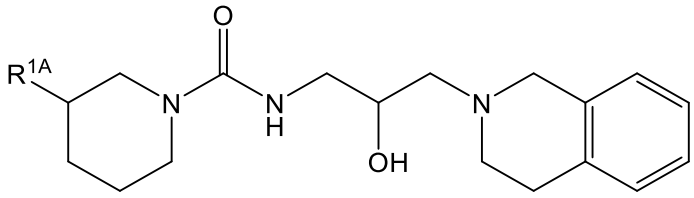
[0005] There is a need to develop compounds that reduce the expression or activity of PRMT5, particularly compounds that can be used in a clinical setting.

SUMMARY

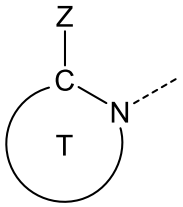
[0005a] In a first aspect of the present disclosure, there is provided a compound of formula (1) or a deuterated form, salt, solvate, or hydrate thereof,



(1)

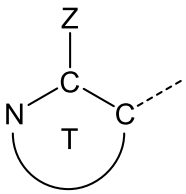
wherein:

R^{1A} is represented by formula (A1) or (A1'),



(A1)

or



(A1')

Z is =O;

T taken together with the intervening carbon and nitrogen atoms (e.g. shown in formula (A1)) is selected from a monocyclic 5- to 7-membered heterocycloalkyl group, a fused bicyclic 6- to 10-membered heterocycloalkyl group and a bridged bicyclic 6- to 9-membered heterocycloalkyl group, wherein each of the monocyclic 5- to 7-membered heterocycloalkyl group, the fused bicyclic 6- to 10-membered heterocycloalkyl group and the bridged bicyclic 6- to 9-membered heterocycloalkyl group is optionally substituted with one or more R^{S1};

R^{S1} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, halo, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}; and

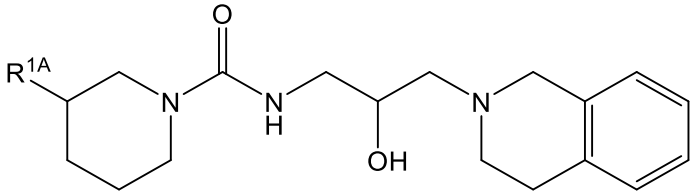
R^{S2} is selected from hydroxy, halo, CN and nitro.

[0005b] In another aspect of the present disclosure, there is provided a pharmaceutical composition which comprises a compound as disclosed herein, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof, and optionally a pharmaceutically acceptable excipient.

[0005c] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof in the manufacture of a medicament for treating or preventing a PRMT5-mediated disorder.

[0005d] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof, for use in therapy.

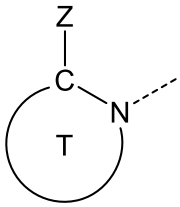
[0006] The present disclosure provides a compound of formula (1) or a deuterated form, salt, solvate, or hydrate thereof,



(1)

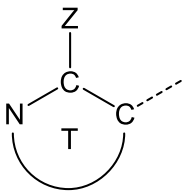
wherein:

R^{1A} is represented by formula (A1) or (A1'),



(A1)

or



(A1')

Z is =O;

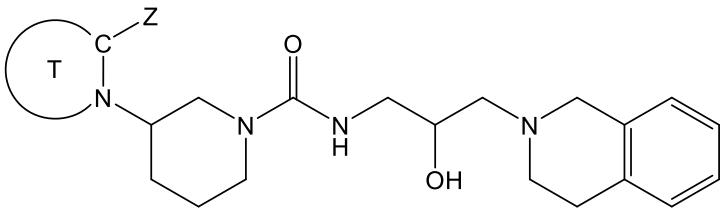
T taken together with the intervening carbon and nitrogen atoms (e.g. shown in formula (A1) and (A1')) is selected from a monocyclic 5- to 7-membered heterocycloalkyl group, a fused bicyclic 6- to 10-membered heterocycloalkyl group and a bridged bicyclic 6- to 9-membered heterocycloalkyl group, wherein each of the monocyclic 5- to 7-membered heterocycloalkyl group, the fused bicyclic 6- to 10-membered heterocycloalkyl group and the bridged bicyclic 6- to 9-membered heterocycloalkyl group is optionally substituted with one or more R^{S1};

