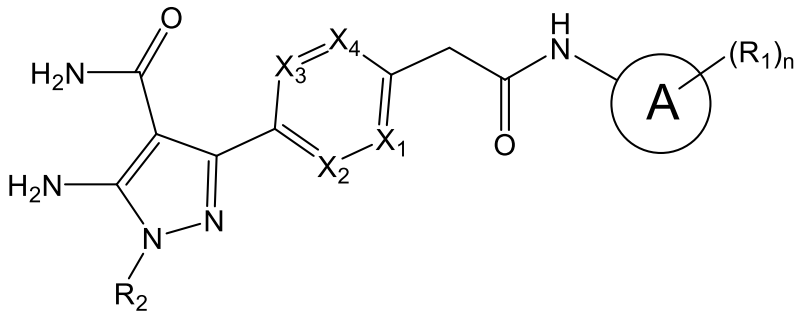
to overactive RET signaling would be of great benefit. Additionally, some RET kinase genetic alterations are altering the conformational structure of a RET kinase to such an extent that a given RET kinase inhibitor may be less effective (or ineffective). In such cases, new RET kinase inhibitors that 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 C_6-C_{10} aryl or C_5-C_6 heteroaryl;

each R_1 is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -(C_1-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_3-C_7 cycloheteroalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloheteroalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclyl), -(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} heterobicyclyl), C_5-C_{12} spiranyl, C_5-C_{12} heterospiranyl, dimethylphosphoryl, adamantyl, C_1-C_6 alkoxy, -(C_1-C_4 alkyl)-SO_2-(C_1-C_4 alkyl), difluoromethylsulfanyl, or pentafluorosulfanyl, wherein each R_1 is unsubstituted or when it is capable of being substituted, it is substituted with one or more substituents that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, mono-, di, or trihalomethoxy, mono-, di-, or tri-halomethyl, and C_0-C_3 alkyl-pyrrolidinyl, where the pyrrolidinyl group is unsubstituted or substituted with one, two or 3 independently selected halogen atoms, 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, 5, or 6;

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_6 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 of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl;

or a pharmaceutically acceptable salt thereof.

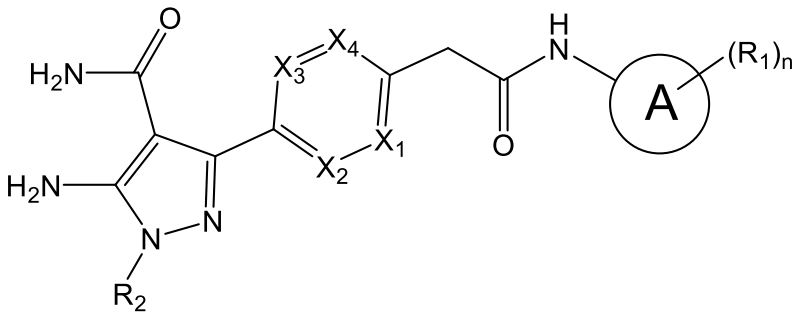
In another aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof, disclosed herein, in the manufacture of a medicament for treating cancer.

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 and at least one pharmaceutically acceptable carrier, diluent, or excipient.

Disclosed herein are compounds of formula I:



I

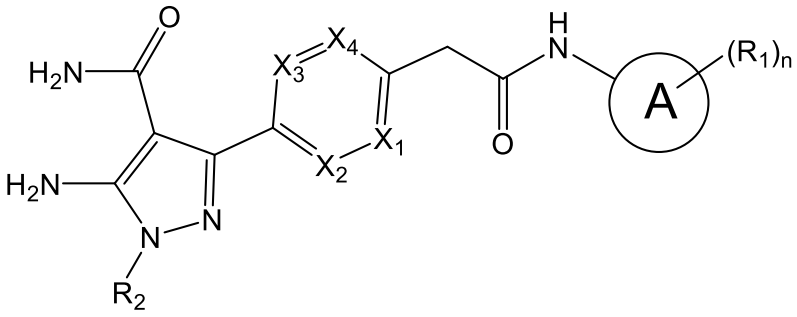
wherein

A is C_6-C_{10} aryl or C_5-C_6 heteroaryl;

each R_1 is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -(C_1-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_3-C_7 cycloheteroalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloheteroalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclyl), -(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} heterobicyclyl), C_5-C_{12} spiranyl, C_5-C_{12} heterospiranyl, dimethylphosphoryl, adamantyl, C_1-C_6 alkoxy, -(C_1-C_4 alkyl)-SO_2-(C_1-C_4 alkyl), difluoromethylsulfanyl, or pentafluorosulfanyl, wherein each R_1 is unsubstituted or when it is capable of being substituted, it is substituted with one or more substituents that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, mono-, di, or trihalomethoxy, mono-, di-, or tri-halomethyl, and C_0-C_3 alkyl-pyrrolidinyl, where the pyrrolidinyl group is unsubstituted or substituted with one, two or 3 independently selected halogen atoms, and wherein two R_1 groups can fuse to form a

