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Electronic Supplementary Information

Discovery of Antipsychotic Loxapine Derivatives against Intracellular Multidrug-Resistant Bacteria

Hsueh-Chun Lin‡[,a] , Yi-Lun Wu‡[,b], Cheng-Yun Hsu[a], Man-Yi Lin[b], Ling-Han Chen[a], Chung-Wai Shiau*[b], and Hao-Chieh Chiu*[ac]

[a]Department of Clinical Laboratory Sciences and Medical Biotechnology, College of Medicine, National Taiwan University, Taipei 10048, Taiwan.

[b]Institute of Biopharmaceutic al Sciences, National Yang Ming Chiao Tung University, Taipei 11221, Taiwan.

[c]Department of Laboratory Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei 10021, Taiwan.

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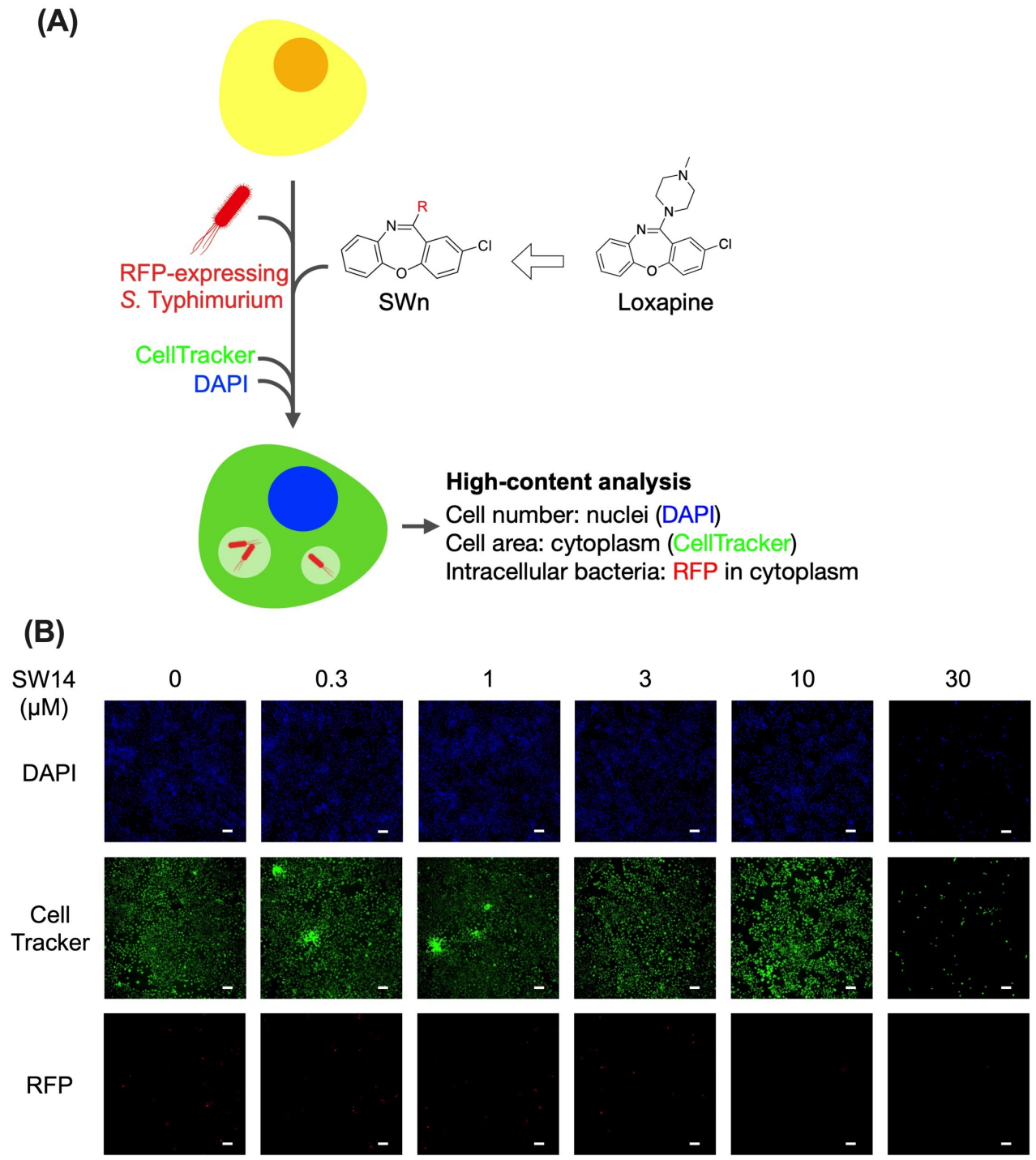


Figure S1. Screening loxapine derivatives by image-based high-content analyses.

(A) Flowchart of the image-based high-content analysis. (B) After 24 h of exposure to elevated concentrations of SW14 combined with 20 mg/L gentamicin, RAW264.7 cells infected by RFP-expressing *S.* Typhimurium were stained with CellTracker™ Green and DAPI and then imaged by a high-content imaging system with a 10× objective. The scale bars shown represent 100 μm, and the images are representative of three independent experiments.

Table S1. Susceptibility of antibiotic-resistant *Salmonella* Typhimurium strains to antibiotics.

	Salmonella Typhimurium					
	ATCC14028		CGC18		NL10	
	MIC (mg/L)	R/I/S[a]	MIC (mg/L)	R/I/S[a]	MIC (mg/L)	R/I/S[a]
SW14	>64	-	>64	-	>64	-
Gentamicin	1	S	2	S	1	S
Tetracycline	4	S	>64	R	>64	R
Streptomycin	16	S	>64	R	>64	R
Chloramphenicol	2	S	>64	R	16	R
Ampicillin	4	S	>64	R	16	R
Ciprofloxacin	<0.125	S	<0.125	S	8	R
Ofloxacin	<0.125	S	<0.125	S	8	R

[a]The susceptibility of bacteria to antibiotics is divided into resistant (R), intermediate (I) and sensitive (S) categories according to CLSI criteria [1].

Biological materials and procedures

Cells

The RAW264.7 murine macrophage cell line, J774.1 murine macrophage cell line, and INT-407 human intestine epithelial cell line were maintained in Dulbecco's modified Eagle's medium (DMEM; HyClone) supplemented with 10% heat-inactivated fetal bovine serum (FBS; Gibco-BRL). The THP-1 human monocytic cell line was maintained in RPMI 1640 medium (Gibco-BRL) supplemented with 10% heat-inactivated FBS. The HT-29 human colon adenocarcinoma cell line and HCT-116 human colon adenocarcinoma cell line were maintained in McCoy's 5A medium (Gibco-BRL) supplemented with 10% heat-inactivated FBS. All cells were purchased from the Bioresource Collection and Research Center (BCRC) and cultured at 37°C in a 5% CO_2 atmosphere.

Bacterial strains

S. Typhimurium ATCC14028 and MRSA USA300 were purchased from the American Type Culture Collection (ATCC). Antibiotic-resistant *S.* Typhimurium isolates NL10 and CGC18 were obtained from the Taiwan Centers for Disease Control. *S.* Typhi Ty2 and *Y. enterocolitica* were from Dr. John S. Gunn, Ohio State University, USA. Red fluorescent protein (RFP)-expressing *S.* Typhimurium was obtained by transforming pBR-RFP.1 [2] into bacteria. Bacteria were cultured in Luria-Bertani (LB) broth (Athena Enzyme Systems) at 37°C and stored in LB medium containing 20% glycerol at -80°C.

