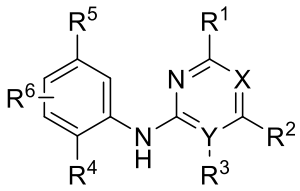
MLL1 present alone has very poor catalytic activity, and can only catalyze the monomethylation of H3K4. When MLL1 forms a core complex with WDR5, RbBP5, Ash2L, and DPY30, the enzymatic catalysis activity is greatly enhanced, especially the catalytic activity for H3K4me2. As a bridge linking a C-terminal 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, ~~a prodrug thereof,~~ and a hydrate or solvate thereof:



(I)

wherein X represents ~~CH or~~ N;

Y represents C~~ or N~~;

R^1, R^2 and R^3 are 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 alkoxyl, nitro,~~ halo, ~~cyano, aldehyde group, hydroxyl,~~ -NR^7R^8, ~~or~~  ~~formed by linking R^2 and R^3,~~ wherein R^7 and R^8 represent hydrogen~~, or C_1-C_4 alkyl, or 3- to 7-membered nitrogenous heterocycle formed by linking R^7 and R^8~~;

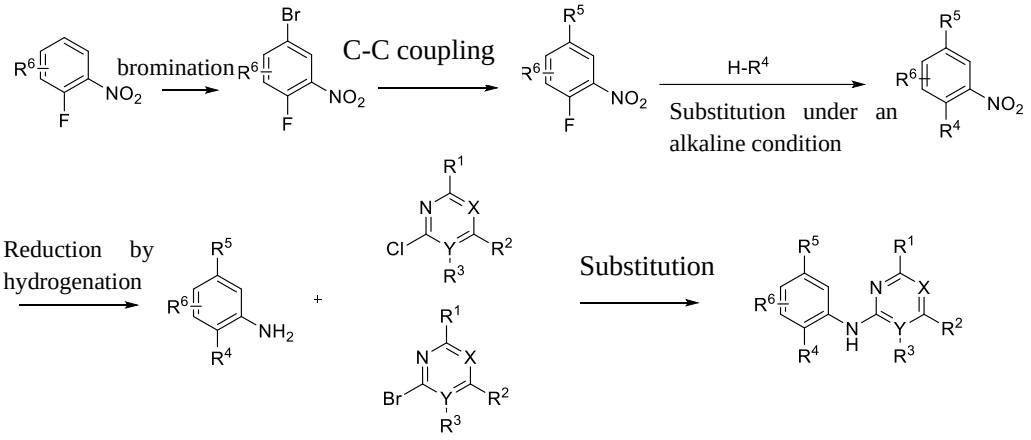
R^4 represents morpholinyl, piperazinyl, 4-substituted piperazinyl, 4-substituted homopiperazinyl, 3-substituted piperazinyl, or 2-substituted piperazinyl, wherein a substituent is C_1-C_4 alkyl~~, 3- to 7-membered cycloalkyl, hydroxyalkyl, or phenyl~~;

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

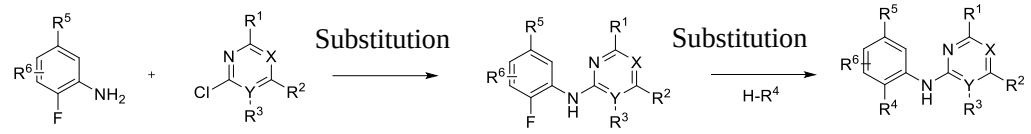
7-membered nitrogenous or oxygenic heterocycle, or 3- to 7-membered nitrogenous or oxygenic heterocycle formed by linking R^{11} and R^{12}; and

R^6 represents hydrogen, halo, or methyl~~, trifluoromethyl, amino, or substituted amino, wherein a substituent is C_1-C_4 alkyl, or allyl~~.

