Supporting Information

2-Aminopyrimidin Derivatives as New Selective Fibroblast Growth Factor Receptor 4 (FGFR4) Inhibitors

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Contents:

Figure S1. The chemical structure of BLU554.

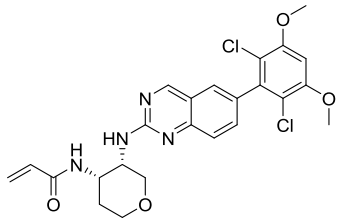
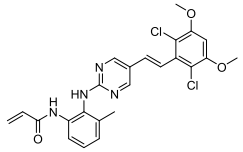


Table S1. Kinase inhibitory activities of compound **3a**



3a

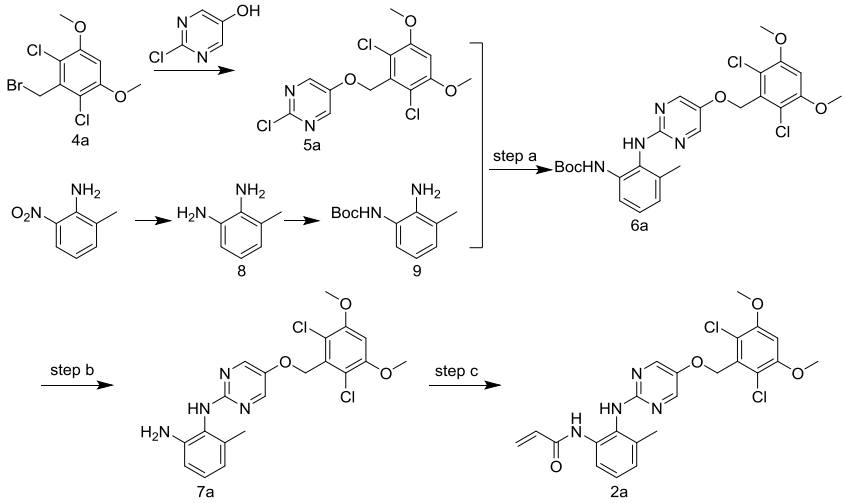
	Kinase activity (IC_{50}, nM)			
	FGFR1	FGFR2	FGFR3	FGFR4
3a	>10,000	2920	756	6.3

Abbreviations. ERK, extracellular signal-regulated kinase; FRS2, fibroblast growth factor substrate 2; IC_{50}, the half maximal (50%) inhibitory concentration (IC) of a substance; SD, standard deviation; TFA, trifluoroacetic acid; DCM, dichloromethane; THF, tetrahydrofuran; DMF, N,N-dimethylformamde; EA, ethylacetate; PE, petroleum ether; Boc_2O, Di-tert-butyl dicarbonate; DIEA, ethyldiisopropylamine;

General Methods for Chemistry. All reagents and solvents were used directly as purchased from commercial sources. Flash chromatography was performed using silica gel (200-300 mesh). All reactions were monitored by TLC, using silica gel plates with fluorescence GF254 and UV light visualization. ^{1}H NMR and ^{13}C NMR spectra were recorded on a AV-400 spectrometer at 400 MHz and AV-500 spectrometer at 125 MHz. Coupling constants (*J*) are expressed in hertz (Hz). Chemical shifts (δ) of NMR are reported in parts per million (ppm) units relative to an internal control (TMS). High resolution ESI-MS on an Applied Biosystems Q-STAR Elite ESI-LC-MS/MS mass spectrometer. The purity of compounds was determined by reverse-phase high performance liquid chromatography (HPLC) analysis to be >95%. HPLC instrument, Dionex Summit HPLC (column: Diamonsil C18, 5.0 μM, 4.6 × 250 mm (Dikma Technologies); detector, PDA-100 photodiode array; injector, ASI-100 autoinjector; pump, p-680A). A flow rate of 1.0 ml/min was used with a mobile phase of MeOH in H_2O with a 0.1% modifier (ammonia or trifluoroacetate, v/v).

Synthetic procedures and compound characterization.

Scheme S1. Synthesis of compound **2a**



2-chloro-5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidine (5a): A mixture of 3-(bromomethyl)-2,4-dichloro-1,5-dimethoxybenzene(6.3g, 21mmol, 1.05eq) (preparation according to WO 2014182829), 2-chloropyrimidin-5-ol(2.61g, 20mmol, 1.0eq), $Bu_4N^+ \cdot I^-$(1.48g, 4mmol, 0.2eq) and K_2CO_3(5.53g, 40mmol, 2.0eq) in DMF(80ml, 4ml/mmol) was stirred at 60℃ for 2h. The resulting mixture was poured into ice and stirred. Then the mixture was filtered, and the filter cake was washed with water for several times and dried in vacuo at 50℃ (6.31g, yield: 90.25%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.68 (s, 2H), 7.02 (s, 1H), 5.42 (s, 2H), 3.95 (s, 6H).

3-methylbenzene-1,2-diamine (8): To a solution of 2-methyl-6-nitroaniline (5g, 2.86mmol) in MeOH (50ml) was added 10% Pd/C (0.25g). The mixture was degassed and purged with hydrogen and stirred at room temperature overnight. The solution was filtered and concentrated. Purification by column chromatography (DCM/MeOH) through silica gel afforded the intermediate (1.83g, yield: 45.68%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 6.41-6.39 (m, 1H), 6.31-6.28 (m, 2H), 4.36 (brs, 2H), 4.13 (brs, 2H), 2.03 (s, 3H).

tert-butyl (2-amino-3-methylphenyl)carbamate(9): To a solution of compound 8 (1.83g, 15.01mmol, 1.0eq) in dry THF (11.26ml) containing triethylamine (2.19ml, 1.05eq) was added Boc_2O (3.28g, 1.0eq) drop-wise at 0℃. Then the mixture was stirred at room temperature overnight. The reaction was diluted with EA and washed with water, brine, dried and concentrated. Purification by column chromatography (PE/EA) through silica gel afforded the intermediate (1.91g, yield: 57.42%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.25 (m, 1H), 7.02 (d, J = 8.0 Hz 1H), 6.77 (d, J = 7.2 Hz 1H), 6.46 (t, J = 7.6 Hz, 1H), 4.52 (s, 2H), 2.08 (s, 3H), 1.45 (s, 9H).

tert-butyl(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-methylphenyl) carbamate (6a):

To a solution of compound 5a（349mg, 1.0mmol, 1.0eq） in 1,4-dioxane (10ml, 10ml/mmol) were added compound 9 (244mg, 1.1mmol, 1.1eq), $Pd(OAc)_2$ (22mg, 0.1mmol, 0.1eq), XantPhos (115mg, 0.2mmol, 0.2eq) and Cs_2CO_3(651mg, 2mmol, 2.0eq). The mixture was degassed and purged again with argon, then heated at 100℃ overnight. After cooling, the solvent was evaporated under reduced pressure. The residue was dissolved in DCM and filtered. The filtrate was concentrated. Purification by column chromatography (PE/EA) through silica gel afforded the intermediate (246mg, yield: 45.95%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.21 (s, 3H), 8.12 (s,

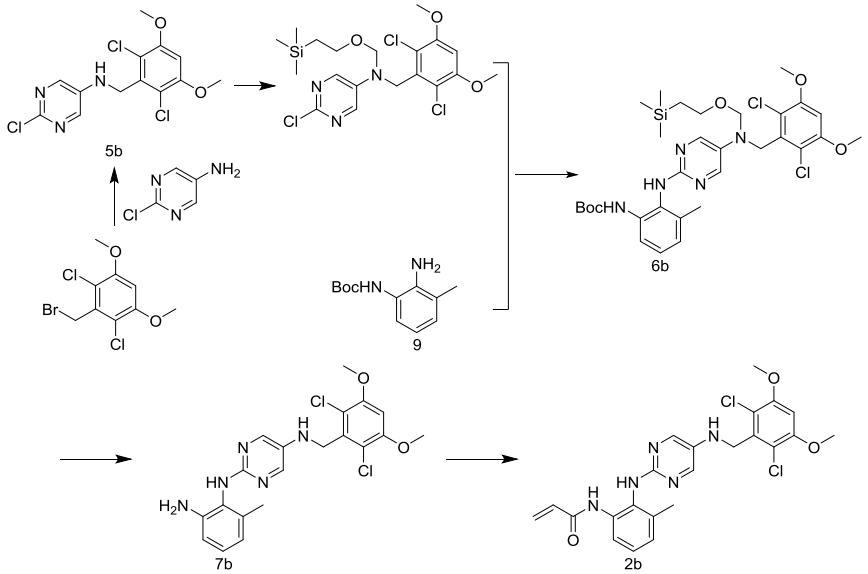
1H), 7.55 (d, J = 7.9 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.99 (s, 1H), 6.95 (d, J = 7.5 Hz, 1H), 5.23 (s, 2H), 3.94 (s, 6H), 2.07 (s, 3H), 1.43 (s, 9H).

N^1-(5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)-6-methylbenzene-1,2-diamine (7a): compound 6a (246mg, 0.4596mmol) was dissolved in DCM/TFA (2:1 volume/volume, 18ml), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with saturated aqueous $NaHCO_3$, brine, dried, and concentrated. Purification by column chromatography (DCM/MeOH) through silica gel afforded the desired product(158mg, 0.363mmol, yield: 78.98%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.16 (s, 2H), 8.03 (s, 1H), 6.99 (s, 1H), 6.83 (t, *J* = 7.7 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.42 (d, *J* = 7.3 Hz, 1H), 5.21 (s, 2H), 4.65 (s, 2H), 3.94 (s, 6H), 2.00 (s, 3H).

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-methylphenyl) acrylamide (2a):

To a solution of compound 7a (158mg, 0.363mmol, 1.0eq) in dry DCM(3ml, 8ml/mmol) containing DIEA(70mg, 0.545mmol, 1.5eq) was added acryloyl chloride(39mg, 0.4356mmol, 1.2eq) drop-wise at 0℃. The mixture was stirred at 0℃ for 3h. Then water was added and diluted with DCM. The organic layer was wash with brine, dried and concentrated. Purification by column chromatography (DCM/MeOH) through silica gel afforded the desired product (122mg, yield: 68.53%). ^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 9.48 (s, 1H), 8.19 (s, 2H), 8.10 (s, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.99 (s, 1H), 6.50 (dd, J = 17.0, 10.2 Hz, 1H), 6.21 (dd, J = 17.0, 1.7 Hz, 1H), 5.70 (dd, J = 10.2, 1.6 Hz, 1H), 5.22 (s, 2H), 3.94 (s, 6H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.39, 157.02, 154.37, 146.48, 146.26, 136.72, 134.75, 132.35, 131.84, 130.70, 126.73, 126.47, 125.62, 120.70, 114.74, 99.14, 67.14, 56.76, 18.40. HRMS (ESI) calcd for C23H22Cl2N4O4 [M+H]+ : 489.10909; found 489.10929. HPLC purity=97.86%, Rt 7.26 min.

Scheme S2. Synthesis of compound **2b**



2-chloro-N-(2,6-dichloro-3,5-dimethoxybenzyl)pyrimidin-5-amine(5b): the title compound was synthesized following the procedure for compound 5a with 2-chloropyrimidin-5-amine and 3-(bromomethyl)-2,4-dichloro-1,5-dimethoxybenzene. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.18 (s, 2H), 6.95 (s, 1H), 6.99 (s, 1H), 6.51 (t, *J* = 4.8 Hz, 1H), 4.45 (d, *J* = 4.8Hz, 3H), 3.93 (s, 1H).

2-chloro-N-(2,6-dichloro-3,5-dimethoxybenzyl)-N-((2-(trimethylsilyl)ethoxy)methyl)pyrimidin-5-a

mine: A mixture compound 5b (174mg, 0.5mmol, 1.0eq) and K_2CO_3(138mg, 1mmol, 2.0eq) was taken in DMF(2ml, 4ml/mmol) and 2-(trimethylsily) ethoxymethyl chloride(125mg, 0.75mmol, 1.5eq) was added drop wise. The reaction mixture was stirred at room temperature for 5h, diluted with water. The aqueous layer was extracted with EA. The organic layer was washed with brine, dried and concentrated. The residue was purified by column chromatography to obtain 2-chloro-N-(2,6-dichloro-3,5-dimethoxybenzyl)-N-((2-(trimethylsilyl)ethoxy)methyl)pyrimidin-5-a mine (100mg, yield: 41.76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.53 (s, 2H), 6.96 (s, 1H), 4.81 (s, 2H), 4.56 (s, 2H), 3.93 (s, 6H), 3.20 (t, *J* =8 Hz, 2H), 0.69 (t, *J* =8 Hz, 2H), -0.11 (s, 9H).

tert-butyl(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)((2-(trimethylsilyl)ethoxy)methyl)amino) pyrimidin-2-yl)amino) -3-methylphenyl)carbamate(6b): the title compound was synthesized following the procedure for compound of 6a, but used directly for the next step.

N^2-(2-amino-6-methylphenyl)-N^5-(2,6-dichloro-3,5-dimethoxybenzyl)pyrimidine-2,5-diamine(7b): the crude of 6b was dissolved in DCM/TFA (2:1 volume/volume), and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with saturated aqueous $NaHCO_3$, brine, dried, and concentrated. Purification by column chromatography (DCM/MeOH) through silica gel afforded the desired product. ^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 7.90 (s, 2H), 7.54 (s, 1H), 6.90 (s, 1H), 6.81 (t, *J* = 7.7 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.41 (d, *J* = 7.3 Hz, 1H), 5.11 (t, *J* = 5.7 Hz, 1H), 4.59 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 3.92 (s, 6H), 1.99 (s, 3H).

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)amino)pyrimidin-2-yl)amino)-3-methylphenyl)acry lamide(2b):

The title compound was synthesized following the procedure for compound 2a.

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.48 (s, 1H), 7.92 (s, 2H), 7.66 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.91 (s, 1H), 6.47 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.20 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.69 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.25 (t, *J* = 5.6 Hz, 1H), 4.34 (d, *J* = 5.6 Hz, 2H), 3.92 (s, 6H), 2.09 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d_6): δ(ppm) 163.35, 154.83, 154.26, 143.33, 136.60, 135.68, 135.22, 134.53, 131.67 (d, *J* = 216 Hz, 1C), , 126.65, 126.49, 125.12, 120.60, 114.22, 97.84, 56.65, 44.03, 18.50. ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.35, 154.83, 154.26, 143.33, 136.60, 135.68, 135.22, 134.53, 131.88, 131.44, 126.65, 126.49, 125.12, 120.60, 114.22, 97.84, 56.65, 44.03, 18.50. HRMS (ESI) calcd for C23H23Cl2N5O3 [M+H]+ : 488.12507; found 488.12494. HPLC purity=96.30%, Rt 6.50 min.

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-6-methylphenyl)acryla mide (2c) was synthesized following the approach outlined in Scheme S1(Example 2a) substituting tert-butyl (2-amino-3-methylphenyl)carbamate with tert-butyl (2-amino-6-methylphenyl)carbamate (prepared by the method outlined below).

^{1}H NMR (400 MHz, DMSO-d6): δ(ppm) 9.57 (s, 1H), 8.33 (s, 2H), 8.00 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.00 (s, 1H), 6.95 (d, J = 7.4 Hz, 1H), 6.51 (dd, J = 17.1, 10.2 Hz, 1H), 6.26 (dd, J = 17.1, 1.8 Hz, 1H), 5.78 (dd, J = 10.2, 1.8 Hz, 1H), 5.29 (s, 2H), 3.94 (s, 6H), 2.18 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d6): δ(ppm) 163.81, 155.39, 154.39, 146.83, 146.30, 136.07, 135.07, 132.26, 131.12, 126.88, 126.43, 126.41, 124.05, 119.06, 114.74, 99.17, 67.12, 56.77, 18.29. HRMS (ESI) calcd for C23H22Cl2N4O4 [M+H]+ : 489.10909; found 489.10929. HPLC purity=99.08%, Rt 7.83 min.

Preparation of tert-butyl (2-amino-6-methylphenyl)carbamate.

a. tert-butyl (2-methyl-6-nitrophenyl)carbamate

To a solution of 2-methyl-6-nitroaniline(1.826g, 12mmol, 1.0eq) in anhydrous THF(120ml, 10ml/mmol) was added Boc_2O(7.857g, 36mmol, 3.0eq) followed by DMAP(0.151g, 1.2mmol, 0.1eq). The mixture was stirred at reflux for 3h then cooled to ambient temperature. The solvent was evaporated. The residue was dissolved in MeOH (100ml) followed by K_2CO_3(4.975g, 3.0eq). The mixture was stirred at reflux for 3h. The mixture was cooled to ambient temperature and concentrated. The residue was dissolved in EA and washed with water, brine, dried and concentrated. Purification by column chromatography (PE/EA) through silica gel afforded the intermediate (0.7g, yield: 35.84%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.10 (s, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 2.27 (d, *J* = 11.0 Hz, 3H), 1.37 (d, *J* = 44.5 Hz, 9H).

b. tert-butyl (2-amino-6-methylphenyl)carbamate

The title compound was synthesized following the procedure of compound 8 in Scheme S1 substituting tert-butyl (2-methyl-6-nitrophenyl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.01 (s, 1H), 6.83 (t, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.41 (d, *J* = 7.3 Hz, 1H), 4.65 (s, 2H), 2.06 (s, 3H), 1.44 (s, 9H).

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-5-methylphenyl) Acrylamide (2d) was synthesized following the approach outlined in Scheme S1 (Example2a) substituting tert-butyl (2-amino-5-methylphenyl)carbamate (prepared by the method outlined below).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.75 (s, 1H), 8.33 (s, 1H), 8.28 (s, 2H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.34 (s, 1H), 6.99 (m, 2H), 6.49 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.26 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.76 (d, *J* = 17.0, 1.8 Hz,1H), 5.27 (s, 2H), 3.94 (s, 6H), 2.28 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d_6): δ(ppm) 163.64, 156.03, 154.38, 146.68, 146.37, 132.31, 132.24, 131.55, 130.49, 129.32, 126.92, 125.82, 124.77, 123.51, 114.76, 99.09, 67.18, 56.73, 20.45. HRMS (ESI) calcd for C23H22Cl2N4O4 [M+H]+ : 489.10909; found 489.10929. HPLC purity=99.18%, Rt 8.44 min.

Preparation of tert-butyl (2-amino-5-methylphenyl)carbamate.

a. tert-butyl (5-methyl-2-nitrophenyl)carbamate

A solution of NaH (1.76g, 2.2eq) in dry THF(27.7ml, 0.63ml/mmol) at 0℃ was slowly treated with a solution of 5-methyl-2-nitroaniline (3.043g, 20mmol, 1.0eq) in dry THF(27.6ml, 1.38ml/mmol). The mixture was stirred for 10 min at 0℃, and then at room temperature for 30 min. A solution of Boc_2O(4.801g, 22mmol, 1.1eq) in dry THF(5.5ml, 0.25ml/mmol) was added to the reaction mixture and stirred at room temperature onvernight. Water was slowly added and the reaction mixture was extracted with EA. The organic phase was wash with brine, dried and concentrated. Purification by column chromatography(PE/EA) through silica gel afforded the intermediate(2.55g, yield: 50.56%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.55 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.08 (dd, *J* = 8.5, 1.2 Hz, 1H), 2.37 (s, 3H), 1.45 (s, 9H).

b. tert-butyl (2-amino-5-methylphenyl)carbamate

The title compound was synthesized following the procedure of compound 8 in Scheme S1 substituting tert-butyl (5-methyl-2-nitrophenyl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.22 (s, 1H), 7.03 (s, 1H), 6.65 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.60 (s, 2H), 2.12 (s, 3H), 1.45 (s, 9H).

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-4-methylphenyl) acrylamide (2e) was synthesized following the approach outlined in Scheme S1 (Example 2a) substituting tert-butyl (2-amino-4-methylphenyl)carbamate (prepared by the method of

corresponding intermediate of 2d).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.77 (s, 1H), 8.37 (s, 1H), 8.32 (s, 2H), 7.63 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.00 (s, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.48 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.25 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.76 (d, *J* = 10.4, 1H), 5.28 (s, 2H), 3.94 (s, 6H), 2.28 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d_6): δ(ppm) 163.70, 155.75, 154.39, 146.80, 146.31, 134.53, 133.09, 132.30, 131.50, 126.86, 126.56, 124.56, 123.60, 123.32, 114.76, 99.15, 67.12, 56.77, 20.81. HRMS (ESI) calcd for C23H22Cl2N4O4 [M+H]+ : 489.10909; found 489.10929. HPLC purity=97.69%, Rt 8.46 min.

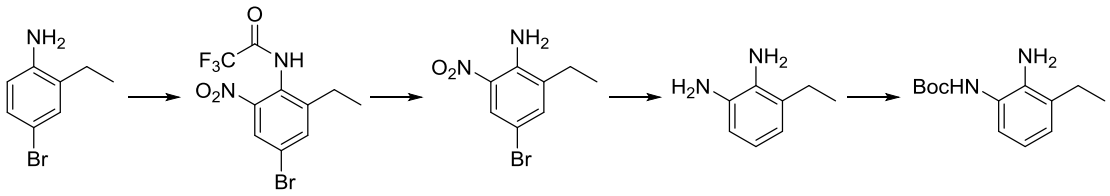
N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2f) was synthesized following the approach outlined in Scheme S1(Example 2a) substituting tert-butyl (2-amino-3-methylphenyl)carbamate with tert-butyl (2-aminophenyl)carbamate (prepared by the method of compound 9 in Scheme S1 with benzene-1,2-diamine).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.83 (s, 1H), 8.44 (s, 1H), 8.31 (s, 2H), 7.80 (d, *J* = 7.1 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.17 (td, *J* = 8.4, 1.4 Hz, 1H), 7.06 (td, *J* = 7.8, 1.4 Hz, 1H), 7.00 (s, 1H), 6.50 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.77 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.28 (s, 2H), 3.94 (s, 6H). ^{13}C NMR (500 MHz, DMSO-d_6): δ(ppm) 163.71, 155.74, 154.38, 146.84, 146.31, 133.14, 132.28, 131.49, 129.15, 127.02, 125.23, 124.62, 123.16, 122.91, 114.73, 99.16, 67.13, 56.76. HRMS (ESI) calcd for C22H20Cl2N4O4 [M+H]+ : 475.09344; found 475.09299. HPLC purity=96.86%, Rt 7.82 min.

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-ethylphenyl)acrylamide (2g) was synthesized following the approach outlined in Scheme S1(Example 2a) substituting tert-butyl (2-amino-3-methylphenyl)carbamate with tert-butyl (2-amino-3-ethylphenyl)carbamate (prepared by the method outlined below).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.39 (s, 1H), 8.18 (s, 2H), 8.07 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.99 (s, 1H), 6.49 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.19 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.68 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.21 (s, 2H), 3.93 (s, 6H), 2.49 (q, *J* = 7.5 Hz, 2H), 1.05 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (500 MHz, DMSO-d_6): δ(ppm) 163.34, 157.48, 154.36, 146.52, 146.24, 142.42, 135.16, 132.34, 131.91, 130.08, 126.60, 126.04, 124.53, 120.66, 114.75, 99.09, 67.17, 56.74, 24.27, 14.00. HRMS (ESI) calcd for C24H24Cl2N4O4 [M+H]+ : 503.12474; found 503.12469. HPLC purity=99.06%, Rt 7.92 min.