Reagents

Loxapine (Sigma–Aldrich) and phorbol 12-myristate 13-acetate (PMA; LC laboratories) were dissolved in dimethyl sulfoxide (DMSO; Sigma–Aldrich). Gentamicin (Bio Basic) and ampicillin (USB) were dissolved in deionized water and filtered through a 0.45 μm filter. Chloramphenicol (Amresco) was dissolved in 95% ethanol as a stock solution.

Image-based high-content analysis of bacterial replication in macrophages

Overnight cultures of RFP-expressing *S.* Typhimurium were prepared for infection by a 1:100 dilution in fresh LB broth and were incubated for 2 h at 37°C. The bacteria were then collected by centrifugation at 6,000 × g for 3 min and suspended in phosphate-buffered saline (PBS; pH 7.2) to an optical density (OD) of 0.6 at 600 nm, which was equivalent to approximately 1×10^8 CFUs/mL. RAW264.7 macrophages were seeded in 96-well black clear bottom plates (Greiner) and incubated for 20 h. Then infection with RFP-expressing *S.* Typhimurium at a multiplicity of infection (MOI) of 50 was conducted for 1 h. The infected macrophages were washed, exposed to 100 mg/L gentamicin for 1 h to eliminate extracellular bacteria, and treated with test compounds combined with gentamicin (20 mg/L) for 24 h. Ciprofloxacin (CIP) and AR12 were used as positive controls for antibacterial assay and cytotoxicity assay, respectively. Afterwards, the cells were washed and stained with CellTracker Green (Thermo Fisher Scientific) for 30 min in serum-free DMEM. Then, the cells were washed, cultured in DMEM with 10% FBS for 30 min and fixed in 3.7% formaldehyde (Sigma–Aldrich) for 20 min followed by a treatment with 0.2 mg/L 4,6-diamidino-2-phenylindole (DAPI; AAT Bioquest) for 30 min. To image the entire well, each well is divided into 21 blocks and the fluorescent pictures of each block at wavelengths of 455nm (DAPI), 525nm (CellTracker Green) or 625nm (RFP) were photographed using a high-content imaging system (ImageXpress Micro 4, Molecular Devices) with a 10× objective lens at three focal lengths and then superimposed to produce clear images. Then, MetaExpress software (Molecular Devices) were used to perform color-coded analysis on captured images. The number of viable cells were determined by the number of nuclei stained by DAPI, the area stained by CellTracker Green was defined as intracellular range, and the total red fluorescence

intensity in the intracellular range was calculated to represent the total intracellular bacterial count. The 50% cytotoxic concentration towards cells (CC_{50}) and 50% effective concentration (EC_{50}) against intracellular bacteria of each compound were determined using CalcuSyn software (Biosoft).

Analysis of the colony-forming units of intracellular bacteria

The overnight cultures of *S.* Typhimurium, *S.* Typhi, *Y.* enterocolitica, *L.* monocytogenes, and MRSA USA300 were diluted 1:100 in fresh LB broth and incubated for 2 h at 37°C. The bacteria were then collected and suspended in PBS to an OD_{600} of 0.6. Cells seeded in a 6-well plate (Greiner) were infected with bacteria at an MOI of 25 for 1 h. After infection, the cells were washed, exposed to 100 mg/L gentamicin for 1 h and treated with SW14 in combination with 20 mg/L gentamicin for 24 h. Then, the infected cells were washed and lysed with 0.1% Triton X-100 in PBS for 10 min at 37°C to release the intracellular bacteria. The cell lysates were serially diluted in PBS, spread on LB agar plates, and incubated at 37°C for 18 h. The bacterial colonies on the plates were enumerated and expressed as CFUs.

Cell viability analysis

Cells were seeded in 96-well plates (Greiner) and incubated for 20 h followed by treatment with test compounds for another 24 h. Then, the cells were treated with 0.5 g/L 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) and incubated at 37°C with 5% CO_2 for 1 h. The culture media were removed, and the reduced MTT products were dissolved in DMSO. The absorbance at 570 nm was detected using a VersaMax Microplate reader (Molecular Devices). The CC_{50} of each compound was determined using CalcuSyn software.

Bacterial growth assay

The *S.* Typhimurium that was grown overnight and cultured in LB medium was inoculated into fresh cation-adjusted Mueller Hinton broth (CAMHB; Becton, Dickinson, and Company) or DMEM supplemented with 10% FBS to a final concentration of 5×10^5 CFU/mL, followed by exposure to different concentrations of SW14 (0.5–64 μM) in a flat-bottom 96-well plate. The plate was incubated at 37°C, and bacterial growth was monitored by measuring the absorbance at 600 nm with the VersaMax Microplate reader at designated times for 24 h.

Dopamine D2 receptor binding assay

The human dopamine binding assay was performed by Eurofins Discovery as a contract service. Briefly, a total of 20 μg human recombinant dopamine D2L receptor expressed in CHO cells is incubated with increasing concentrations of loxapine or SW14 along with 0.16 nM [3H]Spiperone in Tris-HCl buffer pH 7.4 for 120 min at 25°C. Then receptor proteins are filtered, washed, and counted to determine bound [3H]Spiperone. Meanwhile, the non-specific binding is estimated in the presence of 10 μM haloperidol.

Statistical analysis

The data are expressed as the mean ± SD. Differences between group means were analysed using Student's t test or one-way ANOVA with Dunnett's multiple comparison test for independent samples. Differences were considered significant at a P value of <0.05. Statistical analyses were performed using GraphPad Prism (version 9.0; GraphPad Software).

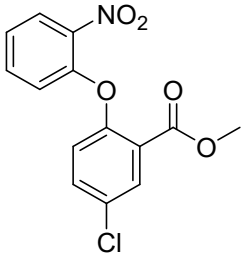
References

1. CLSI. 2017. Performance Standards for Antimicrobial Susceptibility Testing — Eighteenth Informational Supplement: M100.

2. C. L. Birmingham, A. C. Smith, M. A. Bakowski, T. Yoshimori and J. H. Brumell, *J Biol Chem*, 2006, **281**, 11374-11383.

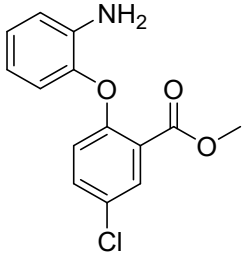
Synthesis procedures, structures and 1H NMR, 13C NMR, and Mass (HRMS) spectroscopy data

Methyl 5-chloro-2-(2-nitrophenoxy)benzoate (C)



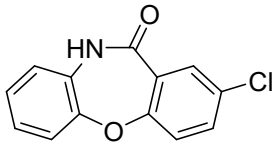
To a 12 mL 1,4-Dioxan solution of methyl 5-chlorosalicylate (7.936 g, 0.043 mol), potassium carbonate(5.88 g, 0.043 mol), 1-fluoro-2-nitrobenzene (4 g, 0.028 mol) were slowly added. The reaction mixture was refluxed for 16 h. After the temperature was cooled to room temperature, water was added to the solution and extracted with toluene. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was collected for next step without purification ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (dd, J = 8.0, 1.6 Hz, 1H), 7.91 (d, J = 2.8 Hz, 1H), 7.74 (dd, J = 8.8, 2.8 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 6.98 (dd, J = 8.4, 0.8 Hz, 1H), 3.68 (s, 3H) ppm.

