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[Continued on next page]

(54) Title: COMPOUNDS FOR TREATMENT OF FIBROSIS DISEASES

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FIG. 1

(57) Abstract: The present invention relates to compounds as inhibitor of WNT signal transduction pathway, as well as a composition comprising the same. Further, the present invention relates to the use of the compounds in the treatment of fibrosis. Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. Fibrosis is the end result of chronic inflammatory reactions induced by a variety of stimuli including persistent infections, autoimmune reactions, allergic responses, chemical insults, radiation, and tissue injury.



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COMPOUNDS FOR TREATMENT OF FIBROSIS DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. Provisional Patent Application Serial No. 61/782,185, filed on March 14, 2013, the entire disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to compounds as inhibitor of WNT signal transduction pathway, as well as compositions comprising the same. Further, the present invention relates to the use of the compounds in the treatment of fibrosis diseases.

BACKGROUND OF THE INVENTION

[0003] Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. Fibrosis is the end result of chronic inflammatory reactions induced by a variety of stimuli including persistent infections, autoimmune reactions, allergic responses, chemical insults, radiation, and tissue injury. Fibrosis is characterized by the accumulation and reorganization of the extracellular matrix (ECM). Despite having obvious etiological and clinical distinctions, most chronic fibrotic disorders have in common a persistent irritant that sustains the production of growth factors, proteolytic enzymes, angiogenic factors, and fibrogenic cytokines, which together stimulate the deposition of connective tissue elements, especially collagens and proteoglycans, which progressively remodel and destroy normal tissue architecture.

[0004] Fibrotic diseases, including pulmonary fibrosis, systemic sclerosis, liver cirrhosis, cardiovascular disease, progressive kidney disease, and macular degeneration, are a leading cause of morbidity and mortality and can affect all tissues and organ systems. Fibrotic tissue remodeling can also influence cancer metastasis and accelerate chronic graft rejection in transplant recipients.

[0005] WNT signaling is important to both embryogenesis and homeostasis in adult animals. The WNT pathway is comprised in general of a network of proteins that regulate the following processes: 1, the production and secretion of WNT proteins; 2, the binding of WNT with cellular receptors; and 3, the intracellular transduction of the biochemical responses triggered by the interaction (Mikels and Nusse, 2006; MacDonald, 2009; Moon, 2005).

[0006] The so-called canonical WNT pathway triggered by binding of WNT proteins to cell surface co-receptors Frizzled LRP5/6 results in a change in the amount of β -catenin that reaches the nucleus where it interacts with TCF/LEF family transcription factors to promote transcription of specific genes.

[0007] The non-canonical WNT pathway transduced by a different set of intracellular proteins controls planar cell polarity in insects and several processes such as gastrulation in vertebrates.

[0008] WNT signaling is also known for its roles in controlling pluripotency and differentiation of embryonic and adult stem cells (Nusse, 2008). For example, formation of the primitive streak during gastrulation was associated with localized WNT activation in the embryoid bodies (Ten Berge, 2008). The derivation of a number of cell types, such as heart cells, pancreatic beta cells, dopaminergic neurons and liver hepatocytes from embryonic stem cells or iPS cells is influenced by WNT modulation (Yang, 2008; D'Amour, 2006; Inestrosa and Arenas, 2010; Sullivan, 2010). The WNT pathway plays a particularly important role in skeletal tissue development such as osteogenesis and chondrogenesis (Hoeppner, 2009; Chun, 2008). WNT signaling is also associated with neuro-regeneration of the adult central nervous system (Lie, 2005).

[0009] Diseases may arise from altered WNT pathway activity. For example, hyperactivation of the canonical WNT pathway can lead to aberrant cell growth (Reya and Clevers, 2005). Notably, 90% of colorectal cancers are initiated by the loss of the adenomatosis polyposis coli (APC) gene, a suppressor of the WNT/β-catenin pathway (Kinzler and Vogelstein, 1996). Increased expression of WNT proteins and loss of extracellular inhibitors that normally suppress WNT protein function may give rise to WNT-dependent tumors (Polakis, 2007). On the other hand, the non-canonical WNT pathway has also been shown to play a role in the progression of certain cancers (Camilli and Weeraratna, 2010). More recently, WNT signaling is also implicated in cancer stem cells (Takahashi-Yanaga and Kahn, 2010).

[0010] Evidence suggests that targeting the Wnt-mediated signal transduction pathway would be therapeutically useful in a broad range of diseases (Barker and Clevers, 2006). Mutations of APC, beta-catenin or axin-1 leading to constitutive activation of the canonical Wnt pathway are critical events in a variety of human cancers including colorectal cancer, melanoma, hepatocellular carcinoma, gastric cancer, ovarian cancer and others (Polakis, 2007). Blockade of the Wnt pathway in a variety of cancers using either genetic or chemical approaches has been shown to abrogate aberrant cell growth (Herbst and Kolligs, 2007). Furthermore, inhibition of this pathway may directly influence the cells that sustain cancer cell growth and enable metastasis, and that are thought to be resistant to traditional chemotherapeutic agents.

[0011] In addition to activation caused by mutations of gene products downstream of the receptors, aberrant Wnt pathway activity caused by other mechanisms have been associated with a broad range of cancers. These cancers include but not limited to: lung (small cell and non-small cell), breast, prostate, carcinoid, bladder, scurcinoma, esophageal, ovarian, cervical, endometrial, mesothelioma, melanoma, sarcoma, osteosarcoma, liposarcoma, thyroid, desmoids, chronic myelocytic leukemia (AML), and chronic myelocytic leukemia (CML). There are now multiple examples of cancer cells dependent upon upregulated autocrine or paracrine Wnt signaling, and cell lines from osteosarcoma, breast, head and neck and ovarian cancers have been shown

to derive protection from apoptosis by autocrine or paracrine Wnt signaling (Kansara, 2009; Bafico, 2004; Akiri, 2009; DeAlmeida, 2007; Chan, 2007; Chen, 2009; Rhee, 2002).

[0012] Furthermore, aberrant Wnt pathway has been implicated in the development of fibrosis, include but are not limited to: lung fibrosis, such as idiopathic pulmonary fibrosis and radiation-induced fibrosis, renal fibrosis and liver fibrosis (Morrisey, 2003; Hwang, 2009; Cheng, 2008), and myocardial fibrosis (cardiac fibrosis) (Duan J. et al., Wnt1/βcatenin injury response activates the epicardium and cardiac fibroblasts to promote cardiac repair. *EMBO J.* 2011 Nov 15;31(2):429-42).

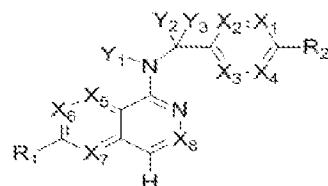
[0013] Other disorders associated with aberrant WNT signaling, include but are not limited to bone and cartilage disorders, such as osteoporosis and osteoarthritis, obesity associated type II diabetes, and neurodegenerative diseases such as Alzheimer's disease (Hoepfner, 2009; Ouchi, 2010; Blom, 2010; Boonen, 2009). WNT signaling also contributes to the self-renewal and 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).

[0014] 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

[0015] 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 treatment of diseases, such as fibrosis diseases.

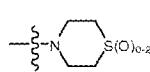
[0016] In one aspect, the present invention provides a method for treating fibrosis disease in a subject that is in need of such treatment, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of the following formula:

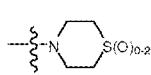


or a physiologically acceptable salt thereof, wherein

$X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8$ are independently CR₄ or N;

Y_1 is hydrogen or CR_4 ; Y_2, Y_3 are independently hydrogen, halo or CR_3 ;

R_1 is morpholinyl, piperazinyl, quinolinyl,  , aryl, C_{1-6} heterocycle, 5 or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

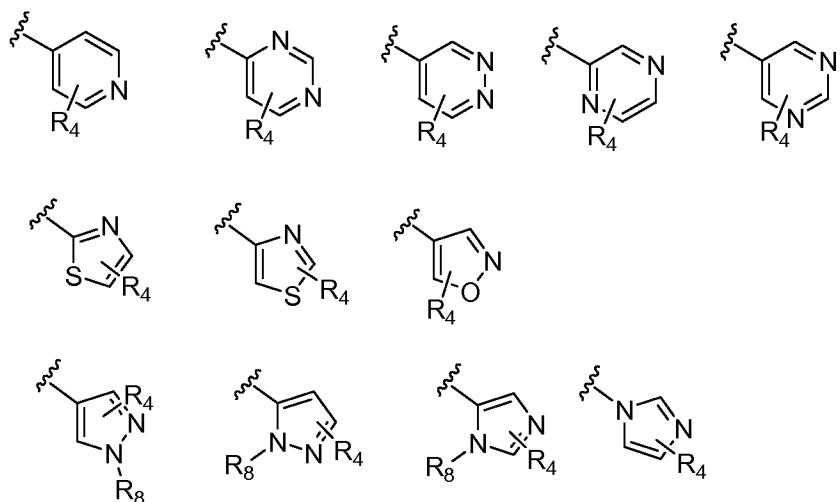
R_2 is hydrogen, halo, morpholinyl, piperazinyl, quinolinyl,  , aryl, C_{1-6} heterocycle, 5 or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R_3 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R_4 is hydrogen, halo, 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 or C_{2-6} alkynyl, each of which can be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

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

[0017] In some embodiments, the 5 or 6 membered heteroaryl is selected from:



wherein,

R_4 is hydrogen, halo, 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 or C_{2-6} alkynyl, each of which can be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R_5 , R_6 and R_7 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano; and

R_8 is hydrogen or C_{1-6} alkyl.

[0018] In some embodiments, R_1 and R_2 is independently substituted with 1 or 2 R_4 groups.

[0019] In some embodiments, the atom in any the substituent groups is H, ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁷O, ¹⁸O, ³⁵S, ¹⁸F, ³⁶I and/or ¹²³I.

[0020] In some embodiments, the compound is selected from N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

N-(4-methoxybenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-fluorobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-chlorobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-bromobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-(trifluoromethyl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
4-((7-(2-methylpyridin-4-yl)quinazolin-4-ylamino)methyl)benzonitrile; N-(4-morpholinobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-phenylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(3-fluoro-4-phenylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-(3-fluorophenyl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
7-(3-fluorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(3-chlorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-m-tolylquinazolin-4-amine;
3-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)benzonitrile;
4-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)benzonitrile;
7-(2-methylpyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(6-methylpyridin-3-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(5-methylpyridin-3-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-2-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-3-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-4-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridazin-4-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyrazin-2-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyrimidin-5-yl)quinazolin-4-amine;
7-(2-fluoropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(2-(trifluoromethyl)pyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(2-methoxypyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(3-methylpyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-morpholinoquinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(piperidin-1-yl)quinazolin-4-amine;
7-(4-methylpiperazin-1-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
1-(4-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)piperazin-1-yl)ethanone;
4-(4-(((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)amino)quinazolin-7-yl)thiomorpholine 1,1-dioxide;
7-(1,2,3,6-tetrahydropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(1,2,3,6-tetrahydropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
1-(4-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)piperidin-1-yl)ethanone;
N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-7-(4-(methylsulfonyl)piperazin-1-yl)quinazolin-4-amine;
7-(1-methyl-1H-pyrazol-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(isoxazol-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(thiazol-2-yl)quinazolin-4-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-(pyrazin-2-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-(2-fluoropyridin-4-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-morpholinoquinazolin-4-amine;
2-(3-fluorophenyl)-N-(4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
2-(3-fluorophenyl)-N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)pyrido[3,4-b]pyrazin-5-amine;
2-(3-fluorophenyl)-N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-2-(3-fluorophenyl)pyrido[3,4-b]pyrazin-5-amine;
2-(2-methylpyridin-4-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;

N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
(S)-6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
(R)-6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
1-(4-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-1-yl)ethanone;
6-(1H-imidazol-1-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
6-(4-methyl-1H-imidazol-1-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-6-(1H-tetrazol-5-yl)-2,7-naphthyridin-1-amine;
6-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
6-(1-methyl-1H-pyrazol-3-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-6-(thiazol-5-yl)-2,7-naphthyridin-1-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-6-(oxazol-5-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(5-methylpyridin-3-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
N-((3-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(5-fluoropyridin-3-yl)-2,7-naphthyridin-1-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
methyl 4-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazine-1-carboxylate;
4-((8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-2-one);
2-(4-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-1-yl)acetonitrile;
2-methyl-4-((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)phenyl)pyridine 1-oxide;
6-(2-chloropyridin-4-yl)-N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-2,7-naphthyridin-1-amine;
6-(2-chloropyridin-4-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
2'-methyl-4-((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)-2H-[1,4'-bipyridin]-2-one;

2-(2-methylpyridin-4-yl)-5-(((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)benzonitrile; N-(3-methoxy-4-(2-methylpyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine; N-((3-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine; 2'-methyl-5-(((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)-[2,4'-bipyridine]-3-carbonitrile; N-(4-(2-(difluoromethyl)pyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;

[0021] In some embodiments, the pharmaceutical composition comprising at least one pharmaceutically acceptable carrier or diluent. In some embodiments, the pharmaceutical composition is oral composition, injectable composition or suppository. In some embodiments, the pharmaceutical composition is oral composition and is tablet or gelatin capsule. In some embodiments, the pharmaceutical composition comprises diluents, lubricants, binders, disintegrants, or additives, or combination thereof. In some embodiments, the diluent is lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine. In some embodiments, the lubricant is silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol. In some embodiments, the binder is magnesium aluminum silicate, starch paste, gelatin, tragamayth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone. In some embodiments, the disintegrant is starches, agar, alginic acid or its sodium salt, or effervescent mixtures. In some embodiments, the additive is absorbent, colorant, flavor and/or sweetener.

[0022] In some embodiments, the pharmaceutical composition is injectable composition and is aqueous isotonic solution or suspension.

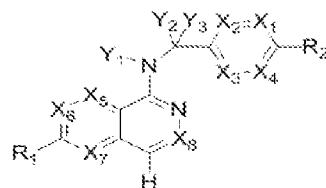
[0023] In some embodiments, the pharmaceutical composition is suppository and is prepared from fatty emulsions or suspensions. In some embodiments, the pharmaceutical composition further comprises adjuvants, wherein the adjuvants are preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In some embodiments, the pharmaceutical composition further contains solubilizers, stabilizers, tonicity enhancing agents, buffers and/or preservatives. In some embodiments, the pharmaceutical composition is for topical application and is aqueous solution, ointment, cream or gel.

[0024] In some embodiments, the therapeutically effective amount of the compound is about 0.03 to 2.5 mg/kg per body weight at daily dosages. In some embodiments, the therapeutically effective amount of the compound from about 0.5 mg to about 500 mg for humans.

[0025] In some embodiments, the pharmaceutical composition is administrated enterally, orally, parenterally, topically or in a nasal or suppository form.

[0026] In some embodiments, fibrosis disease is myocardial remodeling including myocardial fibrosis and hypertrophic growth after MI, lung fibrosis, liver fibrosis, skin fibrosis, or renal fibrosis.

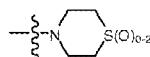
[0027] In yet another aspect, the present invention provides use of a compound for the manufacture of a medicament for treating fibrosis disease, wherein the compound is of the following formula:



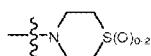
or a physiologically acceptable salt thereof, wherein

X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈ are independently CR₄ or N;

Y₁ is hydrogen or CR₄; Y₂, Y₃ are independently hydrogen, halo or CR₃;

R₁ is morpholinyl, piperazinyl, quinolinyl, , aryl, C₁₋₆ heterocycle, 5 or 6

membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R₂ is hydrogen, halo, morpholinyl, piperazinyl, quinolinyl, , aryl, C₁₋₆ heterocycle, 5

or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R₃ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R₄ is hydrogen, halo, C₁₋₆ alkoxy, -S(O)₂R₅, -C(O)OR₅, -C(O)R₅, -C(O)NR₆R₇, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, each of which can be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R₅, R₆ and R₇ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano.

INCORPORATION BY REFERENCE

[0028] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference

to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0030] **Figure 1** depicts that CGX increased cardiac function after myocardial infarction (MI). Fractional shortening, as a measurement of cardiac function, were determined by echocardiography and are plotted as percentage difference between day 7 and day 14 or 28 after MI (mean + SEM). N=9 for the Vehicle control group, N=10 for the CGX group. *: P < 0.05 in paired t-test.

[0031] **Figure 2** depicts that CGX improved survival after MI. The survival rates of mice after MI for vehicle control group or CGX-treated group are plotted. N=9 for the control group, N=10 for the CGX group.

[0032] **Figure 3** depicts that CGX reduced infarct size after MI. 28 days after MI, heart was sectioned and photographed. The infarct area depicted by the white colored region is significantly smaller in the CGX-treated animals. Pictures shown are representatives of one animal from each group.

[0033] **Figure 4** depicts that CGX decreased myocardial fibrosis after MI. 28 days after MI, heart tissue was formalin fixed, paraffin embedded and sectioned. Masson's Trichrome method is used to detect collagen fibers (blue) and heart muscle (stained red). Sham has no artery ligation, Vehicle has ligation and treated with vehicle, while CGX has ligation and treated with CGX. Pictures shown are representatives of one animal from each group.

[0034] **Figure 5** depicts that CGX improved survival after bleomycin administration. Mice were treated with CGX (10 mg/kg) once daily or Vehicle for 15 days. N = 8 for both groups.

[0035] **Figure 6** depicts that CGX reduced total protein and collagen in BALF after bleomycin administration. Mice were treated with CGX (10 mg/kg) once daily or Vehicle for 15 days. BALF were collected with perfusion for the measurement of total protein and collagen amounts. Left: total protein; Right: soluble collagen. N = 8 for both groups. Results (Mean + SEM) were analyzed by Student's t – test and were considered statistically significant as P values were less than 0.05.

[0036] **Figure 7** depicts that CGX improved overall morphology of the lung after bleomycin administration. Lung tissue sections were stained by H.E. staining. Left: Vehicle control; Right: CGX-treated.

[0037] **Figure 8** depicts that CGX reduced collagen deposition in the lung after bleomycin administration. Lung tissue sections were stained by Masson Trichrome staining for collagen (blue color). Left: Vehicle control; Right: CGX-treated.

[0038] **Figure 9** depicts that CGX reduced myofibroblast (a-SMA) in the lung after bleomycin administration. Lung tissue sections were stained by immunohistochemical staining for a-SMA (dark brown color). Left: Vehicle control; Right: CGX-treated.

[0039] **Figure 10** depicts that CGX reduced the weight of heart organ in a mouse model of cardiac hypertrophy induced by coarctation of the transverse aorta.

[0040] **Figure 11** depicts that CGX increased survival of mice undergone coarctation of the transverse aorta.

DETAILED DESCRIPTION OF THE INVENTION

[0041] Several aspects of the invention are described below with reference to example applications for illustration. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of the invention. One having ordinary skill in the relevant art, however, will readily recognize that the invention can be practiced without one or more of the specific details or with other methods. The present invention is not limited by the illustrated ordering of acts or events, as some acts may occur in different orders and/or concurrently with other acts or events.

[0042] Furthermore, not all illustrated acts or events are required to implement a methodology in accordance with the present invention.

[0043] The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms "including", "includes", "having", "has", "with", or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term "comprising".

[0044] The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless otherwise stated the term "about" meaning within an acceptable error range for the particular value should be assumed.

I. Definitions and Abbreviations

[0045] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry and nucleic acid chemistry and hybridization are those well known and commonly employed in the art. Standard techniques are used for nucleic acid and peptide synthesis. The techniques and procedures are generally performed according to conventional methods in the art and various general references, which are provided throughout this document. The nomenclature used herein and the laboratory procedures in analytical chemistry, and organic synthetic described below are those well-known and commonly employed in the art. Standard techniques, or modifications thereof, are used for chemical syntheses and chemical analyses.

[0046] 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, GSK3 β , 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.

[0047] "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.

[0048] “WNT protein” is a protein binds to Frizzled and LRP5/6 co-receptors so as to activate canonical or non-canonical WNT signaling. Specific examples of WNT proteins include: WNT-1 (NM005430), WNT-2 (NM003391), WNT-2B/WNT-13 (NM004185), WNT-3 (NM030753), WNT3a (NM033131), WNT-4 (NM030761), WNT-5A (NM003392), WNT-5B (NM032642), WNT-6 (NM006522), WNT-7A (NM004625), WNT-7B (NM058238), WNT-8A (NM058244), WNT-8B (NM003393), WNT-9A/WNT-14) (NM003395), WNT-9B/WNT-15 (NM003396), WNT-10A (NM025216), WNT-10B (NM003394), WNT-11 (NM004626), WNT-16 (NM016087).

[0049] “WNT pathway disorder” is a condition or disease state with aberrant WNT signaling. In one aspect, the aberrant WNT signaling is a level of WNT signaling in a cell or tissue suspected of being diseased that exceeds the level of WNT signaling in a normal cell or tissue. In one specific aspect, a WNT-mediated disorder includes cancer or fibrosis.

[0050] The term “cancer” refers to the pathological condition in humans that is characterized by unregulated cell proliferation. Examples include but are not limited to: carcinoma, lymphoma, blastoma, and leukemia. More particular examples of cancers include but are not limited to: lung (small cell and non-small cell), breast, prostate, carcinoid, bladder, gastric, pancreatic, liver (hepatocellular), hepatoblastoma, colorectal, head 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).

[0051] The term “fibrosis” refers to the pathological condition in humans that is typically characterized by uncontrolled proliferation of fibroblast cells and tissue hardening. Specific examples include but not limited to: lung fibrosis (idiopathic pulmonary fibrosis and radiation-induced fibrosis), renal fibrosis, cardiac fibrosis and liver fibrosis including liver cirrhosis.

