

The compounds of the present invention are structurally different and may have improved properties such as for example improved potency, or improved pharmacokinetics (PK) and oral bioavailability, compared with compounds disclosed in the prior art.

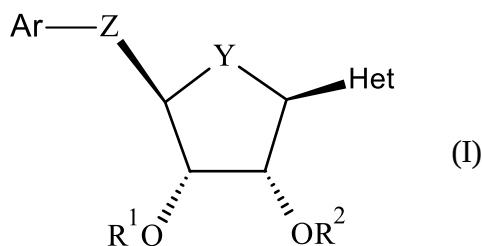
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Summary of the invention

It has been found that the compounds of the present ~~invention~~disclosure are useful as PRMT5 inhibitors. The compounds according to the ~~invention~~disclosure and compositions thereof, may be useful for the treatment or prevention, in particular for the treatment, of diseases such as a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, lung injuries, and the like.

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The present ~~invention~~disclosure concerns novel compounds of Formula (I):



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wherein

R¹ represents hydrogen or $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$;

R² represents hydrogen or $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$;

Y represents $-\text{O}-$, $-\text{CH}_2-$ or $-\text{CF}_2-$;

20 Z represents $-\text{CH}_2-$, $-\text{X}-\text{CR}^{5a}\text{R}^{5b}-$, $-\text{CR}^{5c}=\text{CR}^{5d}-$, $-\text{CR}^{5e}\text{R}^{5g}-\text{CR}^{5f}\text{R}^{5h}-$, or $-\text{C}\equiv\text{C}-$;

and when Y represents $-\text{CH}_2-$ or $-\text{CF}_2-$, then Z can also represent $-\text{O}-$ or $-\text{CR}^{5a}\text{R}^{5b}-\text{X}-$;

R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g}, and R^{5h} each independently represent hydrogen or C₁₋₄alkyl;

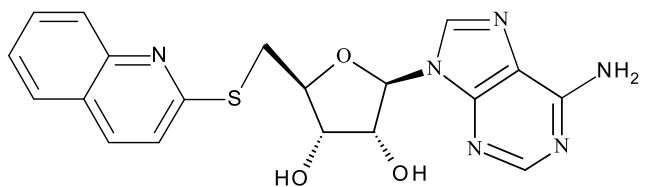
X represents $-\text{O}-$, $-\text{S}-$, or $-\text{NR}^{11}-$;

25 R¹¹ represents hydrogen, C₁₋₄alkyl, or C₁₋₄alkyl substituted with one substituent selected from the group consisting of $-\text{OH}$, $-\text{O}-\text{C}_{1-4}\text{alkyl}$, R¹², $-\text{NH}_2$, $-\text{NH}-\text{C}_{1-4}\text{alkyl}$, and $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$;

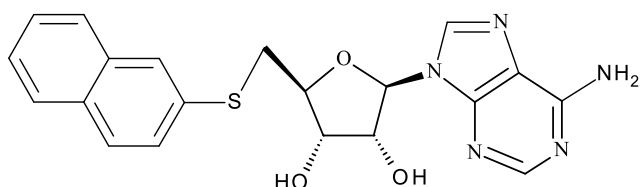
R¹² represents a 4-, 5-, 6- or 7-membered heterocyclic ring containing one nitrogen atom and optionally one oxygen atom; said 4-, 5-, 6- or 7-membered heterocyclic ring being attached to the remainder of the molecule via a ring nitrogen atom;

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and pharmaceutically acceptable addition salts, and solvates thereof;
provided that the following compounds, and pharmaceutically acceptable addition salts,
and solvates thereof are excluded:

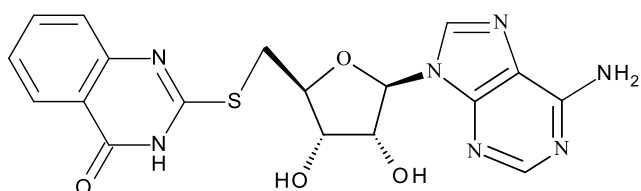


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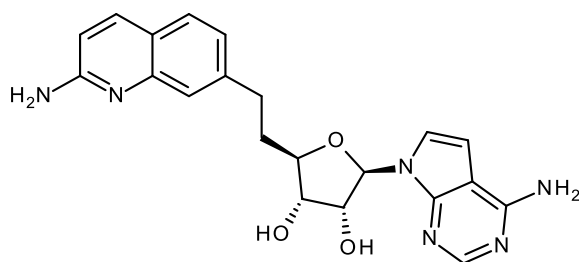
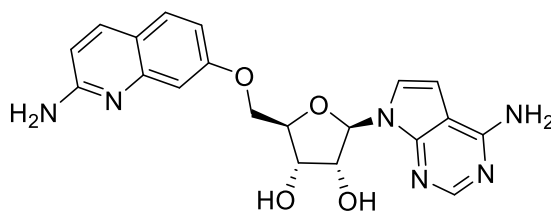
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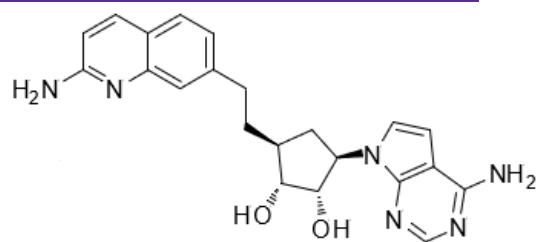
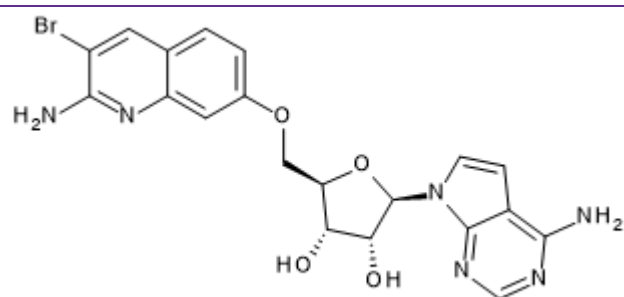
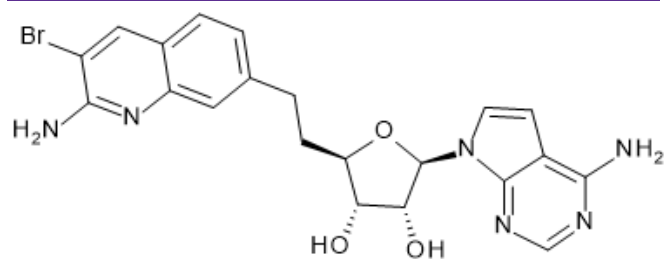
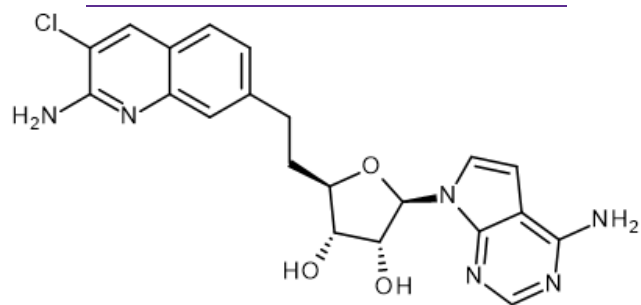
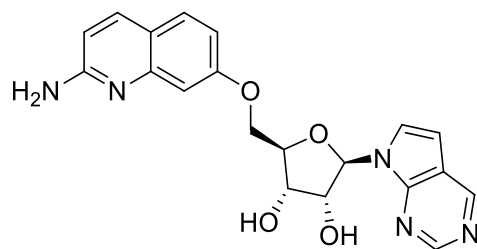
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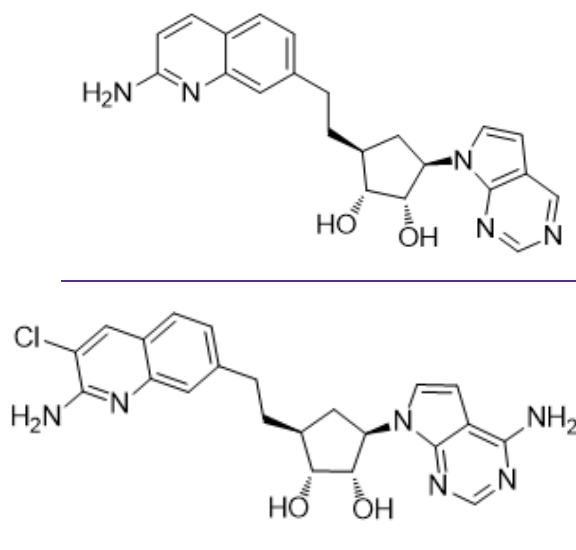
In one aspect, the present disclosure concerns a compound wherein the compound is
selected from the following compounds, or a pharmaceutically acceptable addition salt
or a solvate thereof:



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The present [inventiondisclosure](#) also concerns methods for the preparation of compounds of the present [inventiondisclosure](#) and pharmaceutical compositions comprising them.

[In another aspect, the present disclosure concerns a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as described herein.](#)

The compounds of the present [inventiondisclosure](#) were found to inhibit PRMT5 per se or can undergo metabolism to a (more) active form in vivo (prodrugs), and therefore may be useful in the treatment or prevention, in particular in the treatment, of diseases such as a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, lung injuries, and the like.

In view of the aforementioned pharmacology of the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, it follows that they may be suitable for use as a medicament.

[In another aspect, the present disclosure concerns a compound as described herein or a pharmaceutical composition as described herein for use as a medicament.](#)

In particular the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, may be suitable in the treatment or prevention, in particular in the treatment, of any one of the diseases or conditions mentioned hereinbefore or hereinafter, in particular cancer.

The present [inventiondisclosure](#) also concerns the use of compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, for the manufacture of

a medicament for the inhibition of PRMT5, for the treatment or prevention of any one of the diseases or conditions mentioned hereinbefore or hereinafter, in particular cancer.

In another aspect, the present disclosure concerns use of a compound as described herein or use of a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment or prevention of a disease or condition selected from a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, transplantation rejection, and graft rejection.

The present ~~invention~~disclosure will now be further described. In the following passages, different aspects of the ~~invention~~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 (e.g. Formula (I)), 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.

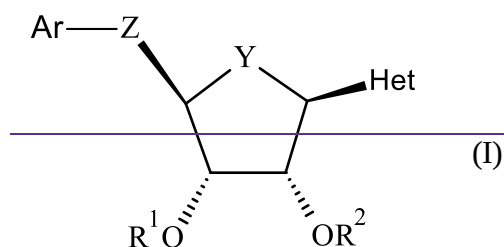
The prefix “C_{x-y}” (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C₁₋₄alkyl group contains from 1 to 4 carbon atoms, a C₁₋₃alkyl group contains from 1 to 3 carbon atoms and so on.

5 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.

