PHENYL TRIAZOLE MLL1-WDR5 PROTEIN-PROTEIN INTERACTION INHIBITOR

Technical field

[0001] The invention is in the medicinal chemistry field, more specifically, is for a class of phenyl triazole MLL1-WDR5 protein-protein interaction inhibitor, its preparation and pharmaceutical uses.

Technical background

[0002] Methylation of histones plays key roles in many biological processes and is the main content of study in epigenetic regulation field. Translocation and re-arrangement of the methyl transferase MLL1 gene for histone H3K4 can lead to mixed lineage leukemia (MLL1, acute myeloid leukemia and acute lymphoid leukemia). About 10% of leukemia patients have MLL1 gene rearrangement. After MLL1 gene arrangement, it fuses with other chaperone proteins to form fusion proteins, and the carcinogenic MLL fusion protein is expressed. The fusion protein can interact with RNA polymerase II (Pol II) related elongation factors to form the super elongation complex (SEC). The complex can lead to abnormal expression of the MLL1 regulated Hox gene, which causes series of serious consequences to induce MLL leukemia onset.

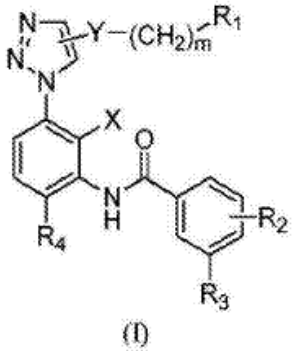
[0003] Rearrangement of the MLL1 gene occur on one allele and the wildtype MLL1 is still present. When the wildtype MLL1 allele is knocked out, the MLL fusion protein alone will not lead to leukemia, and the enzyme activity of the wildtype MLL1 is necessary for the MLL1 fusion protein to cause leukemia. Thus, specific inhibition of the wildtype MLL1 enzyme activity will cure leukemia.

[0004] Catalytic activity on H3K4 methylation by MLL1 alone is very weak and can only result in monomethylation; the catalytic activity improves greatly upon the formation of the MLL1 core catalytic complex, especially the catalytic activity on H3K4me2. The WIN motif on the C-terminus of the MLL binds to WDR5, RbBP5, Ash2L and DPY30 to form complexes. MLL1 interacts with WDR5 directly through the C-terminus WIN motif, to mediate the interaction between the catalytic domain of MLL1SET and other protein complexes. When WDR5 is knocked out, the level of H3K4me2/3 decreases and the Hox gene expression level decreases.

[0005] Thus, the use of small molecule to interfere the protein-protein interaction of MLL1-WDR5 is an effective method to inhibit MLL1 enzymatic activity and lower Hox and Meis-1 gene expression levels and to block the progression of leukemia.

Summary

[0005a] In one aspect, the present disclosure refers to 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 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 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. 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 trisubstitute, 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.