R^{S1} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, halo, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}; and

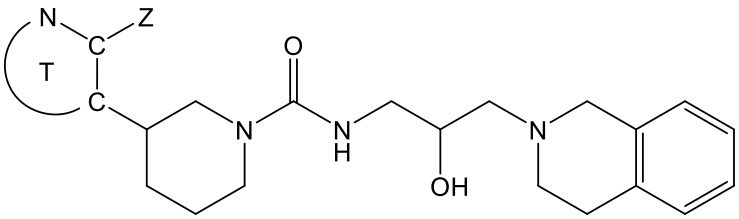
R^{S2} is selected from hydroxy, halo, CN and nitro.

[0007] R^{1A} is represented by formula (A1) and (A1') above, where the dashed bond represents the point of attachment of (A1) or (A1') to formula (1), as shown in formula (1') or (1") below.

[0008] When T is an unsubstituted group, then each constituent atom of the group may be attached to hydrogen atom(s) to satisfy the correct valency of that constituent atom. For example, in formula (A1') above, when the nitrogen atom shown has two single bonds that make up the ring represented by T, the nitrogen atom is bonded to a hydrogen atom (e.g. to ensure that the nitrogen atom is trivalent).



(1')



(1").

[0009] The present disclosure also provides a pharmaceutical composition, which comprises a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof. The pharmaceutical composition may further comprise a pharmaceutically acceptable excipient.

[0010] The compounds of the present disclosure are PRMT5 inhibitors and show excellent inhibitory activity in an *in vitro* PRMT5 assay. In addition to this *in vitro* activity, the compounds of the present disclosure show excellent metabolic stability, which is typically superior to other PRMT5 inhibitors known in the art. This metabolic stability is believed to be due to one or more structural features of the compounds, include the side group represented by formula (A1) or (A1') and the position at which it is attached to the piperidinyl ring in formula (1), (1') or (1").

[0011] The present disclosure further provides a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in therapy and/or for use as a medicament.

[0012] In another example, the present disclosure provides a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment or prevention of a PRMT5-mediated disorder.

[0013] A further example of the present disclosure provides a compound of formula (1), (1') or (1') as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a proliferative disorder.

[0014] In another example, the present disclosure provides a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment cancer.

[0015] In a further example, the present disclosure provides the use of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for the treatment or prevention of a PRMT5-mediated disorder.

[0016] In another example, the present disclosure provides the use of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for the treatment of a proliferative disorder.

[0017] A further example of the present disclosure provides the use of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for the treatment of cancer.

[0018] In another example, the present disclosure provides a method of treating or preventing a PRMT5-mediated disorder, said method comprising administering to a subject in need thereof an effective amount of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0019] In another example, the present disclosure provides a method of treating a proliferative disorder, said method comprising administering to a subject in need thereof an effective amount of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0020] In another example, the present disclosure provides a method of treating cancer, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0021] In another example, the present disclosure provides a method of inhibiting the activity of PRMT5 *in vivo* or *in vitro*. When the method is an *in vivo* or *in vitro* method, then the method

may comprise contacting a cell with an effective amount of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein. When the method is an *in vivo* method, then additionally or alternatively the method may comprise administering to a subject in need thereof a therapeutically effective amount of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0022] In a further example, the present disclosure provides a method of altering gene expression in a cell which comprises contacting a cell with an effective amount of a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0023] In another example, the present disclosure provides a combination comprising a compound of formula (1), (1') or (1") as defined herein, or a deuterated form, a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more additional therapeutic agents.

[0024] In a further example, the present disclosure provides a pharmaceutical composition as defined herein further comprising one or more additional therapeutic agents.

[0025] Preferred, suitable, and optional features of any one particular example of the present disclosure are also preferred, suitable, and optional features of any other example.

