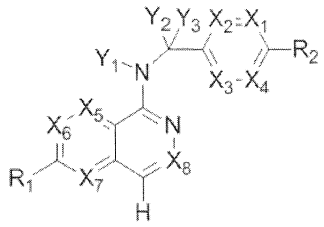
Claims:

1. A compound, ~~as WNT signaling inhibitor which~~ havings the structure of ~~the following~~ Formula I:



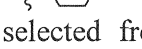
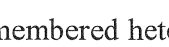
(I)

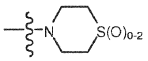
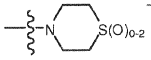
or a physiologically acceptable salt thereof, wherein

X_1, X_2, X_3, X_4, X_5, X_6, X_7 and X_8 are independently CR_4 or N ;

Y_1 is hydrogen or $-C(R_4)_3$, each R_4 is same or different;

Y_2 and Y_3 are independently hydrogen, halogen or $-C(R_3)_3$, each R_3 is same or different;

R_1 is ~~and R_2 are independently~~ selected from hydrogen, halogen, C_{1-6} alkyl, quinolinyl, , C_{6-30} aryl, 3 to 6 membered heterocycloalkyl containing 1-2 heteroatoms selected from N, O and S, and 5 or 6 membered heteroaryl containing 1-4 heteroatoms selected from N, O and S, wherein each of quinolinyl, , C_{6-30} aryl, 3 to 6 membered heterocycloalkyl, and 5 or 6 membered heteroaryl can be optionally substituted with one or two, and same or different R_4;

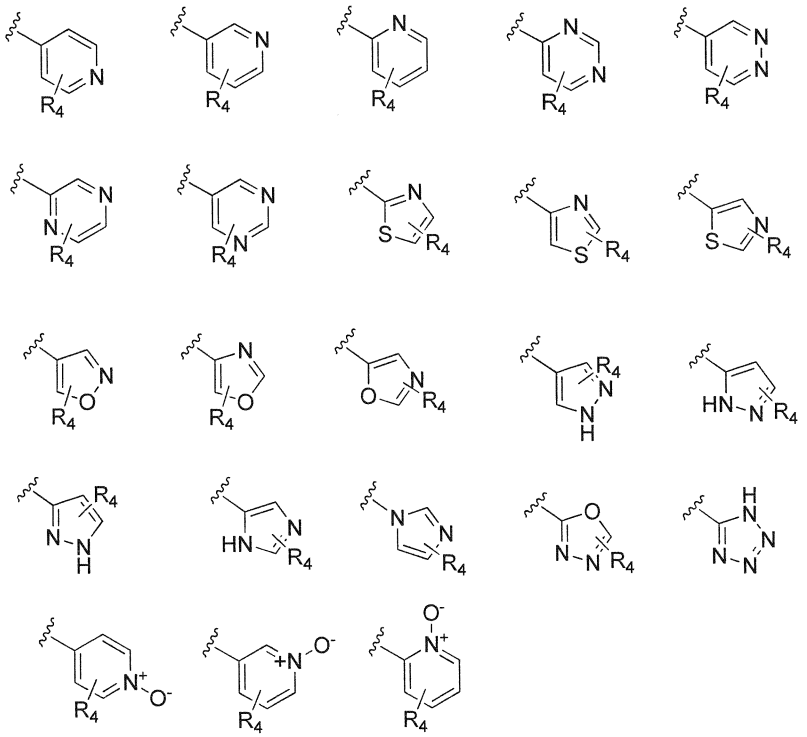
R_2 is selected from C_{1-6} alkyl, quinolinyl, , C_{6-30} aryl, 3 to 6 membered heterocycloalkyl containing 1-2 heteroatoms selected from N, O and S, and 5 or 6 membered heteroaryl containing 1-4 heteroatoms selected from N, O and S, wherein each of quinolinyl, , C_{6-30} aryl, 3 to 6 membered heterocycloalkyl, and 5 or 6 membered heteroaryl can be optionally substituted with one or two, and same or different R_4

each R_3 is independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein each of the C_{1-6} alkyl and C_{1-6} alkoxy can be optionally substituted with halo, amino, hydroxyl, C_{1-6} alkoxy or cyano;

each R_4 is independently selected from hydrogen, halogen, cyano, C_{1-6} alkoxy, $-S(O)_2R_5$, $-C(O)OR_5$, $-C(O)R_5$, $-C(O)NR_6R_7$, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, wherein each of C_{1-6} alkoxy, $-S(O)_2R_5$, $-C(O)OR_5$, $-C(O)R_5$, $-C(O)NR_6R_7$, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl can be optionally substituted with halo, amino, hydroxyl, C_{1-6} alkoxy or cyano;

R_5, R_6 and R_7 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, in which each of the C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl can be optionally substituted with halo, amino, hydroxyl, C_{1-6} alkoxy or cyano.

2. The compound of claim 1, wherein the core structure of Formula I defined by X_5, X_6, X_7 and X_8 is selected from:



5. The compound of any one of claims 2-4, wherein each R_4 is independently selected from hydrogen, chlorine, fluorine, cyano, $-CH_3$,$-CHF_2$, $-CF_3$, $-OCH_3$, $-COOCH_3$.

6. The compound of any one of claims 1-5, wherein at least one atom in Formula I is at least one of corresponding isotope(s) selected from ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl and ^{123}I.

