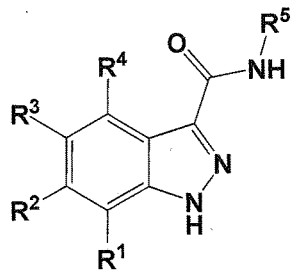
by neuronal activity or experience. Evidence suggests that dysfunction in Wnt signaling contributes to neurological disorders [*Brain Research Reviews* **(2000)**, *33(1)*, 1–12; *Oncogene* **(2006)** *25(57)*, 7545-7553; *Molecular Neurodegeneration* **(2008)**, *3*, 9; *Neurobiology of Disease* **(2010)**, *38(2)*, 148–153; *Journal of Neurodevelopmental Disorders* **(2011)**, *3(2)*, 162–174 and *Cold Spring Harbor Perspectives in Biology February* **(2012)**, *4(2)*].

SUMMARY ~~OF THE INVENTION~~

[0009] The present ~~invention~~ disclosure makes available methods and reagents, involving contacting a cell with an agent, such as an aromatic compound, in a sufficient amount to antagonize Wnt activity, e. g., to reverse or control an aberrant growth state or correct a genetic disorder due to mutations in Wnt signaling components.

[0010] Some embodiments disclosed herein include Wnt inhibitors containing an indazole-3-carboxamide core. Other embodiments disclosed herein include pharmaceutical compositions and methods of treatment using these compounds.

[0011] One embodiment disclosed herein includes a compound having the structure of formula **I**:



I

[0012] In some embodiments of formula **(I)**:

R^1, R^2 and R^4 are independently selected from the group consisting of H, $C_{1\text{-}9}$ alkyl, halide, $-N(R^{10})_2$, $-XR^{10}$, CN, $-OCF_3$ and $-CF_3$;

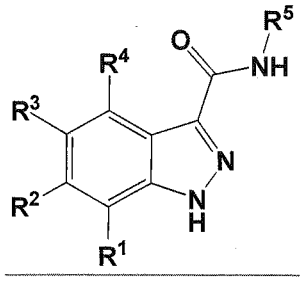
R^3 is selected from the group consisting of carbocyclylR^6, heterocyclylR^6, arylR^6 and heteroarylR^6;

with the proviso that when R^3 is heteroaryl, the heteroaryl is not selected from the group consisting of isoquinoline, 1H-pyrrolo[2,3-*c*]pyridine and tetrazole;

each X is selected from the group consisting of a bond, -O- and -S-; and

each n is 0 or 1.

In one aspect there is provided a compound or pharmaceutically acceptable salt or prodrug thereof having the structure of formula I:



I

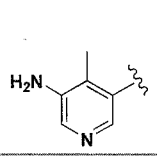
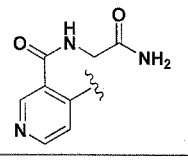
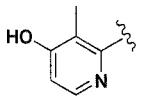
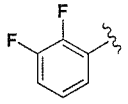
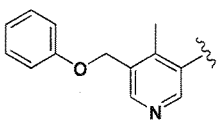
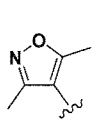
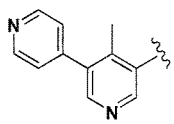
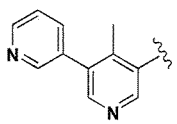
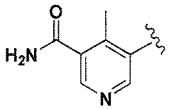
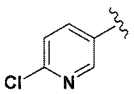
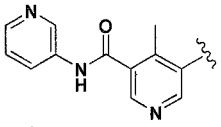
wherein:

R^1, R^2 and R^4 are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-N(R^{10})_2$, $-XR^{10}$, CN, $-OCF_3$ and $-CF_3$;

R^3 is selected from the group consisting of carbocyclylR^6, heterocyclylR^6, arylR^6 and heteroarylR^6;

