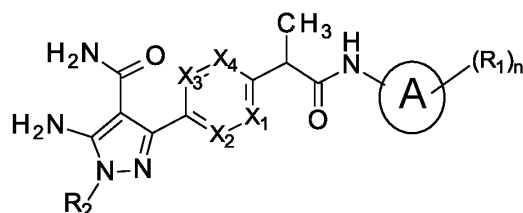


CLAIMS

What is claimed is:

1. A compound of the formula:



wherein

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

Each R₁ is independently hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ heteroalkyl, -(C₀-C₄ alkyl)(C₅-C₆ heteroalkyl), -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(C₄-C₇ cycloheteroalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloheteroalkyl), -(C₀-C₄ alkyl)(C₄-C₁₀ bicyclic), -(C₀-C₄ alkyl)(C₅-C₆ aryl), -(C₀-C₄ alkyl)(C₅-C₆ heteroaryl), -(C₀-C₄ alkyl)(C₄-C₁₀ heterobicyclic), C₅-C₁₂ spirane, C₅-C₁₂ heterospirane, adamantane, difluoromethylsulfane, or pentafluorosulfane, wherein each R₁ 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 R₁ 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;

X₁, X₂, X₃, and X₄ are each independently N, CH, C-CH₃, C-CH₂-OH, C-OCH₃, C-CH₂-OCH₃, or C-halogen; and

R₂ is C₁-C₄ alkyl, -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(C₄-C₇ heterocycloalkyl), -(C₀-C₄ alkyl)(C₄-C₁₀ 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;

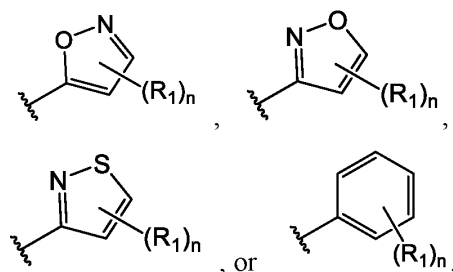
or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein each of X₁, X₂, X₃, and X₄ 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.

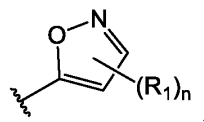
4. The compound according to claim 1, wherein X_2 is N and each of X_1 , X_3 , and X_4 is CH, or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof.

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

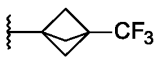
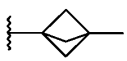


or a pharmaceutically acceptable salt thereof.

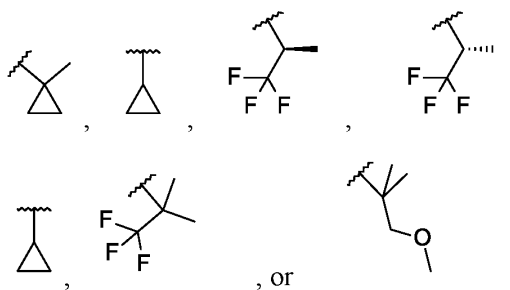
7. The compound according to claim 5 or 6, wherein R_1 is 2,2-dimethylpropyl; 2-chloro-4-fluoro-phenyl; 2,4-dichlorophenyl; 1,1-dimethyl-2,2,2-trifluoroethyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; trifluoromethyl; 1,1-dimethyl-2,2-difluoropropyl; 1,1-dimethyl-3,3,3-trifluoropropyl; 1-methylcyclopropyl; (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,

-CH₂C(CH₃)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.

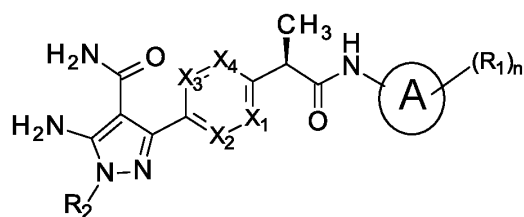
11. The compound according to any one of claims 1-9, wherein R_2 is -CH(CH₃)₂,

-CH(CF₃)CH₃, -CH(CH₃)CHF₂, or , or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of claims 1-9, wherein R_2 is  or

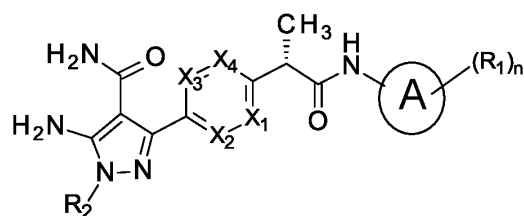
, or a pharmaceutically acceptable salt thereof.