CLAIMS

1. A compound of the formula:



wherein

A is C_6-C_{10} aryl or C_5-C_6 heteroaryl;

each R_1 is independently hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -(C_1-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_3-C_7 cycloheteroalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloheteroalkyl), -(C_0-C_4 alkyl)(C_4-C_{10} bicyclyl), -(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} heterobicyclyl), C_5-C_{12} spiranyl, C_5-C_{12} heterospiranyl, dimethylphosphoryl, adamantyl, C_1-C_6 alkoxy, -(C_1-C_4 alkyl)-SO_2-(C_1-C_4 alkyl), difluoromethylsulfanyl, or pentafluorosulfanyl, wherein each R_1 is unsubstituted or when it is capable of being substituted, it is substituted with one or more substituents that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, mono-, di, or trihalomethoxy, mono-, di-, or tri-halomethyl, and C_0-C_3 alkyl-pyrrolidinyl, where the pyrrolidinyl group is unsubstituted or substituted with one, two or 3 independently selected halogen atoms, 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, 5, or 6;

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_6 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 of 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 or a pharmaceutically acceptable salt thereof according to claim 1, wherein at least one of X_1, X_2, X_3, and X_4 is CH.

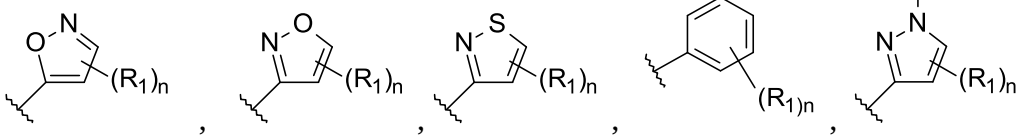
3. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein X_1, X_2, X_3, and X_4 are each CH.

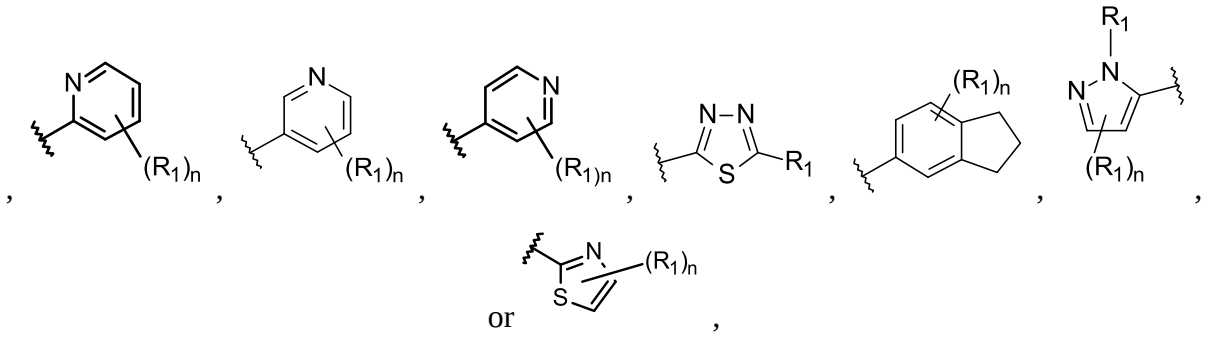
4. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein at least one of X_1, X_2, X_3, and X_4 is N.

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

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

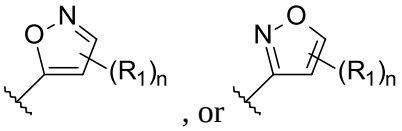
7. The compounds or a pharmaceutically acceptable salts thereof according to any one of claims 1 to 6, wherein A-$(R_1)_n$ is





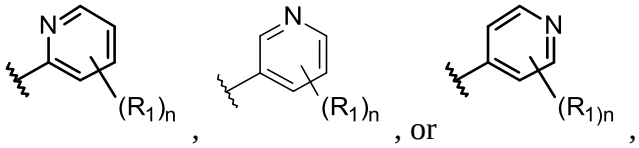
wherein a wavy line indicates connection to the backbone and the maximum value of n depends on the number of substitutable positions on the A-ring.

8. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein A-$(R_1)_n$ is



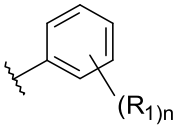
and the maximum value of n depends on the number of substitutable positions on the A-ring.

9. The compound or a pharmaceutically acceptable salts thereof according to any one of claims 1-7, wherein A-$(R_1)_n$ is

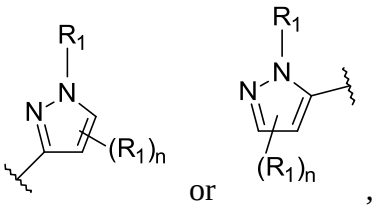


and the maximum value of n depends on the number of substitutable positions on the A-ring.

10. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein A-$(R_1)_n$ is

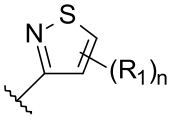
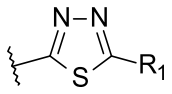
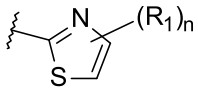


11. The compound or a pharmaceutically acceptable salts thereof according to any one of claims 1-7, wherein A-$(R_1)_n$ is

 or ,

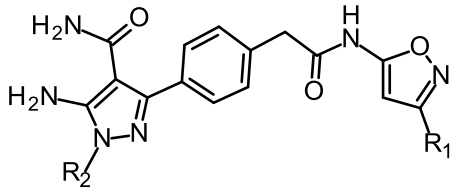
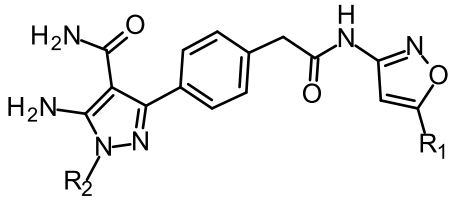
and the maximum value of n depends on the number of substitutable positions on the A-ring.

