SUPPORTING INFORMATION

Second-generation tricyclic pyrimido-pyrrolo-oxazine mTOR inhibitor with predicted blood-brain barrier permeability

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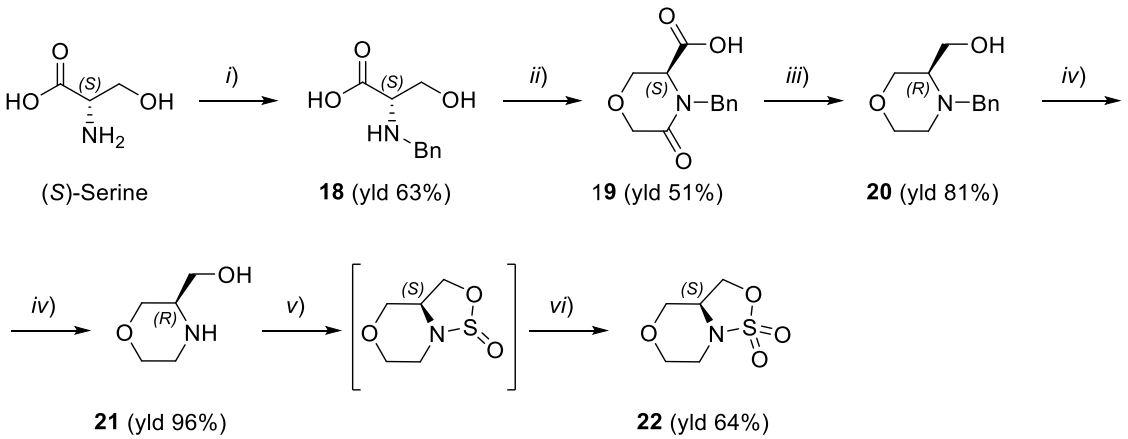
Overview, Summary



Scheme S1. Synthesis of sulfamidate **22**.

Reagents and conditions: (i) 1) benzaldehyde, 2M NaOH, r.t, 30 min; 2) $NaBH_4$, 5 °C → r.t., 1 hr; (ii) 1) chloroacetyl chloride, K_2CO_3, THF / H_2O, 0 °C, 1 hr; 2) NaOH, 5 °C, 2 hrs; (iii) borane-dimethylsulfide complex, Et_3N, THF, 0 °C → 65 °C, 5 hrs; (iv) Pd/C, H_2, 2.8 bar, 48 hrs; (v) thionyl chloride, imidazole, DCM, -5 °C → r.t. → 0 °C, 2 hrs; (vi) ruthenium(IV) oxide hydrate, $NaIO_4$, r.t., o/n. The sulfamidates synthesis is reported in Ref. 1.

Compounds Synthesis and Characterization.

Reagents were purchased at the highest commercial quality from Acros, Sigma-Aldrich or Fluorochem and used without further purification. Solvents were purchased from Acros Organics in AcroSeal® bottles over molecular sieves. Cross coupling reactions were carried out under nitrogen atmosphere in anhydrous solvents, and glassware was oven dried prior to use. Thin layer chromatography (TLC) plates were purchased from Merck KGaA (Polygram SIL / UV254, 0.2 mm silica with fluorescence indicator) and UV light (254 nm) was used to visualize the compounds. Column chromatographic purifications were performed on Merck KGaA silica gel (pore size 60 Å, 230-400 mesh particle size). Alternatively, flash chromatography was performed with Isco CombiFlash Companion systems using prepacked silica gel columns (40−60 μm particle size RediSep). ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer. NMR spectra were obtained in deuterated solvents, such as $CDCl_3$, $(CD_3)_2SO$ or CD_3OD. The chemical shift (δ values) are reported in ppm and corrected to the signal of the deuterated solvents (7.26 ppm (^{1}H NMR) and 77.16 ppm (^{13}C NMR) for $CDCl_3$; 2.50 ppm (^{1}H NMR) and 39.52 ppm (^{13}C NMR) for $(CD_3)_2SO$; and 3.31 ppm (^{1}H NMR) and 49.00 ppm (^{13}C NMR) for CD_3OD). ^{19}F NMR spectra are calibrated relative to $CFCl_3$ (δ = 0 ppm) as external standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), td (triplet of doublets), q (quartet), m (multiplet), br (broadened). Coupling constants, when given, are reported in Hertz (Hz). High resolution mass spectra (HRMS) were recorded on a Bruker maxis 4G, high resolution ESI-QTOF. All analyses were carried out in positive ion mode and in MeOH + 0.1 % formic acid as solvent. Sodium formate was used as calibration standard. MALDI-ToF mass spectra were obtained on a Voyager-De™ Pro measured in *m/z*. The chromatographic purity of final compounds was determined by high performance liquid chromatography (HPLC) analyses on an Ultimate 3000SD System from ThermoFisher with LPG-3400SD pump system, ACC-3000 autosampler and column oven, and DAD-3000 diode array detector. An Acclaim-120 C18 reversed-phase column from ThermoFisher was used as stationary phase. Gradient elution (5:95 for 0.2 min, 5:95 → 100:0 over 10 min, 100:0 for 3 min) of the mobile phase was used at a flow rate of 0.5 ml / min at 40 °C. The mobile phases were consisting in method A of CH_3CN / $MeOH:H_2O_{(10:90)}$ and in method B $CH_3CN:TFA_{(99:1)}$ / $MeOH:H_2O_{(10:90)}$. The purity of all final compounds was higher than 95%.

General Procedure 1

Tricyclic 2-chloropyrimidine precursor (1.0 eq.), boronic acid pinacol ester (1.0 - 1.1 eq.), potassium phosphate (2.0 - 3.0 eq.) and chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (XPhosPdG2, 0.05 eq.) were charged in a flask. Under nitrogen atmosphere, 1,4-dioxane (approx. 1 ml / 0.1 mmol) and deionized water (approx. 1 mL / 0.3 mmol) were

added and the resulting mixture was placed into an oil bath pre-heated at 95 °C and stirred at this temperature for 2 - 15 hours. After completion of the reaction, the mixture was allowed to cool down to room temperature and an aqueous HCl-solution (3 M, 10 eq.) was added. The mixture was stirred at 60 °C for 3 - 15 hours. Then, the mixture was allowed to cool down to room temperature and the pH was adjusted to 10-11 by addition of an aqueous NaOH-solution (2 M). The aqueous layer was separated and extracted with ethyl acetate (3 x). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel.

General Procedure 2

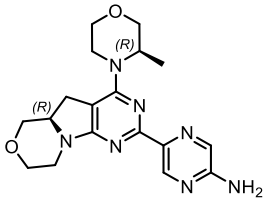
Step 1. Bis(pinacolato)diboron (1.5 eq.), potassium acetate (3.0 eq.), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2$, 0.10 eq.) and the respective bromo derivative (1.0 eq.) were dissolved in absolute 1,4-dioxane (approx. 1 mL / 0.1 mmol) under nitrogen atmosphere. The resulting mixture was heated at 95 °C for 0.5 - 2 hours.

Step 2. Then, the mixture was allowed to cool down to room temperature. Tricyclic 2-chloropyrimidine precursor (1.0 eq.), chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (XPhosPdG2, 0.05 eq.), potassium phosphate (3.0 eq.), and deionized H_2O (approx. 1 mL / 0.3 mmol) were added. The resulting reaction mixture was placed in a preheated oil bath at 95 °C and stirred for 2 - 15 hours.

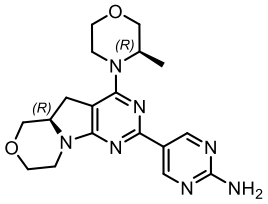
Step 3. After completion of the reaction, the mixture was allowed to cool down to room temperature and an aq. solution of HCl (3 M, 10-20 eq.) was added. The reaction mixture was stirred at 80 °C for 2 hours. The mixture was diluted with deionized H_2O and washed with EtOAc (1 x). The aq. layer was basified to pH = 10 - 11 and then extracted with EtOAc (3 x). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel.

General Procedure 3

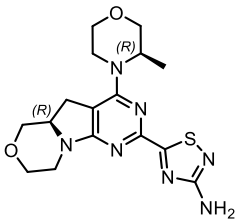
Stannyl derivative **14** (1.0 eq.), 3-bromo-5-chloro-1,2,4-thiadiazole or 3-chloro-6-iodopyridazine (1.0 eq.), CuI (1.0 eq.) and palladium-tetrakis(triphenylphosphine) [$Pd(PPh_3)_4$, 0.1 eq.] were charged in a flask. The system was placed under vacuum and backfilled with nitrogen. 1,4-Dioxane (approx. 1 mL / 0.1 mmol) was added and the reaction mixture was stirred at 90 °C overnight. After completion of the reaction monitored by TLC, a NH_4Cl solution (15%, 15 mL) was added and the aqueous layer was extracted with EtOAc (3x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel.



5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyrazin-2-amine (12b) was prepared according to the literature.[1]

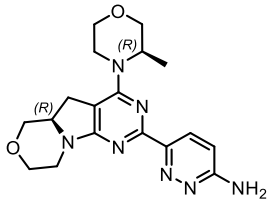


5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyrimidin-2-amine (1) was prepared according to the literature.[1]

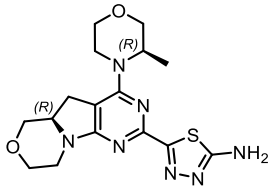


5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,2,4-thiadiazol-3-amine (2). *Step 1*. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(bda)_3$, 9.2 mg, 0.010 mmol, 0.02 eq.) and Xantphos were charged in a flask. Under nitrogen atmosphere 1,4-dioxane (0.55 mL) was added and the mixture was stirred for 15 min at room temperature. The precatalyst solution was added, under nitrogen atmosphere, in a flask charged with compound **15** (220 mg, 0.50 mmol, 1.0 eq.), *tert*-butyl carbamate (88 mg, 0.75 mmol, 1.5 eq.) and Cs_2CO_3 (327 mg, 1.00 mmol, 2.0 eq.). The mixture was stirred at 90 °C overnight. After completion of the reaction, the mixture was cold down to r.t. and a 15% NH_4Cl solution (20 mL) was added. The aqueous layer was extracted with EtOAc (3 x30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. *Step 2*. The crude was dissolved in dioxane and a 4 M HCl solution in dioxane was added. The resulting mixture was stirred for 2 h at 80 °C. After completion of the reaction monitored by TLC, a 2 M NaOH solution (20 mL) was added. The aqueous layer was extracted with EtOAc (3x 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 3:7) gave compound **2** as a colorless solid (19 mg, 0.051 mmol, 10%).

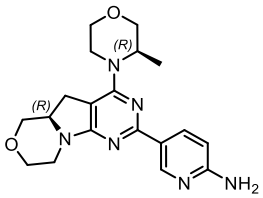
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 (br s, 2 H), 4.29-4.25 (m, 1 H), 4.23 (dd, J = 13.6, 2.8 Hz, 1 H), 4.06-3.96 (m, 3 H), 3.85 (td, J = 11.2, 3.9 Hz, 2 H), 3.77-3.74 (m, 2 H), 3.60 (td, J = 11.8, 2.9 Hz, 1 H), 3.48 (td, J = 11.7, 2.9 Hz, 1 H), 3.40-3.19 (m, 4 H), 2.65 (dd, J = 15.4, 5.4 Hz, 1 H), 1.31 (d, J = 6.8 Hz, 3 H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 188.6 (s), 170.1 (s), 167.6 (s), 157.4 (s), 155.9 (s), 96.1 (s), 71.0 (s), 70.7 (s), 67.2 (s), 66.7 (s), 56.8 (s), 48.1 (s), 42.1 (s), 40.2 (s), 29.7 (s), 14.30 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{16}H_{22}N_7O_2S$ 376.1554; found: 376.1550, $[M + Na]^+$ calc. for $C_{16}H_{21}N_7NaO_2S$ 398.1372; found: 398.1370, $[2M + Na]^+$ calc. for $C_{32}H_{42}N_{14}NaO_4S_2$ 773.2856; found: 773.2847. **HPLC** (method A): t_R = 6.28 min (95.4% purity).



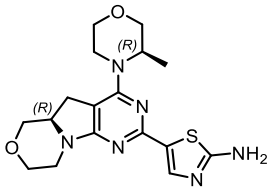
6-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridazin-3-amine (3). To a solution of compound **16** (69 mg, ~0.16 mmol) in DMSO (0.13 mL) in an Ace pressure tube, NH_3 aq. (2 mL) was added. The reaction was stirred at 100 °C overnight. After completion of the reaction monitored by HPLC, the mixture was extracted with DCM (3x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. Purification by column chromatography on silica gel (DCM / MeOH 1:0 → 10:1) gave compound **3** as a colorless solid (30 mg, 0.081 mmol, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15 (d, J = 9.1 Hz, 1 H), 6.82 (d, J = 9.1 Hz, 1 H), 5.60 (br s, 2 H), 4.38-4.25 (m, 2 H), 4.14 (d, J = 10.8 Hz, 1 H), 4.02-3.93 (m, 2 H), 3.86-3.70 (m, 4 H), 3.65-3.57 (m, 1 H), 3.52-3.43 (m, 1 H), 3.42-3.18 (m, 4 H), 2.64 (dd, J = 15.0, 5.3 Hz, 1 H), 1.29 (d, J = 6.8 Hz, 3 H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 168.0 (s), 160.4 (s), 159.8 (s), 157.9 (s), 151.5 (s), 128.7 (s), 114.6 (s), 94.9 (s), 71.1 (s), 70.7 (s), 67.3 (s), 66.7 (s), 56.8 (s), 48.0 (s), 42.1 (s), 40.2 (s), 29.6 (s), 14.2 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{18}H_{24}N_7O_2$ 370.1986; found: 370.1990. **HPLC** (method B): t_R = 4.71 min (96.2% purity).



5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,3,4-thiadiazol-2-amine (4). Thiosemicarbazide (33 mg, 0.37 mmol, 1.1 eq.) and compound **17** (100 mg, 0.33 mmol, 1.0 eq.) were charged in a flash and trifluoroacetic acid (TFA, 10 mL) was added. The mixture was stirred at 65 °C overnight. The reaction mixture was slowly poured into a $NaHCO_3$ saturated solution (30 mL) cooled at 0 °C. The resulting mixture was transferred into a separatory funnel and the aqueous layer was extracted with EtOAc (3x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. Purification by column chromatography on silica gel (DCM / MeOH 1:0 → 10:1) gave compound **4** as a colorless solid (66 mg, 0.18 mmol, 53%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.41 (br s, 2 H), 4.27 (d, J = 7.2 Hz, 1 H), 3.98-3.86 (m, 4 H), 3.76 (ddd, J = 15.3, 11.1, 3.8 Hz, 2 H), 3.69-3.61 (m, 2 H), 3.46 (td, J = 11.7, 2.9 Hz, 1 H), 3.33-3.29 (m, 1 H), 3.26-3.10 (m, 4 H), 2.70 (dd, J = 15.7, 5.0 Hz, 1 H), 1.18 (d, J = 6.7 Hz, 3 H). **^{13}C{^{1}H} NMR** (101 MHz, DMSO-d_6): δ 170.64 (s), 167.52 (s), 158.28 (s), 157.33 (s), 156.21 (s), 95.14 (s), 70.76 (s), 70.16 (s), 66.83 (s), 66.17 (s), 56.81 (s), 47.63 (s), 42.04 (s), 40.12 (s), 29.09 (s), 14.39 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{16}H_{22}N_7O_2S$ 376.1550; found: 376.1552. **HPLC** (method A): t_R = 5.66 min (97.5% purity).

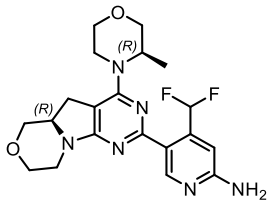


5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridin-2-amine (5) was prepared according to the literature.[1]

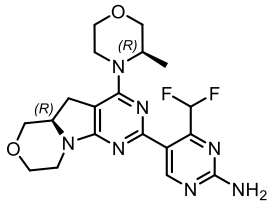


5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazin-2-yl)thiazol-2-amine (6). was prepared according to general procedure 1 from intermediate **13** (200 mg, 0.65 mmol, 1.0 eq.) and 2-(tert-butoxycarbonylamino)-thiazole-5-boronic acid pinacol ester (210 mg, 0.65 mmol, 1.0 eq.). Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 1:1) gave compound **6** as a colorless solid (116 mg, 0.31 mmol, 48%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (s, 1 H), 5.61 (br s, 2 H), 4.30-4.21 (m, 1 H), 4.11 (dd, J = 13.4, 2.9 Hz, 1 H), 4.02-3.88 (m, 3 H), 3.86-3.69 (m, 4 H), 3.58 (td, J = 11.7, 2.9 Hz, 1 H), 3.46 (td, J = 11.7, 3.0 Hz, 1 H), 3.36-3.10 (m, 4 H),

2.57 (dd, J = 14.8, 5.0 Hz, 1 H), 1.26 (d, J = 6.7 Hz, 3 H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 170.07 (s), 167.31 (s), 158.29 (s), 157.63 (s), 139.81 (s), 129.49 (s), 92.52 (s), 71.09 (s), 70.51 (s), 67.25 (s), 66.55 (s), 56.75 (s), 47.91 (s), 41.90 (s), 40.12 (s), 29.60 (s), 14.08 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{17}H_{23}N_6O_2S$ 375.1598; found: 375.1605. **HPLC** (method B): t_R = 4.71 min (96.2% purity).

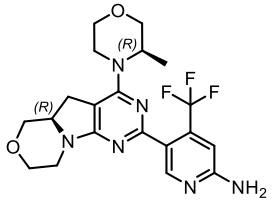


4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridin-2-amine (7) was prepared according to general procedure 1 from intermediate **13** (150 mg, 0.48 mmol, 1.0 eq.) and *N*'-[4-(difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-*N*,*N*-dimethylmethanimidamide (**23**, 158 mg, 0.14 mmol, 1.0 eq.). Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 2:3) gave compound **7** as a colorless solid (156 mg, 0.37 mmol, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.95 (s, 1 H), 7.70 (t, J = 55 Hz, 1 H), 6.82 (s, 1 H), 4.73 (br s, 2 H), 4.33-4.24 (m, 1 H), 4.10 (dd, J = 13, 2.3 Hz, 1 H), 4.04-3.91 (m, 3 H), 3.89-3.70 (m, 4 H), 3.60 (td, J = 12, 2.9 Hz, 1 H), 3.47 (td, J = 12, 2.8 Hz, 1 H), 3.41-3.15 (m, 4 H), 2.62 (dd, J = 15, 4.9 Hz, 1 H), 1.29 (d, J = 6.8 Hz, 3 H). **^{19}F{^{1}H} NMR** (376 MHz, DMSO-d_6): δ − 115.0 (d, J = 289 Hz, 1 F), − 116.2 (d, J = 289 Hz, 1 F). **^{13}C{^{1}H} NMR** (101 MHz, DMSO-d_6): δ 166.9 (s), 160.6 (s), 160.5 (s), 157.4 (s), 151.4 (s), 141.4 (t, J = 21 Hz), 102.2 (t, J = 4.8 Hz), 112.0 (t, J = 273 Hz), 102.8 (t, J = 8.2 Hz), 93.0 (s), 70.3 (s), 69.6 (s), 66.5 (s), 65.7 (s), 56.3 (s), 47.2 (s), 41.6 (s), 39.7 (s), 28.7 (s), 13.8 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{20}H_{25}F_2N_6O_2$ 419.2004; found: 419.2002. **HPLC** (method A): t_R = 7.17 min (97.5% purity). The signal at 39.7 ppm in the ^{13}C{^{1}H} NMR spectra was recorded by DEPT and HMQC experiments.