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



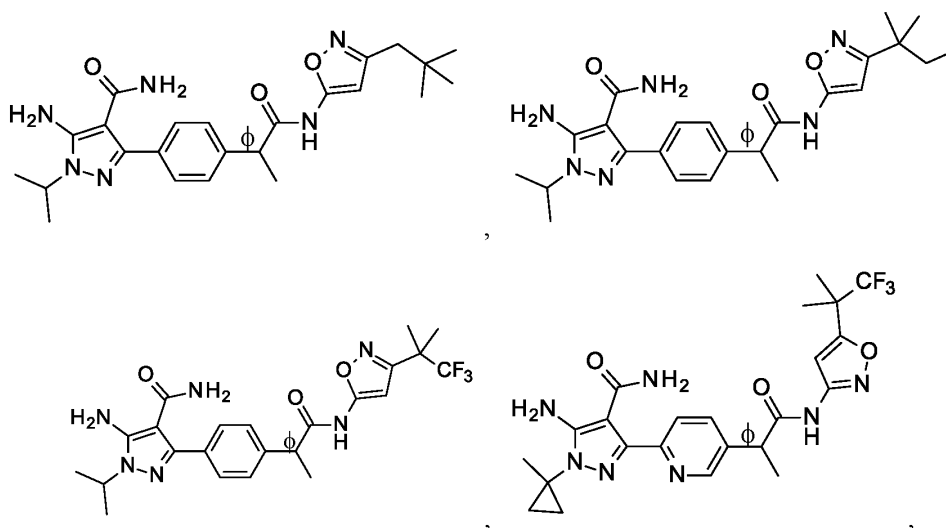
or a pharmaceutically acceptable salt thereof.

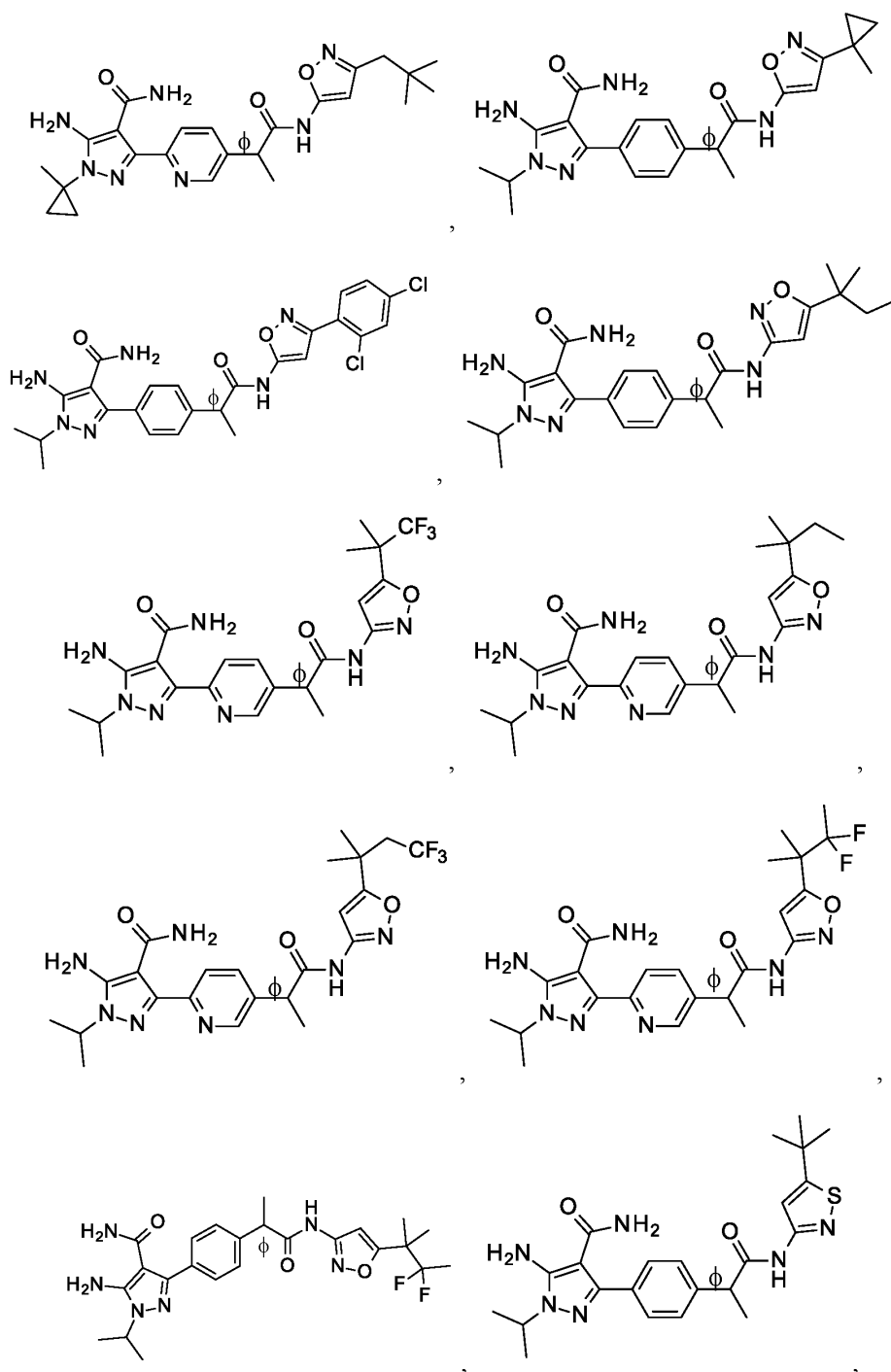
14. The compound according to any of claims 1 to 12 of the formula:

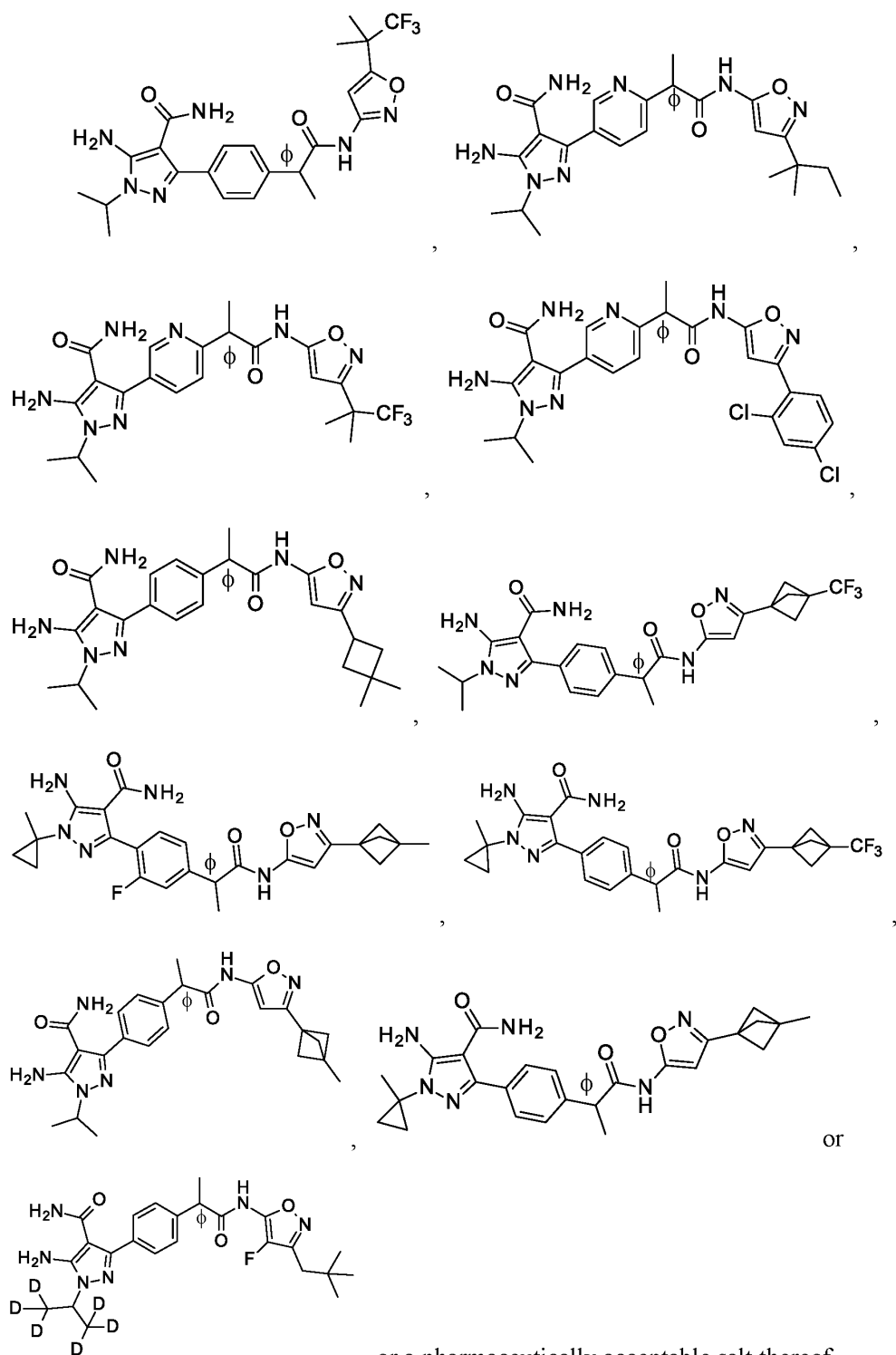


or a pharmaceutically acceptable salt thereof.

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







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. A method of treating cancer in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 17.
19. The method of claim 18, wherein the cancer is a RET-associated cancer.
20. The method 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 method of claim 20, wherein the cancer is medullary thyroid cancer.
22. The method 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. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 17 for the manufacture of a medicament for treating cancer.
30. 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.