7. The compound of claim 1, being ~~is~~ selected from:

~~N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;~~

~~N-((5-(2-methylpyridin-4-yl)pyridin-2-yl)methyl)-7-phenylquinazolin-4-amine;~~

~~N-(4-morpholinobenzyl)-7-phenylquinazolin-4-amine;~~

~~N-((6-morpholinopyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;~~

~~N-((6-(2-methylmorpholino)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;~~

~~N-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;~~

~~4-(5-(((7-phenylquinazolin-4-yl)amino)methyl)pyridin-2-yl)thiomorpholine 1,1-dioxide;~~

~~N-((6-(6-methylpyridin-3-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;~~

~~N-((6-(5-methylpyridin-3-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;~~

7-phenyl-N-((6-(pyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-phenyl-N-((6-(pyridin-3-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-phenyl-N-((6-(pyridin-2-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-phenyl-N-((6-(pyridazin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-phenyl-N-((6-(pyrazin-2-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-phenyl-N-((6-(pyrimidin-5-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

N-((6-(2-fluoropyridin-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;

N-((6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;

N-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;

N-((5-(6-methylpyridin-3-yl)pyridin-2-yl)methyl)-7-phenylquinazolin-4-amine;

N-(4-(2-methylpyridin-4-yl)benzyl)-7-phenylquinazolin-4-amine;

N-(4-(2-fluoropyridin-4-yl)benzyl)-7-phenylquinazolin-4-amine;

N-benzyl-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-methylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-methoxybenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-fluorobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-chlorobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-bromobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-(trifluoromethyl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

4-((7-(2-methylpyridin-4-yl)quinazolin-4-ylamino)methyl)benzonitrile;

N-(4-morpholinobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-phenylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(3-fluoro-4-phenylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-(3-fluorophenyl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

7-(3-fluorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(3-chlorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-m-tolylquinazolin-4-amine;

3-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)benzonitrile;

4-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)benzonitrile;

7-(2-methylpyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(6-methylpyridin-3-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(5-methylpyridin-3-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-2-yl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-3-yl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-4-yl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridazin-4-yl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyrazin-2-yl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyrimidin-5-yl)quinazolin-4-amine;

7-(2-fluoropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(2-(trifluoromethyl)pyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(2-methoxypyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(3-methylpyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-morpholinoquinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(piperidin-1-yl)quinazolin-4-amine;

7-(4-methylpiperazin-1-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

1-(4-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)piperazin-1-yl)ethanone;

4-(4-(((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)amino)quinazolin-7-yl)thiomorpholine1,1-dioxide;

7-(1,2,3,6-tetrahydropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(1,2,3,6-tetrahydropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

1-(4-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)piperidin-1-yl)ethanone;

N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-7-(4-(methylsulfonyl)piperazin-1-yl)quinazolin-4-amine;

7-(1-methyl-1H-pyrazol-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(isoxazol-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(thiazol-2-yl)quinazolin-4-amine;

N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-(2-methylpyridin-4-yl)benzyl)-7-(pyrazin-2-yl)quinazolin-4-amine;

N-(4-(2-methylpyridin-4-yl)benzyl)-7-(2-fluoropyridin-4-yl)quinazolin-4-amine;

N-(4-(2-methylpyridin-4-yl)benzyl)-7-morpholinoquinazolin-4-amine;

2-(3-fluorophenyl)-N-(4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;

2-(3-fluorophenyl)-N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)pyrido[3,4-b]pyrazin-5-amine;

2-(3-fluorophenyl)-N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;

N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-2-(3-fluorophenyl)pyrido[3,4-b]pyrazin-5-amine;

2-(2-methylpyridin-4-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;

N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;

N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;

N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;

N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;

6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

(S)-6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

(R)-6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

1-(4-(8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-1-yl)ethanone;

6-(1H-imidazol-1-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

6-(4-methyl-1H-imidazol-1-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

N-(4-(2-methylpyridin-4-yl)benzyl)-6-(1H-tetrazol-5-yl)-2,7-naphthyridin-1-amine;

6-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

6-(1-methyl-1H-pyrazol-3-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

N-(4-(2-methylpyridin-4-yl)benzyl)-6-(thiazol-5-yl)-2,7-naphthyridin-1-amine;

N-(4-(2-methylpyridin-4-yl)benzyl)-6-(oxazol-5-yl)-2,7-naphthyridin-1-amine;

N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(5-methylpyridin-3-yl)-2,7-naphthyridin-1-amine;

N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;

N-((3-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;

N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(5-fluoropyridin-3-yl)-2,7-naphthyridin-1-amine;

N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;

N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;

methyl 4-(8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazine-1-carboxylate;

4-(8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-2-one;

2-(4-(8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-1-yl)acetonitrile;

2-methyl-4-(4-(((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)phenyl)pyridine 1-oxide;

6-(2-chloropyridin-4-yl)-N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-2,7-naphthyridin-1-amine;

6-(2-chloropyridin-4-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

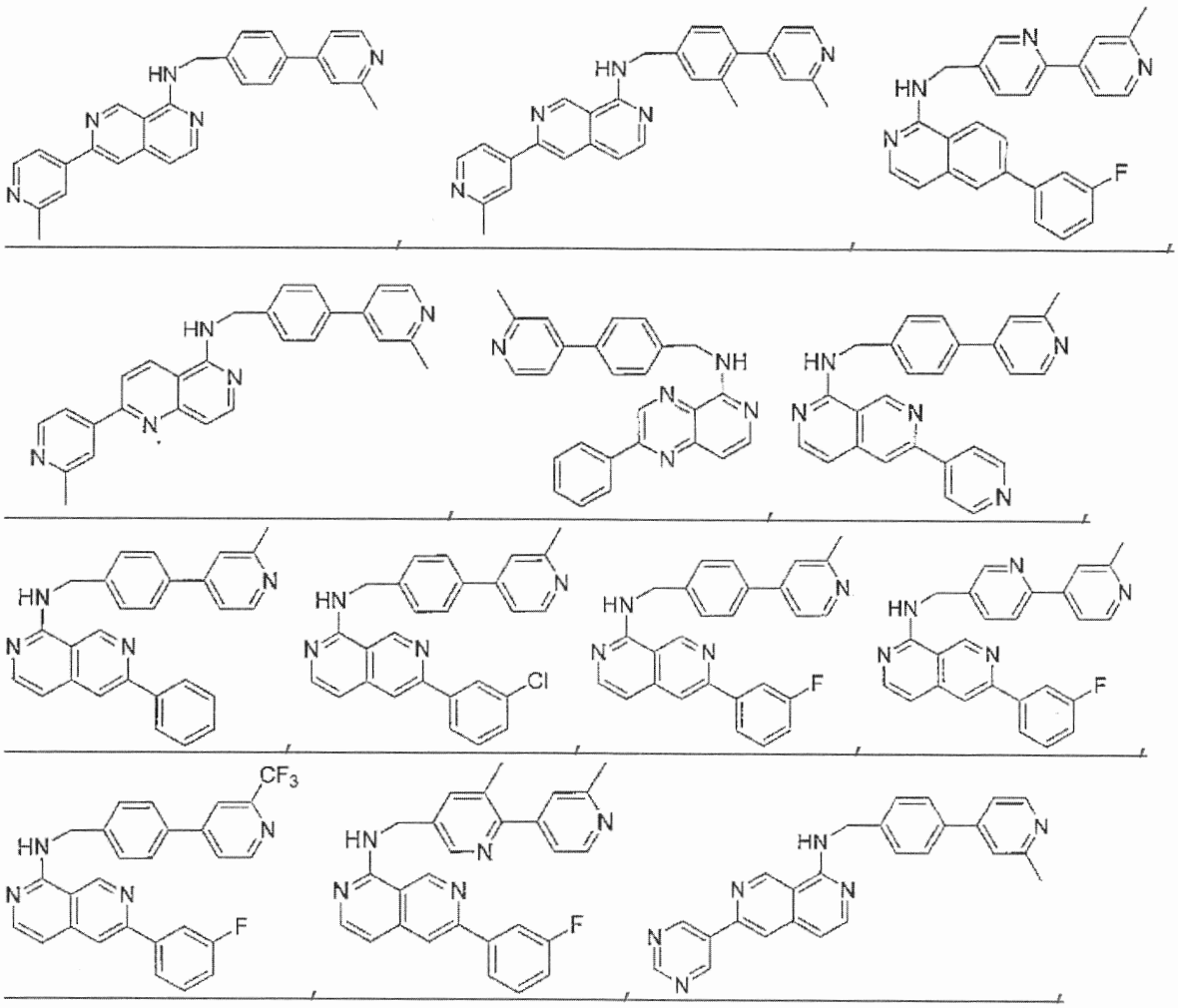
2-(2-methylpyridin-4-yl)-5-(((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)benzonitrile;