The term “C₁₋₄alkyl” as a group or part of a group refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number ranging from 1 to 4. C₁₋₄alkyl groups comprise from 1 to 4 carbon atoms, preferably from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. C₁₋₄alkyl groups may be linear or branched and may be substituted as
10 indicated herein. When a subscript is used herein following a carbon atom, the

Claims

1. — A compound of Formula (I)



wherein

R¹ represents hydrogen or —C(=O)—C₁₋₄alkyl;

R² represents hydrogen or —C(=O)—C₁₋₄alkyl;

Y represents —O—, —CH₂— or —CF₂—;

Z represents —CH₂—, —X—CR^{5a}R^{5b}—, —CR^{5c}=CR^{5d}—, —CR^{5e}R^{5g}—CR^{5f}R^{5h}—, or —C=C—;

and when Y represents —CH₂— or —CF₂—, then Z can also represent —O— or —CR^{5a}R^{5b}—X—;

R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g}, and R^{5h} each independently represent hydrogen or C₁₋₄alkyl;

X represents —O—, —S—, or —NR¹¹—;

R¹¹ represents hydrogen, C₁₋₄alkyl, or C₁₋₄alkyl substituted with one substituent selected from the group consisting of —OH, —O—C₁₋₄alkyl, R¹², —NH₂, —NH—C₁₋₄alkyl, and —N(C₁₋₄alkyl)₂;

R¹² represents a 4-, 5-, 6- or 7-membered heterocyclic ring containing one nitrogen atom and optionally one oxygen atom; said 4-, 5-, 6- or 7-membered heterocyclic ring being attached to the remainder of the molecule via a ring nitrogen atom;

Ar represents a 10-membered bicyclic aromatic ring system consisting of two fused 6-membered rings, wherein optionally 1 or 2 ring carbon atoms are replaced by a nitrogen atom; provided that when the nitrogen atom replaces one of the two fused carbon atoms, a carbonyl group is present in said bicyclic aromatic ring system;

Ar is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo, —OH, —NH₂, —NH—C₁₋₄alkyl, —N(C₁₋₄alkyl)₂, —NHR^{10d}, —NR^{10e}R^{10d}, cyano, —CF₃, —C(=O)—NH₂, —C(=O)—NH—C₁₋₄alkyl, —C(=O)—C₁₋₄alkyl, C₁₋₄alkyloxy, —C(=O)—O—C₁₋₄alkyl, C₃₋₆cycloalkyl, —O—C₃₋₆cycloalkyl, —NH—C₃₋₆cycloalkyl, —N(C₃₋₆cycloalkyl)₂, C₂₋₆alkenyl, C₁₋₄alkyl substituted with one C₁₋₄alkyloxy, and C₁₋₄alkyl optionally substituted with one —NR^{10a}R^{10b};

R^{10a} and R^{10b} each independently represent hydrogen or C₁₋₄alkyl;

R^{10c} and R^{10d} each independently represent C₃₋₆cycloalkyl; R¹³; R¹⁴; C₃₋₆cycloalkyl substituted with one, two or three substituents each independently selected from the group

consisting of halo, OH and O-C₁₋₄alkyl; C₁₋₄alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, OH and O-C₁₋₄alkyl; or C₁₋₄alkyl substituted with one substituent selected from the group consisting of C₃₋₆cycloalkyl, R¹³ and R¹⁴;

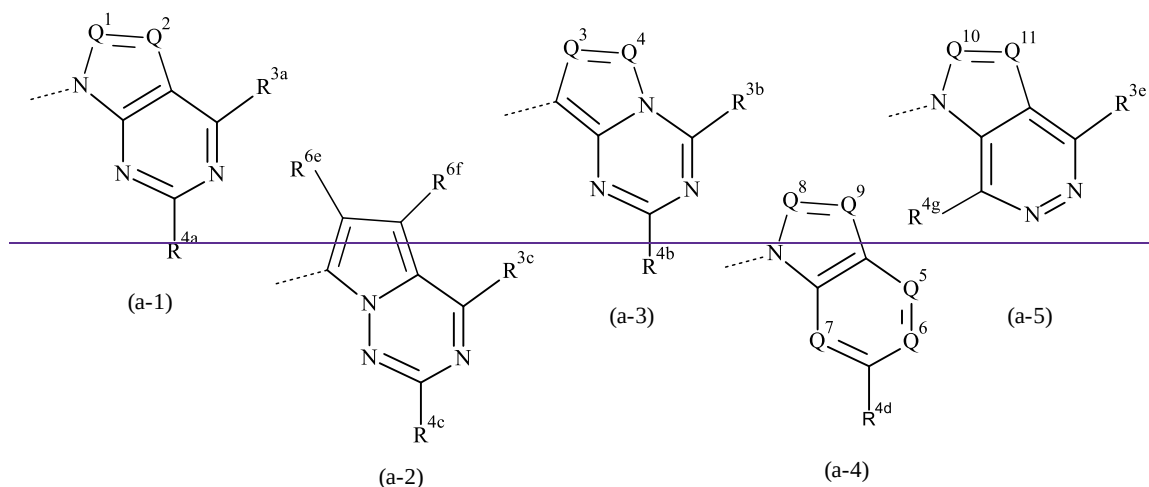
R¹³ represents a 4- to 7-membered monocyclic aromatic ring containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N; or a 6- to 11-membered bicyclic fused aromatic ring containing one, two or three heteroatoms each independently selected from O, S, S(=O)_p and N;

said 4- to 7-membered monocyclic aromatic ring or 6- to 11-membered bicyclic fused aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C₁₋₄alkyl;

p represents 1 or 2;

R¹⁴ represents phenyl optionally substituted with one, two or three substituents each independently selected from the group consisting of halo;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2), (a-3), (a-4) and (a-5):



R^{3a}, R^{3b}, R^{3c}, R^{3d} and R^{3e} each independently represent hydrogen, halo, NR^{7a}R^{7b}, C₁₋₄alkyl, C₂₋₄alkenyl, C₃₋₆cycloalkyl, OH, or O-C₁₋₄alkyl;

R^{7a} represents hydrogen;

R^{7b} represents hydrogen, C₃₋₆cycloalkyl, or C₁₋₄alkyl;

R^{4a}, R^{4b}, R^{4c}, R^{4d}, R^{4e}, R^{4f} and R^{4g} each independently represent hydrogen, halo, NR^{8a}R^{8b}, or C₁₋₄alkyl;

