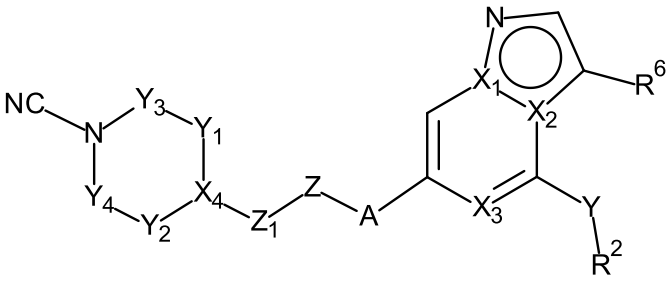
FGFR3 INHIBITOR COMPOUNDS

Background

Fibroblast growth factor (FGF) has been recognized as an important mediator of many physiological processes, such as morphogenesis during development, fibrosis, and angiogenesis. The fibroblast growth factor receptor (FGFR) family consists of five members four of which (FGFR 1-4) are glycoproteins composed of extracellular immunoglobulin (Ig)-like domains, a hydrophobic transmembrane region and a cytoplasmic part containing a tyrosine kinase domain. FGF binding leads to FGFR dimerization, followed by receptor autophosphorylation and activation of downstream signaling pathways. Receptor activation is sufficient for the recruitment and activation of specific downstream signaling partners that participate in the regulation of diverse processes such as cell growth, cell metabolism and cell survival. Thus, the FGF/FGFR signaling pathway has pleiotropic effects on many biological processes critical to tumor cell proliferation, migration, invasion, and angiogenesis.

Summary

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



wherein

A is pyrazole, triazole, thiadiazole or oxadiazole, substituted with R^1 and R^{1A};

R^1 is hydrogen or C_1-C_3 alkyl;

R^{1A} is hydrogen, halo, CN, or C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from halo, OH, and OCH_3;

X_1 and X_2 are independently selected from N and C, wherein when one of X_1 or X_2 is N the other is C;

X_3 is N or CH;

X_4 is N or C-R^9;

Y is NH, O, S or a bond;

Y_1 is a bond, CHR^7, CH_2-CHR^7, CHR^7-CH_2, CF_2, CH_2-CF_2 or CF_2-CH_2;

Y_2 is a bond, CHR^3, CH_2-CHR^3, CHR^3-CH_2, CF_2, CH_2-CF_2 or CF_2-CH_2;

Y_3 is CR^4R^5 or CF_2;

Y_4 is CR^3R^4, or CF_2;

Z is a bond, CHR^{9A}, CR^4R^{4A}, CR^4R^{4A}-CH_2, CH_2-CR^4R^{4A}, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine;

Z_1 is a bond when Z is a bond, CR^4R^{4A}, CR^4R^{4A}-CH_2, CH_2-CR^4R^{4A}, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine, or Z_1 is CH_2 or CH_2-CH_2 when Z is CHR^{9A};

Z_2 is a bond, C(O), SO_2 or -NR^4C(O);

Z_3 is a bond, C(O), SO_2 or -NR^4C(O);

R^2 is C_1-C_5 alkyl or R^8, wherein C_1-C_5 alkyl is optionally substituted with one or more substituents independently selected from halo, OH, CN, oxo, -OC_1-C_4 alkyl, -OC_3-C_5 cycloalkyl, -Z_2-R^{11} and R^{10}, wherein C_1-C_4 alky and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN;

R^3 is hydrogen, F, OH, OCH_3, C_1-C_3 alkyl, cyclopropyl, or one R^3 is fused with R^5 or R^7 to form CH_2, CH_2-CH_2 or CH_2OCH_2;

R^4 is hydrogen or C_1-C_3 alkyl;

R^{4A} is hydrogen, halo, OH, or C_1-C_3 alkyl;

R^5 is hydrogen, F, OH, OCH_3, C_1-C_3 alkyl, cyclopropyl, or is fused with one R^3 to form CH_2, CH_2-CH_2 or CH_2OCH_2;

R^6 is hydrogen, halo, C_1-C_5 alkyl, CN, 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, wherein 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl and 5-6 membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, methyl, halomethyl, OH or OCH_3 and wherein C_1-C_5 alkyl is optionally

substituted with one or more substituents independently selected from halo, OH and OCH_3;

R^7 is hydrogen, F, OH, OCH_3, C_1-C_3 alkyl or is fused with one R^3 to form CH_2, CH_2-CH_2 or CH_2OCH_2;

R^8 is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R^{8A};

R^{8A} is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl;

R^9 is hydrogen, C_1-C_3 alkyl, or is fused with R^{9A} to form CH_2 or CH_2-CH_2;

R^{10} is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R^{8A};

R_{11} is C_1-C_4 alkyl, NH_2, NHC_1-C_3 alkyl, NHC_3-C_5 cycloalkyl or $N(C_1$-C_3 alkyl$)_2$, wherein C_1-C_4 alkyl, C_1-C_3 alkyl and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN;

R^{12} is C_1-C_4 alkyl, C_3-C_5 cycloalkyl, NH_2, NHC_1-C_3 alkyl, NHC_3-C_5 cycloalkyl or $N(C_1$-C_3 alkyl$)_2$, wherein C_1-C_4 alky, C_1-C_3 alkyl and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN; and

R^8, R^{10} and R^{8A} are optionally substituted with one or more substituents independently selected from halo, OH, CN, -OC_1-C_4 alkyl, -OC_3-C_5 cycloalkyl and -Z_3-R^{12} wherein C_1-C_4 alky and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN;

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, as disclosed herein, and a pharmaceutically acceptable carrier, diluent or excipient.

