Design, Synthesis and Biological Evaluation of Substituted Pyrimidines as Potential Phosphatidylinositol 3-Kinase (PI3K) Inhibitors

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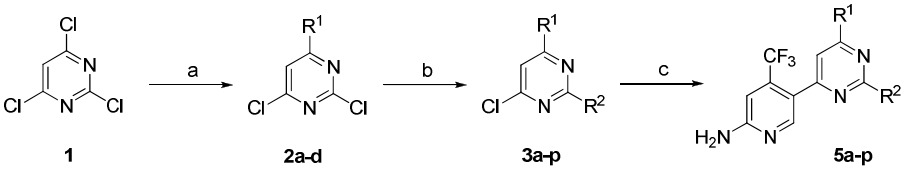
Supporting information

1. Synthetic Schemes

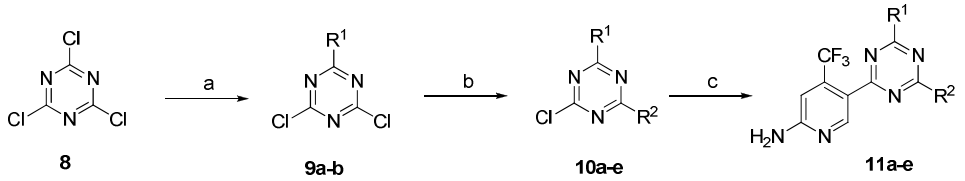


2a: R^1= morpholine
2b: R^1= (2*S*,6*R*)-2,6-dimethylmorpholine
2c: R^1= (4*aR*,7*aS*)-hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole
2d: R^1= (±)-(4*aR*,7*aR*)-hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole

5a: R^1= morpholine, R^2= morpholine
5b: R^1= morpholine, R^2= (2*S*,6*R*)-2,6-dimethylmorpholine
5c: R^1= morpholine, R^2= (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane
5d: R^1= morpholine, R^2= (±)-(4*aS*,7*aS*)-hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole
5e: R^1= morpholine, R^2= (4*aR*,7*aS*)-hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole
5f: R^1= morpholine, R^2= 1-(methylsulfonyl)piperazine
5g: R^1= morpholine, R^2= 4-morpholinoaniline
5h: R^1= morpholine, R^2= 2-morpholinoethanamine
5i: R^1= (2*S*,6*R*)-2,6-dimethylmorpholine, R^2= morpholine
5j: R^1= (2*S*,6*R*)-2,6-dimethylmorpholine, R^2= (2*S*,6*R*)-2,6-dimethylmorpholine
5k: R^1= (2*S*,6*R*)-2,6-dimethylmorpholine, R^2= (4*aR*,7*aS*)-hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole
5l: R^1= (4*aR*,7*aS*)-hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole, R^2= morpholine
5m: R^1=(±)-(4*aR*,7*aR*)-hexahydro-2*H*-[1,4]dioxino[2,3-*c*]pyrrole, R^2= morpholine
5n: R^1= morpholine, R^2= 3-morpholinoaniline
5o: R^1= morpholine, R^2= 4-(4-(methylsulfonyl)piperazin-1-yl)aniline
5p: R^1= morpholine, R^2= (4-aminophenyl)(4-(methylsulfonyl)piperazin-1-yl)methanone

(a) R^1 (1.0 equiv.), DIPEA (1.05 equiv.), CH_2Cl_2, -5 °C-rt, 2.5 h, 60-70%; (b) R^2 (1.2 equiv.), TEA (1.5 equiv.), NaI (1.5 equiv.), THF/EtOH (1:1), 65 °C, 12 h, 50-90% (for aliphatic amines) or R^2 (1.0 equiv.), TsOH (1.0 equiv.), n-BuOH, 100 °C, 24 h, 15-50% (for aromatic amines); (c) 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-amine (**4**, 2.0 equiv.), K_2CO_3 (2 M, 3.0 equiv.), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.05 equiv.), dioxane, 150 °C, 2.0-2.5 h, microwave, 5-30%.

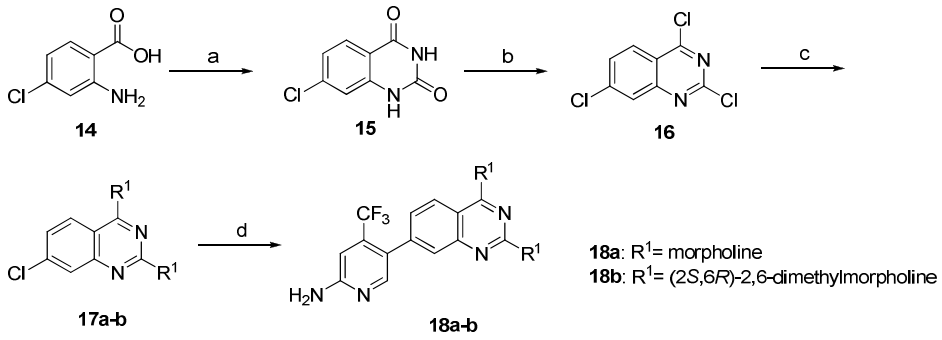
Scheme 1.



9a: R^1= morpholine
9b: R^1= (*2S,6R*)-2,6-dimethylmorpholine
11a: R^1= morpholine, R^2= (*1R,4R*)-2-oxa-5-azabicyclo[2.2.1]heptane
11b: R^1= morpholine, R^2= (*4RS,7RS*)-hexahydro-2*H*-[1,4]dioxino[2,3-c]pyrrole
11c: R^1= (*2S,6R*)-2,6-dimethylmorpholine, R^2= (*1R,4R*)-2-oxa-5-azabicydo[2.2.1]heptane3-c]pyrrole
11d: R^1= (*2S,6R*)-2,6-dimethylmorpholine, R^2= (*2S,6R*)-2,6-dimethylmorpholine
11e: R^1= (*2S,6R*)-2,6-dimethylmorpholine, R^2= (*4aR,7aS*)-hexahydro-2*H*-[1,4]dioxino[2,3-c]pyrrole

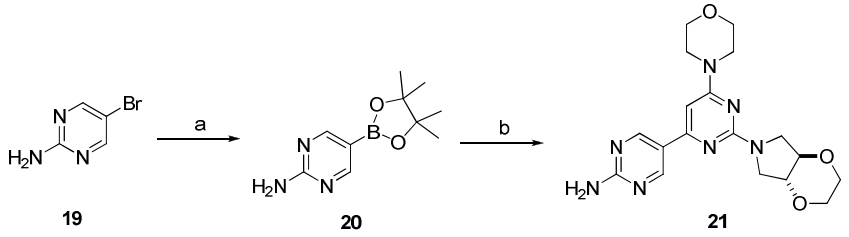
(a) R^1 (0.9 equiv.), DIPEA (0.9 equiv.), CH_2Cl_2, -5-0 °C, 24 h, 60-75%; (b) R^2 (1.0 equiv.), K_2CO_3 (1.5 equiv.), THF, rt, 24 h, 75-90%; (c) **4** (2.0 equiv.), K_2CO_3 (2 M, 3.0 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.05 equiv.), dioxane, 150 °C, 2.0 -2.5 h, microwave, 10-30%.

Scheme 2.



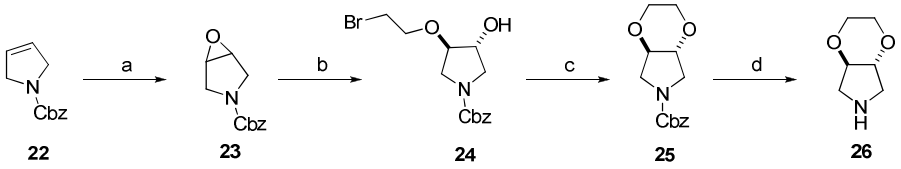
(a) urea (4.0 equiv.), 200 °C, 2 h, 85%; (b) $POCl_3$ (5.5 equiv.), DIPEA (2.8 equiv.), MeCN, 100 °C, 6 h, 90%; (c) R^1 (2.5 equiv.), DIPEA (2.5 equiv.), NaI (2.2 equiv.), DMF, 80 °C, 8 h, 65-80%; (d) **4** (2.0 equiv.), K_2CO_3 (2 M, 3.0 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.05 equiv.), dioxane, 150 °C, 2.0-2.5 h, microwave, 20-30%.

Scheme 3.



(a) 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.05 equiv.), KOAc (3.0 equiv.), dioxane, 115 °C, 12 h, 72%; (b) **3d** (0.5 equiv.), K_2CO_3 (2 M, 1.5 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.025 equiv.), dioxane, 150 °C, 2.0 h, microwave, 62%.

Scheme 4.



(a) m-CPBA (1.25 equiv.), CH_2Cl_2, rt, 16 h, 68%; (b) 2-bromoethanol (1.1 equiv.), $BF_3.OEt_2$ (0.1 equiv.), CH_2Cl_2, rt, 24 h, 29%; (c) KOH (1.1 equiv.), EtOH, reflux, 6 h, 67%; (d) 10% Pd/C, THF, rt, 95%.

Scheme 5.

2. Synthesis of intermediates and target compounds

NMR spectra were recorded on a Bruker Avance III spectrometer with TMS as the internal standard and $CDCl_3$ or DMSO-d_6 as solvent. Low-resolution MS spectra were obtained on an Agilent LC-MS 6120 instrument with an ESI mass detector, and the data were obtained in the positive or negative ion mode. High-resolution ESI-MS data were obtained on a Shimadzu LC-MS-IT-TOF mass spectrometer. The purity of the synthesized compounds was evaluated using a high-performance liquid chromatography (HPLC) equipped with a Chiralcel OD-H, OJ-H or Chiralpak AD-H column (4.6 mm diameter×250 mm length). The purity of all biologically evaluated compounds was > 95%.

Intermediates 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-amine (**4**), 2,4,7-trichloroquinazoline (**16**), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (**20**), (4*aR*,7*aS*)-

hexahydro-2*H*-[1,4]dioxino[2,3-c]pyrrole (**27**), (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptanes (**28**), 3-morpholinoaniline (**29**), 4-(4-(methylsulfonyl)piperazin-1-yl)aniline (**30**) and (4-aminophenyl)(4-(methylsulfonyl) piperazin-1-yl)methanone (**31**) were prepared according to the methods reported previously.[1-7]

2.1 General procedure for the preparation of 4-substituted-2,6-dichloropyrimidines 2a-d

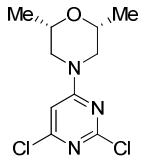
DIPEA (1.05 equiv.) was added to a solution of 2,4,6-trichloropyrimidine **1** (1.0 equiv.) in CH_2Cl_2 (10 mL) and cooled to -5 ^oC. Then morpholine (1.0 equiv.) was added dropwise. The mixture was stirred at -5 ^oC for 0.5 h and rt for 2 h, then H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (20 mL×1), the organic layers were combined, washed with brine (20 mL×1) and dried over Na_2SO_4. The organic solvent was removed under reduced pressure, the crude product was purified by column chromatography (PE/EtOAc = 4/1) to afford **2a** as white solid in 65.81% yield.

Compounds **2b-d** were prepared following the similar procedure with **2a**.

2.1.1 4-(2,6-diChloropyrimidin-4-yl)morpholine (2a)[8]

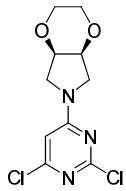
Yield 65.81%. ESI-MS (*m/z*): 234.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.39 (d, *J* = 4.5 Hz, 1H), 3.88-3.49 (m, 8H).

2.1.2 (2R,6S)-4-(2,6-diChloropyrimidin-4-yl)-2,6-dimethylmorpholine (2b)



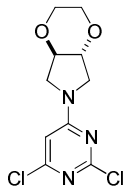
Yield 69.09%. ESI-MS (*m/z*): 262.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.39 (s, 1H), 3.62 (m, 2H), 2.64 (d, *J* = 10.0 Hz, 2H), 1.25 (d, *J* = 6.2 Hz, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.0, 161.1, 160.1, 99.8, 71.4, 49.7, 18.9.

2.1.3 (4aR,7aS)-6-(2,6-diChloropyrimidin-4-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (2c)



Yield 65.81%. ESI-MS (*m/z*): 276.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.23 (d, *J* = 5.6 Hz, 1H), 4.31 (d, *J* = 38.1 Hz, 2H), 3.85 (dd, *J* = 10.8, 5.4 Hz, 3H), 3.65 (ddd, *J* = 28.4, 14.4, 9.2 Hz, 4H), 3.50-3.39 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.0, 159.7, 159.6, 100.3, 72.6, 72.0, 62.9, 61.7, 48.0, 47.1.

2.1.4 (±)-(4aR,7aR)-6-(2,6-diChloropyrimidin-4-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (2d)



Yield 60.28%. ESI-MS (*m/z*): 276.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.21 (s, 1H), 4.11 (dd, *J* = 16.6,

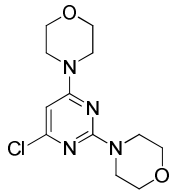
6.3 Hz, 1H), 3.95-3.55 (m, 7H), 3.24 (dt, *J* = 19.1, 10.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.2, 159.9, 159.8, 100.1, 67.1, 47.0, 46.7.

