HETEROCYCLIC COMPOUND CAPABLE OF INHIBITING PRMT5•MTA AND USE THEREOF

Technical Field

The present invention relates to an inhibitor of a PRMT5•MTA complex and the use thereof in the preparation of a drug for treating tumours.

Background Art

Protein arginine methylation catalysed by protein arginine methyltransferases (PRMTs) is an important post-translational modification, in which S-adenosylmethionine (SAM) is used as a methyl donor to methylate the nitrogen atoms of the arginine side chains of proteins. Based on the arginine methylation status, nine identified human PRMTs (PRMT1-9) are further subdivided into type I, type II and type III. Type I PRMTs catalyse the formation of monomethylarginine (MMA) and asymmetric dimethylarginine (aDMA), including PRMT1, PRMT2, PRMT3, PRMT4, PRMT6, and PRTM8; type II PRMTs catalyse the formation of MMA and symmetric dimethylarginine (sDMA), including PRMT5 and PRMT9; and type III PRMT catalyses the formation of MMA, including PRMT7. As a type II PRMT, PRMT5 transfers the methyl group from SAM to the guanidine moiety of arginine residues to form MMA and sDMA, thereby regulating the expression of target genes in an epigenetic manner or regulating key signalling molecules by post-translational methylation modification pathways.

The homozygous deletion of pl6/CDKN2a is common in cancer. These mutations often involve co-occurring deletions of adjacent genes, including the gene encoding methylthioadenosine phosphorylase (MTAP). It is estimated that approximately 15% of human cancers involve homozygous deletions of MTAP genes (e.g., see Firestone & Schramm (2017) J. Am. Chem Soc. 139(39): 13754-13760. doi: 10.1021/jacs.7b05803. Epub 2017 Sep 20).

In MTAP-deficient cells, methylthioadenosine (MTA) overaccumulates and binds to PRMT5 to form a PRMT5•MTA complex, thereby partially inhibiting PRMT5 enzyme activity and increasing the sensitivity of cell proliferation to PRMT5 deficiency or loss of PRMT5 activity. Therefore, MTAP deficiency reduces the methylation activity of PRMT5 and renders cells selectively dependent on PRMT5 activity. In MTAP-deficient cancers, the inhibition of PRMT5 activity

HC(=O)NH(C_{1-6} alkyl), -NHC(=O)NH_2, -NHSO_2(C_{1-6} alkyl), -SO_2N(C_{1-6} alkyl)$_2$, -SO_2NH(C_{1-6} alkyl), -SO_2NH_2, -SO_2C_{1-6} alkyl, etc.

The term "optional" or "optionally" refers to that the events or circumstances subsequently described may but not necessarily occur, and the description includes the occasions where the events or circumstances occur or do not occur. For example, "alkyl optionally substituted with F" means that the alkyl may but not necessarily be substituted with F, and the description includes the case where the alkyl is substituted with F and the case where the alkyl is not substituted with F.

The term "pharmaceutically acceptable salt" refers to a salt of the compound of the present invention, which salt maintains the biological effectiveness and characteristics of a free acid or a free base and is obtained by reacting the free acid with a non-toxic inorganic base or organic base, or reacting the free base with a non-toxic inorganic acid or organic acid.

The term “pharmaceutical composition” represents a mixture of one or more compounds or stereoisomers, deuterated compound, solvates, pharmaceutically acceptable salts or eutectic crystals thereof as described herein and other components including physiologically/pharmaceutically acceptable carriers and/or excipients.

The term “carrier” refers to: a system that does not cause significant irritation to the organism and does not eliminate the biological activity and characteristics of the administered compound and can change the way the drug enters the human body and the distribution of the drug in the body, control the release rate of the drug and delivery the drug to targeted organs. Non-limiting examples of the carrier include microcapsule, microsphere, nanoparticle, liposome, etc.

The term “excipient” refers to: a substance that is not a therapeutic agent per se, but used as a diluent, adjuvant, adhesive and/or vehicle for addition to a pharmaceutical composition, thereby improving the disposal or storage properties thereof, or allowing to or promoting the formation of a compound or a pharmaceutical composition into a unit dosage form for administration. As is known to those skilled in the art, pharmaceutically acceptable excipients can provide various functions and can be described as a wetting agent, a buffer, a suspending agent, a lubricant, an emulsifier, a disintegrating agent, an absorbent, a preservative, a surfactant, a colorant, a flavouring agent, and a sweetening agent. Examples of pharmaceutically acceptable excipients include, but are not limited to: (1) sugars, such as lactose, glucose and sucrose; (2) starch, such as corn starch and potato starch;

(%)=(maximum value negative control-detection signal value)/(maximum value negative control-minimum value blank control) × 100, and IC_{50} values were fitted by using XL-Fit.