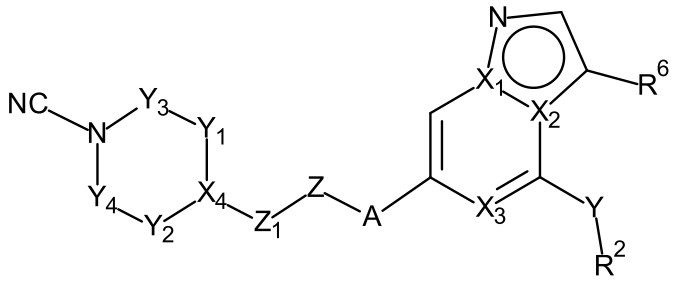
In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating systemic sclerosis, fibrosis, pulmonary fibrosis, achondroplasia,

thanatophoric dysplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), muenke syndrome or cancer.

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

In a further aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, as disclosed herein, for use in the treatment of systemic sclerosis, fibrosis, pulmonary fibrosis, achondroplasia, thanatophoric dysplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), muenke syndrome or cancer.

Provided herein are compounds of the formula:



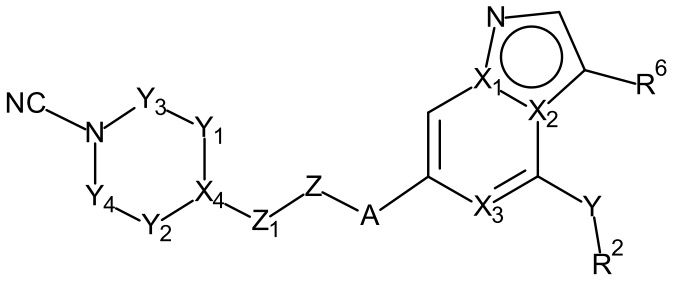
(I)

or a pharmaceutically acceptable salt thereof, wherein A, X_1, X_2, X_3, X_4, Y, Y_1, Y_2, Y_3, Y_4, Z, Z_1, R^2 and R^6 are as defined herein.

Provided herein are compounds of the formula:

CLAIMS

1. A compound of the formula:



wherein

A is pyrazole, triazole, thiadiazole or oxadiazole, substituted with R^1 and R^{1A};

R^1 is hydrogen or C_1-C_3 alkyl;

R^{1A} is hydrogen, halo, CN, or C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from halo, OH, and OCH_3;

X_1 and X_2 are independently selected from N and C, wherein when one of X_1 or X_2 is N the other is C;

X_3 is N or CH;

X_4 is N or C-R^9;

Y is NH, O, S or a bond;

Y_1 is a bond, CHR^7, CH_2-CHR^7, CHR^7-CH_2, CF_2, CH_2-CF_2 or CF_2-CH_2;

Y_2 is a bond, CHR^3, CH_2-CHR^3, CHR^3-CH_2, CF_2, CH_2-CF_2 or CF_2-CH_2;

Y_3 is CR^4R^5 or CF_2;

Y_4 is CR^3R^4, or CF_2;

Z is a bond, CHR^{9A}, CR^4R^{4A}, CR^4R^{4A}-CH_2, CH_2-CR^4R^{4A}, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine;

Z_1 is a bond when Z is a bond, CR^4R^{4A}, CR^4R^{4A}-CH_2, CH_2-CR^4R^{4A}, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine, pyrrolidine or piperidine, or Z_1 is CH_2 or CH_2-CH_2 when Z is CHR^{9A};

Z_2 is a bond, C(O), SO_2 or -NR^4C(O);

Z_3 is a bond, C(O), SO_2 or -NR^4C(O);

R^2 is C_1-C_5 alkyl or R^8, wherein C_1-C_5 alkyl is optionally substituted with one or more substituents independently selected from halo, OH, CN, oxo, -OC_1-C_4 alkyl, -OC_3-

C_5 cycloalkyl, -Z_2-R^{11} and R^{10}, wherein C_1-C_4 alky and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN;

R^3 is hydrogen, F, OH, OCH_3, C_1-C_3 alkyl, cyclopropyl, or one R^3 is fused with R^5 or R^7 to form CH_2, CH_2-CH_2 or CH_2OCH_2;

R^4 is hydrogen or C_1-C_3 alkyl;

R^{4A} is hydrogen, halo, OH, or C_1-C_3 alkyl;

R^5 is hydrogen, F, OH, OCH_3, C_1-C_3 alkyl, cyclopropyl, or is fused with one R^3 to form CH_2, CH_2-CH_2 or CH_2OCH_2;

R^6 is hydrogen, halo, C_1-C_5 alkyl, CN, 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, wherein 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl and 5-6 membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, methyl, halomethyl, OH or OCH_3 and wherein C_1-C_5 alkyl is optionally substituted with one or more substituents independently selected from halo, OH and OCH_3;

R^7 is hydrogen, F, OH, OCH_3, C_1-C_3 alkyl or is fused with one R^3 to form CH_2, CH_2-CH_2 or CH_2OCH_2;

R^8 is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R^{8A};

R^{8A} is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl;

R^9 is hydrogen, C_1-C_3 alkyl, or is fused with R^{9A} to form CH_2 or CH_2-CH_2;

R^{10} is 3-6 membered cycloalkyl, 4-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R^{8A};