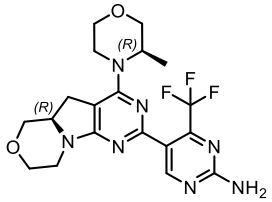


4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyrimidin-2-amine (8) was prepared according to general procedure 2 from intermediate **13** (100 mg, 0.32 mmol, 1.0 eq.) and *tert*-butyl *N*-[5-bromo-4-

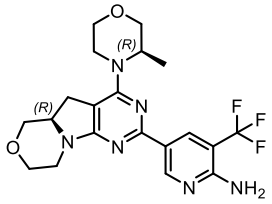
(difluoromethyl)pyrimidin-2-yl]-*N*-[(*tert*-butoxy)carbonyl]carbamate (**24**, 137 mg, 0.32 mmol, 1.0 eq.). Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 3:7) gave compound **8** as a colorless solid (90 mg, 0.22 mmol, 66%). **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 9.05 (s, 1 H), 7.68 (t, J = 54 Hz, 1 H), 7.34 (br s, 2 H), 4.32-4.23 (m, 1 H), 4.00-3.85 (m, 4 H), 3.80-3.59 (m, 4 H), 3.46 (td, J = 12, 2.7 Hz, 1 H), 3.36-3.10 (m, 5 H), 2.69 (dd, J = 16, 4.7 Hz, 1 H), 1.18 (d, J = 6.7 Hz, 3 H). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$): δ − 121.5 (s, 2 F). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 167.5 (s), 162.9 (s), 162.4 (s), 159.5 (s), 158.5 (t, J = 21 Hz), 158.0 (s), 121.4 (t, J = 3.9 Hz), 109.8 (t, J = 240 Hz), 93.4 (s), 71.1 (s), 70.6 (s), 67.3 (s), 66.6 (s), 56.9 (s), 48.1 (s), 42.1 (s), 40.3 (s), 29.7 (s), 14.3 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{19}H_{24}F_2N_7O_2$ 420.1954; found: 420.1961. **HPLC** (method A): t_R = 6.88 min (95.5% purity).



5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (9) was prepared according to general procedure 1 from intermediate **13** (200 mg, 0.64 mmol, 1.0 eq.) and *N*,*N*-dimethyl-*N*'-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-yl]methanimidamide (**25**, 250 mg, 0.73 mmol, 1.1 eq.). Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 1:9) gave compound **9** as a yellowish solid (48 mg, 0.11 mmol, 17%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.62 (s, 1 H), 6.78 (s, 1 H), 4.84 (br s, 2 H),4.36-4.27 (m, 1 H), 4.10 (dd, J = 14, 2.4 Hz, 1 H), 4.06-3.89 (m, 3 H), 3.86-3.68 (m, 4 H), 3.58 (td, J = 12, 2.8 Hz, 1 H), 3.47 (td, J = 12, 2.8 Hz, 1 H), 3.40-3.29 (m, 2 H), 3.27-3.17 (m, 2 H), 2.63 (dd, J = 15, 4.8 Hz, 1 H), 1.27 (d, J = 6.8 Hz, 3 H). **^{19}F{^{1}H} NMR** (376 MHz, $(CD_3)_2SO$): δ − 59.3 (s, 3 F). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 167.7 (s), 161.6 (s), 158.8 (s), 158.8 (s), 158.1 (s), 152.4 (s), 138.0 (d, , J = 32 Hz), 124.2-124.0 (m), 123.1 (d, J = 274 Hz), 105.2 (q, J = 5.7 Hz), 93.3 (s), 71.2 (s), 70.5 (s), 67.4 (s), 66.7 (s), 56.9 (s), 47.9 (s), 42.0 (s), 40.2 (s), 29.8 (s), 14.3 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{20}H_{24}F_3N_6O_2$ 437.1907; found: 437.1907. **HPLC**: t_R = 7.18 min (95.6% purity).

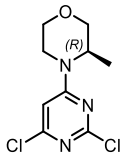


5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine (10). Tricyclic 2-chloropyrimidine precursor (**13**, 43 mg, 0.14 mmol, 1.0 eq.), 2-amino-4-trifluoromethylpyrimidine-5-boronic acid pinacol ester (40 mg, 0.14 mmol, 1.0 eq.), potassium phosphate (59 mg, 0.28 mmol, 2.0 eq.) and chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (XPhos Pd G2, 5.5 mg, 0.0069 mmol, 0.05 eq.) were charged in a flask. Under nitrogen atmosphere, 1,4-dioxane (1.5 mL) and deionized water (approx. 1 ml / 0.4 mmol) were added and the resulting mixture was placed into an oil bath pre-heated at 95 °C and stirred at this temperature overnight. After completion of the reaction, the mixture was allowed to cool down to room temperature, brine was added and the mixture was extracted with dichloromethane (3 x). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 3:7) gave compound **10** as a colorless solid (59 mg, 0.134 mmol, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.89 (s, 1 H), 5.40 (br s, 2 H), 4.37-4.27 (m, 1 H), 4.18-4.06 (m, 1 H), 4.05-3.90 (m, 3 H), 3.88-3.69 (m, 4 H), 3.58 (td, J = 12, 2.8 Hz, 1 H), 3.47(td, J = 12, 2.8 Hz, 1 H), 3.39-3.30 (m, 2 H), 3.29-3.17 (m, 2 H), 2.64 (dd, J = 15, 4.9 Hz, 1 H), 1.28 (d, J = 6.8 Hz, 3 H). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$): δ − 65.3 (s, 3 F). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 167.7 (s), 163.1 (s), 162.1 (s), 160.0 (s), 158.0 (s), 153.7 (q, J = 35 Hz), 122.7-122.6 (m), 120.9 (q, J = 276 Hz), 93.5 (s), 71.2 (s), 70.6 (s), 67.4 (s), 66.7 (s), 56.9 (s), 48.0 (s), 42.0 (s), 40.3 (s), 29.8 (s), 14.4 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{19}H_{23}F_3N_7O_2$ 438.1860; found: 438.1865. **HPLC** (method A): t_R = 7.24 min (97.9% purity).

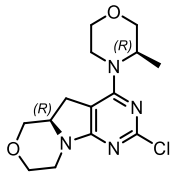


5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-3-(trifluoromethyl)pyridin-2-amine (11) was prepared according to general procedure 1 from intermediate **13** (80 mg, 0.26 mmol, 1.0 eq.) and *N*,*N*-dimethyl-*N*'-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-yl]methanimidamide (**26**, 89 mg, 0.26

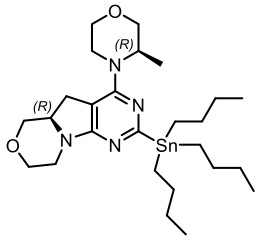
mmol, 1.0 eq.). Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 1:1) gave compound **11** as a colorless solid (90 mg, 0.21 mmol, 80%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 9.04 (d, J = 1.6 Hz, 1 H), 8.44 (d, J = 1.9 Hz, 1 H), 6.82 (br s, 2 H), 4.34-4.26 (s, 1 H), 4.04 (dd, J = 13, 2.6 Hz, 2 H), 3.94-3.83 (m, 2 H), 3.80-3.61 (m, 4 H), 3.47 (td, J = 12, 2.9 Hz, 1 H), 3.33-3.08 (m, 5 H), 2.67 (dd, J = 15, 4.9 Hz, 1 H), 1.18 (d, J = 6.7 Hz, 3 H). **^{19}F{^{1}H} NMR** (376 MHz, DMSO-d_6): δ − 63.2 (s, 3 F). **^{13}C{^{1}H} NMR** (101 MHz, DMSO-d_6): δ 167.1 (s), 159.0 (s), 157.3 (s), 156.3 (s), 152.2 (s), 133.8 (q, J = 5.2 Hz), 124.3 (q, J = 271 Hz), 121.9 (s), 105.1 (q, J = 31 Hz), 93.3 (s), 70.4 (s), 69.7 (s), 66.5 (s), 65.8 (s), 56.4 (s), 47.2 (s), 41.6 (s), 39.6 (s), 28.7 (s), 13.8 (s). **HRMS** (m/z): $[M + H]^+$ calc. for $C_{20}H_{24}F_3N_6O_2$ 437.1907; found: 437.1915. **HPLC** (method A): t_R = 8.67 min (98.4% purity).



(*R*)-4-(2,6-dichloropyrimidin-4-yl)-3-methylmorpholine (12) was prepared according to the literature.[1]

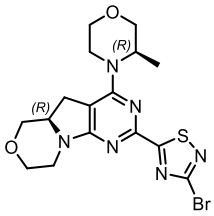


(*R*)-2-chloro-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine (13) was prepared according to the literature.[1]

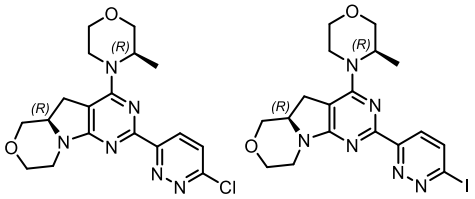


(*R*)-4-((*R*)-3-methylmorpholino)-2-(tributylstannyl)-5a,6,8,9-tetrahydro-5H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazine (14). Tricyclic 2-chloropyrimidine precursor (**13**, 800 mg, 2.58 mmol, 1.0 eq.) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (Pd(amphos)Cl_2, 183 mg, 0.26 mmol, 0.1 eq.) were charged in a flask. Under nitrogen atmosphere 1,4-

dioxane (9.6 mL) was added, followed by bis(tributyltin) (1.92 mL, 3.79 mmol, 1.5 eq.). The reaction mixture was stirred at reflux for 3 hours. After completion of the reaction monitored by TLC, H_2O (20 mL) was added and the aqueous layer was extracted with EtOAc (3x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 4:1) gave compound **14** as a yellowish oil (970 mg, 1.72 mmol, 66%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 4.33-4.25 (m, 1 H), 3.95-3.82 (m, 3 H), 3.81-3.58 (m, 5 H), 3.44 (td, J = 11.7, 2.9 Hz, 1 H), 3.25 (td, J = 11.6, 2.8 Hz, 1 H), 3.21-3.02 (m, 4 H), 2.61 (dd, J = 15.3, 4.7 Hz, 1 H), 1.65-1.48 (m, 6 H), 1.35-1.25 (m, 8 H), 1.15-1.09 (m, 3 H), 1.01-0.96 (m, 4 H), 0.90-0.82 (m, 9 H).

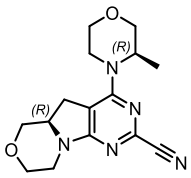


(*R*)-2-(3-bromo-1,2,4-thiadiazol-5-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine (15) was prepared according to general procedure 3 from intermediate **14** (600 mg, 1.06 mmol, 1.0 eq.) and 3-bromo-5-chloro-1,2,4-thiadiazole (212 mg, 1.06 mmol, 1.0 eq.). Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 1:1) gave compound **15** as a yellowish solid (232 mg, 0.53 mmol, 50%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 4.34-3.26 (m, 1 H), 4.03-3.88 (m, 4 H), 3.79 (td, J = 11.0, 3.8 Hz, 2 H), 3.71-3.61 (m, 2 H), 3.47 (td, J = 11.8, 2.9 Hz, 1 H), 3.38-3.32 (m, 1 H), 3.30-3.14 (m, 4 H), 2.78 (dd, J = 16.2, 5.1 Hz, 1 H), 1.21 (d, J = 6.8 Hz, 3 H). **MALDI-MS**: m/z = 439.142 $[M + H]^+$.

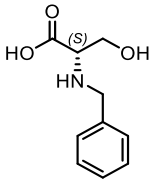


(*R*)-2-(6-chloropyridazin-3-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine and (*R*)-2-(6-iodopyridazin-3-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine (16) was prepared according to general procedure 3 from intermediate **14** (200 mg, 0.35 mmol, 1.0 eq.) and 3-chloro-6-iodopyridazine (85 mg, 0.35 mmol, 1.0 eq.). Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 0:1) gave compound **16** as a mixture of chloro- (50%) and iodo-derivative

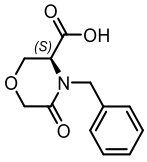
(44% from HPLC) as a dark brown solid (53 mg, ~0.14 mmol, ~39%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 745-7.26 (m, 4 H), 4.45-4.00 (m, 6 H), 3.96-3.57 (m, 12 H), 3.53-3.42 (m, 3 H), 3.28-3.12 (m, 7 H), 2.82-2.57 (m, 4 H), 1.25-1.20 (m, 6 H). **MALDI-MS**: *m/z* = 389.046 $[M + H]^+$ (chloro-derivative); 480.848 $[M + H]^+$ (iodo-derivative).



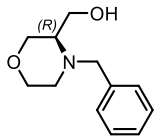
(*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine-2-carbonitrile (17). The tricyclic 2-chloropyrimidine precursor (**13**, 400 mg, 1.29 mmol, 1.0 eq.), tetraethylammonium cyanide (605 mg, 3.87 mmol, 3 eq.), triethylenediamine (DABCO, 434 mg, 3.87 mmol, 3.0 eq.) and DMSO (5 mL) were charged in an Ace pressure tube. The reaction mixture was stirred 1.5 hours at 140 °C. After completion of the reaction monitored by HPLC, the mixture was poured into H_2O (50 mL) and the product was extracted with EtOAc (3x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and reduced to dryness under reduced pressure. Purification by column chromatography on silica gel (cyclohexane / EtOAc 1:0 → 0:1) gave compound **17** as a yellowish oil (169 mg, 0.56 mmol, 43%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 4.27-4.20 (m, 1 H), 3.98-3.81 (m, 4 H), 3.79-3.72 (m, 2 H), 3.67-3.57 (m, 2 H), 3.42 (td, *J* = 11.9, 3.0 Hz, 1 H), 3.36-3.28 (m, 1 H), 3.27-3.09 (m, 4 H), 2.76 (dd, *J* = 16.3, 5.1 Hz, 1 H), 1.17 (d, *J* = 6.8 Hz, 3 H). **^{13}C{^{1}H} NMR** (101 MHz, DMSO-d_6): δ 166.56 (s), 157.05 (s), 142.11 (s), 117.11 (s), 98.74 (s), 70.59 (s), 70.09 (s), 66.70 (s), 66.13 (s), 56.73 (s), 47.70 (s), 42.02 (s), 40.17 (s), 29.13 (s), 14.63 (s). **MALDI-MS**: *m/z* = 302.090 $[M + H]^+$.



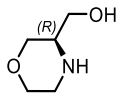
***N*-Benzyl-(*S*)-serine (18)** was prepared according to literature.[1]



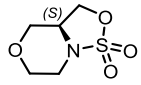
(*S*)-4-Benzyl-5-oxomorpholine-3-carboxylic acid (19) was prepared according to literature.[1]



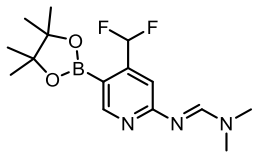
(*R*)-(4-Benzylmorpholin-3-yl)methanol (20) was prepared according to literature.[1]



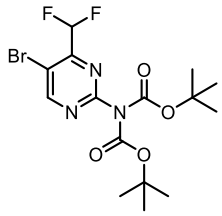
(*R*)-Morpholin-3-ylmethanol (21) was prepared according to literature.[1]



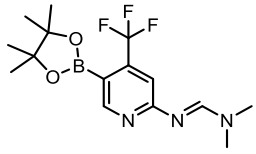
(*S*)-tetrahydro-3*H*-[1,2,3]oxathiazolo[4,3-*c*][1,4]oxazine 1,1-dioxide (22) was prepared according to literature.[1]



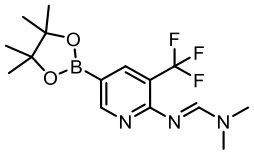
***N*'-[4-(Difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]-*N*,*N*-dimethylmethanimidamide (23)** was prepared according to the literature.[2-4]



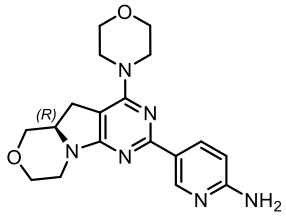
***tert*-Butyl *N*-[5-bromo-4-(difluoromethyl)pyrimidin-2-yl]-*N*-[(*tert*-butoxy)carbonyl]carbamate (24)** was prepared according to the literature.[5]



***N*,*N*-Dimethyl-*N*'-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-yl]methanimidamide (25)** was prepared according to the literature.[6, 7]



(*E*)-*N*,*N*-dimethyl-*N*'-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-yl)formimidamide (26) was prepared according to the literature.[7]



(*R*)-5-(4-morpholino-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridin-2-amine (27) was prepared according to the literature.[1]

Table S1. Apparent permeability and efflux ratio in MDCK-hMDR1$^{cMDR1\text{-}ko}$ cells.

Comp.	Papp A to B (SD) 10^{-6} cm/s	Mass balance A to B % (SD)	Papp B to A (SD) 10^{-6} cm/s	Mass balance B to A % (SD)	ER (SD)
12b (n = 6)	16.3 (2.8)	96.9 (13.6)	154.7 (20.2)	96.1 (25.9)	9.9 (2.9)
PQR620 (n = 6)	111.6 (37.8)	88.3 (14.4)	102.7 (8.9)	79.7 (7.7)	1.1 (0.4)
PQR309 (n = 6)	188.1 (35.9)	124.7 (25.2)	124.7 (24.6)	107.5 (13.6)	0.7 (0.1)
4 (n = 6)	2.2 (0.7)	104.5 (12.1)	87.7 (20.1)	71.9 (62.1)	44.2 (15.5)
6 (n = 3)	2.7 (0.2)	103.3 (7.6)	99.5 (16.1)	107.6 (6.3)	37.6 (8.6)
11 (n = 3)	135.6 (23)	134.8 (14.1)	143.5 (17.4)	123.6 (24.9)	1.1 (0.3)

Table S2. Apparent permeability and efflux ratio in MDCK$^{cMDR1\text{-}ko}$ cells.

Comp.	Papp A to B (SD) 10^{-6} cm/s	Mass balance A to B % (SD)	Papp B to A (SD) 10^{-6} cm/s	Mass balance B to A % (SD)	ER (SD)
12b (n = 6)	55.9 (12.6)	102.1 (13.4)	68.7 (11.6)	91.4 (12.9)	1.3 (0.4)
PQR620 (n = 6)	109 (28)	88.3 (4.9)	95.8 (17.4)	86.4 (2.7)	0.9 (0.2)
PQR309 (n = 6)	178.7 (34.4)	81.6 (8.7)	128.6 (12.1)	84.1 (7.8)	0.8 (0.2)
4 (n = 3)	12.2 (2.3)	99.5 (13.7)	16.4 (3.9)	107.5 (3.2)	1.3 (0.1)
6 (n = 3)	15.5 (0.7)	121.5 (2.8)	19.6 (1.1)	111.6 (2.9)	1.3 (0.0)
11 (n = 3)	109.4 (15.6)	143.9 (40.8)	136.8 (12.2)	142.8 (6.7)	1.2 (0.1)

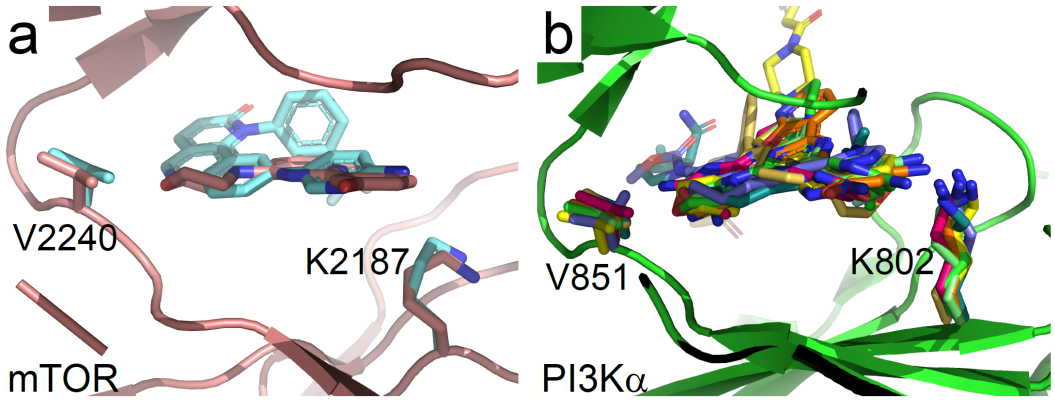


Figure S1. (a, b) Superimposition of mTOR and PI3Kα X-ray crystallographic complexes.

(a) mTOR in complex with (i) 3-(4-morpholin-4-ylpyrido[3',2':4,5]furo[3,2-*d*]pyrimidin-2-yl)phenol (pink, PDB ID 4JT6)[8], and (ii) 9-(6-aminopyridin-3-yl)-1-[3-(trifluoromethyl)phenyl]benzo[h][1,6]naphthyridin-2(1*H*)-one (light blue, PDB ID 4JSX)[8]. **(b)** PI3Kα in complex with (i) PQR530 (green, PDB ID 6OAC)[3], (ii) CNX-1351 (yellow, PDB ID 3ZIM)[9], (iii) GDC-0326 (cyan, PDB ID 5DXH)[10], (iv) (2*S*,3*R*)-*N*[1]-(8-(tert-butyl)-4,5-dihydrothiazolo[4,5-h]quinazolin-2-yl)-3-methylpyrrolidine-1,2-dicarboxamide (deep teal, PDB ID 4ZOP), (v) 1-[4-(3-{4-amino-5-[1-(oxan-4-yl)-1*H*-pyrazol-5-yl]pyrrolo[2,1-*f*][1,2,4]triazin-7-yl}phenyl)piperazin-1-yl]ethan-1-one (sand, PDB ID 5UBR)[11], (vi) 5-(6-azanyl-4-methyl-1-propan-2-yl-pyrazolo[3,4-*d*]pyrimidin-3-yl)-1,3-benzoxazol-2-amine (magenta, PDB ID 6GVG)[12], (vii) 3-amino-5-[4-(morpholin-4-yl)pyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl]phenol (orange, PDB ID 4L2Y)[13], (viii) 3-azanyl-5-(4-morpholin-4-ylthieno[3,2-d]pyrimidin-2-yl)phenol (light green, PDB ID 5XGI).

