

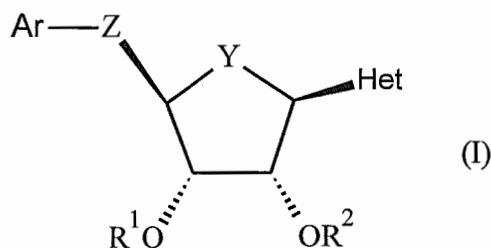
The compounds of the present invention are structurally different and may have improved properties such as for example improved potency, or improved pharmacokinetics (PK) and oral bioavailability, compared with compounds disclosed in the prior art.

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### Summary

It has been found that the compounds of the present disclosure are useful as PRMT5 inhibitors. The compounds according to the disclosure and compositions thereof, may be useful for the treatment or prevention, in particular for the treatment, of diseases  
 10 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.

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



15

wherein

R<sup>1</sup> represents hydrogen or -C(=O)-C<sub>1-4</sub>alkyl;

R<sup>2</sup> represents hydrogen or -C(=O)-C<sub>1-4</sub>alkyl;

Y represents -O-, -CH<sub>2</sub>- or -CF<sub>2</sub>-;

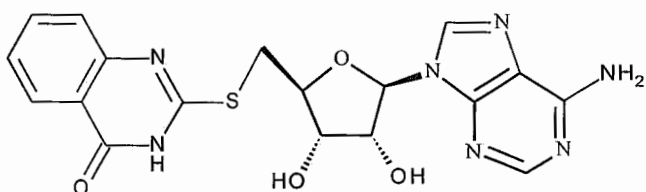
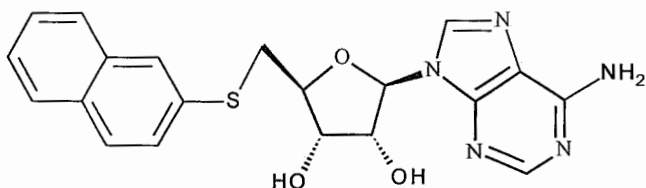
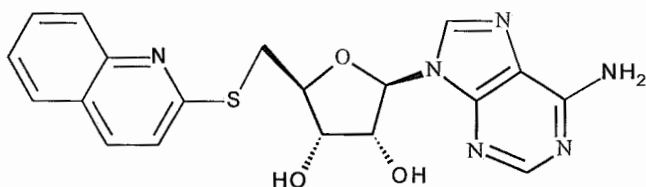
20 Z represents -CH<sub>2</sub>-, -X-CR<sup>5a</sup>R<sup>5b</sup>-, -CR<sup>5c</sup>=CR<sup>5d</sup>-, -CR<sup>5e</sup>R<sup>5g</sup>-CR<sup>5f</sup>R<sup>5h</sup>-, or -C≡C-;  
 and when Y represents -CH<sub>2</sub>- or -CF<sub>2</sub>-, then Z can also represent -O- or -CR<sup>5a</sup>R<sup>5b</sup>-X-;  
 R<sup>5a</sup>, R<sup>5b</sup>, R<sup>5c</sup>, R<sup>5d</sup>, R<sup>5e</sup>, R<sup>5f</sup>, R<sup>5g</sup>, and R<sup>5h</sup> each independently represent hydrogen or C<sub>1-4</sub>alkyl;

X represents -O-, -S-, or -NR<sup>11</sup>-;

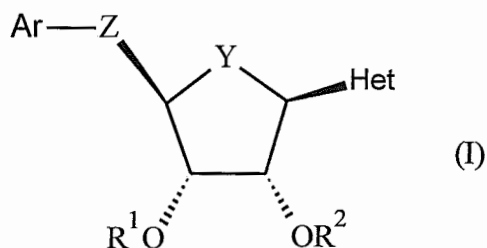
25 R<sup>11</sup> represents hydrogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of -OH, -O-C<sub>1-4</sub>alkyl, R<sup>12</sup>, -NH<sub>2</sub>, -NH-C<sub>1-4</sub>alkyl, and -N(C<sub>1-4</sub>alkyl)<sub>2</sub>;

R<sup>12</sup> 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  
 30 being attached to the remainder of the molecule via a ring nitrogen atom;

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



In one aspect, there is provided a compound of Formula (I)



wherein

10  $R^1$  represents hydrogen or  $-C(=O)-C_{1-4}$ alkyl;

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

Y represents  $-O-$ ,  $-CH_2-$  or  $-CF_2-$ ;