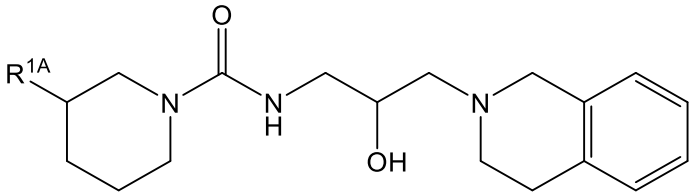
DETAILED DESCRIPTION

Definitions

[0026] The compounds and intermediates described herein may be named according to either the IUPAC (International Union for Pure and Applied Chemistry) or CAS (Chemical Abstracts Service) nomenclature systems. It should be understood that unless expressly stated to the contrary, the terms "compounds of formula (1) or (1')" and the more general term "compounds" refer to and include any and all compounds described by and/or with reference to formula (1) or formula (1'). It should also be understood that these terms encompass all stereoisomers, i.e. *cis* and *trans* isomers, as well as optical isomers, i.e. *R* and *S* enantiomers, of such compounds and all salts thereof, in substantially pure form and/or any mixtures of the foregoing in any ratio. This understanding extends to pharmaceutical compositions and methods of treatment that employ or comprise one or more compounds of formula (1) or (1'), either by themselves or in combination with additional agents.

CLAIMS

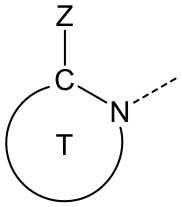
1. A compound of formula (1) or a deuterated form, salt, solvate, or hydrate thereof,



(1)

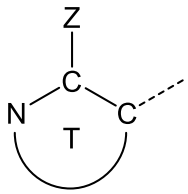
wherein:

R^{1A} is represented by formula (A1) or (A1'),



(A1)

or



(A1')

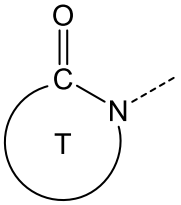
Z is =O;

T taken together with the intervening carbon and nitrogen atoms (e.g. shown in formula (A1)) is selected from a monocyclic 5- to 7-membered heterocycloalkyl group, a fused bicyclic 6- to 10-membered heterocycloalkyl group and a bridged bicyclic 6- to 9-membered heterocycloalkyl group, wherein each of the monocyclic 5- to 7-membered heterocycloalkyl group, the fused bicyclic 6- to 10-membered heterocycloalkyl group and the bridged bicyclic 6- to 9-membered heterocycloalkyl group is optionally substituted with one or more R^{S1};

R^{S1} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, halo, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}; and

R^{S2} is selected from hydroxy, halo, CN and nitro.

2. The compound according to claim 1 or a deuterated form, salt, solvate or hydrate thereof, wherein R^{1A} is represented by formula (A2),



(A2).

3. The compound according to claim 1, or a deuterated form, salt, solvate or hydrate thereof, wherein the monocyclic 5- to 7-membered heterocycloalkyl group is a monocyclic 5- or 6-membered heterocycloalkyl group optionally substituted with one or more R^{S1}.

4. The compound according to claim 1 or a deuterated form, salt, solvate or hydrate thereof, wherein the fused bicyclic 6- to 10-membered heterocycloalkyl group has a first 5- or 6-membered ring including the intervening carbon and nitrogen atoms and a second ring fused to the first 5- or 6-membered ring, and wherein each of the first 5- or 6-membered ring and the second ring is optionally substituted with one or more R^{S1}.

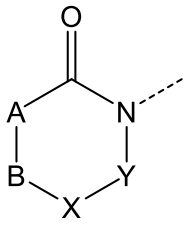
5. The compound according to claim 4 or a deuterated form, salt, solvate or hydrate thereof, wherein the second ring is a 3- to 6-membered ring optionally substituted with one or more R^{S1}.

6. The compound according to claim 1 or a deuterated form, salt, solvate or hydrate thereof, wherein each R^{S1} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, chloro, bromo, fluoro, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}.

