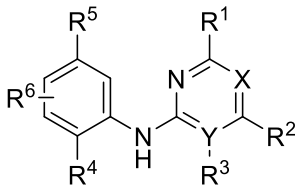
MLL1 present alone has very poor catalytic activity, and can only catalyze the monomethylation of H3K4. When MLL1 forms a core complex with WDR5, RbBP5, Ash2L, and DPY30, the enzymatic catalysis activity is greatly enhanced, especially the catalytic activity for H3K4me2. As a bridge linking a C-terminal WIN motif of MLL1 to other proteins, the WDR5 plays a vital role in the formation of the complex. Therefore, interfering with the WDR5 protein-protein interaction using a micromolecular inhibitor is an effective way to inhibit the enzymatic catalysis activity of MLL1, thereby inhibiting the expression of downstream *Hox* and *Meis-1* genes, and thus blocking the progression of leukemia.

Summary

In a first aspect, the present disclosure refers to an aniline-based WDR5 protein-protein interaction inhibitor, comprising a compound represented by general formula (I), a pharmaceutically acceptable salt thereof, and a hydrate or solvate thereof:



(I)

wherein X represents N;

Y represents C;

R^1, R^2 and R^3 are selected from the group consisting of hydrogen, C_1-C_6 alkyl, halo, -NR^7R^8, wherein R^7 and R^8 represent hydrogen;

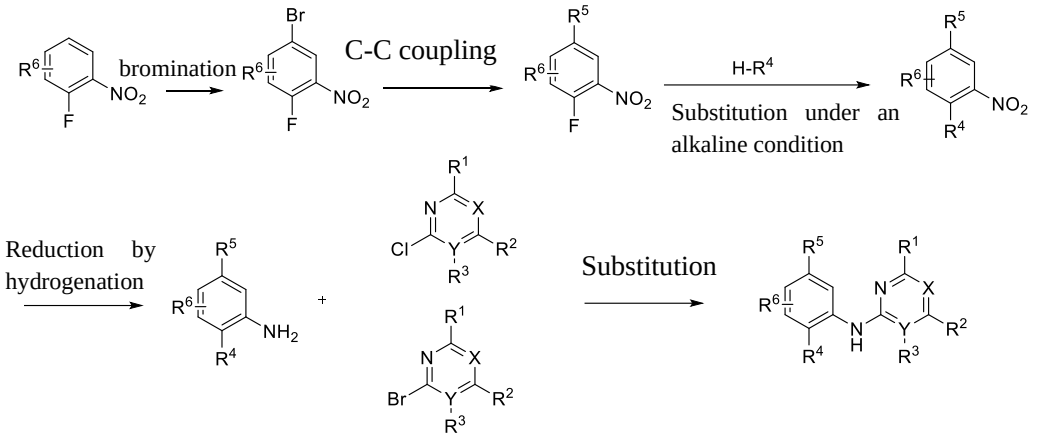
R^4 represents morpholinyl, piperazinyl, 4-substituted piperazinyl, 4-substituted homopiperazinyl, 3-substituted piperazinyl, or 2-substituted piperazinyl, wherein a substituent is C_1-C_4 alkyl;

R^5 represents nitro, amino, phenyl, substituted phenyl, 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, substituted 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, or -$NHCOR^9$; wherein R^9 represents hydroxyl, C_1-C_6 alkoxy, phenyl, substituted phenyl, 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, or substituted 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, wherein a substituent is C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, cyano, -$NHCOR^{10}$, -$CONR^{11}R^{12}$ or -$COOR^{10}$, wherein R^{10} represents hydrogen, C_1-C_6 alkyl, C_1-C_6 amino-substituted alkyl, 3- to 7-membered cycloalkyl, 3- to 7-membered nitrogenous or oxygenic heterocycle, or phenyl; and R^{11} and R^{12} represent hydrogen, C_1-C_6 alkyl, phenyl or substituted phenyl, or substituted or unsubstituted 3- to

