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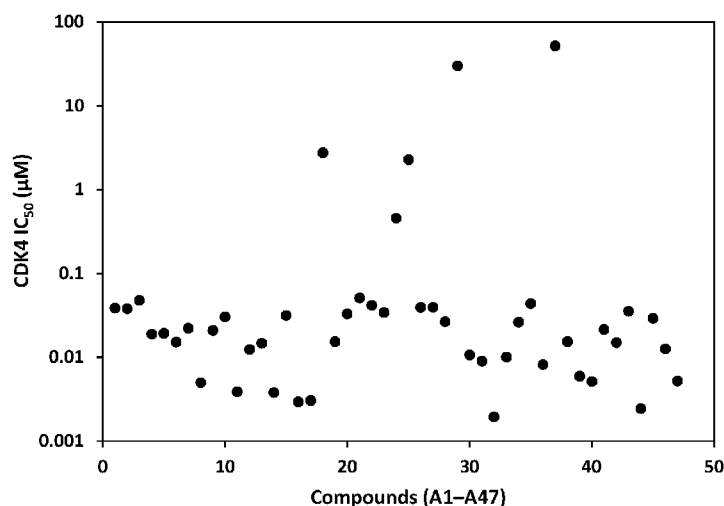
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(54) Title: CYCLIN-DEPENDENT KINASE INHIBITORS

FIG. 1



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

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CYCLIN-DEPENDENT KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of U.S. Provisional Patent Application
5 No. 62/785,857, filed December 28, 2018, which is hereby incorporated herein by reference in its entirety.

TECHNICAL FIELD

Described herein are compounds and their pharmaceutically acceptable salts,
10 pharmaceutical compositions thereof, methods of treatment, and medical uses. The compounds described herein are modulators of cyclin-dependent kinases and are useful in the treatment or alleviation of protein kinase associated disorders, including cancer, infectious diseases, autoimmune diseases, or cardiovascular diseases.

15 BACKGROUND

The cell cycle is a complex series of events that cause a cell to divide and duplicate. The phases of the cell cycle include mitosis (M), gap 1 phase (G1), synthesis phase (S) and gap 2 phase (G2). Checkpoints in the cell cycle ensure that division only occurs after sufficient growth and faithful DNA replication and under favorable conditions. At each checkpoint, a variety of
20 proteins engage in a series of carefully coordinated biochemical reactions. This complexity allows for precise regulation of all steps in the cell cycle.

Cyclin-dependent kinases (CDKs) are powerful protein kinase enzymes that drive cell cycle regulation in biochemical pathways by modulating the activity of various target proteins of the cell cycle. In response to a variety either intra- or extracellular cues, the enzymes function by
25 the transfer of phosphate groups from intracellular adenosine triphosphate (ATP) to the serine or threonine amino acids of target proteins involved in a signaling pathway. These activating or inhibitory phosphorylation events act as the signals that either activate or deactivate target protein activity, and thus stimulate or inhibit the cell from entering the cell cycle and dividing.

CDKs themselves require the presence of cyclin proteins to activate. A variety of cyclin
30 proteins exist, each of which is present at varying protein levels and act during a specific stage of the cell cycle by binding to specific CDKs. The cyclin-CDK complexes then recognize and modify multiple target substrates and thus coordinate multiple events during each phase of the cell cycle. Thus, the various activities of the cell cycle are determined by the specific combination of cyclins and CDKs that are active at each stage. For example, cyclin D and CDK4 and CDK6 have been

found to be active during the G1 phase of the cell cycle and react to external signals such as growth factors and mitogens. Cyclins A and E and CDK2 have been found to be active during G1/S phase of the cell cycle and are thought to regulate centrosome duplication. Some cyclin-CDK complexes are found to be involved in transcription activities, such as cyclin A, cyclin E and CDK2 which are thought to target helicase and polymerase protein enzymes. CDK-cyclin controlled protein phosphorylation thus plays an important role in many key cellular processes including cell division, metabolism, survival, and apoptosis.

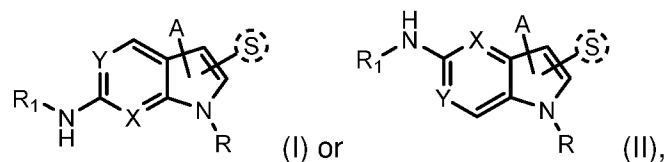
The ubiquitous nature of CDKs coupled with the highly regulated and complex nature of CDK dependent phosphorylation makes it susceptible to malfunction. Thus, CDKs are implicated in a variety of cell-cycle dependent diseases, including cancers, cardiovascular diseases, neurodegenerative disorders, autoimmune diseases and infectious diseases with the CDKs either the causative agents or as therapeutic targets.

Of particular interest are CDK4, CDK6, and CDK9 as therapeutic targets. These cyclin-dependent kinases are involved in cell cycle regulation and have been found to be deregulated and overactive in cancer cells as result of overexpression of relevant genes or loss of naturally occurring, endogenous inhibitors by gene deletion or mutation. Thus, inhibitors of CDK4/6/9 among other cyclin dependent kinases are important targets for cancer therapeutics, alone or in combination with other drugs.

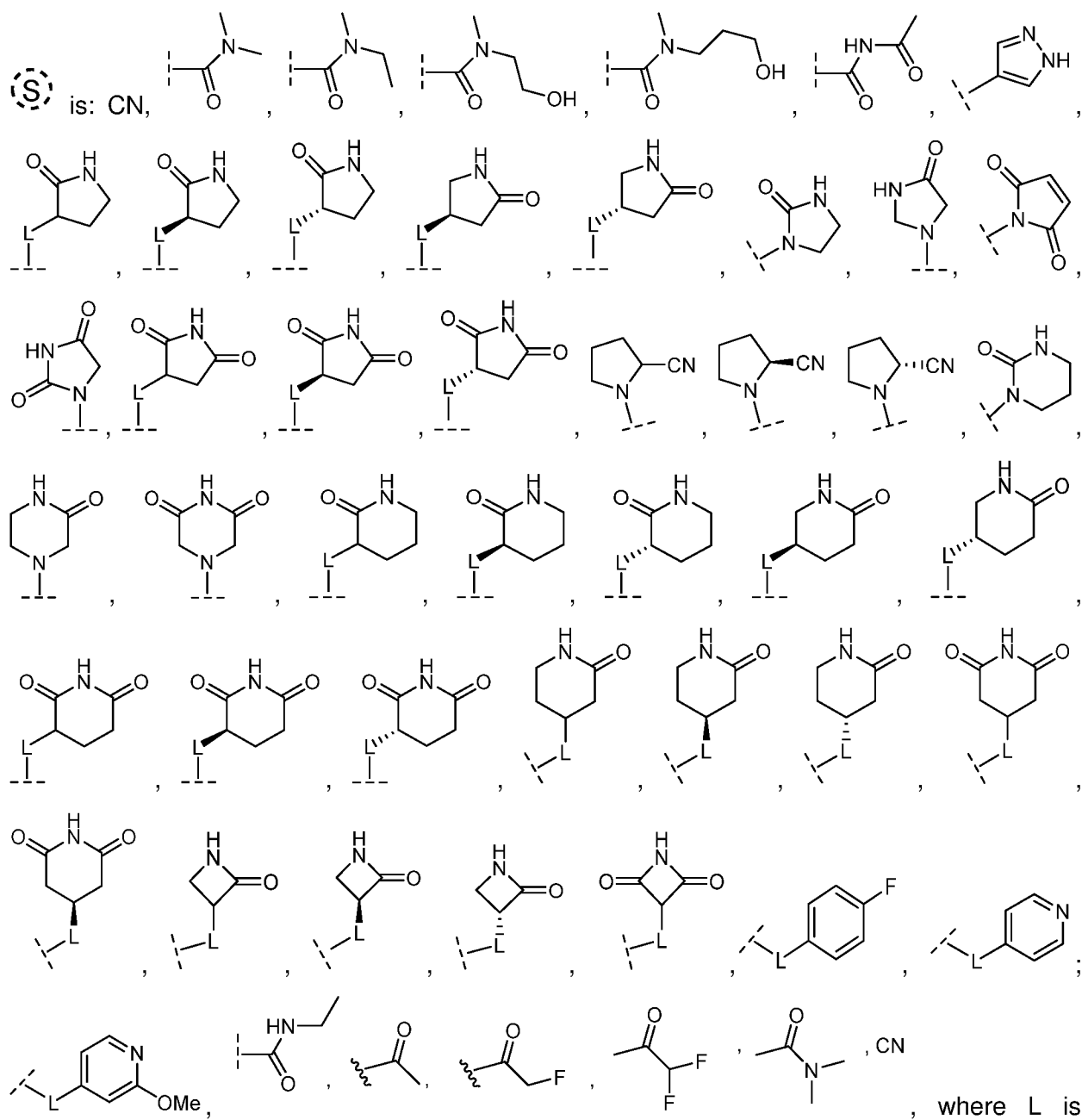
Thus, there remains a need for additional cyclin dependent kinase inhibitors suitable for pharmaceuticals.

SUMMARY

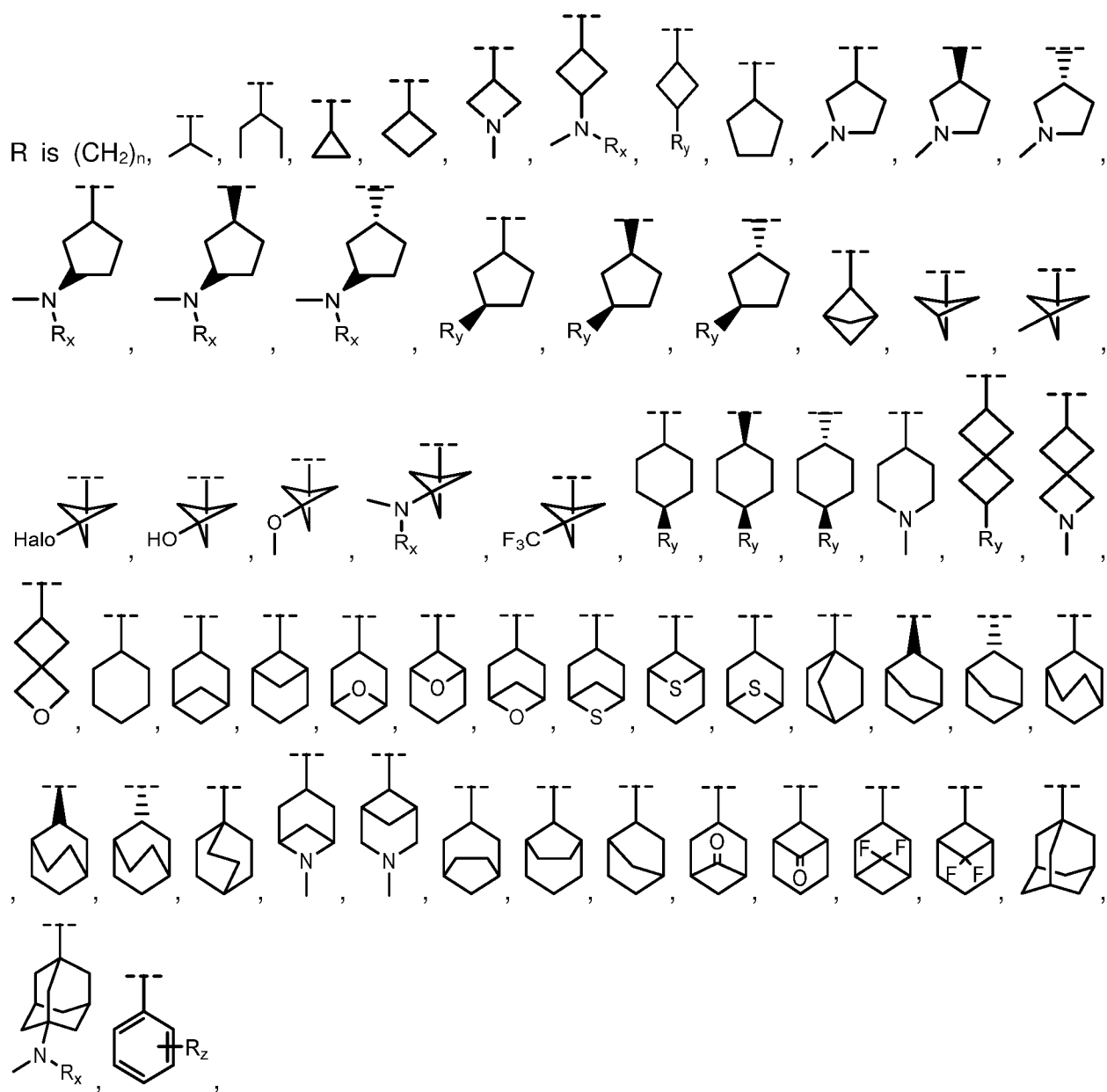
One embodiment described herein is a compound or a pharmaceutically acceptable salt thereof comprising Formula I or II:



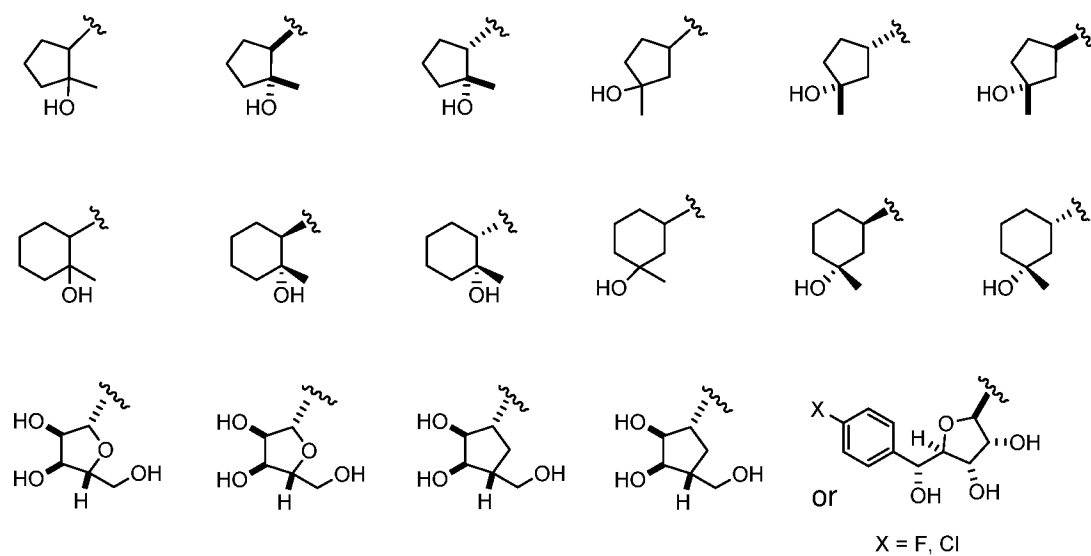
wherein A is H, F, Me, or CON(Me)₂; X and Y are independently, C, N, or C-F;



none, CH₂, CO, NH, O, or S;

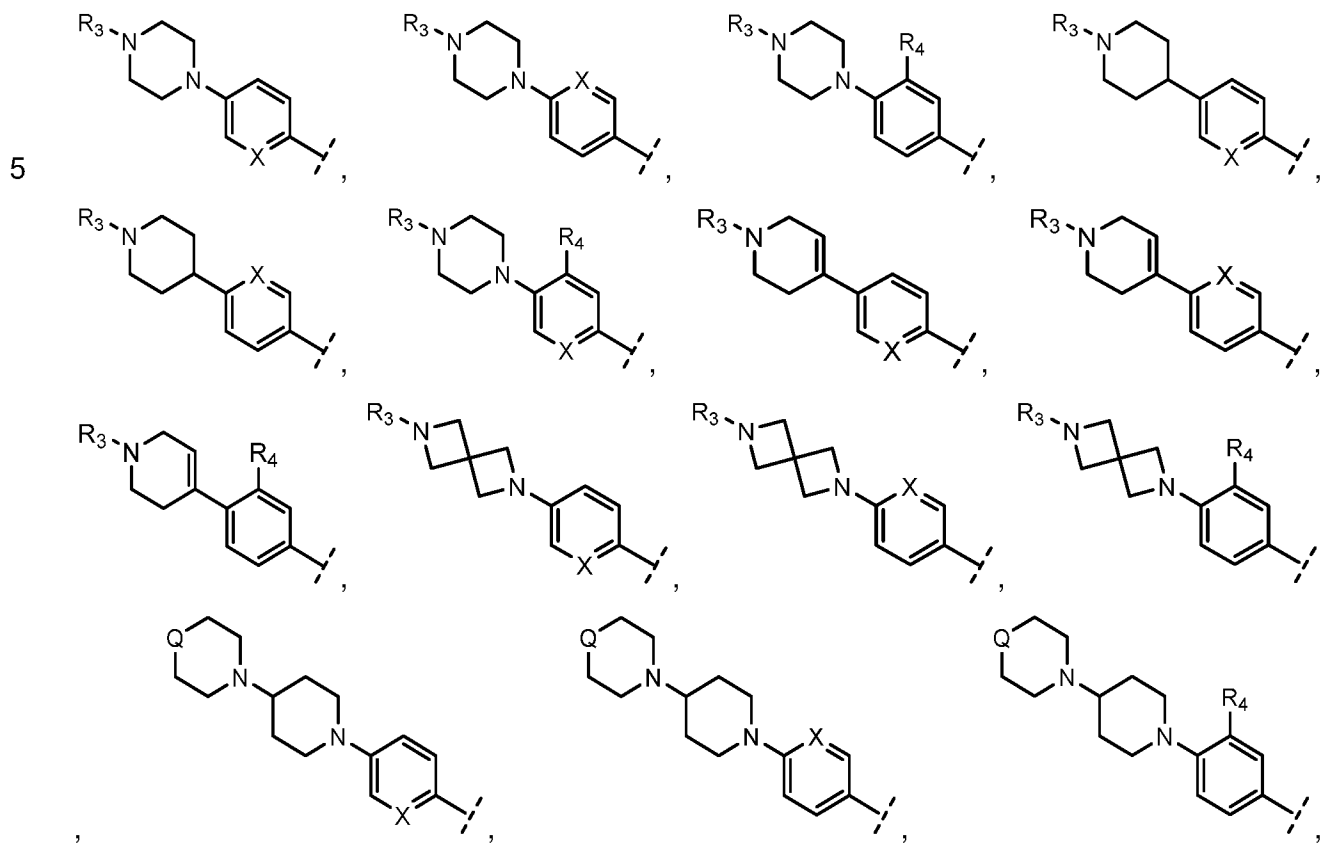


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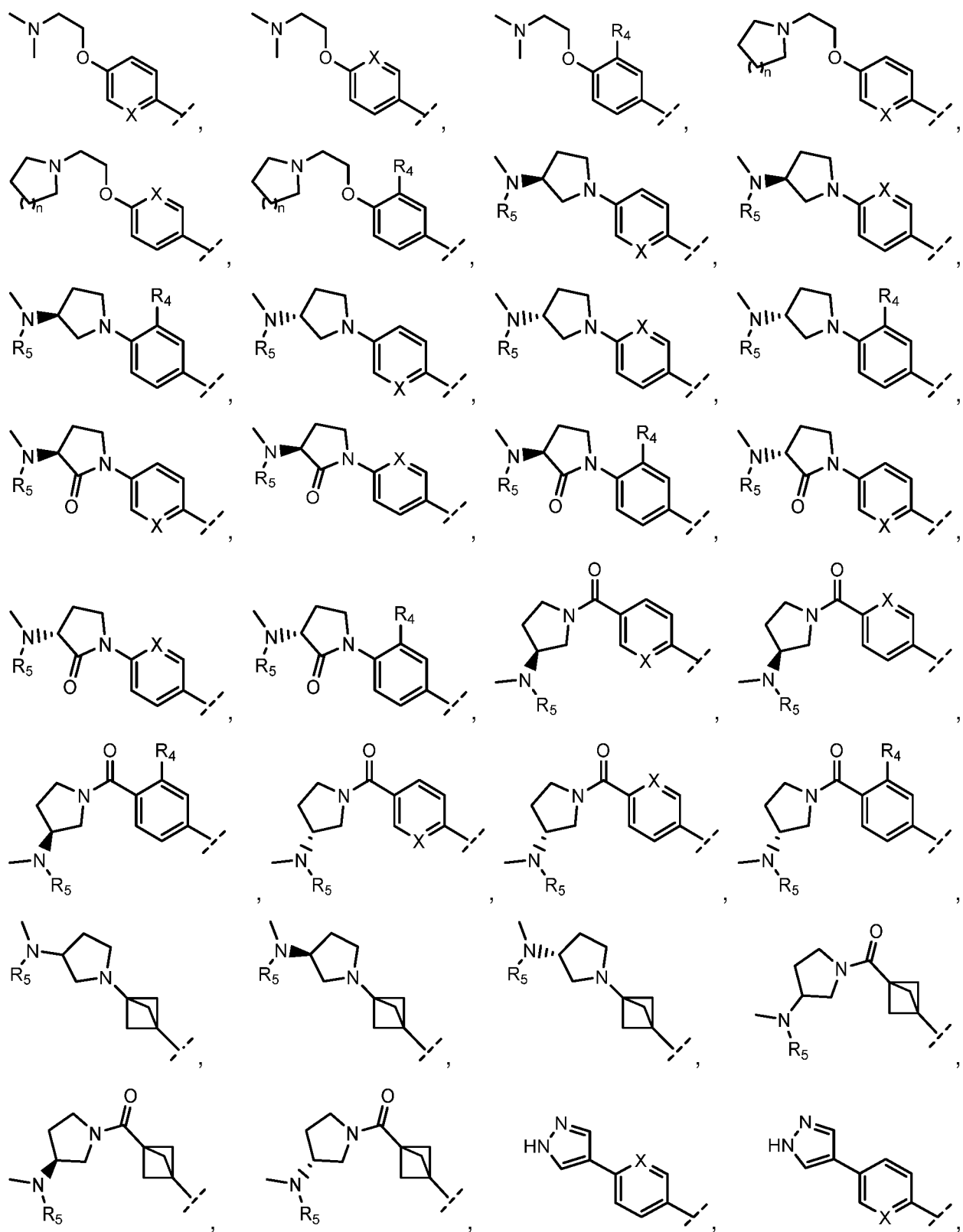


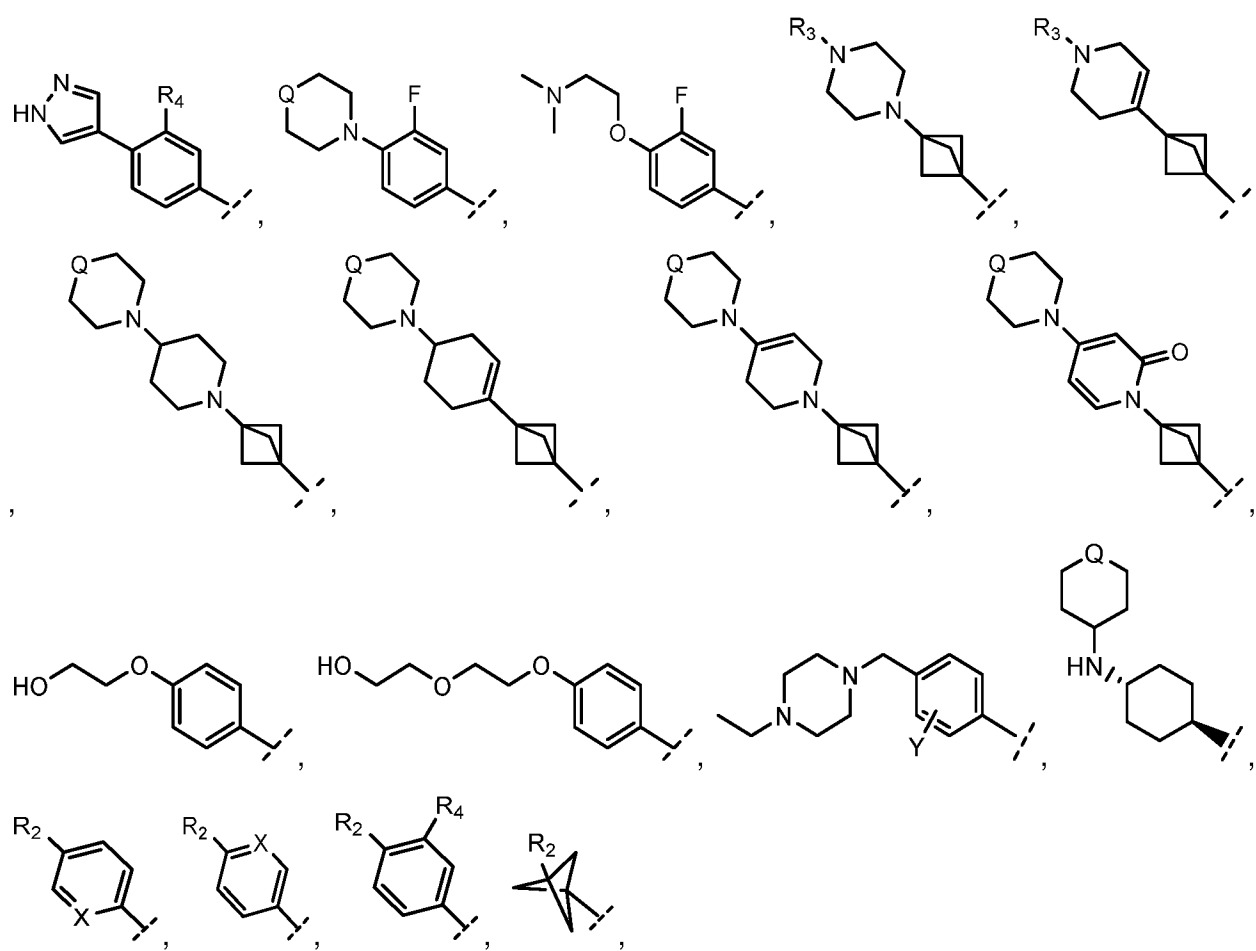
where R_x is H or Me, R_y is Me, OH, or OMe; R_z is H, Me, OMe, OH, N, F, or CF₃; and n is 1 to 11;
and

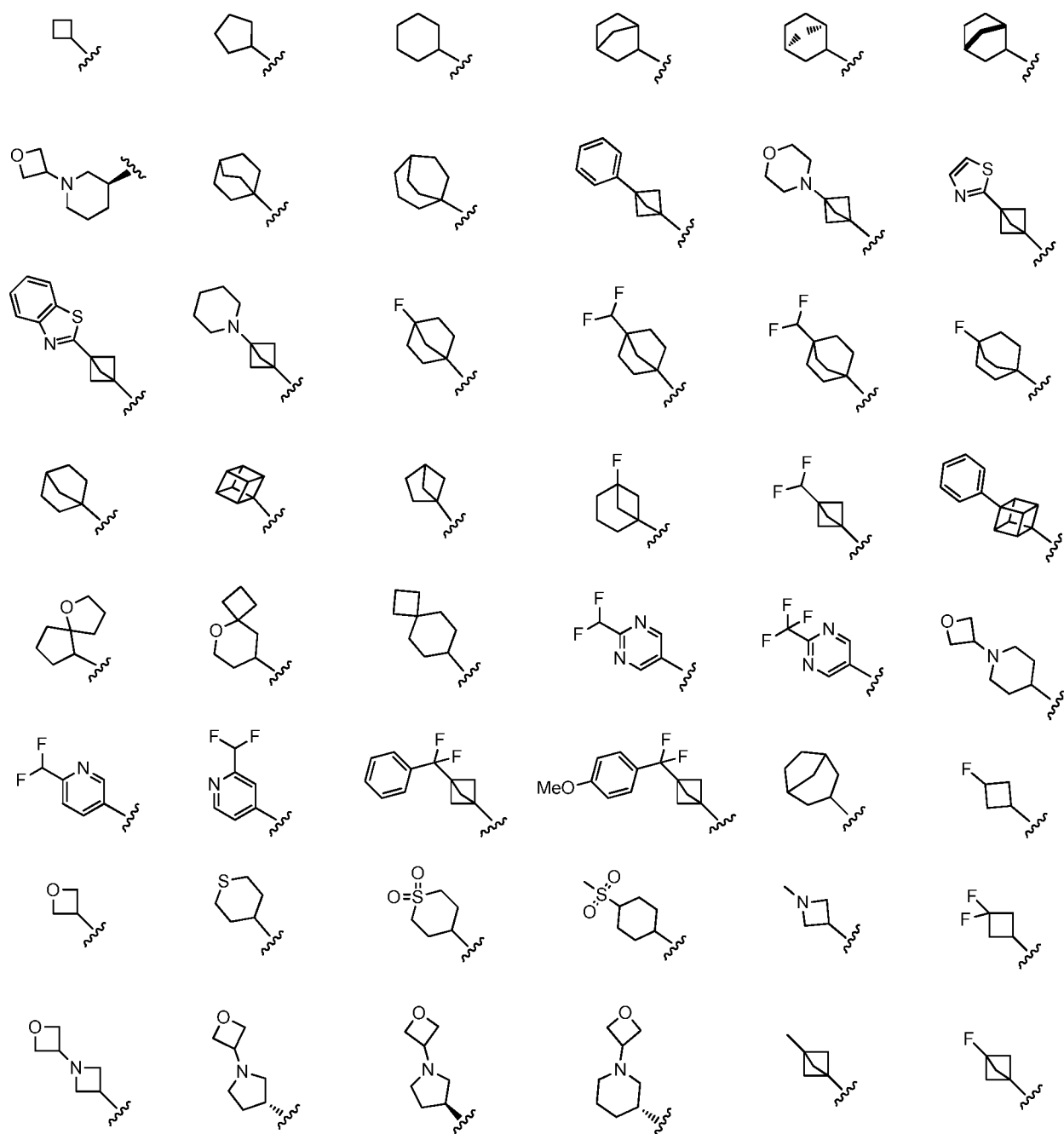
R_1 is

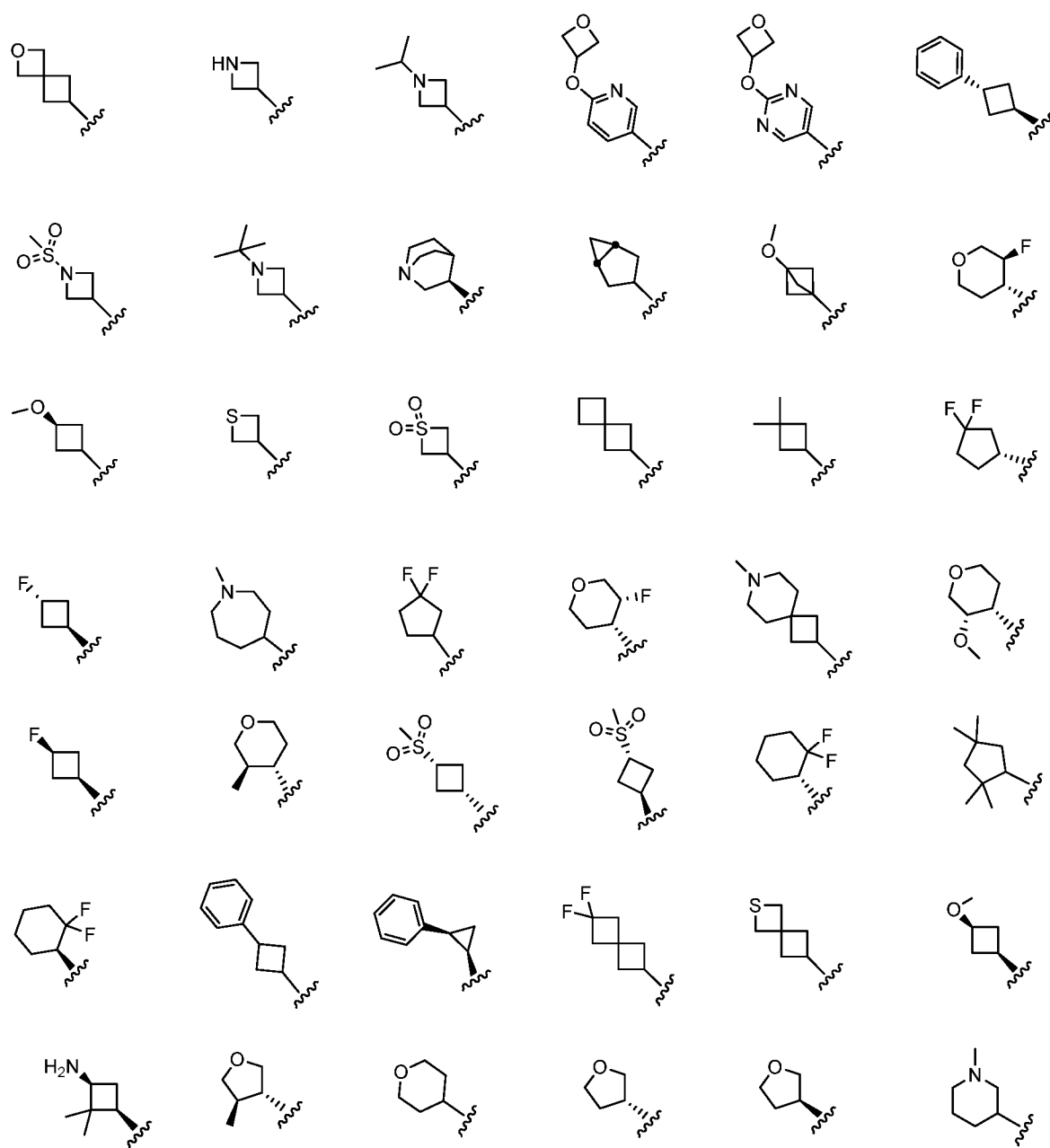


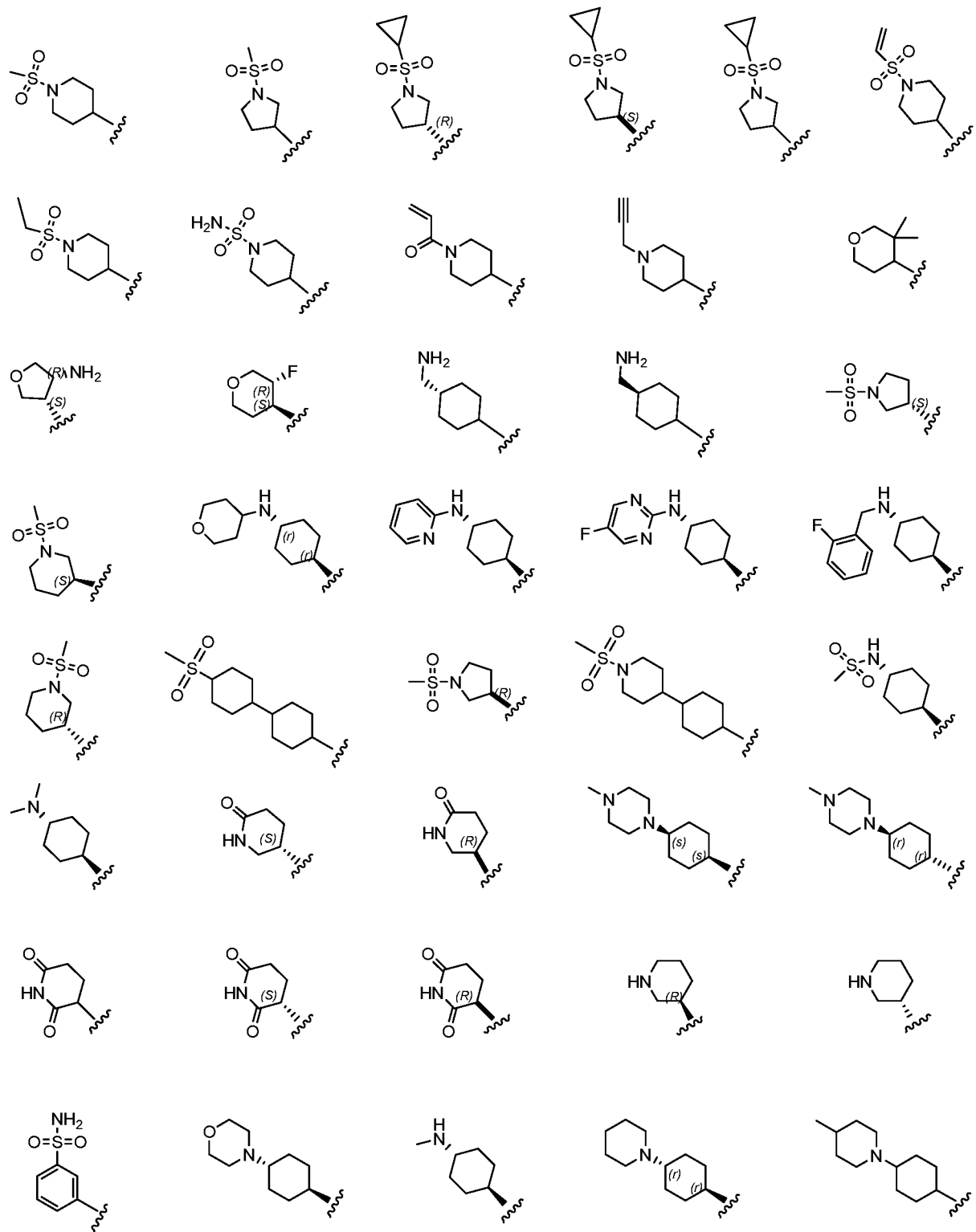
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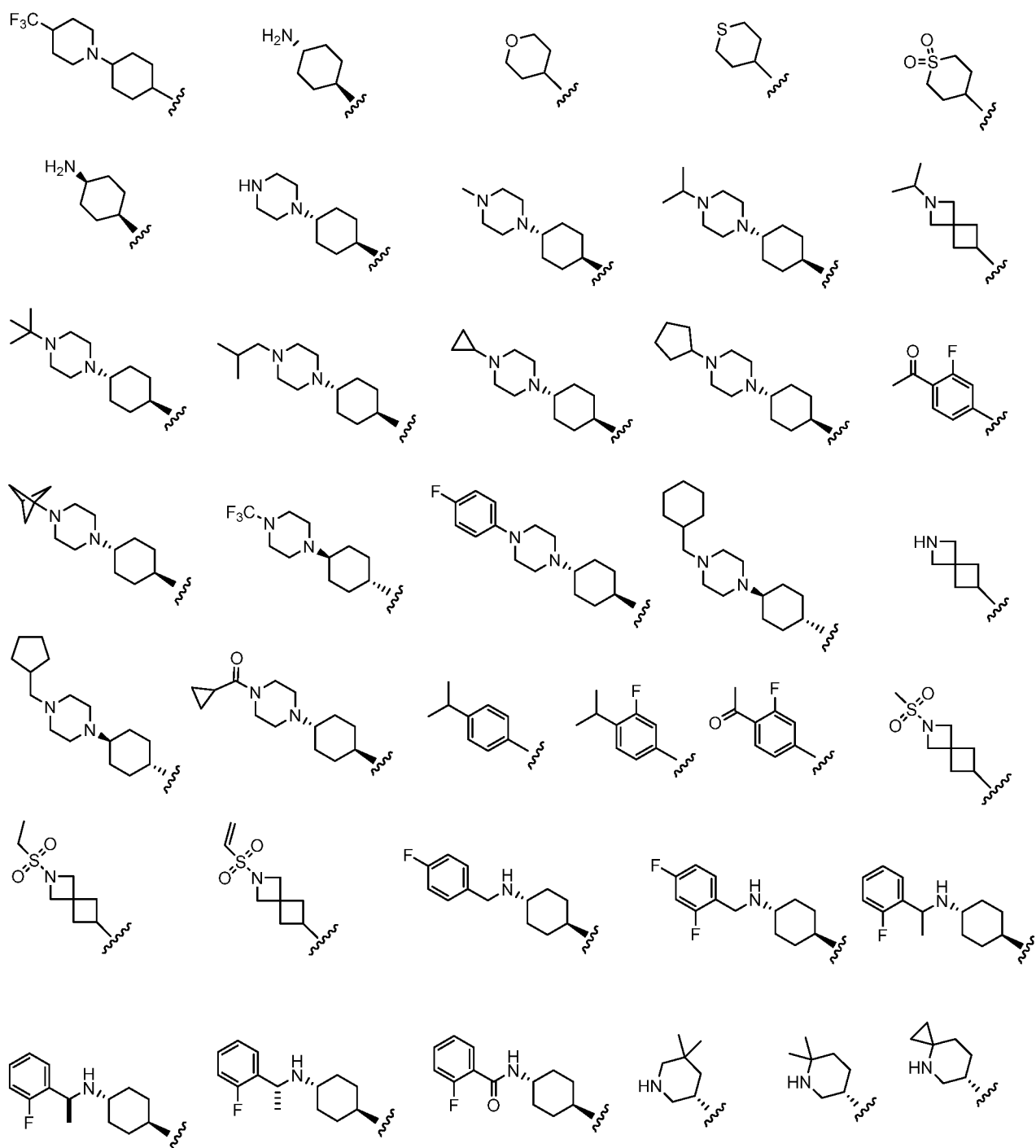


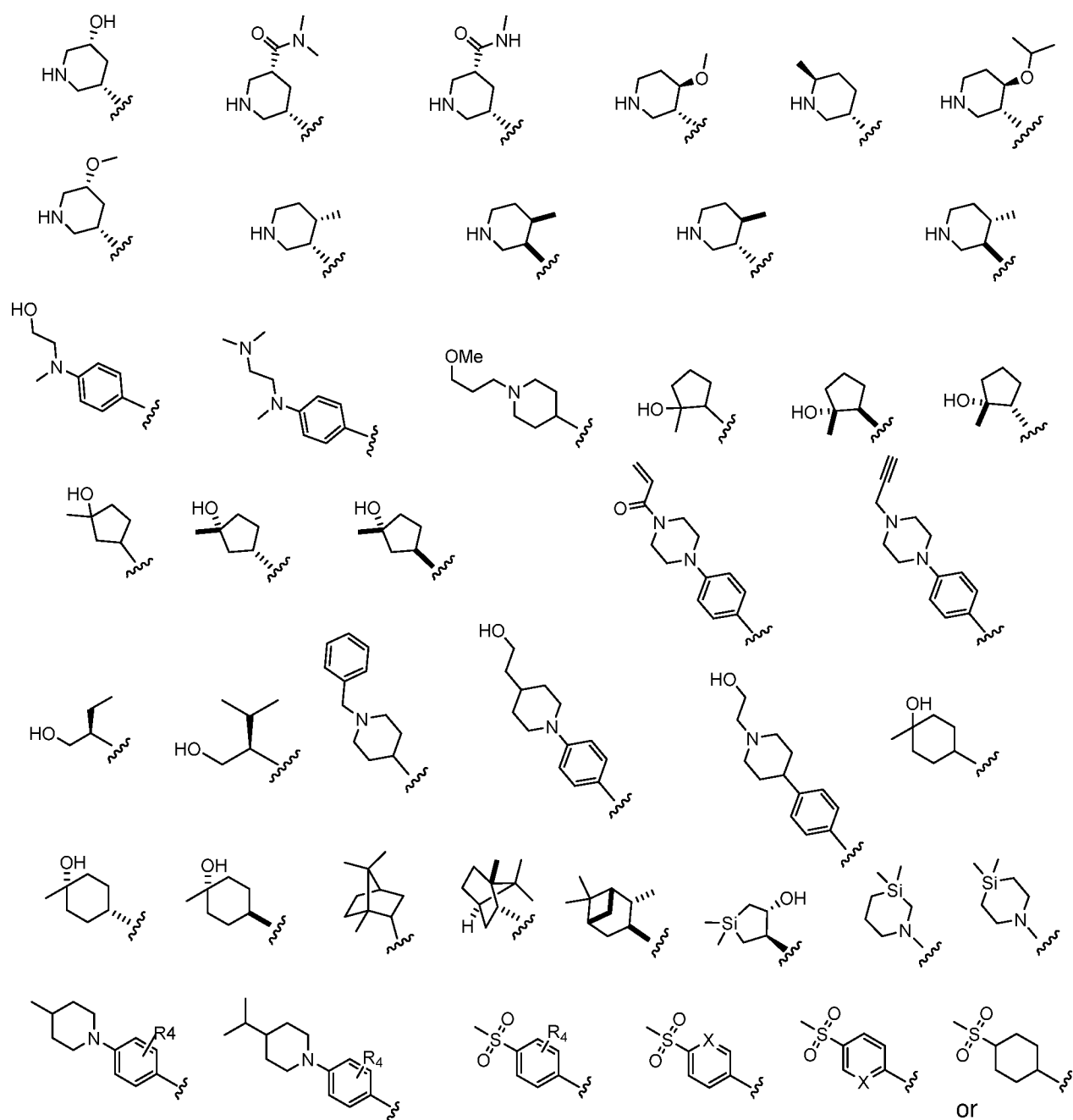












where R_3 is H, Me, $\text{CH}_2\text{CH}_2\text{OH}$, isopropyl, isobutyl, or bicyclo[1.1.1]pentane;

R_4 is H, Me, OMe, CF_3 , or CHF_2 ;

R_5 is H or Me;

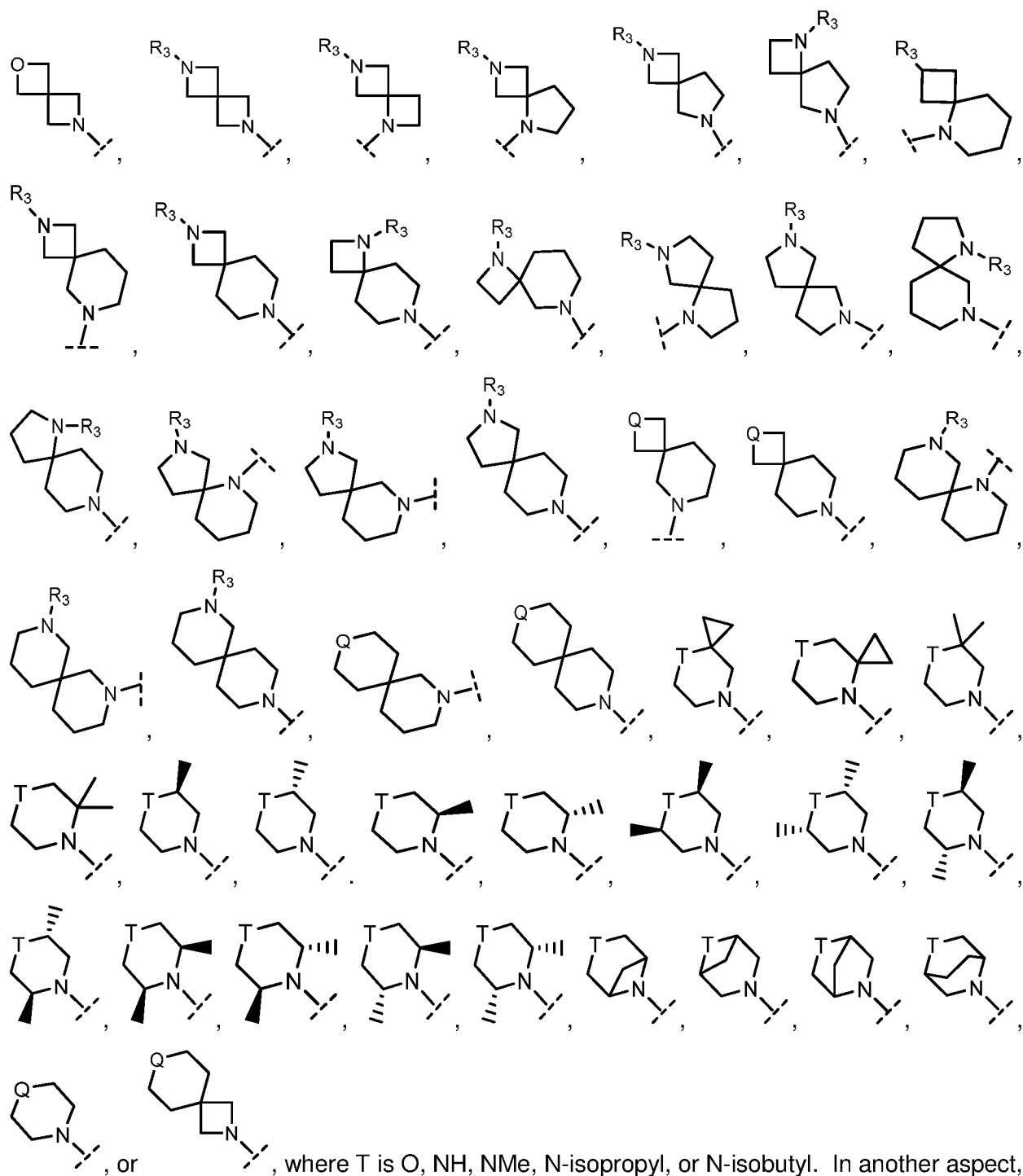
5 X is C-H, N, or C-F;

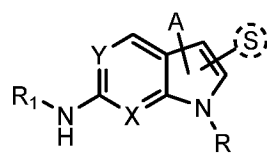
Y is H, N, F, Me, OMe, CF_3 , or CHF_2 ;

Q is O or S;

n is 1, 2, or 3; and

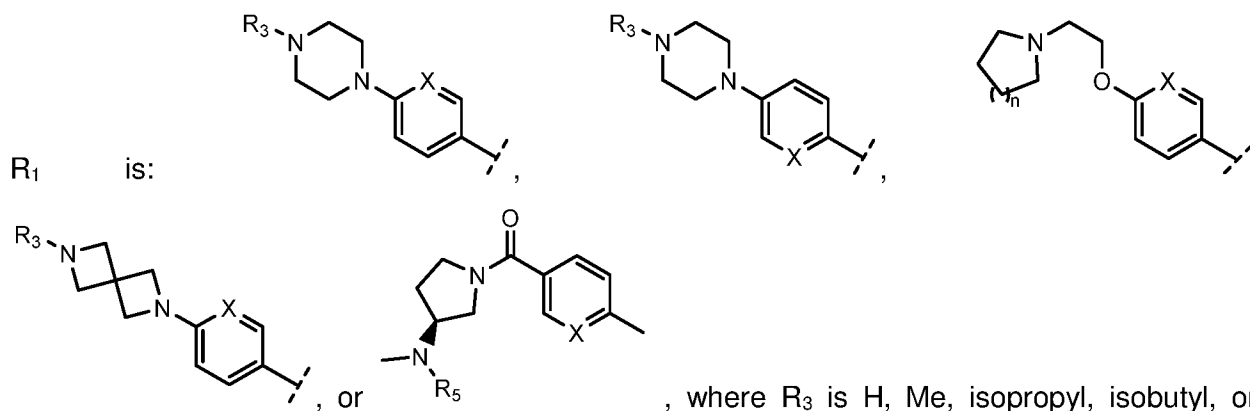
R₂ is:



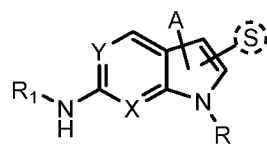


(I), wherein A is H, F, Me, or CON(Me)₂; and X and Y are independently N.

In another aspect, is . In another aspect, R is or . In another aspect,

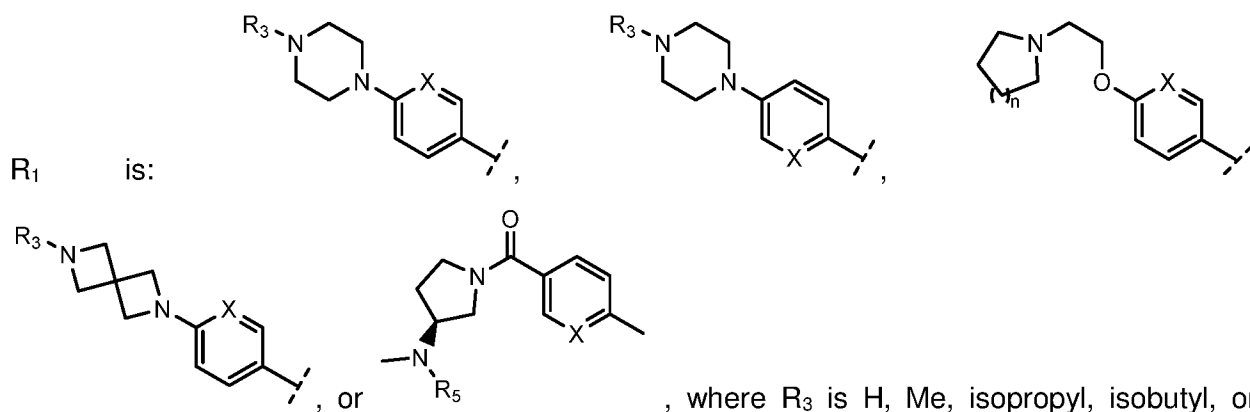


bicyclo[1.1.1]pentane; R₅ is H or Me; and X is C-H, N, or C-F. In another aspect, the compound comprises Formula I:



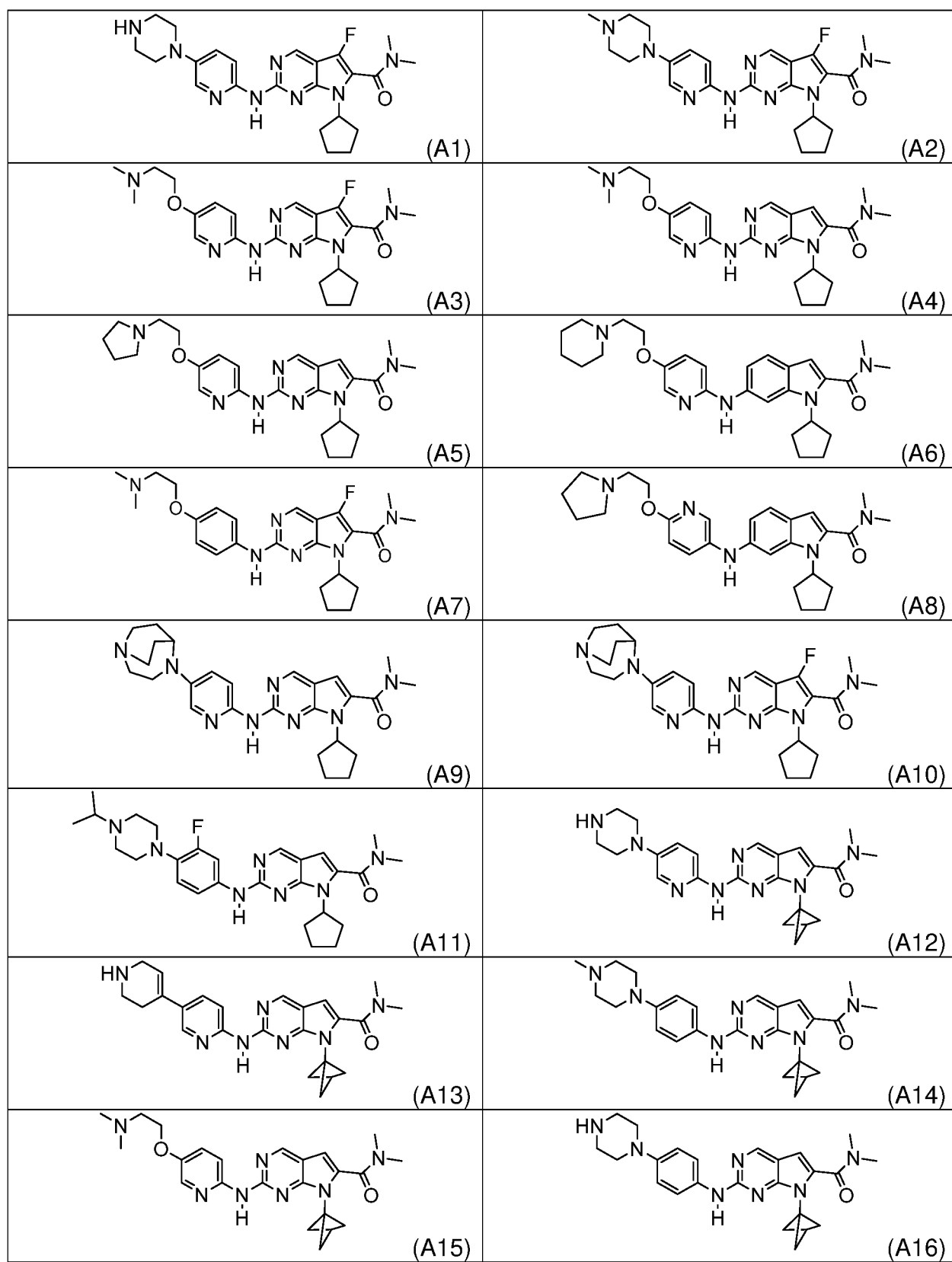
(I),

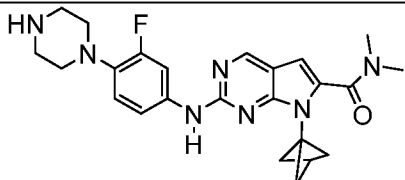
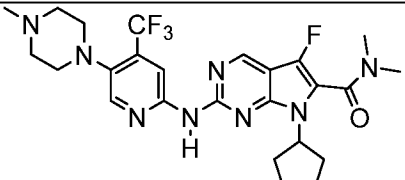
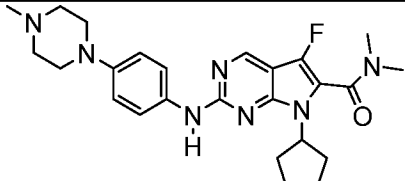
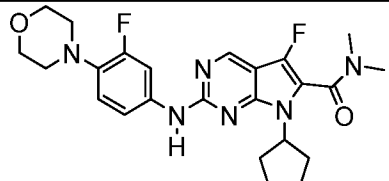
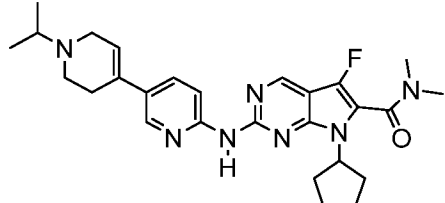
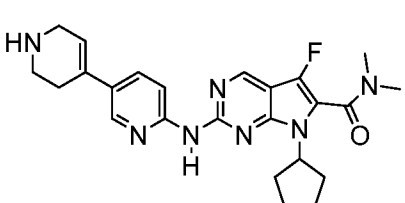
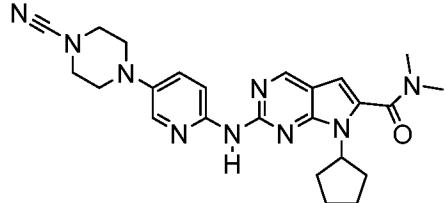
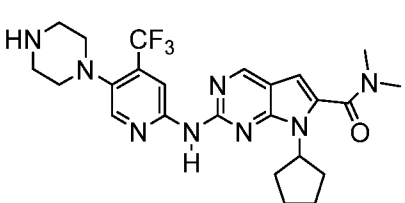
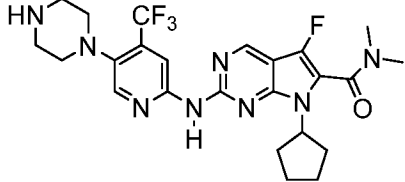
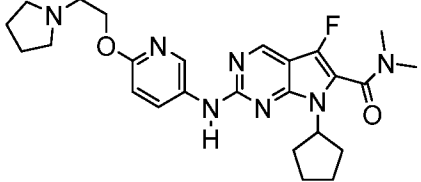
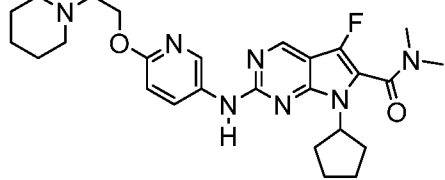
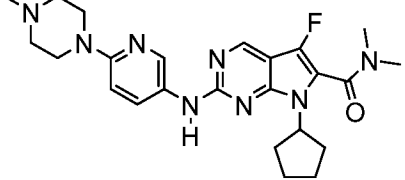
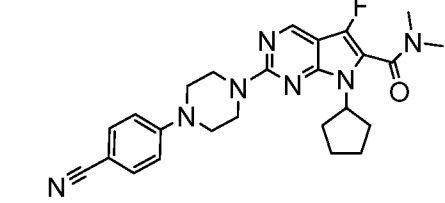
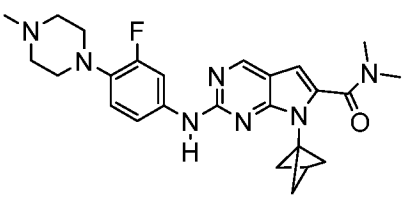
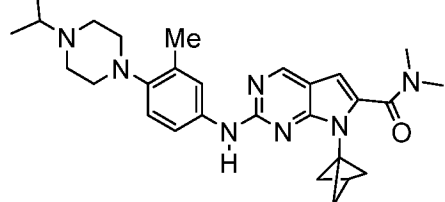
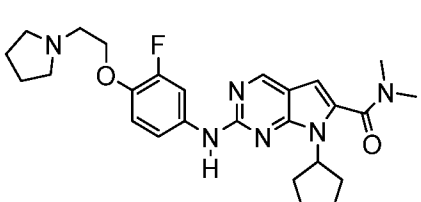
wherein A is H or F; X and Y are independently N; is ; R is or ; and

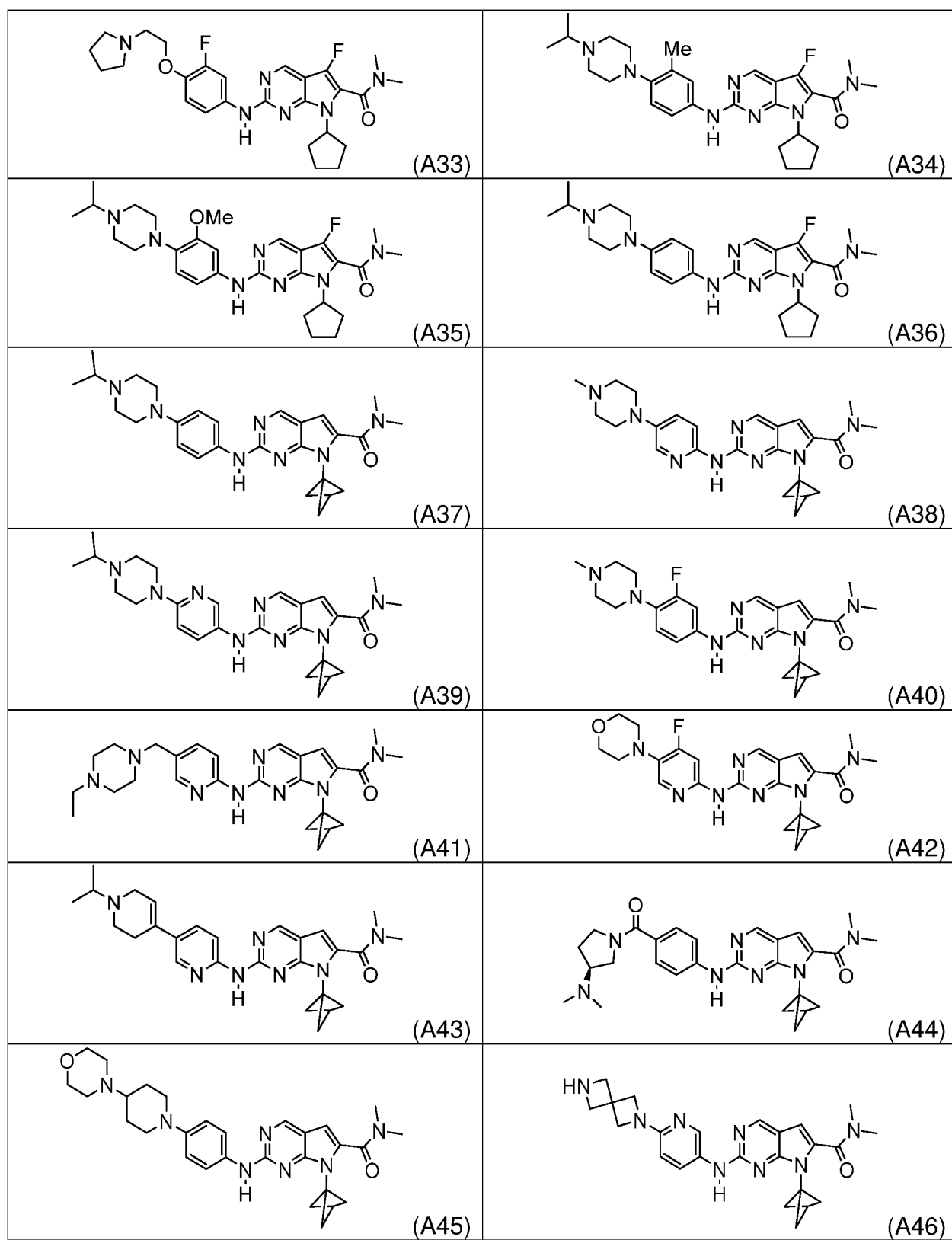


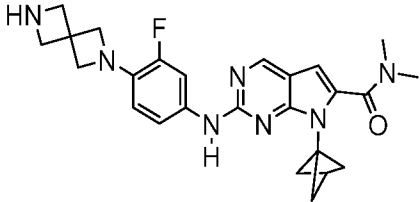
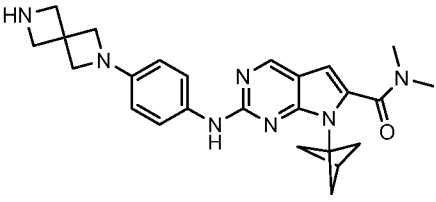
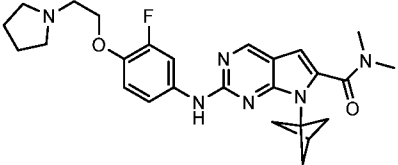
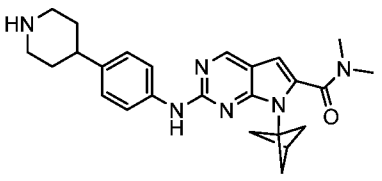
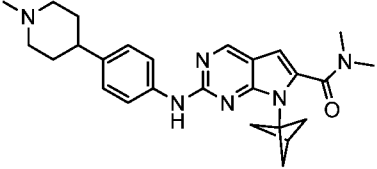
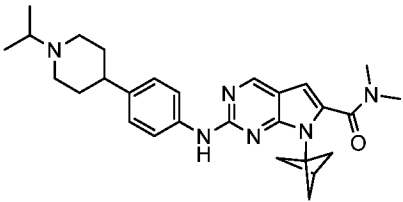
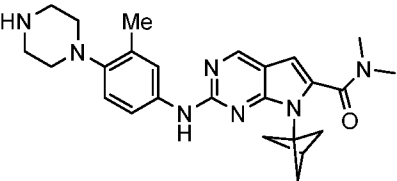
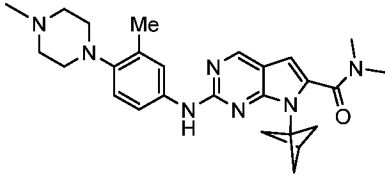
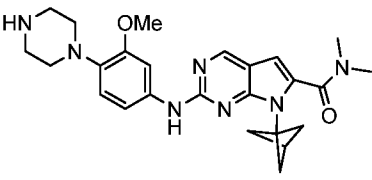
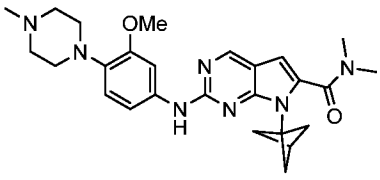
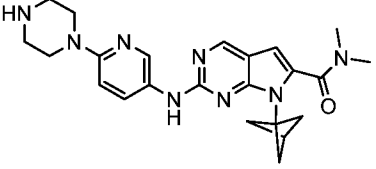
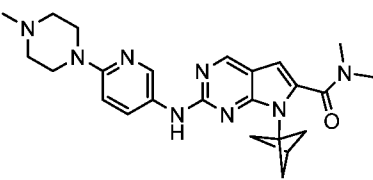
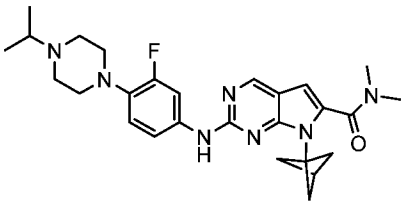
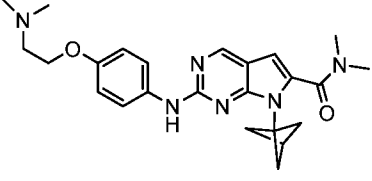
bicyclo[1.1.1]pentane; R₅ is H or Me; and X is C-H, N, or C-F.

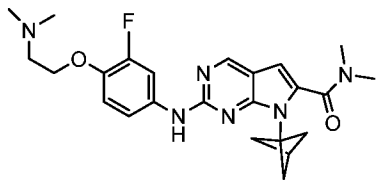
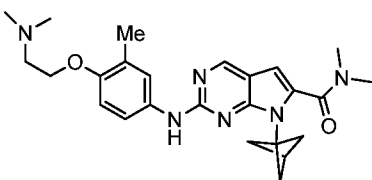
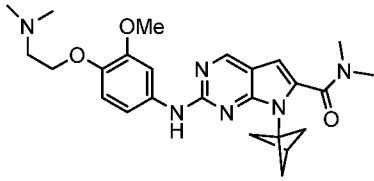
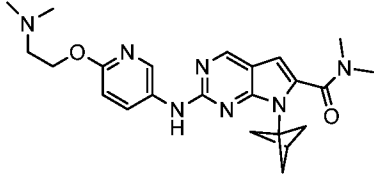
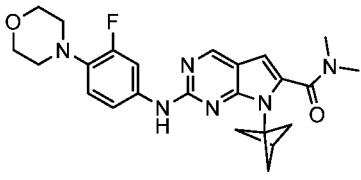
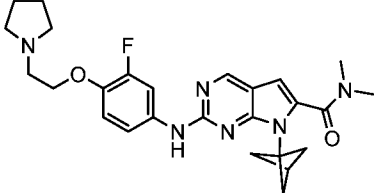
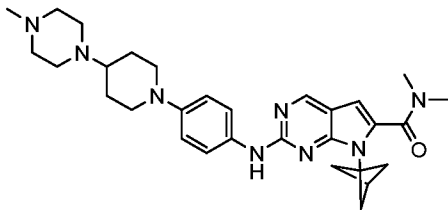
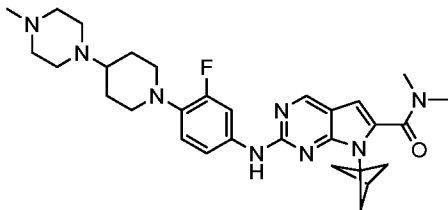
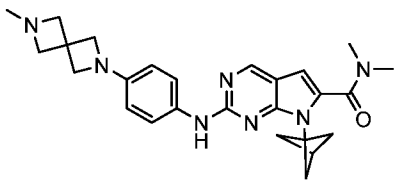
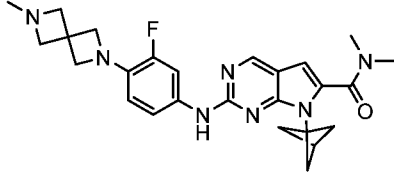
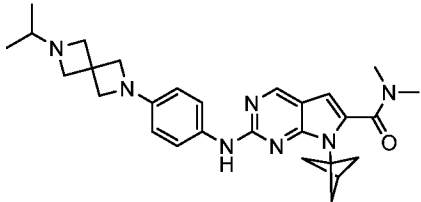
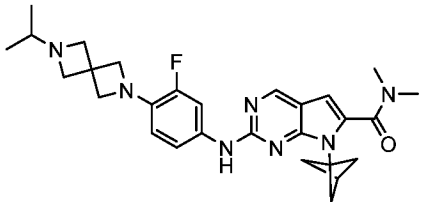
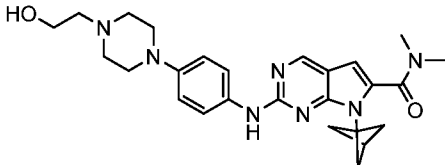
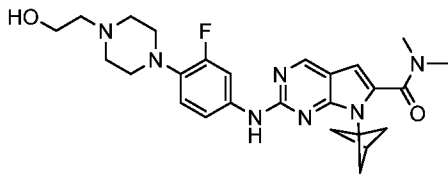
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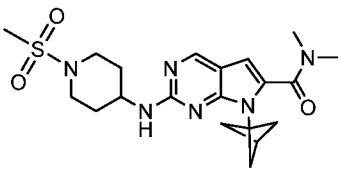
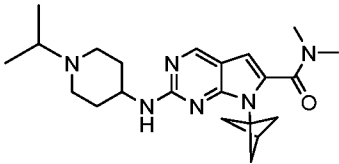
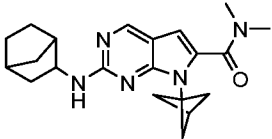
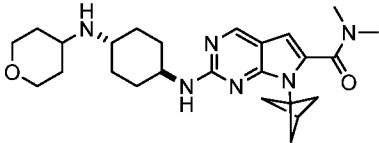
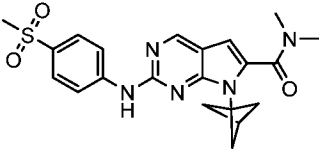
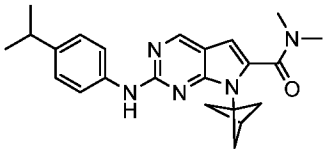
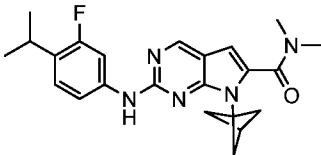
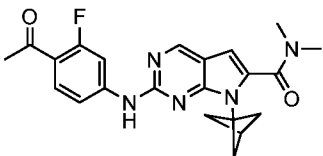
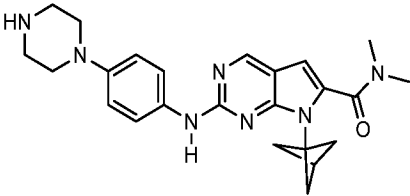
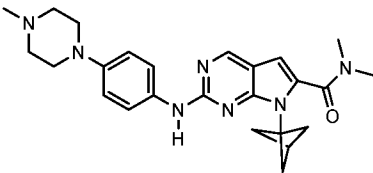
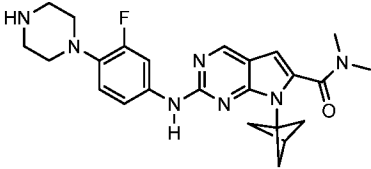
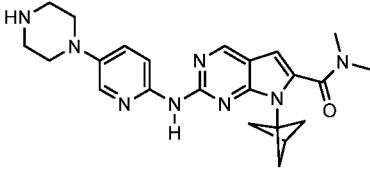
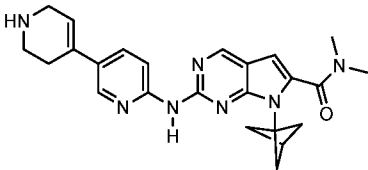
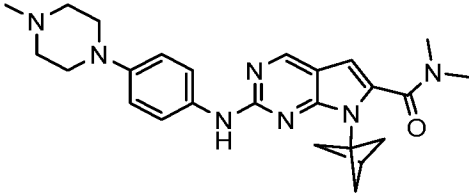


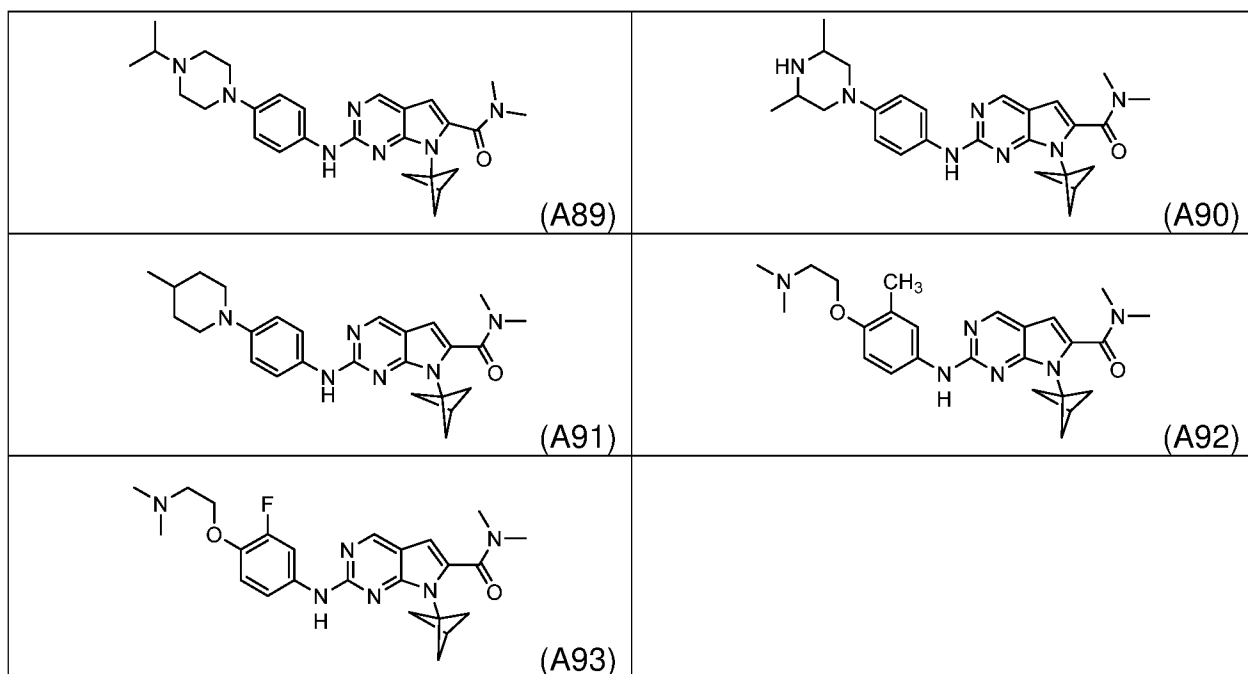
 (A17)	 (A18)
 (A19)	 (A20)
 (A21)	 (A22)
 (A23)	 (A34)
 (A25)	 (A26)
 (A27)	 (A28)
 (A29)	 (A30)
 (A31)	 (A32)



 (A47)	 (A48)
 (A49)	 (A50)
 (A51)	 (A52)
 (A53)	 (A54)
 (A55)	 (A56)
 (A57)	 (A58)
 (A59)	 (A60)

 (A61)	 (A62)
 (A63)	 (A64)
 (A65)	 (A66)
 (A67)	 (A68)
 (A69)	 (A70)
 (A71)	 (A72)
 (A73)	 (A74)

 (A75)	 (A76)
 (A77)	 (A78)
 (A79)	 (A80)
 (A81)	 (A82)
 (A83)	 (A84)
 (A85)	 (A86)
 (A87)	 (A88) . 2HCl



Another embodiment described herein is a pharmaceutical composition comprising one or more of Compounds A1–A93 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

5 Another embodiment described herein is a method of treating cancer or providing a chemotherapeutic protective effect comprising administering an effective amount of one or more of Compounds A1–A93 to a subject in need thereof.