R_{11} is C_1-C_4 alkyl, NH_2, NHC_1-C_3 alkyl, NHC_3-C_5 cycloalkyl or $N(C_1$-C_3 alkyl$)_2$, wherein C_1-C_4 alkyl, C_1-C_3 alkyl and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN;

R^{12} is C_1-C_4 alkyl, C_3-C_5 cycloalkyl, NH_2, NHC_1-C_3 alkyl, NHC_3-C_5 cycloalkyl or $N(C_1$-C_3 alkyl$)_2$, wherein C_1-C_4 alky, C_1-C_3 alkyl and C_3-C_5 cycloalkyl are optionally

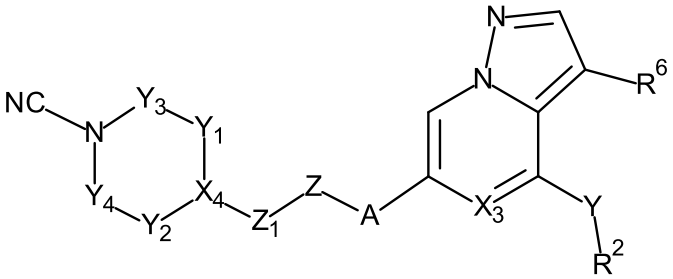
substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN; and

R^8, R^{10} and R^{8A} are optionally substituted with one or more substituents independently selected from halo, OH, CN, -OC_1-C_4 alkyl, -OC_3-C_5 cycloalkyl and -Z_3-R^{12} wherein C_1-C_4 alky and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein X_1 is C, and X_2 is N; or X_1 is N, and X_2 is C.

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



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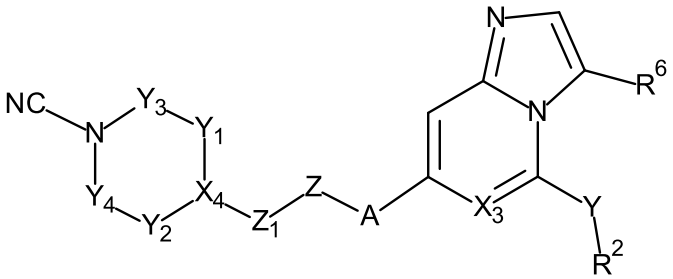
or a pharmaceutically acceptable salt thereof.

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



,

or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1-4, wherein X_3 is CH, or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1-5, wherein R^{1A} is hydrogen or C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from halo, OH, and OCH_3, or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of claims 1-5, wherein R^{1A} is hydrogen or CH_3, or a pharmaceutically acceptable salt thereof.

8. The compound according to any one of claims 1-5, wherein R^{1A} is hydrogen, or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of claims 1-8, wherein R^9 is hydrogen or is fused with R^{9A} to form CH_2 or CH_2-CH_2, or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1-9, wherein R^6 is CN, F, Cl, CH_3, CF_3 or cyclopropyl, or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10, wherein R^6 is CN, F or Cl, or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of claims 1-11 wherein A is pyrazole or triazole, substituted with $R^1$and R^{1A}, or a pharmaceutically acceptable salt thereof.

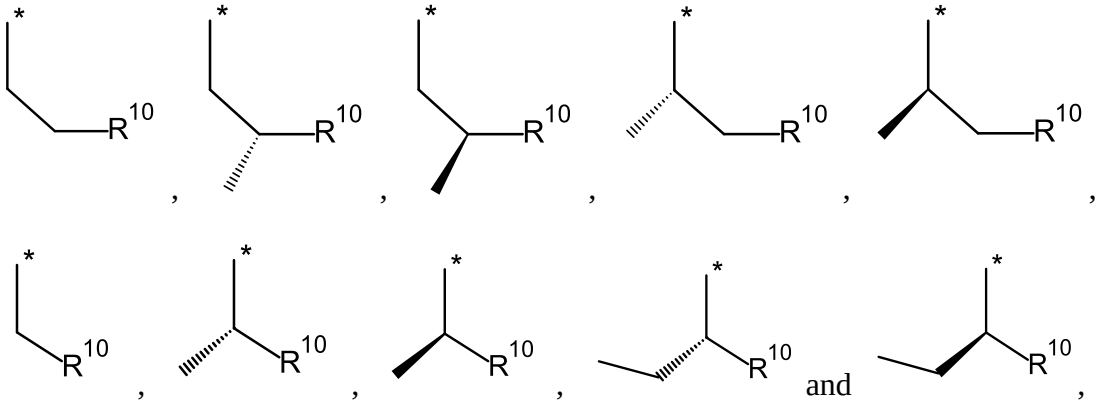
13. The compound according to claim 12, wherein A is triazole, substituted with $R^1$and R^{1A}, or a pharmaceutically acceptable salt thereof.

14. The compound according to any one of claims 1-13, wherein Z is a bond, cyclobutyl, bicyclo(1.1.1)pentane, bicyclo(2.1.1)hexane, azetidine or piperidine, or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 14, wherein Z is a bond, cyclobutyl, azetidine or piperidine, or a pharmaceutically acceptable salt thereof.