2.2 General procedure for the preparation of 2,4-disubstituted-6-chloro-pyrimidines 3a-f, 3h-m

Morpholine (1.0 equiv.) was added to a solution of 4-substituted-2,6-dichloropyrimidine (1.1 equiv.) in THF/EtOH (10 mL, 1:1), followed by the addition of TEA (1.2 equiv.) and NaI (1.1 equiv.). The solution was stirred at 65 ^{o}C for 12 h. Then the solvent was removed, the residue was dissolved in EtOAc (50 mL), washed with H_2O (30 mL) and brine (30 mL) in turn, dried over Na_2SO_4. The solvent was removed under reduced pressure, the crude product was purified by column chromatography (PE/EtOAc = 5/1) to afford **3a** as white solid in 63.51% yield.

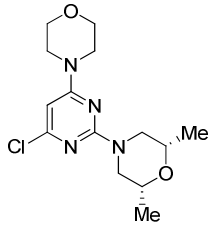
Compounds **3b-f, 3h-m** were prepared following the similar procedure with **3a**.

2.2.1 4,4'-(6-Chloropyrimidine-2,4-diyl)dimorpholine (3a)[9]



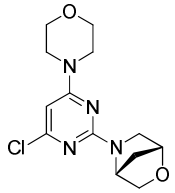
Yield 63.51%. ESI-MS (*m/z*): 285.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.86 (d, *J* = 1.1 Hz, 1H), 3.82-3.64 (m, 12H), 3.59-3.50 (m, 4H).

2.2.2 (2R,6S)-4-(4-Chloro-6-morpholinopyrimidin-2-yl)-2,6-dimethylmorpholine (3b)



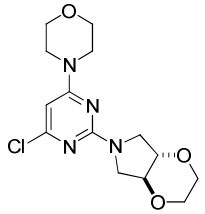
Yield 58.21%. ESI-MS (*m/z*): 313.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 (d, *J* = 1.8 Hz, 1H), 4.45 (d, *J* = 13.3 Hz, 2H), 3.80-3.68 (m, 4H), 3.68-3.46 (m, 6H), 2.53 (t, *J* = 11.3 Hz, 2H), 1.23 (dd, *J* = 6.2, 1.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.0, 160.7, 160.6, 91.1, 71.7, 66.5, 49.3, 44.5, 18.9.

2.2.3 (1R,4R)-5-(4-Chloro-6-morpholinopyrimidin-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane (3c)



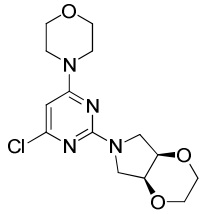
Yield 66.22%. ESI-MS (*m/z*): 297.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 (s, 1H), 4.96 (s, 1H), 4.64 (s, 1H), 3.84 (s, 2H), 3.73 (s, 4H), 3.54 (s, 6H), 1.89 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.3, 160.4, 159.8, 91.1, 76.6, 74.0, 66.5, 56.9, 55.6, 44.4, 36.6.

2.2.4 (±)-(4aS,7aS)-6-(4-Chloro-6-morpholinopyrimidin-2-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (3d)



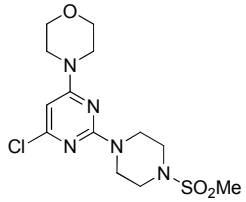
Yield 52.34%. ESI-MS (*m/z*): 327.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.87 (s, 1H), 3.96 (s, 2H), 3.90-3.81 (m, 5H), 3.77-3.64 (m, 7H), 3.58-3.51 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.3, 160.4, 159.5, 91.0, 78.1, 67.2, 66.3, 46.4, 44.4.

2.2.5 (4aR,7aS)-6-(4-Chloro-6-morpholinopyrimidin-2-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (3e)



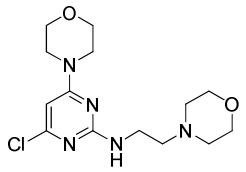
Yield 68.09%. ESI-MS (*m/z*): 327.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.85 (s, 1H), 4.23 (s, 2H), 3.93-3.48 (m, 16H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.3, 160.3, 159.8, 91.0, 73.0, 66.5, 62.4, 46.8, 44.4.

2.2.6 4-(6-Chloro-2-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)morpholine (3f)



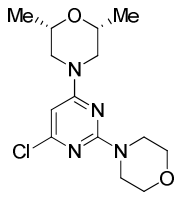
Yield 50.65%. ESI-MS (*m/z*): 362.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.89 (d, J = 2.8 Hz, 1H), 3.90 (d, J = 3.6 Hz, 4H), 3.80-3.70 (m, 4H), 3.55 (s, 4H), 3.24 (d, J = 4.0 Hz, 4H), 2.78 (d, J = 2.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.5, 160.7, 160.5, 91.8, 66.8, 45.8, 44.5, 43.5, 34.5.

2.2.7 4-Chloro-6-morpholino-N-(2-morpholinoethyl)pyrimidin-2-amine (3h)



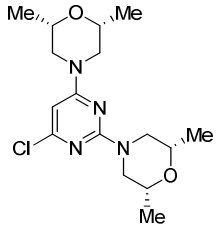
Yield 73.65%. ESI-MS (*m/z*): 328.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.85 (s, 1H), 5.49 (s, 1H), 3.77-3.66 (m, 9H), 3.58-3.51 (m, 5H), 2.53 (t, J = 5.7 Hz, 2H), 2.45 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.0, 161.3, 160.7, 91.1, 66.9, 66.5, 57.3, 53.4, 44.4, 37.6.

2.2.8 (2R,6S)-4-(6-Chloro-2-morpholinopyrimidin-4-yl)-2,6-dimethylmorpholine (3i)



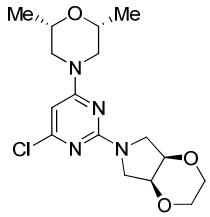
Yield 78.45%. ESI-MS (*m/z*): 313.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.85 (d, *J* = 5.2 Hz, 1H), 4.03 (s, 2H), 3.68 (t, *J* = 23.9 Hz, 10H), 2.54 (td, *J* = 12.7, 4.9 Hz, 2H), 1.23 (t, *J* = 5.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.1, 160.9, 160.5, 91.4, 71.7, 66.9, 49.3, 44.8, 18.9.

2.2.9 (2R,2'R,6S,6'S)-4,4'-(6-Chloropyrimidine-2,4-diyl)bis(2,6-dimethylmorpholine) (3j)



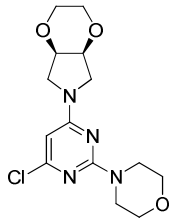
Yield 86.15%. ESI-MS (*m/z*): 341.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 (s, 1H), 4.44 (d, *J* = 12.8 Hz, 2H), 4.02 (s, 2H), 3.68-3.51 (m, 4H), 2.61-2.43 (m, 4H), 1.24 (dd, *J* = 6.1, 3.4 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.1, 160.6, 160.5, 91.1, 71.7, 71.4, 49.6, 49.5, 18.9.

2.2.10 (4aR,7aS)-6-(4-Chloro-6-((2R,6S)-2,6-dimethylmorpholino)pyrimidin-2-yl)hexahydro-2H-[1,4]dioxino [2,3-c]pyrrole (3k)



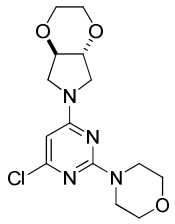
Yield 74.45%. ESI-MS (*m/z*): 355.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.85 (d, *J* = 5.3 Hz, 1H), 4.16 (d, *J* = 63.9 Hz, 4H), 3.93-3.53 (m, 10H), 2.55 (t, *J* = 9.4 Hz, 2H), 1.24 (t, *J* = 5.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.9, 160.2, 159.9, 91.0, 72.8, 71.6, 62.6, 49.1, 47.1, 18.7.

2.2.11 (4aR,7aS)-6-(6-Chloro-2-morpholinopyrimidin-4-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (3l)



Yield 72.37%. ESI-MS (*m/z*): 327.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.68 (d, *J* = 4.4 Hz, 1H), 4.24 (s, 2H), 3.97-3.37 (m, 16H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.1, 160.9, 159.8, 91.5, 72.8, 67.0, 62.6, 47.1, 44.1.

2.2.12 (±)-(4aR,7aR)-6-(6-Chloro-2-morpholinopyrimidin-4-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (3m)



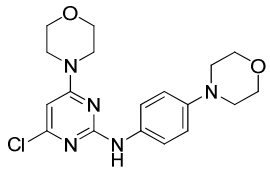
Yield 75.29%. ESI-MS (*m/z*): 327.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.66 (s, 1H), 3.91-3.83 (m, 4H), 3.80-3.57 (m, 12H), 3.17 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.9, 160.8, 159.8, 91.2, 77.8, 67.2, 66.8, 46.2, 44.3.

2.3 General procedure for the preparation of 2,4-disubstituted-6-chloro-pyrimidines 3g, 3n, 3o and 3p

To a solution of **2a** (1.0 equiv.) in *n*-BuOH (20 mL) was added 4-morpholinoaniline (1.0 equiv.), followed by the addition of TsOH•H_2O (1.0 equiv.). After the mixture was stirred at 100 □ for 24 h, the solvent was removed, the residue was dissolved in EtOAc (50 mL), washed with H_2O (50 mL) and brine (50 mL) in turn, dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography (PE/EtOAc = 1/1) to afford **3g** as gray solid in 53.54% yield.

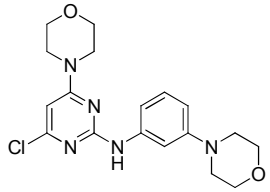
Compounds **3n, 3o-p** were prepared following the similar procedure mentioned above.

2.3.1 4-Chloro-6-morpholino-N-(4-morpholinophenyl)pyrimidin-2-amine (3g)



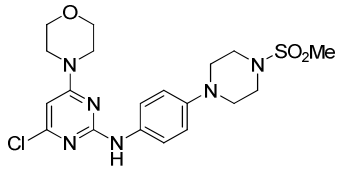
Yield 53.54%. ESI-MS (*m/z*): 376.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.36 (m, 2H), 6.89 (d, J = 7.4 Hz, 2H), 6.83 (s, 1H), 5.97 (d, J = 1.5 Hz, 1H), 3.89-3.82 (m, 4H), 3.78-3.72 (m, 4H), 3.57 (s, 4H), 3.14-3.07 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.7, 160.3, 159.1, 147.2, 132.2, 121.2, 116.4, 92.6, 66.9, 66.4, 50.1, 44.5.

2.3.2 4-Chloro-6-morpholino-N-(3-morpholinophenyl)pyrimidin-2-amine (3n)



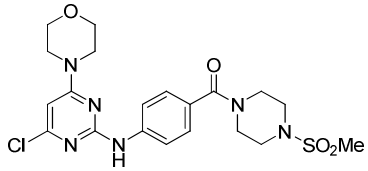
Yield 34.90%. ESI-MS (*m/z*): 376.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.35 (s, 1H), 7.38 (s, 1H), 7.13-7.01 (m, 2H), 6.55 (d, J = 6.8 Hz, 1H), 6.32 (s, 1H), 3.77-3.70 (m, 4H), 3.69-3.58 (m, 8H), 3.09-3.01 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 163.2, 159.1, 158.7, 151.4, 140.6, 128.8, 110.4, 109.0, 106.0, 92.2, 66.1, 65.6, 48.6, 44.3.

2.3.3 4-Chloro-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-6-morpholinopyrimidin-2-amine (3o)



Yield 14.60%. ESI-MS (*m/z*): 453.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.83 (s, 1H), 5.99 (s, 1H), 3.80-3.72 (m, 4H), 3.58 (d, *J* = 4.7 Hz, 4H), 3.42-3.35 (m, 4H), 3.27-3.20 (m, 4H), 2.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.6, 160.3, 159.1, 146.4, 133.2, 121.2, 118.0, 92.8, 66.4, 50.3, 46.1, 44.5, 34.8.

2.3.4 (4-((4-Chloro-6-morpholinopyrimidin-2-yl)amino)phenyl)(4-(methylsulfonyl)piperazin-1-yl) methanone (3p)

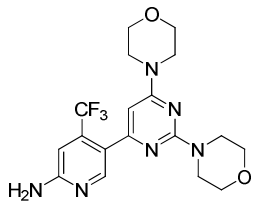


Yield 15.30%. ESI-MS (*m/z*): 481.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.72 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 6.41 (s, 1H), 3.73-3.54 (m, 12H), 3.16 (s, 4H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 169.3, 163.2, 159.3, 158.6, 141.9, 128.1, 127.7, 118.1, 95.5, 65.7, 45.6, 44.6, 42.0, 34.0.