Z represents  $-CH_2-$ ,  $-X-CR^{5a}R^{5b}-$ ,  $-CR^{5c}=CR^{5d}-$ ,  $-CR^{5e}R^{5g}-CR^{5f}R^{5h}-$ , or  $-C\equiv C-$ ;

and when Y represents  $-CH_2-$  or  $-CF_2-$ , then Z can also represent  $-O-$  or  $-CR^{5a}R^{5b}-X-$ ;

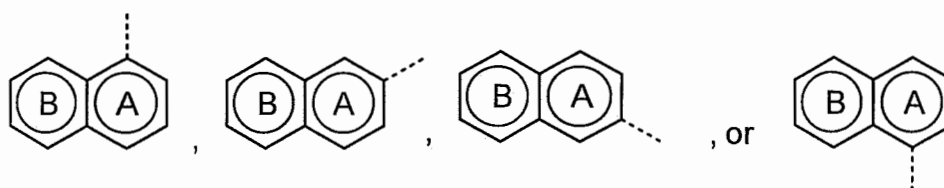
15  $R^{5a}$ ,  $R^{5b}$ ,  $R^{5c}$ ,  $R^{5d}$ ,  $R^{5e}$ ,  $R^{5f}$ ,  $R^{5g}$ , and  $R^{5h}$  each independently represent hydrogen or  $C_{1-4}$ alkyl;

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

$R^{11}$  represents hydrogen,  $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of -OH, -O- $C_{1-4}$ alkyl,  $R^{12}$ , -NH<sub>2</sub>, -NH- $C_{1-4}$ alkyl, and -N( $C_{1-4}$ alkyl)<sub>2</sub>;

5  $R^{12}$  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,



10 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 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;

15 Ar is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo, -OH, -NH<sub>2</sub>, -NH- $C_{1-4}$ alkyl, -N( $C_{1-4}$ alkyl)<sub>2</sub>, -NHR<sup>10d</sup>, -NR<sup>10c</sup>R<sup>10d</sup>, cyano, -CF<sub>3</sub>, -C(=O)-NH<sub>2</sub>, -C(=O)-NH- $C_{1-4}$ alkyl, -C(=O)- $C_{1-4}$ alkyl,  $C_{1-4}$ alkyloxy, -C(=O)-O- $C_{1-4}$ alkyl,  $C_{3-6}$ cycloalkyl, -O- $C_{3-6}$ cycloalkyl, -NH- $C_{3-6}$ cycloalkyl, -N( $C_{3-6}$ cycloalkyl)<sub>2</sub>,  $C_{2-6}$ alkenyl,  $C_{1-4}$ alkyl substituted with one  $C_{1-4}$ alkyloxy, and  $C_{1-4}$ alkyl optionally substituted with one -NR<sup>10a</sup>R<sup>10b</sup>;

20  $R^{10a}$  and  $R^{10b}$  each independently represent hydrogen or  $C_{1-4}$ alkyl;

$R^{10c}$  and  $R^{10d}$  each independently represent  $C_{3-6}$ cycloalkyl;  $R^{13}$ ;  $R^{14}$ ;  $C_{3-6}$ cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O- $C_{1-4}$ alkyl;  $C_{1-4}$ alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O- $C_{1-4}$ alkyl; or  $C_{1-4}$ alkyl substituted with one substituent selected from the group consisting of  $C_{3-6}$ cycloalkyl,  $R^{13}$  and  $R^{14}$ ;

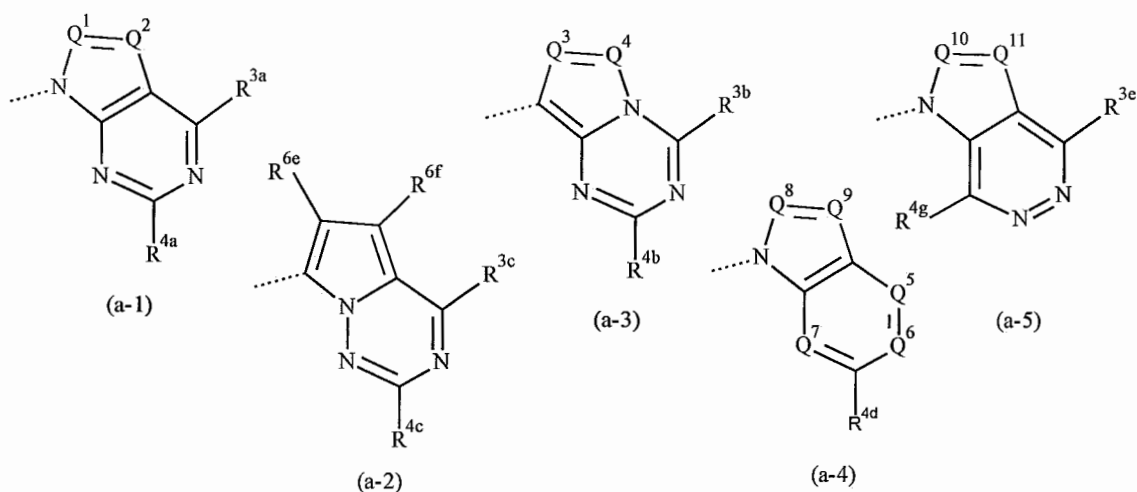
25  $R^{13}$  represents a 4- to 7-membered monocyclic aromatic ring containing one, two or three heteroatoms each independently selected from O, S, S(=O)<sub>p</sub> and N; or a 6- to 11-membered bicyclic fused aromatic ring containing one, two or three heteroatoms each  
30 independently selected from O, S, S(=O)<sub>p</sub> 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 C<sub>1-4</sub>alkyl;

