COMPOUNDS TARGETING PRMT5

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application Nos. 62/828,282, filed April 2, 2019, 62/877,411, filed July 23, 2019 and 62/946,649, filed December 11, 2019.

BACKGROUND

Field

[0002] The present application relates to the fields of chemistry, biochemistry and medicine. Disclosed herein are compounds of Formula (I), or pharmaceutically acceptable salt thereof, pharmaceutical compositions that include a compound described herein (including pharmaceutically acceptable salts of a compound described herein) and methods of synthesizing the same. Also disclosed herein are methods of treating diseases and/or conditions with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

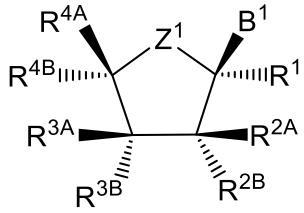
Description

[0003] In mammals, there are nine enzymes in the seven–β-strand family of protein arginine methyltransferases (PRMTs), designated PRMT1–9. These PRMTs are further divided into three types based on the different methylarginine derivatives they produce: Type I PRMTs (PRMT1–4, 6, and 8) catalyze the production of monomethylarginine (MMA) and asymmetric dimethylarginine (ADMA); Type II PRMTs (PRMT5 and 9) catalyze MMA and symmetric dimethylarginine (SDMA) production; and Type III enzymes (PRMT7) catalyze only the production of MMA residues.

SUMMARY

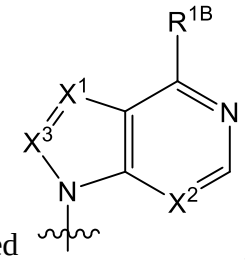
[0004] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

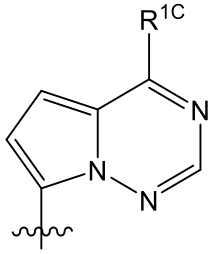
[0004a] In one aspect, disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:

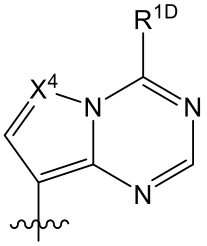


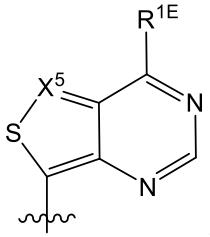
(I)

wherein:

B^1 is an optionally substituted 

, an optionally substituted 

, an optionally substituted 

or an optionally substituted 

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wherein X^1 is N or CR^{C1}; X^2 is N or CR^{C2}; X^3 is N or CR^{C3}; X^4 is N or CR^{C4}; X^5 is N or CR^{C5}; and R^{C1}, R^{C2}, R^{C3}, R^{C4} and R^{C5} are independently hydrogen, halogen or an unsubstituted C_{1-4} alkyl;

R^{1B}, R^{1C}, R^{1D} and R^{1E} are independently hydrogen, halogen, hydroxy, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_3-C_6 cycloalkyl, an unsubstituted C_{1-4} alkoxy or $NR^{A1}R^{A2}$; and

R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, hydroxy, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} alkoxy and

–C(=O)R^{C6}, wherein R^{C6} is hydrogen, an unsubstituted C_{1-4} alkyl or an unsubstituted C_{3-4} monocyclic cycloalkyl;

R^1 is hydrogen;

R^{2A} is hydrogen or an unsubstituted C_{1-4} alkyl;

R^{2B} is halogen, OH, –O-C(=O)-C_{1-4} alkyl or –O-C(=O)-CH($R^{1'}$)-NH_2, wherein $R^{1'}$ is H, -CH_3, -$CH(CH_3)_2$, -CH_2-$CH(CH_3)_2$ or -$CH(CH_3)$-$CH(CH_3)_2$;

R^{3A} is hydrogen, an unsubstituted or a substituted C_{1-4} alkyl, an unsubstituted or a substituted C_{2-4} alkenyl or an unsubstituted or a substituted C_{2-4} alkynyl, wherein when the C_{1-4} alkyl, the C_{2-4} alkenyl and the C_{2-4} alkynyl are substituted, each is independently substituted with 1 or more fluoros;

R^{3B} is halogen, OH, –O-C(=O)-C_{1-4} alkyl or –O-C(=O)-CH($R^{1''}$)-NH_2, wherein $R^{1''}$ is H, -CH_3, -$CH(CH_3)_2$, -CH_2-$CH(CH_3)_2$ or -$CH(CH_3)$-$CH(CH_3)_2$;

R^{4A} is –($CR^{D1}R^{E1}$)($CR^{D2}R^{E2}$)n-R^{F1}, –($CR^{G1}R^{H1}$)–O-R^{J1}, –O-($CR^{K1}R^{L1}$)-R^{M1} or –($CR^{N1}R^{O1}$)p–R^{P1};

wherein R^{D1}, R^{E1}, R^{D2} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; n is 0 or 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

R^{D1} and R^{E1} are taken together with the carbon to which R^{D1} and R^{E1} are attached to form an unsubstituted cyclopropyl ring; and R^{D2} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; n is 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

R^{D1} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; R^{E1} and R^{D2} are taken together with the carbon to which R^{E1} and R^{D2} are attached to form an unsubstituted cyclopropyl ring; n is 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

R^{D1} and R^{E2} are independently selected from the group consisting of hydrogen, halogen and hydroxy; R^{E1} and R^{D2} together form a double bond; n is 1; and R^{F1} is an

unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl;

R^{G1}, R^{H1}, R^{K1}, R^{L1}, R^{N1} and R^{O1} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; R^{J1} and R^{M1} are independently an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; R^{P1} is an unsubstituted or a substituted heteroaryl; and p is 3 or 4;

R^{4B} is a C_{1-4} alkyl substituted with OCH_3, an unsubstituted C_{2-4} alkenyl or an unsubstituted C_{2-4} alkynyl;

Z^1 is $CR^{5A}R^{5B}$, O, S or N(an unsubstituted C_{1-4} alkyl);

R^{5A} and R^{5B} are independently hydrogen, halogen, cyano or an unsubstituted or a substituted C_{1-4} alkyl, wherein when the C_{1-4} alkyl is substituted, the C_{1-4} alkyl is substituted with 1 or more substituents independently selected from the group consisting of fluoro and hydroxy; or

R^{5A} and R^{5B} together with the carbon R^{5A} and R^{5B} are attached form a double bond optionally substituted with one or two halogen, R^{5A} and R^{5B} together with the carbon R^{5A} and R^{5B} are attached form an unsubstituted cyclopropyl or R^{5A} and R^{5B} together with the carbon R^{5A} and R^{5B} are attached form an unsubstituted or a substituted oxetane, wherein when the oxetane is substituted, the oxetane is substituted independently with 1 or 2 halogens; or

R^{2A} and R^{2B} together with the carbon R^{2A} and R^{2B} are attached form a 3, 4 or 5 membered monocyclic cycloalkyl or a 3, 4 or 5 membered monocyclic heterocyclyl; or

R^{3A} and R^{3B} together with the carbon R^{3A} and R^{3B} are attached form a 3, 4 or 5 membered monocyclic cycloalkyl or a 3, 4 or 5 membered monocyclic heterocyclyl; or

R^1 and R^{5B} together with the carbon R^1 and R^{5B} are attached form an unsubstituted cyclopropyl.