Another embodiment described herein is a compound selected from:

- 10 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A1);
- 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A2);
- 7-cyclopentyl-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A3);
- 15 7-cyclopentyl-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A4);
- 7-cyclopentyl-*N,N*-dimethyl-2-((5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A5);
- 1-cyclopentyl-*N,N*-dimethyl-6-((5-(2-(piperidin-1-yl)ethoxy)pyridin-2-yl)amino)-1H-indole-2-carboxamide (A6);
- 20

- 7-cyclopentyl-2-((4-(2-(dimethylamino)ethoxy)phenyl)amino)-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A7);
- 1-cyclopentyl-*N,N*-dimethyl-6-((6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-3-yl)amino)-1H-indole-2-carboxamide (A8);
- 5 2-((5-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-2-yl)amino)-7-cyclopentyl-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A9);
- 2-((5-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-2-yl)amino)-7-cyclopentyl-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A10);
- 7-cyclopentyl-2-((3-fluoro-4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A11);
- 10 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A12);
- 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A13);
- 15 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A14);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A15);
- 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(piperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A16);
- 20 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A17);
- 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(4-methylpiperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A18);
- 25 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A19);
- 7-cyclopentyl-5-fluoro-2-((3-fluoro-4-morpholinophenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A20);
- 30 7-cyclopentyl-5-fluoro-2-((1'-isopropyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A21);
- 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A22);

- 2-((5-(4-cyanopiperazin-1-yl)pyridin-2-yl)amino)-7-cyclopentyl-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A23);
- 7-cyclopentyl-*N,N*-dimethyl-2-((5-(piperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A24);
- 5 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(piperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A25);
- 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-3-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A26);
- 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(2-(piperidin-1-yl)ethoxy)pyridin-3-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A27);
- 10 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A28);
- 2-(4-(4-cyanophenyl)piperazin-1-yl)-7-cyclopentyl-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A29);
- 15 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A30);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)-3-methylphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A31);
- 7-cyclopentyl-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A32);
- 20 7-cyclopentyl-5-fluoro-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A33);
- 7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)-3-methylphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A34);
- 25 7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)-3-methoxyphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A35);
- 7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A36);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A37);
- 30 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A38);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (A39);

- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A40);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A41);
- 5 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-fluoro-5-morpholinopyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A42);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((1'-isopropyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A43);
- 10 (S)-7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(3-(dimethylamino)pyrrolidine-1-carbonyl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A44);
- 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A45);
- 15 2-((6-(2,6-diazaspiro[3.3]heptan-2-yl)pyridin-3-yl)amino)-7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A46);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A47);
- 2-((4-(2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A48);
- 20 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A49);
- 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(piperidin-4-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A50);
- 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(1-methylpiperidin-4-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A51);
- 25 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(1-isopropylpiperidin-4-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A52);
- 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((3-methyl-4-(piperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A53);
- 30 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A54);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-methoxy-4-(piperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A55);

- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A56);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((6-(piperazin-1-yl)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A57);
- 5 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A58);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-isopropylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A59);
- 10 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A60);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-fluorophenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A61);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-methylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A62);
- 15 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A63);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A64);
- 20 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-morpholinophenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A65);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A66);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A67);
- 25 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A68);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A69);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A70);
- 30 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A71);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A72);

- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A73);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A74);
- 5 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A75);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((1-isopropylpiperidin-4-yl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A76);
- 10 7-(bicyclo[1.1.1]pentan-1-yl)-2-(bicyclo[2.2.1]heptan-2-ylamino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A77);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-(((1r,4r)-4-((tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A78);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(methylsulfonyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A79);
- 15 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-isopropylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A80);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-isopropylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A81);
- 2-((4-acetyl-3-fluorophenyl)amino)-7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A82);
- 20 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(piperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A83);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A84);
- 25 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A85);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A86);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A87);
- 30 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide dihydrogen chloride (A88);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A89);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(3,5-dimethylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A90);
7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-methylpiperidin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A91);
5 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-methylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A92);
7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-fluorophenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A93); or
pharmaceutically acceptable salts thereof.

DESCRIPTION OF THE DRAWINGS

Fig. 1 shows CDK4 inhibition data for Compounds A1–A47. The plotted data is shown in Table 2.

Fig. 2 shows CDK6 inhibition data for Compounds A1–A47. The plotted data is shown in Table 2.

DETAILED DESCRIPTION

Described herein are compounds that are useful for treating uncontrolled cell proliferative diseases, including, but not limited to, proliferative diseases such as cancer, restenosis, or rheumatoid arthritis. These compounds are useful for treating inflammation and inflammatory diseases. In addition, these compounds have utility as antiinfective agents. Moreover, these compounds have utility as chemoprotective agents through their ability to inhibit the cell cycle progression of normal untransformed cells. Many of the compounds described herein display unexpected improvements in selectivity for the serine/threonine kinases CDK4, CDK6, CDK9, and other CDKs. The synthesis of these compounds is described herein. These compounds can be administered to patients by a variety of methods including orally or intravenously.

Throughout the specification and claims, a given chemical formula or chemical name shall encompass all optical stereoisomers, as well as racemic mixtures where such isomers or mixtures exist, unless the specific isomer or diastereomer is noted. In addition, the disclosed compounds encompass all pharmaceutically acceptable salts, esters, amides, isotopes, prodrugs, solvates, or crystalline forms thereof.

The term “alkyl” as used herein means a straight or branched hydrocarbon radical having from 1 to 10 carbon atoms and includes, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, iso-pentyl, *n*-hexyl, and the like.

The term "alkenyl" as used means straight and branched hydrocarbon radicals having from 2 to 8 carbon atoms and at least one double bond and includes, but is not limited to, ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like. The term "alkenyl" includes cycloalkenyl, and heteroalkenyl in which 1 to 3 heteroatoms selected from O, S, N, or substituted nitrogen may replace carbon atoms.

The term "alkynyl" as used means straight and branched hydrocarbon radicals having from 2 to 8 carbon atoms and at least one triple bond and includes, but is not limited to, ethynyl, 3-butyne-1-yl, propynyl, 2-butyne-1-yl, 3-pentyne-1-yl, and the like.

The term "cycloalkyl" as used means a monocyclic or polycyclic hydrocarbyl group having from 3 to 8 carbon atoms, for instance, cyclopropyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclobutyl, adamantyl, norpinanyl, decalinyl, norbornyl, cyclohexyl, and cyclopentyl. Such groups can be substituted with groups such as hydroxy, keto, amino, alkyl, and dialkylamino, and the like. Also included are rings in which 1 to 3 heteroatoms replace carbons. Such groups are termed "heterocyclyl," which means a cycloalkyl group also bearing at least one heteroatom selected from O, S, N, or substituted nitrogen. Examples of such groups include, but are not limited to, oxiranyl, pyrrolidinyl, piperidyl, tetrahydropyran, and morpholine.

The term "alkoxy" as used herein means a straight or branched chain alkyl groups having 1–10 carbon atoms and linked through oxygen. Examples of such groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. In addition, alkoxy refers to polyethers such as $\text{—O—(CH}_2\text{)}_2\text{—O—CH}_3$, and the like.

The alkyl, alkenyl, alkoxy, and alkynyl groups described herein are optionally substituted, preferably by 1 to 3 groups selected from NR₄R₅, phenyl, substituted phenyl, thio C₁–C₆ alkyl, C₁–C₆ alkoxy, hydroxy, carboxy, C₁–C₆ alkoxycarbonyl, halo, nitrile, cycloalkyl, and a 5- or 6-membered carbocyclic ring or heterocyclic ring having 1 or 2 heteroatoms selected from nitrogen, substituted nitrogen, oxygen, and sulfur. "Substituted nitrogen" means nitrogen bearing C₁–C₆ alkyl or (CH₂)_pPh where p is 1, 2, or 3. Perhalo and polyhalo substitution is also included.

Examples of substituted alkyl groups include, but are not limited to, 2-aminoethyl, 2-hydroxyethyl, pentachloroethyl, trifluoromethyl, 2-diethylaminoethyl, 2-dimethylaminopropyl, ethoxycarbonylmethyl, 3-phenylbutyl, methanysulfanylmethyl, methoxymethyl, 3-hydroxypentyl, 2-carboxybutyl, 4-chlorobutyl, 3-cyclopropylpropyl, pentafluoroethyl, 3-morpholinopropyl, piperazinylmethyl, and 2-(4-methylpiperaziny)ethyl.

Examples of substituted alkynyl groups include, but are not limited to, 2-methoxyethynyl, 2-ethylsulfanylethynyl, 4-(1-piperazinyl)-3-(butynyl), 3-phenyl-5-hexynyl, 3-diethylamino-3-butynyl, 4-chloro-3-butynyl, 4-cyclobutyl-4-hexenyl, and the like.

Typical substituted alkoxy groups include aminomethoxy, trifluoromethoxy, 2-diethylaminoethoxy, 2-ethoxycarbonylethoxy, 3-hydroxypropoxy, 6-carboxyhexyloxy, and the like.

Further, examples of substituted alkyl, alkenyl, and alkynyl groups include, but are not limited to, dimethylaminomethyl, carboxymethyl, 4-dimethylamino-3-buten-1-yl, 5-ethylmethylamino-3-pentyn-1-yl, 4-morpholinobutyl, 4-tetrahydropyridinylbutyl, 3-imidazolidin-1-ylpropyl, 4-tetrahydrothiazol-3-yl-butyl, phenylmethyl, 3-chlorophenylmethyl, and the like.

The term “anion” as used herein means a negatively charged counterion such as chloride, bromide, trifluoroacetate, and triethylammonium.

The term “acyl” as used herein means an alkyl or aryl (Ar) group having from 1–10 carbon atoms bonded through a carbonyl group, i.e., $R-C(O)-$. For example, acyl includes, but is not limited to, a C_1-C_6 alkanoyl, including substituted alkanoyl, wherein the alkyl portion can be substituted by an amine, amide, carboxylic, or heterocyclic group. Typical acyl groups include acetyl, benzoyl, and the like.

The term “aryl” as used herein refers to an aromatic monocyclic hydrocarbon ring system or a polycyclic ring system where at least one of the rings in the ring system is an aromatic hydrocarbon ring and any other aromatic rings in the ring system include only hydrocarbons. In some embodiments, a monocyclic aryl group can have from 6 to 14 carbon atoms and a polycyclic aryl group can have from 8 to 14 carbon atoms. The aryl group can be covalently attached to the defined chemical structure at any carbon atom(s) that result in a stable structure. In some embodiments, an aryl group can have only aromatic carbocyclic rings, e.g., phenyl, 1-naphthyl, 2-naphthyl, anthracenyl, phenanthrenyl groups, and the like. In other embodiments, an aryl group can be a polycyclic ring system in which at least one aromatic carbocyclic ring is fused (i.e., having a bond in common with) to one or more cycloalkyl or cycloheteroalkyl rings. Examples of such aryl groups include, among others, benzo derivatives of cyclopentane (i.e., an indanyl group, which is a 5,6-bicyclic cycloalkyl/aromatic ring system), cyclohexane (i.e., a tetrahydronaphthyl group, which is a 6,6-bicyclic cycloalkyl/aromatic ring system), imidazoline (i.e., a benzimidazolyl group, which is a 5,6-bicyclic cycloheteroalkyl/aromatic ring system), and pyran (i.e., a chromenyl group, which is a 6,6-bicyclic cycloheteroalkyl/aromatic ring system). Other examples of aryl groups include benzodioxanyl, benzodioxolyl, chromanyl, indolyl groups, and the like.

The terms “halogen” or “halo” as used herein means fluorine, bromine, chlorine, and iodine.

The term “haloalkyl” refers to an alkyl group having one or more halogen substituents. In some embodiments, a haloalkyl group can have 1 to 10 carbon atoms (e.g., from 1 to 8 carbon atoms). Examples of haloalkyl groups include CF₃, C₂F₅, CHF₂, CH₂F, CCl₃, CHCl₂, CH₂Cl, C₂Cl₅, and the like. Perhaloalkyl groups, i.e., alkyl groups wherein all of the hydrogen atoms are replaced with halogen atoms (e.g., CF₃ and C₂F₅), are included within the definition of “haloalkyl.” For example, a C₁₋₁₀ haloalkyl group can have the formula -C_iH_{2i+1-j}X_j, wherein X is F, Cl, Br, or I, *i* is an integer in the range of 1 to 10, and *j* is an integer in the range of 0 to 21, provided that *j* is less than or equal to 2*i*+1.

The term “heteroaryl” as used herein refers to an aromatic monocyclic ring system containing at least one ring heteroatom selected from O, N, and S or a polycyclic ring system where at least one of the rings in the ring system is aromatic and contains at least one ring heteroatom. A heteroaryl group, as a whole, can have from 5 to 14 ring atoms and contain 1–5 ring heteroatoms. In some embodiments, heteroaryl groups can include monocyclic heteroaryl rings fused to one or more aromatic carbocyclic rings, non-aromatic carbocyclic rings, or non-aromatic cycloheteroalkyl rings. The heteroaryl group can be covalently attached to the defined chemical structure at any heteroatom or carbon atom that results in a stable structure. Generally, heteroaryl rings do not contain O–O, S–S, or S–O bonds. However, one or more N or S atoms in a heteroaryl group can be oxidized (e.g., pyridine N-oxide, thiophene S-oxide, thiophene S,S-dioxide). Examples of such heteroaryl rings include pyrrolyl, furyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, isothiazolyl, thiazolyl, thiadiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, indolyl, isoindolyl, benzofuryl, benzothienyl, quinolyl, 2-methylquinolyl, isoquinolyl, quinoxalyl, quinazolyl, benzotriazolyl, benzimidazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzoxadiazolyl, benzoxazolyl, cinnolinyl, 1H-indazolyl, 2H-indazolyl, indoliziny, isobenzofuyl, naphthyridinyl, phthalazinyl, pteridinyl, purinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyridinyl, furopyridinyl, thienopyridinyl, pyridopyrimidinyl, pyridopyrazinyl, pyridopyrdazinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl groups, and the like. Further examples of heteroaryl groups include 4,5,6,7-tetrahydroindolyl, tetrahydroquinolyl, benzothienopyridinyl, benzofuropyridinyl groups, and the like.

The term “lower alkenyl” as used herein refers to alkenyl groups which contains 2 to 6 carbon atoms. An alkenyl group is a hydrocarbyl group containing at least one carbon-carbon double bond. As defined herein, it may be unsubstituted or substituted with the substituents

described herein. The carbon-carbon double bonds may be between any two carbon atoms of the alkenyl group. It is preferred that it contains 1 or 2 carbon-carbon double bonds and more preferably one carbon-carbon double bond. The alkenyl group may be straight chained or branched. Examples include but are not limited to ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-
5 butenyl, 2-methyl-1-propenyl, 1,3-butadienyl, and the like.

The term "lower alkynyl" as used herein, refers to an alkynyl group containing 2–6 carbon atoms. An alkynyl group is a hydrocarbonyl group containing at least one carbon-carbon triple bond. The carbon-carbon triple bond may be between any two carbon atom of the alkynyl group. In an embodiment, the alkynyl group contains 1 or 2 carbon-carbon triple bonds and more preferably
10 one carbon-carbon triple bond. The alkynyl group may be straight chained or branched. Examples include but are not limited to ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl and the like.

The term "carbalkoxy" as used herein refers to an alkoxycarbonyl group, where the attachment to the main chain is through the carbonyl group, e.g., $-\text{C}(\text{O})-$. Examples include but
15 are not limited to methoxy carbonyl, ethoxy carbonyl, and the like.

The term "oxo" as used herein refers to a double-bonded oxygen (i.e., $=\text{O}$). It is also to be understood that the terminology $\text{C}(\text{O})$ refers to a $-\text{C}=\text{O}$ group, whether it be ketone, aldehyde or acid or acid derivative. Similarly, $\text{S}(\text{O})$ refers to a $-\text{S}=\text{O}$ group.

The term "cycloalkyl" as used herein refers to a non-aromatic carbocyclic group including
20 cyclized alkyl, alkenyl, and alkynyl groups. A cycloalkyl group can be monocyclic (e.g., cyclohexyl) or polycyclic (e.g., containing fused, bridged, and/or spiro ring systems), wherein the carbon atoms are located inside or outside of the ring system. A cycloalkyl group, as a whole, can have from 3 to 14 ring atoms (e.g., from 3 to 8 carbon atoms for a monocyclic cycloalkyl group and from 7 to 14 carbon atoms for a polycyclic cycloalkyl group). Any suitable ring position of the
25 cycloalkyl group can be covalently linked to the defined chemical structure. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcaryl, adamantyl, and spiro[4.5]decanyl groups, as well as their homologs, isomers, and the like.

The term "heteroatom" as used herein refers to an atom of any element other than carbon
30 or hydrogen and includes, for example, nitrogen, oxygen, sulfur, phosphorus, and selenium.

The term "cycloheteroalkyl" as used herein refers to a non-aromatic cycloalkyl group that contains at least one (e.g., one, two, three, four, or five) ring heteroatom selected from O, N, and S, and optionally contains one or more (e.g., one, two, or three) double or triple bonds. A cycloheteroalkyl group, as a whole, can have from 3 to 14 ring atoms and contains from 1 to 5

ring heteroatoms (e.g., from 3–6 ring atoms for a monocyclic cycloheteroalkyl group and from 7 to 14 ring atoms for a polycyclic cycloheteroalkyl group). The cycloheteroalkyl group can be covalently attached to the defined chemical structure at any heteroatom(s) or carbon atom(s) that results in a stable structure. One or more N or S atoms in a cycloheteroalkyl ring may be oxidized (e.g., morpholine N-oxide, thiomorpholine S-oxide, thiomorpholine S,S-dioxide). Cycloheteroalkyl groups can also contain one or more oxo groups, such as phthalimidyl, piperidonyl, oxazolidinonyl, 2,4(1H,3H)-dioxo-pyrimidinyl, pyridin-2(1H)-onyl, and the like. Examples of cycloheteroalkyl groups include, among others, morpholinyl, thiomorpholinyl, pyranyl, imidazolidinyl, imidazolyl, oxazolidinyl, pyrazolidinyl, pyrazolyl, pyrrolidinyl, pyrrolyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, piperazinyl, azetidine, and the like.

The compounds described herein may contain chiral centers and therefore may exist in different enantiomeric and diastereomeric forms. One embodiment described herein encompasses all optical isomers or stereoisomers of the compounds described herein both as racemic mixtures and as individual enantiomers or diastereoisomers, or mixtures thereof, and to all pharmaceutical compositions or methods of treatment described herein that contain or employ them, respectively. Individual isomers can be obtained by known methods, such as optical resolution, optically selective reaction, or chiral chromatographic separation in the preparation of the final product or its intermediate.

The compounds described herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope described herein.

Compounds described herein also includes isotopically labelled compounds, which are identical to those described herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{11}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope described herein. Certain isotopically labelled compounds described herein, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14 i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford

certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds described herein and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The term "cancer" as used herein includes, but is not limited to, the following cancers: cancers of the breast, ovary, cervix, prostate, testis, esophagus, stomach, skin, lung, bone, colon, pancreas, thyroid, biliary passages, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, adenocarcinoma, adenocarcinoma, adenoma, adenocarcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, and leukemia.

The term "treating," as used herein refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or ameliorating one or more symptoms of such condition or disorder. The term "treatment," as used herein, refers to the act of treating, as "treating" is defined immediately above.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce a toxic, allergic, or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human. Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. or European Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The compounds described herein are capable of further forming pharmaceutically acceptable formulations comprising salts, including acid addition or base salts, solvents, or N-oxides of any compound described herein.

The term "salts" refers to the relatively non-toxic, inorganic, or organic acid addition salts of compounds described herein. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. In so far as the compounds described herein are basic compounds, they are all capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be

pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the base compound from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert to the free base compound by treatment with an alkaline reagent and thereafter convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of this disclosure.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metal hydroxides, or of organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are *N,N*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, *N*-methylglucamine, and procaine.

The base addition salts of acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in a conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes described herein.

Salts may be prepared from inorganic acids sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorus, and the like. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, laurylsulphonate and isethionate salts, and the like. Salts may also be prepared from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and the like. Representative salts include acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate,

maleate, tartrate, methanesulfonate, and the like. Pharmaceutically acceptable salts may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Also contemplated are the salts of amino acids such as arginate, gluconate, galacturonate, and the like. See Berge et al., *J. Pharm. Sci.* 66: 1-19 (1977) which is incorporated herein by reference.

The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds described herein which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds described herein.

Examples of pharmaceutically acceptable, non-toxic esters of the compounds described herein include C₁–C₆ alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C₅–C₇ cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C₁–C₄ alkyl esters are preferred. Esters of the compounds described herein may be prepared according to conventional methods "March's Advanced Organic Chemistry, 5th Edition," Smith and March, John Wiley & Sons (2001).

Examples of pharmaceutically acceptable, non-toxic amides of the compounds described herein include amides derived from ammonia, primary C₁–C₆ alkyl amines and secondary C₁–C₆ dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C₁–C₃ alkyl primary amines and C₁–C₂ dialkyl secondary amines are preferred. Amides of the compounds described herein may be prepared according to conventional methods such as "March's Advanced Organic Chemistry, 5th Edition," Smith and March, John Wiley & Sons (2001).

The phrase "room temperature," "RT," or "ambient temperature" indicate a temperature of about 25 °C ±10%.

The term "prodrug" as used herein refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in Higuchi, "Pro-drugs as Novel Delivery Systems," ACS Symposium Series 14 (1975), and in Roche, Edward, ed., *Bioreversible Carriers in Drug Design*,

American Pharmaceutical Association, Pergamon Press (1987), both of which are hereby incorporated by reference.

The term “excipient” as used herein refers to a diluent, adjuvant, or vehicle with which the compound is administered. Such pharmaceutical excipients can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water for injection, aqueous saline solutions, aqueous dextrose, or lactated Ringer’s solution are preferably employed as excipients, particularly for injectable solutions. Suitable pharmaceutical excipients are described in “Remington’s Pharmaceutical Sciences” by E. W. Martin.

The phrase “therapeutically effective amount” as used herein means an amount sufficient to reduce by at least about 10 percent, preferably by at least 50 percent, more preferably by at least 90 percent, and most preferably prevent, a clinically significant deficit in the activity, function and response of the host. Alternatively, a therapeutically effective amount is sufficient to cause an improvement in a clinically significant condition/symptom in the host.

The term “analog” as used herein refers to a small organic compound, a nucleotide, a protein, or a polypeptide that possesses similar or identical activity or function(s) as the compound, nucleotide, protein or polypeptide or compound having the desired activity and therapeutic effect (e.g., inhibition of tumor growth), but need not necessarily comprise a sequence or structure that is similar or identical to the sequence or structure of the preferred embodiment.

The term “derivative” as used herein refers to either a compound, a protein or polypeptide that comprises an amino acid sequence of a parent protein or polypeptide that has been altered by the introduction of amino acid residue substitutions, deletions or additions, or a nucleic acid or nucleotide that has been modified by either introduction of nucleotide substitutions or deletions, additions or mutations. The derivative nucleic acid, nucleotide, protein, or polypeptide possesses a similar or identical function as the parent polypeptide.

The phrases “substantial portion” or “significant portion” as used herein mean at least 80%. In alternative embodiments, the portion may be at least 85%, 90%, 95%, 99%, or greater.

The phrase “selective CDK inhibitor” used in the context of the compounds described herein indicates an ability to inhibit CDK4 activity, CDK6 activity, CDK9 activity or other CDK activities at an IC_{50} molar concentration at least about 2000 times less than the IC_{50} molar concentration necessary to inhibit to the same degree as CDK2 activity in a standard phosphorylation assay.

The phrase “induces G1-arrest” mean that a compound described herein induces a quiescent state in a substantial portion of a cell population at the G1 phase of the cell cycle.

The phrase “hematological deficiency” mean reduced hematological cell lineage counts or the insufficient production of blood cells (i.e., myelodysplasia) and/or lymphocytes (i.e., lymphopenia, the reduction in the number of circulating lymphocytes, such as B- and T-cells). Hematological deficiency can be observed, for example, as myelosuppression in form of anemia, reduction in platelet count (i.e., thrombocytopenia), reduction in white blood cell count (i.e., leukopenia), or the reduction in granulocytes (e.g., neutropenia).

The phrase “synchronous reentry into the cell cycle” mean that CDK4/6-replication dependent healthy cells, for example HSPCs, in G1-arrest due to the effect of a compound described herein reenter the cell-cycle within relatively the same collective timeframe or at relatively the same rate upon dissipation of the compound’s effect. Comparatively, by “asynchronous reentry into the cell cycle” is meant that the healthy cells, for example HSPCs, in G1 arrest due to the effect of a CDK4/6 inhibitor compound within relatively different collective timeframes or at relatively different rates upon dissipation of the compound’s effect such as pablociclib or ribociclib.

The phrases “off-cycle” or “drug holiday” mean a time period during which the subject is not administered or exposed to a chemotherapeutic. For example, in a treatment regime wherein the subject is administered the chemotherapeutic in a repeated 21 day cycle, and is not administered the chemotherapeutic at the start of the next 21-day cycle due to hematologic deficiencies, the delayed period of non-administration is considered the “off-cycle” or “drug holiday.” Off-target and drug holiday may also refer to an interruption in a treatment regime wherein the subject is not administered the chemotherapeutic for a time due to a deleterious side effect, for example, myelosuppression or other hematological deficiencies.

The phrase “CDK4/6-replication independent cancer” refers to a cancer that does not significantly require the activity of CDK4/6 for replication. Cancers of such type are often, but not always, characterized by (e.g., has cells that exhibit) an increased level of CDK2 activity or by reduced expression of retinoblastoma tumor suppressor protein or retinoblastoma family member protein(s), such as, but not limited to p107 and p130. The increased level of CDK2 activity or reduced or deficient expression of retinoblastoma tumor suppressor protein or retinoblastoma family member protein(s) can be increased or reduced, for example, compared to normal cells. In some embodiments, the increased level of CDK2 activity can be associated with (e.g., can result from or be observed along with) MYC proto-oncogene amplification or overexpression. In some embodiments, the increased level of CDK2 activity can be associated with overexpression of Cyclin E1, Cyclin E2, or Cyclin A.

The phrase "long-term hematological toxicity" is meant hematological toxicity affecting a subject for a period lasting more than one or more weeks, months, or years following administration of a chemotherapeutic agent. Long-term hematological toxicity can result in bone marrow disorders that can cause the ineffective production of blood cells (i.e., myelodysplasia) and/or lymphocytes (i.e., lymphopenia, the reduction in the number of circulating lymphocytes, such as B- and T-cells). Hematological toxicity can be observed, for example, as anemia, reduction in platelet count (i.e., thrombocytopenia) or reduction in white blood cell count (i.e., neutropenia). In some cases, myelodysplasia can result in the development of leukemia. Long-term toxicity related to chemotherapeutic agents can also damage other self-renewing cells in a subject, in addition to hematological cells. Thus, long-term toxicity can also lead to graying and frailty.

Biological Activity

The compounds described herein are inhibitors of cyclin dependent kinases. For example, compounds described herein are inhibitors of cyclin dependent kinases, and in particular cyclin dependent kinases comprising CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK9, CDK10, CDK11, CDK12, CDK13, or other CDKs. In one aspect, the compounds described herein are inhibitors of CDK4, CDK6, and/or CDK9.

Compounds described herein also have activity against glycogen synthase kinase-3 (GSK-3). As a consequence of their activity in modulating or inhibiting CDK and glycogen synthase kinase, they are expected to be useful in providing a means of arresting, or recovering control of, the cell cycle in abnormally dividing cells. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. It is also envisaged that the compounds described herein will be useful in treating conditions such as viral infections, type II or non-insulin dependent diabetes mellitus, autoimmune diseases, head trauma, stroke, epilepsy, neurodegenerative diseases such as Alzheimer's, motor neuron disease, progressive supranuclear palsy, corticobasal degeneration and Pick's disease for example autoimmune diseases and neurodegenerative diseases.

One sub-group of disease states and conditions where it is envisaged that the compounds described herein will be useful consists of viral infections, autoimmune diseases and neurodegenerative diseases.

CDKs play a role in the regulation of the cell cycle, apoptosis, transcription, differentiation, and CNS function. Therefore, CDK inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis, or differentiation such as cancer. In particular, RB-

ve tumours may be particularly sensitive to CDK inhibitors. These include tumours harbouring mutations in ras, Raf, Growth Factor Receptors or over-expression of Growth Factor Receptors. Furthermore, tumours with hypermethylated promoter regions of CDK inhibitors as well as tumours over-expressing cyclin partners of the cyclin dependent kinases may also display sensitivity. RB-ve tumours may also be sensitive to CDK inhibitors.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g., colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermis, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g., exocrine pancreatic carcinoma, stomach, cervix, thyroid, nose, head and neck, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, chronic lymphocytic leukaemia, B-cell lymphoma (such as diffuse large B cell lymphoma), T-cell lymphoma, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratocanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

The cancers may be cancers which are sensitive to inhibition of any one or more cyclin dependent kinases comprising CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK9, CDK10, CDK11, CDK12, CDK13, or other CDKs for example, one or more CDK kinases selected from CDK4, CDK6, and/or CDK9. Whether or not a particular cancer is one which is sensitive to inhibition by a cyclin dependent kinase inhibitor may be determined by means of a cell growth assay.

CDKs are also known to play a role in apoptosis, proliferation, differentiation and transcription and therefore CDK inhibitors could also be useful in the treatment of the following diseases other than cancer; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for

example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol
5 related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, ophthalmic diseases including age related macular degeneration, uveitis, and cancer pain.

It has also been discovered that some cyclin-dependent kinase inhibitors can be used in
10 combination with other anticancer agents. For example, the cyclin-dependent kinase inhibitor flavopiridol has been used with other anticancer agents in combination therapy. Thus, in the pharmaceutical compositions, uses or methods described herein for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

One group of cancers includes human breast cancers (e.g., primary breast tumours, node-negative breast cancer, invasive duct adenocarcinomas of the breast, non-endometrioid breast cancers); and mantle cell lymphomas. In addition, other cancers are colorectal and endometrial cancers. Another sub-set of cancers includes hematopoietic tumours of lymphoid lineage, for example leukemia, chronic lymphocytic leukaemia, mantle cell lymphoma, and B-cell lymphoma
20 (such as diffuse large B cell lymphoma). One particular cancer is chronic lymphocytic leukaemia. Another particular cancer is mantle cell lymphoma. Another particular cancer is diffuse large B cell lymphoma. Another sub-set of cancers includes breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer, and non-small cell lung carcinomas. Another sub-set of cancers includes breast cancer, pancreatic cancer, colorectal cancer, lung
25 cancer, and melanoma.

A further sub-set of cancers, namely cancers wherein compounds having CDK4 inhibitory activity may be of particular therapeutic benefit, comprises retinoblastomas, small cell lung carcinomas, non-small lung carcinomas, sarcomas, gliomas, pancreatic cancers, head, neck and breast cancers and mantle cell lymphomas.

Another sub-set of cancers wherein compounds having CDK4 inhibitory activity may be of
30 particular therapeutic benefit comprises small cell lung cancer, non-small cell lung cancer, pancreatic cancer, breast cancer, glioblastoma multiforme, T cell acute lymphoblastic leukaemia and mantle cell lymphoma. A further subset of cancers which the compounds described herein

may be useful in the treatment of includes sarcomas, leukemias, glioma, familial melanoma and melanoma.

One embodiment described herein is a method of treating a disorder or condition selected from the group consisting of cell proliferative disorders, such as cancer, vascular smooth muscle proliferation associated with atherosclerosis, postsurgical vascular stenosis, restenosis, and endometriosis; infections, including viral infections such as DNA viruses like herpes and RNA viruses like HIV, and fungal infections; autoimmune diseases such as psoriasis, inflammation like rheumatoid arthritis, lupus, type 1 diabetes, diabetic nephropathy, multiple sclerosis, and glomerulonephritis, organ transplant rejection, including host versus graft disease, in a mammal, including human, comprising administering to said mammal an amount of a compound described herein, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

Another embodiment described herein provides compounds that are useful for treating abnormal cell proliferation such a cancer. One aspect is a method of treating the abnormal cell proliferation disorders such as a cancer selected from the group consisting of cancers of the breast, ovary, cervix, prostate, testis, esophagus, stomach, skin, lung, bone, colon, pancreas, thyroid, biliary passages, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, adenocarcinoma, adenocarcinoma, adenoma, adenocarcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, and leukemia, comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, to a subject in need of such treatment.

A further embodiment described herein is a method of treating subjects suffering from diseases caused by vascular smooth muscle cell proliferation. Compounds within the scope of this disclosure effectively inhibit vascular smooth muscle cell proliferation and migration. The method comprises administering to a subject in need of treatment an amount of a compound described herein, or a pharmaceutically acceptable salt thereof, sufficient to inhibit vascular smooth muscle proliferation, and/or migration.

Another embodiment described herein is a method of treating a subject suffering from gout comprising administering to said subject in need of treatment an amount of a compound described herein, or a pharmaceutically acceptable salt thereof, sufficient to treat the condition.

Another embodiment is a method of treating a subject suffering from kidney disease, such as polycystic kidney disease, comprising administering to said subject in need of treatment an amount of a compound described herein, or a pharmaceutically acceptable salt thereof, sufficient to treat the condition.

5 Because of their inhibitory activity against CDKs and other kinases, the compounds described herein are also useful research tools for studying the mechanism of action of those kinases, both in vitro and in vivo.

10 The above-identified methods of treatment are preferably carried out by administering a therapeutically effective amount of a compound described herein (set forth below) to a subject in need of treatment. Compounds described herein are potent inhibitors of cyclin-dependent kinases. The compounds are readily synthesized and can be administered by a variety of routes, including orally and parenterally, and have little or no toxicity. The compounds described herein are members of the class of compounds described herein.

15 Another embodiment described herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

20 The compounds described herein are selective inhibitors of CDK4, CDK6, or CDK9, which is to say that they inhibit CDK4, CDK6, or CDK9 more potently than they inhibit tyrosine kinases and other serine-threonine kinases including other cyclin-dependent kinases such as CDK2. Despite their selectivity for CDK4, CDK6, or CDK9 inhibition, compounds described herein may inhibit other kinases, albeit at higher concentrations than those at which they inhibit CDK4, CDK6, or CDK9.

Preferred embodiments of this disclosure are compounds described herein inhibit CDK4, CDK6, or CDK9 at least about 100-fold more potently than they inhibit CDK2.

25 A preferred embodiment of this disclosure provides a method of inhibiting CDK4, CDK6, or CDK9 at a lower dose than is necessary to inhibit CDK2 comprising administration of a compound described herein in an effective amount that selectively inhibits CDK4, CDK6, or CDK9 over CDK2.

30 The compounds described herein have useful pharmaceutical and medicinal properties. Many of the compounds described herein exhibit significant selective CDK4, CDK6, or CDK9 inhibitory activity and therefore are of value in the treatment of a wide variety of clinical conditions in which CDK4, CDK6, or CDK9 kinase is abnormally elevated, or activated or present in normal amounts and activities, but where inhibition of the CDKs is desirable to treat a cellular proliferative

disorder. Such disorders include, but are not limited to those enumerated in the paragraphs below.

The compounds described herein are useful for treating cancer (for example, leukemia and cancer of the lung, breast, prostate, and skin such as melanoma) and other proliferative diseases including but not limited to psoriasis, HSV, HIV, restenosis, and atherosclerosis. To utilize a compound of this disclosure to treat cancer, a patient in need of such treatment, such as one having cancer or another proliferative disease, is administered a therapeutically effective amount of a pharmaceutically acceptable composition comprising at least one compound of this disclosure.

Methods of Diagnosis

Prior to administration of a compound described herein, a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against cyclin dependent kinases. For example, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by a genetic abnormality or abnormal protein expression which leads to over-activation of CDKs or to sensitisation of a pathway to normal CDK activity. Examples of such abnormalities that result in activation or sensitisation of the CDK2 signal include up-regulation of cyclin E or loss of p21 or p27, or presence of CDC4 variants. Harwell et al., *J. Biol. Chem.* 279(13): 12695-12705 (2004); Rajagopalan et al., *Nature* 428(6978): 77-81 (2004). Tumours with mutants of CDC4 or up-regulation, in particular over-expression, of cyclin E or loss of p21 or p27 may be particularly sensitive to CDK inhibitors. The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e., multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation, including activation by mutations.

Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of cyclin E, or loss of p21 or p27, or presence of CDC4 variants. The term diagnosis includes screening. Markers include genetic markers such as the measurement of DNA composition to identify mutations of CDC4. The term marker also includes markers which are characteristic of up regulation of cyclin E, including enzyme activity, enzyme levels, enzyme state (e.g., phosphorylated or not) and mRNA levels of the aforementioned proteins. Tumours with upregulation of cyclin E, or loss of p21 or p27 may be particularly sensitive to CDK inhibitors. Tumours may preferentially be screened for upregulation of cyclin E, or loss of p21 or p27 prior

to treatment. Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of cyclin E, or loss of p21 or p27.

The diagnostic tests are typically conducted on a biological sample selected from tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, or urine.

It has been found that there were mutations present in CDC4 (also known as Fbw7 or Archipelago) in human colorectal cancers and endometrial cancers. Rajagopalan et al., *Nature* 428(6978): 77-81 (2004); Spruck et al, *Cancer Res.* 62(16): 4535-4539 (2002). Identification of individual carrying a mutation in CDC4 may mean that the patient would be particularly suitable for treatment with a CDK inhibitor. Tumours may preferentially be screened for presence of a CDC4 variant prior to treatment. The screening process will typically involve direct sequencing, oligonucleotide microarray analysis, or a mutant specific antibody.

Methods of identification and analysis of mutations and up-regulation of proteins are well known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT-PCR) or in-situ hybridization.

In screening by RT-PCR, the level of mRNA in the tumour is assessed by creating a cDNA copy of the mRNA followed by amplification of the cDNA by PCR. Methods of PCR amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons Inc. (2004); Innis, M. A. et al., eds. *PCR Protocols: a guide to methods and applications*, Academic Press, San Diego (1990). Reactions and manipulations involving nucleic acid techniques are also described in Sambrook et al., 3rd ed, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press (2001).

An example of an in-situ hybridization technique for assessing mRNA expression would be fluorescence in-situ hybridization (FISH). Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) prehybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labeled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more

nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for carrying out FISH are described in Ausubel et al. *Current Protocols in Molecular Biology*, 2004, John Wiley & Sons Inc and Fluorescence In Situ Hybridization: Technical Overview by John M. S. Bartlett in *Molecular Diagnosis of Cancer, Methods and Protocols*, 2nd ed, 77-88 (2004).

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumour samples, solid phase immunoassay with microtiter plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, flow cytometry and other methods known in the art for detection of specific proteins. Detection methods would include the use of site specific antibodies. The skilled person will recognize that all such well-known techniques for detection of upregulation of cyclin E, or loss of p21 or p27, or detection of CDC4 variants could be applicable in the present case.

Therefore, all of these techniques could also be used to identify tumours particularly suitable for treatment with the compounds described herein.

Tumours with mutants of CDC4 or up-regulation, in particular over-expression, of cyclin E or loss of p21 or p27 may be particularly sensitive to CDK inhibitors. Tumours may preferentially be screened for up-regulation, in particular over-expression, of cyclin E or loss of p21 or p27 or for CDC4 variants prior to treatment. See Harwell et al., *J. Biol. Chem.* 279(13): 12695-12705 (2004); Rajagopalan et al., *Nature* 428(6978): 77-81 (2004).

Patients with mantle cell lymphoma (MCL) could be selected for treatment with a compound described herein using diagnostic tests outlined herein. MCL is a distinct clinicopathologic entity of non-Hodgkin's lymphoma, characterized by proliferation of small to medium-sized lymphocytes with co-expression of CD5 and CD20, an aggressive and incurable clinical course, and frequent t(11;14) (q13;q32) translocation. Over-expression of cyclin D1 mRNA, found in mantle cell lymphoma (MCL), is a critical diagnostic marker. Yatabe et al., *Blood* 95(7): 2253-2261 (2000) proposed that cyclin D1-positivity should be included as one of the standard criteria for MCL, and that innovative therapies for this incurable disease should be explored on the basis of the new criteria. Jones et al., *J. Mol. Diagn.* 6(2): 84-89 (2004) developed a real-time, quantitative, reverse transcription PCR assay for cyclin D1 (CCND1) expression to aid in the diagnosis of mantle cell lymphoma (MCL). Howe et al., *Clin. Chem.* 50(1): 80-87 (2004) used real-time quantitative RT-PCR to evaluate cyclin D1 mRNA expression and found that quantitative RT-PCR for cyclin D1 mRNA normalized to CD 19 mRNA can be used in the diagnosis of MCL in blood, marrow, and tissue. Alternatively, patients with breast cancer could be selected for treatment with a CDK inhibitor using diagnostic tests outline above. Tumour cells

commonly overexpress cyclin E and it has been shown that cyclin E is over-expressed in breast cancer. Harwell et al., *Cancer Res.* 60: 481-489 (2000). Breast cancer, in particular, may be treated with a CDK inhibitor as described herein.

In addition, the cancer may be analysed for INK4a and RB loss of function, and cyclin D1
5 or CDK4 overexpression or CDK4 mutation. RB loss and mutations inactivating p16INK4a function or hypermethylation of p16INK4a occur in many tumour types. Rb is inactivated in 100% retinoblastomas and in 90% of small cell lung carcinomas. Cyclin D1 is amplified in 40% of head and neck, over-expressed in 50% of breast cancers and 90% of mantle cell lymphomas. p16 is deleted in 60% of non-small lung carcinomas and in 40% of pancreatic cancers. CDK4 is
10 amplified in 20% of sarcomas and in 10% of gliomas. Events resulting in RB or p16INK4a inactivation through mutation, deletion, or epigenetic silencing, or in the overexpression of cyclin D1 or Cdk4 can be identified by the techniques outlined herein. Tumours with up-regulation, in particular over-expression of cyclin D or CDK4 or loss of INK4a or RB may be particularly sensitive to CDK inhibitors. Thus, the patient may be subjected to a diagnostic test to detect a marker
15 characteristic of over-expression of cyclin D or CDK4 or loss of INK4a or RB.

Cancers that experience INK4a and RB loss of function and cyclin D1 or CDK4 overexpression, include small cell lung cancer, non-small cell lung cancer, pancreatic cancer, breast cancer, glioblastoma multiforme, T cell ALL and mantle cell lymphoma. Therefore patients with small cell lung cancer, non-small cell lung cancer, pancreatic cancer, breast cancer,
20 glioblastoma multiforme, T cell ALL or mantle cell lymphoma could be selected for treatment with a CDK inhibitor using diagnostic tests outlined above and may in particular be treated with a CDK inhibitor as provided herein.

Patients with specific cancers caused by aberrations in the D-Cyclin-CDK4/6-INK4-Rb pathway could be identified by using the techniques described herein and then treated with a
25 CDK4 inhibitor as provided. Examples of abnormalities that activate or sensitise tumours to CDK4 signal include, receptor activation e.g., Her-2/Neu in breast cancer, ras mutations for example in pancreatic, colorectal or lung cancer, raf mutations for example in melanoma, p16 mutations for example in melanoma, p16 deletions for example in lung cancer, p16 methylation for example in lung cancer or cyclin D overexpression for example in breast cancer. Thus, a patient could be
30 selected for treatment with a compound described herein using diagnostic tests as outlined herein to identify up-regulation of the D-Cyclin-CDK4/6-INK4-Rb pathway for example by overexpression of cyclin D, mutation of CDK4, mutation or depletion of pRb, deletion of p16-INK4, mutation, deletion or methylation of p16, or by activating events upstream of the CDK4/6 kinase e.g., Ras mutations or Raf mutations or hyperactive or over-expressed receptors such as Her-2/Neu.

The compounds described herein are particularly advantageous in that they are selective inhibitors of CDK4 over other cyclin dependent kinases. Compounds of this class have been previously described, but the compounds described herein have increased potency and selectivity of CDK4 over other cyclin dependent kinases. See *e.g.*, U.S. Pat. Nos. 6,936,612; 8,685,980; 8,324,225; and U.S. Pat. Pub. No. US 20160220569.

The inhibition of protein kinase activity by the compounds described herein may be measured using a number of assays available in the art. Examples of such assays are described in the Exemplification section below.

Pharmaceutical Compositions

The language “effective amount” of the compound is that amount necessary or sufficient to treat or prevent a protein kinase-associated disorder, *e.g.*, prevent the various morphological and somatic symptoms of a protein kinase-associated disorder, and/or a disease or condition described herein. In an example, an effective amount of the compound described herein is the amount sufficient to treat a protein kinase-associated disorder in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound described herein. For example, the choice of the compound described herein can affect what constitutes an “effective amount.” One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds described herein without undue experimentation.

The regimen of administration can affect what constitutes an effective amount. The compound described herein can be administered to the subject either prior to or after the onset of a protein kinase-associated disorder. Further, several divided dosages as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) described herein can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

Compounds described herein may be used in the treatment of states, disorders or diseases as described herein, or for the manufacture of pharmaceutical compositions for use in the treatment of these diseases. Methods of use of the compounds described herein in the treatment of these diseases, or pharmaceutical preparations having the compounds described herein for the treatment of these diseases.

The language “pharmaceutical composition” includes preparations suitable for administration to mammals, *e.g.*, humans. When the compounds described herein are

administered as pharmaceuticals to mammals, e.g., humans, they can be given per se or as a pharmaceutical composition containing, for example, 0.1% to 99.5% (preferably, 1% to 90%) of active ingredient in combination with a pharmaceutically acceptable excipient.

The phrase “pharmaceutically acceptable excipient” includes any pharmaceutically acceptable material, composition, or vehicle, suitable for administering the compounds described herein to mammals. The excipient includes liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each excipient must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable excipients include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers, or lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, α -tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations described herein include those suitable for oral, nasal, topical, buccal, sublingual, rectal, vaginal, and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be combined with an excipient material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1

percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound as described herein with the excipient and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound described herein with liquid excipients, or finely divided solid excipients, or both, and then, if necessary, shaping the product.

Formulations described herein suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound described herein as an active ingredient. A compound described herein may also be administered as a bolus, electuary, or paste.

In solid dosage forms described herein for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof, and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or

dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions described herein, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds described herein include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, or elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluent commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying agents, suspending agents, sweetening, flavoring, coloring, perfuming, preservative agents, or combinations thereof.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions described herein for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds described herein with one or more suitable nonirritating excipients or excipients

comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations described herein which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such excipients as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound described herein include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable excipient, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams, and gels may contain, in addition to an active compound described herein, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound described herein, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound described herein to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this disclosure.

Pharmaceutical compositions described herein suitable for parenteral administration comprise one or more compounds described herein in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous excipients that may be employed in the pharmaceutical compositions described herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, dispersing agents, or combinations thereof. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microcapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

The preparations described herein may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc., administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral and/or IV administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous,

subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, and intrasternal injection or infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

The subject treated is typically a human subject, although it is to be understood the methods described herein are effective with respect to other animals, such as mammals and vertebrate species. More particularly, the term subject can include animals used in assays such as those used in preclinical testing including but not limited to mice, rats, monkeys, dogs, pigs and rabbits; as well as domesticated swine (pigs and hogs), ruminants, equine, poultry, felines, bovines, murines, canines, and the like.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds described herein, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions described herein, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions described herein may be varied to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound described herein employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the

physician or veterinarian could start doses of the compounds described herein employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

5 In general, a suitable daily dose of a compound described herein will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described herein. Generally, intravenous and subcutaneous doses of the compounds described herein for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 200 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably
10 from about 1.0 to about 200 mg per kg per day. An effective amount is that amount treats a protein kinase-associated disorder.

When used in the context of a dosage amount, e.g., mg/m², the numerical weight refers to the weight of a compound described herein, exclusive of any salt, counterion, and so on. Therefore, to obtain the equivalent of 100 mg/m² of a compound described herein, it would be
15 necessary to utilize more than 100 mg/m² of its salt, due to the additional weight of the salt.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound described herein to be administered alone, it is
20 preferable to administer the compound as a pharmaceutical composition.

Synthetic Procedures

The compounds described herein are prepared from commonly available compounds using procedures known to those skilled in the art, including any one or more of the following
25 conditions without limitation:

Within the scope of this disclosure, only a readily removable group that is not a constituent of the particular desired end product of the compounds described herein is designated a "protecting group," unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are
30 described for example in standard reference works, such as e.g., Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag, Stuttgart, Germany (2005); McOmie, "Protective Groups in Organic Chemistry," Plenum Press, London and New York (1973); Greene and Wuts, "Protective Groups in Organic Synthesis," Third edition, Wiley, New York (1999); Gross and Meienhofer, eds., "The Peptides"; Vol. 3 Academic Press, London and New

York (1981). A characteristic of protecting groups is that they can be removed readily (i.e., without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (e.g., by enzymatic cleavage).

Salts of the compounds described herein having at least one salt-forming group may be prepared in a manner known per se. For example, salts of the compounds described herein having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g., the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of the compounds described herein are obtained in customary manner, e.g., by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of the compounds described herein containing acid and basic salt-forming groups, e.g., a free carboxy group and a free amino group, may be formed, e.g., by the neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g., with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable as described herein can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by, e.g., medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials. Intermediates and final products can be worked up and/or purified according to standard methods, e.g., using chromatographic methods, distribution methods, (re-) crystallization, and the like.

General Process Conditions

The following applies in general to all processes mentioned throughout this disclosure. The process steps to synthesize the compounds described herein can be carried out under

reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation
5 exchangers, e.g., in the H⁺ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about –100 °C to about 190 °C., including, for example, from approximately –80 °C to approximately 150 °C., for example at from –80 °C to –60 °C, at room temperature, at from –20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under
10 pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described in Science of Synthesis: Houben-Weyl Methods of Molecular
15 Transformation. Georg Thieme Verlag, Stuttgart, Germany 2005.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic
20 hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear
25 or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or
30 their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

Other embodiments are forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is

used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process as described herein is produced under the process conditions and processed further in situ.

5 Prodrugs

Also described are pharmaceutical compositions containing, and methods of treating protein kinase-associated disorders through administering, pharmaceutically acceptable prodrugs of compounds of the compounds described herein. For example, compounds described herein having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds described herein. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews* 19: 115 (1996). Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described herein, are also encompassed. Prodrugs of this type are described by TenBrink et al., *J. Med. Chem.*, 39: 10 (1996). Free amines can also be derivatized as amides, sulfonamides, or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine, or carboxylic acid functionalities.

Any reference to a compound described herein is therefore to be understood as referring also to the corresponding pro-drugs of the compound described herein, as appropriate and expedient.

Combinations

The compounds described herein may also be used in combination with other agents, e.g., an additional protein kinase inhibitor that is or is not a compound described herein, for treatment of a protein kinase-associated disorder in a subject.

By the term "combination" is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound described herein and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g., synergistic, effect, or any combination thereof.

The compounds described herein may be administered, simultaneously or sequentially, with an antiinflammatory, antiproliferative, chemotherapeutic agent, immunosuppressant, anti-cancer, cytotoxic agent or kinase inhibitor other than a compound described herein or salt thereof. Further examples of agents that may be administered in combination with the compounds described herein include, but are not limited to, a PTK inhibitor, cyclosporin A, CTLA4-Ig, antibodies selected from anti-ICAM-3, anti-IL-2 receptor, anti-CD45RB, anti-CD2, anti-CD3, anti-CD4, anti-CD80, anti-CD86, and monoclonal antibody OKT3, agents blocking the interaction between CD40 and gp39, fusion proteins constructed from CD40 and gp39, inhibitors of NF-kappa B function, non-steroidal antiinflammatory drugs, steroids, gold compounds, antiproliferative agents, FK506, mycophenolate mofetil, cytotoxic drugs, TNF- α inhibitors, anti-TNF antibodies or soluble TNF receptor, rapamycin, leflunomide, cyclooxygenase-2 inhibitors, paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin, etoposide, etoposide phosphate, teniposide, melphalan, vinblastine, vincristine, leurosine, epothilone, vindesine, leurosine, or derivatives thereof.

The compound described herein and any additional agent may be formulated in separate dosage forms. Alternatively, to decrease the number of dosage forms administered to a patient, the compound described herein and any additional agent may be formulated together in any combination. For example, the compound described herein inhibitor may be formulated in one dosage form and the additional agent may be formulated together in another dosage form. Any separate dosage forms may be administered at the same time or different times.

Alternatively, a composition described herein comprises an additional agent as described herein. Each component may be present in individual compositions, combination compositions, or in a single composition.

Chemotherapeutic Agents

As contemplated herein, the compounds described herein are orally or intravenously administered to a subject undergoing an anti-cancer therapeutic treatment regimen, for example a chemotherapeutic treatment regimen, prior to the subject receiving the anti-cancer therapy. As used herein the term “chemotherapy” or “chemotherapeutic agent” refers to treatment with a cytostatic or cytotoxic agent (i.e., a compound) to reduce or eliminate the growth or proliferation of undesirable cells, for example cancer cells. Thus, as used herein, “chemotherapy” or “chemotherapeutic agent” refers to a cytotoxic or cytostatic agent used to treat a proliferative disorder, for example cancer. The cytotoxic effect of the agent can be, but is not required to be, the result of one or more of nucleic acid intercalation or binding, DNA or RNA alkylation, inhibition of RNA or DNA synthesis, the inhibition of another nucleic acid-related activity (e.g., protein synthesis), or any other cytotoxic effect. In one embodiment, the chemotherapeutic agent is selected from etoposide, carboplatin, cisplatin, and topotecan, or a combination thereof. In one embodiment, the chemotherapeutic agent is topotecan. In one embodiment, the chemotherapeutic agent is cisplatin. In one embodiment, the chemotherapeutic agent is carboplatin. In one embodiment, the chemotherapeutic agent is etoposide.

Thus, a “cytotoxic agent” can be any one or any combination of compounds also described as “antineoplastic” agents or “chemotherapeutic agents.” Such compounds include, but are not limited to, DNA damaging compounds and other chemicals that can kill cells. “DNA damaging chemotherapeutic agents” include, but are not limited to, alkylating agents, DNA intercalators, protein synthesis inhibitors, inhibitors of DNA or RNA synthesis, DNA base analogs, topoisomerase inhibitors, and telomerase inhibitors or telomeric DNA binding compounds. For example, alkylating agents include alkyl sulfonates, such as busulfan, improsulfan, and piposulfan; aziridines, such as a benzodizepin, carboquone, meturedopa, and uredopa; ethyleneimines and methylmelamine, such as altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate, and trimethylolmelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cyclophosphamide, estramustine, iphosphamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichine, phenesterine, prednimustine, trofosfamide, and uracil mustard; and nitroso ureas, such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine.

Antibiotics used in the treatment of cancer include dactinomycin, daunorubicin, doxorubicin, idarubicin, bleomycin sulfate, mytomycin, plicamycin, and streptozocin. Chemotherapeutic antimetabolites include mercaptopurine, thioguanine, cladribine, fludarabine phosphate, fluorouracil (5-FU), floxuridine, cytarabine, pentostatin, methotrexate, and

azathioprine, acyclovir, adenine β -1-D-arabinoside, amethopterin, aminopterin, 2-aminopurine, aphidicolin, 8-azaguanine, azaserine, 6-azauracil, 2'-azido-2'-deoxynucleosides, 5-bromodeoxycytidine, cytosine β -1-D-arabinoside, diazooxonorleucine, dideoxynucleosides, 5-fluorodeoxycytidine, 5-fluorodeoxyuridine, and hydroxyurea.

5 Chemotherapeutic protein synthesis inhibitors include abrin, aurintricarboxylic acid, chloramphenicol, colicin E3, cycloheximide, diphtheria toxin, edeine A, emetine, erythromycin, ethionine, fluoride, 5-fluorotryptophan, fusidic acid, guanylyl methylene diphosphonate and guanylyl imidodiphosphate, kanamycin, kasugamycin, kirromycin, and O-methyl threonine. Additional protein synthesis inhibitors include modeccin, neomycin, norvaline, pactamycin, 10 paromomycine, puromycin, ricin, shiga toxin, showdomycin, sparsomycin, spectinomycin, streptomycin, tetracycline, thiostrepton, and trimethoprim. Inhibitors of DNA synthesis, include alkylating agents such as dimethyl sulfate, mitomycin C, nitrogen and sulfur mustards; intercalating agents, such as acridine dyes, actinomycins, adriamycin, anthracenes, benzopyrene, ethidium bromide, propidium diiodide-intertwining; and other agents, such as 15 distamycin and netropsin. Topoisomerase inhibitors, such as coumermycin, nalidixic acid, novobiocin, and oxolinic acid; inhibitors of cell division, including colcemide, colchicine, vinblastine, and vincristine; and RNA synthesis inhibitors including actinomycin D, α -amanitine and other fungal amatoxins, cordycepin (3'-deoxyadenosine), dichlororibofuranosyl benzimidazole, rifampicine, streptovaricin, and streptolydigin also can be used as the DNA 20 damaging compound.

Current chemotherapeutic agents whose toxic effects can be mitigated by the presently disclosed dosages of the compounds described herein include, but are not limited to, adriamycin, 5-fluorouracil (5FU), 6-mercaptopurine, gemcitabine, melphalan, chlorambucil, mitomycin, irinotecan, mitoxantrone, etoposide, camptothecin, topotecan, irinotecan, exatecan, lurtotecan, 25 actinomycin-D, mitomycin, cisplatin, hydrogen peroxide, carboplatin, procarbazine, mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, busulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, tamoxifen, taxol, transplatinum, vinblastine, vinblastin, carmustine, cytarabine, mechlorethamine, chlorambucil, streptozocin, lomustine, temozolomide, thiotepa, altretamine, oxaliplatin, camptothecin, topotecan, and 30 methotrexate, and the like, and similar acting-type agents. In one embodiment, the DNA damaging chemotherapeutic agent is selected from the group consisting of cisplatin, carboplatin, camptothecin, doxorubicin, and etoposide. In one embodiment, the DNA damaging chemotherapeutic agent is topotecan. In one embodiment, the DNA-damaging chemotherapeutic agent is etoposide. In one embodiment, the DNA damaging chemotherapeutic agent is

carboplatin. In one embodiment, the DNA damaging chemotherapeutic agent is a combination of etoposide and carboplatin.

In certain alternative embodiments, compounds described herein in a dosage described herein is also used for an anti-cancer or anti-proliferative effect in combination with a chemotherapeutic to treat a CDK4/6 replication independent, such as an Rb-negative cancer or proliferative disorder. Compounds described herein, under certain conditions, may provide an additive or synergistic effect to the chemotherapeutic, resulting in a greater anti-cancer effect than seen with the use of the chemotherapeutic alone. In one embodiment, the compounds described herein can be combined with one or more of the chemotherapeutic compounds described herein.

In one embodiment, the compounds described herein can be combined with a chemotherapeutic selected from, but not limited to, tamoxifen, midazolam, letrozole, bortezomib, anastrozole, goserelin, an mTOR inhibitor, a PI3 kinase inhibitor, a dual mTOR-PI3K inhibitor, a Bruton's tyrosine kinase (BTK) inhibitor, a spleen tyrosine kinase (Syk) inhibitor, a MEK inhibitor, a RAS inhibitor, an ALK inhibitor, an HSP inhibitor (for example, an HSP70 or an HSP 90 inhibitor, or a combination thereof), a BCL-2 inhibitor, an apoptotic inducing compound, an AKT inhibitor, including but not limited to, MK-2206, GSK690693, Perifosine, (KRX-0401), GDC-0068, Triciribine, AZD5363, Honokiol, PF-04691502, and Miltefosine, a PD-1 inhibitor including but not limited to, nivolumab, CT-011, MK-3475, BMS936558, and AMP-514 or a FLT-3 inhibitor, including but not limited to, P406, dovitinib, quizartinib (AC220), amuvatinib (MP-470), tandutinib (MLN518), ENMD-2076, and KW-2449, or combinations thereof. Examples of mTOR inhibitors include but are not limited to rapamycin and its analogs, everolimus (Afinitor), temsirolimus, ridaforolimus, sirolimus, and deforolimus.

PI3k inhibitors that may be used in this disclosure are well known. Examples of PI3 kinase inhibitors include but are not limited to wortmannin, demethoxyviridin, perifosine, idelalisib, Pictilisib, Palomid 529, ZSTK474, PWT33597, CUDC-907, and AEZS-136, duvelisib, GS-9820, GDC-0032 (2-[4-[2-(2-Isopropyl-5-methyl-1,2,4-triazol-3-yl)-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]pyrazol-1-yl]-2-methylpropanamide), MLN-1117 ((2*R*)-1-Phenoxy-2-butanyl hydrogen (*S*)-methylphosphonate; or Methyl(oxo) {[(2*R*)-1-phenoxy-2-butanyl]oxy}phosphonium), BYL-719 ((2*S*)-N1-[4-Methyl-5-[2-(2,2,2-trifluoro-1,1-dimethylethyl)-4-pyridinyl]-2-thiazolyl]-1,2-pyrrolidinedicarboxamide), GSK2126458 (2,4-Difluoro-N-{2-(methyloxy)-5-[4-(4-pyridazinyl)-6-quinolinyl]-3-pyridinyl}benzenesulfonamide), TGX-221 ((±)-7-Methyl-2-(morpholin-4-yl)-9-(1-phenylaminoethyl)-pyrido[1,2-*a*]-pyrimidin-4-one), GSK2636771 (2-Methyl-1-(2-methyl-3-(trifluoromethyl)benzyl)-6-morpholino-1*H*-benzo[d]imidazole-4-carboxylic acid dihydrochloride), KIN-193 ((*R*)-2-((1-(7-methyl-2-

morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)ethyl)amino)benzoic acid), TGR-1202/RP5264, GS-9820 ((*S*)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morphoxypropan-1-one), GS-1101 (5-fluoro-3-phenyl-2-([*S*])-1-[9H-purin-6-ylamino]-propyl)-3H-quinazolin-4-one), AMG-319, GSK-2269557, SAR245409 (N-(4-(N-(3-((3,5-dimethoxyphenyl)amino)quinoxalin-2-yl)sulfamoyl)phenyl)-3-methoxy-4-methylbenzamide), BAY80-6946 (2-amino-N-(7-methoxy-8-(3-morpholinopropoxy)-2,3-dihydroimidazo[1,2-c]quinaz), AS 252424 (5-[1-[5-(4-Fluoro-2-hydroxyphenyl)-furan-2-yl]-meth-(*Z*)-ylidene]-thiazolidine-2,4-dione), CZ 24832 (5-(2-amino-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide), buparlisib (5-[2,6-Di(4-morpholinyl)-4-pyrimidinyl]-4-(trifluoromethyl)-2-pyridinamine), GDC-0941 (2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-4-(4-morpholinyl)thieno[3,2-d]pyrimidine), GDC-0980 ((*S*)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one (also known as RG7422)), SF1126 ((8*S*,14*S*,17*S*)-14-(carboxymethyl)-8-(3-guanidinopropyl)-17-(hydroxymethyl)-3,6,9,12,15-pentaoxo-1-(4-(4-oxo-8-phenyl-4H-chromen-2-yl)morpholino-4-ium)-2-oxa-7,10,13,16-tetraazaoctadecan-18-oate), PF-05212384 (N-[4-[[4-(Dimethylamino)-1-piperidinyl]carbonyl]phenyl]-N'-[4-(4,6-di-4-morpholinyl-1,3,5-triazin-2-yl)phenyl]urea), LY3023414, BEZ235 (2-Methyl-2-{4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl]phenyl}propanenitrile), XL-765 (N-(3-(N-(3-(3,5-dimethoxyphenylamino)quinoxalin-2-yl)sulfamoyl)phenyl)-3-methoxy-4-methylbenzamide), and GSK1059615 (5-[[4-(4-Pyridinyl)-6-quinolinyl]methylene]-2,4-thiazolidinedione), PX886 ((3*aR*,6*E*,9*S*,9*aR*,10*R*,11*aS*)-6-[[bis(prop-2-enyl)amino]methylidene]-5-hydroxy-9-(methoxymethyl)-9*a*,11*a*-dimethyl-1,4,7-trioxo-2,3,3*a*,9,10,11-hexahydroindeno[4,5*h*]isochromen-10-yl]acetate (also known as sonolisib)). In one embodiment, the compounds described herein are combined in a single dosage form with the Plk3 inhibitor.

BTK inhibitors for use as described herein are well known. Examples of BTK inhibitors include ibrutinib (also known as PCI-32765)(Imbruvica™)(1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one), dianilinopyrimidine-based inhibitors such as AVL-101 and AVL-291/292 (N-(3-((5-fluoro-2-(4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide) (Avila Therapeutics) (see US Patent Publication No 20110117073), Dasatinib ([N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide], LFM-A13 (alpha-cyano-beta-hydroxy-beta-methyl-N-(2,5-ibromophenyl) propenamide), GDC-0834 ([*R*-N-(3-(6-(4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-

yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide], CGI-560 4-(tert-butyl)-N-(3-(8-(phenylamino)imidazo[1,2-a]pyrazin-6-yl)phenyl)benzamide, CGI-1746 4-(tert-butyl)-N-(2-methyl-3-(4-methyl-6-((4-(morpholine-4-carbonyl)phenyl)amino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide), CNX-774 4-(4-((4-((3-acrylamidophenyl)amino)-5-fluoropyrimidin-2-yl)amino)phenoxy)-N-methylpicolinamide), CTA056 (7-benzyl-1-(3-(piperidin-1-yl)propyl)-2-(4-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-g]quinoxalin-6(5H)-one), GDC-0834 ((*R*)-N-(3-(6-((4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide), GDC-0837 ((*R*)-N-(3-(6-((4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide), HM-71224, ACP-196, ONO-4059 (Ono Pharmaceuticals), PRT062607 (4-((3-(2H-1,2,3-triazol-2-yl)phenyl)amino)-2-(((1*R*,2*S*)-2-aminocyclohexyl)amino)pyrimidine-5-carboxamide hydrochloride), QL-47 (1-(1-acryloylindolin-6-yl)-9-(1-methyl-1H-pyrazol-4-yl)benzo[h][1,6]naphthyridin-2(1H)-one), and RN486 (6-cyclopropyl-8-fluoro-2-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-2H-isoquinolin-1-one), and other molecules capable of inhibiting BTK activity, for example those BTK inhibitors disclosed in Akinleye et al, *J. Hemat. Oncol.* 6: 59 (2013), the entirety of which is incorporated herein by reference. In one embodiment, the compounds described herein are combined in a single dosage form with the BTK inhibitor.

Syk inhibitors for use as described herein are well known, and include, for example, cerdulatinib (4-(cyclopropylamino)-2-((4-(4-(ethylsulfonyl)piperazin-1-yl)phenyl)amino)pyrimidine-5-carboxamide), entospletinib (6-(1H-indazol-6-yl)-N-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine), fostamatinib ([6-({5-Fluoro-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinyl}amino)-2,2-dimethyl-3-oxo-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-yl)methyl dihydrogen phosphate), fostamatinib disodium salt (sodium(6-((5-fluoro-2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yl)amino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate), BAY 61-3606 (2-(7-(3,4-Dimethoxyphenyl)-imidazo[1,2-c]pyrimidin-5-ylamino)-nicotinamide HCl), RO9021 (6-[(1*R*,2*S*)-2-Amino-cyclohexylamino]-4-(5,6-dimethyl-pyridin-2-ylamino)-pyridazine-3-carboxylic acid amide), imatinib (Gleevec; 4-[(4-methylpiperazin-1-yl)methyl]-N-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl)benzamide), staurosporine, GSK143 (2-(((3*R*,4*R*)-3-aminotetrahydro-2H-pyran-4-yl)amino)-4-(p-tolylamino)pyrimidine-5-carboxamide), PP2 (1-(tert-butyl)-3-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine), PRT-060318 (2-(((1*R*,2*S*)-2-aminocyclohexyl)amino)-4-(m-tolylamino)pyrimidine-5-carboxamide), PRT-062607 (4-((3-(2H-1,2,3-triazol-2-

yl)phenyl)amino)-2-(((1*R*,2*S*)-2-aminocyclohexyl)amino)pyrimidine-5-carboxamide hydrochloride), R112 (3,3'-((5-fluoropyrimidine-2,4-diyl)bis(azanediyl))diphenol), R348 (3-Ethyl-4-methylpyridine), R406 (6-((5-fluoro-2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yl)amino)-2,2-dimethyl-2H-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one), YM193306, 7-azaindole, piceatannol, ER-27319, Compound D, PRT060318, luteolin, apigenin, quercetin, fisetin, myricetin, or morin. See Singh et al. *J. Med. Chem.* 55: 3614-3643 (2012). In one embodiment, the compounds described herein are combined in a single dosage form with the Syk inhibitor.

MEK inhibitors for use as described herein are well known, and include, for example, tametinib/GSK1120212 (N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*-yl)}phenyl)acetamide), selumetinob (6-(4-bromo-2-chloroanilin)-7-fluoro-N-(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide), pimasertib/AS703026/MSK1935369 ((*S*)-N-(2,3-dihydroxypropyl)-3-((2-fluoro-4-iodophenyl)amino)isonicotinamide), XL-518/GDC-0973 (1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol), refametinib/BAY869766/RDEA119 (N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide), PD-0325901 (N-[(2*R*)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide), TAK733 ((*R*)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamin)-8-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione), MEK162/ARRY438162 (5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1*H*-benzimidazole-6-carboxamide), R05126766 (3-[[3-Fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-4-methyl-7-pyrimidin-2-yloxychromen-2-one), WX-554, R04987655/CH4987655 (3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-5-((3-oxo-1,2-oxazinan-2-yl)methyl)benzamide), or AZD8330 (2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide). In one embodiment, the compounds described herein are combined in a single dosage form with the MEK inhibitor.

