Rational design, synthesis, and biological evaluation of Pan-Raf inhibitors to overcome resistance

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4. Experimental section

4.2. Enzymatic activity test against $BRaf^{V600E}$

Activity of full length $BRaf^{V600E}$ was determined using Hot-Spot^{SM} kinase assay which was performed by Reaction Biology Corp. (Malvern PA). 5 nM of human GST-tagged $BRaf^{V600E}$ protein (AA416-766) (Invitrogen, Cat# PV3894) was mixed with 20 μM of the substrate His 6-Tagged Full-length Human MEK1(K97R) (Reaction Biology Corp.) in reaction buffer (20 mM Hepes pH 7.5, 10 mM $MgCl_2$, 1mM EGTA, 0.02% Brij35, 0.02 mg/mL BSA, 0.1 mM Na_3VO_4, 2 mM DTT, 1% DMSO) at room temperature, the compounds dissolved in 100% DMSO at indicated doses (starting at 30 μM with 3-fold dilution) was delivered into the kinase reaction mixture by Acoustic technology (Echo550; nanoliter range), incubate for 20 min at room temperature. After 10uM ^{33}P-γ-ATP (specific activity 10 μCi/μL) (P-ERKin Elmer, NEG302H001 MC) was added to initiate the reaction, the reactions were carried out at 25°C for 120 min. The kinase activities were detected by filter-binding method. IC_{50} values and curve fits were obtained by Prism (GraphPad Software).

All Raf protomer inhibitory assay was in a manner same as $BRaf^{V600E}$.

4.3. Antiproliferative activity against different cell lines

Cell planking: Vi-Cell XR cell counter was used to count living cells, which collected in exponential phases. After diluting to 3×10^3–1.5×10^4 cells /mL with the complete medium, 90 μL of cells suspension was added to each well of 96-well culture plates and cultured in DMEM (Dulbecco minimum essential medium) or McCoy's 5a/10% fetal bovine serum (Crown Bioscience Corporation) for 24 h, with 5% CO_2 water saturated atmosphere at 37°C.

Compound dispensation: Each selected compounds dissolved in DMSO as the 10 mM storage solution. Then with medium diluted to 10 times solution, each 2 holes (inhibition ratio) or 3 holes (IC_{50} value). The final drug concentration (inhibition ratio) or initial drug concentration was 10 μM. The compound dispensation, which volume was 10 μL, was futher incubated at 37°C for another 72 h in a humidified atmosphere with 5% CO_2.

Plate detection: 50 μL CTG solution, melt in advance and balance to room temperature, was added to each hole. According to the operating instructions of CTG, oscillators with microporous plate blend 2 minutes. At room temperature for 10 min, Envision2104 was used to measure the luminescence signal values.

Data processing: inhibition ratio=$1-V_{sample}/V_{vehicle\ control}\times100\%$. V_{sample} for drug treatment group, $V_{vehicle\ control}$ for solvent control group. Using GraphPad Prism 5.0 software and nonlinear regression model S type dose draw survival rate curve and calculate the IC_{50} value.

4.4. P-ERK cellular assay in A375 and SK-Mel-2 cells

4.4.1. *Recovery, culture and passage of cells*

A375 and SK-MEL-2 human melanoma cell line were both obtained from American Type Culture Collection (Manassas, VA). Removed melanoma cells cryopreserved tube from liquid nitrogen tank, shaking in 37°C water bath to make it melt quickly. The centrifugal tube was added cell suspension in super-clean bench, 5 mL EMEM medium was added. Centrifugalized the mixture 5 min with 1000 rpm, discarded supernatant, joined 2 mL EMEM (Eagle's minimal essential medium) supplemented with 10% serum to suspense cells, vaccinating it in culture bottle. Put culture bottle in incubator with 37°C, saturated humidity, 5% CO_2. The next day,

discarded the original medium, added 6 mL fresh medium to remove dead cells. Passage when cell numbers around 90%. Discarded supernatant, washed twice with PBS (phosphate buffered saline), added 2 mL 0.25% pancreatic enzyme to digest 2–3min. When cells becoming round under microscope, discarded pancreatic enzyme, added 2 mL EMEM medium to terminate digestion. Making the adherent cells blow down to a single suspension cells with a pipette gently. According to the speed of cell growth, culture the cell from one to three or four.

4.4.2 Plating cells and dosing

When the melanoma cells A375 and SK-Mel-2 in the logarithmic phase, vaccinating 3–5×10^5 cells in 96 cell plate with EMEM medium supplemented with 10% heat-inactivated FBS (fetal bovine serum), culturing cells in incubator with 37^{o}C, saturated humidity, 5% CO_2. When cell confluence reached 80–90%, discarding medium, diluting drugs with culture medium into 0.4 μM, 0.2 μM, 0.1 μM, 0.05 μM, 0.025 μM, dosing drugs in 96 cell plate , using DMSO as negative control.

4.4.3 Protein sample preparation

The cells were treated with compounds or DMSO for 24 h. After treatment, digestion cells with 500 μL 0.25% trypsin, then adding 500 μL medium to terminate digestion. Blowed cells evenly, centrifugalized the mixture 5min with 3000 rpm, discarded supernatant, put centrifugal tube on the ice, added suitable amount of protein lysis solution RIPA (Radio–immunoprecipitation assay), protease inhibitor PMSF (Phenylmethanesulfonyl fluoride) (1 mL RIPA/10 μL PMSF) and phosphatase inhibitors (1 mL RIPA/10 μL phosphatase inhibitors), blowed cells evenly, 4^{o}C for 30 min, make cells lysate, every 5 min vortex once. Centrifugalizing the lysate 15 min with 12000 rpm in 4^{o}C, gathering supernatant, using the BCA protein assay kit to determine the total protein concentration. Adding 1/4 volume 5×SDS-PAGE loading buffer, boiling water bath for 10 min to make protein denaturation. The specific signals of bands of interest were quantified by Gel-Pro Analyzer.

4.4.4 Western blot detection

Use 30 μg protein samples in 12% SDS-PAGE (polyacrylamide gel electrophoresis) electrophoresis. Transfer protein from running gel to PVDF (Poly vinylidene fluoride)

membrane with wet transfer method, steady flow 200 mA, according to the 1 kDa/min transfer velocity, according to the interest protein molecular weight to determine the transfer membrane time. Using 10% non-fat milk blocked PVDF membrane for 1.5 h in 37°C. Using 5% BSA diluted primary anti-phospho-ERK1/2 antibody, 4°C incubation overnight. 1×TBST washed the membrane three times, each time 10 min. Using 5% non-fat milk diluted secondary anti-phospho-ERK1/2 antibody with HRP tag, room temperature incubation1h. 1×TBST washed the membrane three times, each time 10 min. Droping appropriate amount ECL luminous on membrane, using Tanon5200 automatic chemiluminescence image analysis system to exposure.

4.5. Solubility Determination

The test substance is dissolved in the solvent system at 37°C. HPLC determination of the concentration of the solute in the solution, which must not contain any undissolved particles, is used to quantify the solubility. Composition of standard buffer solutions: Phosphate buffer pH 7.4: 50 mL of 0.2 M monobasic potassium phosphate solution were placed in a 200 mL volumetric flask, 39.1 mL of 0.2 M sodium hydroxide solution was added followed by water to the appropriate volume. Preparation of the standard solution: The test substance (generally 1 mg) was placed into an amber-glass volumetric flask and dissolved completely in a solution of acetonitrile/methanol (1:1, V/V). The target concentration is between 0.1 and 0.2 mg/mL. The standard solution and test sample (see below) use the same test substance. Preparation of the test sample: The test sample (generally 2-3 mg) was placed into a UniPrep syringeless filter (5 mL; 0.45 μM), 2 mL of solvent (generally 50 mM phosphate buffer at pH 7.4) were added and the sample agitated for 24 h at 37°C. After 24 h, the suspension was filtered and the concentration of dissolved substance determined by HPLC (see Chromatographic Conditions). If the substance has completely dissolved, the result is stated as > x μg/mL, calculated from the sample weight taken and the volume of solvent used.

Chromatographic Conditions: Solvent system: Eluent A: Ultrapure water/formic acid for analysis (999:1, V/V); Eluent B: Acetonitrile/formic acid for analysis (999:1, V/V). Equipment settings: Wavelength range of 190-400 nm, column: Chromolith 18e

100 *3 mm, temperature: 37°C, Gradient program as follows:

Time (Min)	Eluent A (%)	Eluent B (%)	Flow (mL/min)
0	90	10	0.85
0.6	90	10	0.85
4	10	90	0.85
5.5	10	90	0.85
5.51	90	10	2.50
8	90	10	2.50

Quantitative determination: The result is determined quantitatively based the external standard method through integration of the peak areas with reference to figures obtained for the standard substance.

Calculation:

$$L\ (\mu g/mL) = [a\ (A)*c\ (S)*F\ (A)]/a\ (S)*F(S)$$

a (A) = peak area for analyte/mL; a (S) = peak area for standard/mL; c (S) = concentration of standard (μg/mL); F (A) = dilution factor for analyte; F (S) = dilution factor for standard.

4.6. The in vivo pharmacokinetic study of **Y-1** and **I-15** in rats

Every compound: 6 male SD rats. The body weight of them is 180–220 g. Fasted 24 h, divided into two groups randomly (each group is 3). The first group of SD rats by 10 mg/kg dose lavage to give compound suspension, and the second group of SD rats by 2.5 mg/kg dose intravenous to give compound solution. Take blank blood before giving medicine, take venous blood about 150 μL at different time points after the treatment of compounds in eppendorf tube with heparin, centrifuged, took plasma about 50 μL, -20°C saved for testing.

The point time of blood collection:

intravenous injection: 5 min, 15 min, 30 min, 45 min, 60 min, 2 h, 4 h, 8 h, 12 h, 24 h.

oral administration: 5 min, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 8 h, 12 h, 24 h.

Dispensing method:

Injection solution: 15 mg compounds, DMA (dimethylamine, proper quantities), 7.5 mL propylene glycol, diluted with 10% glucose injection to achieve the 2 mg/mL solution of compounds.

Suspension: 15 mg compounds, 0.5% methyl cellulose (proper quantities), grinded evenly in mortar to achieve the 2 mg/mL solution of compounds.

Processing and determination of the 50 μL plasma samples: 50 μL plasma samples in Eppendorf tude, 50 μL acetonitrile and 100 μL acetonitrile solution with internal standard vortex blending. Centrifuged 10 min with 16000 rpm, took supernatant on LC-MS/MS determination.

The calculation method of pharmacokinetic parameters: The blood drug concentration-time data to the DAS 2.1.1 program using the statistical method to calculate pharmacokinetic parameters. Cmax and Tmax are measured, C-t curve established late phase elimination rate constant k for LnC-t linear regression, AUC_{0-t} value calculation method for the trapezoidal area, 0-up time of the area under the curve $AUC=AUC_{0-t}+C_t/k$. C_t is the last blood drug concentration, K is the blood drug concentration late phase elimination rate constant.

The calculation method of absolute bioavailability:

$$F\ (\%) = (AUC_{ev}\times D_{iv})/(AUC_{iv}\times D_{ev})\times 100\%$$

4.7. Chemistry synthesis

All starting materials were obtained from commercial suppliers and used without further purification. NMR spectrum recorded, on a BrukerDPX-300 spectrometer, in DMSO-d_6 using TMS as the internal standard. Chemical shifts (d) were reported in parts per million downfield from the internal standard. The signals were quoted as s (singlet), d (doublet), t (triplet), m (multiplet). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254, 0.25 mm per-coated TLC plates. TLC plates were visualized using UV254. Column chromatography was conducted on silica gel (200–300 mesh). Mass spectra were obtained on a Waters Quattro Micromass instrument using electrospray ionization (ESI) technique.

Diethyl 2-(2-chloropyrimidin-4-yl) malonate (**I-a**)

To a solution of diethyl malonate (16.5 g, 99 mM) in THF (300 mL) was added sodium hydride (60%, 8.0 g, 198 mM) successively. The mixture stirred at 0°C for 0.5 h, followed by addition of the required 2, 4-dichloropyrimidine (9.8 g, 66 mM) and heating to reflux for another 2.5 h. After cooling the reaction, the mixture was diluted in 300 mL saturated ammonium chloride solution, the aqueous layer was extracted

with EtOAc (500 mL×3). The combined organic layers were washed with brine (300 mL×3), dried over anhydrous $MgSO_4$. The mixture was evaporated in *vacuo* and purified by silica gel column chromatography to obtain **I-a** as oil. ESI-MS m/z: 149.0 $[M+H]^+$.

Ethyl 2-(2-chloropyrimidin-4-yl) acetate (**I-b**)

I-a (8.2 g, 30 mM) and sodium ethoxide (0.7 g, 3 mM) in ethanol (100 mL) were heated to reflux for 2.5 h. After cooling the reaction, HCl (1 M) was added to adjust pH to 7. The mixture was evaporated in *vacuo* and purified by silica gel column chromatography to get **I-b** as oil. ESI-MS m/z: 201.0 $[M+H]^+$.

General procedure for the preparation of important intermediate **I-c-1~I-c-3**

Ethyl 1-(2-chloropyrimidin-4-yl) cyclopropane-1-carboxylate (**I-c-1**)

The mixture of **I-b** (5.0 g, 25 mM), sodium hydroxide (2.0 g, 50 mM) and 1, 2-dibromoethane (15.9 g, 100 mM) were stirred at room temperature in DMF (150 mL) for 5 h. The mixture was diluted in 150 mL water, the aqueous layer was extracted with ethyl acetate (250 mL×3). The combined organic phase were evaporated in *vacuo* and purified by silica gel column chromatography to get **I-c-1** as oil. ESI-MS m/z: 227.1 $[M+H]^+$.

Ethyl 2-(2-chloropyrimidin-4-yl)-2-methylpropanoate (**I-c-2**)

I-c-2 (2.1 g, 94.3%) was prepared from **I-b** (2.1 g, 10.3 mM), sodium hydroxide (0.8 g, 20.6 mM) and iodomethane (5.9 g, 41.3 mM), in a manner similar to **I-c-1**. ESI-MS m/z: 229.1 $[M+H]^+$.

Ethyl 1-(2-chloropyrimidin-4-yl) cyclopentane-1-carboxylate (**I-c-3**)

I-c-3 (2.4 g, 90.2%) was prepared from **I-b** (2.1 g, 10.3 mM), sodium hydroxide (0.8 g, 20.6 mM) and 1,4-dibromobutane (8.9 g, 41.3 mM), in a manner similar to **I-c-2**. ESI-MS m/z: 255.1 $[M+H]^+$.

N-(4-chloro-3-(trifluoromethyl)phenyl)-3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methylbenzamide (**I-d-1**)

The mixture of **I-c-1** (0.45 g, 2 mM) and the intermediate **A1** (0.66 g, 2 mM) in anhydrous toluene (10 mL) were degassed for 10min and with nitrogen gas refilled. To the stirred reaction mixture was added a solution of Al $(CH_3)_3$ (2 M solution in toluene, 3.0 mL) dropwise via syringe over 5 min at 0°C. The resulting suspension was stirred for 0.5 h, then heated to 80°C and stirred until all solid was dissolved.

Reaction mixture was further stirred for 4–6 h at 80°C until TLC analysis showed the complete consumption of **A1**, quenched with C_2H_5OH (10 mL). The mixture was evaporated in *vacuo* and purified by silica gel column chromatography to get **I-d-1** (0.88 g, 86.5%) as a yellow solid. ESI-MS *m/z*: 509.1 $[M+H]^+$.

4-chloro-N-(3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methylphenyl)-3-(trifl-uoromethyl)benzamide (**I-d-2**)

I-d-2 (0.90 g, 88.6%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A2** (0.66 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 509.1 $[M+H]^+$.

N-(5-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)-2-methylphenyl)-1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamide (**I-d-3**)

I-d-3 (0.85 g, 81.3%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A3** (0.69 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 524.1 $[M+H]^+$.

N-(4-chloro-3-(trifluoromethyl)phenyl)-3-(2-(2-chloropyrimidin-4-yl)-2-methylpropanamido)-4-methylbenzamide (**I-d-4**)

I-d-4 (0.91 g, 89.1%) was prepared from **I-c-2** (0.46 g, 2 mM) and the intermediate **A1** (0.66 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 511.1 $[M+H]^+$.

N-(4-chloro-3-(trifluoromethyl)phenyl)-3-(1-(2-chloropyrimidin-4-yl)cyclopentane-1-carboxamido)-4-methylbenzamide (**I-d-5**)

I-d-5 (0.98 g, 91.4%) was prepared from **I-c-3** (0.51 g, 2 mM) and the intermediate **A1** (0.66 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 537.1 $[M+H]^+$.

3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methyl-N-(4-morpholino-3-(trifluoromethyl) phenyl) benzamide (**I-d-6**)

I-d-6 (0.94 g, 83.7%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A4** (0.76 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 560.2 $[M+H]^+$.

3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methyl-N-(4-(4-

methylpiperazin-1-yl)-3-(trifluoromethyl) phenyl) benzamide (**I-d-7**)

I-d-7 (0.90 g, 78.4%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A5** (0.78 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 573.2 $[M+H]^+$.

3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methyl-N-(4-(morpholinomethyl)-3-(trifluoromethyl) phenyl) benzamide (**I-d-8**)

I-d-8 (0.95 g, 82.7%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A6** (0.79 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 574.2 $[M+H]^+$.

3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methyl-N-(4-(morpholinomethyl)phenyl)benzamide (**I-d-9**)

I-d-9 (0.88 g, 87.1%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A7** (0.65 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 506.2 $[M+H]^+$.

3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methyl-N-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl)benzamide (**I-d-10**)

I-d-10 (0.89 g, 75.6%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A8** (0.81 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 588.2 $[M+H]^+$.

3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methyl-N-(4-((1-methylpiperidin-4-yl)methoxy)-3-(trifluoromethyl)phenyl)benzamide (**I-d-11**)

I-d-11 (0.85 g, 70.8%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A9** (0.84 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS *m/z*: 588.2 $[M+H]^+$.

3-(1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methyl-N-(4-(3-morpholinopropox-y)-3-(trifluoromethyl)phenyl)benzamide (**I-d-12**)

I-d-12 (1.10 g, 87.2%) was prepared from **I-c-1** (0.45 g, 2 mM) and the intermediate **A10** (0.87 g, 2 mM) as a yellow solid, in a manner same as **I-d-1**. ESI-MS: *m/z*: 618.2 $[M+H]^+$.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cycloprop-ane-1-carboxamido)benzamide (**I-01**)

The mixture of **I-d-1** (0.51 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM) were stirred at room temperature for 2 h.The mixture was evaporated in *vacuo* and purified by silica gel column chromatography to get **I-01** (0.46 g, 91.2%) as a white solid. mp: 235–236°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40-1.41 (2H, m, CH_2-cyclopropyl), 1.56-1.57 (2H, m, CH_2-cyclopropyl), 2.29 (3H, s, $ArCH_3$), 2.81 (3H, d, $NHCH_3$, J = 4.6 Hz), 6.56-6.57 (1H, m, NH), 7.22-7.23 (1H, m, ArH), 7.41 (1H, d, ArH, J = 8.0 Hz), 7.71-7.77 (2H, m, ArH), 8.07-8.08 (1H, m, ArH), 8.14 (1H, dd, ArH, J = 2.0 Hz, J = 8.8 Hz), 8.24 (1H, d, pyrimidine-H, J = 4.6 Hz), 8.36 (1H, d, pyrimidine-H, J = 2.0 Hz), 10.60 (1H, s, NHCO), 10.79 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 169.01, 165.40, 162.00, 158.45, 140.16, 138.68, 136.66, 131.94, 130.25, 124.89, 124.62, 124.41, 118.93, 118.90, 106.30, 106.14, 95.18, 27.76, 17.97. HRMS (ESI) calcd for $C_{24}H_{22}ClF_3N_5O_2$ $[M+H]^+$, 504.1336; found, 504.1406.

4-chloro-N-(4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamido)phenyl)-3-(trifluoromethyl)benzamide (**I-02**)

I-02 (0.45 g, 89.7%) was prepared from **I-d-2** (0.51 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 215–217°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.39-1.40 (2H, m, CH_2-cyclopropyl), 1.52-1.53 (2H, m, CH_2-cyclopropyl), 2.18 (3H, s, $ArCH_3$), 2.81 (3H, d, $NHCH_3$, J = 4.9 Hz), 6.54 (1H, d, NH, J = 4.9 Hz), 7.19-7.22 (2H, m, ArH), 7.58 (1H, dd, ArH, J = 2.0 Hz, J = 8.2 Hz), 7.90-7.93 (2H, m, ArH), 8.23-8.28 (2H, m, ArH), 8.40 (1H, d, NH, J = 1.5 Hz), 10.49 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.70, 168.59, 162.81, 161.93, 158.40, 136.57, 136.46, 134.01, 133.81, 133.30, 131.81, 130.04, 127.01, 126.94, 124.44, 120.85, 117.49, 117.24, 105.86, 27.87, 17.59, 17.33. HRMS (ESI) calcd for $C_{24}H_{22}ClF_3N_5O_2$ $[M+H]^+$, 504.1336; found, 504.1410.