[0005] Disclosed herein is a pharmaceutical composition that can contain an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0005a] In another aspect, disclosed herein is a pharmaceutical composition comprising an effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and excipient.

[0005b] In another aspect, disclosed herein is a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0005c] In another aspect, disclosed herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating a cancer.

[0005d] In another aspect, disclosed herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for modulating PRMT5.

[0005e] In another aspect, disclosed herein is use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for inhibiting PRMT5.

[0006] These are other examples are described in greater detail below.

DETAILED DESCRIPTION

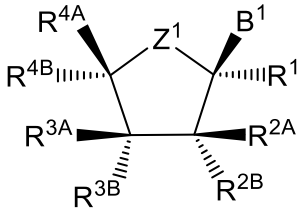
[0007] PRMT5 is a Type II protein arginine methyltransferase that catalyzes SDMA modification in histones and non-histone substrates, including three subunits of the Survival of Motor Neuron (SMN) complex (SmB, SmD1 and SmD3). These proteins are essential components of the spliceosome machinery (See Friesen et al., Molecular and Cellular Biology (2001) 21(24):8289-8300; Matera et al., Nature Reviews Molecular Cell Biology (2014) 14:108-121; and Meister et al., Current Biology (2001) 11(24):1990-1994), and PRMT5 depletion triggers aberrant splicing in the adult hematopoietic compartment (Bezzi et al., Genes & Development (2013) 27:1903-1916; Koh et al., Nature (2015) 523:96-100; and Liu et al., J. Clin. Invest. (2015) 125(9):3532-3544).

[0008] PRMT5 is overexpressed in a variety of human cancers, including several hematological malignancies such as lymphoma and leukemia (Yang et al., Nature Reviews Cancer (2013) 13:37-50 and Chung et al., J. Biol. Chem. (2013) 288(49):35534-35547), as well as liver cancer (Jiang et al., Cancer Medicine (2018) 7(3):869-882), lung cancer (Wei et al., Cancer Science (2012) 103(9): 1640-1650), breast cancer (Powers et al., Cancer Research (2011) 71(16):5579-5587), and colorectal cancer (Cho et al., The EMBO Journal (2012) 31:1785-1797). Enhanced PRMT5 expression correlates with reduced overall survival and higher recurrence rates for patients with hepatocellular carcinoma (HCC) (Jiang et al., Cancer Medicine (2018) 7(3):869-882). Knocking down PRMT5 expression with shRNA can prevent cell proliferation and colony formation in Huh-7 and SK-Hep1 HCC cells. In a mouse xenograph model for HCC, this approach can result in tumor regression.

[0009] Inhibition of PRMT5 has been shown to result in anti-tumor activity in lymphomas (Chan-Penebre et al., Nature Chemical Biology (2015) 11:432-437), MLL-rearranged acute leukemia models (Kaushik et al., Leukemia (2018) 32:499-509), and several other types of leukemia in vitro (Tarighat et al., Leukemia (2016) 30:789-799). In addition, cells lacking MTAP, a critical enzyme in the methionine salvage pathway that is deleted in

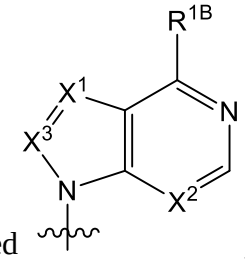
WHAT IS CLAIMED IS:

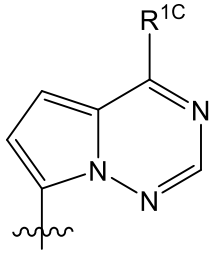
1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:

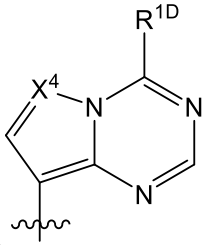


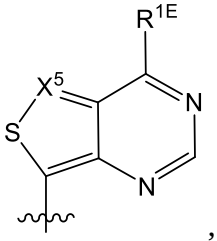
(I)

wherein:

B^1 is an optionally substituted 

, an optionally substituted 

, an optionally substituted 

or an optionally substituted 

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wherein X^1 is N or CR^{C1}; X^2 is N or CR^{C2}; X^3 is N or CR^{C3}; X^4 is N or CR^{C4}; X^5 is N or CR^{C5}; and R^{C1}, R^{C2}, R^{C3}, R^{C4} and R^{C5} are independently hydrogen, halogen or an unsubstituted C_{1-4} alkyl;

R^{1B}, R^{1C}, R^{1D} and R^{1E} are independently hydrogen, halogen, hydroxy, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_3-C_6 cycloalkyl, an unsubstituted C_{1-4} alkoxy or $NR^{A1}R^{A2}$; and

R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, hydroxy, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} alkoxy and $–C(=O)R^{C6}$, wherein R^{C6} is hydrogen, an unsubstituted C_{1-4} alkyl or an unsubstituted C_{3-4} monocyclic cycloalkyl;

R^1 is hydrogen;

R^{2A} is hydrogen or an unsubstituted C_{1-4} alkyl;

R^{2B} is halogen, OH, –O-C(=O)-C_{1-4} alkyl or –O-C(=O)-CH($R^{1'}$)-NH_2, wherein $R^{1'}$ is H, -CH_3, -$CH(CH_3)_2$, -CH_2-$CH(CH_3)_2$ or -CH(CH_3)-$CH(CH_3)_2$;

R^{3A} is hydrogen, an unsubstituted or a substituted C_{1-4} alkyl, an unsubstituted or a substituted C_{2-4} alkenyl or an unsubstituted or a substituted C_{2-4} alkynyl, wherein when the C_{1-4} alkyl, the C_{2-4} alkenyl and the C_{2-4} alkynyl are substituted, each is independently substituted with 1 or more fluoros;

R^{3B} is halogen, OH, –O-C(=O)-C_{1-4} alkyl or –O-C(=O)-CH($R^{1''}$)-NH_2, wherein $R^{1''}$ is H, -CH_3, -$CH(CH_3)_2$, -CH_2-$CH(CH_3)_2$ or -CH(CH_3)-$CH(CH_3)_2$;

R^{4A} is –($CR^{D1}R^{E1}$)($CR^{D2}R^{E2}$)n-R^{F1}, –($CR^{G1}R^{H1}$)–O-R^{J1}, –O-($CR^{K1}R^{L1}$)-R^{M1} or –($CR^{N1}R^{O1}$)p–R^{P1};

wherein R^{D1}, R^{E1}, R^{D2} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; n is 0 or 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

R^{D1} and R^{E1} are taken together with the carbon to which R^{D1} and R^{E1} are attached to form an unsubstituted cyclopropyl ring; and R^{D2} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; n is 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

