

Description

Title of Invention: NOVEL HETEROCYCLIC COMPOUNDS AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

Technical Field

- [1] The present disclosure relates to a novel heterocyclic compound useful as Pol-theta (DNA Polymerase-theta, Polθ) inhibitor and a pharmaceutical composition comprising the same.
- [2]

Background Art

- [3] Targeting DNA repair deficiencies has become a proven and effective strategy in cancer treatment. However, DNA repair deficient cancers often become dependent on backup DNA repair pathways, which present an “Achilles heel” that can be targeted to eliminate cancer cells, and is the basis of synthetic lethality. Synthetic lethality is exemplified by the success of Poly ADP-ribose polymerase (PARP) inhibitors in treating BRCA-deficient breast and ovarian cancers.
- [4]
- [5] Robust repair of DNA double-strand breaks (DSBs) is essential for the maintenance of genome stability and cell viability. DSBs can be repaired by one of three main pathways: homologous recombination (HR), non-homologous end-joining (NHEJ), and alternative NHEJ (alt-NHEJ). Microhomology-mediated end-joining (MMEJ) is the most well characterized alt-NHEJ mechanism.
- [6]
- [7] Polθ is distinct among human DNA polymerases, exhibiting not only a C-terminal DNA polymerase domain but also an N-terminal helicase domain. Numerous genetic studies have highlighted a role for polymerase theta (Polθ) in stimulating MMEJ in higher organisms. It has been shown that cancer cells with deficiency in HR, NHEJ, or ATM (Ataxia-telangiectasia mutated; A-T mutated) are highly dependent on Polθ expression. The expression of Polθ is largely absent in normal cells but upregulated in breast, lung, and ovarian cancers. Additionally, the increase of Polθ expression correlates with poor prognosis in breast cancer. Importantly, Polθ is largely repressed in normal tissues but has been shown to be upregulated in matched cancer samples thus correlating elevated expression with disease. Its suppression or inhibition confers radio-sensitivity in tumor cells. Polθ inhibition could conceivably prevent the MMEJ-dependent functional reversion of BRCA2 mutations that underlies the emergence of cisplatin and PARPi (PARP inhibitor) resistance in tumors. Therefore, Polθ is an

attractive target for novel synthetic lethal therapy in cancers containing DNA repair defects and there is a need to provide effective Polθ inhibitors for the treatment of cancer.

[8]

[9] In view of the above, as a result of studying novel compounds, the present inventors found that a compound having a chemical structure different from Polθ inhibitors reported so far has an excellent Polθ inhibitory effect, thereby completing the present disclosure. The compounds belonging to the present disclosure mainly have Polθ inhibitory activity on their own, but do not exclude a possibility of exhibiting a pharmacological action as an efficacious agent by a special body environment or by products of metabolic process, after absorption into the body.

[10]

Disclosure of Invention

Technical Problem

[11] It is one object of the present disclosure to provide a novel heterocyclic compound useful as a Pol-θeta (Polθ) inhibitor, and a pharmaceutical composition comprising the same.

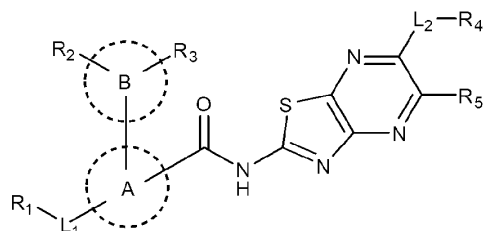
[12]

Solution to Problem

[13] In order to achieve the above objects, there is provided a compound represented by the following Chemical Formula 1, or a pharmaceutically acceptable salt thereof:

[14] [Chemical Formula 1]

[15]



[16] in Chemical Formula 1,

[17] A is a trivalent linker of C₂₋₁₀ heteroaromatic ring containing one to three heteroatoms selected from N, O, or S; or pyridone,

[18] L₁ is a bond; C₁₋₄ alkylene; C₂₋₄ alkenylene; C₂₋₄ alkynylene; -S-; or -O-,

[19] R₁ is hydrogen; C₁₋₄ alkyl; -CONH₂; -CONH(C₁₋₄ alkyl); -CON(C₁₋₄ alkyl)₂; C₂₋₁₀ heterocycloalkyl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl, or C₁₋₄ haloalkyl; or C₂₋₁₀ heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl, or C₁₋₄ haloalkyl,

- [20] B is a bivalent linker of C₆₋₁₀ aromatic ring; C₂₋₁₀ heterocycloalkane ring containing one to three heteroatoms selected from N, O, or S; or C₂₋₁₀ heteroaromatic ring containing one to three heteroatoms selected from N, O, or S,
- [21] R₂ and R₃ are each independently, hydrogen; C₁₋₄ alkyl; C₂₋₄ alkenyl; C₂₋₄ alkynyl; C₁₋₄ haloalkyl; C₁₋₄ alkoxy; halogen; cyano; or C₂₋₆ heterocycloalkyloxy containing one oxygen; or R₂ and R₃ when on adjacent ring vertices, combine to form a C₂₋₆ heterocycloalkyl containing one to three heteroatoms selected from N, O, or S; or C₂₋₆ heteroaryl containing one to three heteroatoms selected from N, O, or S,
- [22] L₂ is a bond; C₁₋₄ alkylene; -CO-; -CONH-; -NHCO-; -S-; or -O-,
- [23] R₄ is -C≡C-R'; C₆₋₁₀ aryl, which is unsubstituted or substituted by halogen, or C₁₋₄ alkoxy; C₃₋₆ cycloalkyl, which is unsubstituted or substituted by hydroxy; C₂₋₁₀ heterocycloalkyl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl, C₁₋₄ haloalkyl, or hydroxy; or C₂₋₁₀ heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by halogen, C₁₋₄ alkyl, or C₁₋₄ haloalkyl,
- [24] R' is hydrogen; C₁₋₄ alkyl, which is unsubstituted or substituted by cyano; (C₁₋₄ alkoxy)C₁₋₄ alkyl; C₁₋₄ hydroxyalkyl; C₂₋₆ heterocycloalkyl containing one oxygen; C₃₋₆ cycloalkyl, which is unsubstituted or substituted by one or two halogens; C₆₋₁₀ aryl, which is unsubstituted or substituted by halogen; C₂₋₁₀ heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl; or C₂₋₁₀ heterocycloalkyl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl,
- [25] R₅ is hydrogen; hydroxy; C₁₋₄ alkyl; C₃₋₆ cycloalkyl; or halogen,
- [26] with the proviso that R₄ is -C≡C-R' when L₂ is a bond.
- [27]
- [28] Further, in order to achieve the above objects, there is provided a pharmaceutical composition comprising the compound, or, a pharmaceutically acceptable salt thereof.
- [29]
- [30] Further, in order to achieve the above objects, there is provided a pharmaceutical composition for the prevention or treatment of cancer, comprising the compound, or a pharmaceutically acceptable salt thereof.
- [31]

Advantageous Effects of Invention

- [32] The compound represented by Chemical Formula 1 according to the present disclosure, or a pharmaceutically acceptable salt thereof can be usefully used for the prevention or treatment of cancers.
- [33]

Best Mode for Carrying out the Invention

[34] Hereinafter, embodiments of the present disclosure will be described in more detail to facilitate understanding of the invention.

[35]

[36] Meanwhile, the present disclosure provides a compound represented by Chemical Formula 1, or a pharmaceutically acceptable salt thereof.

[37]

[38] Preferably, A is a trivalent linker of 1,3-benzodioxole; 2,3-dihydrobenzofuran; 2-pyridone; imidazo[1,5-a]pyridine; imidazole; pyridazine; or pyridine.

[39]

[40] Preferably, L₁ is a bond; -CH₂-; -C≡C-; or -O-.

[41]

[42] Preferably, R₁ is hydrogen; CH₃; -CONH₂; -CONH(CH₃); -CON(CH₃)₂; or any ring selected from the group consisting of 4,7-diazaspiro[2.5]octan-8-onyl, 7-azaspiro[3.5]nonan-6-onyl, 2-pyridonyl, oxadiazolyl, oxopyridazinyl, pyrazolyl, or thiazolyl, which ring is unsubstituted or substituted by CH₃, or CF₃.

[43]

[44] Preferably, B is a bivalent linker of 1,3-benzodioxole; 2-oxa-5-azabicyclo[4.1.0]heptane; 3,4-dihydro-2H-benzo[b][1,4]oxazine; 3-oxa-8-azabicyclo[3.2.1]octane; 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine; 4-oxa-7-azaspiro[2.5]octane; benzene; benzo[d]oxazole; benzo[d]thiazole; morpholine; piperazin-2-one; pyrazole; or pyridine.

[45]

[46] Preferably, R₂ and R₃ are each independently, hydrogen; CH₃; -C≡CH; CHF₂; CF₃; OCH₃; F; Cl; cyano; or (oxetanyl)oxy.

[47]

[48] Preferably, L₂ is a bond; -CH₂-; -CO-; -CONH-; -NHCO-; -S-; or -O-.

[49]

[50] Preferably, R₄ is -C≡C-R'; and R' is hydrogen; methyl; ethyl; propyl; isopropyl; butyl; isobutyl; tert-butyl; -CH(CH₃)(CN); -CH₂-O-CH₃; 2-hydroxyprop-2-yl; 1H-pyrrolo[2,3-b]pyridinyl, which is unsubstituted or substituted by CH₃; oxetanyl; tetrahydrofuranyl; cyclopropyl, which is unsubstituted or substituted by one or two F; cyclobutyl, which is unsubstituted or substituted by one or two F; cyclopentyl, cyclohexyl; spiro[2.2]pentanyl; phenyl, which is unsubstituted or substituted by Cl; pyrazolyl, which is unsubstituted or substituted by CH₃; or pyridinyl.

[51]

[52] Preferably, R_4 is phenyl, which is unsubstituted or substituted by Cl and OCH_3 ; cyclohexyl, which is unsubstituted or substituted by hydroxy; hexahydrofuro[2,3-b]furanlyl; bicyclo[2.2.2]octanyl, which is unsubstituted or substituted by hydroxy; 2,3-dihydrobenzofuranlyl; 4-oxaspiro[2.4]heptanyl; tetrahydrofuranlyl; 1,3-benzodioxolyl; or pyridinyl, which is unsubstituted or substituted by Cl.

[53]

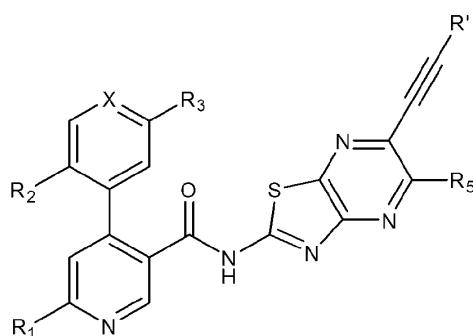
[54] Preferably, R_5 is hydrogen; hydroxy; CH_3 ; cyclopropyl; or Cl.

[55]

[56] Preferably, the Chemical Formula 1 is represented by Chemical Formula 2 below:

[57] [Chemical Formula 2]

[58]



[59] in Chemical Formula 2,

[60] X is N, or CH,

[61] R_1 is C_{1-4} alkyl; or C_{2-10} heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C_{1-4} alkyl, or C_{1-4} haloalkyl,

[62] R_2 is C_{1-4} alkoxy,

[63] R_3 is C_{1-4} haloalkyl; or halogen,

[64] R' is hydrogen; C_{1-4} hydroxyalkyl; C_{2-6} heterocycloalkyl containing one oxygen; C_{3-6} cycloalkyl, which is unsubstituted or substituted by one or two halogens; or C_{2-10} heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C_{1-4} alkyl,

[65] R_5 is hydrogen; hydroxy; C_{1-4} alkyl; C_{3-6} cycloalkyl; or halogen.

[66]

[67] Representative examples of the compound represented by Chemical Formula 1 are as follows:

[68] 1) 2'-chloro-N-(6-ethynylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

[69] 2) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

- [70] 3) 2'-chloro-5'-methoxy-6-methyl-N-(6-((1-methyl-1H-pyrazol-4-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [71] 4) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [72] 5) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide,
- [73] 6) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-(trifluoromethyl)-4,4'-bipyridine-3-carboxamide,
- [74] 7) 2'-chloro-N-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [75] 8) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(4-methyl-6-oxopyridazin-1(6H)-yl)nicotinamide,
- [76] 9) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide,
- [77] 10) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)nicotinamide,
- [78] 11) 2'-chloro-N-(5-cyclopropyl-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [79] 12) 2'-chloro-N-(6-(cyclopropylethynyl)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [80] 13) 2'-chloro-5'-methoxy-6-methyl-N-(6-(oxetan-3-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [81] 14) 2'-chloro-5'-methoxy-N-(6-(3-methoxyprop-1-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4,4'-bipyridine-3-carboxamide,
- [82] 15) 2'-chloro-5'-methoxy-6-methyl-N-(6-(pyridin-2-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [83] 16) 2'-chloro-N-(6-((4-chlorophenyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [84] 17) 2'-chloro-5'-methoxy-6-methyl-N-(6-(spiro[2.2]pentan-1-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [85] 18) 2'-chloro-5'-methoxy-6-methyl-N-(6-((tetrahydrofuran-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [86] 19) 2'-chloro-5'-methoxy-6-methyl-N-(6-((1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [87] 20) 2'-chloro-N-(5-chloro-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [88] 21) 2'-chloro-N-(6-(cyclopropylethynyl)-5-hydroxythiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

- [89] 22) 2'-chloro-5'-methoxy-6-methyl-N-(6-(tetrahydrofuran-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [90] 23) 2'-chloro-N-(6-((5-chloropyridin-2-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [91] 24) 2'-chloro-5'-methoxy-6-methyl-N-(6-((tetrahydrofuran-3-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [92] 25) N-(6-(4-oxaspiro[2.4]heptan-6-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [93] 26) 2'-chloro-N-(6-(5-chloropyridin-2-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [94] 27) 2'-chloro-N-(6-(4-chloro-3-methoxyphenoxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [95] 28) 2-(2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamido)-N-(tetrahydrofuran-3-yl)thiazolo[4,5-b]pyrazine-6-carboxamide,
- [96] 29) 2'-chloro-5'-methoxy-6-methyl-N-(6-(tetrahydrofuran-3-carboxamido)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [97] 30) 2'-chloro-5'-methoxy-6-methyl-N-(6-(morpholine-4-carbonyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [98] 31) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(4-methyl-6-oxopyridazin-1(6H)-yl)-4,4'-bipyridine-3-carboxamide,
- [99] 32) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-(4-methyl-6-oxopyridazin-1(6H)-yl)nicotinamide,
- [100] 33) 2'-chloro-N-(6-(5-chloropyridin-2-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(4-methyl-6-oxopyridazin-1(6H)-yl)-4,4'-bipyridine-3-carboxamide,
- [101] 34) 2'-chloro-5'-methoxy-6-(4-methyl-6-oxopyridazin-1(6H)-yl)-N-(6-(tetrahydrofuran-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [102] 35) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide,
- [103] 36) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)-4,4'-bipyridine-3-carboxamide,
- [104] 37) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2,3-dihydrobenzofuran-6-carboxamide,
- [105] 38) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-4-carboxamide,
- [106] 39) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(6-oxo-7-azaspiro[3.5]nonan-7-yl)-4,4'-bipyridine-3-carboxamide,