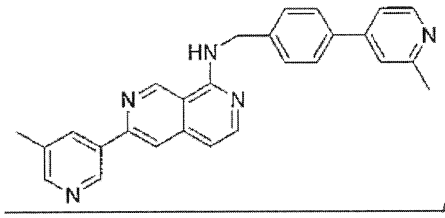
N-(3-methoxy-4-(2-methylpyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;

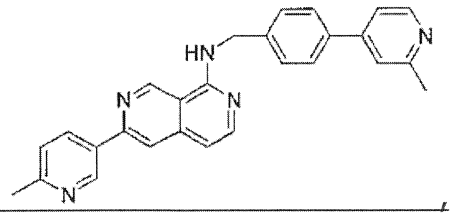
N-((3-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;

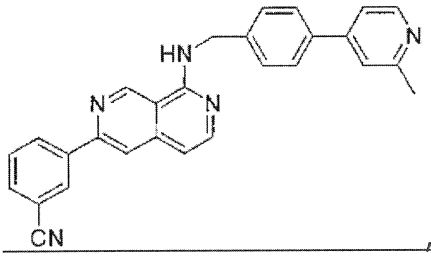
2'-methyl-5-(((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)-[2,4'-bipyridine]-3-carbonitrile;

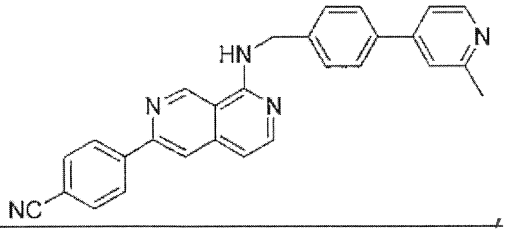
N-(4-(2-(difluoromethyl)pyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine.

