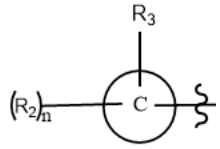
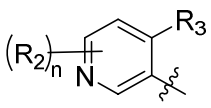
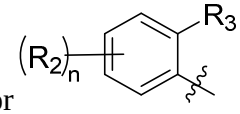
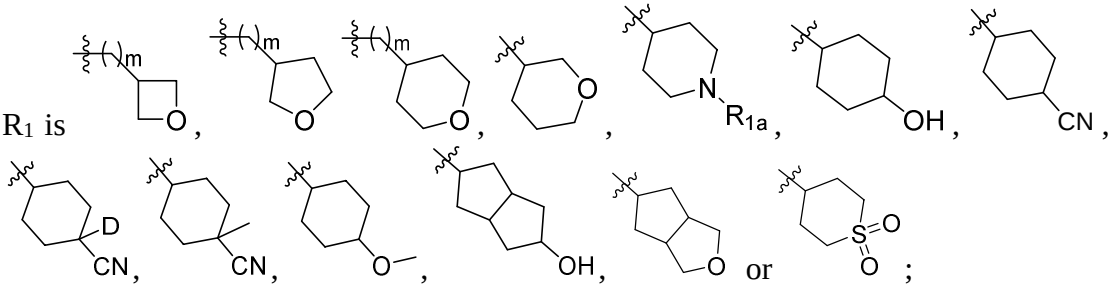

is , n is 1, R_0 is H or methyl, R_2 is methoxy or -$S(=O)_2Me$, and R_3 is methyl.

In one or more embodiments according to the present disclosure,


is  or  ;

R_0 is H, C_{1-4} alkyl, or cyclopropyl, wherein the C_{1-4} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is 

R_{1a} is H, C_{1-6} alkyl or $–C(=O)C_{1-6}$ alkyl;

R_2 is H, cyano, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl; wherein the $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, and halogen;

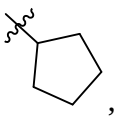
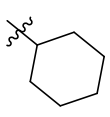
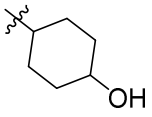
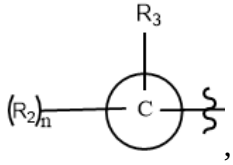
alternatively, R_{2a} and R_{2b} together with the atom to which they are attached form 5- to 6-membered heterocyclyl group containing 1 to 3 heteroatoms selected from N, O and S, wherein the 5- to 6-membered heterocyclyl group is optionally further substituted with one or more substituents selected from OH and halogen;

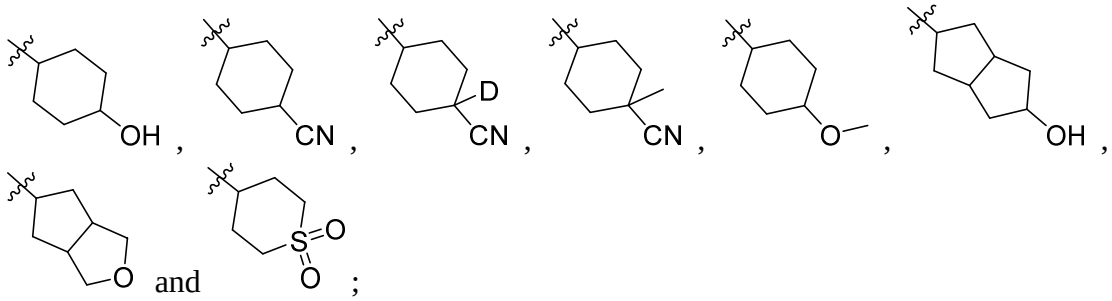
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

m is 0 or 1;

n is 0, 1, or 2;

provided that

R_1 is not  ,  , or  when  , R_0, R_2, and R_3 all satisfy the following condition:


and ;

R_{1a} is selected from H, C_{1-6} alkyl, and –C(=O)C_{1-6} alkyl;

R_2 is selected from cyano, carboxyl, -$NR_{2a}R_{2b}$, -C(=O)$NR_{2a}R_{2b}$, C_{1-6} alkoxy, C_{1-6} alkyl, halogen, -$S(=O)_2R_{2a}$ and -C(=O)OC_{1-6} alkyl; wherein the alkyl or alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are selected from H, C_{1-6} alkyl and 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

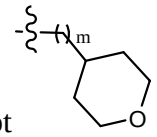
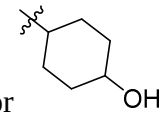
R_{2a} and R_{2b} together with the atom to which they are attached may form 5- to 6-membered heterocyclyl group which may contain 1 to 3 heteroatoms selected from N, O and S, wherein the heterocyclyl group may be further substituted with one or more substituents selected from C_{1-6} alkyl, OH, and halogen;

R_3 is selected from halogen and C_{1-6} alkyl, wherein the alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

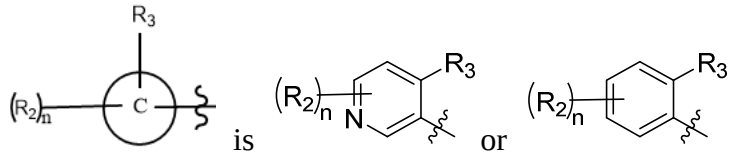
m is selected from 0 and 1; and

n is selected from 0, 1, and 2;

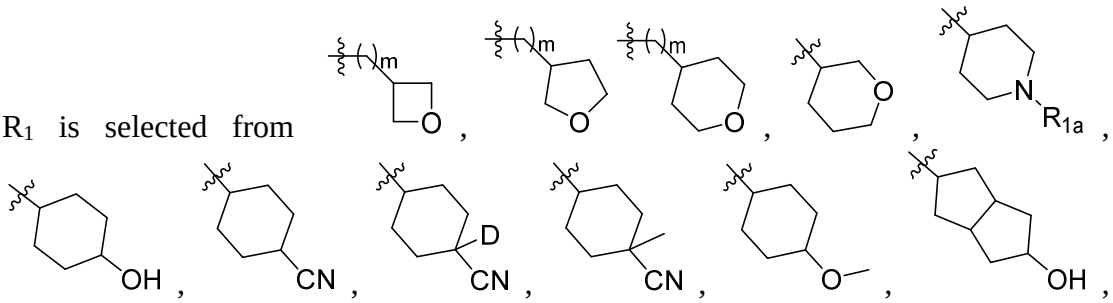
provided that

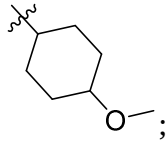
R_1 is not  or  when C is selected from phenyl and a 6-membered monocyclic heterocyclic group and R_0 is H.

In one or more embodiments according to the present disclosure,


is or ;

R_0 is selected from H, C_{1-4} alkyl, and cyclopropyl, wherein the alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is selected from 

 ;

R_2 is selected from cyano, carboxyl, $-NR_{2a}R_{2b}$, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, C_{1-6} alkyl, halogen, $-S(=O)_2R_{2a}$ and $-C(=O)OC_{1-6}$ alkyl; wherein the alkyl is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are selected from H, C_{1-6} alkyl or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

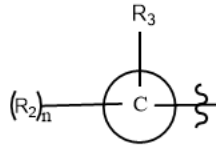
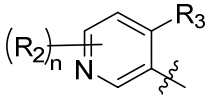
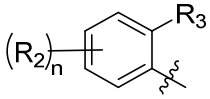
R_{2a} and R_{2b} together with the atom to which they are attached may form 5- to 6-membered heterocyclyl group which may contain 1 to 3 heteroatoms selected from N, O and S, wherein the heterocyclyl group may be further substituted with one or more substituents selected from C_{1-6} alkyl, and halogen;

R_3 is selected from halogen and C_{1-6} alkyl, wherein the alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

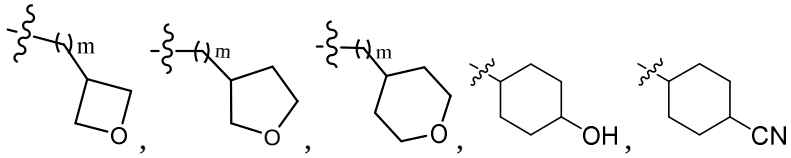
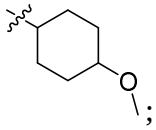
m is selected from 0 and 1; and

n is selected from 1 and 2.

In one or more embodiments according to the present disclosure,

 is selected from  or  ;

R_0 is selected from H and C_{1-4} alkyl, wherein the alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is selected from  , and  ;

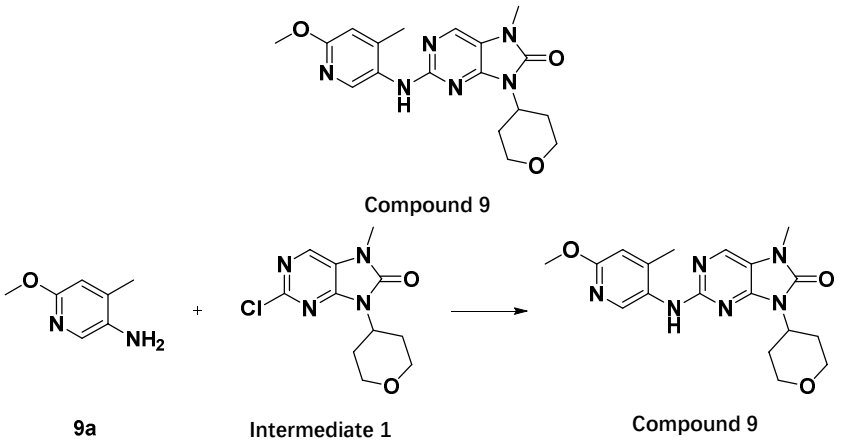
R_2 is selected from cyano, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, $-S(=O)_2R_{2a}$ and $-C(=O)OC_{1-6}$ alkyl; wherein the alkyl is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are selected from H, C_{1-6} alkyl and 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH and halogen;

R_{2a} and R_{2b} together with the atom to which they are attached may form 6-membered heterocyclyl group;

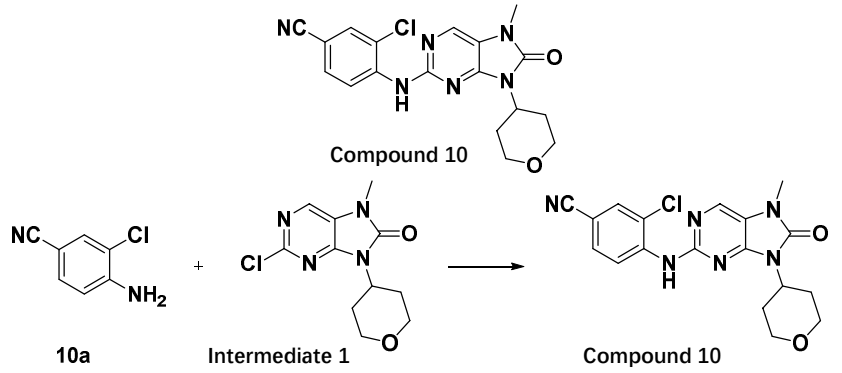
R_3 is selected from halogen and C_{1-6} alkyl, wherein the alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

2-((6-Methoxy-4-methylpyridin-3-yl)amino)-7-methyl-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one (**compound 9**)



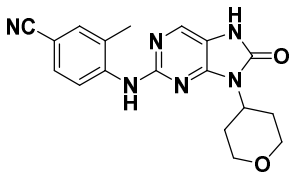
The title compound 2-((6-methoxy-4-methylpyridin-3-yl)amino)-7-methyl-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **compound 9** (white solid, 60 mg, 15.2 % yield) was prepared according to the synthesis method of **compound 1**.
^{1}H NMR (400 MHz DMSO) δ 8.49 (s, 1H), 8.04 (s, 1H), 7.95 (s, 1H), 6.70 (s, 1H), 4.41-4.33 (m, 1H), 3.95 (dd, 2H), 3.81 (s, 3H), 3.40 (t, 2H), 3.27 (s, 3H), 2.54-2.44 (m, 2H), 2.15 (s, 3H), 1.63(dd, 2H).
LC-MS m/z(ESI) = **371.20** [M+1]

Example 10
3-Chloro-4-((7-methyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzonitrile (**compound 10**)

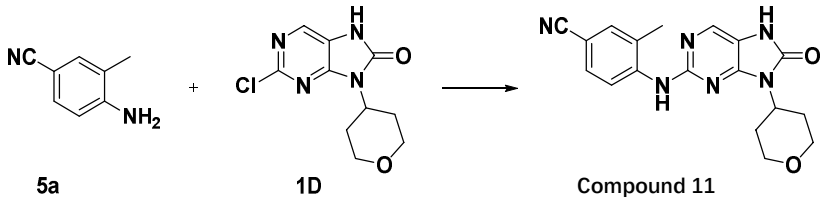


The title compound 3-chloro-4-((7-methyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzonitrile **compound 10** (white solid, 6.4 mg, 7.8 % yield) was prepared according to the synthesis method of **compound 1**.
^{1}H NMR (400 MHz DMSO) δ 8.61 (s, 1H), 8.44 (d, 1H), 8.23 (s, 1H), 8.05 (d, 1H), 7.77 (d, 1H), 4.47-4.41 (m, 1H), 3.97 (dd, 2H), 3.44 (t, 2H), 1.67 (d, 2H).
LC-MS m/z(ESI) = **385.10** [M+1]

Example 11
3-Methyl-4-[8-oxo-9-(tetrahydro-2H-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino]benzonitrile (**compound 11**)



Compound 11



5a 1D Compound 11

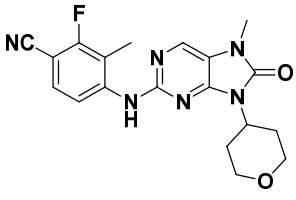
4-Amino-3-methylbenzonitrile **5a** (200 mg, 1.51 mmol), 2-chloro-9-(tetrahydro-2H-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **1D** (380 mg, 1.51 mmol), cesium carbonate (980 mg, 3.02 mmol), and methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (140 mg, 0.15 mmol) were dissolved in dioxane (10 mL), followed by nitrogen purging. The mixture was stirred under nitrogen at 100 °C for 4 h and monitored by TLC. After the reaction was completed. The mixture was poured into ice water, and the solid was collected and purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 100/1) to give obtain the title compound 3-methyl-4-[(9-(oxa-4-yl)-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino]benzonitrile **compound 11** (white solid, 120 mg, 22.68 % yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 8.60 (s, 1H), 8.08 (d, 1H), 7.96 (s, 1H), 7.62 (d, 1H), 7.57 (dd, 1H), 4.42-4.35 (m, 1H), 3.98 (dd, 2H), 3.41 (t, 2H), 2.32 (s, 3H), 1.64 (dd, 2H).

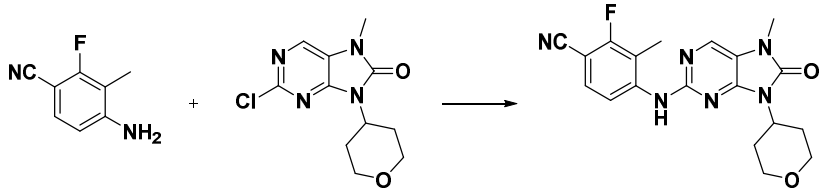
LC-MS m/z(ESI) = **351.10** [M+1]

Example 12

2-Fluoro-3-methyl-4-((7-methyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzonitrile (**compound 12**)



Compound 12



12a Intermediate 1 Compound 12

The title compound 2-fluoro-3-methyl-4-((7-methyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzonitrile **compound 12** (pale yellow solid, 25 mg, 7% yield) was prepared according to the synthesis method of **compound 1**.

^{1}H NMR (400 MHz DMSO) δ 9.00 (s, 1H), 8.20-8.17 (m, 1H), 7.91 (d, 1H), 7.63 (t, 1H), 4.47-4.39 (m, 1H), 3.97 (dd, 2H), 3.45-3.38 (m, 2H), 2.55-2.45 (m, 2H), 2.22 (d, 3H), 1.67 (dd, 2H).

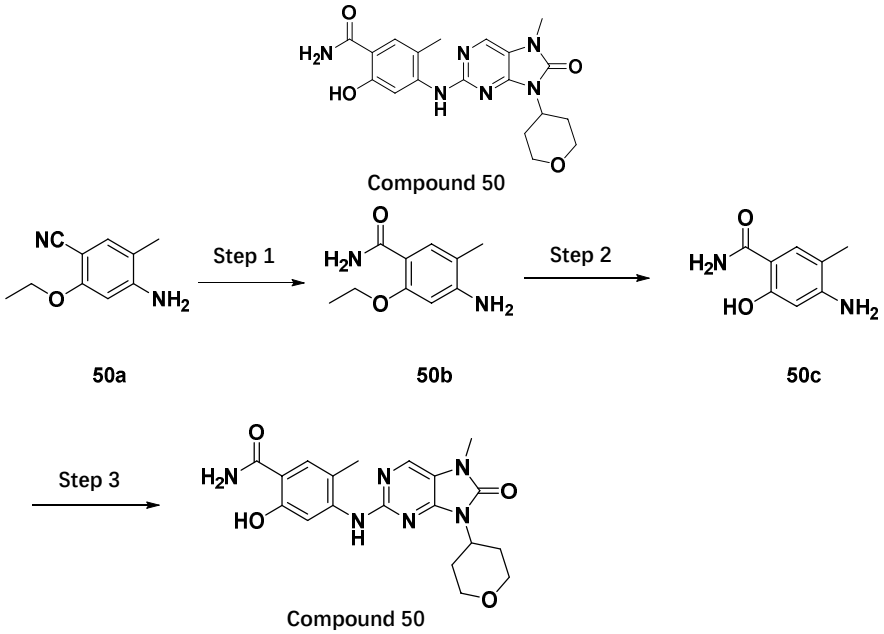
Step 8:
2-Fluoro-4-((9-(3-hydroxy-3-methylcyclobutyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (compound 49)

9-(3-Hydroxy-3-methylcyclobutyl)-7-methyl-2-(methylsulfinyl)-7,9-dihydro-8*H*-purin-8-one **49h** (100 mg, 0.34 mmol) and 4-amino-3-methyl-2-fluorobenzamide intermediate 2 (284 mg, 1.69 mmol) were dissolved in *N*,*N*-dimethylformamide (3 mL), and cesium carbonate (330 mg, 1.01 mmol) was added. The reaction mixture was gradually heated to 80 ℃ and stirred for 3 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into 30 mL of purified water, and extracted with ethyl acetate. Then, the organic layer was concentrated and purified by silica gel column chromatography purification (dichloromethane/methanol (v/v) = 35/1) to obtain the title compound 2-fluoro-4-((9-(3-hydroxy-3-methylcyclobutyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide **compound 49-1** (white solid, 12 mg, 8.88% yield) and **compound 49-2** (white solid, 20 mg, 14.80% yield).