R^{D1} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; R^{E1} and R^{D2} are taken together with the carbon to which R^{E1} and R^{D2} are attached to form an unsubstituted cyclopropyl ring; n is 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

R^{D1} and R^{E2} are independently selected from the group consisting of hydrogen, halogen and hydroxy; R^{E1} and R^{D2} together form a double bond; n is 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl;

R^{G1}, R^{H1}, R^{K1}, R^{L1}, R^{N1} and R^{O1} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; R^{J1} and R^{M1} are independently an

unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; R^{P1} is an unsubstituted or a substituted heteroaryl; and p is 3 or 4;

R^{4B} is a C_{1-4} alkyl substituted with OCH_3, an unsubstituted C_{2-4} alkenyl or an unsubstituted C_{2-4} alkynyl;

Z^1 is $CR^{5A}R^{5B}$, O, S or N(an unsubstituted C_{1-4} alkyl);

R^{5A} and R^{5B} are independently hydrogen, halogen, cyano or an unsubstituted or a substituted C_{1-4} alkyl, wherein when the C_{1-4} alkyl is substituted, the C_{1-4} alkyl is substituted with 1 or more substituents independently selected from the group consisting of fluoro and hydroxy; or

R^{5A} and R^{5B} together with the carbon R^{5A} and R^{5B} are attached form a double bond optionally substituted with one or two halogen, R^{5A} and R^{5B} together with the carbon R^{5A} and R^{5B} are attached form an unsubstituted cyclopropyl or R^{5A} and R^{5B} together with the carbon R^{5A} and R^{5B} are attached form an unsubstituted or a substituted oxetane, wherein when the oxetane is substituted, the oxetane is substituted independently with 1 or 2 halogens; or

R^{2A} and R^{2B} together with the carbon R^{2A} and R^{2B} are attached form a 3, 4 or 5 membered monocyclic cycloalkyl or a 3, 4 or 5 membered monocyclic heterocyclyl; or

R^{3A} and R^{3B} together with the carbon R^{3A} and R^{3B} are attached form a 3, 4 or 5 membered monocyclic cycloalkyl or a 3, 4 or 5 membered monocyclic heterocyclyl; or

R^1 and R^{5B} together with the carbon R^1 and R^{5B} are attached form an unsubstituted cyclopropyl.

2. The compound of Claim 1, wherein Z^1 is $CR^{5A}R^{5B}$; and

R^{5A} and R^{5B} are each hydrogen.

3. The compound of any one of Claims 1-2, wherein R^{2A} is hydrogen; and R^{3A} is hydrogen.

4. The compound of any one of Claims 1-3, wherein R^{2B} is OH; and R^{3B} is OH.

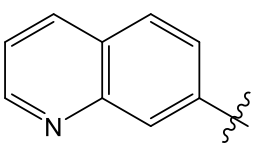
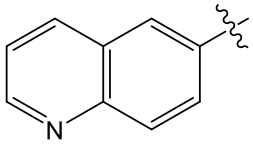
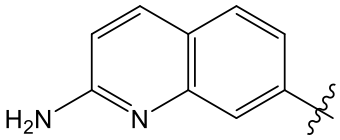
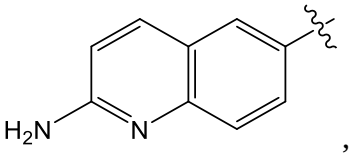
5. The compound of any one of Claims 1-3, wherein R^{2B} is –O-C(=O)-C_{1-4} alkyl; and R^{3B} is –O-C(=O)-C_{1-4} alkyl.

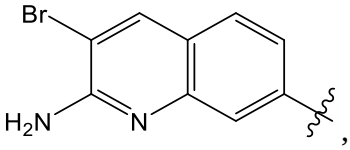
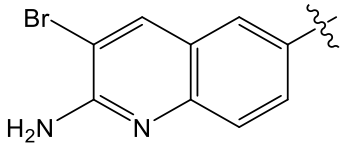
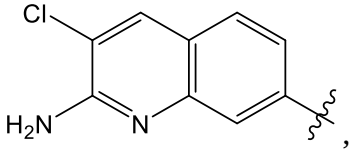
6. The compound of any one of Claims 1-37, wherein R^{4A} is $–(CR^{D1}R^{E1})(CR^{D2}R^{E2})n-R^{F1}$; n is 0; and R^{D1} and R^{E1} are each hydrogen.

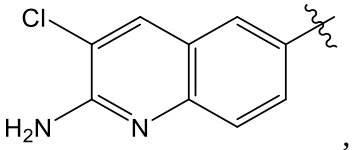
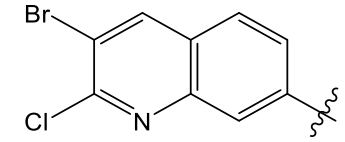
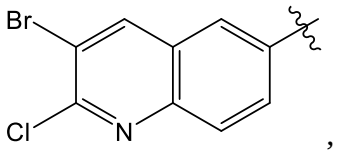
7. The compound of any one of Claims 1-5, wherein R^{4A} is $–(CR^{D1}R^{E1})(CR^{D2}R^{E2})n-R^{F1}$; n is 1; and R^{D1}, R^{E1}, R^{D2} and R^{E2} are each hydrogen.

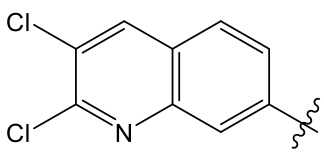
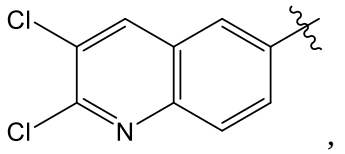
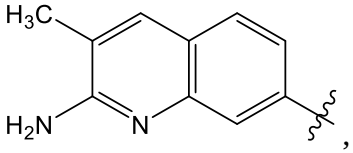
8. The compound of any one of Claim 6, wherein R^{F1} is an unsubstituted or a substituted heteroaryl.

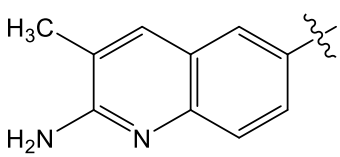
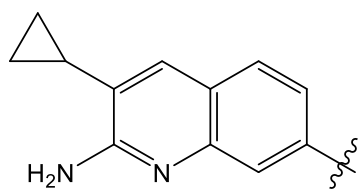
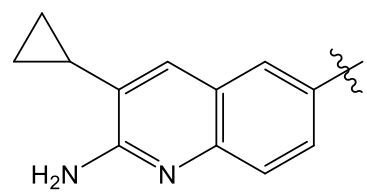
9. The compound of Claim 7, wherein R^{F1} is selected from the group consisting of:

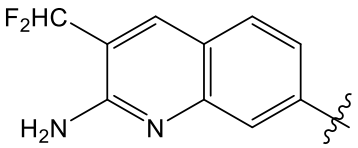
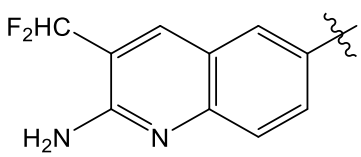
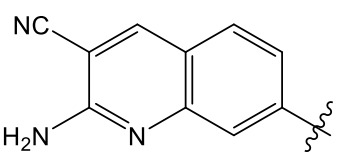
 ,  ,  ,  ,

