

CDC7 Inhibitors

The present invention relates to isoindolinone compounds, or pharmaceutically acceptable salts thereof, that inhibit CDC7 and may be useful for treating cancer.

CDC7 is a serine/threonine kinase that plays a key role in the initiation of DNA replication and regulation of the S phase cell cycle check point. Upregulation of CDC7 has been observed in numerous tumor cell lines. Also, inhibition of CDC7 in such cell lines has resulted in cell cycle arrest. Therefore, CDC7 inhibition may be useful for cancer therapy.

CDC7 inhibitors are known in the art. Isoindolinone compounds are also known in the art. WO 2005/100351 discloses certain isoindolinone compounds as nicotinic acetylcholine receptor-reactive compounds.

There remains a need to provide alternative CDC7 inhibitors for treatment of cancer. Accordingly, the present invention provides inhibitors of CDC7 which may be useful for treating cancer.

In one aspect, the present disclosure provides a compound which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, or a pharmaceutically acceptable salt or hydrate thereof.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound or salt as disclosed above, and a pharmaceutically acceptable carrier, diluent, or excipient.

In another aspect, the present disclosure provides use of a compound or salt as disclosed above in the manufacture of a medicament for the treatment of cancer, wherein the cancer is selected from the group consisting of breast cancer, triple negative breast cancer, ovarian cancer, lung cancer, colorectal cancer, hematologic cancer, and leukemia.

In another aspect, the present disclosure provides the compound or salt as disclosed above for use in therapy.

In another aspect, the present disclosure provides the compound or salt as disclosed above for use in the treatment of cancer.

The present invention provides a compound which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, or a pharmaceutically acceptable salt thereof.

The present invention provides a compound which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, isomer 2, or a pharmaceutically acceptable salt thereof.

The present invention provides a compound which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, isomer 1, or a pharmaceutically acceptable salt thereof.

WE CLAIM:

1. A compound which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, or a pharmaceutically acceptable salt or hydrate thereof.

2. The compound according to Claim 1 which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one.

3. The compound according to Claim 1, which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, ~~isomer 2(3R)-3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one~~, or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 3, which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, ~~isomer 2(3R)-3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one~~.

5. The compound according to Claim 1, which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, ~~isomer 1(3S)-3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one~~, or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 5, which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, ~~isomer 1(3S)-3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one~~.

7. The compound according to Claim 1 which is 3-(5-fluoropyrimidin-4-yl)-3-methyl-6-(1H-pyrazol-4-yl)isoindolin-1-one, or hydrate thereof.

8. The compound according to Claim 7 which is a hydrate in a crystalline form characterized by a X-ray powder diffraction pattern having characteristic peaks, in $2\theta \pm 0.2$, occurring at 22.27 and one or more of 13.46, 16.54, 16.66, 18.10 and 23.13.

9. A pharmaceutical composition comprising the compound or salt according to any one of Claims 1-8, and a pharmaceutically acceptable carrier, diluent, or excipient.

~~10. Use of a compound or salt according to any one of claims 1-8 in the manufacture of a medicament for the treatment of cancer.~~

~~110. Use of a compound or salt according to any one of claims 1-8 in the manufacture of a medicament for the treatment of cancer~~The use according to Claim 10, wherein the cancer is selected from the group consisting of breast cancer, triple negative breast cancer, ovarian cancer, lung cancer, colorectal cancer, hematologic cancer, and leukemia.

~~1211. The use according to Claim 110, wherein the cancer is colorectal cancer.~~

~~1312. The compound or salt according to any one of Claims 1-8 for use in~~ therapy.

~~14~~13. The compound or salt according to any one of Claims 1-8 for use in the treatment of cancer.

~~15~~14. The compound or salt for use according to Claim ~~14~~13, wherein the cancer is selected from the group consisting of breast cancer, triple negative breast cancer,
5 ovarian cancer, lung cancer, colorectal cancer, hematologic cancer, and leukemia.

~~16~~15. The compound or salt for use according to Claim ~~15~~14, wherein the cancer is colorectal cancer.