1.2 Test method for PRMT5·MTA enzyme activity

1× test buffer (10 mM Tris, 1 mM DTT, 0.01% BSA, 0.01% Tween-20, adjusted to pH 8.0) was prepared. The test compound was dissolved in DMSO to prepare a 10 mM mother liquor, and the mother liquor was diluted to a 100-fold final concentration. 100 nL of the compound was added to each well of the administration group, and 100 nL of DMSO solution was added to blank wells and negative control wells. Then, 5 μL of a solution of PRMT5/MEP50 (BPS, Cat# 31921) (final concentration: 1 nM) and MTA (final concentration: 1 μM) was added to the wells of the administration group and negative control wells, and 5 μL of 1× test buffer was added to the blank wells. Incubation was performed at room temperature for 15 minutes. 5 μL of a mixed solution of H4(1-21)S1ac (0.035 μM; GL Biochem, customized) and SAM (0.434 μM; Sigma, Cat# A7007) was added to each well and incubated at room temperature for 1 hour. 1× Epigenetics buffer (PerkinElmer, Cat# AL008F) was prepared and used for diluting acceptor microbeads and donor microbeads. 15 μL of acceptor microbeads (final concentration: 10 μg/mL; PerkinElmer, Cat#AL150C) and donor microbeads (final concentration: 10 μg/mL; PerkinElmer, Cat# AS106M) were added and incubated at room temperature for 1 hour in the dark. Then, detection was performed using the Alpha module of the reader Enspire microplate.

Based on the obtained data, the inhibition rate was calculated in Excel according to: inhibition rate (%) = (maximum value negative control-detection signal value)/(maximum value negative control-minimum value blank control) × 100, and IC_{50} values were fitted by using XL-Fit.

The compounds of the present invention have an IC_{50} value of < 100 nM for PRMT5·MTA, and IC_{50} values of some compounds are shown in Table 2, where AA represents IC_{50} < 1 nM, A represents 1 nM ≤ IC_{50} < 10 nM, B represents 10 nM ≤ IC_{50} < 50 nM, and C represents 50 nM ≤ IC_{50} < 100 nM.

Table 2 Inhibitory activity of compounds on PRMT5•MTA

Compound No.	PRMT5•MTA (nM)	PRMT5 (IC_{50}, nM)
1	A	B
30	AA	A

inhibitor cocktail (CST, Cat# 5872S) and RIPA lysate were prepared in the required volume according to the proportion, and added to the 96-well plate at 50 μL/well. The plate was placed on ice for 10 minutes, during which the cells were repeatedly pipetted until completely lysed. The cells were then centrifuged at 2500 rpm at 4°C for 35 minutes to collect the protein sample of the supernatant. Protein detection was performed using a BCA kit (Beyotime, Cat# P0011). According to the detection results, the protein concentration of the lysate was adjusted to the required concentration using PBS or carbonate-bicarbonate buffer pH 9.6 (Sigma, Cat# C3041), and 100 μL was added to each well of a black high-binding 96-well plate (Nunc Maxisorp, Cat# 437111) and incubated at room temperature for 2 h. After removing the lysate, the plate was washed 4 times with PBST (Cell Signalling, Cat# 9809S), and blocked with 5% BSA blocking solution (solarbio, Cat# SW3015) for 1 hour. After removing the solution, the plate was washed 4 times with PBST. 100 μL of the sDMA antibody (CST, Cat# 13222S) or SMD3 antibody (Abgent, Cat# AP12451A) was added to each well and shaken overnight at 4°C. After removing the antibody, the plate was washed 4 times with PBST. 100 μL of the anti-rabbit secondary antibody (Cell Signalling Technology, Cat# 7074) was added to each well and incubated at room temperature for 1 hour. After removing the secondary antibody, the plate was washed 4 times with PBST. 100 μL of the Immobilon Forte Western HRP substrate (Millipore, Cat# WBLUF0500) was added to each well and incubated with shaking for 15 minutes, followed by chemiluminescence detection using the BMG microplate reader. After data normalization (SDMA reading/SMD3 reading), Graphpad Prism 8.3.0 software was used to plot the data, and the IC_{50} value was calculated.

5.2 SDMA detection in HCT-116 cells

HCT-116 cells were cultured in an RPMI 1640 culture medium (ATCC, Cat# 30-2001; supplemented with 10% FBS and 1% double antibody) until the confluence reached about 85%, and then the cells were plated. The culture medium was discarded, and the cells were rinse with 1× PBS and digested by trypsin (Gibco, Cat# 15400-054). When the cells became round and began to fall off, the digestion was terminated by adding the culture medium. The cells were pipetted, transferred to a sterile centrifuge tube and centrifuged at 1000 rpm for 3 minutes, and after the centrifugation, the supernatant was discarded. The cells were resuspended by adding the culture medium to the centrifuge tube and then counted. According to the

