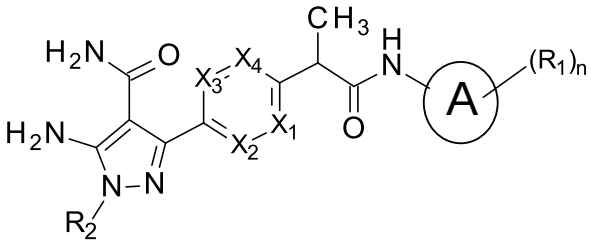
conformational structure of a RET kinase to such an extent that a given RET kinase inhibitor may be less effective (or ineffective). In such cases, new RET kinase inhibitors that are effective to the modified RET kinase would greatly benefit patients.

Summary

In one aspect of the present disclosure, there is provided a compound of the formula:



wherein

A is a five- or six-member aryl or heteroaryl;

Each R_1 is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -(C_0-C_4 alkyl)(C_5-C_6 heteroalkyl), -(C_0-C_4 alkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 alkyl)(C_4-C_7 cycloheteroalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloheteroalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclic), -(C_0-C_4 alkyl)(C_5-C_6 aryl), -(C_0-C_4 alkyl)(C_5-C_6 heteroaryl), -(C_0-C_4 alkyl)(C_4-C_{10} heterobicyclic), C_5-C_{12} spirane, C_5-C_{12} heterospirane, adamantane, difluoromethylsulfane, or pentafluorosulfane, wherein each R_1 is optionally substituted with one or more groups that are independently halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, or mono-, di-, or tri-halomethyl, and wherein two R_1 groups can fuse to form a ring structure that includes a portion of A and is optionally aromatic, and n is 1, 2, or 3;

X_1, X_2, X_3, and X_4 are each independently N, CH, C-CH_3, C-CH_2-OH, C-OCH_3, C-CH_2-OCH_3, or C-halogen; and

R_2 is C_1-C_4 alkyl, -(C_0-C_4 alkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 alkyl)(C_4-C_7 heterocycloalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclic) each optionally substituted with one or more groups that are independently deuterium, halogen, cyano, hydroxyl, oxo, methyl,

methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl;

or a pharmaceutically acceptable salt thereof.

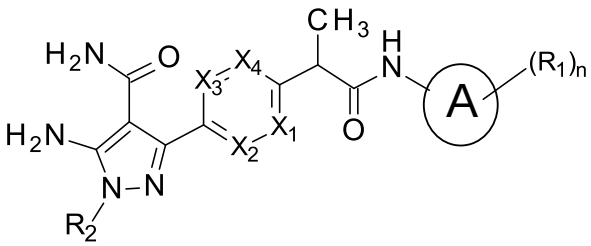
In another aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof, disclosed herein, in the manufacture of a medicament for treating cancer.

In a further aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, disclosed herein for use in therapy.

In another aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, disclosed herein for use in the treatment of cancer.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, disclosed herein with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Compounds of the formula:



(I),

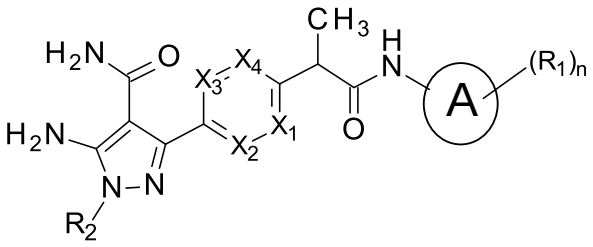
pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, are provided herein. In formula (I), A can be a five- or six-member aryl or heteroaryl; R_1 can be hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -(C_0-C_4 alkyl)(C_5-C_6 heteroalkyl), -(C_0-C_4 alkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 alkyl)(C_4-C_7 cycloheteroalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloheteroalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclic), -(C_0-C_4 alkyl)(C_5-C_6 aryl), -(C_0-C_4 alkyl)(C_5-C_6 heteroaryl), -(C_0-C_4 alkyl)(C_4-C_{10} heterobicyclic), C_5-C_{12} spirane, C_5-C_{12} heterospirane, adamantane, difluoromethylsulfane, or pentafluorosulfane, wherein each R_1 is optionally substituted with one or more groups that are independently halogen, cyano, hydroxyl, oxo, methyl,

methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, or mono-, di-, or tri-halomethyl, and wherein two R_1 groups can fuse to form a ring structure that includes a portion of A and is optionally aromatic, and n is 1, 2, 3, 4 or 5; X_1, X_2, X_3, and X_4 each can be independently N, CH, C-CH_3, C-CH_2-OH, C-OCH_3, C-CH_2-OCH_3 or C-halogen; and R_2 can be C_1-C_4 alkyl, -(C_0-C_4 alkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 alkyl)(C_4-C_7 heterocycloalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclic), with each being optionally substituted with one or more groups that are independently deuterium, halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl. The compounds of

