Discovery of Small Molecule Kappa Opioid Receptor Agonist and Antagonist Chemotypes through a HTS and Hit Refinement Strategy

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Supporting Information Contents:

PDSP Binding Data (numerical K_i values)

CMPD	5ht1a	5ht1b	5ht1d	5ht1e	5ht2a	5ht2b	5ht2c	5ht3	5ht5a	5ht6	5ht7	Alpha1A	Alpha1B	Alpha1D	Alpha2A	Alpha2B	Alpha2C	Beta1	Beta2	Beta3	BZP Rat Brain Site	D1
1{1}																						
2{8}					3,788	1,237			4,986							5,525	9,601			7,312		1,796
3{1}	8,577				3,332	598	4,112		5,442		1,990					1,451	957					
3{39}					2,884	2,269																
4{4}			702			1,922										5,525	9,601					

CMPD	D2	D3	D4	D5	DAT	DOR	GabaA	H1	H2	H3	H4	KOR	M1	M2	M3	M4	M5	MOR	NET	SERT	Sigma 1	Sigma 2
1{1}						1,277						0.6						564				
2{8}				7,018	ND	5,351						2.4					4,418	1,900	5,870			2,905
3{1}		1,234			2,550	1,088		961	4,162			50.4	278	80	284	196	3,726	306	349		379	2,136
3{39}					2,584			9,854				68	4,170	146	361	325	1,905	2,446			642	1,523
4{4}	1,346	250			ND	1,443		454.1	3502			129					6,397	1,585	685	5,326		

Key: Green = primary screen missed or Ki >10,000 nM; ND = not determined

Binding assay protocols are available free of charge via the internet at:

http://pdsp.med.unc.edu/UNC-CH%20Protocol%20Book.pdf

General Experimental Details

All chemicals were used as purchased from commercial suppliers. Methylene chloride, acetonitrile, toluene, ethyl ether and THF were dried by being passed through two packed columns of anhydrous, neutral alumina prior to use.

Parallel syntheses were performed on the Bohdan Miniblock XT parallel solution phase synthesizer obtained from Mettler-Toledo Auto Chem. Automated weighing was performed using the Bohdan Balance Automator (Mettler-Toledo Auto Chem). Parallel evaporation was performed on the GeneVac EZ-2 plus evaporator system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer (operating at 400 and 100 MHz respectively) in $CDCl_3$ with 0.03% TMS as an internal standard, unless otherwise specified. Chemical shifts are reported in parts per million (ppm) downfield from TMS. ^{13}C multiplicities were determined

with the aid of an APT pulse sequence, differentiating the signals for methyl and methyne carbons as "d" from methylene and quarternary carbons as "u". The infrared (IR) spectra were acquired as thin films using a universal ATR sampling accessory on a PerkinElmer Spectrum 100 FT-IR spectrometer and the absorbtion frequencies are reported in cm^{-1}. Melting points were determined on a Stanford Research Systems Optimelt automated melting point system interfaced through a PC and are uncorrected. Microwave syntheses were conducted in a Biotage Initiator constant temperature microwave synthesizer.

HPLC/MS analysis was carried out with gradient elution (5% CH_3CN to 100% CH_3CN) on an Agilent 1200 RRLC with a photodiode array UV detector and an Agilent 6224 TOF mass spectrometer (also used to produce high resolution mass spectra). Purification was carried out by Mass Directed Fractionation with gradient elution (a narrow CH_3CN gradient was chosen based on the retention time of the target from LCMS analysis of the crude sample) on an Agilent 1200 instrument with photodiode array detector, an Agilent 6120 quadrupole mass spectrometer, and a HTPAL LEAP autosampler. Fractions were triggered using an MS and UV threshold determined by HPLC/MS analysis of the crude sample. One of two column/mobile phase conditions were chosen for both analysis and purification to promote the targets neutral state (0.02% formic acid with Waters Atlantis T3 5um, 19 x 150mm; or pH 9.8 NH_4OH with Waters XBridge C18 5µm, 19 x 150mm).

Summary of Assays and Corresponding PubChem Assay Identification (AID) Numbers

Table 1. Listing of agonist assays and PubChem AID numbers for this project

PubChemBioAssay Name	AIDs	Probe Type	Assay Type	Assay Format	Assay Detection & well format

Summary of small molecule agonists of the kappa opioid receptor via a luminescent beta-arrestin assay [Summary]	1786	Agonist	Summary	N/A	N/A
uHTS identification of small molecule agonists of the kappa opioid receptor via a luminescent beta-arrestin assay [Confirmatory]	1777	Agonist	Primary	Cell-based	Luminescence -DiscoveRx β-arrestin & 1536
SAR analysis of small molecule agonists of the kappa opioid receptor via a luminescent beta-arrestin assay [Confirmatory]	2284	Agonist	SAR	Cell-based	Luminescence -DiscoveRx β-arrestin & 1536
HTS Dose response counterscreen for assays utilizing the enzyme, ß-galactosidase [Confirmatory]	1966	Agonist	Counterscreen	Biochemical	Luminescence &1536
HTS Image-Based Screen for Selective Agonists of the KOR Receptor [Confirmatory]	2133	Agonist	Alternate	Cell-based	HCS – Transfluor & 384
HTS Image-Based Screen for Agonists of the MOR Receptor [Confirmatory]	2344	Agonist	Selectivity	Cell-based	HCS – Transfluor & 384
HTS Image-Based Screen for Agonists of the DOR Receptor [Confirmatory]	2343	Agonist	Selectivity	Cell-based	HCS – Transfluor & 384
SAR analysis of Agonists of the Kappa Opioid Receptor (KOR) using an Image-Based Assay [Confirmatory]	2359	Agonist	Alternate	Cell-based	HCS – Transfluor & 384
SAR Analysis of Agonists of the MOR Receptor using an Image-Based Assay [Confirmatory]	2352	Agonist	Selectivity	Cell-based	HCS – Transfluor & 384
SAR Analysis of Agonists of the DOR Receptor using an Image-Based Assay [Confirmatory]	2370	Agonist	Selectivity	Cell-based	HCS – Transfluor & 384

Assay Protocols (for additional details, view the individual AID on the PubChem portal)

KOR ß -Arrestin assay protocol

For the performance of the KOR ß-Arrestin assay, the OPRK1 ß-Arrestin cell line was obtained from DiscoveRx. The KOR ß-Arrestin assay utilized a protocol that was modified from the original DiscoveRx PathHunter™ protocol provided with the cell line. On day one, 500 cells of the OPRK1 ß -Arrestin cell line, grown in MEM supplemented with 10% hiFBS, 1X Pen/Strep/Glu, 125 µg/mL Hygromycin, and 250 ug/mL Geneticin are plated in 5 µL of assay media containing Opti-MEM Medium supplemented with 1% hiFBS, 1X Pen/Strep/Glu, 125 µg/mL Hygromycin, and 250 µg/mL Geneticin in each well of a white, 1536-well, tissue culture treated, assay plate. Assay plates are then incubated overnight at 37 °C, 5% CO_2, and 100% humidity. Following the overnight incubation, varying volumes of test compounds in DMSO are transferred to test compound wells to achieve appropriate test concentrations and range. DMSO is transferred to control wells and test compound wells to equalize DMSO concentrations (< 1.0%). For the agonist assay, immediately following test compound and DMSO transfers, 1 µL of assay media containing 6 µM of dynorphin A (1 uM final) is dispensed to the positive control wells and 1 µL of assay media only is dispensed to test compound and negative control wells. For the antagonist assay, 1 µL of assay media is added to the positive control wells, while 1 µL of 240 nM dynorphin A (40 nM final = EC_{80}) is added to all test compound and negative control wells. Assay plates are then incubated at room temperature for 90 minutes, followed by the addition of 2.5 µL of DiscoveRx detection reagent. Plates are incubated for an additional 60 minutes then read on a PerkinElmer Envision plate reader using a luminescent protocol. EC_{50} values were calculated based on relative luminescence using CBIS software (ChemInnovations) employing a sigmoidal dose-response equation via non-linear regression.

High content imaging ß-arrestin translocation assay protocols

Three U2OS (Human Osteosarcoma) cell lines stably expressing the ß-arrestin GFP and the GPCR target of interest, KOR, DOR and MOR receptors, were utilized in the performance of the HCS secondary assays. On day one, 9000 cells are plated in 45 µL of media containing MEM with L-glutamine, Pen-strep, 10% Fetal Bovine Serum and selection antibiotics – 200 µg/mL G418 and 100ug/mL Zeocin into black, clear bottom, 384-well, tissue culture treated assay plates. Plates are then incubated overnight at 37 °C, 5% CO_2, and 100% humidity. Following the overnight incubation, the media is aspirated from each well of the assay plate and replaced with 45 µL of the same media minus fetal bovine serum. Varying volumes of test compounds in DMSO are transferred to test compound wells to achieve appropriate test concentrations and range. DMSO is transferred to control wells and test compound wells to equalize DMSO concentrations (< 1.0%). For the agonist assays, 5 µL of the positive control ligand in MEM is immediately transferred to the positive control wells. Into the negative control wells, is transferred 5 µL of MEM only. For the antagonist assays, 5 µL of MEM is added to positive control wells, while 5 µL control ligand in MEM is transferred to the test compound and negative control wells to achieve an EC_{80} final assay concentration. For the KOR, DOR, and MOR HCS assays respectively, dynorphin A is utilized at 1µM, SNC80 at 100 nM, and DAMGO at 1 µM as final assay concentrations. Plates were then incubated for 45 minutes at 37 °C and 5% CO_2 prior to being fixed with 4% paraformaldehyde and the cell nuclei stained with 100 ng/mL DAPI. Image acquisition was performed on an Opera QEHS (Perkin Elmer) using a 40 × 0.6 NA air objective with the GFP and DAPI signals acquired via 488 nm laser excitation and 540/70 nm emission filters, and 365 nm Xenon lamp excitation and 450/50 nm emission filters, respectively. Image analysis was performed using the Acapella Spot Detection Algorithm.

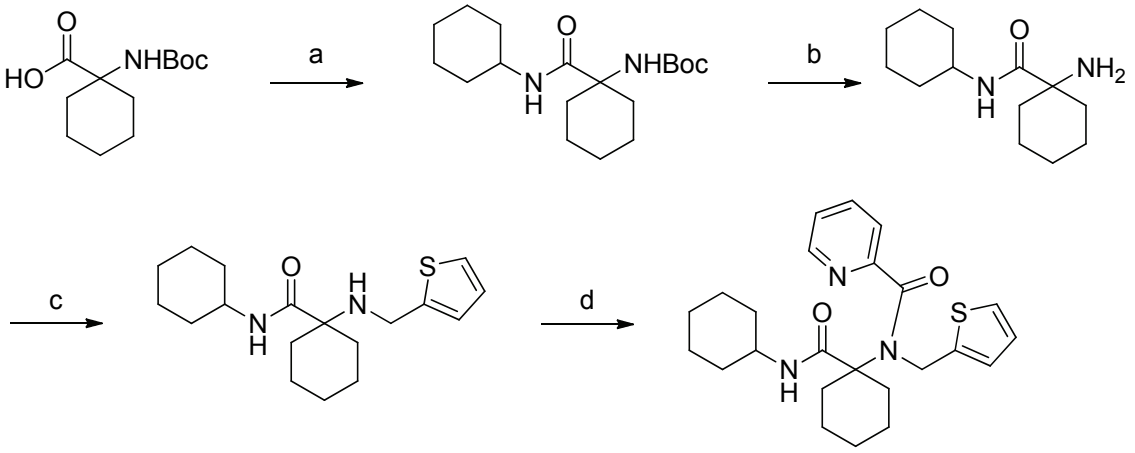
EC_{50} values were calculated based on the number of concentrated fluorescent spots per cell using CBIS software employing a sigmoidal dose-response equation through non-linear regression.

More specific protocol information can be referenced via the NCBI PubChem web portal - http://pubchem.ncbi.nlm.nih.gov/

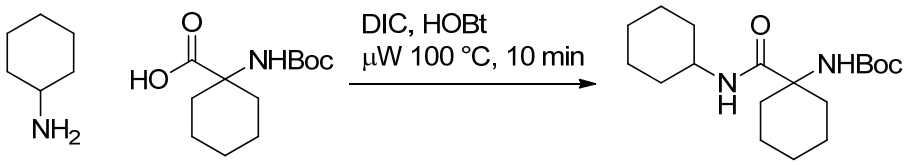
Synthesis of Agonist Chemotype I Compounds 1*{n}*

Compounds **1*{1}*** to **1*{9}*** are available as milligram quantity dry powder samples from several commercial vendors of screening compounds.

Scheme 1. Representative synthetic sequence[a].

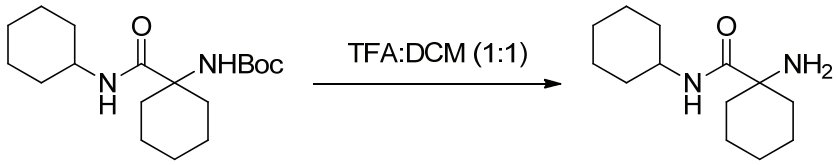


[a] Reagents and conditions: (a) cyclohexylamine, DIC, HOBt, MeCN, microwave irradiation 100 °C, 10 min (73% yield); (b) TFA:CH_2Cl_2 (1:1), rt, 14 h (99% yield); (c) thiophene-2-carboxaldehyde, $NaBH(OAc)_3$, DCE (84% yield); (d) picolynyl chloride, Et_3N, CH_2Cl_2 (86% yield).



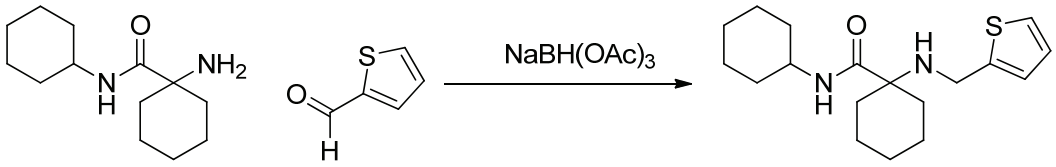
***tert*-Butyl (1-(cyclohexylcarbamoyl)cyclohexyl)carbamate**. A microwave vial (2-5 mL rated capacity) was charged with 1-((tert-butoxycarbonyl)amino)cyclohexanecarboxylic acid[1] (142 mg, 0.58 mmol), cyclohexylamine (75 mg, 0.76 mmol, 1.3 equiv.), HOBt (89 mg, 0.58 mmol,

1.0 equiv.) and diisopropylcarbodiimide (96 mg, 0.76 mmol, 1.3 equiv.) in MeCN (3 mL). The reaction vial was heated in a microwave reactor at 100 °C for 10 min then cooled to rt. The reaction mixture was dissolved in MeOH (4 mL), adsorbed onto Celite and chromatographed to yield the amide product as a white solid (139 mg, 0.43 mmol, 73% yield). R_f = 0.70 (EtOAc:hexanes 1:1); mp = 197-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13-1.19 (complex, 3 H), 1.28-1.45 (complex, 7 H), 1.45 (s, 9 H), 1.61-1.65 (complex, 4 H), 1.84-1.96 (complex, 6 H), 3.74 (m, 1 H), 4.72 (br s, 1 H), 6.72 (br s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 28.2, 47.6; u 21.3, 24.5, 25.1, 25.5, 32.2, 32.8, 59.3, 154.8, 173.6; IR (neat) 3336, 3305, 2931, 2854, 1689, 1641 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{33}N_2O_3$ ($[M+H]^+$), 325.2491, found 325.2498.

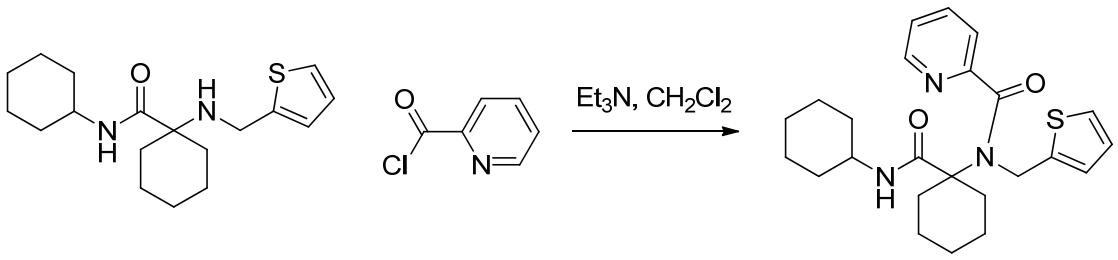


1-Amino-*N*-cyclohexylcyclohexanecarboxamide. *tert*-Butyl (1-(cyclohexylcarbamoyl)cyclohexyl)carbamate (123 mg, 0.38 mmol) was dissolved in a mixture of trifluoroacetic acid (2 mL) and CH_2Cl_2 (2 mL) and stirred at rt for 14 h. The solvents were removed in vacuo and the residue partitioned between saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (3 × 8 mL). The combined organics were dried with Na_2SO_3 and evaporated to yield the deprotected product as a white solid (84 mg, 0.37 mmol, 99% yield), which was used as obtained in the next step. R_f = 0.31 (EtOAc:hexanes 1:1); mp = 98-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.46 (complex, 10 H), 1.57-1.72 (complex, 6 H), 1.86 (dd, *J* = 3.6, 12.8 Hz, 2 H), 1.99 (dt, *J* = 4.0, 13.2 Hz, 2 H), 3.69 (m, 1 H), 7.71 (br s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 47.4; u 21.2 (× 2), 24.7 (× 2), 25.1 (× 2), 25.5 (× 2), 33.0 (× 2), 34.6 (× 2), 56.9, 176.8; IR (neat) 3383,

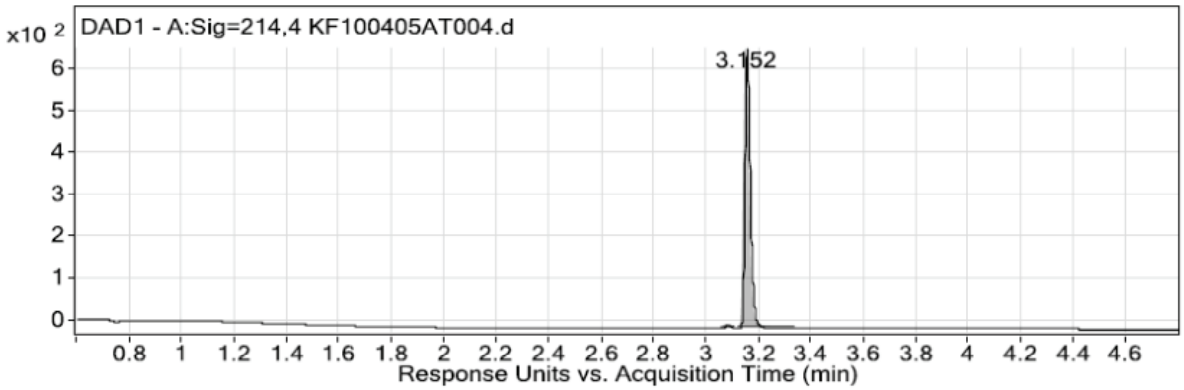
3320, 2929, 2852, 1613 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{25}N_2O$ ($[M+H]^+$), 225.1967, found 225.1977.



***N*-Cyclohexyl-1-((thiophen-2-ylmethyl)amino)cyclohexanecarboxamide**. To a solution of 1-amino-*N*-cyclohexylcyclohexanecarboxamide (84 mg, 0.374 mmol) and thiophene-2-carboxaldehyde (84 mg, 0.749 mmol, 2.0 equiv.) in dichloroethane (5 mL) was added sodium triacetoxyborohydride (238 mg, 1.12 mmol, 3.0 equiv.). The reaction was stirred at rt for 16 h and partitioned between aqueous NaOH (1 N, 10 mL) and CH_2Cl_2 (3 × 10 mL). The combined organics were dried with Na_2SO_3, adsorbed onto Celite and chromatographed to afford the reductive amination product as a light orange oil (101 mg, 0.314 mmol, 84% yield). R_f = 0.72 (EtOAc:hexanes 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.22 (complex, 3 H), 1.32-1.42 (complex, 7 H), 1.57-1.71 (complex, 5 H), 3.68-3.75 (m, 1 H), 3.76 (s, 2 H), 6.94 (dd, *J* = 0.8, 3.2 Hz, 1 H), 6.98 (dd, *J* = 3.2, 5.2 Hz, 1 H), 7.25 (dd, *J* = 1.2, 4.8 Hz , 1 H), 7.54 (br s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 47.5, 124.3, 124.4, 126.7; u 21.5 (× 2), 24.7 (× 2), 25.1, 25.6, 31.8 (× 2), 33.1 (× 2), 42.2, 61.0, 144.2, 175.2; IR (neat) 3345, 2928, 2853, 1644 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2OS$ ($[M+H]^+$), 321.2001, found 321.2007.

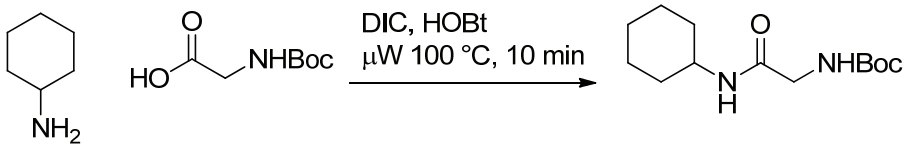


N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-N-(thiophen-2-ylmethyl)picolinamide 1*{1}. To a solution of *N*-cyclohexyl-1-((thiophen-2-ylmethyl)amino)cyclohexanecarboxamide (93 mg, 0.290 mmol) and triethylamine (117 mg, 1.16 mmol, 4.0 equiv.) in CH_2Cl_2 (5 mL) was added picolinoyl chloride hydrochloride (103 mg, 0.58 mmol, 2.0 equiv.). The reaction was stirred at rt for 18 h and partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2 (3 × 8 mL). The combined organics were dried with Na_2SO_3, adsorbed onto Celite and chromatographed to afford the bisamide product as an off-white solid (106 mg, 0.249 mmol, 86% yield). R_f = 0.36 (EtOAc:hexanes 1:1); mp = 102-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06-1.22 (m, 3 H), 1.28-1.38 (m, 2 H), 1.42-1.83 (complex, 11 H), 2.14-2.26 (m, 4 H), 3.66 (m, 1 H), 4.98 (s, 2 H), 6.78 (d, *J* = 2.8 Hz, 1 H), 6.83 (t, *J* = 4.4 Hz, 1 H), 6.95 (br s, 1 H), 7.14 (d, *J* = 5.2 Hz, 1 H), 7.33 (dd, *J* = 0.8, 4.8 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.75 (dt, *J* = 1.6, 7.6 Hz, 1 H), 8.57 (d, *J* = 4.8 Hz, 1 H); ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 47.9, 124.2, 124.7, 125.2, 126.4, 126.5, 137.0, 147.9; u (C, CH_2) 22.4 (× 2), 24.6 (× 2), 25.5, 25.6, 32.7 (× 2), 33.0 (× 2), 44.8, 66.8, 141.8, 155.0, 171.6, 172.7; IR (neat) 2928, 2854, 1655 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_3O_2S$ ($[M+H]^+$), 426.2215, found 426.2207.



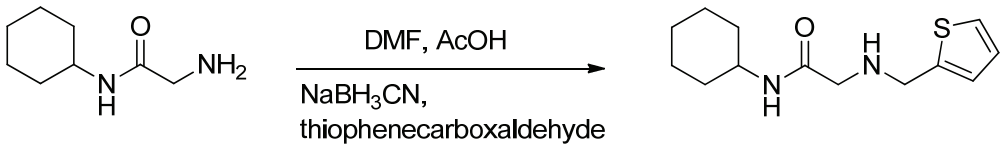
User Chromatogram Peak List

Peak #	RT	Height	Height %	Area	Area %	Area Sum %	Width
1	3.079	6.56	0.99	8.79	0.92	0.91	0.021
2	3.152	660.82	100	953.79	100	99.09	0.022

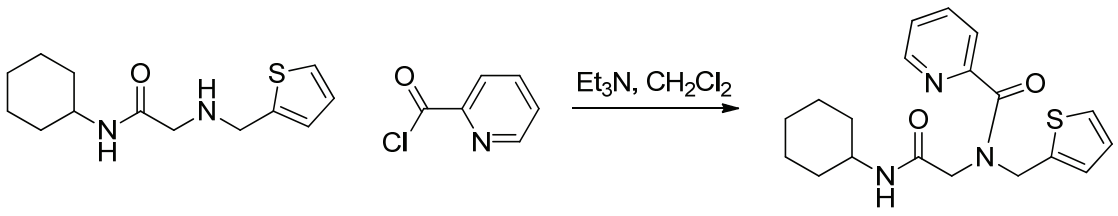


***tert*-Butyl (2-(cyclohexylamino)-2-oxoethyl)carbamate** . A microwave vial (2-5 mL rated capacity) was charged with *N*-Boc glycine[2] (245 mg, 1.40 mmol), cyclohexylamine (180 mg, 1.82 mmol, 1.3 equiv.), HOBt (214 mg, 1.40 mmol, 1.0 equiv.) and diisopropylcarbodiimide (229 mg, 1.82 mmol, 1.3 equiv.) in MeCN (3 mL). The reaction vial was heated in a microwave reactor at 100 °C for 10 min then cooled to rt. The reaction mixture was dissolved in MeOH (4 mL), adsorbed onto Celite and chromatographed to yield the previously reported amide product[3] as a sticky, colorless oil (213 mg, 0.832 mmol, 60% yield). R_f = 0.52 (EtOAc:hexanes 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.22 (complex, 3 H), 1.29-1.40 (m, 2 H), 1.45 (s, 9 H), 1.61 (m, 1 H), 1.71 (td, *J* = 3.6, 13.2 Hz, 2 H), 1.88 (m, 2 H), 3.72-3.77 (complex, 3 H), 5.70 (br s, 1 H), 6.56 (br s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 28.1, 48.0; u 24.6, 25.3, 32.7, 44.3, 79.7, 156.1, 168.4; IR (neat) 3308, 2931, 2856, 1701, 1649 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{25}N_2O_3$ ($[M+H]^+$), 257.1865, found 257.1860.

2-Amino-*N*-cyclohexylacetamide. The above amide, *tert*-butyl (2-(cyclohexylamino)-2-oxoethyl)carbamate (213 mg, 0.83 mmol), was dissolved in a mixture of trifluoroacetic acid (2 mL) and CH_2Cl_2 (3 mL) and stirred at rt for 14 h. The solvents were removed in vacuo to yield the previously reported deprotected product[4] as the crude trifluoroacetate salt, which was used as obtained in the next reaction.

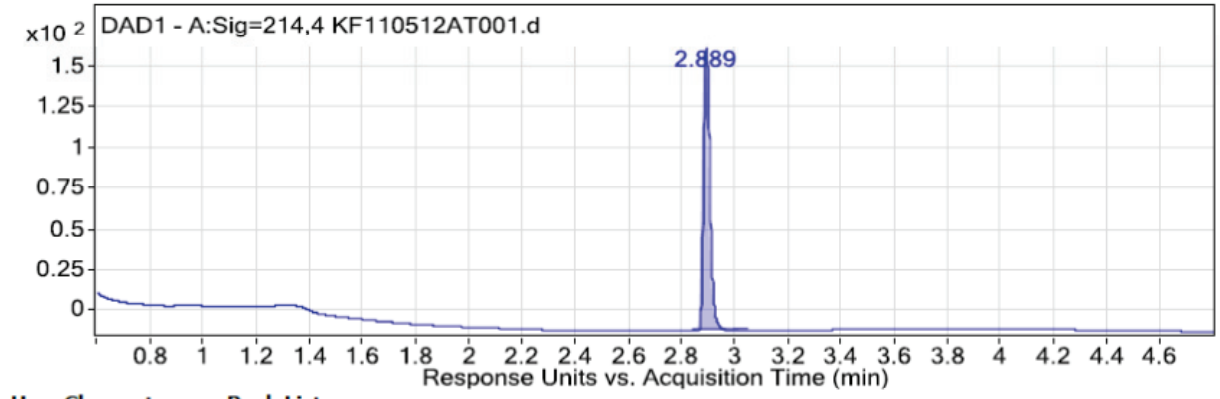


***N*-Cyclohexyl-2-((thiophen-2-ylmethyl)amino)acetamide** . To a solution of the crude 2-amino-*N*-cyclohexylacetamide above (343 mg, 1.27 mmol) and thiophene-2-carboxaldehyde (142 mg, 1.27 mmol, 1.0 equiv.) in DMF (15 mL) was added sodium cyanoborohydride (160 mg, 2.54 mmol, 2.0 equiv.) then AcOH (0.15 mL, 2.54 mmol, 2.0 equiv.). The reaction was stirred at rt for 16 h and partitioned between saturated, aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (3 × 15 mL). The combined organics were dried with Na_2SO_3, adsorbed onto Celite and chromatographed to afford the reductive amination product as a colorless oil (99 mg, 0.392 mmol, 31% yield). R_f = 0.11 (EtOAc:hexanes 3:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.22 (complex, 3 H), 1.13-1.27 (complex, 3 H), 1.32-1.43 (m, 2 H), 1.60 (td, *J* = 4.0, 12.8 Hz, 1 H), 1.71 (td, *J* = 4.0, 13.6 Hz, 2 H), 1.87 (m, 2 H), 3.29 (s, 2 H), 3.78 (m, 1 H), 3.96 (s, 2 H), 6.92 (m, 1 H), 6.95 (m, 1 H),7.15 (br s, 1 H), 7.23 (d, *J* = 4.8 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 47.4, 124.6, 125.2, 126.7; u 24.6(× 2), 25.4, 33.0 (× 2), 48.2, 51.6, 143.0170.0; IR (neat) 3311, 2928, 2853, 1644 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{21}N_2OS$ ($[M+H]^+$), 253.1375, found 253.1385.



N*-(2-(Cyclohexylamino)-2-oxoethyl)-*N*-(thiophen-2-ylmethyl)picolinamide 1*{10} . To a solution of *N*-cyclohexyl-2-((thiophen-2-ylmethyl)amino)acetamide (99 mg, 0.392 mmol) and triethylamine (159 mg, 1.57 mmol, 4.0 equiv.) in CH_2Cl_2 (5 mL) was added picolinoyl chloride

hydrochloride (140 mg, 0.785 mmol, 2.0 equiv.). The reaction was stirred at rt for 18 h and partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2 (3 × 8 mL). The combined organics were dried with Na_2SO_3, adsorbed onto Celite and chromatographed to afford the bisamide product as an off-white solid (77 mg, 0.215 mmol, 55% yield). R_f = 0.43 (EtOAc:hexanes 3:1); mp = 140-143 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.15-1.40 (complex, 5 H), 1.61-1.89 (complex, 5 H), 3.65 (td, *J* = 6.8, 45.6 Hz, 1 H), 4.10 (s, 2 H), 4.96 (s, 2 H), 6.99 (m, 1 H), 7.09 (m, 1 H), 7.39 (d, *J* = 4.8 Hz, 1 H), 7.53 (m, 1 H), 7.78 (t, *J* = 8.0 Hz, 1 H), 7.97 (m, 1 H), 8.62 (dd, *J* = 4.4, 52.0 Hz, 1 H); ^{13}C (100 MHz, CD_3OD) δ d (CH, CH_3) 49.9, 125.5, 126.7, 127.5, 127.8, 129.1, 139.1, 149.3; u (C, CH_2) 26.1, 26.2, 26.7, 33.7, 33.8, 46.7, 52.4, 139.9, 154.6, 169.8, 171.1; IR (neat) 3301, 2930, 2854, 1635 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}N_3O_2S$ ($[M+H]^+$), 358.1589, found 358.1580.



User Chromatogram Peak List

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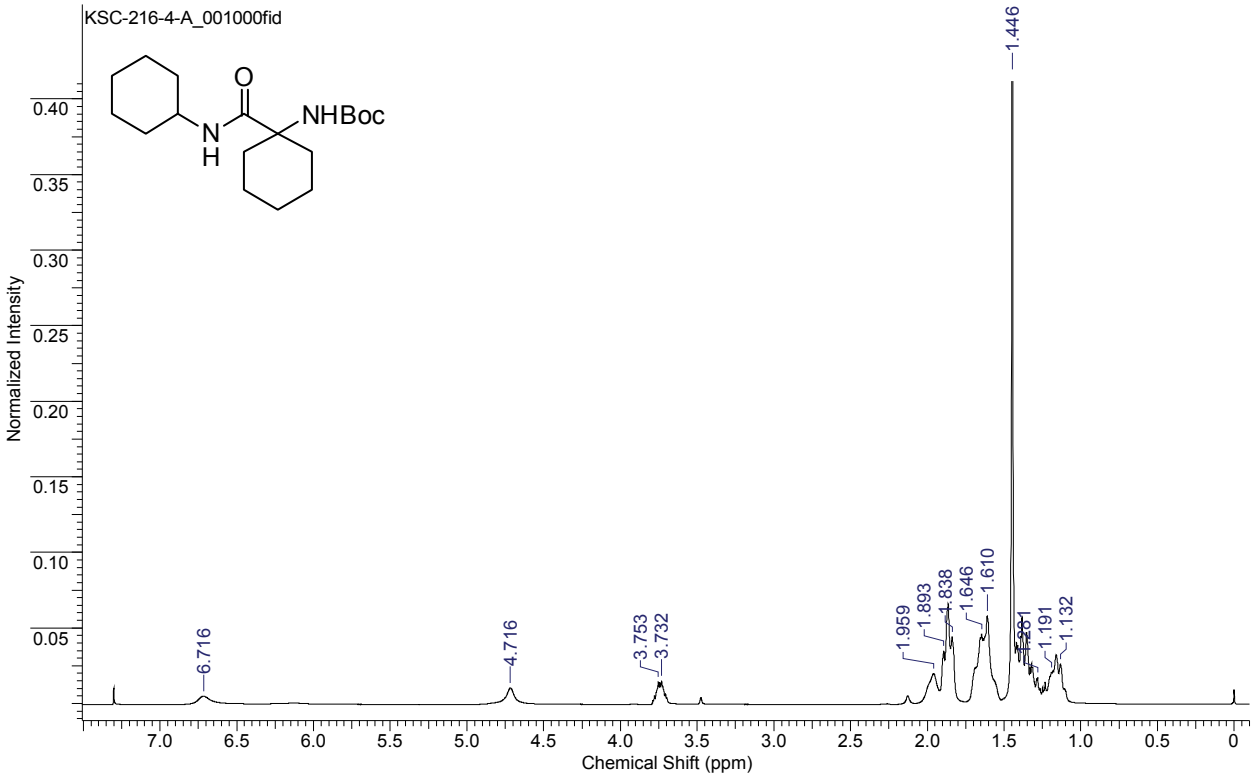
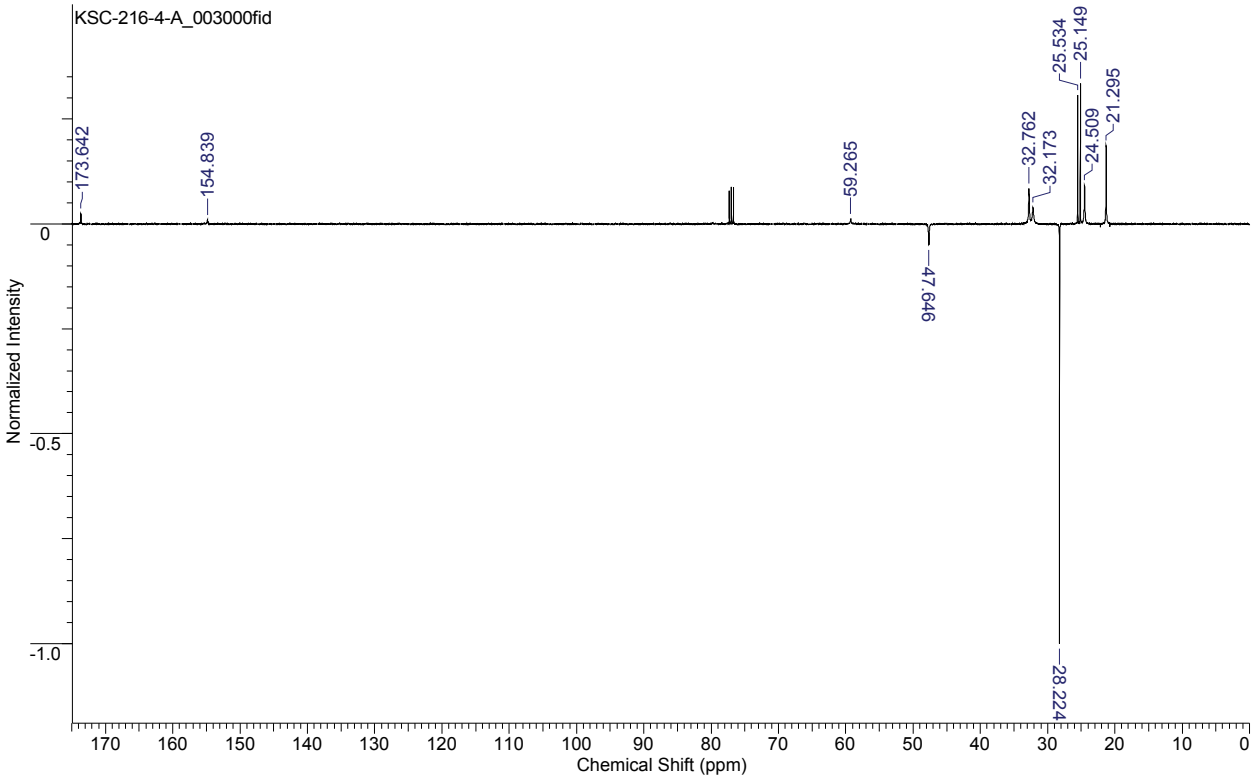
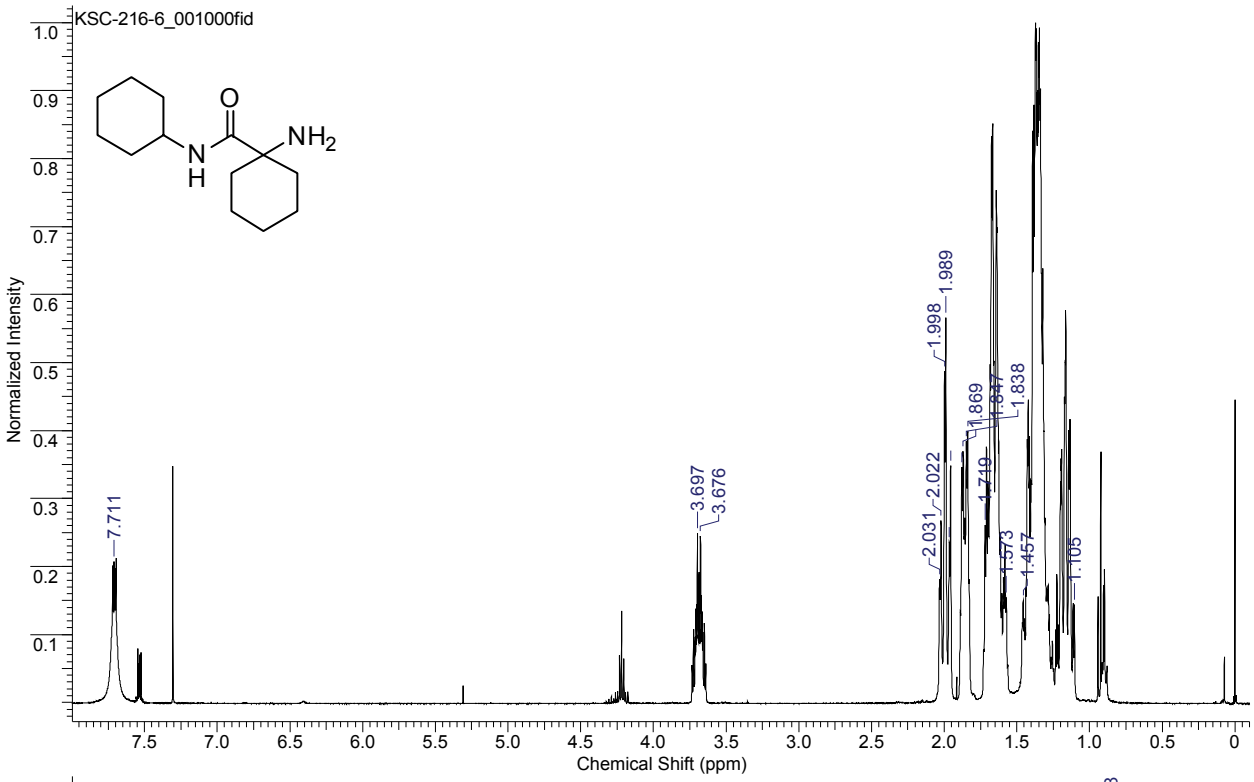
NMR Spectra for Chemotype I Compounds and New Synthetic Intermediates



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N
H
NH2
Normalized Intensity
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3.676
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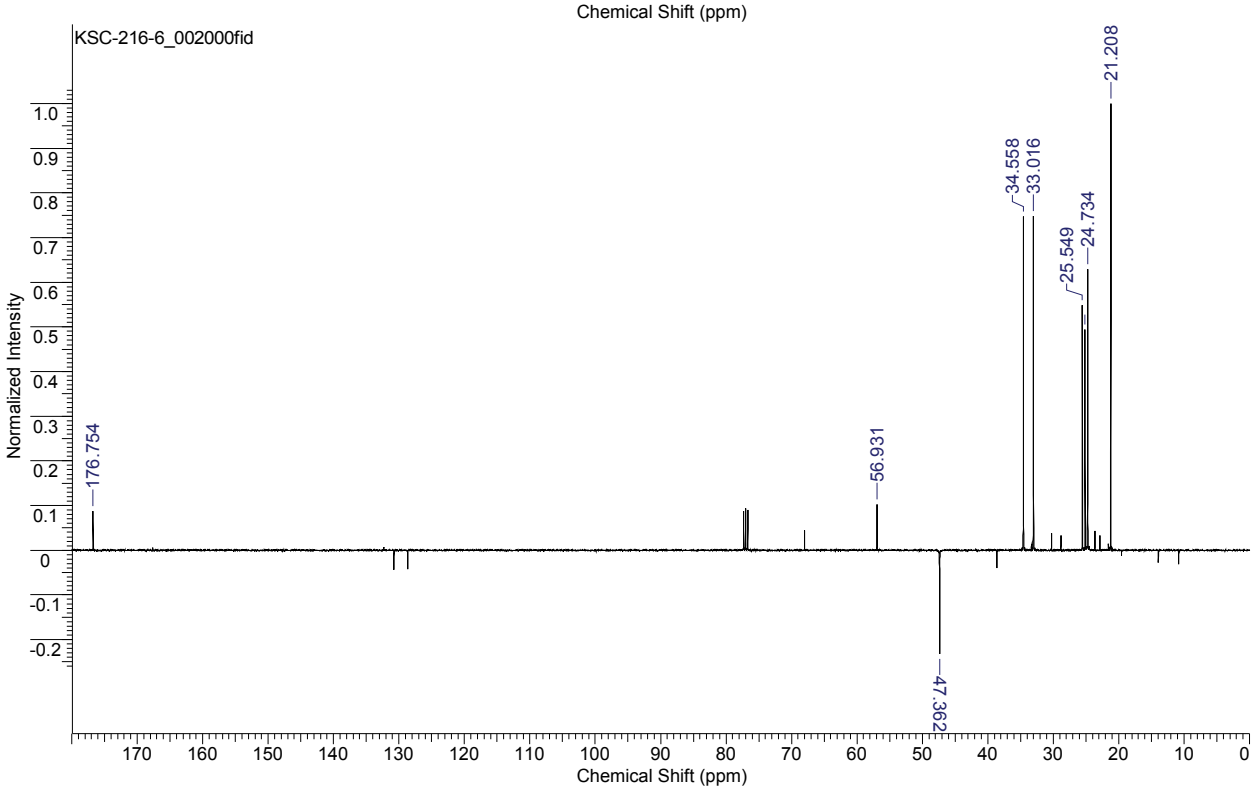
1.457
1.838
1.105
Chemical Shift (ppm)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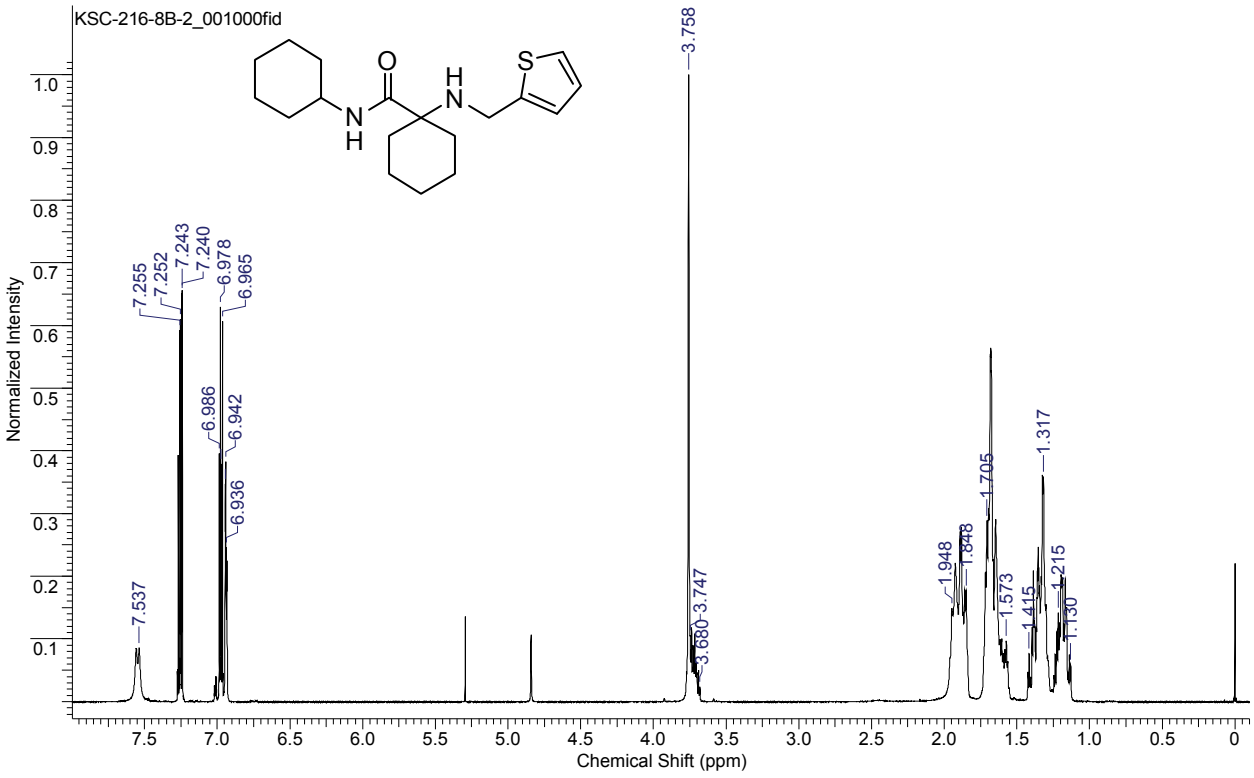
21.208
Chemical Shift (ppm)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Normalized Intensity
Chemical Shift (ppm)
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7.252
7.243
7.240
6.986
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1.573
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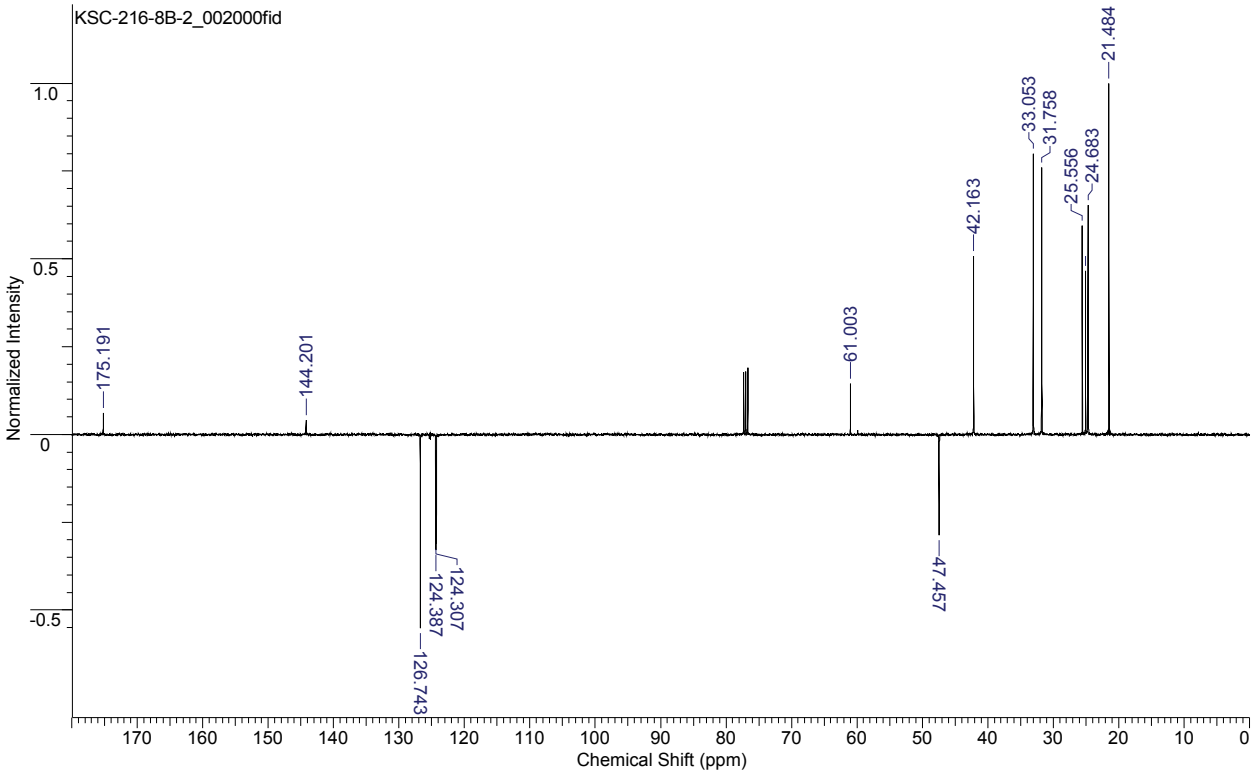
1.317
1.215
1.130


KSC-216-8B-2_002000fid
Normalized Intensity
Chemical Shift (ppm)
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124.307
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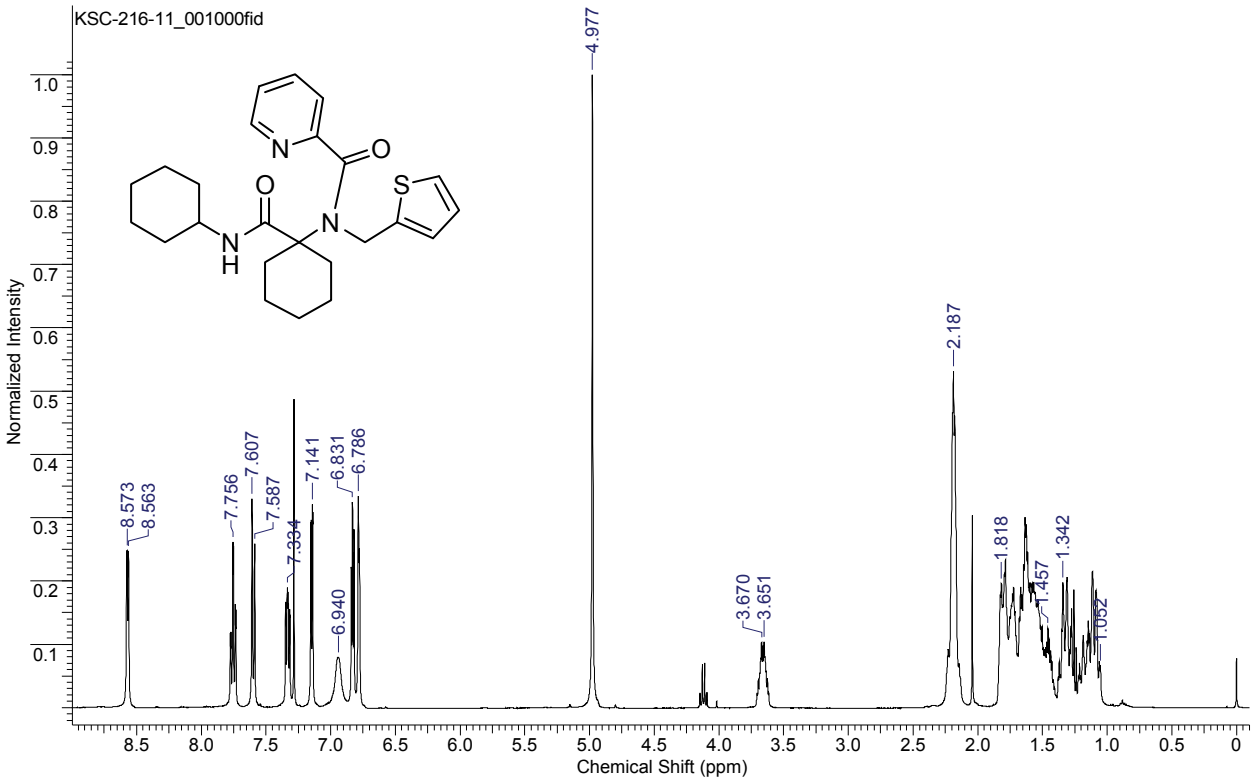
33.053
31.758
25.556
24.683
21.484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Normalized Intensity
Chemical Shift (ppm)
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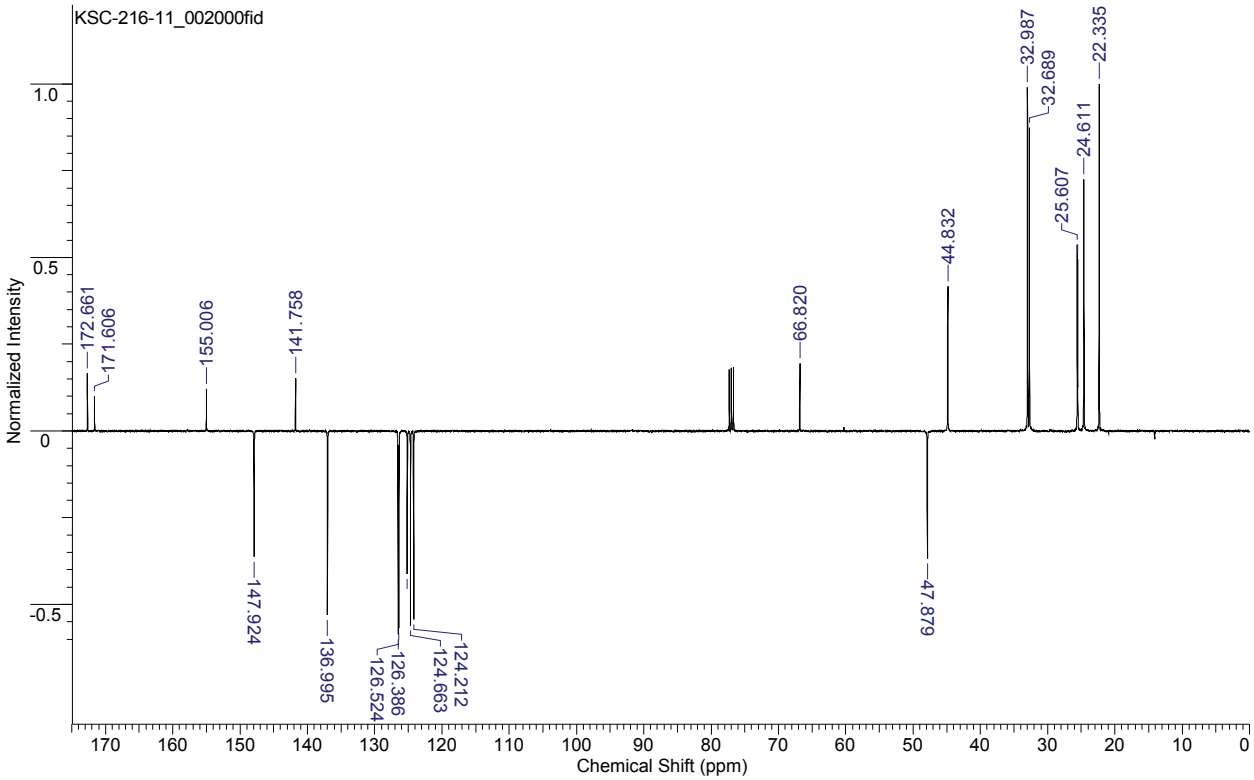
6.940
4.977
3.670
3.651
2.187
1.818
1.457
1.342
1.052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Normalized Intensity
Chemical Shift (ppm)
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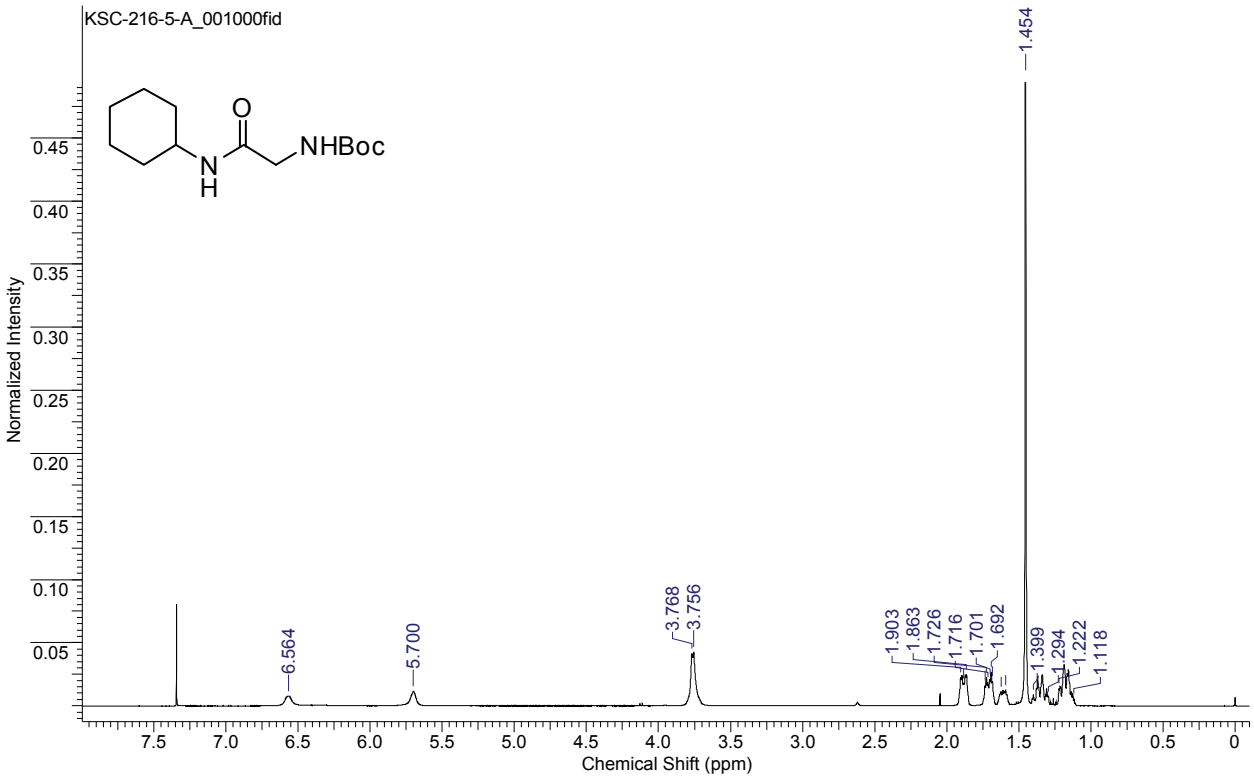
126.524
126.386
124.663
124.212
47.879


KSC-216-5-A_001000fid
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NHBoc
N
H
Normalized Intensity
Chemical Shift (ppm)
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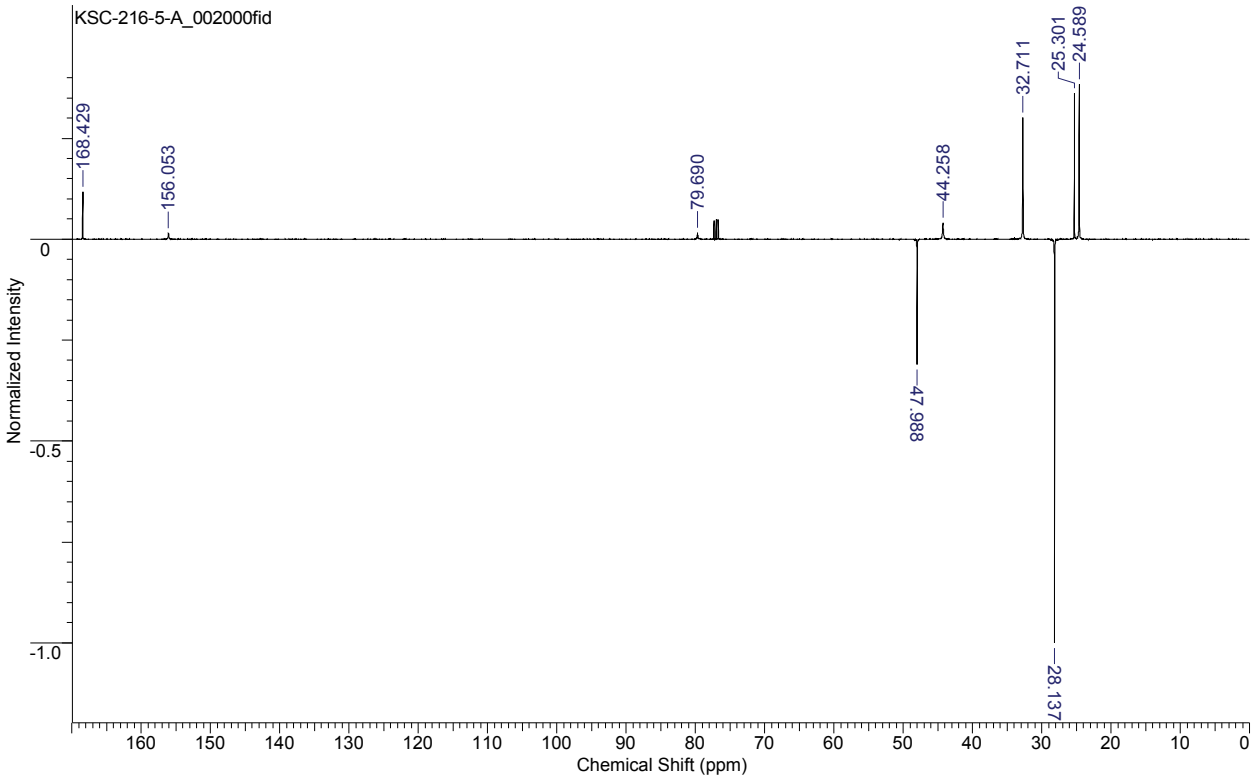
1.701
1.692
1.399
1.294
1.222
1.118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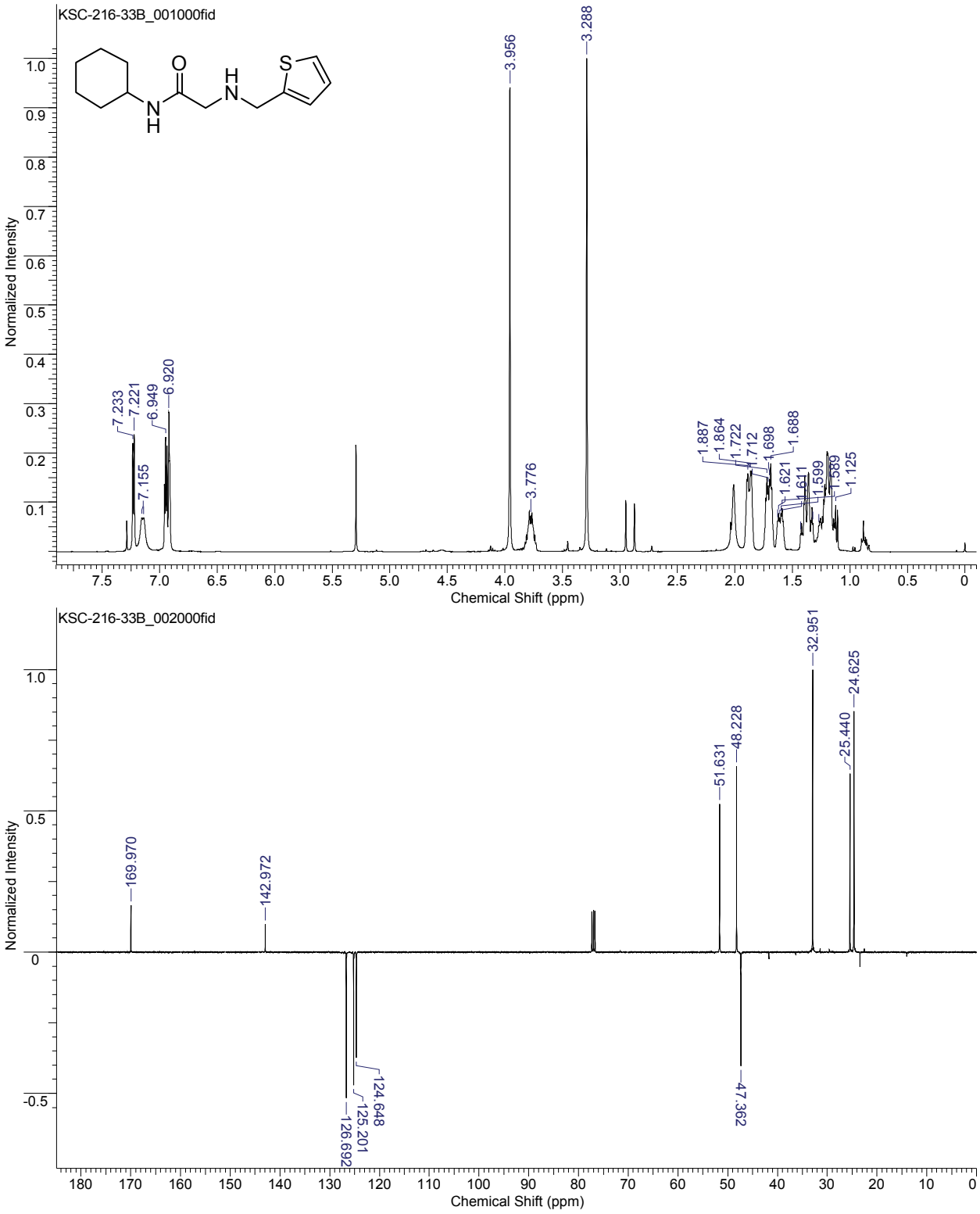
47.988
28.137


KSC-216-33B_001000fid
Normalized Intensity
Chemical Shift (ppm)
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7.221
6.949
6.920
7.155
3.956
3.776
3.288
1.887
1.864
1.722
1.712
1.698
1.688
1.621
1.611
1.599
1.589
1.125
KSC-216-33B_002000fid
Normalized Intensity
Chemical Shift (ppm)
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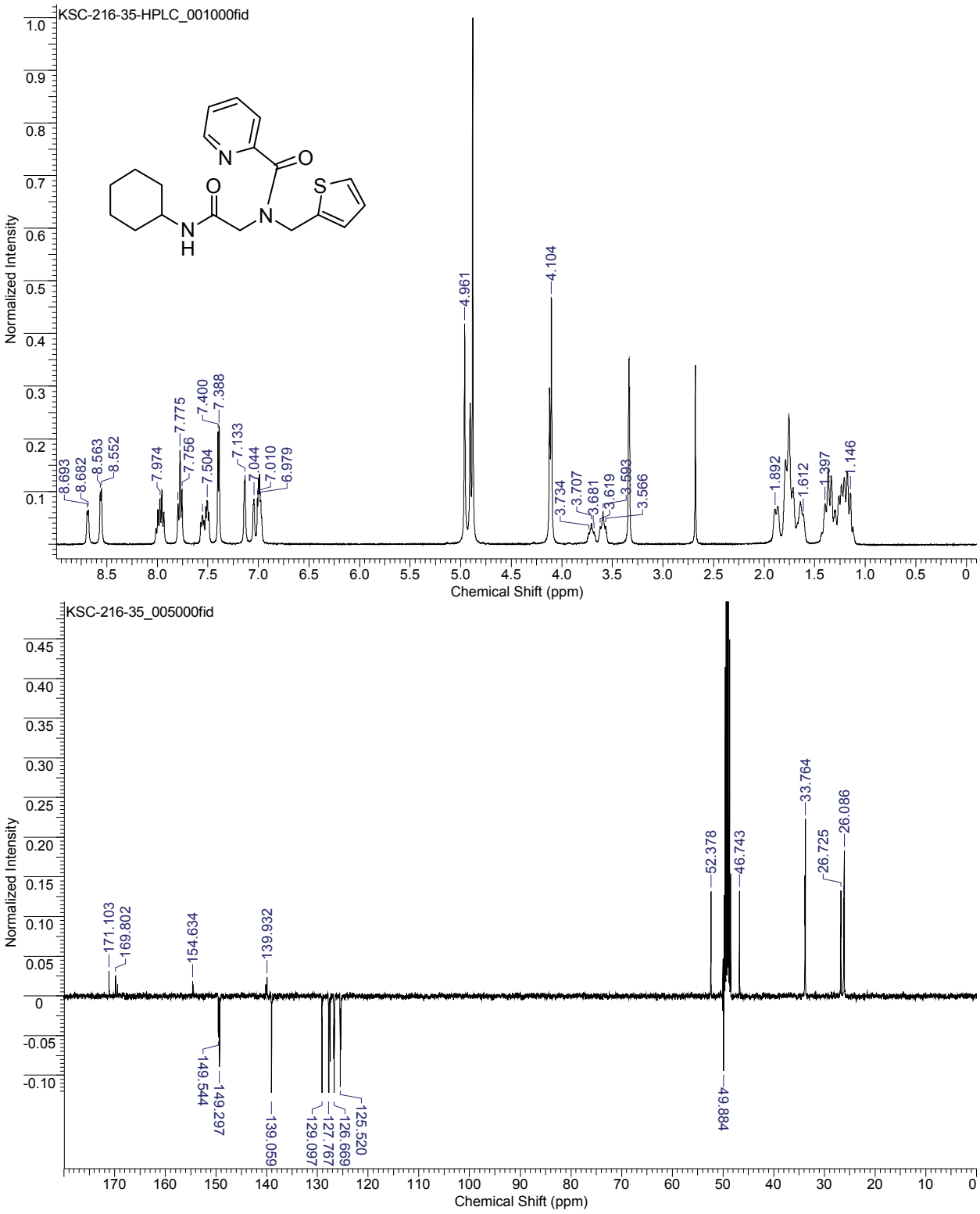
126.692
125.201
124.648
51.631
48.228
47.362
32.951
25.440
24.625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Normalized Intensity
Chemical Shift (ppm)
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7.756
7.504
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7.388
7.133
7.044
7.010
6.979
4.961
4.104
3.734
3.707
3.681
3.619
3.593
3.566
1.892
1.612
1.397
1.146
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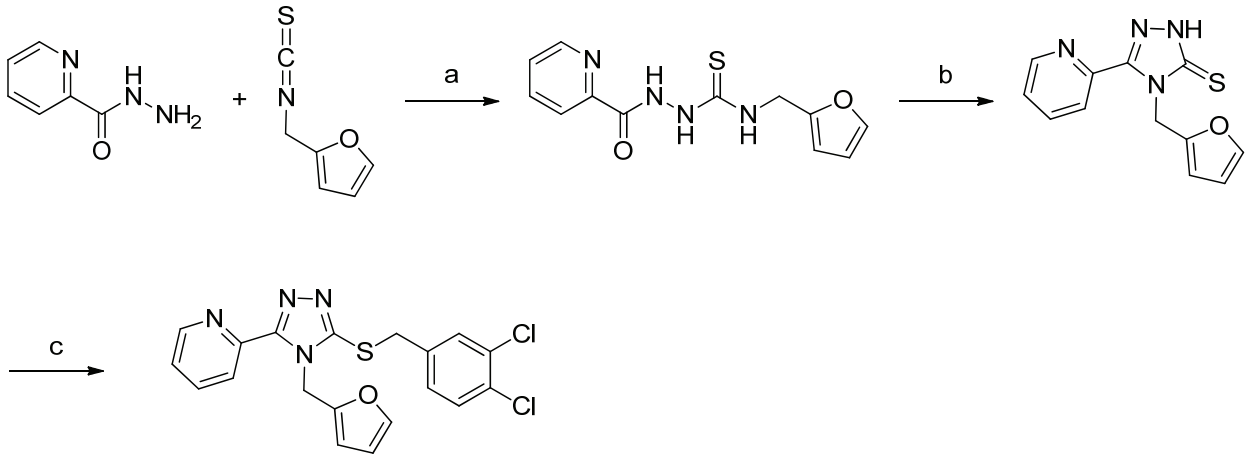
171.103
169.802
154.634
149.544
149.297
139.932
139.059
129.097
127.767
126.669
125.520
52.378
49.884
46.743
33.764
26.725
26.086

Synthesis of Agonist Chemotype II Compounds 2*{n}*

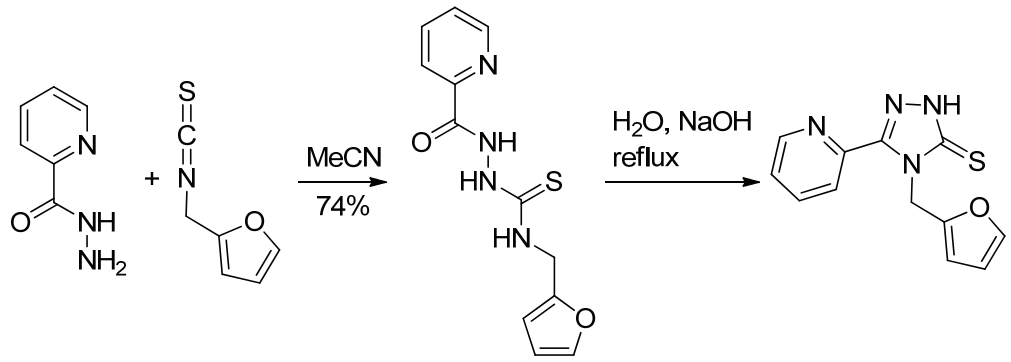
Compounds **2*{1}***, **2*{3}*** and **2*{5}*** to **2*{7}*** are available as milligram quantity dry powder samples from several commercial vendors of screening compounds.

Scheme 2. Representative synthetic sequence[a].



[a] Reagents and conditions: (a) MeCN (74% yield); (b) NaOH, water, reflux (96% yield); (c) 3,4-dichlorobenzyl chloride, K_2CO_3, acetone (77% yield).

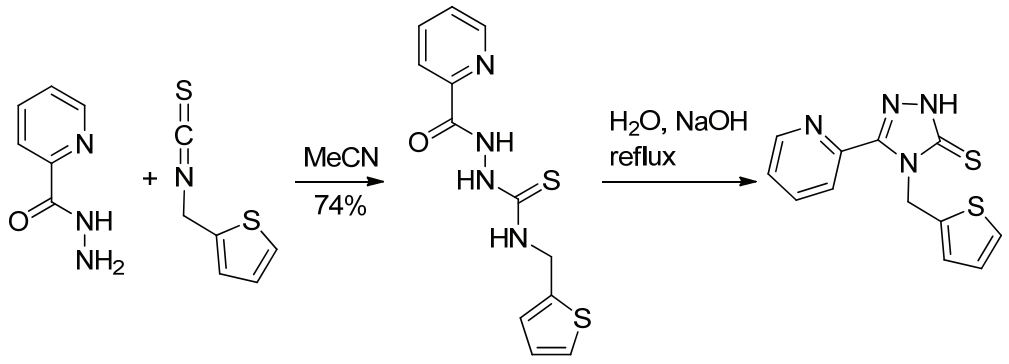
Scaffold synthesis.



***N*-(Furan-2-ylmethyl)-2-picolinoylhydrazinecarbothioamide**. 2-Picolynyl hydrazide (410 mg, 2.99 mmol) and furfuryl isothiocyanate (416 mg, 2.99 mmol) in MeCN (15 mL) were stirred for 16 h at rt. The reaction mixture was filtered, the precipitate washed with additional MeCN (3 × 10 mL) and dried under vacuum to afford the thioamide as an off-white solid (610 mg, 2.21 mmol, 74% yield), which was used without further purification. Mp = 167-169 ºC; ^{1}H NMR

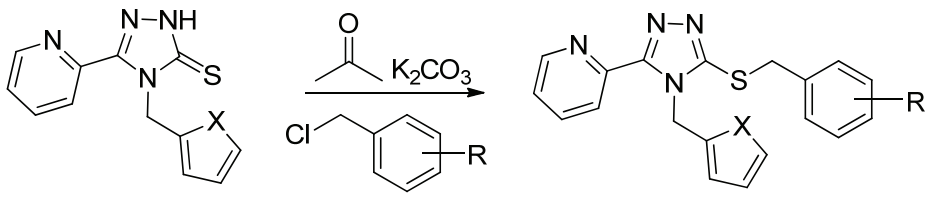
(DMSO-d6) δ 4.67 (d, *J* = 4.8 Hz, 2 H), 6.27 (d, *J* = 2.8 Hz, 1 H), 6.38 (dd, *J* = 2.0, 3.2 Hz, 1 H), 7.54 (s, 1 H), 8.02 (m, 2 H), 8.45 (br s, 1 H), 8.66 (d, *J* = 4.4 Hz, 1 H), 9.52 (br s, 1 H), 10.61 (s, 1 H); ^{13}C NMR (DMSO-d6) δ d 107.0, 110.4, 122.5, 126.9, 137.6, 141.7, 148.4; u 40.6, 149.3, 152.1, 181.8, 202.5; IR (neat) 3135, 1673, 1533, 1500, 1465 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_4O_2S$ ($[M+H]^+$), 277.0759, found 277.0761.

4-(Furan-2-ylmethyl)-3-(pyridin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione. To a slurry of the above thioamide (530 mg, 1.92 mmol) in water (25 mL) was added NaOH (4.00 g, 100 mmol). The reaction was heated at reflux for 2 h, the starting thioamide dissolved promptly upon warming. The reaction was cooled to rt, diluted with aqueous HCl (1 N, 20 mL) and acidified to pH = 6 with concentrated HCl. The solid precipitate was filtered, washed with water (2 × 15 mL) and dried under vacuum to afford the thione as a white solid (478 mg, 1.85 mmol, 96% yield), which was used without further purification. Mp = 181-186 ºC; ^{1}H NMR (DMSO-d6) δ 5.87 (s, 2 H), 6.12 (d, *J* = 1.2 Hz, 1 H), 6.27 (dd, *J* = 0.8, 2.8 Hz, 1 H), 7.45 (s, 1 H), 7.55 (m, 1 H), 7.97 (m, 2 H), 8.73 (d, *J* = 4.8 Hz, 1 H); ^{13}C NMR (DMSO-d6) δ d 108.5, 110.4, 122.9, 125.3, 137.8, 142.6, 149.1; u 41.0, 145.7, 148.3, 149.2, 168.6; IR (neat) 3021, 2894, 2766, 1585, 1550, 1502, 1463 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}N_4OS$ ($[M+H]^+$), 259.0654, found 259.0642.



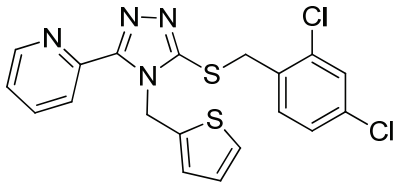
***N*-(Thiophen-2-ylmethyl)-2-picolinoylhydrazinecarbothioamide.** 2-Picolynyl hydrazide (883 mg, 6.44 mmol) and thiophene isothiocyanate (1,000 mg, 6.44 mmol) in MeCN (20 mL) were stirred for 16 h at rt. The reaction mixture was filtered, the precipitate washed with additional MeCN (3 × 10 mL) and dried under vacuum to afford the thioamide as an off-white solid (1,642 mg, 5.62 mmol, 87% yield), which was used without further purification. Mp = 175-178 ºC; ^{1}H NMR (DMSO-d6) δ 4.84 (d, *J* = 6.0 Hz, 2 H), 6.93 (m, 1 H), 7.00 (m, 1 H), 7.36 (dd, *J* = 1.2, 4.8 Hz, 1 H), 7.63 (m, 1 H), 8.03 (m, 2 H), 8.56 (br s, 1 H), 8.66 (d, *J* = 4.8 Hz, 1 H), 9.50 (br s, 1 H), 10.60 (s, 1 H); ^{13}C NMR (DMSO-d6) δ d 122.5, 124.9, 125.8, 126.2, 126.9, 137.6, 148.4; u 42.1, 141.9, 149.3, 181.4, 198.3; IR (neat) 3141, 1672, 1527, 1499, 1466 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_4OS_2$ ([M+H]$^+$), 293.0531, found 293.0516.

4-(Thiophene-2-ylmethyl)-3-(pyridin-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione. To a slurry of the above thioamide (602 mg, 2.06 mmol) in water (25 mL) was added NaOH (4.00 g, 100 mmol). The reaction was heated at reflux for 2 h, the starting thioamide dissolving promptly upon warming. The reaction was cooled to rt, diluted with aqueous HCl (1 N, 20 mL) and acidified to pH = 6 with concentrated HCl. The solid precipitate was filtered, washed with water (2 × 15 mL) and dried under vacuum to afford the thione as a white solid (530 mg, 1.93 mmol, 94% yield), which was used without further purification. Mp = 229-231 ºC; ^{1}H NMR (DMSO-d6) δ 6.02 (s, 2 H), 6.87 (dd, *J* = 3.2, 4.8 Hz, 1 H), 7.09 (d, *J* = 2.4 Hz, 1 H), 7.34 (dd, *J* = 0.8, 5.2 Hz, 1 H), 7.59 (q, *J* = 4.4 Hz, 1 H), 7.99 (d, *J* = 4.4 Hz, 2 H), 8.80 (d, *J* = 4.8 Hz, 1 H), 14.2 (br s, 1 H), 10.60 (s, 1 H); ^{13}C NMR (DMSO-d6) δ d 122.8, 125.5, 126.3, 126.5, 128.1, 138.0, 149.0; u 42.3, 137.8, 145.5, 147.8, 168.3; IR (neat) 3019, 2896, 1584, 1549, 1501, 1462 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{11}N_4S_2$ ([M+H]$^+$), 275.0475, found 275.0412.

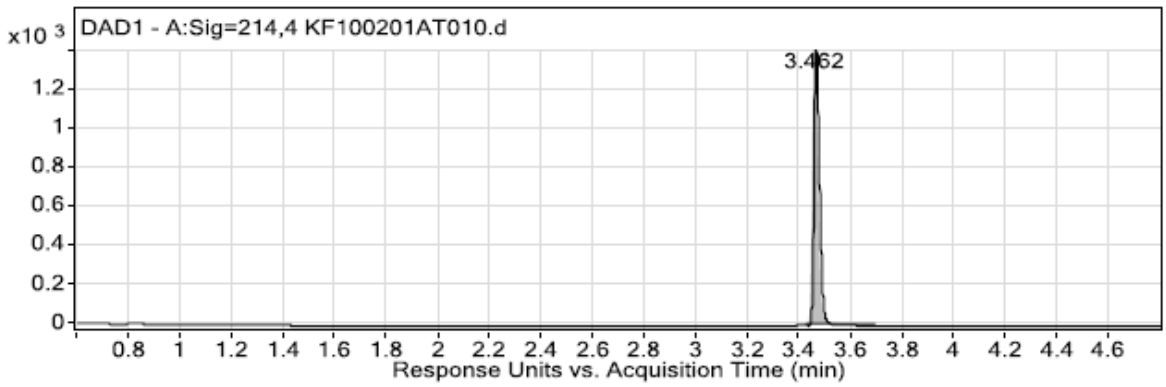


General procedure for the synthesis of series 2 analogs from thiones and benzyl halides.

The thione scaffold (0.1 to 0.3 mmol), K_2CO_3 (2 equiv) and the benzyl halide (1.2 equiv) were combined in acetone (15 mL/mmol substrate) and stirred in a sealed vial. After 15 h, the solvent was removed and the residue washed with CH_2Cl_2 (2 × 3 mL) and filtered. The combined filtrates were evaporated down and either chromatographed on silica or purified by mass-directed, reverse phase preparative HPLC.



2-(5-((2,4-Dichlorobenzyl)thio)-4-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{2}*. (CID 44601469) Following the general procedure above and purification by silica gel chromatography, thiophene thione (65 mg, 0.24 mmol) and 2,4-dichlorobenzyl chloride (56 mg, 0.28 mmol) afforded the product as an off-white solid (78 mg, 0.18 mmol, 76% yield). Mp = 127-128 °C; R_f = 0.28 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.56 (s, 2 H), 5.91 (s, 2 H), 6.83 (dd, *J* = 3.6, 4.8 Hz, 1 H), 6.97 (d, *J* = 3.2 Hz, 1 H), 7.11 (dd, *J* = 2.4, 4.4 Hz, 1 H), 7.13 (dd, *J* = 1.2, 5.6 Hz, 1 H), 7.34 (m, 1 H), 7.37 (d, *J* = 2.0 Hz, 1 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.81 (dt, *J* = 1.6, 8.0 Hz, 1 H), 8.29 (d, *J* = 8.0 Hz, 1 H), 8.66 (d, *J* = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ d 123.1, 124.2, 126.3, 126.4, 127.2, 127.6, 129.4, 132.2, 137.0, 148.5; u 34.9, 43.6, 133.3, 134.3, 134.8, 137.6, 147.5, 152.1, 152.4; IR (neat) 3060, 1587, 1565, 1467 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}Cl_2N_4S_2$ ($[M+H]^+$), 433.0115, found 433.0108.



User Chromatogram Peak List

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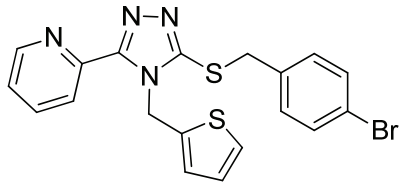
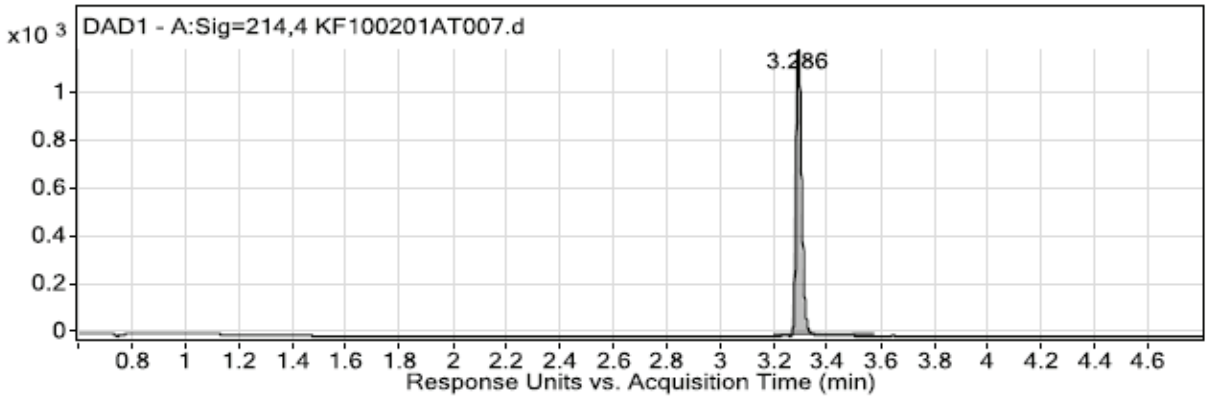


2-(5-((4-Bromobenzyl)thio)-4-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{4}*. (CID 44601472) Following the general procedure above and purification by silica gel chromatography, thiophene thione (65 mg, 0.24 mmol) and 4-bromobenzyl bromide (71 mg, 0.28 mmol) afforded the product as a pale yellow solid (56 mg, 0.13 mmol, 53% yield). Mp = 99-101 °C; R_f = 0.23 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.44 (s, 2 H), 5.92 (s, 2 H), 6.85 (dd, *J* = 3.6, 4.8 Hz, 1 H), 6.97 (d, *J* = 2.8 Hz, 1 H), 7.16 (d, *J* = 5.2 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.35 (dd, *J* = 4.8, 7.6 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 7.82 (dt, *J* = 2.0, 8.0 Hz, 1 H), 8.30 (d, *J* = 8.0 Hz, 1 H), 8.67 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ d 123.2, 124.2, 126.3, 126.4, 127.6, 130.8 (× 2), 131.7 (× 2), 137.0, 148.5; u 37.3, 43.6, 121.7, 135.8, 137.7, 147.6, 152.2, 152.3; IR (neat) 3053, 1589, 1569, 1487 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{16}BrN_4S_2$ ($[M+H]^+$), 443.0000, found 442.9994.



User Chromatogram Peak List

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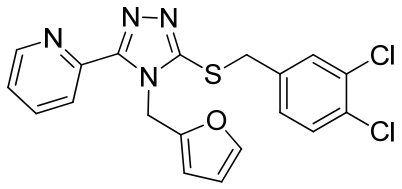
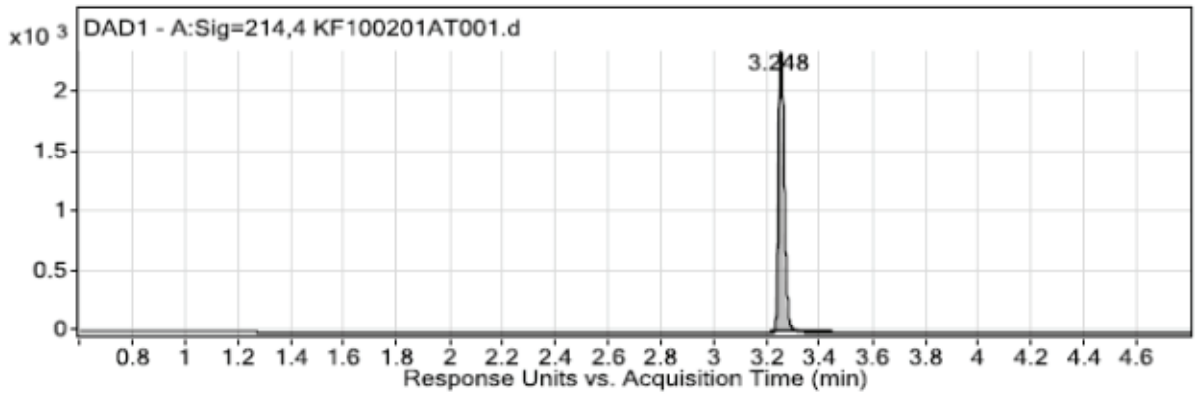


2-(5-(3,4-Dichlorobenzylthio)-4-(furan-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{8}*. (CID44601470). Following the general procedure above and purification by silica gel chromatography, furan thione (93 mg, 0.36 mmol) and 3,4-dichlorobenzyl chloride (84 mg, 0.43 mmol) afforded the product as an off-white solid (116 mg, 0.28 mmol, 77% yield). R_f = 0.24 (1:1 Hexanes: EtOAc); ^{1}H NMR (acetone-d6) δ 4.54 (s, 2 H), 5.91 (s, 2 H), 6.24 (d, *J* = 2.8 Hz, 1 H), 6.29 (dd, *J* = 2.0, 3.2 Hz, 1 H), 7.40-7.51 (complex, 4 H), 7.70 (d, *J* = 2.0 Hz, 1 H), 7.96 (dt, *J* = 1.6, 7.6 Hz, 1 H), 8.24 (d, *J* = 8.0 Hz, 1 H), 8.72 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR (acetone-d6) δ d 109.7, 111.3, 123.7, 125.2, 130.1, 131.4, 132.0, 138.2, 143.8, 149.7; u 36.7, 42.7, 131.7, 132.5, 139.7, 148.8, 150.3, 152.8, 153.4; IR (neat) 1701, 1589, 1463, 1446 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}Cl_2N_4OS$ ($[M+H]^+$), 417.0344, found 417.0353.



User Chromatogram Peak List

Peak #	RT	Height	Height %	Area	Area %	Area Sum %	Width
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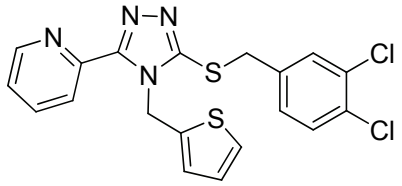
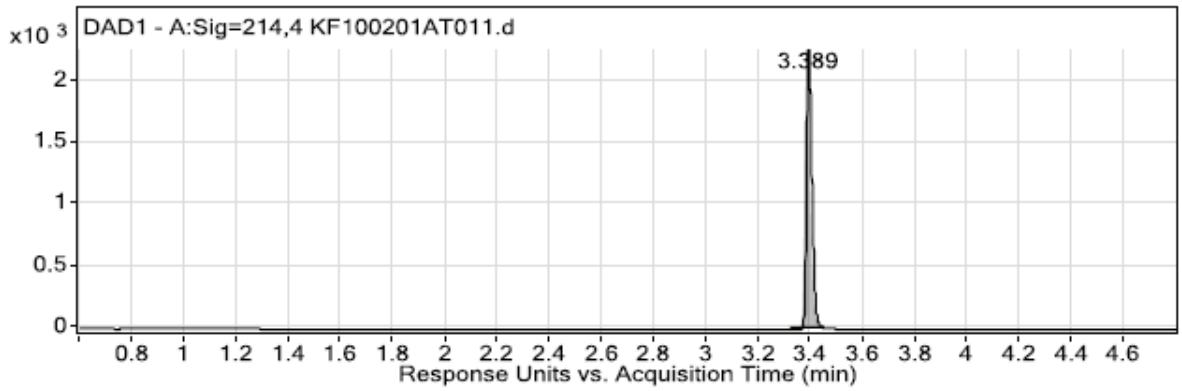


2-(5-((3,4-Dichlorobenzyl)thio)-4-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{9}*. (CID 44601475) Following the general procedure above and purification by silica gel chromatography, thiophene thione (65 mg, 0.24 mmol) and 2,4-dichlorobenzyl chloride (56 mg, 0.28 mmol) afforded the product as an off-white solid (92 mg, 0.21 mmol, 90% yield). Mp = 162-163 °C; R_f = 0.24 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.42 (s, 2 H), 5.93 (s, 2 H), 6.85 (dd, *J* = 3.6, 4.8 Hz, 1 H), 6.98 (d, *J* = 2.4 Hz, 1 H), 7.15 (dd, *J* = 0.8, 4.8 Hz, 1 H), 7.23 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.33 (m, 2 H), 7.48 (d, *J* = 2.0 Hz, 1 H), 7.80 (dt, *J* = 1.6, 8.0 Hz, 1 H), 8.29 (d, *J* = 8.0 Hz, 1 H), 8.66 (d, *J* = 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ d 123.2, 124.3, 126.4, 126.5, 127.7, 128.6, 130.6, 131.0, 137.1, 148.6; u 36.6, 43.8, 131.9, 132.6, 137.7, 147.6 (× 2), 152.0, 152.5; IR (neat) 3052, 1589, 1568, 1463 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}Cl_2N_4S_2$ ($[M+H]^+$), 433.0115, found 433.0108.



User Chromatogram Peak List

Peak #	RT	Height	Height %	Area	Area %	Area Sum %	Width
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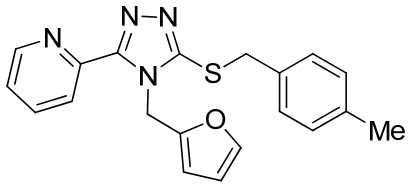
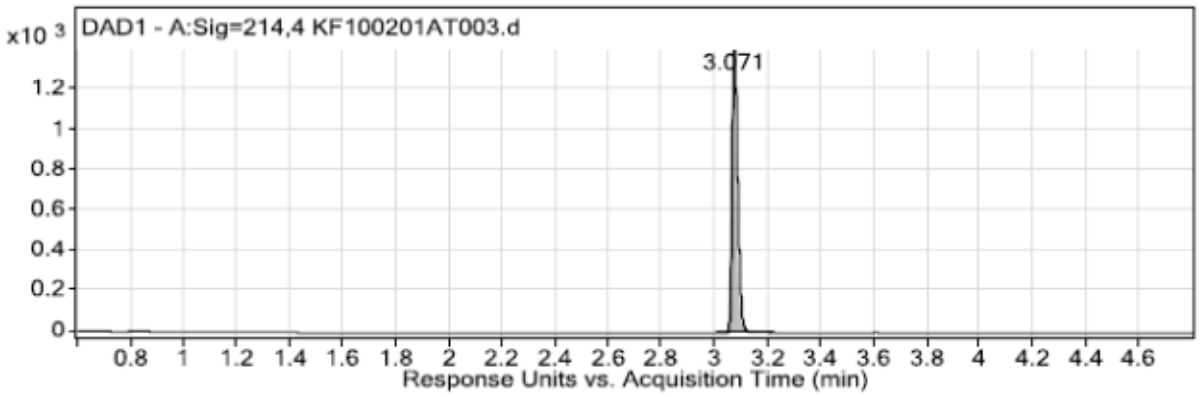


2-(4-(Furan-2-ylmethyl)-5-((4-methylbenzyl)thio)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{10}*. (CID 44601474) Following the general procedure above and purification by silica gel chromatography, furan thione (60 mg, 0.23 mmol) and 4-methylbenzyl bromide (51 mg, 0.28 mmol) afforded the product as a white solid (54 mg, 0.15 mmol, 65% yield). Mp = 102-104 °C; R_f = 0.26 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 4.46 (s, 2 H), 5.80 (s, 2 H), 6.10 (d, *J* = 2.8 Hz, 1 H), 6.19 (m, 1 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 7.23 (d, *J* = 1.2 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.32 (ddd, *J* = 0.8, 4.8, 7.6 Hz, 1 H), 7.80 (dt, *J* = 1.6, 8.0 Hz, 1 H), 8.27 (d, *J* = 8.4 Hz, 2 H), 8.63 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ d 21.1, 108.8, 110.3, 123.3, 124.0, 129.0 (× 2), 129.3 (× 2), 136.9, 142.5, 148.5; u 38.1, 41.8, 133.4, 137.5, 147.8, 149.1, 152.5, 153.0; IR (neat) 2924, 1589, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}N_4OS$ ($[M+H]^+$), 363.1280, found 363.1281.



User Chromatogram Peak List

Peak #	RT	Height	Height %	Area	Area %	Area Sum %	Width
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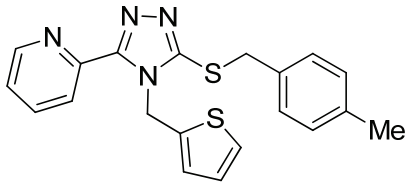
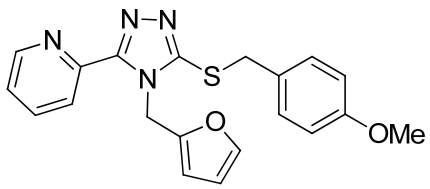
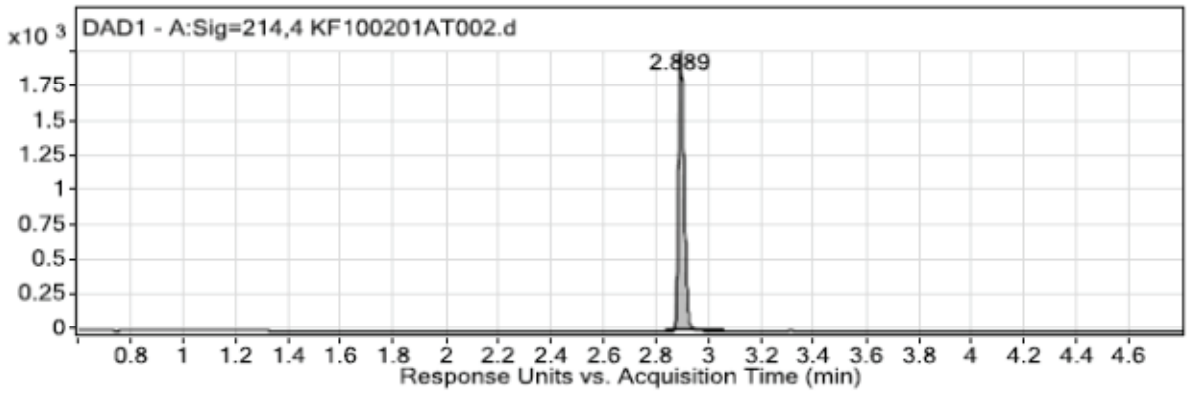


2-(5-((4-Methylbenzyl)thio)-4-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{11}*. (CID 44601473) Following the general procedure above and purification by silica gel chromatography, thiophene thione (65 mg, 0.24 mmol) and 4-methylbenzyl bromide (53 mg, 0.28 mmol) afforded the product as an off-white solid (79 mg, 0.21 mmol, 88% yield). Mp = 97-99 °C; R_f = 0.23 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H), 4.46 (s, 2 H), 5.89 (s, 2 H), 6.83 (dd, *J* = 3.6, 4.8 Hz, 1 H), 6.98 (d, *J* = 3.2 Hz, 1 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 4.8 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.32 (dd, *J* = 4.8, 6.8 Hz, 1 H), 7.79 (dt, *J* = 1.6, 8.0 Hz, 1 H), 8.30 (d, *J* = 7.6 Hz, 1 H), 8.65 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ d 21.1, 123.1, 124.0, 126.2, 126.3, 127.6, 129.0 (× 2), 129.3 (× 2), 136.9, 148.4; u 38.0, 43.5, 133.3, 137.5, 137.8, 147.7, 152.1, 152.7; IR (neat) 3050, 2920, 1589, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}N_4S_2$ ($[M+H]^+$), 379.1051, found 379.1053.



2-(4-(Furan-2-ylmethyl)-5-((4-methoxybenzyl)thio)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{12}*. (CID 2562032) Following the general procedure above and purification by silica gel chromatography, furan thione (57 mg, 0.22 mmol) and 4-methoxybenzyl chloride (42 mg, 0.27 mmol) afforded the product as a white solid (81 mg, 0.21 mmol, 97% yield). Mp = 76-79 °C; R_f = 0.20 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3 H), 4.44 (s, 2 H), 5.78 (s, 2 H), 6.10 (d, *J* = 2.8 Hz, 1 H), 6.18 (dd, *J* = 2.0, 3.2 Hz, 1 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 7.21 (d, *J* = 1.2 Hz, 1 H), 7.30 (m, 3 H), 7.78 (dt, *J* = 1.2, 7.6 Hz, 1 H), 8.26 (d, *J* = 8.0 Hz, 2 H), 8.62 (d, *J* = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ d 55.1, 108.8, 110.2, 114.0 (× 2), 123.2, 123.9, 125.2, 130.2 (× 2), 136.8, 142.4, 148.4; u 37.9, 41.7, 128.4, 147.7, 149.0, 152.4, 152.9, 159.1; IR (neat) 2934, 2836, 1609, 1589, 1511 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}N_4O_2S$ ($[M+H]^+$), 379.1229, found 379.1203.



User Chromatogram Peak List

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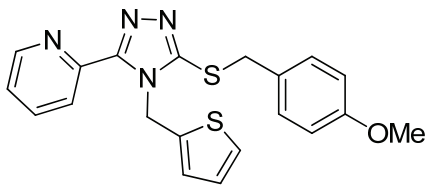
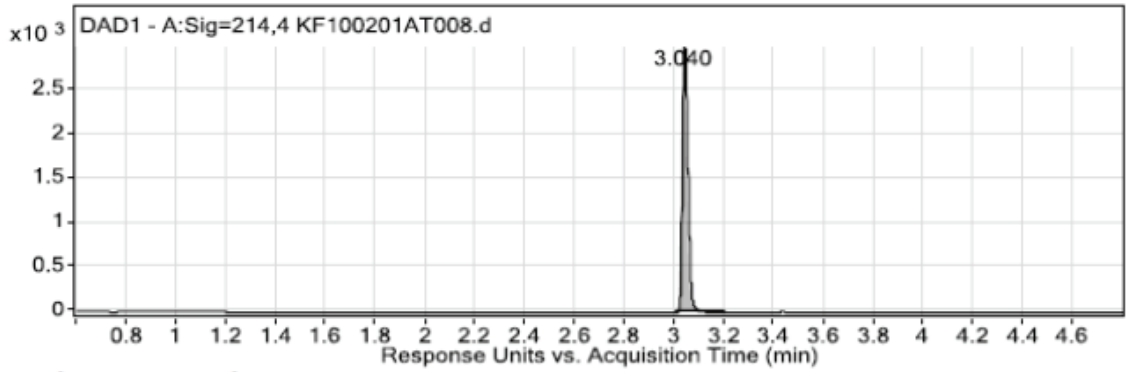
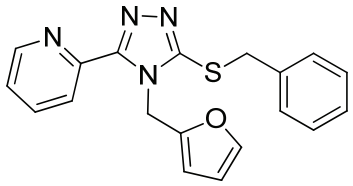


2-(5-((4-Methoxybenzyl)thio)-4-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{13}*. (CID 44601471) Following the general procedure above and purification by silica gel chromatography, thiophene thione (65 mg, 0.24 mmol) and 4-methoxybenzyl bromide (57 mg, 0.28 mmol) afforded the product as an off-white solid (82 mg, 0.21 mmol, 88% yield). Mp = 91-93 °C; R_f = 0.25 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3 H), 4.45 (s, 2 H), 5.89 (s, 2 H), 6.84 (complex, 3 H), 6.98 (d, *J* = 3.2 Hz, 1 H), 7.14 (d, *J* = 4.4 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.34 (d, *J* = 5.6 Hz, 1 H), 7.80 (dt, *J* = 1.2, 8.0 Hz, 1 H), 8.30 (d, *J* = 8.0 Hz, 1 H), 8.67 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ d 55.2, 114.0 (× 2), 123.1, 124.1, 126.2, 126.4, 127.6, 130.3(× 2), 137.0, 148.4; u 37.9, 43.5, 128.4, 137.9, 147.7, 152.1, 152.7, 159.1; IR (neat) 2934, 1609, 1588, 1511, cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}N_4OS_2$ ($[M+H]^+$), 395.1000, found 395.0994.



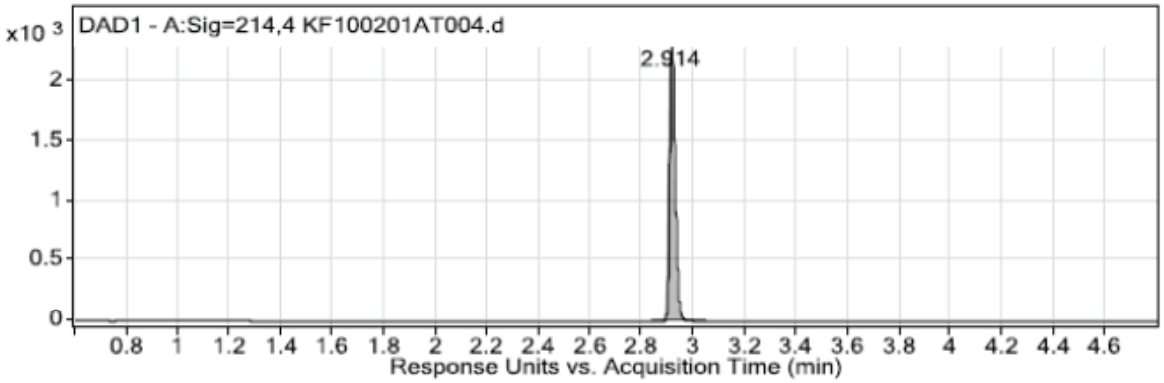
User Chromatogram Peak List

Peak #	RT	Height	Height %	Area	Area %	Area Sum %	Width
1	3.04	2981.16	100	4522.48	100	100	0.024



2-(5-(Benzylthio)-4-(furan-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{14}*. (CID 44601466)

Following the general procedure above and purification by silica gel chromatography, furan thione (60 mg, 0.23 mmol) and benzyl bromide (47 mg, 0.28 mmol) afforded the product as a white solid (56 mg, 0.16 mmol, 70% yield). Mp = 105-106 °C; R_f = 0.19 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.48 (s, 2 H), 5.78 (s, 2 H), 6.10 (d, *J* = 2.8 Hz, 1 H), 6.18 (dd, *J* = 2.4, 3.2 Hz, 1 H), 7.22-7.39 (complex, 7 H), 7.78 (dt, *J* = 1.6, 8.0 Hz, 1 H), 8.27 (d, *J* = 8.0 Hz, 2 H), 8.62 (d, *J* = 4.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ d 108.8, 110.3, 123.3, 124.0, 127.7, 128.6 (× 2), 129.0 (× 2), 136.9, 142.5, 148.4; u 38.3, 41.7, 136.5, 147.7, 149.0, 152.5, 152.8; IR (neat) 3029, 1589, 1496 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}N_4OS$ ($[M+H]^+$), 349.1123, found 349.1127.



User Chromatogram Peak List

Peak #	RT	Height	Height %	Area	Area %	Area Sum %	Width
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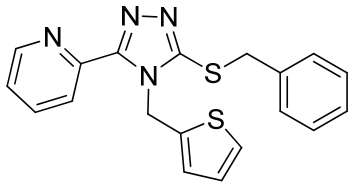
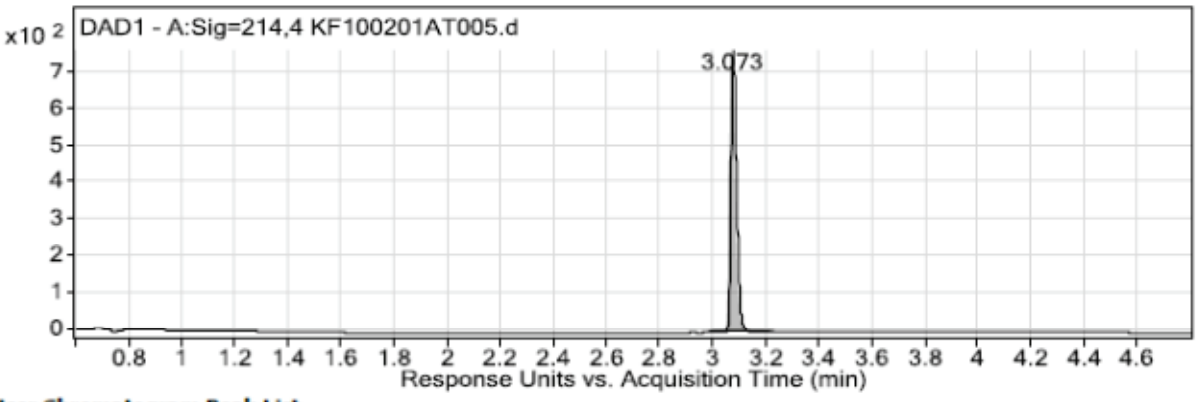


2-(5-(Benzylthio)-4-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{15}*. (CID 44601467) Following the general procedure above and purification by silica gel chromatography, thiophene thione (65 mg, 0.24 mmol) and benzyl bromide (49 mg, 0.28 mmol) afforded the product as an off-white solid (72 mg, 0.20 mmol, 83% yield). Mp = 107-109 °C; R_f = 0.25 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.49 (s, 2 H), 5.89 (s, 2 H), 6.84 (t, *J* = 4.0 Hz, 1 H), 6.99 (m, 1 H), 7.14 (d, *J* = 3.2 Hz, 1 H), 7.26-7.39 (complex, 6 H), 7.81 (t, *J* = 7.2 Hz, 1 H), 8.31 (d, *J* = 8.0 Hz, 2 H), 8.66 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ d 123.2, 124.1, 126.2, 126.4, 127.6, 127.7, 128.6 (× 2), 129.1 (× 2), 137.0, 148.4; u 38.3, 43.5, 136.5, 137.8, 147.7, 152.2, 152.6; IR (neat) 3060, 1588, 1462 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}N_4S_2$ ($[M+H]^+$), 365.0895, found 365.0893.



User Chromatogram Peak List

Peak #	RT	Height	Height %	Area	Area %	Area Sum %	Width
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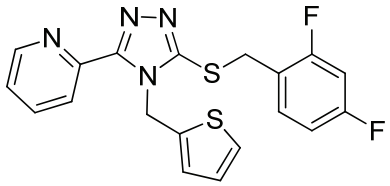
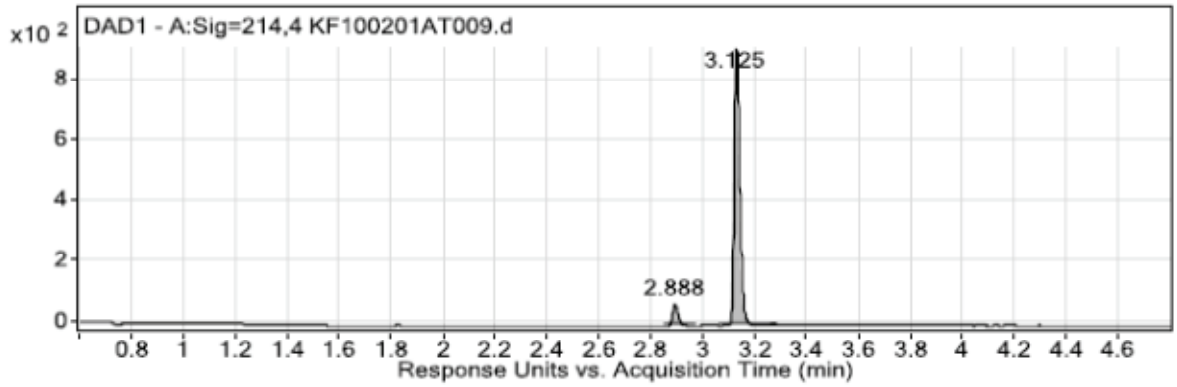


2-(5-((2,4-Difluorobenzyl)thio)-4-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)pyridine 2*{16}*. (CID 44601468) Following the general procedure above and purification by silica gel chromatography, thiophene thione (65 mg, 0.24 mmol) and 2,4-difluorobenzyl bromide (59 mg,

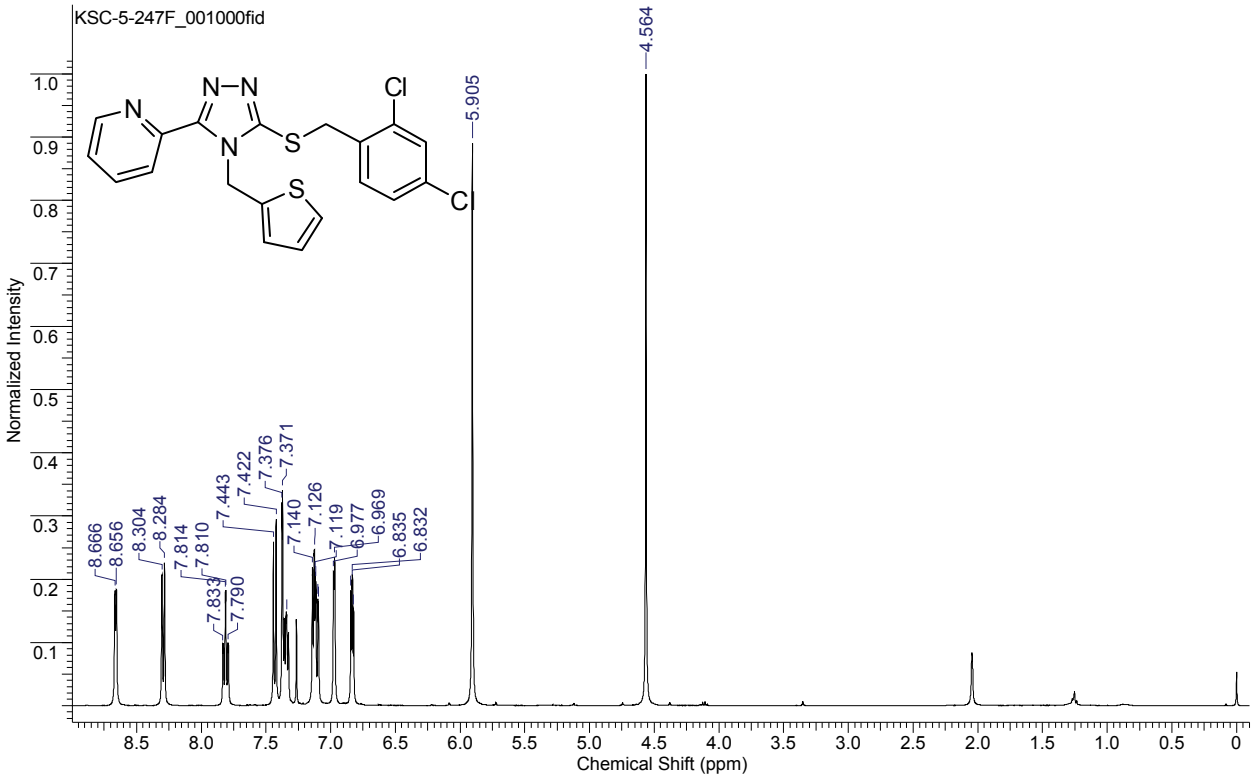
0.28 mmol) afforded the product as a light yellow solid (68 mg, 0.17 mmol, 72% yield). Mp = 122-124 °C; R_f = 0.29 (1:1 Hexanes: EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.49 (s, 2 H), 5.93 (s, 2 H), 6.74-6.85 (complex, 3 H), 6.92 (dd, *J* = 1.2, 3.2 Hz, 1 H), 7.14 (dd, *J* = 1.2, 4.8 Hz, 1 H), 7.34 (dd, *J* = 5.2, 6.8 Hz, 1 H), 7.43 (dt, *J* = 6.4, 8.8 Hz, 1 H), 7.81 (dt, *J* = 1.6, 8.0 Hz, 1 H), 8.30 (d, *J* = 8.4 Hz, 1 H), 8.67 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ d 103.9 (t, *J* = 25 Hz), 111.2 (d, *J* = 25 Hz), 123.1, 124.2, 126.3, 126.4, 127.6, 132.2, 137.0, 148.4; u 30.5, 43.6, 120.0, 120.1, 137.6, 147.5, 152.3, 160.5 (dd, *J* = 12, 172 Hz), 162.9 (dd, *J* = 12, 167 Hz); IR (neat) 3053, 1617, 1603, 1589, 1502 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}F_2N_4S_2$ ($[M+H]^+$), 401.0706, found 401.0704.