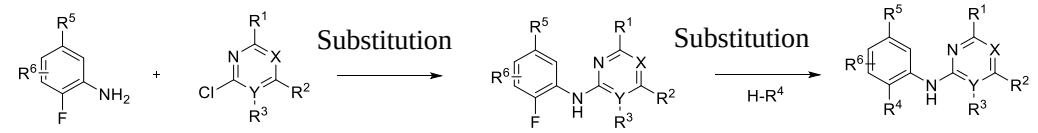
7-membered nitrogenous or oxygenic heterocycle, or 3- to 7-membered nitrogenous or oxygenic heterocycle formed by linking R^{11} and R^{12}; and

R^6 represents hydrogen, halo, or methyl.

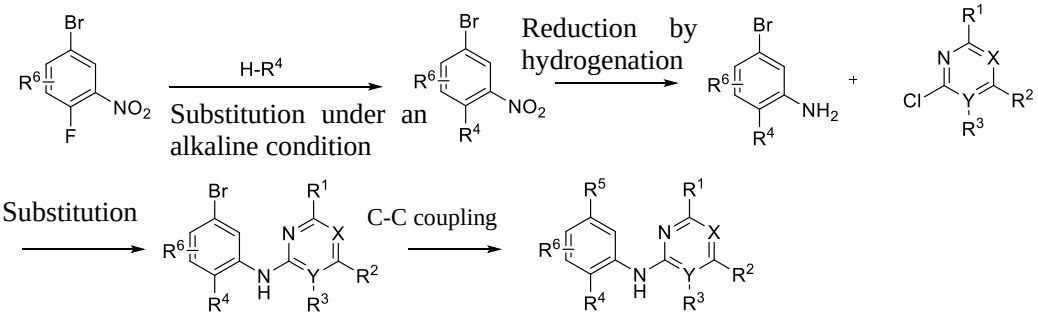
In another aspect, the present disclosure refers to a method for preparing the general formula (I) disclosed herein, comprising following reaction steps:



or:



or:



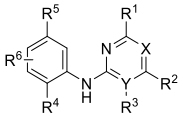
In yet another aspect, the present disclosure refers to a pharmaceutical composition, comprising the WDR5 protein-protein interaction inhibitor disclosed herein.

In a further aspect, the present disclosure refers to a use of the aniline-based WDR5 protein-protein interaction inhibitor disclosed herein in the preparation of a drug for treating a hematological tumor.

In another aspect, the present disclosure refers to an aniline-based WDR5 protein-protein interaction inhibitor disclosed herein, for use in treating a hematological tumor.

Object of the Disclosure: An object of the present disclosure is to provide a WDR5 protein-protein interaction inhibitor, which inhibits the level of a histone methyltransferase and the expression of a downstream hematopoietic gene at the cellular level and inhibits the growth of transplanted tumors in nude mice at the animal level; and use thereof in the treatment of a drug for an indication related to a MLL enzyme function. The inhibitor can be used to treat diseases such as acute leukemia.

Technical Solution: The present disclosure discloses a micromolecular compound that may interfere with WDR5 protein-protein interaction, inhibits the catalytic activity of a MLL1 for methyl transfer and down-regulates the expression levels of *Hox* and *Meis-1* genes by interfering with the WDR5 protein-protein interaction, thereby inducing the apoptosis of leukemia cells for use in the treatment of acute leukemia. The compound of the present disclosure has a structure below:



where X represents CH or N;

Y represents C or N;

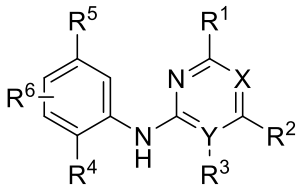
R^1, R^2 and R^3 are identical to or different from each other, and are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted with C_1-C_6 alkoxy, nitro, halo, cyano, aldehyde group, hydroxyl,-NR^7R^8, or  formed by linking R^2 and R^3, where R^7 and R^8 are identical to or different from each other, and each independently represent hydrogen or C_1-C_4 alkyl, or 3- to 7-membered nitrogenous heterocycle formed by linking R^7 and R^8;