Preparation of tert-butyl (2-amino-3-ethylphenyl)carbamate



a. N-(4-bromo-2-ethyl-6-nitrophenyl)-2,2,2-trifluoroacetamide: To trifluoroacetic anhydride(20.85ml, 150mmol, 10.0eq) stirring at 2 ℃ was slowly added 4-bromo-2-ethylaniline(3.0g, 15mmol, 1.0eq) drop-wise followed by anhydrous 2-methyltetrahydrofuran(1.8ml, 0.12ml/mmol). The cold bath was removed and ammonium nitrate(1.56g, 19.5mmol, 1.3eq) was added. A cold water bath was used to control the temperature below 40℃. After 30 min, the cold bath was the removed and stirring continued for another 40 min. Crushed ice was slowly added to the reaction, and the mixture was extracted with EA. The organic layer was washed with brine, dried and concentrated. Purification by column chromatography (PE/EA) through silica gel afforded the intermediate (1.046g, yield: 20.44%). ^{1}H

NMR (500 MHz, DMSO-d_6): δ(ppm) 11.54 (s, 1H), 8.16 (d, *J* = 2.2 Hz, 1H), 8.00 (d, *J* = 2.2 Hz, 1H), 2.64 (q, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H).

b. 4-bromo-2-ethyl-6-nitroaniline: N-(4-bromo-2-ethyl-6-nitrophenyl)-2,2,2-trifluoroacetamide (1.0232g, 3mmol, 1.0eq) was dissolved in 1,4-dioxane(3.6ml, 1.2ml/mmol) and added aqu eous 6M NaOH(1.5ml, 0.5ml/mmol). The reaction mixture was stirred at reflux for 2 days. The mixture was allowed to cool, diluted with EA, and washed with water, saturated aq ueous NH_4Cl, water, brine, dried and concentrated. Purification by column chromatograph y(PE/EA) through silica gel afforded the intermediate (0.703g, yield: 95.61%). ^{1}H NMR (50 0 MHz, DMSO-d_6): δ(ppm) 8.00 (d, *J* = 2.2 Hz, 1H), 7.44 (s, 1H), 7.32 (s, 2H), 2.60 (q, *J* = 7.3 Hz, 2H), 1.15 (t, *J* = 7.4 Hz, 3H).

c. 3-ethylbenzene-1,2-diamine: To a solution of 4-bromo-2-ethyl-6-nitroaniline (0.703g, 2.8683mmol, 1.0eq) in MeOH/THF(4:1 volume/volume 35ml) was added 10% Pd/C (0.050g) followed by KOH(0.177g, 3.1551mmol, 1.1eq). The mixture was degassed and purged with hydrogen and stirred at rt overnight. The solution was filtered and concentrated. Purification by column chromatography (DCM/MeOH) through silica gel afforded the intermediate (0.365g, 2.1885mmol, yield:76.30%.^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 6.41 (dd, *J* = 7.3, 1.4 Hz, 1H), 6.33 (m, 2H), 4.25 (s, 4H), 2.43 (q, *J* = 7.5 Hz, 2H), 1.10 (t, *J* = 7.5 Hz, 3H).

d. tert-butyl (2-amino-3-ethylphenyl)carbamate : the title compound was synthesized following the procedure of compound 9. Yield: 59.38%. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.23 (s, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.50 (t, *J* = 7.7 Hz, 1H), 4.53 (s, 2H), 2.47 (q, *J* = 7.5 Hz, 2H), 1.45 (s, 9H), 1.12 (t, *J* = 7.5 Hz, 3H).

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-fluorophenyl) acrylamide (2k) was synthesized following the approach outlined in Scheme S1(Example 2 a)substituting 2-methyl-6-nitroaniline with 2-fluoro-6-nitroaniline.

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.70 (s, 1H), 8.25 (s, 2H), 8.24 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.23 (td, *J* = 8.3, 6.1 Hz, 1H), 7.03 (dd, *J* = 13.5, 4.9 Hz, 1H), 7.00 (s, 1H), 6.56 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.26 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.75 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.25 (s, 2H), 3.94 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.60, 159.29, 157.33, 156.45, 154.38, 146.83, 146.15, 135.74, 135.71, 132.32, 131.57, 127.31, 125.96, 125.88, 120.21, 120.09, 118.53, 114.74, 111.67, 111.51, 99.14, 67.03, 56.76. HRMS (ESI) calcd for $C_{22}H_{19}Cl_2FN_4O_4$ $[M+H]^+$: 493.08402; found 493.08402. HPLC purity=99.11%, Rt 6.51 min.

N-(3-chloro-2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl) acrylamide (2l) was synthesized following the approach outlined in Scheme S1(Example 2 a)substituting tert-butyl (2-amino-3-methylphenyl)carbamate with tert-butyl (2-amino-3-chlor ophenyl)carbamate (prepared by the method outlined below).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.59 (s, 1H), 8.32 (s, 1H), 8.23 (s, 2H), 8.00 – 7.83 (m, 1H), 7.30 – 7.23 (m, 2H), 6.99 (s, 1H), 6.57 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.24 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.73 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.24 (s, 2H), 3.92 (d, *J* = 12.5 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.58, 156.69, 154.38, 146.68, 146.16, 137.03, 133.07, 132.30, 131.66, 129.21, 127.24, 126.79, 125.25, 121.51, 114.75, 99.14, 66.99, 56.76. HRMS (ESI) calcd for $C_{22}H_{19}Cl_3N_4O_4$ $[M+H]^+$: 509.05446; found 509.05487. HPLC purity=98.22%, Rt 7.45 min.

Preparation of tert-butyl (2-amino-3-chlorophenyl)carbamate

a. 3-chlorobenzene-1,2-diamine

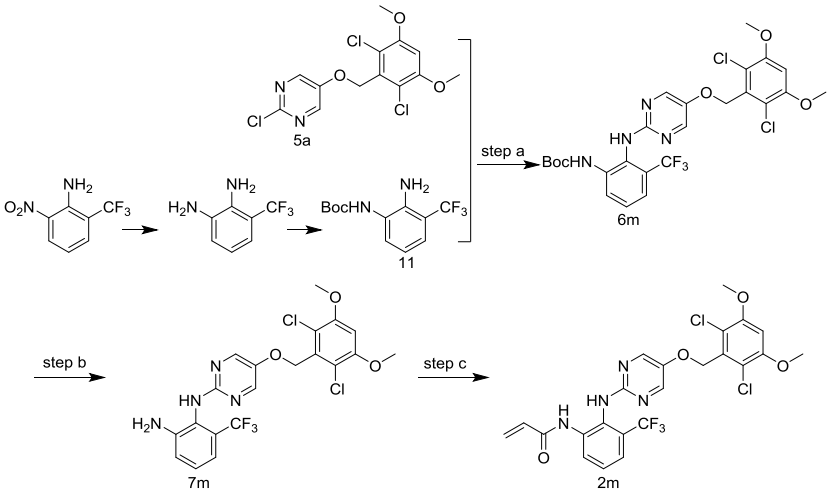
A mixture of 3-chloro-2-nitroaniline (1.51g, 8.75mmol, 1.0eq), iron powder(1.9547g, 35mmol,

4.0eq) and ammonium chloride(2.8082g, 52.5mmol, 6.0eq) in MeOH/water(3;1 volume/volume, 3:1, 100ml) was heated at reflux temperature for 3h. After cooling, the catalyst was removed and the filtrate was concentrated. The residue was dissolved with EA and washed with water, brine, dried and concentrated. Purification by column chromatography (PE/EA) through silica gel afforded the intermediate (0.8557g, yield: 68.59%).^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 6.51-6.46 (m, 2H), 6.38 (t, *J* = 7.8 Hz, 1H), 4.80 (s, 2H), 4.60 (s, 2H).

b. tert-butyl (2-amino-3-chlorophenyl)carbamate (compound 10)

The title compound was synthesized following the procedure of compound 9 in Scheme S1 substituting 3-chlorobenzene-1,2-diamine. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm)8.47 (s, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.56 (t, *J* = 8.0 Hz, 1H), 5.00 (s, 2H), 1.46 (s, 9H).

Scheme S3. Synthesis of compound **2m**



Preparation of tert-butyl (2-amino-3-(trifluoromethyl)phenyl)carbamate (11):

a. 3-(trifluoromethyl)benzene-1,2-diamine

the title compound was synthesized following the procedure of compound 8 in Scheme S1 substituting 2-methyl-6-nitroaniline with 2-nitro-6-(trifluoromethyl)aniline. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 6.74 (d, *J* = 7.6 Hz, 1H), 6.67 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.49 (t, *J* = 7.8 Hz, 1H), 4.90 (s, 2H), 4.79 (s, 2H).

b. tert-butyl (2-amino-3-(trifluoromethyl)phenyl)carbamate (compound 11)

To a solution of 3-(trifluoromethyl)benzene-1,2-diamine (0.1761g, 1.0mmol, 1.0eq) dry THF(2.8ml, 2.8ml/mmol) containing DIEA(0.1258g, 1.0mmol, 1.0eq) was added Boc_2O (0.2162g, 1.0mmol, 1.0eq) and the mixture was heated to reflux overnight. The solution was then cooled, concentrated under reduced pressure, diluted with saturated aqueous EA, and washed brine, dried and concentrated. Purification by column chromatography (PE/EA) through silica gel afforded the intermediate (0.21g, yield: 76.05%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.49 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 6.67 (t, *J* = 7.9 Hz, 1H), 5.16 (s, 2H), 1.46 (s, 9H).

tert-butyl (2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-(trifluoromethyl)phenyl)carbamate (6m):

To a solution of compound 11 (0.0607g, 0.22mmol, 1.1eq), compound 5a (0.070g, 1.0mmol, 1.0eq) and Na_2CO_3 (0.0848g, 0.8mmol, 4.0eq) in tert-amyl alcohol (0.2ml, 10ml/mmol), was

added tris-dibenzylamino dipalladium(0.0274g, 0.03mmol, 0.15eq) and Dave Phos(0.0236g, 0.06mmol, 0.3eq). The mixture was degassed and purged again with argon, then heated at 100℃ overnight. After cooling, the solvent was evaporated under reduced pressure. The residue was dissolved in DCM and filtered. The filtrate was concentrated. Purification by column chromatography(PE/EA) through silica gel afforded the intermediate (0.0280g, yield: 22.76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.22 (s, 1H), 8.13 (s, 1H), 8.12 (s, 1H), 8.04-8.02 (m, 1H), 7.47-7.45 (m, 2H), 6.99 (m, 1H), 5.23 (s, 2H), 3.94 (s, 6H), 1.40 (s, 9H).

N^1-(5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)-6-(trifluoromethyl)benzene-1,2-diamine (7m):

The title compound was synthesized following the procedure of 7a in Scheme S1 substituting 6a with 6m. ^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 8.18 (s, 2H), 8.15 (s, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 6.3 Hz, 2H), 6.85 (d, *J* = 7.2 Hz, 1H), 5.21 (s, 2H), 3.96 (s, 6H).

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-(trifluoromethyl)phenyl)acrylamide (2m):

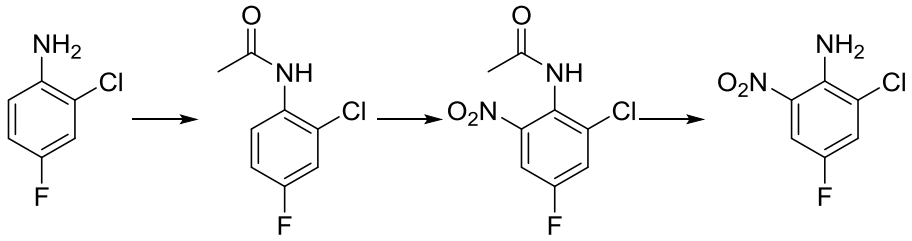
The title compound was synthesized following the procedure of 2a in Scheme S1 substituting 7a with 7m.

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.45 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 8.19 (s, 2H), 8.09 (s, 1H), 7.55-7.47 (m, 2H), 6.99 (s, 1H), 6.50 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.19 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.70 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.22 (s, 2H), 3.94 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.57, 157.49, 154.38, 146.67, 146.08, 138.11, 132.29, 131.53, 129.81, 128.59, 128.36, 127.27, 127.10, 124.66, 122.49, 122.26, 114.74, 99.16, 66.95, 56.76. HRMS (ESI) calcd for C23H19Cl2F3N4O4 [M+H]+ : 543.08082; found 543.08068. HPLC purity=96.34%, Rt 7.06 min.

N-(3-chloro-2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-5-fluorophenyl)acrylamide (2n) was synthesized following the approach outlined in Scheme S3 substituting compound 11 with tert-butyl (2-amino-3-chloro-5-fluorophenyl)carbamate (prepared according to the procedure of compound 10 with 2-chloro-4-fluoro-6-nitroaniline which was prepared by the method outlined below).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.63 (s, 1H), 8.34 (s, 1H), 8.24 (s, 2H), 8.02 (dd, *J* = 11.1, 2.8 Hz, 1H), 7.25 (dd, *J* = 8.2, 2.9 Hz, 1H), 7.00 (s, 1H), 6.65 (dd, *J* = 16.9, 10.2 Hz, 1H), 6.25 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.75 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.24 (s, 2H), 3.94 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.84, 160.20, 158.27, 156.94, 154.38, 146.74, 146.15, 138.71, 138.60, 134.15, 134.05, 132.29, 131.58, 127.72, 125.07, 114.76, 111.79, 111.58, 107.56, 107.35, 99.17, 66.96, 56.76. HRMS (ESI) calcd for C22H18Cl3FN4O4 [M+H]+ : 527.04504; found 527.04544. HPLC purity=99.02%, Rt 8.90 min.

Preparation of 2-chloro-4-fluoro-6-nitroaniline



a. **N-(2-chloro-4-fluorophenyl)acetamide**

Acetic anhydride (20ml) was slowly added to 2-chloro-4-fluoroaniline (4.2212g, 29mmol) at 0℃. The mixture was then stirred at 100℃ for 1h. After that, the reaction was poured into ice

water and extracted with EA. The organic phase was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with EA/PE afforded the desired product (2.801g, yield: 43.29%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.68 (s, 2H), 7.02 (s, 1H), 5.42 (s, 2H), 3.95 (s, 6H).

b. **N-(2-chloro-4-fluoro-6-nitrophenyl)acetamide**

To a solution of N-(2-chloro-4-fluorophenyl)acetamide (2.801g, 14.9339mmol) in acetic acid (2.9ml) and conc. H_2SO_4 (9.8ml) was drop-wise added a mixture of nitric acid (fuming, 1.31ml) and acetic acid (0.33ml) at 0℃. The mixture was stirred at 0℃ for 1.5h. After that, the mixture was poured into ice water and stirred. Then, the mixture was filtered, and the cake was washed with water for several times (2.58g, yield: 74.39%) ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 10.19 (s, 1H), 7.99 (dd, *J* = 19.3, 7.4 Hz, 2H), 2.05 (s, 3H).

c. **2-chloro-4-fluoro-6-nitroaniline**

Conc. HCl (30ml) was slowly added to b. N-(2-chloro-4-fluoro-6-nitrophenyl)acetamide (2.58g, 11.11 mmol) at room temperature. The mixture was then stirred at 120℃ for 1.25h. After that, the reaction was poured into ice water and extracted with EA. The organic phase was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with EA/PE afforded the desired product (1.9404g, yield: 90.0%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 7.88 (s, 1H), 7.86 (s, 1H), 7.21 (s, 2H).

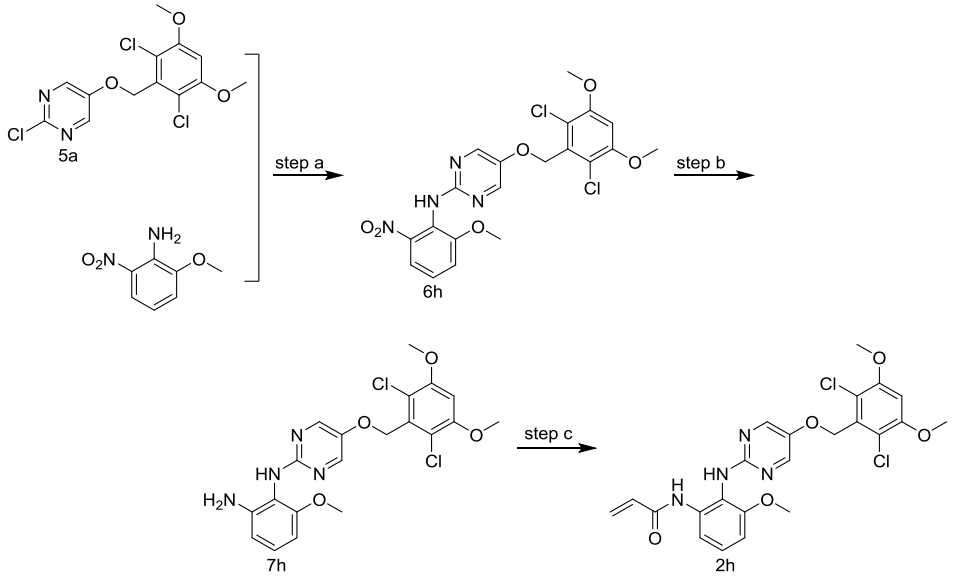
N-(3,5-dichloro-2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2o) was synthesized following the approach outlined in Scheme S3 substituting compound 11 with tert-butyl (2-amino-3,5-dichlorophenyl)carbamate (prepared according to the procedure of tert-butyl (2-amino-3-chlorophenyl)carbamate in compound 2l with 3,5-dichlorobenzene-1,2-diamine).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.65 (s, 1H), 8.44 (s, 1H), 8.24 (s, 2H), 8.17 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 6.99 (s, 1H), 6.62 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.25 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.76 (dd, *J* = 10.4, 1.8 Hz,1H), 5.24 (s, 2H), 3.94 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.82, 156.60, 154.38, 146.83, 146.13, 138.22, 134.10, 132.28, 131.46, 130.35, 127.88, 127.79, 124.18, 120.54, 114.75, 99.15, 66.96, 56.77.HRMS (ESI) calcd for C22H18Cl4N4O4 [M+H]+ : 545.01281; found 545.01328. HPLC purity=95.94%, Rt 10.93 min.

N-(3-chloro-2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-5-(trifluoromethyl)phenyl)acrylamide (2p) was synthesized following the approach outlined in Scheme S3 substituting 3-(trifluoromethyl)benzene-1,2-diamine in with 3-chloro-5-(trifluoromethyl)benzene-1,2-diamine).

^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 9.81 (s, 1H), 8.72 (s, 1H), 8.43 (s, 1H), 8.27 (s, 2H), 7.67 (s, 1H), 7.00 (s, 1H), 6.62 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.27 (d, *J* = 17.0 Hz, 1H), 5.78 (d, *J* = 10.4 Hz, 1H), 5.25 (s, 2H), 3.94 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 164.01, 156.11, 154.39, 147.04, 146.13, 137.61, 133.77, 132.55, 132.24, 131.37, 127.93, 126.98, 126.72, 124.46, 122.29, 121.52, 117.66, 114.75, 99.16, 66.97, 56.77. HRMS (ESI) calcd for C23H18^{35}Cl3F3N4O4 [M+H]+ : 577.04185; found 577.04228. HPLC purity=96.74%, Rt 10.46 min.

Scheme S4. Synthesis of compound **2h**



5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)-N-(2-methoxy-6-nitrophenyl)pyrimidin-2-amine (6h):

The title compound was synthesized following the procedure of 6a in Scheme S1 with compound 5a and 2-methoxy-6-nitroaniline. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.70 (s, 1H), 8.23 (s, 2H), 7.50 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.39 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.31 (t, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 5.25 (s, 2H), 3.94 (s, 6H), 3.85 (s, 3H).

N^1-(5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)-6-methoxybenzene-1,2-diamine (7h): To a solution of compound 6h (0.4144g, 0.8611mmol, 1.0eq) and $NiCl_2 \cdot 6H_2O$(0.3070g, 1.2965mmol, 1.5eq) in MeOH/DCM(1:4, volume/volume, 7ml) was added $NaBH_4$(0.0831g, 2.1527mmol, 2.5eq) in portions at 0℃. The ice-bath was removed, and the resulting mixture was stirred at room temperature for 1.5h. The mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with DCM/MeOH afforded the desired product (0.1930g, yield: 49.65%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.14 (s, 2H), 7.66 (s, 1H), 6.99 (s, 1H), 6.89 (t, *J* = 8.1 Hz, 1H), 6.35 (d, *J* = 7.4 Hz, 1H), 6.22 (d, *J* = 7.6 Hz, 1H), 5.22 (s, 2H), 4.71 (s, 2H), 3.95 (s, 6H), 3.60 (s, 3H).

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-methoxyphenyl)acrylamide (2h): the title compound was synthesized following the procedure of 2a in Scheme S1 with compound 7h.

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.42 (s, 1H), 8.17 (s, 2H), 7.80 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 8.3 Hz, 1H), 6.98 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.53 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.21 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.70 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.23 (s, 2H), 3.93 (s, 6H), 3.67 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.33, 157.33, 155.69, 154.37, 146.35, 146.22, 135.53, 132.39, 131.95, 126.76, 125.94, 120.62, 114.74, 107.96, 99.11, 67.15, 56.76, 55.62. HRMS (ESI) calcd for C23H22Cl2N4O5 [M+H]+ : 505.10400; found 505.10433. HPLC purity=95.27%, Rt 6.63 min.

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-ethoxyphenyl) acrylamide (2i) was synthesized following the approach outlined in Scheme S4 substituting 2-methoxy-6-nitroaniline with 2-ethoxy-6-nitroaniline (prepared by the method outlined below.).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.46 (s, 1H), 8.18 (s, 2H), 7.74 (s, 1H), 7.49 (d, *J* = 8.1 Hz,

1H), 7.14 (t, *J* = 8.2 Hz, 1H), 6.99 (s, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.55 (dd, *J* = 16.9, 10.2 Hz, 1H), 6.22 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.71 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.24 (s, 2H), 3.98 – 3.82 (m, 8H), 1.05 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.31, 157.40, 154.83, 154.36, 146.39, 146.16, 135.28, 132.42, 131.95, 126.75, 125.69, 121.05, 114.69, 109.03, 99.07, 67.27, 63.53, 56.74, 14.43. HRMS (ESI) calcd for C24H24Cl2N4O5 [M+H]+ : 519.11965; found 519.12003. HPLC purity=97.02%, Rt 7.48 min.

Preparation of 2-ethoxy-6-nitroaniline

To a solution of 2-amino-3-nitrophenol(1.2329g, 8mmol, 1.0eq) in DMF(6.4ml, 0.8ml/mmol) at room temperature was added K_2CO_3(1.2162g, 8.8mmol, 1.1eq) and iodoethane (1.3728g, 8.8mmol, 1.1eq). The reaction mixture was stirred overnight, then the solvent was removed in vacuo. The residue was diluted with NH_4Cl (saturated) and extract EA, and the extract was washed water, brine and dried and concentrated. Purification by column chromatography (PE/EA) through silica gel afforded the intermediate (1.2752g, yield: 87.5%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 7.63 – 7.53 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.99 (s, 2H), 6.65 – 6.52 (m, 1H), 4.11 (q, *J* = 6.9 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H).

N-(2-((5-((2,6-dichloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-isopropoxyphenyl)acrylamide (2j) was synthesized following the approach outlined in Scheme S4 substituting 2-methoxy-6-nitroaniline with 2-isopropoxy-6-nitroaniline (prepared according to the procedure of 2-ethoxy-6-nitroaniline).

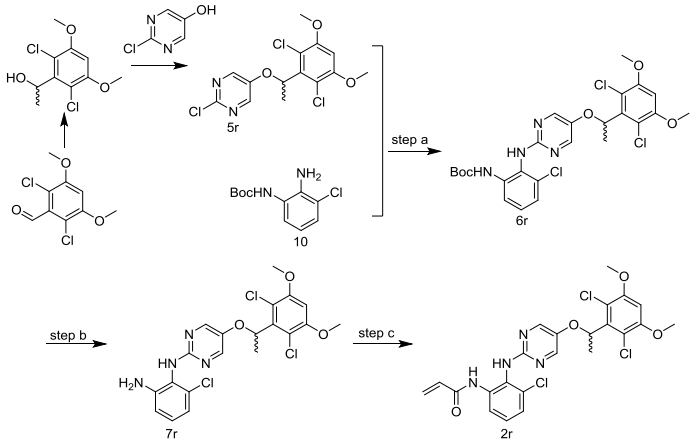
^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 9.43 (s, 1H), 8.17 (s, 2H), 7.67 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 8.2 Hz, 1H), 6.98 (s, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.56 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.22 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.70 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.24 (s, 2H), 4.49-4.44 (m, 1H), 3.93 (s, 6H), 1.04 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.28, 157.58, 154.35, 153.73, 146.38, 146.24, 135.70, 132.43, 132.00, 126.69, 125.66, 121.68, 114.68, 114.35, 110.14, 99.03, 69.75, 67.35, 56.72, 21.68. HRMS (ESI) calcd for C25H26Cl2N4O5 [M+H]+ : 533.13530; found 533.13497. HPLC purity=95.98%, Rt 8.40 min.