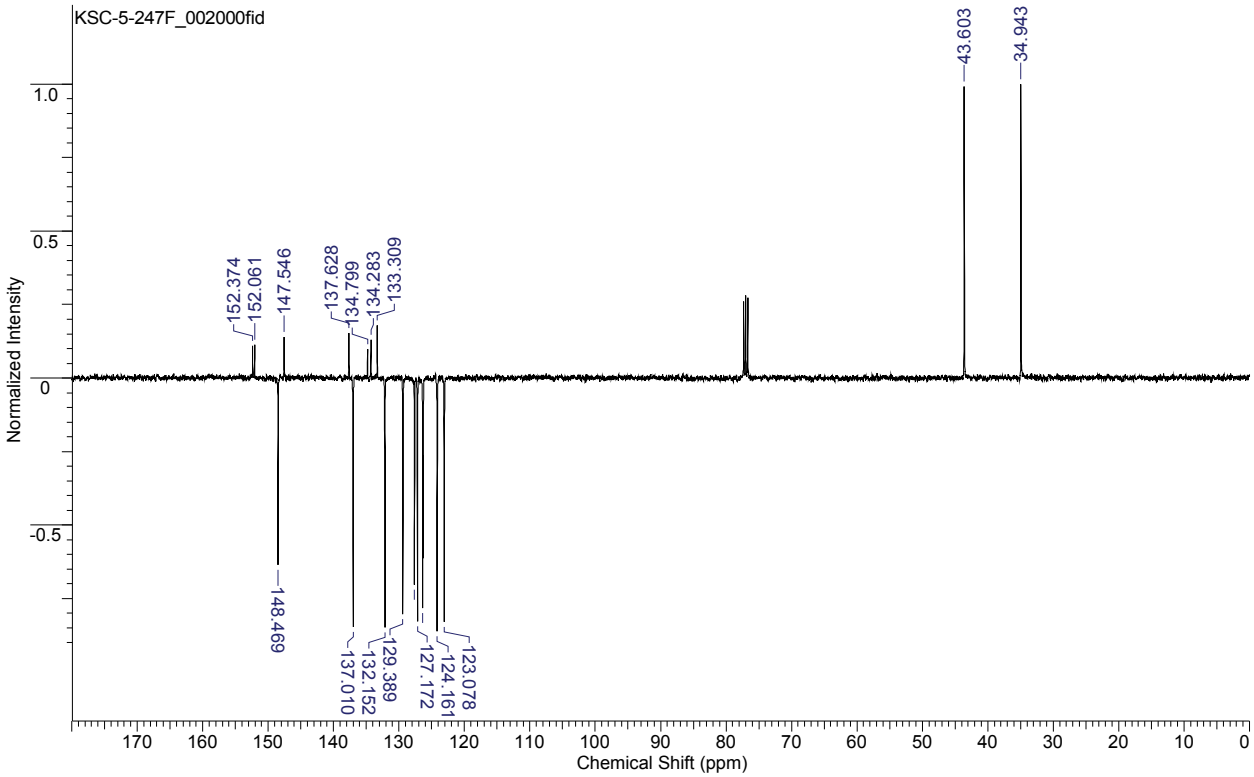


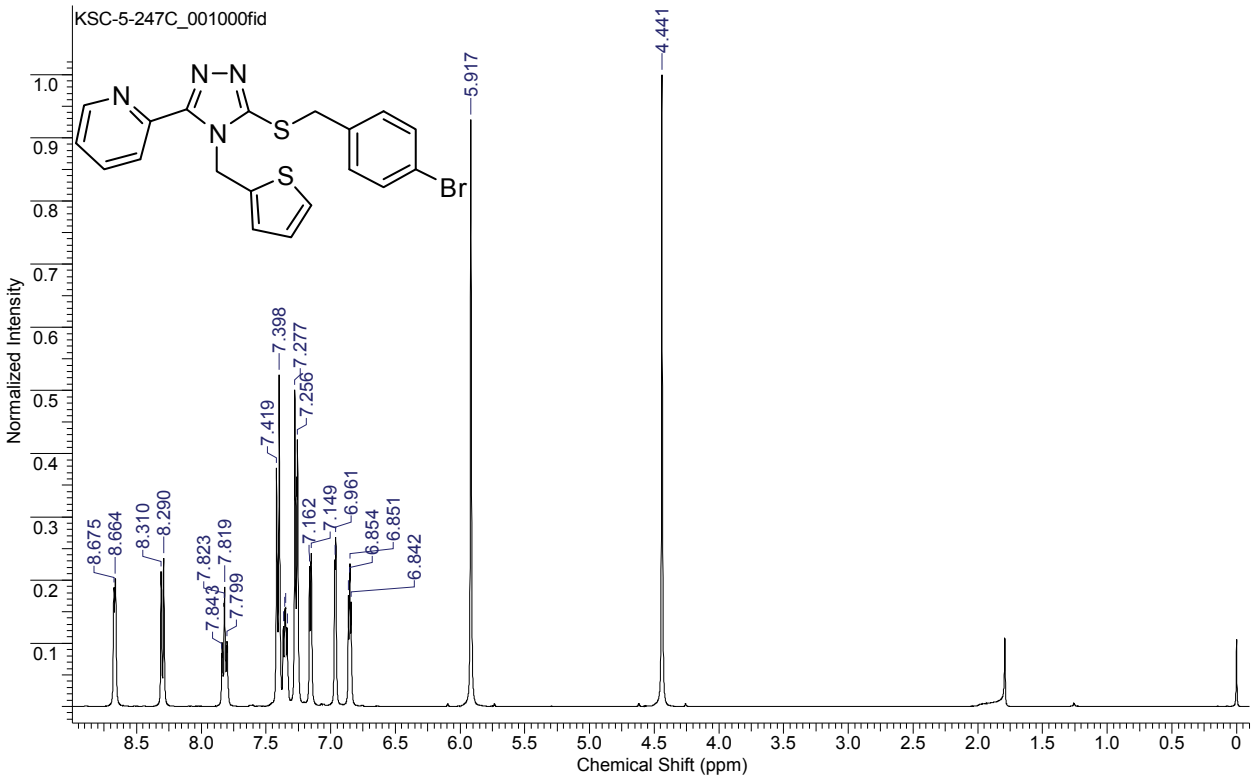
User Chromatogram Peak List

Peak #	RT	Height	Height %	Area	Area %	Area Sum %	Width
1	2.888	67.5	7.47	98.15	7.46	6.94	0.023
2	3.125	903.64	100	1316.28	100	93.06	0.023

NMR spectra for Chemotype II compounds and new synthetic intermediates.



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6.851
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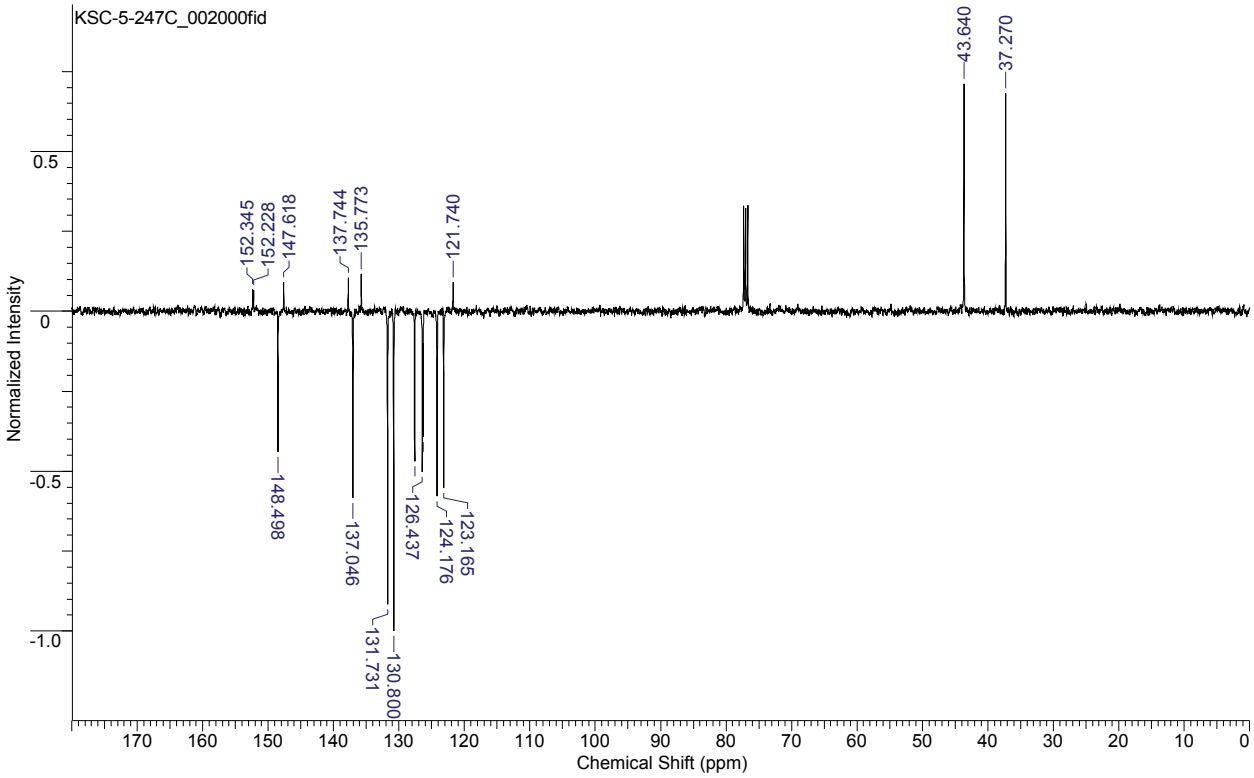
5.917
4.441
Br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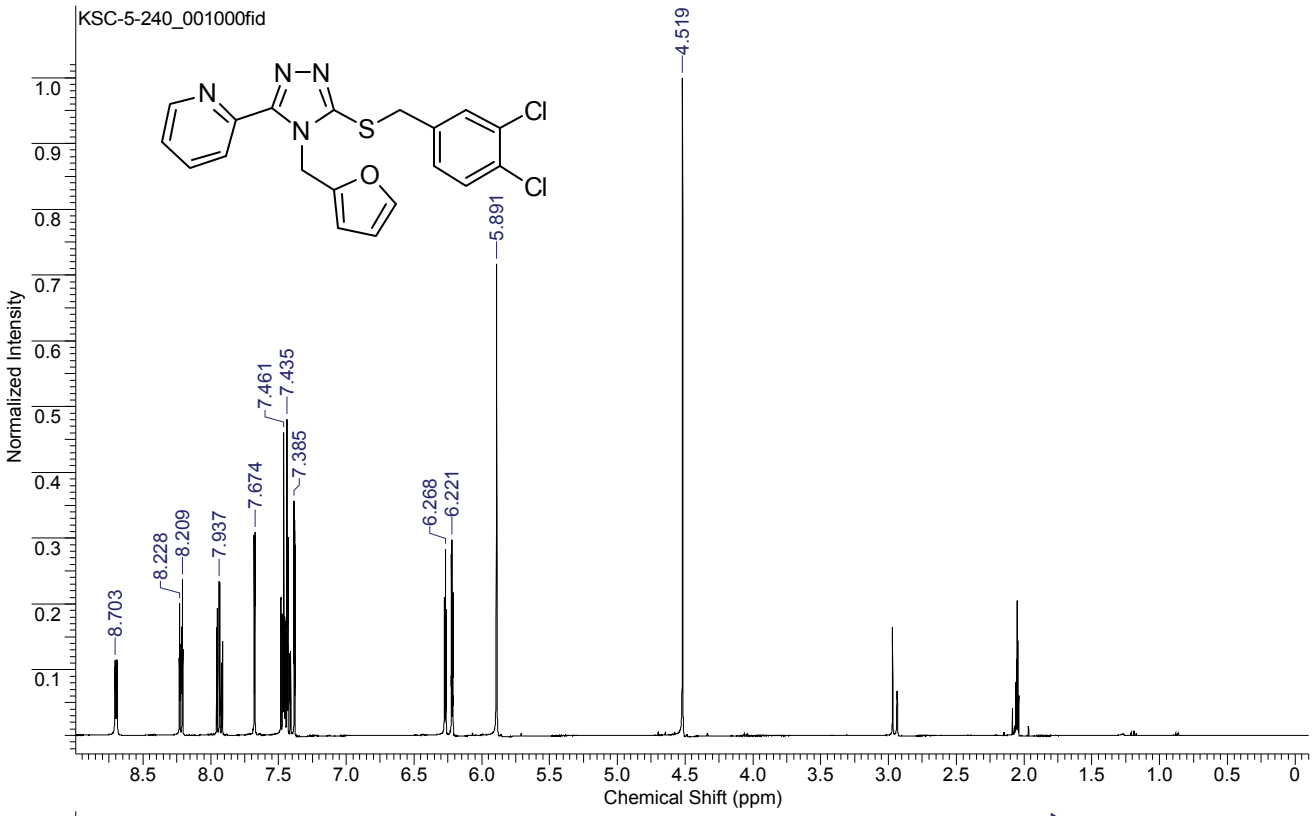
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6.221
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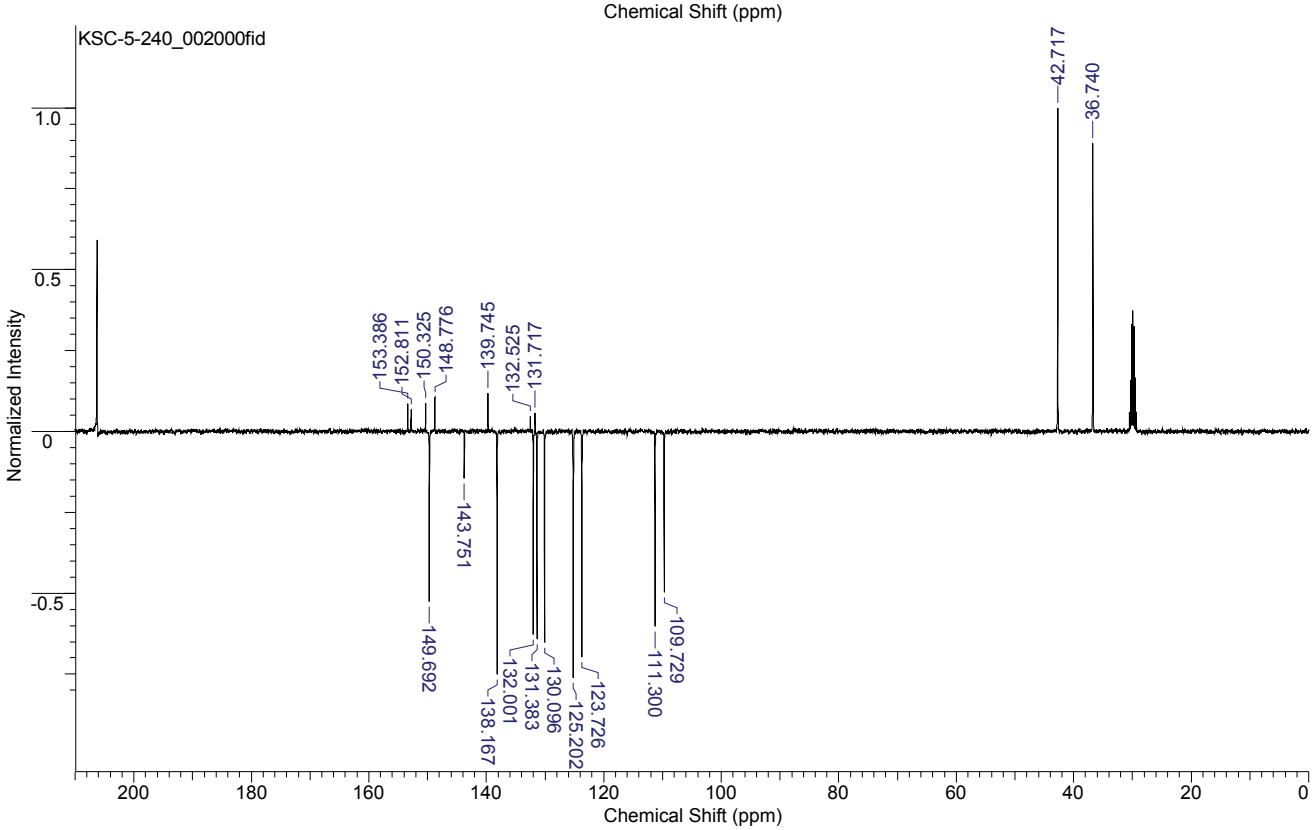
4.519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130.096
125.202
123.726
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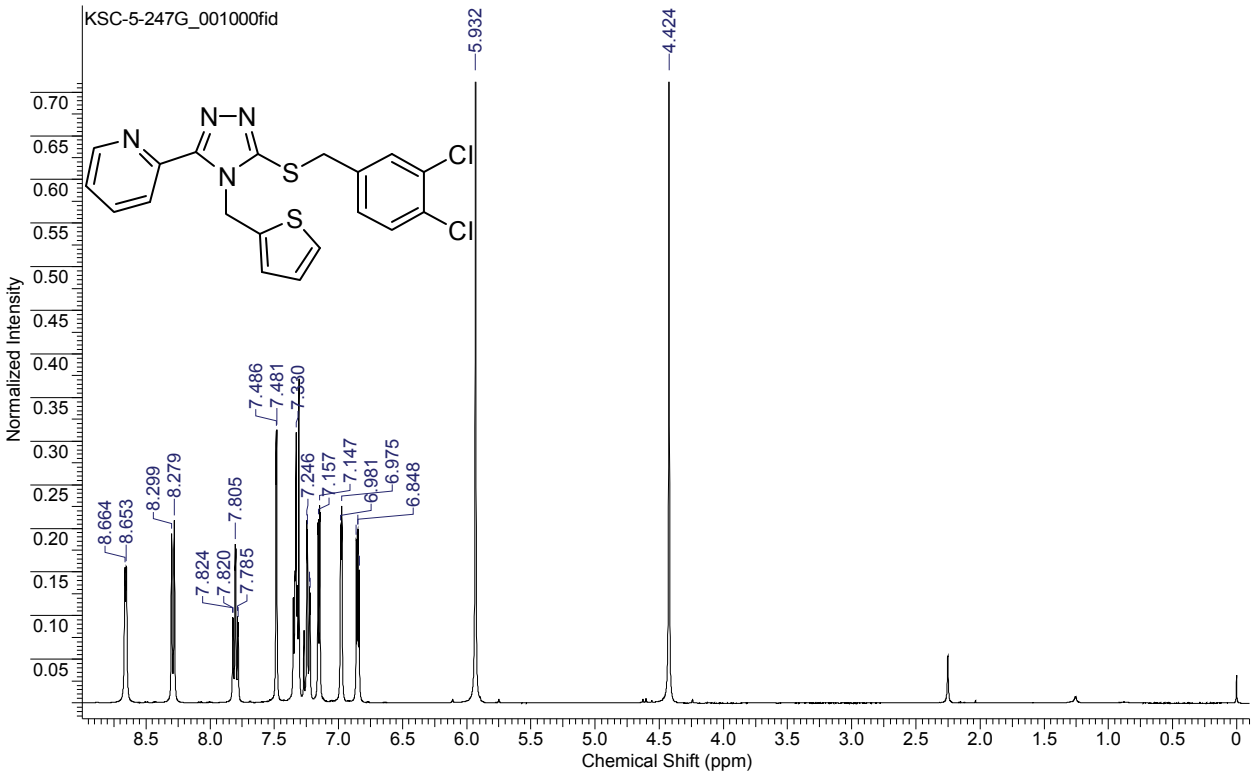
36.740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N–N
N
N
S
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Cl
Cl
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0.30
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0.20
0.15
0.10
0.05
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8.653
8.299
8.279
7.824
7.820
7.805
7.785
7.486
7.481
7.246
7.157
7.147
6.981
6.975
6.848
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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1.5
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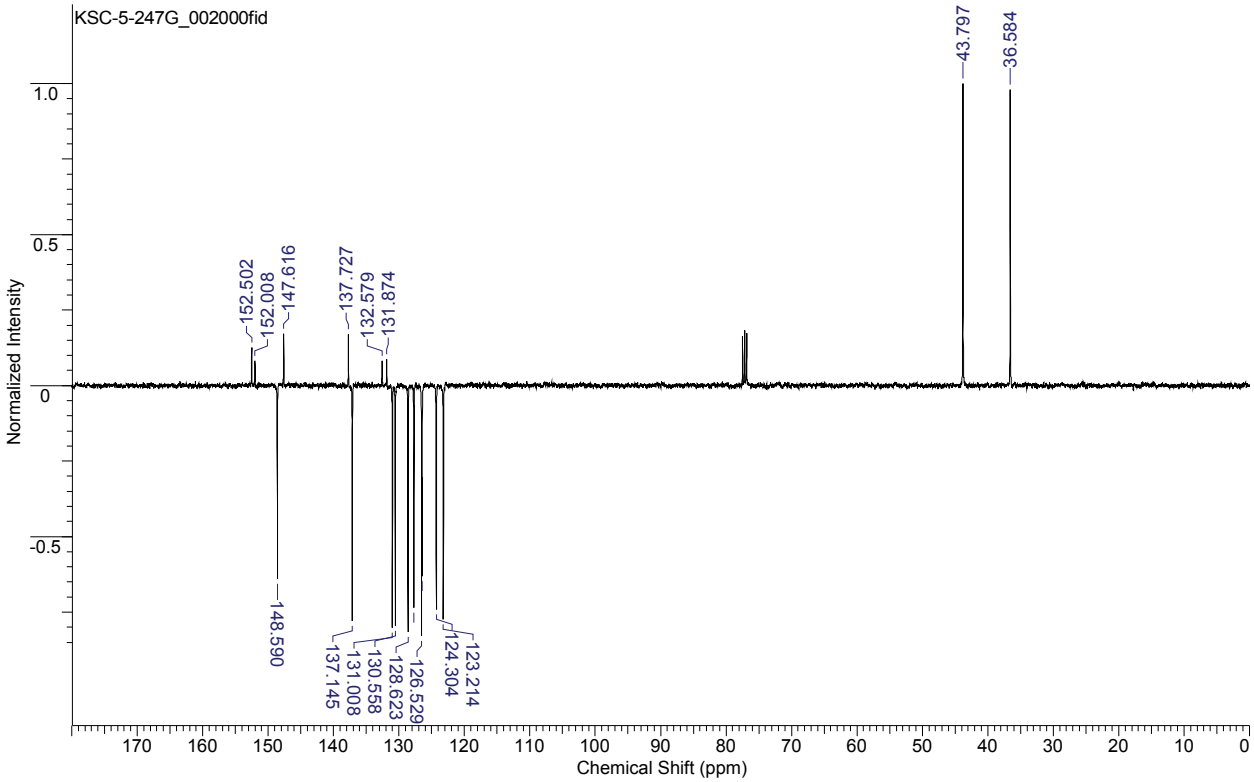
Chemical Shift (ppm)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137.145
131.008
130.558
128.623
126.529
124.304
123.214
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120
110
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90
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70
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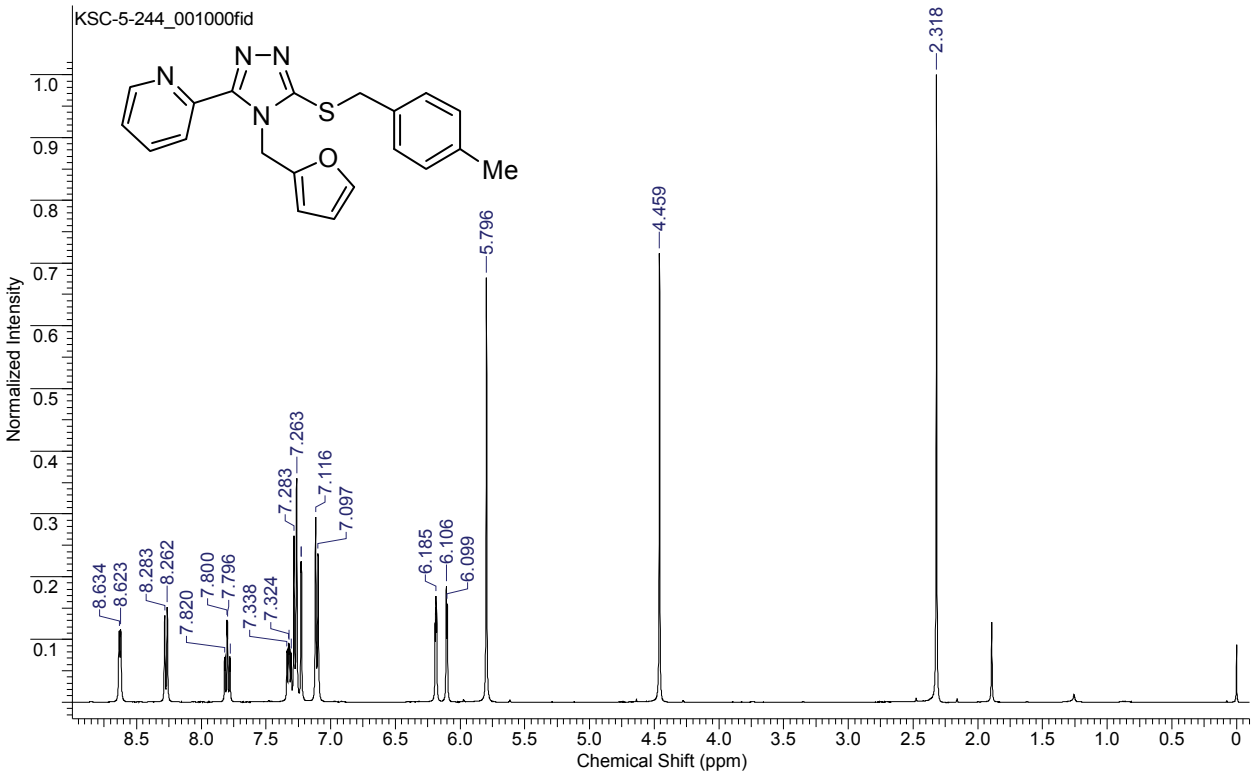
50
40
30
20
10
0
Chemical Shift (ppm)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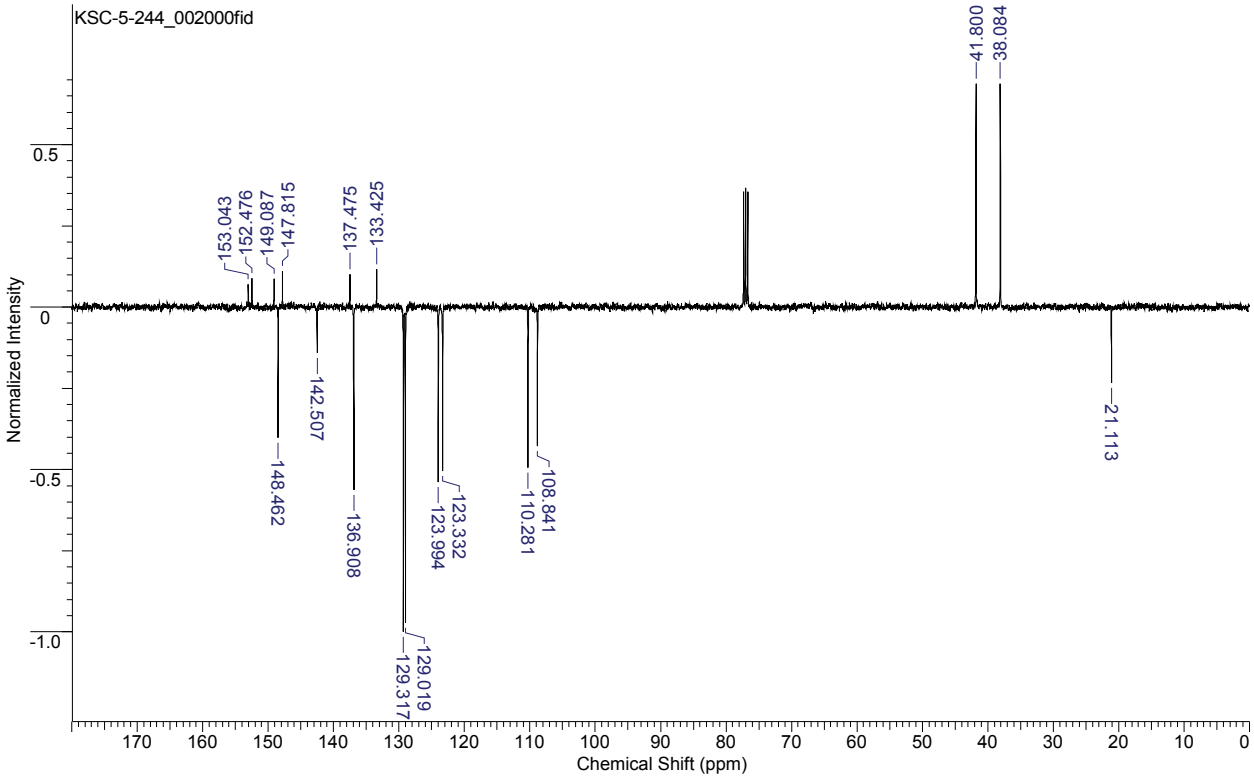
Me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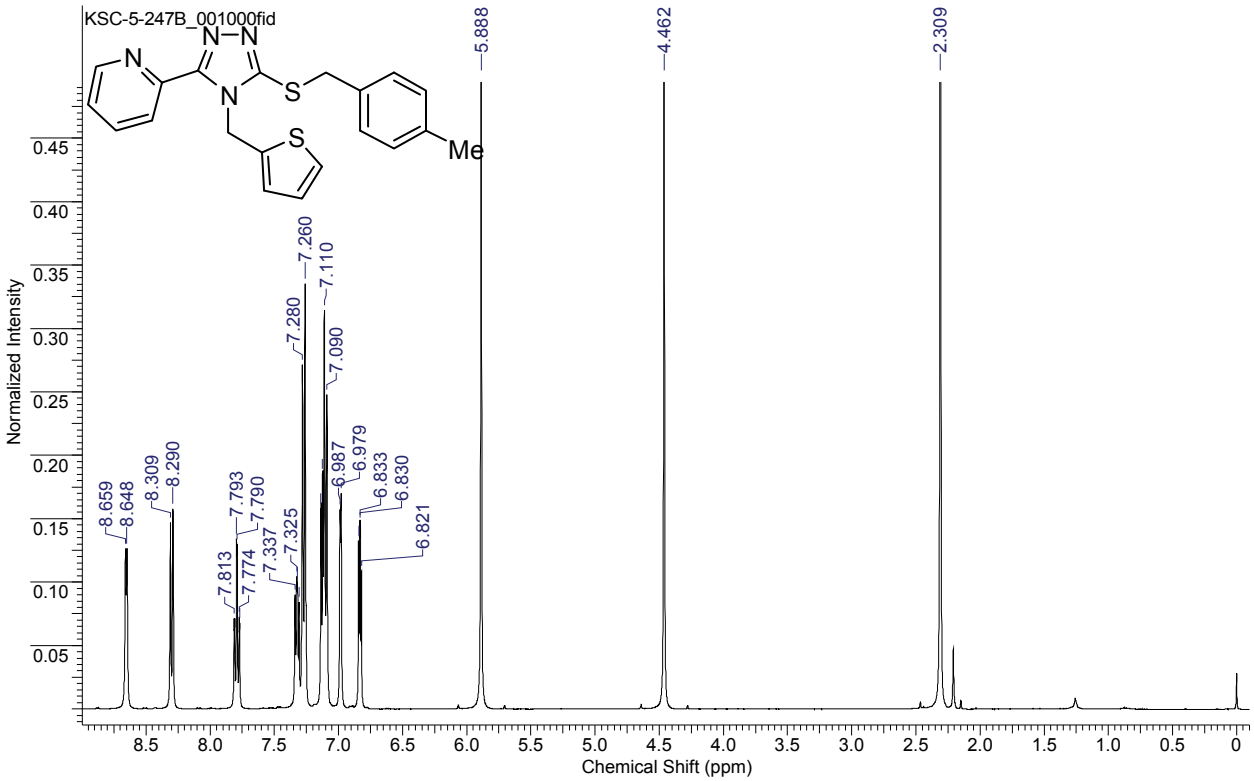
152.476
153.043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7.337
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7.090
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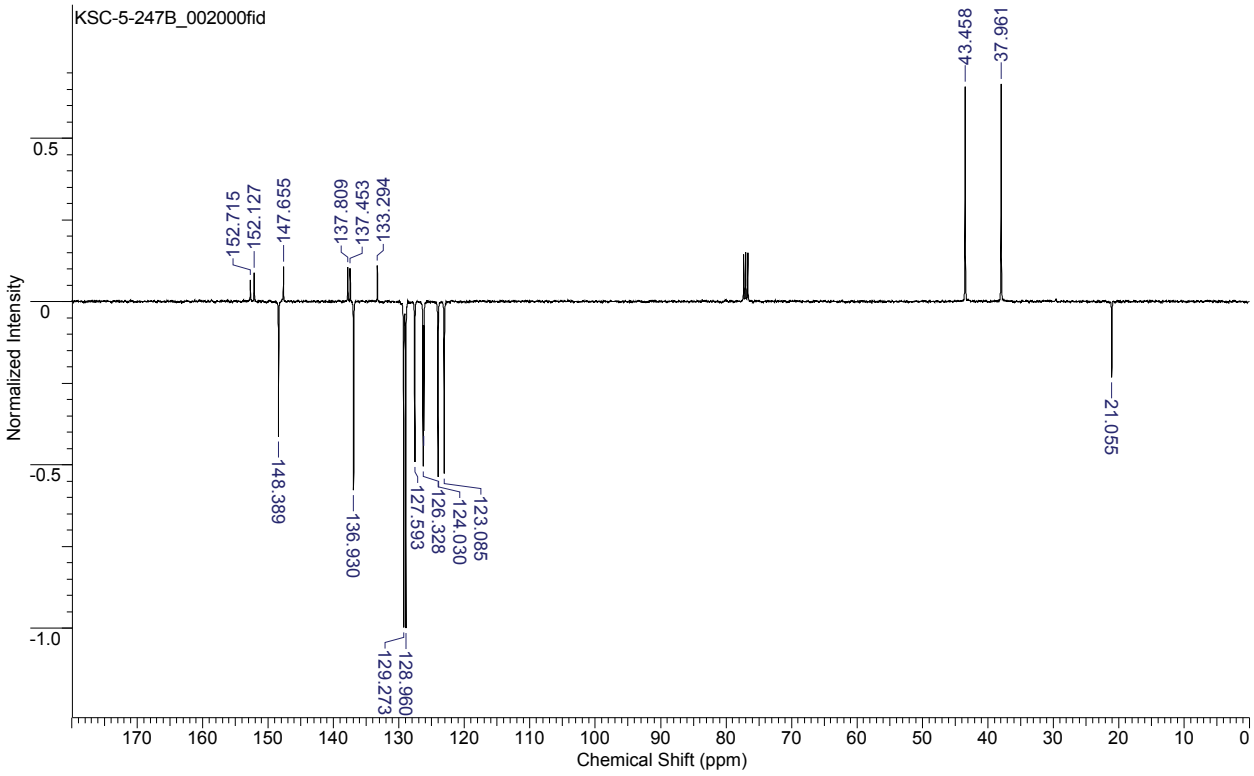
6.830
6.821
Normalized Intensity
Chemical Shift (ppm)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128.960
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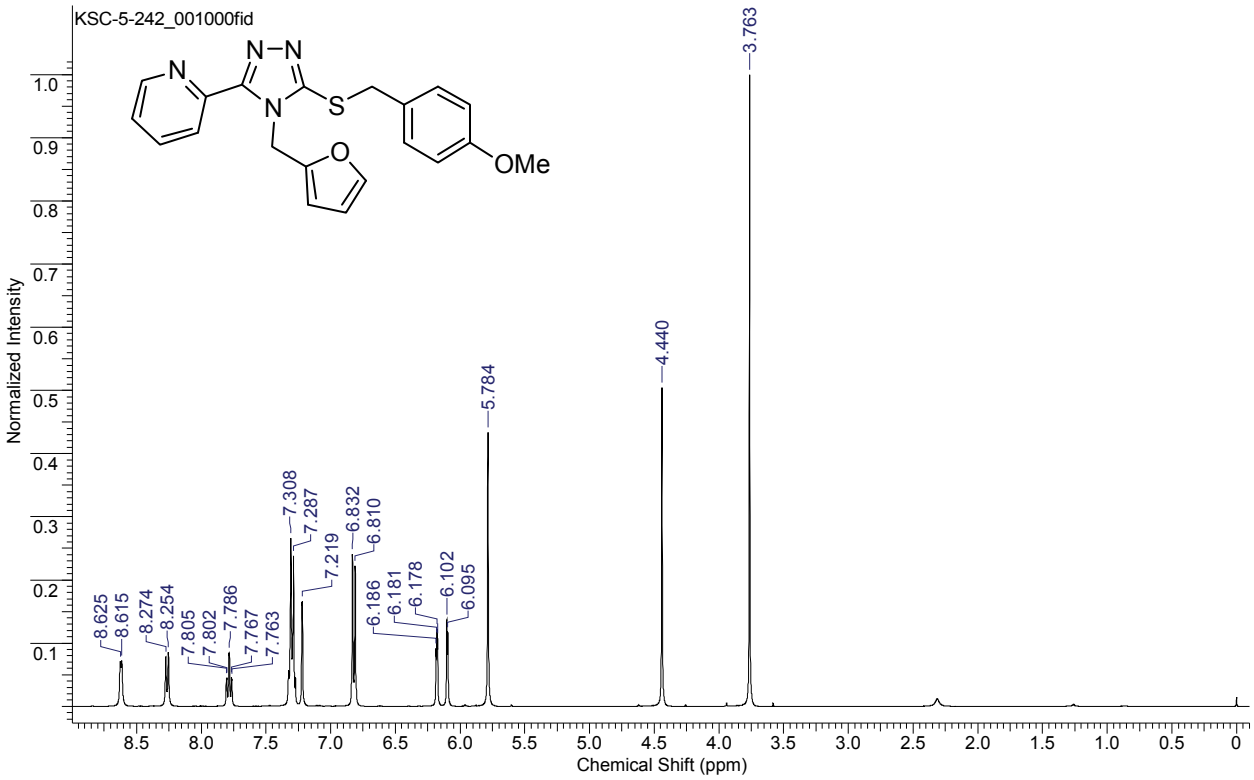
124.030
123.085
21.055
Normalized Intensity
Chemical Shift (ppm)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N–N
N
S
O
OMe
Normalized Intensity
Chemical Shift (ppm)
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8.254
7.805
7.802
7.786
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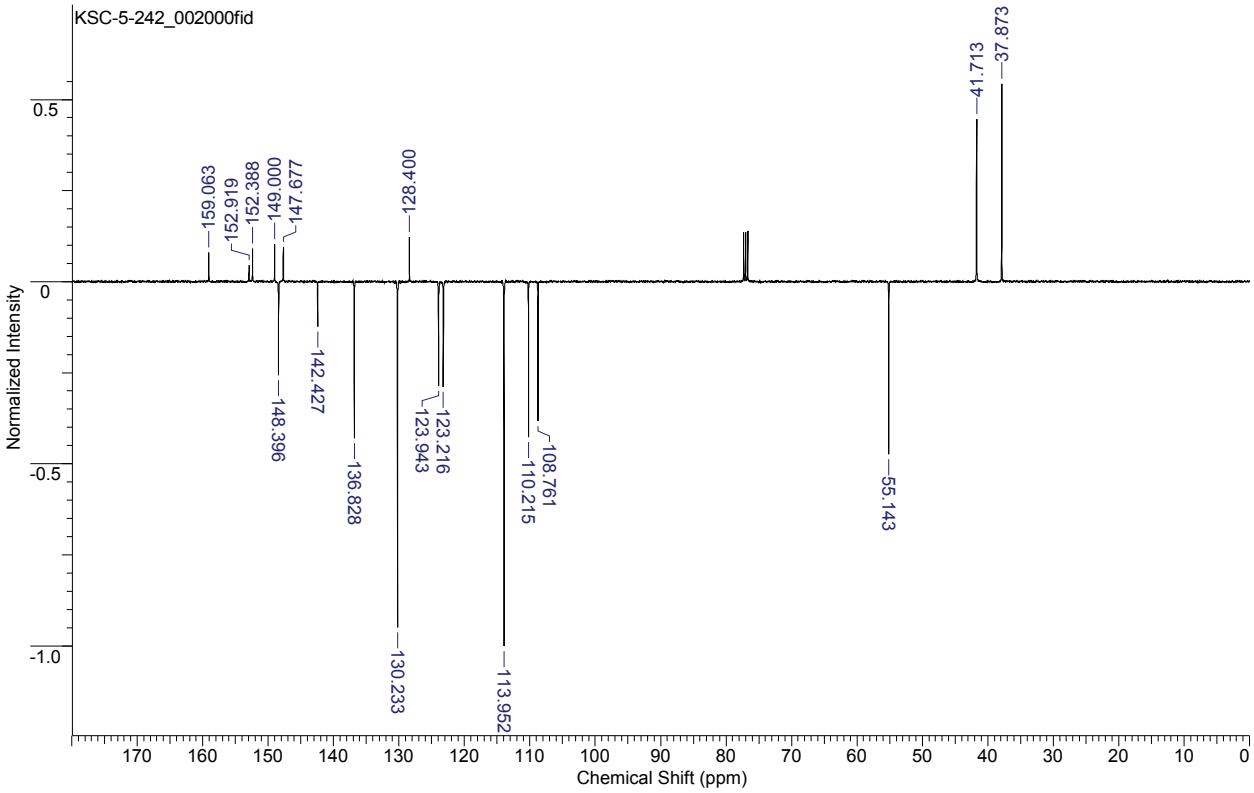
6.810
6.186
6.181
6.178
6.102
6.095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Normalized Intensity
Chemical Shift (ppm)
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113.952
110.215
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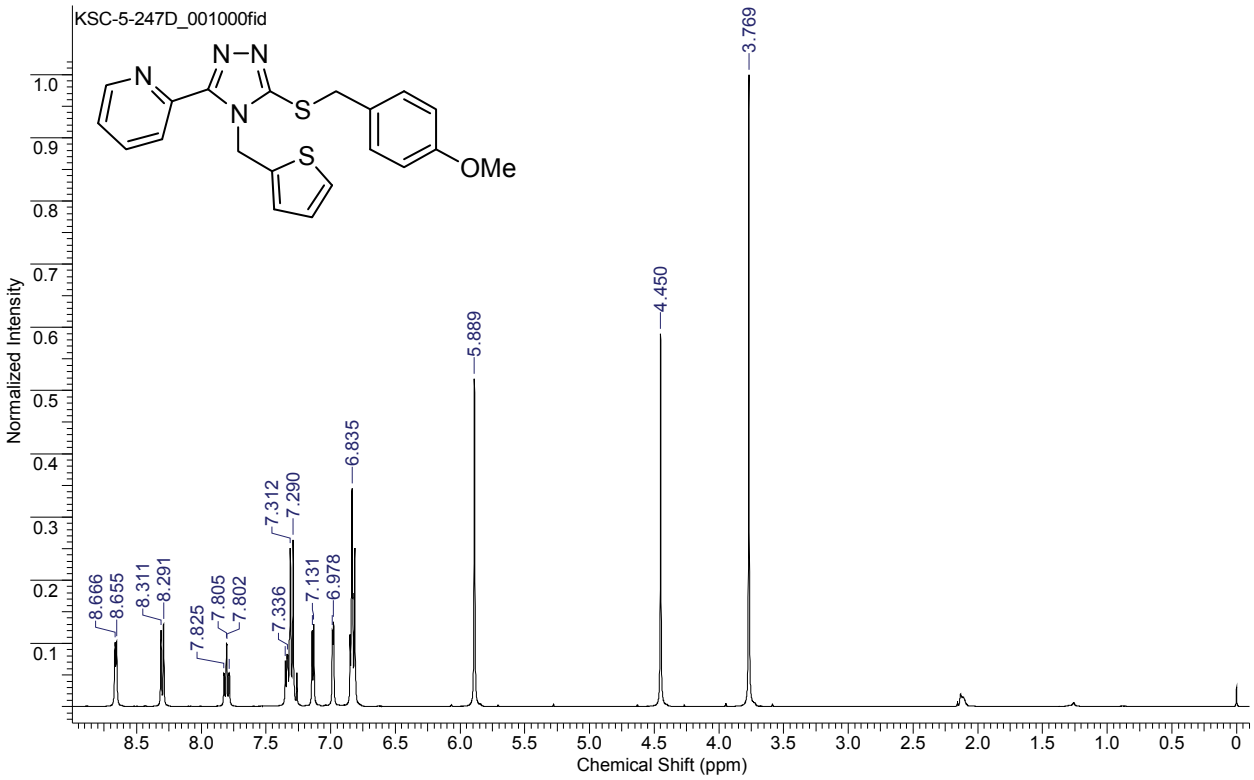
55.143
41.713
37.873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N–N
N
N
S
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OMe
Normalized Intensity
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7.802
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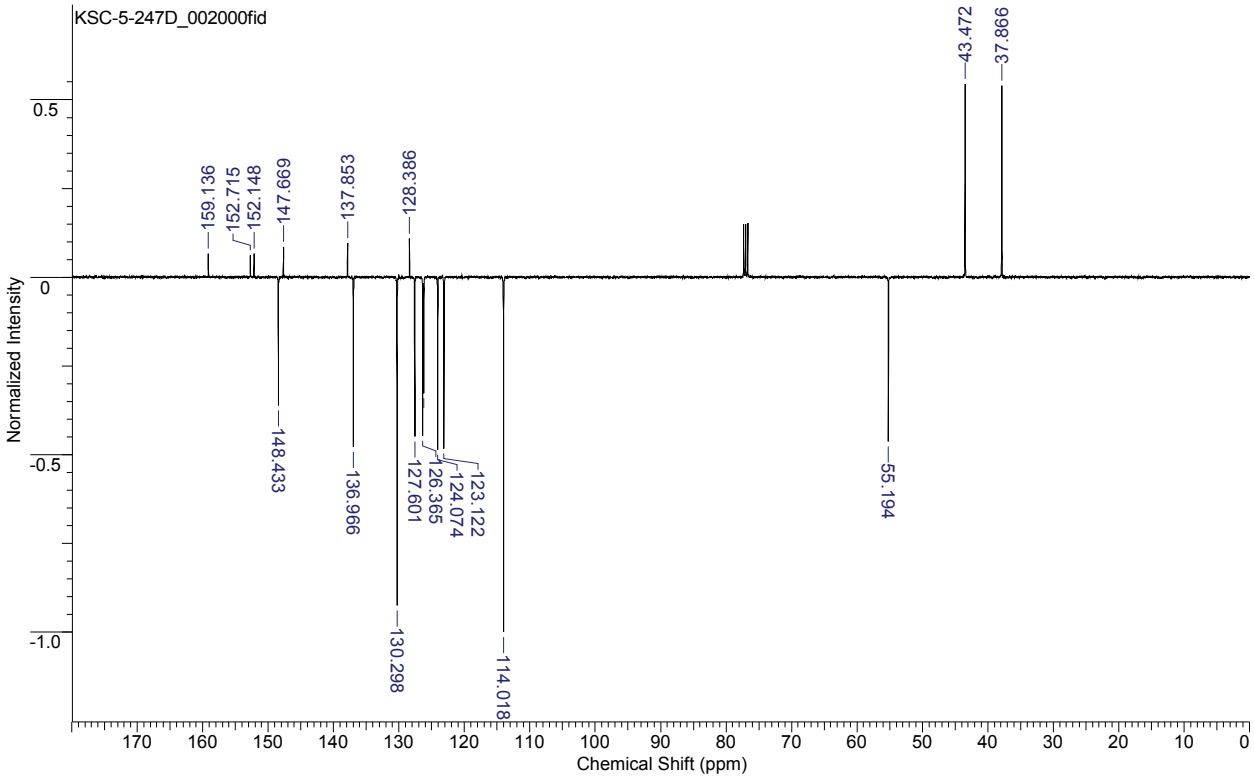
8.311
8.291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Normalized Intensity
Chemical Shift (ppm)
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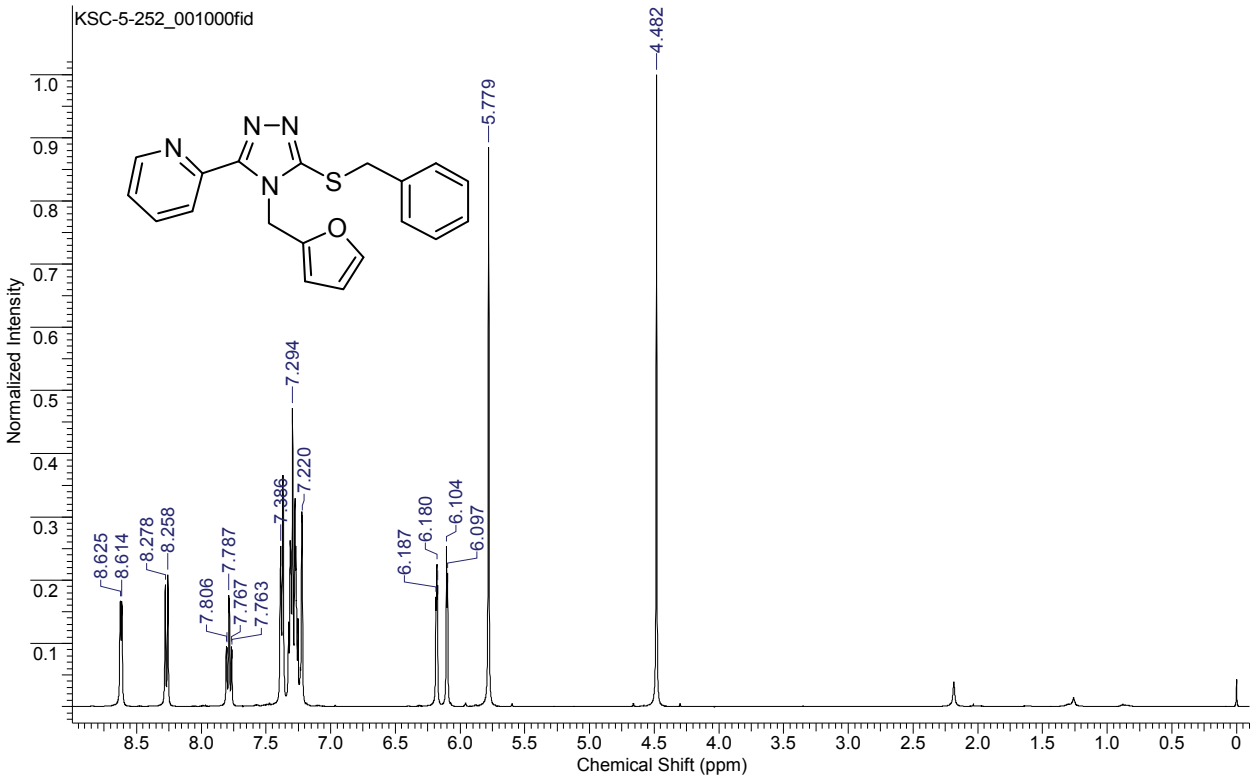
127.601
126.365
124.074
123.122
114.018
55.194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Normalized Intensity
Chemical Shift (ppm)
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7.220
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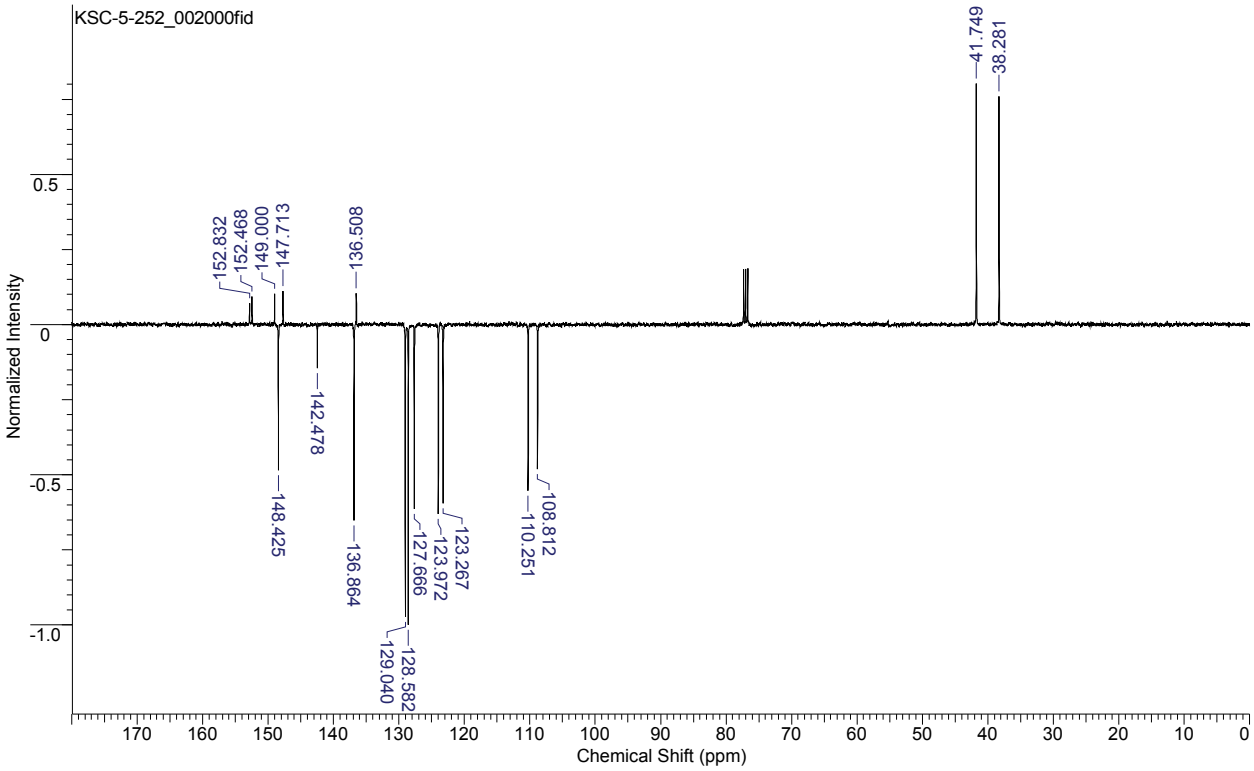
6.180
6.104
6.097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Normalized Intensity
Chemical Shift (ppm)
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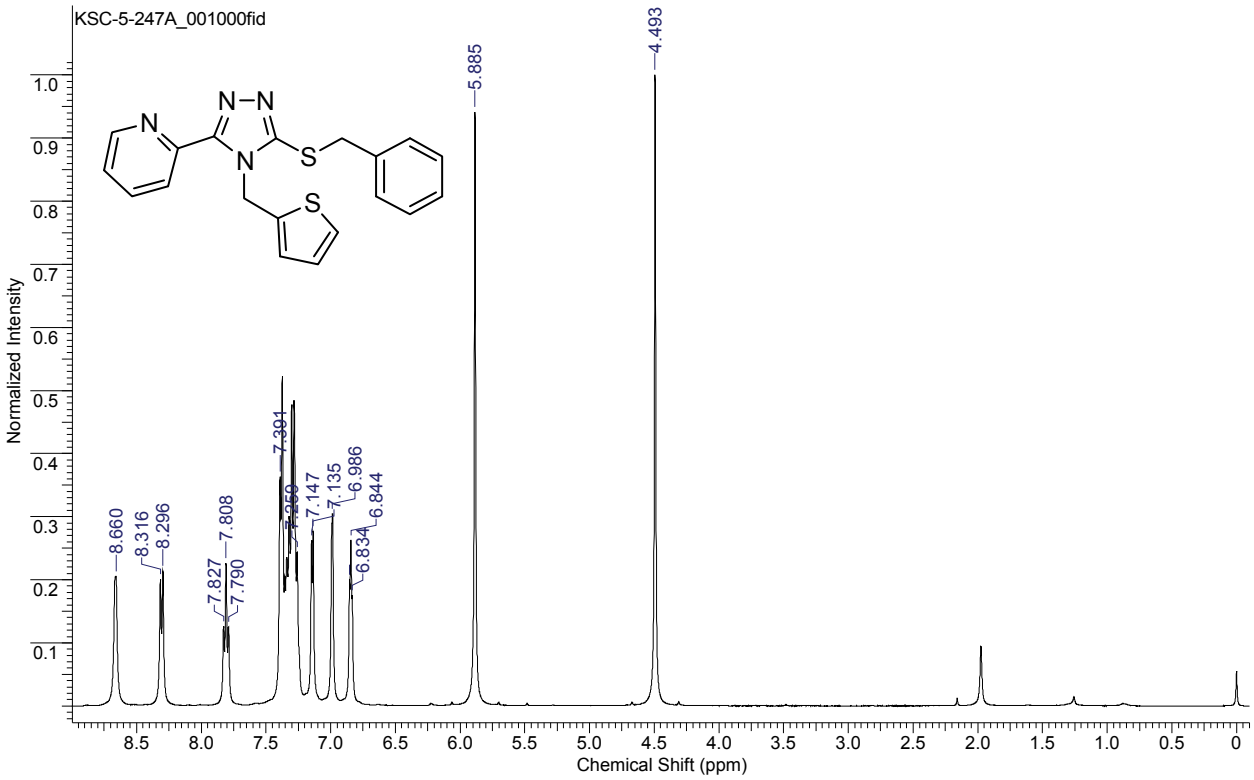
110.251
108.812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Normalized Intensity
Chemical Shift (ppm)
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7.391
7.147
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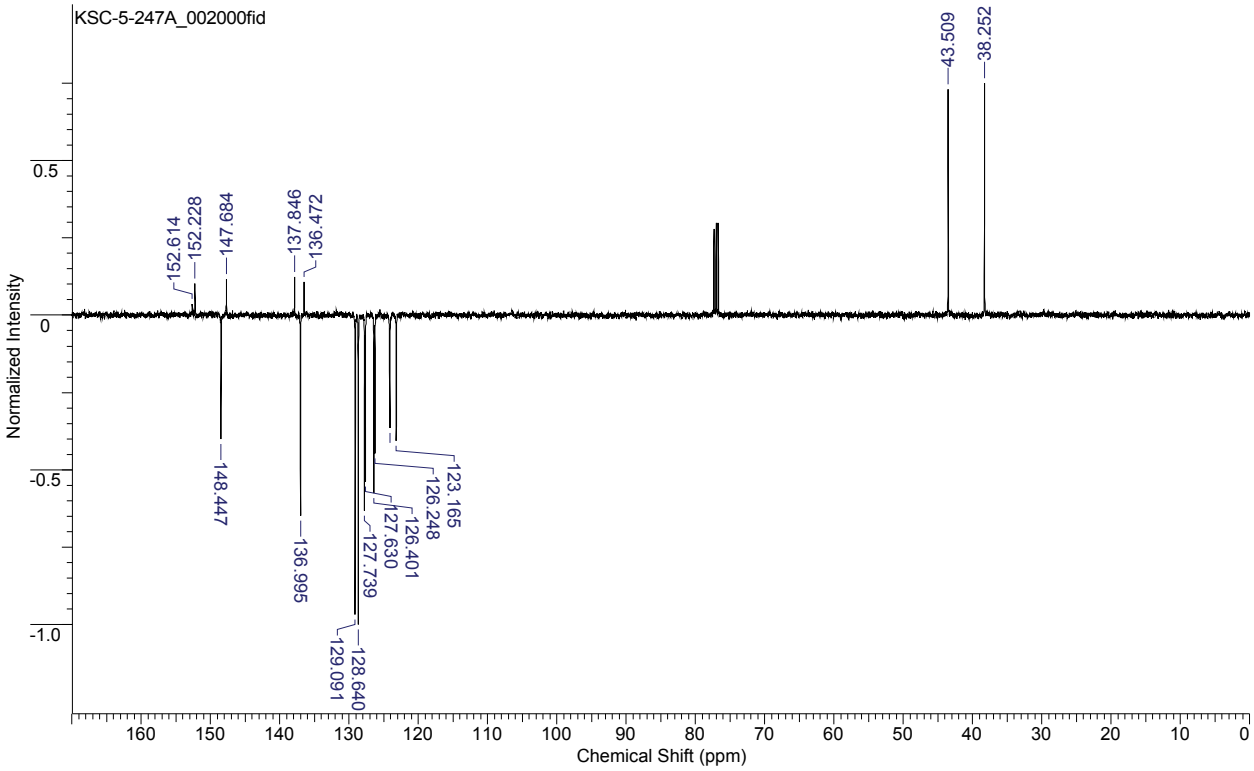
6.844
6.834
5.885
4.493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Normalized Intensity
Chemical Shift (ppm)
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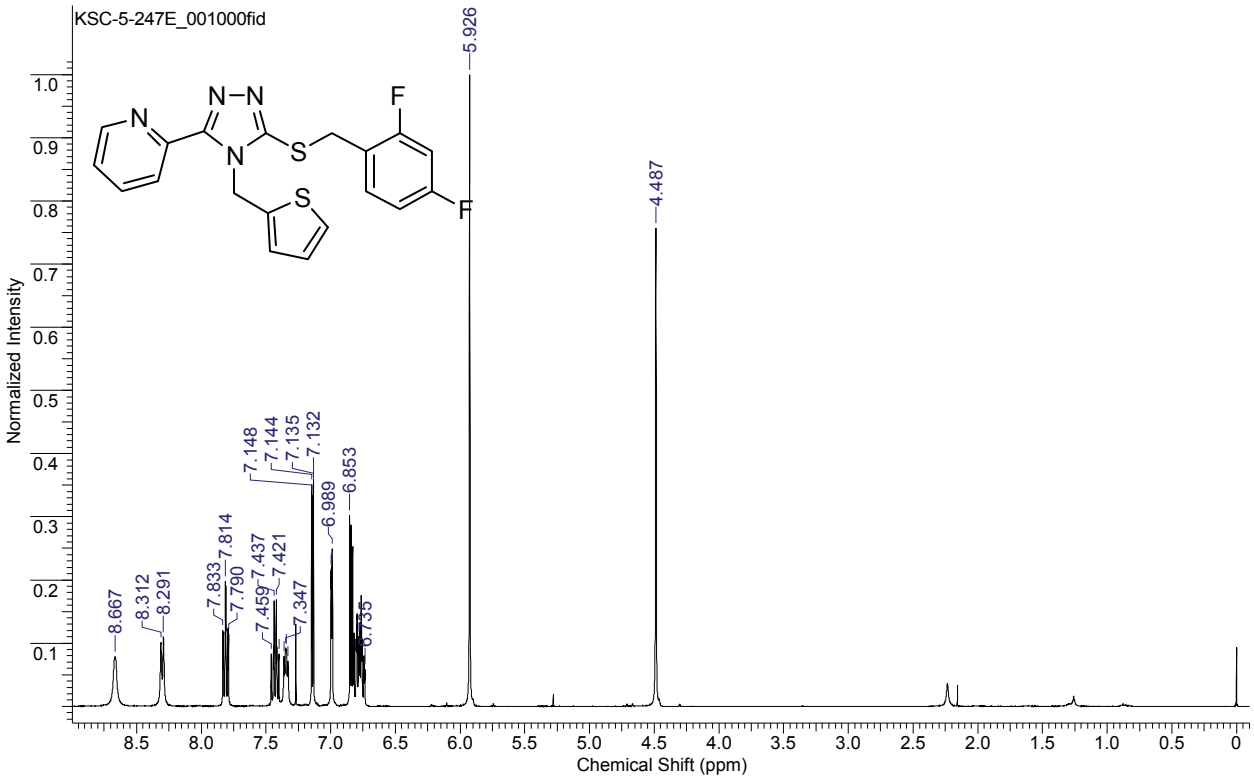
126.401
126.248
123.165
43.509
38.252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Normalized Intensity
Chemical Shift (ppm)
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7.790
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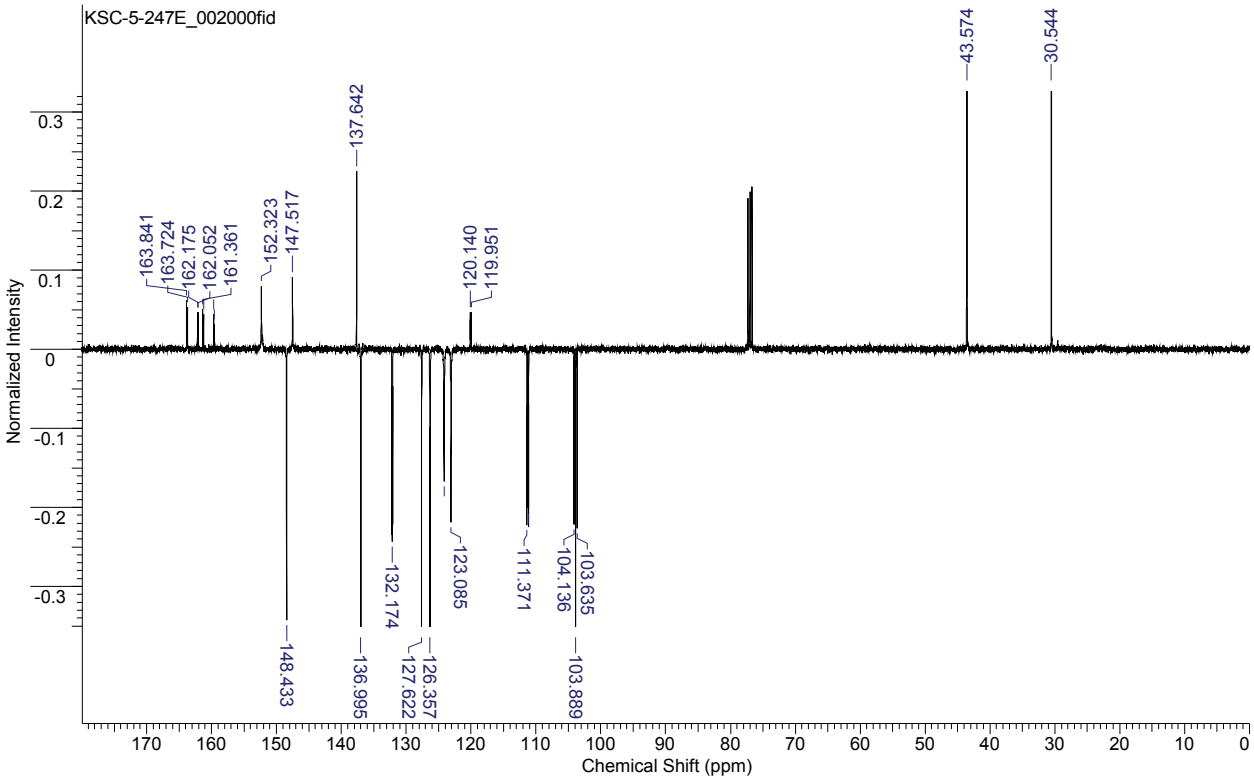
7.148
7.144
7.135
7.132
6.989
6.853
6.735
5.926
4.487


KSC-5-247E_002000fid
Normalized Intensity
Chemical Shift (ppm)
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43.574
30.544
148.433
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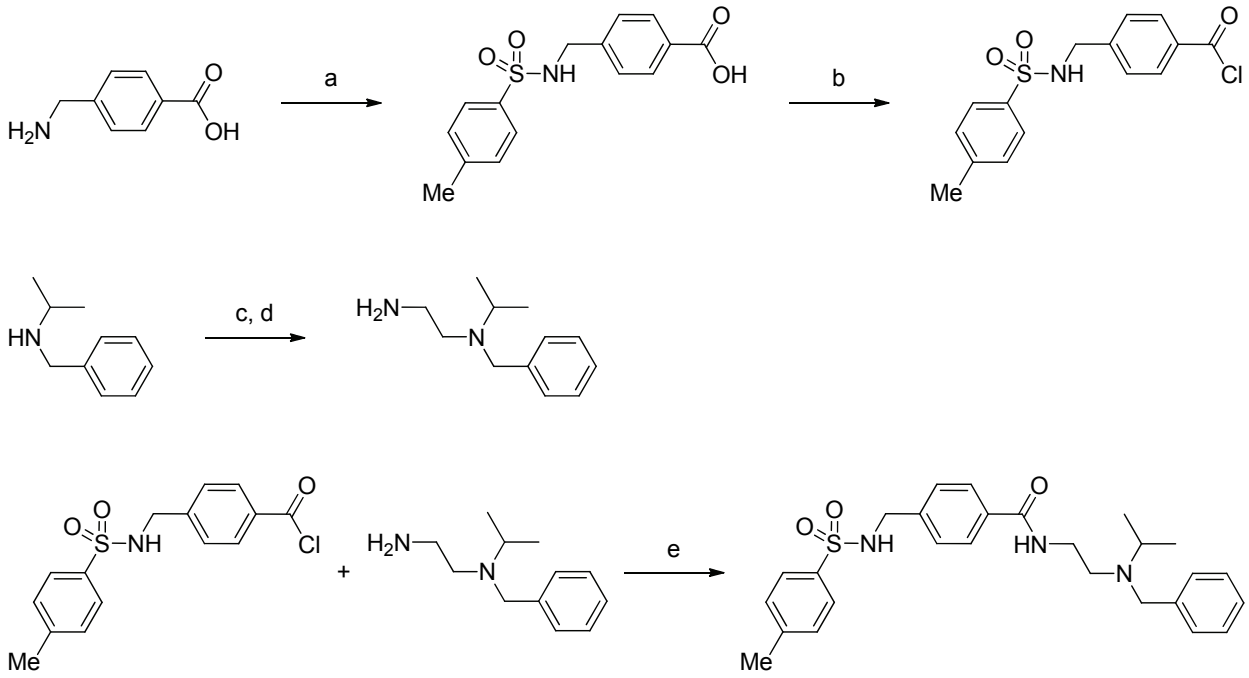
132.174
127.622
126.357
123.085
111.371
104.136
103.635
103.889

Synthesis of Antagonist Chemotype III Compounds 3*{n}*.

Compounds **3*{1}***, **3*{2}*** and **3*{3}*** are available as milligram quantity dry powder samples from several commercial vendors of screening compounds.

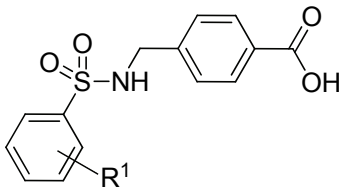
Scheme 3. Representative synthetic sequence[a].



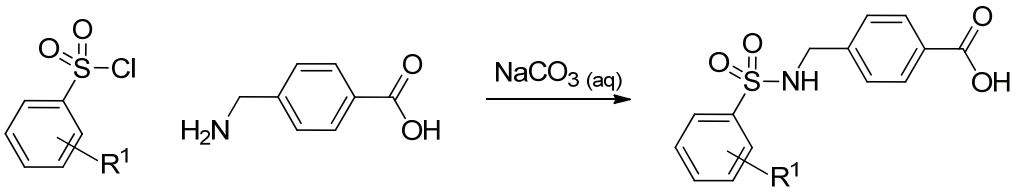
[a] Reagents and conditions: (a) *p*-toluenesulfonyl chloride, Na_2CO_3, water (66 % yield); (b) thionyl chloride, 65 °C (quant.); (c) chloroacetonitrile, KI, K_2CO_3, MeCN (93 % yield); (d) $LiAlH_4$, ether (62 % yield); (e) Et_3N, CH_2Cl_2 (52 % yield).

<u>Chemotype III experimental subsections:</u>

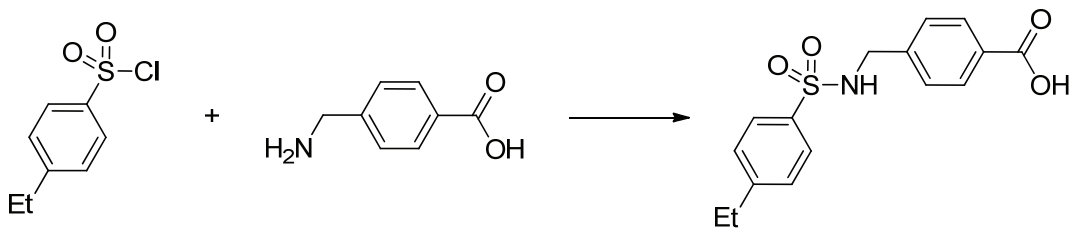
Carboxylic acid scaffold synthesis.



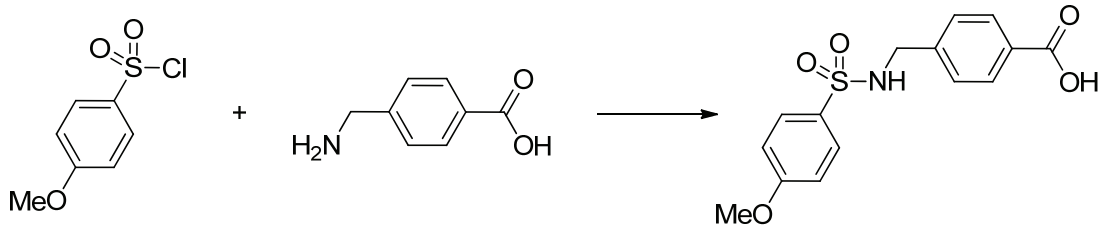
The sulfonamide carboxylic acid fragments 4-(phenylsulfonamidomethyl)benzoic acid,[5] 4-((4-methylphenylsulfonamido)methyl)benzoic acid,[6] 4-((4-bromophenylsulfonamido)methyl)benzoic acid,[5] were prepared according to their published protocols.



General sulfonamide synthesis procedure for the synthesis of sulfonamide carboxylic acid fragments. 4-Methylaminobenzoic acid and the appropriate sulfonyl chloride were reacted according to the protocol of Deng and Mani.[6] Thus, 4-methylaminobenzoic acid and the appropriate sulfonyl chloride (1.0 equiv.) were suspended in water (30 mL) and the pH maintained at ~ 8 by the addition of saturated Na_2SO_4. After approximately 30 min and following the complete dissolution of reactants, the reaction was acidified slowly with concentrated HCl, the precipitate filtered and washed with water. The product was dried under vacuum and used without further purification.

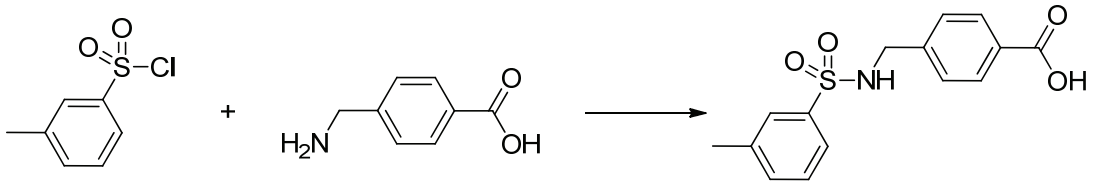


4-((4-Ethylphenylsulfonamido)methyl)benzoic acid . 4-Ethylphenylsulfonyl chloride (677 mg, 3.31 mmol) was reacted according to the general sulfonamide synthesis procedure to afford the sulfonamidebenzoic acid product (969 mg, 3.03 mmol, 92% yield) as a white solid. Mp = 210-211 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 1.20 (t, *J* = 7.2 Hz, 3 H), 2.68 (q, *J* = 7.6 Hz, 2 H), 4.03 (s, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 8.18 (br s, 1 H) ; ^{13}C NMR (101 MHz, DMSO-d6) δ d 15.2, 126.6 (× 2), 127.2 (× 2), 128.5 (× 2), 129.1 (× 2); u 28.0, 45.9, 130.0, 138.0, 141.3, 148.6, 167.8; IR (neat) 3275, 2970, 1672, 1305 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{16}NO_4S$ ([M-H]$^-$), 318.0800, found 318.0817.

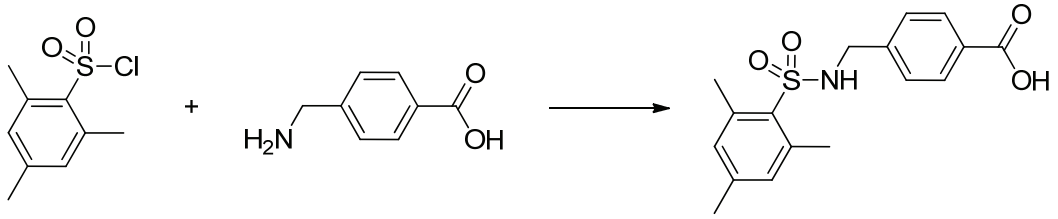


4-((4-Methoxyphenylsulfonamido)methyl)benzoic acid . 4-Methoxyphenylsulfonyl chloride (684 mg, 3.31 mmol) was reacted according to the general sulfonamide synthesis procedure to afford the sulfonamidebenzoic acid product (697 mg, 2.17 mmol, 66% yield) as a white solid. Mp = 161-164 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 3.82 (s, 3 H), 4.02 (d, *J* = 6.0 Hz, 2 H), 7.08 (d, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.73 (d, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 8.1 Hz, 2 H), 8.12 (t, *J* = 6.3 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-d6) δ d 55.6, 114.3 (× 2), 127.6 (×

2), 128.7 (× 2), 129.2 (× 2); u 45.8, 129.6, 132.3, 142.9, 162.1, 167.1; IR (neat) 3276, 1684, 1594, 1498 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}NO_5S$ ($[M+H]^+$), 322.0749, found 322.0741.

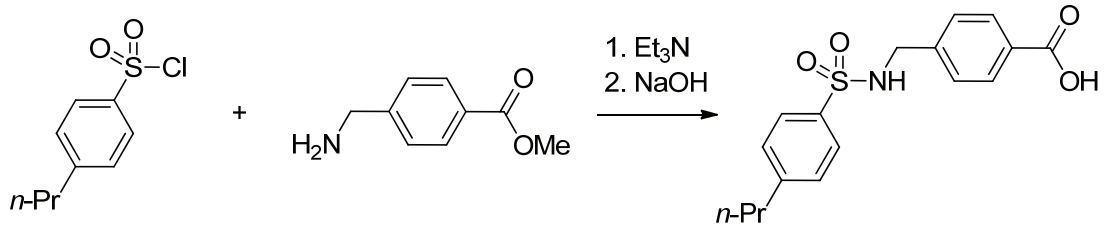


4-((3-Methylphenylsulfonamido)methyl)benzoic acid . 3-Methylphenylsulfonyl chloride (631 mg, 3.31 mmol) was reacted according to the general sulfonamide synthesis procedure to afford the sulfonamidebenzoic acid product (424 mg, 1.39 mmol, 42% yield) as a white solid. Mp = 194-195 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 2.35 (s, 3 H), 4.06 (d, *J* = 6.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.41-7.47 (m, 2 H), 7.57-7.60 (m, 2 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 8.21 (t, *J* = 6.4 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-d6) δ d 20.8, 123.6, 126.7, 127.5 (× 2), 129.0, 129.2 (× 2), 132.9; u 45.8, 138.8, 140.6, 142.8, 166.2, 167.1; IR (neat) 3260, 1687, 1427, 1325, 1152 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}NO_4S$ ($[M-H]^-$), 304.0644, found 304.0654.



4-((4-Trimethylphenylsulfonamido)methyl)benzoic acid. Mesitylenesulfonyl chloride (724 mg, 3.31 mmol) was reacted according to the general sulfonamide synthesis procedure to afford the sulfonamidebenzoic acid product (823 mg, 2.47 mmol, 75% yield) as a white solid. Mp = 144-146 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 2.23 (s, 3 H), 2.53 (s, 6 H), 4.04 (d, *J* = 6.0 Hz, 2 H), 6.96 (s, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H), 8.11 (t, *J* = 6.4 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-d6) δ d 20.3, 22.6, 22.7, 127.4, 129.1, 130.0 (× 2), 131.6; u 45.1,

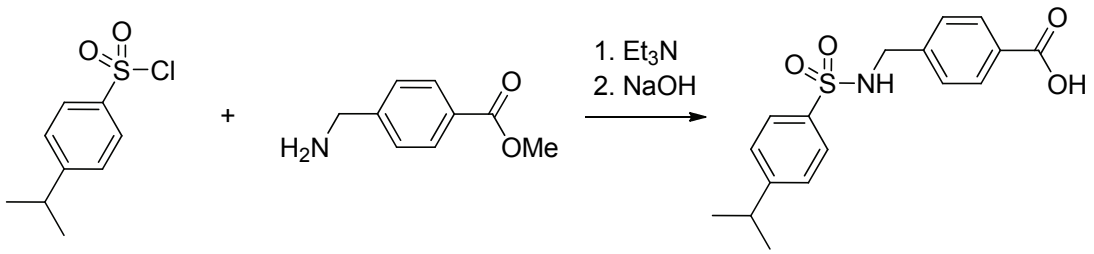
136.0, 136.7, 138.2 (× 2), 141.4, 143.1, 167.1; IR (neat) 3265, 1691, 1426, 1157 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}NO_4S$ ($[M-H]^-$), 332.0957, found 332.0974.



Methyl 4-((4-propylphenylsulfonamido)methyl)benzoate. Methyl 4-aminomethyl-benzoate hydrochloride (300 mg, 1.44 mmol) and triethylamine (0.46 mL, 3.30 mmol, 2.3 equiv.) were dissolved in CH_2Cl_2 (5 mL) then 4-*n*-propylbenzenesulfonylchloride (0.26 mL, 1.45 mmol) was added and the reaction mixture was stirred for 7 hours. The reaction was neutralized with 2N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH. The basic, aqueous solution was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to provide the product as a white solid (465 mg, 1.39 mmol, 93% yield). Rf = 0.85 (EtOAc:hexanes 1:1); mp = 134-138 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.4 Hz, 3 H), 1.56- 1.77 (m, 2 H), 2.65 (t, *J* = 7.6 Hz, 2 H), 3.88 (s, 3 H), 4.18 (d, *J* = 6.4 Hz, 2 H), 5.01 (t, *J* = 6.4 Hz, 1 H), 7.18-7.31 (complex, 4 H), 7.74 (d, *J* = 8.4 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 13.7, 52.2, 127.2, 127.7, 129.2, 129.9; u 24.2, 37.9, 46.9, 127.1, 129.7, 137.0, 141.6, 148.4, 166.7; IR (neat) 1719, 1279, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{18}H_{22}NO_4S$ ($[M+H]^+$), 348.1270, found 348.1262.

4-((4-propylphenylsulfonamido)methyl)benzoic acid. 1N NaOH (2 mL, 2.0 mmol, 4.7 equiv.) was added to a solution of methyl 4-((4-*n*-propyl)phenylsulfonamido)methyl)benzoate (150 mg, 0.43 mmol) in THF (2 mL). The resulting reaction mixture was stirred for 16 hours and

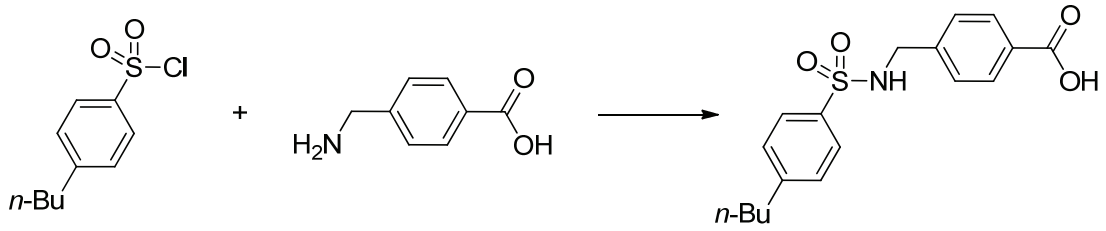
concentrated *in vacuo*. Water was added, and the pH adjusted to 1 with concentrated HCl. The precipitated solid was filtered and dried *in vacuo* to afford the product as a white solid (117 mg, 0.35 mmol, 81% yield). Mp = 207-220 ^{o}C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.88 (t, *J* = 7.2 Hz, 3 H), 1.50-1.68 (m, 2 H), 2.60 (t, J = 7.6 Hz, 2 H), 4.05 (d, *J* = 6.4 Hz, 2 H), 7.25-7.45 (complex, 4 H), 7.68 (d, *J* = 8.3 Hz, 2 H), 7.81 (d, *J* = 8.2 Hz, 2 H), 8.24 (t, *J* = 6.4 Hz, 1 H), 12.89 (br s, 1 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ d 13.5, 126.5, 127.5, 129.0, 129.2; u 23.7, 36.9, 45.7, 129.5, 138.1, 142.8, 147.0, 167.0; IR (neat) 1683, 1318, 1288, 1148 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{17}H_{20}NO_4S$ ([M-H]$^{+}$), 332.0957, found 332.0971.



Methyl 4-((4-isopropylphenylsulfonamido)methyl)benzoate. Methyl 4-aminomethyl-benzoate hydrochloride (300 mg, 1.44 mmol) and triethylamine (0.46 mL, 3.30 mmol, 2.3 equiv.) were dissolved in CH_2Cl_2 (5 mL) then 4-isopropylbenzenesulfonylchloride (316 mg, 1.45 mmol) was added and the reaction mixture was stirred for 7 hours. The reaction was neutralized with 2N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH. The basic, aqueous solution was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to provide the product as a white solid (381 mg, 1.10 mmol, 74% yield). Rf = 0.70 (EtOAc:hexanes 1:1); mp = 156-158 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.8 Hz, 6 H), 2.90-3.03 (m, 1 H), 3.89 (s, 3 H), 4.20 (d, *J* = 6.4 Hz, 2 H), 4.98 (t, *J* = 6.4 Hz, 1 H), 7.20-7.38 (complex, 4 H), 7.75 (d, *J* = 8.6 Hz, 2 H), 7.91 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 23.7, 34.2,

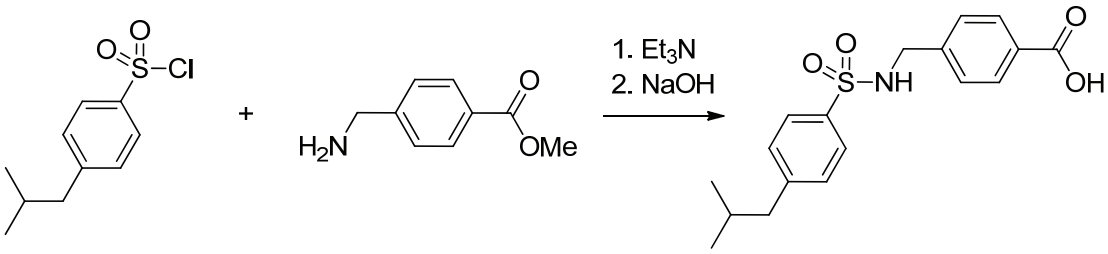
52.2, 127.3, 127.7, 129.9, 129.9; u 46.9, 129.6, 137.1, 141.5, 154.4, 166.7; IR (neat) 1718, 1279, 1159 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{18}H_{22}NO_4S$ ($[M+H]^+$), 348.1270, found 348.1258.

4-((4-Isopropylphenylsulfonamido)methyl)benzoic acid. 1N NaOH (2 mL, 2.0 mmol, 4.7 equiv.) was added to a solution of methyl 4-((4-isopropyl)phenylsulfonamido)methyl)benzoate (150 mg, 0.43 mmol) in THF (2 mL). The resulting reaction mixture was stirred for 16 hours and concentrated *in vacuo*. Water was added, and the pH adjusted to 1 with concentrated HCl. The precipitated solid was filtered and dried *in vacuo* to afford the product as a white solid (132 mg, 0.40 mmol, 92% yield). Mp = 243-247 ^oC; ^1H NMR (400 MHz, d_6-DMSO) δ 1.19 (d, *J* = 6.9 Hz, 6H), 2.93 (dt, *J* = 13.8, 6.9 Hz, 1H), 4.06 (d, *J* = 6.4 Hz, 2H), 7.35 (dd, *J* = 28.7, 8.3 Hz, 4H), 7.72-7.60 (m, 2H), 7.88-7.74 (m, 2H), 8.19 (t, *J* = 6.4 Hz, 1H), 12.87 (br s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ d 23.5, 33.3, 126.6, 127.0, 127.5, 129.2; u 45.8, 129.5, 138.2, 142.8, 153.1, 167.1; IR (neat) 1677, 1318, 1280, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{17}H_{20}NO_4S$ ($[M-H]^+$), 332.0957, found 332.0971.



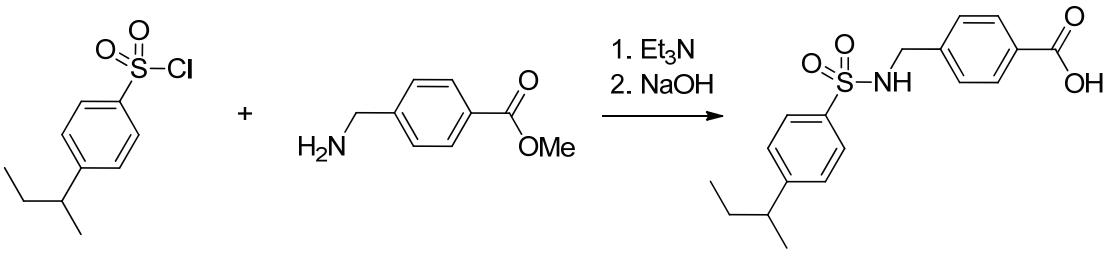
4-((4-*n*-Butylphenylsulfonamido)methyl)benzoic acid. 4-*n*-Butylbenzenesulfonylchloride (794 mg, 3.31 mmol) and 4-(aminomethyl)-benzoic acid (500 mg, 3.31 mmol) in 15 mL of water were reacted according to the general sulfonamide synthesis procedure to afford the desired benzoic acid as a white solid (715 mg, 2.06 mmol, 62 % crude yield). Mp= 214-218 ^oC; ^1H NMR (400 MHz, DMSO-d6) δ 0.90 (t, *J* = 7.3 Hz, 3 H), 1.20-1.36 (m, 2 H), 1.48-1.62 (m, 2 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 4.06 (d, *J* = 6.4 Hz, 2 H), 7.26-7.40 (complex, 4 H), 7.68 (d, *J* = 8.3 Hz, 2 H), 7.82

(d, J = 8.3 Hz, 2 H), 8.20 (t, J = 6.4 Hz, 1 H), 12.88 (br s, 1 H);^{13}C NMR (400 MHz, DMSO-d6) δ d 21.7, 32.7, 34.5, 45.7, 129.5, 138.0, 142.8, 147.26, 167.1; u: 13.7, 126.5, 127.5, 128.9, 129.2; IR (neat) 1676, 1315, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{18}H_{20}NO_4S$ ([M-H]$^+$), 346.1113, found 346.1123.



Methyl 4-((4-isobutylphenylsulfonamido)methyl)benzoate. Methyl 4-aminomethyl-benzoate hydrochloride (224 mg, 1.08 mmol) and triethylamine (0.35 mL, 2.51 mmol, 2.3 equiv.) were dissolved in CH_2Cl_2 5 mL then 4-isobutylbenzenesulfonylchloride (250 mg, 1.07mmol) was added and the reaction mixture was stirred for 7 hours. The reaction was neutralized with 2N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH. The basic, aqueous solution was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to provide the product as a white solid 348 mg, 0.963 mmol, 90% yield). Rf = 0.73 (EtOAc:hexanes 1:1); mp = 173-176 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 6 H), 1.81-1.95 (m,1 H), 2.53 (d, J = 7.2 Hz, 2 H), 3.89 (s, 3 H), 4.21 (d, J = 6.4 Hz, 2 H), 5.01 (t, J = 6.4 Hz, 1 H), 7.18-7.34 (complex, 4 H), 7.75 (d, J = 8.4 Hz, 2 H), 7.98-7.85 (d, J = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ d 22.3, 30.1, 52.2, 127.0, 127.7, 129.8, 129.9; u 45.2, 46.9, 129.7, 137.1, 141.6, 147.4, 166.7; IR (neat) 1719, 1279, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{19}H_{24}NO_4S$ ([M+H]$^+$), 362.1426, found 362.1425.

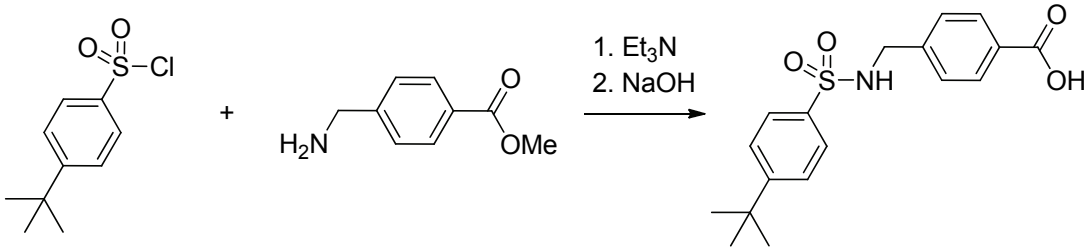
4-((4-Isobutylphenylsulfonamido)methyl)benzoic acid. 1N NaOH (2 mL, 2.0 mmol, 4.7 equiv.) was added to a solution of methyl 4-((4-isobutylphenylsulfonamido)methyl)benzoate (150 mg, 0.42 mmol) in THF (2 mL). The resulting reaction mixture was stirred for 16 hours and concentrated *in vacuo*. Water was added, and the pH adjusted to 1 with concentrated HCl. The precipitated solid was filtered and dried *in vacuo* to afford the product as a white solid (126 mg, 0.36 mmol, 88% yield). Mp = 225-227 ^{o}C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.85 (d, *J* = 6.4 Hz, 6 H), 1.75-1.92 (m, 1 H), 2.51 (d, *J* = 7.2 Hz, 3 H), 4.08 (d, *J* = 6.3 Hz, 2 H), 7.24-7.41 (m, 4 H), 7.68 (d, *J* = 8.3 Hz, 2 H), 7.82 (d, *J* = 8.3 Hz, 2 H), 8.22 (t, *J* = 6.4 Hz, 1 H), 12.88 (br s, 1 H). ^{13}C NMR (100 MHz, d_6-DMSO) δ d 22.0, 29. 5, 126.3, 127.5, 129.2, 129.5; u 44.1, 45.7, 129.5, 138.2, 142.8, 146.0, 167.0; IR (neat) 1679, 1310, 1280, 1154 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{18}H_{20}NO_4S$ ([M-H]$^{+}$), 346.1113, found 346.1126.



Methyl 4-((4-*sec*-butylphenylsulfonamido)methyl)benzoate. Methyl 4-aminomethyl-benzoate hydrochloride (224 mg, 1.08 mmol) and triethylamine (0.35 mL, 2.51 mmol, 2.3 equiv.) were dissolved in CH_2Cl_2 5 mL then 4-*sec*-butylbenzenesulfonylchloride (250 mg, 1.07 mmol) was added and the reaction mixture was stirred for 7 hours. The reaction was neutralized with 2N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH. The basic, aqueous solution was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to provide the product as a white solid (361 mg, 0.999 mmol, 93% yield). Rf = 0.76

(EtOAc:hexanes 1:1); mp = 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.4 Hz, 3 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 1.51-1.70 (m, 2 H), 2.57-2.75 (m, 1 H), 3.88 (s, 3 H), 4.21 (d, *J* = 6.4 Hz, 2 H), 4.99 (t, *J* = 6.4 Hz, 1 H), 7.19-7.35 (complex, 4 H), 7.74 (d, J = 8.4 Hz, 2 H), 7.90 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 12.1, 21.5, 41.7, 52.2, 127.2, 127.7, 127.9, 129.90; u 30.9, 46.9, 129.7, 137.2, 141.6, 153.4, 166.7 IR (neat) 1718, 1278, 1157 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{19}H_{24}NO_4S$ ($[M+H]^+$), 362.1426, found 362.1422.

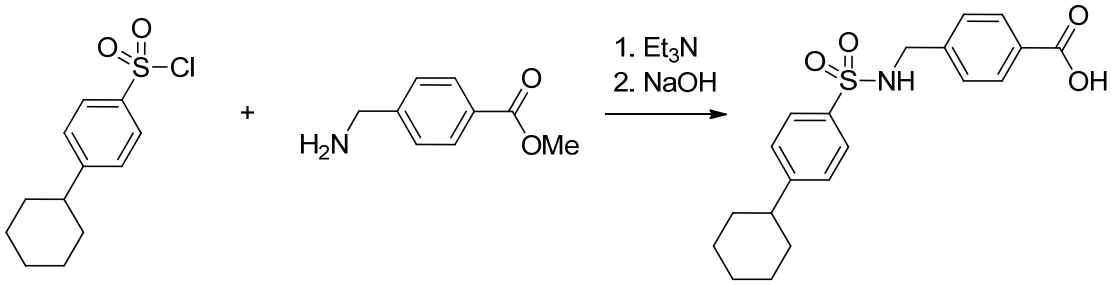
4-((4-*sec*-Butylphenylsulfonamido)methyl)benzoic acid. 1N NaOH (2 mL, 2.0 mmol, 4.8 equiv.) was added to a solution of methyl 4-((4-*sec*-butylphenylsulfonamido)methyl)benzoate (150 mg, 0.42 mmol) in THF (2 mL). The resulting reaction mixture was stirred for 16 hours and concentrated *in vacuo*. Water was added, and the pH adjusted to 1 with concentrated HCl. The precipitated solid was filtered and dried *in vacuo* to afford the product as a white solid (107 mg, 0.31 mmol, 74% yield). Mp = 226-232 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.74 (t, *J* = 7.4 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.69-1.40 (m, 2H), 2.65 (dd, *J* = 14.1, 7.0 Hz, 1H), 4.08 (d, *J* = 6.4 Hz, 2H), 7.32 (dd, *J* = 13.2, 8.3 Hz, 4H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 8.21 (t, *J* = 6.4 Hz, 1H), 12.86 (br s, 1H); ^{13}C NMR (100 MHz, d_6- DMSO) δ d 11.9, 21.3, 40.7, 126.5, 127.5, 127.6, 129.1; u 30.2, 45.8, 129.5, 138.3, 142.8, 151.9, 167.0; IR (neat) 1678, 1311, 1280, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{18}H_{20}NO_4S$ ($[M-H]^+$), 346.1113, found 346.1126.



Methyl 4-((4-*tert*-butylphenylsulfonamido)methyl)benzoate. Methyl 4-aminomethyl-benzoate hydrochloride (300 mg, 1.44 mmol) and triethylamine (0.46 mL, 3.30 mmol, 2.3 equiv.) were dissolved in CH_2Cl_2 (5 mL) then 4-*tert*-butylbenzenesulfonylchloride (343 mg, 1.44 mmol) was added and the reaction mixture stirred for 7 hours. The reaction was acidified with 2N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH. The basic, aqueous solution was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to provide the product as a white solid (513 mg, 1.42 mmol, 98% yield). Rf = 0.87 (EtOAc:hexanes 1:1); mp = 193-195 ^oC; ^1H NMR (400 MHz, d_6-DMSO) δ 1.27 (s, 9 H), 3.82 (s, 3 H), 4.08 (d, *J* = 6.4 Hz, 2 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.66 (m, *J* = 8.8, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 8.23 (t, *J* = 6.5 Hz, 1 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ d 30.7, 52.0, 125.9, 126.3, 127.7, 129.0; u 34.7, 45.7, 128.3, 137.9, 143.2, 155.2, 166.0; IR (neat) 1719, 1279, 1160, 1111 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{19}H_{24}NO_4S$ ($[M+H]^+$), 362.1436, found 362.1426.

4-((4-*tert*-Butylphenylsulfonamido)methyl)benzoic acid. 1N NaOH (4 mL, 4.0 mmol, 9.6 equiv.) was added to a solution of methyl 4-((4-*tert*-butylphenylsulfonamido)methyl)benzoate (150 mg, 0.42 mmol) in THF (4 mL). The resulting reaction mixture was stirred for 16 hours and concentrated *in vacuo*. Water was added, and the pH adjusted to 1 with concentrated HCl. The precipitated solid was filtered and dried *in vacuo* to afford the product as a white solid (138 mg, 0.40 mmol, 96% yield). Mp = 272-283 ^oC; ^1H NMR (400 MHz, d_6-DMSO) δ 1.18-1.35 (m, 9 H), 4.07 (d, *J* = 6.4 Hz, 2 H), 7.31 (d, *J* = 8.3 Hz, 2 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 8.3 Hz, 2 H), 8.26 (t, *J* = 6.4 Hz, 1 H), 12.87 (s, 1 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ d 30.8, 125.8, 126.3, 127.5, 129.1; u 34.7, 45.8, 129.4, 137.9, 142.7, 155.2, 167.0; IR

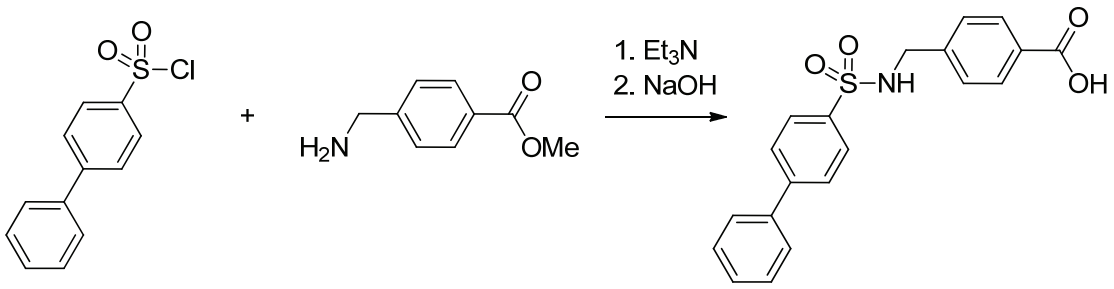
(neat) 1683, 1318, 1150 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{18}H_{21}NO_4S$ ($[M-H]^+$), 346.1113, found 346.1128.



Methyl 4-((4-cyclohexylphenylsulfonamido)methyl)benzoate. Methyl 4-aminomethyl-benzoate hydrochloride (201 mg, 0.97 mmol) and triethylamine (0.31 mL, 2.2 mmol, 2.3 equiv.) were dissolved in CH_2Cl_2 (5 mL) then 4cyclohexylbenzenesulfonylchloride (250 mg, 1.00 mmol) was added and the reaction mixture stirred for 7 hours. The reaction was acidified with 2N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH. The basic, aqueous solution was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to provide the product as a white solid (337 mg, 0.87 mmol, 87% yield). Rf = 0.81 (EtOAc:hexanes 1:1); mp = 189-192 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17-1.49 (complex, 5 H), 1.70-1.98 (complex, 5 H), 2.47-2.67 (m, 1 H), 3.89 (s, 3 H), 4.20 (d, *J* = 6.4 Hz, 2 H), 4.98 (t, *J* = 6.4 Hz, 1 H), 7.18-7.36 (complex, 4 H), 7.74 (d, *J* = 8.4 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δd 44.6, 52.2, 127.2, 127.6, 127.7, 129.9; u 26.0, 26.7, 34.1, 46.9, 129.6, 137.1, 141.6, 153.6, 166.7; IR (neat) 1720, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{21}H_{26}NO_4S$ ($[M+H]^+$), 388.1583, found 388.1578.

4-((4-*tert*-Butylphenylsulfonamido)methyl)benzoic acid. 1N NaOH (2 mL, 2.0 mmol, 5.2 equiv.) was added to a solution of methyl 4-((4-cyclohexylphenylsulfonamido)methyl)benzoate

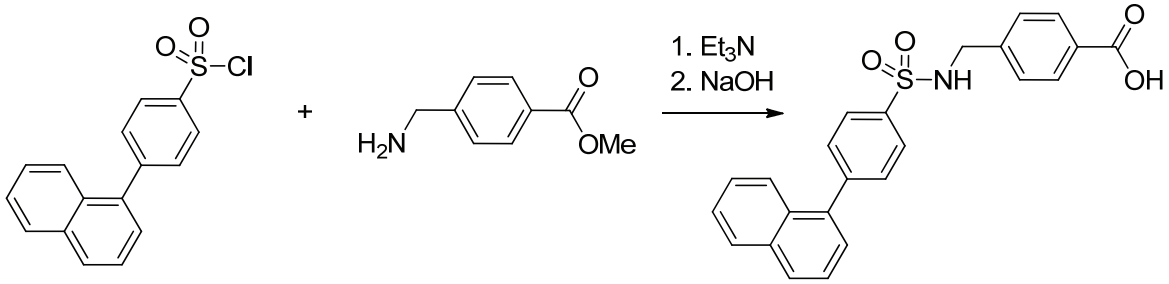
(150 mg, 0.39 mmol) in THF (2 mL). The resulting reaction mixture was stirred for 16 hours and concentrated *in vacuo*. Water was added, and the pH adjusted to 1 with concentrated HCl. The precipitated solid was filtered and dried *in vacuo* to afford the product as a white solid (142 mg, 0.38 mmol, 98% yield). Mp = 238-241 ^{o}C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.08-1.51 (complex, 5 H), 1.57-1.94 (complex, 5 H), 2.52-2.64 (m, 1 H), 4.07 (d, *J* = 6.4 Hz, 2 H), 7.35 (complex, 4 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 8.24 (t, *J* = 6.4 Hz, 1 H), 12.88 (br s, 1 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ d 43.5, 126.6, 127.3, 127.5, 129.1; u 25.4, 26.2, 33.5, 45.8, 129.5, 138.2, 142.8, 152.2, 167.0; IR (neat) 1682, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{20}H_{22}NO_4S$ ($[M-H]^+$), 372.1270, found 372.1283.



Methyl 4-(([1,1'-biphenyl]-4-ylsulfonamido)methyl)benzoate. Methyl 4-aminomethyl-benzoate hydrochloride (318 mg, 1.58 mmol) and triethylamine (0.50 mL, 3.59 mmol, 2.3 equiv.) were dissolved in CH_2Cl_2 (5 mL) then biphenyl-4-sulfonylchloride (399 mg, 1.579 mmol) was added and the reaction mixture stirred for 7 hours. The reaction was acidified with 2N HCl. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH. The basic, aqueous solution was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to provide the product as a white solid (497 mg, 1.30 mmol, 83% yield). Rf = 0.76 (EtOAc:hexanes 1:1); mp = 181-185 ^{o}C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.81 (s, 3 H), 4.12 (d, *J* = 6.3 Hz, 2 H), 7.33-7.58 (complex, 5 H), 7.71 (d, *J* = 7.2 Hz, 2 H), 7.77-7.91 (complex, 6 H),

8.34 (t, J = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ d 52.0, 127.0, 127.1, 127.4, 127.8, 128.4, 129.0, 129.1; u 45.8, 128.8, 138.6, 139.4, 143.3, 143.9, 166.0; IR (neat) 1718, 1276, 1157 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{21}H_{20}NO_4S$ ($[M+H]^+$), 382.1113, found 382.1110.

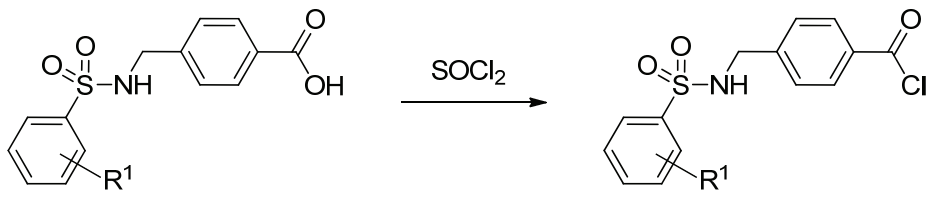
4-(([1,1'-biphenyl]-4-ylsulfonamido)methyl)benzoic acid. 1N NaOH (4 mL, 4.0 mmol, 10 equiv.) was added to a solution of methyl 4-(([1,1'-biphenyl]-4-ylsulfonamido)methyl)benzoate (150 mg, 0.39 mmol) in THF (4 mL). The resulting reaction mixture was stirred for 16 hours and concentrated *in vacuo*. Water was added, and the pH adjusted to 1 with concentrated HCl. The precipitated solid was filtered and dried *in vacuo* to afford the product as a white solid (131 mg, 0.36 mmol, 91% yield). Mp = 264-269 ^{o}C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 4.10 (d, J = 6.3 Hz, 2 H), 7.32-7.56 (complex, 5 H), 7.71 (d, J = 7.2 Hz, 2 H), 7.79-7.91 (complex, 6 H), 8.34 (t, J = 6.4 Hz, 1 H), 12.89 (br s, 1 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ d 127.1, 127.2, 127.4, 127.6, 128.4, 129.1, 129.2; u 45.8, 129.6, 138.6, 139.4, 142.8, 144.0, 167.1; IR (neat) 1684, 1319, 1150 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{20}H_{16}NO_4S$ ($[M-H]^+$), 366.0800, found 366.0815.



Methyl 4-((naphthalene-2-sulfonamido)methyl)benzoate. Methyl 4-aminomethyl-benzoate hydrochloride (300 mg, 1.44 mmol) and triethylamine (0.46 mL, 3.30 mmol, 2.3 equiv.) were dissolved in CH_2Cl_2 (5 mL) then 2-napthalenesulfonylchloride (328 mg, 1.45 mmol) was added and the reaction mixture stirred for 7 hours. The reaction was acidified with 2N HCl. The

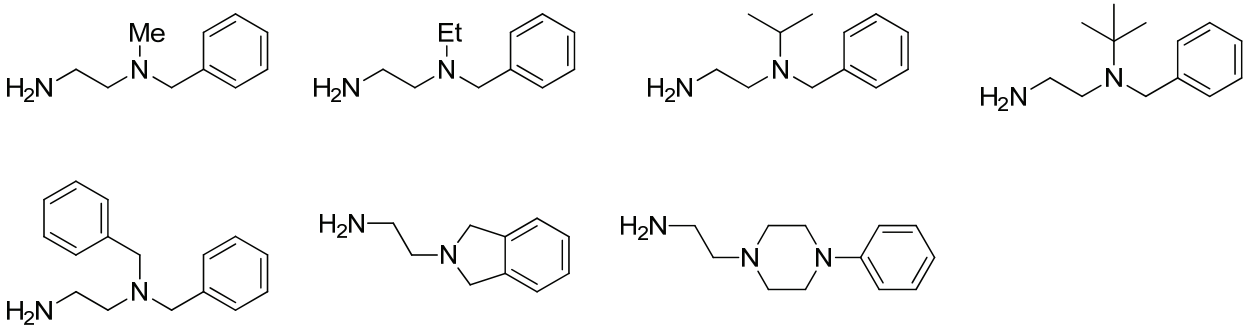
aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N NaOH. The basic, aqueous solution was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to provide the product as a white solid (479 mg, 1.35 mmol, 94% yield). Rf = 0.85 (EtOAc:hexanes 1:1); mp = 144-145 ^oC; ^1H NMR (400 MHz, d_6-DMSO) δ 3.81 (s, 3 H), 4.12 (d, *J* = 6.2 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 7.59-7.74 (complex, 2 H), 7.75-7.88 (complex, 3 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 2 H), 8.30-8.46 (complex, 2 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ d 52.0, 122.2, 127.4, 127.5, 127.7, 127.8, 128.6, 129.0, 129.1, 129.3; u 45.8, 128.3, 131.7, 134.1, 137.6, 143.2, 165.9; IR (neat) 1716, 1316, 1276, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{19}H_{18}NO_4S$ ($[M+H]^+$), 356.0957, found 356.0794.

4-((Naphthalene-2-sulfonamido)methyl)benzoic acid. 1N NaOH (2 mL, 2.0 mmol, 4.7 equiv.) was added to a solution of methyl 4-((naphthalene-2-sulfonamido)methyl)benzoate (150 mg, 0.422 mmol) in THF (2 mL). The resulting reaction mixture was stirred for 16 hours and concentrated *in vacuo*. Water was added, and the pH adjusted to 1 with concentrated HCl. The precipitated solid was filtered and dried *in vacuo* to afford the product as a white solid (135 mg, 0.396 mmol, 94% yield). Mp = 247-252 ^oC; ^1H NMR (400 MHz, d_6-DMSO) δ 4.11 (d, *J* = 6.3 Hz, 2 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 7.63-7.75 (complex, 2 H), 7.77-7.88 (complex, 3 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 8.08-8.20 (complex, 2 H), 8.37 (t, *J* = 6.4 Hz, 1 H), 8.44 (s, 1 H), 12.87 (br s, 1 H). ^{13}C NMR (100 MHz, d_6-DMSO) δ d 122.2, 127.4, 127.5, 127.5, 127.8, 128.7, 129.1, 129.2, 129.4; u 45.8, 129.5, 131.7, 134.1, 137.6, 142.8, 167.0; IR (neat) 1686, 1318, 1153 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{18}H_{14}NO_4S$ ($[M-H]^+$), 340.0644, found 340.0658.

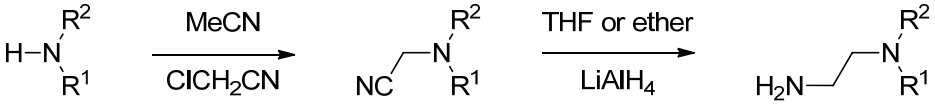


General procedure for the conversion of sulfonamide carboxylic acid fragments to sulfonamide acid chloride fragments. A slurry of the sulfonamide carboxylic acid (1.5 to 3.0 mmol) in thionyl chloride (3.0 mL) was heated at 65 °C for 1 h then cooled to rt. The excess thionyl chloride was blown off under a stream of nitrogen followed by azeotropic codistillation with toluene (2 × 25 mL). The sulfonamide acid chloride thus obtained was used immediately without further purification.

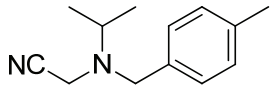
Diamine fragments:



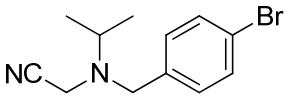
The diamine fragments N^1-benzyl-N^1-methylethane-1,2-diamine,[7] N^1-benzyl-N^1-ethylethane-1,2-diamine,[7] N^1-benzyl-N^1-isopropylethane-1,2-diamine,[7] N^1-benzyl-N^1-*t*-butylethane-1,2-diamine,[7] N^1,N^1-dibenzylethane-1,2-diamine,[7] 2-(isoindolin-2-yl)ethanamine[8] and 2-(4-phenylpiperazin-1-yl)ethanamine[9] were prepared according to their published protocols.



General amine alkylation procedure for the synthesis of the aminoacetonitrile precursors. The aminoacetonitrile precursors were synthesized according to the protocol of Ruchelman et al..[7] Thus, the appropriate secondary amine was combined with chloroacetonitrile (1.1 equiv.), K_2CO_3 (2.0 equiv.) and potassium iodide (1.0 equiv.) in acetonitrile (2.5 mL/ mmol of secondary amine). The reaction was stirred at rt for 13-16 h, diluted with aqueous saturated Na_2CO_3 (50 mL) and extracted with ether (3 × 30 mL). The combined organics were washed with brine and dried with Na_2SO_4. The solvent was removed in vacuo and the residue purified by silica gel chromatography to afford the necessary aminoacetonitrile precursors.

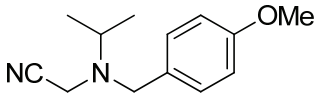


2-(Isopropyl(4-methylbenzyl)amino)acetonitrile. N-Isopropyl(4-methylbenzyl)amine (310 mg, 1.90 mmol) was reacted according to the general amine alkylation procedure to afford the aminonitrile (256 mg, 1.27 mmol, 67% yield) as a colorless oil. R_f = 0.67 (EtOAC:hexanes 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.4 Hz, 6 H), 2.33 (s, 3 H), 3.01 (sept, *J* = 6.4 Hz, 1 H), 3.40 (s, 2 H), 3.70 (s, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 19.7 (× 2), 21.0, 52.8, 128.7 (× 2), 129.2 (× 2); u 37.9, 33.7, 116.7, 134.8, 137.1; IR (neat) 2970, 1514 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}N_2$ ([M+H]$^-$), 203.1548, found 203.1545.

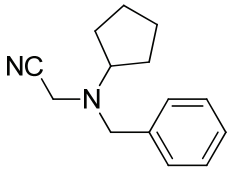


2-((4-Bromobenzyl)(isopropyl)amino)acetonitrile. *N*-Isopropyl(4-bromobenzyl)amine (1.00 g, 4.38 mmol) was reacted according to the general amine alkylation procedure to afford the aminonitrile (731 mg, 2.74 mmol, 62% yield) as a colorless oil. R_f = 0.64 (EtOAC:hexanes 1:3);

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.8 Hz, 6 H), 3.02 (sept, *J* = 6.8 Hz, 1 H), 3.40 (s, 2 H), 3.70 (s, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 19.6 (× 2), 52.9, 130.3 (× 2), 131.6 (× 2); u 37.9, 53.4, 116.5, 121.3, 137.0; IR (neat) 2970, 2830, 1487 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}BrN_2$ ($[M+H]^-$), 267.0497, found 267.0504.

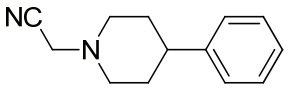


2-((4-Methoxybenzyl)(isopropyl)amino)acetonitrile. *N*-Isopropyl(4-methoxybenzyl)amine[10] (1.25 g, 6.97 mmol) was reacted according to the general amine alkylation procedure to afford the aminonitrile (1.11 g, 5.08 mmol, 73 % yield) as an amber-colored oil. R_f = 0.34 (EtOAC:hexanes 1:9); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.6 Hz, 6 H), 3.04 (sept, *J* = 6.6 Hz, 1 H), 3.43 (s, 2 H), 3.71 (s, 2 H), 3.83 (s, 3 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 7.29 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 19.9, 52.9, 55.3, 114.0 (× 2), 130.0 (× 2); u 37.8, 53.5, 116.8, 129.9, 159.1 IR (neat) 1511, 1247 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{22}N_2$ ($[M+H]^-$), 219.1497, found 219.1522.



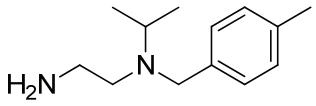
2-((4-Benzyl)(cyclopentyl)amino)acetonitrile. *N*-benzyl-*N*-cyclopentylamine (500 mg, 2.85 mmol) was reacted according to the general amine alkylation procedure to afford the aminonitrile (506 mg, 2.43 mmol, 83 % yield) as a colorless oil. R_f = 0.89 (EtOAc:hexanes 1:1);^{1}H NMR ($CDCl_3$) δ 1.45-1.60 (m, 2 H), 1.64-1.75 (m, 2 H), 1.75-1.87 (m, 2 H), 1.98-2.10

(m, 2 H), 3.04 (tt, J = 6.9, 6.8 Hz, 1 H), 3.44 (s, 2 H), 3.73 (s, 2 H) 7.29-7.40 (complex, 5 H); ^{13}C NMR ($CDCl_3$) δ d 64.1, 127.7, 128.6, 129.0; u 23.9, 31.5, 40.3, 56.8, 115.2, 137.6; IR (neat) 2956, 1354 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{14}H_{20}N_2$ ($[M+H]^+$), 215.1548, found 203.1538.

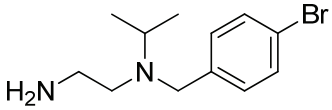


2-(4-Phenylpiperidin-1-yl)acetonitrile. 4-Phenylpiperidine (500 mg, 3.10 mmol) was reacted according to the general amine alkylation procedure to afford the aminonitrile (518 mg, 2.59 mmol, 83 % yield) as a white solid. Mp = 99-101 ^{o}C; R_f = 0.67 (EtOAc:hexanes 1:1);^{1}H NMR ($CDCl_3$) 1.74-2.01 (complex, 4 H), 2.45-2.65 (complex, 3 H), 2.87-3.04 (m, 2 H), 3.60 (s, 2 H), 7.17-7.42 (complex, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 41.5, 126.4, 126.8, 128.5; u 33.1, 46.5, 52.9, 114.8, 145.6; IR (neat) 2809, 1453 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{13}H_{17}N_2$ ($[M+H]^+$), 201.1392, found 201.1383.

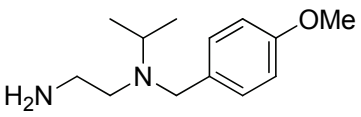
General reduction procedure for the synthesis of the diamine fragments. The diamine fragments were synthesized according to the protocol of Ruchelman et al..[8] Thus, to a solution of the appropriate aminoacetonitrile precursor in THF or ether was added lithium aluminum hydride (3.5 M solution in THF, 1.1 equiv.). The reaction was stirred for 13-16 h, carefully quenched with EtOAc then water, acidified with aqueous HCl (2 M) and extracted with EtOAc (3 × 30 mL). The pH of the aqueous layer was adjusted to > 8 with aqueous NaOH (2 M) and extracted with EtOAc (3 × 30 mL). The combined organics were dried with Na_2SO_4 and the solvent removed in vacuo to afford the diamine fragments which were used without further purification.



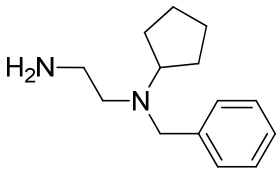
N^1-Isopropyl-N^1-(4-methylbenzyl)ethane-1,2-diamine. 2-(Isopropyl(4-methylbenzyl)amino)acetonitrile (213 mg, 1.05 mmol) was reacted according to the general reduction procedure in THF to afford the diamine (188 mg, 0.91 mmol, 87% yield) as a light yellow oil. R_f = 0.63 (10% MeOH, 1 % Et_3N in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.4 Hz, 6 H), 2.32 (s, 3 H), 2.47 (t, *J* = 5.6 Hz, 2 H), 2.61 (t, *J* = 6.0 Hz, 2 H), 2.92(sept, *J* = 6.4 Hz, 1 H), 3.51 (s, 2 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 17.8 (× 2), 21.0, 49.6, 128.3 (× 2), 128.8 (× 2); u 40.1, 52.0, 54.0, 136.0, 138.0; IR (neat) 2964, 1659 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{23}N_2$ ($[M+H]^+$), 207.1861, found 207.1870.



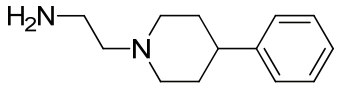
N^1-(4-Bromobenzyl)-N^1-isopropylethane-1,2-diamine. 2-((4-Bromobenzyl)(isopropyl)amino)acetonitrile (459 mg, 1.72 mmol) was reacted according to the general reduction procedure in ether to afford the diamine (384 mg, 1.42 mmol, 82% yield) as a light yellow oil. R_f = 0.62 (10% MeOH, 1 % Et_3N in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.4 Hz, 6 H), 2.47 (t, *J* = 6.0 Hz , 2 H), 2.61 (t, *J* = 6.0 Hz, 2 H), 2.89 (sept, *J* = 6.4 Hz, 1 H), 3.50 (s, 2 H), 7.21 (d, *J* = 8.8 Hz, 2 H), 7.41 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 17.8 (× 2), 49.8, 130.0 (× 2), 131.1 (× 2); u 40.2, 52.3, 53.7, 120.2, 140.3; IR (neat) 2963, 1485 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{20}BrN_2$ ($[M+H]^+$), 271.0810, found 271.0827.