N-(5-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)-2-methylphenyl)-1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamide (**I-03**)

I-03 (0.45 g, 85.8%) was prepared from **I-d-3** (0.52 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 94–96°C. ^{1}H-NMR (300 MHz,

DMSO-d_6): δ 1.38-1.39 (2H, m, CH_2-cyclopropyl), 1.54-1.55 (2H, m, CH_2-cyclopropyl), 2.15 (3H, s, $ArCH_3$), 2.83 (3H, d, $NHCH_3$, J = 4.9 Hz), 6.53 (1H, d, NH, J = 4.9 Hz), 7.12 (1H, d, ArH, J = 8.3 Hz),7.19 (1H, d, ArH, J = 4.7 Hz), 7.23 (1H, dd, ArH, J = 2.0 Hz, J = 8.3 Hz), 7.61-7.63 (2H, m, ArH), 7.65-7.68 (1H, m, ArH), 8.13 (1H, d, ArH, J = 1.6 Hz), 8.24 (1H, d, ArH, J = 4.7 Hz), 8.94 (1H, s, NHCONH), 9.21 (1H, s, NHCONH). ^{13}C NMR (300 MHz, DMSO) δ 172.56, 168.64, 163.28, 158.42, 157.54, 152.22, 139.35, 137.11, 136.69, 131.82, 130.11, 124.61, 122.88, 122.16, 120.98, 116.67, 115.12, 114.34, 106.36, 48.27, 27.05, 25.18, 16.94. HRMS (ESI) calcd for $C_{24}H_{23}ClF_3N_6O_2$ $[M+H]^+$, 519.1445; found, 519.1508.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-methyl-2-(2-(methylamino) pyrimidin-4-yl)propanamido)benzamide (**I-04**)

I-04 (0.45 g, 89.4%) was prepared from **I-d-4** (0.51 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 178–181^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.55 (6H, s, CH_3), 2.09 (3H, s, $ArCH_3$), 2.83 (3H, d, $NHCH_3$, J = 4.7 Hz), 6.65 (1H, d, NH, J = 5.2 Hz), 7.07 (1H, q, ArH, J = 4.7 Hz),7.18 (1H, d, ArH, J = 8.4 Hz), 7.58 (1H, dd, ArH, J = 2.1 Hz, J = 8.2 Hz), 7.73 (1H, d, ArH, J = 1.6 Hz), 7.92 (1H, d, ArH, J = 8.4 Hz), 8.26 (2H, dd, ArH, J = 1.6 Hz, J = 8.2 Hz), 8.40 (1H, d, NH, J = 1.6 Hz), 8.98 (1H, s, NHCO), 10.49 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 172.81, 172.67, 162.80, 162.34, 158.43, 136.49, 136.45, 134.03, 133.79, 133.33, 131.87, 129.98, 128.39, 127.01, 124.42, 117.99, 117.67, 106.14, 49.03, 27.79, 25.19, 17.02. HRMS (ESI) calcd for $C_{24}H_{24}ClF_3N_5O_2$ $[M+H]^+$, 506.1492; found, 506.1564.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopent-ane-1-carboxamido)benzamide (**I-05**)

I-05 (0.47 g, 88.7%) was prepared from **I-d-5** (0.54 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 215–217^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.67-1.69 (4H, m, H-cyclopentyl), 2.05 (3H, s, Ar-CH_3), 2.17-2.21 (2H, t, H-cyclopentyl), 2.38-2.45 (2H, t, H-cyclopentyl), 2.84 (3H, d, $NHCH_3$, J = 4.6 Hz), 6.62 (1H, d, NH, J = 5.1 Hz), 7.08 (1H, q, ArH, J = 4.4 Hz), 7.17 (1H, d, ArH, J = 8.4 Hz), 7.58 (1H, dd, ArH, J = 2.1 Hz, J = 8.3 Hz), 7.71 (1H, d, ArH, J =

2.0 Hz), 7.91 (1H, d, ArH, J = 8.4 Hz), 8.24-8.30 (2H, m, ArH), 8.40 (1H, s, ArH) , 8.94 (1H, s, CONH), 10.48 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 171.77, 171.55, 162.80, 162.44, 158.29, 136.56, 136.44, 134.02, 133.79, 133.31, 131.83, 129.99, 127.93, 127.01, 126.37, 124.44, 120.82, 117.58, 106.68, 61.67, 35.07, 27.78, 24.00, 16.92. HRMS (ESI) calcd for $C_{26}H_{26}ClF_3N_5O_2$ $[M+H]^+$, 532.1649; found, 532.1731.

N-(4-chloro-3-(trifluoromethyl)phenyl)-3-(1-(2-((2-hydroxyethyl)amino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methylbenzamide (**I-06**)

I-d-1 (0.51 g, 1 mM), 2-aminoethan-1-ol (0.31 g, 5 mM) and N, N-diisopropylethylamine (0.65 g, 5 mM) in ethanol were heated to reflux for 5 h. The mixture was evaporated in *vacuo* and purified by silica gel column chromatography to get **I-06** (0.47 g, 87.3%) as a white solid. mp: 224–225^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.34-1.41 (2H, m, CH_2-cyclopropyl), 1.47-1.56 (2H, m, CH_2-cyclopropyl), 2.28 (3H, s, $ArCH_3$), 3.34-3.39 (2H, m, CH_2), 3.48-3.54 (2H, m, CH_2), 4.68 (1H, t, OH, J = 5.4 Hz), 6.55-6.56 (1H, m, NH), 7.21-7.23 (1H, m, ArH), 7.41 (1H, d, ArH, J = 8.0 Hz), 7.74 (2H, t, ArH, J = 9.3 Hz), 8.04-8.07 (1H, m, ArH), 8.14 (1H, dd, ArH, J = 1.8 Hz, J = 8.8 Hz), 8.23 (1H, d, ArH, J = 5.0 Hz), 8.36 (1H, d, ArH, J = 2.0 Hz),10.60 (1H, s, NHCO), 10.80 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.98, 165.49, 164.33, 161.23, 158.40, 143.09, 138.68, 136.51, 131.92, 130.34, 124.90, 124.56, 124.17, 118.98, 115.36, 113.77, 106.39, 59.71, 43.38, 17.88. HRMS (ESI) calcd for $C_{25}H_{24}ClF_3N_5O_3$ $[M+H]^+$, 534.1442; found, 534.1510.

N-(4-chloro-3-(trifluoromethyl)phenyl)-3-(1-(2-((2-methoxyethyl)amino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methylbenzamide (**I-07**)

I-07 (0.48 g, 88.2%) was prepared from **I-d-1** (0.51 g, 1 mM) and 2-methoxyethan-1-amine (0.38 g, 5 mM), in a manner same as **I-06**. mp: 203–204^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40-1.41 (2H, m, CH_2-cyclopropyl), 1.56-1.57 (2H, m, CH_2-cyclopropyl), 2.28 (3H, s, $ArCH_3$), 3.22 (3H, s, OCH_3), 3.35-3.44 (4H, m, $NHCH_2CH_2O$), 6.56-6.57 (1H, m, NH), 7.35 (1H, d, ArH, J = 5.6 Hz), 7.41 (1H, d, ArH, J = 8.1 Hz), 7.74 (2H, t, ArH, J = 9.1 Hz), 8.08 (1H, s, ArH), 8.12 (1H, dd, ArH, J = 2.2 Hz, J = 8.8 Hz), 8.23 (1H, d, ArH, J = 4.9 Hz), 8.36 (1H, d, ArH, J = 2.2 Hz),

10.61 (1H, s, NHCO), 10.85 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.94, 168.62, 165.39, 161.35, 158.43, 138.68, 136.70, 133.85, 131.93, 130.24, 126.36, 124.88, 124.56, 124.14, 120.95, 118.96, 118.87,106.17, 70.31, 57.73, 40.19, 17.86.HRMS (ESI) calcd for $C_{26}H_{26}ClF_3N_5O_3$ $[M+H]^+$, 548.1598; found, 548.1672.

N-(4-chloro-3-(trifluoromethyl)phenyl)-3-(1-(2-((3-methoxypropyl)amino)pyrimidin-4-yl)cyclopr-opane-1-carboxamido)-4-methylbenzamide (**I-08**)

I-08 (0.49 g, 87.9%) was prepared from **I-d-1** (0.51 g, 1 mM) and 3-methoxypropan-1-amine (0.45 g, 5 mM), in a manner same as **I-06**. mp: 195–196^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40-1.41 (2H, m, CH_2, H-cyclopropyl), 1.56-1.57 (2H, m, CH_2, H-cyclopropyl), 1.73-1.77 (2H, m, CH_2, H-$CH_2C\underline{H_2}CH_2$), 2.29 (3H, s, $ArCH_3$), 3.20 (3H, s, OCH_3), 3.28-3.31 (4H, m, $C\underline{H_2}CH2C\underline{H_2}$), 6.56-6.57 (1H, m, NH), 7.24-7.26 (1H, m, ArH), 7.42 (1H, d, ArH, J = 8.0 Hz), 7.74 (2H, t, ArH, J = 9.1 Hz), 8.08 (1H, s, ArH), 8.14 (1H, dd, ArH, J = 2.2 Hz, J = 8.8 Hz), 8.23 (1H, d, ArH, J = 4.7 Hz), 8.36 (1H, d, ArH, J = 2.3 Hz), 10.60 (1H, s, NHCO), 10.82 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.97, 167.85, 165.41, 161.28, 158.46, 138.69, 136.69, 136.33, 131.95, 131.90, 130.23, 126.35, 124.87, 124.57, 124.43, 124.15, 120.95, 118.98, 106.23, 69.77, 57.81, 37.98, 28.98, 17.93. HRMS (ESI) calcd for $C_{26}H_{26}ClF_3N_5O_3$ $[M+H]^+$, 548.1598; found, 548.1664.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(1-(2-((2-(methylamino) ethyl) amino)pyrimidin-4-yl)cyclopropane-1-carboxamido)benzamide (**I-09**)

I-09 (0.46 g, 84.7%) was prepared from **I-d-1** (0.51 g, 1 mM) and N-methylethane-1,2-diamine (0.37 g, 5 mM), in a manner same as **I-06**. mp: 184–185^{o}C. ^{1}H-NMR (300MHz, DMSO-d_6): δ 1.41-1.44 (2H, m, CH_2-cyclopropyl), 1.49-1.53 (2H, m, CH_2-cyclopropyl), 2.26 (3H, s, $ArCH_3$), 2.71 (2H, t, NCH_2, J = 6.8 Hz), 3.12-3.15 (3H, m, CH_3, $NHCH_3$), 3.58 (2H, t, $NHCH_2$, J = 6.8 Hz), 6.64 (1H, d, NH, J = 5.1 Hz), 7.41 (1H, d, ArH, J = 8.2 Hz), 7.72 (1H, d, ArH, J = 8.8 Hz), 7.77 (1H, dd, ArH, J = 1.9 Hz, J = 8.2 Hz), 7.92-7.95 (2H, m, ArH), 8.13 (1H, dd, ArH, J = 2.3 Hz, J = 8.8 Hz), 8.27 (1H, d, ArH, J = 5.1 Hz), 8.36 (1H, d, ArH, J = 2.3 Hz), 9.91 (1H, s, NHCO), 10.56 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 169.27, 168.24, 165.33, 161.08, 157.83, 149.75, 138.67, 137.69, 136.55, 135.23, 131.93, 130.39, 125.59, 124.94,

124.27, 119.00, 118.91, 106.53, 35.59, 31.76, 17.91, 16.79. HRMS (ESI) calcd for $C_{26}H_{27}ClF_3N_6O_2$ $[M+H]^+$, 547.1758; found, 547.1835.

N-(4-chloro-3-(trifluoromethyl)phenyl)-3-(1-(2-((2-(dimethylamino)ethyl)amino) pyrimidin-4-yl)cyclopropane-1-carboxamido)-4-methylbenzamide (**I-10**)

I-10 (0.45 g, 80.3%) was prepared from **I-d-1**(0.51 g, 1 mM) and N,N-dimethylethane-1,2-diamine (0.44 g, 5 mM), in a manner same as **I-06**. mp: 197–199°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.41-1.42 (2H, m, CH_2-cyclopropyl), 1.47-1.48 (2H, m, CH_2-cyclopropyl), 2.15 (6H, s, $N(CH_3)_2$), 2.29 (3H, s, $ArCH_3$), 2.40 (2H, t, CH_2, J = 6.7 Hz), 3.37-3.38 (2H, m, CH_2), 6.56-6.57 (1H, m, NH), 7.10-7.12 (1H, m, ArH), 7.42 (1H, d, ArH, J = 8.0 Hz), 7.71-7.77 (2H, m, ArH), 8.10-8.11 (1H, m, ArH), 8.14 (1H, dd, ArH, J = 2.1 Hz, J = 8.8 Hz), 8.23 (1H, d, ArH, J = 4.8 Hz), 8.37 (1H, d, ArH, J = 2.1 Hz), 10.61 (1H, s, NHCO), 10.84 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 174.99, 168.92, 165.41, 161.22, 158.44, 138.70, 136.66, 134.81, 131.92, 130.24, 126.34, 124.87, 124.52, 124.15, 118.88, 106.51, 106.08, 103.97, 58.46, 38.62, 45.13, 17.92. HRMS (ESI) calcd for $C_{27}H_{29}ClF_3N_6O_2$ $[M+H]^+$, 561.1914; found, 561.1995.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(1-(2-((2-morpholinoethyl)amino)pyrimidin-4-yl)cyclopropane-1-carboxamido)benzamide (**I-11**)

I-11 (0.53 g, 87.1%) was prepared from **I-d-1** (0.51 g, 1 mM) and 2-morpholinoethan-1-amine (0.65 g, 5 mM), in a manner same as **I-06**. mp: 223– 225°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.41-1.42 (2H, m, CH_2-cyclopropyl), 1.57-1.58 (2H, m, CH_2-cyclopropyl), 2.30 (3H, s, $ArCH_3$), 2.37-2.38 (4H, m, $N(CH_2)_2$), 2.46 (2H, t, NCH_2, J = 6.8 Hz), 3.40 (2H, t, $NHCH_2$, J = 6.5 Hz), 3.53-3.55 (4H, m, $O(CH_2)_2$), 6.55-6.56 (1H, m, NH), 7.11-7.13 (1H, m, ArH), 7.42 (1H, d, NH, J = 8.0 Hz), 7.70-7.77 (2H, m, ArH), 8.14 (2H, dd, ArH, J = 2.2 Hz, J = 8.8 Hz), 8.23 (1H, d, NH, J = 4.9 Hz), 8.37 (1H, d, NH, J = 2.2 Hz), 10.62 (1H, s, NHCO), 10.83 (1H, s, NHCO). ^{13}C NMR (300MHz, DMSO) δ 168.96, 168.66, 166.03, 165.33, 158.53, 138.70, 136.64, 131.92, 130.25, 124.89, 124.50, 124.43, 124.34, 124.15, 118.98,

118.90, 106.49, 66.13, 57.25, 53.30, 37.70, 18.01.HRMS (ESI) calcd for $C_{29}H_{31}ClF_3N_6O_3$ $[M+H]^+$, 603.2020; found, 603.2105.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(1-(2-((3-morpholinopropyl) amino)pyrimidin-4-yl)cyclopropane-1-carboxamido)benzamide (**I-12**)

I-12 (0.52 g, 84.8%) was prepared from **I-d-1** (0.51 g, 1 mM) and 3-morpholinopropan-1-amine (0.72 g, 5 mM), in a manner same as **I-06**. mp: 187–188°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40-1.41 (2H, m, CH_2-cyclopropyl), 1.57-1.58 (2H, m, CH_2-cyclopropyl), 1.63-1.72 (2H, m, $NHCH_2C\underline{H_2}CH_2$), 2.28 (3H, s, $ArCH_3$), 2.81-2.82 (7H, m, $NHCH_3$, $N(CH_2)_2$), 3.68-3.72 (4H, m, CH_2OCH_2), 6.53-6.55 (1H, m, NH), 7.31 (1H, s, ArH), 7.41 (1H, d, ArH, J = 8.0 Hz), 7.70-7.78 (2H, m, ArH), 8.12-8.16 (2H, m, ArH), 8.22 (1H, d, ArH, J = 5.0 Hz), 8.40 (1H, d, ArH, J = 2.3 Hz), 10.60 (1H, s, NHCO), 10.80 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.97, 168.77, 165.39, 161.34, 158.48, 138.69, 136.62, 131.92, 130.25, 126.76, 124.87, 124.52, 124.20, 120.88, 118.95, 118.88, 106.17, 66.14, 56.00, 53.29, 39.09, 25.77, 18.02. HRMS (ESI) calcd for $C_{30}H_{33}ClF_3N_6O_3$ $[M+H]^+$, 617.2177; found, 617.2245.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(1-(2-((2-(pyrrolidin-1-yl) ethyl) amino)pyrimidin-4-yl)cyclopropane-1-carboxamido)benzamide (**I-13**)

I-13 (0.49 g, 84.2%) was prepared from **I-d-1** (0.51 g, 1 mM) and 2-(pyrrolidin-1-yl)ethan-1-amine (0.57 g, 5 mM), in a manner same as **I-06**. mp: 204–205°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40~1.41 (2H, m, CH_2- cyclopropyl), 1.47-1.48 (2H,m,CH_2-cyclopropyl),1.62-1.65 (4H, m, CH_2CH_2), 2.29 (3H, s, $ArCH_3$), 2.41-2.44 (4H, m, $N(CH_2)_2$), 2.56 (2H, t, NCH_2, J = 6.8 Hz), 3.39-3.41 (2H, m, $NHCH_2$), 6.54-6.55 (1H, m, NH), 7.15-7.17 (1H, m, ArH), 7.42 (1H, d, ArH, J = 8.0 Hz), 7.70-7.77 (2H, m, ArH), 8.10-8.11 (1H, m, ArH), 8.14 (1H, dd, ArH, J = 1.8 Hz, J = 8.8 Hz), 8.23 (1H, d, ArH, J = 4.8 Hz), 8.37 (1H, d, ArH, J = 2.0 Hz), 10.60 (1H, s, NHCO), 10.84 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.95, 168.56, 165.40, 161.32, 158.46, 138.69, 136.67, 131.92, 130.24, 126.76, 126.35, 124.88, 124.56, 124.50, 124.09, 120.95, 118.96, 118.89, 106.17, 54.71, 53.55, 39.84, 23.07, 17.96. HRMS (ESI) calcd for $C_{29}H_{31}ClF_3N_6O_2$ $[M+H]^+$, 587.2071; found, 587.2137.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(1-(2-((2-(piperidin-1-yl)ethyl) amino) pyrimidin-4-yl)cyclopropane-1-carboxamido)benzamide (**I-14**)

I-14 (0.48 g, 80.6%) was prepared from **I-d-1** (0.51 g, 1 mM) and 2-(piperidin-1-yl)ethan-1-amine (0.64 g, 5 mM) in a manner same as **I-06**. mp: 206–207°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.42-1.47 (8H, m, CH_2-cyclopropyl, $(CH_2)_3$), 1.56-1.57 (2H, m, CH_2-cyclopropyl), 2.30 (3H, s, $ArCH_3$), 2.38-2.39 (6H, m, $N(CH_2)_3$),3.35-3.37 (2H, m, $NHCH_2$),6.55-6.56 (1H, m, NH), 7.10-7.11 (1H, m, ArH), 7.41 (1H, d, ArH, J = 8.0 Hz), 7.70-7.77 (2H, m, ArH), 8.10-8.11 (1H, m, ArH), 8.13 (1H, dd, ArH, J = 2.1 Hz, J = 8.8 Hz), 8.23 (1H, d, ArH, J = 3.9 Hz), 8.37 (1H, d, ArH, J = 2.1Hz), 10.61 (1H, s, NHCO), 10.84 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.93, 168.58, 165.39, 161.24, 158.47, 148.72, 145.96, 145.45, 138.69, 136.68, 131.94, 130.25, 124.85, 124.56, 124.48, 124.14, 118.96, 118.88, 106.19, 57.56, 54.07, 38.19, 25.54, 23.93, 18.01. HRMS (ESI) calcd for $C_{30}H_{33}ClF_3N_6O_2$ $[M+H]^+$, 601.2227; found, 601.2302.

N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methyl-3-(1-(2-((2-(4-methylpiperazin-1-yl)ethyl)amino)pyrimidin-4-yl)cyclopropane-1-carboxamido)benzamide (**I-15**)

I-15 (0.48 g, 77.4%) was prepared from **I-d-1** (0.51 g, 1 mM) and 2-(4-methylpiperazin-1-yl)ethan-1-amine (0.72 g, 5 mM), in a manner same as **I-06**. mp: 190–191°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.41-1.43 (2H, m, CH_2-cyclopropyl), 1.59-1.61 (2H, m, CH_2-cyclopropyl), 2.12 (3H, s, $ArCH_3$), 2.32-2.39 (8H, m, $N(CH_2)_2$), 2.46 (3H, s, NCH_3), 3.41-3.43 (4H, m, $NHCH_2CH_2N$), 6.55-6.56 (1H, m, NH), 7.06-7.08 (1H, m, ArH), 7.41-7.43 (1H, m, ArH), 7.69-7.76 (2H, m, ArH), 8.14-8.17 (2H, m, ArH), 8.24 (1H, s, ArH), 8.39 (1H, s, ArH), 10.60 (1H, s, NHCO), 10.88 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.94, 168.59, 165.39, 161.30, 158.47, 138.69, 136.68, 131.97, 131.87, 130.22, 126.79, 126.38, 125.97, 124.85, 124.56, 124.17, 120.95, 118.90, 106.48, 56.80, 54.66, 52.66, 45.66, 38.13, 18.04. HRMS (ESI) calcd for $C_{30}H_{34}ClF_3N_7O_2$ $[M+H]^+$, 616.2336; found, 616.2422.

4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-N-(4-morpholino-3-(trifluoromethyl)phenyl)benzamide (**I-16**)

I-16 (0.51 g, 92.7%) was prepared from **I-d-6** (0.56 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 222–223°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40-1.41 (2H, m, CH_2-cyclopropyl), 1.57-1.58 (2H, m, CH_2-cyclopropyl), 2.28 (3H, s, $ArCH_3$), 2.81-2.84 (7H, m,$NHC\underline{H}_3$, $C\underline{H}_2NC\underline{H}_2$), 3.69-3.71 (4H, m, CH_2OCH_2), 6.56-6.57 (1H, m, NH), 7.21-7.23 (1H, m, ArH), 7.40 (1H, d, ArH, J = 7.8 Hz), 7.61 (1H, d, ArH, J = 8.8 Hz), 7.75 (1H, d, ArH, J = 7.8 Hz), 8.06-8.09 (2H, m, ArH), 8.16 (1H, s, ArH), 8.25 (1H, s, ArH), 10.42 (1H, s, NHCO), 10.76 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 169.01, 168.55, 165.11, 161.84, 158.43, 147.09, 136.62, 136.48, 132.26, 130.15, 125.75, 125.07, 124.78, 124.45, 122.00, 118.40, 118.33, 106.19, 66.60, 53.44, 27.75, 17.94. HRMS (ESI) calcd for $C_{28}H_{30}F_3N_6O_3$ $[M+H]^+$, 555.2253; found, 555.2327.

4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-N-(4-(4-methylpip-erazin-1-yl)-3-(trifluoromethyl)phenyl)benzamide (**I-17**)

I-17 (0.51 g, 90.2%) was prepared from **I-d-7** (0.57 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 232–233°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40-1.41 (2H, m, CH_2-cyclopropyl), 1.57-1.58 (2H, m, CH_2-cyclopropyl), 2.23 (3H, s, NCH_3), 2.28 (3H, s, $ArCH_3$), 2.44-2.45 (4H, m, piperazin-H), 2.81-2.84 (7H, m, $NHC\underline{H}_3$, piperazin-H), 6.56-6.57 (1H, m, NH), 7.21-7.23 (1H, m, ArH), 7.40 (1H, d, ArH, J = 7.9 Hz), 7.56 (1H, d, ArH, J = 8.7 Hz), 7.75 (1H, d, ArH, J = 7.5 Hz), 8.05 (2H, d, ArH, J = 6.7 Hz), 8.15 (1H, s, ArH), 8.25 (1H, s, ArH), 10.41 (1H, s, NHCO), 10.78 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.99, 168.52, 165.07, 161.82, 158.43, 147.56, 136.59, 136.24, 132.26, 130.15, 125.62, 124.92, 124.74, 124.44, 122.07, 118.43, 118.35, 112.82, 106.48, 55.04, 53.04, 45.77, 27.76, 17.95. HRMS (ESI) calcd for $C_{29}H_{33}F_3N_7O_2$ $[M+H]^+$, 568.2570; found, 568.2644.