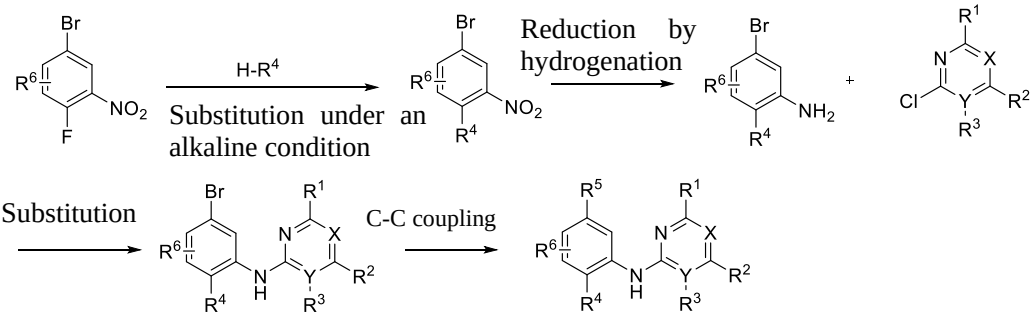
In another aspect, the present disclosure refers to a method for preparing the general formula (I) disclosed herein, comprising following reaction steps:



or:



or:



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

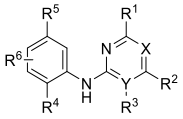
In a further aspect, the present disclosure refers to a use of the aniline-based WDR5 protein-protein interaction inhibitor disclosed herein in the preparation of a drug for treating ~~an indication related to a WDR5 enzyme functiona~~ hematological tumor.

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.~~an indication~~

~~related to a WDR5 enzyme function.~~

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;

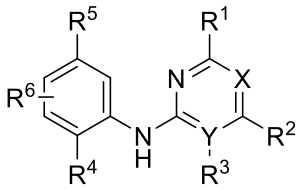
R^1, R^2 and R^3 are identical to or different from each other, and are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted with C_1-C_6 alkoxy, nitro, halo, cyano, aldehyde group, hydroxyl,-NR^7R^8, or  formed by linking R^2 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, ~~a prodrug thereof,~~ and a hydrate or solvate thereof:



(I)

wherein X represents ~~CH or~~ N;

Y represents C~~ or N~~;

R^1, R^2 and R^3 are 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 alkoxyl, nitro,~~ halo, ~~cyano, aldehyde group, hydroxyl,~~ -NR^7R^8, ~~or~~  ~~formed by linking R^2 and R^3,~~ wherein R^7 and R^8 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, wherein 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 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~~, trifluoromethyl, amino, or substituted amino, wherein a substituent is C_1-C_4 alkyl, or allyl~~.

~~2. The aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, wherein X represents CH or N, and Y represents C or N; wherein R^1, R^2 and~~

~~R^3 are selected from the group consisting of hydrogen, methyl, methoxy, nitro, halo, cyano, aldehyde group, $-NR^7R^8$, or~~  ~~formed by linking R^2 and R^3, wherein R^7 and R^8 represent hydrogen, or C_1-C_4 alkyl, or 3- to 5-membered nitrogenous heterocycle formed by linking R^7 and R^8.~~

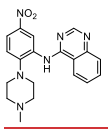
2~~3~~. The aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, wherein R^4 represents morpholinyl, piperazinyl, or 4-substituted piperazinyl, wherein a substituent is methyl, or ethyl~~, cyclopropyl, hydroxyethyl, or phenyl~~.

3~~4~~. 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}.

