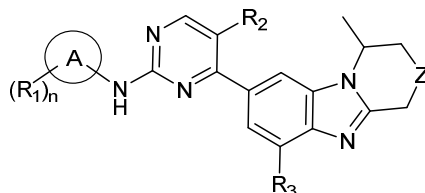


THE CLAIMS

What is claimed is:

1. A compound of Formula I, or a stereoisomer, a tautomer, a polymorph, a solvate, or a pharmaceutically acceptable salt, ~~or a prodrug~~ thereof,



Formula I

wherein,

ring A is a 6-membered heteroaryl comprising one or two heteroatoms of N ~~aryl or heteroaryl~~;

Z is selected from the group consisting of CH₂, NH, O and S;

R₁ is ~~independently~~ selected from the group consisting of ~~hydrogen, halogen, CN, NO₂, OH, NH₂, C₁₋₈alkyl, C₁₋₈alkoxy, C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclyl-(CH₂)_m-, aryl-C₁₋₆alkyl, heteroaryl-C₁₋₆alkyl, NR₁₂R₁₃, NR₁₂-C₁₋₆alkylene-NR₁₂R₁₃, and heterocyclyl-C(O)-~~, wherein the ~~C₁₋₈alkyl, C₁₋₈alkoxy, C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclyl-(CH₂)_m-, aryl-C₁₋₆alkyl, heteroaryl-C₁₋₆alkyl, or and~~ heterocyclyl-C(O)- are each unsubstituted or substituted with at least one substituent selected from halogen, hydroxyl, C₁₋₈alkyl, C₃₋₈cycloalkyl, heterocyclyl, -NR₁₂R₁₃, or -(CH₂)_t-OH;

R₂ and R₃ are each independently selected from H, OH, CN, NO₂, NH₂, halogen, C₁₋₈alkyl, C₁₋₈alkoxy, C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl; wherein the C₁₋₈alkyl, C₁₋₈alkoxy, C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl are each unsubstituted or substituted with at least one substituent selected from halogen, hydroxyl, C₁₋₈alkyl, C₃₋₈cycloalkyl, or heterocyclyl;

R₁₂ and R₁₃ are each independently selected from H, C₁₋₈alkyl, aryl, heteroaryl, heterocyclyl, C₃₋₈cycloalkyl; wherein the C₁₋₈alkyl, aryl, heteroaryl, heterocyclyl, or C₃₋₈cycloalkyl are each unsubstituted or substituted with at least one substituent selected from halogen, hydroxyl, C₁₋₈alkyl, C₃₋₈cycloalkyl, or heterocyclyl;

m is 0, 1, 2, 3 or 4;

n is ~~0, 1, 2, 3 or 4~~;

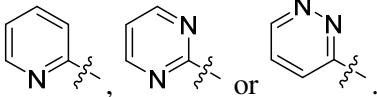
t is 0, 1, 2, 3 or 4.

2. The compound of claim 1, wherein Z is CH₂.

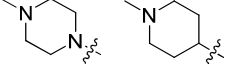
3. The compound of claim 1, wherein Z is O.

~~4. The compound of claim 1, wherein the ring A is a 6-membered heteroaryl comprising one or two heteroatoms of N.~~

~~5.4.~~ The compound of claim 1, wherein the ring A is pyridyl, pyrimidinyl, or pyridazinyl.

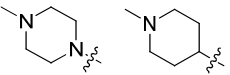
~~6.5.~~ The compound of claim 1, wherein the ring A is , or

~~7.6.~~ The compound of claim 1, wherein R₁ is heterocyclyl-(CH₂)_m-, or heterocyclyl-(CH₂)_m- substituted with C₁₋₈alkyl, -NR₁₂R₁₃, 4 to 6-membered heterocyclyl, C₃₋₆cycloalkyl, or -(CH₂)_t-OH.

~~8.7.~~ The compound of claim 1, wherein R₁ is 5 to 6-membered heterocyclyl-CH₂-, or 5 to 6-membered heterocyclyl-CH₂- substituted with C₁₋₃alkyl, -N(CH₃)₂, -N(CH₂CH₂OH)CH₃, , , , -CH₂OH, -CH₂CH₂OH, or OH.

~~9.8.~~ The compound of claim 1, wherein R₁ is 6-membered heterocyclyl-CH₂-, or 6-membered heterocyclyl-CH₂- substituted with methyl or ethyl.

~~10.9.~~ The compound of claim 1, wherein R₁ is heterocyclyl, or heterocyclyl substituted with C₁₋₈alkyl, NR₁₂R₁₃, 4 to 6-heterocyclyl, C₃₋₆cycloalkyl, or -(CH₂)_t-OH.

~~11.10.~~ The compound of claim 1, wherein R₁ is 5 to 6-membered heterocyclyl, or 5 to 6-membered heterocyclyl substituted with C₁₋₃alkyl, -N(CH₃)₂, -N(CH₂CH₂OH)CH₃, , , , -CH₂OH, -CH₂CH₂OH, or OH.

~~12.11.~~ The compound of claim 1, wherein R₁ is 6-membered heterocyclyl, or 6-membered heterocyclyl substituted with methyl or ethyl.

