selectively kill methylthioadenosine phosphorylase deficient cells. Analogs of MTA are described herein as anti-toxicity agents. Kung, P.-P. et al., Bioorg Med Chem Lett, 2005. **15**: p. 2829-2833, describes the design, synthesis, and biological evaluation of novel human 5'-deoxy-5'-methylthioadenosine phosphorylase (MTAP) substrates. WO2012075500 discloses 7-deazapurine modulators of histone methyltransferase. WO2014035140 discloses compounds and compositions for modulating histone methyltransferase activity. WO9640686 describes heterocyclic substituted cyclopentane compounds and methods of using such compounds for inhibiting adenosine kinase.

WO2016135582 and US20160244475 describe substituted nucleoside derivatives useful as anticancer agents. Boyer *et al* described diaryl-*erythro*-furanosyltubercidin analogies as adenosine kinase inhibitors.

Nucleoside analogues are a class of compounds that have interesting therapeutic activities. They are used clinically for the treatment of wide-ranging diseases and disorders such as viral infections and proliferative disorders. For example, WO2017/032840, WO2017/153186 and WO2018/065365 disclose nucleoside analogues useful for inhibiting Protein Arginine Methyltransferase 5 (PRMT5) activity and for treating PRMT5-mediated disorders.

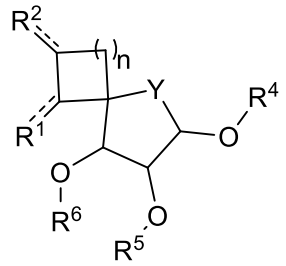
It is desirable to develop intermediates and chemical syntheses to allow the preparation of nucleoside analogues having novel substituent patterns.

Brand *et al.*, JOC 2009, 74, 8779-8786 and Ramakrishna *et al,* RSC Adv., 2015, 5, 8142-8145 describe synthesis of spirocyclic compounds. Nowak *et al,* JOC 2006, 71, 8876-8883 describes addition of difluorocarbene to 4',5'-unsaturated nucleosides. Redlich *et al,* Angew. Chem. Int. Ed. Engl. 28 (1989) 777-778 described synthesis of chiral cyclobutanones.

Summary

It has been determined that spirobicyclic nucleosides show interesting activity, for example against PRMT5. Novel intermediates that may be used to synthesise spirobicyclic nucleoside analogues have been developed. In particular, these intermediates contain functional groups that can be diversified to give access to a variety of spirobicyclic nucleoside analogues, including cyclopentane containing nucleoside analogues. Accordingly, disclosed herein are compounds which are useful as intermediates for the preparation of spirobicyclic nucleoside analogues that may, for example, possess activity against PRMT5. Also disclosed herein are spirocyclic nucleoside compounds which may serve as intermediates for further functionalisation to provide spirobicyclic nucleoside analogues with interesting activity.

In one aspect the present disclosure concerns a compound of Formula (A)



(A)

or a salt or solvate thereof, wherein:

Y is –O– or –CH_2–;

n is 0 or 1;

when n is 1, R^1 is hydrogen and R^2 is -$(CH_2)_mNR^a_2$, -$(CH_2)_mOR^a$, -$(CH_2)_mC(O)OR^a$, -$(CH_2)_mC(O)NR^a_2$, -$(CH_2)_mC(O)R^a$, -$(CH_2)_mB(OR^b)_2$, -$(CH_2)_mS(O)_xR^c$, a silyl group, C_{1-6} alkyl substituted with a silyl group, =O or =CR^a_2; or

when n is 1, R^2 is hydrogen and R^1 is -$(CH_2)_mNR^a_2$, -$(CH_2)_mOR^a$, -$(CH_2)_mOPG$, -$(CH_2)_mC(O)OR^a$, -$(CH_2)_mC(O)NR^a_2$, -$(CH_2)_mC(O)R^a$, -$(CH_2)_mB(OR^b)_2$, -$(CH_2)_mS(O)_xR^c$, a silyl group, C_{1-6} alkyl substituted with a silyl group, -O-aryl, =O or =CR^a_2;

when n is 0, one of R^1 and R^2 is hydrogen and the other is -$(CH_2)_mNR^a_2$,-$(CH_2)_mOR^a$, -$(CH_2)_mOPG$, -$(CH_2)_mC(O)OR^a$, -$(CH_2)_mC(O)NR^a_2$, -$(CH_2)_mC(O)R^a$, -$(CH_2)_mB(OR^b)_2$, -$(CH_2)_mS(O)_xR^c$ or =CH_2;

wherein the bond towards R^1 or R^2 ⎓ is a single bond when R^1 or R^2 is hydrogen, -$(CH_2)_mNR^a_2$, -$(CH_2)_mOR^a$, -$(CH_2)_mOPG$, -$(CH_2)_mC(O)OR^a$, -$(CH_2)_mC(O)NR^a_2$, -$(CH_2)_mC(O)R^a$, -$(CH_2)_mB(OR^b)_2$, -$(CH_2)_mS(O)_xR^c$, a silyl group, C_{1-6} alkyl substituted with a silyl group or -O-aryl, or a double bond when R^1 or R^2 is =O, =CH_2 or =CR^a_2;

each R^a is, independently, hydrogen or C_{1-6} alkyl;

each R^b is hydrogen or both R^b are taken together to form a boronic acid protecting group;

