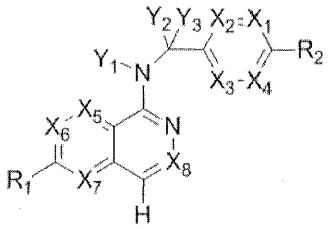
maintenance of HSC's, and dysfunctional WNT signaling is responsible for various disorders resulting from HSC's, such as leukemias and various other blood related cancers (Reya,, 2005). Accordingly, identification of methods and compounds that modulate the WNT- dependent cellular responses may offer an avenue for regulating physiological functions and therapeutic treatment of diseases associated with aberrant activity of the pathways.

SUMMARY OF THE INVENTION

The present invention generally provides a compound and a pharmaceutical composition thereof, while the compound is used as WNT signaling inhibitor, and the use of such compound for inhibiting WNT signaling pathway.

In one aspect, there is provided a compound, having the structure of Formula I:



(I)

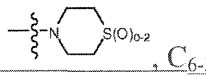
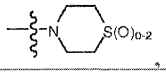
or a physiologically acceptable salt thereof, wherein

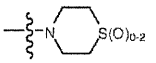
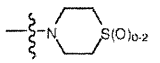
X_1, X_2, X_3, X_4, X_5, X_6 and X_7 are independently CR_4 or N;

X_8 is CR_4;

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 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 halogen, C_{1-6} alkyl, quinolinyl, , 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, ,

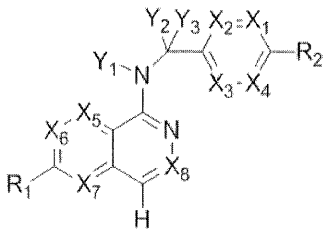
3 to 6 membered heterocycloalkyl, and 5 or 6 membered heteroaryl can be optionally substituted with one or two, and same or different R_4;

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.

In one aspect, there is provided a compound, having the structure of Formula I:



(I)

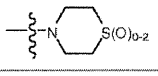
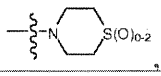
or a physiologically acceptable salt thereof, wherein

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

X_8 is CR_4;

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 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;

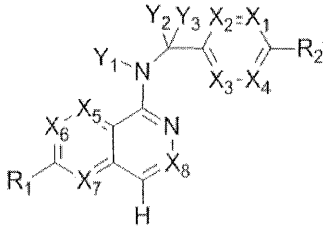
R_2 is C_{6-30} aryl optionally substituted with one R_4 or two different R_4;

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.

In one aspect, there is provided a compound, having the structure of Formula I:



(I)

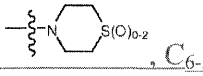
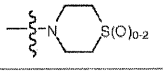
or a physiologically acceptable salt thereof, wherein

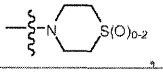
X_1, X_2, X_3, X_4, X_5, X_6 and X_7 are independently CR_4 or N ;

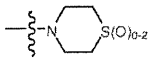
X_8 is CR_4;

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 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 hydrogen, halogen, C_{1-6} alkyl, quinolinyl, , 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,



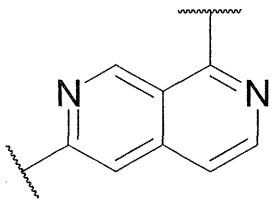
, 3 to 6 membered heterocycloalkyl, and 5 or 6 membered heteroaryl can be optionally substituted with one or two, and same or different R_4, or different R_4;

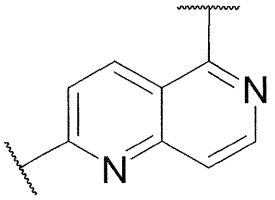
each R_3 is independently selected from hydrogen, halogen, cyano, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein each of the C_{1-6} alkyl and C_{1-6} alkoxy can be optionally substituted with halo, amino, hydroxyl, C_{1-6} alkoxy or cyano; and

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; and

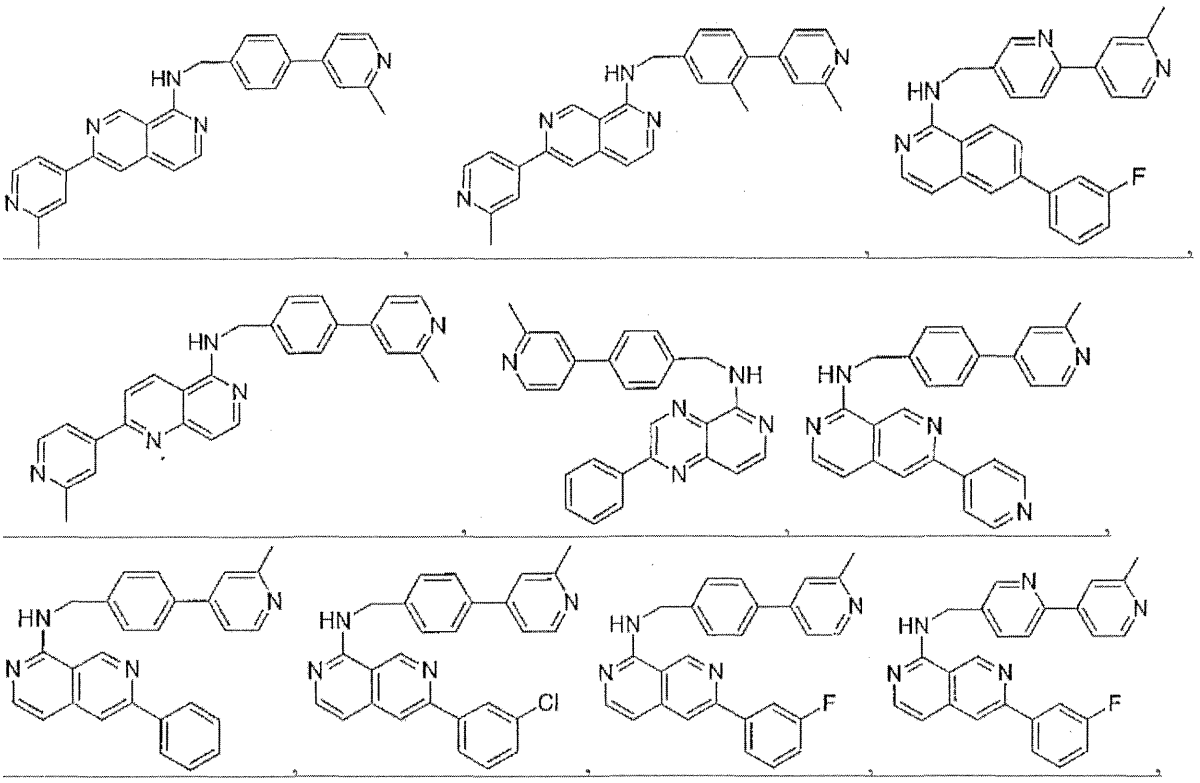
wherein the core structure of Formula I defined by X_5, X_6, X_7 and X_8 is

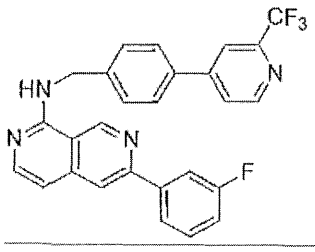


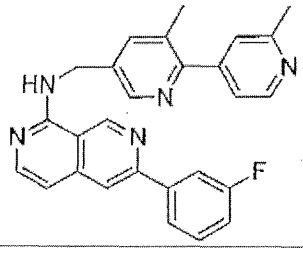
, or


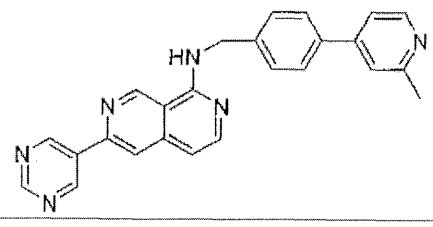
.

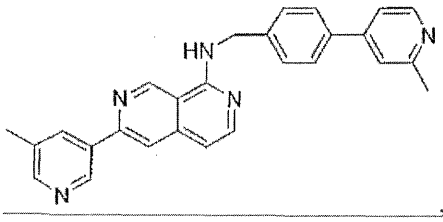
In one aspect, there is provided a compound, being selected from:

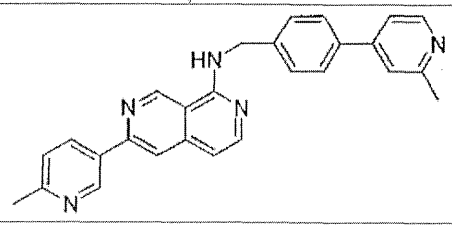


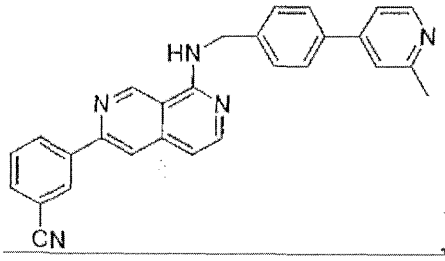


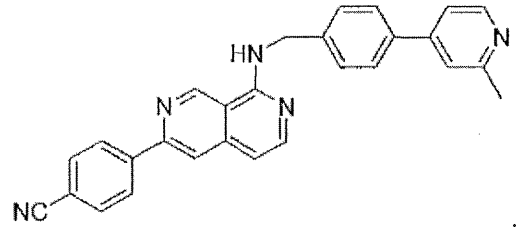


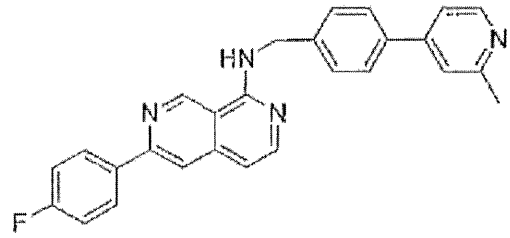


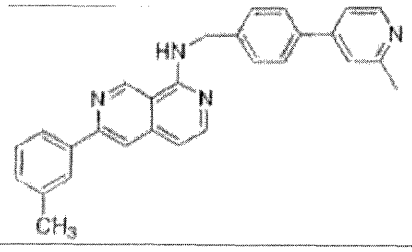


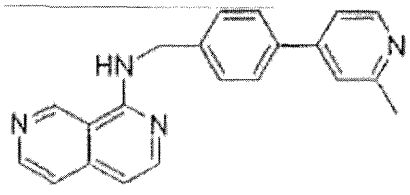


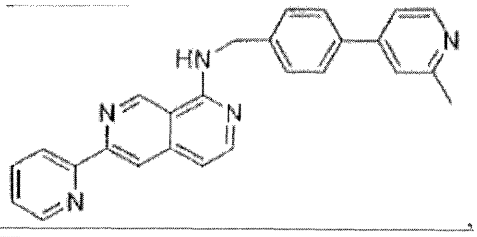


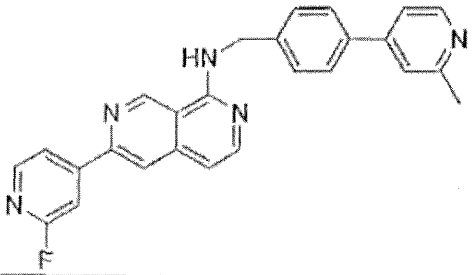


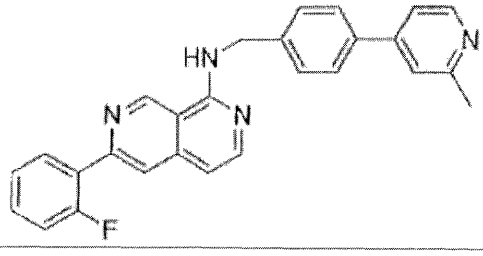


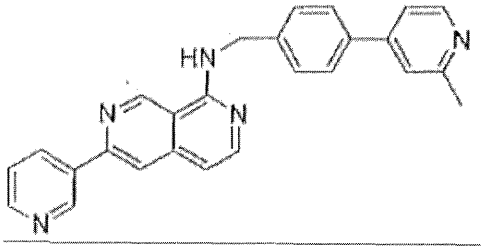


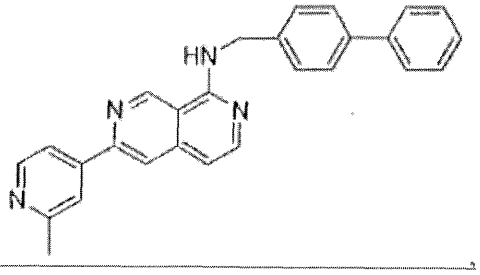


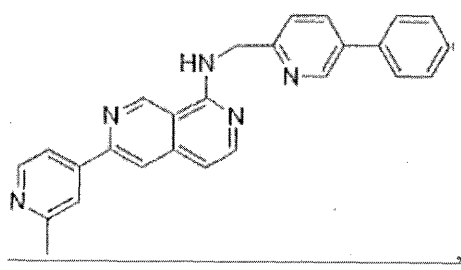


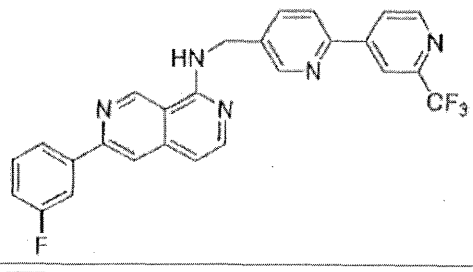


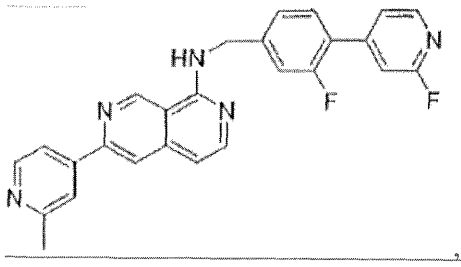


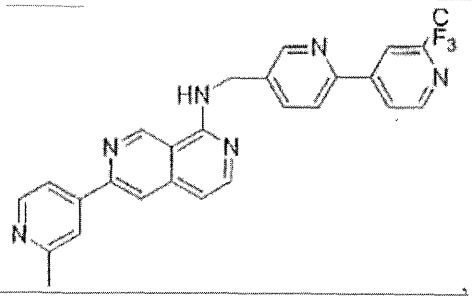


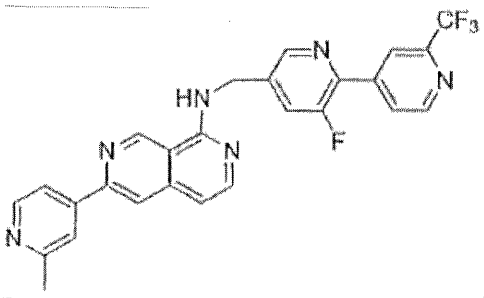


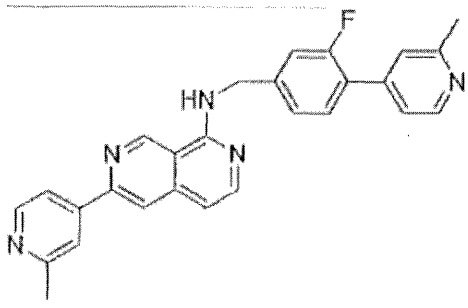


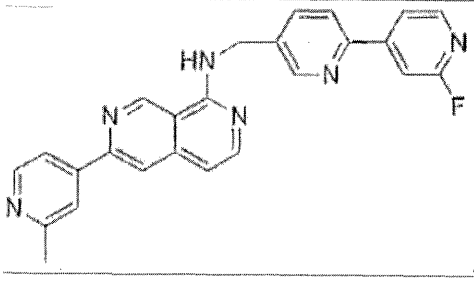


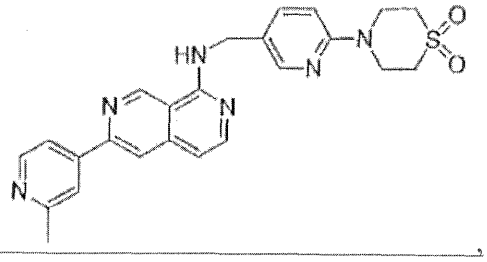


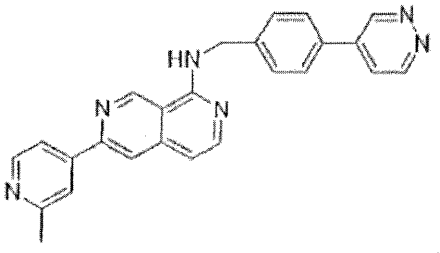


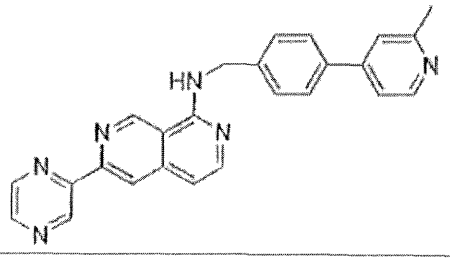


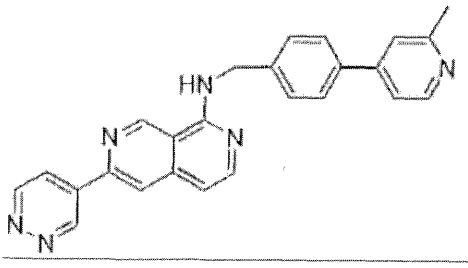


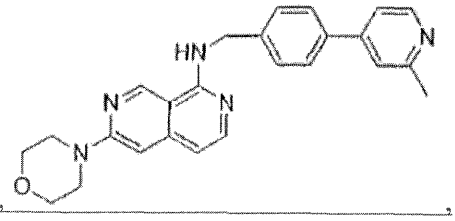


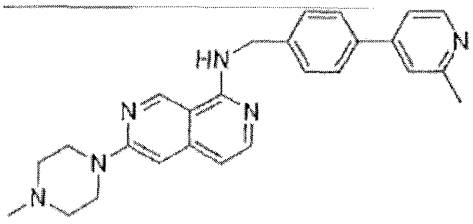


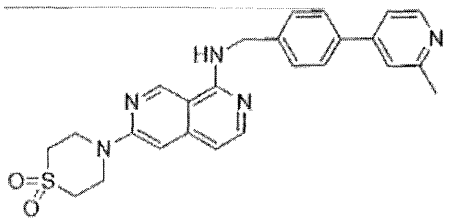


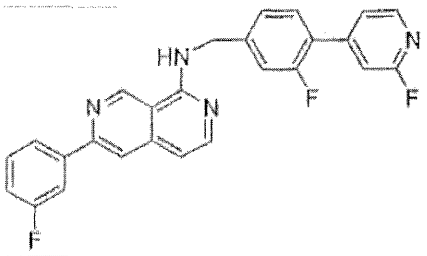


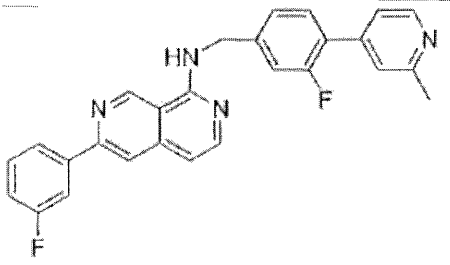


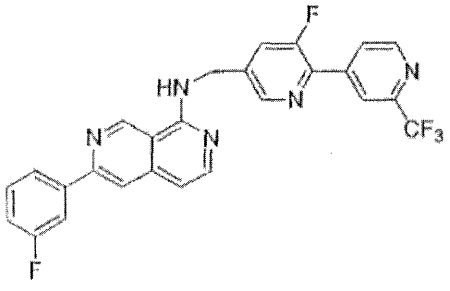


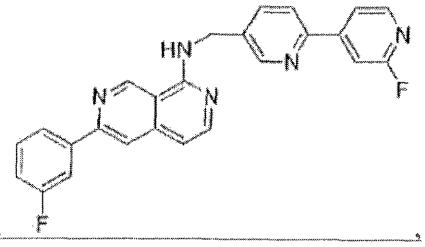


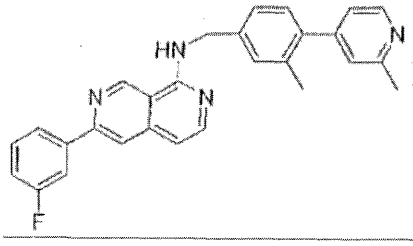


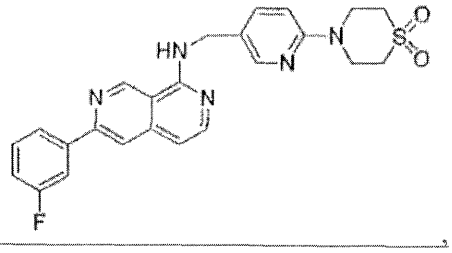


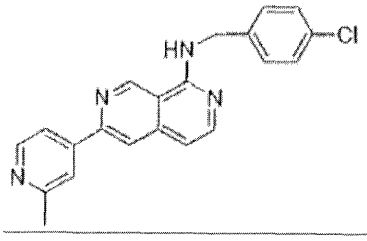


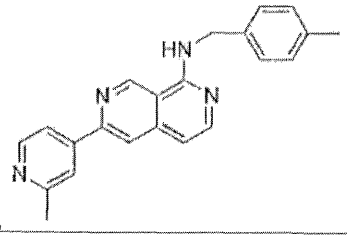


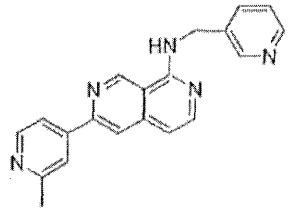


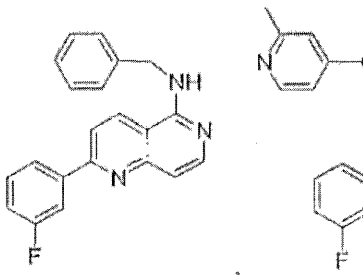


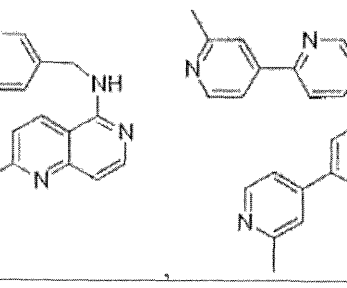


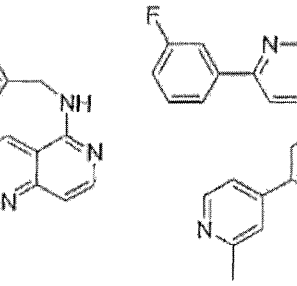


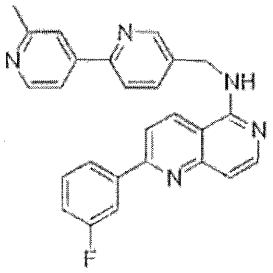


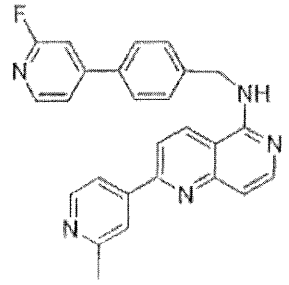


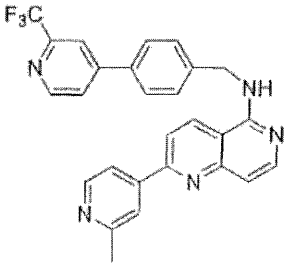


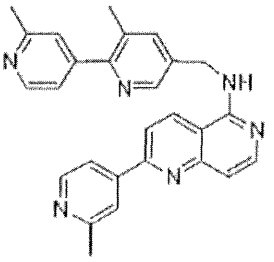


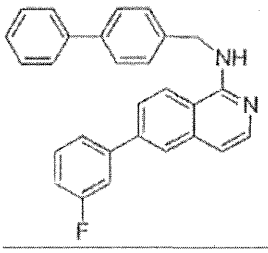


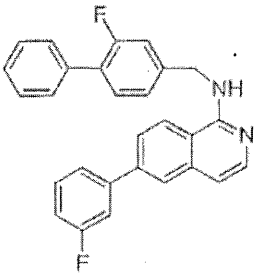


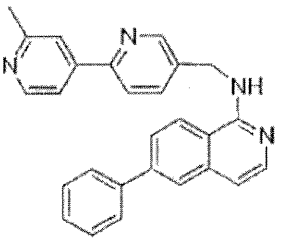


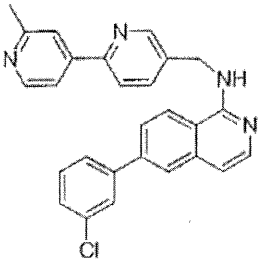


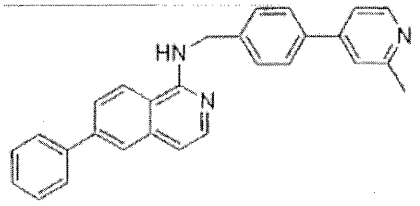


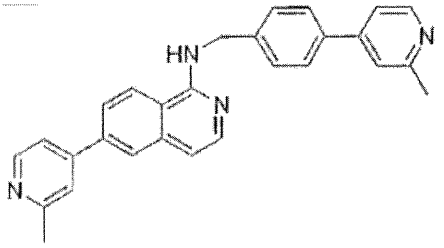


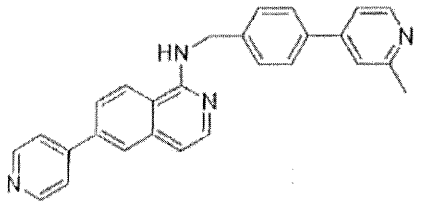


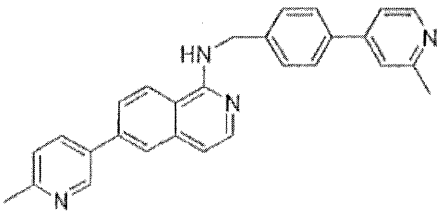


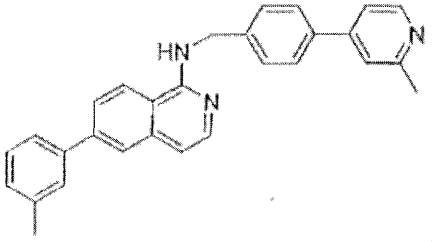


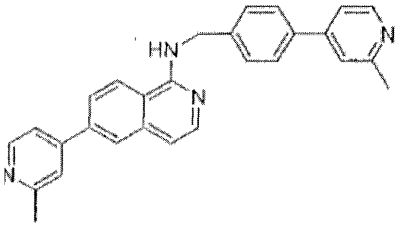


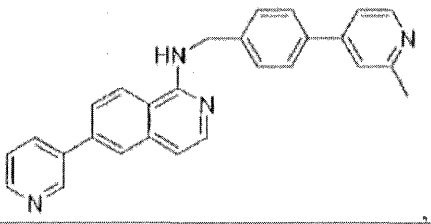


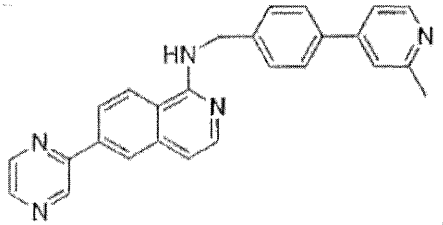


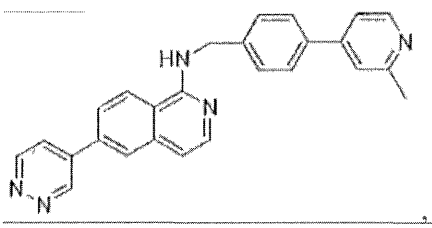


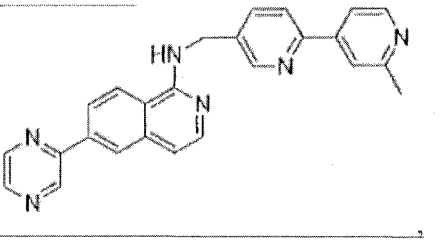


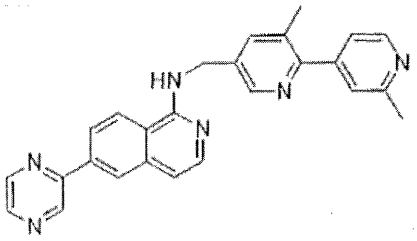


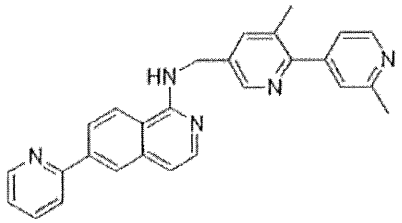


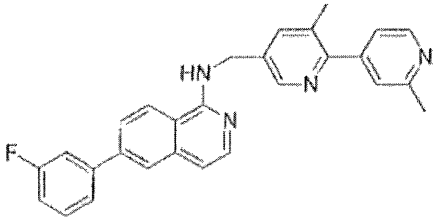


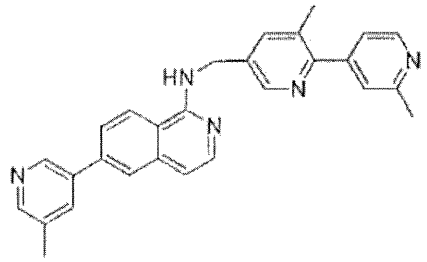


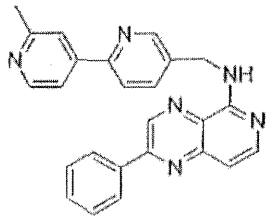


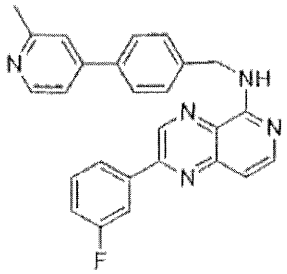


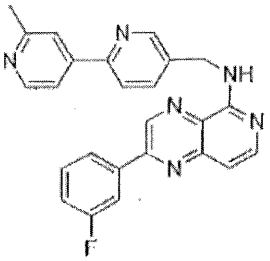


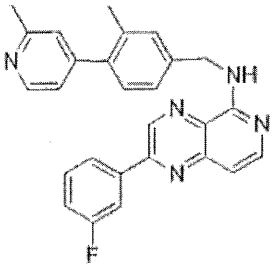


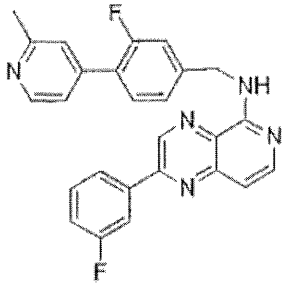


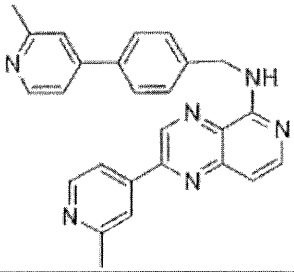


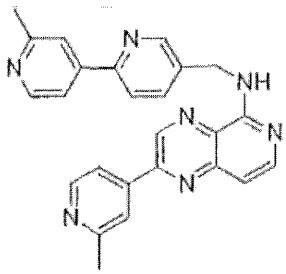


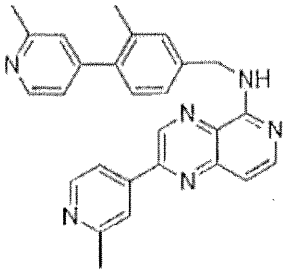


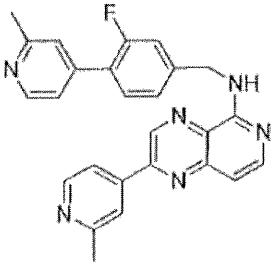


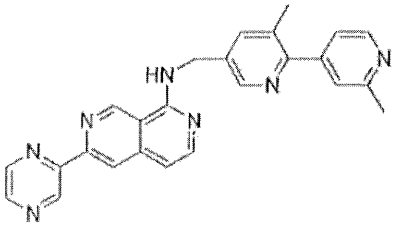


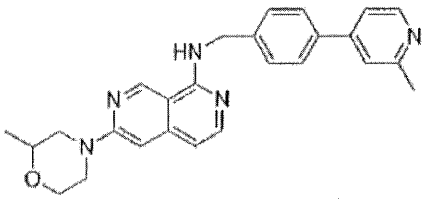


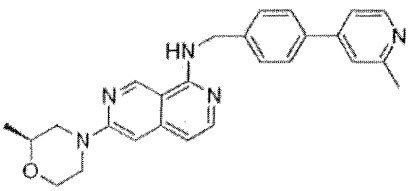


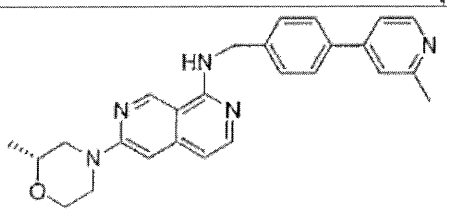


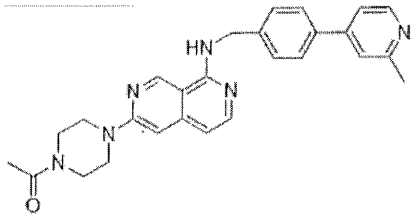


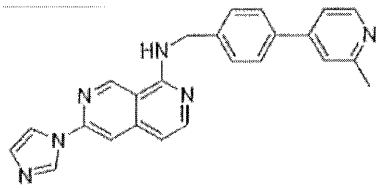


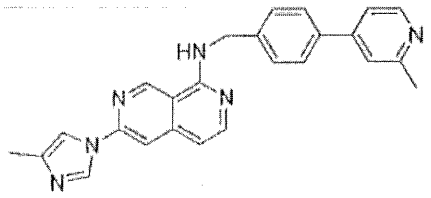


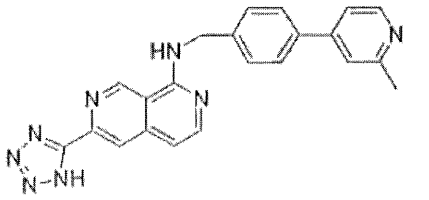


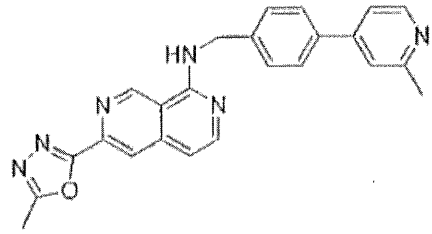


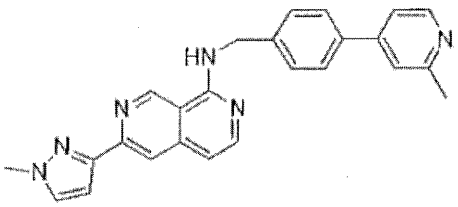


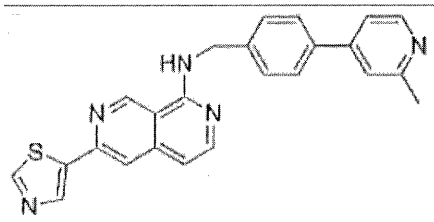


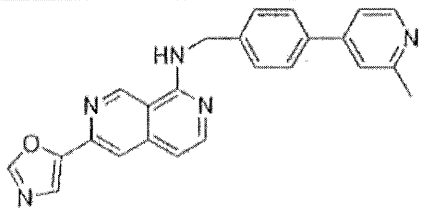


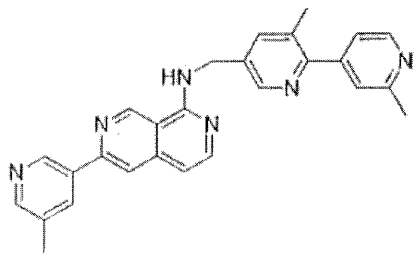


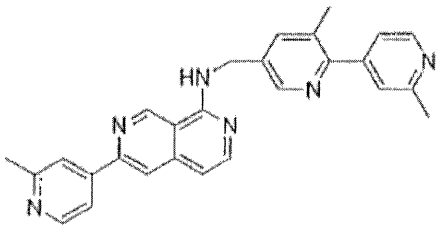


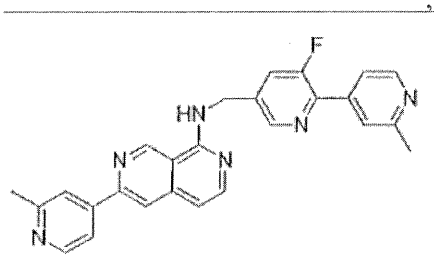


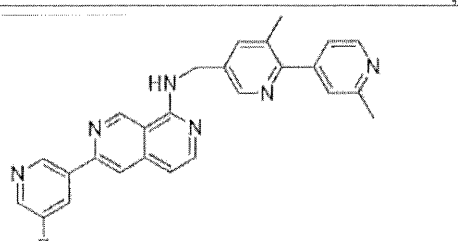


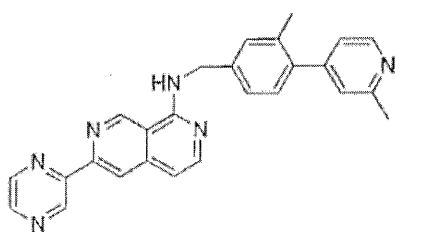


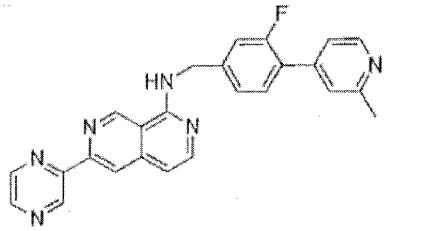


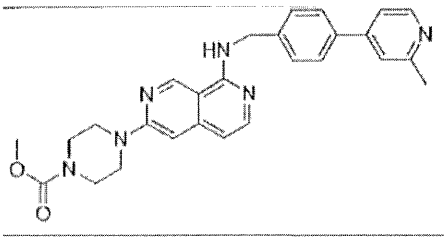


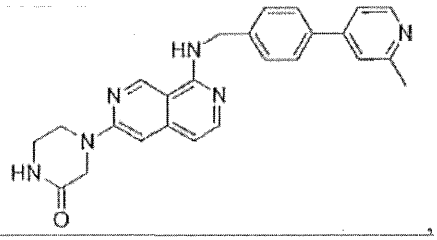


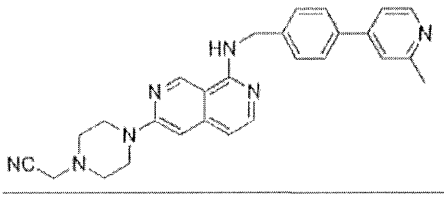


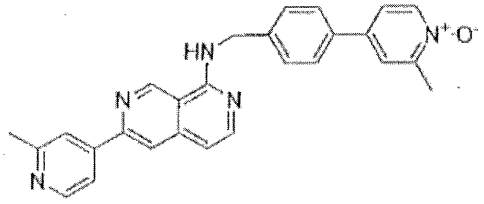


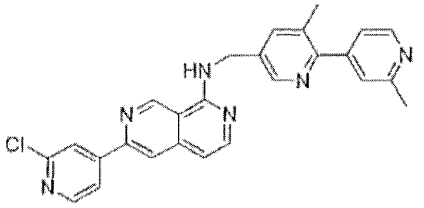


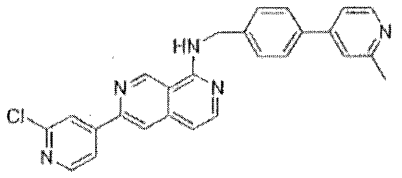


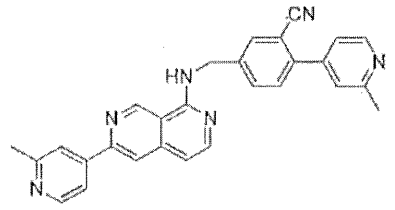


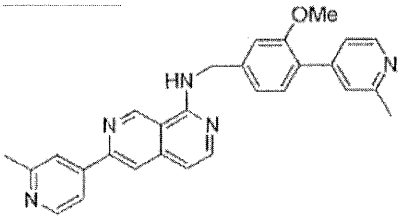