Raf inhibitors for use as described herein are well known, and include, for example, Vemurafinib (N-[3-[[5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]carbonyl]-2,4-difluorophenyl]-1-propanesulfonamide), sorafenib tosylate (4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-N-methylpyridine-2-carboxamide; 4-methylbenzenesulfonate), AZ628 (3-(2-cyanopropan-2-yl)-N-(4-methyl-3-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-ylamino)phenyl)benzamide), NVP-BHG712 (4-methyl-3-(1-methyl-6-(pyridin-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamino)-N-(3-(trifluoromethyl)phenyl)benzamide), RAF-265 (1-methyl-5-[2-[5-(trifluoromethyl)-1*H*-imidazol-2-yl]pyridin-4-yl]oxy-N-[4-

(trifluoromethyl)phenyl]benzimidazol-2-amine), 2-Bromoaldisine (2-Bromo-6,7-dihydro-1H,5H-pyrrolo[2,3-c]azepine-4,8-dione), Raf Kinase Inhibitor IV (2-chloro-5-(2-phenyl-5-(pyridin-4-yl)-1H-imidazol-4-yl)phenol), and Sorafenib N-Oxide (4-[4-[[[4-Chloro-3

(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-Methyl-2pyridinecarboxamide 1-

Oxide). In one embodiment, the compounds described herein are combined in a single dosage form with the Raf inhibitor. In one embodiment, the at least one additional chemotherapeutic agent combined or alternated with the compounds described herein is a protein cell death-1 (PD-1) inhibitor. PD-1 inhibitors are known in the art, and include, for example, nivolumab (BMS), pembrolizumab (Merck), pidilizumab (CureTech/Teva), AMP-244 (Amplimmune/GSK), BMS-936559 (BMS), and MEDI4736 (Roche/Genentech). In one embodiment, the compounds described herein are combined in a single dosage form with the PD-1 inhibitor.

In one embodiment, the at least one additional chemotherapeutic agent combined or alternated with a selected compound disclosed herein is a B-cell lymphoma 2 (Bcl-2) protein inhibitor. BCL-2 inhibitors are known in the art, and include, for example, ABT-199 (4-[4-[[2-(4-Chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl]-N-[[3-nitro-4-[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]sulfonyl]-2-[(1H-pyrrolo[2,3-b]pyridin-5-yl)oxy]benzamide), ABT-737 (4-[4-[[2-(4-chlorophenyl)phenyl]methyl]piperazin-1-yl]-N-[4-[(2R)-4-(dimethylamino)-1-phenylsulfanylbutan-2-yl]amino]-3-nitrophenyl]sulfonylbenzamide), ABT-263 ((R)-4-(4-(4'-chloro-4,4-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-(4-morpholino-1-(phenylthio)butan-2-yl)amino)-3((trifluoromethyl)sulfonyl)phenyl)sulfonylbenzamide), GX15-070 (obatoclax mesylate, (2Z)-2-[(5Z)-5-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-4-methoxypyrrol-2-ylidene]indole; methanesulfonic acid)), 2-methoxy-antimycin A3, YC137 (4-(4,9-dioxo-4,9-dihydronaphtho[2,3-d]thiazol-2-ylamino)-phenyl ester), pogosin, ethyl 2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4H-chromene-3-carboxylate, Nilotinib-d3, TW-37 (N-[4-[[2-(1,1-Dimethylethyl)phenyl]sulfonyl]phenyl]-2,3,4-trihydroxy-5-[[2-(1-methylethyl)phenyl]methyl]benzamide), Apogossypolone (ApoG2), or G3139 (Oblimersen). In one embodiment, the compounds described herein are administered in the dosage described herein and combined in a single dosage form with the at least one BCL-2 inhibitor.

Examples of RAS inhibitors include but are not limited to Reolysin and siGI2D LODER. Examples of ALK inhibitors include but are not limited to Crizotinib, AP26113, and LDK378. HSP inhibitors include but are not limited to Geldanamycin or 17-N-Allylamino-17-demethoxygeldanamycin (17AAG), and Radicicol.

In one embodiment described herein, the compounds described herein are administered in the dosage described herein in combination with a topoisomerase inhibitor. In one aspect, an advantageous treatment of select Rb-negative cancers is disclosed using the compounds described herein in combination with a topoisomerase inhibitor. In one embodiment, the topoisomerase inhibitor is a topoisomerase I inhibitor or a topoisomerase I and II dual inhibitor. In one embodiment, the topoisomerase inhibitor is a topoisomerase II inhibitor.

In one embodiment, the topoisomerase inhibitor is selected from a topoisomerase I inhibitor. Known topoisomerase I inhibitors useful as described herein include (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione monohydrochloride (topotecan), (S)-4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione (camptothecin), (1S,9S)-1-Amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-10H,13H-benzo(de)pyrano(3',4':6,7)indolizino(1,2-b)quinoline-10,13-dione (exatecan), (7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin (lurtotecan), or (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate (irinotecan), (R)-5-ethyl-9,10-difluoro-5-hydroxy-4,5-dihydrooxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15(1H,13H)-dione (diflomotecan), (4S)-11-((E)-((1-Dimethylethoxy)imino)methyl)-4-ethyl-4-hydroxy-1,12-dihydro-14H-pyrano(3',4':6,7)indolizino(1,2-b)quinoline-3,14(4H)-dione (gimatecan), (S)-8-ethyl-8-hydroxy-15-((4-methylpiperazin-1-yl)methyl)-11,14-dihydro-2H-[1,4]dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(3H,8H)-dione (lurtotecan), (4S)-4-Ethyl-4-hydroxy-11-[2-[(1-methylethyl)amino]ethyl]-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione (belotecan), 6-((1,3-dihydroxypropan-2-yl)amino)-2,10-dihydroxy-12-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (edotecarin), 8,9-dimethoxy-5-(2-N,N-dimethylaminoethyl)-2,3-methylenedioxy-5H-dibenzo(c,h)(1,6)naphthyridin-6-one (topovale), benzo[6,7]indolizino[1,2-b]quinolin-11(13H)-one (rosettacin), (S)-4-ethyl-4-hydroxy-11-(2-(trimethylsilyl)ethyl)-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione (cositecan), tetrakis((4S)-9-[[1,4'-bipiperidiny]-1'-carbonyl]oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl}N,N,N',N'-{{methanetetrayltetrakis[methylenepoly(oxyethylene)oxy(1-oxoethylene)]}tetraglycinate tetrahydrochloride (etirinotecan pegol), 10-hydroxy-camptothecin (HOCPT), 9-nitrocampthotecin (rubitecan), SN38 (7-ethyl-10-hydroxycampthotecin), and 10-hydroxy-9-nitrocampthotecin

(CPT109), (*R*)-9-chloro-5-ethyl-5-hydroxy-10-methyl-12-((4-methylpiperidin-1-yl)methyl)-4,5-dihydrooxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15(1H, 13H)-dione (elmotecan).

In a particular embodiment, the topoisomerase inhibitor is the topoisomerase I inhibitor (*S*)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione monohydrochloride (topotecan hydrochloride). In one non-limiting example, the compounds described herein are administered in the dosage described herein in combination with a topoisomerase I inhibitor selected from the group consisting of (*S*)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione monohydrochloride (topotecan), (*S*)-4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14-(4H, 12H)-dione (camptothecin), (1*S*,9*S*)-1-Amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-10H,13H-benzo(de)pyrano(3',4':6,7)indolizino(1,2-b)quinoline-10,13-dione (exatecan), (7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(*S*)-camptothecin (lurtotecan), or (*S*)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'-bipiperidine]-1'-carboxylate (irinotecan). In one embodiment, the topoisomerase I inhibitor is topotecan.

PROTACS

In addition to inhibiting the catalytic function of CDK proteins, another strategy also focuses on their level of expression. Thus the present disclosure also contemplates the use of the novel compounds described herein as Proteolysis Targeting Chimeras or "PROTACS" useful for the suppression of CDK proteins. PROTACS are bivalent inhibitors where the first moiety binds a protein targeted for ubiquitination and the second moiety for binding E3 ubiquitin ligase, thus inducing proximity that leads to ubiquitination of targets and subsequent proteolysis of the target protein in the proteasome. Thus the compounds described herein may readily be made into these chimeras for selective degradation and disruption in the cell. Thus the present disclosure contemplates bivalent compounds or PROTACs, comprising a CDK ligand (or targeting moiety) conjugated to a degradation tag.

As used herein, the term "CDK ligand" encompasses a wide variety of molecules associated with or binding to a CDK protein, including but not limited to CDK1, CDK2, CDK4, CDK6, CDK7 and CDK9. The CDK ligand may be a CDK inhibitor, capable of interfering with the enzymatic activity of the CDK proteins. CDK inhibitors include, but are not limited to, abemaciclib, palbociclib, ribociclib, trilaciclib (GIT28), GIT38 and SHR6390. As used herein, an "inhibitor" may refer to an agent that restrains, retards, or otherwise inhibits enzyme activity.

Inhibitors can refer to a drug, compound, or agent that prevents or reduces the expression, transcription, or translation of a gene or protein.

CDK-Replication Dependent Cells and Cyclin-Dependent Kinase Inhibitors

5 Tissue-specific stem cells and subsets of other resident proliferating cells are capable of self-renewal, meaning that they are capable of replacing themselves throughout the adult mammalian lifespan through regulated replication. Additionally, stem cells divide asymmetrically to produce “progeny” or “progenitor” cells that in turn produce various components of a given organ. For example, in the hematopoietic system, the hematopoietic stem cells give rise to
10 progenitor cells which in turn give rise to all the differentiated components of blood (e.g., white blood cells, red blood cells, and platelets).

Certain proliferating cells, such as HSPCs, require the enzymatic activity of the proliferative kinases cyclin-dependent kinase 4 (CDK4) and/or cyclin-dependent kinase 6 (CDK6) for cellular replication. In contrast, the majority of proliferating cells in adult mammals (e.g.,
15 more differentiated blood-forming cells in the bone marrow) do not require the activity of CDK4 and/or CDK6 (i.e., CDK4/6). These differentiated cells can proliferate in the absence of CDK4/6 activity by using other proliferative kinases, such as cyclin-dependent kinase 2 (CDK2) or cyclin-dependent kinase 1 (CDK1).

The compounds described herein show a marked selectivity for the inhibition of CDK4
20 and/or CDK6 in comparison to other CDKs, for example CDK2. For example, the compounds described herein provide for a dose-dependent G1-arresting effect on a subject's CDK4/6-replication dependent healthy cells, for example HSPCs or renal epithelial cells, and the methods provided for herein are sufficient to afford chemoprotection to targeted CDK4/6-replication dependent healthy cells during chemotherapeutic agent exposure, for example, during the time
25 period that a DNA-damaging chemotherapeutic agent is capable of DNA-damaging effects on CDK4/6-replication dependent healthy cells in the subject, while allowing for the synchronous and rapid reentry into the cell-cycle by these cells shortly after the chemotherapeutic agent dissipates due to the time-limited CDK4/6 inhibitory effect provided by the compound compared to, e.g., ribociclib, palbociclib, or abemaciclib.

30 In some embodiments, a CDK4/6-replication dependent healthy cell is a hematopoietic stem progenitor cell. Hematopoietic stem and progenitor cells include, but are not limited to, long term hematopoietic stem cells (LT-HSCs), short term hematopoietic stem cells (ST-HSCs), multipotent progenitors (MPPs), common myeloid progenitors (CMPs), common lymphoid progenitors (CLPs), granulocyte-monocyte progenitors (GMPs), and megakaryocyte-erythroid

progenitors (MEPs). Administration of the compounds described herein provides temporary, transient pharmacologic quiescence of hematopoietic stem and/or hematopoietic progenitor cells in the subject.

In some embodiments, the CDK4/6-replication dependent healthy cell may be a cell in a non-hematopoietic tissue, such as, but not limited to, the liver, kidney, pancreas, brain, lung, adrenals, intestine, gut, stomach, skin, auditory system, bone, bladder, ovaries, uterus, testicles, gallbladder, thyroid, heart, pancreatic islets, blood vessels, and the like. In some embodiments, the CDK4/6-replication dependent healthy cell is a renal cell, and in particular a renal epithelial cell, for example, a renal proximal tubule epithelial cell. In some embodiments, a CDK4/6-replication dependent healthy cell is a hematopoietic stem progenitor cell. In some embodiments, the CDK4/6-replication dependent healthy cell may be a cell in a non-hematopoietic tissue, such as, but not limited to, the liver, kidney, pancreas, brain, lung, adrenals, intestine, gut, stomach, skin, auditory system, bone, bladder, ovaries, uterus, testicles, gallbladder, thyroid, heart, pancreatic islets, blood vessels, and the like.

Likewise, the compounds described herein provides for a dose-dependent mitigating effect on CDK4/6-replication dependent healthy cells that have been exposed to toxic levels of chemotherapeutic agents, allowing for repair of DNA damage associated with chemotherapeutic agent exposure and synchronous, rapid reentry into the cell-cycle following dissipation of the CDK4/6 inhibitory effect compared to, e.g., ribociclib, palbociclib, or abemaciclib. In one embodiment, the use of the compounds described herein results in the G1-arresting effect on the subject's CDK4/6-replication dependent healthy cells dissipating following administration of the compounds described herein so that the subject's healthy cells return to or approach their pre-administration baseline cell-cycle activity within less than about 24 hours, 30 hours, 36 hours, or 40 hours, of administration. In one embodiment, the G1-arresting effect dissipates such that the subject's CDK4/6-replication dependent healthy cells return to their pre-administration baseline cell-cycle activity within less than about 24 hours, 30 hours, 36 hours, or 40 hours.

In one embodiment, the use of the compounds described herein results in the G1-arresting effect dissipating such that the subject's CDK4/6-dependent healthy cells return to or approach their pre-administration baseline cell-cycle activity within less than about 24 hours, 30 hours, 36 hours, or 40 hours of the chemotherapeutic agent effect. In one embodiment, the G1-arresting effect dissipates such that the subject's CDK4/6-replication dependent cells return to their pre-administration baseline cell-cycle activity within less than about 24 hours, 30 hours, 36 hours, or 40 hours, or within about 48 hours of the cessation of the chemotherapeutic agent administration.

In one embodiment, the CDK4/6-replication dependent healthy cells are HSPCs. In one embodiment, the CDK4/6-dependent healthy cells are renal epithelial cells.

In one embodiment, the use of the compounds described herein results in the G1-arresting effect dissipating so that the subject's CDK4/6-replication dependent healthy cells return to or approach their pre-administration baseline cell-cycle activity within less than about 24 hours, 30 hours, 36 hours, 40 hours, or within less than about 48 hours from the point in which the CDK4/6 inhibitor's concentration level in the subject's blood drops below a therapeutic effective concentration.

In one embodiment, the compounds described herein are used to protect renal epithelium cells during exposure to a chemotherapeutic agent, for example, a DNA damaging chemotherapeutic agent, wherein the renal epithelial cells are transiently prevented from entering S-phase in response to chemotherapeutic agent induced renal tubular epithelium damage for no more than about 24 hours, about 30 hours, about 36 hours, about 40 hours, or about 48 hours from the point in which the compounds described herein concentration level in the subject's blood drops below a therapeutic effective concentration or biological effective concentration, from the cessation of the chemotherapeutic agent effect, or from administration of the compounds described herein.

The compounds described herein may be synchronous in their off-effect, that is, upon dissipation of the G1 arresting effect, CDK4/6-replication dependent healthy cells exposed to the compounds described herein in the concentrations described herein reenter the cell-cycle in a similarly timed fashion. CDK4/6-replication dependent healthy cells that reenter the cell-cycle do so such that the normal proportion of cells in G1 and S are reestablished quickly and efficiently, within less than about 24 hours, 30 hours, 36 hours, 40 hours, or within about 48 hours of the from the point in which the compounds described herein concentration level in the subject's blood drops below a therapeutic effective concentration. This advantageously allows for a larger number of healthy cells to begin replicating upon dissipation of the G1 arrest compared with asynchronous CDK4/6 inhibitors such as ribociclib, palbociclib, or abemaciclib.

In addition, synchronous cell-cycle reentry following G1 arrest using the compounds described herein in concentrations and dosages described herein provides for the ability to time the administration of hematopoietic growth factors to assist in the reconstitution of hematopoietic cell lines to maximize the growth factor effect. In one embodiment described herein, the compounds described herein can be administered in a concerted regimen with a blood growth factor agent. As such, in one embodiment, the use of the compounds described herein and methods described herein are combined with the use of hematopoietic growth factors including,

but not limited to, granulocyte colony stimulating factor (G-CSF, for example, sold as Neupogen (filgrastin), Neulasta (peg-filgrastin), or lenograstin), granulocyte-macrophage colony stimulating factor (GM-CSF, for example sold as molgramostim and sargramostim (Leukine)), M-CSF (macrophage colony stimulating factor), thrombopoietin (megakaryocyte growth development factor (MGDF), for example sold as Romiplostim and Eltrombopag) interleukin (IL)-12, interleukin-3, interleukin-11 (adipogenesis inhibiting factor or oprelvekin), SCF (stem cell factor, steel factor, kit-ligand, or KL) and erythropoietin (EPO), and their derivatives (sold as for example epoetin- α as Darbopoetin, Epocept, Nanokine, Epofit, Epogin, Eprex and Procrit; epoetin- β sold as for example NeoRecormon, Recormon and Micera), epoetin-delta (sold as for example Dynepo), epoetin-omega (sold as for example Epomax), epoetin zeta (sold as for example Silapo and Reacrit) as well as for example Epocept, EPOTrust, Erypro Safe, Repoeitin, Vintor, Epofit, Erykine, Wepox, Espogen, Relipoeitin, Shanpoietin, Zyrop and EPIAO). In one embodiment, the compounds described herein are administered prior to administration of the hematopoietic growth factor. In one embodiment, the hematopoietic growth factor administration is timed so that the compounds described herein inhibitory effect on HSPCs has dissipated.

CDK 4/6-Replication Independent Proliferative Disorders

One aspect described herein is a dosing regimen comprising the administration of the compounds described herein that provides a specific PK and/or PD blood profile followed by the administration of a chemotherapeutic agent for the treatment of the CDK 4/6-replication independent cellular proliferation disorder. The subject treated as described herein may be undergoing therapeutic chemotherapy for the treatment of a proliferative disorder that is CDK4/6 replication independent.

CDK 4/6-replication independent cellular proliferation disorders, for example as seen in certain types of cancer, can be characterized by one or a combination of increased activity of cyclin-dependent kinase 1 (CDK1), increased activity of cyclin-dependent kinase 2 (CDK2), loss, deficiency, or absence of retinoblastoma tumor suppressor protein (Rb)(Rb-null), high levels of MYC expression, increased cyclin E1, E2, and increased cyclin A. The cancer may be characterized by reduced expression of the retinoblastoma tumor suppressor protein or a retinoblastoma family member protein or proteins (such as, but not limited to p107 and p130). In one embodiment, the subject is undergoing chemotherapeutic treatment for the treatment of an Rb-null or Rb-deficient cancer, including but not limited to small cell lung cancer, triple-negative breast cancer, HPV-positive head and neck cancer, retinoblastoma, Rb-negative bladder cancer, Rb negative prostate cancer, osteosarcoma, or cervical cancer. Administration of the compounds

described herein may allow for a higher dose of a chemotherapeutic agent to be used to treat the disease than the standard dose that would be safely used in the absence of administration of the compounds described herein.

The host or subject, including a human, may be undergoing chemotherapeutic treatment of a non-malignant proliferative disorder, or other abnormal cellular proliferation, such as a tumor, multiple sclerosis, lupus, or arthritis.

Proliferative disorders that are treated with chemotherapy include cancerous and non-cancer diseases. In a typical embodiment, the proliferative disorder is a CDK4/6-replication independent disorder. The compounds described herein are effective in protecting healthy CDK4/6-replication dependent cells, for example HSPCs, during chemotherapeutic treatment of a broad range of tumor types, including but not limited to the following: breast, prostate, ovarian, skin, lung, colorectal, brain (i.e., glioma) and renal. Preferably, the compounds described herein should not compromise the efficacy of the chemotherapeutic agent or arrest G1 arrest the cancer cells. Many cancers do not depend on the activities of CDK4/6 for proliferation as they can use the proliferative kinases promiscuously (e.g., can use CDK 1/2/4/or 6) or lack the function of the retinoblastoma tumor suppressor protein (Rb), which is inactivated by the CDKs. The potential sensitivity of certain tumors to CDK4/6 inhibition can be deduced based on tumor type and molecular genetics using standard techniques. Cancers that are not typically affected by the inhibition of CDK4/6 are those that can be characterized by one or more of the group including, but not limited to, increased activity of CDK1 or CDK2, loss, deficiency, or absence of retinoblastoma tumor suppressor protein (Rb), high levels of MYC expression, increased cyclin E (e.g., E1 or E2) and increased cyclin A, or expression of a Rb-inactivating protein (such as HPV-encoded E7). Such cancers can include, but are not limited to, small cell lung cancer, retinoblastoma, HPV positive malignancies like cervical cancer and certain head and neck cancers, MYC amplified tumors such as Burkitts' Lymphoma, and triple negative breast cancer; certain classes of sarcoma, certain classes of non-small cell lung carcinoma, certain classes of melanoma, certain classes of pancreatic cancer, certain classes of leukemia, certain classes of lymphoma, certain classes of brain cancer, certain classes of colon cancer, certain classes of prostate cancer, certain classes of ovarian cancer, certain classes of uterine cancer, certain classes of thyroid and other endocrine tissue cancers, certain classes of salivary cancers, certain classes of thymic carcinomas, certain classes of kidney cancers, certain classes of bladder cancers, and certain classes of testicular cancers.

The loss or absence of retinoblastoma (Rb) tumor suppressor protein (Rb-null) can be determined through any of the standard assays known to one of ordinary skill in the art, including

but not limited to Western Blot, ELISA (enzyme linked immunoadsorbent assay), IHC (immunohistochemistry), and FACS (fluorescent activated cell sorting). The selection of the assay will depend upon the tissue, cell line or surrogate tissue sample that is utilized e.g., for example Western Blot and ELISA may be used with any or all types of tissues, cell lines or surrogate tissues, whereas the IHC method would be more appropriate wherein the tissue utilized in the methods described herein was a tumor biopsy. FACS analysis would be most applicable to samples that were single cell suspensions such as cell lines and isolated peripheral blood mononuclear cells. See e.g., US 20070212736.

Alternatively, molecular genetic testing may be used for determination of retinoblastoma gene status. Molecular genetic testing for retinoblastoma includes the following as described in Lohmann and Gallie "Retinoblastoma. Gene Reviews" (2010) or Parsam et al., *J. Genetics* 88(4): 517-527 (2009).

Increased activity of CDK1 or CDK2, high levels of MYC expression, increased cyclin E and increased cyclin A can be determined through any of the standard assays known to one of ordinary skill in the art, including but not limited to Western Blot, ELISA (enzyme linked immunoadsorbent assay), IHC (immunohistochemistry), and FACS (fluorescent activated cell sorting). The selection of the assay will depend upon the tissue, cell line, or surrogate tissue sample that is utilized e.g., for example Western Blot and ELISA may be used with any or all types of tissues, cell lines, or surrogate tissues, whereas the IHC method would be more appropriate wherein the tissue utilized in the methods described herein was a tumor biopsy. FACS analysis would be most applicable to samples that were single cell suspensions such as cell lines and isolated peripheral blood mononuclear cells.

In some embodiments, the cancer is selected from a small cell lung cancer, retinoblastoma, and triple negative (ER/PR/Her2 negative) or "basal-like" breast cancer, which almost always have inactivate retinoblastoma tumor suppressor proteins (Rb), and therefore do not require CDK4/6 activity to proliferate. Triple negative (basal-like) breast cancer is also almost always genetically or functionally Rb-null. Also, certain virally induced cancers (e.g., cervical cancer and subsets of Head and Neck cancer) express a viral protein (E7) which inactivates Rb making these tumors functionally Rb-null. Some lung cancers are also believed to be caused by HPV. In one particular embodiment, the cancer is small cell lung cancer, and the patient is treated with a DNA-damaging agent selected from the group consisting of etoposide, carboplatin, and cisplatin, or a combination thereof.

The compounds described herein can also be used in protecting healthy CDK4/6-replication dependent cells during chemotherapeutic treatments of abnormal tissues in non-

cancer proliferative diseases, including but not limited to: psoriasis, lupus, arthritis (notably rheumatoid arthritis), hemangiomas in infants, multiple sclerosis, myelodegenerative disease, neurofibromatosis, ganglioneuromatosis, keloid formation, Paget's Disease of the bone, fibrocystic disease of the breast, Peyronie's and Dupuytren's fibrosis, restenosis, and cirrhosis.

5 Further, the compounds described herein can be used to ameliorate the effects of chemotherapeutic agents in the event of accidental exposure or overdose (e.g., methotrexate overdose).

Chemoprotective Regimes

10 In certain embodiments, the compounds described herein or pharmaceutically acceptable compositions, salts, isotopic analogs, or prodrugs thereof, are administered at a dose described herein so that the protection afforded by the compound is short term and transient in nature, allowing a significant portion of the cells to synchronously reenter the cell-cycle quickly following the cessation of the chemotherapeutic agent's effect, for example within less than about 24, 30,

15 36, or 40 hours. Cells that are quiescent within the G1 phase of the cell cycle are more resistant to the damaging effect of chemotherapeutic agents than proliferating cells.

The compounds described herein can be administered to the subject prior to treatment with a chemotherapeutic agent, during treatment with a chemotherapeutic agent, after exposure to a chemotherapeutic agent, or a combination thereof. The compounds described herein are

20 typically administered in a manner that allows the drug facile access to the blood stream, for example via intravenous injection. In one embodiment, the compound is administered to the subject less than about 24 hours, 20 hours, 16 hours, 12 hours, 8 hours, or 4 hours, 2.5 hours, 2 hours, 1 hour, 1/2 hour or less prior to treatment with the chemotherapeutic agent. In an alternative embodiment, the compound is administered to the subject less than about 48 hours,

25 40 hours, 36 hours, or 32 hours or less prior to treatment with the chemotherapeutic agent.

Typically, the compound described herein is administered to the subject prior to treatment with the chemotherapeutic agent such that the compound reaches peak serum levels before or during treatment with the chemotherapeutic agent. In one embodiment, are administered to the subject about 30 minutes prior to administration of the chemotherapeutic agent. In one

30 embodiment, the compounds described herein are administered to the subject over about a 30 minute period and then the subject is administered a chemotherapeutic agent. In one embodiment, the Compound is administered concomitantly, or closely thereto, with the chemotherapeutic agent exposure. If desired, the compound can be administered multiple times during the chemotherapeutic agent treatment to maximize inhibition, especially when the

chemotherapeutic drug is administered over a long period or has a long half-life. In an alternative embodiment, the compounds described herein can be administered following exposure to the chemotherapeutic agent if desired to mitigate healthy cell damage associated with chemotherapeutic agent exposure. In certain embodiments, the compound is administered up to about ½ hour, up to about 1 hour, up to about 2 hours, up to about 4 hours, up to about 8 hours, up to about 10 hours, up to about 12 hours, up to about 14 hours, up to about 16 hours, or up to about 20 hours or greater following the chemotherapeutic agent exposure. In a particular embodiment, the compound is administered up to between about 12 hours and 20 hours following exposure to the chemotherapeutic agent.

Importantly, at the dosing ranges provided herein, the compounds described herein can be used in a multi-day chemotherapeutic regimen without concomitant accumulation in the subject. Accordingly, the PK and/or PD levels provided herein are not significantly altered, that is, by no more than about 10%, across a multi-day dosing regimen. Because of this, the compounds described herein are ideal chemoprotectants in chemotherapeutic treatment regimens that require multi-day chemotherapeutic agent administration, for example as seen in small cell lung cancer, triple negative breast cancer, bladder cancer, and HPV-positive head and neck and cervical cancer.

In one aspect, the use of the compounds described herein at the PK and PD parameters described herein allows for a chemo-protective regimen for use during standard chemotherapeutic dosing schedules or regimens common in many anti-cancer treatments. For example, the compounds described herein can be administered so that CDK4/6-replication dependent healthy cells are G1 arrested during chemotherapeutic agent exposure wherein, due to the rapid dissipation of the G1-arresting effect of the compounds, a significant number of healthy cells reenter the cell-cycle and are capable of replicating shortly after chemotherapeutic agent exposure, for example, within less than about 24, 30, 40, or 48 hours, and continue to replicate until administration of the compounds described herein in anticipation of the next chemotherapeutic treatment. In one embodiment, the compounds described herein are administered to allow for the cycling of the CDK4/6-replication dependent healthy cells between G1-arrest and reentry into the cell-cycle to accommodate a repeated-dosing chemotherapeutic treatment regimen, for example including but not limited to a treatment regimen wherein the chemotherapeutic agent is administered: on day 1–3 every 21 days; on days 1–3 every 28 days; on day 1 every 3 weeks; on day 1, day 8, and day 15 every 28 days, on day 1 and day 8 every 28 days; on days 1 and 8 every 21 days; on days 1–5 every 21 days; 1 day a week for 6–8 weeks; on days 1, 22, and 43; days 1 and 2 weekly; days 1–4 and 22–25; 1–4; 22–25, and 43–46; and

similar type-regimens, wherein the CDK4/6-replication dependent cells are G1 arrested during chemotherapeutic agent exposure. In one embodiment, the compounds described herein can be administered so that the subject's CDK4/6-replication dependent cells are G1-arrested during daily chemotherapeutic agent exposure, for example a contiguous multi-day chemotherapeutic regimen. In one embodiment, the compounds described herein can be administered so that the subject's CDK4/6-replication dependent cells are G1-arrested during chemotherapeutic agent exposure, for example a contiguous multi-day regimen, but a significant portion of healthy cells reenter the cell-cycle and replicate during the off periods before starting the next cycle of chemotherapeutic agent exposure, for example cycle 2, cycle 3, cycle 4, etc. In one embodiment, the compounds described herein are administered so that a subject's CDK4/6-replication dependent cells' G1-arrest is provided during a daily chemotherapeutic agent treatment regimen, for example, a contiguous multi-day treatment regimen, and the arrested cells are capable of reentering the cell-cycle shortly after the multi-day regimen ends.

In one embodiment, the subject has small cell lung cancer and the compounds described herein are administered intravenously over about a 30 minute period about 30 minutes prior to administration of either etoposide or carboplatin on day 1, and etoposide on days 2 and 3 during a 21-day treatment cycle, wherein the subject is administered both etoposide and carboplatin on day 1 and etoposide on day 2 and 3 during a 21-day cycle first line treatment protocol. In one embodiment, the dose of etoposide administered is 100 mg/m² administered intravenously over about 60 minutes daily on days 1, 2, and 3 of each 21-day cycle. In one embodiment, the dose of carboplatin administered to the subject is calculated using the Calvert formula with a target AUC of 5 (maximum dose of 750 mg) administered intravenously over 30 minutes on day1 of each 21-day cycle.

In one embodiment, the subject has small cell lung cancer and the compounds described herein are administered intravenously over about a 30 minute period about 30 minutes prior to administration of topotecan during a 21-day treatment cycle, wherein the subject is administered topotecan on days 1, 2, 3, 4, and 5 during a 21-day cycle second or third line treatment protocol. In one embodiment, the dose of topotecan administered is 1.5 mg/m² administered intravenously over about 30 minutes daily on days 1, 2, 3, 4, and 5 of each 21-day cycle. In one embodiment, the dose of topotecan administered is 1.25 mg/m² administered intravenously over about 30 minutes daily on days 1, 2, 3, 4, and 5 of each 21-day cycle. In one embodiment, the dose of topotecan administered is 0.75 mg/m² administered intravenously over about 30 minutes daily on days 1, 2, 3, 4, and 5 of each 21-day cycle.

In one embodiment, the subject has small cell lung cancer and the compounds described herein are administered intravenously over about a 30 minute period about 30 minutes prior to administration of topotecan during a 21-day treatment cycle, wherein the subject is administered topotecan on days 1, 2, and 3 during a 21-day cycle second or third line treatment protocol. In one embodiment, the dose of topotecan administered is 1.25 mg/m² administered intravenously over about 30 minutes daily on days 1, 2, and 3 of each 21-day cycle.

Administration of the compounds described herein in the doses described herein can result in reduced anemia, reduced lymphopenia, reduced thrombocytopenia, or reduced neutropenia compared to that typically expected after, common after, or associated with treatment with chemotherapeutic agents in the absence of administration of the compounds described herein. The use of the compounds described herein results in a faster recovery from bone marrow suppression associated with long-term use of CDK4/6 inhibitors, such as myelosuppression, anemia, lymphopenia, thrombocytopenia, or neutropenia, following the cessation of use of the compounds described herein. In some embodiments, the use of the compounds described herein results in reduced or limited bone marrow suppression associated with long-term use of CDK4/6 inhibitors, such as myelosuppression, anemia, lymphopenia, thrombocytopenia, or neutropenia.

In one embodiment, the compounds described herein, at the concentrations and doses described herein, is used in a CDK4/6-replication dependent healthy cell cycling strategy wherein a subject is exposed to regular, repeated chemotherapeutic treatments, wherein the healthy cells are G1-arrested when chemotherapeutic agent exposed and allowed to reenter the cell-cycle before the subject's next chemotherapeutic treatment. Such cycling allows CDK4/6-replication dependent cells to regenerate damaged blood cell lineages between regular, repeated treatments, for example those associated with standard chemotherapeutic treatments for cancer, and reduces the risk associated with long term CDK4/6 inhibition. This cycling between a state of G1-arrest and a state of replication is not feasible in limited time-spaced, repeated chemotherapeutic agent exposures using longer acting CDK4/6 inhibitors such as ribociclib, palbociclib, or abemaciclib, as the lingering G1-arresting effects of the compound prohibit significant and meaningful reentry into the cell-cycle before the next chemotherapeutic agent exposure or delay the healthy cells from entering the cell cycle and reconstituting damaged tissues or cells following treatment cessation.

The compounds described herein can be administered to a subject on any chemotherapeutic treatment schedule and in any dose consistent with the prescribed course of treatment. The compounds described herein can be administered prior to, during, or following the administration of the chemotherapeutic agent. In one embodiment, the compounds described

herein can be administered to the subject during the time period ranging from 24 hours prior to chemotherapeutic treatment until 24 hours following exposure. This time period, however, can be extended to time earlier than 24 hours prior to exposure to the agent (e.g., based upon the time it takes the chemotherapeutic agent used to achieve suitable plasma concentrations and/or the compound's plasma half-life). Further, the time period can be extended longer than 24 hours following exposure to the chemotherapeutic agent so long as later administration of the compounds described herein leads to at least some protective effect. Such post-exposure treatment can be especially useful in cases of accidental exposure or overdose. In an alternative embodiment, the compounds described herein can be administered to the subject during the time period ranging from 48 hours prior to chemotherapeutic treatment until 48 hours following exposure.

In some embodiments, the compounds described herein can be administered to the subject at a time period prior to the administration of the chemotherapeutic agent, so that plasma levels of the compounds described herein are peaking at the time of administration of the chemotherapeutic agent. If convenient, the compounds described herein can be administered at the same time as the chemotherapeutic agent, in order to simplify the treatment regimen. In some embodiments, the chemoprotectant and chemotherapeutic can be provided in a single formulation.

In some embodiments, the compounds described herein can be administered to the subject such that the chemotherapeutic agent can be administered either at higher doses (increased chemotherapeutic dose intensity) or more frequently (increased chemotherapeutic dose density) or at a dose that achieves equivalent AUC therapeutic levels as seen when the chemotherapeutic agent is administered alone.

Dose-dense chemotherapy is a chemotherapy treatment plan in which drugs are given with less time between treatments than in a standard chemotherapy treatment plan. Chemotherapy dose intensity represents unit dose of chemotherapy administered per unit time. Dose intensity can be increased or decreased through altering dose administered, time interval of administration, or both. Myelosuppression continues to represent the major dose-limiting toxicity of cancer chemotherapy, resulting in considerable morbidity and mortality along with frequent reductions in chemotherapy dose intensity, which may compromise disease control and survival. The compounds and their use as described herein represent a way of increasing chemotherapy dose density and/or dose intensity while mitigating adverse events such as, but not limited to, myelosuppression.

If desired, multiple doses of the compounds described herein can be administered to the subject. Alternatively, the subject can be given a single dose of the compounds described herein. For example, the compounds described herein can be administered so that CDK4/6-replication dependent healthy cells are G1 arrested during chemotherapeutic agent exposure wherein, due to the rapid dissipation of the G1-arresting effect of the compounds, a significant number of healthy cells reenter the cell-cycle and are capable of replicating shortly after chemotherapeutic agent exposure, for example, within about 24–48 hours or less, and continue to replicate until administration of the CDK4/6-inhibitor in anticipation of the next chemotherapeutic treatment. In one embodiment, the compounds described herein are administered to allow for the cycling of the CDK4/6-replication dependent healthy cells between G1-arrest and reentry into the cell-cycle to accommodate a repeated-dosing chemotherapeutic treatment regimen, for example, including but not limited to a treatment regimen wherein the chemotherapeutic agent is administered: on day 1–3 every 21 days; on days 1–3 every 28 days; on day 1 every 3 weeks; on day 1, day 8, and day 15 every 28 days; on day 1 and day 8 every 28 days; on days 1 and 8 every 21 days; on days 1–5 every 21 days; 1 day a week for 6–8 weeks; on days 1, 22, and 43; days 1 and 2 weekly; days 1–4 and 22–25; 1–4; 22–25, and 43–46; and similar type-regimens, wherein the CDK4/6-replication dependent cells are G1 arrested during chemotherapeutic agent exposure and a significant portion of the cells reenter the cell-cycle in between chemotherapeutic agent exposure.

As contemplated herein, the compounds described herein can be used as a chemoprotectant in conjunction with a number of standard of care chemotherapeutic treatment regimens used to provide chemoprotection to a subject's CDK4/6-replication dependent healthy cells during a CDK4/6-replication independent cancer treatment protocol. In alternative embodiments, for example, the compounds described herein can be administered to provide chemoprotection in a small cell lung cancer therapy protocol such as, but not limited to: cisplatin 60 mg/m² IV on day 1 plus etoposide 120 mg/m² IV on days 1–3 every 21 d for 4 cycles; cisplatin 80 mg/m² IV on day 1 plus etoposide 100 mg/m² IV on days 1–3 every 28 d for 4 cycles; cisplatin 60–80 mg/m² IV on day 1 plus etoposide 80–120 mg/m² IV on days 1–3 every 21–28 d (maximum of 4 cycles); carboplatin AUC 5–6 min·mg/mL IV on day 1 plus etoposide 80–100 mg/m² IV on days 1–3 every 28 d (maximum of 4 cycles); Cisplatin 60–80 mg/m² IV on day 1 plus etoposide 80–120 mg/m² IV on days 1–3 every 21–28 d; carboplatin AUC 5–6 min·mg/mL IV on day 1 plus etoposide 80–100 mg/m² IV on days 1–3 every 28 d (maximum 6 cycles); cisplatin 60 mg/m² IV on day 1 plus irinotecan 60 mg/m² IV on days 1, 8, and 15 every 28 d (maximum 6 cycles); cisplatin 30 mg/m² IV on days 1 and 8 or 80 mg/m² IV on day 1 plus irinotecan 65 mg/m² IV on days 1 and 8 every 21 d (maximum 6 cycles); carboplatin AUC 5 min·mg/mL IV on day 1 plus

irinotecan 50 mg/m² IV on days 1, 8, and 15 every 28 d (maximum 6 cycles); carboplatin AUC 4–5 IV on day 1 plus irinotecan 150–200 mg/m² IV on day 1 every 21 d (maximum 6 cycles); cyclophosphamide 800–1000 mg/m² IV on day 1 plus doxorubicin 40–50 mg/m² IV on day 1 plus vincristine 1–1.4 mg/m² IV on day 1 every 21–28 d (maximum 6 cycles); Etoposide 50 mg/m² PO daily for 3 wk every 4 wk; topotecan 2.3 mg/m² PO on days 1–5 every 21 d; topotecan 1.5 mg/m² IV on days 1–5 every 21 d; carboplatin AUC 5 min·mg/mL IV on day 1 plus irinotecan 50 mg/m² IV on days 1, 8, and 15 every 28 d; carboplatin AUC 4–5 IV on day 1 plus irinotecan 150–200 mg/m² IV on day 1 every 21 d; cisplatin 30 mg/m² IV on days 1, 8, and 15 plus irinotecan 60 mg/m² IV on days 1, 8, and 15 every 28 d; cisplatin 60 mg/m² IV on day 1 plus irinotecan 60 mg/m² IV on days 1, 8, and 15 every 28 d; cisplatin 30 mg/m² IV on days 1 and 8 or 80 mg/m² IV on day 1 plus irinotecan 65 mg/m² IV on days 1 and 8 every 21 d; paclitaxel 80 mg/m² IV weekly for 6 wk every 8 wk; paclitaxel 175 mg/m² IV on day 1 every 3 wk; etoposide 50 mg/m² PO daily for 3 wk every 4 wk; topotecan 2.3 mg/m² PO on days 1–5 every 21 d; topotecan 1.5 mg/m² IV on days 1–5 every 21 d; carboplatin AUC 5 min·mg/mL IV on day 1 plus irinotecan 50 mg/m² IV on days 1, 8, and 15 every 28 d; carboplatin AUC 4–5 IV on day 1 plus irinotecan 150–200 mg/m² IV on day 1 every 21 d; cisplatin 30 mg/m² IV on days 1, 8, and 15 plus irinotecan 60 mg/m² IV on days 1, 8, and 15 every 28 d; cisplatin 60 mg/m² IV on day 1 plus irinotecan 60 mg/m² IV on days 1, 8, and 15 every 28 d; cisplatin 30 mg/m² IV on days 1 and 8 or 80 mg/m² IV on day 1 plus irinotecan 65 mg/m² IV on days 1 and 8 every 21 d; paclitaxel 80 mg/m² IV weekly for 6 wk every 8 wk; and paclitaxel 175 mg/m² IV on day 1 every 3 wk. In alternative embodiments, the compounds described herein are administered to provide chemoprotection in a small cell lung cancer therapy protocol such as, but not limited to: topotecan 2.0 mg/m² PO on days 1–5 every 21 d; topotecan 1.5–2.3 mg/m² PO on days 1–5 every 21 d; etoposide 100 mg/m² intravenously (IV) on days 1 through 3 plus cisplatin 50 mg/m² IV on days 1 and 2 (treatment cycles administered every 3 weeks to a maximum of six cycles); etoposide 100 mg/m² intravenously (IV) on days 1 through 3 plus carboplatin 300 mg/m² IV on day 1 (treatment cycles administered every 3 weeks to a maximum of six cycles); carboplatin (300 mg/m² IV on day 1) and escalating doses of etoposide starting with 80 mg/m² IV on days 1–3; carboplatin 125 mg/m²/day combined with etoposide 200 mg/m²/day administered for 3 days; etoposide 80–200 mg/m² intravenously (IV) on days 1 through 3 plus carboplatin 125–450 mg/m² IV on day 1 (treatment cycles administered every 21–28 days); carboplatin AUC 5–6 min·mg/mL IV on day 1 plus etoposide 80–200 mg/m² IV on days 1–3 every 28 d (maximum of 4 cycles).

In one embodiment, the compounds described herein are administered in a dosage describe herein to a subject with small cell lung cancer on days 1, 2, and 3 of a treatment protocol

wherein the DNA damaging agent selected from the group consisting of carboplatin, etoposide, and cisplatin, or a combination thereof, is administered on days 1, 2, and 3 every 21 days.

In one embodiment, the compounds described herein are used to provide chemoprotection to a subject's CDK4/6–replication dependent healthy cells during a CDK4/6–replication independent head and neck cancer treatment protocol. In one embodiment, the compounds described herein are administered to provide chemoprotection in a CDK4/6–replication independent head and neck cancer therapy protocol such as, but not limited to: cisplatin 100 mg/m² IV on days 1, 22, and 43 or 40–50 mg/m² IV weekly for 6–7 wk; cetuximab 400 mg/m² IV loading dose 1 wk before the start of radiation therapy, then 250 mg/m² weekly (premedicate with dexamethasone, diphenhydramine, and ranitidine); cisplatin 20 mg/m² IV on day 2 weekly for up to 7 wk plus paclitaxel 30 mg/m² IV on day 1 weekly for up to 7 wk; cisplatin 20 mg/m²/day IV on days 1–4 and 22–25 plus 5–FU 1000 mg/m²/day by continuous IV infusion on days 1–4 and 22–25; 5–FU 800 mg/m² by continuous IV infusion on days 1–5 given on the days of radiation plus hydroxyurea 1 g PO q12h (11 doses per cycle); chemotherapy and radiation given every other week for a total of 13 wk; carboplatin 70 mg/m²/day IV on days 1–4, 22–25, and 43–46 plus 5–FU 600 mg/m²/day by continuous IV infusion on days 1–4, 22–25, and 43–46; carboplatin AUC 1.5 IV on day 1 weekly plus paclitaxel 45 mg/m² IV on day 1 weekly; cisplatin 100 mg/m² IV on days 1, 22, and 43 or 40–50 mg/m² IV weekly for 6–7 wk; docetaxel 75 mg/m² IV on day 1 plus cisplatin 100 mg/m² IV on day 1 plus 5–FU 100 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk for 3 cycles, then 3–8 wk later, carboplatin AUC 1.5 IV weekly for up to 7 wk during radiation therapy; docetaxel 75 mg/m² IV on day 1 plus cisplatin 75 mg/m² IV on day 1 plus 5–FU 750 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk for 4 cycles; cisplatin 100 mg/m² IV on day 1 every 3 wk for 6 cycles plus 5–FU 1000 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk for 6 cycles plus cetuximab 400 mg/m² IV loading dose on day 1, then 250 mg/m² IV weekly until disease progression (premedicate with dexamethasone, diphenhydramine, and ranitidine); carboplatin AUC 5 min·mg/mL IV on day 1 every 3 wk for 6 cycles plus 5–FU 1000 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk for 6 cycles plus cetuximab 400 mg/m² IV loading dose on day 1, then 250 mg/m² IV weekly until disease progression (premedicate with dexamethasone, diphenhydramine, and ranitidine); cisplatin 75 mg/m² IV on day 1 plus docetaxel 75 mg/m² IV on day 1 every 3 wk; cisplatin 75 mg/m² IV on day 1 plus paclitaxel 175 mg/m² IV on day 1 every 3 wk; carboplatin AUC 6 IV on day 1 plus docetaxel 65 mg/m² IV on day 1 every 3 wk; carboplatin AUC 6 IV on day 1 plus paclitaxel 200 mg/m² IV on day 1 every 3 wk; cisplatin 75–100 mg/m² IV on day 1 every 3–4 wk plus cetuximab 400 mg/m² IV loading dose on day 1, then 250 mg/m² IV weekly (premedicate

with dexamethasone, diphenhydramine, and ranitidine); cisplatin 100 mg/m² IV on day 1 plus 5–FU 1000 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk; methotrexate 40 mg/m² IV weekly (3 wk equals 1 cycle); paclitaxel 200 mg/m² IV every 3 wk; docetaxel 75 mg/m² IV every 3 wk; cetuximab 400 mg/m² IV loading dose on day 1, then 250 mg/m² IV weekly until disease

5 progression (premedicate with dexamethasone, diphenhydramine, and ranitidine); cisplatin 100 mg/m² IV on day 1 every 3 wk for 6 cycles plus 5–FU 1000 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk for 6 cycles plus cetuximab 400 mg/m² IV loading dose on day 1, then 250 mg/m² IV weekly (premedicate with dexamethasone, diphenhydramine, and ranitidine); carboplatin AUC 5 min·mg/mL IV on day 1 every 3 wk for 6 cycles plus 5–FU 1000 mg/m²/day by

10 continuous IV infusion on days 1–4 every 3 wk for 6 cycles plus cetuximab 400 mg/m² IV loading dose on day 1, then 250 mg/m² IV weekly (premedicate with dexamethasone, diphenhydramine, and ranitidine); cisplatin 75 mg/m² IV on day 1 plus docetaxel 75 mg/m² IV on day 1 every 3 wk; cisplatin 75 mg/m² IV on day 1 plus paclitaxel 175 mg/m² IV on day 1 every 3 wk; carboplatin AUC 6 IV on day 1 plus docetaxel 65 mg/m² IV on day 1 every 3 wk; carboplatin AUC 6 IV on day 1

15 plus paclitaxel 200 mg/m² IV on day 1 every 3 wk; cisplatin 75–100 mg/m² IV on day 1 every 3–4 wk plus cetuximab 400 mg/m² IV loading dose on day 1, then 250 mg/m² IV weekly (premedicate with dexamethasone, diphenhydramine, and ranitidine); cisplatin 100 mg/m² IV on day 1 plus 5–FU 1000 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk; methotrexate 40 mg/m² IV weekly (3 wk equals 1 cycle); paclitaxel 200 mg/m² IV every 3 wk; docetaxel 75 mg/m² IV every

20 3 wk; cetuximab 400 mg/m² IV loading dose on day 1, then 250 mg/m² IV weekly until disease progression (premedicate with dexamethasone, diphenhydramine, and ranitidine); cisplatin 100 mg/m² IV on days 1, 22, and 43 with radiation, then cisplatin 80 mg/m² IV on day 1 plus 5–FU 1000 mg/m²/day by continuous IV infusion on days 1–4 every 4 wk for 3 cycles; cisplatin 75 mg/m² IV on day 1 plus docetaxel 75 mg/m² IV on day 1 every 3 wk; cisplatin 75 mg/m² IV on day 1 plus

25 paclitaxel 175 mg/m² IV on day 1 every 3 wk; carboplatin AUC 6 IV on day 1 plus docetaxel 65 mg/m² IV on day 1 every 3 wk; carboplatin AUC 6 IV on day 1 plus paclitaxel 200 mg/m² IV on day 1 every 3 wk; cisplatin 100 mg/m² IV on day 1 plus 5–FU 1000 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk; cisplatin 50–70 mg/m² IV on day 1 plus gemcitabine 1000 mg/m² IV on days 1, 8, and 15 every 4 wk; gemcitabine 1000 mg/m² IV on days 1, 8, and 15 every 4 wk

30 or gemcitabine 1250 mg/m² IV on days 1 and 8 every 3 wk; methotrexate 40 mg/m² IV weekly (3 wk equals 1 cycle); paclitaxel 200 mg/m² IV every 3 wk; docetaxel 75 mg/m² IV every 3 wk; cisplatin 75 mg/m² IV on day 1 plus docetaxel 75 mg/m² IV on day 1 every 3 wk; cisplatin 75 mg/m² IV on day 1 plus paclitaxel 175 mg/m² IV on day 1 every 3 wk; carboplatin AUC 6 IV on day 1 plus docetaxel 65 mg/m² IV on day 1 every 3 wk; carboplatin AUC 6 IV on day 1 plus

paclitaxel 200 mg/m² IV on day 1 every 3 wk; cisplatin 100 mg/m² IV on day 1 plus 5-FU 1000 mg/m²/day by continuous IV infusion on days 1–4 every 3 wk; cisplatin 50–70 mg/m² IV on day 1 plus gemcitabine 1000 mg/m² IV on days 1, 8, and 15 every 4 wk; gemcitabine 1000 mg/m² IV on days 1, 8, and 15 every 4 wk or gemcitabine 1250 mg/m² IV on days 1 and 8 every 3 wk; methotrexate 40 mg/m² IV weekly (3 wk equals 1 cycle); paclitaxel 200 mg/m² IV every 3 wk; and docetaxel 75 mg/m² IV every 3 wk.

In one embodiment, the compounds described herein are used to provide chemoprotection to a subject's CDK4/6-replication dependent healthy cells during a CDK4/6-replication independent triple negative breast cancer treatment protocol. In one embodiment, the compounds described herein are administered to provide a blood plasma concentration described herein to provide chemoprotection in a CDK4/6-replication independent triple negative breast cancer therapy protocol such as, but not limited to: dose-dense doxorubicin (adriamycin) and cyclophosphamide (cytoxan) every two weeks for four cycles followed by dose-dense paclitaxel (Taxol) every two weeks for four cycles; adriamycin/paclitaxel/cyclophosphamide every three weeks for a total of four cycles; adriamycin/paclitaxel/cyclophosphamide every two weeks for a total of four cycles; adriamycin/cyclophosphamide followed by paclitaxel (Taxol) every three weeks for four cycles each; and adriamycin/cyclophosphamide followed by paclitaxel (Taxol) every two weeks for four cycles each.

In one embodiment, the compounds described herein are used to provide chemoprotection to a subject's CDK4/6-replication dependent healthy cells during a CDK4/6-replication independent bladder cancer treatment protocol. In one embodiment, the compounds described herein are administered to provide a blood plasma concentration described herein to provide chemoprotection in a CDK4/6-replication independent bladder cancer therapy protocol such as, but not limited to: postoperative adjuvant intravesical chemotherapy for non-muscle invasive bladder cancer, first-line chemotherapy for muscle-invasive bladder cancer, and second-line chemotherapy for muscle invasive bladder cancer. Non-limiting examples of postoperative chemotherapy for bladder cancer include one dose or mitomycin (40 mg), epirubicin (80 mg), thiotepa (30 mg), or doxorubicin (50 mg). Non-limiting examples of first-line chemotherapy for bladder cancer include: gemcitabine 1000 mg/m² on days 1, 8, and 15 plus cisplatin 70 mg/m² on day 1 or 2 repeating cycle every 28 days for a total of four cycles; dosing methotrexate 30 mg/m² IV on days 1, 15, and 22 plus vinblastine 3 mg/m² IV on days 2, 15, and 22 plus doxorubicin 30 mg/m² IV on day 2 plus cisplatin 70 mg/m² IV on day 2, repeat cycle every 28 d for a total of 3 cycles; and dose-dense regimens of the above administered along with doses of growth factor stimulants.

In one embodiment, the compounds described herein are used to provide chemoprotection to a subject's CDK4/6-replication dependent healthy cells during a CDK4/6-replication independent retinoblastoma treatment protocol. In one embodiment, the compounds described herein are administered to provide a blood plasma concentration described herein to provide chemoprotection in a CDK4/6-replication independent retinoblastoma therapy protocol such as, but not limited to the administration of carboplatin, vincristine, or etoposide in conjunction with surgery, radiotherapy, cryotherapy, thermotherapy, or other local therapy techniques.

In one embodiment, the compounds described herein are used to provide chemoprotection to a subject's CDK4/6-replication dependent healthy cells during a CDK4/6-replication independent cervical cancer treatment protocol. In one embodiment, the compounds described herein are administered to provide a blood plasma concentration described herein to provide chemoprotection in a CDK4/6-replication independent cervical cancer therapy protocol such as, but not limited to the administration of cisplatin 40 mg/m² IV once weekly, cisplatin 50–75 mg/m² IV on day 1 plus 5-fluorouracil (5-FU) 1000 mg/m² continuous IV infusion on days 2–5 and days 30–33, cisplatin 50–75 mg/m² IV on day 1 plus 5-FU 1000 mg/m² IV infusion over 24 hour on days 1–4 every 3 weeks for 3–4 cycles, bevacizumab 15 mg/kg IV over 30–90 minutes plus cisplatin on day 1 or 2 plus paclitaxel on day 1 every 3 weeks, bevacizumab plus paclitaxel on day 1 plus topotecan on days 1–3 every 3 weeks, paclitaxel followed by cisplatin on day 1 every 3 weeks, topotecan on days 1–3 followed by cisplatin on day 1 every 3 weeks, and paclitaxel on day 1 every 3 weeks. In another embodiment, the cervical cancer therapy protocol is as above in addition to radiation, surgery, or another procedure.

Triple-negative breast cancer (TNBC) is defined as the absence of staining for estrogen receptor, progesterone receptor, and HER2/neu. TNBC is insensitive to some of the most effective therapies available for breast cancer treatment including HER2-directed therapy such as trastuzumab and endocrine therapies such as tamoxifen or the aromatase inhibitors. Combination cytotoxic chemotherapy administered in a dose-dense or metronomic schedule remains the standard therapy for early-stage TNBC. Platinum agents have recently emerged as drugs of interest for the treatment of TNBC with carboplatin added to paclitaxel and adriamycin plus cyclophosphamide chemotherapy in the neoadjuvant setting. The poly (ADP-ribose) polymerase (PARP) inhibitors are emerging as promising therapeutics for the treatment of TNBC. PARPs are a family of enzymes involved in multiple cellular processes, including DNA repair.

As a nonlimiting illustration, the subject is exposed to chemotherapeutic agent at least 5 times a week, at least 4 times a week, at least 3 times a week, at least 2 times a week, at least 1 time a week, at least 3 times a month, at least 2 times a month, or at least 1 time a month, wherein

the subject's CDK4/6-replication dependent healthy cells are G1 arrested during treatment and allowed to cycle in between chemotherapeutic agent exposure, for example during a treatment break. In one embodiment, the subject is undergoing 5 times a week chemotherapeutic treatment, wherein the subject's CDK4/6-replication dependent healthy cells are G1 arrested during the chemotherapeutic agent exposure and allowed to reenter the cell-cycle during the 2 day break, for example, over the weekend.

In one embodiment, using the compounds described herein at the dosage described herein, the subject's CDK4/6-replication dependent healthy cells are arrested during the entirety of the chemotherapeutic agent exposure time-period, for example, during a contiguous multi-day regimens, the cells are arrested over the time period that is required to complete the contiguous multi-day course, and then allowed to recycle at the end of the contiguous multi-day course. In one embodiment, using the compounds described herein at the dosage described herein, the subject's CDK4/6-replication dependent healthy cells are arrested during the entirety of the chemotherapeutic regimen, for example, in a daily chemotherapeutic exposure for three weeks, and rapidly reenter the cell-cycle following the completion of the therapeutic regimen.

In one embodiment, the subject has been exposed to a chemotherapeutic agent, and, using the compounds described herein at the dosage described herein, the subject's CDK4/6-replication dependent healthy cells are placed in G1 arrest following exposure in order to mitigate, for example, DNA damage. In one embodiment, the compounds described herein at the dosage described herein is administered at least 1/2 hour, at least 1 hour, at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours, at least 6 hours, at least 7 hours, at least 8 hours, at least 10 hours, at least 12 hours, at least 14 hours, at least 16 hours, at least 18 hours, at least 20 hours or more post chemotherapeutic agent exposure.

In some embodiments, the CDK4/6-replication dependent healthy cells can be arrested for longer periods to allow for intensified chemotherapeutic treatment, for example, over a period of hours, days, and/or weeks, through multiple, time separated administrations of a CDK4/6 inhibitor described herein. Because of the rapid and synchronous reentry into the cell cycle by CDK4/6-replication dependent healthy cells, for example HSPCs, upon dissipation of the CDK4/6 inhibitors intra-cellular effects, the cells are capable of reconstituting the cell lineages faster than CDK4/6 inhibitors with longer G1 arresting profiles, for example, ribociclib, palbociclib, or abemaciclib.

The reduction in chemotoxicity afforded by the compounds described herein at the dosage described herein can allow for dose intensification (e.g., more therapy can be given in a fixed period of time) in medically related chemotherapies, which will translate to better efficacy.

Therefore, the presently disclosed methods can result in chemotherapy regimens that are less toxic and more effective.

The use of the compounds described herein at the dosage described herein can induce selective G1 arrest in CDK4/6-dependent cells (e.g., as measured in a cell-based in vitro assay).
5 In one embodiment, the compounds described herein at the dosage described herein is capable of increasing the percentage of CDK4/6-dependent cells in the G1 phase, while decreasing the percentage of CDK4/6-dependent cells in the G2/M phase and S phase. In one embodiment, the compounds described herein at the dosage described herein induces substantially pure (i.e., “clean”) G1 cell cycle arrest in the CDK4/6-dependent cells (e.g., wherein treatment with the
10 compounds described herein induces cell cycle arrest such that the majority of cells are arrested in G1 as defined by standard methods (e.g., propidium iodide (PI) staining or others) with the population of cells in the G2/M and S phases combined being less than about 30%, about 25%, about 20%, about 15%, about 10%, about 5%, about 3% or less of the total cell population. Methods of assessing the cell phase of a population of cells are known in the art (*see*, for example,
15 in U.S. Patent Application Publication No. 20020224522) and include cytometric analysis, microscopic analysis, gradient centrifugation, elutriation, fluorescence techniques including immunofluorescence, and combinations thereof. Cytometric techniques include exposing the cell to a labeling agent or stain, such as DNA-binding dyes, e.g., PI, and analyzing cellular DNA content by flow cytometry. Immunofluorescence techniques include detection of specific cell cycle
20 indicators such as, for example, thymidine analogs (e.g., 5-bromo-2-deoxyuridine (BrdU) or an iododeoxyuridine), with fluorescent antibodies.

In some embodiments, the use of the compounds described herein at the dosage described herein results in reduced or substantially free off-target effects, particularly related to inhibition of kinases other than CDK4 and or CDK6 such as CDK2, as the compounds described
25 herein at the dosage described herein is a poor inhibitor (e.g., $>1 \mu\text{M}$ IC_{50}) of CDK2. Furthermore, because of the high selectivity for CDK4/6, the use of the compounds described herein should not induce cell cycle arrest in CDK4/6-independent cells. In addition, because of the short transient nature of the G1-arrest effect, the CDK4/6-replication dependent cells more quickly reenter the cell-cycle than, comparatively, use of palbociclib provides, resulting in the reduced
30 risk of, in one embodiment, hematological toxicity development during long term treatment regimens due to the ability of HSPCs to replicate between chemotherapeutic treatments.

In some embodiments, the use of the compounds described herein at the dosage described herein reduces the risk of undesirable off-target effects including, but not limited to, long term toxicity, anti-oxidant effects, and estrogenic effects. Anti-oxidant effects can be

determined by standard assays known in the art. For example, a compound with no significant anti-oxidant effects is a compound that does not significantly scavenge free-radicals, such as oxygen radicals. The anti-oxidant effects of a compound can be compared to a compound with known anti-oxidant activity, such as genistein. Thus, a compound with no significant anti-oxidant activity can be one that has less than about 2, 3, 5, 10, 30, or 100-fold anti-oxidant activity relative to genistein. Estrogenic activities can also be determined via known assays. For instance, a non-estrogenic compound is one that does not significantly bind and activate the estrogen receptor. A compound that is substantially free of estrogenic effects can be one that has less than about 2, 3, 5, 10, 20, or 100-fold estrogenic activity relative to a compound with estrogenic activity, e.g., genistein.

Dosing Profiles

One embodiment described herein is the particular dosing and blood profile ranges of the CDK4/6 inhibitor compounds described herein, and methods using said dosages, for treating a subject undergoing DNA-damaging chemotherapeutic therapy for the treatment of a CDK 4/6-replication independent cellular proliferation disorder.

As contemplated herein and for purposes of the disclosed ranges herein, all ranges described herein include any and all numerical values occurring within the identified ranges. For example, a range of 1 to 10, as contemplated herein, would include the numerical values 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, as well as fractions thereof.

The term "AUC" (amount·time/volume) as used herein means the area under the plasma concentration-time curve.

The term " AUC_{inf} " (amount·time/volume) as used herein means the area under the plasma concentration-time curve from time zero to infinity.

The term " AUC_t " (amount·time/volume) as used herein means the area under the plasma concentration time curve from time zero to time t.

The term " AUC_τ " (amount·time/volume) as used herein means the area under the plasma concentration-time curve during a dosage interval (τ).

The term " AUC_{last} " (amount·time/volume) as used herein means the area under the plasma concentration-time curve from time zero to time of the last measurable concentration.

The term " C_{max} " (amount/volume) as used herein means the maximum (peak) plasma drug concentration.

The term "CL" (volume/time or volume/time/kg) as used herein means the apparent total body clearance of the drug from plasma.

The term "CL/F" (volume/time or volume/time/kg) as used herein means the apparent total clearance of the drug from plasma after administration.

The term " κ " (time^{-1}) as used herein means first-order rate constant.

5 The term " κ_{12} " (time^{-1}) as used herein means the transfer rate constant (first-order) from the central (1) to the peripheral (2) compartment.

The term " κ_{21} " (time^{-1}) as used herein means the transfer rate constant (first-order) from the peripheral (2) to the central (1) compartment.

The term " κ_{31} " (time^{-1}) as used herein means the transfer rate constant (first-order) from the deep peripheral (3) to the central (1) compartment.

10 The term " κ_z " (time^{-1}) as used herein means the terminal disposition rate constant/terminal rate constant.

The term " MRT_{inf} " (time) as used herein means mean residence time.

The term " T_{max} " (time) as used herein means time to reach maximum (peak) plasma concentration following drug administration.

15 The term " $T_{1/2}$ " (time) as used herein means the elimination half-life as used in one or non-compartmental models.

The term " $T_{1/2\beta}$ " (time) as used herein means the terminal elimination half-life as used in two-compartmental models.

20 The term " $T_{1/2\gamma}$ " (time) as used herein means the terminal or elimination half-life as used in three compartmental models.

The term " V_{ss} " (volume or volume/kg) as used herein means the apparent volume of distribution at steady state.

In one embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single
25 dose of the compounds described herein provides a specific PK and/or PD blood profile as described herein. In one embodiment, the dose administered to the subject is between about 180 and about 215 mg/m^2 . In one embodiment, the dose is between about 180 and about 280 mg/m^2 . In one embodiment, the dose administered is between about 170 to about 215 mg/m^2 . In one embodiment, the dose administered is between about 170 to about 280 mg/m^2 . For example, the
30 dose is about 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, or 280 mg/m^2 . In one embodiment, the dose is about 190 mg/m^2 . In one embodiment, the dose is about 200 mg/m^2 . In one embodiment, the dose is about 240 mg/m^2 . In one embodiment, the dose administered provides for a mean AUC_{last} measured at 24.5 hours or a mean C_{max} as described below.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile dosage-corrected mean $C_{\max}$ ((ng/mL)/(mg/m²)) of between about 1 (ng/mL)/(mg/m²) and 20 (ng/mL)/(mg/m²),
5 between about 2.5 (ng/mL)/(mg/m²) and 15 (ng/mL)/(mg/m²), or of between about 4 (ng/mL)/(mg/m²) and 12 (ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean $C_{\max}$ ((ng/mL)/(mg/m²)) is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 ((ng/mL)/(mg/m²)). In one embodiment, the dosage-corrected mean $C_{\max}$ ((ng/mL)/(mg/m²)) is about 8.0 (ng/mL)/(mg/m²) $\pm$ 3.5 (ng/mL)/(mg/m²), about 8.5 (ng/mL)/(mg/m²) $\pm$ 2.5
10 (ng/mL)/(mg/m²), about 9.5 (ng/mL)/(mg/m²) $\pm$ 2.0 (ng/mL)/(mg/m²), or about 10.2 (ng/mL)/(mg/m²) $\pm$ 1.5 (ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean $C_{\max}$ is about 6.0 $\pm$ 20%. The dosage corrected mean $C_{\max}$ is mean $C_{\max}$ divided by the number of milligrams/m² of the compounds described herein in the formulation. In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one
15 embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m².

Another embodiment is a method of treating a subject undergoing chemotherapy for the treatment of an CDK 4/6-replication independent cellular proliferation disorder by providing an intravenously administered formulation of the compounds described herein wherein a single-dose
20 provides a blood plasma level profile dosage-corrected mean $C_{\max}$ ((ng/mL)/(mg/m²)) of between about 4.6 (ng/mL)/(mg/m²) and about 17.1 (ng/mL)/(mg/m²) or about 1.8 (ng/mL)/(mg/m²) to about 16.8 (ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean $C_{\max}$ ((ng/mL)/(mg/m²)) is about at least 8.5 (ng/mL)/(mg/m²) or about at least 3.8 (ng/mL)/(mg/m²).

In another embodiment, the compounds described herein are administered to a subject
25 prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a dosage-corrected mean $C_{\max}$ (ng/mL)/(mg/m²) of between of between about 1
30 (ng/mL)/(mg/m²) and 20 (ng/mL)/(mg/m²), between about 2.5 (ng/mL)/(mg/m²) and 15 (ng/mL)/(mg/m²), or of between about 4 (ng/mL)/(mg/m²) and 14 (ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean $C_{\max}$ ((ng/mL)/(mg/m²)) is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 ((ng/mL)/(mg/m²)). In one embodiment, the dosage-corrected mean $C_{\max}$ ((ng/mL)/(mg/m²)) is about 9.5 (ng/mL)/(mg/m²) $\pm$ 1.5 (ng/mL)/(mg/m²). In

an alternative embodiment the dosage-corrected mean $C_{\max}$ is about $9.5 \text{ (ng/mL)/(mg/m}^2\text{)} \pm 1.9 \text{ (ng/mL)/(mg/m}^2\text{)}$ or $9.5 \text{ (ng/mL)/(mg/m}^2\text{)} \pm \text{about } 20\%$. In one embodiment, the mean dose-corrected $C_{\max}$ ($\text{(ng/mL)/(mg/m}^2\text{)}$) is about $10.45 \text{ (ng/mL)/(mg/m}^2\text{)} \pm \text{about } 20\%$. In one embodiment, the dosage-corrected mean $C_{\max}$ is about $6.0 \text{ ((ng/mL)/(mg/m}^2\text{))} \pm 20\%$. In one embodiment, the dosage-corrected mean $C_{\max}$ is about $6.5 \text{ ((ng/mL)/(mg/m}^2\text{))} \pm 20\%$. In one embodiment, the compounds described herein are administered on days 1 and 2 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, and 3 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, and 4 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, 4, and 5 of the treatment regime.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile dosage-corrected with a mean $C_{\max}$ (ng/mL) of between about 1000 ng/mL and about 3500 ng/mL, or between about 1400 ng/mL and about 3100 ng/mL, or between about 1700 ng/mL and about 2500 ng/mL, or between about 1900 ng/mL and about 2150 ng/mL. In one embodiment, the mean $C_{\max}$ (ng/mL) is about 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, or 3500 (ng/mL). In one embodiment, the mean $C_{\max}$ (ng/mL) is about $2030 \text{ ng/mL} \pm 555 \text{ ng/mL}$. In one embodiment, the mean $C_{\max}$ (ng/mL) is about 1900 ng/mL, about 1950 ng/mL, about 1975 ng/mL, about 2000 ng/mL, about 2025 ng/mL, about 2030 ng/mL, about 2040 ng/mL, about 2050 ng/mL, about 2075 ng/mL, or about 2100 ng/mL. In one embodiment, the maximum mean concentration occurs at the end of the infusion period of the formulation. In one embodiment, the single dose is between about 170 mg/m^2 and 280 mg/m^2 or 170 mg/m^2 and 215 mg/m^2 . In one embodiment, the single dose is about 190 mg/m^2 . In one embodiment, the single dose is about 200 mg/m^2 . In one embodiment, the single dose is about 240 mg/m^2 .

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile dosage-corrected a mean $C_{\max}$ (ng/mL) of between about 885 ng/mL and about 3280 ng/mL, or between about 355 ng/mL and about 3360 ng/mL. In one embodiment, the mean $C_{\max}$ (ng/mL) is about at least 1705 ng/mL. In one embodiment, the $C_{\max}$ (ng/mL) is about at least 752 ng/mL.

In another embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment

regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a mean $C_{\max}$ (ng/mL) of between about 1000 ng/mL and 3500 ng/mL. In one embodiment, the mean $C_{\max}$ (ng/mL) is between about 1400 ng/mL and about 3100 ng/mL. In one embodiment, the mean $C_{\max}$ (ng/mL) of about 1000, 1100, 1200, 1300, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, 1800, 1850, 1900, 1950, 2000, 2050, 2100, 2150, 2200, 2250, 2300, 2400, 2450, 2500, 2600, 2650, 2700, 2750, 2800, 2850, 2900, 2950, 3000, 3050, 3100, 3200, 3300, 3400, 3500 (ng/mL). In one embodiment, the mean $C_{\max}$ (ng/mL) is about 2030 ng/mL $\pm$ 555 ng/mL. In an alternative embodiment, the mean $C_{\max}$ is about 2030 ng/mL $\pm$ 406 ng/mL or about 2030 ng/mL about 20%. In an alternative embodiment, the mean $C_{\max}$ is about 2230 ng/mL $\pm$ about 20%. In one embodiment, the mean $C_{\max}$ is at least about 1020 ng/mL. In one embodiment, the maximum mean concentration occurs at the end of the infusion period of the compounds described herein. In one embodiment, the compounds described herein are administered on days 1 and 2 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, and 3 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, and 4 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, 4, and 5 of the treatment regime.

In another embodiment, provided is a method of treating a subject undergoing chemotherapy for the treatment of a CDK 4/6-replication independent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein wherein a single-dose provides a blood plasma level profile with a mean $T_{\max}$ (h) of between about 0.10 hrs and about 1.0 hrs, of between about 0.20 hrs and about 0.6 hrs, or of between about 0.30 hrs and about 0.5 hrs. In one embodiment, the $T_{\max}$ (h) is about 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.85, 0.90, 0.95, or 1.0 (h). In one embodiment, the mean $T_{\max}$ (h) is about 0.417 hrs 0.129 hrs. In one embodiment, the mean $T_{\max}$ (h) is about 0.3 hrs, about 0.35 hrs, about 0.375 hrs, about 0.40 hrs, about 0.415 hrs, about 0.425 hrs, about 0.45 hrs, about 0.475 hrs, or about 0.5 hrs. In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the

compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a $T_{\max}$ (h) as described herein.