- [107] 40) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- [108] 41) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- [109] 42) 1-(2-amino-2-oxoethyl)-5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- [110] 43) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-(2-(methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- [111] 44) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-(2-(dimethylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- [112] 45) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(thiazol-2-ylloxy)-4,4'-bipyridine-3-carboxamide,
- [113] 46) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(oxetan-3-ylethynyl)-4,4'-bipyridine-3-carboxamide,
- [114] 47) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-((1-methyl-1H-pyrazol-4-yl)ethynyl)-4,4'-bipyridine-3-carboxamide,
- [115] 48) 7-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)imidazo[1,5-a]pyridine-6-carboxamide,
- [116] 49) 1-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1H-imidazole-5-carboxamide,
- [117] 50) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)pyridazine-4-carboxamide,
- [118] 51) 6-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)benzo[d][1,3]dioxole-5-carboxamide,
- [119] 52) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4-morpholinonicotinamide,
- [120] 53) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [121] 54) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-(trifluoromethyl)-4,4'-bipyridine-3-carboxamide,
- [122] 55) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide,

- [123] 56) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methylnicotinamide,
- [124] 57) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-ethynyl-2-methoxyphenyl)-6-methylnicotinamide,
- [125] 58) 4-(5-cyano-2-methoxyphenyl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- [126] 59) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4-(2-(oxetan-3-yloxy)phenyl)nicotinamide,
- [127] 60) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinamide,
- [128] 61) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-methylnicotinamide,
- [129] 62) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-6-methylnicotinamide,
- [130] 63) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide,
- [131] 64) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4-(2-methyl-3-oxopiperazin-1-yl)nicotinamide,
- [132] 65) 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- [133] 66) 4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- [134] 67) 4-(benzo[d]thiazol-7-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- [135] 68) 4-(benzo[d]oxazol-7-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- [136] 69) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-methylnicotinamide,
- [137] 70) 2'-chloro-5'-methoxy-6-methyl-N-(6-(prop-2-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [138] 71) 2'-chloro-N-(6-(3-cyclopropylprop-2-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [139] 72) 2'-chloro-5'-methoxy-6-methyl-N-(6-(3-(oxetan-3-yl)prop-2-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [140] 73) 2'-chloro-5'-methoxy-6-methyl-N-(6-(3-(1-methyl-1H-pyrazol-4-yl)prop-2-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [141] 74) 2'-chloro-N-(6-(3-cyanobut-1-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

- [142] 75) 2'-chloro-N-(5-chloro-6-((tetrahydrofuran-3-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [143] 76) 2'-chloro-5'-methoxy-6-methyl-N-(5-methyl-6-((tetrahydrofuran-3-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [144] 77) 2'-chloro-5'-methoxy-6-methyl-N-(5-methyl-6-(tetrahydrofuran-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [145] 78) 2'-chloro-N-(6-((5-chloropyridin-2-yl)methyl)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [146] 79) 2'-chloro-N-(6-(5-chloropyridin-2-yloxy)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [147] 80) 2'-chloro-5'-methoxy-6-methyl-N-(6-(tetrahydrofuran-3-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [148] 81) 2'-chloro-5'-methoxy-6-methyl-N-(5-methyl-6-(tetrahydrofuran-3-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- [149] 82) 2'-chloro-N-(6-(5-chloropyridin-2-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [150] 83) 2'-chloro-N-(6-(5-chloropyridin-2-ylthio)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [151] 84) 2'-chloro-N-(6-(4-hydroxycyclohexyloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [152] 85) 2'-chloro-N-(6-(hexahydrofuro[2,3-b]furan-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [153] 86) 2'-chloro-N-(6-(5-hydroxybicyclo[2.2.2]octan-2-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [154] 87) N-(6-(benzo[d][1,3]dioxol-4-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [155] 88) 2'-chloro-N-(6-(2,3-dihydrobenzofuran-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [156] 89) 2'-chloro-N-(6-(4-chloro-3-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [157] 90) 2'-chloro-N-(6-((4-hydroxycyclohexyl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [158] 91) N-(6-(4-oxaspiro[2.4]heptan-6-ylmethyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [159] 92) 2'-chloro-N-(6-((hexahydrofuro[2,3-b]furan-3-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [160] 93) 2'-chloro-N-(6-((5-hydroxybicyclo[2.2.2]octan-2-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

- [161] 94) 2'-chloro-N-(6-(4-chloro-3-methoxyphenylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [162] 95) 2'-chloro-N-(6-(4-hydroxycyclohexylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [163] 96) N-(6-(4-oxaspiro[2.4]heptan-6-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [164] 97) 2'-chloro-N-(6-(hexahydrofuro[2,3-b]furan-3-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [165] 98) 2'-chloro-N-(6-(5-hydroxybicyclo[2.2.2]octan-2-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- [166] 99) 4-(2-chloro-5-methoxypyridin-4-yl)-N-[6-(cyclopentylethynyl)[1,3]thiazolo[4,5-b]pyrazin-2-yl]-6-methylpyridine-3-carboxamide,
- [167] 100) 4-(2-chloro-5-methoxypyridin-4-yl)-N-[6-(3,3-dimethylbut-1-ynyl)[1,3]thiazolo[4,5-b]pyrazin-2-yl]-6-methylpyridine-3-carboxamide,
- [168] 101) 2'-chloro-N-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide, and
- [169] 102) 4-(2-chloro-5-methoxypyridin-4-yl)-N-[6-(cyclohexylethynyl)[1,3]thiazolo[4,5-b]pyrazin-2-yl]-6-methylpyridine-3-carboxamide.

[170]

- [171] In addition, the compounds of the present disclosure may exist in the form of salts, especially pharmaceutically acceptable salts. As salts, salts commonly used in the art, such as acid addition salts formed by pharmaceutically acceptable free acids can be used without limitation. The term "pharmaceutically acceptable salt" as used herein refers to any organic or inorganic addition salt of the compound represented by Chemical Formula 1, whose concentration is relatively non-toxic and harmless to a patient and activates effectively and whose side effects do not degrade the beneficial efficacy of the above compound.

[172]

- [173] As the free acid, an organic acid and an inorganic acid can be used. Examples of the inorganic acids include hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, tartaric acid, and the like. Examples of the organic acids include methanesulfonic acid, p-toluenesulfonic acid, acetic acid, trifluoroacetic acid, maleic acid, succinic acid, oxalic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, propionic acid, citric acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonic acid, vanillic acid, hydroiodic acid, and the like, but are not limited thereto. Preferably, the salt may be a hydrochloride salt.

[174]

[175] Further, a pharmaceutically acceptable metal salt can be obtained by a conventional method using a base. For example, the compound represented by Chemical Formula 1 is dissolved in an excess amount of an alkali metal hydroxide or an alkaline earth metal hydroxide solution, the non-soluble salt is filtered, and then the filtrate is evaporated and dried to obtain a pharmaceutically acceptable metal salt. At this time, it is particularly preferable to prepare a sodium salt, a potassium salt, or a calcium salt as the metal salt.

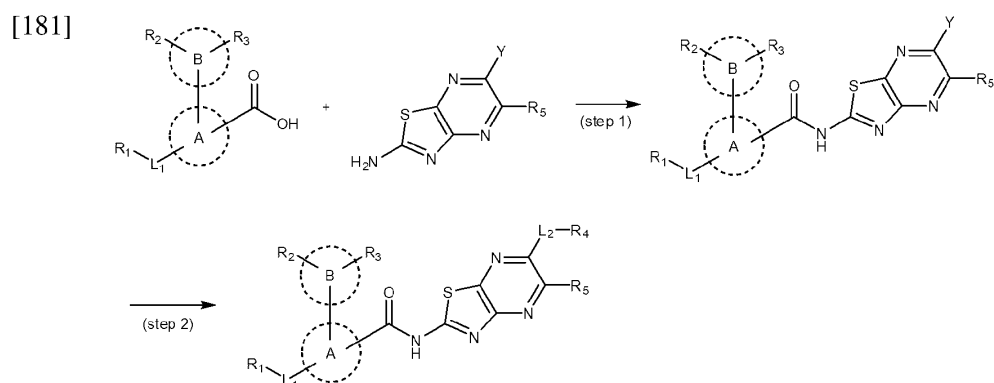
[176]

[177] In addition, a pharmaceutically unacceptable salt or solvate of the compound of Chemical Formula 1 may be used as an intermediate when preparing the compound of Chemical Formula 1, or the pharmaceutically acceptable salt or the solvate thereof.

[178]

[179] In one embodiment, the compound represented by Chemical Formula 1 may be prepared through Reaction Formula 1 below.

[180] [Reaction Scheme 1]



[182]

[183] In Reaction Scheme 1, A , L_1 , R_1 , B , R_2 , R_3 , L_2 , R_4 , and R_5 are as defined above, and Y is halogen. Preferably, Y is bromo, or chloro.

[184]

[185] Step 1 is a step of preparing a compound represented by Chemical Formula 3' by reacting a compound represented by Chemical Formula 1' with a compound represented by Chemical Formula 2', which is the amidation reaction. Step 2 is a step of preparing a compound represented by Chemical Formula 1, in which $-L_2-R_4$ is substituted while a halogen (Y) is eliminated.

[186]

[187] The above preparation method will be more specifically described in the Examples described hereinafter.

[188]

- [189] According to a further embodiment of the present disclosure, there is provided a pharmaceutical composition comprising the compound represented by Chemical Formula 1, or a pharmaceutically acceptable salt thereof.
- [190]
- [191] According to a further embodiment of the present disclosure, there is provided a pharmaceutical composition for the prevention or treatment of cancer diseases, which is effective for Polθ inhibitory actions, comprising the compound represented by Chemical Formula 1, or a pharmaceutically acceptable salt thereof as an active ingredient.
- [192]
- [193] In this case, the cancer may be blood cancer, extranodal marginal zone B-cell lymphoma, glioblastoma, lymphoplasmacytic lymphoma, acute myelogenous leukemia, macroglobulinemia, B cell lymphoma, chronic lymphocytic leukemia, follicular lymphoma, non-Hodgkin's lymphoma, diffuse large B cell lymphoma, hairy cell leukemia, mantle cell lymphoma, glioblastoma, bladder cancer, pancreatic cancer, ovarian cancer, colorectal cancer, renal cancer, gastric cancer, transitional cell carcinoma, a carcinoid tumor, breast cancer, non-small cell lung cancer, or multiple myeloma.
- [194]
- [195] As used herein, the term "prevention" refers to any act to delay or inhibit occurrence, spread, or recurrence of the above-mentioned diseases by administration of the composition of the present disclosure, and "treatment" refers to any act to improve or change the symptoms of the above diseases for the better by administration of the composition of the present disclosure.
- [196]
- [197] The pharmaceutical composition according to the present disclosure can be formulated in types for oral or parenteral administrations according to a standard pharmaceutical practice. These formulations may contain additives such as a pharmaceutically acceptable carrier, an adjuvant, or a diluent in addition to the active ingredient.
- [198]
- [199] Suitable carriers include, for example, physiological saline, polyethylene glycol, ethanol, vegetable oil, isopropyl myristate, and the like. Diluents include, for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine, and the like, but are not limited thereto. Further, the compounds of the present disclosure can be dissolved in oils, propylene glycol, or other solvents commonly used in the preparation of injection solutions. Furthermore, the compounds of the present disclosure can be formulated in ointments or creams for topical application.

[200]

[201] A preferred dose of the compound of the present disclosure may be varied according to the condition and weight of a patient, the severity of a disease, the type of a drug, and the route and duration of administration, but it may be suitably selected by those skilled in the art. In order to achieve the desirable effects, however, the compound of the present disclosure may be administrated daily at a dose of 0.0001 to 100 mg/kg (body weight), and preferably 0.001 to 100 mg/kg (body weight). The administration may be performed once a day or in divided doses each day through an oral or parenteral route.

[202]

[203] Depending on the method of administration, the pharmaceutical composition may contain the compound of the present disclosure in an amount of 0.001 to 99 % by weight, preferably 0.01 to 60 % by weight.

[204]

[205] The pharmaceutical composition according to the present disclosure may be administered to mammals such as a rat, a mouse, a domestic animal, or a human, through various routes. The administration may be carried out through all possible methods, for example, oral, rectal, intravenous, intramuscular, subcutaneous, intra-endometrial, intracerebroventricular injection.

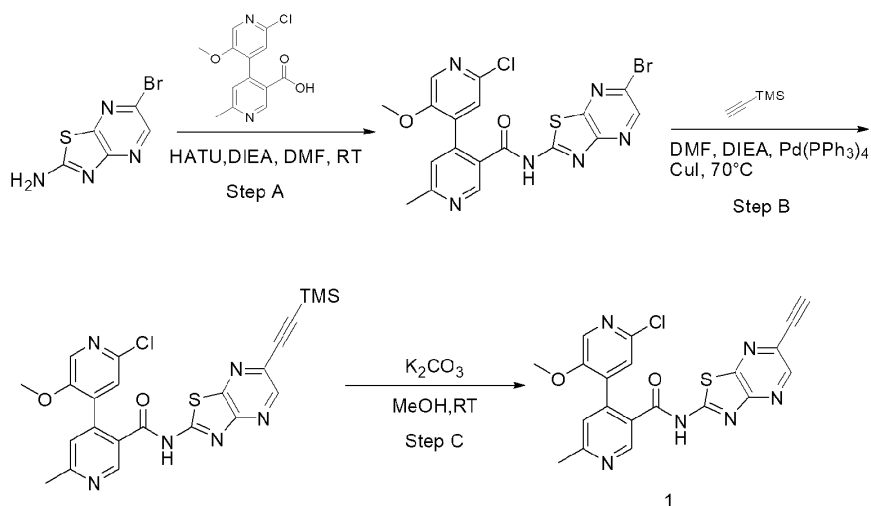
[206]

[207] Below, the present disclosure will be described in more detail by way of examples. However, these examples are provided for illustrative purposes only, and should not be construed as limiting the scope of the present disclosure to these examples.

[208]

[209] Example 1: Synthesis of Compound 1

[210]



[211]

[212] **Step A: N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide**

[213] To a solution of 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxylic acid (241.22 mg, 0.87 mmol) in DMF (2 mL) were added 6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-amine (200 mg, 0.87 mmol), DIEA (335.59 mg, 2.60 mmol) and HATU (493.67 mg, 1.30 mmol) at 25 °C, the reaction was stirred at 25 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by pre-HPLC (FA condition) to give N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (40.0 mg, 0.08 mmol) as yellow solid.

[214] LCMS: m/z (M+H)⁺ = 491.0/493.0

[215]

[216] **Step B: 4-(2-chloro-5-methoxypyridin-4-yl)-6-methyl-N-{6-[(trimethylsilyl)ethynyl][1,3]thiazolo[4,5-b]pyrazin-2-yl}pyridine-3-carboxamide**

[217] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (10 mg, 0.02 mmol) in DMF (1 mL) were added CuI (0.77 mg), ethynyltrimethylsilane (2.00 mg, 0.02 mmol), DIEA (0.01 mL, 0.04 mmol) and tetrakis(triphenylphosphine)palladium(0) (4.70 mg) at 25 °C, the mixture was degassed with N₂ three times and stirred at 70 °C for 1 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by pre-HPLC (FA condition) to give 4-(2-chloro-5-methoxypyridin-4-yl)-6-methyl-N-{6-[(trimethylsilyl)ethynyl][1,3]thiazolo[4,5-b]pyrazin-2-yl}pyridine-3-carboxamide (8 mg, 0.02 mmol) as white solid.

[218] LCMS: m/z (M+H)⁺ = 509.2

[219]

[220] **Step C: 2'-chloro-N-(6-ethynylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide**

[221] To a solution of 4-(2-chloro-5-methoxypyridin-4-yl)-6-methyl-N-{6-[(trimethylsilyl)ethynyl][1,3]thiazolo[4,5-b]pyrazin-2-yl}pyridine-3-carboxamide (8 mg, 0.02 mmol) in MeOH (1 mL) was added K₂CO₃ (5.43 mg, 0.04 mmol) at 25 °C, the reaction was stirred at 25 °C for 1 h. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by pre-HPLC (FA condition) to give 2'-chloro-N-(6-ethynylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide (3.1 mg, 0.01 mmol) as white solid.