p represents 1 or 2;

- 5 R<sup>14</sup> 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):



10

R<sup>3a</sup>, R<sup>3b</sup>, R<sup>3c</sup>, R<sup>3d</sup> and R<sup>3e</sup> each independently represent hydrogen, halo, -NR<sup>7a</sup>R<sup>7b</sup>, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>3-6</sub>cycloalkyl, -OH, or -O-C<sub>1-4</sub>alkyl;

R<sup>7a</sup> represents hydrogen;

R<sup>7b</sup> represents hydrogen, C<sub>3-6</sub>cycloalkyl, or C<sub>1-4</sub>alkyl;

- 15 R<sup>4a</sup>, R<sup>4b</sup>, R<sup>4c</sup>, R<sup>4d</sup>, R<sup>4e</sup>, R<sup>4f</sup> and R<sup>4g</sup> each independently represent hydrogen, halo, -NR<sup>8a</sup>R<sup>8b</sup>, or C<sub>1-4</sub>alkyl;

R<sup>8a</sup> and R<sup>8b</sup> each independently represent hydrogen or C<sub>1-4</sub>alkyl;

Q<sup>1</sup> represents N or CR<sup>6a</sup>;

Q<sup>2</sup> represents N or CR<sup>6b</sup>;

- 20 Q<sup>3</sup> represents N or CR<sup>6c</sup>;

Q<sup>4</sup> represents N or CR<sup>6d</sup>;

provided that maximum one of Q<sup>3</sup> and Q<sup>4</sup> represents N;

Q<sup>8</sup> represents N or CR<sup>6g</sup>;

- $Q^9$  represents N or  $CR^{6h}$ ;  
 $Q^{10}$  represents N or  $CR^{6i}$ ;  
 $Q^{11}$  represents N or  $CR^{6j}$ ;  
 $Q^5$  represents  $CR^{3d}$ ;  $Q^6$  represents N; and  $Q^7$  represents  $CR^{4f}$ ; or  
5  $Q^5$  represents  $CR^{3d}$ ;  $Q^6$  represents  $CR^{4e}$ ; and  $Q^7$  represents N; or  
 $Q^5$  represents N;  $Q^6$  represents  $CR^{4e}$ ; and  $Q^7$  represents  $CR^{4f}$ ; or  
 $Q^5$  represents N;  $Q^6$  represents  $CR^{4e}$ ; and  $Q^7$  represents N; or  
 $Q^5$  represents N;  $Q^6$  represents N; and  $Q^7$  represents  $CR^{4f}$ ; or  
 $Q^5$  represents N;  $Q^6$  represents N; and  $Q^7$  represents N;  
10  $R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$ ,  $R^{6d}$ ,  $R^{6e}$ ,  $R^{6f}$ ,  $R^{6g}$ ,  $R^{6h}$ ,  $R^{6i}$  and  $R^{6j}$  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;  
or a pharmaceutically acceptable addition salt or a solvate thereof.
- 15 The present disclosure also concerns methods for the preparation of compounds of the present disclosure and pharmaceutical compositions comprising them. In another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined herein.
- 20 The compounds of the present disclosure 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,
25 graft rejection, lung injuries, and the like. Hence, in another aspect, there is provided a compound as defined herein 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,
30 transplantation rejection, graft rejection, and lung

injuries. In another aspect, there is provided a compound as defined herein for use in the treatment of a proliferative disorder.

In view of the aforementioned pharmacology of the compounds of Formula (I) and pharmaceutically acceptable addition salts, and solvates thereof, it follows that they  
5 may be suitable for use as a medicament. Hence, in another aspect, there is provided a compound as defined 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  
10 in the treatment, of any one of the diseases or conditions mentioned hereinbefore or hereinafter, in particular cancer.

The present disclosure 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, there is provided use of a compound as defined 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, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.