Methyl 2-(2-aminophenoxy)-5-chlorobenzoate (D)



To a 12 mL ethanol solution of **Methyl 5-chloro-2-(2-nitrophenoxy)benzoate** (4 g, 0.013 mol), $SnCl_2$ (12.3 g, 0.065 mol) were slowly added. The reaction mixture was refluxed for 16 h in a nitrogen atmosphere. The reaction mixture was quenched with ice and 10% NaOH solution and filtrated with Celite. The filtrate was extracted with ethyl acetate and washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by chromatography on a silica gel using EtOAc/Hexane as eluent (ratio1/10) to give **Methyl 2-(2-aminophenoxy)-5-chlorobenzoate** (1.3 g, yield: 36%) ◦ ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.2, 0.8 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 2H), 6.76 (d, J = 9.2 Hz, 1H), 6.56 (t, J = 7.6 Hz, 1H), 4.99 (s, 2H), 3.81 (s, 4H) ppm.

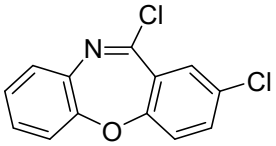
2-chlorodibenzo[b,f][1,4]oxazepin-11(10H)-one (E)



To a 5 mL dimethylformamide solution of **Methyl 2-(2-aminophenoxy)-5-chlorobenzoate** (1.3 g, 4.68 mmol), H_2SO_4 (105.6 mg, 1.08 mmol) were slowly added in room temperature. The reaction mixture was refluxed for 16 h in a nitrogen atmosphere. The reaction mixture was cooled to room temperature and added with water to generate precipitate. Ethyl acetate was applied to dissolve

the precipitate. The solution was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give **2-chlorodibenzo[b,f][1,4]oxazepin-11(10H)-one** (1.1 g，yield: 95.7%)。^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 7.70 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.21 – 7.12 (m, 3H) ppm.

2,11-dichlorodibenzo[b,f][1,4]oxazepine (S4)

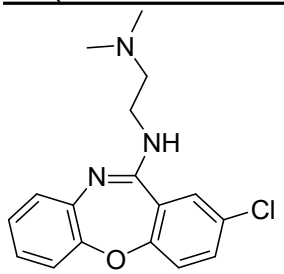


To a flask with **2-chlorodibenzo[b,f][1,4]oxazepin-11(10H)-one** (500 mg, 2.04 mmol), $POCl_3$ (4 ml, 23 equiv) were added. The mixture was stirred for 10 minutes and *N*, *N*-dimethylaniline (99 mg, 0.82 mmol) was slowly added to the solution. The reaction mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature. The excess of POCl3 was evaporated with vacuum rotavapor. The residue was dissolved with water and extracted with toluene. The solution was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure for the next reaction

General procedures for the synthesis of compounds SW1-26

A mixture of amine derivatives(2-10 equiv) and 2,11-dichlorodibenzo[b,f][1,4]oxazepine (1 equiv) in xylene was refluxed for 16 h, quenched with NaOH (aq) and extracted with ethyl acetate. The solvent was removed under vacuum and the crude residue purified by chromatography on a silica gel column using various eluent composition. This procedure afforded the expected coupling product from 29.0% to 88.5% yield.

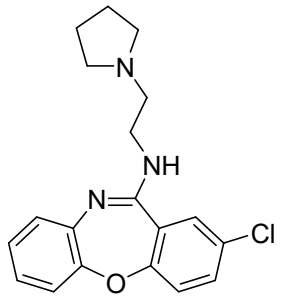
N1-(2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)-N2,N2-dimethylethane-1,2-diamine (SW1)



N,N-Dimethylethylenediamine (5.0 equiv); methanol/dichloromethane = 1/50; yield: 60.7%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.39 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.06 (t, J = 7.6 Hz, 2H), 6.92 (t, J = 7.6 Hz, 1H), 5.50 (brs, 1H), 3.58 (brs, 2H), 2.58 (t, J = 6.0 Hz, 2H), 2.27 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.53, 155.69, 151.89, 141.27, 132.58, 130.58, 127.73, 127.50, 127.28, 126.03, 123.90, 122.48, 120.49, 57.62, 45.38, 39.09 ppm. HRMS calculated for $C_{17}H_{18}ON_3Cl$ $(M+H)^+$: 316.1211. Found: 316.1213.

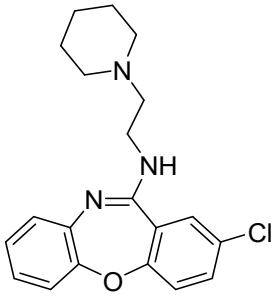
2-chloro-N-(2-(pyrrolidin-1-yl)ethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW2)



1-(2-Aminoethyl)pyrrolidine (10.0 equiv); methanol/dichloromethane = 1/100; yield: 43.7%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.39 (s, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 5.50 (brs, 1H), 3.61 (s, 2H), 2.77 (brs, 2H), 2.56 (s, 4H), 1.78 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.51, 155.78, 151.91, 141.24, 132.57, 130.57, 127.73, 127.63, 127.27, 126.03, 123.89, 122.46, 120.49, 54.55, 54.09, 40.47, 23.70 ppm. HRMS calculated for $C_{19}H_{20}ON_3Cl$ $(M+H)^+$: 342.1368. Found: 342.1371.

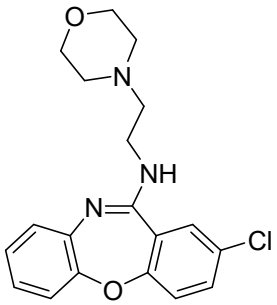
2-chloro-N-(2-(piperidin-1-yl)ethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW3)



1-(2-Aminoethyl)piperidine (2.0 equiv); methanol/ dichloromethane = 1/50; yield: 66.6%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.38 – 7.35 (m, 2H), 7.15 – 7.12 (m, 2H), 7.05 (t, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 5.60 (brs, 1H), 3.58 (s, 2H), 2.61 – 2.60 (m, 2H), 2.43 (brs, 4H), 1.57 – 1.56 (m, 4H), 1.44 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.48, 155.63, 151.87, 141.31, 132.55, 130.62, 127.85, 127.47, 127.31, 126.03, 123.85, 122.52, 120.49, 56.90, 54.47, 38.37, 26.26, 24.66 ppm. HRMS calculated for $C_{20}H_{22}ON_3Cl$ $(M+H)^+$: 356.1524. Found: 356.1528.