Another embodiment is a method of treating a subject undergoing chemotherapy for the treatment of a CDK 4/6-replication independent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein wherein a single-dose provides a blood plasma level profile with a mean $T_{\max}$ (h) of between about 0.25 hrs and about 0.48 hrs. In one embodiment, the mean $T_{\max}$ (h) is about at least 0.47 hrs.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile mean AUC_{inf} (h·ng/mL) measured over 24.5 hours after administration of between about 2000 h·ng/mL to about 4500 h·ng/mL, of between about 2300 h·ng/mL to about 4000 h·ng/mL, of between about 2500 h·ng/mL to about 3500 h·ng/mL, or of between about 2700 h·ng/mL to about 3200 h·ng/mL. In one embodiment, the mean AUC_{inf} (h·ng/mL) is about 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, or 4000 (h·ng/mL). In one embodiment, the mean AUC_{inf} (h·ng/mL) measured over 24.5 hours after administration is about 3050 h·ng/mL $\pm$ 513 h·ng/mL. In one embodiment, the mean AUC_{inf} (h·ng/mL) measured over 24.5 hours after administration is about 2500 h·ng/mL, is about 2750 h·ng/mL, about 2900 h·ng/mL, about 3000 h·ng/mL, about 3050 h·ng/mL, about 3100 h·ng/mL, about 3250 h·ng/mL, about 3300 h·ng/mL. In one embodiment, the mean AUC_{inf} (h·ng/mL) measured over 72.5 hours after administration is between about 2000 h·ng/mL to about 4500 h·ng/mL, of between about 2300 h·ng/mL to about 4000 h·ng/mL, of between about 2500 h·ng/mL to about 3500 h·ng/mL, or of between about 2700 h·ng/mL to about 3200 h·ng/mL. In one embodiment, the mean AUC_{inf} (h·ng/mL) measured over 72.5 hours after administration is about 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, or 4000 (h·ng/mL). In one embodiment, the mean AUC_{inf} (h·ng/mL) measured over 72.5 hours after administration is about 3160 h·ng/mL $\pm$ 522 h·ng/mL. In one embodiment, the mean AUC_{inf} (h·ng/mL) measured over 72.5 hours after administration is about 2500 h·ng/mL, is about 2600 h·ng/mL, about 2900 h·ng/mL, about 3000 h·ng/mL, about 3050 h·ng/mL, about 3100 h·ng/mL, about 3250 h·ng/mL, about 3300 h·ng/mL, about 3500 h·ng/mL, about 3600 h·ng/mL, about 3700 h·ng/mL, or about 3800 h·ng/mL. In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is

about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on
5 any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a AUC_{inf} (h·ng/mL) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single
10 dose of the compounds described herein provides a blood plasma level profile with a mean AUC_{inf} (h·ng/mL) measured over 24.5 hours after administration of between about 2379 h·ng/mL to about 3762 h·ng/mL or about 1530 h·ng/mL to about 3300 h·ng/mL. In one embodiment, the mean AUC_{inf} h·ng/mL measured over 24.5 hours after administration is about at least 2991 h·ng/mL or about at least 2140 h·ng/mL. In one embodiment, the mean AUC_{inf} h·ng/mL measured over 72.5
15 hours after administration of between about 2379 h·ng/mL to about 3762 h·ng/mL or about 1530 h·ng/mL to about 3300 h·ng/mL. In one embodiment, the mean AUC_{inf} h·ng/mL measured over 72.5 hours after administration is about at least 2991 h·ng/mL or about at least 2140 h·ng/mL.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single
20 dose of the compounds described herein provides a blood plasma level profile with a mean AUC_t (ng·hr/mL) measured over 24.5 hours after administration of between about 2000 h·ng/mL to about 4500 h·ng/mL, between about 2600 h·ng/mL to about 3700 h·ng/mL, between about 2800 h·ng/mL to about 3500 h·ng/mL, or between about 3000 h·ng/mL to about 3200 h·ng/mL. In one embodiment, the mean AUC_t (ng·hr/mL) measured over 24.5 hours after administration is about
25 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, 4000, 4100, 4200, 4300, 4400, or 4500 (h·ng/mL). In one embodiment, the mean AUC_t (ng·hr/mL) measured over 24.5 hours after administration is about 2830 (ng·hr/mL) ± 474 (ng·hr/mL). In one embodiment, the mean AUC_t (ng·hr/mL) measured over 72.5 hours after administration is between about 2000 h·ng/mL to about 4500 h·ng/mL,
30 between about 2600 h·ng/mL to about 3700 h·ng/mL, between about 2800 h·ng/mL to about 3500 h·ng/mL, or between about 3000 h·ng/mL to about 3200 h·ng/mL. In one embodiment, the mean AUC_t (ng·hr/mL) measured over about 72.5 hours after administration is about 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, 4000, 4100, 4200, 4300, 4400, or 4500 (ng·hr/mL). In one embodiment, the mean

AUC_t (ng·hr/mL) measured over 72.5 hours after administration is about 3110 (ng·hr/mL) ± 515 (ng·hr/mL). In one embodiment, the mean AUC_t (ng·hr/mL) measured over 72.5 hours after administration is about 3000 (ng·hr/mL), is about 3050 (ng·hr/mL), is about 3100 (ng·hr/mL), is about 3110 (ng·hr/mL), is about 3150 (ng·hr/mL), is about 3200 (ng·hr/mL), or is about 3250 (ng·hr/mL). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m².

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a mean AUC_t (ng·hr/mL) of between about 2360 h·ng/mL to about 3750 h·ng/mL or about 1530 h·ng/mL to about 3300 h·ng/mL. In one embodiment, the mean AUC_t (ng·hr/mL) is about at least 2991 h·ng/mL or about at least 2140 h·ng/mL.

In another embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a mean AUC_t (ng·hr/mL) measured over about 24.5 hours after administration of between about 2300 h·ng/mL to about 4000 h·ng/mL. In one embodiment, the mean AUC_t (ng·hr/mL) measured over about 24.5 hours after administration is about 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, or 4000 (ng·hr/mL). In one embodiment, the mean AUC_t (ng·hr/mL) measured over about 24.5 hours after administration is about 2830 (ng·hr/mL) ± 550 (ng·hr/mL). In an alternative embodiment, the mean AUC_t (ng·hr/mL) measured over about 24.5 hours after administration is about 2830 (ng·hr/mL) ± 560 (ng·hr/mL) or about 2830 (ng·hr/mL) ± about 20%. In one embodiment, the mean AUC_t (ng·hr/mL) measured over about 24.5 hours after administration is about 3020 (ng·hr/mL) about 20%. In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a mean AUC_t (ng·hr/mL) measured over about 24.5 hours after

administration of at least about 2040 ng·hr/mL. In one embodiment, the mean AUC_t (ng·hr/mL) measured over about 72.5 hours after administration is between about 2300 h·ng/mL to about 4100 h·ng/mL. In one embodiment, the mean AUC_t (ng·hr/mL) measured over about 72.5 hours after administration is about 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000, 3100, 3200, 3300, 3400, 3500, 3600, 3700, 3800, 3900, 4000, or 4100 (ng·hr/mL). In an alternative embodiment, the mean AUC_t (ng·hr/mL) measured over about 72.5 hours after administration is about 3100 (ng·hr/mL) $\pm$ about 20% or about 3100 (ng·hr/mL) $\pm$ about 20%. In one embodiment, the mean AUC_t (ng·hr/mL) measured over about 72.5 hours after administration is about 3410 (ng·hr/mL) $\pm$ about 20%. In one embodiment, the compounds described herein are administered on days 1 and 2 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, and 3 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, and 4 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, 4, and 5 of the treatment regime.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) of between about 6 (h·ng/mL)/(mg/m²) and 20 (h·ng/mL)/(mg/m²), of between about 8 (h·ng/mL)/(mg/m²) and 15 (h·ng/mL)/(mg/m²), of between about 10 (h·ng/mL)/(mg/m²) and 13 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is about 12.5 (h·ng/mL)/(mg/m²) $\pm$ 2.2 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is about 10.5 (h·ng/mL)/(mg/m²), about 11.0 (h·ng/mL)/(mg/m²), about 11.5 (h·ng/mL)/(mg/m²), about 12.0 (h·ng/mL)/(mg/m²), about 12.5 (h·ng/mL)/(mg/m²), or about 13.0 (h·ng/mL)/(mg/m²). The dosage corrected mean AUC_t is mean AUC_t divided by the number of milligrams/m² of the compounds described herein in the formulation. In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m².

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a dosage-

corrected mean AUC_t (h·ng/mL)/(mg/m²) of between about 12.3 (h·ng/mL)/(mg/m²) to about 19.5 (h·ng/mL)/(mg/m²) or about 7.6 (h·ng/mL)/(mg/m²) to about 16.5 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is about at least 15.6 (h·ng/mL)/(mg/m²) or about at least 10.7 (h·ng/mL)/(mg/m²).

5 In another embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described
10 herein with a dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) of between about 6 (h·ng/mL)/(mg/m²) and 20 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is about 15.0 (h·ng/mL)/(mg/m²) $\pm$ 3.0 (h·ng/mL)/(mg/m²) or about 15.0 (h·ng/mL)/(mg/m²) $\pm$ about 20%. In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is at least about 8.35 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-
15 corrected mean AUC_t (h·ng/mL)/(mg/m²) is about 16.5 (h·ng/mL)/(mg/m²) $\pm$ about 20%. In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is at least about 10.0 (h·ng/mL)/(mg/m²). The dosage corrected AUC_t is AUC_t divided by the number of milligrams/m² of the compounds described herein in the formulation. In one embodiment, the compounds described herein are administered on days 1 and 2 of the treatment regime. In one embodiment,
20 the compounds described herein are administered on days 1, 2, and 3 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, and 4 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, 4, and 5 of the treatment regime.

In another embodiment, the compounds described herein are orally or intravenously
25 administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a dosage-corrected mean AUC_{inf} (h·ng/mL)/(mg/m²) of between about 6 (h·ng/mL)/(mg/m²) and 20 (h·ng/mL)/(mg/m²), of between about 8 (h·ng/mL)/(mg/m²) and 15 (h·ng/mL)/(mg/m²), of between about 10 (h·ng/mL)/(mg/m²) and 13 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-
30 corrected mean AUC_{inf} (h·ng/mL)/(mg/m²) is about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_{inf} (h·ng/mL)/(mg/m²) is about 12.7 (h·ng/mL)/(mg/m²) $\pm$ 2.5 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_{inf} (h·ng/mL)/(mg/m²) is about 10.5 (h·ng/mL)/(mg/m²), about 11.0 (h·ng/mL)/(mg/m²), about 11.5 (h·ng/mL)/(mg/m²), about 12.0 (h·ng/mL)/(mg/m²), about 12.5

(h·ng/mL)/(mg/m²), about 13.0 (h·ng/mL)/(mg/m²), or about 13.5 (h·ng/mL)/(mg/m²). The dosage corrected mean AUC_{inf} is mean AUC_{inf} divided by the number of milligrams/m² of the compounds described herein in the formulation. In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m².

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a dosage-corrected mean AUC_{inf} (h·ng/mL)/(mg/m²) measured over 24.5 hours after administration of between about 12.4 (h·ng/mL)/(mg/m²) to about 19.6 (h·ng/mL)/(mg/m²) or about 7.6 (h·ng/mL)/(mg/m²) to about 16.5 (h·ng/mL)/(mg/m²). In one embodiment, the mean AUC_{inf} (h·ng/mL)/(mg/m²) measured over 24.5 hours after administration is about at least 15. (h·ng/mL)/(mg/m²) or about at least 10.7 (h·ng/mL)/(mg/m²). In one embodiment, the mean AUC_{inf} (h·ng/mL)/(mg/m²) measured over 72.5 hours after administration of between about 12.4 (h·ng/mL)/(mg/m²) to about 19.6 (h·ng/mL)/(mg/m²) or about 7.6 (h·ng/mL)/(mg/m²) to about 16.5 (h·ng/mL)/(mg/m²). In one embodiment, the mean AUC_{inf} (h·ng/mL)/(mg/m²) measured over 72.5 hours after administration is about at least 15.6 h·(h·ng/mL)/(mg/m²) or about at least 10.7 (h·ng/mL)/(mg/m²).

In another embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) of between about 6 (h·ng/mL)/(mg/m²) and 20 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 (h·ng/mL)/(mg/m²). In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is about 15.0 (h·ng/mL)/(mg/m²) ± 3.0 (h·ng/mL)/(mg/m²) or about 15.0 (h·ng/mL)/(mg/m²) ± about 20%. In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is about 8.35 (h·ng/mL)/(mg/m²) ± about 20%. In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is about 16.5 (h·ng/mL)/(mg/m²) ± about 20%. In one embodiment, the dosage-corrected mean AUC_t (h·ng/mL)/(mg/m²) is at least about 10.0 (h·ng/mL)/(mg/m²). The dosage corrected AUC_t is AUC_t divided by the number of milligrams/m² of the compounds

described herein in the formulation. In one embodiment, the compounds described herein are administered on days 1 and 2 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, and 3 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, and 4 of the treatment regime. In one embodiment, the compounds described herein are administered on days 1, 2, 3, 4, and 5 of the treatment regime.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a mean CL (L/h/m²) measured over 24.5 hours after administration of between about 45 L/h/m² and about 85 L/h/m². In one embodiment, the mean CL (L/h/m²) measured over 24.5 hours after administration is 45, 50, 55, 60, 65, 70, 75, 80, or 85 (L/h/m²). In one embodiment, the mean CL (L/h/m²) measured over 24.5 hours after administration is about 65 (L/h/m²) $\pm$ 15 (L/h/m²). In one embodiment, the mean CL (L/h/m²) measured over 24.5 hours after administration is about 64.4 (L/h/m²) $\pm$ 10.6 (L/h/m²). In one embodiment, the mean CL (L/h/m²) measured over 72.5 hours after administration is between about 45 (L/h/m²) to about 80 (L/h/m²). In one embodiment, the mean CL (L/h/m²) measured over 72.5 hours after administration is about 60 (L/h/m²) $\pm$ 15 (L/h/m²). In one embodiment, the mean CL (L/h/m²) measured over 72.5 hours after administration is about 62.1 (L/h/m²) $\pm$ 10.3 (L/h/m²). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a CL (L/h/m²) as described herein.

In another embodiment, provided is a method of treating a subject undergoing chemotherapy for the treatment of a CDK 4/6-replication independent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein wherein a single-dose provides a blood plasma level profile with a mean V_{ss} (L/m²) measured over 24.5 hours after final administration of between about 320 (L/m²) and about 630 (L/m²). In one embodiment, the mean V_{ss} (L/m²) measured over 24.5 hours is 320, 370, 400, 420, 470, 500, 520, 570, 600, or 630 (L/m²). In one embodiment, the mean V_{ss} (L/m²) measured over 24.5 hours

is about $425 \text{ (L/m}^2\text{)} \pm 150 \text{ (L/m}^2\text{)}$. In one embodiment, the mean $V_{ss} \text{ (L/m}^2\text{)}$ measured over 24.5 hours is about $421 \text{ (L/m}^2\text{)} \pm 101 \text{ (L/m}^2\text{)}$. In one embodiment, the mean $V_{ss} \text{ (L/m}^2\text{)}$ measured over 72.5 hours after final administration of between about 390 $\text{(L/m}^2\text{)}$ and about 825 $\text{(L/m}^2\text{)}$. In one embodiment, the mean $V_{ss} \text{ (L/m}^2\text{)}$ measured over 72.5 hours after final administration is 400, 450, 500, 550, 600, 650, 700, 750, 800, or 825 $\text{(L/m}^2\text{)}$. In one embodiment, the mean $V_{ss} \text{ (L/m}^2\text{)}$ measured over 72.5 hours after final administration is about $550 \text{ (L/m}^2\text{)} \pm 175 \text{ (L/m}^2\text{)}$. In one embodiment, the mean $V_{ss} \text{ (L/m}^2\text{)}$ measured over 72.5 hours after final administration is about $547 \text{ (L/m}^2\text{)} \pm 147 \text{ (L/m}^2\text{)}$. In one embodiment, the single dose is between about 170 mg/m^2 and 280 mg/m^2 or 170 mg/m^2 and 215 mg/m^2 . In one embodiment, the single dose is about 190 mg/m^2 . In one embodiment, the single dose is about 200 mg/m^2 . In one embodiment, the single dose is about 240 mg/m^2 . In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a $V_{ss} \text{ (L/m}^2\text{)}$ as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a mean MRTs (h) measured over 24.5 hours of between about 4.75 (h) and about 9.25 (h). In one embodiment, the mean $\text{MRT}_{inf} \text{ (h)}$ measured over 24.5 hours is 4.75, 5.25, 5.75, 6.25, 6.75, 7.25, 7.75, 8.25, 8.75, or 9.25 (h). In one embodiment, the mean $\text{MRT}_{inf} \text{ (h)}$ measured over 24.5 hours is about $6.5 \text{ (h)} \pm 1.75 \text{ (h)}$. In one embodiment, the mean $\text{MRT}_{inf} \text{ (h)}$ measured over 24.5 hours is about $6.59 \text{ (h)} \pm 1.33 \text{ (h)}$. In one embodiment, the mean $\text{MRT}_{inf} \text{ (h)}$ measured over 72.5 hours is between about 6 (h) and about 13 (h). In one embodiment, the mean $\text{MRT}_{inf} \text{ (h)}$ measured over 72.5 hours is about $9 \text{ (h)} \pm 2.5 \text{ (h)}$. In one embodiment, the mean $\text{MRT}_{inf} \text{ (h)}$ measured over 72.5 hours is about $8.86 \text{ (h)} \pm 2.12 \text{ (h)}$. In one embodiment, the single dose is between about 170 mg/m^2 and 280 mg/m^2 or 170 mg/m^2 and 215 mg/m^2 . In one embodiment, the single dose is about 190 mg/m^2 . In one embodiment, the single dose is about 200 mg/m^2 . In one embodiment, the single dose is about 240 mg/m^2 . In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic

treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a V_{ss} (L/m²) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a mean λ_z (1/h) measured over 24.5 hours of between about 0.07 and 0.15. In one embodiment, the mean λ_z (1/h) measured over 24.5 hours is 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, or 0.15 (1/h). In one embodiment, the mean λ_z (1/h) measured over 24.5 hours is about 0.09 ± 0.025 . In one embodiment, the mean λ_z (1/h) measured over 24.5 hours is about 0.0899 ± 0.0157 . In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a λ_z (1/h) measured over 24.5 hours as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a mean $t_{1/2}$ (h) measured over 24.5 hours of between about 5 h and 9.5 h. In one embodiment, the mean $t_{1/2}$ (h) measured over 24.5 hours is 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, or 9.5 h. In one embodiment, the mean $t_{1/2}$ (h) measured over 24.5 hours is about 8 ± 1.5 (h). In one embodiment, the mean $t_{1/2}$ (h) measured over 24.5 hours is about 7.87 ± 1.14 (h). In one embodiment, the mean $t_{1/2\beta}$ (h) measured over 72.5 hours is between about 5.5 (h) and about 9 (h). In one embodiment, the mean $t_{1/2\beta}$ (h) measured over 24.5 hours is 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, or 9 h. In one embodiment, the mean $t_{1/2\beta}$ (h) measured over 72.5 hours is about 8 (h) ± 1.5 (h). In one embodiment, the mean $t_{1/2\beta}$ (h) measured over 72.5 hours is about 7.87 (h) ± 1.14 (h). In one embodiment, the mean $t_{1/2\gamma}$ (h) measured over 72.5 hours is between about 15 (h) and about 22 (h). In one embodiment, the mean $t_{1/2\gamma}$ (h) measured over 72.5 hours is 15, 16, 17, 18, 19, 20, 21, or 22 (h). In one embodiment, the mean $t_{1/2\gamma}$ (h) measured over 72.5 hours is about 18 (h) ± 2.25 (h). In one embodiment, the mean $t_{1/2\gamma}$ (h) measured over 72.5 hours is about 18.0 (h) ± 1.92 (h). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215

mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a t_{1/2} (h), t_{1/2β} (h), and/or t_{1/2γ} (h) measured over 24.5 hours and/or 72.5 hours as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a mean t_{1/2} (h) of between about 11.9 h and 17.3 h.

In one embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a blood plasma level profile with a mean concentration (ng/mL) at 24.5 hours after the end of administration of between about 5 (ng/mL) and about 35 (ng/mL). In one embodiment, the mean concentration at 24.5 hours after the end of administration is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 (ng/mL). In one embodiment, the mean concentration at 24.5 hours after the end of administration is about 19 (ng/mL) ± 5.24 (ng/mL). In one embodiment, the mean concentration at 24.5 hours after the end of administration is about 20 (ng/mL) ± 7.5 (ng/mL). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean concentration (ng/mL) at 24.5 hours after the end of administration as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single

dose of the compounds described herein provides a blood plasma level profile with a mean concentration (ng/mL) at 72.5 hours after the end of administration of between about 0.7 (ng/mL) and about 3 (ng/mL). In one embodiment, the mean concentration at 72.5 hours after the end of administration is about 0.7, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, or 3 (ng/mL). In one
5 embodiment, the mean concentration at 72.5 hours after the end of administration is about 2.25 (ng/mL) $\pm$ 1.5 (ng/mL). In one embodiment, the mean concentration at 72.5 hours after the end of administration is about 1.79 (ng/mL) $\pm$ 0.731 (ng/mL). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one
10 embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level
15 profile of the compounds described herein with a with a mean concentration (ng/mL) at 72.5 hours after the end of administration as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a primary pharmacokinetic blood plasma level
20 profile with a mean α (1/h) of between about 1 (1/h) and 15 (1/h). In one embodiment, a single-dose provides a primary pharmacokinetic blood plasma level profile with a mean α (1/h) of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 (1/h). In one embodiment, a single-dose provides a primary pharmacokinetic blood plasma level profile with a mean α (1/h) of about 11 (1/h) $\pm$ 9 (1/h). In one embodiment, a single-dose provides a primary pharmacokinetic blood plasma level profile
25 with a mean α (1/h) of about 11.3 (1/h) $\pm$ 7.06 (1/h). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent
30 in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean α (1/h) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a primary pharmacokinetic blood plasma level profile with a mean β (1/h) of about $0.4 \text{ (1/h)} \pm 0.3 \text{ (1/h)}$. In one embodiment, provided is a primary pharmacokinetic blood plasma level profile with a mean β (1/h) of about $0.362 \text{ (1/h)} \pm 0.110 \text{ (1/h)}$. In one embodiment, the single dose is between about 170 mg/m^2 and 280 mg/m^2 or 170 mg/m^2 and 215 mg/m^2 . In one embodiment, the single dose is about 190 mg/m^2 . In one embodiment, the single dose is about 200 mg/m^2 . In one embodiment, the single dose is about 240 mg/m^2 . In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean β (1/h) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a primary pharmacokinetic blood plasma level profile with a mean γ (1/h) of about $0.05 \text{ (1/h)} \pm 0.01 \text{ (1/h)}$. In one embodiment, provided is a primary pharmacokinetic blood plasma level profile with a mean γ (1/h) of about $0.0497 \text{ (1/h)} \pm 0.00442 \text{ (1/h)}$. In one embodiment, the single dose is between about 170 mg/m^2 and 280 mg/m^2 or 170 mg/m^2 and 215 mg/m^2 . In one embodiment, the single dose is about 190 mg/m^2 . In one embodiment, the single dose is about 200 mg/m^2 . In one embodiment, the single dose is about 240 mg/m^2 . In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean γ (1/h) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean K_{21} (1/h) of about $1 \text{ (1/h)} \pm 0.6$. In one embodiment, a single-dose provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean K_{21} (1/h) of about $0.993 \text{ (1/h)} \pm 0.439$. In one embodiment, the single dose is between

about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean K₂₁ (1/h) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean K₃₁ (1/h) of about 0.08 (1/h) ± 0.03 (1/h). In one embodiment, a single-dose provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean K₃₁ (1/h) of about 0.0750 (1/h) ± 0.0160 (1/h). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean K₃₁ (1/h) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean V₁ (L/m²) of about 25 ± 15. In one embodiment, a single-dose provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean V₁ (L/m²) of about 25.6 ± 9.51. In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds

described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean V_1 (L/m²) as described herein.

5 In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean $C_{\max}$ (ng/mL) of about 2000 (ng/mL) $\pm$ 650 (ng/mL). In one embodiment, a single-dose provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean $C_{\max}$ (ng/mL) of about 2020 (ng/mL) $\pm$ 505 (ng/mL). In one embodiment, 10 the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 15 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean $C_{\max}$ (ng/mL) as described herein.

20 In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a primary pharmacokinetic blood plasma level profile with a mean $t_{1/2\alpha}$ of about 0.1 (h) $\pm$ 0.05 (h). In one embodiment, a single-dose provides a primary pharmacokinetic blood plasma level profile with a mean $t_{1/2\alpha}$ of about 0.0776 (h) $\pm$ 0.0329 (h). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 25 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to 30 administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean $t_{1/2\alpha}$ (h) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 2-compartment primary pharmacokinetic blood plasma level profile with a mean $t_{1/2\beta}$ of about 2 (h) $\pm$ 0.75 (h). In one embodiment, a single-dose provides a 2-compartment primary pharmacokinetic blood plasma level profile with a mean $t_{1/2\beta}$ of about 2.03 (h) $\pm$ 0.444 (h). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean $t_{1/2\beta}$ (h) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean $t_{1/2\gamma}$ of about 15 (h) $\pm$ 3 (h). In one embodiment, a single-dose provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean $t_{1/2\gamma}$ of about 14.0 (h) $\pm$ 1.35 (h). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean $t_{1/2\gamma}$ (h) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean AUC (h·ng/mL) of about 3200(h·ng/mL) $\pm$ 750 (h·ng/mL). In one embodiment, a single-dose provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean AUC (h·ng/mL) of about 3220(h·ng/mL) $\pm$ 559 (h·ng/mL). In one

embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean AUC (h·ng/mL) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean CL (L/h/m²) of about 60 (L/h/m²) ± 15 (L/h/m²). In one embodiment, a 3-compartment primary pharmacokinetic blood plasma level profile with a mean CL (L/h/m²) of about 61.1 (L/h/m²) ± 10.6 (L/h/m²). In one embodiment, the single dose is between about 170 mg/m² and 240 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean CL (L/h/m²) as described herein.

In another embodiment, the compounds described herein are orally or intravenously administered to a subject prior to administration of a chemotherapeutic agent so that a single dose of the compounds described herein provides a 3-compartment primary pharmacokinetic blood plasma level profile with a mean V_{ss} (L/m²) of about 500 (L/m²) ± 200 (L/m²). In one embodiment, a 3-compartment primary pharmacokinetic blood plasma level profile with a mean V_{ss} (L/m²) of about 508 (L/m²) ± 131 (L/m²). In one embodiment, the single dose is between about 170 mg/m² and 280 mg/m² or 170 mg/m² and 215 mg/m². In one embodiment, the single dose is about 190 mg/m². In one embodiment, the single dose is about 200 mg/m². In one embodiment, the single dose is about 240 mg/m². In one embodiment, the compounds described herein are administered to a subject prior to administration of a chemotherapeutic agent in a multi-day chemotherapeutic treatment regime, for example, 2 days, 3 days, 4 days, or 5 days, wherein the

compounds described herein, following administration on any day of the multi-day chemotherapeutic treatment regime, for example day 2, 3, 4, or 5, provides a blood plasma level profile of the compounds described herein with a with a mean V_{ss} (L/m²) as described herein.

In another embodiment, the compounds described herein at the dosages described about
5 is administered daily for more than 1, more than 2, more than 3, more than 4, more than 5, more than 6, more than 7, more than 8, more than 9, more than 10, more than 11, more than 12, more than 13, more than 14, more than 15, more than 16, more than 17, more than 18, more than 19, more than 20, more than 21, more than 22, more than 23, more than 24, more than 25 more than 26, more than 27, or more than 28 days. In one embodiment, provided is a method of treating a
10 subject undergoing chemotherapy for the treatment of a CDK 4/6-replication independent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein at a dosage described herein daily for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 days or more.

In another embodiment, provided is a method of treating a subject undergoing
15 chemotherapy for the treatment of a CDK 4/6-replication independent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein wherein a single-dose of the compounds described herein followed by a single-dose of Topotecan at 1.5 mg/m² provides a mean C_{max} (ng/mL) of Topotecan between about 30 ng/mL to about 150 ng/mL. In one embodiment, the mean C_{max} (ng/mL) of Topotecan at 1.5 mg/m² is about 30 ng/mL,
20 about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, about 130 ng/mL, about 140 ng/mL or about 150 ng/mL. In one embodiment, a single-dose of the compounds described herein followed by a single-dose of Topotecan at 1.25 mg/m² provides a mean C_{max} (ng/mL) of Topotecan between about 20 ng/mL and 120 ng/mL. In one embodiment, the mean C_{max} (ng/mL) of
25 Topotecan at 1.25 mg/m² is about 20 ng/mL, about 30 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 110 ng/mL, or about 120 ng/mL. In one embodiment, a single-dose of the compounds described herein followed by a single-dose of Topotecan at 0.75 mg/m² provides a mean C_{max} (ng/mL) of Topotecan between about 10 ng/mL and 70 ng/mL. In one embodiment, the mean C_{max} (ng/mL)
30 of Topotecan at 0.75 mg/m² is about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 45 ng/mL, about 50 ng/mL, about 55 ng/mL, about 60 ng/mL, about 65 ng/mL, or about 70 ng/mL.

In another embodiment, provided is a method of treating a subject undergoing chemotherapy for the treatment of a CDK 4/6-replication independent cellular proliferation

disorder by providing an intravenous administered formulation of the compounds described herein wherein a single-dose of the compounds described herein followed by a single-dose of Topotecan at 1.5 mg/m² provides a mean $C_{\max}$ (ng/mL) of Topotecan between about 40.2 ng/mL and about 122 ng/mL. In one embodiment, a single-dose of the compounds described herein followed by a single-dose of Topotecan at 1.25 mg/m² provides a mean $C_{\max}$ (ng/mL) of Topotecan between about 33.1 ng/mL and 104 ng/mL. In one embodiment, a single-dose of the compounds described herein followed by a single-dose of Topotecan at 0.75 mg/m² provides a mean $C_{\max}$ (ng/mL) of Topotecan between about 17.9 ng/mL and 38.5 ng/mL.

In another embodiment, provided is a method of treating a subject undergoing chemotherapy for the treatment of a CDK 4/6-replication independent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein wherein a single-dose of the compounds described herein followed by a single-dose of Topotecan at 1.5 mg/m² provides a mean AUC_t (h·ng/mL) of Topotecan between about 100 h·ng/mL and about 300 h·ng/mL. In one embodiment, the mean AUC_t (h·ng/mL) of Topotecan at 1.5 mg/m² is about 100 h·ng/mL, about 110 h·ng/mL, about 120 h·ng/mL, about 130 h·ng/mL, about 140 h·ng/mL, about 150 h·ng/mL, about 160 h·ng/mL, about 170 h·ng/mL, about 180 h·ng/mL, about 190 h·ng/mL, about 200 h·ng/mL, about 220 h·ng/mL, about 240 h·ng/mL, about 260 h·ng/mL, about 280 h·ng/mL, or about 300 h·ng/mL. In one embodiment, a single-dose of the compounds described herein followed by a single-dose of Topotecan at 1.25 mg/m² provides a mean AUC_t (h·ng/mL) of Topotecan between about 80 h·ng/mL and about 300 h·ng/mL. In one embodiment, the mean AUC_t (h·ng/mL) of Topotecan at 1.25 mg/m² is about 80 h·ng/mL, about 90 h·ng/mL, about 100 h·ng/mL, about 110 h·ng/mL, about 120 h·ng/mL, about 130 h·ng/mL, about 140 h·ng/mL, about 150 h·ng/mL, about 160 h·ng/mL, about 170 h·ng/mL, about 180 h·ng/mL, about 190 h·ng/mL, about 200 h·ng/mL, about 220 h·ng/mL, about 240 h·ng/mL, about 260 h·ng/mL, about 280 h·ng/mL, or about 300 h·ng/mL. In one embodiment, a single-dose of the compounds described herein followed by a single-dose of Topotecan at 0.75 mg/m² provides a mean AUC_t (h·ng/mL) of Topotecan between about 50 h·ng/mL and about 200 h·ng/mL. In one embodiment, the mean AUC_t (h·ng/mL) of Topotecan at 0.75 mg/m² is about 50 h·ng/mL, about 60 h·ng/mL, about 70 h·ng/mL, about 80 h·ng/mL, about 90 h·ng/mL, about 100 h·ng/mL, about 110 h·ng/mL, about 120 h·ng/mL, about 130 h·ng/mL, about 140 h·ng/mL, about 150 h·ng/mL, about 160 h·ng/mL, about 170 h·ng/mL, about 180 h·ng/mL, about 190 h·ng/mL, or about 200 h·ng/mL.

In another embodiment, provided is a method of treating a subject undergoing chemotherapy for the treatment of a CDK 4/6-replication independent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein

wherein a single-dose of the compounds described herein followed by a single-dose of Topotecan at 1.5 mg/m² provides a mean AUC_t (h·ng/mL) of Topotecan between about 132 h·ng/mL and about 181 h·ng/mL. In one embodiment, a single-dose of the compounds described herein followed by a single-dose of Topotecan at 1.25 mg/m² provides a mean AUC_t (h·ng/mL) of Topotecan between about 121 h·ng/mL and about 254 h·ng/mL. In one embodiment, a single-dose of the compounds described herein followed by a single-dose of Topotecan at 0.75 mg/m² provides a mean AUC_t (h·ng/mL) of Topotecan between about 74.4 h·ng/mL and about 120 h·ng/mL.

As provided herein, the compounds described herein can be administered wherein any one or more of the described PK or PD blood profile parameters described herein is reached to treat a subject undergoing chemotherapy for the treatment of any CDK-replication independent cellular proliferation disorder.

In another embodiment, provided is a method of treating a subject having a CDK-replication dependent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein in a dosage providing a blood plasma profile as described herein.

In another embodiment, provided is method of treating a subject having a CDK-replication independent cellular proliferation disorder by providing an intravenous administered formulation of the compounds described herein in a dosage providing a combination of two or more blood plasma parameters at levels described herein. Non-limiting examples of parameters that can be provided in combinations of two or more at levels described herein include: mean C_{max}, mean dosage-corrected C_{max}, mean T_{max}, mean AUC_{inf}, dosage-corrected mean AUC_{inf}, mean AUC_t, dosage-corrected mean AUC_t, and mean t_{1/2}.

Another embodiment described herein is a kit for dispensing a pharmaceutical dosage form comprising any of the compounds described herein, the kit comprising: (a) at least one dosage form comprising a compound described herein; (b) at least one moisture proof dispensing receptacle comprising blister or strip packs, an aluminum blister, a transparent or opaque polymer blister with pouch, polypropylene tubes, colored blister materials, tubes, bottles, and bottles optionally containing a child-resistant feature, optionally comprising a desiccant, such as a molecular sieve or silica gel; and optionally (c) an insert comprising instructions or prescribing information for the compound 1 comprised by the oral pharmaceutical composition; or (d) directions for administration or any contraindications.

Another embodiment is a kit comprising one or more pre-filled syringes comprising a solution or suspension of one or more compounds described herein. In one embodiment, such a

kit comprises a pre-filled syringe comprising compounds described herein in a blister pack or a sealed sleeve. The blister pack or sleeve may be sterile on the inside. In one aspect, pre-filled syringes as described herein may be placed inside such blister packs or sleeves prior to undergoing sterilization, for example terminal sterilization.

5 Such a kit may further comprise one or more needles for administration of the compounds described herein. Such kits may further comprise instructions for use, a drug label, contraindications, warnings, or other relevant information. One embodiment described herein is a carton or package comprising one or more pre-filled syringes comprising one or more compounds as described herein contained within a blister pack, a needle, and optionally
10 instructions for administration, a drug label, contraindications, warnings, or other relevant information.

A terminal sterilization process may be used to sterilize the syringe and such a process may use a known process such as an ethylene oxide or a hydrogen peroxide (H₂O₂) sterilization process. Needles to be used with the syringe may be sterilised by the same method, as may kits
15 described herein. In one aspect, a package is exposed to the sterilising gas until the outside of the syringe is sterile. Following such a process, the outer surface of the syringe may remain sterile (whilst in its blister pack) for up to 6 months, 9 months, 12 months, 15 months, 18 months, 24 months or longer. Thus, in one embodiment, a pre-filled syringe as described herein (in its blister pack) may have a shelf life of up to 6 months, 9 months, 12 months, 15 months, 18 months,
20 24 months, or even longer. In one embodiment, less than one syringe in a million has detectable microbial presence on the outside of the syringe after 18 months of storage. In one aspect, the pre-filled syringe has been sterilised using ethylene oxide with a Sterility Assurance Level of at least 10⁻⁶. In another aspect, the pre-filled syringe has been sterilised using hydrogen peroxide with a Sterility Assurance Level of at least 10⁻⁶. Significant amounts of the sterilising gas should
25 not enter the variable volume chamber of the syringe. The term "significant amounts" As used herein, refers to an amount of gas that would cause unacceptable modification of the compound solution or suspension within the variable volume chamber. In one embodiment, the pre-filled syringe has been sterilised using ethylene oxide, but the outer surface of the syringe has ≤1 ppm, preferably ≤0.2 ppm ethylene oxide residue. In one embodiment, the pre-filled syringe has been
30 sterilised using hydrogen peroxide, but the outer surface of the syringe has ≤1 ppm, preferably ≤0.2 ppm hydrogen peroxide residue. In another embodiment, the pre-filled syringe has been sterilised using ethylene oxide, and the total ethylene oxide residue found on the outside of the syringe and inside of the blister pack is ≤0.1 mg. In another embodiment, the pre-filled syringe

has been sterilised using hydrogen peroxide, and the total hydrogen peroxide residue found on the outside of the syringe and inside of the blister pack is ≤ 0.1 mg.

Another aspect is a kit of parts. For liquid and suspension compositions, and when the administration device is simply a hypodermic syringe, the kit may comprise the syringe, a needle and a container comprising the compounds described herein for use with the syringe. In case of a dry composition, the container may have one chamber containing the dry compound, and a second chamber comprising a reconstitution solution. In one embodiment, the injection device is a hypodermic syringe adapted so the separate container with compound can engage with the injection device such that in use the liquid or suspension or reconstituted dry composition in the container is in fluid connection with the outlet of the injection device. Examples of administration devices include but are not limited to hypodermic syringes and pen injector devices. Particularly preferred injection devices are the pen injectors, in which case the container is a cartridge, preferably a disposable cartridge.

Another embodiment comprises a kit comprising a needle and a container containing the compounds described herein and optionally further containing a reconstitution solution, the container being adapted for use with the needle. In one aspect, the container is a pre-filled syringe. In another aspect, the container is dual chambered syringe. Another embodiment is a cartridge containing a composition of the compounds described herein for use with a pen injector device. The cartridge may contain a single dose or plurality of doses of drug delivery system.

In another embodiment composition comprises a compound described herein and one or more excipients, and also other biologically active agents, either in their free form or as drugs or combined with other drug delivery systems such as pegylated drugs or hydrogel linked drugs. In one aspect, such additional one or more biologically active agents is a free form drug or a second drug delivery system. In another embodiment, one or more compounds described herein are simultaneously administered, with each compound having either separate or related biological activities or targets.

In an alternative embodiment, the compound is combined with a second biologically active compound in such way that the composition is administered to a subject in need thereof first, followed by the administration of the second compound. Alternatively, the compounds described herein are administered to a subject in need thereof after another compound has been administered to the same subject.

It will be apparent to one of ordinary skill in the relevant art that suitable modifications and adaptations to the compositions, formulations, methods, processes, and applications described herein can be made without departing from the scope of any embodiments or aspects thereof.

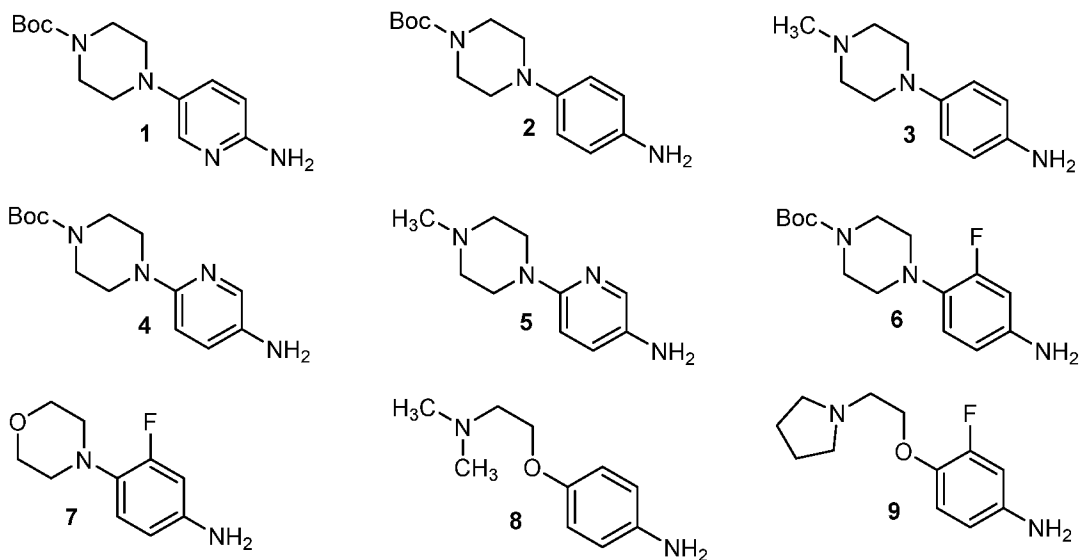
The compositions, methods, and experiments provided are exemplary and are not intended to limit the scope of any of the specified embodiments. All of the various embodiments, aspects, and options disclosed herein can be combined in any variations or iterations. The scope of the compositions, formulations, methods, and processes described herein include all actual or potential combinations of embodiments, aspects, options, examples, and preferences herein described. The exemplary compositions and formulations described herein may omit any component, substitute any component disclosed herein, or include any component disclosed elsewhere herein. The ratios of the mass of any component of any of the compositions or formulations disclosed herein to the mass of any other component in the formulation or to the total mass of the other components in the formulation are hereby disclosed as if they were expressly disclosed. Should the meaning of any terms in any of the patents or publications incorporated by reference conflict with the meaning of the terms used in this disclosure, the meanings of the terms or phrases in this disclosure are controlling. All patents and publications cited herein are incorporated by reference herein for the specific teachings thereof.

The present disclosure includes duplicates. Duplicates are intended to be supplementary and additive.

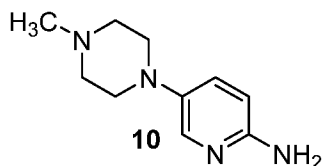
EXAMPLES**Example 1****Synthesis of R₁ Groups**

The following amines were purchased from commercial sources:

5

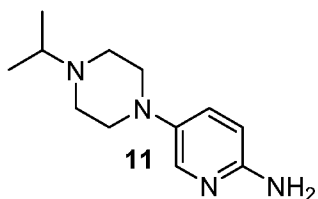


The following amines were synthesized using reported methods.

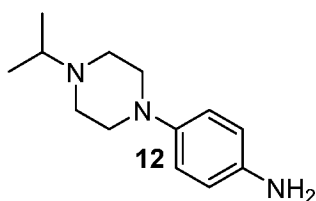


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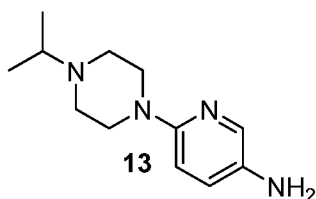
Compound **10** was synthesized using the procedure reported in Int. Pat. App. Publication No. WO 2009156284.



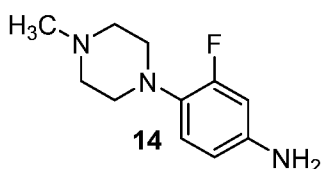
Compound **11** was synthesized using the reported procedures reported in Int. Pat. App. Publication No. WO 2011112995 and U.S. Pat. No. 7,713,994.



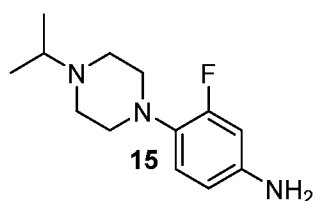
Compound **12** was synthesized using the procedure reported in Int. Pat. App. Publication No. WO 2007131991.



5 Compound **13** was synthesized using the procedure reported by Li et al., *ACS Med. Chem. Lett.*, 4(7): 647-650 (2013).



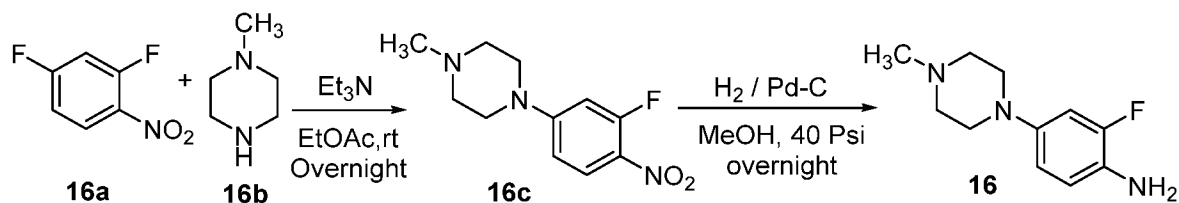
Compound **14** was synthesized using the procedures reported in Int. Pat. App. Publication No. WO 2014012360 and Tsou et al., *J. Med. Chem.* 51(12): 3507-3525 (2008).



10

Compound **15** was synthesized using the procedures reported in Int. Pat. App. Publication No. WO 2014012360 and Tsou et al., *J. Med. Chem.* 51(12): 3507-3525 (2008).

Synthesis of 2-fluoro-4-((4-methylpiperazin-1-yl)aniline) (**16**):



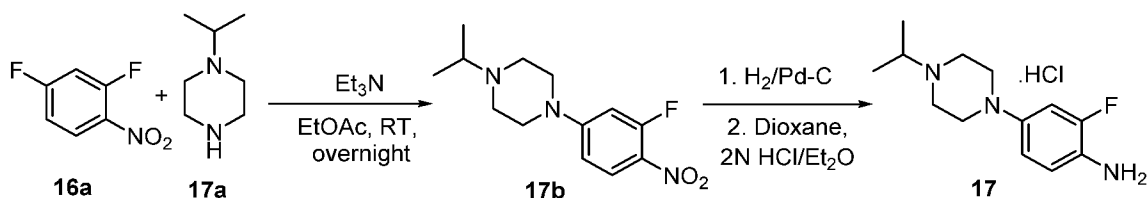
15

Step 1: Synthesis of **16c**: To a solution of **16a** (1.4 g, 13.9 mmol) and Et₃N (1.4 g, 13.9 mmol) in EtOAc (15 mL) was added 1,3-difluoro-4-nitrobenzene **16a** (2 g, 12.6 mmol) dropwise with stirring and the mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (100

mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the title compound **16c** as a yellow solid (3.0 g, quantitative). This product is used as such in the next step.

- 5 Step 2: Synthesis of **16**: To a solution of Compound **16c** (3 g, 12.9 mmol) in methanol (100 mL) was added catalytic amount of 10% Pd/C-50% wet (2 g). The mixture was hydrogenated on a Parr apparatus at 35–40 psi for 3 h at RT. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **16** as a solid (2.4 g, 78% yield). MS(ESI) m/z 210.2 $[\text{M}+\text{H}]^+$. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 6.71 (dd, $J = 10.7, 2.5$ Hz, 1H), 6.65–6.61 (m, 2H), 4.53 (s, 2H), 2.80 (s, 4H), 2.52–2.49 (m, 2H), 2.23 (s, 3H).
- 10

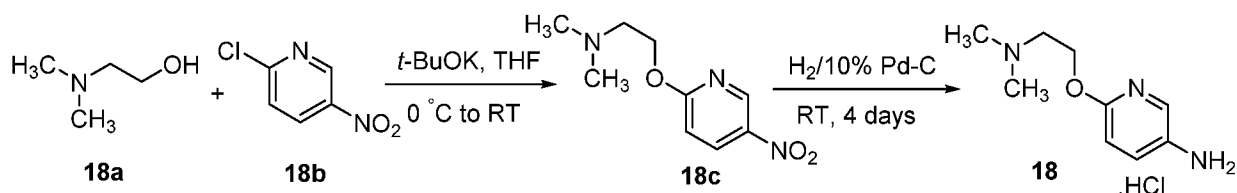
Synthesis of 2-fluoro-4-(4-isopropylpiperazin-1-yl)aniline hydrochloride (**17**):



- Step 1: Synthesis of **17b**: Prepared according to the procedure described for compound **16c** (quantitative yield).
- 15

- Step 1: Synthesis of **17**: 30 g (112 mmol) of **17b** was hydrogenated following the procedure described for the preparation of compound **16**. The resultant crude amine was dissolved in dioxane and treated with 2 *N* HCl in Et_2O . After stirring for 1 h at RT, the solid is filtered and dried to give 12 g (34%) of **17** as white solid. MS(ESI) m/z 238.2 $[\text{M}+\text{H}]^+$. ^1H NMR (600 MHz, $\text{Chloroform}-d$) δ 6.74 (dt, $J = 10.2, 1.6$ Hz, 1H), 6.63 (dd, $J = 6.9, 1.6$ Hz, 2H), 3.78 (s, 2H), 2.93 (s, 4H), 2.67 (s, 3H), 1.09 (d, $J = 6.6$ Hz, 6H).
- 20

Synthesis of 6-(2-(dimethylamino)ethoxy)pyridin-3-amine (**18**):



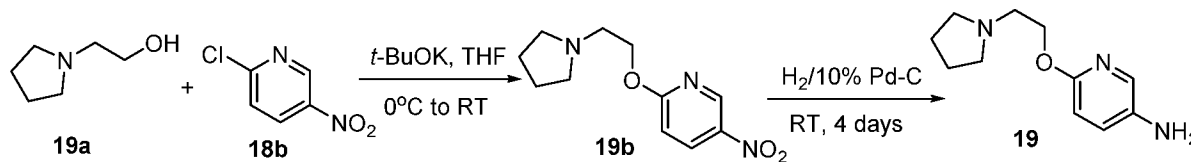
- Step 1: Synthesis of **18c**: To a solution of 2-(dimethylamino)ethanol **18a** (18.55 g, 208 mmol) in THF (200 mL) was added potassium tert-butoxide (18.6 g, 166.6 mmol) portion wise at 0 °C. After
- 25

stirring at room temperature for 1.5 h, 2-chloro-5-nitropyridine **18b** (29.8 g, 187.2 mmol) was added in portion wise 0 °C. The reaction was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated under reduced pressure, diluted with water (250 mL), and then extracted with Dichloromethane (3 × 250 mL). The organic extracts were combined, washed with water, brine, dried over (Na₂SO₄) and concentrated to afford crude material which was further purified by column chromatography on silica gel using 0–7% methanol/methylene chloride to give 2-(5-nitropyridin-2-yloxy)-N, N-dimethylethanamine **18** as a light-yellow solid (20 g, 58%, purity 80%). MS(ESI) m/z 212.2 (M+H)⁺.

Step 1: Synthesis of **18**: To a solution of Compound **18c** (20 g, 96.1 mmol) in a 1:2 mixture (200 mL) of ethanol and ethyl acetate, catalytic amount of 10% palladium on carbon-50% H₂O (10 g) was added carefully under an argon atmosphere. The flask was flushed three times with hydrogen (standard hydrogenation procedure) and then stirred at room temperature under a hydrogen atmosphere (balloon of H₂ was connected) for 4 days. The reaction mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to afford the crude product (15 g) as a brown oil. Purification by column chromatography on silica gel using 0–20%percent methanol/methylene chloride (containing 0.25% NH₃ in MeOH) gave 2-(dimethylamino)ethoxy]pyridin-3-amine **18** as a syrup (5.3 g, 31%). MS(ESI) m/z 182.2 [M+H]⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.01 (s, 2H), 8.31 (d, *J* = 2.5 Hz, 1H), 7.86 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 4.72–4.60 (m, 2H), 3.56–3.46 (m, 2H), 2.82 (d, *J* = 4.0 Hz, 6H).

LC-MS of this compound showed two peaks. 6-[2-(dimethylamino)ethoxy]pyridin-3-amine was converted to di-Boc derivative using standard reaction conditions. Purification by column chromatography on silica gel using 0–4%percent methanol/methylene chloride and then di de-Boc with methanolic hydrochloride gave ~3 g of 6[2-(dimethylamino)ethoxy]pyridin-3-amine hydrochloride salt **18**.

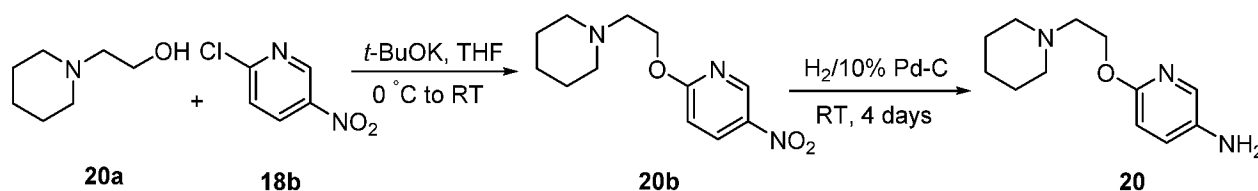
Synthesis of 6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-3-amine (**19**)



Step 1: Synthesis of **19b**: Prepared according to the procedure described for compound **18c** (16 g, 32% yield). MS(ESI) m/z 238.2 $[M+H]^+$.

Step 1: Synthesis of **19**: Prepared according to the procedure described for compound of **18** (4 g, 29% yield). MS(ESI) m/z 208.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.63 (d, J = 2.9 Hz, 1H), 7.02 (dd, J = 8.7, 3.0 Hz, 1H), 6.63 (d, J = 8.7 Hz, 1H), 4.36 (t, J = 5.9 Hz, 2H), 3.35 (s, 2H), 2.88 (t, J = 5.9 Hz, 2H), 2.68–2.53 (m, 4H), 1.81 (p, J = 3.2 Hz, 4H).

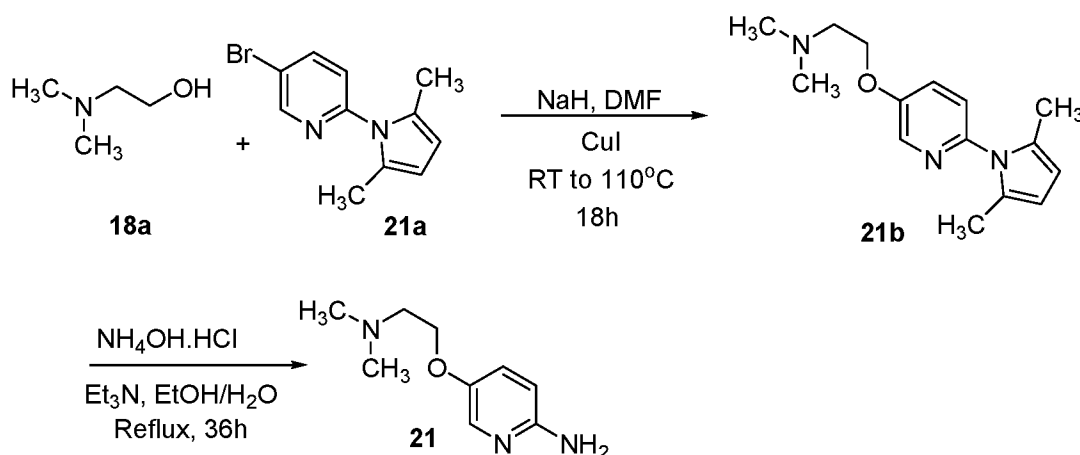
Synthesis of 6-(2-(piperidin-1-yl)ethoxy)pyridin-3-amine (**20**)



Step 1: Synthesis of **20b**: Prepared according to the procedure described for compound **18c** (18 g, 34% yield). MS(ESI) m/z 252.2 $[M+H]^+$

Step 1: Synthesis of **20**: Prepared according to the procedure described for compound **18c** (8 g, 51% yield). MS(ESI) m/z 222.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.64 (d, J = 2.9 Hz, 1H), 7.01 (dd, J = 8.7, 2.9 Hz, 1H), 6.61 (d, J = 8.7 Hz, 1H), 4.34 (t, J = 6.1 Hz, 2H), 3.36 (s, 2H), 2.73 (t, J = 6.1 Hz, 2H), 2.49 (s, 4H), 1.60 (p, J = 5.6 Hz, 4H), 1.49–1.38 (m, 2H).

Synthesis of 5-(2-(dimethylamino)ethoxy)pyridin-2-amine (**21**):

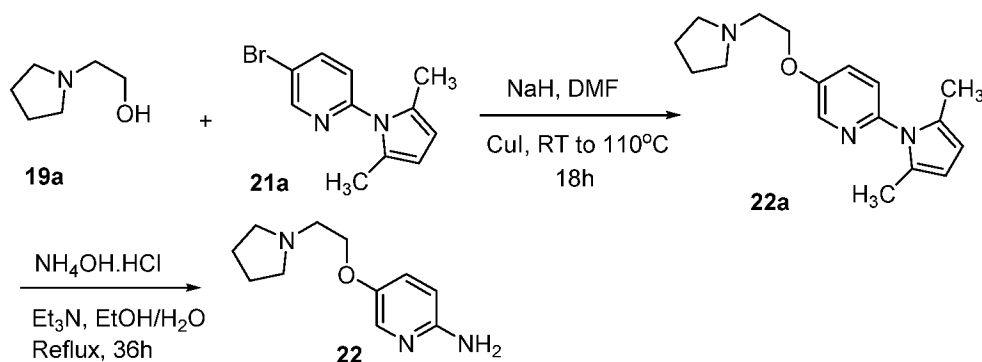


Step 1: Synthesis of **21b**: To a solution of 2-(dimethylamino)ethanol **18a** (68.8 g, 772 mmol) in DMF (400 mL) was added sodium hydride (60% dispersion in mineral oil) (18.5 g, 454.1 mmol) portion wise at 0 °C. The mixture was stirred at room temperature for 1.5 h, cooled to 0 °C again,

CuI (7.35 g, 38.6 mmol) and 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-bromo-pyridine **21a** (55 g, 219.0 mmol) were added. The reaction mixture was stirred at 110 °C for overnight. The Reaction mixture was cooled to RT and the solids were filtered over Celite and the filtrate was diluted with water (1.5 lit.) and extracted five times (4 × 200 mL) with dichloromethane. The combined organic phases were washed with 10% aqueous NH₄OH solution, dried with Na₂SO₄ and concentrated under reduced pressure to yield the crude product which was purified by flash chromatography (silica gel, 0–5% methanol/dichloromethane) to afford the desired product **21b** (45 g, 64%, purity: 70–80%). MS(ESI) m/z 260.3 [M+H]⁺.

Step 2: Synthesis of **21**: A mixture of **21b** (45 g, 179.2 mmol), hydroxylamine hydrochloride (78.17 g, 1.12 mol), triethylamine (47.11 mL, 335.3 mmol), ethanol (350 mL) and water (150 mL) was refluxed for 36 h. The solution was cooled to RT and the solvent was removed under reduced pressure. The pH was adjusted to 9–10 with 6 M NaOH solution and the resulting mixture was extracted (4 × 200 mL) with dichloromethane. The combined organic phases were dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The oily residue was purified by column chromatography on silica gel (gradient elution: dichloromethane/methanol) to give 5-(2-(dimethylamino)ethoxy)pyridin-2-amine **21** (6 g, 19%). MS(ESI) m/z 182.2 [M+H]⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 2.9 Hz, 1H), 7.12 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.47 (d, *J* = 8.8 Hz, 1H), 4.21 (bs, 2H), 4.01 (t, *J* = 5.7 Hz, 2H), 2.70 (t, *J* = 5.7 Hz, 2H), 2.33 (s, 6H).

Synthesis of 5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-amine (**22**):

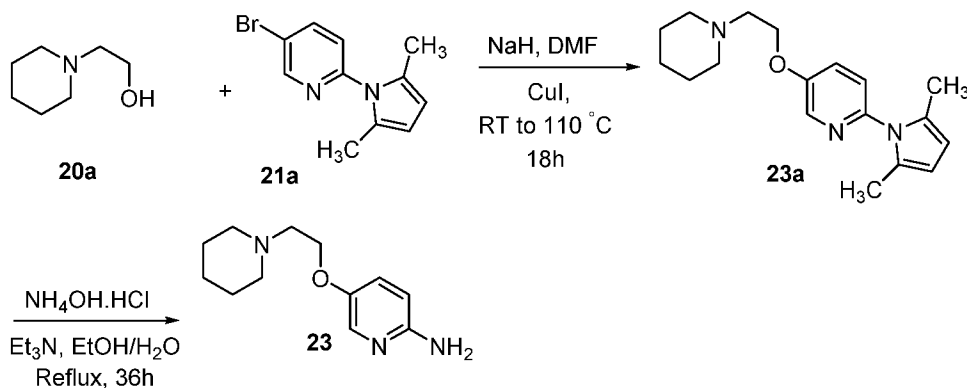


Step 1: Synthesis of **22a**: Prepared according to the procedure described for compound **21b** (2 g, 67%).

Step 2: Synthesis of **22**: Prepared according to the procedure described for compound **21** (6 g, 33% yield). MS(ESI) m/z 208.2 [M+H]⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 2.9 Hz,

1H), 7.12 (dd, $J = 8.8, 2.9$ Hz, 1H), 6.47 (d, $J = 8.8$ Hz, 1H), 4.23 (s, 2H), 4.05 (t, $J = 5.9$ Hz, 2H), 2.86 (t, $J = 5.9$ Hz, 2H), 2.66–2.57 (m, 4H), 1.81 (p, $J = 3.1$ Hz, 4H).

Synthesis of 5-(2-(piperidin-1-yl)ethoxy)pyridin-2-amine (**23**):



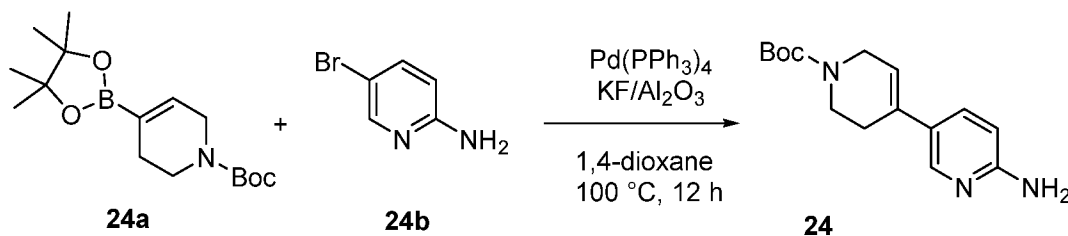
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Step 1: Synthesis of **23a**: Prepared according to the procedure described for compound **21b** (45 g, 81% yield).

Step 1: Synthesis of **23**: Prepared according to the procedure described for compound **21** (8.5 g, 38% yield). MS(ESI) m/z 222.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.78 (d, $J = 2.9$ Hz, 1H), 7.10 (dd, $J = 8.8, 2.9$ Hz, 1H), 6.46 (d, $J = 8.8$ Hz, 1H), 4.25 (s, 2H), 4.04 (t, $J = 6.0$ Hz, 2H), 2.72 (t, $J = 6.0$ Hz, 2H), 2.48 (s, 4H), 1.60 (p, $J = 5.6$ Hz, 4H), 1.50–1.38 (m, 2H).

10

Synthesis of tert-butyl 6-amino-3',6'-dihydro-[3,4'-bipyridine]-1'-(2'H)-carboxylate (**24**):



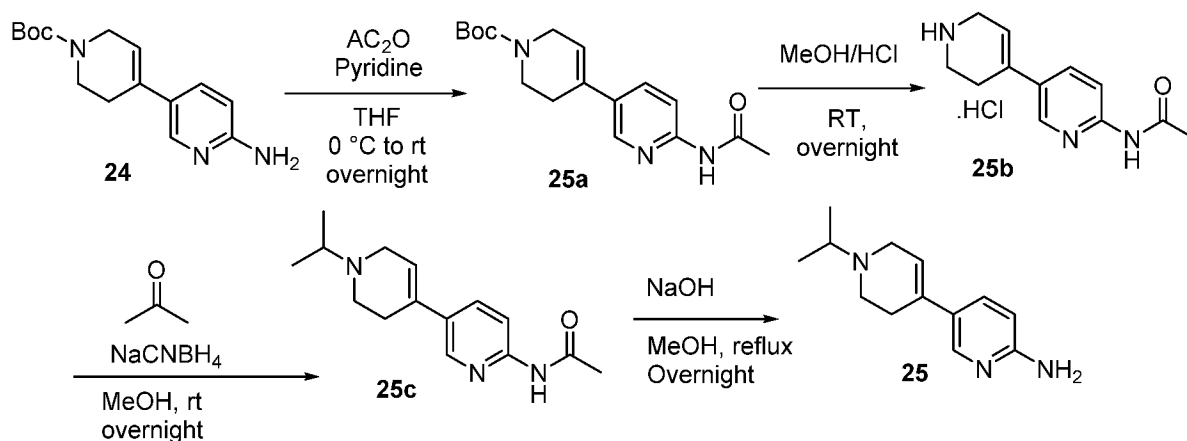
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Step 1: Synthesis of **24**: To a mixture of 5-bromo-2-aminopyridine **24b** (100 g, 0.578 mol) and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tertbutylester **24a** (121.3 g, 0.578 mol) in 1,4-dioxane (2L) were added $Pd(PPh_3)_4$ (10 g) and KF/Al_2O_3 (200 g, 1:1 ratio). The mixture was degassed for 0.5 h and then heated at 100 °C for 12 h under argon. The reaction mixture was concentrated, and the crude was diluted with EtOAc (2 L), filtered through a pad of Celite, and the filter cake was rinsed with EtOAc (2 $\times$ 250 mL). The combined filtrates were dried over Na_2SO_4 , filtered, and concentrated in vacuo. Purification by SiO_2 column chromatography (EtOAc/n-hexanes) provided **24** (35 g, 22% yield) as a brownish

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solid. MS(ESI) m/z 276.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 8.08 (s, 1H), 7.47 (dd, J = 8.6, 2.3 Hz, 1H), 6.48 (d, J = 8.6 Hz, 1H), 5.90 (s, 1H), 4.54 (s, 2H), 4.05 (s, 2H), 3.68–3.53 (m, 2H), 2.45 (s, 2H), 1.49 (s, 9H).

5 Synthesis of 1'-isopropyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-amine (**25**):



Step 1: Synthesis of **25a**: To a solution of tert-butyl 6-amino-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate **24** (10 g, 36.2 mmol) and 5 mL pyridine in THF (100 mL) was added acetic anhydride (4.4 g, 43.6 mmol) dropwise at 0 °C. The mixture was stirred at room temperature for overnight. The solvent was removed, reaction mixture partitioned between water (50 mL) and dichloromethane (100 mL). The two layers were separated, and the aqueous layer further extracted with dichloromethane (2 × 100 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated to give the crude material as a brown syrup. Purification by column chromatography on silica gel using 0–3% methanol/methylene chloride yielded **25a** as a light-yellow solid (9.1 g, purity 80%). MS(ESI) m/z 318.2 $[M+H]^+$.

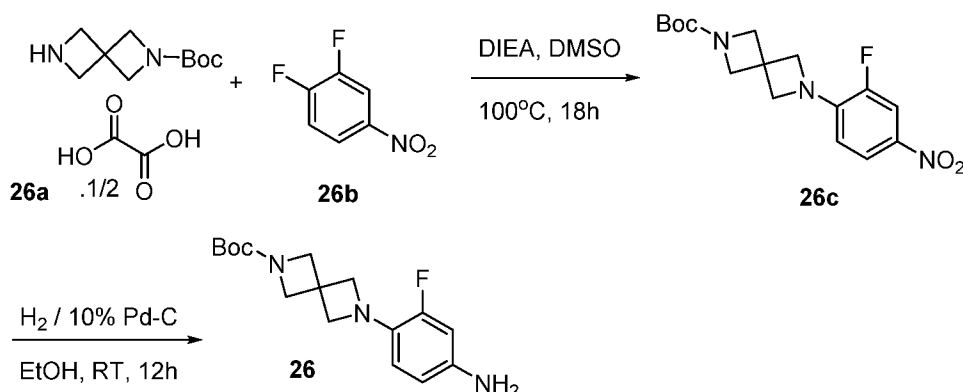
Step 2: Synthesis of **25b**: tert-butyl 6-acetamido-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-carboxylate **25a** (9.12 g, 14.3 mmol) was dissolved in 3 N methanolic hydrochloride (200 mL) and stirred for overnight. The reaction mixture was concentrated to afford crude N-(1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)acetamide hydrochloride salt, **25b** (8.2 g).

Step 3: Synthesis of **25c**: A solution of N-(1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl) acetamide hydrochloride **25b** (4.0 g, 15.8 mmol) in 50 mL of methanol was added to a mixture of acetone (2 mL) and sodium cyanoborohydride (3.92 g, 63.2 mmol) and the resultant mixture was stirred at room temperature for overnight. The reaction mixture was concentrated and evaporated to

dryness. The residue was partitioned between dichloromethane (100 mL) and saturated sodium bicarbonate (50 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (4 × 100 mL). The organic phases were combined and washed with brine, dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (dichloromethane: methanol = 95: 5, v/v) to afford of **25c** as a light-yellow syrup (2.1 g, 53% yield).

Step 4: Synthesis of **25**: To a solution of compound **25c** (1.8 g, 6.9 mmol) in MeOH (100 mL), NaOH (2.78 g, 69 mmol) was added and the resultant mixture was stirred at reflux temperature for 18 h. The standard work-up and chromatography purification (see Preston et al., *Dalton Transactions*, 45(19): 8050-8060 (2016)) afforded compound **25** (0.888g, 60%) as a light-yellow solid. MS(ESI) m/z 218.2 [M+H]⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 7.95 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 6.40 (d, *J* = 8.6 Hz, 1H), 5.93 (s, 1H), 5.89 (s, 2H), 3.09 (s, 2H), 2.77–2.65 (m, 1H), 2.65–2.54 (m, 2H), 2.35 (s, 2H), 1.01 (d, *J* = 6.4 Hz, 6H).

Synthesis of tert-butyl 6-(4-amino-2-fluorophenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (**26**):

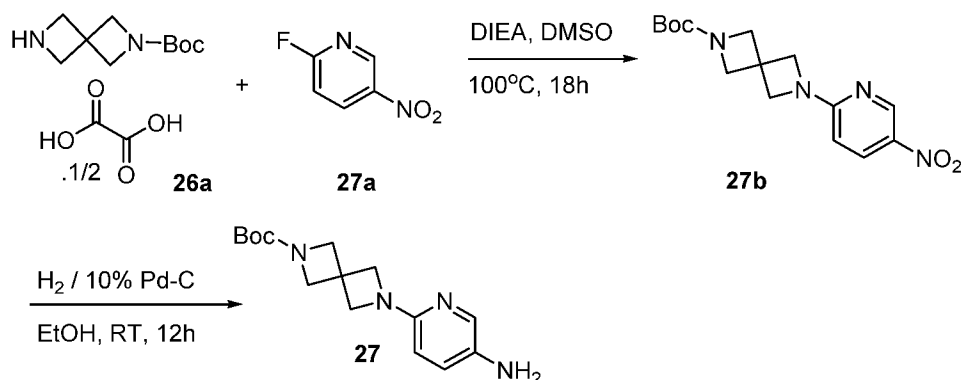


Step 1: Synthesis of **26c**: To a mixture of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate hemioxalate **26a** (1.5 g, 6.17 mmol) and DIEA (3.3 mL, 19 mmol) in DMSO (15 mL) was added 1,3-difluoro-4-nitrobenzene **26b** (1 g, 6.3 mmol) dropwise over a period of 5 minutes. The resultant reaction mixture was stirred at 100 °C for 18 h and then cooled to room temperature. The reaction mixture was and then poured into H₂O (100 mL) and extracted with EtOAc (3 × 50 mL). Th combined organic layer was washed with water (2 × 25 mL), brine (1 × 25 mL), dried (Na₂SO₄) and concentrated to afford the product **26c** as a yellow solid (~1.8 g) which was used as such for the next step.

Step 2: Synthesis of **26**: The Parr-hydrogenator flask (500 mL) was charged with nitro compound **26c** (1.8 g, 5.6 mmol) and ethanol (100 mL). A 10% Pd-C (1 g, 50% H₂O) was introduced carefully

under argon. The resultant mixture was hydrogenated at ~33 Psi 12 h at RT. The reaction mixture was filtered through pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to afford the title product **26** as a gray solid (1.36 g 72% yield). MS(ESI) m/z 308.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.43–6.29 (m, 3H), 4.07 (s, 4H), 3.92 (d, J = 1.5 Hz, 4H), 1.44 (s, 9H).

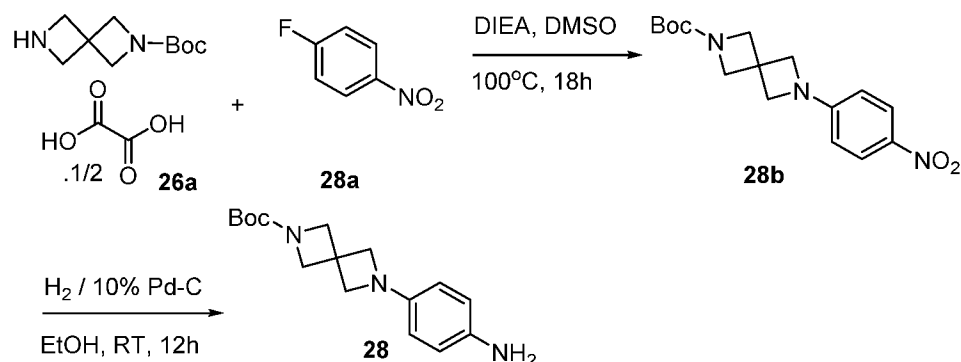
Synthesis of tert-butyl 6-(5-aminopyridin-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (**27**):



Step 1: Synthesis of **27b**: Prepared according to the procedure described for compound **26c**.

Step 2: Synthesis of **27**: Prepared according to the procedure described for compound **26** (1.36 g, 76% yield). MS(ESI) m/z 291.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.73 (d, J = 2.6 Hz, 1H), 6.97 (dd, J = 8.6, 2.7 Hz, 1H), 6.24 (d, J = 8.6 Hz, 1H), 4.08 (s, 4H), 4.02 (s, 4H), 1.44 (s, 9H).