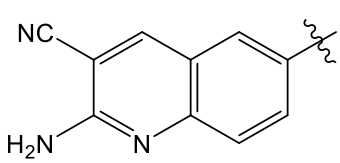
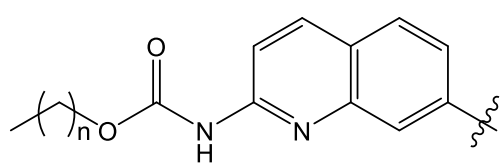
 ,  ,  ,

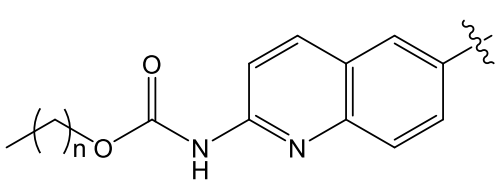
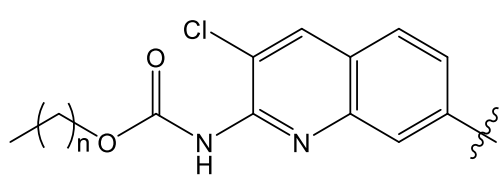
 ,  ,  ,

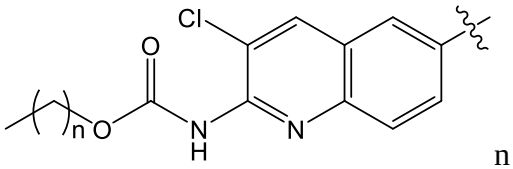
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  n = 1, 2, 3, 4, 5 or 6,

 n = 1, 2, 3, 4, 5 or 6, 

n = 1, 2, 3, 4, 5 or 6, 
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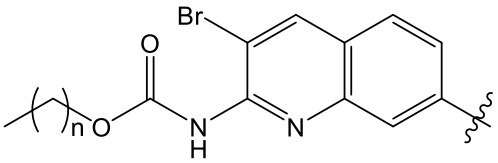
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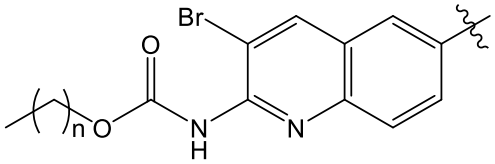
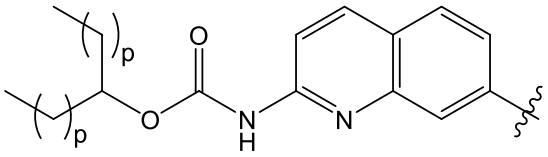