[0052] “Inhibiting” or “treating” or “treatment” refers to reduction, therapeutic treatment and prophylactic or preventative treatment, wherein the objective is to reduce or prevent the aimed pathologic disorder or condition. In one example, following administering of a WNT signaling inhibitor, a cancer patient may experience a reduction in tumor size. “Treatment” or “treating” includes (1) inhibiting a disease in a subject experiencing or displaying the pathology or symptoms of the disease, (2) ameliorating a disease in a subject that is experiencing or displaying the pathology or symptoms of the disease, and/or (3) affecting any measurable decrease in a disease in a subject or patient that is experiencing or displaying the pathology or symptoms of the disease. To the extent the WNT pathway inhibitor may prevent growth and/or kill cancer cells, it may be cytostatic and/or cytotoxic.

[0053] The term “therapeutically effective amount” refers to an amount of a WNT pathway inhibitor effective to “treat” a WNT pathway disorder in a subject or mammal. In the case of cancer, the therapeutically effective amount of the drug may either reduce the number of cancer cells, reduce the tumor size, inhibit cancer cell infiltration into peripheral organs, inhibit tumor metastasis, inhibit tumor growth to certain extent, and/or relieve one or more of the symptoms associated with the cancer to some extent.

[0054] Administration “in combination with” one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order. As used herein, the term “pharmaceutical combination” refers to a product obtained from mixing or combining active ingredients, and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, e.g. a compound of Formula (1) and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g. a compound of Formula (1) and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the active ingredients in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[0055] A “chemotherapeutic agent” is a chemical compound useful in the treatment of cancer. Examples are but not limited to: Gemcitabine, Irinotecan, Doxorubicin, 5-Fluorouracil, Cytosine arabinoside (“Ara-C”), Cyclophosphamide, Thiotepa, Busulfan, Cytoxin, TAXOL, Methotrexate, Cisplatin, Melphalan, Vinblastine and Carboplatin.

[0056] The term “alkyl,” by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term “alkyl,” unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below, such as “heteroalkyl.” Alkyl groups, which are limited to hydrocarbon groups, are termed “homoalkyl”.

[0057] The term “alkylene” by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, and further includes those groups described below as “heteroalkylene.” Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0058] The terms “alkoxy,” “alkylamino” and “alkylthio” (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0059] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_3$, $-\text{CH}_2\text{SCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{S(O)CH}_3$, $-\text{CH}_2\text{CH}_2\text{S(O)}_2\text{CH}_3$, $-\text{CH}=\text{CH-OCH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}=\text{N-OCH}_3$, and $-\text{CH}=\text{CH-N}(\text{CH}_3)\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2\text{NH-OCH}_3$ and $-\text{CH}_2\text{O-Si}(\text{CH}_3)_3$. Similarly, the term “heteroalkylene” by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_2-$ and $-\text{CH}_2\text{SCH}_2\text{CH}_2\text{NHCH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkyleneedioxy, alkyleneamino, alkylidendiamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'-$ represents both $-\text{C}(\text{O})_2\text{R}'-$ and $-\text{R}'\text{C}(\text{O})_2-$.

[0060] In general, an “acyl substituent” is also selected from the group set forth above. As used herein, the term “acyl substituent” refers to groups attached to, and fulfilling the valence of a carbonyl carbon that is either directly or indirectly attached to the polycyclic nucleus of the compounds of the present invention.

[0061] The terms “cycloalkyl” and “heterocycloalkyl”, by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl”, respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the

remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0062] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl,” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0063] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings), which are fused together or linked covalently. The term “heteroaryl” refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0064] For brevity, the term “aryl” when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term “arylalkyl” is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxyethyl, 2-pyridyloxymethyl, 3-(1-naphthoxy)propyl, and the like).

[0065] Each of the above terms (e.g., “alkyl,” “heteroalkyl,” “aryl” and “heteroaryl”) include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0066] Substituents for the alkyl, and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generally referred to as “alkyl substituents” and “heteroalkyl substituents,” respectively, and they can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'', R''' and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, e.g., aryl substituted with 1-3 halogens, substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term “alkyl” is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0067] Similar to the substituents described for the alkyl radical, the aryl substituents and heteroaryl substituents are generally referred to as “aryl substituents” and “heteroaryl substituents,” respectively and are varied and selected from, for example: halogen, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''' and R'''' are preferably independently selected from hydrogen, (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C₁-C₄)alkyl, and (unsubstituted aryl)oxy-(C₁-C₄)alkyl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present.

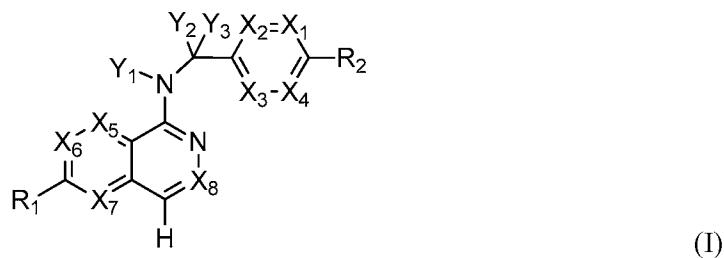
[0068] Two of the aryl substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR' - or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the

substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently $-CRR'$ -, $-O-$, $-NR-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2NR'$ - or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X-(CR''R''')_d-$, where s and d are independently integers of from 0 to 3, and X is $-O-$, $-NR'$ -, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'$ -. The substituents R, R', R'' and R''' are preferably independently selected from hydrogen or substituted or unsubstituted (C₁-C₆) alkyl.

[0069] As used herein, the term “heteroatom” includes oxygen (O), nitrogen (N), sulfur (S), phosphorus (P) and silicon (Si).

II. The Compositions

[0070] In one aspect, the present invention provides a compound as WNT signaling inhibitor, which has the structure of Formula I:

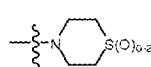


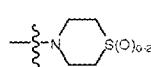
or a physiologically acceptable salt thereof, wherein,

X1, X2, X3, X4, X5, X6, X7, X8 are independently CR₄ or N

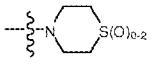
Y₁ is hydrogen or CR₄;

Y₂, Y₃ are independently hydrogen, halo or CR₃;

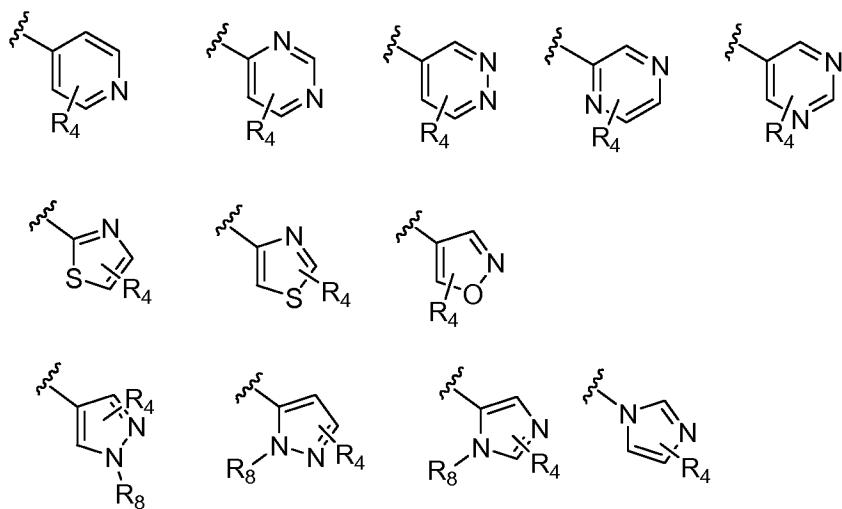
R₁ is morpholinyl, piperazinyl, quinolinyl,  , aryl, C₁-6 heterocycle, 5 or 6 membered



heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R₂ is hydrogen, halo, morpholinyl, piperazinyl, quinolinyl,  , aryl, C₁-6 heterocycle, 5 or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

wherein 5 or 6 membered heteroaryl includes the following selected groups but is not limited to:



R₁ and R₂ could be independently and optionally substituted with 1-2 R₄ groups;

R₃ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R₄ is hydrogen, halo, C₁₋₆ alkoxy, -S(O)₂R₅, -C(O)OR₅, -C(O)R₅, -C(O)NR₆R₇, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, each of which can be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R₅, R₆ and R₇ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R₈ is hydrogen or C₁₋₆ alkyl.

[0071] As used herein, an H atom in any substituent groups (e.g., CH₂) encompasses all suitable isotopic variations, e.g., H, ²H and ³H.

[0072] As used herein, other atoms in any substituent groups encompasses all suitable isotopic variations, including but not limited to ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁷O, ¹⁸O, ³⁵S, ¹⁸F, ³⁶I and/or ¹²³I.

[0073] In some embodiments, example of the compound of the invention includes but is not limited to:

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

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

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

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

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

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

4-((5-((7-phenylquinazolin-4-yl)amino)methyl)pyridin-2-yl)thiomorpholine 1,1-dioxide;
N-((6-(6-methylpyridin-3-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
N-((6-(5-methylpyridin-3-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
7-phenyl-N-((6-(pyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyridin-3-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyridin-2-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyridazin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyrazin-2-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyrimidin-5-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-fluoropyridin-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
N-((6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
N-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
N-((5-(6-methylpyridin-3-yl)pyridin-2-yl)methyl)-7-phenylquinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-phenylquinazolin-4-amine;
N-(4-(2-fluoropyridin-4-yl)benzyl)-7-phenylquinazolin-4-amine;
N-benzyl-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-methylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-methoxybenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-fluorobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-chlorobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-bromobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-(trifluoromethyl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
4-((7-(2-methylpyridin-4-yl)quinazolin-4-ylamino)methyl)benzonitrile; N-(4-morpholinobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-phenylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(3-fluoro-4-phenylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;

N-(4-(3-fluorophenyl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
7-(3-fluorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(3-chlorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-m-tolylquinazolin-4-amine;
3-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)benzonitrile;
4-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)benzonitrile;
7-(2-methylpyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(6-methylpyridin-3-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(5-methylpyridin-3-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-2-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-3-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-4-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridazin-4-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyrazin-2-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyrimidin-5-yl)quinazolin-4-amine;
7-(2-fluoropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(2-(trifluoromethyl)pyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(2-methoxypyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(3-methylpyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-morpholinoquinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(piperidin-1-yl)quinazolin-4-amine;
7-(4-methylpiperazin-1-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
1-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)piperazin-1-yl)ethanone;
4-(4-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)amino)quinazolin-7-yl)thiomorpholine 1,1-dioxide;
7-(1,2,3,6-tetrahydropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(1,2,3,6-tetrahydropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

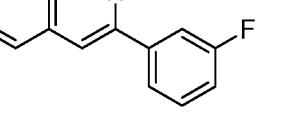
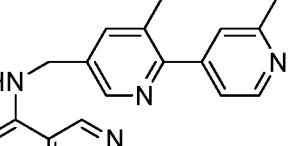
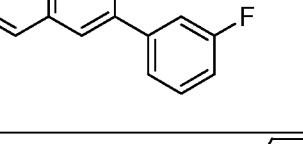
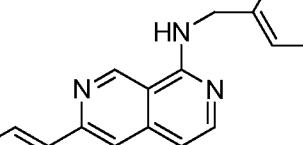
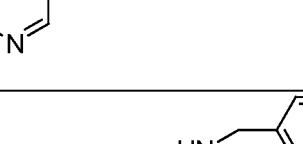
1-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)piperidin-1-yl)ethanone;
N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-7-(4-(methylsulfonyl)piperazin-1-yl)quinazolin-4-amine;
7-(1-methyl-1H-pyrazol-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(isoxazol-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(thiazol-2-yl)quinazolin-4-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-(pyrazin-2-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-(2-fluoropyridin-4-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-morpholinoquinazolin-4-amine;
2-(3-fluorophenyl)-N-(4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
2-(3-fluorophenyl)-N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)pyrido[3,4-b]pyrazin-5-amine;
2-(3-fluorophenyl)-N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-2-(3-fluorophenyl)pyrido[3,4-b]pyrazin-5-amine;
2-(2-methylpyridin-4-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
(S)-6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
(R)-6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
1-(4-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-1-yl)ethanone;
6-(1H-imidazol-1-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
6-(4-methyl-1H-imidazol-1-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-6-(1H-tetrazol-5-yl)-2,7-naphthyridin-1-amine;

6-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
6-(1-methyl-1H-pyrazol-3-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-6-(thiazol-5-yl)-2,7-naphthyridin-1-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-6-(oxazol-5-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(5-methylpyridin-3-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
N-((3-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(5-fluoropyridin-3-yl)-2,7-naphthyridin-1-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
methyl 4-((8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazine-1-carboxylate);
4-((8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-2-one);
2-((8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-1-yl)acetonitrile;
2-methyl-4-((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)phenyl)pyridine 1-oxide;
6-(2-chloropyridin-4-yl)-N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-2,7-naphthyridin-1-amine;
6-(2-chloropyridin-4-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
2'-methyl-4-((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)-2H-[1,4'-bipyridin]-2-one;
2-(2-methylpyridin-4-yl)-5-((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)benzonitrile;
N-(3-methoxy-4-(2-methylpyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
N-((3-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
2'-methyl-5-((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)-[2,4'-bipyridine]-3-carbonitrile;
N-(4-(2-(difluoromethyl)pyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
or physiologically acceptable salts thereof.

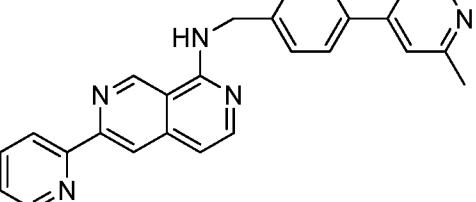
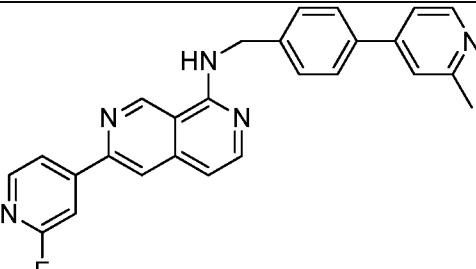
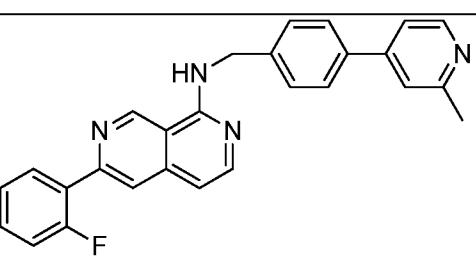
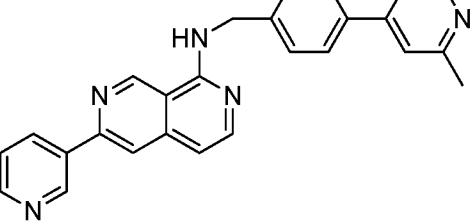
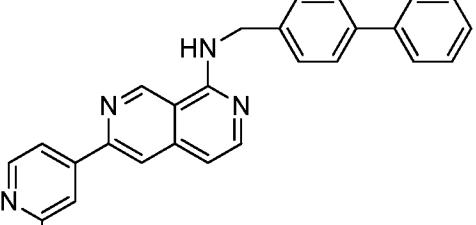
[0074] In some embodiments, examples of the compound of the invention include but are not limited to the compounds provided in Examples 1-5 and Table 1. A person skilled in the art can clearly understand and know that the other compounds could be prepared by the same strategy as examples 1-5.

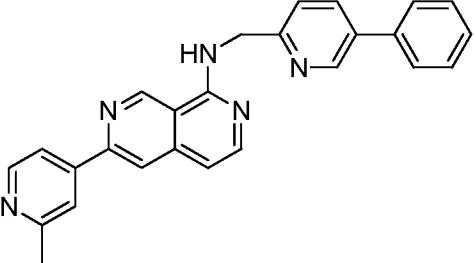
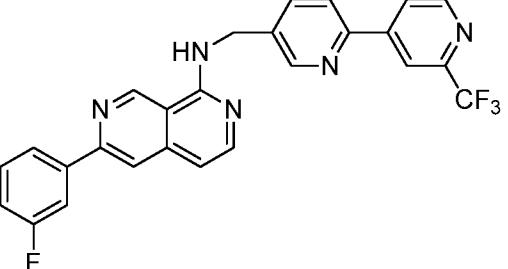
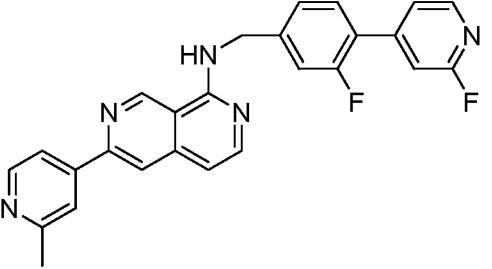
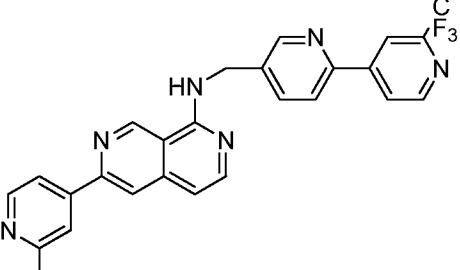
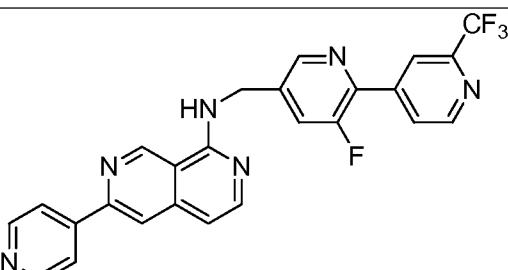
Table 1 Compounds Table

No.	Compound Structure	Compound physical characterization
6		MS m/z=404.2 (M+1);
7		MS m/z=403.2 (M+1);
8		MS m/z=437.2 (M+1);
9		MS m/z=421.2 (M+1); ¹ H NMR (400MHz, DMSO-d6) δ 9.82 (s, 1H), 8.76 (d, J=6.0Hz, 1H), 8.39(s, 1H), 8.17 (s, 1H), 7.95-8.18 (m, 6H), 7.58-7.66 (m, 3H), 7.35 (t, J=8.0Hz, 1H), 7.07 (d, J=6.0Hz, 1H), 5.77 (s, 1H), 4.92 (d, J=6.0Hz, 1H), 2.70 (s, 3H)
10		MS m/z=422.2 (M+1);

11		MS m/z=475.2 (M+1);
12		MS m/z=436.2 (M+1);
13		MS m/z=405.2 (M+1);
14		MS m/z=418.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ 2.46 (s, 3H), 2.63 (s, 3H), 4.94 (d, J = 5.10 Hz, 2H), 5.94 (br, 1H), 6.97 (d, J = 5.70 Hz, 1H), 7.31 (d, J = 4.20 Hz, 1H), 7.36 (s, 1H), 7.54 (d, J = 8.10 Hz, 2H), 7.63 (d, J = 8.40 Hz, 2H), 7.90 (s, 1H), 8.19 (d, J = 6.00 Hz, 1H), 8.22 (s, 1H), 8.51 (m, 2H), 9.08 (s, 1H), 9.30 (s, 1H).
15		MS m/z=418.2 (M+1);

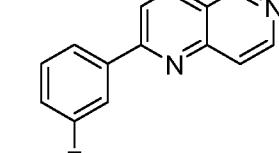
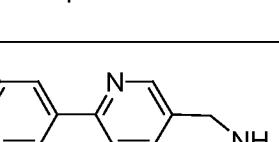
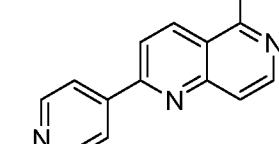
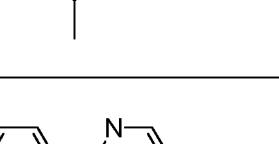
16		MS m/z=428.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.64 (s, 3H), 4.96 (d, J = 5.10 Hz, 2H), 5.99 (br, 1H), 7.31 (d, J = 5.10 Hz, 1H), 7.37 (s, 1H), 7.63 (m, 1H), 7.73 (m, 1H), 7.91 (s, 1H), 8.22 (d, J = 5.70 Hz, 1H), 8.33 (m, 1H), 8.44 (s, 1H), 8.53 (d, J = 5.10 Hz, 1H), 9.33 (s, 1H).
17		MS m/z=428.2 (M+1);
18		MS m/z=420.2 (M+1);
19		MS m/z=417.2 (M+1);
20		MS m/z=326.1 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.58 (s, 3H), 4.90 (d, J = 5.1 Hz, 2H), 5.96 (br, 1H), 6.91 (d, J=6.0Hz, 1H), 7.48-7.58 (m, 4H), 7.62 (d, J=5.7Hz, 1H), 7.70 (d, J=8.4Hz, 2H), 8.02 (d, J=5.7Hz, 1H), 8.40 (d, J=5.1Hz, 1H), 8.53 (d, J=5.7Hz, 1H), 9.50 (s, 1H).