4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-N-(4-(morpholino-methyl)-3-(trifluoromethyl)phenyl)benzamide (**I-18**)

I-18 (0.53 g, 93.1%) was prepared from **I-d-8** (0.57 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 202–204°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.41-1.42 (2H, m, CH_2-cyclopropyl), 1.57-1.58 (2H, m, CH_2-

cyclopropyl), 2.29 (3H, s, $ArCH_3$), 2.36-2.39 (4H, m, $N(CH_2)_2$), 2.82 (3H, d, $NHCH_3$, J = 4.7 Hz), 3.57-3.60 (6H, m, $O(CH_2)_2$ and $ArCH_2$), 6.55-6.57 (1H, m, NH), 7.21-7.23 (1H, m, ArH), 7.40 (1H, d, ArH, J = 8.0 Hz), 7.72-7.77 (2H, m, ArH), 8.06-8.08 (2H, m, ArH), 8.21-8.25 (2H, m, ArH), 10.47 (1H, s, NHCO), 10.78 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.99, 168.50, 165.24, 161.79, 158.43, 138.33, 136.60, 132.23, 131.36, 131.27, 130.17, 127.19, 124.70, 124.46, 123.43, 122.48, 117.29, 117.20, 106.15, 66.19, 57.83, 53.24, 27.76, 17.95. HRMS (ESI) calcd for $C_{29}H_{32}F_3N_6O_3$ $[M+H]^+$, 568.2410; found, 568.2490.

4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-N-(4-(morpholino-methyl)phenyl)benzamide (**I-19**)

I-19 (0.47 g, 89.1%) was prepared from **I-d-9** (0.51 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 109–110°C. ^1H-NMR (300 MHz, DMSO-d_6): δ 1.40-1.41 (2H, m, CH_2-cyclopropyl), 1.55-1.57 (2H, m, CH_2-cyclopropyl), 2.27 (3H, s, $ArCH_3$), 2.34 (4H, t, $N(C\underline{H}_2)_2$, J = 4.4 Hz), 2.81 (3H, d, $NHCH_3$, J = 4.6 Hz), 3.42 (2H, s, CH_2), 3.57 (4H, t, $O(C\underline{H}_2)_2$, J = 4.4 Hz), 6.56 (1H, d, NH, J = 4.6 Hz), 7.21 (1H, s, ArH), 7.27 (2H, d, ArH, J = 8.4 Hz), 7.38 (1H, d, ArH, J = 8.0 Hz), 7.72 (3H, d, ArH, J = 8.4 Hz), 8.02-8.04 (1H, s, ArH), 8.24 (1H, d, ArH, J = 4.6 Hz), 10.19 (1H, s, NHCO), 10.78 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.96, 168.50, 164.89, 161.87, 158.42, 149.86, 138.00, 136.51, 132.88, 132.77, 130.08, 129.12, 124.72, 124.43, 120.18, 106.38, 66.16, 62.02, 53.09, 27.77, 17.93. HRMS (ESI) calcd for $C_{28}H_{33}N_6O_3$ $[M+H]^+$, 501.2536; found, 501.2606.

4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-N-(4-((1-methylpip-eridin-4-yl)oxy)-3-(trifluoromethyl)phenyl)benzamide (**I-20**)

I-20 (0.50 g, 86.1%) was prepared from **I-d-10** (0.59 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 198–200°C. ^1H-NMR (300 MHz, DMSO-d_6): δ 1.41-1.42 (2H, m, CH_2-cyclopropyl), 1.58-1.59 (2H, m, CH_2-cyclopropyl), 1.70-1.71 (2H, m, CH_2, $CHCH_2$), 1.90-1.91 (2H, m, CH_2, $CHCH_2$), 2.17 (3H, s, $ArCH_3$), 2.28-2.31 (4H, m, $N(CH_2)_2$), 2.83 (3H, d, $NHCH_3$, J = 4.6 Hz), 2.91(3H, s, NCH_3), 4.56-4.57 (1H, m, CH), 6.56-6.57 (1H, m, NH), 7.21-7.23 (1H, m, ArH), 7.32 (1H, d, ArH, J = 9.2 Hz), 7.39 (1H, d, ArH, J = 8.0 Hz), 7.76 (1H, d, ArH,

J = 7.8 Hz), 7.99-8.02 (1H, m, ArH), 8.08-8.10 (2H, m, ArH), 8.25 (1H, d, ArH, *J* = 4.7 Hz), 10.31 (1H, s, NHCO), 10.77 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 169.08, 168.51, 164.84, 161.93, 158.30, 150.85, 141.87, 136.48, 135.89, 132.42, 131.80, 130.14, 125.63, 125.43, 124.40, 121.75, 118.97, 115.15, 106.33, 72.30, 51.66, 45.84, 30.14, 27.67, 17.88. HRMS (ESI) calcd for $C_{30}H_{34}F_3N_6O_3$ $[M+H]^+$, 583.2566; found, 583.2638.

4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-N-(4-((1-methylpip-eridin-4-yl)methoxy)-3-(trifluoromethyl)phenyl)benzamide (**I-21**)

I-21 (0.51 g, 84.9%) was prepared from **I-d-11** (0.60 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 191–192^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.33-1.41 (4H, m, CH_2), 1.56-1.57 (2H, m, CH_2), 1.69-1.72 (3H, m, CH_2, CH), 1.82-1.89 (2H, m, CH_2), 2.15 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.77-2.82 (5H, m, NHC<u>H</u>$_3$ and CH_2), 3.94 (2H, d, CH_2, *J* = 4.7 Hz), 6.56-6.57 (1H, m, NH), 7.23-7.27 (2H, m, ArH), 7.39 (1H, d, ArH, *J* = 7.8 Hz), 7.74 (1H, d, ArH, *J* = 7.8 Hz), 7.99-8.08 (3H, m, ArH), 8.24 (1H, d, ArH, *J* = 4.7 Hz), 10.30 (1H, s, NHCO), 10.74 (1H, s, NHCO). ^{13}C NMR (300 MHz, DMSO) δ 168.98, 168.56, 164.84, 161.80, 158.42, 152.42, 136.54, 132.37, 131.84, 130.12, 125.67, 124.40, 121.85, 118.88, 118.80, 116.74, 116.28, 113.56, 106.19, 72.80, 59.76, 54.88, 46.09, 34.85, 28.21, 27.83, 18.01, 13.98. HRMS (ESI) calcd for $C_{31}H_{36}F_3N_6O_3$ $[M+H]^+$, 597.2723; found, 597.2793.

4-methyl-3-(1-(2-(methylamino)pyrimidin-4-yl)cyclopropane-1-carboxamido)-N-(4-(3-morpholin-opropoxy)-3-(trifluoromethyl)phenyl)benzamide (**I-22**)

I-22 (0.56 g, 90.7%) was prepared from **I-d-12** (0.62 g, 1 mM) and methylamine (33%, 0.7 mL, 5 mM), in a manner same as **I-01**. mp: 172–173^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.40-1.41 (2H, m, CH_2-cyclopropyl), 1.55-1.56 (2H, m, CH_2-cyclopropyl), 1.86-1.90 (2H, m, NCH_2C<u>H</u>$_2$-CH_2O), 2.28 (3H, s, $ArCH_3$), 2.35-2.45 (6H, m, 3 × NCH_2), 2.81 (3H, d, $NHCH_3$, *J* = 4.0 Hz), 3.57 (4H, s, CH_2OCH_2), 4.11-4.13 (2H, m, OCH_2), 6.55-6.56 (1H, m, NH), 7.26 (1H, s, ArH), 7.28 (1H, d, ArH, *J* = 9.0 Hz), 7.40 (1H, d, ArH, *J* = 7.8 Hz), 7.72 (1H, m, ArH), 7.98-8.08 (3H, m, ArH), 8.22-8.28 (1H, m, ArH), 10.30 (1H, s, NHCO), 10.70 (1H, s, NHCO). ^{13}C NMR (300

MHz, DMSO) δ 169.00, 168.54, 164.86, 161.87, 158.43, 152.36, 136.58, 132.36, 131.89, 130.14, 125.72, 124.32, 121.82, 118.88, 118.81, 117.29, 116.92, 113.84, 106.43, 66.63, 66.14, 54.51, 53.31, 27.75, 25.66, 17.92. HRMS (ESI) calcd for $C_{31}H_{36}F_3N_6O_4$ $[M+H]^+$, 613.2672; found, 613.2747.

3-amino-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-4-methylbenzamide (**A1**)

4-methyl-3-nitrobenzoic acid (2.7 g, 15 mM), oxalyl chloride (2.5 mL, 30 mM) and DMF (several drops) in dichloromethane (50 mL) were stirred at room temperature for 2 h. Then, the solvent and oxalyl chloride were evaporated under reduced pressure to get 4-methyl-3-nitrobenzoyl chloride. The benzoyl chloride (1 M solution in dichloromethane, 15 mL) in constant pressure funnel was added to a solution of 4-chloro-3-(trifluoromethyl) aniline (2.44 g,12.5 mM) and triethylamine (5.2 mL, 37.5 mM) in dichloromethane (40 mL) successively. The reaction mixture was stirred at room temperature for 5 h. Subsequently, the solvent and triethylamine were evaporated under reduced pressure to get substituted amide. Then, reduction of the nitro group was carried out by using Fe/NH_4Cl (50 mM/37.5 mM) in ethanol/H_2O (75 mL/ 25 mL). The mixture was heated to reflux for about 3 h, evaporated in *vacuo*, purified with silica gel column chromatography. Desired aniline (3 g, 72.6%) was afforded as a pale yellow solid. ESI-MS m/z: 329.1 $[M+H]^+$.

N-(3-amino-4-methylphenyl)-4-chloro-3-(trifluoromethyl)benzamide (**A2**)

A2 (2.6 g, 80.4%) was prepared from 4-chloro-3-(trifluoromethyl)benzoic acid (3.4 g, 15 mM), in a manner same as **A1**. ESI-MS m/z: 329.1 $[M+H]^+$.

1-(3-amino-4-methylphenyl)-3-(4-chloro-3-(trifluoromethyl) phenyl) urea (**A3**)

Commercially available 4-chloro-3-(trifluoromethyl) aniline (2.9 g, 15 mM) and CDI (2.6 g, 16 mM) in dichloromethane (50 mL) were stirred at room temperature for 16 h, followed by addition of the required 4-methyl-3-nitroaniline (2.3 g, 15 mM) and stirring at room temperature for another 18 h. The precipitate formed was filtered, washed with ethanol, and then dried under vacuum. The intermediate substituted amide was converted to **A3** (4.8 g, 92.6%) through reduction reaction in a manner same as **A1**. ESI-MS m/z: 344.1 $[M+H]^+$.

4-(4-nitro-2-(trifluoromethyl) phenyl) morpholine (**1a**)

1-fluoro-4-nitro-2-(trifluoromethyl)benzene (2.1 g, 10 mM) and morpholine (2.6 mL, 30 mM) in DMSO (20 mL) were heated to 100°C for 5 h. The mixture was partitioned between ethyl acetate (80×2 mL) and water (40×2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to get **2a** (2.6 g, 9.4 mM) as yellow solid in 94.2%. ESI-MS m/z: 277.1 $[M+H]^+$.

1-methyl-4-(4-nitro-2-(trifluoromethyl)phenyl)piperazine (**1b**)

1b (2.6 g, 91.4%) was prepared from N-methyl piperazine (3.3 mL, 30 mM), in a manner same as **1a**. ESI-MS m/z: 290.1 $[M+H]^+$.

3-amino-4-methyl-N-(4-morpholino-3-(trifluoromethyl)phenyl)benzamide (**A4**)

A4 (3.0 g, 85.4%) was prepared from **1a** (2.6 g, 9.4 mM), in a manner same as **A1**. ESI-MS m/z: 380.2 $[M+H]^+$.

3-amino-4-methyl-N-(4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl) benzamide (**A5**)

A5 (2.7 g, 76.2%) was prepared from **1b** (2.6 g, 9 mM), in a manner same as **A1**. ESI-MS m/z: 393.2 $[M+H]^+$.

1-(bromomethyl)-4-nitrobenzene (**2a**)

1-methyl-4-nitro-2-(trifluoromethyl) benzene (2.1 g, 10 mM) and NBS (2.1 g, 12 mM) in DCE (25 mL) were heated to reflux for 5 h. The mixture was partitioned between ethyl acetate (80 mL) and water (50 mL), the organic layer was evaporated. The oily residue was purified with column chromatography on silica gel, crystallized with ethyl acetate/n-hexane (1:4) to give **2a** (2.5 g, 86.4%) as a pale yellow solid.

1-(bromomethyl)-4-nitro-2-(trifluoromethyl) benzene (**2b**)

2b (1.9 g, 89.2%) was prepared from 1-methyl-4-nitrobenzene (1.4 g, 10 mM), in a manner same as **2a**.

4-(4-nitro-2-(trifluoromethyl)benzyl)morpholine (**3a**)

The mixture of **2a** (1.9 g, 8.8 mM), morpholine (1.1 mL, 13.2 mM) and triethylamine (1.8 mL, 13.2 mM) were heated to reflux in THF for 2 h. The mixture was partitioned between ethyl acetate (60×2 mL) and water (40×2 mL), the combined organic layers were evaporated. The oily residue **3a** utilized as materials without further purification.

4-(4-nitrobenzyl)morpholine (**3b**)

3b was prepared from **2b**, in a manner same as **3a**.

3-amino-4-methyl-N-(4-(morpholinomethyl)-3-(trifluoromethyl) phenyl) benzamide (**A6**)

A6 was prepared from **3a**, in a manner same as **A1**.

3-amino-4-methyl-N-(4-(morpholinomethyl) phenyl) benzamide (**A7**)

A7 was prepared from **3b**, in a manner same as **A1**.

1-methyl-4-(4-nitro-2-(trifluoromethyl) phenoxy) piperidine (**4a**)

To a solution of 1-methylpiperidin-4-ol (1.15 g, 10 mM) in DMF (10 mL) were added NaH (0.48 g, 12 mM) successively. The mixture was stirred at 0^{o}C for 0.5 h, followed by addition of the required 1-fluoro-4-nitro-2-(trifluoromethyl)benzene and heating to reflux for another 5 h. After cooling to room temperature, the mixture was partitioned between ethyl acetate (100×2 mL) and water (40×2 mL). The combined organic layers were evaporated, the resulting residue **4a** utilized as materials without further purification.

1-methyl-4-((4-nitro-2-(trifluoromethyl) phenoxy) methyl) piperidine (**4b**)

4b was prepared from (1-methylpiperidin-4-yl) methanol, in a manner same as **4a**.

4-(3-(4-nitro-2-(trifluoromethyl) phenoxy) propyl) morpholine (**4c**)

4c was prepared from 3-morpholinopropan-1-ol (1.45g, 10mM), in a manner same as **4a**.

3-amino-4-methyl-N-(4-((1-methylpiperidin-4-yl)oxy)-3-(trifluoromethyl)phenyl) benzamide (**A8**)

A8 (3.6 g, 89.4%) was prepared from **4a** (3.0 g, 10 mM), in a manner same as **A1**. ESI-MS m/z: 408.2 $[M+H]^{+}$.

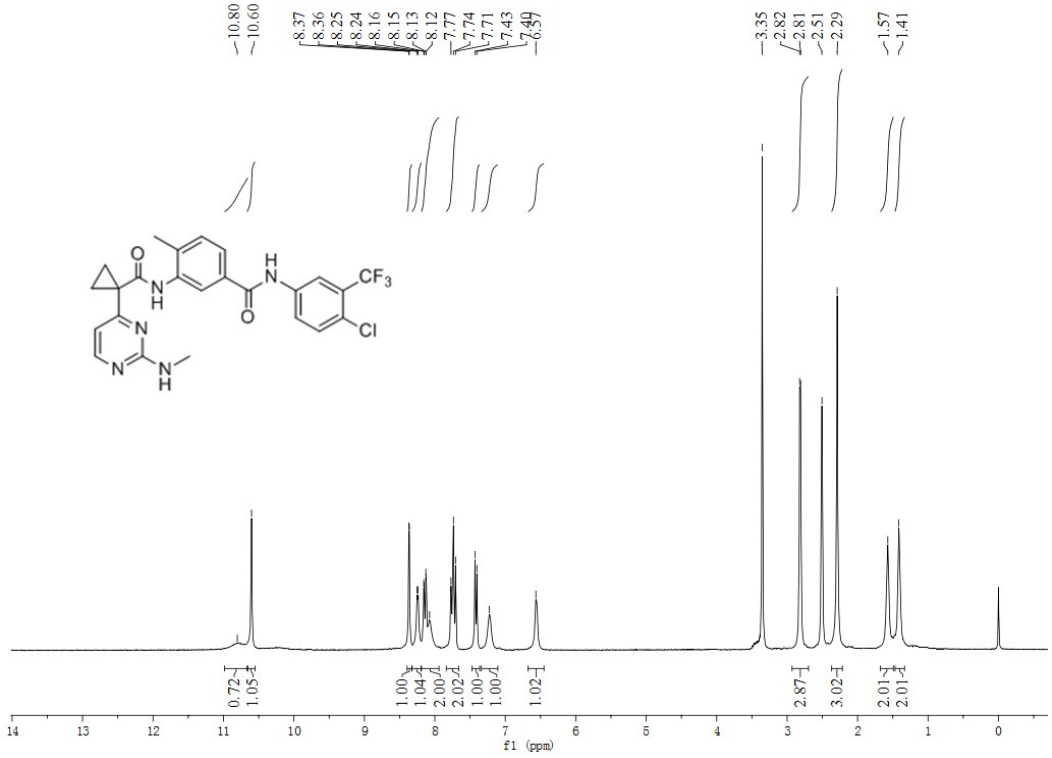
3-amino-4-methyl-N-(4-((1-methylpiperidin-4-yl)methoxy)-3-(trifluoromethyl)phenyl)benzamide (**A9**)

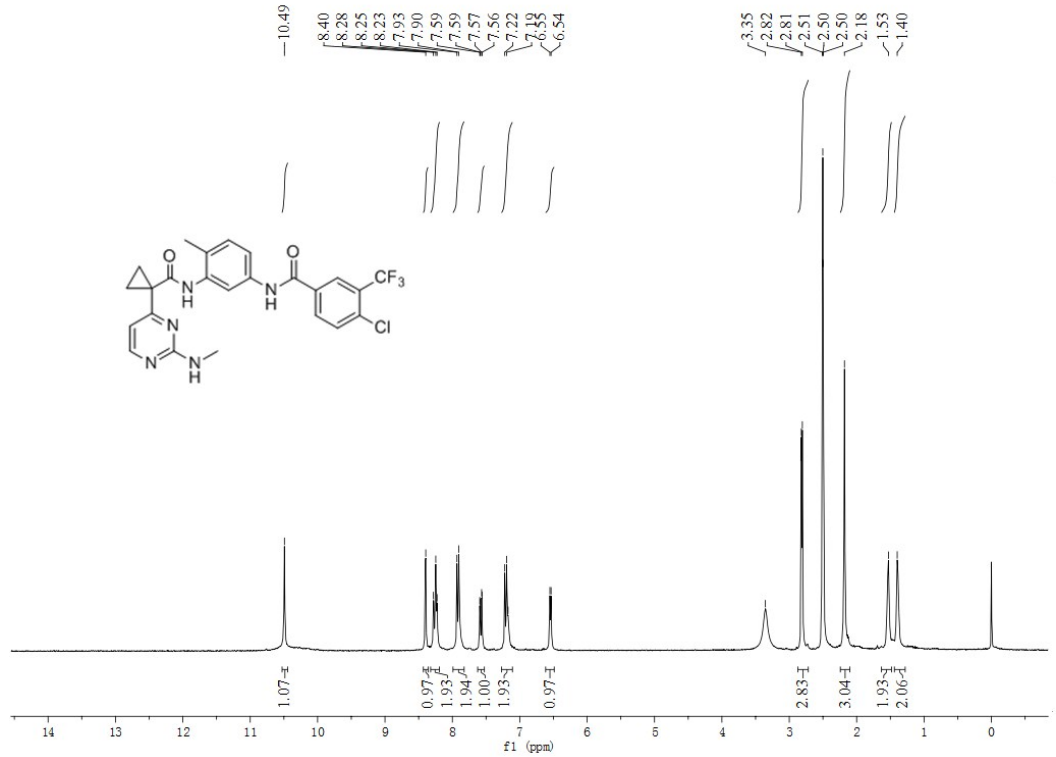
A9 (3.6 g, 86.4%) was prepared from **4b** (3.2 g, 10 mM), in a manner same as **A1**. ESI-MS m/z: 422.2 $[M+H]^{+}$.

3-amino-4-methyl-N-(4-(3-morpholinopropoxy)-3-(trifluoromethyl)phenyl) benzamide (**A10**)

A10 (3.7 g, 85.2%) was prepared from **4c** (3.3 g, 10 mM), in a manner same as **A1**. ESI-MS m/z: 438.2 $[M+H]^+$.