counting results, the cell suspension was adjusted to an appropriate concentration and poured into a loading slot. 100 μL of the cell suspension was added to each well of the 96-well plate. The compound was dissolved in DMSO to 10 mM and stored for later use. During the experiment, the compound was subjected to 5-fold serial dilution by using the culture medium. 100 μL of the diluted compound was added to the 96-well plate in which the cells were already plated, and a DMSO vehicle control group was also set up. Incubation was performed at 37°C, 5% CO_2 for 3 days. After 3 days, each well was washed twice with cold PBS. The protease and phosphatase inhibitor cocktail (CST, Cat# 5872S) and RIPA lysate were prepared in the required volume according to the proportion, and added to the 96-well plate at 50 μL/well. The plate was placed on ice for 10 minutes, during which the cells were repeatedly pipetted until completely lysed. The cells were then centrifuged at 2500 rpm at 4°C for 35 minutes to collect the protein sample of the supernatant. Protein detection was performed using a BCA kit (Beyotime, Cat# P0011). According to the detection results, the protein concentration of the lysate was adjusted to the required concentration using PBS or carbonate-bicarbonate buffer pH 9.6 (Sigma, Cat# C3041), and 100 μL was added to each well of a black high-binding 96-well plate (Nunc Maxisorp, Cat# 437111) and incubated at room temperature for 2 h. After removing the lysate, the plate was washed 4 times with PBST (Cell Signalling, Cat# 9809S), and blocked with 5% BSA blocking solution (solarbio, Cat# SW3015) for 1 hour. After removing the solution, the plate was washed 4 times with PBST. 100 μL of the sDMA antibody (CST, Cat# 13222S) or SMD3 antibody (Abgent, Cat# AP12451A) was added to each well and shaken overnight at 4°C. After removing the antibody, the plate was washed 4 times with PBST. 100 μL of the anti-rabbit secondary antibody (Cell Signalling Technology, Cat# 7074) was added to each well and incubated at room temperature for 1 hour. After removing the secondary antibody, the plate was washed 4 times with PBST. 100 μL of the Immobilon Forte Western HRP substrate (Millipore, Cat# WBLUF0500) was added to each well and incubated with shaking for 15 minutes, followed by chemiluminescence detection using the BMG microplate reader. After data normalization (SDMA reading/SMD3 reading), Graphpad Prism 8.3.0 software was used to plot the data, and the IC_{50} value was calculated.

Table 6 Inhibitory activity of compounds on SDMA production in HCT-116 cells

Compound No.	HCT-116 SDMA (IC_{50}, nM)
30	499

Conclusion: The compounds of the present invention, such as the compounds of the examples, have weak inhibitory activity on the production of SDMA in HCT-116 cells.

5.3 SDMA detection in HCT-116 $MTAP^{-/-}$ cells

HCT-116 MTAP-/- cells were cultured in an RPMI 1640 culture medium (ATCC, #30-2001; supplemented with 10% FBS and 1% double antibody) until the confluence reached about 85%, and then the cells were plated. The culture medium was discarded, and the cells were rinse with 1× PBS and digested by trypsin (Gibco, Cat# 15400-054). When the cells became round and began to fall off, the digestion was terminated by adding the culture medium. The cells were pipetted, transferred to a sterile centrifuge tube and centrifuged at 1000 rpm for 3 minutes, and after the centrifugation, the supernatant was discarded. The cells were resuspended by adding the culture medium to the centrifuge tube and then counted. According to the counting results, the cell suspension was adjusted to an appropriate concentration and poured into a loading slot. 100 μL of the cell suspension was added to each well of the 96-well plate. The compound was dissolved in DMSO to 10 mM and stored for later use. During the experiment, the compound was subjected to 5-fold serial dilution by using the culture medium. 100 μL of the diluted compound was added to the 96-well plate in which the cells were already plated, and a DMSO vehicle control group was also set up. Incubation was performed at 37°C, 5% CO_2 for 3 days. After 3 days, each well was washed twice with cold PBS. The protease and phosphatase inhibitor cocktail (CST, Cat# 5872S) and RIPA lysate were prepared in the required volume according to the proportion, and added to the 96-well plate at 50 μL/well. The plate was placed on ice for 10 minutes, during which the cells were repeatedly pipetted until completely lysed. The cells were then centrifuged at 2500 rpm at 4°C for 35 minutes to collect the protein sample of the supernatant. Protein detection was performed using a BCA kit (Beyotime, Cat# P0011). According to the detection results, the protein concentration of the lysate was adjusted to the required concentration using PBS or carbonate-bicarbonate buffer pH 9.6 (Sigma, Cat# C3041), and 100 μL was added to each well of a black high-binding 96-well plate (Nunc Maxisorp, Cat# 437111) and incubated at room temperature for 2 h. After removing

Test compound	Mode of administration	CL (mL/min/kg)	$T_{1/2}$ (h)	AUC_{0-t} (hr × ng/mL)
Compound 30	i.v. (1 mg/kg)	0.313	-	-
	i.g. (5 mg/kg)	-	16.1	178458

-: not applicable.

Conclusion: The compounds of the present invention, such as the compounds in the examples, have good pharmacokinetic profiles in beagle dogs.

11. Pharmacokinetic test in monkeys

11.1 Experimental animals: Male cynomolgus monkeys, 3-5 kg, 3-6 years old, 4 monkeys/compound, purchased from Suzhou Xishan Biotechnology Inc.

11.2 Experimental method: On the day of the experiment, (4×number of test compounds (n)) monkeys were randomly divided into groups according to their body weights. The animals were fasted but with water available for 14 to 18 h one day before the administration and were fed 4 h after the administration.

Before and after the administration, 1.0 mL of blood was taken from the limb veins and placed in an EDTAK2 centrifuge tube. Centrifugation was performed at 5000 rpm at 4°C for 10 min, and the plasma was collected. The blood collection time points for the intravenous administration group and intragastric administration group were 0 min, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 48 h and 72 h. Before analysis and detection, all samples were stored at -80°C, and a quantitative analysis of samples was performed using LC-MS/MS.