7. The compound according to claim 6 or a deuterated form, salt, solvate or hydrate thereof, wherein each R^{S1} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy and chloro, wherein the C_{1-6}alkyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}.

8. The compound according to claim 7 or a deuterated form, salt, solvate or hydrate thereof, wherein each R^{S1} is selected from unsubstituted C_{1-6}alkyl, fluoro-C_{1-6}alkyl, fluoro and chloro.

9. The compound according to claim 1 or a deuterated form, salt, solvate or hydrate thereof, wherein R^{1A} is represented by formula (B1),



(B1)

(a) X-Y is selected from $CR^{3A}=CR^{2A}$, $CR^{3A}=N$, $N=CR^{2A}$, $N=N$, $C(R^{3A})_2$-$C(R^{2A})_2$, $C(R^{3A})_2$-NR^{2A}, NR^{3A}-$C(R^{2A})_2$, NR^{3A}-NR^{2A}, $C(R^{3A})_2$-O, O-$C(R^{2A})_2$ $C(R^{3A})_2$-S and S^A-$C(R^{2A})_2$; and

A-B is selected from $CR^{5A}=CR^{4A}$, $CR^{5A}=N$, $N=CR^{4A}$, $N=N$, $C(R^{5A})_2$-$C(R^{4A})_2$, $C(R^{5A})_2$-NR^{4A}, NR^{5A}-$C(R^{4A})_2$, NR^{5A}-NR^{4A}, $C(R^{5A})_2$-O, O-$C(R^{4A})_2$, $C(R^{5A})_2$-S and S-$C(R^{4A})_2$; or

(b) A is selected from $C(R^{5A})_2$, NR^{5A}, O and S;

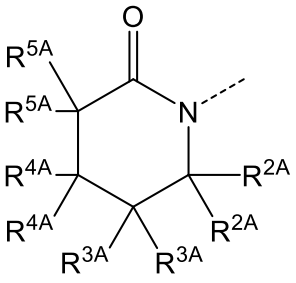
Y is selected from $C(R^{2A})_2$ and NR^{2A}; and

B-X is selected from $CR^{4A}=CR^{3A}$, $CR^{4A}=N$ and $N=CR^{3A}$;

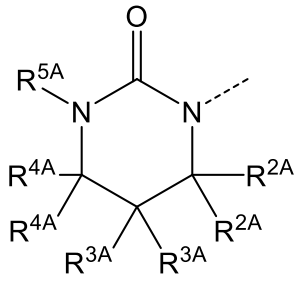
wherein each R^{2A}, R^{3A}, R^{4A} and R^{5A} is the same or different and is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, halo, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}; and

each R^{S2} is selected from hydroxy, halo, CN and nitro.

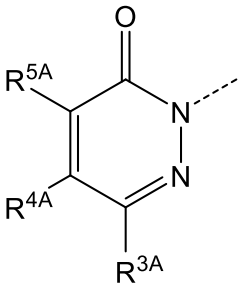
10. The compound according to claim 9 or a deuterated form, salt, solvate, or hydrate thereof, wherein R^{1A} is represented by one of the following formulae,



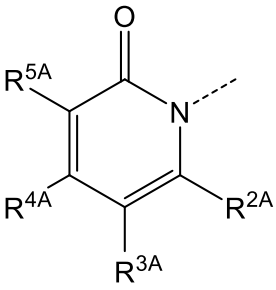
(B1a)



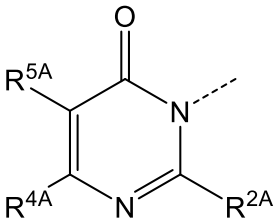
(B1b)



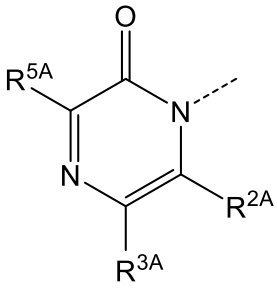
(B1c)


(B1d)

