**CDK kinase assays.**

* Kinase assays for CDKs were carried out using recombinant CDK/cyclins purchased from Carna Biosciences (CDK2/cyclin E, CDK4/cyclin D3, and CDK6/cyclin D3). All activity assays were performed in duplicate in white low volume 384-well plates. Reactions were carried out in 40 mM Tris-HCl pH 7.5, containing 20 mM MgCl2, 0.1 % BSA, and 50 μM DTT. The reactions were initiated by the addition of ATP and substrate peptides. The plates were incubated at 37°C for 30 min and followed by two-step ADP-Glo detection. The plates were finally read out using a TecanSpark plate reader. Data was analyzed using curve-fitting software (GraphPad Prism version 9). IC50 values were determined from a 12-point concentration curve using ATP concentrations approximating Km values. Ki values were calculated according to the equation: *K*i = IC50/(1 + S/*K*m), where S is the ATP concentration in the assay and Km is the Michaelis-Menten constant for ATP. Molecule10-25 were purchased from Enamine and molecule 73 was synthesized internal. Reversed-phase HPLC analyses were performed on an Agilent 1260 HPLC system. Purity of all compounds for biological evaluation was confirmed by HPLC to be >95%.

Supplementary

(R)-N-(2,3-dihydro-1H-inden-1-yl)-5-(morpholinomethyl)pyridin-2-amine **(Molecule10)**. HPLC analysis: retention time = 0.554min; peak area, 100%

2-((1H-pyrazol-4-yl)methyl)-3,5,6,7,8,9-hexahydro-4H-cyclohepta[4,5]thieno[2,3-d]pyrimidin-4-one **(Molecule11)**.HPLC analysis: retention time = 0.894min; peak area, 100%

(1R,3s,5S)-N-(4-(3-fluorophenyl)-1,3,5-triazin-2-yl)-8-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-3-amine **(Molecule17).** HPLC analysis: retention time = 1.239min; peak area, 100%

2-(1H-indazol-6-yl)-N-(5-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-3-yl)acetamide **(Molecule18)**. HPLC analysis: retention time = 0.958min; peak area, 97.4%

1-(((1R,2R,4R,5R)-5-hydroxybicyclo[2.2.1]heptan-2-yl)methyl)-3-(5-(tetrahydro-2H-pyran-4-yl)thiazol-2-yl)urea **(Molecule20)**. HPLC analysis: retention time = 1.066min; peak area, 100%

(R)-N-(5-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-3-yl)-2-(1,2,3,4-tetrahydronaphthalen-2-yl)acetamide **(Molecule21)**. HPLC analysis: retention time = 1.089min; peak area, 100%

4-(6-isopropyl-4-oxo-3,4-dihydroquinazolin-2-yl)benzenesulfonamide **(Molecule23)**. HPLC analysis: retention time = 1.193min; peak area, 95.33%

(S)-1-((3-methyltetrahydrofuran-3-yl)methyl)-3-(5-(tetrahydro-2H-pyran-4-yl)thiazol-2-yl)urea **(Molecule25)**. HPLC analysis: retention time = 0.924min; peak area, 100%

4-((2-(((1R,2R)-2-hydroxycyclohexyl)amino)benzo[d]thiazol-6-yl)oxy)-N-methylpicolinamide (**PB01-001**). Peak area, 99%

4-(3-methoxy-4-((4-methoxybenzyl)oxy)phenoxy)-N-methylpicolinamide (**PB01-002**). Peak area, 95%

5-(3-methoxy-4-((4-methoxybenzyl)oxy)benzyl)pyrimidine-2,4-diamine (**PB01-003**). Peak area, 97%

4-((5-methoxy-6-((5-methoxypyridin-2-yl)methoxy)pyridin-3-yl)methyl)-2-(1-methyl-1H-pyrazol-4-yl)pyrimidine (PB01-004). Peak area, 97%

N-(4-((2-((1-ethyl-3,3-dimethyl-2-oxoindolin-5-yl)amino)-5-methylpyrimidin-4-yl)oxy)-2-methylphenyl)acetamide (**PB01-005**). Peak area, 97%

1-ethyl-5-((4-methoxy-5-methylpyrimidin-2-yl)amino)-3,3-dimethylindolin-2-one (**PB01-006**). Peak area, 99.67%

4-((2-acetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)-2-((4-(tert-butyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (**PB01-007**). Peak area, 90%

2-((6-(7-acetyl-2,7-diazaspiro[3.5]nonan-2-yl)-2-(pyridin-3-yl)pyrimidin-4-yl)amino)isonicotinonitrile **(PB02-001)**. Peak area, 99.06%

1-(2-(6-((4-ethylpyridin-2-yl)amino)-2-(pyridin-3-yl)pyrimidin-4-yl)-2,7-diazaspiro[3.5]nonan-7-yl)ethan-1-one **(PB02-002)**. Peak area, 99.22%

1-(2-(2-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-6-((4-(trifluoromethoxy)pyridin-2-yl)amino)pyrimidin-4-yl)-2-azaspiro[3.4]octan-6-yl)ethan-1-one (**PB02-003**). Peak area, 97%

(R)-N-((5,5-difluoro-1-(3-methyl-6-((4-(trifluoromethyl)pyridin-2-yl)amino)picolinoyl)piperidin-2-yl)methyl)acetamide (**PB03-001**). Peak area, 94.71%

N-(4-bromo-2,5-difluorophenyl)-6-chloro-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide **(PB04-001)**. Peak area, 95%

N-(4-bromo-2,5-difluorophenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-3-sulfonamide **(PB04-002)**. Peak area, 95%

2-((1R,5S,6R)-3-(2-((S)-2-methylazetidin-1-yl)-6-(trifluoromethyl)pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexan-6-yl)acetic acid (**PB05-001**). Peak area, 97%

2-(3-(2-((S)-2-methylazetidin-1-yl)-6-(trifluoromethyl)pyrimidin-4-yl)-2-oxo-3-azabicyclo[3.1.0]hexan-6-yl)acetic acid (**PB05-002**). Peak area, 97.61%