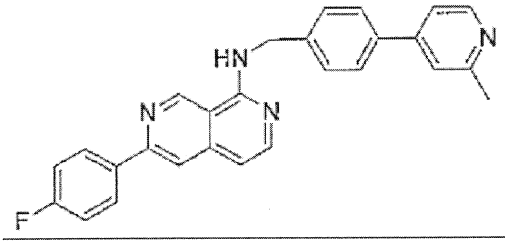


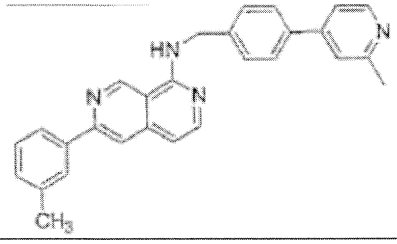


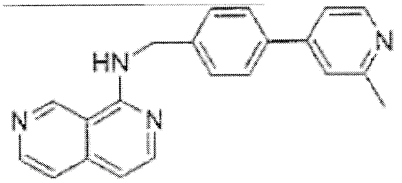


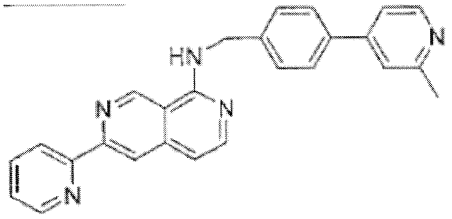


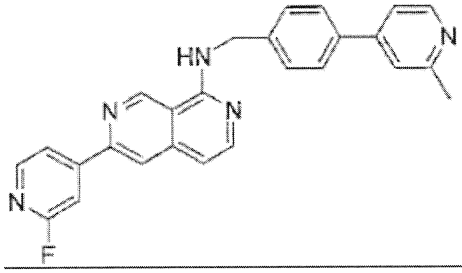


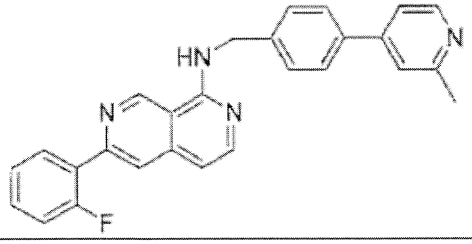


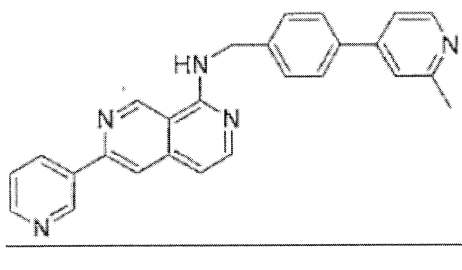


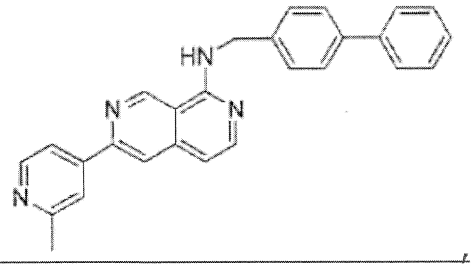


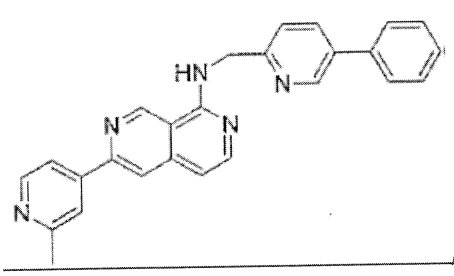


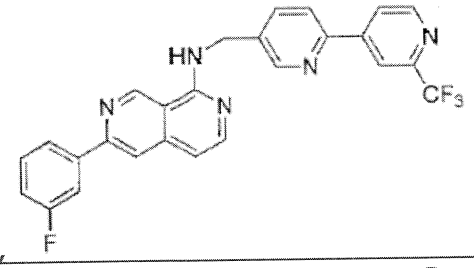


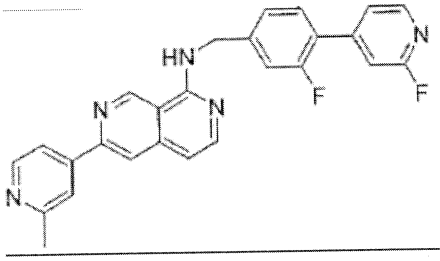


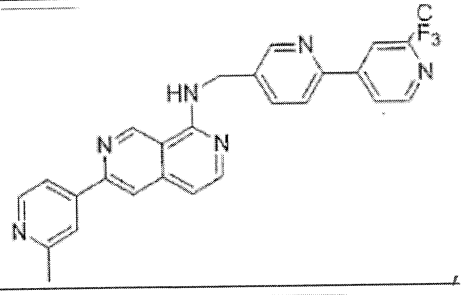


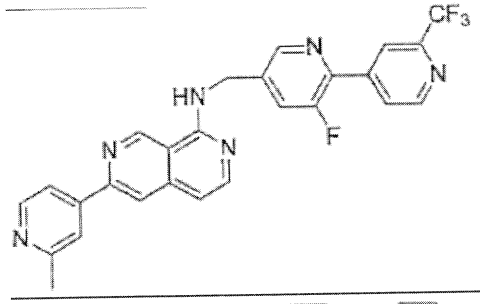


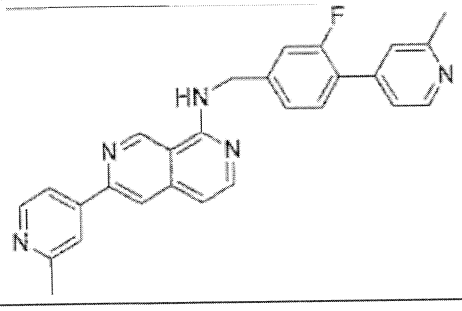


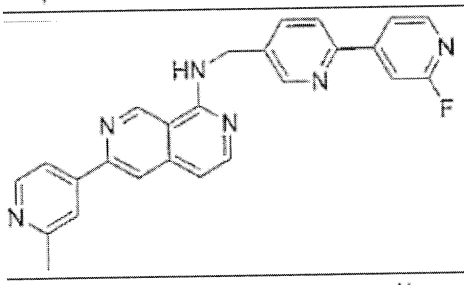


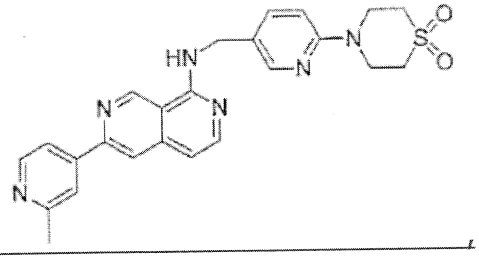


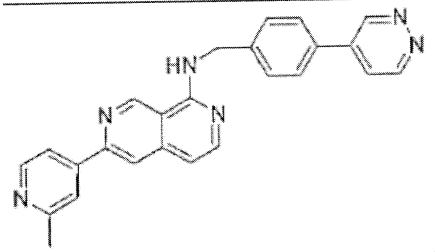


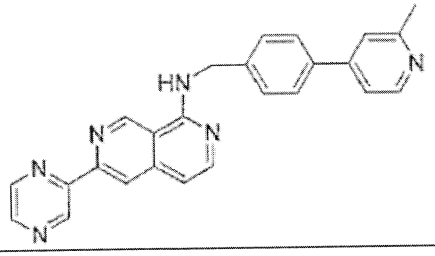


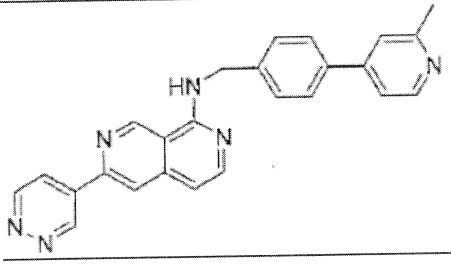


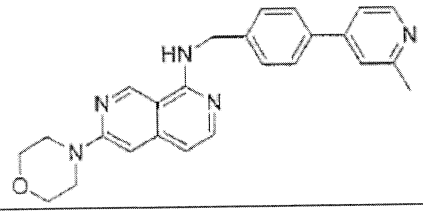


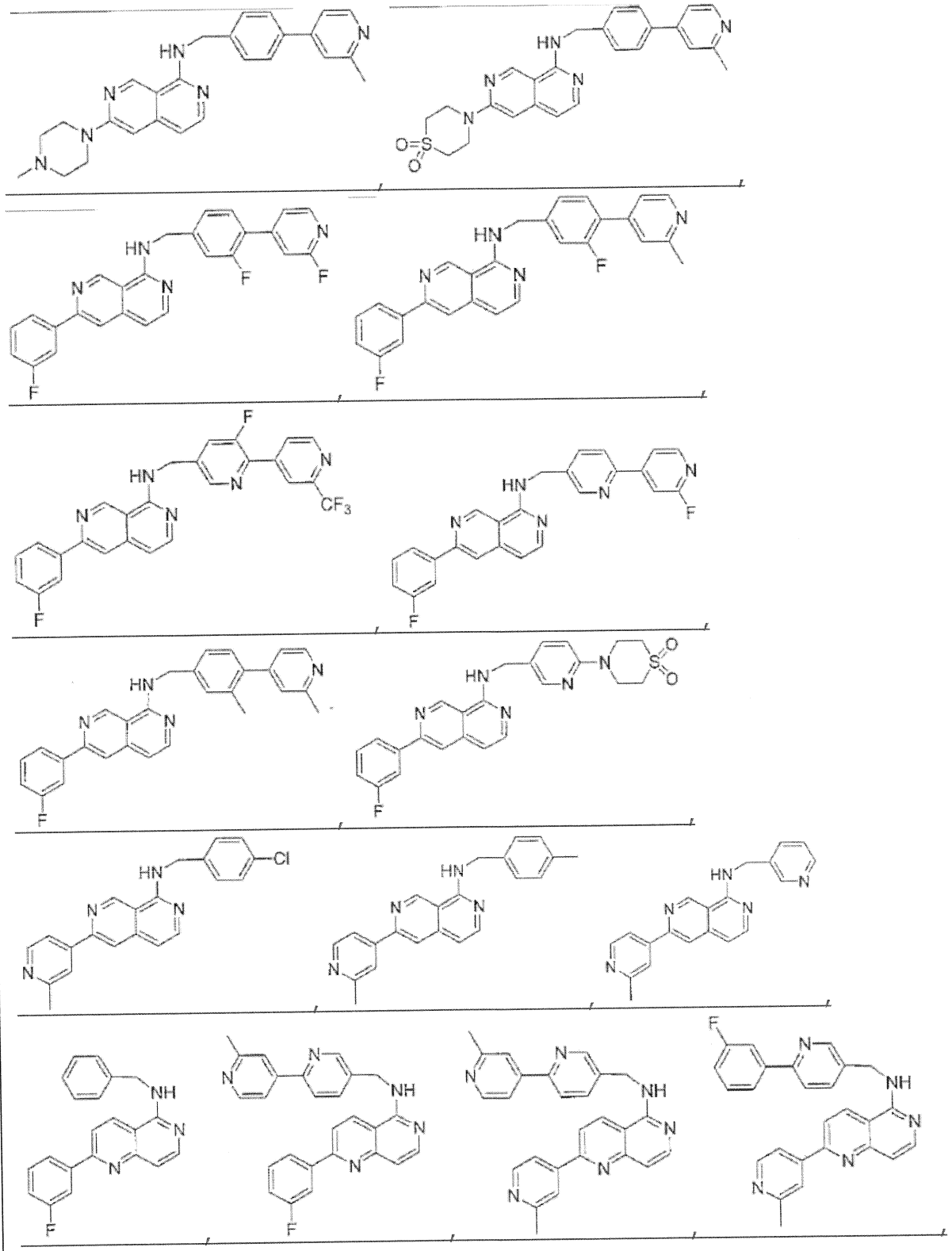


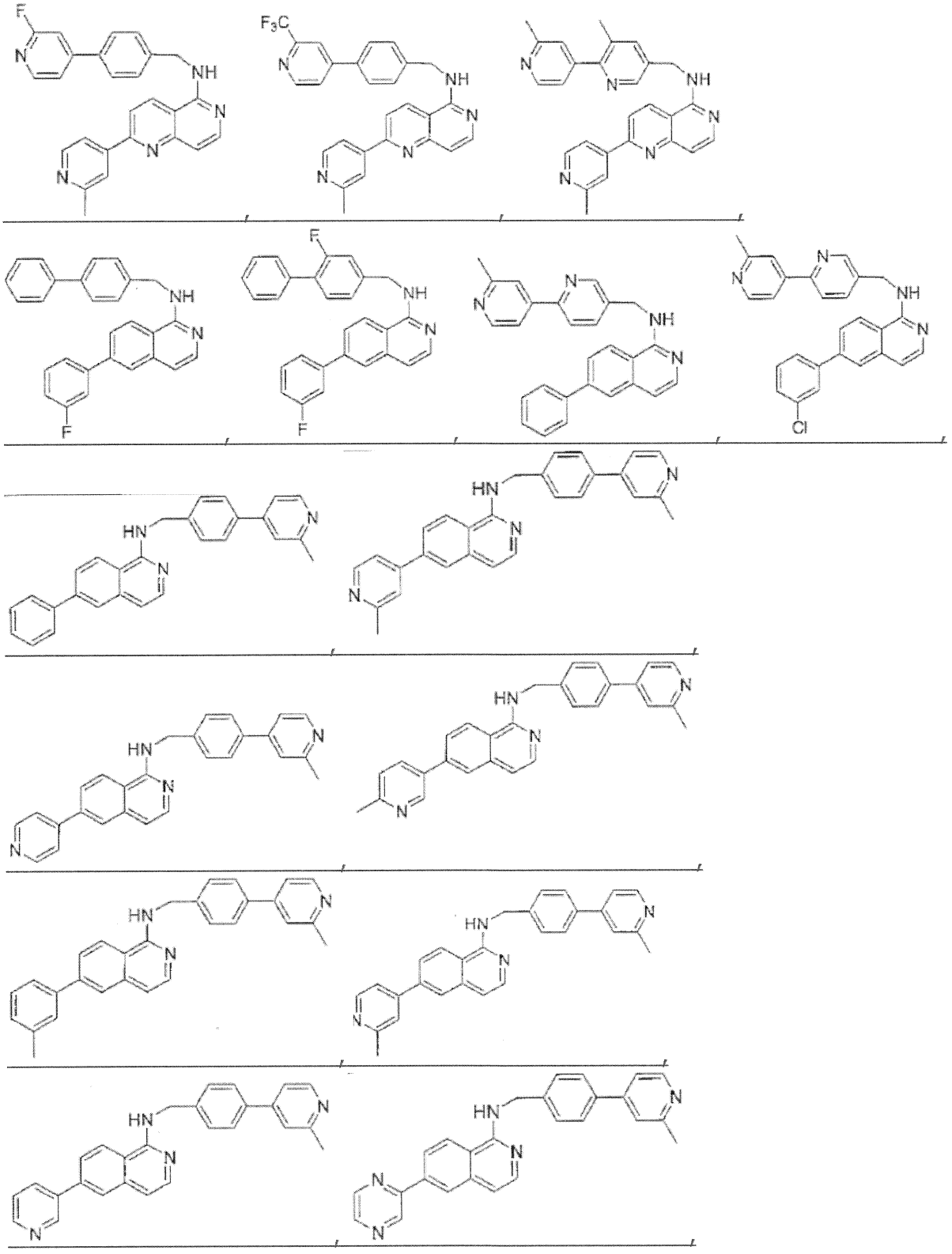


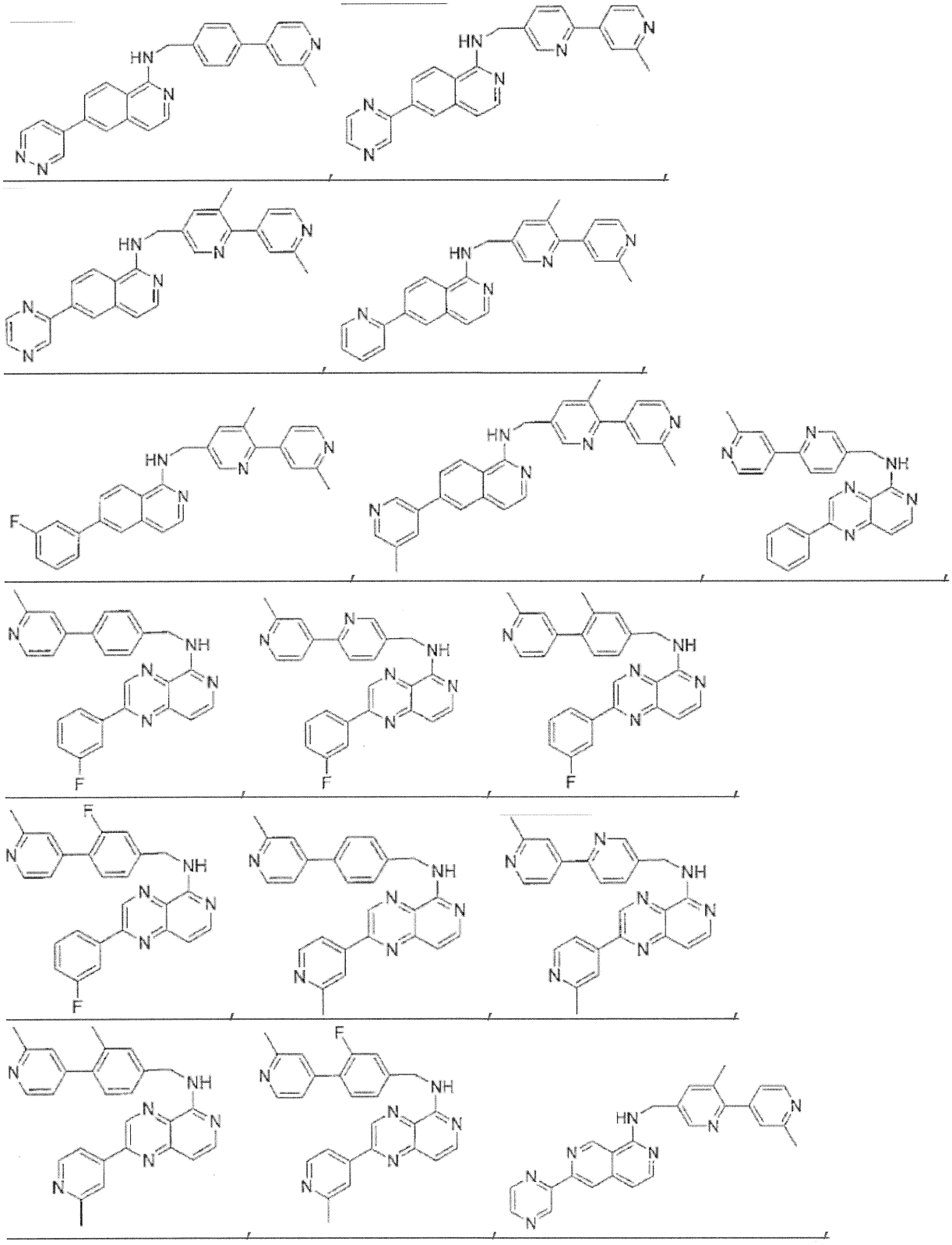


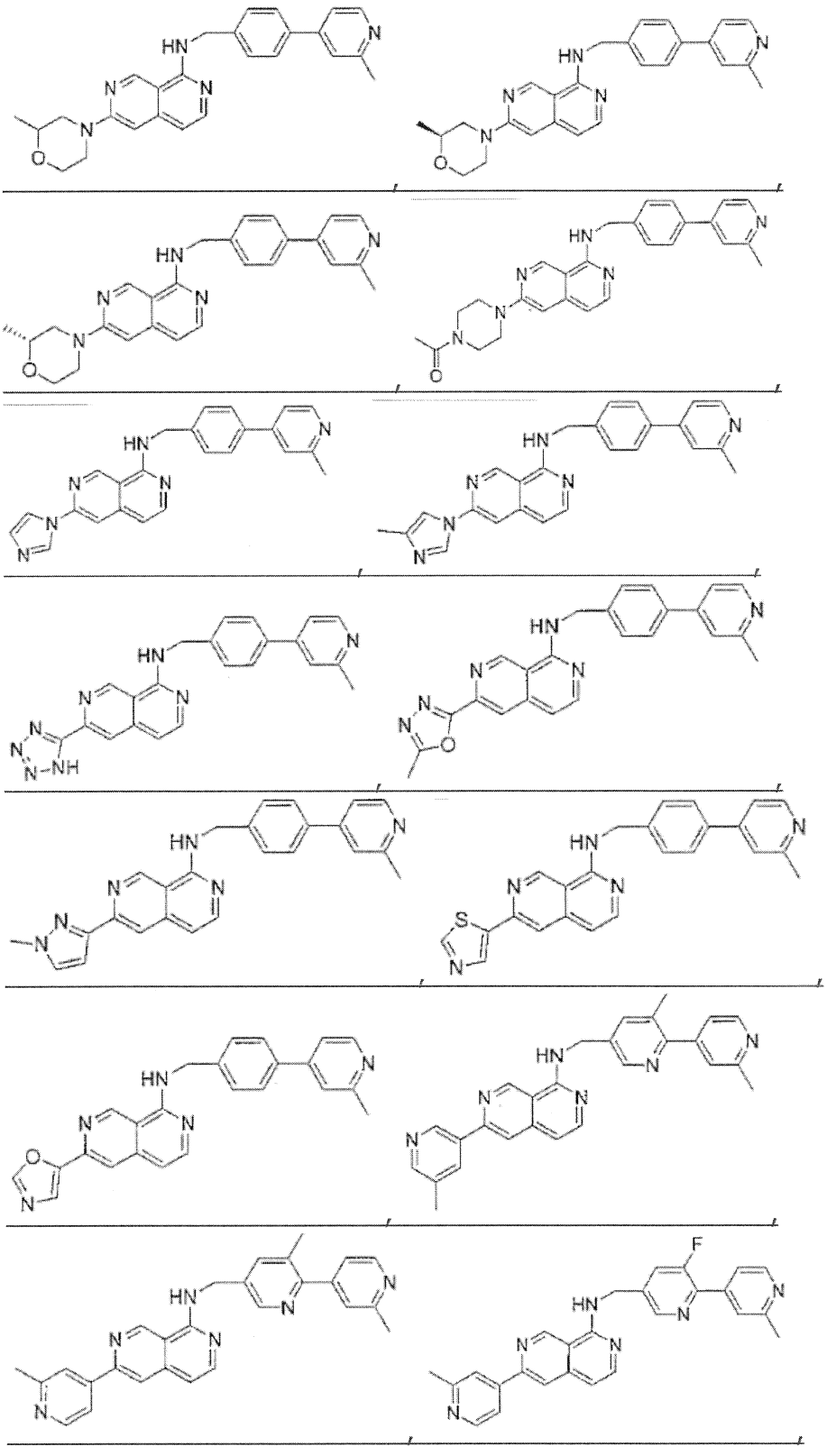


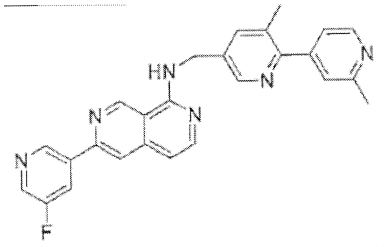


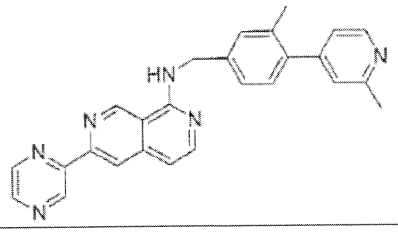


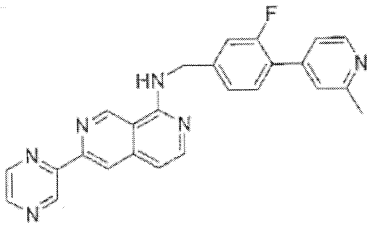


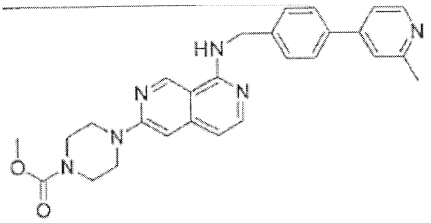


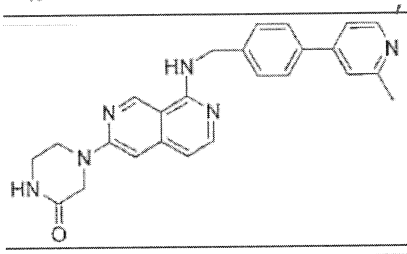


