VINYL INDAZOLYL COMPOUNDS

Fibroblast growth factor (FGF) has been recognized as an important mediator of many physiological processes, such as morphogenesis during development and angiogenesis. The fibroblast growth factor receptor (FGFR) family consists of four members (FGFR1-FGFR4), which are glycoproteins composed of extracellular immunoglobulin (Ig)-like domains, a hydrophobic transmembrane region and a cytoplasmic part containing a tyrosine kinase domain. FGF binding leads to FGFR dimerization, followed by receptor autophosphorylation and activation of downstream signaling pathways. Receptor activation is sufficient for the recruitment and activation of specific downstream signaling partners that participate in the regulation of diverse processes such as cell growth, cell metabolism and cell survival. Thus, the FGF/FGFR signaling pathway has pleiotropic effects on many biological processes critical to tumor cell proliferation, migration, invasion, and angiogenesis.

Vinyl indazoles are known in the art for the treatment of cancer. See for example, WO0210137 and WO2003101968. FGFR inhibitors are also known in the art. See for example, WO2002022598.

The present disclosure~~invention~~ provides novel vinyl indazolyl compounds believed to have clinical use for treatment of proliferative disorders such as cancer and particularly in disorders mediated by FGF and/or FGFR dysregulation.

Additionally, certain compounds of the present disclosure~~invention~~ have superior FGFR1 and FGFR3 potency compared to certain previously known FGFR inhibitors.

In one aspect, there is~~The present invention~~ provide~~s~~d a compound which is (E)-2-(4-(2-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)vinyl)-1H-pyrazol-1-yl)ethanol, or a pharmaceutically acceptable salt thereof.

The present disclosure~~invention~~ also provides the compound which is (R)-(E)-2-(4-(2-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)vinyl)-1H-pyrazol-1-yl)ethanol or a pharmaceutically acceptable salt thereof.

The present disclosure~~invention~~ provides a method of treating cancer wherein the cancer is selected from the group consisting of breast cancer, non-small cell lung (NSCL) cancer, bladder cancer, gastric cancer, pancreatic cancer, prostate cancer, colon

cancer, multiple myeloma, liver cancer, melanoma, head and neck cancer, thyroid cancer, renal cell cancer, glioblastoma, and testicular cancer in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound or salt of the present disclosure~~invention~~.

In another aspect, there is~~This invention also~~ provided~~s~~ a pharmaceutical composition~~s~~ comprising a compound or salt as defined above~~of the present invention~~ in combination with a~~one or more~~ pharmaceutically acceptable carrier~~s~~, diluent~~s~~, or excipient~~s~~. The pharmaceutical composition as defined above may also be in combination with more than one pharmaceutically acceptable carrier, diluent, or excipient. In a particular embodiment the composition further comprises one or more other therapeutic agents.

In another aspect, there is~~This invention also~~ provided~~s~~ a compound or salt as defined above~~of the present invention~~ for use in therapy. In another aspect, there is provided a compound or salt as defined above for the treatment of cancer. Additionally, this disclosure~~invention~~ provides use of a compound or salt as defined above~~of the present invention~~ in the manufacture of a medicament for treating cancer. In particular these cancers are selected from the group consisting of breast cancer, lung cancer, bladder cancer, gastric cancer, pancreatic cancer, prostate cancer, colon cancer, multiple myeloma AML, liver cancer, melanoma, head and neck cancer, thyroid cancer, renal cell cancer, glioblastoma, and testicular cancer. More particularly, the cancers are selected from the group consisting of breast cancer, non-small cell lung cancer, bladder cancer, gastric cancer, pancreatic cancer, prostate cancer, colon cancer, multiple myeloma, liver cancer, melanoma, head and neck cancer, thyroid cancer, renal cell cancer, glioblastoma, and testicular cancer. Most particularly the cancer is non-small cell lung cancer. Most particularly the cancer is gastric cancer. Most particularly the cancer is multiple myeloma. Furthermore, this disclosure~~invention~~ provides a pharmaceutical composition for treating cancer selected from the group consisting of breast cancer, non-small cell lung cancer, bladder cancer, gastric cancer, pancreatic cancer, prostate cancer, colon cancer, multiple myeloma, liver cancer, melanoma, head and neck cancer, thyroid cancer, renal cell cancer, glioblastoma, and testicular cancer comprising a compound or salt of the present invention as an active ingredient.

The skilled artisan will appreciate that racemic (E)-2-(4-(2-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)vinyl)-1H-pyrazol-1-yl)ethanol can be made essentially as described for (R)-(E)-2-(4-(2-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)vinyl)-1H-pyrazol-1-yl)ethanol starting from racemic 1-

(3,5-dichloropyridin-4-yl)ethanol in place of (S)-1-(3,5-dichloropyridin-4-yl)ethanol. Additionally, the skilled artisan will appreciate that (E)-2-(4-(2-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)vinyl)-1H-pyrazol-1-yl)ethanol contains one chiral center. It is preferred that (E)-2-(4-(2-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)vinyl)-1H-pyrazol-1-yl)ethanol exists as a single enantiomer. The single enantiomer may be prepared beginning with chiral reagents or by stereoselective or stereospecific synthetic techniques. Alternatively, the single enantiomer may be isolated from mixtures by standard chiral chromatographic or crystallization techniques.

It will be understood by the skilled reader that all of the compounds of the present disclosure~~invention~~ are capable of forming salts. The compounds of the present ~~invention~~disclosure are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Such pharmaceutically acceptable acid addition salts and common methodology for preparing them are well known in the art. *See, e.g.*, P. Stahl, *et al.*, HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION AND USE, (VCHA/Wiley-VCH, 2008); S.M. Berge, *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Sciences*, Vol 66, No. 1, January 1977.

The compounds of the present disclosure~~invention~~ can be prepared as illustrated in the preparations and examples below. The naming of the following preparations and examples is done using the Struct=Name naming feature in ChemDraw® Ultra 10.0.

Preparation 1

1-(3,5-Dichloropyridin-4-yl)ethanol

To a 3-neck 12 L round bottom flask add tetrahydrofuran (THF, 3 L) and diisopropylamine (DIPA, 315 mL, 2.24 mol) and cool to -78 °C. Add slowly n-butyllithium (1.6 M in hexanes, 1400 mL, 2.24 mol). After the addition is complete and the temperature has settled at -78 °C slowly add a solution of 3,5-dichloropyridine (296.7 g, 2.00 mol) which immediately forms a yellow solution that changes to a rust colored suspension. After the addition is complete and the temperature has settled at -78 °C slowly add acetaldehyde (230 mL, 4.05 mol) in THF (600 mL). Continue