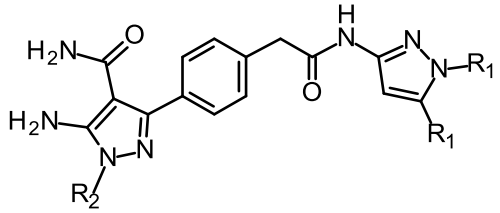
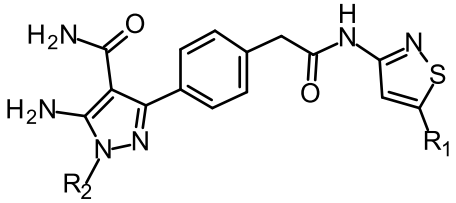
12. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein A-$(R_1)_n$ is

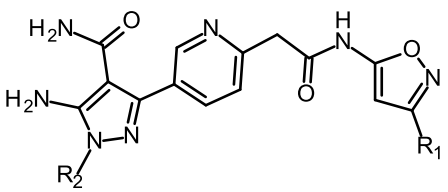
 ,  , or  ,

and the maximum value of n depends on the number of substitutable positions on the A-ring.

13. The compound or a pharmaceutically acceptable salt thereof according to any one of claim 1, wherein the compound is selected from the group consisting of

 ,  ,

 ,  ,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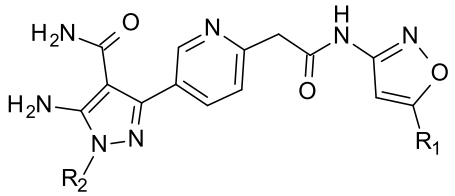
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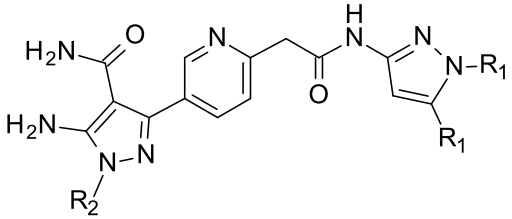
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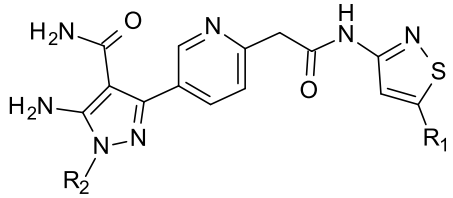
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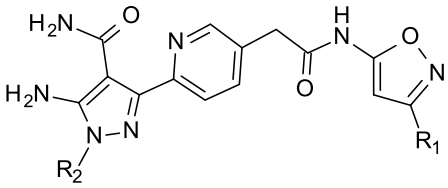
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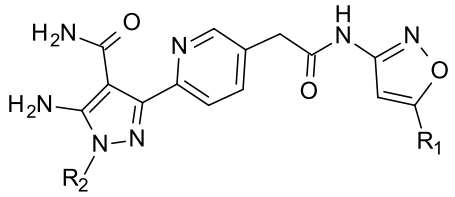
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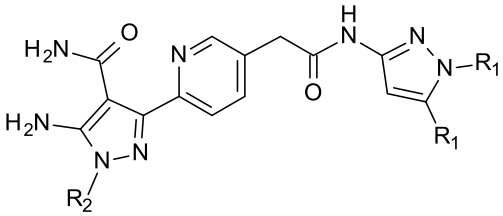
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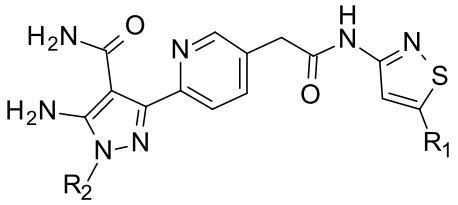
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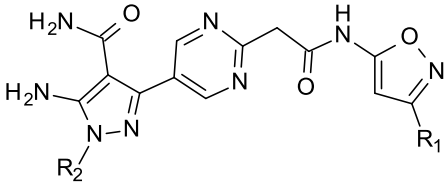
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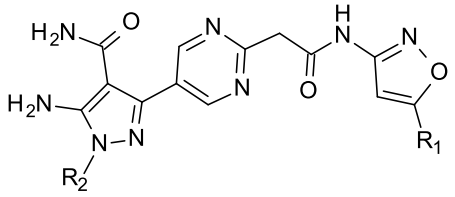
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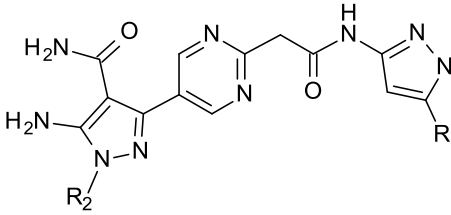
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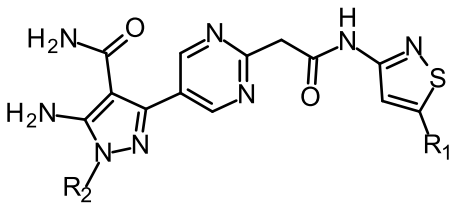
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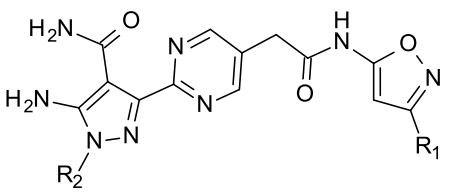
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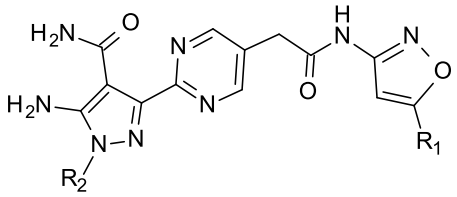
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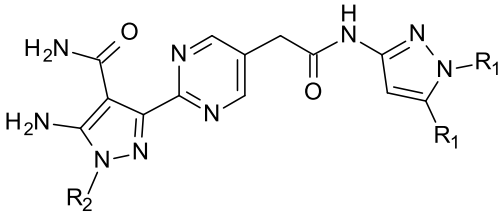
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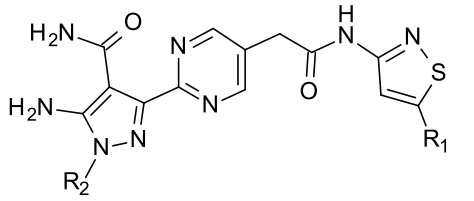