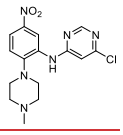
4~~5~~. The aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, wherein the pharmaceutically acceptable salt is an inorganic acid salt or an organic acid salt represented by general formula (I); wherein the inorganic acid salt is a hydrochloride, a hydrobromide, or a sulfate; 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:

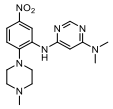
Example 1



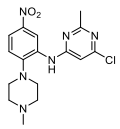
Example 2



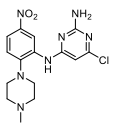
Example 3



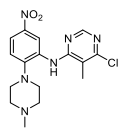
Example 4



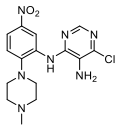
Example 5



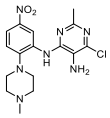
Example 6



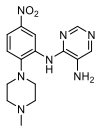
Example 7



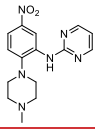
Example 8



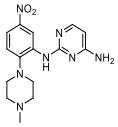
Example 9



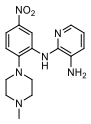
Example 10



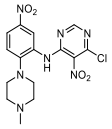
Example 11



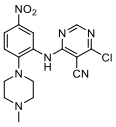
Example 12



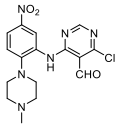
Example 13



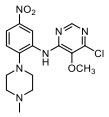
Example 14



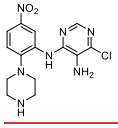
Example 15



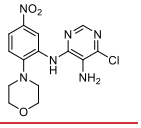
Example 16



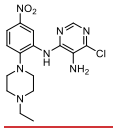
Example 17



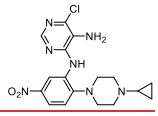
Example 18

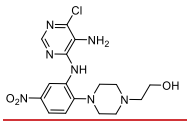
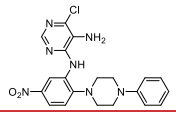
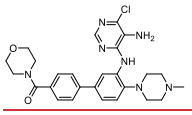
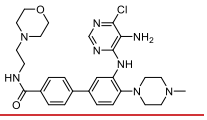
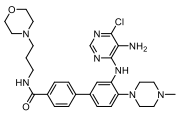
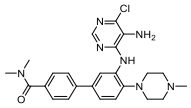
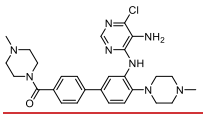
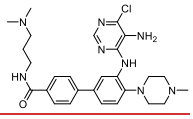
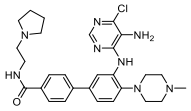
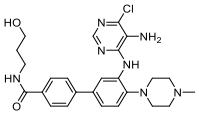
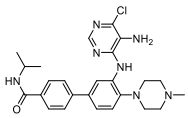
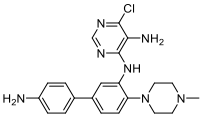
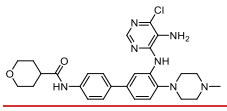
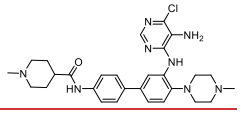
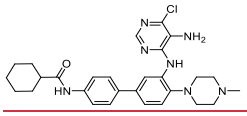
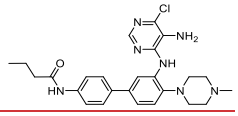
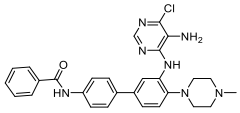
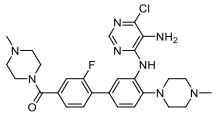


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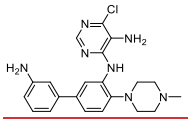


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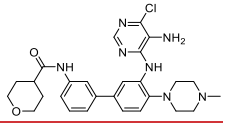