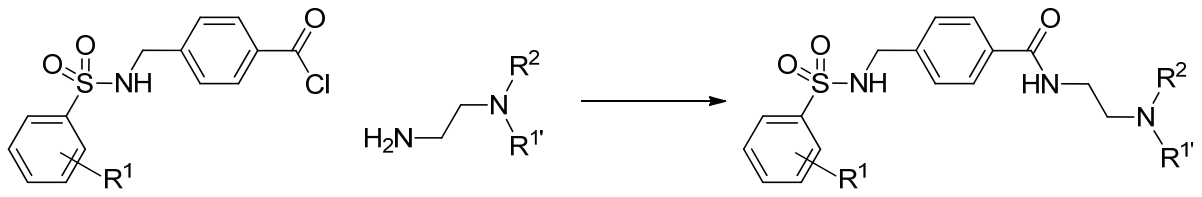
***N*^{1}-(4-Methoxybenzyl)-*N*^{1}-isopropylethane-1,2-diamine**. 2-((4-Methoxybenzyl)(isopropyl)amino)acetonitrile (898 mg, 4.11 mmol) was reacted according to the general reduction procedure in ether to afford the diamine (835 mg, 3.76 mmol, 91% yield) as a colorless oil. R_f = 0.19 (1:25:75 Et_3N:acetone:CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, *J* = 6.8 Hz, 6 H), 2.44-2.68 (m, 3 H), 2.86-3.00 (m, 2 H), 3.50 (s, 2 H), 3.79 (s, 3 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 17.9 (× 2), 49.9, 55.3, 113.8 (× 2), 129.6 (× 2); u 39.6, 50.9, 53.8, 132.6, 158.5; IR (neat) 2963, 1508, 1246 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{23}N_2O$ ([M+H]$^+$), 223.1810, found 223.1822.



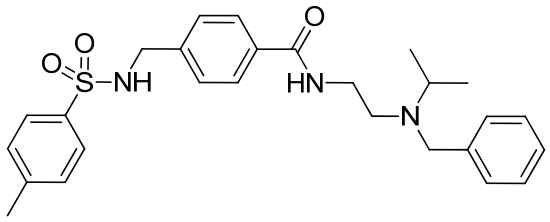
***N*^{1}-(4-Methoxybenzyl)-*N*^{1}-cyclopentylethane-1,2-diamine**. 2-((4-2-(Benzyl(cyclopentyl)amino)acetonitrile (410 mg, 1.91 mmol) was reacted according to the general reduction procedure in ether to afford the diamine (418 mg, 1.91 mmol, quantiative crude yield) as a yellow oil. R_f = 0.23 (1:25:75 Et_3N:acetone:CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.56 (m, 4 H), 1.57-1.70 (m, 2 H), 1.71-1.85 (m, 2 H), 2.62 (t, *J* = 5.6 Hz, 2 H), 2.69 (t, *J* = 5.6 Hz, 2 H), 3.13-3.21 (m, 1 H), 3.63 (s, *J* = 6.0 Hz, 2 H), 7.15-7.44 (m, 5 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ d 58.3, 121.7, 123.1, 123.3, u 19.0, 23.4, 34.1, 47.6, 51.5, 135.1; IR (neat) 2952, 2868, 1452 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{14}H_{23}N_2$ ([M+H]$^+$), 219.1861, found 219.1846.



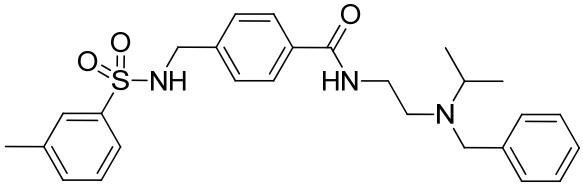
***N*^{1}-(4-Methoxybenzyl)-*N*^{1}-cyclopentylethane-1,2-diamine**. 2-(4-Phenylpiperidin-1-yl)acetonitrile (400 mg, 2.00mmol) was reacted according to the general reduction procedure in THF to afford the previously reported diamine[11] (mg, 1.919 mmol, 96 % crude yield) as an amber oil, which was used without further purification. R_f = 0.29 (1:25:75 Et_3N:acetone:CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73-1.96 (m, 4 H), 2.05-2.22 (m, 2 H), 2.43-2.62 (complex, 3 H), 2.85 (t, *J* = 6.3 Hz, 2 H), 2.98-3.14 (m, 2 H), 7.16-7.40 (complex, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 42.7, 126.1, 127.0, 128.4; u 33.1, 38.9, 54.6, 61.5, 146.3; IR (neat) 2933, 1666 1452 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{13}H_{21}N_2$ ([M+H]$^+$), 205.1705, found 205.1701.



General procedure for the coupling of the sulfonamide acid chloride and diamine fragments. The sulfonamide acid chloride fragment (1.0 equiv.) was added to a solution of the diamine fragment (1.0 equiv.) and triethylamine (2.5 equiv.) in CH_2Cl_2 (3 mL) and stirred at rt 14 – 18 h. The reaction was diluted with saturated aqueous $NaHCO_3$ (2 mL) and all solvents evaporated in vacuo. The residue was extracted with MeOH (3 × 5 mL) and the combined methanol extracts evaporated in vacuo. The crude product was purified by preparative reverse phase HPLC purification to afford the pure sulfonamide amide products.

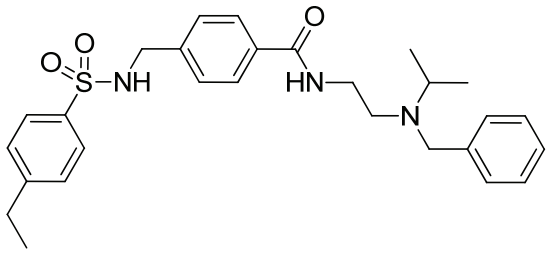


N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-methylphenylsulfonamido)methyl)benzamide 3*{1} (CID03342390). 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (120 mg, 0.37 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (71 mg, 0.37 mmol) were reacted according to the general procedure to afford the product as a white solid (92 mg, 0.19 mmol, 52% yield). R_f = 0.21 (EtOAc:hexanes 1:1); mp = 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.8 Hz, 6 H), 2.42 (s, 3 H), 2.67 (t, *J* = 6.0 Hz, 2 H), 3.00 (sept, *J* = 6.8 Hz, 1 H), 3.34 (q, *J* = 5.2 Hz, 2 H), 3.55 (s, 2 H), 4.14 (s, 2 H), 5.34 (br s, 1 H), 6.56 (br s, 1 H), 7.21-7.31 (complex, 9 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H). ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 18.0, 21.5, 49.7, 126.9, 127.0, 127.1, 127.7, 128.4, 128.5, 129.7; u (C, CH_2) 37.5, 46.8, 47.8, 53.6, 134.0, 136.9, 139.8, 140.7, 143.5, 166.6; IR (neat) 2964, 1639, 1156 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{33}N_3O_3S$ ($[M+H]^+$), 480.2315, found 480.2316.

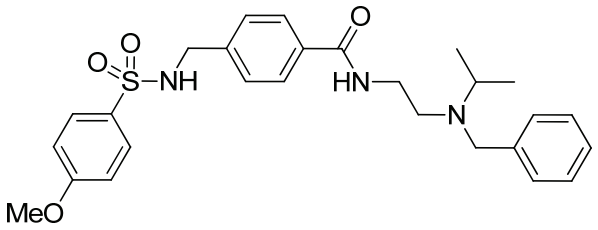


N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((3-methylphenylsulfonamido)methyl)benzamide 3*{4}(CID44608030). 4-((3-Methylphenylsulfonamido)methyl)benzoyl chloride (60 mg, 0.19 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (36 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as a tan solid (50 mg, 0.10 mmol, 56% yield). Mp = 112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.8 Hz, 6 H), 2.39 (s, 3 H),

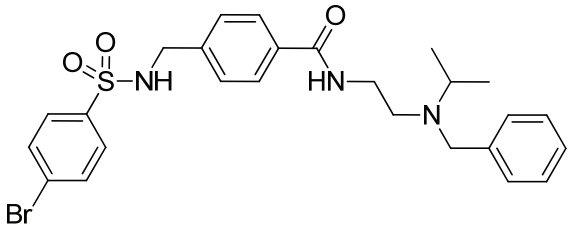
2.66 (t, J = 5.6 Hz, 2 H), 3.00 (sept, J = 6.8 Hz, 1 H), 3.34 (m, 2 H), 3.55 (s, 2 H), 4.15 (s, 2 H), 5.62 (br s, 1 H), 6.58 (br s, 1 H), 7.19-7.22 (complex, 3 H), 7.25-7.31 (complex, 6 H), 7.37 (m, 2 H), 7.44 (d, J = 7.6 Hz, 2 H), 7.68 (m, 2 H). ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 18.0 (× 2), 21.3, 49.6, 124.1, 127.0(× 2), 127.4, 127.7 (× 2), 128.4 (× 2), 128.5 (× 2), 128.9, 133.4; u (C, CH_2) 37.5, 46.8, 47.7, 53.6, 133.9, 139.3, 139.8, 139.9, 140.6, 166.7; IR (neat) 2964, 1638, 1152 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_3O_3S$ ($[M+H]^+$), 480.2315, found 480.2315.



N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-ethylphenylsulfonamido)methyl)benzamide 3*{5} (CID44601476). 4-((4-Ethylphenylsulfonamido)methyl)benzoyl chloride (68 mg, 0.20 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (38 mg, 0.20 mmol) were reacted according to the general procedure to afford the product as a white solid (58 mg, 0.12 mmol, 59% yield). mp = 90-92 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.06 (d, J = 6.8 Hz, 6 H), 1.23 (t, J = 7.6 Hz, 3 H), 2.65-2.73 (m, 4 H), 3.00 (sept, J = 6.8 Hz, 1 H), 3.34 (t, J = 6.8 Hz, 2 H), 3.62 (s, 2 H), 4.11 (s, 2 H), 7.17-7.35 (complex, 9 H), 7.60 (d, J = 8.0 Hz, 2 H), 7.72 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ d 15.9, 18.4 (× 2), 51.4, 128.0, 128.3 (× 2), 128.4 (× 2), 129.0 (× 2), 129.4 (× 2), 129.7 (× 2), 129.9 (× 2); u 29.8, 40.0, 47.6, 49.7, 55.5, 134.8, 139.5, 142.2, 142.7, 151.0, 169.6; IR (neat) 2965, 1637, 1449, 1159 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}N_3O_3S$ ($[M+H]^+$), 494.2477, found 494.2471.

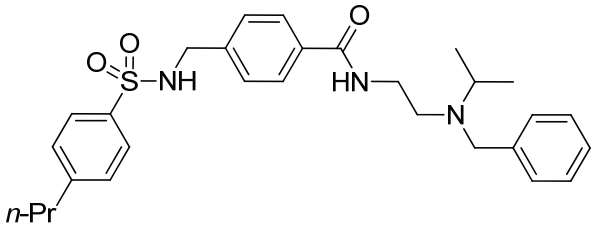


N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-methoxyphenylsulfonamido)methyl)benzamide 3*{6} (CID44620904). 4-((4-Methoxyphenylsulfonamido)methyl)benzoyl chloride (63 mg, 0.19 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (36 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as an off white solid (58 mg, 0.12mmol, 63% yield). Mp = 124-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.8 Hz, 6 H), 2.67 (t, *J* = 6.6 Hz, 2 H), 3.00 (sept, *J* = 6.8 Hz, 1 H), 3.34 (m, 2 H), 3.55 (s, 2 H), 3.85 (s, 3 H), 4.13 (d, *J* = 5.2 Hz, 2 H), 5.38 (br s, 1 H), 6.57 (br s, 1 H), 6.95 (d, *J* = 8.8 Hz, 2 H) 7.21-7.28 (complex, 7 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 9.2 Hz, 2 H); ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 18.0 (× 2), 49.6, 55.6, 114.2 (× 2), 127.0, 127.1 (× 2), 127.7 (× 2), 128.5 (× 2), 129.2 (× 2); u (C, CH_2) 37.5, 46.7, 47.8, 53.6, 131.5, 134.0, 139.8, 140.7, 162.9, 166.6; IR (neat) 2964, 1639, 1496, 1152 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_3O_4S$ ($[M+H]^+$), 496.2270, found 496.2261.

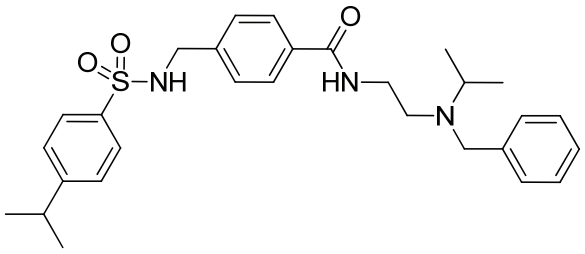


N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-bromophenylsulfonamido)methyl)benzamide 3*{7} (CID44620910). 4-((4-Bromophenylsulfonamido)methyl)benzoyl chloride (72 mg, 0.19 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (36 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as a white solid (60 mg, 0.11 mmol,

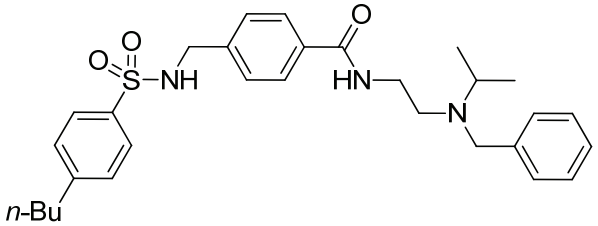
60% yield). mp = 149-150 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.07 (d, *J* = 6.4 Hz, 6 H), 2.27 (t, *J* = 6.0 Hz, 2 H), 3.00 (sept, *J* = 6.4 Hz, 1 H), 3.32 (m, 2 H), 3.55 (s, 2 H), 4.13 (s, 2 H), 5.97 (br s, 1 H), 6.58 (br s, 1 H), 7.17-7.30 (complex, 7 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.61 (d, *J* = 8.8 Hz, 2 H), 7.75 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ d 18.0 (× 2), 49.7, 126.9, 127.0 (× 2), 127.7 (× 2), 128.4 (× 2), 128.5(× 2), 128.6 (× 2), 132.3 (× 2); u 37.5, 46.8, 47.8, 49.7, 53.6, 127.5, 133.9, 139.2, 139.6, 140.7, 166.8; IR (neat) 3376, 3109, 2848, 1637 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{31}BrN_3O_3S$ ([M+H+isotope (+2)]$^{+}$), 546.1249, found 546.1238.



N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-propylphenylsulfonamido)methyl)benzamide 3*{8} (CID45115590). 4-((4-*n*-propylphenylsulfonamido)methyl)benzoyl chloride (104 mg, 0.29 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (57 mg, 0.29 mmol) were reacted according to the general procedure to afford the product as a white solid (69 mg, 0.1359 mmol., 47% yield). Mp = 138-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.3 Hz, 3 H), 1.07 (d, *J* = 6.6 Hz, 6 H), 1.57-1.76 (m, 2 H), 2.62-2.72 (complex, 4 H), 2.96-3.06 (m, 1 H), 3.35 (dt, *J* = 6.4, 5.6 Hz, 2 H), 3.56 (s, 2 H), 4.18 (d, *J* = 5.4 Hz, 2 H), 4.96 (br s, 1 H), 6.55 (br s, 1 H), 7.18-7.36 (complex, 9 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 13.8, 18.1, 49.8, 127.0, 127.2, 127.2, 127.8, 128.5, 128.6, 129.2; u 24.3, 37.5, 37.9, 46.9, 47.9, 53.7, 134.3, 137.2, 139.8, 140.8, 148.4, 166.6; IR (neat) 1638, 1326, 1154 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{29}H_{38}N_3O_3S$ ([M+H]$^{+}$), 508.2634, found 508.2623.

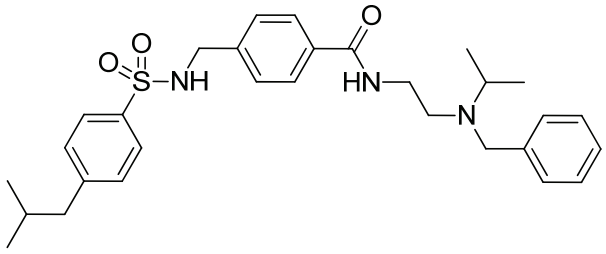


N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-*iso*-propylphenylsulfonamido)methyl)benzamide 3*{9} (CID45479162). 4-((4-*iso*-propylphenylsulfonamido)methyl)benzoyl chloride (117 mg, 0.33 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (64 mg, 0.333 mmol) were reacted according to the general procedure to afford the product as a white solid (101 mg, 0.1989 mmol., 60% yield). Mp = 122-125 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.6 Hz, 6 H), 1.27 (d, *J* = 6.9 Hz, 6 H), 2.64-2.73 (m, 2 H), 2.92-3.07 (complex, 2 H), 3.35 (dt, *J* = 6.4, 5.6 Hz, 2 H), 3.56 (s, 2 H), 4.18 (d, *J* = 6.1 Hz, 2 H), 5.08 (t, *J* = 6.2 Hz, 1H), 6.55 (br s, 1H), 7.19-7.32 (complex, 7 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 18.0, 23.7, 34.3, 49.7, 127.1, 127.2, 127.3, 127.4, 127.8, 128.5, 128.6; u 37.5, 46.9, 47.8, 53.7, 134.3, 137.2, 139.8, 140.7, 154.4, 166.6; IR (neat) 1639, 1324, 1161 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{29}H_{38}N_3O_3S$ ($[M+H]^+$), 508.2634, found 508.2627.

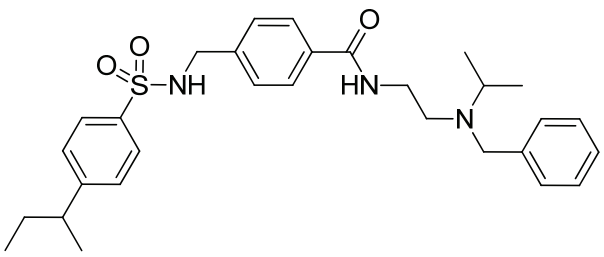


N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-butylphenylsulfonamido)methyl)benzamide 3*{10} (CID45115593). 4-((4-butylphenylsulfonamido)methyl)benzoyl chloride (107 mg, 0.29 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (56 mg, 0.29 mmol) were reacted according to the general procedure to afford the product as a viscous oil (13 mg, 0.025 mmol, 9%

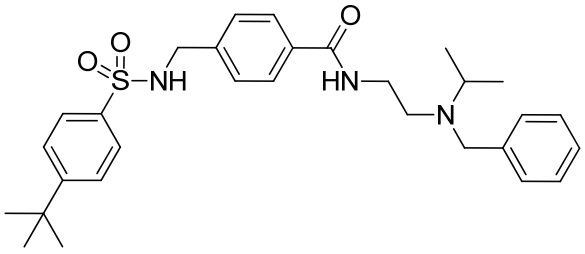
yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.4 Hz, 3 H), 1.08 (d, *J* = 6.8 Hz, 6 H), 1.31-1.44 (m, 2 H), 1.57-1.68 (m, 2 H), 2.65-2.75 (complex, 4 H), 2.97-3.09 (m, 1 H), 3.36 (dt, *J* = 6.4 Hz, 5.6 Hz, 2 H), 3.57 (s, 2 H), 4.20 (d, *J* = 6.1 Hz, 2 H), 4.82 (t, *J* = 6.2 Hz, 1 H), 6.56 (br s, 1 H), 7.19-7.41 (complex, 9 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ d 14.0, 18.1, 49.7, 127.1, 127.2, 127.2, 127.8, 128.5, 128.6, 129.2; u 22.4, 33.2, 35.6, 37.5, 47.0, 47.9, 53.8, 134.1, 134.3, 139.7, 140.7, 166.9; IR (neat) 1639, 1327, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{30}H_{40}N_3O_3S$ ($[M+H]^+$), 522.2790, found 522.2778.



N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-isobutylphenylsulfonamido)methyl)benzamide 3*{11} (CID45115591). 4-((4-isobutylphenylsulfonamido)methyl)benzoyl chloride (114 mg, 0.31 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (60 mg, 0.31 mmol) were reacted according to the general procedure to afford the product as a white solid (76 mg, 0.15 mmol, 47% yield). Mp = 107-113 ^{o}C.^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, 6 H), 1.07 (d, *J* = 6.6 Hz, 6 H), 1.82-1.98 (m, 1 H), 2.55 (d, *J* = 7.2 Hz, 2 H), 2.68 (t, *J* = 5.6 Hz, 2 H), 2.95-3.07 (m, 1 H), 3.35 (dt, *J* = 6.4, 5.6 Hz, 2 H), 3.56 (s, 2 H), 4.19 (d, *J* = 6.2 Hz, 2 H), 4.97 (t, *J* = 6.3 Hz, 1 H), 6.54 (br s, 1 H), 7.18 – 7.34 (complex, 9 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ d 18.1, 22.3, 30.2, 49.7, 127.0, 127.0, 127.2, 127.8, 128.5, 128.6, 129.9; 37.5, 45.2, 46.9, 47.8, 53.7, 134.2, 137.2, 139.7, 140.7, 147.4, 166.6; IR (neat) 1638, 1326, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{30}H_{40}N_3O_3S$ ($[M+H]^+$), 522.2790, found 522.2780.

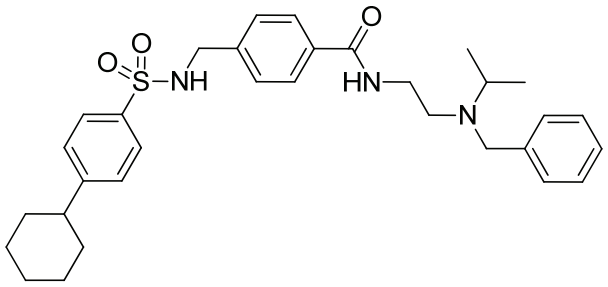


N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-*sec*-butylphenylsulfonamido)methyl)benzamide 3*{12} (CID45115586). 4-((4-*sec*-butylphenylsulfonamido)methyl)benzoyl chloride (84 mg, 0.23 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (44 mg, 0.23 mmol) were reacted according to the general procedure to afford the product as a white solid (24 mg, 0.046 mmol, 20% yield). Mp = 106-110 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.4 Hz, 3 H), 1.07 (d, *J* = 6.6 Hz, 6 H), 1.25 (d, *J* = 6.8 Hz, 3 H), 1.56-1.67 (complex, 2 H), 2.63-2.73 (complex, 3 H), 2.94-3.08 (m, 1 H), 3.35 (dt, *J* = 6.4, 5.6 Hz, 2 H), 3.56 (s, 2 H), 4.20 (br s, 2 H), 4.88 (br s, 1 H), 6.54 (br s, 1H), 7.17-7.36 (complex, 9 H), 7.51 (d, J = 8.4 Hz, 2 H), 7.80 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 12.2, 18.1, 21.6, 41.8, 49.7, 127.1, 127.2, 127.8, 127.8, 127.9, 128.5, 128.6; u 30.9, 37.5, 46.9, 47.8, 53.6, 134.3, 137.2, 139.8, 140.8, 153.4, 166.6; IR (neat) 1639, 1327, 1161 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{30}H_{40}N_3O_3S$ ($[M+H]^+$), 522.2790, found 522.2782.



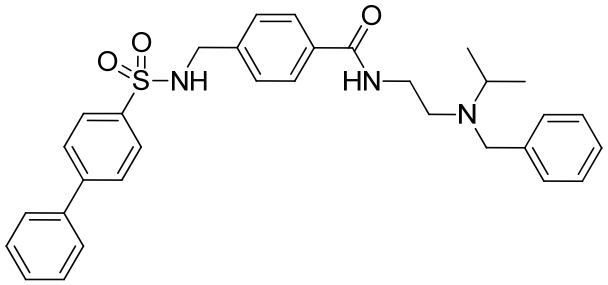
N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-*tert*-butylphenylsulfonamido)methyl)benzamide 3*{13} (CID45115588). 4-((4-*tert*-butylphenylsulfonamido)methyl)benzoyl chloride (124 mg, 0.34 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (65 mg, 0.34 mmol) were reacted according to the general procedure to afford the product as a white solid (84 mg, 0.16 mmol,

48% yield). Mp = 143-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.6 Hz, 6 H), 1.34 (s, 9 H), 2.68 (t, *J* = 5.6 Hz, 2 H), 2.94-3.90 (m, 1 H), 3.35 (dt, *J* = 6.4, 5.6 Hz, 2 H), 3.56 (s, 2 H), 4.19 (d, *J* = 6.3 Hz, 2 H), 4.98 (t, *J* = 6.3 Hz, 1 H), 6.55 (br s, 1 H), 7.18-7.34 (complex, 7 H), 7.48-7.54 (complex, 4 H), 7.80 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 18.1, 31.1, 49.7, 126.2, 127.0, 127.1, 127.2, 127.8, 128.5, 128.6; u 29.6, 37.5, 46.9, 47.8, 53.7, 134.3, 136.8, 139.8, 140.8, 156.7, 166.6; IR (neat) 1639, 1327, 1161 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{30}H_{40}N_3O_3S$ ($[M+H]^+$), 522.2790, found 522.2781.

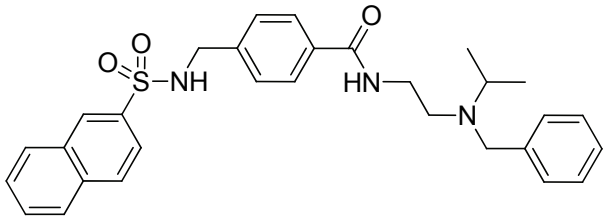


N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((4-cyclohexylphenylsulfonamido)methyl)benzamide 3*{14} (CID45115594). 4-((4-Cyclohexylphenylsulfonamido)methyl)benzoyl chloride (141 mg, 0.36 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (69 mg, 0.36 mmol) were reacted according to the general procedure to afford the product as a white solid (84 mg, 0.15 mmol, 43% yield). Mp = 120-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.6 Hz, 6 H), 1.32 – 1.48 (m, 4 H), 1.70 – 1.80 (m, 2 H), 1.81-1.90 (m, 4 H), 2.52-2.59 (m, 1 H), 2.67 (t, *J* = 5.6 Hz, 2 H), 2.95-3.06 (m, 1 H), 3.34 (dt, *J* = 6.4, 5.6 Hz, 2 H), 3.55 (s, 2 H), 4.17 (d, *J* = 6.0 Hz, 2 H), 5.22 (t, *J* = 6.1 Hz, 1 H), 6.55 (br s, 1 H), 7.19-7.35 (complex, 9 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.78 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) d 18.1, 44.6, 49.7, 127.1, 127.2, 127.2, 127.6, 127.8, 128.5, 128.6; u 26.0, 26.7, 34.2, 37.5, 46.9, 47.9, 53.7, 134.2, 137.2, 139.9, 140.8, 153.5, 166.6; IR (neat)

2926, 1641, 1319, 1157 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{32}H_{42}N_3O_3S$ ($[M+H]^+$), 548.2947, found 548.2938.

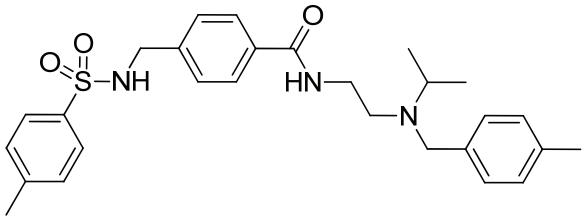


4-(([1,1'-Biphenyl]-4-ylsulfonamido)methyl)-*N*-(2-benzyl(isopropyl)amino)ethyl)benzamide *3{15}* (CID45115592). 4-(([1,1'-Biphenyl]-4-ylsulfonamido)methyl)benzoyl chloride (116 mg, 0.30 mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (58 mg, 0.30 mmol) were reacted according to the general procedure to afford the product as a white solid (39 mg, 0.072 mmol, 24% yield). Mp = 128-131 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.6 Hz, 6 H), 2.67 (t, *J* = 5.6 Hz, 2 H), 2.96-3.06 (m, 1 H), 3.35 (dt, *J* = 6.4 Hz, 5.6 Hz, 2 H), 3.56 (s, 2 H), 4.24 (d, *J* = 5.2 Hz, 2 H), 5.25 (br, 1 H), 6.55 (br, 1 H), 7.19-7.33 (complex, 7 H), 7.40-7.56 (complex, 5 H), 7.58-7.65 (m, 2 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.95 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 18.0, 49.7, 127.0, 127.2, 127.3, 127.7, 127.8, 127.9, 128.5, 128.5, 128.6, 129.1; u 37.5, 47.0, 47.8, 53.7, 134.3, 138.5, 139.3, 139.7, 140.7, 145.8, 166.6; IR (neat) 1639, 1328, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{32}H_{36}N_3O_3S$ ($[M+H]^+$), 542.2477, found 542.2467.



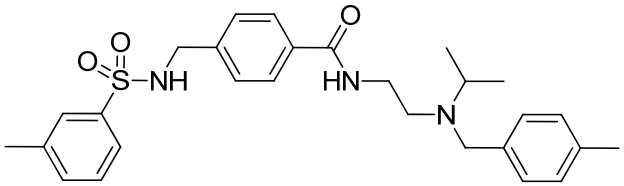
N*-(2-(Benzyl(isopropyl)amino)ethyl)-4-((naphthalene-2-sulfonamido)methyl)benzamide *3{16} (CID45115585). 4-((Naphthalene-1-sulfonamido)methyl)benzoyl chloride (122 mg, 0.34

mmol) and N^1-benzyl-N^1-isopropylethane-1,2-diamine (66 mg, 0.34mmol) were reacted according to the general procedure to afford the product as a white solid (39 mg, 0.072 mmol, 24% yield). Mp = 124-132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J = 6.6 Hz, 6 H), 2.66 (t, J = 5.6 Hz, 2 H), 2.95-3.05 (m, 1 H), 3.33 (dt, J = 6.4, 5.6 Hz, 2 H), 3.55 (s, 2 H), 4.21 (d, J = 5.8 Hz, 2 H), 5.23 (t, J = 5.7 Hz, 1 H), 6.49 (br s, 1 H), 7.16 – 7.33 (complex, 7 H), 7.46 (d, J = 8.0 Hz, 2 H), 7.57-7.70 (m, 2 H), 8.02-7.82 (m, 4H), 8.45 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 18.0, 49.7, 122.3, 127.0, 127.2, 127.7, 127.8, 128.0, 128.5, 128.5, 128.6, 128.9, 129.3, 129.6; u 37.5, 47.0, 47.8, 53.7, 132.2, 134.3, 134.9, 136.7, 139.7, 140.8, 166.6; IR (neat) 1638, 1326, 1154 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{30}H_{34}N_3O_3S$ ($[M+H]^+$), 516.2321, found 516.2312.

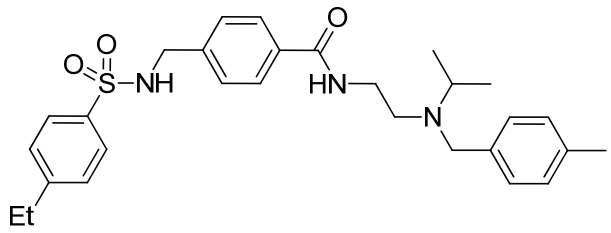


N*-(2-((4-Methylbenzyl)(isopropyl)amino)ethyl)-4-((4-methylphenylsulfonamido)methyl)-benzamide 3*{17}(CID44620902). 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (30 mg, 0.093 mmol) and N^1-isopropyl-N^1-(4-methylbenzyl)ethane-1,2-diamine (19 mg, 0.093 mmol) were reacted according to the general procedure to afford the product as a tan solid (10 mg, 0.02 mmol, 21% yield). Mp = 110-112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, J = 7.0 Hz, 6 H), 2.31 (s, 3 H), 2.45 (s, 3 H), 2.67 (t, J = 5.5 Hz, 2 H), 3.01 (sept, J = 6.5 Hz, 1 H), 3.35 (q, J = 5.5 Hz, 2 H), 3.52 (s, 2 H), 4.19 (d, J = 6.0 Hz, 2 H), 4.70 (br s, 1 H), 6.60 (br s, 1 H), 7.09 (d, J = 8.0 Hz, 2 H), 7.18 (d, J = 8.0 Hz, 2H),7.27 (m, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.55 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 8.5 Hz, 2 H); ^{13}C (125 MHz, $CDCl_3$) δ d (CH, CH_3) 18.2 (× 2),

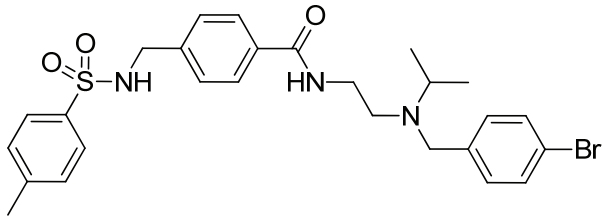
21.4, 21.8, 49.8, 127.4 (× 2), 127.5 (× 2), 128.0 (× 2), 128..8 (× 2), 129.4 (× 2), 130.1 (× 2); u (C, CH_2) 37.7, 47.1, 47.8, 53.5, 134.6, 136.9, 137.0, 137.8, 139.8, 144.0, 166.7; IR (neat) 2964, 1640, 1154 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}N_3O_3S$ ($[M+H]^+$), 494.2477, found 494.2470.



N*-(2-(Isopropyl(4-methylbenzyl)amino)ethyl)-4-((3-methylphenylsulfonamido)methyl)-benzamide 3*{18} (CID44608029). 4-((3-Methylphenylsulfonamido)methyl)benzoyl chloride (60 mg, 0.19 mmol) and N^1-isopropyl-N^1-benzylethane-1,2-diamine (38 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as a tan solid (51 mg, 0.10 mmol, 56% yield). Mp = 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.8 Hz, 6 H), 2.30 (s, 3 H), 2.39 (s, 3 H), 2.65 (t, *J* = 5.6 Hz, 2 H), 2.99 (sept, *J* = 6.8 Hz, 1 H), 3.34 (m, 2 H), 3.51 (s, 2 H), 4.16 (s, 2 H), 5.53 (br s, 1 H), 6.61 (br s, 1 H), 7.07 (d, *J* = 7.6 Hz, 2 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.38 (m, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.68 (m, 2 H); ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 18.0 (× 2), 21.1, 21.3, 49.6, 124.1, 127.0 (× 2), 127.4, 127.7 (× 2), 128.5 (× 2), 128.9, 129.1 (× 2), 133.4; u (C, CH_2) 37.5, 46.8, 47.6, 53.3, 134.0, 136.5, 137.5, 139.3, 139.8 (× 2), 166.6; IR (neat) 2965, 1639, 1152 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}N_3O_3S$ ($[M+H]^+$), 494.2477, found 494.2472.

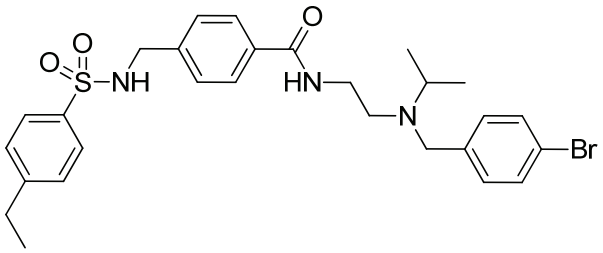


4-((4-Ethylphenylsulfonamido)methyl)-*N*-(2-(isopropyl(4-methylbenzyl)amino)ethyl)-benzamide 3*{19}* (CID44608031). 4-((4-Ethylphenylsulfonamido)methyl)benzoyl chloride (60 mg, 0.19 mmol) and N^1-isopropyl-N^1-(4-methylbenzyl)ethane-1,2-diamine (38 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as an off-white solid (47 mg, 0.09 mmol, 50% yield). Mp = 103-104 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.06 (d, *J* = 6.8 Hz, 6 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 2.30 (s, 3 H), 2.65 (t, *J* = 5.6 Hz, 2 H), 2.72 (q, *J* = 7.2 Hz, 2 H), 2.99 (sept, *J* = 6.8 Hz, 1 H), 3.34 (m, 2 H), 3.51 (s, 2 H), 4.16 (s, 2 H), 5.43 (br s, 1 H), 6.61 (br s, 1 H), 7.07 (d, *J* = 7.6 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 7.6 Hz, 2 H), 7.46 (d, *J* = 7.6 Hz, 2 H), 7.79 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ d 15.1, 18.0 (× 2), 21.1, 49.5, 127.1 (× 2), 127.2 (× 2), 127.7 (× 2), 128.5 (× 2), 128.6 (× 2), 129.1 (× 2); u 28.8, 37.5, 46.8, 47.6, 53.3, 134.0, 136.5, 137.1, 137.5, 139.8, 149.6, 166.6; IR (neat) 2966, 1640, 1157 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{38}N_3O_3S$ ($[M+H]^+$), 508.2634, found 508.2631.

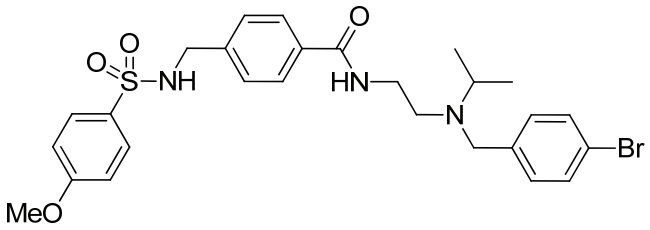


N*-(2-((4-Bromobenzyl)(isopropyl)amino)ethyl)-4-((4-methylphenylsulfonamido)methyl)-benzamide 3*{20} (CID 44620907). 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (318 mg, 0.98 mmol) and N^1-(4-bromobenzyl)-N^1-isopropylethane-1,2-diamine (266 mg, 0.98 mmol) were reacted according to the general procedure to afford the product as a white solid (248 mg, 0.44 mmol, 45% yield). Mp = 97-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.4 Hz, 6 H), 2.41 (s, 3 H), 2.64 (t, *J* = 5.6 Hz, 2 H), 2.96 (sept, *J* = 6.4 Hz, 1 H), 3.34 (m, 2 H),

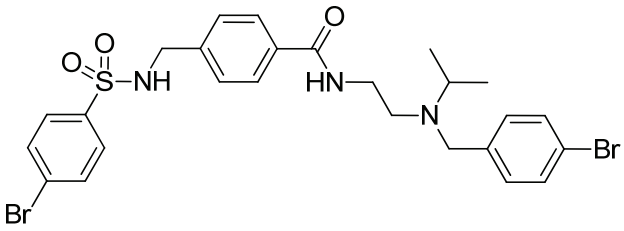
3.55 (s, 2 H), 3.49 (s, 2 H), 4.12 (s, 2 H), 5.71 (br s, 1 H), 6.53 (br s, 1 H), 7.15 (d, J = 8.8 Hz, 2 H), 7.23 (d, J = 8.4 Hz, 2 H),7.28 (d, J = 8.4 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.45 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 8.4 Hz, 2 H). ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 17.9 (× 2), 21.4, 49.7, 126.9 (× 2), 127.0 (× 2), 127.7 (× 2), 129.6 (× 2), 130.2 (× 2), 131.4 (× 2); u (C, CH_2) 37.6, 46.7, 47.9, 53.0, 120.5, 133.7, 136.9, 139.7, 140.0, 143.4, 166.8; IR (neat) 2965, 1639, 1157 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{33}BrN_3O_3S$ ([M+H + isotope]$^+$), 560.1406, found 560.1400.



4-((4-Ethylphenylsulfonamido)methyl)-*N*-(2-(isopropyl(4-bromobenzyl)amino)ethyl)-benzamide 3*{21}* (CID44608037). 4-((4-Ethylphenylsulfonamido)methyl)benzoyl chloride (60 mg, 0.19 mmol) and N^1-(4-bromobenzyl)-N^1- isopropylethane-1,2-diamine (50 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as an off-white solid (41 mg, 0.07 mmol, 39% yield). Mp = 106-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J = 6.8 Hz, 6 H), 1.26 (t, J = 7.2 Hz, 3 H), 2.65 (t, J = 5.6 Hz, 2 H), 2.72 (q, J = 7.6 Hz, 2 H), 2.97 (sept, J = 6.8 Hz, 1 H), 3.35 (m, 2 H), 3.50 (s, 2 H), 4.16 (d, J = 5.2 Hz, 2 H), 5.36 (br s, 1 H), 6.47 (br s, 1 H), 7.15 (d, J = 8.8 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 7.35 (d, J = 8.8 Hz, 2 H), 7.45 (d, J = 8.4 Hz, 2 H), 7.80 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 15.1, 18.0 (× 2), 49.7, 127.0 (× 2), 127.2 (× 2), 127.8 (× 2), 128.6 (× 2), 130.2 (× 2), 131.5(× 2); u 28.8, 37.6, 46.8, 48.0, 53.1, 120.6, 134.0, 137.1, 139.8, 139.9, 149.7, 166.8; IR (neat) 2966, 1638, 1324, 1156 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{35}BrN_3O_3S$ ([M+H]$^+$ + isotope), 574.1562, found 574.1554.

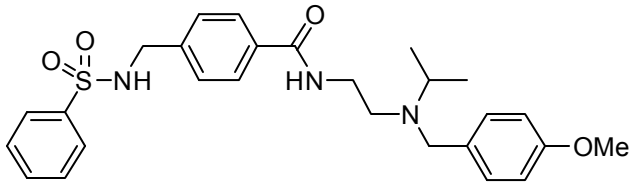


N*-(2-((4-Bromobenzyl)(isopropyl)amino)ethyl)-4-((4-methoxyphenylsulfonamido)methyl)-benzamide 3*{22} (CID44620903). 4-((4-Methoxyphenylsulfonamido)methyl)benzoyl chloride (63 mg, 0.19 mmol) and N^1-(4-bromobenzyl)-N^1-isopropylethane-1,2-diamine (50 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as a white solid (65 mg, 0.11 mmol, 61% yield). Mp = 106-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.4 Hz, 6 H), 2.64 (t, *J* = 5.6 Hz, 2 H), 2.97 (sept, *J* = 6.8 Hz, 1 H), 3.34 (m, 2 H), 3.49 (s, 2 H), 3.85 (s, 3 H), 4.13 (s, 2 H), 5.48 (br s, 1 H), 6.50 (br s, 1 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H),7.24 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 9.2 Hz, 2 H); ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 18.0 (× 2), 49.7, 55.6, 114.2 (× 2), 127.0 (× 2), 127.8 (× 2), 129.2 (× 2), 130.2 (× 2), 131.4 (× 2); u (C, CH_2) 37.7, 46.7, 48.0, 53.1, 120.6, 133.9, 139.8, 140.0 (× 2), 162.9, 166.8; IR (neat) 2966, 1641, 1497, 1153 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{33}BrN_3O_4S$ ([M+H + isotope (2)]$^+$), 576.1355, found 576.1349.

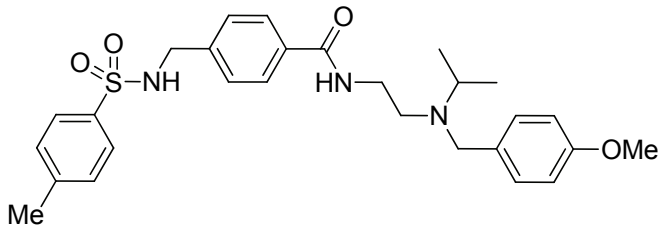


N*-(2-((4-Bromobenzyl)(isopropyl)amino)ethyl)-4-((4-methoxyphenylsulfonamido)methyl)-benzamide 3*{23} (CID44620900). 4-((4-Bromophenylsulfonamido)methyl)benzoyl chloride (72 mg, 0.19 mmol) and N^1-(4-bromobenzyl)-N^1-isopropylethane-1,2-diamine (50 mg, 0.19 mmol)

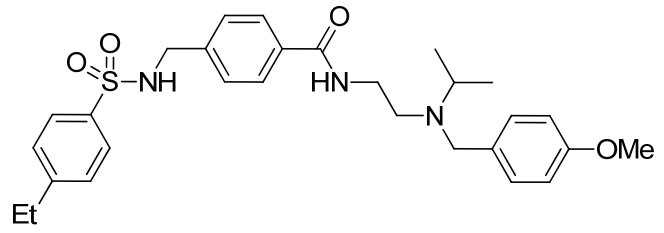
were reacted according to the general procedure to afford the product as a white solid (70 mg, 0.11 mmol, 60% yield). Mp = 108-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.4 Hz, 6 H), 2.65 (t, *J* = 5.6 Hz, 2 H), 2.97 (sept, *J* = 6.4 Hz, 1 H), 3.35 (m, 2 H), 3.49 (s, 2 H), 4.15 (s, 3 H), 5.77 (br s, 1 H), 6.49 (br s, 1 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H),7.34 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.8 Hz, 2 H), 7.75 (d, *J* = 8.8 Hz, 2 H); ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 18.0 (× 2), 49.8, 127.0 (× 2), 127.8 (× 2), 128.6 (× 2), 130.2 (× 2), 131.5 (× 2), 132.3 (× 2); u (C, CH_2) 37.7, 46.8, 48.1, 53.1, 120.6, 127.6, 134.0, 139.2, 139.7, 139.8, 166.8; IR (neat) 3102, 1637, 1497, 1486 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{30}Br_2N_3O_3S$ ([M+H + isotope (2)]$^{+}$), 624.0354, found 624.0338.



N*-(2-((4-Methoxybenzyl)(isopropyl)amino)ethyl)-4-(phenylsulfonamidomethyl)-benzamide 3*{24} (CID44665684). 4-(Phenylsulfonamidomethyl)benzoyl chloride (130 mg, 0.42 mmol) and N^1-(4-methoxybenzyl)-N^1-isopropylethane-1,2-diamine (93 mg, 0.42 mmol) were reacted according to the general procedure to afford the product as a viscous oil (40 mg, 0.081 mmol, 19% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.6 Hz, 6 H), 2.66 (t, *J* = 5.6 Hz 2 H), 2.96-3.08 (m, 1 H), 3.34 (dt, *J* = 6.4 Hz, 5.6 Hz, 2 H), 3.48 (s, 2 H), 3.76 (s, *J* = 3.0, 3 H), 4.20 (d, *J* = 5.6 Hz, 2 H), 4.91 (br s, 1 H), 6.52 (br s, 1 H), 6.74-6.82 (m, 2 H), 7.13-7.31 (complex, 4 H), 7.45-7.64 (complex, 5 H),7.90 (ddd, *J* = 7.0, 3.2, 1.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 18.1, 49.7, 55.3, 114.0, 127.1, 127.3, 127.8, 129.2, 129.7, 132.9; u 37.6, 47.0, 47.8, 53.0, 132.6, 134.5, 139.5, 140.0, 158.7, 166.6; IR (neat) 1639, 1510, 1327, 1159 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{27}H_{34}N_3O_4S$ ([M+H]$^{+}$), 496.2270, found 496.2261.

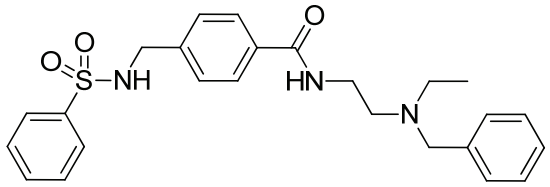


N*-(2-((4-Methoxybenzyl)(isopropyl)amino)ethyl)-4-((4-methylphenylsulfonamido)methyl)-benzamide 3*{25} (CID44620909). 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (146 mg, 0.45 mmol) and N^1-(4-methoxybenzyl)-N^1-isopropylethane-1,2-diamine (100 mg, 0.45 mmol) were reacted according to the general procedure to afford the product as a white solid (16 mg, 0.031 mmol, 7% yield). Mp = 122-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.8 Hz, 6 H), 2.47 (s, 3 H), 2.69 (t, *J* = 5.7 Hz, 2 H), 2.94-3.06 (m, 1 H), 3.37 (dt, J = 5.7, 6.0 Hz, 2 H), 3.52 (s, 2 H), 3.80 (s, 3 H), 4.20 (d, *J* = 5.2 Hz, 2 H), 4.91 (br s, 1 H), 6.55 (br s, 1 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 18.0, 21.6, 49.6, 55.3, 113.9, 127.2, 127.2, 127.8, 129.7, 129.8; u 37.5, 46.9, 47.7, 52.9, 132.6, 134.3, 136.9, 139.6, 143.7, 158.6, 166.7; IR (neat) 1638, 1509, 1326, 1243, 1156 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}N_3O_4S$ ($[M+H]^+$), 510.2427, found 510.2416.



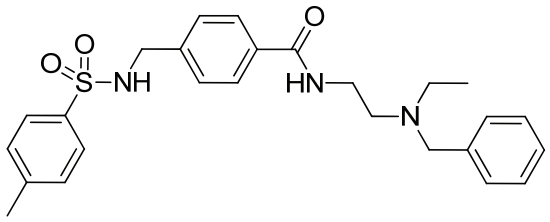
N*-(2-((4-Methoxybenzyl)(isopropyl)amino)ethyl)-4-((4-methylphenylsulfonamido)methyl)-benzamide 3*{26} (CID44620896). 4-((4-Ethylphenylsulfonamido)methyl)benzoyl chloride (149 mg, 0.44 mmol) and N^1-(4-methoxybenzyl)-N^1-isopropylethane-1,2-diamine (98 mg, 0.44 mmol)

were reacted according to the general procedure to afford the product as a viscous oil (13 mg, 0.025 mmol, 6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.8 Hz, 6 H), 1.19 (t, *J* = 7.6 Hz, 3 H), 2.58 (t, *J* = 5.2 Hz, 2 H), 2.65 (q, *J* = 7.6 Hz, 2 H), 2.86-2.98 (m, 1 H), 3.26 (m, 2 H), 3.40 (s, 2 H), 3.69 (s, 3 H), 4.10 (d, *J* = 6.0 Hz, 2 H), 4.78 (br s, 1 H), 6.43 (br s, 1 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 15.2, 18.0, 49.6, 55.3, 113.9, 127.2, 127.3, 127.8, 128.7, 129.7; u 28.8, 37.5, 46. 9, 47.7, 52.9, 132.6, 134.3, 137.0, 139.6, 149.8, 158.6, 166.6; IR (neat) 1639, 1509, 1326, 1243, 1156 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{38}N_3O_4S$ ($[M+H]^+$), 524.2578, found 524.2574.

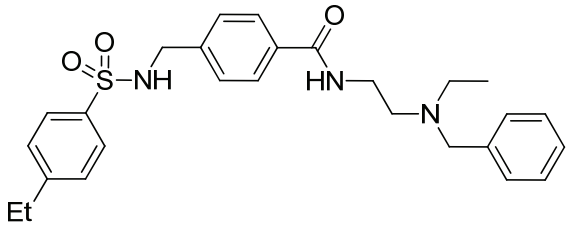


N*-(2-(Benzyl(ethyl)amino)ethyl)-4-(phenylsulfonamidomethyl)benzamide 3*{27}

(CID44665688). 4-((4-Phenylsulfonamido)methyl)benzoyl chloride (116 mg, 0.38 mmol) and N^1-benzyl-N^1-ethylethane-1,2-diamine (67 mg, 0.38 mmol) were reacted according to the general procedure to afford the product as a viscous oil (35 mg, 0.078 mmol, 21% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, *J* = 7.1 Hz, 3 H), 2.61 (q, *J* = 7.1 Hz, 2 H), 2.66 (t, *J* = 5.8 Hz, 2 H), 3.43 (dt, *J* = 5.8, 6.4 Hz, 2 H), 3.60 (s, 2 H), 4.20 (d, *J* = 5.6 Hz), 4.99 (br s, 1 H), 6.65 (br s, 1 H), 7.21-7.33 (m, 7 H), 7.48-7.56 (m, 5 H), 7.89 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 12.0, 127.1, 127.2, 127.3, 127.8, 128.5, 128.9, 129.2; u 37.5, 47.3, 51.6, 58.3, 134.3, 139.5, 139.6, 140.0, 166.9; IR (neat) 1638, 1325, 1157 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{29}N_3O_3S$ ($[M+H]^+$), 452.2008, found 452.2005.

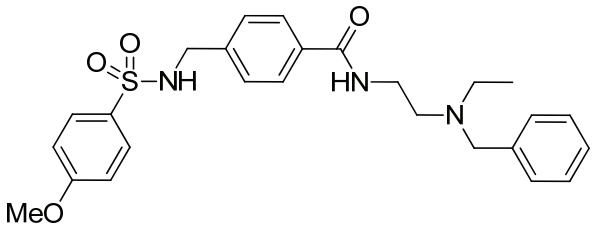


N*-(2-(Benzyl(ethyl)amino)ethyl)-4-((4-methylphenylsulfonamido)methyl)benzamide 3*{28} (CID44608034). 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (147 mg, 0.45 mmol) and N^1-benzyl-N^1-ethylethane-1,2-diamine (81 mg, 0.45 mmol) were reacted according to the general procedure to afford the product as a white solid (23 mg, 0.050 mmol, 11% yield). Mp = 85-88 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3 H), 2.47 (s, 3 H), 2.64 (q, *J* = 7.2 Hz, 2 H), 2.69 (t, *J* = 6.0, 2 H), 3.46 (dt, *J* = 5.1, 6.0 Hz, 2 H), 3.63 (s, 2 H), 4.21 (s, 2 H), 4.91 (br s, 1 H), 6.66 (br s, 1 H), 7.25-7.37 (m, 9 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* =8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 12.0, 21.6, 127.2, 127.3, 127.8, 128.5, 128.9, 129.8; u 37.3, 46.9, 47.5, 51.4, 58.0, 134.3, 136.8, 139.6, 139.7, 143.7, 166.6; IR (neat) 1638, 1325, 1149 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{31}N_3O_3S$ ($[M+H]^+$), 466.2159, found 466.2159.

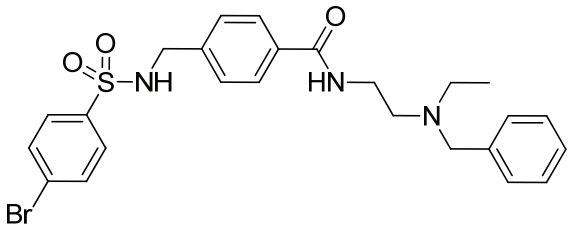


N*-(2-(Benzyl(ethyl)amino)ethyl)-4-((4-ethylphenylsulfonamido)methyl)benzamide 3*{29} (CID44608039). 4-((4-Ethylphenylsulfonamido)methyl)benzoyl chloride (121 mg, 0.36 mmol) and N^1-benzyl-N^1-ethylethane-1,2-diamine (64 mg, 0.36 mmol) were reacted according to the general procedure to afford the product as a viscous oil (14 mg, 0.029 mmol, 8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.5 Hz, 3 H), 2.65 (q, *J* = 7.2 Hz, 2 H),

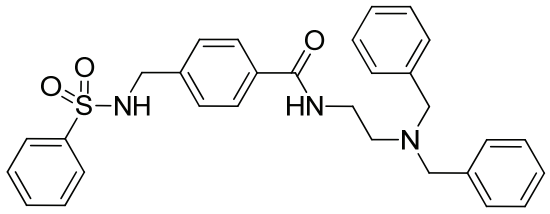
2.70 (t, *J* = 5.2 Hz, 2 H), 2.76 (q, *J* = 7.5 Hz, 2 H), 3.46 (dt, *J* = 5.2, 6.4 Hz, 2 H), 3.63 (s, 2 H), 4.22 (d, *J* = 6.0 Hz, 2 H), 4.80 (t, *J* = 6.3 Hz, 1 H), 6.66 (br s, 1 H), 7.24-7.40 (m, 9 H), 7.60 (d, *J* = 7.2 Hz, 2 H), 7.83 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 12.0, 15.2, 127.1, 127.2, 127.3, 127.8, 128.5, 128.7, 128. 9; u 28.8, 37.3, 46.9, 47.5, 51.4, 58.0, 134.3, 137.1, 139.6, 139.7, 149.9, 166.7; IR (neat) 1641, 1328, 1156 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_3O_3S$ ($[M+H]^+$), 480.2315, found 480.2318.



N*-(2-(benzyl(ethyl)amino)ethyl)-4-((4-methoxyphenylsulfonamido)methyl)benzamide 3*{30} (CID44620901). 4-((4-Methoxyphenylsulfonamido)methyl)benzoyl chloride (153 mg, 0.45 mmol) and N^1-benzyl-N^1-ethylethane-1,2-diamine (80 mg, 0.45 mmol) were reacted according to the general procedure to afford the product as a white solid (35 mg, 0.0727 mmol, 16% yield). Mp = 72-77 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3 H), 2.64 (t, *J* = 5.2 Hz, 2 H), 2.68 (q, *J* = 7.0 Hz, 2 H), 3.46 (dt, *J* = 5.2, 6.1 Hz, 2 H), 3.62 (s, 2 H), 3.90 (s, 3 H), 4.20 (d, *J* = 5.2 Hz, 2 H), 4.89 (br s, 1 H), 6.66 (br s, 1 H), 7.01 (d, *J* = 9.6 Hz , 2 H), 7.24-7.36 (m, 7 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.85 (d, *J* = 9.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 12.0, 55.7, 114.3, 127.2, 127.2, 127.8, 128.5, 128.9, 129.3; u 37.2, 46.8, 47.4, 51.3, 57.9, 131.3, 134.2, 139.6, 139.8, 163.0, 166.7; IR (neat) 1639, 1496, 1301, 1258, 1152 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{32}N_3O_4S$ ($[M+H]^+$), 482.2108, found 482.2109.

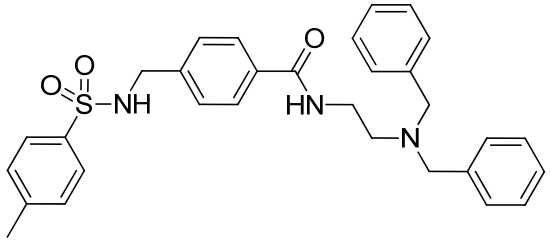


N*-(2-(benzyl(ethyl)amino)ethyl)-4-((4-bromophenylsulfonamido)methyl)benzamide 3*{31} (CID44620906). 4-((4-Bromophenylsulfonamido)methyl)benzoyl chloride (181 mg, 0.47 mmol) and N^1-benzyl-N^1-ethylethane-1,2-diamine (83 mg, 0.47 mmol) were reacted according to the general procedure to afford the product as a white solid (27 mg, 0.051 mmol, 11% yield). Mp = 99-101 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, *J* = 7.0 Hz, 3 H), 2.57 (t, *J* = 7.1 Hz, 2 H), 2.68 (q, *J* = 7.0 Hz, 2 H), 3.46 (dt, *J* = 4.9, 7.1 Hz, 2 H), 3.56 (s, 2 H), 4.16 (s, 2 H), 6.60 (br s, 1 H), 7.16-7.31 (m, 7 H), 7.50 (d, *J* = 8.3 Hz , 2 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 12.0, 127.2, 127.3, 127.8, 128.5, 128.7, 128.9, 132.5; u 37.2, 46.9, 47.4, 51.3, 57.9, 127.8, 134.3, 139.0, 139.4, 139.6, 167. 7; IR (neat) 1638, 1331, 1159 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{29}BrN_3O_3S$ ($[M+H]^+$ and $[M+H+Isotope\ (A+2)]^+$), 530.1108, 532.1090, found 530.1104, 532.1087.

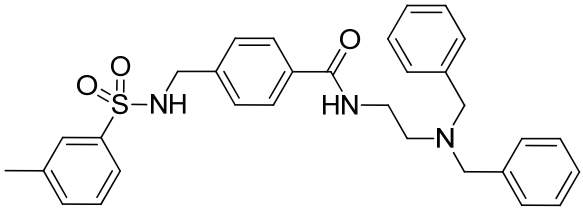


N*-(2-(Dibenzylamino)ethyl)-4-(phenylsulfonamidomethyl)benzamide 3*{32} (CID44665683). 4-((Phenylsulfonamido)methyl)benzoyl chloride (82 mg, 0.27 mmol) and N^1, N^1-dibenzylethane-1,2-diamine (64 mg, 0.27 mmol) were reacted according to the general procedure to afford the product as a white solid (62 mg, 0.121 mmol, 45% yield). Mp = 100-102 ^{o}C; ^{1}H NMR (400

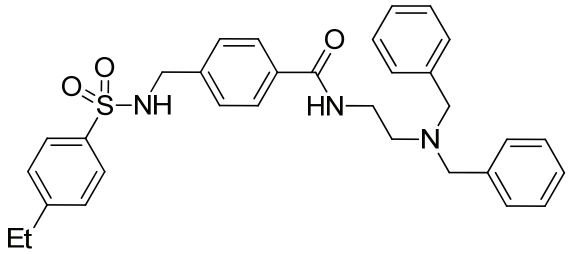
MHz, $CDCl_3$) δ 2.66-2.75 (m, 2 H), 3.48 (dd, *J* = 11.2, 4.9 Hz, 2 H), 3.63 (s, 4 H), 4.23 (s, 2 H), 4.90 (br s, 1 H), 6.42 (br s, 1 H), 7.20-7.38 (complex, 12 H), 7.48-7.58 (complex, 4 H), 7.58-7.66 (m, 1 H), 7.88-7.96 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 127.1, 127.3, 127.8, 128.5, 129.0, 129.2, 132.9; u 37.4, 47.0, 51.8, 58.6, 134.3, 139.1, 139.7, 166.6; IR (neat) 1638, 1327, 1157 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_3O_3S$ ($[M+H]^+$), 514.2164, found 514.2158.



N*-(2-(Dibenzylamino)ethyl)-4-((4-methylphenylsulfonamido)methyl)benzamide 3*{33} (CID44608028). 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (146 mg, 0.45 mmol) and N^1, N^1-dibenzylethane-1,2-diamine (104 mg, 0.45 mmol) were reacted according to the general procedure to afford the product as a white solid (79 mg, 0.1497 mmol, 33% yield). Mp = 134-136 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 2.73 (t, *J* = 6.0 Hz, 2 H), 3.50 (dt, *J* = 4.8, 6.0 Hz, 2 H), 3.65 (s, 4 H), 4.23 (s, 2 H), 4.89 (br s, 1 H), 6.45 (br s, 1 H), 7.25-7.38 (m, 14 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.82 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 21.6, 127.2, 127.3, 127.4, 127.8, 128.5, 129.0, 129.9; u 37.4, 46.9, 51.8, 58.5, 134.3, 136.9, 139.2, 139.9, 143.8, 166.7; IR (neat) 1639, 1326, 1155 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{34}N_3O_3S$ ($[M+H]^+$), 528.2315, found 528.2310.

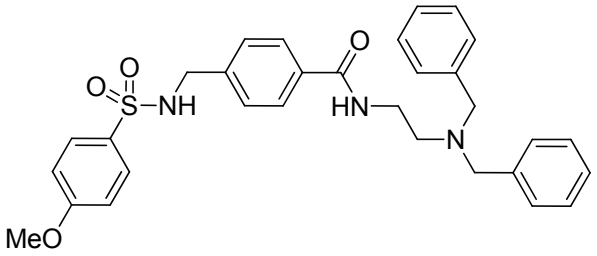


N*-(2-(Dibenzylamino)ethyl)-4-((3-methylphenylsulfonamido)methyl)benzamide 3*{34} (CID CID44608038). 4-((3-Methylphenylsulfonamido)methyl)benzoyl chloride (46 mg, 0.142 mmol) and N^1, N^1-dibenzylethane-1,2-diamine (34 mg, 0.142 mmol) were reacted according to the general procedure to afford the product as a white solid (39 mg, 0.074 mmol, 53% yield). Mp = 117-119 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 2.73 (t, *J* = 5.7 Hz, 2 H), 3.50 (dt, *J* = 5.0, 5.7 Hz, 2 H), 3.65 (s, 4 H), 4.25 (s, 2 H), 6.45 (br s, 1 H), 7.24-7.35 (m, 12 H), 7.43-7.45 (m, 2 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.72-7.75 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 21.4, 124.2, 127.2, 127.3, 127.5, 127.8, 128.5, 129.0, 129.1, 133.6; u 37.3, 46.9, 51.8, 58.5, 134.3, 139.1, 139.5, 139.7, 139.8, 166.7; IR (neat) 1639, 1327, 1152 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{34}N_3O_3S$ ($[M+H]^+$), 528.2315, found 528.2317.

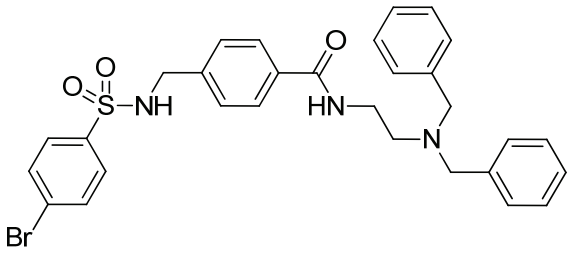


N*-(2-(Dibenzylamino)ethyl)-4-((4-ethylphenylsulfonamido)methyl)benzamide 3*{35} (CID44608033). 4-((4-Ethylphenylsulfonamido)methyl)benzoyl chloride (117 mg, 0.35 mmol) and N^1, N^1-dibenzylethane-1,2-diamine (83 mg, 0.35 mmol) were reacted according to the general procedure to afford the product as a white solid (51 mg, 0.094 mmol 27% yield). Mp = 141-145 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.6 Hz, 3 H), 2.69-2.80 (m, 4 H), 3.50 (dt, *J* = 4.5, 6.4 Hz, 2 H), 3.65 (s, 4 H), 4.24 (s, 2H), 6.44 (br s, 1 H), 7.25-7.35 (complex, 12 H), 7.38 (d, *J* = 7.6 Hz, 2 H), 7.55 (d, *J* = 7.6 Hz, 2 H), 7.84 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 15.2, 127.3, 127.3, 127.8, 128.5, 128.7, 129.0; u 28.8, 37.3, 46.9, 51.8, 58.5,

134.2, 137.1, 139.1, 139.8, 149.9, 166.7; IR (neat) 1639, 1325, 1155 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{32}H_{36}N_3O_3S$ ($[M+H]^+$), 542.2472, found 542.2469.

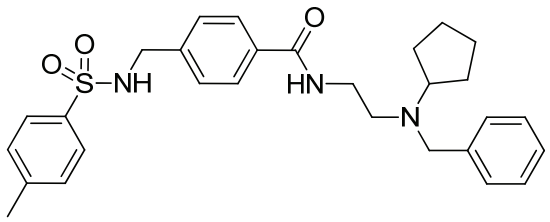


N*-(2-(Dibenzylamino)ethyl)-4-((4-methoxyphenylsulfonamido)methyl)benzamide 3*{36} (CID44620905). 4-((4-Methoxyphenylsulfonamido)methyl)benzoyl chloride (132 mg, 0.39 mmol) and N^1, N^1-dibenzylethane-1,2-diamine (93 mg, 0.39 mmol) were reacted according to the general procedure to afford the product as a white solid (46 mg, 0.085 mmol, 22% yield). Mp = 128-135 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.73 (t, *J* = 5.6 Hz, 2 H), 3.50 (dt, *J* = 5.2, 5.6 Hz, 2 H), 3.65 (s, 4 H), 3.90 (s, 3 H), 4.22 (d, *J* = 7.2 , 2 H), 4.80 (br s, 1 H), 6.44 (br s, 1 H), 7.02 (d, *J* = 8.0, 2 H), 7.24-7.37 (complex, 12 H), 7.55 (d, *J* = 8.0, 2 H), 7.86 (d, *J* = 8.0, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 55.7, 114.4, 127.3, 127.3, 127.8, 128.5, 129.0, 129.3; u 37.3, 46.9, 51.7, 58.5, 131.3, 134.2, 139.1, 139.8, 163.1, 166.7; IR (neat) 1639, 1495, 1301, 1256, 1150 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{31}H_{34}N_3O_4S$ ($[M+H]^+$), 544.2265, found 544.2260.



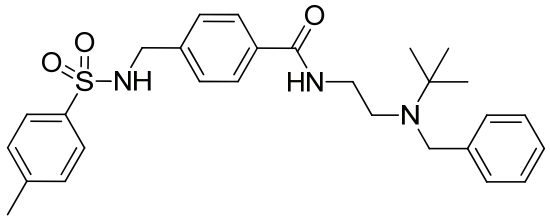
N*-(2-(Dibenzylamino)ethyl)-4-((4-bromophenylsulfonamido)methyl)benzamide 3*{37} (CID44620908). 4-((4-Bromophenylsulfonamido)methyl)benzoyl chloride (160 mg, 0.41 mmol)

and N^1, N^1-dibenzylethane-1,2-diamine (99 mg, 0.41 mmol) were reacted according to the general procedure to afford the product as a white solid (41 mg, 0.069 mmol, 17% yield). Mp = 150-155 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 2.73 (t, J = 5.6 Hz, 2 H), 3.50 (dt, J = 5.3, 5.6 Hz, 2 H), 3.65 (s, 4 H), 3.90 (s, 3 H), 4.24 (s, 2 H), 5.10 (br s, 1 H), 6.44 (br s, 1 H), 7.24-7.37 (complex, 12 H), 7.53 (d, J = 8.4, 2 H), 7.69 (d, J = 8.4, 2 H), 7.79 (d, J = 8.4, 2 H); ^{13}CNMR (100 MHz, $CDCl_3$) δ d 127.3, 127.8, 128.5, 128.7, 129.0, 132.5; u 37.3, 46.9, 51.7, 58.5, 127.8, 134.4, 139.0, 139.1, 139.4, 166.7; IR (neat) 1640, 1332, 1161 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{30}H_{31}BrN_3O_3S$ ($[M+H]^+$ and $[M+H+Isotope\ (A+2)]^+$), 592.1264, 594.1247, found 592.1252, 594.1236.

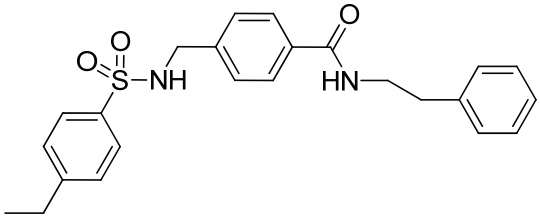


N*-(2-(benzyl(cyclopentyl)amino)ethyl)-4-((4-methylphenylsulfonamido)methyl)benzamide** (CID45479167) ***3{38}. 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (101 mg, 0.31 mmol) and N^1-benzyl-N^1-cyclopentylethane-1,2-diamine (68 mg, 0.3114 mmol) were reacted according to the general procedure to afford the product as a white solid (37 mg, 0.073 mmol., 24% yield). Mp = 140-146 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ1.40-1.58 (m, 4 H), 1.59-1.73 (m, 2 H), 1.74-1.86 (m, 2 H), 2.43 (s, 3 H), 2.68-2.76 (m, 2 H), 3.17-3.28 (m, 1 H), 3.37 (dt, J = 6.4, 5.6 Hz, 2 H), 3.62 (s, 2 H), 4.16 (s, 2 H), 5.05 (br s, 1 H), 6.52 (br s, 1 H), 7.17-7.38 (m, 9 H), 7.51 (d, J = 8.4 Hz, 2 H), 7.77(d, J = 8.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ d 21.5, 63.1, 127.0, 127.1, 127.2, 127.8, 128.5, 128.7, 129.8; u 24.2, 28.5, 37.6, 46.9, 50.1, 56.0, 134.2, 136.9, 139.8,

140.5, 143.7, 166.7; IR (neat) 1642, 1327, 1157 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{29}H_{36}N_3O_3S$ ($[M+H]^+$), 506.2477, found 506.2472.

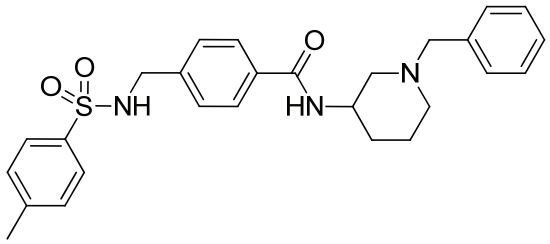


N*-(2-(Benzyl(*tert*-butyl)amino)ethyl)-4-((4-methylphenylsulfonamido)methyl)benzamide** (CID45115589) ***3{39}. 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (75 mg, 0.23 mmol) and N^1-benzyl-N^1-(*tert*-butyl)ethane-1,2-diamine (48 mg, 0.23 mmol) were reacted according to the general procedure to afford the product as a white solid (33 mg, 0.067 mmol, 19% yield). Mp = 136-139; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9 H), 2.44 (s, 3 H), 2.83 (t, *J* = 5.9 Hz, 2 H), 3.18 (dt, *J* = 6.4, 5.9 Hz, 2 H), 3.70 (s, 2 H), 4.16 (s, 2 H), 4.94 (br s, 1 H), 6.25 (br s, 1 H), 7.16 (m, 1 H), 7.21-7.28 (complex, 4 H), 7.29-7.38 (complex, 4 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 27.5, 41.0, 126.8, 127.2, 127.2, 127.8, 127.9, 128.5, 129.8; u 39.8, 46.9, 50.1, 55.3, 55.5, 134.4, 137.0, 139.6, 142.9, 143.7, 166.5; IR (neat) 1638, 1509, 1326, 1243, 1156 cm^{-1}; IR (neat) 1638, 1509, 1326, 1154 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{28}H_{36}N_3O_3S$ ($[M+H]^+$), 494.2477, found 494.2470.



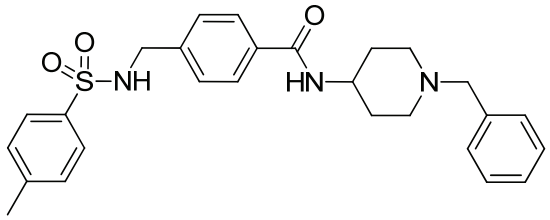
4-((4-Ethylphenylsulfonamido)methyl)-*N*-phenethylbenzamide (CID44601477) ***3{40}***. 4-((4-Ethylphenylsulfonamido)methyl)benzoyl chloride (42 mg, 0.13 mmol) and phenethylamine (32

mg, 0.25 mmol, 2.0 equiv.) afforded the product as a white solid (42 mg, 0.10 mmol, 80% yield). mp = 173-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.6 Hz, 3 H), 2.73 (q, *J* = 7.6 Hz, 2 H), 2.93 (t, *J* = 6.8 Hz, 2 H), 3.71 (m, 2 H), 4.17 (s, 2 H), 4.72 (br s, 1 H), 6.08 (br s, 1 H), 7.22-7.26 (complex, 5 H), 7.31-7.34 (complex, 4 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.78 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ d 15.2 (× 2), 126.5, 127.2 (× 2), 127.3 (× 2), 127.9 (× 2), 128.6 (× 2), 128.7 (× 2), 128.8 (× 2); u 28.8, 35.7, 41.1, 46.8, 138.0, 138.8, 139.9, 152.4, 170.4; IR (neat) 3410, 3132, 1635, 1542, 1154 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{27}N_2O_3S$ ($[M+H]^+$), 423.1742, found 423.1733.

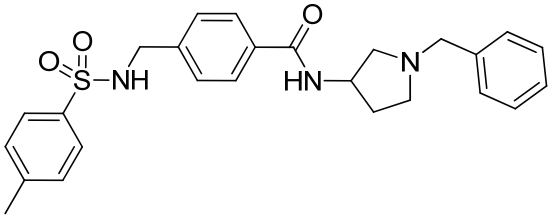


N*-(1-benzylpiperidin-3-yl)-4-((4-methylphenylsulfonamido)methyl)benzamide** (CID45479165) ***3{41}. 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (71 mg, 0.22 mmol) and the commercially available 1-benzylpiperidine-3-amine (42 mg, 0.22 mmol) were reacted according to the general procedure to afford the product as a white solid (65 mg, 0.14 mmol, 65% yield). Mp = 159-170 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53-1.65 (complex, 2 H), 1.66-1.91 (complex, 2 H), 2.16-2.30 (m,1 H), 2.36-2.50 (complex, 4 H), 2.53-2.66 (m, 1 H), 2.66-2.80 (m, 1 H), 3.45 (d, *J* = 12.8 Hz, 1 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 4.18 (d, *J* = 6.3 Hz, 2 H), 4.24 (br s, 1 H), 4.77 (t, *J* = 6.4 Hz, 1 H), 6.83 (br s, 1 H), 7.21 – 7.39 (complex, 9 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 21.6, 45.4, 127.0, 127.3, 127.8, 127.9, 128.4, 129.0, 129.8; u 21.9, 28.9, 46.9, 54.1, 57.8, 63.1, 134.6, 138.3, 139.8, 143.

8, 165.8; IR (neat) 3300, 1636, 1324, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{27}H_{32}N_3O_3S$ ($[M+H]^+$), 478.2164, found 478.2155.

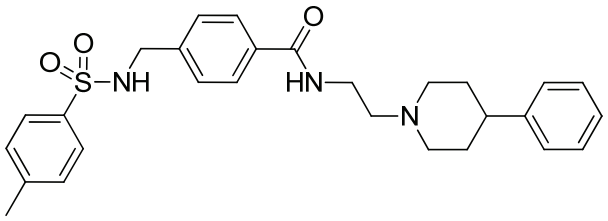


N*-(1-Benzylpiperidin-4-yl)-4-((4-methylphenylsulfonamido)methyl)benzamide** (CID45479171) ***3{42}. 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (103 mg, 0.32 mmol) and the commercially available 1-benzylpiperidine-4-amine (60 mg, 0.32 mmol) were reacted according to the general procedure to afford the product as a white solid (68 mg, 0.14 mmol, 46% yield). Mp = 160-167 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49-1.61 (m, 2 H), 1.95-2.05 (m, 2 H), 2.11-2.24 (m, 2 H), 2.44 (s, 3 H), 2.79-2.91 (m, 2 H), 3.51 (s, 2 H), 3.93-4.05 (m, 1 H), 4.15 (s, 2 H), 4.90 (br s, 1 H), 5.95 (d, *J* = 7.7 Hz, 1H), 7.21-7.35 (complex, 9 H), 7.64 (d, *J* = 8.3 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d 21.6, 47.1, 127.1, 127.2, 127.2, 127.9, 128.3, 129.1, 129.8; u 32.4, 46.9, 52.4, 63.1, 134.4, 136.8, 138.4, 140.0, 143.7, 166.3; IR (neat) 1637, 1330, 1156 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{27}H_{32}N_3O_3S$ ($[M+H]^+$), 478.2164, found 478.2159.

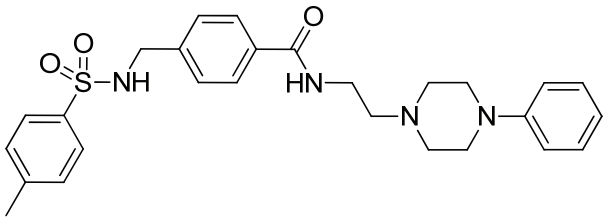


N*-(1-Benzylpyrrolidin-3-yl)-4-((4-methylphenylsulfonamido)methyl)benzamide** (CID45479170) ***3{43}. 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (113 mg, 0.35

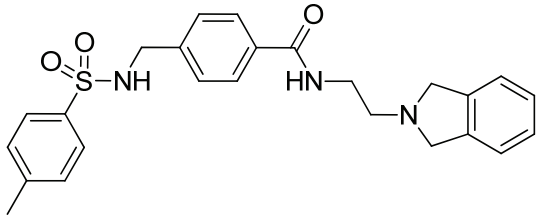
mmol) and the commercially available 1-benzylpyrrolidine-3-amine (61 mg, 0.35 mmol) were reacted according to the general procedure to afford the product as a white solid (70 mg, 0.1511 mmol, 49% yield). Mp = 160-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67-1.76 (m, 1 H), 2.25-2.42 (complex, 2 H), 2.44 (s, 3 H), 2.57-2.65 (m, 1 H), 2.71 (dd, *J* = 9.6, 2.4 Hz, 1 H), 2.88-2.96 (m, 1 H), 3.62 (s, 2 H), 4.14 (s, 2 H), 4.71 – 4.58 (m, 1 H), 5.02 (br s, 1 H), 6.58 (d, *J* = 8.3 Hz, 1 H), 7.21-7.40 (complex, 9 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 7.76 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ d u 21.6, 49.2, 127.2, 127.2, 127.3, 127.9, 128.4, 128.9, 129.8; u 32.7, 46.9, 52.8, 60.1, 60.8, 134.0, 136.8, 138.4, 139.9, 143.7, 166.2 IR (neat) 2926, 1641, 1319, 1157 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{26}H_{30}N_3O_3S$ ($[M+H]^+$), 464.2008, found 464.2005.



4-((4-Methylphenylsulfonamido)methyl)-*N*-(2-(4-phenylpiperidin-1-yl)ethyl)benzamide (CID45479163) ***3{44}***. 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (101 mg, 0.31 mmol) and 2-(4-phenylpiperidin-1-yl)ethanamine (64 mg, 0.31 mmol) were reacted according to the general procedure to afford the product as a white solid (23 mg, 0.047 mmol, 15% yield). Mp = 134-141 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69-1.82 (m, 2 H), 1.83-1.93 (m, 2 H), 2.09-2.22 (m, 2 H), 2.44 (s, 3 H), 2.49-2.58 (m, 1 H), 2.59-2.66 (m, 2 H), 3.04 (m, 2 H), 3.55 (dt, *J* = 6.4, 5.7 Hz, 2H), 4.17 (s, 2 H), 4.90 (s, 1 H), 6.89 (s, 1 H), 7.16-7.36 (complex, 9 H), 7.71 (d, 2 H), 7.76 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ d 21.6, 42.5, 126.6, 126.8, 127.2, 127.3, 127.9, 128.5, 129.8; u 33.5, 36.6, 46.9, 54.1, 56.7, 134.3, 136.9, 139.9, 143.7, 146.1, 166.9; IR (neat) 1638, 1325, 1155 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{28}H_{34}N_3O_3S$ ($[M+H]^+$), 492.2321, found 492.2319.

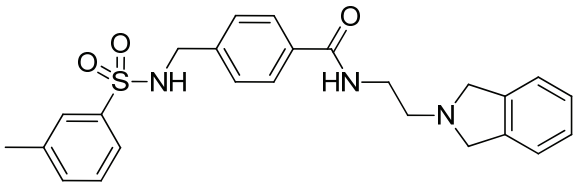


4-((4-Methylphenylsulfonamido)methyl)-*N*-(2-(4-phenylpiperazin-1-yl)ethyl)benzamide (CID6621922) ***3{45}***. 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (101 mg, 0.31 mmol) and 2-(4-phenylpiperazin-1-yl)ethanamine (64 mg, 0.31 mmol) were reacted according to the general procedure to afford the product as a white solid (30 mg, 0.061 mmol, 20% yield). Mp = 145-155 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.62-2.70 (complex, 6 H), 3.16-3.25 (m, 4 H), 3.57 (dt, *J* = 6.4, 5.6 Hz, 2 H), 4.13 (s, 2 H), 5.28 (br s, 1 H), 6.84-6.90 (m, 2 H), 6.93 (d, *J* = 8.8, Hz, 2 H), 7.21-7.33 (complex, 6 H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ d 21.6, 116.1, 120.0, 127.2, 127.3, 127.9, 129.2, 129.8; u 36.3, 46.8, 49.3, 52.9, 56.4, 134.0, 136.9, 140.2, 143.6, 151.2, 167.0; IR (neat) 1637, 1599, 1499, 1325, 1154 cm^{-1}; HRMS (APCI/ES) *m/z* calcd for $C_{27}H_{33}N_4O_3S$ ($[M+H]^+$), 493.2273, found 493.2266.



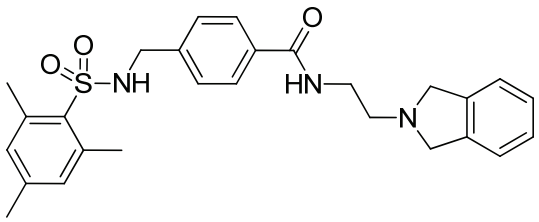
N*-(2-(Isoindolin-2-yl)ethyl)-4-((4-methylphenylsulfonamido)methyl)benzamide** (CID44620897) ***3{46}. 4-((4-Methylphenylsulfonamido)methyl)benzoyl chloride (60 mg, 0.19 mmol) and 2-(isoindolin-2-yl)ethanamine (30 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as a tan solid (30 mg, 0.07 mmol, 36% yield). Mp = 161-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 2.99 (t, *J* = 5.6 Hz, 2 H), 3.62 (q, *J* = 5.6

Hz, 2 H), 3.98 (s, 4 H), 4.06 (d, J = 6.0 Hz, 2 H), 5.50 (t, J = 6.4 Hz, 1 H), 6.97 (t, J = 4.8 Hz, 1 H), 7.17-7.23 (complex, 6 H), 7.28 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 8.4 Hz, 2 H), 7.72 (d, J = 8.4 Hz, 2 H); ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 21.5, 122.3 (× 2), 127.0 (× 2), 127.1 (× 2), 127.4 (× 2), 127.8 (× 2), 129.7; u (C, CH_2) 38.4, 46.7, 54.4, 58.9 (× 2), 133.9, 136.9, 139.5, 140.0 (× 2), 143.5, 167.1; IR (neat) 1638, 1323, 1305, 1153 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_3O_3S$ ($[M+H]^+$), 450.1851, found 450.1846.



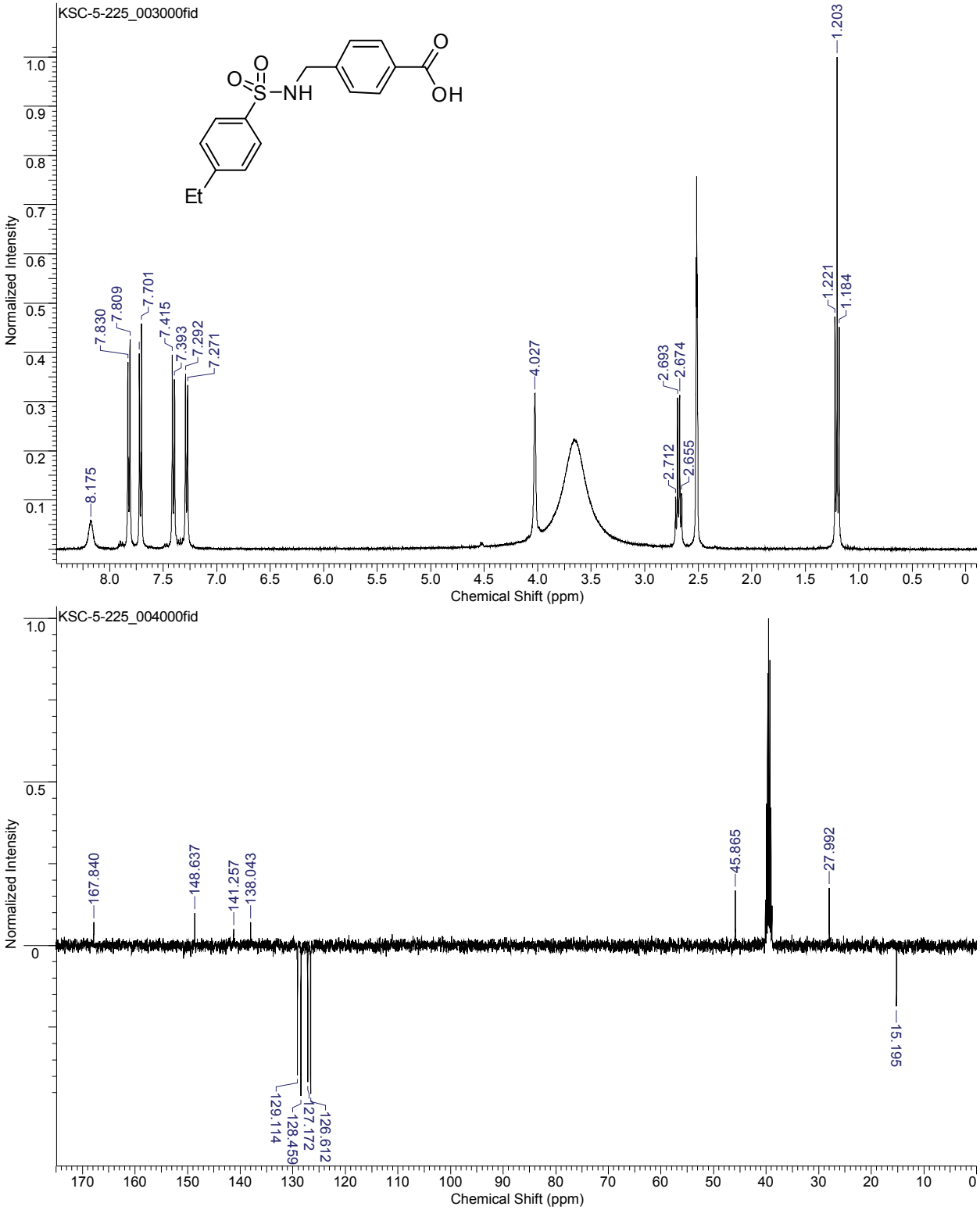
***N*-(2-(Isoindolin-2-yl)ethyl)-4-((3-methylphenylsulfonamido)methyl)benzamide**

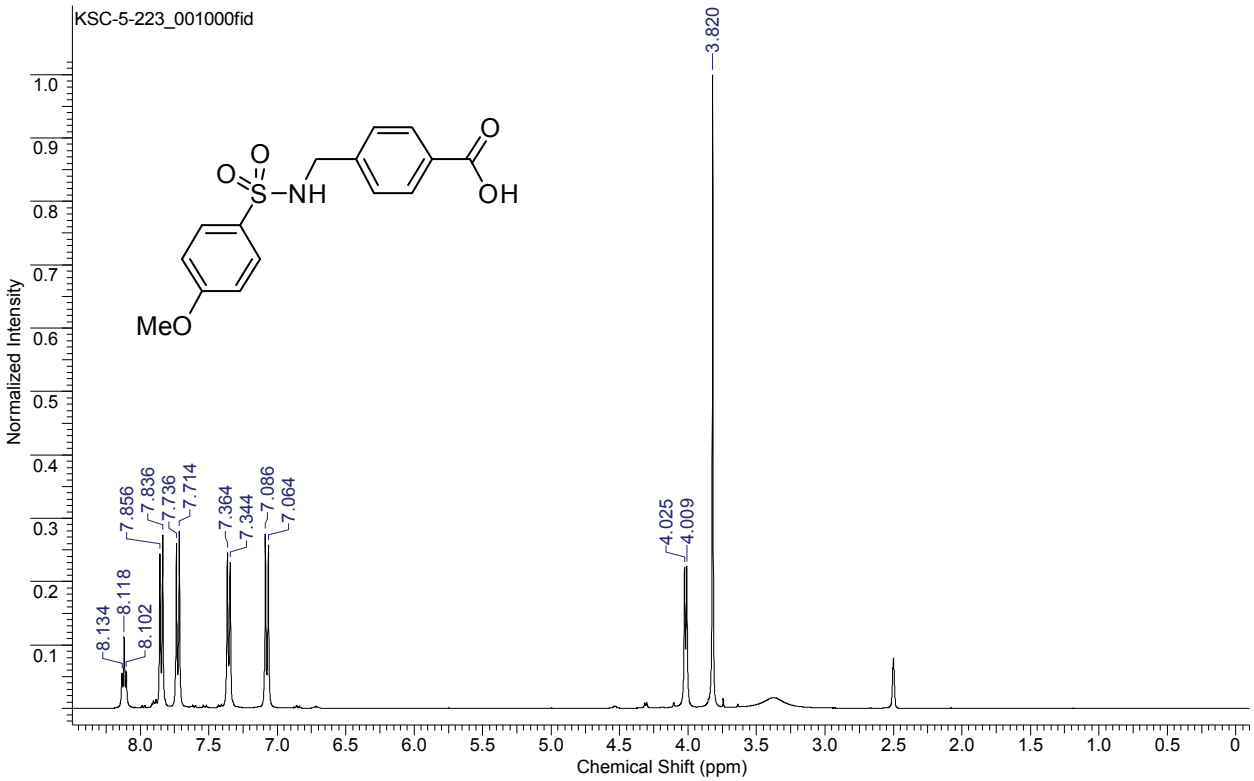
(CID44608035) ***3{47}***. 4-((3-Methylphenylsulfonamido)methyl)benzoyl chloride (60 mg, 0.19 mmol) and 2-(isoindolin-2-yl)ethanamine (30 mg, 0.19 mmol) were reacted according to the general procedure to afford the product as an off-white solid (20 mg, 0.04 mmol, 24% yield). Mp = 130-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H), 2.99 (t, J = 5.6 Hz, 2 H), 3.63 (q, J = 5.6 Hz, 2 H), 3.99 (s, 4 H), 4.12 (d, J = 5.2 Hz, 2 H), 5.20 (br s, 1 H), 6.91 (br s, 1 H), 7.20-7.26 (complex, 6 H), 7.37 (m, 2 H), 7.65 (m, 2 H); ^{13}C (100 MHz, $CDCl_3$) δ d (CH, CH_3) 21.3, 122.3 (× 2), 124.2, 127.0 (× 2), 127.3 (× 2), 127.4, 127.8 (× 2), 129.0, 133.5; u (C, CH_2) 38.4, 46.8, 54.3, 58.8 (× 2), 134.0, 139.4, 139.6 (× 2), 139.7, 139.9, 167.1; IR (neat) 1639, 1545, 1325, 1308, 1152 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_3O_3S$ ($[M+H]^+$), 450.1851, found 450.1847.



N*-(2-(Isoindolin-2-yl)ethyl)-4-((2,4,6-trimethylphenylsulfonamido)methyl)benzamide** (CID44601478) ***3{48}. 4-((2, 4, 6-Trimethylphenylsulfonamido)methyl)benzoyl chloride (102 mg, 0.29 mmol) and 2-(isoindolin-2-yl)ethanamine (47 mg, 0.29 mmol) were reacted according to the general procedure to afford the product as a viscous orange oil (106 mg, 0.22 mmol, 76% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 2.26 (s, 3 H), 2.59 (s, 6 H), 2.98 (t, J = 5.6 Hz, 2 H), 3.62 (t, J = 6.8 Hz, 2 H), 4.00 (s, 4 H), 4.11 (s, 2 H), 6.95 (s, 2 H), 7.20-7.26 (complex, 6 H), 7.71 (d, J = 8.0 Hz, 2 H), 7.63 (d, J = 8.4 Hz, 2 H), 7.72 (d, J = 8.4 Hz, 2 H); ^{13}C (100 MHz, CD_3OD) δ d (CH, CH_3) 21.1, 23.3, 122.4 (× 2), 128.3 (× 2), 128.4 (× 2), 128.9 (× 2), 133.0 (× 2); u (C, CH_2) 39.8, 46.8, 56.1, 60.1 (× 2), 134.5, 136.0, 140.2, 140.9 (× 2), 142.9, 143.6, 169.8; IR (neat) 3302, 1640, 1323, 1152 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{32}N_3O_3S$ ($[M+H]^+$), 478.2164, found 478.2150.

NMR spectra for Chemotype III compounds and new synthetic intermediates

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4.009
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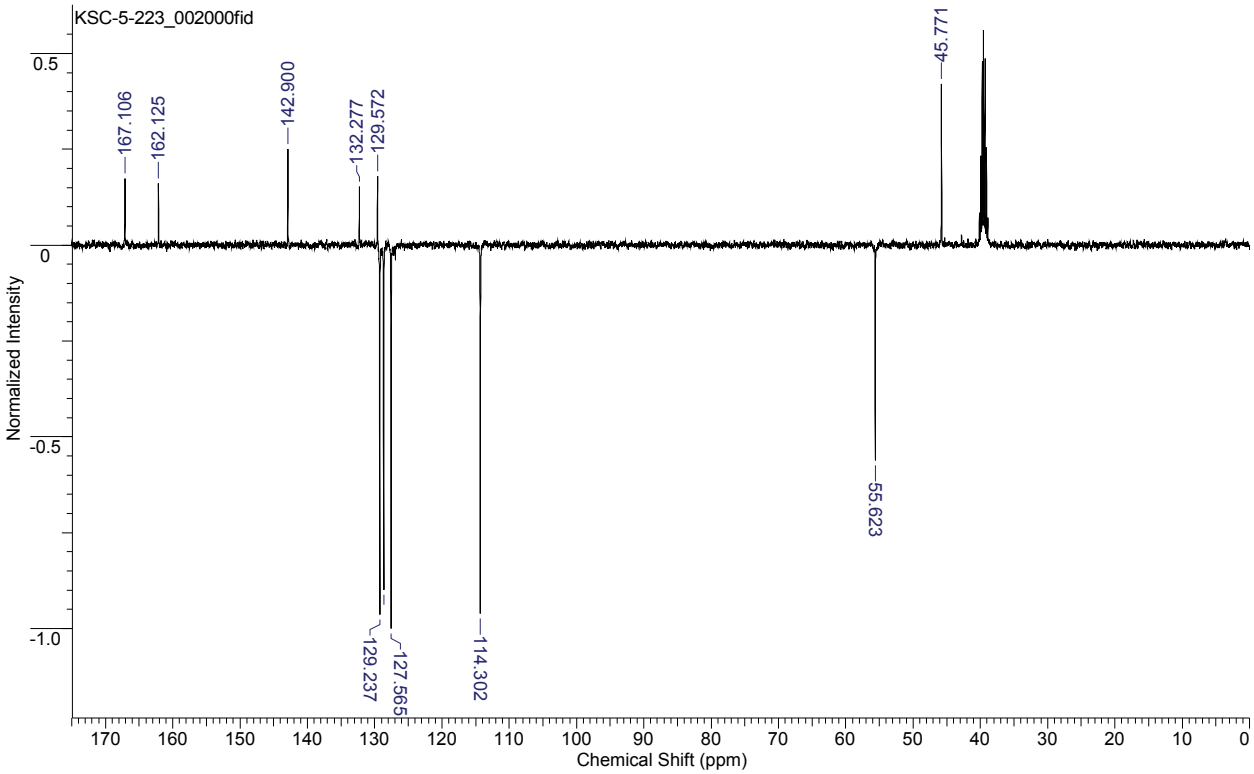
O
S
NH
OH
MeO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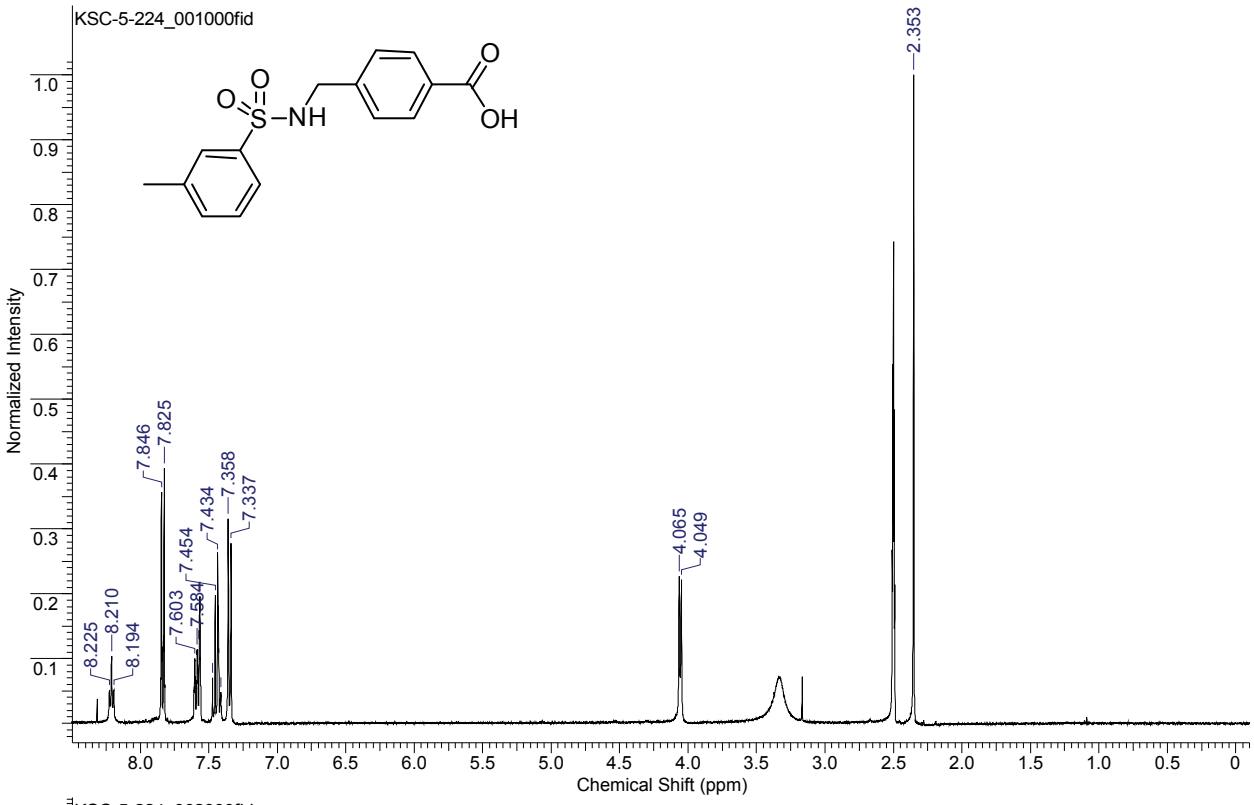
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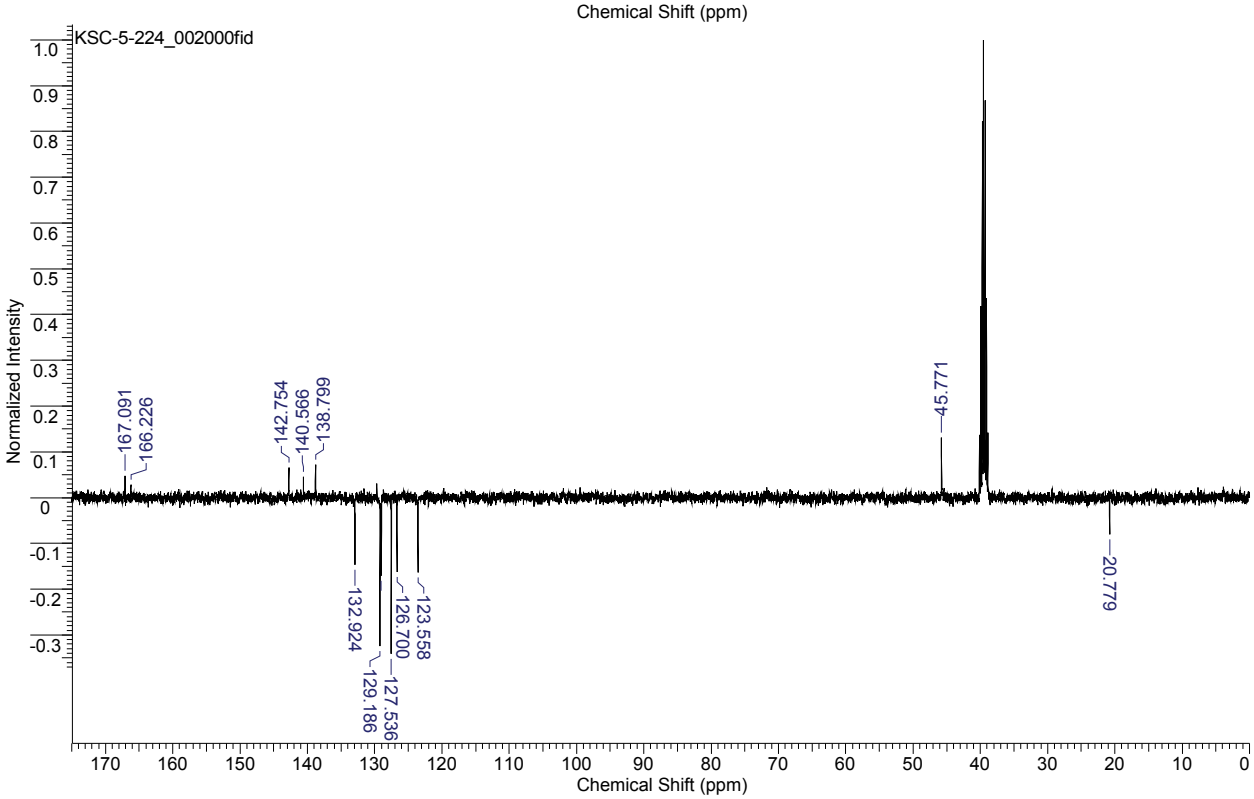
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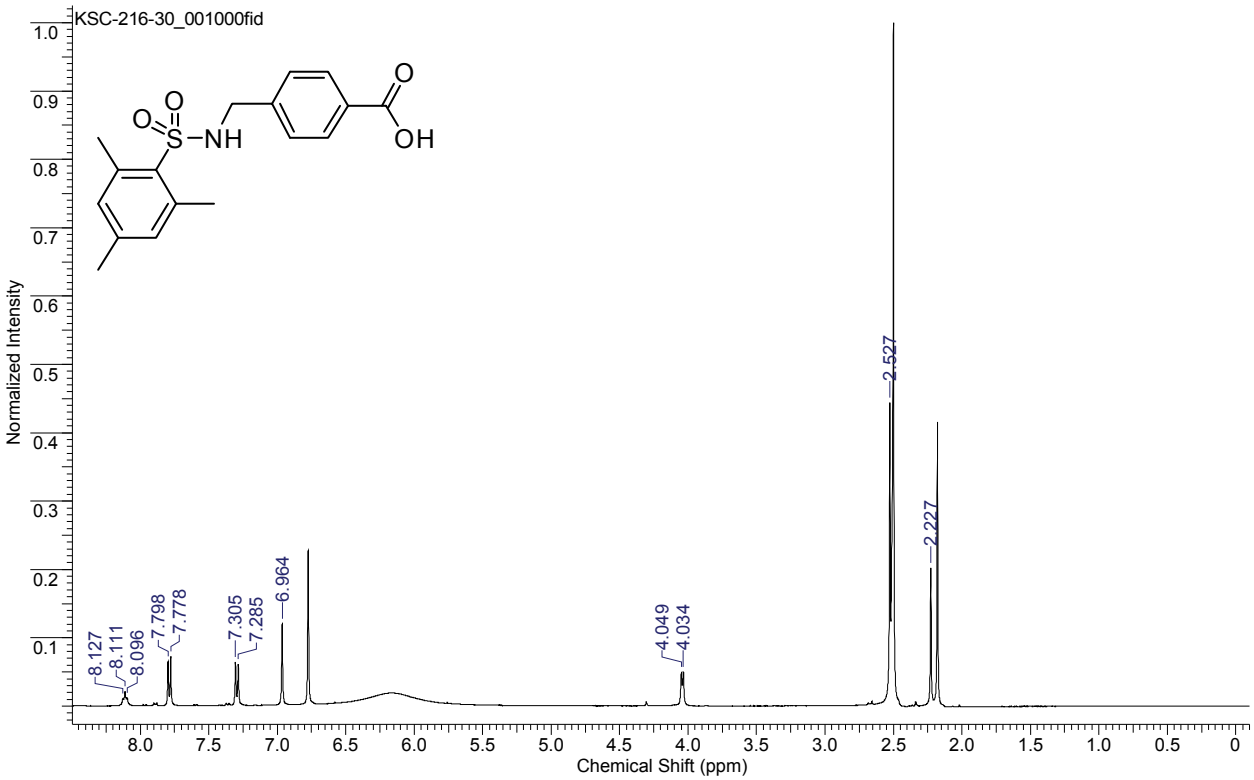
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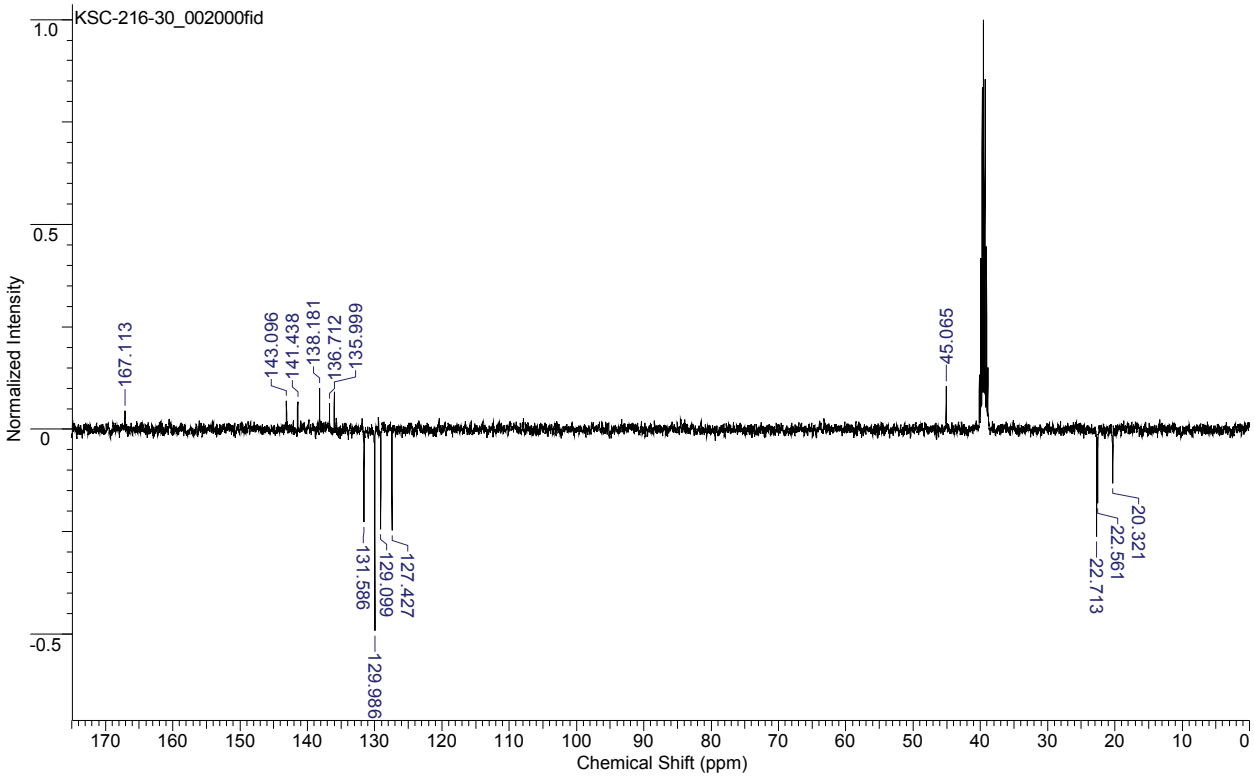
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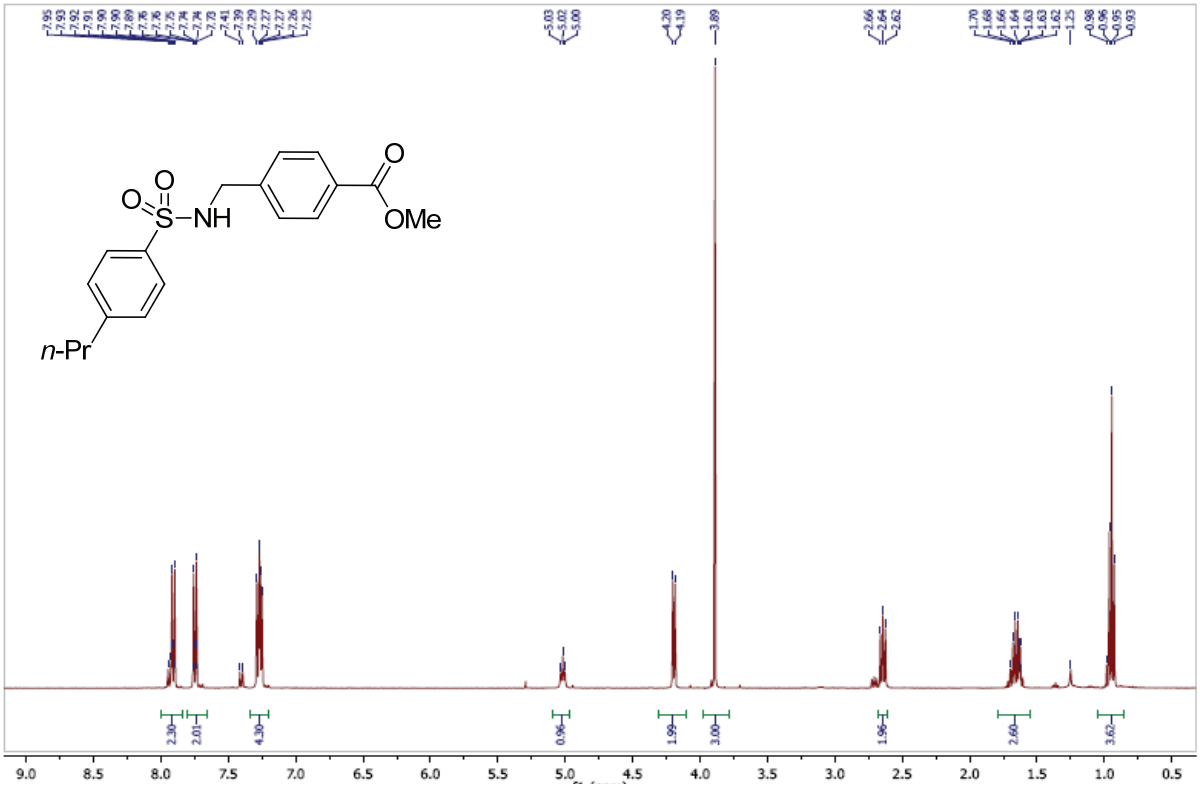
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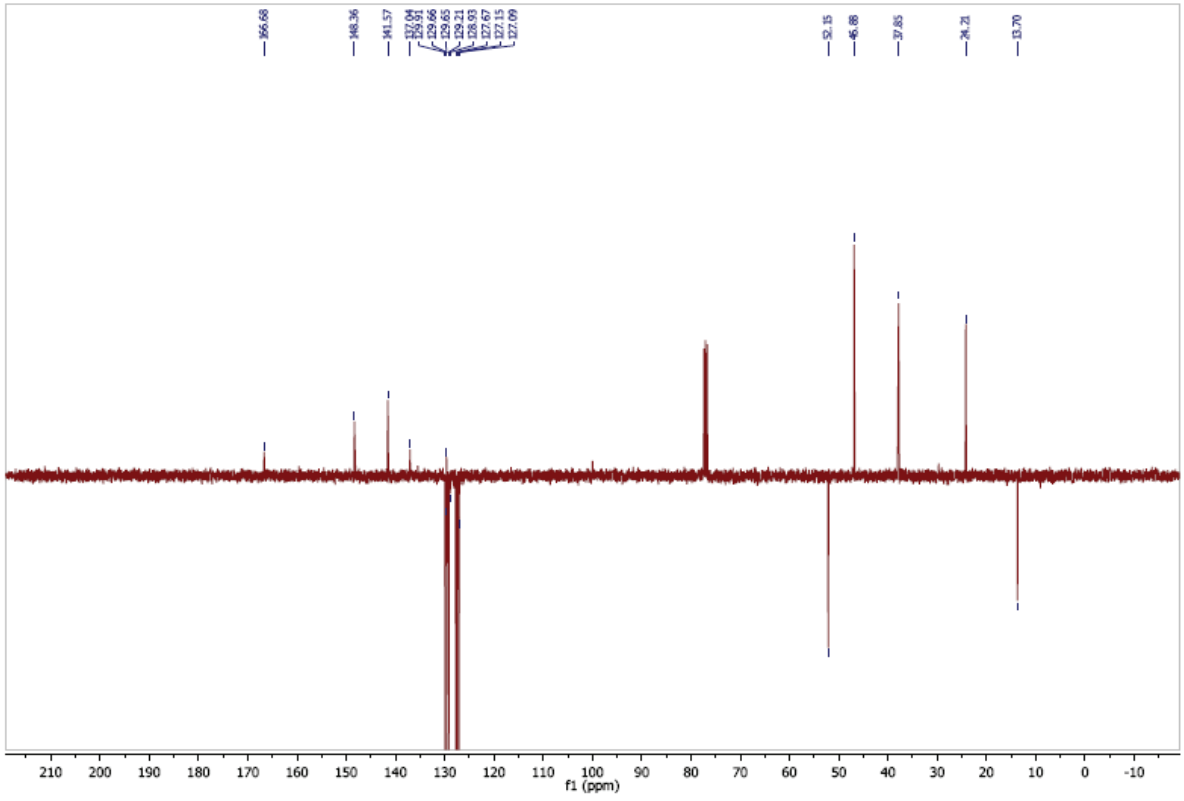
O
OMe
n-Pr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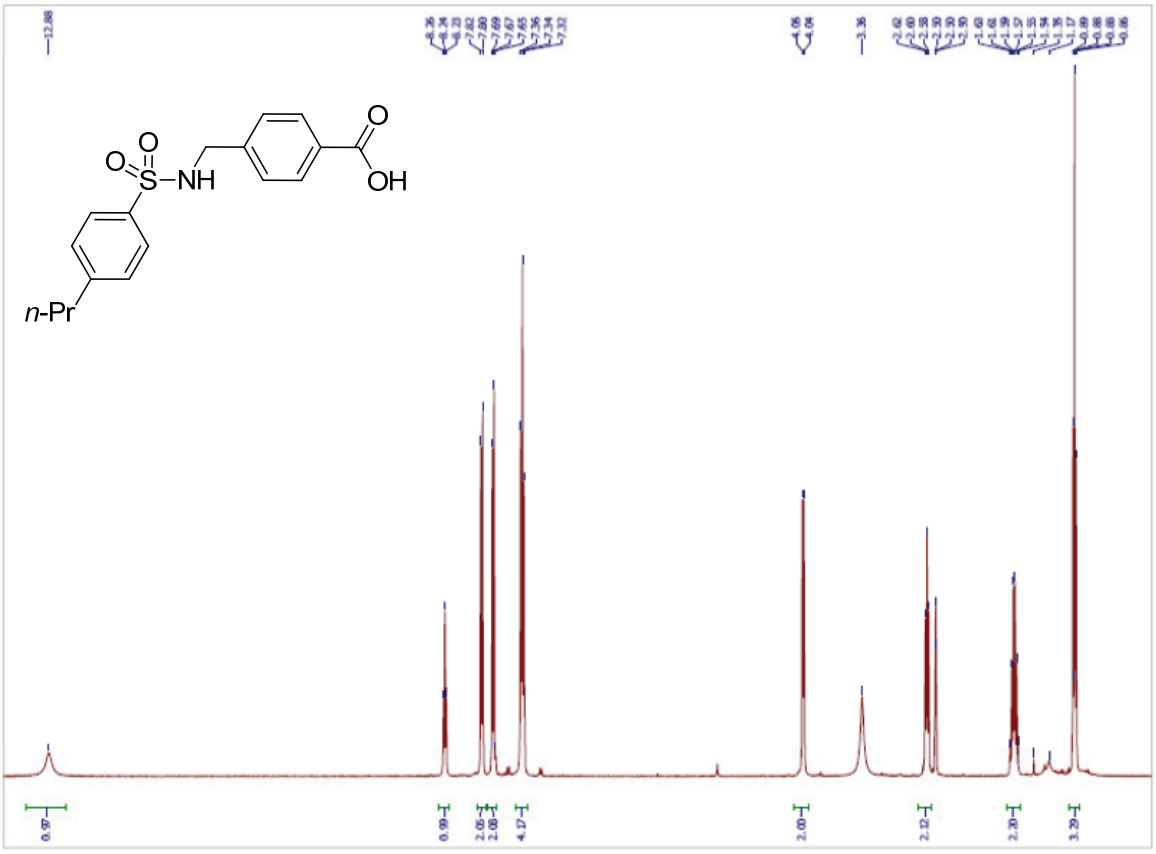
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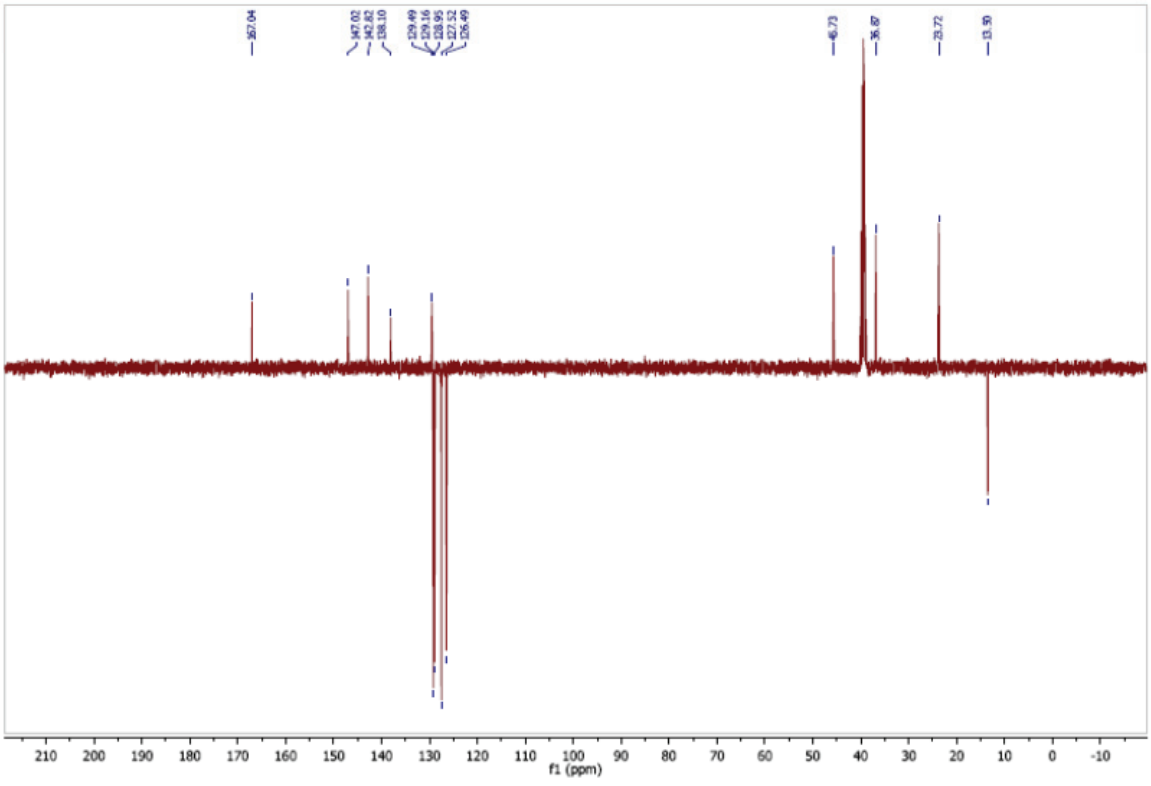
n-Pr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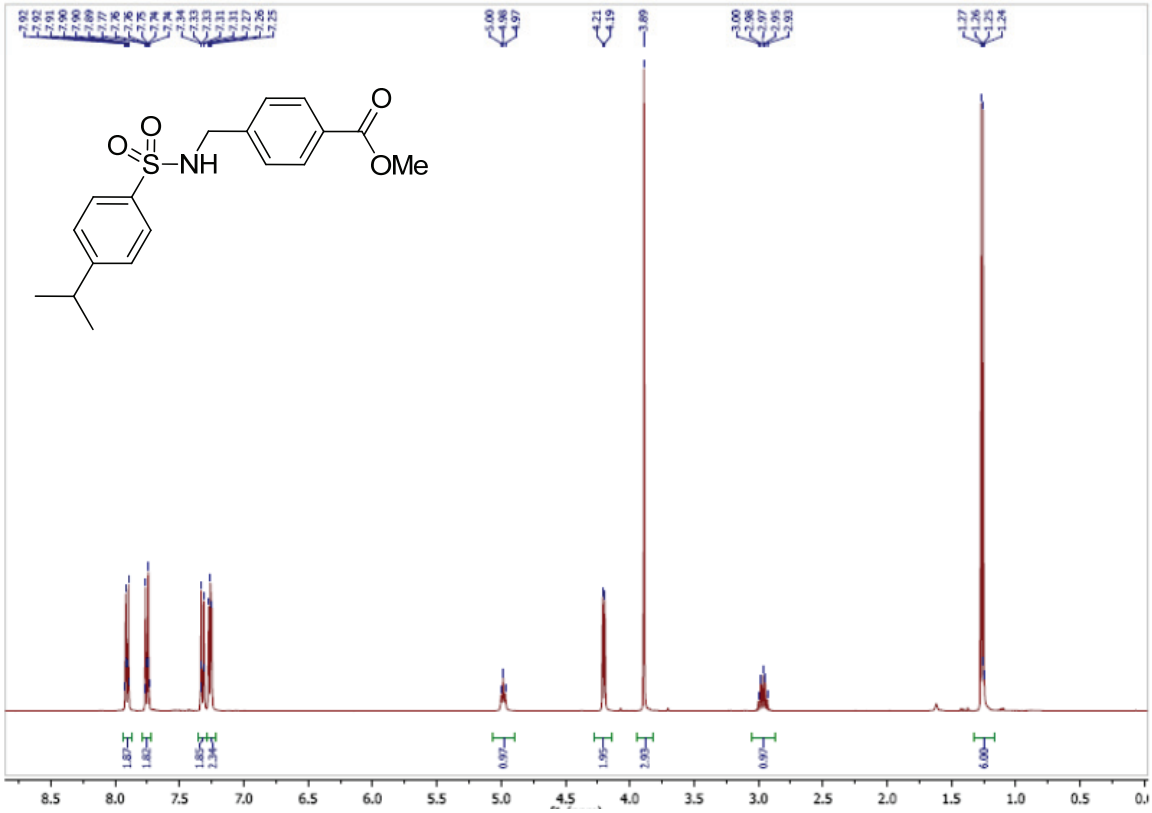
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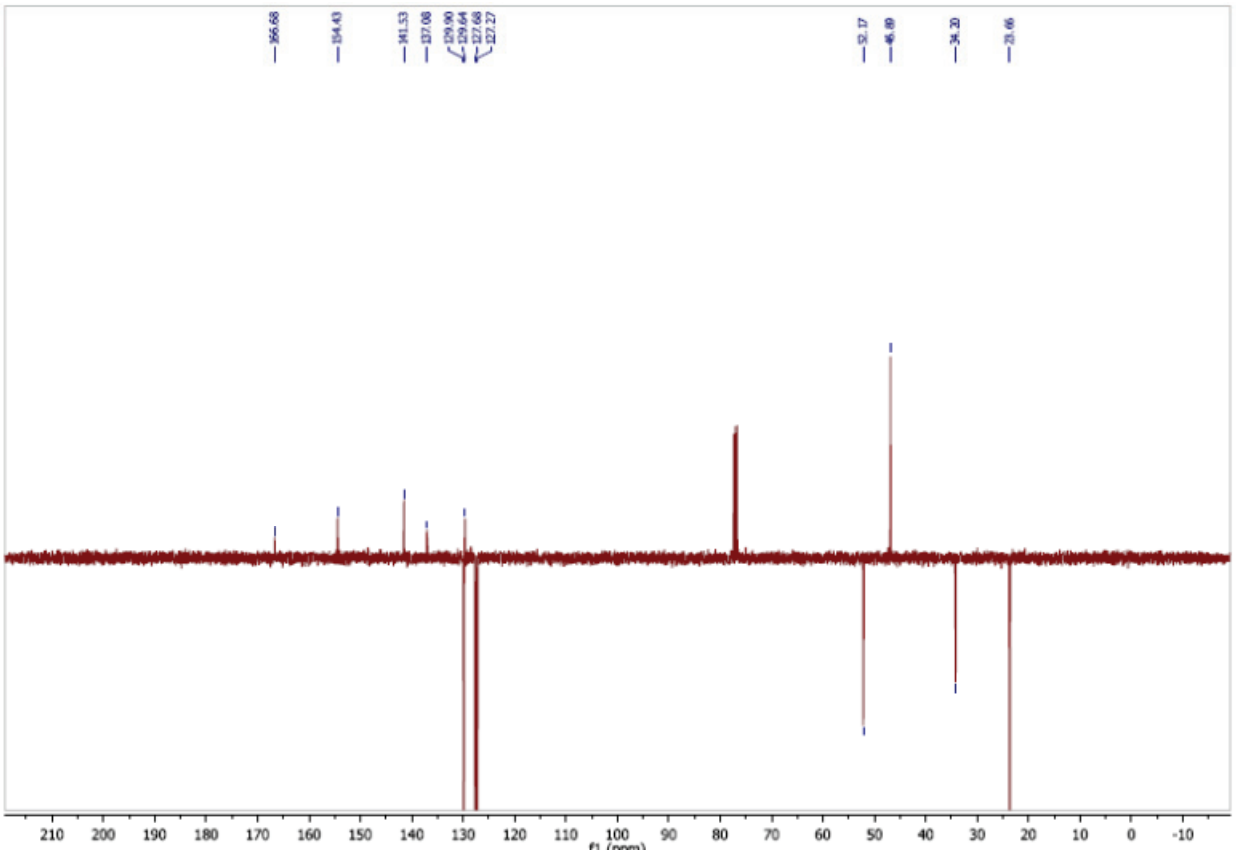
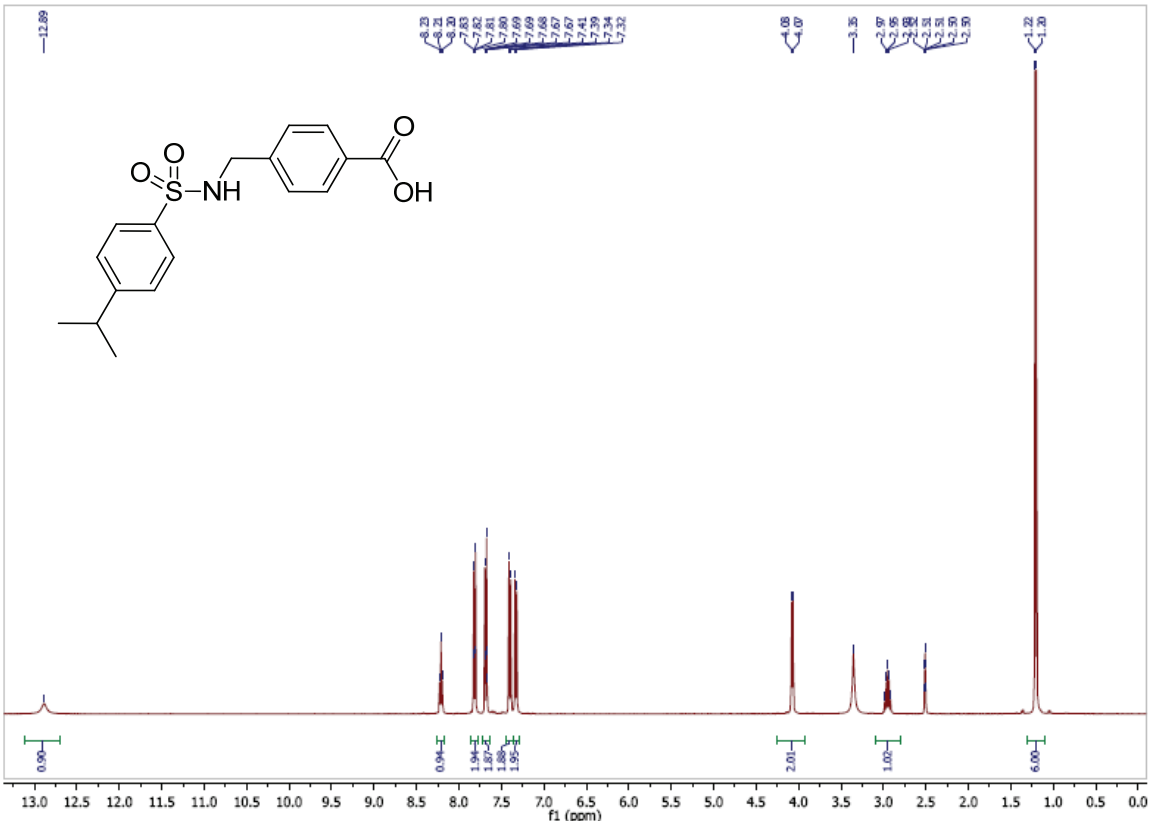
O
OMe