R^4 represents morpholinyl, piperazinyl, 4-substituted piperazinyl, 4-substituted homopiperazinyl, 3-substituted piperazinyl, or 2-substituted piperazinyl, where a substituent is C_1-C_4 alkyl, 3- to 7-membered cycloalkyl, hydroxyalkyl, or phenyl;

R^5 represents nitro, amino, phenyl, substituted phenyl, 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, substituted 5- to 6-membered oxygenic

Claims

1. An aniline-based WDR5 protein-protein interaction inhibitor, comprising a compound represented by general formula (I), a pharmaceutically acceptable salt thereof, and a hydrate or solvate thereof:



(I)

wherein X represents N;

Y represents C;

R^1, R^2 and R^3 are selected from the group consisting of hydrogen, C_1-C_6 alkyl, halo, -NR^7R^8, wherein R^7 and R^8 represent hydrogen;

R^4 represents morpholinyl, piperazinyl, 4-substituted piperazinyl, 4-substituted homopiperazinyl, 3-substituted piperazinyl, or 2-substituted piperazinyl, wherein a substituent is C_1-C_4 alkyl;

R^5 represents nitro, amino, phenyl, substituted phenyl, 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, substituted 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, or -$NHCOR^9$; wherein R^9 represents hydroxyl, C_1-C_6 alkoxy, phenyl, substituted phenyl, 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, or substituted 5- to 6-membered oxygenic or nitrogenous aromatic heterocycle, wherein a substituent is C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, cyano, -$NHCOR^{10}$, -$CONR^{11}R^{12}$ or -$COOR^{10}$, wherein R^{10} represents hydrogen, C_1-C_6 alkyl, C_1-C_6 amino-substituted alkyl, 3- to 7-membered cycloalkyl, 3- to 7-membered nitrogenous or oxygenic heterocycle, or phenyl; and R^{11} and R^{12} represent hydrogen, C_1-C_6 alkyl, phenyl or substituted phenyl, or substituted or unsubstituted 3- to 7-membered nitrogenous or oxygenic heterocycle, or 3- to 7-membered nitrogenous or oxygenic heterocycle formed by linking R^{11} and R^{12}; and

R^6 represents hydrogen, halo, or methyl.

2. The aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, wherein R^4 represents morpholinyl, piperazinyl, or 4-substituted piperazinyl, wherein a substituent is methyl, or ethyl.

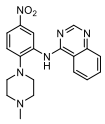
3. The aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, wherein R^5 represents nitro, amino, -$NHCOR^9$, furyl, pyrimidinyl, pyridinyl, substituted triazolyl, or substituted phenyl, wherein a substituent is a mono- or

di-substituted halo, -NHCOR^{10}, -CONR^{11}R^{12}, or -COOR^{10}, wherein R^{9} represents phenyl, R^{10} represents hydrogen, C_1-C_6 alkyl, C_1-C_6 amino-substituted alkyl, 3- to 7-membered cycloalkyl, 3- to 7-membered nitrogenous or oxygenic heterocycle, or phenyl; and R^{11} and R^{12} represent hydrogen, C_1-C_6 alkyl, phenyl or substituted phenyl, substituted or unsubstituted 3- to 7-membered nitrogenous or oxygenic heterocycle, or 3- to 7-membered nitrogenous or oxygenic heterocycle formed by linking R^{11} and R^{12}.

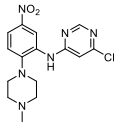
4. The aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, wherein the pharmaceutically acceptable salt is an inorganic acid salt or an organic acid salt represented by general formula (I); wherein the inorganic acid salt is a hydrochloride, a hydrobromide, or a sulfate; and the organic acid salt is an acetate, a lactate, a succinate, a fumarate, a maleate, a citrate, a benzoate, a methanesulfonate, or a p-toluenesulfonate.

