wherein X is hydrogen, methyl, methoxy or halogen;
Y is $–CH_2$-, -O-, -S-, -CO-, $-CH_2O$-, $-NR_5$-, $-CONR_6$- or $–NR_7CO$-, wherein R_5, R_6, or R_7 each independently is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, phenyl or substituted phenyl, the substituent is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, hydroxyl, thiol, carboxyl, cyano, trifluoromethyl or imidazolyl;
M is 0≃ - 6;
R_1 is hydrogen, amino, hydroxyl, thiol, carboxyl, cyano, $-CONH_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, substituted phenyl, substituted or unsubstituted nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring, $-NR_8COR_9$, $-CONR_{10}R_{11}$ or $–NR_{10}R_{11}$, wherein R_8 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, phenyl or substituted phenyl, R_9 is amino, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl or substituted phenyl, substituted or unsubstituted nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring, R_{10}, R_{11} independently is hydrogen, C_1-C_4 alkyl, phenyl or substituted phenyl, substituted or unsubstituted nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring, or R_{10} and R_{11} are bonded to form nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring, wherein the substituent is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, hydroxyl, thiol, carboxyl, cyano, trifluoromethyl or imidazolyl;
R_2 is disubstituted or trisubstituted wherein the substituent is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, nitro or cyano;
R_3 is amino, methylamino, aminomethyl, hydroxyl, hydroxymethyl, thiol or $–CONH_2$;
R_4 is N-methylpiperazine, 1,2-dimethyl piperazine or N-methylhomopiperazine.

[0005b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carrier.

[0005c] In yet another aspect, the present disclosure refers to a use of a compound disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of acute leukemia.

[0005d] In a further aspect, the present disclosure refers to a compound disclosed herein or a pharmaceutically acceptable salt thereof for use in treating acute leukemia.

Content of the invention

[0006] This invention publishes a small molecule compound that regulates MLL1-WDR5 protein-protein interactions, through interference of which, it inhibits the enzymatic activities of catalysis, down-regulates the methylation levels of H3K4, and gene expression levels of Hox and Meis-1 genes, which in turn to induce the apoptosis of leukemia cells for the applications of leukemia treatment. The structure of the compound in this invention is:

Claims:

1. A compound of the formula (I) or a pharmaceutically acceptable salt thereof:



(I)

Wherein X is hydrogen, methyl, methoxy or halogen;

Y is $–CH_2$-, -O-, -S-, -CO-, $-CH_2O$-, $-NR_5$-, $-CONR_6$- or $–NR_7CO$-, wherein R_5, R_6, or R_7 each independently is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, phenyl or substituted phenyl, the substituent is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, hydroxyl, thiol, carboxyl, cyano, trifluoromethyl or imidazolyl;

M is 0 - ~~~6;

R_1 is hydrogen, amino, hydroxyl, thiol, carboxyl, cyano, $-CONH_2$, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, substituted phenyl, substituted or unsubstituted nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring, $-NR_8COR_9$, $-CONR_{10}R_{11}$ or $–NR_{10}R_{11}$, wherein R_8 is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, phenyl or substituted phenyl, R_9 is amino, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl or substituted phenyl, substituted or unsubstituted nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring, R_{10}, R_{11} independently is hydrogen, C_1-C_4 alkyl, phenyl or substituted phenyl, substituted or unsubstituted nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring, or R_{10} and R_{11} are bonded to form nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring, wherein the substituent is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, hydroxyl, thiol, carboxyl, cyano, trifluoromethyl or imidazolyl;

R_2 is disubstituted or trisubstituted wherein the substituent is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, nitro or cyano;

R_3 is amino, methylamino, aminomethyl, hydroxyl, hydroxymethyl, thiol or $–CONH_2$;

R_4 is N-methylpiperazine, 1,2-dimethyl piperazine or N-methylhomopiperazine.

2. The~~A~~ compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein X is hydrogen, fluorine, chlorine or methyl.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is $–NR_5$-, -$CONR_6$- or-NR_7CO-; R_5, R_6 or R_7 each independently is hydrogen, methyl, ethyl, propyl, cyclopropyl or isopropyl.
4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is $–NR_5$-, -$CONR_6$- or-NR_7CO-; R_5, R_6 or R_7 each independently is substituted phenyl, and the substituent is methyl, ethyl, isopropyl, t-butyl, cyclopropyl, methoxy, cyano, halogen, trifluoromethyl or imidazolyl.
5. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein said substituted or unsubstituted nitrogen- or oxygen-containing 3 to 7 membered heterocyclic ring is aziridine, azetidine, tetrahydrogen pyrrole, piperidine, cycloheximide, lactam, tetrahydrofuran, tetrahydropyran, morpholine, 1,4-oxazaxane, hexahydropyridazine, imidazoline, pyrazolidine, piperazine, the substituent is methyl, ethyl, phenyl, hydroxyl, amino, hydroxymethyl, or aminomethyl, the substituent is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, hydroxyl, thiol, carboxyl, cyano, or trifluoromethyl.
6. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R_1 is –NR_8COR_9, -$CONR_{10}R_{11}$ or $–NR_{10}R_{11}$, wherein R_8, R_9, R_{10} or R_{11} is C1-C4 alkyl.
7. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R2 is trisubstituted, and the substituent is fluorine, chlorine, bromine, methyl, methoxy, nitro, trifluoromethyl or cyano.
8. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carrier.
9. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of acute leukemia.
10. The use of claim 9, wherein the acute leukemia is an acute leukemia having MLL1 gene rearrangement.
11. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use in treating acute leukemia.