R^c is C_{1-6} alkyl or aryl;

PG is a hydroxyl protecting group;

m is 0 or 1;

x is 0, 1 or 2;

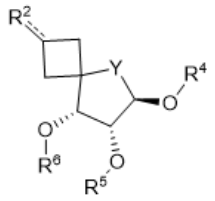
R^4, R^5 and R^6 are each independently hydrogen or a hydroxyl protecting group;

or R^5 and R^6 taken together are a diol protecting group;

or R^4 and R^5 taken together are a diol protecting group;

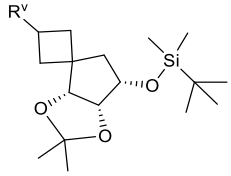
provided that:

(a) the compound is not a compound of formula:



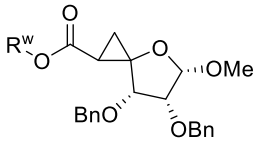
, wherein Y is –O– or –CH_2–; R^4 is hydrogen or a hydroxyl protecting group such as for example C_{1-4}alkyl, t-butyldimethylsilyl, C_{1-4}alkyl-O-C_{1-4}alkyl, tetrahydropyranyl, allyl, t-butyldiphenylsilyl, benzyl, -C(=O)-C_{1-4}alkyl, or -C(=O)-phenyl; R^2 is -OH, =O, -CH_2-OH or =CH_2; and R^5 and R^6 are each independently -C(=O)-C_{1-4}alkyl, benzoyl, benzyl, or -CH_2-naphthyl, wherein benzyl, -CH_2-naphthyl, and benzoyl are optionally substituted with one or two substituents each independently selected from -CH_3 and -OCH_3; or R^5 and R^6 taken together are -C(C_{1-4}alkyl)$_2$-; or wherein Y is –O– or –CH_2, R^4 is methyl, R^2 is =O, or =CH_2, and R^5 and R^6 are each independently hydrogen or –C(=O)-C_{1-4}alkyl; and

(b) the compound is not a compound of formula:

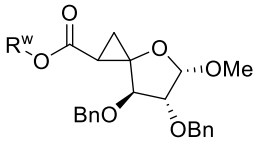


, wherein R^v is =O, -OH or =CH_2; and

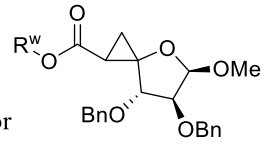
(c) the compound is not a compound of formula:



,

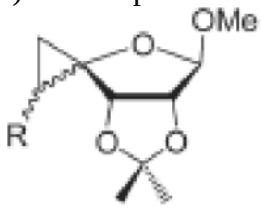


or



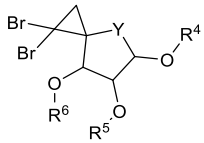
, wherein R^w is methyl or H; and

(d) the compound is not a compound of formula:



wherein R is CO_2Et or CH_2OH or any stereoisomer thereof.

In another aspect the present disclosure concerns a compound of formula (B):

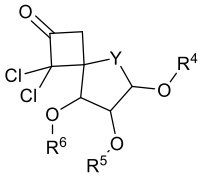


(B)

or a salt or solvate thereof, wherein:

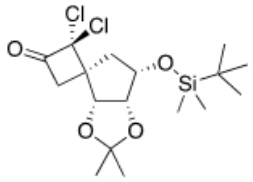
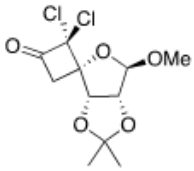
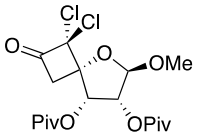
Y is –O– or –CH_2–;
R^4, R^5 and R^6 are each, independently, hydrogen or a hydroxyl protecting group;
or R^5 and R^6 taken together are a diol protecting group;
or R^4 and R^5 taken together are a diol protecting group.

In another aspect the present disclosure concerns a compound of formula (C):

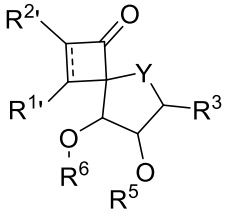


(C)

wherein:
Y is –O– or –CH_2–;
R^4, R^5 and R^6 are each, independently, hydrogen or a hydroxyl protecting group; or
R^4 and R^5 taken together are a diol protecting group; or
R^5 and R^6 taken together are a diol protecting group;
provided that the compound is not:


, 
or 
.