The chemical structures of compounds were confirmed by ^{1}H-NMR and ^{13}C-NMR

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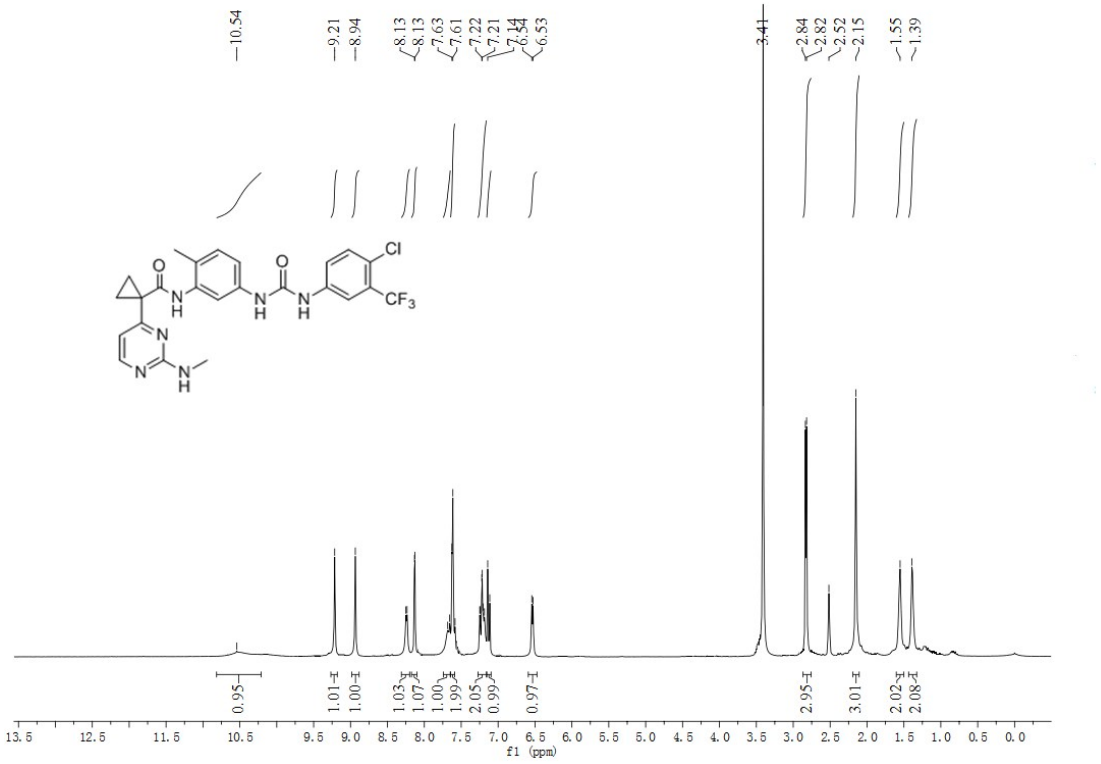
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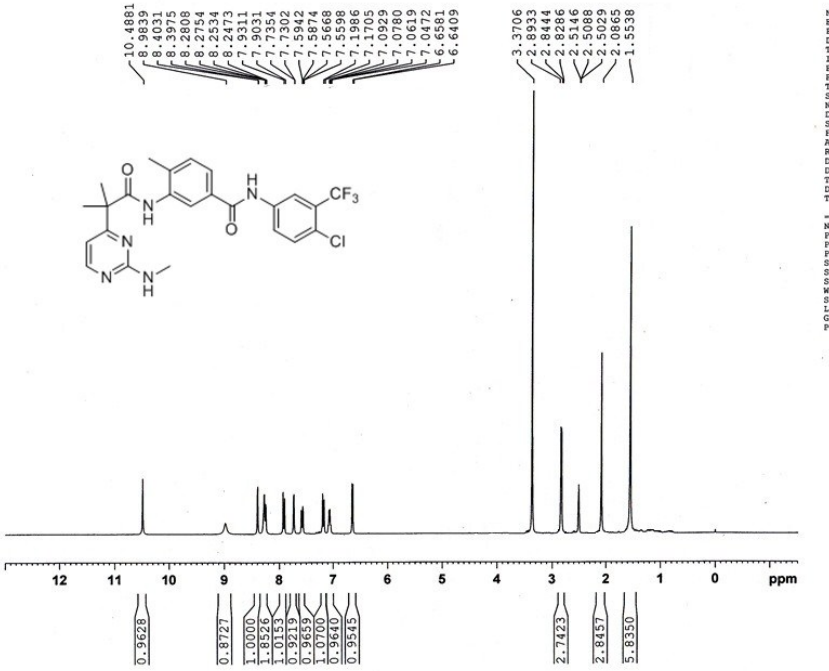


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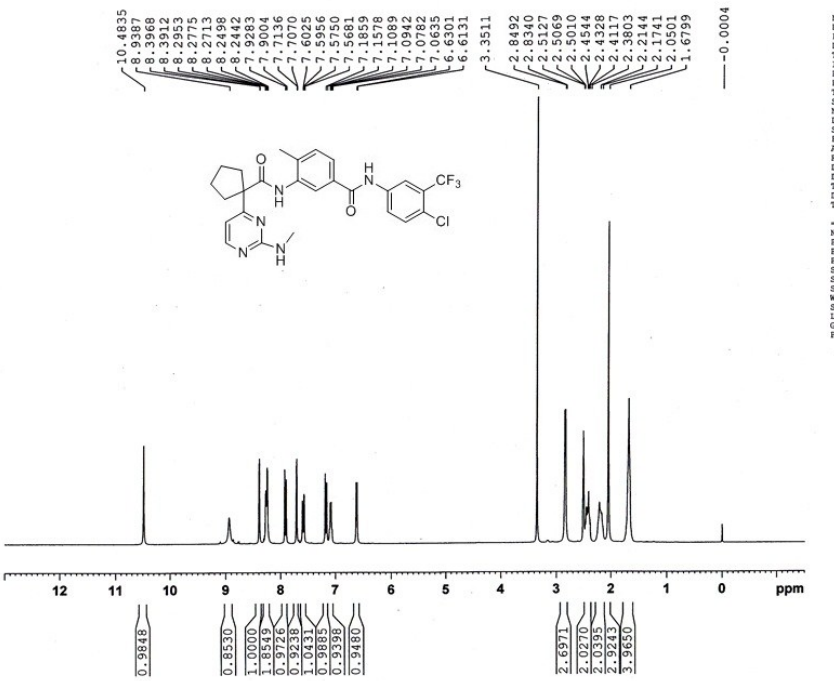