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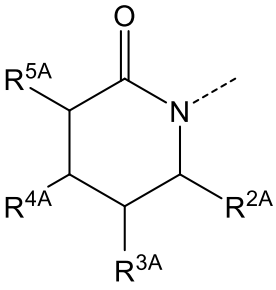

(B1e)

or

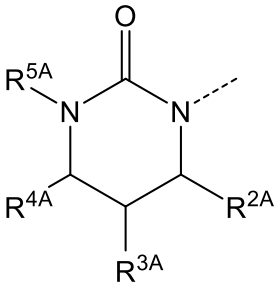

(B1f)

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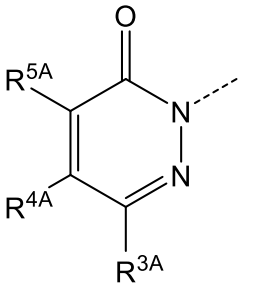
11. The compound according to claim 10 or a deuterated form, salt, solvate, or hydrate thereof, wherein R^{1A} is represented by one of the following formulae:


(B1a)

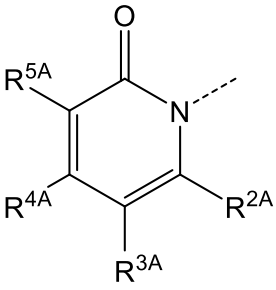
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(B1b)

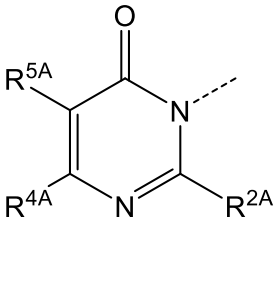
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(B1c)

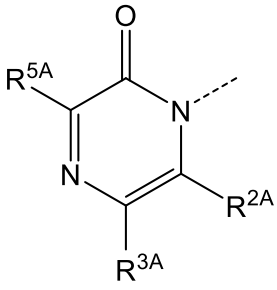
,


(B1d)

,


(B1e)

or


(B1f)

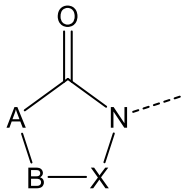
.

12. The compound according to claim 9 or a deuterated form, salt, solvate, or hydrate thereof, wherein each R^{2A}, R^{3A}, R^{4A} and R^{5A} is the same or different and is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, chloro, bromo, fluoro, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}.

13. The compound according to claim 12 or a deuterated form, salt, solvate or hydrate thereof, wherein each R^{2A}, R^{3A}, R^{4A} and R^{5A} is the same or different and is

independently selected from hydrogen, unsubstituted C_{1-6}alkyl, halo-C_{1-6}alkyl, fluoro and chloro.

14. The compound according to claim 1 or a deuterated form, salt, solvate or hydrate thereof, wherein R^{1A} is represented by formula (C1),



(C1)

wherein either:

(a) X is selected from $C(R^{2A})_2$ and NR^{2A}; and

A-B is selected from $CR^{4A}=CR^{3A}$, $CR^{4A}=N$, $N=CR^{3A}$, $N=N$, $C(R^{4A})_2$-$C(R^{3A})_2$, $C(R^{4A})_2$-NR^{3A}, NR^{4A}-$C(R^{3A})_2$, NR^{4A}-NR^{3A}, $C(R^{4A})_2$-O, O-$C(R^{3A})_2$, $C(R^{4A})_2$-S and S-$C(R^{3A})_2$; or

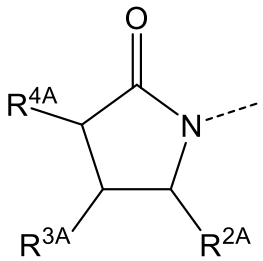
(b) A is selected from $C(R^{4A})_2$, NR^{4A}, O and S; and

B-X is selected from $CR^{3A}=CR^{2A}$, $CR^{3A}=N$, $N=CR^{2A}$ and $N=N$;

wherein each R^{2A}, R^{3A}, R^{4A} and R^{5A} is the same or different and is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, halo, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}; and

each R^{S2} is selected from hydroxy, halo, CN and nitro.