Experimental Section.

Structure Modelling of PI3K and mTOR Kinase Complexes

The coordinates of PI103 in mTOR complex (PDB code 4JT6, resolution of 3.6 Å) was used as starting points to dock compounds **1-6**, **11** into the ATP-binding site. The coordinates of PQR530 in PI3Kα complex (PDB code 6OAC, resolution of 3.15 Å) were used as starting points to dock compound **11** into the ATP-binding site of PI3Kα. The ligand in the crystal structure was manually replaced using Maestro 11.1 and energy minimization was carried out. Further measurements and figures were generated in Maestro 11.1, Chimera UCSF and PyMOL 2.3.5 Schrödinger LLC.

Determination of Inhibitor Dissociation Constants

Dissociation constants of compounds (K_i) for p110α and mTOR were determined by commercial LanthaScreen (Life Technologies) and evaluated as described in Ref. 7. Briefly, AlexaFluor647-labeled Kinase Tracer314 (#PV6087) with a K_d of 2.2 nM was used at 20 nM for p110α, and at a final concentration of 10 nM for mTOR (K_d of 19 nM). Recombinant N-terminally $(His)_6$-tagged p110α was detected with biotinylated anti-$(His)_6$-tag antibody (2 nM, #PV6089) and LanthaScreen Eu-Steptavidin (2 nM, #PV5899); N-terminal GST fused to truncated mTOR (amino acids 1360-2549; #PR8683B) was detected with a LanthaScreen Eu-labelled anti-GST antibody (2 nM, #PV5594). The p110α assay buffer was composed of 50 mM HEPES pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, and 0.01% (v/v) Brij-35, and the mTOR assay buffer contained 50 mM HEPES; 5 mM $MgCl_2$; 1 mM EGTA; 0.01% Pluronic F-127. Further details and calculations are explained in Ref. 6.

Cellular PI3K and mTOR Signalling

Downstream signals emerging from mTORC2 (phosphorylation of Ser473 of PKB/Akt; rabbit polyclonal antibody from Cell Signalling Technology (CST), #4058) and mTORC1 (phosphorylation of Ser235/236 on the ribosomal protein S6; rabbit monoclonal antibody from CST, #4856) were measured in In-Cell Western assays plating $2x10^4$ A2058 cells/well in 96-well plates (Cell Carrier, Perkin Elmer) for 24 h (37°C, 5%CO_2), before exposing cells for 1 h to inhibitors or DMSO. Then, cells were fixed (4% PFA in PBS for 30 min at RT), blocked (1% BSA/0.1% Triton X-100/5% goat serum in PBS for 30 min, RT), and stained with CST primary antibodies (1:500). Tubulin staining (mouse anti-a-tubulin, 1:2000, Sigma #T9026) was assessed as internal standard. Secondary antibody [IRDye680-conjugated goat anti-mouse, and IRDye800-conjugated goat anti-rabbit antibodies (LICOR # 926-68070 and # 926-32211), both 1:500] fluorescence was detected on an Odyssey CLx infrared imaging scanner (LICOR). Remaining phospho-protein signals were normalized to cellular tubulin and related to DMSO controls. ICW analysis and determination of IC_{50} were done as described in Ref. 7.

CYP reactive phenotyping with human recombinant CYP1A1 and CYP1A2 isoenzymes

Human recombinant isoenzymes from insect cells infected by baculovirus and containing cDNA of a single human CYP isoenzyme (Supersomes^{TM}, Corning) were used. The test item stock solutions were diluted in DMSO/H2O (1:8, v/v) to obtain 50-fold concentrated working solutions (solvent content 12.5% DMSO/87.5% H_2O) for CYP1A1 and CYP1A2. The test compound concentration applied in the CYP reactive phenotyping assay was 1 µM in presence of 0.25% DMSO. The assays were performed in duplicate using human recombinant enzymes systems from Corning (BD Gentest P450 High Throughput Inhibitor Screening Kits). The cofactor-mix, containing the NADP+-regenerating system, was prepared according to the instructions of the manufacturer. For CYP1A1 and CYP1A2, 4 µL of the 50-fold concentrated working solution was added to 96 µL cofactor-mix. Cofactor mix and test item were pipetted into the respective wells of a pre-warmed 96-well-plate and pre-warmed for 10 minutes on a shaker with fitted heating block. The reactions were initiated by addition of 100 µL pre-warmed enzyme-mix. By default, the final protein concentration of all CYP isoenzymes was 25 pmol/mL. Incubations with a final volume of 200 µL were performed at 37 °C. After 0 and 60 min (30 min for positive control substrates), the reactions were stopped by the addition of 200 µL stop solution, i.e. ACN containing the internal standard. Two control groups were run in parallel for every assay: positive controls (PC, n = 2) using specific probe substrates for each CYP isoform as reference compounds (CYP1A1 = Melatonin and CYP1A2 = Phenacetin) to prove the quality of the enzyme activity of the used batches as well as a negative control (NC, n = 2), which were performed without cofactors and glucose-6-phosphate-dehydrogenase to ensure that the potential loss of parent compound is due to CYP-mediated metabolism.

For quantitative analysis of compound **4** and **6**, LC-MS systems were used: (i) LC-MS: Accela U-HPLC pump and an Accela auto sampler (Thermo Fisher Scientific, USA) connected to an Exactive mass spectrometer (Orbitrap with accurate mass (Thermo Fisher Scientific, USA)); data handling with the standard software Xcalibur 2.1; (ii) LC-HRMS: Accela U-HPLC pump and an Accela Open auto sampler (Thermo Fisher Scientific, USA) connected to an Q-Exactive mass spectrometer (Orbitrap); data handling with the standard software Xcalibur 2.2. (iii) LC-MS: Surveyor MS Plus HPLC (Thermo Electron) HPLC system connected to a TSQ Quantum Discovery Max (Thermo Electron) triple quadrupole mass spectrometer equipped with an electrospray (ESI) or APCI interface (Thermo Fisher Scientific, USA); connected to a PC running the standard software Xcalibur 2.0.7.

The pump flow rate was set to 600 µL/min and the analytes were separated on a Kinetex Phenyl-Hexyl analytical column 2.6 µm, 50x2.1 mm (Phenomenex, Germany).

MDCK TransWell assay (P_{app}, ER)

Apparent permeability across MDCLK monolayers was assessed using MDCK-hMDR1$^{cMDR1\text{-}ko}$ and MDCK$^{cMDR1\text{-}ko}$ cultivated in DMEM containing Glutamax (cat. no. 14190), 10% fetal bovine serum (cat. no. 10270) and 5% Penicillin-Streptomycin (cat. no. 10687) and Hygromycin B (cat. no. 10687) as selection antibiotic for cells expressing hMDR1. Cells were grown for four to five days prior the experiment at a seeding density of 100'000 cells/well and cell media was exchanged every second day and 24 h before the beginning of the experiment. The cells were washed with pre-warmed HBSS for 30 minutes (37°C, 300 rpm) prior to addition of fresh HBSS to the receiver chamber and addition of 1 µM drug solution to the donor chamber. The volume was 0.4 in the apical chamber and 1.2 ml the in the basolateral chamber. Samples of 100 µL were retrieved from the receiver chamber at time points 5, 10 and 20 minutes and replaced with fresh buffer. 100 µL were retrieved from the donor chamber at the end of the experiment for calculation of mass balance. Trans-epithelial electrical resistance (TEER) values were measured prior addition of drug and 30 minutes after sampling of last time point (Epithelial Volt/Ohm Meter (EVOM), World Precision Instrument, equipped with Chopstick Electrode STX2). Positive controls (PQR620[2] and PQR309[7]) and a negative control (**12b**)[1] were included into each series of experiments. Experiments were performed in triplicates, and on at least two independent occasions.

Immediately after the final sampling, the samples and calibration standards were diluted with an equal volume of acetonitrile containing the internal standard, vortexed, centrifuged at 2000 x g for 15 minutes and the supernatant was analysed by UPLC-MS/MS. The UPLC-MS/MS system consisted of an Agilent 1290 Infinity Binary Pump coupled to an Agilent 6460 Triple Quad Mass Spectrometer with an AJS ESI interface. Mobile phases consisted of (A) water with 5% acetonitrile, 0.05% formic acid and 10 mM ammonium formate and (B) acetonitrile with 0.05% formic acid. Separation was performed on an Acquity UPLC column (BEH C18 1.7µm, 2.1 x 50mm for **12b**, PQR620, PQR309 and CSH Phenyl-Hexyl 1.7µm, 2.1 x 50mm for **4**, **6** and **11**) with an integrated pre-filter. Acquisition and quantification were performed with the Agilent MassHunter Workstation (Version 10.1). The mass transitions in positive mode were (precursor ion → quantifier ion, qualifier ion): **12b**: 370.4 → 312.1, 67.1; PQR309: 412.4 → 69.1, 113.1; PQR620: 446.5 → 426.3, 41.1; compound **4**: 376.5 → 318.1, 132; compound **6**: 375.5 → 317.1, 258.1; compound **11**: 437.4 → 379.1, 359.1).

Finally, P_{app} was calculated according to literature[14] using the equation:

$$P_{app} = (dQ/dt)(1/AC0)$$

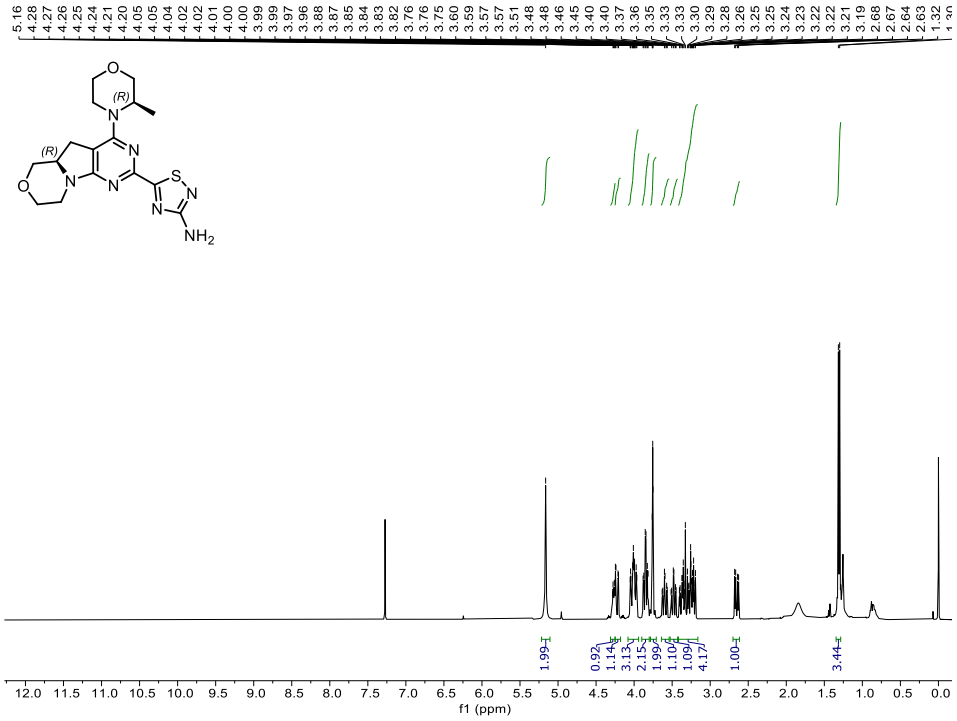
Where dQ/dt is the steady-state flux (µmol/s), A is the surface area of the filter (cm^2) and C_0 is the initial concentration in the donor chamber (µM),

The efflux ratio is the ratio between the secretory permeability and the absorptive permeability (P_{app} B to A / P_{app} A to B).

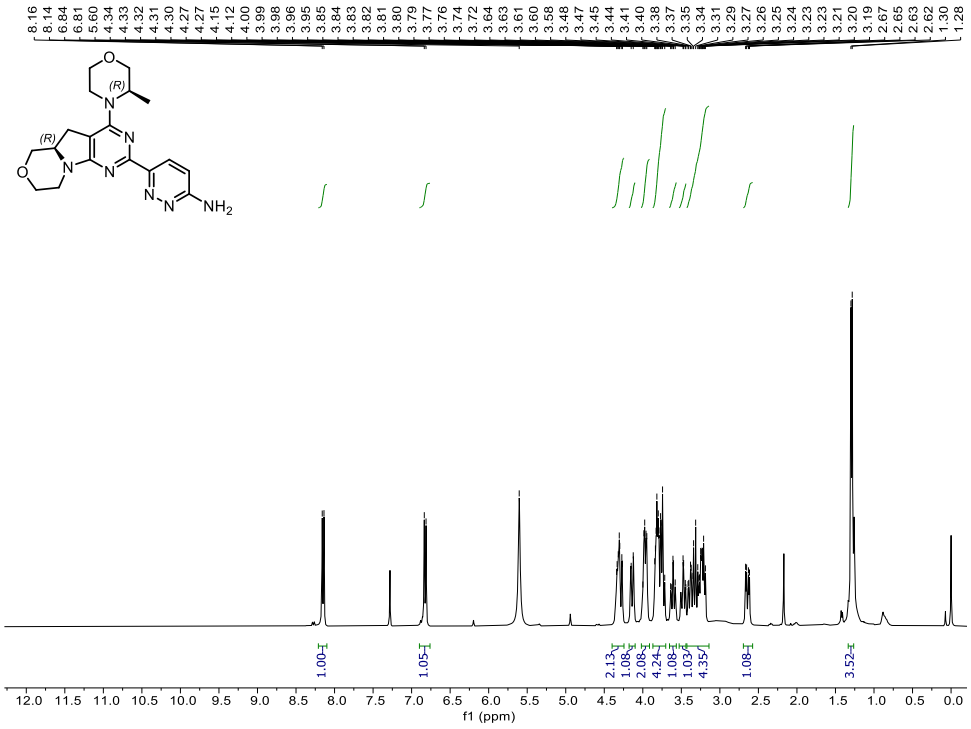
P_{app} values were retained for experiments with a mass balance >75% and TEER in the range of 160-180 $\Omega \cdot cm^2$.

[1]H NMR Spectra.

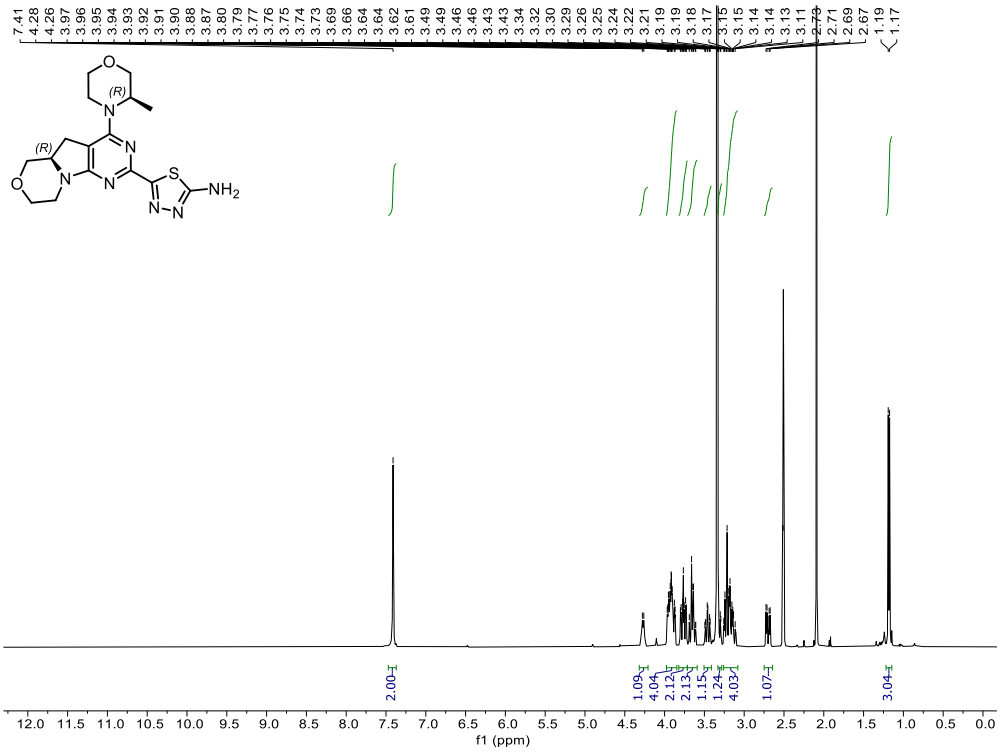
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,2,4-thiadiazol-3-amine (**2**):



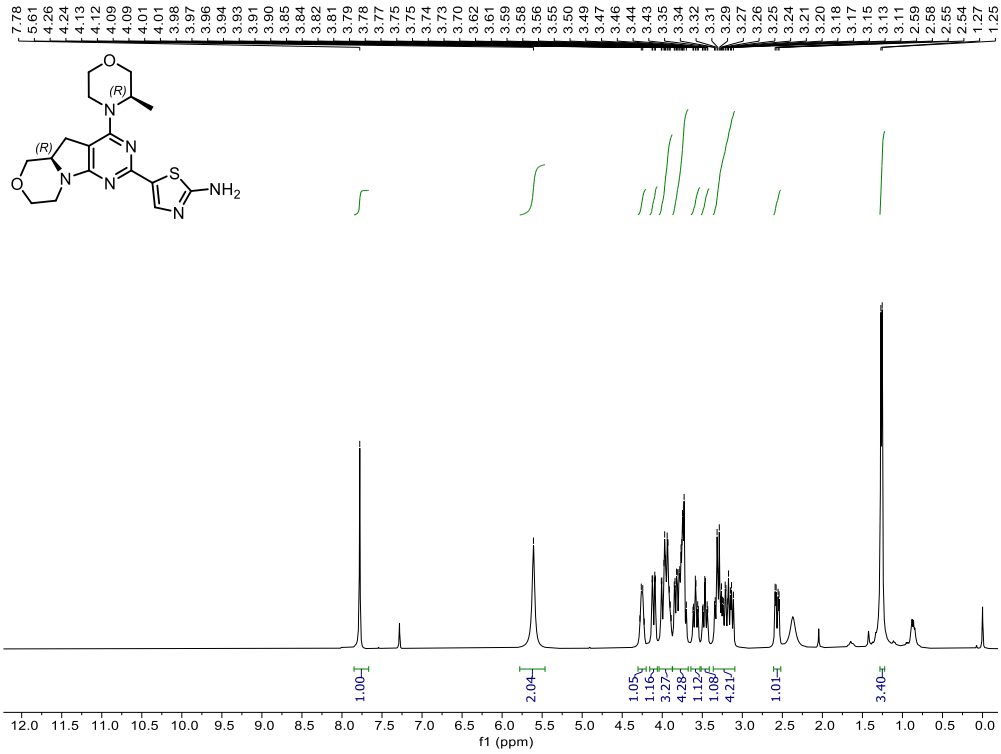
6-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridazin-3-amine (**3**):