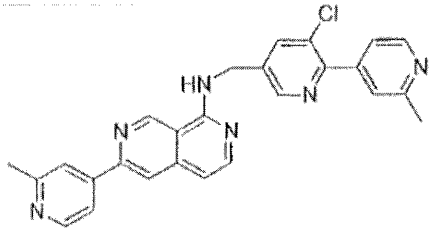


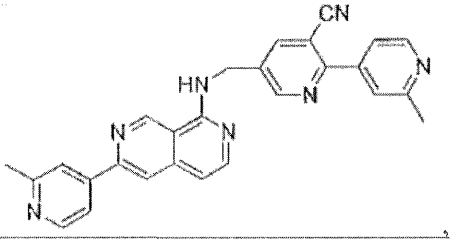


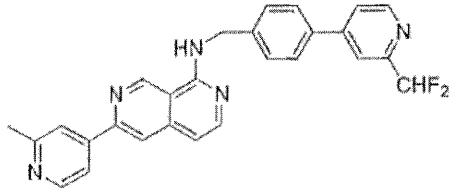












Wherein:

In one aspect, there is provided a pharmaceutical composition comprising the compound or physiologically acceptable salt thereof as described herein.

In one aspect, there is provided an *ex vivo* method of inhibiting WNT secretion from a cell, comprising contacting the cell with an effective amount of the compound or physiologically acceptable salt thereof as described herein, or the pharmaceutical composition as described herein.

In one aspect, there is provided an *ex vivo* method of inhibiting WNT signaling in a cell, comprising contacting the cell with an effective amount of the compound or physiologically acceptable salt thereof as described herein, or the pharmaceutical composition as described herein.

In one aspect, there is provided the use of a compound or physiologically acceptable salt thereof as described herein, or a pharmaceutical composition as described herein for the manufacture of a medicament for treating a WNT pathway mediated disorder.

Definition

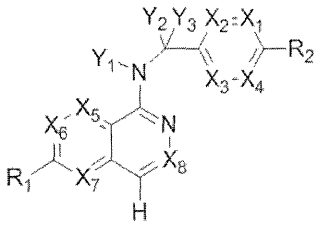
As used herein, "WNT signaling pathway" or "WNT pathway" refers to the pathway by which binding of the WNT protein to cellular receptors results in changes of cell behavior. The WNT pathway involves a variety of proteins including Frizzled, Disheveled, Axin, APC, GSK3β, β-catenin, LEF/TCF transcription factors, and molecules involved in the synthesis and secretion of WNT proteins. Examples of proteins implicated in the secretion of functional WNTs include, but are not limited to wntless/evenness interrupted (Wls/Evi), porcupine (Porcn), and Vps35p. Wls/Evi is a 7 pass transmembrane protein which resides in the Golgi apparatus and is required for secretion of Wg (drosophila) MOM-2 (c. elegans) and Wnt3A. It contains a conserved structural motif whose structure and function are both unknown. Porcupine (Porcn) is a member of the membrane-bound O- acyltransferase (MBOAT) family of palmitoyl transferases. Fatty acid modification of Wnts is critical for their function. Wnts are palmitoylated on one or two highly conserved sites. Inhibitors of Porcn may therefore block all functional Wnt signaling. Vps35p is a subunit of a multiprotein complex called the retromer complex which is involved in intracellular protein trafficking. Vps35p functions in binding target proteins like WNTs for recruitment into vesicles.

"WNT pathway inhibitor" or "WNT signaling inhibitor" is a small organic molecule that inhibits WNT signaling activity and typically has a molecular weight of about 800 g/mol or less.

The term "a method of inhibiting WNT pathway" refers to methods of inhibiting known biochemical events associated with production of functional WNT proteins or with cellular responses to WNT proteins. As discussed herein, small organic molecules may inhibit WNT response in accordance with this definition.

Claims:

1. A compound, having the structure of 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 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 or 6 membered heteroaryl can be optionally substituted with one or two, and same or different R_4;

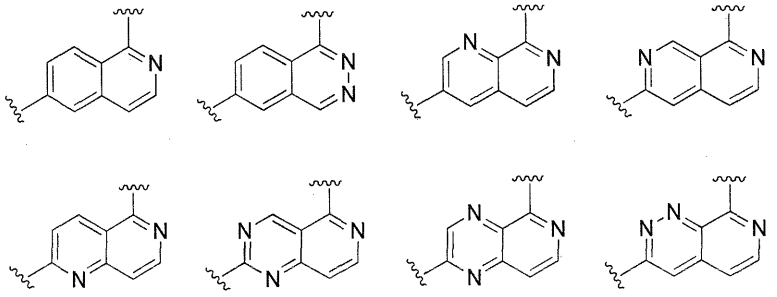
R_2 is selected from C_{1-6} alkyl, quinolinyl, , C_{6-30} aryl, 3 to 6 membered heterocycloalkyl containing 1-2 heteroatoms selected from N, O and S, and 5 or 6 membered heteroaryl containing 1-4 heteroatoms selected from N, O and S, wherein each of quinolinyl, , C_{6-30} aryl, 3 to 6 membered heterocycloalkyl, 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;

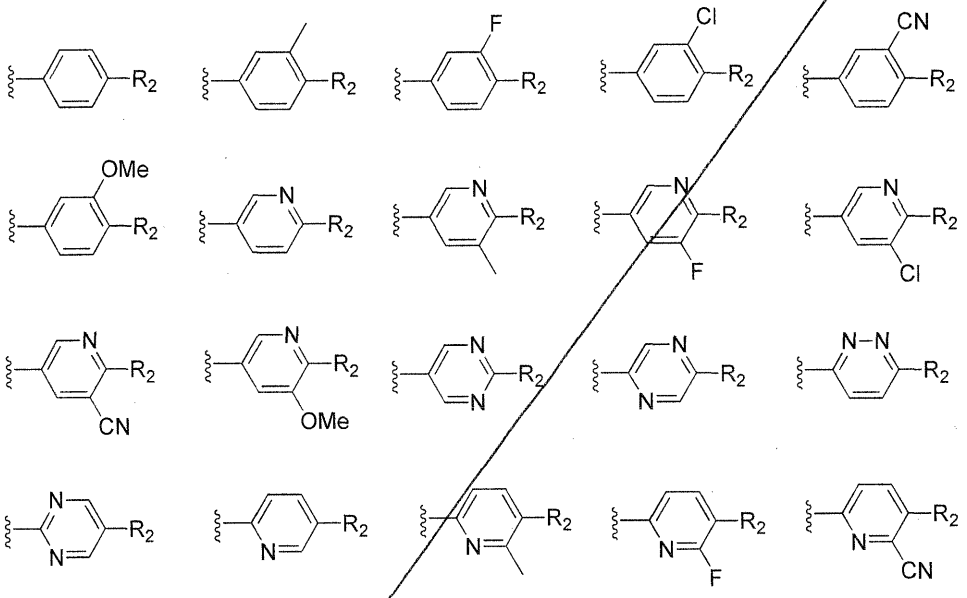
each R_4 is independently selected from hydrogen, halogen, cyano, C_{1-6} alkoxy, $-S(O)_2R_5$, $-C(O)OR_5$, $-C(O)R_5$, $-C(O)NR_6R_7$, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, wherein each of C_{1-6} alkoxy, $-S(O)_2R_5$, $-C(O)OR_5$, $-C(O)R_5$, $-C(O)NR_6R_7$, C_{1-6} alkyl, C_{2-6} alkenyl 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.

