

- 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
25 failure, kidney diseases, platelet aggregation, sperm motility, transplantation rejection, 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,
30 pancreatitis, transplantation rejection, and graft rejection.

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
 5 selected from a blood disorder, metabolic disorders, autoimmune disorders, cancer, inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, pancreatitis, transplantation rejection, and graft rejection.

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
 10 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

15 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.

20 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
 25 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
 30 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.

diseases, neurodegenerative diseases, pancreatitis, transplantation rejection, and graft rejection.

23. The compound for use according to claim 22 for the treatment 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.
24. The compound for use 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 for use according to claim 24 wherein the disease or condition is cancer.
26. The compound for use according to claim 25 wherein the cancer is a hematopoietic cancer.
27. The compound for use according to claim 26 wherein the hematopoietic cancer is leukemia.
28. The compound for use according to claim 27 wherein the leukemia is acute myelocytic leukemia, chronic lymphocytic leukemia or acute lymphocytic leukemia.
29. The compound for use according to claim 25 wherein the cancer is non-Hodgkin lymphoma.
30. The compound for use according to claim 29 wherein the non-Hodgkin lymphoma is B-cell non-Hodgkin lymphoma.
31. The compound for use according to claim 25 wherein the cancer is myelodysplastic syndrome.
32. The compound for use according to claim 25 wherein the cancer is lung cancer.

33. The compound for use according to claim 32 wherein the lung cancer is non-small cell lung cancer or small cell lung cancer.
34. A compound as defined in claim 17 or 18 for use in the treatment of a proliferative disorder.
35. 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, transplantation rejection, and graft rejection.