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 (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.

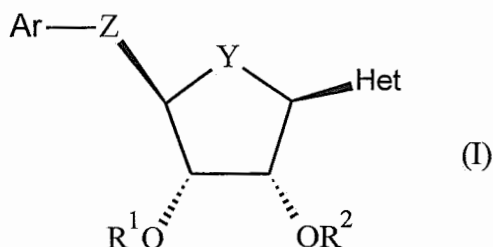
The prefix “C<sub>x-y</sub>” (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C<sub>1-4</sub>alkyl group contains from 1 to 4 carbon atoms, a C<sub>1-3</sub>alkyl group contains from 1 to 3 carbon atoms and so on.

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.

- 5 The term "C<sub>1-4</sub>alkyl" as a group or part of a group refers to a hydrocarbyl radical of Formula C<sub>n</sub>H<sub>2n+1</sub> wherein n is a number ranging from 1 to 4. C<sub>1-4</sub>alkyl groups comprise from 1 to 4 carbon atoms, preferably from 1 to 3 carbon atoms, more preferably 1 to 2 carbon atoms. C<sub>1-4</sub>alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the

### Claims

1. A compound of Formula (I)



wherein

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

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

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

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

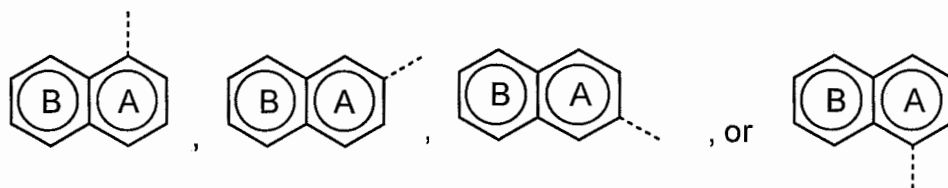
$\text{R}^{5a}$ ,  $\text{R}^{5b}$ ,  $\text{R}^{5c}$ ,  $\text{R}^{5d}$ ,  $\text{R}^{5e}$ ,  $\text{R}^{5f}$ ,  $\text{R}^{5g}$ , and  $\text{R}^{5h}$  each independently represent hydrogen or  $\text{C}_{1-4}\text{alkyl}$ ;

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

$\text{R}^{11}$  represents hydrogen,  $\text{C}_{1-4}\text{alkyl}$ , or  $\text{C}_{1-4}\text{alkyl}$  substituted with one substituent selected from the group consisting of  $-\text{OH}$ ,  $-\text{O}-\text{C}_{1-4}\text{alkyl}$ ,  $\text{R}^{12}$ ,  $-\text{NH}_2$ ,  $-\text{NH}-\text{C}_{1-4}\text{alkyl}$ , and  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ;

$\text{R}^{12}$  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;

$\text{Ar}$  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 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;

$\text{Ar}$  is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo,  $-\text{OH}$ ,  $-\text{NH}_2$ ,  $-\text{NH}-\text{C}_{1-4}\text{alkyl}$ ,  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ,

$-\text{NHR}^{10\text{d}}$ ,  $-\text{NR}^{10\text{c}}\text{R}^{10\text{d}}$ , cyano,  $-\text{CF}_3$ ,  $-\text{C}(=\text{O})-\text{NH}_2$ ,  $-\text{C}(=\text{O})-\text{NH}-\text{C}_{1-4}\text{alkyl}$ ,  
 $-\text{C}(=\text{O})-\text{C}_{1-4}\text{alkyl}$ ,  $\text{C}_{1-4}\text{alkyloxy}$ ,  $-\text{C}(=\text{O})-\text{O}-\text{C}_{1-4}\text{alkyl}$ ,  $\text{C}_{3-6}\text{cycloalkyl}$ ,  $-\text{O}-\text{C}_{3-6}\text{cycloalkyl}$ ,  $-\text{NH}-$   
 $\text{C}_{3-6}\text{cycloalkyl}$ ,  $-\text{N}(\text{C}_{3-6}\text{cycloalkyl})_2$ ,  $\text{C}_{2-6}\text{alkenyl}$ ,  $\text{C}_{1-4}\text{alkyl}$  substituted with one  
 $\text{C}_{1-4}\text{alkyloxy}$ , and  $\text{C}_{1-4}\text{alkyl}$  optionally substituted with one  $-\text{NR}^{10\text{a}}\text{R}^{10\text{b}}$ ;  
 $\text{R}^{10\text{a}}$  and  $\text{R}^{10\text{b}}$  each independently represent hydrogen or  $\text{C}_{1-4}\text{alkyl}$ ;

$Q^1$  represents N or  $CR^{6a}$ ;

