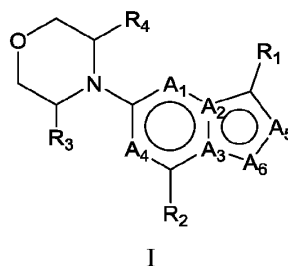


WHAT IS CLAIMED IS:

1. A compound of Formula I:

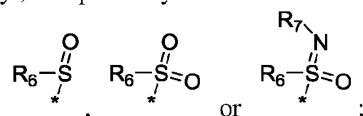


or a stereoisomer, a tautomer, a N-oxide, a hydrate, an isotope-substituted derivative, a solvate or a pharmaceutically acceptable salt thereof, or a mixture thereof, or a prodrug thereof, wherein:

A₁ and A₄-A₆ are independently CR₅ or N;

A₂ and A₃ are independently N or C, with the proviso that at least one of A₂ and A₃ is N;

R₁ is an optionally substituted aryl, an optionally substituted heterocyclic group, an optionally substituted cycloalkyl, an optionally substituted heteroaryl,



wherein * indicates an attachment position of the group to the rest of the compound;

R₂ is halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, carbocyclic group, heterocyclic group, aryl, heteroaryl, -NR₈R₉, -(CO)R₈, -(CO)OR₈, -(CO)NR₈R₉, -(SO)R₆, -(SO₂)R₆, -SR₆, -(SO₂)NR₈R₉, -NR₈(SO₂)R₆, -((SO)=NR₇)R₁₀, -N=(SO)R₆R₁₀, -SiR₇R₁₀R₁₁, -(PO)(OR₈)₂, -(PO)(OR₈)R₁₀ or -(PO)(R₁₀)₂, wherein the said C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, carbocyclic group, heterocyclic group, aryl and heteroaryl each are optionally substituted;

R₃ and R₄ are independently hydrogen or C₁-C₆ alkyl;

R₅ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, amino, nitro, cyano, acylamino, acyloxy, hydroxy, thiol, alkylthiol, azido or carboxy; wherein the said C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, amino, acylamino, acyloxy, hydroxy, thiol, alkylthiol and carboxy each are optionally substituted;

R₆ is an optionally substituted alkyl or an optionally substituted phenyl;

R₇ is hydrogen, an optionally substituted alkyl, -(CO)OR₈ or -(CO)NR₈R₉;

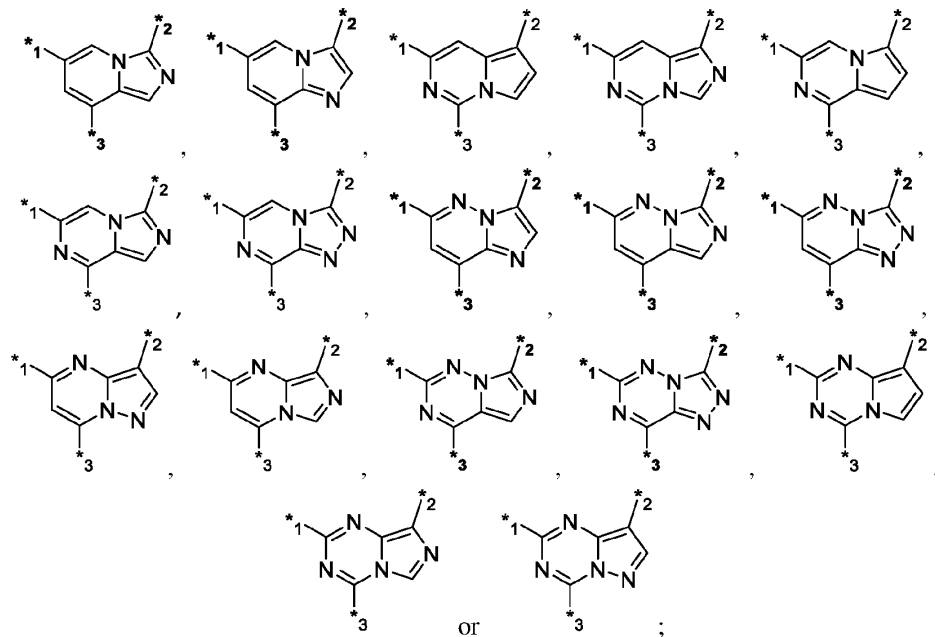
R₈ and R₉ are independently hydrogen, an optionally substituted C₁-C₁₀ alkyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclic group, an optionally substituted aryl or an optionally substituted heteroaryl; or R₈ and R₉ in the -(CO)NR₈R₉ group together with the N and C to which they are attached form an optionally substituted 4-7