5. The aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, represented by any of the following structures:

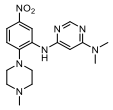
Example 1



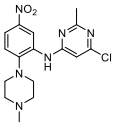
Example 2



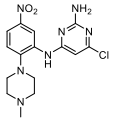
Example 3



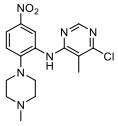
Example 4



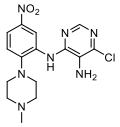
Example 5



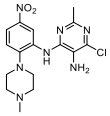
Example 6



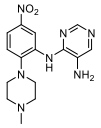
Example 7



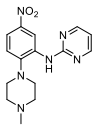
Example 8



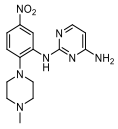
Example 9



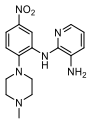
Example 10



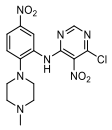
Example 11



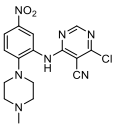
Example 12



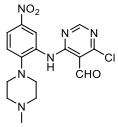
Example 13



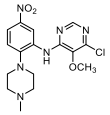
Example 14



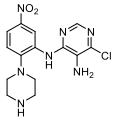
Example 15



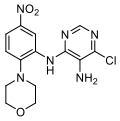
Example 16



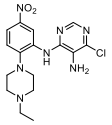
Example 17



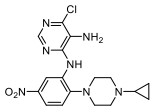
Example 18



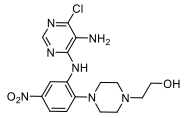
Example 19



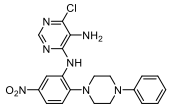
Example 20



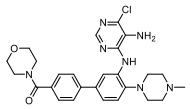
Example 21



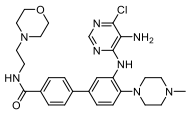
Example 22



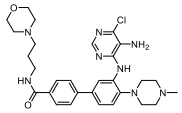
Example 23



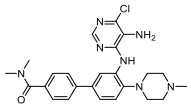
Example 24



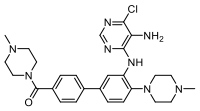
Example 25



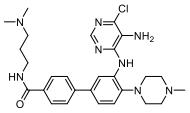
Example 26



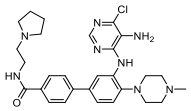
Example 27



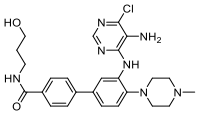
Example 28



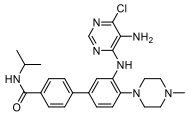
Example 29



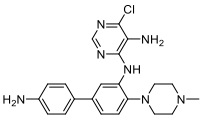
Example 30



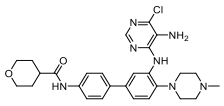
Example 31



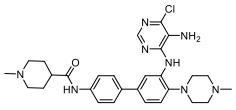
Example 32



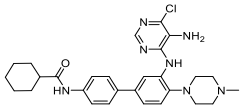
Example 33



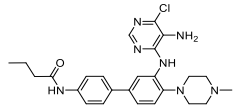
Example 34



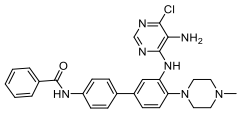
Example 35



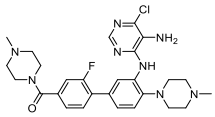
Example 36



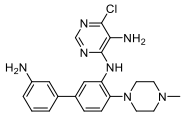
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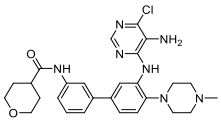
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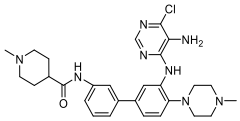
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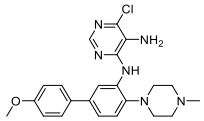
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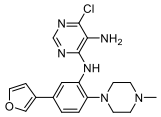
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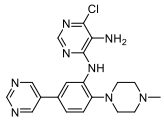
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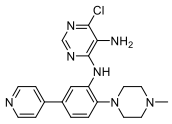
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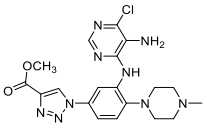
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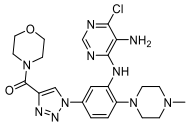
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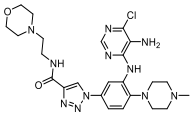
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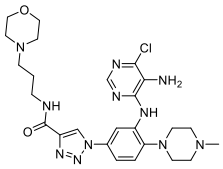
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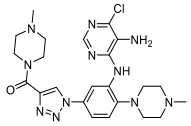
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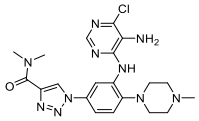
Example 49