$Q^2$  represents N or  $CR^{6b}$ ;

$Q^3$  represents N or  $CR^{6c}$ ;

$Q^4$  represents N or  $CR^{6d}$ ;

provided that maximum one of  $Q^3$  and  $Q^4$  represents N;

$Q^8$  represents N or  $CR^{6g}$ ;

$Q^9$  represents N or  $CR^{6h}$ ;

$Q^{10}$  represents N or  $CR^{6i}$ ;

$Q^{11}$  represents N or  $CR^{6j}$ ;

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

$Q^5$  represents  $CR^{3d}$ ;  $Q^6$  represents  $CR^{4e}$ ; and  $Q^7$  represents N; or

$Q^5$  represents N;  $Q^6$  represents  $CR^{4e}$ ; and  $Q^7$  represents  $CR^{4f}$ ; or

$Q^5$  represents N;  $Q^6$  represents  $CR^{4e}$ ; and  $Q^7$  represents N; or

$Q^5$  represents N;  $Q^6$  represents N; and  $Q^7$  represents  $CR^{4f}$ ; or

$Q^5$  represents N;  $Q^6$  represents N; and  $Q^7$  represents N;

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$ ,  $R^{6d}$ ,  $R^{6e}$ ,  $R^{6f}$ ,  $R^{6g}$ ,  $R^{6h}$ ,  $R^{6i}$  and  $R^{6j}$  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;

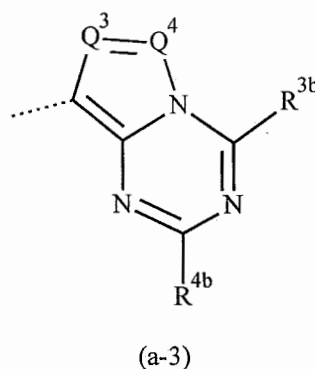
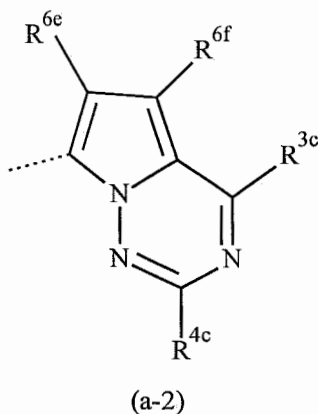
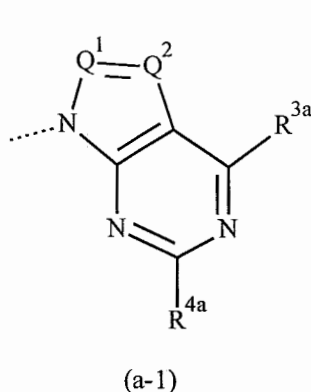
$R^{9a}$  and  $R^{9b}$  each independently represent hydrogen or  $C_{1-4}$ alkyl;

or a pharmaceutically acceptable addition salt or a solvate thereof.

2. The compound according to claim 1, wherein

Ar is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo, -OH, -NH<sub>2</sub>, -NH-C<sub>1-4</sub>alkyl, -N(C<sub>1-4</sub>alkyl)<sub>2</sub>, -NHR<sup>10d</sup>, -NR<sup>10c</sup>R<sup>10d</sup>, cyano, -CF<sub>3</sub>, -C(=O)-NH<sub>2</sub>, -C(=O)-NH-C<sub>1-4</sub>alkyl, -C(=O)-C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyloxy, -C(=O)-O-C<sub>1-4</sub>alkyl, C<sub>3-6</sub>cycloalkyl, C<sub>2-6</sub>alkenyl, C<sub>1-4</sub>alkyl substituted with one C<sub>1-4</sub>alkyloxy, and C<sub>1-4</sub>alkyl optionally substituted with one -NR<sup>10a</sup>R<sup>10b</sup>, R<sup>10c</sup> and R<sup>10d</sup> each independently represent C<sub>3-6</sub>cycloalkyl; C<sub>3-6</sub>cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH and -O-C<sub>1-4</sub>alkyl; or C<sub>1-4</sub>alkyl substituted with one substituent selected from the group consisting of C<sub>3-6</sub>cycloalkyl, R<sup>13</sup> and R<sup>14</sup>;

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



R<sup>3a</sup>, R<sup>3b</sup> and R<sup>3c</sup> each independently represent hydrogen, halo, -NR<sup>7a</sup>R<sup>7b</sup>, C<sub>1-4</sub>alkyl, or -O-C<sub>1-4</sub>alkyl;

R<sup>7b</sup> represents hydrogen or C<sub>1-4</sub>alkyl;