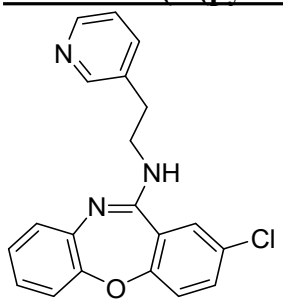
2-chloro-N-(2-morpholinoethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW4)



4-(2-Aminoethyl)morpholine (2.0 equiv); methanol/dichloromethane = 1.5/100; yield: 60.6%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.39 – 7.37 (m, 2H), 7.16 – 7.04 (m, 4H), 6.93 (t, *J* = 7.6 Hz, 1H), 5.41 (brs, 1H), 3.72 (t, *J* = 4.4 Hz, 4H), 3.61 (q, *J* = 4.4 Hz, 2H), 2.67 (t, *J* = 6.0 Hz, 2H), 2.51 (brs, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.50, 155.54, 151.84, 141.13, 132.68, 130.65, 127.70, 127.35, 127.29, 126.07, 124.05, 122.60, 120.52, 67.20, 56.84, 53.56, 37.95 ppm. HRMS calculated for $C_{19}H_{20}O_2N_3Cl$ $(M+H)^+$: 358.1317. Found: 358.1325.

2-chloro-N-(2-(pyridin-3-yl)ethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW5)

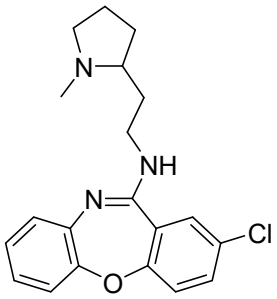


3-(2-Aminoethyl)pyridine (2.0 equiv); methanol/ dichloromethane = 1/100; yield: 67.3%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 8.53 (s, 1H), 8.48 (d, *J* = 4.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.26 – 7.24 (m, 2H), 7.14 (t, *J* = 7.2 Hz, 2H), 7.10 – 7.07 (m, 2H), 6.95 (t, *J*

= 7.2 Hz, 1H), 4.80 (brs, 1H), 3.80 (q, *J* = 6.4 Hz, 2H), 3.06 (t, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.58, 155.05, 151.81, 150.45, 148.23, 140.96, 136.61, 135.05, 132.80, 130.69, 127.42, 127.35, 127.07, 126.10, 124.27, 123.72, 122.65, 120.56, 42.76, 32.53 ppm. HRMS calculated for $C_{20}H_{16}ON_3Cl$ $(M+H)^+$: 350.1055. Found: 350.1059.

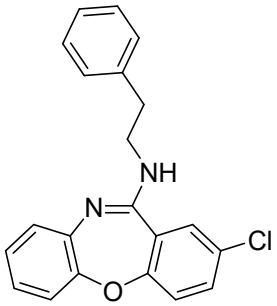
2-chloro-N-(2-(1-methylpyrrolidin-2-yl)ethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW6)



2-(2-Aminoethyl)-1-methylpyrrolidine (2.0 equiv); methanol/dichloromethane = 2.5/100; yield: 73.8%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.35 –7.32 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.07 – 6.99 (m, 3H), 6.90 (t, *J* = 7.6 Hz, 1H), 3.74 – 3.72 (m, 1H), 3.55 – 3.54 (m, 1H), 3.04 – 3.02 (m, 1H), 2.42 (brs, 1H), 2.36 (s, 3H), 2.17 (q, *J* = 8.0 Hz, 1H), 1.92 – 1.90 (m, 2H), 1.84 – 1.75 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.50, 155.51, 151.88, 141.54, 132.31, 130.45, 128.08, 127.34, 127.29, 126.00, 123.60, 122.47, 120.48, 65.25, 57.25, 40.83, 39.13, 29.10, 28.64, 22.74 ppm. HRMS calculated for $C_{20}H_{22}ON_3Cl$ $(M+H)^+$: 356.1524. Found: 356.1515.

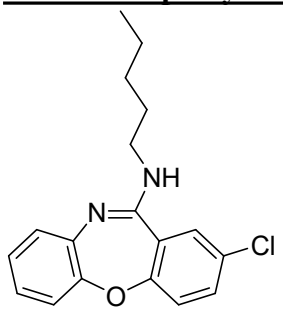
2-chloro-N-phenethyldibenzo[b,f][1,4]oxazepin-11-amine (SW7)



Phenethylamine (10.0 equiv); ethyl acetate/hexane = 1/33; yield: 78.0%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.35 – 7.06 (m, 11H), 6.94 (t, *J* = 7.2 Hz, 1H), 4.69 (brs, 1H), 3.80 (q, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.54, 155.16, 151.84, 141.15, 139.51, 132.66, 130.62, 129.11, 128.91, 127.62, 127.37, 127.16, 126.76, 126.06, 124.07, 122.57, 120.52, 42.95, 35.20 ppm. HRMS calculated for $C_{21}H_{17}ON_2Cl$ $(M+H)^+$: 349.1102. Found: 349.1103.

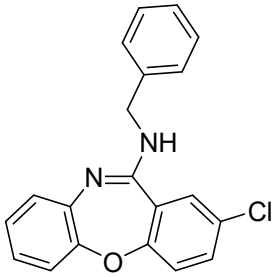
2-chloro-N-pentyldibenzo[b,f][1,4]oxazepin-11-amine (SW8)



Amylamine (10.0 equiv); ethyl acetate/hexane = 1/28; yield: 61.3%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.35 (s, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 7.07 – 7.06 (m, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 4.67 (brs, 1H), 3.51 (s, 2H), 1.70 – 1.67 (m, 3H), 1.40 (brs, 4H), 0.93 (brs, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.61, 155.49, 151.87, 141.23, 132.60, 130.60, 127.78, 127.30, 127.19, 126.04, 123.92, 122.57, 120.47, 42.01, 29.56, 29.14, 22.69, 14.24 ppm. HRMS calculated for $C_{18}H_{19}ON_2Cl$ $(M+H)^+$: 315.1259. Found: 315.1260.

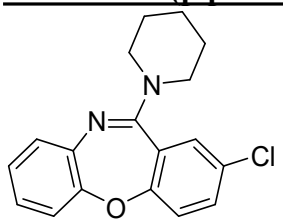
N-benzyl-2-chlorodibenzo[b,f][1,4]oxazepin-11-amine (SW9)



Benzylamine (5.0 equiv); ethyl acetate/hexane = 1/32; yield: 88.5%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.45 – 7.29 (m, 7H), 7.16 (brs, 2H), 7.08 (t, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 4.94 (brs, 1H), 4.72 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.63, 155.15, 151.91, 140.96, 138.69, 132.81, 130.68, 129.01, 128.54, 127.85, 127.43, 127.37, 127.18, 126.10, 124.26, 122.65, 120.55, 46.28 ppm. HRMS calculated for $C_{20}H_{15}ON_2Cl$ $(M+H)^+$: 335.0946. Found: 335.0936.

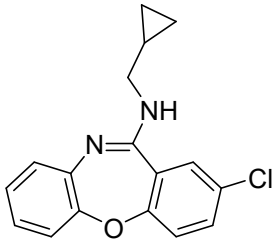
2-chloro-11-(piperidin-1-yl)dibenzo[b,f][1,4]oxazepine (SW10)



Piperidine (5.0 equiv); ethyl acetate/hexane = 1/33; yield: 59.5%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.35 (d, *J* = 8.8 Hz, 1H), 7.29 (s, 1H), 7.16 – 7.11 (m, 2H), 7.08 – 7.03 (m, 2H), 6.94 (t, *J* = 7.6 Hz, 1H), 3.46 (s, 4H), 1.68 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.55, 159.37, 152.07, 140.70, 132.45, 130.33, 129.30, 127.24, 125.93, 125.73, 124.28, 122.77, 120.19, 48.70, 26.05, 25.10 ppm. HRMS calculated for $C_{18}H_{17}ON_2Cl$ $(M+H)^+$: 313.1102. Found: 313.1103.