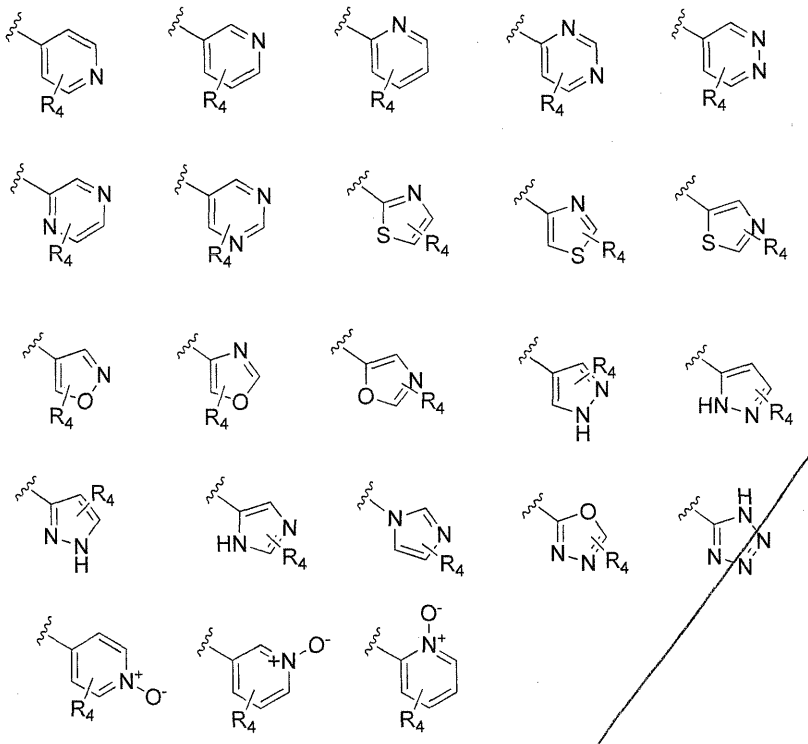
2. The compound of claim 1, wherein the core structure of Formula I defined by X_5, X_6, X_7 and X_8 is selected from:



3. The compound of claim 1 or 2, wherein the ring in Formula I defined by X_1, X_2, X_3 and X_4 is selected from:



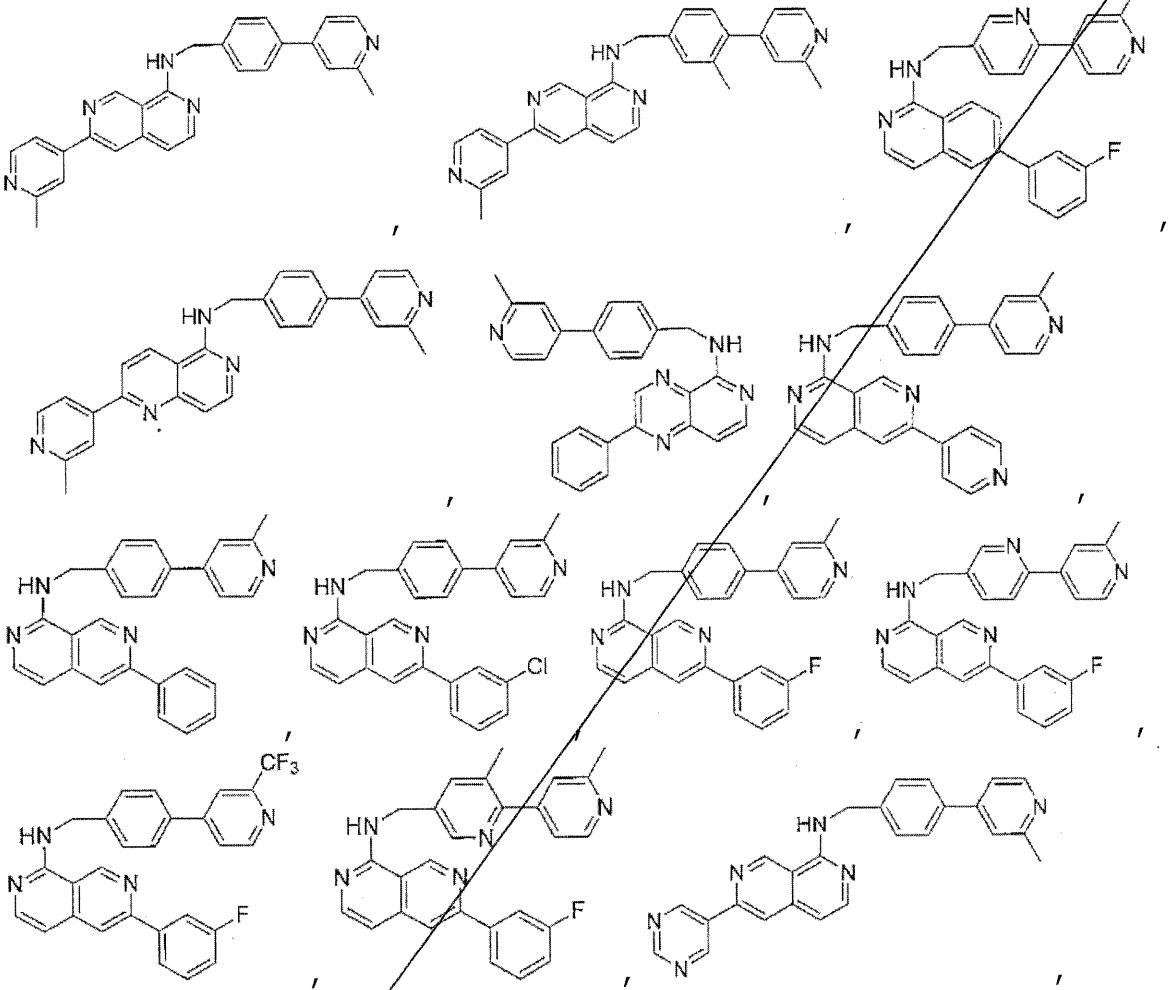
4. The compound of claim 2 or 3, wherein R_1 and R_2 are independently selected from hydrogen, fluorine, chlorine, methyl,  , phenyl, morpholinyl, piperazinyl, and the 5 or 6 membered heteroaryl is selected from:

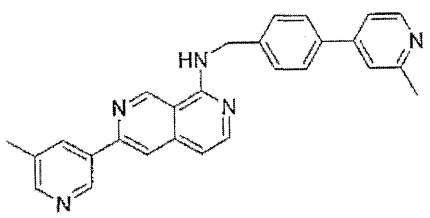
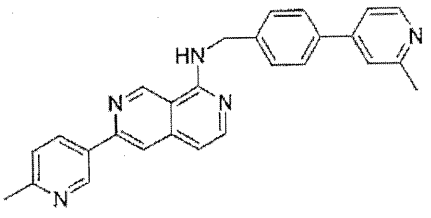
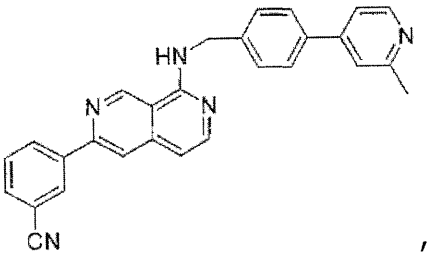
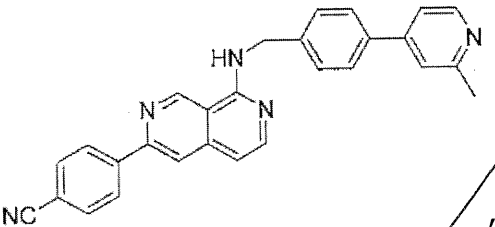
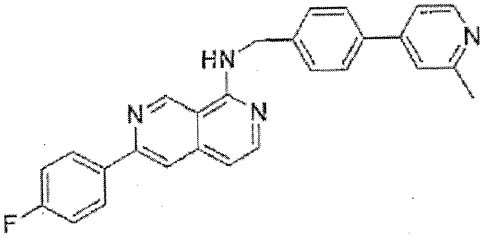
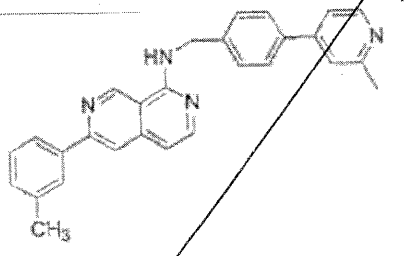
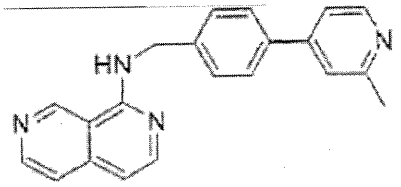
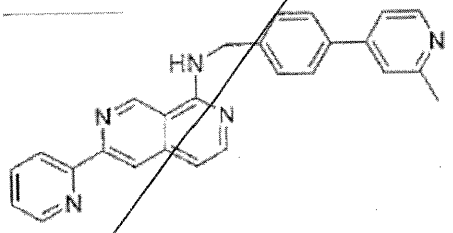
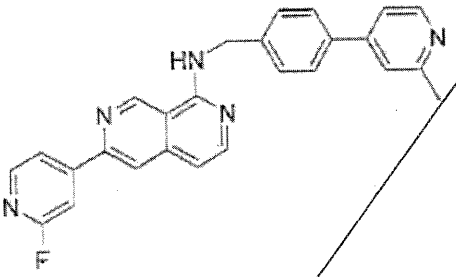
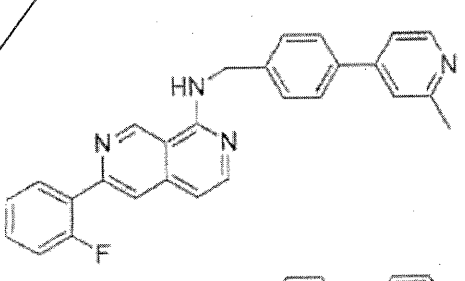
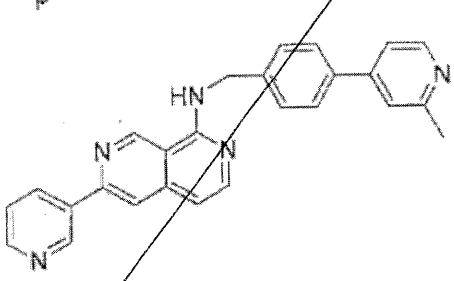
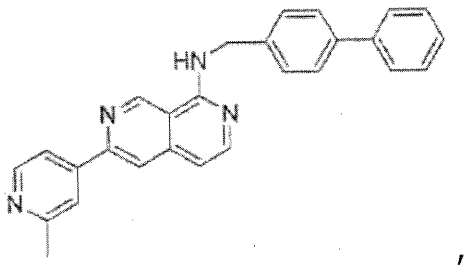


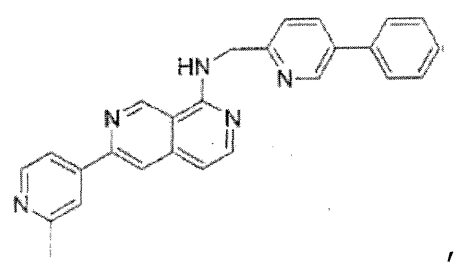
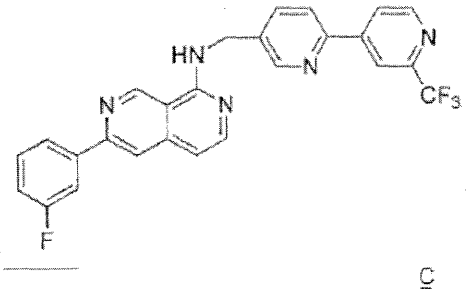
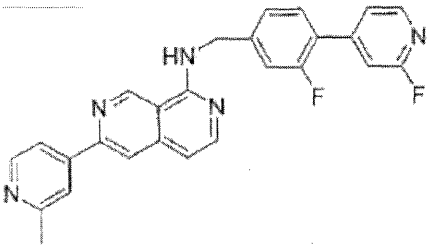
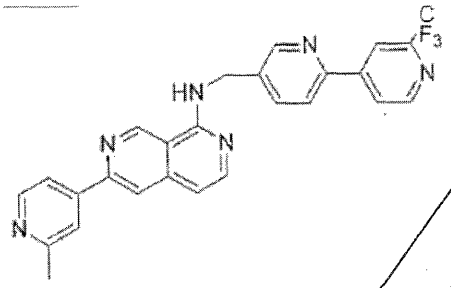
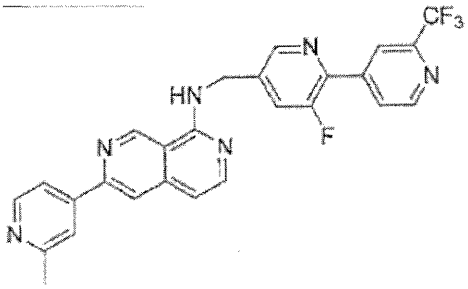
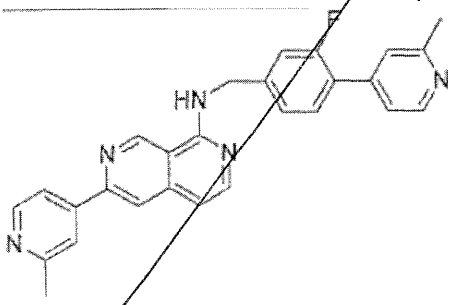
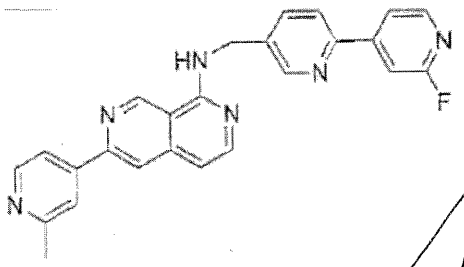
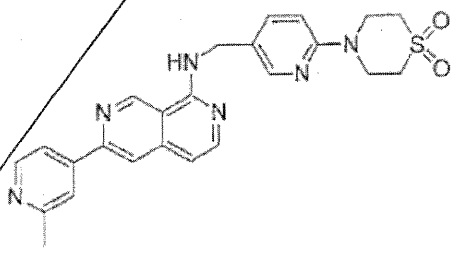
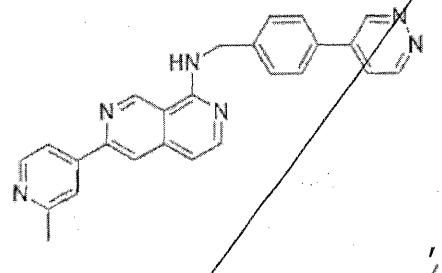
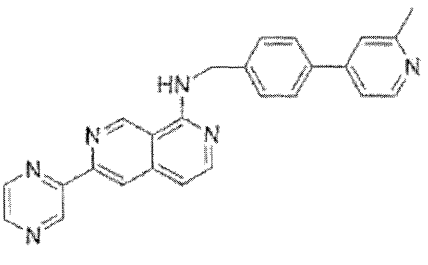
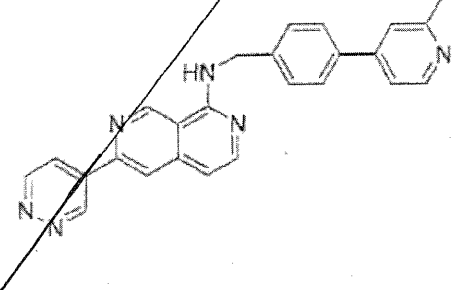
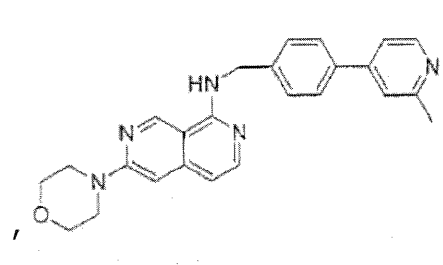
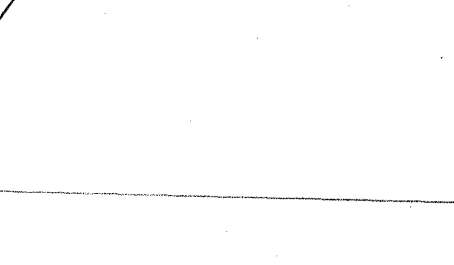
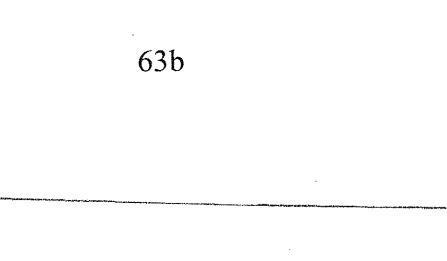
5. The compound of any one of claims 2-4, wherein each R_4 is independently selected from hydrogen, chlorine, fluorine, cyano, $-CH_3$,$-CHF_2$, $-CF_3$, $-OCH_3$, $-COOCH_3$.