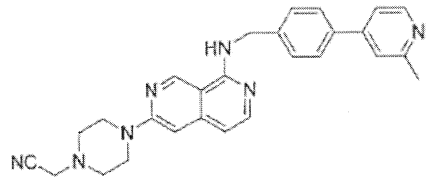


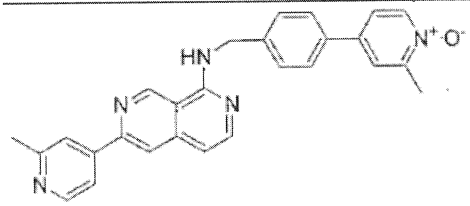


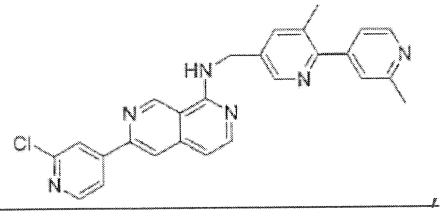


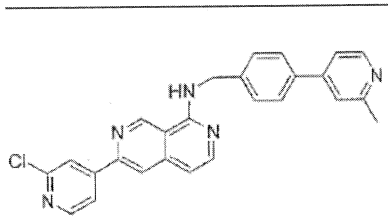


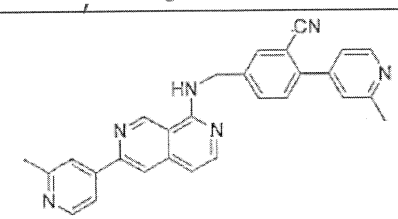


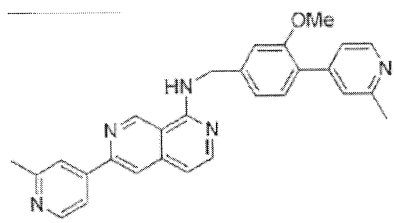


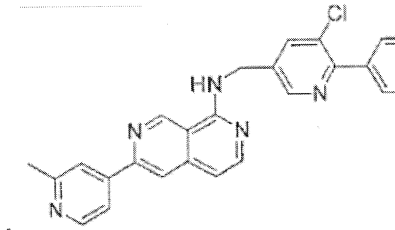


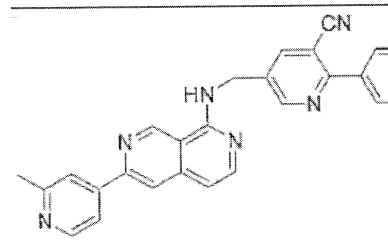


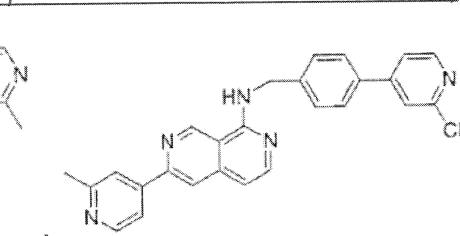


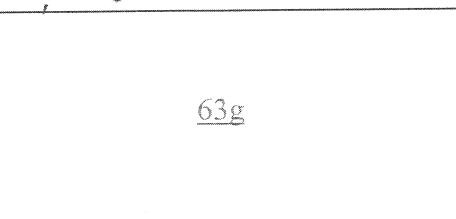












8. A pharmaceutical composition comprising the compound or physiologically acceptable salt thereof of any one of the preceding claims.

9. The pharmaceutical composition of claim 8 is an oral composition, an injectable composition or a suppository.

10. The pharmaceutical composition of claim 9, wherein the oral composition is tablet or gelatin capsule; the injectable composition is aqueous isotonic solution or suspension; and the suppository is prepared from fatty emulsions or suspensions.

11. The pharmaceutical composition of claim 8, further comprises at least one of diluents selected from lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and glycine; lubricants selected from silica, talcum, stearic acid, its magnesium and calcium salt and polyethyleneglycol; binders selected from magnesium