R^{8a} and R^{8b} each independently represent hydrogen or C₁₋₄alkyl;

Q¹ represents N or CR^{6a};

~~Q² represents N or CR^{6b};~~

~~Q³ represents N or CR^{6c};~~

~~Q⁴ represents N or CR^{6d};~~

~~provided that maximum one of Q³ and Q⁴ represents N;~~

~~Q⁸ represents N or CR^{6g};~~

~~Q⁹ represents N or CR^{6h};~~

~~Q¹⁰ represents N or CR⁶ⁱ;~~

~~Q¹¹ represents N or CR^{6j};~~

~~Q⁵ represents CR^{3d}; Q⁶ represents N; and Q⁷ represents CR^{4f}; or~~

~~Q⁵ represents CR^{3d}; Q⁶ represents CR^{4e}; and Q⁷ represents N; or~~

~~Q⁵ represents N; Q⁶ represents CR^{4e}; and Q⁷ represents CR^{4f}; or~~

~~Q⁵ represents N; Q⁶ represents CR^{4e}; and Q⁷ represents N; or~~

~~Q⁵ represents N; Q⁶ represents N; and Q⁷ represents CR^{4f}; or~~

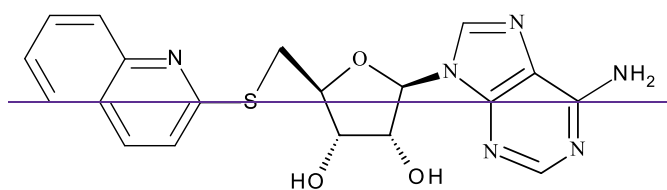
~~Q⁵ represents N; Q⁶ represents N; and Q⁷ represents N;~~

~~R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e}, R^{6f}, R^{6g}, R^{6h}, R⁶ⁱ and R^{6j} each independently represent hydrogen, halogen, C₁₋₄alkyl, NR^{9a}R^{9b}, or C₁₋₄alkyl substituted with one, two or three halo atoms;~~

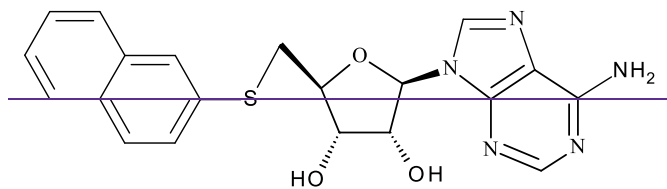
~~R^{9a} and R^{9b} each independently represent hydrogen or C₁₋₄alkyl;~~

~~or a pharmaceutically acceptable addition salt or a solvate thereof;~~

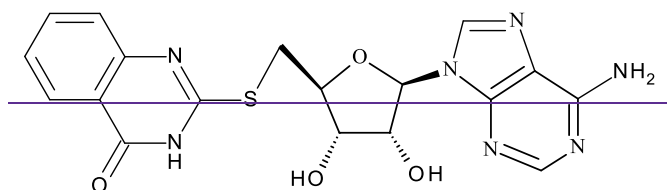
~~provided that the following compounds, and pharmaceutically acceptable addition salts, and solvates thereof are excluded:~~



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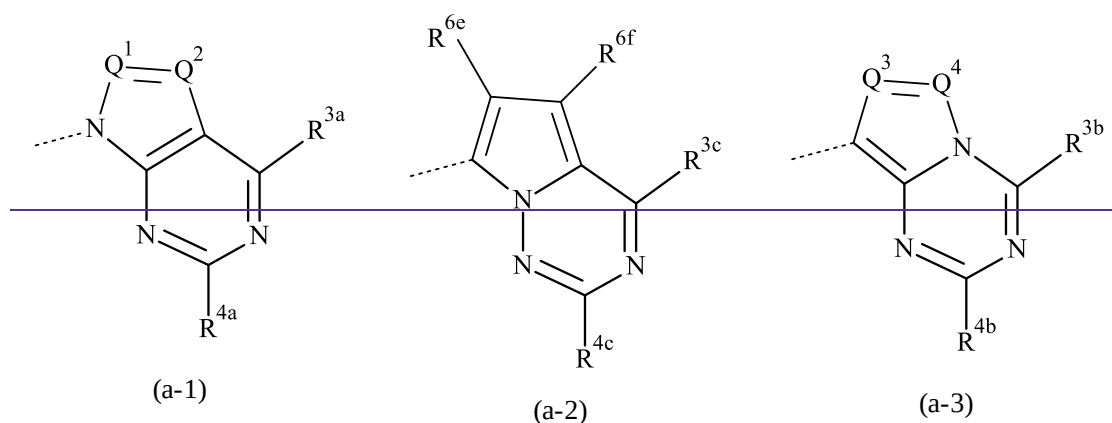
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2.—The compound according to claim 1, wherein

Ar represents a 10-membered bicyclic aromatic ring system consisting of two fused 6-membered rings, wherein optionally 1 or 2 ring carbon atoms are replaced by a nitrogen atom; provided that when the nitrogen atom replaces one of the two fused carbon atoms, a carbonyl group is present in said bicyclic aromatic ring system;

Ar is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo, —OH, —NH₂, —NH—C₁₋₄alkyl, —N(C₁₋₄alkyl)₂, cyano, —CF₃, —C(=O)—NH—C₁₋₄alkyl, —C(=O)—C₁₋₄alkyl, C₁₋₄alkyloxy, and C₁₋₄alkyl optionally substituted with one —NR^{10a}R^{10b};

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1), (a-2) and (a-3):



R^{3a}, R^{3b} and R^{3c} each independently represent hydrogen, halo, —NR^{7a}R^{7b}, or —O—C₁₋₄alkyl;

R^{7b} represents hydrogen or C₁₋₄alkyl;

R^{4a}, R^{4b} and R^{4c} each independently represent hydrogen, halo, —NR^{8a}R^{8b}, or C₁₋₄alkyl;

Q¹ represents N or CR^{6a};

Q² represents N or CR^{6b};

Q³ represents N or CR^{6c};

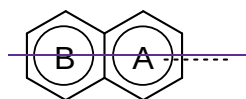
Q⁴ represents N or CR^{6d};

provided that maximum one of Q³ and Q⁴ represents N;

R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e} and R^{6f} each independently represent hydrogen, halogen, C₁₋₄alkyl, —NR^{9a}R^{9b}, or C₁₋₄alkyl substituted with one, two or three halo atoms.