2.4 General procedure for the preparation of 2,4,6-trisubstituted pyrimidines5a-m

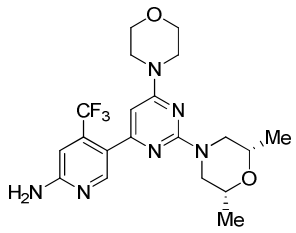
To a solution of **3a**-**m** (1.0 equiv.), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-amine (**4**, 2.0 equiv.) and Pd(dppf)Cl_2•CH_2Cl_2 (0.05 equiv.) in degassed dioxane (6 mL) was added 2 M K_2CO_3 (3.0 equiv.). The mixture was heated under microwave at 150 ^{o}C for 2.0-2.5 h. The solvent was removed, the residue was dissolved in EtOAc (50 mL), washed with H_2O (30 mL×3) and brine (30 mL) in turn, dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was first separated by column chromatography (PE/EtOAc = 5/1 to 1/2), then further purified by column chromatography (CH_2Cl_2/MeOH = 50/1) to afford white or off-white solid in 5-30% yield.

2.4.1 5-(2,6-diMorpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5a)[1]



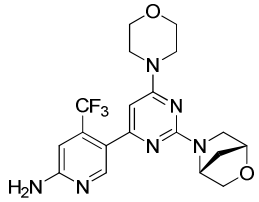
Yield 27.78%. HPLC purity 99.31% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 12.86 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{18}H_{22}F_3N_6O_2]^+$: 411.1751, found: 411.1736; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (s, 1H), 6.77 (s, 1H), 5.96 (s, 1H), 4.88 (s, 2H), 3.74 (dd, *J* = 12.0, 4.0 Hz, 12H), 3.59 (d, *J* = 4.0 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.3, 161.4, 159.4, 150.6, 137.7, 131.6, 128.7, 123.8, 105.7, 92.8, 67.0, 66.6, 44.4, 30.9.

2.4.2 5-(2-((2S,6R)-2,6-diMethylmorpholino)-6-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5b)



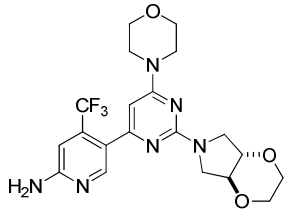
Yield 22.05%. HPLC purity 96.10% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 9.34 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{20}H_{26}F_3N_6O_2]^+$: 439.2064, found: 439.2070; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 6.77 (s, 1H), 5.95 (s, 1H), 4.83 (s, 2H), 4.54 (d, *J* = 12.7 Hz, 2H), 3.86-3.70 (m, 4H), 3.71-3.50 (m, 6H), 2.54 (dd, *J* = 13.1, 10.7 Hz, 2H), 1.22 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.3, 162.6, 161.1, 158.4, 151.0, 138.4, 124.8, 121.5, 105.4, 92.4, 72.0, 66.5, 49.7, 44.5, 18.9.

2.4.3 5-(2-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-6-morpholinopyrimidin-4-yl)-4-(trifluoromethyl) pyridin-2-amine (5c)



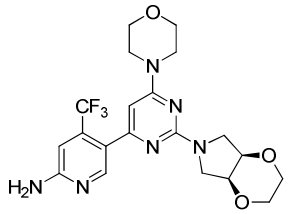
Yield 20.15%. HPLC purity 97.20% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 12.58 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{19}H_{22}F_3N_6O_2]^+$: 423.1751, found: 423.1772; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 6.76 (s, 1H), 5.94 (s, 1H), 4.99 (s, 1H), 4.83 (s, 2H), 4.64 (s, 1H), 3.87 (dd, *J* = 20.0, 7.2 Hz, 2H), 3.81-3.66 (m, 5H), 3.62-3.56 (m, 5H), 1.90 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.0, 160.7, 158.8, 151.0, 147.4, 138.1, 124.4, 121.9, 105.3, 92.1, 73.3, 67.2, 56.8, 55.5, 53.2, 44.8, 36.4.

2.4.4 (±)-5-(2-((4aS,7aR)-diHydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholinopyrimidin-4- yl)-4-(trifluoromethyl)pyridin-2-amine (5d)



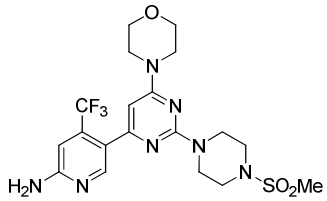
Yield 16.97%. HPLC purity 98.92% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 16.89 and 18.06 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{20}H_{24}F_3N_6O_3]^+$: 453.1856, found: 453.1852; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 6.76 (s, 1H), 5.95 (s, 1H), 5.29 (s, 1H), 4.82 (s, 2H), 4.01 (s, 2H), 3.87 (s, 3H), 3.79-3.70 (m, 6H), 3.63-3.56 (m, 4H), 3.26 (t, *J* = 10.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.0, 160.7, 159.1, 150.3, 138.1, 124.4, 121.9, 105.3, 100.1, 93.0, 78.8, 67.8, 66.5, 46.8, 44.2.

2.4.5 5-(2-((4aR,7aS)-diHydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5e)



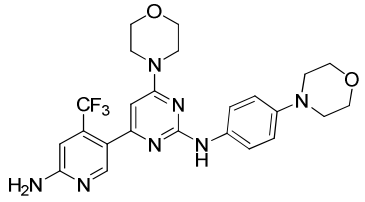
Yield 15.05%. HPLC purity 95.60% (Chiralcel OJ-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 15.16 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{20}H_{24}F_3N_6O_3]^+$: 453.1856, found: 453.1838; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, *J* = 4.5 Hz, 1H), 6.75 (d, *J* = 4.5 Hz, 1H), 5.94 (d, *J* = 4.9 Hz, 1H), 4.84 (s, 2H), 4.25 (d, *J* = 3.9 Hz, 2H), 3.94-3.55 (m, 16H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.0, 162.7, 160.3, 158.7, 150.9, 138.4, 124.4, 121.5, 105.3, 92.4, 73.3, 67.2, 62.9, 47.4, 44.5.

2.4.6 5-(2-(4-(Methylsulfonyl)piperazin-1-yl)-6-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5f)



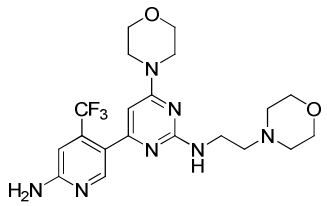
Yield 14.54%. HPLC purity 97.34% (Chiralpak AD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 25.56 min). HRMS (ESI): *m/z* $[M-H]^-$ calcd. for $[C_{19}H_{23}F_3N_7O_3S]^-$: 486.1507, found: 486.1498; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.23 (s, 1H), 6.79 (s, 1H), 5.98 (s, 1H), 4.94 (s, 2H), 3.99-3.89 (m, 4H), 3.84-3.74 (m, 4H), 3.66-3.53 (m, 4H), 3.31-3.20 (m, 4H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.3, 162.9, 160.9, 158.8, 150.7, 144.3, 137.7, 124.1, 105.4, 92.7, 66.6, 45.8, 44.3, 43.6, 34.3.

2.4.7 4-(6-Amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholino-N-(4-morpholinophenyl)pyrimidin-2-amine (5g)



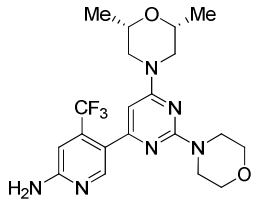
Yield 9.50%. HPLC purity 98.96% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 20.80 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{27}F_3N_7O_2]^+$: 502.2173, found: 502.2163; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 7.47 (d, *J* = 7.7 Hz, 2H), 6.92-6.85 (m, 3H), 6.76 (s, 1H), 6.06 (s, 1H), 4.84 (s, 2H), 3.88-3.83 (m, 4H), 3.81-3.76 (m, 4H), 3.62 (d, *J* = 4.0 Hz, 4H), 3.13-3.07 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.3, 163.0, 159.6, 158.7, 151.0, 146.8, 137.7, 137.3, 133.1, 123.9, 120.8, 116.6, 104.8, 94.7, 67.0, 66.7, 50.3, 44.4.

2.4.8 4-(6-Amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholino-N-(2-morpholinoethyl)pyrimidin-2-amine (5h)



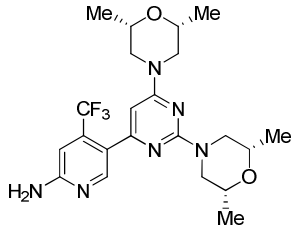
Yield 8.41%. HPLC purity 98.57% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 11.40 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{20}H_{27}F_3N_7O_2]^+$: 454.2173, found: 454.2142; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (s, 1H), 6.75 (s, 1H), 5.94 (s, 1H), 5.37 (s, 1H), 4.79 (s, 2H), 3.82-3.65 (m, 8H), 3.63-3.56 (m, 4H), 3.50 (dd, *J* = 11.4, 5.7 Hz, 2H), 2.56 (t, *J* = 6.0 Hz, 2H), 2.47 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.2, 163.0, 161.8, 158.6, 150.8, 137.7, 131.6, 124.1, 105.0, 93.1, 67.0, 66.6, 57.6, 53.5, 44.2, 37.7.

2.4.9 5-(6-((2S,6R)-2,6-diMethylmorpholino)-2-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5i)



Yield 14.30%. HPLC purity 96.30% (Chiralcel OJ-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 7.91 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{20}H_{26}F_3N_6O_2]^+$: 439.2064, found: 439.2072; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 6.77 (s, 1H), 5.96 (s, 1H), 4.84 (s, 2H), 4.23-4.04 (m, 2H), 3.87-3.57 (m, 10H), 2.66-2.51 (m, 2H), 1.25 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.8, 161.5, 158.8, 150.9, 138.0, 137.6, 124.4, 121.5, 105.2, 92.7, 71.7, 67.2, 50.0, 44.5, 18.9.

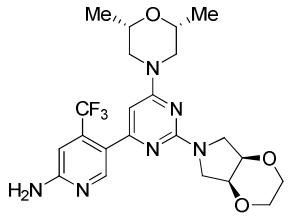
2.4.10 5-(2,6-bis((2S,6R)-2,6-diMethylmorpholino)pyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5j)



Yield 5.35%. HPLC purity 97.82% (Chiralcel OJ-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 7.22 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{22}H_{30}F_3N_6O_2]^+$: 467.2377, found: 467.2308; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 6.78 (s, 1H), 5.94 (s, 1H), 4.80 (s, 2H), 4.54 (d, *J* = 12.8 Hz, 2H), 4.12 (d, *J* = 12.2 Hz, 2H), 3.74-3.58 (m, 4H), 2.68-2.46 (m, 4H), 1.25 (dd, *J* = 10.7, 6.2 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.9, 162.7, 161.2, 158.7, 150.9, 138.1, 131.9, 124.5, 105.0, 92.4, 71.7, 49.7, 18.9.

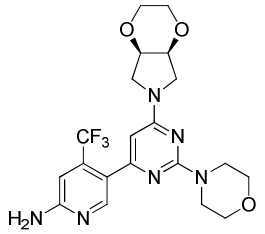
2.4.11 5-(2-((4aR,7aS)-diHydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-((2R,6S)-2,6-dimethyl

morpholino)pyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5k)



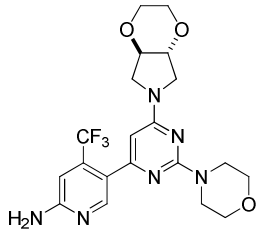
Yield 22.42%. HPLC purity 98.35% (Chiralcel OJ-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 9.20 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{22}H_{28}F_3N_6O_3]^+$: 481.2170, found: 481.2149; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, *J* = 4.0 Hz, 1H), 6.77 (d, *J* = 4.0 Hz, 1H), 5.93 (d, *J* = 4.3 Hz, 1H), 4.78 (s, 2H), 4.34-3.97 (m, 4H), 3.96-3.55 (m, 10H), 2.56 (dd, *J* = 16.2, 7.3 Hz, 2H), 1.29-1.17 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.7, 162.6, 160.4, 158.8, 151.0, 138.1, 124.8, 121.2, 105.3, 92.4, 73.3, 71.7, 62.6, 49.7, 46.0, 19.3.

2.4.12 5-(6-((4aR,7aS)-diHydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-2-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5l)



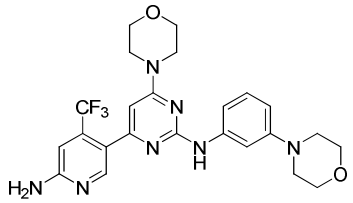
Yield 23.35%. HPLC purity 95.61% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 11.40 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{20}H_{24}F_3N_6O_3]^+$: 453.1856, found: 453.1876; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.25 (s, 1H), 6.76 (s, 1H), 5.95 (s, 1H), 4.82 (s, 2H), 4.01 (s, 2H), 3.87 (s, 2H), 3.80-3.67 (m, 6H), 3.64-3.52 (m, 5H), 3.26 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.6, 159.1, 154.3, 151.0, 150.1, 127.0, 124.4, 109.8, 105.0, 93.0, 72.7, 67.1, 62.9, 46.8, 44.5.