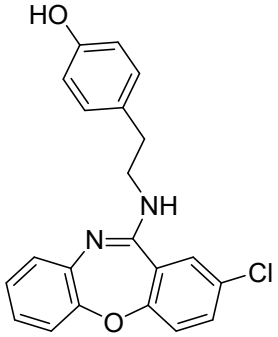
2-chloro-N-(cyclopropylmethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW11)



Cyclopropanemethylamine (5.0 equiv); ethyl acetate/hexane = 1/2; yield: 64.6%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.41 (s, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.15 – 7.04 (m, 4H), 6.93 (t, *J* = 7.2 Hz, 1H), 4.84 (s, 1H), 3.37 (s, 2H), 1.15 – 1.13 (m, 1H), 0.58 (d, *J* = 6.8 Hz, 2H), 0.30 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.64, 155.46, 151.90, 141.20, 132.64, 130.62, 127.71, 127.29, 126.05, 123.98, 122.57, 120.49, 47.16, 10.60, 3.83 ppm. HRMS calculated for $C_{17}H_{15}ON_2Cl$ $(M+H)^+$: 299.0946. Found: 299.0949.

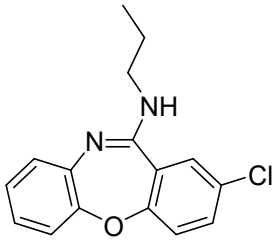
4-(2-((2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)amino)ethyl)phenol (SW12)



Tyramine (5.0 equiv); ethyl acetate/hexane = 1/6; yield: 77.0%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.34 (d, *J* = 8.8 Hz, 1H), 7.21 (s, 1H), 7.17 – 7.11 (m, 4H), 7.06 (brs, 2H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 4.97 (brs, 1H), 4.68 (brs, 1H), 3.76 – 3.75 (m, 2H), 2.95 (t, *J* = 7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.56, 155.31, 154.49, 151.89, 141.08, 132.69, 131.47, 130.64, 130.20, 127.62, 127.32, 127.18, 126.08, 124.11, 122.58, 120.53, 115.75, 43.16, 34.30 ppm. HRMS calculated for $C_{21}H_{17}O_2N_2Cl$ $(M+H)^+$: 365.1051. Found: 365.1057.

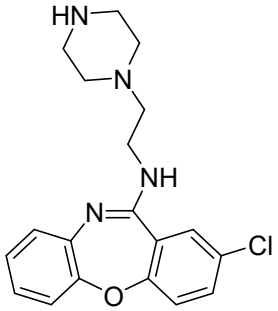
2-chloro-N-propyldibenzo[b,f][1,4]oxazepin-11-amine (SW13)



Propylamine (5.0 equiv); elute: ethyl acetate/hexane = 1/32; yield: 60.8%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.36 – 7.35 (m, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.06 (t, *J* = 7.2 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 4.69 (brs, 1H), 3.49 (q, *J* = 5.6 Hz, 2H), 1.72 (sextet, *J* = 7.2 Hz, 2H), 1.03 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.62, 155.50, 151.88, 141.24, 132.60, 130.61, 127.80, 127.30, 127.18, 126.05, 123.93, 122.58, 120.48, 43.74, 22.69, 11.94 ppm. HRMS calculated for $C_{16}H_{15}ON_2Cl$ $(M+H)^+$: 287.0946. Found: 287.0950.

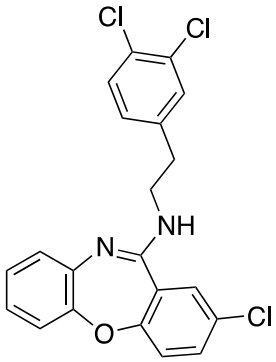
2-chloro-N-(2-(piperazin-1-yl)ethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW14)



1-(2-Aminoethyl)piperazine (6.0 equiv); elute: ethyl acetate/methanol = 4/1; yield: 72.8%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.38 – 7.36 (m, 2H), 7.13 (t, *J* = 7.2 Hz, 2H), 7.06 (t, *J* = 7.2 Hz, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 5.50 (brs, 1H), 3.60 (brs, 2H), 2.89 (s, 4H), 2.65 (brs, 2H), 2.48 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.48, 155.56, 151.84, 141.20, 132.61, 130.62, 127.76, 127.39, 127.29, 126.04, 123.95, 122.55, 120.50, 56.87, 54.39, 46.33, 38.05 ppm. HRMS calculated for $C_{19}H_{21}ON_4Cl$ $(M+H)^+$: 357.1477. Found: 357.1484.

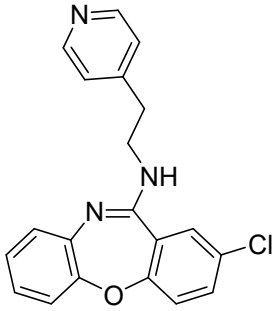
2-chloro-N-(3,4-dichlorophenethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW15)



3,4-Dichlorophenethylamine (5.0 equiv); elute: hexane/dichloromethane = 3/1; yield: 49.0%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.38 – 7.36 (brs, 3H), 7.24 (s, 1H), 7.17 – 7.07 (m, 5H), 6.97 (t, *J* = 7.2 Hz, 1H), 4.75 (brs, 1H), 3.76 (s, 2H), 3.01 (t, *J* = 6.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.57, 155.19, 151.85, 139.83, 132.93, 132.76, 131.05, 130.74, 128.57, 127.26, 127.16, 126.14, 124.41, 122.70, 120.59, 42.83, 34.45 ppm. HRMS calculated for $C_{21}H_{15}ON_2Cl_3$ $(M+H)^+$: 417.0323. Found: 417.0327.

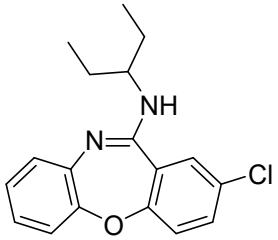
2-chloro-N-(2-(pyridin-4-yl)ethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW16)



4-(2-Aminoethyl)pyridine (3.0 equiv); elute: methanol/dichloromethane = 1/100; yield: 70.6%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 8.50 (s, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.24 – 7.06 (m, 7H), 6.97 (t, *J* = 7.6 Hz, 1H), 4.92 (brs, 1H), 3.82 (t, *J* = 6.4 Hz, 2H), 3.06 (t, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.55, 155.18, 151.83, 150.04, 148.78, 140.62, 133.03, 132.91, 130.70, 127.25, 127.18, 126.13, 124.54, 124.42, 122.67, 120.59, 42.21, 34.68 ppm. HRMS calculated for $C_{20}H_{16}ON_3Cl$ $(M+H)^+$: 350.10547. Found: 350.10550.