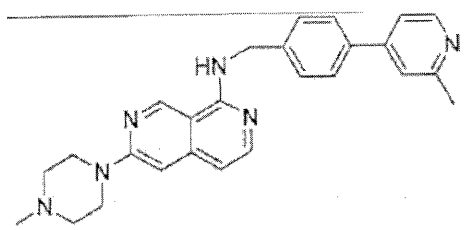
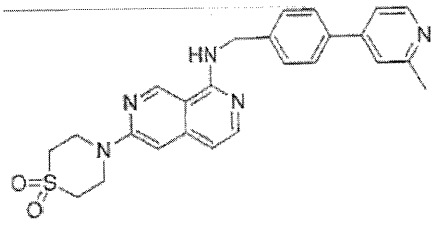
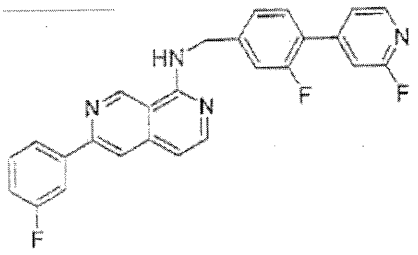
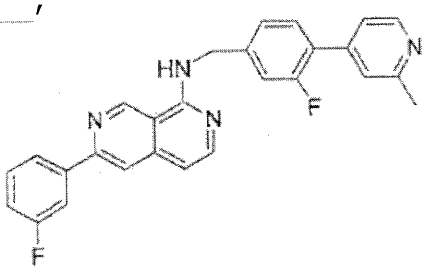
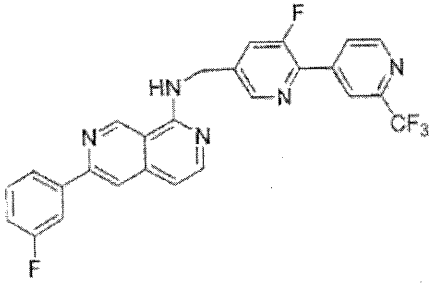
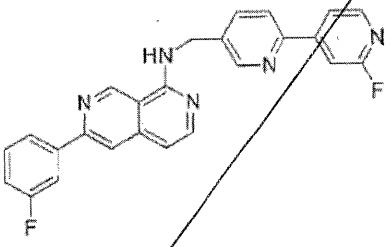
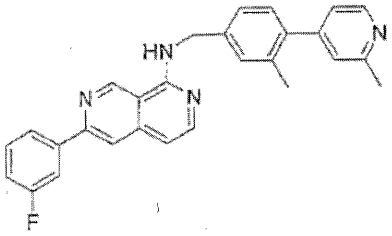
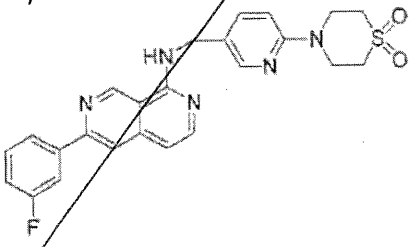
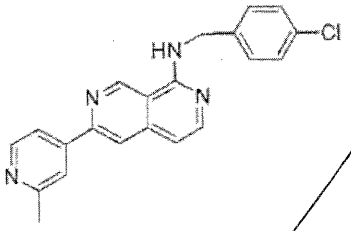
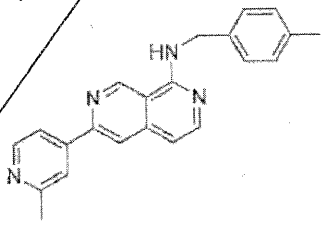
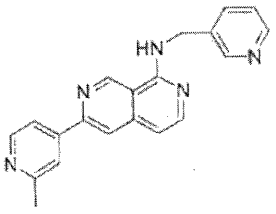
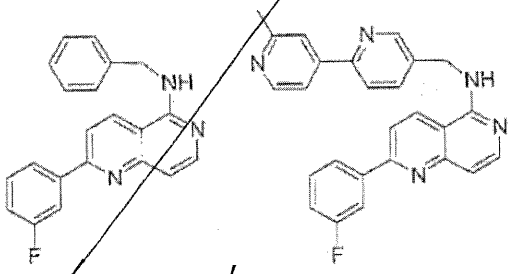
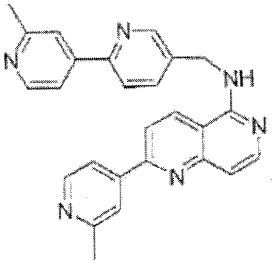
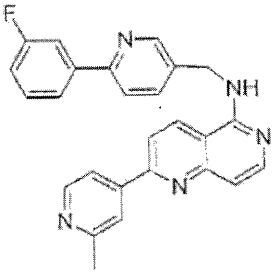
6. The compound of any one of claims 1-5, wherein at least one atom in Formula I is at least one of corresponding isotope(s) selected from ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl and ^{123}I.

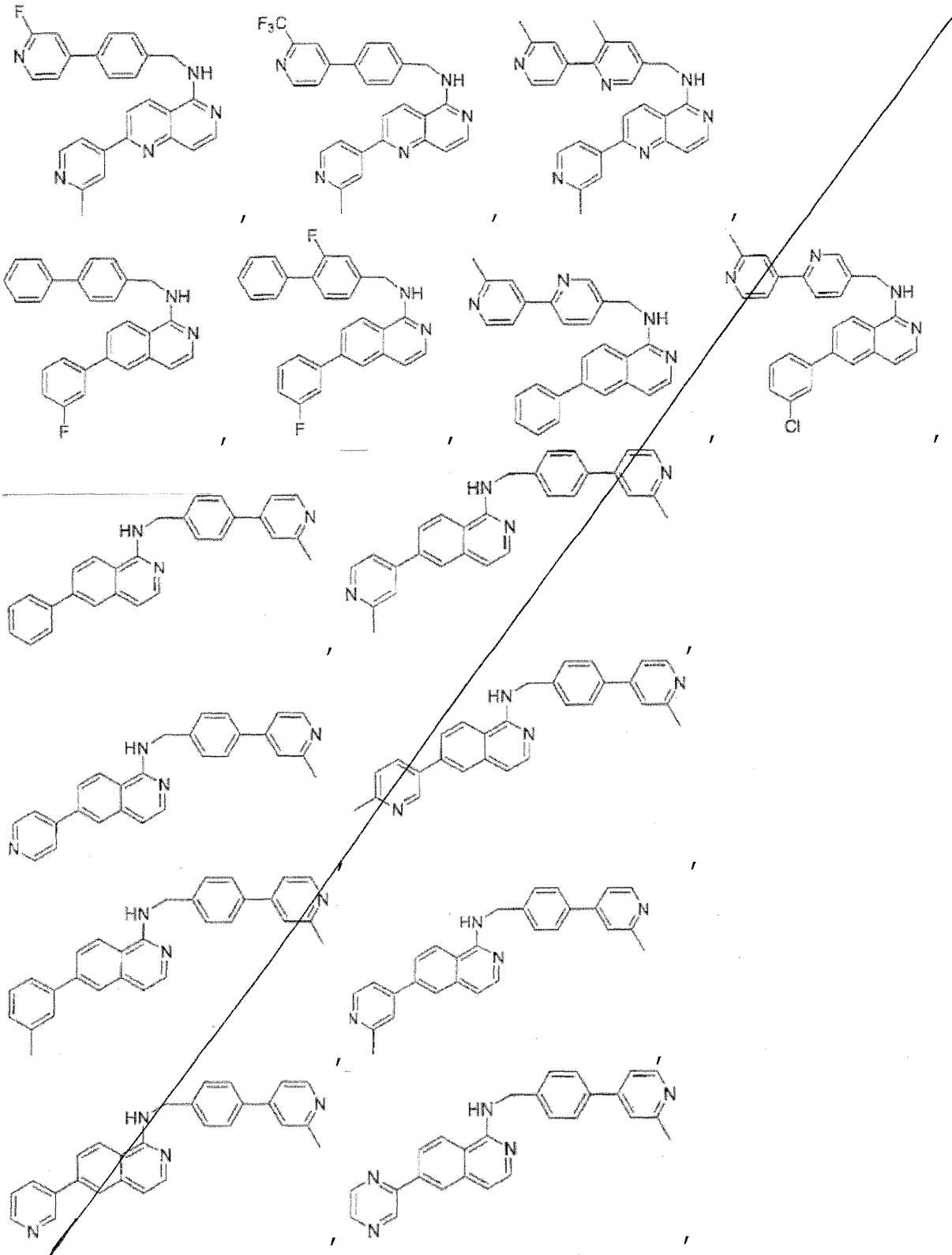
7. The compound of claim 1, being selected from:

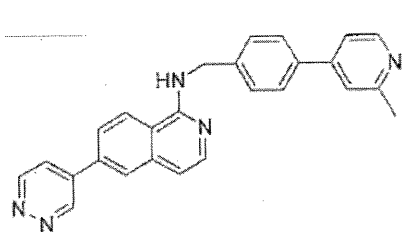
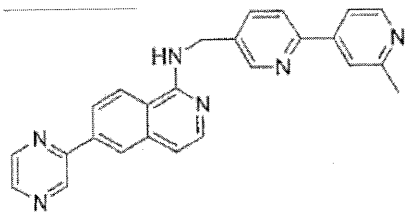
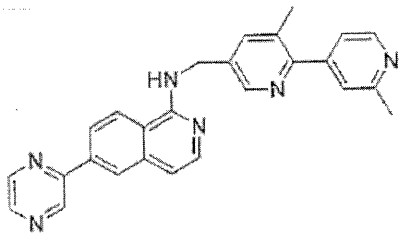
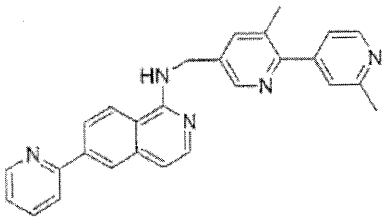
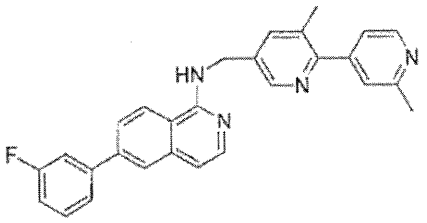
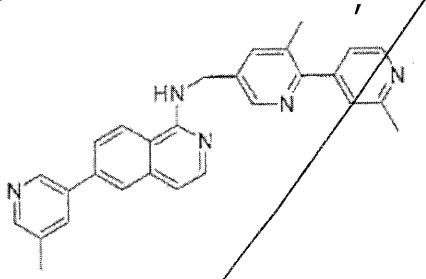
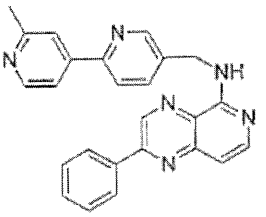
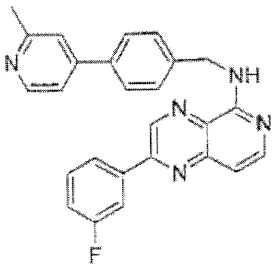
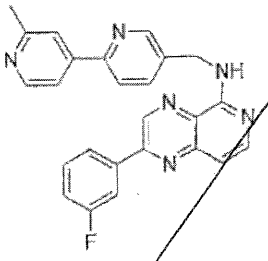
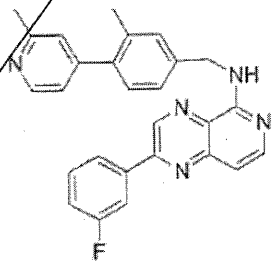
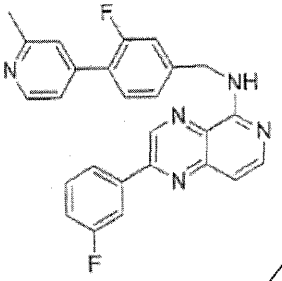
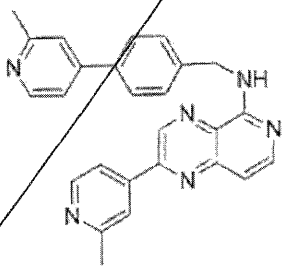
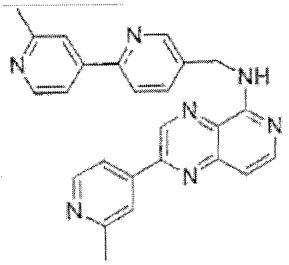
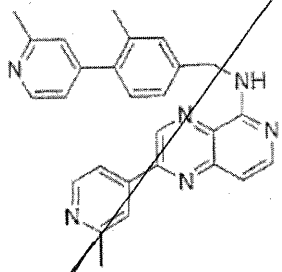
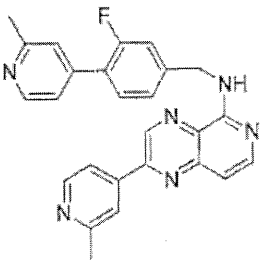
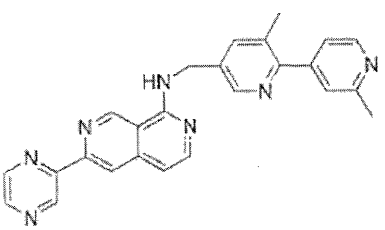