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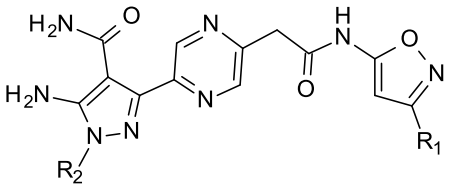
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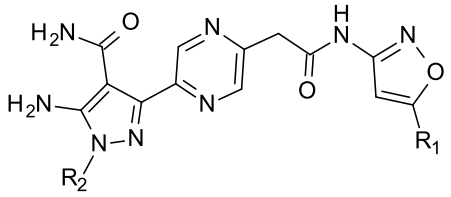
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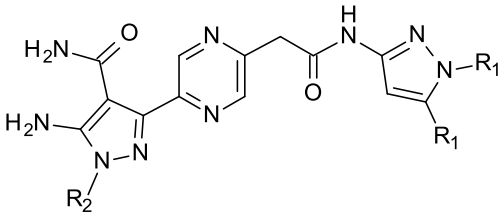
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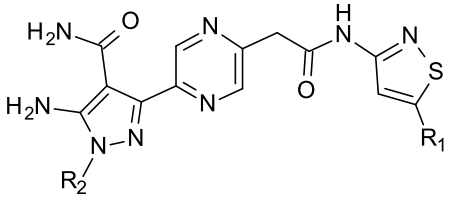
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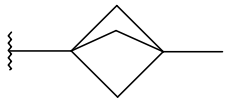
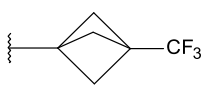
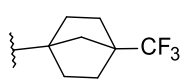
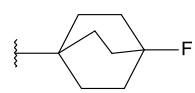
14. The compound according to any one of claims 1 to 13, wherein each R_1 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_4-C_{10} bicyclyl and C_5-C_{12} spiranyl, wherein the C_4-C_{10} bicyclyl is a C_4-C_8 bridged bicycloalkyl, and wherein each R_1 is optionally substituted with one or more of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, or mono-, di-, or tri-halomethyl.

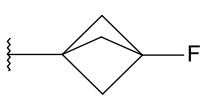
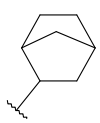
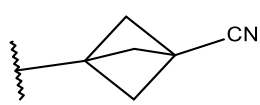
15. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is independently 2,2-dimethylpropyl; 2-chloro-4-fluoro-phenyl; 2,4-dichlorophenyl; 1,1-dimethyl-2,2,2-trifluoroethyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; trifluoromethyl; 1,1-dimethyl-2,2-difluoropropyl; 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; or (3,3-dimethylcyclobutyl)methyl.

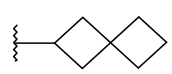
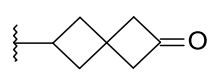
16. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is a C_4-C_8 bridged bicycloalkyl that is unsubstituted or substituted with 1 or 2 groups independently selected from the group consisting of methyl, ethyl, CF_3, halo, and CN.