2.4.13 (±)-5-(6-((4aR,7aR)-diHydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-2-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5m)



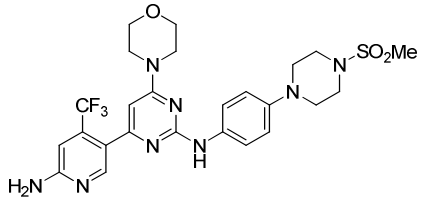
Yield 10.44%. HPLC purity 97.02% (Chiralcel OJ-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 14.03 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{20}H_{24}F_3N_6O_3]^+$: 453.1856, found: 453.1836; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 6.77 (s, 1H), 5.76 (s, 1H), 4.81 (s, 2H), 3.88 (s, 4H), 3.81-3.58 (m, 12H), 3.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.1, 161.5, 161.3, 158.6, 151.0, 137.9, 124.3, 120.3, 105.0, 92.7, 78.0, 67.3, 67.0, 46.0, 44.3.

2.4.14 4-(6-Amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholino-N-(3-morpholinophenyl)pyrimidin-2-amine (5n)



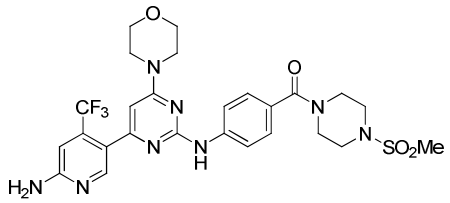
Yield 21.83%. HPLC purity 99.39% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 19.08 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{27}F_3N_7O_2]^+$: 502.2173, found: 502.2203; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.36 (s, 1H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.09-6.97 (m, 2H), 6.76 (s, 1H), 6.62-6.53 (m, 1H), 6.10 (s, 1H), 4.86 (s, 2H), 3.88-3.75 (m, 8H), 3.65 (s, 4H), 3.21-3.09 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.1, 162.8, 159.4, 158.9, 151.9, 150.9, 141.0, 137.6, 129.4, 123.5, 121.4, 111.1, 109.7, 106.7, 104.7, 94.9, 67.0, 66.5, 49.5, 44.5.

2.4.15 4-(6-Amino-4-(trifluoromethyl)pyridin-3-yl)-N-(4-(4-(methylsulfonyl)piperazin-1-yl)phenyl)-6-morpholinopyrimidin-2-amine (5o)



Yield 19.33%. HPLC purity 98.50% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 8.21 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{25}H_{30}F_3N_8O_3S]^+$: 579.2108, found: 579.2132; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.85 (s, 1H), 8.09 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.78 (s, 1H), 6.67 (s, 2H), 6.21 (s, 1H), 3.66 (s, 4H), 3.57 (s, 4H), 3.21 (s, 4H), 3.11 (s, 4H), 2.90 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 162.9, 162.7, 160.1, 159.2, 150.5, 145.0, 135.3, 134.2, 133.7, 121.0, 120.0, 116.8, 103.8, 94.1, 66.0, 49.2, 45.6, 44.0, 34.0.

2.4.16 (4-((4-(6-Amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholinopyrimidin-2-yl)amino)phenyl)(4-(methyl sulfonyl)piperazin-1-yl)methanone (5p)



Yield 19.80%. HPLC purity 99.39% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 19.08 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{26}H_{30}F_3N_8O_4S]^+$: 607.2057, found: 607.2049; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.78 (s, 1H), 6.16 (s, 1H), 4.89 (s, 2H), 3.79 (dd, *J* =

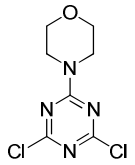
14.2, 9.1 Hz, 8H), 3.65 (d, *J* = 4.5 Hz, 4H), 3.24 (s, 4H), 2.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.8, 163.1, 162.9, 159.0, 150.9, 142.2, 128.5, 127.3, 124.3, 123.3, 121.5, 118.3, 104.9, 100.1, 95.7, 66.5, 45.9, 44.5, 34.8.

2.5 General procedure for the preparation of 2-substituted-4,6-dichloro-1,3,5-triazines 9a-b

To a solution of DIPEA (1.0 equiv.) and morpholine (1.0 equiv.) in CH_2Cl_2 (20 mL) was added 2,4,6-trichloro-1,3,5-triazine **8** (1.1 equiv.) in CH_2Cl_2 (20 mL) at -5 ^{o}C slowly. The mixture was stirred at -5 ^{o}C for 1 h and 0 ^{o}C overnight. The solution was diluted with CH_2Cl_2 (50 mL), washed with 1M HCl (50 mL×2） and brine (50 mL×1) in turn, dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography (PE/EtOAc = 10/1 to 5/1) to afford **9a** as white solid in 59.74% yield.

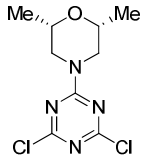
Compound **9b** was prepared following the similar procedure mentioned above.

2.5.1 4-(4,6-diChloro-1,3,5-triazin-2-yl)morpholine (9a)[9]



Yield 59.74%. ESI-MS (*m/z*): 235.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.97-3.80 (m, 4H), 3.80-3.65 (m, 4H).

2.5.2 (2S,6R)-4-(4,6-diChloro-1,3,5-triazin-2-yl)-2,6-dimethylmorpholine (9b)



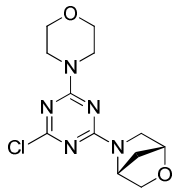
Yield 74.42%. ESI-MS (*m/z*): 263.10 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.56 (d, *J* = 13.1 Hz, 2H), 3.59 (m, 2H), 2.67 (dd, *J* = 13.3, 10.8 Hz, 2H), 1.25 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.7, 164.0, 71.6, 49.3, 18.7.

2.6 General procedure for the preparation of 2-chloro-4,6-disubstituted-1,3,5-triazines 10a-e

To a solution of 2-substituted-4,6-dichloro-1,3,5-triazine **10a** (1.0 equiv.) in THF (10 mL) was added (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane (**28**, 1.0 equiv.) and K_2CO_3 (1.5 equiv.). The mixture was stirred at room temperature overnight. Then the solvent was removed and the residue was dissolved in EtOAc (50 mL). The solution was washed with H_2O (50 mL) and brine (50 mL) in turn, dried over Na_2SO_4. The organic solvent was removed under reduced pressure, the residue was purified by column chromatography (PE/EtOAc = 5/1) to afford **10a** as white solid in 84.46% yield.

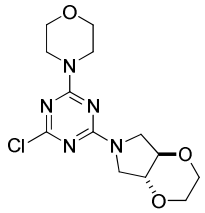
Compounds **10b-e** were prepared following the similar procedure mentioned above.

2.6.1 (1R,4R)-5-(4-Chloro-6-morpholino-1,3,5-triazin-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane (10a)



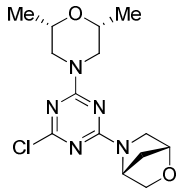
Yield 84.46%. ESI-MS (*m/z*): 298.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.02 (d, *J* = 35.7 Hz, 1H), 4.67 (s, 1H), 3.94-3.64 (m, 10H), 3.52 (dt, *J* = 27.2, 11.2 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.1, 164.6, 163.3, 76.1, 73.6, 66.8, 56.8, 55.2, 43.8, 36.7.

2.6.2 (±)-(4aR,7aR)-6-(4-Chloro-6-morpholino-1,3,5-triazin-2-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (10b)



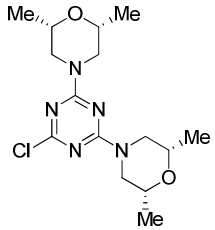
Yield 82.23%. ESI-MS (*m/z*): 328.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.08-3.41 (m, 16H), 3.31-3.14 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.2, 164.2, 163.8, 77.8, 67.2, 66.6, 46.2, 43.8.

2.6.3 (1R,4R)-5-(4-Chloro-6-((2S,6R)-2,6-dimethylmorpholino)-1,3,5-triazin-2-yl)-2-oxa-5-azabicyclo[2.2.1] heptane (10c)



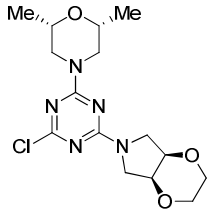
Yield 83.04%. ESI-MS (*m/z*): 326.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.01 (d, *J* = 28.1 Hz, 1H), 4.67 (s, 1H), 4.51 (s, 2H), 3.84 (s, 2H), 3.65-3.39 (m, 4H), 2.68-2.42 (m, 2H), 2.02-1.80 (m, 2H), 1.30-1.05 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.4, 164.2, 163.3, 76.1, 74.0, 71.7, 56.8, 55.2, 48.7, 36.6, 18.7.

2.6.4 (2S,2'S,6R,6'R)-4,4'-(6-Chloro-1,3,5-triazine-2,4-diyl)bis(2,6-dimethylmorpholine) (10d)



Yield 76.53%. ESI-MS (*m/z*): 342.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.48 (dd, *J* = 36.4, 12.6 Hz, 4H), 3.57 (s, 4H), 2.56 (t, *J* = 11.9 Hz, 4H), 1.23 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.5, 164.2, 71.6, 48.8, 18.8.

2.6.5 (4aR,7aS)-6-(4-Chloro-6-((2S,6R)-2,6-dimethylmorpholino)-1,3,5-triazin-2-yl)hexahydro-2H-[1,4] dioxino[2,3-c]pyrrole (10e)

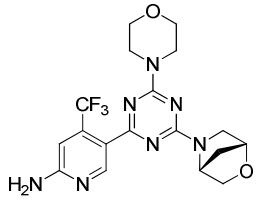


Yield 88.73%. ESI-MS (*m/z*): 356.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.52 (d, *J* = 13.3 Hz, 2H), 4.23 (s, 2H), 3.92-3.72 (m, 4H), 3.72-3.49 (m, 6H), 2.56 (t, *J* = 11.4 Hz, 2H), 1.23 (d, *J* = 5.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.2, 163.9, 163.7, 72.6, 71.4, 62.0, 48.8, 47.1, 18.7.

2.7 General procedure for the preparation of 2,4,6-trisubstituted-1,3,5-triazines 11a-e

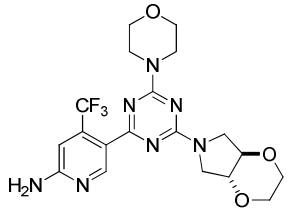
Compounds **11a-e** were prepared from **10a-e** following the similar procedure for **5a-m.**

2.7.1 5-(4-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-6-morpholino-1,3,5-triazin-2-yl)-4-(trifluoro methyl)pyridin-2-amine (11a)



Yield 16.85%. HPLC purity 95.32% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 10.96 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{18}H_{21}F_3N_7O_2]^+$: 424.1703, found: 424.1692; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (s, 1H), 6.77 (s, 1H), 5.06 (d, *J* = 35.4 Hz, 1H), 4.95 (s, 2H), 4.68 (s, 1H), 3.93-3.46 (m, 12H), 1.92 (q, *J* = 10.0 Hz, 1H), 1.84 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.5, 164.6, 163.6, 159.4, 152.6, 138.4, 122.5, 121.5, 105.3, 76.3, 74.1, 66.8, 56.6, 54.9, 43.6, 36.6.

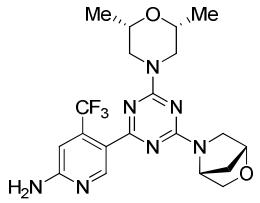
2.7.2 (±)-5-(4-((4aR,7aR)-dihydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (11b)



Yield 7.80%. HPLC purity 95.72% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, *t* = 12.72 min). ESI-MS (*m/z*): 454.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 6.77 (s, 1H), 4.90 (s, 2H), 4.16-3.60 (m,

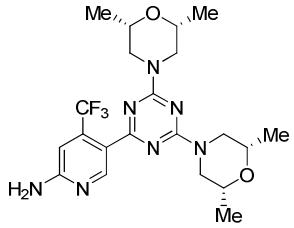
16H), 3.26 (dt, J = 14.9, 10.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.7, 164.5, 163.9, 159.8, 152.7, 138.1, 122.3, 105.3, 99.7, 78.0, 67.3, 66.8, 45.8, 43.6.

2.7.3 5-(4-((1R,4R)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-6-((2S,6R)-2,6-dimethylmorpholino)-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (11c)



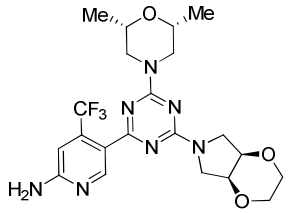
Yield 20.05%. HPLC purity 95.80% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, t = 8.95 min). HRMS (ESI): m/z $[M+H]^+$ calcd. for $[C_{20}H_{24}F_3N_7O_2]^+$: 452.2016, found: 452.2020; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (s, 1H), 6.77 (s, 1H), 5.07 (d, J = 27.8 Hz, 1H), 4.95 (s, 2H), 4.68 (s, 2H), 4.61 (s, 1H), 3.87 (d, J = 11.9 Hz, 2H), 3.69-3.49 (m, 4H), 2.56 (t, J = 11.8 Hz, 2H), 1.97-1.89 (m, 2H), 1.23 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.2, 163.9, 163.3, 159.5, 152.4, 127.3, 122.0, 105.6, 100.0, 74.0, 71.6, 56.4, 55.0, 48.6, 36.5, 30.9, 18.7.

