

## AMINOPYRIDYLOXYPYRAZOLE COMPOUNDS

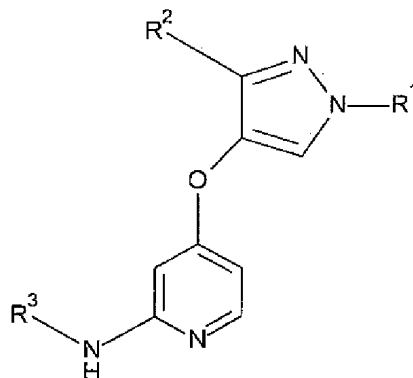
The present invention relates to novel aminopyridyloxypyrazole compounds that inhibit activity of transforming growth factor beta receptor 1 (TGF $\beta$ R1), pharmaceutical compositions comprising the compounds, and methods of using the compounds to treat cancer, preferably colon cancer, melanoma, hepatocellular carcinoma (HCC), renal cancer, glioblastoma (GBM), pancreatic cancer, myelodysplastic syndrome (MDS), lung cancer, and gastric cancer, and/or fibrosis, preferably liver fibrosis and chronic kidney disease.

Transforming growth factor beta (TGF-beta or TGF $\beta$ ) is a multi-functional cytokine which binds to the heteromeric complexes of TGF-beta type I and type II serine/threonine kinase receptors and activates the TGF-beta receptor complex, which phosphorylates and activates SMAD2 and SMAD3, which then associate with SMAD4 and migrate into the nucleus and regulate expression of different target genes. Key players of TGF-beta receptor signal transduction pathway include TGF $\beta$ 1, TGF $\beta$ 2, TGF $\beta$ 3, TGF $\beta$ R1, TGF $\beta$ R2, SMADs, SnoN, SARA, SKI, DAB, TRAP, TAK1, SMIF, E2F4, E2F5, RBL1, RBL2, RB1, TFDP1, TFDP2, SMURF1, SMURF2, P300, CBP, and JUN. The SMAD mediated TGF-beta receptor pathway regulates various cellular and physiological processes such as proliferation, differentiation, growth, migration, myelination, cell cycle arrest, apoptosis and development.

Small molecule inhibitors of TGF $\beta$ R1 are already known in the art for the treatment of cancer and/or fibrosis. See for example, WO2012/002680, WO2009/022171, WO2004/048382, and WO2002/094833. Unfortunately, there is no known curative treatments for many types of cancers or fibrosis. It would be desirable to have additional small molecule inhibitors of TGF $\beta$ R1 for the treatment of cancer, preferably colon cancer, melanoma, hepatocellular carcinoma (HCC), renal cancer, glioblastoma (GBM), pancreatic cancer, myelodysplastic syndrome (MDS), lung cancer, and gastric cancer, and/or fibrosis, preferably liver fibrosis and chronic kidney disease, in particular compounds that are more selective for TGF $\beta$ R1.

### Summary

In a first aspect of the present disclosure, there is provided a compound of the formula:



wherein:

5 R<sup>1</sup> is hydrogen, isopropyl, difluoromethyl, difluoroethyl, or cyclopropyl;

R<sup>2</sup> is ethyl, tert-butyl, pyridin-2-yl, tetrahydropyran-4-yl, tetrahydrofuran-3-yl, cyclopropyl, or cyclobutyl; and

10 R<sup>3</sup> is carbamoylphenyl, pyridin-2-yl, (1-hydroxy-1-methylethyl)pyridinyl, 1-methyl-2-oxo-1H-pyridin-4-yl, 1-methylpyrazolyl, pyrazin-2-yl, 2-methoxypyrimidin-4-yl, 1-methyl-2-oxo-1H-pyrimidin-4-yl, pyridazin-3-yl, 6-chloropyridazin-3-yl, 6-methylpyridazin-3-yl, or 6-methoxypyridazin-3-yl;  
or a pharmaceutically acceptable salt thereof.

15 In a second aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound or salt according to the first aspect and one or more pharmaceutically acceptable excipients, carriers, or diluents.

In a third aspect of the present disclosure, there is provided a use of 2-{4-[(4-{[1-cyclopropyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]oxy}pyridin-2-yl)amino]pyridin-2-yl}propan-2-ol, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

20 In a fourth aspect of the present disclosure, there is provided a use of 2-{4-[(4-{[1-cyclopropyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]oxy}pyridin-2-yl)amino]pyridin-2-yl}propan-2-ol, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating fibrosis in a patient.

In a fifth aspect of the present disclosure, there is provided a compound or salt according to the first aspect for use in therapy.

In a sixth aspect of the present disclosure, there is provided a compound or salt according to the first aspect for use in the treatment of cancer.

