

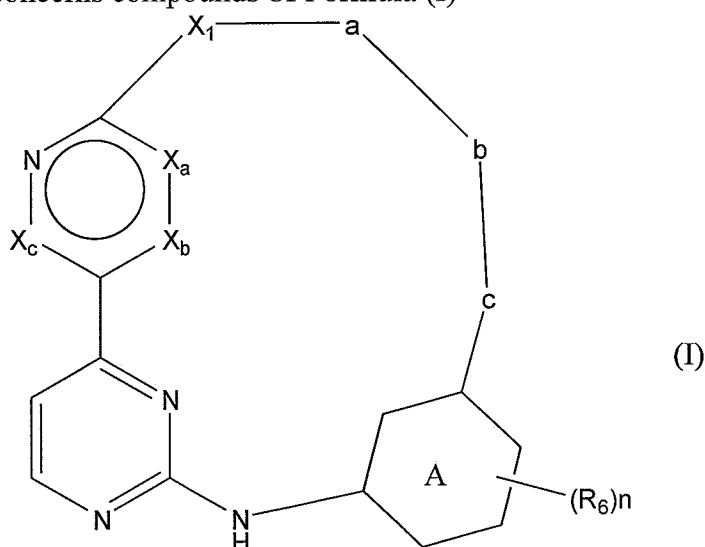
et al., *Cell Death Differ.* 2009, 16(1):87-93) may be most susceptible to Vps34 inhibition.

WO 2009/112439 describes 4-aryl-2-anilino-pyrimidines as PLK kinase inhibitors.

- 5 There is a strong need for novel compounds which have EF2K inhibitory activity and optionally also have Vps34 inhibitory activity, thereby opening new avenues for the treatment of cancer. It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative. It is accordingly an object of the present invention to provide such novel compounds.

Summary

- 10 It has been found that the compounds of the present disclosure have EF2K inhibitory activity and optionally also have Vps34 inhibitory activity. The compounds according to the disclosure and the pharmaceutical compositions comprising such compounds may be useful for treating or preventing, in particular treating, diseases such as cancer, depression, and memory and learning disorders. In particular, the compounds according to the present disclosure and the pharmaceutical compositions thereof may be useful in the treatment of a haematological malignancy or solid tumour. In a specific embodiment said solid tumour is selected from the group consisting of glioblastoma, medulloblastoma, prostate cancer, breast cancer, ovarian cancer and colorectal cancer, and the like.
- 20 This disclosure concerns compounds of Formula (I)



tautomers and stereochemically isomeric forms thereof, wherein X_a , X_b and X_c each independently represent CH or N;

substituted with 1 to 4 substituents each independently selected from C_{1-4} alkyl, halo, hydroxyl or halo C_{1-4} alkyl;

n represents an integer of value 1 or 2;

m represents an integer of value 1 or 2 ;

5 p represents an integer of value 1 or 2;

p1 represents an integer of value 1 or 2;

each p2 independently represents an integer of value 0, 1 or 2;

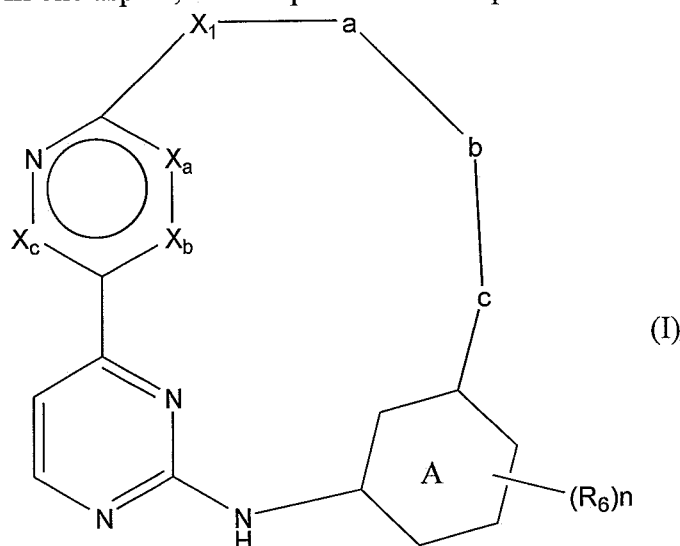
r represents an integer of value 0, 1 or 2;

each p3 independently represents an integer of value 0 or 1;

10 each s independently represents an integer of value 0, 1 or 2;

and the pharmaceutically acceptable addition salts, and the solvates thereof.