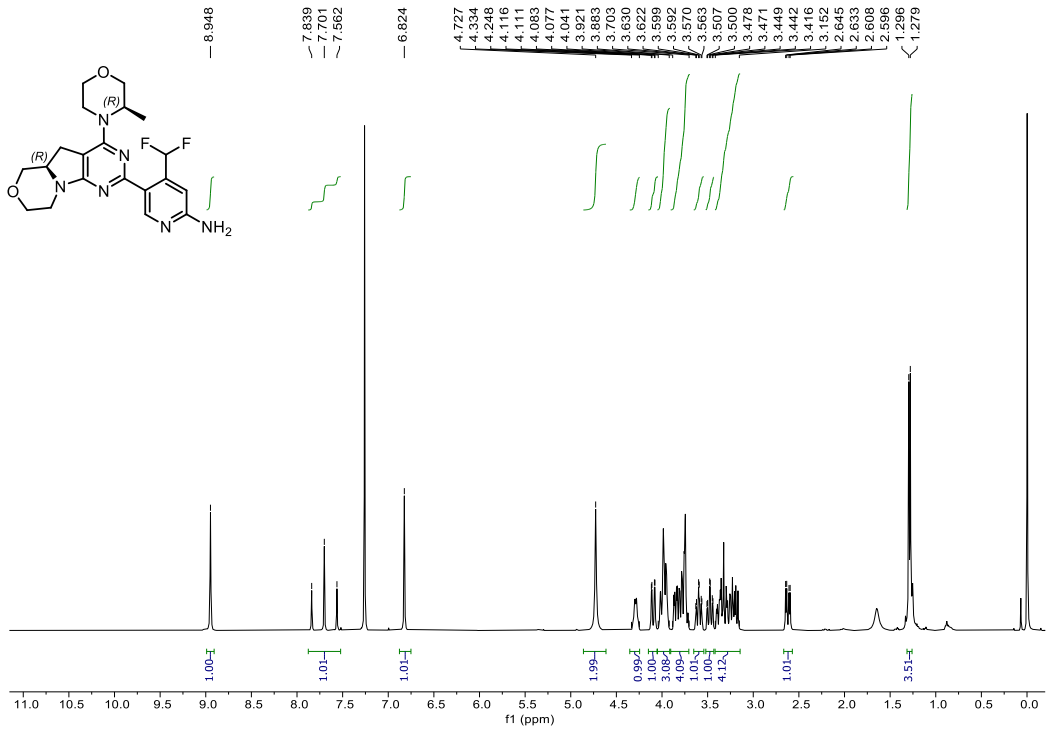
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,3,4-thiadiazol-2-amine (**4**):



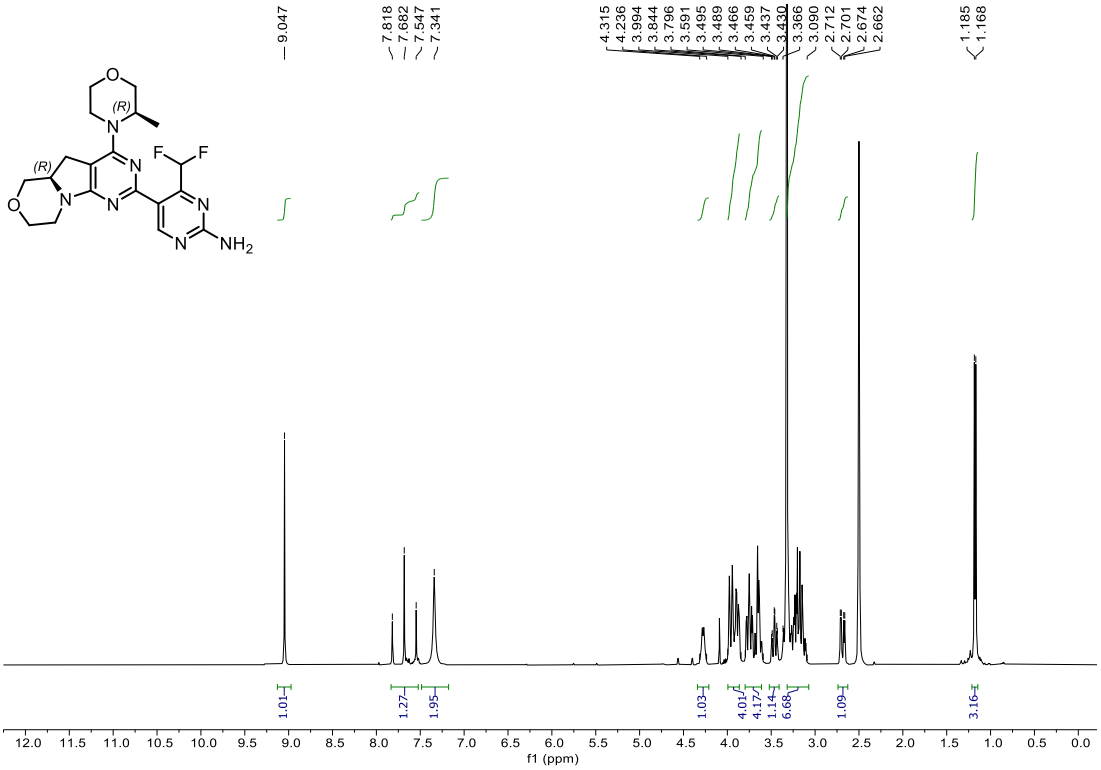
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazin-2-yl)thiazol-2-amine (**6**):



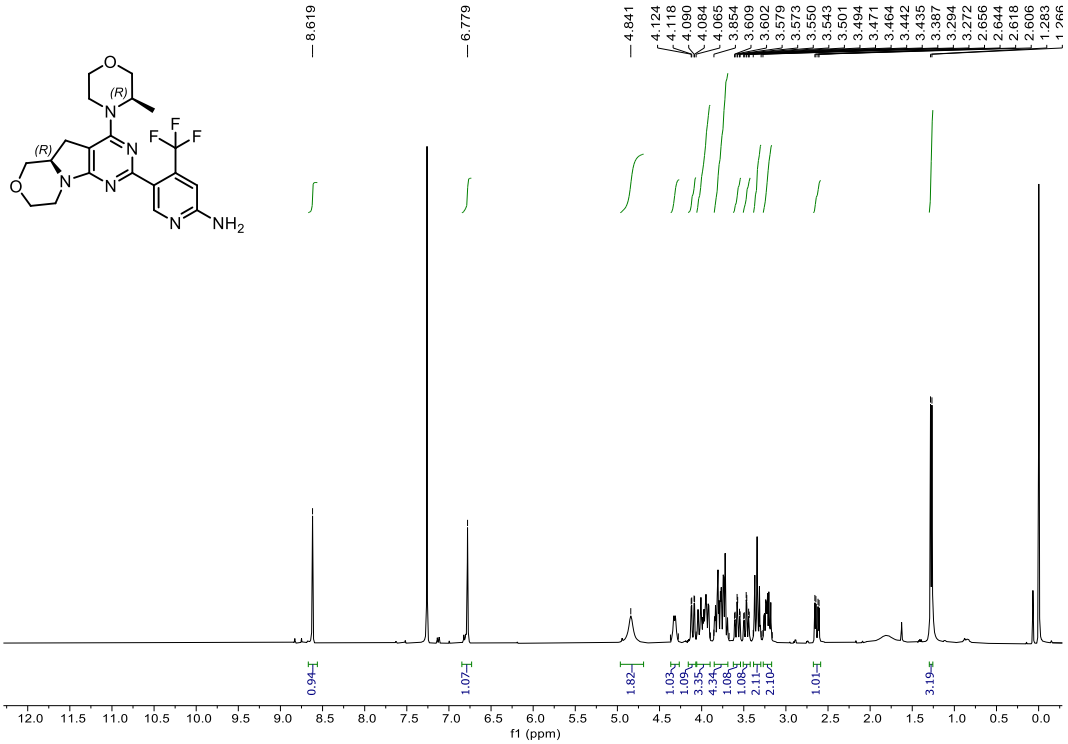
4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridin-2-amine (**7**):



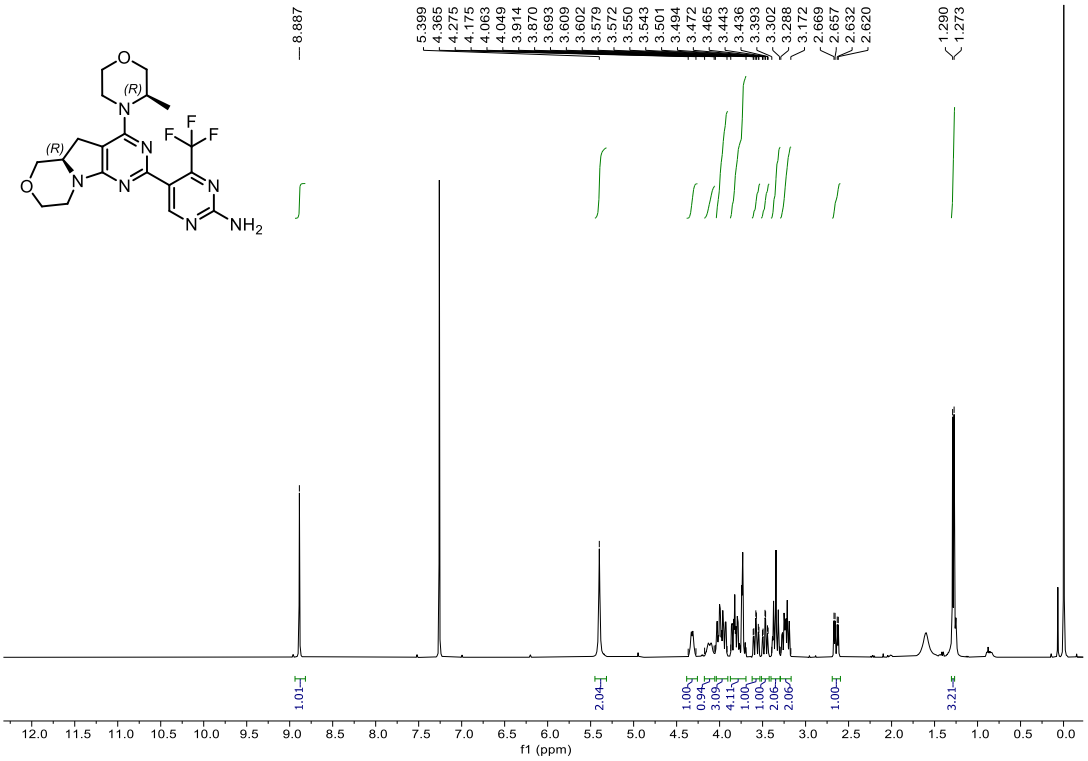
4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyrimidin-2-amine (**8**):



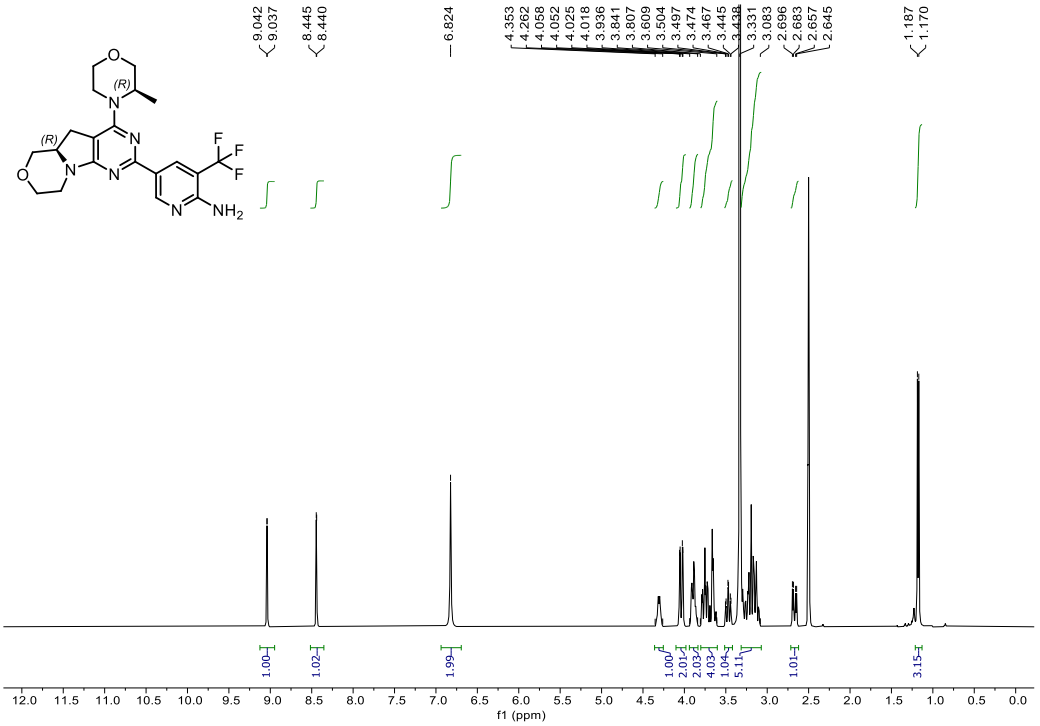
5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (**9**):



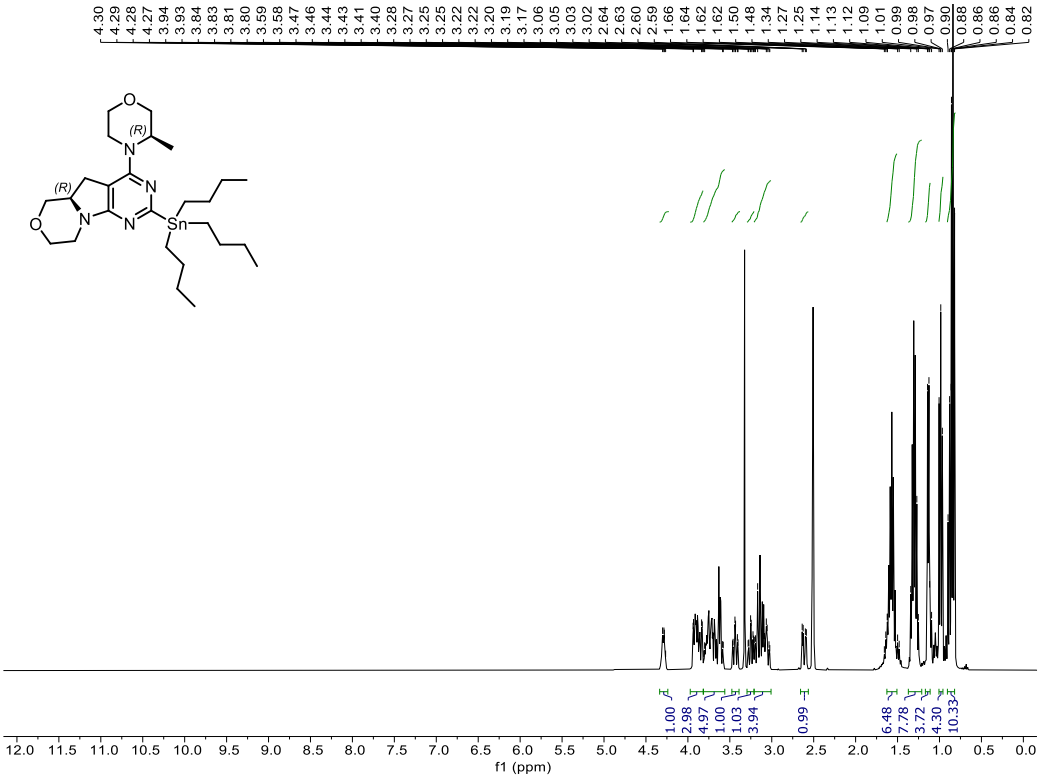
5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine (**10**):



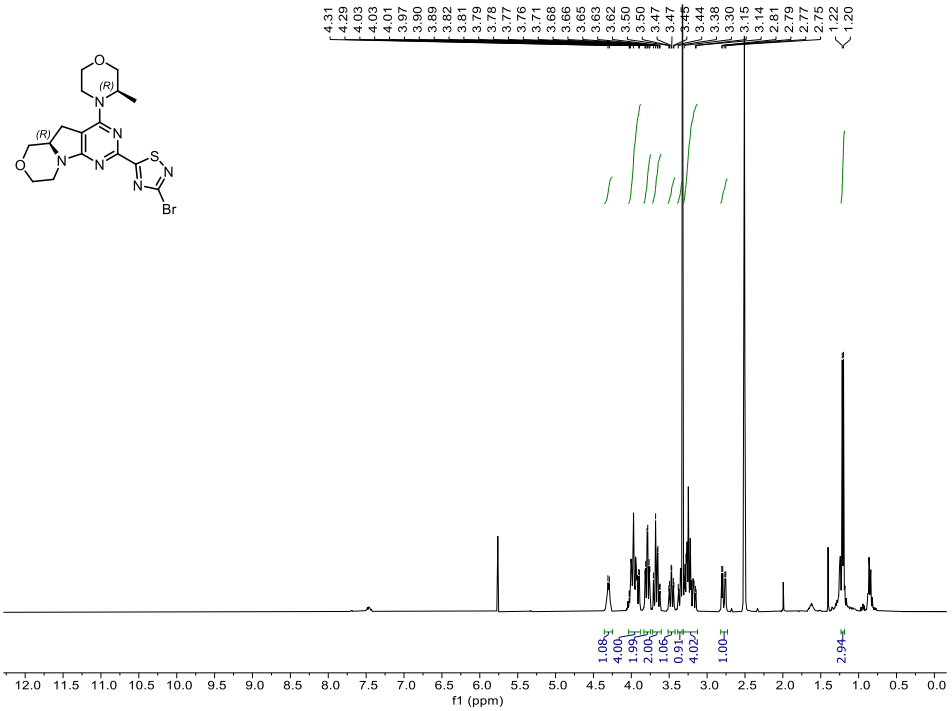
5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-3-(trifluoromethyl)pyridin-2-amine (**11**):



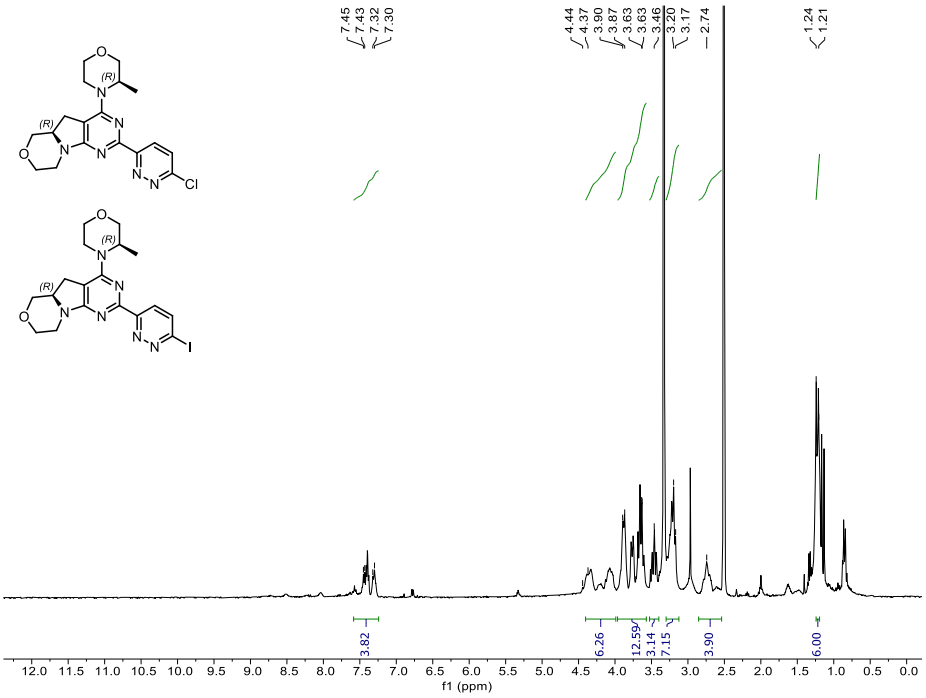
(*R*)-4-((*R*)-3-methylmorpholino)-2-(tributylstannyl)-5a,6,8,9-tetrahydro-5H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazine (**14**):



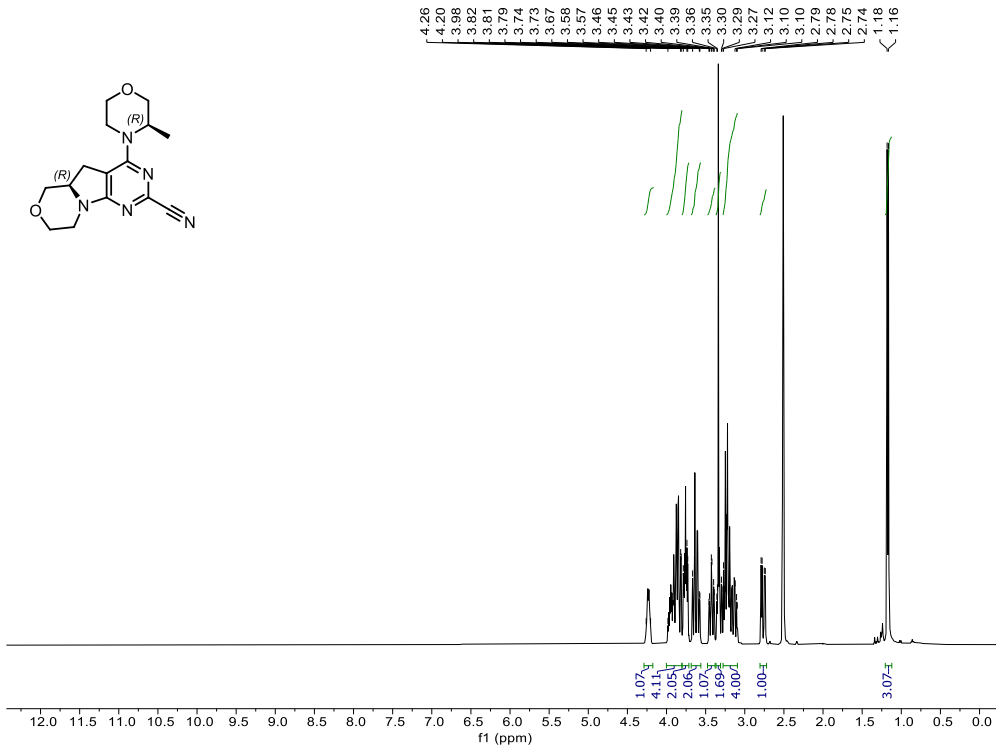
(*R*)-2-(3-bromo-1,2,4-thiadiazol-5-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine (**15**):



(*R*)-2-(6-chloropyridazin-3-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine and (*R*)-2-(6-iodopyridazin-3-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine (**16**):

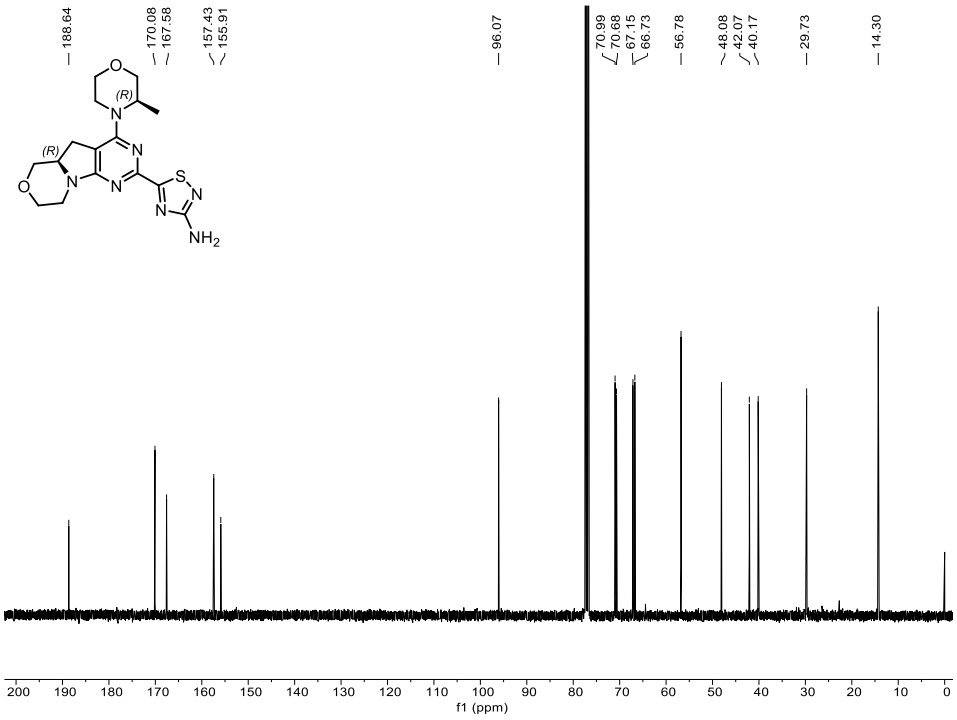


(*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine-2-carbonitrile (**17**):

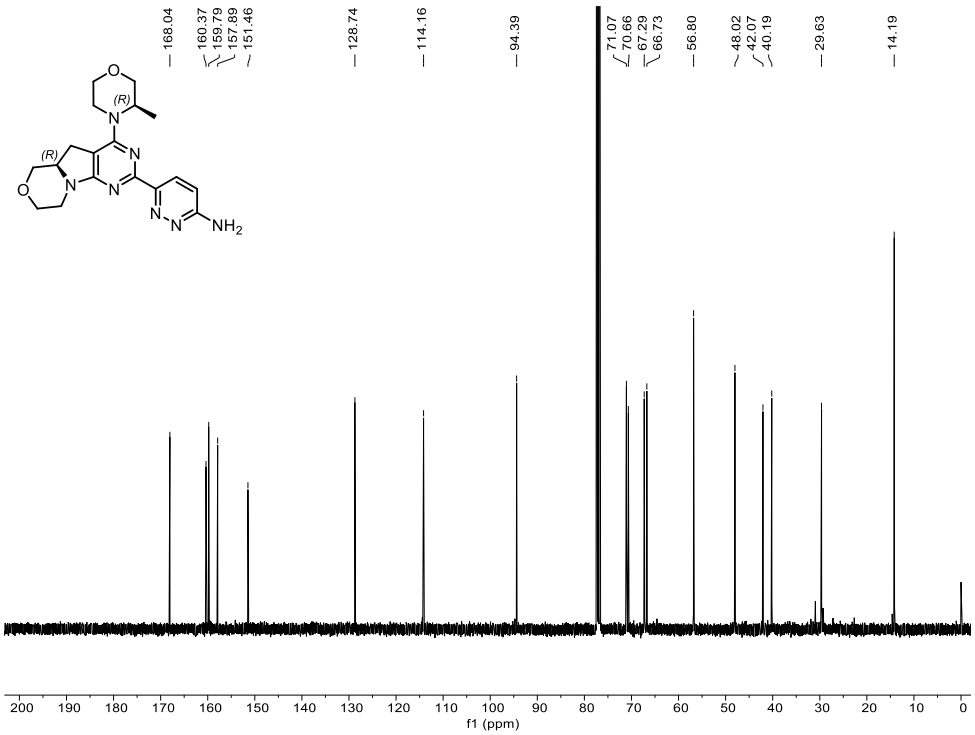


$^{13}C\{^{1}H\}$ NMR Spectra.

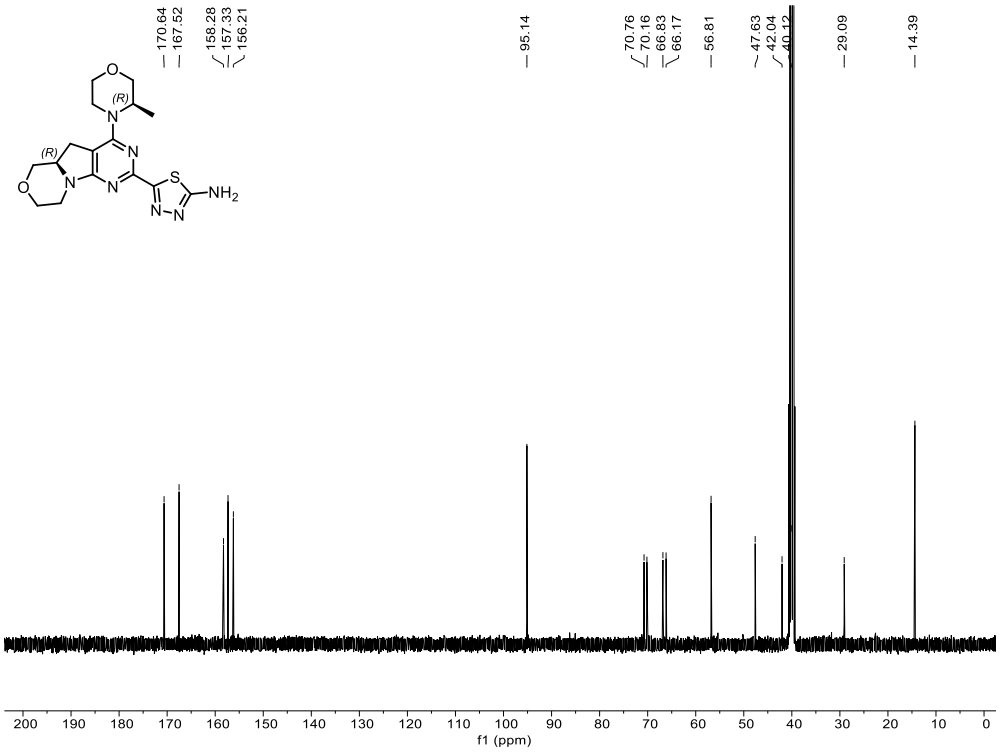
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,2,4-thiadiazol-3-amine (**2**):



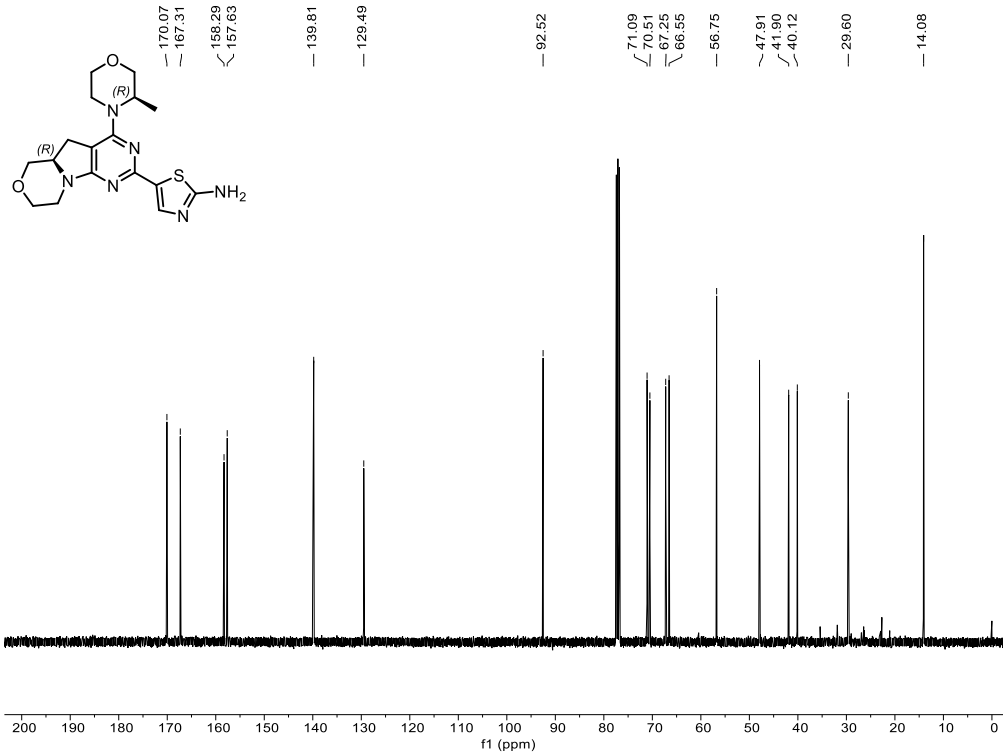
6-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridazin-3-amine (**3**):



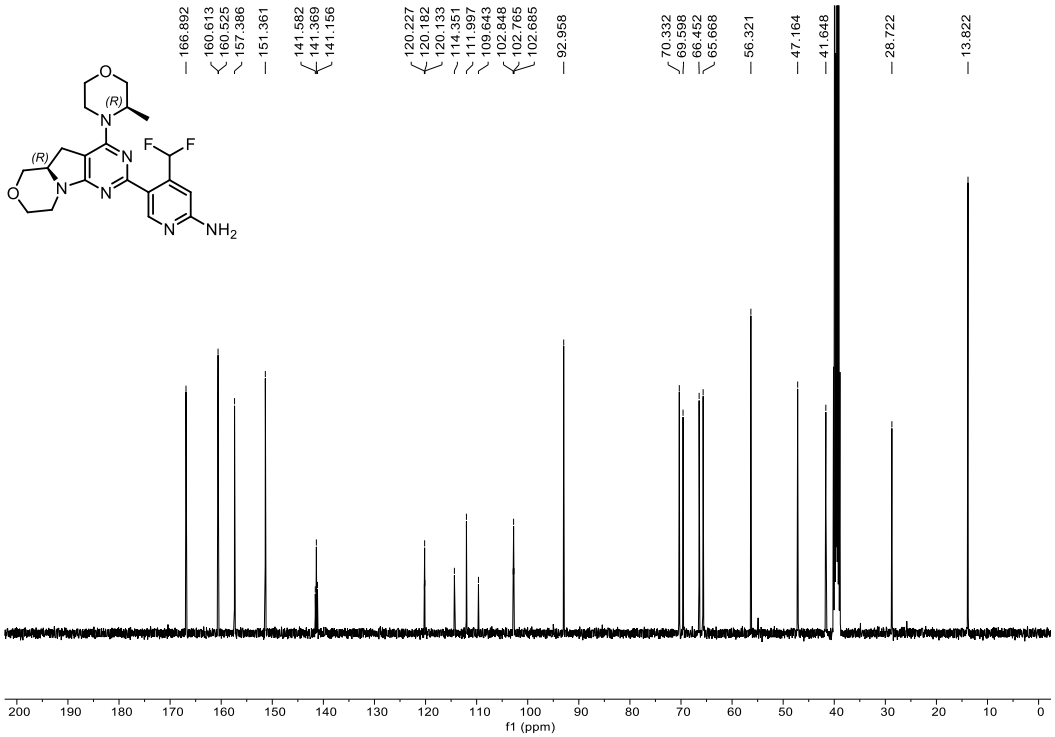
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,3,4-thiadiazol-2-amine (**4**):



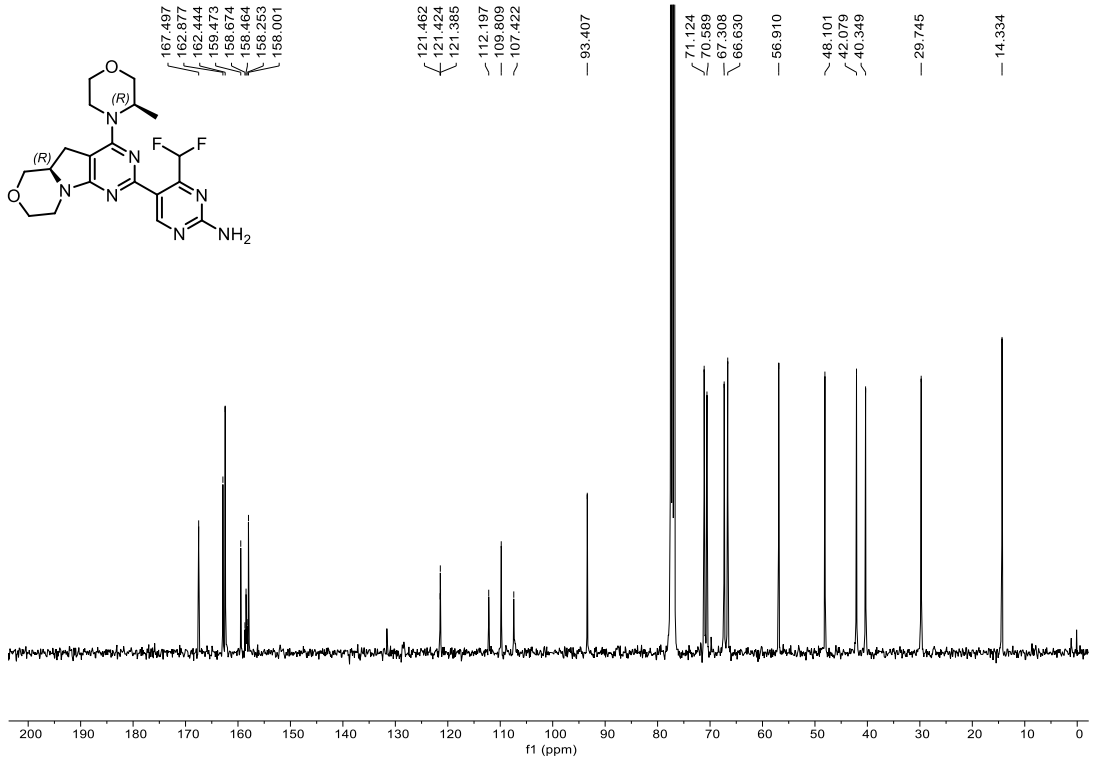
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazin-2-yl)thiazol-2-amine (**6**):



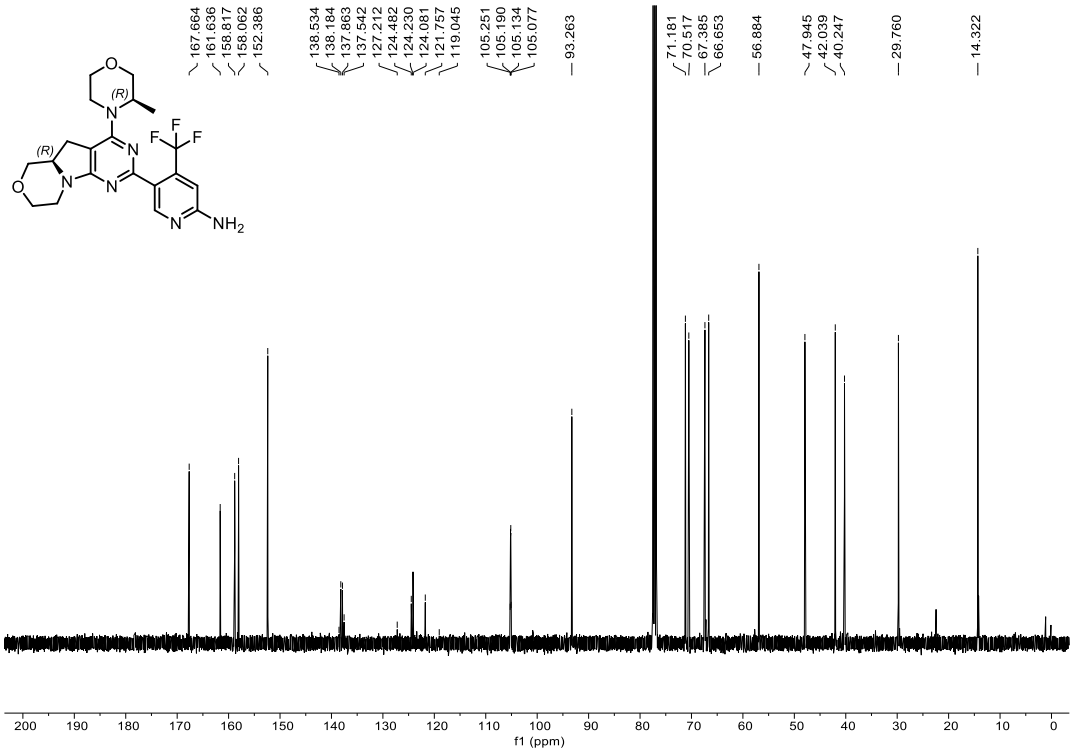
4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridin-2-amine (**7**):



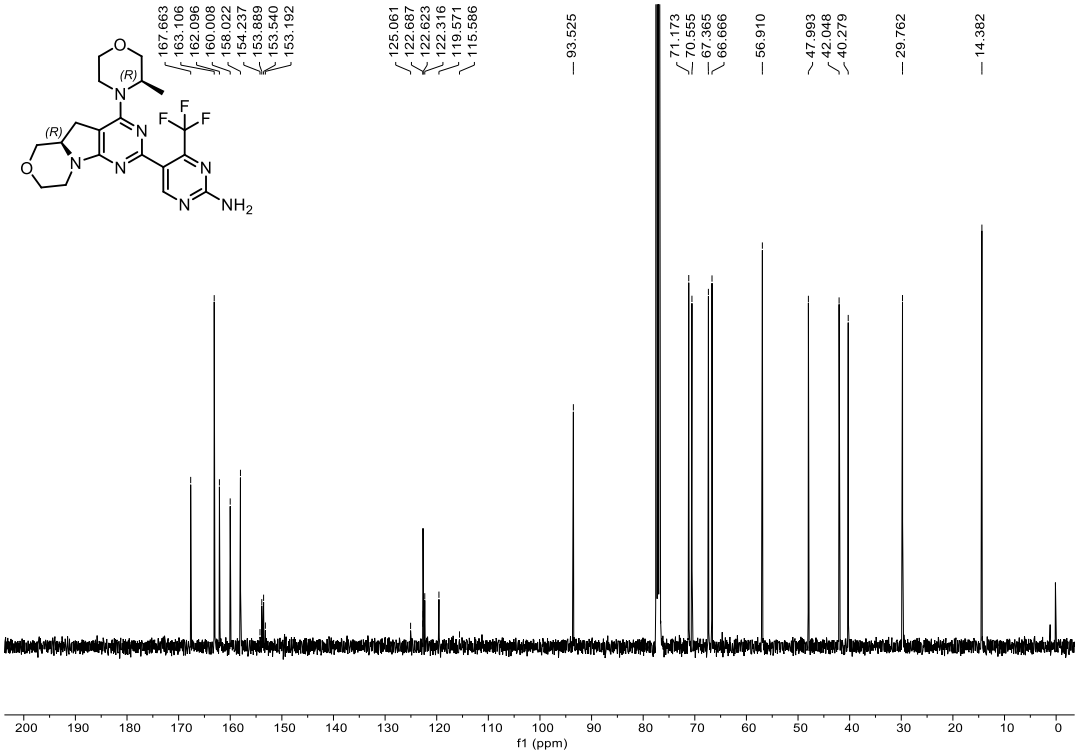
4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyrimidin-2-amine (**8**):