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4.07
3.35
2.97
2.95
2.51
2.50
1.22
1.20
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O
S
NH
O
OH
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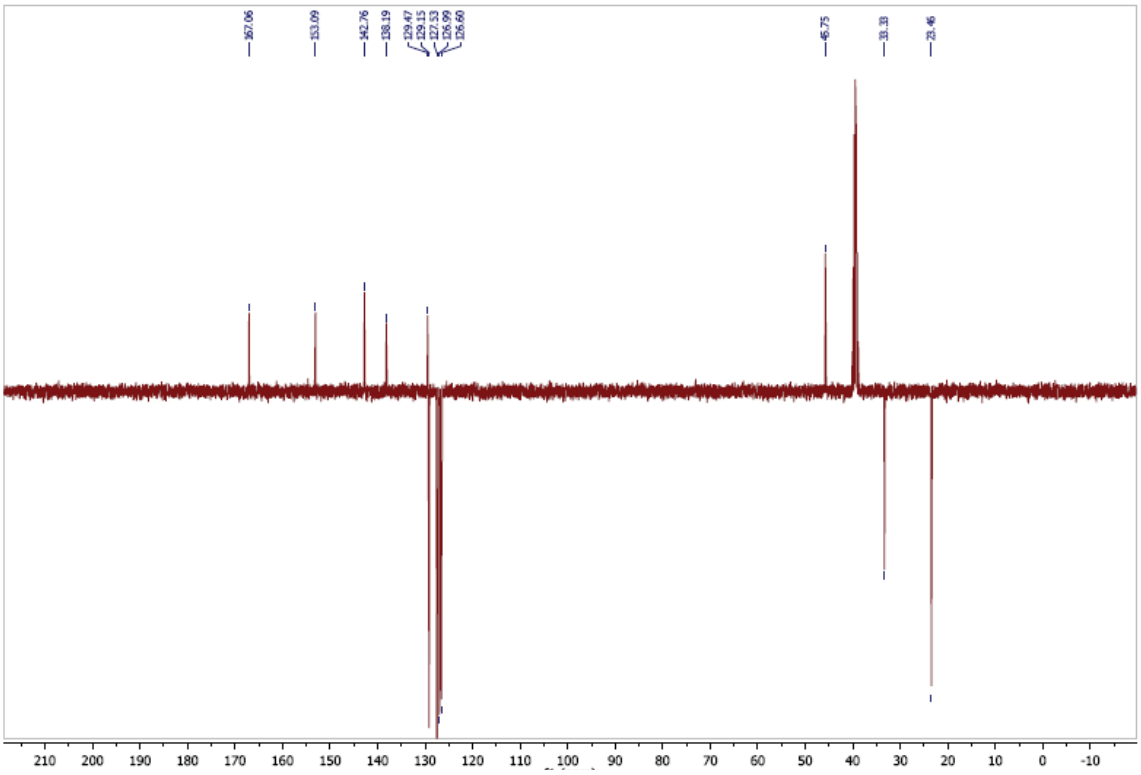
0.94
1.94
1.87
1.88
1.95
2.01
1.02
6.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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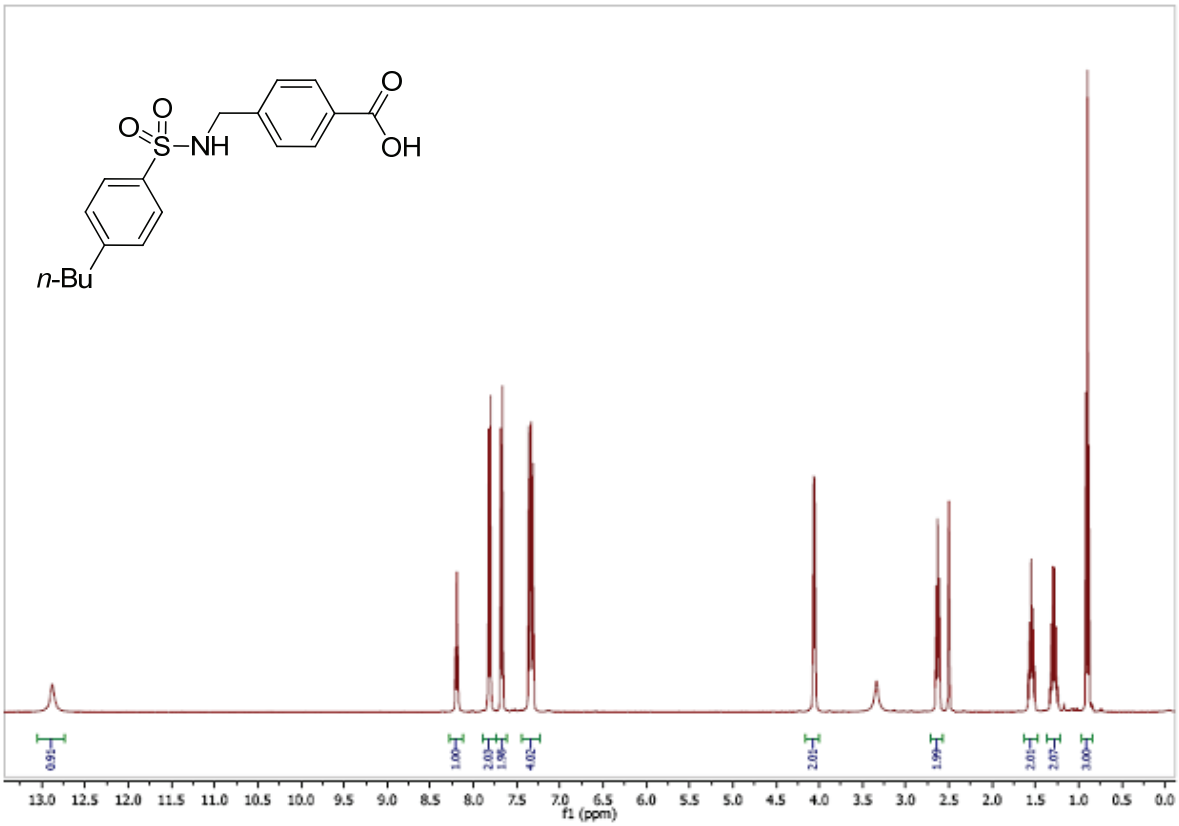
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OH
n-Bu
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1.98
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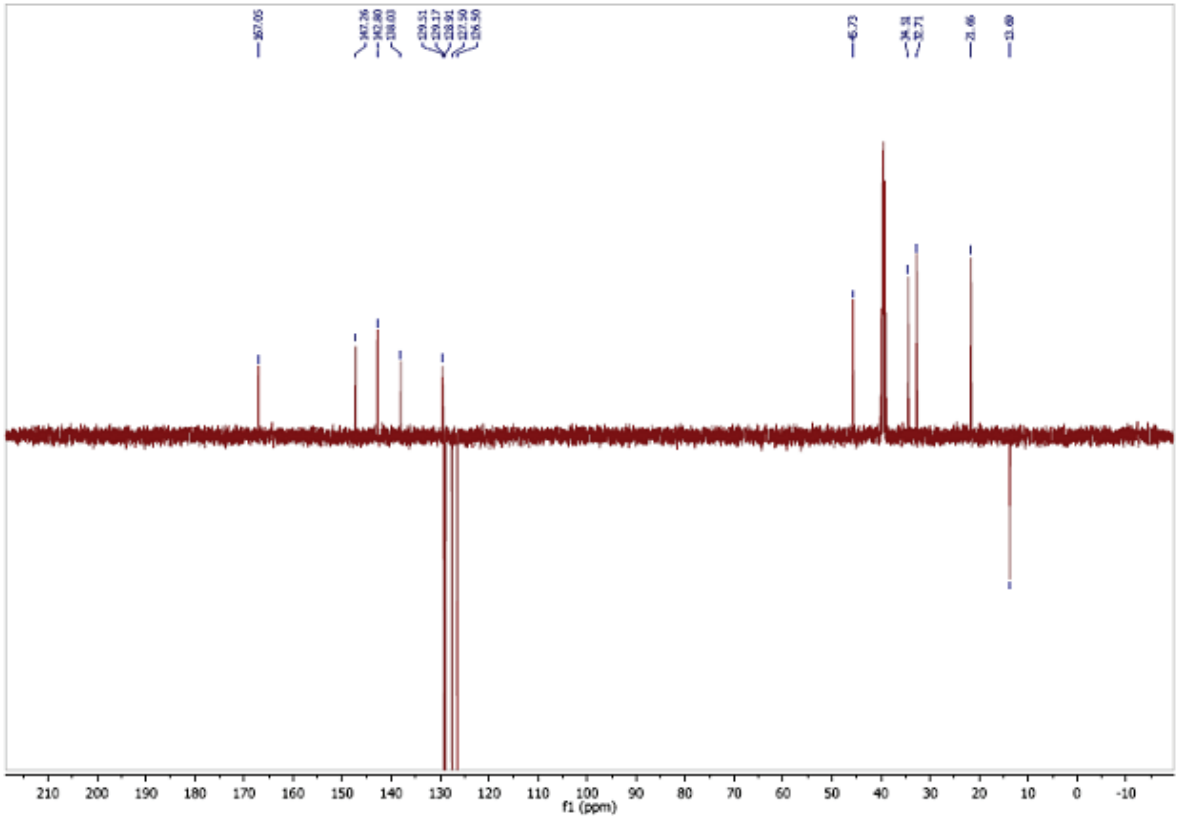
2.01
1.99
2.01
2.07
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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128.91
127.50
126.50
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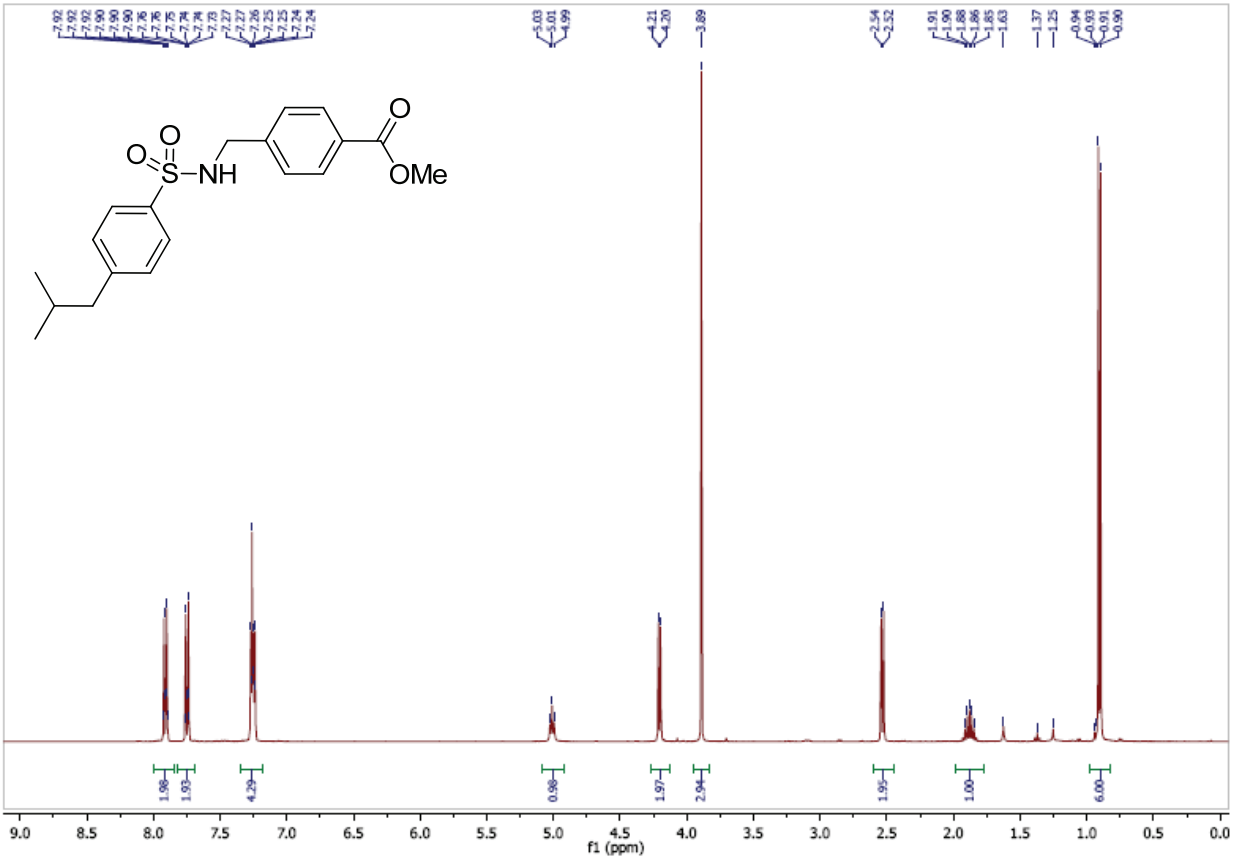
30.71
21.46
13.69
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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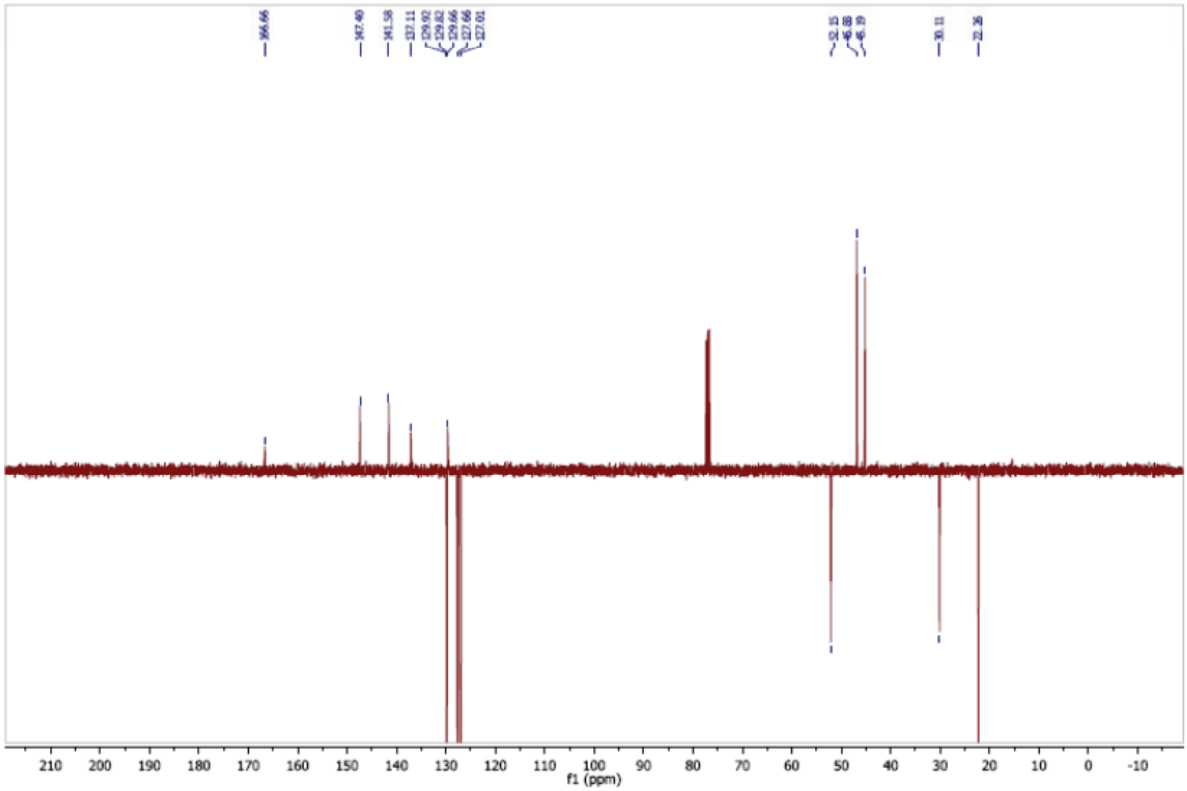
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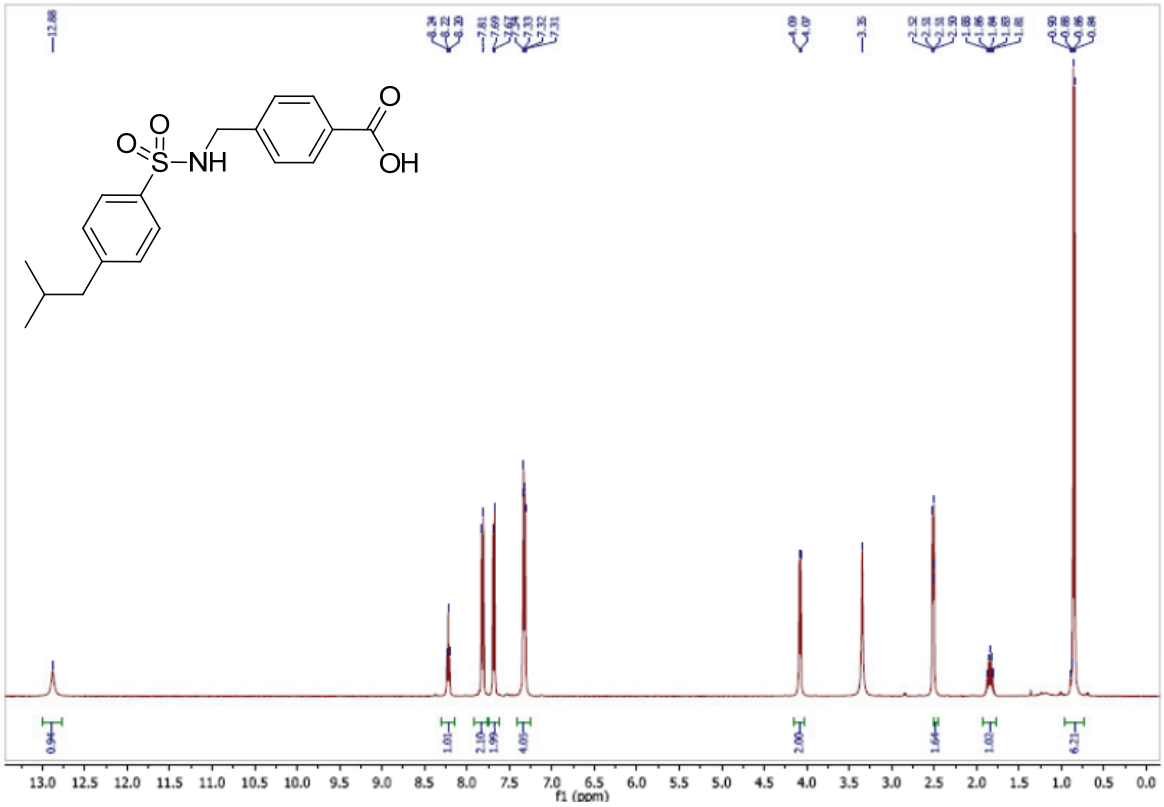
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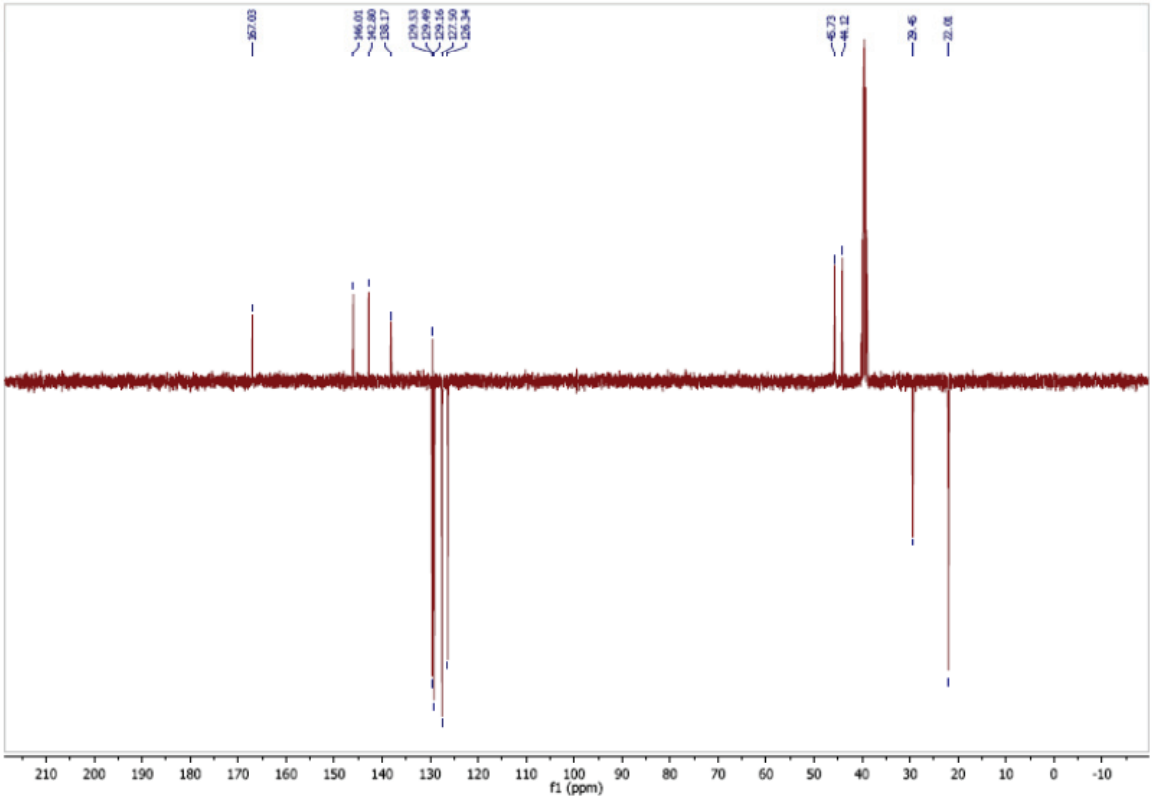
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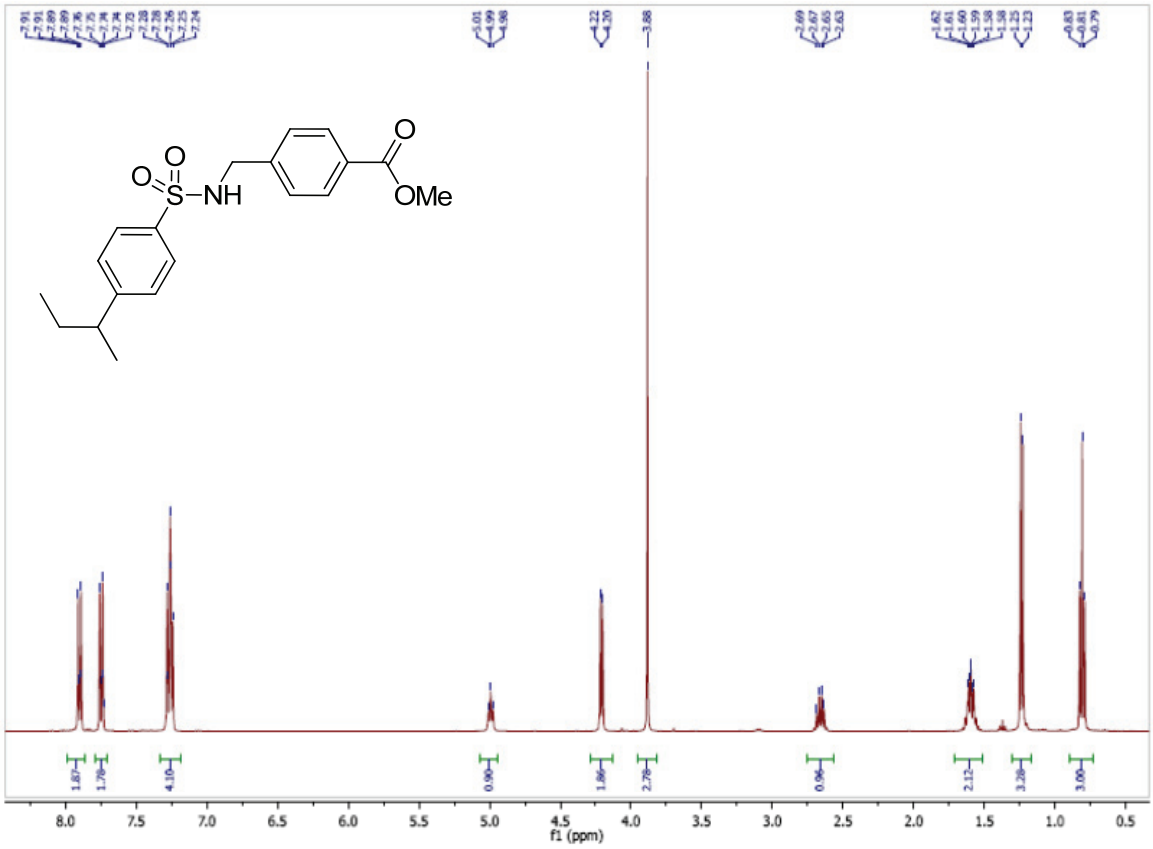
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S
NH
O
OMe
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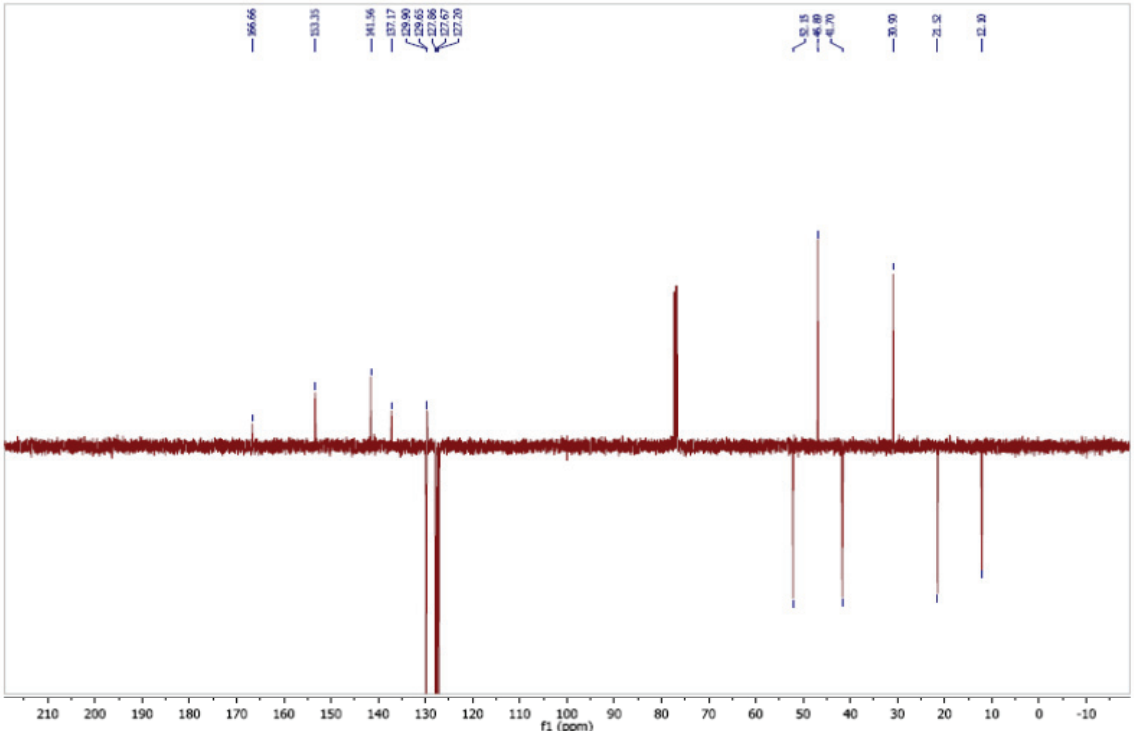
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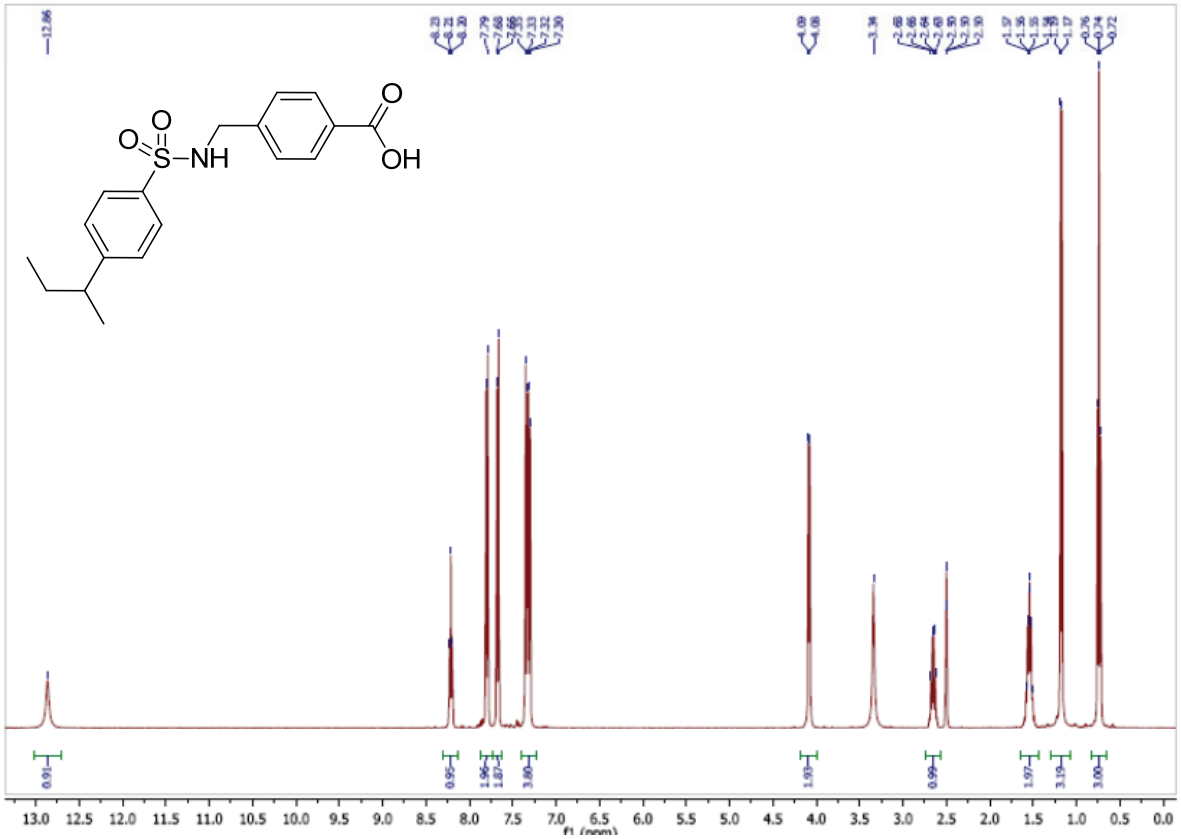
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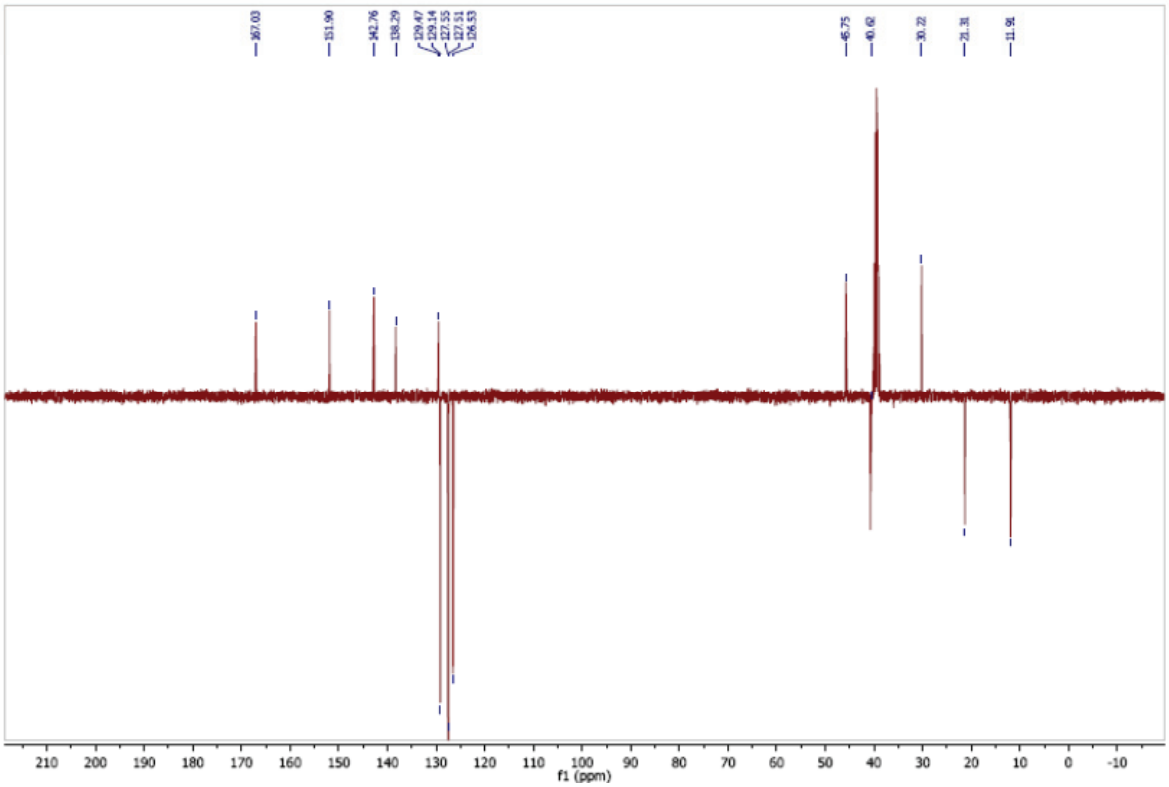
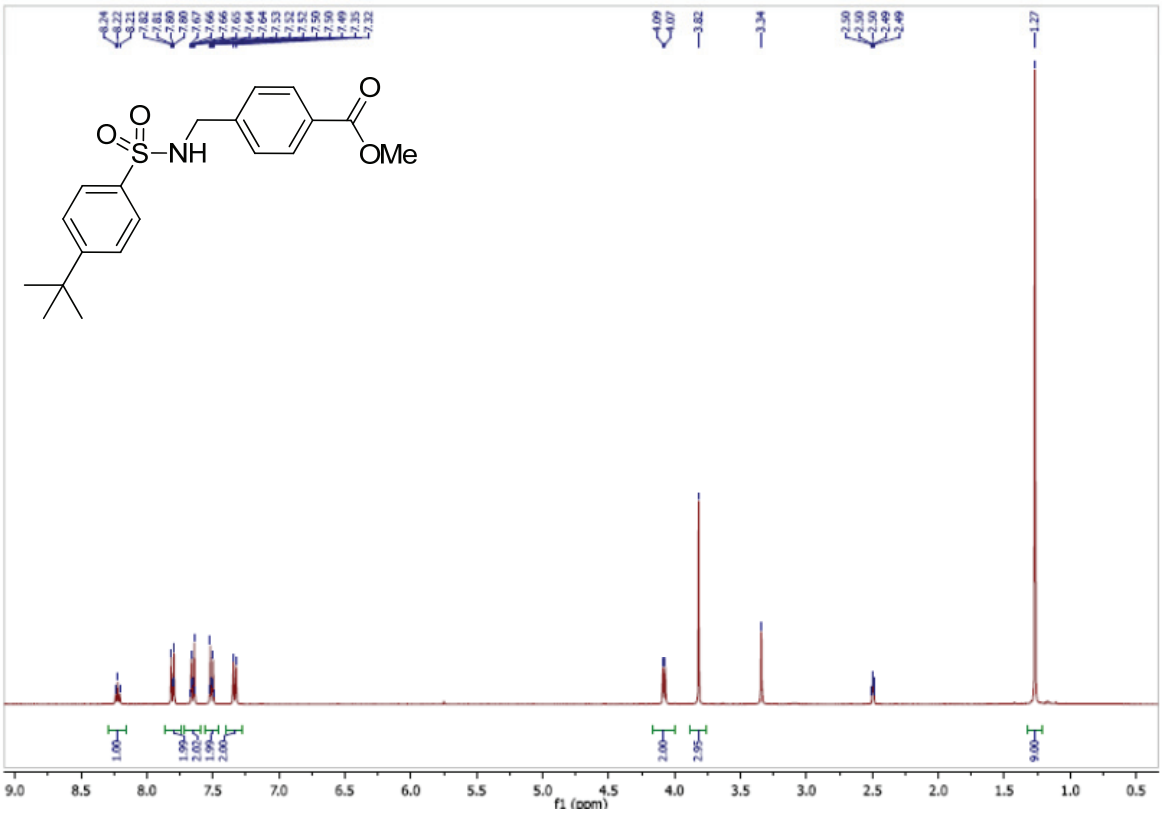
S
NH
O
OH

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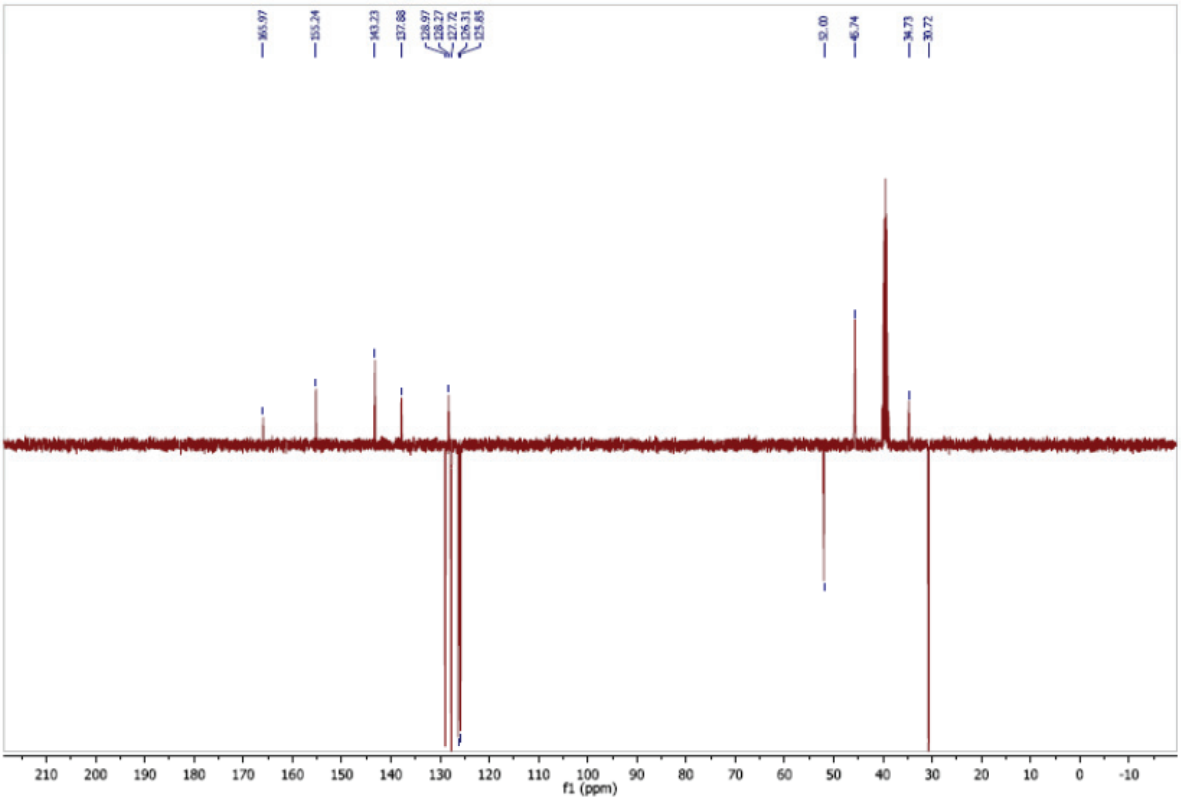
O
S
NH
O
OMe
f1 (ppm)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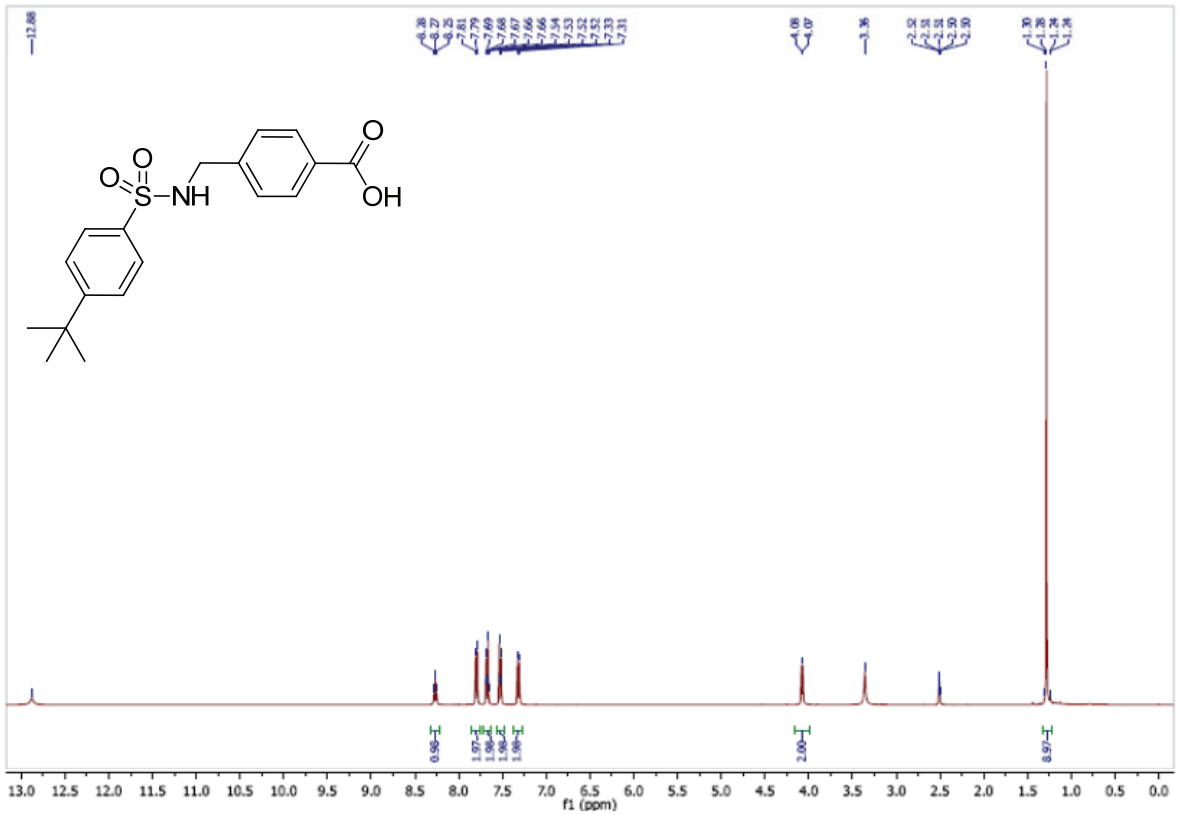
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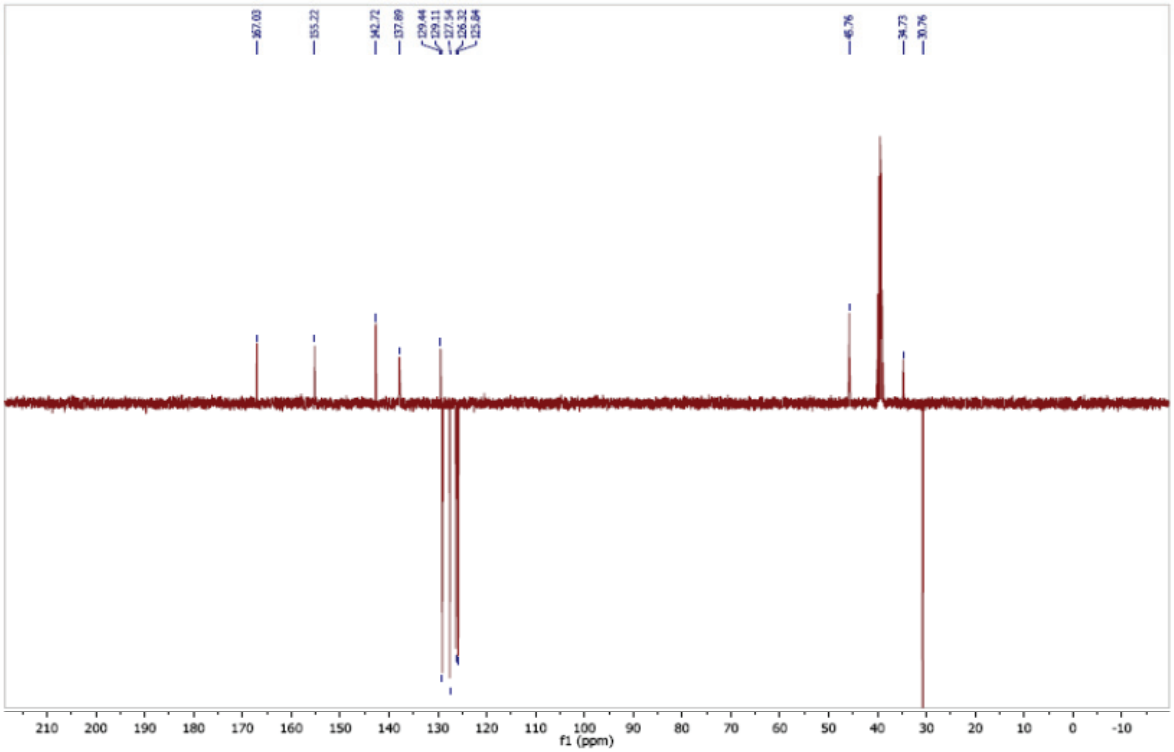
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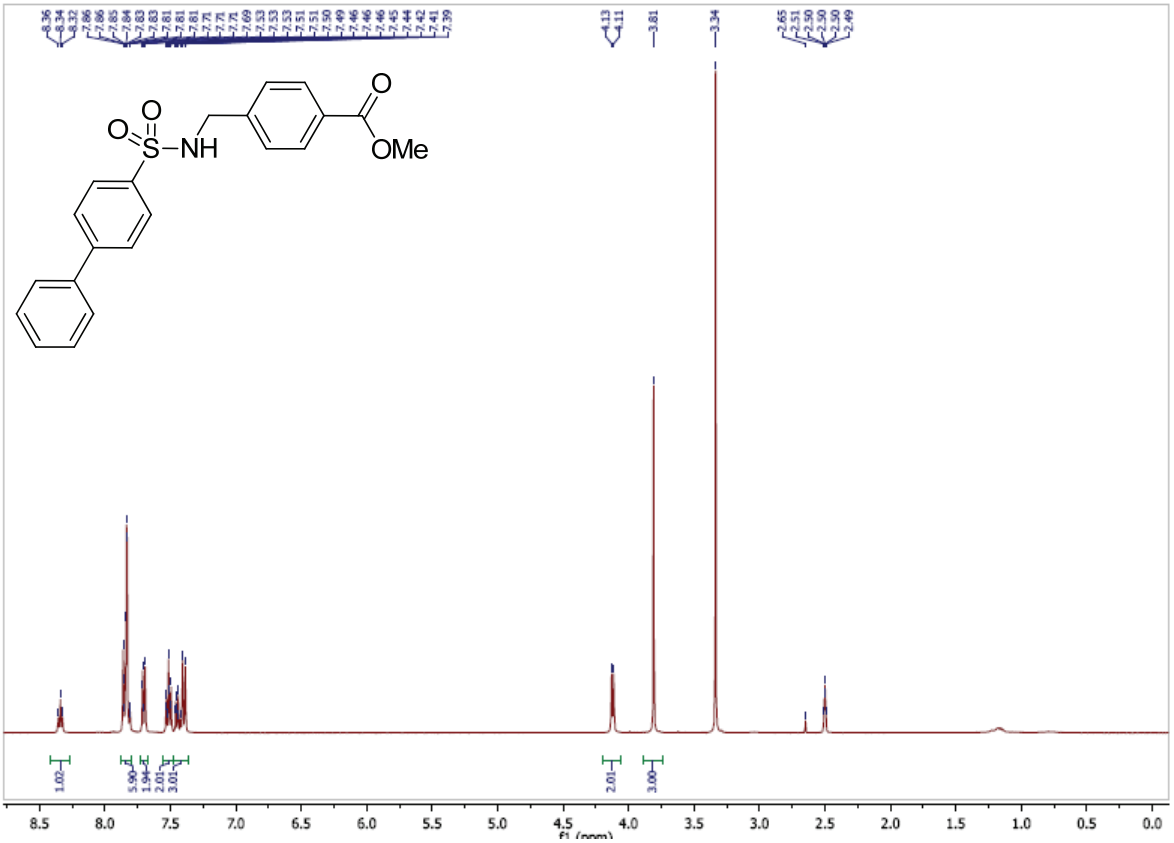
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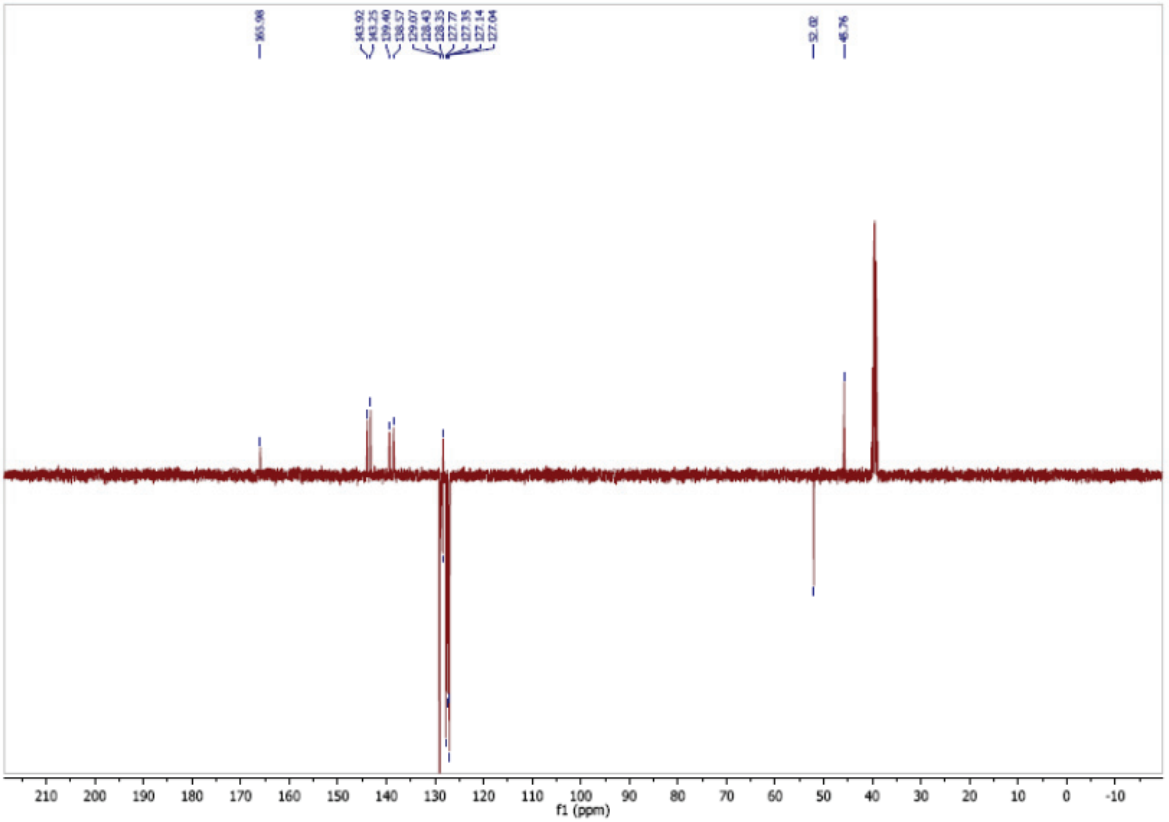

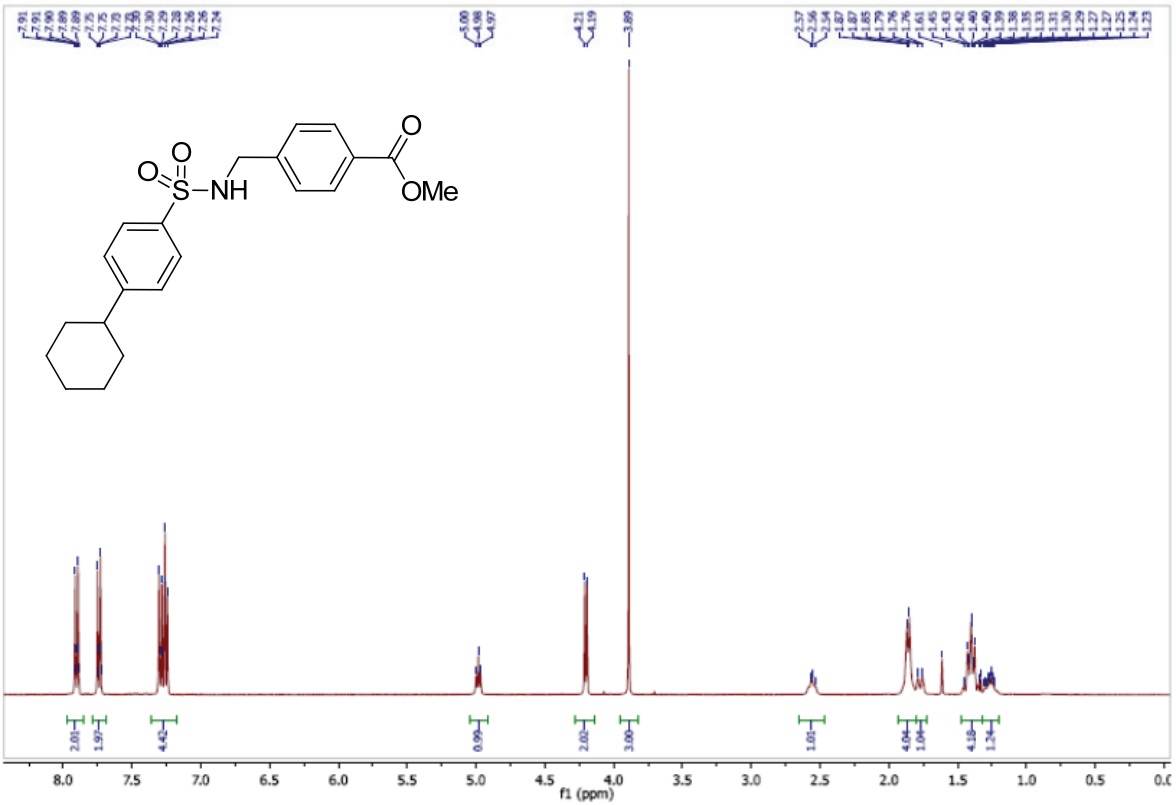
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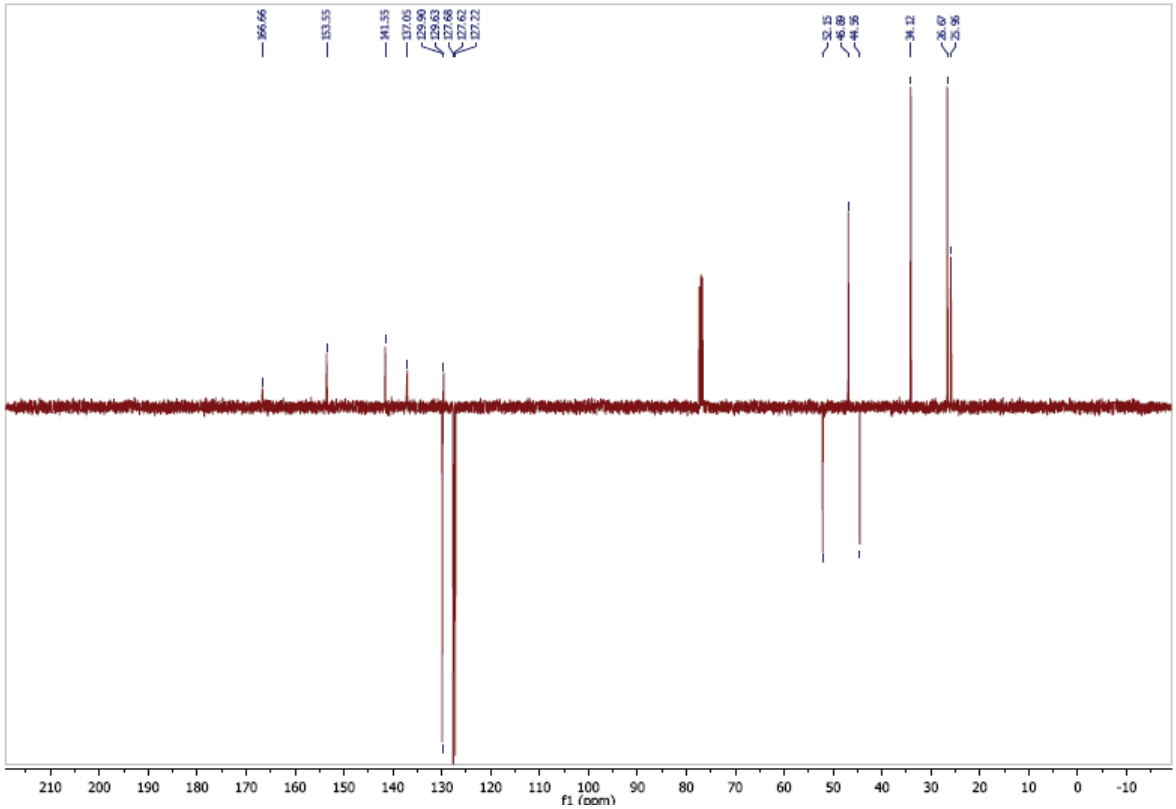
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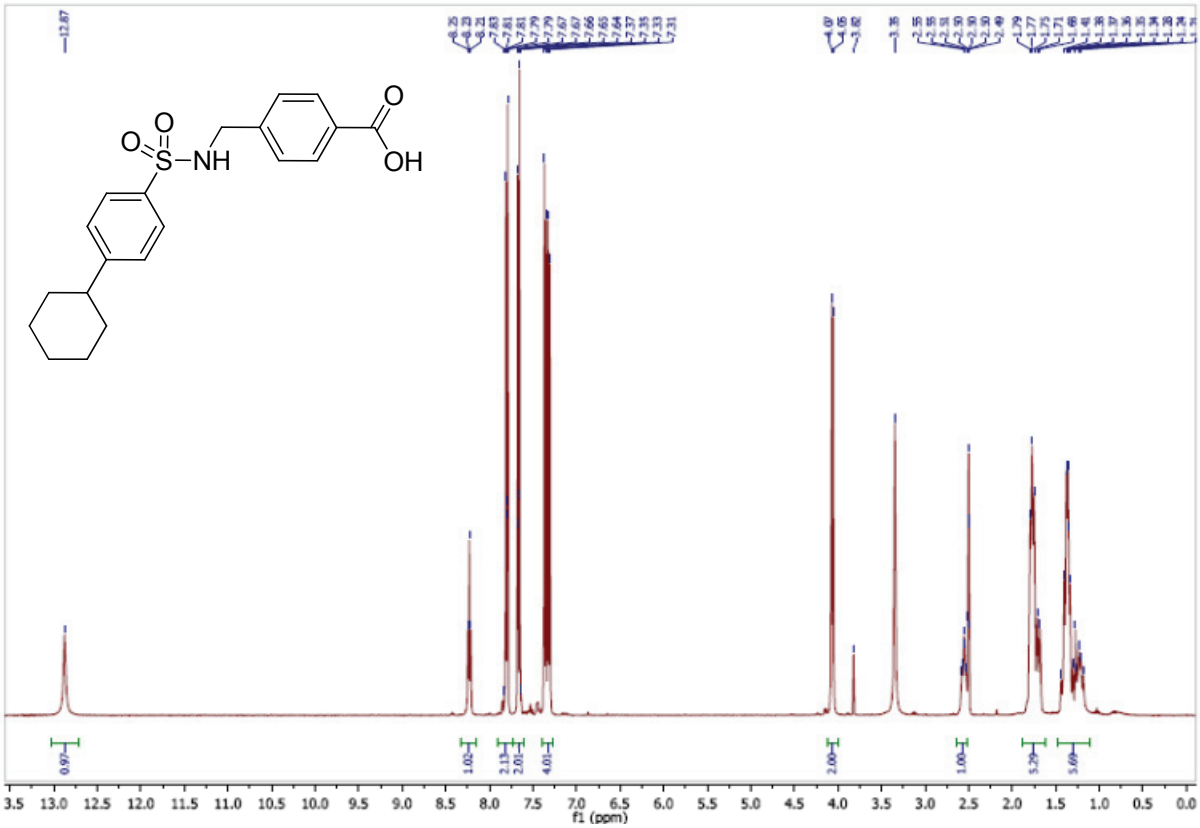
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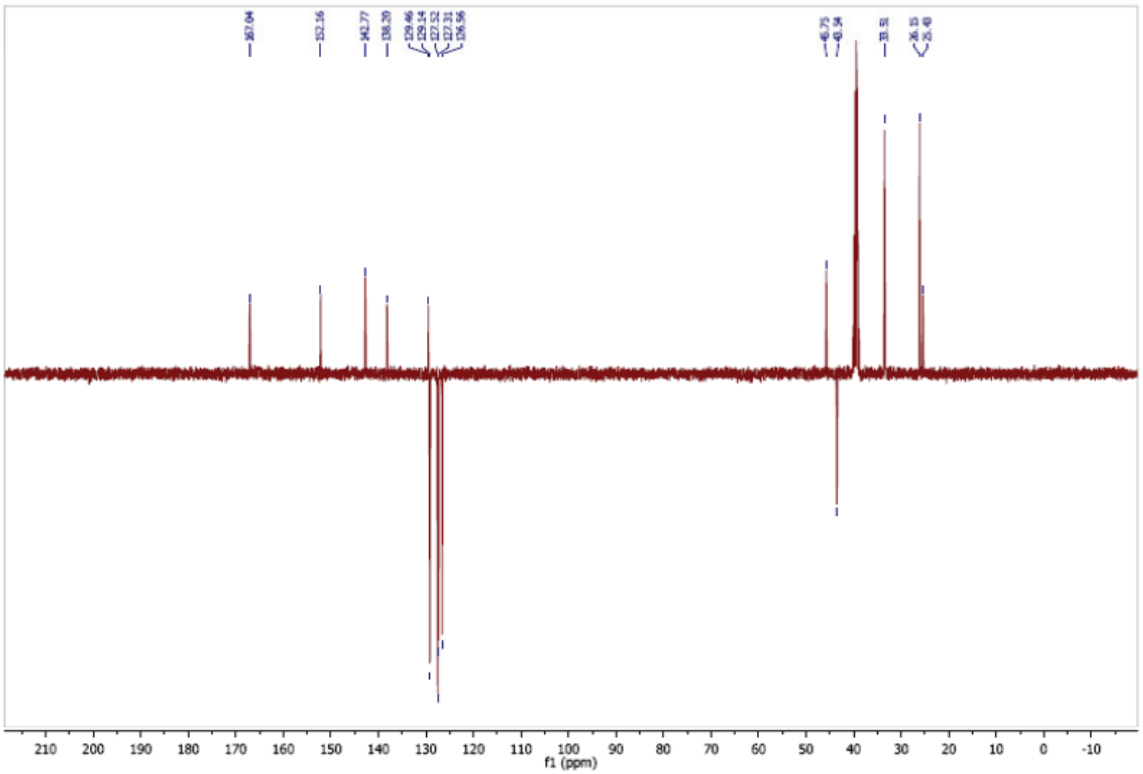
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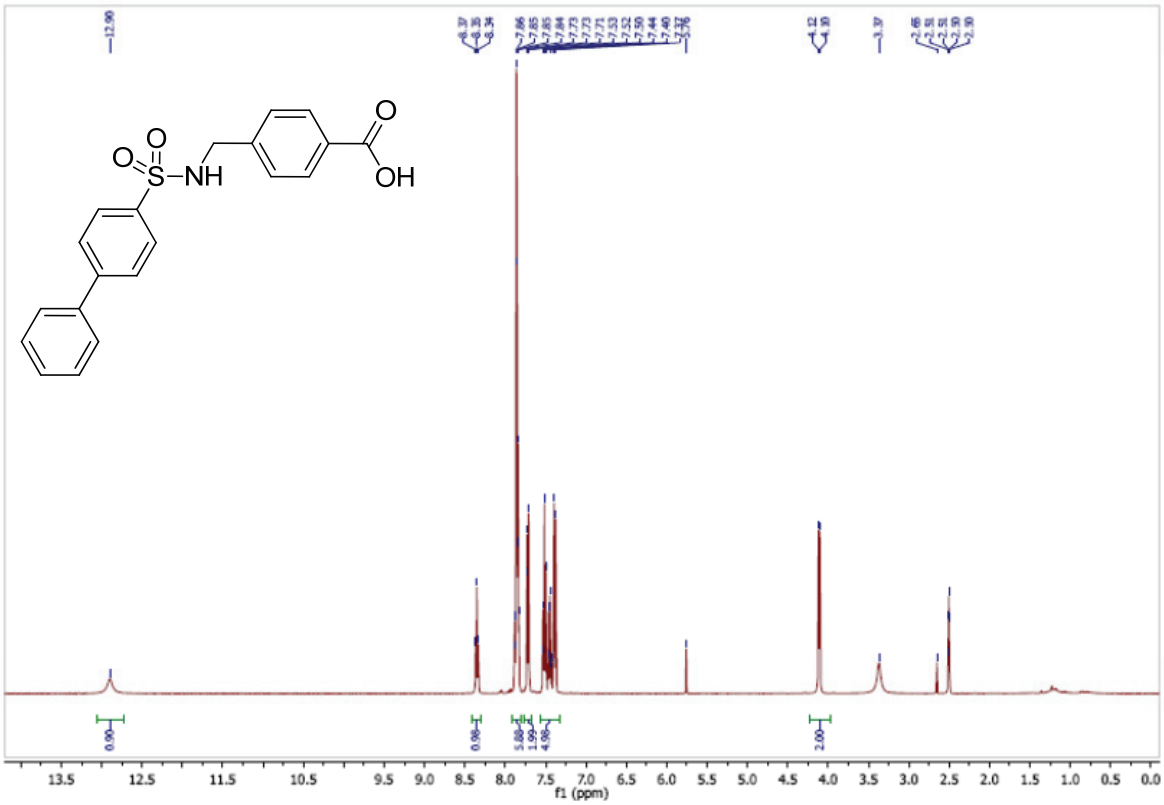
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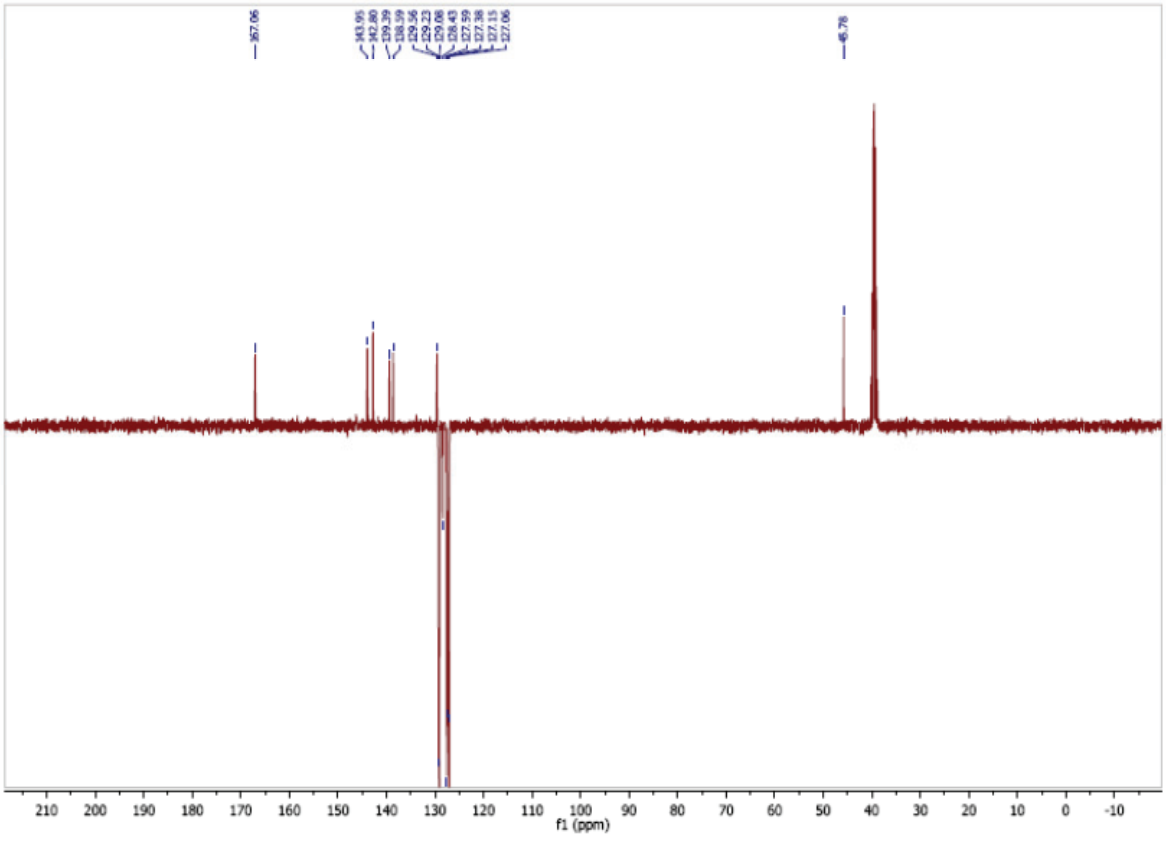
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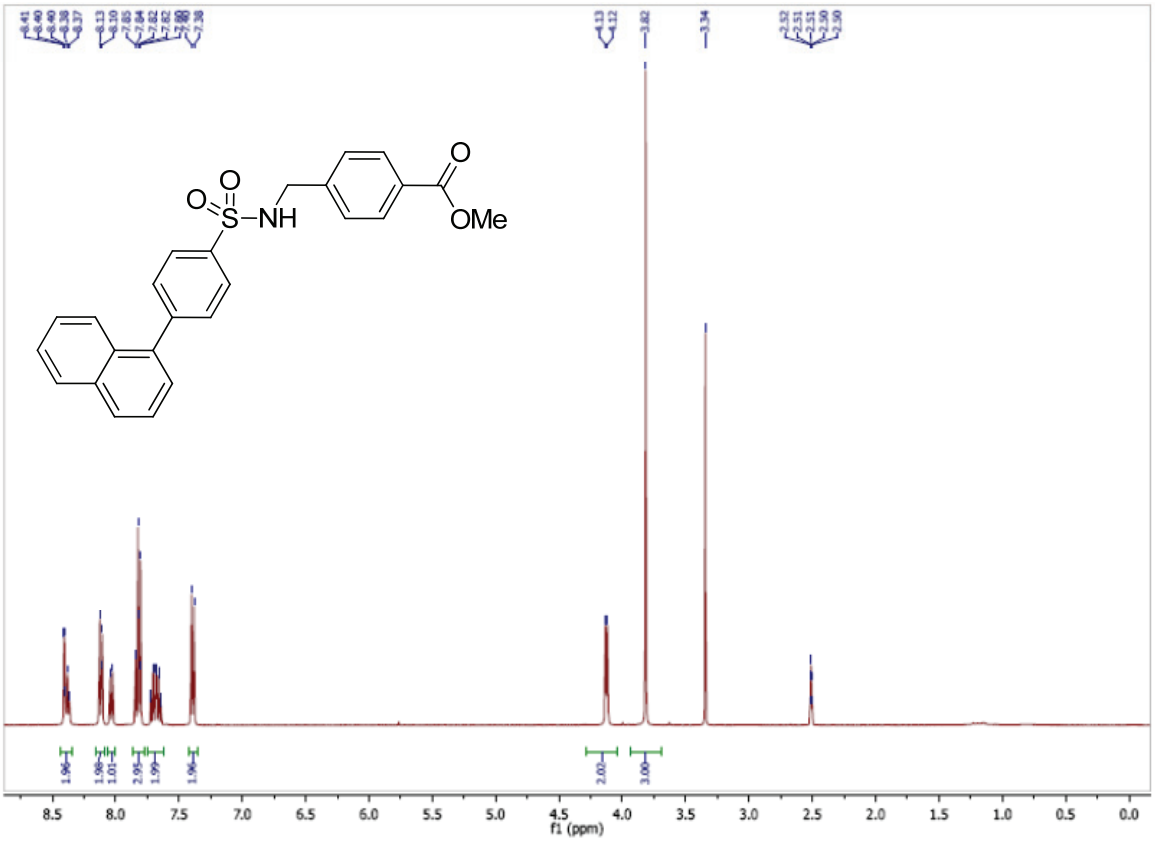
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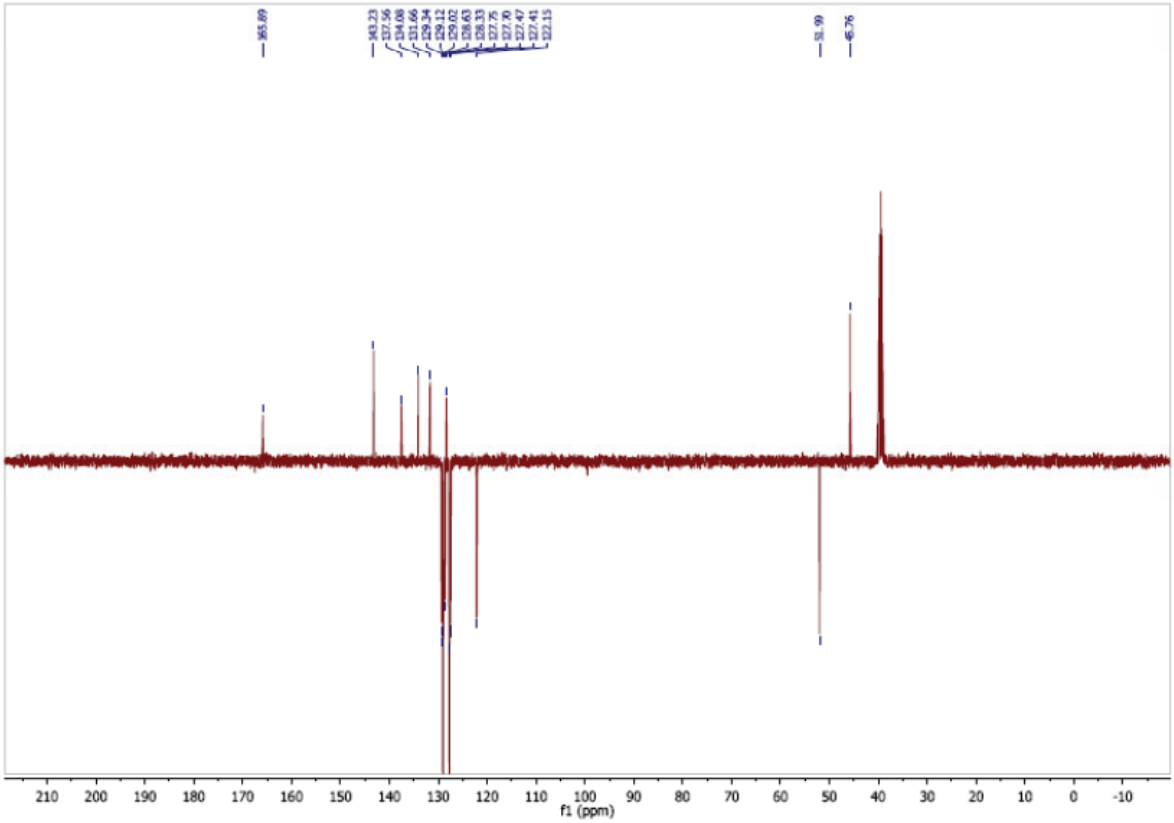
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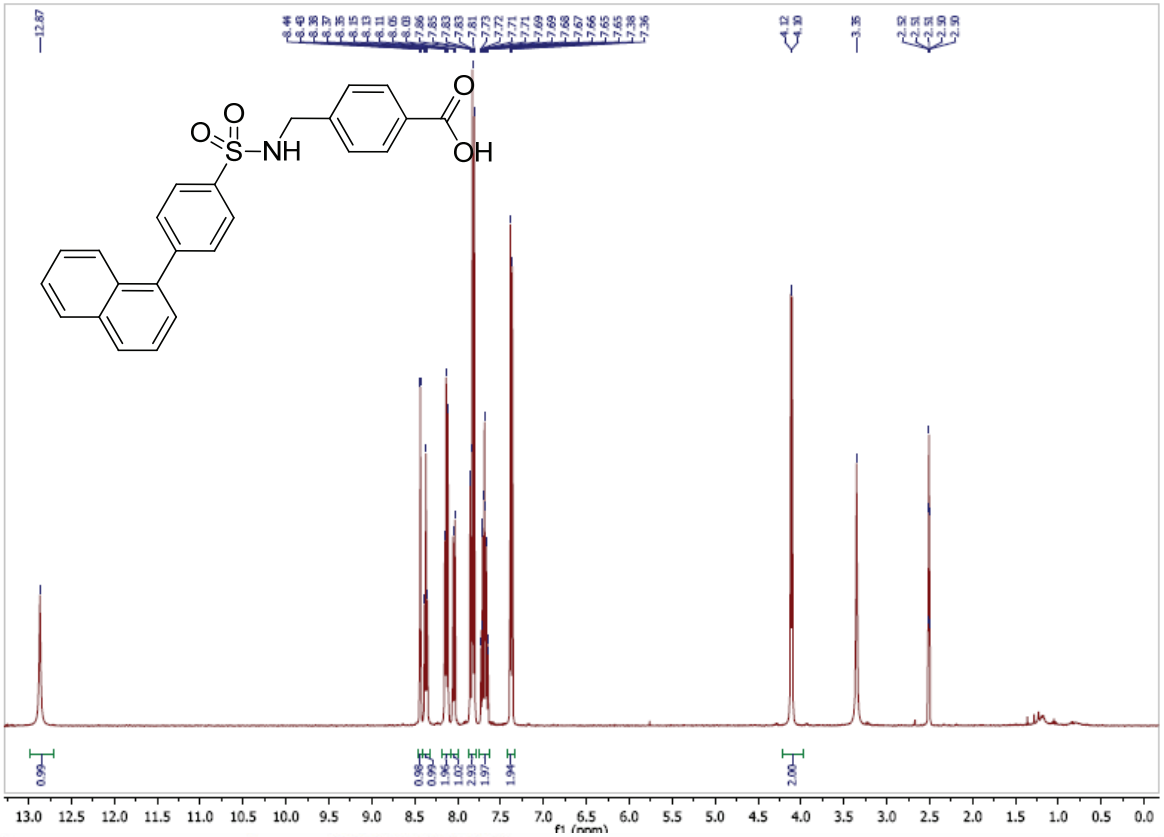
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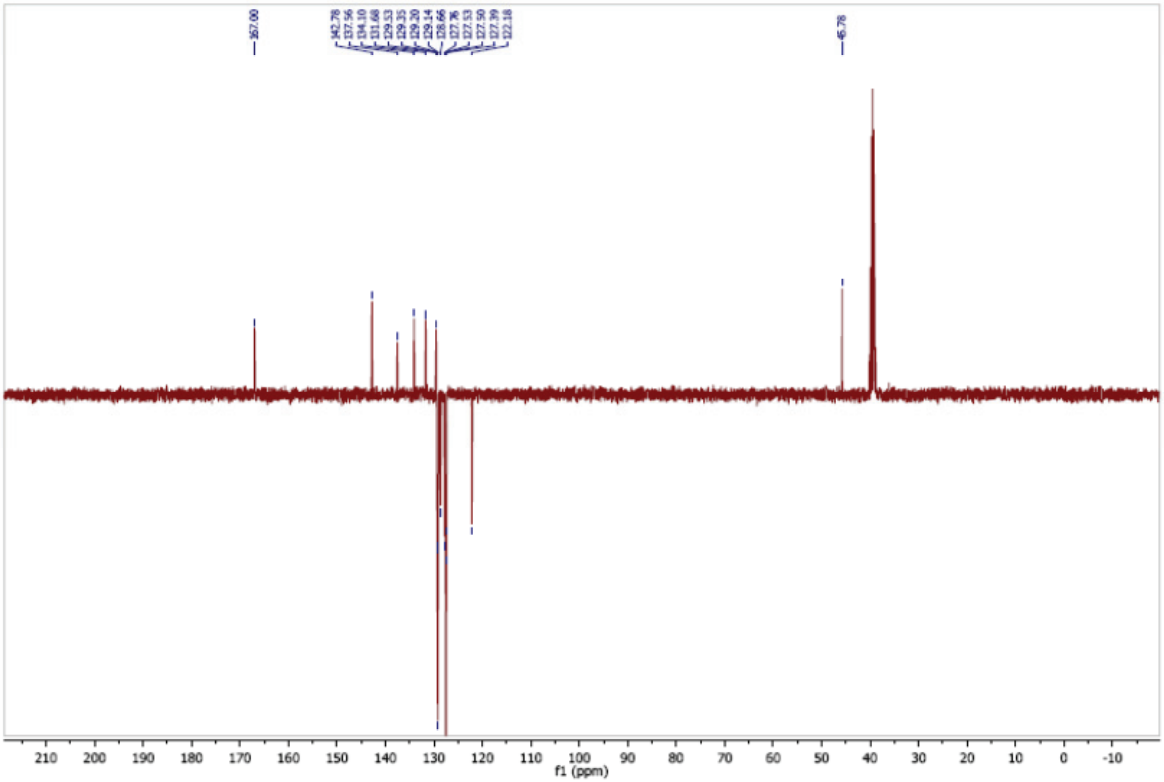
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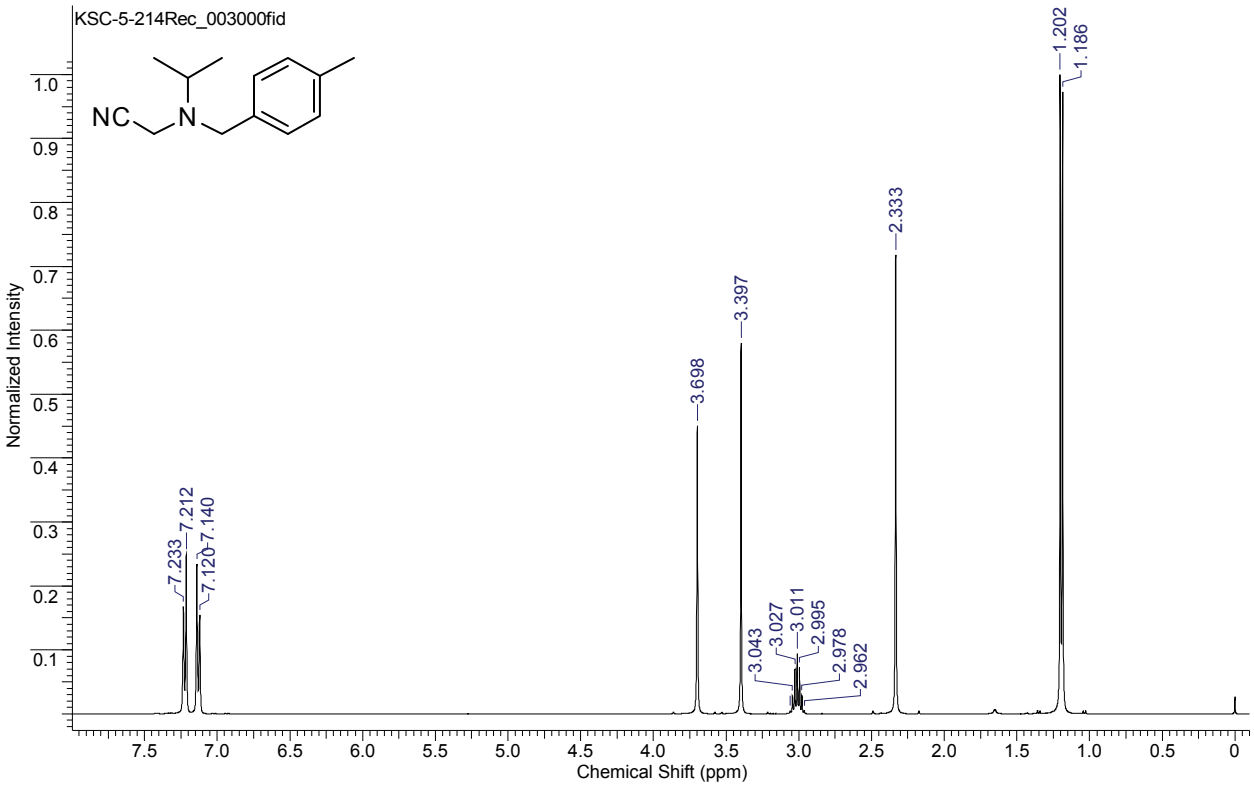
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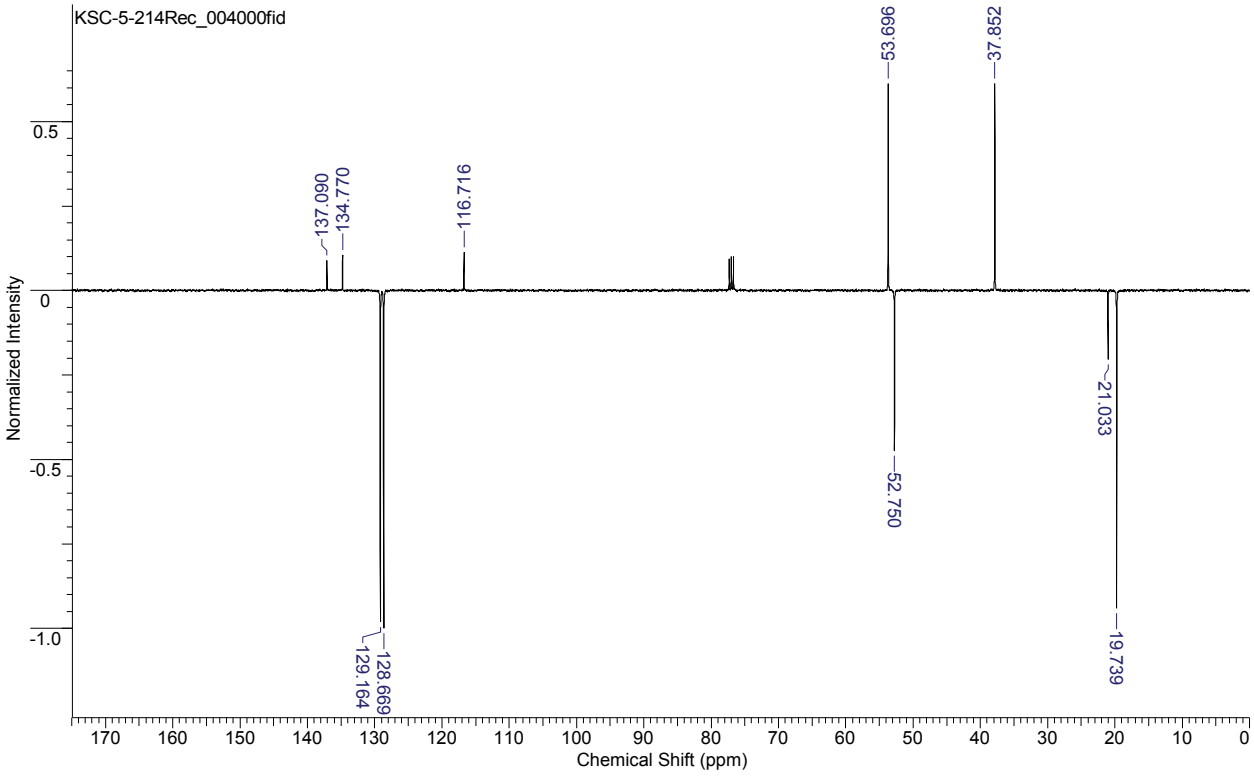
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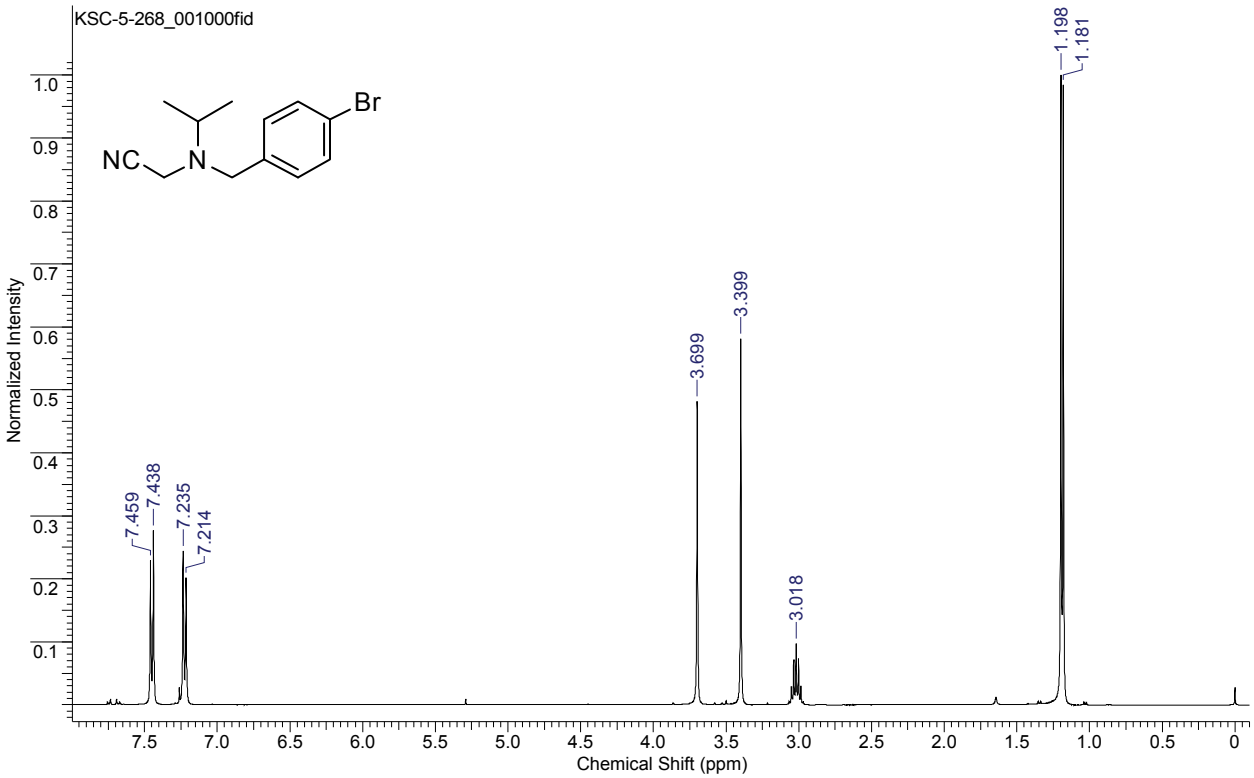
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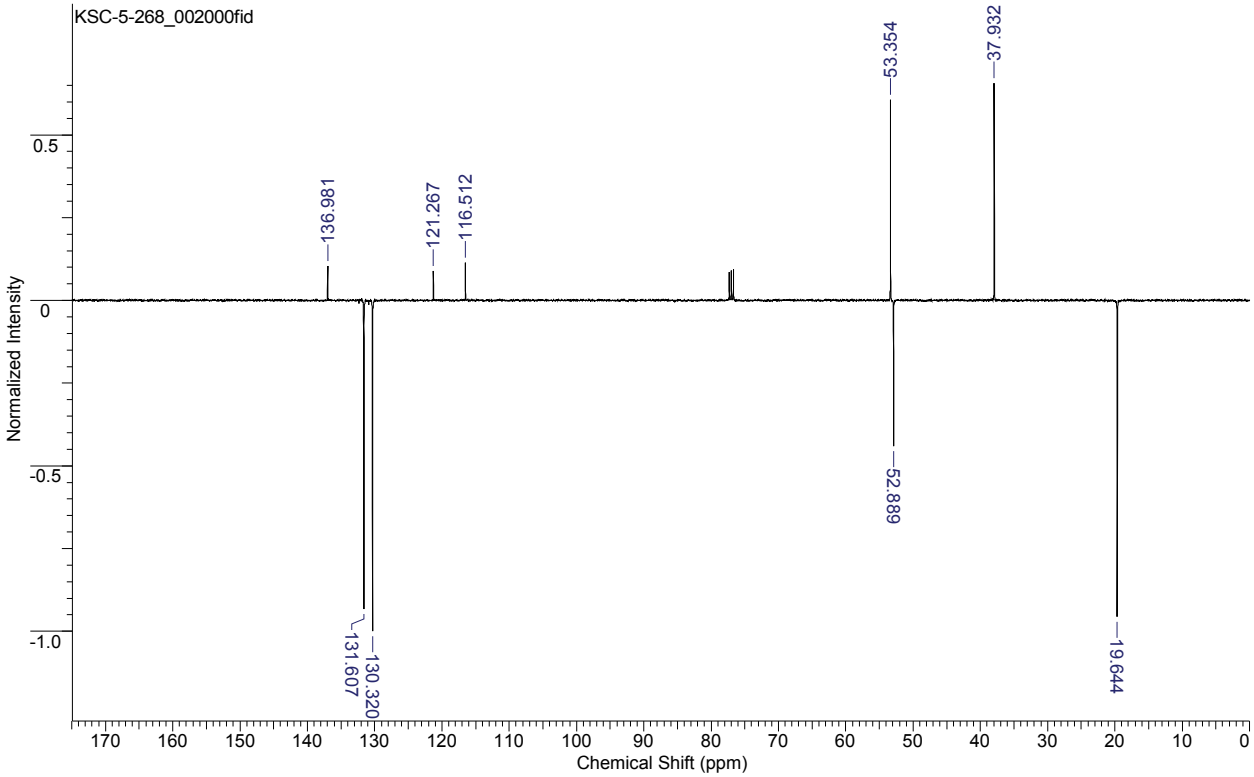
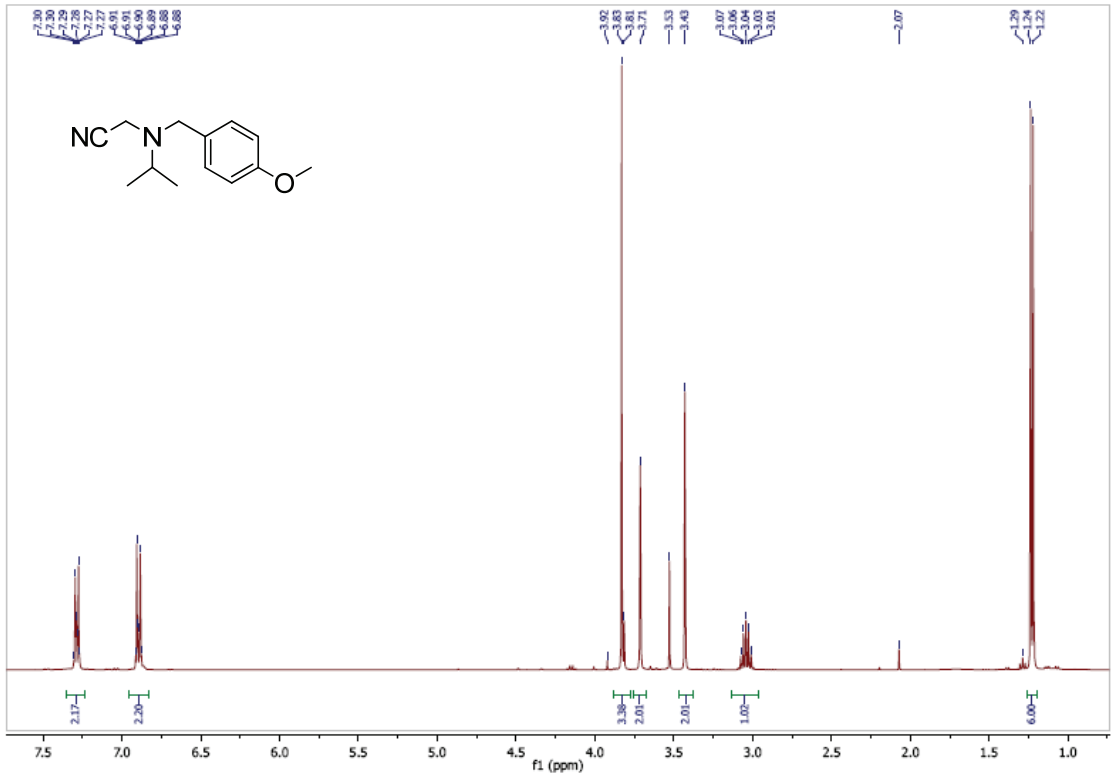
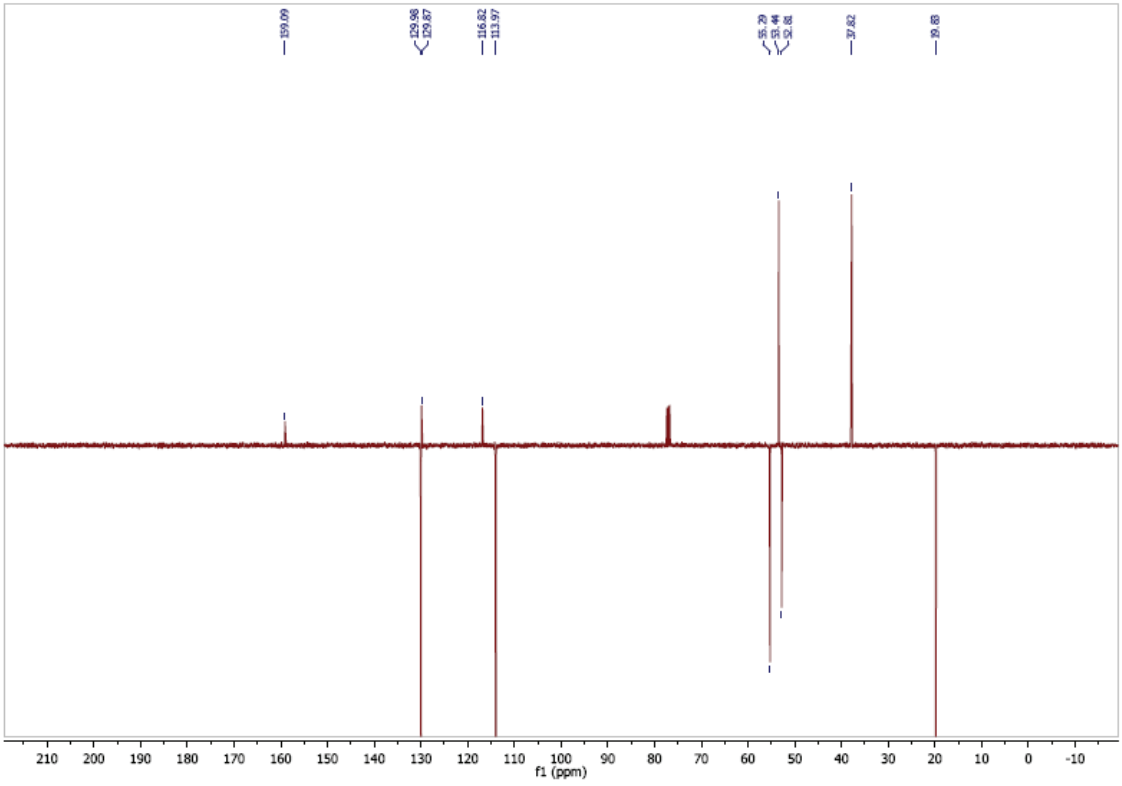
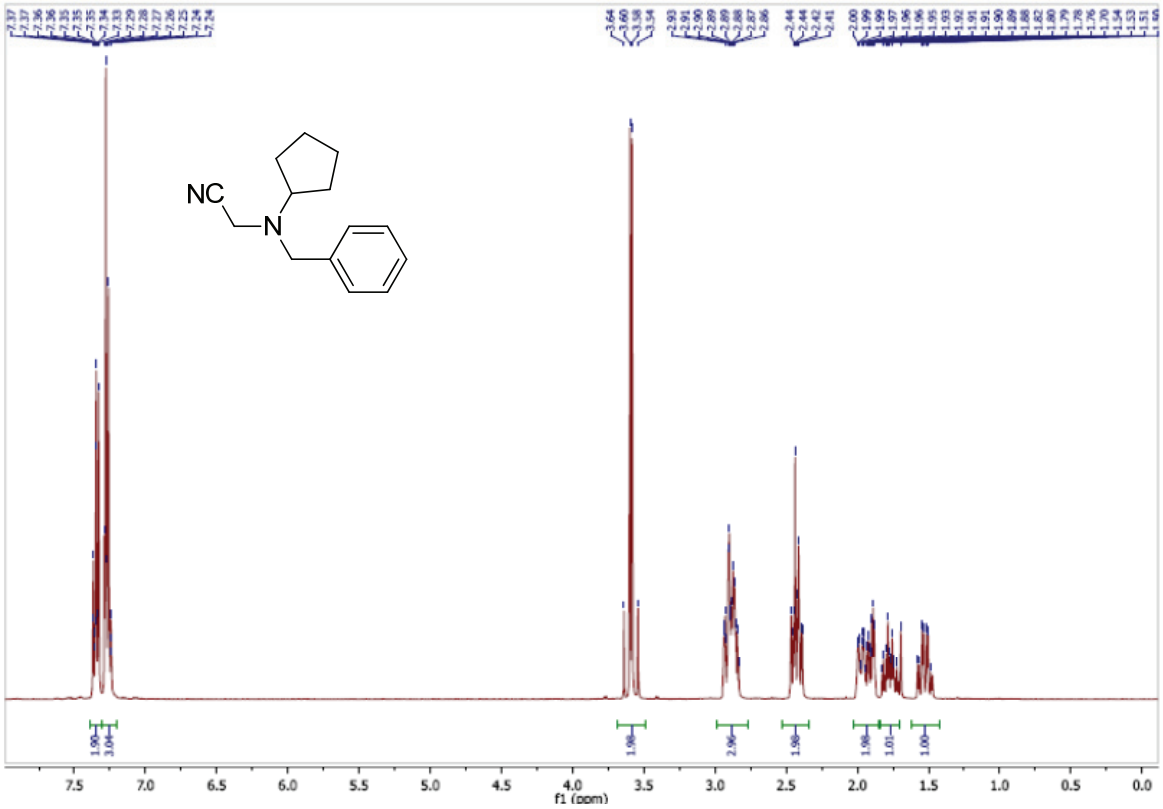
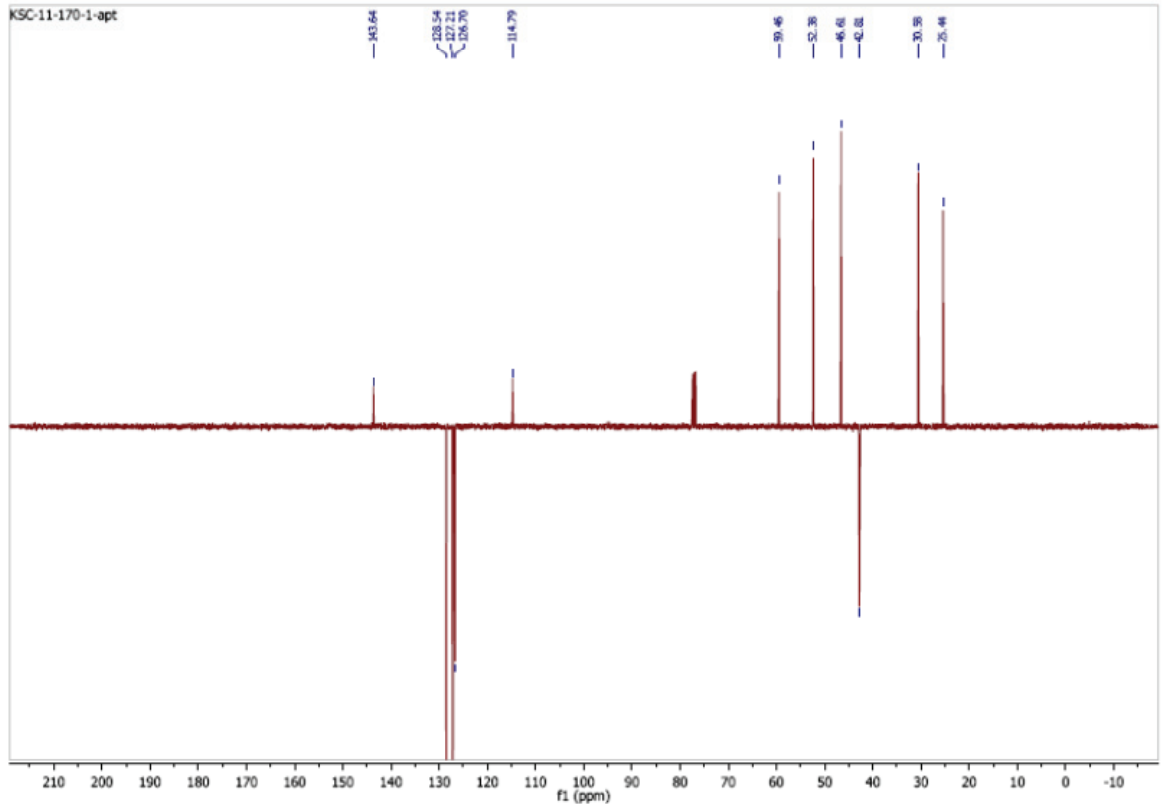
3.018
7.459
7.438
7.235
7.214

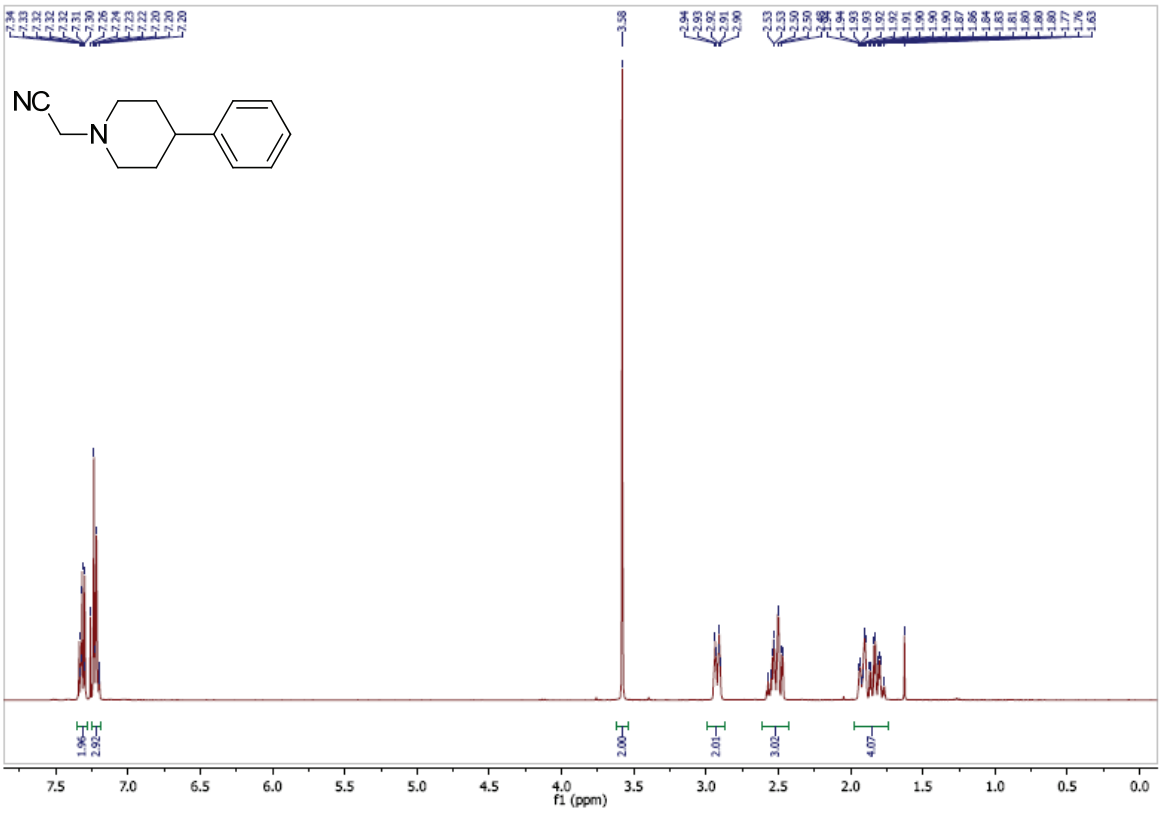

KSC-5-268_002000fid
Normalized Intensity
Chemical Shift (ppm)
136.981
121.267
116.512
53.354
37.932
52.889
131.907
130.320
19.644

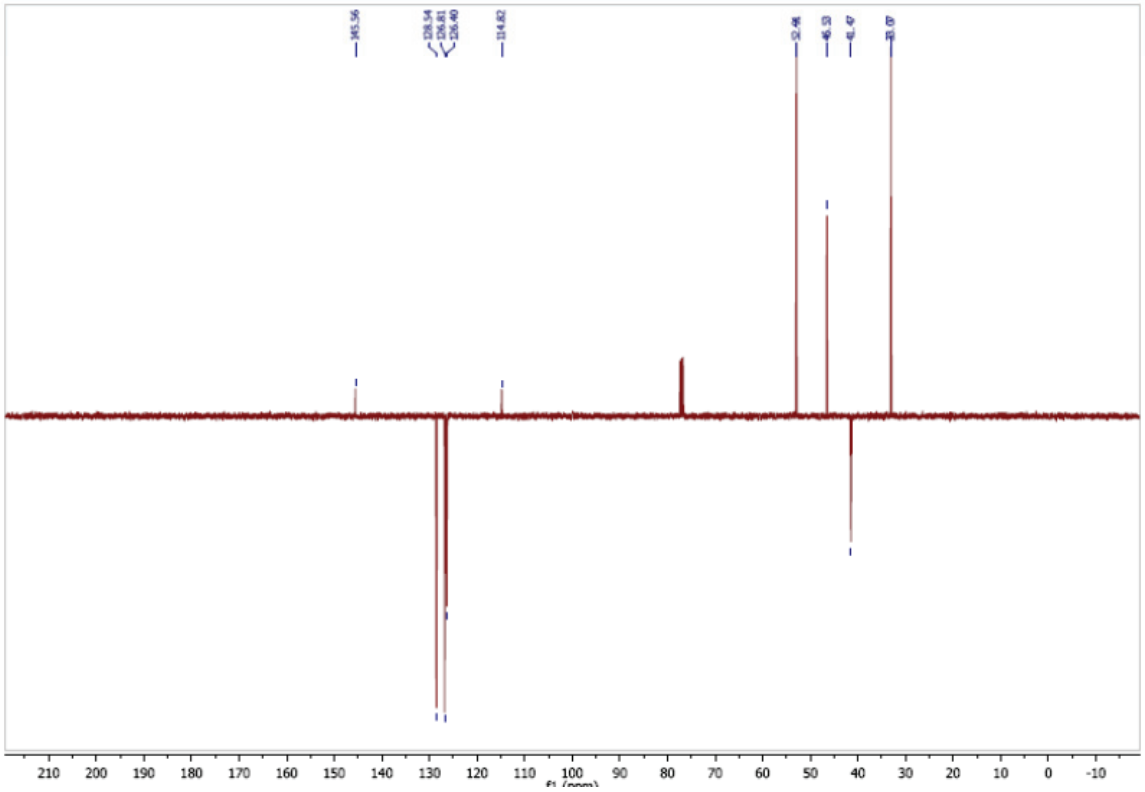

NC
N
O
f1 (ppm)