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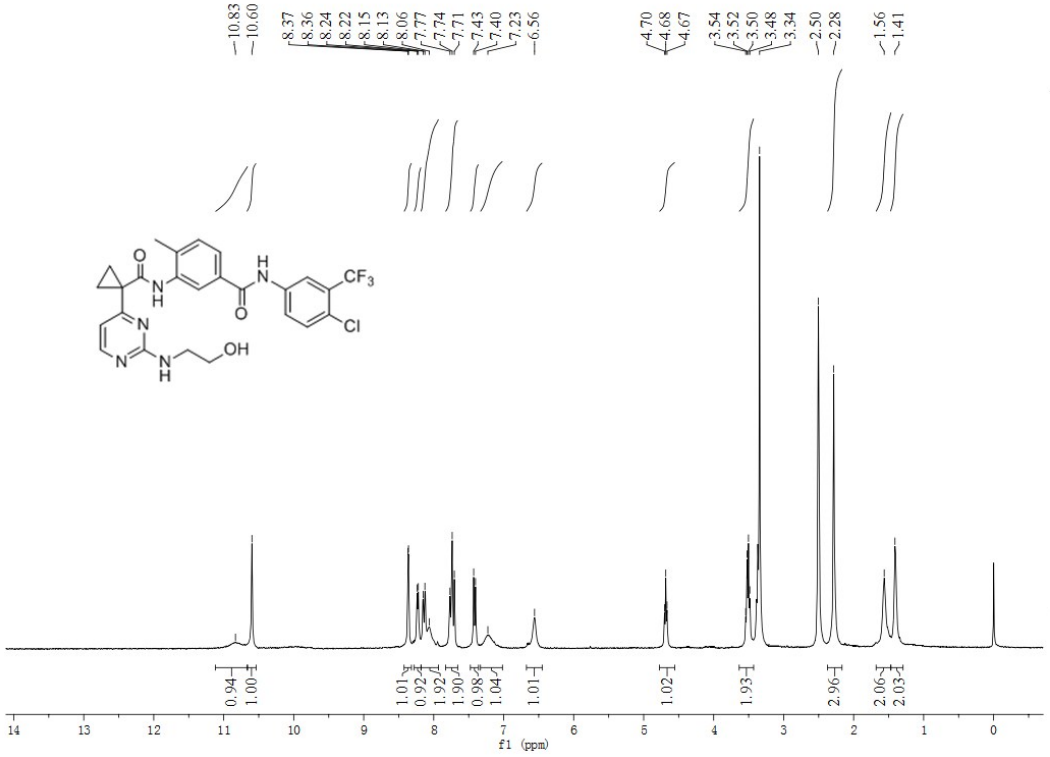
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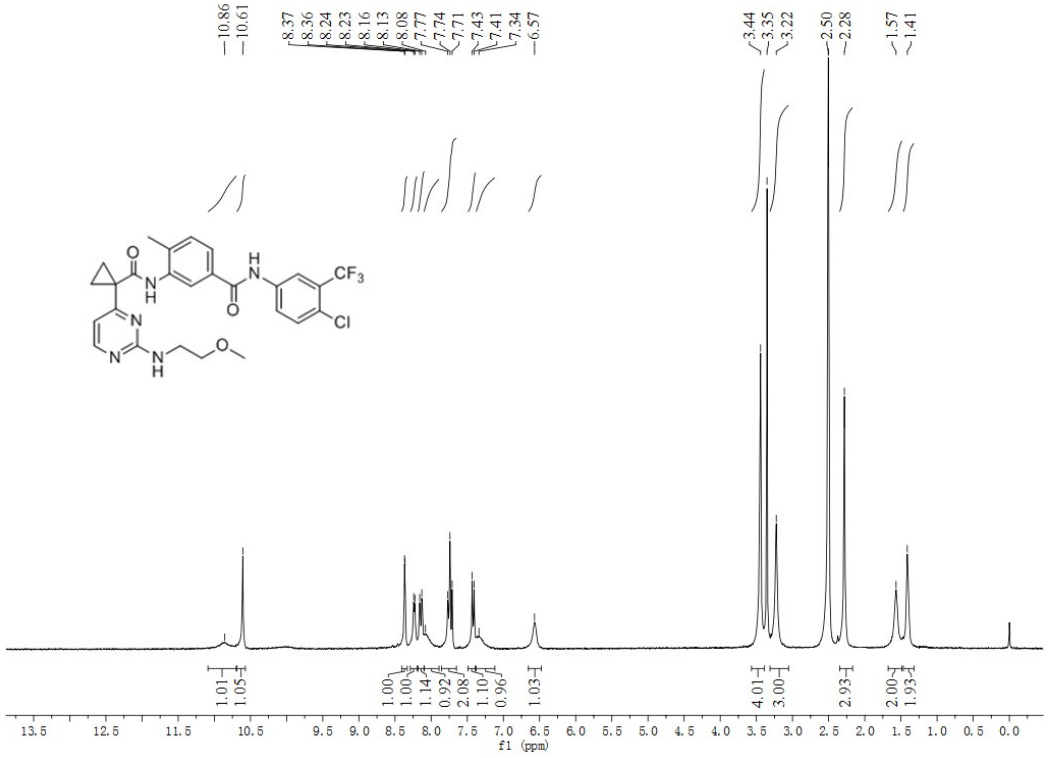
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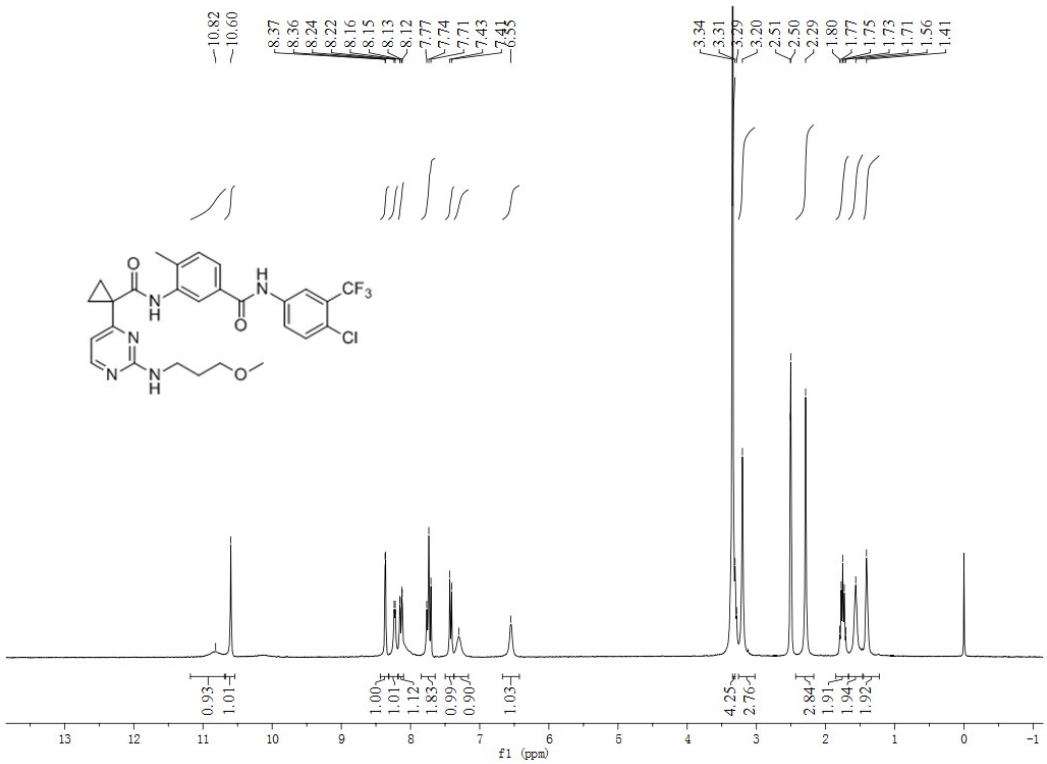
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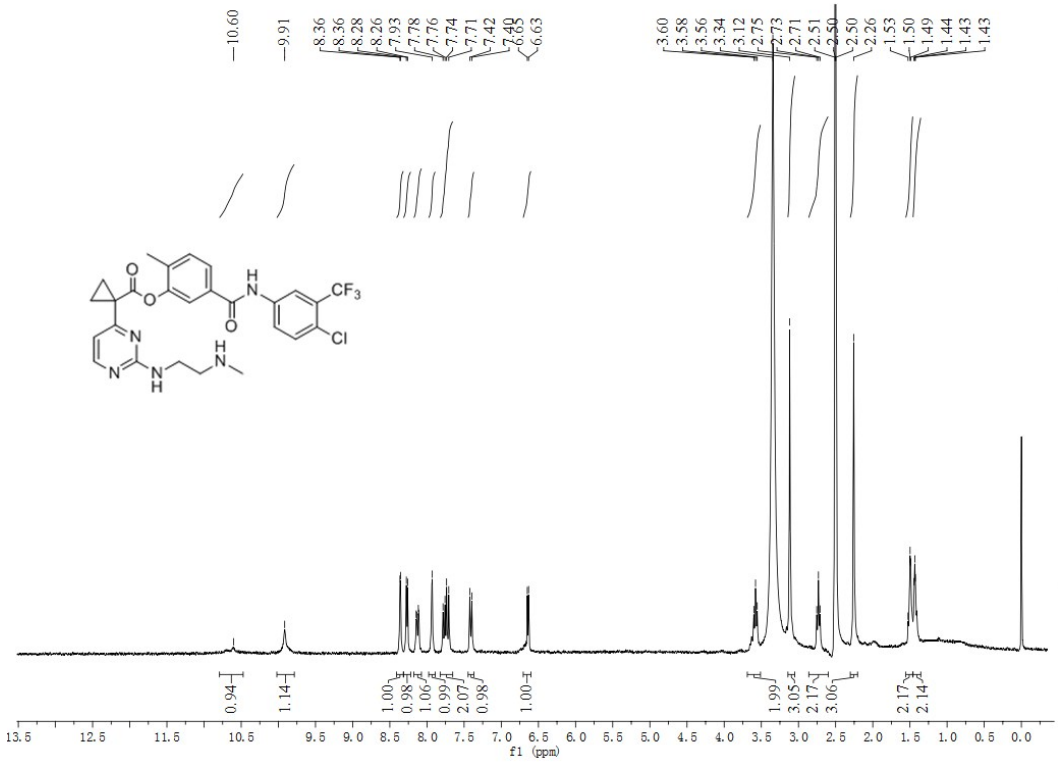
1.92
f1 (ppm)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6.65
6.63
3.60
3.58
3.56
3.34
3.12
2.75
2.73
2.71
2.51
2.50
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1.53
1.50
1.49
1.44
1.43
1.43
CF3
Cl
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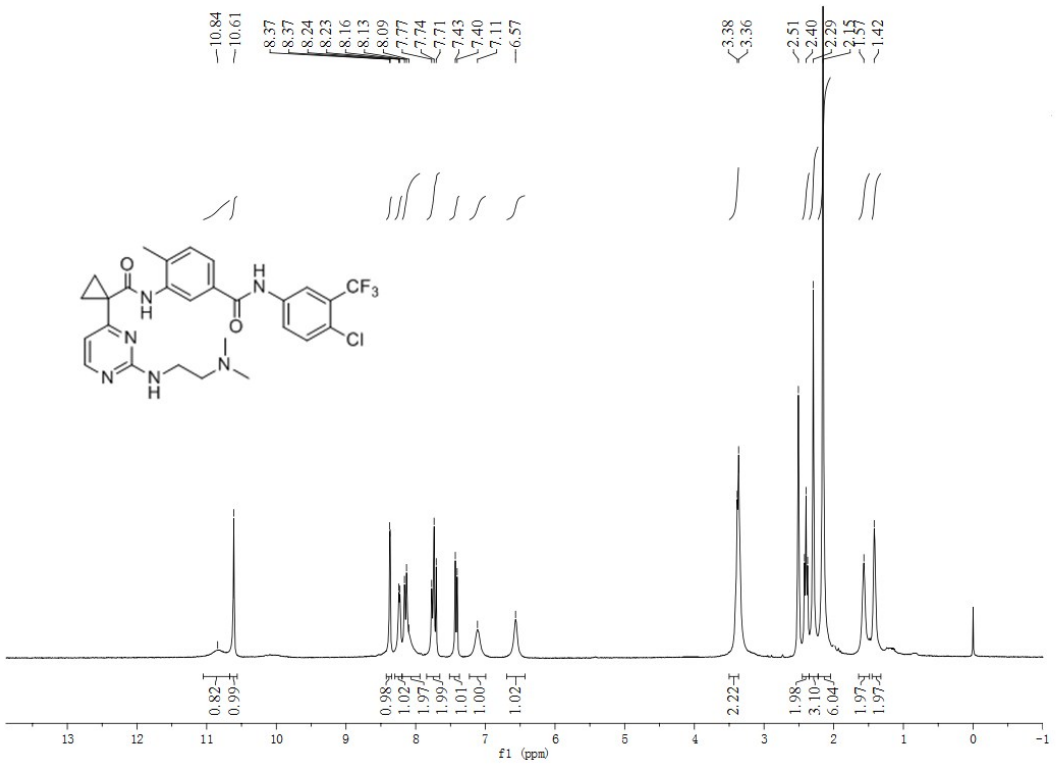
f1 (ppm)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7.40
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3.36
2.51
2.40
2.29
2.15
1.57
1.42
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0.98
1.02
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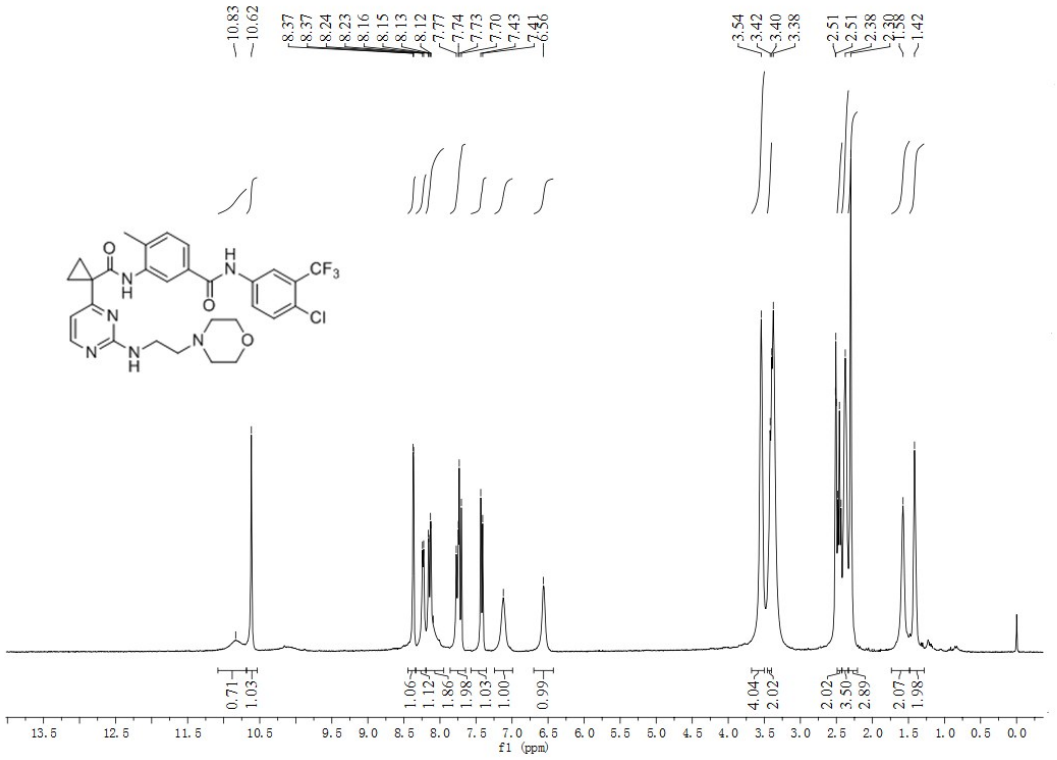
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7.43
7.41
6.56
3.54
3.42
3.40
3.38
2.51
2.51
2.38
2.30
1.58
1.42
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1.06
1.12
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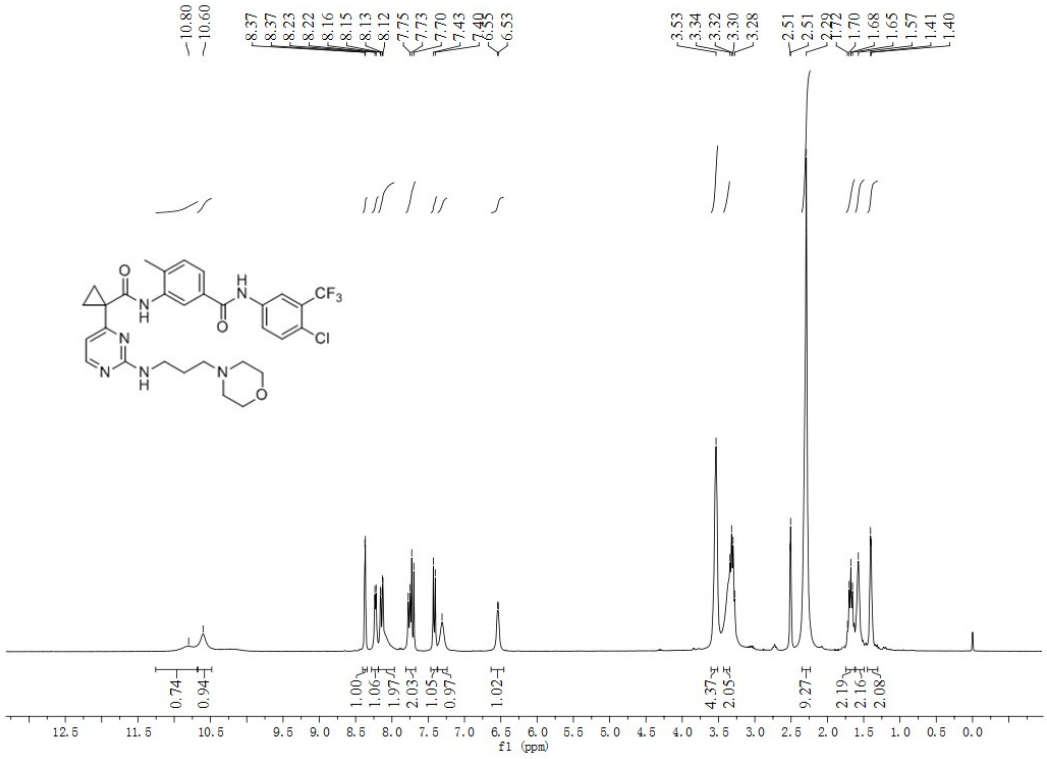
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7.40
6.55
6.53
3.53
3.34
3.32
3.30
3.28
2.51
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1.41
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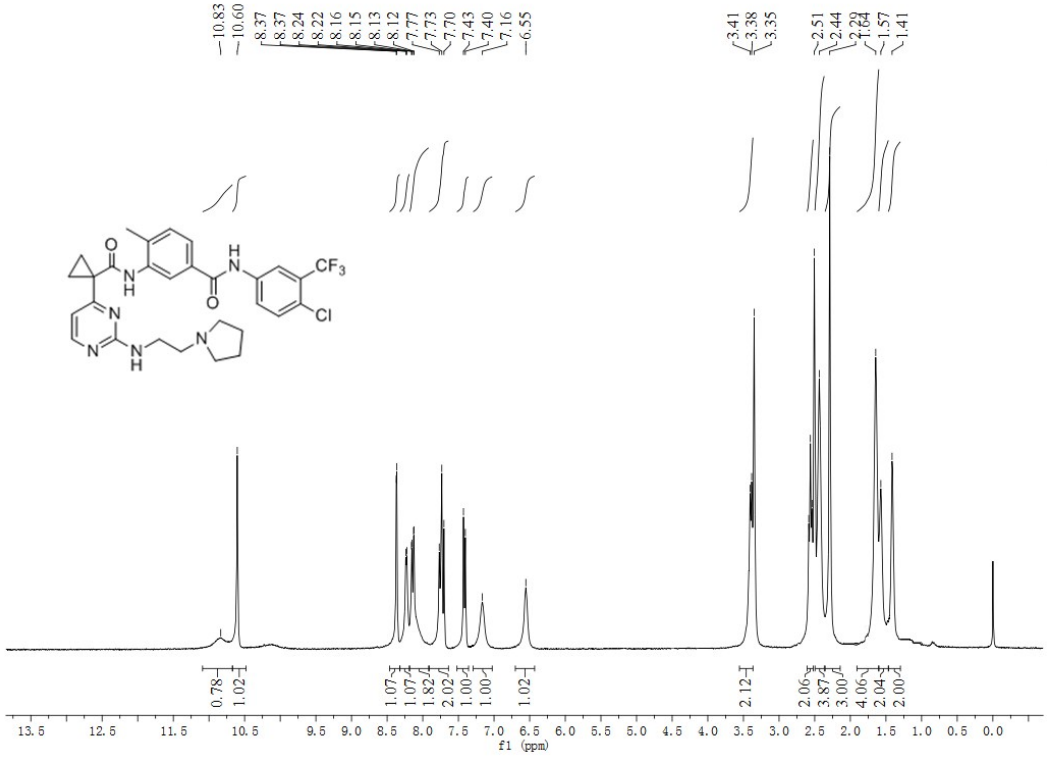
CF3
Cl
f1 (ppm)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7.40
7.16
6.55
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CF3
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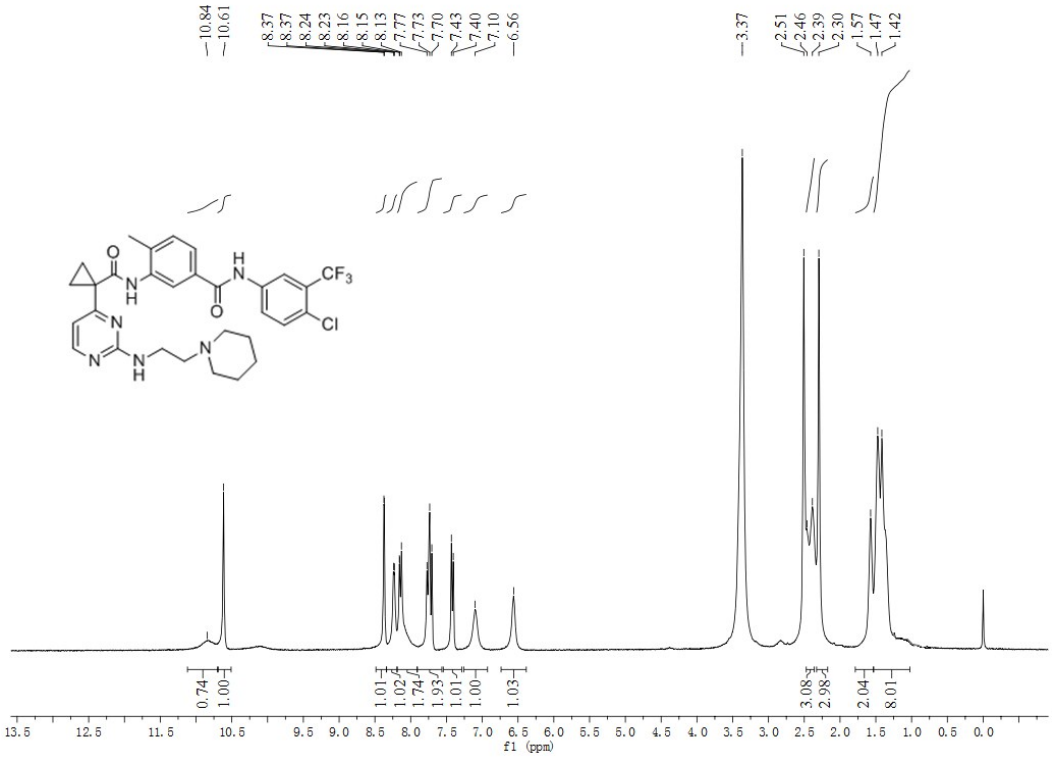
f1 (ppm)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7.43
7.40
7.10
6.56
3.37
2.51
2.46
2.39
2.30
1.57
1.47
1.42
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1.00
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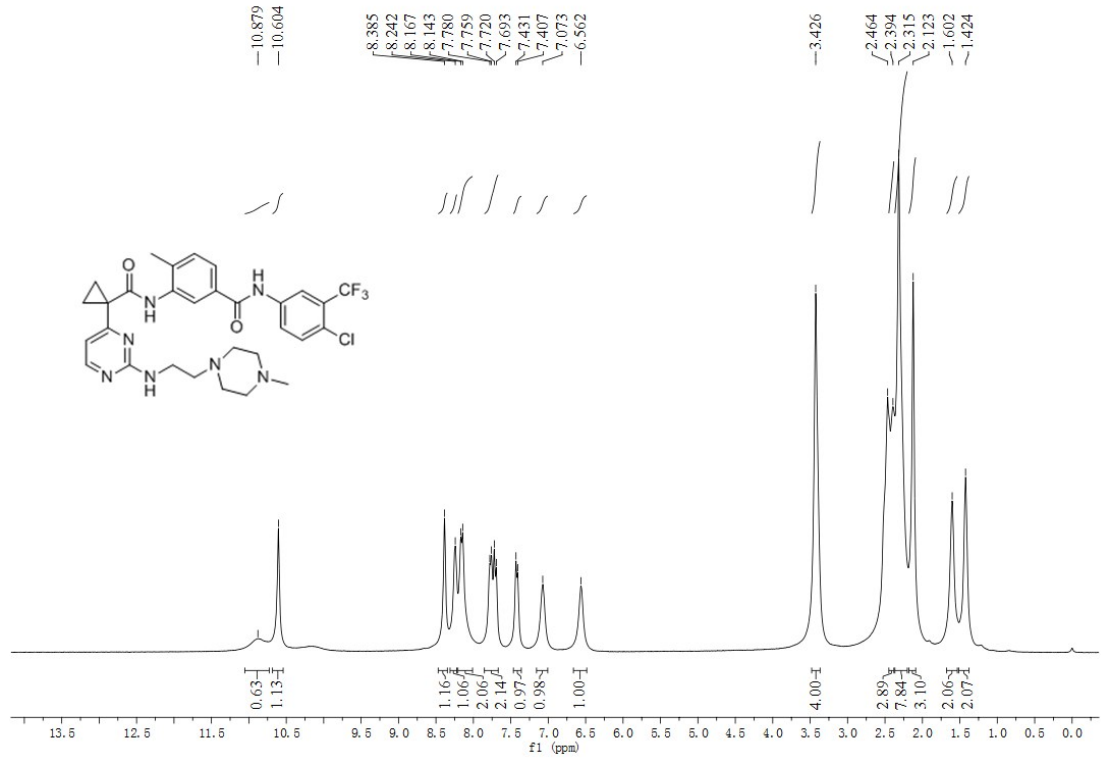
8.01
f1 (ppm)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7.073
6.562
3.426
2.464
2.394
2.315
2.123
1.602
1.424
0.63
1.13
1.16
1.06
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2.14
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4.00
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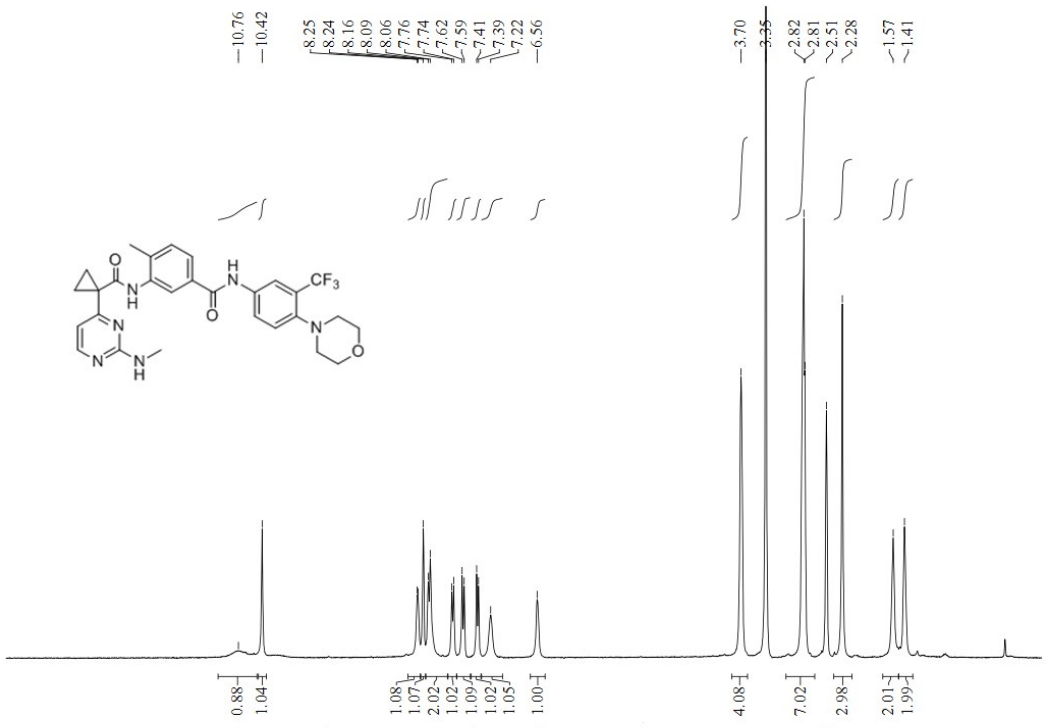
3.10
2.06
2.07
f1 (ppm)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7.22
6.56
3.70
3.35
2.82
2.81
2.51
2.28
1.57
1.41
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1.04
1.08
1.07
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1.09
1.02
1.05
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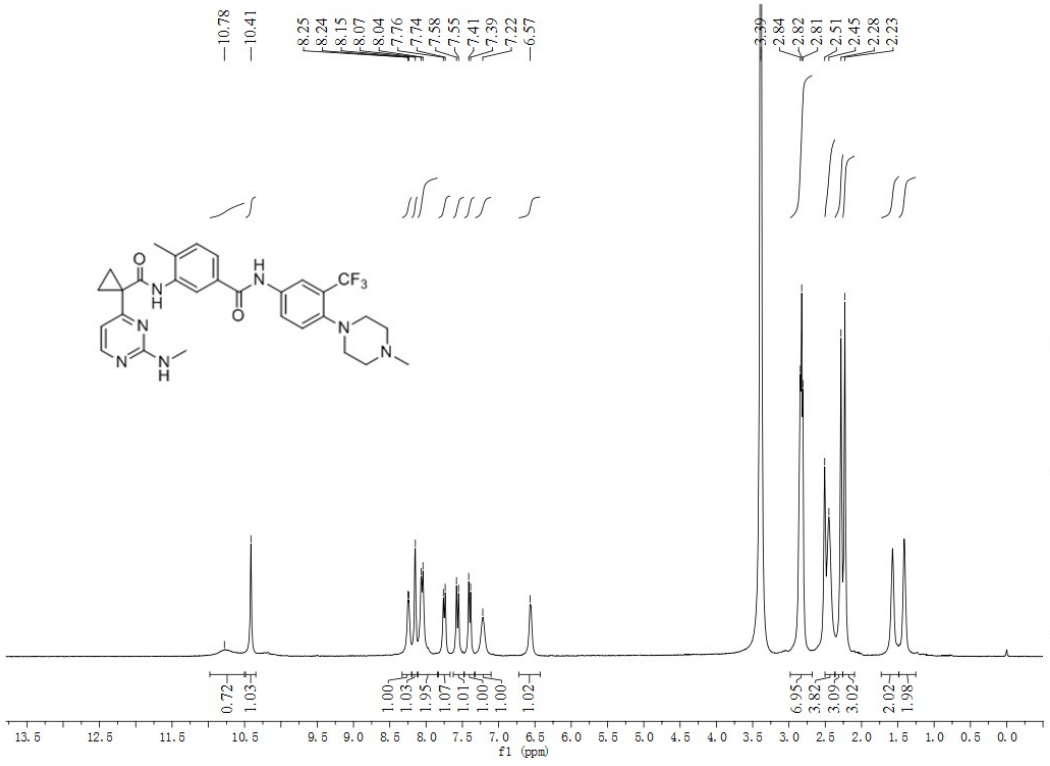
4.08
7.02
2.98
2.01
1.99