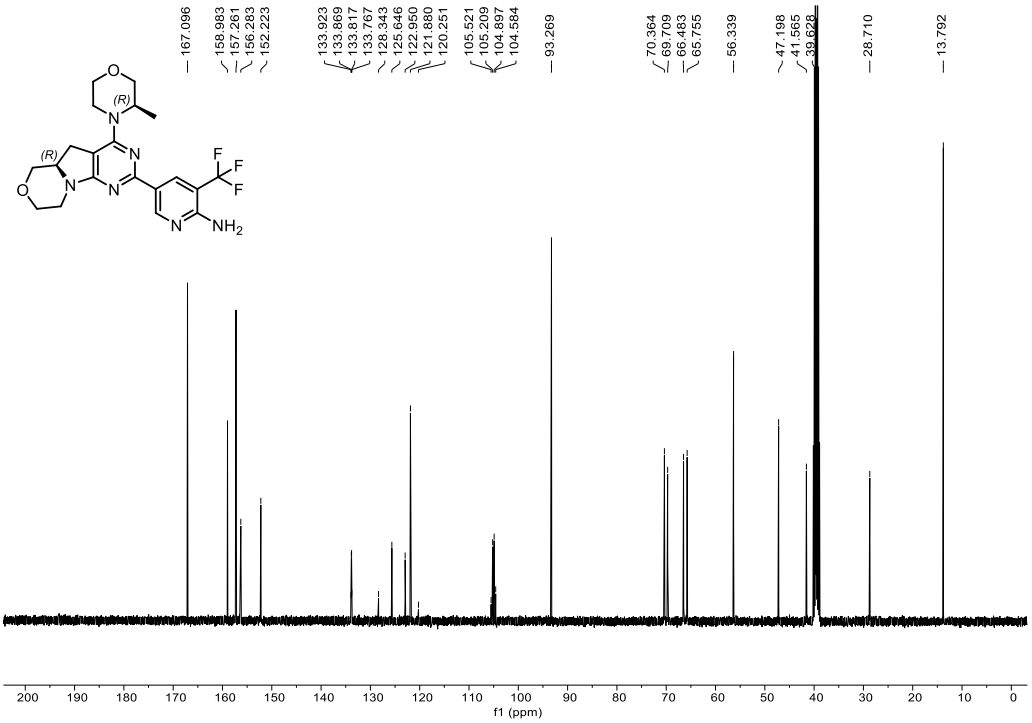
5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (**9**):



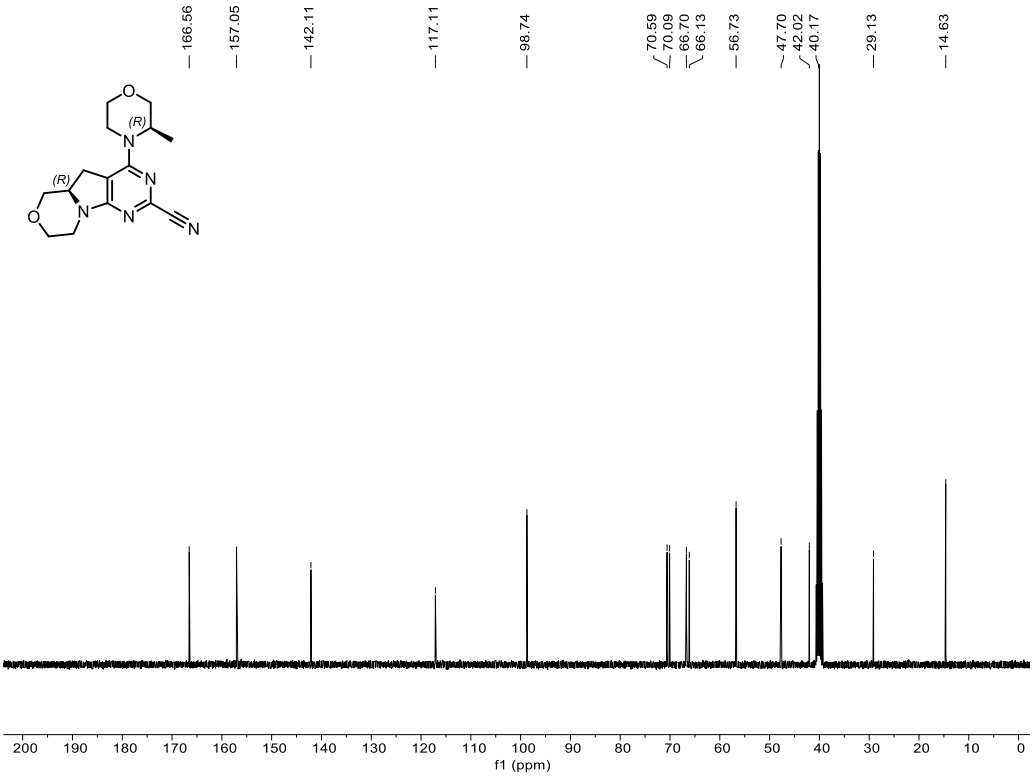
5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine (**10**):



5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-3-(trifluoromethyl)pyridin-2-amine (**11**):

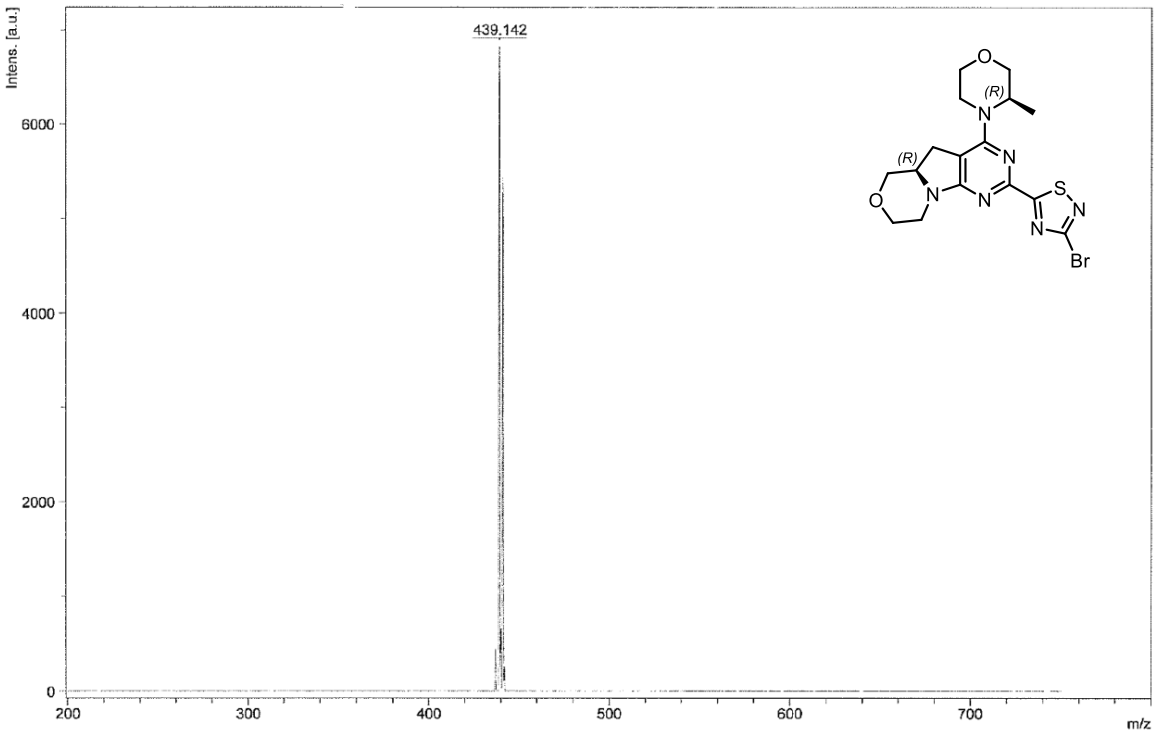


(*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine-2-carbonitrile (**17**):

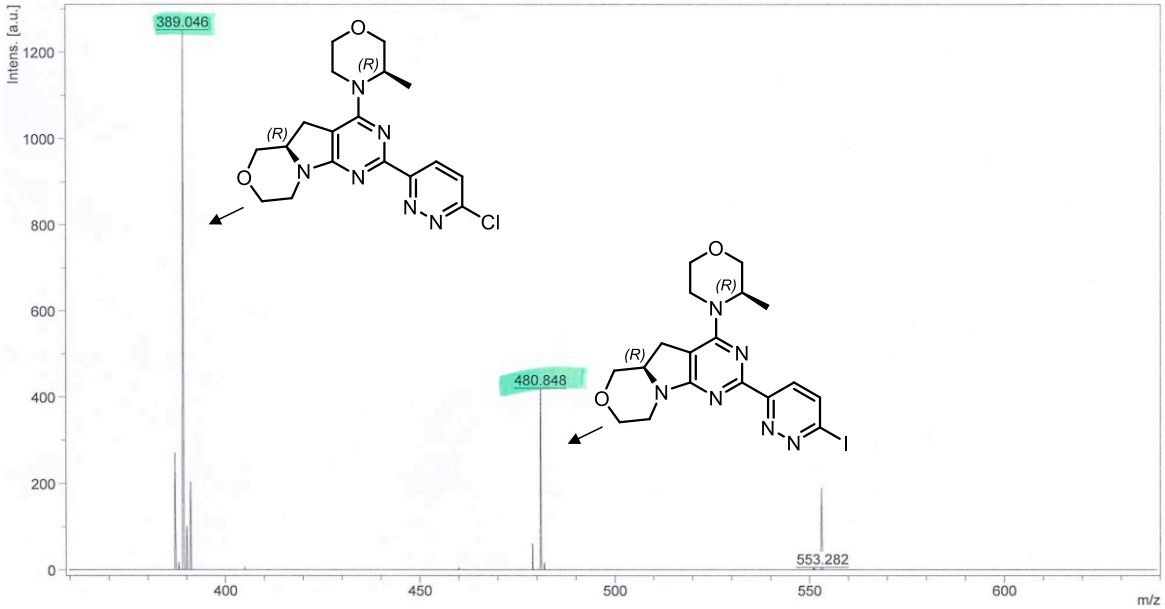


MALDI-MS Spectra.

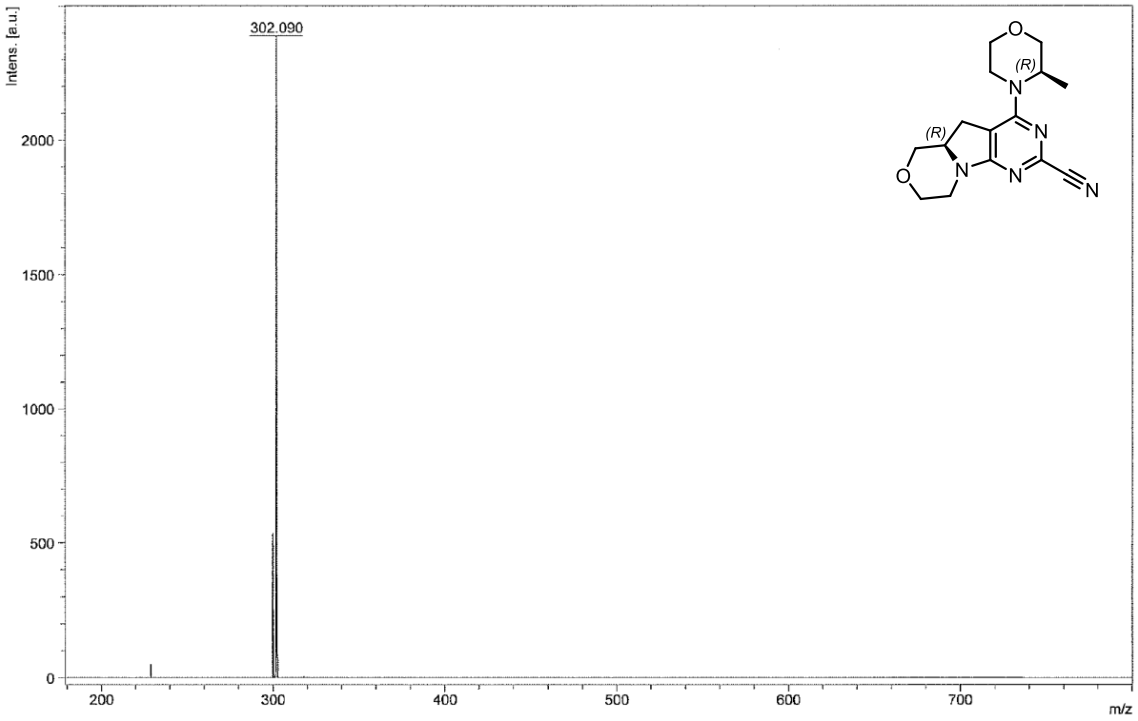
(*R*)-2-(3-bromo-1,2,4-thiadiazol-5-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine (**15**):



(*R*)-2-(6-chloropyridazin-3-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine and (*R*)-2-(6-iodopyridazin-3-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine (**16**):

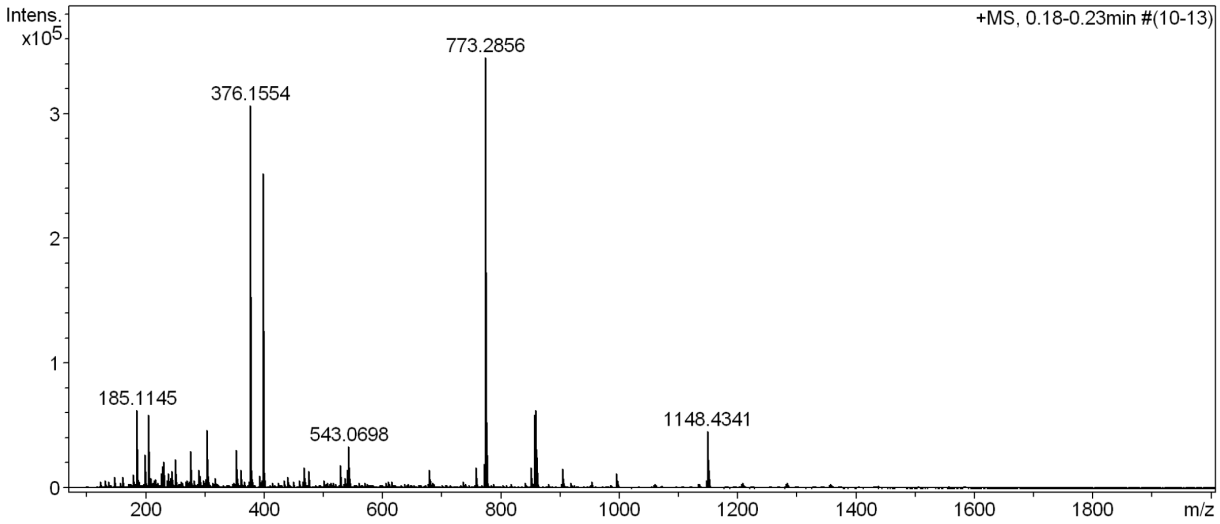


(*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine-2-carbonitrile (**17**):

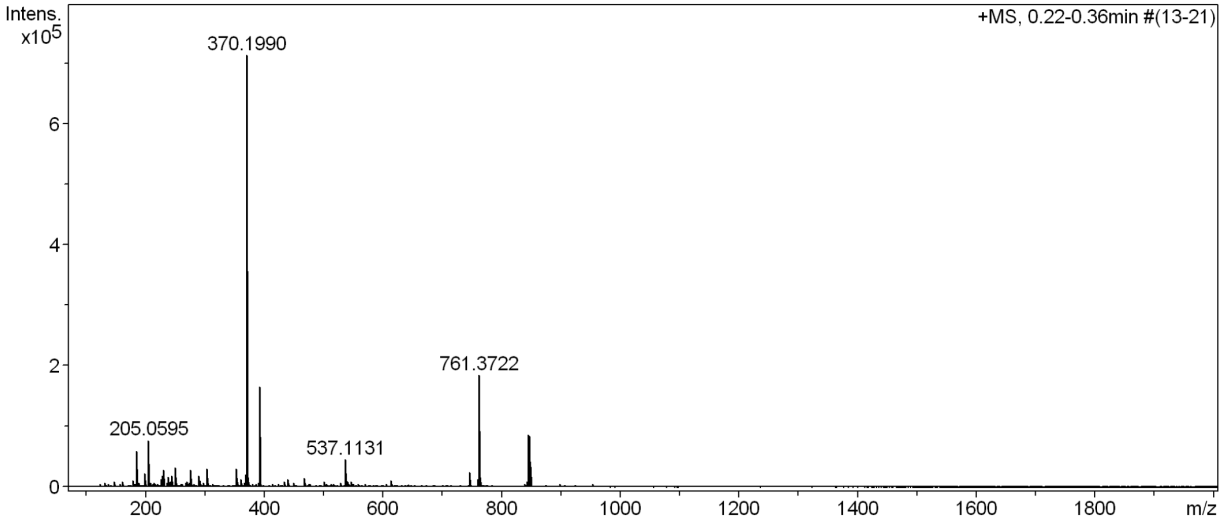


HRMS Spectra.

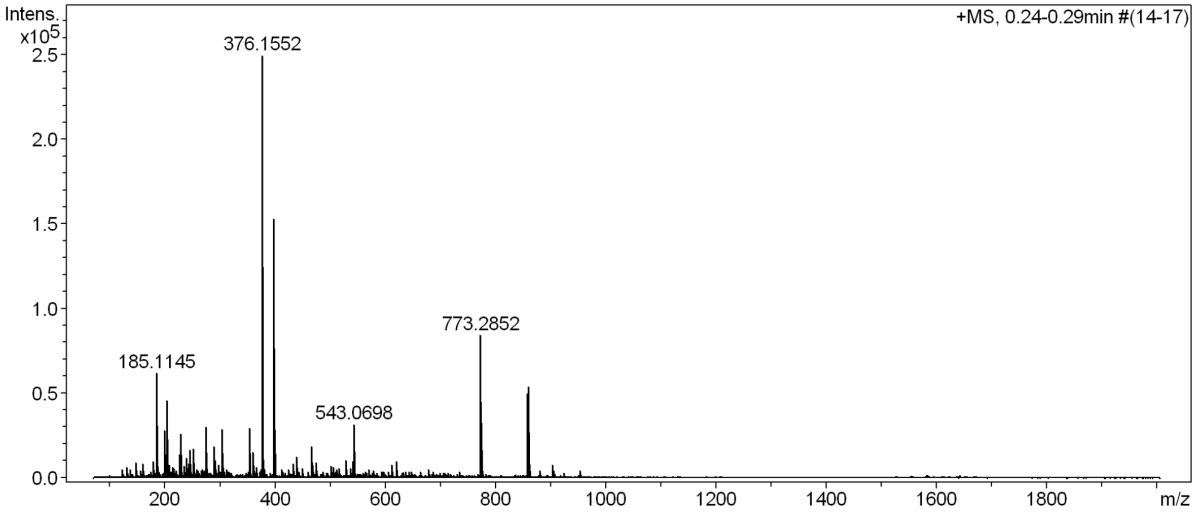
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,2,4-thiadiazol-3-amine (**2**):



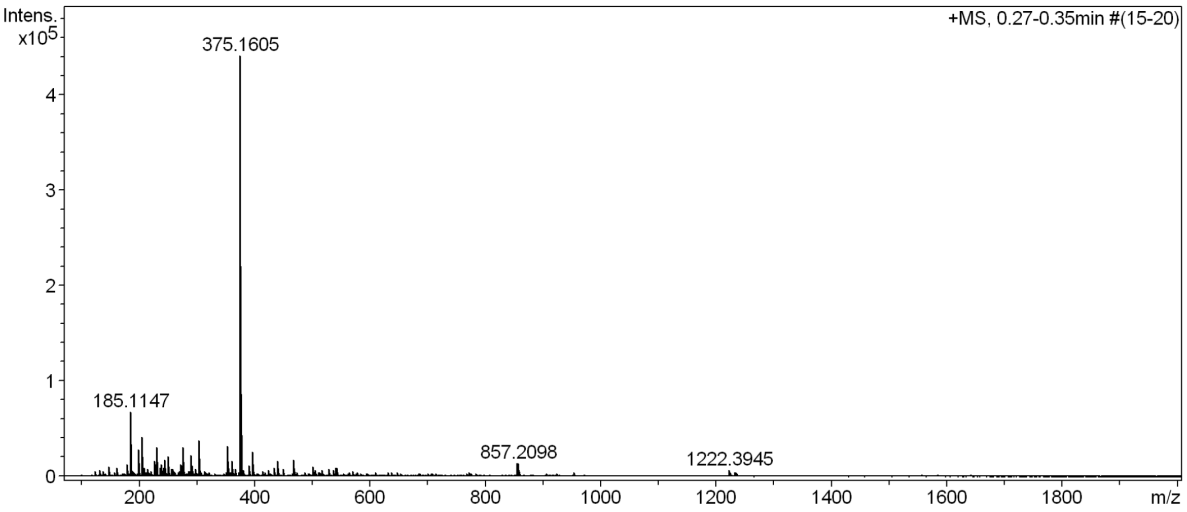
6-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridazin-3-amine (**3**):