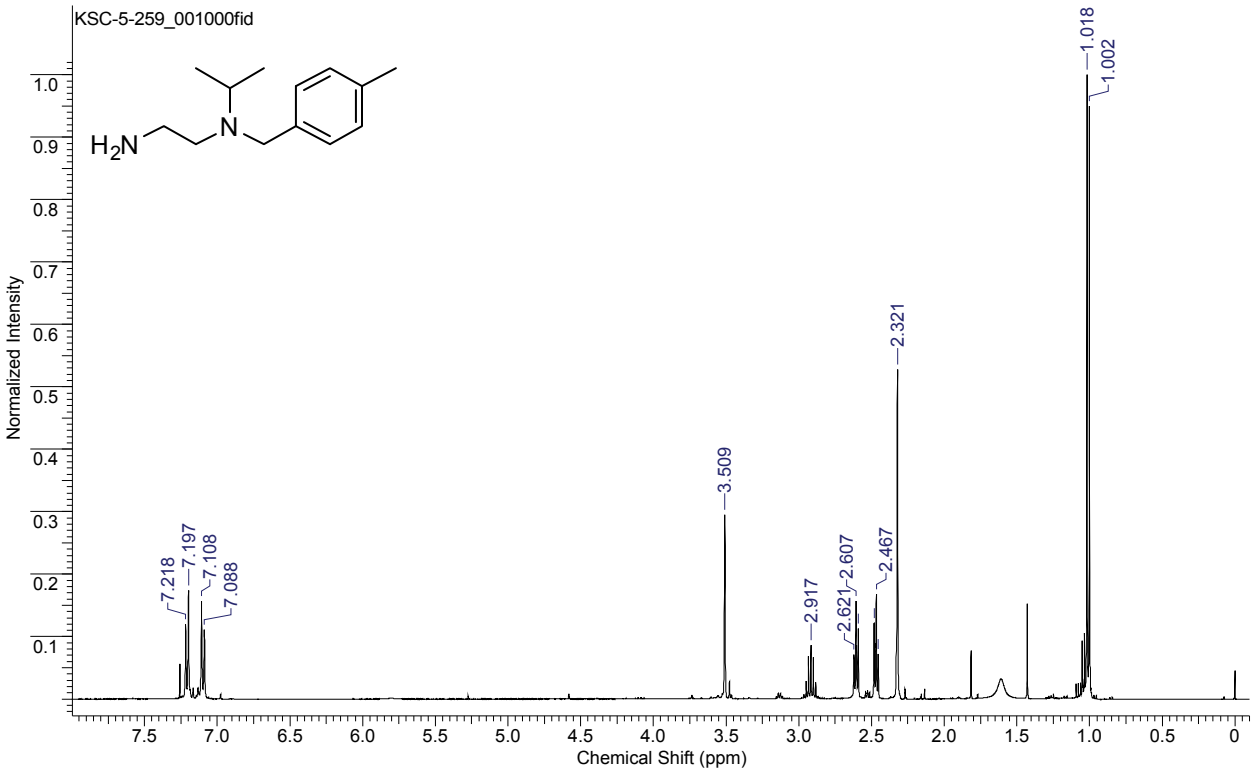

f1 (ppm)

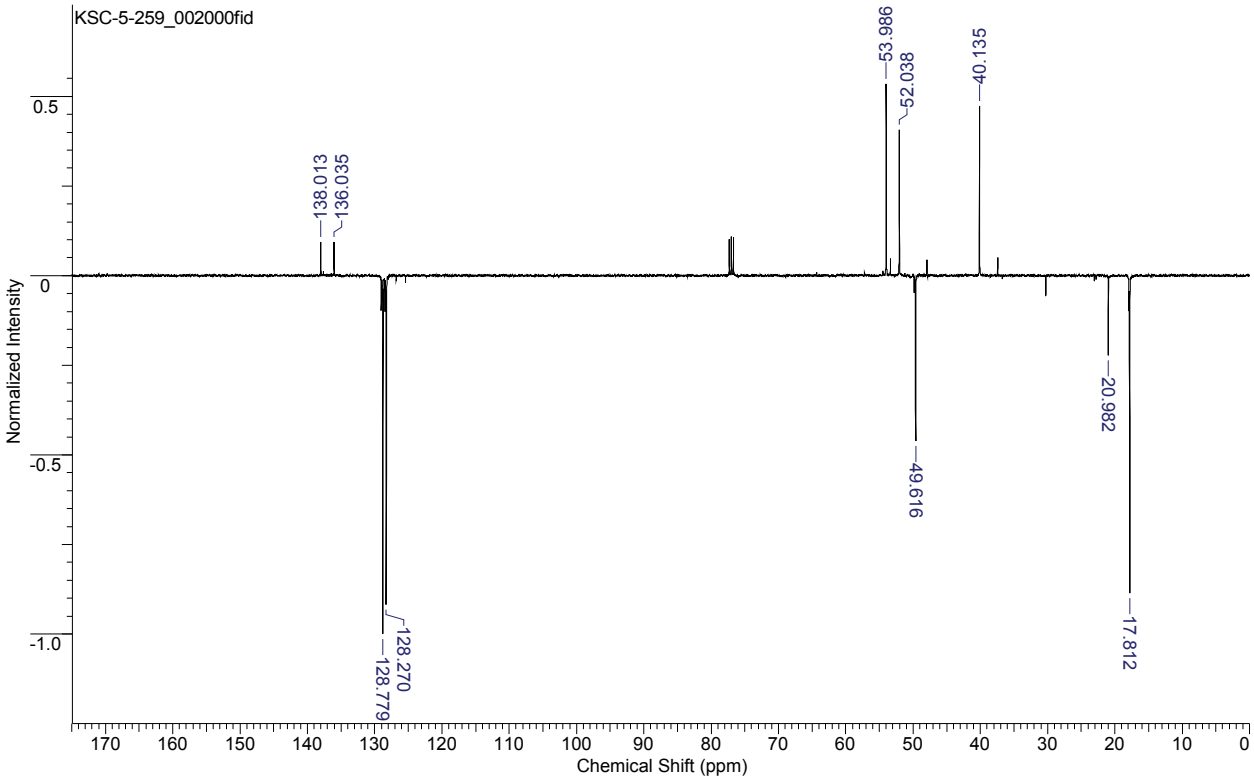

NC
N
f1 (ppm)

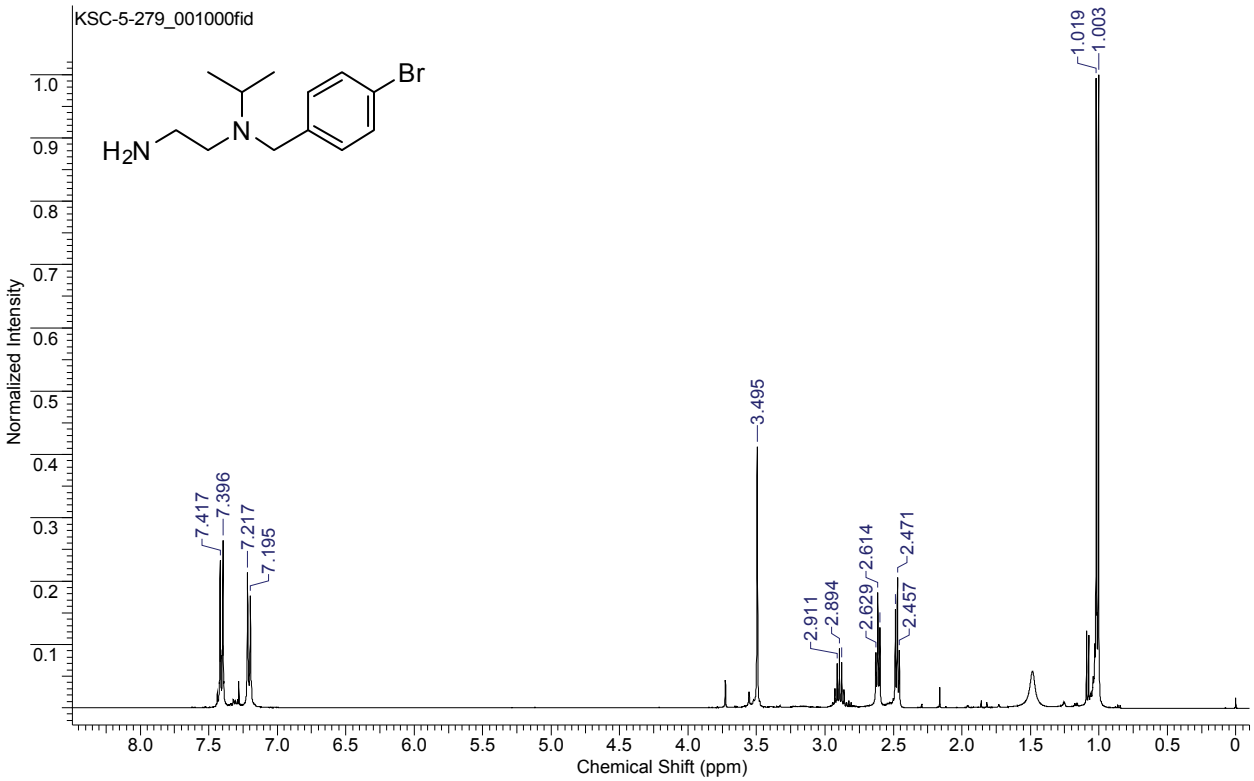

KSC-11-170-1-apt
f1 (ppm)

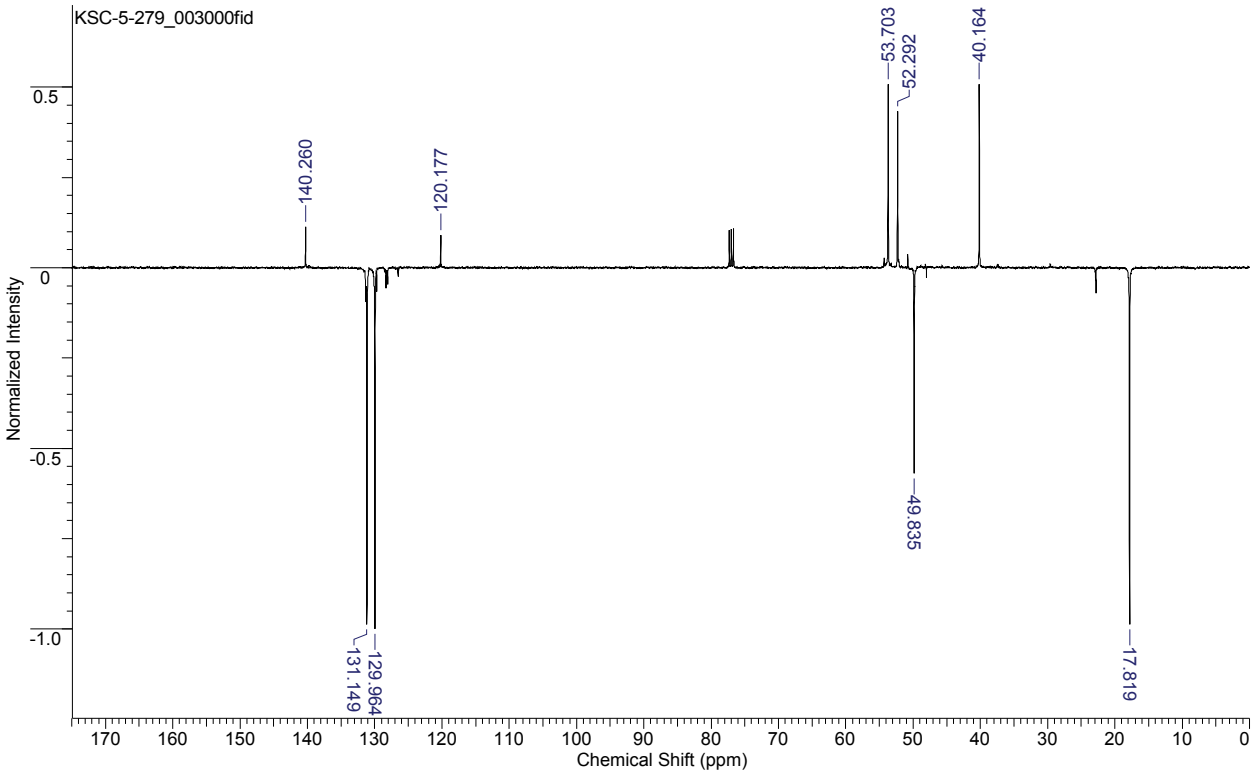

NC
N
f1 (ppm)

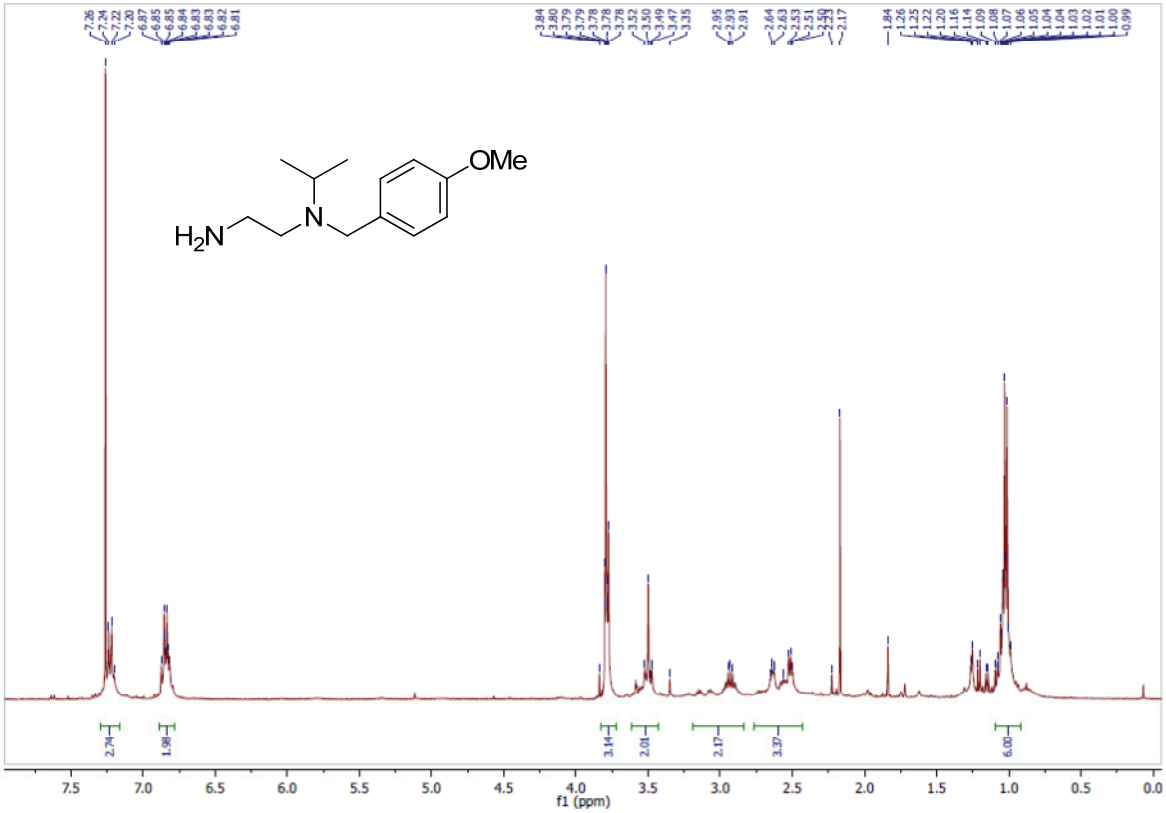


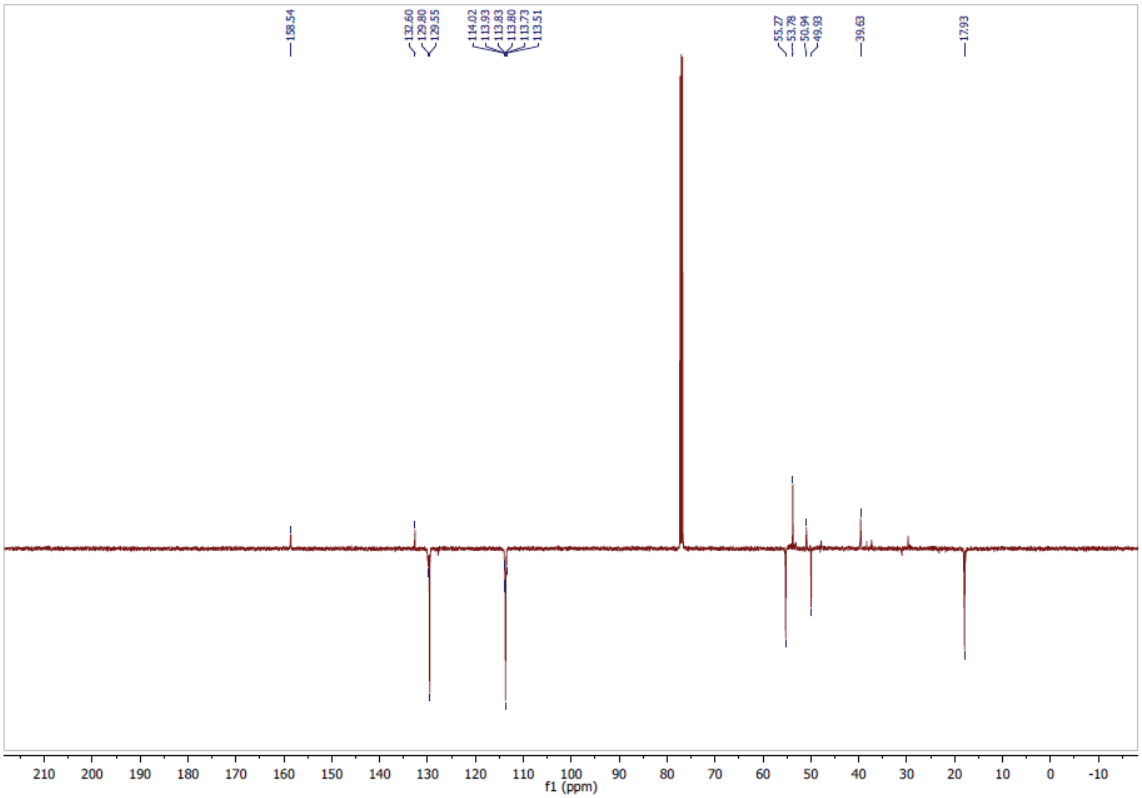

KSC-5-259_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.218
7.197
7.108
7.088
3.509
2.917
2.621
2.607
2.467
2.321
1.018
1.002

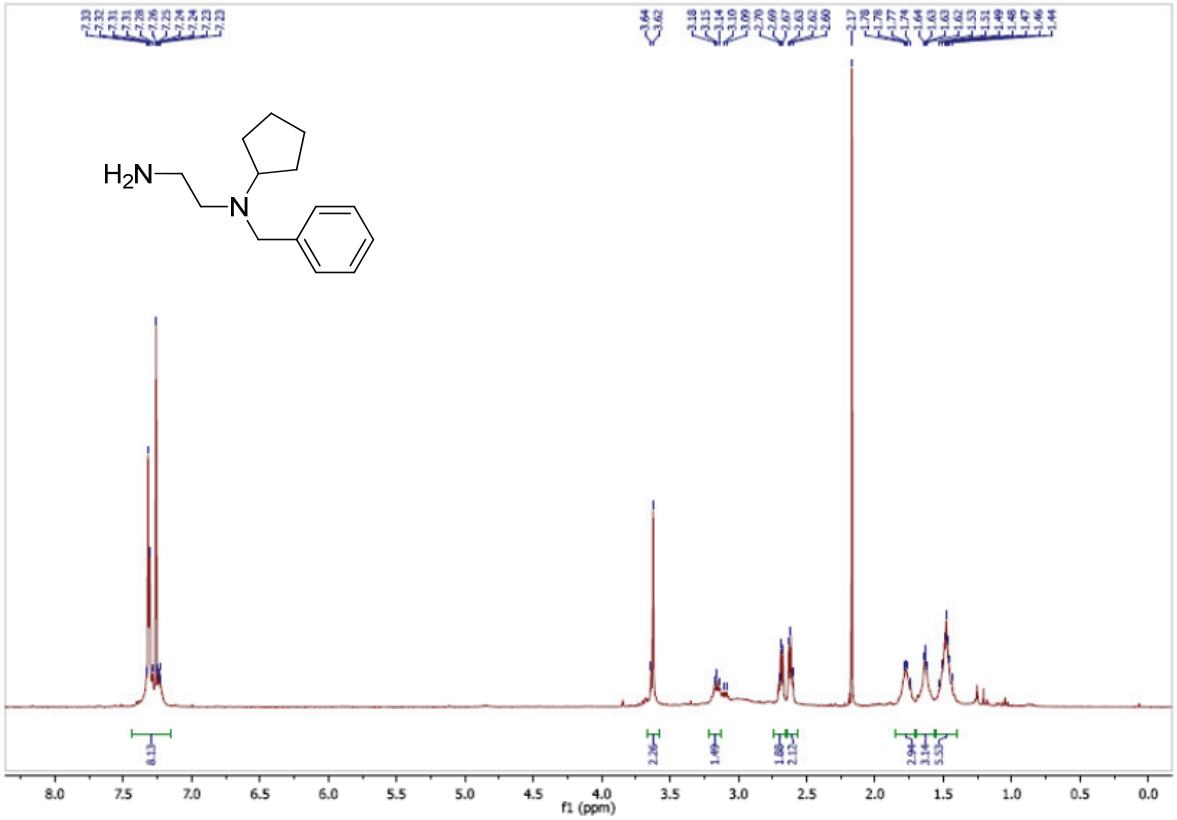

KSC-5-259_002000fid
Normalized Intensity
Chemical Shift (ppm)
138.013
136.035
128.779
128.270
53.986
52.038
49.616
40.135
20.982
17.812

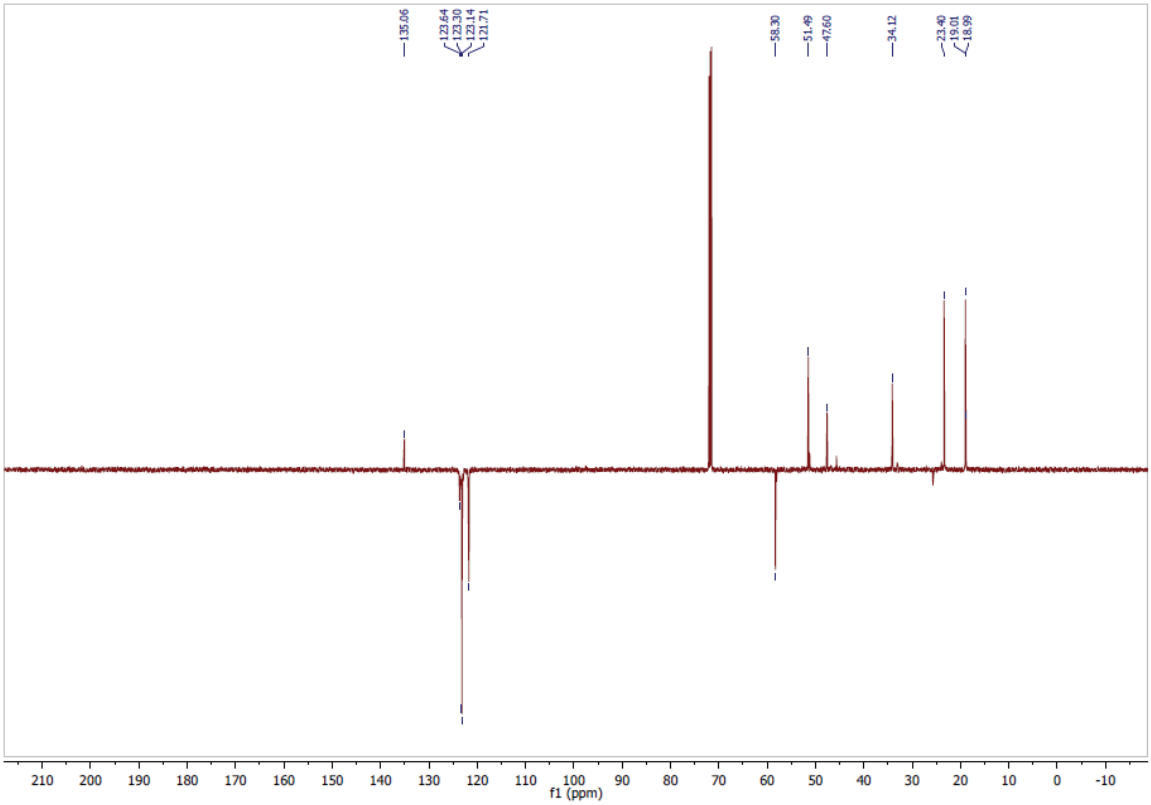

KSC-5-279_001000fid
Br
N
H2N
Normalized Intensity
Chemical Shift (ppm)
7.417
7.396
7.217
7.195
3.495
2.911
2.894
2.629
2.614
2.471
2.457
1.019
1.003

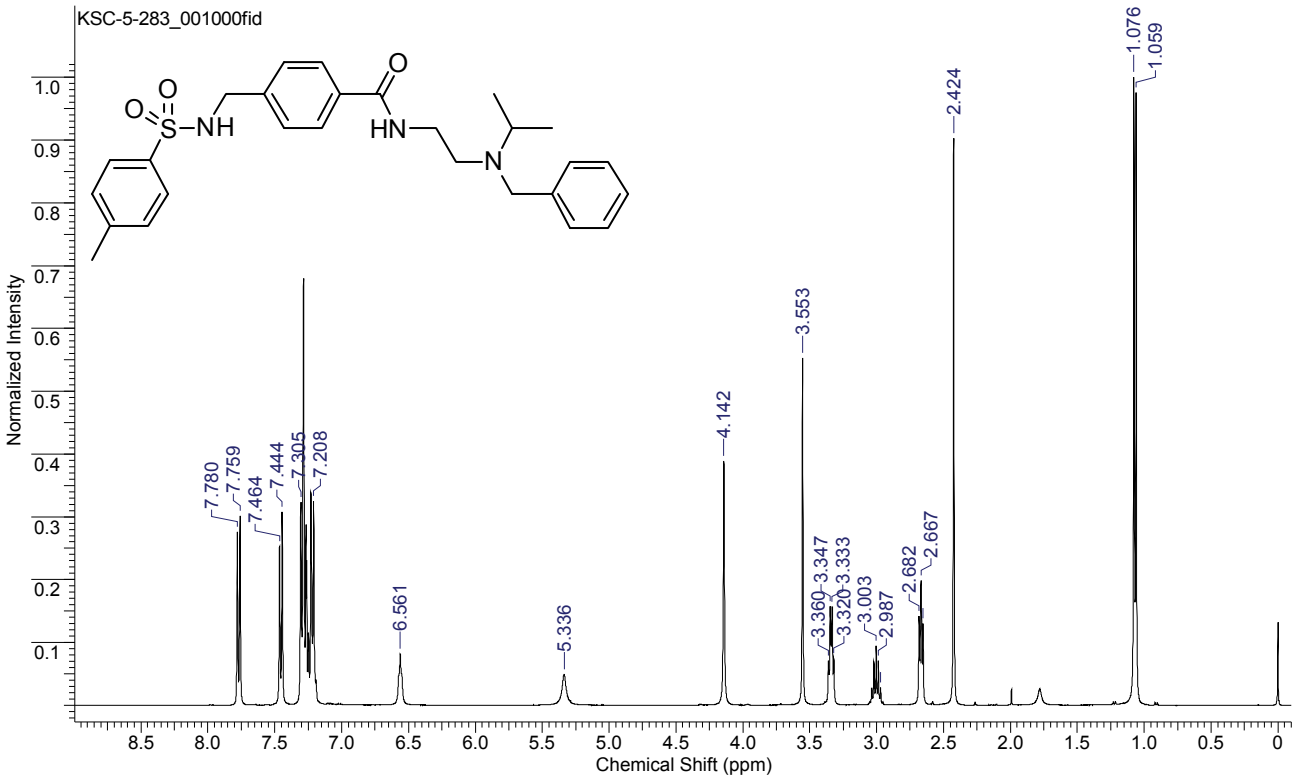

KSC-5-279_003000fid
Normalized Intensity
Chemical Shift (ppm)
140.260
120.177
53.703
52.292
40.164
49.835
131.149
129.964
17.819

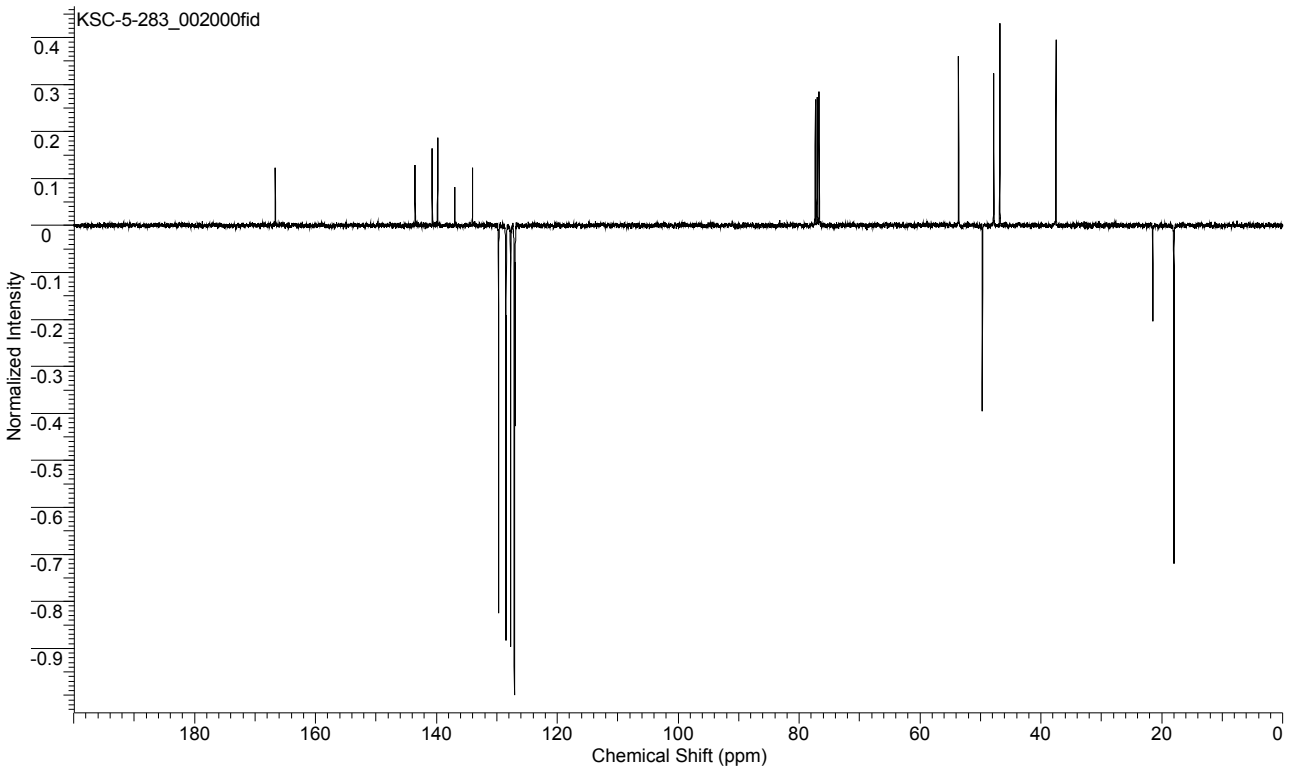

OMe
N
H2N
f1 (ppm)

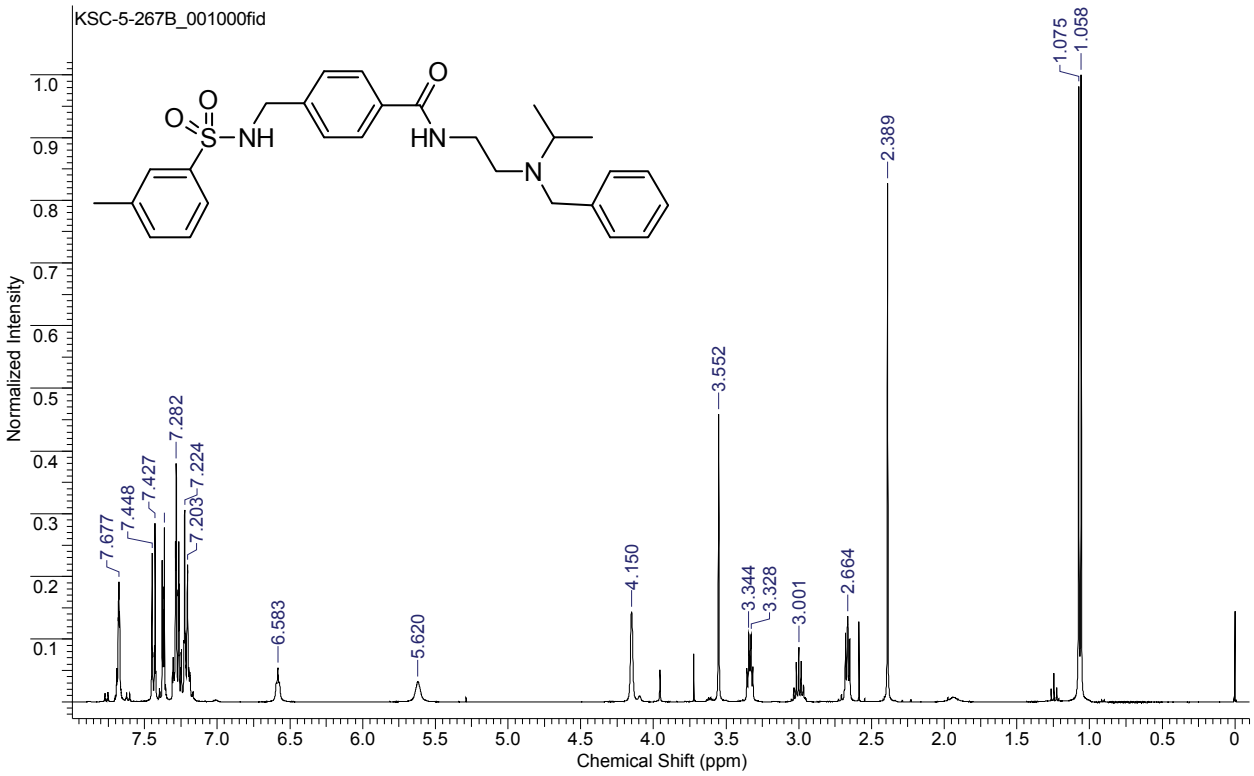

f1 (ppm)

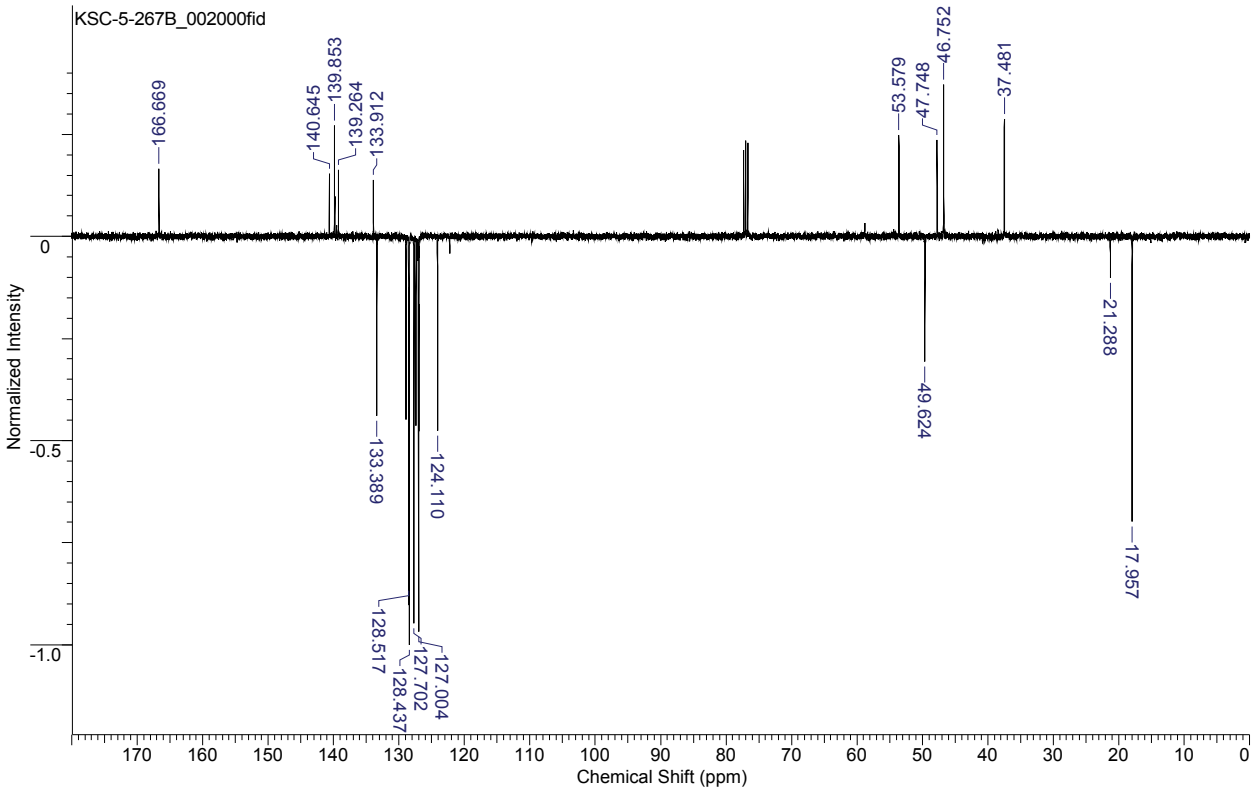

H2N
N
f1 (ppm)

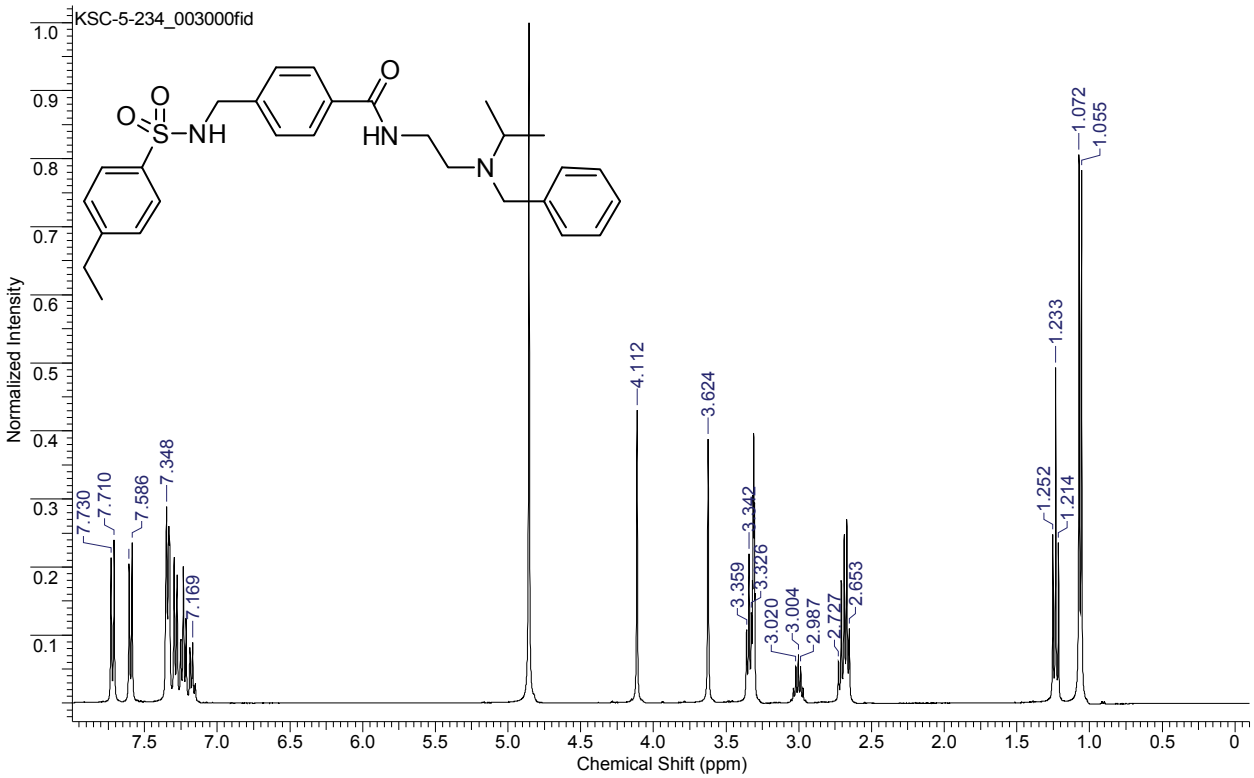

f1 (ppm)

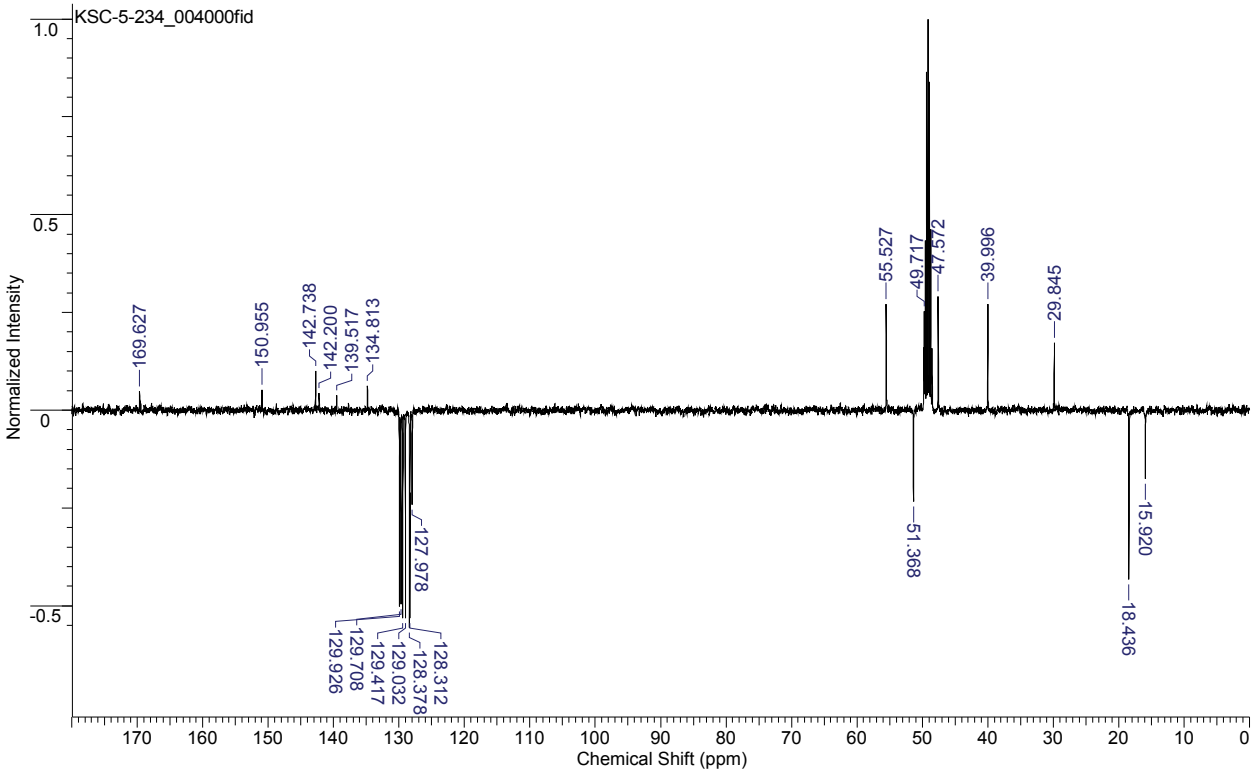

KSC-5-283_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.780
7.759
7.464
7.444
7.305
7.208
6.561
5.336
4.142
3.553
3.360
3.347
3.320
3.333
3.003
2.987
2.682
2.667
2.424
1.076
1.059

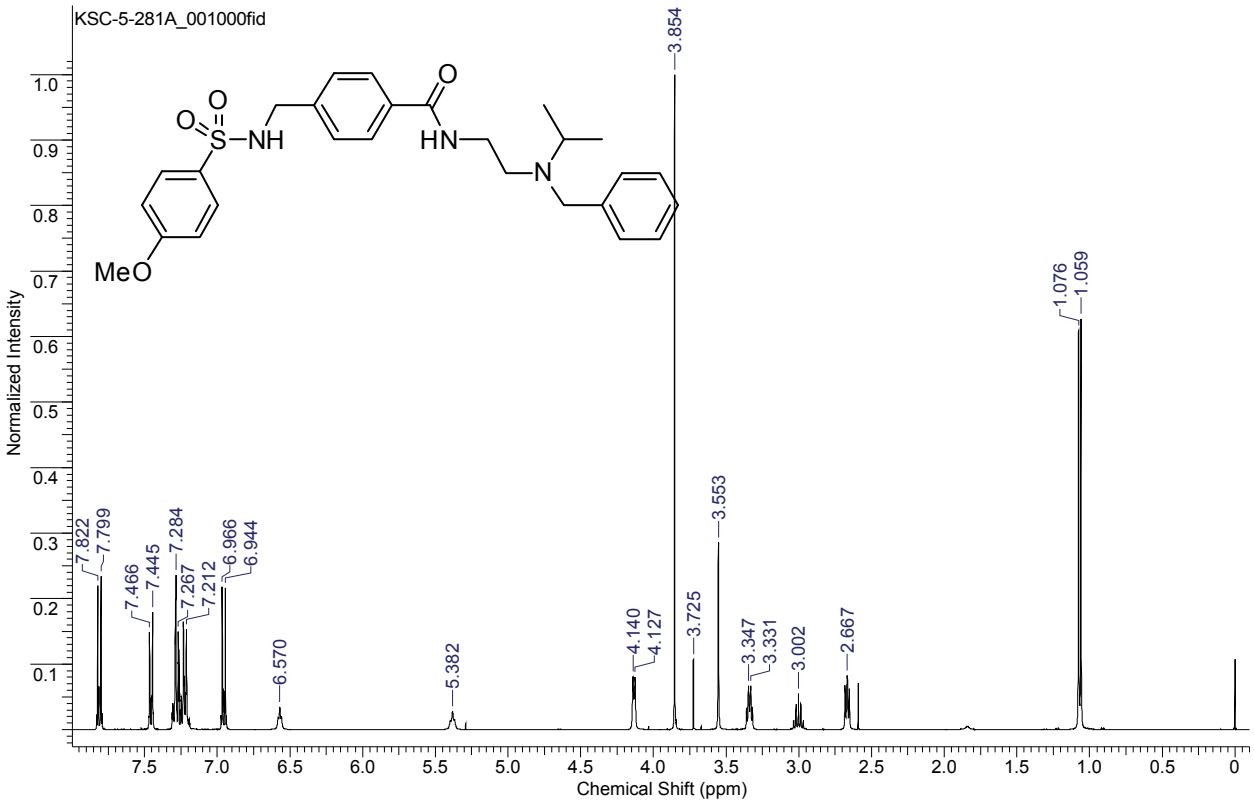

KSC-5-283_002000fid
Normalized Intensity
Chemical Shift (ppm)

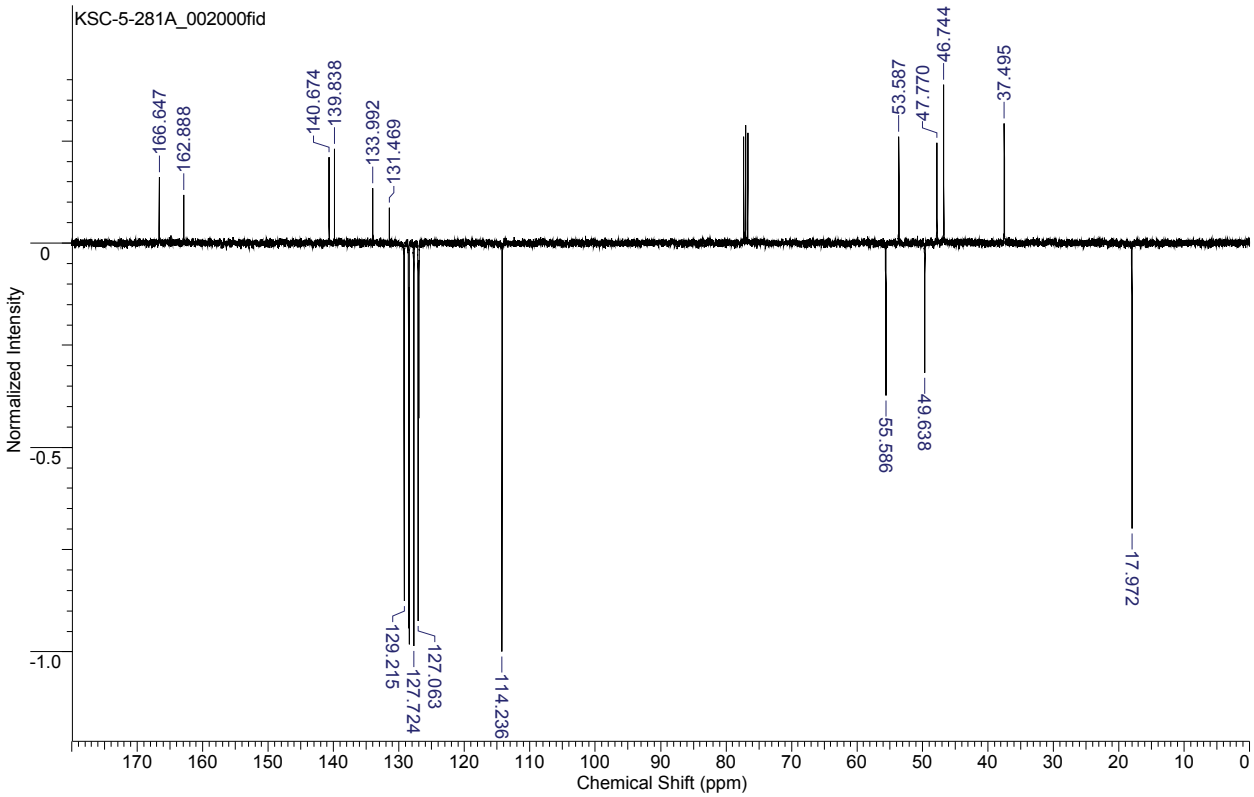

KSC-5-267B_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.677
7.448
7.427
7.282
7.224
7.203
6.583
5.620
4.150
3.552
3.344
3.328
3.001
2.664
2.389
1.075
1.058

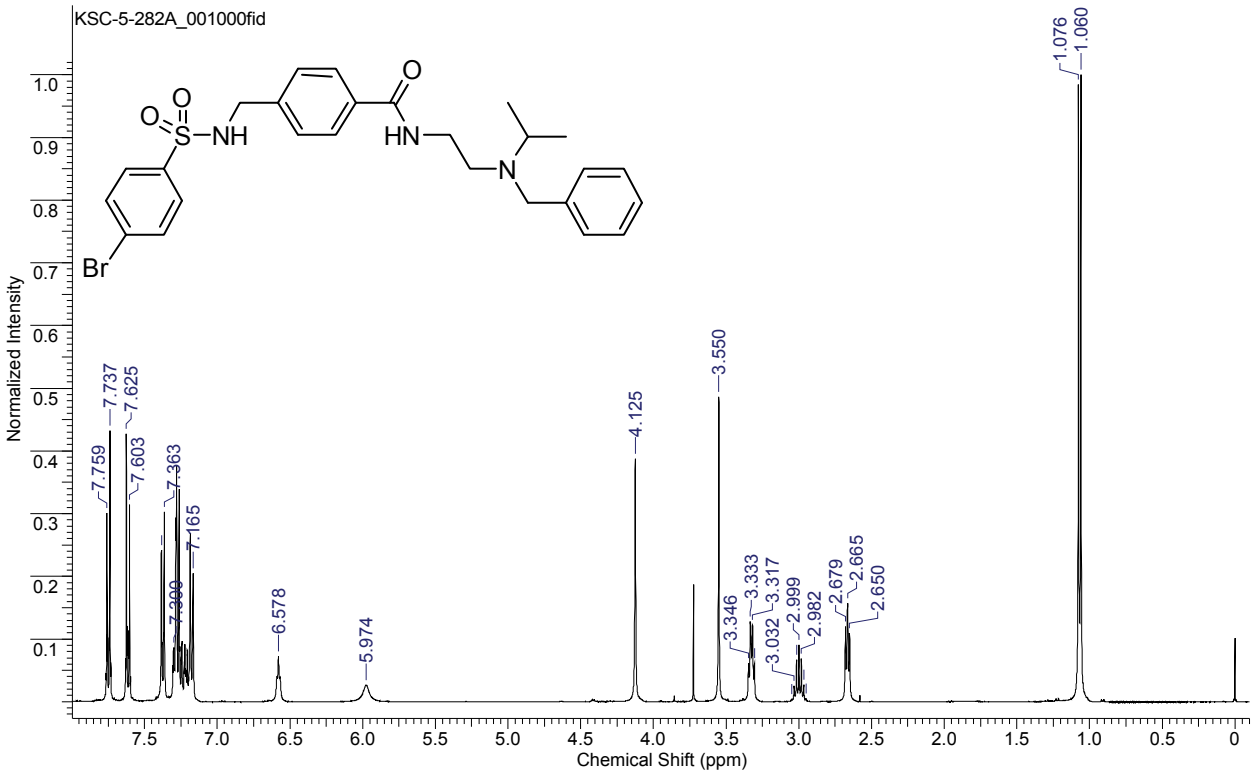

KSC-5-267B_002000fid
Normalized Intensity
Chemical Shift (ppm)
166.669
140.645
139.853
139.264
133.912
133.389
128.517
128.437
127.702
127.004
124.110
53.579
47.748
46.752
49.024
37.481
21.288
17.957

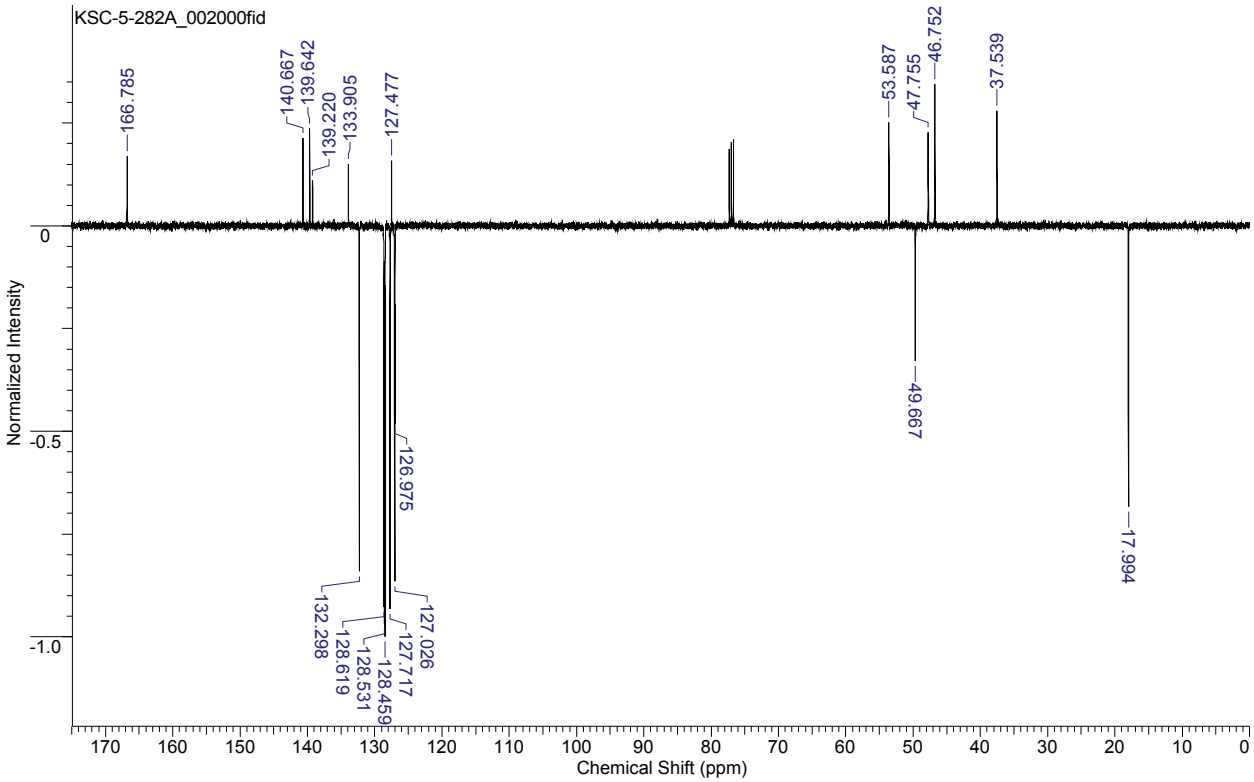

KSC-5-234_003000fid
Normalized Intensity
Chemical Shift (ppm)
7.730
7.710
7.586
7.348
7.169
4.112
3.624
3.359
3.342
3.326
3.020
3.004
2.987
2.727
2.653
1.252
1.233
1.214
1.072
1.055


KSC-5-234_004000fid
Normalized Intensity
Chemical Shift (ppm)
169.627
150.955
142.738
142.200
139.517
134.813
127.978
129.926
129.708
129.417
129.032
128.378
128.312
55.527
49.717
47.572
51.368
39.996
29.845
15.920
18.436


KSC-5-281A_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.822
7.799
7.466
7.445
7.284
7.267
7.212
6.966
6.944
6.570
5.382
4.140
4.127
3.854
3.725
3.553
3.347
3.331
3.002
2.667
1.076
1.059


KSC-5-281A_002000fid
Normalized Intensity
Chemical Shift (ppm)
166.647
162.888
140.674
139.838
133.992
131.469
129.215
127.724
127.063
114.236
56.586
53.587
49.638
47.770
46.744
37.495
17.972


KSC-5-282A_001000fid
Br
Normalized Intensity
Chemical Shift (ppm)
7.759
7.737
7.625
7.603
7.363
7.165
6.578
5.974
4.125
3.550
3.346
3.333
3.317
3.032
2.999
2.982
2.679
2.665
2.650
1.076
1.060


KSC-5-282A_002000fid
Normalized Intensity
Chemical Shift (ppm)
166.785
140.667
139.642
139.220
133.905
127.477
126.975
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128.459
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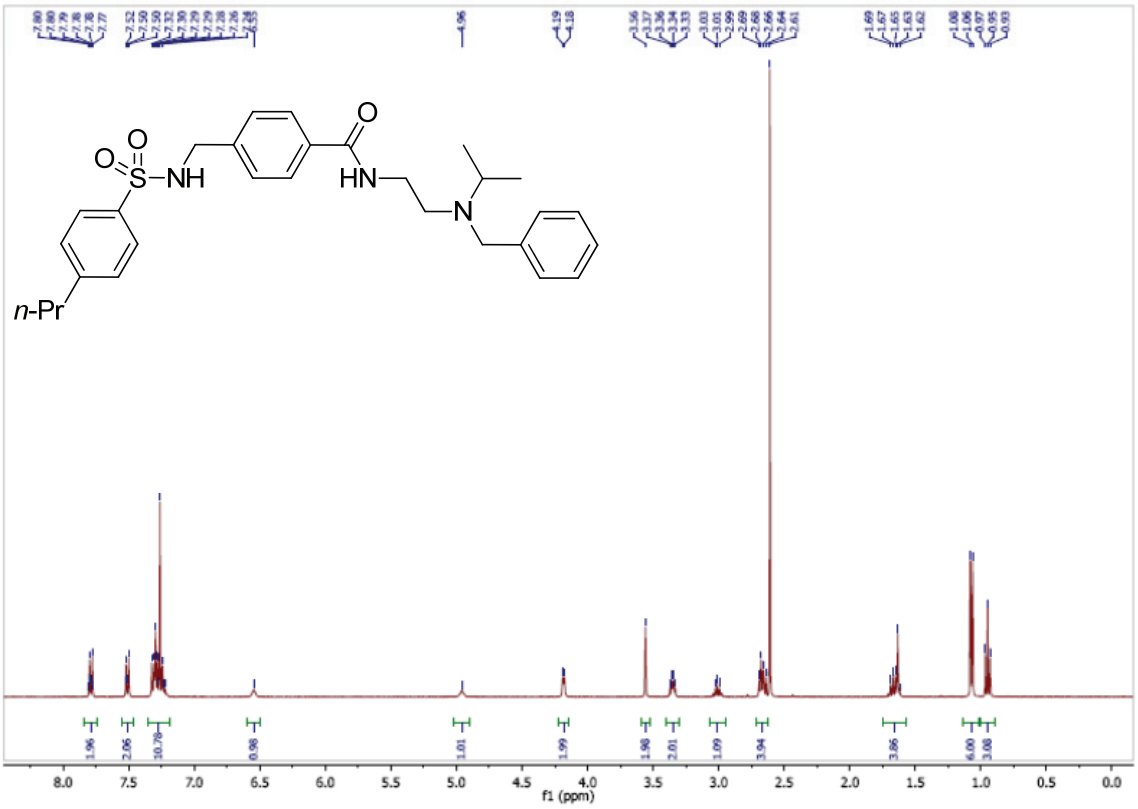
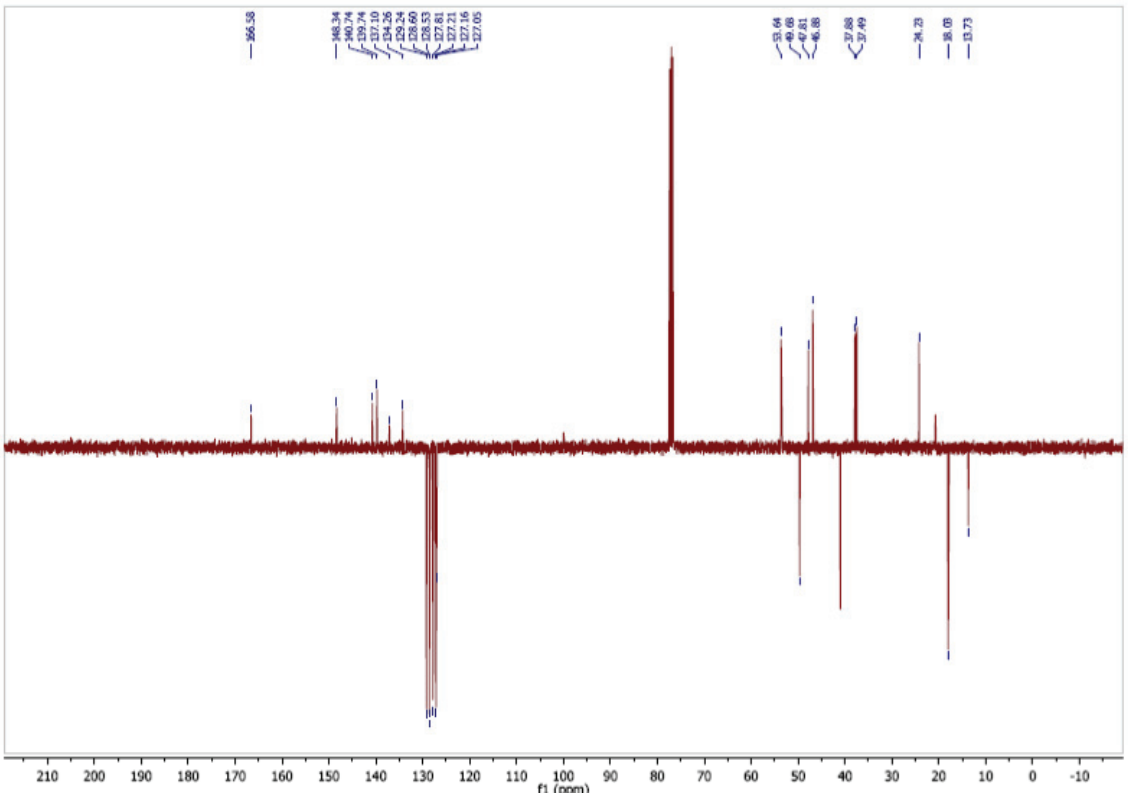
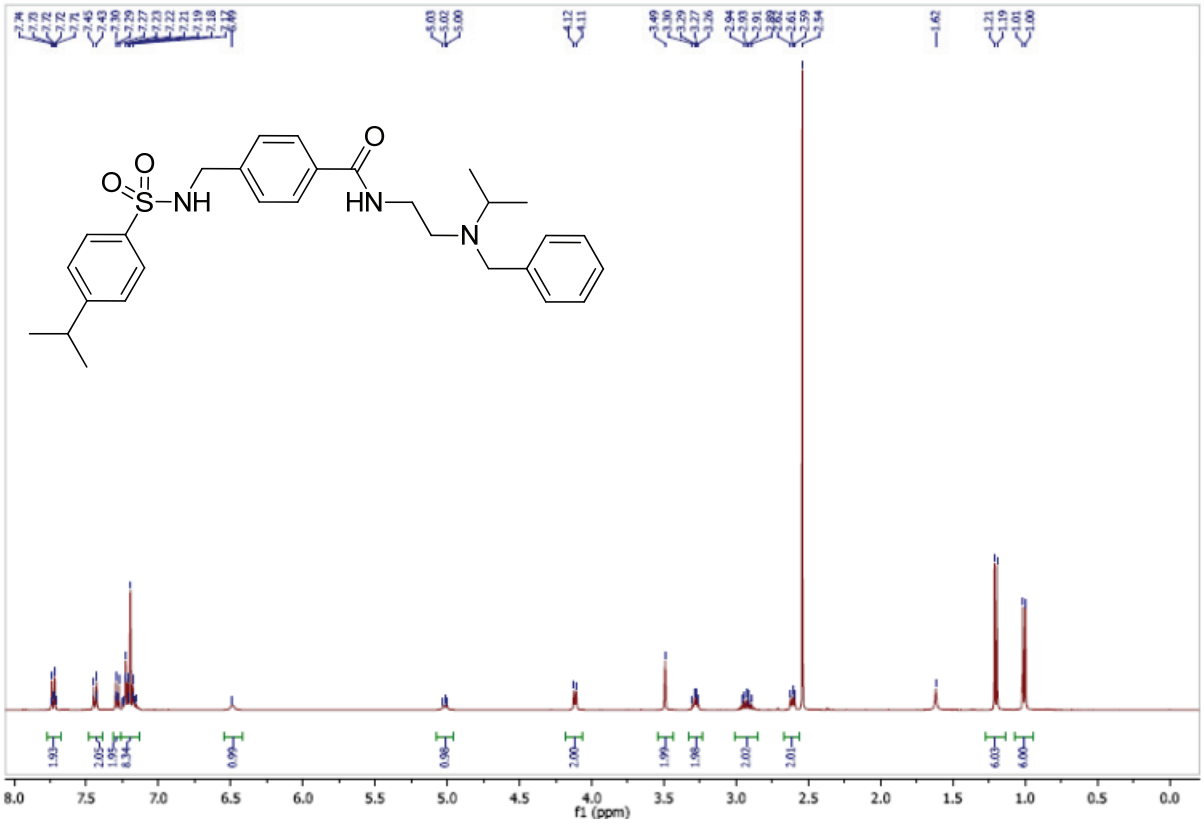
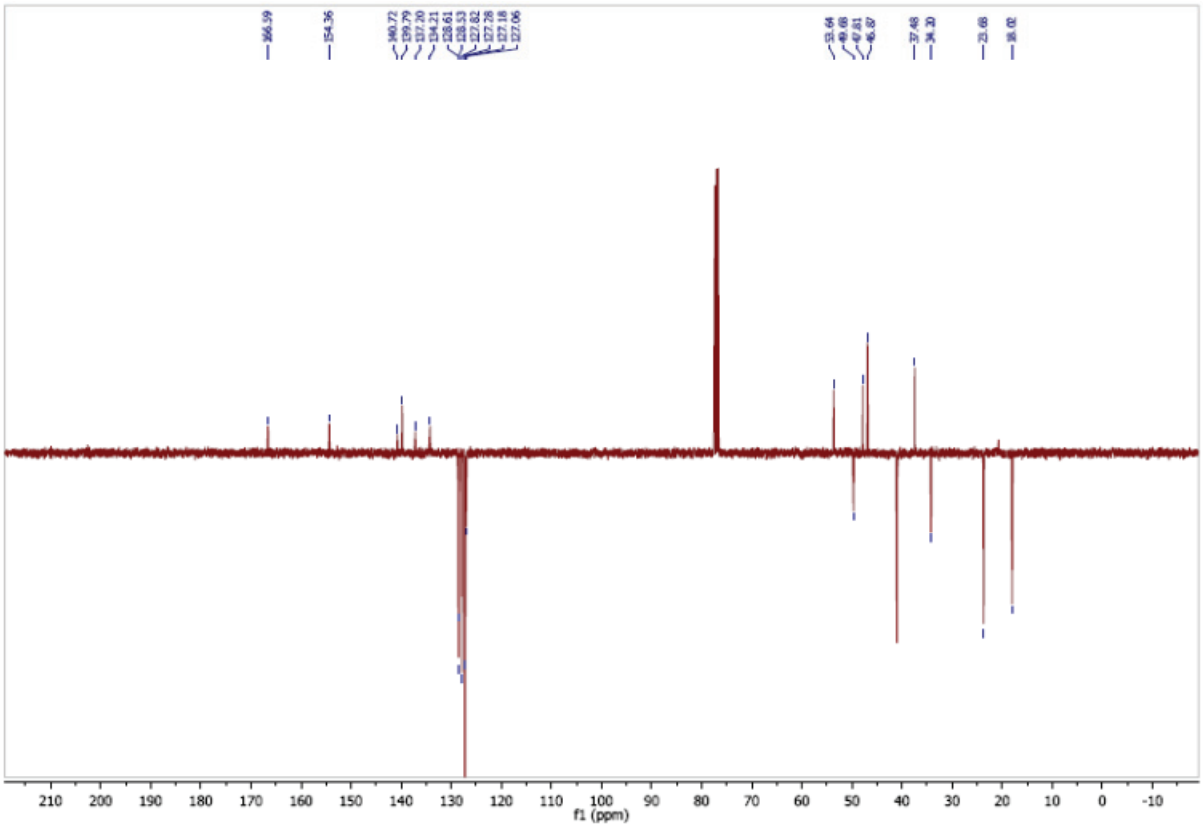
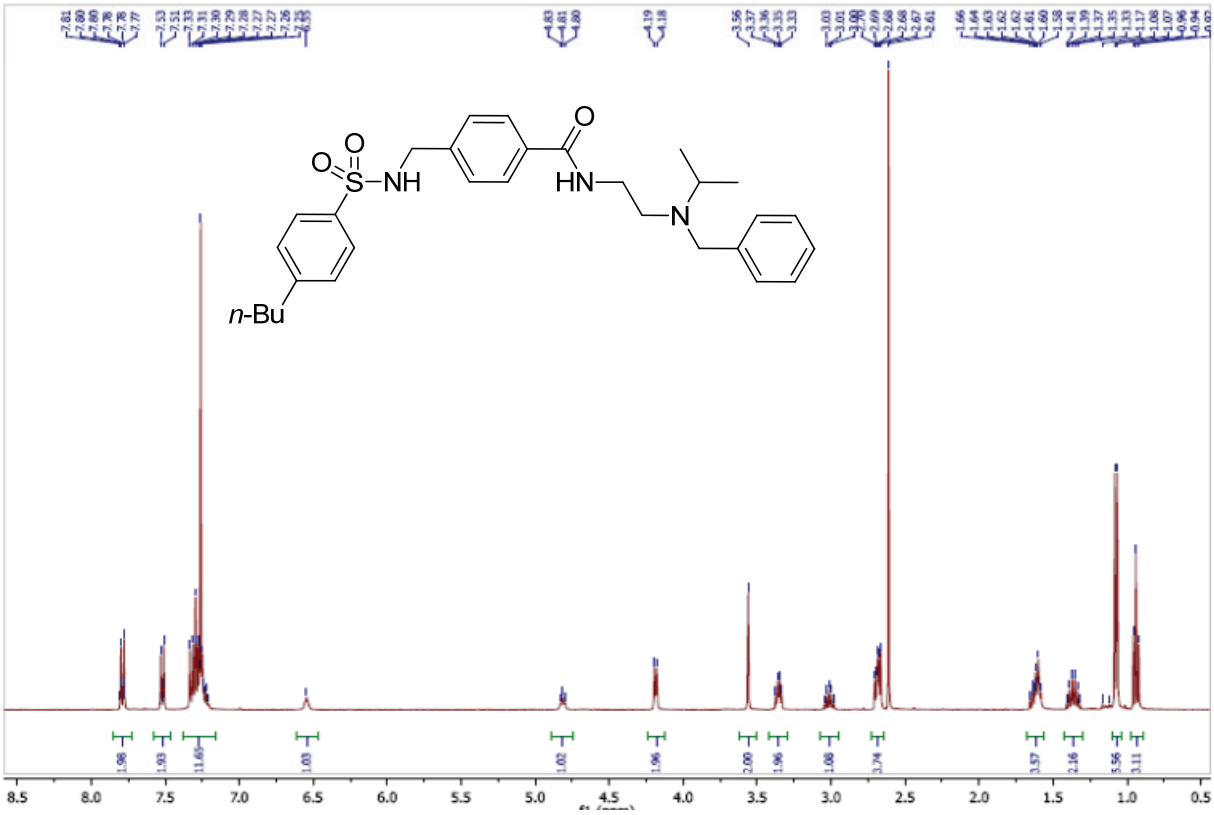
53.587
47.755
46.752
37.539
49.667
17.994

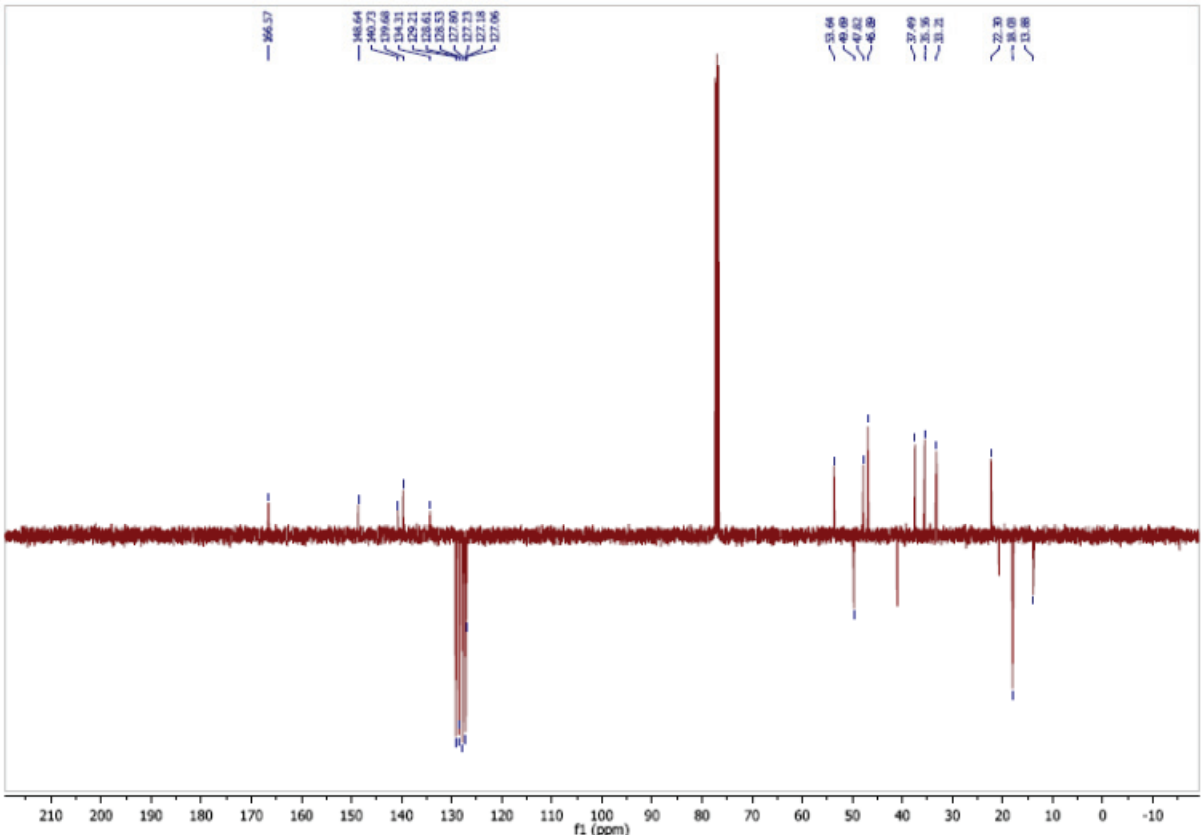

O
O
S
NH
HN
N
n-Pr
f1 (ppm)

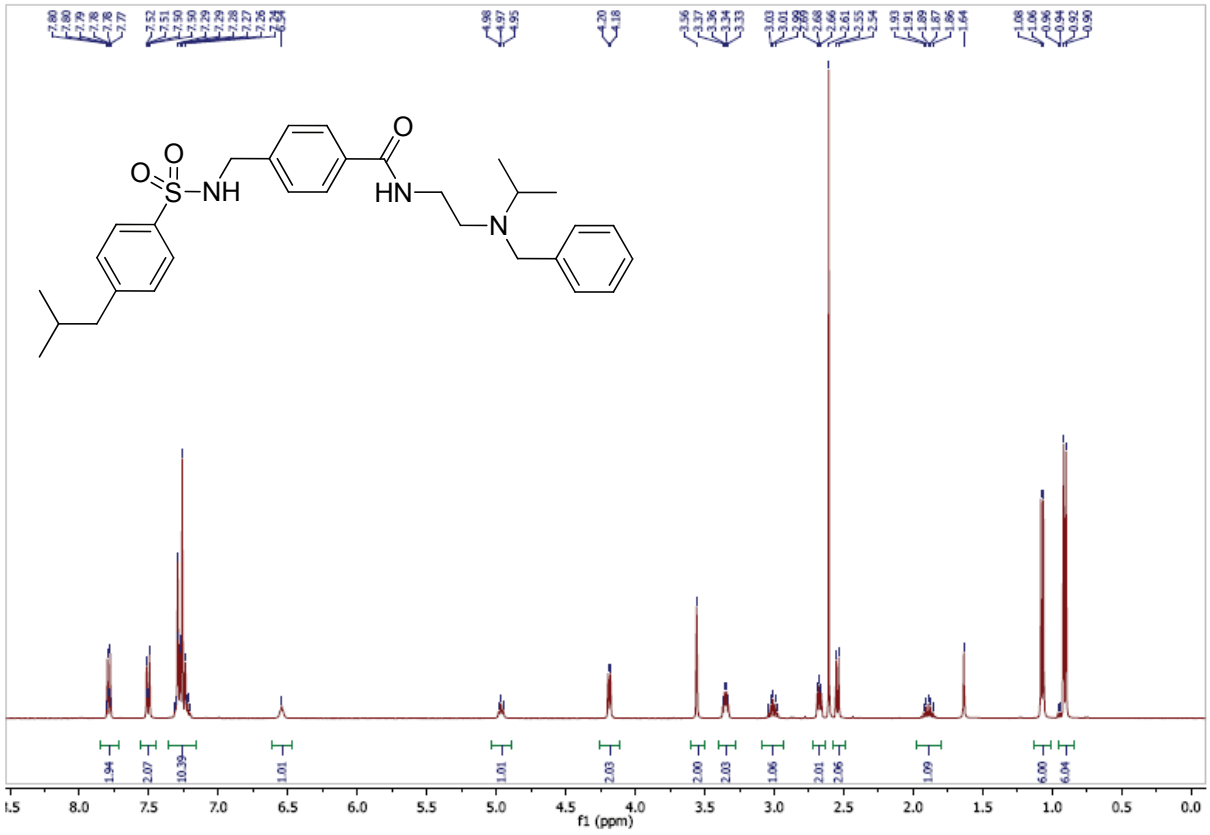

f1 (ppm)

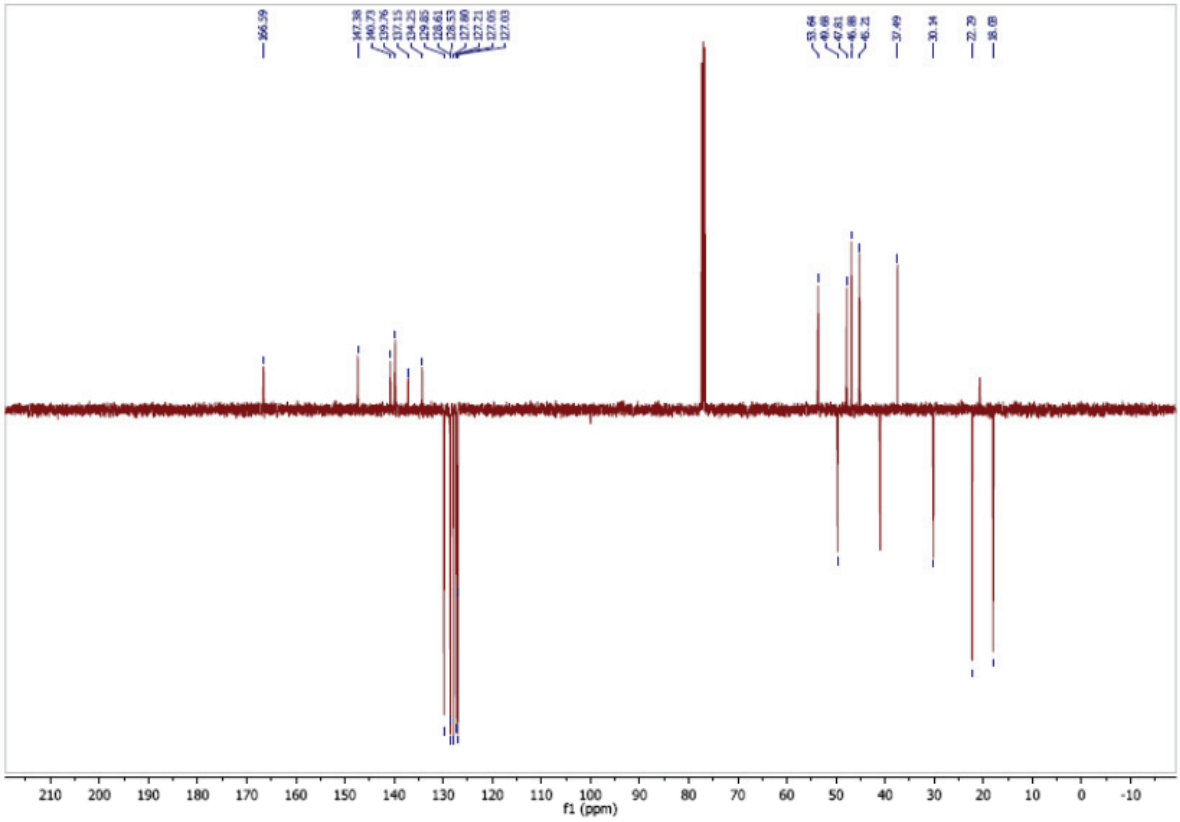

O
O
S
NH
HN
O
N
f1 (ppm)

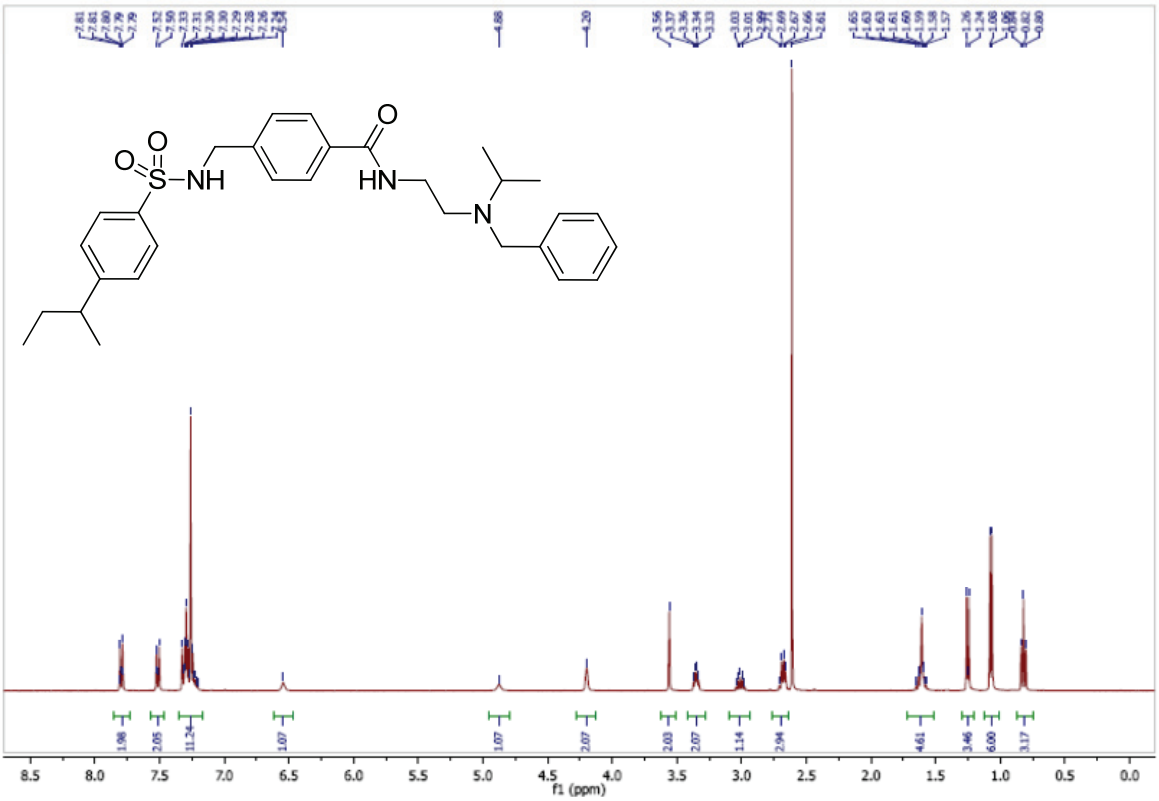

f1 (ppm)

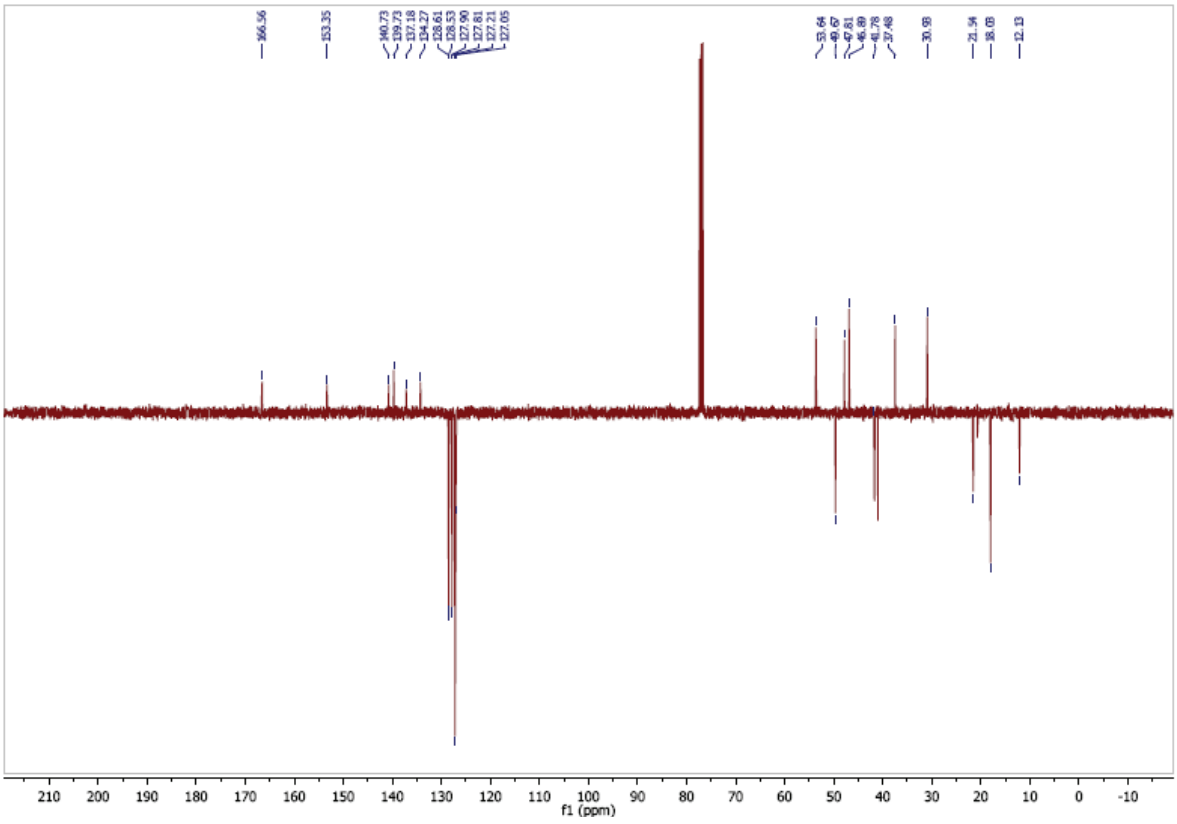

O
O
S
NH
HN
O
N
n-Bu

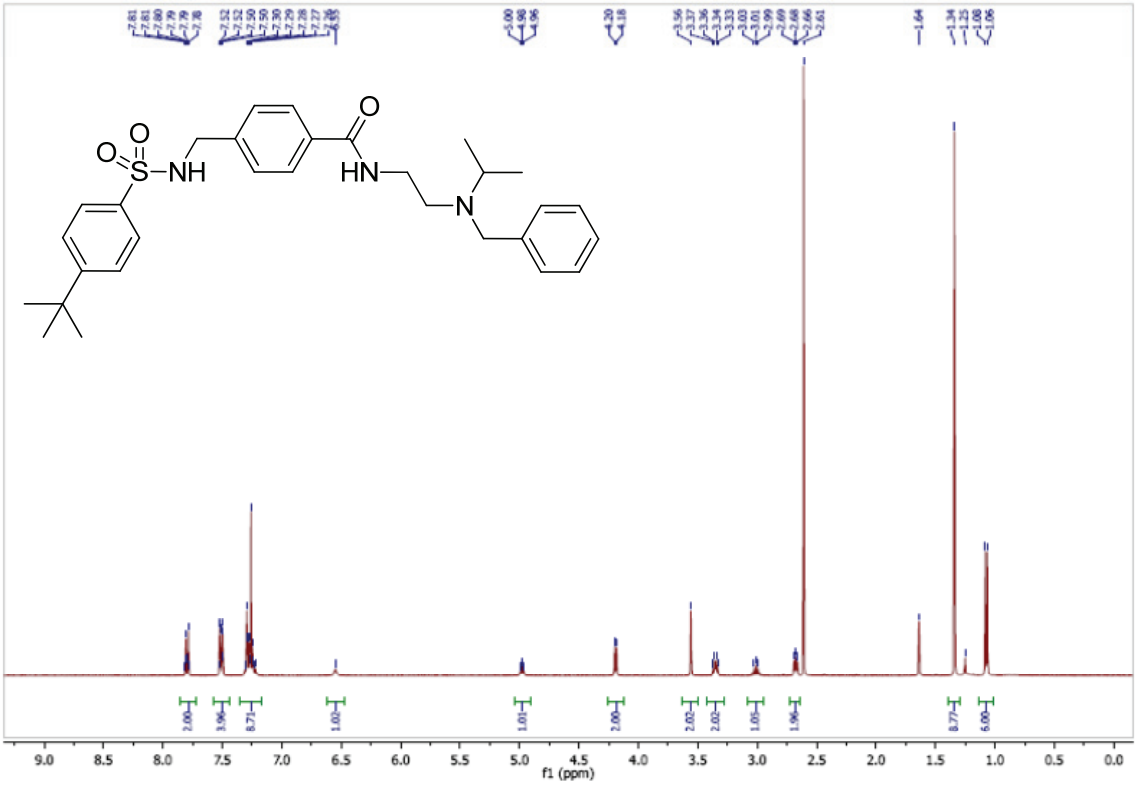


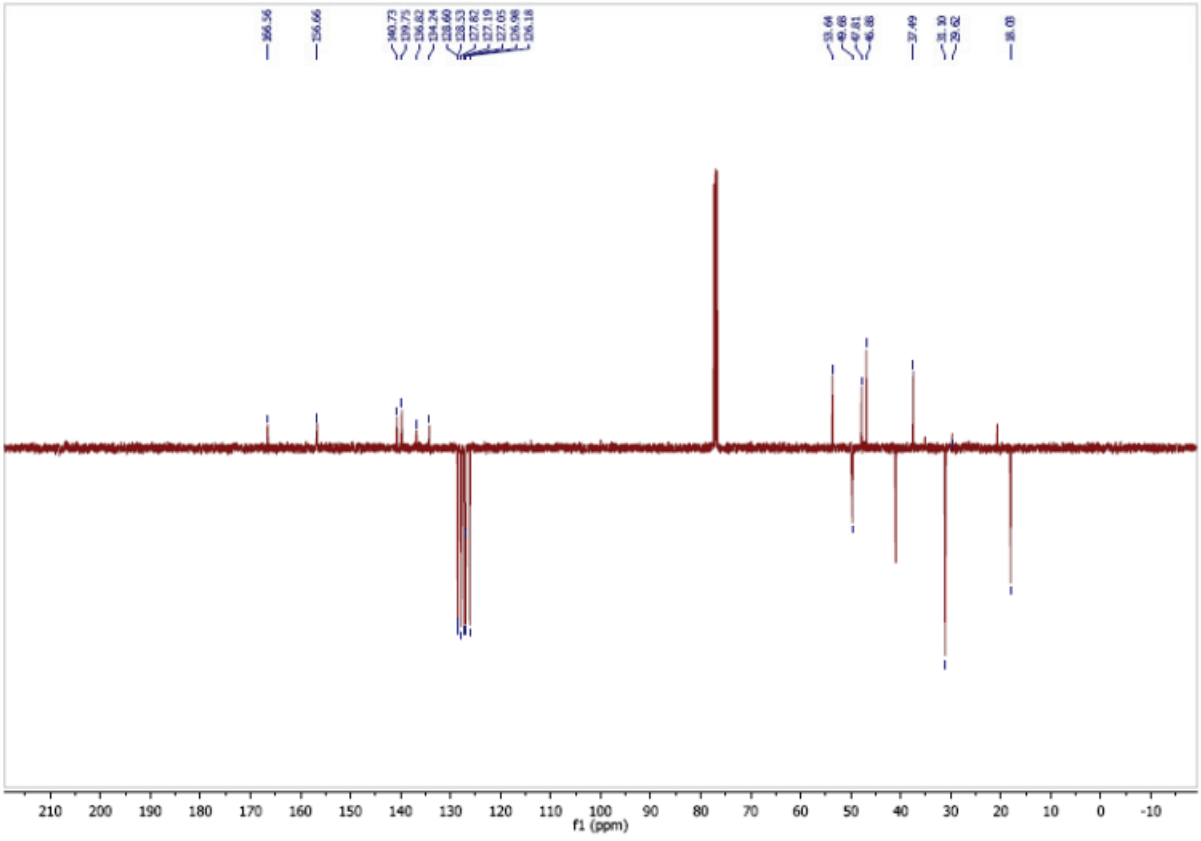

O
O
S
NH
HN
N
f1 (ppm)

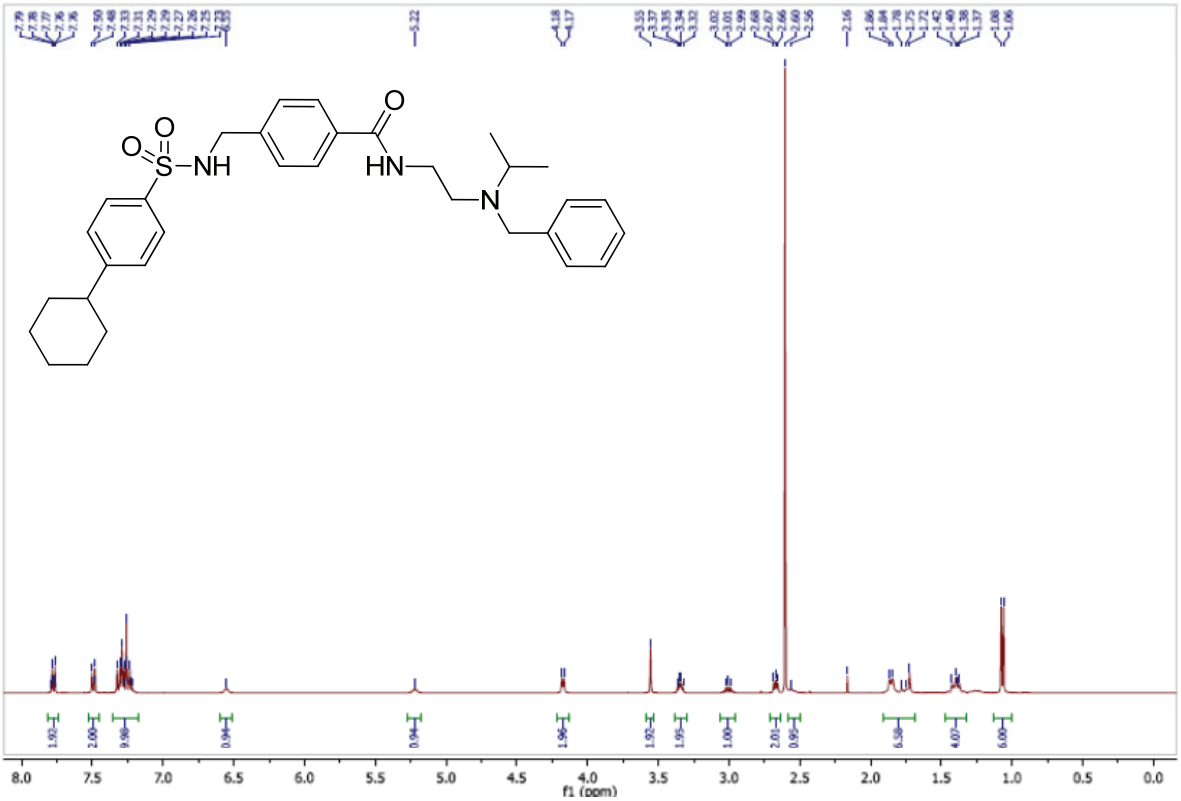

f1 (ppm)

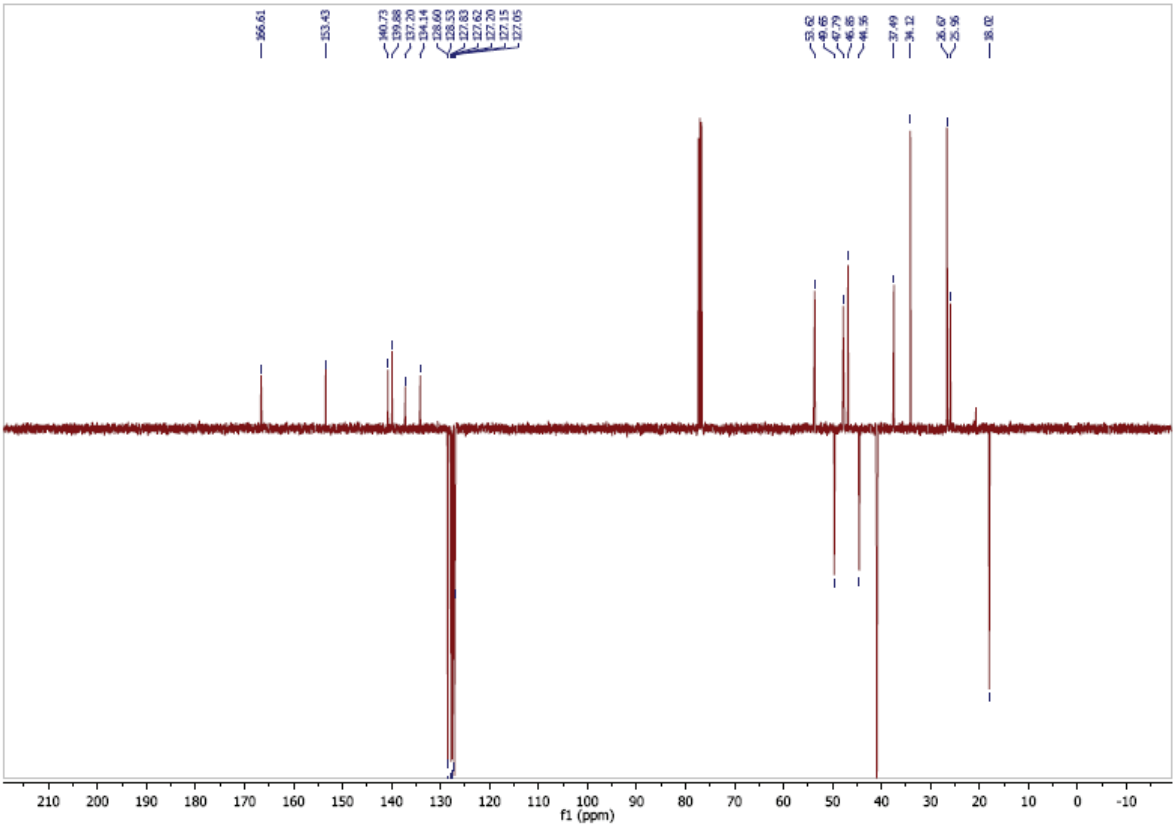

O
O
S
NH
HN
N
f1 (ppm)

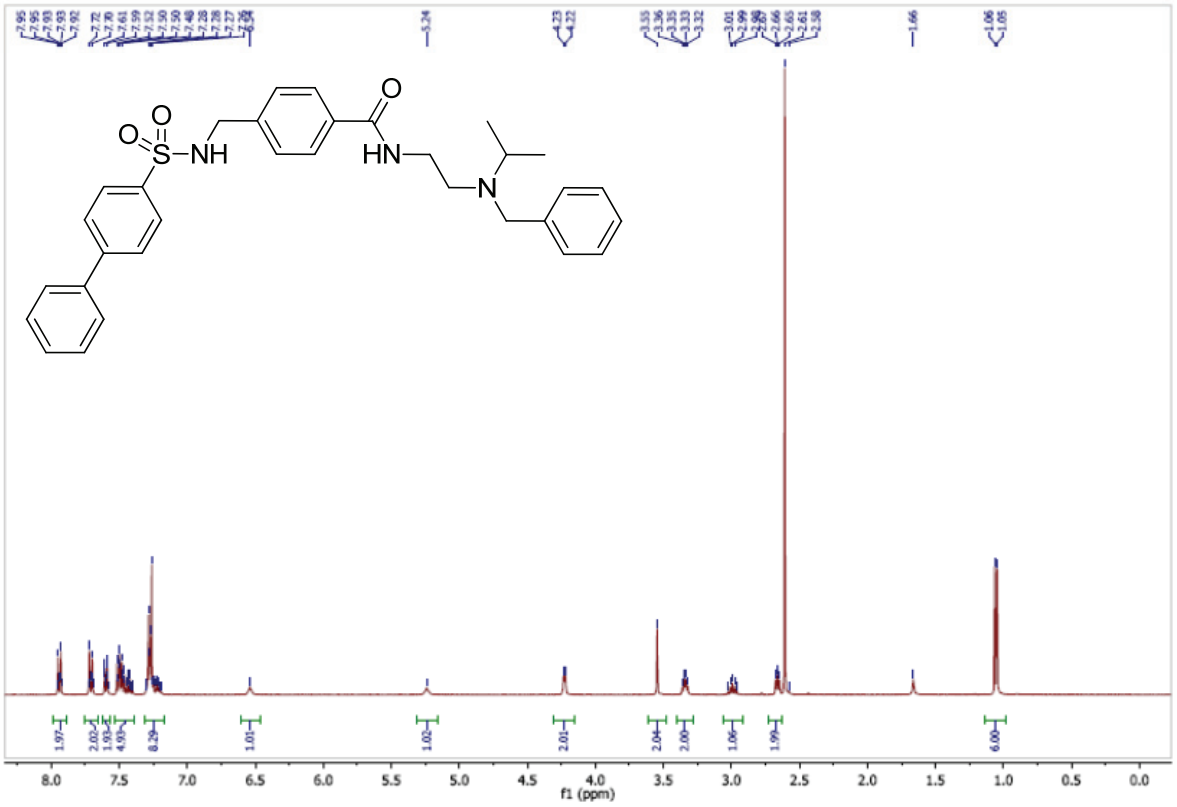

f1 (ppm)

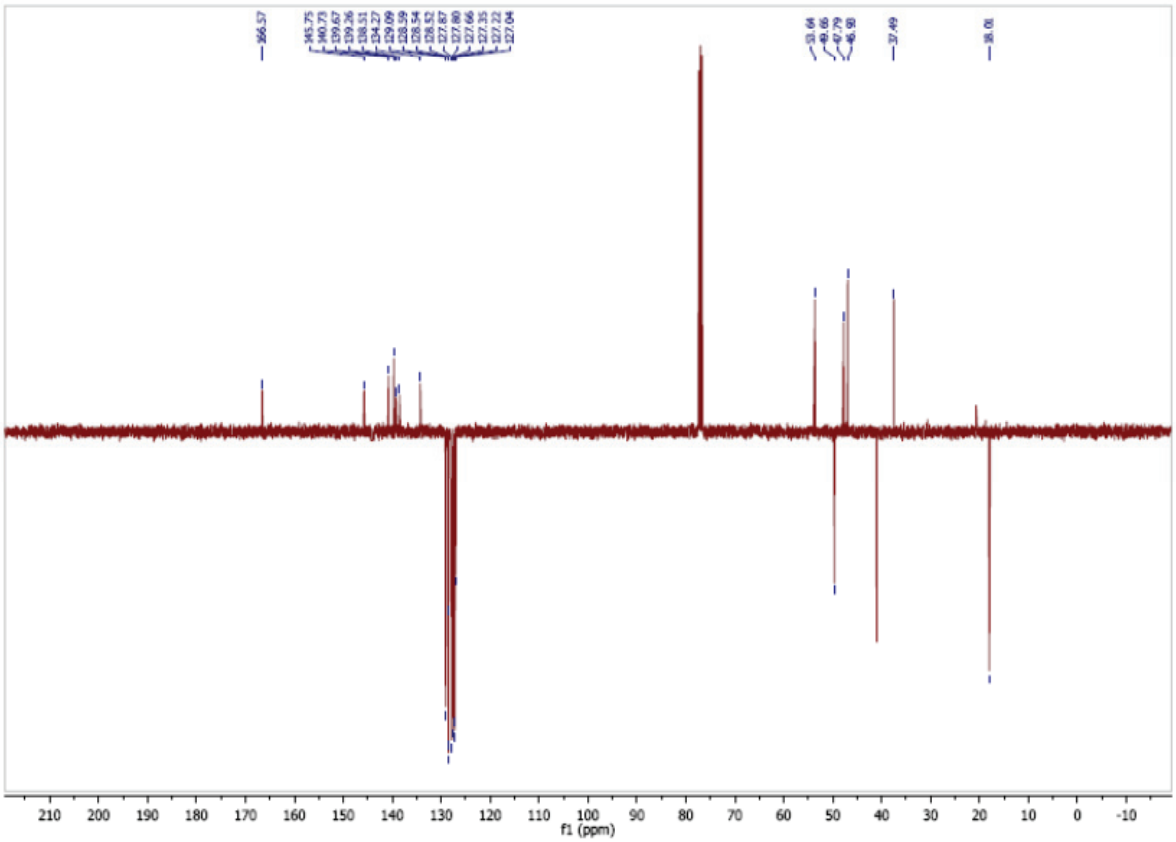

O
O
S
NH
HN
O
N
f1 (ppm)

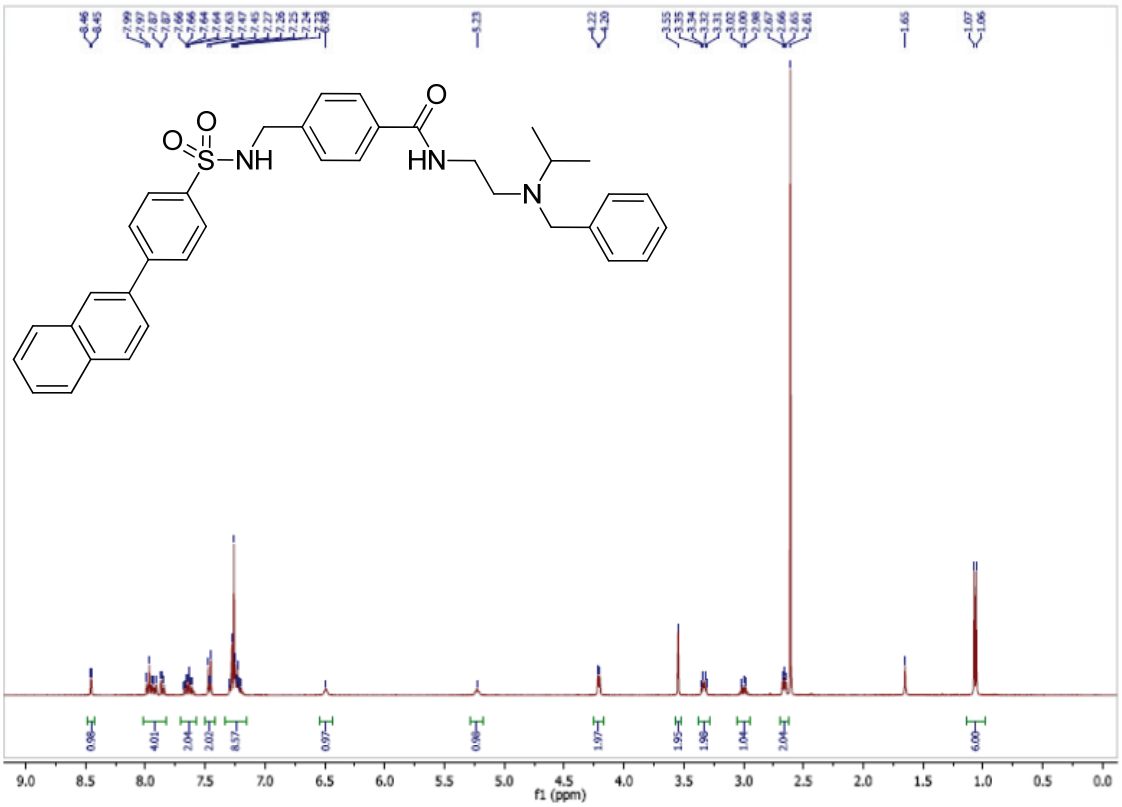

f1 (ppm)

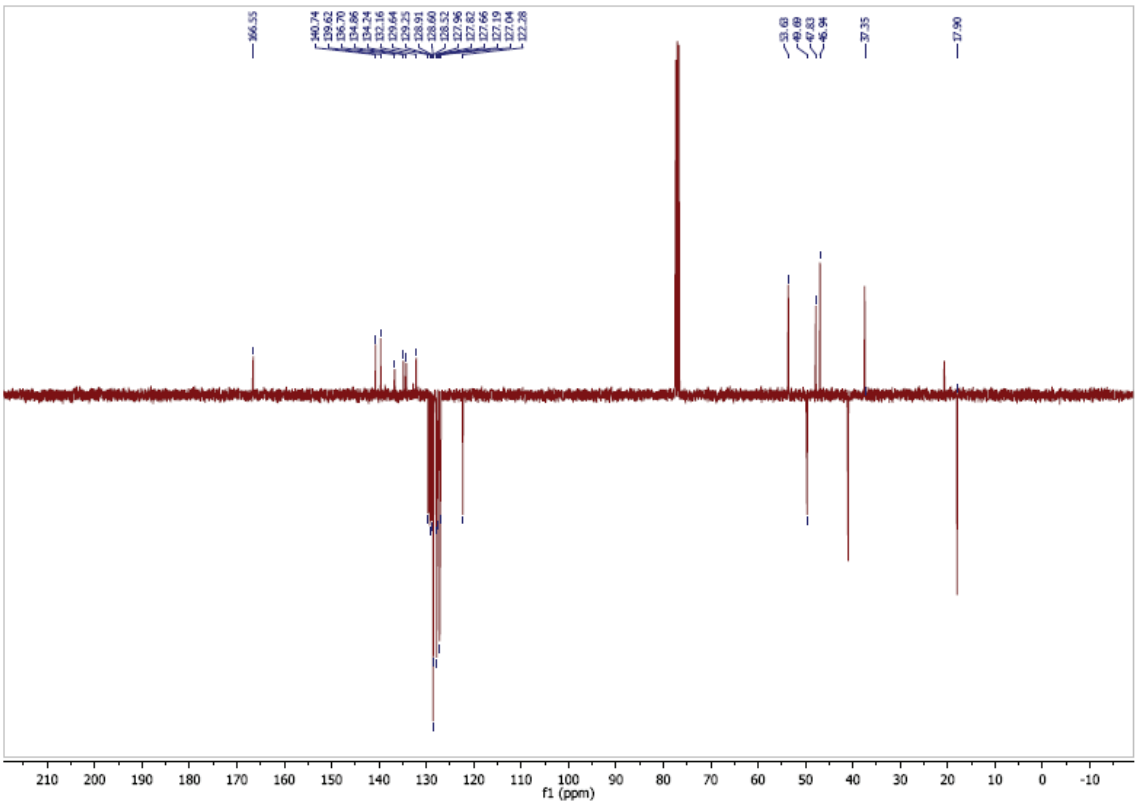

O
O
S
NH
HN
O
N
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

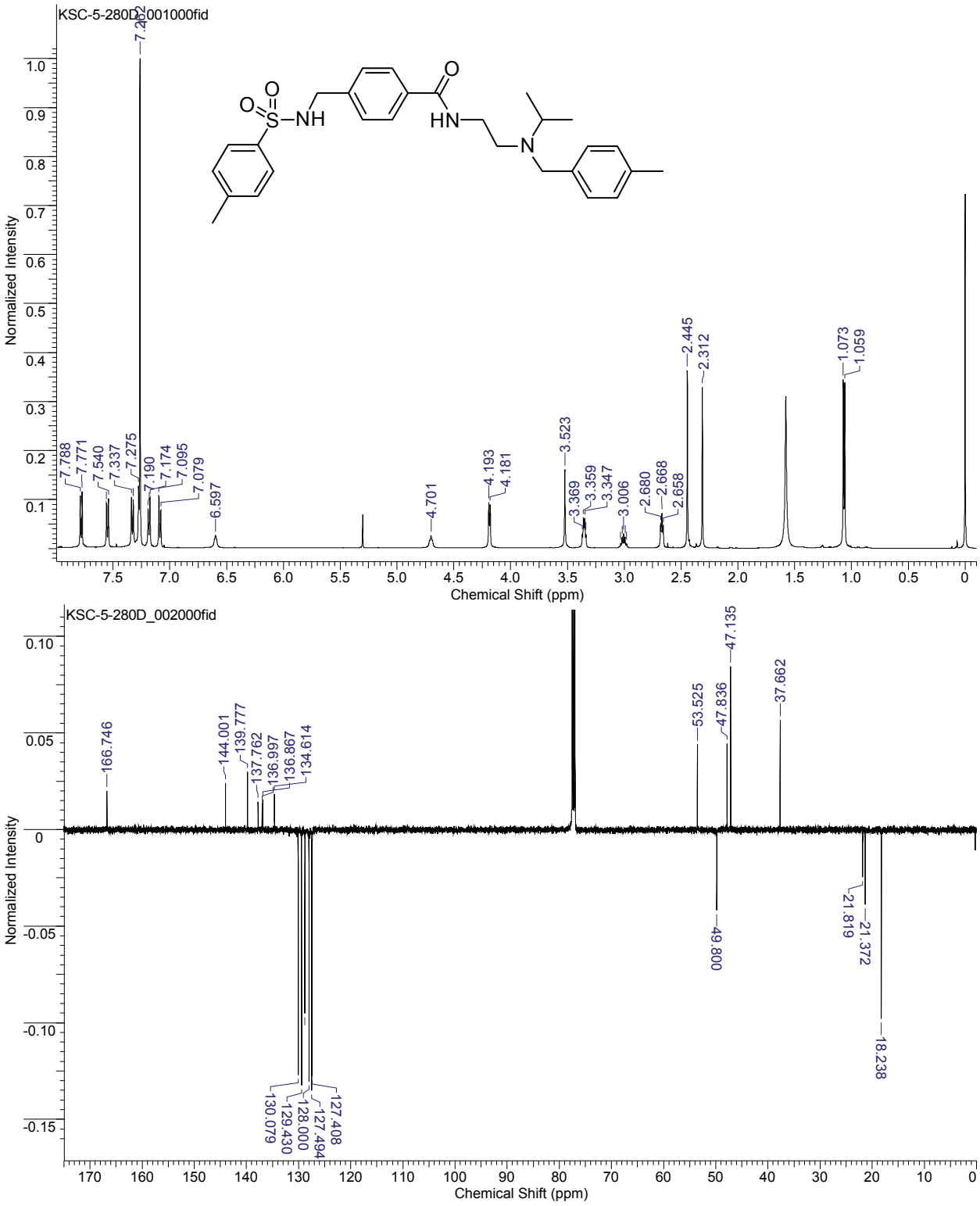

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

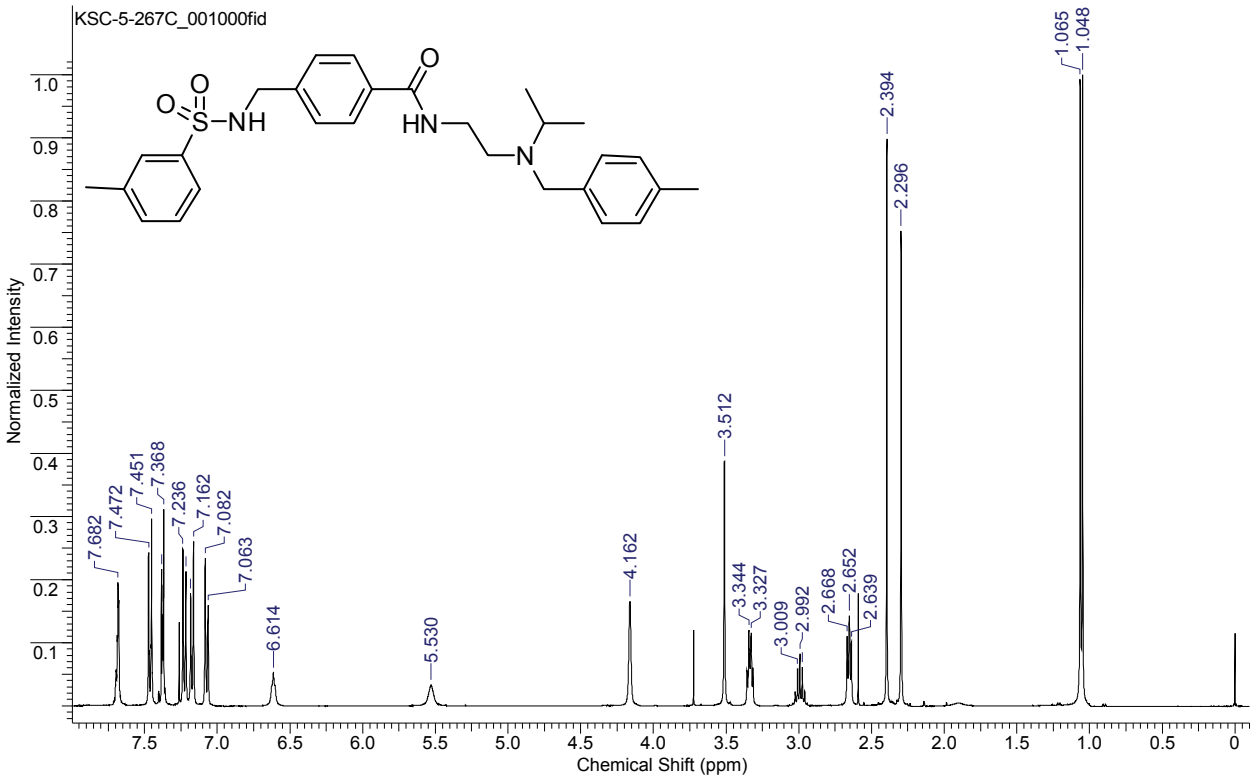

O
O
S
NH
HN
N
f1 (ppm)