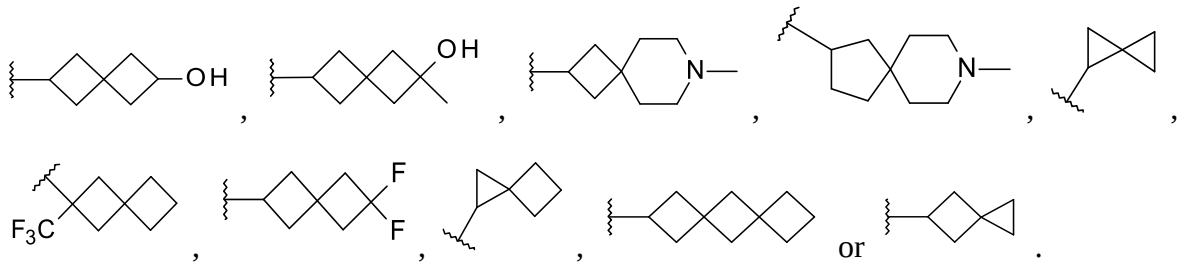
17. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, or claim 16, wherein each R_1 is independently

 ,  ,  ,  ,  ,

 ,  , or  .

18. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein n is 1 and R_1 is a C_5-C_{12} spirane that is unsubstituted or substituted with 1 or 2 groups that are independently selected from the group consisting of =O, -OH, methyl, ethyl, CF_3, and halo.

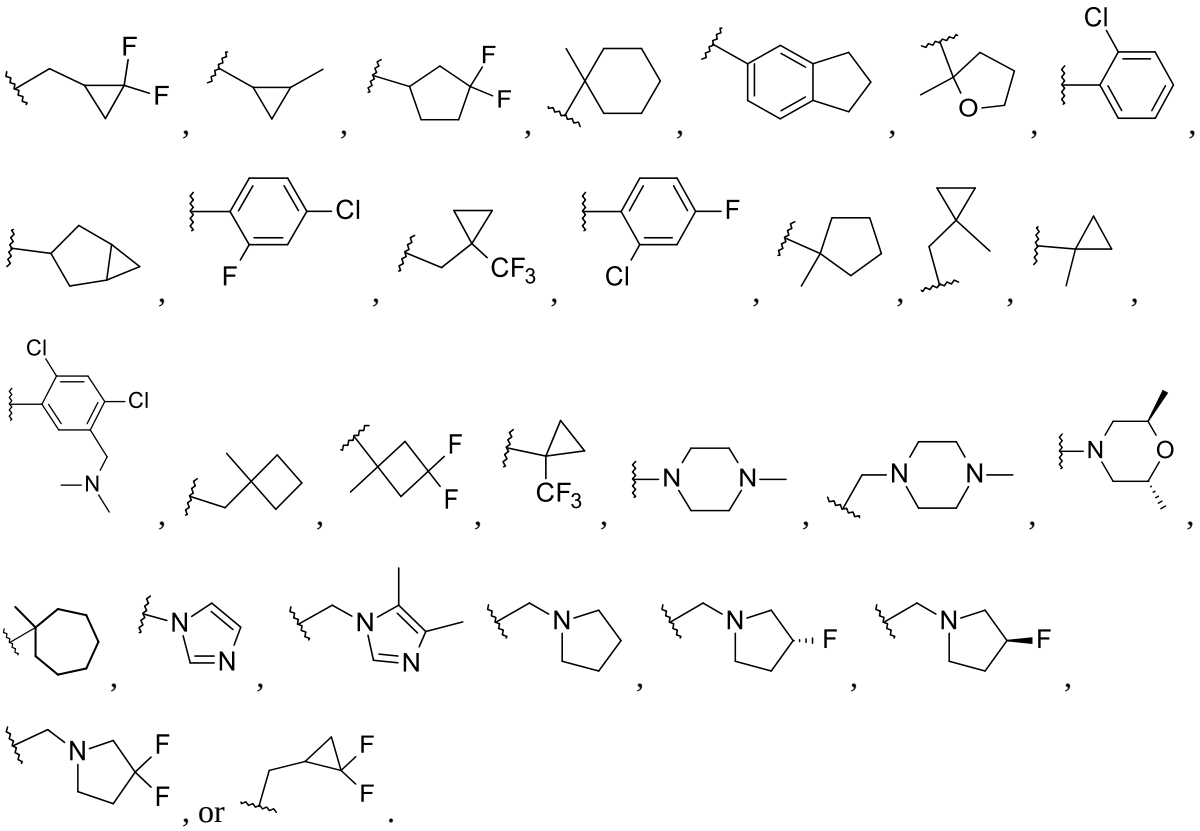
19. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is independently  ,  ,

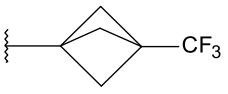


20. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is independently halogen, C_1-C_6 alkyl, -(C_0-C_4 alkyl)(C_3-C_7 cycloalkyl), -(C_0-C_4 alkyl)(phenyl), -(C_1-C_4 alkyl)(C_5-C_6 heteroalkyl), -(C_0-C_4 heteroalkyl)(C_3-C_7 cycloheteroalkyl), or -(C_0-C_4 alkyl)(C_5-C_6 heteroaryl), wherein each R_1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, and mono-, di-, or tri-halomethyl.