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



a tautomer or a stereoisomeric form thereof, wherein

15 X_a , X_b and X_c each independently represent CH or N;

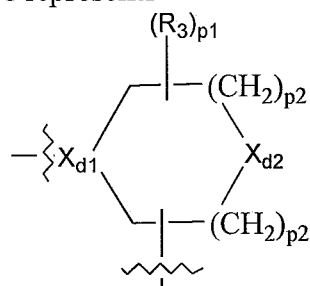
$-X_1-$ represents $-(CHR_{12})_s-NR_1-X_e-C_{1-4}$ alkanediyl- $(SO_2)_{p3}-$ or

$-(CH_2)_s-O-X_e-C_{1-4}$ alkanediyl- $(SO_2)_{p3}-$; wherein each of said C_{1-4} alkanediyl moieties are optionally substituted with hydroxyl or hydroxy C_{1-4} alkyl;

$-X_e-$ represents $-C(R_2)_2-$ or $-C(=O)-$;

20 a represents $-NR_4-C(=O)-[C(R_{5b})_2]_r-$ or $-NR_4-C(R_{5b})_2-C(=O)-$ or $-C(=O)-NR_4-C(R_{5b})_2-$;

b represents



, wherein said b ring may contain extra bonds to form a bridged

ring system selected from 2,5-diazabicyclo[2.2.2]octanyl, 3,8-

diazabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 3,9-

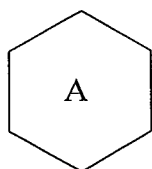
5 diazabicyclo[3.3.1]nonyl;

X_{d1} represents CH or N;

X_{d2} represents CH_2 or NH;

provided that at least one of X_{d1} and X_{d2} represents nitrogen;

c represents a bond, $-[C(R_{5a})_2]_m-$, $-C(=O)-$, $-O-$, $-NR_{5a}-$, $-SO_2-$, or $-SO-$;



10 ring represents phenyl or pyridyl;

R_1 represents hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, cyano C_{1-4} alkyl,

$-C(=O)-C_{1-4}$ alkyl, $-C(=O)-haloC_{1-4}$ alkyl, hydroxy C_{1-4} alkyl, halo C_{1-4} alkyl,

C_{1-4} alkyloxy C_{1-4} alkyl, halo C_{1-4} alkyloxy C_{1-4} alkyl, $-C(=O)NR_7R_8$, $-SO_2-NR_7R_8$, $-SO_2-R_9$,

R_{11} , C_{1-4} alkyl substituted with R_{11} , $-C(=O)-R_{11}$, or $-C(=O)-C_{1-4}$ alkyl- R_{11} ;

15 each R_2 independently represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyl substituted with

C_{3-6} cycloalkyl, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, carboxyl, $-C(=O)-O-C_{1-4}$ alkyl

wherein C_{1-4} alkyl is optionally substituted with C_{1-4} alkyloxy, $-C(=O)-NH_2$, $-C(=O)-$

$NH(C_{1-4}alkyl)$ wherein $C_{1-4}alkyl$ is optionally substituted with $C_{1-4}alkyloxy$, or $-C(=O)-$

$N(C_{1-4}alkyl)_2$ wherein each $C_{1-4}alkyl$ is optionally substituted with $C_{1-4}alkyloxy$;

20 or R_1 and one R_2 are taken together to form C_{1-4} alkanediyl or C_{2-4} alkenediyl, each of

said C_{1-4} alkanediyl and C_{2-4} alkenediyl optionally being substituted with 1 to 4

substituents each independently selected from hydroxyl, oxo, halo, cyano, N_3 ,

hydroxy C_{1-4} alkyl, $-NR_7R_8$, $-SO_2-NR_7R_8$, $-NH-SO_2-NR_7R_8$, $-C(=O)-NR_7R_8$, or $-NH-$

$C(=O)-NR_7R_8$;

25 or R_1 and R_{12} are taken together to form C_{1-4} alkanediyl or C_{2-4} alkenediyl, each of said

C_{1-4} alkanediyl and C_{2-4} alkenediyl optionally being substituted with 1 to 4 substituents

each independently selected from hydroxyl, oxo, halo, cyano, N_3 , hydroxy C_{1-4} alkyl,

$-NR_7R_8$, $-SO_2-NR_7R_8$, $-NH-SO_2-NR_7R_8$, $-C(=O)-NR_7R_8$, or $-NH-C(=O)-NR_7R_8$;