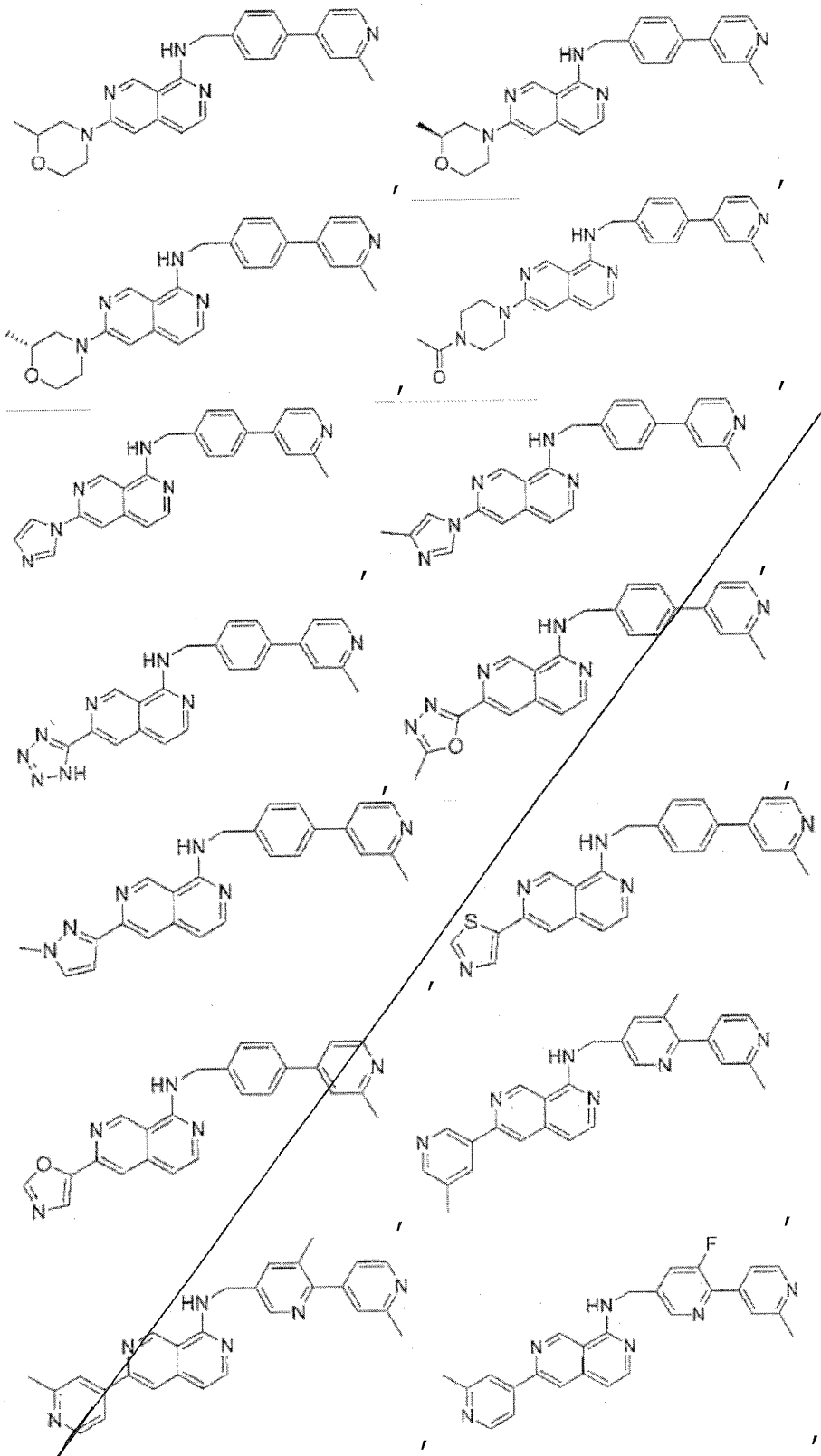













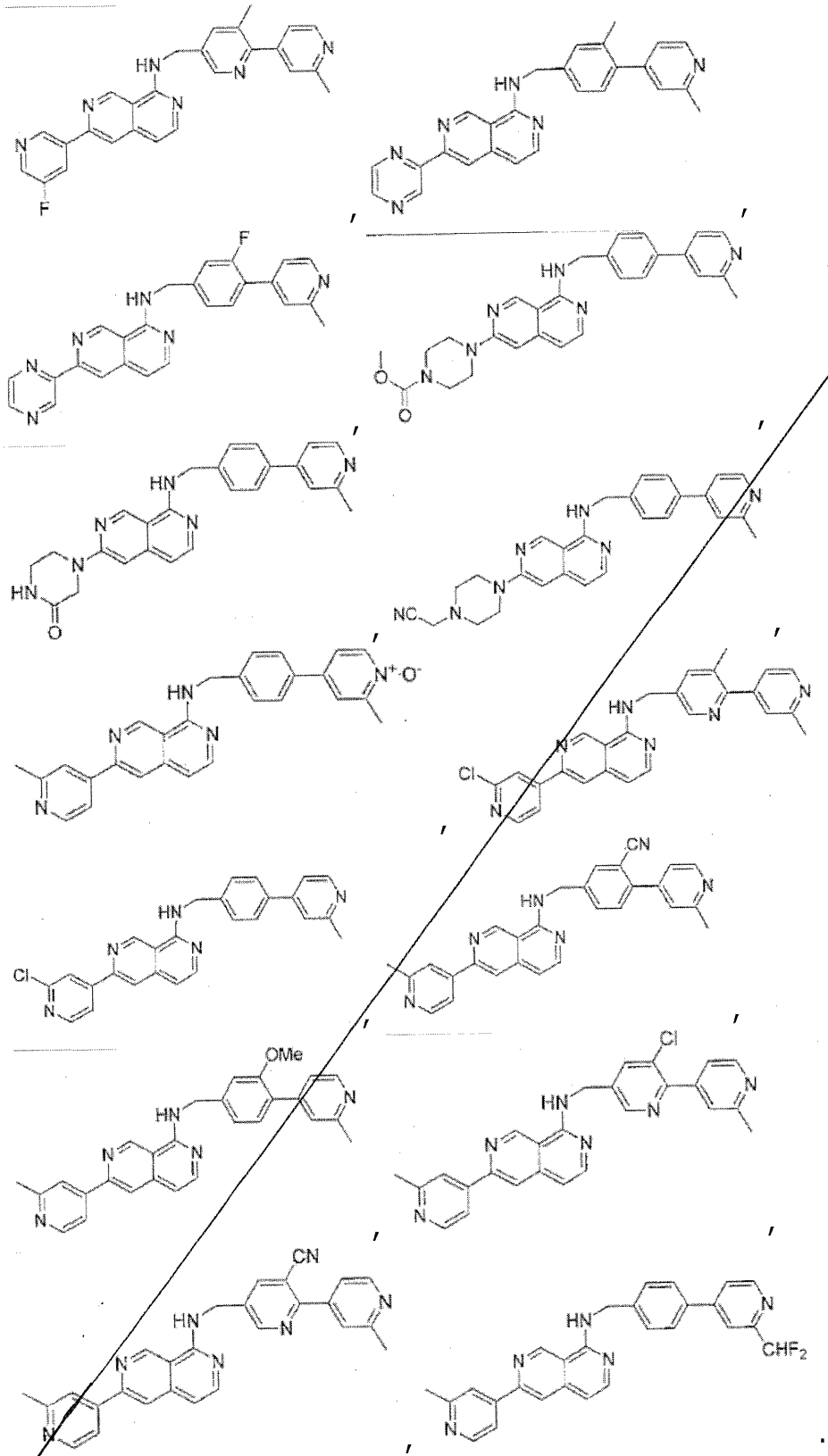





















8. A pharmaceutical composition comprising the compound or physiologically acceptable salt thereof of any one of the preceding claims.

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. The use of claim 17, wherein said disorder is cancer, fibrosis, osteoarthritis, Parkinson's disease, retinopathy, macular degeneration.

19. The use of claim 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).

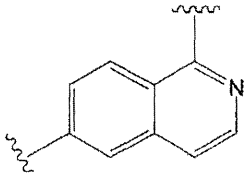
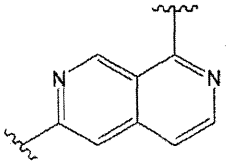
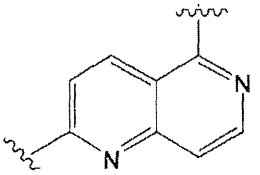
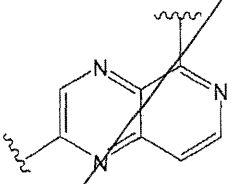
20. The use of claim 18, wherein the fibrosis is selected from systemic sclerosis, skin fibrosis, idiopathic pulmonary fibrosis, renal fibrosis, liver fibrosis, drug-induced fibrosis and radiation-induced fibrosis.

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

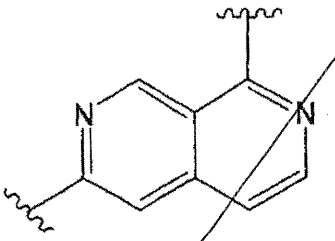
22. The use of claim 21, wherein the therapeutically effective amount is about 0.5 mg to about 1000 mg for humans.

23. The use of any one of claims 17-22, 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:

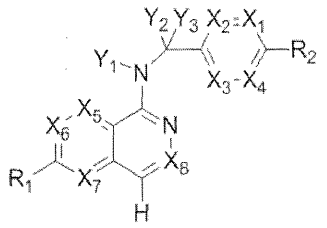





25. The compound of claim 24, having the core structure of:



Claims:

1. A compound, having the structure of Formula I:



(I)

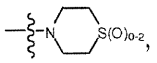
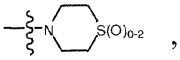
or a physiologically acceptable salt thereof, wherein

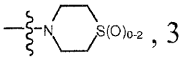
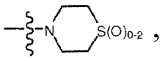
X_1, X_2, X_3, X_4, X_5, X_6 and X_7 are independently CR_4 or N;

X_8 is CR_4;

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 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;

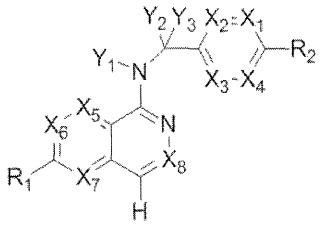
R_2 is selected from halogen, C_{1-6} alkyl, quinolinyl,  , 3 to 6 membered heterocycloalkyl containing 1-2 heteroatoms selected from N, O and S, and 5 or 6 membered heteroaryl containing 1-4 heteroatoms selected from N, O and S, wherein each of quinolinyl,  , 3 to 6 membered heterocycloalkyl, and 5 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. A compound, having the structure of Formula I:



(I)

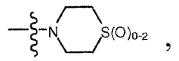
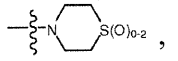
or a physiologically acceptable salt thereof, wherein

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

X_8 is CR_4;

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 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;

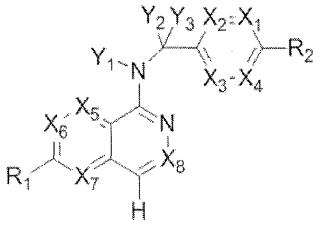
R_2 is C_{6-30} aryl optionally substituted with one R_4 or two different R_4;

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.

3. A compound, having the structure of Formula I:



(I)

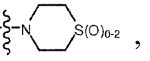
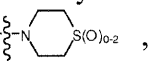
or a physiologically acceptable salt thereof, wherein

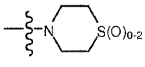
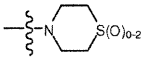
X_1, X_2, X_3, X_4, X_5, X_6 and X_7 are independently CR_4 or N ;

X_8 is CR_4;

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 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;

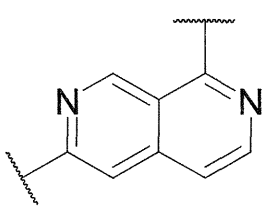
R_2 is selected from hydrogen, halogen, C_{1-6} alkyl, quinolinyl , , 3 to 6 membered heterocycloalkyl containing 1-2 heteroatoms selected from N, O and S, and 5 or 6 membered heteroaryl containing 1-4 heteroatoms selected from N, O and S, wherein each of quinolinyl, , 3 to 6 membered heterocycloalkyl,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

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; and

wherein the core structure of Formula I defined by X_5, X_6, X_7 and X_8 is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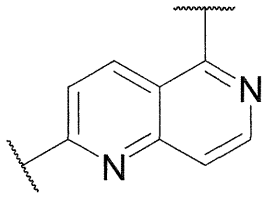
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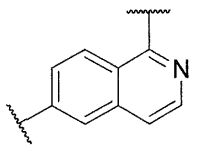
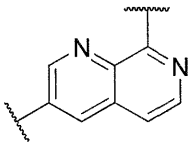
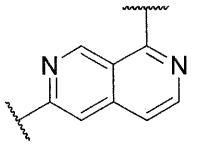
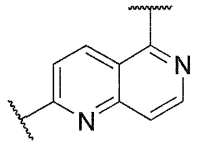
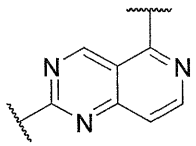
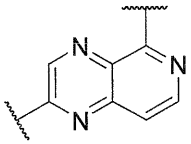
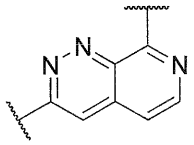
4. The compound of claim 1, 2 or 3, wherein the core structure of Formula I defined by X_5, X_6, X_7 and X_8 is selected from: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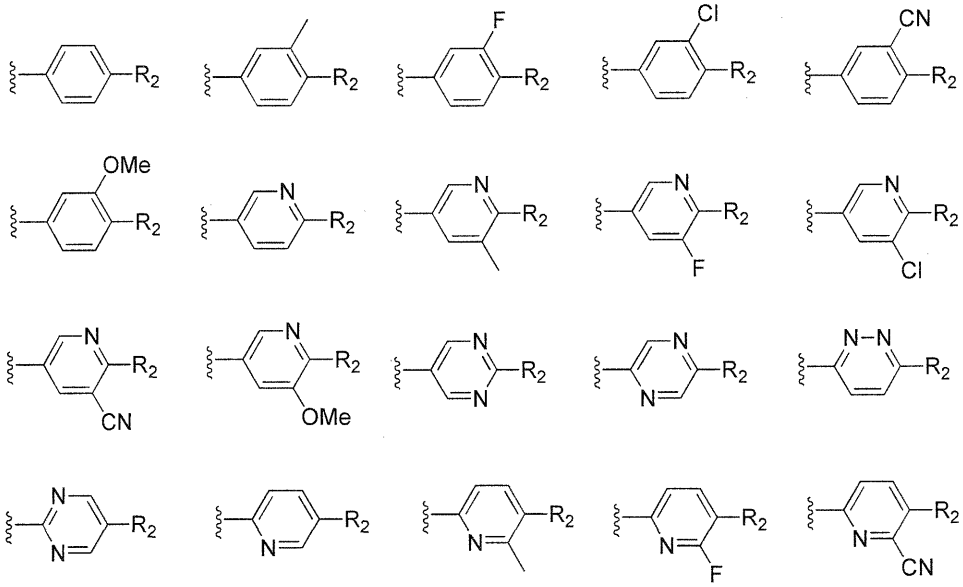
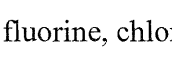
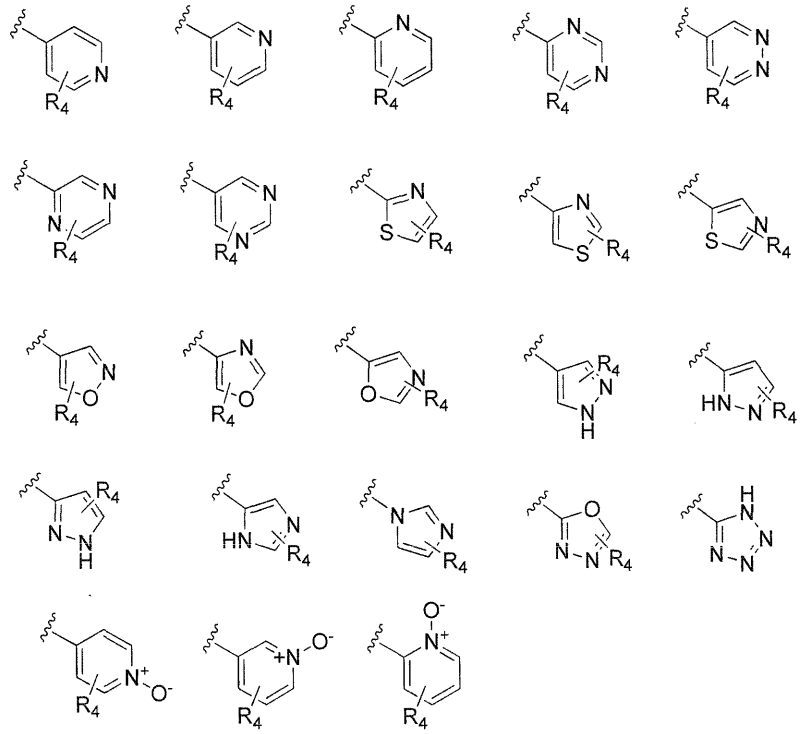
5. The compound of claim 1, 2, 3 or 4, wherein the ring in Formula I defined by X_1, X_2, X_3 and X_4 is selected from:



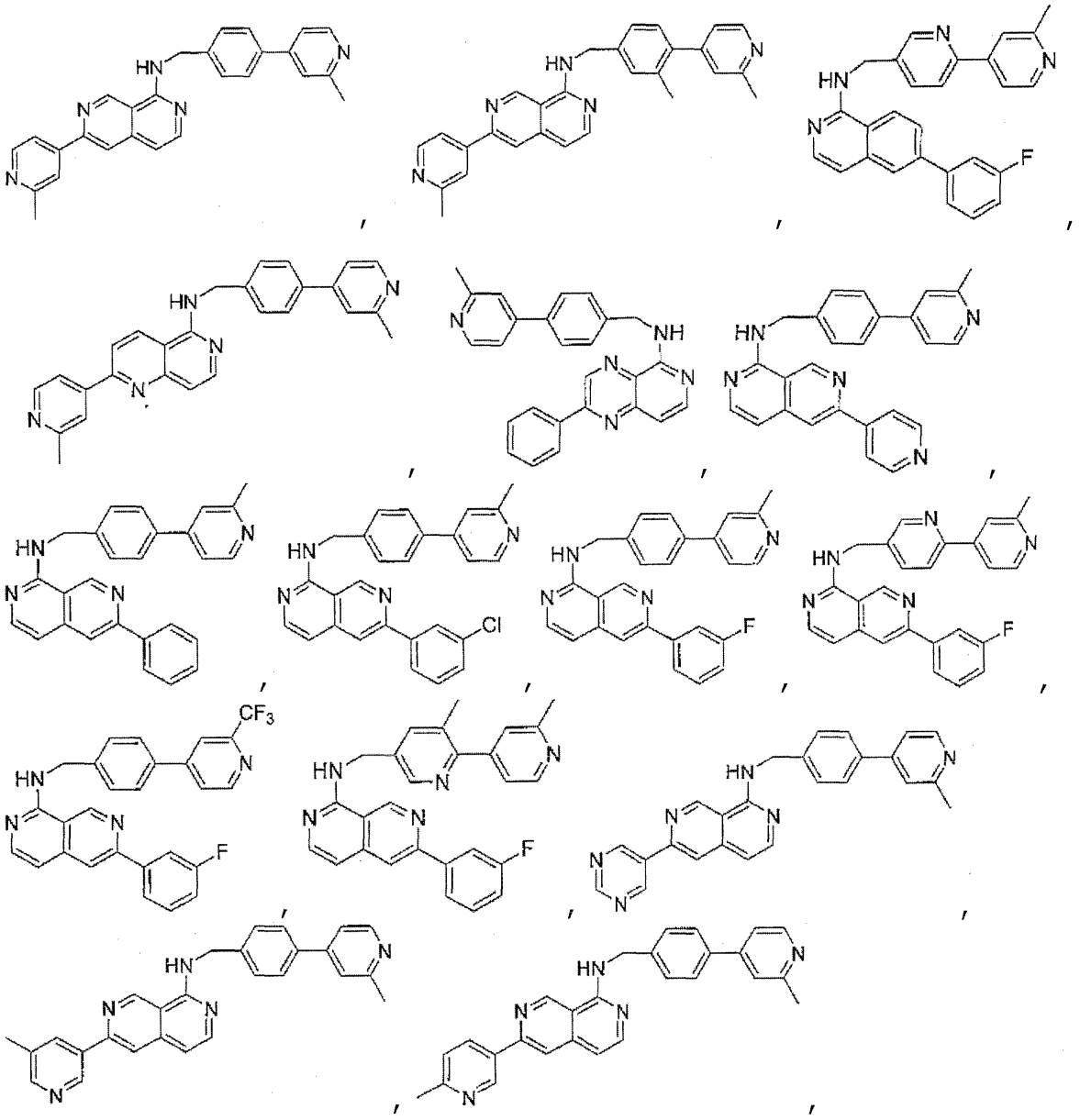
6. The compound of claim 2, 3, 4, or 5, wherein R_1 and R_2 are independently selected from hydrogen, fluorine, chlorine, methyl, , phenyl, morpholinyl, piperazinyl, and the 5 or 6 membered heteroaryl is selected from:

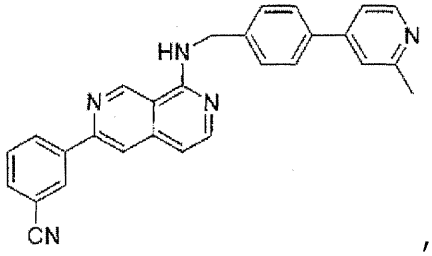
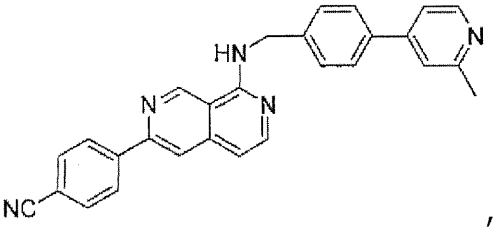
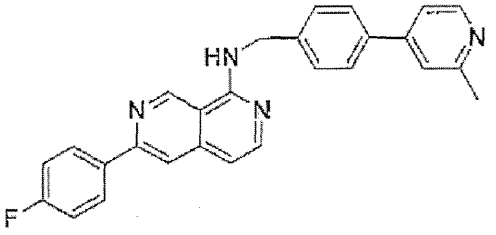
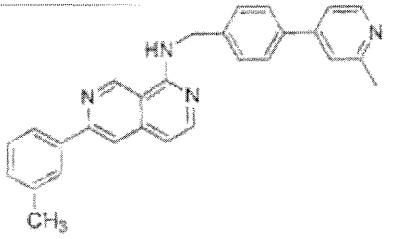
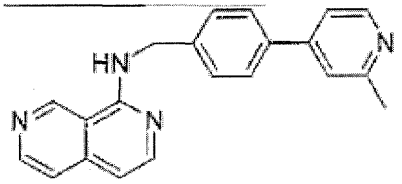
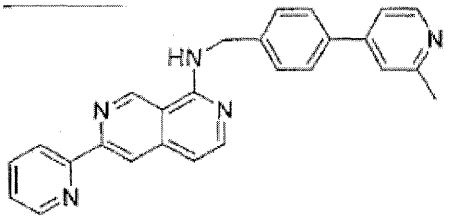
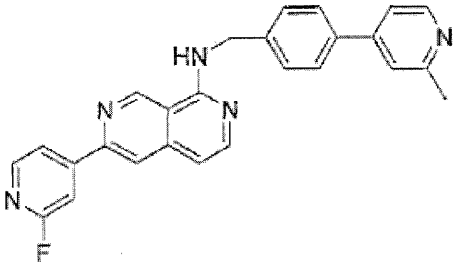
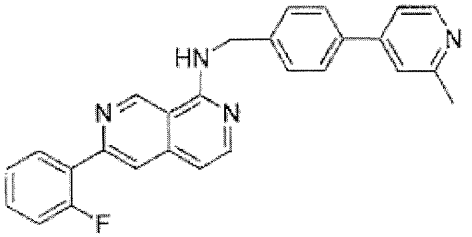
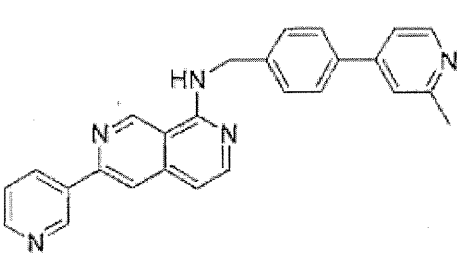
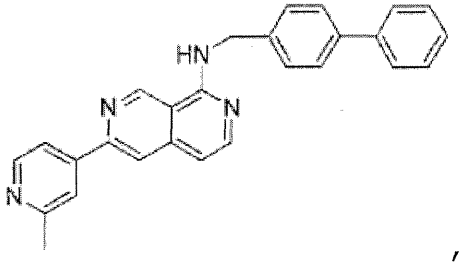


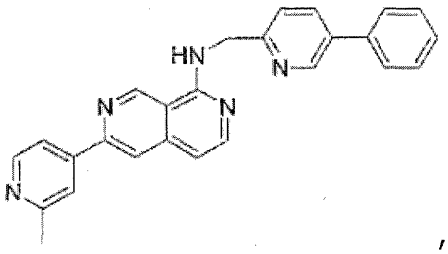
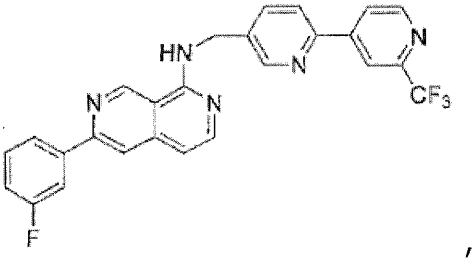
7. The compound of any one of claims 2, 3 and 4-6, wherein each R_4 is independently selected from hydrogen, chlorine, fluorine, cyano, $-CH_3$,$-CHF_2$, $-CF_3$, $-OCH_3$, $-COOCH_3$.

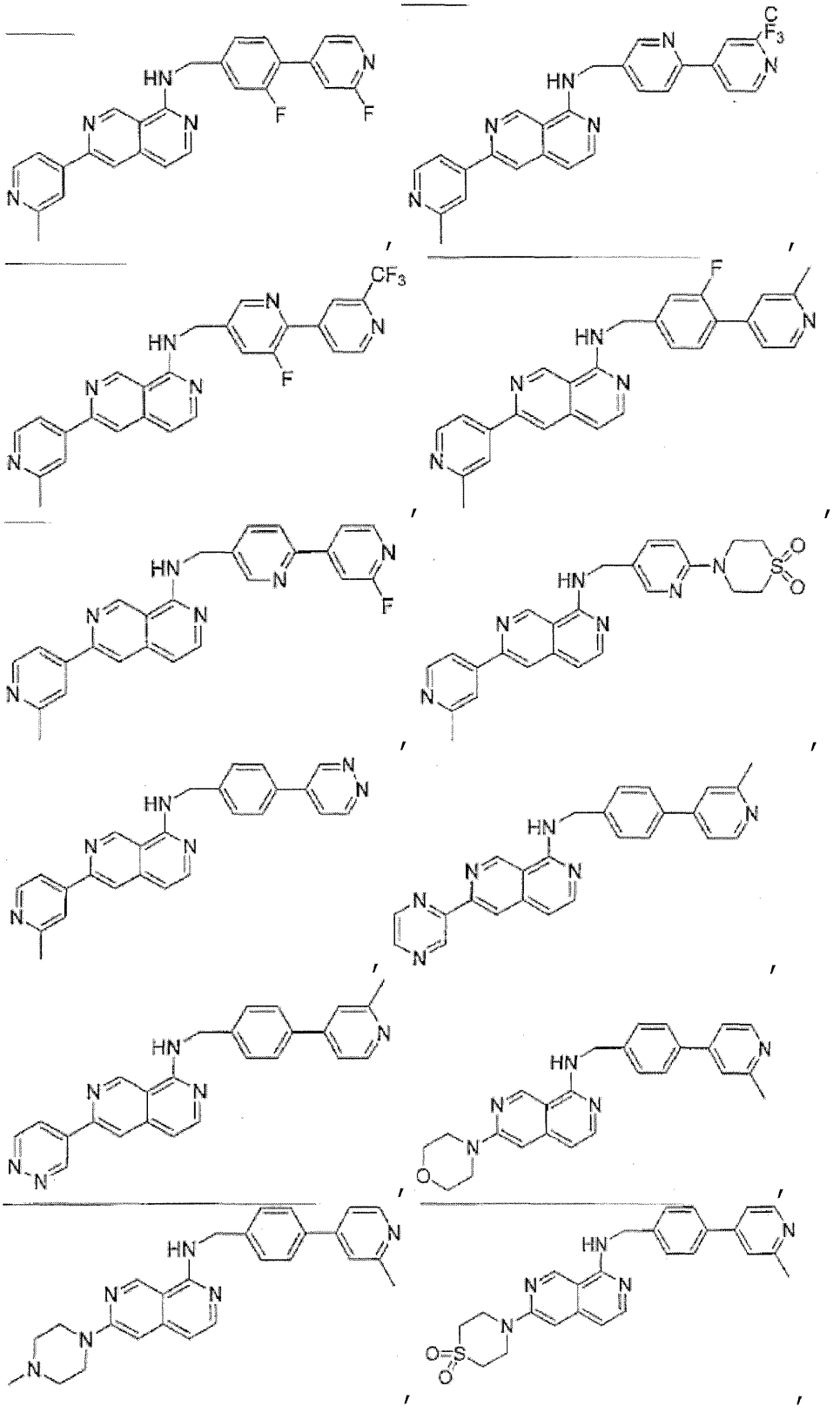
8. The compound of any one of claims 1-7, wherein at least one atom in Formula I is at least one of corresponding isotope(s) selected from ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl and ^{123}I.

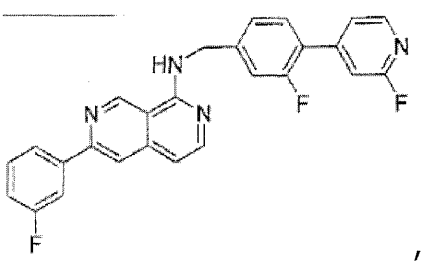
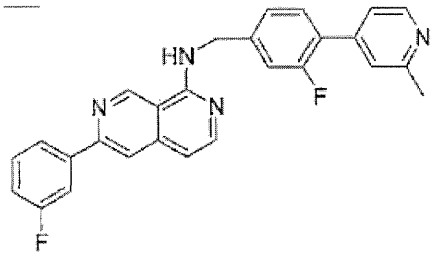
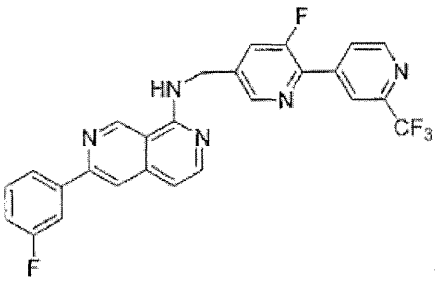
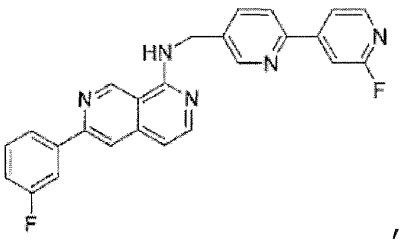
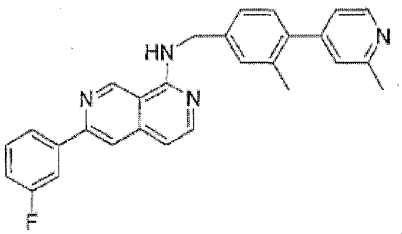
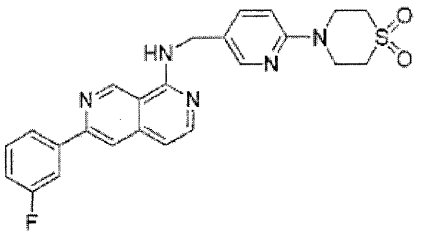
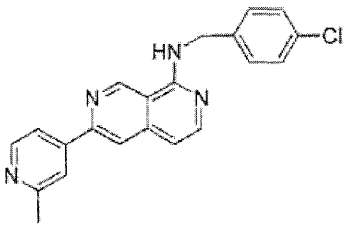
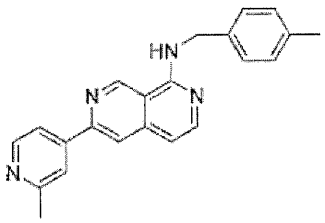
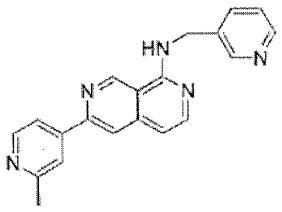
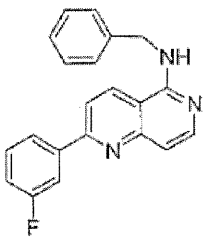
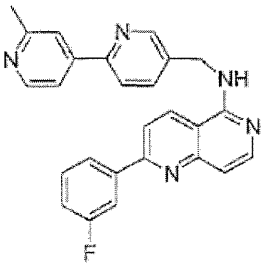
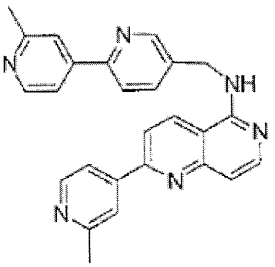
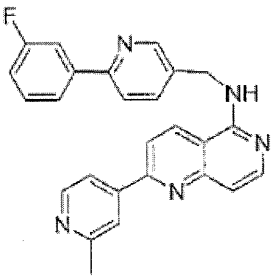
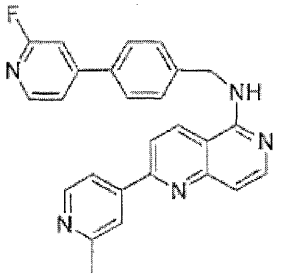
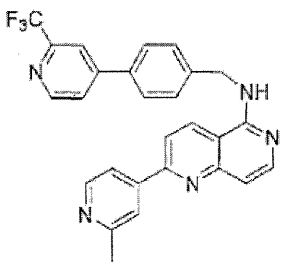
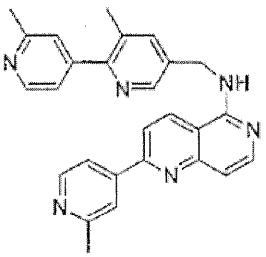
9. A compound, being selected from:

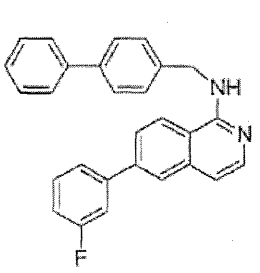
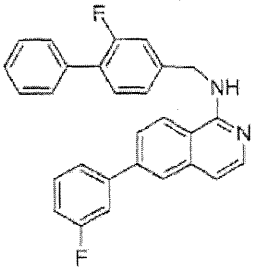
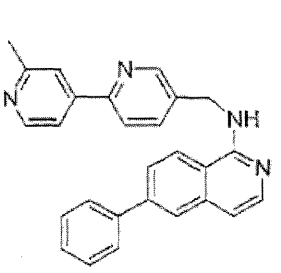
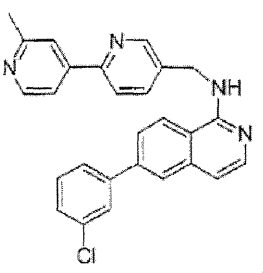
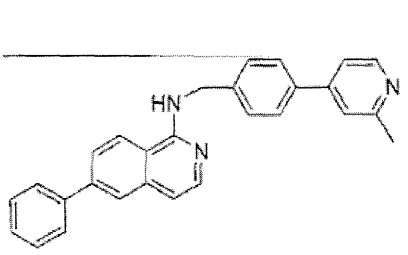
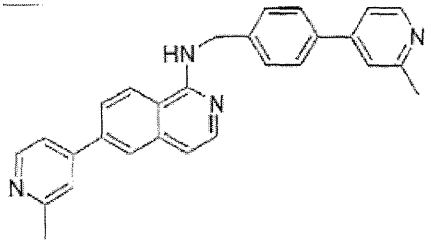
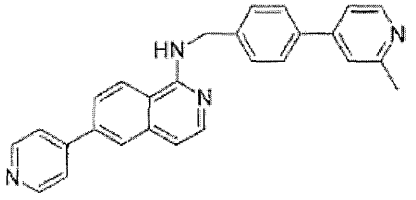
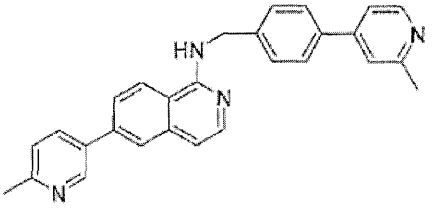
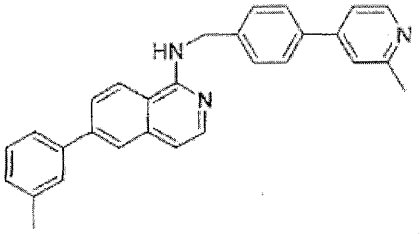
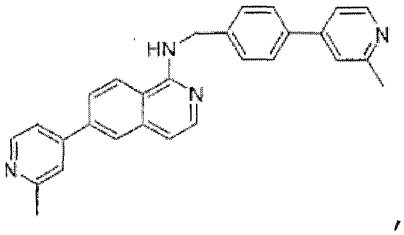
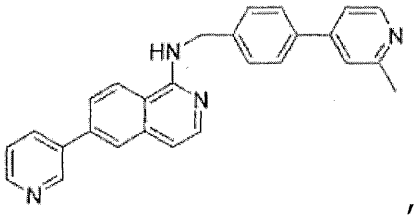
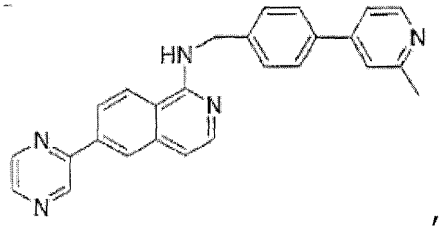
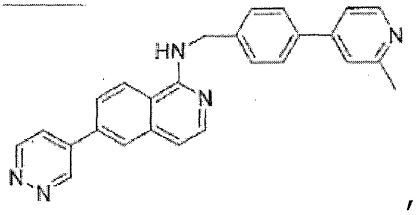
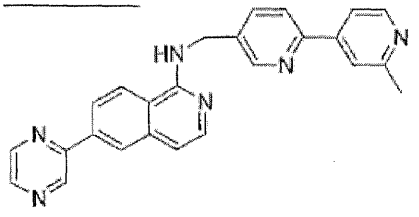