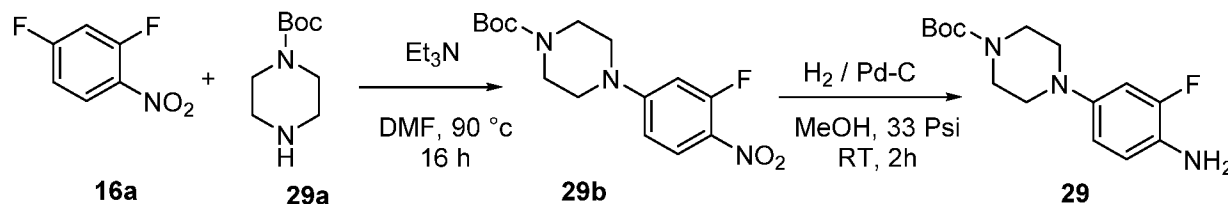
Synthesis of tert-butyl 6-(4-aminophenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (**28**):



Step 1: Synthesis of **28b**: Prepared according to the procedure described for compound **26c**.

Step 2: Synthesis of **28**: Prepared according to the procedure described for compound **26** (7.12 g, 98% yield). MS(ESI) m/z 290.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.63 (d, J = 8.5 Hz, 2H), 6.35 (d, J = 8.5 Hz, 2H), 3.33 (s, 2H), 4.06 (s, 4H), 1.44 (s, 9H).

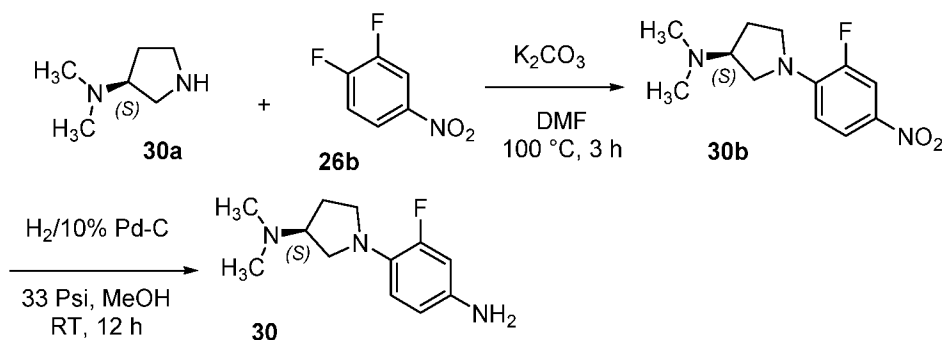
5 Synthesis of tert-butyl 4-(4-amino-3-fluorophenyl)piperazine-1-carboxylate (**29**):



Step 1: Synthesis of **29b**: (Ref: US 20090093497): A mixture of 2,4-difluoro-nitro-benzene **16a** (20 g, 126 mmol), piperazine-1-carboxylic acid tert-butyl ester **29a** (23.4 g, 126 mmol), and triethylamine (63 mL, 378 mmol) in anhydrous DMF (200 mL) was stirred at 90 °C for 16 h. The reaction mixture was partitioned between water and ethyl acetate, layers were separated, and the aqueous layer was extracted with ethyl acetate twice. Organic layers were collected, combined, washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica-gel column with ethyl acetate and hexanes as eluting solvents to give the product **29b** as a light-yellow solid (25.1 g, 62% yield). MS(ESI) m/z 326.1 $[M+H]^+$.

Synthesis of **29**: (Ref: WO 2015038417): The solution of compound **29b** (25g, 89.2 mmol) in Methanol (300 mL) in the presence of 10% palladium on carbon (12.5 g, 50% wet) was shaken under the hydrogen with a pressure of 33 psi at room temperature for 12 hr. The reaction mixture was filtered through a plug of Celite and the filtration pad was washed with methanol. The organic layer was collected, concentrated, and dried to give compound **29** (26g, 99%) as a light red gummy material, which was used as such without further purification. MS(ESI) m/z 296.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.74–6.70 (m, 1H), 6.66–6.63 (m, 1H), 6.59–6.55 (m, 1H), 3.56 (t, J = 5.1 Hz, 4H), 2.96 (d, J = 5.6 Hz, 4H), 1.48 (s, 9H).

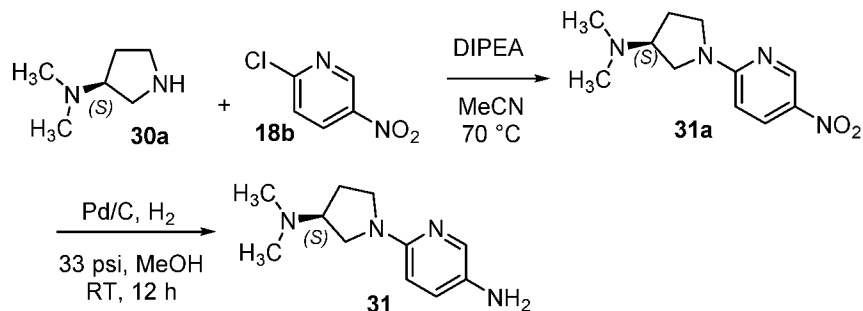
Synthesis of (*S*)-1-(4-amino-2-fluorophenyl)-*N,N*-dimethylpyrrolidin-3-amine (**30**):



Step 1: Synthesis of **30b**: (Ref: WO 2015038417): To a stirred mixture of compound **30a** (2.0 g, 16.9 mmol) in DMF (50 mL) at room temperature were added **26b** (3.0 g, 18.9 mmol) and K_2CO_3 (13.1 g, 94.5 mmol). The resulting mixture was stirred at $110\text{ }^\circ\text{C}$ for 16 h. After cooling down to room temperature, the reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 × 150 mL). The organic layer was washed with brine solution (50 mL), dried (Na_2SO_4), and concentrated to provide crude residue. The crude was triturated with n-hexane and filtered to give compound **30b** as a yellow solid (3.8 g, 80% yield). MS(ESI) m/z 254.2 $[M+H]^+$.

Step 2: Synthesis of **30**: (Ref: WO 2015038417): The solution of compound **30b** (3.75 g 15 mmol) in Methanol (200 mL) in the presence of 10% palladium on carbon (2 g, 50% H_2O) was shaken under the hydrogen with a pressure of 33 psi at room temperature for 12 hr. The reaction mixture was filtered through a plug of Celite and the filtration pad was washed with methanol. The organic layer was collected, concentrated, and dried to give compound **30** (3.2g, 96%) as a light red solid, which was directly used in the next step reaction without further purification. MS(ESI) m/z 224.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.62–6.52 (m, 1H), 6.49–6.34 (m, 2H), 3.49–3.31 (m, 4H), 3.31–3.18 (m, 1H), 3.18–3.09 (m, 1H), 2.83 (p, $J = 7.6$ Hz, 1H), 2.28 (s, 6H), 2.21–2.07 (m, 1H), 1.92–1.80 (m, 1H).

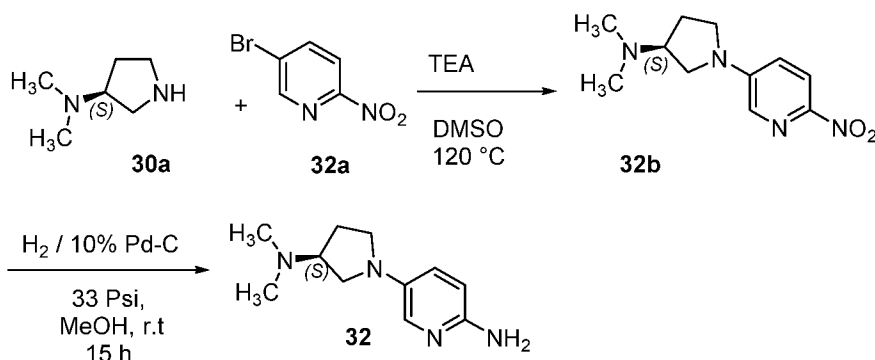
Synthesis of (*S*)-6-(3-(dimethylamino)pyrrolidin-1-yl)pyridin-3-amine (**31**):



Step 1: Synthesis of **31a**: (Ref: WO 20050261307): To a stirred mixture of compound **30a** (1.5 g, 12.5 mmol) in MeCN (25 mL) at room temperature, nitro compound **18b** (1.8 g, 11.4 mmol) and diisopropylethylamine (4 mL, 23 mmol) were added and stirred at 70 °C for overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (150 mL) and then washed with H₂O (2 × 30 mL), brine, dried over sodium sulfate and concentrated to give **31a** as yellow solid (2.3 g, 85% yield). MS(ESI) m/z 237.2 [M+H]⁺.

Step 2: Synthesis of **31**: Prepared according to the procedure described for compound **30** (1.85 g, 92%). MS(ESI) m/z 207.2 [M+H]⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 7.60 (d, *J* = 2.6 Hz, 1H), 7.34 (s, 2H), 7.01 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.40 (d, *J* = 8.8 Hz, 1H), 3.85 (q, *J* = 7.4 Hz, 1H), 3.69 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.55–3.47 (m, 2H), 3.24 (q, *J* = 8.5 Hz, 2H), 2.73 (s, 6H), 2.38–2.30 (m, 1H), 2.29–2.20 (m, 1H).

Synthesis of (*S*)-5-(3-(dimethylamino)pyrrolidin-1-yl)pyridin-2-amine (**32**):

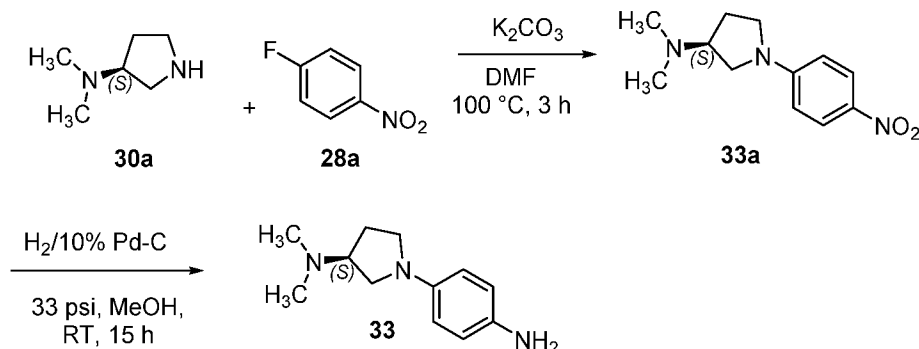


Step 1: Synthesis of **32b**: (Ref: WO 20180072707): To a stirred mixture of compound **30a** (1.5 g, 12.5 mmol) and nitro compound **32a** (1.8 g, 11.4 mmol) in DMSO (15 mL) was added triethylamine (4 mL, 23 mmol) at room temperature and stirred at 120 °C for overnight. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 × 150 mL). The organic layer was washed with brine solution (50 mL), dried (Na₂SO₄), and concentrated to provide crude residue. The crude residue was further purified by silica-gel column using 0–20% MeOH in DCM to give **32b** as yellow solid (3.3 g, 80% yield). MS(ESI) m/z 237.2 [M+H]⁺.

Step 2: Synthesis of **32**: Prepared according to the procedure described for compound **30** (2.8 g, quantitative yield). MS(ESI) m/z 207.2 [M+H]⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 7.48 (d, *J* =

2.9 Hz, 1H), 6.84 (dd, $J = 8.8, 3.0$ Hz, 1H), 6.50 (d, $J = 8.7$ Hz, 1H), 3.43–3.37 (m, 1H), 3.37–3.30 (m, 1H), 3.30–3.24 (m, 1H), 3.10 (t, $J = 8.2$ Hz, 1H), 2.91–2.84 (m, 1H), 2.31 (s, 6H), 2.23–2.15 (m, 1H), 1.97–1.88 (m, 1H).

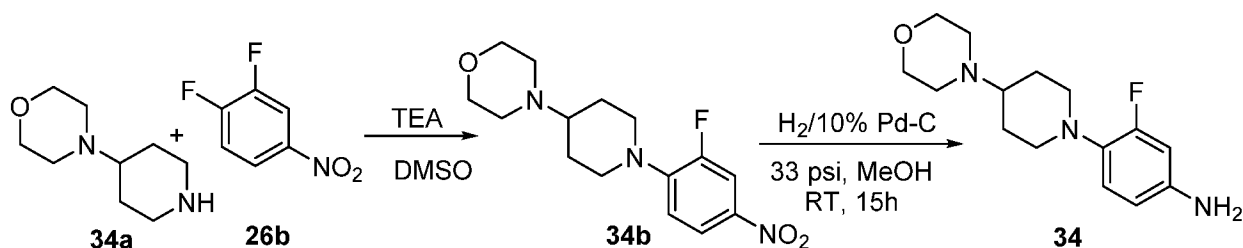
5 Synthesis of (*S*)-1-(4-aminophenyl)-*N,N*-dimethylpyrrolidin-3-amine (**33**):



Step 1: Synthesis of **33a**: Prepared according to the procedure described for compound **30b**. (3.8 g, 81% yield) as yellow solid. MS(ESI) m/z 236.2 $[M+H]^+$.

Step 1: Synthesis of **33**: Prepared according to the procedure described for compound **30** (3.23 g, 99% yield). MS(ESI) m/z 206.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.67 (d, $J = 8.6$ Hz, 2H), 6.45 (d, $J = 8.6$ Hz, 2H), 3.41 (t, $J = 7.9$ Hz, 1H), 3.38–3.23 (m, 2H), 3.09 (t, $J = 8.2$ Hz, 1H), 2.89–2.80 (m, 1H), 2.30 (s, 6H), 2.22–2.13 (m, 1H), 1.97–1.84 (m, 1H).

Synthesis of 3-fluoro-4-(4-morpholinopiperidin-1-yl)aniline (**34**):

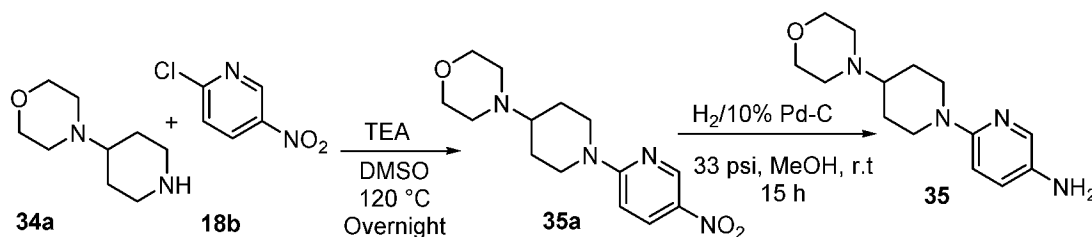


Step 1: Synthesis of **34b**: (Ref: WO 20160400858): To a stirred mixture of compound **34a** (4.0 g, 23.5 mmol) and compound **26b** (3.4 g, 21.4 mmol) in DMSO (20 mL) at room temperature was added triethylamine (9.8 mL, 71 mmol) and stirred at 120 °C for overnight. After TLC showed completion of starting material the mixture was diluted with water (100 mL) and the solid formed

was filtered and dried under vacuum to give the product **34b** (6.3 g, 84% yield) as yellow solid which is used in the next step without further purification. MS(ESI) m/z 310.1 $[M+H]^+$.

Step 1: Synthesis of **34**: (Ref: WO 2015038417): The solution of compound **34b** (6.3 g, 0.4 mmol) in Methanol (mL) in the presence of 10% palladium on carbon was shaken under the hydrogen with a pressure of 50 psi at room temperature for 2 hr. The reaction mixture was filtered through a plug of Celite and the filtration pad was washed with methanol. The organic layer was collected, concentrated, and dried to give compound **34** (4.9g, 86%) as a light red solid, which was directly used in the next step reaction without further purification. MS(ESI) m/z 280.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.80 (t, J = 8.9 Hz, 1H), 6.49–6.34 (m, 2H), 3.77–3.69 (m, 3H), 3.53 (s, 2H), 3.34 (d, J = 11.6 Hz, 2H), 2.67–2.53 (m, 5H), 2.38–2.27 (m, 1H), 1.94–1.85 (m, 2H), 1.81–1.61 (m, 3H).

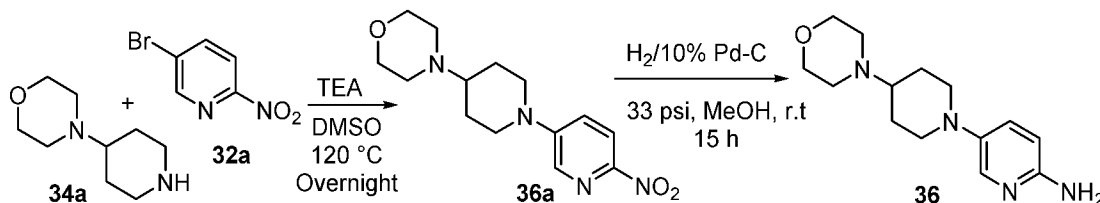
Synthesis of 6-(4-morpholinopiperidin-1-yl)pyridin-3-amine (**35**):



Synthesis of **35a**: Prepared according to the procedure described for compound **34b** (3.6 g, 69% yield). MS(ESI) m/z 293.2 $[M+H]^+$.

Synthesis of **35**: Prepared according to the procedure described for compound **34** (1.25 g, 40% yield). MS(ESI) m/z 263.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.78 (d, J = 2.7 Hz, 1H), 6.97 (dd, J = 8.8, 2.9 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 4.10 (d, J = 12.8 Hz, 2H), 3.75–3.71 (m, 3H), 3.28 (s, 2H), 2.73 (td, J = 12.6, 2.0 Hz, 2H), 2.64–2.51 (m, 4H), 2.41–2.30 (m, 1H), 1.92 (d, J = 12.5 Hz, 2H), 1.64–1.48 (m, 2H).

Synthesis of 5-(4-morpholinopiperidin-1-yl)pyridin-2-amine (**36**):

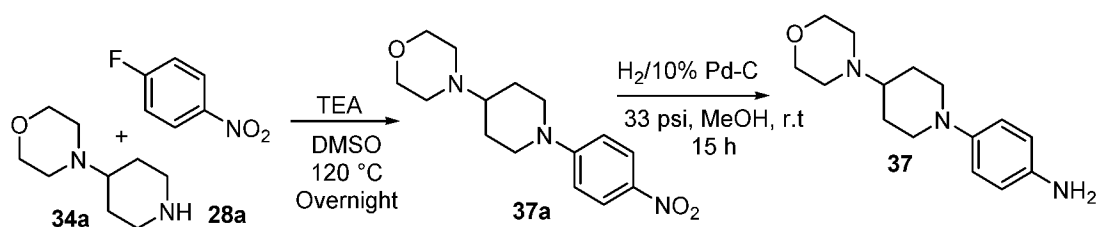


Synthesis of **36a**: Prepared according to the procedure described for compound **34b** (3.5 g, 68% yield). MS(ESI) m/z 293.2 $[M+H]^+$.

- 5 Synthesis of **37**: Prepared according to the procedure described for compound **34** (1.25 g, 40% yield). MS(ESI) m/z 263.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.78 (d, J = 2.8 Hz, 1H), 7.18 (dd, J = 8.8, 2.9 Hz, 1H), 6.47 (d, J = 8.8 Hz, 1H), 3.76–3.72 (m, 5H), 3.47 (d, J = 12.3 Hz, 2H), 2.67–2.61 (m, 2H), 2.61–2.56 (m, 4H), 2.32–2.26 (m, 1H), 1.94 (d, J = 12.5 Hz, 2H), 1.72–1.63 (m, 2H).

10

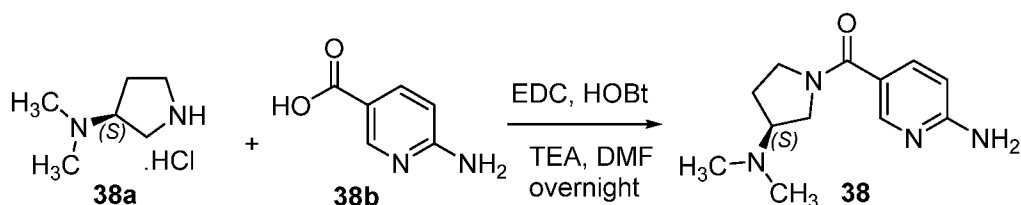
Synthesis of 4-(4-morpholinopiperidin-1-yl)aniline (**37**):



- 15 Synthesis of **37a**: Prepared according to the procedure described for compound **34b** (3.6 g, 70% yield). MS(ESI) m/z 292.2 $[M+H]^+$.

- 20 Synthesis of **37**: Prepared according to the procedure described for compound **34** (1.25 g, 40% yield). MS(ESI) m/z 262.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.86–6.78 (m, 2H), 6.70–6.58 (m, 2H), 3.77–3.68 (m, 3H), 3.52 (d, J = 12.3 Hz, 2H), 3.42 (s, 2H), 2.63–2.60 (m, 1H), 2.60–2.56 (m, 4H), 2.34–2.24 (m, 1H), 1.96–1.88 (m, 2H), 1.77–1.62 (m, 3H).

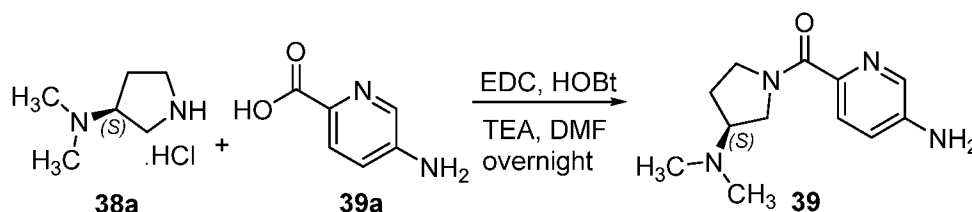
Synthesis of (S)-(6-aminopyridin-3-yl)(3-(dimethylamino)pyrrolidin-1-yl)methanone (**38**):



- 25 Synthesis of **38**: (Ref: WO 2016015605): To a solution of compound **38b** (1.1 g, 8.0 mmol) in DMF (25 mL) were added EDC (1.53 g, 8 mmol), HOBt (1.22 g, 8 mmol) and triethylamine (5.5 mL, 40 mmol). After stirring the mixture for 10 min, compound **38a** (1.5 g, 8 mmol) was added.

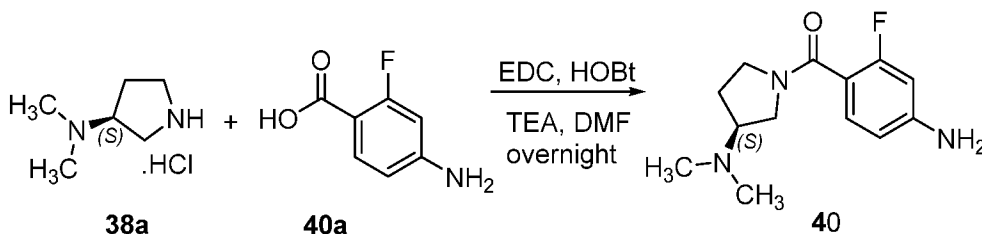
The resulting mixture was stirred at room temperature for overnight. The reaction mixture was concentrated in vacuo and the residue was purified by silica-gel chromatography using 0–10% MeOH in DCM to give **38** as a light-yellow solid (0.61 g, 34% yield). MS(ESI) m/z 235.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 8.31 (s, 1H), 7.74–7.63 (m, 1H), 6.49 (d, J = 8.5 Hz, 1H), 4.81 (s, 2H), 3.82–3.54 (m, 2H), 3.45–3.37 (m, 1H), 2.79–2.61 (m, 1H), 2.26 (d, J = 40.6 Hz, 6H), 2.20–2.05 (m, 2H), 1.88–1.79 (m, 1H).

Synthesis of (S)-(5-aminopyridin-2-yl)(3-(dimethylamino)pyrrolidin-1-yl)methanone (**39**):



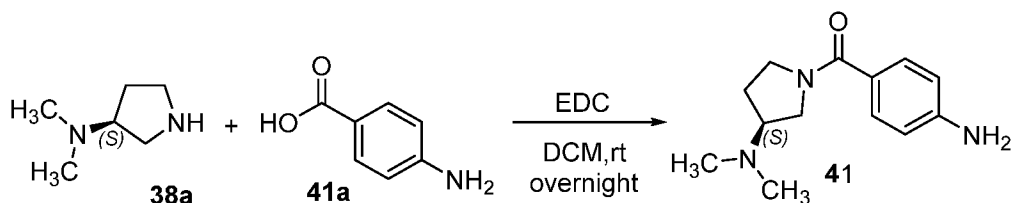
Synthesis of **39**: Prepared according to the procedure described for compound **38** (0.95 g, 50% yield). MS(ESI) m/z 235.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 8.00 (dd, J = 11.5, 2.7 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.00 (dd, J = 8.5, 2.7 Hz, 1H), 4.14–4.10 (m, 0.5H), 4.05–4.00 (m, 0.5H), 3.98 (d, J = 12.2 Hz, 2H), 3.91–3.83 (m, 1H), 3.65–3.59 (m, 1H), 3.45–3.38 (m, 1H), 2.76–2.67 (m, 1H), 2.30 (s, 3H), 2.26 (s, 3H), 2.16–2.08 (m, 1H), 1.87–1.74 (m, 3H).

Synthesis of (S)-(4-amino-2-fluorophenyl)(3-(dimethylamino)pyrrolidin-1-yl)methanone (**40**):



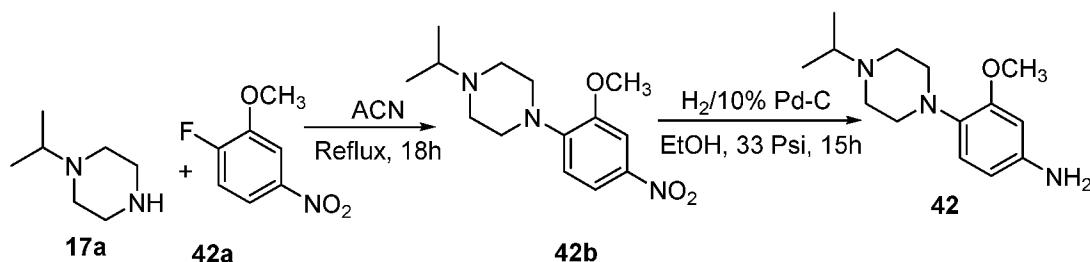
Synthesis of **40**: Prepared according to the procedure described for compound **38** (1.0 g, 50% yield). MS(ESI) m/z 252.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.22–7.15 (m, 1H), 6.46–6.40 (m, 1H), 6.35–6.28 (m, 1H), 4.15 (d, J = 14.1 Hz, 2H), 3.94–3.86 (m, 0.5H), 3.84–3.75 (m, 0.5H), 3.63–3.40 (m, 2H), 3.40–3.33 (m, 0.5H), 3.33–3.24 (m, 0.5H), 2.81–2.71 (m, 0.5H), 2.72–2.64 (m, 0.5H), 2.28 (s, 3H), 2.21 (s, 3H), 2.19–2.12 (m, 0.5H), 2.10–2.02 (m, 0.5H), 1.87–1.73 (m, 1H).

Synthesis of (S)-(4-aminophenyl)(3-(dimethylamino)pyrrolidin-1-yl)methanone (**41**):



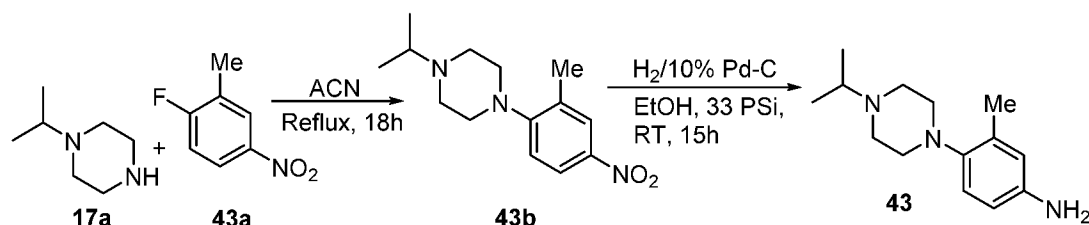
Synthesis of **41**: Prepared according to the procedure described for compound **38** (0.63 g, 45% yield). MS(ESI) m/z 234.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.39 (d, J = 8.0 Hz, 2H), 6.64 (d, J = 8.3 Hz, 2H), 3.89 (s, 3H), 3.83–3.50 (m, 3H), 3.45–3.30 (m, 1H), 2.68 (d, J = 68.0 Hz, 1H), 2.26 (d, J = 44.2 Hz, 6H), 1.83–1.77 (m, 1H).

Synthesis of 4-(4-isopropylpiperazin-1-yl)-3-methoxyaniline (**42**):



Following the above scheme, the title compound **42** (4.75 g, 64% for two steps) was synthesized. MS(ESI) m/z 250.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.78 (d, J = 8.2 Hz, 1H), 6.31–6.15 (m, 2H), 3.81 (s, 3H), 3.48 (s, 2H), 3.01 (s, 4H), 2.81–2.65 (m, 5H), 1.10 (d, J = 6.5 Hz, 6H).

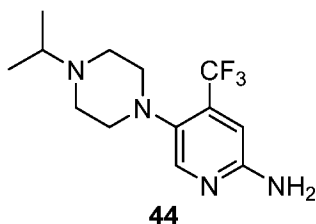
Synthesis of 4-(4-isopropylpiperazin-1-yl)-3-methylaniline (**43**):



Following the scheme, the title compound **43**, (4.46 g, 64% for two steps), was synthesized. MS(ESI) m/z 234.3 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.89 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 2.6 Hz, 1H), 6.50 (dd, J = 8.3, 2.7 Hz, 1H), 3.44 (s, 2H), 2.91–2.81 (m, 4H), 2.75–2.67 (m, 2H), 2.65 (s, 3H), 2.23 (s, 3H), 1.09 (d, J = 6.5 Hz, 6H).

The amines **44**, **45**, and **46** were prepared by following the reported methods. See Walia et al., *J. Org. Chem.* 78(21): 10931-10937 (2013).

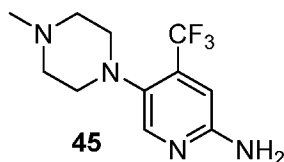
Synthesis of 5-(4-isopropylpiperazin-1-yl)-4-(trifluoromethyl)pyridin-2-amine (**44**):



5

MS(ESI) m/z 289.3 $[M+H]^+$.

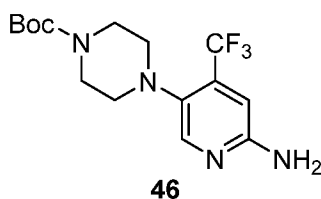
Synthesis of 5-(4-methylpiperazin-1-yl)-4-(trifluoromethyl)pyridin-2-amine (**45**):



10

MS(ESI) m/z 261.3 $[M+H]^+$.

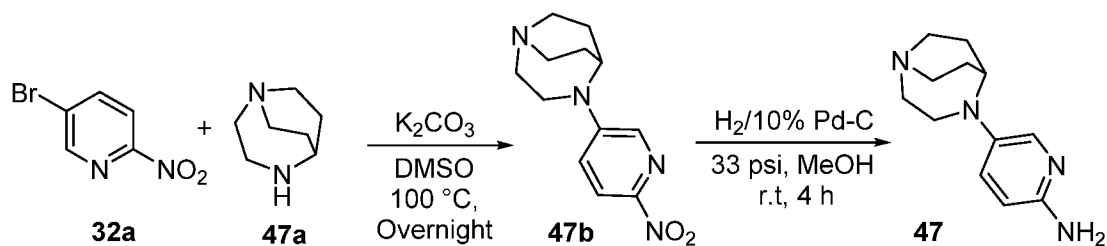
Synthesis of tert-butyl 4-(6-amino-4-(trifluoromethyl)pyridin-3-yl)piperazine-1-carboxylate (**46**):



MS(ESI) m/z 347.3 $[M+H]^+$.

15

Synthesis of 5-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-2-amine (**47**):

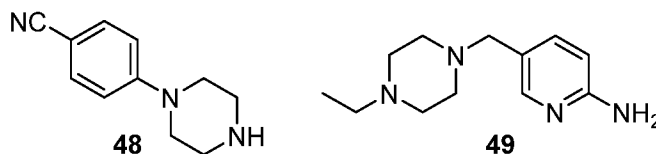


Step 1: Synthesis of **47b**: Prepared according to the procedure described for the preparation of compound **30b** (12 g, 52% yield).

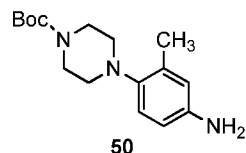
20

Step 2: Synthesis of **47**: Prepared according to the procedure described for the preparation of compound 32 (4 g, 66% yield). MS(ESI) m/z 219.3 [M+H]⁺.

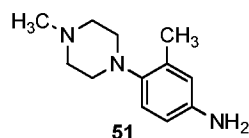
5 Compounds **48** and **49** were purchased from commercial sources:



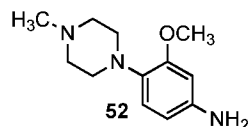
The following amines were synthesized using a reported procedure:



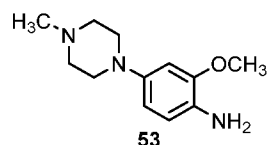
10 Compound **50** was synthesized using procedure reported in WO2001068643.



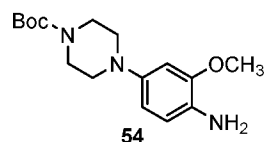
Compound **51** was synthesized using procedure reported in WO2012059932.



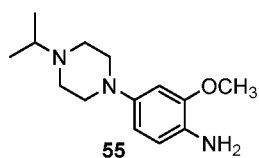
Compound **52** was synthesized using procedure reported in WO2008051547.



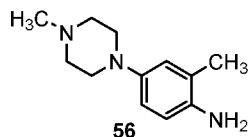
15 Compound **53** was synthesized using procedure reported in WO2017076355 and US20180208564



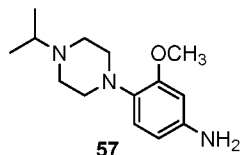
20 Compound **54** was synthesized using procedure reported in WO2017143842 and JMC 2019, 62, 4401-4410



Compound **55** was synthesized using procedure reported in WO2004080980

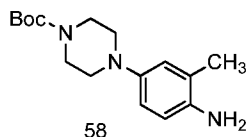


Compound **56** was synthesized using procedure reported in WO2008051547

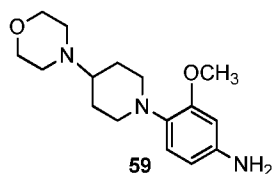


5

Compound **57** was synthesized using procedure reported in WO2005009443

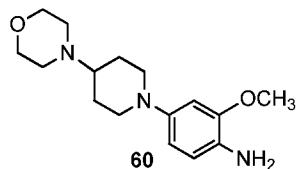


Compound **58** was synthesized using procedure reported in WO2007089768 and WO2006004200

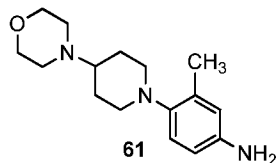


10

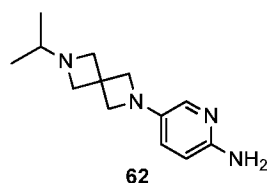
Compound **59** was synthesized using procedure reported in WO2016049211



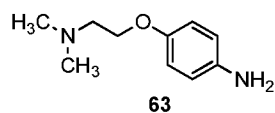
Compound **60** was synthesized using procedure reported in WO2018183112



15 Compound **61** was synthesized using procedure reported in WO2012053606

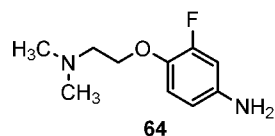


Synthesis of 62: Prepared according to the procedure described for the preparation of compound **91**. MS (ESI) m/z 233.2 $[M+H]^+$.

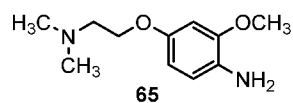


5

Compound **63** was synthesized using procedure reported in WO2008152013

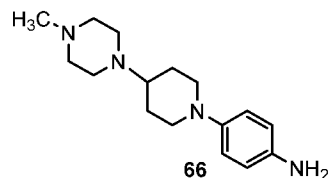


Compound **64** was synthesized using procedure reported in WO2009076140 and BMCL 2015, 23, 1044-1054

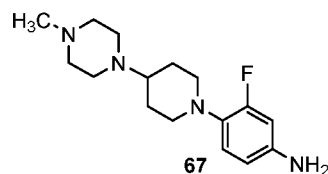


10

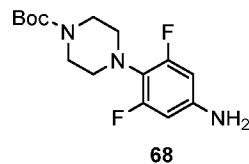
Compound **65** was synthesized using procedure reported in WO2014134308



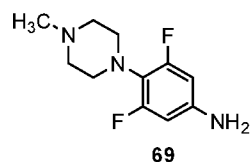
Compound **66** was synthesized using procedure reported in eJMC 2019, 163, 690-709



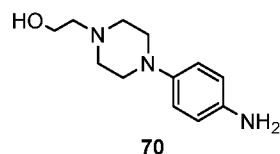
15 Compound **67** was synthesized using procedure reported in WO2012053605



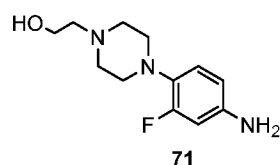
Compound **68** was synthesized using procedure reported in WO20120220572



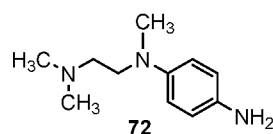
Compound **69** was synthesized using procedure reported in WO2017066428



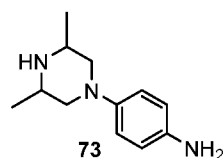
Compound **70** was synthesized using procedure reported in JMC 2005, 48, 2371-2387 and
5 WO2003037872



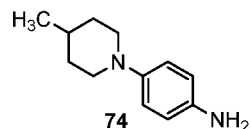
Compound **71** was synthesized using procedure reported in WO2010090764



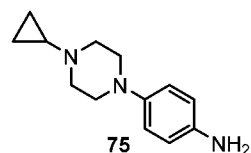
Compound **72** was synthesized using procedure reported in WO2004011438 and
10 WO2008152013



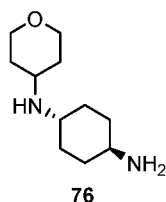
Compound **73** was synthesized using procedure reported in WO2015092431 and JMC 2008,
51, 3507-3525



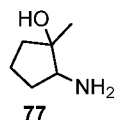
Compound **74** was synthesized using procedure reported in JMC 2012, 55, 10685-10699



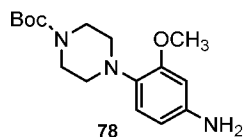
Compound **75** was synthesized using procedure reported in WO2017211216



Compound **76** was synthesized using procedure reported in WO2012058392



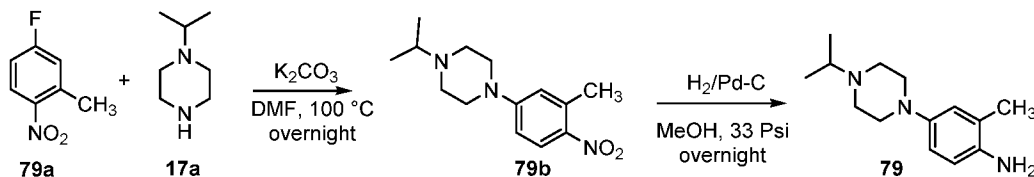
Compound **77** was synthesized using procedure reported in JMC 2016, 59, 750-755



5

Compound **78** was synthesized using procedure reported in Part in WO2009079597 and WO2002010146

Synthesis of 4-4-(isopropylpiperazin-1-yl)-2-methylaniline (79):

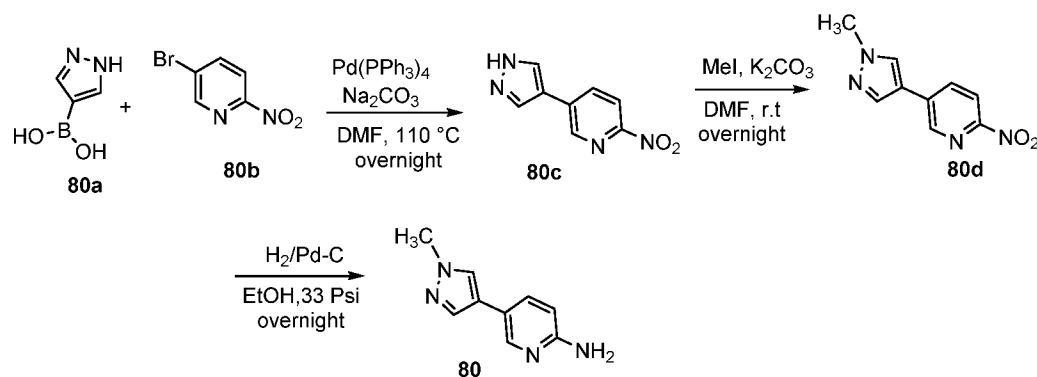


10 **Step1: Synthesis of 79b:** (Part in WO2009079597) To a stirred mixture of compound **79a** (3.6 g, 23.4 mmol) in DMF (25 mL) at room temperature were added **17a** (3.0 g, 23.4 mmol) and K_2CO_3 (9.7 g, 70.2 mmol). The resulting mixture was stirred at 100 °C for overnight. After cooling to room temperature, the reaction mixture was diluted with water (200 mL) and the solid obtained was filtered, washed with water (3 x 25 mL), and dried under vacuum to give

15 compound **79b** as a yellow solid (5.1 g, 75% yield). MS (ESI) m/z 264.2 $[M+H]^+$. This product was used as such in the next step.

Step 2: Synthesis of 79: (Part in WO2002010146) To a solution of compound **79b** (4.5 g, 17.1 mmol) in methanol (200 mL) was added a 10% Pd/C-50% wet (2.3 g). The mixture was hydrogenated on a par apparatus at 33 psi for overnight at RT. The reaction mixture was filtered

20 through a pad of Celite and the filtrate was concentrated to afford **79** as a solid (3.5 g, 88% yield). MS (ESI) m/z 233.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.73 (d, J = 2.8 Hz, 1H), 6.70 (dd, J = 8.4, 2.8 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.74 – 2.66 (m, 5H), 2.17 (s, 2H), 2.16 (s, 3H), 1.09 (d, J = 6.5 Hz, 6H).

Synthesis of 5-(1-methyl-1H-pyrazol-4-yl)pyridine-2-amine (80):**Step1: Synthesis of 80c:** (Part in WO2012082817) To a mixture of compound **80a** (5.0 g, 45

mmol) and compound **80b** (9.1 g, 45 mmol) in DMF (100 mL) was added 2M Na_2CO_3 solution (10 mL) and the reaction mixture was degassed for 5 min and then

tetrakis(triphenylphosphine)palladium(0) (0.52 g, 0.45 mmol) was added at room temperature under Argon. The resulting mixture was stirred at 110°C for overnight. Reaction mixture was cooled and poured onto H_2O (1000 mL). The solid obtained was filtered and washed with

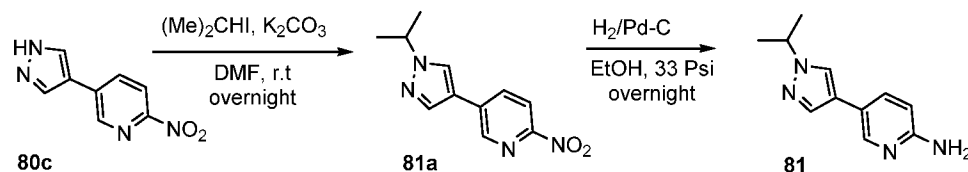
methanol to give compound **80c** as a solid (2.1 g, 25% yield). MS (ESI) m/z 191.2 $[\text{M}+\text{H}]^+$

Step2: Synthesis of 80d: (Part in WO2018124001) To a stirred mixture of compound **80c** (1.0 g, 5.3 mmol) in DMF (20 mL) at room temperature were added MeI (1.5 g, 10.5 mmol) and K_2CO_3 (2.2 g, 16 mmol). The resulting mixture was stirred at room temperature for overnight.

Reaction mixture was cooled and poured onto H_2O (200 mL). The solid obtained was filtered

and dried to give compound **80d** as a solid (0.75 g, 75% yield). MS (ESI) m/z 205.1 $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of 80: (Part in WO2002010146) Following the standard hydrogenation conditions and isolation techniques gave **80** as a solid (240 mg, 38% yield). MS (ESI) m/z 175.1 $[\text{M}+\text{H}]^+$.

Synthesis of 5-(1-isopropyl-1H-pyrazol-4-yl)pyridine-2-amine (81):

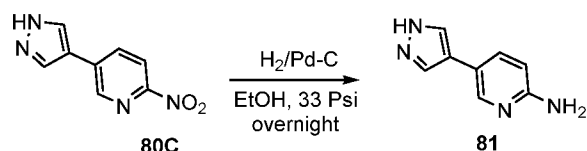
Step 1: Synthesis of 81b: (Part in WO2018124001) To a stirred mixture of compound **80c** (1.0 g, 5.3 mmol) in DMF (20 mL) at room temperature were added $(\text{Me})_2\text{CHI}$ (1.8 g, 10.5 mmol) and K_2CO_3 (2.2 g, 16 mmol). The resulting mixture was stirred at room temperature for overnight. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL).

The organic layer was washed with brine solution (50 mL), dried (Na_2SO_4), and concentrated to provide crude residue. The crude residue was further purified by silica-gel column using 0-20% MeOH in DCM to give **81b** as a solid (0.9 g, 75% yield). MS (ESI) m/z 233.1 $[\text{M}+\text{H}]^+$.

Step 2: Synthesis of 81: (Part in WO2002010146) Following the standard hydrogenation

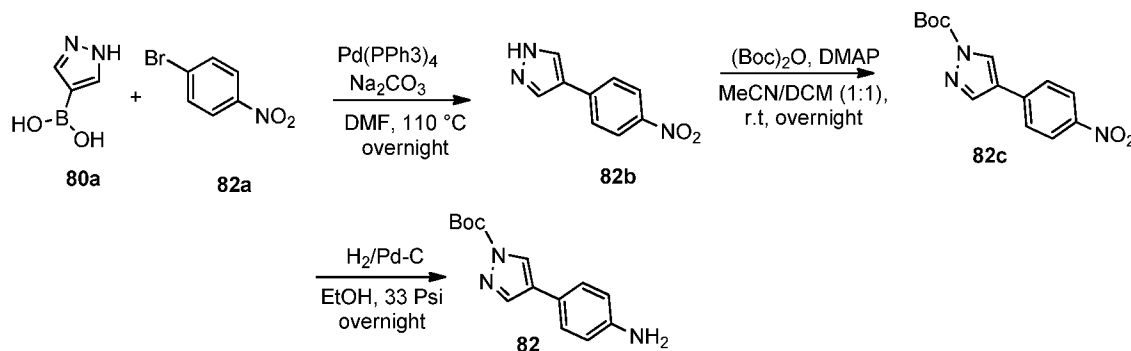
conditions and isolation techniques gave **81** as a solid (670 mg, 86% yield). MS (ESI) m/z 203.2 $[\text{M}+\text{H}]^+$. δ ^1H NMR (600 MHz, Chloroform- d) δ 8.22 (dd, $J = 2.4, 0.8$ Hz, 1H), 7.69 – 7.66 (m, 1H), 7.58 (d, $J = 0.8$ Hz, 1H), 7.54 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.27 (s, 1H), 6.53 (dd, $J = 8.5, 0.9$ Hz, 1H), 4.62 – 4.47 (m, 1H), 4.41 (s, 2H), 1.81 (s, 1H), 1.54 (d, $J = 6.7$ Hz, 6H).

Synthesis of 5-(1H-pyrazol-4-yl)pyridin-2-amine (82):



Step 1: Synthesis of 82: (Part in WO2002010146) To a solution of compound **80c** (1.1 g, 3.8 mmol) in ethanol (100 mL) was added catalytic amount of 10% Pd/C-50% wet (600 mg). The mixture was hydrogenated on a par apparatus at 33 psi for overnight at RT. Following standard isolation techniques gave **81** as a solid (660 mg, 76% yield). MS (ESI) m/z 161.2 $[\text{M}+\text{H}]^+$.

Synthesis of tert-butyl-4-(6-aminopheyl)-1H-pyrazole-1carboxylate (82):



Step1: Synthesis of 82b: (Part in WO2012082817) The procedure used for making **80c** was used to isolate **82b** as a solid (3.7 g, 44% yield). MS (ESI) m/z 190.1 $[\text{M}+\text{H}]^+$.

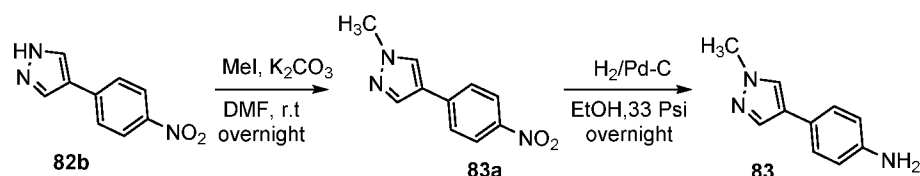
Step2: Synthesis of 82c: (Part in WO2018005193) To a stirred mixture of compound **82b** (1.0 g, 5.3 mmol) in MeCN/DCM (1:1) (50 mL) at room temperature were added $(\text{Boc})_2\text{O}$ (5.8 g, 27

mmol) and DMAP (324 mg, 2.7 mmol). The resulting mixture was stirred at room temperature for overnight. The work-up and column chromatography gave **82c** as a solid (1.1 g, 66% yield). MS (ESI) m/z 291.1 $[M+H]^+$.

- 5 **Step 3: Synthesis of 82:** (Part in WO2002010146) The hydrogenation of **82c** (1.1 g, 0.8 mmol) in ethanol (100 mL) using catalytic amount of 10% Pd/C-50% wet (600 mg) gave **82** as a solid (950 mg, 96% yield). MS (ESI) m/z 260.1 $[M+H]^+$. δ ^1H NMR (600 MHz, Chloroform- d) δ 8.17 (d, J = 0.9 Hz, 1H), 7.91 (d, J = 0.9 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 1.67 (s, 9H).

10

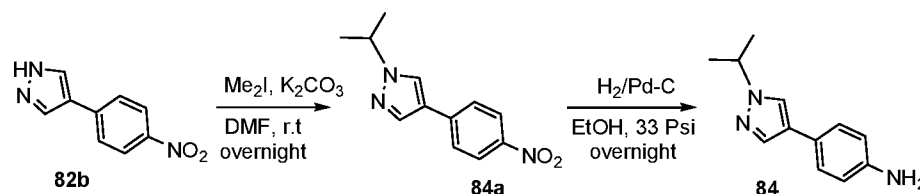
Synthesis of tert-butyl-4-(1-methyl-1H-pyrazol-4-yl)aniline (83):



- 15 **Step1: Synthesis of 83a:** (Part in WO2018124001) To a stirred mixture of compound **82b** (1.0 g, 5.3 mmol) in DMF (20 mL) at room temperature were added MeI (1.5 g, 10.5 mmol) and K_2CO_3 (2.2 g, 16 mmol). The resulting mixture was stirred at room temperature for overnight. The work-up and purification gave **83a** as a solid (0.8 g, 73% yield). MS (ESI) m/z 204.1 $[M+H]^+$.

- 20 **Step 2: Synthesis of 83:** (Part in WO2002010146) Following the standard hydrogenation technique and isolation procedure gave **83** as a gray solid (660 mg, 97% yield). MS (ESI) m/z 174.1 $[M+H]^+$. δ ^1H NMR (600 MHz, Chloroform- d) δ 7.66 (s, 1H), 7.49 (s, 1H), 7.28 – 7.25 (m, 2H), 6.69 (d, J = 8.4 Hz, 2H), 3.91 (s, 3H), 3.66 (s, 2H).

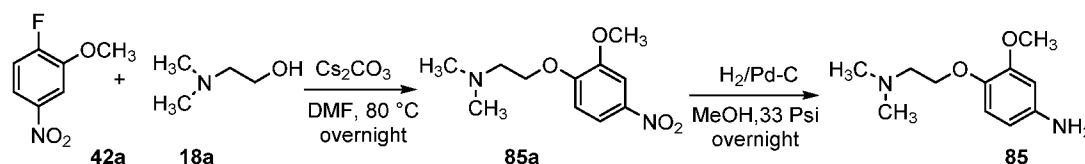
- 25 **Synthesis of 4-(1-isopropyl-1H-pyrazol-4-yl)aniline (84):**



Step 1: Synthesis of 84a: (Part in WO2018124001) The procedure described for **81a** was employed to isolate **84a** as a solid (0.9 g, 75% yield). MS (ESI) m/z 233.2 $[M+H]^+$.

Step 2: Synthesis of **84:** (Part in WO2002010146) (750 mg, 96% yield). Following the standard hydrogenation technique and isolation procedure gave **84** as a gray solid MS (ESI) m/z 203.1 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.68 (s, 1H), 7.55 (s, 1H), 7.27 (dd, J = 8.9, 6.9 Hz, 2H), 6.72 – 6.66 (m, 2H), 4.55 – 4.46 (m, 1H), 1.53 (d, J = 6.7 Hz, 6H).

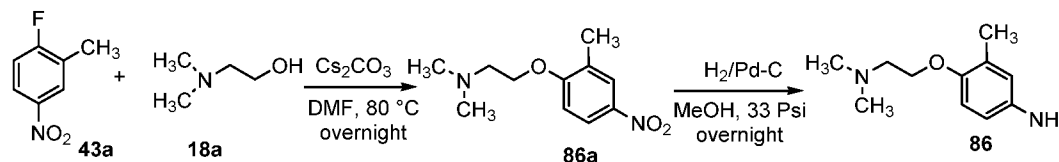
Synthesis of 4-(2-(dimethylamino)ethoxy)-3-methoxyaniline (85**):**



Step1: Synthesis of **85a:** (Part in 2009076140) To a stirred mixture of compound **42a** (5.0 g, 29 mmol) in DMF (50 mL) at room temperature were added **18a** (3.9 g, 44 mmol) and Cs_2CO_3 (29 g, 188 mmol). The resulting mixture was stirred at 80 °C for overnight. Reaction mixture was cooled, diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The organic layer was washed with brine solution (100 mL), dried (Na_2SO_4), and concentrated to provide crude residue. The crude residue was further purified by silica-gel column using 0-20% MeOH in DCM to give **85a** as a solid (5.0 g, 71% yield). MS (ESI) m/z 241.1 $[M+H]^+$.

Step 2: Synthesis of **85:** (Part in WO2002010146) To a solution of compound **85a** (5.0 g, 21 mmol) in methanol (200 mL) was added catalytic amount of 10% Pd/C-50% wet (2.5 g). The mixture was hydrogenated on a par apparatus at 40 psi for overnight at RT. The reaction mixture was filtered and concentrated to afford **85** as a solid (3.9 g, 89% yield). MS (ESI) m/z 211.2 $[M+H]^+$. ^1H NMR (600 MHz, DMSO- d_6) δ 7.95 (s, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.26 (d, J = 2.6 Hz, 1H), 6.04 (dd, J = 8.4, 2.5 Hz, 1H), 3.84 (t, J = 6.1 Hz, 2H), 3.67 (s, 3H), 2.55 – 2.48 (m, 3H), 2.19 (s, 6H).

Synthesis of 4-(2-(dimethylamino)ethoxy)-3-methylaniline (86**):**

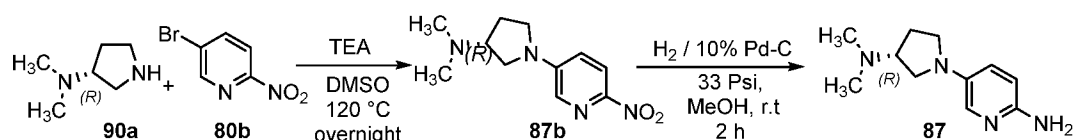


Step1: Synthesis of **86a:** (Part in 2009076140) The procedure to make **85a** was used to isolate **86a** as a solid (7.0 g, 97% yield). MS (ESI) 225.1 m/z $[M+H]^+$.

Step 2: Synthesis of 86: (Part in WO2002010146) The standard hydrogenation technique and isolation procedure was used to isolate **86** as a solid (6.0 g, 99% yield). MS (ESI) m/z 195.2 $[M+H]^+$. ^1H NMR (600 MHz, DMSO- d_6) δ 7.95 (s, 1H), 6.62 (s, 1H), 6.38 (s, 1H), 6.33 (s, 1H), 3.86 (s, 2H), 2.21 (s, 6H), 2.03 (s, 3H).

5

Synthesis of (R)-5-(3-(dimethylamino)pyrrolidin-1-yl)pyridin-2-amine (87):

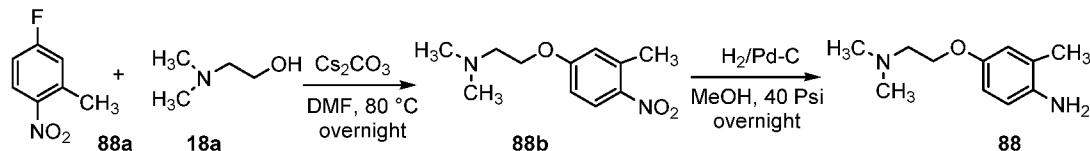


- 10 **Step1: Synthesis of 87b:** (Part in Ref: WO 20180072707 A1): To a stirred mixture of compound **90a** (5.0 g, 44 mmol) and bromo compound **80b** (8.4 g, 42 mmol) in DMSO (25 mL) was added triethylamine (31 mL, 220 mmol) at room temperature and stirred at 120°C for overnight. The reaction mixture was cooled and diluted with water (300 mL) and extracted with EtOAc (3 x 150 mL). The organic layer was washed with brine solution (100 mL), dried
- 15 (Na_2SO_4), and concentrated to provide crude residue. The crude residue was further purified by silica-gel column using 0-20% MeOH in DCM to give **87b** as yellow solid (8.0 g, 78% yield). MS (ESI) m/z 237.2 $[M+H]^+$.

- Step 2: Synthesis of 87:** (Part in WO 2015038417 A1) Hydrogenation of **87b** by following
- 20 standard hydrogenation technique and isolation method afforded **90** as a solid (6.8 g, 97% yield). MS (ESI) m/z 207.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 7.48 (d, $J = 3.0$ Hz, 1H), 6.84 (dd, $J = 8.8, 3.0$ Hz, 1H), 6.50 (d, $J = 8.7$ Hz, 1H), 3.42 – 3.36 (m, 1H), 3.32 (dd, $J = 8.8, 2.7$ Hz, 1H), 3.30 – 3.23 (m, 1H), 3.10 (t, $J = 8.2$ Hz, 1H), 2.90 – 2.84 (m, 1H), 2.31 (s, 6H), 2.23 – 2.15 (m, 1H), 1.96 – 1.87 (m, 1H).

25

Synthesis of 4-(2-(dimethylamino)ethoxy)-2-methylaniline (88):

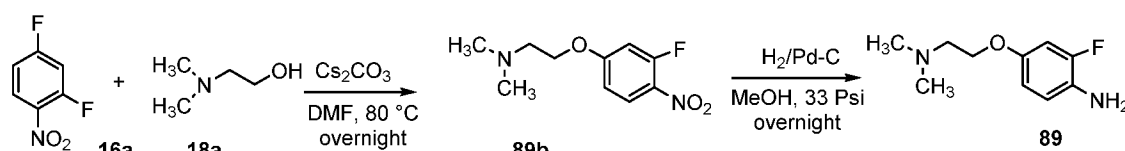


Step1: Synthesis of 88b: (Part in WO2014134308) The procedure to make **85b** was used to isolate **88b** as a solid

(4.1 g, 57% yield). MS (ESI) m/z 225.2 $[M+H]^+$.

Step 2: Synthesis of 88: (Part in WO2002010146) Hydrogenation and then filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **91** as a solid (3.0 g, 83% yield). MS (ESI) m/z 195.1 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.69 (d, J = 2.8 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 6.61 (s, 1H), 3.99 (t, J = 5.8 Hz, 2H), 2.68 (t, J = 5.8 Hz, 2H), 2.32 (s, 6H), 2.15 (s, 3H)

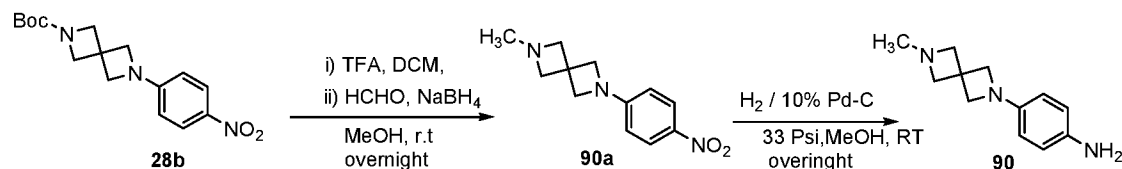
Synthesis of 4-(2-(dimethylamino)ethoxy)-2-fluoroaniline (89):



Step1: Synthesis of 89b: (Part in WO2009076140) The procedure to make **85a** was used to isolate **89b** as a solid (6.3 g, 44% yield). MS (ESI) 229.1 m/z $[M+H]^+$.

Step 2: Synthesis of 89: (Part in WO2002010146) Standard hydrogenation of **89b** was followed. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **89** as a solid (5.1 g, 94% yield). MS (ESI) m/z 199.1 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.62 (dd, J = 8.5, 5.7 Hz, 1H), 6.57 (dd, J = 10.2, 2.7 Hz, 1H), 6.51 (td, J = 8.5, 2.7 Hz, 1H), 4.07 (t, J = 5.7 Hz, 2H), 2.76 (t, J = 5.7 Hz, 2H), 2.35 (s, 6H).

Synthesis of 4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)amine (90):

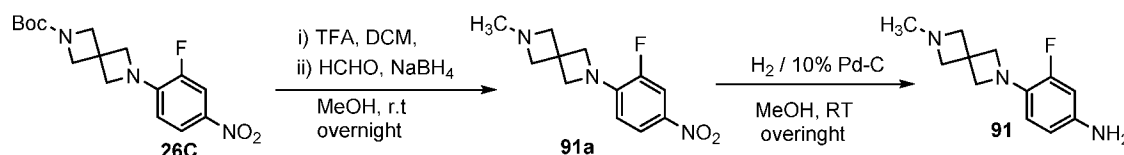


Step 2: Synthesis of 90a: To compound **28b** (1.5 g, 5 mmol) was added 25% TFA in DCM (100 mL) and stirred at room temperature for 1 h. After completion of the reaction, removed solvent under vacuum and used as such for the next step. The crude reaction mixture and formaldehyde (2 mL, 25 mmol, 37% aqueous solution) were added to methanol (30 mL), stirred at room temperature for 1 h, then sodium borohydride (946 mg, 25 mmol) was added to the reaction mixture in portions and reaction was continued for overnight. After the reaction is completed, removed solvents under vacuum and the crude residue was purified by silica-gel

column using 0-20% MeOH in DCM to give **90a** as liquid (701 mg, 60% yield). MS (ESI) 234.1 m/z

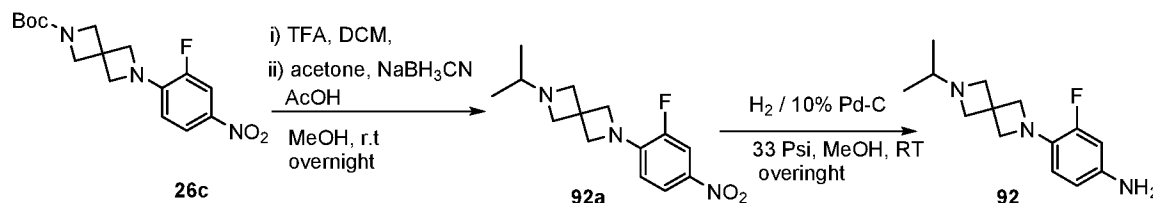
Step 3: Synthesis of 90: (WO2002010146) To a solution of compound **97c** (0.7 g, 3 mmol) in methanol (100 mL) was added catalytic amount of 10% Pd/C-50% wet (0.4 g). The mixture was hydrogenated on a par apparatus at 40 psi for overnight. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **90** as a solid (560 mg, 93% yield). MS (ESI) m/z 204.1 ¹H NMR (600 MHz, Chloroform-*d*) δ 6.62 (d, *J* = 8.6 Hz, 2H), 6.35 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 3.39 (s, 4H), 2.33 (s, 4H).

10 **Synthesis of 3-fluoro-4-(6-methyl-2,6-diazaspiro[3,3]heptan-2-yl)amine (91):**



Step 2: Synthesis of 91a: The procedure described for making **90a** was used to isolate **91** (601 mg, 48% yield). MS (ESI) m/z 252.1 (VP-HB5-227A)

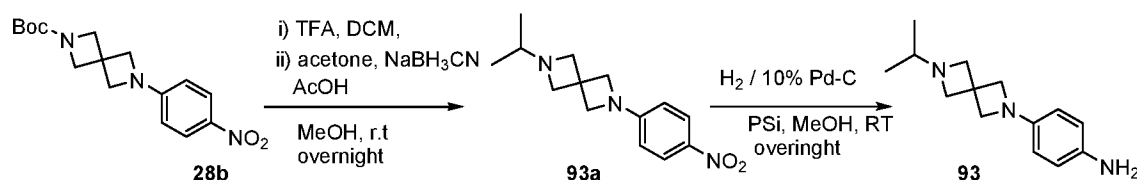
15 **Synthesis of 3-fluoro-4-(6-isopropyl-2,6-diazaspiro[3,3]heptan-2-yl)amine (92):**



Step 1: Synthesis of 92a: To compound **26c** (1.7 g, 5.1 mmol) was added 25% TFA in DCM (100 mL) and stirred at room temperature for 1 h. After completion of the reaction, removed solvent under vacuum and used as such for the next step. The crude reaction mixture, acetic acid (2.5 mL) and acetone (2.5 mL, 51 mmol, 37% aqueous solution) were added to methanol (30 mL), stirred at room temperature for 1 h, then sodium cyanoborohydride (3.2 g, 51 mmol) was added to the reaction mixture in portions and reaction was continued for overnight. After the reaction is completed, removed solvents under vacuum and the crude residue was purified by silica-gel column using 0-20% MeOH in DCM to give **92a** as liquid (0.85 g, 61% yield). MS (ESI) m/z 280.1

Step 2: Synthesis of 92: (WO2002010146) To a solution of compound **92a** (0.85 g, 3 mmol) in methanol (100 mL) was added catalytic amount of 10% Pd/C-50% wet (0.5 g). The mixture was hydrogenated on a par apparatus at 40 psi for overnight. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **92** as a solid (0.71 g, 93% yield). MS (ESI) m/z 250.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.42 – 6.30 (m, 3H), 3.90 (s, 4H), 3.33 (s, 4H), 0.93 (d, J = 6.2 Hz, 6H).

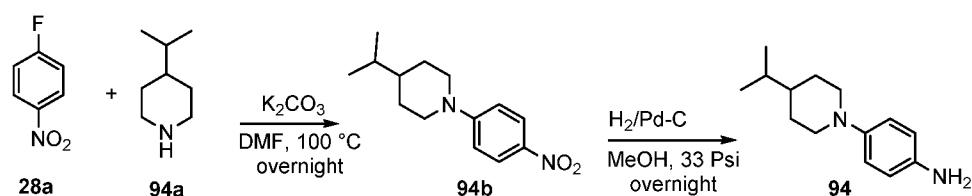
Synthesis of 4-(6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)amine (93):



Step 1: Synthesis of 93a: To compound **28b** (1.5 g, 5 mmol) was added 25% TFA in DCM (100 mL) and stirred at room temperature for 1 h. After completion of the reaction, removed solvent under vacuum and used as such for the next step. The crude reaction mixture, acetic acid (2.5 mL) and acetone (2.5 mL, 50 mmol, 37% aqueous solution) were added to methanol (30 mL), stirred at room temperature for 1 h, then sodium cyanoborohydride (3.1 g, 50 mmol) was added to the reaction mixture in portions and reaction was continued for overnight. After the reaction is completed, removed solvents under vacuum and the crude residue was purified by silica-gel column using 0-20% MeOH in DCM to give **93a** as liquid (0.86 g, 66% yield). MS (ESI) m/z 262.1

Step 2: Synthesis of 93: (WO2002010146) To a solution of compound **93a** (0.86 g, 3.3 mmol) in methanol (100 mL) was added catalytic amount of 10% Pd/C-50% wet (0.5 g). The mixture was hydrogenated on a par apparatus at 40 psi for overnight. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford **93** as a solid (0.74 g, 97% yield). MS (ESI) m/z 232.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.63 (d, J = 8.6 Hz, 2H), 6.35 (d, J = 8.6 Hz, 2H), 3.84 (s, 4H), 3.32 (s, 4H), 2.24 (dt, J = 12.4, 6.2 Hz, 1H), 0.93 (d, J = 6.2 Hz, 6H).

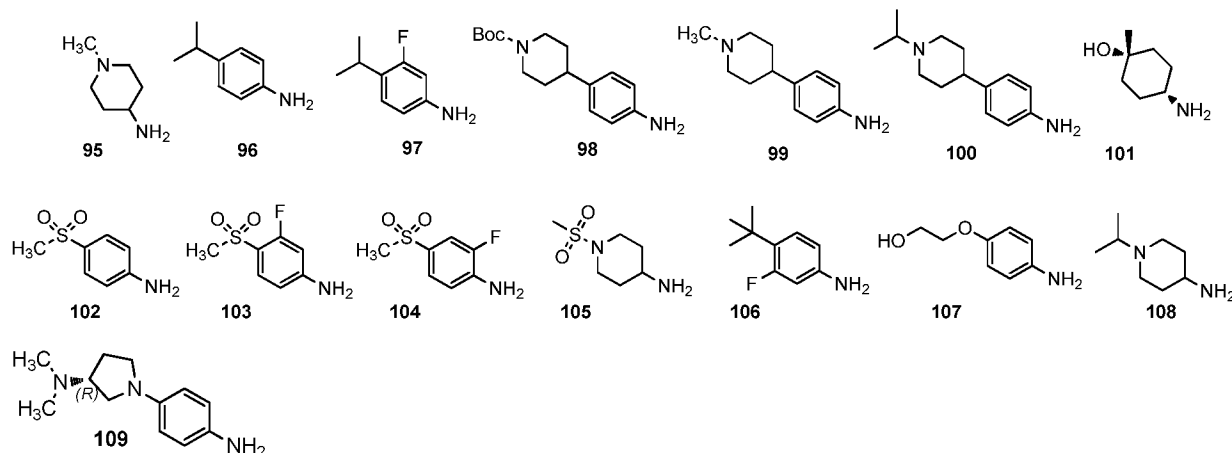
Synthesis of 4-(4-isopropylpiperidin-1-yl)aniline (94):



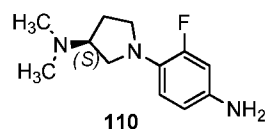
Step1: Synthesis of 94: (Part in WO2009079597) To a stirred mixture of compound **28a** (1.1 g, 8 mmol) in DMF (25 mL) at room temperature were added **101a** (1.0 g, 8 mmol) and K_2CO_3 (3.3 g, 24 mmol). The resulting mixture was stirred at 80 °C for overnight. Reaction mixture was cooled and diluted with water (200 mL) and the solid obtained was filtered and washed with water (3x25 mL) and dried under vacuum to give compound **94a** as a yellow solid (1.7 g, 87% yield). MS (ESI) m/z 249.1 $[M+H]^+$. This product is used as such in the next step.

Step 2: Synthesis of 94: (WO2002010146) The standard hydrogenation technique and isolation procedure afforded **94** as a solid (1.3 g, 87% yield). MS (ESI) m/z 219.2 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 6.83 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 8.7 Hz, 2H), 3.52 – 3.44 (m, 2H), 2.58 – 2.46 (m, 2H), 1.80 – 1.70 (m, 2H), 1.54 – 1.37 (m, 3H), 1.09 (dddd, J = 15.5, 11.9, 6.8, 3.7 Hz, 1H), 0.91 (d, J = 6.8 Hz, 6H).

The following amines were purchased from commercial sources:

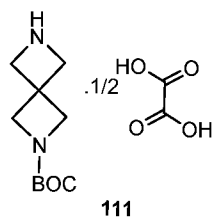


Synthesis of 109: Prepared according to the procedure described for the preparation of compound **33**. MS (ESI) m/z 206.2 $[M+H]^+$.



Synthesis of 110: Prepared according to the procedure described for the preparation of compound **30**. MS (ESI) m/z 224.2 $[M+H]^+$.

Some of the amines that are not mentioned here are commercially available and might have used to make the final target molecules.



Procured from a commercial source.

Example 2

General Synthesis and Schemes

General Methods. General reaction conditions are described in International Pat. App. Publication No. WO 2018009625, which is incorporated by reference for such teachings. The reactions were generally carried out under a dry argon atmosphere using anhydrous solvents (Sigma-Aldrich, St. Louis, MO). All common chemicals were purchased from commercial sources. The purification of the molecules was carried out using Combi Flash Rf from Teledyne ISCO, regular silica gel columns, and C18 columns. Chiral HPLC columns (Chiral Technologies) and lyophilization techniques (VirTis Genesis 25L Pilot Lyophilizer) were used wherever necessary to isolate the desired products. The isolated target products are excellent powder/fluffy material and possess the purity, in general, of >97%. ¹H NMR spectra were recorded on a 600 MHz Fourier Transform Brücker Spectrometer. Spectra were obtained from samples prepared in 5 mm diameter tubes in CDCl₃, CD₃OD or DMSO-d₆. The spin multiplicities are indicated by the symbols, s (singlet), d (doublet), t (Triplet), m (multiplet) and, br (broad). Coupling constants (J) are reported in Hz. MS spectra were obtained using electrospray ionization (ESI) on an Agilent Technologies' 6120 quadrupole LCMS system.

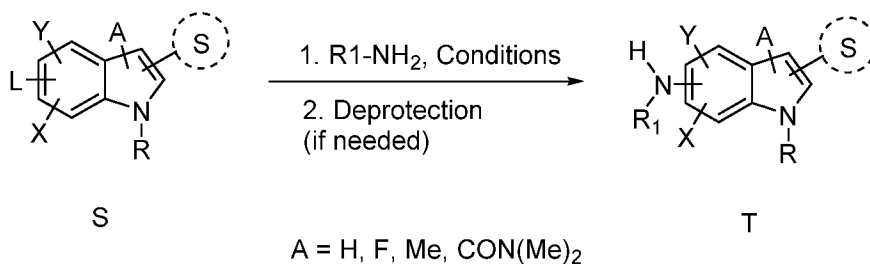
The compounds described herein may be synthesized by many methods available to those skilled in the art of organic chemistry. Mafrand et al., *Heterocycles* 16(1): 35-37 (1981). General synthetic schemes for preparing compounds described herein are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds described herein will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds. Examples of compounds described herein prepared by methods described in the general schemes are shown below.

Preparation of homochiral examples may be carried out by techniques known to one having ordinary skill in the art. For example, homochiral compounds may be prepared by separation of racemic products by chiral phase preparative HPLC. Alternatively, the example compounds may be prepared by methods known to give enantiomerically enriched products such as asymmetric synthesis and enantioselective synthesis. These include, but are not limited to, the incorporation of chiral auxiliary functionalities into racemic intermediates that serve to control the diastereoselective of transformations, providing enantio-enriched products upon cleavage of the chiral auxiliary. The compounds described herein can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds described herein can be synthesized

using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being affected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one process scheme over another in order to obtain a desired compound described herein. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described herein. An authoritative account describing the many alternatives to the trained practitioner is Greene et al., *Protective Groups in Organic Synthesis*, 4th ed, Wiley-Interscience (2006).

General Scheme for Compounds

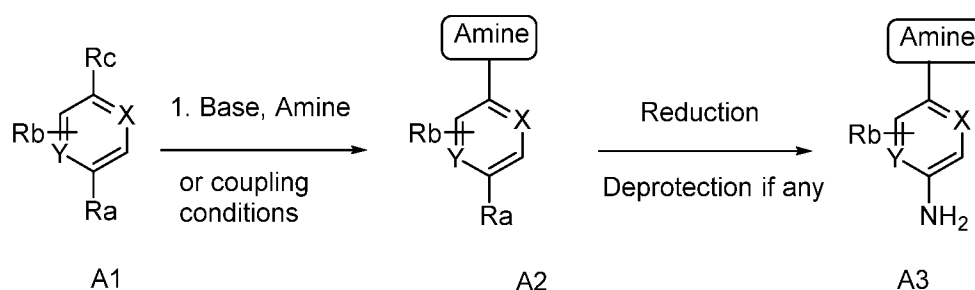
Scheme T



Scheme T can be followed to make the final target molecules. The synthesis of variously substituted starting materials (S) can be made using one or more of the schemes shown below. It may be modified the proposed synthetic plan to affect the desired transformation. R₁NH₂ can be obtained from the commercial source, or it can be made using the standard reactions (Scheme A) that are appreciated by those skilled in the art. Group L may be changed to L1 (e.g., SMe to SOMe/SO₂Me) before reacting with R₁NH₂ in the sequence.

General Scheme for making R₁NH₂

Scheme A

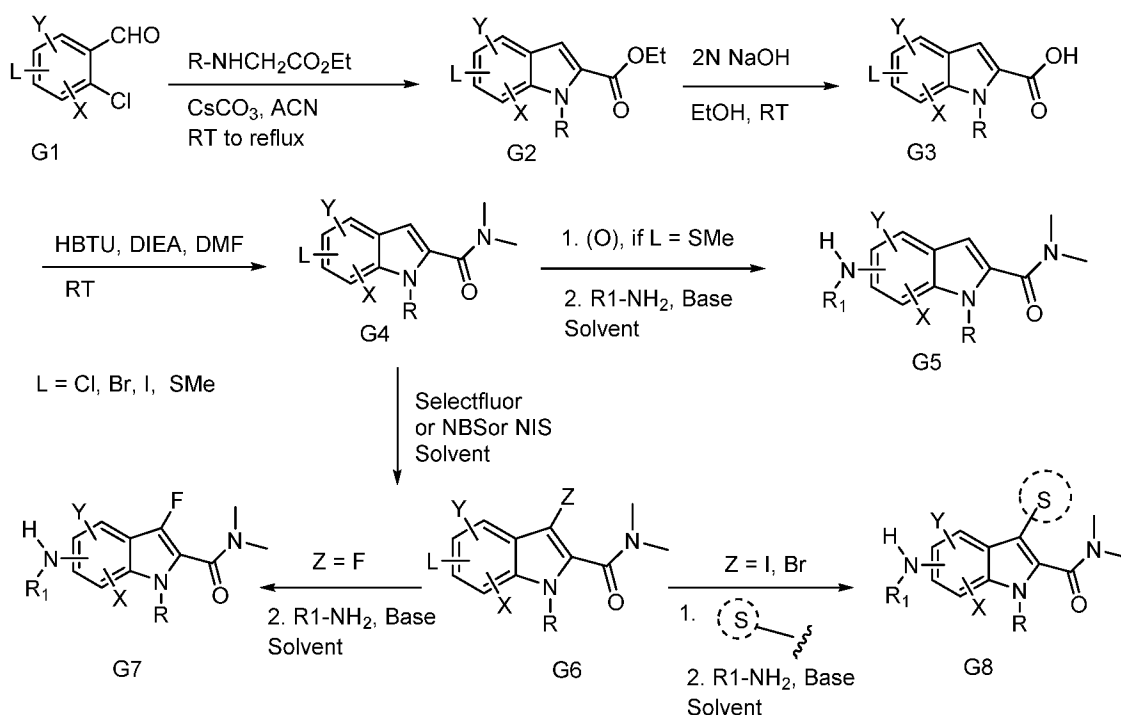


Ra = NO₂, Masked amine or Amine
 Rb = F, Me, OMe, CF₃, CHF₂
 X = Y = Independently C or N
 Rc = Halogen (Cl, Br, F), -CO₂H

The R₁NH₂ required for making the final targets would be synthesized via a sequence shown in the scheme A. The appropriately substituted **A1** can give the intermediate or the final amine **A2** via a reaction(s) such as displacement of halogen atom or amide bond formation reactions that are appreciated by those skilled in the art. The desired **A3** (R₁NH₂) can be obtained from **A2** by reduction of a nitro group or de-masking the amine as needed.

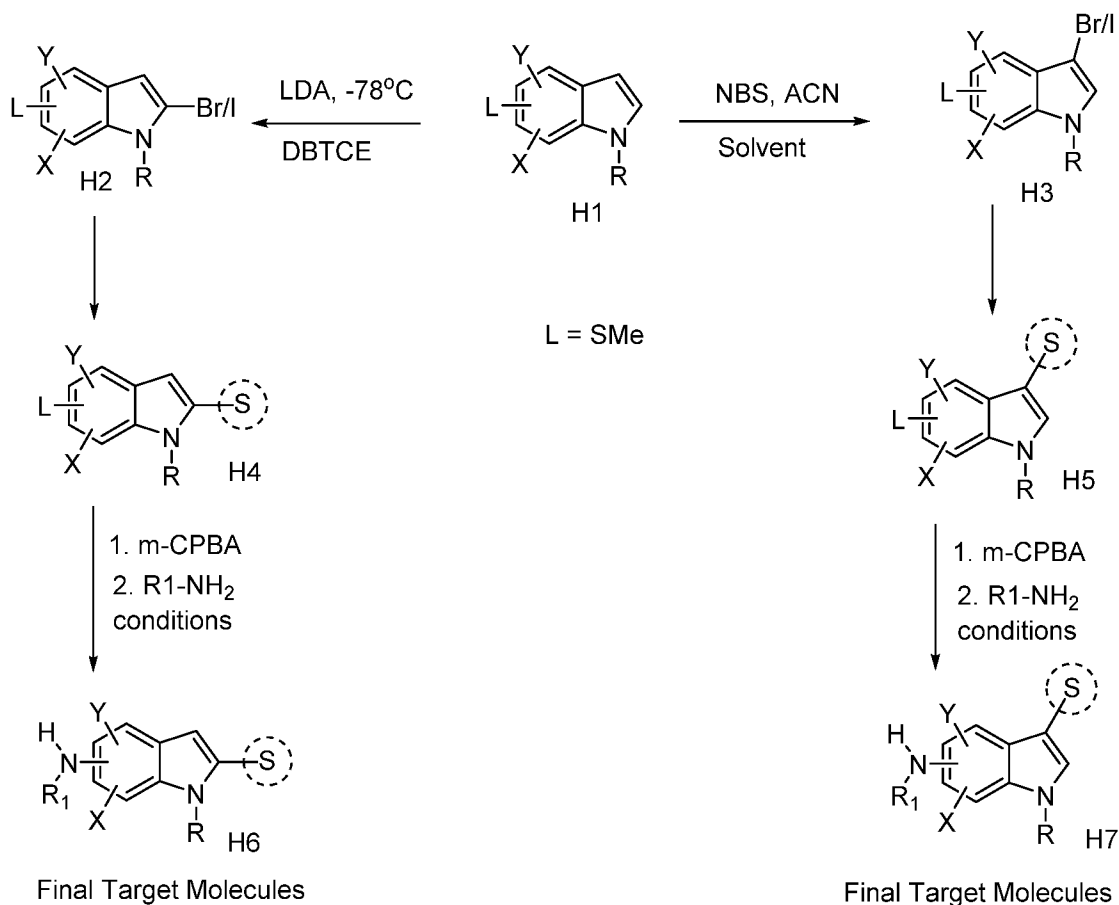
General schemes to make building blocks and final target molecules

Scheme G



As shown in Scheme G, compounds depicted in the general claim may be synthesized from a readily available starting material. The required intermediates and the target molecules can be made using standard synthetic organic chemistry procedures. The reported standard reaction conditions on a substrate can be extended to perform the reactions on analogous substrates to effect the transformation. The proposed routes or slightly modified schemes may be performed.

General Scheme H



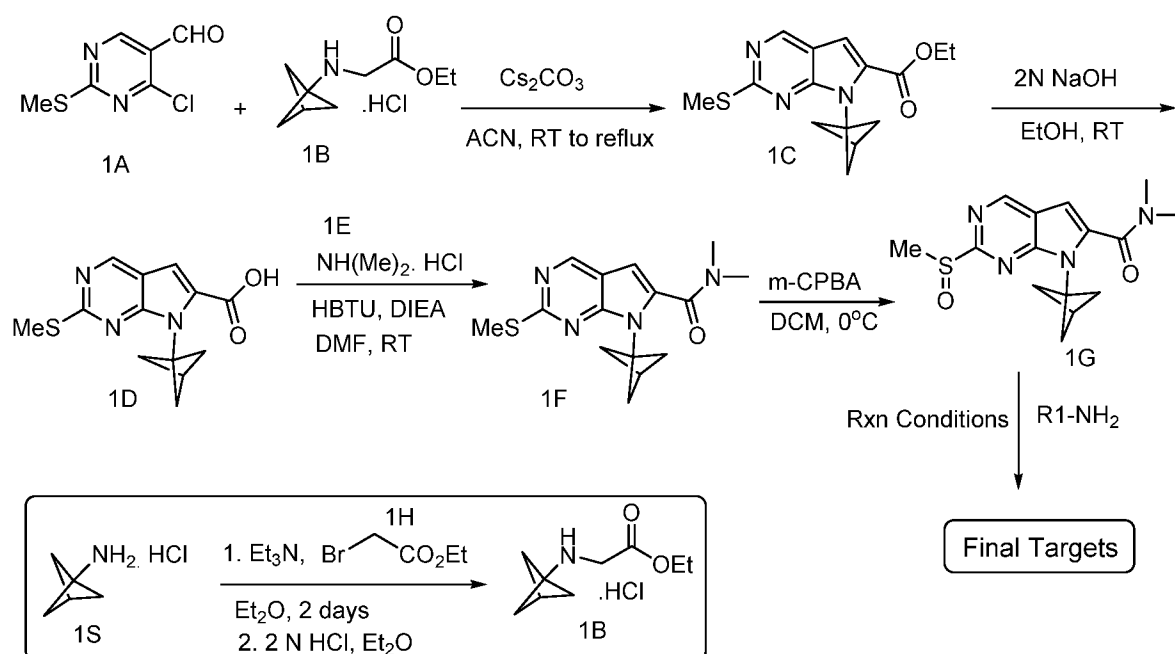
Scheme H can be used to synthesize different types of intermediates and subsequently the final target molecules. The starting bicyclic compound **H1** can serve as a starting material to make two different compounds **H2** and **H3**. The compound **H3** can be obtained upon treating with N-bromosuccinimide (NBS). See Axten et al., *J. Med. Chem.* 55(16): 7193-7207 (2012). The 2-bromo compound **H2** can be achieved using different conditions. See WO 2009037467; Lawhorn et al., *J. Med. Chem.* 58(18): 7431-7448, (2015). The compound **H2** can be reacted with the desired amine or amide (circled "C") to afford the compound of the type **H4**. The required target molecules of the type **H6** can be realized through a sulfoxide intermediate and the

subsequent reaction with R_1-NH_2 to afford the final target molecules. Similarly, the compound **H3** can be transformed into the final targets of the type **H7** using the identical conditions. See WO 2010027005; WO 2015128334; WO 2010149755.

The proposed routes or slightly modified schemes may be used to synthesize targets.

5

Scheme 1



10 The bicyclic ester **1C** was synthesized starting from aldehyde **1A** and amino ester **1B** (prepared from amine **1S** and **1H** as an HCl salt) under base mediated reaction conditions. See Zhu et al., *Eur. J. Org. Chem.* 2014(3): 511-514 (2014). The amide substrate **1F** was prepared via two step sequence, saponification of an ester followed by a reaction with amine **1E**. The oxidation of methyl sulfide **1F** with m-CPBA gave the penultimate compound **1G**. The sulfoxide

15 **1G** was used to synthesize the final target molecules by reacting with R_1-NH_2 using standard reaction conditions that are well know to those skilled in the art. See WO 2018005860.

Example 3

General Procedures for the Synthesis of Compounds A1–A47

General Procedure A

Parts of the procedure were described in WO 2010020675, which is incorporated by reference herein for such teachings. A mixture of corresponding amine (1.5 eq), amide (1 eq), BINAP (20 mole percentage) and sodium-tert-butoxide (2 eq) in dioxane was degassed and Pd₂(dba)₃ (10 mole percentage) was added under argon. The reaction mixture was heated to 100 °C for 2 h in an oil bath. After completion, the reaction mixture was quenched with MeOH, concentrated and purified using silica gel chromatography (0 to 100% MeOH in dichloromethane). The obtained residue was dissolved and stirred in 5 mL of 30% TFA/DCM solution for 2 h at RT. The mixture was concentrated to dryness and treated with 7 N NH₃/MeOH solution. The mixture was concentrated again and purified using a C18 column (0 to 100% CH₃CN in H₂O with 0.025% AcOH). The fractions containing desired compound were combined and lyophilized.

General Procedure B

Parts of the procedure were described in WO 2010020675, which is incorporated by reference herein for such teachings. A mixture of corresponding amine (1.5 eq), amide (1 eq), BINAP (20 mole percentage) and sodium-tert-butoxide (2 eq) in dioxane was degassed and Pd₂(dba)₃ (10 mole percentage) was added under argon. The reaction mixture was heated to 100 °C for 2 h in an oil bath. After completion, the reaction mixture was quenched with MeOH, concentrated, concentrated, and purified using silica gel chromatography (0 to 100% MeOH in dichloromethane). The fractions containing required compound were collected, concentrated and further purified on a C18 column (0 to 100% ACN in H₂O) to give the desired compound. The fractions containing desired compound were combined and lyophilized.

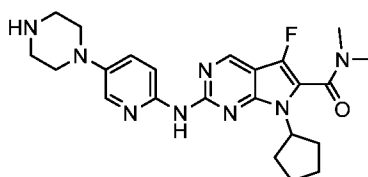
General Procedure C

Parts of the procedure were described in Chinese Patent Application No. CN 106749259, published as CN 201510800951, both of which are incorporated by reference herein for such teachings. To a solution of corresponding amine (3 eq) in anhydrous toluene was added 1 M LiHMDS in toluene (3.6 eq) dropwise at RT. After stirring for 30 minutes, a solution of amide (1 eq) in anhydrous toluene was added dropwise and stirring was continued for 1 h. The reaction mixture is then quenched with AcOH, concentrated and purified using silica gel chromatography (0 to 100% methanol in dichloromethane). The fractions containing required compound were collected and concentrated under reduced pressure. The obtained residue was dissolved and

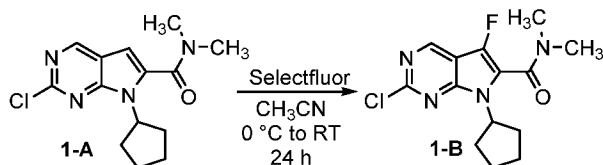
stirred in 5 mL of 30% TFA/DCM solution for 2 h at RT. The mixture was concentrated to dryness and treated with 7 *N*NH₃/MeOH solution. The mixture was concentrated again and purified using a C18 column (0 to 100% CH₃CN in H₂O with 0.025% AcOH). The fractions containing desired compound were combined and lyophilized.

5

Example 1: Compound A1



Step 1: Synthesis of 2-chloro-7-cyclopentyl-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (**1-B**):



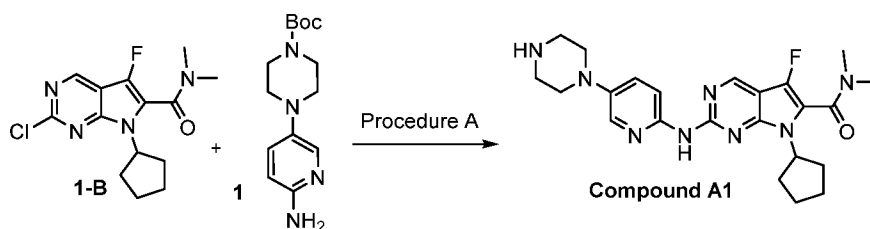
10

To a stirred solution of **1-A** (900 mg, 3.07 mmol) in acetonitrile (40 mL) was added selectfluor (1.1 g, 3.22 mmol) at 0 °C in three portions with an interval of 10 min. The reaction mixture was stirred at 0 °C for 30 minutes, then at RT for 24 h. After completion, the reaction mixture was quenched with saturated NaHCO₃ and extracted with DCM. The organic layer was dried over sodium sulfate, filtered, concentrated and used as such for the next step (735 mg, 77% yield). MS(ESI) *m/z* 311.1 (*M*+*H*)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.84 (d, *J* = 27.5 Hz, 1H), 4.96–4.80 (m, 1H), 3.22–3.06 (m, 6H), 2.37–2.28 (m, 2H), 2.10 (s, 2H), 2.06–1.97 (m, 2H), 1.72–1.62 (m, 2H).

15

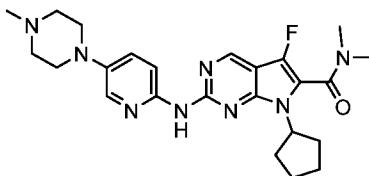
Step 2: Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A1**):

20

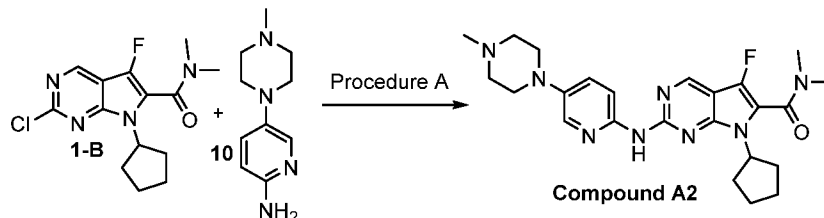


Compound **A1** was synthesized following the general procedure **A**, 24 mg (9% yield). MS(ESI) *m/z* 453.3 (*M*+*H*)⁺.

Example 2: Compound A2



Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A2**):

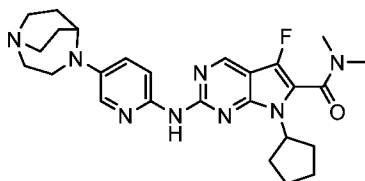


5

Compound **A2** was synthesized following the general procedure **A**, 10 mg (4% yield). MS(ESI) m/z 467.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.77–8.71 (m, 1H), 8.30 (d, J = 9.1 Hz, 1H), 8.02 (d, J = 2.9 Hz, 1H), 7.86 (s, 1H), 7.32 (dd, J = 9.1, 3.0 Hz, 1H), 4.81–4.72 (m, 1H), 3.23–3.18 (m, 7H), 3.15 (s, 3H), 2.65 (s, 4H), 2.59–2.46 (m, 2H), 2.40 (s, 3H), 2.08 (s, 2H), 2.04–1.95 (m, 2H), 1.74–1.68 (m, 2H).

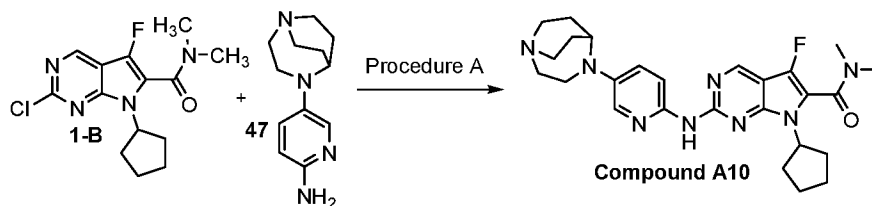
10

Example 3: Compound A10



Synthesis of 2-((5-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-2-yl)amino)-7-cyclopentyl-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A10**):

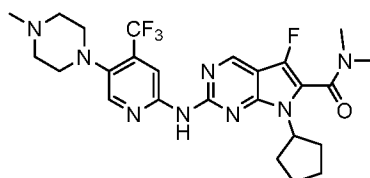
15



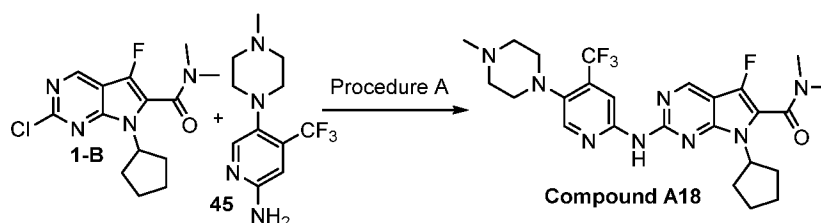
Compound **A10** was synthesized following the general procedure **A**, 3 mg (1% yield). MS(ESI) m/z 493.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 8.20 (d, J = 9.1 Hz, 1H), 7.91 (d, J = 3.0 Hz, 1H), 7.71 (s, 1H), 7.16 (dd, J = 9.1, 3.1 Hz, 1H), 4.77 (p, J = 9.0 Hz, 1H), 4.00–3.92 (m, 1H), 3.52–3.44 (m, 2H), 3.20 (d, J = 2.4 Hz, 3H), 3.15 (s, 3H), 3.14–3.09 (m, 4H), 3.06–2.97 (m, 2H), 2.58–2.48 (m, 2H), 2.16–2.04 (m, 4H), 2.04–1.96 (m, 2H), 1.78–1.66 (m, 4H).

20

Example 4: Compound A18

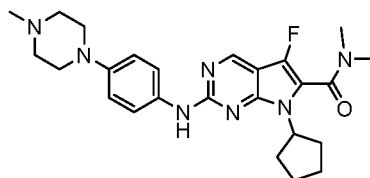


Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(4-methylpiperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A18**):

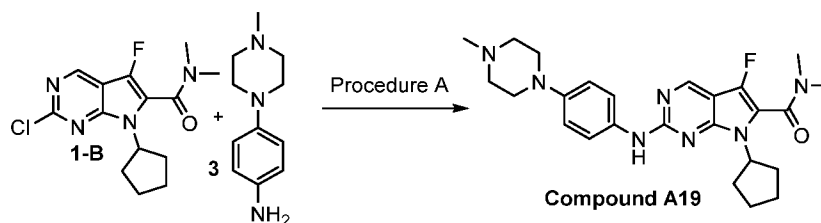


Compound **A18** was synthesized following the general procedure **A**, 4 mg. MS(ESI) m/z 535.5 ($M+H$)⁺.

Example 5: Compound A19

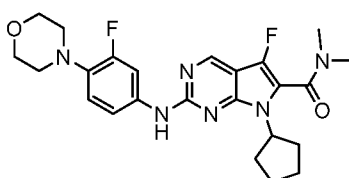


Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A19**):

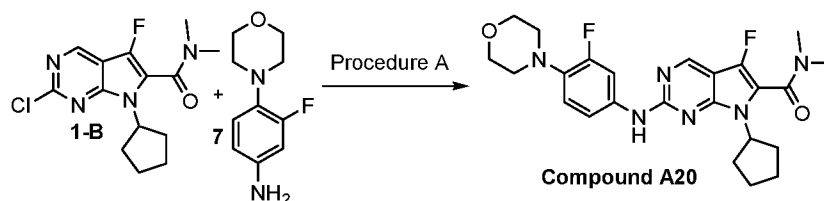


Compound **A19** was synthesized following the general procedure **A**, 2 mg. MS(ESI) m/z 466.3 ($M+H$)⁺.

Example 6: Compound A6



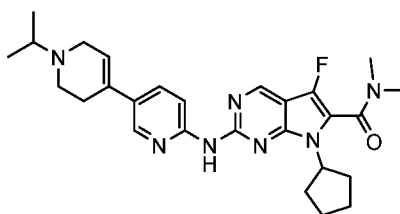
Synthesis of 7-cyclopentyl-5-fluoro-2-((3-fluoro-4-morpholinophenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A20**):



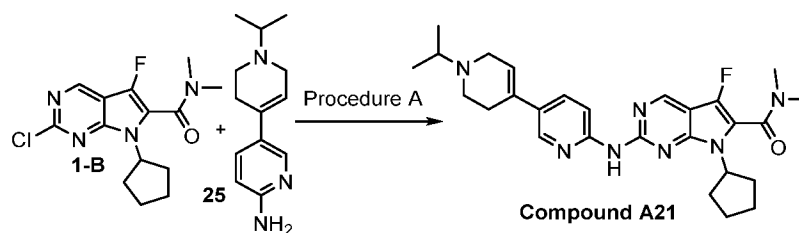
- 5 Compound **A20** was synthesized following the general procedure **A**, 46 mg. MS(ESI) *m/z* 471.3 (*M*+*H*)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 7.84 (dd, *J* = 14.8, 2.5 Hz, 1H), 7.17 (s, 1H), 7.10–7.04 (m, 1H), 6.92 (t, *J* = 9.0 Hz, 1H), 4.73 (p, *J* = 9.0 Hz, 1H), 3.93–3.86 (m, 4H), 3.22–3.18 (m, 3H), 3.15 (s, 2H), 3.12 (s, 1H), 3.09–3.05 (m, 4H), 2.62–2.49 (m, 2H), 2.11–2.01 (m, 4H), 1.74–1.63 (m, 2H).

10

Example 7: Compound **A21**



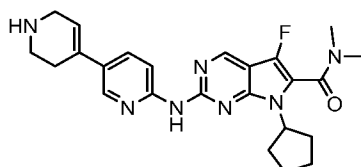
Synthesis of 7-cyclopentyl-5-fluoro-2-((1'-isopropyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A21**):



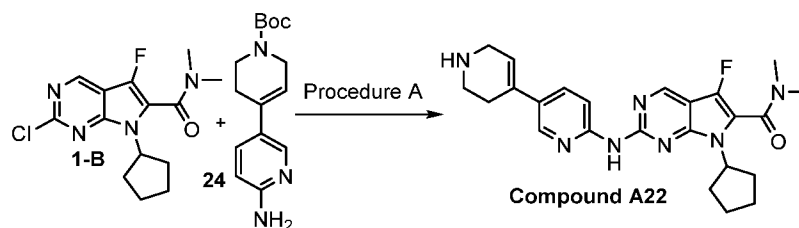
15

Compound **A21** was synthesized following the general procedure **A**, 28 mg. MS(ESI) *m/z* 492.3 (*M*+*H*)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 8.44 (d, *J* = 8.8 Hz, 2H), 8.39 (d, *J* = 2.5 Hz, 1H), 7.71 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.01 (d, *J* = 3.5 Hz, 1H), 4.79 (p, *J* = 9.0 Hz, 1H), 3.65–3.56 (m, 3H), 3.23–3.19 (m, 4H), 3.17 (s, 3H), 3.12 (s, 1H), 2.58–2.48 (m, 2H), 2.11 (s, 2H), 2.07–1.96 (m, 3H), 1.78–1.69 (m, 3H), 1.53 (d, *J* = 6.6 Hz, 6H).

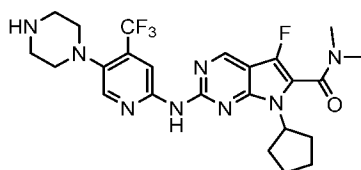
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Example 8: Compound **A22**

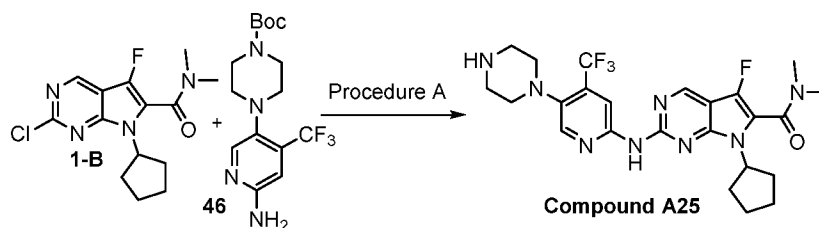
Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example 8):



Example 8 was synthesized following the general procedure **A**, 27 mg. MS(ESI) m/z 450.3 ($M+H$)⁺.

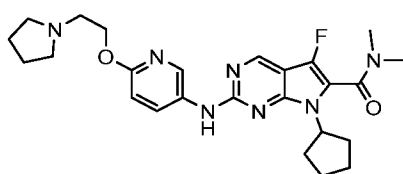
10 Example 9: Compound **A25**

Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(piperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A25**):

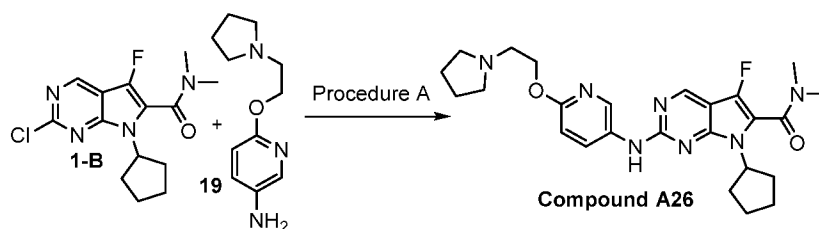


15 Compound **A25** was synthesized following the general procedure **A**, 5 mg. MS(ESI) m/z 521.3 ($M+H$)⁺.

Example 10: Compound **A26**

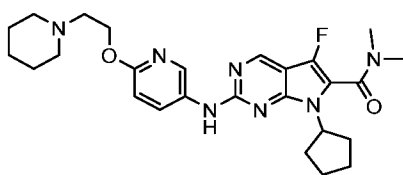


Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A26**):

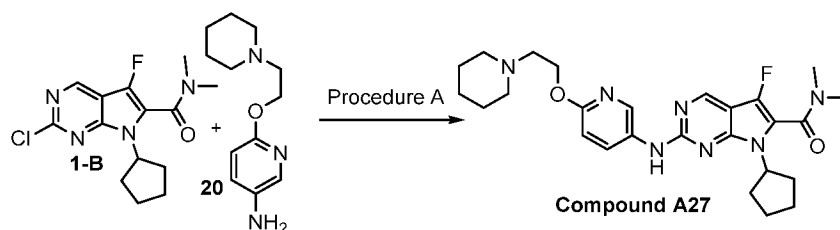


- 5 Compound **A26** was synthesized following the general procedure **A**, 7 mg. MS(ESI) m/z 482.3 (M+H)⁺.

Example 11: Compound **A27**



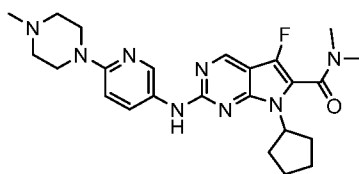
- 10 Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(2-(piperidin-1-yl)ethoxy)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A27**):



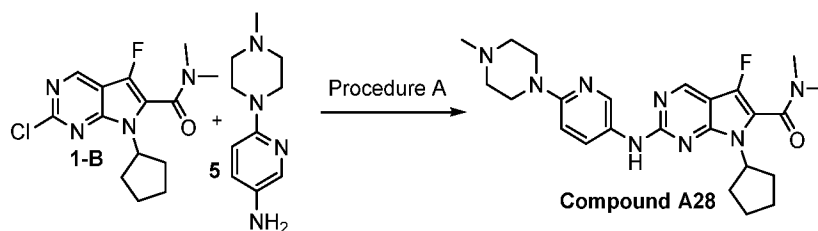
Compound **A27** was synthesized following the general procedure **A**, 15 mg. MS(ESI) m/z 496.3 (M+H)⁺.

15

Example 12: Compound **A28**

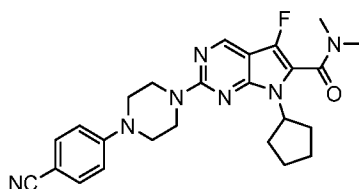


Synthesis of 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A28**):

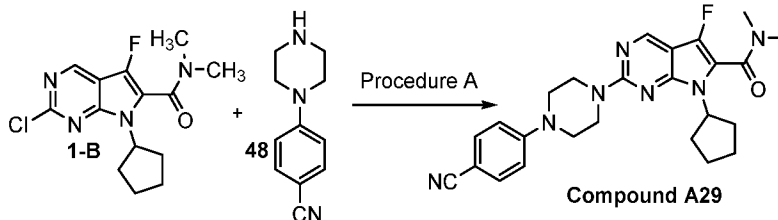


Compound **A28** was synthesized following the general procedure **A**, 9 mg. MS(ESI) m/z 467.3 (M+H)⁺.

Example 13: Compound **A29**

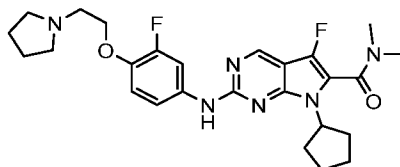


Synthesis of 2-(4-(4-cyanophenyl)piperazin-1-yl)-7-cyclopentyl-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A29**):

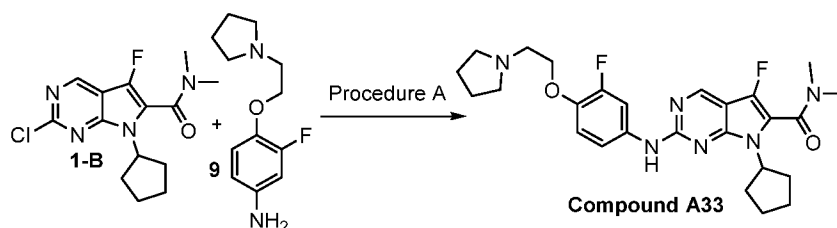


Compound **A29** was synthesized following the general procedure **A**, 10 mg. MS(ESI) m/z 462.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.64 (s, 0.5H), 8.60 (s, 0.5H), 7.57–7.49 (m, 2H), 6.96–6.87 (m, 2H), 4.75 (p, J = 8.8 Hz, 0.5H), 4.55 (p, J = 8.8 Hz, 0.5H), 4.02 (t, J = 5.3 Hz, 4H), 3.46 (t, J = 5.3 Hz, 4H), 3.18 (d, J = 5.8 Hz, 3H), 3.14 (s, 2H), 3.10 (s, 1H), 2.47–2.33 (m, 2H), 2.10–2.02 (m, 1H), 2.02–1.90 (m, 3H), 1.73–1.61 (m, 2H).

Example 14: Compound **A33**

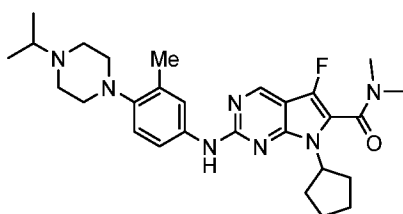


Synthesis of 7-cyclopentyl-5-fluoro-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A33**):

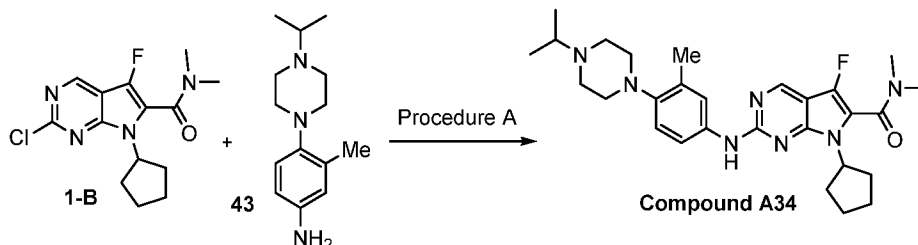


Compound **A33** was synthesized following the general procedure **A**, 6 mg. MS(ESI) m/z 499.3 (M+H)⁺.

Example 15: Compound **A34**

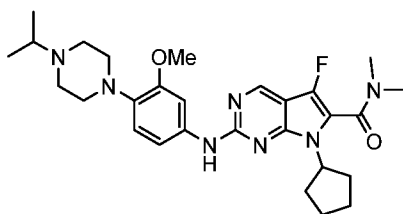


Synthesis of 7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)-3-methylphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A34**):

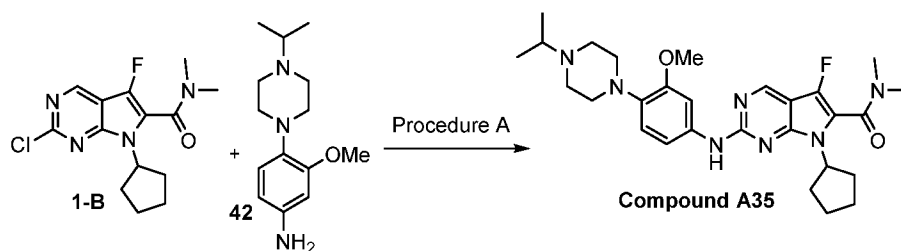


Compound **A34** was synthesized following the general procedure **A**, 9 mg. MS(ESI) m/z 508.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.69–8.63 (m, 1H), 7.47 (d, J = 2.6 Hz, 1H), 7.46–7.43 (m, 1H), 7.09 (s, 1H), 7.05 (d, J = 8.5 Hz, 1H), 4.72 (p, J = 9.0 Hz, 1H), 3.19 (s, 3H), 3.15 (s, 3H), 2.51 (q, J = 9.5, 8.2 Hz, 2H), 2.33 (s, 3H), 2.08–2.01 (m, 2H), 1.98 (q, J = 7.8 Hz, 2H), 1.61 (s, 17H).

Example 16: Compound **A35**

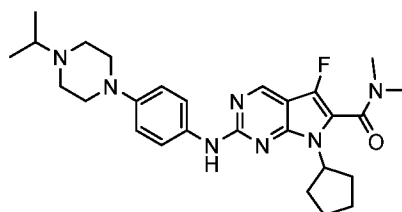


Synthesis of 7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)-3-methoxyphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A35**):

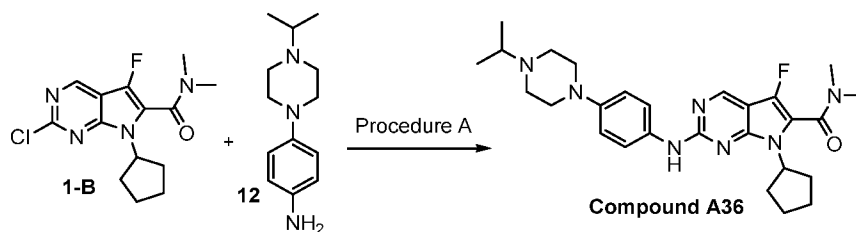


Compound **A35** was synthesized following the general procedure **A**, 11 mg. MS(ESI) *m/z* 524.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 7.22 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.11 (s, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 4.83 (p, *J* = 9.0 Hz, 1H), 3.89 (s, 3H), 3.22–3.17 (m, 3H), 3.14 (s, 3H), 3.11 (s, 4H), 2.76 (s, 5H), 2.49–2.35 (m, 2H), 2.05 (d, *J* = 16.6 Hz, 3H), 1.97–1.86 (m, 3H), 1.12 (d, *J* = 6.5 Hz, 6H).

Example 17: Compound A36

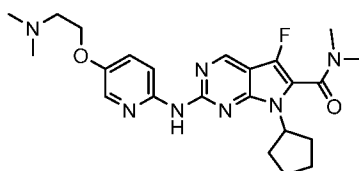


Synthesis of 7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A36**):

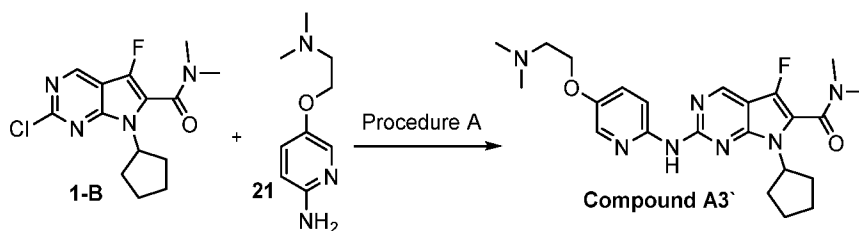


Compound **A36** was synthesized following the general procedure **A**, 12 mg. MS(ESI) *m/z* 494.3 (M+H)⁺.

Example 18: Compound A3

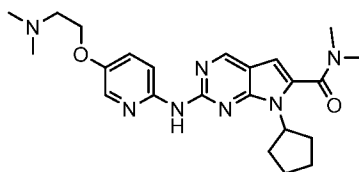


Synthesis of 7-cyclopentyl-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A3**):

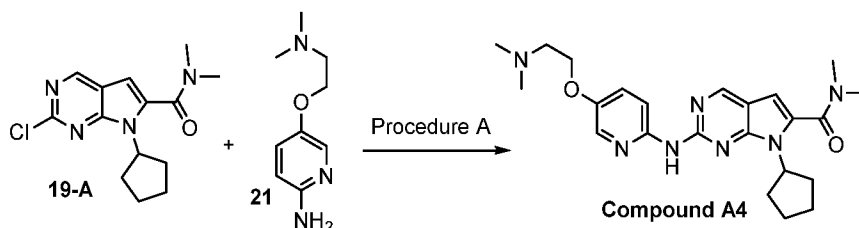


Compound **A3** was synthesized following the general procedure A, 26 mg (12% yield). MS(ESI) m/z 456.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 8.33 (d, J = 9.1 Hz, 1H), 8.07–8.01 (m, 2H), 7.32 (dd, J = 9.1, 3.0 Hz, 1H), 4.76 (p, J = 9.0 Hz, 1H), 4.11 (t, J = 5.6 Hz, 2H), 3.20 (s, 3H), 3.16 (s, 3H), 2.75 (t, J = 5.6 Hz, 2H), 2.58–2.47 (m, 2H), 2.36 (s, 6H), 2.08 (s, 2H), 2.05–1.96 (m, 2H), 1.78–1.62 (m, 2H).

10 Example 19: Compound A4

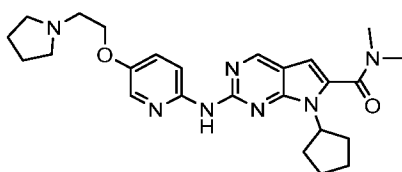


Synthesis of 7-cyclopentyl-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A4**):

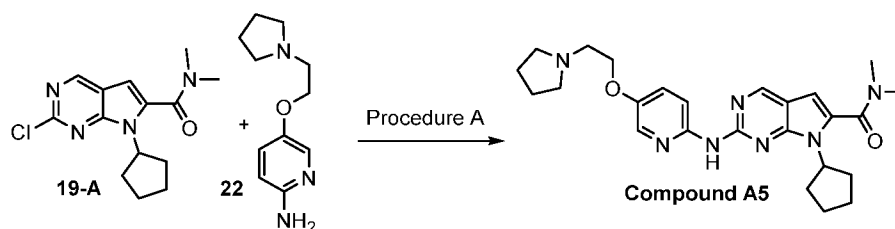


Compound **A4** was synthesized following the general procedure A, 26 mg (12% yield). MS(ESI) m/z 438.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.37 (d, J = 9.1 Hz, 1H), 8.02 (d, J = 3.0 Hz, 1H), 7.79 (s, 1H), 7.32 (dd, J = 9.1, 3.0 Hz, 1H), 6.44 (s, 1H), 4.78 (p, J = 8.9 Hz, 1H), 4.11 (t, J = 5.6 Hz, 2H), 3.16 (s, 6H), 2.75 (t, J = 5.6 Hz, 2H), 2.62–2.53 (m, 2H), 2.36 (s, 6H), 2.12–2.00 (m, 4H), 1.77–1.65 (m, 2H).

20 Example 20: Compound A5



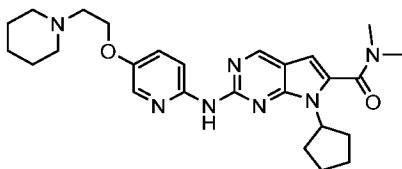
Synthesis of 7-cyclopentyl-*N,N*-dimethyl-2-((5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A5**):



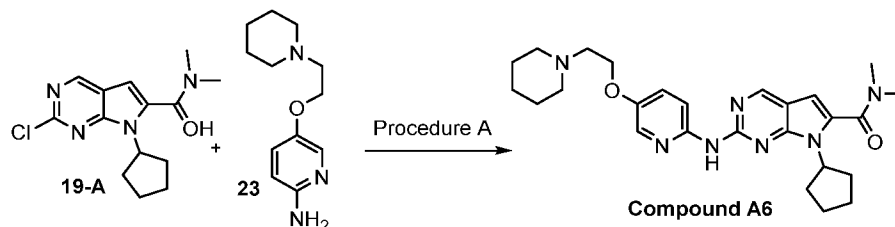
- 5 Compound **A5** was synthesized following the general procedure **A**, 35 mg (15% yield). MS(ESI) m/z 464.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 8.37 (d, J = 9.1 Hz, 1H), 8.02 (d, J = 3.0 Hz, 1H), 7.81 (s, 1H), 7.31 (dd, J = 9.1, 3.0 Hz, 1H), 6.44 (s, 1H), 4.78 (p, J = 9.0 Hz, 1H), 4.16 (t, J = 5.8 Hz, 2H), 3.16 (s, 6H), 2.94 (t, J = 5.8 Hz, 2H), 2.66 (s, 4H), 2.63–2.52 (m, 2H), 2.12–1.99 (m, 5H), 1.88–1.79 (m, 5H).

10

Example 21: Compound **A6**



Synthesis of 7-cyclopentyl-*N,N*-dimethyl-2-((5-(2-(piperidin-1-yl)ethoxy)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A6**):

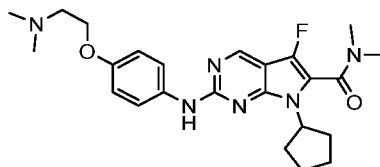


15

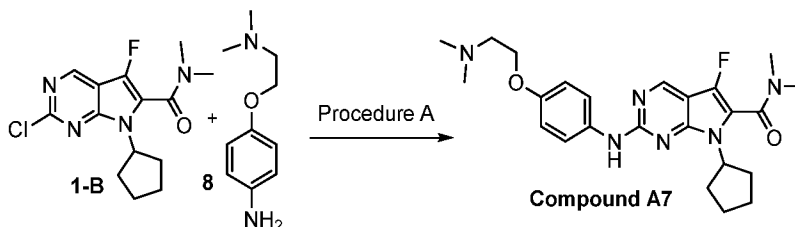
Compound **A6** was synthesized following the general procedure **A**, 215 mg (45% yield). MS(ESI) m/z 478.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.36 (d, J = 9.1 Hz, 1H), 8.01 (d, J = 3.0 Hz, 1H), 7.83 (s, 1H), 7.30 (dd, J = 9.1, 3.0 Hz, 1H), 6.44 (s, 1H), 4.78 (p, J = 9.0 Hz, 1H), 4.14 (t, J = 6.0 Hz, 2H), 3.16 (s, 6H), 2.78 (t, J = 6.0 Hz, 2H), 2.62–2.55 (m, 2H), 2.52 (s, 4H), 2.11–2.00 (m, 4H), 1.76–1.69 (m, 2H), 1.62–1.60 (m, 4H), 1.49–1.41 (m, 2H).

20

Example 22: Compound A7



Synthesis of 7-cyclopentyl-2-((4-(2-(dimethylamino)ethoxy)phenyl)amino)-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A7**):

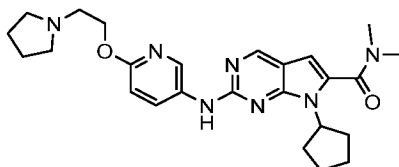


5

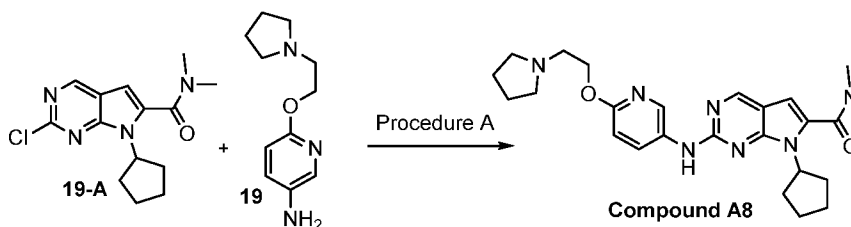
Compound **A7** was synthesized following the general procedure **A**, 2 mg (1% yield). MS(ESI) m/z 455.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 7.55 (d, J = 8.9 Hz, 2H), 7.03 (s, 1H), 6.93–6.90 (m, 2H), 4.72 (p, J = 9.0 Hz, 1H), 4.09 (t, J = 5.7 Hz, 2H), 3.19 (s, 3H), 3.14 (s, 3H), 2.76 (s, 2H), 2.48 (d, J = 9.8 Hz, 2H), 2.37 (s, 7H), 2.04 (s, 2H), 1.97 (s, 3H).

10

Example 23: Compound A8



Synthesis of 7-cyclopentyl-*N,N*-dimethyl-2-((6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A8**):

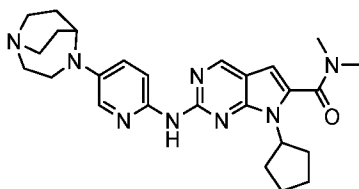


15

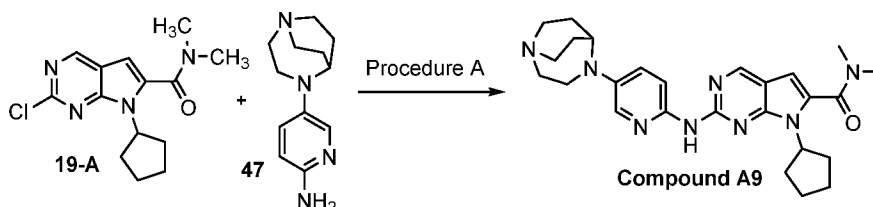
Compound **A8** was synthesized following the general procedure **A**, 47 mg (10% yield). MS(ESI) m/z 464.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.26 (d, J = 2.8 Hz, 1H), 8.05 (dd, J = 8.9, 2.8 Hz, 1H), 7.09 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H), 6.41 (s, 1H), 4.75 (s, 1H), 4.44 (t, J = 5.9 Hz, 2H), 3.14 (s, 6H), 2.90 (t, J = 5.9 Hz, 2H), 2.66–2.59 (m, 4H), 2.53–2.42 (m, 2H), 2.07–1.99 (m, 2H), 1.99–1.89 (m, 2H), 1.81 (s, 5H), 1.68–1.60 (m, 2H).

20

Example 24: Compound A9



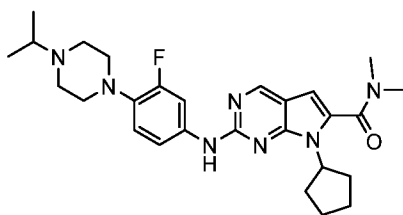
Synthesis of 2-((5-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-2-yl)amino)-7-cyclopentyl-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A9**):



5

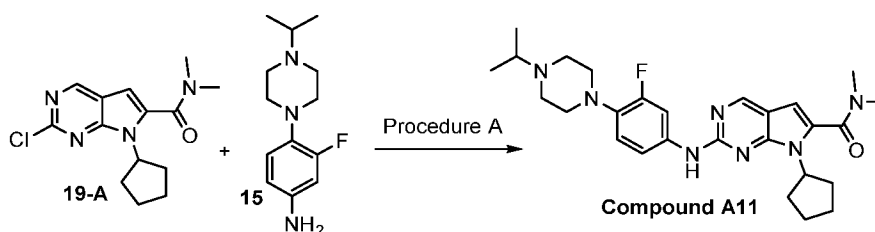
Compound **A9** was synthesized following the general procedure **A**, 12 mg (3% yield). MS(ESI) m/z 475.3 ($M+H$)⁺.

Example 25: Compound A11



10

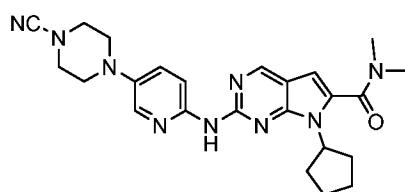
Synthesis of 7-cyclopentyl-2-((3-fluoro-4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A11**):



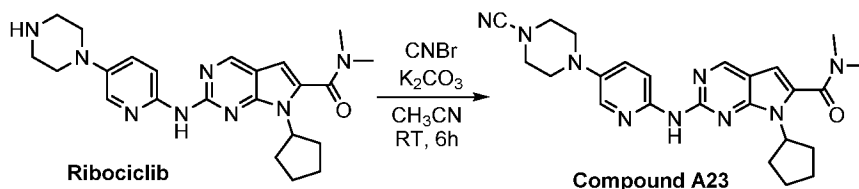
15

Compound **A11** was synthesized following the general procedure **A**, 2 mg (1% yield). MS(ESI) m/z 494.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 7.87 (dd, J = 14.8, 2.4 Hz, 1H), 7.09 (d, J = 3.7 Hz, 1H), 7.07–7.04 (m, 1H), 6.94 (t, J = 9.0 Hz, 1H), 6.42 (s, 1H), 4.75 (p, J = 9.0 Hz, 1H), 3.15 (s, 6H), 3.14–3.07 (m, 4H), 2.75 (s, 5H), 2.65–2.54 (m, 3H), 2.08 (d, J = 12.5 Hz, 5H), 1.57 (s, 75H).

20 Example 26: Compound A23



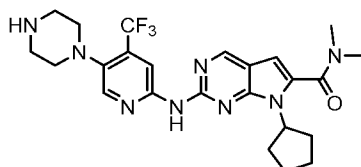
Synthesis of 2-((5-(4-cyanopiperazin-1-yl)pyridin-2-yl)amino)-7-cyclopentyl-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A23**):



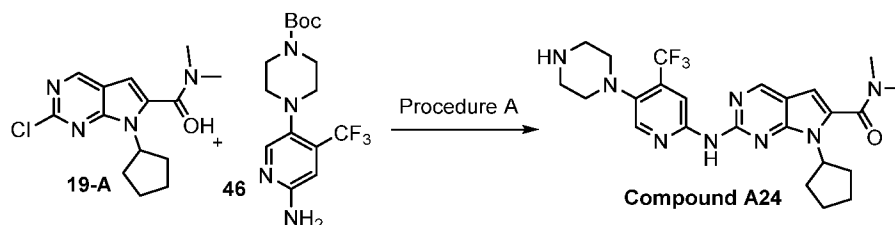
- 5 To a solution of **26-A** (120 mg, 0.28 mmol) in acetonitrile were added K₂CO₃ (116 mg, 0.84 mmol) and CNBr (59 mg, 0.56 mmol). The resulting mixture was stirred at RT for 6 h. The reaction mixture was concentrated under reduced pressure, diluted with DCM and washed with water and brine. The organic layer was dried over sodium sulfate, concentrated, and purified on column (19:1, DCM/MeOH). (20 mg, 16% yield). MS(ESI) *m/z* 460.3 (M+H)⁺.

10

Example 27: Compound A24



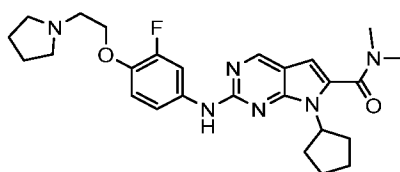
Synthesis of 7-cyclopentyl-*N,N*-dimethyl-2-((5-(piperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A24**):



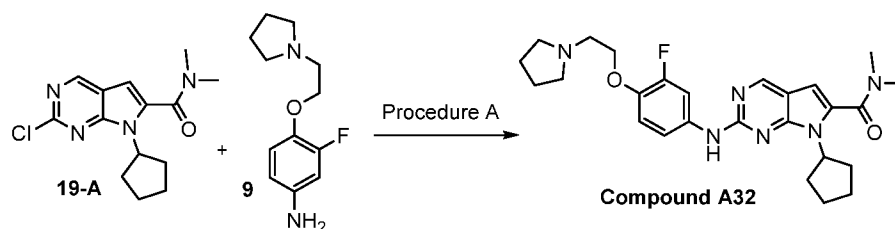
15

Compound **A24** was synthesized following the general procedure **A**, 4 mg. MS(ESI) *m/z* 503.3 (M+H)⁺.

Example 28: Compound A32



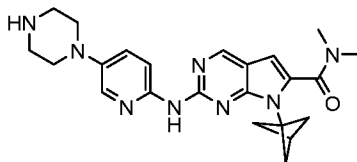
Synthesis of 7-cyclopentyl-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A32**):



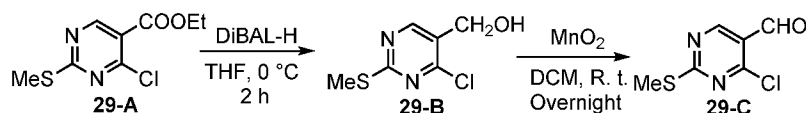
- 5 Compound **A32** was synthesized following the general procedure **A**, 7 mg. MS(ESI) m/z 481.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.61 (s, 1H), 7.90 (dd, J = 13.8, 2.6 Hz, 1H), 7.55 (s, 1H), 7.11–7.04 (m, 1H), 6.95 (t, J = 9.0 Hz, 1H), 6.42 (s, 1H), 4.75 (p, J = 9.0 Hz, 1H), 4.30 (t, J = 5.3 Hz, 2H), 3.24 (t, J = 5.3 Hz, 2H), 3.15 (s, 6H), 3.08 (s, 4H), 2.64–2.54 (m, 2H), 2.07 (d, J = 4.2 Hz, 4H), 1.98 (t, J = 3.5 Hz, 4H), 1.75–1.64 (m, 2H).

10

Example 29: Compound A12



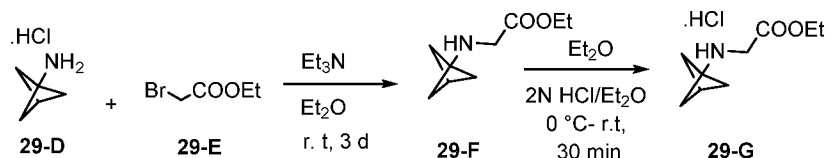
Step 1: Synthesis of 4-chloro-2-(methylthio)pyrimidine-5-carbaldehyde (**29-C**):



- 15 Synthesis of **29-B**: (Ref: WO 2015161285): To a stirred solution of compound **29-A** (40 g, 172 mmol) in anhydrous THF (500 mL) at 0 °C was added DIBAL-H (516 mL, 3 mmol) dropwise and stirred at 0 °C for 1 h and quenched with 600 mL of saturated NH₄Cl at 0 °C and warmed to RT and added 600 mL of saturated Rochelle Salt. To this, added 600 mL of ethyl acetate and stirred for 30 minutes. Two layers separated, and aqueous layer was washed with ethyl acetate and
- 20 combined organic layers dried on Na₂SO₄ and concentrated to get the crude compound which is purified by column chromatography (0 to 40% ethyl acetate in hexanes) to give compound 29-B (27 g, 67% yield). MS(ESI) m/z 191.1 [$M+H$]⁺.

Synthesis of **29-C**: (Ref: Reddy et al., *J. Med. Chem.* 57(3): 578–599 (2014)): The compound **29-B** (20 g, 105 mmol) was dissolved in dichloromethane to which manganese dioxide (MnO_2) (137 g, 1572 mmol) was added and stirred for 48 h. The solids were removed by filtration through a Celite pad and washed with dichloromethane. Solvent evaporated under reduced pressure to get crude compound which is purified by column chromatography (0 to 20% ethyl acetate in hexanes) to give compound **29-C** (13.3 g, 68% yield) as yellow solid. MS(ESI) m/z 189.0 $[\text{M}+\text{H}]^+$.

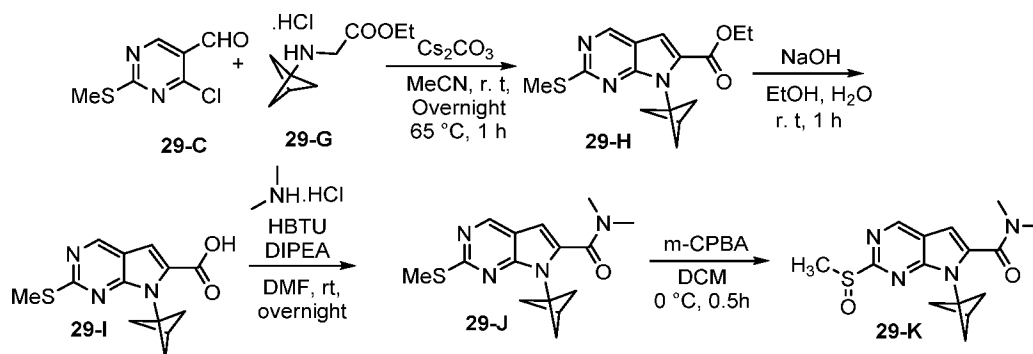
Step 2: Synthesis of ethyl 2-(cyclopentylamino)acetate hydrochloride (**26-G**):



Synthesis of **29-F**: (Ref: part in WO 199948858): To a solution of compound **29-D** (6 g, 70.46 mmol) in ether (100 mL) was added compound **29-E** (5.9 g, 35.23 mmol) and stirred at room temperature for 3 days. The solid was filtered and the filtrate was concentrated to get the crude product **29-F**.

Synthesis of **29-G**: Compound **29-F** was dissolved in ether and treated with 2 N HCl/ Et_2O (2 eq). The obtained solid is filtered and dried to get **29-G** (6.4 g, 89% yield) MS(ESI) m/z 170.2 $[\text{M}+\text{H}]^+$. ^1H NMR (600 MHz, Chloroform- d) δ 10.51 (s, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 3.77 (s, 2H), 2.68 (s, 1H), 2.21 (s, 6H), 1.32 (t, $J = 7.1$ Hz, 3H).

Step 3: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-(methylsulfinyl)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (**29-J**):



Synthesis of **29-H**: To a solution of compound **29-C** (2.5 g, 8 mmol) and Cs_2CO_3 (7.9 g, 24 mmol) in acetonitrile (100 mL) was added compound **29-G** (1.5 g, 8 mmol) under argon and the reaction mixture was stirred for overnight at RT and then at 65 °C for 1 h. After cooling to RT, solvent is

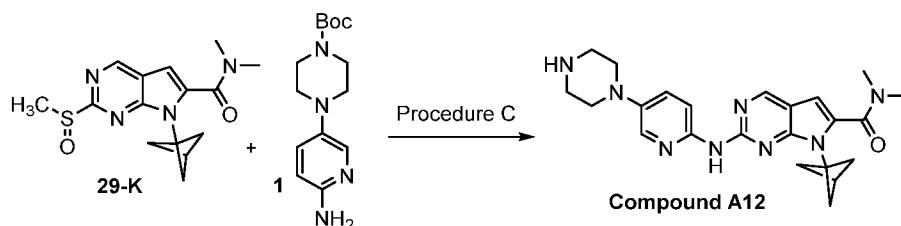
removed under reduced pressure and partitioned between with ethyl acetate (50 mL) and water (30 mL). The organic layer is separated, and aqueous layer was washed 3 times with ethyl acetate. Combined organic layers were dried on Na₂SO₄ and concentrated to get the crude compound which is purified by column chromatography (0 to 10% ethyl acetate in hexanes) to give compound **29-H** (1.6 g, 67% yield) as a white solid. MS(ESI) *m/z* 304.1 [M+H]⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 7.19 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.67 (s, 6H), 2.62 (s, 3H), 2.61 (s, 1H), 1.41 (t, *J* = 7.1 Hz, 3H).

Synthesis of **29-I**: To a solution of compound **29-H** (1.6 g, 5.2 mmol) in ethanol (20 mL) was added 10 mL of aqueous 2 *N* NaOH and stirred at room temperature for 1 h. The Solvent removed under reduced pressure, diluted with 10 mL of water and acidified with 2 *N* HCl. The solid was filtered and dried to give **29-I** as a white solid (1.4 g, 98% yield). MS(ESI) *m/z* 276.1 [M+H]⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.78 (s, 1H), 7.13 (s, 1H), 2.66 (s, 6H), 2.61 (s, 3H), 1.89 (s, 1H).

Synthesis of **29-J**: (Ref: WO 2010020675): To a solution of Compound **29-I** (6 g, 22.6 mmol), HBTU (12.9 g, 33.7 mmol) and diisopropylethylamine (11.8 mL, 67.8 mmol) in DMF (50 mL) was added *N,N*-dimethylamine hydrochloride (5.4 g, 27.1 mmol) and the reaction mixture was stirred for 2 h at room temperature. After completion, the reaction mixture was diluted with ethyl acetate (200 mL) and washed sequentially with saturated aqueous sodium bicarbonate (150 mL), water (100 mL), then 4X brine (100 mL). The organic phase is dried on Na₂SO₄ and concentrated to get the crude compound which is further purified by column chromatography (0 to 40% ethyl acetate in hexanes) to give compound **1-D** (9.5 g, 94% yield) as a light-yellow solid. MS(ESI) *m/z* 303.3 [M+H]⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 6.38 (s, 1H), 3.14 (s, 3H), 2.98 (s, 3H), 2.61 (s, 3H), 2.60 (s, 1H), 2.49 (s, 6H).

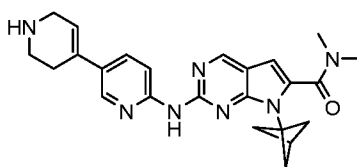
Synthesis of **29-K**: To a solution of **29-J** (2 g, 4.9 mmol) in DCM (400 mL) at 0 °C was added *m*-CPBA in one portion. The resulting mixture was stirred at same temperature for 30 min. The reaction mixture was washed with saturated NaHCO₃ solution and brine respectively. The organic layer is then dried over sodium sulfate, filtered and concentrated under reduced pressure to give **29-K** which was used as such for next step (2 g, quantitative). MS(ESI) *m/z* 319.2 [M+H]⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 9.06 (s, 1H), 6.56 (s, 1H), 3.17 (s, 3H), 3.00 (s, 3H), 2.98 (s, 3H), 2.65 (s, 1H), 2.52 (s, 6H).

Step 4: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A12**):

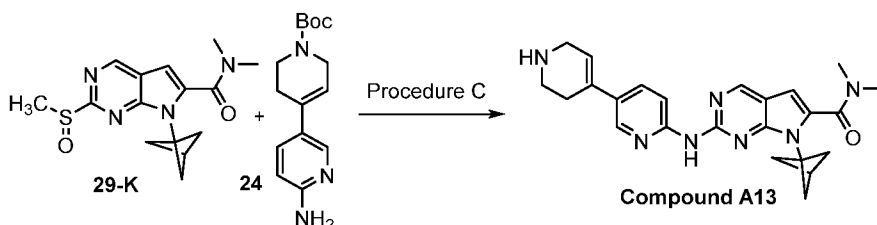


Compound **A12** was synthesized following the general procedure **C**, 25 mg (19% yield). MS(ESI) m/z 433.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 8.34 (d, J = 9.1 Hz, 1H), 7.99 (d, J = 3.0 Hz, 1H), 7.73 (s, 1H), 7.36 (dd, J = 9.1, 3.0 Hz, 1H), 6.35 (s, 1H), 3.16–3.10 (m, 7H), 3.10–3.05 (m, 4H), 3.01 (s, 3H), 2.62 (s, 1H), 2.50 (s, 6H).

Example 30: Compound A13

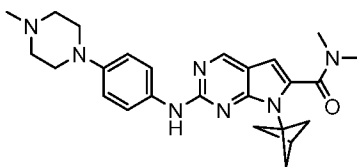


Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A13**):

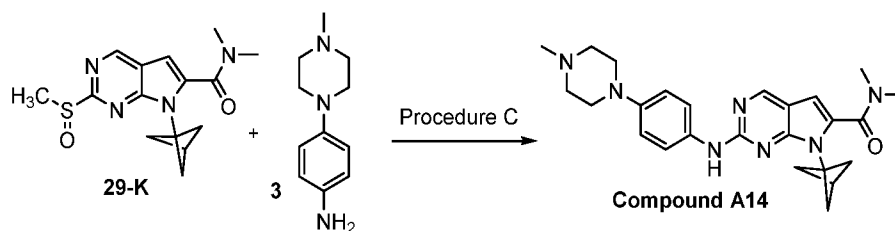


Compound **A13** was synthesized following the general procedure **C**, 9 mg (7% yield). MS(ESI) m/z 430.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.48 (d, J = 8.8 Hz, 1H), 8.32 (d, J = 2.5 Hz, 1H), 8.05 (s, 1H), 7.72 (dd, J = 8.9, 2.5 Hz, 1H), 6.39 (s, 1H), 6.04 (s, 1H), 3.88 (s, 2H), 3.47 (t, J = 6.0 Hz, 2H), 3.15 (s, 3H), 3.02 (s, 3H), 2.82 (s, 2H), 2.64 (s, 1H), 2.51 (s, 5H), 2.17 (s, 1H).

Example 31: Compound A14

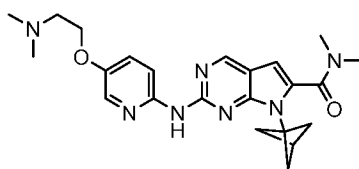


Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A14**):

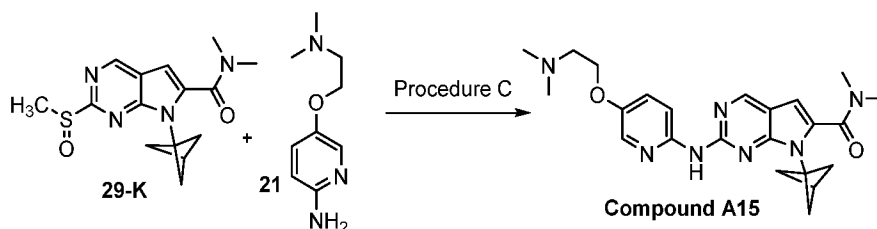


Compound **A14** was synthesized following the general procedure **C**, 33 mg (25% yield). MS(ESI) m/z 446.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 7.58 (d, J = 9.0 Hz, 2H), 7.01 (s, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.32 (s, 1H), 3.22 (t, J = 4.9 Hz, 4H), 3.13 (s, 3H), 3.00 (s, 3H), 2.68 (s, 4H), 2.59 (s, 1H), 2.47 (s, 6H), 2.42 (s, 3H).

Example 32: Compound A15

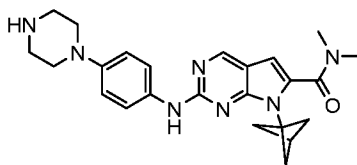


Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A15**):

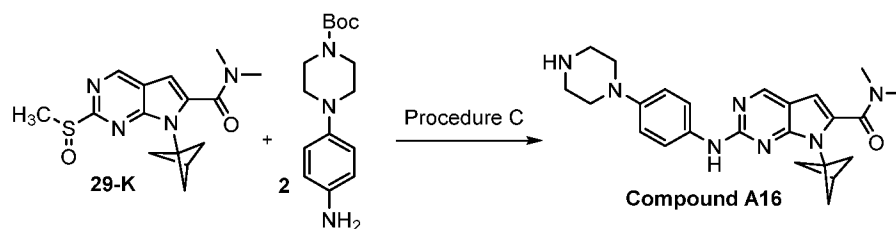


Compound **A15** was synthesized following the general procedure **C**, 54 mg (42% yield). MS(ESI) m/z 436.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 8.35 (d, J = 9.1 Hz, 1H), 8.03 (d, J = 3.0 Hz, 1H), 7.88 (s, 1H), 7.34 (dd, J = 9.1, 3.0 Hz, 1H), 6.35 (s, 1H), 4.11 (t, J = 5.6 Hz, 2H), 3.14 (s, 3H), 3.01 (s, 3H), 2.75 (t, J = 5.6 Hz, 2H), 2.62 (s, 1H), 2.49 (s, 6H), 2.36 (s, 6H).

Example 33: Compound A16

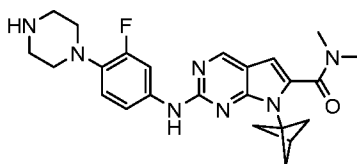


Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(piperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A16**):

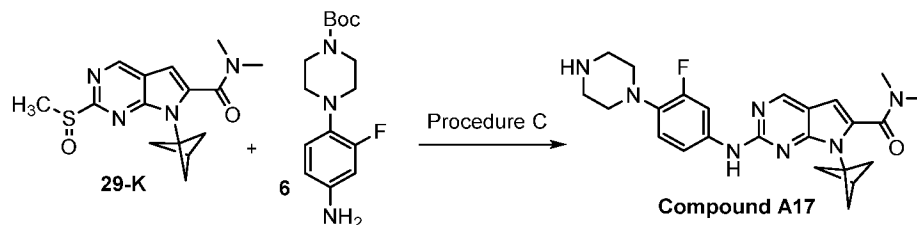


Compound **A16** was synthesized following the general procedure **C**, 18 mg (28% yield). MS(ESI) m/z 432.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 7.66–7.61 (m, 2H), 6.99–6.94 (m, 2H), 6.34 (s, 1H), 3.41–3.34 (m, 8H), 3.13 (s, 3H), 3.01 (s, 3H), 2.61 (s, 1H), 2.48 (s, 6H).