aluminum silicate, starch paste, gelatin, tragamayth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone; disintegrants selected from starches, agar, alginic acid and its sodium salt and effervescent mixtures; additives selected from absorbent, colorant, flavor and sweetener.

12. The pharmaceutical composition of claim 8, further comprises at least one adjuvant selected from preserving agents, stabilizing agents, wetting agents, emulsifying agents, solution promoters, salts for regulating osmotic pressure and buffers.

13. The pharmaceutical composition of claims 8 or 12, further contains solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

14. The pharmaceutical composition of claim 13, wherein the pharmaceutical composition is for topical application and is in a form of aqueous solution, ointment, cream or gel.

15. A method of inhibiting WNT secretion from a cell, comprising contacting the cell with an effective amount of the compound or physiologically acceptable salt thereof of any one of claims 1-7, or the pharmaceutical composition of any one of claims 8-14.

16. A method of inhibiting WNT signaling in a cell, comprising contacting the cell with an effective amount of the compound or physiologically acceptable salt thereof of any one of claims 1-7, or the pharmaceutical composition of any one of claims 8-14.

17. The use of a compound or physiologically acceptable salt thereof of any one of claims 1-7, or a pharmaceutical composition of any one of claims 8-14 for the manufacture of a medicament for treating a WNT pathway mediated disorder.

~~18. A method for treating a WNT pathway mediated disorder in a subject suffering therefrom, comprising administering to the subject a therapeutically effective amount of the compound or physiologically acceptable salt thereof of any one of claims 1-7, or the pharmaceutical composition of any one of claims 8-14.~~

18~~19~~. The use of claim 17 ~~or the method of claim 18~~, wherein said disorder is cancer, fibrosis, osteoarthritis, Parkinson's disease, retinopathy, macular degeneration.

19~~20~~. The use ~~or the method~~ of claim ~~19~~18, wherein the cancer is selected from: lung, including small cell and non-small cell, breast, prostate, carcinoid, bladder, gastric, pancreatic, liver or hepatocellular, hepatoblastoma, colorectal, renal and head cancer and neck squamous cell carcinoma, esophageal, ovarian, cervical, endometrial, mesothelioma, melanoma, sarcoma, osteosarcoma, liposarcoma, thyroid, desmoids, chronic myelocytic leukemia (AML), and chronic myelocytic leukemia (CML).