2.7.4 5-(4,6-bis((2S,6R)-2,6-diMethylmorpholino)-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (11d)



Yield 10.10%. HPLC purity 95.54% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, t = 7.17 min). HRMS (ESI): m/z $[M+H]^+$ calcd. for $[C_{21}H_{29}F_3N_7O_2]^+$: 468.2329, found: 468.2312; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (s, 1H), 6.78 (s, 1H), 4.91 (d, J = 9.8 Hz, 2H), 4.62 (d, J = 54.7 Hz, 4H), 3.61 (s, 4H), 2.69-2.47 (m, 4H), 1.24(s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.0, 164.7, 159.5, 152.7, 138.1, 124.3, 122.3, 105.3, 71.7, 48.8, 19.0.

2.7.5 5-(4-((2S,6R)-2,6-diMethylmorpholino)-6-((4aR,7aS)-tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (11e)



Yield 13.14%. HPLC purity 98.35% (Chiralcel OJ-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, t = 9.20 min). HRMS (ESI): m/z $[M+H]^+$ calcd. for $[C_{21}H_{27}F_3N_7O_3]^+$: 482.2122, found: 482.2120; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (s, 1H), 6.78 (s, 1H), 4.85 (s, 2H), 4.26 (s, 2H), 4.00-3.80 (m, 6H), 3.72-3.53 (m, 6H), 2.57 (t, J = 13.0 Hz, 2H), 1.29-1.18 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.7, 164.0, 163.8, 159.5, 152.4, 146.0, 122.3, 112.0,

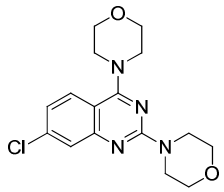
105.3, 72.6, 71.4, 62.0, 48.8, 30.7, 19.0.

2.8 General procedure for the preparation of 7-chloro-2,4-disubstitutedquinazolines 17a-b

To a solution of **16** (1.0 equiv.) in DMF (10 mL) was added DIPEA (2.5 equiv.) and NaI (2.2 equiv.), followed by the addition of morpholine (2.5 equiv.). The mixture was heated to 80 □ for 8 h, then cooled to rt and diluted with EtOAc (50 mL). The solution was washed with H_2O (50 mL×5) and brine (50 mL) in turn, dried over Na_2SO_4. The organic solvent was removed under reduced pressure, the residue was purified by column chromatography (PE/EtOAc = 5/1) to afford **17a** as yellow solid in 66.76% yield.

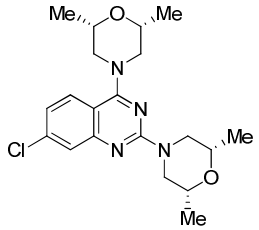
Compound **17b** was prepared following the similar procedure mentioned above.

2.8.1 4,4'-(7-Chloroquinazoline-2,4-diyl)dimorpholine (17a)



Yield 66.76%. ESI-MS (*m/z*): 335.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.01 (dd, *J* = 8.8, 1.7 Hz, 1H), 3.90-3.83 (m, 8H), 3.80-3.74 (m, 4H), 3.66-61 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.4, 158.8, 155.3, 138.6, 126.2, 125.4, 121.5, 110.3, 67.0, 66.6, 50.4, 44.5.

2.8.2 (2R,2'R,6S,6'S,)-4,4'-(7-Chloroquinazoline-2,4-diyl)bis(2,6-dimethylmorpholine) (17b)

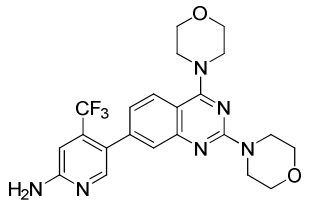


Yield 79.46%. ESI-MS (*m/z*): 391.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.00 (dd, *J* = 8.8, 1.9 Hz, 1H), 4.64 (d, *J* = 12.8 Hz, 2H), 3.98 (d, *J* = 13.0 Hz, 2H), 3.90-78 (m, 2H), 3.71-3.59 (m, 2H), 2.84 (dd, *J* = 12.7, 10.8 Hz, 2H), 2.61 (dd, *J* = 12.9, 10.8 Hz, 2H), 1.26 (dd, *J* = 13.8, 6.2 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.3, 158.4, 155.5, 136.7, 126.4, 125.4, 121.5, 110.5, 71.9, 71.5, 55.4, 49.6, 18.8.

2.9 General procedure for the preparation of 5-(2,4-disubstitutedquinazolin-7-yl)-4-(trifluoromethyl)pyridin-2-amines 18a-b

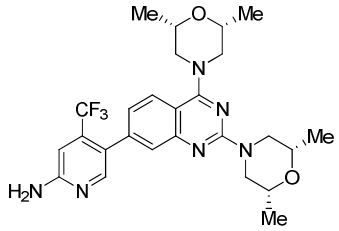
Compounds **18a**-**e** were prepared from **17a**-**b** following the similar procedure for **5a**.

2.9.1 5-(2,4-diMorpholinoquinazolin-7-yl)-4-(trifluoromethyl)pyridin-2-amine (18a)



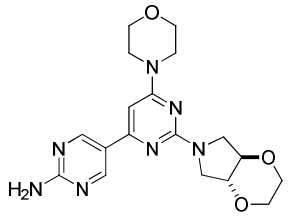
Yield 31.64%. HPLC purity 98.65% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, t = 14.84 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{22}H_{24}F_3N_6O_2]^+$: 461.1907, found: 461.1898; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.80 (s, 1H), 4.81 (s, 2H), 3.99-3.60 (m, 16H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.7, 158.6, 158.1, 153.9, 150.8, 141.2, 137.7, 137.3, 127.0, 124.8, 124.6, 122.6, 111.3, 104.7, 67.0, 66.7, 50.3, 44.4.

2.9.2 5-(2,4-bis((2R,6S)-2,6-diMethylmorpholino)quinazolin-7-yl)-4-(trifluoromethyl)pyridin-2-amine (18b)



Yield 18.50%. HPLC purity 97.82% (Chiralcel OJ-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, t = 7.22 min). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{26}H_{32}F_3N_6O_2]^+$: 517.2533, found: 517.2528; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.45 (s, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.80 (s, 1H), 4.82 (s, 2H), 4.66 (d, J = 12.5 Hz, 2H), 4.06 (d, J = 12.9 Hz, 2H), 3.88 (dd, J = 8.6, 6.3 Hz, 2H), 3.67 (dd, J = 8.3, 6.0 Hz, 2H), 2.87 (dd, J = 12.7, 10.8 Hz, 2H), 2.62 (dd, J = 12.9, 10.8 Hz, 2H), 1.26 (t, J = 6.0 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.3, 158.4, 158.1, 154.1, 150.9, 140.9, 137.4, 126.9, 124.8, 124.5, 124.3, 122.6, 111.3, 104.6, 71.9, 71.5, 55.4, 49.7, 19.0, 18.9.

2.10 (±)-2-((4aR,7aR)-dihydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholino-4,5'-bipyrimidin-2'-amine (21)

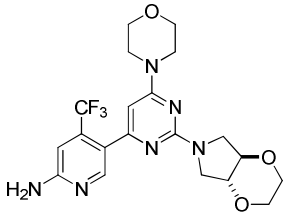


To a mixture of **4d** (0.25 g, 0.77 mmol, 1.0 equiv.), **20** (0.34 g, 1.53 mmol, 2.0 equiv.) and $Pd(dppf)Cl_2•CH_2Cl_2$ (32 mg, 0.038 mmol, 0.05 equiv.) in degassed dioxane (3.6 mL) was added 2 M K_2CO_3 (1.20 mL, 2.40 mmol, 3.0 equiv.). The mixture was heated under microwave to 150 ℃ for 2 h. The solvent was removed and the residue was dissolved in EtOAc (50 mL), washed with H_2O (30 mL×3) and brine (30 mL) in turn, dried over Na_2SO_4. The solvent was removed under reduced pressure, the crude product was first separated by column chromatography (PE/EtOAc = 5/1 to 1/2), then further purified by column chromatography (CH_2Cl_2/MeOH = 50/1)

to give **21** as off-white solid (157 mg, 52.25% yield). HPLC purity 98.95% (Chiralcel OD-H, 0.5 mL/min, hexane/*i*-PrOH = 60/40, t = 20.80 min). HRMS (ESI): m/z $[M+H]^+$ calcd. for $[C_{18}H_{24}N_7O_3]^+$: 386.1935, found: 386.1916; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.93 (d, J = 2.7 Hz, 2H), 6.99 (s, 2H), 6.57 (s, 1H), 3.83 (t, J = 9.1 Hz, 4H), 3.79-3.56 (m, 12H), 3.19-3.08 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 164.1, 163.3, 159.8, 159.3, 156.8, 119.9, 86.4, 78.0, 66.5, 65.9, 45.8, 44.0.

2.11 (-)-5-(2-((4aR,7aR)-diHydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (6)

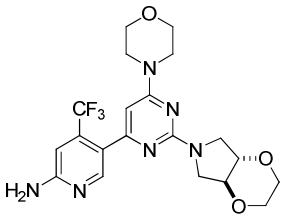
(-)



The title compound was obtained via chiral preparative column (Phenomenex Lux, cellulose-2, 250 ×10 mm, 5 μm). HPLC purity 99.90% (Phenomenex Lux, 3.0 mL/min, MeOH/H_2O = 95/5, t = 11.25 min). HRMS (ESI): m/z $[M+H]^+$ calcd. for $[C_{20}H_{24}F_3N_6O_3]^+$: 453.1856, found: 453.1845; $[a]_D^{30}$ = -34.2 (c = 0.20, $CHCl_3$).

2.12 (+)-5-(2-((4aS,7aS)-diHydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (7)

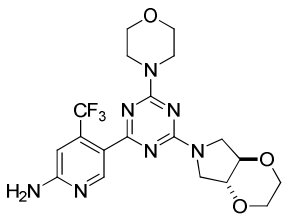
(+)



The title compound was obtained via chiral preparative column (Phenomenex Lux, cellulose-2, 250 ×10 mm, 5 μm). HPLC purity 99.90% (Phenomenex Lux, 3.0 mL/min, MeOH/H_2O = 95/5, t = 12.30 min). HRMS (ESI): m/z $[M+H]^+$ calcd. for $[C_{20}H_{24}F_3N_6O_3]^+$: 453.1856, found: 453.1863; $[a]_D^{30}$ = 46.8 (c = 0.21, $CHCl_3$).

2.13 (-)-5-(4-((4aR,7aR)-dihydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (12)

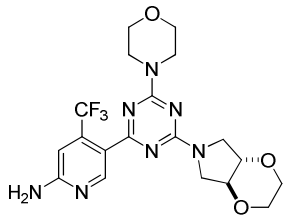
(-)



The title compound was obtained via chiral preparative column (Phenomenex Lux, cellulose-2, 250 ×10 mm, 5 μm). HPLC purity 97.70% (Phenomenex Lux, 3.0 mL/min, MeOH/H_2O = 95/5, *t* = 12.25 min). ESI-MS (*m/z*): 454.2 $[M+H]^+$; $[a]_D^{30}$ = -29.5 (c = 0.21, $CHCl_3$).

2.14 (+)-5-(4-((4aS,7aR)-dihydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (13)

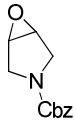
(+)



The title compound was obtained via chiral preparative column (Phenomenex Lux, cellulose-2, 250 ×10 mm, 5 μm). HPLC purity 98.62% (Phenomenex Lux, 3.0 mL/min, MeOH/H_2O = 95/5, *t* = 14.25 min). ESI-MS (*m/z*): 454.2 $[M+H]^+$; $[a]_D^{30}$ = 50.7 (c = 0.22, $CHCl_3$).

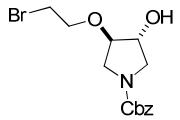
2.15 Preparation of (±)-(4aR,7aR) hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (26)

2.15.1 Benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (23)[10]



To a solution of 3-chlorobenzoperoxoic acid (10.55 g, 61.14 mmol) in CH_2Cl_2 (70 mL) was added benzyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate **22** (10 g, 49.24 mmol) in CH_2Cl_2 (30 mL) dropwise. The mixture was stirred at rt for 16 h, and the formed precipitate was filtered off. Then the solution was washed with saturated $Na_2S_2O_3$ (100 mL×1), $NaHCO_3$ (100 mL×1) and NaCl (100 mL×1) in turn, dried over Na_2SO_4. The solvent was removed under reduced pressure, the residue was further purified by column chromatography (PE/EtOAc = 3/1) to afford **23** (7.39 g, 68.49% yield). ESI-MS (*m/z*): 220.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.41-7.29 (m, 5H), 5.16-5.04 (m, 2H), 3.86 (dd, *J* = 19.1, 12.8 Hz, 2H), 3.73-3.63 (m, 2H), 3.38 (dd, *J* = 12.7, 6.0 Hz, 2H).