N-(3-chloro-2-((5-(1-(2,6-dichloro-3,5-dimethoxyphenyl)ethoxy)pyrimidin-2-yl)amino)phenyl) Propionamide (2q):

To a solution of compound 6l (see compound 2l) (0.3645g, 0.7998mmol, 1.0eq) in dry DCM(6.4ml, 8ml/mmol) containing DIEA(0.1547g, 1.2mmol, 1.5eq) was added propionyl chloride (0.0884g, 0.96mmol, 1.2eq) drop-wise at 0℃. The mixture was stirred at 0℃ for 3h. Then water was added and diluted with DCM. The organic layer was wash with brine, dried and concentrated. Purification by column chromatography (DCM/MeOH) through silica gel afforded the desired product (0.2g, yield: 48.85%).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm): 9.31 (s, 1H), 8.29 (s, 1H), 8.23 (s, 2H), 7.81 (d, *J* = 7.0 Hz, 1H), 7.34 – 7.15 (m, 2H), 6.99 (s, 1H), 5.24 (s, 2H), 3.94 (s, 6H), 2.31 (q, *J* = 7.5 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm): 172.39, 156.64, 154.39, 146.66, 146.24, 137.14, 132.92, 132.31, 129.00, 126.70, 124.88, 121.48, 114.75, 99.11, 67.04, 56.76, 29.27, 9.60. ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 172.39, 156.64, 154.39, 146.66, 146.24, 137.14, 132.92, 132.31, 129.00, 126.70, 124.88, 121.48, 114.75, 99.11, 67.04, 56.76, 29.27, 9.60. HRMS (ESI) calcd for C22H21Cl3N4O4 [M+H]+ : 511.07012; found 511.07033. HPLC purity=99.06%, Rt 7.92min.

Scheme S5. Synthesis of compound **2r**



Preparation of 2-chloro-5-(1-(2,6-dichloro-3,5-dimethoxyphenyl)ethoxy)pyrimidine (5r):

a. 1-(2,6-dichloro-3,5-dimethoxyphenyl)ethan-1-ol

Under an atmosphere of argon, a solution of methylmagnesium bromide(1.3ml, 1.5eq, 1M) was added to a solution of 2,6-dichloro-3,5-dimethoxybenzaldehyde (prepared according to the procedure reported in Synthetic Communication, 30(12), 2133-2141; 2000) (0.2077g, 0.8838mmol, 1.0eq) in anhydrous THF(1.5ml, 1.7ml/mmol) at 0℃. The ice bath was removed, and the reaction was stirred for 2h. The reaction was quenched with a solution of saturated aqueous ammonium chloride. The organic layer were washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo. Column chromatography (PE/EA) afforded the intermediate alcohol (0.171g, yield: 77.08%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 6.82 (s, 1H), 5.50 (qd, *J* = 6.8, 4.8 Hz, 1H), 5.24 (d, *J* = 4.7 Hz, 1H), 3.90 (d, *J* = 7.1 Hz, 6H), 1.44 (d, *J* = 6.8 Hz, 3H).

b. 2-chloro-5-(1-(2,6-dichloro-3,5-dimethoxyphenyl)ethoxy)pyrimidine (5r)

To a solution of triphenylphosphine(1.0765g, 4.104mmol, 6.0eq) in dry THF(13.5ml, 3.3ml/mmol) at 0℃ was added drop-wise DIAD(0.8298g, 4.104mmol, 6.0eq). The suspension was stirred at 0 ℃ for 15 min. A solution of 1-(2,6-dichloro-3,5-dimethoxyphenyl)ethan-1-ol (0.171g, 0.6840mmol, 1.0eq) in THF(3.67ml, 5.36ml/mmol) was added drop-wise , followed by 2-chloropyrimidin-5-ol (0.3571g, 2.736mmol, 4.0eq) as a solid. The ice-bath was removed and the mixture stirred at rt overnight. 1M NaOH(2.8ml) and water(6ml) were added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried, and concentrated. Purification by column chromatography (PE/EA) through silica gel afforded the desired product (0.1271g, yield: 51.12%). ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.29 (s, 2H), 6.89 (s, 1H), 6.25 (q, *J* = 6.6 Hz, 1H), 3.89 (s, 6H), 1.74 (d, *J* = 6.6 Hz, 3H).

tert-butyl (3-chloro-2-((5-(1-(2,6-dichloro-3,5-dimethoxyphenyl)ethoxy)pyrimidin-2-yl)amino) phenyl)carbamate (6r):

The title compound was synthesized following the procedure of compound 6a in Scheme S1 with compound 5r and compound 10. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.32 (s, 1H), 8.30 (s, 1H), 7.94 (s, 2H), 7.71 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.28 – 7.07 (m, 2H), 6.86 (s, 1H), 6.01 (q, *J* = 6.6 Hz, 1H), 3.88 (s, 6H), 1.69 (d, *J* = 6.6 Hz, 3H), 1.40 (s, 9H).

6-chloro-N1-(5-(1-(2,6-dichloro-3,5-dimethoxyphenyl)ethoxy)pyrimidin-2-yl)benzene-1,2-diamine(7r):

The title compound was synthesized following the procedure of compound 7a in Scheme S1 with

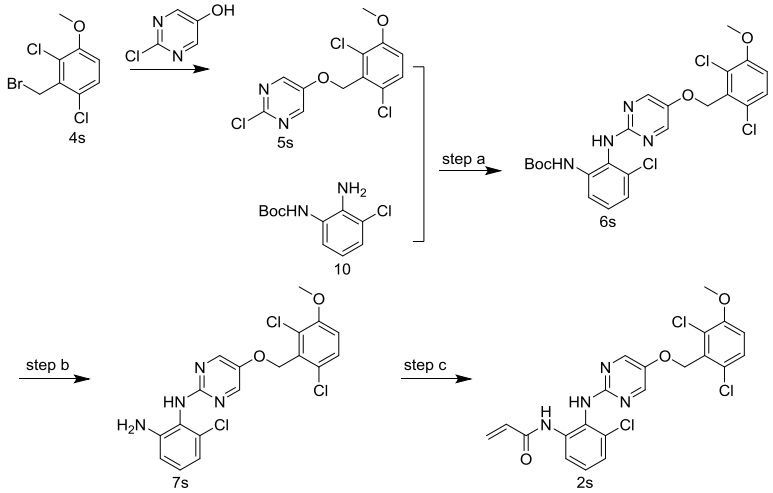
compound 6r. ^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.13 (s, 1H), 7.91 (s, 2H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 6.63 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.58 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.99 (q, *J* = 6.6 Hz, 1H), 5.03 (s, 2H), 3.89 (s, 6H), 1.68 (d, *J* = 6.6 Hz, 3H).

N-(3-chloro-2-((5-(1-(2,6-dichloro-3,5-dimethoxyphenyl)ethoxy)pyrimidin-2-yl)amino)phenyl) Acrylamide (2r):

The title compound was synthesized following the procedure of compound 2a in Scheme S1 with compound 7r.

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.55 (s, 1H), 8.28 (s, 1H), 7.94 (s, 2H), 7.89 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.29 – 7.13 (m, 2H), 6.86 (s, 1H), 6.52 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.20 (dd, *J* = 17.0, 1.8 Hz, 1H), 6.01 (q, *J* = 6.5 Hz, 1H), 5.69 (dd, *J* = 10.2, 1.7 Hz, 1H), 3.89 (s, 6H), 1.69 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.55, 156.37, 154.57, 145.95, 144.99, 136.91, 135.38, 132.83, 131.63, 129.08, 127.10, 126.69, 125.23, 121.55, 112.39, 98.08, 74.02, 56.63. HRMS (ESI) calcd for C23H21Cl3N4O4 [M+H]+ : 523.07012; found 523.06996. HPLC purity=98.79%, Rt 9.72min.

Scheme S6. Synthesis of compound **2s**



2-chloro-5-((2,6-dichloro-3-methoxybenzyl)oxy)pyrimidine (5s):

The title compound was synthesized following the procedure of compound 5a in Scheme S1 substituting 2-(bromomethyl)-1,3-dichloro-4-methoxybenzene (prepared by the according to the procedure in WO 2006049952).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.70 (s, 2H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 5.42 (s, 2H), 3.90 (s, 3H).

tert-butyl (2-((5-((2,6-dichloro-3-methoxybenzyl)oxy)pyrimidin-2-yl)amino)-3-methylphenyl) carbamate (6s):

The title compound was synthesized following the procedure of compound 6a in Scheme S1 with compound 10 and compound 5s.

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.40 (s, 1H), 8.34 (s, 1H), 8.26 (s, 2H), 7.76 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 7.23-7.18 (m, 2H), 5.24 (s, 2H), 3.89 (s, 3H), 1.44 (s, 9H).

6-chloro-N^1-(5-((2,6-dichloro-3-methoxybenzyl)oxy)pyrimidin-2-yl)benzene-1,2-diamine (7s):

The title compound was synthesized following the procedure of compound 7a in Scheme S1 with compound 6s.

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.21 (d, *J* = 4.3 Hz, 3H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.25 (d, *J* =

9.0 Hz, 1H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.22 (s, 2H), 5.08 (s, 2H), 3.89 (s, 3H).

N-(3-chloro-2-((5-((2,6-dichloro-3-methoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2s):

The title compound was synthesized following the procedure of compound 2a in Scheme S1 with compound 7s.

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.61 (s, 1H), 8.35 (s, 1H), 8.25 (s, 2H), 7.93 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.35 – 7.20 (m, 3H), 6.58 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.24 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.73 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.23 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.57, 156.71, 154.04, 146.66, 146.19, 137.02, 133.07, 132.05, 131.66, 129.20, 128.56, 127.24, 126.80, 126.33, 125.25, 124.21, 121.51, 114.33, 67.02, 56.64.HRMS (ESI) calcd for C21H17Cl3N4O3 [M+H]+ : 479.04390; found 479.04415. HPLC purity=95.61%, Rt 7.52 min.

N-(3-chloro-2-((5-((2-chloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2t) was synthesized following the approach outlined in Scheme S6 (example 2s) with modified procedure of step b (as shown below) starting with 1-(bromomethyl)-2-chloro-3,5-dimethoxybenzene (prepared according to the procedure reported in Journal of Chemistry, 78 (9), 420-4626; 2013).

^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 9.59 (s, 1H), 8.30 (s, 1H), 8.22 (s, 2H), 7.92 (d, *J* = 7.3 Hz, 1H), 7.32 – 7.15 (m, 2H), 6.76 (d, *J* = 2.6 Hz, 1H), 6.72 (d, *J* = 2.6 Hz, 1H), 6.56 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.23 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.73 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.10 (s, 2H), 3.86 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.57, 158.79, 156.52, 155.56, 146.43, 146.08, 137.00, 135.53, 133.03, 131.65, 129.23, 127.24, 126.77, 125.26, 121.52, 112.22, 106.53, 99.66, 68.82, 56.30, 55.57. HRMS (ESI) calcd for C22H20Cl2N4O4 [M+H]+ : 475.09344; found 475.09355. HPLC purity=97.23%, Rt 7.80 min.

Modified procedure of step b:

To the solution of tert-butyl (3-chloro-2-((5-((2-chloro-3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)carbamate (6r) (0.4974g, 0.9534mmol, 1.0eq) in toluene(2ml, 40ml/g) was added silica gel(0.05728g, 9.534mmol, 10eq) (100-200 mesh), the mixture was refluxed overnight. The solution was evaporated under reduced pressure and purified by silica gel column chromatography (DCM/MeOH) (0.1305g, yield: 28.79%).

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 8.18 (s, 3H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 2.6 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.37 (s, 1H).

N-(3-chloro-2-((5-((2,6-dichlorobenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2u) was synthesized following the approach outlined in Scheme S6 (example 2s) starting with 2-(bromomethyl)-1,3-dichlorobenzene.

^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 9.60 (s, 1H), 8.34 (s, 1H), 8.26 (s, 2H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.47 (dd, *J* = 8.7, 7.4 Hz, 1H), 7.24 – 7.30 (m, 2H), 6.57 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.24 (dd, *J* = 17.0, 1.6 Hz, 1H), 5.74 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.24 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.57, 156.74, 146.63, 146.23, 137.03, 136.03, 133.07, 131.70, 131.66, 131.30, 129.19, 128.77, 127.25, 126.81, 125.25, 121.52, 66.74. HRMS (ESI) calcd for C20H15Cl3N4O2 [M+H]+ : 449.03334; found 449.03365. HPLC purity=97.84%, Rt 8.16 min.

Compounds **2v-2z** were synthesize according to procedures for compound **2t** with corresponding substituted benzyl bromides.

N-(3-chloro-2-((5-((2-chloro-3-methoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2v):

^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 9.60 (s, 1H), 8.30 (s, 1H), 8.22 (s, 2H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.29-7.24 (m, 2H), 7.18-7.15 (m, 2H), 6.56 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.23 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.73 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.14 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.57, 156.50, 154.79, 146.47, 146.01, 136.98, 135.23, 133.04, 131.65, 129.24, 127.69, 127.24, 126.76, 125.26, 121.59, 121.52, 120.71, 112.56, 68.74, 56.23. HRMS (ESI) calcd for C21H18Cl2N4O3 [M+H]+ : 445.08287; found 445.08328. HPLC purity=98.52%, Rt 7.04 min.

N-(3-chloro-2-((5-((2-chloro-5-methoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2w):

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.59 (s, 1H), 8.31 (s, 1H), 8.24 (s, 2H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.32 – 7.19 (m, 2H), 7.17 (d, *J* = 3.0 Hz, 1H), 6.97 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.56 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.23 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.73 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.10 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.59, 158.20, 156.56, 146.43, 146.11, 137.02, 134.84, 133.05, 131.65, 130.19, 129.24, 127.24, 126.77, 125.26, 123.79, 121.52, 115.99, 115.29, 68.72, 55.50. HRMS (ESI) calcd for C21H18Cl2N4O3 [M+H]+ : 445.08287; found 445.08328. HPLC purity=98.52%, Rt 7.04 min.

N-(3-chloro-2-((5-((3,5-dimethoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2x):

^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 9.60 (s, 1H), 8.26 (s, 1H), 8.19 (s, 2H), 7.92 (d, *J* = 6.9 Hz, 1H), 7.35 – 7.16 (m, 2H), 6.64 – 6.49 (m, 3H), 6.45 (s, 1H), 6.23 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.72 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.03 (s, 2H), 3.73 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.57, 160.53, 156.32, 146.40, 145.90, 138.88, 136.98, 133.03, 131.65, 129.28, 127.24, 126.74, 125.25, 121.49, 105.60, 99.69, 70.62, 55.18. HRMS (ESI) calcd for C22H21ClN4O4 [M+H]+ : 441.13241; found 441.13218. HPLC purity=96.52%, Rt 6.80 min.

N-(3-chloro-2-((5-((2-chlorobenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2y):

^{1}H NMR (400 MHz, DMSO-d_6): δ(ppm) 9.60 (s, 1H), 8.31 (s, 1H), 8.24 (s, 2H), 7.92 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.67 – 7.56 (m, 1H), 7.56 – 7.46 (m, 1H), 7.46 – 7.33 (m, 2H), 7.32 – 7.17 (m, 2H), 6.56 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.24 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.73 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.15 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.57, 156.53, 146.47, 146.05, 136.99, 133.87, 133.05, 132.82, 131.64, 130.51, 130.11, 129.41, 129.24, 127.33, 127.24, 126.77, 125.26, 121.52, 68.69. HRMS (ESI) calcd for C20H16Cl2N4O2 [M+H]+ : 415.07231; found 415.07259. HPLC purity=99.08%, Rt 7.66 min.

N-(3-chloro-2-((5-((3-methoxybenzyl)oxy)pyrimidin-2-yl)amino)phenyl)acrylamide (2z):

^{1}H NMR (500 MHz, DMSO-d_6): δ(ppm) 9.60 (s, 1H), 8.27 (s, 1H), 8.20 (s, 2H), 7.92 (d, *J* = 7.4 Hz, 1H), 7.31-7.23 (m, 3H), 6.99 (s, 2H), 6.90 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.56 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.23 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.72 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.07 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ(ppm) 163.58, 159.34, 156.32, 146.46, 145.90, 138.12, 136.99, 133.05, 131.66, 129.56, 129.30, 127.25, 126.74, 125.27, 121.51, 119.92, 113.53, 113.30. HRMS (ESI) calcd for C21H19ClN4O3 [M+H]+ : 411.12184; found 411.12159. HPLC purity=96.82%, Rt 6.44 min.

Computational Study. All the procedure was performed in Maestro 9.9 (Schrodinger LLC). The crystal structures of FGFR4 and FGFR1 were taken from PDB ID 4XCU and 3TT0, respectively. The covalent bond between the inhibitor (BLU9931) and the protein (FGFR4, PDB ID: 4XCU) was delete, Then, the protein was processed using the "Protein Preparation Wizard" workflow in Maestro 9.9 (Schrodinger LLC) to adding bond orders and add hydrogens. All hetatm residues and crystal water molecules beyond 5A from het group were removed. 2a were built by in LigPrep module using OPLS-2005 force field. Glide module (Covalent Docking) was used as docking program. Michael Addition was chose as the reaction type. CYS552 was chose as the reactive residue. The docking box was placed on the centroid of the binding ligand in the optimized crystal structure as described above. Covalent docking approach of Glide was adopted to dock 2a to FGFR4 with the default parameters.

In Vitro Enzymatic Activity Assay. $FGFR^{WT}$ (FGFR1, PV3146; FGFR2, PV3368; FGFR3, PV3145; FGFR4, P3054) and the Z'-Lyte Kinase Assay Kit were purchased from Invitrogen. The experiments were performed according to the instructions of the manufacturer. The concentrations of kinases were determined by optimization experiments and the respective concentration was: FGFR 0.22 μg/ μL. First, the compounds were diluted three-fold from 5.1×10^{-9} M to1×10^{-4} M in DMSO and a 400 μM compound solution was prepared (4 μL compound dissolved in 96 μL water). Second, a 100 μL ATP solution in 1.33×Kinase Buffer was prepared. Third, a kinase/peptide mixture containing 2×kinase and 4 μM Tyr 4 peptide (Invitrogen, PV3193) was prepared right before use. The final 10 μL reaction consists of 0.002 ng of FGFR, 2 μM Tyr4 peptide in 1×kinase buffer. For each assay, 10 μL kinase reactions were made at first (including 2.5 μL compound solution, 5 μL Kinase/Peptide Mixture, and 2.5 μL ATP solution). Mixed the plate thoroughly and incubated for one hour at room temperature. Then 5 μL development solution was added to each well and the plate was incubated for 1h at room temperature; the nonphosphopeptides were cleaved at this time. In the end, 5 μL stop reagent was loaded to stop the reaction. For the control setting, 5 μL phospho-peptide solution instead of kinase/peptide mixture was used as 100% phosphorylation control. 2.5 μL 1.33×Kinase Buffer instead of ATP solution was used as 100% inhibition control, and 2.5 μL 4% DMSO instead of compound solution was used as the 0% inhibitor control. The plate was measured on an EnVision Multilabel Reader (Perkin-Elmer). Curve fitting and data presentations were performed using Graph Pad Prism, version 5.0. Every experiment was repeated at least 3 times.

Cell Culture. The human breast cancer cell lines MDA-MB-453, MDA-MB-231 and MCF-7 were purchased from American type culture collection (ATCC). MDA-MB-453 and MDA-MB-231 cells were maintained in RPMI-1640, and MCF-7 cells were maintained in DMEM. They all were supplemented with 10% FBS, 100 U/mL penicillin, 50 mg/mL streptomycin, and 2 mmol/L glutamine in a humidified CO_2 incubator at 37℃. All cells were passaged for less than 3 months before renewal from frozen, early-passage stocks obtained from the indicated sources.

Cell Proliferation Assay. Tumor cells were seeded (2,500 cells per well) in 96-well plates in complete medium and cultured overnight, and then were treated with a dilution series of test compounds for 72 h. Cell proliferation was evaluated by Cell Counting Kit 8(CCK8, CK04, Dojindo laboratories, Japan). IC50 values were calculated by concentration-response cure fitting using GraphPad Prism 5.0 software. Each IC50 value was expressed as mean±SD.

Western Blot Analysis. The western blot analysis was carried out by following the protocol described before. Briefly, after the indicated treatment, cell lysates were collected dissolving cells in 1×SDS sample lysis buffer (CST recommended). After being sonicated and boiled, the supernatant of cell lysate were used for western blot analysis. Cell lysates were loaded to 8-12% SDS-PAGE and separated by electrophoresis. Separated proteins were then electrically transferred to a PVDF film. After being blocked with 1×TBS containing 0.5% Tween-20 and 5% non-fat milk, the film was incubated with corresponding primary antibody followed by HRP-conjugated secondary antibody. And the protein lanes were visualized using ECL Western Blotting Detection Kit (Thermo Scientific, USA).

KINOMEscan™: kinase-tagged T7 phase strains were prepared in an E. coli host derived from the BL21 strain. E. coil were grown to log-phase and infected with T7 phage and incubated with shaking at 32℃ until lysis. The lysates were centrifuged and filtered to remove cell debris. The remaining kinases were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock (Pierce), 0.17x BSA, 0.05% Tween 20, 1mM DTT). All reactions were performed in polystyrene 96-well plates in a final volume of 0.135 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 μM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

For Kd determination, an 11-point 3-fold serial dilution of compound 2n was prepared in 100% DMSO at 100x final test concentration and subsequently diluted to 1x in the assay (final DMSO concentration = 1%). Binding constants (Kds) were calculated with a standard dose-response curve using the Hill equation.

For primary screening, compound 2n was screened at the concentration of 1μM/L, and the results are reported as '% Ctrl'.