R<sup>4a</sup>, R<sup>4b</sup> and R<sup>4c</sup> each independently represent hydrogen, halo, -NR<sup>8a</sup>R<sup>8b</sup>, or C<sub>1-4</sub>alkyl;

Q<sup>1</sup> represents N or CR<sup>6a</sup>;

Q<sup>2</sup> represents N or CR<sup>6b</sup>;

Q<sup>3</sup> represents N or CR<sup>6c</sup>;

Q<sup>4</sup> represents N or CR<sup>6d</sup>;

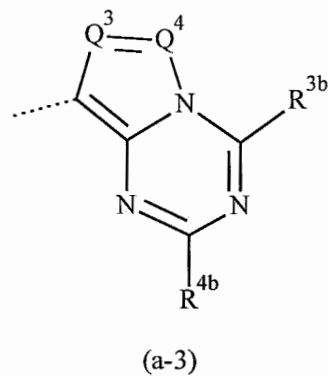
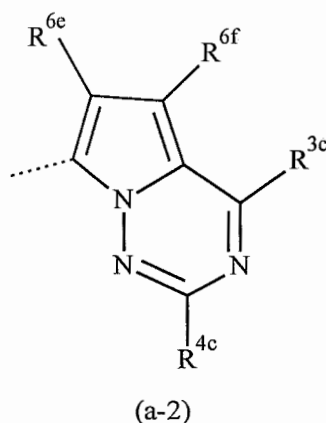
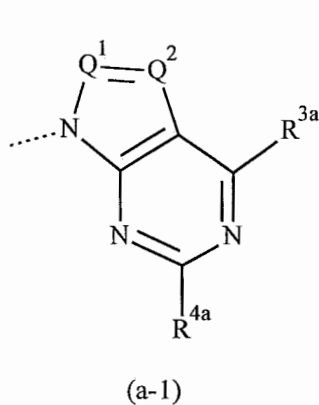
provided that maximum one of  $Q^3$  and  $Q^4$  represents N;

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$ ,  $R^{6d}$ ,  $R^{6e}$  and  $R^{6f}$  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.

3. The compound according to claim 1 or 2, wherein

Ar is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo,  $-OH$ ,  $-NH_2$ ,  $-NH-C_{1-4}$ alkyl,  $-N(C_{1-4}alkyl)_2$ , cyano,  $-CF_3$ ,  $-C(=O)-NH-C_{1-4}alkyl$ ,  $-C(=O)-C_{1-4}alkyl$ ,  $C_{1-4}$ alkyloxy, and  $C_{1-4}$ alkyl 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  $-O-C_{1-4}alkyl$ ;

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

$R^{4a}$ ,  $R^{4b}$  and  $R^{4c}$  each independently represent hydrogen, halo,  $-NR^{8a}R^{8b}$ , or  $C_{1-4}alkyl$ ;

$Q^1$  represents N or  $CR^{6a}$ ;

$Q^2$  represents N or  $CR^{6b}$ ;

$Q^3$  represents N or  $CR^{6c}$ ;

$Q^4$  represents N or  $CR^{6d}$ ;

provided that maximum one of  $Q^3$  and  $Q^4$  represents N;

$R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$ ,  $R^{6d}$ ,  $R^{6e}$  and  $R^{6f}$  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.

4. The compound according to claim 1, wherein

$R^1$  represents hydrogen;

$R^2$  represents hydrogen;

Y represents  $-O-$  or  $-CH_2-$ ;

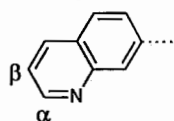
Z represents  $-X-CR^{5a}R^{5b}-$  or  $-CR^{5c}R^{5g}-CR^{5f}R^{5h}-$ ;

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  $\alpha$  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  $\beta$  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  $\alpha$  or  $\beta$ ;

$R^{10d}$  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;

5. The compound according to any one of claims 1 to 4, wherein

$R^1$  represents hydrogen;

$R^2$  represents hydrogen;

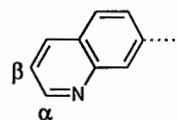
Y represents  $-O-$  or  $-CH_2-$ ;

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

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

X represents  $-O-$ ;

Ar represents



wherein Ar is optionally substituted in the position indicated by  $\alpha$  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  $\beta$  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  $\alpha$  or  $\beta$ ;

$R^{10d}$  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);

$R^{3a}$  represents 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  $C_{1-4}alkyl$ ;

$R^{4a}$  represents hydrogen or halo;

$Q^1$  represents  $CR^{6a}$ ;

$Q^2$  represents  $CR^{6b}$ ;

$R^{6a}$  and  $R^{6b}$  represent hydrogen.