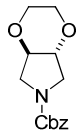
2.15.2 (±)-(3R,4R)-benzyl 3-(2-bromoethoxy)-4-hydroxypyrrolidine-1-carboxylate (24)



To a solution of **23** (3.16 g, 14.42 mmol) in dry CH_2Cl_2 (40 mL) was added 2-bromoethanol (1.97 g, 15.87 mmol) and BF_3•Et_2O (0.22 g, 0.19 mmol) slowly. The mixture was stirred at rt overnight, then diluted with CH_2Cl_2 (30 mL). The solution was washed with H_2O (50 mL) and brine (50 mL) in turn, dried over Na_2SO_4. Then the

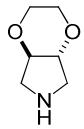
solvent was removed and the residue was purified by column chromatography (PE/EtOAc = 1/2) to give **24** (1.44 g, 29.03% yield). ESI-MS (*m/z*): 344.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, *J* = 3.4 Hz, 5H), 5.09 (s, 2H), 3.80 (d, *J* = 35.3 Hz, 3H), 3.63 (td, *J* = 12.2, 4.4 Hz, 2H), 3.56-3.28 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.7, 137.1, 128.5, 128.0, 127.8, 83.3, 82.5, 73.3, 72.4, 69.4, 66.9, 30.4.

2.15.3 (±)-(4aR,7aR)-benzyl tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrole-6(3H)-carboxylate (25)



A solution of KOH (0.26 g, 4.59 mmol) in absolute ethanol (3 mL) was added to **24** (1.43 g, 4.14 mmol) in ethanol (10 mL). The mixture was refluxed for 6 h, the formed precipitate was filtered off and the cake was washed with EtOAc (50 mL). The organic layers were combined and concentrated to give a residue, which was further purified by column chromatography (PE/EtOAc = 1/1) to afford **25** (0.74 g, 67.27% yield). ESI-MS (*m/z*): 264.2 $[M+H]^+$; LC-MS: 264.1 (M+1); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, *J* = 4.6 Hz, 5H), 5.13 (d, *J* = 3.1 Hz, 2H), 3.92-3.70 (m, 6H), 3.60 (s, 2H), 3.15 (dd, *J* = 9.5, 4.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.2, 136.4, 128.5, 128.1, 128.0, 76.6, 67.5, 61.2, 45.5.

2.15.4 (±)-(4aR,7aR)-hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole (26)



To a solution of **25** (0.30 g, 1.14 mmol) in THF (10 mL) was added 10% Pd/C (0.10 g). The mixture was stirred under H_2 atmosphere at rt for 6 h. Then the catalyst was filtered off, the solvent was removed to give **26**, which was used for next step directly. ESI-MS (*m/z*): 130.1 $[M+H]^+$.

3. Enzyme assays

In this study, the compounds were evaluated in terms of their ability to inhibit class I PI3K enzymes P110α/p85 and p110δ/p85 via the Kinase-Glo Luminescent Kinase Assays, as well as p110β/p85 and p110γ/p101 via the ADP-Glo Luminescent Kinase Assay. PI3K reactions were performed in 50 mM HEPES at pH 7.5 with 1 mM EGTA, 100 mM NaCl, 3 mM $MgCl_2$, 2 mM DTT, and 0.03% CHAPS; all tested compounds were dissolved in 100% DMSO. PIP2 and ATP were used as substrates, and the final reaction volume was 10 μL. To evaluate the PI3Kα inhibitors, 1.65 nM enzyme, 50 μM PIP2, and 25 μM ATP were used for every 10 μL reaction volume with inhibitor concentrations ranging from 0.5 nM to 10 μM. After incubating for 1 h at room temperature, the reactions were quenched by adding 10 μL of Kinase-Glo reagent (5 μL of ADP-Glo reagent for p110β/p85 and p110γ/p101). Raw data were collected from Flexstation program (SnygerMax for p110β/p85 and p110γ/p101) and the IC_{50} values were defined *via* curves that plotted using Graphpad Prism software.

4. Cell proliferation assay

The following cell lines were used in the experiment: K562, HL60, Huh7, MOLT-4, MCF-7, DU145, U937, NCI-N87, HT1080, BGC-823, BEL-7402, A431, A549, Hela, SGC-7901, PANC-1, MDA-MB-231, PC3 and

SK-BR-3. Cells were maintained at 37 ^{o}C in a 5% CO_2 incubator in RPMI1640 (Gibco, Invitrogen) or DMEM (Gibco, Invitrogen) containing 10% fetal bovine serum (Gibco, Invitrogen). Cell proliferation was determined by CCK8 assay (DOjinDo, Japan). Cells were seeded data density of 800-1000 cells/well in 384 well plates and treated with various concentrations of compounds or the solvent control. After incubating for 72 h, CCK8 reagent was added, and absorbance was measured at 450 nm by using Envision 2104 multi-label Reader (PerkinElmer, USA). All the experiments were repeated at least three times. Dose-response curves were plotted using Prism 5.0 (Graph Pad Software Inc., USA) to determine the IC_{50} values.

Cell viability in Figure 7 was assessed by WST-8 assay (Dojindo) according to the manufacturer's instructions. Cells were seeded in the 96-well plate. After different treatment, 10 μL WST-8 solutions were added to each well and cells were incubated at 37 ˚C for 4 h. The absorbance was finally determined at 450 nm.

5. Western blot assay

Suppressive activities of Akt and phospho-Akt (p-Akt, S473) in U937 cells were determined by Western blot. U937 cells were treated with different compounds for 24 h. Cell lysates were clarified by centrifugation at 12,000 rpm for 20 min at 4 ^{o}C, and supernatant was collected. Equal amounts of protein were subjected to SDS-PAGE and transferred to nitrocellulose membranes (Merck Millipore, Billerica, MA, USA). The membrane were blocked and incubated overnight at 4 °C with primary antibodies against p-Akt, Akt (Cell Signaling Technology Corp., Beverly, MA, USA), and β-actin (Santa Cruz Biotechnology, Santa Cruz, CA, USA), followed by incubation with appropriate secondary antibodies. Antibody binding was detected with chemiluminescence reagents (Sigma-Aldrich, St. Louis, MO, USA).

6. Tumor growth in xenografts

MDA-MB-231 cells (10^6) were injected into the right flank of 4-week-old female nude mice (n=5). When the tumor size reached 50 mm^3, mice were randomly distributed into two groups that were treated intragastrically every two days with either a vehicle control or with 30 mg/kg **5d** dissolved in PEG300. The tumor volumes ($A\times B^2/2$; A being the greatest diameter and B being the diameter perpendicular to A) were measured by calipers. Other indicators of general health, such as body weight, feeding behavior, and motor activity, of each animal were also monitored. After administering the drug or vehicle for 19 days, the mice were sacrificed and the tumor xenografts were immediately dissected and weighed. All animal procedures were approved by the Institutional Animal Care and Use Committee of the Sun Yat-sen University Cancer Center.

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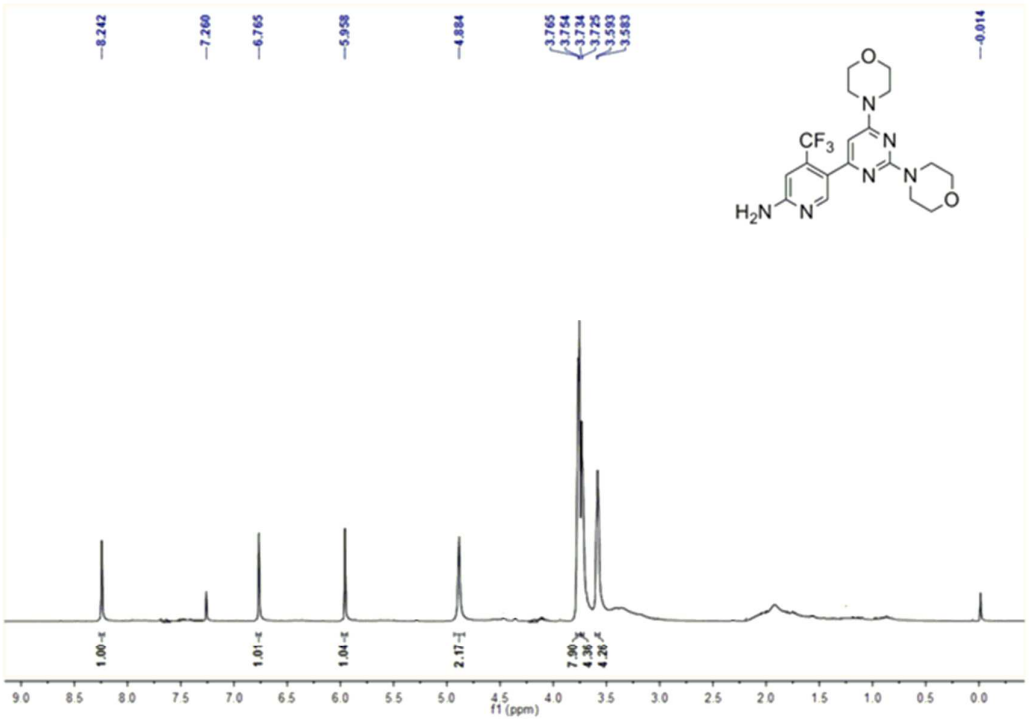
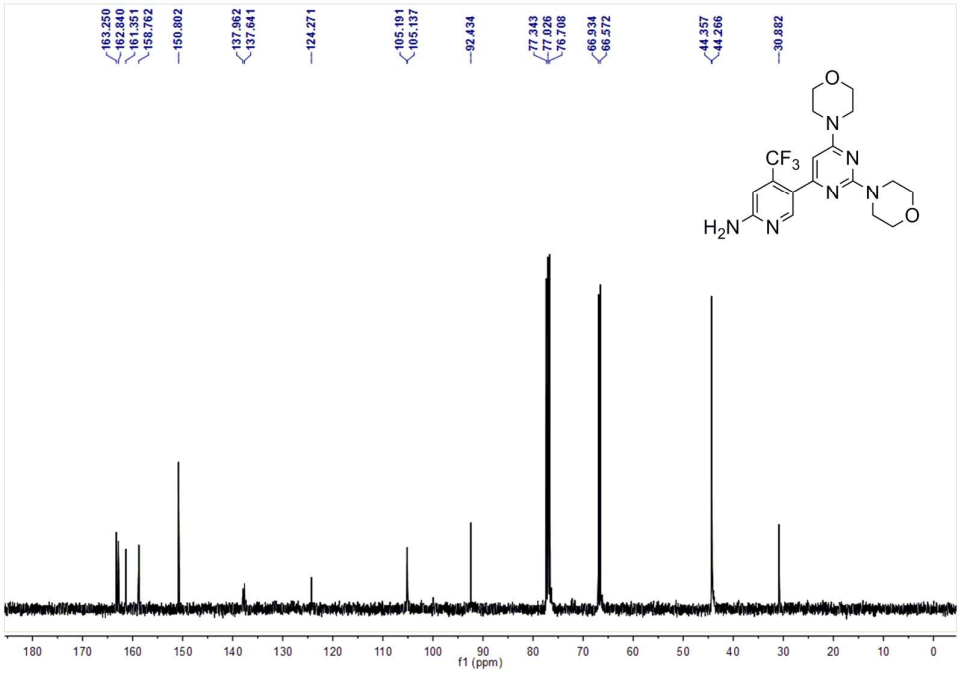
7. ^{1}H NMR and ^{13}C NMR spectra for selected compounds

5-(2,6-diMorpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5a)