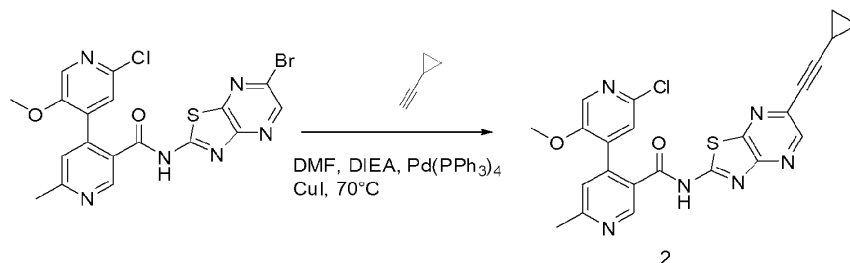
[222] ¹H NMR (400 MHz, MeOD) δ 8.89 (s, 1H), 8.69 (s, 1H), 8.10 (s, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 4.00 (s, 1H), 3.73 (s, 3H), 2.71 (s, 3H)

[223] LCMS: m/z (M+H)⁺ = 437.2

[224]

[225] **Example 2: Synthesis of Compound 2**

[226]



[227] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (20 mg, 0.04 mmol) in DMF (1 mL) were added ethynylcyclopropane (2.69 mg, 0.03 mmol), CuI (1.55 mg, 0.01 mmol), DIEA (0.01 mL, 0.08 mmol) and tetrakis(triphenylphosphine)palladium(0) (9.40 mg, 0.01 mmol) at 25 °C, the mixture was degassed with N₂ three times and stirred at 70 °C for 1 h. After filtration, the mixture was concentrated under reduced pressure. The residue was purified by pre-HPLC (FA condition) to give 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide (4.5 mg, 0.01 mmol) as a white solid.

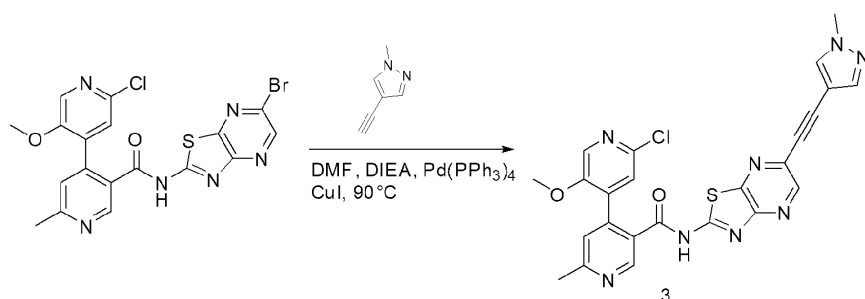
[228] ¹H NMR (400 MHz, MeOD) δ 8.85 (s, 1H), 8.54 (s, 1H), 8.08 (s, 1H), 7.53 (s, 1H), 7.48 (s, 1H), 3.71 (s, 3H), 2.69 (s, 3H), 1.63 - 1.54 (m, 1H), 1.00 (s, 2H), 0.88 (s, 2H)

[229] LCMS: m/z (M+H)⁺ = 477.2

[230]

[231] **Example 3: Synthesis of Compound 3**

[232]



[233] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (10 mg, 0.02 mmol) in DMF (1 mL) were added 4-ethynyl-1-methylpyrazole (2.55 mg, 0.02 mmol), DIEA (0.01 mL, 0.04 mmol), CuI (0.76 mg, 0.001 mmol) and tetrakis(triphenylphosphine)palladium(0) (4.62 mg) at 25 °C, the mixture was degassed with N₂ three times and stirred at 90 °C for 1 h. After filtration, the filtrate was concentrated under reduced

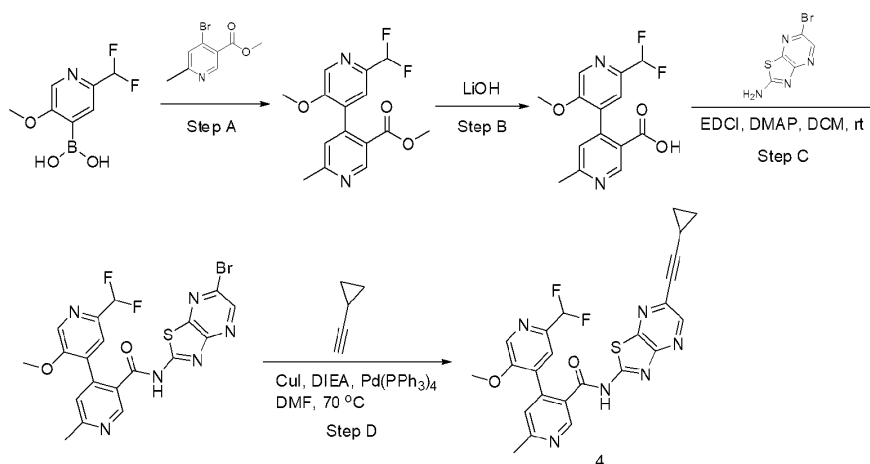
pressure. The residue was purified by pre-HPLC (NH_4HCO_3 condition) to give 2'-chloro-5'-methoxy-6-methyl-N-((1-methyl-1H-pyrazol-4-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide (0.41 mg, 0.001 mmol) as yellow solid.

[234] LCMS: m/z ($M+H$)⁺ = 517.2

[235]

[236] **Example 4: Synthesis of Compound 4**

[237]



[238]

[239] **Step A: methyl 2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate**

[240] To a solution of [2-(difluoromethyl)-5-methoxypyridin-4-yl]boranediol (200 mg, 0.99 mmol) in Dioxane (8.0 mL) were added methyl 4-bromo-6-methylpyridine-3-carboxylate (249 mg, 1.08 mmol), potassium carbonate (408 mg, 2.95 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (144 mg, 0.20 mmol) at 25 °C under N_2 , the mixture was stirred at 100 °C for 2 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether: EtOAc = 10:1 to 5:1) to give methyl 2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (180 mg, 0.58 mmol) as yellow oil.

[241] LCMS: m/z ($M+H$)⁺ = 309.1

[242]

[243] **Step B: 2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylic acid**

[244] To a stirred solution methyl 2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylate (180 mg, 0.58 mmol) in MeOH/ H_2O (4:1) (5.0 mL) was added lithium hydroxide (28 mg, 1.17 mmol) at 25 °C, the mixture was stirred at 25 °C for 18 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (TFA condition) to give 2'-(difluoromethyl)-

5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylic acid (130 mg, 0.44 mmol) as white solid.

[245] LCMS: m/z (M+H)⁺ = 295.0

[246]

[247] **Step C: N-(6-bromothiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide**

[248] To a solution of 2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxylic acid (130 mg, 0.44 mmol) in DCM (5 mL) were added 6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-amine (122 mg, 0.53 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (127 mg, 0.66 mmol) and 4-dimethylaminopyridine (161 mg, 1.32 mmol) at 25 °C, the mixture was stirred at 25 °C for 18 h. Upon completion, the reaction was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: petroleum ether: EtOAc = 10: 1 to 3: 1) to give N-(6-bromothiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (70 mg) as yellow oil.

[249] LCMS: m/z (M+H)⁺ = 507.0/509.0

[250]

[251] **Step D: N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide**

[252] To a solution of N-(6-bromothiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (70 mg, 0.14 mmol) in N,N-dimethylmethanamide (5 mL) were added ethynylcyclopropane (18 mg, 0.27 mmol), copper(I) iodide (10 mg, 0.05 mmol), tetrakis(triphenylphosphine)palladium(0) (31 mg, 0.03 mmol), N,N-diisopropylethylamine (53 mg, 0.41 mmol) at 25 °C under N₂, the mixture was stirred at 70 °C under N₂ for 18 h. After filtration, the mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC ((ACN: water (1% FA)) to give N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide (0.82 mg, 0.01 mmol) as white solid.

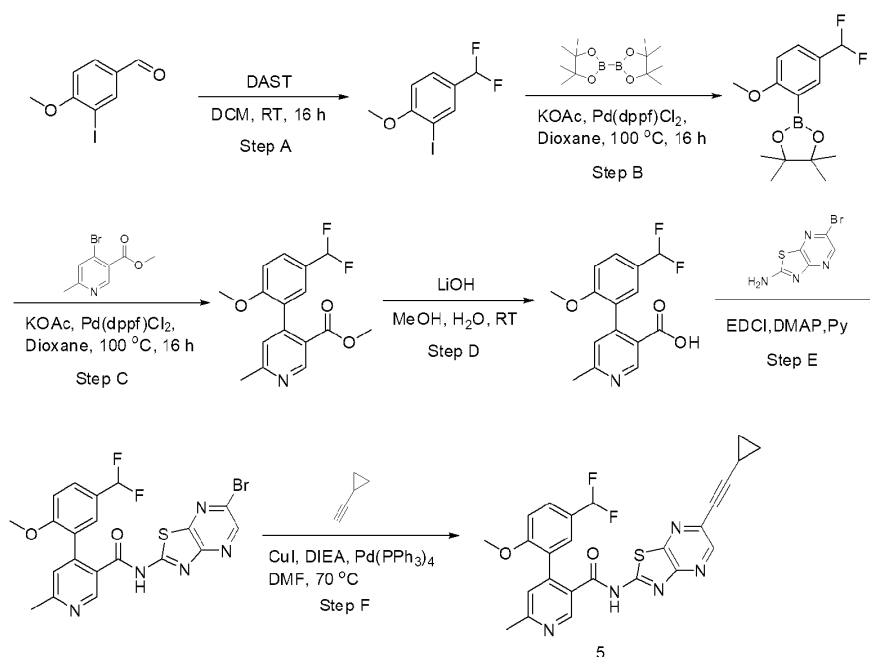
[253] ¹H NMR (400 MHz, DMSO) δ 9.04 (s, 1H), 8.40 (d, J = 21.6 Hz, 1H), 8.15 (s, 1H), 7.59 (s, 1H), 7.28 (s, 1H), 7.22 - 6.38 (m, 2H), 3.69 (s, 3H), 2.57 (s, 3H), 1.24 (s, 1H), 0.94 - 0.92 (m, 2H), 0.82 - 0.79 (m, 2H)

[254] LCMS: m/z (M+H)⁺ = 493.2

[255]

[256] **Example 5: Synthesis of Compound 5**

[257]



[258]

[259] **Step A: 4-(difluoromethyl)-2-iodo-1-methoxybenzene**

[260] To a solution of 3-iodo-4-methoxybenzaldehyde (5000 mg, 19.08 mmol) in DCM (50 mL) was added DAST (5.04 mL, 38.16 mmol) at 0 °C, the reaction was stirred at 25 °C for 16 h. Upon completion, the mixture was quenched with NaHCO₃ aq. (100 mL) and extracted with DCM (100 mL * 2), the organic layers were washed with brine (100 mL) and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Pet.ether: EtOAc = 100:1 to 10:1) to give 4-(difluoromethyl)-2-iodo-1-methoxybenzene (3400 mg, 10.77 mmol) as colorless oil.

[261]

[262] **Step B: 2-[5-(difluoromethyl)-2-methoxyphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**

[263] To a solution of 4-(difluoromethyl)-2-iodo-1-methoxybenzene (3400 mg, 11.97 mmol) in dioxane (40 mL) were added KOAc (3524.25 mg, 35.91 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (6079.40 mg, 23.94 mmol) and Pd(dppf)Cl₂ (875.87 mg, 1.20 mmol) at 25 °C, the reaction was degassed N₂ three times and stirred at 100 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Pet.ether: EtOAc = 10:1 to 5:1) to give 2-[5-(difluoromethyl)-2-methoxyphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3100 mg, 9.82 mmol) as colorless oil.

[264] LCMS: m/z (M+H)⁺ = 285.2

[265]

[266] **Step C: methyl 4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxylate**

[267] To a solution of methyl 4-chloro-6-methylpyridine-3-carboxylate (2200 mg, 11.85 mmol) in dioxane (30 mL) were added 2-[5-(difluoromethyl)-2-methoxyphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3704.25 mg, 13.04 mmol), KOAc (3489.70 mg, 35.56 mmol) and PdCl₂(dppf) (867.28 mg, 1.19 mmol) at 25 °C. The reaction was degassed N₂ three times and stirred at 100 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Pet.ether: EtOAc = 10:1 to 1:2) to give methyl 4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxylate (3100 mg, 10.09 mmol) as a white solid.

[268] LCMS: m/z (M+H)⁺ = 308.2

[269]

[270] **Step D: 4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxylic acid**

[271] To a solution of methyl 4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxylate (2700 mg, 8.79 mmol) in MeOH (20 mL) and Water (5 mL) was added LiOH (737.66 mg, 17.58 mmol), the reaction was stirred at 25 °C for 16 h. Upon completion, the mixture was concentrated under vacuum. The residue was purified by pre-HPLC (FA condition) to give 4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxylic acid (510 mg, 1.63 mmol) as a white solid.

[272] LCMS: m/z (M+H)⁺ = 294.2

[273]

[274] **Step E: N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxamide**

[275] To a solution of 6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-amine (100 mg, 0.43 mmol) in Py (2 mL) were added 4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxylic acid (126.92 mg, 0.43 mmol), DMAP (52.87 mg, 0.43 mmol) and EDCI (165.92 mg, 0.87 mmol) at 25 °C, the reaction was stirred at 35 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (DCM: MeOH = 20:1 to 10:1) to give N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxamide (95 mg, 0.17 mmol) as a yellow solid.

[276] LCMS: m/z (M+H)⁺ = 506.0/508.0

[277]

[278] **Step F: N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide**

[279] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[5-(difluoromethyl)-2-methoxyphenyl]-6-methylpyridine-3-carboxamide (50 mg, 0.10 mmol) in DMF (1 mL) were added ethynylcyclopropane (0.02 mL, 0.20 mmol), CuI (3.76 mg, 0.02 mmol), DIEA (0.03 mL, 0.20 mmol) and tetrakis(triphenylphosphine)palladium(0) (22.82 mg, 0.02 mmol) at 25 °C, the reaction was degassed N₂ three times and stirred at 75 °C for 1 h. After filtration, the filtrate was purified by pre-HPLC (FA condition) to give N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide (10 mg, 0.02 mmol) as a white solid.

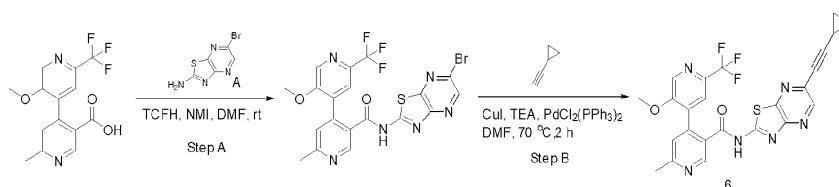
[280] ¹H NMR (400 MHz, CDCl₃) = 8.96 (s, 1H), 8.52 (s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.48 (s, 1H), 7.22 (s, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.68 (t, J = 56.6 Hz, 1H), 3.77 (s, 3H), 2.73 (s, 3H), 1.56 - 1.54 (m, 1H), 1.01 - 0.88 (m, 4H).

[281] LCMS: m/z (M+H)⁺ = 492.2

[282]

[283] **Example 6: Synthesis of Compound 6**

[284]



[285]

[286] **Step A: N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[5-methoxy-2-(trifluoromethyl)pyridin-4-yl]-6-methylpyridine-3-carboxamide**

[287] To a solution of 4-[5-methoxy-2-(trifluoromethyl)pyridin-4-yl]-6-methylpyridine-3-carboxylic acid (50 mg, 0.16 mmol) and 6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-amine (37.00 mg, 0.16 mmol) in DMF (3 mL) were added TCFH (58.41 mg, 0.21 mmol) and 1-methylimidazole (0.04 mL, 0.48 mmol) at 25 °C, the mixture was stirred at 25 °C for 2 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (DCM:MeOH = -0 to 10%) to give N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[5-methoxy-2-(trifluoromethyl)pyridin-4-yl]-6-methylpyridine-3-carboxamide (63 mg, 0.07 mmol) as white solid.