n = 1, 2, 3, 4, 5 or 6, 
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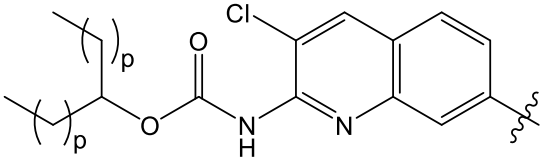
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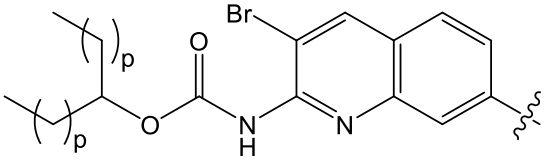
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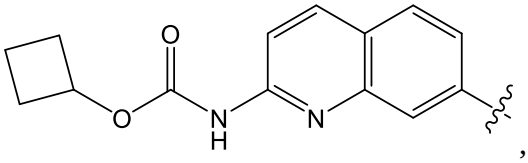
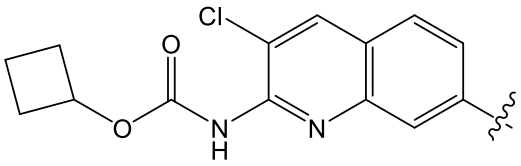
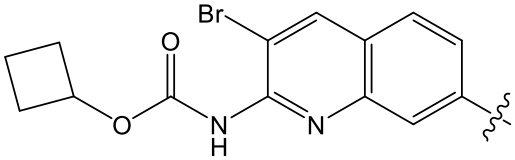
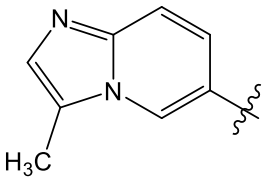
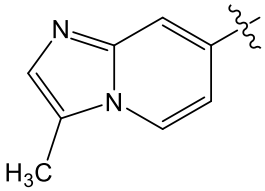
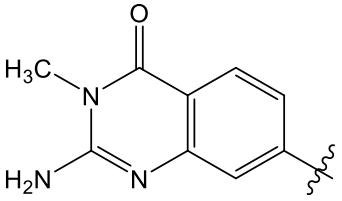
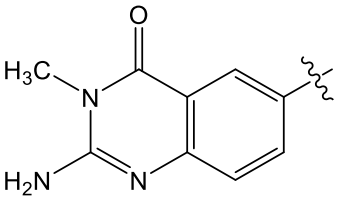
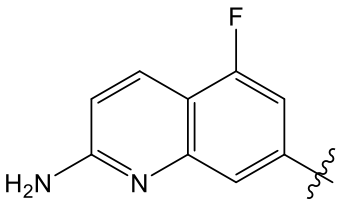
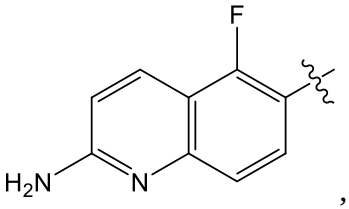
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,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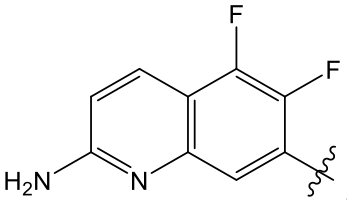
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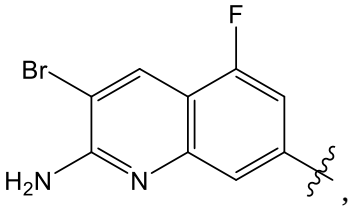
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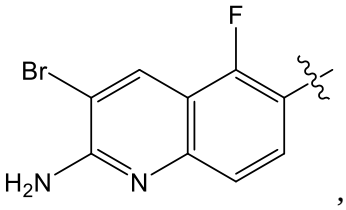
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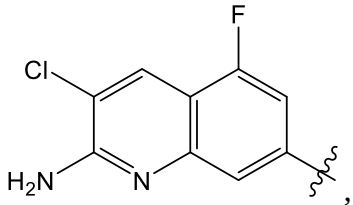
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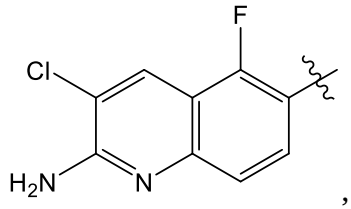
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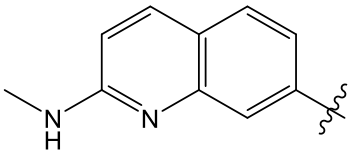
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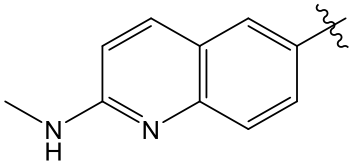
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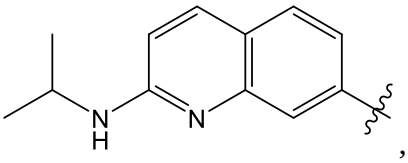
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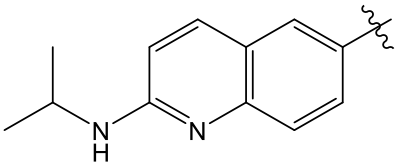
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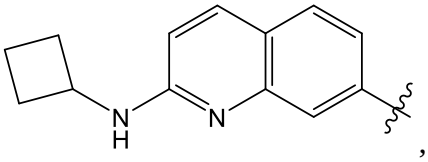
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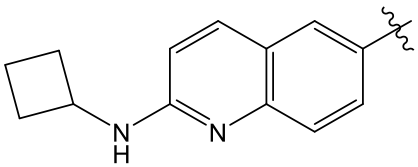
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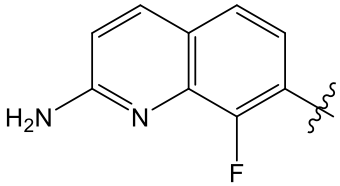
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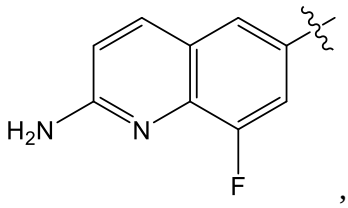
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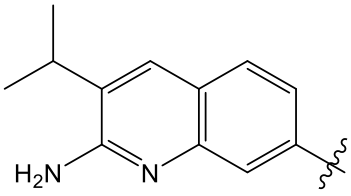
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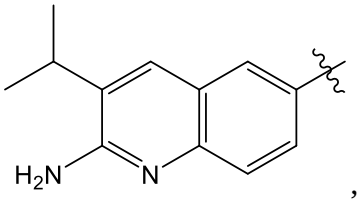
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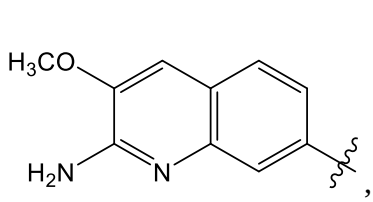
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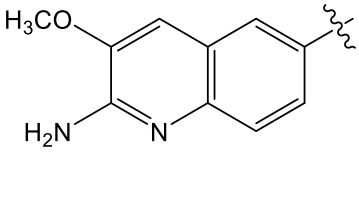
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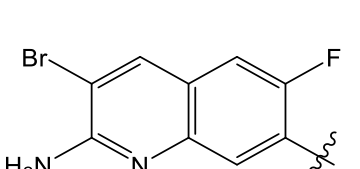
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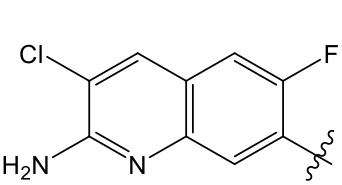
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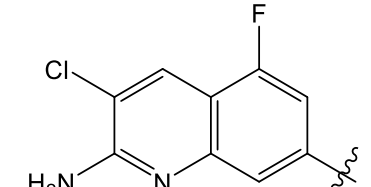
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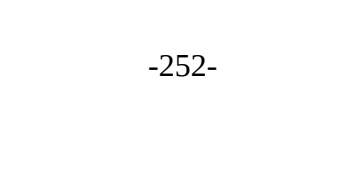
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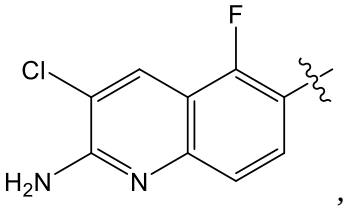
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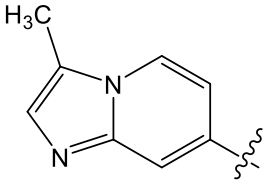
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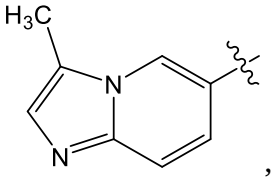
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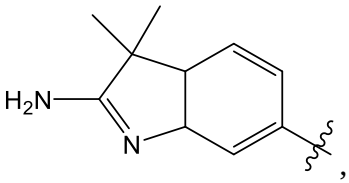
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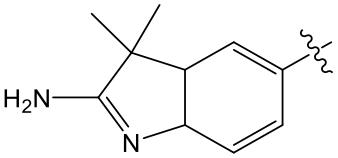
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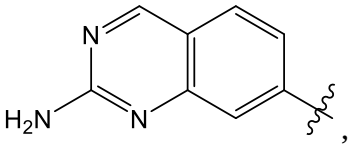
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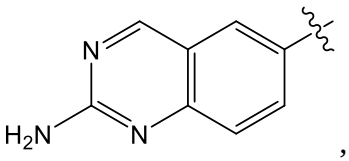
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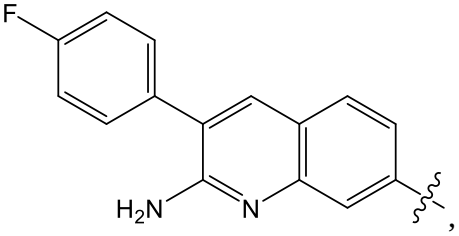
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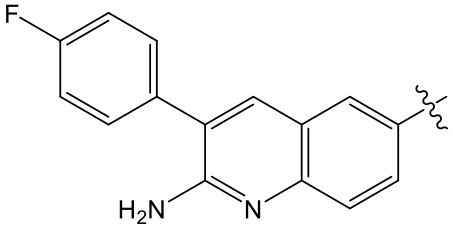
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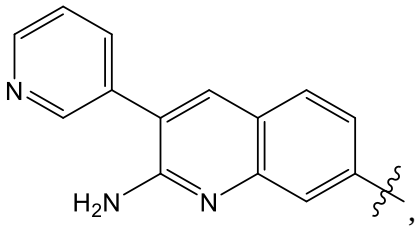
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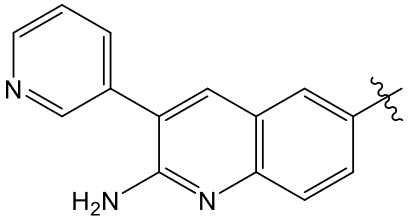
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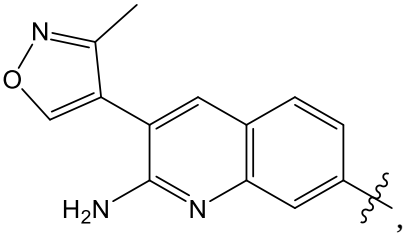
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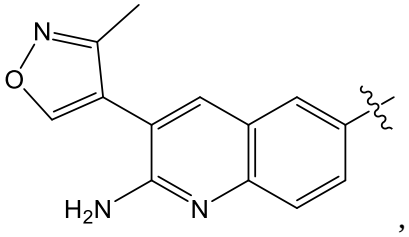
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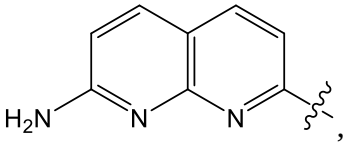
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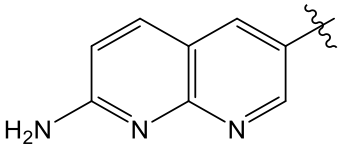
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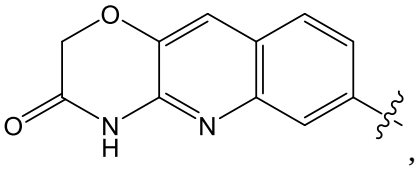
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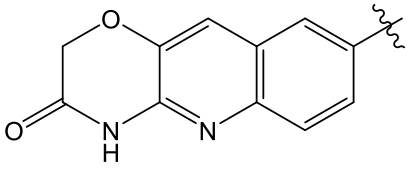
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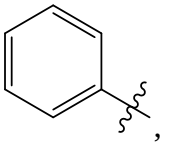
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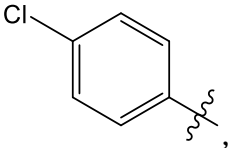
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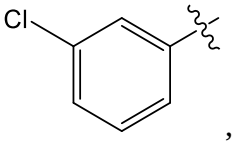
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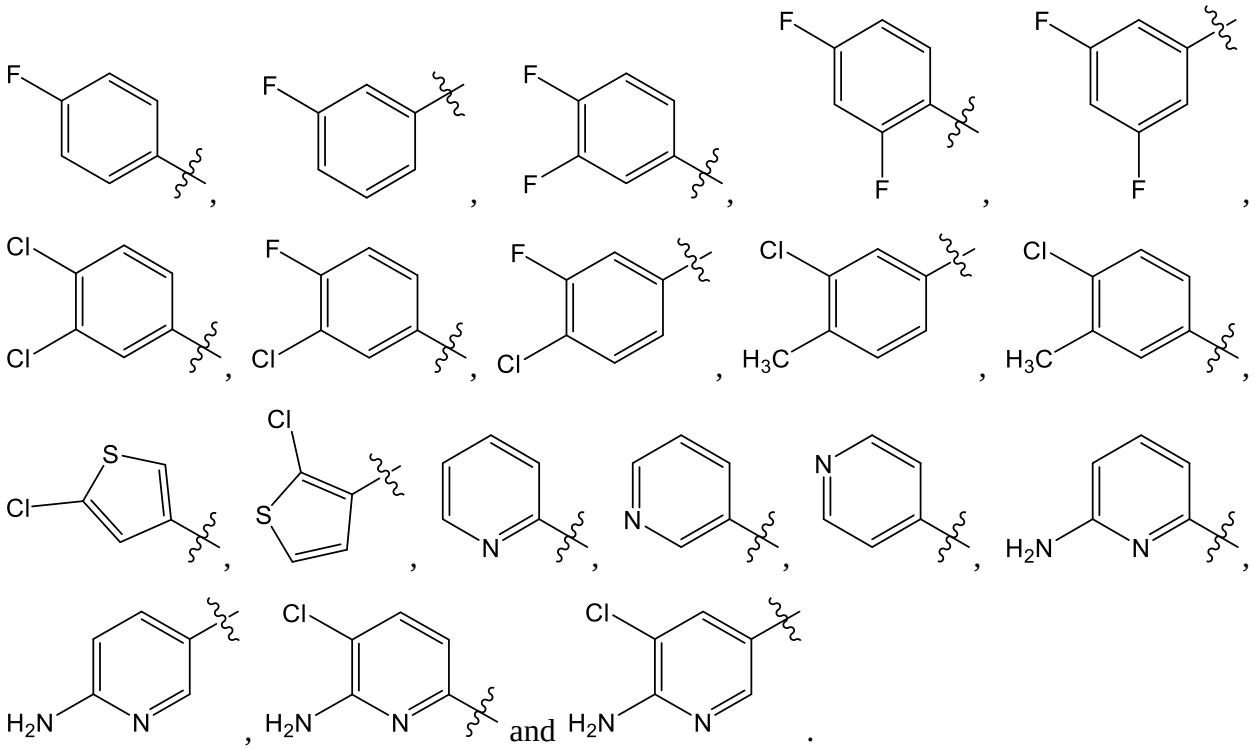