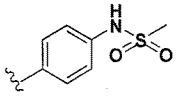
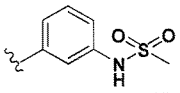
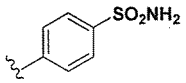
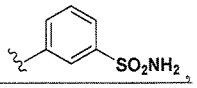
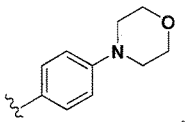
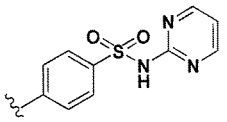
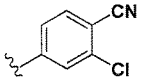
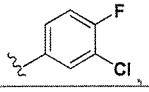
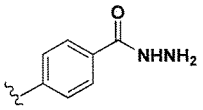
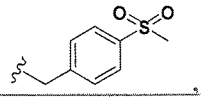
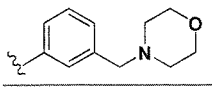
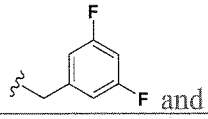
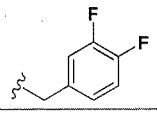
with the proviso that when R^3 is heteroaryl, the heteroaryl is not selected from the group consisting of isoquinoline, 1H-pyrrolo[2,3-*c*]pyridine and tetrazole;

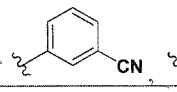
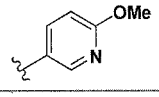
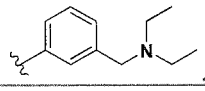
R^5 is selected from the group consisting of $-(C_{1-9}$ alkyl$)_n$carbocyclylR^7, $-(C_{1-9}$ alkyl$)_n$heterocyclylR^7, $-(C_{1-9}$ alkyl$)_n$arylR^7 and $-(C_{1-9}$ alkyl$)_n$heteroarylR^7;

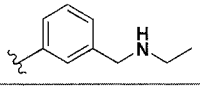
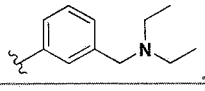
with the proviso that R^5 is not 4-pyridylR^7 when R^1, R^2 and R^4 are H, R^3 is selected from the group consisting of 3-pyridylR^6, 4-pyridylR^6, 2-pyridylR^6, phenylR^6, thiazoleR^6, imidazoleR^6, pyrimidineR^6, oxazoleR^6,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  , and R^6 and R^7 are both H;

with the proviso that R^5 is not $-(CH_2)$(3-pyridyl)R^7 when R^1, R^2 and R^4 are H, R^3 is selected from the group consisting of 3-pyridylR^6, 4-pyridylR^6 and thiazoleR^6, and R^6 and R^7 are both H;

with the proviso that R^5 is not phenylR^7 when R^1, R^2 and R^4 are H, R^3 is 4-pyridylR^6 and R^6 and R^7 are both H;

with the proviso that R^3 is not 3-pyridylR^6 when R^1, R^2 and R^4 are H, R^5 is selected from the group consisting of phenylR^7,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  , and R^6 and R^7 are both H;

with the proviso that R^3 is not oxazoleR^6 when R^1, R^2 and R^4 are H, R^5 is selected from the group consisting of  ,  and  , and R^6 is H;

with the proviso that R^3 is not thiazoleR^6 when R^1, R^2 and R^4 are H, R^5 is selected from the group consisting of  and  , and R^6 is H;

each R^6 is 1-5 substituents each selected from the group consisting of H, $C_{1\text{-}9}$ alkyl, halide, amino, $-OCF_3$, $-CF_3$, -CN, $-XR^{10}$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{carbocyclyl}R^8$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{heterocyclyl}R^8$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{aryl}R^8$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{heteroaryl}R^8$, $-C(=O)R^{11}$, $-N(R^{10})C(=O)R^{11}$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^{10})_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^{10})SO_2R^{11}$ and $-SO_2R^{11}$;

each R^7 is 1-5 substituents each selected from the group consisting of H, $C_{1\text{-}9}$ alkyl, halide, amino, $-OCF_3$, $-CF_3$, -CN, $-XR^{10}$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{carbocyclyl}R^9$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{heterocyclyl}R^9$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{aryl}R^9$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{heteroaryl}R^9$, $-C(=O)R^{11}$, $-N(R^{10})C(=O)R^{11}$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^{10})_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^{10})SO_2R^{11}$ and $-SO_2R^{11}$;