^{1}H NMR

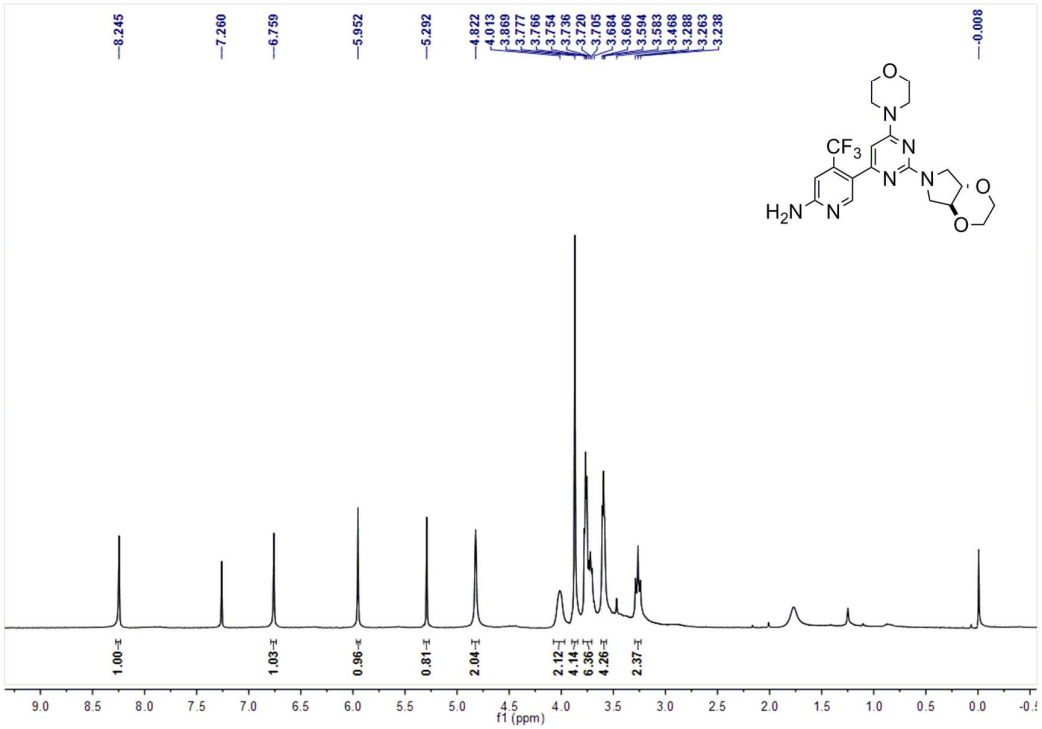


^{13}C NMR

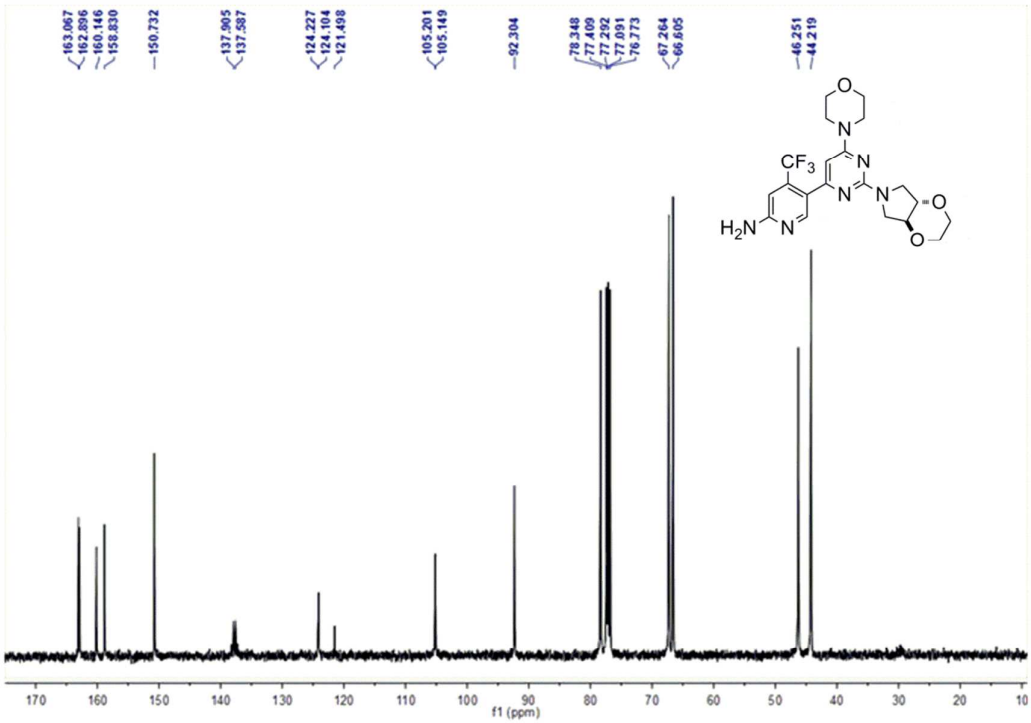


(±)-5-(2-((4aS,7aR)-diHydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5d)

^{1}H NMR

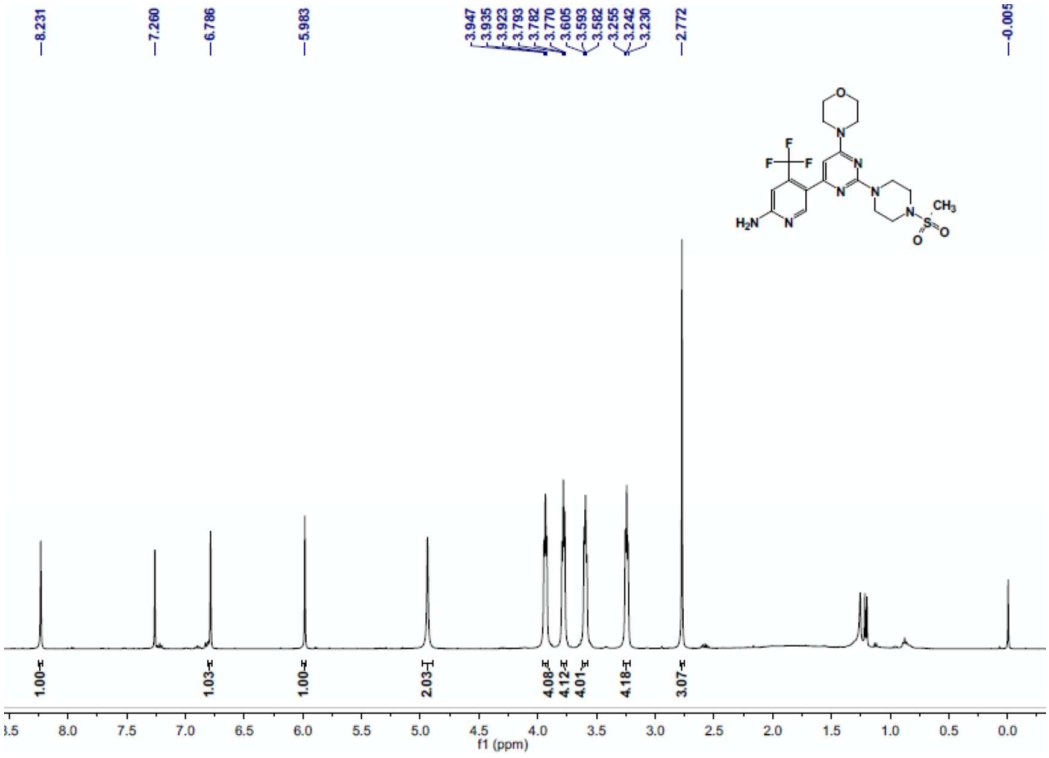


^{13}C NMR

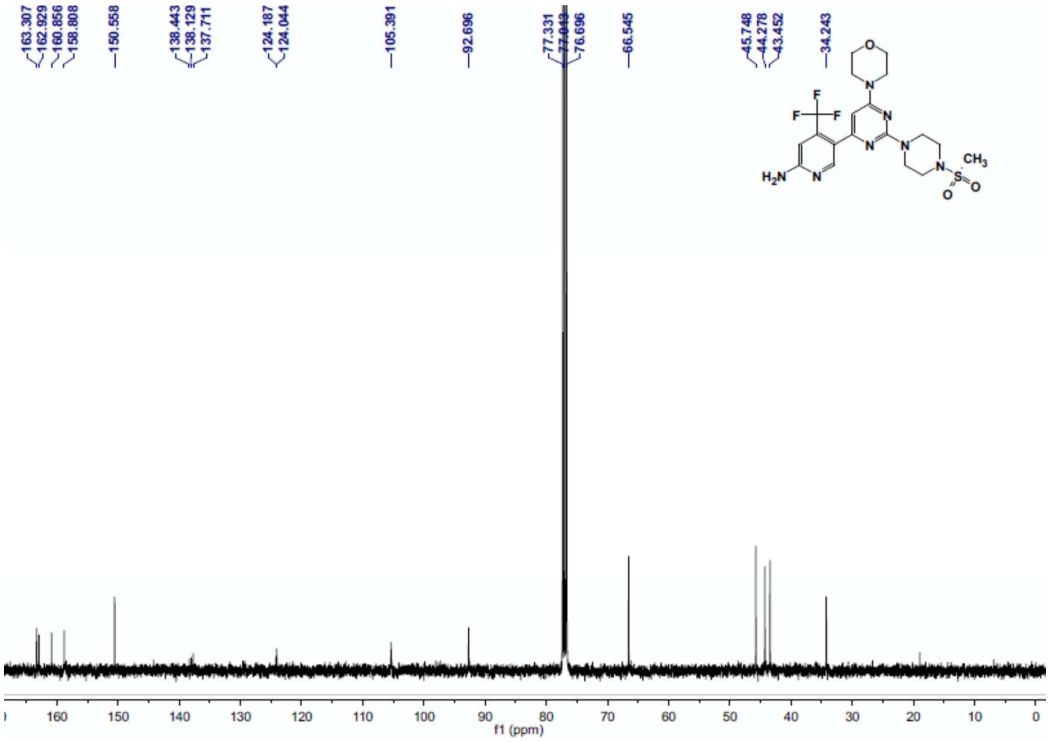


5-(2-(4-(Methylsulfonyl)piperazin-1-yl)-6-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine (5f)

^{1}H NMR

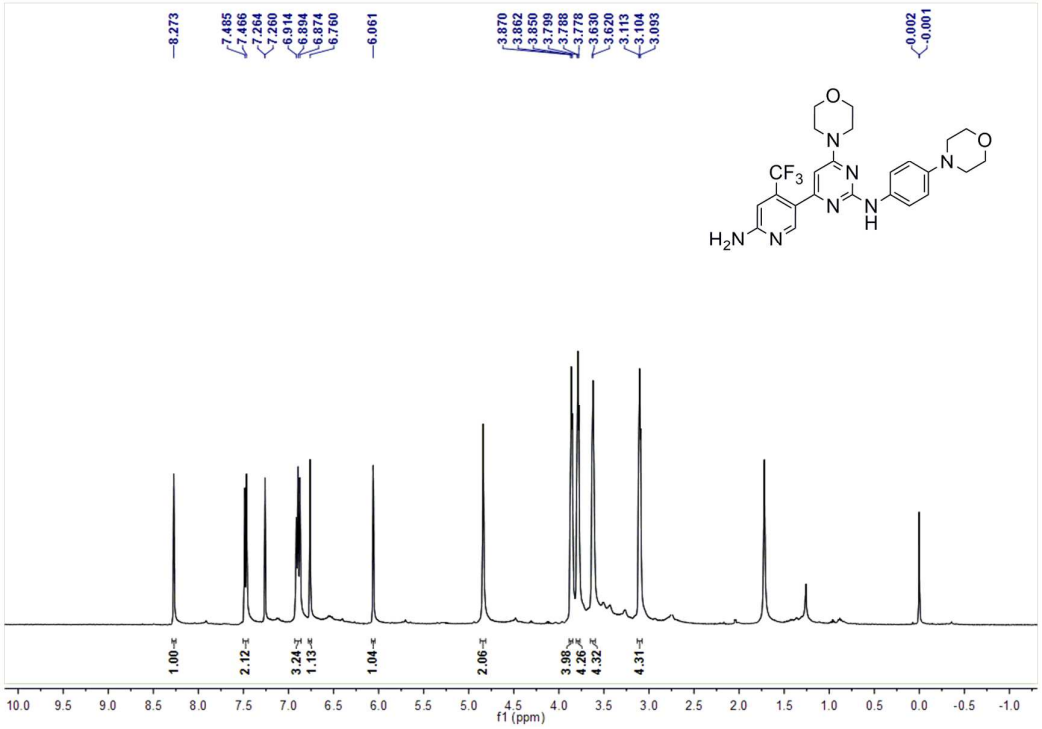


^{13}C NMR

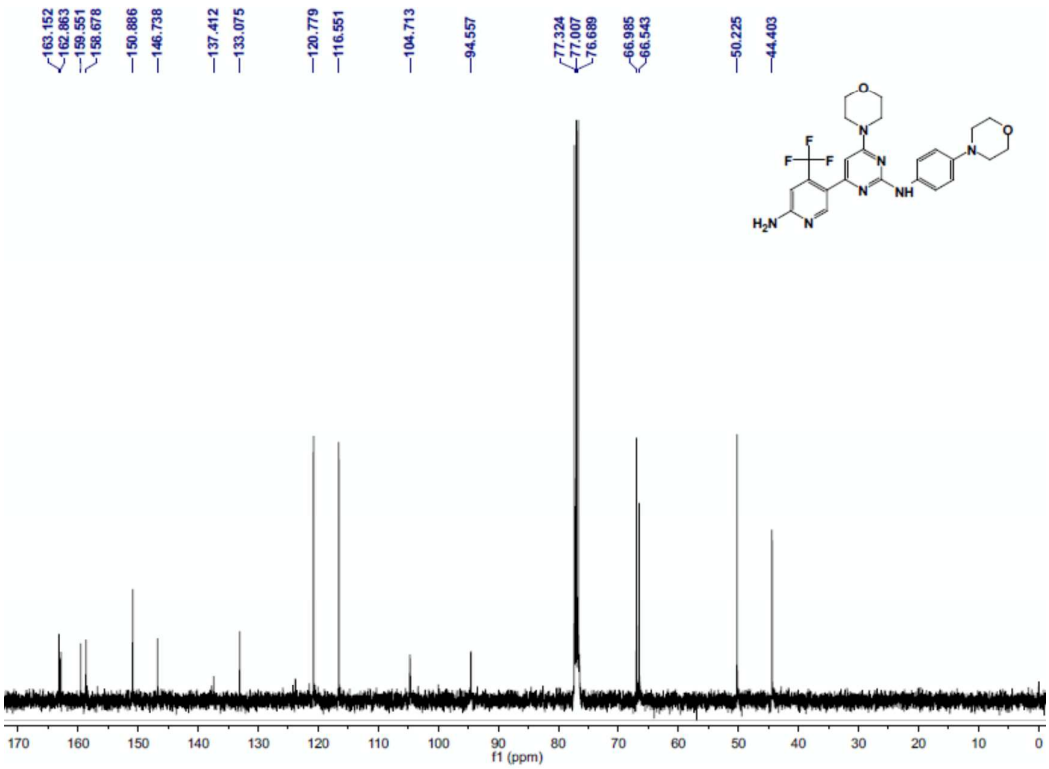


4-(6-Amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholino-N-(4-morpholinophenyl)pyrimidin-2-amine (5g)