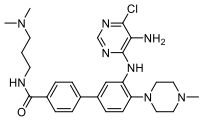
Example 50



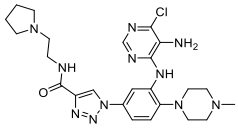
Example 51



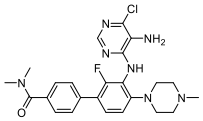
Example 52



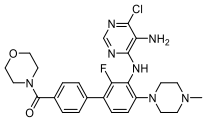
Example 53



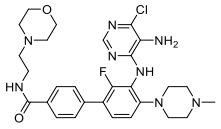
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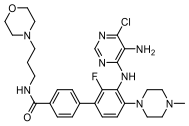
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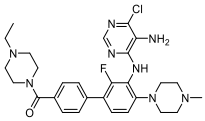
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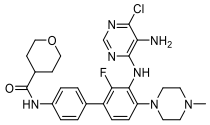
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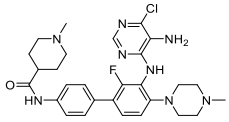
Example 58:



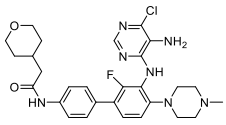
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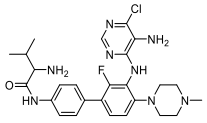
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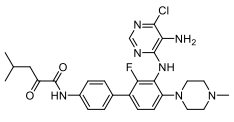
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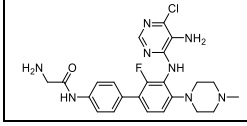
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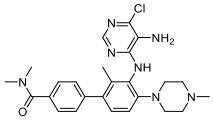
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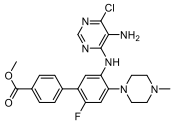
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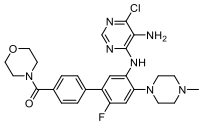
Example 65



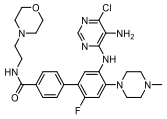
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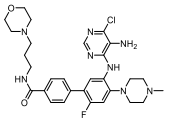
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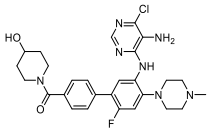
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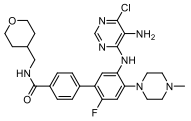
Example 69