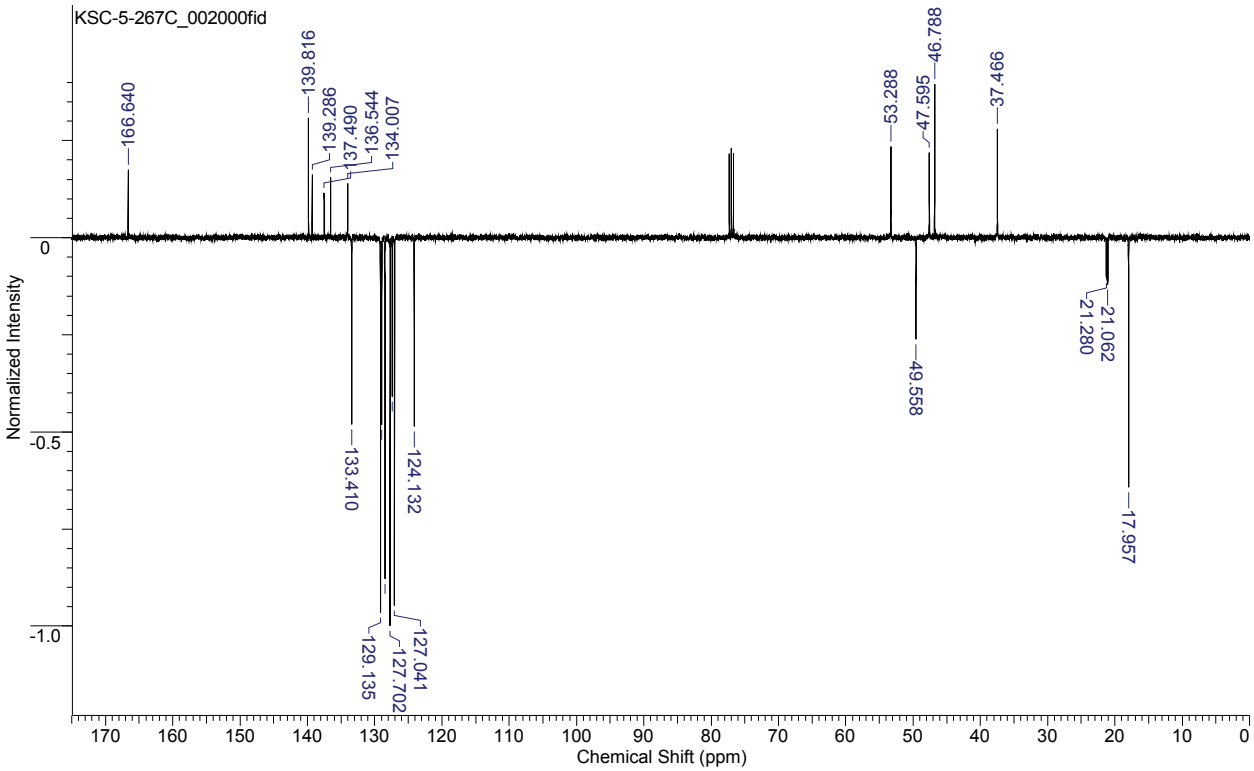

f1 (ppm)

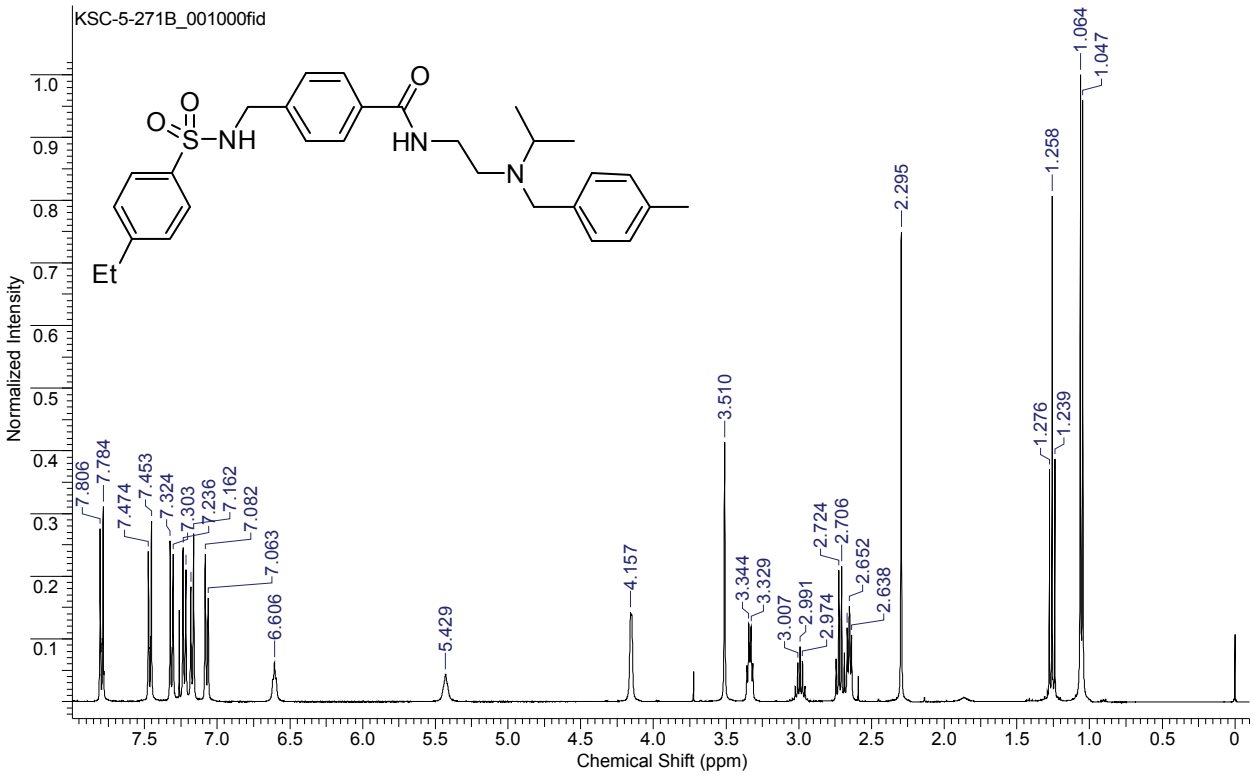

O
O
S
NH
HN
O
N
f1 (ppm)

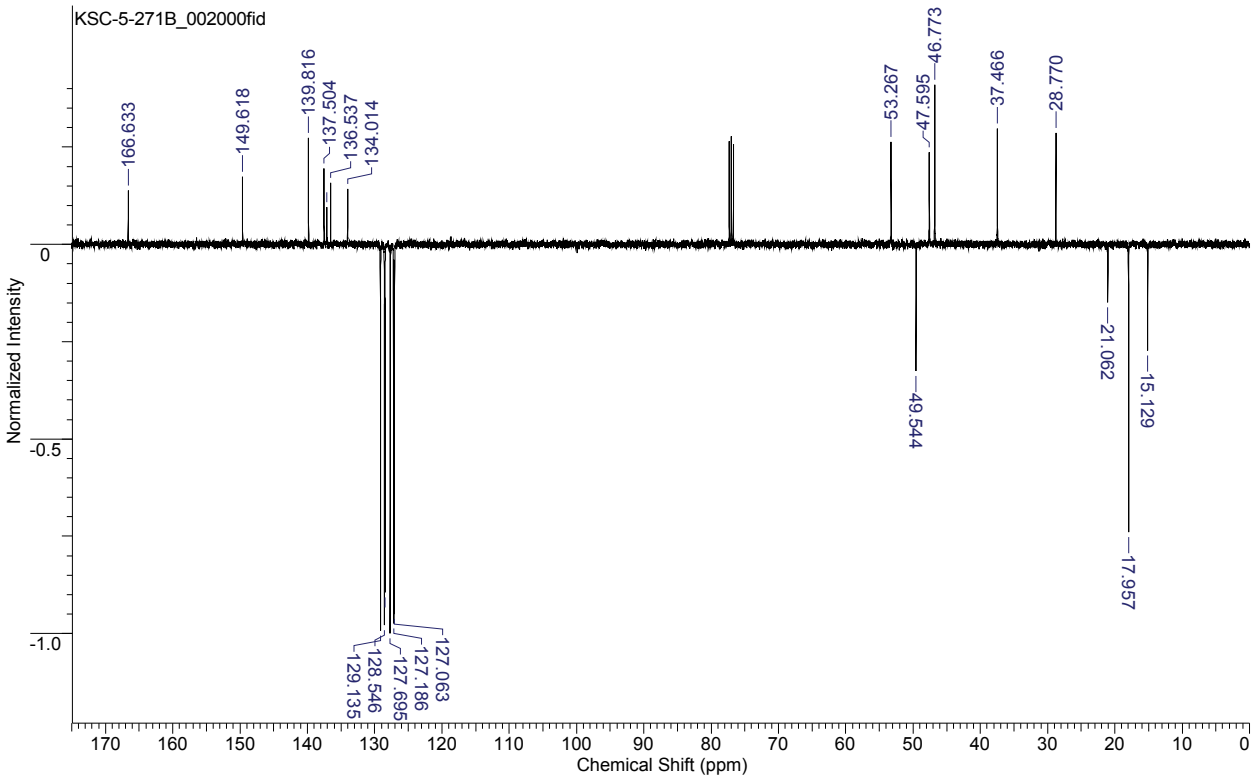

f1 (ppm)

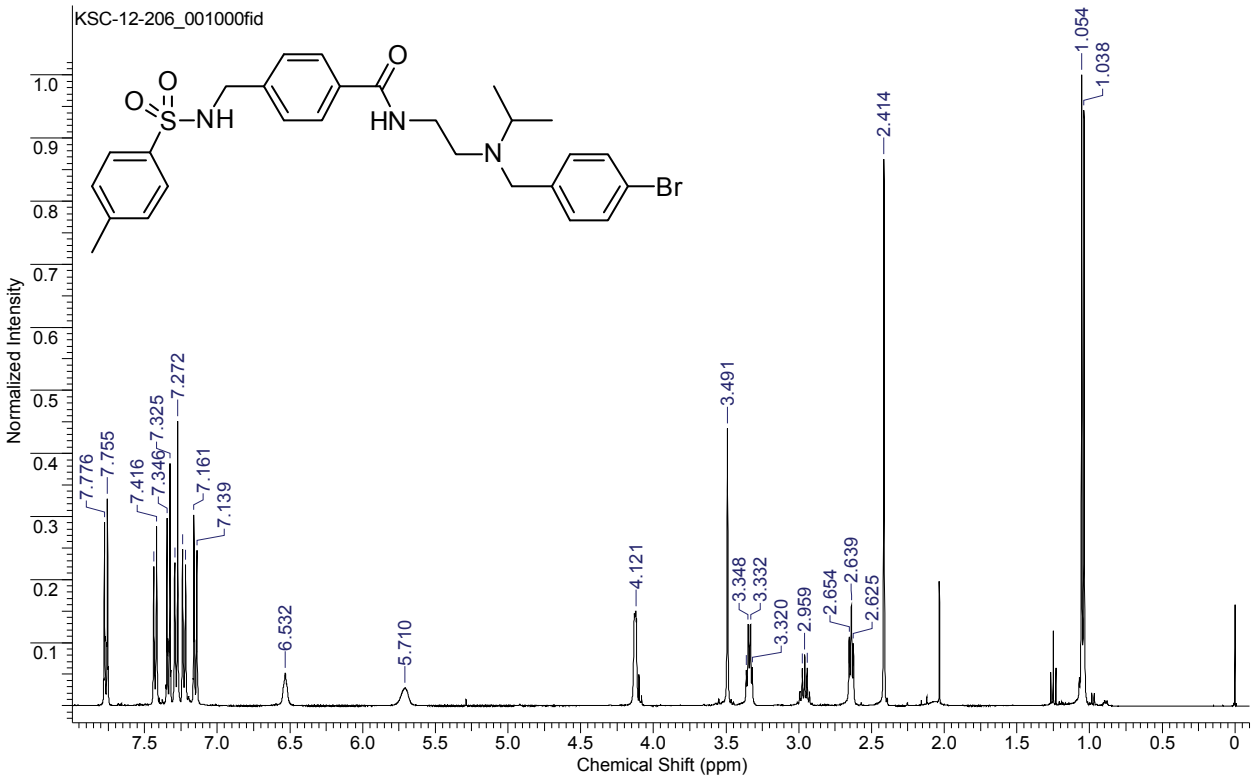

KSC-5-280D_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.260
7.788
7.771
7.540
7.337
7.275
7.190
7.174
7.095
7.079
6.597
4.701
4.193
4.181
3.523
3.369
3.359
3.347
3.006
2.680
2.668
2.658
2.445
2.312
1.073
1.059
KSC-5-280D_002000fid
166.746
144.001
139.777
137.762
136.997
136.867
134.614
130.079
129.430
128.000
127.494
127.408
53.525
47.836
47.135
37.662
49.800
21.819
21.372
18.238

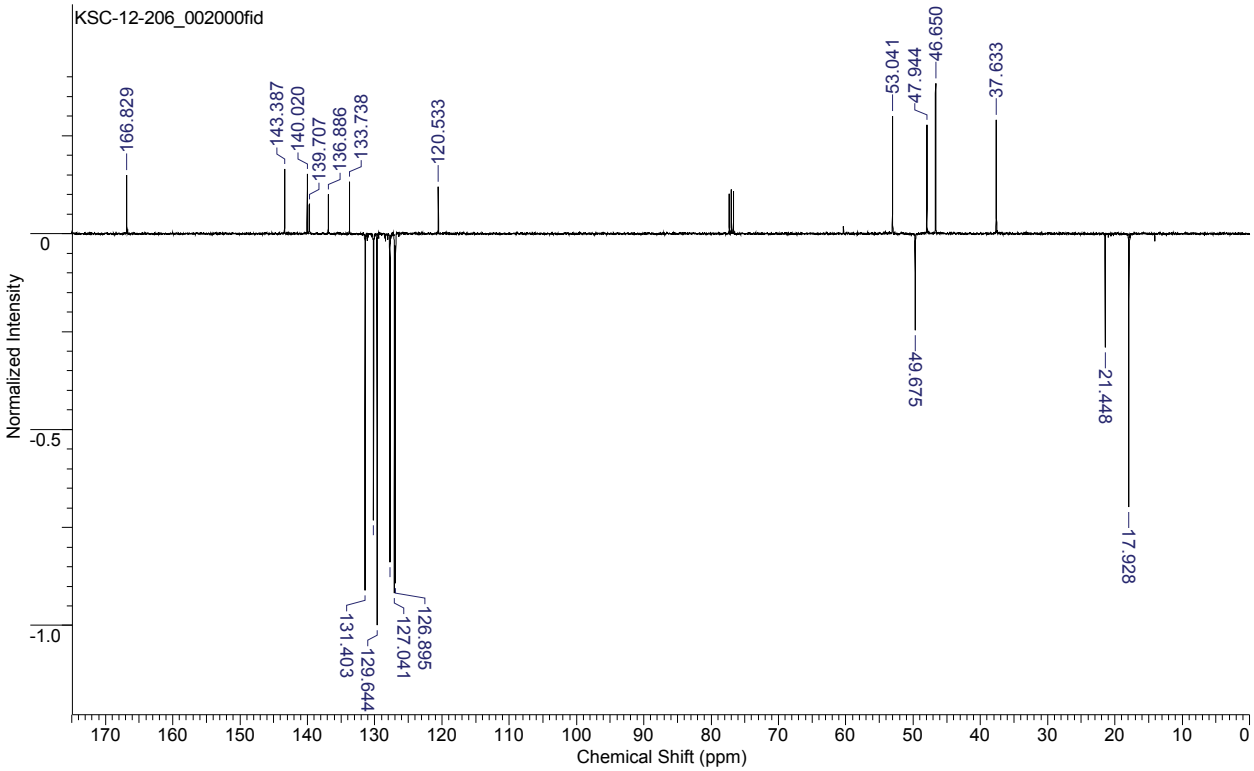

KSC-5-267C_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.682
7.472
7.451
7.368
7.236
7.162
7.082
7.063
6.614
5.530
4.162
3.512
3.344
3.327
3.009
2.992
2.668
2.652
2.639
2.394
2.296
1.065
1.048

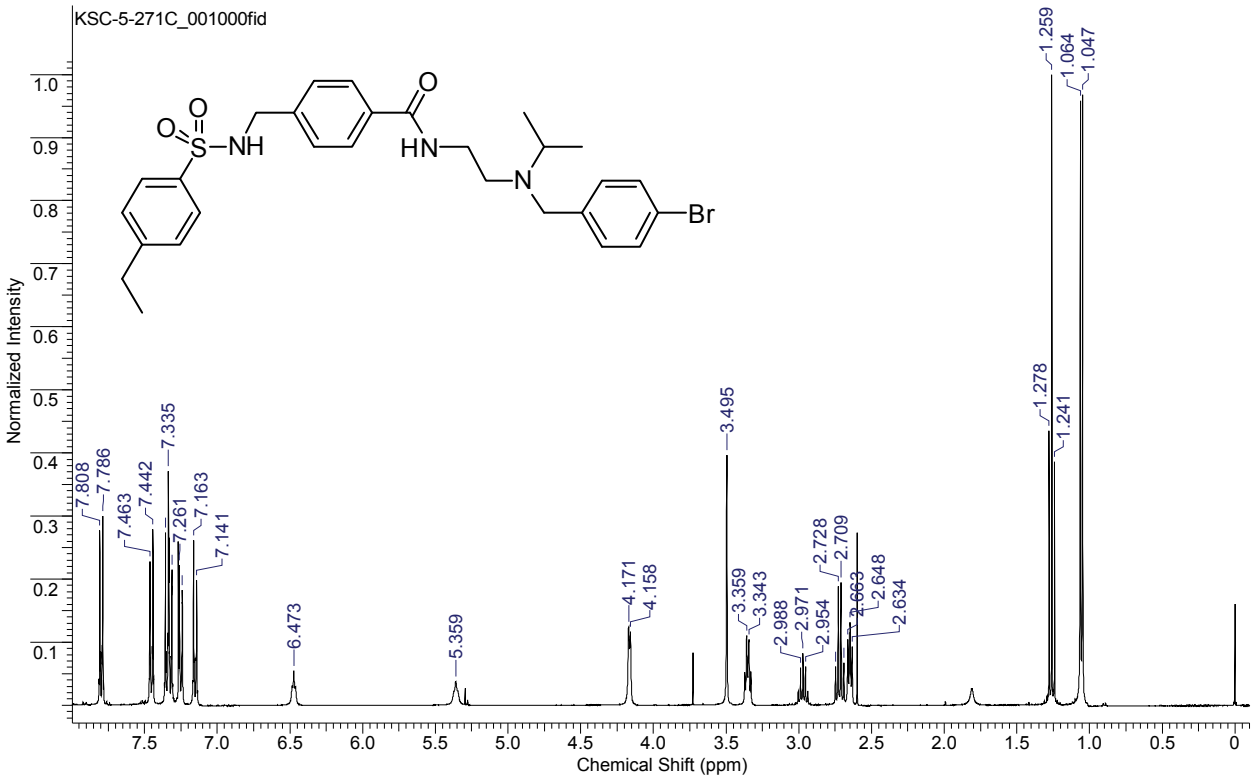

KSC-5-267C_002000fid
Normalized Intensity
Chemical Shift (ppm)
166.640
139.816
139.286
137.490
136.544
134.007
133.410
129.135
127.702
127.041
124.132
53.288
47.595
46.788
37.466
49.558
21.280
21.062
17.957

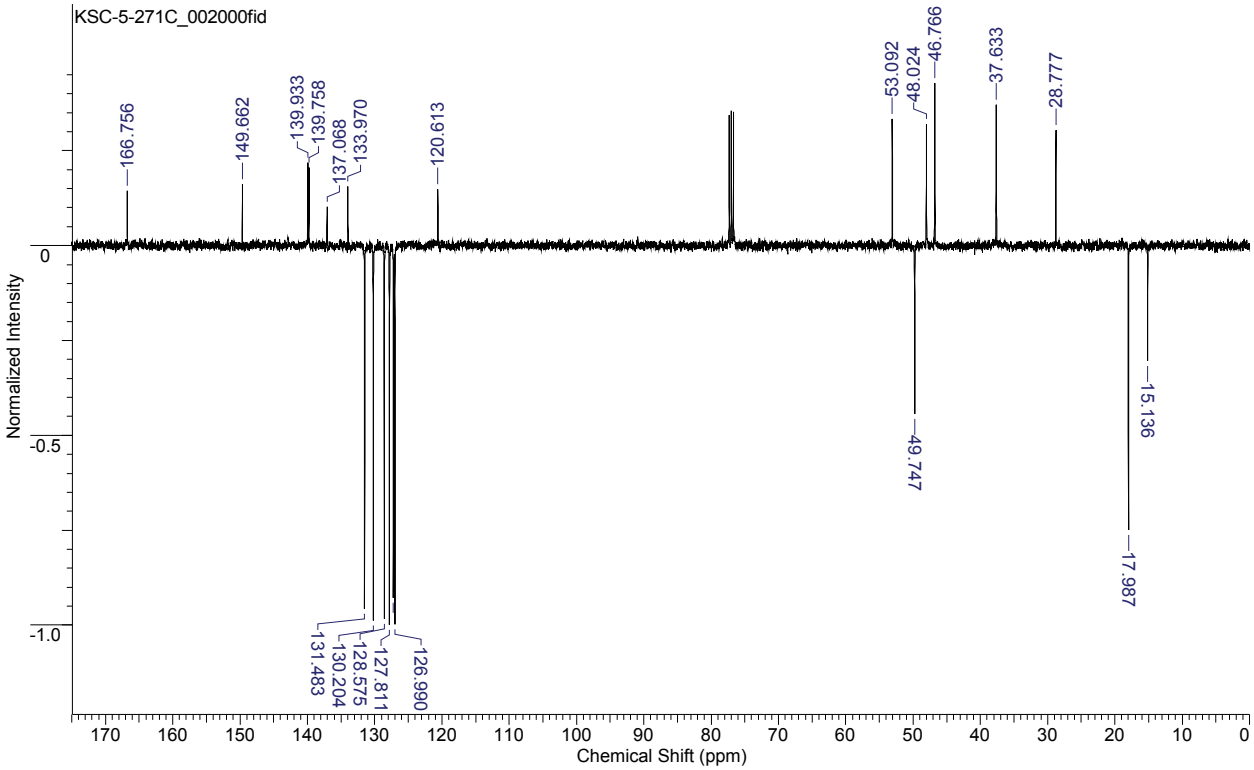

KSC-5-271B_001000fid
Et
Normalized Intensity
Chemical Shift (ppm)
7.806
7.784
7.474
7.453
7.324
7.303
7.236
7.162
7.082
7.063
6.606
5.429
4.157
3.510
3.344
3.329
3.007
2.991
2.974
2.724
2.706
2.652
2.638
2.295
1.276
1.258
1.239
1.064
1.047

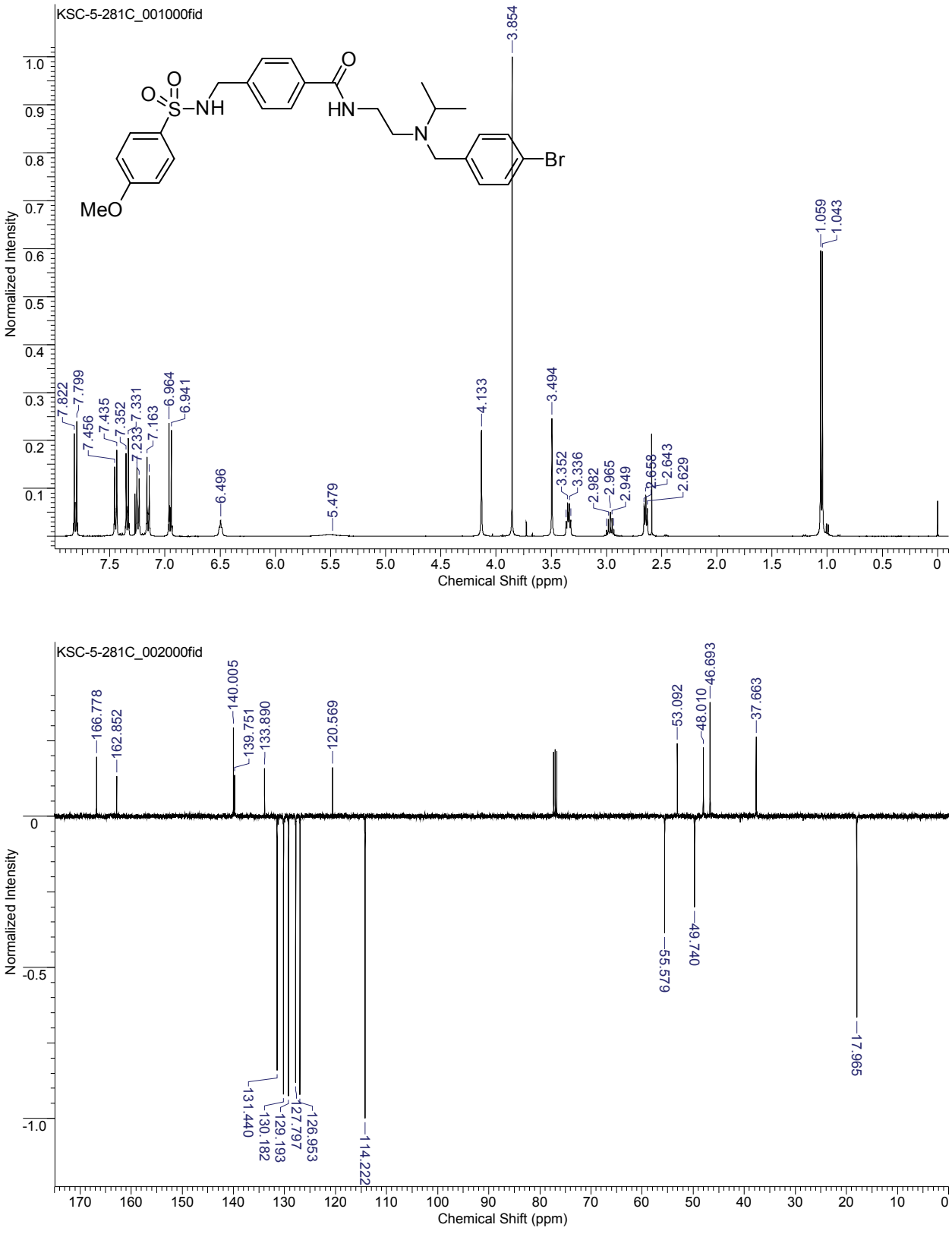

KSC-5-271B_002000fid
Normalized Intensity
Chemical Shift (ppm)
166.633
149.618
139.816
137.504
136.537
134.014
129.135
128.546
127.695
127.186
127.063
53.267
47.595
46.773
37.466
28.770
49.544
21.092
17.957
15.129

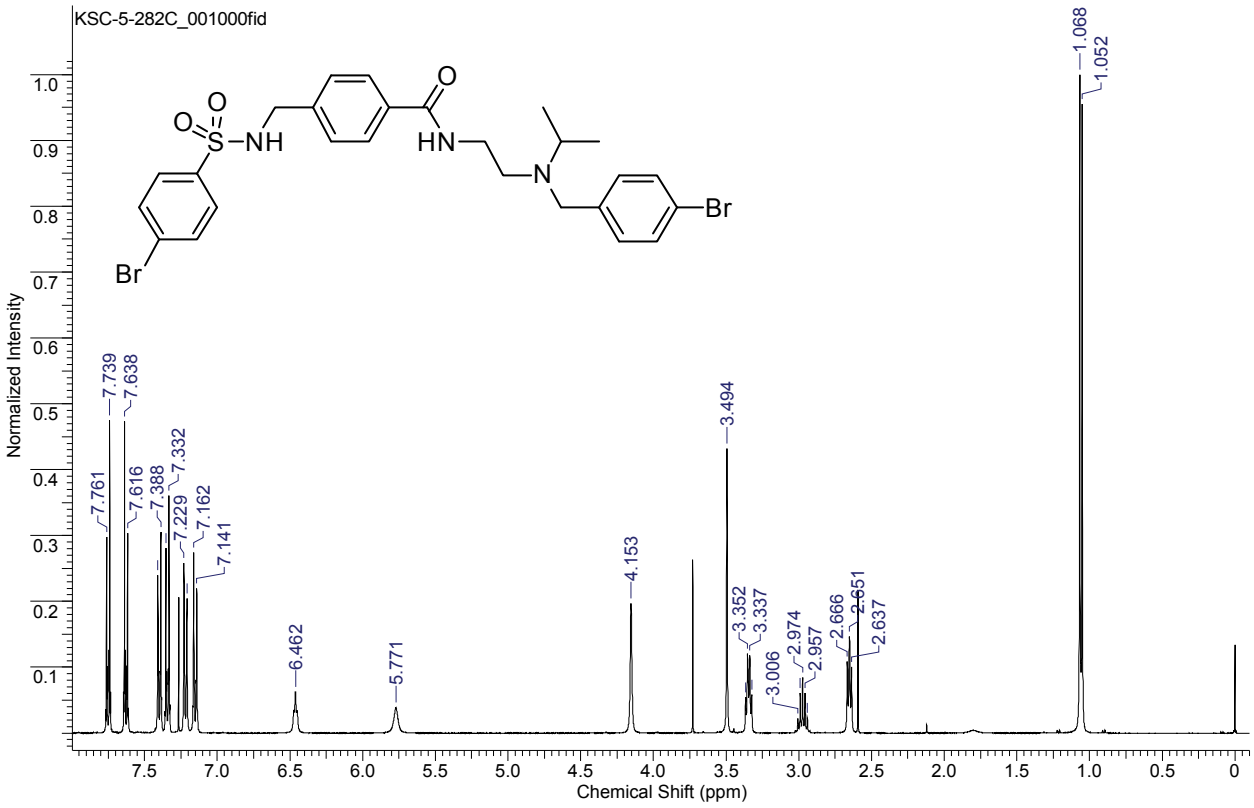

KSC-12-206_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.776
7.755
7.416
7.346
7.325
7.272
7.161
7.139
6.532
5.710
4.121
3.491
3.348
3.332
3.320
2.959
2.654
2.639
2.625
2.414
1.054
1.038
Br

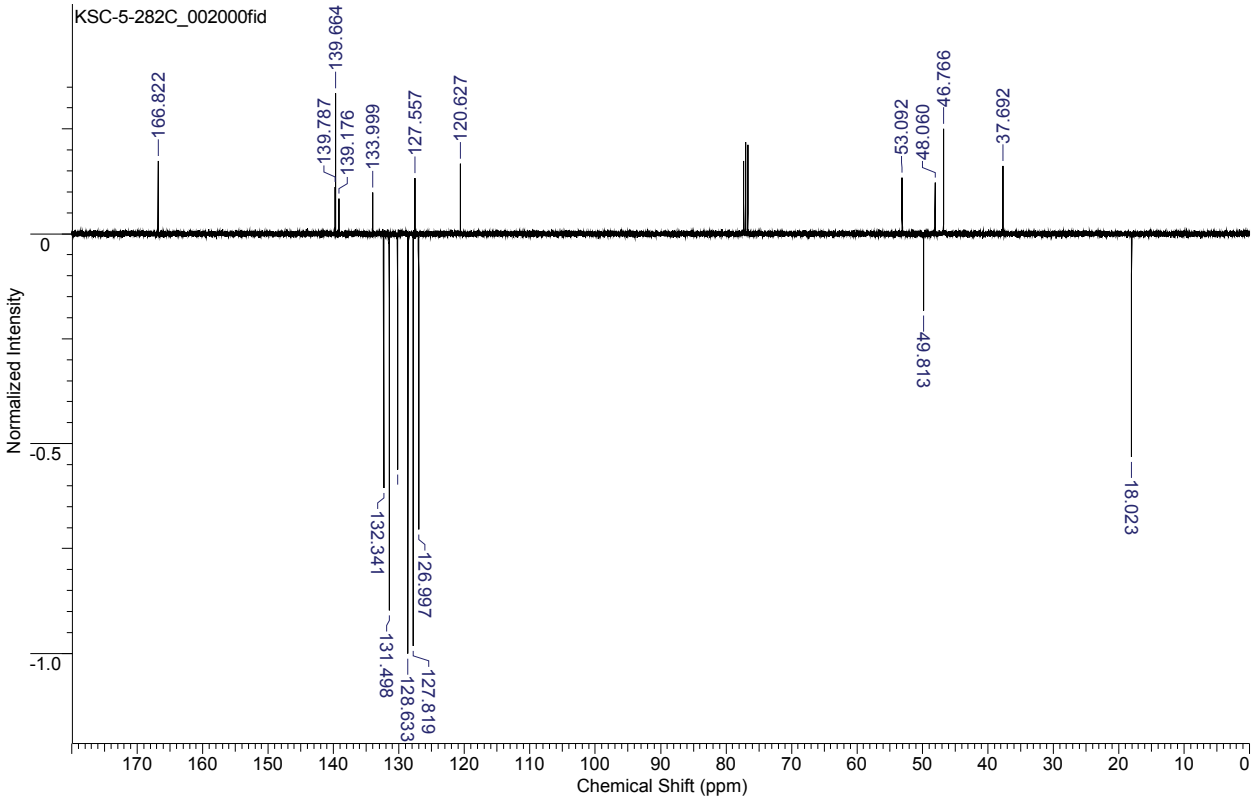

KSC-12-206_002000fid
Normalized Intensity
Chemical Shift (ppm)
166.829
143.387
140.020
139.707
136.886
133.738
120.533
53.041
47.944
46.650
37.633
49.675
21.448
17.928
131.403
129.644
127.041
126.895


KSC-5-271C_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.808
7.786
7.463
7.442
7.335
7.261
7.163
7.141
6.473
5.359
4.171
4.158
3.495
3.359
3.343
2.988
2.971
2.954
2.728
2.709
2.663
2.648
2.634
1.278
1.259
1.241
1.064
1.047


KSC-5-271C_002000fid
Normalized Intensity
Chemical Shift (ppm)
166.756
149.662
139.933
139.758
137.068
133.970
120.613
53.092
48.024
46.766
37.633
28.777
131.483
130.204
128.575
127.811
126.990
49.747
17.987
15.136


KSC-5-281C_001000fid
KSC-5-281C_002000fid
Normalized Intensity
Chemical Shift (ppm)
MeO
Br
3.854
1.059
1.043
7.822
7.799
7.456
7.435
7.352
7.331
7.233
7.163
6.964
6.941
6.496
5.479
4.133
3.494
3.352
3.336
2.982
2.965
2.949
2.658
2.643
2.629
166.778
162.852
140.005
139.751
133.890
120.569
53.092
48.010
46.693
37.663
131.440
130.182
129.193
127.797
126.953
114.222
55.579
49.740
17.995


KSC-5-282C_001000fid
Normalized Intensity
Chemical Shift (ppm)
7.761
7.739
7.638
7.616
7.388
7.332
7.229
7.162
7.141
6.462
5.771
4.153
3.494
3.352
3.337
3.006
2.974
2.957
2.666
2.651
2.637
1.068
1.052
Br
Br


KSC-5-282C_002000fid
Normalized Intensity
Chemical Shift (ppm)
166.822
139.664
139.787
139.176
133.999
127.557
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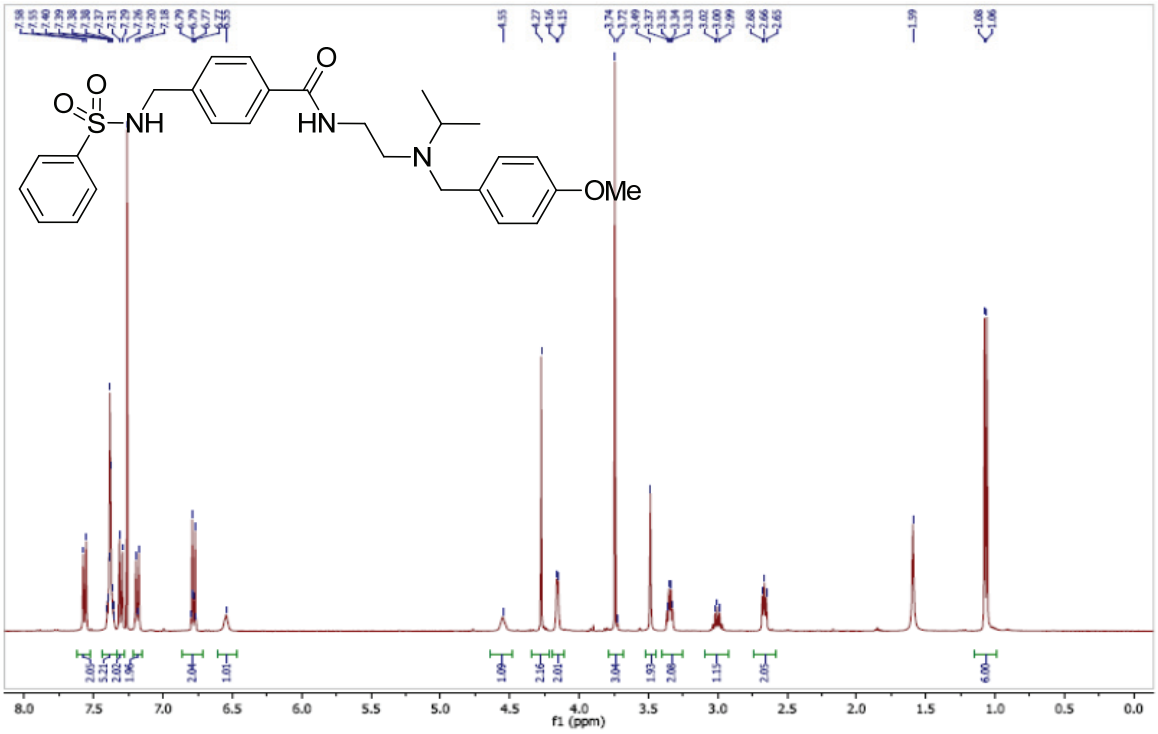
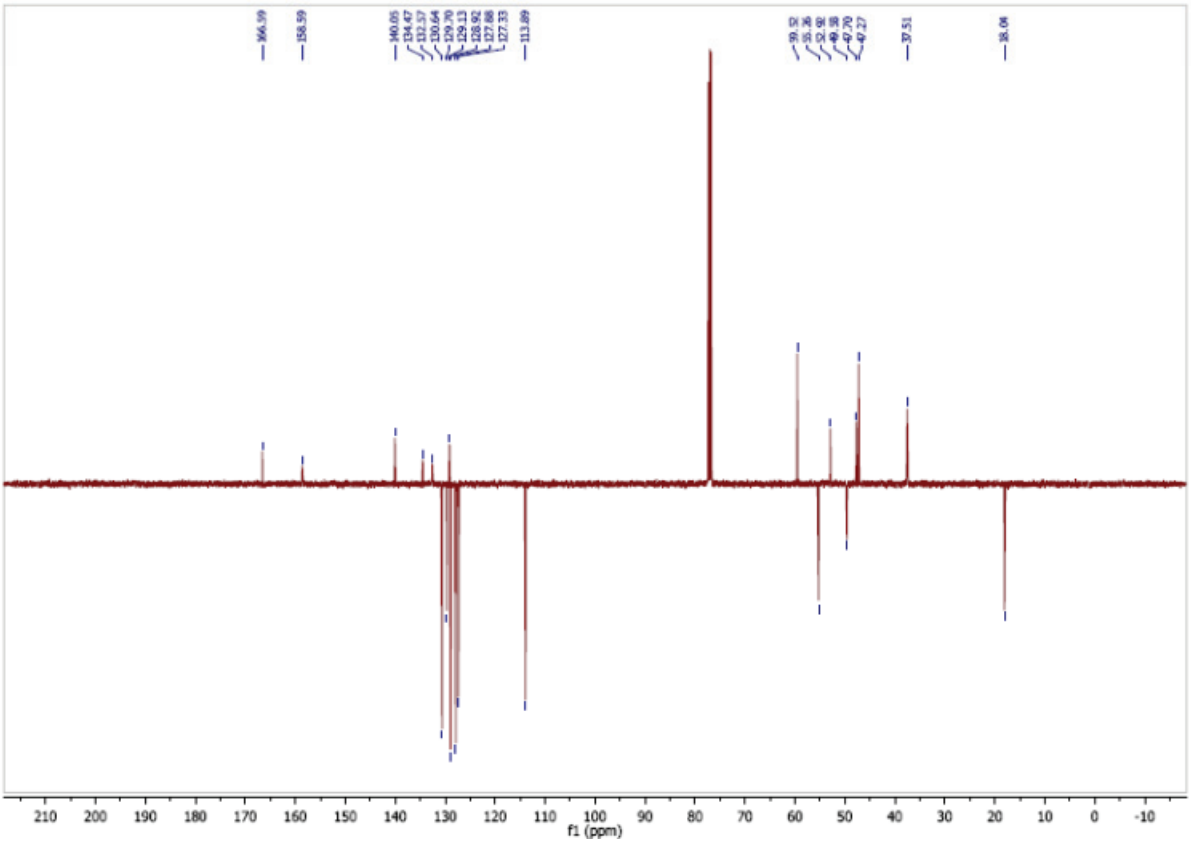
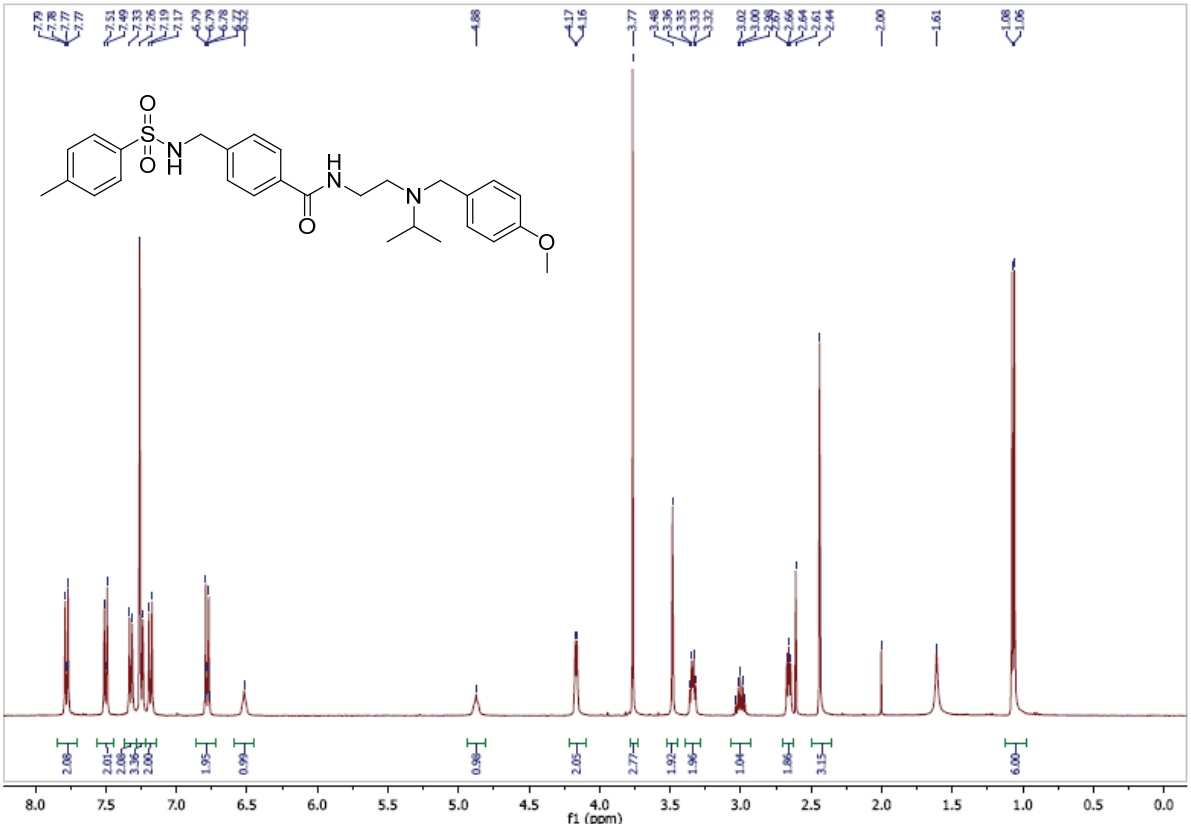
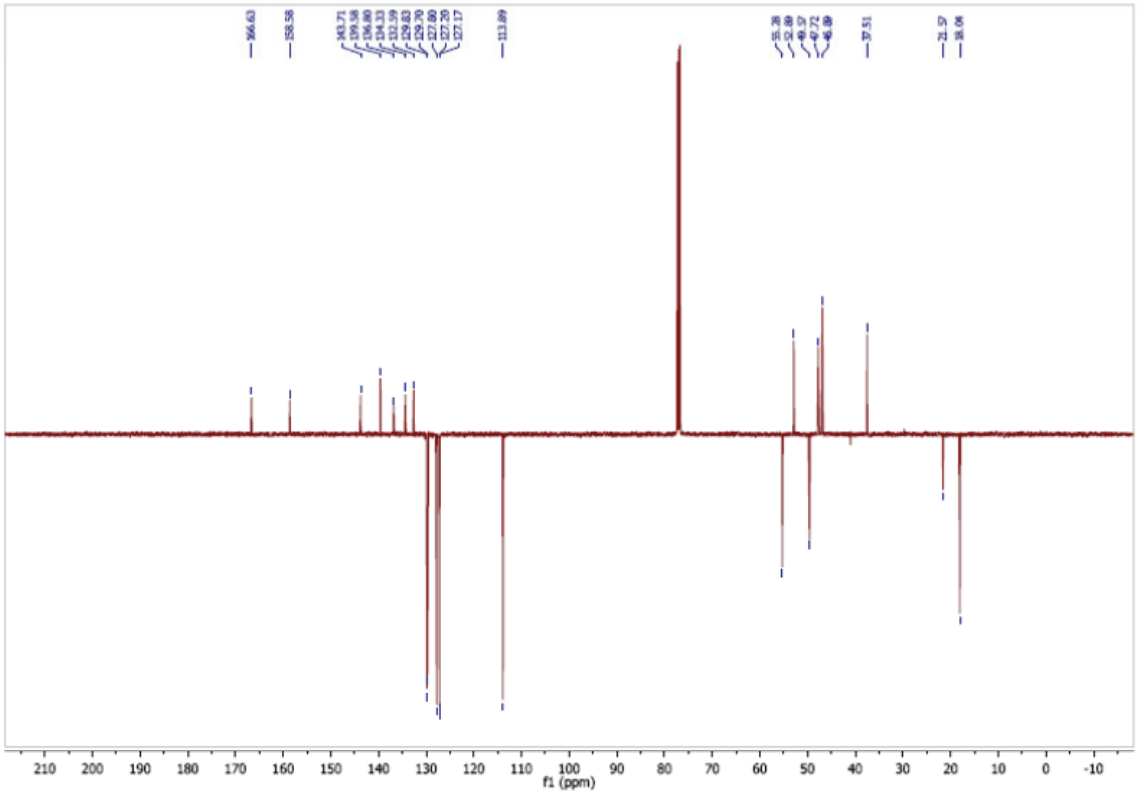
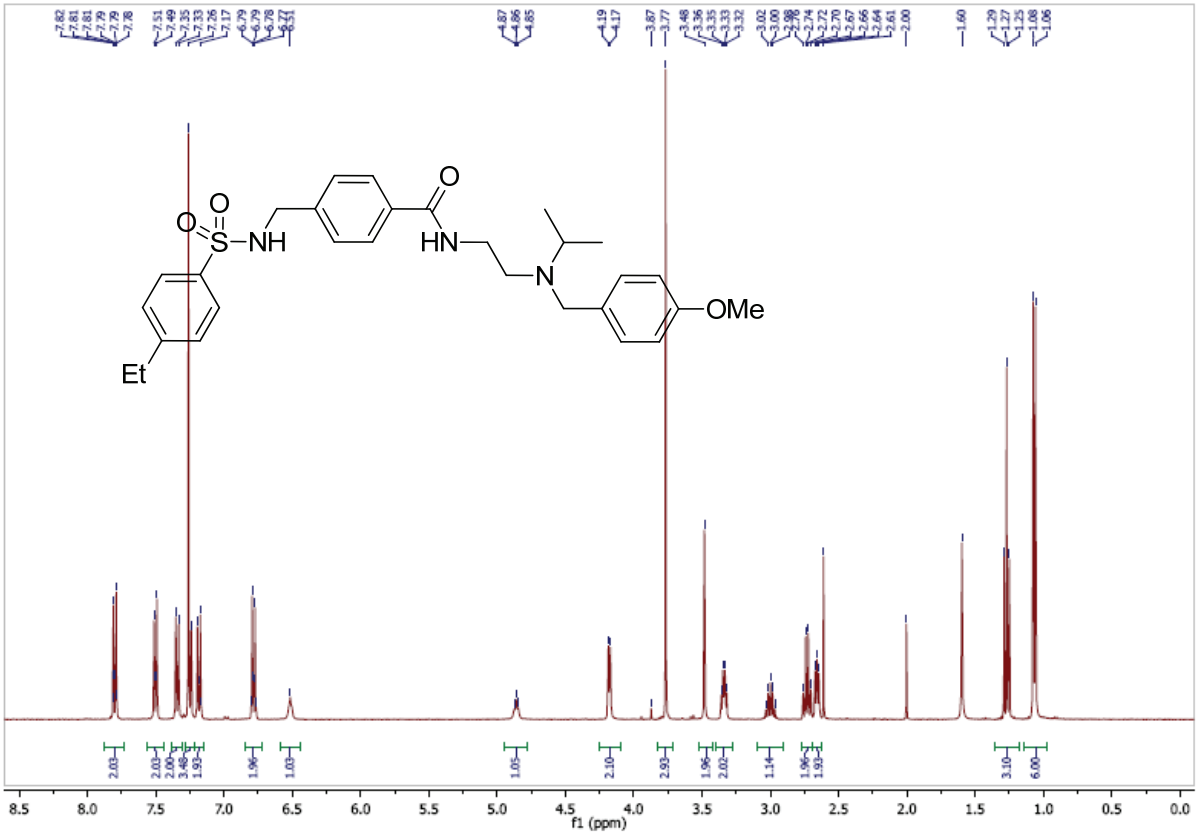
132.341
131.498
128.633
127.819
126.997

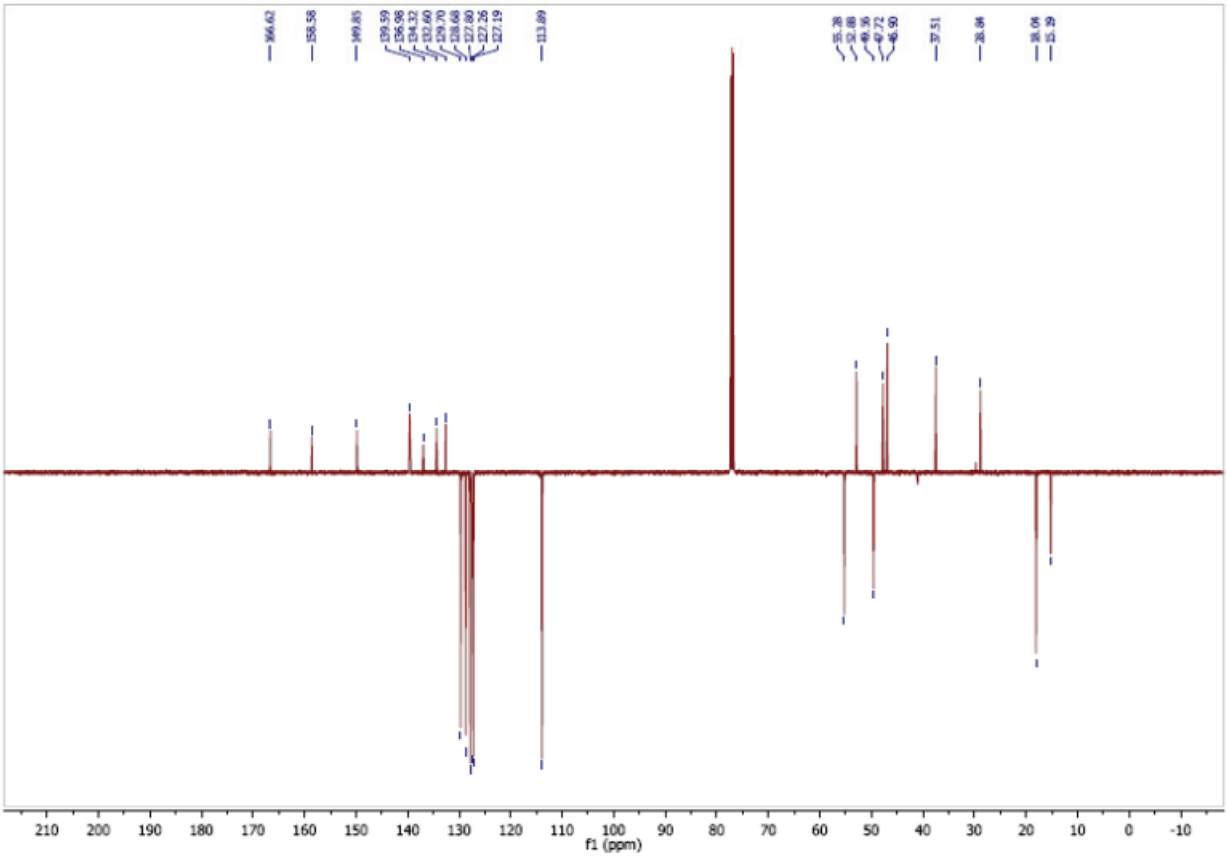

O
O
S
NH
HN
O
N
OMe
f1 (ppm)

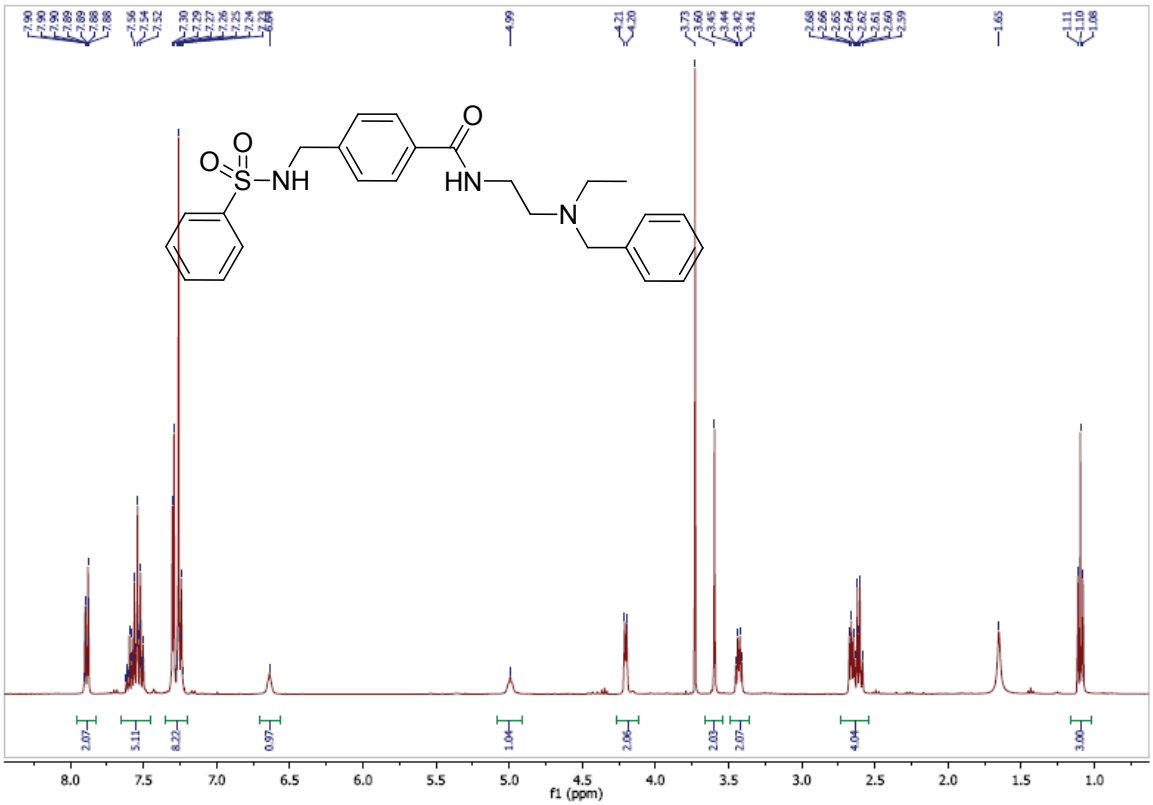

f1 (ppm)

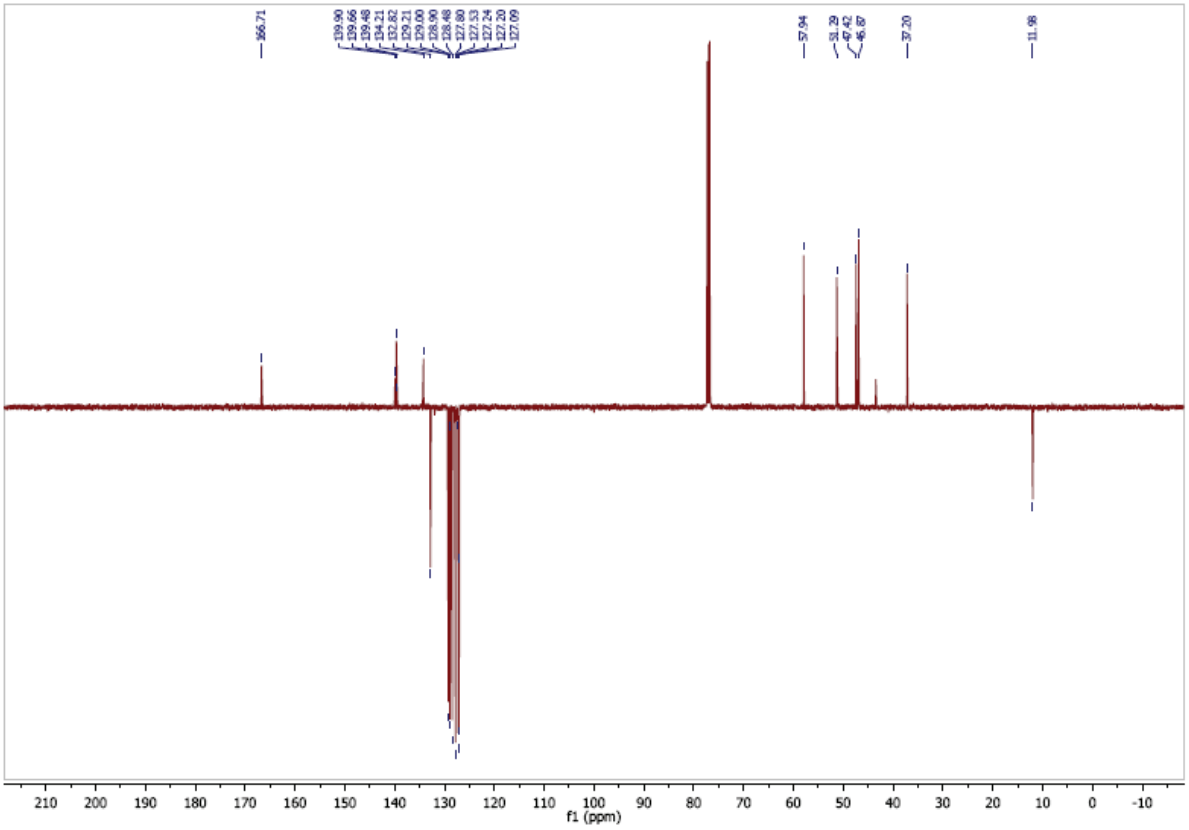

f1 (ppm)

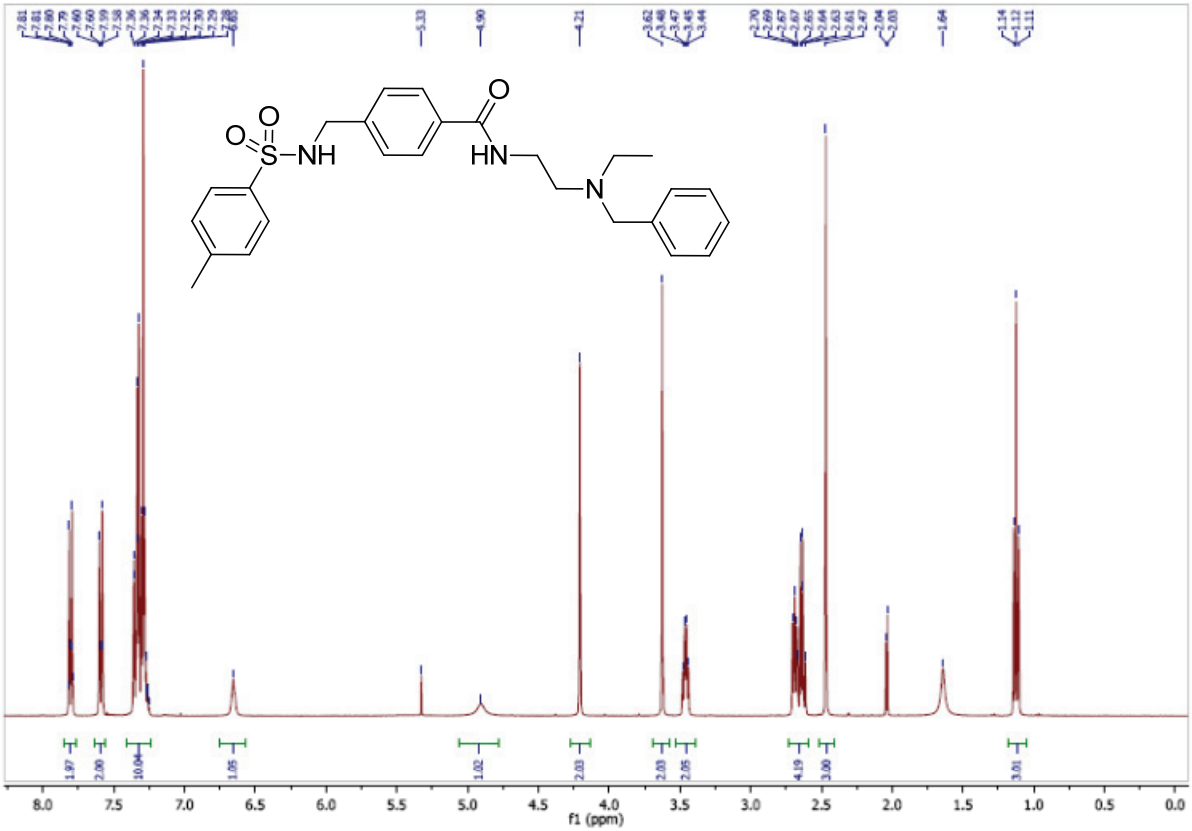

f1 (ppm)

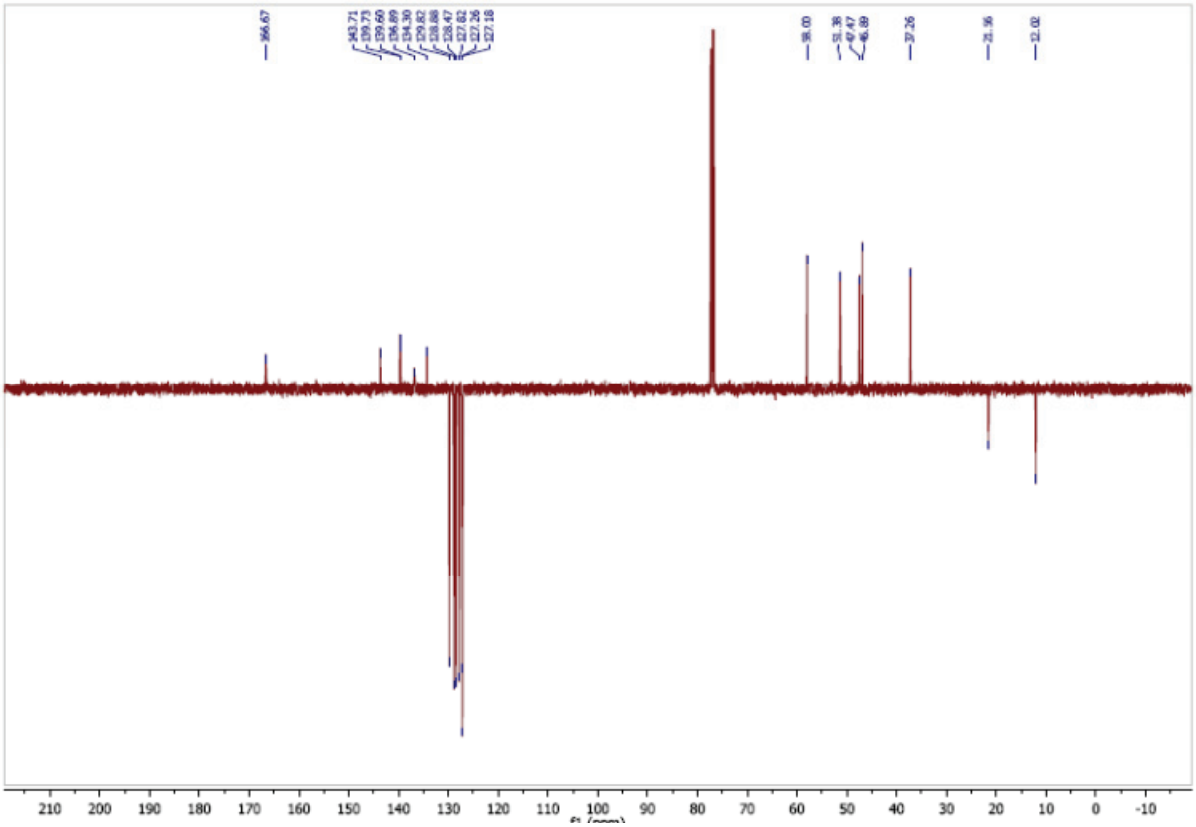

O
O
S
NH
HN
N
OMe
Et
f1 (ppm)

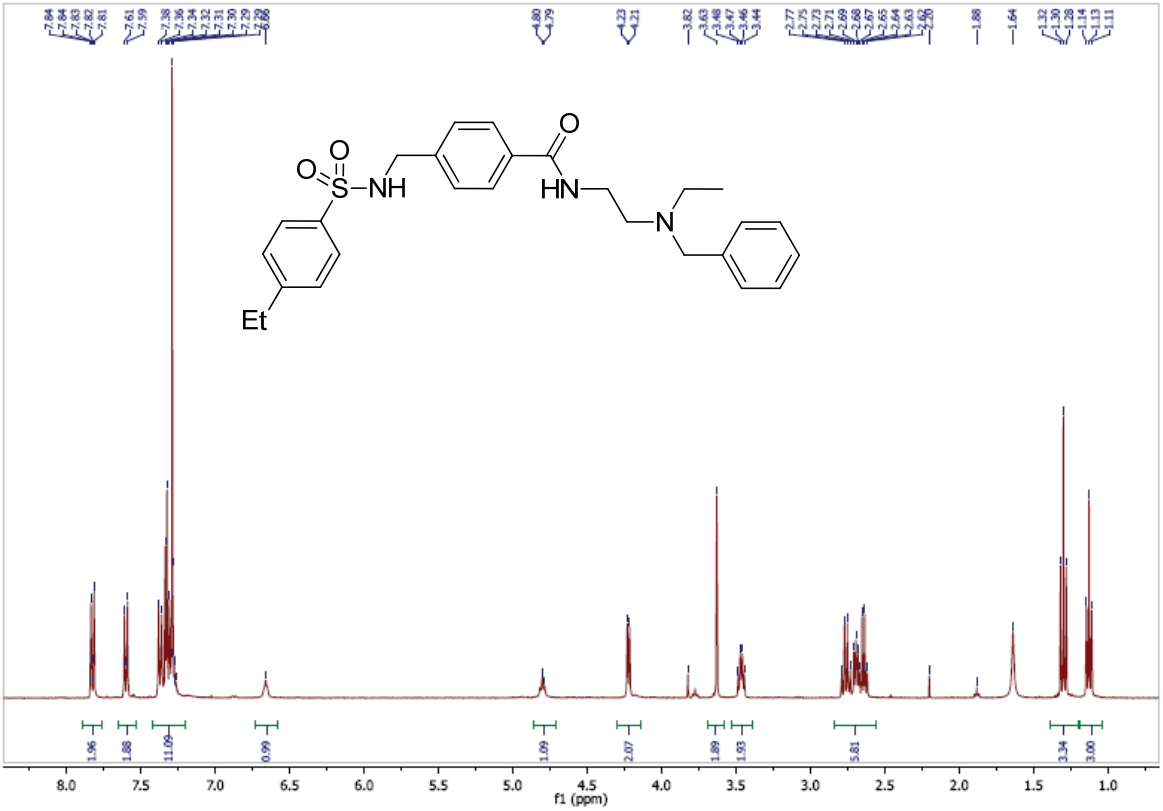

f1 (ppm)

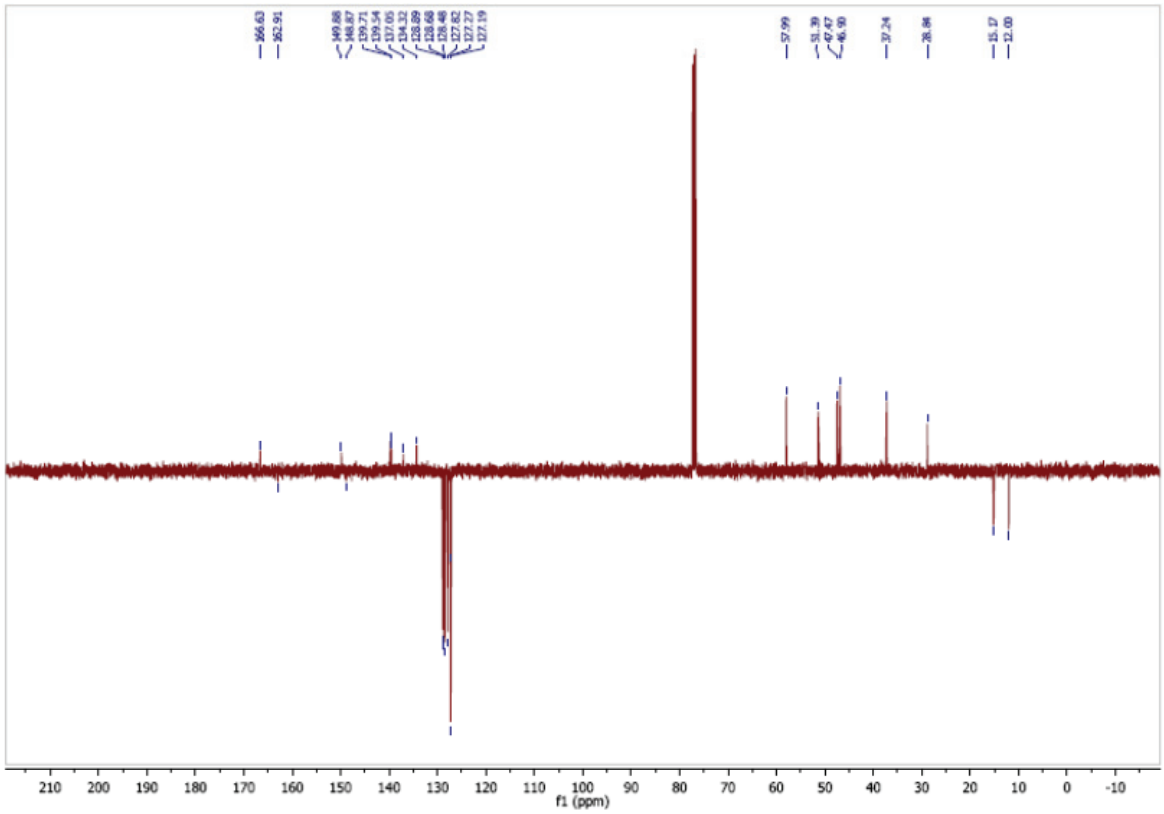

O
O
S
NH
HN
N
f1 (ppm)

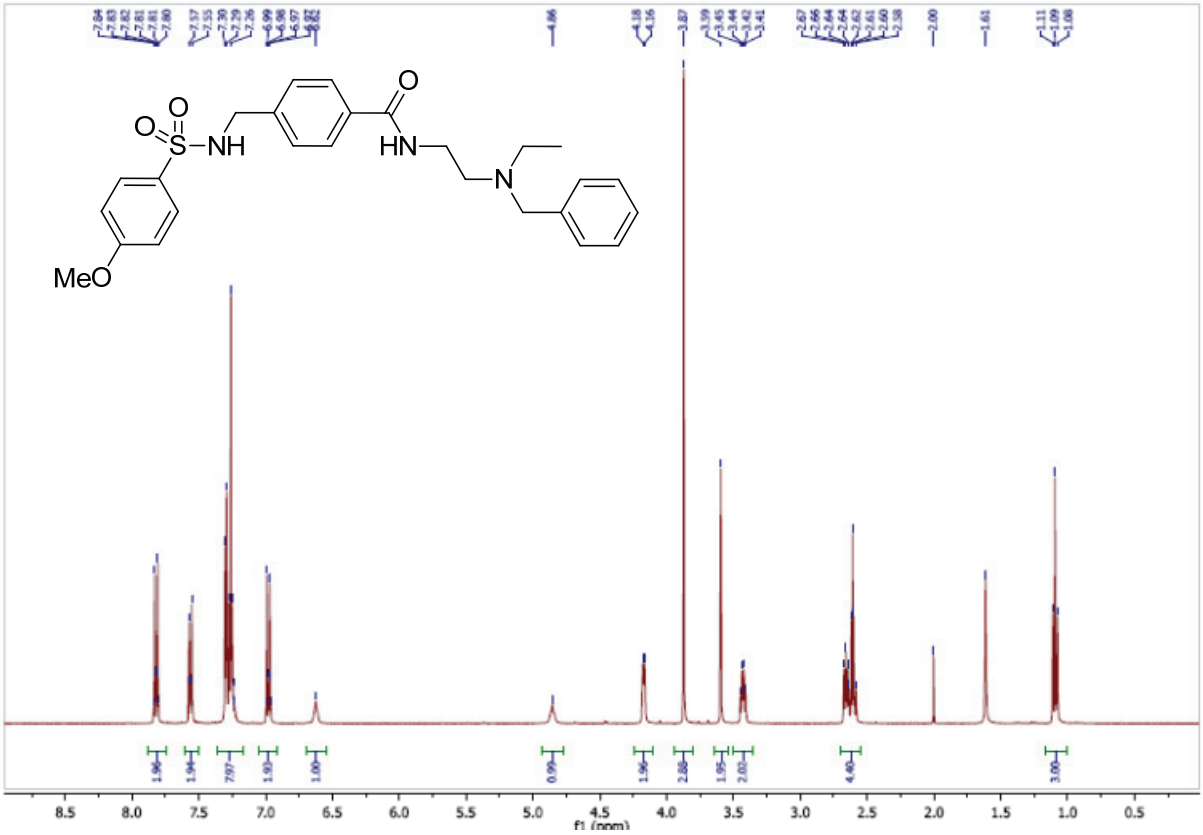

f1 (ppm)

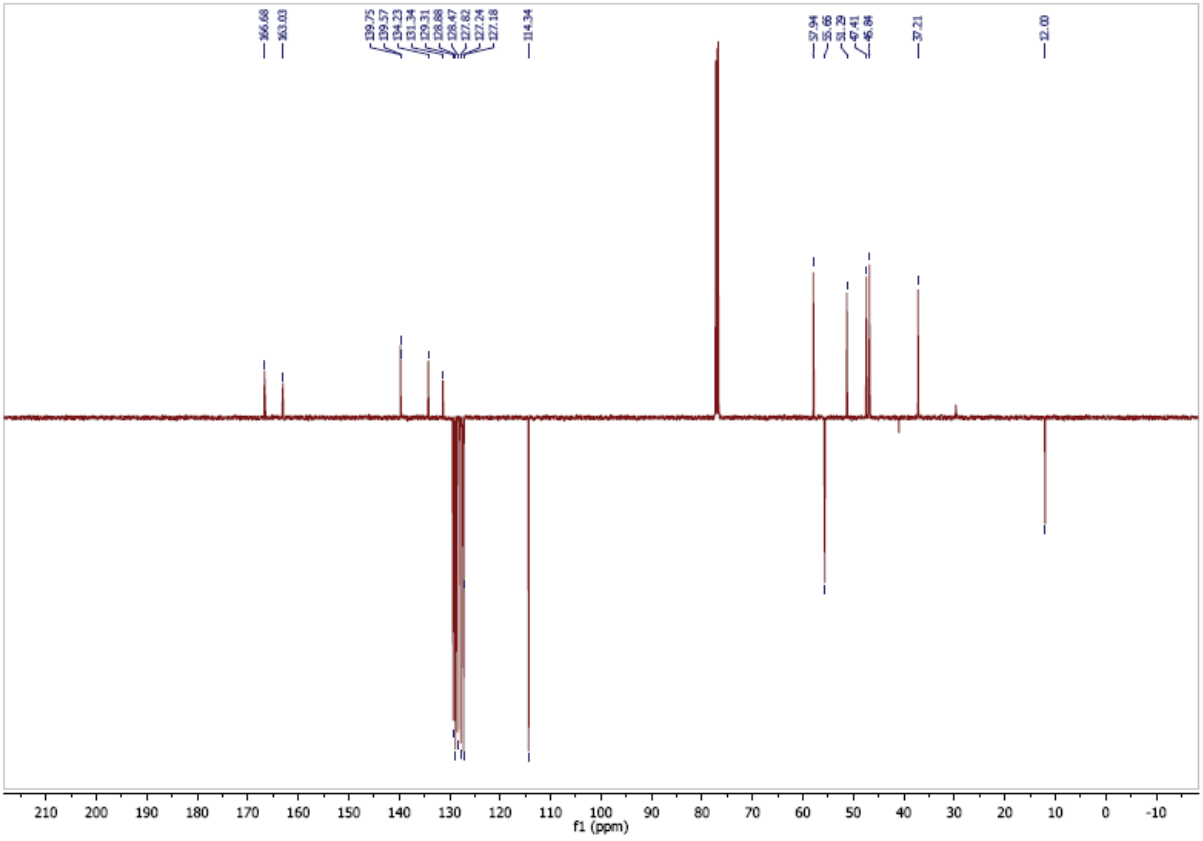

O
O
S
NH
O
HN
N
f1 (ppm)

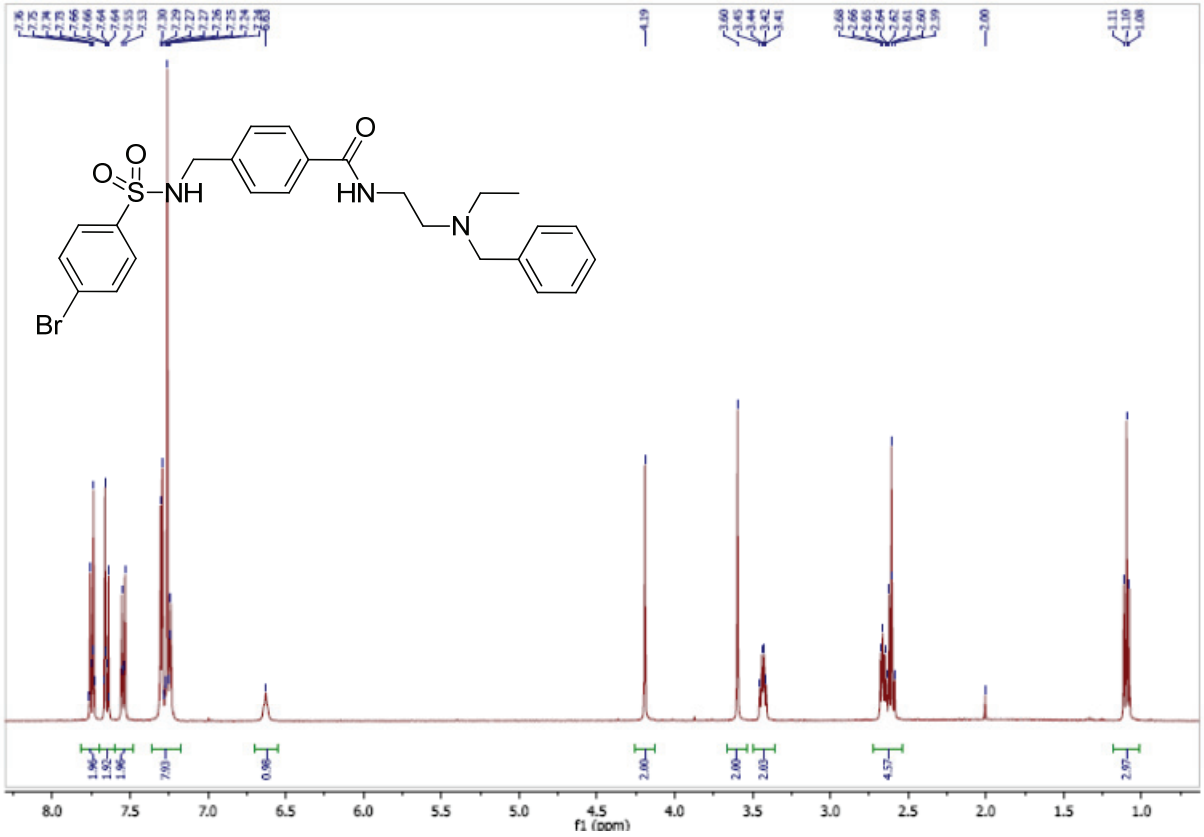


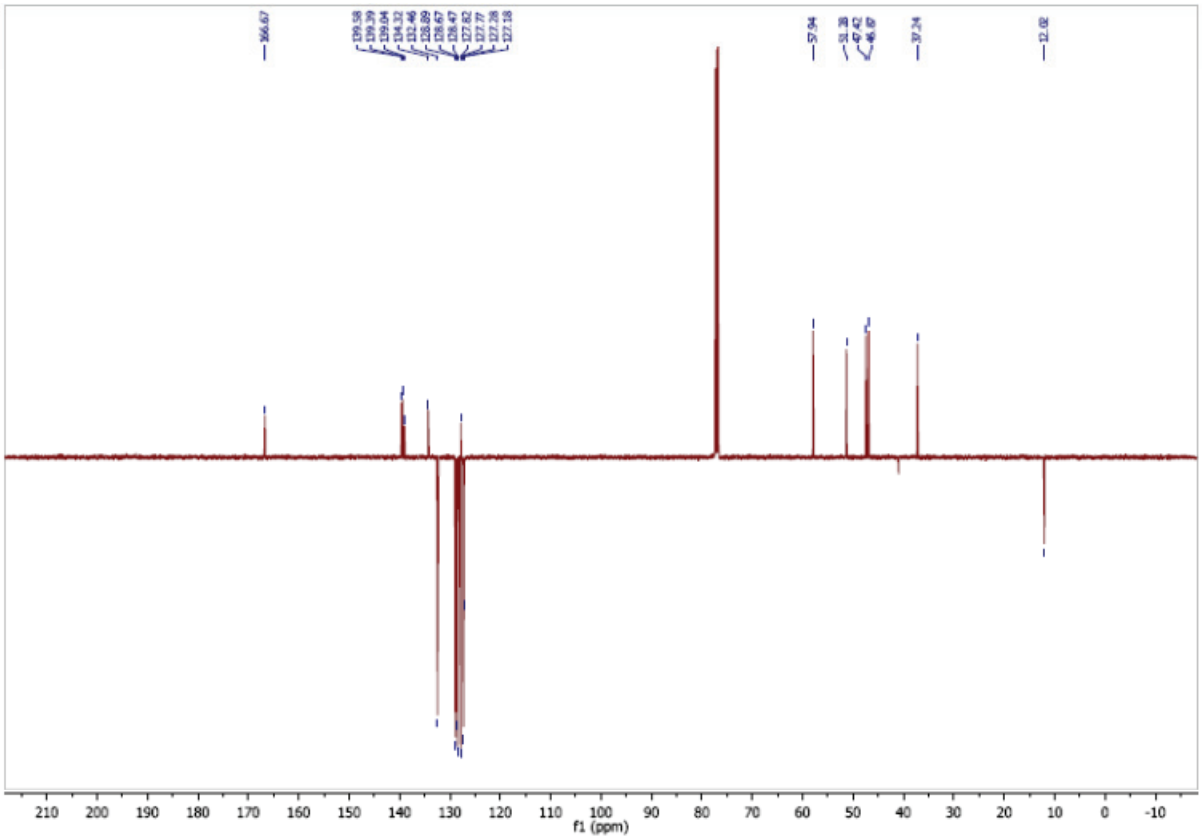

O
O
S
NH
HN
O
N
Et
f1 (ppm)

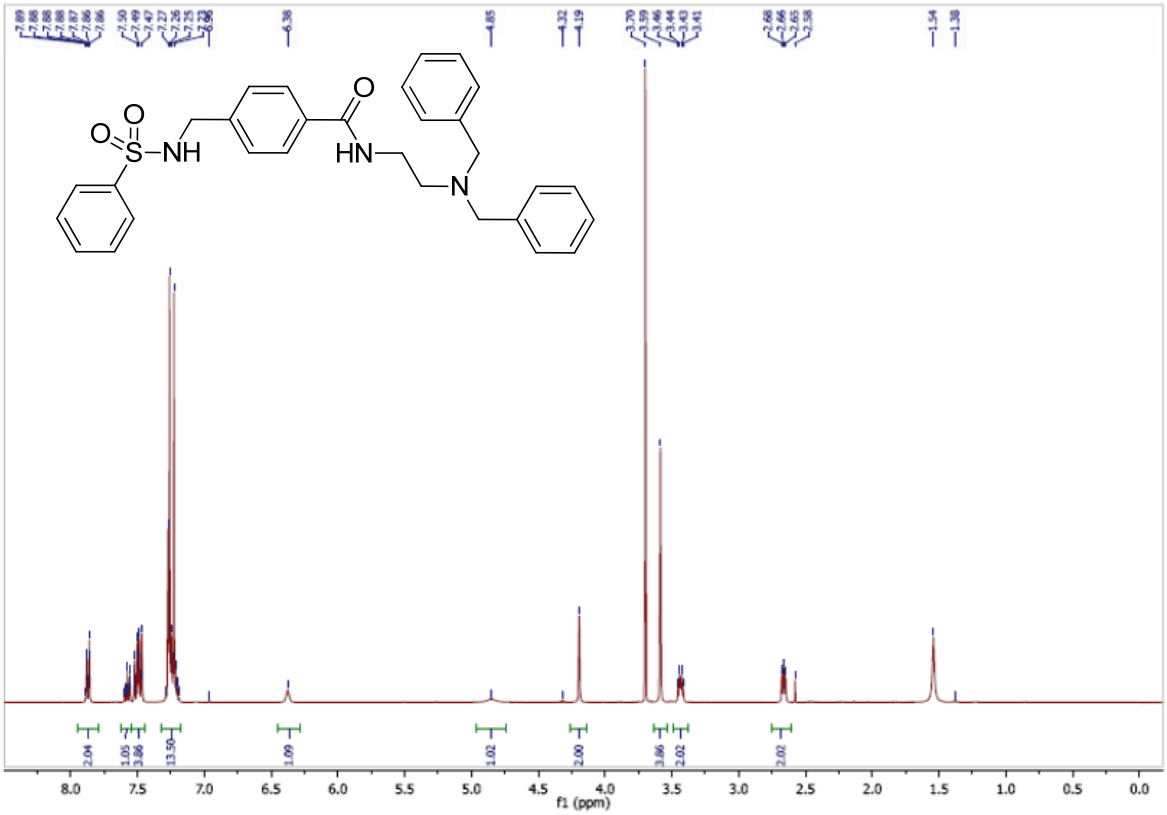

f1 (ppm)

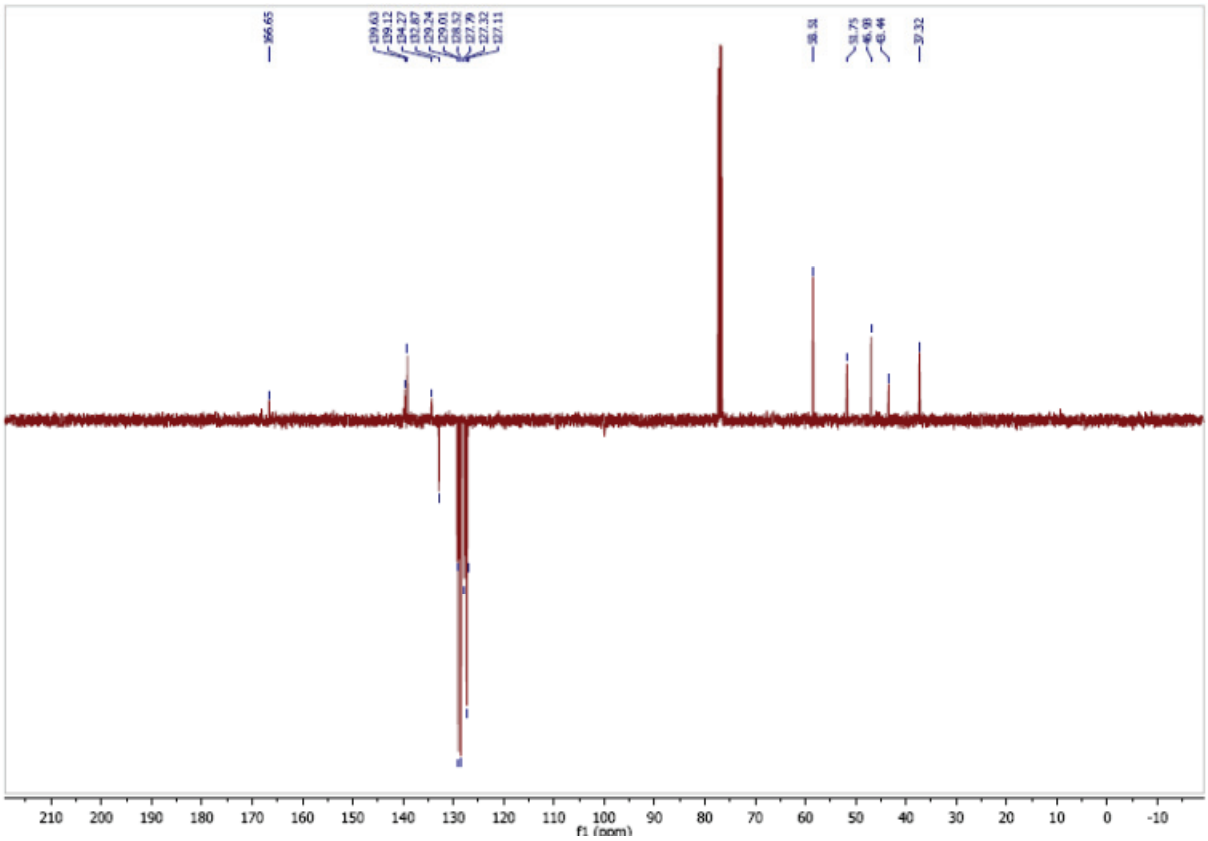

O
O
S
NH
HN
N
MeO
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

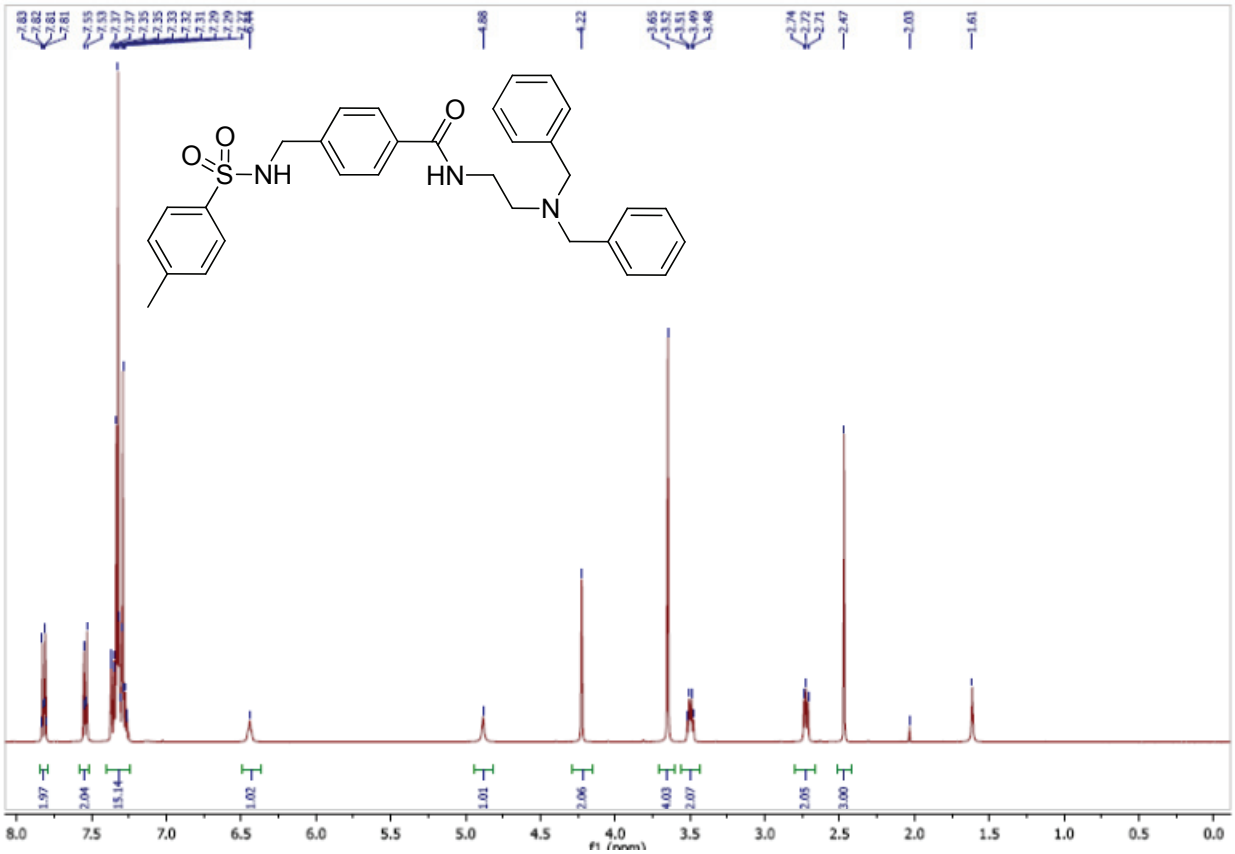

166.68
163.03
139.75
139.57
134.33
131.34
129.31
128.88
128.47
127.82
127.24
127.18
114.34
57.94
55.66
51.29
47.41
45.84
37.21
12.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

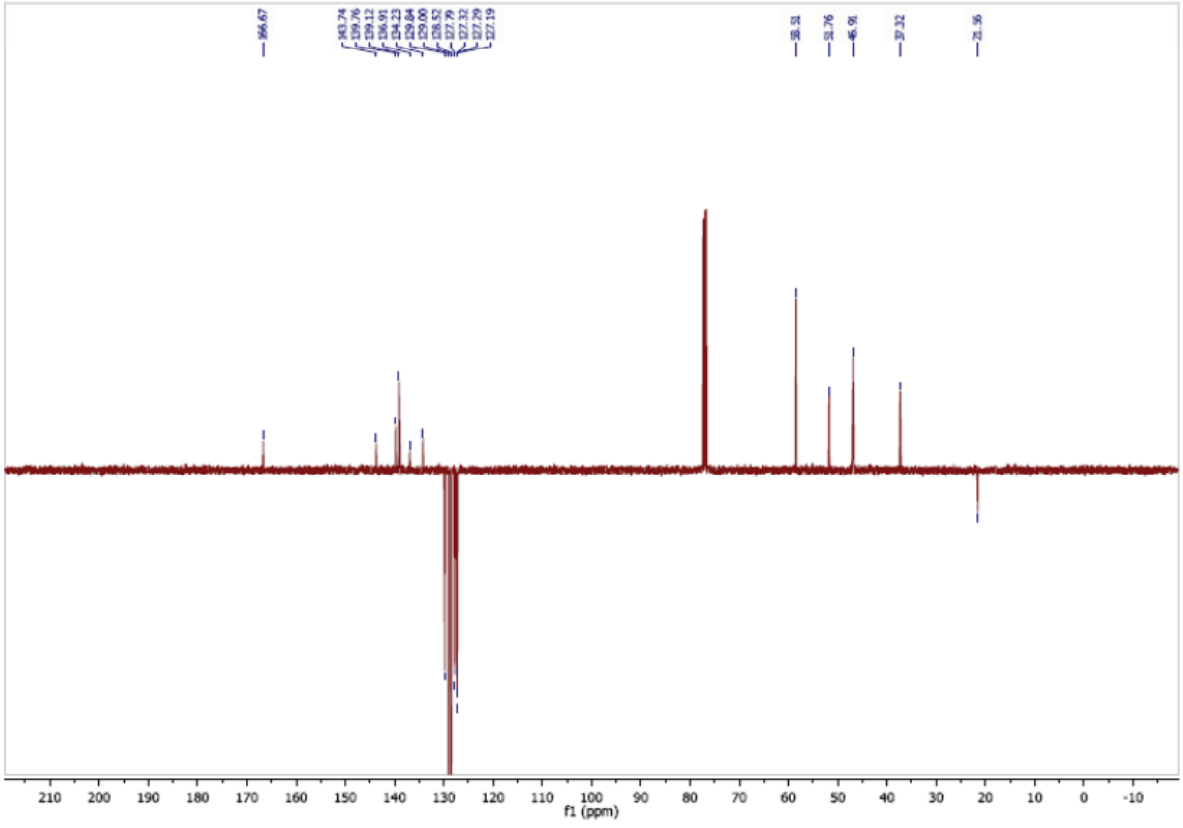

O
O
S
NH
HN
O
N
Br
f1 (ppm)

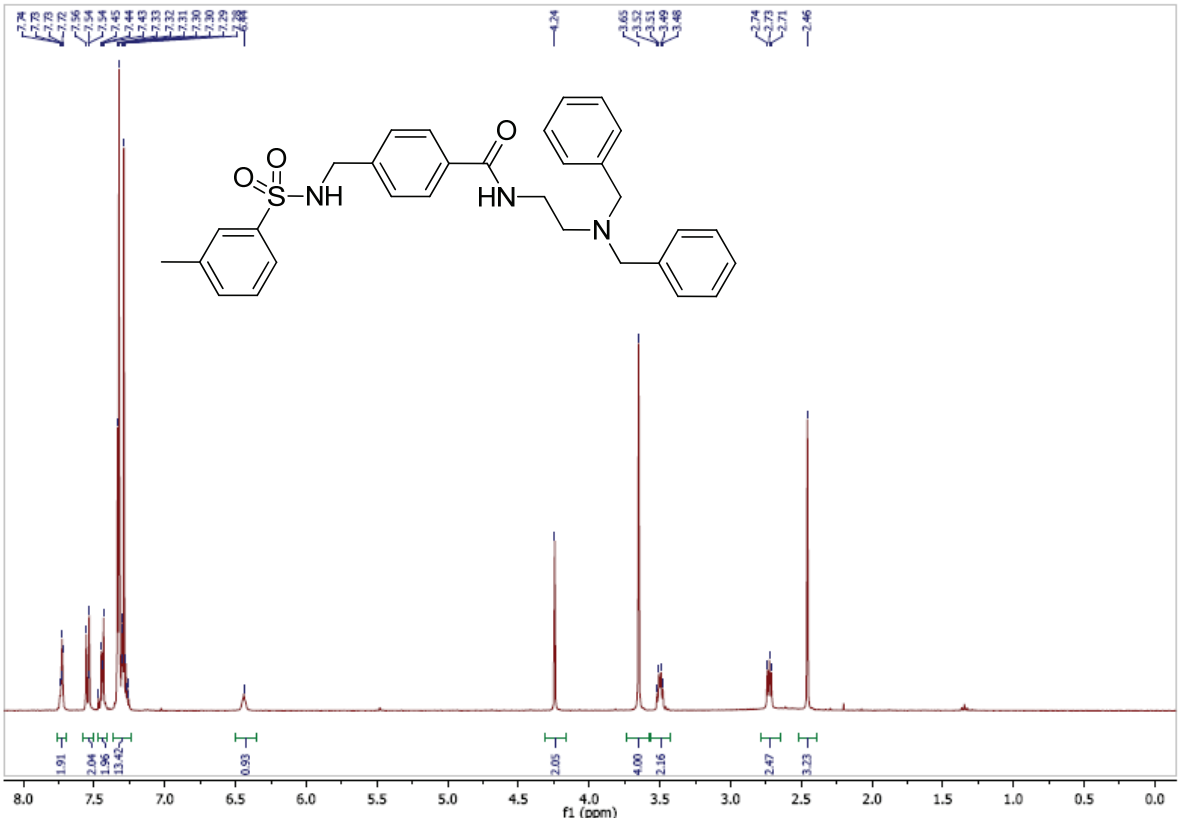

f1 (ppm)

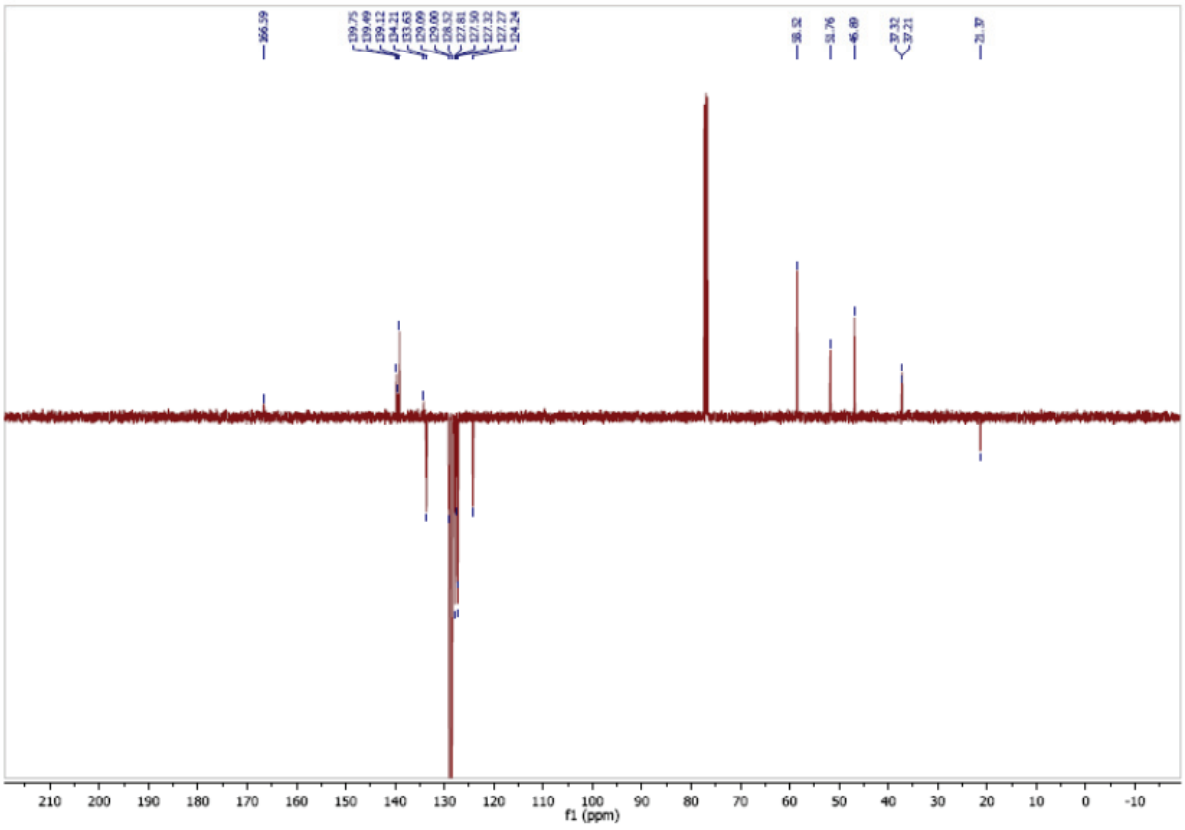

O
O
S
NH
HN
N
f1 (ppm)

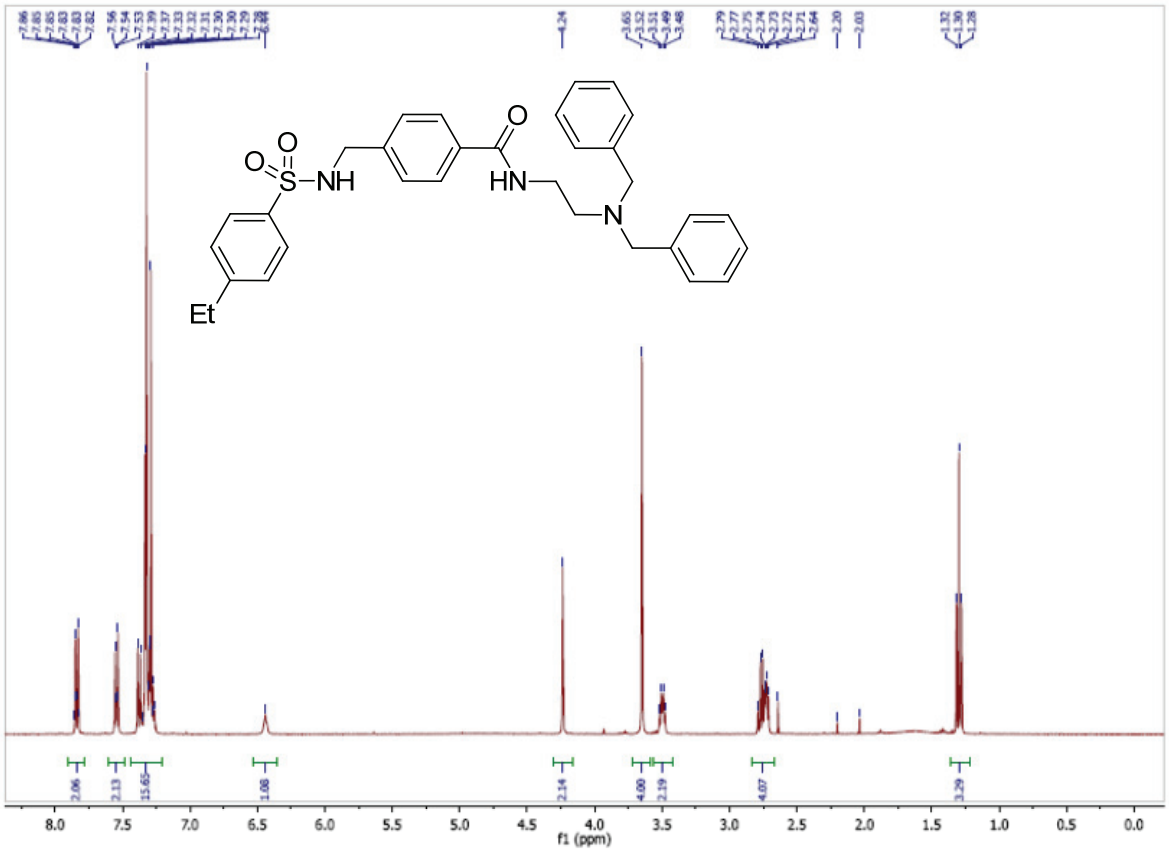

f1 (ppm)

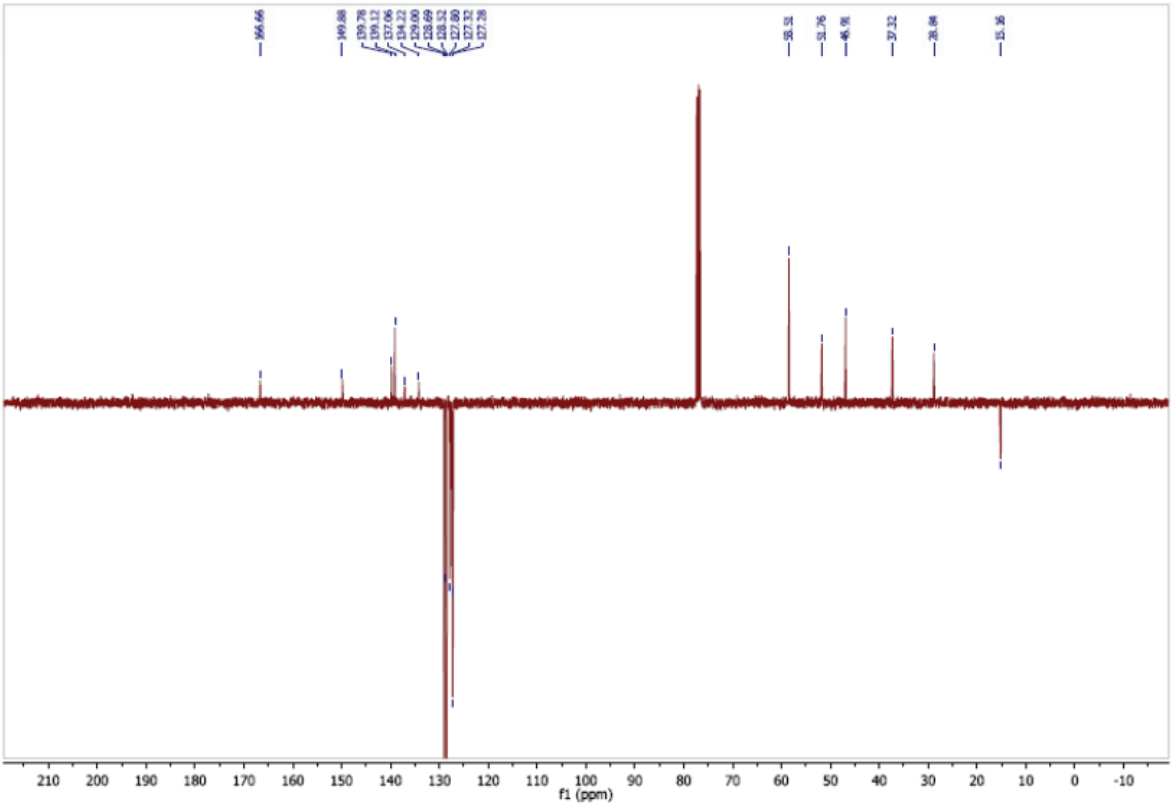

O
O
S
NH
HN
O
N

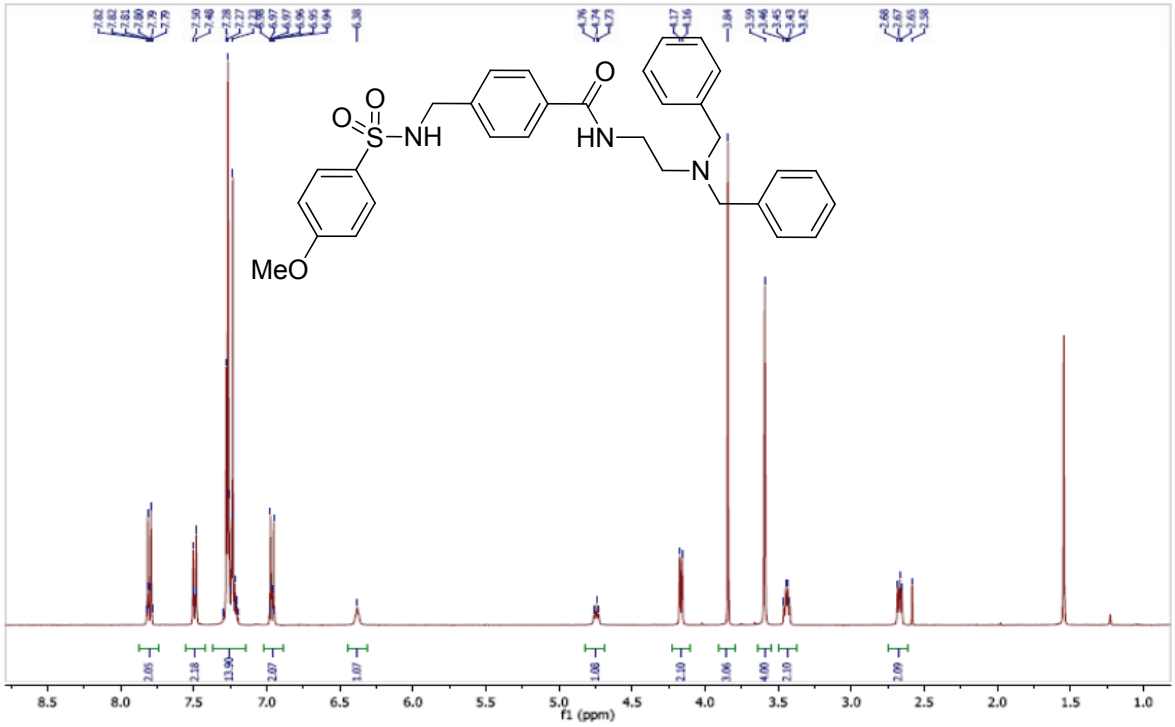


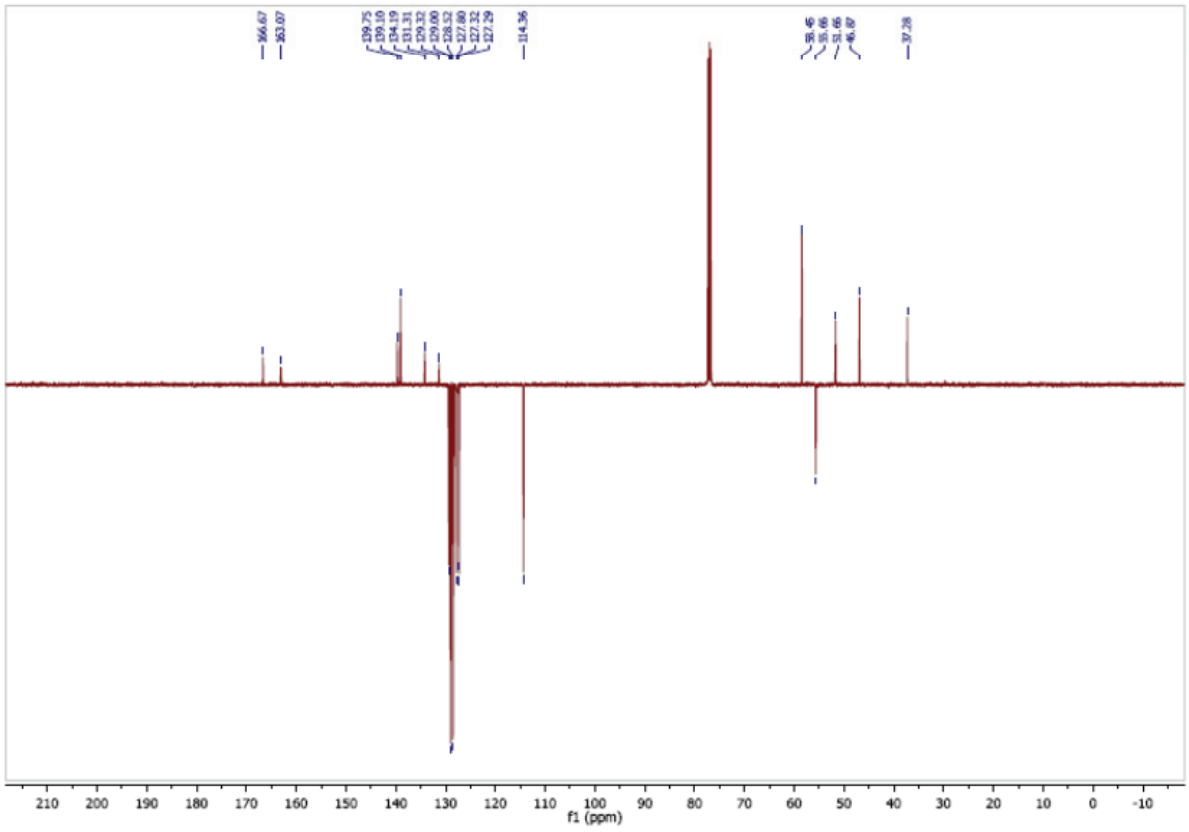

O
O
S
NH
HN
O
N
f1 (ppm)

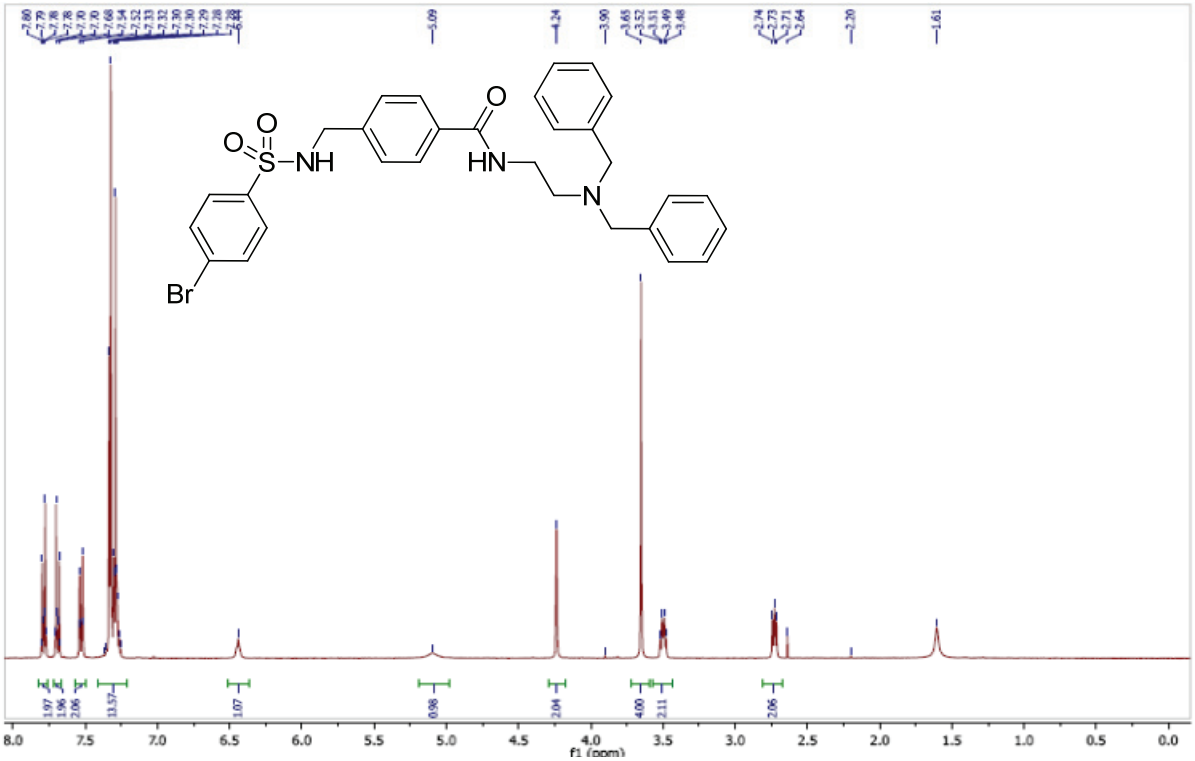

f1 (ppm)

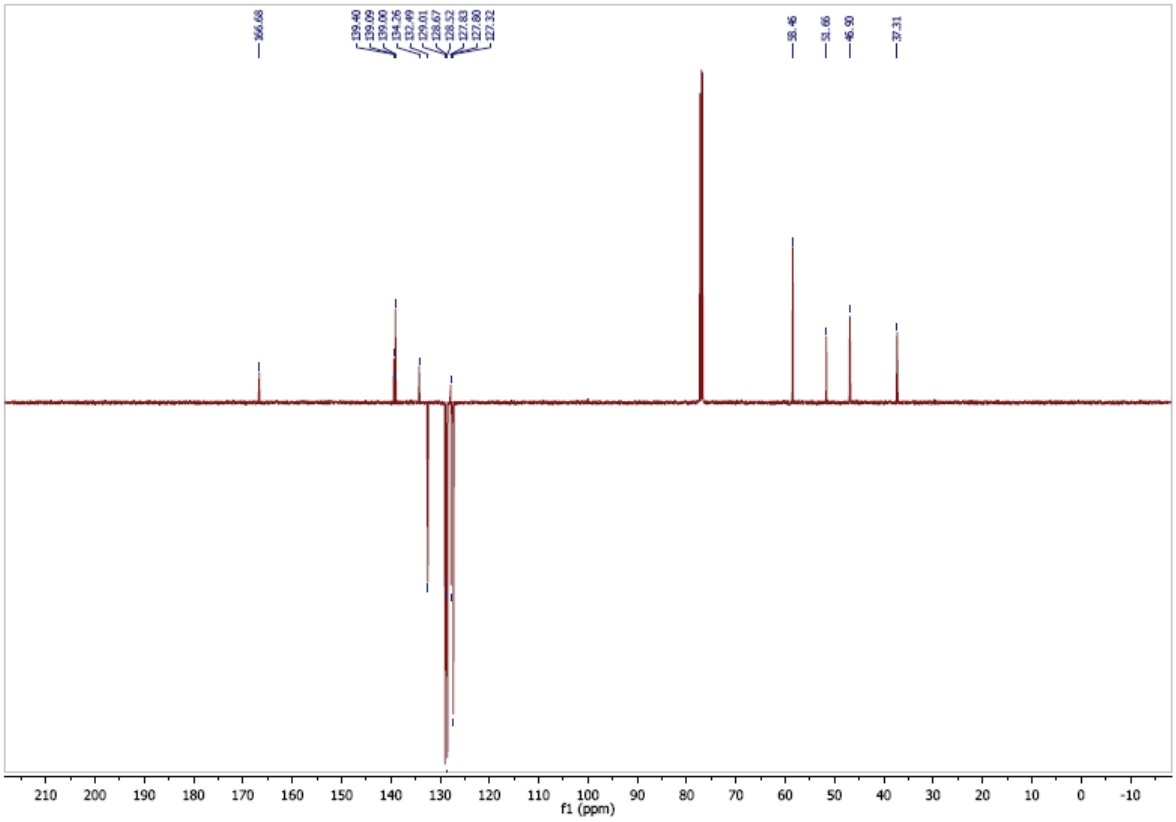

O
O
S
NH
HN
O
N
Et
f1 (ppm)