In another aspect the present disclosure concerns a compound of formula (D):



(D)

or a salt or solvate thereof, wherein:
Y is –O– or –CH_2–;
wherein  is a single bond or a double bond; and
when is a single bond, one of $R^{1'}$ and $R^{2'}$ is hydrogen or C_{1-6} alkyl and the other is a silyl group, C_{1-6} alkyl optionally substituted with a silyl group, -O-C_{1-6} alkyl, -$B(OR^b)_2$, -S-C_{1-6} alkyl, -S-aryl, -O-aryl or $C(O)R^a$;
when is a double bond, one of $R^{1'}$ and $R^{2'}$ is hydrogen or C_{1-6} alkyl and the other is a silyl group, C_{1-6} alkyl optionally substituted with a silyl group, -O-C_{1-6} alkyl, or $C(O)R^a$;

and

R^a is hydrogen or C_{1-6} alkyl;

each R^b is hydrogen or both R^b are taken together to form a boronic acid protecting group;

R^3 is OR^4 or R^{10};

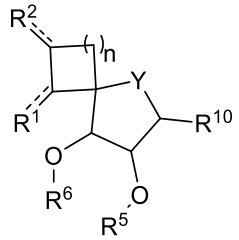
R^{10} is a nucleobase or nucleobase derivative;

R^4, R^5 and R^6 are each, independently, hydrogen or a hydroxyl protecting group; or

R^4 and R^5 taken together are a diol protecting group; or

R^5 and R^6 taken together are a diol protecting group.

In another aspect the present disclosure concerns a compound of formula (E):



(E)

or a salt or solvate thereof, wherein:

Y is –O- or $–CH_2–$;

n is 0 or 1;

when n is 1, R^1 is hydrogen and R^2 is $-(CH_2)_mNR^a_2$, $-(CH_2)_mOR^a$, $-(CH_2)_mC(O)OR^a$, $-(CH_2)_mC(O)NR^a_2$, $-(CH_2)_mC(O)R^a$, $-(CH_2)_mB(OR^b)_2$, $-(CH_2)_mS(O)_xR^c$, a silyl group, C_{1-6} alkyl substituted with a silyl group, =O or $=CR^a_2$; or

when n is 1, R^2 is hydrogen and R^1 is $-(CH_2)_mNR^a_2$, $-(CH_2)_mOR^a$, $-(CH_2)_mOPG$, $-(CH_2)_mC(O)OR^a$, $-(CH_2)_mC(O)NR^a_2$, $-(CH_2)_mC(O)R^a$, $-(CH_2)_mB(OR^b)_2$, $-(CH_2)_mS(O)_xR^c$, a silyl group, C_{1-6} alkyl substituted with a silyl group, -O-aryl, =O or $=CR^a_2$;

when n is 0, one of R^1 and R^2 is hydrogen and the other is $-(CH_2)_mNR^a_2$, $-(CH_2)_mOR^a$, $-(CH_2)_mOPG$, $-(CH_2)_mC(O)OR^a$, $-(CH_2)_mC(O)NR^a_2$, $-(CH_2)_mC(O)R^a$, $-(CH_2)_mB(OR^b)_2$, $-(CH_2)_mS(O)_xR^c$ or $=CH_2$;

wherein the bond towards R^1 or R^2 ═ is a single bond when R^1 or R^2 is hydrogen, $-(CH_2)_mNR^a_2$, $-(CH_2)_mOR^a$, $-(CH_2)_mOPG$, $-(CH_2)_mC(O)OR^a$, $-(CH_2)_mC(O)NR^a_2$, $-(CH_2)_mC(O)R^a$, $-(CH_2)_mB(OR^b)_2$, $-(CH_2)_mS(O)_xR^c$, a silyl group, C_{1-6} alkyl substituted with a silyl group or -O-aryl, or a double bond when R^1 or R^2 is =O, $=CH_2$ or $=CR^a_2$;

each R^a is, independently, hydrogen or C_{1-6} alkyl;

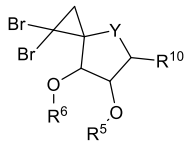
each R^b is hydrogen or both R^b are taken together to form a boronic acid protecting group;

R^c is C_{1-6} alkyl or aryl;

x is 0, 1 or 2;

m is 0 or 1;

In another aspect the present disclosure concerns a compound of formula (H):



(H)

or a salt or solvate thereof, wherein:
R^5 and R^6 are each, independently, hydrogen or a hydroxyl protecting group; or R^5 and R^6 taken together are a diol protecting group; and
R^{10} is a nucleobase or nucleobase derivative.

The present disclosure will now be further described. In the following passages, different aspects of the disclosure are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Detailed description

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise.
When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence.
Whenever the term “substituted” is used in the present invention, it is meant, unless otherwise is indicated or is clear from the context, to indicate that one or more hydrogens, in particular from 1 to 3 hydrogens, preferably 1 or 2 hydrogens, more preferably 1 hydrogen, on the atom or radical indicated in the expression using “substituted” are replaced with a selection from the indicated group, provided that the normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.
When two or more substituents are present on a moiety they may, unless otherwise is indicated or is clear from the context, replace hydrogens on the same atom or they may replace hydrogen atoms on different atoms in the moiety.
The prefix “C_{x-y}” (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-4}alkyl group contains from 1 to 4 carbon atoms, a C_{1-3}alkyl group contains from 1 to 3 carbon atoms and so on.
The term “halo” as a group or part of a group is generic for fluoro, chloro, bromo, iodo unless otherwise is indicated or is clear from the context.