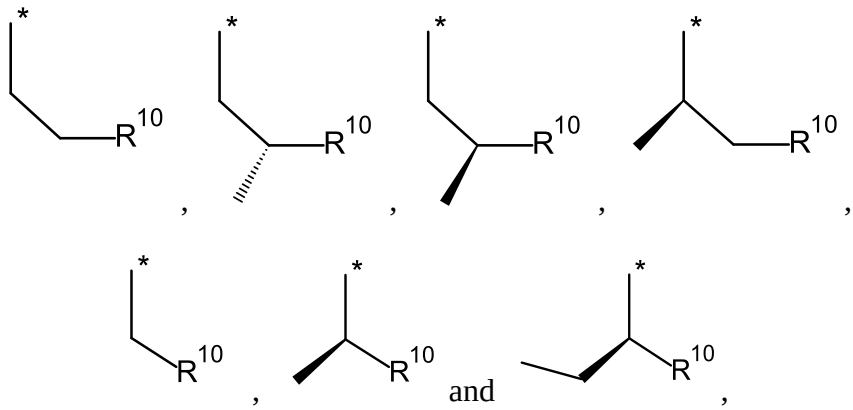
16. The compound according to any one of claims 1-15, wherein R^2 is C_1-C_3 alkyl optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, -OC_1-C_4 alkyl, -OC_3-C_5 cycloalkyl, -Z_2-R^{11} and R^{10}, wherein C_1-C_4 alkyl and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN, or a pharmaceutically acceptable salt thereof.

17. The compound according to any one of claims 1-15, wherein R^2 is selected from:



optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, -OC_1-C_4 alkyl, -OC_3-C_5 cycloalkyl, -Z_2-R^{11} and R^{10}, wherein C_1-C_4 alkyl and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y, or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 17, wherein R^2 is selected from:



optionally substituted with one, two, three or four substituents independently selected from halo, OH, CN, oxo, -OC_1-C_4 alkyl, -OC_3-C_5 cycloalkyl, -Z_2-R^{11} and R^{10}, wherein C_1-C_4 alkyl and C_3-C_5 cycloalkyl are optionally substituted with one or more substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN, wherein * indicates the connection point to Y, or a pharmaceutically acceptable salt thereof.

19. The compound according to any one of claims 17-18, wherein R^2 is optionally substituted with one, two, three or four substituents independently selected from F, OH, CN, oxo, -OCH_3 and -OC_3 cycloalkyl, or a pharmaceutically acceptable salt thereof.

20. The compound according to any one of claims 1-19, wherein R^{10} is 4-6 membered heterocycloalkyl or 5-6 membered heteroaryl, optionally fused with R^{8A}, or a pharmaceutically acceptable salt thereof.

21. The compound according to any one of claims 1-19, wherein R^{10} is 5-6 membered heteroaryl, optionally fused with R^{8A}, or a pharmaceutically acceptable salt thereof.

22. The compound according to any one of claims 1-21, wherein R^{10} and R^{8A} are optionally substituted with one, two or three substituents independently selected from halo, OH, CN, -OC_1-C_4 alkyl, -OC_3-C_5 cycloalkyl and -Z_3-R^{12} wherein C_1-C_4 alkyl and C_3-C_5 cycloalkyl are optionally substituted with one, two or three substituents independently selected from halo, OH, OCH_3, methylamine, N,N-dimethylamine and CN, or a pharmaceutically acceptable salt thereof.

23. The compound according to any one of claims 1-21, wherein R^{10} and R^{8A} are optionally substituted with one, two or three substituents independently selected from F, Cl, CN, CH_3, CH_2F, CHF_2, CF_3, -OCH_3, -$C(O)NH_2$ and -$S(O)_2CH_3$, or a pharmaceutically acceptable salt thereof.

24. The compound according to any one of claims 1-23, wherein Y_1 is a bond, CHR^7, CH_2-CHR^7 or CHR^7-CH_2, wherein R^7 is selected from hydrogen, F, OH and CH_3, or a pharmaceutically acceptable salt thereof.

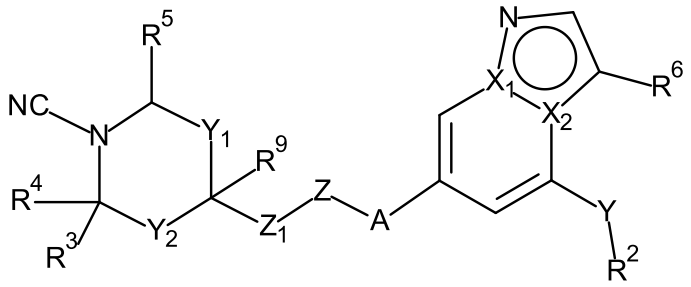
25. The compound according to any one of claims 1-24, wherein Y_2 is a bond, CHR^3, CH_2-CHR^3 or CHR^3-CH_2, wherein R^3 is selected from hydrogen, F, OH and CH_3, or a pharmaceutically acceptable salt thereof.

26. The compound according to any one of claims 1-25, wherein Y_3 is CR^4R^5 or CF_2 wherein R^4 is hydrogen or CH_3 and R^5 is hydrogen, F, OH or CH_3, or a pharmaceutically acceptable salt thereof.

27. The compound according to any one of claims 1-25, wherein Y_3 is CR^4R^5 wherein R^4 is hydrogen and R^5 is fused with one R^3 to form CH_2, CH_2-CH_2 or CH_2OCH_2, or a pharmaceutically acceptable salt thereof.

28. The compound according to any one of claims 1-27, wherein Y_4 is CR^3R^4 or CF_2 wherein R^4 is hydrogen or CH_3 and R^3 is hydrogen, F, OH or CH_3, or a pharmaceutically acceptable salt thereof.