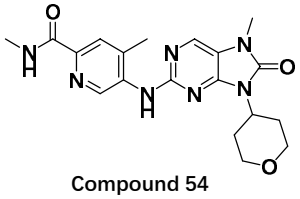
Compound 49-1:
1H NMR (600 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.21 (s, 1H), 7.87 (d, 1H), 7.55 (d, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 5.13 (s, 1H), 4.41-4.33 (m, 1H), 3.35 (s, 3H), 3.07-2.98 (m, 2H), 2.53 (s, 3H), 2.35-2.30 (m, 2H), 1.36 (s, 3H).
LC-MS m/z(ESI) = 401.20 [M+1]

Compound 49-2:
1H NMR (600 MHz, DMSO-d6) δ 8.59 (s, 1H), 8.20 (s, 1H), 7.87 (d, 1H), 7.55 (d, 1H), 7.46 (s, 1H), 7.42 (s, 1H), 5.14 (s, 1H), 4.39-4.31 (m, 1H), 3.32 (s, 3H), 3.05-2.97 (m, 2H), 2.54 (s, 3H), 2.33-2.29 (m, 2H), 1.35 (s, 3H).
LC-MS m/z(ESI) = 401.20 [M+1]

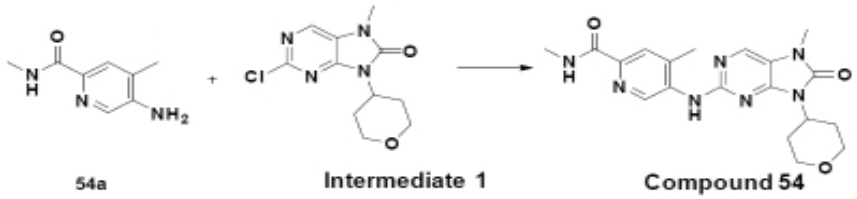
Example 50
2-Hydroxy-5-methyl-4-((7-methyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzamide (**compound 50**)



Step 1:



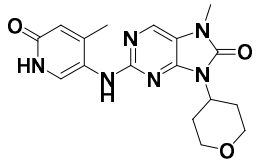
Compound 54



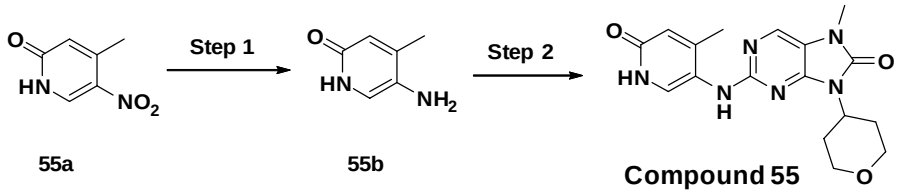
54a Intermediate 1 Compound 54

The title compound *N*,4-dimethyl-5-((7-methyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)picolinamide **compound 54** (pale yellow solid, 30 mg, 23.2% yield) was prepared according to the synthesis method of compound 1.
^{1}H NMR (400 MHz DMSO) δ 9.84 (s, 1H), 8.93 (d, 2H), 8.26 (d, 1H), 8.13 (s, 1H), 4.44-4.38 (m, 1H), 3.97-3.93 (m, 2H), 3.44-3.38 (m, 2H), 3.34 (s, 3H), 2.83 (d, 3H), 2.43-2.37 (m, 5H), 2.15 (s, 3H), 1.68 (dd, 2H).
LC-MS m/z(ESI) = **398.10** [M+1]

Example 55
7-Methyl-2-((4-methyl-6-oxo-1,6-dihydropyridin-3-yl)amino)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one (**compound 55**)



Compound 55



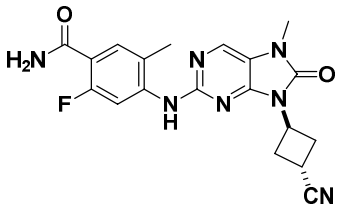
55a 55b Compound 55

Step 1:
5-Amino-4-methylpyridin-2(1*H*)-one (**55b**)

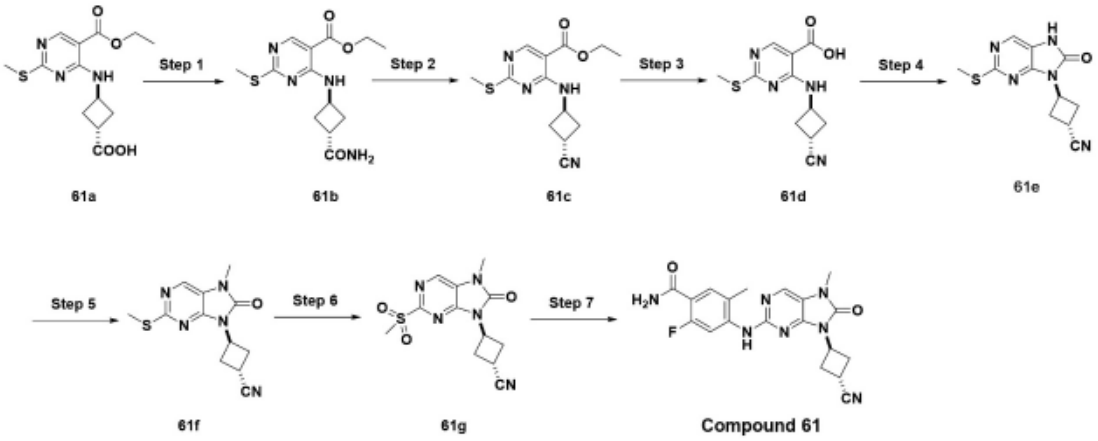
4-Methyl-5-nitropyridine-2(1*H*)-one **55a** (5.0 g, 32.44 mmol) and iron powder (9.0 g, 162.2 mmol) were added to a dry reaction flask and well mixed with ethanol/water (v/v=10/1, 110 mL), and then hydrochloric acid (7 mL, 2 mol/L) was added dropwise. The reaction mixture was stirred at 85 °C for 3 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered, and the filter cake was washed with an appropriate amount of ethanol. The filtrate was concentrated, the pH was adjusted to about 8 with saturated sodium bicarbonate and purified by silica gel column chromatography (dichloromethane:methanol (v/v) = 10:1) to give the title compound 5-amino-4-methylpyridin-2(1*H*)-one **55b** (dark green solid, 2.5 g, 62.08% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 10.63 (s, 1H), 6.75 (s, 1H), 6.11 (s, 1H), 4.06 (s, 2H), 2.02 (s, 3H).

Example 61

4-((9-(*trans*-3-Cyanocyclobutyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide (**compound 61**)



Compound 61



Step 1:

Ethyl 4-((*trans*-3-carbamoylcyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate (**61b**)

The starting material *trans*-3-((5-(ethoxycarbonyl)-2-(methylthio)pyrimidin-4-yl)amino)cyclobutane-1-carboxylic acid **61a** (13.0 g, 41.8 mmol) was added to dichloromethane (130 mL), and *N*,*N*,*N*',*N*'-tetramethyl-*O*-(7-azabenzotriazol-1-yl)urea hexafluorophosphate (19.1 g, 50.2 mmol) and triethylamine (16.9 g, 167.2 mmol) were added. The mixture was stirred at room temperature for 10 min, and ammonium chloride (6.7 g, 125.4 mmol) was added. The reaction mixture was stirred for 2 h. The reaction was monitored by TLC. After completion of the reaction, 50 mL of saturated aqueous sodium bicarbonate and dichloromethane was added to the reaction mixture. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude title compound ethyl 4-((*trans*-3-carbamoylcyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate **61b** (yellow viscous liquid, 12.5 g, 96.5% yield).

LCMS m/z(ESI) = 311.20 [M+1]

Step 2:

Ethyl 4-((*trans*-3-cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate (**61c**)

Ethyl 4-((*cis*-3-carbamoylcyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate **61b** (12.5 g, 4.03 mmol) was added to dichloromethane (130 mL), and pyridine (13.2 g, 167.2 mmol) and trifluoroacetic anhydride (26.3 g, 125.4 mmol) were added. The

reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion of the reaction, the pH of reaction mixture was adjusted to 3 with 2 N hydrochloric acid and extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was then purified by column chromatography (petroleum ether/ethyl acetate (v/v) = 5:1) to give the title compound ethyl 4-((*trans*-3-cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate **61c** (white solid, 1.7 g, 10.2% yield).
1H NMR (400 MHz, DMSO-d6) δ 8.65 (s, 1H), 8.46 (d, 1H), 4.70-4.61 (m, 1H), 4.37-4.31 (m, 2H), 2.92-2.81 (m, 3H), 2.52 (s, 3H), 2.46-2.35 (m, 2H), 1.38(t, 3H).
LC-MS m/z(ESI) = 293.20 [M+1]

Step 3:
4-((*trans*-3-Cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylic acid (**61d**)

Ethyl 4-((*cis*-3-Cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate **61c** (1.7 g, 5.8 mmol) was dissolved in a mixture of tetrahydrofuran (10 mL) and water (10 mL), and lithium hydroxide (487 mg, 11.6 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran and the pH was adjusted to 4–5, and a white solid was precipitated. The mixture was filtered, and the filter cake was washed twice with petroleum ether/ethyl acetate (v/v = 10/1) and concentrated to obtain the title compound 4-((*trans*-3-cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylic acid 61d (white solid, 1.5 g, 97.4% yield).
LC-MS m/z(ESI) = 265.10 [M+1]

Step 4:
trans-3-(2-(Methylthio)-8-oxo-7,8-dihydro-9*H*-purin-9-yl)cyclobutane-1-carbonitrile (**61e**)

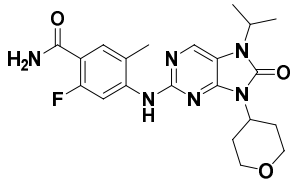
4-((*trans*-3-Cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylic acid **61d** (1.5 g, 5.7 mmol) was dissolved in *N*,*N*-dimethylformamide (15 mL), and triethylamine (576 mg, 5.7 mmol) and diphenylphosphoryl azide (1.57 g, 5.7 mmol) were added. The reaction mixture was gradually heated to 110 °C and stirred for 1.5 h. The reaction was monitored by TLC. After completion of the reaction,the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate (v/v) = 5:1 to 1:10) to obtain the title compound *trans*-3-(2-(methylthio)-8-oxo-7,8-dihydro-9*H*-purin-9-yl)cyclobutane-1-carbonitrile **61e** (white solid, 1.0 g, 67% yield).
1H NMR (400 MHz, DMSO-d6) δ 11.35 (s, 1H), 8.11 (s, 1H), 4.92-3.92 (m, 1H), 3.37-3.26 (m, 2H), 3.27-3.15 (m, 1H), 2.78-2.67 (m, 2H), 2.58 (s, 3H).
LC-MS m/z(ESI) = 262.10 [M+1]

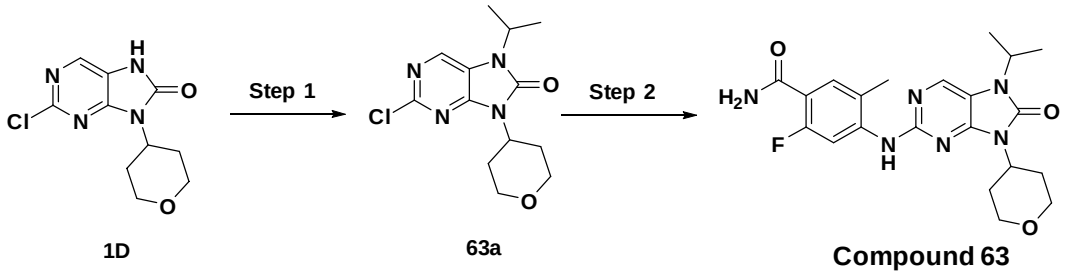
Step 5:
trans-3-(7-Methyl-2-(methylthio)-8-oxo-7,8-dihydro-9*H*-purin-9-yl)cyclobutane-1-carbonitrile (**61f**)

trans-3-(2-(Methylthio)-8-oxo-7,8-dihydro-9*H*-purin-9-yl)cyclobutane-1-carbonitrile **61e** (500 mg, 19.1 mmol) was dissolved in dimethylformamide (5 mL), and dimethyl

^{1}H NMR (400 MHz, DMSO-d6) δ 8.53 (s, 1H), 8.25 (s, 1H), 7.89 (d, 1H), 7.55 (d, 1H), 7.42 (d, 2H), 4.48-4.40 (m, 1H), 3.98 (dd, 2H), 3.85 (q, 2H), 3.43 (t, 2H), 2.58-2.54 (m, 2H), 2.30 (s, 3H) 1.71-1.68 (m, 2H), 1.25 (t, 3H).
LC-MS m/z(ESI) = **415.20** [M+1]

Example 63
2-Fluoro-4-((7-isopropyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (**compound 63**)





Step 1:
2-Chloro-7-isopropyl-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one (**63a**)

2-Chloro-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **1D** (520 mg, 2.04 mmol) was dissolved in *N*,*N*-dimethylformamide (10 mL), and cesium carbonate (665 mg, 2.04 mmol) and 2-iodopropane (416 mg, 2.45 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h. The reaction was monitored by TLC. After completion of the reaction,then 20 mL of water was added, and the resulting mixture was extracted 3 times with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated to afford the title compound 2-chloro-7-isopropyl-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **63a** (white solid, 465 mg, 76.74% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.52 (s, 1H), 4.65-4.56 (m, 1H), 4.49-4.40 (m, 1H), 3.99-3.95 (m, 2H), 3.44 (t, 2H), 2.46-2.42 (m, 2H), 1.70-1.67 (m, 2H), 1.43 (d, 6H).
LC-MS m/z(ESI) = **297.10** [M+1]

Step 2:
2-Fluoro-4-((7-isopropyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (**compound 63**)

The title compound 2-fluoro-4-((7-isopropyl-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide **compound 63** (white solid, 58 mg, 20.06% yield) was prepared according to the synthesis method of **compound 62**.
^{1}H NMR (400 MHz, Chloroform-d) δ 10.17 (s, 1H), 7.98 (d, 1H), 7.93 (s, 1H), 7.76 (d, 1H), 6.79 (d, 1H), 6.39 (s, 1H), 4.73 (t, 1H), 4.52 (t, 1H), 4.11 (dd, 2H), 3.49 (t, 2H), 2.63-2.55 (m, 1H), 2.40 (s, 3H), 1.75 (d, 2H), 1.51 (d, 6H).
LC-MS m/z(ESI) = **429.20** [M+1]

3-Aminocyclopentane-1-ol hydrochloride **67c** (6.91 g, 50.22 mmol) and ethyl 2,4-dichloropyrimidine-5-carboxylate (13.32 g, 60.26 mmol) were added to 75 mL of acetonitrile, and after being stirred at room temperature until dissolved, the reaction mixture was added slowly with potassium carbonate (17.35 g, 125.54 mmol) and stirred for 10 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to remove acetonitrile, and water was added and the organics were extracted with ethyl acetate. The organic phase was concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate (v/v) = 1/1) to yield the title compound ethyl 2-chloro-4-((3-hydroxycyclopentyl)amino)pyrimidine-5-carboxylate **67d** (yellow oily liquid, 7.78 g, 54% yield).
LC-MS m/z(ESI) = **286.10** [M+1]

Step 4:
2-Chloro-4-((3-hydroxycyclopentyl)amino)pyrimidine-5-carboxylic acid (**67e**)

Ethyl 2-chloro-4-((3-hydroxycyclopentyl)amino)pyrimidine-5-carboxylate **67d** (7.78 g, 27.23 mmol) was dissolved in 50 mL of tetrahydrofuran, lithium hydroxide (1.3 g, 54.46 mmol) was dissolved in 50 mL of water, an aqueous solution of lithium hydroxide was slowly added to the THF solution in an ice bath and the reaction mixture was stirred for 2 h. The reaction was monitored by TLC. After completion of the reaction,the reaction mixture was concentrated by rotary evaporation under reduced pressure to remove tetrahydrofuran and the pH was adjusted to about 4 with hydrochloric acid solution, and a solid was precipitated. The solid was collected by filtration, and the filtrate was extracted with ethyl acetate. The organic phase and the filter residue were combined and concentrated to obtain the title compound 2-chloro-4-((3-hydroxycyclopentyl)amino)pyrimidine-5-carboxylic acid **67e** (pale yellow solid, 6.78 g, 96% yield).
LC-MS m/z(ESI) = **258.10** [M+1]

Step 5:
2-Chloro-9-(3-hydroxycyclopentyl)-7,9-dihydro-8*H*-purin-8-one (**67f**)

2-Chloro-4-((3-hydroxycyclopentyl)amino)pyrimidine-5-carboxylic acid **67e** (6.0 g, 23.29 mmol) was dissolved in 60 mL of *N*,*N*-dimethylacetamide, diphenylphosphoryl azide (6.41 g, 23.29 mmol) and triethylamine (2.36 g, 23.29 mmol) were slowly added in an ice bath, and the reaction mixture was stirred at room temperature for 1 h, and then stirred at 90 °C for 5 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was added dropwise to 200 mL of water, and extracted with ethyl acetate. The organic phase was collected and concentrated to obtain the title compound 2-chloro-9-(3-hydroxycyclopentyl)-7,9-dihydro-8*H*-purin-8-one **67f** (yellow oily liquid, 5.47 g, 92% yield).
LC-MS m/z(ESI) = **255.10** [M+1]

Step 6:
2-Chloro-9-(3-hydroxycyclopentyl)-7-methyl-7,9-dihydro-8*H*-purin-8-one (**67g**)

2-Chloro-9-(3-hydroxycyclopentyl)-7,9-dihydro-8*H*-purin-8-one **67f** (2.5 g, 9.82 mmol) and cesium carbonate (4.16 g, 12.76 mmol) were dissolved in 40 mL of DMF,

and the reaction mixture was stirred in an ice bath for 10 min, then added slowly with dimethyl sulfate (1.24 g, 9.82 mmol) and reacted for 1 h. The reaction was monitored by TLC. After completion of the reaction, 100 mL of water was added and the organics were extracted with ethyl acetate, and the organic phase was collected, concentrated and purified by column chromatography to yield the title compound 2-chloro-9-(3-hydroxycyclopentyl)-7-methyl-7,9-dihydro-8*H*-purin-8-one **67g** (orange solid, 900 mg, 34% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 4.90 (d, 1H), 4.71-4.62 (m, 1H), 4.16-4.08 (m, 1H), 3.35 (s, 3H), 2.29-2.23 (m, 1H), 2.17-2.10(m, 2H), 1. 92-1.77 (m, 3H).
LC-MS m/z(ESI) = **269.10** [M+1]

Step 7:
2-Fluoro-4-((9-(3-hydroxycyclopentyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzonitrile (**67h**)

2-Chloro-9-(3-hydroxycyclopentyl)-7-methyl-7,9-dihydro-8*H*-purin-8-one **67g** (600 mg, 2.23 mmol), 4-amino-2-fluoro-5-methylbenzonitrile **2A** (335 mg, 2.23 mmol), cesium carbonate (2.18 g, 6.70 mmol), and methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (303 mg, 0.34 mmol) were dissolved in 1,4-dioxane (10 mL), and the reaction mixture was purged with nitrogen and stirred at 110 °C for 6 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 20/1) to obtain the title compound 2-fluoro-4-((9-(3-hydroxycyclopentyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzonitrile **67h** (pale yellow solid, 460 mg, 54% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.74 (d, 1H), 8.25 (d, 1H), 8.20-8.15 (m, 1H), 7.66 (d, 1H), 5.05-4.96 (m, 0.5H), 4.83 (d, 0.5H), 4.73-4.64 (m, 0.5H), 4.66 (s, 0.5H), 4.13-4.08 (m, 1H), 3.34 (d, 3H), 2.31 (s, 3H), 2.15-2.09 (m, 3H), 1.96-1.75 (m, 3H).
LC-MS m/z(ESI) = **383.20** [M+1]

Step 8:
2-Fluoro-4-((9-(3-hydroxycyclopentyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (**compound 67**)

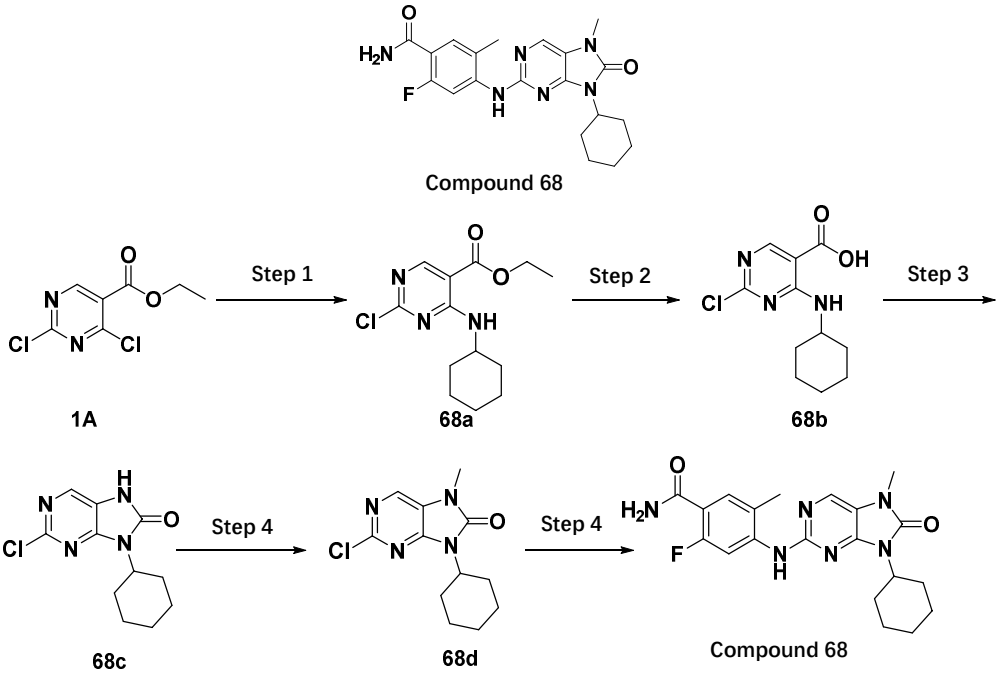
2-Fluoro-4-((9-(3-hydroxycyclopentyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzonitrile **67h** (400 mg, 1.05 mmol) and potassium carbonate (43.4 mg, 313.81 mmol) were dissolved in 20 mL of dimethyl sulfoxide, and hydrogen peroxide (1.05 mL, 10.46 mmol) was slowly added with stirring at room temperature. The reaction mixture was stirred for 3 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by preparative medium pressure liquid chromatography, followed by Pre-HPLC to obtain the title compound 2-fluoro-4-((9-(3-hydroxycyclopentyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide **compound 67**, which was then resolved by SFC to yield **compound 67-1** (white solid, 70 mg, 17% yield, dr = 99%) and **compound 67-2** (white solid, 58 mg, 14% yield, dr = 99%). (OZ), mobile phase: CO_2/isopropanol = 70/30; column temperature: 35 °C; column pressure: 80 bar; flow rate: 1 mL/min; detector signal channel: 220 nm@4 nm; diode array detector at a wavelength of 200–400 nm.
Compound 67-1:

^{1}H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 8.19 (s, 1H), 7.88 (d, 1H), 7.54 (d, 1H), 7.47 (s, 1H), 7.37 (d, 1H), 4.86 (d, 1H), 4.72-4.63 (m, 1H), 4.14-4.06 (m, 1H), 3.32(s, 3H), 2.42-2.32 (m, 1H), 2.28 (s, 3H), 2.16-2.10 (m, 2H), 1.93-1.76 (m,3H).
LC-MS m/z(ESI) = **400.20** [M+1]

Compound 67-2:
^{1}H NMR (400 MHz, DMSO-d6) δ 8.51 (s, 1H), 8.18 (s, 1H), 7.86 (d, 1H), ,7.54 (d, 1H), 7.46 (s, 1H), 7.38 (d,1H), 5.03-4.94 (m, 1H), 4.64(d, 1H), 4.35 (s,1H), 3.32(s,3H), 2.38-2.31(m,1H), 2.28 (s, 3H), 2.15-2.03(m,3H)1.85-1.80(m, 1H), 1.62-1.57(m, 1H).
LC-MS m/z(ESI) = **400.20** [M+1]

Example 68

4-((9-Cyclohexyl-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide (**compound 68**)



Step 1:

Ethyl 2-chloro-4-(cyclohexylamino)pyrimidine-5-carboxylate (**68a**)