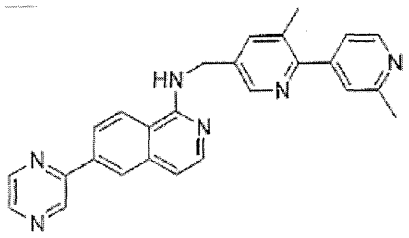
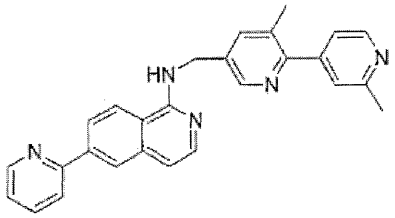
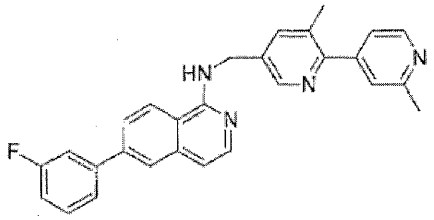
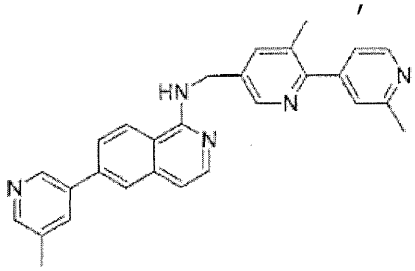
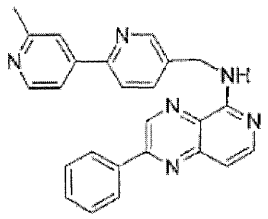
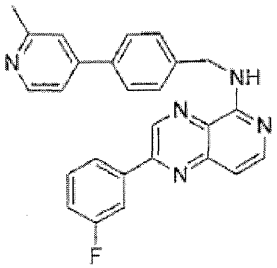
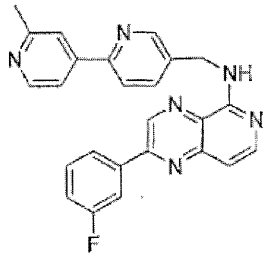
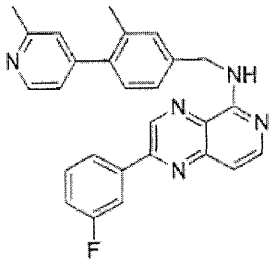
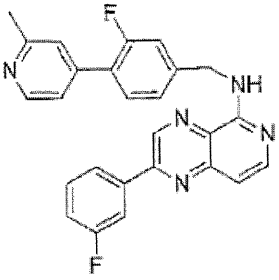
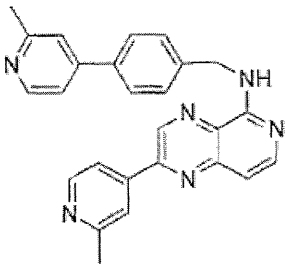
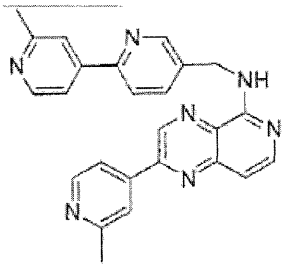
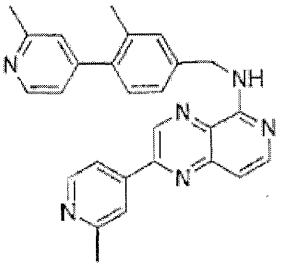
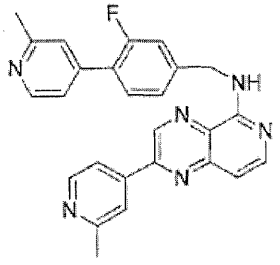
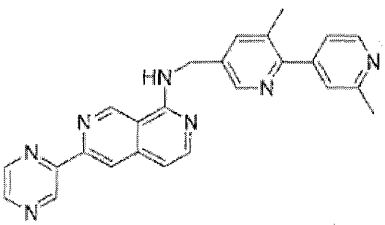
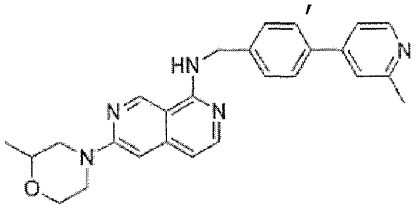
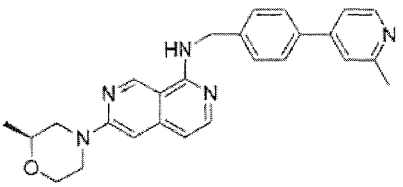











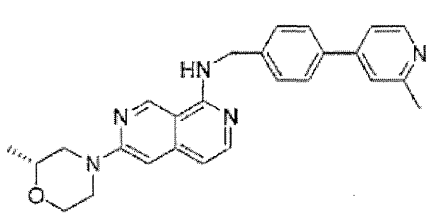
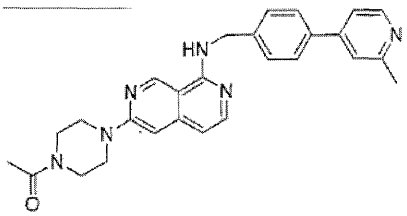
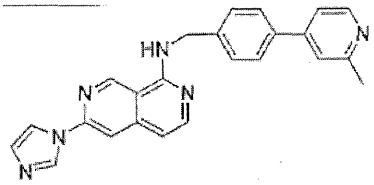
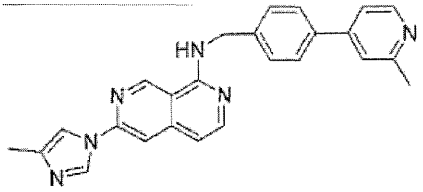
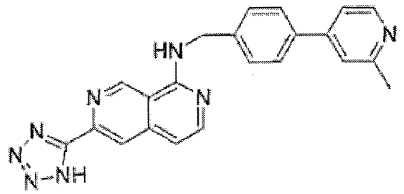
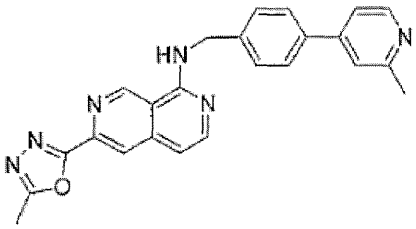
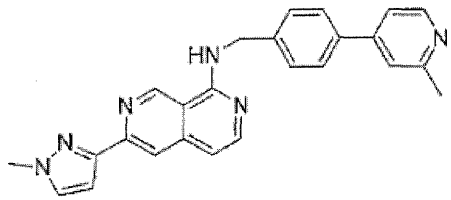
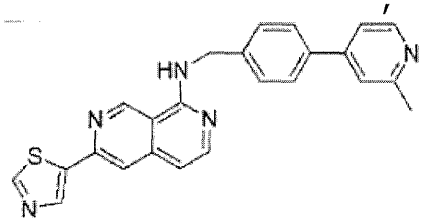
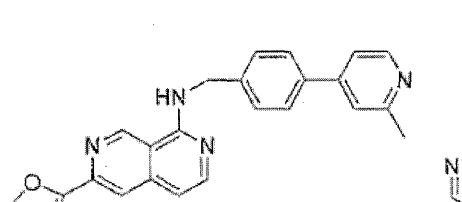
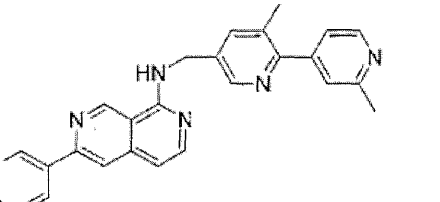



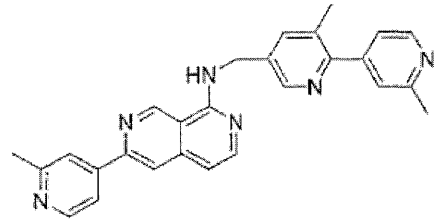
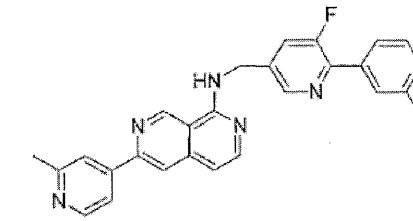
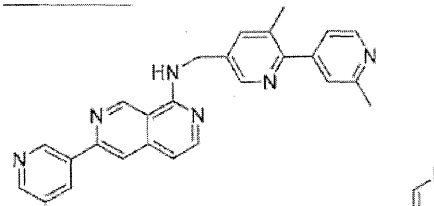
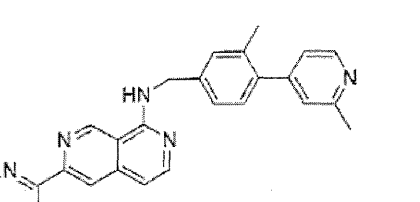


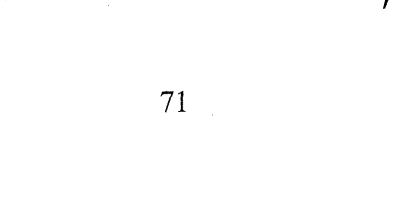

















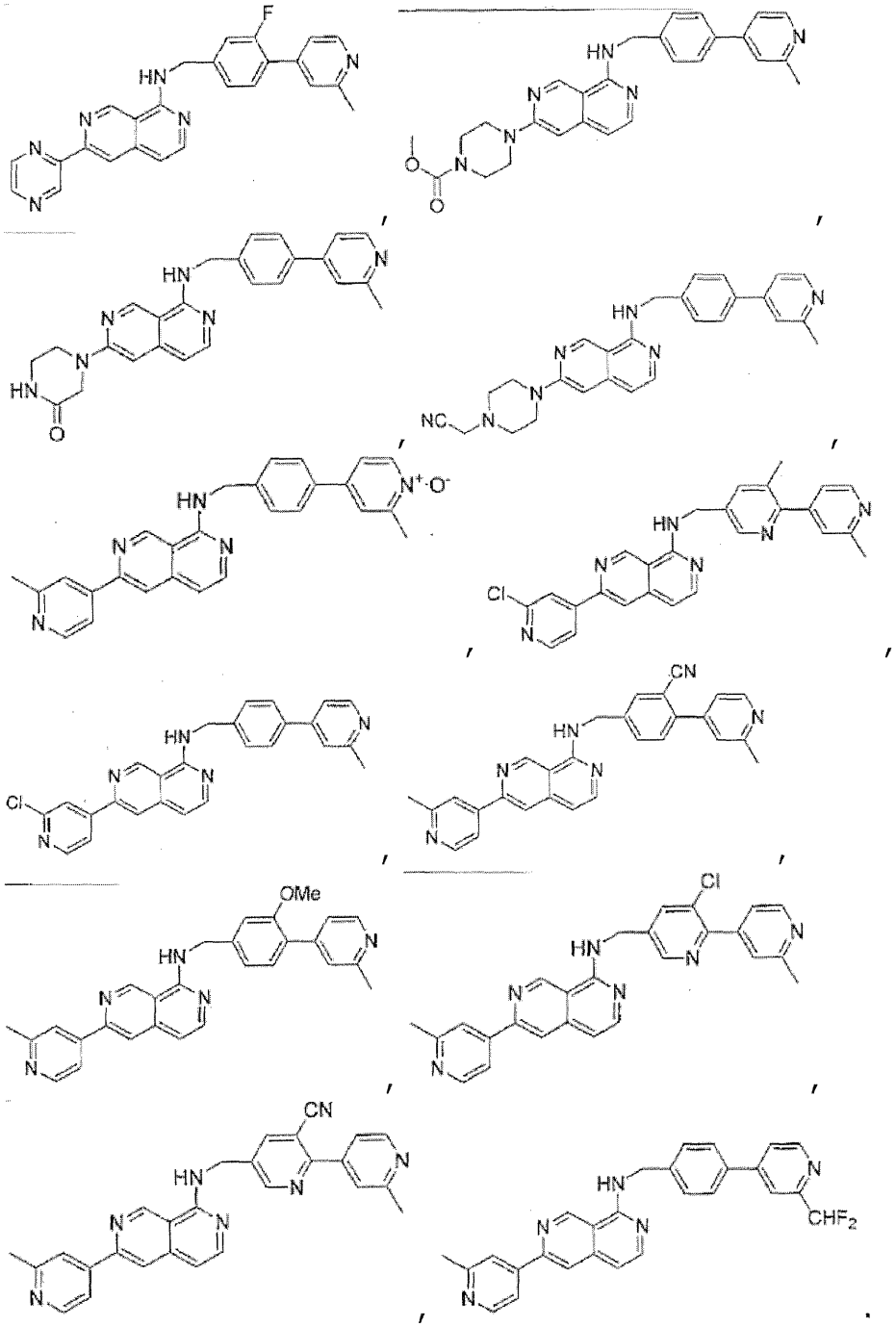



















10. A pharmaceutical composition comprising the compound or physiologically acceptable salt thereof of any one of the preceding claims.

11. The pharmaceutical composition of claim 10 is an oral composition, an injectable composition or a suppository.

12. The pharmaceutical composition of claim 11, 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.

13. The pharmaceutical composition of claim 10, 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.

14. The pharmaceutical composition of claim 10, 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.

15. The pharmaceutical composition of claims 10 or 14, further contains solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

16. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition is for topical application and is in a form of aqueous solution, ointment, cream or gel.

17. An *ex vivo* 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 1-9, or the pharmaceutical composition of any one of claims 10-16.

18. An *ex vivo* 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 1-9, or the pharmaceutical composition of any one of claims 10-16.

19. The use of a compound or physiologically acceptable salt thereof of any one of claims 1-9, or a pharmaceutical composition of any one of claims 10-16 for the manufacture of a medicament for treating a WNT pathway mediated disorder.

20. The use of claim 19, wherein said disorder is cancer, fibrosis, osteoarthritis, Parkinson's disease, retinopathy, macular degeneration.

21. The use of claim 20, 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).

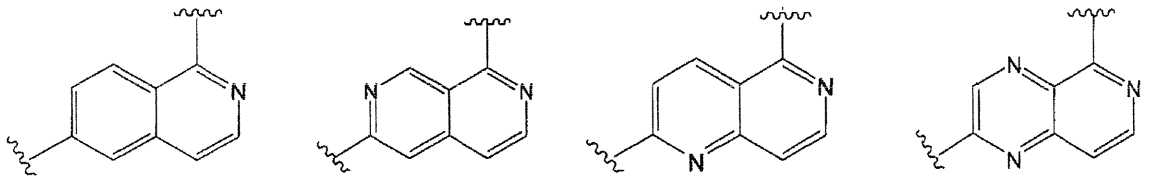
22. The use of claim 20, wherein the fibrosis is selected from systemic sclerosis, skin fibrosis, idiopathic pulmonary fibrosis, renal fibrosis, liver fibrosis, drug-induced fibrosis and radiation-induced fibrosis.

23. The use of any one of claims 19-22, wherein the compound or physiologically acceptable salt thereof of any one of claims 1-9, or a pharmaceutical composition of any one of claims 10-16 is formulated for administration at a therapeutically effective amount of about 0.03 to about 2.5 mg/kg per body weight at daily dosages.

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

25. The use of any one of claims 19-24, wherein the compound is formulated for administration enterally, orally, parenterally, topically or in a nasal or suppository form.

26. The compound of any one of claims 1-2 and 4-8, having one of the following core structures:



27. The compound of claim 26, having the core structure of:

