Title: P53 ACTIVATOR SMALL MOLECULES

Abstract: Disclosed are small molecules of formula (I) which can inhibit WNT secretion from a cell or restore mutant P53 function in a cell, pharmaceutical compositions and their use in the treatment of abnormal conditions, such as malignant tumors.
P53 ACTIVATOR SMALL MOLECULES

Field of the Invention
The present invention relates to field of medicine, specially relates to a P53 activator small molecules, its preparation method and its use in therapeutic applications.

Background of the Invention
p53 is best known as a tumor suppressor that transcriptionally regulates, in response to cellular stresses such as DNA damage or oncogene activation, the expression of various target genes that mediate cell-cycle arrest, DNA repair, senescence or apoptosis. Loss of p53 activity - either by somatic mutation of the TP53 gene or by functional inhibition of the p53 protein - is a common feature of human tumors. TP53 is the most frequently mutated gene in human cancer with mutation frequencies ranging from 38%-50% in some reports to as high as 75% and 96% in pancreatic adenocarcinoma and high-grade serous ovarian carcinomas, respectively (Hingorani et al., 2005; Cancer Genome Atlas Research Network, 2011; Petitjean et al., 2007). The majority of mutations are mis-sense mutations that occur most frequently in six "hotspot" codons within the DNA binding domain (Olivier et al., 2010). These mutant proteins are classified as either DNA contact mutants (e.g., p53R273H) when the mutation occurs in a DNA binding residue or conformational mutants (e.g., p53R175H) when a conformational change causes a loss of WT p53 DNA binding. Mutant p53 proteins are found at high concentrations in tumor cells relative to WT p53, mostly because of a loss of WT p53 transcription of the MDM2 gene that negatively regulates p53, as well as other tumor-specific alterations, such as loss of p16INK4a (Haupt et al., 1997; Midgley and Lane, 1997; Terzian et al., 2008). The concept that these mutant proteins are functional and regulate important processes relevant to tumor biology is referred to as the mutant p53 gain-of-function (GOF) phenotype (Sigal and Rotter, 2000). Properties attributed to mutant p53 GOF include enhanced tumorigenesis, invasion, and metastasis (Adorno et al., 2009; Dittmer et al., 1993; Liu et al., 2000; Muller et al., 2009). Taken together, these properties make mutant p53 an attractive target for drug development.

The next generation of anticancer drugs will be defined by compounds that selectively kill cancer cells while leaving normal cells undisturbed. Small molecule compounds that selectively kill cancer cells with a p53R175 or p53R273H mutation without toxicity in normal cells will be an ideal drug for development. Those small molecules restore WT structure and function to the p53R175 Δφ 53R273Fl protein, may allow to be developed as new anti-cancer drug.

Summary of the Invention
The present invention is to restore WT structure and function to the p53R175 or p53R273H protein by small molecules and to apply in therapeutic applications.
Therefore, one aspect of the present invention is to provide p53 activators which can be used therapeutically, for example, a compound having the general structural formulae (I):

![Formula I](image)

Wherein the group R can be selected from the group consisting of:

![ Structures II, III, IV, V, VI, VII](images)

that is, the compound of formula I can be selected from the group consisting of:

Wherein,
R₁ R₂, R₃ and R₄ are independently hydrogen, halogen, C₁₋₆ alkoxy, -S(0)₂R₅, -C(0)OR₆, -C(0)NR₆R₇, C₁₋₆ alkyl, C₂₋₆ alkenyl, cyclopropyl, or C₂₋₆ alkynyl, each of which can be optionally substituted with halogen, amino, hydroxyl, alkoxy or cyano, morpholinyl, piperazinyl, quinolinyl, aryl, C₁₋₆ heterocycle, 5 or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S:

R₅, R₆, R₇ is independently hydrogen, halogen, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, each of which can be optionally substituted with halogen, amino, hydroxyl, alkoxy or cyano.

In one preferred embodiment, R₁, R₂, R₃ and R₄ are independently hydrogen, halogen, methyl, ethyl, aryl, cyano, ethoxy, -C(0)NH₂, -C(0)NHC₁₋₆ alkyl, C₁₋₆ heterocycle; R₅, R₆, R₇ are independently methyl.

Said halogen is preferred F or Cl.

As used herein, some of the terms are as defined as follows.

"Halogen" refers to fluorine, chlorine, bromine and iodine.

"Alkyl" when used as a substituent or part of a substituent, refers to a linear or branched aliphatic hydrocarbon substituent. Most preferable one is C₁₋₆ alkyl, unless otherwise indicated. Examples of linear or branched Ci-C₆ alkyl include but not limited to methyl, ethyl, n-propyl, 2-propyl, n-butyl, isobutyl, tert-butyl, hexyl and the like.

"Alkoxyl" refers to a substituent of (alkyl-O-), in which the alkyl is as defined herein. Preferably, it is Q-alkoxy. Examples include but not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy and the like.

"Alkenyl" when used as a substituent or part of a substituent, refers to an aliphatic hydrocarbon substituent with at least one carbon carbon double bond, and may be linear or branched. Most preferable one is C₂₋C₆ alkenyl. The said substituent may contain multiple double bonds in its backbone which may independently be E configuration or Z configuration. Examples of said alkenyl include but not limited to vinyl, propenyl, allyl, butylene and the like.

"Alkynyl" refers to an aliphatic hydrocarbon substituent with at least one carbon carbon triple bond, and may be linear or branched. Most preferable one is C₂₋C₆ alkynyl. Examples of said alkynyl include but not limited to all isomers of hexynyl, pentynyl, butynyl, propynyl and ethynyl.

"Aryl" refers to aromatic carbon-ring system with one or two rings, including such as phenyl, naphthyl and tetrahydronaphthyl. Preferred aryl is phenyl.

As used herein, an H atom in any substituent groups (e.g., CH₂) encompasses all suitable isotopic variations, e.g., H,²H and ³H.
As used herein, other atoms in any substituent groups encompasses all suitable isotopic variations, including but not limited to $^{11}$C, $^{13}$C, $^{14}$C, $^{15}$N, $^{17}$O, $^{18}$O, $^{32}$S, $^{18}$F, $^{35}$I and/or $^{129}$I.

The preferred compounds of formula I of the present invention comprise the following compounds:

(1-((6-methylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
6-((3-(hydroxymethyl)-1H-indol-1-yl)methyl)picolinonitrile;  
(1-((6-chloropyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((5-methylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((4-methylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((3-methylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((6-phenylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-(pyridin-2-ylmethyl)-1H-indol-3-yl)methanol;  
(1-(pyridin-3-ylmethyl)-1H-indol-3-yl)methanol;  
(1-(pyridin-4-ylmethyl)-1H-indol-3-yl)methanol;  
(1-((6-ethylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((6-methoxypyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((6-fluoropyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
6-((3-(hydroxymethyl)-1H-indol-1-yl)methyl)picolinamide;  
N-ethyl-6-((3-(hydroxymethyl)-1H-indol-1-yl)methyl)picolinamide;  
(1-((6-piperidin-1-yl)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((6-morpholinopyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((6-pyridin-1-yl)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((6-(cyclopropylamino)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-(quinolin-2-ylmethyl)-1H-indol-3-yl)methanol;  
(1-(isoquinolin-3-ylmethyl)-1H-indol-3-yl)methanol;  
(1-(isoquinolin-1-ylmethyl)-1H-indol-3-yl)methanol;  
(1-((8-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((7-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol;  
(1-((6-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol.

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 in the art, for example, by mixing, granulating or coating methods.

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.

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

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

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

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.

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 earners, 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.

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.

In another aspect, the present invention provides a method of inhibiting WNT secretion from a cell.
In another aspect, the present invention provides a method of restoring mutant P53 function in a cell with an effective amount of the present compound. In one embodiment, the cell is contained within a mammal, and the administered amount is a therapeutically effective amount. In another embodiment, the restoring mutant P53 function 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.

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.

The present invention also provides a method for treating cancers related to the P53 mutation 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 P53 mutation 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 P53 mutation using immune and nucleic acid detection methods.

Furthermore, the invention provides a method for treating P53 disorder in a subject suffering from the disorder by administering to the subject a therapeutically effective amount of a mutant P53 activator. In one embodiment, the disorder is a cell proliferative disorder associated with aberrant, e.g., decreased, activity of P53 signaling. 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, carcinoma, 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, acute myelocytic leukemia (AML), and chronic myelocytic leukemia (CML).

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 100mg. 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 100 mg active ingredient. 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.

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.

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, selected from the group consisting of an aurora kinase inhibitor, a tyrosine kinase inhibitor and a histone deacetylase inhibitor. In addition, the kit may comprise instructions for its administration.

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.

In another aspect, the present invention provides a process for preparing the compound of the present invention or the salts or derivatives thereof.
In one embodiment, the compound having Formula (I), preferably Formula (II), (III), (IV), (V), (VI) and (VII) 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.

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 hydrides, 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.

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), preferably Formula (II), (III), (IV), (V), (VI) and (VII) 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), preferably Formula (II), (III), (IV), (V), (VI) and (VII) with a basic nitrogen atom with organic or inorganic acids.

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

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, azelaiic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic 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.

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.

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 phosphate, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like. Preferably, the invert organic solvent is acetonitrile, ethanol, aqueous dioxane, or the like.

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-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like.

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.

In yet another embodiment, compound of the present invention may be prepared as their individual stereoisomers. The process includes steps: 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 earned 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,

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.

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.

**Description of the Figures**

Figure 1a shows mRNA levels of p53 targets p21, DR5, GADD45, PUMA and Noxa in SW620 (having p53 R273H mutation) cells upon treatment of compound 1.

Figure 1b shows mRNA levels of p53 targets p21, DR5, GADD45, PUMA and Noxa in Saos2(without p53 R273H mutation) cells upon treatment of compound 1.

**Embodiments**

**Methods of Preparation**

The compounds of the present invention may be prepared by methods such as those illustrated in the following scheme 1.

Wherein, solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared using procedures generally known to those skilled in the art.

**Scheme 1**
Step 1

1H-indole-3-carboxaldehyde is reacted with substituted chloromethylpyridine or chloromethylquinoline in the presence of a base, such as cesium carbonate, preferably at elevated temperatures (50°C~100°C) to afford 1H-indole-3-carboxaldehyde derivatives of compound of formula (Γ) of scheme I.

Step 2

1H-indole-3-carboxaldehyde derivatives of compound of formula (Γ) of scheme I can be reduced with a reducing agent, such as sodium borohydride to obtain alcohol derivatives of compound of formula (I) of scheme I.

Detailed embodiments

The invention will now be further described by the following working examples, which are preferred embodiments of the invention. All temperatures are in degrees Celsius (°C) unless otherwise indicated. Preparative Reverse Phase (RP) HPLC purifications were done on C18 reverse phase (RP) columns using water/methanol mixtures. All the synthesized compounds were characterized by at least NMR or LC/MS. During work up of reactions, the organic extract was dried over sodium sulfate, purified by silica gel column chromatography or (RP) HPLC, unless mentioned otherwise.

These examples are illustrative rather than limiting and it is to be understood that there may be other embodiments that fall within the spirit and scope of the invention as defined by the claims appended hereto.

Example 1
(L-((6-methylpyridin-2-yl)methyl)-lH-indol-3-yl)methanol (compound 1)

Step 1
To a stirred solution of lH-indole-3-carboxaldehyde (145.2mg, 1mmol) and 2-(chloromethyl)-6-methylpyridine (155.2mg, 1.1mmol) in 5.0 mL of MeCN was added Cs₂CO₃ (980mg, 3mmol) at room temperature. The mixture was then heated to 80°C and kept stirring for 3h. When lH-indole-3-carboxaldehyde was consumed monitored by TLC, MeCN was evaporated. The residue was partitioned in 15 mL of water and 15 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried, and concentrated. The crude product was purified by silica gel column chromatography to give L-((6-methylpyridin-2-yl)methyl)-lH-indole-3-carbaldehyde (200mg, 80% yield). ESI-MS m/z 251.1 [M+H].

Step 2
L-((6-methylpyridin-2-yl)methyl)-lH-indole-3-carbaldehyde (20mg, 0.08mmol) was dissolved in THF: MeOH (6mL: 2mL), then sodium borohydride (6.0mg, 0.16mmol) was added. After the mixture was stirred at room temperature for 2h, a small amount of acetone was added to stop the reaction. The mixture was concentrated and purified to give title compound (17.1mg, 85% yield).

^1H NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 7.4 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.25-7.12 (m, 4H), 7.02 (d, J = 7.6 Hz, 1H), 6.45 (d, J = 7.8 Hz, 1H), 5.38 (s, 2H), 4.90 (s, 2H), 2.59 (s, 3H). ESI-MS m/z 235.1 [M+H^+-H₂O].

Example 2

6-((3-(hydroxymethyl)-lH-indol-1-yl)methyl)picolinonitrile (compound 2)

Step 1
To a stirred solution of lH-indole-3-carboxaldehyde (145.2mg, 1mmol) and 6-(chloromethyl)picolinonitrile (167.8mg, 1.1mmol) in 5.0 mL of MeCN was added Cs₂CO₃ (980mg, 3mmol) at room temperature. The mixture was then heated to 80°C and kept stirring for 3h. When lH-indole-3-carboxaldehyde was consumed monitored by TLC, MeCN was evaporated. The residue was partitioned in 15 mL of water and 15 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried, and concentrated. The crude
product was purified by silica gel column chromatography to give 6-((3-formyl-1H-indol-1-yl)methyl)picolinonitrile (214mg, 82% yield). ESI-MS m/z 262.1 [M+H].

Step 2

6-((3-formyl-1H-indol-1-yl)methyl)picolinonitrile (20.8mg, 0.08mmol) was dissolved in THF: MeOH (6mL: 2mL), then sodium borohydride (6.0mg, 0.16mmol) was added. After the mixture was stirred at room temperature for 2h, a small amount of acetone was added to stop the reaction. The mixture was concentrated and purified to give title compound (17.1mg, 81% yield).

\[ 1^1H \text{ NMR (400 MHz, DMSO)} \delta 8.01-7.88 \text{ (m, 2H), 7.63 (d, } J = 7.8 \text{ Hz, 1H), 7.41 (s, 1H), 7.38 (d, } J = 8.2 \text{ Hz, 1H), 7.21 (d, } J = 7.5 \text{ Hz, 1H), 7.11 (t, } J = 7.5 \text{ Hz, 1H), 7.04 (t, } J = 7.4 \text{ Hz, 1H), 5.55 (s, 2H), 4.85 (t, } J = 5.3 \text{ Hz, 1H), 4.66 (d, } J = 5.3 \text{ Hz, 2H). ESI-MS m/z 246.3 [M+H–H_2O].} \]

Example 3

(I-((6-chloropyridin-2-yl)methyl)-1H-indol-3-yl)methanol (compound 3)

Step 1

To a stirred solution of 1H-indole-3-carboxaldehyde (145.2mg, 1mmol) and 2-chloro-6-(chloromethyl)pyridine (178.2mg, 1.1mmol) in 5.0 mL of MeCN was added Cs_{2}CO_{3}(980mg, 3mmol) at room temperature. The mixture was then heated to 80°C and kept stirring for 3h. When 1H-indole-3-carboxaldehyde was consumed monitored by TLC, MeCN was evaporated. The residue was partitioned in 15 mL of water and 15 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried, and concentrated. The crude product was purified by silica gel column chromatography to give 1-((6-chloropyridin-2-yl)methyl)-1H-indole-3-carbaldehyde (232.8mg, 86% yield). ESI-MS m/z 271.7 [M+H].

Step 2

1-((6-chloropyridin-2-yl)methyl)-1H-indole-3-carbaldehyde (21.7mg, 0.08mmol) was dissolved in THF: MeOH (6mL: 2mL), then sodium borohydride (6.0mg, 0.16mmol) was added. After the mixture was stirred at room temperature for 2h, a small amount of acetone was added to stop the reaction. The mixture was concentrated and purified to give title compound (19.4mg, 89% yield).
NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.26-7.12 (m, 4H), 7.04 (d, J = 7.6 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 5.38 (s, 2H), 4.90 (s, 2H). ESI-MS m/z 255.1 [M+H⁺-H₂O].

The following compounds were prepared using a procedure similar to that described for the preparation of example 1.

Table 1

<table>
<thead>
<tr>
<th>Example #</th>
<th>Structure</th>
<th>NMR/MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image" alt="Structure 4" /></td>
<td>¹H NMR (400 MHz, DMSO) δ 8.36 (s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.40-7.34 (m, 2H), 7.08 (t, J = 7.3 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 5.40 (s, 2H), 4.81 (t, J = 5.4 Hz, 1H), 4.64 (d, J = 5.4 Hz, 2H), 2.23 (s, 3H). ESI-MS m/z 235.3 [M+H⁺-H₂O].</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 5" /></td>
<td>¹H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.51 (s, 1H), 7.40-7.34 (m, 2H), 7.10 (t, J = 7.1 Hz, 1H), 7.03 (t, J = 7.0 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 5.42 (s, 2H), 4.82 (t, J = 5.4 Hz, 1H), 4.69 (d, J = 5.4 Hz, 2H), 2.25 (s, 3H). ESI-MS m/z 235.3 [M+H⁺-H₂O].</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Structure 6" /></td>
<td>¹H NMR (400 MHz, DMSO) δ 8.32 (d, J = 4.7 Hz, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 8.2 Hz, 1H), 7.26-7.22 (m, 1H), 7.21 (s, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 5.45 (s, 2H), 4.79 (t, J = 5.4 Hz, 1H), 4.62 (d, J = 5.4 Hz, 2H), 2.29 (s, 3H). ESI-MS m/z 235.3 [M+H⁺-H₂O].</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure 7" /></td>
<td>¹H NMR (400 MHz, CDCl₃) δ 7.9-7.84 (m, 2H), 7.43-7.25 (m, 6H), 7.20-7.14 (m, 1H), 7.10-7.00 (m, 2H), 6.99-6.93 (m, 1H), 6.49-6.38 (m, 1H), 5.50 (s, 2H), 4.76 (s, 2H). ESI-MS m/z 328.2 [M+H⁺-H₂O].</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure 8" /></td>
<td>¹H NMR (400 MHz, DMSO) δ 8.56 (d, J = 4.9 Hz, 1H), 7.59-7.57 (m, 1H), 7.56-7.50 (m, 1H), 7.49 (s, 1H), 7.48-7.15 (m, 4H), 6.77 (d, J = 7.6 Hz, 1H), 5.61 (s, 2H), 4.95 (t, J = 5.4 Hz, 1H), 4.71 (d, J = 5.4 Hz, 2H). ESI-MS m/z 221.1 [M+H⁺-H₂O].</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Molecule 9" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.54 (s, 1H), 8.47 (d, $J = 5.6$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.70-7.60 (m, 2H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.47 (s, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.06 (t, $J = 7.3$ Hz, 1H), 5.54 (s, 2H), 4.85 (t, $J = 5.4$ Hz, 1H), 4.64 (d, $J = 5.4$ Hz, 2H). ESI-MS $m/z$ 221.1 [M+H$^+$-H$_2$O].</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Molecule 10" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.49 (d, $J = 6.4$ Hz, 2H), 7.65 (d, $J = 8.1$ Hz, 1H), 7.42 (s, 1H), 7.41-7.26 (m, 3H), 7.13-7.03 (m, 2H), 5.61 (s, 2H), 4.85 (t, $J = 5.2$ Hz, 1H), 4.66 (d, $J = 5.2$ Hz, 2H). ESI-MS $m/z$ 221.1 [M+H$^+$-H$_2$O].</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Molecule 11" /></td>
<td>ESI-MS $m/z$ 249.1 [M+H$^+$-H$_2$O].</td>
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<tr>
<td>12</td>
<td><img src="image" alt="Molecule 12" /></td>
<td>ESI-MS $m/z$ 251.1 [M+H$^+$-H$_2$O].</td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Molecule 13" /></td>
<td>ESI-MS $m/z$ 239.1 [M+H$^+$-H$_2$O].</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Molecule 14" /></td>
<td>ESI-MS $m/z$ 264.1 [M+H$^+$-H$_2$O].</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>ESI-MS $m/z 292.2 [M+H^- - H_2O]$.</td>
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<tr>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>ESI-MS $m/z 304.2 [M+H^- - H_2O]$.</td>
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<tr>
<td>17</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>ESI-MS $m/z 306.2 [M+H^- - H_2O]$.</td>
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<tr>
<td>18</td>
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<td>ESI-MS $m/z 290.2 [M+H^- - H_2O]$.</td>
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<td>ESI-MS $m/z 276.1 [M+H^- - H_2O]$.</td>
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<tr>
<td>20</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>ESI-MS $m/z 271.1 [M+H^- - H_2O]$.</td>
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</table>
The compounds obtained from Examples 4-25 are listed as follows:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular Structure</th>
<th>ESI-MS m/z</th>
<th>Description</th>
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<td><img src="image" alt="Structure 21" /></td>
<td>m/z271.1</td>
<td>[M+H-H_2O].</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 22" /></td>
<td>m/z271.1</td>
<td>[M+H-H_2O].</td>
</tr>
<tr>
<td>23</td>
<td><img src="image" alt="Structure 23" /></td>
<td>m/z295.2</td>
<td>[M+H-H_2O].</td>
</tr>
<tr>
<td>24</td>
<td><img src="image" alt="Structure 24" /></td>
<td>m/z295.2</td>
<td>[M+H-H_2O].</td>
</tr>
<tr>
<td>25</td>
<td><img src="image" alt="Structure 25" /></td>
<td>m/z295.2</td>
<td>[M+H-H_2O].</td>
</tr>
</tbody>
</table>

compound 4: (1-((5-methylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 5: (1-((4-methylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 6: (1-((3-methylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 7: (1-((6-phenylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 8: (1-(pyridin-2-ylmethyl)-1H-indol-3-yl)methanol;
compound 9: (1-(pyridin-3-ylmethyl)-1H-indol-3-yl)methanol;
compound 10: (1-(pyridin-4-ylmethyl)-1H-indol-3-yl)methanol;
compound 11: (1-((6-ethylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 12: (1-((6-methoxypyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 13: (1-((6-fluoropyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 14: 6-((3-(hydroxymethyl)-1H-indol-1-yl)methyl)picolinamamide;
compound 15: N-ethyl-6-((3-(hydroxymethyl)-1H-indol-1-yl)methyl)picolinamamide;
compound 16: (1-((6-(piperidin-1-yl)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 17: (1-((6-morpholinopyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 18: (1-((6-(pyrrolidin-1-yl)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 19: (1-((6-(cyclopropylamino)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 20: (1-(quinolin-2-ylmethyl)-1H-indol-3-yl)methanol;
compound 21: (1-(isoquinolin-3-ylmethyl)-1H-indol-3-yl)methanol;
compound 22: (1-(isoquinolin-1-ylmethyl)-1H-indol-3-yl)methanol;
compound 23: (1-((8-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 24: (1-((7-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol;
compound 25: (1-((6-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol.

Cellular Assays Using the Compounds of this Invention

Methods
Commercially available colorectal cancer with p53 R273H mutation (HT29, SW480, SW620) in log-phase growth were plated using cell growth media and 10% fetalbovine serum in 96-well plates at a density of 3,000-5,000 cells per well. An equal volume of cell culture media (no FBS) containing drug solution (0.1%) was added. Concentrations ranging from $10^{-10}$ to $10^{-3}$ M were evaluated at half-log intervals in triplicate. The cells were allowed to proliferate for 3 days at the end of which cell viability was determined using CellTiter-Glo® Luminescent Cell Viability (Promega) reagent according to the manufacturer’s instructions. The resulting absorbance values were represented as a percentage of untreated control and fit using a four parameter logistic model in Sigma
Plot© (Systat Software) to determine IC50 values. The selected compounds' results are presented in the following Table 2.

Table 2

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>HT29 (IC50)</th>
<th>SW480 (IC50)</th>
<th>SW620 (IC50)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.60</td>
<td>0.07</td>
<td>0.16</td>
</tr>
<tr>
<td>2</td>
<td>1.09</td>
<td>0.78</td>
<td>1.10</td>
</tr>
<tr>
<td>3</td>
<td>1.72</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>4</td>
<td>2.90</td>
<td>1.32</td>
<td>1.55</td>
</tr>
<tr>
<td>5</td>
<td>0.68</td>
<td>0.29</td>
<td>0.52</td>
</tr>
<tr>
<td>6</td>
<td>1.50</td>
<td>0.80</td>
<td>0.92</td>
</tr>
<tr>
<td>7</td>
<td>1.36</td>
<td>0.75</td>
<td>0.80</td>
</tr>
<tr>
<td>8</td>
<td>1.44</td>
<td>0.78</td>
<td>0.91</td>
</tr>
<tr>
<td>9</td>
<td>1.25</td>
<td>0.73</td>
<td>1.01</td>
</tr>
<tr>
<td>10</td>
<td>0.58</td>
<td>0.07</td>
<td>0.20</td>
</tr>
<tr>
<td>11</td>
<td>0.99</td>
<td>0.89</td>
<td>1.05</td>
</tr>
<tr>
<td>12</td>
<td>1.65</td>
<td>0.80</td>
<td>1.02</td>
</tr>
<tr>
<td>13</td>
<td>1.03</td>
<td>0.38</td>
<td>0.69</td>
</tr>
<tr>
<td>14</td>
<td>3.80</td>
<td>1.92</td>
<td>3.55</td>
</tr>
<tr>
<td>15</td>
<td>3.35</td>
<td>1.74</td>
<td>2.89</td>
</tr>
<tr>
<td>16</td>
<td>1.20</td>
<td>0.58</td>
<td>0.75</td>
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<tr>
<td>17</td>
<td>1.65</td>
<td>0.79</td>
<td>0.98</td>
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<tr>
<td>18</td>
<td>1.90</td>
<td>1.22</td>
<td>1.67</td>
</tr>
<tr>
<td>19</td>
<td>1.21</td>
<td>0.90</td>
<td>1.25</td>
</tr>
<tr>
<td>20</td>
<td>0.70</td>
<td>0.12</td>
<td>0.14</td>
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<tr>
<td>21</td>
<td>1.18</td>
<td>0.65</td>
<td>0.69</td>
</tr>
<tr>
<td>22</td>
<td>1.29</td>
<td>0.78</td>
<td>0.95</td>
</tr>
<tr>
<td>23</td>
<td>1.10</td>
<td>0.55</td>
<td>0.59</td>
</tr>
<tr>
<td>24</td>
<td>0.89</td>
<td>0.19</td>
<td>0.62</td>
</tr>
<tr>
<td>25</td>
<td>0.85</td>
<td>0.15</td>
<td>0.51</td>
</tr>
</tbody>
</table>

RNA Extraction and Quantitative RT-PCR

RNA is extracted from the cells SW620 (having p53 R273H mutation) and Saos2 (without p53 R273H mutation) using a QiagenRNeasy Kit, and the gene expression level is measured by quantitative RT-PCR using TaqMan gene expression assays (Applied Biosciences, Carlsbad, CA, USA). The gene expression level is normalized with b-actin, and the average is presented with standard deviation from duplicates or triplicates of repeated experiments. To compare the mRNA levels of p53 targets p21, DR5, GADD45, PUMA and Noxa in SW620 and Saos2 cells, upon treatment of compound 1, all 5 target genes expression were increased in SW620 cells but no change in Saos2 cells. The data showed the restoration of p53 transactivational function through the "WT-like" conformational change induced by compound 1.
Claims

1. A compound having the general structural formulae (I):

Wherein, the group R can be selected from the group consisting of:

\[ R_1, R_2, R_3, R_4 \]

\[ R_5, R_6, R_7 \]

\[ R_i, R_2, R_3, R_4 \]

are independently hydrogen, halogen, \(Ci_{-6}\) alkoxy, -S(0) \_2\_R_5, -C(0)OR \_5, -C(0)R \_5, -C(0)NR \_6\_R_7. \(Ci_{-6}\) alkyl, \(C_{2-6}\) alkenyl, cyclopropyl, or \(C_{2-6}\) alkynyl, each of which can be optionally substituted with halogen, amino, hydroxyl, alkoxy or cyano, morpholinyl, piperazinyl, quinolinyl, aryl, \(Ci_{-6}\) heterocycle, 5 or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

\[ R_5, R_6, R_7 \]

is independently hydrogen, halogen, \(Ci_{-6}\) alkoxy, \(Ci_{-6}\) alkyl, \(C_{2-6}\) alkenyl or \(C_{2-6}\) alkynyl, each of which can be optionally substituted with halogen, amino, hydroxyl, alkoxy or cyano;

or pharmaceutical acceptable salts thereof.

2. The compound according to claim 1, wherein the compound of formula I can be selected from the group consisting of:

\[ (II) \]

\[ (III) \]

\[ (IV) \]

\[ (V) \]
Wherein, Ri, R2, R3, and R4 are independently hydrogen, halogen, C1-6 alkoxy, -S(0) R5, -C(0)OR 5, -C(0)NR 6 R7, C1-6 alkyl, C2-6 alkenyl, cyclopropyl or C2-6 alkylnyl, each of which can be optionally substituted with halogen, amino, hydroxyl, alkoxy or cyano, morpholinyl, piperazinyl, quinolinyl, aryl, C]6 heterocycle, 5 or 6 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S;

R5, R6, R7 is independently hydrogen, halogen, C1-6 alkoxy,Ci-6 alkyl, C2-6 alkenyl or C2-6 alkynyl, each of which can be optionally substituted with halogen, amino, hydroxyl, alkoxy or cyano; or pharmaceutical acceptable salts thereof.

3. The compound according to claim 1 or 2, wherein Ri, R2, R3 and R4 are independently hydrogen, halogen, methyl, ethyl, aryl, cyano, ethyloxy, -C(0)NH 2, -C(0)NHCi.6 alkyl, C1-6 heterocycle.

4. The compound according to claim 1 or 2, wherein R5, R6, R7 are independently methyl.

5. The compound according to any one of claims 1 to 4, wherein halogen is F or Cl.

6. The compound according to claim 1 or 2, said compound is selected from the group consisting of:

(1-((6-methylpyridin-2-yl)methyl)- 1H-indol-3-yl)methanol;
6-((3-(hydroxymethyl)- 1H-indol-1-yl)methyl)picolinonitrile;
(1-((6-chloropyridin-2-yl)methyl)- 1H-indol-3-yl)methanol;
(1-((5-methylpyiidin-2-yl)methyl)- 1H-indol-3-yl)methanol;
(1-((4-methylpyridin-2-yl)methyl)-IH-indol-3-yl)methanol;
(1-((3-methylpyridin-2-yl)methyl)- 1H-indol-3-yl)methanol;
(1-((6-phenylpyridin-2-yl)methyl)- 1H-indol-3-yl)methanol;
(1-(pyridin-2-ylmethyl)- 1H-indol-3-yl)methanol;
(1-(pyridin-3-ylmethyl)-1H-indol-3-yl)methanol;
(1-(pyridin-4-ylmethyl)-1H-indol-3-yl)methanol;
(1-((6-ethylpyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
(1-((6-methoxypyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
(1-((6-fluoropyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
6-((3-(hydroxymethyl)-1H-indol-1-yl)methyl)picolinamide;
N-ethyl-6-((3-(hydroxymethyl)-1H-indol-1-yl)methyl)picolinamide;
(1-((6-(piperidin-1-yl)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
(1-((6-morpholopyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
(1-((6-(pyrrolidin-1-yl)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
(1-((6-(cyclopropylamino)pyridin-2-yl)methyl)-1H-indol-3-yl)methanol;
(1-(quinolin-2-ylmethyl)-1H-indol-3-yl)methanol;
(1-(isoquinolin-3-ylmethyl)-1H-indol-3-yl)methanol;
(1-(isoquinolin-1-ylmethyl)-1H-indol-3-yl)methanol;
(1-((8-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol;
(1-((7-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol; and
(1-((6-methylquinolin-2-yl)methyl)-1H-indol-3-yl)methanol; or pharmaceutical acceptable salts thereof.

7. A pharmaceutical composition, comprising the compound according to any one of claims 1-6 or pharmaceutical acceptable salts thereof.

8. The pharmaceutical composition according to claim 7, wherein said composition can be an oral composition, injectable composition or suppository.

9. A process for preparing the compound of any one of claims 1 to 6, comprising steps:
Step 1:

lH-indole-3-carboxaldehyde is reacted with substituted chloromethylpyridine or chloromethylquinolone in the presence of a base, such as cesium carbonate, preferably at 50°C~100°C to afford lH-indole-3-carboxaldehyde derivatives of compound of formula (Γ) of the scheme;

Step 2:

lH-indole-3-carboxaldehyde derivatives of compound of formula (Γ) of the scheme can be reduced with a reducing agent, such as sodium borohydride to obtain alcohol derivative compound of formula (I) of the scheme.

10. Use of the compound according to any one of claims 1 to 6 in preparation of medicament for inhibiting WNT secretion from a cell or for restoring mutant P53 function in a cell.

11. A method for inhibiting WNT secretion from a cell of with an effective amount of the compound according to any one of claims 1 to 6.

12. A method for restoring mutant P53 function in a cell with an effective amount of the compound according to any one of claims 1 to 6.

13. The method according to any one of claims 11 to 12, wherein the cell is a cancer cell.

14. The method according to claim 13, wherein the cell is a fibrogenic cell.

15. A method for treating cancers related to the P53 mutation with an effective amount of the compound according to any one of claims 1 to 6.

16. The method according to claim 15, wherein said cancers can be selected from the group consisting of lung cancer, such as small cell and non-small cell, breast cancer, prostate cancer, carcinoid cancer, bladder cancer, gastric cancer, pancreatic cancer, liver cancer, colorectal cancer, head cancer and neck squamous cell carcinoma, esophageal cancer, ovarian cancer, cervical cancer, endometrial cancer, mesothelioma cancer, melanoma cancer, sarcoma cancer, osteosarcoma cancer, liposarcoma cancer, thyroid cancer, desmoid cancer, acute myelocytic leukemia, and chronic myelocytic leukemia.
Drawings

Figure 1a

Figure 1b

Figure 1
# A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/06(2006.01)i; C07D 401/14(2006.01)i; A61K 31/4439(2006.01)i; A61K 31/4725(2006.01)i; A61P 35/00(2006.01)i

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)

C07D401; A61K31; A61P35

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

WPI, EPODOC, CNABS, CNTXT, CNKIP, GISTRY (STN), CAPLUS (STN); indol, methanol, pyridin, picolin, quinolin, isoquinolin, p53, oncrasin, tumo?, cancer

# C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>description, paragraphs [0001]-[0003], [0034], [0037]-[0040] and [0043]-[0045], examples 1, 11, 18 and 20</td>
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<td>JP 2009091326 A (NIPPON KAYAKUKK) 30 April 2009 (2009-04-30)</td>
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<td>description, paragraphs [0001]-[0003], [0034], [0037]-[0040] and [0043]-[0045], examples 1, 11, 18 and 20</td>
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<td>CN 102603717 A (UNIV PLA SECOND MILITARY MEDICAL) 25 July 2012 (2012-07-25)</td>
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* Further documents are listed in the continuation of Box C. See patent family annex.

* 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
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- "O" document referring to an oral disclosure, use, exhibition or other means
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Date of the actual completion of the international search

15 February 2015

Date of mailing of the international search report

25 March 2015

Name and mailing address of the ISA/CN

STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA(ISA/CN)
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Authorized officer

HAN, Tao

Facsimile No. (86-10)62019451

Telephone No. (86-10)61648369

Form PCT/ISA/210 (second sheet) (July 2009)
### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>1-2, 4-5</td>
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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.: 11-16**
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   [1] The subject matter of claims 11-16 relates to methods for the treatment of human body by therapy as defined in PCT Rule 39.1(IV). This search has been carried out on the basis of the subject matter of the use in manufacture of medicaments for treating the alleged diseases.

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.:**
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
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