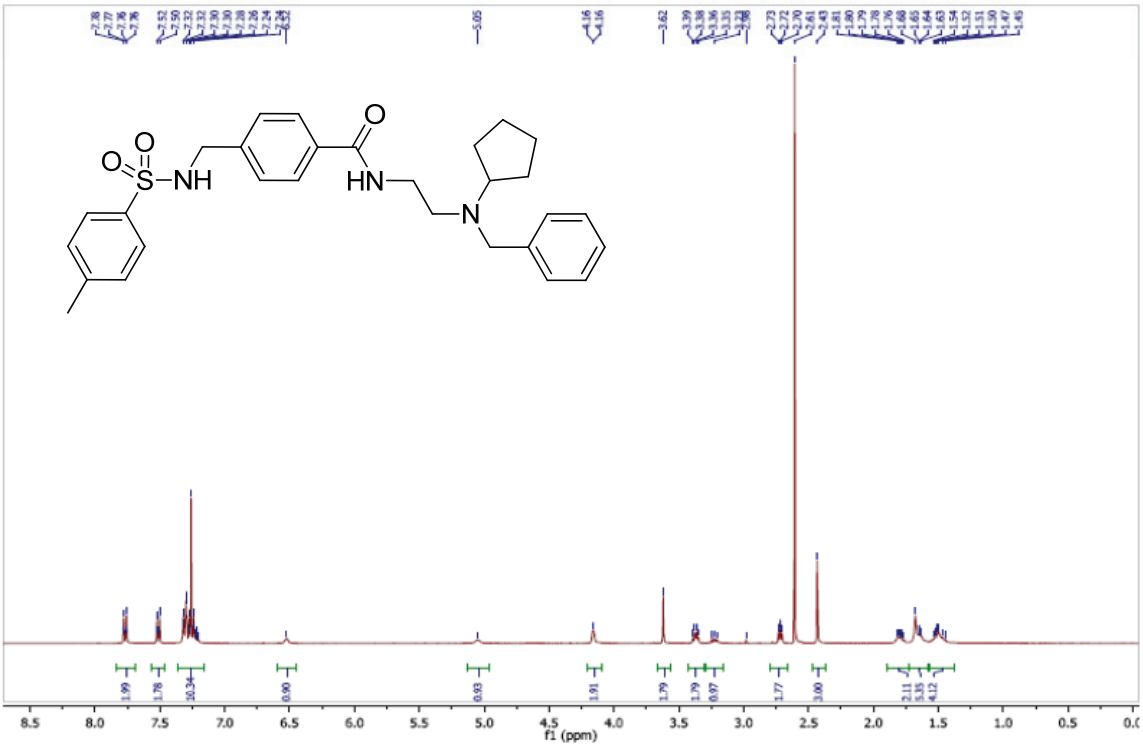

f1 (ppm)

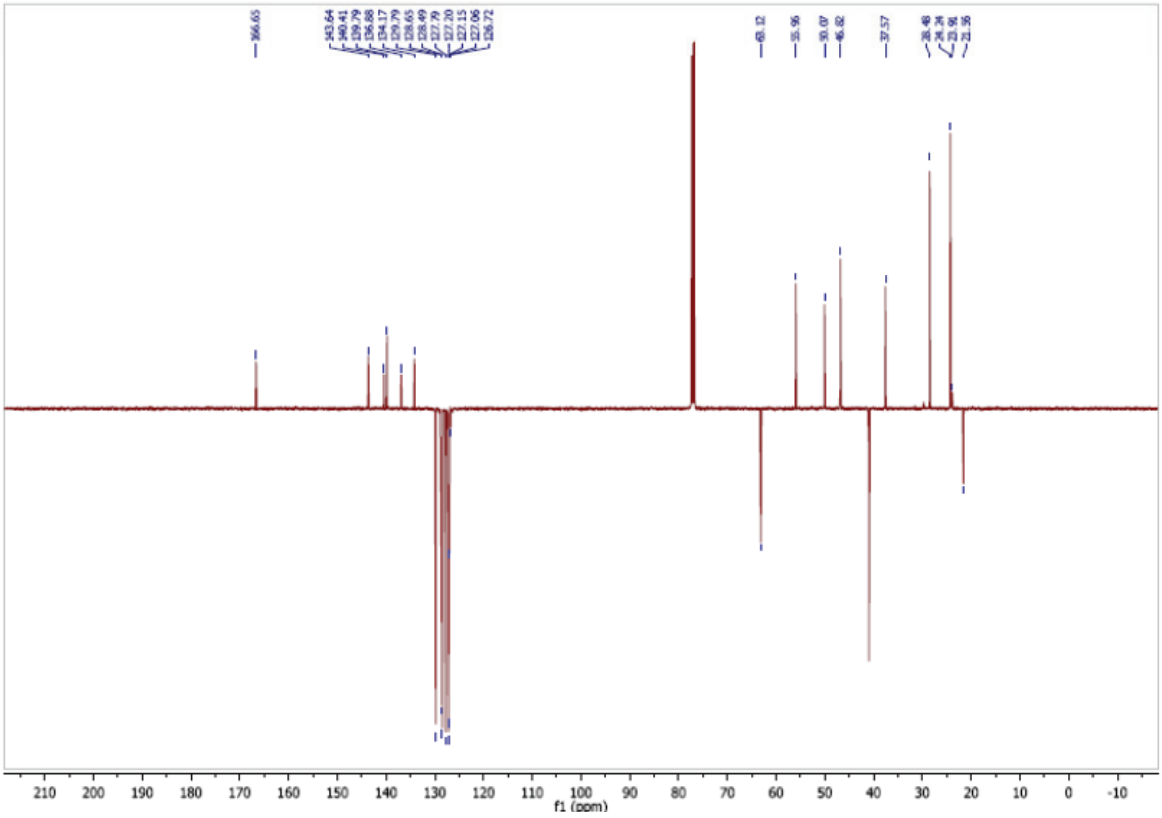

O
O
S
NH
HN
O
N
MeO
f1 (ppm)


f1 (ppm)


O
O
S
NH
HN
O
N
Br
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


166.68
139.40
139.09
139.00
134.26
132.49
129.01
128.67
128.52
127.83
127.80
127.32
58.46
51.66
45.90
37.31
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
S
NH
HN
N
f1 (ppm)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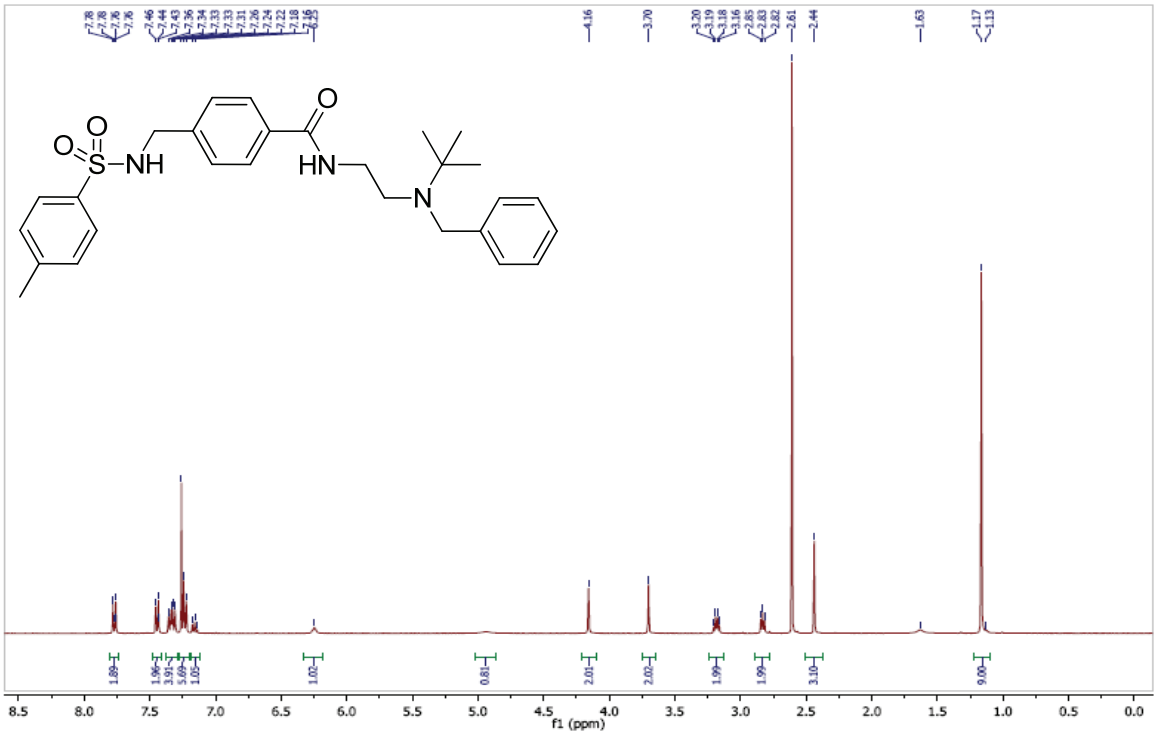
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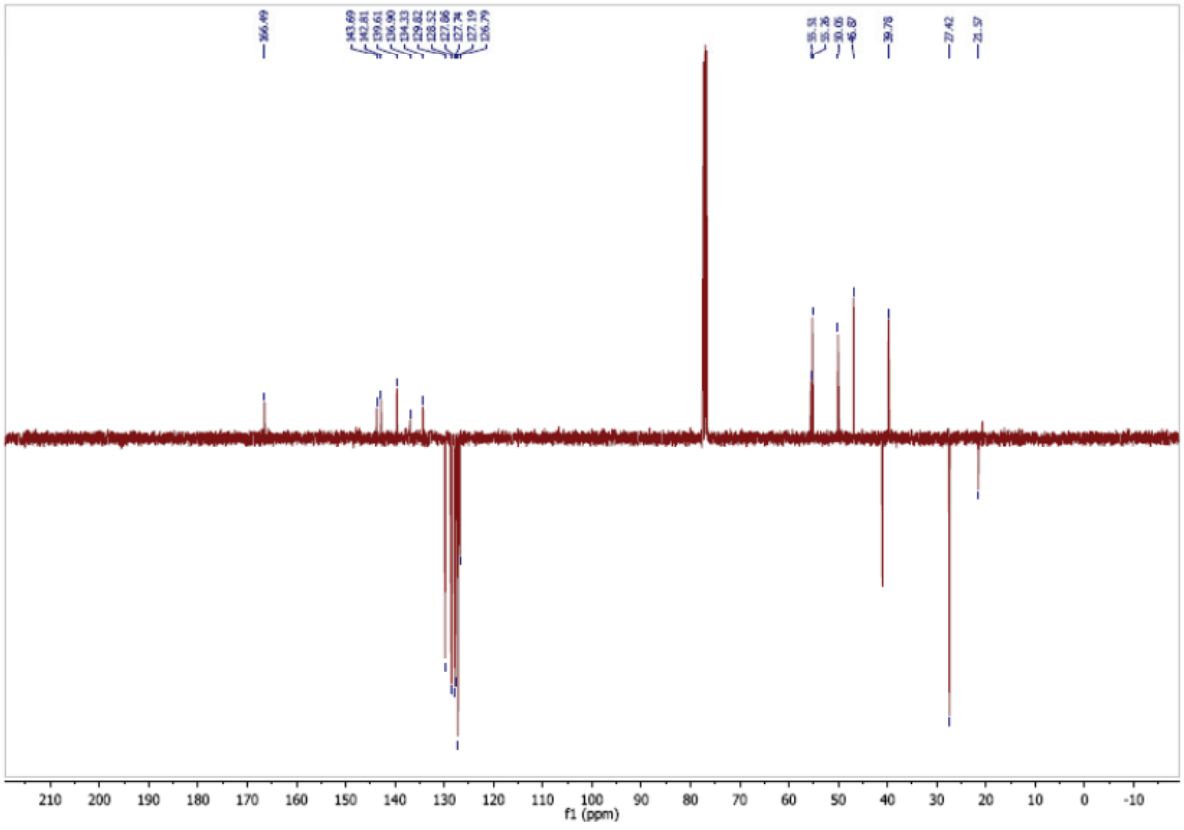
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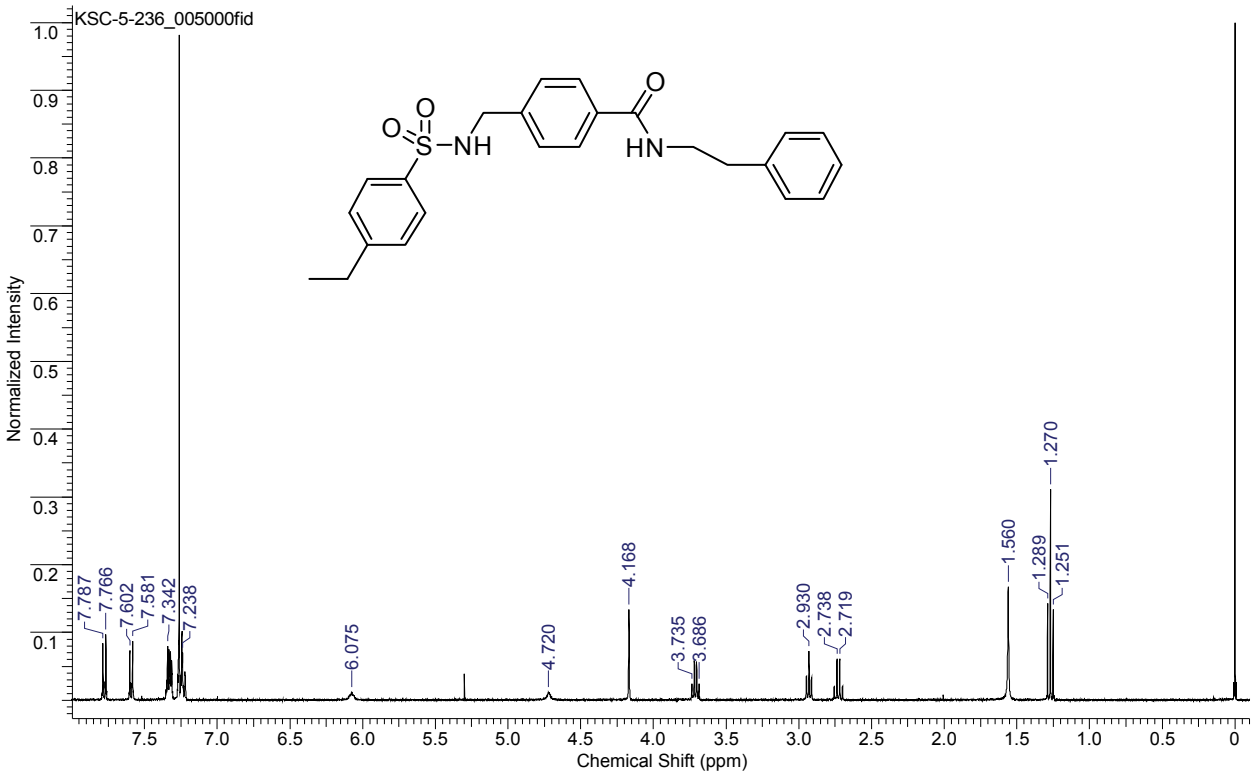
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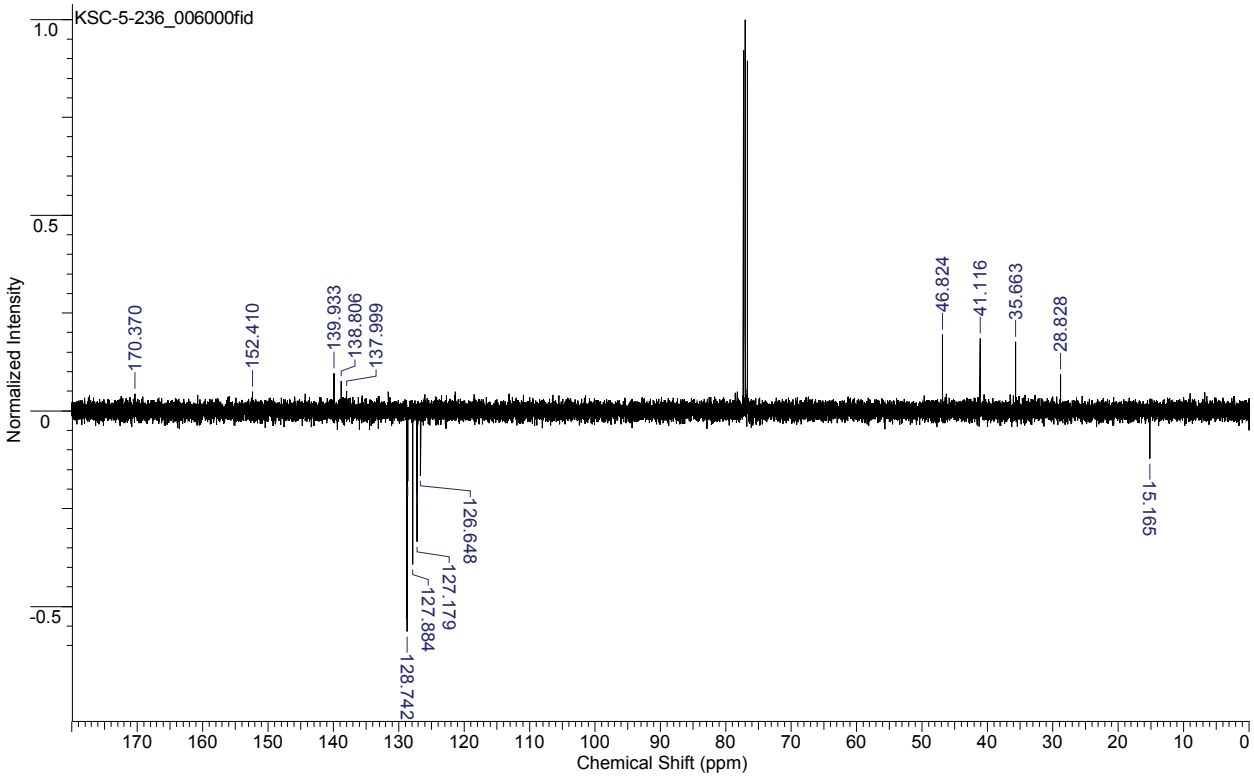
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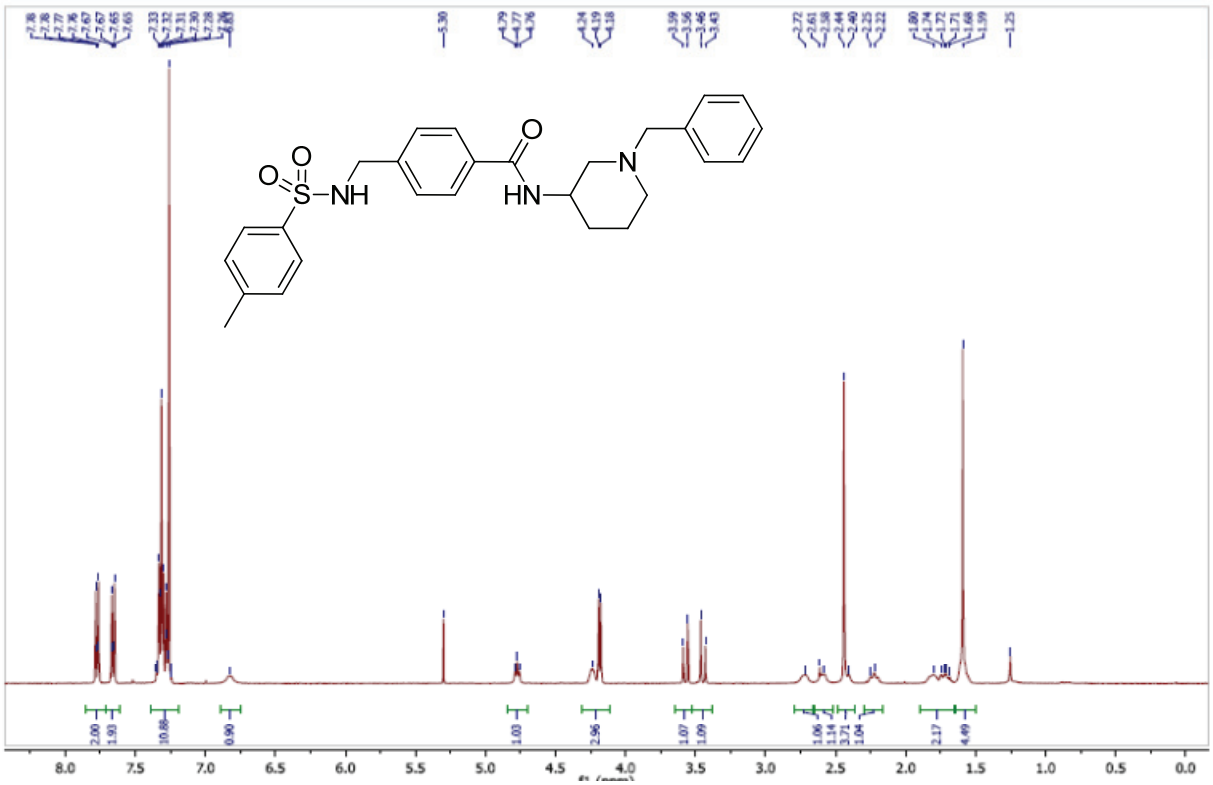
15.165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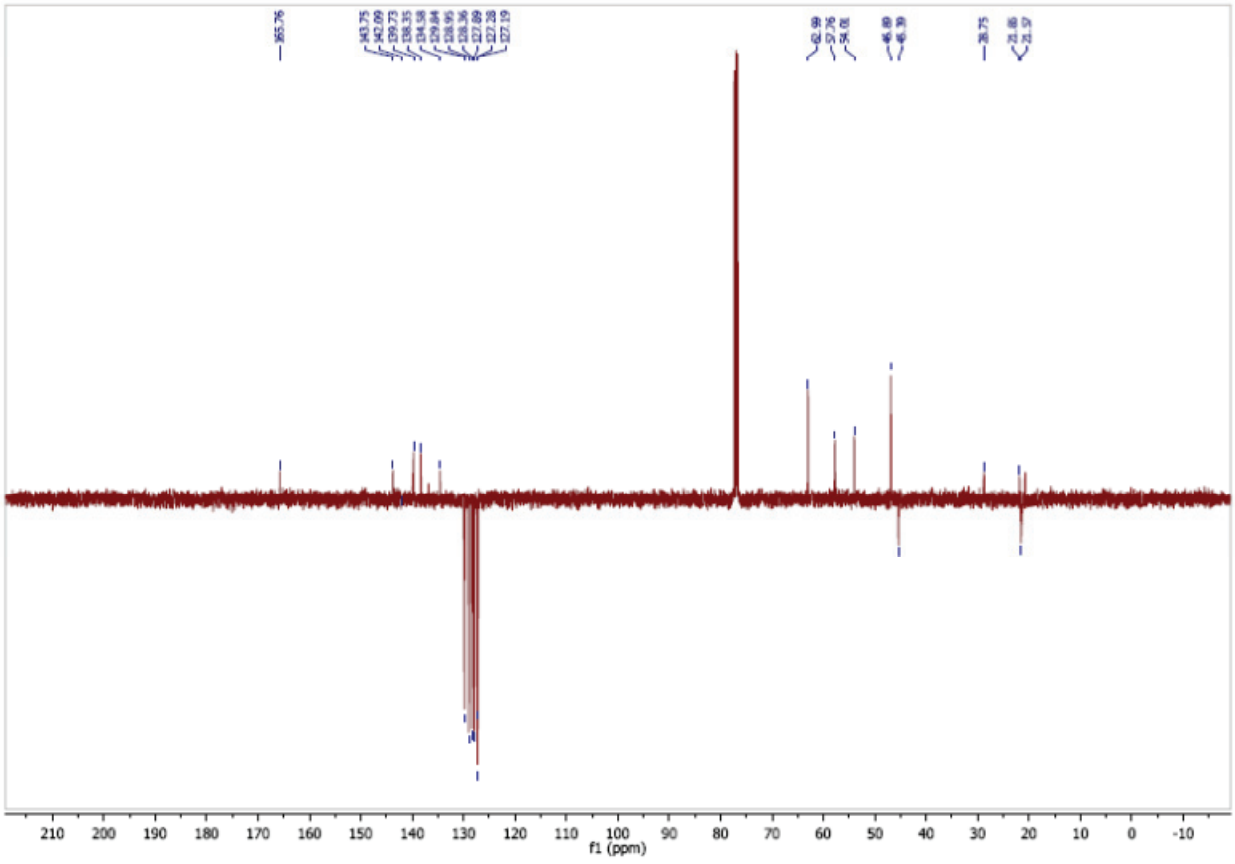
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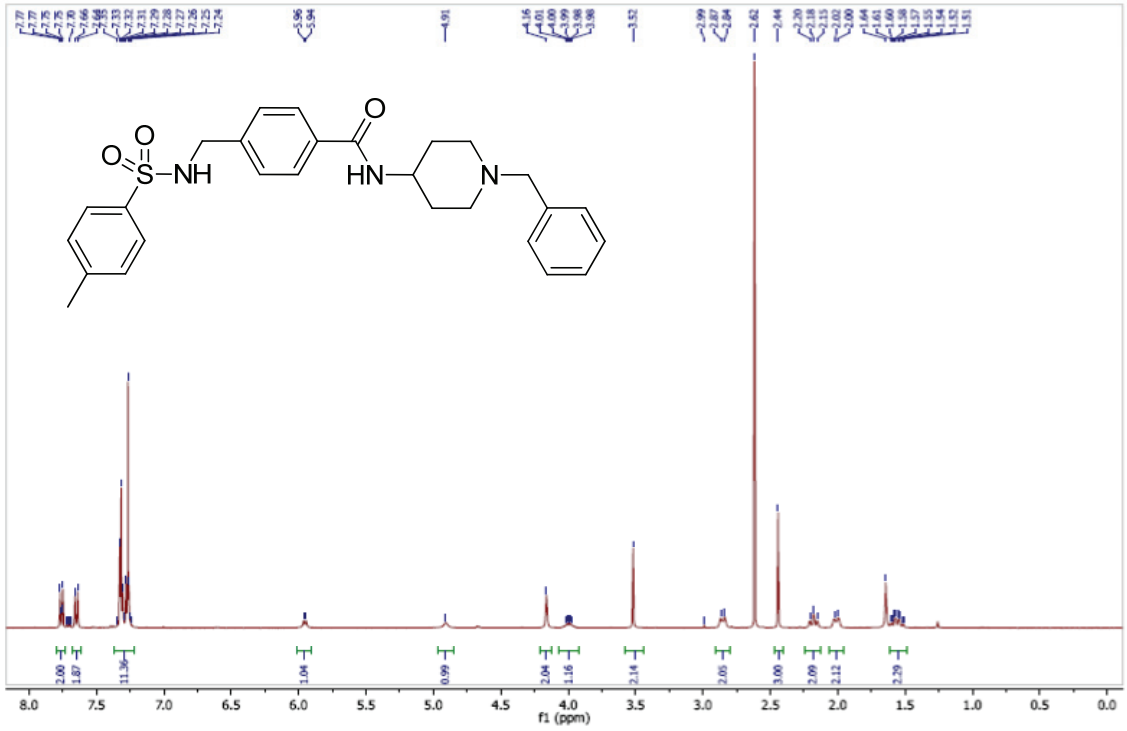
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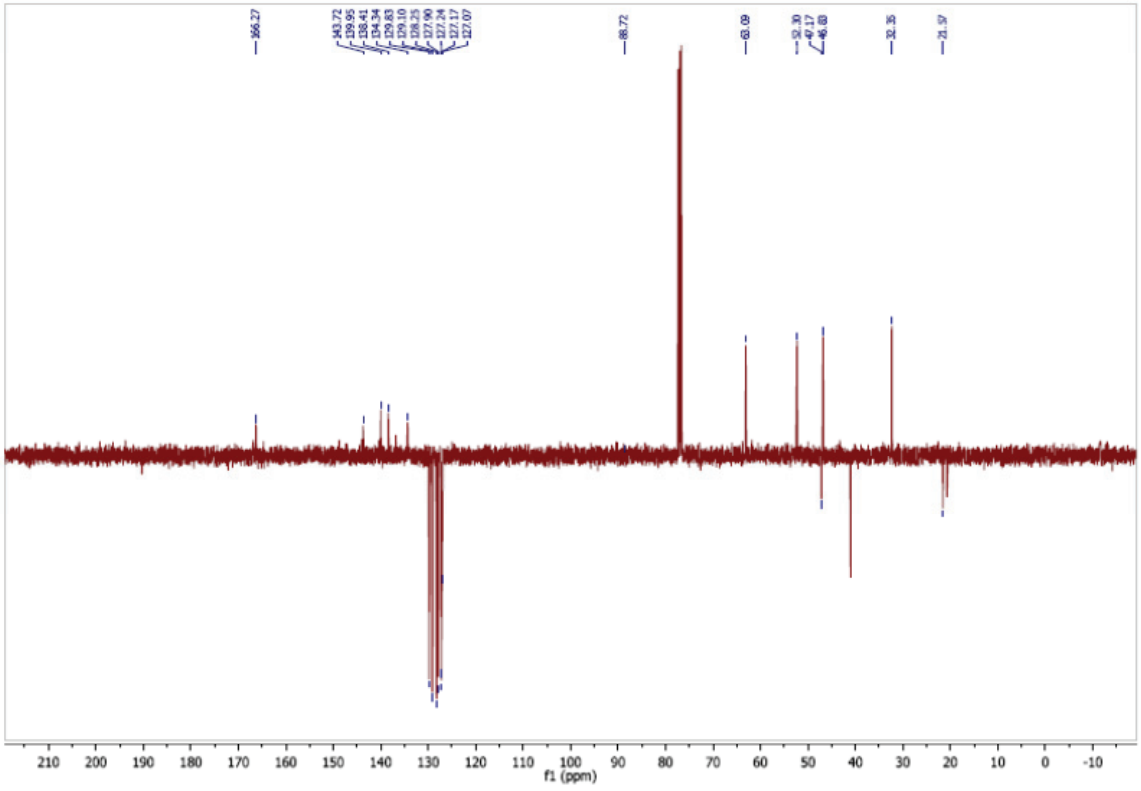
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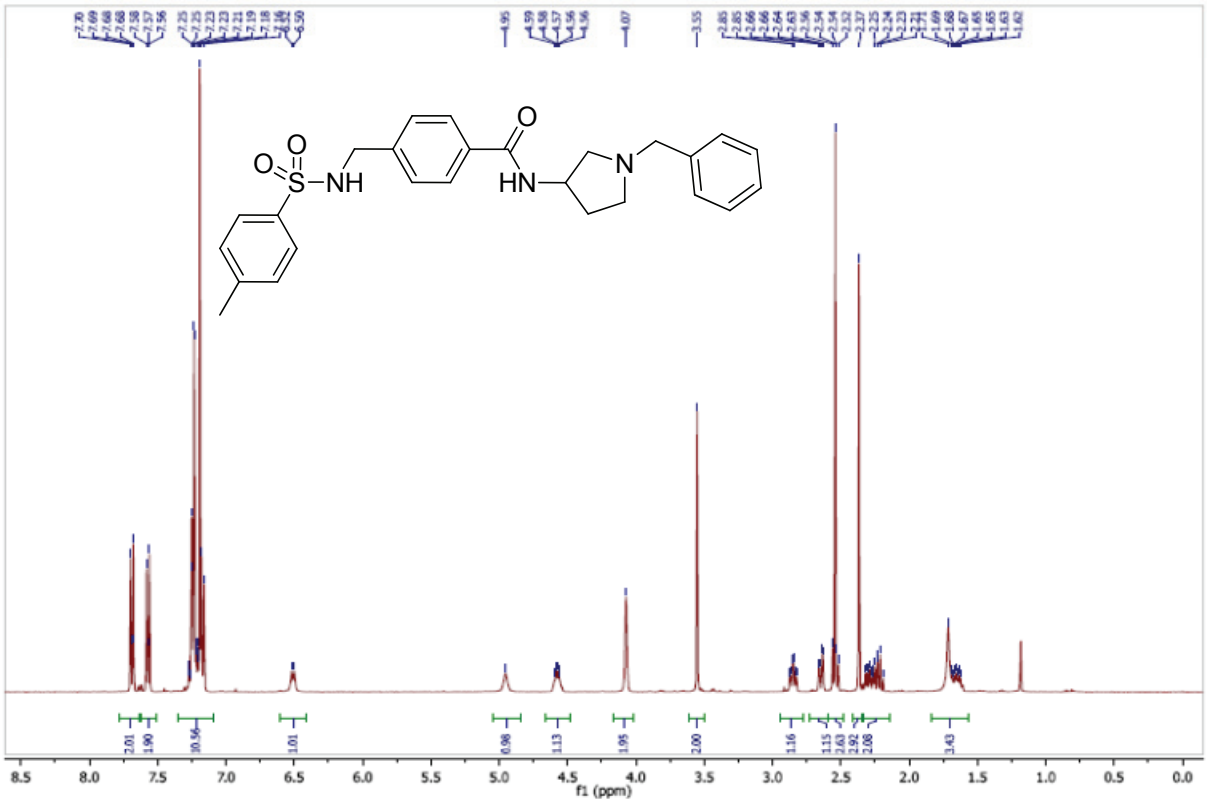
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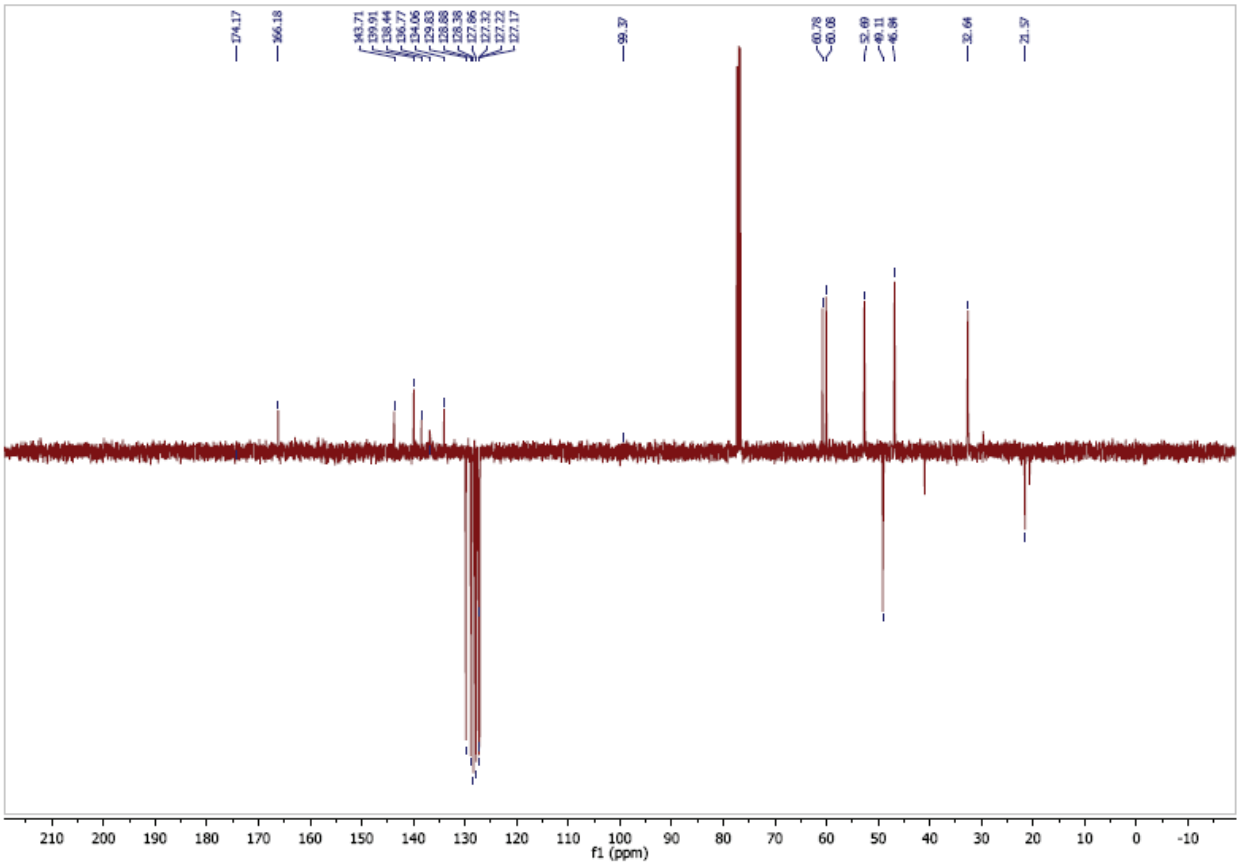
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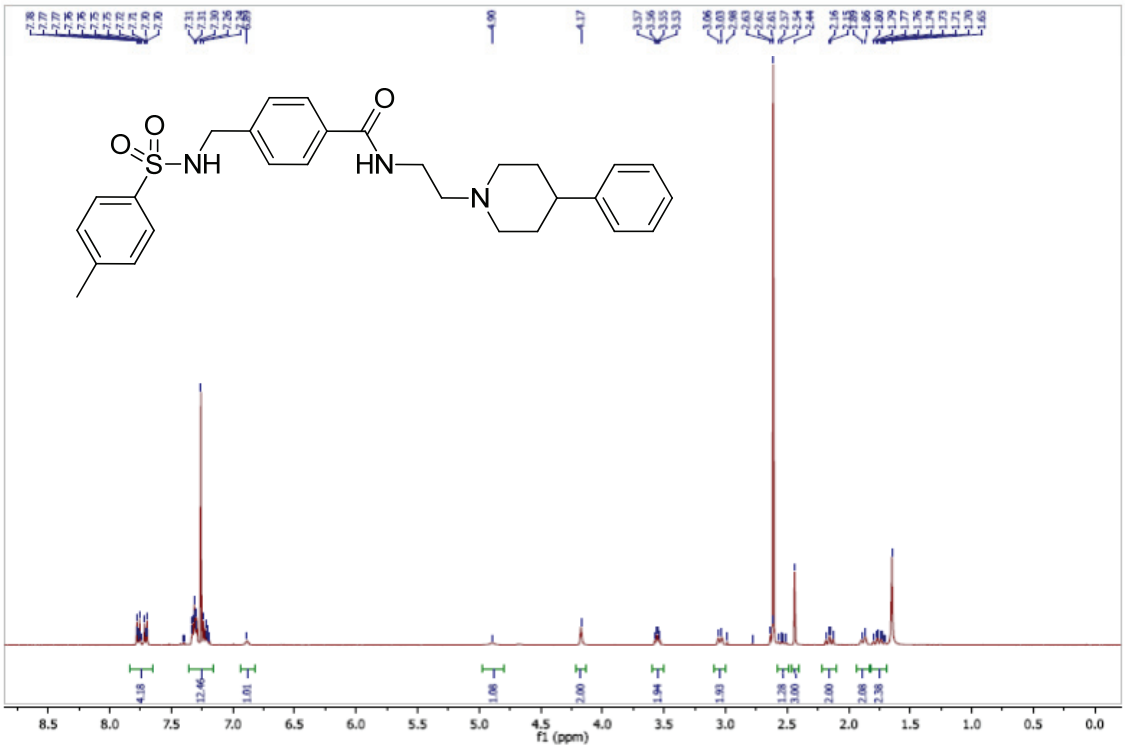
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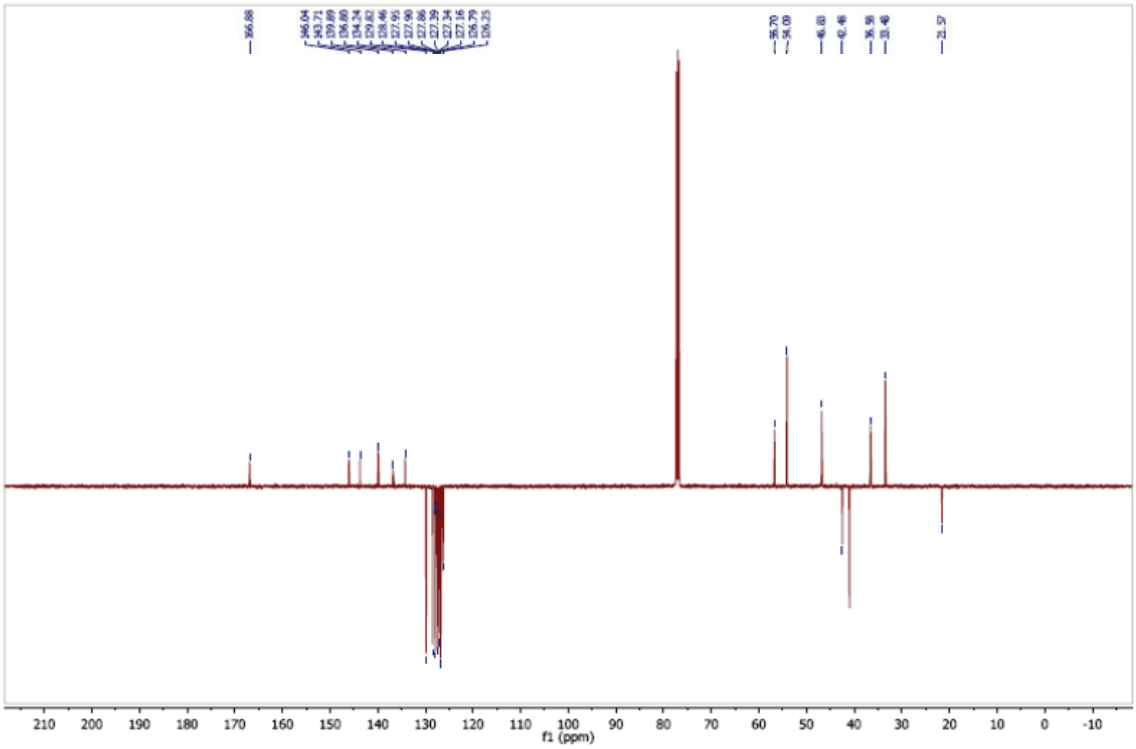
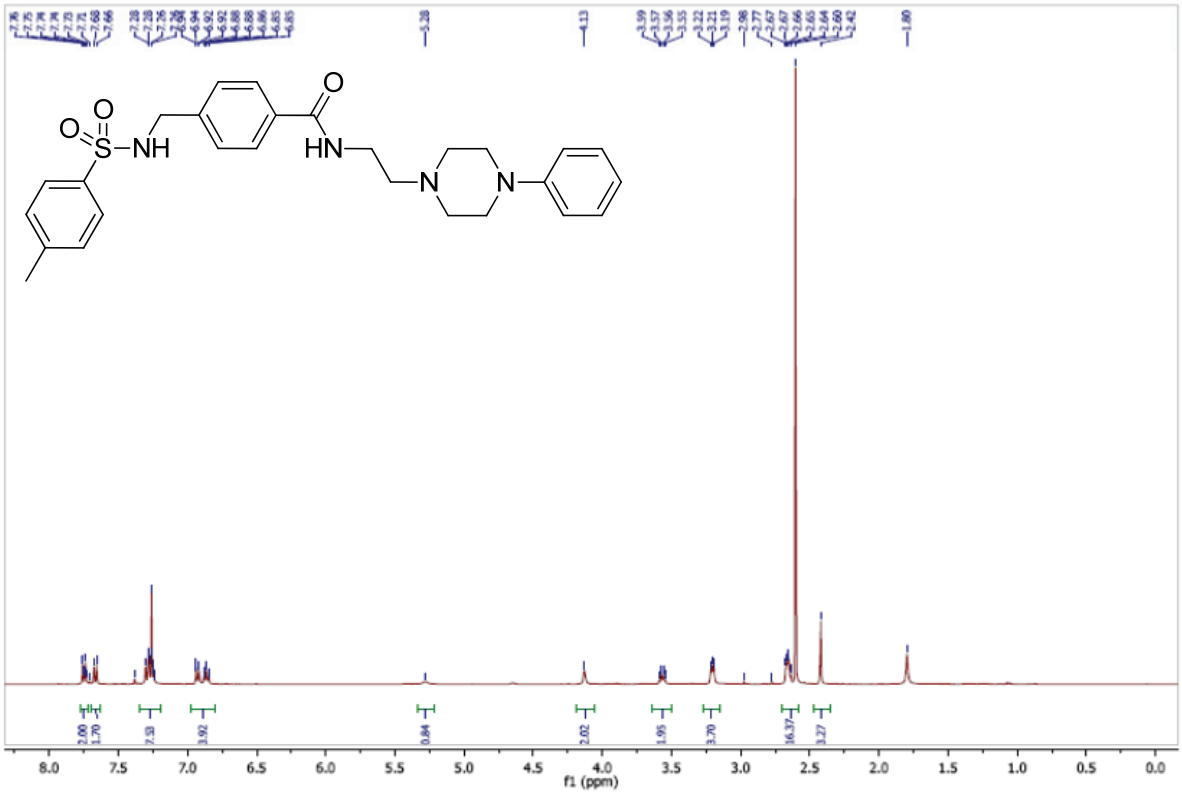
f1 (ppm)


f1 (ppm)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NH
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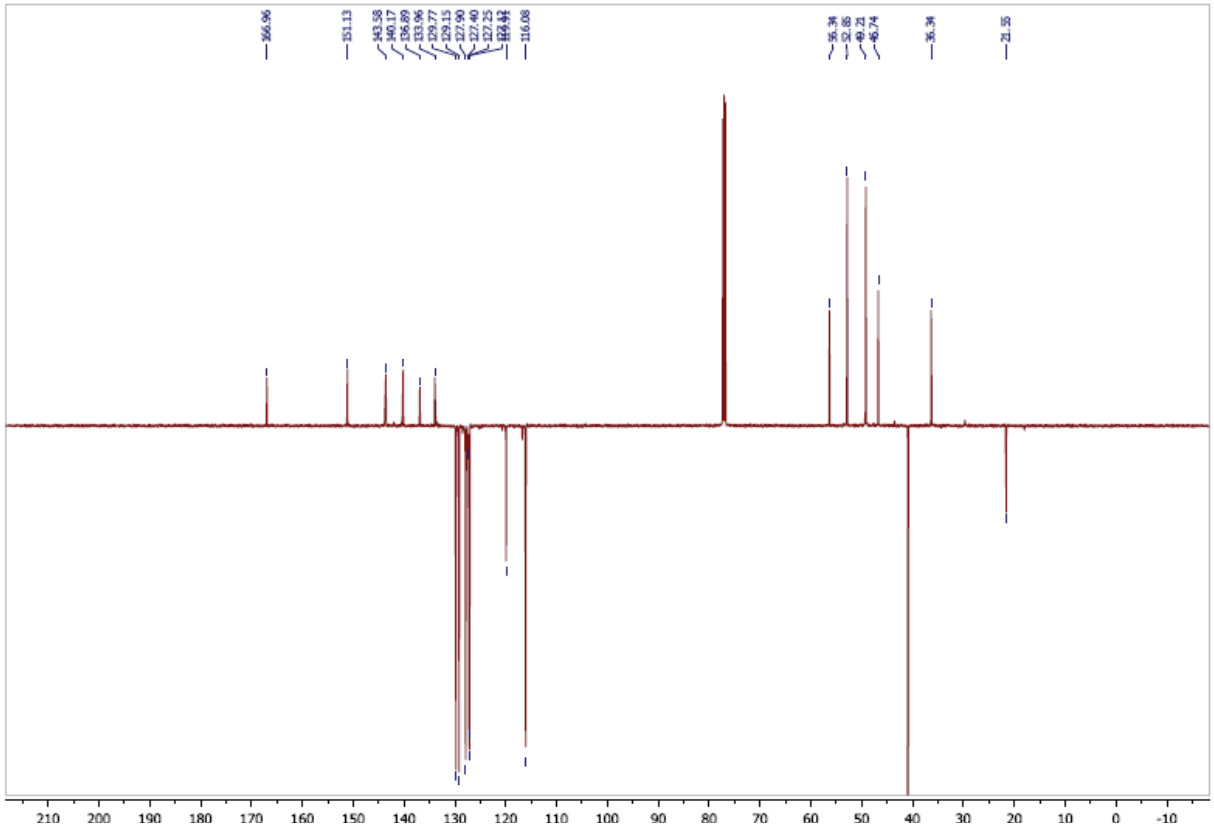
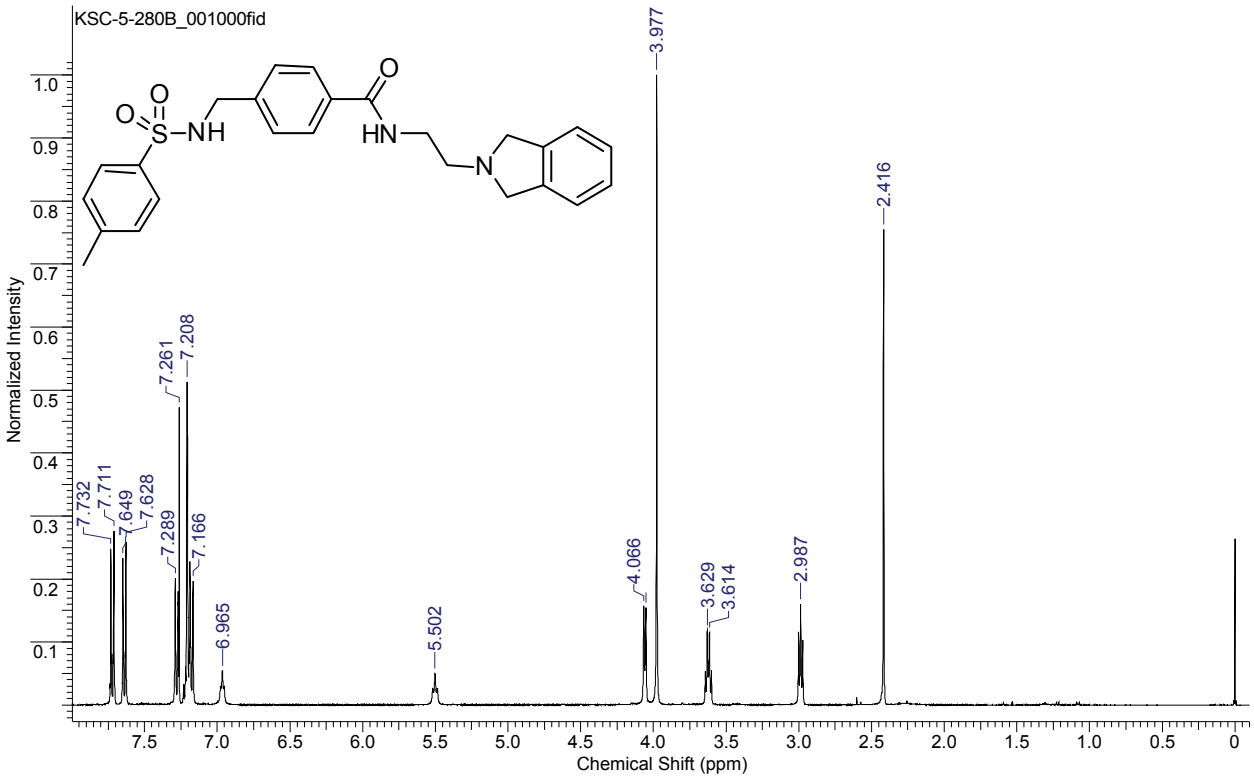
f1 (ppm)

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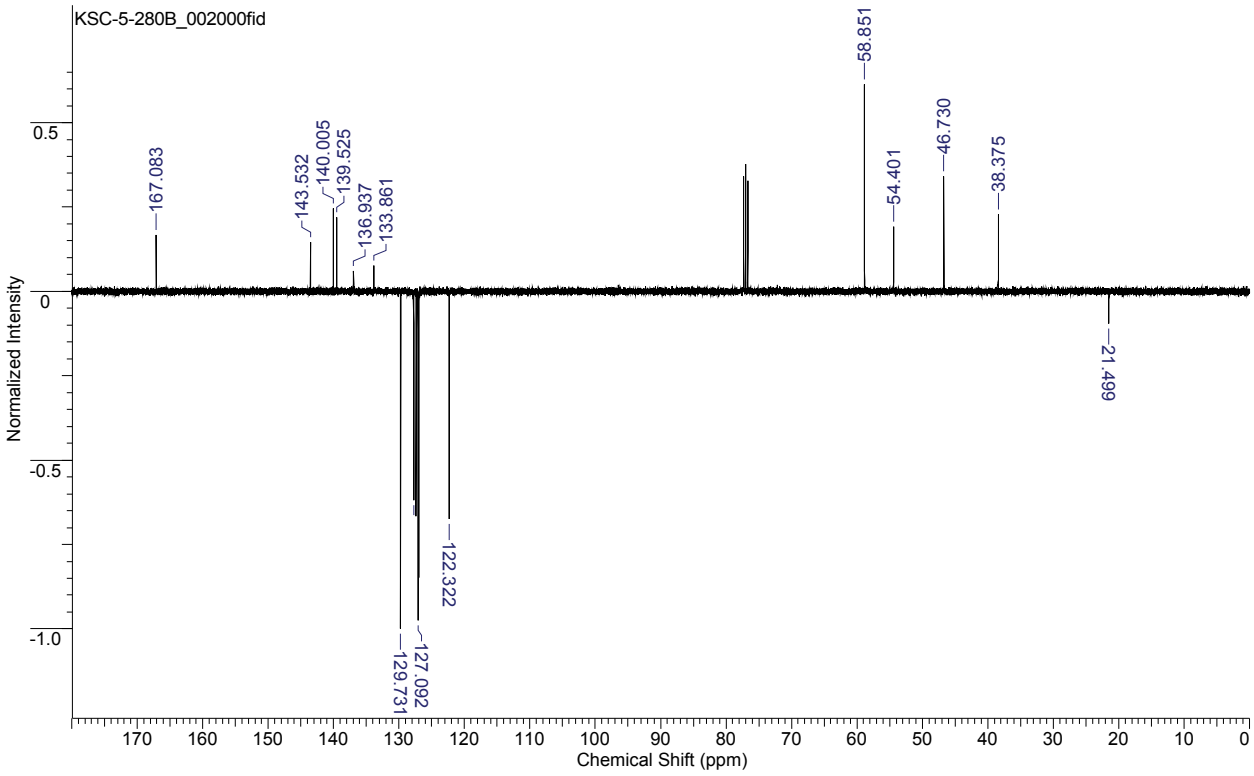
3.629
3.614
2.987
2.416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Normalized Intensity
Chemical Shift (ppm)
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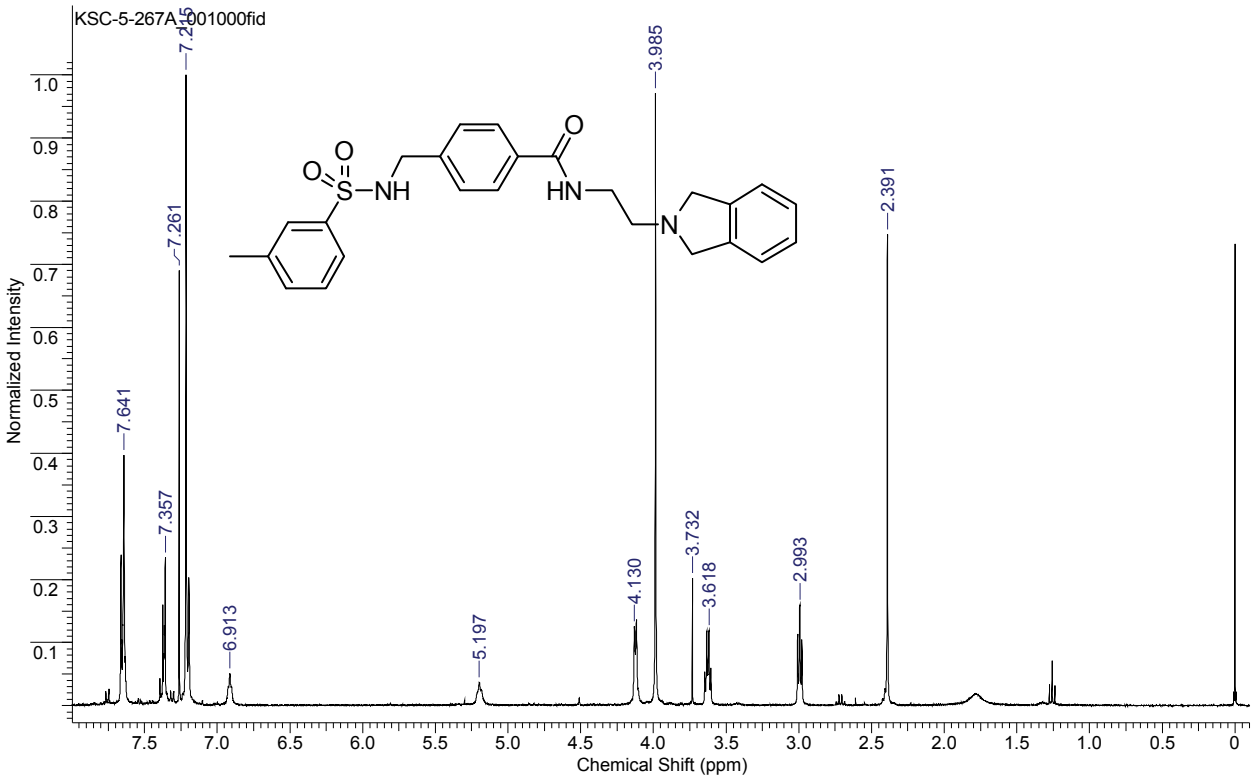
21.499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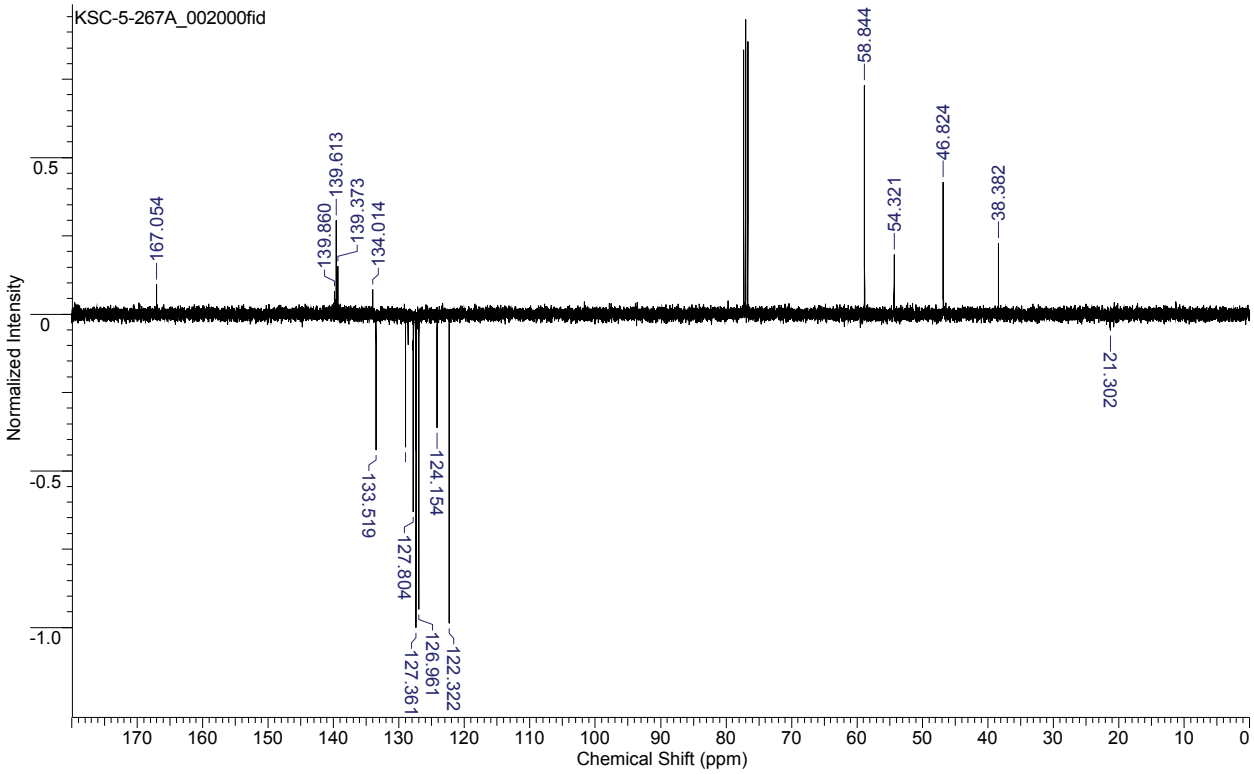
S
NH
HN
N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126.961
124.154
122.322
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54.321
46.824
38.382
21.302


KSC-5-250B_003000fid
Normalized Intensity
Chemical Shift (ppm)
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3.990
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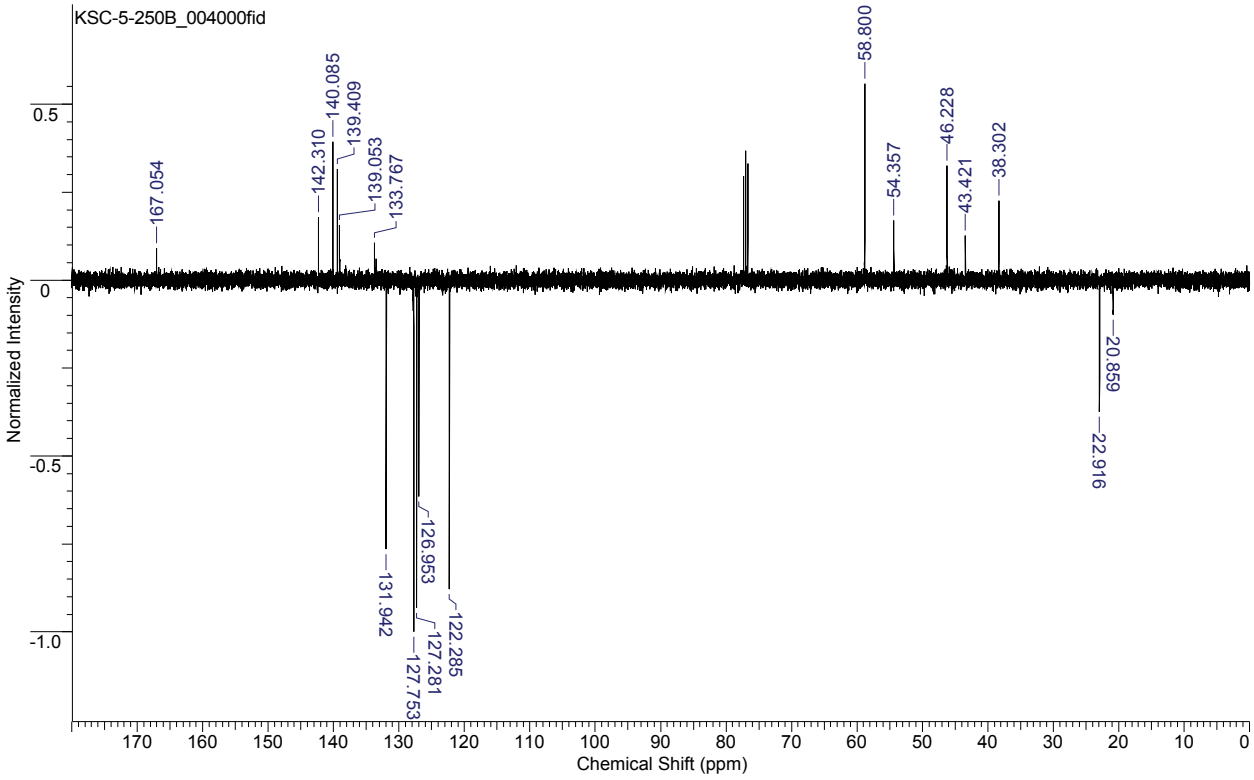
2.987
2.607
2.280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127.753
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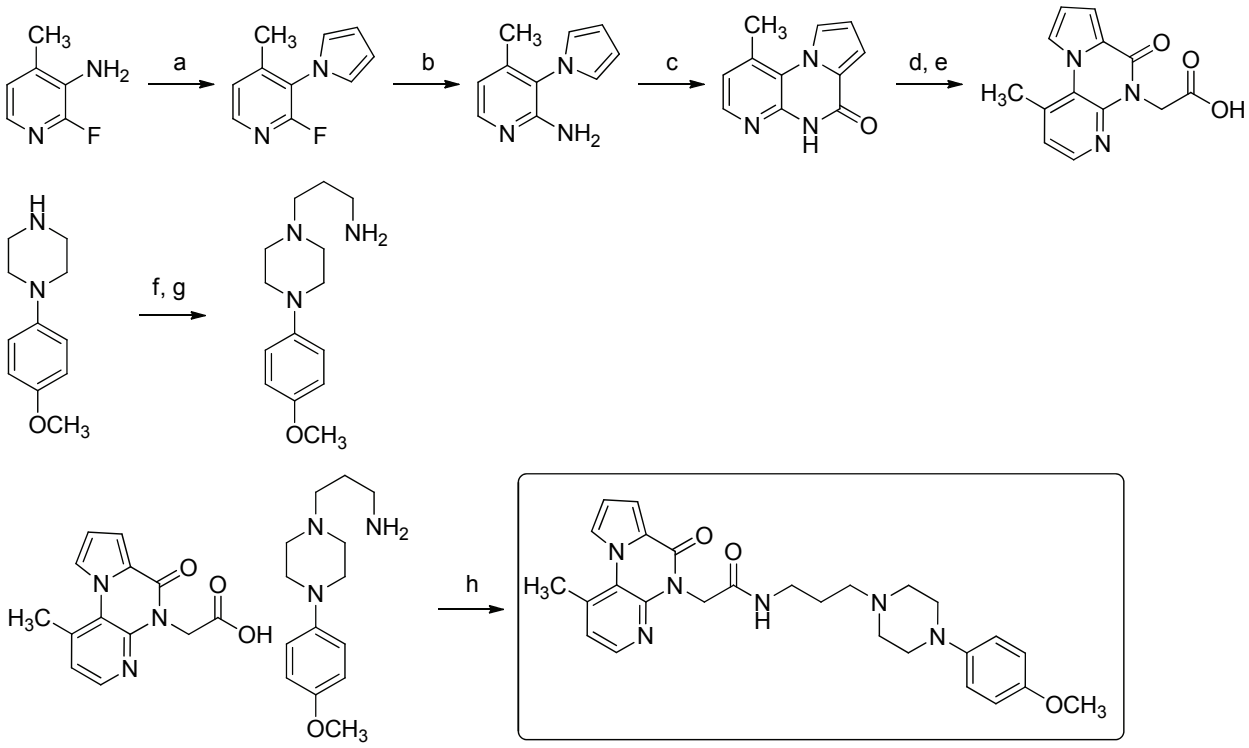
58.800
54.357
46.228
43.421
38.302
20.859
22.916

Synthesis of antagonist Chemotype IV compounds 4*{n}*.

Compounds **4*{1}*** to **4*{12}*** were available as milligram quantity dry powder samples from several commercial vendors of screening compounds.

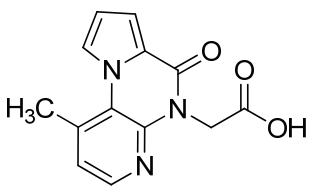
Scheme 4. Representative synthetic sequence[a].



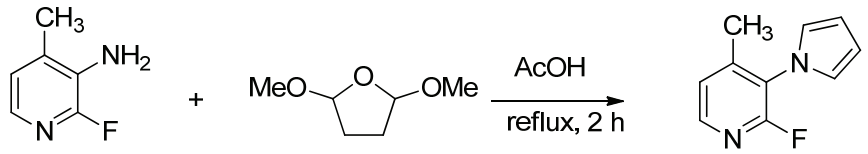
[a] Reagents and conditions: (a) 2,5-dimethoxytetrahydrofuran, AcOH (72% yield); (b) ammonia, MeOH, 150 ºC (76% yield); (c) triphosgene, toluene (43% yield); (d) sodium hydride, methyl bromoacetate, DMF (54% yield); (e) LiOH, MeOH:THF:H_2O (73% yield); (f) acryl nitrile (73% yield); (g) lithium aluminum hydride, ether (70% yield); (h) DIC, DMAP, CH_2Cl_2 (53% yield).

Scaffold synthesis.

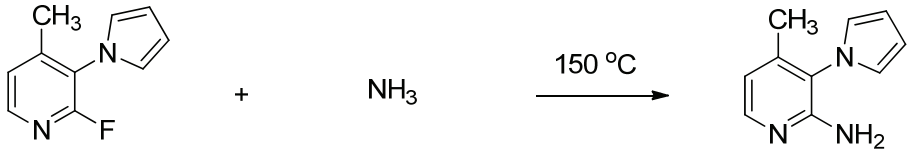
Pyroloquinoxalinylacetic acid scaffolds:



Synthetic sequence to the methyl substituted scaffold:

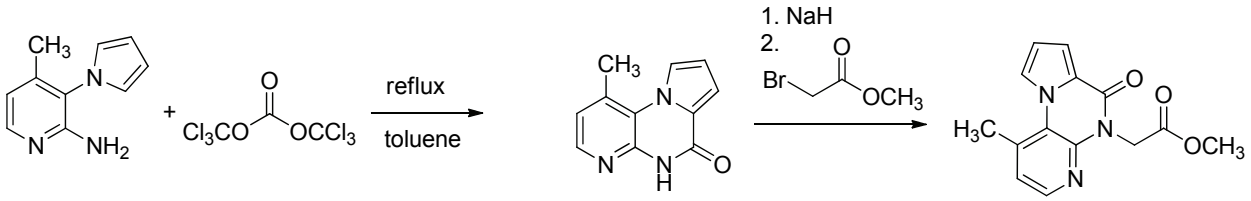


2-Fluoro-4-methyl-3-(1*H*-pyrrol-1-yl)pyridine. The protocol of Melander and coworkers was utilized.[12] Thus, 2-fluoro-4-methylpyridin-3-amine (1.00 g, 7.93 mmol) and 2,5-dimethoxytetrahydrofuran (1.08 mL, 1.05 equiv.) were suspended in acetic acid (3 mL), refluxed for 2 h and the reaction allowed to cool to rt. The solvents were removed in vacuo and the residue was purified by silca gel chromatography to afford the product as a light colored oil (1.00 g, 5.68 mmol, 72% yield). R_f = 0.3 (EtOAc:hexanes, 1:8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 6.40 (t, *J* = 2.1 Hz, 2H), 6.74 (td, *J* = 2.1, 0.9 Hz, 2H), 7.17 (d, *J* = 5.1 Hz, 1H), 8.10 (dd, *J* = 0.8, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.2, 17.3, 109.8, 122.1, 123.7, 123.8, 145.4, 145.5, 149.5, 149.6, 157.8, 160.2; HRMS (ESI) m/z calcd for $C_{10}H_{10}FN_2$ ($[M+H]^+$), 177.0828, found 177.0827.



4-Methyl-3-(1*H*-pyrrol-1-yl)pyridin-2-amine. 2-Fluoro-4-methyl-3-(1*H*-pyrrol-1-yl)pyridine (3.9 g, 22.1 mmol) was dissolved in 80 mL of ammonia (7N in MeOH) in a sealed tube (250 mL). The mixture was heated at 150 °C for 2 days protected with a blast shield. The mixture was cooled to room temperature, then cooled in an ice bath for 30 min and filtered cold. The filtrate was evaporated to dryness and purified by flash chromatography to give the product as a white solid (2.9 g 76% yield). R_f = 0.5 (EtOAc:Hexanes, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 4.52 (s, 2H), 6.41 (t, *J* = 2.1 Hz, 2H), 6.67 (t, *J* = 2.1 Hz, 2H), 6.60 (d, *J* = 5.2 Hz, 1H), 7.96

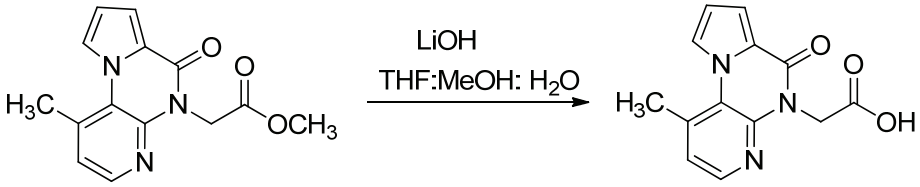
(d, J = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.7, 116.0, 121.2, 121.5, 145.9, 147.2, 156.1; HRMS (ESI) m/z calcd for $C_{10}H_{12}N_3$ ($[M+H]^+$) 174.1031; found 174.1026.



1-Methylpyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5*H*)-one. 4-Methyl-3-(1H-pyrrol-1-yl)pyridin-2-amine (1.0 g, 5.8 mmol) and triphosgene (2.6 g, 8.7 mmol) were dissolved in 100 mL of toluene. The mixture was refluxed for 3 h, then cooled to room temperature. The red solid was collected after filtration and washed with CH_3CN to afford the crude product (0.5 g, 43% yield). The material was used directly for next step reaction without purification. ^{1}H NMR (400 MHz, DMSO) δ 2.81 (s, 3H), 6.75 (dd, J = 2.9, 3.9 Hz, 1H), 7.20-7.08 (m, 2H), 8.13 (d, J = 4.9 Hz, 1H), 8.15 (dd, J = 1.4, 2.9 Hz, 1H), 11.64 (s, 1H); HRMS (ESI) m/z calcd for $C_{11}H_{10}N_3O$ ($[M+H]^+$) 200.0824; found 200.0819.

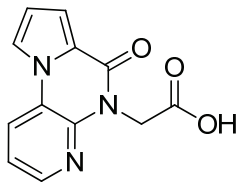
Methyl 2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetate. To a solution of 1-methylpyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (50 mg, 0.25 mmol) in 2 mL of DMF, was added NaH (60%, 11 mg, 0.28 mmol). The mixture was stirred at room temperature for 1 h. Methyl bromoacetate (0.03 mL, 0.28 mmol) was added. The mixture was stirred for 16 h, the solvents removed under vacuum and the residue was purified by silca gel flash chromatography to afford the product as a light yellow solid (37 mg, 54% yield). R_f = 0.5 (DCM/MeOH, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 3H), 3.77 (s, 3H), 5.25 (s, 2H), 6.71 (dd, J = 2.9, 4.0 Hz, 1H), 7.00 (d, J = 4.9 Hz, 1H), 7.36 (dd, J = 1.5, 4.0 Hz, 1H), 7.95 (dd, J = 1.5, 2.9 Hz, 1H), 8.15 (d, J = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.9, 41.9, 52.3, 113.4, 113.5, 120.4, 122.6,

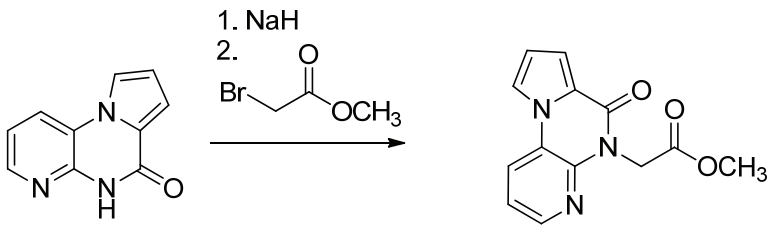
122.7, 124.2, 134.8, 142.1, 143.1, 155.5, 169.3; HRMS (ESI) m/z calcd for $C_{14}H_{14}N_3O_3$ ($[M+H]^+$) 272.1035; found 272.1042.



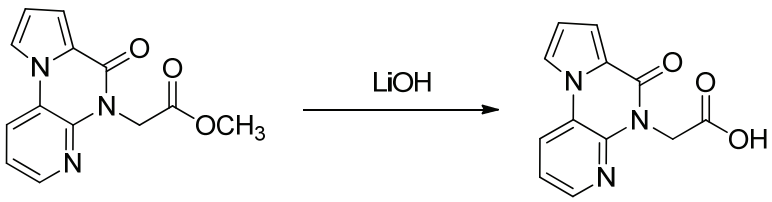
2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid. Methyl 2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)acetate (517 mg, 1.91 mmol) was dissolved in 20 mL of MeOH/H2O/THF (1:1:4). Lithium hydroxide monohydrate (68.5 mg, 2.86 mmol, 1.5 equiv.) was added. The mixture was stirred at room temperature for 16 h. The solvents were removed and residue was dissolved in water, washed with ether, then neutralized with 2N HCl to pH = 3. The precipitate was filtered and dried under vacuum to afford the product as a white solid (356 mg, 73% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.85 (s, 3H), 5.02 (s, 2H), 6.80 (dd, *J* = 2.9, 3.9 Hz, 1H), 7.29-7.19 (m, 2H), 12.90 (s, 1H), 8.27-8.17 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 22.2, 41.6, 112.7, 113.3, 119.5, 122.8, 123.3, 123.9, 135.9, 141.4, 143.1, 154.5, 169.8; HRMS (ESI) m/z calcd for $C_{13}H_{12}N_3O_3$ ($[M+H]^+$) 258.0879; found 258.0894.

Synthetic sequence to the unsubstituted scaffold:



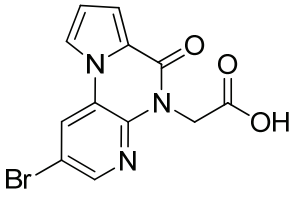


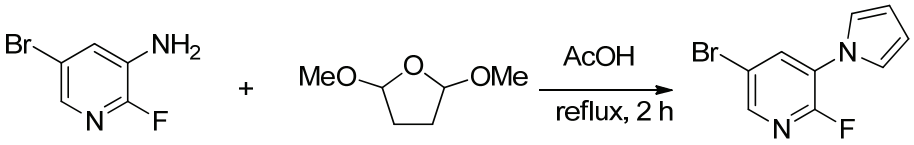
Methyl 2-(6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetate. To a solution of pyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one[13] (1.03 g, 5.55 mmol) in 20 mL of DMF, was added NaH (60%, 249 mg, 6.22 mmol, 1.1 equiv.). The mixture was stirred at room temperature for 1 h. Methyl bromoacetate (0.59 mL, 6.22 mmol, 1.1 equiv.) was added. The mixture was stirred for 16 h, the solvents removed under vacuum and the residue was purified by silca gel flash chromatography to afford the product as a light yellow solid (400 mg, 1.55 mmol, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.25 (s, 2H), 6.71 (dd, *J* = 2.8, 3.9 Hz, 1H), 7.19 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.30 (dd, *J* = 1.2, 3.7 Hz, 1H), 7.66 (dd, *J* = 1.5, 2.8 Hz, 1H), 7.94 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.30 (dd, *J* = 1.5, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 41.3, 52.4, 113.9, 114.1, 117.0, 118.5, 120.2, 121.7, 122.9, 141.4, 144.3, 155.6, 169.2; HRMS (ESI) m/z calcd for $C_{13}H_{12}N_3O_3$ ($[M+H]^+$), 258.0879, found 258.0872.



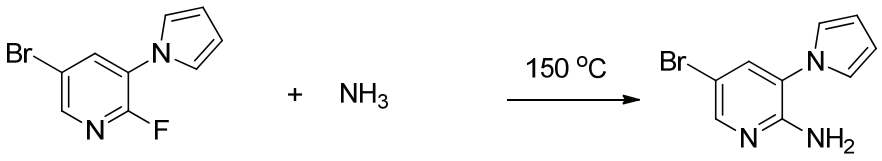
2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid. Methyl 2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)acetate (418 mg, 1.62 mmol) was dissolved in 20 mL of MeOH/H2O/THF (1:1:4). Lithium hydroxide monohydrate (102 mg, 2.43 mmol, 1.5 equiv.) was added. The mixture was stirred at room temperature for 16 h. The solvents were removed and residue was dissolved in water, washed with ether, then neutralized with 2N HCl to pH = 3. The precipitate was filtered and dried under vacuum to afford the product as a white solid (304 mg, 1.25 mmol, 77% yield). ^{1}H NMR (400 MHz, DMSO) δ 5.02 (s, 2H), 6.79 (dd, *J* = 2.8, 3.8 Hz, 1H), 7.17 (dd, *J* = 1.4, 3.9 Hz, 1H), 7.38 (dd, *J* = 4.8, 8.1 Hz, 1H), 8.32 (dd, *J* = 1.5, 2.8 Hz, 1H), 8.37 (dd, *J* = 1.4, 4.8 Hz, 1H), 8.58 (dd, *J* = 1.4, 8.1 Hz, 1H), 12.97 (s, 1H); ^{13}C

NMR (101 MHz, DMSO) δ 41.0, 113.0, 113.8, 119.2, 119.6, 122.1, 123.2, 140.8, 144.4, 154.7, 169.7; HRMS (ESI) m/z calcd for $C_{12}H_{10}N_3O_3$ ([M+H]$^+$), 244.0722; found 244.0717.

Synthetic sequence to the bromo substituted scaffold: 

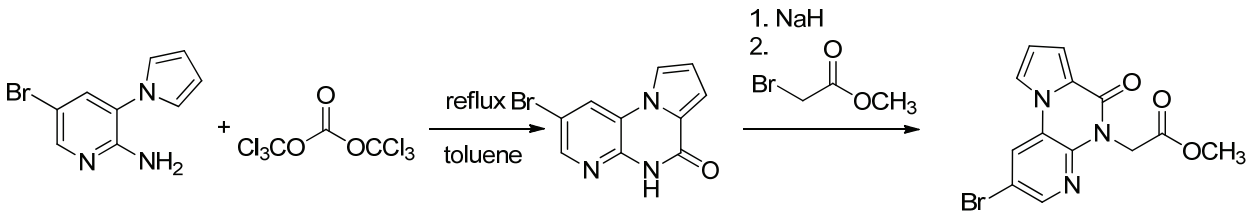


5-Bromo-2-fluoro-3-(1*H*-pyrrol-1-yl)pyridine. 5-Bromo-2-fluoropyridin-3-amine (4.98 g, 2.60 mmol) and 2,5-dimethoxytetrahydrofuran (361 mg, 2.73 mmol, 1.05 equiv.) were suspended in acetic acid (10 mL), refluxed for 2 h and the reaction allowed to cool to rt. The solvents were removed in vacuo and the residue was purified by silca gel chromatography to afford the product as a light colored oil (5.40 g, 2.24 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, J = 2.0 Hz, 2H), 7.09 (d, J = 2.0 Hz, 2H), 7.93 (d, J = 8.3 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ111.7, 116.5, 116.6, 120.8, 120.9, 125.1, 125.4, 135.7, 135.8, 143.9, 144.1, 152.9, 155.3; HRMS (ESI) m/z calcd for $C_9H_6FBrFN_2$ ([M]$^+$), 239.9698, found 239.9685.



5-Bromo-3-(1H-pyrrol-1-yl)pyridin-2-amine. 5-Bromo-2-fluoro-3-(1H-pyrrol-1-yl)pyridine (5.06 g, 21.0 mmol) was dissolved in 80 mL of ammonia (7N in MeOH) in a sealed tube (250 mL). The mixture was heated at 150 ^{o}C for 2 days protected with a blast shield. The mixture was cooled to room temperature, then cooled in an ice bath for 30 min and filtered cold. The filtrate

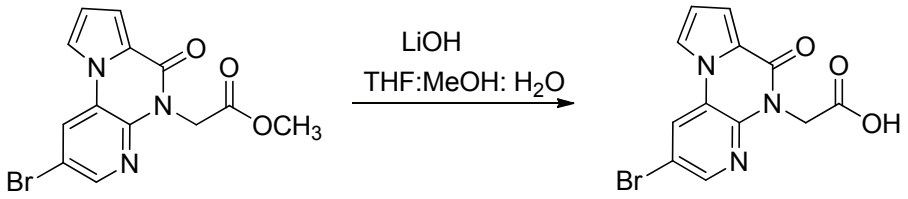
was evaporated to dryness and purified by flash chromatography to give the previously reported product[14] as a white solid (3.0 g, 12.6 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 2H), 6.49-6.33 (m, 2H), 6.86-6.84 (m, 2H), 7.54 (d, J = 2.2 Hz, 1H), 8.13 (d, J = 2.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.0, 110.7, 121.2, 123.2, 136.4, 147.7, 153.2.



2-Bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one. 5-Bromo-3-(1H-pyrrol-1-yl)pyridin-2-amine (2.00 g, 8.40 mmol) and triphosgene (3.74 g, 12.6 mmol, 1.5 equiv.) were dissolved in 100 mL of toluene. The mixture was refluxed for 3 h, then cooled to room temperature. The red solid was collected after filtration and washed with CH_3CN to afford the crude product (1.93 g, 7.31 mmol, 87% yield). The material was used directly for next step reaction without further purification. ^{1}H NMR (400 MHz, DMSO) δ 6.75 (dd, J = 2.8, 3.8 Hz, 1H), 7.09 (dd, J = 1.4, 3.8 Hz, 1H), 8.28 (dd, J = 1.4, 2.9 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H), 8.81 (d, J = 2.0 Hz, 1H), 11.87 (s, 1H). HRMS (ESI) m/z calcd for $C_{10}H_7BrN_3O$ ($[M+H]^+$), 263.9772, found 263.9755.

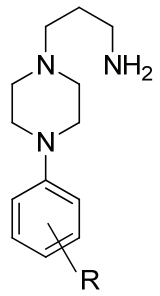
Methyl 2-(2-bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)acetate. To a solution of 2-bromopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (1.00 g, 3.79 mmol) in 20 mL of DMF, was added NaH (60%, 167 mg, 4.17 mmol, 1.1 equiv.). The mixture was stirred at room temperature for 1 h. Methyl bromoacetate (0.39 mL, 4.17 mmol, 1.1 equiv.) was added. The mixture was stirred for 16 h, the solvents removed under vacuum and the residue was purified by silca gel flash chromatography to afford the product as a light yellow solid (613 mg, 1.82 mmol, 48% yield). R_f = 0.5 (DCM/MeOH, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 5.20 (s,

2H), 6.69 (dd, *J* = 2.9, 4.0 Hz, 1H), 7.26 (dd, *J* = 1.3, 4.0 Hz, 1H), 7.58 (dd, *J* = 1.4, 2.9 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 8.29 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 41.4, 52.4, 113.5, 114.6, 114.7, 117.2, 120.9, 122.8, 124.2, 140.3, 144.8, 155.2, 168.9; HRMS (ESI) m/z calcd for $C_{13}H_{11}BrN_3O_3$ ($[M+H]^+$) 337.9963; found 337.9952.

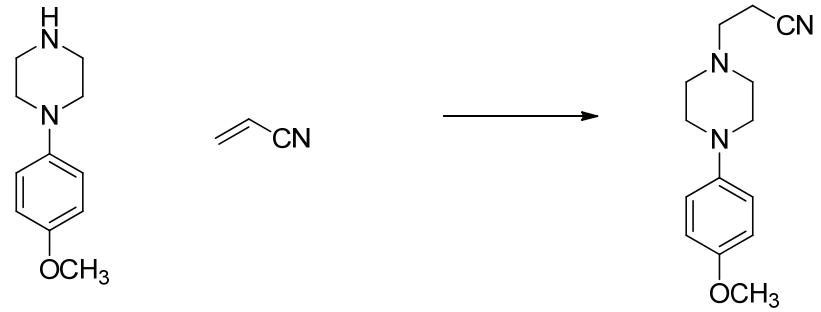


2-(2-Bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid. Methyl 2-(2-bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetate (287 mg, 0.89 mmol) was dissolved in 20 mL of MeOH/H2O/THF (1:1:4). Lithium hydroxide monohydrate (56 mg, 1.34 mmol, 1.5 equiv.) was added. The mixture was stirred at room temperature for 16 h. The solvents were removed and residue was dissolved in water, washed with ether, then neutralized with 2N HCl to pH = 3. The precipitate was filtered and dried under vacuum to afford the product as a white solid (212 mg, 0.66 mmol, 74% yield). ^{1}H NMR (400 MHz, DMSO) δ 4.97 (s, 2H), 6.81 (dd, *J* = 2.9, 3.8 Hz, 1H), 7.19 (dd, *J* = 1.4, 3.9 Hz, 1H), 8.36 (dd, *J* = 1.4, 2.9 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 8.93 (d, *J* = 2.0 Hz, 1H), 13.04 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d6) δ 41.1, 113.2, 113.6, 114.2, 111.9, 120.6, 122.0, 125.5, 139.9, 144.4, 154.4, 169.5; HRMS (ESI) m/z calcd for $C_{12}H_9BrN_3O_3$ ($[M+H]^+$) 321.9827; found 321.9812.

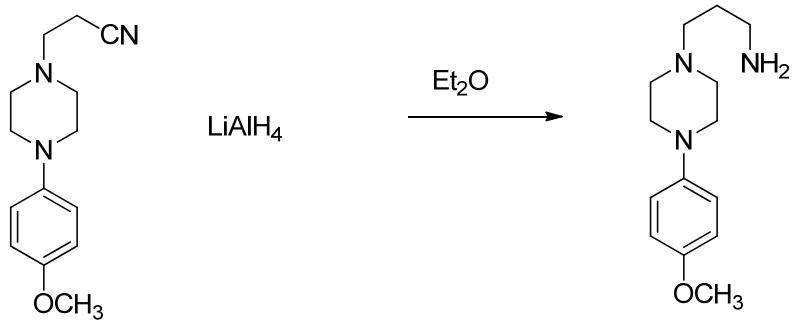
Aminopropylpiperazine fragments:



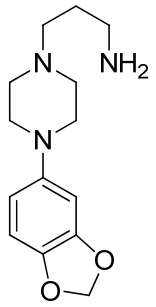
The preparation of aminopiperazine fragments for R = 4-methoxy,[15], [16] 4-chloro,[25, 17] 4-methyl,[25, 26, 18, 19] 4-fluoro[20] and hydrogen[26, 29, 21, 22] have been previously reported. The preparations of 4-methoxy, 2,4-dimethoxy, 3,4-dioxomethylene aminopiperazine fragments are given below.



3-(4-(4-methoxyphenyl)piperazin-1-yl)propanenitrile. 4-methoxyphenypiperazine (0.92 g, 4.68 mmol) and acrylonitrile (0.31 mL, 4.68 mmol) were mixed together neat in a 10 mL reaction tube and stirred for 16 h at rt. The crude reaction mixture was purified by silica gel chromatography to give the product as a white solid (0.80 g, 3.26 mmol, 70% yield). R_f = 0.3 (EtOAC:hexanes 1:8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (t, *J* = 7.0 Hz, 2H), 2.74 – 2.64 (m, 4H), 2.78 (t, *J* = 7.0 Hz, 2H), 3.17-3.07 (m, 4H), 3.79 (s, 3H), 6.90 – 6.82 (m, 2H), 6.98 – 6.90 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9, 50.6, 52.8, 53.4, 55.6, 114.5, 118.4, 118.8, 145.5, 154.0. This data is consistent with that previously reported.[9]

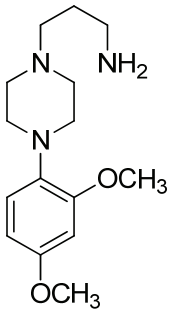


3-(4-(4-methoxyphenyl)piperazin-1-yl)propan-1-amine. A solution of 3-(4-(4-methoxyphenyl)piperazin-1-yl)propanenitrile (0.80 g, 3.26 mmol) in ether (15 mL) was added to a suspension of $LiAlH_4$ (0.19 g, 4.89 mmol) in ether (5 mL). The mixture was stirred at room temperature for 16 h, then quenched with 2N NaOH (1 mL). The organics were separated, dried over MgSO4 and evaporated to give the previously reported aminopiperazine[1, 2] (0.68 g, 2.73 mmol, 84% yield) as a white solid, which was used directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75-1.54 (m, 2H), 2.51-2.37 (m, 2H), 2.67-2.53 (m, 4H), 2.76 (t, *J* = 6.8 Hz, 2H), 2.87 (br s, 2H), 3.15-3.04 (m, 4H), 3.75 (s, 3H), 6.82 (d, *J* = 9.1 Hz, 2H), 6.89 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 30.1, 40.6, 50.6, 53.5, 55.5, 56.4, 114.4, 118.1, 145.7. HRMS (m/z): calcd for $C_{14}H_{24}N_3O$ ($[M+H]^+$) 250.1914; found 250.1912.

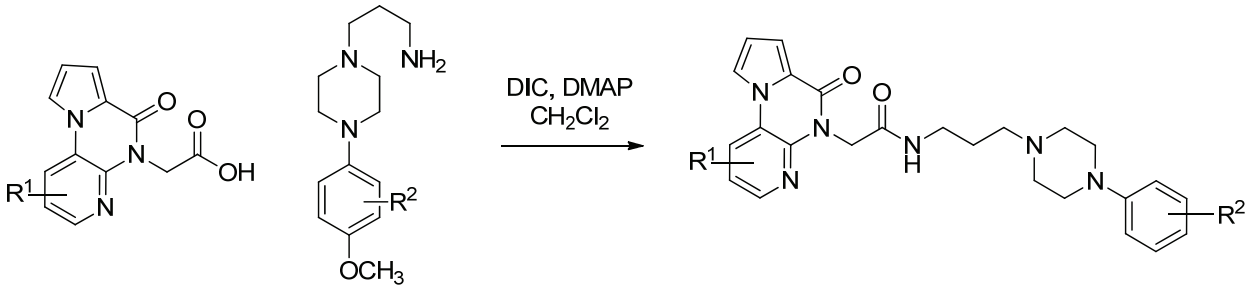


3-(4-(Benzo[d][1,3]dioxol-5-yl)piperazin-1-yl)propan-1-amine. The sequence described above was applied to 1-(benzo[d][1,3]dioxol-5-yl)piperazine to give the amino piperazine fragment, which was used for the coupling step without further purification ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 2.4, 8.5 Hz, 1H), 5.91 (s, 2H),

3.15-3.05 (m, 4H), 2.79 (t, J = 6.8 Hz, 2H), 2.67-2.56 (m, 4H), 2.53-2.42 (m, 2H), 1.73-1.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 147.5, 141.5, 108.9, 108.2, 100.8, 99.9, 56.4, 53.4, 50.8, 40.8, 30.6; HRMS (m/z): calcd for $C_{14}H_{22}N_3O_2$ ($[M+H]^+$) 264.1712; found 264.1703.



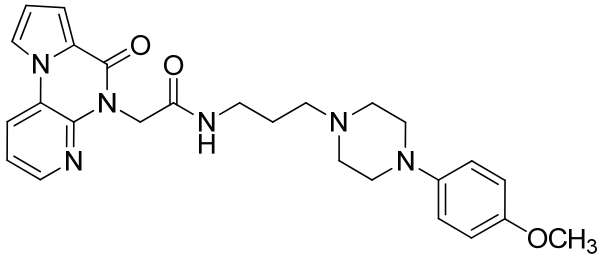
3-(4-(2,4-Dimethoxyphenyl)piperazin-1-yl)propan-1-amine. The sequence described above was applied to 1-(3,4-dimethoxyphenyl)piperazine to give the amino piperazine fragment, which was used for the coupling step without further purification ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, J = 8.6 Hz, 1H), 6.40 (d, J = 2.7 Hz, 1H), 6.35 (dd, J = 2.7, 8.6 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.95 (s, br., 4H), 2.70 (t, J = 6.8 Hz, 2H), 2.58 (s, br., 4H), 2.45-2.34 (m, 2H), 1.65-1.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 153.4, 135.3, 118.5, 103.3, 99.9, 56.6, 55.4, 55.4, 53.6, 51.2, 40.9, 30.6. HRMS (m/z): calcd for $C_{15}H_{26}N_3O_2$ ($[M+H]^+$) 280.2025; found 280.2026.



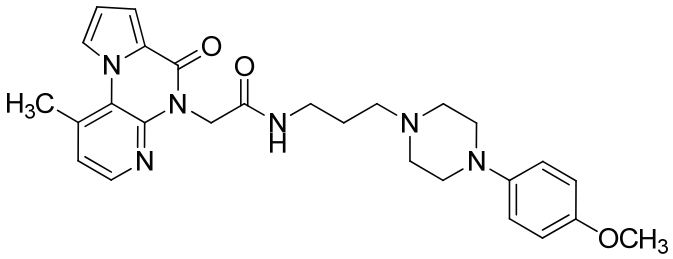
General procedure for the coupling of the acid scaffold and amino fragment.

The carboxylic acid scaffold (1 equiv.), amine fragment (1.4 equiv.) and DMAP (0.1 equiv.) were dissolved in 1 mL of DCM. Diisopropylcarbodiimide (4.8 equiv.) was added. The mixture

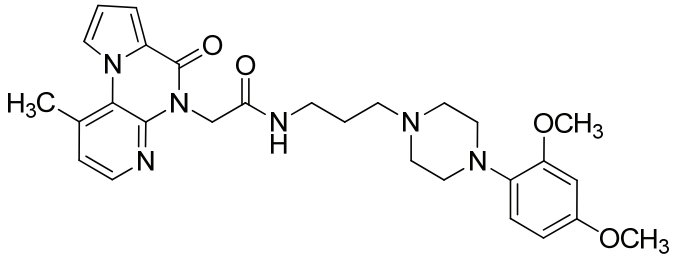
was stirred at room temperature for 16 h. The reaction mixture was purified directly by silica gel flash chromatography (DCM/MeOH) to afford the coupled product.



N*-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propyl)-2-(6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetamide 4*{1} (CID22553442). 2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(4-methoxyphenyl)piperazin-1-yl)propan-1-amine (42 mg, 0.17 mmol) were reacted according the general procedure to afford the product as an off-white solid (19 mg, 0.040 mmol, 32% yield). ^{1}H NMR (400 MHz, CDCl3) δ 8.22 (dd, *J* = 1.5, 4.8 Hz, 1H), 7.77 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.48 (dd, *J* = 1.4, 2.8 Hz, 1H), 7.16 (dd, *J* = 1.4, 3.9 Hz, 1H), 7.12 (s, 1H), 7.07 (dd, *J* = 4.8, 8.0 Hz, 1H), 6.76 (s, 4H), 6.58 (dd, *J* = 2.8, 3.9 Hz, 1H), 5.02 (s, 2H), 3.69 (s, 3H), 3.34 (dd, *J* = 5.8, 11.9 Hz, 2H), 2.96 – 2.83 (m, 4H), 2.57 – 2.47 (m, 4H), 2.42 (t, *J* = 6.3 Hz, 2H), 1.71 – 1.58 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 155.9, 153.8, 145.4, 144.4, 141.6, 122.9, 121.8, 120.2, 118.5, 118.0, 116.9, 114.4, 114.1, 113.9, 57.3, 55.6, 53.4, 50.4, 43.5, 39.5, 25.1. HRMS (ESI) m/z calcd for $C_{26}H_{31}N_6O_3$ ($[M+H]^+$) 475.2452; found 475.2448.

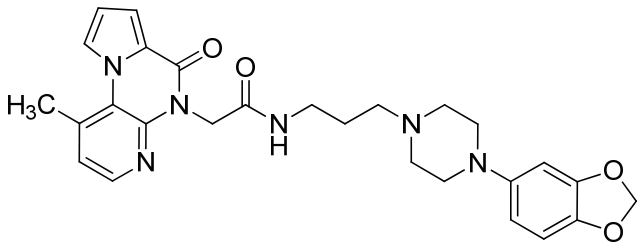


N*-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propyl)-2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetamide 4*{13} (CID44665680). 2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(4-methoxyphenyl)piperazin-1-yl)propan-1-amine (44 mg, 0.17 mmol) were reacted according the general procedure to afford the product as a white solid (30 mg, 0.061 mmol, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75-1.69 (m, 2H), 2.49 (t, *J* = 6.4 Hz, 2H), 2.63-2.54 (m, 4H), 2.74 (s, 3H), 3.02-2.91 (m, 4H), 3.41 (dd, *J* = 5.8, 12.0 Hz, 2H), 3.78 (s, 3H), 5.11 (s, 2H), 6.68 (dd, *J* = 2.9, 4.0 Hz, 1H), 6.84 (s, 4H), 6.99 (d, *J* = 5.0 Hz, 1H), 7.12 (s, 1H), 7.33 (dd, *J* = 1.4, 4.0 Hz, 1H), 7.87 (dd, *J* = 1.4, 2.9 Hz, 1H), 8.17 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.8, 25.2, 39.4, 44.2, 50.4, 53.4, 55.6, 57.3, 113.4, 113.5, 114.4, 118.0, 122.6, 122.8, 124.1, 134.8, 142.3, 143.2, 145.4, 153.8, 155.8, 167.9; HRMS (ESI) m/z: calcd for $C_{27}H_{33}N_6O_3$ ($[M+H]^+$) 489.2609; found 489.2600.

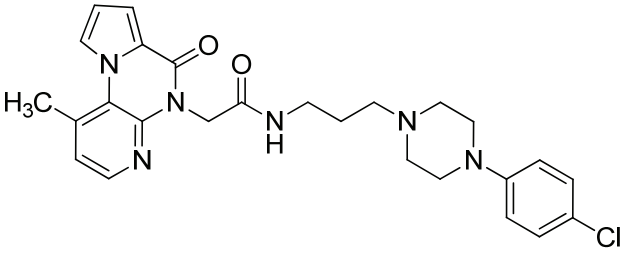


N*-(3-(4-(2,4-Dimethoxyphenyl)piperazin-1-yl)propyl)-2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetamide 4*{14} (CID44665679). 2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(2, 4-dimethoxyphenyl)piperazin-1-yl)propan-1-amine (47 mg, 0.17 mmol) were reacted according the general procedure to afford the product as a white solid (38 mg, 0.073 mmol, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72-1.55 (m, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 2.56 (s, br. 4H), 2.68 (s, 3H), 2.87 (s, br. 4H), 3.31 (dd, *J* = 5.9, 11.9 Hz, 2H), 3.69 (s, 3H), 3.75 (s, 3H), 5.03 (s, 2H),

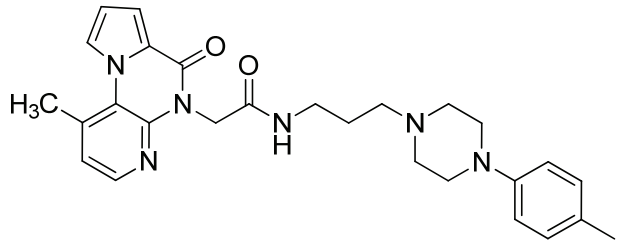
6.32 (dd, *J* = 2.7, 8.6 Hz, 1H), 6.39 (d, *J* = 2.7 Hz, 1H), 6.59 (dd, *J* = 2.9, 4.0 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 7.14 (s, 1H), 6.89 (d, *J* = 4.9 Hz, 1H), 7.24 (dd, *J* = 1.4, 4.0 Hz, 1H), 7.81 (dd, *J* = 1.4, 2.9 Hz, 1H), 8.06 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.9, 25.2, 39.3, 44.1, 51.2, 53.5, 55.4, 55.5, 57.3, 100.0, 103.4, 113.4, 118.5, 120.4, 122.6, 122.7, 124.2, 134.8, 135.0, 142.3, 143.2, 153.3, 155.8, 156.1, 167.8; HRMS (ESI) m/z calcd for $C_{28}H_{35}N_6O_4$ ($[M+H]^+$) 519.2714; found 519.2710.



N*-(3-(4-(benzo[d][1,3]dioxol-5-yl)piperazin-1-yl)propyl)-2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetamide 4*{15} (CID44665685). 2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(benzo[d][1,3]dioxol-5-yl)piperazin-1-yl)propan-1-amine (45 mg, 0.17 mmol) were reacted according the general procedure to afford the product as a white solid (24 mg, 0.048 mmol, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69-1.56 (m, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.52-2.43 (m, 4H), 2.67 (s, 3H), 2.89-2.80 (m, 4H), 3.32 (dd, *J* = 5.8, 12.0 Hz, 2H), 5.02 (s, 2H), 5.82 (s, 2H), 6.20 (dd, *J* = 2.4, 8.5 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.66-6.58 (m, 2H), 6.91 (d, *J* = 4.9 Hz, 1H), 6.96 (s, 1H), 7.25 (dd, *J* = 1.4, 4.0 Hz, 1H), 7.80 (dd, *J* = 1.4, 2.9 Hz, 1H), 8.08 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.9, 25.2, 39.4, 44.3, 50.6, 53.3, 57.3, 99.7, 100.9, 108.2, 108.8, 113.5, 113.6, 120.4, 122.6, 122.8, 124.1, 134.8, 141.3, 142.3, 143.2, 147.1, 148.3, 155.7, 167.9; HRMS (ESI) m/z calcd for $C_{27}H_{31}N_6O_4$ ($[M+H]^+$) 503.2401; found 503.2397.

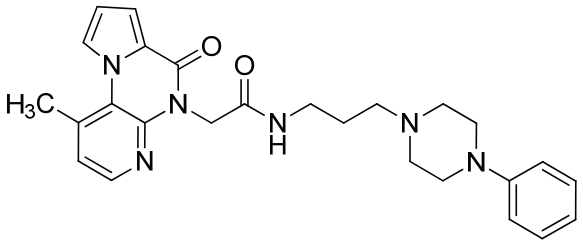


N*-(3-(4-(4-chlorophenyl)piperazin-1-yl)propyl)-2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetamide 4*{16} (CID44665687). 2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(4-chlorophenyl)piperazin-1-yl)propan-1-amine (43 mg, 0.17 mmol) were reacted according the general procedure to afford the product as an off-white solid (34 mg, 0.069 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75-1.68 (m, 2H), 2.47 (t, *J* = 6.4 Hz, 2H), 2.61-2.51 (m, 4H), 2.74 (s, 3H), 3.06-2.94 (m, 4H), 3.41 (dd, *J* = 5.9, 12.0 Hz, 2H), 6.67 (dd, *J* = 2.9, 4.0 Hz, 1H), 5.11 (s, 2H), 6.80-6.73 (m, 2H), 6.99 (d, *J* = 4.9 Hz, 1H), 7.25-7.16 (m, 2H), 7.02 (s, 1H), 7.32 (dd, *J* = 1.4, 4.0 Hz, 1H), 7.87 (dd, *J* = 1.5, 2.9 Hz, 1H), 8.17 (d, *J* = 4.9 Hz, 1H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.8, 25.3, 39.3, 44.3, 48.9, 53.1, 57.2, 113.5, 113.6, 117.0, 120.4, 122.6, 122.8, 124.1, 124.4, 128.9, 134.8, 142.3, 143.2, 149.6, 155.8, 167.9; HRMS (ESI) m/z calcd for $C_{26}H_{30}ClN_6O_2$ ($[M+H]^+$) 493.2113; found 493.2108.



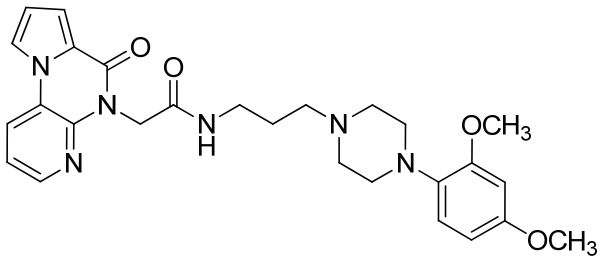
2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)-*N*-(3-(4-(p-tolyl)piperazin-1-yl)propyl)acetamide 4*{17}* (CID44665686). 2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(4-methylphenyl)piperazin-1-

yl)propan-1-amine (40 mg, 0.17 mmol) were reacted according the general procedure to afford the product as an off-white solid (29 mg, 0.061 mmol, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72-1.66 (m, 2H), 2.26 (s, 3H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.60-2.51 (m, 4H), 2.70 (s, 3H), 3.03-2.92 (m, 4H), 3.39 (dd, *J* = 5.8, 12.0 Hz, 2H), 5.08 (s, 2H), 6.65 (dd, *J* = 2.9, 4.0 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 4.9 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 7.09 (s, 1H), 7.31 (dd, *J* = 1.4, 4.0 Hz, 1H), 7.84 (dd, *J* = 1.4, 2.9 Hz, 1H), 8.14 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.4, 22.8, 25.2, 39.4, 44.2, 49.5, 53.3, 57.3, 113.4, 113.5, 116.2, 120.4, 122.6, 122.8, 124.1, 129.2, 129.6, 134.9, 142.3, 143.2, 148.9, 155.8, 167.9; HRMS (ESI) m/z calcd for $C_{27}H_{33}N_6O_2$ ($[M+H]^+$) 473.2600; found 473.2657.

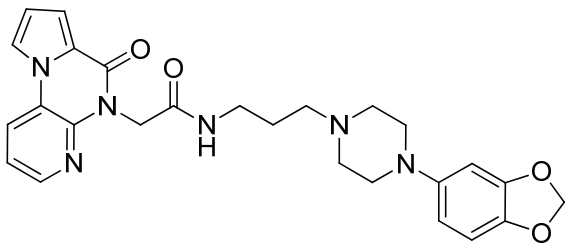


2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)-*N*-(3-(4-phenylpiperazin-1-yl)propyl)acetamide 4*{18}* (CID44665682). 2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (17 mg, 0.066 mmol) and 3-(4-phenylpiperazin-1-yl)propan-1-amine (20 mg, 0.092 mmol) were reacted according the general procedure to afford the product as an off-white solid (24 mg, 0.052 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67-1.52 (m, 2H), 2.38 (t, *J* = 6.3 Hz, 2H), 2.50-2.42 (m, 4H), 2.62 (s, 3H), 2.99-2.84 (m, 4H), 3.33 (dd, *J* = 5.8, 12.0 Hz, 2H), 5.02 (s, 2H), 6.58 (dd, *J* = 2.9, 4.0 Hz, 1H), 6.77 (dd, *J* = 7.7, 8.5 Hz, 3H), 6.90 (d, *J* = 4.9 Hz, 1H), 7.00 (s, 1H), 7.17 (dd, *J* = 1.7, 6.8 Hz, 2H), 7.25 (dd, *J* = 1.4, 4.0 Hz, 1H), 7.76 (dd, *J* = 1.4, 2.9 Hz, 1H), 8.08 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.8, 25.1, 39.5, 44.4, 48.9, 53.3, 57.4, 113.5, 113.6, 115.9, 119.7, 120.4, 122.7, 122.8, 124.0,

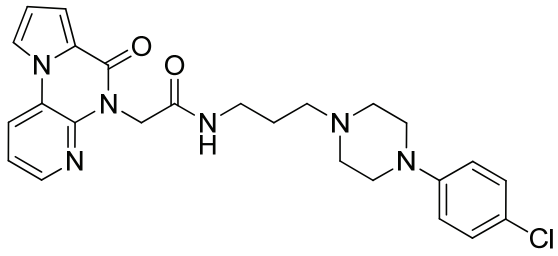
129.1, 134.9, 142.3, 143.2, 151.0, 155.8, 167.9; HRMS (ESI) m/z calcd for $C_{26}H_{31}N_6O_2$ ($[M+H]^+$) 459.2503; found 459.2507.



N*-(3-(4-(2,4-dimethoxyphenyl)piperazin-1-yl)propyl)-2-(6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetamide 4*{19} (CID44828478). 2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(2,4-dimethoxyphenyl)piperazin-1-yl)propan-1-amine (47 mg, 0.17 mmol) were reacted according the general procedure to afford the product as an off-white solid (36 mg, 0.071 mmol, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82-1.68 (m, 2H), 2.54 (t, *J* = 6.3 Hz, 3H), 2.67 (s, br. 4H), 2.98 (s, br. 4H), 3.43 (dd, *J* = 5.8, 11.8 Hz, 2H), 3.78 (s, 3H), 3.85 (s, 3H), 5.12 (s, 2H), 6.42 (dd, *J* = 2.7, 8.6 Hz, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 2.8, 3.9 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 7.15 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.25 (dd, *J* = 1.4, 3.9 Hz, 1H), 7.37 (s, 1H), 7.61 (dd, *J* = 1.4, 2.8 Hz, 1H), 7.90 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.29 (dd, *J* = 1.5, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.1, 39.4, 43.4, 51.2, 53.5, 55.5, 55.6, 57.3, 99.9, 103.3, 113.8, 114.0, 116.9, 118.4, 118.5, 120.2, 121.8, 122.9, 135.0, 141.6, 144.3, 153.4, 155.9, 156.2, 167.6; HRMS (ESI) m/z calcd for $C_{27}H_{33}N_6O_4$ ($[M+H]^+$) 505.2558; found 505.2552.

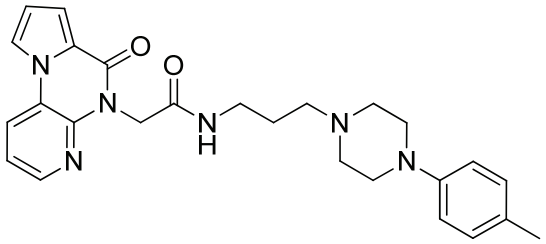


N-(3-(4-(benzo[d][1,3]dioxol-5-yl)piperazin-1-yl)propyl)-2-(6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)acetamide 4*{20}* (CID44828479). 2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(benzo[d][1,3]dioxol-5-yl)piperazin-1-yl)propan-1-amine (45 mg, 0.17 mmol) were reacted according the general procedure to afford the product as an off-white solid (24 mg, 0.49 mmol, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.57 (m, 2H), 2.40 (t, *J* = 6.3 Hz, 2H), 2.54-2.44 (m, 4H), 2.93-2.80 (m, 4H), 3.33 (dd, *J* = 5.8, 11.9 Hz, 2H), 5.01 (s, 2H), 5.82 (s, 2H), 6.21 (dd, *J* = 2.4, 8.5 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.58 (dd, *J* = 2.8, 3.9 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 4.8, 8.0 Hz, 2H), 7.16 (dd, *J* = 1.4, 3.9 Hz, 1H), 7.50 (dd, *J* = 1.4, 2.8 Hz, 1H), 7.79 (dd, *J* = 1.4, 8.1 Hz, 1H), 8.22 (dd, *J* = 1.4, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.2, 39.4, 43.6, 50.7, 53.3, 57.3, 99.7, 100.9, 108.1, 108.8, 113.9, 114.1, 116.9, 118.5, 120.2, 121.8, 122.8, 141.5, 141.6, 144.4, 147.1, 148.2, 155.9, 167.7; HRMS (ESI) m/z calcd for $C_{26}H_{29}N_6O_4$ ($[M+H]^+$) 489.2245; found 489.2237.

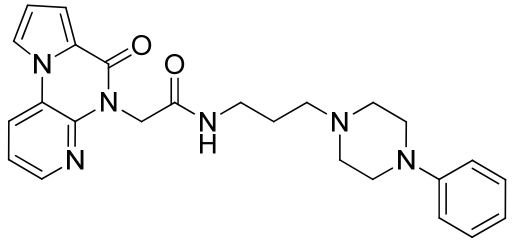


N*-(3-(4-(4-Chlorophenyl)piperazin-1-yl)propyl)-2-(6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetamide 4*{21} (CID44828476). 2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(4-chlorophenyl)piperazin-1-yl)propan-1-amine (43 mg, 0.17 mmol) were reacted according the general procedure to afford the product as an off-white solid (35 mg, 0.073 mmol, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (p, *J* = 6.3 Hz, 2H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.52-2.44 (m, 4H), 2.98-2.87 (m, 4H), 3.33

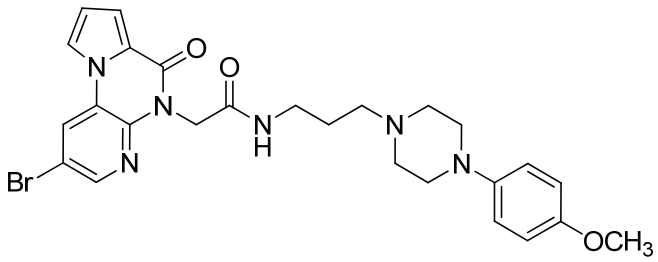
(dd, *J* = 5.9, 11.9 Hz, 2H), 5.01 (s, 2H), 6.60-6.51 (m, 1H), 6.73-6.63 (m, 2H), 7.02 (s, 1H), 7.17-7.05 (m, 4H), 7.47 (dd, *J* = 1.4, 2.7 Hz, 1H), 7.77 (dd, *J* = 1.3, 8.0 Hz, 1H), 8.22 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.2, 39.4, 43.6, 49.0, 53.1, 57.3, 113.9, 114.1, 116.9, 117.1, 118.5, 120.2, 121.8, 122.8, 124.5, 128.9, 141.6, 144.4, 149.6, 155.9, 167.7; HRMS (ESI) m/z calcd for $C_{25}H_{28}ClN_6O_2$ ($[M+H]^+$) 479.1957; found 479.1949.



2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)-N-(3-(4-(p-tolyl)piperazin-1-yl)propyl)acetamide 4*{22}* (CID44828480) 2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-(4-methylphenyl)piperazin-1-yl)propan-1-amine (40 mg, 0.17 mmol) were reacted according the general procedure to afford the product as an off-white solid (30 mg, 0.065 mmol, 53% yield). ^{1}H NMR (400 MHz, CDCl3) δ 1.63 (p, *J* = 6.3 Hz, 2H), 2.19 (s, 3H), 2.40 (t, *J* = 6.3 Hz, 2H), 2.54-2.45 (m, 4H), 2.99-2.85 (m, 4H), 3.33 (dd, *J* = 5.8, 11.9 Hz, 2H), 5.00 (s, 2H), 6.56 (dd, *J* = 2.8, 3.9 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 7.05 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.14 (dt, *J* = 4.2, 8.3 Hz, 2H), 7.46 (dd, *J* = 1.4, 2.8 Hz, 1H), 7.75 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.20 (dd, *J* = 1.5, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.4, 25.1, 39.5, 43.5, 49.6, 53.3, 57.4, 113.9, 114.1, 116.3, 117.0, 118.5, 120.2, 121.8, 122.8, 129.2, 129.6, 141.6, 144.3, 148.9, 155.9, 167.6; HRMS (ESI) m/z calcd for $C_{26}H_{31}N_6O_2$ ($[M+H]^+$) 459.2503; found 459.2501.

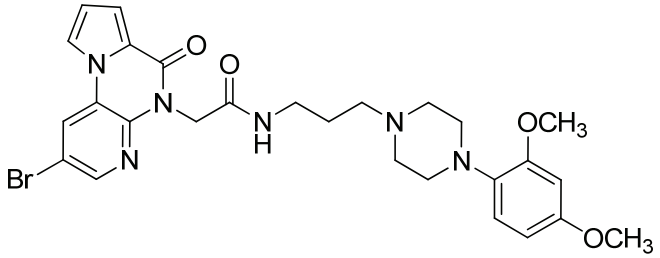


2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)-*N*-(3-(4-phenylpiperazin-1-yl)propyl)acetamide 4*{23}* (CID44828477). 2-(6-Oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (30 mg, 0.12 mmol) and 3-(4-phenylpiperazin-1-yl)propan-1-amine (37 mg, 0.17 mmol) were reacted according the general procedure to afford the product as a-white solid (40 mg, 0.090 mmol, 73% yield). ^{1}H NMR (400 MHz, CDCl3) δ 1.73 (p, *J* = 6.3 Hz, 2H), 2.50 (t, *J* = 6.3 Hz, 2H), 2.64-2.54 (m, 3H), 3.13-2.98 (m, 4H), 3.43 (dd, *J* = 5.8, 11.9 Hz, 2H), 5.10 (s, 2H), 6.64 (dd, *J* = 2.8, 3.9 Hz, 1H), 6.93-6.82 (m, 3H), 7.14 (dd, *J* = 4.8, 8.0 Hz, 1H), 7.34-7.18 (m, 4H), 7.54 (dd, *J* = 1.4, 2.8 Hz, 1H), 7.83 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.30 (dd, *J* = 1.5, 4.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.1, 39.6, 43.6, 49.0, 53.3, 57.4, 113.9, 114.1, 115.9, 117.0, 118.5, 119.7, 120.1, 121.8, 122.8, 129.1, 141.6, 144.3, 151.0, 155.9, 167.7; HRMS (ESI) m/z calcd for $C_{25}H_{29}N_6O_2$ ($[M+H]^+$) 445.2347; found 445.2344.