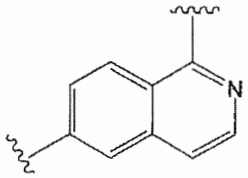
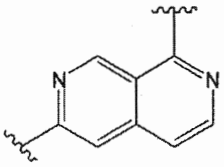
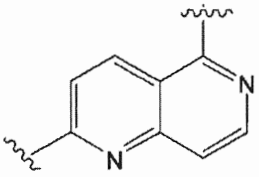
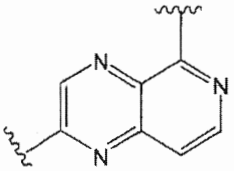
20~~21~~. The use ~~or the method~~ of claim 18~~19~~, wherein the fibrosis is selected from systemic sclerosis, skin fibrosis, idiopathic pulmonary fibrosis, renal fibrosis, liver fibrosis, drug-induced fibrosis and radiation-induced fibrosis.

21~~22~~. The ~~method~~ use of any one of claims 17~~18~~-20~~21~~, wherein the therapeutically effective amount is about 0.03 to about 2.5 mg/kg per body weight at daily dosages.

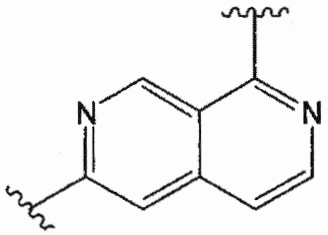
22~~23~~. The ~~method~~ use of claim 21~~22~~, wherein the therapeutically effective amount is about 0.5 mg to about 1000 mg for humans.

23~~24~~. The ~~method~~ use of any one of claims 17~~18~~-22~~23~~, wherein the compound is to be administrated enterally, orally, parenterally, topically or in a nasal or suppository form.

24. The compound of any one of claims 1 to 6, having one of the following core structures:

25. The compound of claim 24, having the core structure of:



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