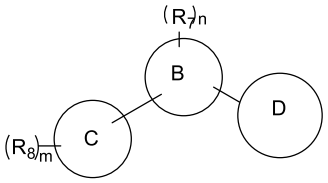
Conclusion: The compounds of the present invention, such as the compounds in the examples, have good pharmacokinetic profiles in monkeys.

12. *In-vivo* efficacy experiment

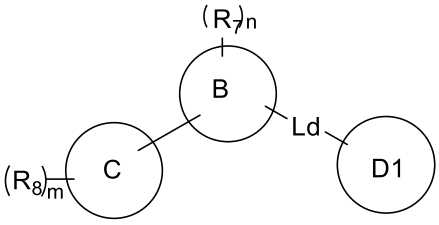
HCT-116 MTAP-/- cells were cultured in an RPMI-1640 culture medium in a 37°C incubator containing 5% CO2. The cells were passaged every 2 to 3 days. When the number reached the requirement, the cells were collected and counted. The cell concentration was adjusted to an appropriate concentration with PBS and then diluted to 2.5×10^7 cells/ml with Matrigel at a ratio of 1 : 1. According to 5×10^6 cells/200 μL/mouse (purchased from Vital River Laboratory Animal Technology Co., Ltd., Balb/c nude, female), the cells were inoculated into the axilla of the right forelimb. When the tumour grew to 80-100 mm^3 (Day 5-7 after the inoculation), the animals were sorted by tumour size and grouped for administration (the day of grouping for administration was recorded as Day 0). During the

CLAIMS

1. A compound represented by formula (I-a) or (I-b), or a stereoisomer, a deuterated compound, a solvate or a pharmaceutically acceptable salt thereof,

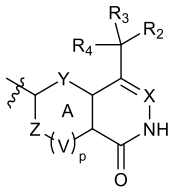
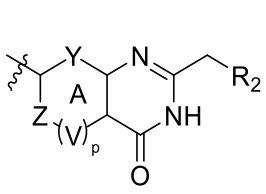
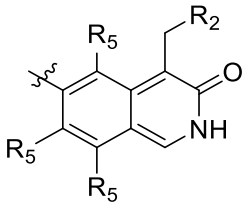
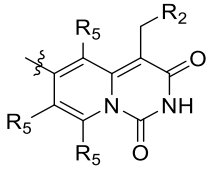
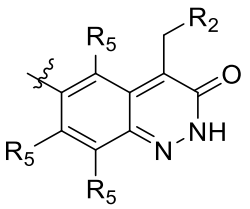
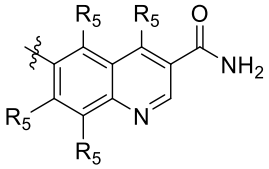
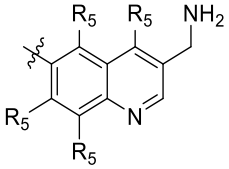
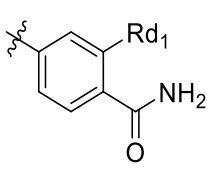
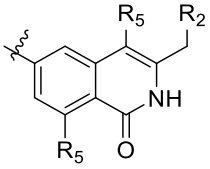
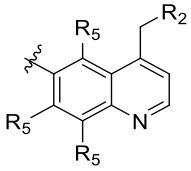
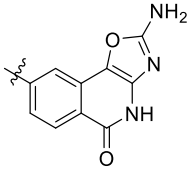
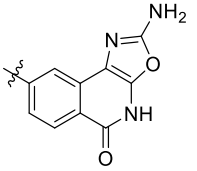
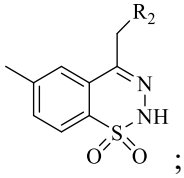


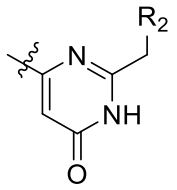
I-a



I-b

characterized in that

D is selected from: , , , , , , , , , , , , ;

D1 is selected from:  ;

Ld is selected from C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl;

Rd1 is selected from 5-membered heteroaryl, wherein the heteroaryl is optionally substituted with 1-3 groups selected from halogen, D, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy and NH_2;

X is selected from CR_1 or N;

Y, Z and V are independently CR_5, $C(R_5)_2$, NR_6, N, O or S, and the total number of O and S is not greater than 1;

ring A is phenyl, 5- to 7-membered heterocycloalkyl containing 1-3 heteroatoms selected from N, O or S, or 5- to 6-membered heteroaryl containing 1-3 heteroatoms selected from N, O or S;

ring B is C_{3-12} carbocycle, or 4- to 12-membered heterocycle containing 1-3 heteroatoms selected from N, O or S;

ring C is C_{3-12} carbocycle, or 4- to 12-membered heterocycle containing 1-3 heteroatoms selected from N, O or S;

R_1 is H, D, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, CN, OH, NH_2 or COOH, wherein the alkyl, alkoxy, alkenyl or alkynyl is optionally substituted with 1-3 groups selected from halogen, D, CN, OH and NH_2;

R_2 is OH, NH_2, $-CH_2NH_2$ or -NH-OH;