Example 21	Example 22
	
Example 23	Example 24
	
Example 25	Example 26
	
Example 27	Example 28
	
Example 29	Example 30
	
Example 31	Example 32
	
Example 33	Example 34
	
Example 35	Example 36
	
Example 37	Example 38
	

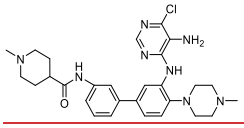
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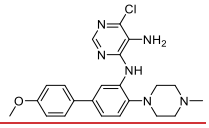
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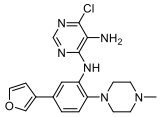
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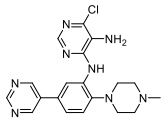
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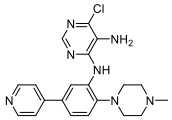
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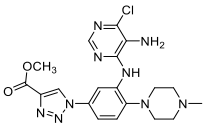
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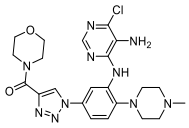
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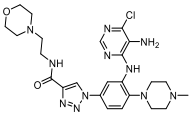
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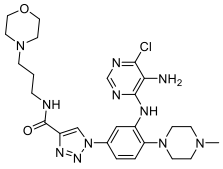
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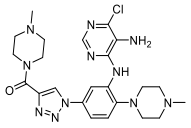
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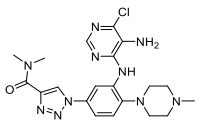
Example 49



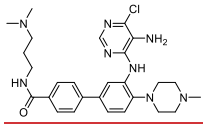
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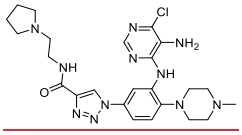
Example 51



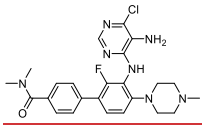
Example 52



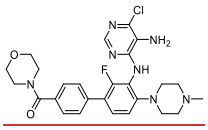
Example 53



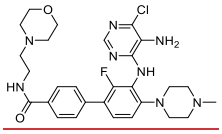
Example 54



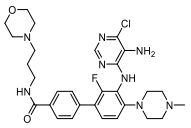
Example 55



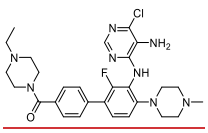
Example 56



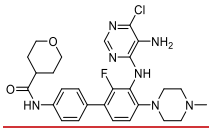
Example 57



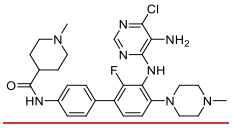
Example 58:



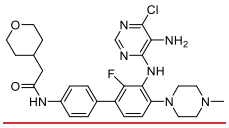
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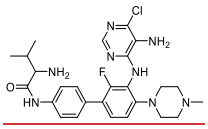
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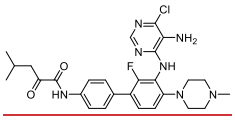
Example 61



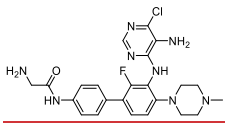
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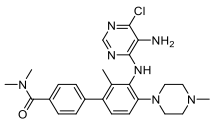
Example 63



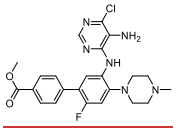
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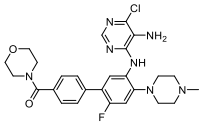
Example 65