6. The compound according to claim 1 or 2, wherein

$R^1$  represents hydrogen;

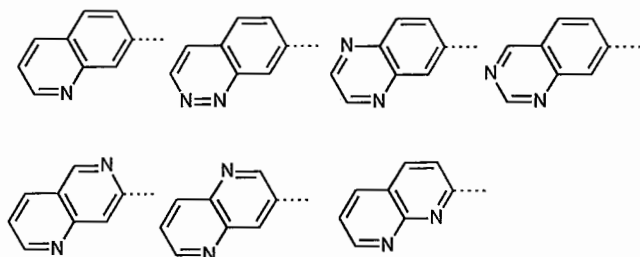
$R^2$  represents hydrogen;

Y represents  $-\text{CH}_2-$ ;

Z represents  $-\text{CR}^{5e}\text{R}^{5g}-\text{CR}^{5f}\text{R}^{5h}-$ ;

$R^{5e}$ ,  $R^{5f}$ ,  $R^{5g}$ , and  $R^{5h}$  represent hydrogen;

Ar represents any one of the following 10-membered bicyclic aromatic ring systems:



Ar is optionally substituted with one, two, three or four substituents each independently selected from the group consisting of halo,  $-\text{NH}_2$ ,  $-\text{NH}-\text{C}_{1-4}\text{alkyl}$ ,  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ,  $-\text{NHR}^{10d}$ ,  $-\text{NR}^{10c}\text{R}^{10d}$ ,

$R^{10c}$  and  $R^{10d}$  each independently represent  $\text{C}_{3-6}\text{cycloalkyl}$ ;  $\text{C}_{3-6}\text{cycloalkyl}$  substituted with one, two or three substituents each independently selected from the group consisting of halo,  $-\text{OH}$  and  $-\text{O}-\text{C}_{1-4}\text{alkyl}$ ;  $\text{C}_{1-4}\text{alkyl}$  substituted with one, two or three substituents each independently selected from the group consisting of halo,  $-\text{OH}$  and  $-\text{O}-\text{C}_{1-4}\text{alkyl}$ ; or  $\text{C}_{1-4}\text{alkyl}$  substituted with one  $\text{C}_{3-6}\text{cycloalkyl}$  substituent;

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

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

$R^{7a}$  represents hydrogen;

$R^{7b}$  represents hydrogen or  $\text{C}_{1-4}\text{alkyl}$ ;

$R^{4a}$  represents hydrogen;

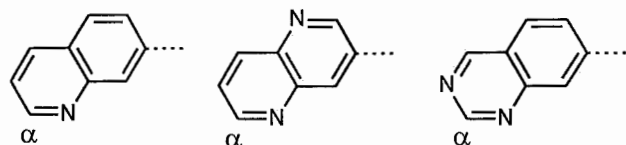
$Q^1$  represents  $\text{CR}^{6a}$ ;

$Q^2$  represents  $\text{CR}^{6b}$ ;

$R^{6a}$  and  $R^{6b}$  represent hydrogen.

7. The compound according to claim 1, 2 or 6, wherein

Ar is selected from the group consisting of:



wherein each Ar is optionally substituted in position  $\alpha$  with a substituent selected from the

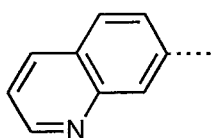
group consisting of  $-\text{NH}_2$ ,  $-\text{NH}-\text{C}_{1-4}\text{alkyl}$ ,  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ,  $-\text{NHR}^{10d}$ , and  $-\text{NR}^{10c}\text{R}^{10d}$ , and wherein Ar is optionally substituted in another position with a halo substituent.

8. The compound according to claim 1, wherein

Y represents  $-\text{O}-$  or  $-\text{CH}_2-$ ; Z represents  $-\text{X}-\text{CR}^{5a}\text{R}^{5b}-$  or  $-\text{CH}_2\text{CH}_2-$ ;

$\text{R}^{5a}$  and  $\text{R}^{5b}$  represent hydrogen; X represents  $-\text{O}-$ ;

$\text{R}^{11}$  represents hydrogen;



Ar represents ;

Ar is optionally substituted with one or two substituents each independently selected from the group consisting of halo,  $-\text{OH}$ ,  $-\text{NH}_2$ ,  $-\text{NH}-\text{C}_{1-4}\text{alkyl}$ ,  $-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ , cyano, and  $-\text{CF}_3$ ;

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

$\text{R}^{3a}$  represents  $-\text{NR}^{7a}\text{R}^{7b}$ ;

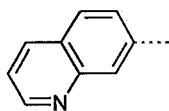
$\text{R}^{7a}$  represents hydrogen;

$\text{R}^{7b}$  represents hydrogen;

$\text{R}^{4a}$  represents hydrogen;

$\text{Q}^1$  represents  $\text{CR}^{6a}$ ;  $\text{Q}^2$  represents  $\text{CR}^{6b}$ ;  $\text{R}^{6a}$  and  $\text{R}^{6b}$  represent hydrogen.