Example 34: Compound A17

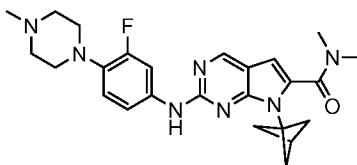


10 Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A17**):

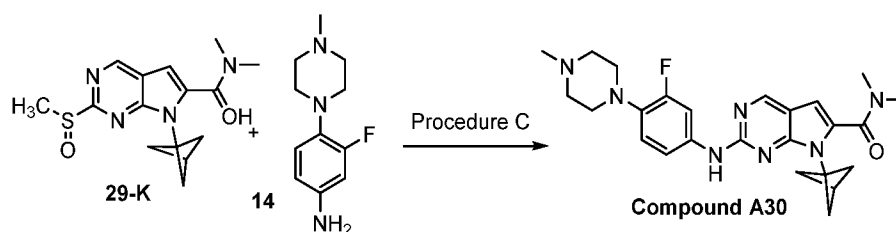


15 Compound **A17** was synthesized following the general procedure **C**, 33 mg (49% yield). MS(ESI) m/z 450.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.60 (s, 1H), 7.84 (dd, J = 14.5, 2.5 Hz, 1H), 7.18 (dd, J = 8.9, 2.4 Hz, 1H), 6.95 (t, J = 9.0 Hz, 1H), 6.36 (s, 1H), 3.42–3.30 (m, 8H), 3.14 (s, 3H), 3.01 (s, 3H), 2.64 (s, 1H), 2.50 (s, 6H).

Example 35: Compound A30

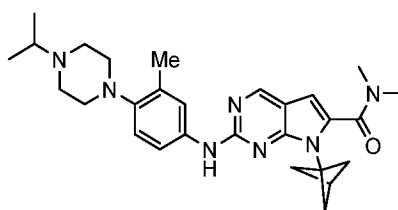


20 Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (Compound **A30**):

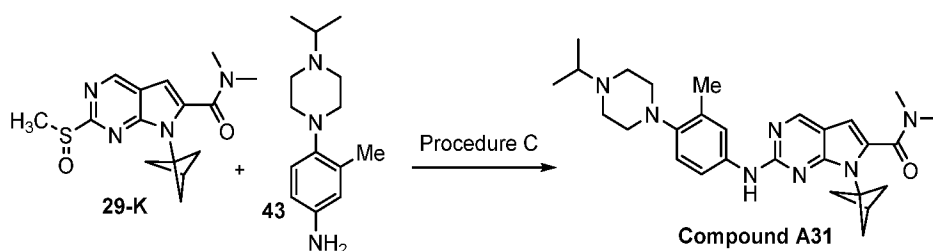


Compound **A30** was synthesized following the general procedure **C**, 4 mg. MS(ESI) m/z 464.3 ($M+H$)⁺.

5 Example 36: Compound A31

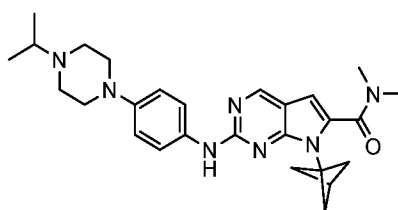


Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)-3-methylphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A31**):

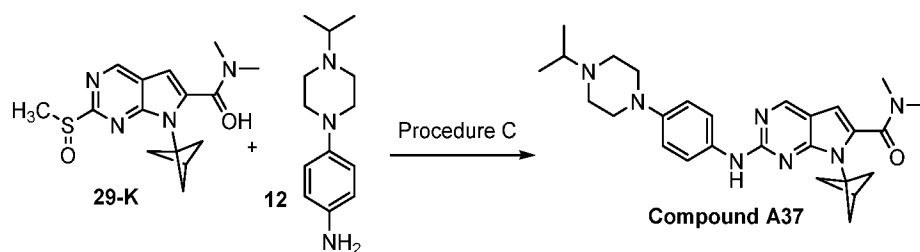


Compound **A31** was synthesized following the general procedure **C**, 10 mg. MS(ESI) m/z 488.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 7.54 (dd, J = 21.1, 3.4 Hz, 3H), 7.07 (d, J = 8.5 Hz, 1H), 6.33 (s, 1H), 3.13 (s, 8H), 3.00 (s, 4H), 2.63 (s, 1H), 2.50 (s, 6H), 2.32 (s, 4H), 2.09 (s, 2H), 1.30 (d, J = 6.6 Hz, 6H).

Example 37: Compound A37



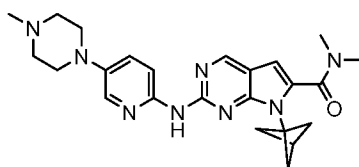
Step 4: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A37**):



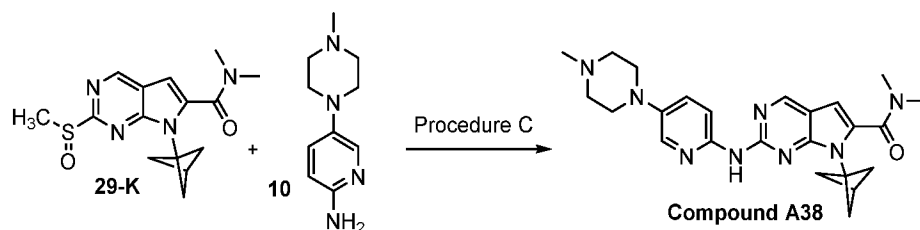
Compound **A37** was synthesized following the general procedure **C**, 7 mg. MS(ESI) m/z 474.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 6.87–6.76 (m, 3H), 6.70–6.61 (m, 3H), 3.09–3.00 (m, 6H), 2.75–2.62 (m, 7H), 1.59 (s, 8H), 1.09 (d, J = 6.5 Hz, 8H).

5

Example 38: Compound A38



Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A38**):

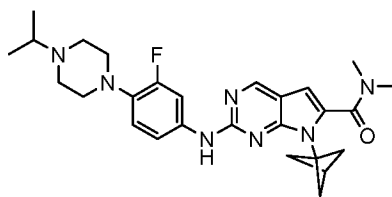


10

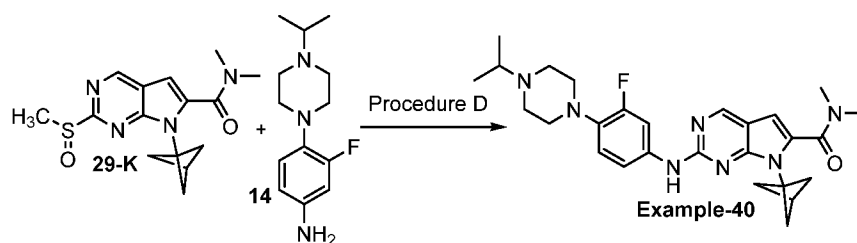
Compound **A38** was synthesized following the general procedure **C**, 9 mg. MS(ESI) m/z 447.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 8.42 (d, J = 9.0 Hz, 1H), 8.03 (d, J = 2.9 Hz, 1H), 7.94 (s, 1H), 7.42 (dd, J = 9.1, 3.0 Hz, 1H), 6.37 (s, 1H), 3.55 (s, 6H), 3.14 (s, 3H), 3.01 (s, 3H), 2.84 (s, 3H), 2.65 (s, 1H), 2.50 (s, 6H), 2.01 (s, 2H).

15

Example 39: Compound A39

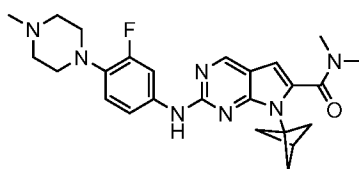


Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A39**):

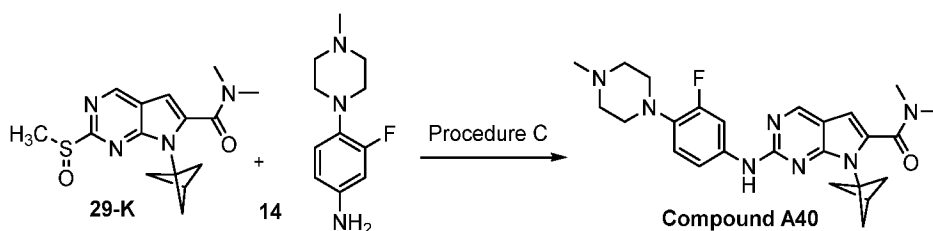


Compound **A39** was synthesized following the general procedure **C**, 3 mg. MS(ESI) m/z 475.3 (M+H)⁺.

5 Example 40: Compound A40

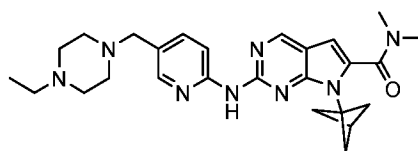


Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A40**):

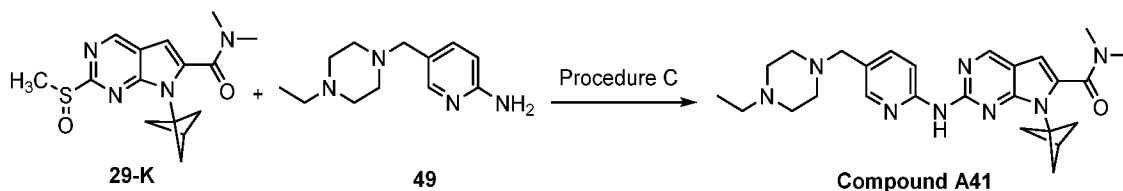


10 Compound **A40** was synthesized following the general procedure **C**, 8 mg. MS(ESI) m/z 492.3 (M+H)⁺.

Example 41: Compound A41

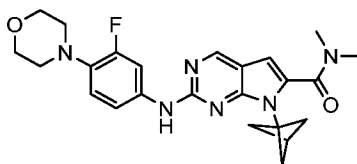


15 Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A41**):



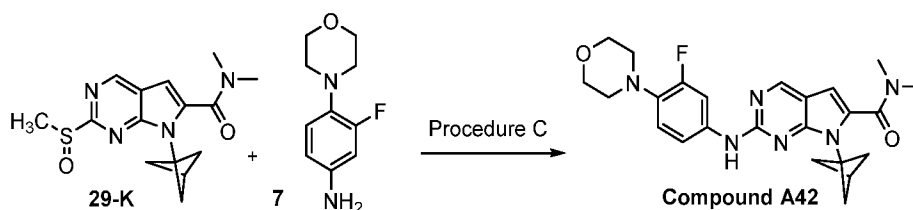
Compound **A41** was synthesized following the general procedure **C**, 25 mg (34% yield). MS(ESI) m/z 475.3 (M+H)⁺.

Example 42: Compound A42



5

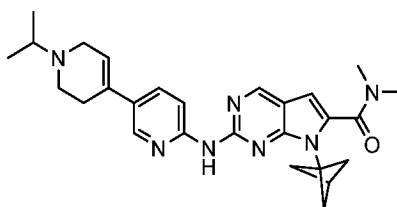
Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-morpholinophenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A42**):



Compound **A42** was synthesized following the general procedure **C**, 9 mg. MS(ESI) m/z 451.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 7.83 (dd, J = 15.0, 2.5 Hz, 1H), 7.35 (s, 1H), 7.19–7.10 (m, 1H), 6.93 (t, J = 9.1 Hz, 1H), 6.34 (s, 1H), 3.95–3.78 (m, 5H), 3.13 (s, 2H), 3.09–3.04 (m, 3H), 3.00 (s, 3H), 2.62 (s, 1H), 2.50 (s, 6H), 2.12 (s, 1H).

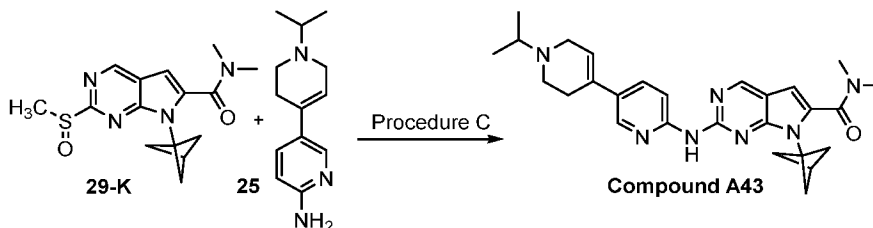
10

Example 43: Compound A43



15

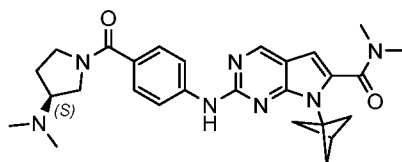
Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((1'-isopropyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A43**):



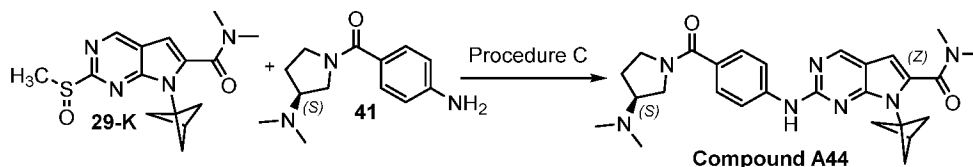
Compound **A43** was synthesized following the general procedure **D**, 5 mg (4% yield). MS(ESI) m/z 472.3 (M+H)⁺.

20

Example 44: Compound A44

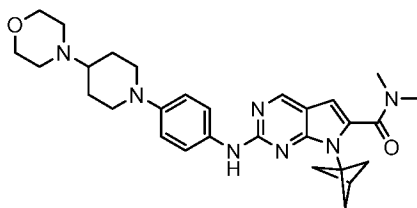


Synthesis of (S)-7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(3-(dimethylamino)pyrrolidine-1-carbonyl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A44**):

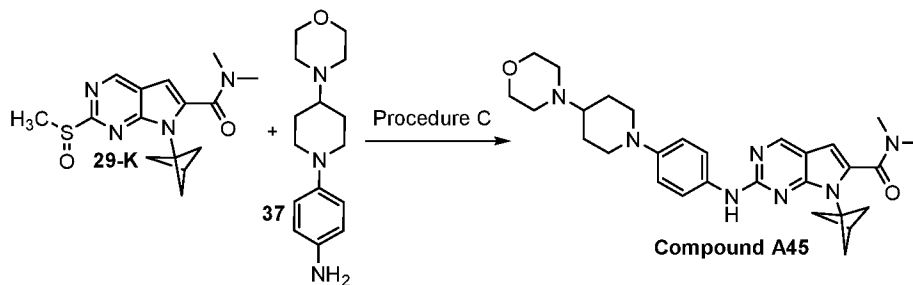


Compound **A44** was synthesized following the general procedure **D**, 6 mg. MS(ESI) m/z 488.3 (M+H)⁺.

Example 45: Compound A45

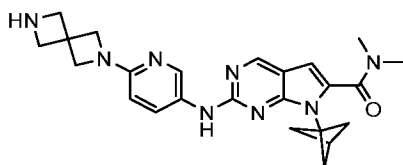


Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A45**):

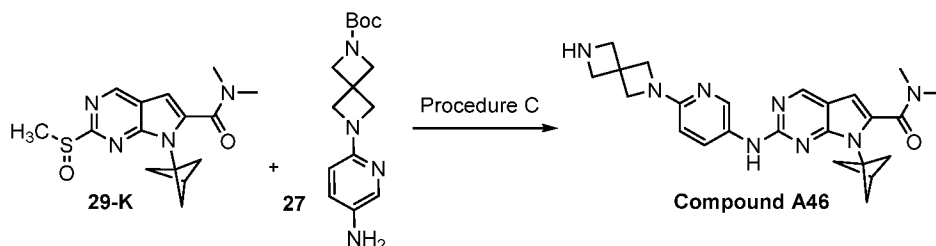


Compound **A45** was synthesized following the general procedure **C**, 12 mg (16% yield). MS(ESI) m/z 516.3 (M+H)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 7.56 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.31 (s, 1H), 3.79–3.71 (m, 3H), 3.68 (d, J = 12.3 Hz, 2H), 3.13 (s, 2H), 3.00 (s, 2H), 2.70 (t, J = 11.2 Hz, 2H), 2.64–2.54 (m, 4H), 2.47 (s, 4H), 2.38–2.29 (m, 1H), 1.95 (d, J = 12.3 Hz, 2H), 1.75–1.65 (m, 2H), 1.58 (s, 6H).

Example 46: Compound A46

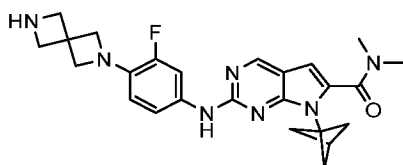


Synthesis of 2-((6-(2,6-diazaspiro[3.3]heptan-2-yl)pyridin-3-yl)amino)-7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A46**):

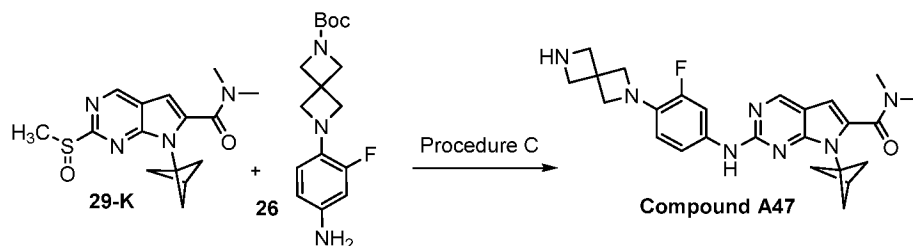


Compound **A46** was synthesized following the general procedure **C**, 16 mg (36% yield). MS(ESI) m/z 445.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.98 (dd, J = 8.8, 2.6 Hz, 1H), 7.12 (s, 1H), 6.40 (d, J = 8.8 Hz, 1H), 6.32 (s, 1H), 4.28 (s, 4H), 4.19 (s, 4H), 3.13 (s, 3H), 3.00 (s, 3H), 2.59 (s, 1H), 2.43 (s, 6H).

Example 47: Compound A47



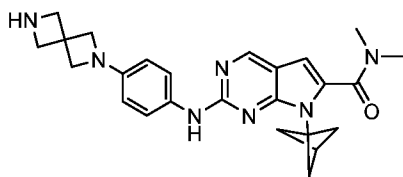
Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Compound **A47**):



Compound **A47** was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 462.3 ($M+H$)⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 7.70 (dd, J = 14.5, 2.1 Hz, 1H), 7.43 (s, 1H), 7.17–7.05 (m, 1H), 6.46 (t, J = 9.2 Hz, 1H), 6.34 (s, 1H), 4.27 (s, 4H), 4.10 (s, 4H), 3.13 (s, 3H), 3.00 (s, 3H), 2.63 (s, 1H), 2.48 (s, 6H).

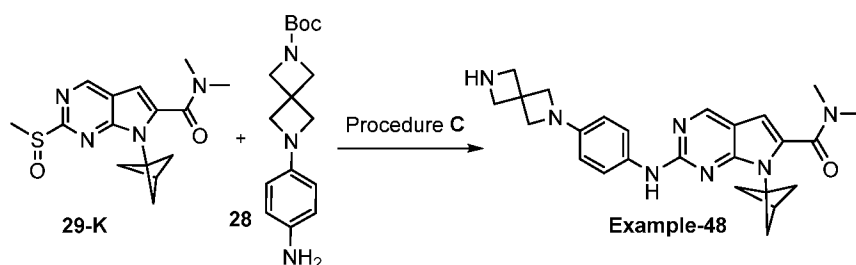
Example 4General Procedure D:

(Ref: Part in US7776869): A mixture of amide (1 eq), corresponding amine (1.5 eq), TFA (10 eq.)
 5 in 2-propanol were heated at 100 °C in a sealed tube for 24 h. After completion, the reaction mixture was concentrated and purified using silica gel chromatography (0 to 100% Methanol in dichloromethane). The fractions containing required compound were collected and concentrated under reduced pressure. The obtained residue was dissolved and stirred in 5 mL of 30% TFA/DCM solution for 2 h at RT. The mixture was concentrated to dryness and treated with 7N
 10 NH₃/MeOH solution. The mixture was concentrated again and purified using a C18 column (0 to 100% CH₃CN in H₂O with 0.025% AcOH). The fractions containing desired compound were combined and lyophilized.

Example-48 (VP-7-148A, SPV-426)

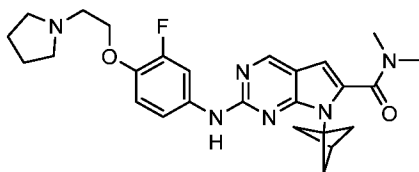
15

Step 1: Synthesis of 2-((4-(2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-48):

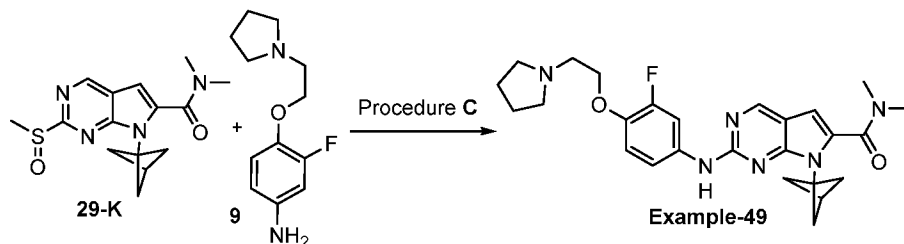


20

Example-48 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 444.3 (M+H)⁺.

Example-49 (VP-7-155A, SPV-427)

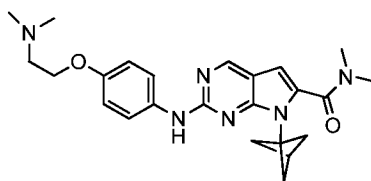
Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-49):



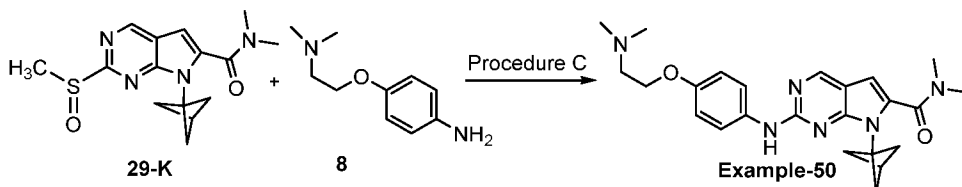
- 5 Example-49 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 479.3 ($M+H$)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.44 (s, 1H), 8.64 (s, 1H), 7.81 (dd, J = 14.5, 2.6 Hz, 1H), 7.33 (dt, J = 8.9, 1.8 Hz, 1H), 7.05 (t, J = 9.4 Hz, 1H), 6.40 (s, 1H), 4.03 (t, J = 5.9 Hz, 2H), 2.72 (t, J = 5.9 Hz, 2H), 2.55 (s, 1H), 2.47 (d, J = 3.6 Hz, 4H), 2.34 (s, 5H), 1.84 (s, 1H), 1.65 – 1.57 (m, J = 3.8, 3.3 Hz, 4H).

10

Example-50 (VP-8-31B, SPV-534)



Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-50):

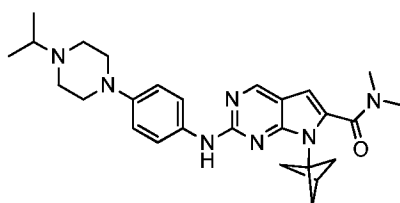


15

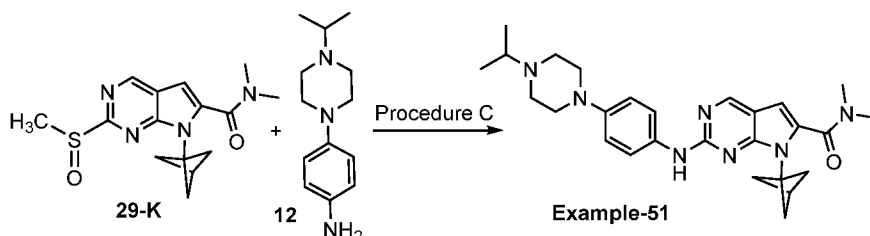
Example-50 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 435.2 ($M+H$)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 8.67 (s, 1H), 7.70 – 7.66 (m, 2H), 6.91 – 6.87 (m, 2H), 6.44 (s, 1H), 4.01 (t, J = 5.9 Hz, 2H), 3.01 (s, 3H), 2.95 (s, 3H), 2.62 – 2.59 (m, 3H), 2.39 (s, 6H), 2.22 (s, 6H).

20

Example-51 (VP-NR11-145A, SPV-539)

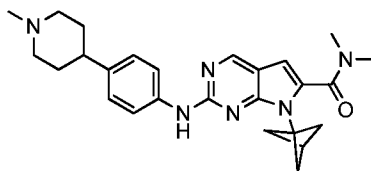


Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-51):

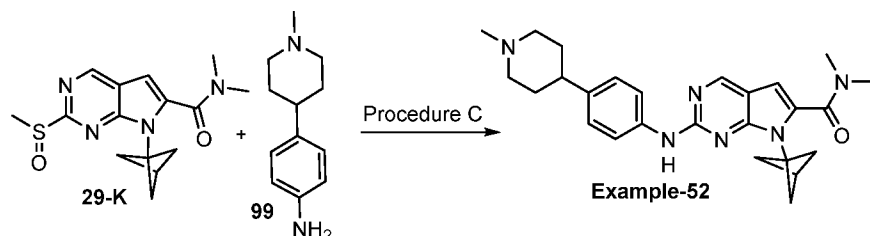


5 Example-51 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 474.2 ($M+H$)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 8.71 (s, 1H), 7.74 – 7.68 (m, 2H), 6.98 – 6.92 (m, 2H), 6.49 (s, 1H), 3.11 (t, J = 4.9 Hz, 4H), 2.74 (p, J = 6.5 Hz, 1H), 2.65 (dd, J = 10.3, 5.4 Hz, 5H), 2.56 (s, 2H), 1.07 (d, J = 6.5 Hz, 6H).

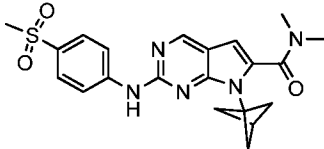
10 Example-52 (VP-NR11-146A, SPV-540)



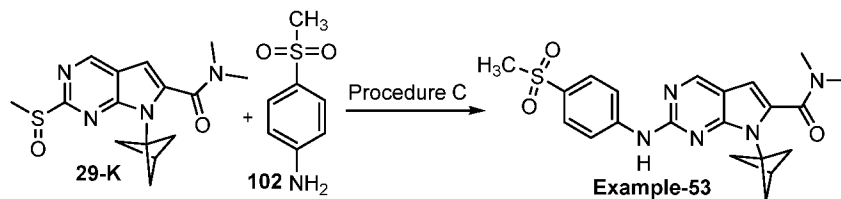
Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(1-methylpiperidin-4-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-52):



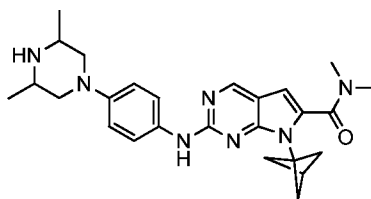
15 Example-52 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 445.2 ($M+H$)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.33 (s, 1H), 8.62 (s, 1H), 7.69 – 7.64 (m, 2H), 7.11 – 7.06 (m, 2H), 6.39 (s, 1H), 2.80 (dt, J = 11.7, 3.1 Hz, 2H), 2.55 (s, 1H), 2.43 (d, J = 3.8 Hz, 3H), 2.34 (s, 6H), 2.13 (s, 3H), 1.91 (td, J = 11.7, 2.5 Hz, 2H), 1.83 (s, 3H), 1.69 – 1.62 (m, 2H), 1.58 (qd, J = 12.3, 3.7 Hz, 2H).

Example-53 (VP-NR11-154C, SPV-541)

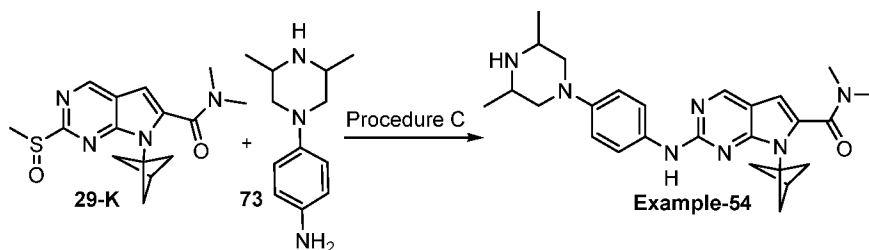
Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(methylsulfonyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-53):



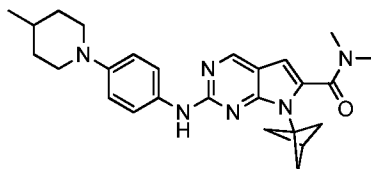
Example-53 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 445.2 (M+H)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.04 (s, 1H), 8.75 (s, 1H), 8.03 – 7.97 (m, 2H), 7.79 – 7.74 (m, 2H), 6.47 (s, 1H), 3.09 (s, 3H), 2.96 (s, 3H), 2.89 (s, 3H), 2.58 (s, 1H), 2.37 (s, 6H).

Example-54 (VP-NR11-164A, SPV-543)

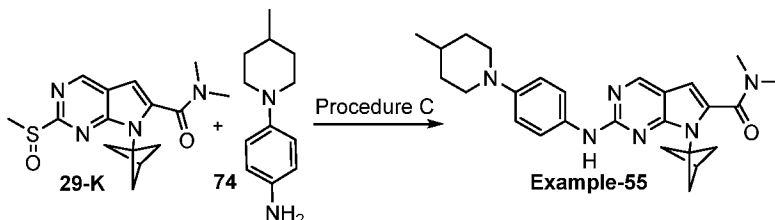
Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(3,5-dimethylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-54):



Example-54 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 460.2 (M+H)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.21 (s, 1H), 8.65 (s, 1H), 7.67 – 7.62 (m, 2H), 6.91 – 6.86 (m, 2H), 6.43 (s, 1H), 3.49 – 3.43 (m, 2H), 2.98 (d, J = 35.3 Hz, 5H), 2.90 (s, 2H), 2.61 (s, 1H), 2.09 (d, J = 6.4 Hz, 3H), 1.91 (s, 2H), 1.04 (d, J = 6.3 Hz, 5H).

Example-55 (VP-NR11-166B, SPV-544)

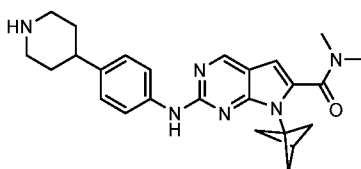
Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-methylpiperidin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-55):



5

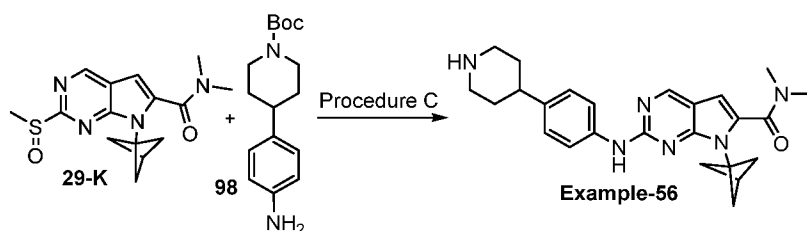
Example-55 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 445.2 (M+H)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.19 (s, 1H), 8.65 (s, 1H), 7.66 – 7.60 (m, 2H), 6.91 – 6.86 (m, 2H), 6.43 (s, 1H), 3.54 (dt, *J* = 12.6, 3.5 Hz, 2H), 2.98 (d, *J* = 35.4 Hz, 6H), 2.60 (s, 1H), 2.60 – 2.54 (m, 2H), 2.39 (s, 6H), 1.72 – 1.66 (m, 2H), 1.25 (qd, *J* = 12.1, 4.0 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H).

10

Example-56 (VP-NR11-155A, SPV-545)

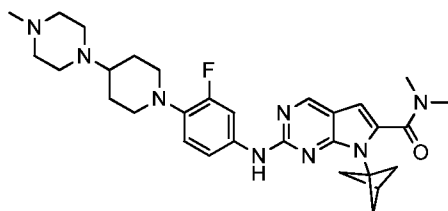
Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(piperidin-4-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-56):

15

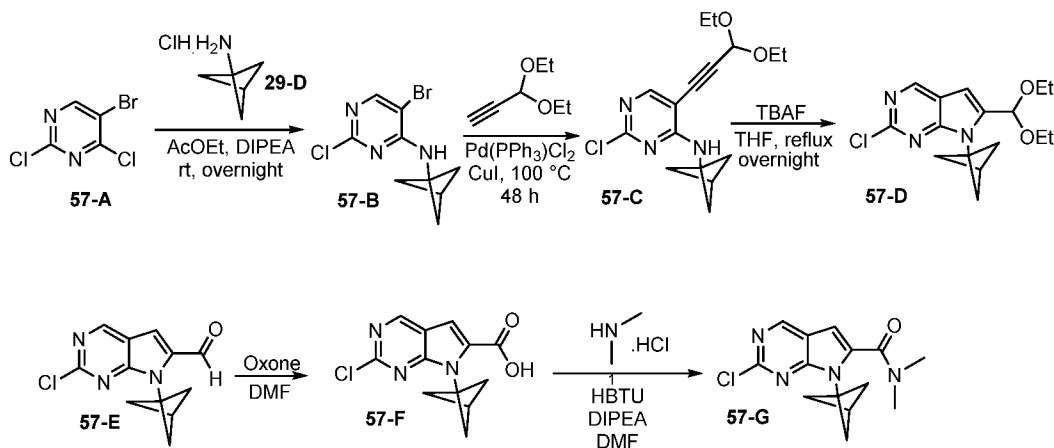


Example-56 was synthesized following the general procedure **C**, 6 mg (13% yield). MS(ESI) m/z 431.2 (M+H)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.46 (s, 1H), 8.70 (s, 1H), 7.80 – 7.75 (m, 2H), 7.18 – 7.13 (m, 2H), 6.47 (s, 1H), 2.98 (d, *J* = 2.9 Hz, 2H), 2.93 (d, *J* = 2.8 Hz, 1H), 2.80 – 2.73 (m, 1H), 2.62 (s, 1H), 1.93 (d, *J* = 3.6 Hz, 1H), 1.91 (s, 2H), 1.74 (tt, *J* = 12.9, 6.6 Hz, 3H).

20

Example-57 (VP-NR11-73C, SPV-535)

Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-chloro-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (**57-G**):



Synthesis of **57-B**: (Ref : Green Chemistry Letters and Reviews, 10(1), 42-47; 2017) : To a solution of 5-bromo-2,4-dichloropyrimidine (25 g, 110.7 mmol) in AcOEt (400 mL) was added **29-D** (20.4 g, 240 mmol) and DIPEA (36 g, 277 mmol) at room temperature. The mixture thus obtained was stirred at room temperature for 24 h. The reaction mixture was then diluted with ethyl acetate, washed with brine, and dried over MgSO₄. The solvent was evaporated to give compound **57-B** which was used in next step without further purification. (30 g, 92%). MS (ESI) m/z: 273.8 [M + H]⁺. ¹H NMR (600 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 5.88 (s, 1H), 2.56 (s, 1H), 2.23 (s, 6H).

Synthesis of **57-C**: (Ref: WO2010020675): To a stirred solution of **57-B** (30 g, 110 mmol) in DMF (200 mL) were added Et₃N (22.2 g, 220 mmol) and 3,3-diethoxypropyne (21.1 g, 165 mmol) sequentially at room temperature. The mixture was degassed under a stream of N₂ and stirred at room temperature for 10 minutes before CuI (29 mg, 0.154 mmol) and PdCl₂(PPh₃)₂ (7.7 g, 11 mmol) were added. The reaction vessel is evacuated and backfilled with N₂ (×3) and heated at 100 °C for 48 hours. The mixture was allowed to cool to rt, diluted with EtOAc, filtered on celite and partitioned between H₂O and ethyl acetate. The phases are separated, and the aqueous layer

is further extracted with EtOAc ($\times 3$), combined organic extracts are dried (Na_2SO_4), filtered and concentrated. The residue was purified by SiO_2 chromatography (hexane/EA) to give **57-C** (5.2 g, 25%). MS (ESI) m/z : 322.2

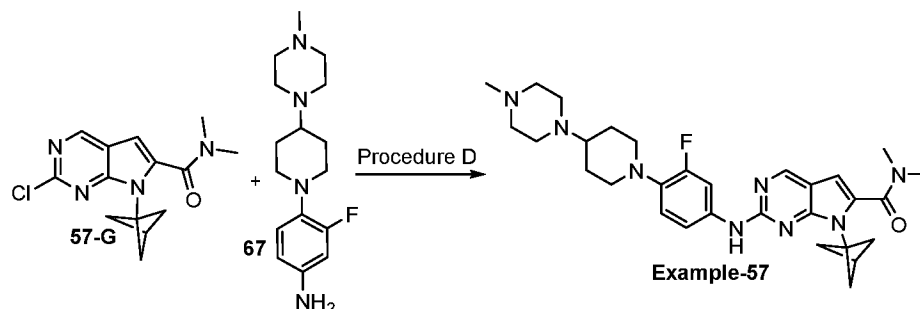
Synthesis of 57-D: (Ref: WO2010020675): To a stirred solution of **57-C** (5.2 g, 16.2 mmol) in THF (35 mL) is added 1N TBAF in THF (70 mL, 81 mmol) at room temperature. The reaction mixture is heated under reflux overnight. After cooling to rt, the mixture is partitioned between H_2O and dichloromethane. The phases are separated, and the aqueous layer is extracted with dichloromethane ($\times 2$). The combined organic extracts are dried (MgSO_4), filtered and concentrated. The residue is purified by SiO_2 chromatography eluting with a gradient of 10% EtOAc/Hexane to 30% EtOAc/Hexane to give **57-D** (2.3 g, 44%). ^1H NMR (600 MHz, Chloroform- d) δ 8.71 (s, 1H), 6.68 (d, $J = 0.9$ Hz, 1H), 5.74 (d, $J = 0.8$ Hz, 1H), 3.58 (q, $J = 7.0$ Hz, 4H), 2.61 (s, 7H), 1.24 (t, $J = 7.1$ Hz, 6H).

Synthesis of 57-E: To A mixture of **57-D** (2.3 g, 7.16 mmol) in dioxane (30 mL) is added concentrated HCl (10 mL). After reaction is completed within 10 min, water is added and then extracted with ethyl acetate. Solvent is removed to give a brown color crude product **57-E**. Used as such for the next step (1.8 g, 100%). ^1H NMR (600 MHz, Chloroform- d) δ 10.02 (s, 1H), 8.97 (s, 1H), 7.30 (s, 1H), 2.67 (s, 7H).

Synthesis of 57-F: To a solution of **57-E** (1.8 g, 7.1 mmol) in DMF (30 mL) is added oxone (4 g, 13 mmol) and the resulting mixture is stirred for 30 h. After the reaction is complete, water is added, and the yellow solid is filtered to give **57-F** (1.4 g, 75% yield). ^1H NMR (600 MHz, Chloroform- d) δ 8.91 (s, 1H), 7.37 (s, 1H), 3.50 (s, 1H), 2.68 (s, 2H), 2.62 (d, $J = 12.2$ Hz, 1H), 2.47 (s, 1H), 0.91 – 0.77 (m, 2H).

Synthesis of 57-G: (Ref: Part in WO 2010020675): **57-F** (1.4 g, 5.6 mmol), HBTU (2.54 g, 6.72 mmol) and diisopropylethylamine (2.9 mL, 16.8 mmol) are dissolved in dimethylformamide (20 mL). Dimethyl amine. HCl (0.55 g, 6.8 mmol) is added and the mixture is stirred for 3 h to achieve complete conversion. The reaction mixture is diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate, water, then brine. The organic phase is dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on silicagel (ethyl acetate:hexane) provides **57-G** (1.1 g, 67% yield). ^1H NMR (600 MHz, Chloroform- d) δ 8.78 (s, 1H), 6.46 (s, 1H), 3.15 (s, 3H), 2.97 (s, 3H), 2.62 (s, 1H), 2.50 (s, 6H).

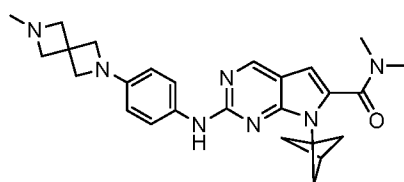
Step 2: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-57):



- 5 Example-57 was synthesized following the general procedure **D**, 6 mg (13% yield). MS(ESI) m/z 547.2 ($M+H$)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.53 (s, 1H), 8.71 (s, 1H), 7.85 (dd, J = 15.6, 2.5 Hz, 1H), 7.41 – 7.36 (m, 1H), 6.98 (dd, J = 10.1, 8.8 Hz, 1H), 6.47 (s, 1H), 2.98 (d, J = 40.1 Hz, 6H), 2.66 – 2.59 (m, 6H), 2.48 (s, 4H), 2.41 (s, 6H), 2.09 (s, 1H), 1.91 (s, 1H), 1.88 – 1.83 (m, 2H), 1.62 – 1.57 (m, 1H), 1.55 (d, J = 9.1 Hz, 1H).

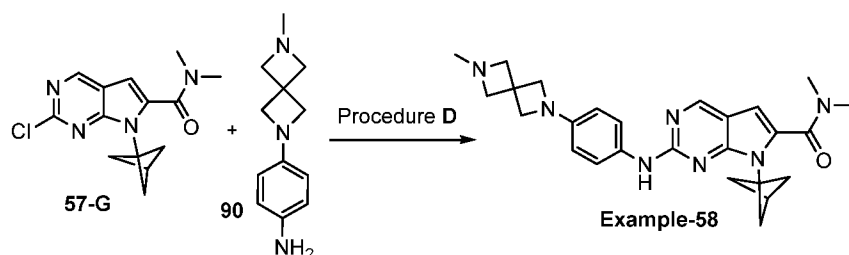
10

Example-58 (VP-NR11-74B, SPV-536)



Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-58):

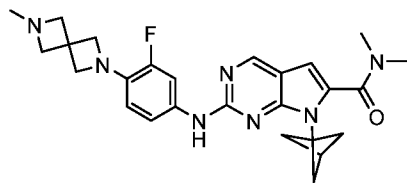
15



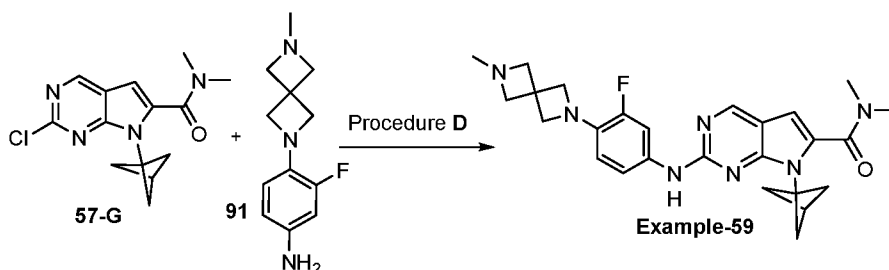
Example-58 was synthesized following the general procedure **D**, 6 mg (13% yield). MS(ESI) m/z 458.2 ($M+H$)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.99 (s, 1H), 8.55 (s, 1H), 7.48 – 7.43 (m, 2H), 6.60 – 6.55 (m, 2H), 6.35 (s, 1H), 5.33 (s, 1H), 3.49 (s, 2H), 3.15 (s, 2H), 2.94 (s, 4H), 2.88 (s, 3H), 2.69 (s, 3H), 2.52 (s, 1H), 2.33 (s, 1H), 2.31 (s, 6H), 2.02 (s, 1H), 1.84 (s, 1H).

20

Example-59 (VP-NR11-75D, SPV-537)

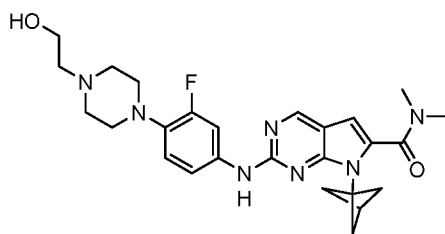


Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-59):

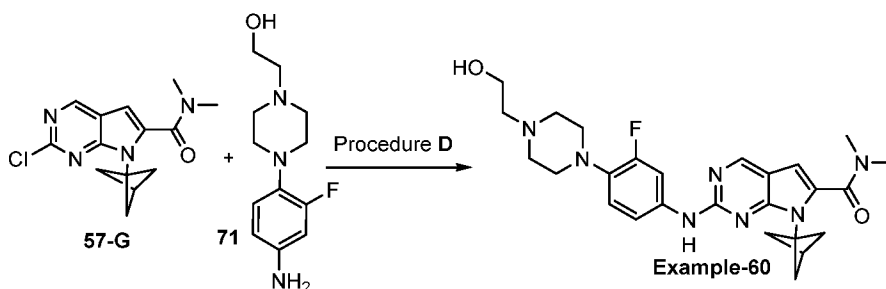


Example-59 was synthesized following the general procedure **D**, 6 mg (13% yield). MS(ESI) m/z 476.2 ($M+H$)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.30 (s, 1H), 8.67 (s, 1H), 7.75 (dd, J = 14.7, 2.5 Hz, 1H), 7.30 (dd, J = 8.8, 2.4 Hz, 1H), 6.78 (t, J = 9.4 Hz, 1H), 6.56 – 6.51 (m, 1H), 6.45 (s, 1H), 5.33 (t, J = 6.5 Hz, 1H), 3.79 (s, 2H), 3.57 (s, 2H), 3.26 (d, J = 5.9 Hz, 3H), 3.01 (s, 3H), 2.95 (s, 3H), 2.69 (s, 2H), 2.61 (s, 1H), 2.40 (s, 6H), 1.91 (s, 3H).

Example-60 (VP-NR11-79, SPV-538)

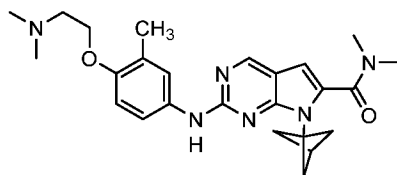


Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-60):



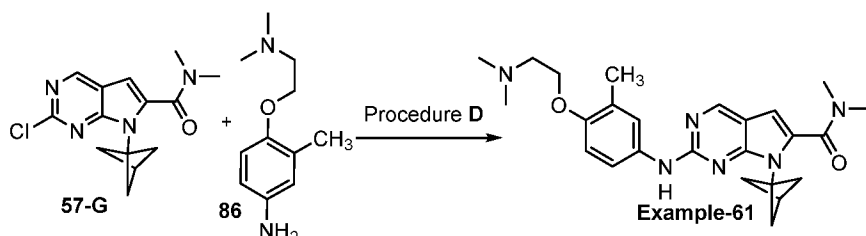
Example-60 was synthesized following the general procedure **D**, 6 mg (13% yield). MS(ESI) m/z 494.2 (M+H)⁺.

Example-61 (VP-NR11-80B, SPV-546)



5

Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-methylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-61):

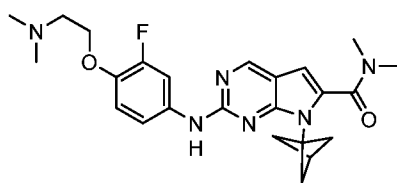


10

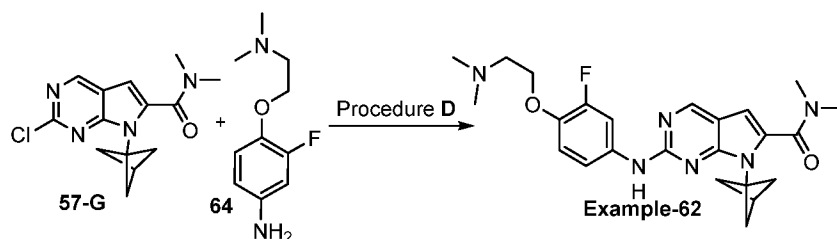
Example-61 was synthesized following the general procedure **D**, 6 mg (13% yield). MS(ESI) m/z 449.2 (M+H)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 8.66 (s, 1H), 7.68 (d, J = 2.7 Hz, 1H), 7.47 (dd, J = 8.7, 2.7 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.43 (s, 1H), 4.01 (t, J = 5.8 Hz, 2H), 3.01 (s, 3H), 2.95 (s, 3H), 2.64 (t, J = 5.8 Hz, 2H), 2.61 (s, 1H), 2.40 (s, 6H), 2.24 (s, 6H), 2.16 (s, 3H).

15

Example-62 (VP-NR11-82B, SPV-547)



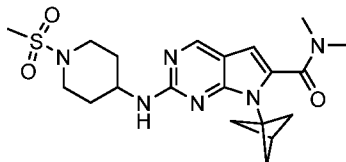
Step 1: Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-fluorophenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-62):



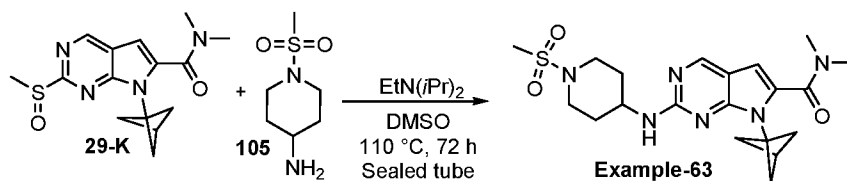
Example-62 was synthesized following the general procedure **D**, 6 mg (13% yield). MS(ESI) m/z 453.2 (M+H)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.51 (s, 1H), 8.71 (s, 1H), 7.88 (dd, J = 14.5, 2.6 Hz, 1H), 7.40 (ddd, J = 8.9, 2.6, 1.3 Hz, 1H), 7.12 (t, J = 9.4 Hz, 1H), 6.47 (s, 1H), 4.08 (t, J = 5.8 Hz, 2H), 3.02 (s, 3H), 2.95 (s, 3H), 2.64 – 2.59 (m, 3H), 2.41 (s, 6H), 2.22 (s, 6H).

5

Example-63 (VP-NR11-160C, SPV-542)



Synthesis of 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (Example-63):



10

To a solution of **29-K** and the amine (2 eq) in 3 mL of DMSO was added DIPEA (10 eq). The resulting mixture was stirred in a pressure tube at 110 °C for 72 h. The mixture was poured onto water, extracted with 10% MeOH in DCM solution, concentrated and purified on C18 column (H₂O/ACN) to obtain **63** as a white solid, 6 mg (13% yield). MS(ESI) m/z 453.2 (M+H)⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.52 (s, 1H), 6.35 (s, 1H), 3.56 (d, J = 12.1 Hz, 2H), 2.99 (s, 3H), 2.96 – 2.90 (m, 5H), 2.89 (s, 3H), 2.87 (d, J = 2.8 Hz, 1H), 2.56 (s, 1H), 2.35 (s, 6H), 2.04 (d, J = 12.7 Hz, 2H), 1.91 (s, 1H), 1.60 – 1.54 (m, 2H).

15

Example 5

Inhibition Assays

Inhibition assays were performed using microfluidic LabChip 300 Drug Discovery System from Caliper Life Sciences. The assays were performed in Six-point to 12-point concentration-response format (IC_{50}) (Nanosyn, Santa Clara, CA). The assay has a total volume of 10 μ L consisting of 5 μ L of enzyme and buffer and 5 μ L of substrate and buffer. The test compounds were diluted in 100% dimethylsulfoxide (DMSO) using 3-fold dilution steps. The compounds were diluted in 100% dimethylsulfoxide (DMSO) and plated at 100-fold greater than the screening composition and serially diluted using 3-fold dilution steps. Compounds were tested in a single well for each dilution and the final concentration of DMSO was maintained at 1%.

The assay buffer contained 100 mM HEPES, pH 7.5, 0.01% Triton X-100, 0.1% bovine serum albumin (BSA), 5 mM $MgCl_2$; 1 mM dithiothreitol (DTT), 10 μ M sodium orthovanadate, and 10 μ M β -glycerophosphate.

The assay was conducted by adding 5 μ L of enzyme, adenosine triphosphate (ATP) and buffer to an assay plate. A 100 nL aliquot of the diluted compounds were added to the plate. The assay was initiated by the addition of 5 μ L of phosphoenolpyruvate substrate (PEP) in buffer. Specific concentrations for the enzyme, ATP, and PEP are shown in Table 1. The assays were incubated at 25 °C for 3 min for CDK2, CDK4 and CDK6 or 17 min for CDK9. The reaction was terminated by the addition of EDTA. The plates were analyzed using a Caliper LabChip 3000.

Table 1. Inhibition Assay Components and Concentrations

Enzyme	Vendor	ENZ Stock Conc (μ M)	ENZ Assay Conc (nM)	ATP Conc (μ M)	PEP Conc (μ M)	Assay Time
CDK2-CYCLINA	Millipore	1.8	0.1	50	1	3
CDK2-CYCLINE	Millipore	0.93	0.15	100	1	3
CDK4-CYCLIND1	Invitrogen	3.5	1	200	1	3
CDK6-CYCLIND3	Carna	3.13	2	300	1	3
CDK9-CYCLINT1	Carna	2.86	5	10	1	17

Results for controls and compounds described herein are shown in the table below. The results are graphically shown in Fig. 1 (CDK4) and Fig. 2 (CDK6).

Table 2. Inhibition Assay Results		
Compound	CDK4 IC50 (μM)	CDK6 IC50 (μM)
Staurosporine	0.0535	0.0619
Ribociclib	0.00908	0.0243
A1	0.0387	0.0543
A2	0.0379	0.0543
A3	0.048	0.0645
A4	0.0189	0.0349
A5	0.0193	0.0506
A6	0.0152	0.0364
A7	0.0222	0.063
A8	0.00498	0.0236
A9	0.021	0.0549
A10	0.0304	0.05
A11	0.00388	0.012
A12	0.0124	0.01
A13	0.0147	0.00829
A14	0.00381	0.00708
A15	0.0315	0.0238
A16	0.00294	0.00768
A17	0.00304	0.00804
A18	2.74	12.6
A19	0.0154	0.0453
A20	0.033	0.0746
A21	0.0512	0.0986
A22	0.0417	0.082
A23	0.0343	0.097
A24	0.457	1.43
A25	2.29	4.86
A26	0.0393	0.119
A27	0.0396	0.116
A28	0.0266	0.0819
A29	>30	>30
A30	0.0107	0.0317
A31	0.009	0.0337
A32	0.00195	0.0101
A33	0.0101	0.0374
A34	0.0262	0.103
A35	0.0438	0.217
A36	0.00817	0.0325
A37	52	100
A38	0.0154	0.0235
A39	0.00593	0.0134
A40	0.00516	0.0173

A41	0.0214	0.0402
A42	0.015	0.0434
A43	0.0356	0.0329
A44	0.00245	0.0101
A45	0.0293	0.0733
A46	0.0126	0.0282
A47	0.00522	0.0165

Example 6

Additional inhibition assays were performed as described above. The data is shown in Tables 3a and 3b.

Table 3a. Inhibition Assay Results						
Compound	CDK1/B IC₅₀ (μM)	CDK2 CyclinA IC₅₀ (μM)	CDK4 CyclinD1 IC₅₀ (μM)	CDK6 CyclinD3 IC₅₀ (μM)	CDK7 CyclinH IC₅₀ (μM)	CDK9 CyclinT1 IC₅₀ (μM)
A48		0.666	0.0164	0.044	4.86	0.0149
A49		0.179	0.00579	0.0103	1.66	0.0021
A83		0.289	0.00675	0.015	3.41	0.0127
A84		0.185	0.00244	0.0061	1.43	0.00584
A85		0.162	0.00413	0.0101	1.14	0.00618
A86		18.9	0.016	0.0201	27.4	0.67
A87		50	0.0252	0.02	>100	0.553
A88	0.379	0.354	<0.0032		1.65	0.0051
A60	0.955	0.8	0.0079		3.42	<0.0032
A68	0.562	0.632	0.00378		2.68	0.00755
A69	1.83	1.47	0.014		>10	0.0051
A70	0.732	0.631	0.0159		5.01	0.00476
A74	0.25	0.245	<0.0032		0.938	<0.0032
A89	0.44	0.4	<0.0032		1.52	0.00406
A51	0.453	0.66	0.00452		2.06	0.00546
A79	0.0971	0.0302	0.036		>10	<0.0032
A75	0.066	0.0457	0.0172		8.13	0.0114
A90	1.15	0.913	0.0111		5.61	0.00926
A91	1.33	0.69	0.0255		5.79	0.00714
A49	>10	>10	3.36		>10	>10
A92	0.62	0.713	0.0147		2.65	<0.0032
A93	0.655	0.742	0.00698		2.14	<0.0032

Table 3b. Inhibition Assay Results						
Compound	CDK1/B IC₅₀ (μM)	CDK2 CyclinA IC₅₀ (μM)	CDK4 CyclinD1 IC₅₀ (μM)	CDK6 CyclinD3 IC₅₀ (μM)	CDK7 CyclinH IC₅₀ (μM)	CDK9 CyclinT1 IC₅₀ (μM)
A48		0.666	0.0164	0.044	4.86	0.0149
A49		0.179	0.00579	0.0103	1.66	0.0021
A60	0.955	0.8	0.0079		3.42	<0.0032
A89	0.44	0.4	<0.0032		1.52	0.00406
A51	0.453	0.66	0.00452		2.06	0.00546
A79	0.0971	0.0302	0.036		>10	<0.0032
A90	1.15	0.913	0.0111		5.61	0.00926
A91	1.33	0.69	0.0255		5.79	0.00714
A49	>10	>10	3.36		>10	>10
A68	0.562	0.632	0.00378		2.68	0.00755
A69	1.83	1.47	0.014		>10	0.0051
A70	0.732	0.631	0.0159		5.01	0.00476
A74	0.25	0.245	<0.0032		0.938	<0.0032
A92	0.62	0.713	0.0147		2.65	<0.0032
A93	0.655	0.742	0.00698		2.14	<0.0032
A75	0.066	0.0457	0.0172		8.13	0.0114
A83		0.289	0.00675	0.015	3.41	0.0127
A84		0.185	0.00244	0.0061	1.43	0.00584
A85		0.162	0.00413	0.0101	1.14	0.00618
A86		18.9	0.016	0.0201	27.4	0.67
A87		50	0.0252	0.02	>100	0.553
A88	0.379	0.354	<0.0032		1.65	0.0051
A89	0.44	0.4	<0.0032		1.52	0.00406

Example 7**2D Cell Proliferation Assay**

Viability of the cells was analyzed by using the CellTiter-Blue® Cell Viability Assay (Promega), and was performed according to manufacturer's instructions. Briefly, cells were harvested from exponential phase cultures (Chapter 6.6), counted and plated in 96-well flat-bottom microtiter plates at a cell density of 4,000 – 60,000 cells/well in a volume of 140 µl per well. After a 24 hours recovery period, 10 µL cell culture medium (six control wells/plate) or culture medium with test compound were added (Chapter 6.2). The compounds were applied at five concentrations in full-log increments up to 100 µM in duplicate. Cultures were incubated at 37 °C and 5 % CO₂ in a humidified atmosphere for another three days. After three days of treatment, 20 µl/well CellTiter-Blue® reagent was added. Following incubation with CellTiter-Blue® reagent for up to four hours, fluorescence (FU) was measured by using the Enspire Multimode Plate Reader (excitation λ = 570 nm, emission λ = 600 nm). For calculations, the mean values of duplicate / sextuplicate (untreated control) data were used.

Data Evaluation for Efficacy Assessment

An assay was considered fully evaluable if the following quality control criteria were fulfilled:

- control/background ratio > 3.0 - Z'-factor calculated within the assay plate > 0.5
- [7] - coefficient of variation in the growth control wells < 30%

Drug effects were expressed in terms of the percentage of the fluorescence signal, obtained by comparison of the mean signal in the treated wells with the mean signal of the untreated controls (expressed by the test-versus-control value, T/C-value [%]):

$$\frac{T}{C} [\%] = \frac{\text{mean fluorescence signal}_{\text{treated group}}}{\text{mean fluorescence signal}_{\text{control group}}} \cdot 100$$

IC values are reported as relative IC₅₀ values and absolute IC₅₀ and IC₇₀ values. The absolute IC₅₀ value reflects the concentration of the test compound that achieves T/C = 50 %. The absolute IC₇₀ value gives the concentration of the test compound that achieves T/C = 30 %. The relative IC₅₀ value is the concentration of test compound that gives a response half way between the top and bottom plateau of the sigmoidal concentration-response curve (inflection

point of the curve). Calculation was done by 4parameter non-linear curve fit (Oncotest Data Warehouse Software).

If an IC₅₀ or IC₇₀ value could not be determined within the examined dose range (because a compound was either too active or lacked activity), the lowest or highest concentration studied was used for calculation of the geometric mean value.

The overall potency of a compound was determined by the geometric mean IC₅₀ / IC₇₀ values of all individual IC₅₀ / IC₇₀ values. In the heatmap representation of IC₅₀ and IC₇₀ values, the distribution of the IC₅₀ or IC₇₀ values obtained for a test compound in the individual cell lines is given in relation to the geometric mean IC₅₀ or IC₇₀ value, obtained over all PDX models tested. The individual IC values range from 1/32-fold geometric mean IC (corresponding to very potent compound activity or high tumor sensitivity) to 32-fold geometric mean IC (corresponding to lack of compound activity or tumor resistance). The heatmap presentation, therefore, represents an antiproliferative “fingerprint” profile of a test compound. The results may be found in Table 4.

Table 4. Tumor Sensitivity Results

Compound Cell Line	SPV113 (Compound A14) IC	Compound Cell Line	SPV113 (Compound A14) IC
BXF 5637	0.476	MAXFHER SK-BR-3	2.037
CEXF HeLa	0.329	MAXFLB MCF7 (ER+)	0.173
CNXF U-87 MG	100	MAXFLB T47D (ER+)	3.468
CXF Caco-2	100	MAXFTN BT-549	0.713
CXF COLO 205	0.148	MAXFTN MDA-MB-231 (ER-)	0.34
CXF HCT-15	0.202	MAXFTN MDA-MB-453	0.177
CXF HT-29	0.437	MAXFTN MDA-MB-468 (ER-)	0.29
GXA MKN45	1.076	MAXFTN ZR-75-1 (ER+)	12.55
LEXFAL MOLT-4	0.567	MEXF A2058	1.512
LEXFAM MV4-11	0.01	MEXF A-375	0.101
LEXFCL MEC-1	0.01	MEXF M14	1.013
LEXFCM K-562	1.151	MEXF MDA-MB-435	0.296
LIXAH HLE	0.229	MEXF WM-266-4	3.3
LIXAH SNU-398	0.148	MMXF U-266	0.655
LIXFH Hep G2	0.124	OVXF SK-OV-3	3.152
LIXFH HEP-3B	0.367	PAXF BxPC-3	0.193
LXFA A549	1.232	PAXF MIA-Pa-Ca-2	0.105
LXFA NCI-H1975	0.122	PRXF 22Rv1	0.01
LXFE Calu-1	1.561	PRXF DU-145	0.253

LXFL NCI-H1299	1.634	PRXF LNCaP	0.116
LXFL NCI-H460	0.291	PRXF VCap	0.015
LYXFNH Daudi	0.01	UXF EFE-184	0.906
LYXFNH U-937	0.01	UXF MFE-319	0.667
MAXFHER BT-474	0.802	Geomean abs. IC₅₀ value	0.391
		[μM]:	

Example 8

PK Data Table of SPV113 (compound A14)

Nonclinical pharmacokinetic (PK) parameters of lead CDK4/6/9 inhibitors were determined in an intravenous (IV) and oral study (p.o.) conducted in rats. Lead compounds were each administered as a single oral dose at 100 mg/kg or by IV bolus via the caudal vein at the dose of 30 mg/kg. Blood samples were collected at 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours post i.v. administration, and at 1, 2, 4, 8, 24 and 48 hours post oral administration. Plasma was processed for drug concentration analysis using a validated LCMS/MS method, and PK parameters were calculated by using WinNonlin. The lead compound exhibited excellent exposure following oral administration with oral bioavailability. High exposure level and excellent bioavailability enable a once-daily oral dose regimen. The results are shown in Table 5.