R_3 and R_4 are independently H, D, halogen, C_{1-4} alkyl, CN, OH, NH_2, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-6} cycloalkyl, wherein the alkyl, alkoxy, alkenyl, alkynyl or cycloalkyl is optionally substituted with 1-3 groups selected from halogen, D, CN, OH and NH_2;

alternatively, R_3 and R_4 together form =NH;

each R_5 is independently H, D, =O, OH, C_{1-4} alkyl, CN, halogen, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, 5- to 6-membered heteroaryl containing 1-3 heteroatoms selected from N, O or S, 4- to 7-membered heterocycloalkyl containing 1-3 heteroatoms selected from N, O or S, or C_{3-6} cycloalkyl, wherein the alkyl, alkoxy, alkenyl, alkynyl, heteroaryl or cycloalkyl is optionally substituted with 1-3 groups selected from halogen, D, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy and NH_2;

R_6 is H, D, C_{1-4} alkyl or C_{3-6} cycloalkyl, wherein the alkyl or cycloalkyl is optionally substituted with 1-3 groups selected from halogen, D, CN, OH and NH_2;

each R_7 is independently H, =O, D, OH, CN, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $N(R_7')_2$, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl or 4- to 7-membered heterocycloalkyl containing 1-3 heteroatoms selected from N, O or S, wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl or heterocycloalkyl is optionally substituted with 1-3 groups selected from halogen, D, OH, NH_2, CN, C_{1-4} alkyl, -$C(O)C_{1-4}$ alkyl, -$C(O)NHC_{1-4}$ alkyl, -$C(O)NH_2$, -$NHC(O)C_{1-4}$ alkyl and C_{1-4} alkoxy;

each R_8 is independently H, D, nitro, amino, C_{1-6} alkoxy, =O, OH, CN, halogen, C_{2-6} alkenyl, C_{2-6} alkynyl, -SF_5, N_3, C_{1-6} alkyl, -COC_{1-4} alkyl, -$N(R_7')_2$, -$C(=O)N(R_7')_2$, -$NR_7'C(=O)$-R_7', -$C(=O)$-R_7', -$(CH_2)_r$-O-$(CH_2)_r$-R_8', -S-C_{1-6} alkyl, -$S(O)$-C_{1-6} alkyl, -$S(O)_2$-C_{1-6} alkyl, -S-$(CH_2)_r$-R_8', -NR_7'-$(CH_2)_r$-R_8' or -$(CH_2)_r$-R_8', wherein the alkyl, alkenyl or alkynyl is optionally substituted with 1-5 groups selected from $R_{8''}$;

each R_7' is independently H, D, amino, hydroxyl, C_{1-6} alkyl, halo C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{1-6} alkoxy, halo C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-12} heterocycloalkyl, -NHC_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$ or deuterated C_{1-6} alkoxy, wherein the cycloalkyl or heterocycloalkyl is optionally substituted with 1 to 3 groups selected from deuterium, halogen, cyano, amino, hydroxyl, C_{1-6} alkyl, halo C_{1-6} alkyl, deuterated C_{1-6} alkyl, C_{1-6} alkoxy, halo C_{1-6} alkoxy or deuterated C_{1-6} alkoxy;

each R_8' is independently H, D, C_{1-6} alkyl, C_{1-4} alkoxy, C_{3-12} carbocycle, or 4- to 12-membered heterocycle containing 1-3 heteroatoms selected from N, O or S, wherein the alkyl or alkoxy is optionally substituted with 1-3 groups selected from halogen, =O, D, OH, NH_2, CN, C_{1-6} alkyl, halo C_{1-6} alkyl, deuterated C_{1-6} alkyl, -$C(O)C_{1-4}$ alkyl, -$C(O)NHC_{1-4}$ alkyl, -$C(O)NH_2$, -$NHC(O)C_{1-4}$ alkyl, C_{1-6} alkoxy, halo C_{1-6} alkoxy and deuterated C_{1-6} alkoxy; the carbocycle or heterocycle is optionally substituted with 1-5 groups selected from $R_{8''}$;

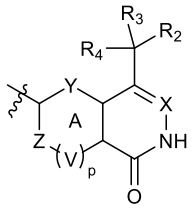
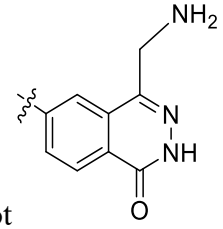
$R_{8''}$ is selected from halogen, D, OH, NH_2, CN, C_{1-6} alkyl and C_{1-6} alkoxy, wherein the alkyl or alkoxy is optionally further substituted with 1 to 5 groups selected from halogen, deuterium, cyano, amino, hydroxyl, C_{1-6} alkyl or C_{1-6} alkoxy;

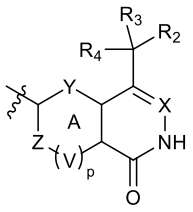
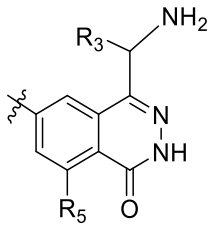
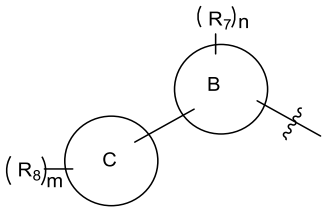
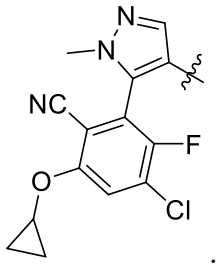
each r is independently 0, 1, 2 or 3;

p is 0, 1 or 2;

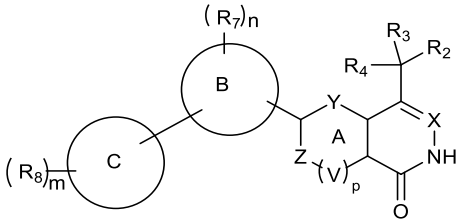
n and m are independently an integer of 0-5;

provided that:

1. the group  is not ;

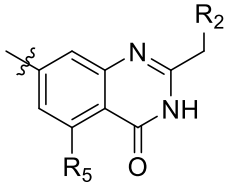
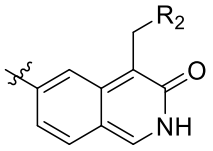
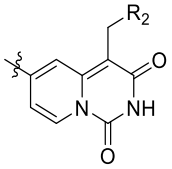
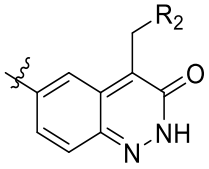
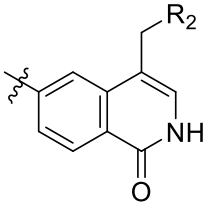
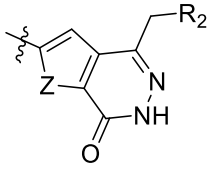
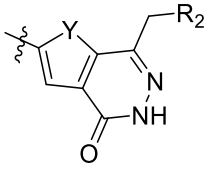
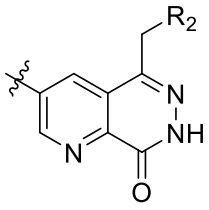
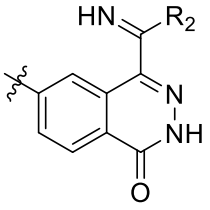
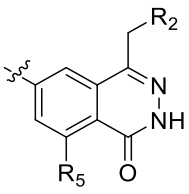
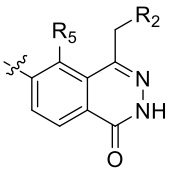
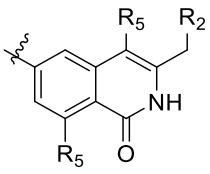
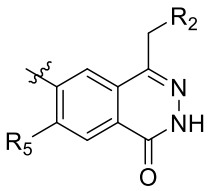
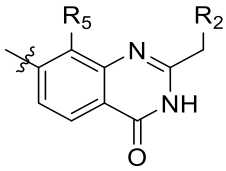
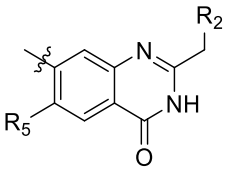
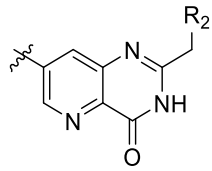
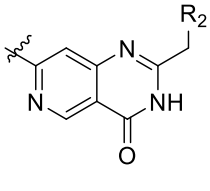
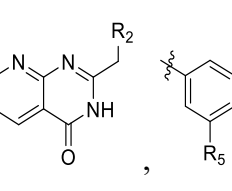
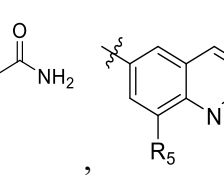
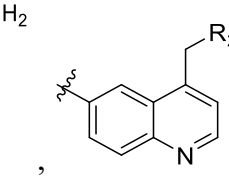
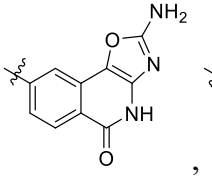
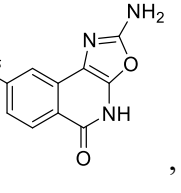
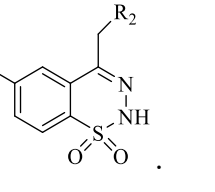
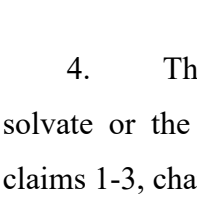
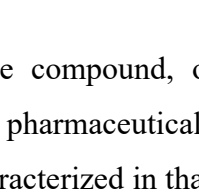
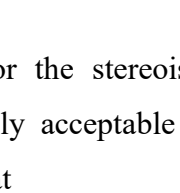
2. when  is , R_3 is H, C_{1-4} alkyl or C_{1-4} haloalkyl, R_5 is H, halogen, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} haloalkyl, and R_3 and R_5 are not both H, the group  is .

2. The compound represented by formula (I-a), or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 1, characterized in that the compound has a structure of formula (I) below:



I .

3. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 1, characterized in that

D is selected from , , , , , , , , , , , , , , , , , , , , , , , , , , , .

4. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to any one of claims 1-3, characterized in that

X is selected from CR_1 or N;

Y, Z and V are independently CR_5, N, O or S, and the total number of O and S is not greater than 1;

ring A is phenyl, or 5- to 6-membered heteroaryl containing 1-3 heteroatoms selected from N, O or S;

ring B is phenyl, C_{3-6} cycloalkyl, 4- to 7-membered heterocycloalkyl containing 1-3 heteroatoms selected from N, O or S, or 5- to 6-membered heteroaryl containing 1-3 heteroatoms selected from N, O or S;

ring C is phenyl, C_{3-6} cycloalkyl, 4- to 7-membered heterocycloalkyl containing 1-3 heteroatoms selected from N, O or S, or 5- to 6-membered heteroaryl containing 1-3 heteroatoms selected from N, O or S;

R_1 is H, D, C_{1-4} alkyl, halogen or CN, wherein the alkyl is optionally substituted with 1-3 groups selected from halogen, D, CN and OH;

R_2 is OH, NH_2, $-CH_2NH_2$ or -NH-OH;

R_3 and R_4 are independently H, D, halogen, C_{1-4} alkyl, CN, OH or NH_2, wherein the alkyl is optionally substituted with 1-3 groups selected from halogen, D, CN, OH and NH_2;

each R_5 is independently H, D, OH, C_{1-4} alkyl, CN, halogen, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, 5-membered heteroaryl containing 1-3 heteroatoms selected from N, O or S, 4- to 5-membered heterocycloalkyl containing 1-3 heteroatoms selected from N, O or S, or C_{3-4} cycloalkyl, wherein the alkyl, alkoxy, alkenyl, alkynyl, heteroaryl, heterocycloalkyl or cycloalkyl is optionally substituted with 1-3 groups selected from halogen, D, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy and NH_2;

each R_7 is independently H, =O, D, OH, CN, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $N(R_7')_2$, C_{2-4} alkenyl or C_{2-4} alkynyl, wherein the alkyl, alkoxy, alkenyl or alkynyl is optionally substituted with 1-3 groups selected from halogen, D, OH, NH_2, CN, C_{1-4} alkyl, $-C(O)C_{1-4}$ alkyl, $-C(O)NHC_{1-4}$ alkyl, $-C(O)NH_2$, $-NHC(O)C_{1-4}$ alkyl and C_{1-4} alkoxy;

each R_8 is independently H, D, =O, OH, CN, halogen, C_{2-4} alkenyl, C_{2-4} alkynyl, N_3, C_{1-4} alkyl, $-COC_{1-4}$ alkyl, $-CONR_7'C_{1-4}$ alkyl, $-NR_7'COC_{1-4}$ alkyl, $N(R_7')_2$, $-O-(CH_2)r-R_8'$ or $-(CH_2)r-R_8'$, wherein the alkyl, alkenyl or alkynyl is optionally substituted with 1-3 groups selected from halogen, D, OH, NH_2, CN, C_{1-4} alkyl and C_{1-4} alkoxy;

each R_7' is independently H, C_{1-4} alkyl or halo C_{1-4} alkyl;

each R_8' is independently H, C_{1-4} alkoxy, C_{3-6} cycloalkyl, phenyl, 4- to 7-membered heterocycloalkyl containing 1-3 heteroatoms selected from N, O or S, or 5- to 6-membered heteroaryl containing 1-3 heteroatoms selected from N, O or S, wherein the cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally

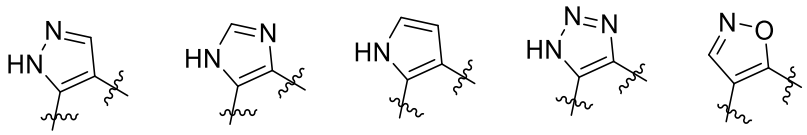
substituted with 1-3 groups selected from halogen, =O, D, OH, NH_2, CN, C_{1-4} alkyl, halo C_{1-4} alkyl and C_{1-4} alkoxy;

each r is independently 0, 1 or 2;

p is 0 or 1;

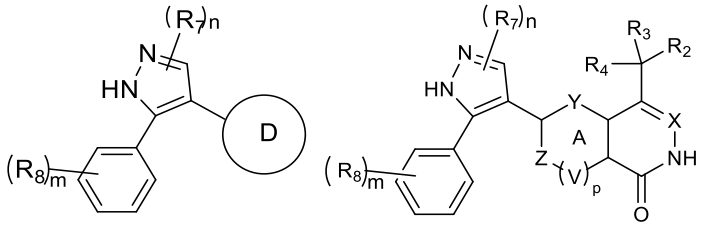
n and m are independently 0, 1, 2, 3 or 4.

5. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 1, characterized in that ring B is selected from



.

6. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 1, characterized in that the compound has a structure of formula (II-a) or formula (II):



II-a II

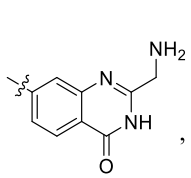
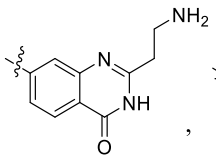
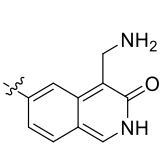
.

7. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 6, characterized in that

X is selected from CR_1 or N;

Y, Z and V are independently CR_5, N, O or S, and the total number of O and S is not greater than 1;

ring A is phenyl, thienyl, thiazolyl, pyrrolyl, imidazolyl, oxazolyl, pyridyl, pyrazinyl, pyrimidyl or pyridazinyl;

D is selected from , , ,

selected from N, O or S, or C_{3-4} cycloalkyl, wherein the alkyl, alkoxy, alkenyl, alkynyl, heteroaryl, heterocycloalkyl or cycloalkyl is optionally substituted with 1-3 groups selected from F, Cl, Br, I, D, CN, OH, methoxy and NH_2;

each R_7 is independently H, D, OH, CN, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, $N(R_7')_2$, C_{2-4} alkenyl or C_{2-4} alkynyl, wherein the alkyl, alkoxy, alkenyl or alkynyl is optionally substituted with 1-3 groups selected from halogen, D, OH, NH_2, CN, C_{1-4} alkyl and C_{1-4} alkoxy;

each R_8 is independently H, D, OH, CN, F, Cl, Br, I, C_{2-4} alkenyl, C_{2-4} alkynyl, N_3, C_{1-4} alkyl, $-COC_{1-4}$ alkyl, $-CONR_7'C_{1-4}$ alkyl, $-NR_7'COC_{1-4}$ alkyl, $N(R_7')_2$, $-O-(CH_2)r-R_8'$ or $-(CH_2)r-R_8'$, wherein the alkyl, alkenyl or alkynyl is optionally substituted with 1-3 groups selected from halogen, D, OH, NH_2, CN, C_{1-4} alkyl and C_{1-4} alkoxy;

each R_7' is independently H, C_{1-4} alkyl or halo C_{1-4} alkyl;

each R_8' is independently H, C_{1-4} alkoxy, C_{3-6} cycloalkyl, phenyl, 4- to 7-membered heterocycloalkyl containing 1-3 heteroatoms selected from N, O or S, or 5- to 6-membered heteroaryl containing 1-3 heteroatoms selected from N, O or S, wherein the cycloalkyl, phenyl, heterocycloalkyl or heteroaryl is optionally substituted with 1-3 groups selected from halogen, =O, D, OH, NH_2, CN, C_{1-4} alkyl, halo C_{1-4} alkyl and C_{1-4} alkoxy;

each r is independently 0, 1 or 2;

p is 0 or 1;

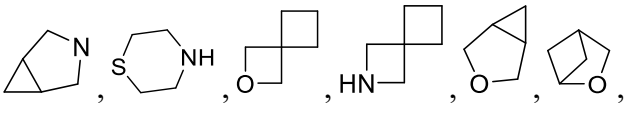
n is 0, 1, 2 or 3;

m is 0, 1, 2, 3 or 4.

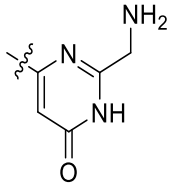
8. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 7, characterized in that

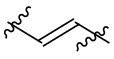
each R_8 is independently D, CN, F, Cl, Br, C_{2-4} alkenyl, C_{2-4} alkynyl, N_3, C_{1-4} alkyl, $-O-(CH_2)r-R_8'$ or $-(CH_2)r-R_8'$, wherein the alkyl, alkenyl or alkynyl is optionally substituted with 1-3 groups selected from halogen, D, OH, NH_2, CN, C_{1-2} alkyl and C_{1-2} alkoxy.

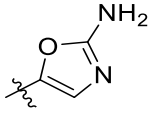
9. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 6, characterized in that

R_8' is independently C_{1-4} alkoxy, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, tetrahydropyrrolyl, azetidinyl, piperidyl, piperazinyl, morpholinyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, , , thienyl, thiazolyl, pyrrolyl, imidazolyl, oxazolyl, pyridyl, pyrazinyl, pyrimidyl or pyridazinyl optionally substituted with 1-3 groups selected from F, Cl, Br, I, =O, D, OH, NH_2, CN, C_{1-4} alkyl, halo C_{1-2} alkyl and C_{1-2} alkoxy.

10. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 1, characterized in that

D1 is selected from: ;

Ld is selected from C_{2-4} alkenyl, preferably ;

Rd1 is selected from 5-membered heteroaryl, wherein the heteroaryl is optionally substituted with 1-2 groups selected from NH_2, and Rd1 is preferably .

11. The compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to claim 1, characterized in that the compound has a structure selected from those in Table 1.

12. A pharmaceutical composition, characterized in comprising the compound, or the stereoisomer, the deuterated compound, the solvate or the

pharmaceutically acceptable salt thereof according to any one of claims 1-11, and a pharmaceutically acceptable carrier and/or excipient.

13. Use of the compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to any one of claims 1-11, or the composition according to claim 12 in the preparation of a drug for treating/preventing PRMT5•MTA-mediated diseases.

14. The use according to claim 13, characterized in that the PRMT5•MTA-mediated diseases are selected from liver cancer, breast cancer, skin cancer, bladder cancer, pancreatic cancer, or head and neck cancer.

15. The use according to claim 13, characterized in that the amount of the compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof is 1-1500 mg.

16. A pharmaceutical composition or pharmaceutical preparation, characterized in that the pharmaceutical composition or pharmaceutical preparation comprises 1-1500 mg of the compound, or the stereoisomer, the deuterated compound, the solvate or the pharmaceutically acceptable salt thereof according to any one of claims 1-11, and a pharmaceutically acceptable excipient.