- each R_3 independently represents hydrogen; oxo; hydroxyl; carboxyl; $-NR_{3a}R_{3b}$; $-C(=O)-NR_{3a}R_{3b}$; hydroxyc₁₋₄alkyl; haloC₁₋₄alkyl; $-C(=O)-C_{1-4}$ alkyl; $-C(=O)-O-C_{1-4}$ alkyl wherein said C₁₋₄alkyl may optionally be substituted with phenyl; C₁₋₄alkyl optionally substituted with cyano, carboxyl, C₁₋₄alkyloxy, $-C(=O)-O-C_{1-4}$ alkyl, $-O-C(=O)-C_{1-4}$ alkyl, $-NR_{3e}R_{3f}$, $-C(=O)-NR_{3e}R_{3f}$, $-SO_2-NR_{3e}R_{3f}$, Q, $-C(=O)-Q$, or $-SO_2-Q$;
- 5 hydroxyc₁₋₄alkyloxyC₁₋₄alkyl; C₁₋₄alkyloxyhydroxyc₁₋₄alkyl; hydroxyc₁₋₄alkyloxyhydroxyc₁₋₄alkyl; or C₁₋₄alkyloxyC₁₋₄alkyl optionally substituted with cyano, carboxyl, C₁₋₄alkyloxy, $-C(=O)-O-C_{1-4}$ alkyl, $-O-C(=O)-C_{1-4}$ alkyl, $-NR_{3e}R_{3f}$, $-C(=O)-NR_{3e}R_{3f}$, $-SO_2-NR_{3e}R_{3f}$, R_{10} , $-C(=O)-R_{10}$, or $-SO_2-R_{10}$;
- 10 or two R_3 substituents attached to the same carbon atom are taken together to form C₂₋₅alkanediyl or $-(CH_2)_p-O-(CH_2)_p-$;
- each R_{3a} and R_{3b} independently represent hydrogen; $-C(=O)-C_{1-4}$ alkyl; $-SO_2-NR_{3c}R_{3d}$; or C₁₋₄alkyl optionally substituted with C₁₋₄alkyloxy; or R_{3a} and R_{3b} are taken together with the nitrogen to which they are attached to form a
- 15 to 7 membered saturated monocyclic heterocyclic ring which optionally contains 1 or 2 further heteroatoms selected from N, O or SO₂, said heterocyclic ring being optionally substituted with 1 to 4 substituents each independently selected from C₁₋₄alkyl, halo, hydroxyl, or haloC₁₋₄alkyl;
- each R_{3c} and R_{3d} independently represent hydrogen, C₁₋₄alkyl or $-C(=O)-C_{1-4}$ alkyl; or
- 20 R_{3c} and R_{3d} are taken together with the nitrogen to which they are attached to form a 4 to 7 membered saturated monocyclic heterocyclic ring which optionally contains 1 or 2 further heteroatoms selected from N, O or SO₂, said heterocyclic ring being optionally substituted with 1 to 4 substituents each independently selected from C₁₋₄alkyl, halo, hydroxyl, or haloC₁₋₄alkyl;
- 25 each R_{3e} and R_{3f} independently represent hydrogen, C₁₋₄alkyl optionally substituted with C₁₋₄alkyloxy, $-C(=O)-C_{1-4}$ alkyl, or $-SO_2-NR_{3c}R_{3d}$;
- R_4 represents hydrogen, C₁₋₄alkyl or C₁₋₄alkyloxyC₁₋₄alkyl;
- each R_{5a} independently represents hydrogen or C₁₋₄alkyl; or
- two R_{5a} substituents attached to the same carbon atom are taken together to form
- 30 C₂₋₅alkanediyl or $-(CH_2)_p-O-(CH_2)_p-$;
- $R_{5a'}$ represents hydrogen or C₁₋₄alkyl;
- each R_{5b} independently represents hydrogen; C₁₋₄alkyl; C₁₋₄alkyl substituted with $NR_{5b1}R_{5b2}$; C₁₋₄alkyloxyC₁₋₄alkyl; hydroxyc₁₋₄alkyl; hydroxyl; C₃₋₆cycloalkyl; or phenyl optionally substituted with C₁₋₄alkyl, halo, hydroxyl or C₁₋₄alkyloxy; or
- 35 two R_{5b} substituents attached to the same carbon atom are taken together to form C₂₋₅alkanediyl or $-(CH_2)_p-O-(CH_2)_p-$;