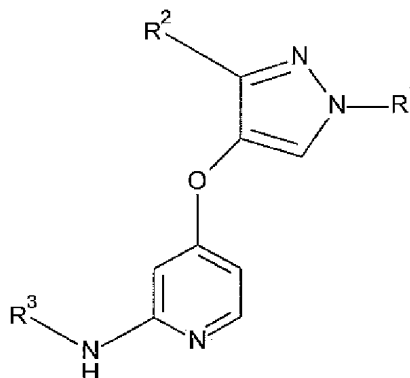
- 5        In a seventh aspect of the present disclosure, there is provided a compound or salt according to the first aspect for use in the treatment of fibrosis.

### **Description**

The present invention provides a compound of the formula:

We Claim:

1. A compound of the formula:



5 wherein:

R<sup>1</sup> is hydrogen, isopropyl, difluoromethyl, difluoroethyl, or cyclopropyl;

R<sup>2</sup> is ethyl, tert-butyl, pyridin-2-yl, tetrahydropyran-4-yl, tetrahydrofuran-3-yl, cyclopropyl, or cyclobutyl; and

R<sup>3</sup> is carbamoylphenyl, pyridin-2-yl, (1-hydroxy-1-methylethyl)pyridinyl, 1-methyl-2-oxo-1H-pyridin-4-yl, 1-methylpyrazolyl, pyrazin-2-yl, 2-methoxypyrimidin-4-yl, 1-methyl-2-oxo-1H-pyrimidin-4-yl, pyridazin-3-yl, 6-chloropyridazin-3-yl, 6-methylpyridazin-3-yl, or 6-methoxypyridazin-3-yl;  
or a pharmaceutically acceptable salt thereof.

15 2. The compound according to Claim 1 which is 2-{4-[(4-{[1-cyclopropyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]oxy}pyridin-2-yl)amino]pyridin-2-yl}propan-2-ol or a pharmaceutically acceptable salt thereof.

20 3. The compound or salt according to either Claim 1 or 2 which is 2-{4-[(4-{[1-cyclopropyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]oxy}pyridin-2-yl)amino]pyridin-2-yl}propan-2-ol 4-methylbenzenesulfonate.

25 4. The compound or salt according to any one of Claims 1-3 which is crystalline 2-{4-[(4-{[1-cyclopropyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]oxy}pyridin-2-yl)amino]pyridin-2-yl}propan-2-ol 4-methylbenzenesulfonate.

5. The compound or salt according to Claim 4 which is crystalline 2-{4-[(4-{[1-cyclopropyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]oxy}pyridin-2-yl)amino]pyridin-2-yl}propan-2-ol 4-methylbenzenesulfonate characterized by an X-ray powder diffraction pattern (Cu radiation,  $\lambda$ -1.54060 Å) comprising a peak at 17.8° with one or more peaks selected from the group consisting of 19.7°, 18.4°, and 22.0° ( $2\theta \pm 0.2^\circ$ ).
6. A pharmaceutical composition comprising a compound or salt according to any one of Claims 1-5 and one or more pharmaceutically acceptable excipients, carriers, or diluents.
7. Use of 2-{4-[(4-{[1-cyclopropyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]oxy}pyridin-2-yl)amino]pyridin-2-yl}propan-2-ol, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.
8. The use according to Claim 7 wherein the salt is a 4-methylbenzenesulfonate.
9. The use according to Claim 7 or 8 wherein the cancer is selected from the group consisting of colon cancer, melanoma, hepatocellular carcinoma, renal cancer, glioblastoma, pancreatic cancer, myelodysplastic syndrome, lung cancer, and gastric cancer.
10. Use of 2-{4-[(4-{[1-cyclopropyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]oxy}pyridin-2-yl)amino]pyridin-2-yl}propan-2-ol, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating fibrosis in a patient.
11. The use according to Claim 10 wherein the salt is a 4-methylbenzenesulfonate.

12. The use according to Claim 10 or 11 wherein the fibrosis is selected from the group consisting of liver fibrosis and chronic kidney disease.

5 13. A compound or salt according to any one of Claims 1-5 for use in therapy.

14. A compound or salt according to any one of Claims 1-5 for use in the treatment of cancer.

10 15. A compound or salt for use according to Claim 14 wherein the cancer is selected from the group consisting of colon cancer, melanoma, hepatocellular carcinoma, renal cancer, glioblastoma, pancreatic cancer, myelodysplastic syndrome, lung cancer, and gastric cancer.

15 16. A compound or salt according to any one of Claims 1-5 for use in the treatment of fibrosis.

17. A compound or salt for use according to Claim 16 wherein the fibrosis is selected from the group consisting of liver fibrosis and chronic kidney disease.