15. The compound according to claim 14 or a deuterated form, salt, solvate, or hydrate thereof, wherein R^{1A} is represented by formula (C3),



(C3)

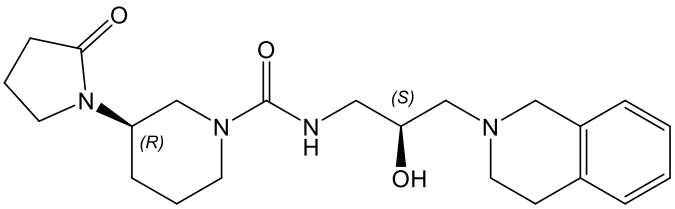
wherein R^{2A}, R^{3A} and R^{4A} is each independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, halo, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}; and

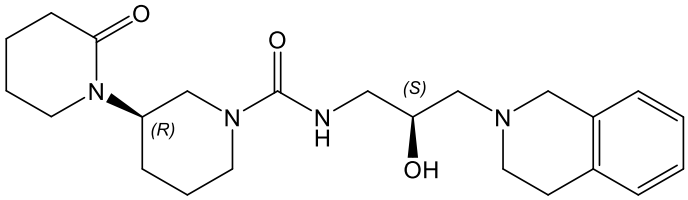
each R^{S2} is selected from hydroxy, halo, CN and nitro.

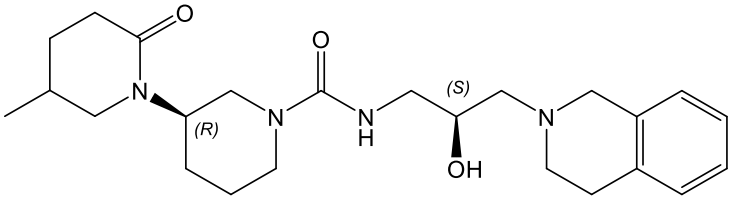
16. The compound according to claim 14 or a deuterated form, salt, solvate, or hydrate thereof, wherein each R^{2A}, R^{3A} and R^{4A} is the same or different and is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{3-12}cycloalkyl, hydroxy, chloro, bromo, fluoro, CN and nitro, wherein the C_{1-6}alkyl, the C_{2-6}alkenyl, the C_{2-6}alkynyl and the C_{3-12}cycloalkyl is each optionally substituted with one or more R^{S2}.

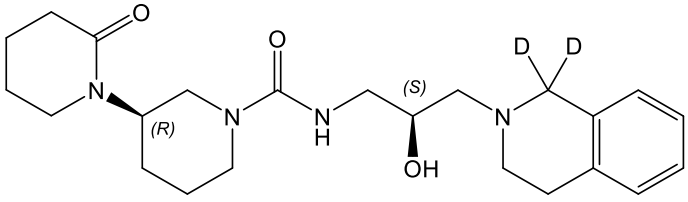
17. The compound according to claim 16 or a deuterated form, salt, solvate or hydrate thereof, wherein each R^{2A}, R^{3A} and R^{4A} is the same or different and is independently selected from hydrogen, unsubstituted C_{1-6}alkyl, halo-C_{1-6}alkyl, fluoro and chloro.

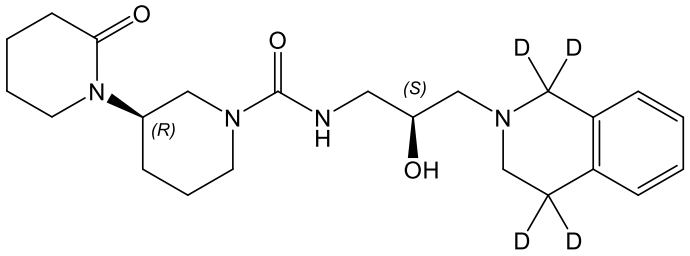
18. The compound according to claim 1 selected from:

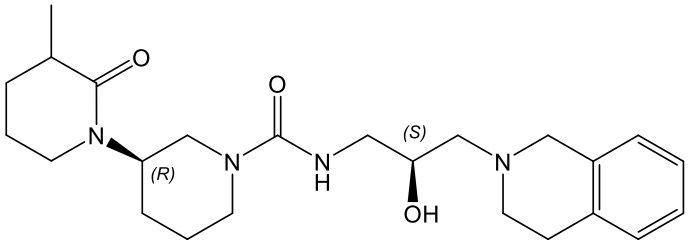

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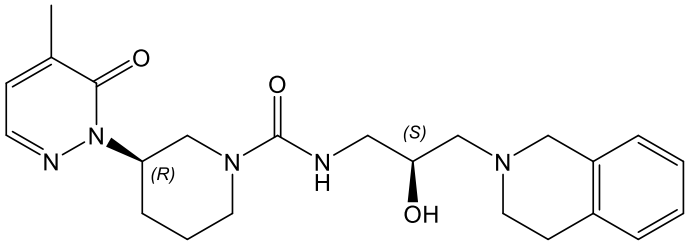

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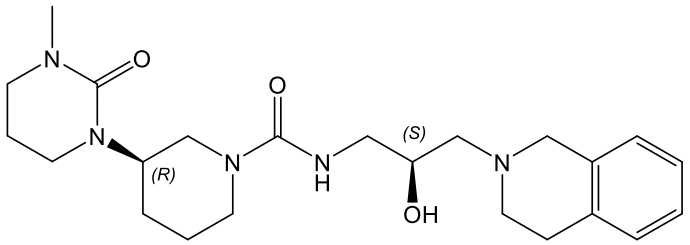

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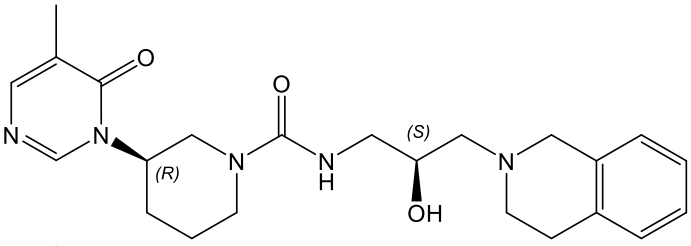

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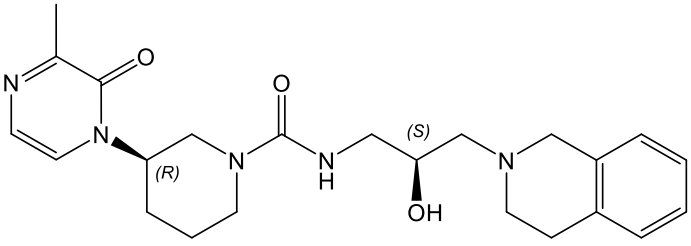

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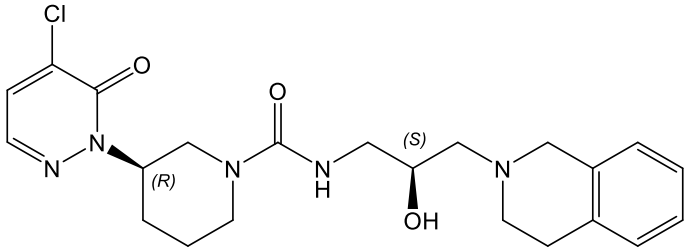