Table S2. Matrix of Compound Screen for inhibitor **2n**

Gene Symbol	%Ctrl @ 1000nM
BRK	100
BRSK1	100
BRSK2	99
BTK	100
BUB1	93
CAMK1	100
CAMK1B	100
CAMK1D	5.3
CAMK1G	100
CAMK2A	91
CAMK2B	97
CAMK2D	100
CAMK2G	100
CAMK4	86
CAMKK1	98
CAMKK2	99
CASK	95
CDC2L1	100
CDC2L2	100
CDC2L5	100
CDK11	92
CDK2	98
CDK3	92
CDK4	100
CDK4-cyclinD1	96
CDK4-cyclinD3	100
CDK5	89
CDK7	100
CDK8	63
CDK9	100
CDKL1	91
CDKL2	93
CDKL3	94
CDKL5	100
CHEK1	100
CHEK2	100
CIT	86
CLK1	99
CLK2	94
CLK3	100
CLK4	99
CSF1R	100
CSF1R-autoinhibited	100
CSK	100
CSNK1A1	100
CSNK1A1L	100
CSNK1D	96
CSNK1E	100
CSNK1G1	100

Gene Symbol	%Ctrl @ 1000nM
AAK1	100
ABL1(E255K)-phosphorylated	100
ABL1(F317I)-nonphosphorylated	100
ABL1(F317I)-phosphorylated	100
ABL1(F317L)-nonphosphorylated	100
ABL1(F317L)-phosphorylated	100
ABL1(H396P)-nonphosphorylated	100
ABL1(H396P)-phosphorylated	100
ABL1(M351T)-phosphorylated	100
ABL1(Q252H)-nonphosphorylated	100
ABL1(Q252H)-phosphorylated	100
ABL1(T315I)-nonphosphorylated	100
ABL1(T315I)-phosphorylated	96
ABL1(Y253F)-phosphorylated	100
ABL1-nonphosphorylated	87
ABL1-phosphorylated	97
ABL2	100
ACVR1	100
ACVR1B	82
ACVR2A	100
ACVR2B	99
ACVRL1	76
ADCK3	100
ADCK4	100
AKT1	100
AKT2	97
AKT3	80
ALK	90
ALK(C1156Y)	100
ALK(L1196M)	92
AMPK-alpha1	96
AMPK-alpha2	100
ANKK1	100
ARK5	100
ASK1	98
ASK2	92
AURKA	100
AURKB	90
AURKC	90
AXL	100
BIKE	89
BLK	100
BMPR1A	100
BMPR1B	100
BMPR2	97
BMX	100
BRAF	100
BRAF(V600E)	100

Gene Symbol	%Ctrl @ 1000nM
CSNK1G2	100
CSNK1G3	96
CSNK2A1	99
CSNK2A2	100
CTK	100
DAPK1	87
DAPK2	91
DAPK3	83
DCAMKL1	82
DCAMKL2	94
DCAMKL3	86
DDR1	100
DDR2	96
DLK	100
DMPK	89
DMPK2	100
DRAK1	100
DRAK2	100
DYRK1A	88
DYRK1B	37
DYRK2	98
EGFR	87
EGFR(E746-A750del)	96
EGFR(G719C)	96
EGFR(G719S)	80
EGFR(L747-E749del, A750P)	89
EGFR(L747-S752del, P753S)	100
EGFR(L747-T751del,Sins)	64
EGFR(L858R)	97
EGFR(L858R,T790M)	100
EGFR(L861Q)	88
EGFR(S752-I759del)	93
EGFR(T790M)	100
EIF2AK1	100
EPHA1	100
EPHA2	100
EPHA3	100
EPHA4	100
EPHA5	88
EPHA6	100
EPHA7	92
EPHA8	99
EPHB1	100
EPHB2	100
EPHB3	100
EPHB4	100
EPHB6	100
ERBB2	83
ERBB3	55

Gene Symbol	%Ctrl @ 1000nM
ERBB4	100
ERK1	99
ERK2	82
ERK3	100
ERK4	92
ERK5	100
ERK8	94
ERN1	100
FAK	96
FER	95
FES	100
FGFR1	100
FGFR2	100
FGFR3	100
FGFR3(G697C)	96
FGFR4	0.5
FGR	98
FLT1	92
FLT3	81
FLT3(D835H)	84
FLT3(D835V)	95
FLT3(D835Y)	100
FLT3(ITD)	91
FLT3(ITD,D835V)	100
FLT3(ITD,F691L)	100
FLT3(K663Q)	100
FLT3(N841I)	62
FLT3(R834Q)	100
FLT3-autoinhibited	100
FLT4	94
FRK	100
FYN	93
GAK	100
GCN2(Kin.Dom.2,S808G)	88
GRK1	100
GRK2	100
GRK3	100
GRK4	7.8
GRK7	100
GSK3A	98
GSK3B	83
HASPIN	90
HCK	90
HIPK1	85
HIPK2	100
HIPK3	99
HIPK4	100
HPK1	92
HUNK	100

Gene Symbol	%Ctrl @ 1000nM
ICK	100
IGF1R	87
IKK-alpha	91
IKK-beta	90
IKK-epsilon	100
INSR	100
INSRR	100
IRAK1	100
IRAK3	100
IRAK4	100
ITK	100
JAK1(JH1domain-catalytic)	100
JAK1(JH2domain-pseudokinase)	100
JAK2(JH1domain-catalytic)	89
JAK3(JH1domain-catalytic)	49
JNK1	100
JNK2	100
JNK3	100
KIT	100
KIT(A829P)	100
KIT(D816H)	100
KIT(D816V)	99
KIT(L576P)	99
KIT(V559D)	100
KIT(V559D,T670I)	100
KIT(V559D,V654A)	100
KIT-autoinhibited	100
LATS1	94
LATS2	100
LCK	96
LIMK1	100
LIMK2	100
LKB1	86
LOK	91
LRRK2	100
LRRK2(G2019S)	100
LTK	98
LYN	100
LZK	98
MAK	97
MAP3K1	91
MAP3K15	100
MAP3K2	90
MAP3K3	100
MAP3K4	100
MAP4K2	100
MAP4K3	100
MAP4K4	100
MAP4K5	100

Gene Symbol	%Ctrl @ 1000nM
MAPKAPK2	70
MAPKAPK5	100
MARK1	98
MARK2	81
MARK3	100
MARK4	100
MAST1	61
MEK1	100
MEK2	92
MEK3	100
MEK4	100
MEK5	92
MEK6	100
MELK	100
MERTK	100
MET	100
MET(M1250T)	77
MET(Y1235D)	99
MINK	100
MKK7	97
MKNK1	100
MKNK2	100
MLCK	100
MLK1	100
MLK2	100
MLK3	97
MRCKA	100
MRCKB	100
MST1	100
MST1R	97
MST2	91
MST3	99
MST4	100
MTOR	54
MUSK	100
MYLK	89
MYLK2	93
MYLK4	100
MYO3A	100
MYO3B	93
NDR1	98
NDR2	100
NEK1	100
NEK10	100
NEK11	100
NEK2	100
NEK3	79
NEK4	95
NEK5	100

Gene Symbol	%Ctrl @ 1000nM	Gene Symbol	%Ctrl @ 1000nM
NEK6	77	PIP5K1A	100
NEK7	100	PIP5K1C	68
NEK9	81	PIP5K2B	90
NIK	100	PIP5K2C	88
NIM1	100	PKAC-alpha	82
NLK	94	PKAC-beta	58
OSR1	100	PKMYT1	98
p38-alpha	100	PKN1	100
p38-beta	96	PKN2	92
p38-delta	100	PKNB(M.tuberculosis)	95
p38-gamma	92	PLK1	100
PAK1	100	PLK2	100
PAK2	100	PLK3	88
PAK3	99	PLK4	100
PAK4	100	PRKCD	100
PAK6	100	PRKCE	64
PAK7	100	PRKCH	98
PCTK1	100	PRKCI	100
PCTK2	100	PRKCQ	71
PCTK3	100	PRKD1	98
PDGFRA	100	PRKD2	100
PDGFRB	100	PRKD3	99
PDPK1	100	PRKG1	66
PFCDPK1(P.falciparum)	76	PRKG2	100
PFPK5(P.falciparum)	100	PRKR	99
PFTAIRE2	96	PRKX	100
PFTK1	100	PRP4	100
PHKG1	100	PYK2	100
PHKG2	86	QSK	81
PIK3C2B	100	RAF1	100
PIK3C2G	100	RET	100
PIK3CA	100	RET(M918T)	100
PIK3CA(C420R)	100	RET(V804L)	99
PIK3CA(E542K)	99	RET(V804M)	100
PIK3CA(E545A)	99	RIOK1	99
PIK3CA(E545K)	63	RIOK2	100
PIK3CA(H1047L)	100	RIOK3	97
PIK3CA(H1047Y)	100	RIPK1	99
PIK3CA(I800L)	93	RIPK2	100
PIK3CA(M1043I)	100	RIPK4	98
PIK3CA(Q546K)	100	RIPK5	88
PIK3CB	100	ROCK1	100
PIK3CD	100	ROCK2	100
PIK3CG	96	ROS1	94
PIK4CB	99	RPS6KA4(Kin.Dom.1-N-terminal)	66
PIKFYVE	66	RPS6KA4(Kin.Dom.2-C-terminal)	100
PIM1	94	RPS6KA5(Kin.Dom.1-N-terminal)	100
PIM2	97	RPS6KA5(Kin.Dom.2-C-terminal)	100
PIM3	100	RSK1(Kin.Dom.1-N-terminal)	100

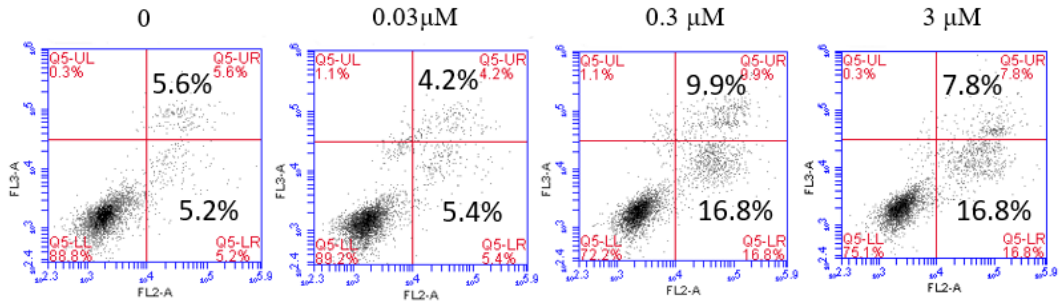
Gene Symbol	%Ctrl @ 1000nM
RSK1(Kin.Dom.2-C-terminal)	100
RSK2(Kin.Dom.1-N-terminal)	98
RSK2(Kin.Dom.2-C-terminal)	100
RSK3(Kin.Dom.1-N-terminal)	96
RSK3(Kin.Dom.2-C-terminal)	95
RSK4(Kin.Dom.1-N-terminal)	97
RSK4(Kin.Dom.2-C-terminal)	90
S6K1	98
SBK1	100
SGK	100
SgK110	100
SGK2	89
SGK3	100
SIK	86
SIK2	100
SLK	97
SNARK	100
SNRK	91
SRC	75
SRMS	100
SRPK1	100
SRPK2	100
SRPK3	12
STK16	100
STK33	97
STK35	100
STK36	100
STK39	72
SYK	97
TAK1	100
TAOK1	100
TAOK2	100
TAOK3	100
TBK1	92
TEC	100
TESK1	100
TGFBR1	100
TGFBR2	86
TIE1	100
TIE2	94
TLK1	100
TLK2	100
TNIK	94
TNK1	100
TNK2	100
TNNI3K	100
TRKA	100
TRKB	100
TRKC	100

Gene Symbol	%Ctrl @ 1000nM
TRPM6	100
TSSK1B	100
TSSK3	58
TTK	65
TXK	100
TYK2(JH1domain-catalytic)	100
TYK2(JH2domain-pseudokinase)	100
TYRO3	100
ULK1	100
ULK2	99
ULK3	100
VEGFR2	100
VPS34	100
VRK2	100
WEE1	95
WEE2	100
WNK1	100
WNK2	100
WNK3	100
WNK4	100
YANK1	100
YANK2	100
YANK3	100
YES	97
YSK1	100
YSK4	100
ZAK	100
ZAP70	91

Table S3. S-score Table for **2n**

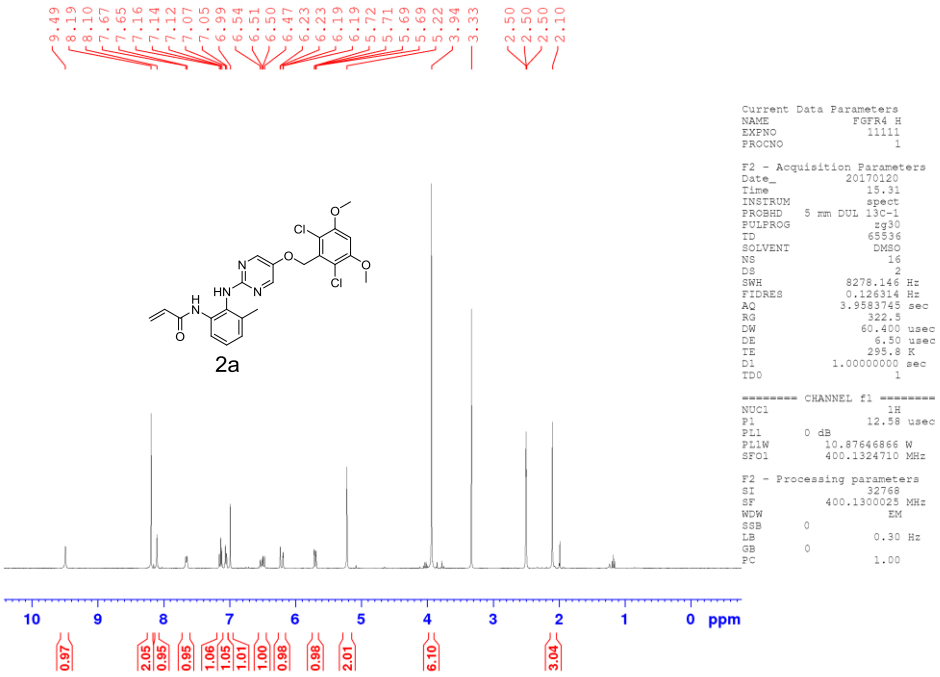
Compd	Selectivity Score Type	Number of hits	Number of Non-Mutant Kinases	Screening Concentration (nM)	Selectivity Score
2n	S(35)	4	403	1000	0.01
	S(10)	3	403	1000	0.007
	S(1)	1	403	1000	0.002

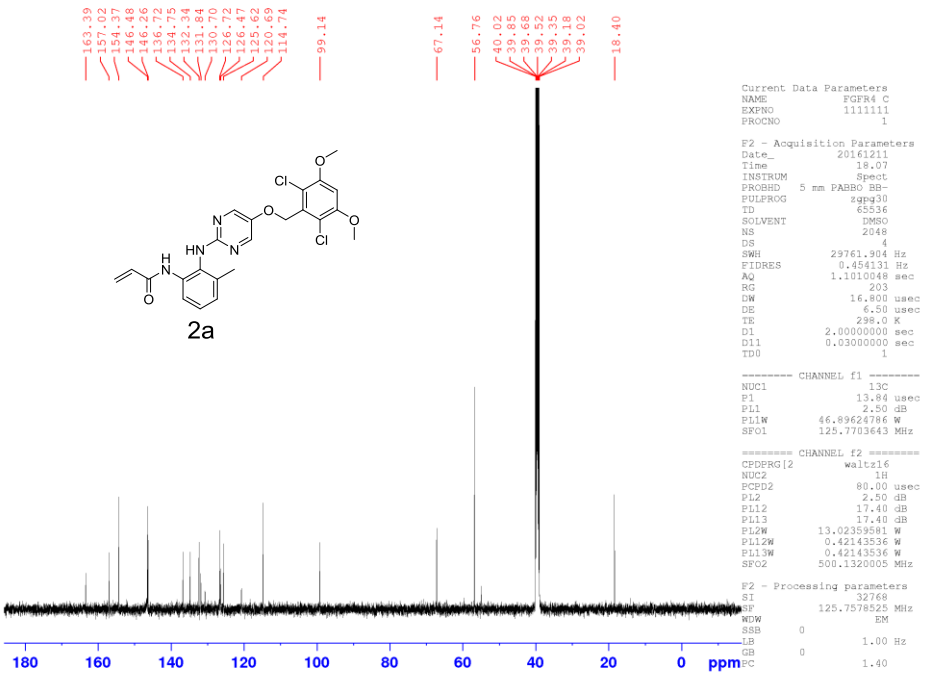
Figure S2. Compound **2n** induces apoptosis in MDA-MB-453.

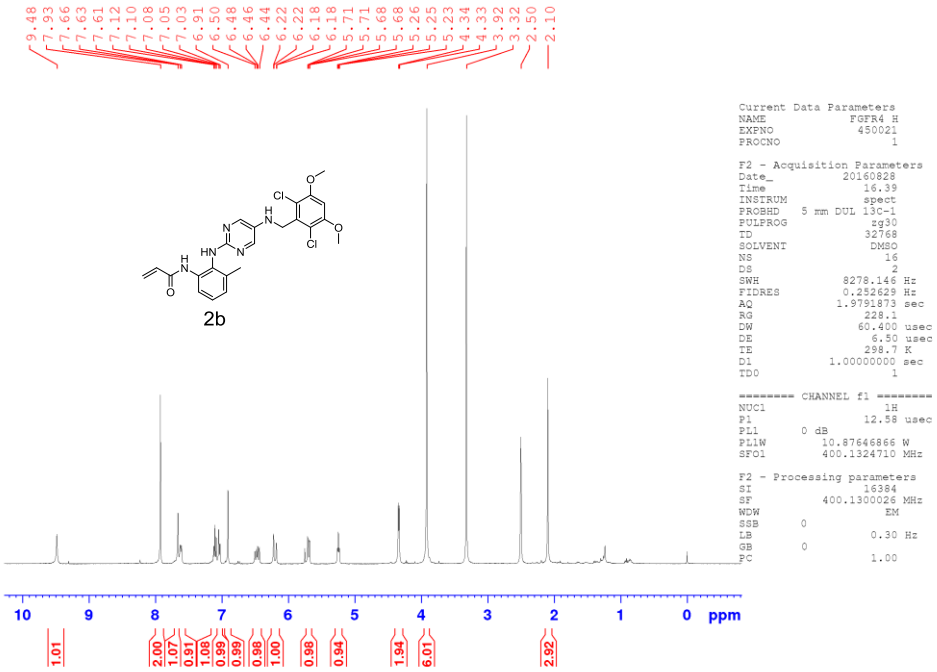


*MDA-MB-453 Cells were treated with 0.03 μM, 0.3 μM, 3 μM compound **2n** for 48h before analysis by annexin V/7-ADD staining.

^{1}H NMR and ^{13}C NMR spectra of compound **2a-2z** (Solvent: DMSO-d_6 for all compounds)



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EXPNO 450021
PROCNO 1
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Time 16.39
INSTRUM spect
PROBHD 5 mm DUL 13C-1
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.252629 Hz
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RG 228.1
DW 60.400 usec
DE 6.50 usec
TE 298.7 K
D1 1.00000000 sec
TD0 1
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NUC1 1H
P1 12.58 usec
PL1 0 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 16384
SF 400.1300026 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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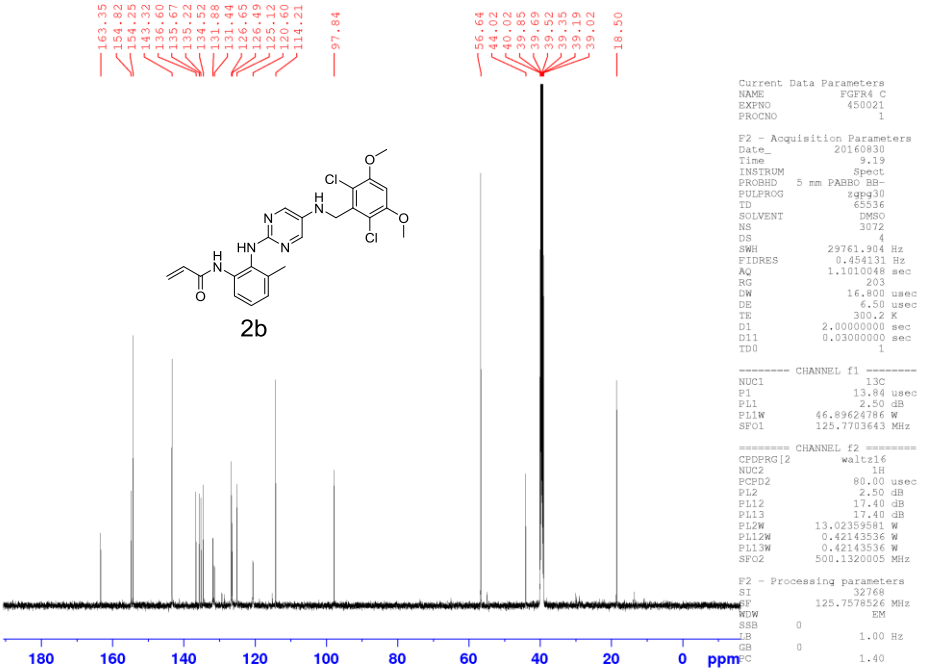
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Time 9.19
INSTRUM spect
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RG 203
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TE 300.2 K
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D11 0.03000000 sec
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PL1 2.50 dB
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SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
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PL12W 0.42143536 W
PL13W 0.42143536 W
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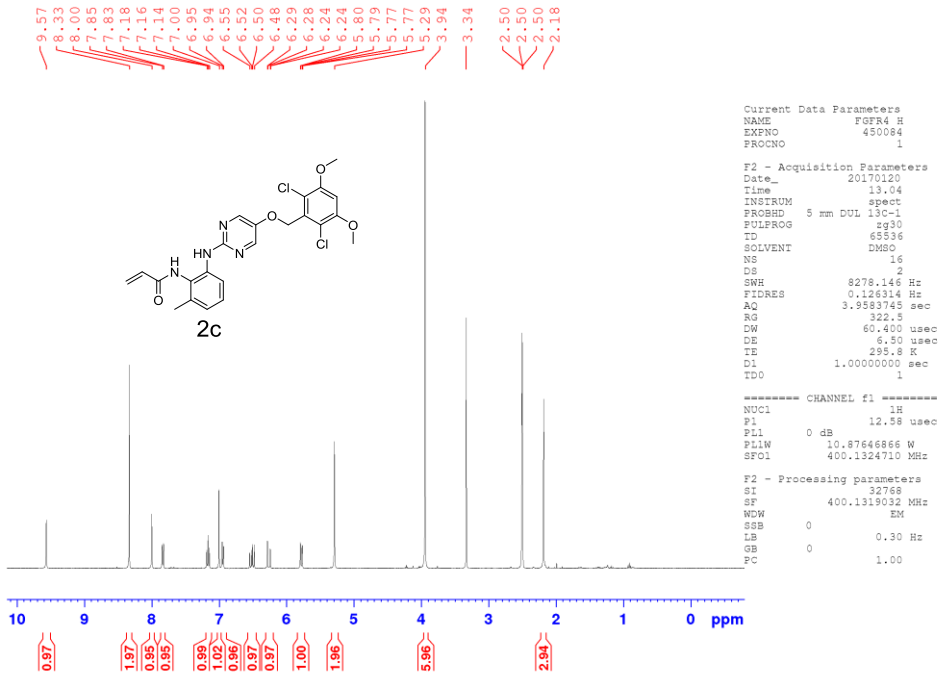


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PROCNO                      1

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TD                    65536
SOLVENT               DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                     322.8
DW                    60.400 usec
DE                     6.50 usec
TE                    295.8 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1                 0 dB
PL1W               10.87646866 W
SFO1              400.1324710 MHz

F2 - Processing parameters
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WDW                        EM
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PC                      1.00
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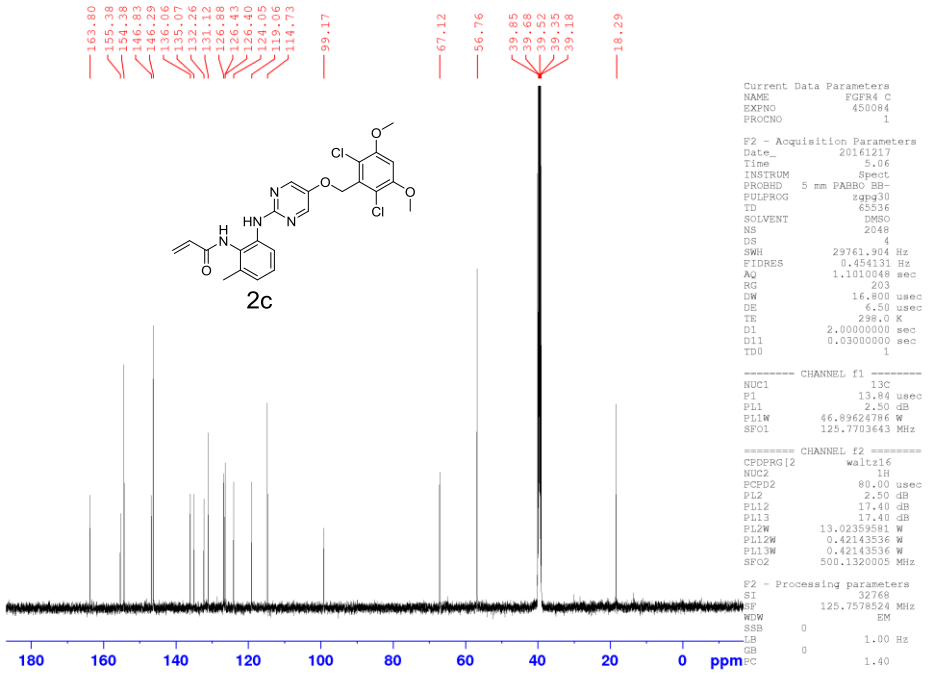


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EXPNO                  450084
PROCNO                      1