21		MS m/z=404.2 (M+1);
22		MS m/z=422.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.64 (s, 3H), 4.96 (d, J = 5.40 Hz, 2H), 5.96 (br, 1H), 7.01 (d, J = 6.00 Hz, 1H), 7.31 (m, 1H), 7.37 (s, 1H), 7.56 (d, J = 8.10 Hz, 2H), 7.64 (d, J = 8.10 Hz, 2H), 7.88 (m, 1H), 7.99 (s, 1H), 8.25 (d, J = 6.00 Hz, 1H), 8.36 (d, J = 8.10 Hz, 1H), 9.32 (s, 1H).
23		MS m/z=421.2 (M+1);
24		MS m/z=404.2 (M+1);
25		MS m/z=403.2 (M+1);

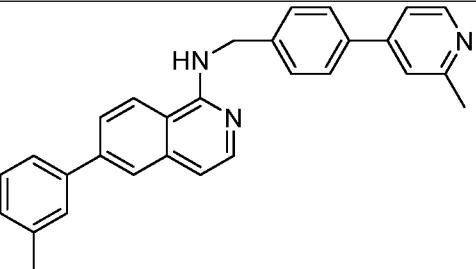
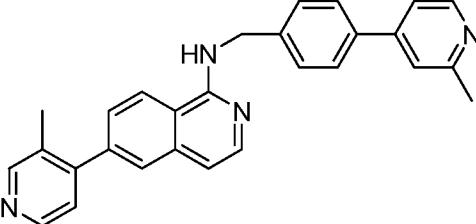
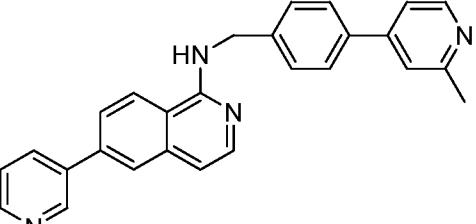
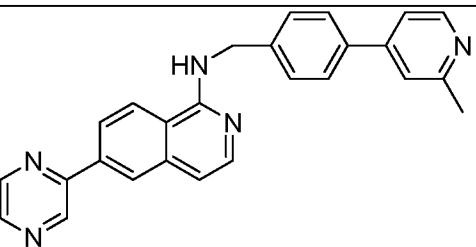
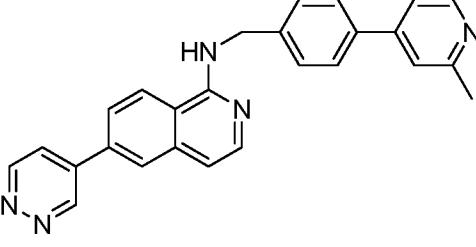
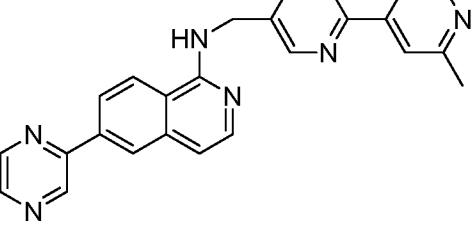
26		MS m/z=404.2 (M+1);
27		MS m/z=476.2 (M+1);
28		MS m/z=440.2 (M+1); 1H NMR (300 MHz, CDCl3): 82.61 (s, 3H), 4.88 (d, J = 5.70 Hz, 2H), 5.98 (br, 1H), 6.92 (d, J = 5.7 Hz, 1H), 7.02 (s, 1H), 7.26 (m, 3H), 7.37 (t, J=7.8Hz, 1H), 7.68 (d, J = 5.4 Hz, 1H), 7.79 (s, 1H), 7.89 (s, 1H), 8.11 (d, J= 6.0 Hz, 1H), 8.17 (d, J=5.1Hz, 1H), 8.55 (d, J=5.4Hz, 1H), 9.26 (s, 1H).
29		MS m/z=473.2 (M+1);
30		MS m/z=497.2 (M+1);

31		MS m/z=436.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.63 (s, 3H), 2.70 (s, 3H), 4.96 (d, J = 5.70 Hz, 2H), 6.02 (br, 1H), 7.02 (d, J = 5.70 Hz, 1H), 7.34 (s, 1H), 7.45 (d, J = 7.80 Hz, 2H), 7.61 (s, 1H), 7.78 (d, J = 4.80 Hz, 2H), 7.88 (s, 1H), 7.98 (s, 1H), 8.22 (d, J = 5.70 Hz, 1H), 8.55 (d, J = 5.10 Hz, 2H), 8.64 (d, J = 5.10 Hz, 2H), 9.34 (s, 1H).
32		MS m/z=423.2 (M+1);
33		MS m/z=461.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.69 (s, 3H), 3.06 (t, 4H), 4.18 (t, 4H), 4.79 (d, J = 5.40 Hz, 2H), 5.85 (br, 1H), 6.76 (d, J = 8.70 Hz, 1H), 6.99 (d, J = 6.00 Hz, 1H), 7.69 (q, 1H), 7.76 (q, 1H), 7.86 (s, 1H), 7.96 (s, 1H), 8.22 (d, J = 6.00 Hz, 1H), 8.31 (s, 1H), 8.63 (d, J = 5.40 Hz, 1H), 9.27 (s, 1H).
34		MS m/z=405.2 (M+1);

35		MS m/z=405.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.64 (s, 3H), 4.96 (d, J = 5.40 Hz, 2H), 5.96 (br, 1H), 7.05 (d, J = 5.70 Hz, 1H), 7.31 (m, 1H), 7.37 (s, 1H), 7.56 (d, J = 8.40 Hz, 2H), 7.64 (d, J = 8.40 Hz, 2H), 8.23 (d, J = 5.70 Hz, 1H), 8.54 (d, J = 5.40 Hz, 1H), 8.57 (s, 1H), 8.64 (d, J = 2.40 Hz, 1H), 8.67 (m, 1H), 9.32 (s, 1H), 9.71 (d, J = 1.50 Hz, 1H).
36		MS m/z=405.2 (M+1);
37		MS m/z=412.2 (M+1);
38		MS m/z=425.2 (M+1);
39		MS m/z=460.2 (M+1); ¹ H NMR (300 MHz, CD ₃ OD): δ2.56 (s, 3H), 3.13 (t, 4H), 4.28 (t, 4H), 4.81 (s, 2H), 6.79 (d, J = 6.30 Hz, 1H), 6.99 (s, 1H), 7.47 (m, 2H), 7.51 (s, 1H), 7.55 (d, J = 6.60 Hz, 2H), 7.71 (d, J = 8.40 Hz, 2H), 8.38 (d, J = 5.40 Hz, 1H), 9.27 (s, 1H).

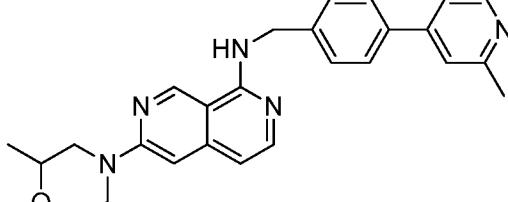
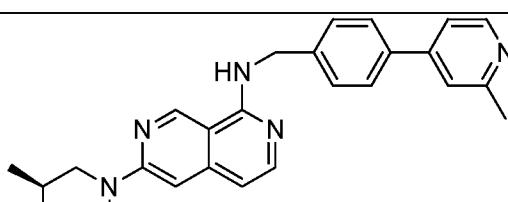
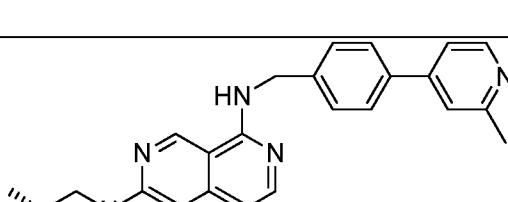
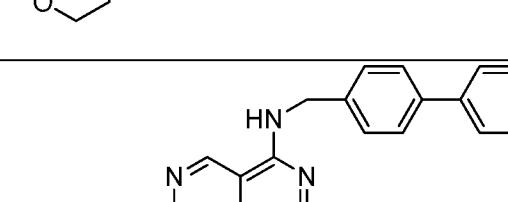
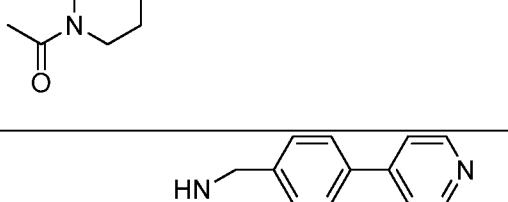
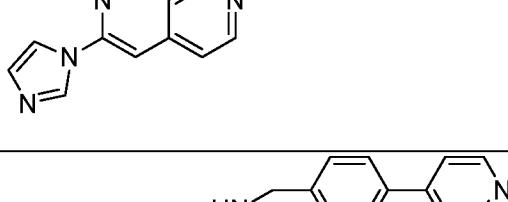
50		MS $m/z=422.2$ ($M+1$); 1H NMR (400MHz, DMSO-d6) δ 8.96 (d, $J=8.4$ Hz, 1H), 8.87 (s, 1H), 8.76 (d, $J=6.0$ Hz, 1H), 8.02-8.37 (m, 8H), 7.61-7.67 (m, 1H), 7.42 (t, $J=8.0$ Hz, 1H), 7.19 (d, $J=6.4$ Hz, 1H), 5.76 (s, 1H), 4.93 (d, $J=5.6$ Hz, 2H), 2.69 (s, 3H).
51		MS $m/z=419.2$ ($M+1$);
52		MS $m/z=422.2$ ($M+1$);
53		MS $m/z=422.2$ ($M+1$);

59		MS m/z=437.2 (M+1);
60		MS m/z=402.2 (M+1);
61		MS m/z=417.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.45 (s, 3H), 2.64 (s, 3H), 4.94 (d, J = 5.10 Hz, 2H), 5.93 (br, 1H), 7.00 (d, J = 5.70 Hz, 1H), 7.32 (d, J = 5.10 Hz, 1H), 7.36 (s, 1H), 7.54 (d, J = 8.10 Hz, 2H), 7.63 (d, J = 8.10 Hz, 2H), 7.80 (m, 2H), 8.20 (d, J = 6.00 Hz, 1H), 8.21 (s, 1H), 8.53 (m, 2H), 9.10 (s, 1H), 9.31 (s, 1H).
62		MS m/z=403.2 (M+1);
63		MS m/z=417.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.63 (s, 3H), 2.65 (s, 3H), 4.93 (d, J = 5.10 Hz, 2H), 7.06 (d, J = 6.00 Hz, 1H), 7.30 (m, 2H), 7.37 (s, 1H), 7.55 (d, J = 8.10 Hz, 2H), 7.63 (d, J = 8.10 Hz, 2H), 7.67 (m, 1H), 7.88 (m, 3H), 8.07 (d, J = 6.00 Hz, 1H), 8.53 (d, J = 5.10 Hz, 1H), 8.82 (d, J = 2.40 Hz, 1H).

64		MS m/z=416.2 (M+1);
65		MS m/z=417.2 (M+1);
66		MS m/z=403.2 (M+1);
67		MS m/z=404.2 (M+1);
68		MS m/z=404.2 (M+1);
69		MS m/z=405.2 (M+1); ¹ H NMR (400MHz, DMSO-d6) δ 9.52 (d, J=1.2Hz, 1H), 8.92 (d, J=2.0Hz, 1H), 8.84-8.86 (m, 1H), 8.75-8.82 (m, 4H), 8.56 (d, J=8.8Hz, 1H), 8.42 (s, 1H), 8.31 (d, J=8.8Hz, 2H), 8.12 (d, J=8.0Hz, 1H), 7.78 (d, J=6.8Hz, 1H), 7.40 (d, J=6.8Hz, 1H),

		5.76 (s, 1H), 5.00 (d, $J=5.6\text{Hz}$, 2H), 2.73 (s, 1H).
70		MS $m/z=419.2$ ($M+1$);
71		MS $m/z=418.2$ ($M+1$);
72		MS $m/z=435.2$ ($M+1$);
73		MS $m/z=432.2$ ($M+1$);
74		MS $m/z=405.2$ ($M+1$);

79		MS m/z=419.2 (M+1);
80		MS m/z=420.2 (M+1);
81		MS m/z=433.2 (M+1);
82		MS m/z=437.2 (M+1);
83		MS m/z=420.2 (M+1);

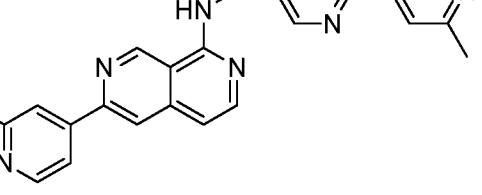
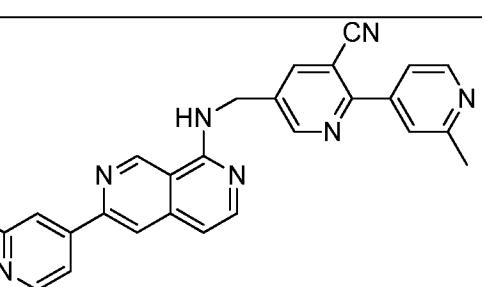
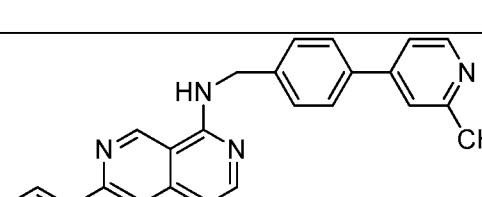
84		MS m/z=426.2 (M+1);
85		MS m/z=426.2 (M+1);
86		MS m/z=426.2 (M+1);
87		MS m/z=453.2 (M+1);
88		MS m/z=393.1 (M+1);
89		MS m/z=407.2 (M+1);

90		MS m/z=395.1 (M+1);
91		MS m/z=409.2 (M+1);
92		MS m/z=407.2 (M+1);
93		MS m/z=410.2 (M+1);
94		MS m/z=394.1 (M+1);
95		MS m/z=433.2 (M+1);

96		MS m/z=433.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.30 (s, 3H), 2.55 (s, 3H), 2.61 (s, 3H), 4.86 (d, J = 5.4 Hz, 2H), 5.98 (br, 1H), 6.94 (d, J = 5.7Hz, 1H), 7.17 (m, 1H), 7.24 (s, 1H), 7.61 (s, 1H), 7.70 (d, J=5.1Hz, 1H), 7.79 (s, 1H), 7.89 (s, 1H), 8.14 (d, J=6.0Hz, 1H), 8.49 (d, J=5.1Hz, 1H), 8.56 (m, 2H), 9.25 (s, 1H).
97		MS m/z=437.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): δ2.31 (s, 3H), 2.61 (s, 3H), 4.90 (d, J = 5.4 Hz, 2H), 6.00 (br, 1H), 6.94 (d, J = 5.7Hz, 1H), 7.18 (m, 1H), 7.24 (s, 1H), 7.63 (s, 1H), 7.70 (d, J=5.1Hz, 1H), 7.80 (s, 1H), 7.90 (s, 1H), 8.14 (d, J=6.0Hz, 1H), 8.33 (s, 1H), 8.50 (d, J=5.1Hz, 1H), 8.54 (m, 1H), 9.25 (s, 1H).
98		MS m/z=437.2 (M+1);
99		MS m/z=419.2 (M+1);

100		MS m/z=423.2 (M+1);
101		MS m/z= 469.2(M+1);
102		MS m/z=425.2 (M+1);
103		MS m/z=450.2 (M+1);
104		MS m/z=434.2 (M+1);

105		MS m/z=453.2 (M+1);
106		MS m/z=438.2 (M+1);
107		MS m/z=435.2 (M+1);
108		MS m/z=443.2 (M+1); ¹ H NMR (300 MHz, CDCl ₃): 82.30 (s, 3H), 2.61 (s, 3H), 4.98 (d, J = 5.7 Hz, 2H), 6.00 (br, 1H), 7.03 (d, J = 5.70 Hz, 1H), 7.35 (s, 1H), 7.45 (d, J = 7.8 Hz, 2H), 7.62 (s, 1H), 7.79 (d, J = 5.1 Hz, 2H), 7.89 (s, 1H), 7.98 (s, 1H), 8.20 (d, J = 5.70 Hz, 1H), 8.56 (d, J = 5.10 Hz, 2H), 8.66 (d, J = 5.10 Hz, 2H), 9.30 (s, 1H).
109		MS m/z=448.2 (M+1);

110		MS m/z=453.2 (M+1);
111		MS m/z=444.2 (M+1);
112		MS m/z=454.2 (M+1);

III. Medical and Pharmaceutical Uses

[0075] Compounds of the invention are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of the invention, as hereinbefore (but without any provisos, where applicable), for use as a pharmaceutical. There is also provided a synthetic form of a compound of the invention (but without any provisos, where applicable), for use as a pharmaceutical.

[0076] For the avoidance of doubt, although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. “protected”) derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be metabolized in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the “active” compounds to which they are metabolized) may therefore be described as “prodrugs” of compounds of the invention.

[0077] By “prodrug of a compound of the invention”, we include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time (e.g. about 1 hour),

following oral or parenteral administration. All prodrugs of the compounds of the invention are included within the scope of the invention.

[0078] Furthermore, certain compounds of the invention may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds of the invention that possess pharmacological activity as such. Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the “active” compounds of the invention to which they are metabolised), may also be described as “prodrugs”.

[0079] Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds which possess pharmacological activity.

[0080] Compounds of the invention (as hereinbefore defined but without the proviso(s)) may be useful in the treatment of a cancer. By “cancer”, we mean any disease that arises from an uncontrolled growth of cells (e.g. uncontrolled division), invasion (e.g. direct growth into adjacent tissue) or metastasis. By “uncontrolled growth”, we include an increase in the number and/or size of cancer cells (also referred to herein as “proliferation”). By “metastasis” we mean the movement or migration (e.g. invasiveness) of cancer cells from a primary tumor site in the body of a subject to one or more other areas within the subject’s body (where the cells can then form secondary tumors). Thus, in one embodiment the invention provides compounds and methods for inhibiting, in whole or in part, the formation of secondary tumors in a subject with cancer.

[0081] Advantageously, the compounds of the invention may be capable of inhibiting the proliferation and/or metastasis of cancer cells selectively.

[0082] By “selectively” we mean that the compounds of the invention may inhibit the proliferation and/or metastasis of cancer cells to a greater extent than it modulates the function (e.g. proliferation) of non-cancer cells. Preferably, the compounds of the invention inhibit the proliferation and/or metastasis of cancer cells only.

[0083] In another aspect, the present invention provides a pharmaceutical composition comprising the compound of the present invention and at least one pharmaceutically acceptable carrier or diluent, wherein said compound is in free form or in a pharmaceutically acceptable salt form. Such composition may be an oral composition, injectable composition or suppository. And the composition may be manufactured in a conventional manner by mixing, granulating or coating methods.

[0084] In an embodiment of the invention, the composition is an oral composition and it may be a tablet or gelatin capsule. Preferably, the oral composition comprises the present compound together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets, together with c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragamayth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; and if desired, d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) additives, e.g., absorbents, colorants, flavors and sweeteners.

[0085] In another embodiment of the invention, the composition is an injectable composition, and may be an aqueous isotonic solution or suspension.

[0086] In yet another embodiment of the invention, the composition is a suppository and may be prepared from fatty emulsion or suspension.

[0087] Preferably, the composition is sterilized and/or contains adjuvant. Such adjuvant can be preserving, stabilizing, wetting or emulsifying agent, solution promoter, salt for regulating the osmotic pressure, buffer and/or any combination thereof.

[0088] Alternatively or in addition, the composition may further contain other therapeutically valuable substances for different applications, like solubilizers, stabilizers, tonicity enhancing agents, buffers and/or preservatives.

[0089] In an embodiment of the invention, the composition may be a formulation suitable for transdermal application. Such formulation includes an effective amount of the compound of the present invention and a carrier. Preferably, the carrier may include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. A transdermal device contain the formulation may also be used. The transdermal device may be in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Otherwise, a matrix transdermal formulation may also be used.

[0090] In another embodiment of the invention, the composition may be a formulation suitable for topical application, such as to the skin and eyes, and may be aqueous solution, ointment, cream or gel well known in the art.

[0091] In another aspect, the present invention provides a method of inhibiting WNT secretion from a cell.

[0092] In one embodiment, the cell is contained within a mammal, and the administered amount is a therapeutically effective amount. In another embodiment, the inhibition of WNT signaling further results in the inhibition of the growth of the cell. In a further embodiment, the cell is a cancer cell. In yet another embodiment, the cell is a fibrogenic cell.

[0093] Cell proliferation is measured by using methods known to those skilled in the art. For example, a convenient assay for measuring cell proliferation is the CellTiter-Glo™ Assay commercially available from Promega (Madison, WI). The assay procedure involves adding the CellTiter-Glo® reagent to cells cultured on multi-well dishes. The luminescent signal, measured by a luminometer or an imaging device, is proportional to the amount of ATP present, which is directly proportional to the number of viable cells present in culture. In addition, cell proliferation may also be measured using colony formation assays known in the art.

[0094] The present invention also provides a method for treating cancers or fibroses related to the WNT signaling pathway with an effective amount of the present compound. Those skilled in the art would readily be able to determine whether a cancer is related to the Wnt pathway by analyzing cancer cells using one of several techniques known in the art. For example, one could examine cancer cells for aberrations in the levels of proteins or mRNAs involved in Wnt signaling using immune and nucleic acid detection methods.

[0095] Cancers or fibroses related to the Wnt pathway include those in which activity of one or more components of the Wnt signaling pathways are upregulated from basal levels. In one embodiment, inhibiting the Wnt pathway may involve inhibiting Wnt secretion. As another example, inhibiting the Wnt pathway may involve inhibiting components downstream of the cell surface receptors. In another embodiment, inhibition of Wnt secretion may involve inhibiting the activity of any of the proteins implicated in the secretion of functional WNTs.

[0096] Furthermore, the invention provides a method for treating a WNT pathway disorder in a subject suffering from the disorder by administering to the subject a therapeutically effective amount of a WNT inhibitor. In one embodiment, the disorder is a cell proliferative disorder associated with aberrant, e.g., increased, activity of WNT signaling. In another embodiment, the disorder results from increased amount of a WNT protein. In yet another embodiment, the cell proliferative disorder is cancer, include but are not limited to: lung (small cell and non-small cell), breast, prostate, carcinoid, bladder, gastric, pancreatic, liver (hepatocellular), hepatoblastoma, colorectal, 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). In yet another embodiment, the cell proliferative disorder is fibrosis, include but are not limited

to: lung fibrosis, such as idiopathic pulmonary fibrosis and radiation-induced fibrosis, renal fibrosis, cardiac fibrosis and liver fibrosis including liver cirrhosis. In yet another embodiment, the disorder is osteoarthritis, Parkinson's disease, retinopathy, macular degeneration.