membered cyclic amino group, which optionally comprises one additional heteroatom selected from O, N and S;

R_{10} is C_1 - C_4 alkyl, or in the case of $-N=(SO)R_6R_{10}$, R_6 and R_{10} together with the S to which they attached form a 5-8 membered heterocycloalkyl; and

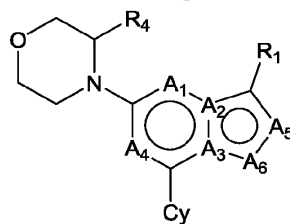
R_{11} is hydrogen or C_1 - C_4 alkyl.

2. The compound of claim 1, wherein A_1 is N or CH; the penta-fused hexa-heteroaryl containing A_1 , A_2 , A_3 , A_4 , A_5 and A_6 is:



wherein, $*_1$, $*_2$ and $*_3$ are the attachment positions of the group to morpholinyl, R_1 and R_2 of the compound, respectively.

3. The compound of claim 1, wherein the compound is a compound of Formula II:



or a stereoisomer, a tautomer, a N-oxide, hydrate, an isotope-substituted derivative, a solvate or a pharmaceutically acceptable salt thereof, or a mixture thereof, or a prodrug thereof, wherein:

A_1 - A_6 , R_1 and R_4 are as defined in claim 1;

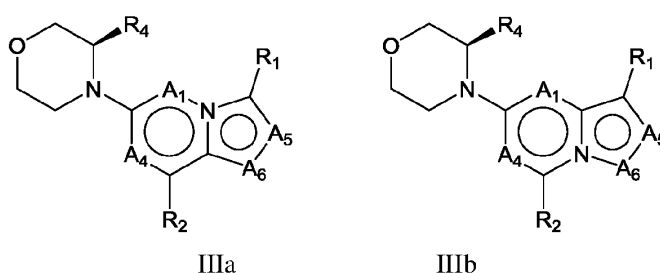
Cy is C_3 - C_6 cycloalkyl, carbocyclic group, heterocyclic group, aryl, heteroaryl, $-NR_8R_9$, $-NR_8(SO_2)R_6$ or $-N=(SO)R_6R_{10}$; wherein the said C_3 - C_6 cycloalkyl, carbocyclic group, heterocyclic group, aryl and heteroaryl each are optionally substituted;

R₆ is an optionally substituted alkyl or an optionally substituted phenyl;

R₈ and R₉ each are independently hydrogen, an optionally substituted C₁-C₁₀ alkyl, an optionally substituted cycloalkyl, an optionally substituted heterocyclic group, an optionally substituted aryl, or an optionally substituted heteroaryl; or R₈ and R₉ together is a optionally substituted 4-7 membered cyclic amino group, which optionally comprises one additional heteroatom selected from O, N and S;