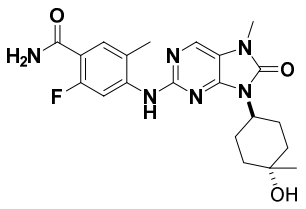
Ethyl 2,4-dichloropyrimidine-5-carboxylate **1A** (5.0 g, 22.6 mmol) and potassium carbonate (6.2 g, 45.2 mmol) were dissolved in acetonitrile (50 mL), and cyclohexylamine (2.2 g, 22.6 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The reaction was monitored by TLC. After completion of the reaction, water was added and the organics were extracted with ethyl acetate., and the organic phase was dried over anhydrous sodium sulfate and purified by silica gel column chromatography (*n*-hexane/ethyl acetate (v/v) = 10:1) to obtain the title compound ethyl 2-chloro-4-(cyclohexylamino)pyrimidine-5-carboxylate **68a** (white solid, 4.1 g, 64% yield).
^{1}H NMR (400 MHz, Chloroform-d) δ 8.64 (s, 1H), 8.53-8.23 (m, 1H), 4.35 (q, 2H), 4.25-4.05 (m, 1H), 2.01-1.95 (m, 2H), 1.77-1.72(m, 2H), 1.64-1.61 (m, 1H), 1.50-1.41 (m, 3H), 1.39 (t, 3H), 1.35-1.18 (m, 2H).
LC-MS m/z(ESI) = **284.10** [M+1]

Step 2:

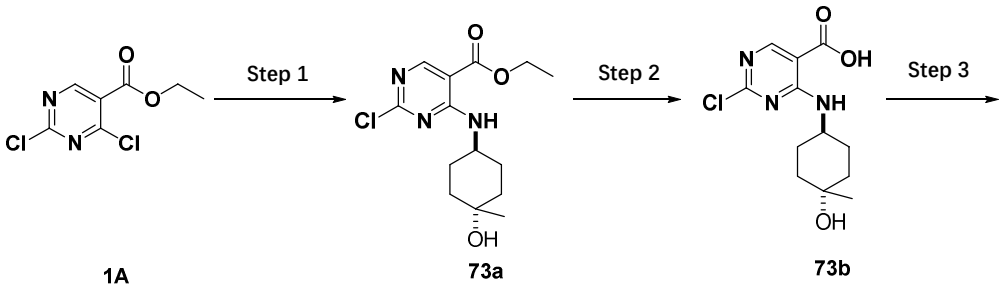
purin-2-yl)amino)-5-methylbenzamide (**compound 72**)

2-Chloro-9-(*cis*-4-hydroxy-4-methylcyclohexyl)-7-methyl-7,9-dihydro-8*H*-purin-8-one **72d** (250 mg, 0.84 mmol), 4-amino-3-methyl-2-fluorobenzamide **intermediate 2** (282 mg, 1.68 mmol), cesium carbonate (446 mg, 1.68 mmol) and methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (76 mg, 0.084 mmol) were dissolved in dioxane (4 mL), followed by nitrogen purging. The reaction mixture was stirred under nitrogen at 110 °C for 4 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 35/1) to obtain the title compound 2-fluoro-4-((9-(*cis*-4-hydroxy-4-methylcyclohexyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide **compound 72** (white solid, 80 mg, 22 % yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.40 (s, 1H), 8.15 (s, 1H), 7.92 (d, 1H), 7.54 (d, 1H), 7.46 (s, 1H), 7.35 (d, 1H), 4.20-4.06 (m, 1H), 4.02 (s, 1H), 3.31 (s, 3H), 2.78-2.57 (m, 2H), 2.28 (s, 3H), 1.68 (d, 2H), 1.49-1.40 (m, 4H), 1.15 (s, 3H).
LC-MS m/z (ESI) = **429.20** [M+1]

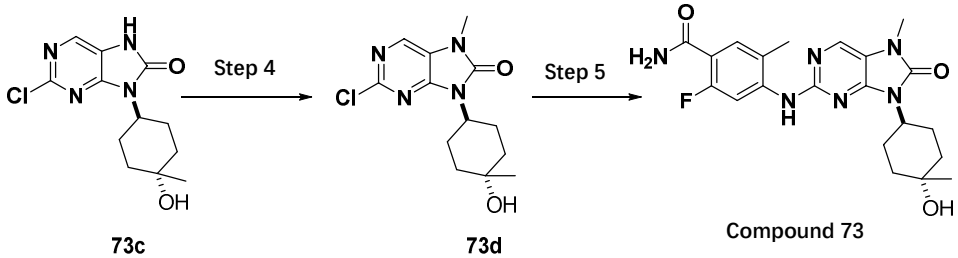
Example 73
2-Fluoro-4-((9-(*trans*-4-hydroxy-4-methylcyclohexyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (**compound 73**)



Compound 73



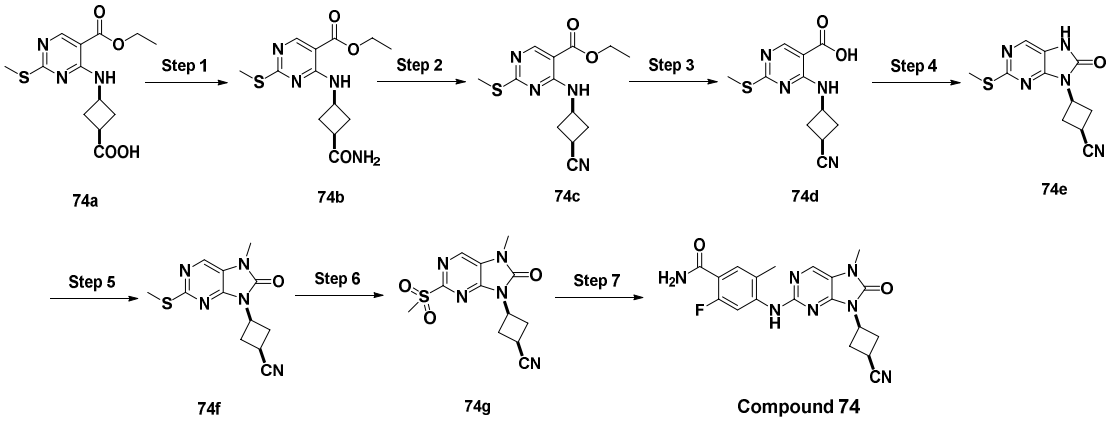
1A 73a 73b



73c 73d Compound 73

Step 1:
Ethyl 2-chloro-4-((*trans*-4-hydroxy-4-methylcyclohexyl)amino)pyrimidine-5-carboxylate (**73a**)

Ethyl 2,4-dichloro-5-pyrimidinecarboxylate **1A** (5.00 g, 30.18 mmol) was dissolved in



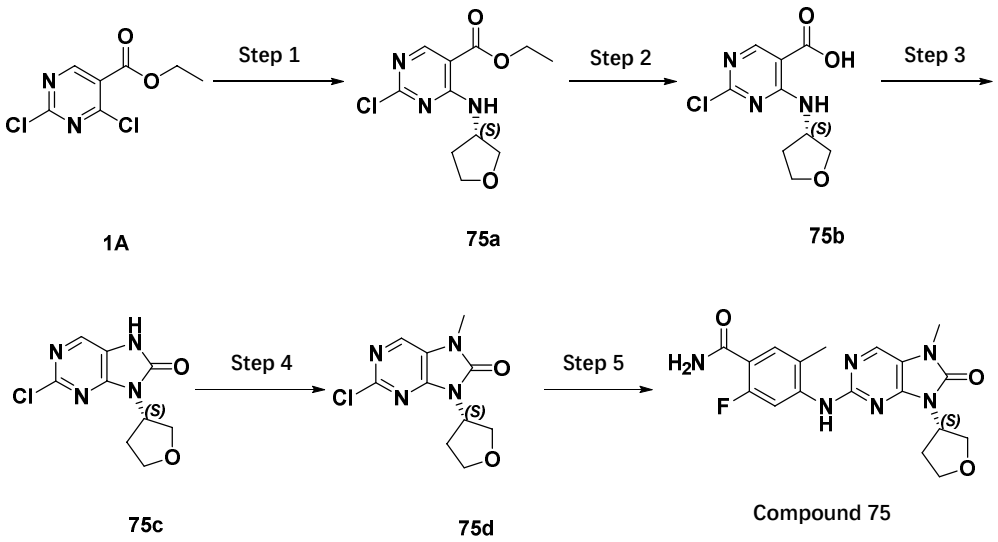
Step 1:
Ethyl 4-((*cis*-3-carbamoylcyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate (**74b**)

The starting material *cis*-3-((5-(ethoxycarbonyl)-2-(methylthio)pyrimidine-4-yl)amino)cyclobutane-1-carboxylic acid **74a** (13.0 g, 41.8 mmol) was added to dichloromethane (130 mL), and *N*,*N*,*N*',*N*'-tetramethyl-O-(7-azabenzotriazol-1-yl)urea hexafluorophosphate (19.1 g, 50.2 mmol) and triethylamine (16.9 g, 167.2 mmol) were added. The mixture was stirred at room temperature for 10 min, and then ammonium chloride (6.7 g, 125.4 mmol) was added. The reaction mixture was stirred for 2 h. The reaction was monitored by TLC. After completion of the reaction, 50 mL of saturated aqueous sodium bicarbonate were added to the reaction mixture and the organics were extracted with dichloromethane, and the organic layer was concentrated, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude title compound ethyl 4-((*cis*-3-carbamoylcyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate **74b** (yellow viscous liquid, 17.5 g, 134.6% yield).
LC-MS m/z(ESI) = 311.20 [M+1]

Step 2:
Ethyl 4-((*cis*-3-cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate (74c)

Ethyl 4-((*cis*-3-carbamoylcyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate 74b (17.5 g, 5.64 mmol) was added to dichloromethane (130 mL), and pyridine (13.2 g, 167.2 mmol) and trifluoroacetic anhydride (26.3 g, 125.4 mmol) were added. The reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion of the reaction, the pH of reaction mixture was adjusted to 3 with 2 N hydrochloric acid and extracted with dichloromethane, and the organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to get a crude product, which was then purified by column chromatography (petroleum ether/ethyl acetate (v/v) = 5:1) to obtain the title compound ethyl 4-((*cis*-3-cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylate **74c** (white solid, 3.5 g, 21.2 % yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (s, 1H), 8.46 (d, 1H), 4.70-4.61 (m, 1H), 4.37-4.31 (m, 2H), 2.94-2.84 (m, 3H), 2.52 (s, 3H), 2.48-2.38 (m, 2H), 1.38(t, 3H).
LC-MS m/z(ESI) = 293.20 [M+1]

Step 3:
4-((*cis*-3-Cyanocyclobutyl)amino)-2-(methylthio)pyrimidine-5-carboxylic acid **(74d)**



Step 1:
Ethyl (*S*)-2-chloro-4-((tetrahydrofuran-3-yl)amino)pyrimidine-5-carboxylate (**75a**)

Ethyl 2,4-dichloropyrimidine-5-carboxylate **1A** (5 g, 5.35 mmol) and potassium carbonate (1.4 g, 22.6 mmol) were dissolved in acetonitrile (20 mL), and (*S*)-tetrahydrofuran-3-amine (660 mg, 5.35 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 20 h. Water was added and the organics were extracted three times with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate and purified by silica gel column chromatography (*n*-hexane/ethyl acetate (v/v) = 10:1) followed by concentration to obtain the title compound ethyl (*S*)-2-chloro-4-((tetrahydrofuran-3-yl)amino)pyrimidine-5-carboxylate **75a** (white solid, 2.2 g, 36% yield).
^{1}H NMR (400 MHz DMSO) δ 8.68 (s, 1H), 8.58 (d, 1H), 4.79-4.77 (m, 1H), 4.39-4.33 (m, 2H), 4.04-3.98 (m, 2H), 3.90-3.87 (m, 1H), 3.76-3.73 (m, 1H), 2.43-2.33 (m, 1H), 1.95-1.88 (m, 1H), 1.39 (t, 3H).
LC-MS m/z(ESI) = **272.00** [M+1]

Step 2:
(*S*)-2-Chloro-4-((tetrahydrofuran-3-yl)amino)pyrimidine-5-carboxylic acid (**75b**)

Ethyl (*S*)-2-chloro-4-((tetrahydrofuran-3-yl)amino)pyrimidine-5-carboxylate **75a** (2.2 g, 8.1 mmol) was dissolved in tetrahydrofuran/water (5 mL/5 mL), and lithium hydroxide (681 mg, 16.2 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated by rotary evaporation under reduced pressure to remove tetrahydrofuran and the pH was adjusted to 4–5, and a white solid was precipitated. The mixture was filtered, and the filter cake was washed twice with petroleum ether/ethyl acetate (v/v = 10/1) and concentrated to obtain the title compound (*S*)-2-chloro-4-((tetrahydrofuran-3-yl)amino)pyrimidine-5-carboxylic acid **75b** (white solid, 1.7 g, 89% yield).
^{1}H NMR (400 MHz DMSO) δ 13.83 (s, 1H), 8.65 (s, 1H), 8.63 (d, 1H), 4.61 (s, 1H), 3.89-3.80 (m, 2H), 3.76-3.70 (m, 1H), 3.65-3.63 (m, 1H), 2.50-2.25 (m, 1H), 1.87-1.86 (m, 1H).
LC-MS m/z(ESI) = **244.20** [M+1]

Step 3:
(*S*)-2-Chloro-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one (**75c**)

(*S*)-2-Chloro-4-((tetrahydrofuran-3-yl)amino)pyrimidine-5-carboxylic acid **75b** (1.7 g, 7 mmol) was dissolved in dimethylacetamide (10 mL), and triethylamine (707 mg, 7 mmol) and diphenylphosphoryl azide (1.9 g, 7 mmol) were added. The reaction mixture was gradually heated to 110 °C and stirred for 1.5 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate (v/v) = 1:6) to obtain the title compound (*S*)-2-chloro-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one **75c** (white solid, 1.4 g, 87% yield).
^{1}H NMR (400 MHz DMSO) δ 8.13 (s, 1H), 5.00-4.93 (m, 1H), 4.12-4.06 (dd, 1H), 3.97 (t, 1H), 3.88-3.87 (m, 2H), 3.33 (s, 3H), 2.43-2.37 (m, 1H), 2.25-2.20 (m, 1H).
LC-MS m/z(ESI) = **241.20** [M+1]

Step 4:
(*S*)-2-Chloro-7-methyl-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one (**75d**)

(*S*)-2-Chloro-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one **75c** (1.4 g, 5.8 mmol) was dissolved in dimethylformamide (10 mL), and dimethyl sulfate (735 mg, 5.8 mmol) and cesium carbonate (2.85 g, 8.7 mmol) were added at 0 °C. The reaction mixture was stirred for 0.5 h. The reaction was monitored by TLC. After completion of the reaction, water was added to the reaction mixture, and a solid was precipitated. The solid was collected by filtration to get the title compound (*S*)-2-chloro-7-methyl-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one **75d** (white solid, 1.2 g, 85% yield).
^{1}H NMR (400 MHz DMSO) δ 8.35 (s, 1H), 5.04-4.97 (m, 1H), 4.13-4.07 (dd, 1H), 3.98 (t, 1H),3.90-3.84 (m, 2H), 3.35(s, 3H), 2.44-2.37 (m, 1H), 2.28-2.27 (m,1H).
LC-MS m/z(ESI) = **255.20** [M+1]

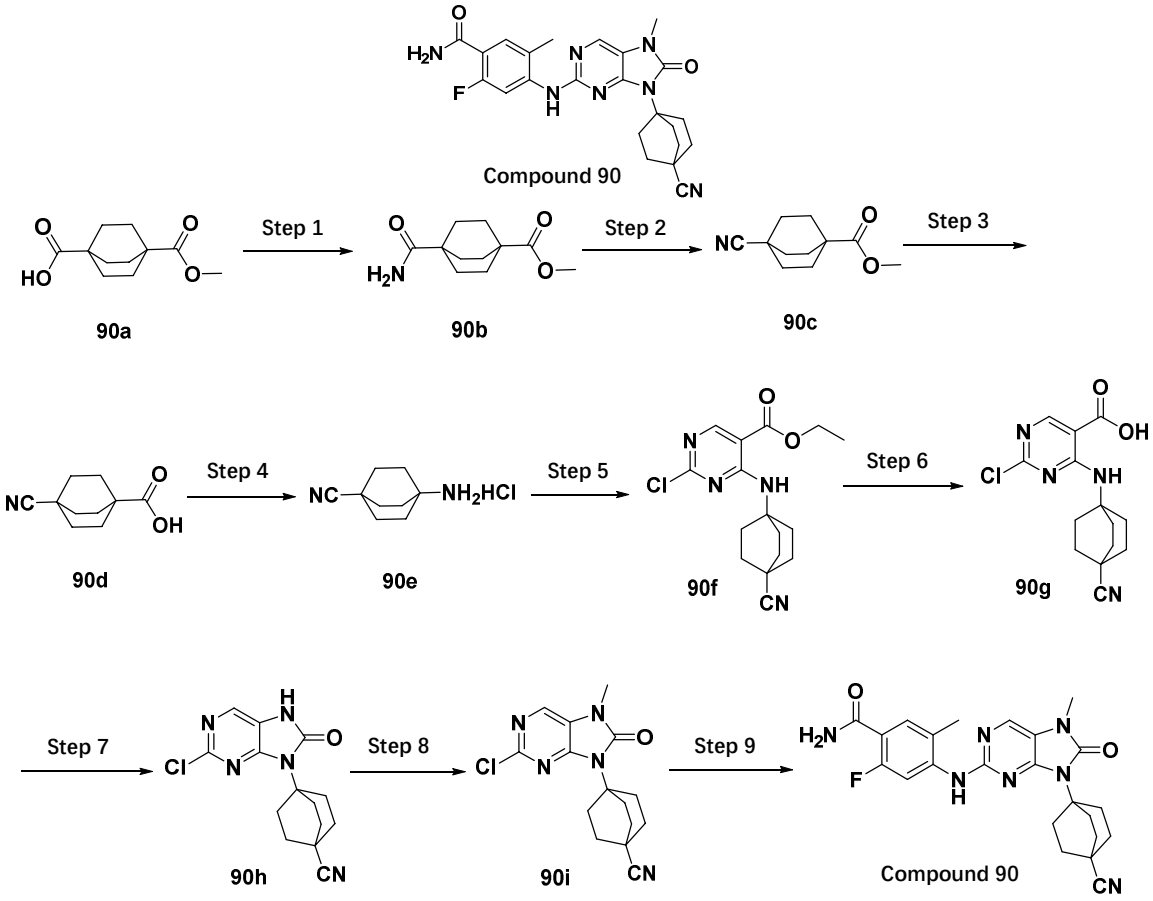
Step 5:
(*S*)-2-Fluoro-5-methyl-4-((7-methyl-8-oxo-9-(tetrahydrofuran-3-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzamiderile (**compound 75**)

(*S*)-2-Chloro-7-methyl-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one **75d** (200 mg, 0.78 mmol), 4-amino-2-fluoro-5-methylbenzamide **intermediate 2** (264 mg, 1.57 mmol), cesium carbonate (770 mg, 2.36 mmol) and methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (71.4 mg, 0.078 mmol) were dissolved in dioxane (3 mL), followed by nitrogen purging. The reaction mixture was stirred under nitrogen at 110 °C for 4 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 35/1) to obtain the title compound (*S*)-2-fluoro-5-methyl-4-((7-methyl-8-oxo-9-(tetrahydrofuran-3-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzamiderile **compound 75** (white solid, 58 mg, 19 % yield).
^{1}H NMR (400 MHz DMSO) δ 8.49 (s, 1H), 8.20 (s, 1H), 7.89 (d, 1H),7.55 (d, 1H), 7.44(d, 2H), 4.95-5.02 (m, 1H), 4.07-4.13 (dd, 1H), 3.91-3.99(m,2H), 3.82-3.85(m,1H),3.32 (s, 3H), 2.44-2.50(m, 1H), 2.28(S, 3H), 2.20-2.27(m, 1 H).
LC-MS m/z(ESI) = **387.10** [M+1]

Example 76

Example 90

4-((9-(4-Cyanobicyclo[2.2.2]octan-1-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide (**compound 90**)



Step 1:

Methyl 4-carbamoylbicyclo[2.2.2]octane-1-carboxylate (**90b**)

4-(Methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid **90a** (10.0 g, 47.12 mmol) was dissolved in anhydrous dichloromethane (200 mL), and 2-(7-azabenzotriazole)-*N*,*N*,*N'*,*N'*-tetramethylurea hexafluorophosphate (18.81 g, 49.47 mmol) was added in an ice bath. The mixture was stirred for 30 min with the temperature maintained. *N*,*N*-Diisopropylethylamine (24.62 mL, 141.35 mmol) was added, and then solid ammonium chloride (3.78 g, 70.67 mmol) was slowly added several times. The reaction mixture was gradually warmed to room temperature and stirred overnight. The reaction was monitored by TLC. After completion of the reaction, 100 mL of 0.5 N hydrochloric acid solution was added, the organic phase was separated, washed successively with water and saturated brine (100 mL each), dried and concentrated to give the title compound methyl 4-carbamoylbicyclo[2.2.2]octane-1-carboxylate **90b** (white solid, 21 g, crude).

^{1}H NMR (400 MHz, DMSO-d6) δ 6.94 (s, 1H), 6.73 (s, 1H), 3.57 (s, 3H), 1.72-1.63 (m, 12 H).

LC-MS m/z(ESI) = **212.10** [M+1]

Step 2:

Methyl 4-cyanobicyclo[2.2.2]octane-1-carboxylate (**90c**)

Step 3:
Ethyl 2-chloro-4-((4-cyano-4-methylcyclohexyl)amino)pyrimidine-5-carboxylate (92d)

Ethyl 2,4-dichloro-5-pyrimidinecarboxylate **1A** (6.72 g, 30.39 mmol) was dissolved in acetonitrile (30 mL), and potassium carbonate (8.40 g, 60.78 mmol) was added with stirring at 0 °C, followed by the slow dropwise addition of a solution of 4-amino-1-methylcyclohexane-1-carbonitrile **92c** (2.80 g, 20.26 mmol) in acetonitrile (10 mL). The reaction mixture was stirred for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through celite, and the filtrate was purified by silica gel column chromatography (petroleum ether/ethyl acetate (v/v) = 20:1) to obtain the title compound ethyl 2-chloro-4-((4-cyano-4-methylcyclohexyl)amino)pyrimidine-5-carboxylate **92d** (white solid, 2.63 g, 40.22% yield).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (d, 1H), 4.38 (p, 2H), 2.23-1.82 (m, 4H), 1.79-1.49 (m, 6H), 1.46-1.36 (m, 6H).
LC-MS m/z(ESI) = **323.10** [M+1]

Step 4:
2-Chloro-4-((4-cyano-4-methylcyclohexyl)amino)pyrimidine-5-carboxylic acid (**92e**)

Ethyl 2-chloro-4-((4-cyano-4-methylcyclohexyl)amino)pyrimidine-5-carboxylate **92d** (2.63 g, 8.15 mmol) was dissolved in tetrahydrofuran/water (20 mL/10 mL), and lithium hydroxide monohydrate (1.00 g, 24.45 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated to evaporate tetrahydrofuran and the pH was adjusted to about 3–4 with 2 N HCl, and a white solid was precipitated. The mixture was filtered, and the filter cake was washed twice with water and petroleum ether/ethyl acetate (v/v = 10/1) to obtain the title compound 2-chloro-4-((4-cyano-4-methylcyclohexyl)amino)pyrimidine-5-carboxylic acid **92e** (white solid, 2.20 g, 91.59% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 13.75 (s, 1H), 8.59 (s, 1H), 8.52 (d, 1H), 3.97 (m, 1H), 2.06-1.92 (m, 4H), 1.63-1.47 (m, 4H), 1.35 (s, 3H).
LC-MS m/z(ESI) = **295.10** [M+1]

Step 5:
4-(2-Chloro-8-oxo-7,8-dihydro-9*H*-purin-9-yl)-1-methylcyclohexane-1-carbonitrile (**92f**)

2-Chloro-4-((4-cyano-4-methylcyclohexyl)amino)pyrimidine-5-carboxylic acid **92e** (2.20 g, 7.46 mmol) was dissolved in *N*,*N*-dimethylacetamide (15 mL), and triethylamine (1.04 mL, 7.46 mmol) and diphenylphosphoryl azide (1.61 mL, 7.46 mmol) were added with stirring at room temperature. The reaction mixture was stirred for 2 h, then heated to 110 °C and refluxed for 2.5 h. The reaction was monitored by TLC. After completion of the reaction, water was added and the organics were extracted three times with ethyl acetate. The organic layer was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 80/1) to obtain the title compound 4-(2-chloro-8-oxo-7,8-dihydro-9*H*-purin-9-yl)-1-methylcyclohexane-1-carbonitrile **92f** (white solid, 0.9 g, 41.35% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 11.64 (s, 1H), 8.13 (s, 1H), 4.31-4.20 (m, 1H), 2.45-2.33 (m, 2H), 2.01-1.94 (m, 4H), 1.71-1.64 (m, 2H), 1.49 (s, 3H).
LC-MS m/z(ESI) = **292.10** [M+1]

Step 6:
4-(2-Chloro-7-methyl-8-oxo-7,8-dihydro-9*H*-purin-9-yl)-1-methylcyclohexane-1-carbonitrile (**92g**)

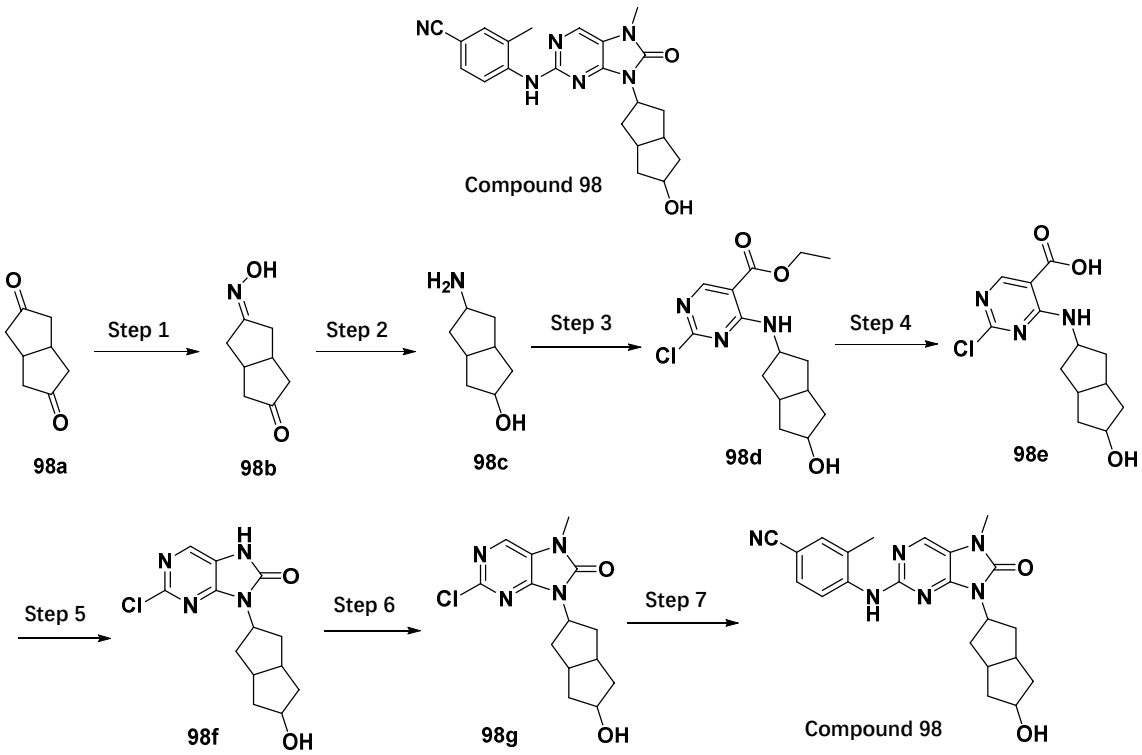
4-(2-chloro-8-oxo-7,8-dihydro-9*H*-purin-9-yl)-1-methylcyclohexane-1-carbonitrile **92f** (0.90 g, 3.08 mmol) was dissolved in *N*,*N*-dimethylformamide (10 mL), and dimethyl sulfate (0.29 mL, 3.08 mmol) and cesium carbonate (1.51 g, 4.62 mmol) were added with stirring at 0 °C. The reaction mixture was stirred for 2 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was slowly added dropwise to ice water. The mixture was stirred, and a white solid was precipitated. The solid was washed 3 times with water and petroleum ether and collected by filtration to give the title compound 4-(2-chloro-7-methyl-8-oxo-7,8-dihydro-9*H*-purin-9-yl)-1-methylcyclohexane-1-carbonitrile **92g** (white solid, 0.85 g, 90.26% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 4.35-4.20 (m, 1H), 3.36 (s, 3H), 2.48-2.31 (m, 2H), 2.06-1.95 (m, 3H), 1.83-1.76 (m, 1H), 1.71-1.57 (m, 2H), 1.48 (s, 1H), 1.36 (s, 2H).
LC-MS m/z(ESI) = **306.10** [M+1]

Step 7:
4-((9-(4-Cyano-4-methylcyclohexyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide (**compound 92**)

4-(2-Chloro-7-methyl-8-oxo-7,8-dihydro-9H-purin-9-yl)-1-methylcyclohexane-1-carbonitrile **92g** (200 mg, 0.67 mmol), 4-amino-2-fluoro-5-methylbenzamide **intermediate 2** (338 mg, 2.01 mmol), cesium carbonate (473 mg, 1.34 mmol) and Brettphos Pd G3 (61 mg, 0.067 mmol) were dissolved in dioxane, followed by nitrogen purging. The reaction mixture was stirred under nitrogen atmosphere at 110 °C for 4 h. The reaction was s monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 30/1) to obtain the title compound 4-((9-(4-cyano-4-methylcyclohexyl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide **compound 92**, which was resolved by SFC to give **compound 92-1** (white solid, 12 mg, 4.1% yield, RT = 3.58 min) and **compound 92-2** (white solid, 22 mg, 7.5% yield, RT = 4.17 min). (OZ), mobile phase: CO_2/ethanol = 70/30; column temperature: 35 °C; column pressure: 80 bar; flow rate: 1 mL/min; detector signal channel: 215 nm@4.8 nm; diode array detector at a wavelength of 200–400 nm.
Compound 92-1:
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.18 (s, 1H), 7.65 (d, 1H), 7.57 (d, 1H), 7.47 (s, 1H), 7.38 (s, 1H), 4.27-4.16 (m, 1H), 2.45-2.31 (m, 5H), 2.26 (s, 3H), 1.97-1.89 (m, 4H), 1.69-1.59 (m, 2H), 1.32 (s, 3H).
LC-MS m/z(ESI) = **438.20** [M+1]

Compound 92-2:

yl)amino]-3-methylbenzonitrile (**compound 98**)



Step 1:
5-(hydroxyimino)hexahydropentalen-2(1H)-one (**98b**)

Hydroxylamine hydrochloride (9.05 g, 130.28 mmol) and potassium carbonate (18.01, 130.28 mmol) were dissolved in 100 mL of water, and the resulting solution was added to a solution of tetrahydropentalene-2,5(1H,3H)-dione **98a** (20 g, 144.76 mmol) in ethanol (200 mL). The reaction mixture was refluxed at 90 °C for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated to remove ethanol, then diluted with 100 mL of water and extracted with ethyl acetate. The organic phases were combined, dried and filtered, and the filtrate was concentrated to get a crude product, which was then purified by column chromatography (dichloromethane:methanol = 100:1) to give the title compound 5-(hydroxyimino)hexahydropentalen-2(1H)-one **98b** (white solid, 7 g, 31.57% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 2.79-2.69 (m, 2H), 2.66-2.54 (m, 2H), 2.42-2.34 (m, 2H), 2.23-2.13 (m, 2H), 2.05-1.99 (m, 1H), 1.96-1.90 (m, 1H).
LC-MS m/z(ESI) = **154.10** [M+1]

Step 2:
5-Amino-octahydropentalen-2-ol (98c)

5-(hydroxyimino)hexahydropentalen-2(1H)-one **98b** (4 g, 26.11 mmol) was dissolved in tetrahydrofuran (100 mL), and cobalt chloride (12.42 g, 52.22 mmol) was added. The solution was cooled to -30 °C, and sodium borohydride (4.94 g, 130.55 mmol) was added in batches. The reaction mixture was stirred for 1 h with the temperature maintained at -25 °C to -30 °C throughout the reaction. The reaction was monitored by TLC. After completion of the reaction, saturated brine was added to the reaction

mixture until no bubbles were formed. The reaction mixture was warmed to room temperature, stirred for another 0.5 h and filtered, and the filtrate was concentrated and dried to give the crude product 5-amino-octahydropentalen-2-ol **98c** (oily solid, 1 g, 27.12% yield).
LC-MS m/z(ESI) = **142.10** [M+1]

Step 3:
Ethyl 2-chloro-4-[(5-hydroxy-octahydropentalen-2-yl)amino]pyrimidine-5-carboxylate (**98d**)

Ethyl 2,4-dichloropyrimidine-5-carboxylate **1A** (2.0 g, 9.05 mmol) and 5-amino-octahydropentalen-2-ol **98c** (1 g, 7.08 mmol) were dissolved in acetonitrile (40 mL), and potassium carbonate (2.5 g, 18.10 mmol) was added in an ice bath. The reaction mixture was stirred at room temperature for 12 h. The reaction was monitored by TLC. After completion of the reaction, 50 mL water was added and the organics were extracted with ethyl acetate. The organic phases were combined, dried and concentrated, and the residue was purified by column chromatography (petroleum ether: ethyl acetate = 4:1) to obtain the title compound ethyl 2-chloro-4-[(5-hydroxy-octahydropentalen-2-yl)amino]pyrimidine-5-carboxylate **98d** (yellow solid, 1 g, 33.92% yield).
^{1}H NMR (400 MHz, Chloroform-d) δ 8.63 (s, 1H), 4.48-4.41 (m, 1H), 4.33 (q, 2H), 2.58 -2.46 (m, 2H), 2.42-2.36 (m, 2H), 2.11-2.05 (m, 2H), 1.57-1.48 (m, 4H), 1.37 (t, 3H).
LC-MS m/z(ESI) = **326.10** [M+1]

Step 4:
2-Chloro-4-[(5-hydroxy-octahydropentalen-2-yl)amino]pyrimidine-5-carboxylic acid (**98e**)

Ethyl 2-chloro-4-[(5-hydroxy-octahydropentalen-2-yl)amino]pyrimidine-5-carboxylate **98d** (1 g, 3.07 mmol) was dissolved in 10 mL of tetrahydrofuran and 10 mL of water, and lithium hydroxide (0.15 g, 6.14 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated to remove tetrahydrofuran and the pH was adjusted to 5 with 6 N hydrochloric acid, and a solid was precipitated. The mixture was filtered, and the filter cake was washed twice with petroleum ether and collected to obtain the title compound 2-chloro-4-[(5-hydroxy-octahydropentalen-2-yl)amino]pyrimidine-5-carboxylic acid **98e** (white solid, 0.57 g, 62.36% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 13.77 (s, 1H), 8.59 (d, 1H), 8.56 (s, 1H), 4.55 (s, 1H), 4.29-4.22 (m, 1H), 4.12-4.10 (m, 1H), 2.41-2.37 (m, 2H), 2.28-2.22 (m, 2H), 1.89-1.83 (m, 2H), 1.53-1.42 (m, 4H).
LC-MS m/z(ESI) = **298.10** [M+1]

Step 5:
2-Chloro-9-(5-hydroxy-octahydropentalen-2-yl)-7,9-dihydro-8*H*-purin-8-one (**98f**)

2-Chloro-4-[(5-hydroxy-octahydropentalen-2-yl)amino]pyrimidine-5-carboxylic acid **98e** (0.57 g, 1.91 mmol) was dissolved in *N*,*N*-dimethylacetamide (20 mL), and diphenylphosphoryl azide (0.53 g, 1.91 mmol) and triethylamine (0.19 g, 1.91 mmol) were

added in an ice bath. The reaction mixture was stirred at room temperature for 1 h, heated to 90 °C and stirred for another 3 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was naturally cooled to room temperature, diluted with 40 mL of water and extracted with ethyl acetate. The organic phases were combined, dried and concentrated to obtain the title compound 2-chloro-9-(5-hydroxy-octahydropentalen-2-yl)-7,9-dihydro-8*H*-purin-8-one **98f** (yellow solid, 0.5 g, 54.65% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.11 (s, 1H), 4.67 (d, 1H), 4.58-4.49 (m, 1H), 4.05 (m, 1H), 2.40-2.24 (m, 4H), 2.06-2.01 (m, 4H), 1.39-1.33 (m, 2H).
LC-MS m/z(ESI) = **295.10** [M+1]

Step 6:
2-Chloro-9-(5-hydroxy-octahydropentalen-2-yl)-7-methyl-7,9-dihydro-8*H*-purin-8-one (**98g**)

2-Chloro-9-(5-hydroxy-octahydropentalen-2-yl)-7,9-dihydro-8*H*-purin-8-one **98f** (0.3 g, 1.02 mmol) was dissolved in dimethylformamide (10 mL), and cesium carbonate (0.66 g, 2.04 mmol) and dimethyl sulfate (0.13 g, 1.02 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion of the reaction, 20 mL of water was added, and a solid was precipitated. The solid was collected by filtration and dried to give the title compound 2-chloro-9-(5-hydroxy-octahydropentalen-2-yl)-7-methyl-7,9-dihydro-8*H*-purin-8-one **98g** (pale yellow solid, 0.14 g, 44.45% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.34 (s, 1H), 4.63 (d, 1H), 4.60-4.52 (m, 1H), 4.10-4.01 (m, 1H), 3.34 (s, 3H), 2.40-2.24 (m, 4H), 2.07-1.99 (m, 4H), 1.40-1.33 (m, 2H).
LC-MS m/z(ESI) = **309.10** [M+1]

Step 7:
4-[(9-(5-Hydroxy-octahydropentalen-2-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino]-3-methylbenzonitrile (**compound 98**)

4-Amino-3-methylbenzonitrile **5a** (50 mg, 0.38 mmol), 2-chloro-9-(5-hydroxy-octahydropentalen-2-yl)-7-methyl-7,9-dihydro-8*H*-purin-8-one **98g** (117 mg, 0.38 mmol), cesium carbonate (248 mg, 0.76 mmol) and methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (34.45 mg, 0.04 mmol) were dissolved in dioxane (5 mL), followed by nitrogen purging. The reaction mixture was stirred under nitrogen atmosphere at 100 °C for 4 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water, and the solid was collected and purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 100/1) to obtain the title compound 4-[(9-(5-hydroxy-octahydropentalen-2-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino]-3-methylbenzonitrile **compound 98** (white solid, 60 mg, 38.12% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.50 (s, 1H), 8.27 (d, 1H), 8.20 (s, 1H), 7.73 (dd, 1H),7.62 (d, 1H), 4.82 (d, 1H), 4.63-4.55 (m, 1H), 4.13-4.04 (m, 1H), 3.34 (s, 3H), 2.33-2.29 (m, 7H), 2.09-2.02 (m, 4H), 1.34-1.30 (m, 2H).
LC-MS m/z(ESI) = **405.20** [M+1]

Example 99
2-Fluoro-4-((9-((3a*S*,6a*S*)-hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-8-oxo-

Dimethyl 4-(benzylamino)cyclopentane-1,2-dicarboxylate **99b** (2.0 g, 6.86 mmol) was dissolved in tetrahydrofuran (40 mL), and lithium aluminum hydride (0.63 g, 17.15 mmol) was added in batches at 0 °C. The reaction was monitored by TLC. After completion of the reaction, the lithium aluminum hydride was quenched with 10% aqueous sodium hydroxide, and the reaction mixture was filtered. The filtrate was directly concentrated to obtain the title compound (4-(benzylamino)cyclopentane-1,2-diyl)dimethanol **99c** (white solid, 1.1 g, 68.32% yield).
LC-MS m/z(ESI) = **236.20** [M+1]

Step 3:
tert-Butyl benzyl(3,4-bis(hydroxymethyl)cyclopentyl)carbamate (**99d**)

(4-(Benzylamino)cyclopentane-1,2-diyl)dimethanol **99c** (8 g, 34.0 mmol) was dissolved in methanol (50 mL), and triethylamine (3.64 g, 35.97 mmol) was added, followed by the addition of di-*tert*-butyl dicarbonate (8.16 g, 37.40 mmol). The reaction mixture was stirred for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 50:1) to obtain the title compound *tert*-butyl benzyl(3,4-bis(hydroxymethyl)cyclopentyl)carbamate **99d** (white solid, 7.18 g, 63% yield).
^{1}H NMR (400 MHz, Chloroform-d) δ 7.32-7.16 (m, 5H), 4.37 (s, 2H), 3.72-3.61 (m,1H), 3.38-3.32 (m, 2H), 1.90-1.75 (m, 4H), 1.47-1.44 (m, 3H), 1.38 (s, 9H).
LC-MS m/z(ESI) = **236.10** [M+1]

Step 4:
tert-Butyl benzyl (hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)carbamate (**99e**)

tert-Butyl benzyl (3,4-bis(hydroxymethyl)cyclopentyl)carbamate **99d** (8 g, 23.85 mmol) was dissolved in tetrahydrofuran (100 mL), and *n*-butyllithium (10.7 mL, 26.75 mmol, 2.5 mol/L) was added dropwise at -20 °C under nitrogen atmosphere. The reaction mixture was stirred for 1 h, and a solution of *p*-toluenesulfonyl chloride (5 g, 26.23 mmol) in tetrahydrofuran (10 mL) was added dropwise. The reaction mixture was stirred for 0.5 h, and *n*-butyllithium (10.7 mL, 26.75 mmol, 2.5 mol/L) was added dropwise again. The reaction mixture was stirred for 10 min and heated at reflux for 48 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with ice water and extracted three times with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate (v/v) = 5:1) to obtain the title compound *tert*-butyl benzyl(hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)carbamate **99e** (white solid, 4.0 g, 52.84% yield).
^{1}H NMR (400 MHz, CDCl3) δ 7.32-7.17 (m, 5H), 4.37 (s, 2H), 3.73-3.63 (m, 2H), 3.40-3.34 (m, 2H), 2.06-1.25 (m, 16H).
LC-MS m/z(ESI) = **262.10** [M+1]

Step 5:
N-Benzylhexahydro-1*H*-cyclopenta[*c*]furan-5-amine (**99f**)

mL of water, and lithium hydroxide (104.38 mg, 4.36 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated by rotary evaporation under reduced pressure to remove tetrahydrofuran and the pH was adjusted to about 4, and a white solid was precipitated. The mixture was filtered, and the filter cake was washed twice with petroleum ether/ethyl acetate (v/v = 10/1) and concentrated to obtain the title compound 2-chloro-4-((hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)amino)pyrimidine-5-carboxylic acid **99i** (white solid, 520 mg, 67.26% yield).
LC-MS m/z(ESI) = **284.10** [M+1]

Step 9:
2-Chloro-9-(hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7,9-dihydro-8*H*-purin-8-one (**99j**)

2-Chloro-4-((hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)amino)pyrimidine-5-carboxylic acid **99i** (0.5 g, 1.76 mmol) was dissolved in *N*,*N*-dimethylacetamide (20 mL), and diphenylphosphoryl azide (0.48 g, 1.76 mmol) and triethylamine (0.18 g, 1.76 mmol) were added in an ice bath. The reaction mixture was stirred at room temperature for 1 h, then heatedto 90 °C and stirred for another 3 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was naturally cooled to room temperature, and 40 mL water was added and the organics were extracted with ethyl acetate. The organic phases were combined, dried and concentrated to yield the title compound 2-chloro-9-(hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7,9-dihydro-8*H*-purin-8-one **99j** (yellow solid, 0.45 g, 54.65% yield).
LC-MS m/z(ESI) = **281.00** [M+1]

Step 10:
2-Chloro-9-(hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-7,9-dihydro-8*H*-purin-8-one (**99k**)

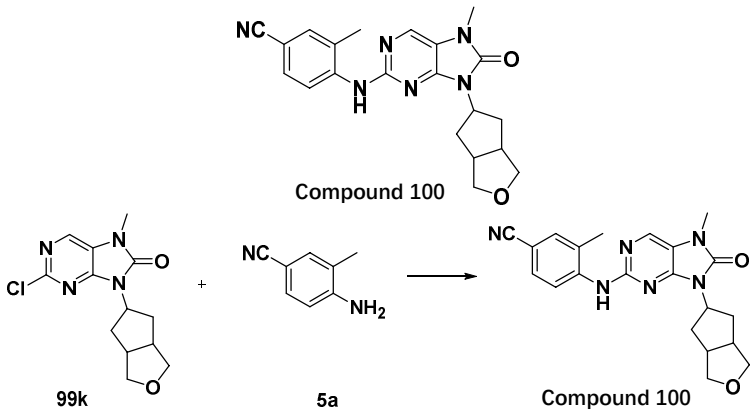
2-Chloro-9-(hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7,9-dihydro-8*H*-purin-8-one **99j** (0.45 g, 0.96 mmol) was dissolved in dimethylformamide (10 mL), and cesium carbonate (0.47 g, 1.44 mmol) and dimethyl sulfate (0.11 mL, 1.15 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC. After completion of the reaction, then 20 mL of water was added, and a solid was precipitated. The solid was collected by filtration and dried to yield the title compound 2-chloro-9-(hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-7,9-dihydro-8*H*-purin-8-one **99k** (pale yellow solid, 0.14 g, 49.48% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 5.49-5.21 (m, 1H), 3.82-3.77 (m, 2H), 3.37 (s, 3H), 3.35-3.27 (m, 2H), 3.23-3.18 (m, 2H), 2.96-2.84 (m, 1H), 2.15-2.03 (m, 2H), 1.94-1.85 (m, 2H).
LC-MS m/z(ESI) = **295.10** [M+1]

Step 11:
2-Fluoro-4-((9-((3a*S*,6a*S*)-hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (**compound 99**)

2-Chloro-9-((3a*S*,6a*S*)-hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-7,9-dihydro-8*H*-purin-8-one **99k** (100 mg, 0.34 mmol), 4-amino-2-fluoro-5-methylbenzamide **intermediate 2** (114 mg, 0.68 mmol), cesium carbonate (221 mg, 0.68 mmol) and

methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (30 mg, 0.03 mmol) were dissolved in 1,4-dioxane (10 mL), followed by nitrogen purging. The reaction mixture was stirred under nitrogen atmosphere at 110 °C for 4 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 10/1) to obtain the title compound 2-fluoro-4-((9-((3a*S*,6a*S*)-hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide **compound 99** (white solid, 8 mg, 6% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.18 (s, 1H), 7.64 (d, 1H), 7.54 (d, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 3.74 (t, 1H), 3.68 (t, 1H), 3.32 (s, 3H), 3.22-3.13 (m, 3H), 2.81-2.71 (m, 1H), 2.25 (s, 3H), 2.03-1.99 (m, 2H), 1.92-1.84 (m, 3H).
LC-MS m/z(ESI) = 427.2 [M+1]

Example 100
4-((9-(Hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-3-methylbenzonitrile (**compound 100**)



4-Amino-3-methylbenzonitrile **5a** (50 mg, 0.38 mmol), 2-chloro-9-(hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-7,9-dihydro-8*H*-purin-8-one **99k** (112 mg, 0.38 mmol), cesium carbonate (247.62 mg, 0.76 mmol) and methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (34.45 mg, 0.04 mmol) were dissolved in dioxane (10 mL), followed by nitrogen purging. The reaction mixture was stirred under nitrogen atmosphere at 100 °C for 4 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water, and the solid was collected and purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 100/1) to obtain the title compound 4-((9-(hexahydro-1*H*-cyclopenta[*c*]furan-5-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-3-methylbenzonitrile **compound 100** (pale yellow solid, 45 mg, 30.09% yield).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, 1H), 7.93 (s, 1H), 7.53 (dd, 1H), 7.48 (d, 1H), 7.05 (s, 1H), 5.47-5.40 (m, 1H), 3.96 (q, 2H), 3.48 (dd, 1H), 3.43 (s, 3H), 3.37 (dd, 1H), 5.38-5.31 (m, 1H), 2.38 (s, 3H), 2.92- 2.21 (m, 5H).
LC-MS m/z(ESI) = **391.20** [M+1]

Example 101
4-((9-(1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-3-methylbenzonitrile (**compound 101**)

the reaction, water was added to the reaction mixture, and a solid was precipitated. The mixture was filtered, and the filter cake was eluted with water and petroleum ether and concentrated under reduced pressure to give the title compound 9-(3-fluorotetrahydro-2*H*-pyran-4-yl)-2-(methylthio)-7,9-dihydro-8*H*-purin-8-one **104f** (white solid, 1.27 g, 73.89% yield).
LC-MS m/z(ESI) = 285.10 [M+1]

Step 6:
9-(3-Fluorotetrahydro-2*H*-pyran-4-yl)-7-methyl-2-(methylthio)-7,9-dihydro-8*H*-purin-8-one (**104g**)

9-(3-fluorotetrahydro-2*H*-pyran-4-yl)-2-(methylthio)-7,9-dihydro-8*H*-purin-8-one **104f** (1.27 g, 4.45 mmol) was dissolved in dimethylformamide (10 mL), and dimethyl sulfate (433 μL, 4.45 mmol) and cesium carbonate (1.84 g, 13.35 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h. The reaction was monitored by TLC. After completion of the reaction, then water was added and the organics were extracted with ethyl acetate, and the organic layer was concentrated to obtain the title compound 9-(3-fluorotetrahydro-2*H*-pyran-4-yl)-7-methyl-2-(methylthio)-7,9-dihydro-8*H*-purin-8-one **104g** (white solid, 800 mg, 60.27% yield).
LC-MS m/z(ESI) = 299.10 [M+1]

Step 7:
9-(3-Fluorotetrahydro-2*H*-pyran-4-yl)-7-methyl-2-(methylsulfonyl)-7,9-dihydro-8*H*-purin-8-one (**104h**)

9-(3-Fluorotetrahydro-2*H*-pyran-4-yl)-7-methyl-2-(methylthio)-7,9-dihydro-8*H*-purin-8-one **104g** (800 mg, 2.68 mmol) was dissolved in dichloromethane (6 mL), and *m*-chloroperoxybenzoic acid (1.85 g, 10.73 mmol) was added with stirring at room temperature. The reaction mixture was stirred for 1 h. The reaction was monitored by TLC. After completion of the reaction, The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 100:1 to 60:1) to obtain the title compound 9-(3-fluorotetrahydro-2*H*-pyran-4-yl)-7-methyl-2-(methylsulfonyl)-7,9-dihydro-8*H*-purin-8-one **104h** (white solid, 1.05 g, 119% yield).
LC-MS m/z(ESI) = 331.10 [M+1]

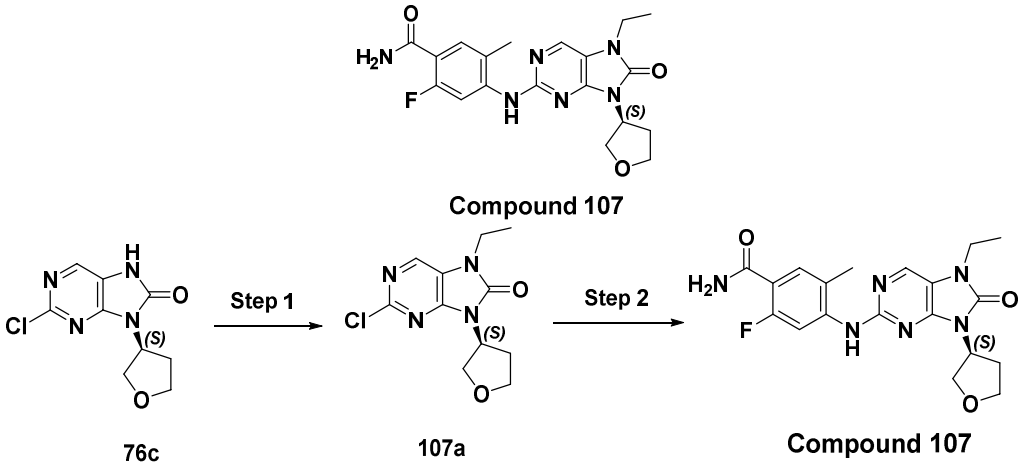
Step 8:
2-Fluoro-4-((9-(3-fluorotetrahydro-2*H*-pyran-4-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (**compound 104**)

9-(3-Fluorotetrahydro-2*H*-pyran-4-yl)-7-methyl-2-(methylsulfonyl)-7,9-dihydro-8*H*-purin-8-one **104h** (300 mg, 0.91 mmol), 4-amino-3-methylbenzamide intermediate 2 (458 mg, 2.72 mmol) and potassium *tert*-butoxide (305 mg, 2.72 mmol) were dissolved in dimethylformamide (10 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC. After completion of the reaction, water was added and the organics were extracted with ethyl acetate. The organic layer was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/ethyl acetate (v/v) = 5:1 to 1:1) to get the title compound 2-fluoro-4-((9-(3-fluorotetrahydro-2*H*-pyran-4-yl)-7-methyl-8-oxo-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide compound **104-1** (pale yellow solid, 130 mg, 34.21%

Step 3:
4-((7-(2,2-Difluoroethyl)-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide

7-(2,2-Difluoroethyl)-2-(methylsulfinyl)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **106b** (200 mg, 0.58 mmol), 4-amino-3-methylbenzamide intermediate 2 (388 mg, 2.31 mmol) and cesium carbonate (564 mg, 1.73 mmol) were dissolved in dimethylformamide (5 mL). The reaction mixture was heated to 80 °C and stirred for 3 h. The reaction was monitored by TLC. After completion of the reaction, water was added and the organics were extracted with dichloromethane. The organic layer was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 30:1), followed by recrystallization to obtain the title compound 4-((7-(2,2-difluoroethyl)-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide **compound 106** (white solid, 65 mg, 24.99% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.64 (s, 1H), 8.21 (s, 1H), 7.84 (d, 1H), 7.54 (d, 1H), 7.47 (s, 1H), 7.41 (s, 1H), 6.54-6.22 (m, 1H), 4.51-4.41 (m, 1H), 4.37-4.25 (m, 2H), 3.98 (dd, 2H), 3.46-3.38 (m, 2H), 2.58-2.50 (m, 2H), 2.29 (s, 3H), 1.75-1.67 (m, 2H).
LC-MS m/z(ESI) = 451.20 [M+1]

Example 107
(*S*)-4-((7-Ethyl-8-oxo-9-(tetrahydrofuran-3-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide (**compound 107**)



Step 1:
(*S*)-2-Chloro-7-ethyl-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one (**107a**)

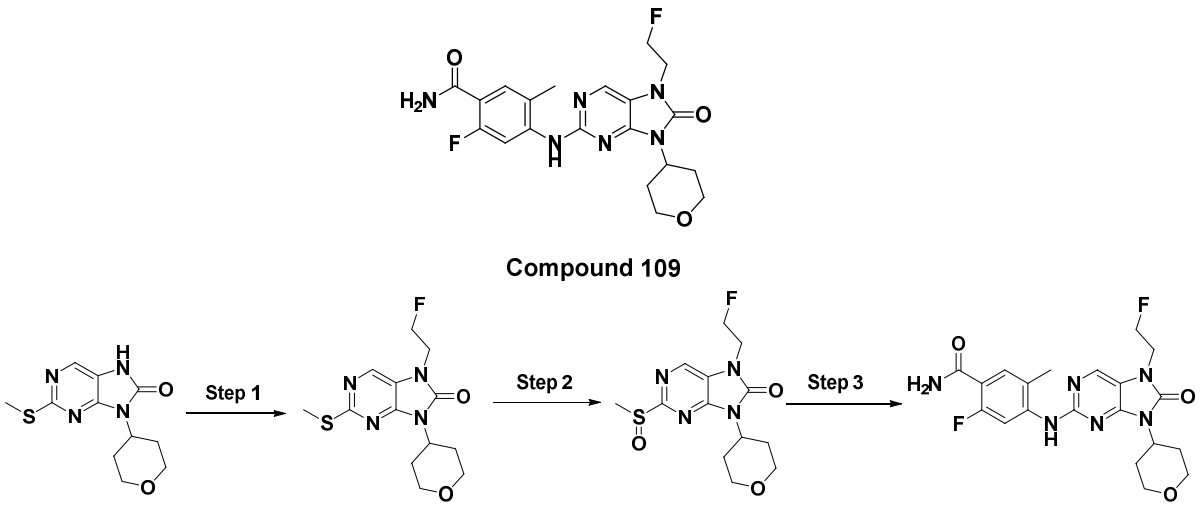
(*S*)-2-Chloro-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one **76c** (2 g, 8.31 mmol) was dissolved in dimethylformamide (20 mL), and cesium carbonate (2.71 g, 8.31 mmol) and iodoethane (1.56 g, 9.97 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h. The reaction was monitored by TLC. After completion of the reaction, then the reaction mixture was poured into 60 mL of water, and a large amounts of solid was precipitated The solid was collected by filtration and dried to give the title compound (*S*)-2-chloro-7-ethyl-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one **107a** (white solid, 1.1 g, 49.26% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.43 (s, 1H), 5.04-4.97 (m, 1H), 4.15-4.06 (m, 1H), 3.98 (t, 1H), 3.91-3.84 (m, 4H), 2.44-2.37 (m, 1H), 2.30-2.19 (m, 1H), 1.26 (s, 3H).

8*H*-purin-8-one 108a (white solid, 1.08 g, 69.09% yield).
LC-MS m/z(ESI) = 269.10 [M+1]

Step 2:
(*R*)-4-((7-Ethyl-8-oxo-9-(tetrahydrofuran-3-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-2-fluoro-5-methylbenzamide (**compound 108**)

(*R*)-2-Chloro-7-ethyl-9-(tetrahydrofuran-3-yl)-7,9-dihydro-8*H*-purin-8-one **108a** (300 mg, 1.12 mmol), 4-amino-2-fluoro-5-methylbenzamide intermediate 2 (939 mg, 5.58 mmol), cesium carbonate (1.09 g, 3.35 mmol) and methanesulfonato(2-dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (202 mg, 0.22 mmol) were dissolved in 1,4-dioxane (10 mL), followed by nitrogen purging. The reaction mixture was stirred under nitrogen atmosphere at 110 °C for 4 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 20/1) followed by Pre-HPLC to obtain the title compound (*R*)-2-fluoro-5-methyl-4-((7-methyl-8-oxo-9-(tetrahydrofuran-3-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzamide **compound 108** (white solid, 100 mg, 22.37% yield).
^{1}H NMR (400 MHz, DMSO-d6) δ 8.53 (s, 1H), 8.28 (s, 1H), 7.87 (d, 1H), 7.55 (d, 1H), 7.47 (s, 1H), 7.41 (s, 1H), 5.03-4.97 (m, 1H), 4.11-4.05 (m, 1H), 3.96 (t, 3H), 3.94-3.85 (m, 4H), 2.77-2.70 (m, 1H), 2.36-2.23 (m, 1H), 2.28 (s, 3H), 1.26 (t, 3H).
LC-MS m/z(ESI) = 401.20 [M+1]

Example 109
2-Fluoro-4-((7-(2-fluoroethyl)-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (compound 109)



Step 1:
7-(2-Fluoroethyl)-2-(methylthio)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one (**109a**)

2-(Methylthio)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **105d** (1.0 g, 3.75 mmol), 1-fluoro-2-iodoethane (0.71 g, 4.1 mmol) and potassium carbonate (1.5 g, 11.2 mmol) were added to a dry reaction flask, followed by the addition of DMF (10

mL). The reaction mixture was stirred at room temperature for 2.5 h. The reaction was monitored by TLC. After completion of the reaction, water was added and the organics were extracted with dichloromethane, and the organic phases were combined, dried and concentrated to yield the title compound 7-(2-fluoroethyl)-2-(methylthio)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **109a** (white solid, 1.0 g, 85.47% yield).
LC-MS m/z (ESI) = 313.10 [M+1]

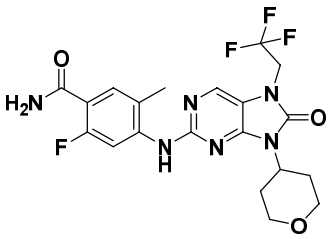
Step 2:
7-(2-Fluoroethyl)-2-(methylsulfinyl)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one (**109b**)

7-(2-Fluoroethyl)-2-(methylthio)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **109a** (0.9 g, 2.88 mmol) was added to a dry reaction flask and dissolved in DCM (10 mL), and *m*-chloroperoxybenzoic acid (0.5 g, 3.17 mmol) was added in three batches at room temperature. After addition, the reaction mixture was stirred for 3 h. The reaction was monitored by TLC. After completion of the reaction, water was added and the organics were extracted with dichloromethane, and the organic phases were combined, dried and concentrated to yield the title compound 7-(2-fluoroethyl)-2-(methylsulfinyl)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **109b** (white solid, 0.8 g, 85.11% yield).
LC-MS m/z (ESI) = 329.10 [M+1]

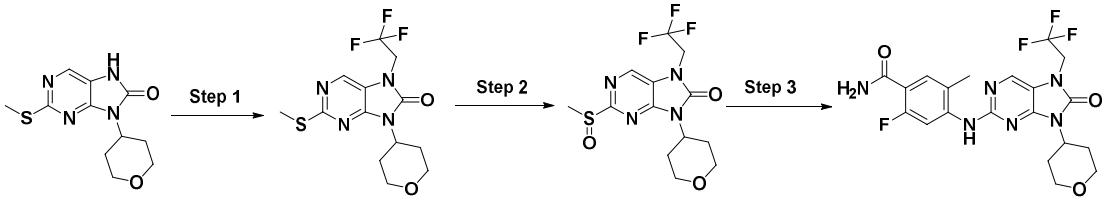
Step 3:
2-Fluoro-4-((7-(2-fluoroethyl)-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide (**compound 109**)

7-(2-Fluoroethyl)-2-(methylsulfinyl)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **109b** (200 mg, 0.61 mmol), 4-amino-2-fluoro-5-methylbenzamide intermediate 2 (410 mg, 2.44 mmol) and cesium carbonate (590 mg, 1.83 mmol) were added to a dry reaction tube, followed by the addition of DMF (3 mL). The reaction mixture was stirred at 80 °C for 2.5 h. Water was added and the organics were extracted with dichloromethane, and the organic phases were combined, dried and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20:1) to obtain the title compound 2-fluoro-4-((7-(2-fluoroethyl)-8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-8,9-dihydro-7*H*-purin-2-yl)amino)-5-methylbenzamide **compound 109** (white solid, 21 mg, 7.98% yield).
^{1}H NMR (600 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.21 (s, 1H), 7.87 (d, 1H), 7.55 (d, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 4.75-4.66 (m, 2H), 4.48-4.43 (m, 1H), 4.19-4.13 (m, 2H), 4.00-3.97 (m, 2H), 3.43 (t, 2H), 2.59-2.53 (m, 2H), 2.29 (s, 3H), 1.74-1.68 (m, 2H).
LC-MS m/z (ESI) = 433.20 [M+1]

Example 110
2-Fluoro-5-methyl-4-((8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-7-(2,2,2-trifluoroethyl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzamide (**compound 110**)



Compound 110



105d 110a 110b Compound 110

Step 1:
2-(Methylthio)-9-(tetrahydro-2*H*-pyran-4-yl)-7-(2,2,2-trifluoroethyl)-7,9-dihydro-8*H*-purin-8-one (**110a**)

2-(Methylthio)-9-(tetrahydro-2*H*-pyran-4-yl)-7,9-dihydro-8*H*-purin-8-one **105d** (1.0 g, 3.75 mmol), 2-iodo-1,1,1-trifluoroethane (444 mg, 4.5 mmol) and cesium carbonate (3.67 g, 11.26 mmol) were added to a dry reaction flask, followed by the addition of DMF (10 mL). The reaction mixture was stirred at room temperature for 2.5 h. The reaction was monitored by TLC. After completion of the reaction, water was added and the organics were extracted with ethyl acetate, and the organic phases were combined, dried and concentrated to give the title compound 2-(methylthio)-9-(tetrahydro-2*H*-pyran-4-yl)-7-(2,2,2-trifluoroethyl)-7,9-dihydro-8*H*-purin-8-one **110a** (pale yellow solid, 1.18 g, 90.22% yield).
^{1}H NMR (600 MHz, DMSO-d6) δ 8.43 (s, 1H), 4.83 (q, 2H), 4.52-4.43 (m, 1H), 3.98 (dd, 2H), 3.51-3.42 (m, 2H), 2.53 (s, 3H), 2.50-2.44 (m, 2H), 1.76-1.68 (m, 2H).
LC-MS m/z (ESI) = 349.10 [M+1]

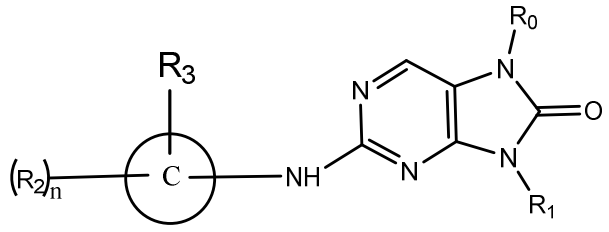
Step 2:
2-(Methylsulfinyl)-9-(tetrahydro-2*H*-pyran-4-yl)-7-(2,2,2-trifluoroethyl)-7,9-dihydro-8*H*-purin-8-one (**110b**)

2-(methylthio)-9-(tetrahydro-2*H*-pyran-4-yl)-7-(2,2,2-trifluoroethyl)-7,9-dihydro-8*H*-purin-8-one **110a** (1.17 g, 3.36 mmol) was added to a dry reaction flask and dissolved in DCM (10 mL), and *m*-chloroperoxybenzoic acid (754 mg, 4.37 mmol) was added at room temperature. The reaction mixture was stirred for 1.5 h. The reaction was monitored by TLC. After completion of the reaction, saturated sodium bicarbonate and dichloromethane were added to the reaction mixture for extraction, and the organic phases were combined, dried and concentrated to obtain the title compound 2-(methylsulfinyl)-9-(tetrahydro-2*H*-pyran-4-yl)-7-(2,2,2-trifluoroethyl)-7,9-dihydro-8*H*-purin-8-one **110b** (white solid, 1 g, 81.72% yield).
LC-MS m/z (ESI) = 365.10 [M+1]

Step 3:
2-Fluoro-5-methyl-4-((8-oxo-9-(tetrahydro-2*H*-pyran-4-yl)-7-(2,2,2-trifluoroethyl)-8,9-dihydro-7*H*-purin-2-yl)amino)benzamide (**compound 110**)

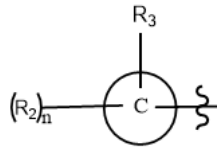
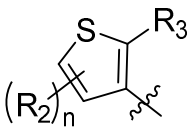
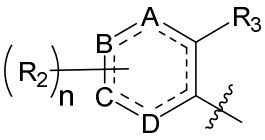
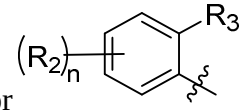
Claims

1. A compound of general formula (I), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt, or co-crystal thereof,

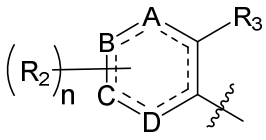


(I)

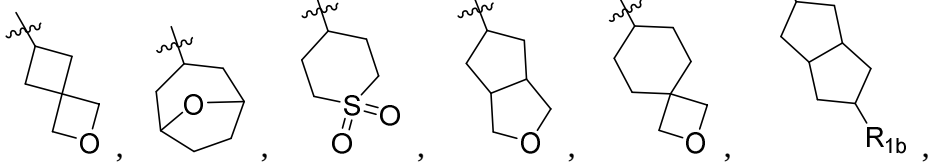
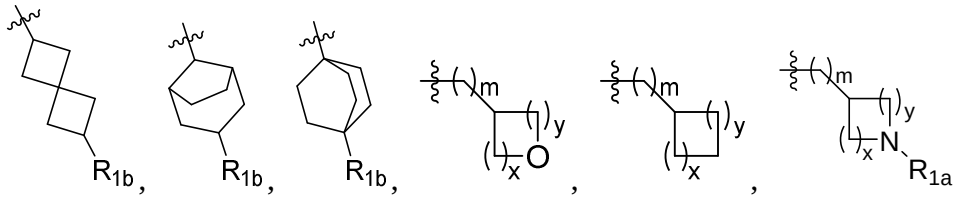
wherein

 is  ,  or  ;

 is a single bond or a double bond;

A, B, C, and D in the  are each independently C or N, and at least one of A, B, C, and D is N;

R_0 is H, C_{1-6} alkyl, or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium (D);

R_1 is  ,  or pyridyl, and R_1 is optionally further substituted with one or two substituents selected from D, halogen, cyano, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy;

R_{1a} is H or C_{1-6} alkyl;

R_{1b} is H, OH, cyano, or hydroxyl-substituted C_{1-6} alkyl;

R_2 is H, cyano, =O, carboxyl, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, C_{1-6} alkyl, halogen, $-S(=O)_2R_{2a}$ or a $-C(=O)OC_{1-6}$ alkyl; wherein the C_{1-6} alkyl, $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl or 3- to 5 -membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

alternatively, R_{2a} and R_{2b} together with the atom to which they are attached form a 5- to 6-membered heterocyclyl group containing 1, 2 or 3 heteroatoms selected from N, O and S, wherein the 5- to 6-membered heterocyclyl group is optionally further substituted with one or more substituents selected from C_{1-6} alkyl, OH, and halogen;

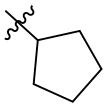
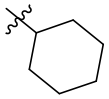
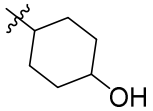
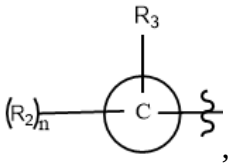
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

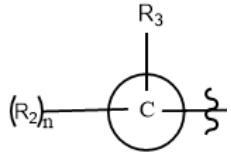
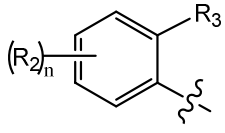
m is 0 or 1;

n is 0, 1, or 2; and

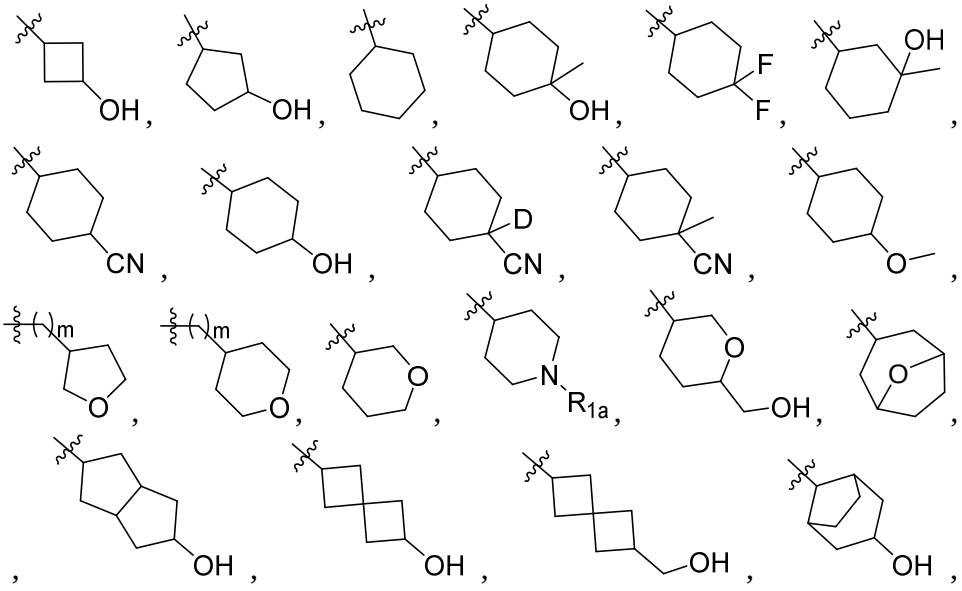
x and y are each independently 1, 2, or 3;

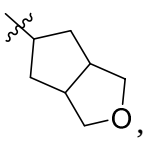
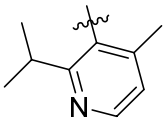
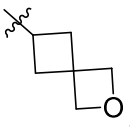
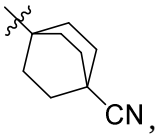
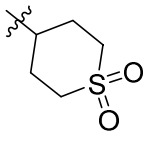
provided that

R_1 is not  ,  , or  when  , R_0, R_2, and R_3 all satisfy the following condition:

 is  , n is 1, R_0 is H or methyl, R_2 is methoxy or -$S(=O)_2Me$, and R_3 is methyl.

2. The compound according to claim 1, or a stereoisomer, solvate, metabolite, prodrug, pharmaceutically acceptable salt, or co-crystal thereof, wherein

R_1 is 

 ,  ,  ,  , or  ;

R_{1a} is H or C_{1-6} alkyl;

R_2 is H, cyano, -C(=O)$NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, -S(=O)$_2R_{2a}$ or -C(=O)OC_{1-6} alkyl; wherein the -C(=O)OC_{1-6} alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, and halogen;

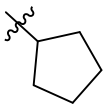
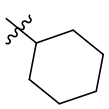
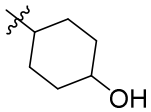
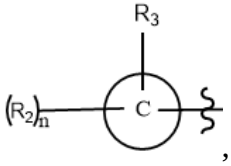
alternatively, R_{2a} and R_{2b} together with the atom to which they are attached form a 5- to 6-membered heterocyclyl group containing 1 to 3 heteroatoms selected from N, O and S, wherein the heterocyclyl group is optionally further substituted with one or more substituents selected from OH and halogen;

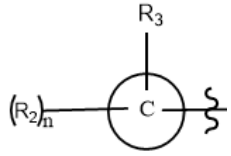
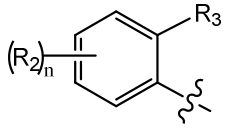
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

m is 0 or 1; and

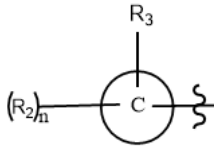
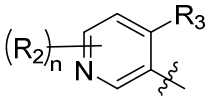
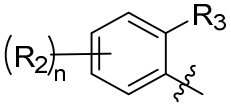
n is 0, 1, or 2;

provided that

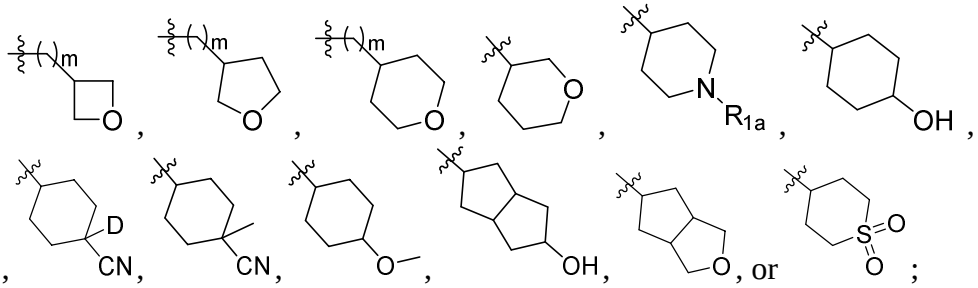
R_1 is not  ,  , or  when  , R_0, R_2, and R_3 all satisfy the following condition:

 is  , n is 1, R_0 is H or methyl, R_2 is methoxy or -S(=O)$_2$Me, and R_3 is methyl.

3. The compound according to claim 1, or a stereoisomer, solvate, metabolite, prodrug, pharmaceutically acceptable salt, or co-crystal thereof, wherein

 is  or  ;

R_0 is H, C_{1-4} alkyl, or cyclopropyl, wherein the C_{1-4} alkyl is optionally further substituted with one or more substituents selected from halogen and D;

$R_1$is  ;

R_{1a} is H, a C_{1-6} alkyl or a –C(=O)C_{1-6} alkyl;

R_2 is H, cyano, -C(=O)N$R_{2a}R_{2b}$, a C_{1-6} alkoxy, halogen, -S(=O)$_2R_{2a}$ or a -C(=O)OC_{1-6} alkyl; wherein the -C(=O)OC_{1-6} alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, and halogen;

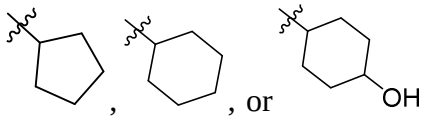
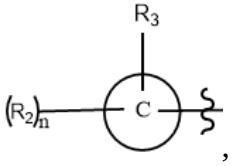
alternatively, R_{2a} and R_{2b} together with the atom to which they are attached form 5- to 6-membered heterocyclyl group containing 1 to 3 heteroatoms selected from N, O and S, wherein the 5- to 6-membered heterocyclyl group is optionally further substituted with one or more substituents selected from OH and halogen;

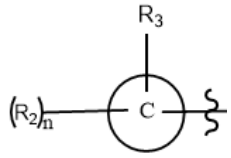
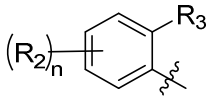
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

m is 0 or 1; and

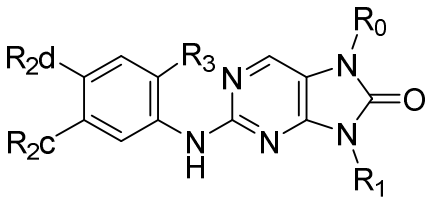
n is 0, 1, or 2;

provided that

R_1 is not  , when  , R_0, R_2, and R_3 all satisfy the following condition:

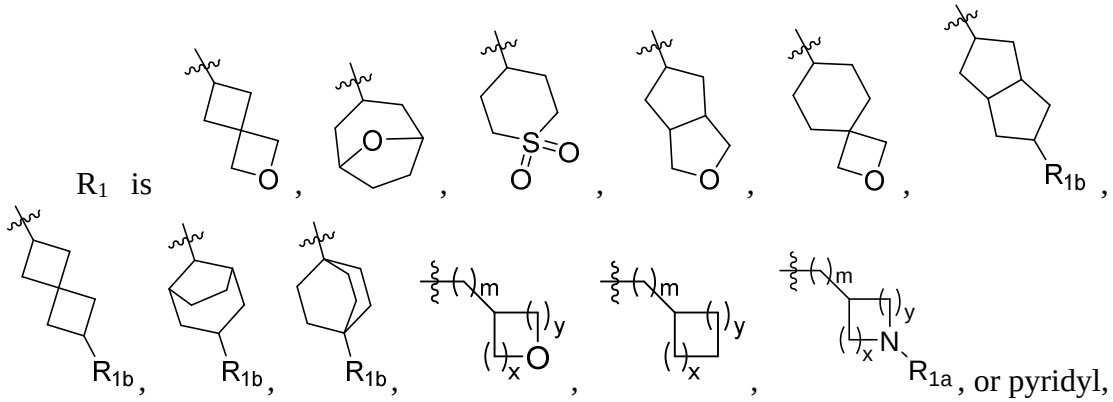
 is  , n is 1, R_0 is H or methyl, R_2 is methoxy or -S(=O)$_2$Me, and R_3 is methyl.

4. The compound according to claim 1, or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt, or co-crystal thereof, wherein the compound is a compound of general formula (II):

 (II)

wherein

R_0 is H, C_{1-6} alkyl, or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is  , or pyridyl, and R_1 is optionally further substituted with one or two substituents selected from D, halogen, cyano, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy;

R_{1a} is H or C_{1-6} alkyl;

R_{1b} is H, OH, cyano, or hydroxyl-substituted C_{1-6} alkyl;

R_{2c} is H, cyano, halogen, or C_{1-6} alkoxy;

R_{2d} is H, cyano, carboxyl, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkyl, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl; wherein the C_{1-6} alkyl or $-C(=O)OC_{1-6}$ alkyl is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

alternatively, R_{2a} and R_{2b} together with the atom to which they are attached form 5- to 6-membered heterocyclyl group containing 1 to 3 heteroatoms selected from N, O and S, wherein the 5- to 6-membered heterocyclyl group is optionally further substituted with one or more substituents selected from C_{1-6} alkyl, OH, and halogen;

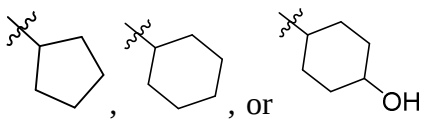
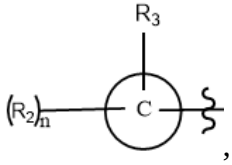
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

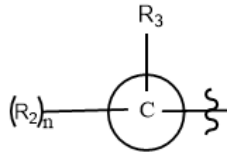
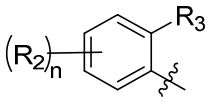
m is 0 or 1;

n is 0, 1, or 2; and

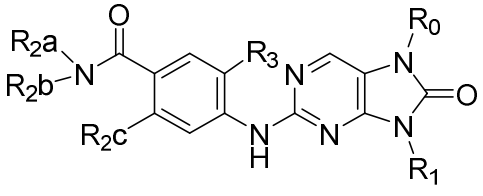
x and y are each independently 1, 2, or 3;

provided that

R_1 is not  , when  , R_0, R_2, and R_3 all satisfy the following condition:

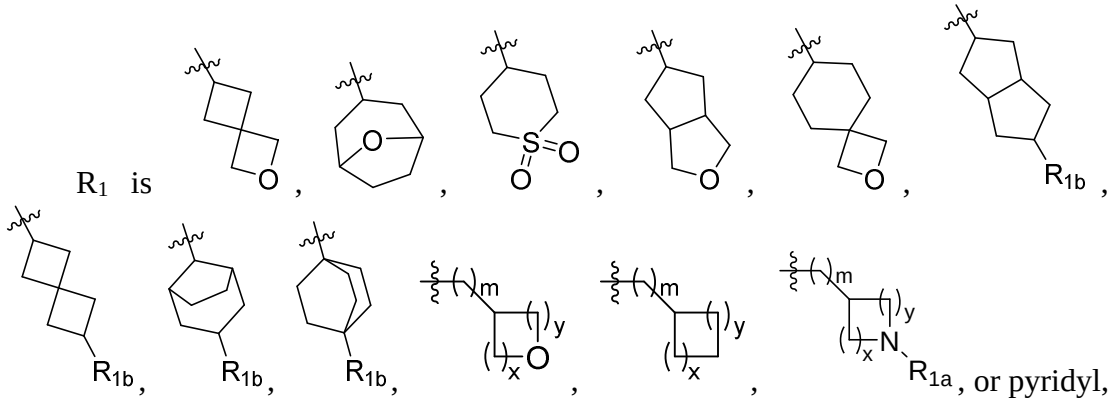
 is selected from  , n is 1, R_0 is H or methyl, R_2 is methoxy or -S(=O)$_2$Me, and R_3 is methyl.

5. The compound according to claim 4, or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt, or co-crystal thereof, wherein the compound is a compound of general formula (III):

 (III)

wherein

R_0 is H, C_{1-6} alkyl, or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is  , or pyridyl, and R_1 is optionally further substituted with one or two substituents selected from D, halogen, cyano, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy;

R_{1b} is H, OH, cyano, or hydroxyl-substituted C_{1-6} alkyl;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from D and halogen;

alternatively, R_{2a} and R_{2b} together with the atom to which they are attached form 5- to 6-membered heterocyclyl group containing 1 to 3 heteroatoms selected from N, O and S, wherein the 5- to 6-membered heterocyclyl group is optionally further substituted with one or more substituents selected from C_{1-6} alkyl, OH, and halogen;

R_{2c} is H, cyano, halogen, or C_{1-6} alkoxy, wherein the C_{1-6} alkoxy is optionally substituted with one or more D;

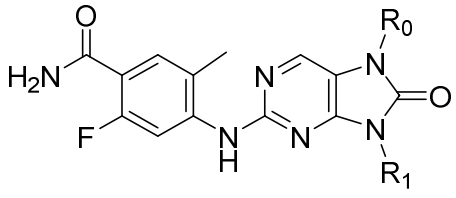
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

m is 0 or 1;

n is 0, 1, or 2; and

x and y are each independently 1, 2, or 3.

6. A compound of general formula (IV), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt, or co-crystal thereof,



(IV)

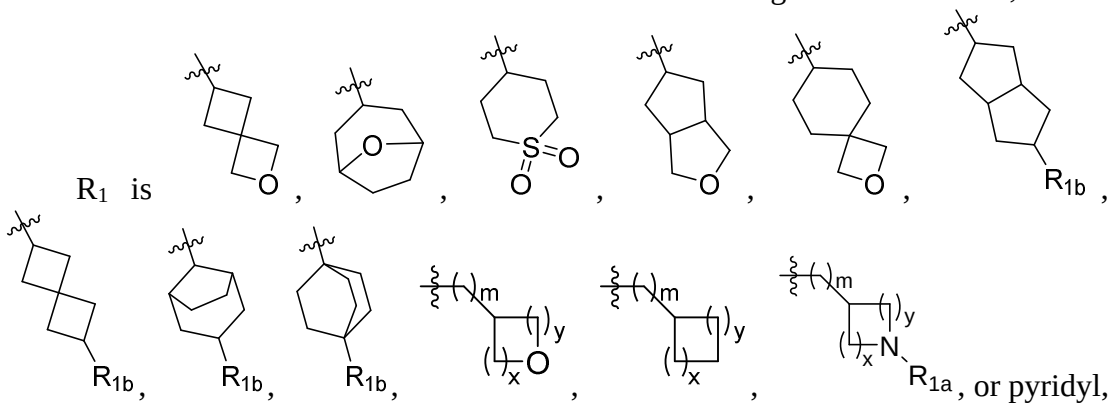
wherein

R_0 is H, C_{1-6} alkyl, or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium; and

R_1 is -$(CH)_m$- 4 to 7-membered carbocyclyl, -$(CH)_m$- 4 to 7-membered heterocyclyl, -$(CH)_m$- 8 to 12-membered bridged ring, or -$(CH)_m$- 7 to 12 membered spiro, wherein the -$(CH)_m$- 4 to 7-membered carbocyclyl, -$(CH)_m$- 4 to 7-membered heterocyclyl, -$(CH)_m$- 8 to 12-membered bridged ring, or -$(CH)_m$- 7 to 12 membered spiro is optionally further substituted with one or more substituents selected from hydroxy, cyano, halogen, =O, C_{1-6} alkyl, C_{1-6} alkoxy, and hydroxyl-substituted C_{1-6} alkyl.

7. The compound according to claim 6, or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt, or co-crystal thereof, wherein

R_0 is H, C_{1-6} alkyl, or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is  , or pyridyl,

and R_1 is optionally further substituted with one or two substituents selected from D, halogen, cyano, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy;

R_{1a} is H or C_{1-6} alkyl;

R_{1b} is H, OH, cyano, or hydroxyl-substituted C_{1-6} alkyl;

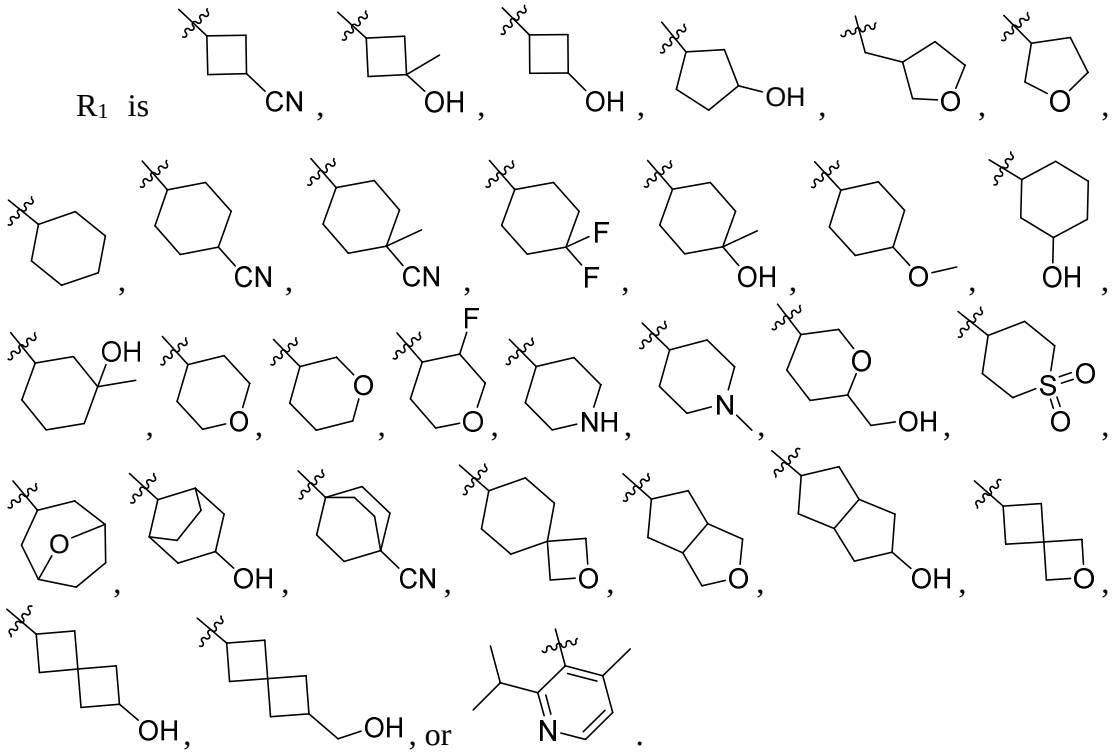
m is 0 or 1; and

x and y are each independently 1, 2, or 3.

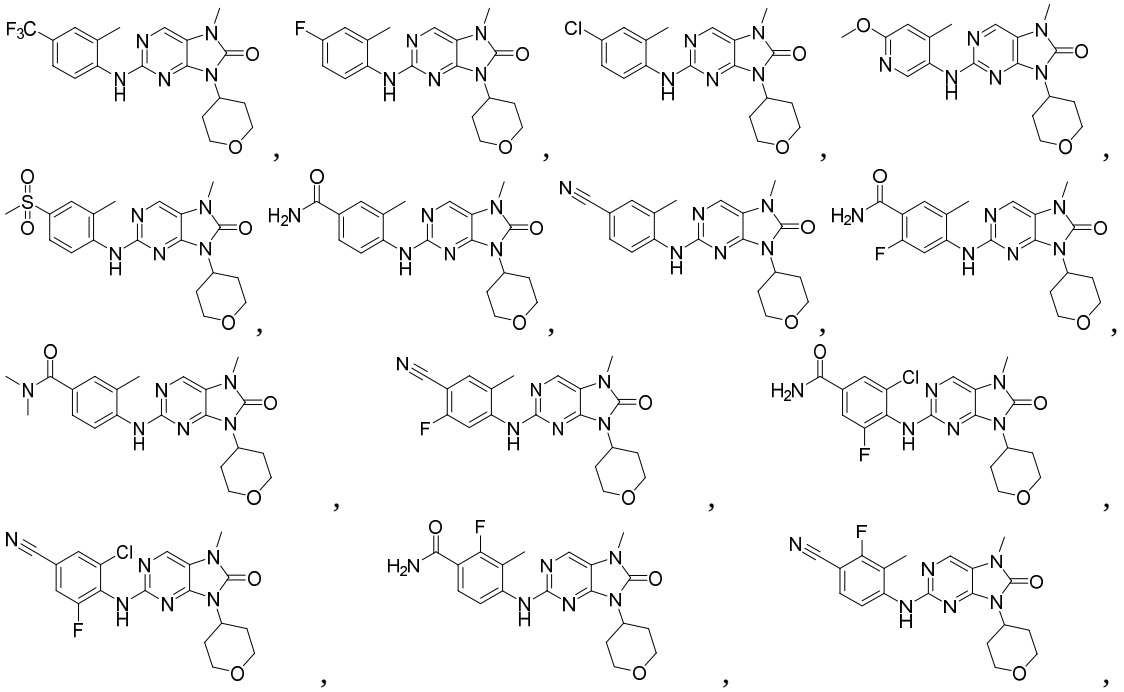
8. The compound according to claim 7, or a stereoisomer, solvate, prodrug, metabolite,

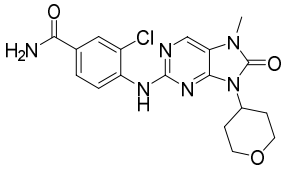
pharmaceutically acceptable salt, or co-crystal thereof, wherein

R_0 is C_{1-4} alkyl, wherein the C_{1-4} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium; and

R_1 is 

9. The compound according to any one of claims 1 to 8, or a stereoisomer, solvate, metabolite, prodrug, pharmaceutically acceptable salt, or co-crystal thereof, wherein the compound is:

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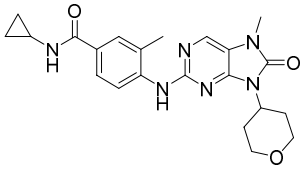
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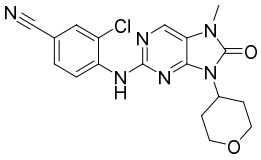
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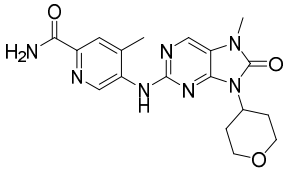
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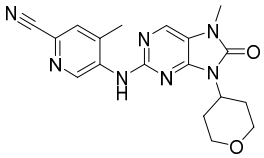
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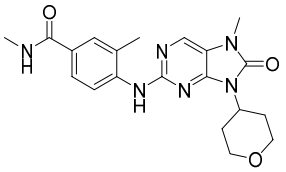
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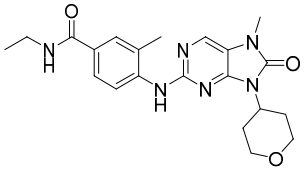
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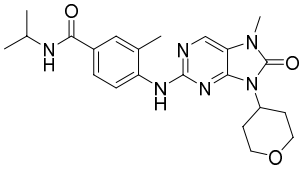
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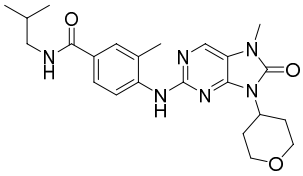
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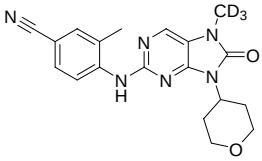
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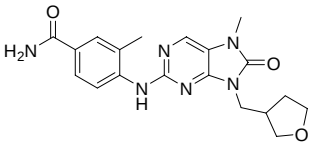
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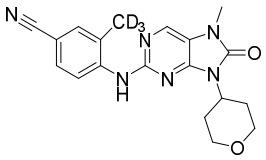
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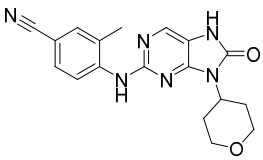
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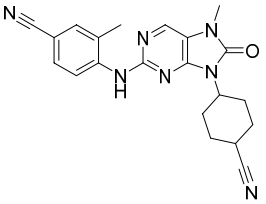
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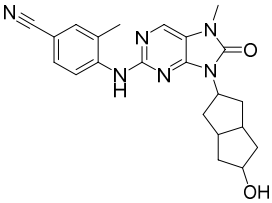
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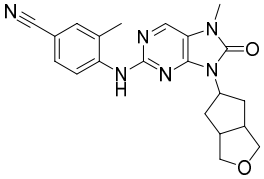
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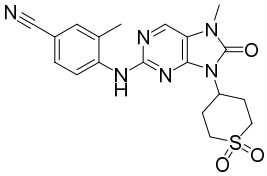
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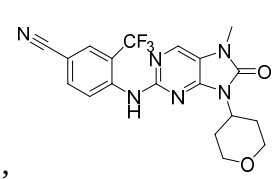
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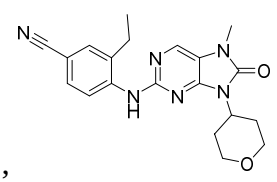
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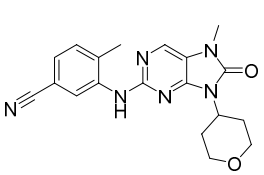
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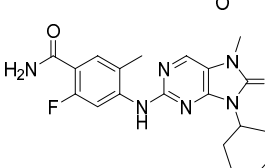
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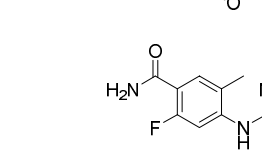
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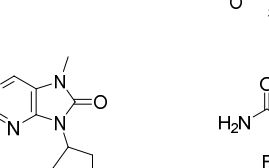
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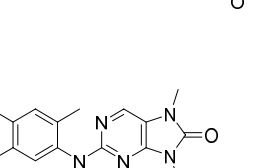
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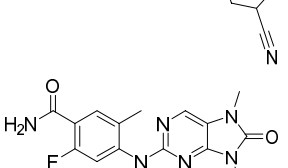
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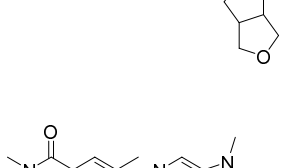
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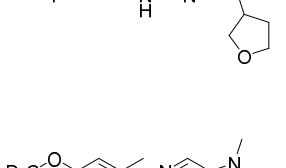
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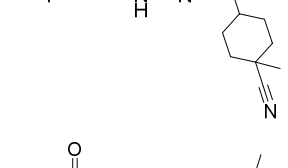
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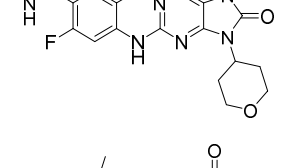
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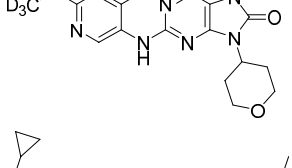
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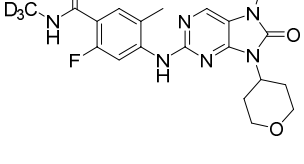
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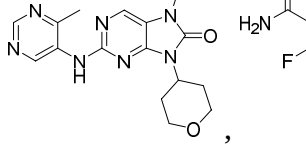
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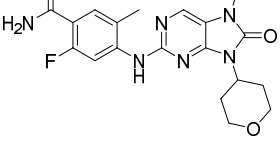
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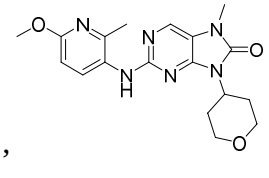
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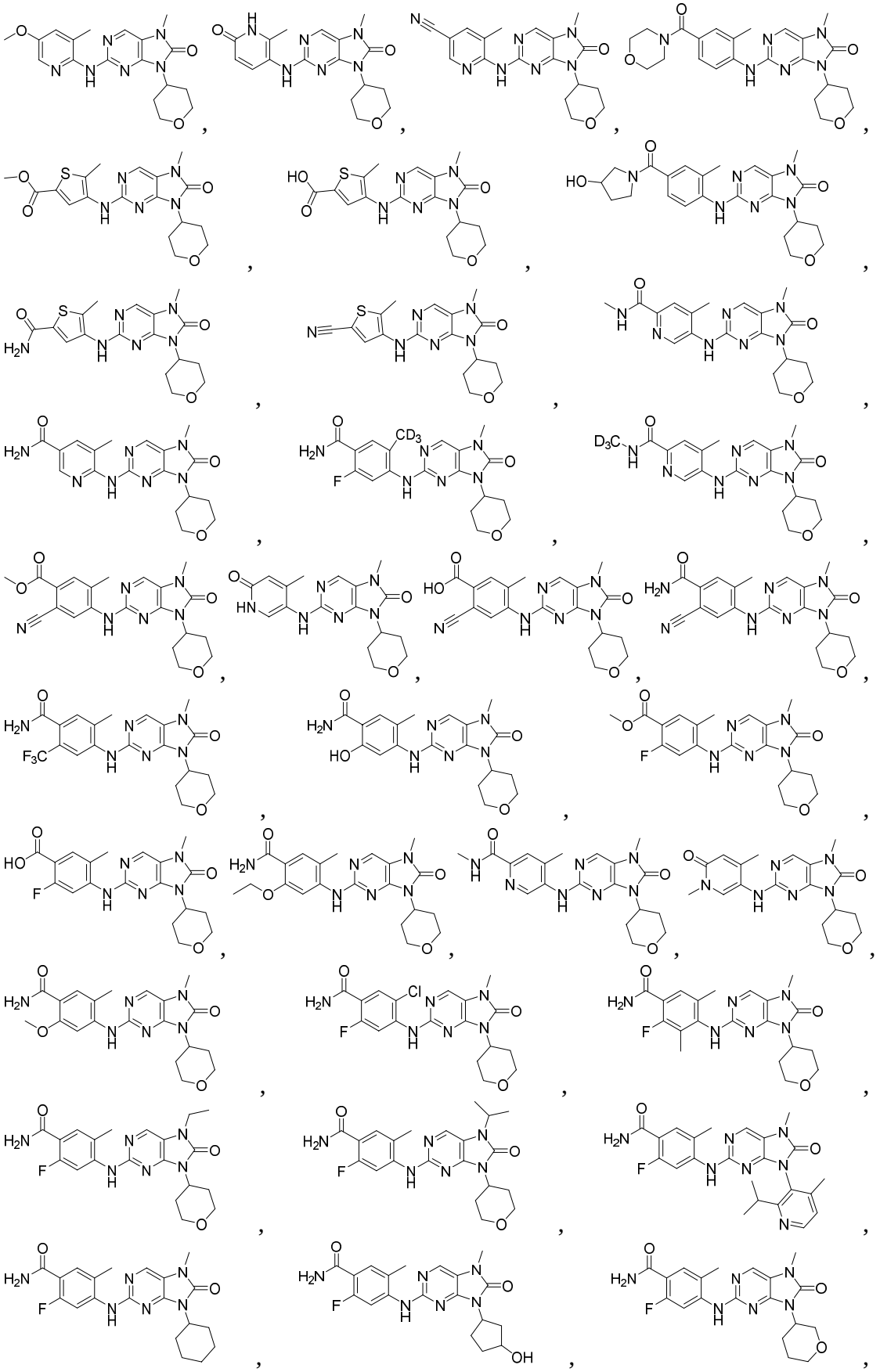

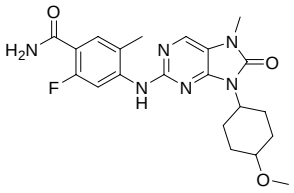
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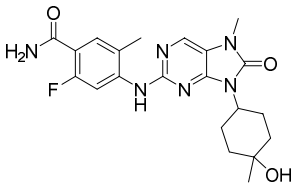
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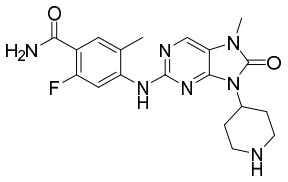
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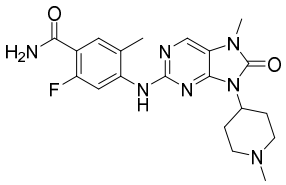
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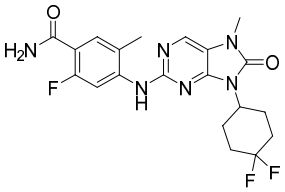
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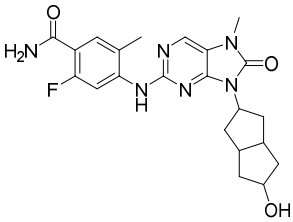
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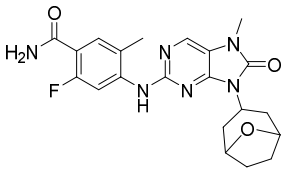
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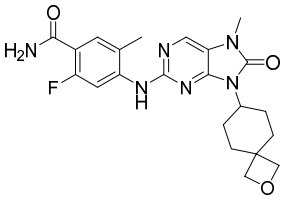
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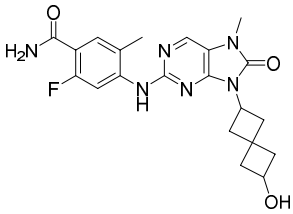
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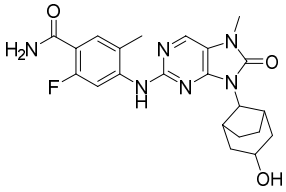
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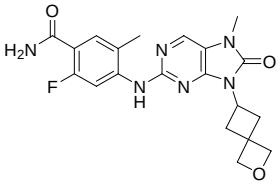
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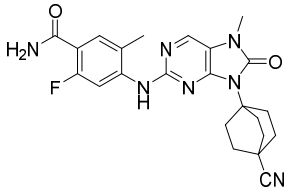
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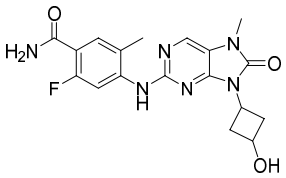
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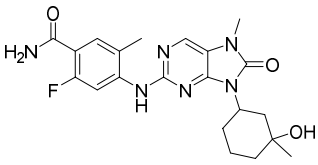
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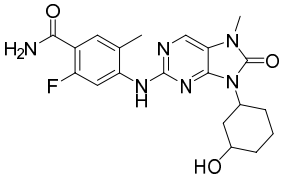
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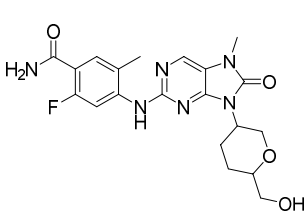
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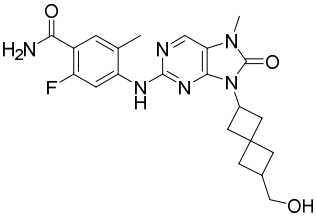
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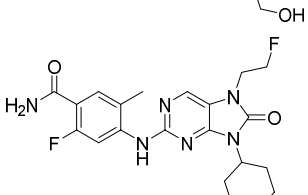
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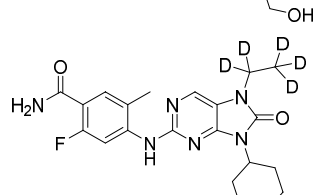
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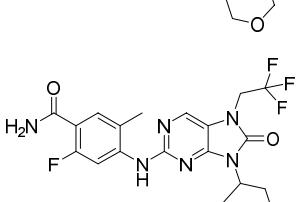
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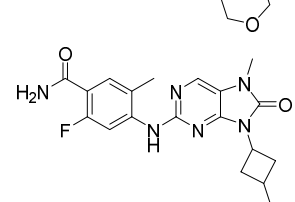
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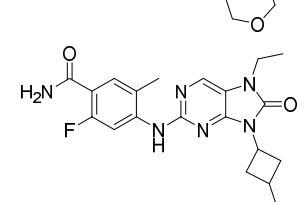
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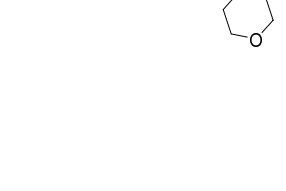
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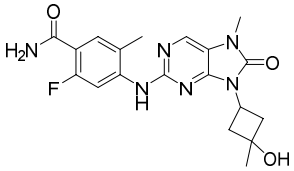
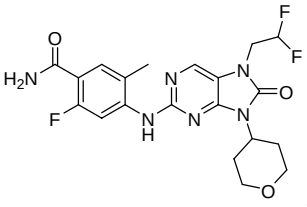
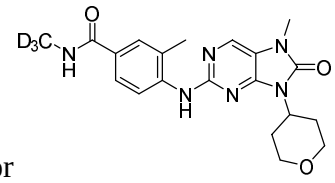
 ,  , or  .

10. A pharmaceutical composition, comprising:

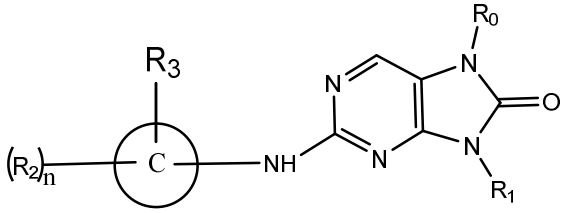
(1) a compound according to any one of claims 1 to 9, or a stereoisomer, solvate, metabolite, pharmaceutically acceptable salt, co-crystal, or prodrug thereof,

(2) optionally one or more additional active ingredients; and

(3) a pharmaceutically acceptable carrier and/or excipient.

11. Use of the compound according to any one of claims 1 to 9, or a stereoisomer, solvate, metabolite, pharmaceutically acceptable salt, co-crystal, or prodrug thereof, or the pharmaceutical composition according to claim 10, in the manufacture of a medicament for treatment of cancer; wherein the medicament for treatment of cancer is preferably a DNA-PK inhibitor.