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



wherein

A is pyrazole, triazole, thiadiazole or oxadiazole, optionally substituted with R^1;

R^1 is C_1-C_3 alkyl;

X_1 and X_2 are independently selected from N and C, wherein when one of X_1 or X_2 is N the other is C;

Y is NH, O, or a bond;

Y_1 is a bond, CHR^7, CH_2-CHR^7 or CHR^7-CH_2;

Y_2 is a bond, CH_2, CF_2, CHR^3, CH_2-CHR^3 or CHR^3-CH_2;

Z is a bond, CHR^{9A}, azetidine, pyrrolidine or piperidine;

Z_1 is a bond when Z is a bond, azetidine, pyrrolidine or piperidine, or Z_1 is CH_2 or CH_2-CH_2 when Z is CHR^{9A};

R^2 is C_1-C_5 alkyl or R^8, wherein C_1-C_5 alkyl is optionally substituted with one or more substituents independently selected from OH, methoxy, halomethyl and R^{10};

R^3 is hydrogen, C_1-C_3 alkyl, or one R^3 is fused with R^5 or R^7 to form CH_2 or CH_2-CH_2;

R^4 is hydrogen, or C_1-C_3 alkyl;

R^5 is hydrogen, or is fused with one R^3 to form CH_2 or CH_2-CH_2;

R^6 is hydrogen, CH_3, CN, Cl or F;

R^7 is hydrogen, or is fused with one R^3 to form CH_2 or CH_2-CH_2;

R^8 is 3-6 membered cycloalkyl, 5-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R^{8A};

R^{8A} is 3-6 membered cycloalkyl, 5-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl;

R^9 is hydrogen or is fused with R^{9A} to form CH_2 or CH_2-CH_2;

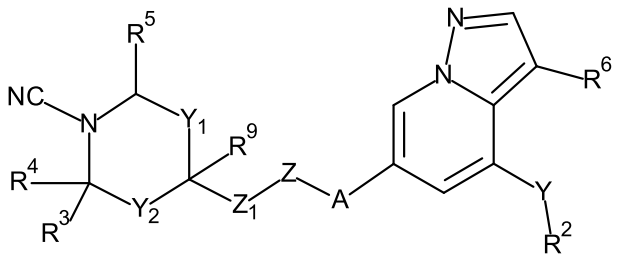
R^{10} is 3-6 membered cycloalkyl, 5-6 membered heterocycloalkyl, 5-6 membered aryl or 5-6 membered heteroaryl, optionally fused or substituted with R^{8A}; and

R^8, R^{10} and R^{8A} are optionally substituted with one or more substituents independently selected from halo, CN, methyl, halomethyl, methoxy, ethyl, ethoxy, methylamine, $S(O)_2CH_3$, $C(O)NH_2$, N,N-dimethylamine and C(O)N,N-dimethylamine;

or a pharmaceutically acceptable salt thereof.

30. The compound according to claim 29 wherein X_1 is C, and X_2 is N; or X_1 is N, and X_2 is C.

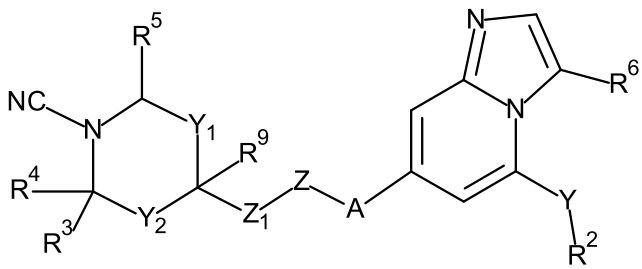
31. The compound according to claim 29 of the formula:



,

or a pharmaceutically acceptable salt thereof.

32. The compound according to claim 29 of the formula:



,

or a pharmaceutically acceptable salt thereof.

33. The compound according to any one of claims 29-32, wherein A is pyrazole or triazole, optionally substituted with R^1, or a pharmaceutically acceptable salt thereof.

34. The compound according to claim 33, wherein A is triazole, optionally substituted with R^1, or a pharmaceutically acceptable salt thereof.

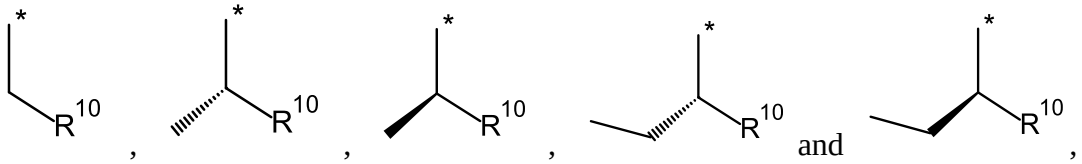
35. The compound according to any one of claims 1-34, wherein R^1 is methyl, or a pharmaceutically acceptable salt thereof.

36. The compound according to any one of claims 1-35, wherein Y is NH or O, or a pharmaceutically acceptable salt thereof.

37. The compound according to claim 36, wherein Y is O, or a pharmaceutically acceptable salt thereof.

38. The compound according to any one of claims 29-37, wherein R^2 is C_1-C_3 alkyl optionally substituted with one, two or three substituents independently selected from OH, methoxy, halomethyl and R^{10}, or a pharmaceutically acceptable salt thereof.

39. The compound according to claim 37, wherein R^2 is selected from:



optionally substituted with one or two substituents independently selected from OH, CF_3 and methoxy, wherein * indicates the connection point to Y, or a pharmaceutically acceptable salt thereof.