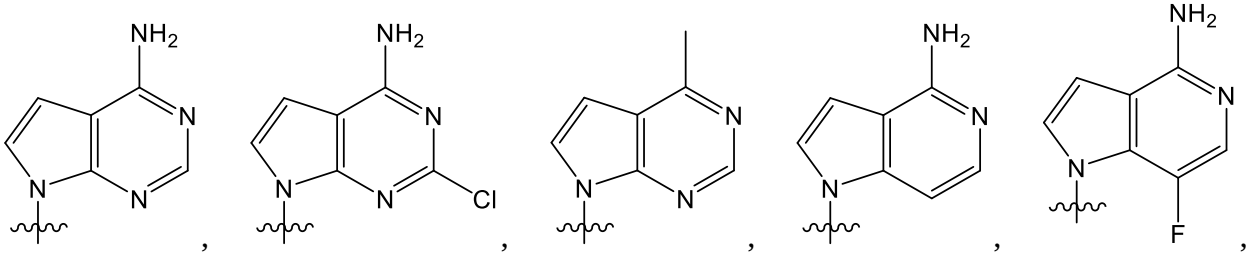
10. The compound of any one of Claims 1-5, wherein R^{4A} is $–(CR^{G1}R^{H1})–O-R^{J1}$, $–O-(CR^{K1}R^{L1})-R^{M1}$ or $–(CR^{N1}R^{O1})p–R^{P1}$.

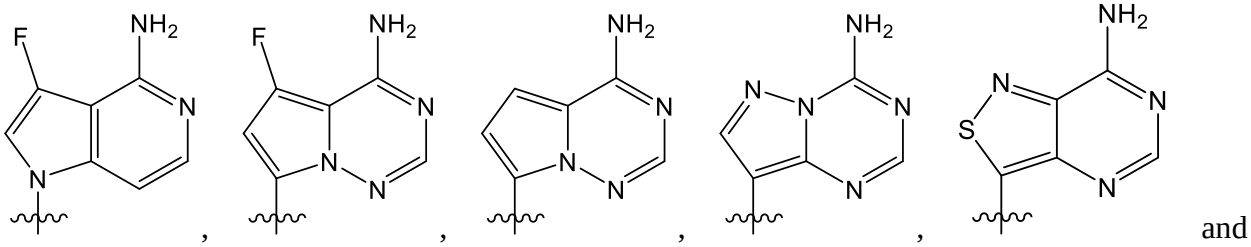
11. The compound of any one of Claims 1-10, wherein R^{4B} is a C_{1-4} alkyl substituted with OCH_3.