CLAIMS

What is claimed is:

1. A compound of the formula:



wherein

A is a five- or six-member aryl or heteroaryl;

Each R_1 is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -(C_0-C_4 alkyl)(C_5-C_6 heteroalkyl), -(C_0-C_4 alkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 alkyl)(C_4-C_7 cycloheteroalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloheteroalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclic), -(C_0-C_4 alkyl)(C_5-C_6 aryl), -(C_0-C_4 alkyl)(C_5-C_6 heteroaryl), -(C_0-C_4 alkyl)(C_4-C_{10} heterobicyclic), C_5-C_{12} spirane, C_5-C_{12} heterospirane, adamantane, difluoromethylsulfane, or pentafluorosulfane, wherein each R_1 is optionally substituted with one or more groups that are independently halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, or mono-, di-, or tri-halomethyl, and wherein two R_1 groups can fuse to form a ring structure that includes a portion of A and is optionally aromatic, and n is 1, 2, or 3;

X_1, X_2, X_3, and X_4 are each independently N, CH, C-CH_3, C-CH_2-OH, C-OCH_3, C-CH_2-OCH_3, or C-halogen; and

R_2 is C_1-C_4 alkyl, -(C_0-C_4 alkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 alkyl)(C_4-C_7 heterocycloalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclic) each optionally substituted with one or more groups that are independently deuterium, halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl;

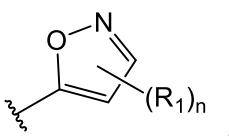
or a pharmaceutically acceptable salt thereof.

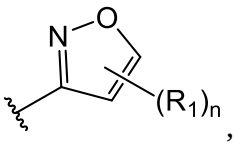
2. The compound according to claim 1, wherein each of X_1, X_2, X_3, and X_4 is CH, or a pharmaceutically acceptable salt thereof.

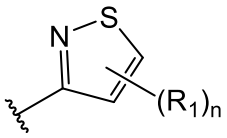
3. The compound according to claim 1, wherein X_1 is N and each of X_2, X_3, and X_4 is CH, or a pharmaceutically acceptable salt thereof.

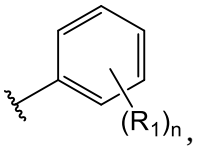
4. The compound according to claim 1, wherein X_2 is N and each of X_1, X_3, and X_4 is CH, or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1 to 4, wherein A-$(R_1)_n$ is



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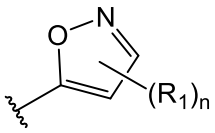
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or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1-5, wherein A-$(R_1)_n$ is

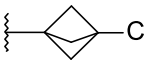


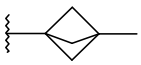
,

or a pharmaceutically acceptable salt thereof.

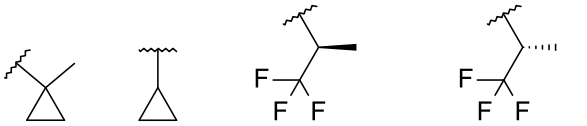
7. The compound according to claim 5 or 6, wherein R_1 is 2,2-dimethylpropyl; 2-chloro-4-fluoro-phenyl; 2,4-dichlorophenyl; 1,1-dimethyl-2,2,2-trifluoroethyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; trifluoromethyl; 1,1-dimethyl-2,2-difluoropropyl; 1,1-dimethyl-3,3,3-trifluoropropyl; 1-methylcyclopropyl; (1-methylcyclopropyl)methyl; 3-methylbicyclo[1.1.1]pentan-1-yl; 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl; (3,3-dimethylcyclobutyl)methyl or a pharmaceutically acceptable salt thereof.

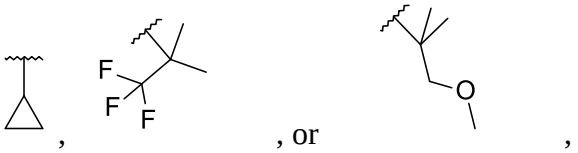
8. The compound according to claim 5, 6 or 7, wherein R_1 is 2,2-dimethylpropyl, or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 5 or 6, wherein at least one R_1 is halogen, $-CH_2C(CH_3)_3$, 

,  or a pharmaceutically acceptable salt thereof.