[288] LCMS: m/z (M+H)⁺ = 525.2/527.2

[289]

[290] **Step B: N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-(trifluoromethyl)-4,4'-bipyridine-3-carboxamide**

[291] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[5-methoxy-2-(trifluoromethyl)pyridin-4-yl]-6-methylpyridine-3-carboxamide (31 mg, 0.06 mmol) and ethynylcyclopropane (0.01 mL, 0.12 mmol) in DMF (2 mL) were added palladium chloride bis(triphenylphosphane) (4.21 mg, 0.01 mmol), CuI (2.25 mg, 0.01 mmol) and TEA (0.02 mL, 0.12 mmol) at 25 °C, the mixture was stirred at 70 °C under N₂ for 2 h. After filtration, the filtrate was purified by high performance liquid phase (TFA/ acetonitrile/water) to give N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-(trifluoromethyl)-4,4'-bipyridine-3-carboxamide (4.54 mg, 0.01 mmol) as white solid.

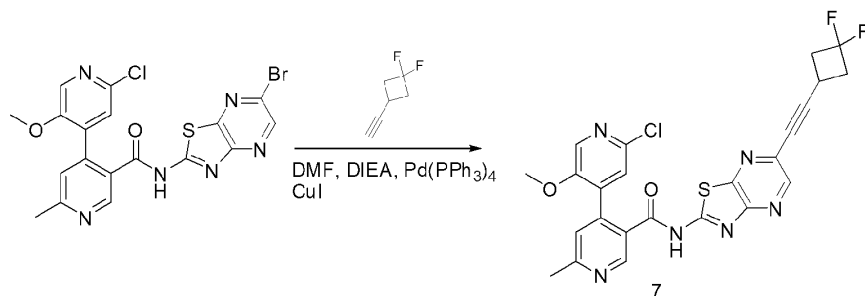
[292] ¹H NMR (400 MHz, CDCl₃) δ 8.96 (s, 1H), 8.43 (d, J = 5.2 Hz, 2H), 7.60 (s, 1H), 7.23 (s, 1H), 3.85 (s, 3H), 2.72 (s, 3H), 1.56 (m, 1H), 0.98 (m, 4H)

[293] LCMS: m/z (M+H)⁺ = 511.2

[294]

[295] **Example 7: Synthesis of Compound 7**

[296]



[297] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (300 mg, 0.61 mmol) in DMF (4 mL) were added 3-ethynyl-1,1-difluorocyclobutane (77.92 mg, 0.67 mmol), CuI (11.62 mg, 0.06 mmol), DIEA (0.20 mL, 1.22 mmol) and tetrakis(triphenylphosphine)palladium(0) (35.25 mg, 0.03 mmol) at 25 °C. The reaction was degassed N₂ three times and stirred at 70°C for 1 h. After filtration, the filtrate was purified by pre-HPLC (FA condition) to give 2'-chloro-N-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide (135 mg, 0.25 mmol) as a white solid.

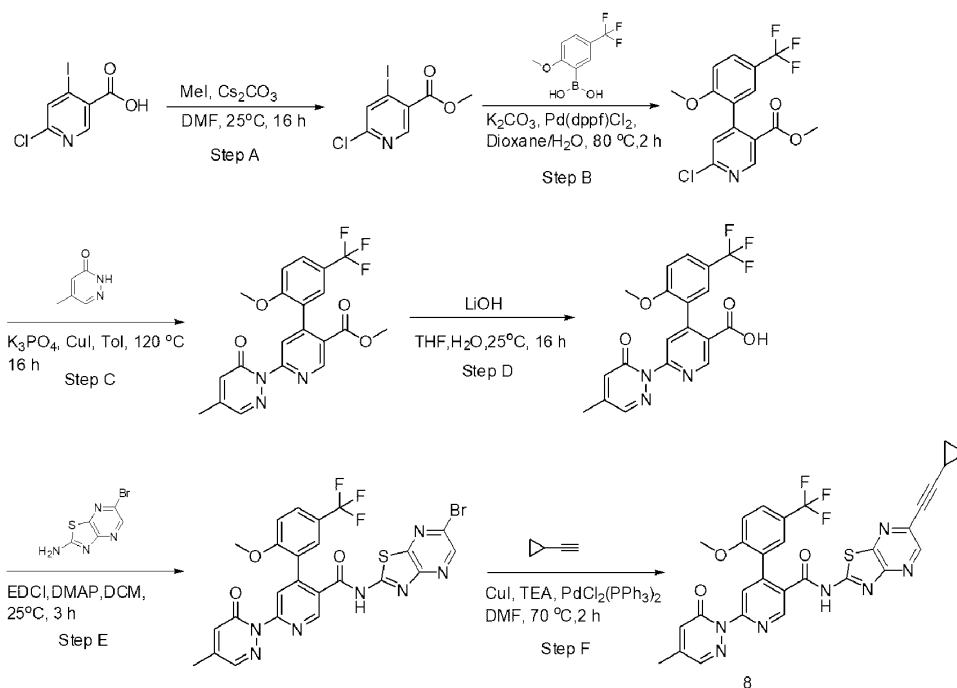
[298] ¹H NMR (400 MHz, DMSO-d₆) δ 8.91 - 8.87 (m, 1H), 8.71 (s, 1H), 8.18 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 3.63 (s, 3H), 3.27 - 2.99 (m, 3H), 2.88 - 2.74 (m, 2H), 2.61 (s, 3H)

[299] LCMS: m/z (M+H)⁺ = 527.2

[300]

[301] **Example 8: Synthesis of Compound 8**

[302]



[303]

[304] **Step A: methyl 6-chloro-4-iodopyridine-3-carboxylate**

[305] To a solution of 6-chloro-4-iodopyridine-3-carboxylic acid (300 mg, 1.06 mmol) and Cs_2CO_3 (1034.53 mg, 3.18 mmol) in DMF (10 mL) was added iodomethane (0.07 mL, 1.06 mmol) at 25 °C, the mixture was stirred at 25 °C for 16 h to give a yellow solution. Upon completion, the mixture was quenched with H_2O (200 mL) and extracted with EtOAc (200 mL * 3), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Pet.ether: EtOAc = 0 to 5%) to give methyl 6-chloro-4-iodopyridine-3-carboxylate (300 mg, 1.00 mmol) as white solid.

[306] LCMS: m/z (M+H)⁺ = 298.0

[307]

[308] **Step B: methyl 6-chloro-4-[2-methoxy-5-(trifluoromethyl) phenyl] pyridine-3-carboxylate**

[309] To a solution of methyl 6-chloro-4-iodopyridine-3-carboxylate (300 mg, 1.01 mmol) and [2-methoxy-5-(trifluoromethyl) phenyl] boranediol (221.81 mg, 1.01 mmol) in dioxane (8 mL) and H_2O (2 mL) were added $\text{Pd}(\text{dppf})\text{Cl}_2$ (73.79 mg, 0.10 mmol) and K_2CO_3 (418.11 mg, 3.03 mmol) at 25 °C under N_2 , the mixture was stirred at 80 °C under N_2 for 2 h to give a black suspension. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Pet.ether: EtOAc = 0 to 20%) to give methyl 6-chloro-4-[2-methoxy-

5-(trifluoromethyl) phenyl] pyridine-3-carboxylate (290 mg, 0.69 mmol) as white solid.

[310] LCMS: m/z (M+H)⁺ = 346.0

[311]

[312] **Step C: methyl 4-[2-methoxy-5-(trifluoromethyl) phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl) pyridine-3-carboxylate**

[313] To a solution of methyl 6-chloro-4-[2-methoxy-5-(trifluoromethyl)phenyl]pyridine-3-carboxylate (270 mg, 0.78 mmol) and 5-methyl-2H,3H-1,2-diazin-3-one (172.01 mg, 1.56 mmol) in toluene (10 mL) were added tripotassium phosphate (331.56 mg, 1.56 mmol), CuI (14.87 mg, 0.08 mmol) and 2,5-diazahehexane (0.02 mL, 0.16 mmol) at 25 °C under N₂, the mixture was stirred at 120 °C under N₂ for 16 h to give a brown solution. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by high performance liquid phase (Trifluoroacetic acid/ acetonitrile/water) to give methyl 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl) pyridine-3-carboxylate (100 mg, 0.21 mmol) as white solid.

[314] LCMS: m/z (M+H)⁺ = 420.3

[315]

[316] **Step D: 4-[2-methoxy-5-(trifluoromethyl) phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl) pyridine-3-carboxylic acid**

[317] To a solution of methyl 4-[2-methoxy-5-(trifluoromethyl) phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl)pyridine-3-carboxylate (100 mg, 0.24 mmol) in THF (3 mL) and H₂O (2 mL) was added LiOH (12.01 mg, 0.29 mmol) at 25 °C, the mixture was stirred at 25 °C for 16 h to give a yellow solution. Upon completion, the mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL). The aqueous phase was adjusted to pH=3 with HCl (2 N in H₂O) in an ice bath and extracted with EtOAc (20 mL * 2), the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (DCM:MeOH = 0 to 10%) to give 4-[2-methoxy-5-(trifluoromethyl) phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl)pyridine-3-carboxylic acid (30 mg, 0.06 mmol) as white solid.

[318] LCMS: m/z (M+H)⁺ = 406.2

[319]

[320] **Step E: N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl)pyridine-3-carboxamide**

[321] To a solution of 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl)pyridine-3-carboxylic acid (80 mg, 0.01 mmol) and 6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-amine (2.31 mg, 0.01 mmol) in DCM (3 mL) were added DMAP (1.83 mg, 0.02 mmol) and EDCI (2.88 mg, 0.02 mmol) at 25 °C, the mixture was stirred at 25 °C for 3 h to give a brown solution. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (DCM:MeOH = 0 to 6%) to give N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl)pyridine-3-carboxamide (30 mg, 0.03 mmol) as white solid.

[322] LCMS: m/z (M+H)⁺ = 618.2/620.2

[323]

[324] **Step F: N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(4-methyl-6-oxopyridazin-1(6H)-yl)nicotinamide**

[325] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(4-methyl-6-oxo-1,2-diazin-1-yl)pyridine-3-carboxamide (30 mg, 0.05 mmol) and ethynylcyclopropane (0.01 mL, 0.10 mmol) in DMF (2 mL) were added palladium chloride bis(triphenylphosphane) (3.41 mg), CuI (1.85 mg, 0.01 mmol) and TEA (0.01 mL, 0.10 mmol) at 25 °C under N₂, the mixture was stirred at 70 °C for 2 h under N₂ to give a brown solution. After filtration, the filtrate was purified by high performance liquid phase (TFA/acetonitrile/water) to give N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(4-methyl-6-oxopyridazin-1(6H)-yl)nicotinamide (9.34 mg, 0.01 mmol) as white solid.

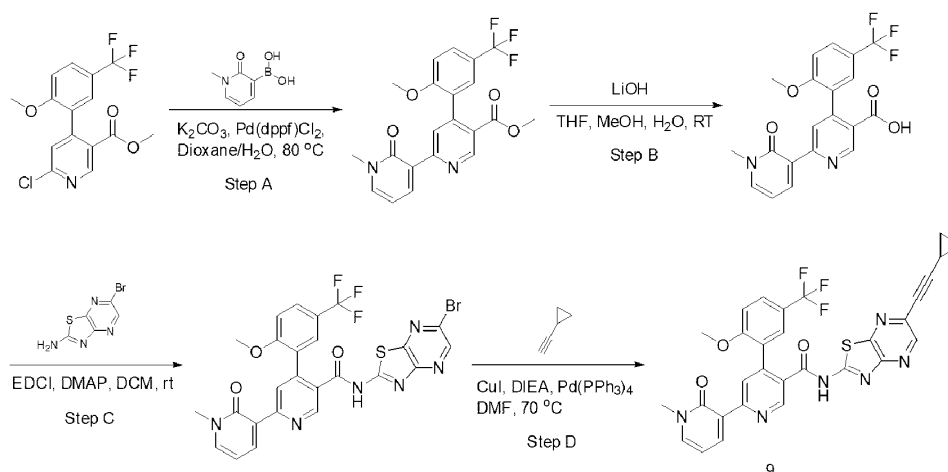
[326] ¹H NMR (400 MHz, CDCl₃) δ 11.55 (s, 1H), 8.85 (s, 1H), 8.43 (s, 1H), 7.77 (d, J = 26.2 Hz, 2H), 7.60 (dd, J = 8.8, 2.2 Hz, 1H), 7.49 (s, 1H), 6.88 - 6.74 (m, 2H), 3.58 (s, 3H), 2.25 (s, 3H), 1.46 (m, 1H), 0.94 - 0.77 (m, 4H)

[327] LCMS: m/z (M+H)⁺ = 604.4

[328]

[329] **Example 9: Synthesis of Compound 9**

[330]



[331]

[332] **Step A: methyl 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxylate**

[333] To a solution of methyl 6-chloro-4-[2-methoxy-5-(trifluoromethyl)phenyl]pyridine-3-carboxylate (100 mg, 0.29 mmol) in dioxane (2 mL), H₂O (0.5 mL) were added K₂CO₃ (39.98 mg, 0.29 mmol), 3-(4-methoxy-2-oxo-1,2-dihydropyridin-3-yl)-1-methyl-1,2-dihydropyridin-2-one (44.24 mg, 0.29 mmol) and bis[5-(diphenylphosphanyl)cyclopenta-1,3-dienyl]- λ 2-iron(II) palladium chloride (21.17 mg, 0.03 mmol) at 20 °C under N₂, the mixture was stirred at 80 °C for 16 h. Upon completion, the reaction was concentrated under reduced pressure. The residue was purified silica-gel column chromatography (Pet.ether: EtOAc = 10:1 to 3:1) to give methyl 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxylate (100 mg, 0.24 mmol) as a yellow solid.

[334] LCMS: m/z (M+H)⁺ = 419.2

[335]

[336] **Step B: 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxylic acid**

[337] To a solution of methyl 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxylate (100 mg, 0.24 mmol) in THF (4 mL), MeOH (0.5 mL) and H₂O (1 mL) was added LiOH (10.03 mg, 0.24 mmol) at 20 °C, the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was adjusted pH to 2 with 2M HCl and extracted with EtOAc (10 mL * 3). The organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxylic acid (60 mg, 0.13 mmol) as a white solid.

[338] LCMS: m/z (M+H)⁺ = 405.2

[339]

[340] **Step C: N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxamide**

[341] To a solution of 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxylic acid (40 mg, 0.10 mmol) in DCM (3 mL) were added DMAP (18.13 mg, 0.15 mmol), EDCI (28.45 mg, 0.15 mmol) and 6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-amine (22.86 mg, 0.10 mmol) at 20 °C, the mixture was stirred at 20 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified silica-gel column chromatography (Pet.ether: EtOAc = 10:1 to 1:1) to give N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxamide (25 mg, 0.04 mmol) as a yellow solid.