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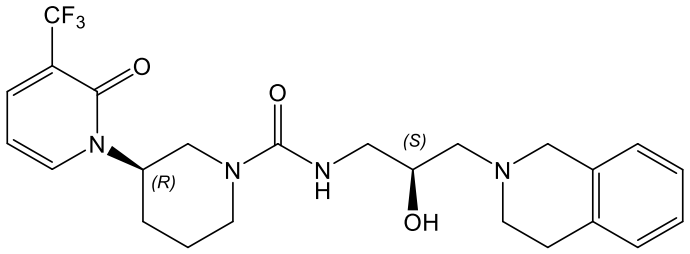
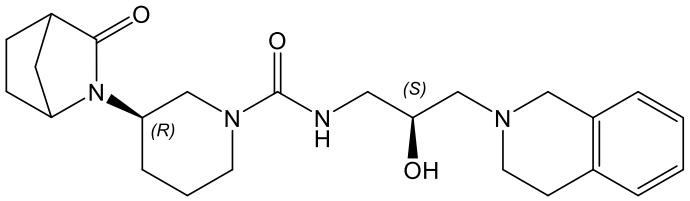
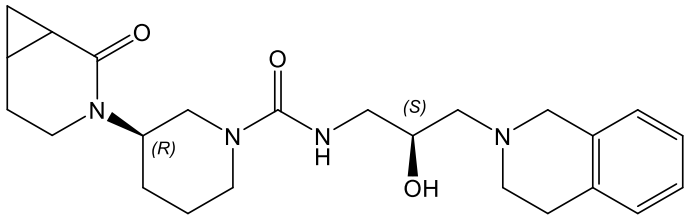
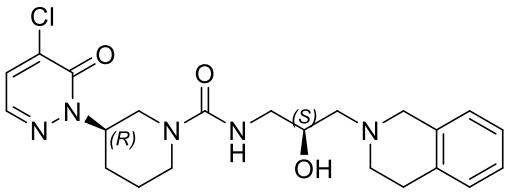
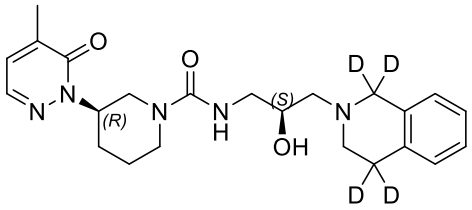
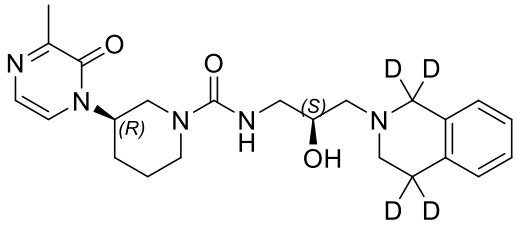
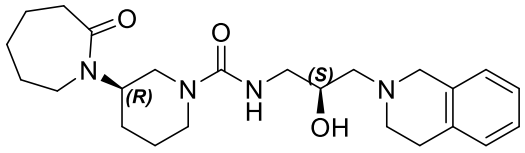
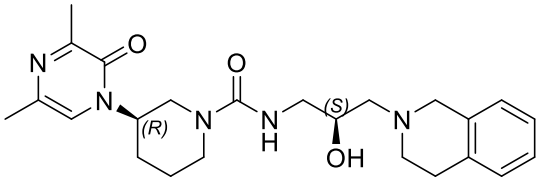
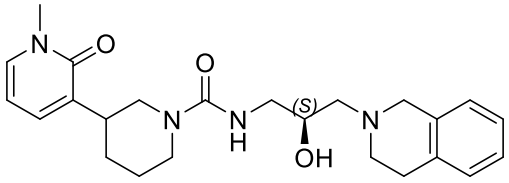
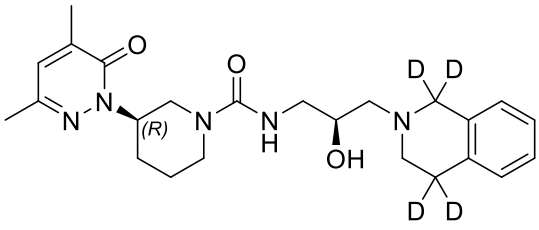

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or a salt, solvate, or hydrate thereof.

19. A pharmaceutical composition which comprises a compound according to claim 1, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof, and optionally a pharmaceutically acceptable excipient.

20. Use of a compound according to claim 1, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof in the manufacture of a medicament for treating or preventing a PRMT5-mediated disorder.

21. A compound according to claim 1, or a deuterated form, pharmaceutically acceptable salt, hydrate or solvate thereof, for use in therapy.