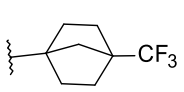
21. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is independently -$CH_2C(CH_3)_3$, -$CH(CH_2CH_3)_2$, -CF_2CH_3, -$CH_2CH_2CF_3$, -$C(CH_3)_2F$, -$C(CH_3)_2CF_3$, -CH_2-cyclopentyl, -CH_2-cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-morpholinyl, -CH_2-pyrrolidinyl, phenyl, naphthyl, pyran-4-yl, 4-methylphenyl, 4-methoxyphenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, 3-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2,4-dimethylphenyl, 4-chlorophenyl, 2-methylphenyl, 3-fluorophenyl, 3-chlorophenyl, 2-methoxyphenyl, 4-difluoromethoxyphenyl, -$C(CH_3)_2SO_2CH_3$, 4-fluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3-chlorophenyl, methyl, ethyl, *tert*-butyl, isopropyl, trifluoromethyl, 3-methoxyphenyl, 3-bromophenyl, 4-bromophenyl, 2,4,6-trifluoromethylphenyl, 3-tetrahydrofuranyl, -$C(CH_3)_2CH_2CH_3$, -$C(CH_3)_2OH$, 3,3-dimethylcyclobut-1-yl, 2,3-dichlorobenzyl, 3,3-difluoromethylcyclobutyl, 2,2-dimethylcycloprop-1-yl, 2,2-difluorocyclopropyl, N-methylimidazolyl, 2-methyl-4-chlorophenyl, 2,4-dichloro-3-fluorophenyl, -CH_2OCH_3, -CH_2CF_3, -CF_2CH_3, -$CF_2C(CH_3)_3$, -$CH(CH_3)$cyclopropyl, 2,6-difluorophenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 3-chloropyrid-2-

yl, 2-methylpyrid-3-yl, 4-methylpyrid-3-yl, 3,5-dichloropyrid-2-yl, 3,3-difluorocyclopentyl, fluoro, chloro, bromo, 2-methoxy-4-chloro-phenyl, 2-fluoro-4-chlorophenyl, 3-fluoro-4-chlorophenyl, benzyl, piperidinyl, 4-methyl-piperidinyl, 4-methoxy-piperidinyl, N-methylpyrazol-3-yl, -C(O)-piperidinyl, $-OCHF_2$,



22. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein n is 1 and R_1 is 2,2-dimethylpropyl or  .

23. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein R_1 is independently



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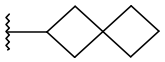
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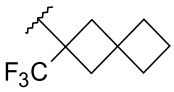

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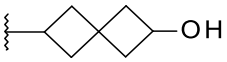

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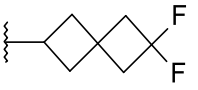

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24. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-13, wherein R_1 is C_1-C_6 alkyl, which is unsubstituted or substituted with one or more substituents that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, and mono-, di-, and tri-halomethyl and n is 1 or 2.

25. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R_2 is -C_1-C_6 alkyl, -C_1-C_4 alkyl-tetrahydrofuranyl, C_3-C_6 cycloalkyl, tetrahydrofuranyl, pyranyl, -C_1-C_4 alkyl – tetrahydropyranyl, -C_1-C_4 alkyl –C_3-C_6 cycloalkyl, and azetidinyl, wherein each is unsubstituted or substituted with one or two groups that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl.

26. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R_2 is of *tert*-butyl, -CH(CH_3)-cyclopropyl, -2-tetrahydrofuranyl, -3-tetrahydrofuranyl, -3-pyranyl, -4-pyranyl, -CH(CH_3)CH_2OH, -C(CH_3)$_2CH_2OH$, -CH_2-(2-tetrahydrofuranyl), -CH_2-(3-tetrahydrofuranyl), -$(CH_2)_3OH$, -C(CH_3)$_2CH_2OCH_3$, -CH(CH_3)CF_3, -CH_2CF_3, -C(CH_3)$_2CH_2OCH_3$, cyclopentyl,


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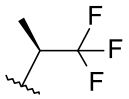

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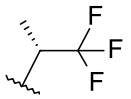

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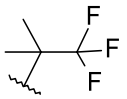

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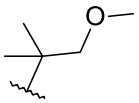

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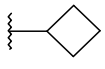
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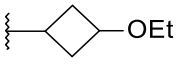

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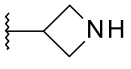

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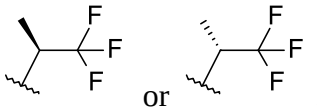
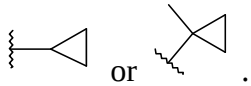
27. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R_2 is