each R^8 is 1-5 substituents each selected from the group consisting of H, $C_{1\text{-}3}$ alkyl, halide, amino, OCF_3, $-CF_3$ -CN, $-XR^{12}$, $-C(=O)R^{13}$, $-N(R^{12})C(=O)R^{13}$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^{12})_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^{12})SO_2R^{13}$ and $-SO_2R^{13}$;

each R^9 is 1-5 substituents each selected from the group consisting of H, $C_{1\text{-}3}$ alkyl, halide, amino, $-OCF_3$, $-CF_3$ -CN, $-XR^{12}$, $-C(=O)R^{13}$, $-N(R^{12})C(=O)R^{13}$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^{12})_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^{12})SO_2R^{13}$ and $-SO_2R^{13}$;

each R^{10} is independently selected from the group consisting of H, C_{1-9} alkyl, -(C_{1-9} alkyl)$_n$N(R^{14})$_2$, -(C_{1-9} alkyl)$_n$carbocyclylR^8, -(C_{1-9} alkyl)$_n$heterocyclylR^8, -(C_{1-9} alkyl)$_n$arylR^8 and -(C_{1-9} alkyl)$_n$heteroarylR^8;

each R^{11} is independently selected from the group consisting of C_{1-9} alkyl, -N(R^{14})$_2$, -(C_{1-9} alkyl)$_n$carbocyclylR^8, -(C_{1-9} alkyl)$_n$heterocyclylR^8, -(C_{1-9} alkyl)$_n$arylR^8 and -(C_{1-9} alkyl)$_n$heteroarylR^8;

each R^{12} is independently selected from the group consisting of H, C_{1-9} alkyl, -(C_{1-9} alkyl)$_n$N(R^{14})$_2$, -(C_{1-9} alkyl)$_n$carbocyclyl, -(C_{1-9} alkyl)$_n$heterocyclyl, -(C_{1-9} alkyl)$_n$aryl and -(C_{1-9} alkyl)$_n$heteroaryl;

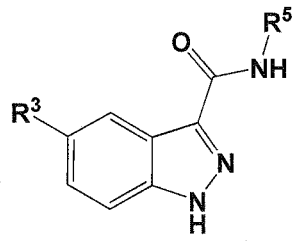
each R^{13} is independently selected from the group consisting of C_{1-9} alkyl, -N(R^{14})$_2$, -(C_{1-9} alkyl)$_n$carbocyclyl, -(C_{1-9} alkyl)$_n$heterocyclyl, -(C_{1-9} alkyl)$_n$aryl and -(C_{1-9} alkyl)$_n$heteroaryl;

each R^{14} is independently selected from the group consisting of H, C_{1-3} alkyl, carbocyclyl and aryl;

each X is selected from the group consisting of a bond, -O- and -S-; and

each n is 0 or 1.

In another aspect, there is provided a compound or pharmaceutically acceptable salt or prodrug thereof having the structure of formula **Ia**:



Ia

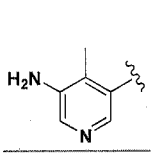
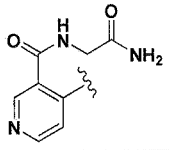
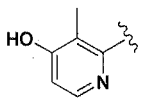
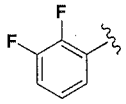
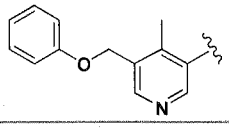
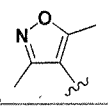
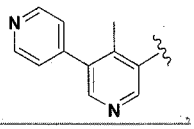
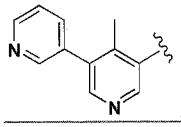
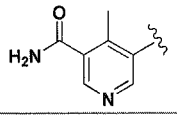
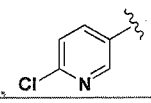
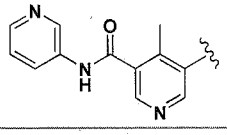
wherein:

R^3 is selected from the group consisting of arylR^6 and heteroarylR^6;

with the proviso that when R^3 is heteroaryl, the heteroaryl is not selected from the group consisting of isoquinoline, 1H-pyrrolo[2,3-*c*]pyridine and tetrazole;

R^5 is selected from the group consisting of -carbocyclylR^7, -heterocyclylR^7, -arylR^7, -heteroarylR^7, and -(C_{1-2} alkyl)heteroarylR^7;

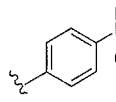
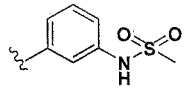
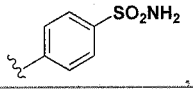
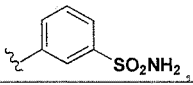
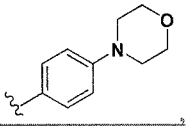
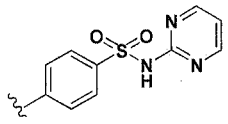
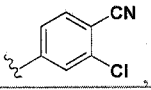
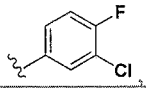
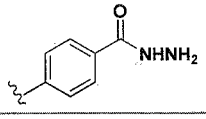
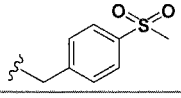
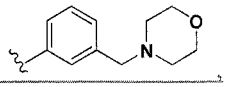
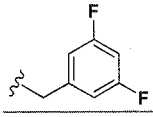
with the proviso that R^5 is not 4-pyridylR^7 when R^3 is selected from the group consisting of 3-pyridylR^6, 4-pyridylR^6, 2-pyridylR^6, phenylR^6, thiazoleR^6, imidazoleR^6, pyrimidineR^6, oxazoleR^6,












and , and R^6 and R^7 are both H;

with the proviso that R^5 is not $-(CH_2)$(3-pyridyl)R^7 when R^3 is selected from the group consisting of 3-pyridylR^6, 4-pyridylR^6 and thiazoleR^6, and R^6 and R^7 are both H;

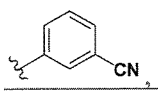
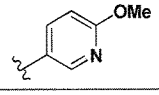
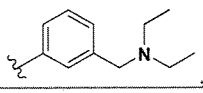
with the proviso that R^5 is not phenylR^7 when R^3 is 4-pyridylR^6 and R^6 and R^7 are both H;

with the proviso that R^3 is not 3-pyridylR^6 when R^5 is selected from the group consisting of phenylR^7,

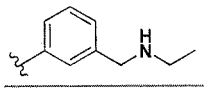
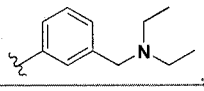













and , and R^6 and R^7 are both H;

with the proviso that R^3 is not oxazoleR^6 when R^5 is selected from the group consisting of



and  , and R^6 is H;

with the proviso that R^3 is not thiazoleR^6 when R^5 is selected from the group consisting of


and  , and R^6 is H;

each R^6 is 1-2 substituents each selected from the group consisting of H, C_{1-3} alkyl, halide, amino, $-OCF_3$, $-CF_3$, -CN, $-OR^{10}$, $-(C_{1-2}$ alkyl)heterocyclylR^8, -heterocyclylR^8, $-(C_{1-2}$ alkyl)arylR^8, $-C(=O)R^{11}$, $-N(R^{10})C(=O)R^{11}$ and $-(C_{1-2}$ alkyl)$N(R^{10})_2$;

each R^7 is 1-2 substituents each selected from the group consisting of H, C_{1-3} alkyl, halide, amino, $-OCF_3$, $-CF_3$, -CN, $-OR^{10}$, $-(C_{1-2}$ alkyl)heterocyclylR^9, -heterocyclylR^9, -arylR^9, $-(C_{1-2}$ alkyl)arylR^9, $-C(=O)R^{11}$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})_2$, $-(C_{1-2}$ alkyl)$N(R^{10})_2$, $-N(R^{10})SO_2R^{11}$ and $-SO_2R^{11}$;