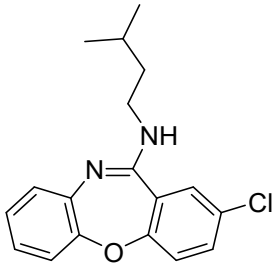
2-chloro-N-(pentan-3-yl)dibenzo[b,f][1,4]oxazepin-11-amine (SW17)



1-Ethylpropylamine (3.0 equiv); elute: ethyl acetate/eexane = 1/45; yield: 55.9%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.37 – 7.34 (m, 2H), 7.12 (t, *J* = 9.2 Hz, 2H), 7.05 (t, *J* = 7.6 Hz, 2H), 6.91 (t, *J* = 7.6 Hz, 1H), 4.44 (brs, 1H), 4.16 (brs, 1H), 1.77 – 1.67 (m, 2H), 1.62 – 1.52 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.57, 155.10, 151.76, 141.36, 132.51, 130.55, 128.06, 127.27, 127.01, 125.98, 123.67, 122.61, 120.41, 53.14, 27.02, 10.44 ppm. HRMS calculated for $C_{18}H_{19}ON_2Cl$ $(M+H)^+$: 315.1259. Found: 315.1260.

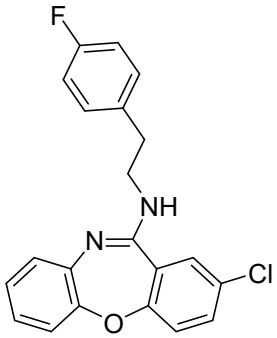
2-chloro-N-isopentyldibenzo[b,f][1,4]oxazepin-11-amine (SW18)



Isopentylamine (5.0 equiv); elute: dichloromethane / hexane = 5/1; yield: 37.2%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.37 – 7.35 (m, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.08 – 7.06 (m, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 4.60 (brs, 1H), 3.54 (q, *J* = 6.4 Hz, 2H), 1.79 – 1.69 (m, 1H), 1.61 – 1.56 (m, 2H), 0.98 (d, *J* = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.62, 155.47, 151.88, 141.27, 132.60, 130.61, 127.81, 127.34, 127.17, 126.05, 123.93, 122.59, 120.48, 40.27, 38.49, 26.35, 22.86 ppm. HRMS calculated for $C_{18}H_{19}ON_2Cl$ $(M+H)^+$: 315.1259. Found: 315.1267.

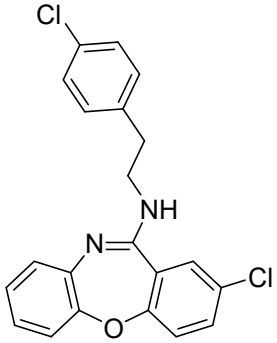
2-chloro-N-(4-fluorophenethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW19)



4-Fluorophenethylamine (6.0 equiv); elute: ethyl acetate/hexane =1/19; yield: 60.3%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.35 (d, *J* = 8.4 Hz, 1H), 7.24 – 7.21 (m, 4H), 7.16 – 7.12 (m, 2H), 7.07 (d, *J* = 6.8 Hz, 2H), 7.02 – 6.93 (m, 3H), 4.69 (brs, 1H), 3.77 (d, *J* = 6.0 Hz, 2H), 3.01 (t, *J* = 6.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 161.90 (d, *J* = 242.9 Hz), 159.55, 155.13, 151.83, 141.07, 135.16, 132.72, 130.65, 130.47 (d, *J* = 7.7 Hz), 127.55, 127.34, 127.10, 126.08, 124.16, 122.61, 120.54, 115.66 (d, *J* = 21.1 Hz), 43.07, 34.43 ppm. HRMS calculated for $C_{21}H_{16}ON_2ClF$ $(M+H)^+$: 367.1008. Found: 367.1009.

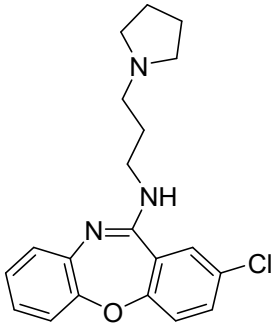
2-chloro-N-(4-chlorophenethyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW20)



2-(4-Chlorophenyl)ethylamine (5.0 equiv); elute: ethyl acetate/hexane =1/19; yield: 63.5%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.35 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.16 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 2H), 6.95 (t, *J* = 7.2 Hz, 1H), 4.70 (brs, 1H), 3.76 (q, *J* = 4.4 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.54, 155.16, 151.83, 140.96, 137.98, 132.79, 132.54, 130.68, 130.44, 128.98, 127.44, 127.30, 127.13, 126.10, 124.24, 122.64, 120.55, 42.95, 34.61 ppm. HRMS calculated for $C_{21}H_{16}ON_2Cl_2$ $(M+H)^+$: 383.0712. Found: 383.0713.

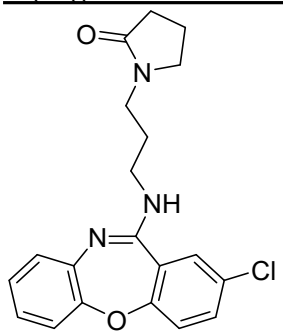
2-chloro-N-(3-(pyrrolidin-1-yl)propyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW22)



1-(3-Aminopropyl)pyrrolidine (8.0 equiv); elute: methanol /dichloromethane = 2.5/100; yield: 65.0%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.88 (brs, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.30 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.89 (t, *J* = 7.2 Hz, 1H), 3.63 (s, 2H), 2.72 (brs, 2H), 2.54 (s, 4H), 1.86 (brs, 2H), 1.74 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.56, 155.79, 151.93, 141.71, 132.24, 130.33, 128.27, 127.23, 127.20, 125.99, 123.43, 122.45, 120.45, 56.37, 54.30, 43.32, 25.73, 23.57 ppm. HRMS calculated for $C_{20}H_{22}ON_3Cl$ $(M+H)^+$: 356.1524. Found: 356.1533.

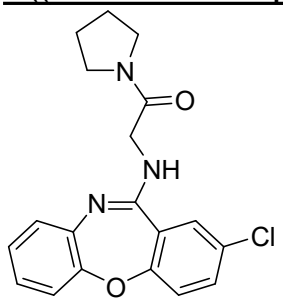
1-(3-((2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)amino)propyl)pyrrolidin-2-one (SW23)



N-(3-Aminopropyl)-2-pyrrolidinone (7.4 equiv); elute: methanol/dichloromethane = 1/100; yield: 47.0%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.52 (s, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.12 – 7.02 (m, 4H), 6.90 (t, *J* = 7.4 Hz, 1H), 5.97 (brs, 1H), 3.51 (q, *J* = 5.6 Hz, 2H), 3.42 (s, 4H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.04 (qui, *J* = 7.2 Hz, 2H), 1.91 – 1.88 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 176.08, 159.35, 155.34, 151.81, 141.35, 132.53, 130.77, 127.76, 127.54, 127.09, 125.92, 123.66, 122.31, 120.45, 47.54, 40.10, 37.81, 31.14, 25.81, 18.16 ppm. HRMS calculated for $C_{20}H_{20}O_2N_3Cl$ $(M+H)^+$: 370.1317. Found: 370.1304.