- R_{5b1} and R_{5b2} independently represent hydrogen, C₁₋₄alkyl optionally substituted with C₁₋₄alkyloxy, -(C=O)-C₁₋₄alkyl, or -SO₂-NR_{5b3}R_{5b4};
- R_{5b3} and R_{5b4} independently represent hydrogen, C₁₋₄alkyl or -(C=O)-C₁₋₄alkyl; or
- R_{5b3} and R_{5b4} are taken together with the nitrogen to which they are attached to form a 4 to 7 membered saturated monocyclic heterocyclic ring which optionally contains 1 or 2 further heteroatoms selected from N, O or SO₂, said heterocyclic ring being optionally substituted with 1 to 4 substituents each independently selected from C₁₋₄alkyl, halo, hydroxyl, or haloC₁₋₄alkyl;
- each R₆ independently represents hydrogen, halo, hydroxyl, carboxyl, cyano, C₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, hydroxyC₁₋₄alkyl, haloC₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, -NR_{6a}R_{6b}, or -C(=O)NR_{6a}R_{6b};
- each R_{6a} and R_{6b} independently represent hydrogen or C₁₋₄alkyl;
- each R₇ and R₈ independently represent hydrogen, C₁₋₄alkyl, haloC₁₋₄alkyl, or C₃₋₆cycloalkyl; or
- R₇ and R₈ are taken together with the nitrogen to which they are attached to form a 4 to 7 membered saturated monocyclic heterocyclic ring which optionally contains 1 further heteroatom selected from N, O or SO₂, said heterocyclic ring being optionally substituted with 1 to 4 substituents each independently selected from C₁₋₄alkyl, halo, hydroxyl, or haloC₁₋₄alkyl;
- R₉ represents C₁₋₄alkyl, haloC₁₋₄alkyl, or C₃₋₆cycloalkyl;
- each R₁₀ independently represents a 4 to 7 membered saturated monocyclic heterocyclic ring containing up to 2 heteroatoms selected from N, O or SO₂, said heterocyclic ring being optionally substituted with 1 to 4 substituents each independently selected from C₁₋₄alkyl, halo, hydroxyl or haloC₁₋₄alkyl;
- each R₁₁ independently represents C₃₋₆cycloalkyl, phenyl, or a 4 to 7 membered monocyclic heterocyclic ring containing up to 3 heteroatoms selected from N, O or SO₂, said heterocyclic ring being optionally substituted with 1 to 4 substituents each independently selected from C₁₋₄alkyl, halo, hydroxyl, or haloC₁₋₄alkyl;
- each R₁₂ independently represents hydrogen or C₁₋₄alkyl;
- Q represents a 4 to 7 membered saturated monocyclic heterocyclic ring containing up to 3 heteroatoms selected from N, O or SO₂, said heterocyclic ring being optionally substituted with 1 to 4 substituents each independently selected from C₁₋₄alkyl, halo, hydroxyl or haloC₁₋₄alkyl;
- n represents an integer of value 1 or 2;
- m represents an integer of value 1 or 2 ;
- p represents an integer of value 1 or 2;
- p1 represents an integer of value 1 or 2;

- each p₂ independently represents an integer of value 0, 1 or 2;
r represents an integer of value 0, 1 or 2;
each p₃ independently represents an integer of value 0 or 1;
each s independently represents an integer of value 0, 1 or 2;
5 or a N-oxide, a pharmaceutically acceptable addition salt or a solvate thereof.

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
10 compound of the present disclosure.

The compounds of the present disclosure were found to have EF2K inhibitory activity and optionally also have Vps34 inhibitory activity. Therefore the compounds of the present disclosure may be useful in the treatment or prevention, in particular in the
15 treatment, of diseases such as cancer, depression, neuroplasticity (synaptic plasticity and non-synaptic plasticity), and memory and learning disorders. In particular, the compounds according to the present disclosure and the pharmaceutical compositions thereof may be useful in the treatment of a haematological malignancy or solid tumour. In a specific embodiment said solid tumour is selected from the group
20 consisting of glioblastoma, medulloblastoma, prostate cancer, breast cancer, ovarian cancer and colorectal cancer, 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, there is provided a
25 compound of the present disclosure for use as a medicament. In another aspect, there is provided a compound of the present disclosure for use in the treatment or prevention of a disease or condition selected from cancer, depression, and memory and learning disorders.

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
30 in the treatment, of 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 treatment or prevention, in particular treatment, of diseases such as cancer, depression, neuroplasticity (synaptic plasticity and non-synaptic plasticity),
5 and memory and learning disorders.

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.

Combinations of substituents and/or variables are permissible only if such combinations result in chemically stable compounds. "Stable compound" is meant to indicate 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 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 a radical or group is defined as "optionally substituted" in the present invention, it is meant that said radical or group is unsubstituted or is substituted.

Lines drawn from substituents into ring systems indicate that the bond may be attached to any of the suitable ring atoms.

Whenever the term "substituted with 1 to 4 substituents" is used in the present invention, it is meant, to indicate that from 1 to 4 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.

Whenever the term "substituted with" without an indication of the number of substituents is used in the present invention, it is meant, unless otherwise is indicated or is clear from the context, to indicate that one hydrogen, on the atom or radical indicated in the expression using "substituted" is replaced with a substituent from the indicated group, provided 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