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Time                    5.06
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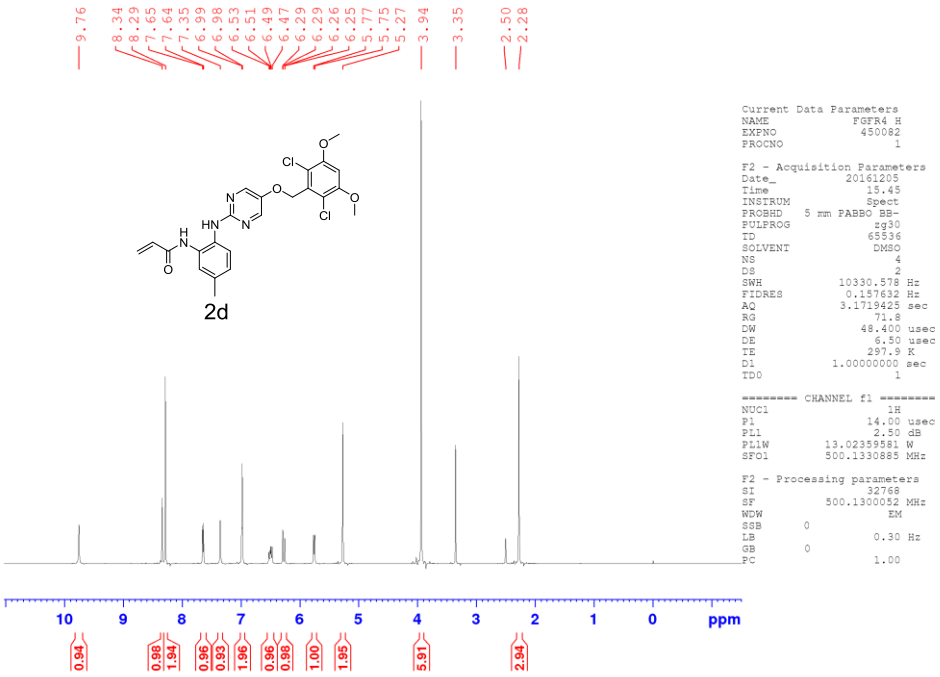
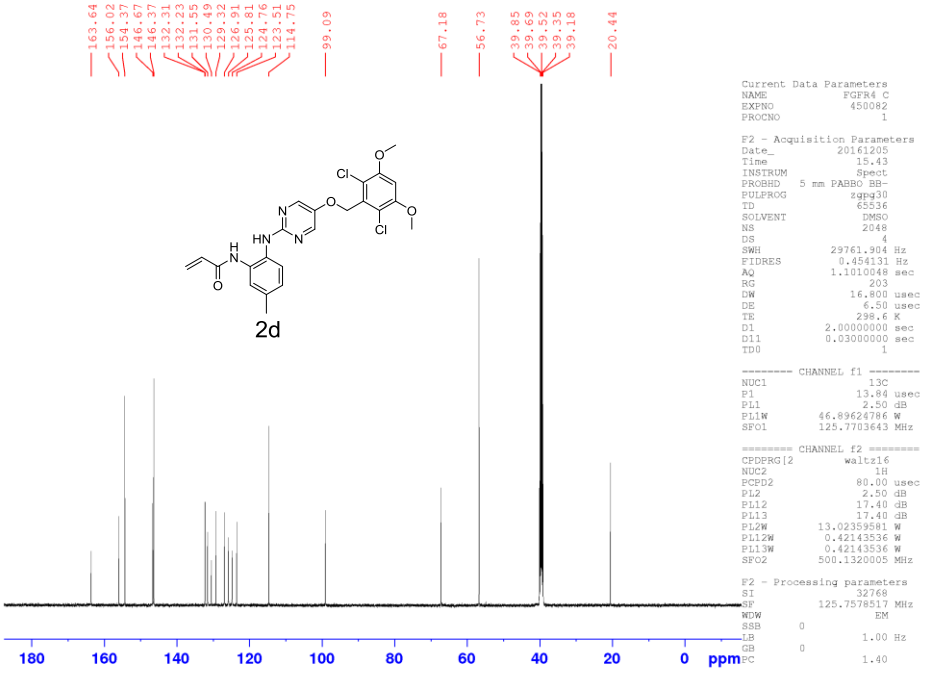
PULPROG             zgpg30
TD                    65536
SOLVENT               DMSO
NS                       2048
DS                          4
SWH                29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                      203
DW                    16.800 usec
DE                     6.50 usec
TE                    298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

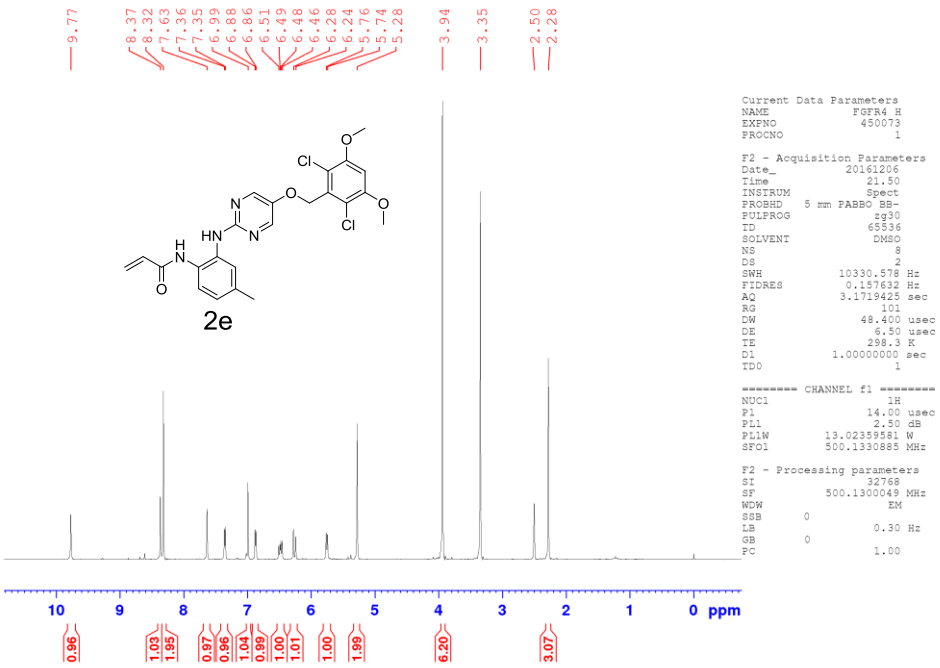
======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                    2.50 dB
PL1W              46.89624786 W
SFO1             125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                    2.50 dB
PL12                  17.40 dB
PL13                  17.40 dB
PL2W              13.02359581 W
PL12W              0.42143536 W
PL13W              0.42143536 W
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7578524 MHz
WDW                        EM
SSB                 0
LB                      1.00 Hz
GB                  0
PC                      1.40
```


9.76
8.34
8.29
7.65
7.64
7.35
6.99
6.98
6.53
6.51
6.49
6.47
6.29
6.29
6.26
6.25
5.77
5.75
5.27
3.94
3.35
2.50
2.28
2d
Current Data Parameters
NAME FGFR4 H
EXPNO 450082
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161205
Time 15.45
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 4
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 71.8
DW 48.400 usec
DE 6.50 usec
TE 297.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 2.50 dB
PL1W 13.02359581 W
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300052 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 0 ppm
0.94 0.98 1.94 0.96 0.93 1.96 0.96 0.98 1.00 1.95 5.91 2.94


163.64
156.02
154.37
146.67
146.37
132.31
132.23
131.55
130.49
129.32
126.91
125.81
124.76
123.51
114.75
99.09
67.18
56.73
39.85
39.69
39.52
39.35
39.18
20.44
2d
Current Data Parameters
NAME FGFR4 C
EXPNO 450082
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161205
Time 15.43
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578517 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 0 ppm



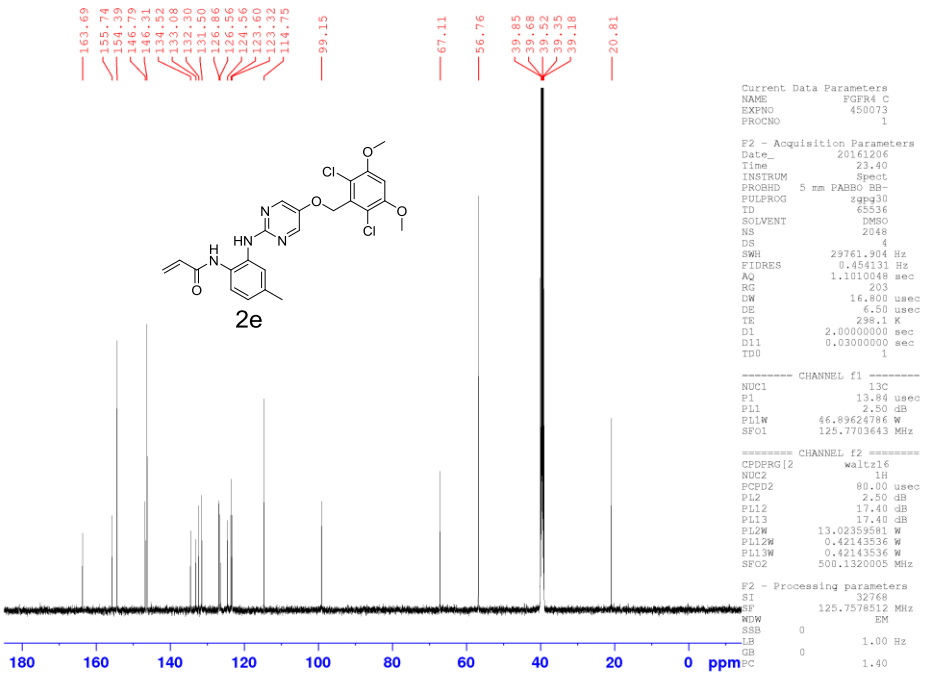
Current Data Parameters
NAME FGFR4 H
EXPNO 450073
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161206
Time 21.50
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 101
DW 48.400 usec
DE 6.50 usec
TE 298.3 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 2.50 dB
PL1W 13.02359581 W
SFO1 500.1330885 MHz

F2 - Processing parameters
SI 32768
SF 500.1300049 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Bruker



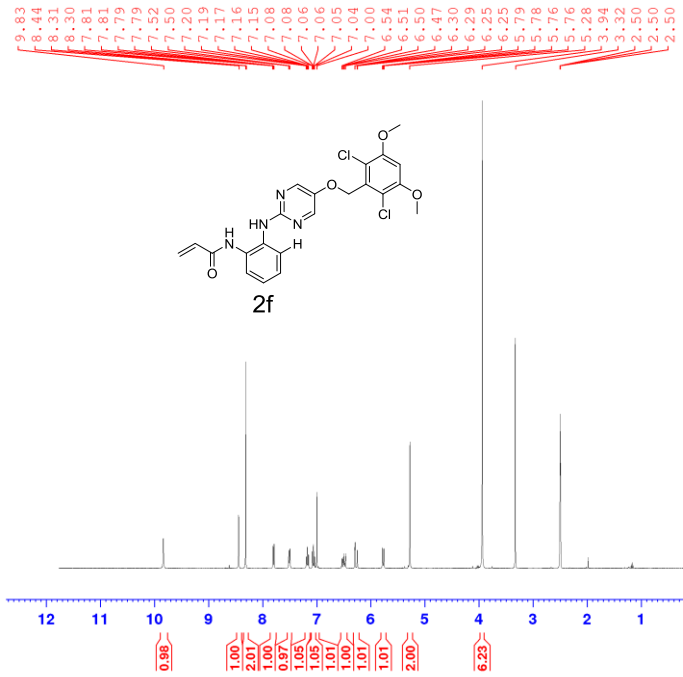
Current Data Parameters
NAME FGFR4 C
EXPNO 450073
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161206
Time 23.40
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz

F2 - Processing parameters
SI 32768
SF 125.7578512 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

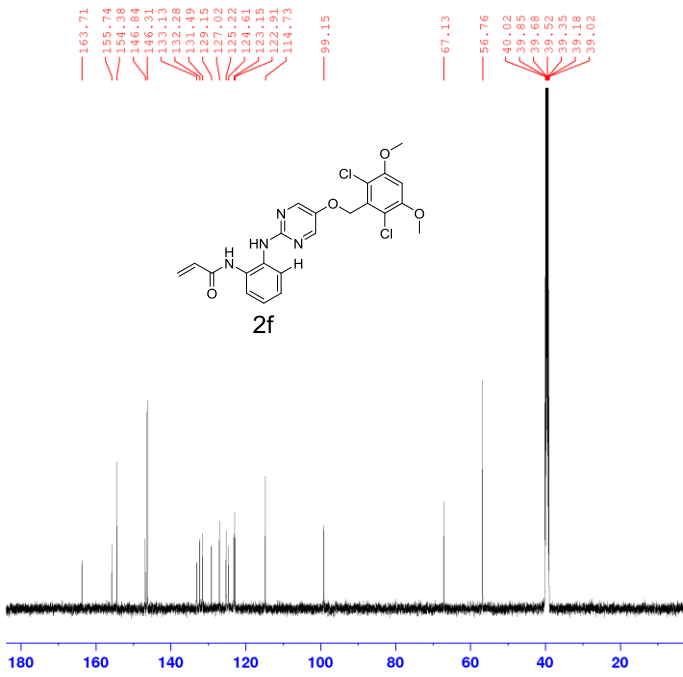



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 5960093
PROCNO                      1

F2 - Acquisition Parameters
Date_               20170120
Time                   13.09
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT               DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                      362
DW                   60.400 usec
DE                    6.50 usec
TE                   295.8 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1             0 dB
PL1W             10.87646866 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1319033 MHz
WDW                        EM
SSB             0
LB                      0.30 Hz
GB              0
PC                      1.00
```



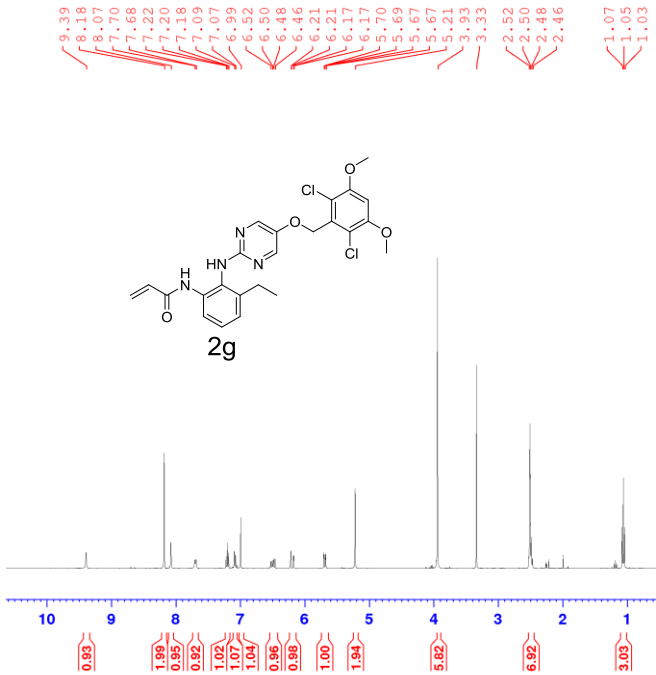

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 5960093
PROCNO                      1

F2 - Acquisition Parameters
Date_               20161214
Time                   11.20
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               DMSO
NS                     2048
DS                        4
SWH                29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                      203
DW                   16.800 usec
DE                    6.50 usec
TE                   298.3 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                    2.50 dB
PL1W            46.89624786 W
SFO1            125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                    2.50 dB
PL12                  17.40 dB
PL13                  17.40 dB
PL2W            13.02359581 W
PL12W            0.42143536 W
PL13W            0.42143536 W
SFO2            500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7578510 MHz
WDW                        EM
SSB             0
LB                      1.00 Hz
GB              0
PC                      1.40
```

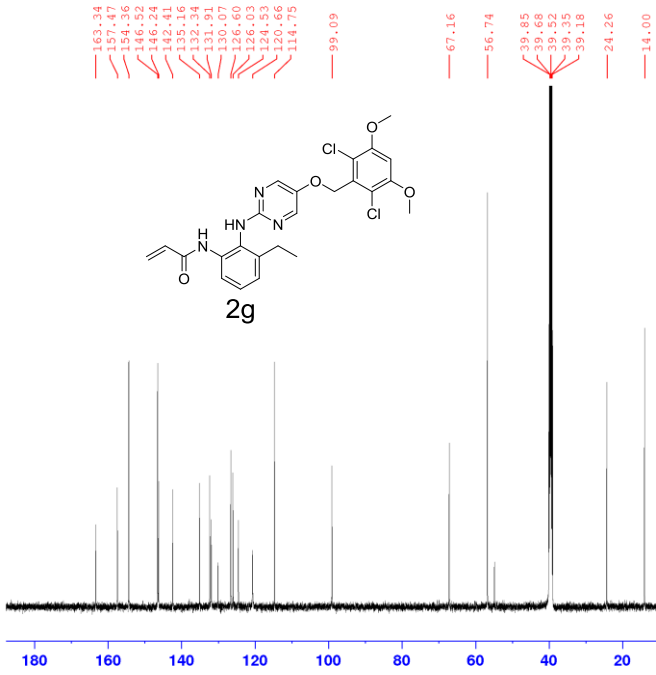



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                  450063
PROCNO                      1

F2 - Acquisition Parameters
Date_               20170120
Time                   12.59
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                 8278.146 Hz
FIDRES                0.126314 Hz
AQ                  3.9583745 sec
RG                      322.8
DW                     60.400 usec
DE                      6.50 usec
TE                     295.8 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1             0 dB
PL1W              10.87646866 W
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1300000 MHz
WDW                        EM
SSB             0
LB                      0.30 Hz
GB              0
PC                      1.00
```



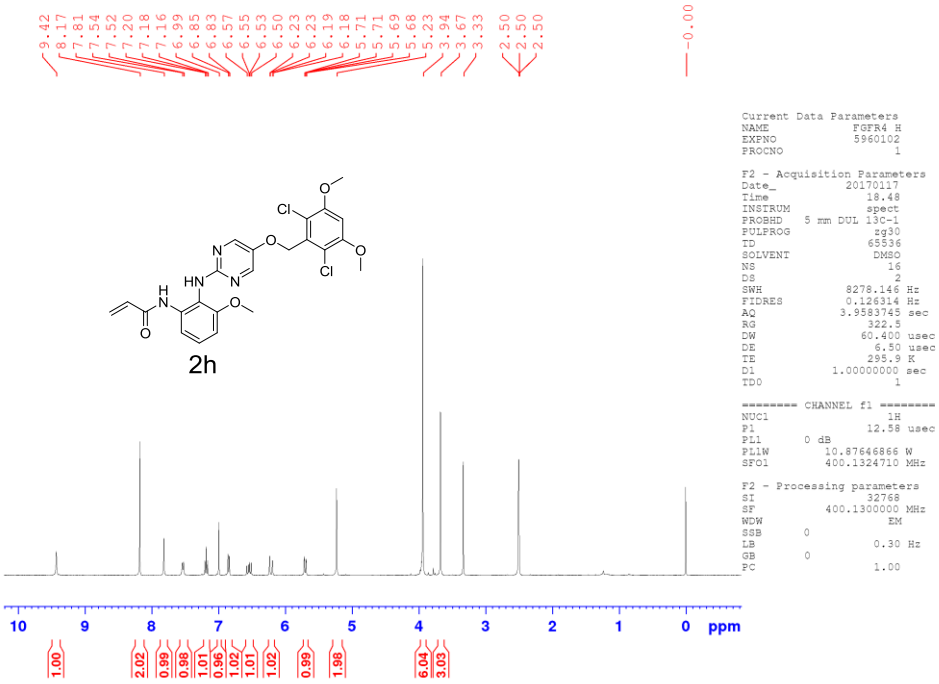

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                  450063
PROCNO                      1

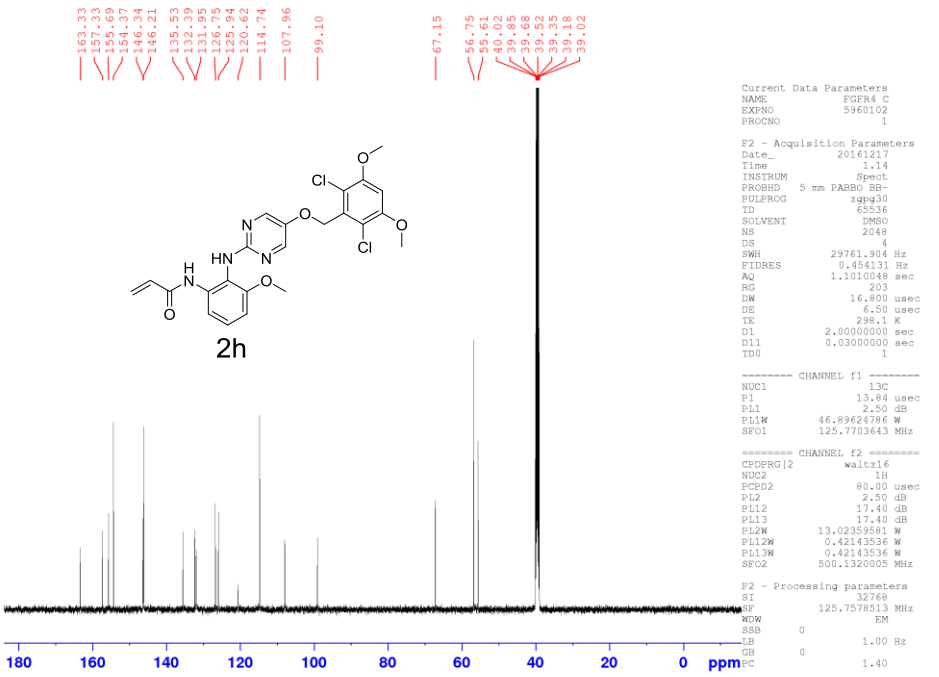
F2 - Acquisition Parameters
Date_               20161208
Time                    6.05
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                       2048
DS                          4
SWH                29761.904 Hz
FIDRES                0.454131 Hz
AQ                  1.1010048 sec
RG                        203
DW                     16.800 usec
DE                      6.50 usec
TE                     298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

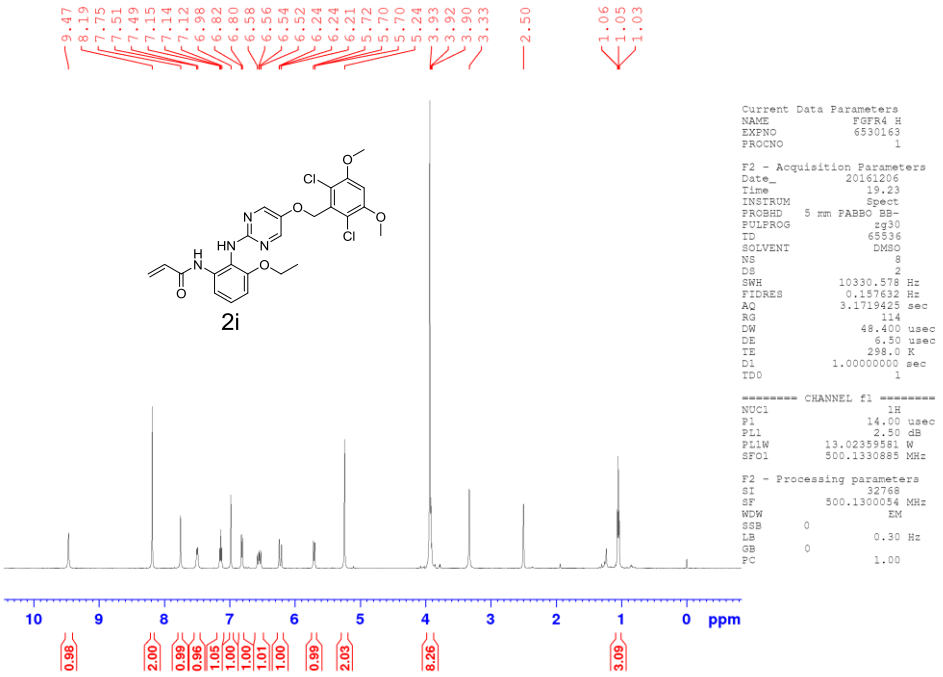
======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                     2.50 dB
PL1W              46.89624786 W
SFO1             125.7703643 MHz

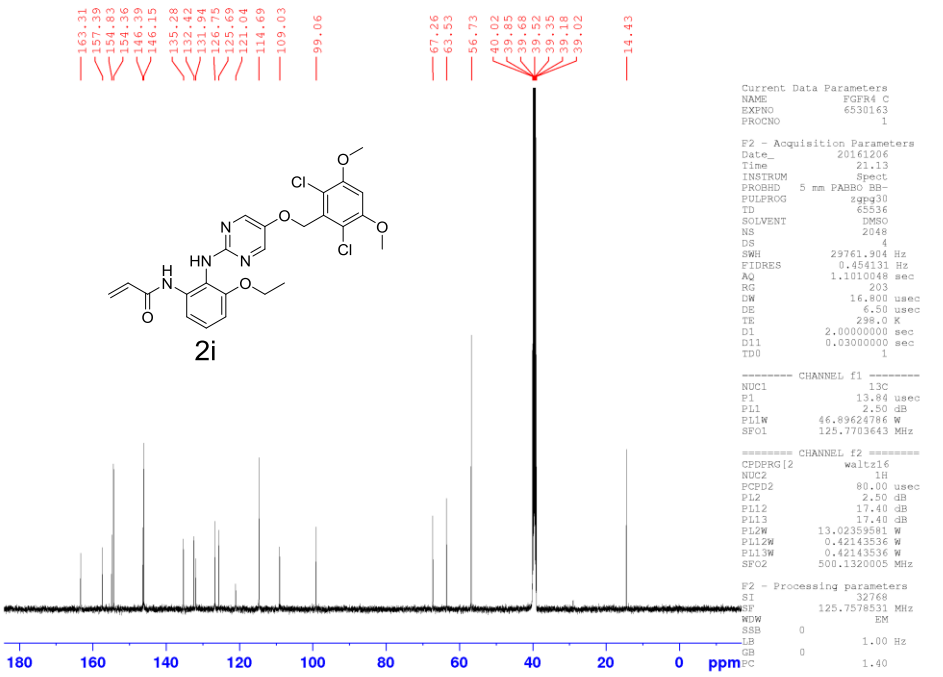
======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                     2.50 dB
PL12                   17.40 dB
PL13                   17.40 dB
PL2W              13.02359581 W
PL12W              0.42143536 W
PL13W              0.42143536 W
SFO2             500.1320005 MHz