3.—The compound according to claim 1, wherein

Ar represents a 10-membered bicyclic aromatic ring system consisting of two fused 6-membered rings;



wherein at least 1 ring carbon atom of ring B is replaced by a nitrogen atom;

wherein optionally 1 additional ring carbon atom of ring A or ring B is replaced by a nitrogen atom; provided that when a nitrogen atom replaces one of the two fused carbon atoms, a carbonyl group is present in said bicyclic aromatic ring system;

Ar is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo, OH , NH_2 , $\text{NH-C}_{1-4}\text{alkyl}$, $\text{N}(\text{C}_{1-4}\text{alkyl})_2$, NHR^{10d} , $\text{NR}^{10e}\text{R}^{10d}$, cyano, CF_3 , C(=O)-NH_2 , $\text{C(=O)-NH-C}_{1-4}\text{alkyl}$, $\text{C(=O)-C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkyloxy}$, $\text{C(=O)-O-C}_{1-4}\text{alkyl}$, $\text{C}_{3-6}\text{cycloalkyl}$, $\text{O-C}_{3-6}\text{cycloalkyl}$, $\text{NH-C}_{3-6}\text{cycloalkyl}$, $\text{N}(\text{C}_{3-6}\text{cycloalkyl})_2$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{1-4}\text{alkyl}$ substituted with one $\text{C}_{1-4}\text{alkyloxy}$, and $\text{C}_{1-4}\text{alkyl}$ optionally substituted with one $\text{NR}^{10a}\text{R}^{10b}$.

4.——The compound according to claim 1, wherein

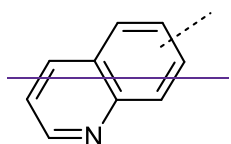
R^1 represents hydrogen or $\text{C(=O)-C}_{1-4}\text{alkyl}$;

R^2 represents hydrogen or $\text{C(=O)-C}_{1-4}\text{alkyl}$;

Y represents O ; Z represents $\text{X-CR}^{5a}\text{R}^{5b}$;

R^{5a} and R^{5b} each independently represent hydrogen or $\text{C}_{1-4}\text{alkyl}$;

X represents O , S , or NR^{11} ; R^{11} represents hydrogen;



Ar represents- ;

Ar is optionally substituted with one or two substituents each independently selected from the group consisting of halo, OH , NH_2 , $\text{NH-C}_{1-4}\text{alkyl}$, $\text{N}(\text{C}_{1-4}\text{alkyl})_2$, cyano, CF_3 , $\text{C(=O)-NH-C}_{1-4}\text{alkyl}$, $\text{C(=O)-C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkyloxy}$, and $\text{C}_{1-4}\text{alkyl}$ optionally substituted with one $\text{NR}^{10a}\text{R}^{10b}$;

R^{10a} and R^{10b} each independently represent hydrogen or $\text{C}_{1-4}\text{alkyl}$;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1);

R^{3a} represents hydrogen, halo, $\text{NR}^{7a}\text{R}^{7b}$, or $\text{O-C}_{1-4}\text{alkyl}$;

R^{7a} represents hydrogen;

R^{7b} represents hydrogen;

R^{4a} represents hydrogen, halo, $\text{NR}^{8a}\text{R}^{8b}$, or $\text{C}_{1-4}\text{alkyl}$;

R^{8a} and R^{8b} each independently represent hydrogen or C_{1-4} alkyl;

Q^1 represents CR^{6a} ;

Q^2 represents CR^{6b} ;

R^{6a} and R^{6b} each independently represent hydrogen, halogen, C_{1-4} alkyl, $NR^{9a}R^{9b}$, or C_{1-4} alkyl substituted with one, two or three halo atoms;

R^{9a} and R^{9b} each independently represent hydrogen or C_{1-4} alkyl.

5. — The compound according to claim 1, wherein

R^1 represents hydrogen;

R^2 represents hydrogen;

Y represents O or CH_2 ;

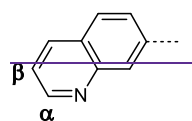
Z represents $X-CR^{5a}R^{5b}$ or $CR^{5c}R^{5g}-CR^{5f}R^{5h}$;

and when Y represents CH_2 , then Z can also represent $CR^{5a}R^{5b}-X$;

R^{5a} , R^{5b} , R^{5c} , R^{5f} , R^{5g} , and R^{5h} represent hydrogen;

X represents O ;

Ar represents



wherein Ar is optionally substituted in the position indicated by α with a substituent selected from the group consisting of NH_2 , $NH-C_{1-4}$ alkyl, and NHR^{10d} ; and

wherein Ar is optionally substituted in the position indicated by β with a substituent selected from the group consisting of halo and CF_3 ;

provided however that Ar is substituted in at least one of the positions indicated by α or β ;

R^{10d} represents C_{3-6} cycloalkyl; C_{1-4} alkyl substituted with one, two or three halo substituents;

or C_{1-4} alkyl substituted with one C_{3-6} cycloalkyl substituent;

Het represents a bicyclic aromatic heterocyclic ring system selected from the group consisting of (a-1) and (a-4);

R^{3a} and R^{3d} each independently represent hydrogen, halo, $NR^{7a}R^{7b}$, C_{1-4} alkyl, or $O-C_{1-4}$ alkyl;

R^{7a} represents hydrogen;

R^{7b} represents hydrogen or C_{1-4} alkyl;

R^{4a} , R^{4d} and R^{4f} each independently represent hydrogen or halo;

Q^1 represents CR^{6a} ;

Q^2 represents CR^{6b} ;

Q^8 represents CR^{6g} ;

Q^9 represents CR^{6h} ;

Q^5 represents CR^{3d} ; Q^6 represents N; and Q^7 represents CR^{4f} ;

R^{6a} , R^{6b} , R^{6g} , and R^{6h} represent hydrogen;

6.—The compound according to any one of claims 1 to 4, wherein R^1 and R^2 represent hydrogen.

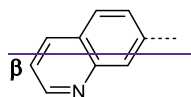
7.—The compound according to any one of claims 1 to 3 and claims 5 to 6, wherein Y represents —O—.

8.—The compound according any one of claims 1 to 3 and claims 5 to 7, wherein Het represents a bicyclic aromatic heterocyclic ring system of Formula (a-1).

9.—The compound according to claim 8, wherein

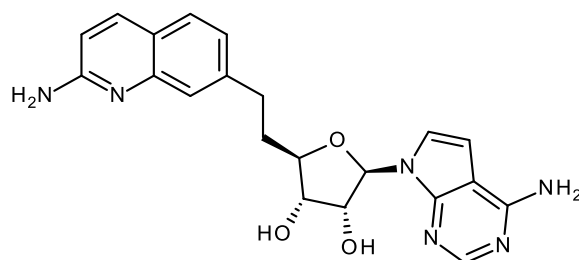
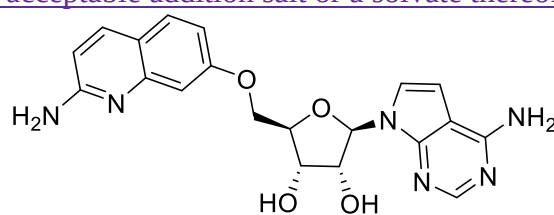
R^{3a} represents $NR^{7a}R^{7b}$; and R^{7a} and R^{7b} represent hydrogen.

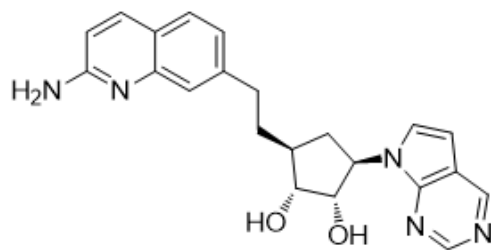
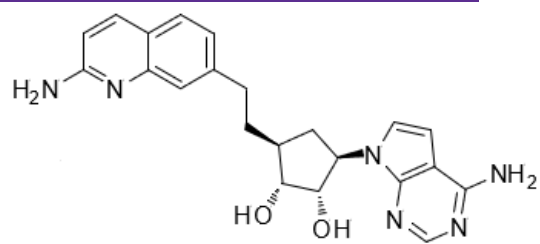
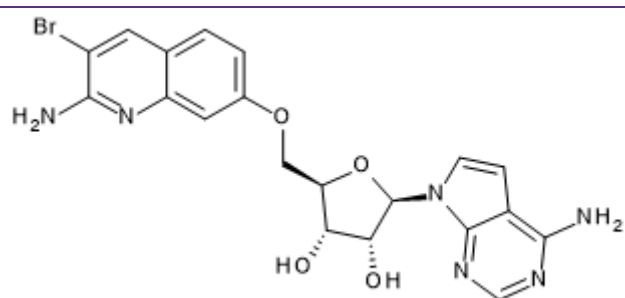
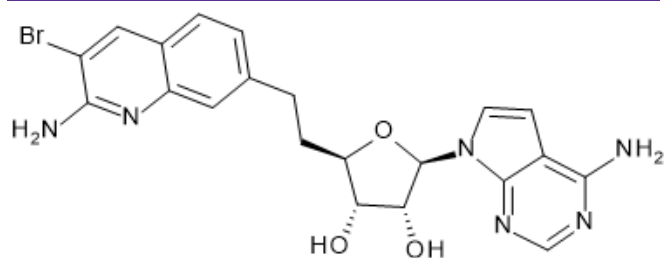
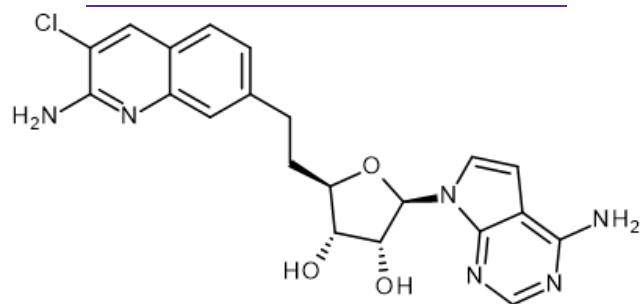
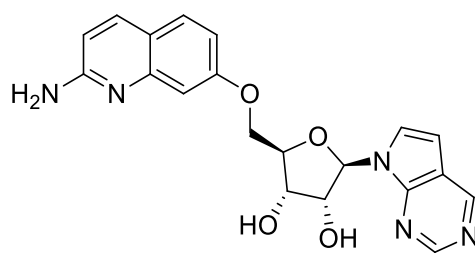
10.—The compound according to any one of claims 1 to 9, wherein Ar represents

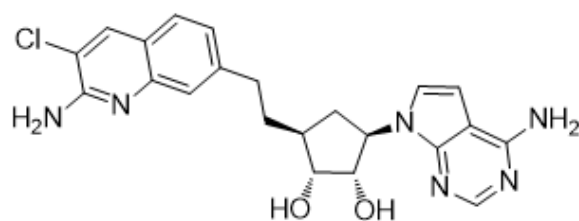


wherein Ar is substituted in the position indicated by β with a halo substituent.