[342] LCMS: m/z (M+H)⁺ = 617.2/619.2

[343]

[344] **Step D: N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide**

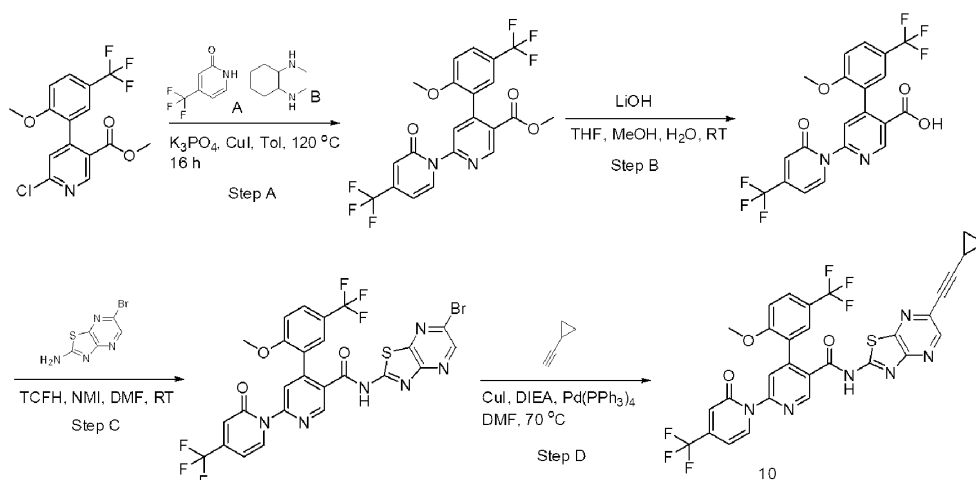
[345] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-(1-methyl-2-oxopyridin-3-yl)pyridine-3-carboxamide (40 mg, 0.06 mmol) in DMF (1.5 mL) were added the DIEA (0.02 mL, 0.13 mmol), CuI (2.47 mg, 0.01 mmol), ethynylcyclopropane (0.01 mL, 0.06 mmol) and Pd(PPh₃)₄ (4.55 mg, 0.01 mmol) at 20 °C under N₂, the mixture was stirred at 70 °C under N₂ for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by high performance liquid phase (TFA/acetonitrile/water) to give N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide (1.55 mg) as a white solid.

[346] LCMS: m/z (M+H)⁺ = 603.4

[347]

[348] **Example 10: Synthesis of Compound 10**

[349]



[350]

[351] **Step A: methyl 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxylate**

[352] To a solution of methyl 6-chloro-4-[2-methoxy-5-(trifluoromethyl)phenyl]pyridine-3-carboxylate (50 mg, 0.14 mmol) in Tol (3 mL) were added K_3PO_4 (92.10 mg, 0.43 mmol), CuI (5.51 mg, 0.03 mmol), 4-(trifluoromethyl)pyridin-2-ol (23.59 mg, 0.14 mmol) and methyl[2-(methylamino)cyclohexyl]amine (2.06 mg, 0.01 mmol) at 20 °C, the mixture was stirred at 120 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified silica-gel column chromatography (Pet.ether: EtOAc = 10:1 to 1:1) to give methyl 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxylate (41 mg, 0.08 mmol) as a yellow solid.

[353] LCMS: m/z (M+H)⁺ = 473.2

[354]

[355] **Step B: 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxylic acid**

[356] To a solution of methyl 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxylate (83 mg, 0.18 mmol) in THF (4 mL), MeOH (0.5 mL) and H₂O (1 mL) was added LiOH (10.03 mg, 0.24 mmol) at 20 °C, the mixture was stirred at 20 °C for 2 h. Upon completion, the reaction mixture was adjusted pH to 2 with 2M HCl and extracted with EtOAc (10 mL*3). The organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxylic acid (38 mg, 0.08 mmol) as a white solid.

[357] LCMS: m/z (M+H)⁺ = 459.2

[358]

[359] **Step C: N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxamide**

[360] To a solution of 4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxylic acid (80 mg, 0.17 mmol) in DCM (3 mL) were added DMAP (31.99 mg, 0.26 mmol), EDCI (50.19 mg, 0.26 mmol) and 6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-amine (40.33 mg, 0.17 mmol) at 20 °C, the mixture was stirred at 20 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Pet.ether: EtOAc = 10:1 to 1:1) to give N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxamide (90 mg, 0.12 mmol) as a yellow solid.

[361] LCMS: m/z (M+H)⁺ = 671.2/673.2

[362]

[363] **Step D: N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)nicotinamide**

[364] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-[2-methoxy-5-(trifluoromethyl)phenyl]-6-[2-oxo-4-(trifluoromethyl)pyridin-1-yl]pyridine-3-carboxamide (90 mg, 0.15 mmol) in DMF (1.5 mL) were added DIEA (0.04 mL, 0.27 mmol), CuI (5.11 mg, 0.03 mmol), ethynylcyclopropane (0.02 mL, 0.27 mmol) and Pd(PPh₃)₄ (9.41 mg, 0.01 mmol) at 20 °C under N₂, the mixture was stirred at 70 °C under N₂ for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by high performance liquid phase (FA/ acetonitrile/water) to give N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)nicotinamide (1.72 mg) as a white solid.

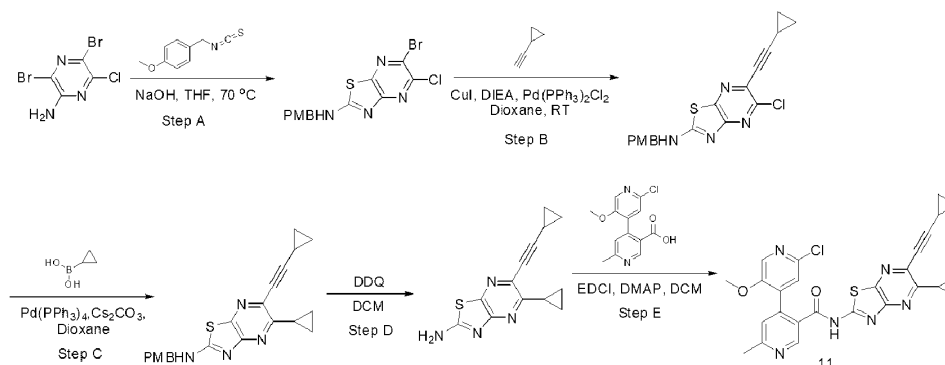
[365] ¹H NMR (400 MHz, MeOD) δ 8.99 (s, 1H), 8.56 (s, 1H), 8.30 (d, J = 7.4 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.76 - 7.67 (m, 1H), 7.63 - 7.48 (m, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.01 (s, 1H), 6.72 (dd, J = 7.4, 2.0 Hz, 1H), 3.72 (s, 3H), 1.61 (m, 1H), 1.06 - 0.97 (m, 2H), 0.95 - 0.86 (m, 2H)

[366] LCMS: m/z (M+H)⁺ = 657.4

[367]

[368] **Example 11: Synthesis of Compound 11**

[369]



[370]

[371] **Step A: 6-bromo-5-chloro-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine**

[372] To a solution of 3,5-dibromo-6-chloropyrazin-2-amine (1.7 g, 5.92 mmol) in THF (20 mL) were added NaOH (0.83 g, 20.71 mmol) and {[(4-methoxyphenyl)methyl]azanylidene}methanethione (1.12 mL, 6.80 mmol) at 20 °C, the reaction was stirred at 70 °C by Microwave for 2 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Pet.ether: EtOAc = 10:1 to 3:1) to give 6-bromo-5-chloro-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine (1.6 g, 2.66 mmol) as a white solid.

[373] LCMS: m/z (M+H)⁺ = 384.7/386.7

[374]

[375] **Step B: 5-chloro-6-(cyclopropylethynyl)-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine**

[376] A mixture of 6-bromo-5-chloro-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine (50 mg, 0.13 mmol), ethynylcyclopropane (219.74 μ L, 2.59 mmol), CuI (10 mg, 0.03 mmol), DIEA (53.91 μ L, 0.39 mmol) and Pd(PPh₃)₂Cl₂ (9.10 mg, 0.01 mmol) in dioxane (3 mL) was degassed and purged 3 times with N₂ and then stirred at 25 °C for 2 h. Upon completion, the reaction mixture was evaporated and the crude residue was purified by column chromatography (20 % EtOAc in PE) to give 5-chloro-6-(cyclopropylethynyl)-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine (35 mg, 0.07 mmol) as a yellow oil.

[377] LCMS: m/z (M+H)⁺ = 370.9

[378]

[379] **Step C: 5-cyclopropyl-6-(cyclopropylethynyl)-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine**

[380] A mixture of cyclopropylboronediol (231.62 mg, 2.70 mmol), 5-chloro-6-(cyclopropylethynyl)-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine (50 mg, 0.13 mmol), Cs₂CO₃ (87.86 mg, 0.27 mmol), Pd(PPh₃)₄ (31.16 mg, 0.03 mmol) in

Dioxane (5 mL) was degassed and purged 3 times with N₂ and then stirred at 120 °C for 2 h under N₂. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude residue purified by p-TLC (5% EtOAc in PE) to give 5-cyclopropyl-6-(cyclopropylethynyl)-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine (10 mg, 0.01 mmol) as a yellow oil.

[381] LCMS: m/z (M+H)⁺ = 377.2

[382]

[383] **Step D: 5-cyclopropyl-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-amine**

[384] To a stirred solution of 5-cyclopropyl-6-(cyclopropylethynyl)-N-(4-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-amine (15 mg, 0.04 mmol) in DCM (10 mL) was added DDQ (18.09 mg, 0.08 mmol) at 0 °C, the mixture was stirred at 25 °C for 16 h. Upon completion, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and stirred vigorously for ten minutes, then the mixture was extracted with DCM (30 mL * 3), the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (Pet.ether:EtOAc = 10:1 to 2: 1) to give 5-cyclopropyl-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-amine (8 mg, 0.01 mmol) as a yellow solid.

[385] LCMS: m/z (M+H)⁺ = 257.0

[386]

[387] **Step E: 2'-chloro-N-(5-cyclopropyl-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide**

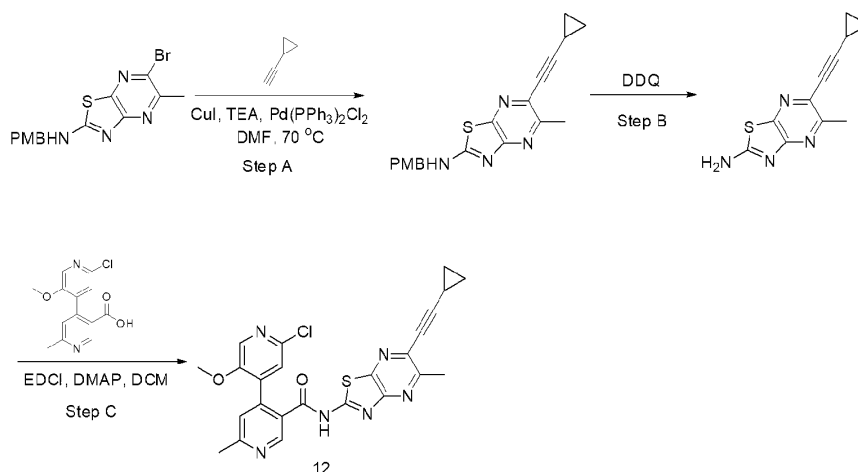
[388] To a solution of 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxylic acid (11.96 mg, 0.04 mmol) in DCM (2 mL) were added 5-cyclopropyl-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-amine (10 mg, 0.04 mmol), DMAP (12.33 mg, 0.10 mmol) and EDCI (19.35 mg, 0.10 mmol) at 25 °C, the mixture was stirred at 25 °C for 2 h. Upon completion, the reaction was concentrated under reduced pressure. The residue was purified by preparative HPLC (FA condition) to give 2'-chloro-N-(5-cyclopropyl-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide (1 mg, 0.01 mmol) as white solid.

[389] LCMS: m/z (M+H)⁺ = 517.2

[390]

[391] **Example 12: Synthesis of Compound 12**

[392]



[393]

[394] **Step A: 6-(cyclopropylethynyl)-N-(4-methoxybenzyl)-5-methylthiazolo[4,5-b]pyrazin-2-amine**

[395] To a solution of 6-bromo-N-(4-methoxybenzyl)-5-methylthiazolo[4,5-b]pyrazin-2-amine (200 mg, 0.55 mmol) in DMF (5 mL) were added ethynylcyclopropane (0.09 mL, 1.10 mmol), CuI (10 mg, 0.11 mmol), TEA (0.23 mL, 1.64 mmol) and Pd(PPh₃)₂Cl₂ (38.43 mg, 0.05 mmol), the mixture was degassed and purged 3 times with N₂ and stirred at 70 °C for 2 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (Pet.ether:EtOAc = 100:1 to 5:1) to give 6-(cyclopropylethynyl)-N-(4-methoxybenzyl)-5-methylthiazolo[4,5-b]pyrazin-2-amine (80 mg, 0.21 mmol) as a yellow oil.

[396] LCMS: m/z (M+H)⁺ = 351.2

[397]

[398] **Step B: 6-(cyclopropylethynyl)-5-methylthiazolo[4,5-b]pyrazin-2-amine**

[399] To a solution of 6-(cyclopropylethynyl)-N-(4-methoxybenzyl)-5-methylthiazolo[4,5-b]pyrazin-2-amine (50 mg, 0.14 mmol) in DCM (20 mL) was added DDQ (64.78 mg, 0.29 mmol) at 0 °C, the mixture was stirred at 25 °C for 18 h. Upon completion, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and stirred vigorously for ten minutes, then the mixture was extracted with DCM (20 mL * 2), the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purification by column chromatography on silica gel (Pet.ether:EtOAc = 10:1 to 2:1) to give 6-(cyclopropylethynyl)-5-methylthiazolo[4,5-b]pyrazin-2-amine (21 mg, 0.07 mmol) as a brown solid.

[400] LCMS: m/z (M+H)⁺ = 231.1

[401]

[402] **Step C: 2'-chloro-N-(6-(cyclopropylethynyl)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide**

[403] To a solution of 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxylic acid (20.63 mg, 0.07 mmol) in DCM (2 mL) were added 6-(cyclopropylethynyl)-5-methylthiazolo[4,5-b]pyrazin-2-amine (21 mg, 0.07 mmol), DMAP (12.33 mg, 0.10 mmol) and EDCI (19.35 mg, 0.10 mmol) at 25 °C, the mixture was stirred at 25 °C for 16 h. Upon completion, the mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (FA condition) to give 2'-chloro-N-(6-(cyclopropylethynyl)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide (9 mg, 0.02 mmol) as white solid.

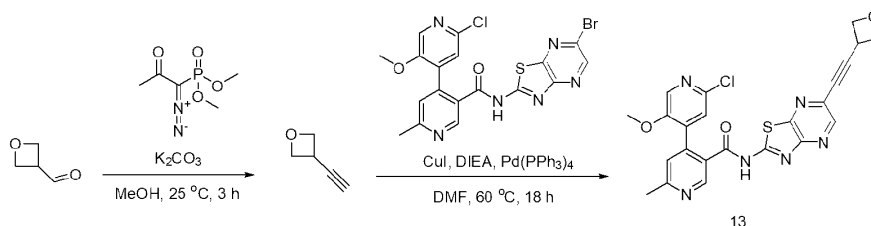
[404] ¹H NMR (400 MHz, DMSO) δ 13.46 (s, 1H), 8.91 (s, 1H), 8.17 (s, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 3.62 (s, 3H), 2.63 (s, 3H), 2.60 (s, 3H), 1.73 - 1.62 (m, 1H), 1.03 - 0.95 (m, 2H), 0.89 - 0.82 (m, 2H)

[405] LCMS: m/z (M+H)⁺ = 491.2

[406]

[407] **Example 13: Synthesis of Compound 13**

[408]



[409]

[410] **Step A: 3-ethynyloxetane**

[411] To a solution of oxetane-3-carbaldehyde (50 mg, 0.58 mmol), (1Z)-1-(diazyn-1-iumyl)-1-[dimethoxy(oxo)-λ5-phosphanyl]prop-1-en-2-olate (111.42 mg, 0.58 mmol) and K₂CO₃ (120.40 mg, 0.87 mmol) in EtOH (1 mL) was reacted at 25°C for 3 h. The mixture was filtered, and the filtrate was used for next step without further purification.