40. The compound according to any one of claims 29-39, wherein R^{10} is 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl, optionally fused with R^{8A}, or a pharmaceutically acceptable salt thereof.

41. The compound according to claim 40, wherein R^{10} is 5-6 membered heterocycloalkyl or 5-6 membered heteroaryl, or a pharmaceutically acceptable salt thereof.

42. The compound according to claim 40, wherein R^{10} is 5-6 membered heteroaryl, or a pharmaceutically acceptable salt thereof.

43. The compound according to any one of claims 1-42, wherein R^6 is CN or Cl, or a pharmaceutically acceptable salt thereof.

44. The compound according to claim 43, wherein R^6 is CN, or a pharmaceutically acceptable salt thereof.

45. The compound according to claim 43, wherein R^6 is Cl, or a pharmaceutically acceptable salt thereof.

46. The compound according to any one of claims 1-45, wherein Z is a bond, azetidine or piperidine, or a pharmaceutically acceptable salt thereof.

47. The compound according to any one of claims 1-46, wherein Z_1 is a bond, or a pharmaceutically acceptable salt thereof.

48. The compound according to any one of claims 1-45, wherein Z is CHR^{9A}, Z_1 is CH_2 and R^9 is fused with R^{9A} to form CH_2, or a pharmaceutically acceptable salt thereof.

49. The compound according to any one of claims 29-48, wherein R^3 and R^4 are hydrogen or CH_3, or a pharmaceutically acceptable salt thereof.

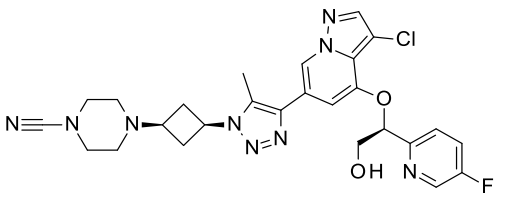
50. The compound according to any one of claims 29-49, wherein R^5 is hydrogen, or a pharmaceutically acceptable salt thereof.

51. The compound according to any one of claims 29-49, wherein R^5 is fused with one R^3 to form CH_2-CH_2, or a pharmaceutically acceptable salt thereof.

52. The compound according to any one of claims 29-51, wherein Y_1 is a bond or CH_2, or a pharmaceutically acceptable salt thereof.

53. The compound according to any one of claims 29-52, wherein Y_2 is a bond or CH_2, or a pharmaceutically acceptable salt thereof.