CF3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7.55
7.41
7.39
7.22
6.57
3.39
2.84
2.82
2.81
2.51
2.45
2.28
2.23
0.72
1.03
1.00
1.03
1.95
1.07
1.01
1.00
1.00
1.02
6.95
3.82
3.09
3.02
2.02
1.98
CF3
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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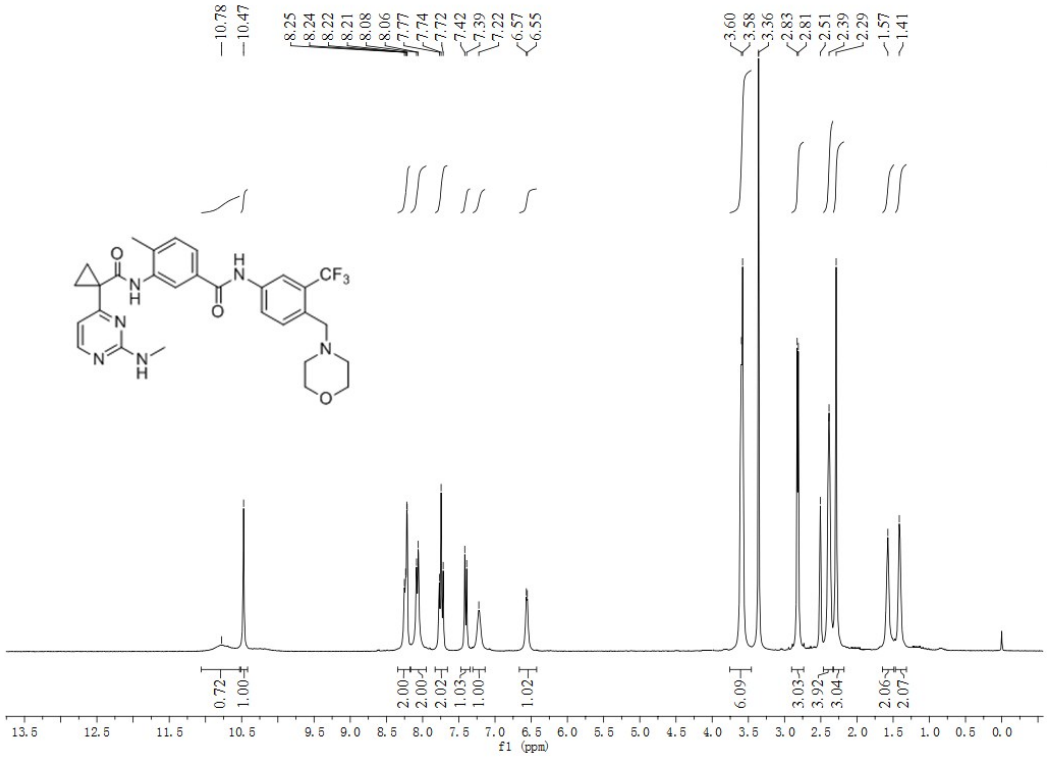
f1 (ppm)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7.74
7.72
7.42
7.39
7.22
6.57
6.55
3.60
3.58
3.36
2.83
2.81
2.51
2.39
2.29
1.57
1.41
CF3
0.72
1.00
2.00
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1.00
1.02
6.09
3.03
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3.04
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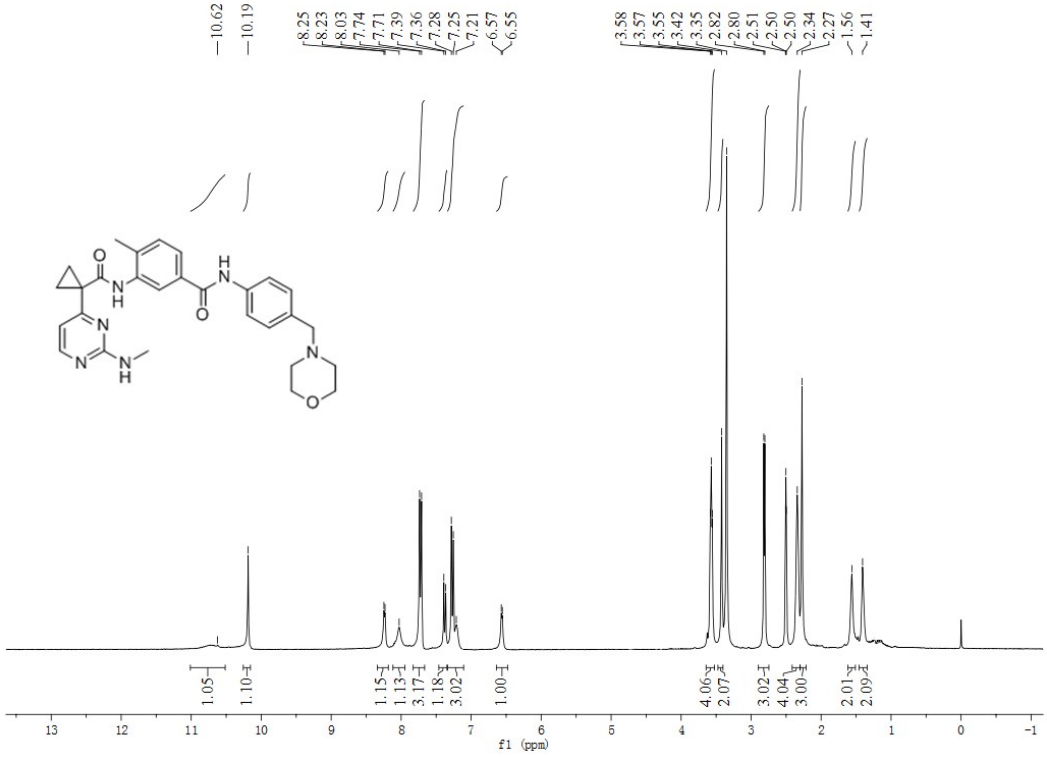
2.07
f1 (ppm)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7.21
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6.55
3.58
3.57
3.55
3.42
3.35
2.82
2.80
2.51
2.50
2.50
2.34
2.27
1.56
1.41
1.05
1.10
1.15
1.13
3.17
1.18
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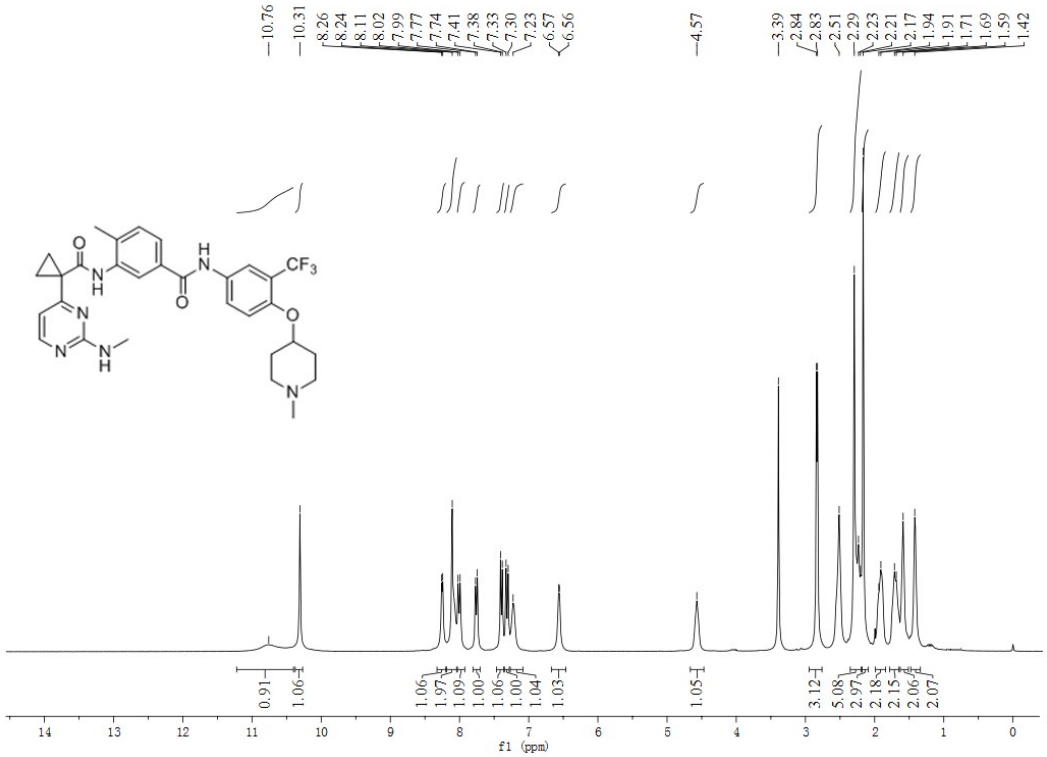
1.00
4.06
2.07
3.02
4.04
3.00
2.01
2.09
f1 (ppm)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7.23
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6.56
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3.39
2.84
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2.23
2.21
2.17
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1.91
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1.06
1.06
1.97
1.09
1.00
1.06
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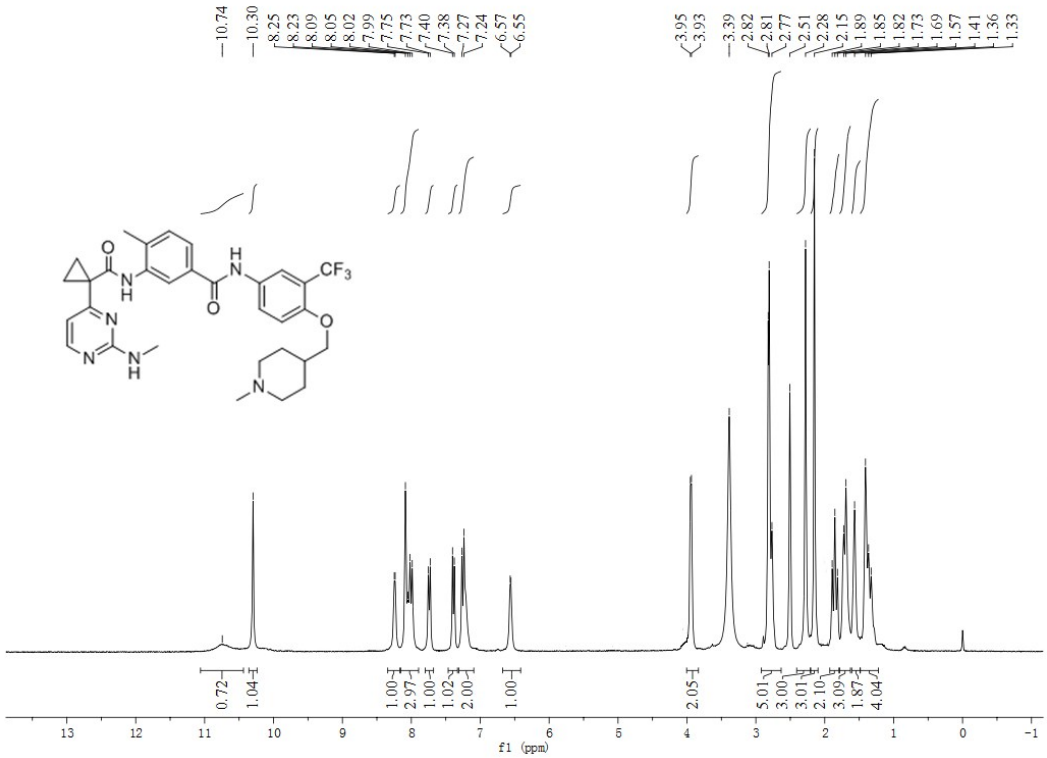
1.05
3.12
5.08
2.97
2.18
2.15
2.06
2.07
f1 (ppm)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7.27
7.24
6.57
6.55
3.95
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3.39
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2.81
2.77
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2.28
2.15
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1.41
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1.33
0.72
1.04
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2.97
1.00
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3.01
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3.09
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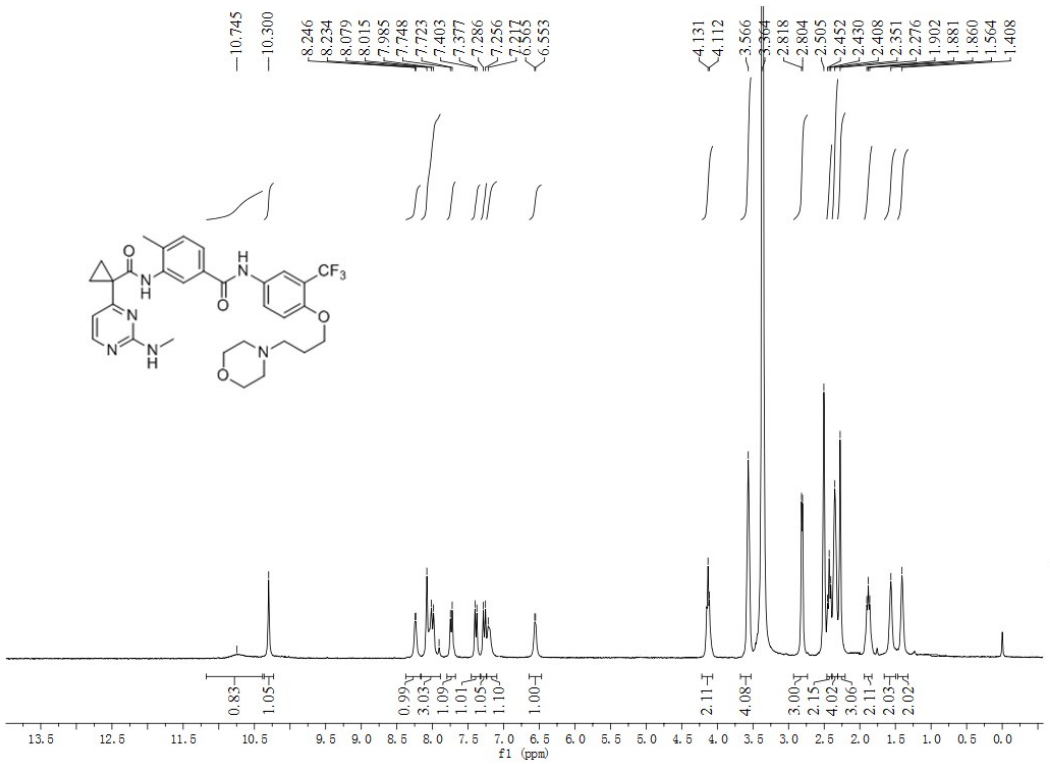
f1 (ppm)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7.286
7.256
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6.553
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1.408
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1.05
0.99
3.03
1.09
1.01
1.05
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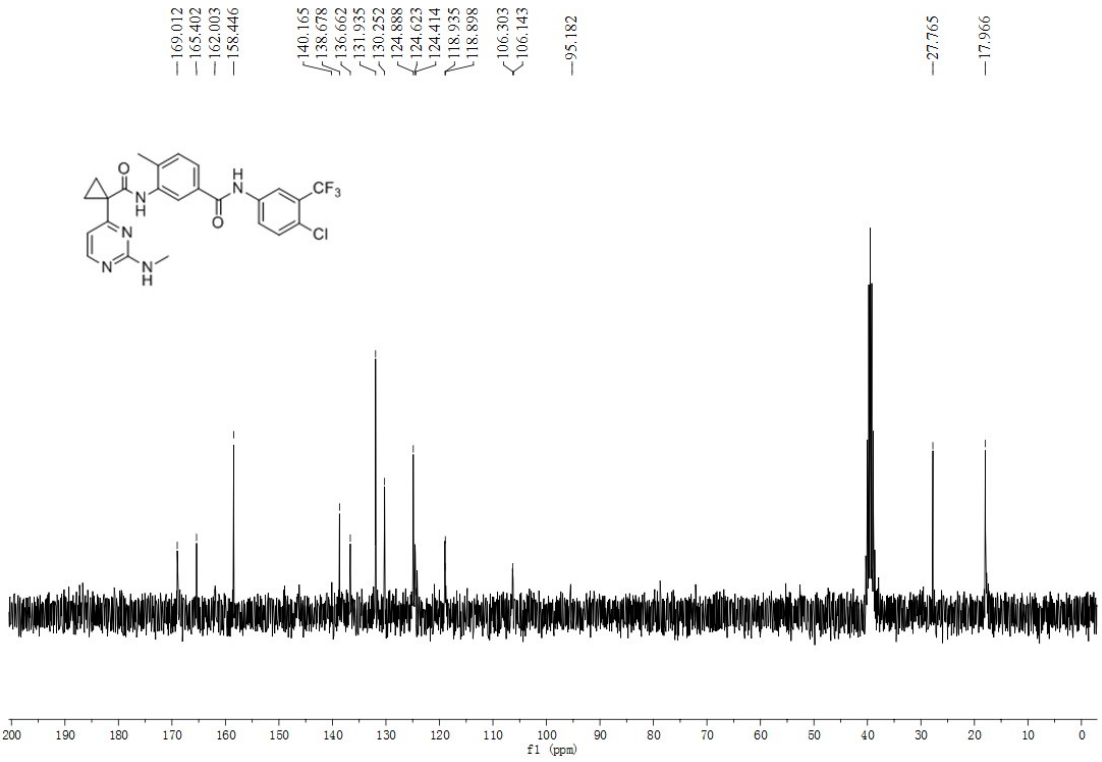
2.02
f1 (ppm)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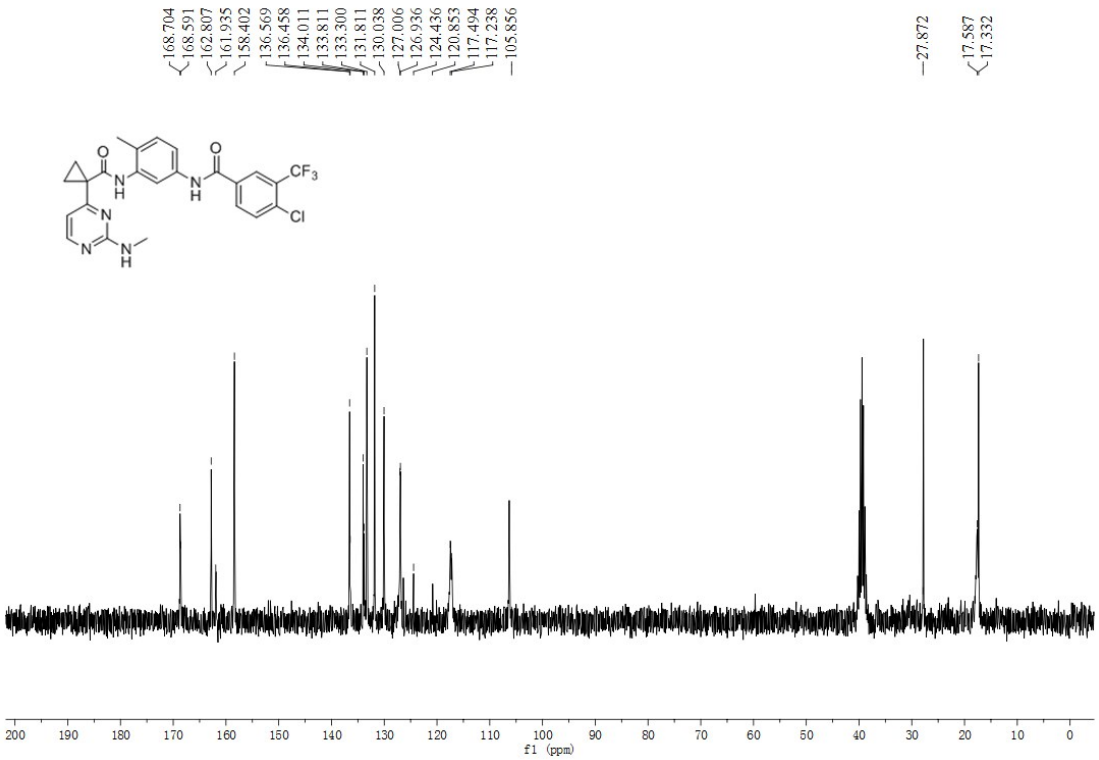