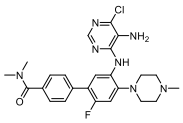
Example 70



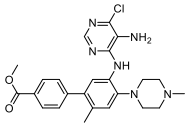
Example 71



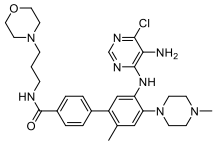
Example 72



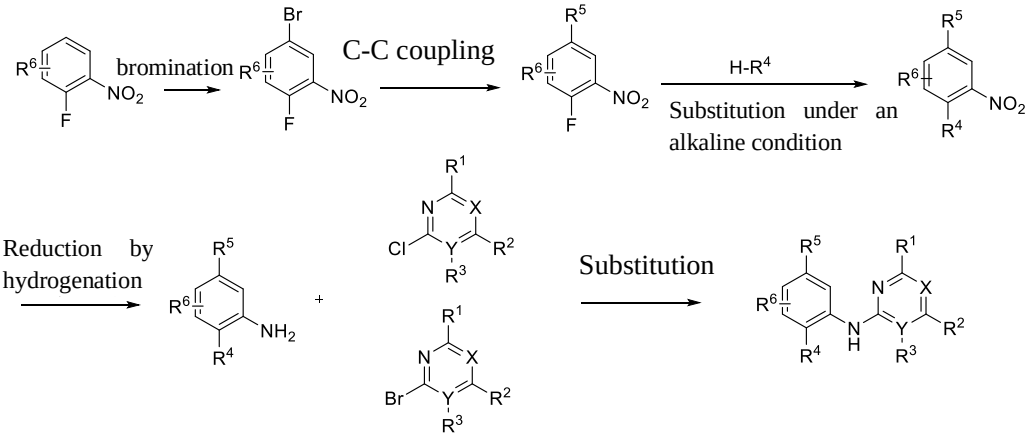
Example 73



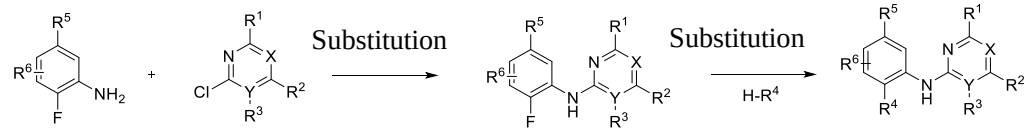
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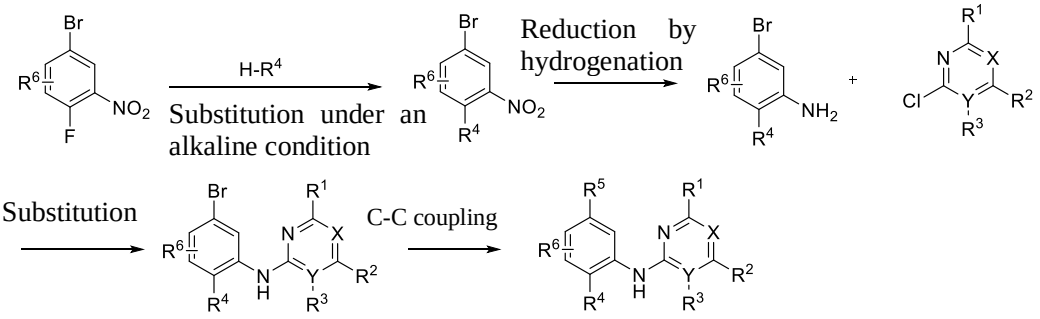
6. A method for preparing the general formula (I) according to claim 1, comprising following reaction steps:



or:



or:



7. A pharmaceutical composition, comprising the WDR5 protein-protein interaction inhibitor according to claim 1.

8. Use of the aniline-based WDR5 protein-protein interaction inhibitor according to claim 1 in the preparation of a drug for treating a hematological tumor.

9. The use according to claim 8, wherein the hematological tumor is acute leukemia.

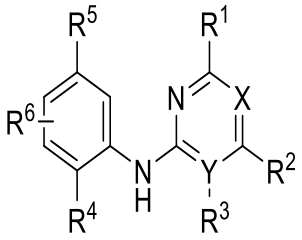
10. An aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, for use in treating a hematological tumor.

11. The aniline-based WDR5 protein-protein interaction inhibitor for use according to claim 10, wherein the hematological tumor is acute leukemia.

Aniline-based WDR5 Protein-Protein Interaction Inhibitor, Method for Preparing the Same, and Use thereof

Abstract

The present disclosure discloses a WDR5 protein-protein interaction inhibitor, including a compound having a structure represented by general formula (I). Experiments show that the inhibitor acts on a WDR5 protein and an interacting protein thereof including, but not limited to, MLL, selectively inhibits the proliferation of leukemia cells, and inhibits the methylation of H3K4 and the expression of downstream Hox/Meis-1 gene at the cellular level. The present disclosure also discloses a method for preparing the inhibitor and use thereof in the preparation of a drug for treating acute leukemia and other related diseases.



(I)

[Figure 3]