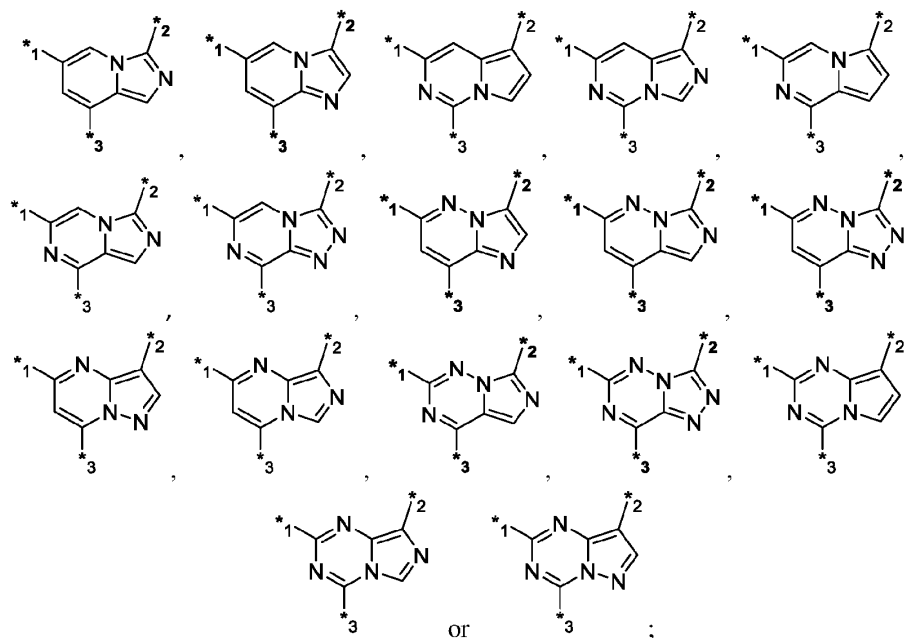
R₁₀ is C₁-C₄ alkyl, or in the case of -N=(SO)R₆R₁₀, R₆ and R₁₀ together with the S to which they attached form a 5-8 membered heterocycloalkyl.

4. The compound of claim 1, wherein the compound is a compound of Formulae IIIa and IIIb:



or a stereoisomer, a tautomer, a N-oxide, a hydrate, an isotope-substituted derivative, a solvate or a pharmaceutically acceptable salt thereof, or a mixture thereof, or a prodrug thereof, wherein A₁, A₄, A₅, A₆, R₁, R₂ and R₄ are as defined in claim 1.

5. The compound of claim 4, wherein the penta-fused hexa-heteroaryl containing A₁, A₄, A₅ and A₆ is:



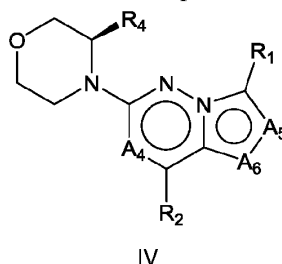
wherein $*_1$, $*_2$ and $*_3$ refer to the attachment position of the group to morpholinyl, R_1 and R_2 of the compound, respectively;

R_1 is an optionally substituted alkylsulfonyl, an optionally substituted aryl, an optionally substituted heterocyclic group, an optionally substituted cycloalkyl, or an optionally substituted heteroaryl;

R_2 is an optionally substituted C_3 - C_6 cycloalkyl, an optionally substituted aryl, an optionally substituted heterocyclic group, or an optionally substituted heteroaryl; and

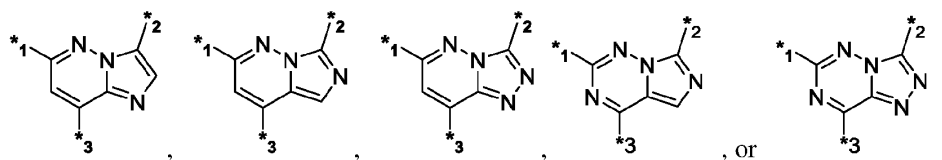
R_4 is C_1 - C_4 alkyl.

6. The compound of claim 1, wherein the compound is a compound of Formula IV:



or a stereoisomer, a tautomer, a N-oxide, a hydrate, an isotope-substituted derivative, a solvate or a pharmaceutically acceptable salt thereof, or a mixture thereof, or a prodrug thereof; wherein A_4 , A_5 , A_6 , R_1 , R_2 and R_4 are as defined in claim 1.