f1 (ppm)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126.936
124.436
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CF3
Cl
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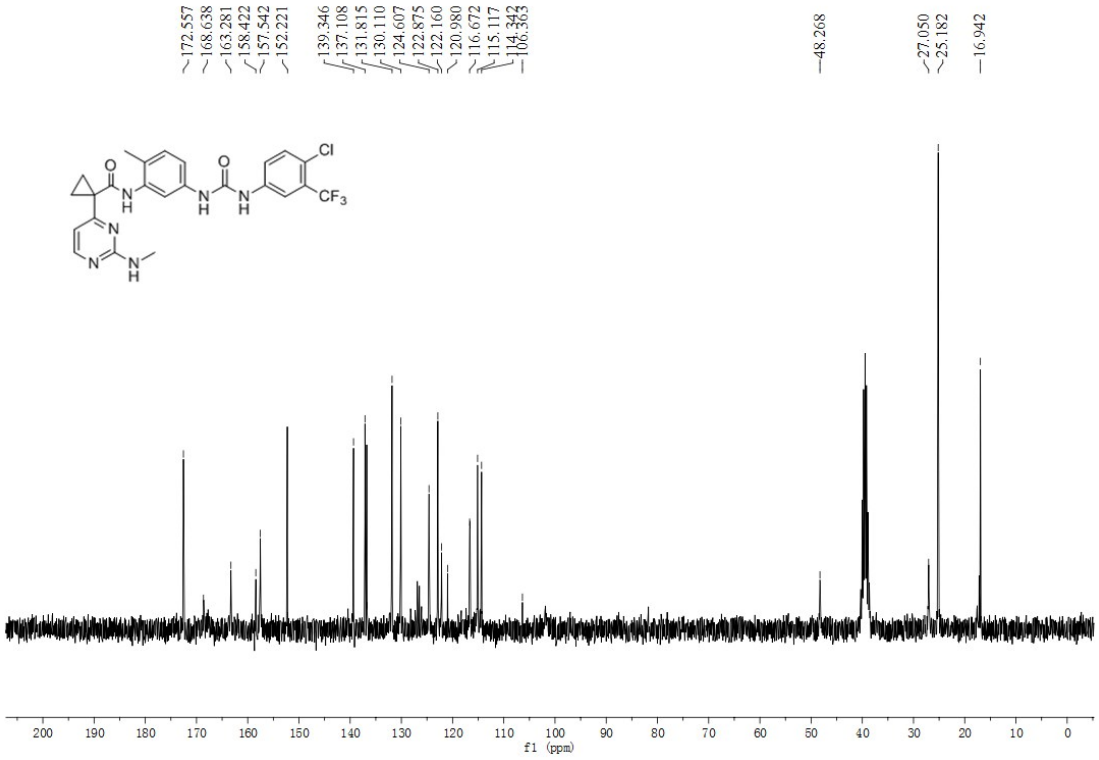
f1 (ppm)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Cl
CF3
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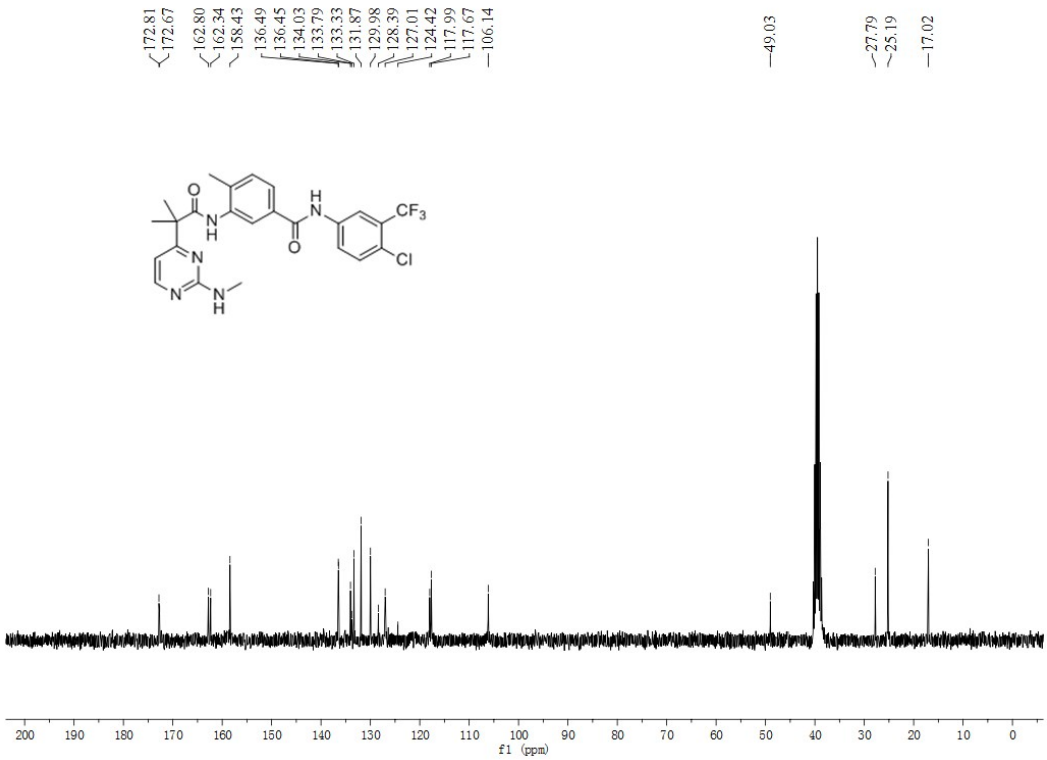
f1 (ppm)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25.19
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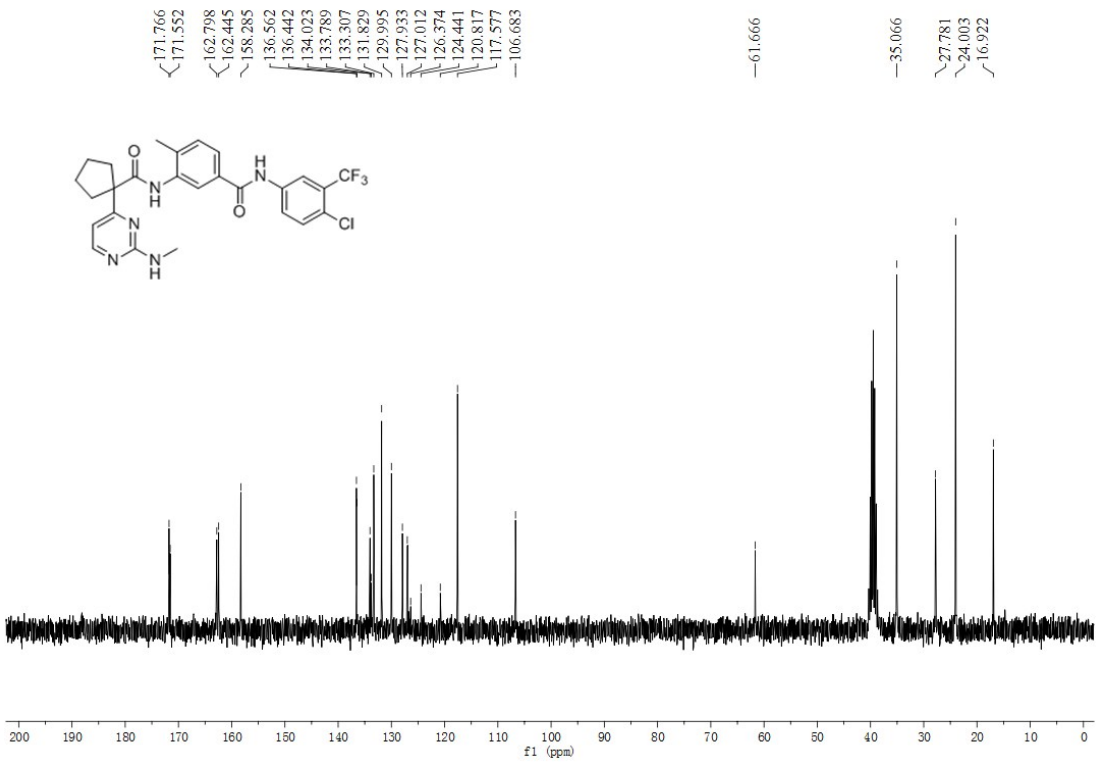
CF3
Cl
f1 (ppm)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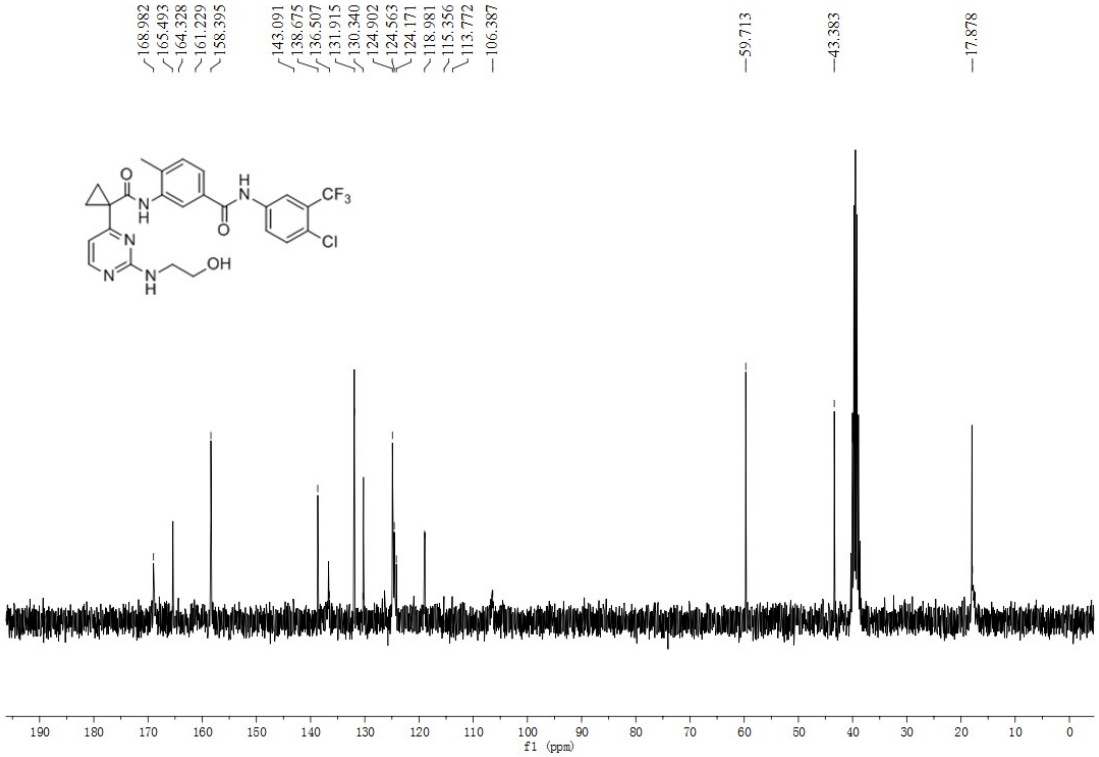
Cl
f1 (ppm)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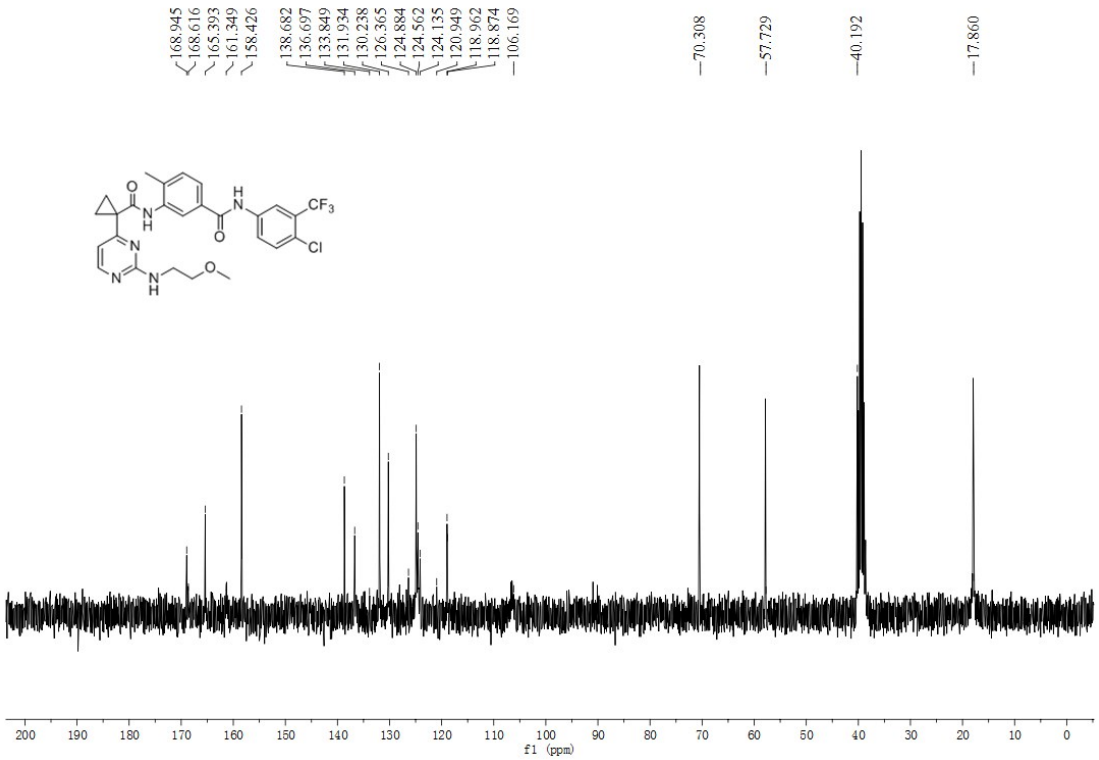
Cl
OH
f1 (ppm)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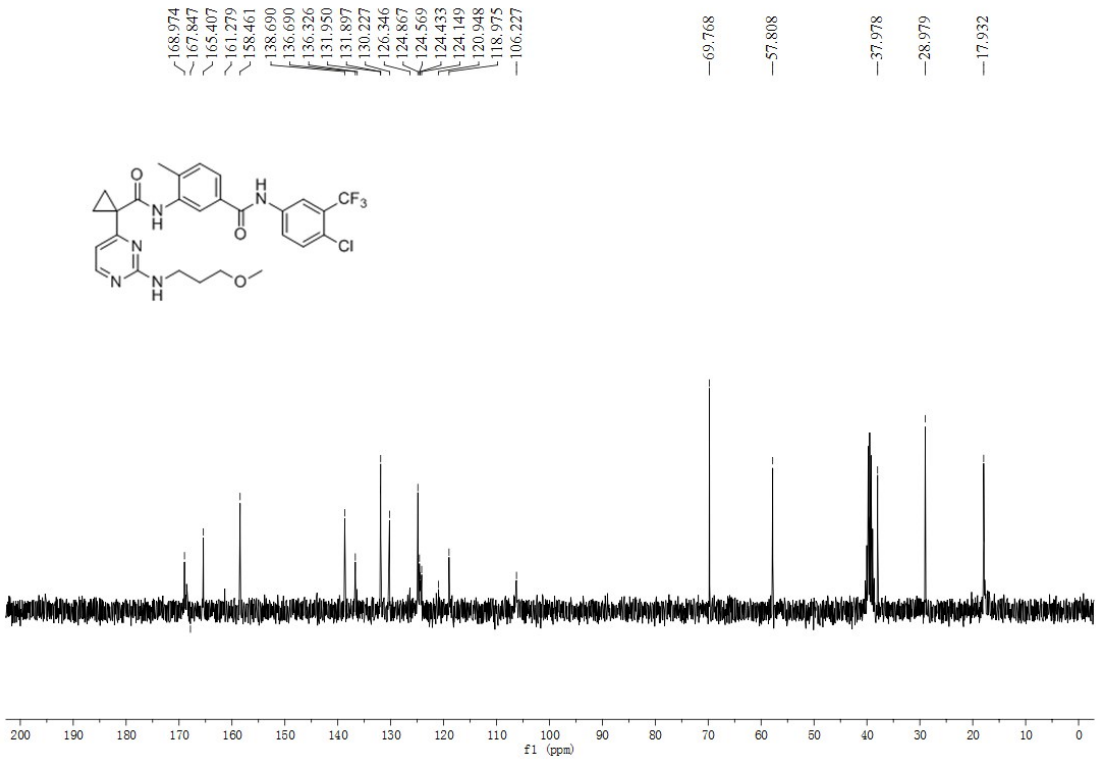
CF3
Cl
O
f1 (ppm)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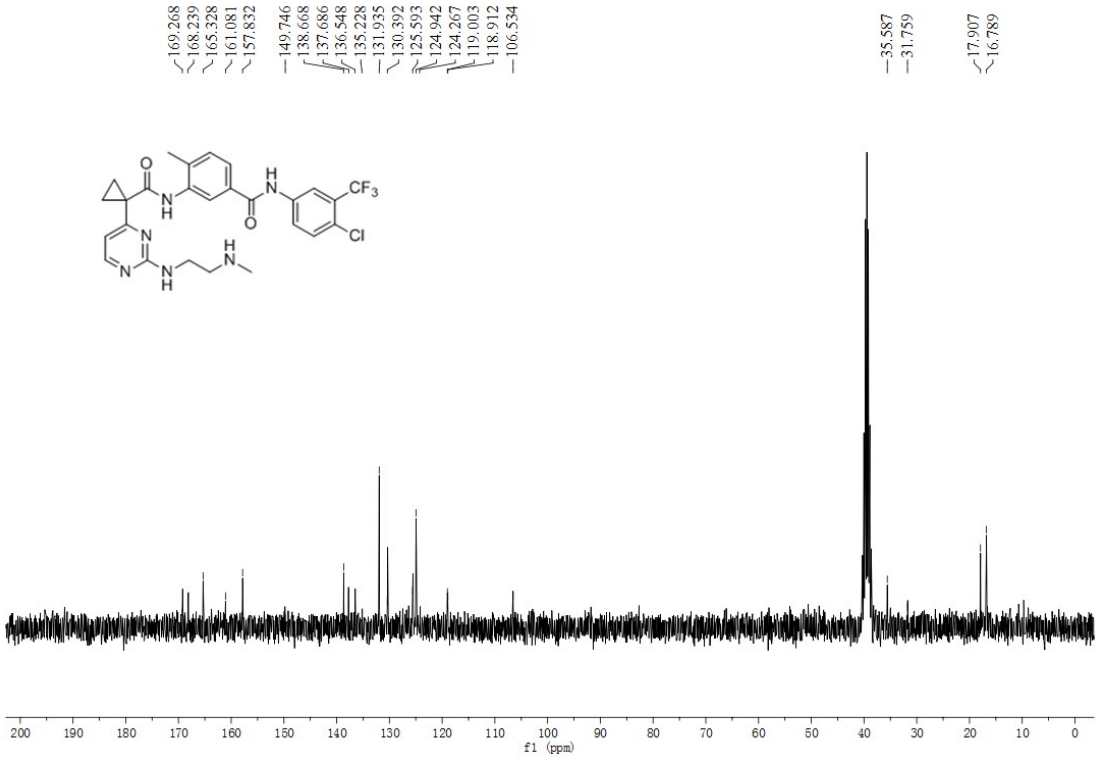
f1 (ppm)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17.907
16.789
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Cl
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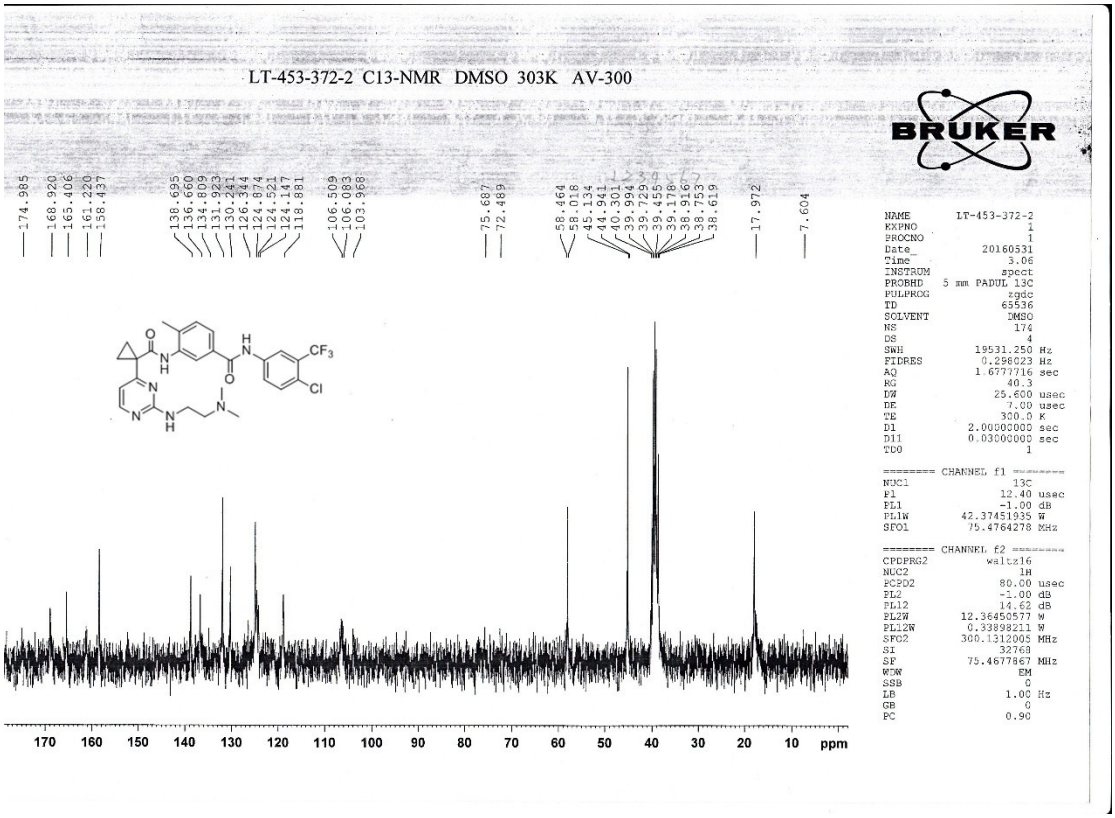
f1 (ppm)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103.968
75.687
72.489
58.464
58.018
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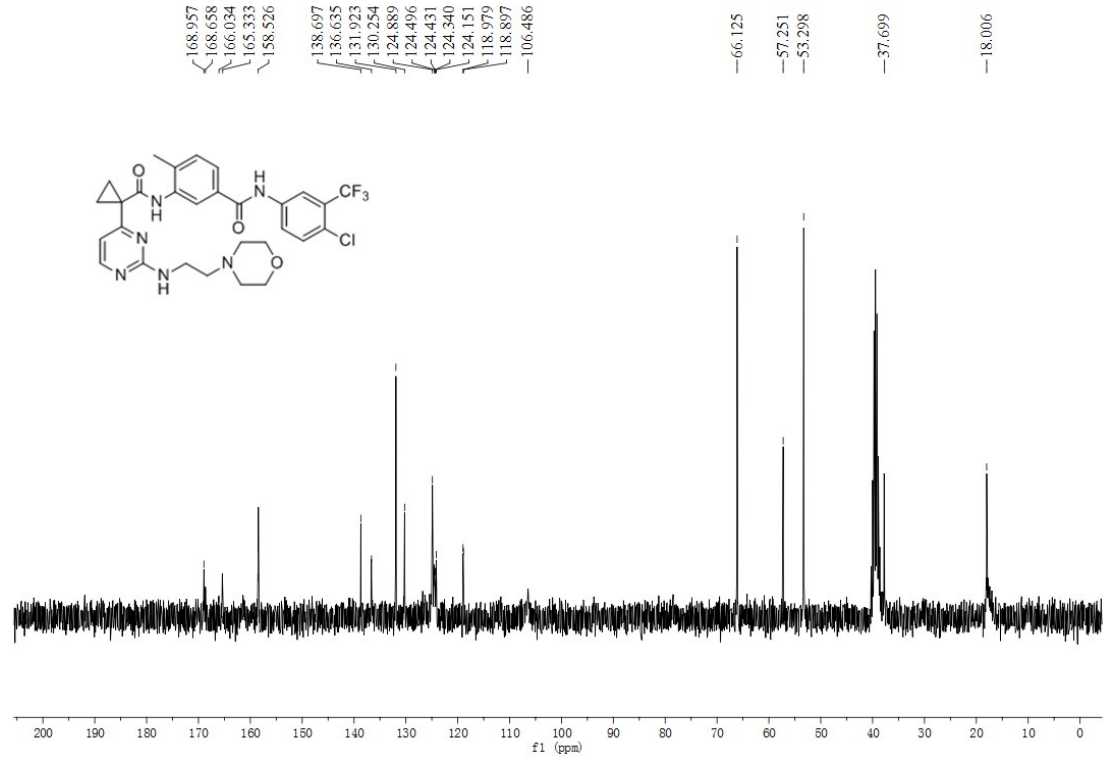
38.619
17.972
7.604
NAME LT-453-372-2
EXPNO 1
PROCNO 1
Date_ 20160531
Time 3.06
INSTRUM spect
PROBHD 5 mm PADUL 13C
PULPROG zgdc
TD 65536
SOLVENT DMSO
NS 174
DS 4
SWH 19531.250 Hz
FIDRES 0.298023 Hz
AQ 1.6777716 sec
RG 40.3
DW 25.600 usec
DE 7.00 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 12.40 usec
PL1 -1.00 dB
PL1W 42.37451935 W
SFO1 75.4764278 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.00 dB
PL12 14.62 dB
PL2W 12.36450577 W
PL12W 0.33898211 W
SFO2 300.1312005 MHz
SI 32768
SF 75.4677867 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 0.90
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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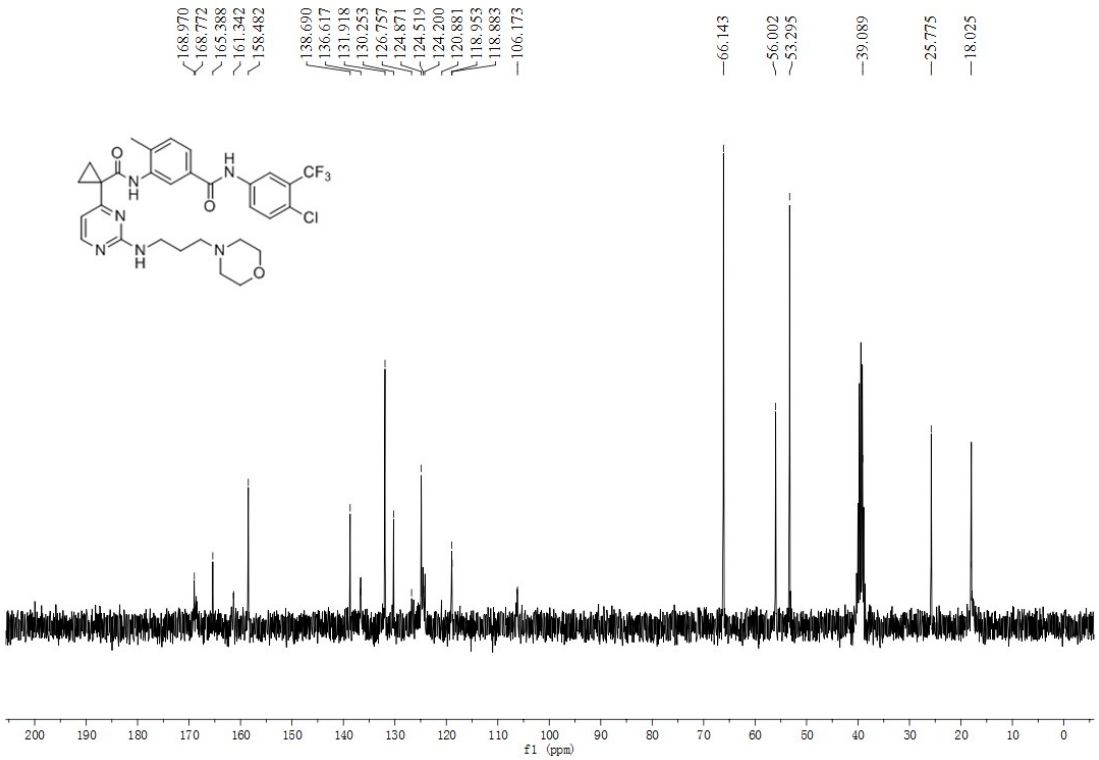
168.658
166.034
165.333
158.526
138.697
136.635
131.923
130.254
124.889
124.496
124.431
124.340
124.151
118.979
118.897
106.486
66.125
57.251
53.298
37.699
18.006
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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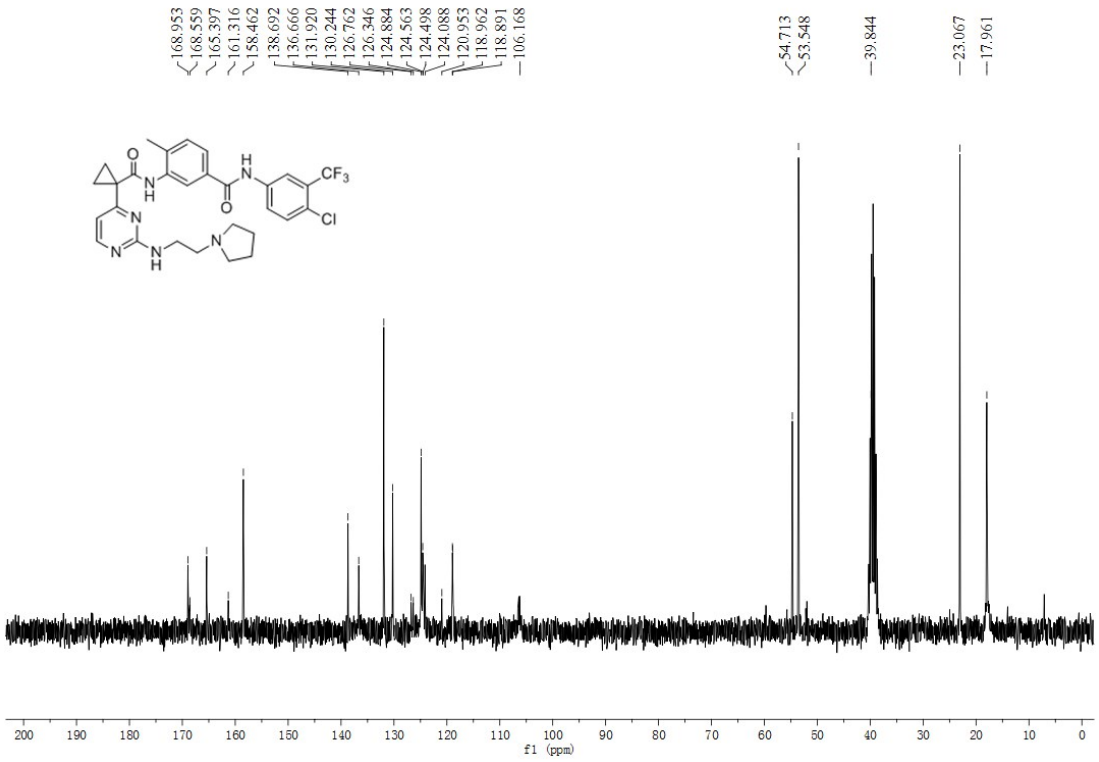
165.388
161.342
158.482
138.690
136.617
131.918
130.253
126.757
124.871
124.519
124.200
120.881
118.953
118.883
106.173
66.143
56.002
53.295
39.089
25.775
18.025
CF3
Cl
f1 (ppm)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168.559
165.397
161.316
158.462
138.692
136.666
131.920
130.244
126.762
126.346
124.884
124.563
124.498
124.088
120.953