~~13.12.~~ The compound of claim 1, wherein R₁ is 6-membered heterocyclyl-C(O)- or 6-membered heterocyclyl-C(O)- substituted with C₁₋₃alkyl.

~~14.13.~~ The compound of claim 1, wherein R₁ is 6-membered heterocyclyl-C(O)- substituted with methyl.

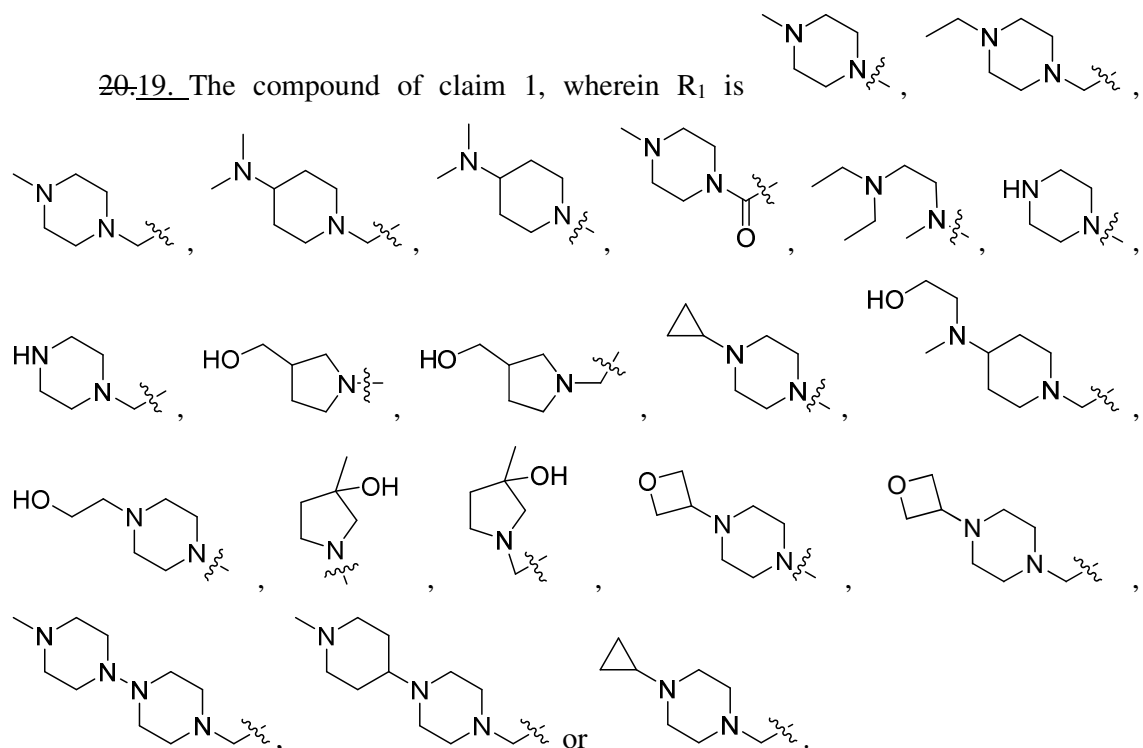
~~15.14.~~ The compound of claim 1, wherein the heterocyclyl comprises one or two heteroatoms of N or O as ring atoms.

~~16.15.~~ The compound of claim 1, wherein the heterocyclyl comprises one or two heteroatoms of N as ring atoms.

~~17.16.~~ The compound of claim 1, wherein R₁ is -NR₁₂-C₁₋₃alkylene-NR₁₂R₁₃.

~~18.17.~~ The compound of claim 1, wherein R₁₂ and R₁₃ are each independently H, (CH₂)₁-OH or C₁₋₃alkyl.

~~19.18.~~ The compound of claim 1, wherein R₁₂ and R₁₃ are each independently OH, CH₂CH₂OH, methyl or ethyl.



~~21.20.~~ The compound of claim 1, wherein m is 1.

~~22.~~ The compound of claim 1, wherein n is 1.

~~23.~~21. The compound of claim 1, wherein t is 0, 1, or 2.

~~24.~~22. The compound of claim 1, wherein R₂ and R₃ are each independently H, OH, halogen, C₁₋₆alkyl, C₁₋₆alkyl substituted with halogen, C₁₋₆alkoxy, C₁₋₆alkoxy substituted with halogen.

~~25.~~23. The compound of claim 1, wherein R₂ and R₃ are each independently H, OH, F, Cl, CH₃, CH₂CH₃, CF₃, OCH₃, or OCF₃.

~~26.~~24. The compound of claim 1, wherein R₂ and R₃ are both F.

~~27.~~25. The compound of claim 1, wherein the compound is:

- 1) 4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)-N-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)pyrimidin-2-amine;
- 2) N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)pyrimidin-2-amine;
- 3) 5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)-N-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)pyrimidin-2-amine;
- 4) 5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)-N-(6-((4-methylpiperazin-1-yl)methyl)pyridin-3-yl)pyrimidin-2-amine;
- 5) 5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)-N-(5-((4-methylpiperazin-1-yl)methyl)pyrimidin-2-yl)pyrimidin-2-amine;
- 6) N-(5-((4-(dimethylamino)piperidin-1-yl)methyl)pyrimidin-2-yl)-5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)pyrimidin-2-amine;
- 7) N-(5-((4-(dimethylamino)piperidin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)pyrimidin-2-amine;
- 8) N-(5-(4-(dimethylamino)piperidin-1-yl)pyridin-2-yl)-5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)pyrimidin-2-amine;
- 9) (2-((5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)pyrimidin-2-yl)amino)pyrimidin-5-yl)(4-methylpiperazin-1-yl)methanone;
- 10) (6-((5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)pyrimidin-2-yl)amino)pyridin-3-yl)(4-methylpiperazin-1-yl)methanone;

- 11) N5-(2-(diethylamino)ethyl)-N2-(5-fluoro-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)pyrimidin-2-yl)-N5-methylpyridine-2,5-diamine;
- 12) N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-4-(6-fluoro-1-methyl-1,2,3,4,4a,5-hexahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)-5-(trifluoromethyl)pyrimidin-2-amine;
- 13) N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-4-(6-fluoro-1-methyl-1,2,3,4,4a,5-hexahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)-5-methylpyrimidin-2-amine;
- 14) 5-chloro-N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-4-(6-fluoro-1-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridin-8-yl)pyrimidin-2-amine;
- 15) 5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)-N-(5-(4-methylpiperazin-1-yl)pyridin-2-yl)pyrimidin-2-amine;
- 16) N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-amine;
- 17) N-(5-(4-(dimethylamino)piperidin-1-yl)pyridin-2-yl)-5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-amine;
- 18) N-(5-((4-(dimethylamino)piperidin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-amine;
- 19) 5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)-N-(5-(piperazin-1-yl)pyridin-2-yl)pyrimidin-2-amine;
- 20) 5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)-N-(5-(piperazin-1-yl)methyl)pyridin-2-yl)pyrimidin-2-amine;
- 21) N-(5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-yl)-6-(4-methylpiperazin-1-yl)pyridazin-3-amine;
- 22) 6-((4-ethylpiperazin-1-yl)methyl)-N-(5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-yl)pyridazin-3-amine;
- 23) (1-(6-((5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-yl)amino)pyridin-3-yl)pyrrolidin-3-yl)methanol;
- 24) (1-((6-((5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)pyrrolidin-3-yl)methanol;
- 25) N-(5-(4-cyclopropylpiperazin-1-yl)pyridin-2-yl)-5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-amine;

- 26) N-(5-((4-cyclopropylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-amine;
- 27) 2-((1-((6-((5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)piperidin-4-yl)(methyl)amino)ethan-1-ol;
- 28) 1-(6-((5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-yl)amino)pyridin-3-yl)-3-methylpyrrolidin-3-ol;
- 29) 1-((6-((5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)pyrimidin-2-yl)amino)pyridin-3-yl)methyl)-3-methylpyrrolidin-3-ol;
- 30) 5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)-N-(5-((4-(oxetan-3-yl)piperazin-1-yl)methyl)pyridin-2-yl)pyrimidin-2-amine;
- 31) 5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)-N-(5-(4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)pyrimidin-2-amine;
- 32) N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(9-fluoro-4-methyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-7-yl)pyrimidin-2-amine;
- 33) 5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)-N-(5-((4'-methyl-[1,1'-bipiperazin]-4-yl)methyl)pyridin-2-yl)pyrimidin-2-amine;
- 34) 5-fluoro-4-(9-fluoro-4-methyl-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazin-7-yl)-N-(5-((4-(1-methylpiperidin-4-yl)piperazin-1-yl)methyl)pyridin-2-yl)pyrimidin-2-amine.

~~28,26.~~ The compound of claim 1, wherein the compound is the (-) enantiomer of the compound.

~~29,27.~~ The compound of claim 1, wherein the compound is the (+) enantiomer of the compound.

~~30,28.~~ A pharmaceutical composition comprising a therapeutically effective amount of the compound according to claim 1, and a pharmaceutically acceptable excipient.

~~31,29.~~ The pharmaceutical composition according to claim ~~30,28~~, wherein a weight ratio of the said compound to the said excipient is in the range from about 0.001 to about 10.

32.30. Use of the compound of claim 1, or the pharmaceutical composition of claim 28, in the manufacture of a medicament for ~~A method of treating a disease mediated by CDK in a subject, comprising administering the compound of claim 1 or the pharmaceutical composition comprising a therapeutically effective amount of the compound according to claim 1 and a pharmaceutically acceptable excipient,~~ wherein the disease mediated by CDK is cancer, wherein the cancer is colon cancer, rectal cancer, mantle cell lymphoma, multiple myeloma, breast cancer, prostate cancer, glioblastoma, squamous cell esophageal cancer, liposarcoma, T-cell lymphoma melanoma, pancreatic cancer, brain cancer or lung cancer.

33.31. The ~~method use~~ of claim ~~32.30~~, wherein the subject is a human.