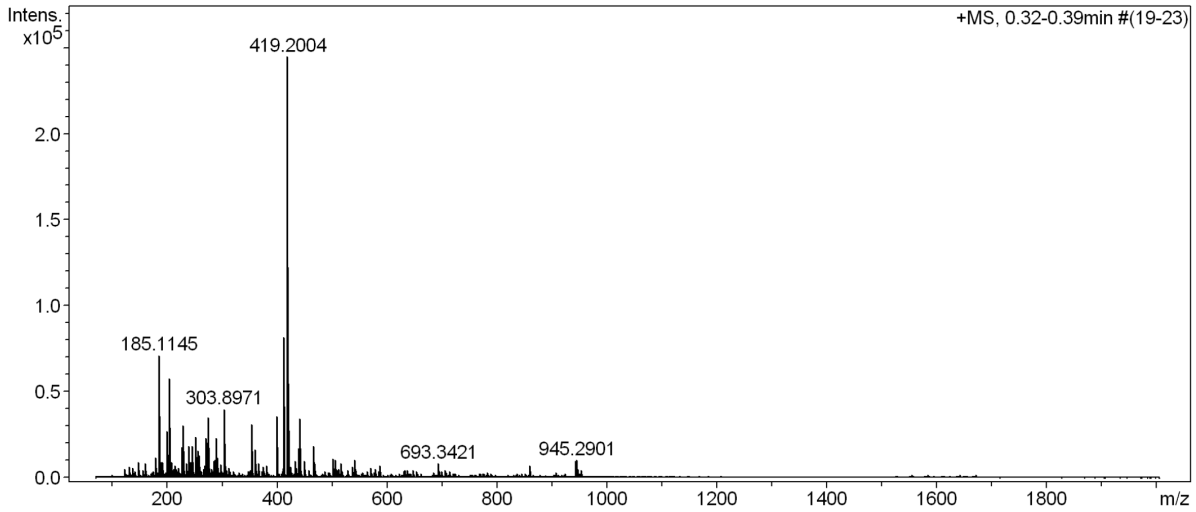
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,3,4-thiadiazol-2-amine (**4**):



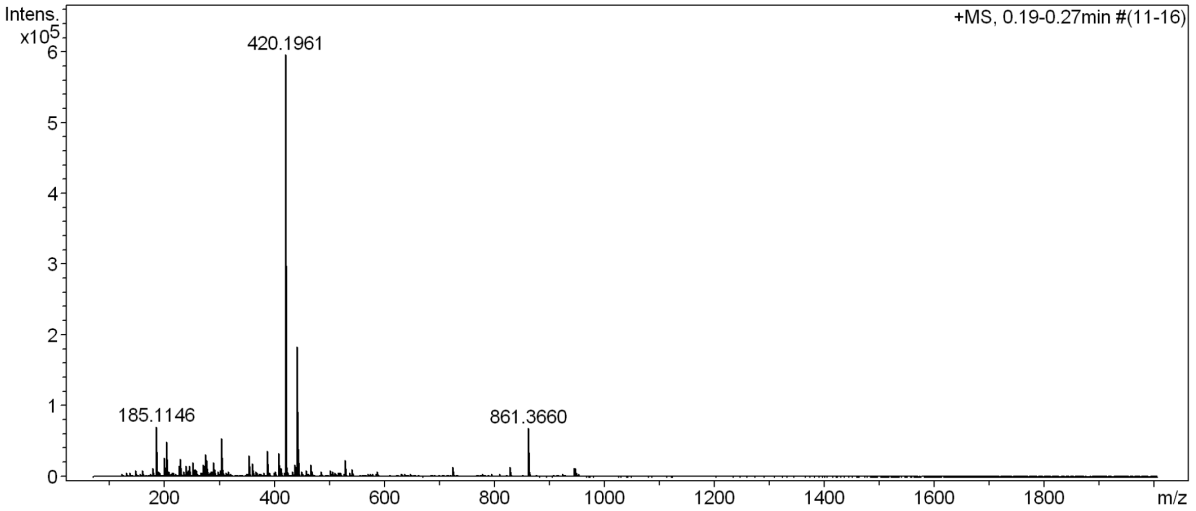
5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazin-2-yl)thiazol-2-amine (**6**):



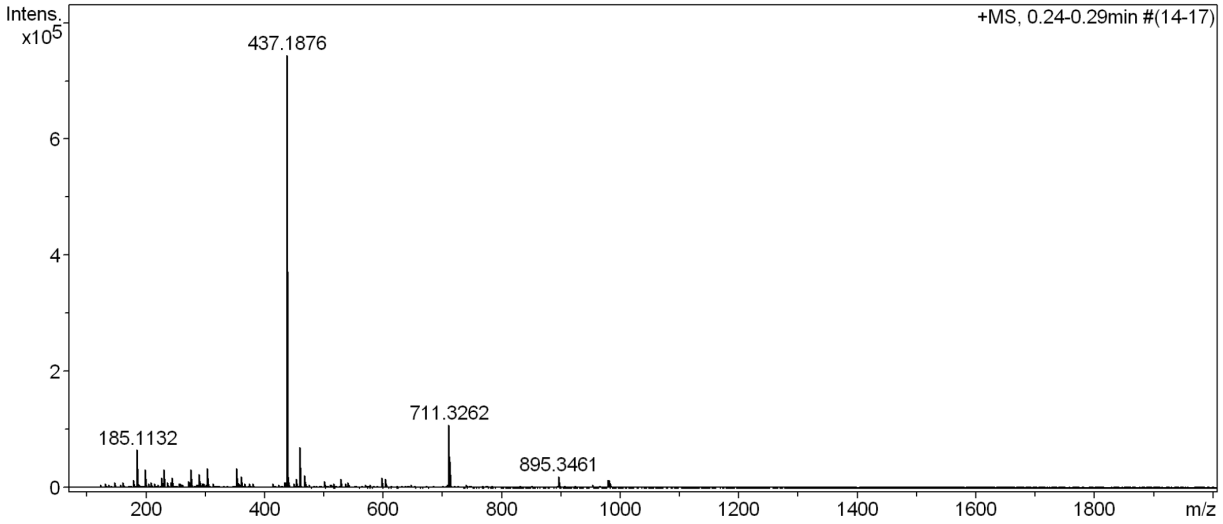
4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridin-2-amine (**7**):



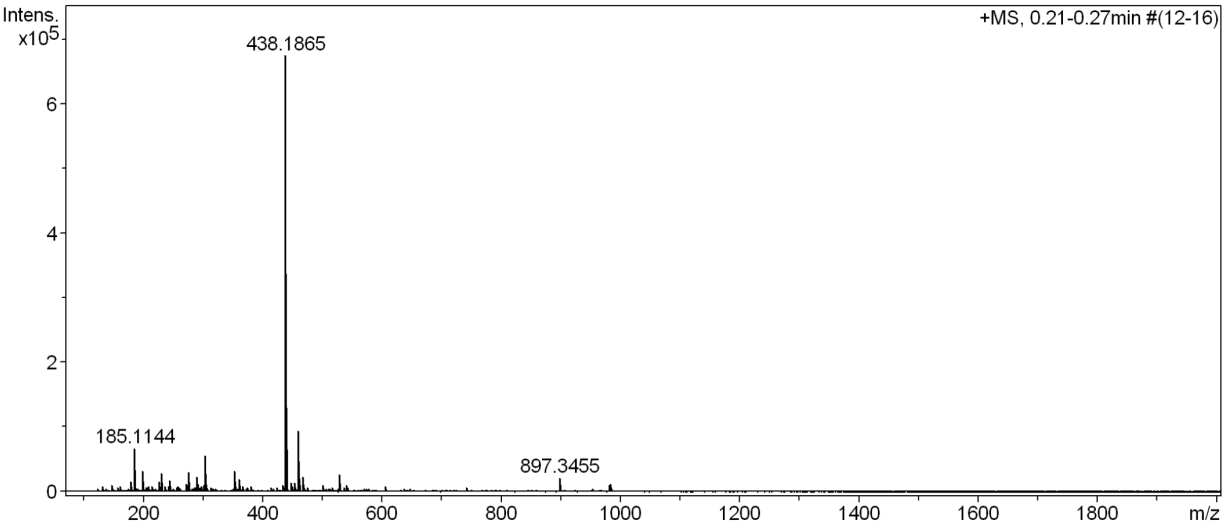
4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyrimidin-2-amine (**8**):



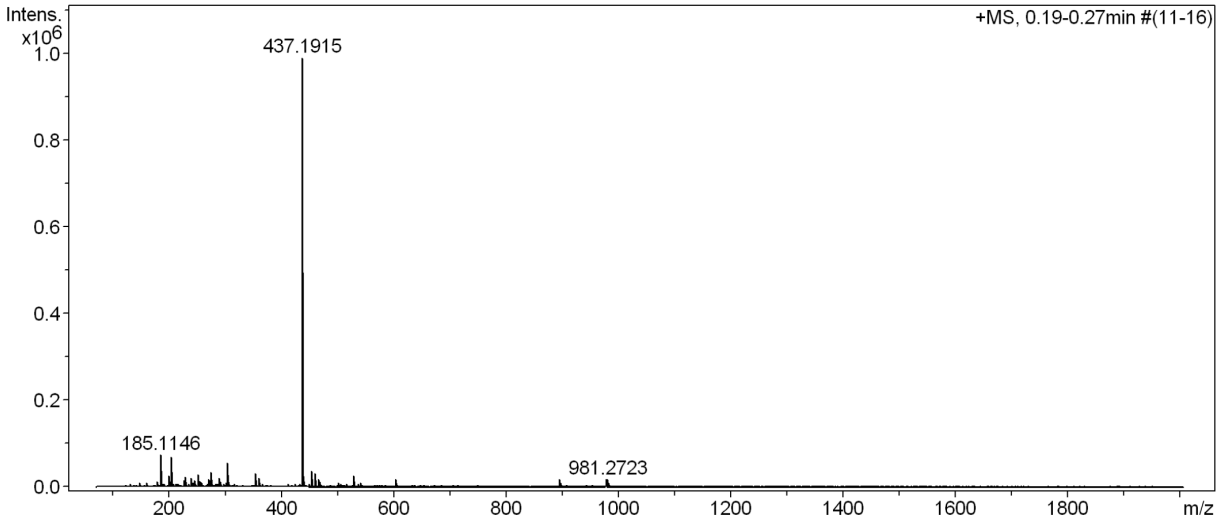
5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (**9**):



5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine (**10**):

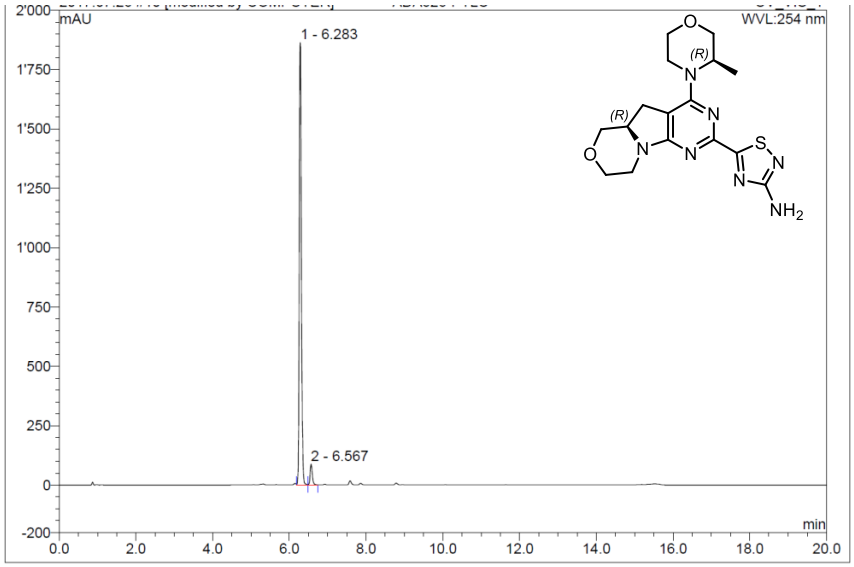


5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-3-(trifluoromethyl)pyridin-2-amine (**11**):



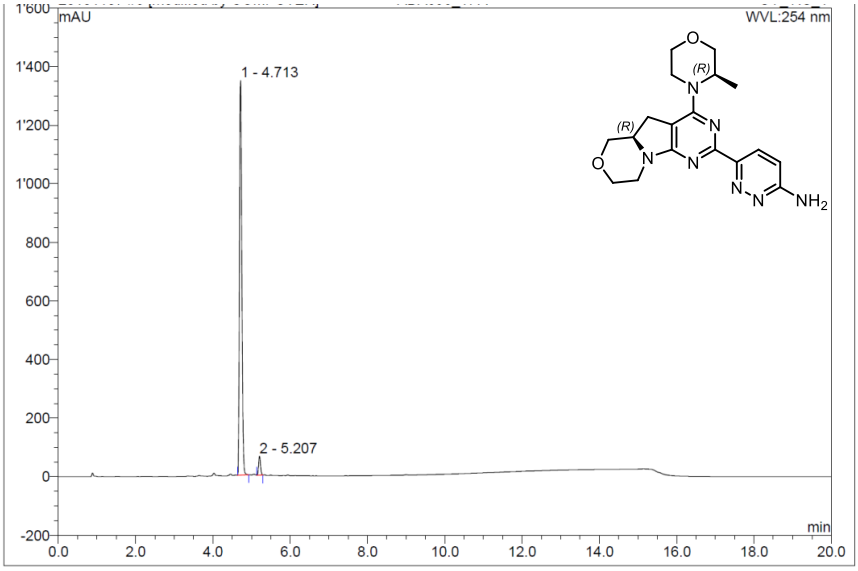
HPLC Chromatograms.

5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,2,4-thiadiazol-3-amine (**2**):



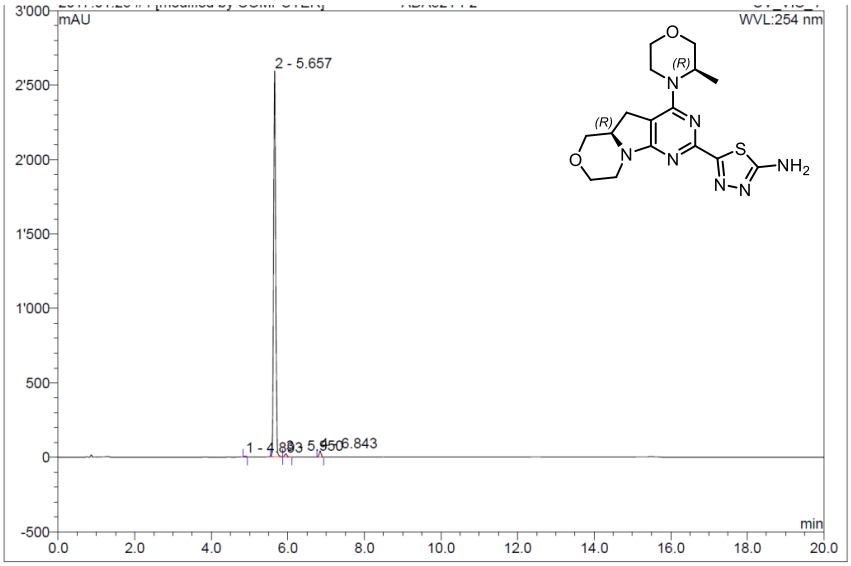
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.28	n.a.	1862.945	118.061	95.40	n.a.	M *
2	6.57	n.a.	87.319	5.691	4.60	n.a.	MB*
Total:			1950.264	123.752	100.00	0.000	

6-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridazin-3-amine (**3**):



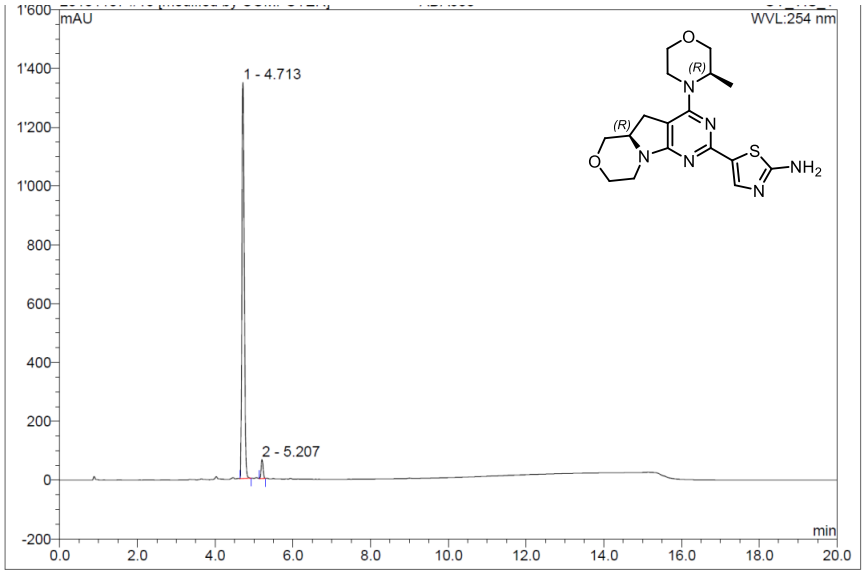
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.71	n.a.	1346.976	94.298	96.17	n.a.	BMB
2	5.21	n.a.	64.905	3.757	3.83	n.a.	BMB
Total:			1411.881	98.055	100.00	0.000	

5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-1,3,4-thiadiazol-2-amine (**4**):



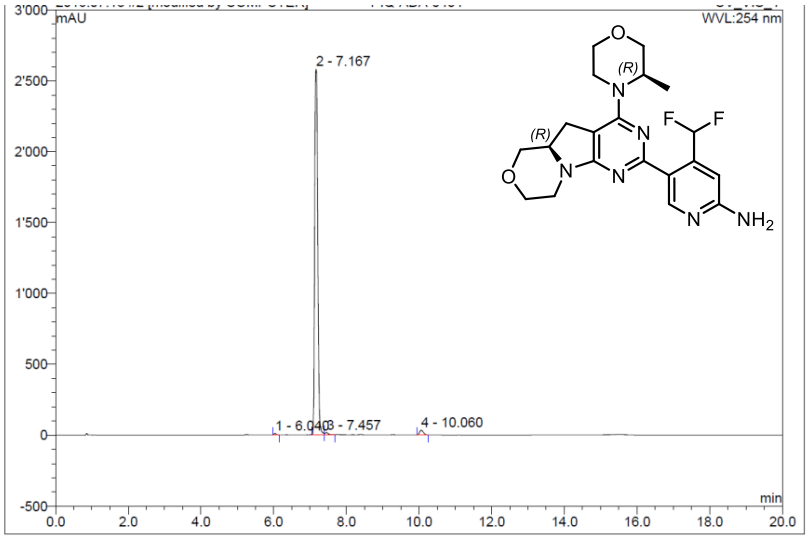
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.89	n.a.	6.415	0.337	0.20	n.a.	BMB*
2	5.66	n.a.	2591.400	166.156	97.47	n.a.	BMB
3	5.95	n.a.	22.191	1.432	0.84	n.a.	BMB
4	6.84	n.a.	40.207	2.537	1.49	n.a.	BMB*
Total:			2660.213	170.462	100.00	0.000	

5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5H-pyrimido[5',4':4,5]pyrrolo[2,1-c][1,4]oxazin-2-yl)thiazol-2-amine (**6**):