^{1}H NMR

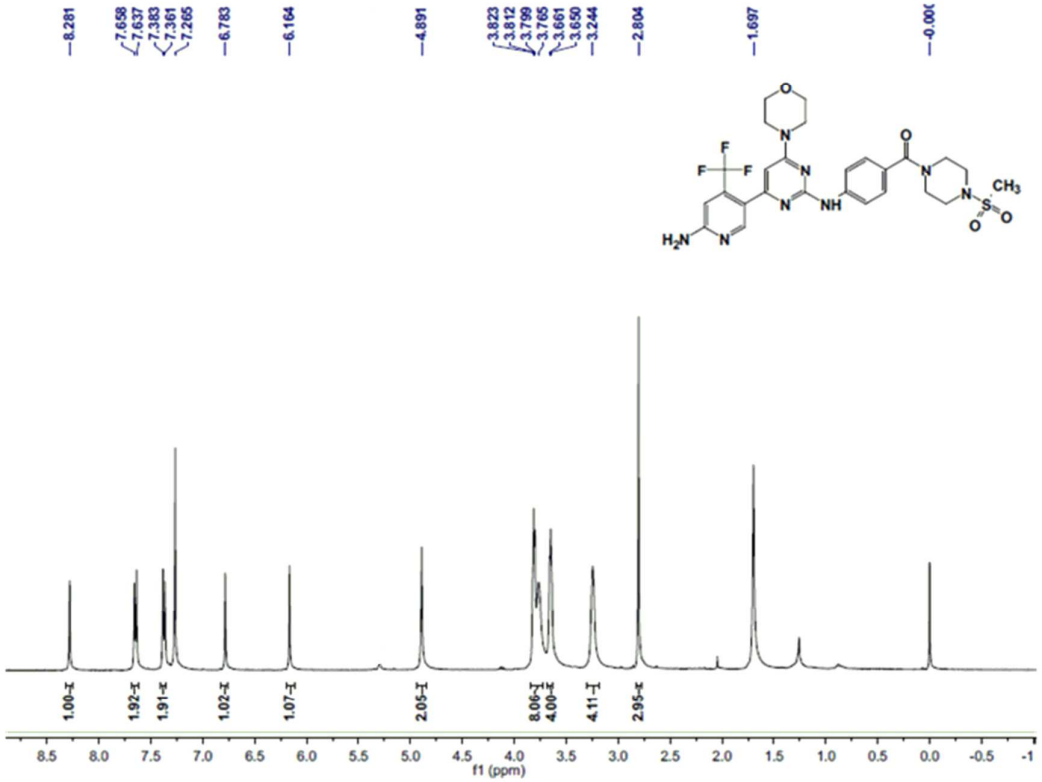


^{13}C NMR

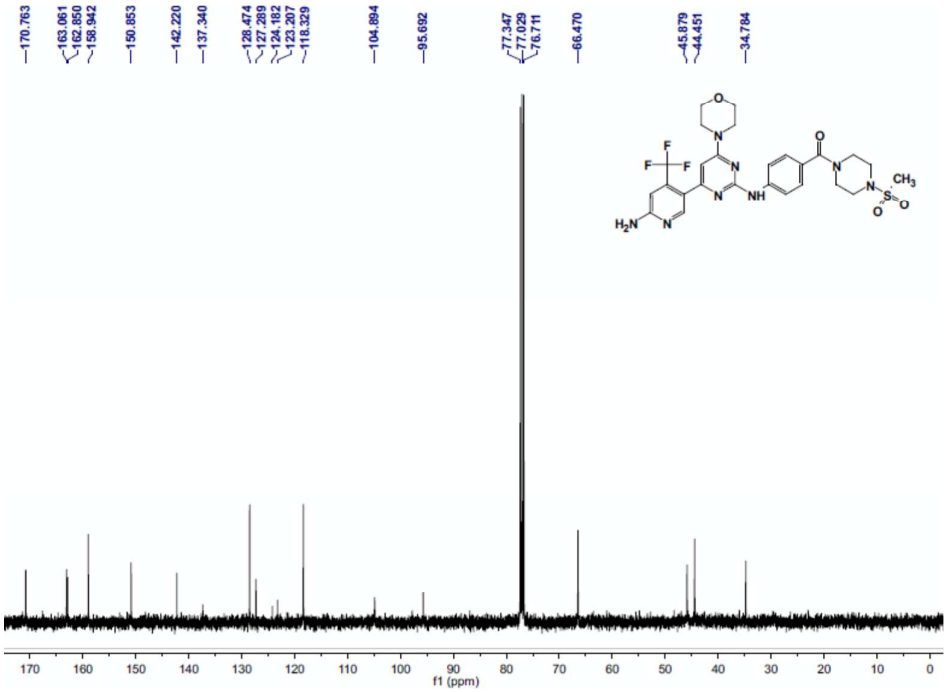


(4-((4-(6-Amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholinopyrimidin-2-yl)amino)phenyl)(4-(methylsulfonyl) piperazin-1-yl)methanone (5p)

^{1}H NMR

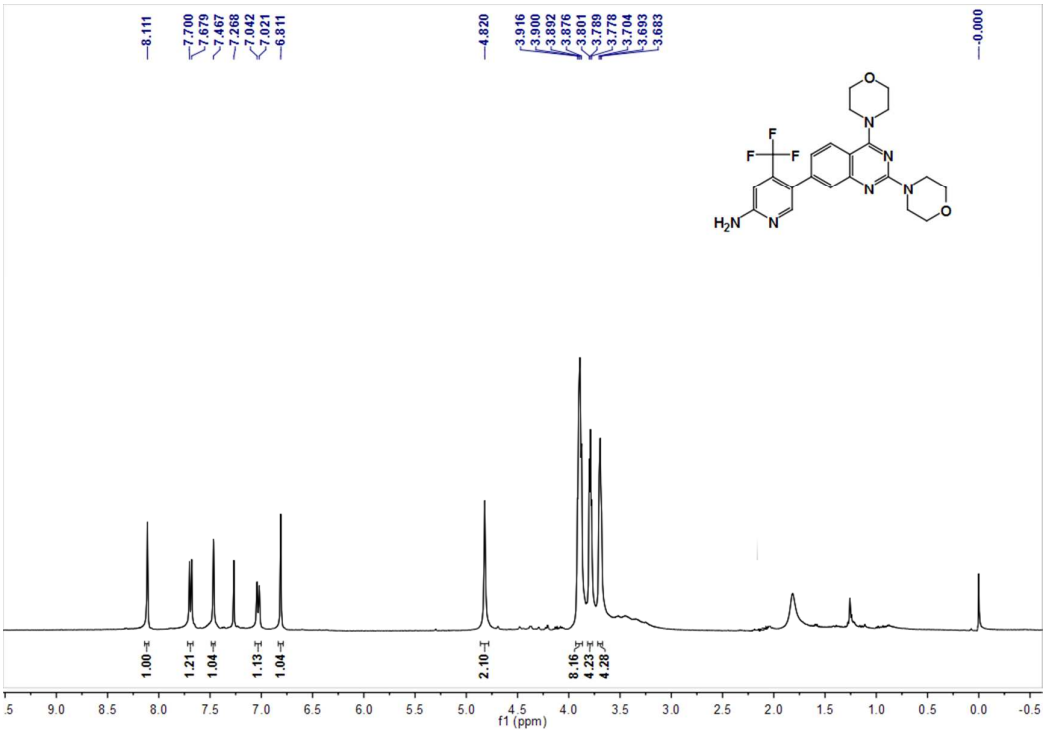


^{13}C NMR

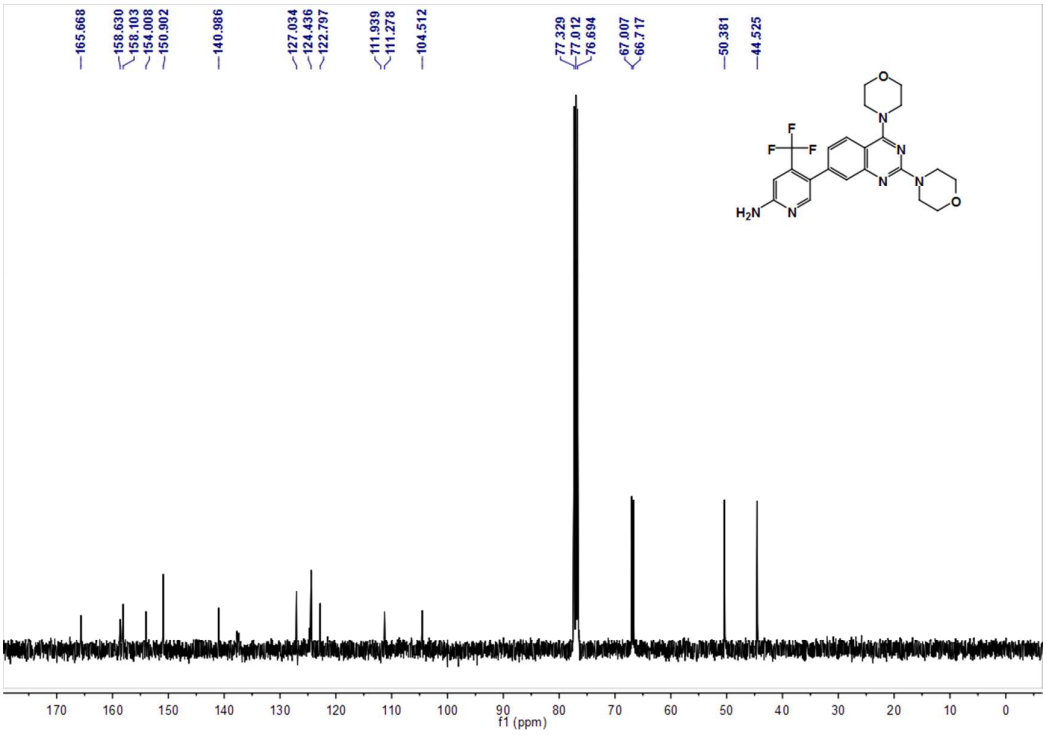


5-(2,4-diMorpholinoquinazolin-7-yl)-4-(trifluoromethyl)pyridin-2-amine (18a)

^{1}H NMR

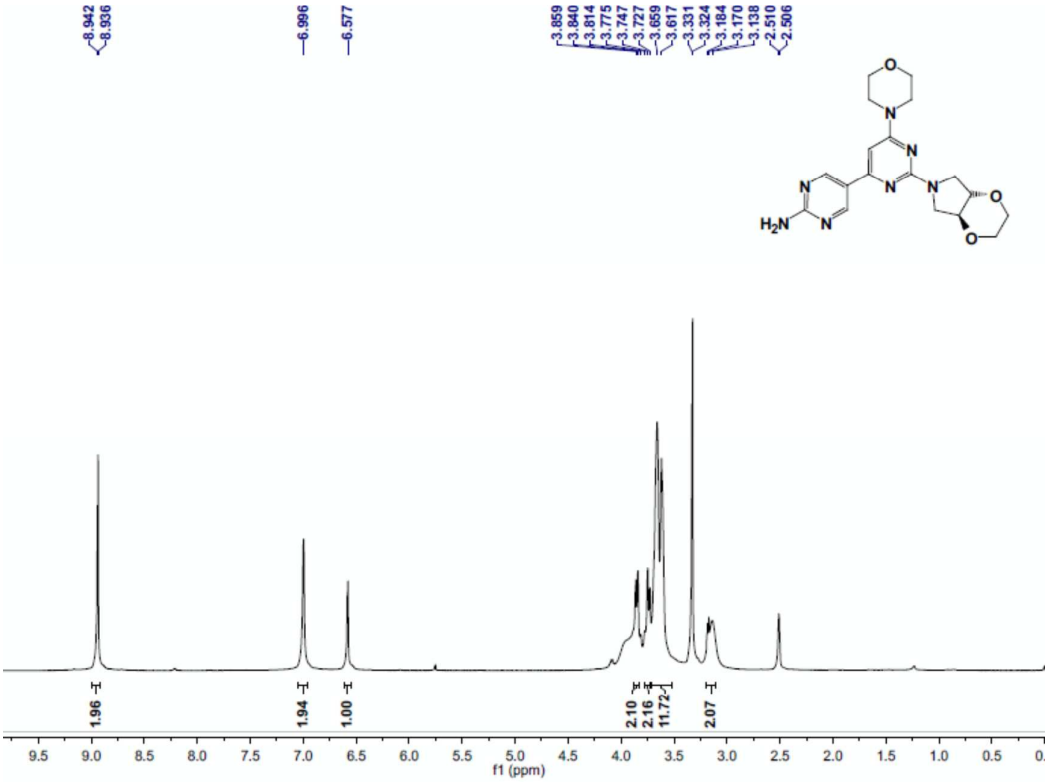


^{13}C NMR



(±)-2-((4aR,7aR)-dihydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H,7H,7aH)-yl)-6-morpholino-4,5'-bipyrimidin-2'-amine (21)

^{1}H NMR



^{13}C NMR