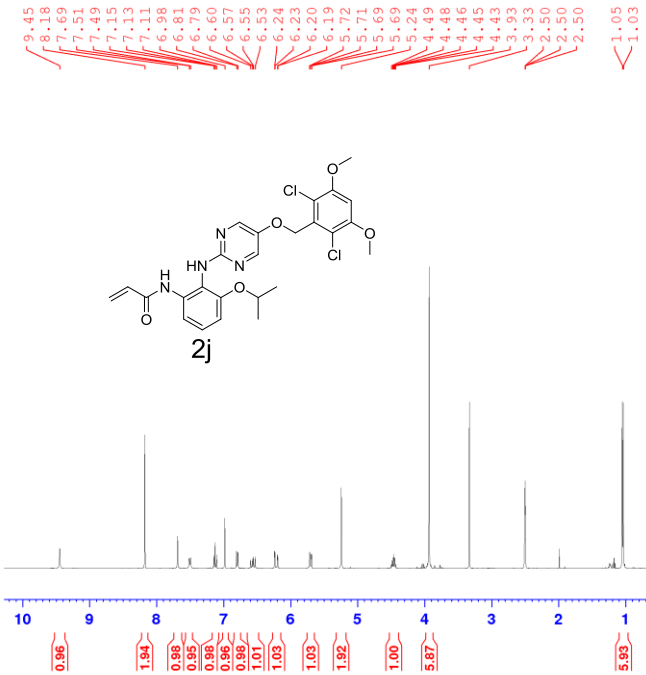
F2 - Processing parameters
SI                        32768
SF                 125.7578522 MHz
WDW                        EM
SSB             0
LB                      1.00 Hz
GB              0
PC                      1.40
```


9.42
8.17
7.81
7.54
7.52
7.20
7.18
7.16
6.99
6.85
6.83
6.57
6.55
6.53
6.50
6.23
6.23
6.19
6.18
5.71
5.71
5.69
5.68
5.23
3.94
3.67
3.33
2.50
2.50
2.50
0.00
Cl
Cl
HN
H
N
O
2h
Current Data Parameters
NAME FGFR4 H
EXPNO 5960102
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170117
Time 18.48
INSTRUM spect
PROBHD 5 mm DUL 13C-1
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9583745 sec
RG 322.8
DW 60.400 usec
DE 6.50 usec
TE 295.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 2.02 0.99 0.98 1.01 0.96 1.02 1.01 1.02 0.99 1.98 6.04 3.03


163.33
157.33
155.69
154.37
146.34
146.21
135.53
132.39
131.95
126.75
125.94
120.62
114.74
107.96
99.10
67.15
56.75
55.61
40.02
39.85
39.68
39.52
39.35
39.18
39.02
Cl
Cl
HN
H
N
O
2h
Current Data Parameters
NAME FGFR4 C
EXPNO 5960102
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161217
Time 1.14
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359981 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578513 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 0 ppm


9.47
8.19
7.75
7.51
7.49
7.15
7.14
7.12
6.98
6.82
6.80
6.58
6.56
6.54
6.52
6.24
6.24
6.21
5.72
5.70
5.70
5.24
3.93
3.92
3.90
3.33
2.50
1.06
1.05
1.03
2i
Current Data Parameters
NAME FGFR4 H
EXPNO 6530163
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161206
Time 19.23
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 114
DW 48.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 2.50 dB
PL1W 13.02359581 W
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 0 ppm
0.98 2.00 0.99 0.96 1.05 1.00 1.00 1.01 1.00 0.99 2.03 8.26 3.09


163.31
157.39
154.83
154.36
146.39
146.15
135.28
132.42
131.94
126.75
125.69
121.04
114.69
109.03
99.06
67.26
63.53
56.73
40.02
39.85
39.68
39.52
39.35
39.18
39.02
14.43
2i
Current Data Parameters
NAME FGFR4 C
EXPNO 6530163
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161206
Time 21.13
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578531 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 0 ppm

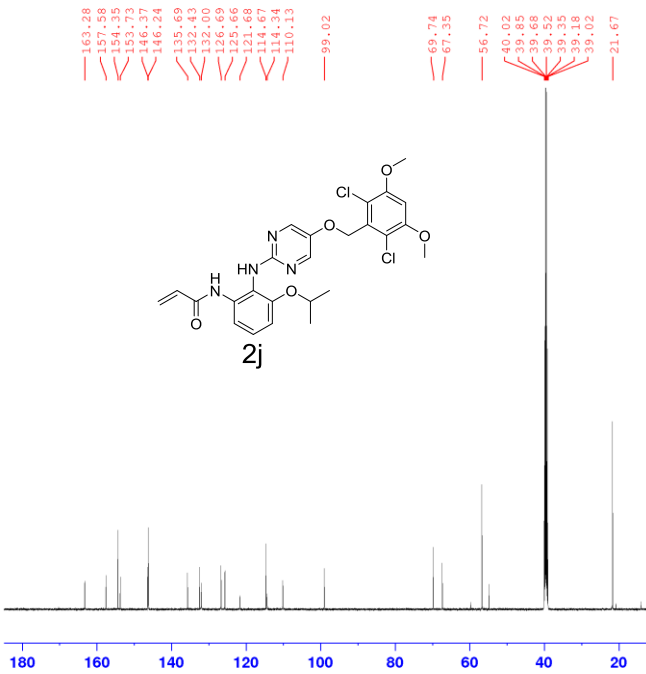



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530173
PROCNO                      1

F2 - Acquisition Parameters
Date_               20170120
Time                   15.21
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                      256
DW                   60.400 usec
DE                    6.50 usec
TE                   295.8 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1             0 dB
PL1W              10.87646866 W
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1300025 MHz
WDW                        EM
SSB             0
LB                      0.30 Hz
GB              0
PC                      1.00
```



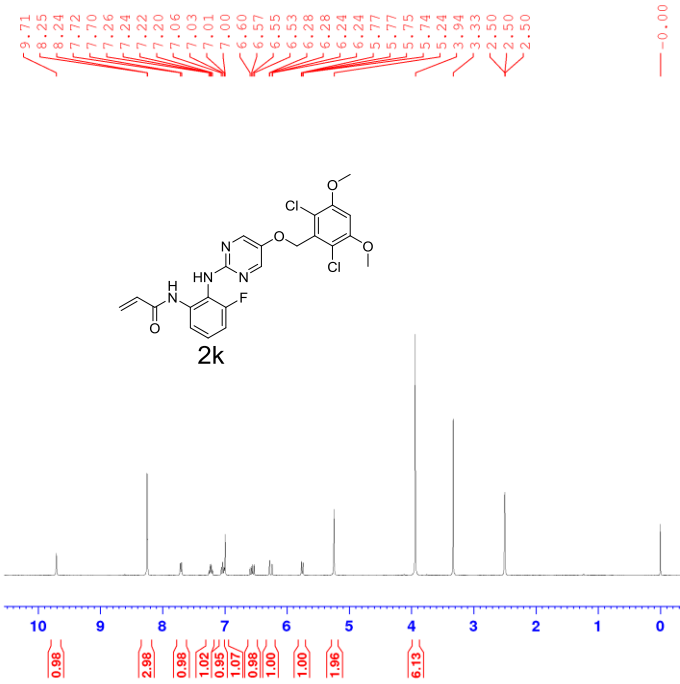

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530173
PROCNO                      1

F2 - Acquisition Parameters
Date_               20161218
Time                   12.39
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                       2048
DS                          4
SWH                29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                        203
DW                   16.800 usec
DE                    6.50 usec
TE                   298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                     2.50 dB
PL1W              46.89624786 W
SFO1             125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2              waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                     2.50 dB
PL12                   17.40 dB
PL13                   17.40 dB
PL2W              13.02359581 W
PL12W              0.42143536 W
PL13W              0.42143536 W
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7578526 MHz
WDW                        EM
SSB             0
LB                      1.00 Hz
GB              0
PC                      1.40
```

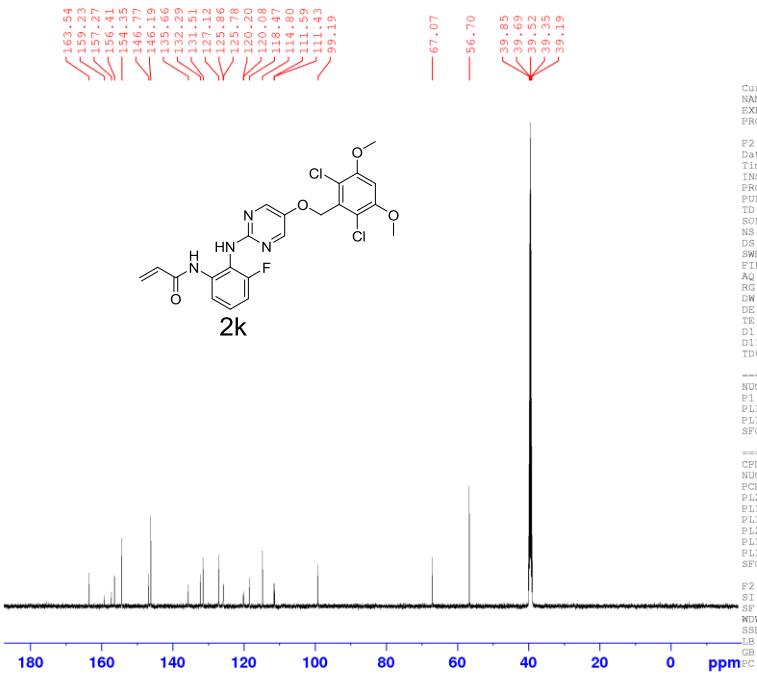



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 5960096
PROCNO                      1

F2 - Acquisition Parameters
Date_              20170119
Time                  15.06
INSTRUM               spect
PROBHD    5 mm DUL 13C-1
PULPROG               zg30
TD                    65536
SOLVENT               DMSO
NS                    16
DS                    2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                 3.9583745 sec
RG                    362
DW                    60.400 usec
DE                    6.50 usec
TE                    296.1 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      1H
P1                     12.58 usec
PL1          0 dB
PL1W           10.87646866 W
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF               400.1300026 MHz
WDW                     EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```



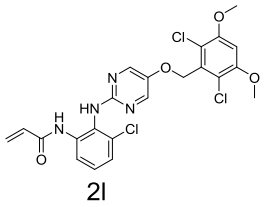

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 5960096
PROCNO                      1

F2 - Acquisition Parameters
Date_              20170121
Time                   2.34
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               DMSO
NS                    697
DS                    4
SWH                29761.904 Hz
FIDRES             0.454131 Hz
AQ                 1.1010048 sec
RG                    203
DW                    16.800 usec
DE                    6.50 usec
TE                    310.3 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                     13C
P1                     8.80 usec
PL1                   -1.00 dB
PL1W          104.98761749 W
SFO1          125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL2                    2.50 dB
PL12                  17.46 dB
PL13                  17.46 dB
PL2W           13.02359581 W
PL12W           0.41565308 W
PL13W           0.41565308 W
SFO2          500.1320005 MHz

F2 - Processing parameters
SI                    32768
SF               125.7578627 MHz
WDW                     EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```



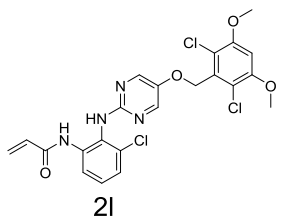
2l


```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 5960090
PROCNO                      1

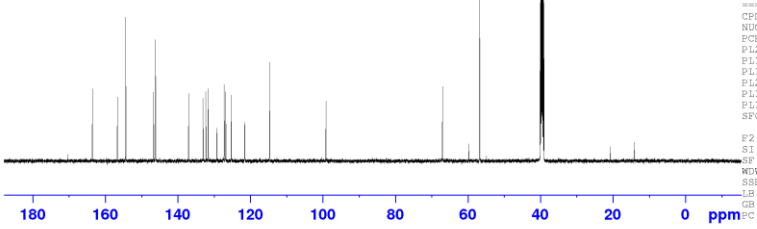
F2 - Acquisition Parameters
Date_               20170119
Time                   15.01
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                     322.8
DW                    60.400 usec
DE                     6.50 usec
TE                    296.1 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     12.58 usec
PL1            0 dB
PL1W             10.87646866 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1300026 MHz
WDW                       EM
SSB            0
LB                     0.30 Hz
GB             0
PC                     1.00
```



2l



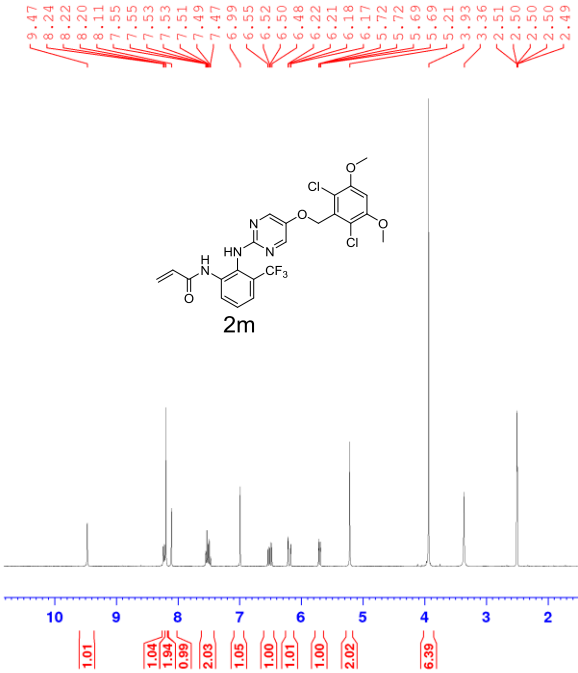

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 5960090
PROCNO                      1

F2 - Acquisition Parameters
Date_               20161211
Time                   19.59
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                      2048
DS                         4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                       203
DW                    16.800 usec
DE                     6.50 usec
TE                    298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     13.84 usec
PL1                    2.50 dB
PL1W            46.89624786 W
SFO1            125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2              waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL2                    2.50 dB
PL12                  17.40 dB
PL13                  17.40 dB
PL2W            13.02359581 W
PL12W            0.42143536 W
PL13W            0.42143536 W
SFO2            500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7578522 MHz
WDW                       EM
SSB            0
LB                     1.00 Hz
GB             0
PC                     1.40
```

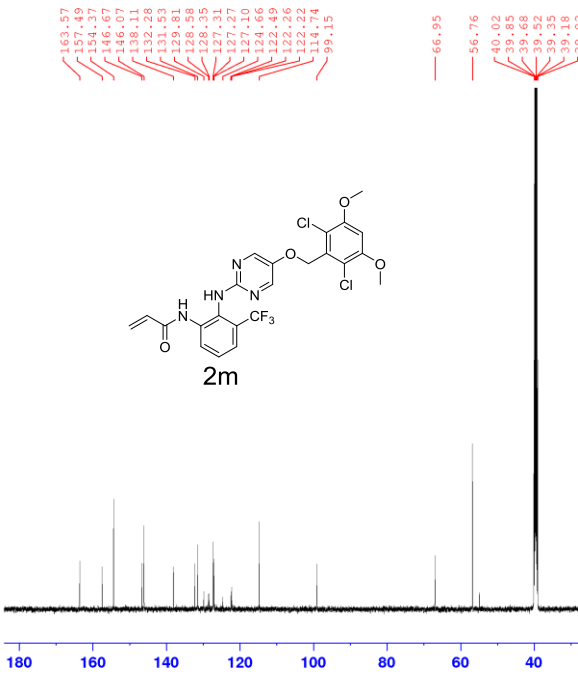



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530188
PROCNO                      1

F2 - Acquisition Parameters
Date_              20170120
Time                   15.26
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                      362
DW                   60.400 usec
DE                    6.50 usec
TE                   295.8 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1             0 dB
PL1W              10.87646866 W
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1300025 MHz
WDW                        EM
SSB             0
LB                      0.30 Hz
GB              0
PC                      1.00
```



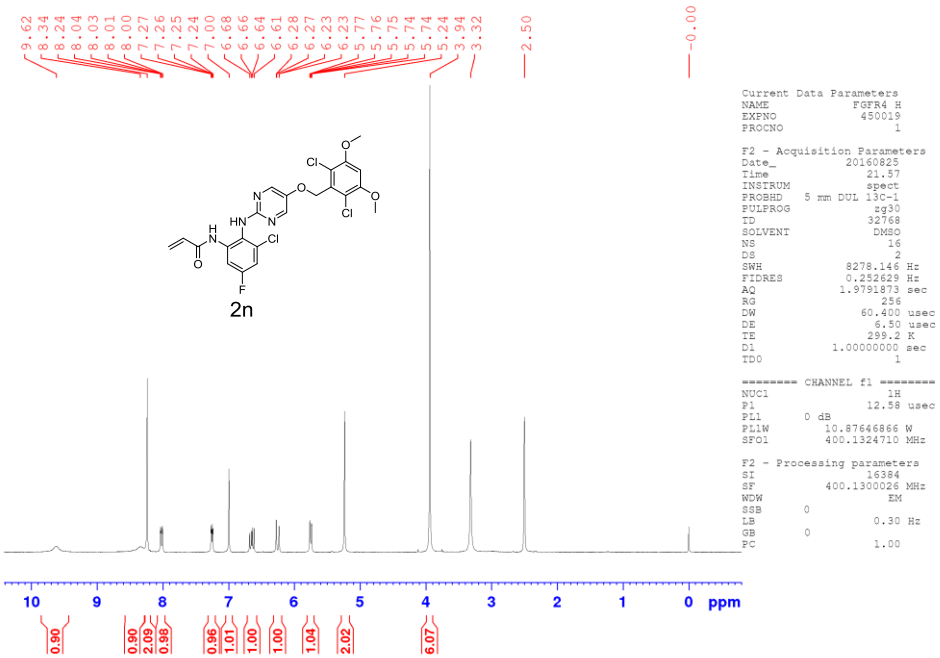

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530188
PROCNO                      1

F2 - Acquisition Parameters
Date_              20161210
Time                    7.46
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      2048
DS                         4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                      203
DW                   16.800 usec
DE                    6.50 usec
TE                   298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                      2.50 dB
PL1W              46.89624786 W
SFO1             125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2              waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                      2.50 dB
PL12                    17.40 dB
PL13                    17.40 dB
PL2W              13.02359581 W
PL12W              0.42143536 W
PL13W              0.42143536 W
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7578520 MHz
WDW                        EM
SSB             0
LB                      1.00 Hz
GB              0
PC                      1.40
```

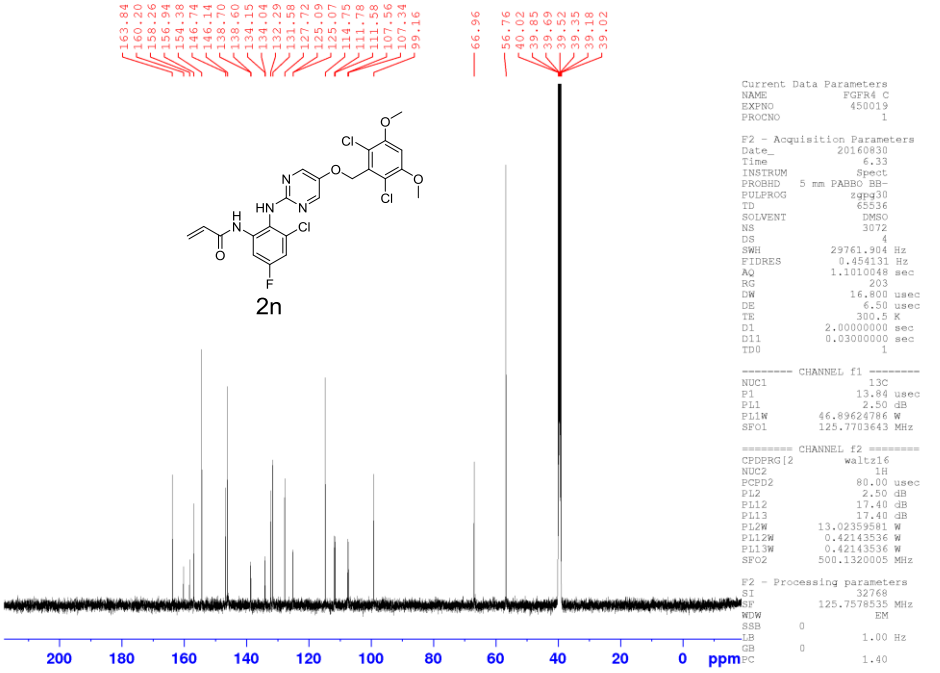



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                  450019
PROCNO                      1

F2 - Acquisition Parameters
Date_               20160825
Time                   21.57
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    32768
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.252629 Hz
AQ                 1.9791873 sec
RG                      256
DW                   60.400 usec
DE                    6.50 usec
TE                   299.2 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1             0 dB
PL1W             10.87646866 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                      16384
SF                 400.1300026 MHz
WDW                        EM
SSB             0
LB                      0.30 Hz
GB              0
PC                      1.00
```



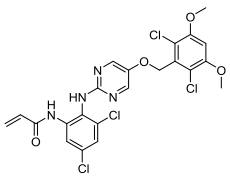

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                  450019
PROCNO                      1

F2 - Acquisition Parameters
Date_               20160830
Time                    6.33
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      3072
DS                         4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                      203
DW                   16.800 usec
DE                    6.50 usec
TE                   300.5 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       13C
P1                      13.84 usec
PL1                    2.50 dB
PL1W            46.89624786 W
SFO1            125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                    2.50 dB
PL12                  17.40 dB
PL13                  17.40 dB
PL2W            13.02359581 W
PL12W            0.42143536 W
PL13W            0.42143536 W
SFO2            500.1320005 MHz

F2 - Processing parameters
SI                      32768
SF                 125.7578535 MHz
WDW                        EM
SSB             0
LB                      1.00 Hz
GB              0
PC                      1.40
```



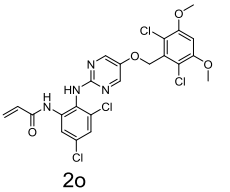
2o


```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530148
PROCNO                      1

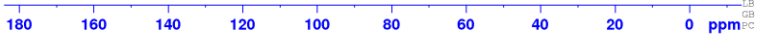
F2 - Acquisition Parameters
Date_               20170120
Time                   12.54
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                     322.8
DW                    60.400 usec
DE                     6.50 usec
TE                    295.9 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     12.58 usec
PL1             0 dB
PL1W              10.87646866 W
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                400.1300000 MHz
WDW                       EM
SSB             0
LB                     0.30 Hz
GB              0
PC                     1.00
```



2o



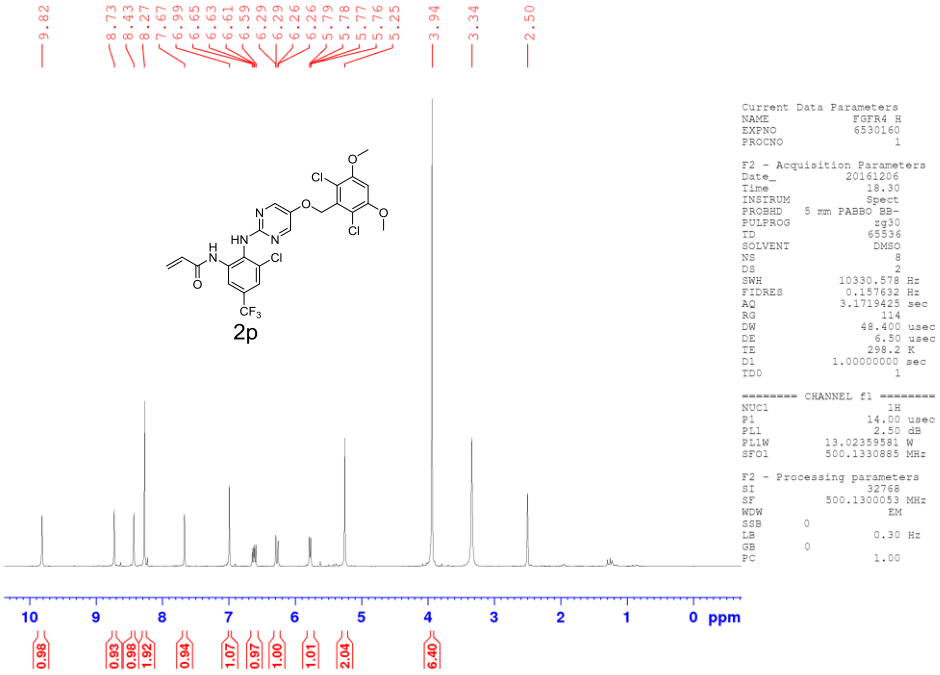

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530148
PROCNO                      1