2-((2-chlorodibenzo[b,f][1,4]oxazepin-11-yl)amino)-1-(pyrrolidin-1-yl)ethan-1-one (SW24)

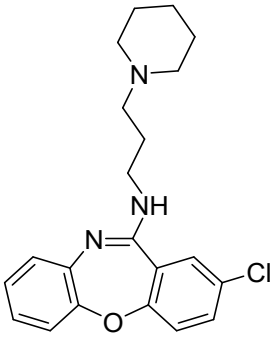


2-Oxo-2-pyrrolidin-1-ylethanamine (4.7 equiv); elute: ethyl acetate/hexane = 1/1; yield: 29.0%

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.49 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.14 – 7.04 (m, 4H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.07 (s, 1H), 4.24 (s, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 3.50 (t, *J* = 6.8 Hz, 2H), 2.02 (qui, *J* = 6.4 Hz, 2H), 1.91 (qui, *J* = 6.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 167.19, 159.52,

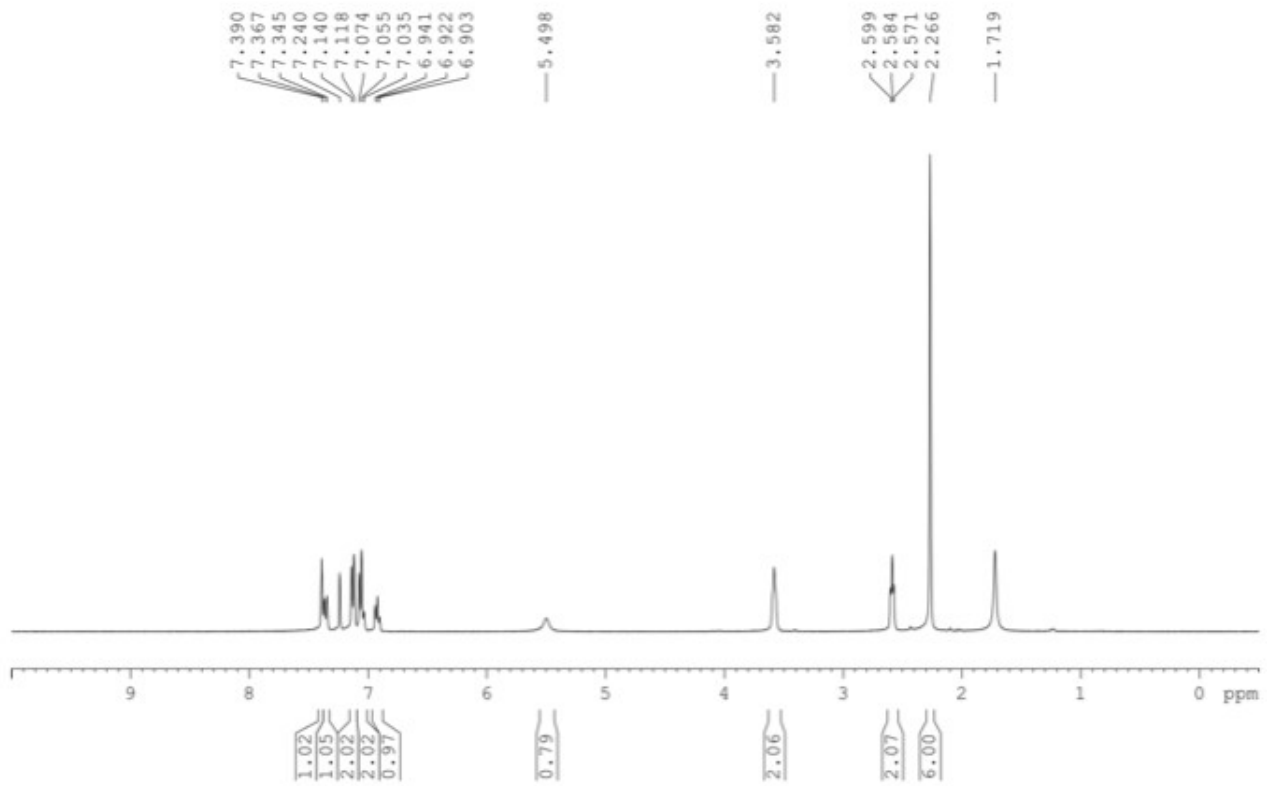
155.00, 151.99, 141.03, 132.82, 130.85, 127.61, 127.30, 127.23, 126.03, 124.22, 122.43, 120.65, 46.27, 45.78, 44.28, 26.17, 24.42 ppm. HRMS calculated for $C_{19}H_{18}O_2N_3Cl$ $(M+H)^+$: 356.1160. Found: 356.1165.

2-chloro-N-(3-(piperidin-1-yl)propyl)dibenzo[b,f][1,4]oxazepin-11-amine (SW26)



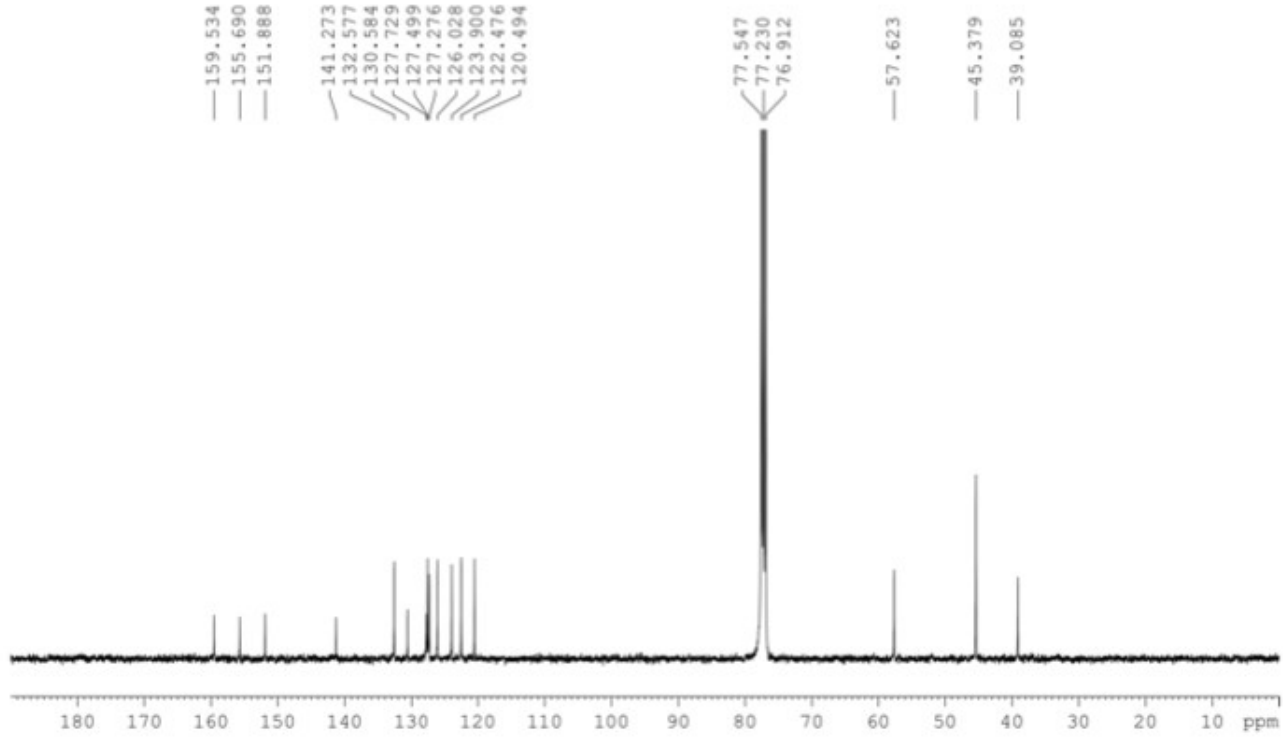
1-(3-aminopropyl)piperidine (5.0 equiv); elute: methanol/dichloromethane = 1/200; yield: 63.0%