9. The compound according to claim 1, 2, 3 or 6, wherein Ar represents



10. The compound according to claim 1, 2, 3, 7, 8 or 9, wherein  $\text{R}^1$  and  $\text{R}^2$  represent hydrogen.

11. The compound according to any one of claims 1 to 5 and claim 8, wherein Y represents  $-\text{O}-$ .

12. The compound according to any one of claims 1 to 5 and claims 7 to 10, wherein Y represents  $-\text{CH}_2-$ .

13. The compound according to claim 12 wherein Z represents  $-\text{CH}_2\text{CH}_2-$ .

14. The compound according to any one of claims 1 to 4, claim 7, and claims 9 to 13, wherein Het represents a bicyclic aromatic heterocyclic ring system of Formula (a-1).

15. The compound according to claim 14, wherein  $R^{3a}$  represents  $-NR^{7a}R^{7b}$ ; and  $R^{7a}$  and  $R^{7b}$  represent hydrogen.

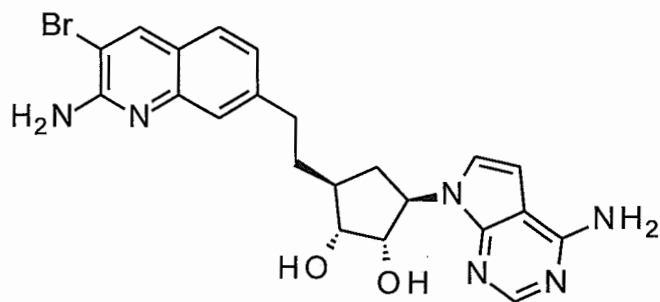
16. The compound according to any one of claims 1 to 5, wherein  $R^{5b}$ ,  $R^{5g}$  and  $R^{5h}$  represent hydrogen;

Y represents  $-\text{CH}_2-$ ;

Het represents (a-1);

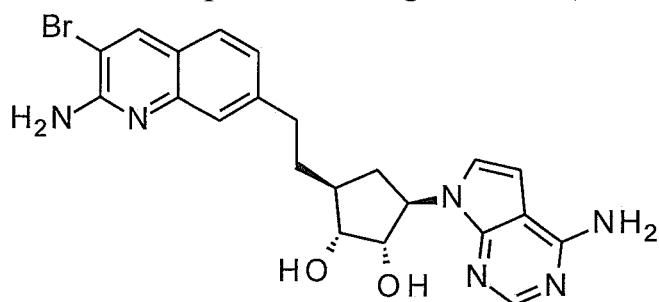
$Q^1$  represents  $\text{CH}$ ; and  $Q^2$  represents  $\text{CH}$ .

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

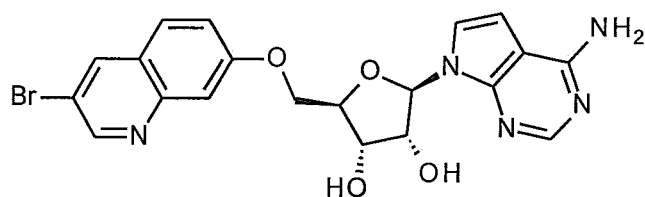


or a pharmaceutically acceptable addition salt or a solvate thereof.

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



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



or a pharmaceutically acceptable addition salt or a solvate thereof.

20. 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 19.
21. A compound as defined in any one of claims 1 to 19 for use as a medicament.
22. A compound as defined in any one of claims 1 to 19 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.

**23.** The compound according to claim 22 for use in the treatment 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.

**24.** The compound according to claim 22 or 23 wherein the disease or condition is an autoimmune disorder, cancer, inflammatory disease, or a neurodegenerative disease.

**25.** The compound according to claim 24 wherein the disease or condition is cancer.

**26.** The compound according to claim 25 wherein the cancer is non-Hodgkin lymphoma.

**27.** The compound according to claim 26 wherein the non-Hodgkin lymphoma is B-cell non-Hodgkin lymphoma.

**28.** The compound according to claim 25 wherein the cancer is lung cancer.

**29.** The compound according to claim 28 wherein the lung cancer is non-small cell lung cancer or small cell lung cancer.

**30.** A compound as defined in claim 17 or 18 for use in the treatment of a proliferative disorder.

**31.** Use of a compound as defined in any one of claims 1 to 19 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, multiorgan failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, graft rejection, and lung injuries.