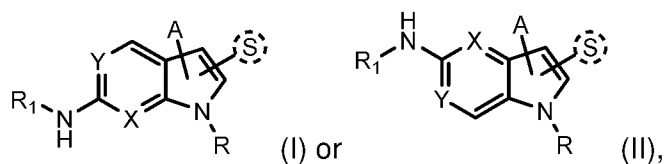
Table 5. PK Data of SPV 113 (A14)

	IV BOLUS AT 30 MG/KG N = 3			ORAL ADMINISTRATION, 100 MG/KG N = 3				BIO-AVAILABILITY
	C_{max} ng/ml	Clearance L/hr/kg	T_{1/2} hr	C_{max}	T_{1/2} hr	MRT hr	AUC ng.hr/ml	F %*
SPV113 (A14)	6830	1.12	5.73	2517	6.0	25.5	33798	33.3

CLAIMS

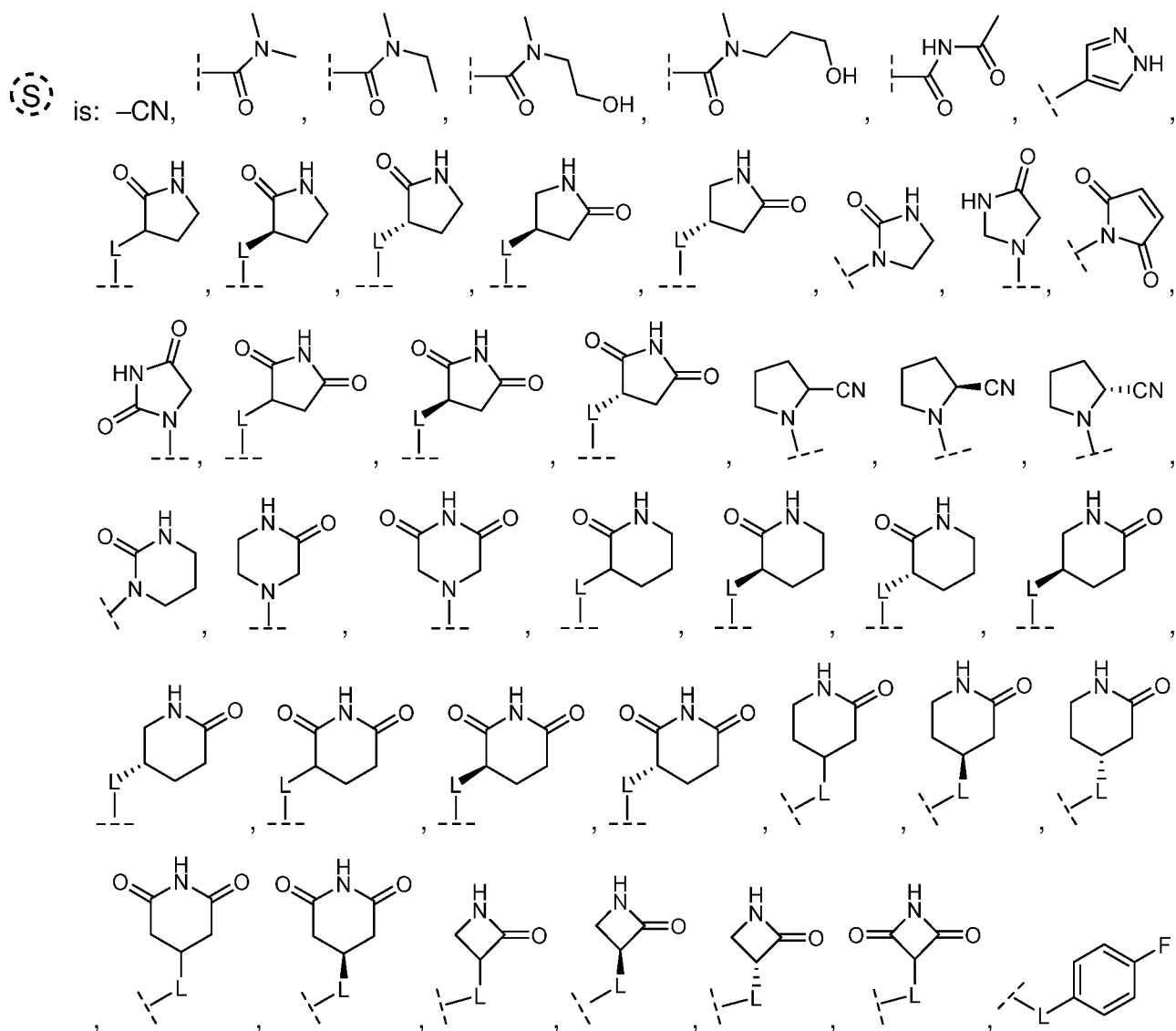
What is claimed:

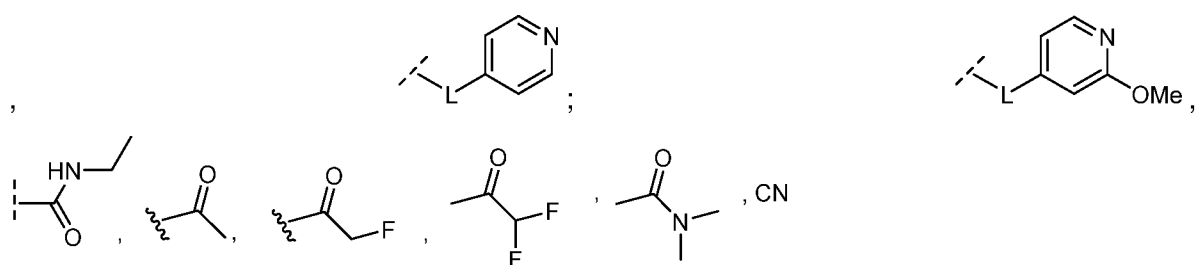
1. A compound or a pharmaceutically acceptable salt thereof comprising Formula I or II:



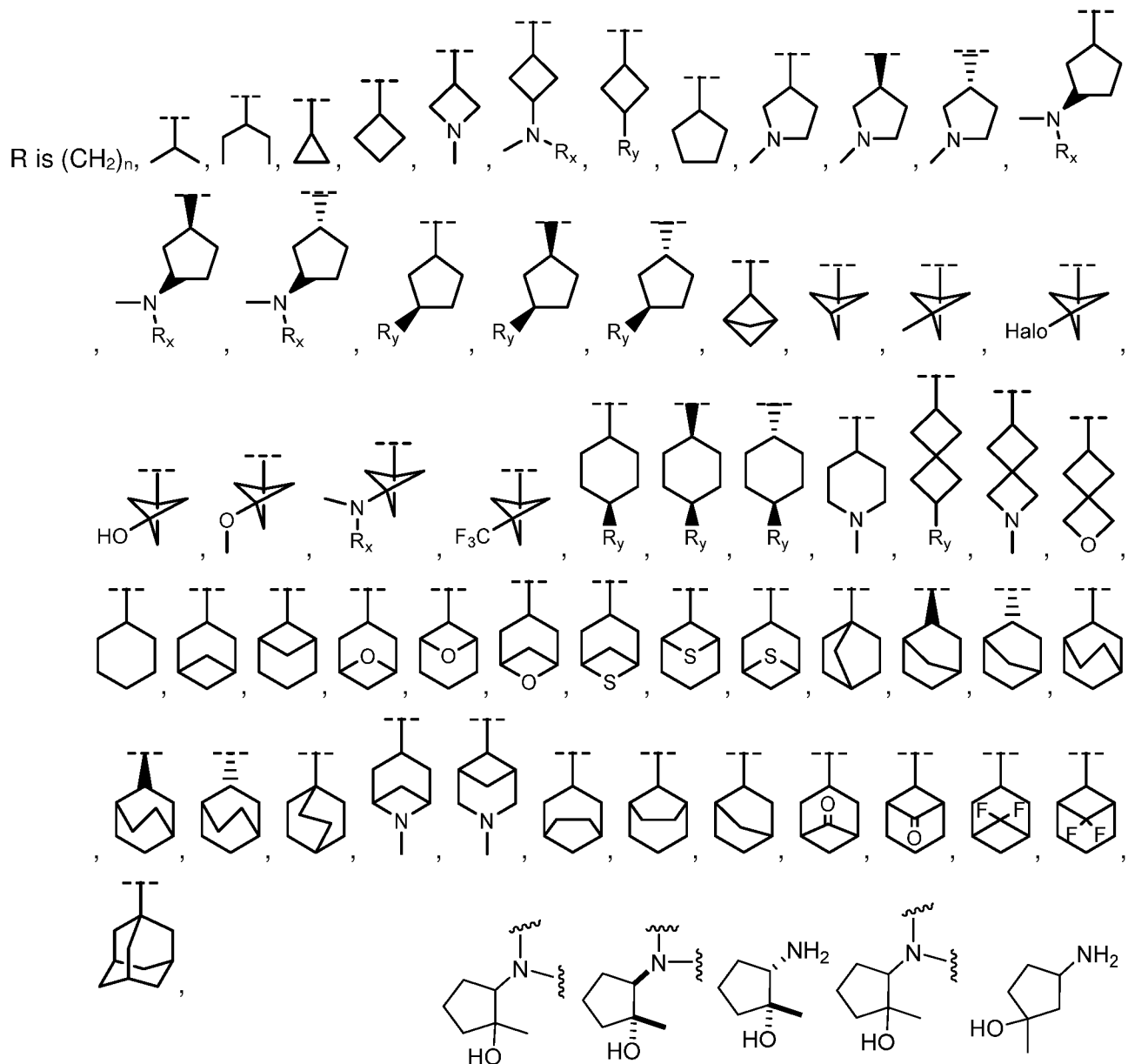
wherein A is H, F, Me, or CON(Me)₂;

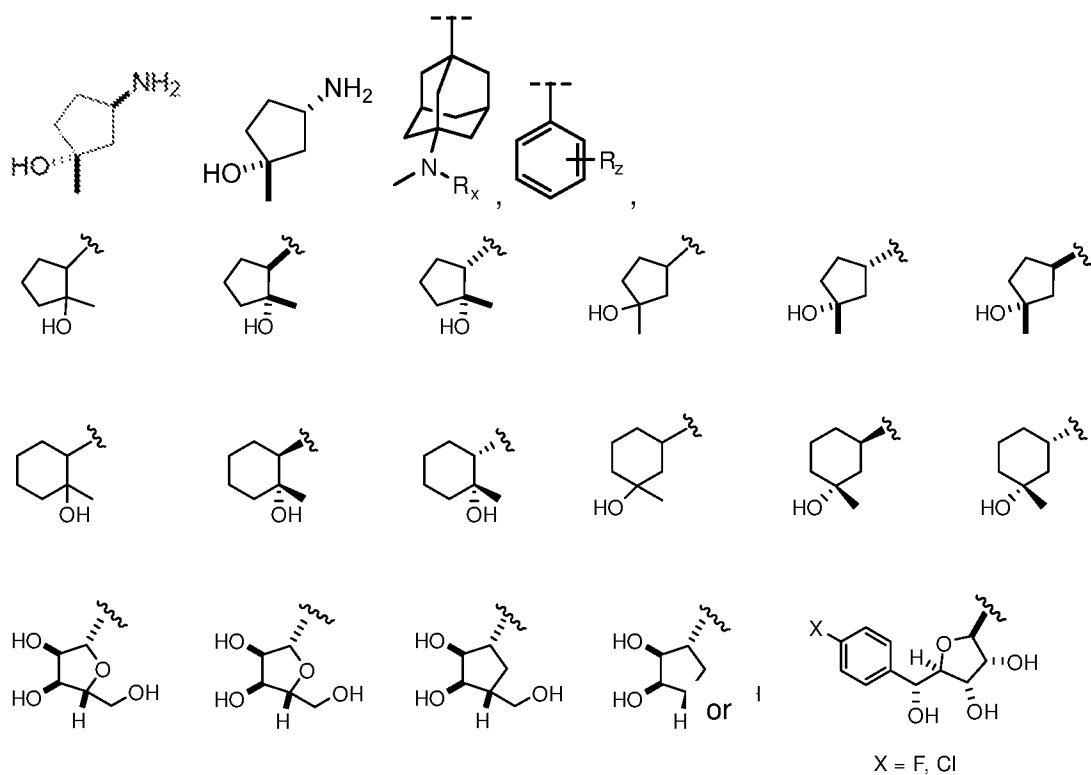
X and Y are independently, C, N, or C-F;





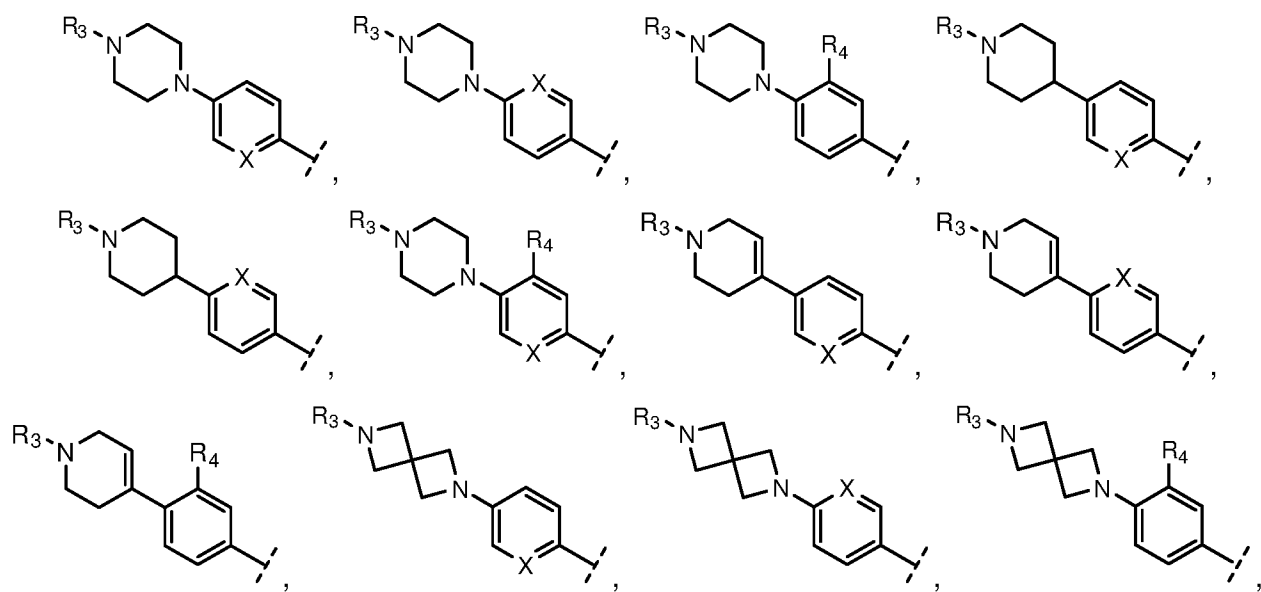
where L is none, CH₂, CO, NH, O, or S;

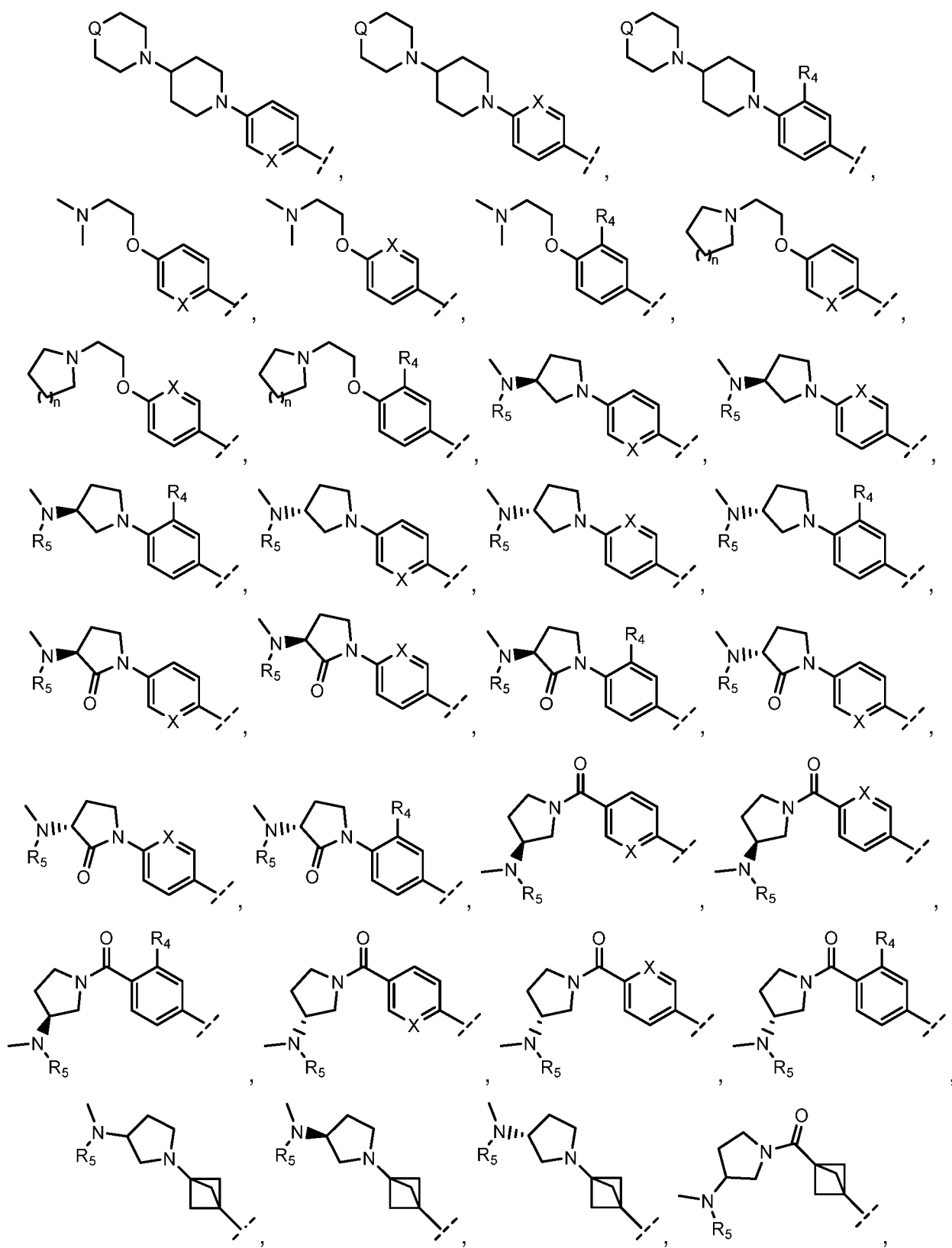


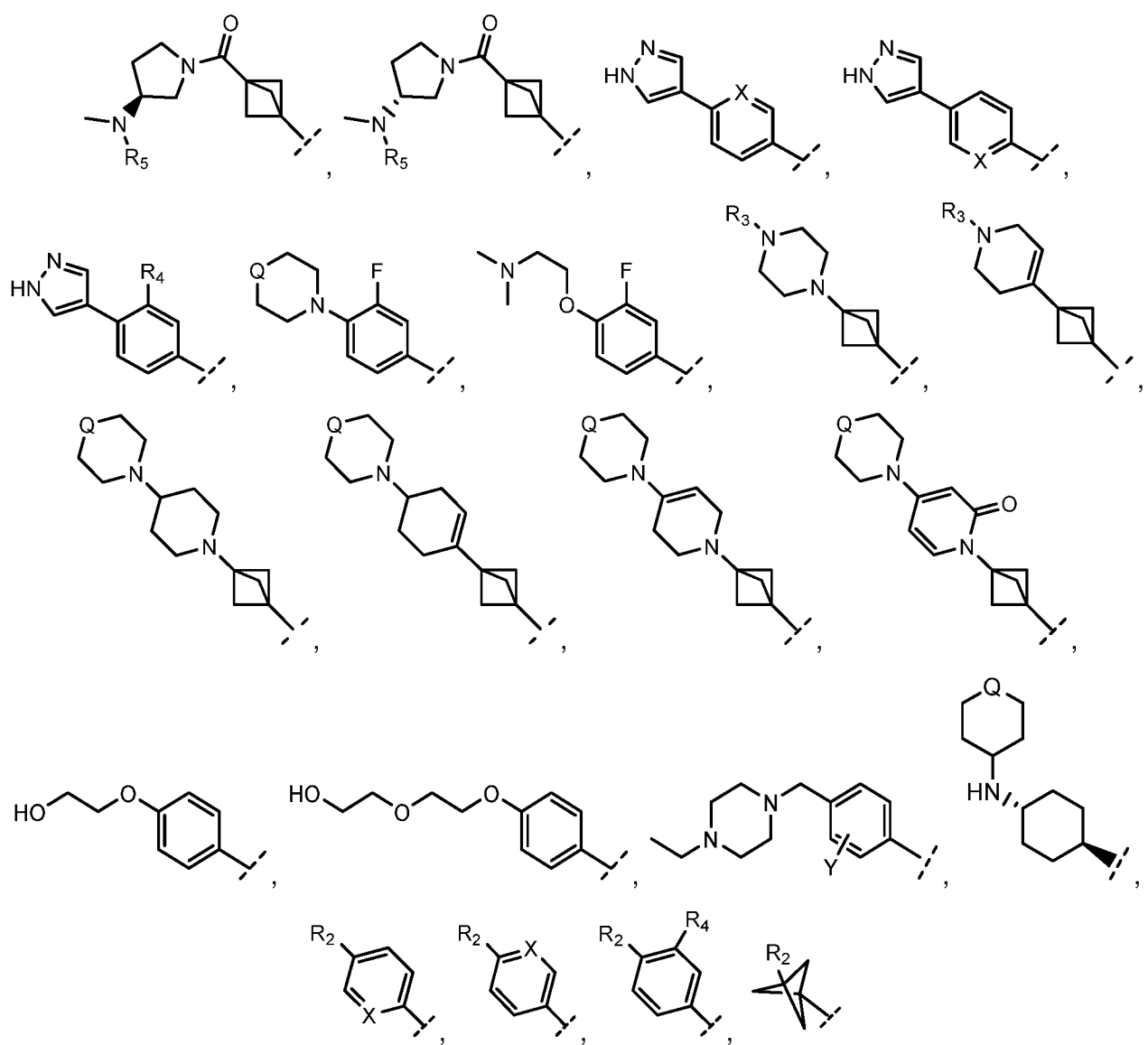


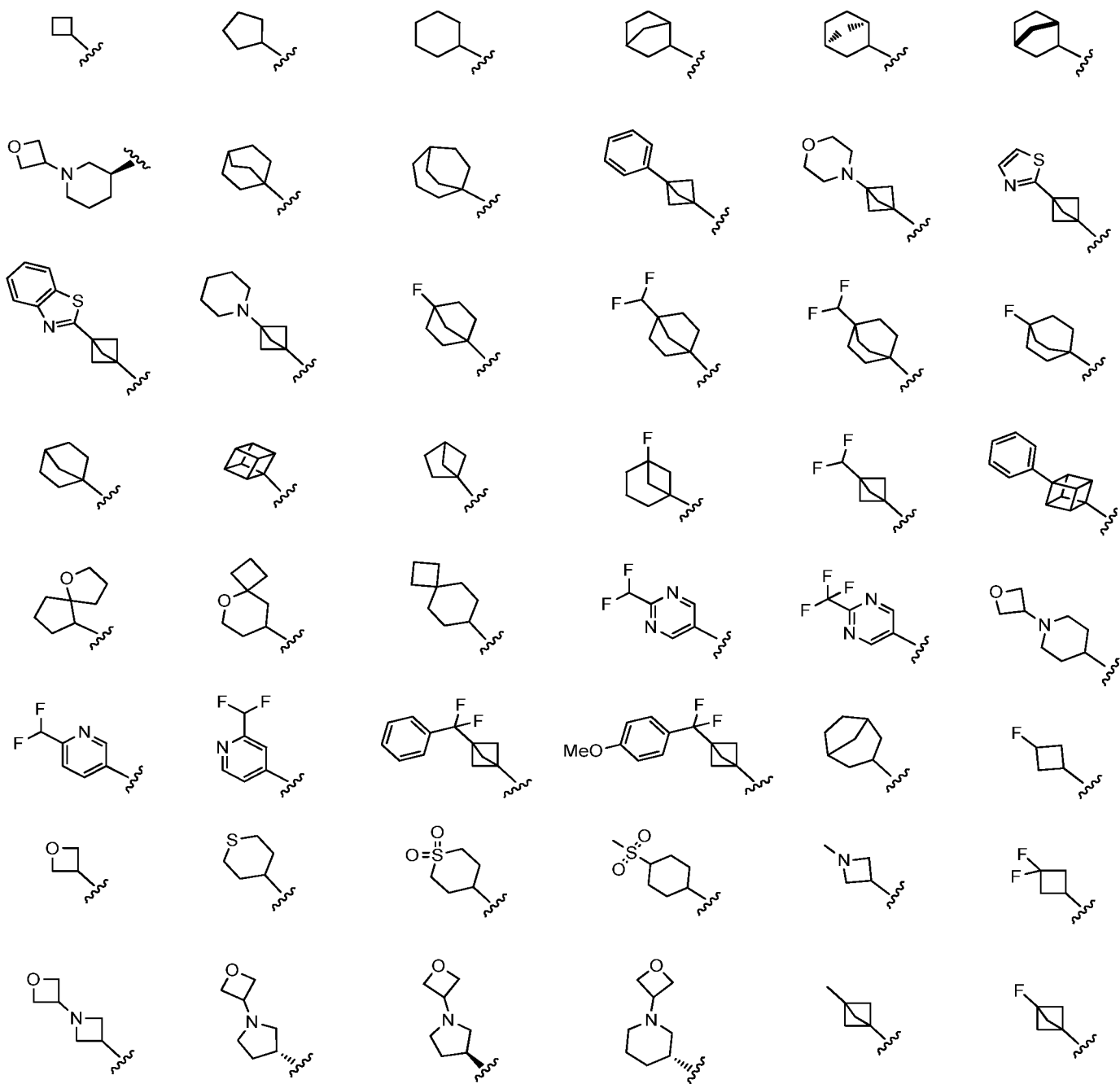
where R_x is H or Me, R_y is Me, OH, or OMe; R_z is H, Me, OMe, OH, N, F, or CF₃; and n is 1 to 11;
and

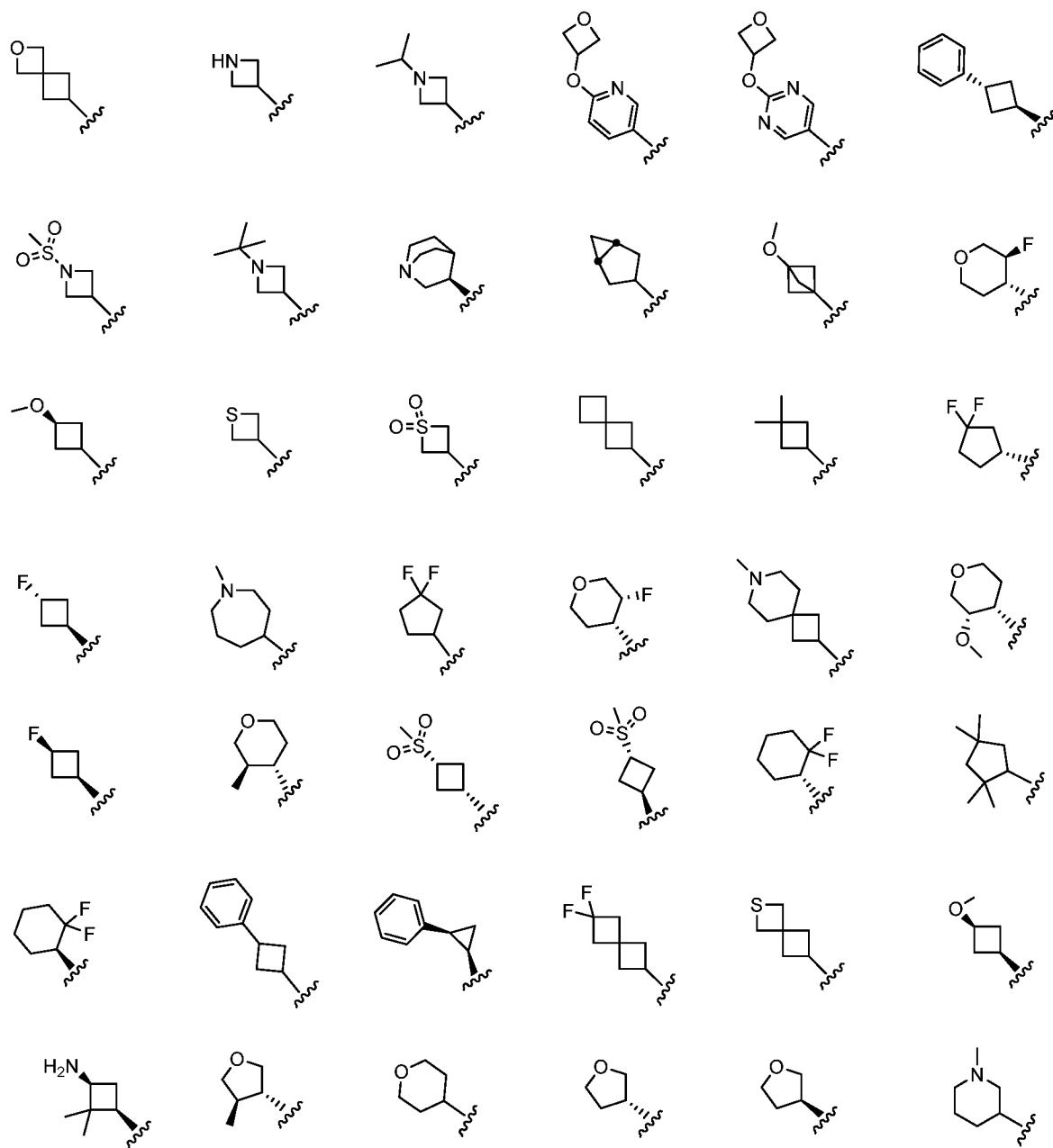
R_1 is

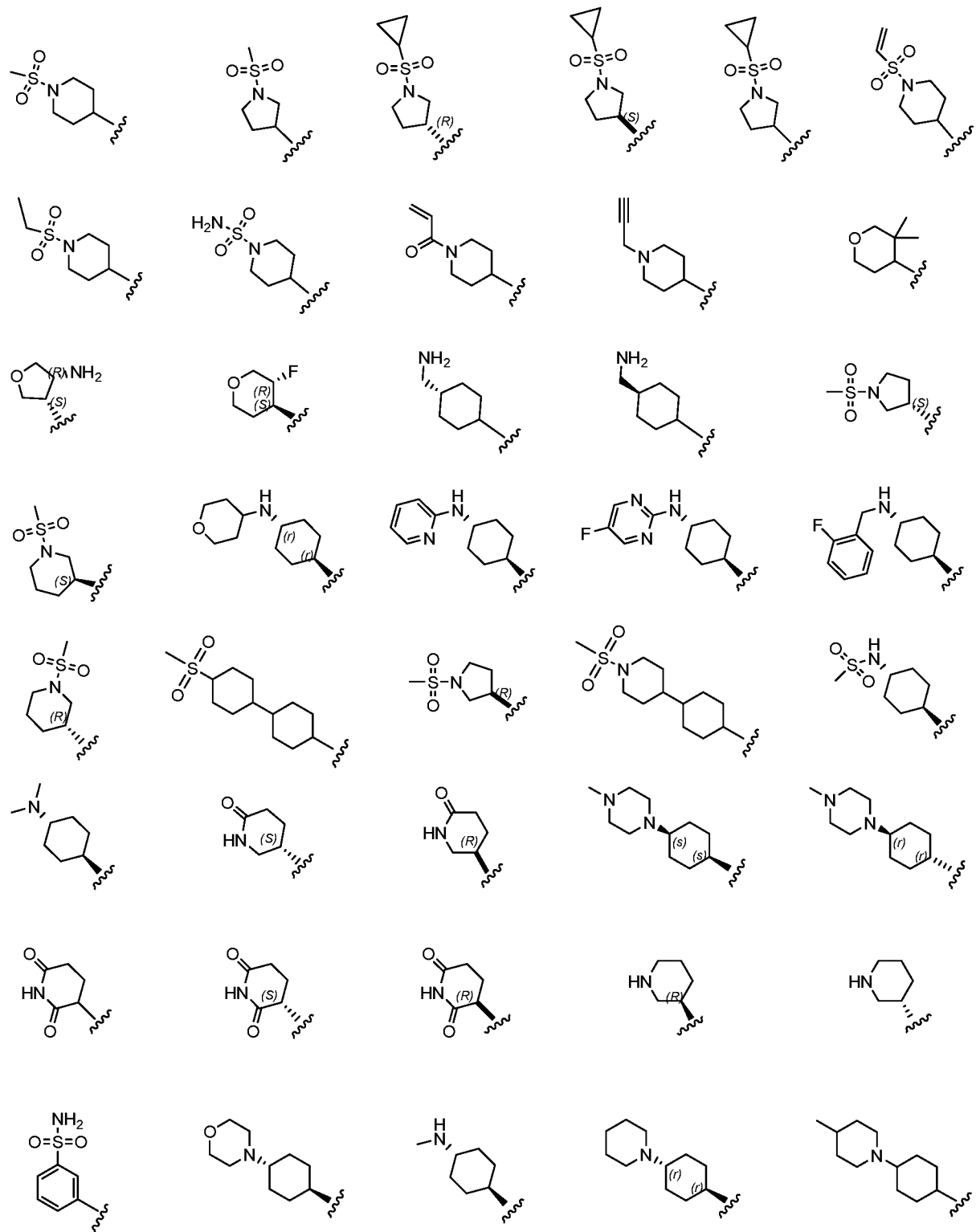


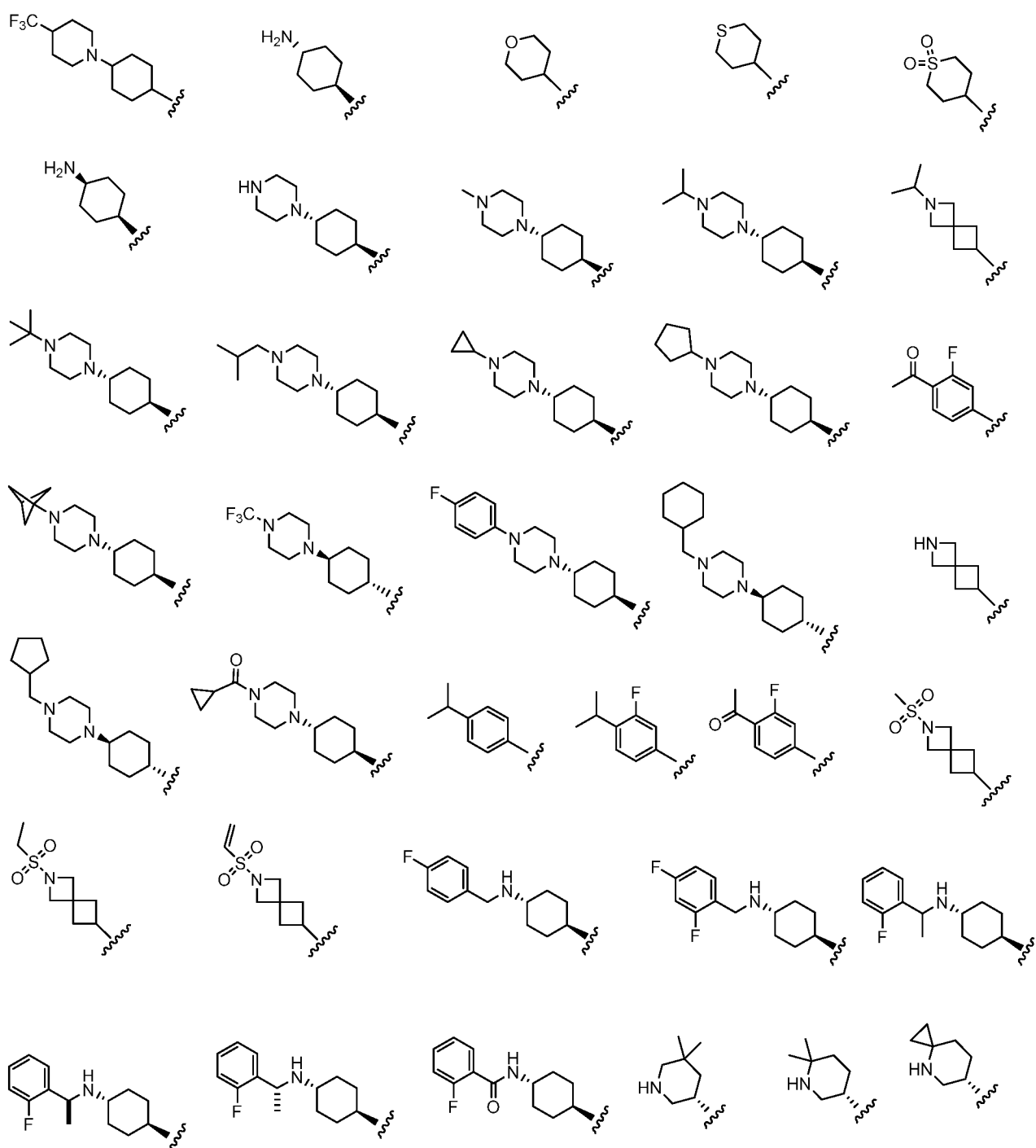


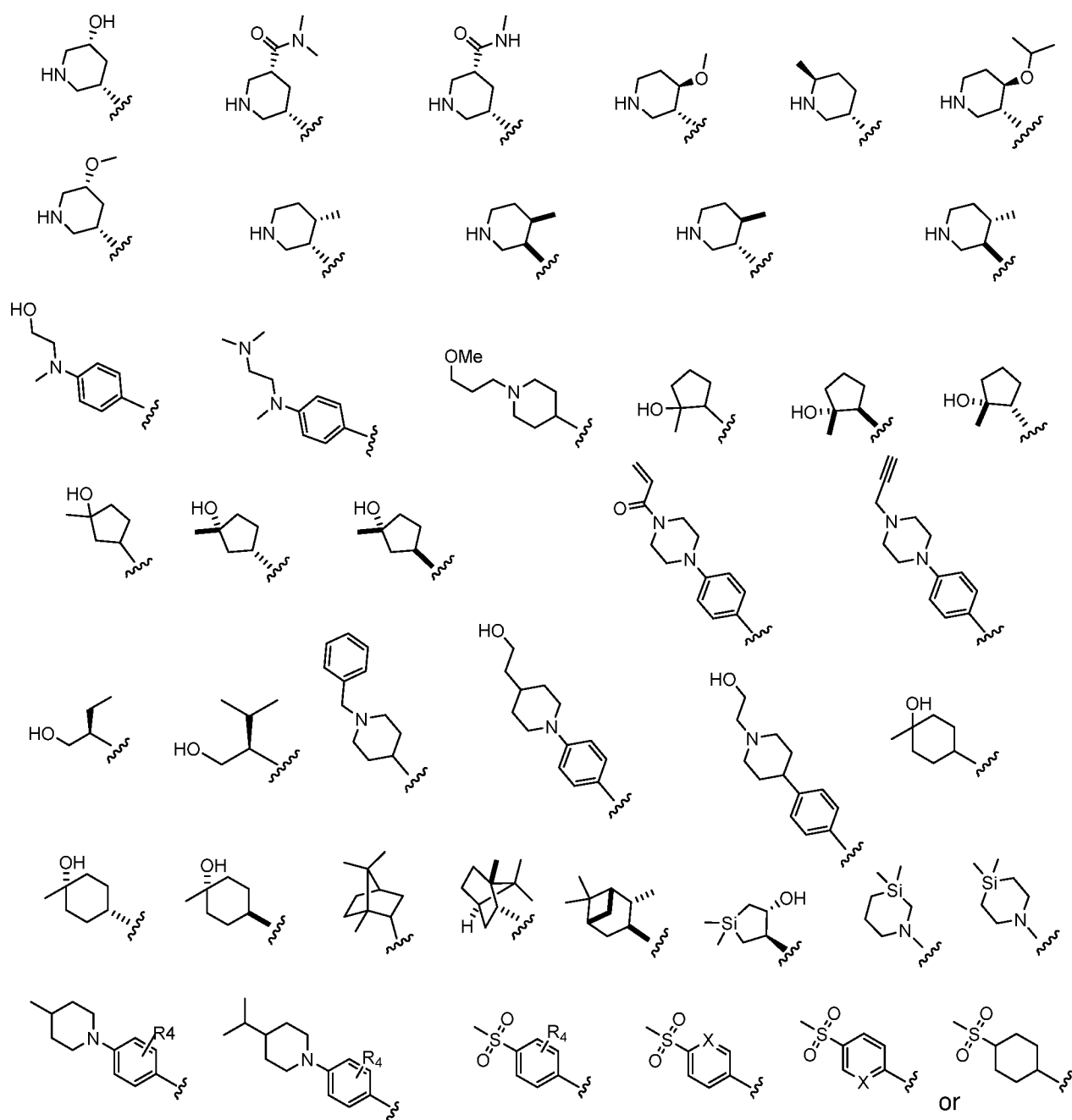












or

where R_3 is H, Me, $\text{CH}_2\text{CH}_2\text{OH}$, isopropyl, isobutyl, or bicyclo[1.1.1]pentane;

R_4 is H, Me, OMe, CF_3 , or CHF_2 ;

R_5 is H or Me;

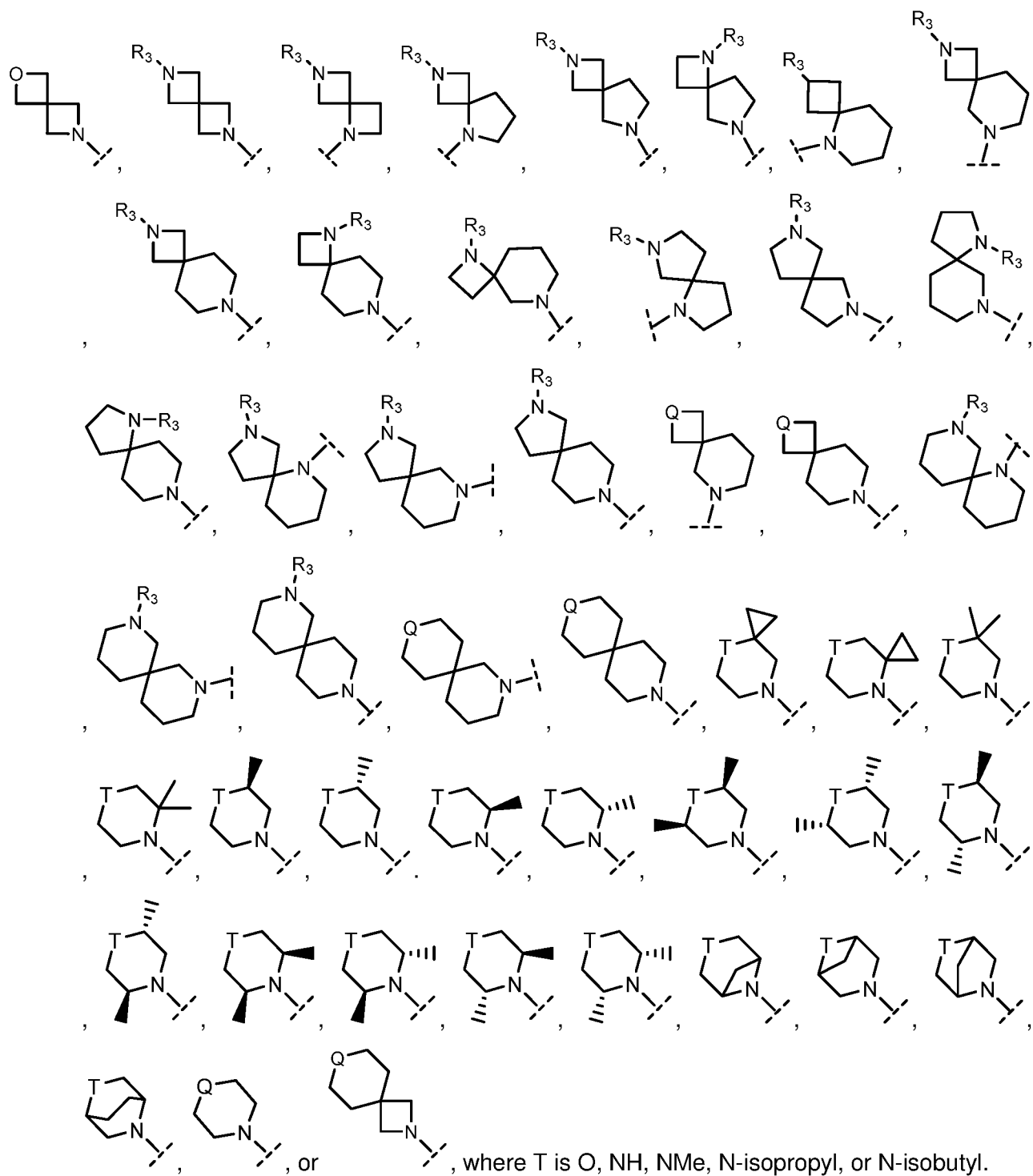
X is C-H, N, or C-F;

Y is H, N, F, Me, OMe, CF_3 , or CHF_2 ;

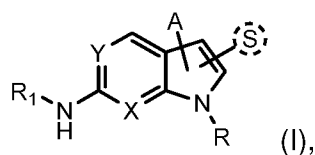
Q is O or S;

n is 1, 2, or 3; and

R₂ is:



6. The compound of claim 1, wherein the compound comprises Formula I:



wherein A is H, F, Me, or CON(Me)₂;

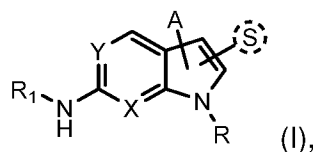
X and Y are independently N.

7. The compound of claim 6, wherein is:

8. The compound of claim 6, wherein R is or .

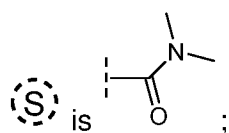
9. The compound of claim 6, wherein R₁ is:
-
- , where R₃ is H, Me, isopropyl, isobutyl, or bicyclo[1.1.1]pentane; R₅ is H or Me; and X is C-H, N, or C-F.

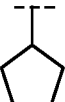
10. The compound of claim 1, wherein the compound comprises Formula I:

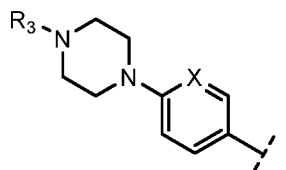
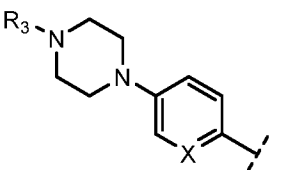
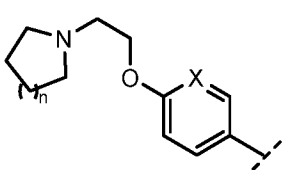
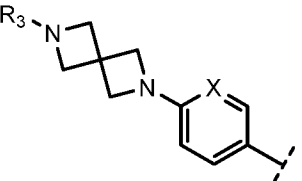


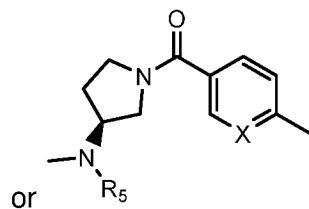
wherein A is H or F;

X and Y are independently N;

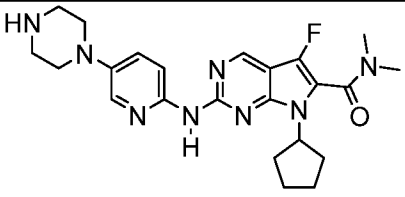
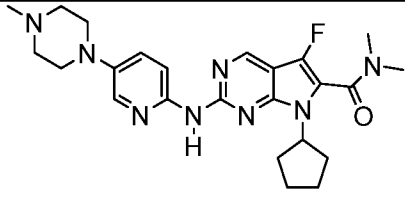
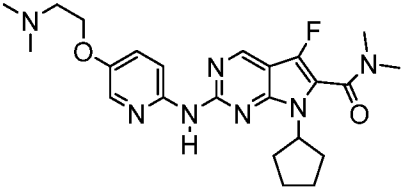
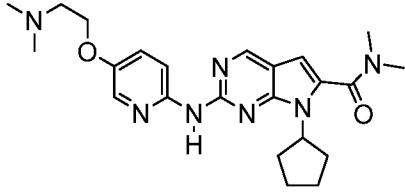
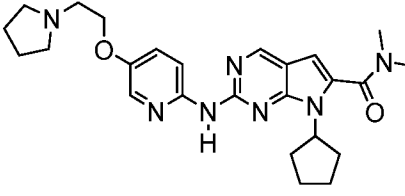
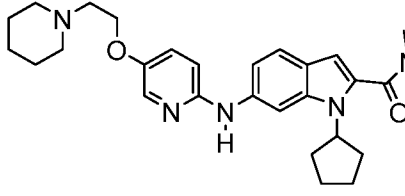
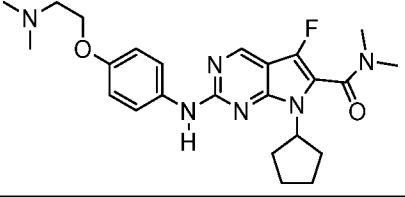
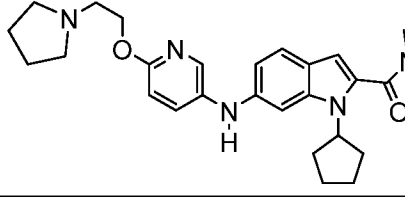


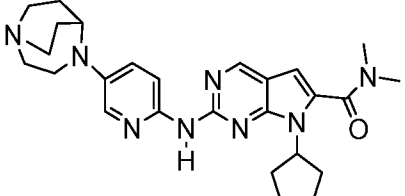
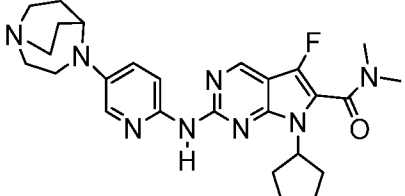
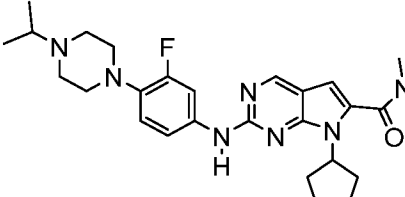
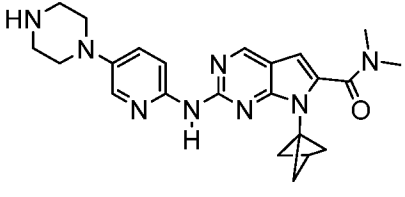
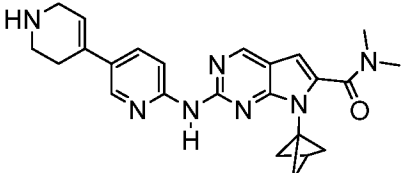
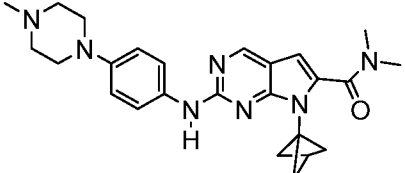
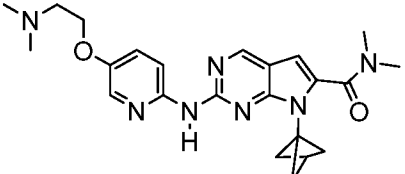
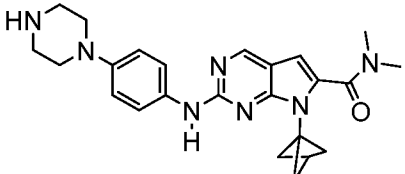
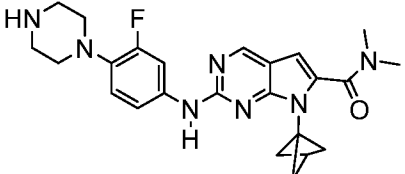
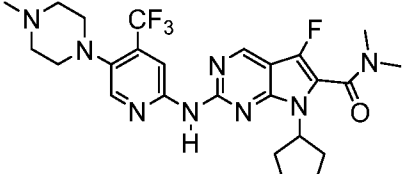
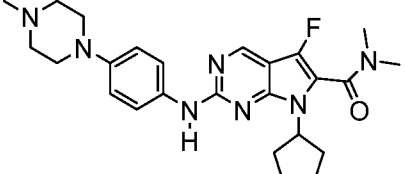
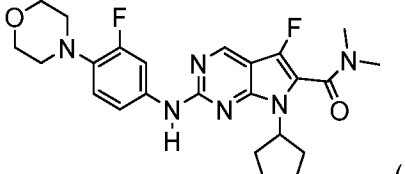
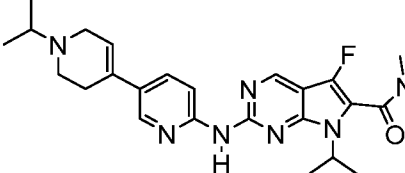
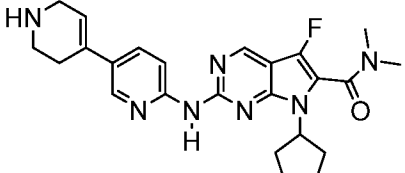
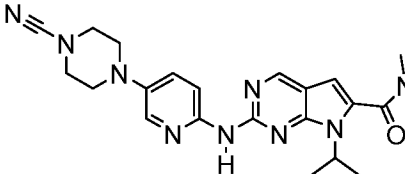
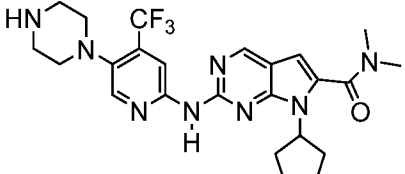
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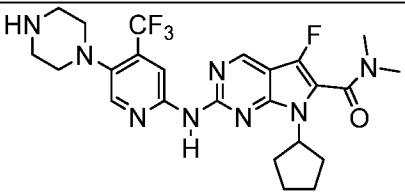
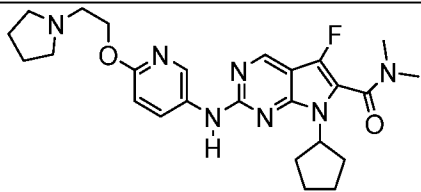
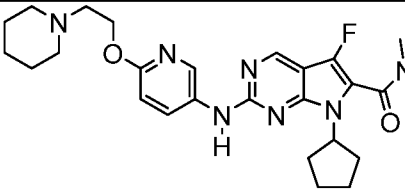
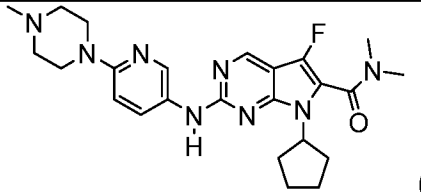
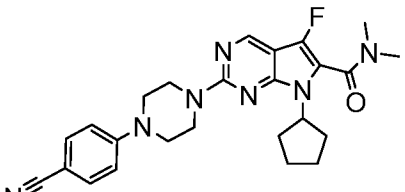
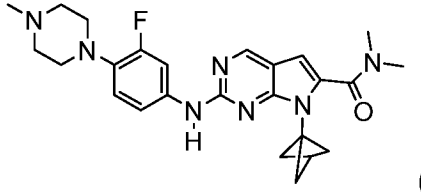
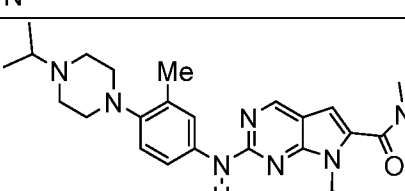
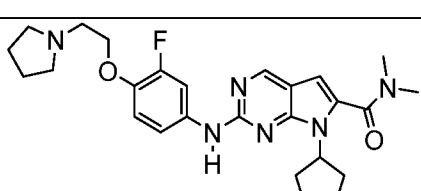
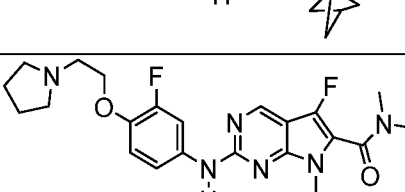
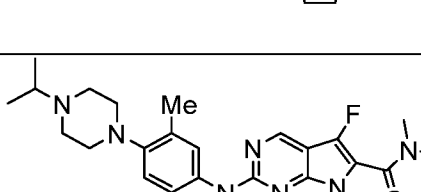
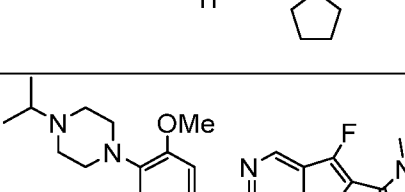
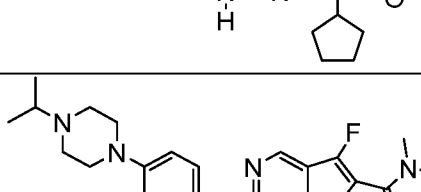
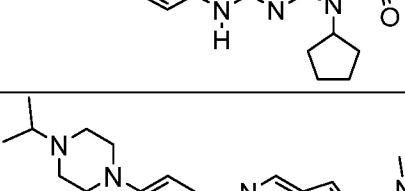
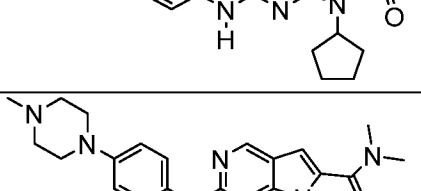
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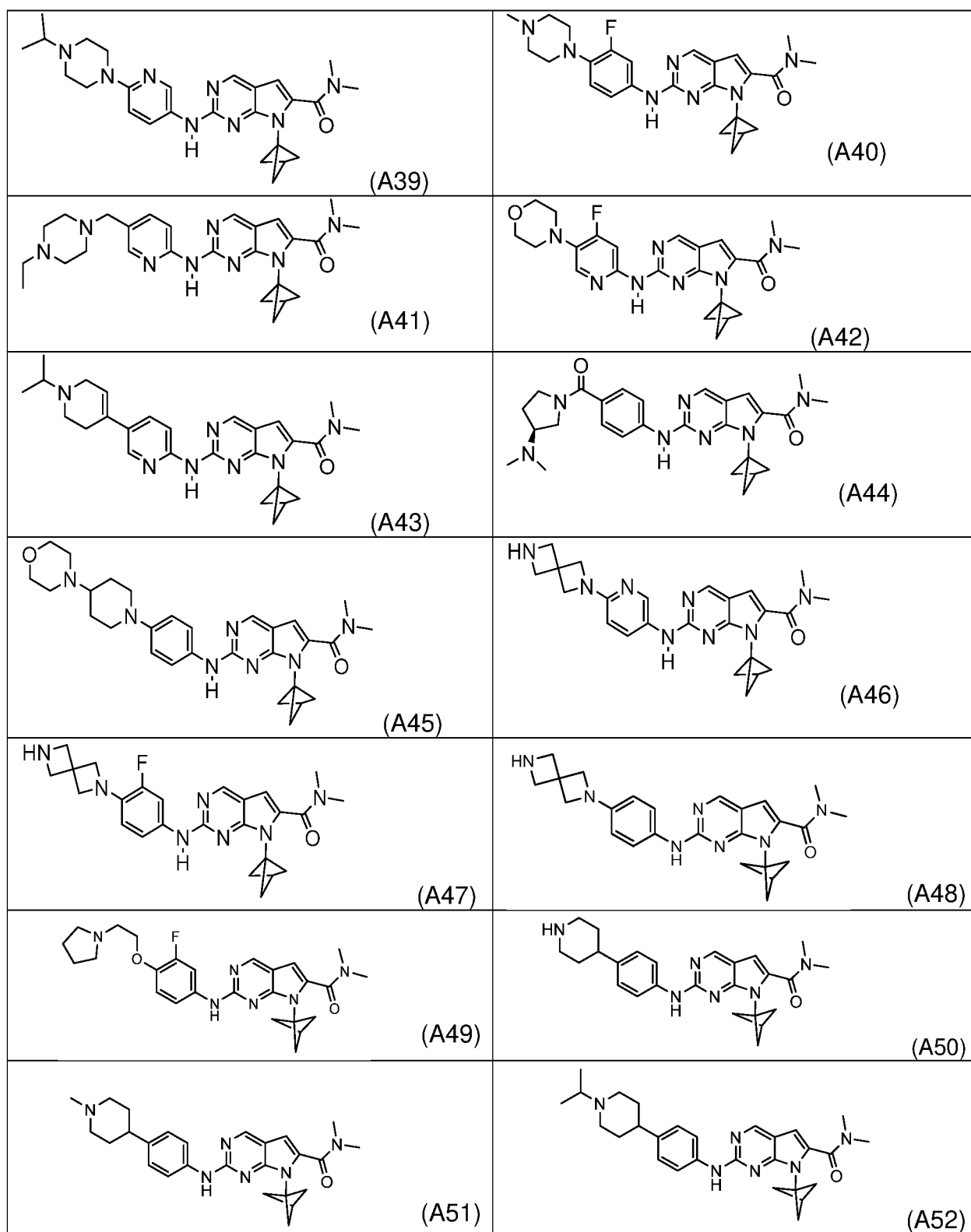


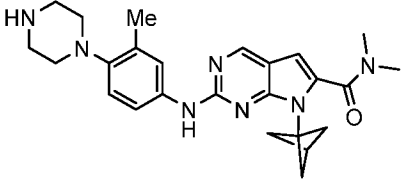
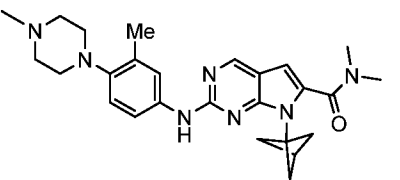
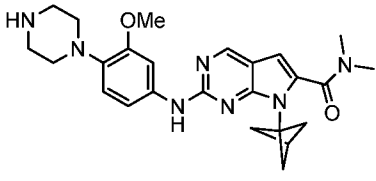
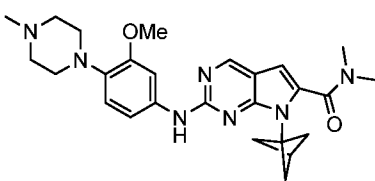
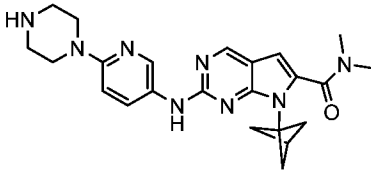
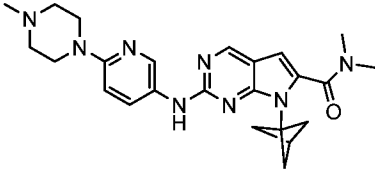
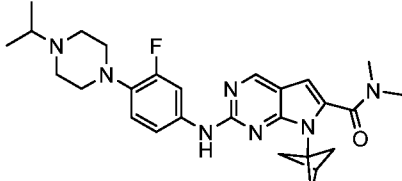
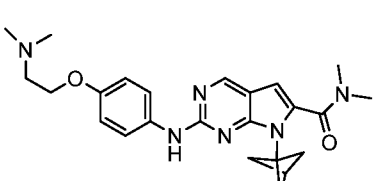
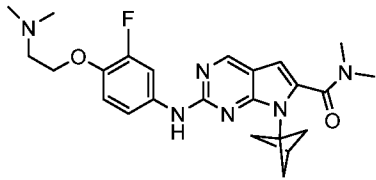
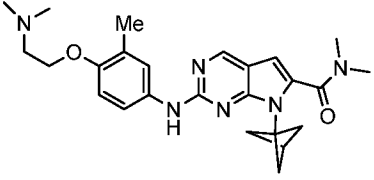
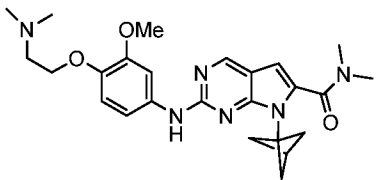
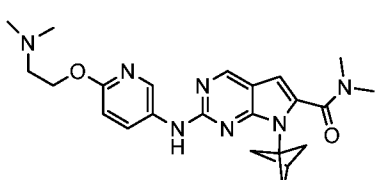
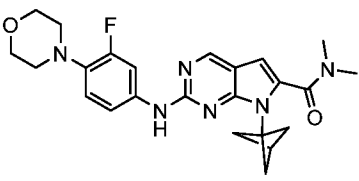
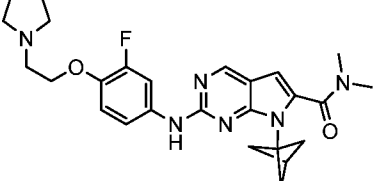
11. A compound selected from A1–A93 or pharmaceutically acceptable salts thereof:

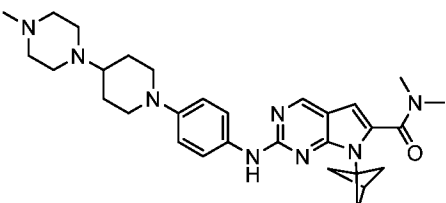
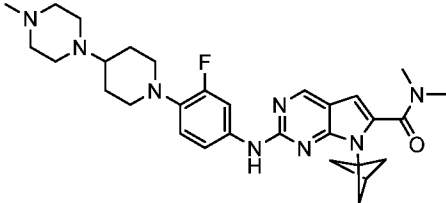
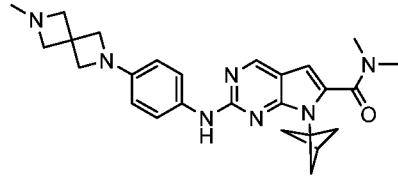
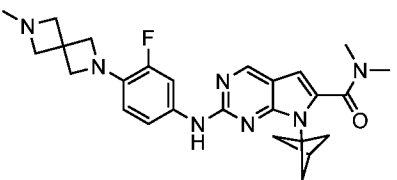
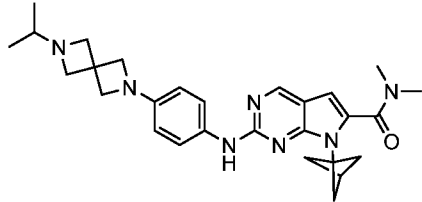
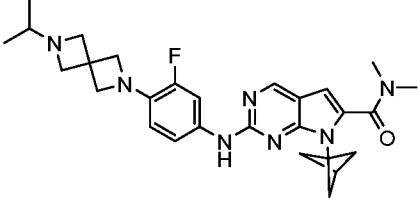
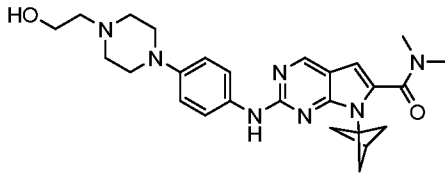
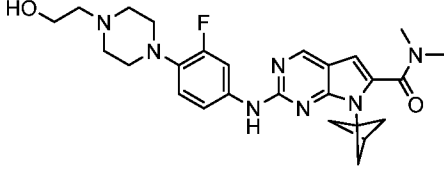
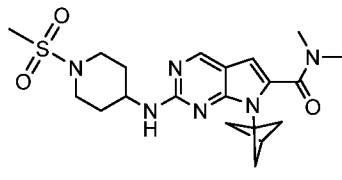
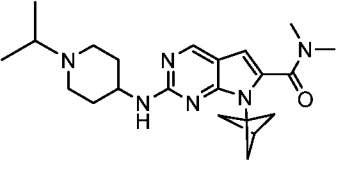
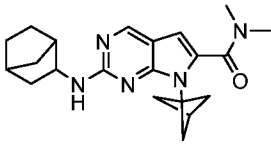
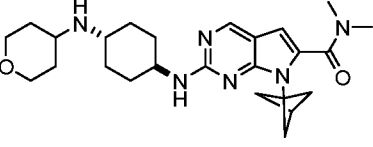
	
	
	
	

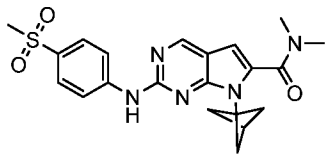
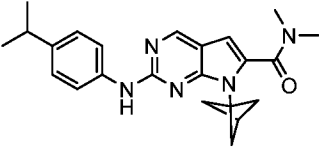
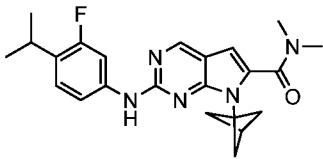
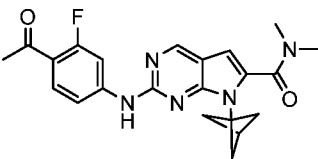
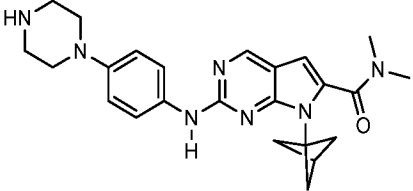
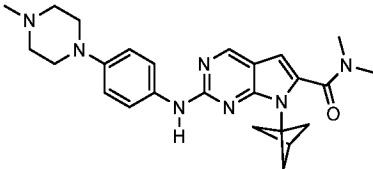
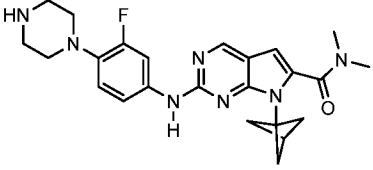
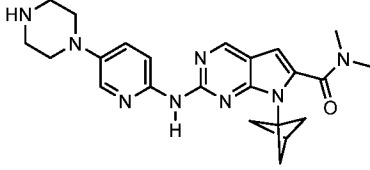
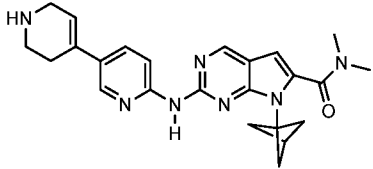
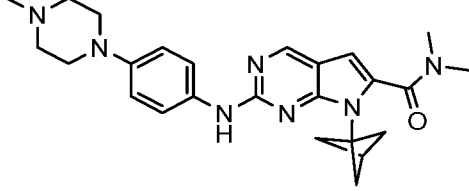
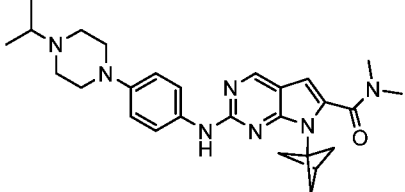
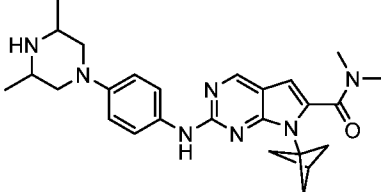
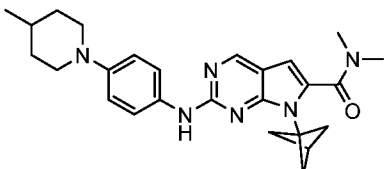
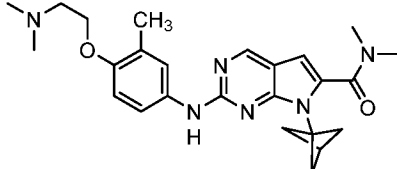
 (A9)	 (A10)
 (A11)	 (A12)
 (A13)	 (A14)
 (A15)	 (A16)
 (A17)	 (A18)
 (A19)	 (A20)
 (A21)	 (A22)
 (A23)	 (A34)

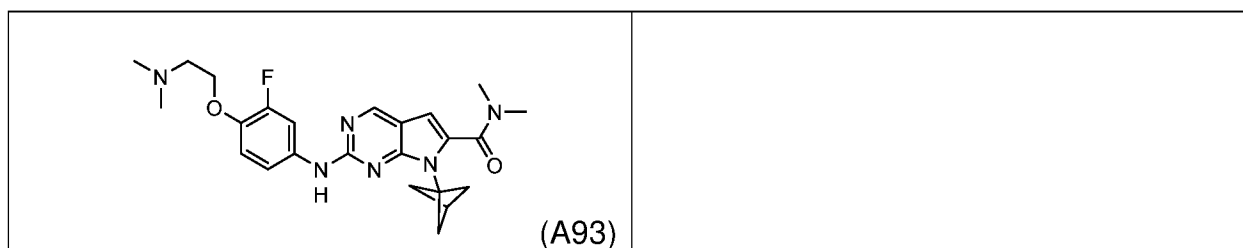
 (A25)	 (A26)
 (A27)	 (A28)
 (A29)	 (A30)
 (A31)	 (A32)
 (A33)	 (A34)
 (A35)	 (A36)
 (A37)	 (A38)



 (A53)	 (A54)
 (A55)	 (A56)
 (A57)	 (A58)
 (A59)	 (A60)
 (A61)	 (A62)
 (A63)	 (A64)
 (A65)	 (A66)

 (A67)	 (A68)
 (A69)	 (A70)
 (A71)	 (A72)
 (A73)	 (A74)
 (A75)	 (A76)
 (A77)	 (A78)

 (A79)	 (A80)
 (A81)	 (A82)
 (A83)	 (A84)
 (A85)	 (A86)
 (A87)	 (A88) . 2HCl
 (A89)	 (A90)
 (A91)	 (A92)



12. A pharmaceutical composition comprising one or more of Compounds A1–A93 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.
13. A method of treating cancer or providing a chemotherapeutic protective effect comprising administering an effective amount of one or more of Compounds A1–A93 to a subject in need thereof.
14. A compound selected from:
 - 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A1);
 - 7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A2);
 - 7-cyclopentyl-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A3);
 - 7-cyclopentyl-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A4);
 - 7-cyclopentyl-*N,N*-dimethyl-2-((5-(2-(pyrrolidin-1-yl)ethoxy)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A5);
 - 1-cyclopentyl-*N,N*-dimethyl-6-((5-(2-(piperidin-1-yl)ethoxy)pyridin-2-yl)amino)-1H-indole-2-carboxamide (A6);
 - 7-cyclopentyl-2-((4-(2-(dimethylamino)ethoxy)phenyl)amino)-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A7);
 - 1-cyclopentyl-*N,N*-dimethyl-6-((6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-3-yl)amino)-1H-indole-2-carboxamide (A8);
 - 2-((5-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-2-yl)amino)-7-cyclopentyl-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A9);

2-((5-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridin-2-yl)amino)-7-cyclopentyl-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A10);

7-cyclopentyl-2-((3-fluoro-4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A11);

7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A12);

7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A13);

7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A14);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A15);

7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((4-(piperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A16);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A17);

7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(4-methylpiperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A18);

7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A19);

7-cyclopentyl-5-fluoro-2-((3-fluoro-4-morpholinophenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A20);

7-cyclopentyl-5-fluoro-2-((1'-isopropyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A21);

7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A22);

2-((5-(4-cyanopiperazin-1-yl)pyridin-2-yl)amino)-7-cyclopentyl-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A23);

7-cyclopentyl-*N,N*-dimethyl-2-((5-(piperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A24);

7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((5-(piperazin-1-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A25);

7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(2-(pyrrolidin-1-yl)ethoxy)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A26);

7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(2-(piperidin-1-yl)ethoxy)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A27);

7-cyclopentyl-5-fluoro-*N,N*-dimethyl-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A28);

2-(4-(4-cyanophenyl)piperazin-1-yl)-7-cyclopentyl-5-fluoro-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A29);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A30);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)-3-methylphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A31);

7-cyclopentyl-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A32);

7-cyclopentyl-5-fluoro-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A33);

7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)-3-methylphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A34);

7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)-3-methoxyphenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A35);

7-cyclopentyl-5-fluoro-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A36);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A37);

7-(bicyclo[1.1.1]pentan-1-yl)-*N,N*-dimethyl-2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A38);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A39);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A40);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A41);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-fluoro-5-morpholinopyridin-2-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A42);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((1'-isopropyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-*N,N*-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A43);

(S)-7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(3-(dimethylamino)pyrrolidine-1-carbonyl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A44);

7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A45);

2-((6-(2,6-diazaspiro[3.3]heptan-2-yl)pyridin-3-yl)amino)-7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A46);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A47);

2-((4-(2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A48);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A49);

7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(piperidin-4-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A50);

7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(1-methylpiperidin-4-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A51);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(1-isopropylpiperidin-4-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A52);

7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((3-methyl-4-(piperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A53);

7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A54);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-methoxy-4-(piperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A55);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A56);

7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((6-(piperazin-1-yl)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A57);

7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A58);

7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-isopropylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A59);

- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A60);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-fluorophenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A61);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-methylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A62);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A63);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A64);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-morpholinophenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A65);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A66);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A67);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A68);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A69);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A70);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A71);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(6-isopropyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A72);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A73);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(4-(2-hydroxyethyl)piperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A74);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((1-(methylsulfonyl)piperidin-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A75);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((1-isopropylpiperidin-4-yl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A76);

- 7-(bicyclo[1.1.1]pentan-1-yl)-2-(bicyclo[2.2.1]heptan-2-ylamino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A77);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-(((1r,4r)-4-((tetrahydro-2H-pyran-4-yl)amino)cyclohexyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A78);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(methylsulfonyl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A79);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-isopropylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A80);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-isopropylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A81);
- 2-((4-acetyl-3-fluorophenyl)amino)-7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A82);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(piperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A83);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A84);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A85);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A86);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((1',2',3',6'-tetrahydro-[3,4'-bipyridin]-6-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A87);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide dihydrogen chloride (A88);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(4-isopropylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A89);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(3,5-dimethylpiperazin-1-yl)phenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A90);
- 7-(bicyclo[1.1.1]pentan-1-yl)-N,N-dimethyl-2-((4-(4-methylpiperidin-1-yl)phenyl)amino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A91);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-methylphenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A92);
- 7-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(2-(dimethylamino)ethoxy)-3-fluorophenyl)amino)-N,N-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide (A93);

or pharmaceutically acceptable salts thereof.

FIG. 1

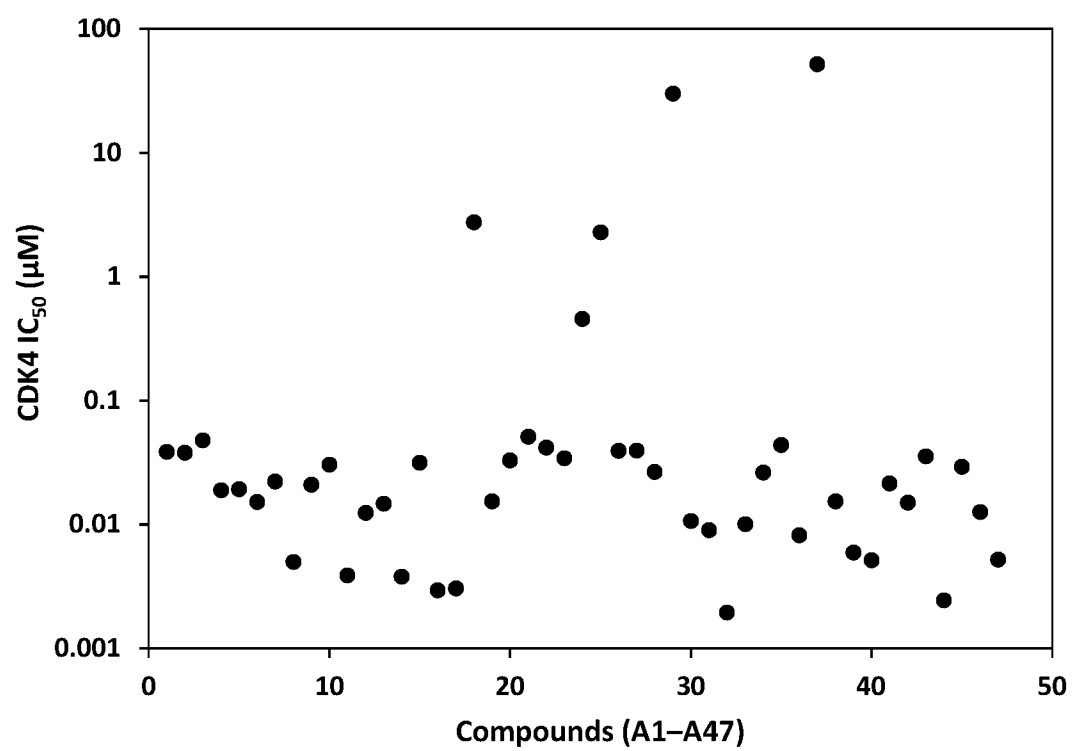
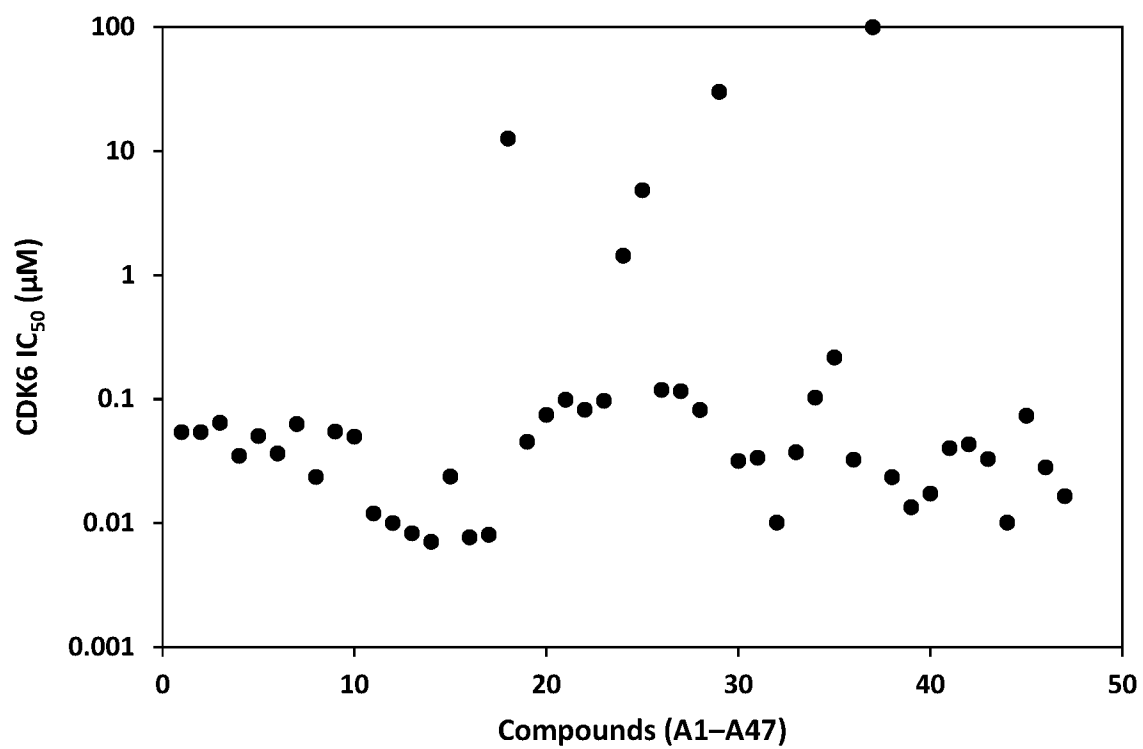


FIG. 2



A. CLASSIFICATION OF SUBJECT MATTER**C07D 487/04(2006.01)i, C07D 401/12(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 487/04; A61K 031/519; A61K 31/519; A61K 31/5377; A61P 35/02; C07D 417/14; C07D 401/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN(Registry, Caplus) & keywords: cyclin-dependent kinase inhibitor, cancer, pyrrolopyrimidine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2018-0155351 A1 (NOVARTIS AG et al.) 07 June 2018 claims 1, 13-14, 19, 21-22; example 63; table 1	1,6-12,14
X	US 2013-0035336 A1 (BORLAND, M. et al.) 07 February 2013 claims 1-2, 34, 55	1,6-12,14
A	WO 2007-140222 A2 (NOVARTIS AG et al.) 06 December 2007 the whole document	1,6-12,14
A	US 2005-0222163 A1 (ECK, S. L. et al.) 06 October 2005 the whole document	1,6-12,14
A	WO 2009-085185 A1 (AMGEN INC.) 09 July 2009 the whole document	1,6-12,14



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

01 May 2020 (01.05.2020)

Date of mailing of the international search report

01 May 2020 (01.05.2020)

Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea

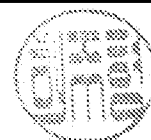


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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/068771

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 13 pertains to methods for treatment of the human body by surgery or therapy, as well as diagnostic methods(PCT Article 17(2)(a)(i) and Rule 39.1(iv)).
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2019/068771

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2018-0155351 A1	07/06/2018	AR 073116 A1	13/10/2010
		AR 111763 A2	14/08/2019
		AU 2009-284098 A1	25/02/2010
		AU 2009-284098 B2	29/03/2012
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		CA 2734802 E	25/02/2010
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