each R^8 is 1-2 substituents each selected from the group consisting of H, C_{1-3} alkyl, halide, amino, OCF_3, $-CF_3$ –CN and $-OR^{12}$;

each R^9 is 1-2 substituents each selected from the group consisting of H, C_{1-3} alkyl, halide, amino, -OCF_3, -CF_3 –CN and -OR^{12};

each R^{10} is independently selected from the group consisting of H, C_{1-3} alkyl, -(C_{1-3} alkyl)$N(R^{14})_2$ and -arylR^8;

each R^{11} is independently selected from the group consisting of C_{1-3} alkyl, -$N(R^{14})_2$, -carbocyclylR^8 and -heterocyclylR^8;

each R^{12} is independently selected from the group consisting of H and C_{1-3} alkyl;

each R^{14} is independently selected from the group consisting of H, C_{1-3} alkyl and carbocyclyl.

[0013] Some embodiments include stereoisomers and pharmaceutically acceptable salts of a compound of general formula (**I**).

[0014] Some embodiments include pro-drugs of a compound of general formula (**I**).

[0015] Some embodiments of the present disclosure~~invention~~ include pharmaceutical compositions comprising a compound of general formula (**I**) or in a pharmaceutically acceptable carrier, diluent, or excipient.

In one aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0016] Other embodiments disclosed herein include methods of inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins by administering to a subject affected by a disorder or disease in which aberrant Wnt signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, cell cycling and mutations in Wnt signaling components, a compound according to formula (I). Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation and correct a genetic disorder due to mutations in Wnt signaling components. Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, scleroderma, mycotic and viral infections, osteochondrodysplasia, Alzheimer's disease, lung disease, osteoarthritis, polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-ameliasyndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X synd 7 ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease and Rett syndrome.

In one aspect there is provided a use of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a disorder or disease in which aberrant Wnt signaling is implicated in a patient.

In another aspect, there is provided a use of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a disease or disorder mediated by the Wnt pathway in a patient.

In another aspect, there is provided a use of at least one compound according as defined herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a disease or disorder mediated by kinase activity in a patient.

In another aspect, there is provided a use of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting the activity of a protein kinase receptor, wherein the medicament is to be contacted with the receptor.

In another aspect, there is provided a use of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a disease or disorder associated with aberrant cellular proliferation in a patient.

In another aspect, there is provided a use of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for preventing or reducing angiogenesis in a patient.

In another aspect, there is provided a use of at least one compound as defined herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for preventing or reducing abnormal cellular proliferation in a patient.

In another aspect, there is provided a use of a pharmaceutical composition comprising one or more of the compounds as defined herein for the manufacture of a medicament for treating a disease or disorder associated with aberrant cellular proliferation in a patient, wherein the medicament is to be administered with a pharmaceutically acceptable carrier and one or more other agents.

[0017] Some embodiments of the present ~~invention~~ disclosure include methods to prepare a compound of general formula (**I**).

[0018] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

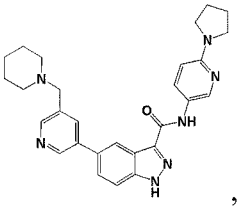
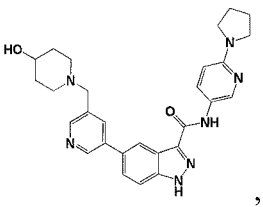
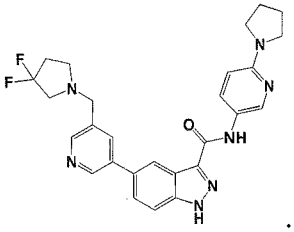
DETAILED DESCRIPTION OF THE INVENTION

[0019] Compositions and methods for inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins would be of tremendous benefit. Certain embodiments provide such compositions and methods.