F2 - Acquisition Parameters
Date_               20161217
Time                    3.13
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      2048
DS                         4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                       203
DW                    16.800 usec
DE                     6.50 usec
TE                    298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     13.84 usec
PL1                    2.50 dB
PL1W              46.89624786 W
SFO1             125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2              waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL2                    2.50 dB
PL12                  17.40 dB
PL13                  17.40 dB
PL2W              13.02359581 W
PL12W              0.42143536 W
PL13W              0.42143536 W
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF               125.7578519 MHz
WDW                       EM
SSB             0
LB                     1.00 Hz
GB              0
PC                     1.40
```

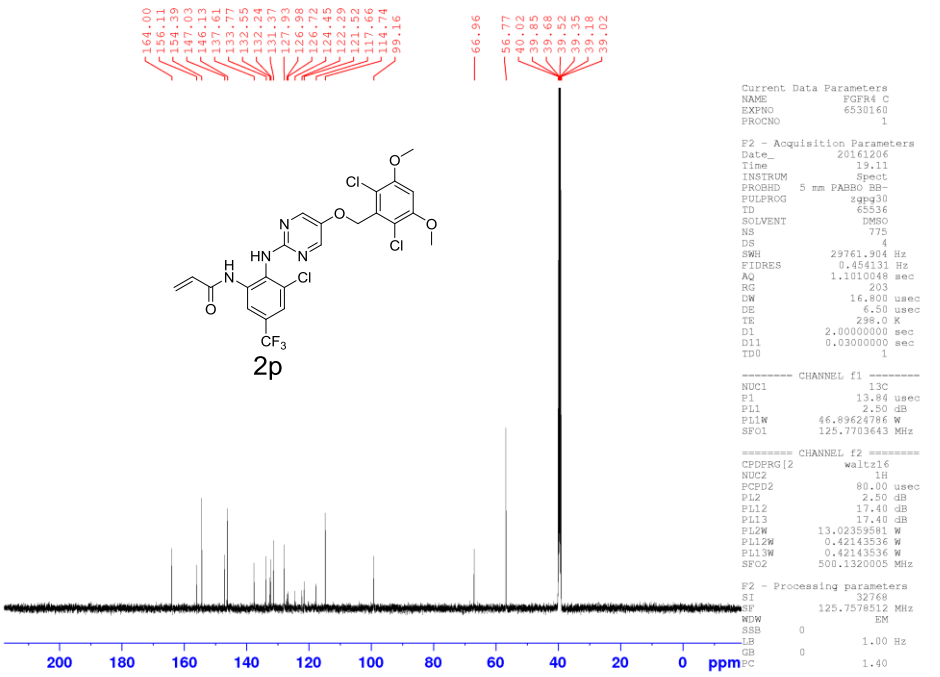



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530160
PROCNO                      1

F2 - Acquisition Parameters
Date_               20161206
Time                   18.30
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        8
DS                        2
SWH               10330.578 Hz
FIDRES                0.157632 Hz
AQ                    3.1719425 sec
RG                      114
DW                     48.400 usec
DE                      6.50 usec
TE                     298.2 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      14.00 usec
PL1                      2.50 dB
PL1W               13.02359581 W
SFO1               500.1330885 MHz

F2 - Processing parameters
SI                        32768
SF                 500.1300053 MHz
WDW                        EM
SSB           0
LB                      0.30 Hz
GB            0
PC                      1.00
```



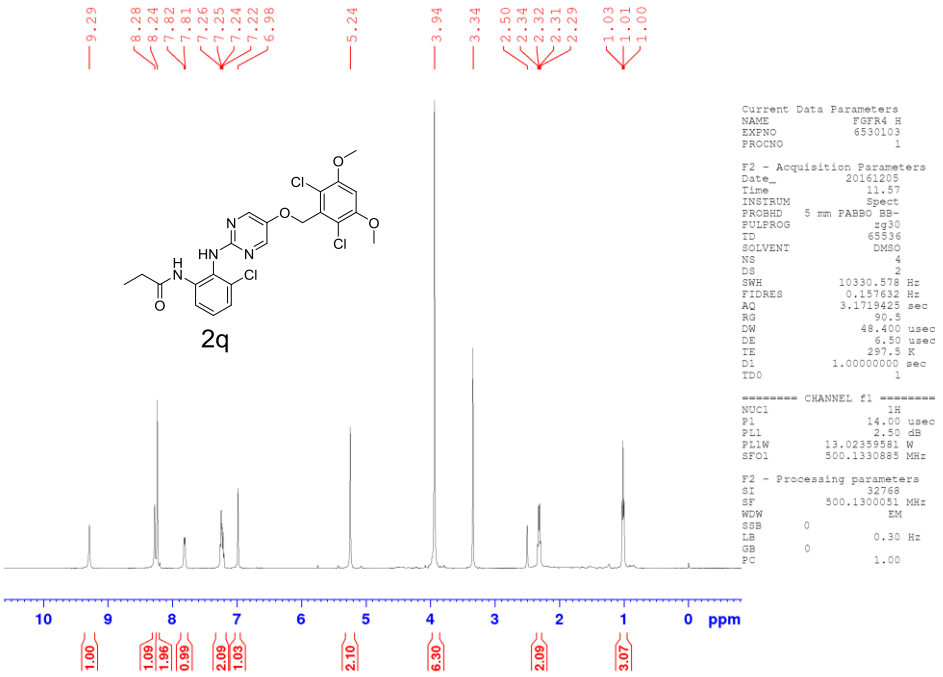

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530160
PROCNO                      1

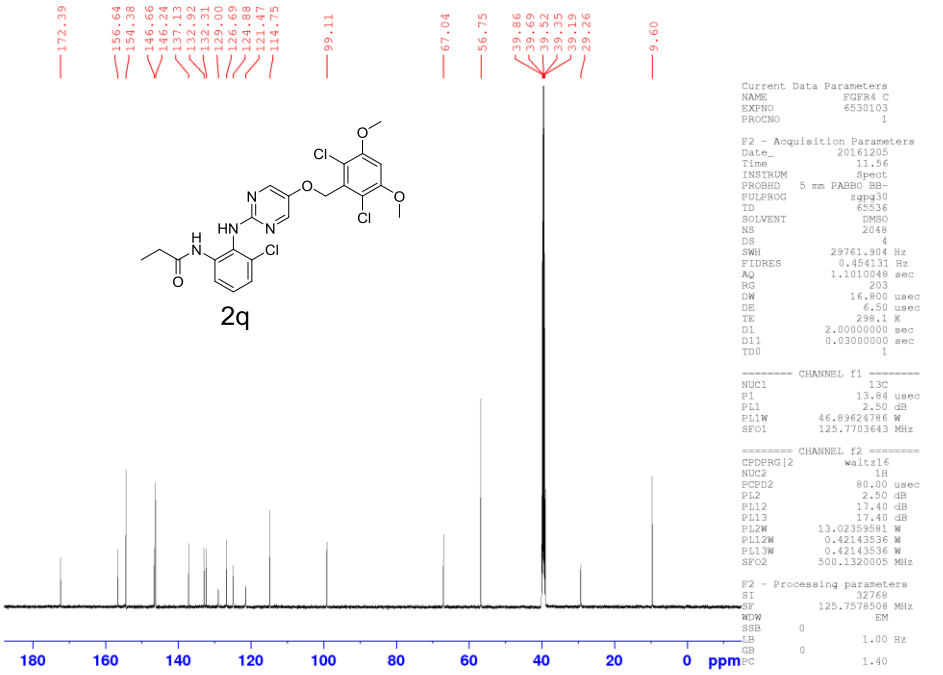
F2 - Acquisition Parameters
Date_               20161206
Time                   19.11
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                      775
DS                        4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                    1.1010048 sec
RG                      203
DW                     16.800 usec
DE                      6.50 usec
TE                     298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

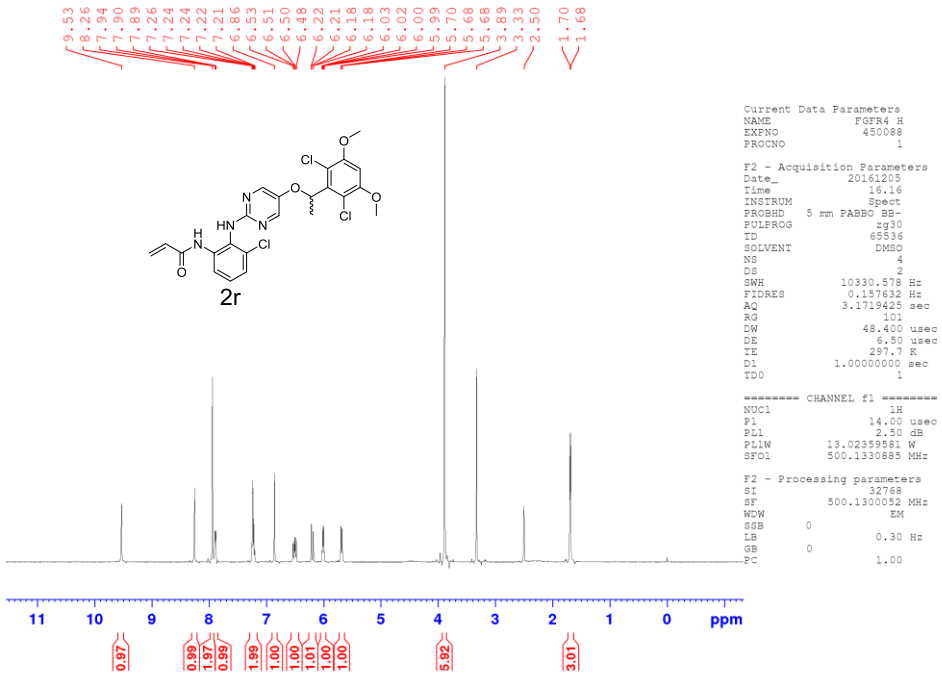
======== CHANNEL f1 ========
NUC1                       13C
P1                      13.84 usec
PL1                      2.50 dB
PL1W               46.89624786 W
SFO1               125.7703643 MHz

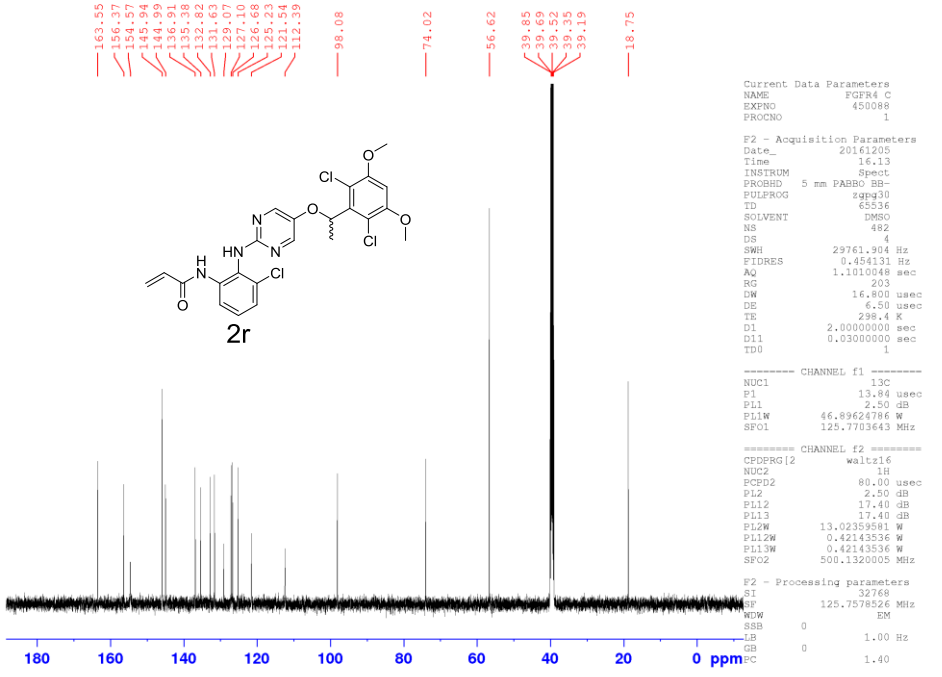
======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                      2.50 dB
PL12                    17.40 dB
PL13                    17.40 dB
PL2W               13.02359581 W
PL12W               0.42143536 W
PL13W               0.42143536 W
SFO2               500.1320005 MHz

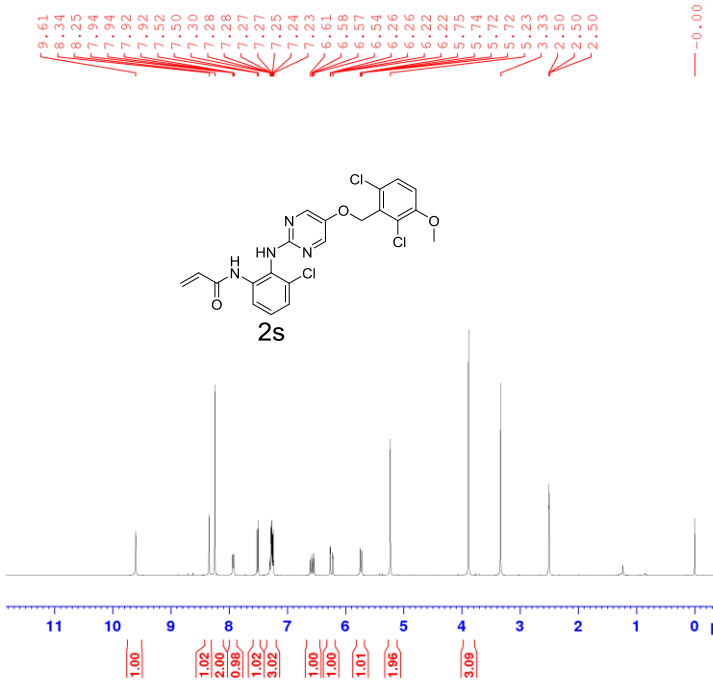
F2 - Processing parameters
SI                        32768
SF                 125.7578512 MHz
WDW                        EM
SSB           0
LB                      1.00 Hz
GB            0
PC                      1.40
```


9.29
8.28
8.24
7.82
7.81
7.26
7.25
7.24
7.22
6.98
5.24
3.94
3.34
2.50
2.34
2.32
2.31
2.29
1.03
1.01
1.00
2q
Current Data Parameters
NAME FGFR4 H
EXPNO 6530103
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161205
Time 11.57
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 4
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 80.8
DW 48.400 usec
DE 6.50 usec
TE 297.5 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 2.50 dB
PL1W 13.02359581 W
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300051 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.09 1.96 0.99 2.09 1.03 2.10 6.30 2.09 3.07


172.39
156.64
154.38
146.66
146.24
137.13
132.92
132.31
129.00
126.69
124.88
121.47
114.75
99.11
67.04
56.75
39.86
39.69
39.52
39.35
39.19
29.26
9.60
2q
Current Data Parameters
NAME FGFR4 C
EXPNO 6530103
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161205
Time 11.56
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578508 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 0 ppm


9.53
8.26
7.94
7.90
7.89
7.26
7.24
7.24
7.22
7.21
6.86
6.53
6.51
6.50
6.48
6.22
6.21
6.18
6.18
6.03
6.02
6.00
5.99
5.70
5.68
5.68
3.89
3.33
2.50
1.70
1.68
2r
Current Data Parameters
NAME FGFR4 H
EXPNO 450088
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161205
Time 16.16
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 4
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 101
DW 48.400 usec
DE 6.50 usec
TE 297.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 2.50 dB
PL1W 13.02359581 W
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300052 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.97 0.99 1.97 0.99 1.99 1.00 1.00 1.01 1.00 1.00 5.92 3.01


163.55
156.37
154.57
145.94
144.99
136.31
132.82
131.63
129.07
127.10
126.68
125.23
121.54
112.39
98.08
74.02
56.62
39.85
39.69
39.52
39.35
39.19
18.75
2r
Current Data Parameters
NAME FGFR4 C
EXPNO 450088
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161205
Time 16.13
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 482
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578526 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 0 ppm

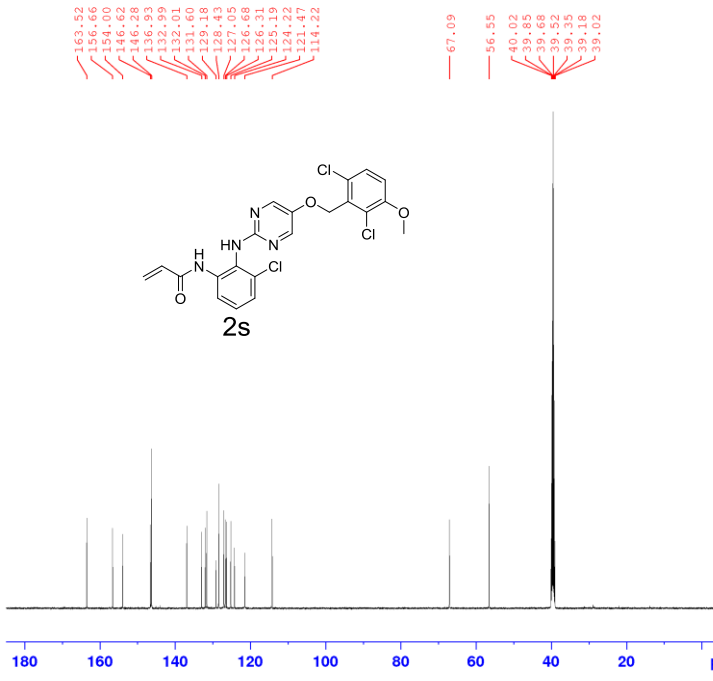



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530105
PROCNO                      1

F2 - Acquisition Parameters
Date_              20170119
Time                  15.11
INSTRUM               spect
PROBHD    5 mm DUL 13C-1
PULPROG               zg30
TD                    65536
SOLVENT               DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                      256
DW                   60.400 usec
DE                    6.50 usec
TE                   296.1 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1            0 dB
PL1W            10.87646866 W
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1300027 MHz
WDW                        EM
SSB            0
LB                      0.30 Hz
GB             0
PC                      1.00
```



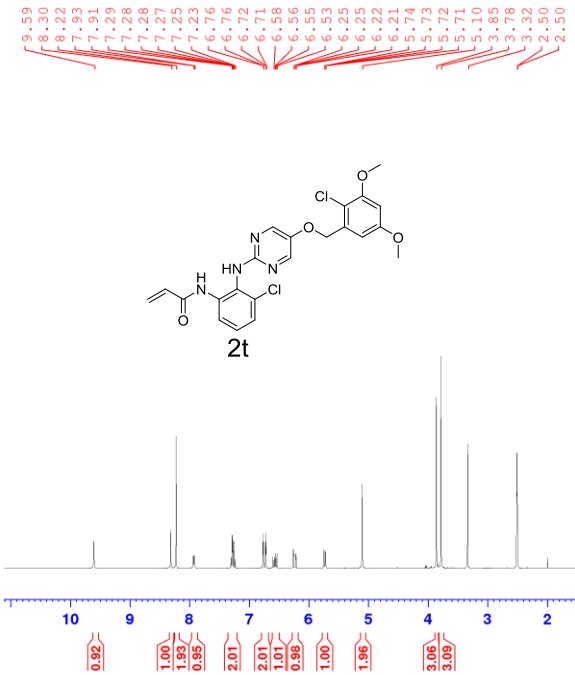

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530105
PROCNO                      1

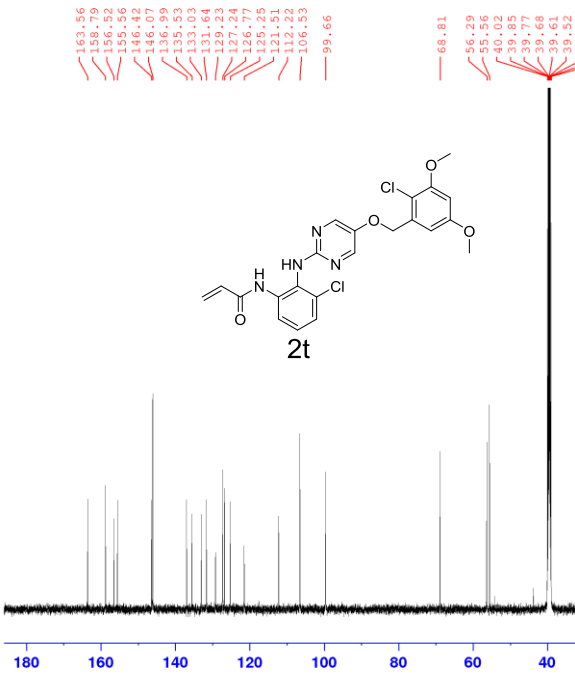
F2 - Acquisition Parameters
Date_              20170123
Time                   6.03
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               DMSO
NS                     2364
DS                        4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                      203
DW                   16.800 usec
DE                    6.50 usec
TE                   310.1 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

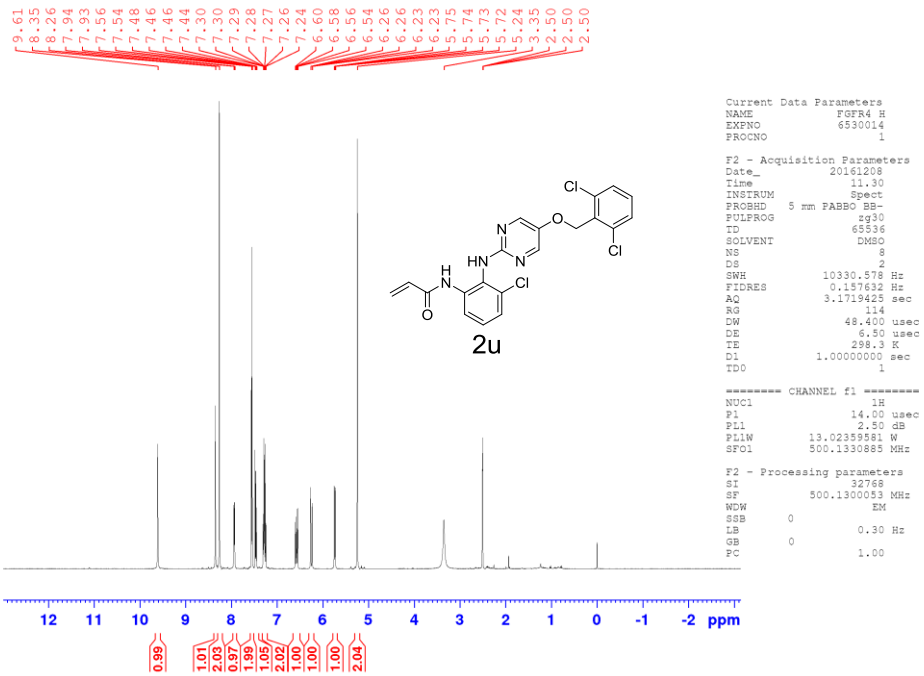
======== CHANNEL f1 ========
NUC1                      13C
P1                      8.80 usec
PL1                    -1.00 dB
PL1W           104.98761749 W
SFO1           125.7703643 MHz

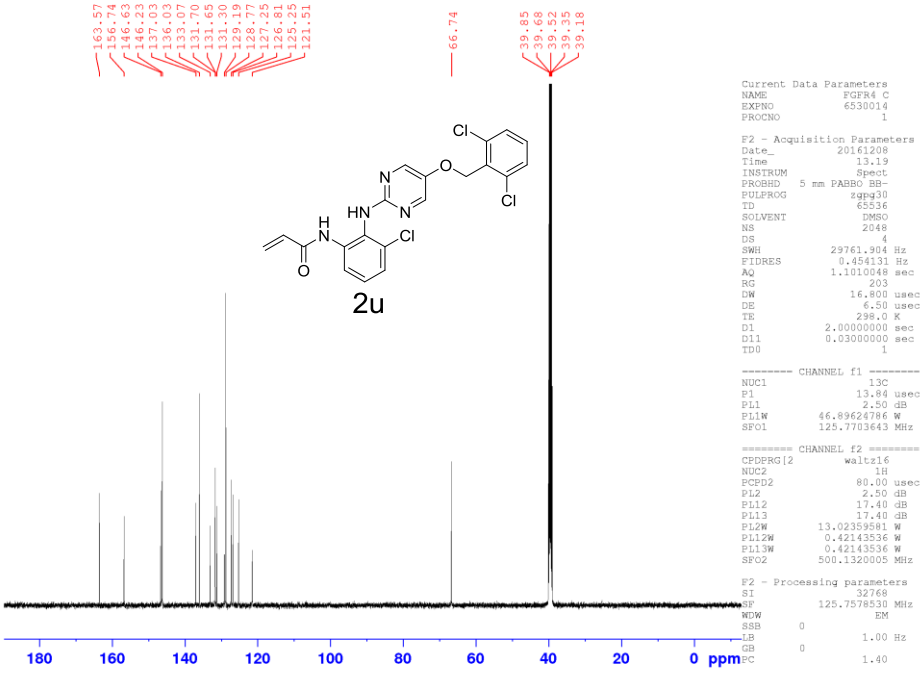
======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                       1H
PCPD2                 80.00 usec
PL2                    2.50 dB
PL12                  17.46 dB
PL13                  17.46 dB
PL2W           13.02359581 W
PL12W           0.41565308 W
PL13W           0.41565308 W
SFO2           500.1320005 MHz