7. The compound of claim 6, wherein the penta-fused hexa-heteroaryl containing A_4 , A_5 and A_6 is:



R_1 is an optionally substituted alkylsulfonyl, an optionally substituted aryl, an optionally substituted heterocyclic group, an optionally substituted cycloalkyl, or an optionally substituted heteroaryl;

R_2 is an optionally substituted C_3 - C_6 cycloalkyl, an optionally substituted aryl, an optionally substituted heterocyclic group, or an optionally substituted heteroaryl; and

R_4 is C_1 - C_4 alkyl.

8. The compound of any of claims 1-7, wherein

R_1 is sulfonyl substituted with C_1 - C_4 alkyl; or pyrazolyl, pyrrolyl, or imidazolyl optionally substituted with 1 or 2 substituents selected from a group consisting of C_1 - C_4 alkyl, halogen, hydroxyl, C_1 - C_4 alkoxy and amino; and/or

Cy or R_2 is an optionally substituted cyclopropyl, an optionally substituted phenyl, an optionally substituted pyrazolyl, an optionally substituted pyrrolyl, an optionally substituted imidazolyl, an optionally substituted triazolyl, an optionally substituted furanyl, an optionally

substituted pyridyl, an optionally substituted pyrimidinyl, an optionally substituted morpholinyl, an optionally substituted dihydropyranyl, an optionally substituted tetrahydropyranyl, or an optionally substituted pyrrolopyridyl; wherein the substituent on R₂ is selected from a group consisting of optionally substituted C₁-C₆ alkyl, cyano, hydroxy, carboxyl, amino, halogen, optionally substituted alkylsulfinyl and optionally substituted alkylsulfonyl.

9. The compound of claim 1, wherein

A₁ is N, A₂ is N, A₃ is C, A₄ is CR₅, A₅ is CR₅, A₆ is N; R₁ is a heteroaryl (preferably pyrazolyl, pyrrolyl and imidazolyl) optionally substituted with 1-2 C₁-C₄ alkyl, such as pyrazolyl optionally substituted by a C₁-C₃ alkyl; R₂ is a heteroaryl (preferably pyrazolyl, pyridinyl, pyrrolopyridinyl and imidazolyl) optionally substituted by one or two C₁-C₄ alkyl, an aryl (preferably phenyl) optionally substituted with 1-2 substituents selected from the group consisting of C₁-C₄ alkylsulfonyl and halogen, or a heterocyclic group (preferably morpholinyl) optionally substituted by one or two C₁-C₄ alkyl, such as 2,6-diC₁-C₄ alkyl-morpholinyl; one of R₃ and R₄ is H, the other is C₁-C₄ alkyl; and each R₅ is independently H or C₁-C₄ alkyl, preferably H; or

A₁ is N, A₂ is N, A₃ is C, A₄ is CR₅, A₅ is N, A₆ is CR₅; R₁ is a heteroaryl (preferably pyrazolyl, pyrrolyl and imidazolyl, more preferably pyrazolyl) optionally substituted with 1-2 C₁-C₄ alkyl, such as pyrazolyl optionally substituted by a C₁-C₃ alkyl; R₂ is a heteroaryl (preferably pyrazolyl, pyrrolyl, pyridinyl, pyrrolopyridinyl, pyrimidinyl, triazolyl, and imidazolyl) optionally substituted by one or two substituents selected from the group consisting of halogen, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylsulfinyl, C₁-C₄ alkyl optionally substituted by one to three halogen atoms, an aryl (preferably phenyl) optionally substituted with 1-2 substituents selected from the group consisting of C₁-C₄ alkyl, -CN, C₁-C₄ alkylsulfonyl and halogen, or a heterocyclic group (preferably morpholinyl, dihydropyranyl and tetrahydropyranyl) optionally substituted by one or two C₁-C₄ alkyl; R₃ and R₄ are independently selected from the group consisting of H and C₁-C₄ alkyl; and each R₅ is independently H or C₁-C₄ alkyl, preferably H; or

