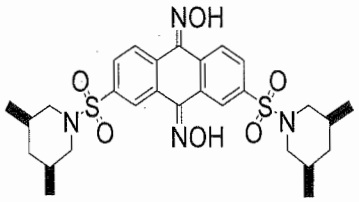
SUMMARY OF THE INVENTION

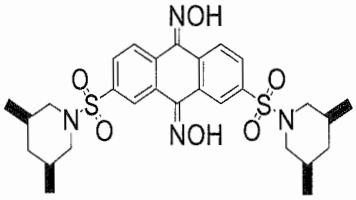
~~The present invention provides~~Disclosed herein are methods for treating disease or disorders by administering a therapeutically effective amount of an agent that inhibits transducin β-like protein 1 (TBL1) from binding disease-associated molecules. In particular, the provided methods and compositions relate to the treatment, diagnosis, and/or prevention of β-catenin signaling pathway disorders.

In one aspect, the present invention refers to use of a therapeutically effective amount of an agent that disrupts TBL1 interaction with a coactivator molecule in the manufacture of a medicament for treating and/or preventing a disorder selected from the group consisting of a myeloproliferative neoplasia, chronic myeloid leukemia and acute myeloid leukemia, wherein the agent is defined below:



or a pharmaceutically acceptable salt thereof. In another preferred ~~embodiment~~example, the β-catenin related disorder includes myeloproliferative neoplasia (MPN), chronic myeloid leukemia (CML) and acute myeloid leukemia (AML).

In the most preferred ~~embodiment~~example, the provided agent has the following structure:



or a pharmaceutically acceptable salt thereof. This agent is referred to as Compound 1 throughout this application.

In a preferred ~~embodiment~~example, TBL1 is selected from the group consisting of transducin (beta)-like 1X-linked (TBL1X), transducin (beta)-like 1Y-linked (TBL1Y) and transducin (beta)-like R1-linked TBLR1 proteins.

In one example~~embodiment~~, the activator is beta-catenin.

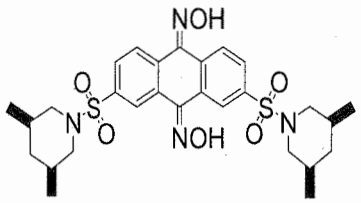
In another example~~embodiment~~, the activator is a beta-catenin related protein.

In another example~~embodiment~~, the provided agent can be used in combination with other therapeutic agents, including but not limited to tyrosine kinase inhibitor (including but not limited to nilotinib), histone deacetylase inhibitor (including, but not limited to panobinostat), other anti-cancer agents and other therapeutic agents.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of an agent that disrupts TBL1 interaction with a coactivator molecule in the manufacture of a medicament for treating and/or preventing a disorder selected from the group consisting of a myeloproliferative neoplasia, chronic myeloid leukemia and acute myeloid leukemia, wherein the agent is defined below:



or a pharmaceutically acceptable salt thereof.

2. The use of claim 1, wherein said disorder is myeloproliferative neoplasia.

3. The use of claim 1, wherein said disorder is chronic myeloid leukemia.

4. The use of claim 1, wherein said disorder is acute myeloid leukemia.

5. The use of claim 1, wherein said coactivator molecule is beta-catenin.

6. The use of claim 1, wherein said agent is provided further in combination with an agent that inhibits JAK2 kinase, BCR-ABL kinase, or histone deacetylase.

7. The use of claim 1, wherein said TBL1 is selected from the group consisting of Transducin (beta)-like 1X-linked (TBL1X), Transducin (beta)-like 1Y-linked (TBL1Y) and Transducin (beta)-like R1-linked TBLR1 proteins.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of an agent that disrupts TBL1 interaction with a coactivator molecule in the manufacture of a medicament for treating and/or preventing a disorder selected from the group consisting of a myeloproliferative neoplasia, chronic myeloid leukemia and acute myeloid leukemia.

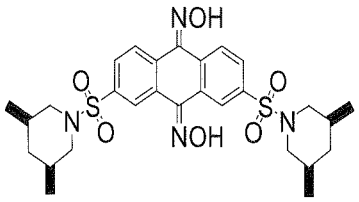
2. The use of claim 1, wherein said disorder is myeloproliferative neoplasia.

3. The use of claim 1, wherein said disorder is chronic myeloid leukemia.

4. The use of claim 1, wherein said disorder is acute myeloid leukemia.

5. The use of claim 1, wherein said coactivator molecule is beta-catenin.

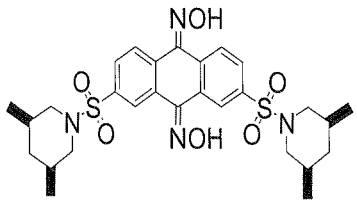
6. The use of claim 1, wherein said agent has the following structure:



or a pharmaceutically acceptable salt thereof.

7. The use of claim 1, wherein said agent is provided further in combination with an agent that inhibits JAK2 kinase, BCR-ABL kinase, or histone deacetylase.

8. The use of claim 7, wherein said agent has the following structure:



or a pharmaceutically acceptable salt thereof.

9. The use of claim 8, wherein said TBL1 is selected from the group consisting of Transducin (beta)-like 1X-linked (TBL1X), Transducin (beta)-like 1Y-linked (TBL1Y) and Transducin (beta)-like R1-linked TBLR1 proteins.