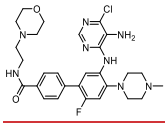
Example 66



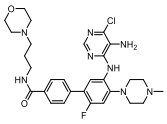
Example 67



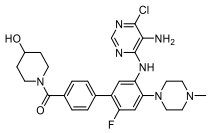
Example 68



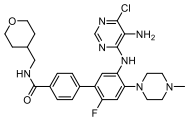
Example 69



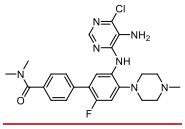
Example 70



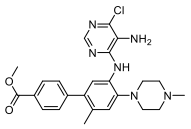
Example 71



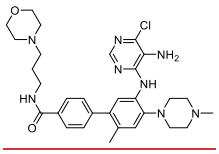
Example 72



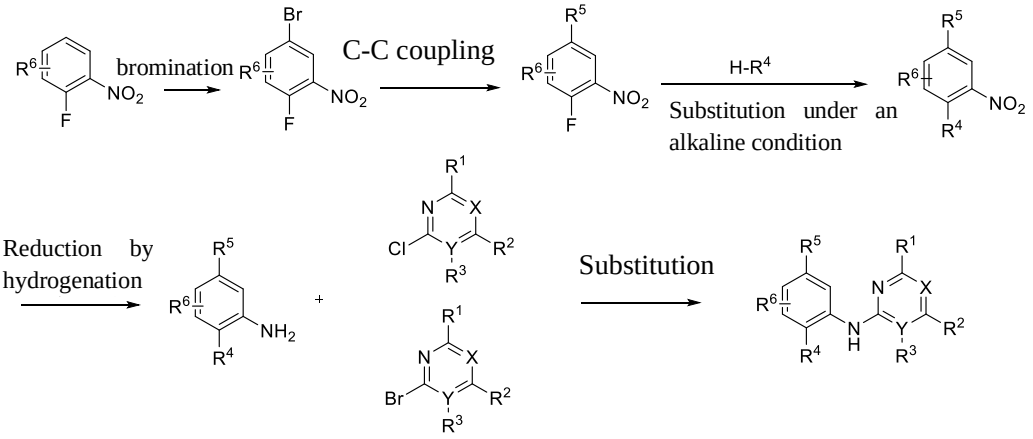
Example 73



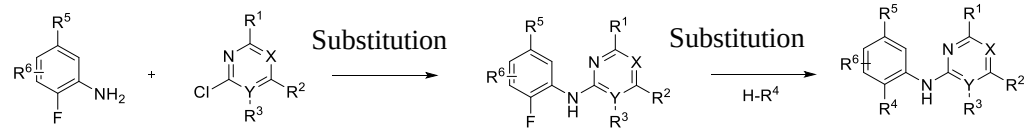
Example 74



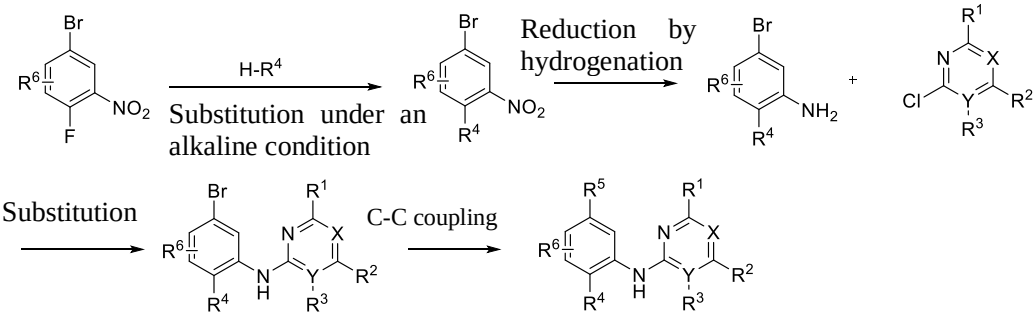
6. A method for preparing the general formula (I) according to claim 1, comprising following reaction steps:



or:



or:



7. A pharmaceutical composition, comprising the ~~aniline-based~~ 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~~an indication related to a WDR5 enzyme function~~.

~~9. The use according to claim 8, wherein the related indication is a hematological tumor.~~

9~~10~~. The use according to claim 8~~9~~, wherein the hematological tumor is acute leukemia.

10~~11~~. An aniline-based WDR5 protein-protein interaction inhibitor according to claim 1, for use in treating a hematological tumor~~an indication related to a WDR5 enzyme function~~.

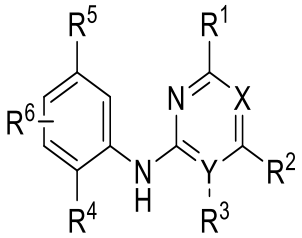
~~12. The aniline-based WDR5 protein-protein interaction inhibitor for use according to claim 11, wherein the related indication is a hematological tumor.~~

11~~13~~. The aniline-based WDR5 protein-protein interaction inhibitor for use according to claim ~~12~~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]