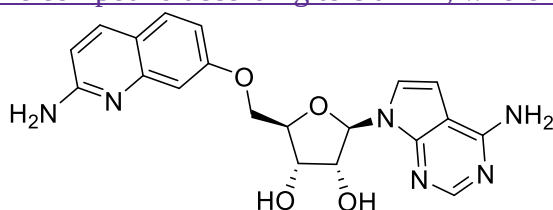
1. A compound wherein the compound is selected from the following compounds, or a pharmaceutically acceptable addition salt or a solvate thereof:





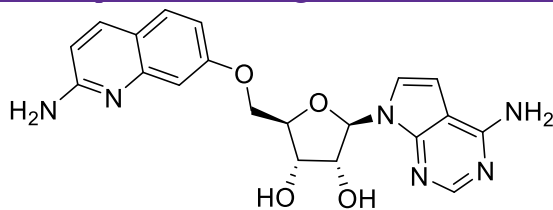


2. The compound according to claim 1, wherein the compound is

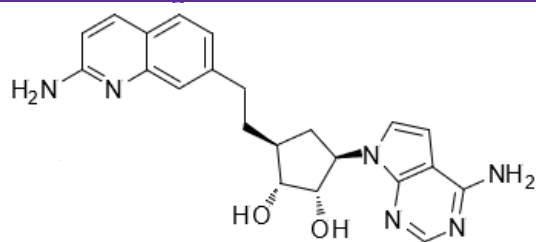


or a pharmaceutically acceptable addition salt or a solvate thereof.

3. The compound according to claim 2, wherein the compound is

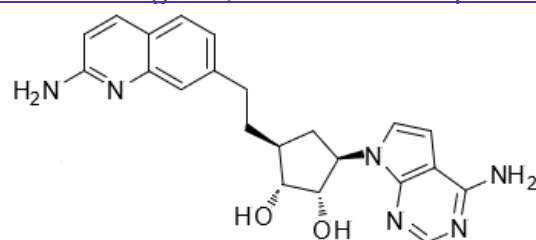


4. The compound according to claim 1, wherein the compound is

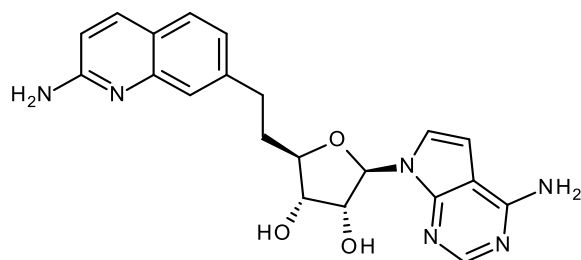


or a pharmaceutically acceptable addition salt or a solvate thereof.

5. The compound according to 4, wherein the compound is

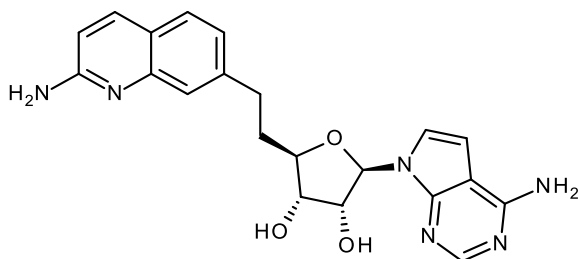


6. The compound according to claim 1, wherein the compound is

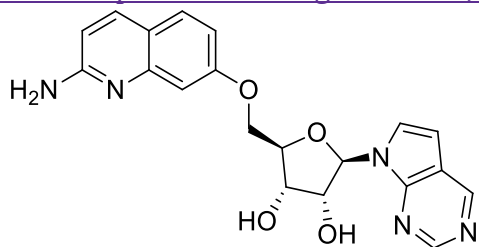


or a pharmaceutically acceptable addition salt or a solvate thereof.

7. The compound according to claim 6, wherein the compound is

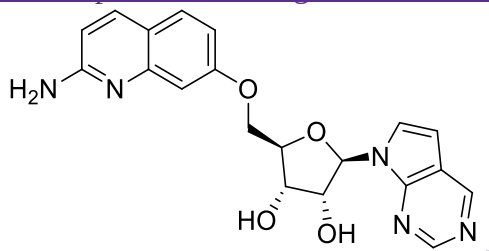


8. The compound according to claim 1, wherein the compound is

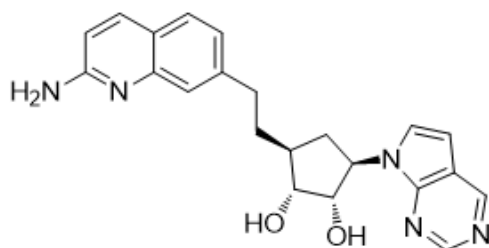


or a pharmaceutically acceptable addition salt or a solvate thereof.

9. The compound according to claim 8, wherein the compound is

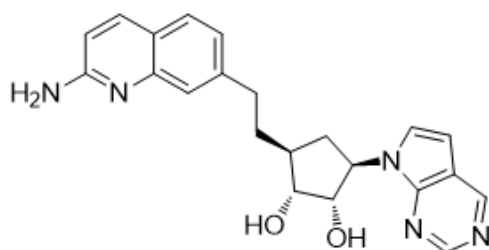


10. The compound according to claim 1, wherein the compound is

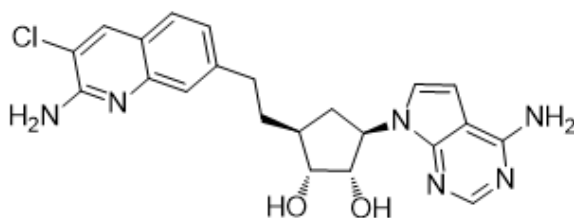


or a pharmaceutically acceptable addition salt or a solvate thereof.