[0097] For therapeutically use, the compound of the present invention could be administered in a therapeutically effective amount via any acceptable way known in the art singly. As used herein, the therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. Generally, the satisfactory result is indicated to be obtained systemically at a daily dosage of about 0.03 to 2.5 mg/kg per body weight of the subject. In one embodiment, the indicated daily dosage for larger mammal as human is in the range from about 0.5mg to about 500mg. Preferably, the compound is administered in divided doses up to four times a day or in retard form. In another embodiment, suitable unit dosage forms for oral administration comprise from ca. 1 to 500 mg active ingredient.

[0098] Alternatively, the compound of the present invention may be administered in a therapeutically effective amount as the active ingredient in combination with one or more therapeutic agents, such as pharmaceutical combinations. There may be synergistic effects when the compound of the present invention is used with a chemotherapeutic agent known in the art. The dosage of the co-administered compounds could vary depending on the type of co-drug employed, the specific drug employed, the condition being treated and so forth.

[0099] The compound of the present invention or the composition thereof may be administered by any conventional route. In one embodiment, it is administered enterally, such as orally, and in the form of tablets or capsules. In another embodiment, it is administered parenterally and in the form of injectable solutions or suspensions. In yet another embodiment, it is administered topically and in the form of lotions, gels, ointments or creams, or in a nasal or suppository form.

[0100] In another aspect, the invention also provides a pharmaceutical combination, preferably, a kit, comprising a) a first agent which is the compound of the present invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. In addition, the kit may comprise instructions for its administration.

[0101] The combination of the present invention may be used in vitro or in vivo. Preferably, the desired therapeutic benefit of the administration may be achieved by contacting cell, tissue or organism with a single composition or pharmacological formulation that includes the compound of the present invention and one or more agents, or by contacting the cell with two or more distinct compositions or formulations, wherein one composition includes one agent and the other includes another. The agents of the

combination may be administered at the same time or separately within a period of time. Preferably, the separate administration can result in a desired therapeutic benefit. The present compound may precede, be co-current with and /or follow the other agents by intervals ranging from minutes to weeks. A person skilled in the art could generally ensure the interval of the time of each delivery, wherein the agents administered separately could still be able to exert an advantageously combined effect on the cell, tissue or organism. In one embodiment, it is contemplated that one may contact the cell, tissue or organism with two, three, four or more modalities substantially simultaneously as the candidate substance, i.e., with less than about one minute. In another embodiment, one or more agents may be administered about between 1 minute to 14 days.

[0102] In another aspect, the present provides a process for preparing the compound of the present invention or the salts or derivatives thereof.

[0103] In one embodiment, the compound having Formula (I) may be prepared following any one of the synthetic methodologies described in Examples below. In the reactions described, reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice (see e.g., T.W. Greene and P. G. M. Wuts in “Protective Groups in Organic Chemistry”, John Wiley and Sons, 1991). Suitable leaving groups for use in the synthetic methodologies described include halogen leaving groups and other conventional leaving groups known in the art. Preferably, the leaving group is chloro or bromo.

[0104] In another embodiment, the compound of the invention or the salts thereof may also be obtainable in the form of hydrates, or their crystals may include for example the solvent used for crystallization (present as solvates). Salts can usually be converted to compounds in free form by treating with suitable basic agents, preferably with alkali metal carbonates, alkali metal hydrogen carbonates, or alkali metal hydroxides, more preferably with potassium carbonate or sodium hydroxide. A compound of the invention in a base addition salt form may be converted to the corresponding free acid by treating with a suitable acid, such as hydrochloric acid. In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that may be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds is to be understood as referring also to the corresponding salts, as appropriate.

[0105] Salts of the present compound with a salt-forming group may be prepared in a manner known in the art. Acid addition salts of compound of Formula (I) may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. Pharmaceutically acceptable salts of the compound of the

invention may be formed as acid addition salts from compound of Formula (I) with a basic nitrogen atom with organic or inorganic acids.

[0106] Preferably, suitable inorganic acids include, but are not limited to, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid.

[0107] Preferably, suitable organic acids include, but are not limited to, carboxylic, phosphoric, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantane carboxylic acid, benzoic acid, salicylic acid, 4 aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4 methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

[0108] Alternatively, it is also possible to use pharmaceutically unacceptable salts for isolation or purification, for example picrates or perchlorates. But for therapeutic use, only pharmaceutically acceptable salts or free compounds are employed, where applicable in the form of pharmaceutical preparations.

[0109] In yet another embodiment, compound of the present invention in unoxidized form may be prepared from N-oxides of compound of the invention by treating with a reducing agent in a suitable inert organic solvent at 0 to 80°C. Preferably, the reducing agent is sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like. Preferably, the inert organic solvent is acetonitrile, ethanol, aqueous dioxane, or the like.

[0110] In yet another embodiment, prodrug derivatives of the compound of the present invention may be prepared by methods known in the art (for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). In a preferable embodiment, an appropriate prodrug may be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent such as 1,1-acycloxyalkylcarbanochloride, para-nitrophenyl carbonate, or the like.

[0111] In yet another embodiment, protected derivatives of the compound of the present invention may be made by means known in the art. A detailed description of techniques applicable to the creation of

protecting groups and their removal may be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[0112] In yet another embodiment, compound of the present invention may be prepared as their individual stereoisomers. The process includes reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. Resolution of enantiomers may be carried out using covalent diastereomeric derivatives of the compound of the present invention, or by using dissociable complexes such as crystalline diastereomeric salts. Diastereomers have distinct physical properties presented by melting points, boiling points, solubilities, reactivity, etc., and may be readily separated by taking advantage of these dissimilarities. The diastereomers may be separated by fractionated crystallization, chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture may be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[0113] In conclusion, the compound of the present invention could be made by the process described in the Examples;

optionally a pharmaceutically acceptable salt may be converted from the compound of the present invention;

optionally a pharmaceutically acceptable N-oxide may be converted from an unoxidized form of the compound the present invention;

optionally an individual isomer of the compound of the present invention is resolved from a mixture of isomers; and

optionally a pharmaceutically acceptable prodrug derivative may be converted from a non-derivatized compound of the present invention.

[0114] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter. One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well-known methods can similarly be used.

IV. Treatment of Fibrosis Diseases

[0115] In another aspect, the present invention provides compositions and methods for prevention and/or treatment of fibrosis or fibrotic diseases (or fibrosis diseases) including fibrogenic and hypertrophic remodeling after myocardial infarction, scleroderma, systemic sclerosis, scleroderma-like disorders, sine scleroderma, liver cirrhosis, interstitial pulmonary fibrosis, Dupuytren's contracture, keloids, chronic kidney disease, chronic graft rejection, and other scarring/wound healing abnormalities, post operative adhesions, and reactive fibrosis comprising administering to a subject in need thereof, a composition that comprises a therapeutically effective amount of a compound of the formula (I) or its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, pharmaceutically acceptable salts thereof, polymorphs, or a combination thereof, to the subject.

1. Fibrotic Diseases

[0116] Fibrosis is the abnormal accumulation of fibrous tissue that can occur as a part of the wound-healing process in damaged tissue. Examples of fibrosis include liver fibrosis, lung fibrosis (e.g., silicosis, asbestosis, idiopathic pulmonary fibrosis), myocardial fibrosis, oral fibrosis, endomyocardial fibrosis, fibrogenic and hypertrophic remodeling after myocardial infarction, retroperitoneal fibrosis, deltoid fibrosis, kidney fibrosis (including diabetic nephropathy), and glomerulosclerosis. Liver fibrosis, for example, occurs as a part of the wound-healing response to chronic liver injury. Fibrosis can occur as a complication of haemochromatosis, Wilson's disease, alcoholism, schistosomiasis, viral hepatitis, bile duct obstruction, exposure to toxins, and metabolic disorders. The formation of fibrotic tissue is believed to represent an attempt by the body to encapsulate injured tissue. Liver fibrosis is characterized by the accumulation of extracellular matrix that can be distinguished qualitatively from that in normal liver. Left unchecked, hepatic fibrosis progresses to cirrhosis (defined by the presence of encapsulated nodules), liver failure, and death. Endomyocardial fibrosis is an idiopathic disorder that is characterized by the development of restrictive cardiomyopathy. In endomyocardial fibrosis, the underlying process produces patchy fibrosis of the endocardial surface of the heart, leading to reduced compliance and, ultimately, restrictive physiology as the endomyocardial surface becomes more generally involved. Endocardial fibrosis principally involves the inflow tracts of the right and left ventricles and may affect the atrioventricular valves, leading to tricuspid and mitral regurgitation. Oral submucous fibrosis is a chronic, debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). It results in marked rigidity and an eventual inability to open the mouth. The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx. Retroperitoneal fibrosis is characterized by the development of extensive fibrosis throughout the retroperitoneum, typically centered over the anterior

surface of the fourth and fifth lumbar vertebrae. This fibrosis leads to entrapment and obstruction of retroperitoneal structures, notably the ureters. In most cases, the etiology is unknown.

[0117] Scleroderma is a fibrotic disease that affects approximately 19 cases per 1 million persons. The cause of scleroderma is unknown. Abnormalities involve autoimmunity and alteration of endothelial cell and fibroblast function are believed to be involved. Indeed, systemic sclerosis is probably the most severe of the auto-immune diseases with 50% mortality within 5 years of diagnosis.

[0118] Scleroderma is a disease of the connective tissue characterized by fibrosis of the skin and internal organs, leading to organ failure and death. Scleroderma has a spectrum of manifestations and a variety of therapeutic implications. It comprises localized scleroderma, systemic sclerosis, scleroderma-like disorders, and sine scleroderma.

[0119] While localized scleroderma is a rare dermatologic disease associated with fibrosis and manifestations limited to skin, systemic sclerosis is a multi-system disease with variable risk for internal organ involvement and variation in the extent of skin disease. Systemic sclerosis can be diffuse or limited. Limited systemic sclerosis is also called CREST (calcinosis, Raynaud's esophageal dysfunction, sclerodactyl, telangiectasiae). Systemic sclerosis comprises: scleroderma lung disease, scleroderma renal crisis, cardiac manifestations, muscular weakness including fatigue or limited CREST, gastrointestinal dysmotility and spasm, and abnormalities in the central, peripheral and autonomic nervous system. Scleroderma-like disorders are believed to be related to industrial environment exposure. In sine disease, there is internal organ involvement without skin changes.

[0120] The major symptoms or manifestations of scleroderma and in particular of systemic sclerosis are inappropriate excessive collagen synthesis and deposition, endothelial dysfunction, spasm, collapse and obliteration by fibrosis. In terms of diagnosis, an important clinical parameter is skin thickening proximal to the metacarpophalangeal joints. Raynaud's phenomenon is a frequent, almost universal component of scleroderma. It is diagnosed by color changes of the skin upon cold exposure. Ischemia and skin thickening are symptoms of Raynaud's disease.

[0121] Several underlying biological processes are implicated in the initiation, severity and progression of the disease and include vascular dysfunction, endothelial cell activation and damage, leukocyte accumulation, auto-antibody production and crucially, an uncontrolled fibrotic response which may lead to death. Fibroblasts have a pivotal role in the pathogenesis of this disease. Primary fibroblasts obtained from patients with scleroderma exhibit many of the characteristic properties of the disease seen *in vivo*, notably increased extracellular matrix synthesis and deposition, notably of collagen and fibronectin, and

altered growth factor and cytokine production such as of TGF-beta and CTGF (“Increased collagen synthesis by scleroderma skin fibroblasts in vitro” J. Clin. Invest. 54, p. 880-89 LeRoy (1974)) [2].

[0122] Recent investigations implicate WNT signaling in abnormal wound repair leading to fibrosis. In patients with fibrotic diseases, there is an elevated expression in components of the pathway. In animal models, activation of the WNT canonical signaling participates in injury repair that leads to fibrogenesis Lam AP, Gottardi CJ. Curr Opin Rheumatol. 2011 Nov;23(6):562-7.

[0123] Several types of fibrosis have been linked to the WNT pathway. For example, idiopathic pulmonary fibrosis (IPF) patients have aberrant activation of the WNT/β-catenin signaling in the lungs Königshoff et al, PLoS One. 2008 May 14;3(5):e2142. Also, it was found that significant increase in nuclear levels of β-catenin occur in fibroblasts in systemic sclerosis skin compared to fibroblasts in the skin of healthy individuals. It was further showed that the nuclear accumulation of β-catenin has direct implications for the development of fibrosis in mice with fibroblast-specific stabilization of β-catenin. In contrast, fibroblast-specific deletion of β-catenin significantly reduced bleomycin-induced dermal fibrosis. Beyer C et al., Ann Rheum Dis. 2012 May;71(5):761-7.

[0124] A link between the canonical WNT pathway and the well-known fibrogenic pathway, transforming growth factor-β (TGF-β) pathway has been made recently. While activation of the canonical Wnt pathway stimulates fibroblasts in vitro and induces fibrosis in vivo, TGF-β stimulates canonical WNT signaling by decreasing the expression of the WNT antagonist DKK-1. Transgenic over-expression of DKK-1 ameliorates skin fibrosis induced by constitutively active TGF-β receptor signaling. This finding not only demonstrated that canonical WNT pathway is necessary for TGF-β-mediated fibrosis but also implicated the novel interaction between the two key pathways in fibrosis (Akhmetshina et al., Nat Commun. 2012 Mar 13;3:735).

[0125] In yet another aspect, the present invention provide a combination therapy for fibrosis using a Wnt inhibitor provided herein and a medicine used in standard-of-care. In some embodiments, the present invention provides a combination for treatment of lung fibrosis using a combination of a Wnt inhibitor provided herein and a standard-of-care medicine, such as a steroid (prednisone), or Esbriet (pirfenidone).

2. Acute Myocardiac Infarction

[0126] Myocardial infarction is an important complication of coronary artery disease and usually results from a critical reduction in coronary blood flow secondary to coronary thrombosis. The two important pathological changes of the cardiac tissue after acute myocardial infarction are fibrosis and hypertrophic growth of the cardiac tissues. Both changes (“remodeling”) significantly contribute to the pathogenesis of

heart failure. Intravenous thrombolytic agent therapy has been widely used to restore flow to the occluded coronary artery. A thrombolytic agent is a medicament capable of lysing the fibrin-platelet thrombus, and thereby permitting blood to again flow through the affected blood vessel. Such agents include streptokinase, urokinase, prourokinase, reteplase, alteplase and tissue-type plasminogen activator (t-PA). The mortality of patients with acute myocardial infarction even if treated with thrombolytic agents remains high.

[0127] By “acute myocardial infarction” herein is meant immediate or sudden (not chronic) infarction of the heart muscle, i.e. an insufficiency of arterial blood flow as a result of occlusion of a coronary artery due to at least partial blockage of the artery by an embolus or thrombus.

[0128] As an important regulator of differentiation and morphogenesis that control stem cell fates, WNT pathway is one of the important signals that form the heart. Indeed, the organogenesis of the heart is tightly controlled by WNT signaling (Tzahor, Dev Cell. 2007 Jul;13(1):10-3).

[0129] This knowledge has been used in the induction of mesoderm and subsequent cardiac differentiation from human ES cells in culture by using modulators of the WNT pathway. In the early phase, activation of the canonical WNT signaling enhances mesoderm induction, while the later cardiac differentiation requires inhibition of the canonical signal. This biphasic control of the WNT pathway permits efficient generation of cardiomyocytes from human ES or iPS cells, and modulators of the WNT signaling have been postulated as useful tools or drugs for basic studies or cardiac repair applications (Paige, J Bone Miner Res. 2011 Jan;26(1):19-26; Lian, Proc Natl Acad Sci U S A. 2012 Jul 3;109(27):E1848-57.)

[0130] Upon myocardial infarction, the heart reactivates several signaling pathways involved in the developing heart in an attempt to regenerate itself. It has been shown that inhibition of the canonical WNT signaling significantly reduced post-infarct mortality and functional decline. In addition, WNT signaling is activated during left ventricular (LV) remodeling by soluble frizzled-related proteins (sFRPs) which block WNT-dependent activation of the canonical WNT pathway. In animal studies, sFRPs injected into the heart attenuated LV remodeling. Notably, sFRPs are secreted from bone marrow-derived mononuclear cells, which may serve as a mechanism for the therapeutic action of such cells in human heart failure patients (Bergmann, Circ Res. 2010 Nov 12;107(10):1198-208).

[0131] The cellular mechanism by which WNT signaling is involved in cardiac remodeling processes may relate to its action on fibrosis. As mentioned above, the WNT pathway plays a key role in fibrosis of various organs. Much is needed to learn for its role and to more effectively explore its potential in therapeutic development for heart failure (Dawson K, Aflaki M, Nattel S. Role of the Wnt-Frizzled

System in Cardiac Pathophysiology: A Rapidly Developing, Poorly Understood Area with Enormous Potential. *J Physiol.* 2012 Dec 3. [Epub ahead of print]).

[0132] As used herein, “thrombus” or “embolus” refer to a blood clot within the blood vessel. “At least partial” blockage of the artery means that the artery contains an embolus or thrombus, which reduces the cross sectional area of the artery.

[0133] In another aspect, the present invention provides a combination therapy that combines the compound of formula (I) provided herein and a thrombolytic agent to provide synergistic effect.

[0134] By “thrombolytic agent: herein is meant any agent effective in helping to dissolving or breaking up an occluding thrombus. A thrombolytic agent may be selected from those thrombolytic agents, which are known in the art. These include, but are not limited to, streptokinase, urokinase, prourokinase, alteplase, reteplase, anistreplase and tissue plasminogen activator (t-PA) and biologically active variants thereof. A combination of two or several thrombolytic agents may be also used.

[0135] The active ingredients are preferably administered concurrently as soon as possible, preferably within six hours, after the onset of symptoms of an acute myocardial infarction. If it is desired to avoid other medication during the thrombolytic therapy, which may be given e.g. as an intravenous bolus or infusion, the compound of formula(I) may be administered sequentially after the administration of the thrombolytic agent.

[0136] While it is preferred to administer the compound of formula (I) during or immediately after the thrombolytic therapy, the synergistic effect of the combination is still obtained, if compound of formula (I) administration is started not later than five days, preferably not later than three days, more preferably not later than 48 hours, from the thrombolytic therapy or, preferably, from the onset of symptoms of an acute myocardial infarction.

[0137] The administration routes of the active ingredients include, but are not limited to, enteral, e.g. oral or rectal, or parenteral, e.g. intravenous, intramuscular, intraperitoneal or transdermal. In the treatment of myocardial infarction, the active ingredients are preferably administered parenterally, intravenous route being particularly preferred. Single or multiple dosages may be given. Preferably, the active agents are administered via continuous infusion.

[0138] Preferably, the method comprises administering to a patient an amount of the combination, which is synergistically effective in reducing mortality of patients with myocardial infarction.

[0139] Compound of formula (I) may be administered intravenously using an infusion rate which is from about 0.05 to 0.4 μ g/kg/min. For an intravenous bolus a suitable dose is in the range from about 5 to 30

µg/kg. In the treatment of patients with acute myocardial infarction an intravenous bolus followed by continuous infusion may be needed.

[0140] Compound of formula (I) may be administered orally to man in daily dose ranging from about 0.1 to 8 mg given once a day or divided into several doses a day, depending on the age, body weight and condition of the patient. The effective amount of compound of formula (I) to be administered to a subject depends upon the condition to be treated, the route of administration, age, weight and the condition of the patient.

[0141] Preferred thrombolytic agents include streptokinase, urokinase, prourokinase, alteplase, reteplase, anistreplase and tissue plasminogen activator (t-PA) and biologically active variants thereof as well as any combinations thereof. The thrombolytic agent may be administered using the conventional dosage ranges for these agents, for example a daily dosage used when the agent is administered in thrombolytic therapy as a monotherapy. The range will, of course, vary depending on the thrombolytic agent employed. Examples of normal dosage ranges are as follows: urokinase - 500,000 to 6,250,000 units/patient; streptokinase - 140,000 to 2,500,000 units/patient; prourokinase - 5,000 to 100,000 units/patient; anistreplase- 10 to 100 units/patient; t-PA - 0.5 to 2.0 mg/kg body weight.

[0142] Thrombolytic therapy is typically given as an intravenous bolus alone or followed by intravenous infusion or as an infusion alone. The infusion is normally administered over a time ranging from less than one hour to about 12 hours, typically from about 1 to 3 hours. For example, the thrombolytic therapy may comprise administration of up to 10 % of the total dose as bolus injection over 1 to 5 minutes and the remaining 90 % then as a constant infusion during the next hour.

[0143] When the symptoms have been alleviated to the desired level, treatment can be stopped.

[0144] The combination may be supplemented with one or more other active ingredients, e.g. anticoagulants, or surgical methods such as angioplasty.

[0145] The active ingredients can be formulated into pharmaceutical dosage forms suitable for the treatment according to the present invention using the principles known in the art. They are given to a patient as such or preferably in combination with suitable pharmaceutical excipients in the form of tablets, granules, capsules, suppositories, emulsions, suspensions or solutions whereby the contents of the active compound in the formulation is from about 0.5 to 100 % per weight. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds, release controlling components and other ingredients normally used in this field of technology may be also used.

[0146] The active ingredients may be formulated in the same pharmaceutical formulation. Preferably, such pharmaceutical composition of thrombolytic agent and compound of formula (I) is adapted to intravenous administration. Such compositions may be prepared for storage by mixing these compounds with optional pharmaceutically acceptable carriers, excipients or stabilizers, e.g. into the form of infusion concentrates or aqueous solutions, or powders adapted to be reconstituted with sterile water or aqueous infusion vehicles for infusion.