A₁ is N, A₂ is N, A₃ is C, A₄ is CR₅, A₅ is N, A₆ is CR₅; R₁ is pyrazolyl optionally substituted by a C₁-C₃ alkyl; R₂ is pyrazolyl optionally substituted by one or two substituents selected from the group consisting of unsubstituted C₁-C₄ alkyl and C₁-C₄ alkyl substituted by one to three halogen atoms; R₃ and R₄ are independently selected from the group consisting of H and C₁-C₄ alkyl; and each R₅ is independently H or C₁-C₄ alkyl, preferably H. In further preferred embodiments, R₂ is pyrazolyl substituted by one or two substituents selected from the group consisting of unsubstituted C₁-C₄ alkyl and C₁-C₄ alkyl substituted by one to three halogen atoms, with at most one of the nitrogen atoms of the pyrazolyl is substituted by the

substituent, preferably one of the nitrogen of the pyrazolyl is substituted. In further or alternative embodiments, one of R₃ and R₄ is H and the other is R-methyl; or

A₁ and A₄-A₆ are independently N or CR₅; A₂ and A₃ are independently C or N; R₁ is pyrazolyl optionally substituted by a C₁-C₃ alkyl; R₂ is pyrazolyl optionally substituted by one or two substituents selected from the group consisting of unsubstituted C₁-C₄ alkyl and C₁-C₄ alkyl substituted by one to three halogen atoms; R₃ and R₄ are independently selected from the group consisting of H and C₁-C₄ alkyl; and each R₅ is independently H or C₁-C₄ alkyl, preferably H.

10. The compound of claim 1, wherein the compound is selected from a group consisting of:

(R)-3-methyl-4-(8-(1-methyl-1H-pyrazol-5-yl)-3-(1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-6-yl)morpholine;

(R)-3-methyl-4-(8-(1-methyl-1H-pyrazol-5-yl)-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(8-(1-ethyl-1H-pyrazol-5-yl)-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(8-(1-isopropyl-1H-pyrazol-5-yl)-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(8-(1-methyl-1H-imidazol-5-yl)-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(8-(6-methylpyridin-3-yl)-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(8-(4-(methylsulfonyl)phenyl)-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(8-(2-fluorophenyl)-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(8-morpholinyl-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(2S,6R)-2,6-dimethyl-4-(6-((R)-3-methylmorpholino)-3-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-8-yl)morpholine;

4-(4-(1-methyl-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

4-(8-(1-methyl-1H-pyrazol-5-yl)-3-(1H-pyrazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(4-(1-methyl-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-methyl-4-(3-(1H-pyrazol-5-yl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)imidazo[1,2-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(8-(1-methyl-1H-pyrazol-5-yl)-3-(1H-pyrazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)morpholine;

(R)-3-methyl-4-(7-(1-methyl-1H-pyrazol-5-yl)-3-(1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrimidin-5-yl)morpholine;

(R)-3-methyl-4-(5-(methylsulfonyl)-1-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrrolo[1,2-c]pyrimidin-3-yl)morpholine;

(R)-3-methyl-4-(1-(methylsulfonyl)-5-(1H-pyrrolo[2,3-b]pyridin-4-yl)imidazo[1,5-c]pyrimidin-7-yl)morpholine;

(R)-3-methyl-4-(6-(methylsulfonyl)-1-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrrolo[1,2-a]pyrazin-3-yl)morpholine;

(R)-3-methyl-4-(3-(methylsulfonyl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyrazin-6-yl)morpholine;