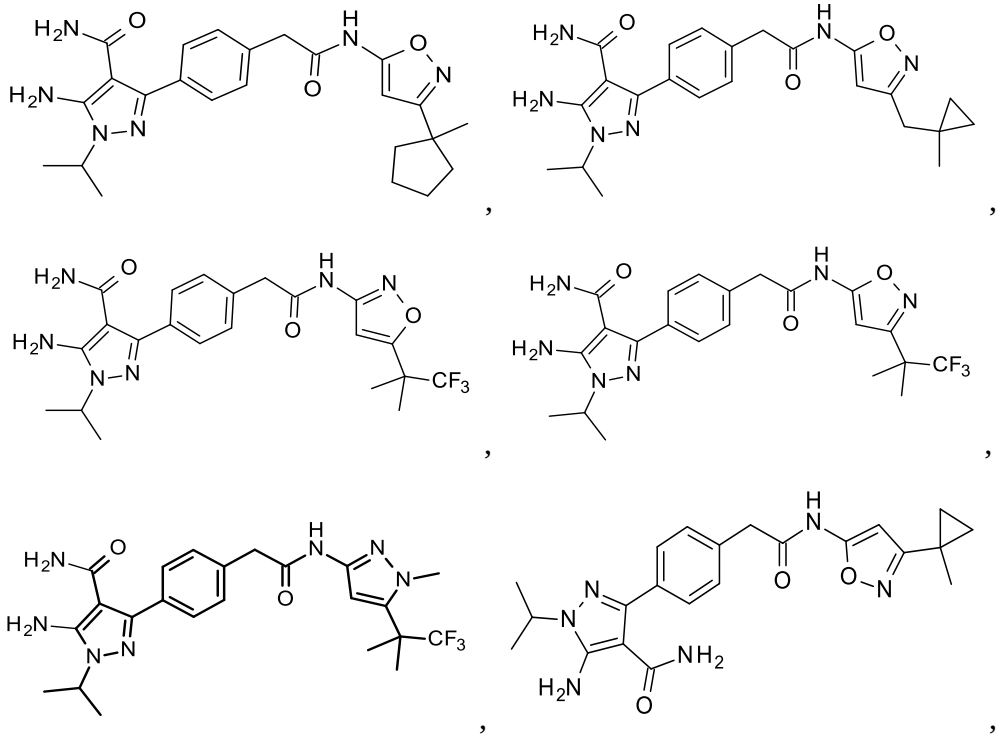
28. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R_2 is