10. The compound according to any of claims 1 to 9, wherein R_2 is



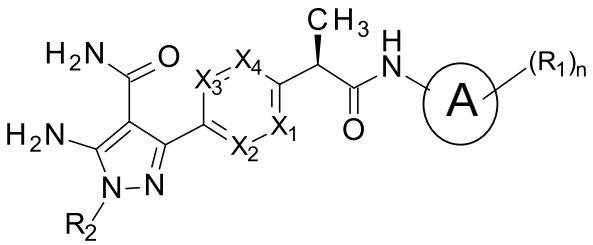


or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of claims 1-9, wherein R_2 is $-CH(CH_3)_2$, $-CH(CF_3)CH_3$, $-CH(CH_3)CHF_2$, or , or a pharmaceutically acceptable salt thereof.

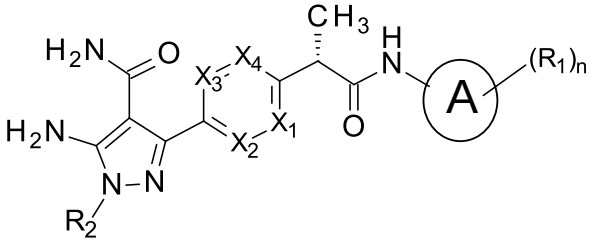
12. The compound according to any one of claims 1- 9, wherein R_2 is  or , or a pharmaceutically acceptable salt thereof.

13. The compound according to any of claims 1 to 12 of the formula:



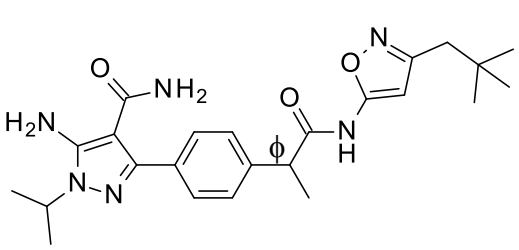
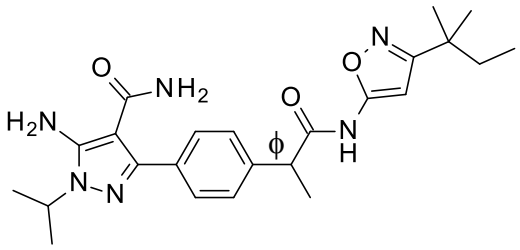
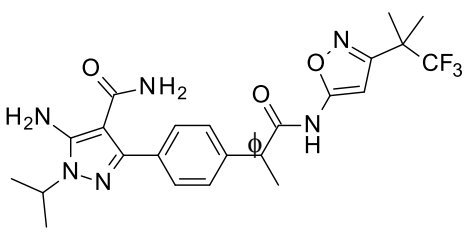
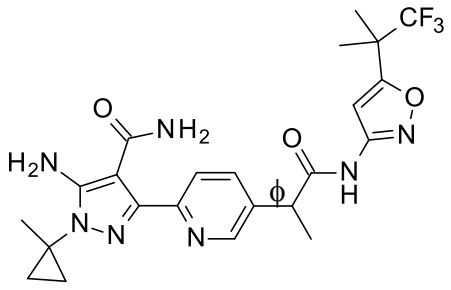
or a pharmaceutically acceptable salt thereof.