[0147] Alternatively, the active ingredients are formulated as separate pharmaceutical dosage forms. The combination of the two pharmaceutical dosage forms may be packaged as a single medical product or kit for use in the method of the invention, optionally together with a package insert instructing to the correct use of the medical product.

[0148] Formulations suitable for intravenous administration such as injection or infusion formulation, comprise sterile isotonic solutions of the active ingredient and vehicle, preferably aqueous solutions. Typically an intravenous infusion solution of compound of formula (I) comprises from about 0.01 to 0.1 mg/ml of compound of formula (I). Compound of formula (I) composition as stored before use is preferably an infusion concentrate product, which can be reconstituted with sterile water or aqueous infusion vehicle for infusion.

[0149] For oral administration of compound of formula (I) in tablet form, suitable carriers and excipients include e.g. lactose, corn starch, magnesium stearate, calcium phosphate and talc. For oral administration in capsule form, useful carriers and excipients include e.g. lactose, corn starch, magnesium stearate and talc. For controlled release oral compositions release controlling components can be used. Typical release controlling components include hydrophilic gel forming polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl celluloses, alginic acid or a mixture thereof; vegetable fats and oils including vegetable solid oils such as hydrogenated soybean oil, hardened castor oil or castor seed oil (sold under trade name Cutina HR), cotton seed oil (sold under the trade names Sterotex or Lubritab) or a mixture thereof; fatty acid esters such as triglycerides of saturated fatty acids or their mixtures e.g. glyceryl tristearates, glyceryl tripalmitates, glyceryl trimyristates, glyceryl tribehenates (sold under the trade name Compritol) and glyceryl palmitostearic acid ester.

[0150] Tablets can be prepared by mixing compound of formula (I) with the carriers and excipients and compressing the powdery mixture into tablets. Capsules can be prepared by mixing compound of formula (I) with the carriers and excipients and placing the powdery mixture in capsules, e.g. hard gelatin capsules. Typically a tablet or a capsule comprises from about 0.1 to 8 mg, more typically 0.2 to 5 mg, of compound of formula (I).

[0151] Thrombolytic agent compositions as used in clinical practice comprises generally water as a carrier and pharmaceutical adjuvants known in the art, i.e. isotonizing agents; acid, base or buffer substances to adjust the pH of the solution; and stabilizing agents for the thrombolytic agent. Said thrombolytic agent composition as stored before use is preferably a sterile lyophilized product, which can be reconstituted with sterile water for injection.

[0152] The concentration of the thrombolytic agent in the composition depends on the nature of the thrombolytic agent. For example, tissue plasminogen activator may be present in an amount from 20 mg to 100 mg per dosage form. The concentration of tissue plasminogen activator in a lyophilized product is typically in the range of from 1.5 to 2 % (w/w). As pH adjusting agents, phosphoric acid and optionally sodium hydroxide may be used, so that upon reconstitution with sterile water for injection, a pH of about 7.3 is reached. As stabilizing agent for the thrombolytic agent, an amino acid may be used, for example L-arginine in the case of tissue plasminogen activator. The stabilizing agent makes up the bulk of the lyophilized thrombolytic agent, typically from about 70 % to about 80 % (w/w).

[0153] In another aspect, the present invention provide a combination therapy of the compounds provided herein (e.g., a compound of formula (I)) and a hemodynamic agents such as ACE inhibitor and beta blocker, and other medicines that are the standard-of-care. First-line therapy for all heart failure patients is angiotensin-converting enzyme (ACE) inhibitors (i.e., enalapril, captopril, lisinopril, ramipril). Other drugs, such as oral loop diuretics, beta-blockers, angiotensin receptor blockers, vasodilators, and aldosterone receptor antagonists, are also frequently used and can be combined with WNT inhibitors provided herein.

[0154] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

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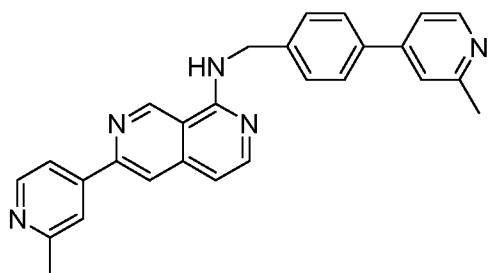
EXAMPLES

[0156] The present invention is further exemplified, but not limited, by the following and Examples that illustrate the preparation of the compounds of the invention.

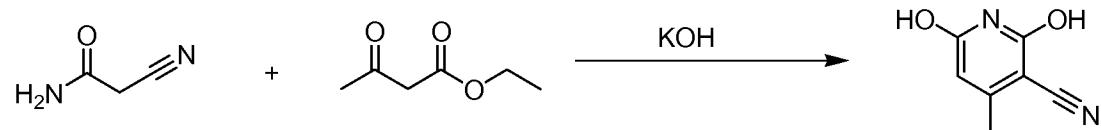
Abbreviation	Definition or Explanation
DCM	Dichloromethane
DIEA	N,N'-Diisopropylethylamine
DMF	N,N-Dimethylformamide
eq.	equivalents
TEA	Triethylamine
THF	Tetrahydrofuran
RT	Room Temperature
EA	Ethyl acetate
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
s-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium

Example 1

[0157] Synthesis of N-(4-(2-methylpyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine (Compound No. 1)

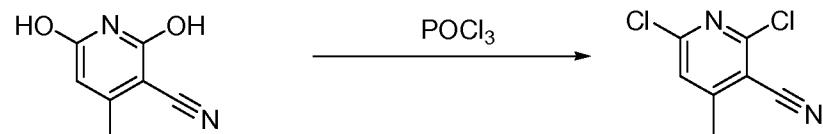


[0158] Step 1:



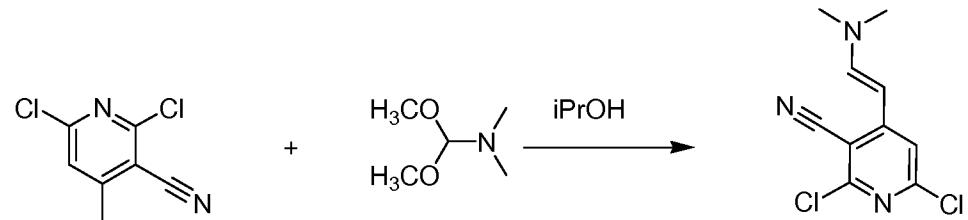
[0159] 2-Cyanoacetamide (50 g, 601.8 mmol) and ethyl acetoacetate (75 mL, 601.8 mmol) were dissolved in MeOH. KOH (37.0 g, 1.1 eq) was dissolved in MeOH, and added dropwise into the mixture, some white solid came out. The mixture was heated up to reflex at oil bath for 8h, and then cooled down to RT. The solid was filtered and then re-dissolved into hot water, and then filtered again. 6N HCl was added into the filtration to neutralize till pH<7. The white solid was out again and filtered. The solid was further washed with MeOH, water and MeOH, and then dried by vacuum to get the final product 3-ethynyl-4-methylpyridine-2,6-diol (yield ~41%).

[0160] Step 2:



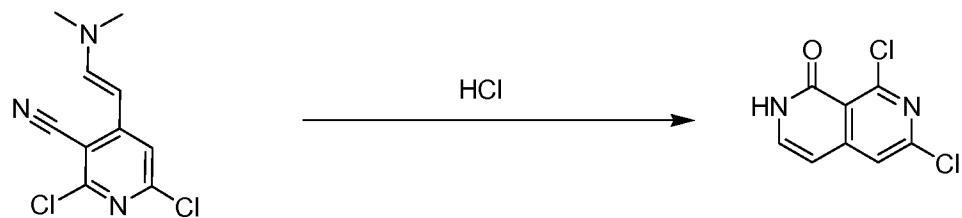
[0161] 3-ethynyl-4-methylpyridine-2,6-diol (28.0 g, 195.2 mmol) was dissolved in POCl₃ (60.0 mL). The reaction mixture was sealed in a pressure tube and heated up to 180°C for 6h. After the reaction was cooled down to room temperature, the excessive POCl₃ was removed under the vacuum. Slowly added crushed ice into the mixture, and the solid came out. Filtered the solid out and dried under the vacuum to get the final product 2,6-dichloro-4-methylpyridine-3-carbonitrile (yield ~92%) without further purity.

[0162] Step 3:



[0163] 2,6-dichloro-4-methylpyridine-3-carbonitrile (20.0 g, 107.5mmol) in 200 mL of isopropyl alcohol was added N,N-dimethylformamide dimethylacetal (12.82 g, 107.5mmol) and the reaction was stirred at 65°C for 18 h. After cooling down the reaction to RT, the precipitate was collected by filtration and washed with 50 mL of isopropyl alcohol, and air dried to give the product 2,6-dichloro-4-((E)-2-(dimethylamino)vinyl)pyridine-3-carbonitrile (yield ~ 26%) without further purification.

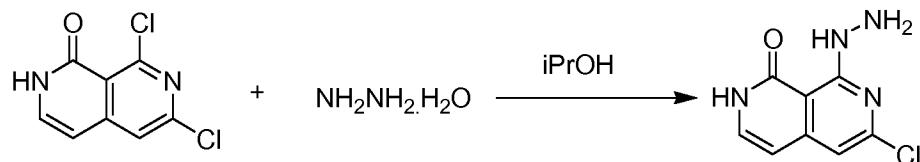
[0164] Step 4:



[0165] 2,6-dichloro-4-((E)-2-(dimethylamino)vinyl)pyridine-3-carbonitrile (4.0g, 16.6mmol) was added with 20mL concentrated HCl in a sealed tube. The reaction is stirred at 45°C for 18h. After cooling down the reaction to RT, ice water was added to the solution resulting heavy yellow slurry. The precipitate was collected by filtration, washed with cold water, ether and ethyl acetate, and dried under vacuum to get light yellow solid 6,8-dichloro-2,7-naphthyridin-1(2H)-one (yield ~80%). MS *m/z* 215.0 (M + 1).

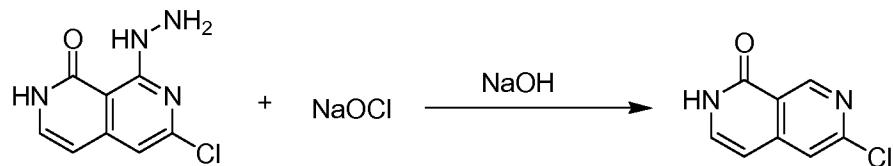
¹H NMR (300 MHz, DMSO-*d*6): δ 11.75 (s, 1H), 7.76 (s, 1H), 7.50 (t, J=6.6Hz, 1H), 6.52 (d, J=6.6Hz, 1H).

[0166] Step 5:



[0167] 6,8-dichloro-2,7-naphthyridin-1(2H)-one (3.0 g, 13.96 mmol) was dissolved in iPrOH (120 mL) to form a kind of suspension. The solution was cooled down to 0 °C in ice bath, and then hydrazine solution (5.6 g, 80%, 10eq) was added dropwise. The mixture was stirred at RT for 15 minutes, and then heated in oil bath at 55 °C for overnight. After the reaction mixture was cooled down to RT, filtered to get the solid directly, and then the solid was washed with 70 mL MeOH and dried by vaccum. The product 6-chloro-8-hydrazinyl-2,7-naphthyridin-1(2H)-one (yield ~98%) was used in the next step reaction directly without further purification.

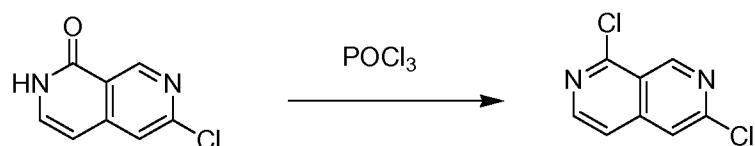
[0168] Step 6:



[0169] 6-chloro-8-hydrazinyl-2,7-naphthyridin-1(2H)-one (1.50 g, 7.12 mmol) was dissolved into MeCN (90 mL) to form a kind of suspension. 1N NaOH (17.80 mL, 2.5 eq) was added, and then equal amount of

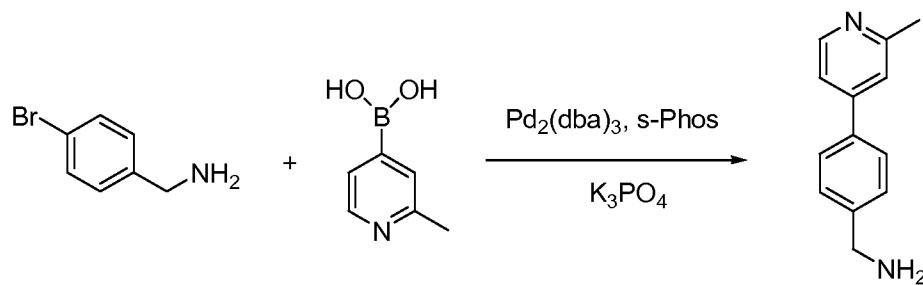
water (107.80 mL) was added into the mixture. The reaction mixture was heated at 50 °C, stirred till becoming the clear solution. The solution was cooled down to 0°C again, and NaOCl (11.05 g, 12% solution, 2.5 eq) was added dropwise, and then reaction was stirred at RT for overnight. After the reaction was done, the solution was cooled down to 0°C and then added into 1N HCl to neutralize (pH ~6). Precipitate was collected and the filtrate was extracted with 100mL x 2 EA. The organic layer was combined and dried over Na₂SO₄ and evaporated to give additional crude product. The combined solid material 6-chloro-2,7-naphthyridin-1(2H)-one (yield ~93%) was used in the next reaction without further purification. MS *m/z* 181.1 (M + 1).

[0170] Step 7:



[0171] 6-chloro-2,7-naphthyridin-1(2H)-one (400 mg, 2.2 mmol) was added in POCl₃ (20.0 mL) in a pressure tube. The reaction mixture was heated up to 160°C for 4 h to get a clear solution. The solution was cooled down to room temperature and poured in DCM, and added crushed ice slowly. Saturated NaHCO₃ was added into the mixture to neutralize HCl generated in the reaction. Vacuum to remove DCM and the left water solution was extracted by 100mL x 2 EA. The combined organic layers were washed with brine once, and dried by Na₂SO₄, and then evaporated under the vacuum to get the solid 1,6-dichloro-2,7-naphthyridine (yield ~73%) to use in the next step reaction without further purifications. MS *m/z* 199.0 (M + 1).

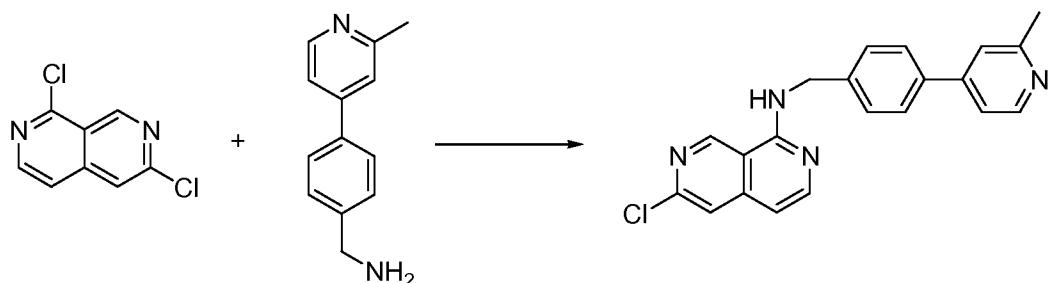
[0172] Step 8:



[0173] (4-bromophenyl)methanamine (1.00 g, 5.37 mmol) and 2-methylpyridin-4-yl-4-boronic acid (883.30 mg, 6.45 mmol) were dissolved in BuOH (10.0 mL) and water (2.0 mL). K₃PO₄ (2.28 g, 10.75 mmol), Pd₂(dba)₃ (120.20 mg, 0.27 mmol) and S-phos (220.70 mg, 0.54 mmol) were added in under N₂. The reaction mixture was sealed in a pressure tube and heated up to 125°C for 1h. After cooling down the reaction to RT, the mixture was poured into the water and extracted by 100mL x 3 EA. The combined

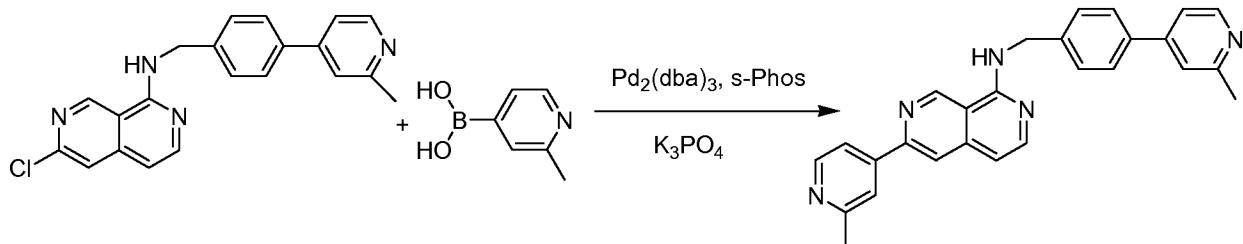
organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under the vacuum to give the crude product. The solid was purified by silicone gel column with 10% MeOH (containing $\sim 2\text{N NH}_3$) in DCM to get the pure (4-(2-methylpyridin-4-yl)phenyl)methanamine (yield $\sim 89\%$). MS m/z 199.1 ($\text{M} + 1$).

[0174] Step 9:



[0175] 1,6-dichloro-2,7-naphthyridine (160 mg, 0.80 mmol) and (4-(2-methylpyridin-4-yl)phenyl)methanamine (239.10 mg, 1.21 mmol) were dissolved in BuOH (5.0 mL) and heated up to 115°C for overnight. After the reaction was cooled down to RT, the organic solvent was removed under the vacuum. The crude product was purified by silicone gel flash chromatography with EA/Hexane (1:1) to get the solid N-(4-(2-methylpyridin-4-yl)benzyl)-6-chloro-2,7-naphthyridin-1-amine (yield $\sim 90\%$). MS m/z 361.1 ($\text{M} + 1$).

[0176] Step 10:

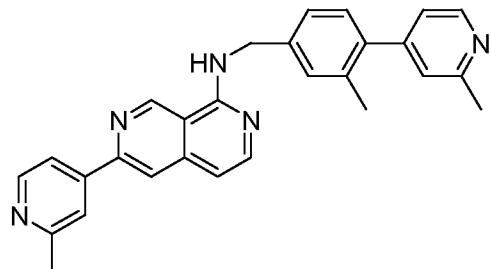


[0177] N-(4-(2-methylpyridin-4-yl)benzyl)-6-chloro-2,7-naphthyridin-1-amine (50.00 mg, 0.14 mmol) and 2-methylpyridin-4-yl-4-boronic acid (56.90 mg, 0.42 mmol) were dissolved in BuOH (3.0 mL) and water (0.6 mL). K_3PO_4 (88.20 mg, 0.028 mmol), $\text{Pd}_2(\text{dba})_3$ (6.20 mg, 0.014 mmol) and S-phos (11.40 mg, 0.011 mmol) were added into the mixture under N_2 . The reaction was sealed in a pressure tube and heated up to 105°C for overnight. After cooling down the reaction to RT, the mixture was poured in water and extracted by EA for three times. The combined organic layer was washed with brine, dried by Na_2SO_4 , and concentrated under the vacuum. The crude product was further purified by prep-TLC with 5% MeOH in DCM to get the final product N-(4-(2-methylpyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine (yield $\sim 70\%$). MS m/z 418.2 ($\text{M} + 1$). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 2.46 (s, 3H), 2.63 (s, 3H), 4.94 (d, $J = 5.10$ Hz, 2H), 5.94 (br, 1H), 6.97 (d, $J = 5.70$ Hz, 1H), 7.31 (d, $J = 4.20$ Hz, 1H),

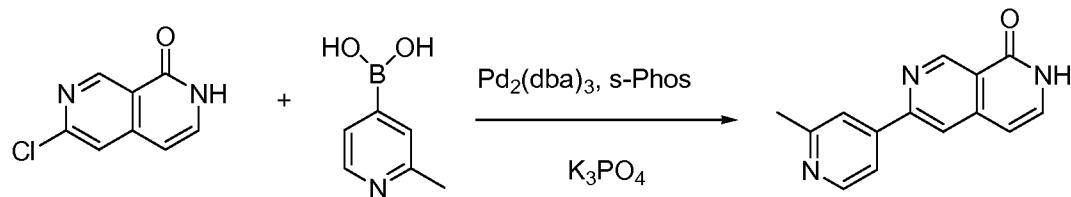
7.36 (s, 1H), 7.54 (d, J = 8.10 Hz, 2H), 7.63 (d, J = 8.40 Hz, 2H), 7.90 (s, 1H), 8.19 (d, J = 6.00 Hz, 1H), 8.22 (s, 1H), 8.51 (m, 2H), 9.08 (s, 1H), 9.30 (s, 1H).

Example 2

[0178] Synthesis of N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine (Compound No. 2)

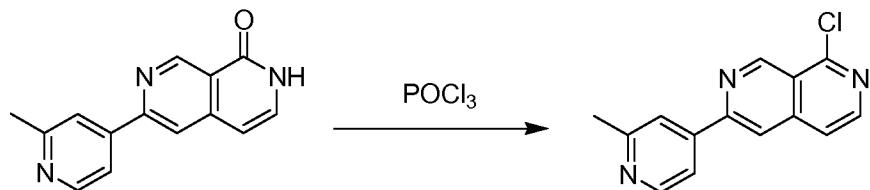


[0179] Step 1:



[0180] 6-chloro-2,7-naphthyridin-1(2H)-one (200 mg, 1.10 mmol) and 2-methylpyridin-4-yl-4-boronic acid (227.60 mg, 1.66 mmol) were dissolved in BuOH (5.0 mL) and water (1.0 mL). K_3PO_4 (705.20 g, 3.32 mmol), $Pd_2(dba)_3$ (49.60 mg, 0.22 mmol) and S-phos (91.00 mg, 0.11 mmol) were added under N_2 . The reaction mixture in the pressure tube was heated up to 130°C for 1h. After cooling down the reaction to RT, poured the mixture into the water, extracted by EA for three times. The combined organic layer was washed with brine, dried over Na_2SO_4 , concentrated under the vacuum to get the crude. The crude product was purified by column with 5% MeOH in DCM to get the final compound 6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1(2H)-one (yield ~ 61%). MS m/z 238.1 (M + 1).