(R)-3-methyl-4-(4-(1-methyl-1H-pyrazol-5-yl)-7-(1H-pyrrol-3-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-methyl-4-(4-(1-methyl-1H-pyrazol-5-yl)-7-(1H-pyrrol-2-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-4-(7-(1H-imidazol-4-yl)-4-(1-methyl-1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-3-methyl-4-(4-(6-methylpyridin-3-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-4-(4-(2-fluorophenyl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1-isopropyl-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4,7-di(1H-pyrazol-5-yl)imidazol[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-3-methyl-4-(4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)imidazo[1,5-a]pyrimidin-2-yl)morpholine;

(R)-3-methyl-4-(4-(1-methyl-1H-pyrazol-5-yl)-7-(1H-pyrazol-3-yl)imidazo[5,1-f][1,2,4]triazin-2-yl)morpholine;

(R)-3-methyl-4-(8-(1-methyl-1H-pyrazol-5-yl)-3-(1H-pyrazol-5-yl)-[1,2,4]triazolo[3,4-f][1,2,4]triazin-6-yl)morpholine;

(R)-3-methyl-4-(4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)imidazo[1,5-a][1,3,5]triazin-2-yl)morpholine;

(R)-4-(4-cyclopropyl-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(S)-3-methyl-4-(4-(1-methyl-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(3R,5R)-3,5-dimethyl-4-(4-(1-methyl-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-methyl-4-(4-(4-(methylsulfonyl)phenyl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-4-(4-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1-ethyl-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-3-methyl-4-(4-(3-methyl-1H-pyrazol-4-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-methyl-4-(7-(3-methyl-1H-pyrazol-5-yl)-4-(6-methylpyridin-3-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-4-(7-(1H-pyrazol-5-yl)-4-(o-tolyl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1,4-dimethyl-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-3-methyl-4-(4-(2-methylpyridin-3-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-4-(4-(3-fluoropyridin-4-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-3-methyl-4-(4-(4-methyl-6-(methylsulfonyl)pyridin-3-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-methyl-4-(4-(4-methylpyrimidin-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-methyl-4-(4-morpholino-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-4-(7-(1H-pyrazol-5-yl)-4-(2-(trifluoromethyl)pyridin-3-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-3-methyl-4-(4-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-methyl-4-(4-(2-methyl-4-(methylsulfonyl)phenyl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(3R)-3-methyl-4-(4-(2-methyl-6-(methylsulfinyl)pyridin-3-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-methyl-4-(4-(3-methylpyridin-4-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-3-(2-(3-methylmorpholino)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-4-yl)benzonitrile;

(R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(7-(1H-pyrazol-5-yl)-4-(tetrahydro-2H-pyran-4-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(7-(1H-pyrazol-5-yl)-4-(1H-pyrrolo[2,3-b]pyridin-4-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1,5-dimethyl-1H-pyrazol-4-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-3-methyl-4-(4-(1-methyl-1H-imidazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)morpholine;

(R)-4-(4-(1,3-dimethyl-1H-pyrazol-4-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1,5-dimethyl-1H-1,2,3-triazol-4-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1-(2-fluoroethyl)-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1-(2-fluoroethyl)-1H-pyrazol-3-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1-(difluoromethyl)-1H-pyrazol-5-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

(R)-4-(4-(1-(difluoromethyl)-1H-pyrazol-3-yl)-7-(1H-pyrazol-5-yl)imidazo[1,5-b]pyridazin-2-yl)-3-methylmorpholine;

or a stereoisomer, a tautomer, a N-oxide, a hydrate, an isotope-substituted derivative, a solvate or a pharmaceutically acceptable salt thereof, or a mixture thereof.

11. Use of the compound of any of claims 1-10 or a stereoisomer, a tautomer, a N-oxide, a hydrate, an isotope-substituted derivative, a solvate or a pharmaceutically acceptable salt thereof, or a mixture thereof or a prodrugs thereof in the manufacture of a medicament for treatment or prevention of an ATR kinase mediated disease; preferably, the disease is cancer.