12. The compound of any one of Claims 1-10, wherein R^{4B} is an unsubstituted C_{2-4} alkenyl.

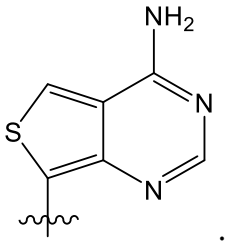
13. The compound of any one of Claims 1-10, wherein R^{4B} is an unsubstituted C_{2-4} alkynyl.

14. The compound of any one of Claims 1-13, wherein B^1 is selected from the group consisting of:





and



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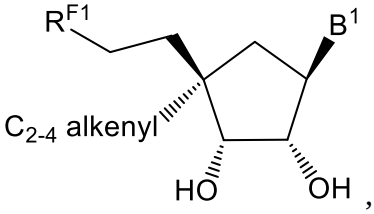
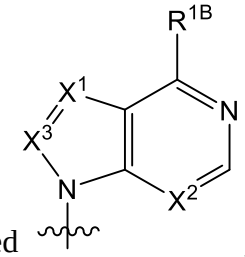
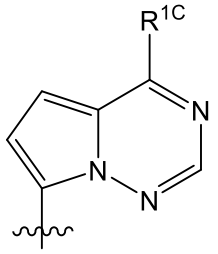
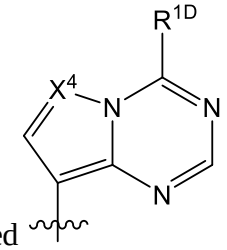
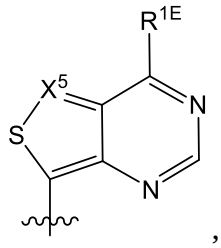
15. The compound of Claim 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

16. The compound of Claim 1, wherein:

B^1 is an optionally substituted  , an optionally substituted  , an optionally substituted  or an optionally substituted  ,

wherein X^1 is N or CR^{C1}; X^2 is N or CR^{C2}; X^3 is N or CR^{C3}; X^4 is N or CR^{C4}; X^5 is N or CR^{C5}; and R^{C1}, R^{C2}, R^{C3}, R^{C4} and R^{C5} are independently hydrogen, halogen or an unsubstituted C_{1-4} alkyl;

R^{1B}, R^{1C}, R^{1D} and R^{1E} are independently hydrogen, halogen, hydroxy, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_3-C_6 cycloalkyl, an unsubstituted C_{1-4} alkoxy or $NR^{A1}R^{A2}$; and

R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, hydroxy, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{1-4} alkoxy and $–C(=O)R^{C6}$, wherein R^{C6} is hydrogen, an unsubstituted C_{1-4} alkyl or an unsubstituted C_{3-4} monocyclic cycloalkyl;

R^1 is hydrogen;

R^{2A} is hydrogen;

R^{2B} is halogen, OH, $–O\text{-}C(=O)\text{-}C_{1-4}$ alkyl or $–O\text{-}C(=O)\text{-}CH(R^{1'})\text{-}NH_2$, wherein $R^{1'}$ is H, $\text{-}CH_3$, $\text{-}CH(CH_3)_2$, $\text{-}CH_2\text{-}CH(CH_3)_2$ or $\text{-}CH(CH_3)\text{-}CH(CH_3)_2$;

R^{3A} is hydrogen, an unsubstituted or a substituted C_{1-4} alkyl, an unsubstituted or a substituted C_{2-4} alkenyl or an unsubstituted or a substituted C_{2-4} alkynyl, wherein when the C_{1-4} alkyl, the C_{2-4} alkenyl and the C_{2-4} alkynyl are substituted, each is independently substituted with 1 or more fluoros;

R^{3B} is halogen, OH, $–O\text{-}C(=O)\text{-}C_{1-4}$ alkyl or $–O\text{-}C(=O)\text{-}CH(R^{1''})\text{-}NH_2$, wherein $R^{1''}$ is H, $\text{-}CH_3$, $\text{-}CH(CH_3)_2$, $\text{-}CH_2\text{-}CH(CH_3)_2$ or $\text{-}CH(CH_3)\text{-}CH(CH_3)_2$;

R^{4A} is $–(CR^{D1}R^{E1})(CR^{D2}R^{E2})n\text{-}R^{F1}$;

wherein R^{D1}, R^{E1}, R^{D2} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; n is 0 or 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

R^{D1} and R^{E1} are taken together with the carbon to which R^{D1} and R^{E1} are attached to form an unsubstituted cyclopropyl ring; and R^{D2} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; n is 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

R^{D1} and R^{E2} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; R^{E1} and R^{D2} are taken together with the carbon to which R^{E1} and R^{D2} are attached to form an unsubstituted cyclopropyl ring; n is 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; or

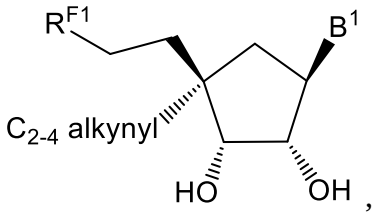
R^{D1} and R^{E2} are independently selected from the group consisting of hydrogen, halogen and hydroxy; R^{E1} and R^{D2} together form a double bond; n is 1; and R^{F1} is an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl;

R^{G1}, R^{H1}, R^{K1}, R^{L1}, R^{N1} and R^{O1} are independently selected from the group consisting of hydrogen, halogen, hydroxy and an unsubstituted C_{1-3} alkyl; R^{J1} and R^{M1} are independently an unsubstituted or a substituted aryl, an unsubstituted or a substituted heteroaryl or an unsubstituted or a substituted heterocyclyl; R^{P1} is an unsubstituted or a substituted heteroaryl; and p is 3 or 4;

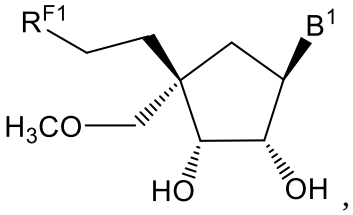
R^{4B} is a substituted C_{1-4} alkyl substituted with OCH_3, an unsubstituted C_{2-4} alkenyl or an unsubstituted C_{2-4} alkynyl,

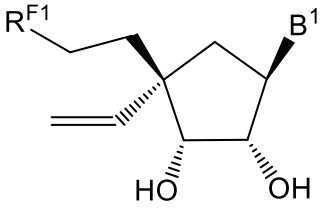
Z^1 is $CR^{5A}R^{5B}$; and

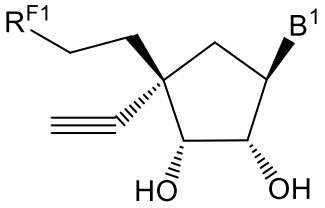
R^{5A} and R^{5B} are each hydrogen.