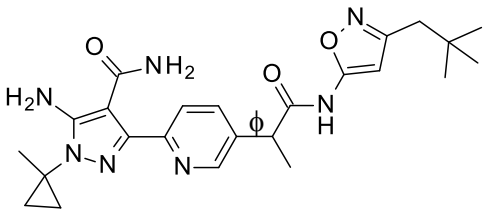
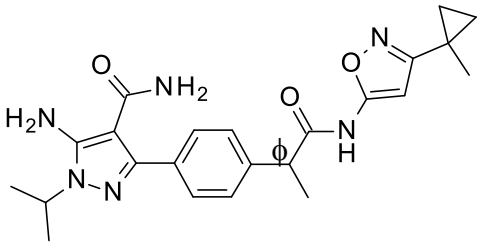
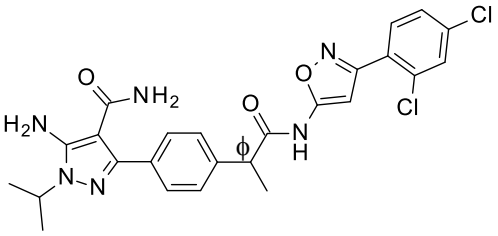
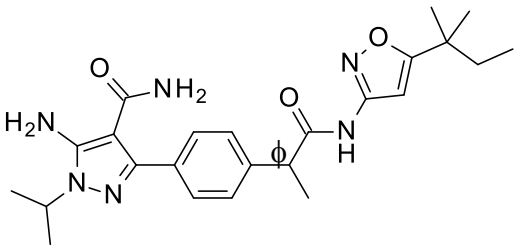
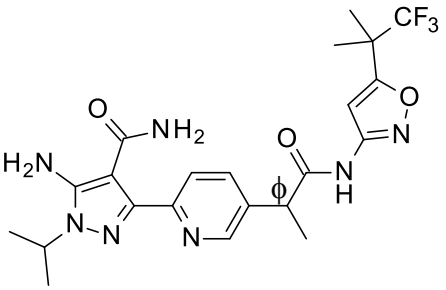
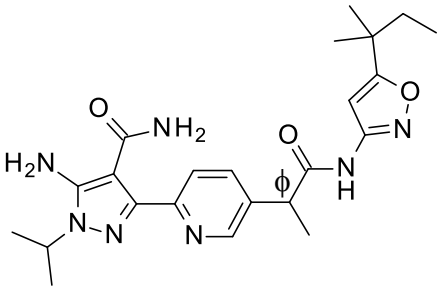
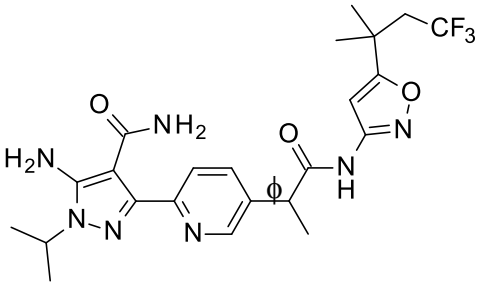
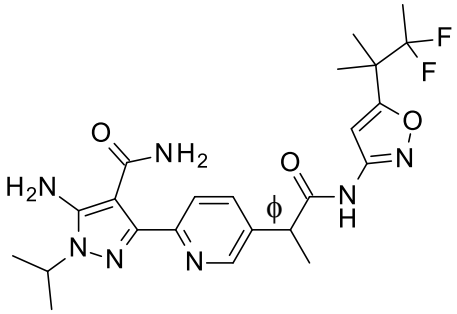
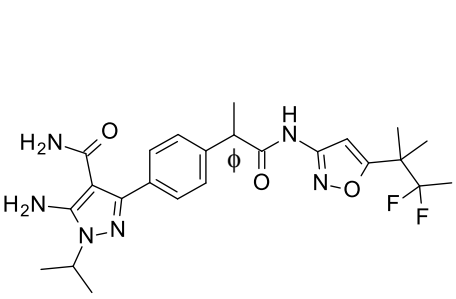
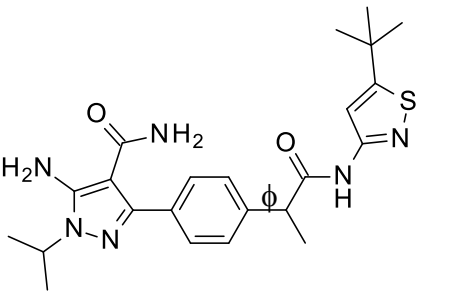
14. The compound according to any of claims 1 to 12 of the formula:



or a pharmaceutically acceptable salt thereof.