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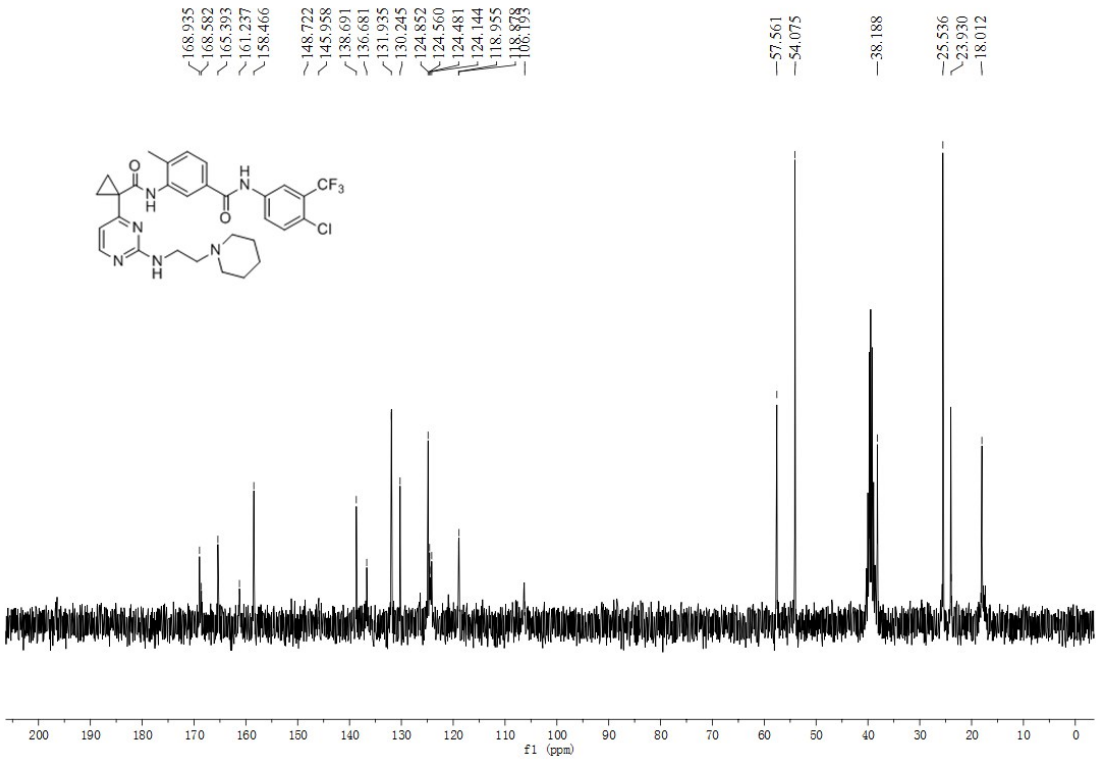
118.891
106.168
54.713
53.548
39.844
23.067
17.961
CF3
Cl
f1 (ppm)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130.245
124.852
124.560
124.481
124.144
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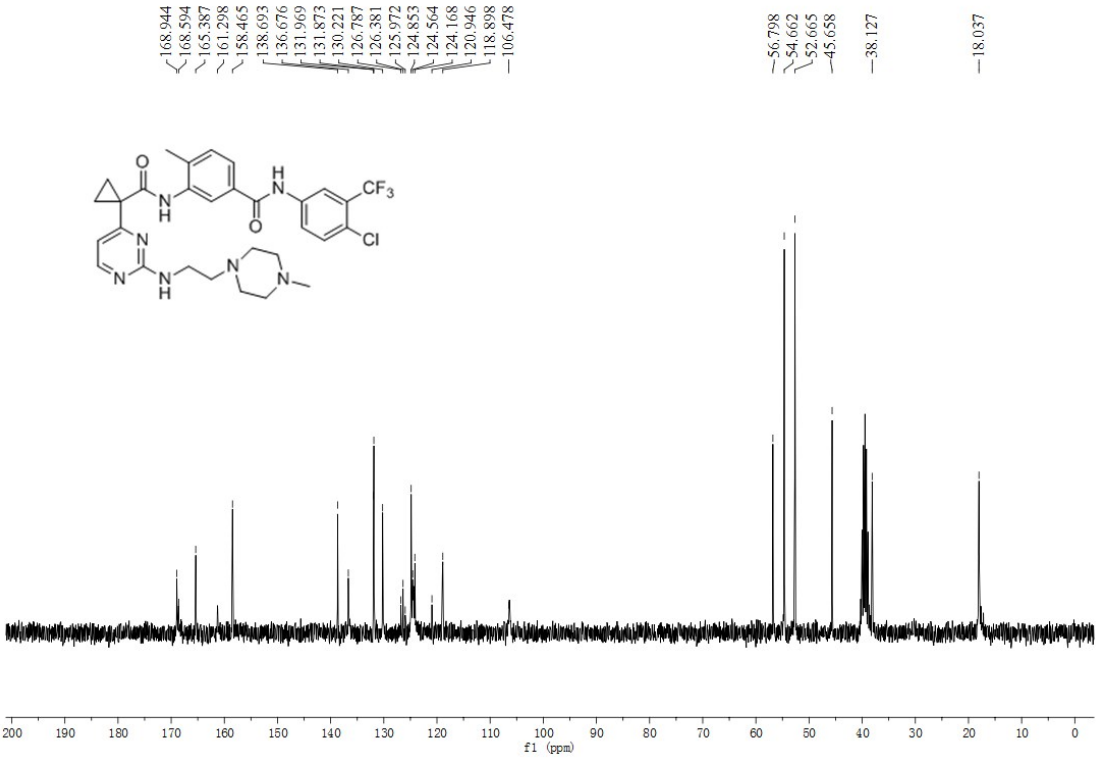
106.193
57.561
54.075
38.188
25.536
23.930
18.012
CF3
Cl
f1 (ppm)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124.853
124.564
124.168
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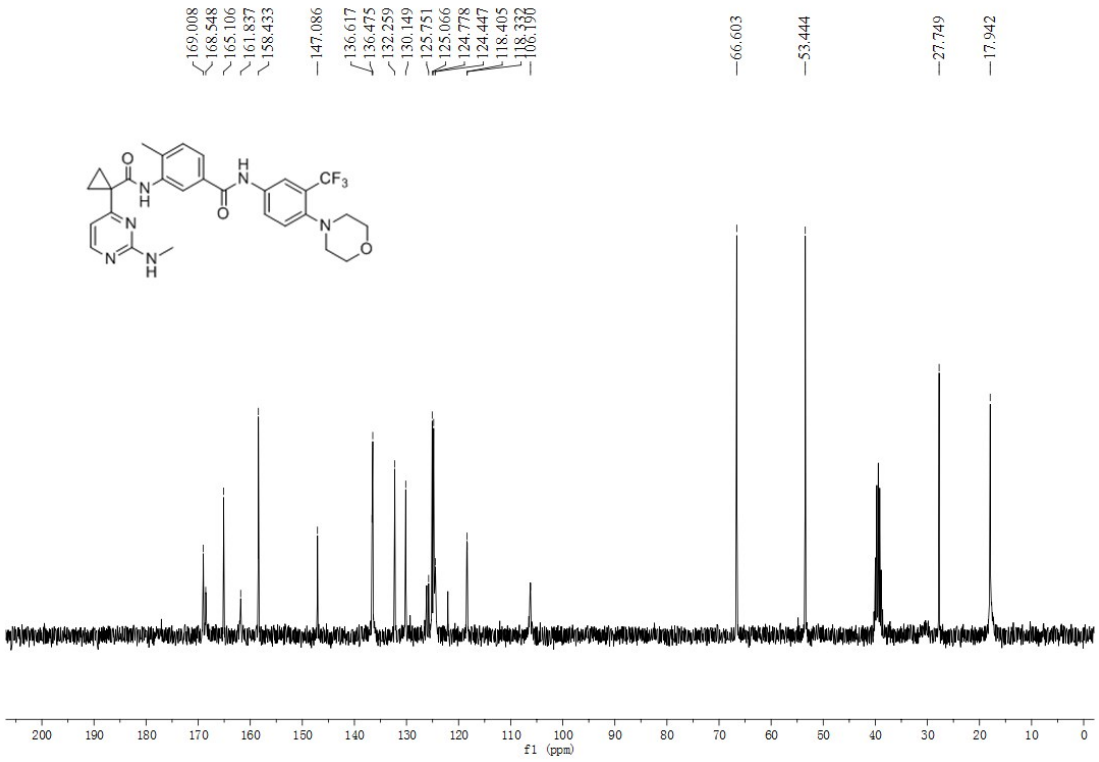
38.127
18.037
CF3
Cl
f1 (ppm)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158.433
147.086
136.617
136.475
132.259
130.149
125.751
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118.405
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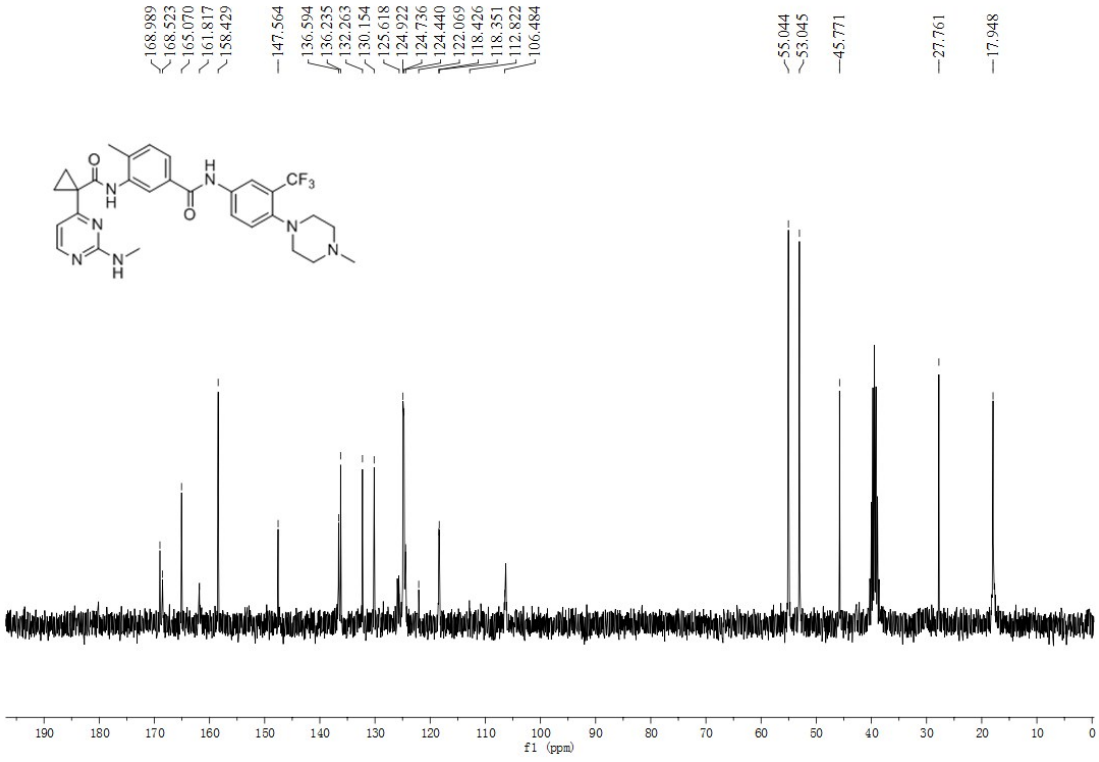
106.190
66.603
53.444
27.749
17.942
f1 (ppm)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147.564
136.594
136.235
132.263
130.154
125.618
124.922
124.736
124.440
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118.351
112.822
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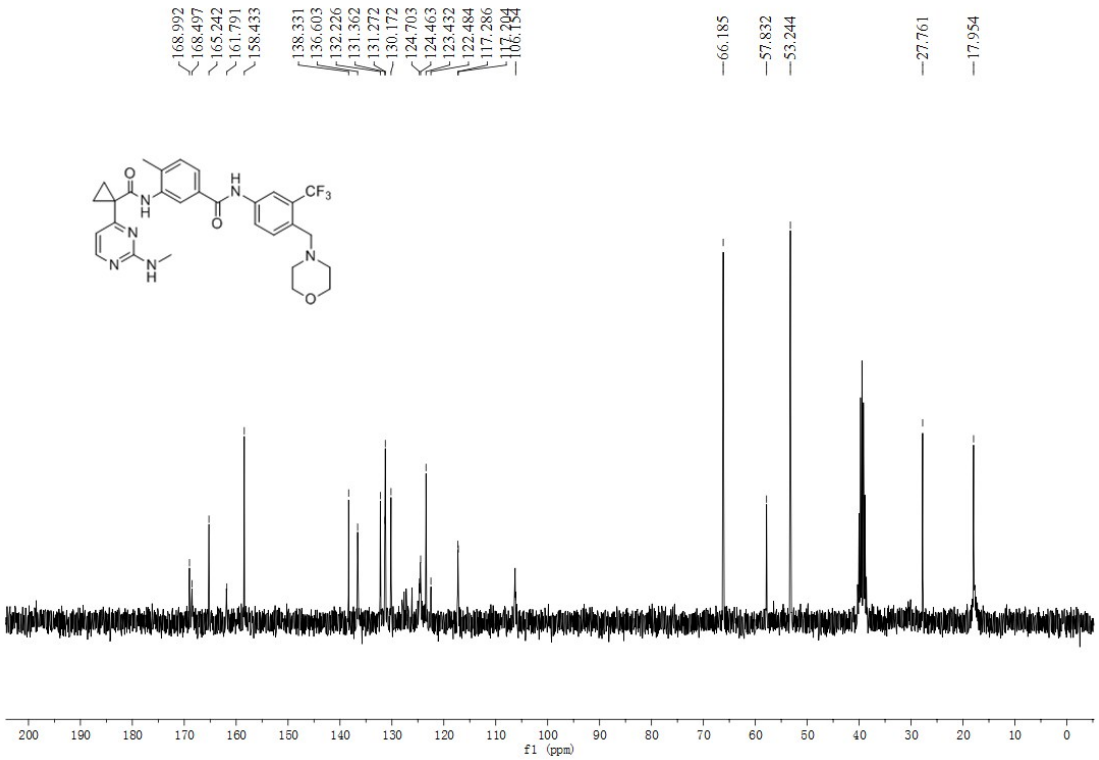
45.771
27.761
17.948
f1 (ppm)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131.272
130.172
124.703
124.463
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117.286
117.204
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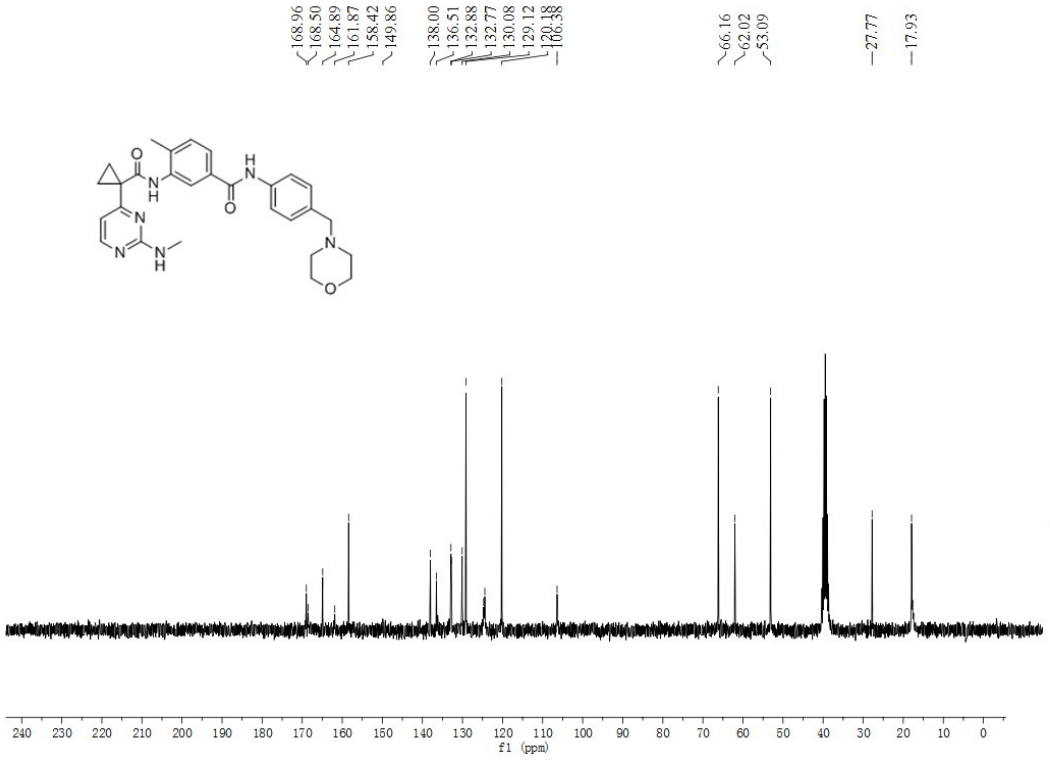
66.185
57.832
53.244
27.761
17.954
CF3
f1 (ppm)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158.42
149.86
138.00
136.51
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129.12
120.18
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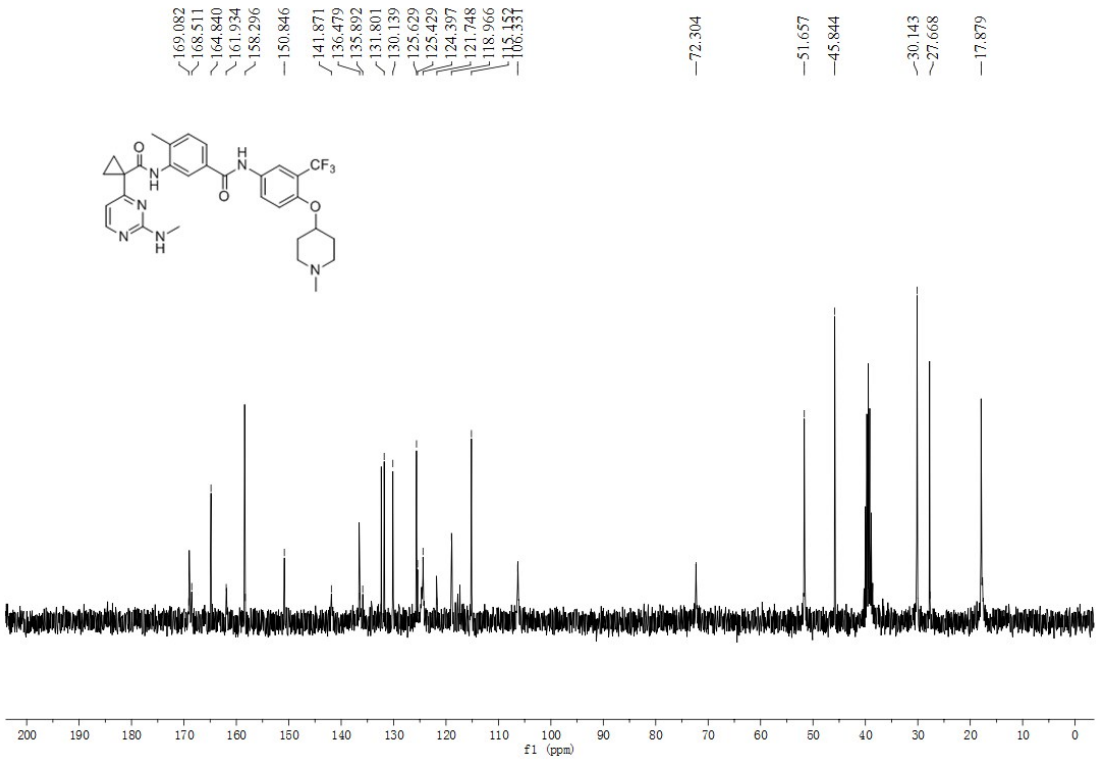
66.16
62.02
53.09
27.77
17.93
f1 (ppm)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164.840
161.934
158.296
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141.871
136.479
135.892
131.801
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125.629
125.429
124.397
121.748
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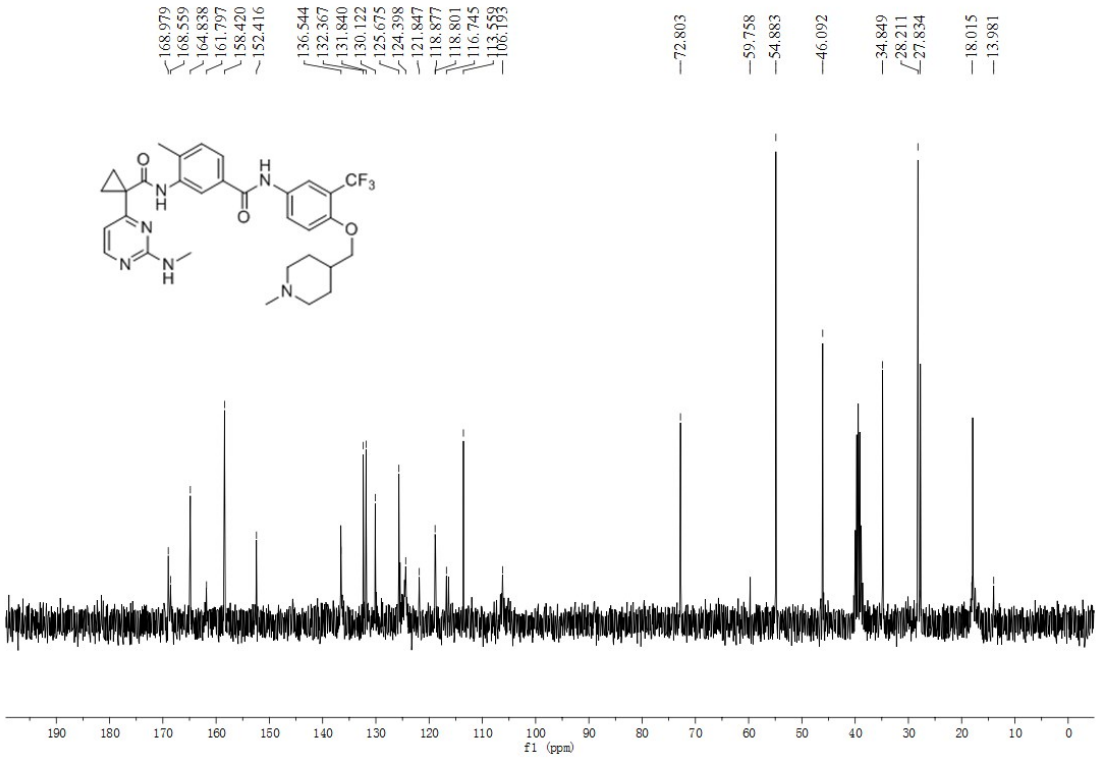
106.331
72.304
51.657
45.844
30.143
27.668
17.879
CF3
f1 (ppm)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124.398
121.847
118.877
118.801
116.745
113.559
106.593
72.803
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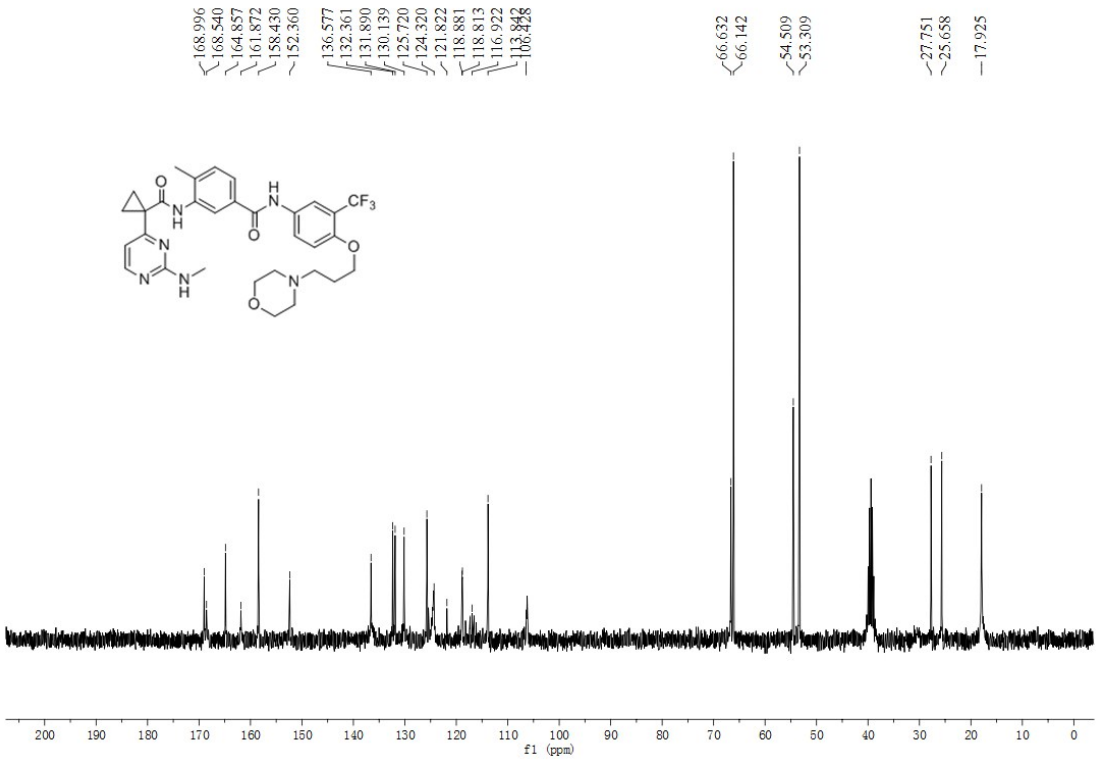
54.883
46.092
34.849
28.211
27.834
18.015
13.981
CF3
f1 (ppm)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152.360
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132.361
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125.720
124.320
121.822
118.881
118.813
116.922
66.632
66.142
54.509
53.309
27.751
25.658
17.925
CF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)