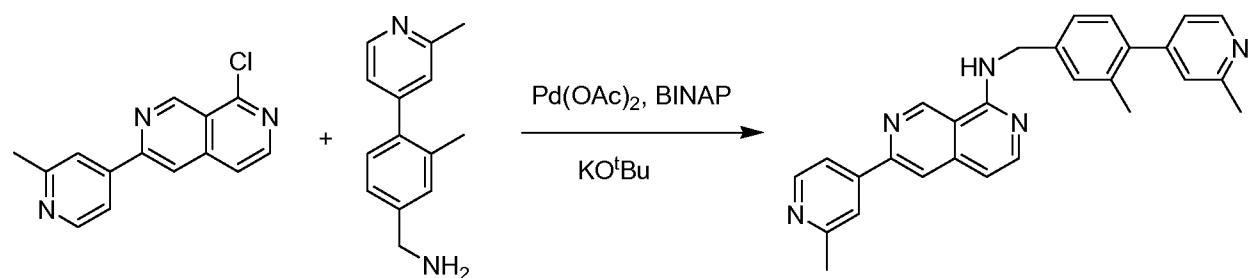
[0181] Step 2:



[0182] 6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1(2H)-one (150 mg, 0.63 mmol) was dissolved in $POCl_3$ (15.0 mL), the pressure tube was sealed and heated up to 160°C for 4 h. After cooling down the

reaction to RT, excessive POCl_3 was removed under vacuum. Crushed ice was slowly added into the mixture, and then added into NaHCO_3 to neutralize until $\text{pH} \sim 7.5$. Extracted the solution by EA three times, the combined organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The crude was purified by column with EA/Hexane (1:1) to get the compound 1-chloro-6-(2-methylpyridin-4-yl)-2,7-naphthyridine (yield $\sim 55\%$). MS m/z 256.1 ($\text{M} + 1$).

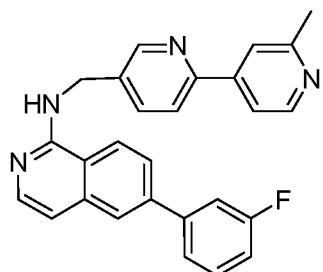
[0183] Step 3:



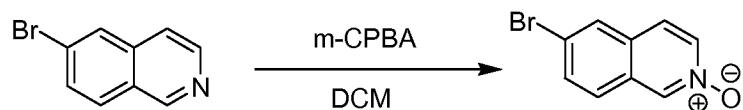
[0184] 1-chloro-6-(2-methylpyridin-4-yl)-2,7-naphthyridine (10.00 mg, 0.039 mmol) and (3-methyl-4-(2-methylpyridin-4-yl)phenyl)methanamine (10.00 mg, 0.047 mmol) were dissolved in Toluene (1.0 mL). KO^tBu (8.80 mg, 0.078 mmol), $\text{Pd}(\text{OAc})_2$ (0.90 mg, 0.0039 mmol) and BINAP (4.90 mg, 0.0078 mmol) was added into the mixture under N_2 . The reaction was heated up to 100°C for overnight. After cooling down the reaction to RT, poured the mixture into the water, extracted by EA for three times. The combined organic layer was washed with brine, dried over Na_2SO_4 , then concentrated under vacuum. The crude product was purified by prep-TLC by EA/Hexane (4:1) to get N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridine-1-amine (8.8mg, yield $\sim 52\%$). ^1H NMR (300 MHz, CDCl_3): δ 2.31 (s, 3H), 2.63 (s, 3H), 2.70 (s, 3H), 4.91 (d, $J = 5.10$ Hz, 2H), 5.88 (br, 1H), 7.00 (d, $J = 5.40$ Hz, 1H), 7.08 (d, $J = 5.10$ Hz, 1H), 7.12 (s, 1H), 7.22 (d, $J = 7.50$ Hz, 1H), 7.36 (m, 2H), 7.77 (d, $J = 4.50$ Hz, 1H), 7.88 (s, 1H), 7.98 (s, 1H), 8.24 (d, $J = 6.00$ Hz, 1H), 8.53 (d, $J = 4.80$ Hz, 1H), 8.64 (d, $J = 5.40$ Hz, 1H), 9.31 (s, 1H). MS m/z 432.2 ($\text{M} + 1$).

Example 3

[0185] Synthesis of 6-(3-fluorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)isoquinolin-1-amine (Compound No. 3)

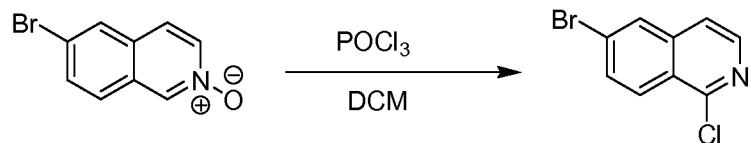


[0186] Step 1:



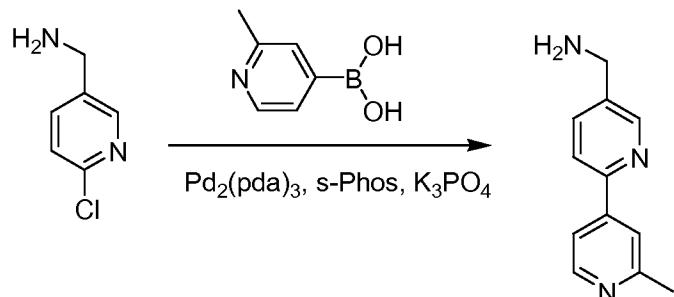
[0187] 6-bromoisoquinoline (1.80g, 8.66 mmol) was dissolved in DCM (40 mL), after cooling down the reaction to 0°C m-CPBA (2.30 g, 1.3 eq, 77% max) was added slowly in small portion. The reaction was warmed up to RT to become a kind of white suspension. In 4 hours, 100mL DCM was added into the solution, and washed with saturated Na_2CO_3 solution, water and brine. The separated organic layer was dried over Na_2SO_4 and removed under the vacuum to get the yellow solid N-oxide 6-bromoisoquinoline without further purification (1.82 g, yield ~93%).

[0188] Step 2:



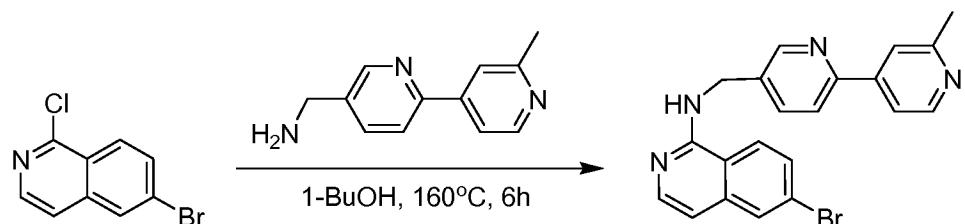
[0189] N-oxide 6-bromoisoquinoline (1.82 g, 8.12 mmol) was dissolved in dry DCM (80 mL), POCl_3 (1.12 ml, 1.5 eq) was added dropwise at RT. The reaction was heated to 45°C for 2 hours. After cooling down the reaction to RT, DCM and excessive POCl_3 were removed under the vacuum. The crude was redissolved into 100mL DCM and was washed by saturated Na_2CO_3 , water and brine. The separated organic layer was dried over Na_2SO_4 , and concentrated to give brown solid. The crude was purified by flash column using 2% MeOH in DCM to get the pale yellow solid 6-bromo-1-chloroisoquinoline (1.27g, yield ~65%). MS m/z 242.0 (M + 1).

[0190] Step 3:



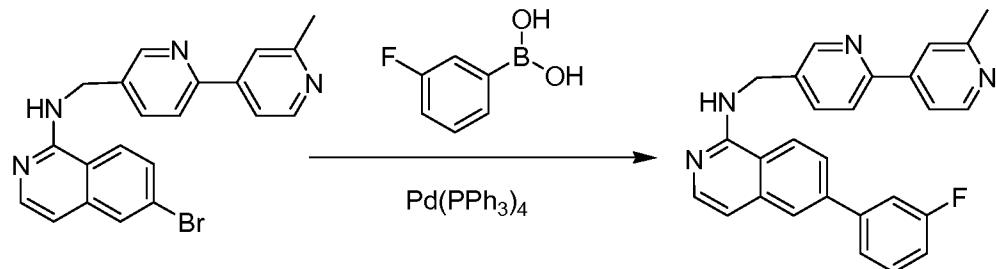
[0191] (6-chloropyridin-3-yl)methanamine (300mg, 2.1 mmol) and 2-methylpyridin-4-ylboronic acid (345mg, 2.52 mmol) were dissolved in a pressure tube with n-butanol (10 mL) and water (2 mL). K_3PO_4 (893mg, 4.2mmol), $\text{Pd}_2(\text{dba})_3$ (96.3 mg, 0.105 mmol), and S-phos (86.4 mg, 0.21mmol) were added under the nitrogen protection. The reaction was heated to 125°C for 30 minutes and then cooled down to room temperature. The solution was pull in water and extracted by EA for three times. The combined organic layer was washed by brine and dried over Na_2SO_4 , and concentrated under the vacuum. The crude was further purified by flash chromatography with 10% MeOH (containing ~2N NH_3) in DCM to get the pure (6-(2-methylpyridin-4-yl)pyridin-3-yl)methanamine (0.19g, yield ~45%). MS m/z 200.1 (M + 1).

[0192] Step 4:



[0193] 6-bromo-1-chloroisouquinoline (100mg, 0.41mmol) and (6-(2-methylpyridin-4-yl)pyridin-3-yl)methanamine (165mg, 0.82mmol) were dissolved in 0.5mL n-BuOH in a sealed tube. The reaction was heat up to 160°C for 6h and cooled down to RT. The crude was purified by flash chromatography using 8% MeOH (containing ~2N NH_3) in DCM to get the pure 6-bromo-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)isoquinolin-1-amine (116mg, ~70%). MS m/z 405.2 (M + 1).

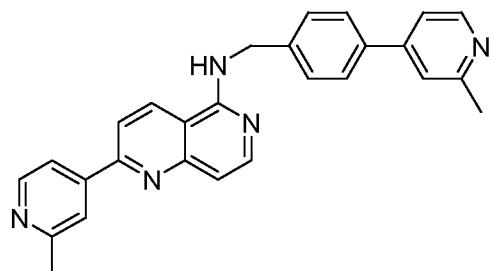
[0194] Step 5:



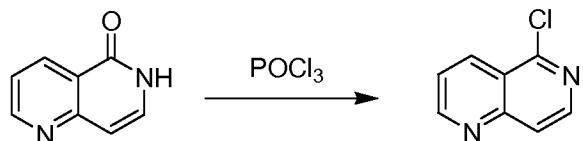
[0195] 6-bromo-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)isoquinolin-1-amine (20mg, 0.05mmol), 3-fluorophenylboronic acid (10.5mg, 0.075mmol), Na_2CO_3 (21mg, 0.2mmol) and Tetrakis(triphenylphosphine)palladium (5.8mg, 0.005mmol) were added in a pressure tube. Dioxane/water (3:1, 2mL) was added into the tube and heated to 125°C for 10 minutes. After cooling down the reaction to RT, the solution was diluted by 50mL water and extracted by EA for 3 times. The combined organic layer was dried over Na_2SO_4 , and concentrated under the vacuum. The crude was further purified by flash chromatography with 10% MeOH (containing ~2N NH3) in DCM to get the pure 6-(3-fluorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)isoquinolin-1-amine (15.8mg, ~75%). ^1H NMR (400 MHz, CDCl_3): δ 2.71 (s, 3H), 5.00 (d, $J=5.6\text{Hz}$, 2H), 7.32-7.38 (m, 2H), 7.59-7.65 (m, 1H), 7.75-7.83 (m, 3H), 8.10 (d, $J=8.4\text{Hz}$, 1H), 8.21 (d, $J=8.8\text{Hz}$, 1H), 8.27-8.31 (m, 2H), 8.39 (s, 2H), 8.72 (d, $J=8.8\text{Hz}$, 1H), 8.79 (d, $J=6.0\text{Hz}$, 1H), 8.91 (d, $J=1.6\text{Hz}$, 1H), 10.02 (s, 1H). MS m/z 421.2 ($M + 1$).

Example 4

[0196] Synthesis of N-(4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)-1,6-naphthyridin-5-amine (Compound No. 4)

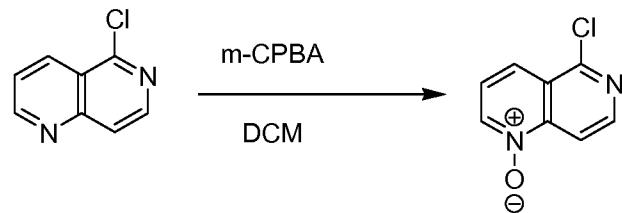


[0197] Step 1:



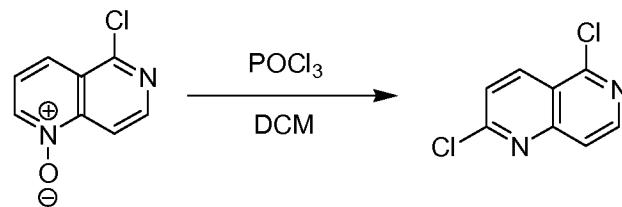
[0198] 1,6-naphthyridin-5(6H)-one (2.9 g, 19.84 mmol) was dissolved in POCl_3 (40 mL) and heated up to 100°C for 24 h. After cooling down the reaction to room temperature, the excessive POCl_3 was removed under the vacuum. Small amount crushed ice in saturated Na_2CO_3 solution was added slowly, and lots of bubbles and solid came out. The solid was filtered, and the solution was extracted by EA for 3 times. The combined organic layer was dried over Na_2SO_4 , and concentrated under the vacuum. The combined solid was further dried under the vacuum to get 5-chloro-1,6-naphthyridine without further purification (2.6g, yield ~80%). MS m/z 165.1 (M + 1).

[0199] Step 2:



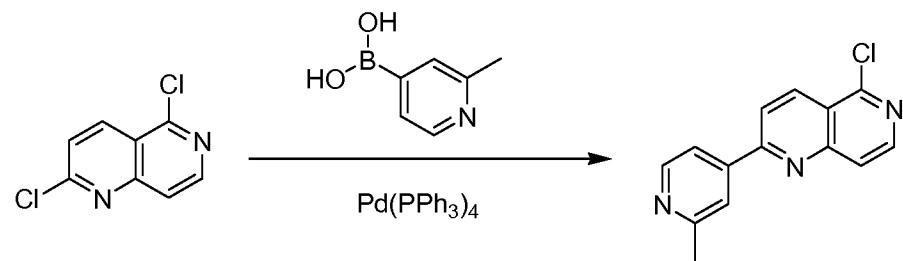
[0200] 5-chloro-1,6-naphthyridine (1.5 g, 9.11 mmol) was dissolved in DCM (45 mL) and cooled down by ice bath, m-CPBA (3.7 g, 2 eq, 77% max) was added in small portion and slowly. The reaction was warmed up to RT and continued for 3 hours. 100mL more DCM was added into the solution, and washed with saturated Na_2CO_3 solution, water and brine. The organic layer was dried over Na_2SO_4 , and concentrated under the vacuum to get yellow solid N-oxide 5-chloro-1,6-naphthyridine without further purification (1.25 g, yield ~76%).

[0201] Step 3:



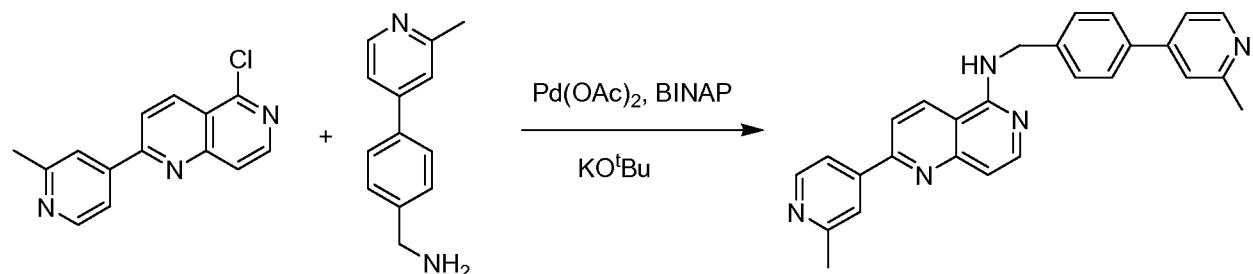
[0202] N-oxide 5-chloro-1,6-naphthyridine (1.2g, 6.64mmol) was dissolved in dry DCM (30 mL), Et3N (1.85 mL, 13.29mmol) was added and followed by dropwise adding POCl_3 (0.93mL, 9.97 mmol) in 5mL dry DCM. The reaction was heated to 48°C for 2 hours. 100mL more DCM was added into the solution, and washed with saturated Na_2CO_3 solution, water and brine. The organic layer was dried over Na_2SO_4 , and concentrated under the vacuum to get the yellow solid. The crude was further purified by silicon column using EA/Hexane (1:4) to get white solid 2,5-dichloro-1,6-naphthyridine (0.6g, yield ~45%). MS m/z 199.0 (M + 1)

[0203] Step 4:



[0204] 2,5-dichloro-1,6-naphthyridine (200mg, 1.0mmol), 2-methylpyridin-4-yl-4-boronic acid (137mg, 1.0mmol), Na₂CO₃ (424mg, 4.0mmol) and Tetrakis(triphenylphosphine)palladium (116mg, 0.1mmol) were added in a flask, dioxane 16mL and water 4mL were further added. The reaction was stirred very well and heated to 90°C for 4 hours. After cooling down the reaction to RT, the solution was diluted by 100mL water and extracted by EA for 3 times. The combined organic layer was dried over Na₂SO₄, and concentrated under the vacuum. The crude was further purified by flash chromatography with EA/Hexane (1:1) to get the solid 5-chloro-2-(2-methylpyridin-4-yl)-1,6-naphthyridine (143mg, yield ~56%). MS m/z 256.1 (M + 1)

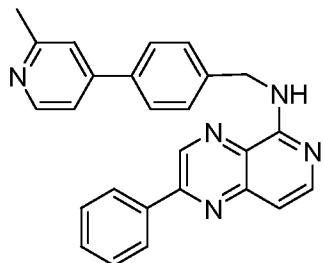
[0205] Step 5:



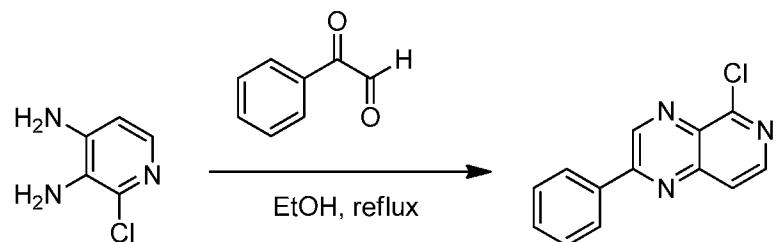
[0206] 5-chloro-2-(2-methylpyridin-4-yl)-1,6-naphthyridine (20.00 mg, 0.078 mmol) and (4-(2-methylpyridin-4-yl)phenyl)methanamine (25 mg, 0.118 mmol) were dissolved in Toluene (2.0 mL). KO^tBu (13.2 mg, 0.118 mmol), Pd(OAc)₂ (2.7 mg, 0.012 mmol) and BINAP (15.0 mg, 0.024 mmol) were added into the mixture under N₂. The reaction was heated up to 100°C for overnight. After cooling down the reaction to RT, poured the mixture into the water, extracted by EA for three times. The combined organic layer was washed with brine, dried over Na₂SO₄, then concentrated under vacuum. The crude product was purified by prep-TLC by 8% MeOH in DCM to N-(4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)-1,6-naphthyridin-5-amine (31mg, yield ~61%). ¹H NMR (400 MHz, DMSO-d₆): δ9.12 (d, J=8.8Hz, 1H), 8.77-8.83 (m, 2H), 8.49 (d, J=8.4Hz, 1H), 8.40 (s, 1H), 8.31 (d, J=6.4Hz, 1H), 8.21 (s, 1H), 8.11 (d, J=5.6Hz, 1H), 8.06 (d, J=6.4Hz, 1H), 7.99 (d, J=8.4Hz, 2H), 7.65 (d, J=8.4Hz, 2H), 7.23 (d, J=6.4Hz, 1H), 5.76 (s, 1H), 4.93 (d, J=5.6Hz, 2H), 2.72 (s, 6H). MS m/z 432.2 (M + 1).