12. The use of claim 11, wherein the cancer is selected from liver cancer, melanoma, Hodgkin's disease, non-Hodgkin's lymphomas, acute lymphocytic leukemia, chronic

lymphocytic leukemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, choriocarcinoma, mycosis fungoide, head and neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer, or prostatic carcinoma.

13. The use of claim 12, wherein the medicament further comprises at least one known anticancer drug or a pharmaceutically acceptable salt thereof; preferably, the anticancer drug is selected from a group consisting of: busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin, epirubicin, aclarubicin, mitoxantrone, methylhydroxy ellipticine, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, capecitabine, methotrexate, 5-fluoro-2'-deoxy-uridine, fludarabine, nelarabine, ara-C, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, mAb, panitumumab, necitumumab, nivolumab, pembrolizumab, ramucirumab, bevacizumab, pertuzumab, trastuzumab, cetuximab, obinutuzumab, ofatumumab, rituximab, alemtuzumab, ibritumomab, tositumomab, brentuximab, daratumumab, elotuzumab, T-DM1, Ofatumumab, Dinutuximab, Blinatumomab, ipilimumab, avastin, herceptin, mabthera, imatinib, gefitinib, erlotinib, osimertinib, afatinib, ceritinib, alectinib, crizotinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, torisel, everolimus, vorinostat, romidepsin, panobinostat, belinostat, tamoxifen, letrozole, fulvestrant, mitoguanzone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, carfilzomib, ixazomib, vismodegib, sonidegib, denosumab, thalidomide, lenalidomide, Venetoclax, Aldesleukin (recombinant human interleukin-2), sipueucel-T (prostate cancer therapeutic vaccine), palbociclib, olaparib, niraparib, rucaparib, talazoparib and senaparib.

14. The use of claim 11, wherein the medicament is used in combination with radiotherapy.

15. A pharmaceutical composition comprising the compound of any one of claims 1-10 and a pharmaceutically acceptable carrier; preferably the composition further includes at least one known anticancer drug or pharmaceutically acceptable salts thereof; preferably, the at least one known anticancer drug is selected from the group consisting of: busulfan, melphalan, chlorambucil, cyclophosphamide, ifosfamide, temozolomide, bendamustine, cis-platin, mitomycin C, bleomycin, carboplatin, camptothecin, irinotecan, topotecan, doxorubicin,

epirubicin, aclarubicin, mitoxantrone, methylhydroxy ellipticine, etoposide, 5-azacytidine, gemcitabine, 5-fluorouracil, capecitabine, methotrexate, 5-fluoro-2'-deoxy-uridine, fludarabine, nelarabine, ara-C, pralatrexate, pemetrexed, hydroxyurea, thioguanine, colchicine, vinblastine, vincristine, vinorelbine, paclitaxel, ixabepilone, cabazitaxel, docetaxel, mAb, panitumumab, necitumumab, nivolumab, pembrolizumab, ramucirumab, bevacizumab, pertuzumab, trastuzumab, cetuximab, obinutuzumab, ofatumumab, rituximab, alemtuzumab, ibritumomab, tositumomab, brentuximab, daratumumab, elotuzumab, T-DM1, Ofatumumab, Dinutuximab, Blinatumomab, ipilimumab, avastin, herceptin, mabthera, imatinib, gefitinib, erlotinib, osimertinib, afatinib, ceritinib, alectinib, crizotinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, torisel, everolimus, vorinostat, romidepsin, panobinostat, belinostat, tamoxifen, letrozole, fulvestrant, mitoguazone, octreotide, retinoic acid, arsenic trioxide, zoledronic acid, bortezomib, carfilzomib, Ixazomib, vismodegib, sonidegib, denosumab, thalidomide, lenalidomide, Venetoclax, Aldesleukin (recombinant human interleukin-2), sipueucel-T (prostate cancer therapeutic vaccine), palbociclib, olaparib, niraparib, rucaparib, talazoparib and senaparib.