54. The compound according to claim 1, selected from the group consisting of: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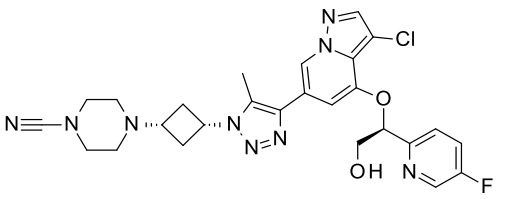
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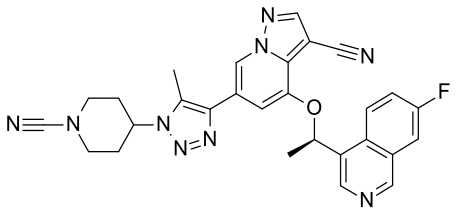
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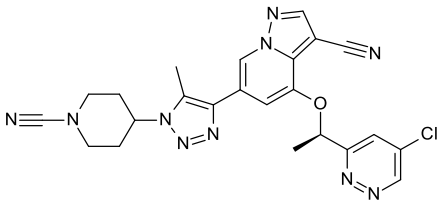
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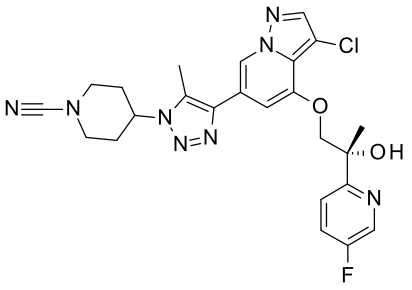
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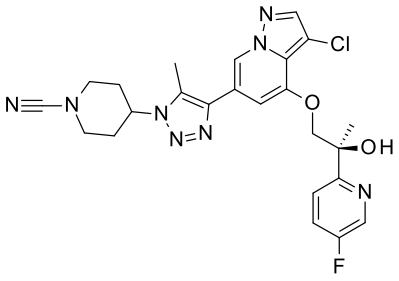
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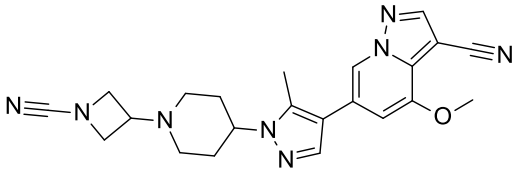
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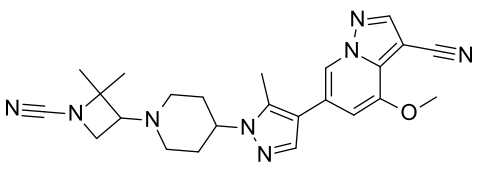
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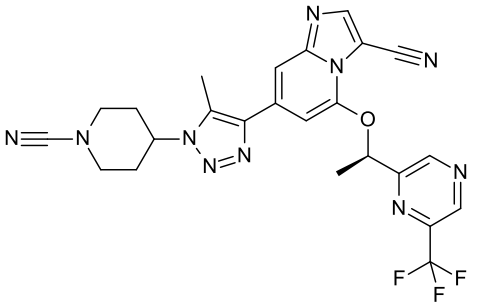
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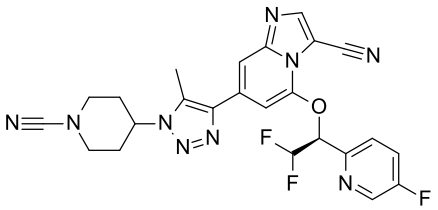
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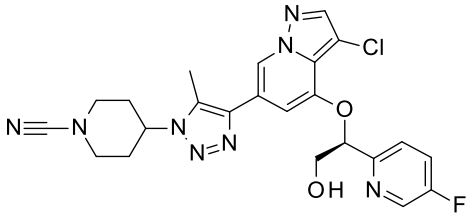
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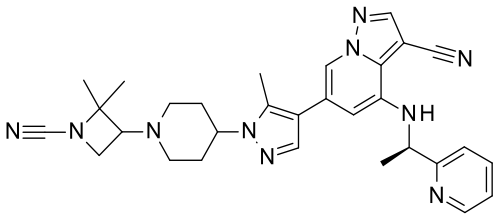
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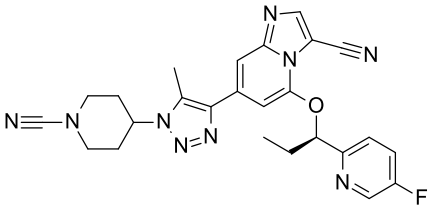
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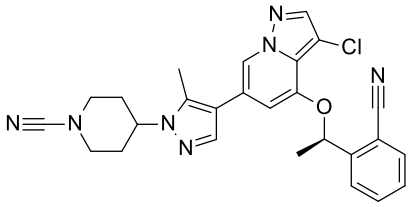
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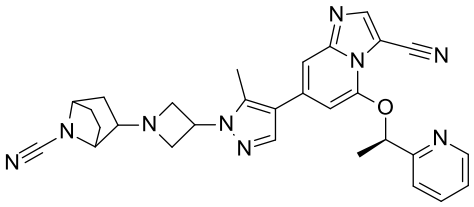
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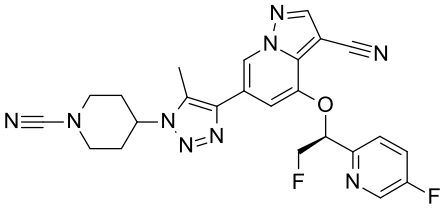
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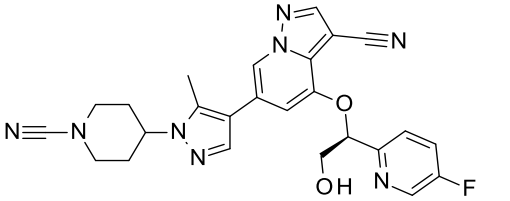
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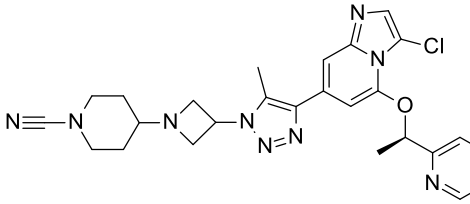
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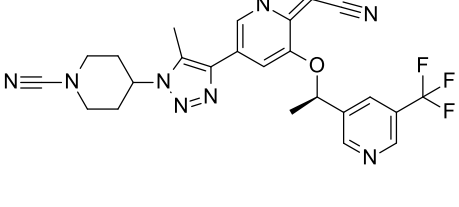
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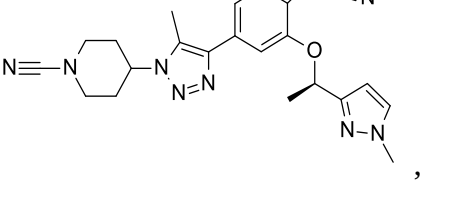
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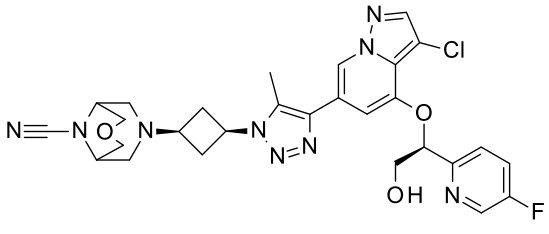
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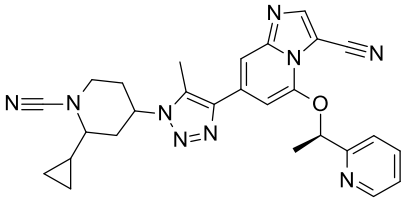
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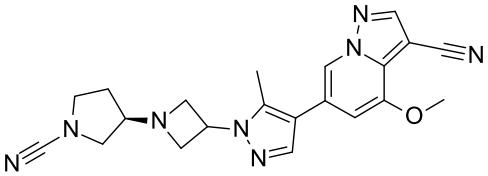
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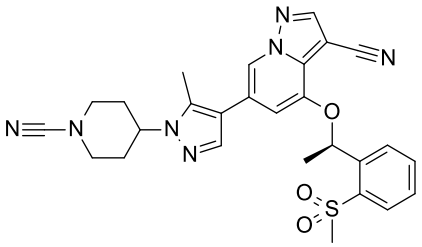
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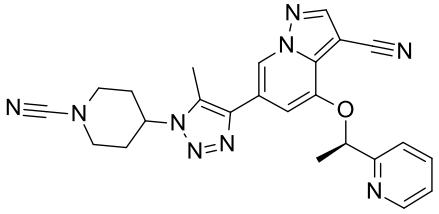
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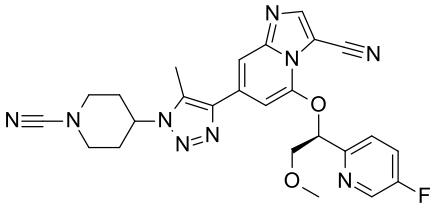
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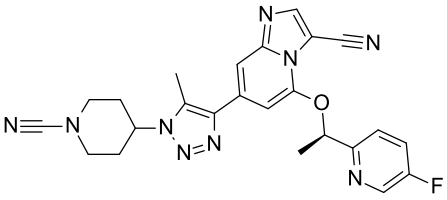
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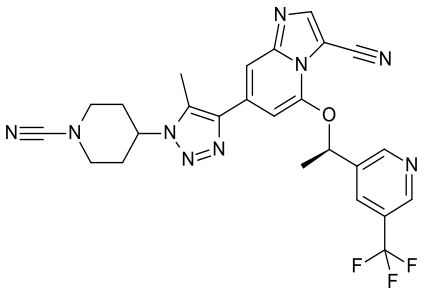
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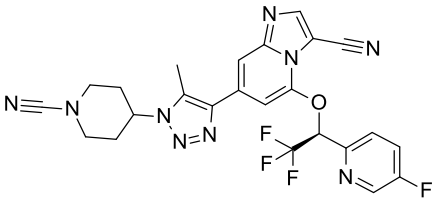
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or a pharmaceutically acceptable salt thereof.

55. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-52, and a pharmaceutically acceptable carrier, diluent or excipient.

56. Use of a compound of any one of claims 1-54, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating systemic sclerosis, fibrosis,

pulmonary fibrosis, achondroplasia, thanatophoric dysplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), muenke syndrome or cancer.

57. The use of claim 56, wherein the disease is cancer and the cancer is selected from the group consisting of breast cancer, invasive ductal breast cancer, invasive lobular breast cancer, lung cancer, non-small-cell lung cancer, lung adenocarcinoma, squamous cell lung cancer, small-cell lung cancer, urothelial cancer, bladder cancer, urothelial bladder cancer, non-muscle invasive bladder cancer, muscle invasive bladder cancer, upper tract cancer, urothelial upper tract cancer, urethral cancer, gastric cancer, pancreatic cancer, prostate cancer, colorectal cancer, multiple myeloma, liver cancer, melanoma, cutaneous melanoma, head and neck cancer, oral cancer, thyroid cancer, renal cancer, renal pelvis cancer, glioblastoma, endometrial cancer, cervical cancer, ovarian cancer, and testicular cancer.

58. The use of claim 57, wherein the cancer is selected from the group consisting of breast cancer, invasive ductal breast cancer, invasive lobular breast cancer, lung cancer, non-small-cell lung cancer, lung adenocarcinoma, squamous cell lung cancer, small-cell lung cancer, urothelial cancer, bladder cancer, urothelial bladder cancer, non-muscle invasive bladder cancer, muscle invasive bladder cancer upper tract cancer, urothelial upper tract cancer, and glioblastoma.

59. The use of claim 58, wherein the cancer is selected from the group consisting of bladder cancer, urothelial bladder cancer, non-muscle invasive bladder cancer and muscle invasive bladder cancer.

60. The use according to any one of claims 56-59, wherein the cancer is FGFR3-associated cancer.

61. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-54, for use in therapy.

62. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-54, for use in the treatment of systemic sclerosis, fibrosis, pulmonary fibrosis, achondroplasia, thanatophoric dysplasia, severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), muenke syndrome or cancer.

63. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 62, wherein the cancer is selected from the group consisting of breast cancer, invasive ductal breast cancer, invasive lobular breast cancer, lung cancer, non-small-cell

lung cancer, lung adenocarcinoma, squamous cell lung cancer, small-cell lung cancer, urothelial cancer, bladder cancer, urothelial bladder cancer, non-muscle invasive bladder cancer, muscle invasive bladder cancer, upper tract cancer, urothelial upper tract cancer, urethral cancer, gastric cancer, pancreatic cancer, prostate cancer, colorectal cancer, multiple myeloma, liver cancer, melanoma, cutaneous melanoma, head and neck cancer, oral cancer, thyroid cancer, renal cancer, renal pelvis cancer, glioblastoma, endometrial cancer, cervical cancer, ovarian cancer, and testicular cancer.

64. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 62, wherein the cancer is selected from the group consisting of breast cancer, invasive ductal breast cancer, invasive lobular breast cancer, lung cancer, non-small-cell lung cancer, lung adenocarcinoma, squamous cell lung cancer, small-cell lung cancer, urothelial cancer, bladder cancer, urothelial bladder cancer, non-muscle invasive bladder cancer, muscle invasive bladder cancer, upper tract cancer, urothelial upper tract cancer and glioblastoma.

65. The compound, or a pharmaceutically acceptable salt thereof, for use according to claim 62, wherein the cancer is selected from the group consisting of bladder cancer, urothelial bladder cancer, non-muscle invasive bladder cancer and muscle invasive bladder cancer.

66. The compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 61-65, wherein the cancer is FGFR3-associated cancer.