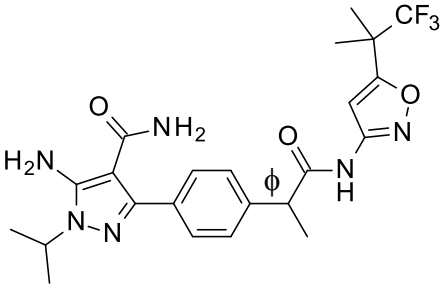
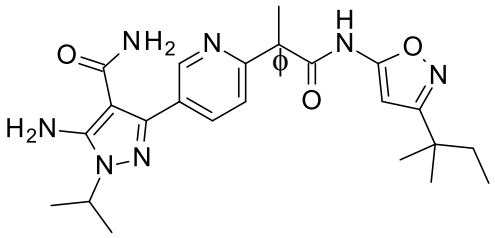
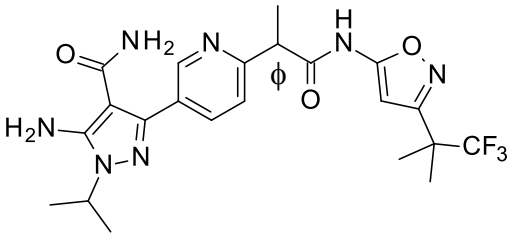
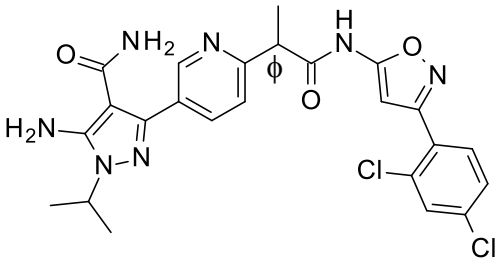
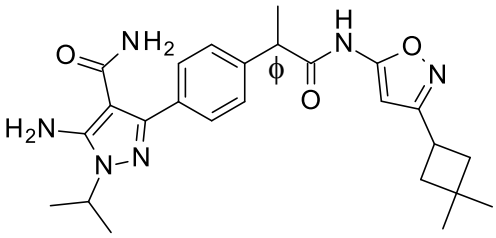
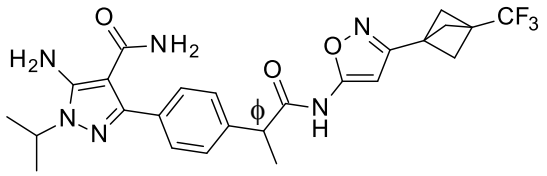
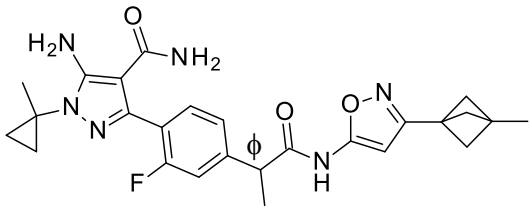
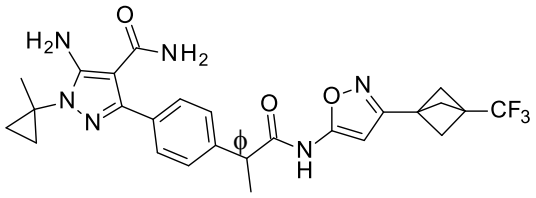
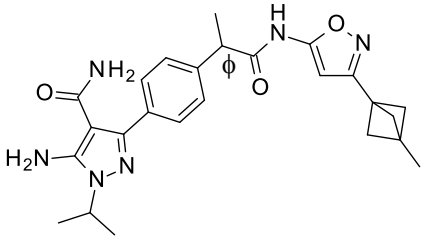
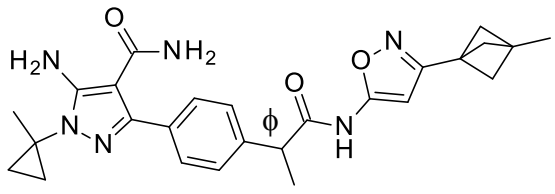
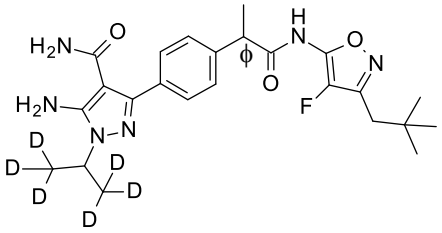
15. The compound according to claim 1 of the formula:


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or

, or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 15, wherein the formulas have R-enantiomeric chirality at the ϕ position.

17. The compound according to claim 15, wherein the formulas have S-enantiomeric chirality at the ϕ position.

18. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 17, in the manufacture of a medicament for treating cancer.

19. The use of claim 18, wherein the cancer is a RET-associated cancer.

20. The use according to claim 18 or 19, wherein the cancer is selected from the group consisting of: lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, and cervical cancer.

21. The use of claim 20, wherein the cancer is medullary thyroid cancer.

22. The use of claim 20, wherein the lung cancer is small cell lung carcinoma, non-small cell lung cancer, bronchioles lung cell carcinoma, RET fusion lung cancer, or lung adenocarcinoma.

23. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 17 for use in therapy.

24. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 17 for use in the treatment of cancer.

25. The compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer of claim 24, wherein the cancer is a RET-associated cancer.

26. The compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer of claim 24 or 25, wherein the cancer is selected from the group consisting of: lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, and cervical cancer.

27. The compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer of claim 26, wherein the cancer is medullary thyroid cancer.

28. The compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer of claim 26, wherein the lung cancer is small cell lung carcinoma, non-small cell lung cancer, bronchioles lung cell carcinoma, RET fusion lung cancer, or lung adenocarcinoma.

29. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 17 with one or more pharmaceutically acceptable carriers, diluents, or excipients.