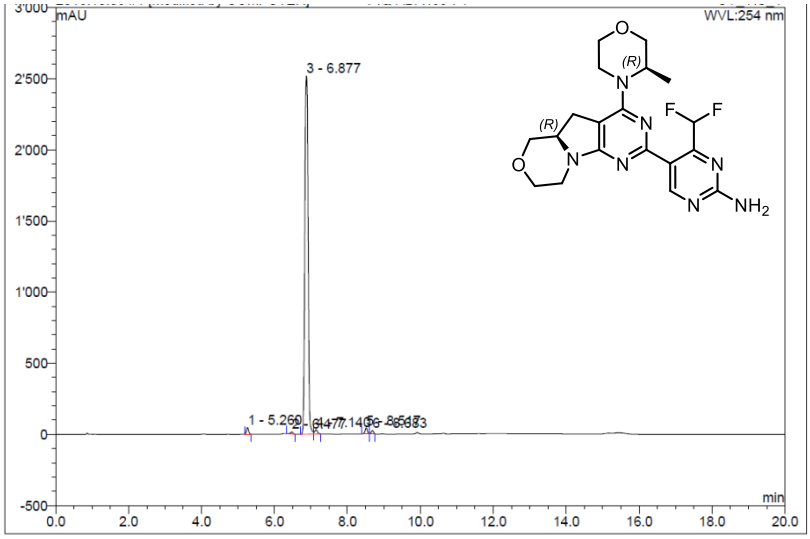
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.71	n.a.	1346.976	94.298	96.17	n.a.	BMB
2	5.21	n.a.	64.905	3.757	3.83	n.a.	BMB
Total:			1411.881	98.055	100.00	0.000	

4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyridin-2-amine (**7**):



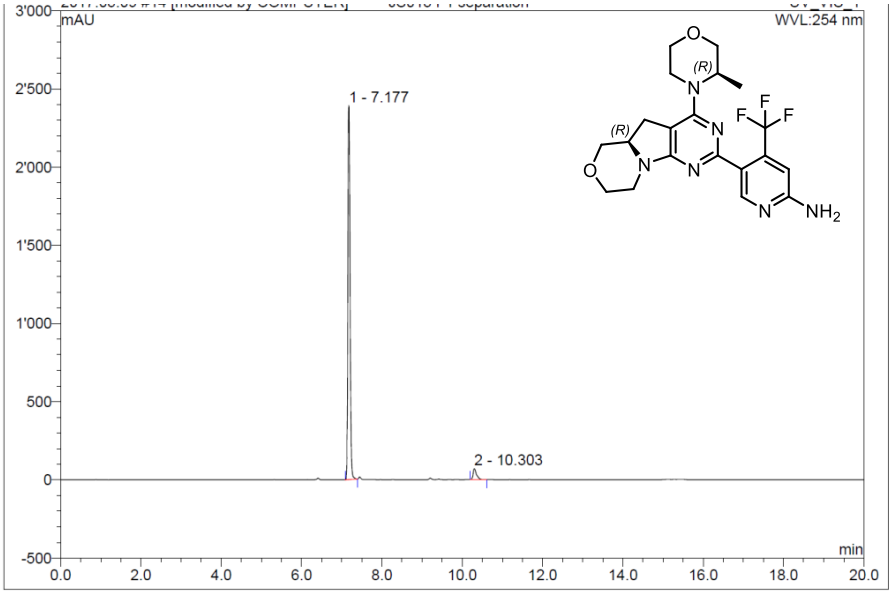
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.04	n.a.	11.235	0.761	0.29	n.a.	BMB*
2	7.17	n.a.	2579.323	257.119	97.52	n.a.	BM
3	7.46	n.a.	15.458	1.560	0.59	n.a.	MB
4	10.06	n.a.	33.908	4.213	1.60	n.a.	BMB*
Total:			2639.924	263.653	100.00	0.000	

4-(Difluoromethyl)-5-((*R*)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)pyrimidin-2-amine (**8**):



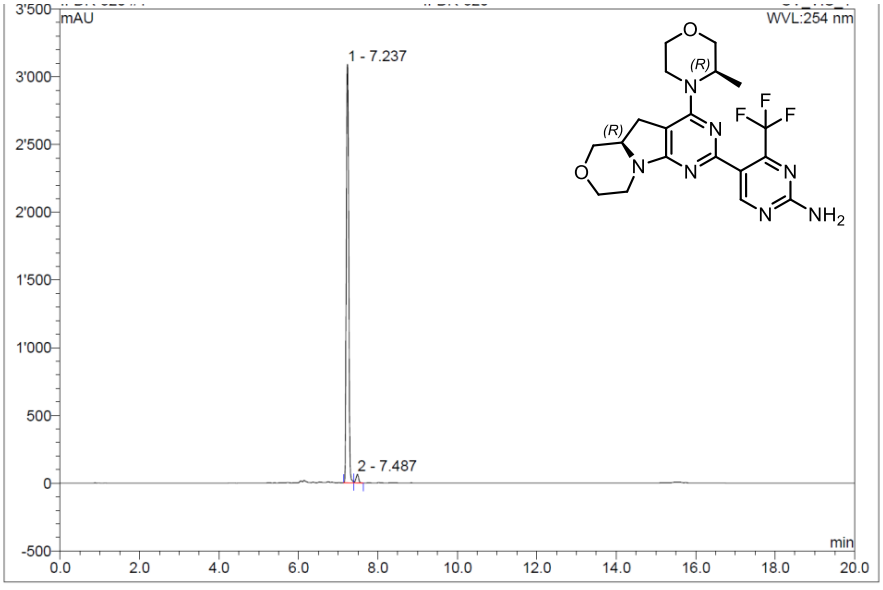
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.26	n.a.	46.326	3.144	1.14	n.a.	BMB*
2	6.48	n.a.	14.151	1.116	0.40	n.a.	BMB*
3	6.88	n.a.	2517.525	264.739	95.84	n.a.	BM *
4	7.14	n.a.	29.432	2.598	0.94	n.a.	MB*
5	8.52	n.a.	41.009	3.035	1.10	n.a.	BM *
6	8.68	n.a.	23.224	1.613	0.58	n.a.	MB*
Total:			2671.667	276.244	100.00	0.000	

5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (**9**):



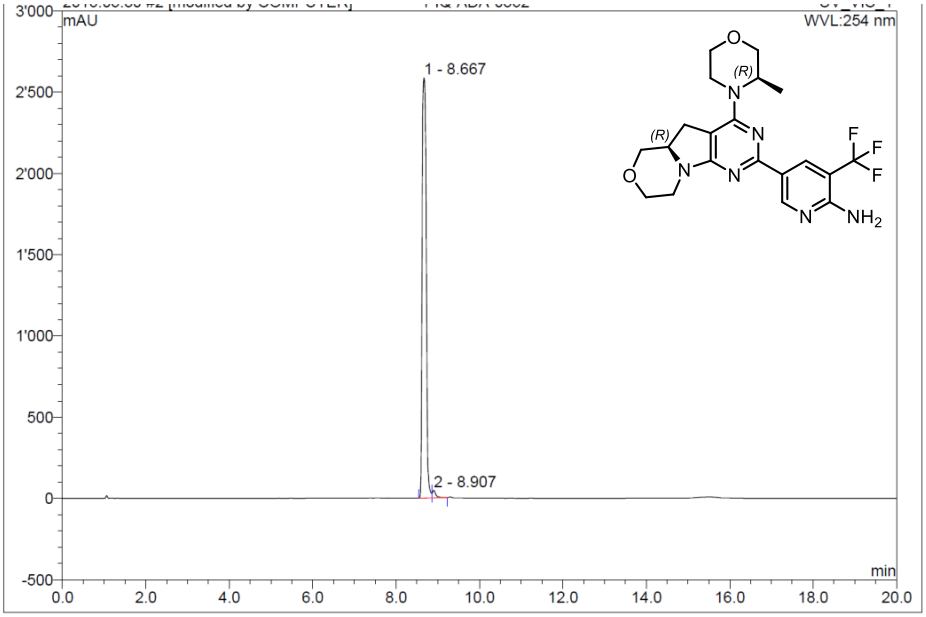
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.18	n.a.	2392.216	147.767	95.55	n.a.	BMB*
2	10.30	n.a.	69.027	6.884	4.45	n.a.	BMB
Total:			2461.243	154.651	100.00	0.000	

5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-4-(trifluoromethyl)pyrimidin-2-amine (**10**):



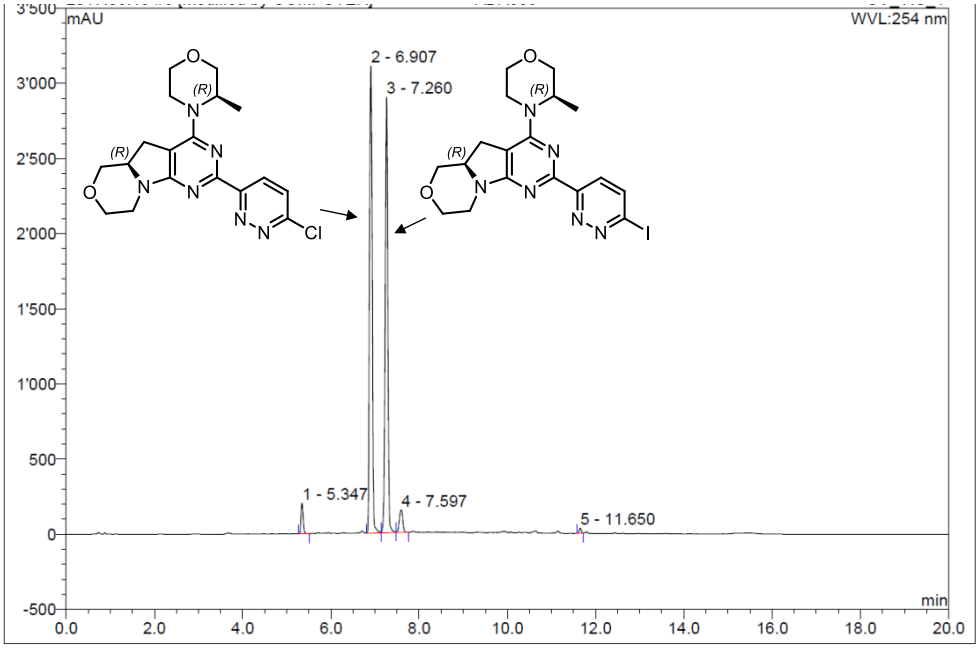
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.24	n.a.	3089.199	217.495	97.86	n.a.	BM
2	7.49	n.a.	63.683	4.755	2.14	n.a.	MB
Total:			3152.882	222.250	100.00	0.000	

5-((*R*)-4-((*R*)-3-Methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazin-2-yl)-3-(trifluoromethyl)pyridin-2-amine (**11**):



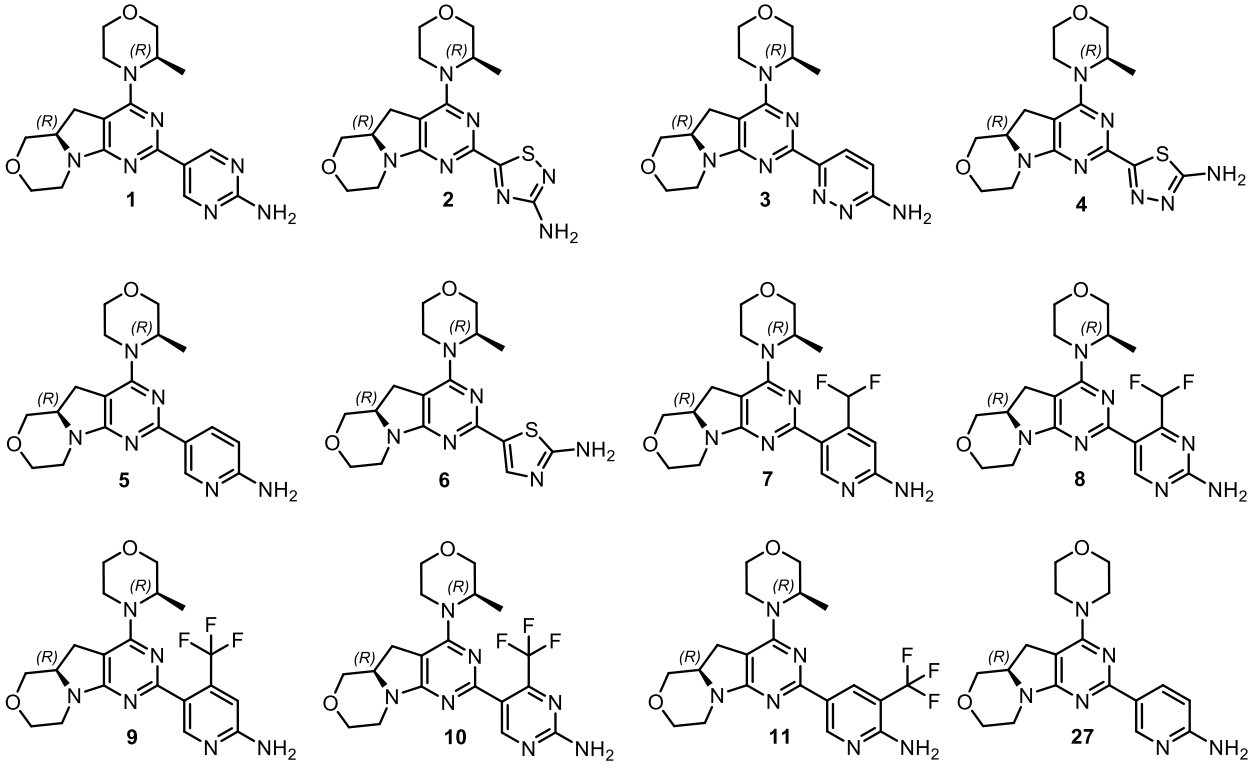
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.67	n.a.	2586.235	291.648	98.43	n.a.	BM
2	8.91	n.a.	45.831	4.660	1.57	n.a.	MB
Total:			2632.066	296.308	100.00	0.000	

(*R*)-2-(6-chloropyridazin-3-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine and (*R*)-2-(6-iodopyridazin-3-yl)-4-((*R*)-3-methylmorpholino)-5a,6,8,9-tetrahydro-5*H*-pyrimido[5',4':4,5]pyrrolo[2,1-*c*][1,4]oxazine (**16**):

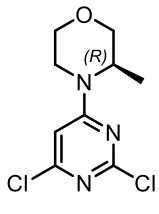


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.35	n.a.	204.636	11.719	2.65	n.a.	BMB
2	6.91	n.a.	3107.569	220.635	49.93	n.a.	BM
3	7.26	n.a.	2899.062	194.258	43.96	n.a.	M
4	7.60	n.a.	149.685	13.432	3.04	n.a.	MB
5	11.65	n.a.	33.307	1.840	0.42	n.a.	BMB
Total:			6394.259	441.884	100.00	0.000	

Final Compounds.



Intermediates.



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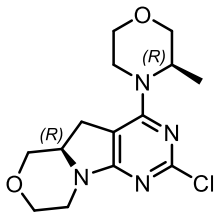

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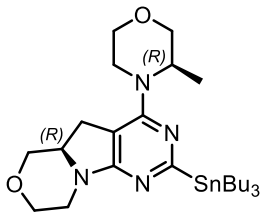

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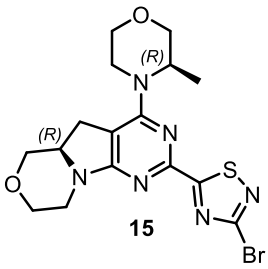

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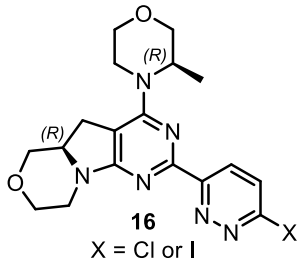

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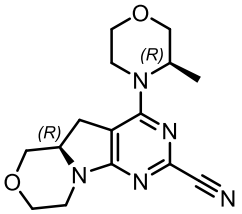

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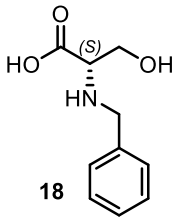

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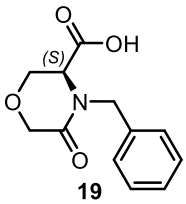

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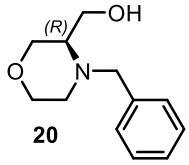

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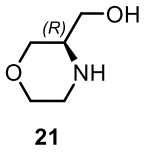

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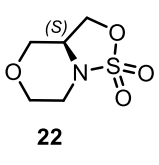

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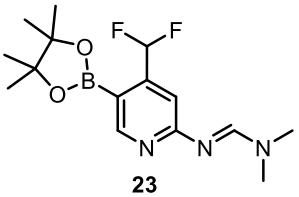

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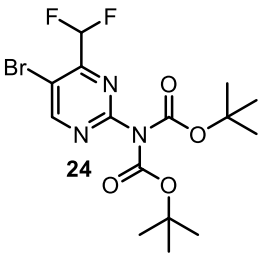

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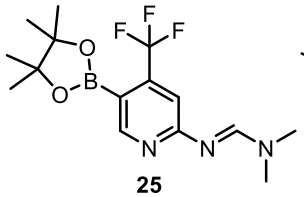

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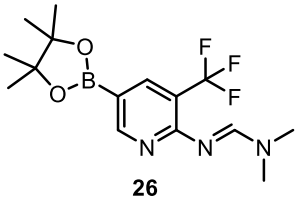

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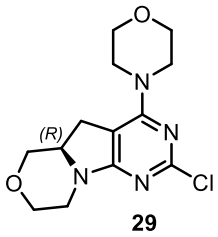

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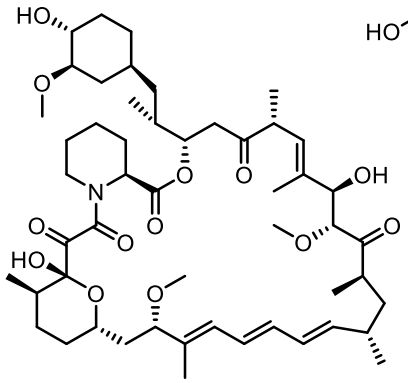
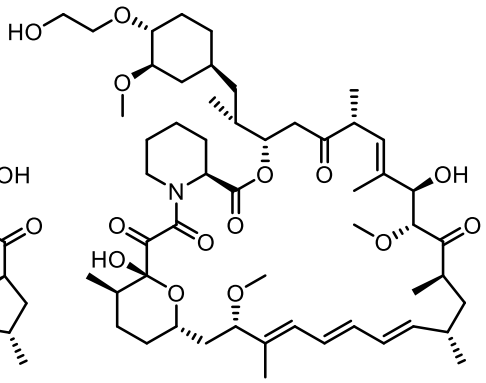
Rapamycin, Rapalogs and ATP-Competitive mTOR Inhibitors.



Rapamycin



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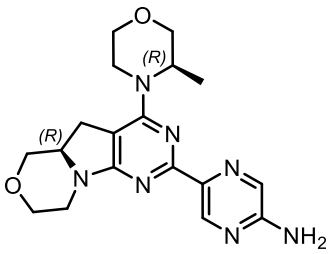

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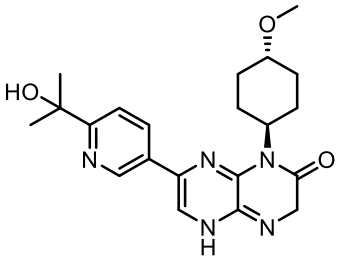

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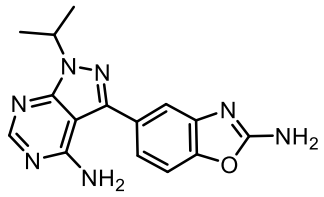

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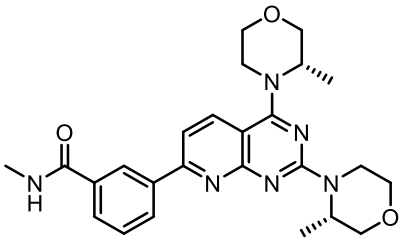

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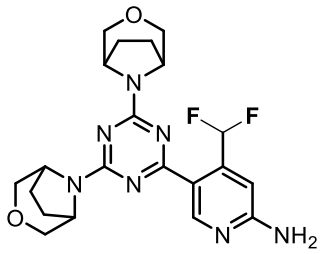

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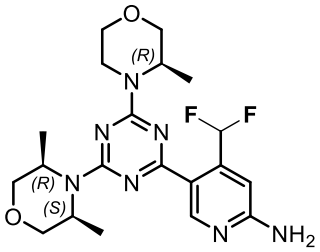

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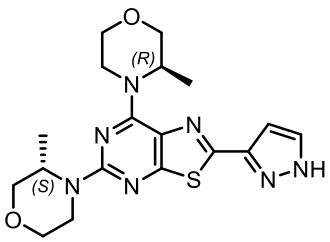

thiazolopyrimidine derivative

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