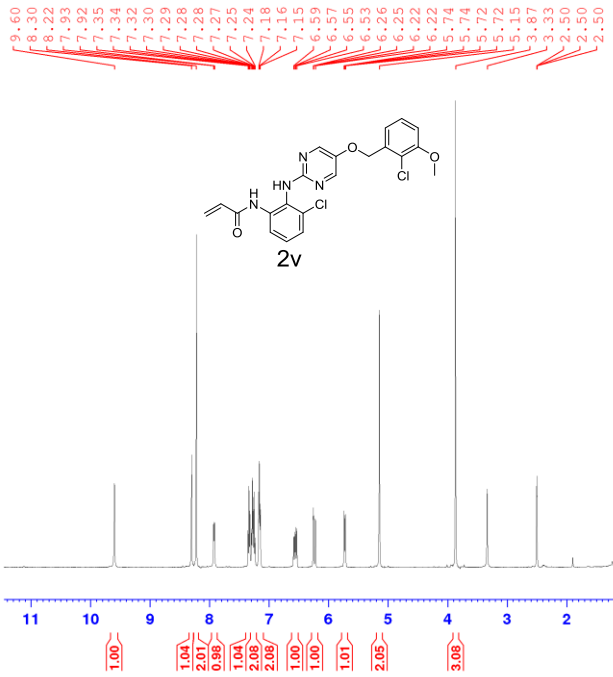
F2 - Processing parameters
SI                        32768
SF                 125.7578629 MHz
WDW                        EM
SSB            0
LB                      1.00 Hz
GB             0
PC                      1.40
```


9.59
8.30
8.22
7.93
7.91
7.29
7.28
7.28
7.27
7.25
7.23
6.76
6.76
6.72
6.71
6.58
6.56
6.55
6.53
6.25
6.22
6.21
5.74
5.73
5.72
5.71
5.10
3.85
3.78
3.32
2.50
2.50
Cl
O
N
HN
N
H
N
Cl
O
O
2t
Current Data Parameters
NAME FGFR4 H
EXPNO 6530016
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170120
Time 12.44
INSTRUM spect
PROBHD 5 mm DUL 13C-1
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9583745 sec
RG 362
DW 60.400 usec
DE 6.50 usec
TE 295.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10 9 8 7 6 5 4 3 2 1 0 ppm
0.92 1.00 1.93 0.95 2.01 2.01 1.01 0.98 1.00 1.96 3.06 3.09


163.56
158.79
156.52
155.56
146.42
146.07
136.99
135.53
133.03
131.64
129.23
127.24
126.77
125.25
121.51
112.22
106.53
99.66
68.81
56.29
55.56
40.02
39.85
39.77
39.68
39.61
39.52
39.35
39.18
39.02
Cl
O
N
HN
N
H
N
Cl
O
O
2t
Current Data Parameters
NAME FGFR4 C
EXPNO 6530016
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161211
Time 16.15
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578526 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 ppm


9.61
8.35
8.26
7.94
7.93
7.56
7.54
7.48
7.46
7.46
7.44
7.30
7.30
7.29
7.28
7.27
7.26
7.24
6.60
6.58
6.56
6.54
6.26
6.26
6.23
6.23
5.75
5.74
5.73
5.72
5.24
3.35
2.50
2.50
2.50
2u
Current Data Parameters
NAME FGFR4 H
EXPNO 6530014
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161208
Time 11.30
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 114
DW 48.400 usec
DE 6.50 usec
TE 298.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 2.50 dB
PL1W 13.02359581 W
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300053 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
0.99 1.01 2.03 0.97 1.99 1.05 2.02 1.00 1.00 1.00 2.04


163.57
156.74
146.63
146.23
137.03
136.03
133.07
131.70
131.65
131.30
129.19
128.77
127.25
126.81
125.25
121.51
66.74
39.85
39.68
39.52
39.35
39.18
2u
Current Data Parameters
NAME FGFR4 C
EXPNO 6530014
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161208
Time 13.19
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578530 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 0 ppm

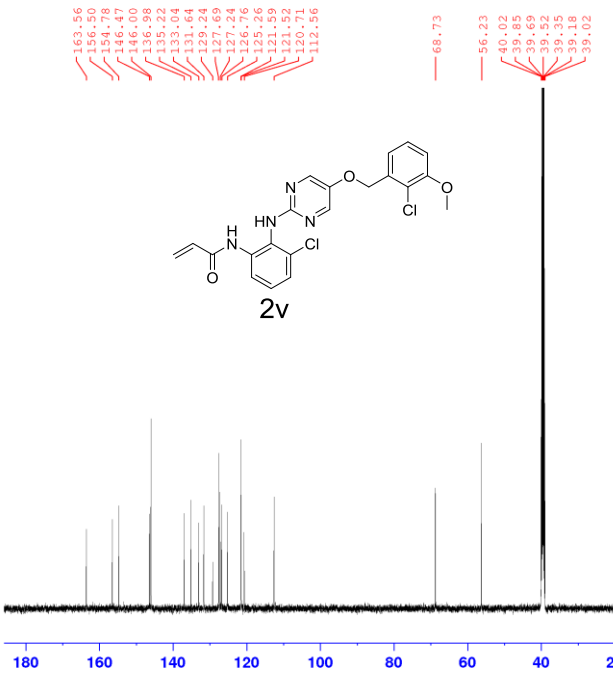



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530036
PROCNO                      1

F2 - Acquisition Parameters
Date_              20161206
Time                  17.32
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        8
DS                        2
SWH               10330.578 Hz
FIDRES                0.157632 Hz
AQ                    3.1719425 sec
RG                      114
DW                    48.400 usec
DE                     6.50 usec
TE                    298.0 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      14.00 usec
PL1                      2.50 dB
PL1W               13.02359581 W
SFO1              500.1330885 MHz

F2 - Processing parameters
SI                        32768
SF                500.1300052 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```



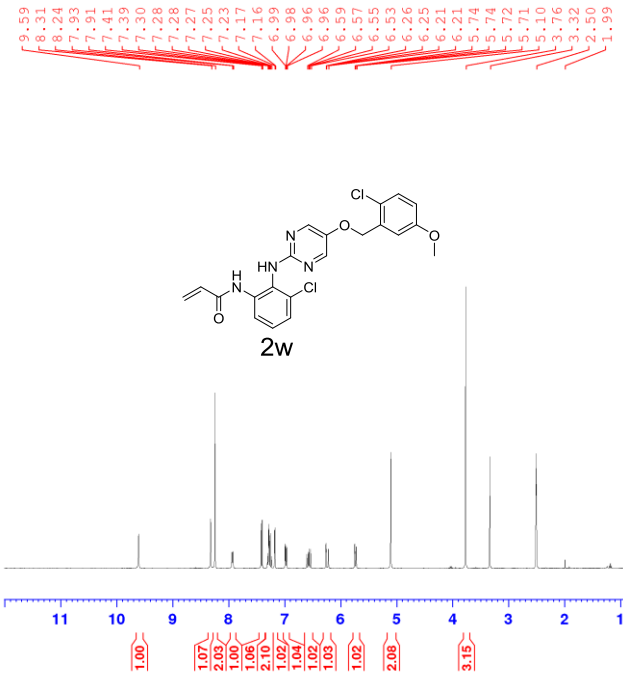

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530036
PROCNO                      1

F2 - Acquisition Parameters
Date_              20161206
Time                  18.25
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                      974
DS                        4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                    1.1010048 sec
RG                      203
DW                    16.800 usec
DE                     6.50 usec
TE                    298.1 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                      2.50 dB
PL1W               46.89624786 W
SFO1              125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2              waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                      2.50 dB
PL12                    17.40 dB
PL13                    17.40 dB
PL2W               13.02359581 W
PL12W               0.42143536 W
PL13W               0.42143536 W
SFO2              500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                125.7578532 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

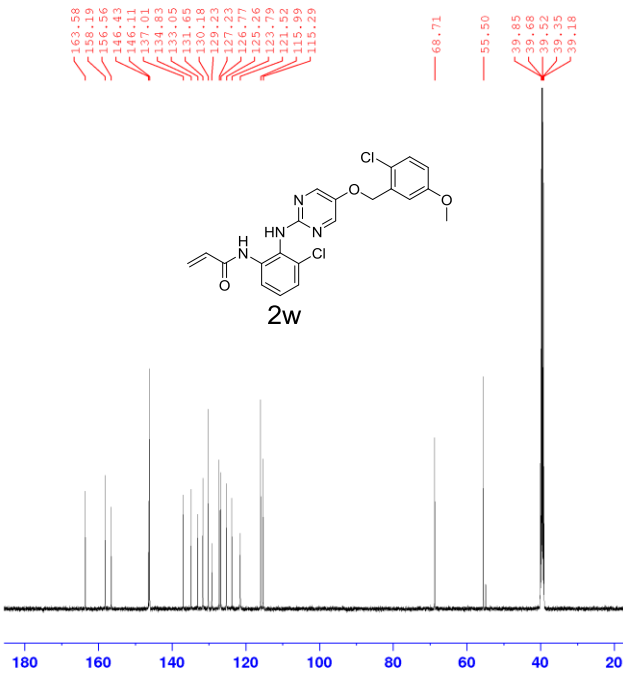



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530012
PROCNO                      1

F2 - Acquisition Parameters
Date_              20170120
Time                  12.39
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                     322.8
DW                    60.400 usec
DE                     6.50 usec
TE                    295.9 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1             0 dB
PL1W              10.87646866 W
SFO1             400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1300000 MHz
WDW                        EM
SSB             0
LB                       0.30 Hz
GB              0
PC                       1.00
```



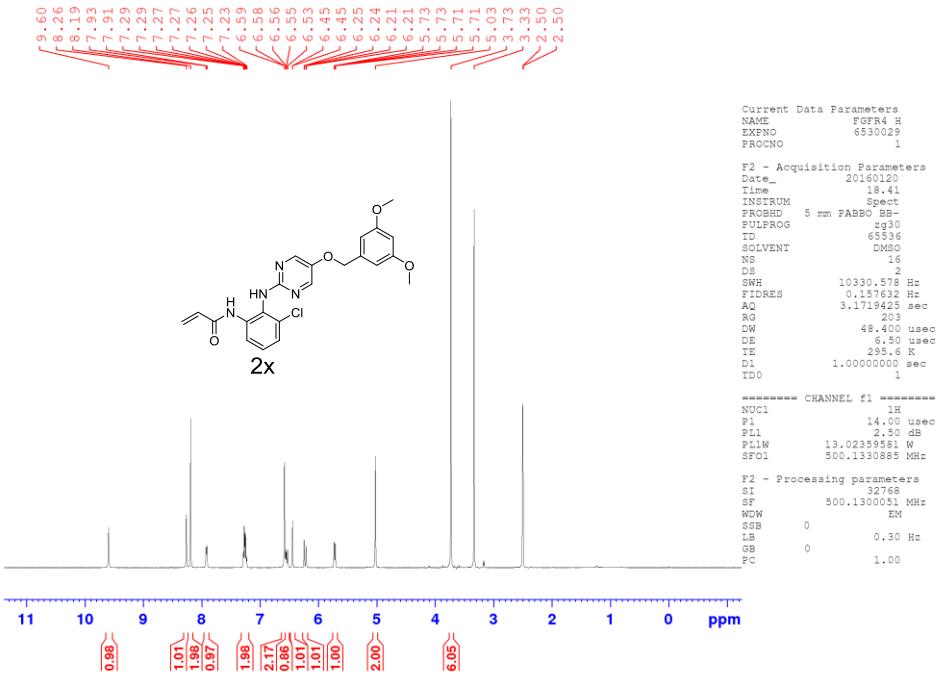

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530012
PROCNO                      1

F2 - Acquisition Parameters
Date_              20161208
Time                  15.52
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      1708
DS                         4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                       203
DW                    16.800 usec
DE                     6.50 usec
TE                    298.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                      2.50 dB
PL1W              46.89624786 W
SFO1             125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                      2.50 dB
PL12                    17.40 dB
PL13                    17.40 dB
PL2W              13.02359981 W
PL12W              0.42143536 W
PL13W              0.42143536 W
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7578520 MHz
WDW                        EM
SSB             0
LB                       1.00 Hz
GB              0
PC                       1.40
```

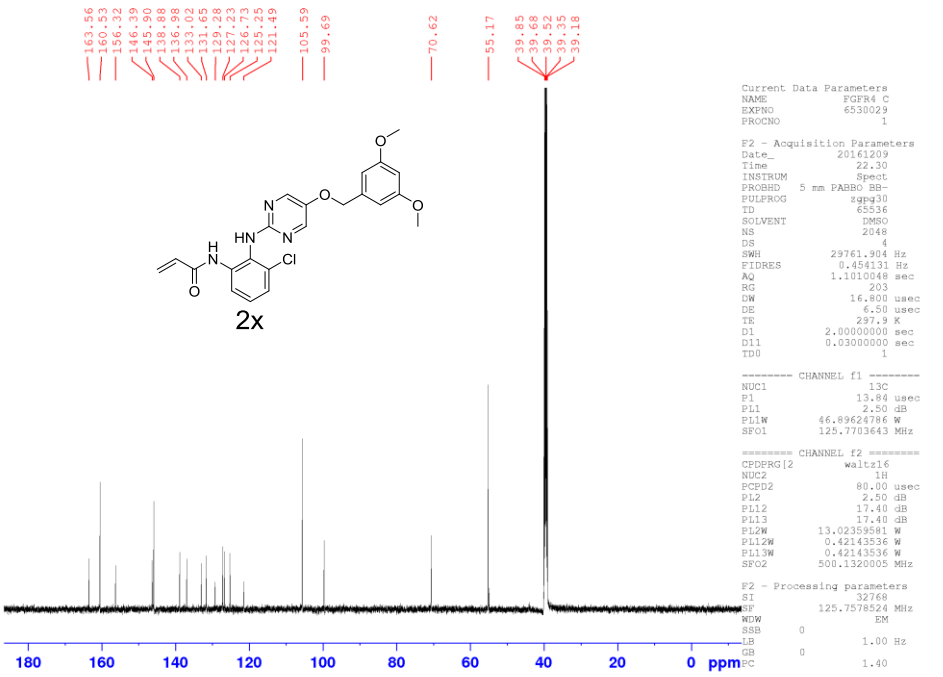



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530029
PROCNO                      1

F2 - Acquisition Parameters
Date_              20160120
Time                   18.41
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH               10330.578 Hz
FIDRES             0.157632 Hz
AQ                 3.1719425 sec
RG                      203
DW                   48.400 usec
DE                    6.50 usec
TE                   295.6 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      14.00 usec
PL1                      2.50 dB
PL1W               13.02359581 W
SFO1              500.1330885 MHz

F2 - Processing parameters
SI                        32768
SF                500.1300051 MHz
WDW                         EM
SSB          0
LB                       0.30 Hz
GB           0
PC                       1.00
```



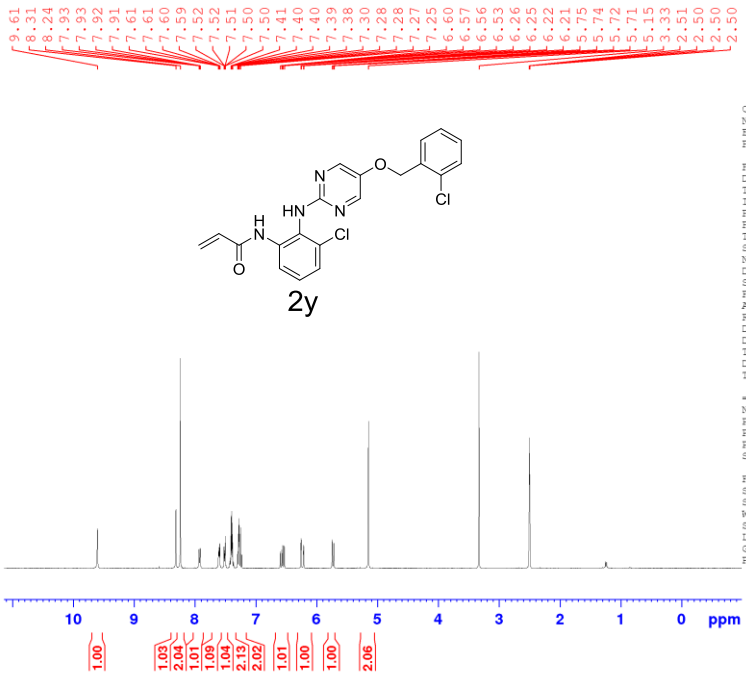

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530029
PROCNO                      1

F2 - Acquisition Parameters
Date_              20161209
Time                   22.30
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                     2048
DS                        4
SWH               29761.904 Hz
FIDRES             0.454131 Hz
AQ                 1.1010048 sec
RG                      203
DW                   16.800 usec
DE                    6.50 usec
TE                   297.9 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                      2.50 dB
PL1W              46.89624786 W
SFO1             125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                   80.00 usec
PL2                      2.50 dB
PL12                    17.40 dB
PL13                    17.40 dB
PL2W               13.02359581 W
PL12W               0.42143536 W
PL13W               0.42143536 W
SFO2              500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                125.7578524 MHz
WDW                         EM
SSB          0
LB                       1.00 Hz
GB           0
PC                       1.40
```

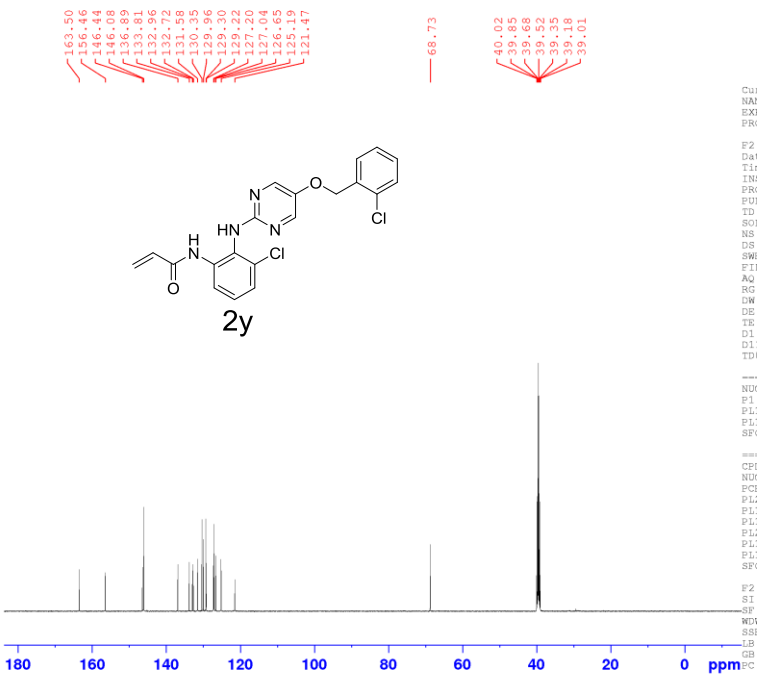



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530100
PROCNO                      1

F2 - Acquisition Parameters
Date_              20170120
Time                   15.16
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                      362
DW                   60.400 usec
DE                    6.50 usec
TE                   295.8 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1            0 dB
PL1W             10.87646866 W
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1300026 MHz
WDW                        EM
SSB            0
LB                      0.30 Hz
GB             0
PC                      1.00
```



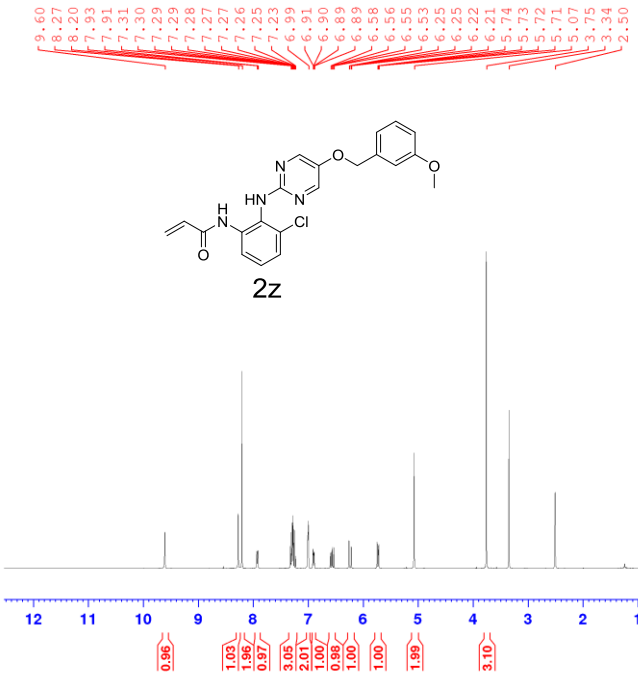

```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                 6530100
PROCNO                      1

F2 - Acquisition Parameters
Date_              20170121
Time                   22.41
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                     3072
DS                        4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                      203
DW                   16.800 usec
DE                    6.50 usec
TE                   310.2 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      8.80 usec
PL1                    -1.00 dB
PL1W            104.98761749 W
SFO1            125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                     2.50 dB
PL12                   17.46 dB
PL13                   17.46 dB
PL2W            13.02359581 W
PL12W            0.41565308 W
PL13W            0.41565308 W
SFO2            500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7578646 MHz
WDW                        EM
SSB            0
LB                      1.00 Hz
GB             0
PC                      1.40
```

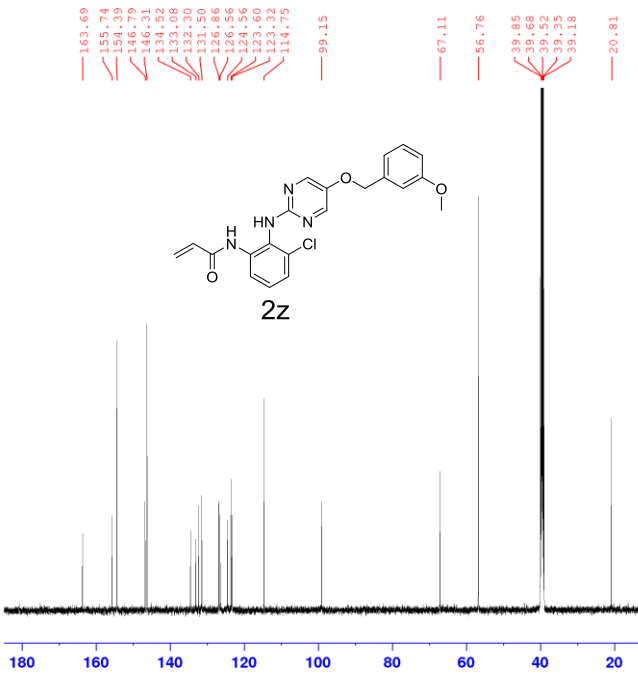



```
Current Data Parameters
NAME                  FGFR4 H
EXPNO                 6530073
PROCNO                      1

F2 - Acquisition Parameters
Date_               20170120
Time                   12.49
INSTRUM                spect
PROBHD    5 mm DUL 13C-1
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES                0.126314 Hz
AQ                 3.9583745 sec
RG                     228.1
DW                    60.400 usec
DE                     6.50 usec
TE                    295.9 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.58 usec
PL1                 0 dB
PL1W               10.87646866 W
SFO1              400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                 400.1300000 MHz
WDW                        EM
SSB                 0
LB                      0.30 Hz
GB                  0
PC                      1.00
```




```
Current Data Parameters
NAME                  FGFR4 C
EXPNO                  450073
PROCNO                      1

F2 - Acquisition Parameters
Date_               20161206
Time                   23.40
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG              zgpg30
TD                    65536
SOLVENT                DMSO
NS                       2048
DS                          4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                 1.1010048 sec
RG                      203
DW                    16.800 usec
DE                     6.50 usec
TE                    298.1 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      13.84 usec
PL1                    2.50 dB
PL1W              46.89624786 W
SFO1             125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                    2.50 dB
PL12                  17.40 dB
PL13                  17.40 dB
PL2W              13.02359581 W
PL12W              0.42143536 W
PL13W              0.42143536 W
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                 125.7578512 MHz
WDW                        EM
SSB                 0
LB                      1.00 Hz
GB                  0
PC                      1.40
```