[412]

[413] **Step B: 2'-chloro-5'-methoxy-6-methyl-N-(6-(oxetan-3-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide**

[414] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (2 mL) were added DIEA (78.85 mg, 0.61 mmol), 3-ethynyloxetane (20.03 mg, 0.24 mmol), CuI (2.32 mg, 0.01 mmol) and Pd(PPh₃)₄ (7.05 mg, 0.01 mmol). The resulting mixture was degassed and purged with N₂ for three times, it was stirred at 60°C for 18 h under N₂ protection to give a brown solution. LCMS showed starting material

was consumed and desired product was formed. The cooled reaction was filtered. The filtrate was purified by prep-HPLC(FA condition) to afford the desired product 2'-chloro-5'-methoxy-6-methyl-N-(6-(oxetan-3-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide (52.47 mg, 0.11 mmol, 52.34%) as a yellow solid.

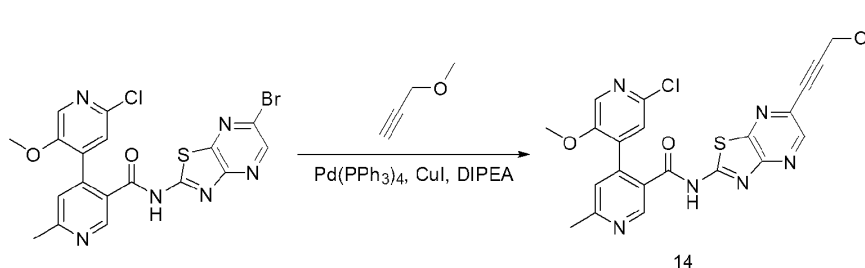
[415] LCMS: m/z (M+H)⁺ = 493.1.

[416] ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.59 (s, 1H), 8.89 (s, 1H), 8.73 (s, 1H), 8.18 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 4.84 (dd, *J* = 8.8, 5.6 Hz, 2H), 4.67 (dd, *J* = 7.2, 5.6 Hz, 2H), 4.34 - 4.17 (m, 1H), 3.63 (s, 3H), 2.61 (s, 3H).

[417]

[418] **Example 14: Synthesis of Compound 14**

[419]



[420] To a solution of N-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (10 mL) were added 3-methoxyprop-1-yne (15.42 mg, 0.22 mmol), CuI (2.32 mg, 0.01 mmol), DIPEA (78.85 mg, 0.61 mmol) and Pd(PPh₃)₄ (37.05 mg, 0.01 mmol) at 25°C. The reaction was degassed N₂ three times and stirred at 70°C for 18 h. After filtration, the filtrate was purified by pre-HPLC (FA condition) to give 2'-chloro-5'-methoxy-N-(6-(3-methoxyprop-1-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4,4'-bipyridine-3-carboxamide (21.68 mg, 0.05 mmol) as a yellow solid.

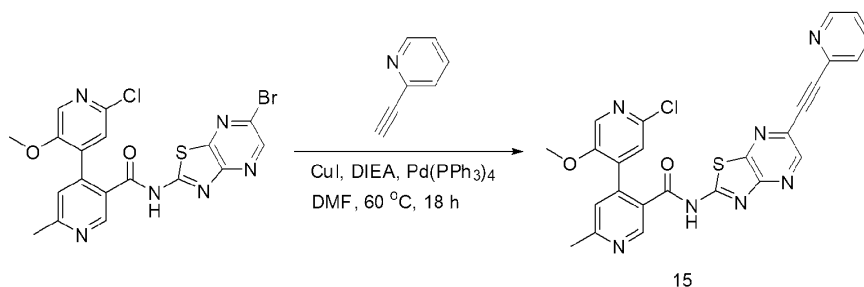
[421] LCMS: m/z (M+H)⁺ = 481.0.

[422] ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.61 (s, 1H), 8.91 (s, 1H), 8.73 (s, 1H), 8.18 (s, 1H), 7.59 (s, 1H), 7.47 (s, 1H), 4.43 (s, 2H), 3.63 (s, 3H), 3.37 (s, 3H), 2.61 (s, 3H).

[423]

[424] **Example 15: Synthesis of Compound 15**

[425]



[426] To a solution of *N*-(6-bromo[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (2 mL) were added DIEA (78.85 mg, 0.61 mmol), 2-ethynylpyridine (31.46 mg, 0.31 mmol), CuI (2.32 mg, 0.01 mmol) and Pd(PPh₃)₄ (7.05 mg, 0.01 mmol). The resulting mixture was degassed and purged with N₂ for three times, it was stirred at 60°C for 18 h under N₂ protection to give a brown solution. LCMS showed starting material was consumed and desired product was formed. The cooled reaction was filtered. The filtrate was purified by prep-HPLC(FA condition) to afford the desired product 2'-chloro-5'-methoxy-6-methyl-*N*-(6-(pyridin-2-ylethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide (73 mg, 0.14 mmol) as a yellow solid.

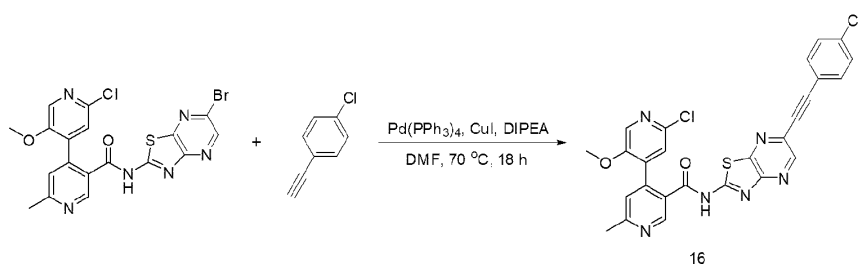
[427] LCMS: *m/z* (M+H)⁺ = 514.0.

[428] ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.67 (s, 1H), 8.91 (d, *J* = 6.2 Hz, 2H), 8.68 (d, *J* = 4.8 Hz, 1H), 8.19 (s, 1H), 7.92 (dt, *J* = 7.8, 3.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.62 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 3.64 (s, 3H), 2.62 (s, 3H).

[429]

[430] **Example 16: Synthesis of Compound 16**

[431]



[432] To a solution of *N*-(6-bromo[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (10 mL) were added 1-chloro-4-ethynylbenzene (30.05 mg, 0.22 mmol), CuI (2.32 mg, 0.01 mmol), DIPEA (78.85 mg, 0.61 mmol) and Pd(PPh₃)₄ (37.05 mg, 0.01 mmol) at 25°C. The reaction was degassed N₂ three times and stirred at 70°C for 18 h. After filtration, the filtrate was purified by pre-HPLC (FA condition) to give 2'-chloro-*N*-(6-((4-chlorophenyl)ethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide (47.51 mg, 0.09 mmol) as a yellow solid.

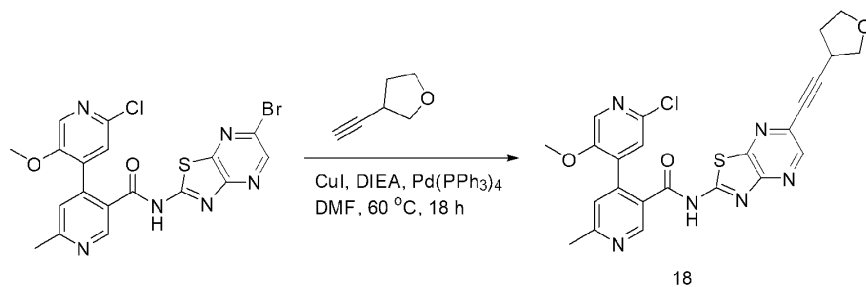
[433] LCMS: *m/z* (M+H)⁺ = 547.0.

[434] ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.64 (s, 1H), 8.88 (d, *J* = 12.6 Hz, 2H), 8.19 (s, 1H), 7.72 - 7.67 (m, 2H), 7.61 (s, 1H), 7.59 - 7.54 (m, 2H), 7.49 (s, 1H), 3.64 (s, 3H), 2.61 (s, 3H).

[435]

[436] **Example 18: Synthesis of Compound 18**

[437]



[438] To a solution of *N*-(6-bromo[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (2 mL) were added DIEA (78.85 mg, 0.61 mmol), 3-ethynyltetrahydrofuran (23.07 mg, 0.24 mmol), CuI (2.32 mg, 0.01 mmol) and Pd(PPh₃)₄ (7.05 mg, 0.01 mmol). The resulting mixture was degassed and purged with N₂ for three times, it was stirred at 60°C for 18 h under N₂ protection to give a brown solution. LCMS showed starting material was consumed and desired product was formed. The cooled reaction was filtered. The filtrate was purified by prep-HPLC(FA condition) to afford the desired product 2'-chloro-5'-methoxy-6-methyl-*N*-(6-((tetrahydrofuran-3-yl)ethynyl)thiazolo[4,5-*b*]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide (38 mg, 0.07 mmol) as a yellow solid.

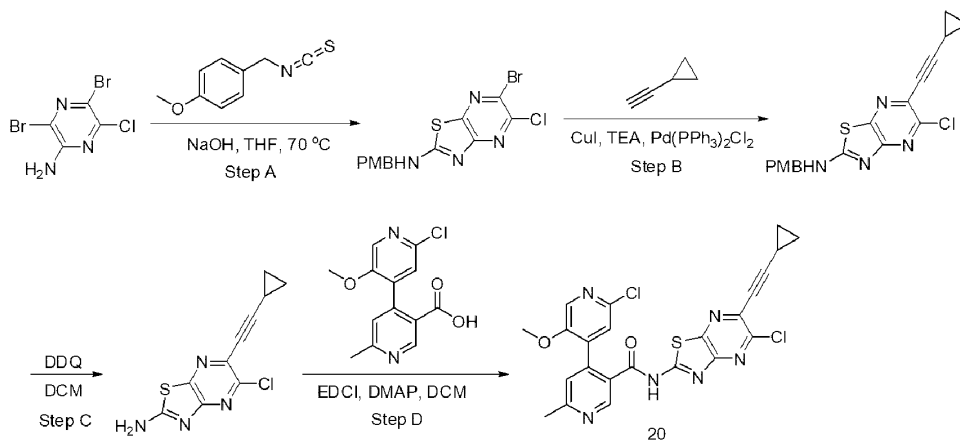
[439] LCMS: *m/z* (M+H)⁺ = 507.0.

[440] ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.56 (s, 1H), 8.92 (s, 1H), 8.64 (s, 1H), 8.17 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 4.00 (t, *J* = 7.8 Hz, 1H), 3.90 - 3.83 (m, 1H), 3.80 - 3.74 (m, 1H), 3.70 - 3.65 (dm, 1H), 3.63 (s, 3H), 3.41 - 3.35 (m, 1H), 2.60 (s, 3H), 2.35 - 2.26 (m, 1H), 2.07 - 1.96 (m, 1H).

[441]

[442] **Example 20: Synthesis of Compound 20**

[443]



[444]

[445] **Step A: 6-bromo-5-chloro- *N*-(4-methoxybenzyl)thiazolo[4,5- *b*]pyrazin-2-amine**

[446] To a solution of 3,5-dibromo-6-chloropyrazin-2-amine (1.7 g, 5.92 mmol) in THF (20 mL) was added NaOH (0.83 g, 20.71 mmol) and {[4-methoxyphenyl)methyl]azanylidene}methanethione (1.12 mL, 6.80 mmol). It was stirred for 2 h at 70°C (Microwave). The reaction was complete detected by LC-MS. The solvent was removed under vacuum. The resulting residue was dissolved in DCM (3 mL) and purified by Combi Flash (Biotage Isolera Prime) which applied to a 40 g silica gel column, eluted with 0-40% PE in EA within 30 min to afford 6-bromo-5-chloro-*N*-(4-methoxybenzyl)thiazolo[4,5-*b*]pyrazin-2-amine (1.6 g, 2.66 mmol, 44.88%) as a white solid.

[447] LCMS: m/z (M+H)⁺= 384.7, 386.7

[448]

[449] **Step B: 5-chloro-6-(cyclopropylethynyl)- *N*-(4-methoxybenzyl)thiazolo[4,5- *b*]pyrazin-2-amine**

[450] A mixture of 6-bromo-5-chloro-*N*-(4-methoxybenzyl)thiazolo[4,5-*b*]pyrazin-2-amine (50 mg, 0.13 mmol), ethynylcyclopropane (219.74 μ L, 2.59 mmol), CuI (0.88 μ L, 0.03 mmol), TEA (53.91 μ L, 0.39 mmol) and Pd(PPh₃)₂Cl₂ (9.10 mg, 0.01 mmol) in dioxane (3 mL) was degassed and purged 3 times with N₂ and then stirred at 25°C for 2 h. The reaction was complete detected by LC-MS. The reaction mixture was evaporated and the crude residue purified by column chromatography (20% EtOAc in PE) to afford 5-chloro-6-(cyclopropylethynyl)-*N*-(4-methoxybenzyl)thiazolo[4,5-*b*]pyrazin-2-amine (35 mg, 0.07 mmol, 56.78%) as a yellow oil.

[451] LCMS: m/z (M+H)⁺= 370.9

[452]

[453] **Step C: 5-chloro-6-(cyclopropylethynyl)thiazolo[4,5- *b*]pyrazin-2-amine**

[454] DDQ was added portionwise to a stirred solution of 5-chloro-6-(cyclopropylethynyl)-2-{[(4-methoxyphenyl)methyl]amino}[1,3]thiazolo[5,4-*b*]pyrazine (15 mg, 0.04 mmol) in DCM (2 mL) and stirred at 25°C. The reaction was complete detected by LC-MS. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and stirred vigorously for ten minutes before extracting with EA. The combined organic extracts were dried (MgSO₄), filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane: EtOAc=2: 1) to give 5-chloro-6-(cyclopropylethynyl)[1,3]thiazolo[5,4-*b*]pyrazin-2-amine (10 mg, 0.02 mmol, 56.21%) as a colorless oil.

[455] LCMS: m/z (M+H)⁺= 257.0

[456]

[457] **Step D: 2'-chloro-N-(5-chloro-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide**

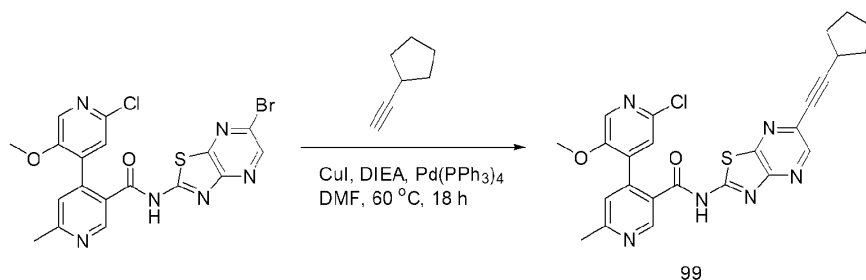
[458] A mixture of 4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxylic acid (12.23 mg, 0.04 mmol), 5-chloro-6-(cyclopropylethynyl)[1,3]thiazolo[5,4-b]pyrazin-2-amine (10 mg, 0.04 mmol), DMAP (7.31 mg, 0.06 mmol) in DCM (2 mL) was added EDCI (11.47 mg, 0.06 mmol). Then the mixture was stirred for 2 h at 25°C. The reaction was complete detected by LC-MS. The reaction mixture was poured into water (20 mL) and extracted with EA (3 x 50 mL). The combined ether layers were washed with water (50 mL) and sat. aq. NaCl solution (50 mL). The organic layer was dried (Na₂SO₄) and solvent removed in vacuo. The residue was purified by preparative HPLC (FA condition) to give 2'-chloro-N-(5-chloro-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide (2 mg, 0.01 mmol, 9.22%) as white solid.