Example 5

[0207] Synthesis of N-(4-(2-methylpyridin-4-yl)benzyl)-2-phenylpyrido[4,3-b]pyrazin-5-amine (Compound No. 5)

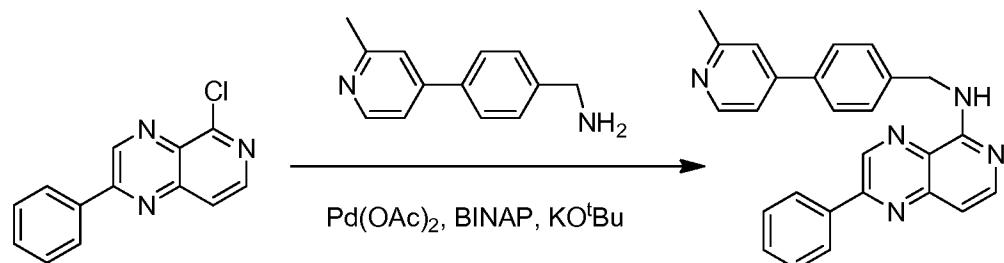


[0208] Step 1:



[0209] To 20mL of ethanol was added phenyl glyoxal monohydrate (940mg, 6.99mmol) and 2-chloro-3,4-diaminopyridine (1000mg, 6.99mmol). The mixture was refluxed for overnight. After cooling down the reaction, the crude precipitated product was filtered and washed with 15mL ethanol and dried under vacuum to get 5-chloro-2-phenylpyrido[3,4-b]pyrazine without further purification (1.28g, yield ~76%), MS m/z 241.0 (M + 1); 1H NMR (300 MHz, DMSO-d6): δ 9.82 (s, 1H), 8.64 (d, J=6.0Hz, 1H), 8.38-8.43 (m, 2H), 8.07 (d, J=6.0Hz, 1H), 7.64-7.68 (m, 3H).

[0210] Step 2:



[0211] N-(4-(2-methylpyridin-4-yl)benzyl)-2-phenylpyrido[3,4-b]pyrazin-5-amine (50mg, 0.21mmol) and (4-(2-methylpyridin-4-yl)phenyl)methanamine (42mg, 0.21mmol) were dissolved in Toluene (4.0 mL). KOtBu (24 mg, 0.21 mmol), Pd(OAc)2 (4.5 mg, 0.021 mmol) and BINAP (26.4 mg, 0.042 mmol) was added into the mixture under N2. The reaction was heated up to 100°C for overnight. After cooling

down the reaction to RT, poured the mixture into the water, extracted by EA for three times. The combined organic layer was washed with brine, dried over Na_2SO_4 , then concentrated under vacuum. The crude product was purified by flash chromatography using 7% MeOH in DCM to get N-(4-(2-methylpyridin-4-yl)benzyl)-2-phenylpyrido[4,3-b]pyrazin-5-amine (61mg, yield ~72%). MS m/z=404.2 (M+1); ^1H NMR (400MHz, DMSO-d6) δ 9.53 (s, 1H), 8.77 (d, $J=6.4\text{Hz}$, 1H), 8.35-8.39 (m, 2H), 8.21 (s, 1H), 8.11 (d, $J=6.0\text{Hz}$, 1H), 8.07 (d, $J=6.4\text{Hz}$, 1H), 7.96 (d, $J=8.4\text{Hz}$, 2H), 7.60-7.65 (m, 5H), 7.14 (d, $J=6.0\text{Hz}$, 1H), 5.76 (s, 1H), 4.90 (d, $J=6.4\text{Hz}$, 2H), 2.71 (s, 3H).

Example 6

[0212] WNT Pathway Reporter Gene Assay

[0213] Materials and Methods: NIH3T3 mouse fibroblast cells (American Type Culture Collection, Manassas, VA) were transfected with a plasmid containing a luciferase gene driven by 5 copies of TCF elements. Stable cells selected with 1 $\mu\text{g}/\text{mL}$ of Zeocin (Gibco/Invitrogen, Carlsbad, CA) are cultured in Dulbecco's modified Eagle's medium (Invitrogen, Carlsbad, CA) supplemented with 10% FBS (Invitrogen), 50 unit/mL penicillin and 50 $\mu\text{g}/\text{mL}$ of streptomycin (Invitrogen) at 37°C with 5% CO₂ in air atmosphere. Suspension HEK293 cells (ATCC) were transfected with a plasmid containing full-length human WNT-3a cDNA sequence driven by a CMV promoter, and stable cells were selected in FreeStyle 293 medium (Invitrogen) supplemented with 100ug/mL G418.

[0214] The NIH3T3 TCF-Luc cells and 293 WNT3a cells were co-cultured in a 96-well plate with DMEM medium supplemented with 0.5% FBS. After 16 hours, the firefly luciferase activities are measured with the Steady-Glo™ Luciferase Assay System (Promega). The cells were treated with different concentrations of compounds of this invention during the co-culture. The IC₅₀s were defined as the concentration when the compounds reduce the luminescence intensity by 50%. To normalize for cell quantity and viability, CellTiter Glo assay is next performed in a duplicate plate.

[0215] All compounds presented in the patent have IC₅₀ < 5 μM in WNT pathway reporter gene assay. Selective examples were listed in Table 2 below.

Table 2

Compound No.	IC ₅₀ (μM)
1	<0.003
2	<0.003
3	0.010

4	0.005
5	0.070
9	0.010
14	0.003
16	0.015
20	0.050
22	0.005
23	0.020
28	<0.003
33	0.050
35	<0.003
37	0.020
39	0.070
47	1.25
50	0.035
61	0.005
63	0.005
68	0.025
69	0.015
70	<0.003
75	0.005
84	0.015
96	0.001
97	0.001
104	0.005

108	0.008
110	0.002

Example 7

[0216] Mechanistic Studies of the WNT Pathway Inhibitors

[0217] Compounds that inhibited the TCF reporter gene activity induced by the co-cultured Wnt-3a cells in the primary assay were followed up in a mechanistic study to identify the point of action of the compounds. Two different of activators were assessed, one with purified recombinant Wnt-3a protein (StemRD Inc., Burlingame, CA), the other with a GSK-3b inhibitor 6-bromoindirubin-3'-oxime (StemRD Inc., Burlingame, CA).

[0218] Results of such mechanistic studies showed that some of the active compounds in this invention inhibit WNT pathway activation at a point before the WNT-3a interaction with the receptors, as they did not inhibit the TCF reporter gene activation by recombinant WNT-3a protein. The candidates of such action include, but are not limited to wntless/evenness interrupted (Wls/Evi), porcupine (Porcn), and Vps35p. The direct target of the active compounds is most likely to be Porcn because transfection of Porcn into WNT-3a expressing cells abolished the inhibitory effect of the compounds

Example 8

[0219] Efficacy of CGX in Myocardial Infarction Animal Model

[0220] Model for myocardial infarction (MI): A model for myocardial infarction was created in mice by left coronary artery ligation, which produced infarcts in the anterolateral wall of the left ventricle (LV).

[0221] Drug Treatment: Starting from 1 day prior to the ligation, 2.5 mg/kg CGX was given intraperitoneally once daily for 28 days.

[0222] Data in Figures 1, 2 and 3 show that cardiac function measured by echocardiography as fractional shortening at day 14 or 28 after MI was significantly strengthened by CGX treatment. CGX treatment also improved animal survival after MI, likely through improved cardiac function and reduced the size of infarct area. Histology examination of the heart tissue for collagen also indicated that CGX treatment significantly reduced myocardial fibrosis as compared to Vehicle control after 28 days.

Example 9

[0223] Efficacy of CGX in Animal Model for Lung Fibrosis

[0224] Animal Model for Lung fibrosis: Mouse model of lung fibrosis was established in Balb/c mice by intratracheal administration of bleomycin (10 mg/g body weight). Starting from 1 day prior to bleomycin administration, animal were treated with WNT inhibitor CGX compound orally at 10mg/kg once daily or with the same volume of vehicle. Treatment was repeated daily for 15 days. Bronchoalveolar lavage fluid (BALF) and lung tissues were harvested at day 15 for protein measurement and histology, respectively.

[0225] Collagen Assay: The Sircol collagen assay was performed following the manufacturer's instructions. Samples were from BALF.

[0226] Histology Analysis: Lung tissues were formalin-fixed, dehydrated and then embedded with paraffin. The H.E. staining, Masson Trichrome staining and immunohistochemical staining for alpha smooth muscle actin (a-SMA) were performed on paraffin sections.

[0227] Data in Figures 5, 6, 7, 8 and 9 show that CGX treatment improved animal survival after bleomycin-induced lung fibrosis. Amounts of total protein and collagen in BALF were significantly reduced by CGX treatment, indicating reduction of fibrogenic response. Histology examination of the lung tissue of showed improved overall lung structure, reduced collagen deposition and decreased myofibroblast infiltration with CGX treatment.

Example 11

[0228] Efficacy of CGX in Cardiac Hypertrophy Animal Model

[0229] Model for cardiac hypertrophy: A model for load-induced cardiac hypertrophy was created in mice by coarctation of the transverse aorta (Webpage: www.ncbi.nlm.nih.gov/pubmed/18287666).

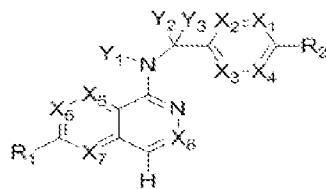
[0230] Drug Treatment: 2.5 mg/kg CGX was given intraperitoneally once daily for 28 days.

[0231] Data in Fig. 10 shows that the weight of the heart was reduced by CGX treatment compared with vehicle control. Data in Fig. 11 shows that CGX treatment also improved animal survival after coarctation of the transverse aorta, likely through improved cardiac function.

Claims

1. A method for treating a fibrosis related disease in a subject that is in need of such treatment, comprising:

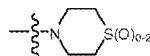
administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound of the following formula:



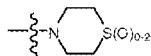
or a physiologically acceptable salt thereof, wherein

X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈ are independently CR₄ or N;

Y₁ is hydrogen or CR₄; Y₂, Y₃ are independently hydrogen, halo or CR₃;

R₁ is morpholinyl, piperazinyl, quinolinyl,  , aryl, C₁₋₆ heterocycle, 5 or 6

membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R₂ is hydrogen, halo, morpholinyl, piperazinyl, quinolinyl,  , aryl, C₁₋₆ heterocycle, 5

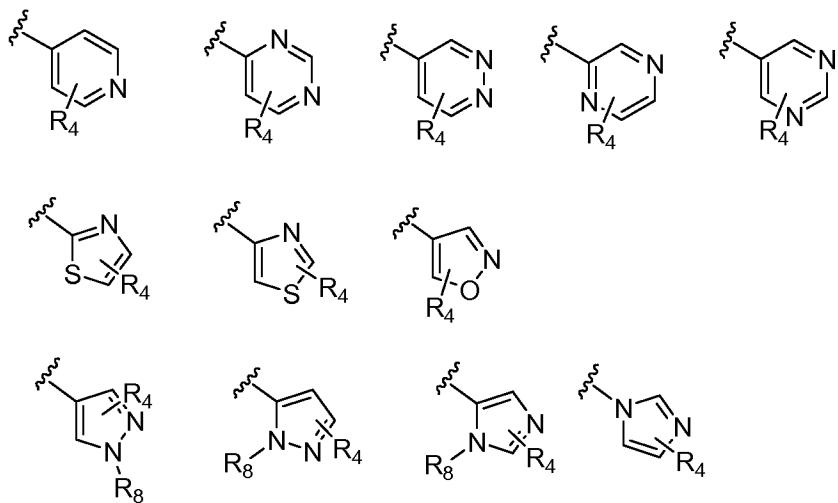
or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R₃ is hydrogen, halo, cyano, C₁₋₆ alkyl, C₁₋₆ alkoxy optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R₄ is hydrogen, halo, C₁₋₆ alkoxy, -S(O)₂R₅, -C(O)OR₅, -C(O)R₅, -C(O)NR₆R₇, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, each of which can be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R₅, R₆ and R₇ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano.

2. The method of claim 1, wherein said 5 or 6 membered heteroaryl is selected from:



wherein,

R_4 is hydrogen, halo, 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 or C_{2-6} alkynyl, each of which can be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R_5 , R_6 and R_7 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, each of which may be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano; and

R_8 is hydrogen or C_{1-6} alkyl.

3. The method of claim 1 or 2, wherein R_1 and R_2 is independently substituted with 1 or 2 R_4 groups.

4. The method of any one of claims 1-3, wherein atom in any said substituent groups is H, ^{2}H , ^{3}H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{35}S , ^{18}F , ^{36}I and/or ^{123}I .

5. The method of any one of claims 1-3, wherein said compound is selected from N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;

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

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

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

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

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

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

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

N-((6-(5-methylpyridin-3-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
7-phenyl-N-((6-(pyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyridin-3-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyridin-2-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyridazin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyrazin-2-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-phenyl-N-((6-(pyrimidin-5-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-fluoropyridin-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
N-((6-(4-methyl-1H-imidazol-1-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
N-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-7-phenylquinazolin-4-amine;
N-((5-(6-methylpyridin-3-yl)pyridin-2-yl)methyl)-7-phenylquinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-phenylquinazolin-4-amine;
N-(4-(2-fluoropyridin-4-yl)benzyl)-7-phenylquinazolin-4-amine;
N-benzyl-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-methylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-methoxybenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-fluorobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-chlorobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-bromobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-(trifluoromethyl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
4-((7-(2-methylpyridin-4-yl)quinazolin-4-ylamino)methyl)benzonitrile; N-(4-morpholinobenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-phenylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(3-fluoro-4-phenylbenzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-(3-fluorophenyl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
7-(3-fluorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;

7-(3-chlorophenyl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-m-tolylquinazolin-4-amine;
3-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)benzonitrile;
4-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)benzonitrile;
7-(2-methylpyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(6-methylpyridin-3-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(5-methylpyridin-3-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-2-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-3-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridin-4-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyridazin-4-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyrazin-2-yl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(pyrimidin-5-yl)quinazolin-4-amine;
7-(2-fluoropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(2-(trifluoromethyl)pyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(2-methoxypyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(3-methylpyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-morpholinoquinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(piperidin-1-yl)quinazolin-4-amine;
7-(4-methylpiperazin-1-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
1-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)piperazin-1-yl)ethanone;
4-(4-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)amino)quinazolin-7-yl)thiomorpholine 1,1-dioxide;
7-(1,2,3,6-tetrahydropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(1,2,3,6-tetrahydropyridin-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
1-(4-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methylamino)quinazolin-7-yl)piperidin-1-yl)ethanone;
N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-7-(4-(methylsulfonyl)piperazin-1-yl)quinazolin-4-amine;

7-(1-methyl-1H-pyrazol-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
7-(isoxazol-4-yl)-N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)quinazolin-4-amine;
N-((6-(2-methylpyridin-4-yl)pyridin-3-yl)methyl)-7-(thiazol-2-yl)quinazolin-4-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-7-(2-methylpyridin-4-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-(pyrazin-2-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-(2-fluoropyridin-4-yl)quinazolin-4-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-7-morpholinoquinazolin-4-amine;
2-(3-fluorophenyl)-N-(4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
2-(3-fluorophenyl)-N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)pyrido[3,4-b]pyrazin-5-amine;
2-(3-fluorophenyl)-N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-2-(3-fluorophenyl)pyrido[3,4-b]pyrazin-5-amine;
2-(2-methylpyridin-4-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)pyrido[3,4-b]pyrazin-5-amine;
N-((2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-2-(2-methylpyridin-4-yl)pyrido[3,4-b]pyrazin-5-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
(S)-6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
(R)-6-(2-methylmorpholino)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
1-(4-(8-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-1-yl)ethanone;
6-(1H-imidazol-1-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
6-(4-methyl-1H-imidazol-1-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-6-(1H-tetrazol-5-yl)-2,7-naphthyridin-1-amine;
6-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
6-(1-methyl-1H-pyrazol-3-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;

N-(4-(2-methylpyridin-4-yl)benzyl)-6-(thiazol-5-yl)-2,7-naphthyridin-1-amine;
N-(4-(2-methylpyridin-4-yl)benzyl)-6-(oxazol-5-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(5-methylpyridin-3-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
N-((3-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-6-(5-fluoropyridin-3-yl)-2,7-naphthyridin-1-amine;
N-(3-methyl-4-(2-methylpyridin-4-yl)benzyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
N-(3-fluoro-4-(2-methylpyridin-4-yl)benzyl)-6-(pyrazin-2-yl)-2,7-naphthyridin-1-amine;
methyl 4-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazine-1-carboxylate;
4-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-2-one;
2-(4-((4-(2-methylpyridin-4-yl)benzyl)amino)-2,7-naphthyridin-3-yl)piperazin-1-yl)acetonitrile;
2-methyl-4-((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)phenyl)pyridine 1-oxide;
6-(2-chloropyridin-4-yl)-N-((2',3-dimethyl-[2,4'-bipyridin]-5-yl)methyl)-2,7-naphthyridin-1-amine;
6-(2-chloropyridin-4-yl)-N-(4-(2-methylpyridin-4-yl)benzyl)-2,7-naphthyridin-1-amine;
2'-methyl-4-((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)-2H-[1,4'-bipyridin]-2-one;
2-(2-methylpyridin-4-yl)-5-(((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)benzonitrile;
N-(3-methoxy-4-(2-methylpyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
N-((3-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)methyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;
2'-methyl-5-(((6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-yl)amino)methyl)-[2,4'-bipyridine]-3-carbonitrile;
N-(4-(2-(difluoromethyl)pyridin-4-yl)benzyl)-6-(2-methylpyridin-4-yl)-2,7-naphthyridin-1-amine;

6. The method of any one of claims 1 to 5, wherein said pharmaceutical composition comprising at least one pharmaceutically acceptable carrier or diluent.

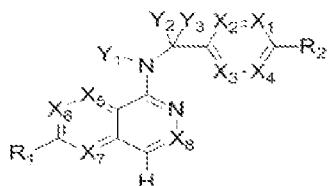
7. The method of claim 6, wherein said pharmaceutical composition is oral composition, injectable composition or suppository.

8. The method of claim 7, wherein said pharmaceutical composition is oral composition and is tablet or gelatin capsule.

9. The method of claim **8**, wherein said pharmaceutical composition comprises diluents, lubricants, binders, disintegrants, or additives, or combination thereof.
10. The method claim **9**, wherein the diluent is lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine.
11. The method of claim **9** or **10**, wherein said lubricant is silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol.
12. The method of claim **9** or **10**, wherein said binder is magnesium aluminum silicate, starch paste, gelatin, tragamayth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone.
13. The method of claim **9** or **10**, wherein said disintegrant is starches, agar, alginic acid or its sodium salt, or effervescent mixtures.
14. The method of claim **9** or **10**, wherein the additive is absorbent, colorant, flavor and/or sweetener.
15. The method of claim **7**, wherein said pharmaceutical composition is injectable composition and is aqueous isotonic solution or suspension.
16. The method of claim **7**, wherein said pharmaceutical composition is suppository and is prepared from fatty emulsions or suspensions.
17. The method of claim **9**, wherein said pharmaceutical composition further comprises adjuvants, wherein the adjuvants are preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers.
18. The method of claim **17**, wherein the pharmaceutical composition further contains solubilizers, stabilizers, tonicity enhancing agents, buffers and/or preservatives.
19. The method of claim **18**, wherein said pharmaceutical composition is for topical application and is aqueous solution, ointment, cream or gel.
20. The method of any one of claims **1-19**, wherein the therapeutically effective amount of the compound is about 0.03 to 2.5 mg/kg per body weight at daily dosages.
21. The method of claim **20**, wherein the therapeutically effective amount of the compound from about 0.5 mg to about 500 mg for humans.
22. The method of any one of claims **1-21**, wherein said pharmaceutical composition is administrated enterally, orally, parenterally, topically or in a nasal or suppository form.

23. The method of any one of claims 1- 22, wherein said fibrosis disease is myocardial remodeling including myocardial fibrosis and hypertrophic growth after MI, lung fibrosis, liver fibrosis, skin fibrosis, or renal fibrosis.

24. Use of a compound for the manufacture of a medicament for treating fibrosis disease, wherein said compound is of the following formula:



or a physiologically acceptable salt thereof, wherein

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

Y_1 is hydrogen or CR_4 ; Y_2, Y_3 are independently hydrogen, halo or CR_3 ;

R_1 is morpholinyl, piperazinyl, quinolinyl, , aryl, C_{1-6} heterocycle, 5 or 6

membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R_2 is hydrogen, halo, morpholinyl, piperazinyl, quinolinyl, , aryl, C_{1-6} heterocycle, 5

or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R_3 is hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkoxy optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

R_4 is hydrogen, halo, 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 or C_{2-6} alkynyl, each of which can be optionally substituted with halo, amino, hydroxyl, alkoxy or cyano;

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

25. The use of claim 24, wherein said fibrosis disease is myocardial remodeling including myocardial fibrosis and hypertrophic growth after MI, lung fibrosis, liver fibrosis, skin fibrosis, or renal fibrosis.

