An Aurora A Kinase Inhibitor for Use in the Treatment of Neuroblastoma

The present invention relates to the use of an Aurora A kinase inhibitor, and salts thereof, for the treatment of neuroblastoma.

Neuroblastoma is one of the most common solid tumors in children, and more than 650 neuroblastoma cases are diagnosed each year in North America. Neuroblastoma can be subdivided into two defined patient subsets, referred to generally as low risk and high risk. Low risk neuroblastoma is usually found in children younger than 18 months of age with limited disease burden resulting in a favorable prognosis. However, high-risk neuroblastoma generally occurs in children older than 18 months, frequently metastatic in bone tissue, resulting in poor prognosis. Although advances in multimodal treatment strategies have led to improved outcomes for neuroblastoma patients, survival rates for the high-risk category patients remain poor with less than 50% survival five years after diagnosis.

High-risk neuroblastoma is associated with the MYCN gene which encodes the N-myc proto-oncogene protein (N-MYC). Although incompletely understood, N-MYC and Aurora A Kinase appear to interact, and Aurora A kinase expression and amplification are thought to stabilize N-MYC and/or slow its degradation, which in turn would cause an increase in N-MYC levels. Michaelis, M, et al., "Aurora Kinases as Targets in Drug–Resistant Neuroblastoma Cells", PLOS One, 2014, **9**(9) e108758.

Aurora A kinase inhibitors are known in the art (see, for example, PCT Patent Application Publication, WO2016/077191, which discloses the compound of Formula I (see below). Use of certain Aurora kinase inhibitors, including an Aurora A selective inhibitor, alisertib, and a pan Aurora inhibitor, tozasertib, have been associated with unacceptably high levels of neutropenia and other toxic effects.

A need exists for novel approaches and medications to treat neuroblastoma, in particular, high-risk neuroblastoma. In addition, there is a need to provide methods of inhibiting Aurora kinases, in particular Aurora A kinase, and decreasing the expression and/or activity of N-MYC. The present invention addresses these needs and provides a method of treating neuroblastoma.

Summary

In one aspect of the present disclosure, there is provided a use of a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating neuroblastoma.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient, in the manufacture of a medicament for treating neuroblastoma.

In a further aspect of the present disclosure, there is provided a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use in the treatment of neuroblastoma.

In another aspect of the present disclosure, there is provided a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient, for use in the treatment of neuroblastoma.

Description

In one form, the present invention provides a method for treating neuroblastoma in a patient in need of treatment. Preferably the present invention provides a method for treating high neuroblastoma in a patient in need of treatment. The method comprises

What is Claimed is:

1. Use of a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating neuroblastoma.

2. The use according to claim 1 wherein the compound is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid.

3. The use according to claim 1 wherein the compound is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : 2-methylpropan-2-amine (1:1) salt.

4. The use according to claim 1 wherein the compound is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : amine (1:1) salt.

5. Use of a pharmaceutical composition comprising a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient, in the manufacture of a medicament for treating neuroblastoma.

6. The use of claim 5 wherein the composition comprises a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid.

7. The use of claim 5 wherein the composition comprises a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : 2-methylpropan-2-amine (1:1) salt.

8. The use of claim 5 wherein the composition comprises a compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : amine (1:1) salt.

9. A compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use in the treatment of neuroblastoma.

10. The compound for use according to claim 9 which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid.

11. The compound for use according to claim 9 which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : 2-methylpropan-2-amine (1:1) salt.

12. The compound according to claim 9 which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : amine (1:1).

13. A compound which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient, for use in the treatment of neuroblastoma.

14. The compound for use according to claim 13 which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid.

15. The compound for use according to claim 13 which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : 2-methylpropan-2-amine (1:1) salt.

16. The compound according to claim 13 which is (2R,4R)-1-[(3-chloro-2-fluoro-phenyl)methyl]-4-[[3-fluoro-6-[(5-methyl-1H-pyrazol-3-yl)amino]-2-pyridyl]methyl]-2-methyl-piperidine-4-carboxylic acid : amine (1:1).