[459] LCMS: m/z (M+H)⁺ = 510.8

[460]

[461] **Example 99: Synthesis of Compound 99**

[462]



[463] To a solution of *N*-(6-bromo[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (2 mL) were added DIEA (78.85 mg, 0.61 mmol), ethynylcyclopentane (22.60 mg, 0.24 mmol), CuI (2.32 mg, 0.01 mmol) and Pd(PPh₃)₄ (7.05 mg, 0.01 mmol). The resulting mixture was degassed and purged with N₂ for three times, it was stirred at 60°C for 18 h under N₂ protection to give a brown solution. LCMS showed starting material was consumed and desired product was formed. The cooled reaction was filtered. The filtrate was purified by prep-HPLC(FA condition) to afford the desired product 4-(2-chloro-5-methoxypyridin-4-yl)-*N*-[6-(cyclopentylethynyl)[1,3]thiazolo[4,5-*b*]pyrazin-2-yl]-6-methylpyridine-3-carboxamide (46 mg, 0.09 mmol) as a yellow solid.

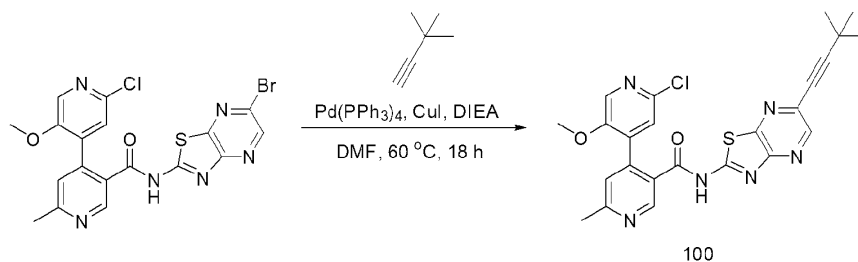
[464] LCMS: m/z (M+H)⁺ = 505.0.

[465] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.55 (s, 1H), 8.89 (s, 1H), 8.64 (s, 1H), 8.18 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 3.63 (s, 3H), 3.02 - 2.92 (m, 1H), 2.61 (s, 3H), 2.08 - 1.97 (m, 2H), 1.76 - 1.56 (m, 6H).

[466]

[467] **Example 100: Synthesis of Compound 100**

[468]



[469] To a solution of *N*-(6-bromo[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (2 mL) were added DIEA (78.85 mg, 0.61 mmol), 3,3-dimethylbut-1-yn-1-ol (33.41 mg, 0.41 mmol), CuI (2.32 mg, 0.01 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (11.75 mg, 0.01 mmol). The resulting mixture was degassed and purged with N_2 for three times, it was stirred at 60°C for 18 h under N_2 protection to give a brown solution. LCMS showed starting material was consumed and desired product was formed. The cooled reaction was filtered. The filtrate was purified by prep-HPLC(FA condition) to afford the desired product 4-(2-chloro-5-methoxypyridin-4-yl)-*N*-[6-(3,3-dimethylbut-1-ynyl)[1,3]thiazolo[4,5-*b*]pyrazin-2-yl]-6-methylpyridine-3-carboxamide (7.27 mg, 0.01 mmol) as a white solid.

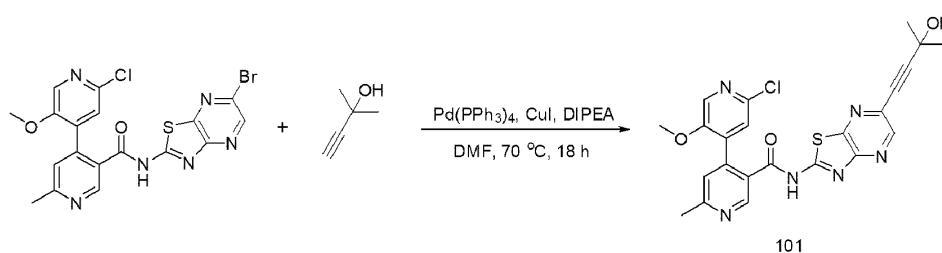
[470] LCMS: m/z ($\text{M}+\text{H}$) $^+$ = 493.0.

[471] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.56 (s, 1H), 8.93 (s, 1H), 8.55 (s, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 7.42 (s, 1H), 3.63 (s, 3H), 2.60 (s, 3H), 1.33 (s, 9H).

[472]

[473] **Example 101: Synthesis of Compound 101**

[474]



[475] To a solution of *N*-(6-bromo[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (10 mL) were added 2-methylbut-3-yn-2-ol (20.19 mg, 0.22 mmol), CuI (2.32 mg, 0.01 mmol), DIEA (78.85 mg, 0.61 mmol) and tetrakis(triphenylphosphine)palladium

(0) (37.05 mg, 0.01 mmol) at 25°C. The reaction was degassed N₂ three times and stirred at 70°C for 18 h. After filtration, the filtrate was purified by pre-HPLC (FA condition) to give 2'-chloro-N-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide (47.26 mg, 0.10 mmol) as a yellow solid.

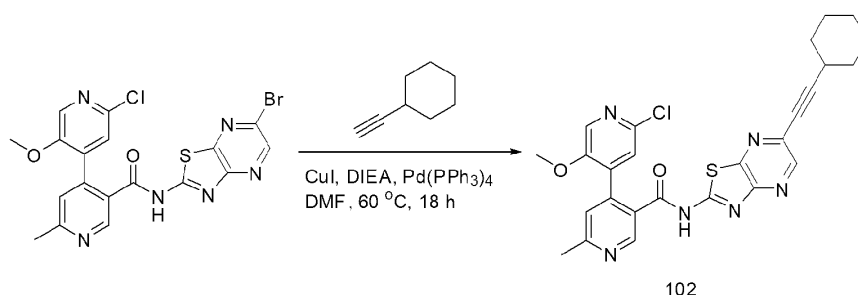
[476] LCMS: m/z (M+H)⁺ = 495.0.

[477] ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.59 (s, 1H), 8.89 (s, 1H), 8.65 (s, 1H), 8.18 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 5.68 (s, 1H), 3.63 (s, 3H), 2.61 (s, 3H), 1.51 (s, 6H).

[478]

[479] **Example 102: Synthesis of Compound 102**

[480]



[481] To a solution of *N*-(6-bromo[1,3]thiazolo[4,5-b]pyrazin-2-yl)-4-(2-chloro-5-methoxypyridin-4-yl)-6-methylpyridine-3-carboxamide (100 mg, 0.20 mmol) in DMF (2 mL) were added DIEA (78.85 mg, 0.61 mmol), ethynylcyclohexane (25.96 mg, 0.24 mmol), CuI (2.32 mg, 0.01 mmol) and Pd(PPh₃)₄ (7.05 mg, 0.01 mmol). The resulting mixture was degassed and purged with N₂ for three times, it was stirred at 60°C for 18 h under N₂ protection to give a brown solution. LCMS showed starting material was consumed and desired product was formed. The cooled reaction was filtered. The filtrate was purified by prep-HPLC(FA condition) to afford the desired product 4-(2-chloro-5-methoxypyridin-4-yl)-*N*-[6-(cyclohexylethynyl)[1,3]thiazolo[4,5-b]pyrazin-2-yl]-6-methylpyridine-3-carboxamide (59 mg, 0.11 mmol) as a yellow solid.

[482] LCMS: m/z (M+H)⁺ = 519.0.

[483] ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.55 (s, 1H), 8.89 (s, 1H), 8.64 (s, 1H), 8.18 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 3.63 (s, 3H), 2.81 - 2.71 (m, 1H), 2.61 (s, 3H), 1.93 - 1.81 (m, 2H), 1.76 - 1.65 (m, 2H), 1.60 - 1.46 (m, 3H), 1.44 - 1.30 (m, 3H).

[484]

[485] **Experimental example 1: Inhibitory activity against Polθ**

[486] Inhibitory activities against Polθ were measured for the compounds prepared in the above examples as follows.

[487] An ADP-GLO assay was used to measure the ability of compounds to inhibit the activity of Polθ-Helicase in vitro. A Recombinant Polθ-Helicase domain (aa 1-987)

was purchased from SignalChem Biotech (Catalog No. D681-31G) and stored at -80 °C in aliquots, Single stranded DNA was produced by Genscrip (30mer ssDNA (CT)15). Reactions were performed at room temperature, in freshly prepared assay buffer (25 mM Tris-HCl pH 7.5, 6 mM NaCl, 1.5 mM MgCl₂, 5% (v/v) glycerol, 0.01% v/v Triton x-100, 0.01% (w/v) Bovine γ -Globulin, 1 mM dithiothreitol). The compounds were dispensed on a 384-well plate (PerkinElmer# 6007290) using a Labcyte Echo 655 at varying concentrations (10 point, 1:3 dilution), 2 μ L of 2 X helicase domain Pol θ and DNA mix (3 nM helicase domain Pol θ and 2 nM DNA in assay buffer) was added to plates that had been pre-dispensed with compound. The plates were covered and left to incubate for 30 minutes at room temperature. then 2 μ L of 2 X substrate mix (80 μ M ATP in assay buffer) was added to the plates to start the enzyme reaction. The plates were covered and left to incubate for 1 hour at room temperature before the addition of the ADP-Glo™ Reagent. 4 μ L ADP-Glo™ Reagent containing 10mM MgCl₂ was added, and plates incubated for 40 minutes. 8 μ L kinase detection reagent was then added to the plates and incubated for 40 minutes. The luminescence was read on a 2105-0020 EnVision Multilabel Reader and raw data analyzed using log(inhibitor) vs. response - variable slope (four parameters) to generate IC₅₀ values. The results are shown in Table 1 below.

[488] [Table 1]

Example No.	Pol θ / IC ₅₀ (nM)
Example 1	22.16
Example 2	0.49
Example 3	60.51
Example 4	2.14
Example 5	0.78
Example 6	1.12
Example 7	0.5
Example 8	1.31
Example 9	9.15
Example 10	8.87
Example 11	13.93
Example 12	1.49
Example 13	3.41
Example 14	3.28

Example 15	0.42
Example 16	0.36
Example 18	1.61
Example 20	0.88
Example 99	0.22
Example 100	8.30
Example 101	9.65
Example 102	0.30

[489]

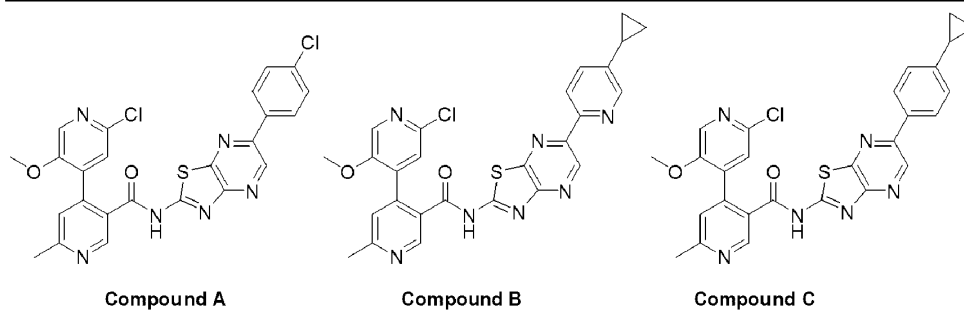
[490] **Experimental example 2: Evaluation of kinetic solubility** The stock solutions of test compounds were prepared in DMSO at the concentrations of 10 mM. Add 8.71 g K_2HPO_4 into 500 mL deionized water to prepare 100 mM K_2HPO_4 solution. Add 2.05 g KH_2PO_4 into 150 mL deionized water to prepare 100 mM KH_2PO_4 solution. Mix 405 mL of 100 mM K_2HPO_4 and 95 mL of 100 mM KH_2PO_4 and adjust the mixed solution to pH 7.4 with 100 mM K_2HPO_4 / KH_2PO_4 solution. 16 μ L of the compound 10 mM stock solution were added into 784 μ L different buffer in the 96 deep well plates ($n = 3$). The plate was sealed and shaken at room Temperature (PBS=7.4) for 1.5 h at 1000 rpm. After incubation, the solutions were transferred into the filter plate. All the samples were filtered by using the vacuum manifold. Aliquot of 5 μ L and 5 μ L DMSO were taken from the filtrate followed by addition of 490 μ L of a mixture of H_2O and acetonitrile containing internal standard (1:1). The mixture of H_2O and acetonitrile was used to dilute the diluent according to the signal response. The dilution factor was changed according to the solubility values and the UPLC-MS/MS signal response. 10 mM stock solution was diluted with DMSO to obtain 2, 20 and 200 μ M STD. Then 5 μ L DMSO STD and 5 μ L buffer were transferred into the remaining empty plate, and then 490 μ L of a mixture of H_2O and acetonitrile containing internal standard (1:1). A certain proportion of mixture of H_2O and acetonitrile was used to dilute the diluent according to the signal response. The dilution factor was changed according to the solubility values and the UPLC-MS/MS signal response. Mix well and analyze samples using UPLC-MS/MS. The results are shown in Table 2 below. For comparison, compounds A, B and C in which the right-hand side were substituted by aryl moieties were synthesized and tested the solubilities. As shown in table 2, the solubilities of substituted alkynyl analogues (example 2 and example 7) are much better than substituted aryl analogues (compounds A, B and C).

[491]

[492] [Table 2]

Example No.	Test systems	Solubility (μ M)
Example 2	PBS (pH=7.4)	122.33
Example 7	PBS (pH=7.4)	29.53
Compound A	PBS (pH=7.4)	0.41
Compound B	PBS (pH=7.4)	3.93
Compound C	PBS (pH=7.4)	<0.00033

[493]

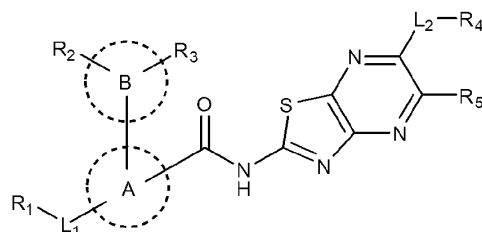


Claims

[Claim 1]

A compound represented by Chemical Formula 1 below, or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



in Chemical Formula 1,

A is a trivalent linker of C₂₋₁₀ heteroaromatic ring containing one to three heteroatoms selected from N, O, or S; or pyridone,

L₁ is a bond; C₁₋₄ alkylene; C₂₋₄ alkenylene; C₂₋₄ alkynylene; -S-; or -O-,

R₁ is hydrogen; C₁₋₄ alkyl; -CONH₂; -CONH(C₁₋₄ alkyl); -CON(C₁₋₄ alkyl)₂; C₂₋₁₀ heterocycloalkyl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl, or C₁₋₄ haloalkyl; or C₂₋₁₀ heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl, or C₁₋₄ haloalkyl,

B is a bivalent linker of C₆₋₁₀ aromatic ring; C₂₋₁₀ heterocycloalkane ring containing one to three heteroatoms selected from N, O, or S; or C₂₋₁₀ heteroaromatic ring containing one to three heteroatoms selected from N, O, or S,

R₂ and R₃ are each independently, hydrogen; C₁₋₄ alkyl; C₂₋₄ alkenyl; C₂₋₄ alkynyl; C₁₋₄ haloalkyl; C₁₋₄ alkoxy; halogen; cyano; or C₂₋₆ heterocycloalkyloxy containing one oxygen; or R₂ and R₃ when on adjacent ring vertices, combine to form a C₂₋₆ heterocycloalkyl containing one to three heteroatoms selected from N, O, or S; or C₂₋₆ heteroaryl containing one to three heteroatoms selected from N, O, or S,

L₂ is a bond; C₁₋₄ alkylene; -CO-; -CONH-; -NHCO-; -S-; or -O-,
R₄ is -C≡C-R'; C₆₋₁₀ aryl, which is unsubstituted or substituted by halogen, or C₁₋₄ alkoxy; C₃₋₆ cycloalkyl, which is unsubstituted or substituted by hydroxy; C₂₋₁₀ heterocycloalkyl containing one to

three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl, C₁₋₄ haloalkyl, or hydroxy; or C₂₋₁₀ heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by halogen, C₁₋₄ alkyl, or C₁₋₄ haloalkyl,

R' is hydrogen; C₁₋₄ alkyl, which is unsubstituted or substituted by cyano; (C₁₋₄ alkoxy)C₁₋₄ alkyl; C₁₋₄ hydroxyalkyl; C₂₋₆ heterocycloalkyl containing one oxygen; C₃₋₆ cycloalkyl, which is unsubstituted or substituted by one or two halogens; C₆₋₁₀ aryl, which is unsubstituted or substituted by halogen; C₂₋₁₀ heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl; or C₂₋₁₀ heterocycloalkyl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl,

R₅ is hydrogen; hydroxy; C₁₋₄ alkyl; C₃₋₆ cycloalkyl; or halogen, with the proviso that R₄ is -C≡C-R' when L₂ is a bond.