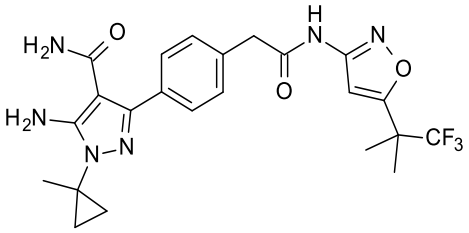


29. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R_2 is



30. The compound or a pharmaceutically acceptable salt thereof, according to claim 1 that is:

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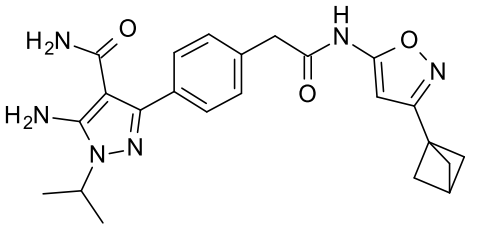
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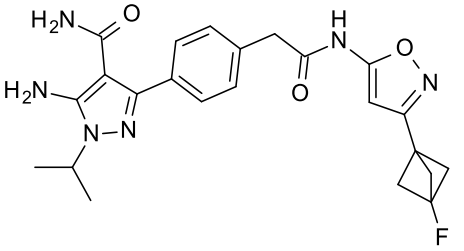
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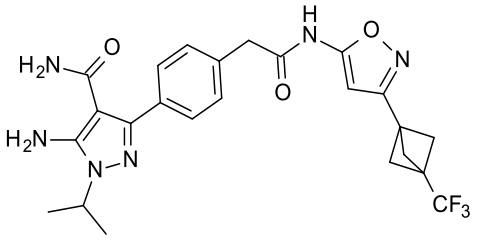
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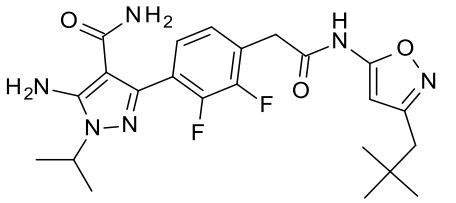
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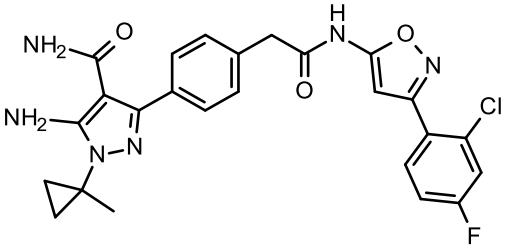
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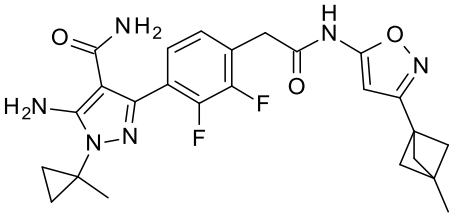
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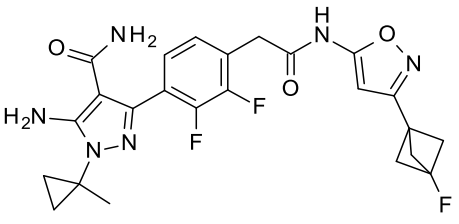
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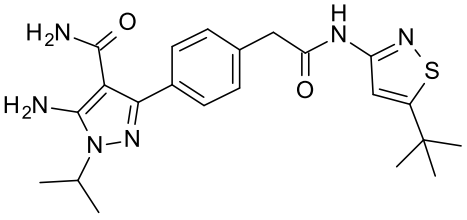
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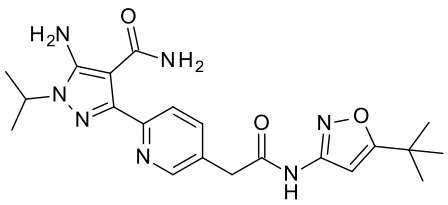
31. The compound or a pharmaceutically acceptable salt thereof, according to claim 1 that is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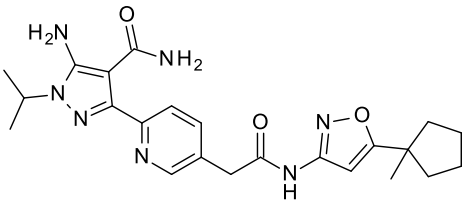
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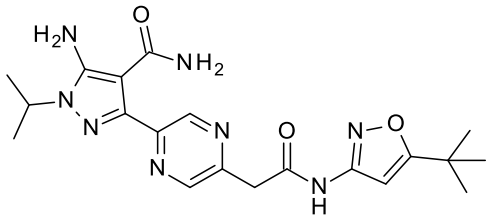
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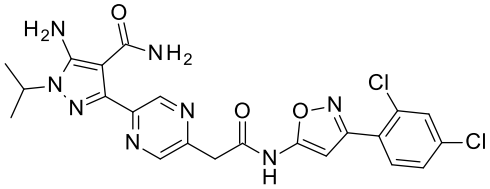
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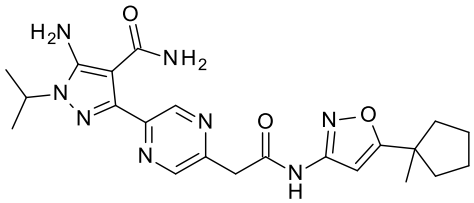
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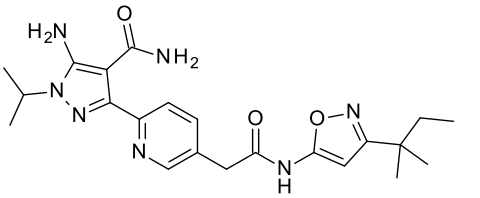
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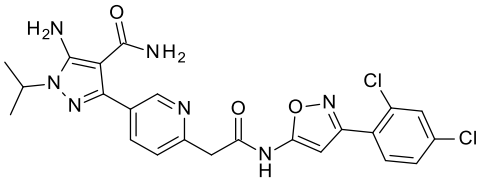
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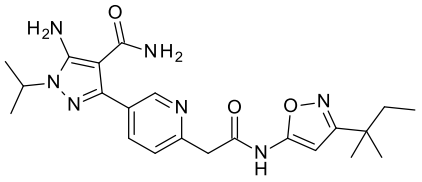
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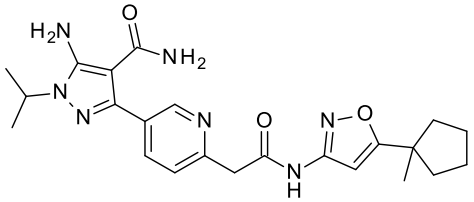
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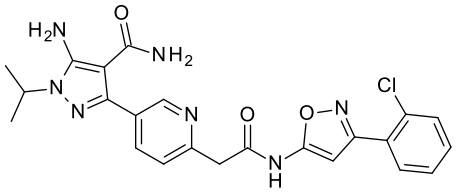
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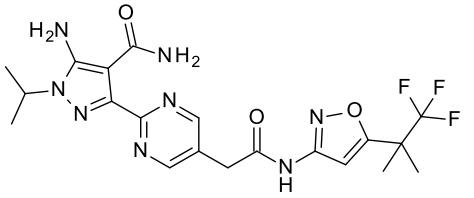
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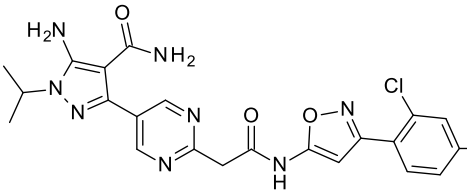
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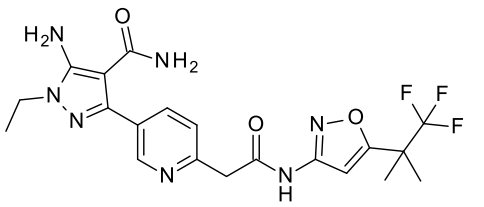

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32. Use of~~A method of treating cancer in a patient, comprising administering to a patient in need of such treatment an effective amount of~~ a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31, in the manufacture of a medicament for treating cancer.

33. The use~~method~~ of claim 32, wherein the cancer is a RET-associated cancer.

34. The use~~method~~ according to claim 32 or 33, 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.

35. The use~~method~~ of claim 34, wherein the cancer is medullary thyroid cancer.

36. The use~~method~~ of claim 34, 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.

37. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31 for use in therapy.

38. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31 for use in the treatment of cancer.

39. A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 38, wherein the cancer is a RET-associated cancer.

40. A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 38 or 39, 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.

41. A compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 38-39, wherein the cancer is medullary thyroid cancer.

42. The compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 38-40, 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.

~~43. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31 for the manufacture of a medicament for treating cancer.~~

43~~44~~. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31 and at least one pharmaceutically acceptable carrier, diluent, or excipient.