11. The compound according to claim 10, wherein the compound is

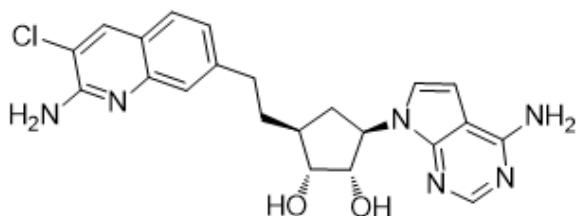


12. The compound according to claim 1, wherein the compound is

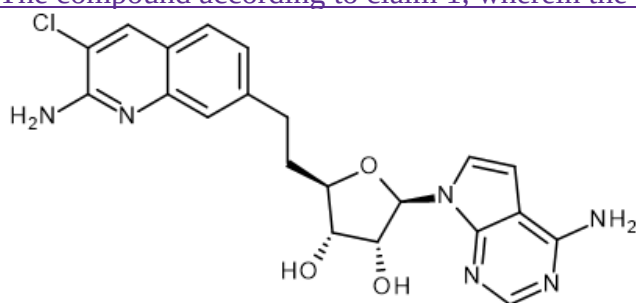


or a pharmaceutically acceptable addition salt or a solvate thereof.

13. The compound according to claim 12, wherein the compound is

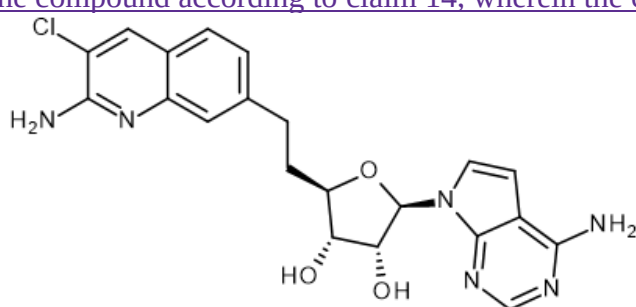


14. The compound according to claim 1, wherein the compound is

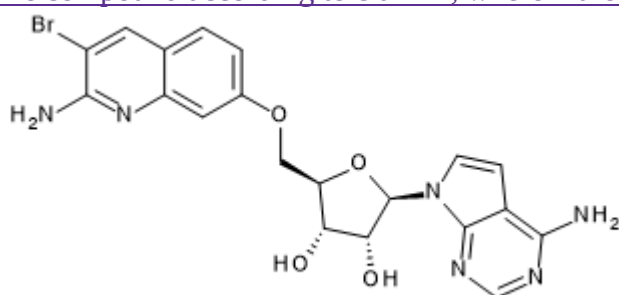


or a pharmaceutically acceptable addition salt or a solvate thereof.

15. The compound according to claim 14, wherein the compound is

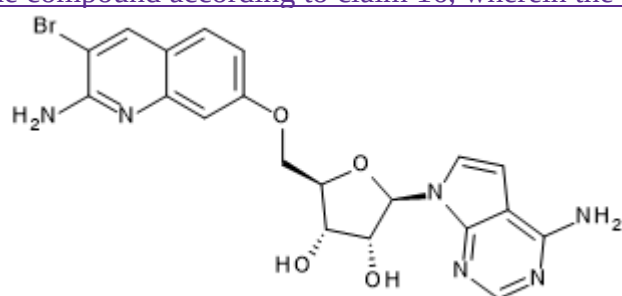


16. The compound according to claim 1, wherein the compound is

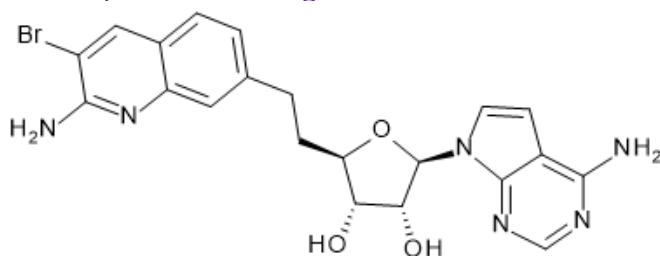


or a pharmaceutically acceptable addition salt or a solvate thereof.

17. The compound according to claim 16, wherein the compound is

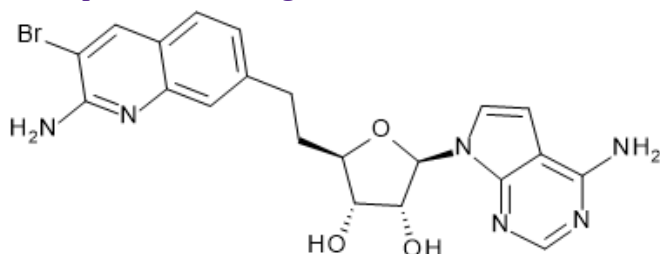


18. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable addition salt or a solvate thereof.

19. The compound according to claim 18, wherein the compound is



1420. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to any one of claims 1 to ~~40~~19.

1421. A compound as defined in any one of claims 1 to ~~40~~19 or a pharmaceutical composition as defined in claim 20 for use as a medicament.

22. Use of a compound as defined in any one of claims 1 to 19 or use of a pharmaceutical composition as defined in claim 20 in the manufacture of a medicament for the treatment or prevention of a disease or condition selected from a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, transplantation rejection, and graft rejection.

~~13. A compound as defined in any one of claims 1 to 10 for use in the treatment or prevention of a disease or condition selected from a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases,~~

neurodegenerative diseases, pancreatitis, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.

14. The compound according to claim 13 wherein the disease or condition is an autoimmune disorder, cancer, inflammatory disease, or a neurodegenerative disease.

15. The compound according to claim 14 wherein the disease or condition is cancer.