12. A compound of general formula (I'), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt, or co-crystal thereof,

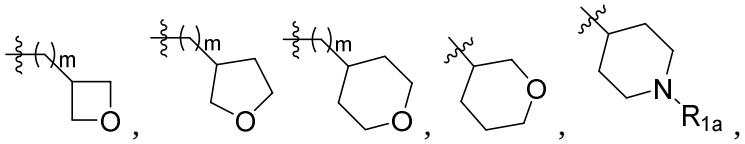
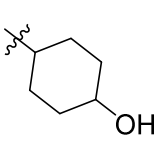
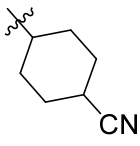
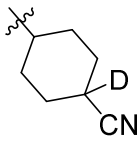
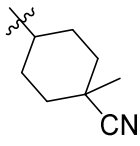
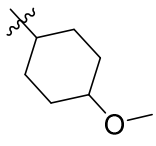
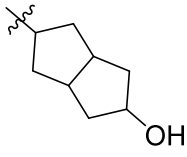
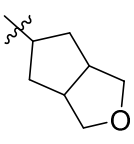
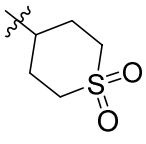


(I')

wherein

C is selected from phenyl and 6-membered monocyclic heterocyclic group, wherein the heterocyclic group may contain 1 to 3 heteroatoms selected from N;

R_0 is selected from H, C_{1-6} alkyl, and cyclopropyl, wherein the alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ;

R_{1a} is selected from H, C_{1-6} alkyl, and $-C(=O)C_{1-6}$ alkyl;

R_2 is selected from cyano, carboxyl, -$NR_{2a}R_{2b}$, -$C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, C_{1-6} alkyl, halogen, -$S(=O)_2R_{2a}$ and -$C(=O)OC_{1-6}$ alkyl; wherein the alkyl or alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are selected from H, C_{1-6} alkyl and 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

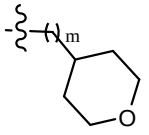
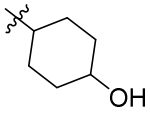
R_{2a} and R_{2b} together with the atom to which they are attached may form 5- to 6-membered heterocyclyl group which may contain 1 to 3 heteroatoms selected from N, O and S, wherein the heterocyclyl group may be further substituted with one or more substituents selected from C_{1-6} alkyl, OH, and halogen;

R_3 is selected from halogen and C_{1-6} alkyl, wherein the alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

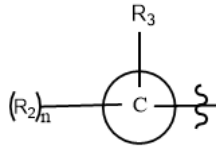
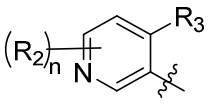
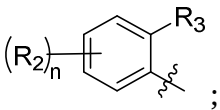
m is selected from 0 and 1; and

n is selected from 0, 1, and 2;

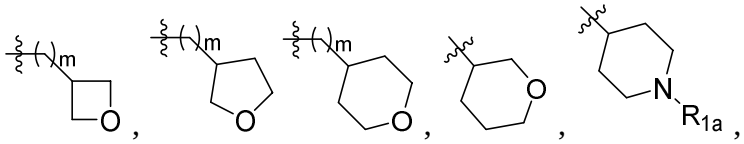
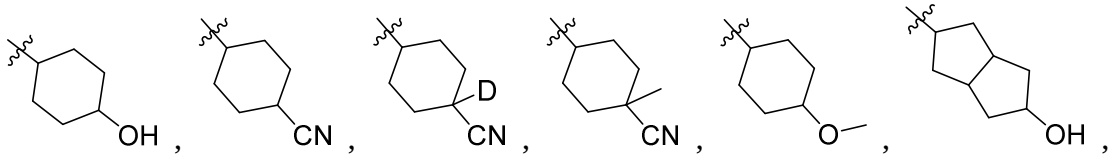
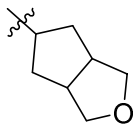
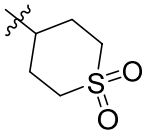
provided that

R_1 is not  or  when C is selected from phenyl and 6-membered monocyclic heterocyclic group and R_0 is H.

13. The compound according to claim 12, or a stereoisomer, solvate, metabolite, prodrug, pharmaceutically acceptable salt, or co-crystal thereof, wherein

 is  or  ;

R_0 is selected from H, C_{1-4} alkyl, and cyclopropyl, wherein the alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is selected from    , and  ;

R_{1a} is selected from H, C_{1-6} alkyl, and –$C(=O)C_{1-6}$ alkyl;

R_2 is selected from cyano, -$C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, -$S(=O)_2R_{2a}$ and

-C(=O)OC_{1-6} alkyl; wherein the alkyl or alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are selected from H, C_{1-6} alkyl and 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl may be further substituted with one or more substituents selected from OH, D, and halogen;

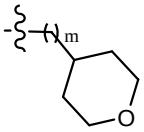
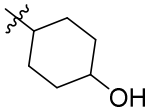
R_{2a} and R_{2b} together with the atom to which they are attached may form 5- to 6-membered heterocyclyl group which may contain 1 to 3 heteroatoms selected from N, O and S, wherein the heterocyclyl group may be further substituted with one or more substituents selected from OH and halogen;

R_3 is selected from halogen or C_{1-6} alkyl, wherein the alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

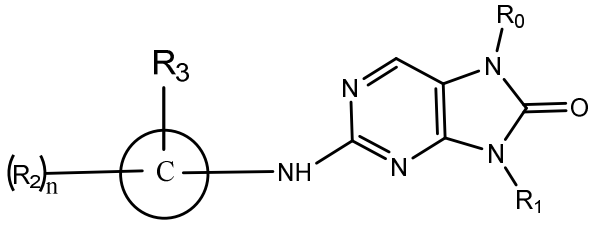
m is selected from 0 and 1; and

n is selected from 0, 1, and 2;

provided that

R_1 is not  or  when C is selected from phenyl and 6-membered monocyclic heterocyclic group and R_0 is H.

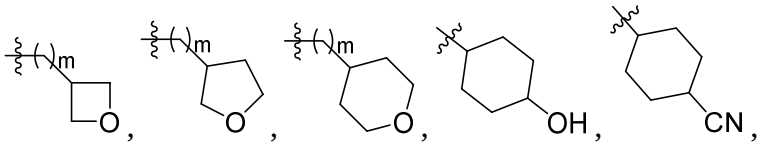
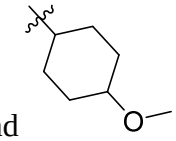
14. A compound of general formula (I''), or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt, or co-crystal thereof,


(I'')

wherein

C is selected from phenyl and 6-membered monocyclic heterocyclic group, wherein the heterocyclic group may contain 1 to 3 heteroatoms selected from N;

R_0 is selected from H and C_{1-6} alkyl, wherein the alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is selected from  ,  and ;

R_2 is selected from cyano, carboxyl, -$NR_{2a}R_{2b}$, -C(=O)$NR_{2a}R_{2b}$, C_{1-6} alkoxy, C_{1-6} alkyl, halogen, -$S(=O)_2R_{2a}$ and -C(=O)OC_{1-6} alkyl; wherein the alkyl is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are selected from H, C_{1-6} alkyl and 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

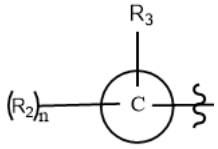
R_{2a} and R_{2b} together with the atom to which they are attached may form 5- to 6-membered heterocyclyl group which may contain 1 to 3 heteroatoms selected from N, O and S, wherein the heterocyclyl group may be further substituted with one or more substituents selected from C_{1-6} alkyl and halogen;

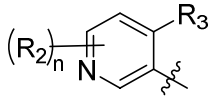
R_3 is selected from halogen and C_{1-6} alkyl, wherein the alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

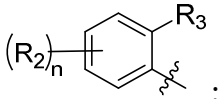
m is selected from 0 and 1; and

n is selected from 1 and 2.

15. The compound according to claim 14, or a stereoisomer, solvate, metabolite, prodrug, pharmaceutically acceptable salt, or co-crystal thereof, wherein

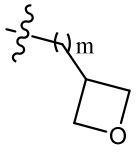


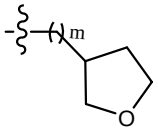
is selected from 

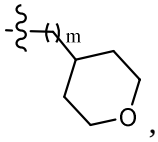
and 

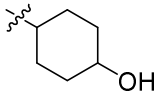
;

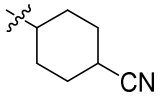
R_0 is selected from H and C_{1-4} alkyl, wherein the alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

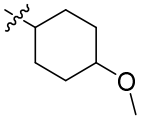
R_1 is selected from 

, 

, 

, 

, 

and 

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R_2 is selected from cyano, -C(=O)$NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, -S(=O)$_2R_{2a}$ and -C(=O)OC_{1-6} alkyl; wherein the alkyl is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are selected from H, C_{1-6} alkyl and 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH and halogen;

R_{2a} and R_{2b} together with the atom to which they are attached may form 6-membered heterocyclyl group;

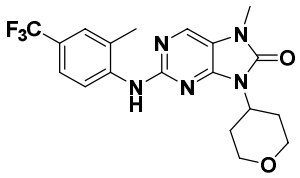
R_3 is selected from halogen and C_{1-6} alkyl, wherein the alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

m is selected from 0 and 1; and

n is selected from 1 and 2.

16. The compound according to claim 14 or 15, or a stereoisomer, solvate, metabolite, prodrug, pharmaceutically acceptable salt, or co-crystal thereof, wherein the compound

is selected from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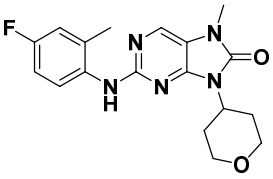
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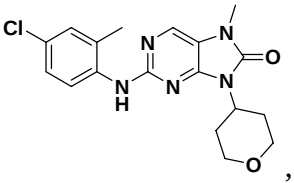
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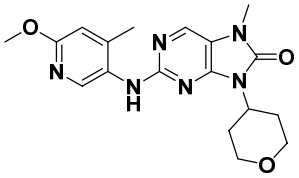
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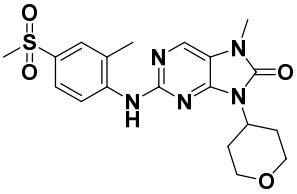
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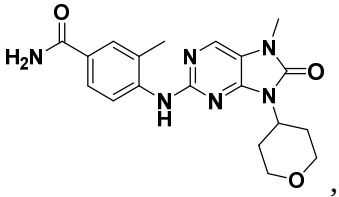
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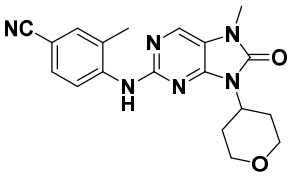
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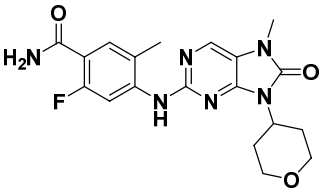
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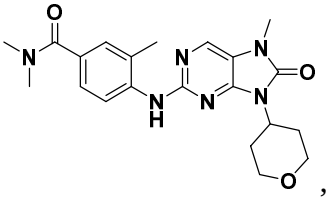
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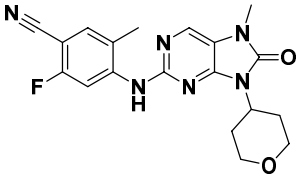
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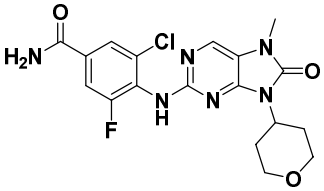
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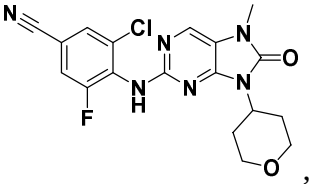
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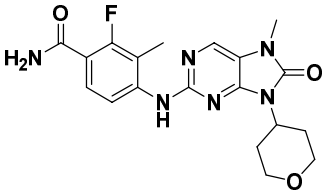
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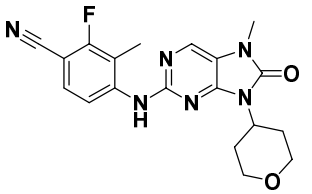
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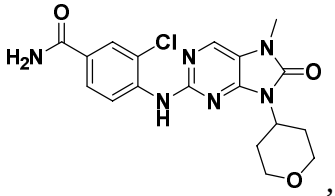
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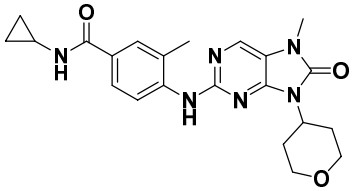
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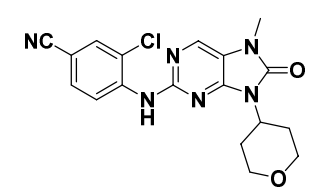
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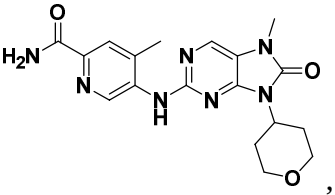
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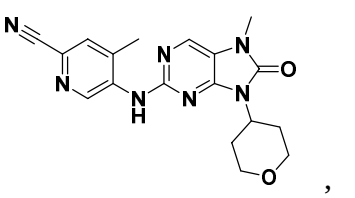
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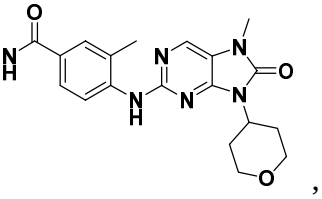
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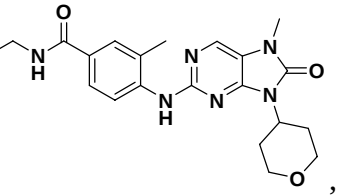
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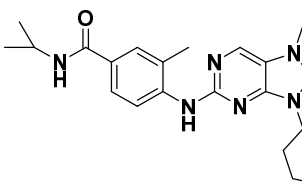
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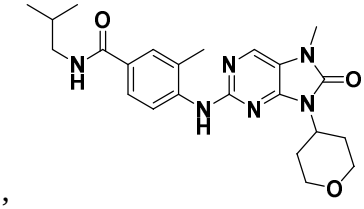
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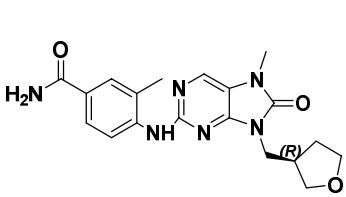
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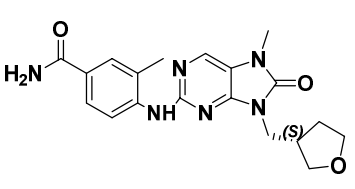
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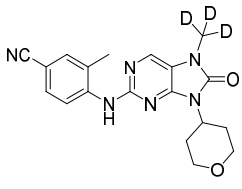
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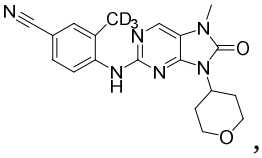
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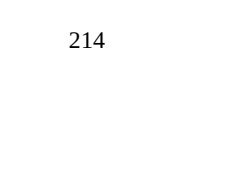
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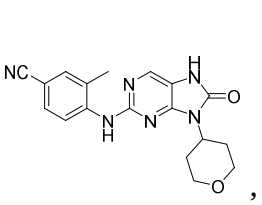
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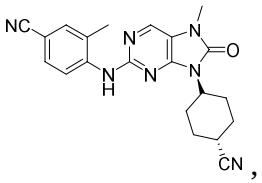
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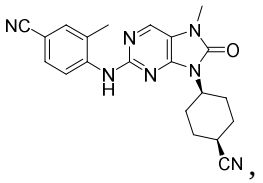
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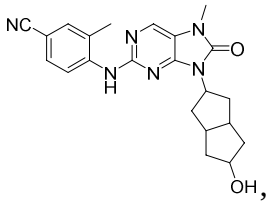
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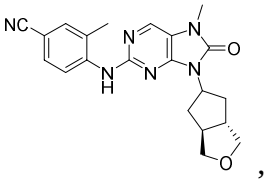
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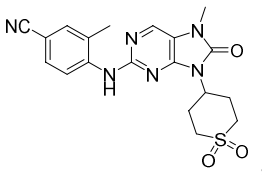
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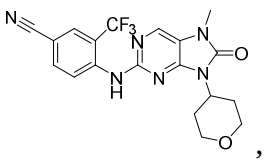
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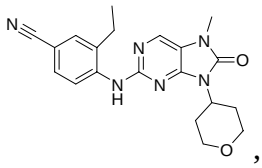
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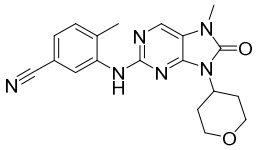
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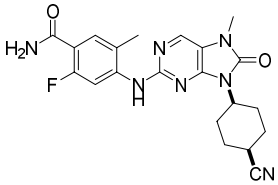
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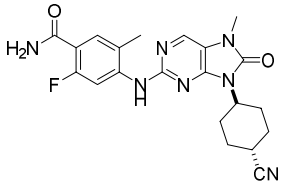
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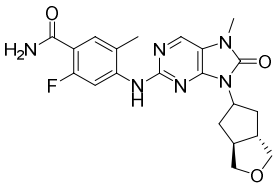
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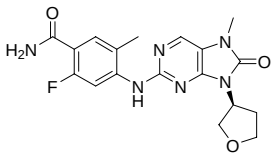
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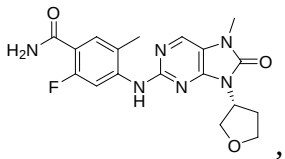
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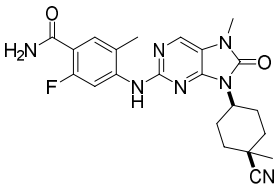
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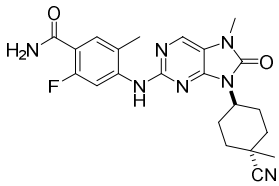
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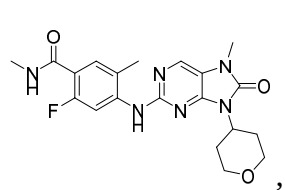
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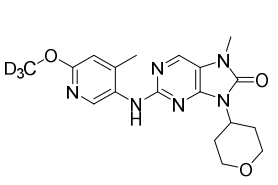
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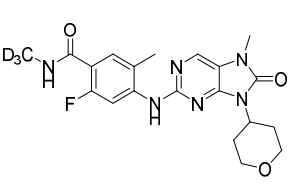
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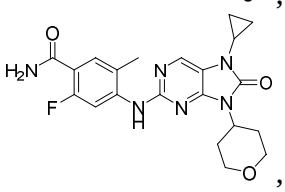
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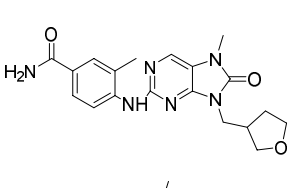
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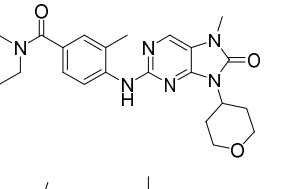
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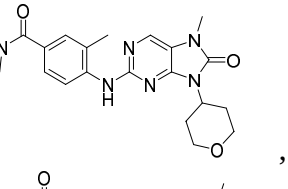
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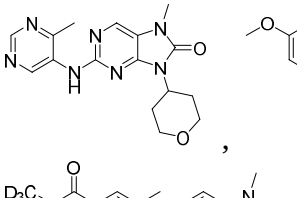
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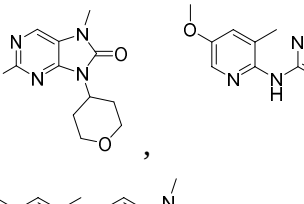
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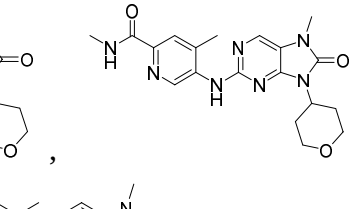
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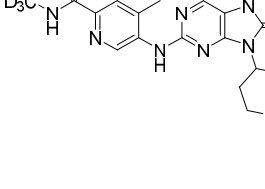
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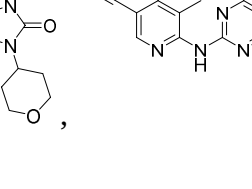
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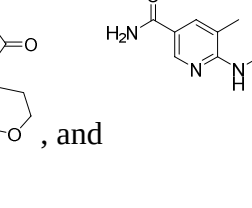
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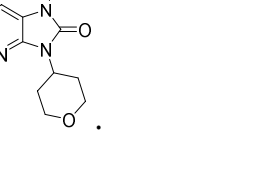
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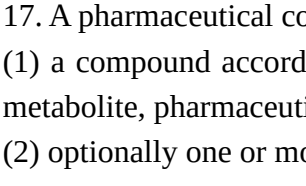
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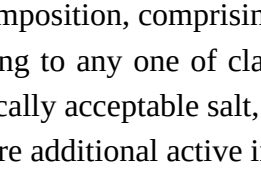
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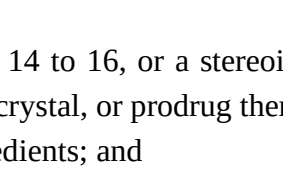
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17. A pharmaceutical composition, comprising:

(1) a compound according to any one of claims 14 to 16, or a stereoisomer, solvate, metabolite, pharmaceutically acceptable salt, co-crystal, or prodrug thereof,

(2) optionally one or more additional active ingredients; and

(3) a pharmaceutically acceptable carrier and/or excipient.

18. Use of the compound according to any one of claims 14 to 16, or stereoisomer, solvate, metabolite, pharmaceutically acceptable salt, co-crystal, or prodrug thereof, or the pharmaceutical composition according to claim 17, in the manufacture of DNA-PK inhibitor.