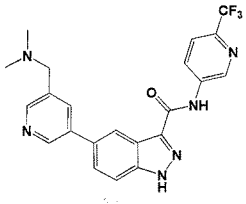
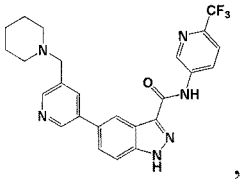
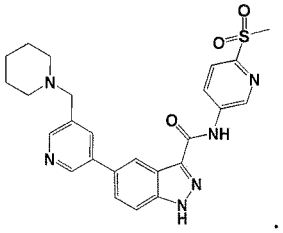
[0020] Some embodiments relate to a method for treating a disease including, but not limited to, cancers, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, scleroderma, mycotic and viral infections, bone and cartilage diseases, Alzheimer's disease, lung disease, osteoarthritis, polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman's syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease and Rett syndrome.

[0021] In some embodiments, pharmaceutical compositions are provided that are effective for treatment of a disease of an animal, *e.g.*, a mammal, caused by the pathological activation or mutations of the Wnt pathway. The composition includes a pharmaceutically acceptable carrier and a Wnt pathway inhibitor as described herein.

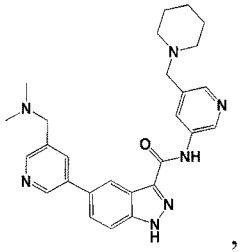
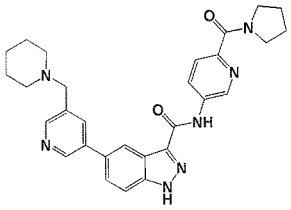
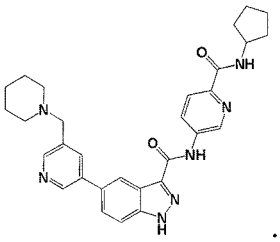
Definitions

 ,  , and  .

34. The compound of claim 30 having a structure selected from the group consisting of:

 ,  , and  .

35. The compound of claim 30 having a structure selected from the group consisting of:

 ,  , and  .

36. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

37. Use of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for ~~A method of~~ treating a disorder or disease in which aberrant Wnt signaling is implicated in a patient.~~, the method comprising administering to the patient a therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof.~~

38. A use~~method~~ of claim 37, wherein the disorder or disease is cancer.

39. A use~~method~~ of claim 37, wherein the disorder or disease is diabetic retinopathy.

40. A use~~method~~ of claim 37, wherein the disorder or disease is rheumatoid arthritis.

41. A use~~method~~ of claim 37, wherein the disorder or disease is a mycotic or viral infection.

42. A ~~method~~ use of claim 37, wherein the disorder or disease is a bone or cartilage disease.

43. A ~~method~~use of claim 37, wherein the disorder or disease is a neurological condition, disorder or disease, wherein the neurological condition/disorder/disease is selected from: Alzheimer's disease, frontotemporal dementias, dementia with lewy bodies, prion diseases, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, corticobasal degeneration, mutiple system atrophy, amyotrophic lateral sclerosis (ALS), inclusion body myositis, autism, degenerative myopathies, diabetic neuropathy, other metabolic neuropathies, endocrine neuropathies, orthostatic hypotension, multiple sclerosis and Charcot-Marie-Tooth disease.

44. A ~~method~~ use of claim 37, wherein the disorder or disease is lung disease.

45. A ~~method~~use of claim 37, wherein the disorder or disease is osteoarthritis.

46. A ~~method~~use of claim 37, wherein the disorder or disease is a genetic disease caused by mutations in Wnt signaling components, wherein the genetic disease is selected from: polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome, Norrie disease and Rett syndrome.

47. A ~~method~~ use of claim 37, wherein the disorder or disease is a fibrotic disorder, wherein the fibrotic disorder is selected from: skin fibrosis; scleroderma; progressive systemic fibrosis; lung fibrosis; muscle fibrosis; kidney fibrosis; glomerulosclerosis; glomerulonephritis; hypertrophic scar formation; uterine fibrosis; renal fibrosis; cirrhosis of the liver, liver fibrosis; adhesions, such as those occurring in the abdomen, pelvis, spine or tendons; chronic obstructive pulmonary disease; fibrosis following myocardial infarction; pulmonary fibrosis; fibrosis and scarring associated with diffuse/interstitial lung disease; central nervous system fibrosis, such as fibrosis following stroke; fibrosis

associated with neuro-degenerative disorders such as Alzheimer's Disease or multiple sclerosis; fibrosis associated with proliferative vitreoretinopathy (PVR); restenosis; endometriosis; ischemic disease and radiation fibrosis.