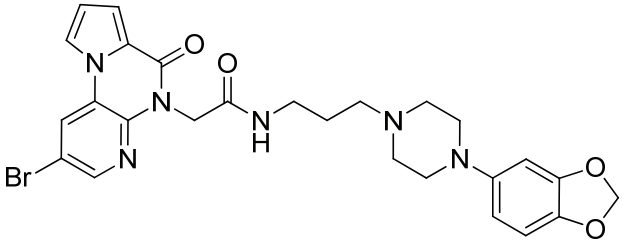
2-(2-Bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)-*N*-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propyl)acetamide 4*{24}* (CID45100475). 2-(2-Bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (20 mg, 0.062 mmol) and 3-(4-(4-bromophenyl)piperazin-1-yl)propan-1-amine (22 mg, 0.087 mmol) were reacted according the

general procedure to afford the product as an off-white solid (31 mg, 0.056 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78-1.71 (m, 2H), 2.54 (t, *J* = 6.2 Hz, 2H), 2.68-2.59 (m, 4H), 3.07-2.95 (m, 4H), 3.44 (dd, *J* = 5.7, 11.7 Hz, 2H), 3.79 (s, 3H), 5.05 (s, 2H), 6.68 (dd, *J* = 2.9, 3.8 Hz, 1H), 6.86 (s, 4H), 7.26 (dd, *J* = 1.4, 3.9 Hz, 1H), 7.36 (s, 1H), 7.51 (dd, *J* = 1.4, 2.8 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9, 39.8, 43.5, 50.5, 53.4, 55.6, 57.6, 113.5, 114.4, 114.5, 114.6, 117.2, 118.0, 120.8, 122.8, 124.3, 140.5, 144.8, 145.4, 153.8, 155.5, 167.2; HRMS (ESI) m/z calcd for $C_{26}H_{30}BrN_6O_3$ ($[M+H]^+$) 553.1557; found 553.1544.

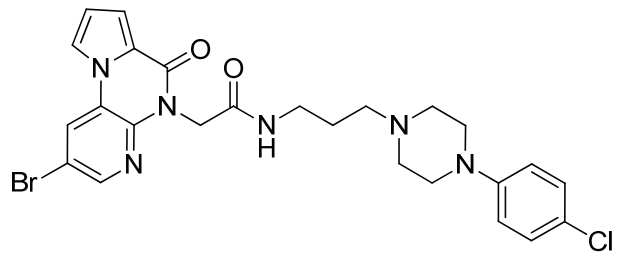


2-(2-Bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)-*N*-(3-(4-(2,4-dimethoxyphenyl)piperazin-1-yl)propyl)acetamide 4*{25}* (CID45100477). 2-(2-Bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (20 mg, 0.062 mmol) and 3-(4-(2, 4-dimethoxyphenyl)piperazin-1-yl)propan-1-amine (24 mg, 0.087 mmol) were reacted according the general procedure to afford the product as an off-white solid (34 mg, 0.058 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.73 (m, 2H), 2.58 (d, *J* = 6.0H, 2H), 2.71 (s, br. 4H), 3.01 (s, br. 4H), 3.44 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 3.86 (s, 3H), 5.07 (s, 2H), 6.44 (d, *J* = 8.7 Hz, 1H), 6.50 (s, 1H), 6.70 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 1H), 7.28 (dd, *J* = 2.7, 5.7 Hz, 2H), 7.50 (s, 1H), 7.57 (s, 1H), 8.02 (s, 1H), 8.33 (s, 1H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.8, 39.7, 43.4, 51.2, 53.5, 55.4, 55.5, 57.5, 99.9, 103.3, 113.4, 114.5, 114.6, 117.1, 118.5, 120.9, 122.9, 124.2,

134.8, 140.6, 144.8, 153.4, 155.5, 156.2, 167.1; HRMS (ESI) m/z calcd for $C_{27}H_{32}BrN_6O_4$ ($[M+H]^+$) 585.1647; found 585.1637.

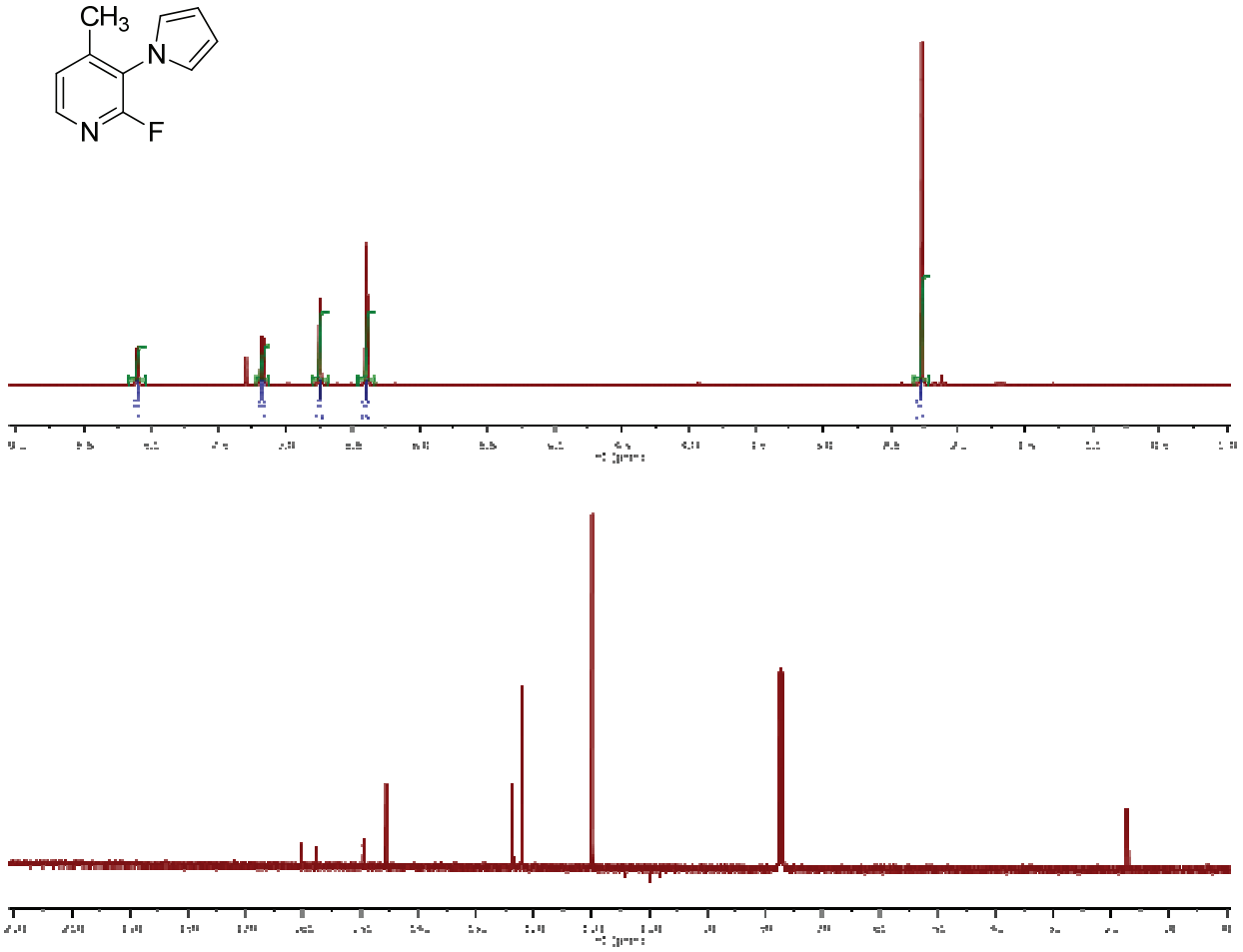


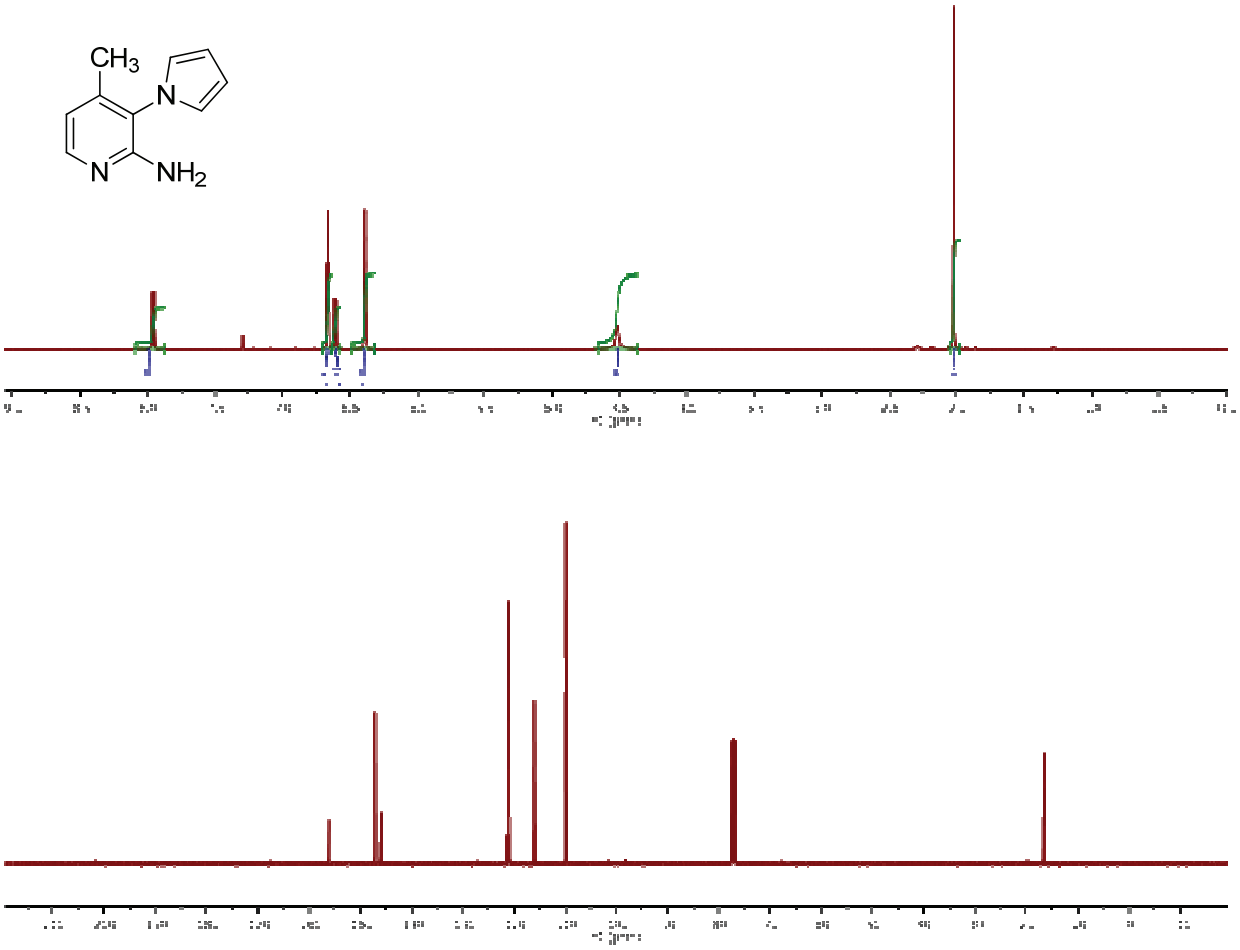
N*-(3-(4-(Benzo[d][1,3]dioxol-5-yl)piperazin-1-yl)propyl)-2-(2-bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetamide 4*{26} (CID45100476). 2-(2-Bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (20 mg, 0.062 mmol) and 3-(4-(benzo[d][1,3]dioxol-5-yl)piperazin-1-yl)propan-1-amine (23 mg, 0.087 mmol) were reacted according the general procedure to afford the product as an off-white solid (31 mg, 0.055 mmol, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70-1.58 (m, 2H), 2.44 (t, *J* = 6.2 Hz, 2H), 2.53 (s, 4H), 2.88 (d, *J* = 4.9 Hz, 4H), 3.34 (d, *J* = 5.9 Hz, 2H), 4.96 (s, 2H), 5.83 (s, 2H), 6.23 (dd, *J* = 2.4, 8.5 Hz, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 6.69-6.56 (m, 2H), 7.26-7.14 (m, 3H), 7.45 (s, 1H), 7.89 (d, *J* = 1.9 Hz, 1H), 8.24 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.9, 39.6, 43.5, 50.6, 53.3, 57.4, 99.8, 100.9, 108.2, 108.8, 113.5, 114.6, 114.7, 117.1, 120.9, 124.3, 140.5, 141.6, 144.8, 147.0, 148.2, 155.5, 167.2; HRMS (ESI) m/z calcd for $C_{26}H_{28}BrN_6O_4$ ($[M+H]^+$) 569.1333; found 569.1321.



2-(2-Bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)-*N*-(3-(4-(4-chlorophenyl)piperazin-1-yl)propyl)acetamide 4*{27}* (CID45100474). 2-(2-Bromo-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6*H*)-yl)acetic acid (20 mg, 0.062 mmol) and 3-(4-(4-chlorophenyl)piperazin-1-yl)propan-1-amine (22 mg, 0.087 mmol) were reacted according the general procedure to afford the product as an off-white solid (30 mg, 0.054 mmol, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78-1.71 (m, 2H), 2.52 (t, *J* = 6.2 Hz, 2H), 2.66-2.57 (m, 4H), 3.10-2.98 (m, 4H), 3.44 (dd, *J* = 5.8, 11.8 Hz, 2H), 5.05 (s, 2H), 6.69 (dd, *J* = 2.9, 3.9 Hz, 1H), 6.85-6.76 (m, 2H), 7.28-7.17 (m, 4H), 7.52 (dd, *J* = 1.4, 2.8 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.0, 39.7, 43.6, 49.0, 53.1, 57.5, 113.5, 114.6, 114.7, 117.1, 117.2, 120.8, 122.8, 124.3, 124.6, 128.9, 140.5, 144.9, 155.5, 167.2; HRMS (ESI) m/z calcd for $C_{25}H_{27}BrClN_6O_2$ ($[M+H]^+$) 559.1042; found 559.1031.

NMR spectra for Chemotype IV compounds and new synthetic intermediates

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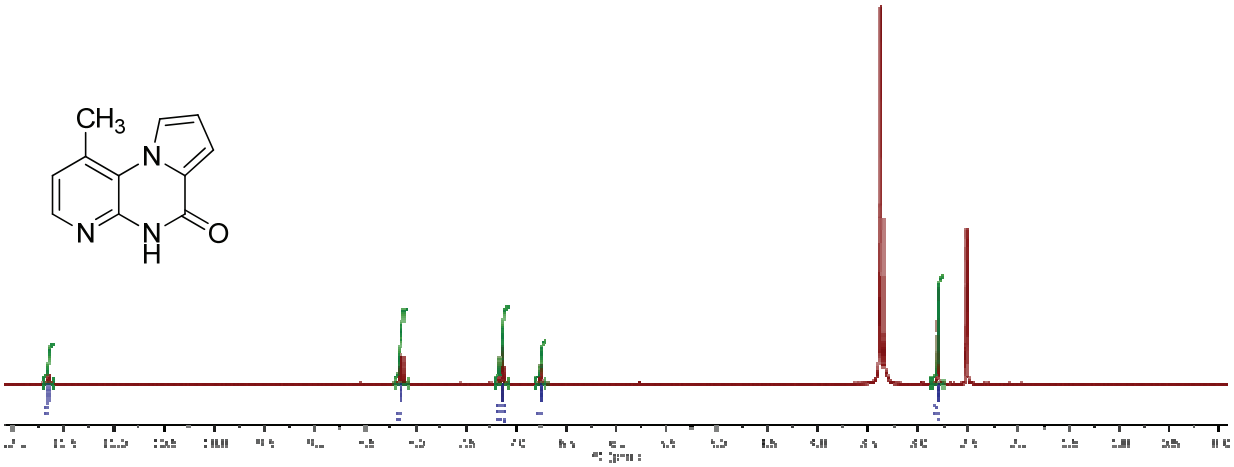
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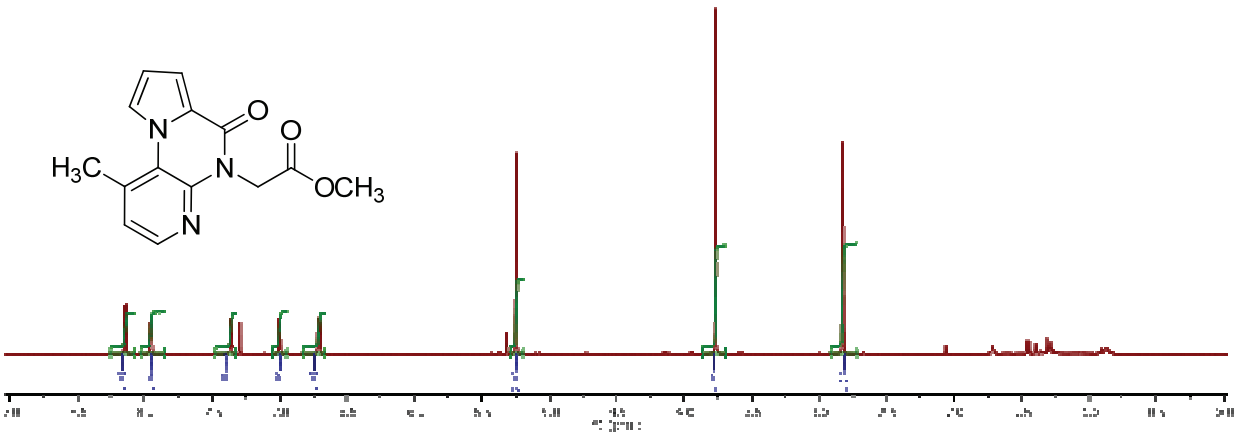
H
O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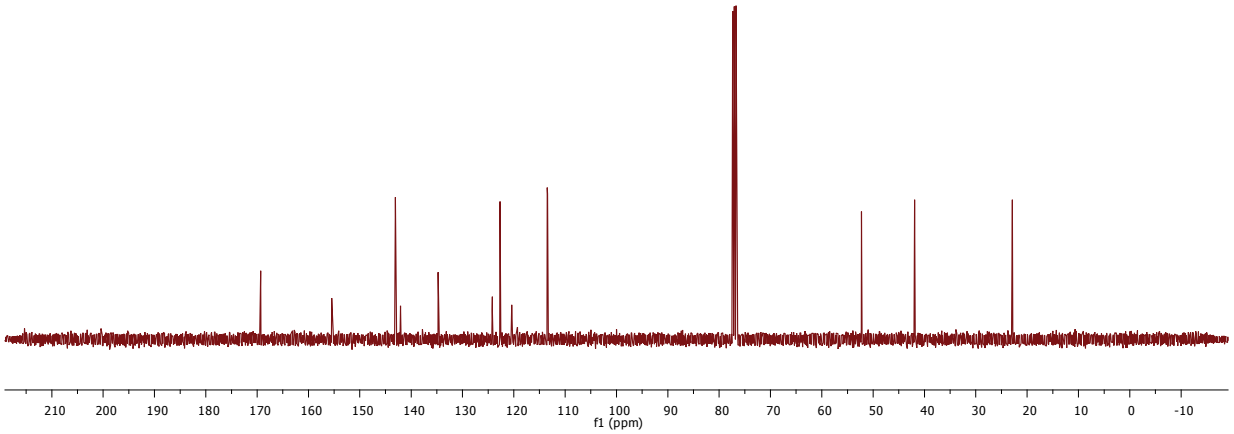
N
H3C
OCH3
N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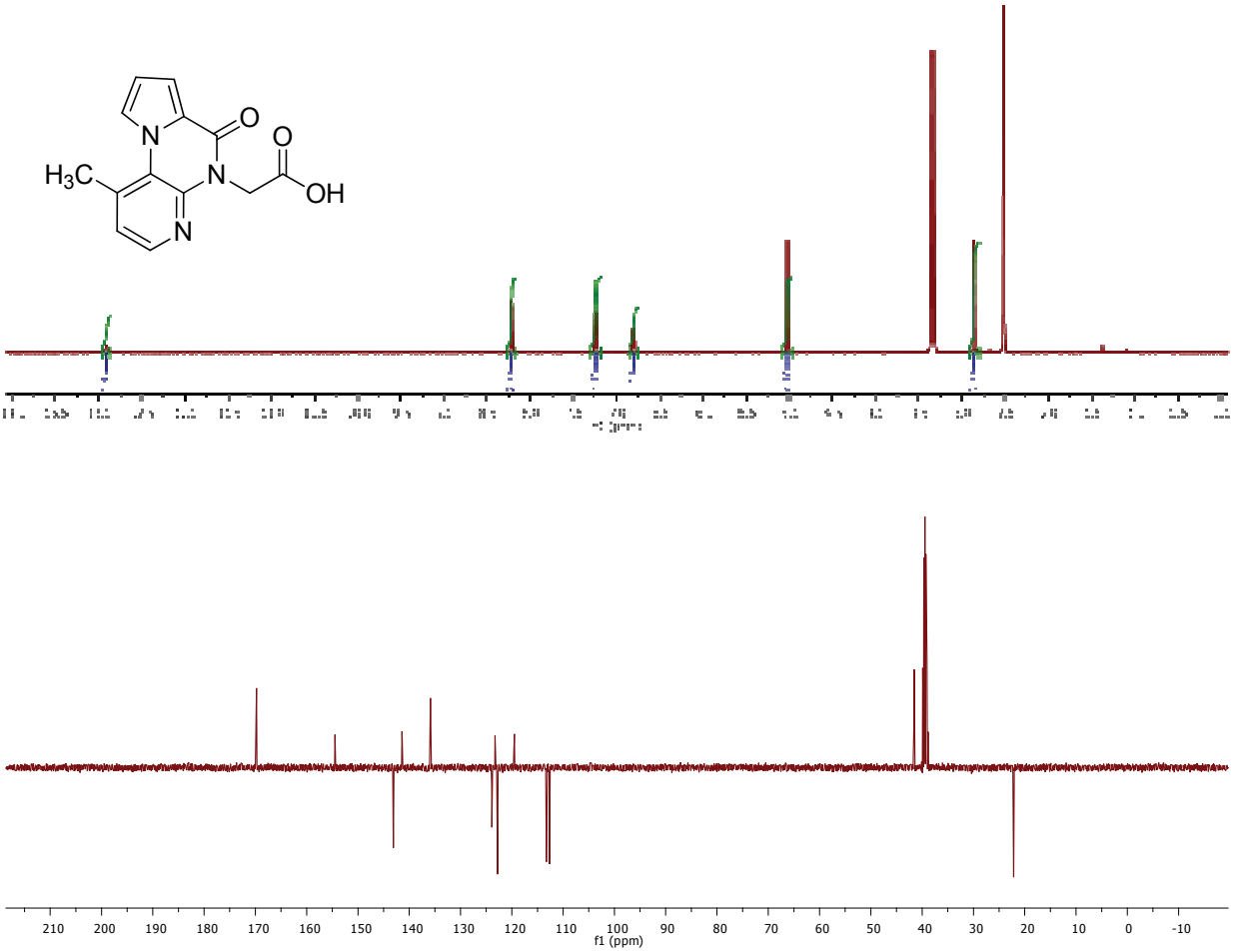
f1 (ppm)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N
H3C
OH
N
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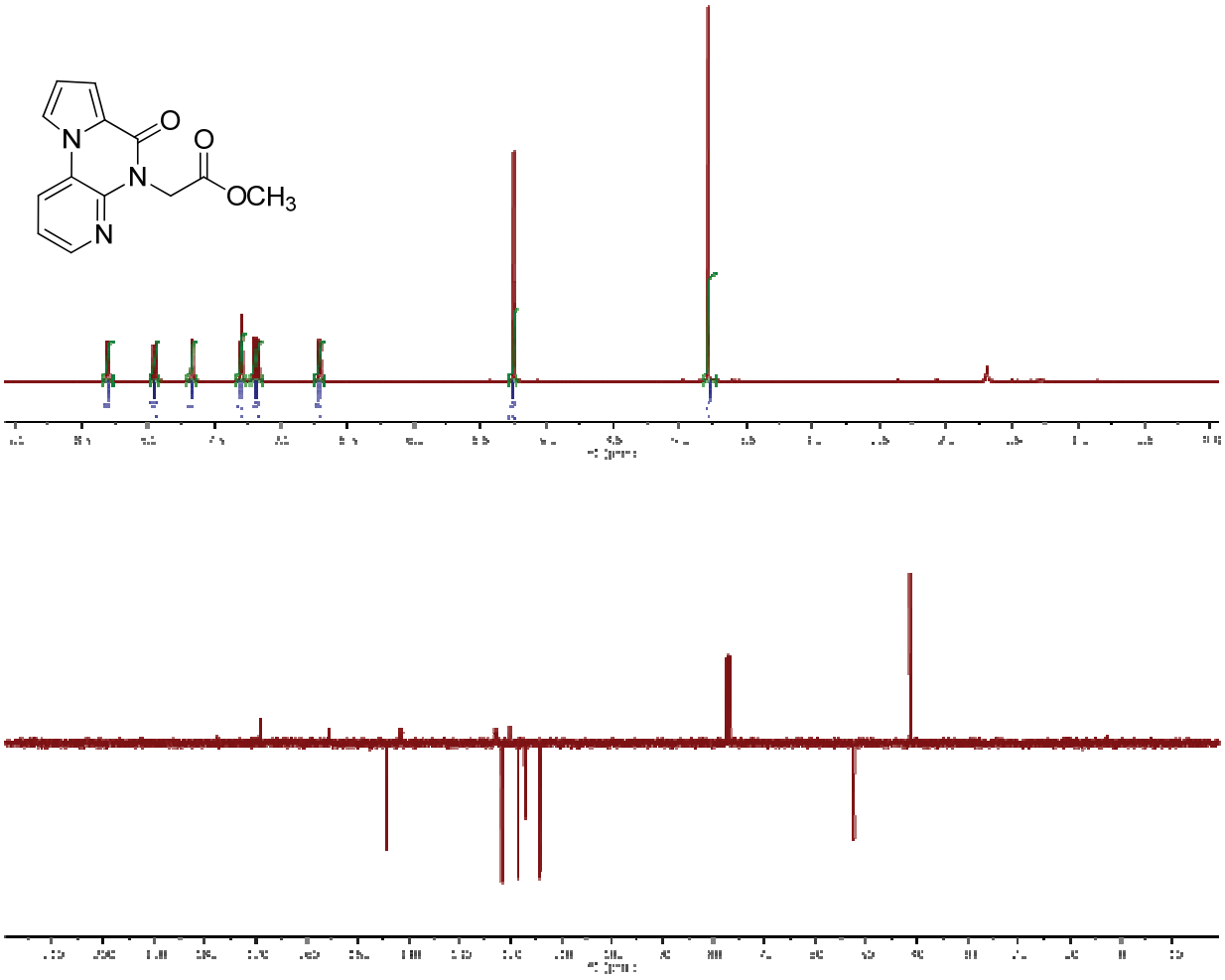
f1 (ppm)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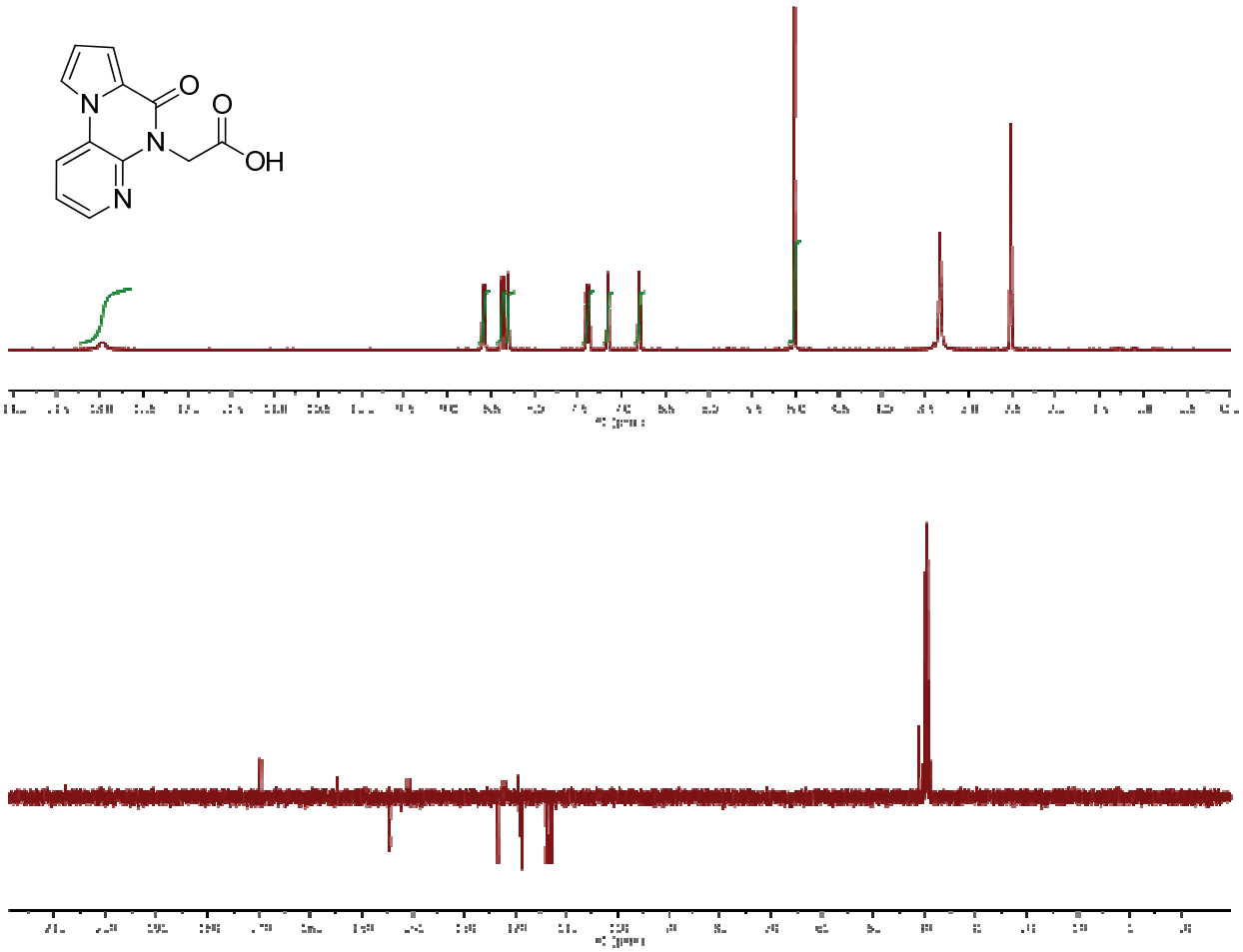
N
N
OCH3
N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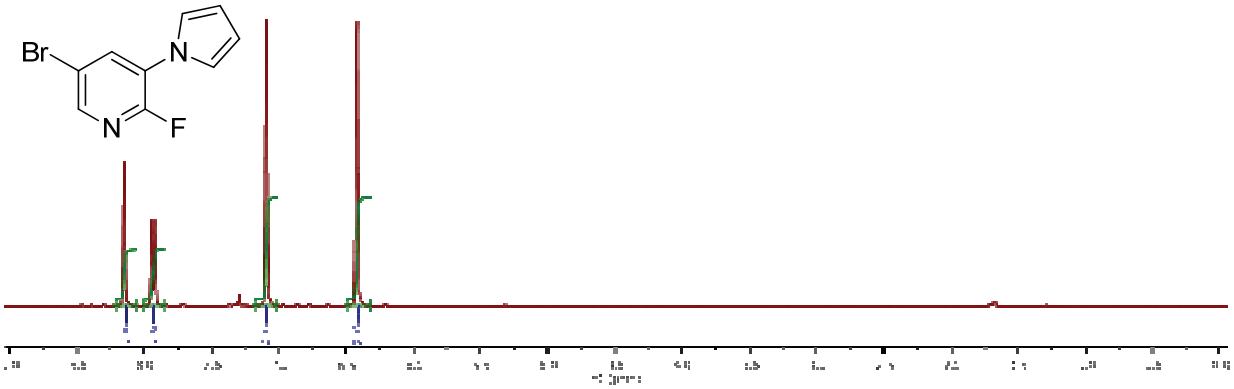
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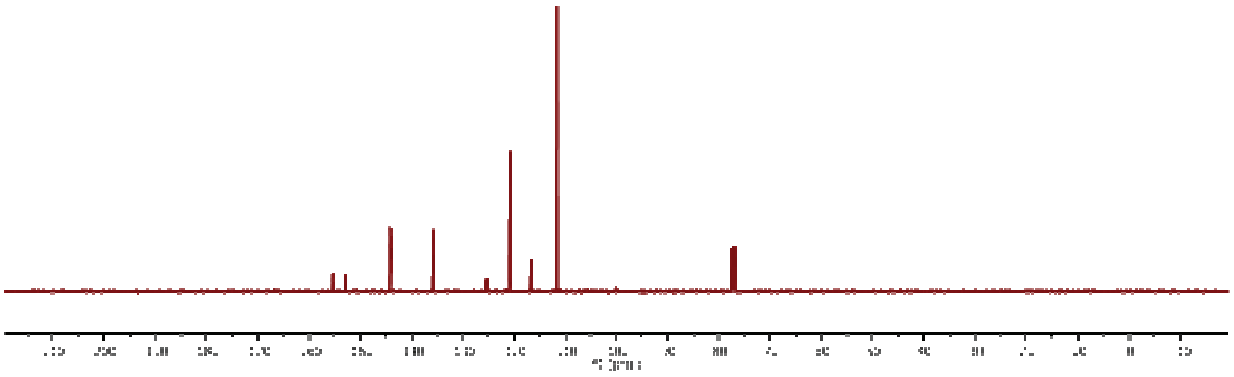
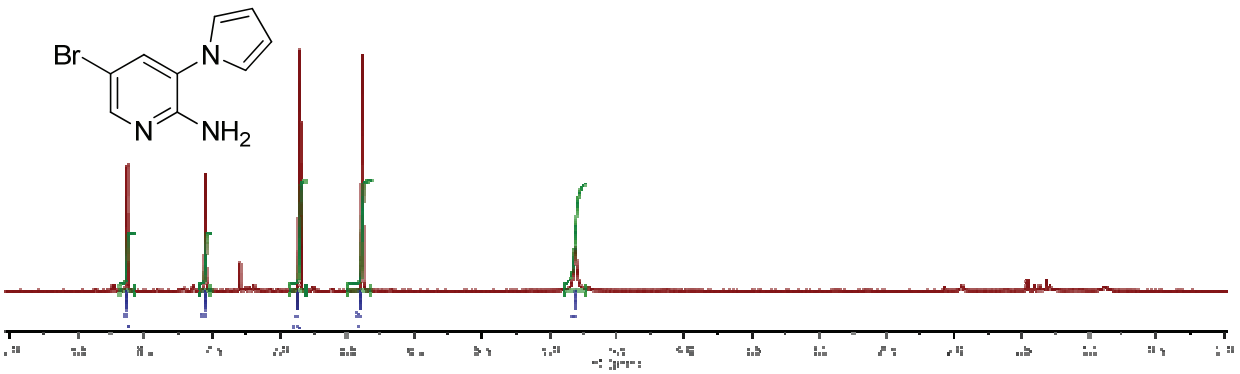
N
F

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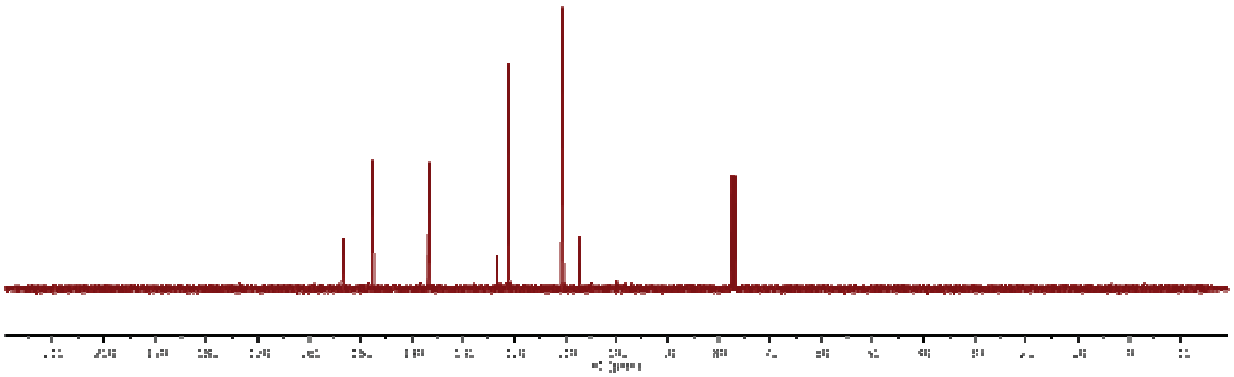

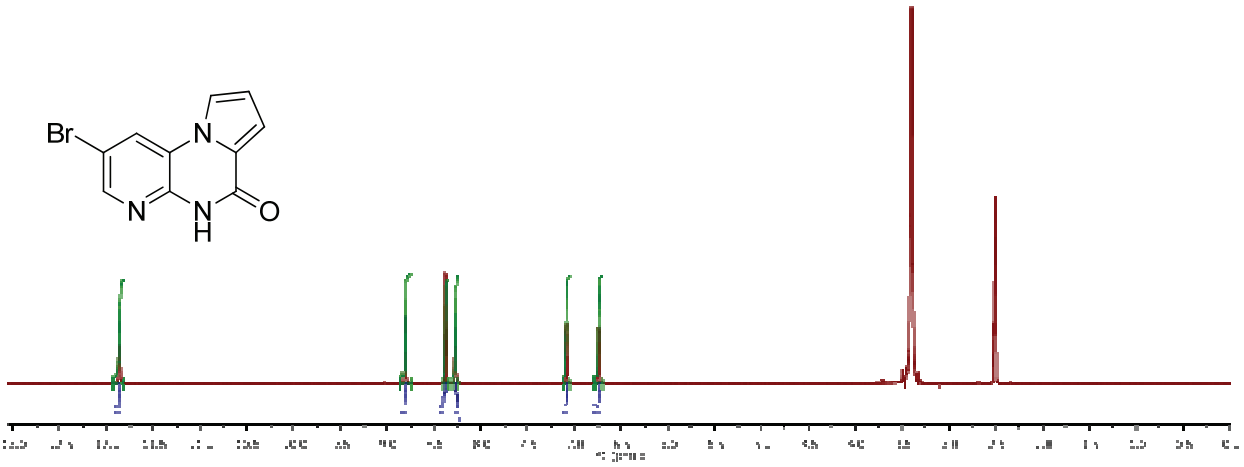
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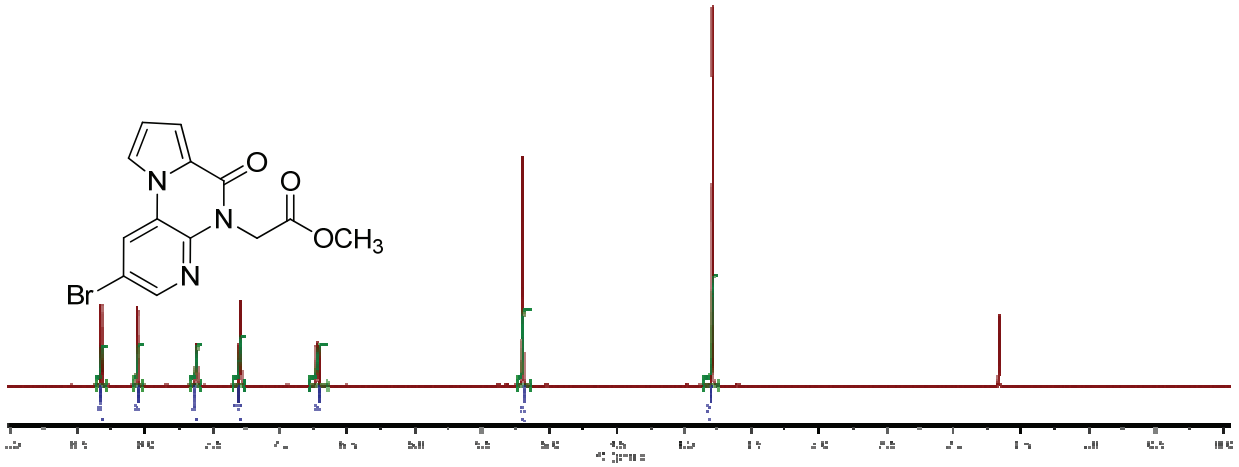
O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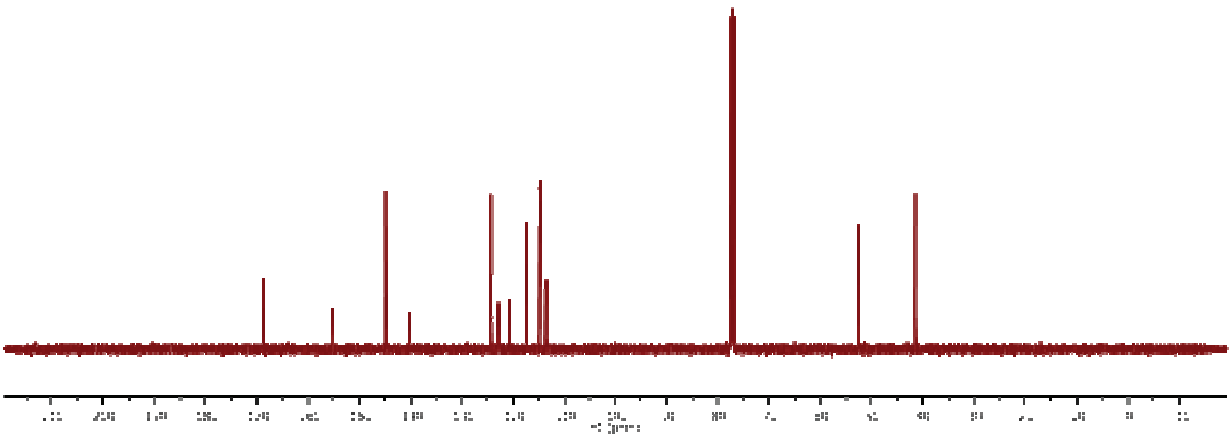
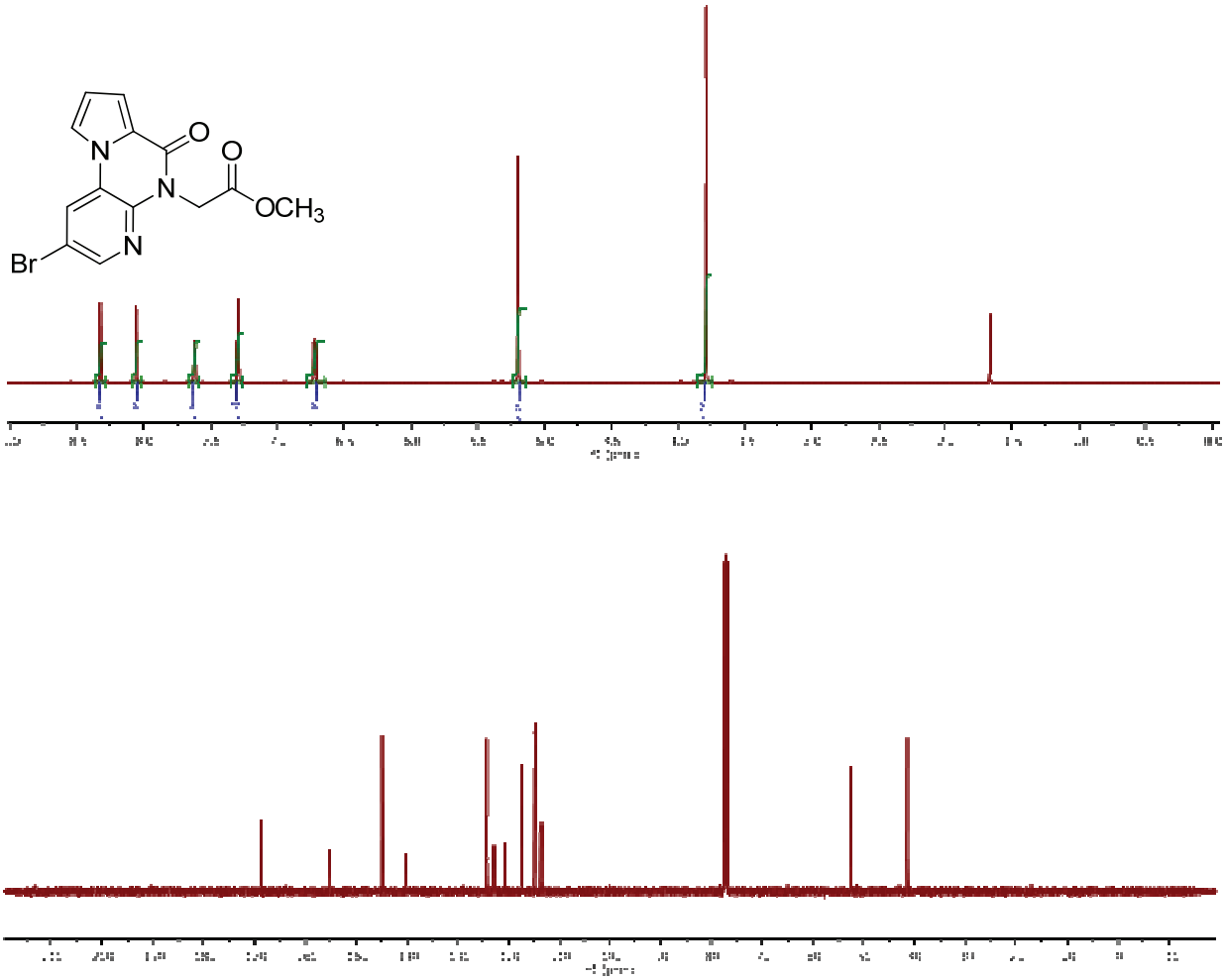
N
OCH3
N
Br

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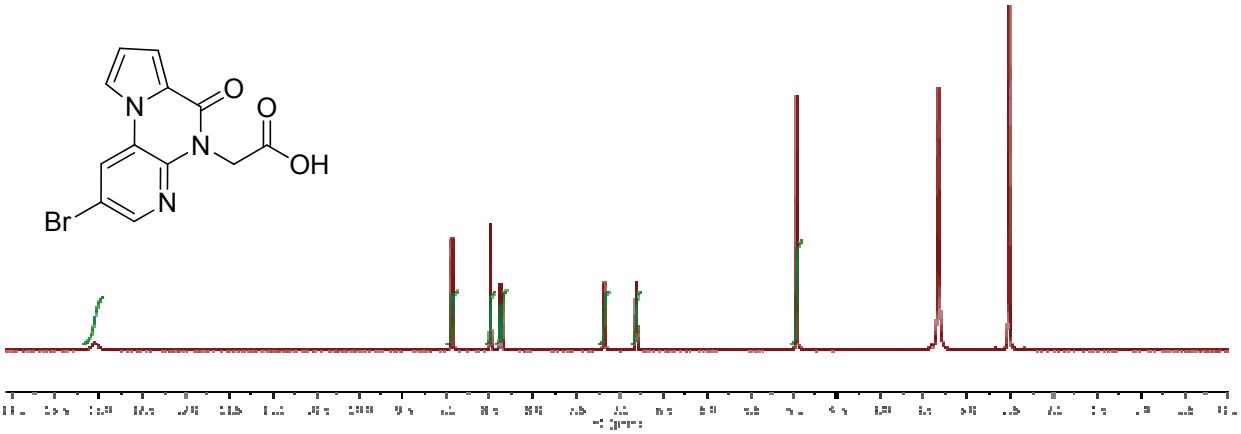
N
N
OCH3
N
Br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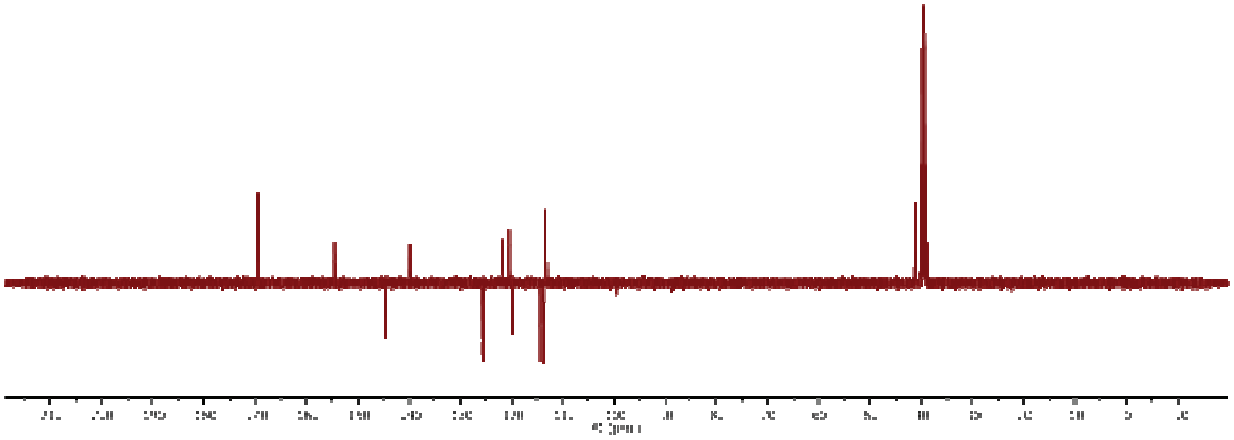

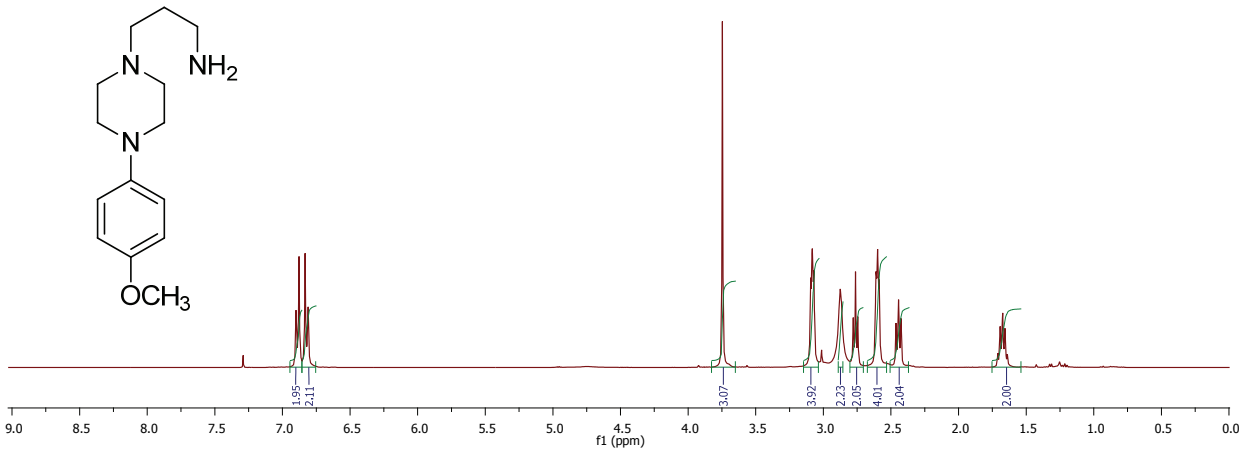
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2.05
4.01
2.04
2.00
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8.5
8.0
7.5
7.0
6.5
6.0
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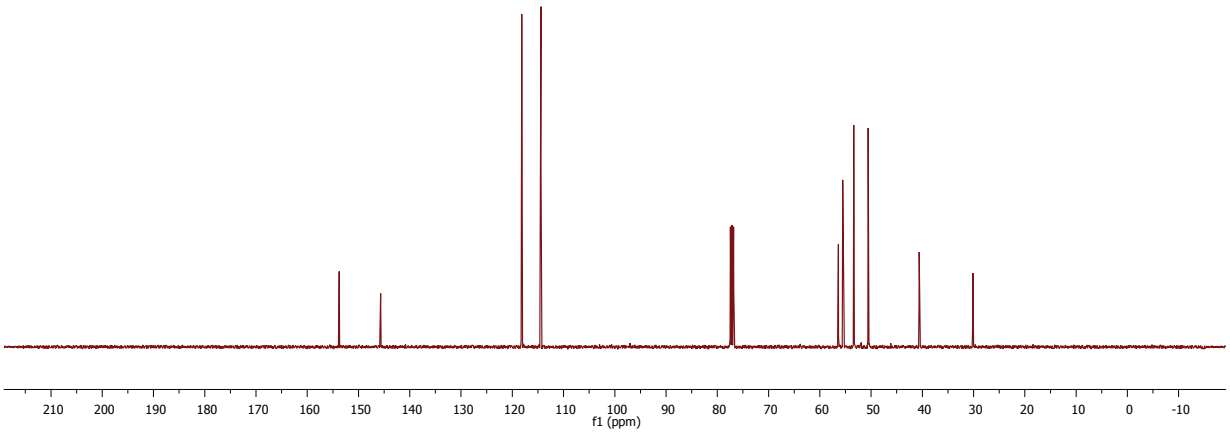
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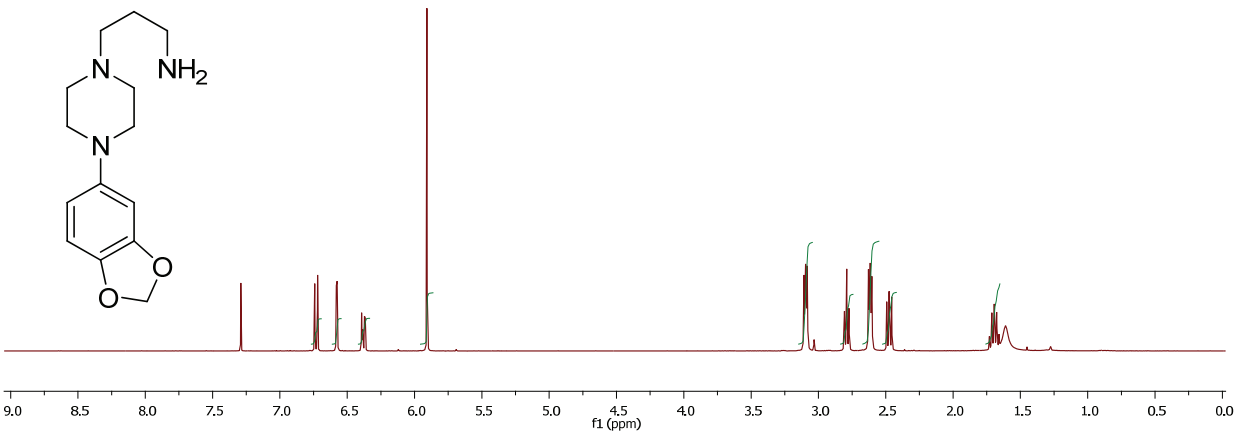
f1 (ppm)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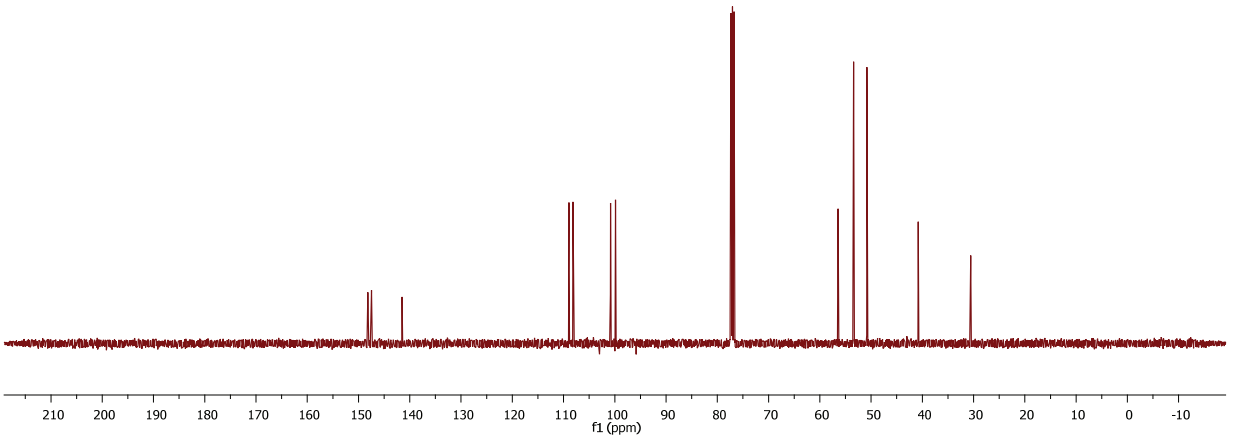
f1 (ppm)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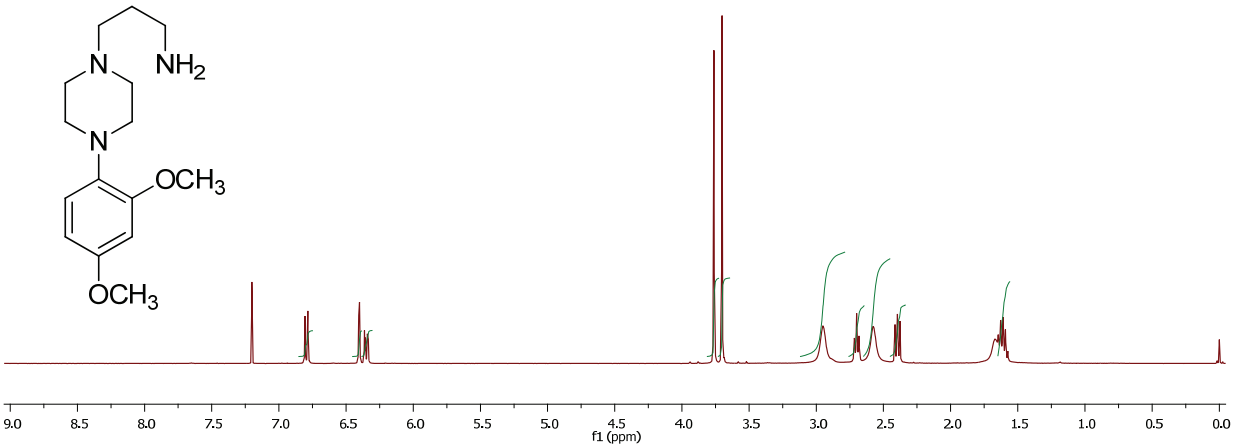
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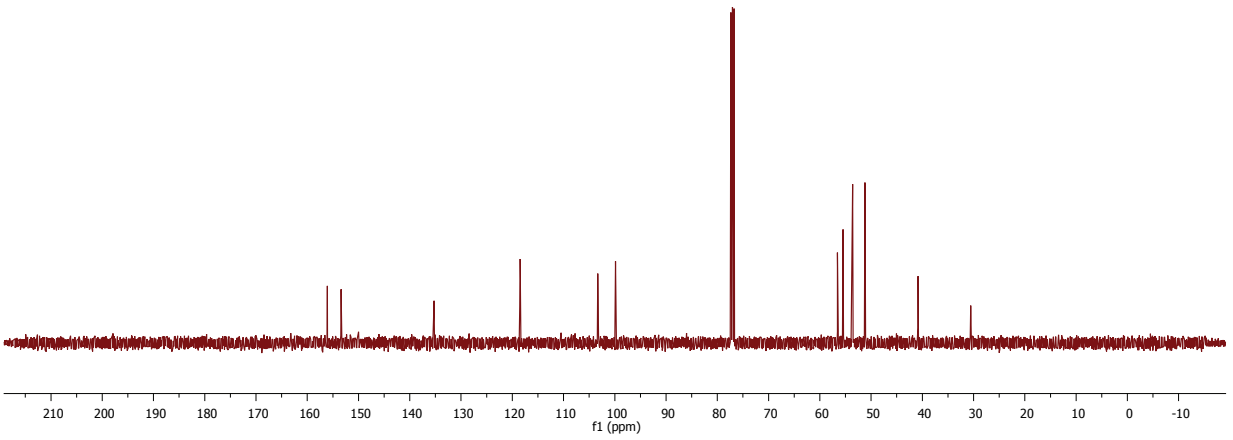
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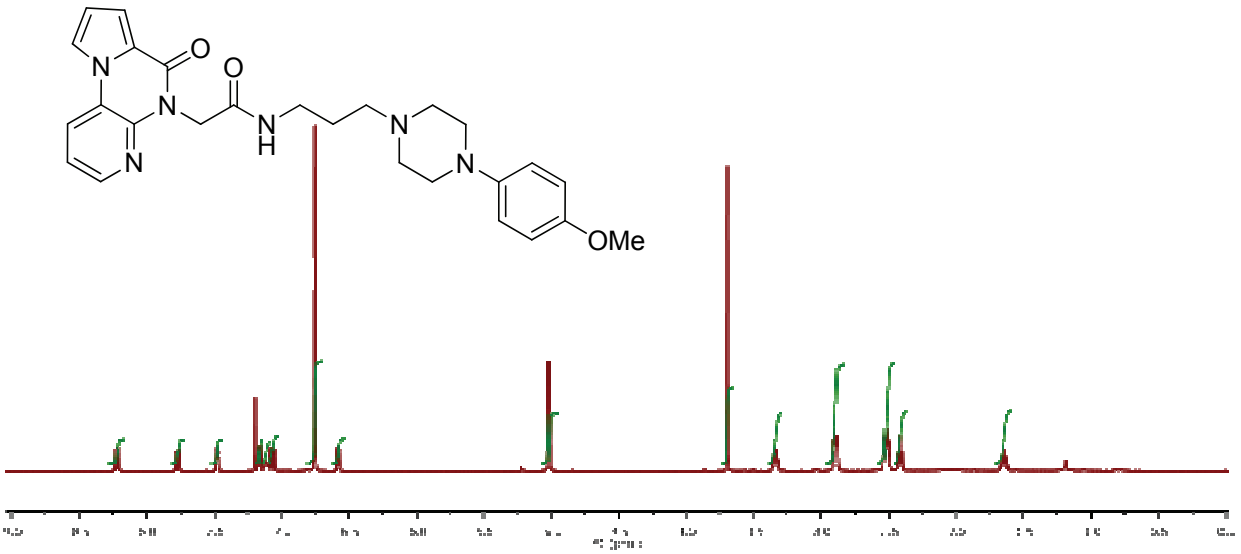
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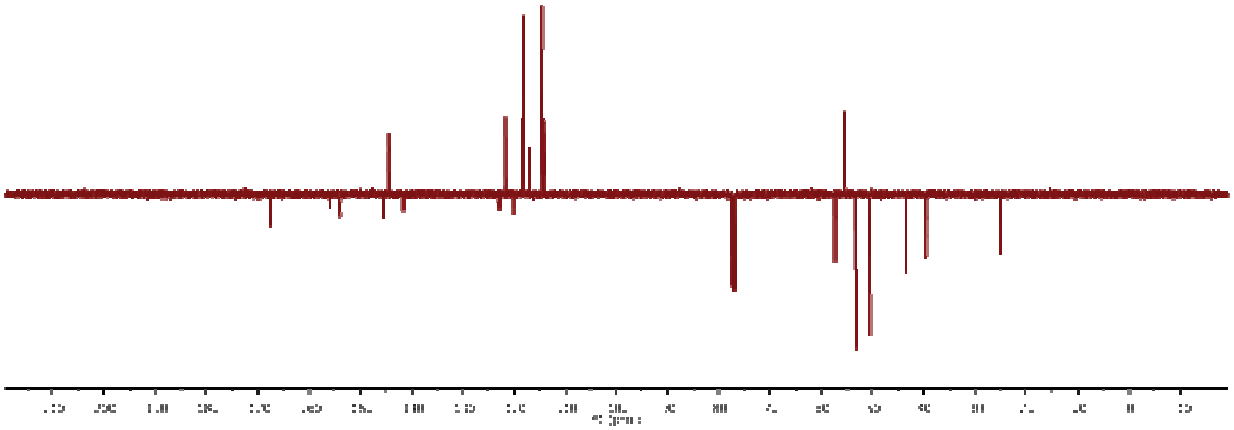
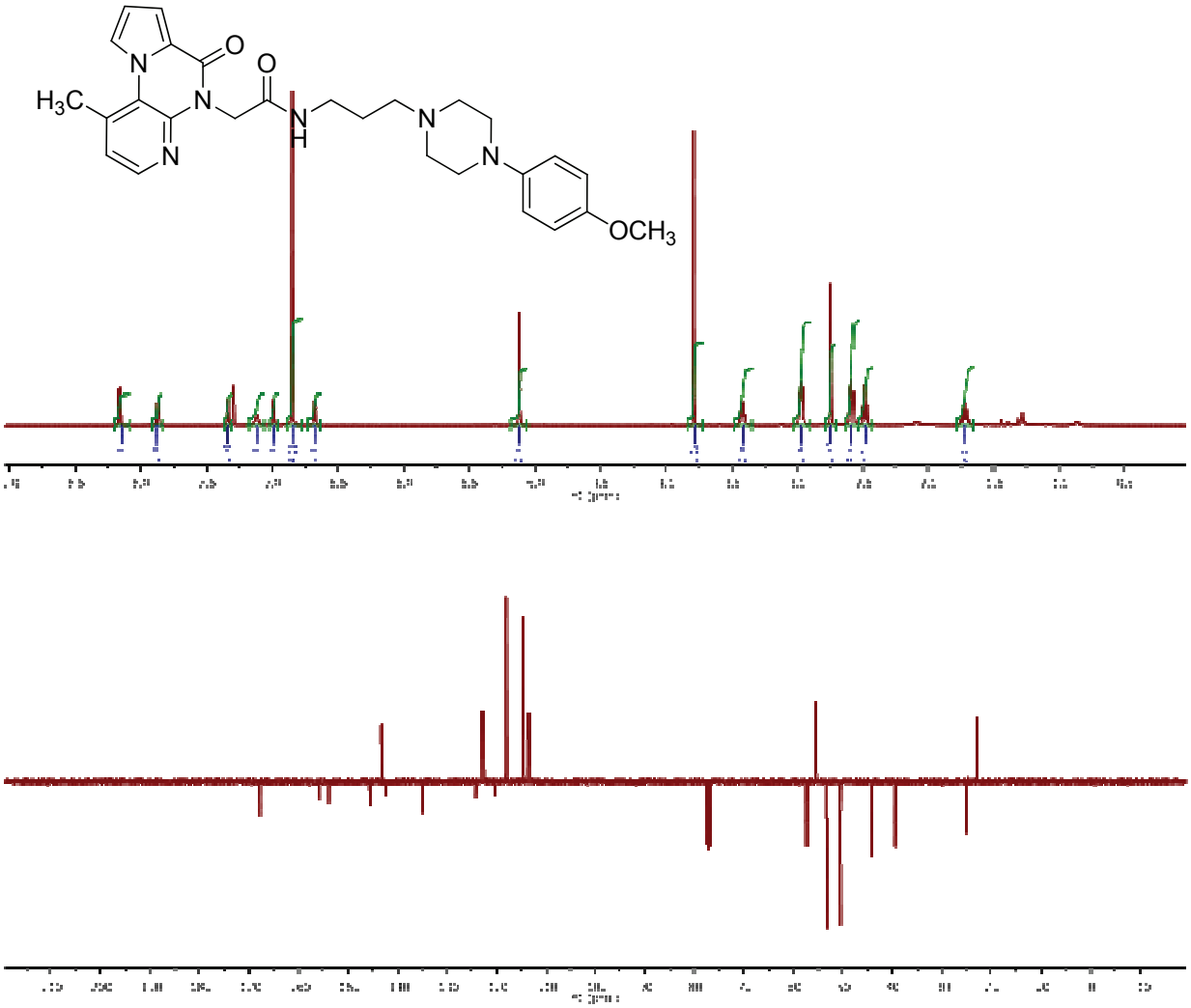
N
N
OMe

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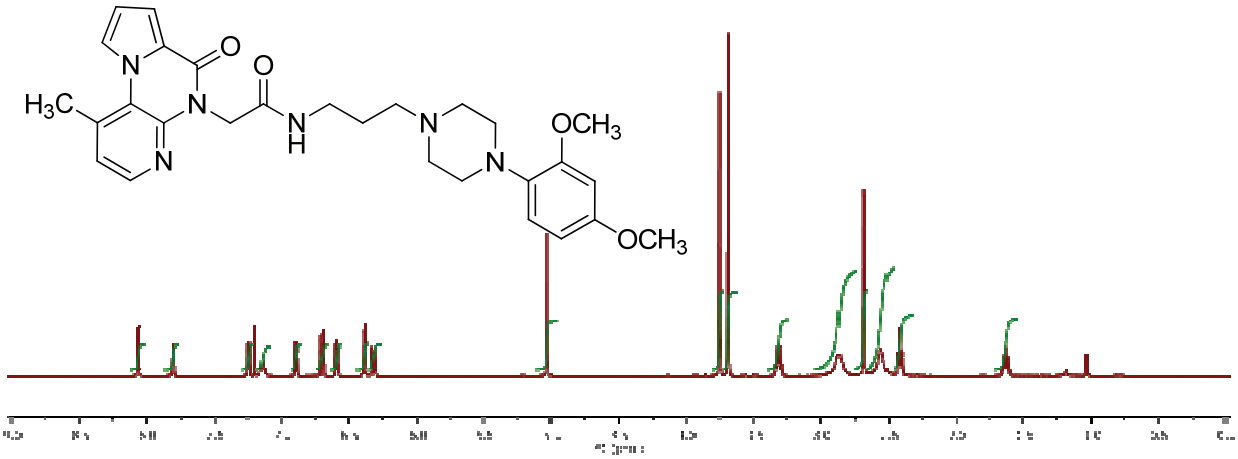
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H3C
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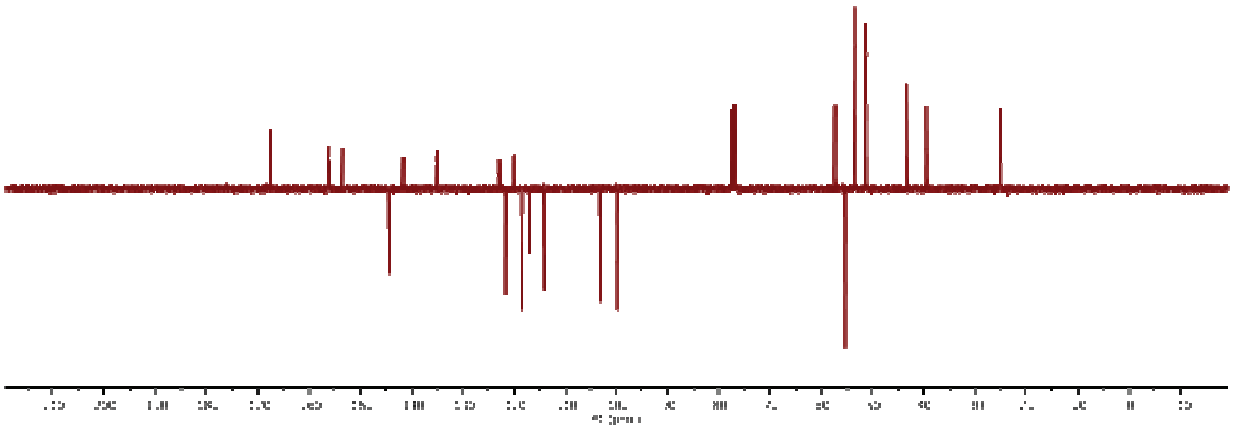
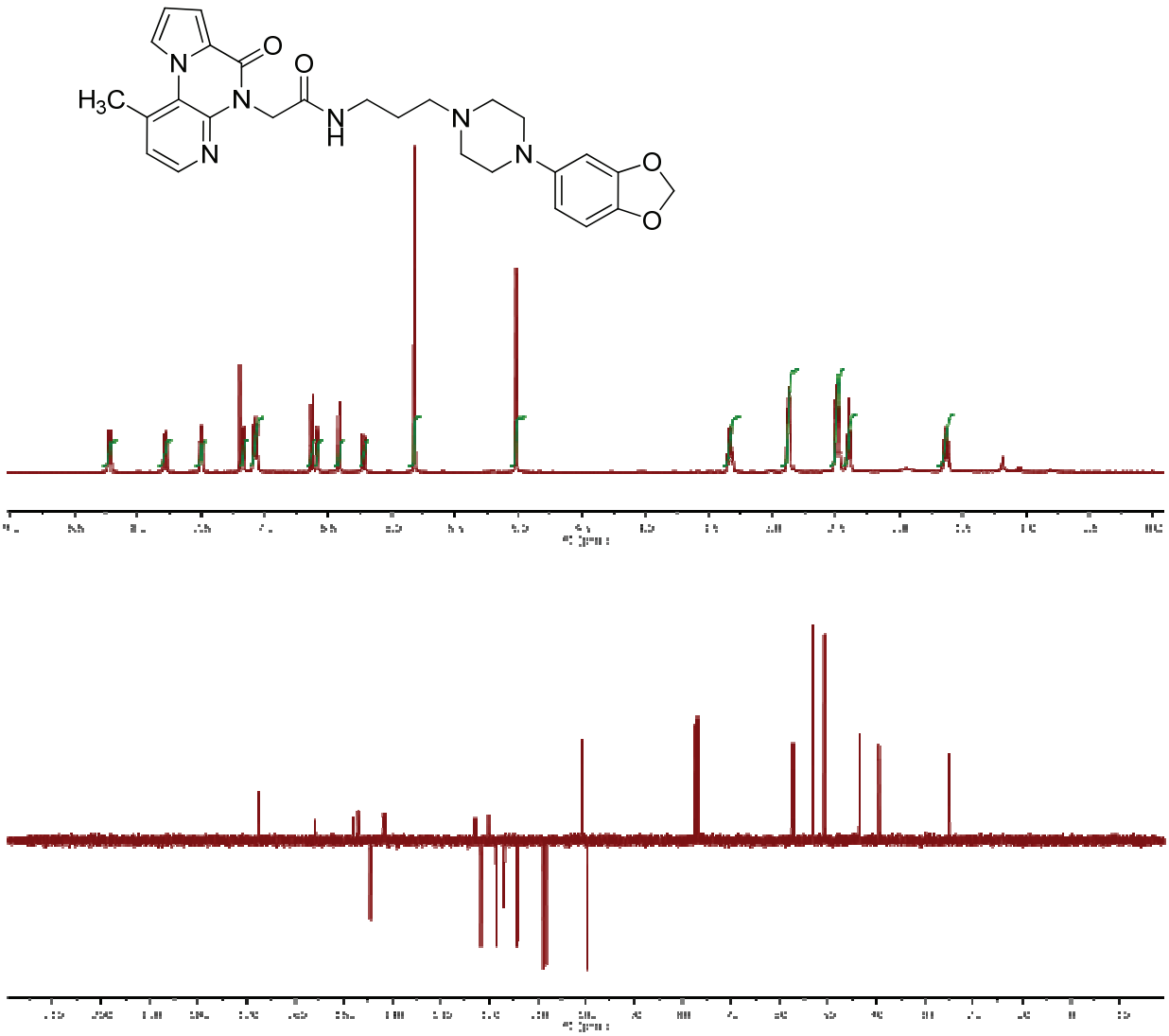
OCH3

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O
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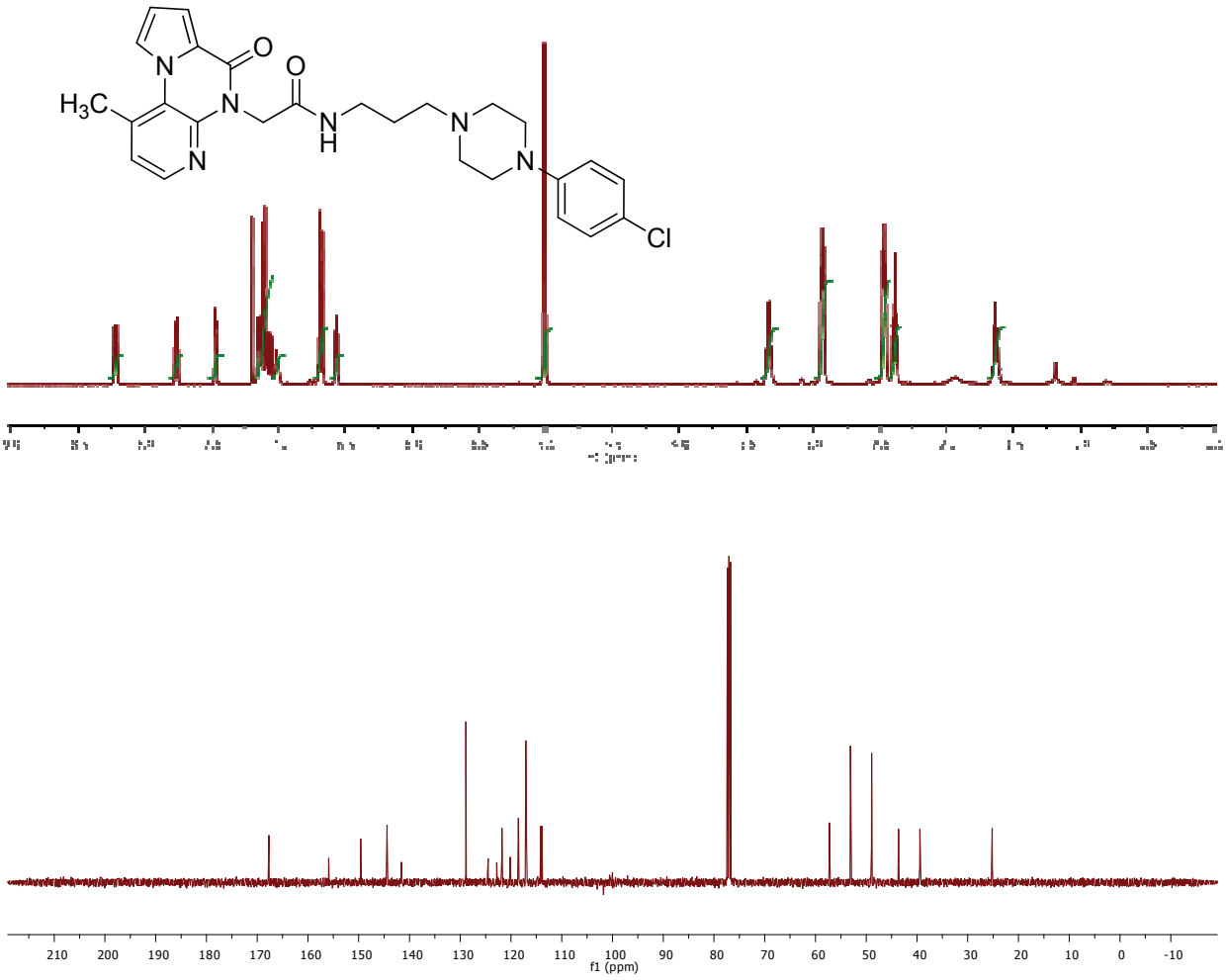
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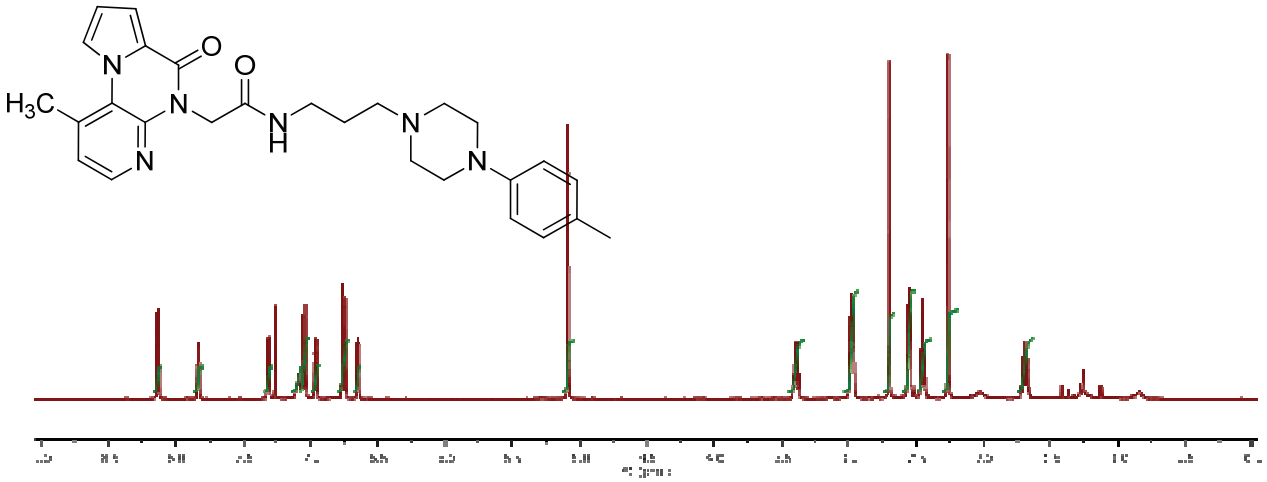
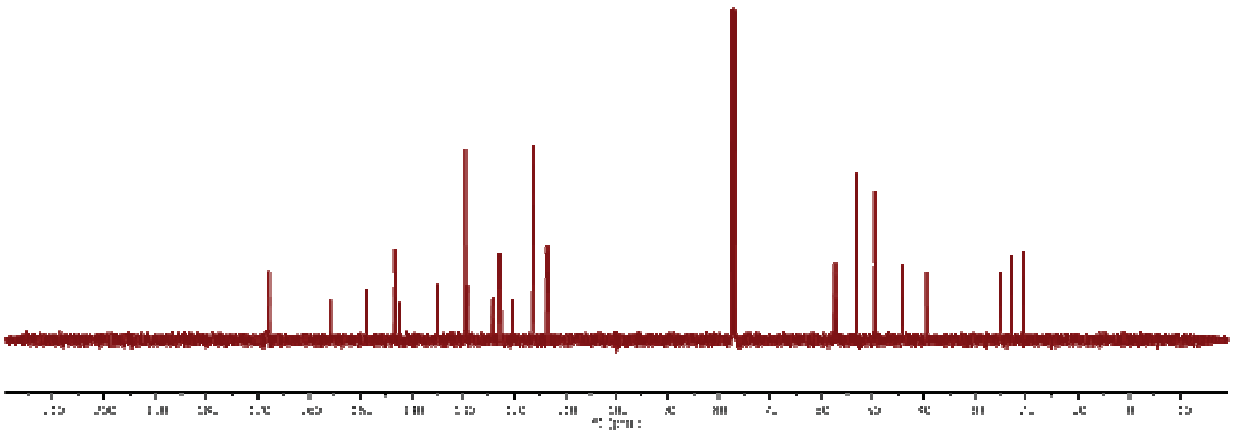
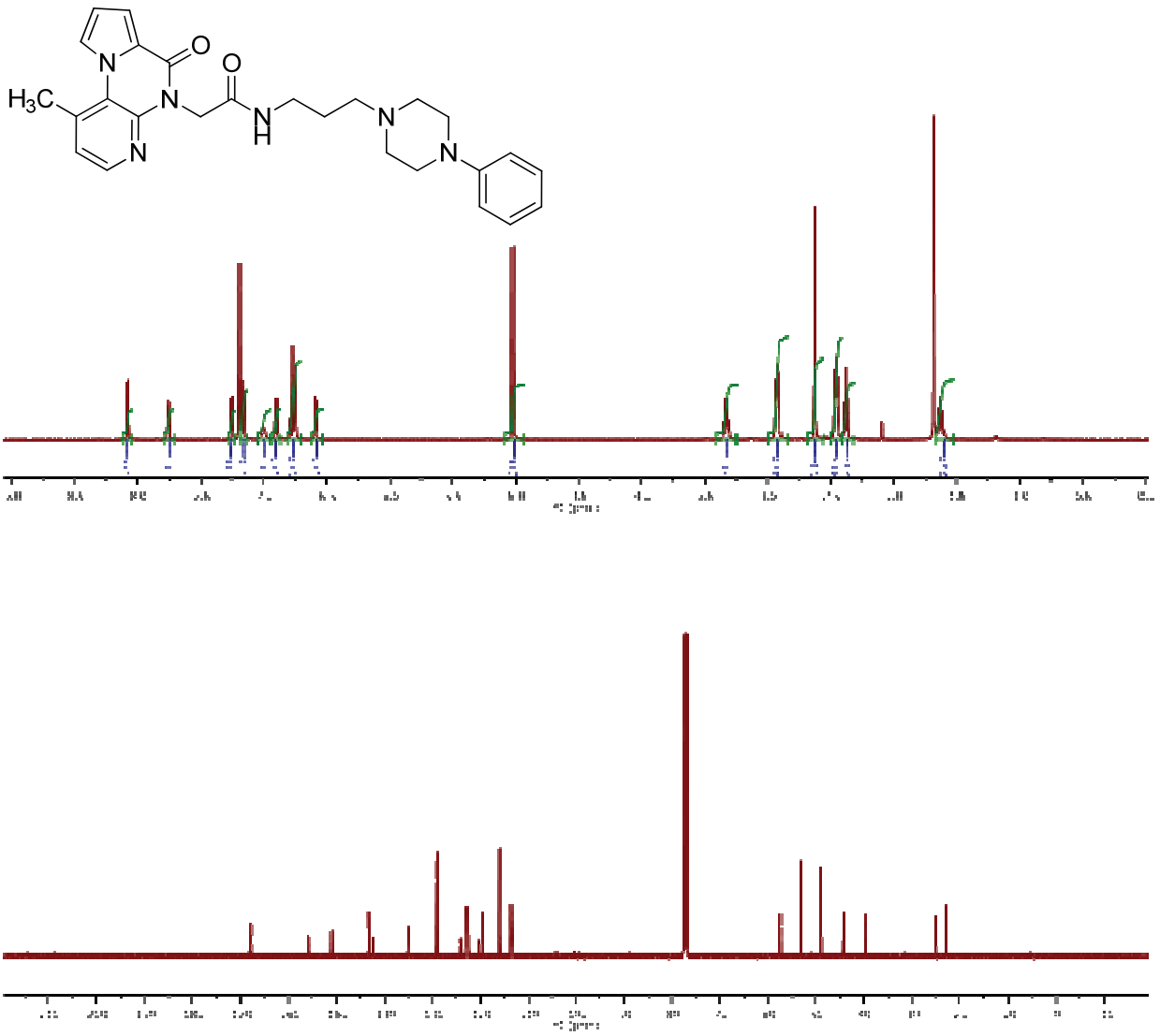
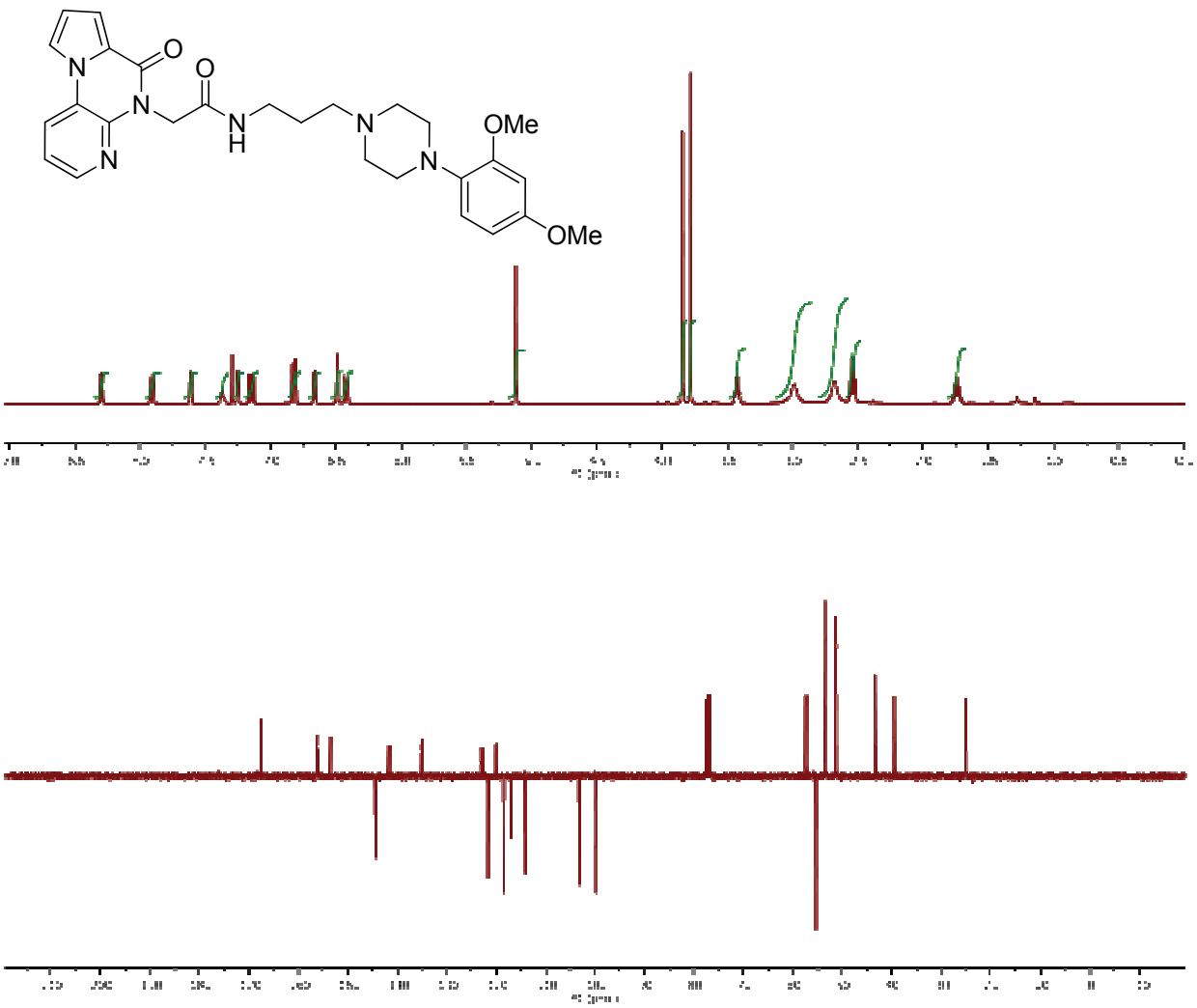
f1 (ppm)


O
O
N
N
H3C
N
N
N
N



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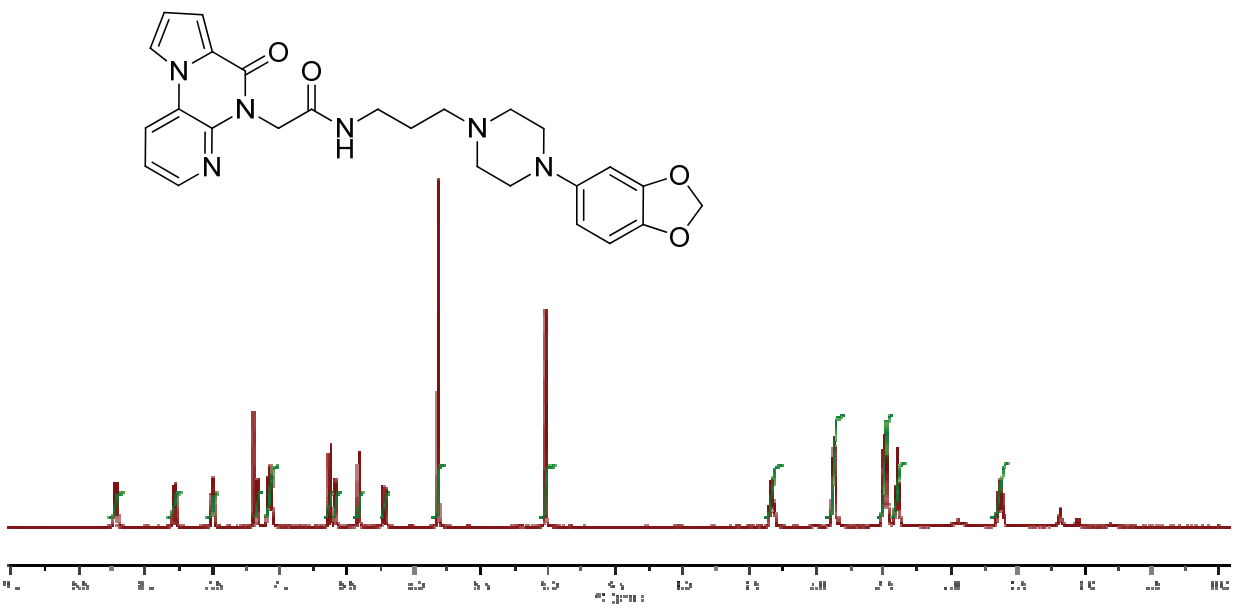
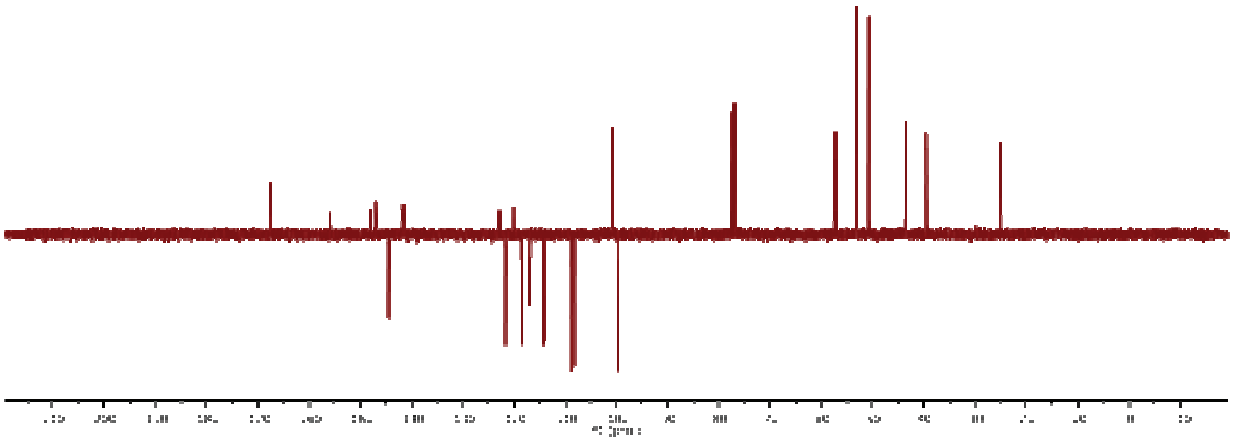
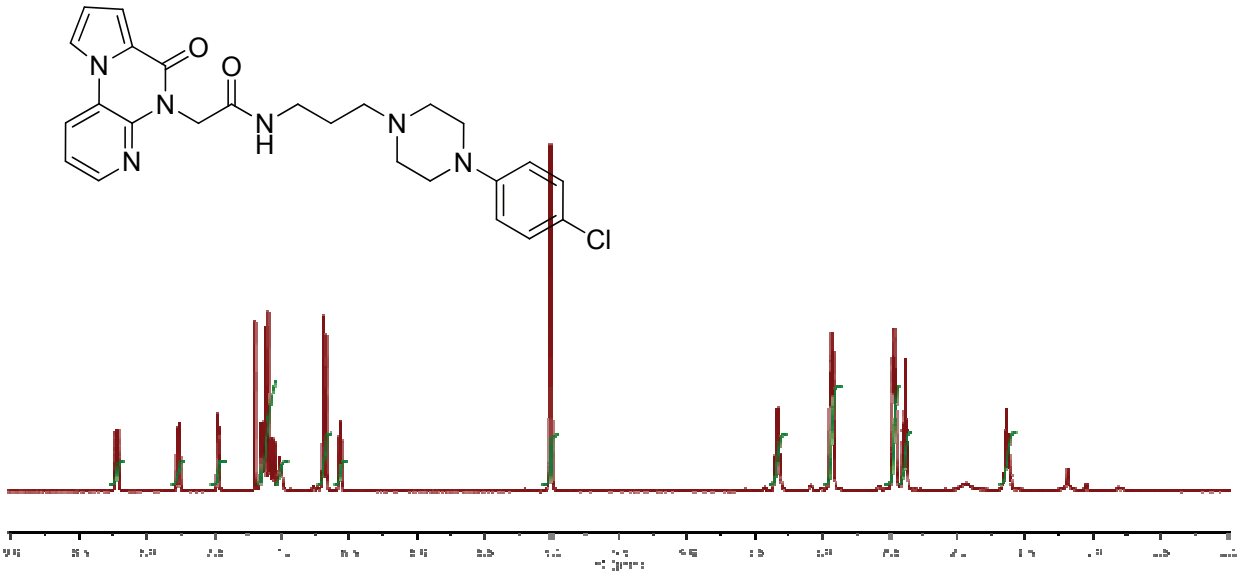
O
N
N
N
N
H
N
N
OMe
OMe






O
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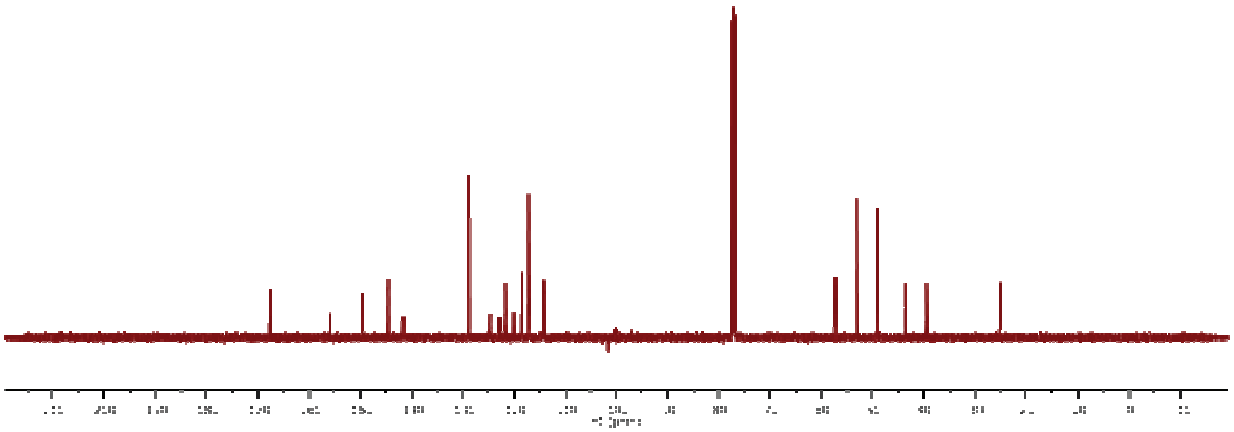
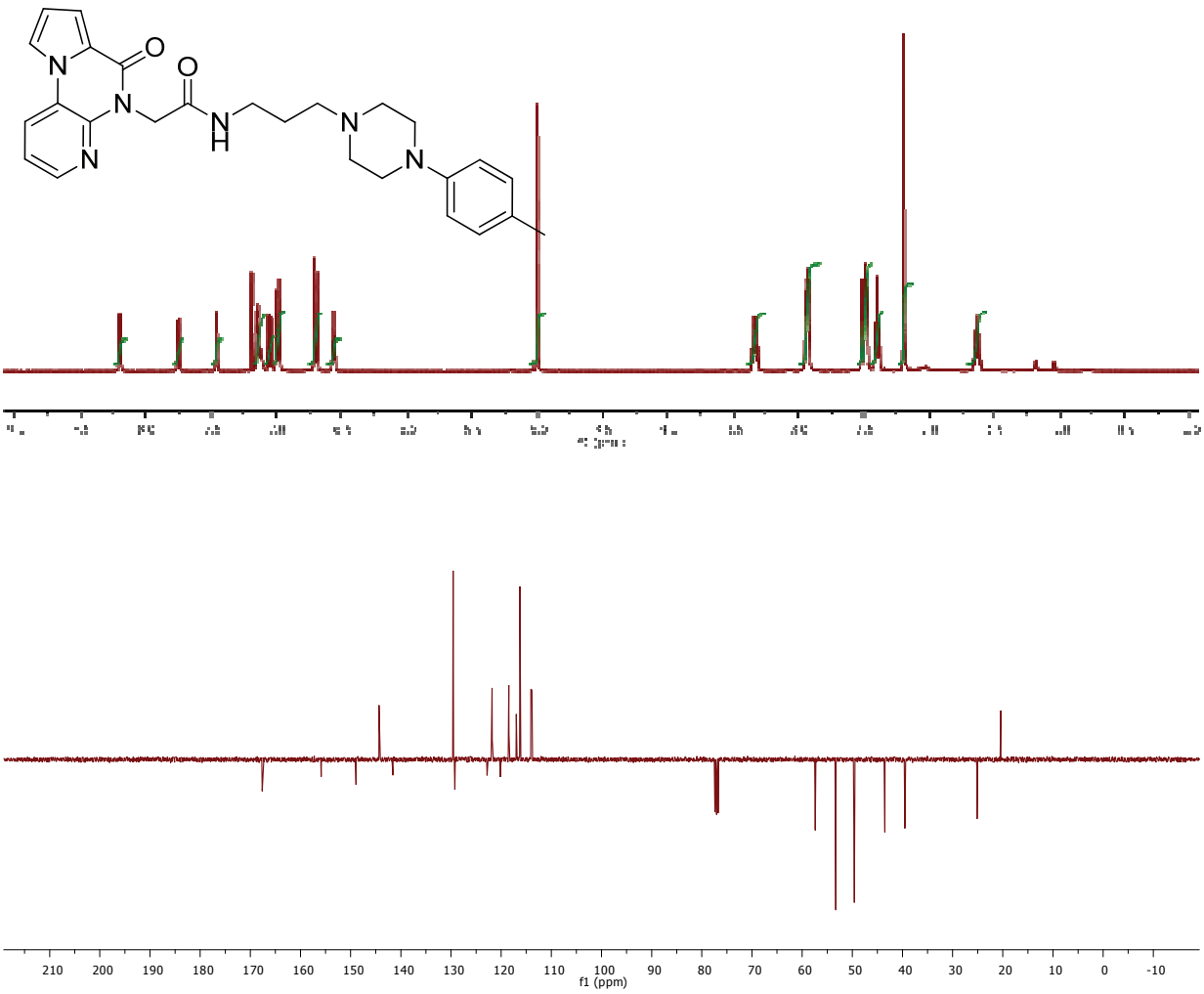
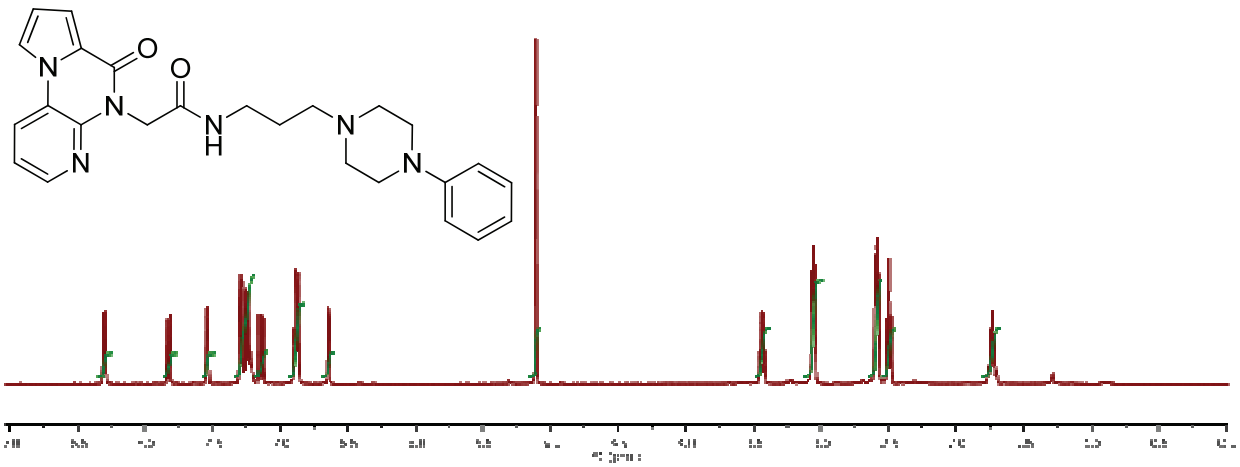
N
N
N
H
N
N
N
Cl




O
O
N
N
N
H
N
N
N
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
O
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N
H
N
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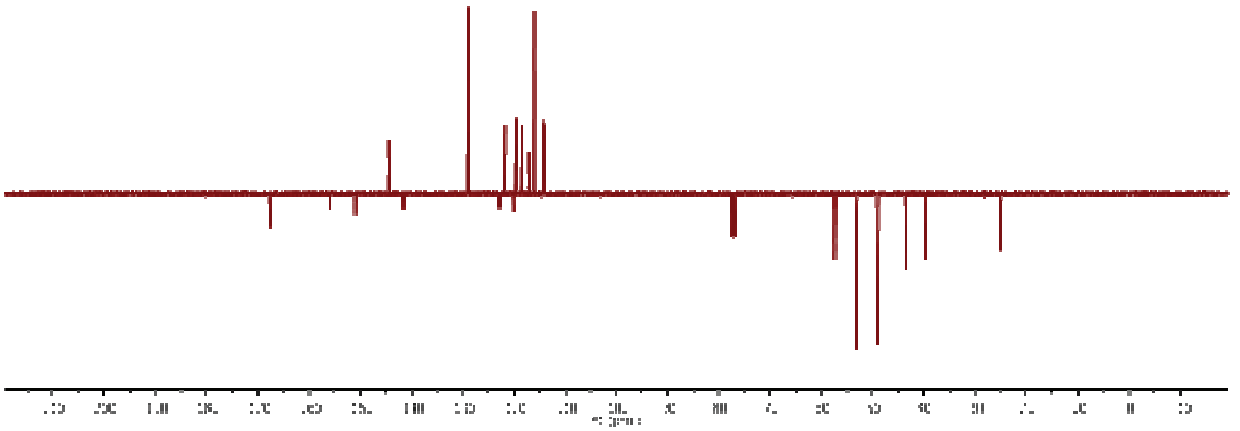
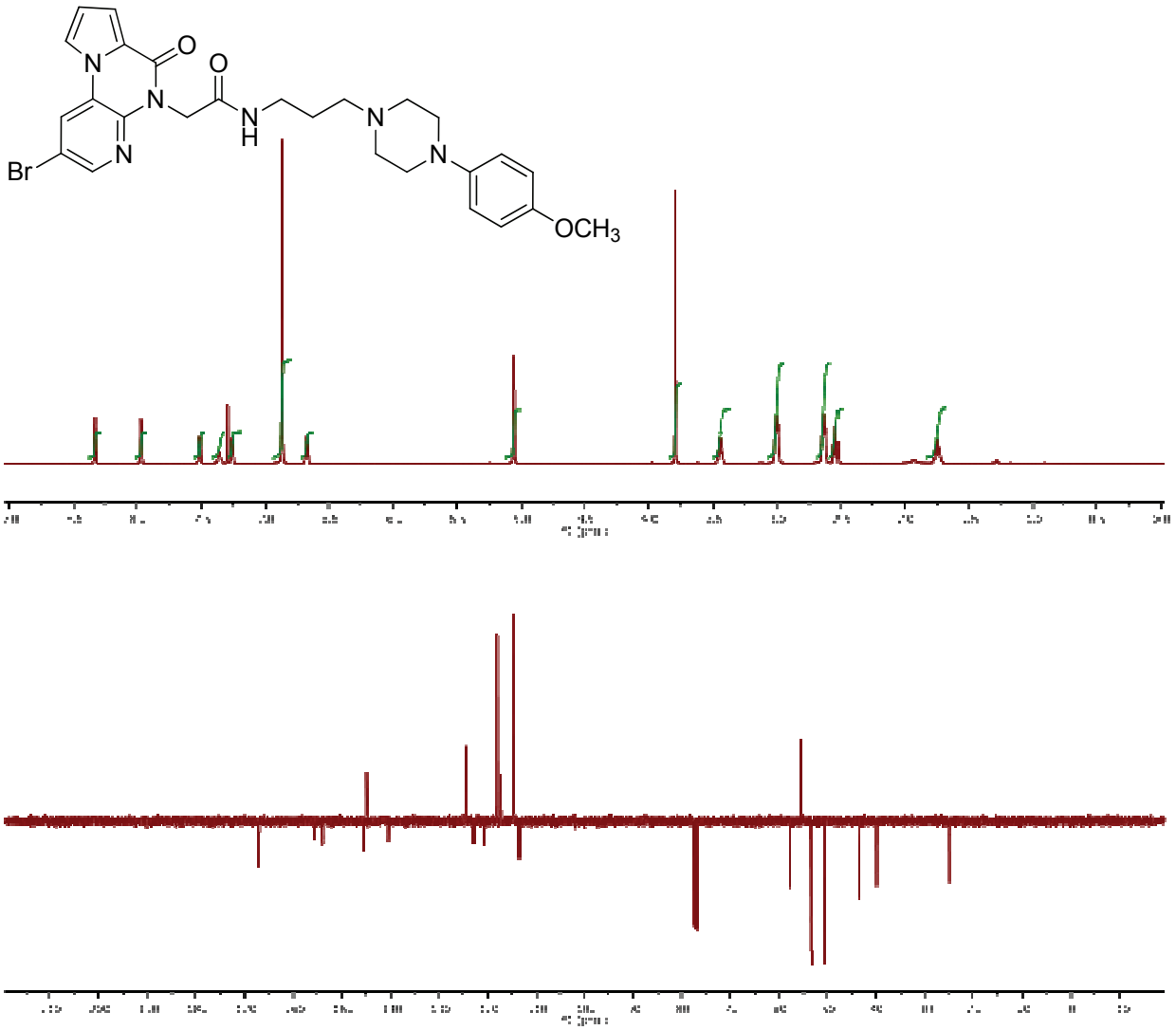
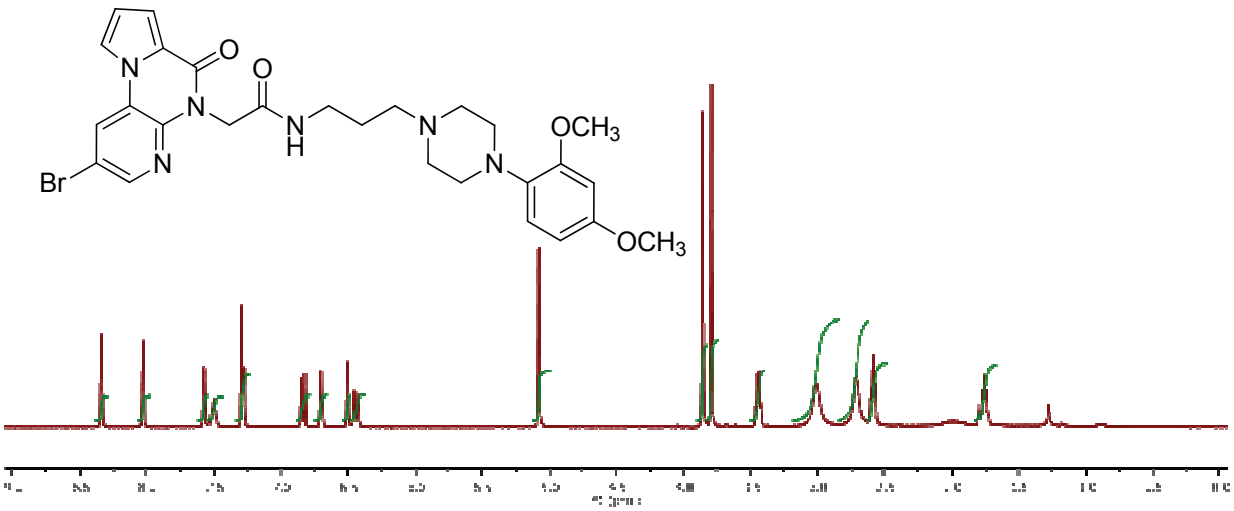
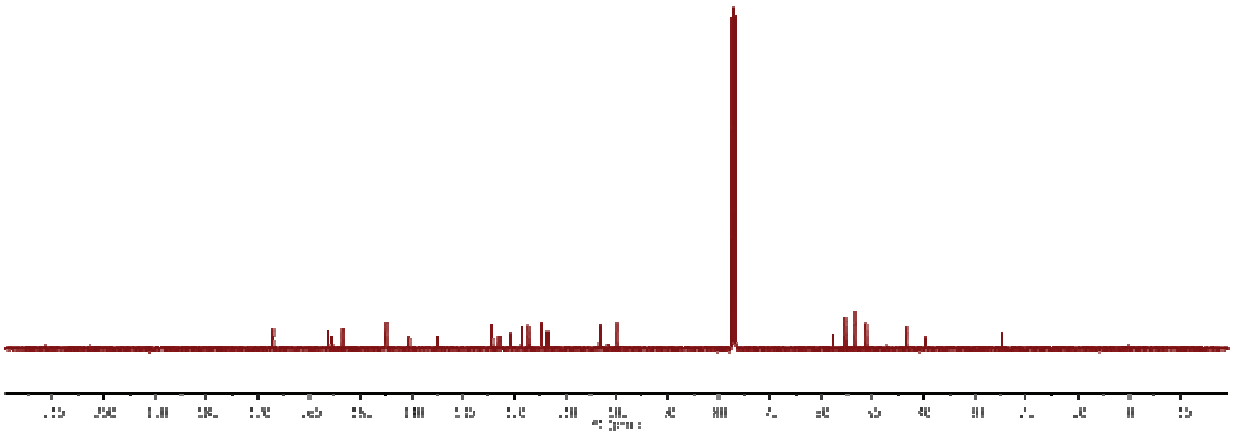
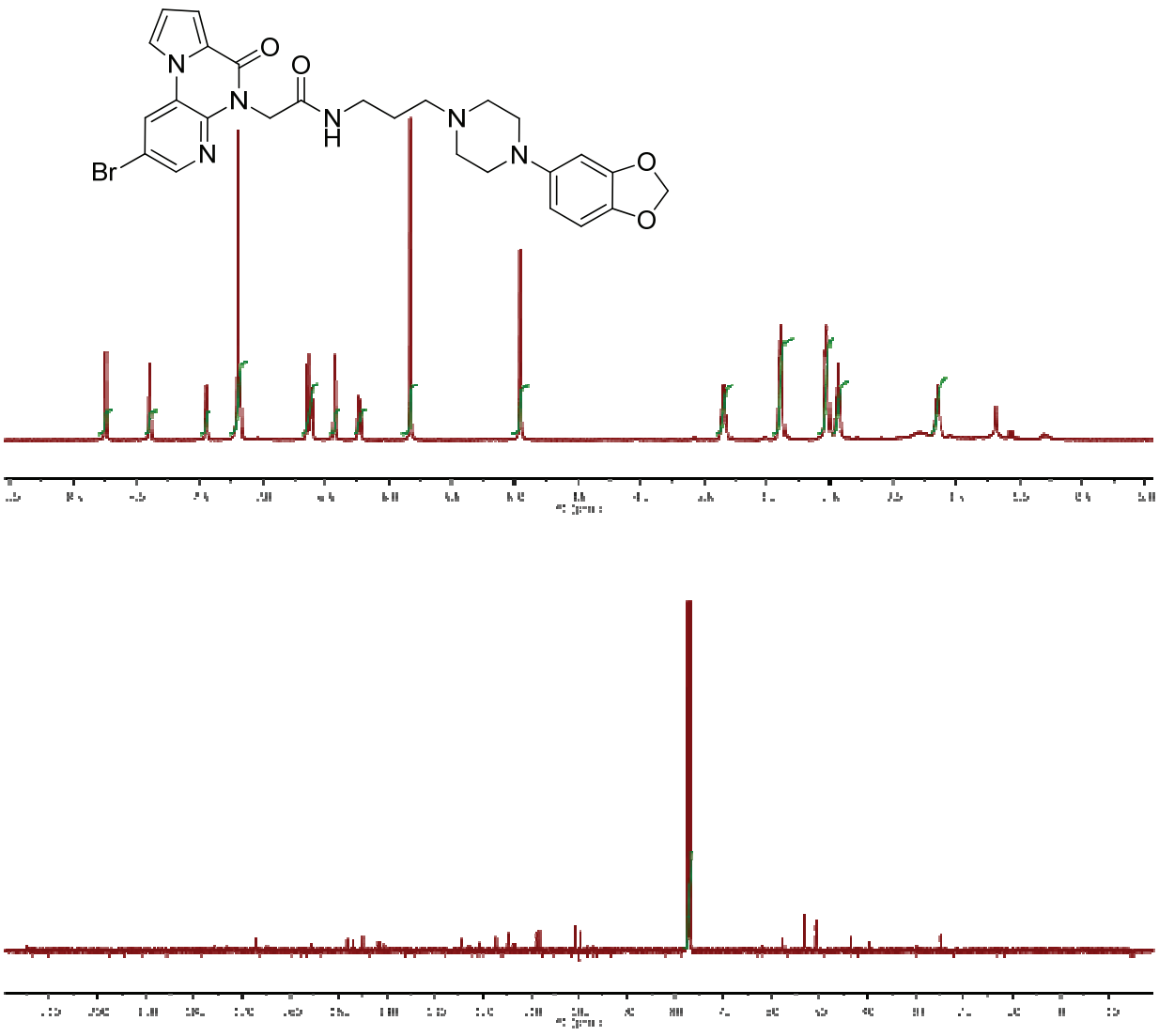
N

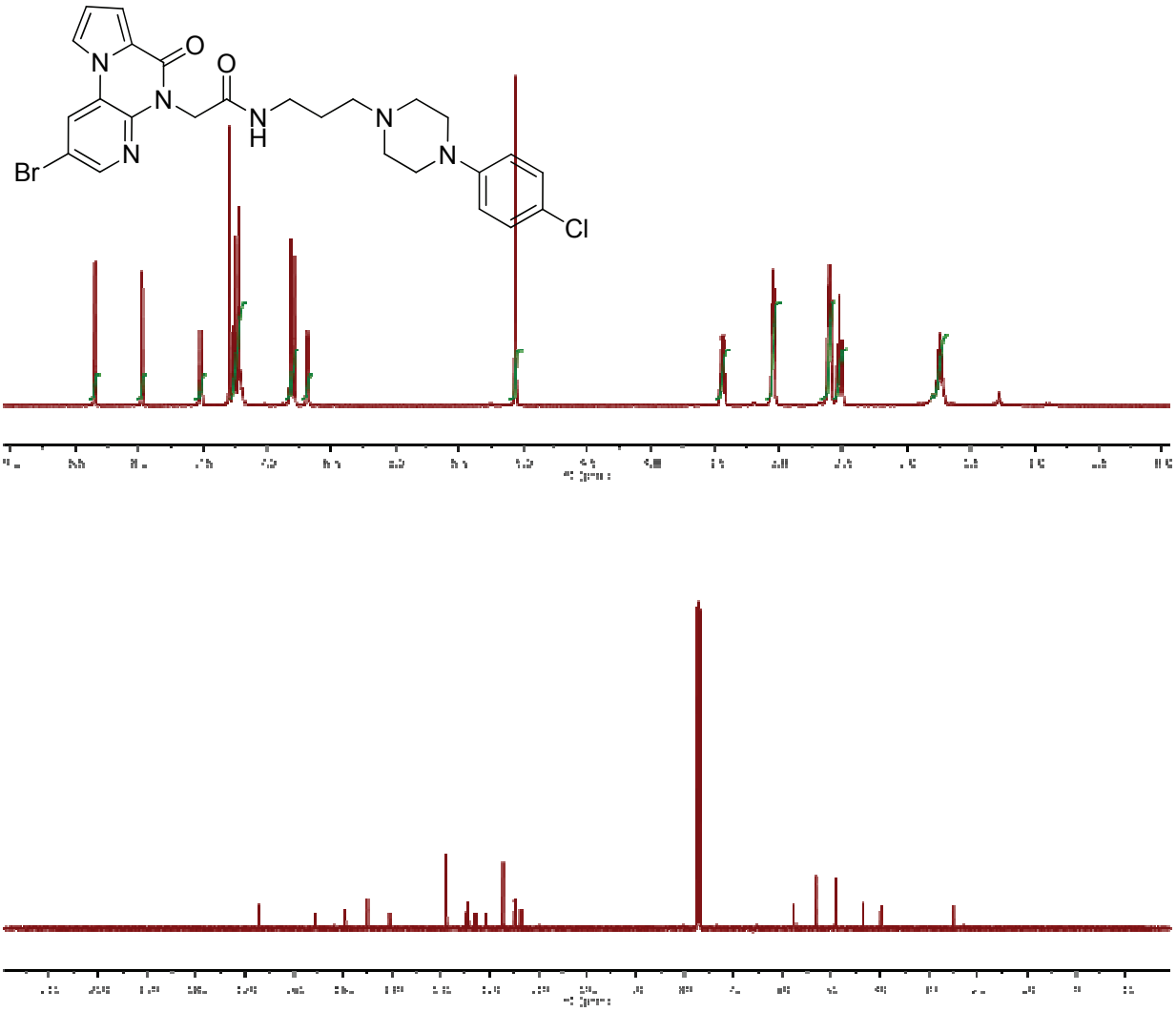



O
O
N
N
N
H
N
N
Br
N
OCH3


O
O
N
N
N
H
N
N
Br
OCH3
OCH3




O
O
N
N
N
N
N
H
N
N
O
O
Br



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