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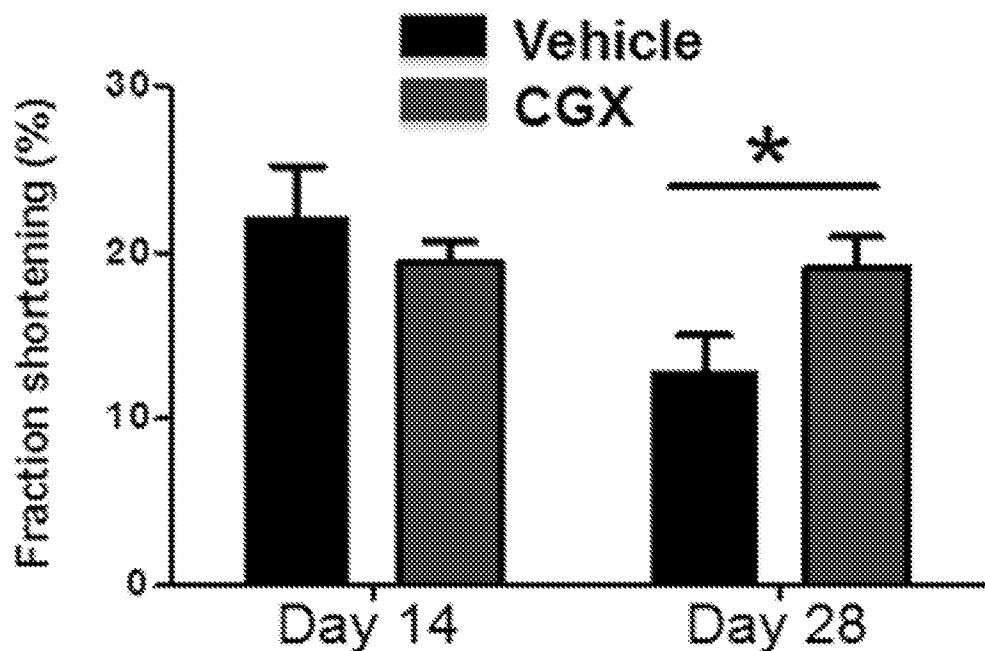


FIG. 1

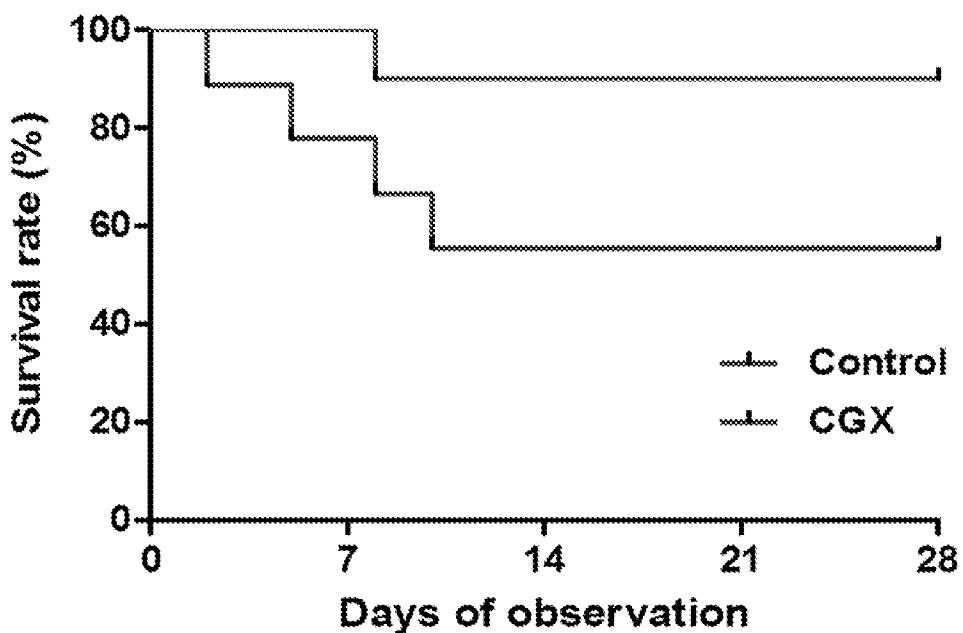


FIG. 2

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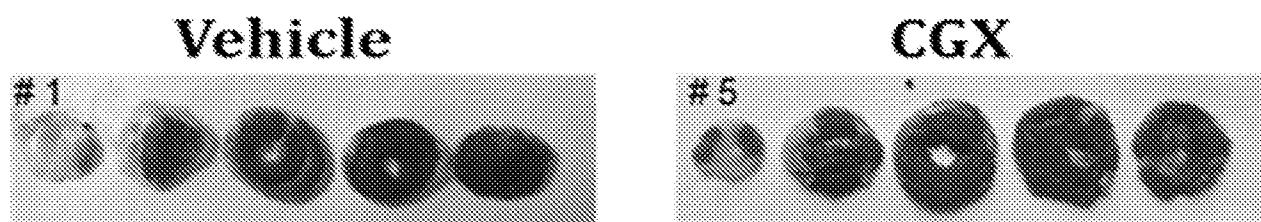


FIG. 3

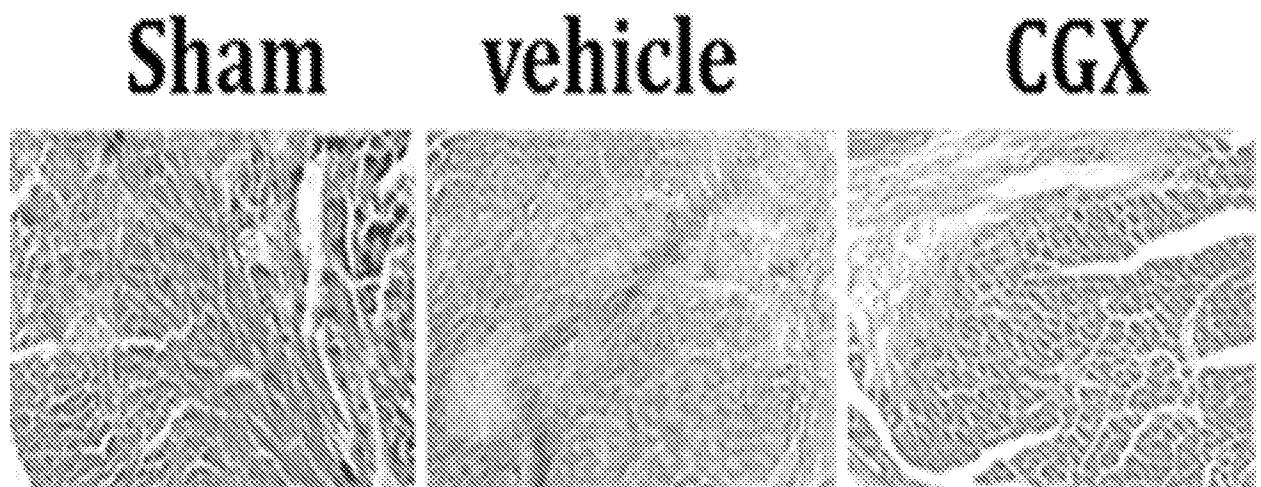


FIG. 4

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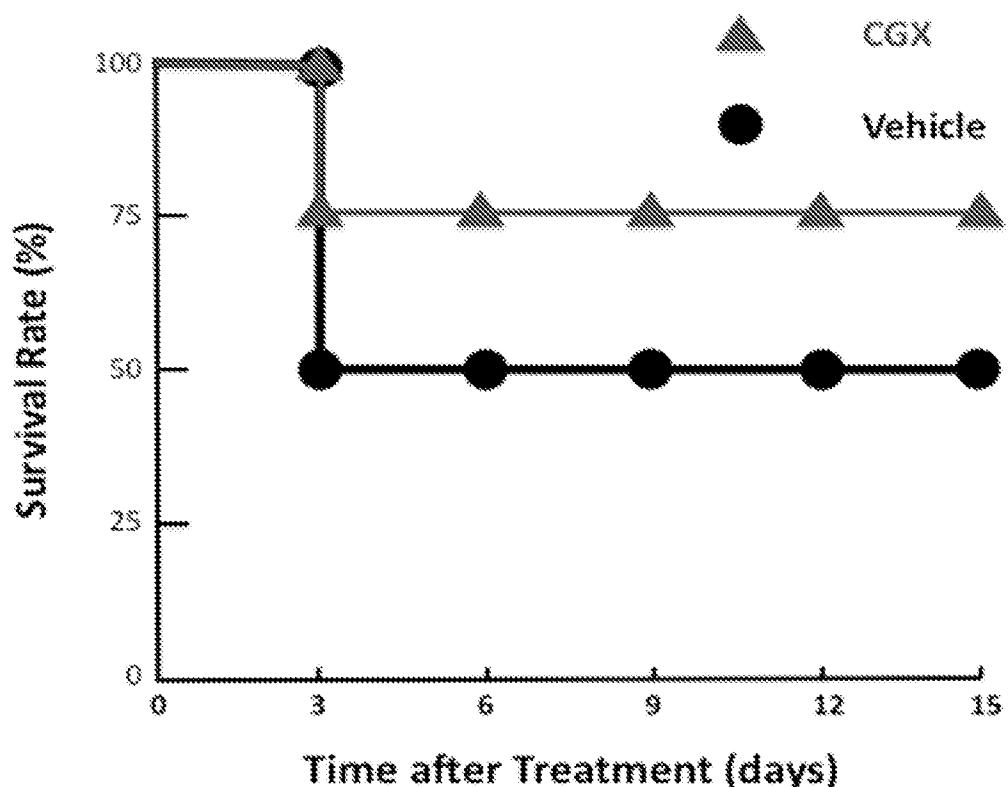


FIG. 5

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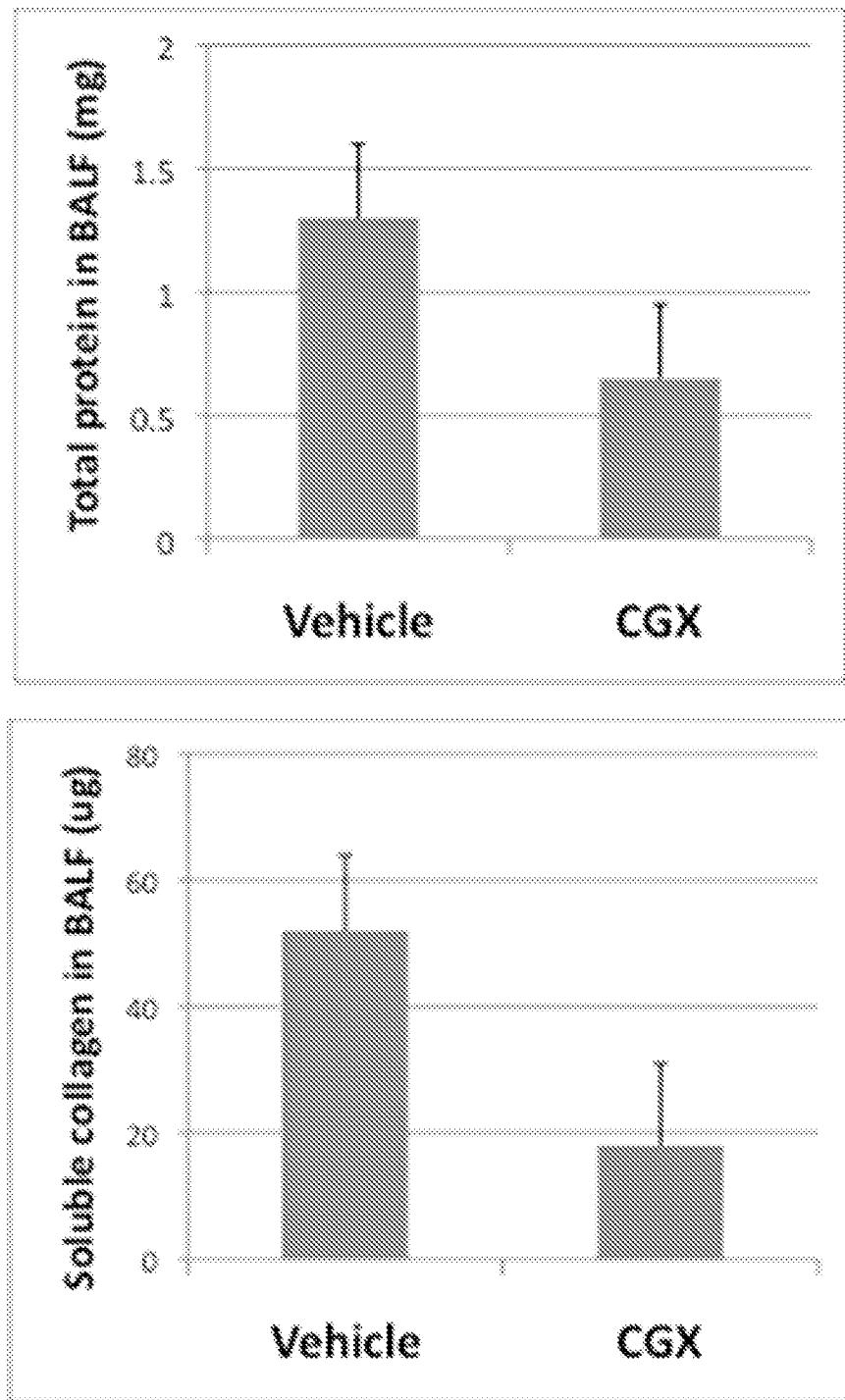


FIG. 6

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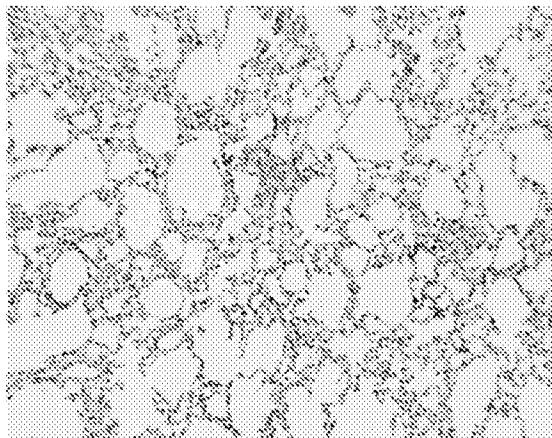
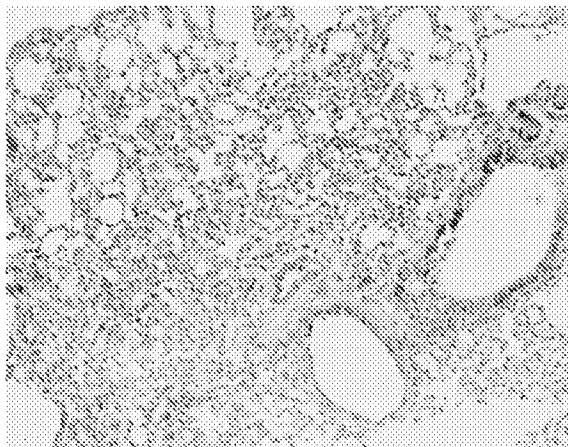


FIG. 7

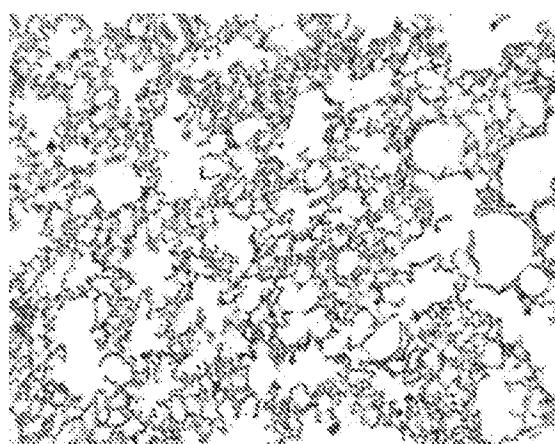
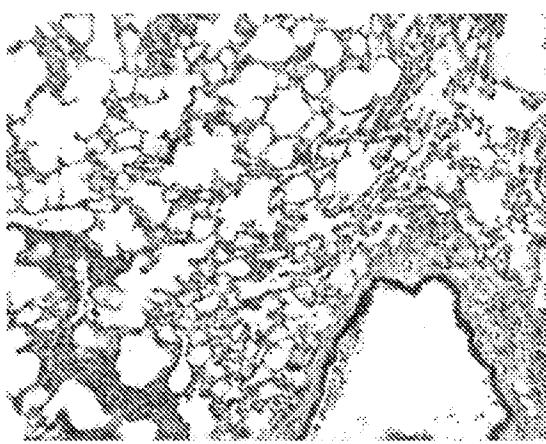


FIG. 8

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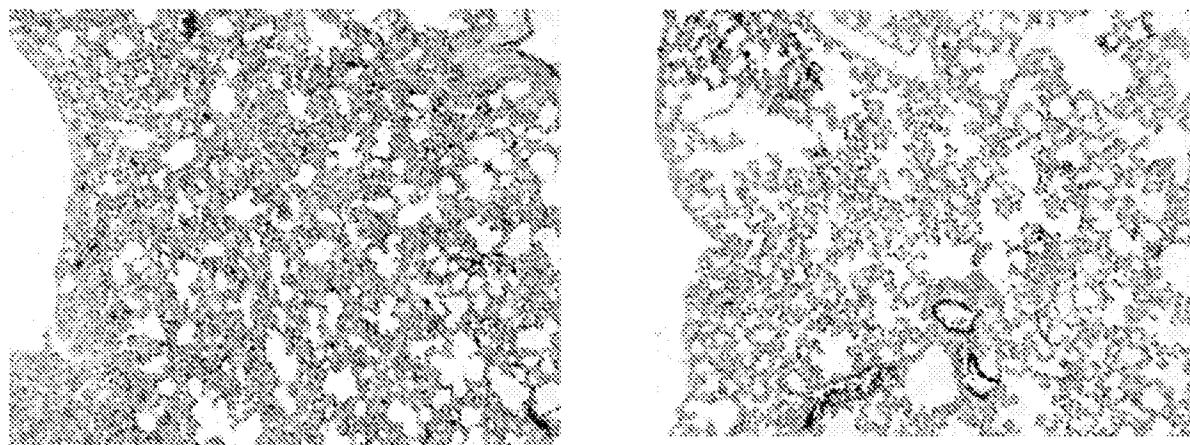


FIG. 9

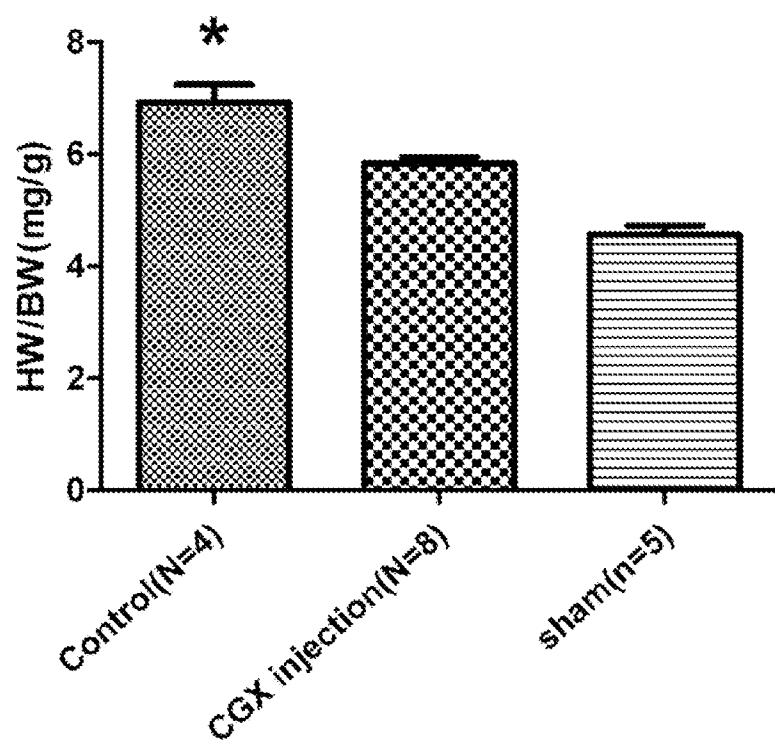


FIG. 10

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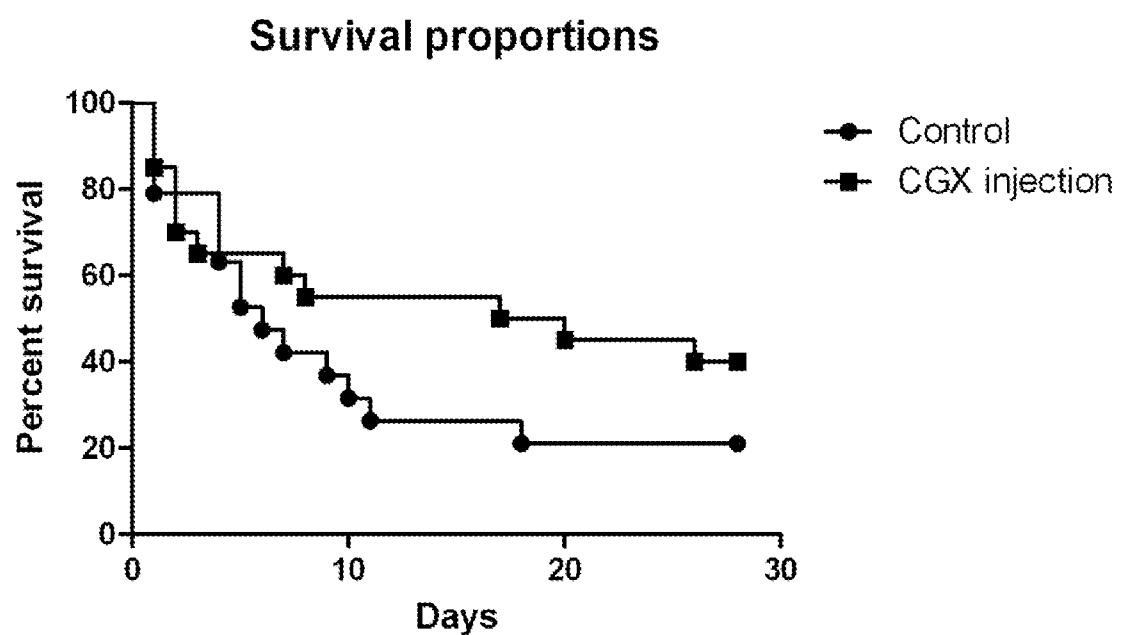


FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/024922

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/4985 (2014.01)

USPC - 514/310

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/4725, 31/498, 31/4985 (2014.01)

USPC - 514/248, 310

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/4725, 31/498, 31/4985 (2014.02)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Orbit, STN, PubChem

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102558173 A (SONGZHU et al) 11 July 2012 (11.07.2012) see machine translation	1-3, 24, 25

 Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 June 2014

Date of mailing of the international search report

08 JUL 2014

Name and mailing address of the ISA/US

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Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/024922

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 4-23 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.