48. The ~~method~~ use of claim 37, wherein the patient is a human.

49. The ~~method~~use of claim 38, wherein the cancer is chosen from: hepatocellular carcinoma, colon cancer, breast cancer, pancreatic cancer, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, chronic lymphocytic leukemia (CLL), acute myeloid leukemia, acute lymphocytic leukemia, Hodgkin lymphoma, lymphoma, sarcoma and ovarian cancer.

50. The ~~method~~use of claim 38, wherein the cancer is chosen from: lung cancer - non-small cell, lung cancer - small cell, multiple myeloma, nasopharyngeal cancer, neuroblastoma, osteosarcoma, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer - basal and squamous cell, skin cancer – melanoma, small intestine cancer, stomach cancers, testicular cancer, thymus cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, laryngeal or hypopharyngeal cancer, kidney cancer, Kaposi sarcoma, gestational trophoblastic disease, gastrointestinal stromal tumor, gastrointestinal carcinoid tumor, gallbladder cancer, eye cancer (melanoma and lymphoma), Ewing tumor, esophagus cancer, endometrial cancer, colorectal cancer, cervical cancer, brain or spinal cord tumor, bone metastasis, bone cancer, bladder cancer, bile duct cancer, anal cancer and adrenal cortical cancer.

51. The ~~method~~ use of claim 37, wherein the compound inhibits one or more proteins in the Wnt pathway.

52. The ~~method~~use of claim 51, wherein the compound inhibits signaling induced by one or more Wnt proteins.

53. The ~~method~~use of claim 52, wherein the Wnt proteins are chosen from: WNT1, WNT2, WNT2B, WNT3, WNT3A, WNT4. WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT9A, WNT9B, WNT10A, WNT10B, WNT11, and WNT16.

54. The ~~method~~use of claim 37, wherein the compound inhibits a kinase activity.

55. Use of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for ~~A method of~~ treating a disease or disorder mediated by the Wnt pathway in a patient.~~, the method comprising administering to the patient a therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof.~~

56. The ~~method~~ use of claim 55, wherein the compound inhibits one or more Wnt proteins.

57. Use of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for ~~A method of~~ treating a disease or disorder mediated by kinase activity in a patient.~~, the method comprising administering to the patient a therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof.~~

58. The ~~method~~use of claim 57, wherein the disease or disorder comprises tumor growth, cell proliferation, or angiogenesis.

59. Use of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for ~~A method of~~ inhibiting the activity of a protein kinase receptor, wherein the medicament is to be contacted with the receptor. ~~the method comprising contacting the receptor with an effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof.~~

60. Use of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for ~~A method of~~ treating a disease or disorder associated with aberrant cellular proliferation in a patient.~~, the method comprising administering to the patient a therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof.~~

61. Use of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for ~~A method of~~ preventing or reducing angiogenesis in a patient.~~, the method comprising administering to the patient a therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof.~~

62. Use of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for ~~A method of~~ preventing or reducing abnormal cellular proliferation in a patient.~~, the method comprising administering to the patient a therapeutically effective amount of at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof.~~

63. Use of a pharmaceutical composition comprising one or more of the compounds of claim 1 for the manufacture of a medicament for ~~A method of~~ treating a disease or disorder associated with aberrant cellular proliferation in a patient,~~ the method comprising administering to the patient a pharmaceutical composition comprising one or more of the compounds of claim 1 in combination with a pharmaceutically acceptable carrier and one or more other agents.~~ wherein the medicament is to be administered with a pharmaceutically acceptable carrier and one or more other agents.