17. The compound of Claim 1, wherein the compound is 

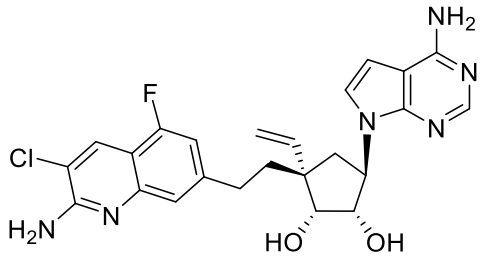
, or a pharmaceutically acceptable salt thereof.

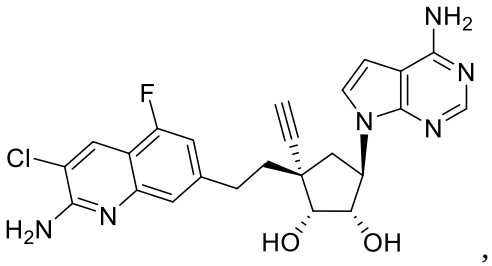
18. The compound of Claim 1, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

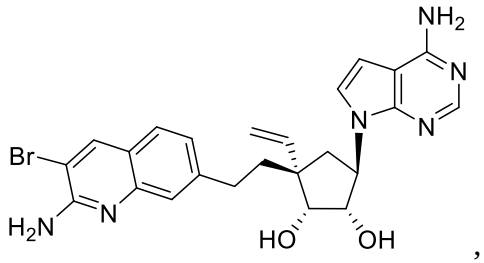
19. The compound of Claim 1, wherein the compound is  , or a pharmaceutically acceptable salt thereof

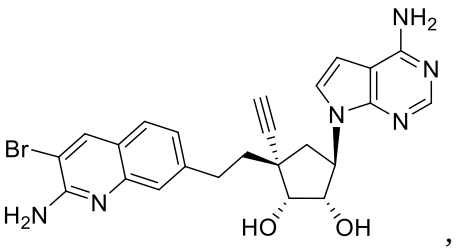
20. The compound of Claim 1, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

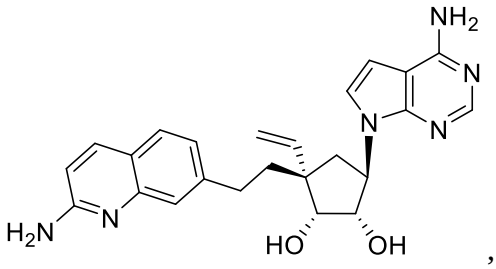
21. The compound of Claim 1, wherein the compound is selected from the group consisting of:

 ,

 ,

 ,

 ,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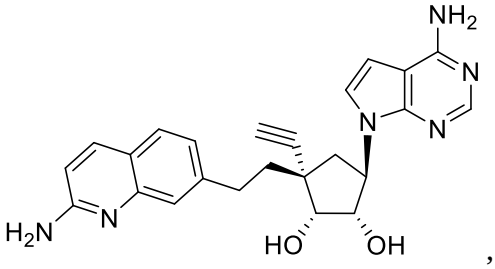
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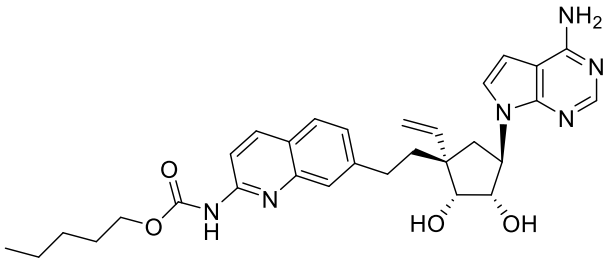
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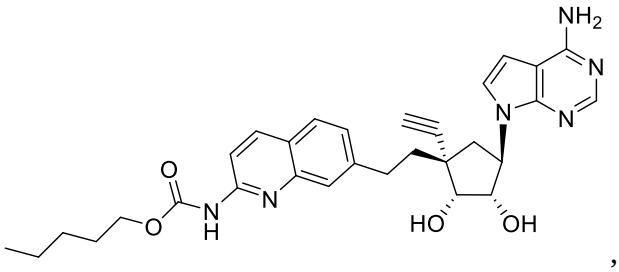
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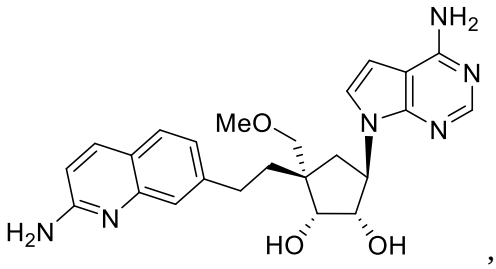
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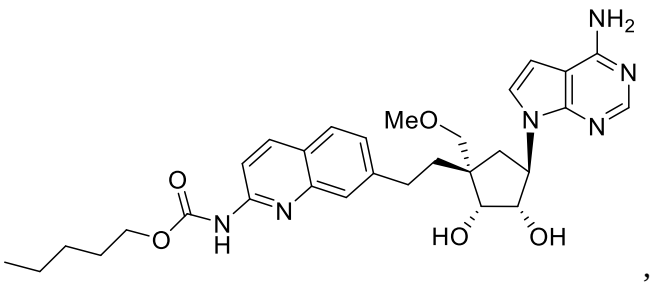
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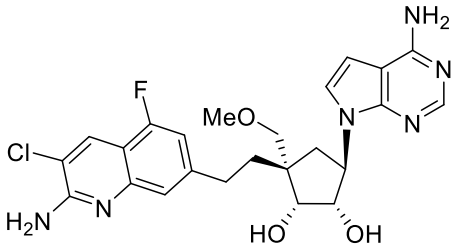
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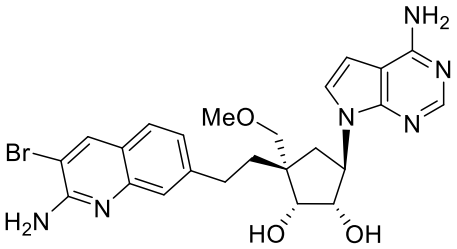
,or a pharmaceutically acceptable salt of any of the foregoing.

22. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-21, or a pharmaceutically acceptable salt thereof, and excipient.

23. A compound of any one of Claims 1-21, or a pharmaceutically acceptable salt thereof, for use in therapy.

24. Use of a compound of any one of Claims 1-21, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating a cancer.

25. Use of a compound of any one of Claims 1-21, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for modulating PRMT5.

26. Use of a compound of any one of Claims 1-21, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for inhibiting PRMT5.

27. The use of any one of Claims 24-26, wherein the use further comprises the use of an additional agent selected from the group consisting of a kinase inhibitor, a checkpoint inhibitor/modulator and an anti-VEGF antibody.