[Claim 2]

The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein

A is a trivalent linker of 1,3-benzodioxole; 2,3-dihydrobenzofuran; 2-pyridone; imidazo[1,5-a]pyridine; imidazole; pyridazine; or pyridine.

[Claim 3]

The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein

L₁ is a bond; -CH₂-; -C≡C-; or -O-.

[Claim 4]

The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein

R₁ is hydrogen; CH₃; -CONH₂; -CONH(CH₃); -CON(CH₃)₂; or any ring selected from the group consisting of 4,7-diazaspiro[2.5]octan-8-onyl, 7-azaspiro[3.5]nonan-6-onyl, 2-pyridonyl, oxadiazolyl, oxopyridazinyl, pyrazolyl, or thiazolyl, which ring is unsubstituted or substituted by CH₃, or CF₃.

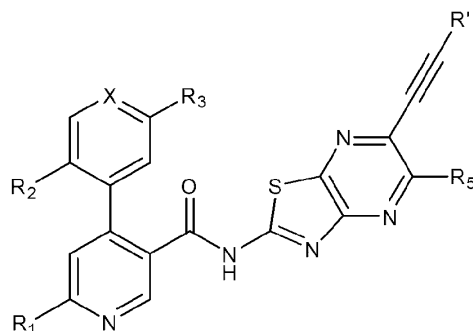
[Claim 5]

The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein

B is a bivalent linker of 1,3-benzodioxole; 2-oxa-5-azabicyclo[4.1.0]heptane; 3,4-dihydro-2H-benzo[b][1,4]oxazine; 3-oxa-8-azabicyclo[3.2.1]octane; 4,5,6,7-tetrahydropyrazolo[1

- ,5-a]pyrimidine; 4-oxa-7-azaspiro[2.5]octane; benzene; benzo[d]oxazole; benzo[d]thiazole; morpholine; piperazin-2-one; pyrazole; or pyridine.
- [Claim 6] The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein R_2 and R_3 are each independently, hydrogen; CH_3 ; $-C\equiv CH$; CHF_2 ; CF_3 ; OCH_3 ; F; Cl; cyano; or (oxetanyl)oxy.
- [Claim 7] The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein L_2 is a bond; $-CH_2-$; $-CO-$; $-CONH-$; $-NHCO-$; $-S-$; or $-O-$.
- [Claim 8] The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein R_4 is $-C\equiv C-R'$; R' is hydrogen; methyl; ethyl; propyl; isopropyl; butyl; isobutyl; tert-butyl; $-\text{CH}(\text{CH}_3)(\text{CN})$; $-\text{CH}_2-\text{O}-\text{CH}_3$; 2-hydroxyprop-2-yl; 1H-pyrrolo[2,3-b]pyridinyl, which is unsubstituted or substituted by CH_3 ; oxetanyl; tetrahydrofuranyl; cyclopropyl, which is unsubstituted or substituted by one or two F; cyclobutyl, which is unsubstituted or substituted by one or two F; cyclopentyl, cyclohexyl; spiro[2.2]pentanyl; phenyl, which is unsubstituted or substituted by Cl; pyrazolyl, which is unsubstituted or substituted by CH_3 ; or pyridinyl.
- [Claim 9] The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein R_4 is phenyl, which is unsubstituted or substituted by Cl and OCH_3 ; cyclohexyl, which is unsubstituted or substituted by hydroxy; hexahydrofuro[2,3-b]furanyl; bicyclo[2.2.2]octanyl, which is unsubstituted or substituted by hydroxy; 2,3-dihydrobenzofuranyl; 4-oxaspiro[2.4]heptanyl; tetrahydrofuranyl; 1,3-benzodioxolyl; or pyridinyl, which is unsubstituted or substituted by Cl.
- [Claim 10] The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein R_5 is hydrogen; hydroxy; CH_3 ; cyclopropyl; or Cl.
- [Claim 11] The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein the Chemical Formula 1 is represented by Chemical Formula 2 below:

[Chemical Formula 2]



in Chemical Formula 2,

X is N, or CH,

R₁ is C₁₋₄ alkyl; or C₂₋₁₀ heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl, or C₁₋₄ haloalkyl,

R₂ is C₁₋₄ alkoxy,R₃ is C₁₋₄ haloalkyl; or halogen,

R' is hydrogen; C₁₋₄ hydroxyalkyl; C₂₋₆ heterocycloalkyl containing one oxygen; C₃₋₆ cycloalkyl, which is unsubstituted or substituted by one or two halogens; or C₂₋₁₀ heteroaryl containing one to three heteroatoms selected from N, O, or S, which is unsubstituted or substituted by C₁₋₄ alkyl,

R₅ is hydrogen; hydroxy; C₁₋₄ alkyl; C₃₋₆ cycloalkyl; or halogen.

[Claim 12]

The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein

the compound represented by Chemical Formula 1 is any one selected from the group consisting of the following:

- 1) 2'-chloro-N-(6-ethynylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 2) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 3) 2'-chloro-5'-methoxy-6-methyl-N-(6-((1-methyl-1H-pyrazol-4-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 4) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

- 5) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide,
- 6) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-(trifluoromethyl)-4,4'-bipyridine-3-carboxamide,
- 7) 2'-chloro-N-(6-((3,3-difluorocyclobutyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 8) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(4-methyl-6-oxopyridazin-1(6H)-yl)nicotinamide,
- 9) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)nicotinamide,
- 10) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-(2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)nicotinamide,
- 11) 2'-chloro-N-(5-cyclopropyl-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 12) 2'-chloro-N-(6-(cyclopropylethynyl)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 13) 2'-chloro-5'-methoxy-6-methyl-N-(6-(oxetan-3-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 14) 2'-chloro-5'-methoxy-N-(6-(3-methoxyprop-1-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4,4'-bipyridine-3-carboxamide,
- 15) 2'-chloro-5'-methoxy-6-methyl-N-(6-(pyridin-2-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 16) 2'-chloro-N-(6-((4-chlorophenyl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 17) 2'-chloro-5'-methoxy-6-methyl-N-(6-(spiro[2.2]pentan-1-ylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,

- 18) 2'-chloro-5'-methoxy-6-methyl-N-(6-((tetrahydrofuran-3-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 19) 2'-chloro-5'-methoxy-6-methyl-N-(6-((1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)ethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 20) 2'-chloro-N-(5-chloro-6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 21) 2'-chloro-N-(6-(cyclopropylethynyl)-5-hydroxythiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 22) 2'-chloro-5'-methoxy-6-methyl-N-(6-(tetrahydrofuran-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 23) 2'-chloro-N-(6-((5-chloropyridin-2-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 24) 2'-chloro-5'-methoxy-6-methyl-N-(6-((tetrahydrofuran-3-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 25) N-(6-(4-oxaspiro[2.4]heptan-6-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 26) 2'-chloro-N-(6-(5-chloropyridin-2-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 27) 2'-chloro-N-(6-(4-chloro-3-methoxyphenoxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 28) 2-(2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamido)-N-(tetrahydrofuran-3-yl)thiazolo[4,5-b]pyrazine-6-carboxamide,
- 29) 2'-chloro-5'-methoxy-6-methyl-N-(6-(tetrahydrofuran-3-carboxamido)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 30) 2'-chloro-5'-methoxy-6-methyl-N-(6-(morpholine-4-carbonyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,

- 31) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(4-methyl-6-oxopyridazin-1(6H)-yl)-4,4'-bipyridine-3-carboxamide,
- 32) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-(4-methyl-6-oxopyridazin-1(6H)-yl)nicotinamide,
- 33) 2'-chloro-N-(6-(5-chloropyridin-2-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(4-methyl-6-oxopyridazin-1(6H)-yl)-4,4'-bipyridine-3-carboxamide,
- 34) 2'-chloro-5'-methoxy-6-(4-methyl-6-oxopyridazin-1(6H)-yl)-N-(6-(tetrahydrofuran-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 35) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamide,
- 36) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(4-methyl-8-oxo-4,7-diazaspiro[2.5]octan-7-yl)-4,4'-bipyridine-3-carboxamide,
- 37) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2,3-dihydrobenzofuran-6-carboxamide,
- 38) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-4-carboxamide,
- 39) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(6-oxo-7-azaspiro[3.5]nonan-7-yl)-4,4'-bipyridine-3-carboxamide,
- 40) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-(5-methyl-1,3,4-oxadiazol-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- 41) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- 42) 1-(2-amino-2-oxoethyl)-5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2-oxo-1,2-dihydropyridine-4-carboxamide,

- 43) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-(2-(methylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- 44) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1-(2-(dimethylamino)-2-oxoethyl)-2-oxo-1,2-dihydropyridine-4-carboxamide,
- 45) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(thiazol-2-yloxy)-4,4'-bipyridine-3-carboxamide,
- 46) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-(oxetan-3-ylethynyl)-4,4'-bipyridine-3-carboxamide,
- 47) 2'-chloro-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-((1-methyl-1H-pyrazol-4-yl)ethynyl)-4,4'-bipyridine-3-carboxamide,
- 48) 7-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)imidazo[1,5-a]pyridine-6-carboxamide,
- 49) 1-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-1H-imidazole-5-carboxamide,
- 50) 5-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)pyridazine-4-carboxamide,
- 51) 6-(2-chloro-5-methoxypyridin-4-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)benzo[d][1,3]dioxole-5-carboxamide,
- 52) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4-morpholinonicotinamide,
- 53) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-(difluoromethyl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 54) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-2'-(trifluoromethyl)-4,4'-bipyridine-3-carboxamide,

- 55) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-(difluoromethyl)-2-methoxyphenyl)-6-methylnicotinamide,
- 56) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2-methoxy-5-(trifluoromethyl)phenyl)-6-methylnicotinamide,
- 57) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(5-ethynyl-2-methoxyphenyl)-6-methylnicotinamide,
- 58) 4-(5-cyano-2-methoxyphenyl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- 59) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4-(2-(oxetan-3-yloxy)phenyl)nicotinamide,
- 60) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)-6-methylnicotinamide,
- 61) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-methylnicotinamide,
- 62) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-6-methylnicotinamide,
- 63) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4-(4-oxa-7-azaspiro[2.5]octan-7-yl)nicotinamide,
- 64) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methyl-4-(2-methyl-3-oxopiperazin-1-yl)nicotinamide,
- 65) 4-(2-oxa-5-azabicyclo[4.1.0]heptan-5-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- 66) 4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- 67) 4-(benzo[d]thiazol-7-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- 68) 4-(benzo[d]oxazol-7-yl)-N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide,
- 69) N-(6-(cyclopropylethynyl)thiazolo[4,5-b]pyrazin-2-yl)-4-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-6-methylnicotinamide,
- 70) 2'-chloro-5'-methoxy-6-methyl-N-(6-(prop-2-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 71) 2'-chloro-N-(6-(3-cyclopropylprop-2-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

- 72) 2'-chloro-5'-methoxy-6-methyl-N-(6-(3-(oxetan-3-yl)prop-2-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 73) 2'-chloro-5'-methoxy-6-methyl-N-(6-(3-(1-methyl-1H-pyrazol-4-yl)prop-2-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 74) 2'-chloro-N-(6-(3-cyanobut-1-ynyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 75) 2'-chloro-N-(5-chloro-6-((tetrahydrofuran-3-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 76) 2'-chloro-5'-methoxy-6-methyl-N-(5-methyl-6-((tetrahydrofuran-3-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 77) 2'-chloro-5'-methoxy-6-methyl-N-(5-methyl-6-(tetrahydrofuran-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 78) 2'-chloro-N-(6-((5-chloropyridin-2-yl)methyl)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 79) 2'-chloro-N-(6-(5-chloropyridin-2-yloxy)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 80) 2'-chloro-5'-methoxy-6-methyl-N-(6-(tetrahydrofuran-3-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 81) 2'-chloro-5'-methoxy-6-methyl-N-(5-methyl-6-(tetrahydrofuran-3-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-4,4'-bipyridine-3-carboxamide,
- 82) 2'-chloro-N-(6-(5-chloropyridin-2-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 83) 2'-chloro-N-(6-(5-chloropyridin-2-ylthio)-5-methylthiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 84) 2'-chloro-N-(6-(4-hydroxycyclohexyloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

- 85) 2'-chloro-N-(6-(hexahydrofuro[2,3-b]furan-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 86) 2'-chloro-N-(6-(5-hydroxybicyclo[2.2.2]octan-2-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 87) N-(6-(benzo[d][1,3]dioxol-4-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 88) 2'-chloro-N-(6-(2,3-dihydrobenzofuran-3-yloxy)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 89) 2'-chloro-N-(6-(4-chloro-3-methoxybenzyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 90) 2'-chloro-N-(6-((4-hydroxycyclohexyl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 91) N-(6-(4-oxaspiro[2.4]heptan-6-ylmethyl)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 92) 2'-chloro-N-(6-((hexahydrofuro[2,3-b]furan-3-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 93) 2'-chloro-N-(6-((5-hydroxybicyclo[2.2.2]octan-2-yl)methyl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 94) 2'-chloro-N-(6-(4-chloro-3-methoxyphenylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 95) 2'-chloro-N-(6-(4-hydroxycyclohexylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 96) N-(6-(4-oxaspiro[2.4]heptan-6-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-2'-chloro-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 97) 2'-chloro-N-(6-(hexahydrofuro[2,3-b]furan-3-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,

- 98) 2'-chloro-N-(6-(5-hydroxybicyclo[2.2.2]octan-2-ylthio)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-4,4'-bipyridine-3-carboxamide,
- 99) 4-(2-chloro-5-methoxypyridin-4-yl)-N-[6-(cyclopentylethynyl)[1,3]thiazolo[4,5-b]pyrazin-2-yl]-6-methylpyridine-3-carboxamide,
- 100) 4-(2-chloro-5-methoxypyridin-4-yl)-N-[6-(3,3-dimethylbut-1-ynyl)[1,3]thiazolo[4,5-b]pyrazin-2-yl]-6-methylpyridine-3-carboxamide,
- 101) 2'-chloro-N-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)thiazolo[4,5-b]pyrazin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide, and
- 102) 4-(2-chloro-5-methoxypyridin-4-yl)-N-[6-(cyclohexylethynyl)[1,3]thiazolo[4,5-b]pyrazin-2-yl]-6-methylpyridine-3-carboxamide.

[Claim 13]

A pharmaceutical composition for the prevention or treatment of cancer, comprising the compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.