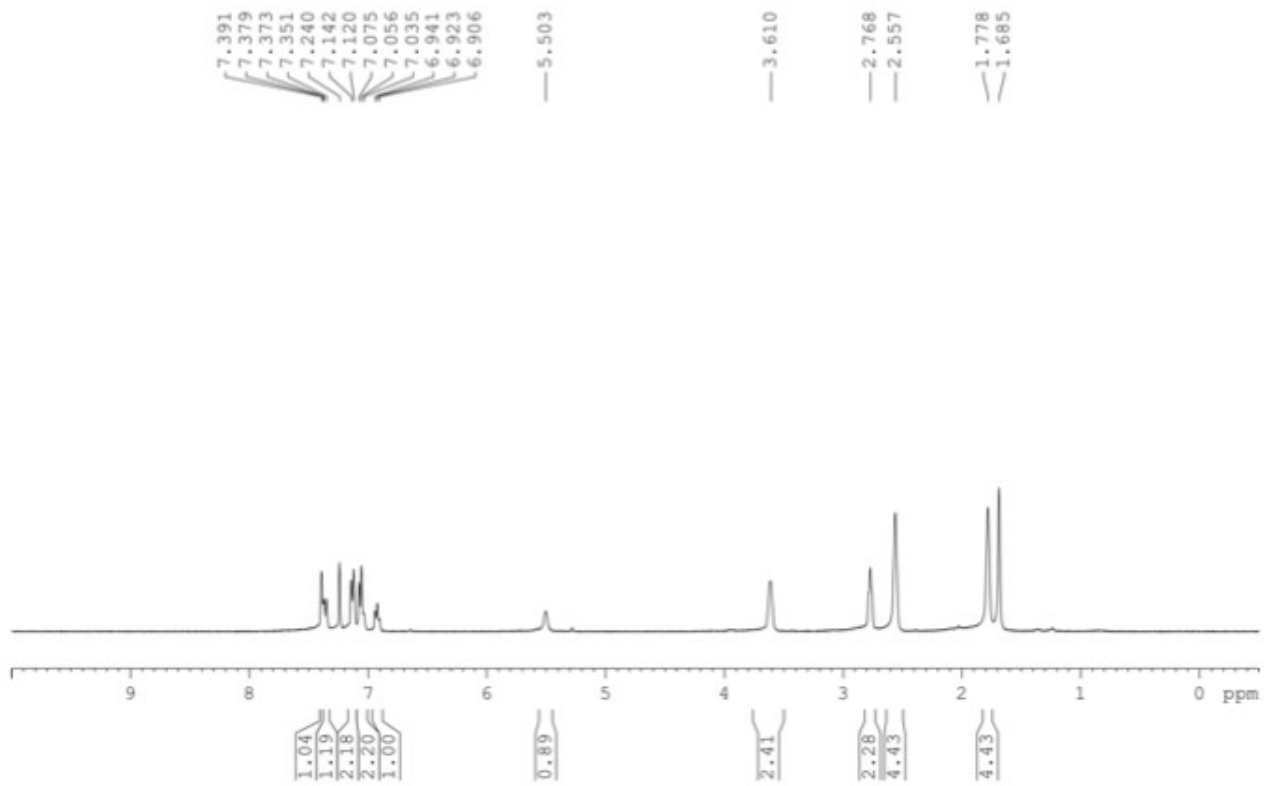
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ 7.85 (brs, 1H), 7.44 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 9.6 Hz, 2H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.90 (t, *J* = 7.6 Hz, 1H), 3.62 (brs, 2H), 2.55 – 2.42 (m, 6H), 1.84 – 1.81 (m, 2H), 1.49 (s, 4H), 1.41 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$-*d*) δ 159.60, 155.95, 151.95, 141.73, 132.28, 130.37, 128.09, 127.75, 127.26, 126.00, 123.43, 122.38, 120.46, 59.66, 54.95, 43.49, 26.10, 24.47, 23.66 ppm. HRMS calculated for $C_{21}H_{24}ON_3Cl$ $(M+H)^+$: 370.1681. Found: 370.1693.



SW1 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

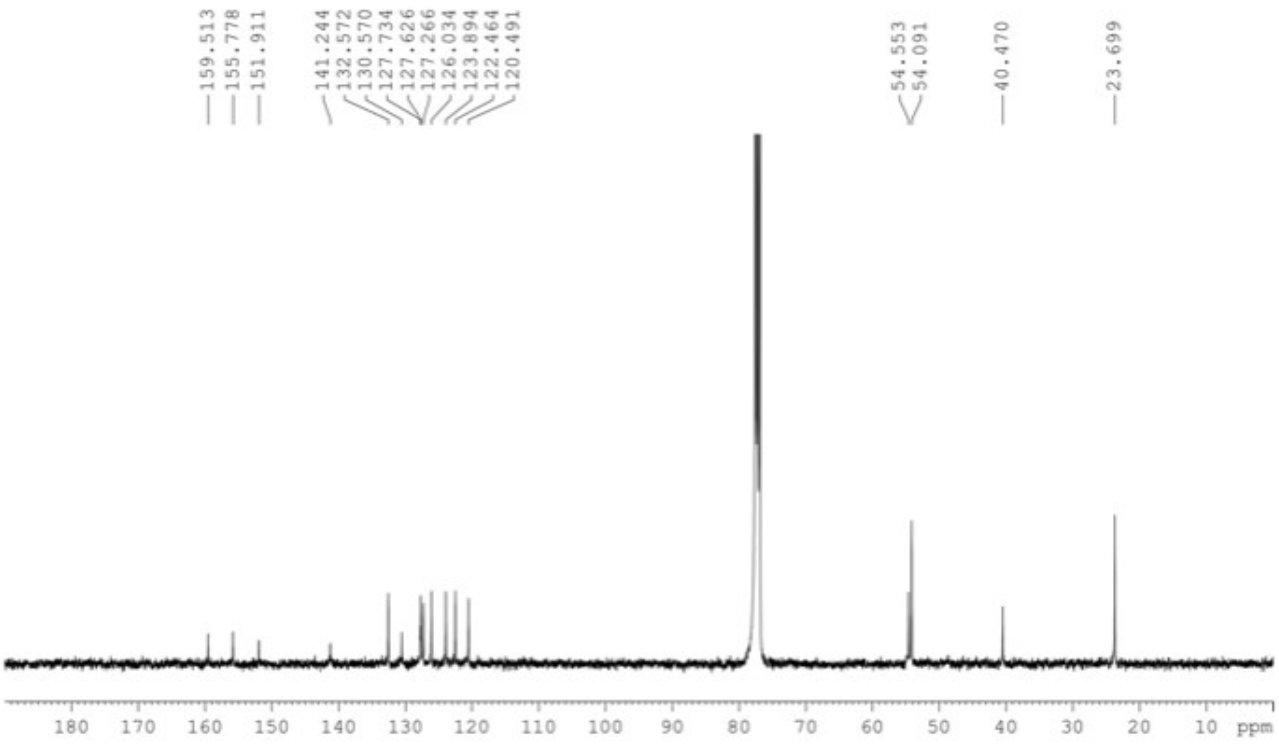
SW1 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



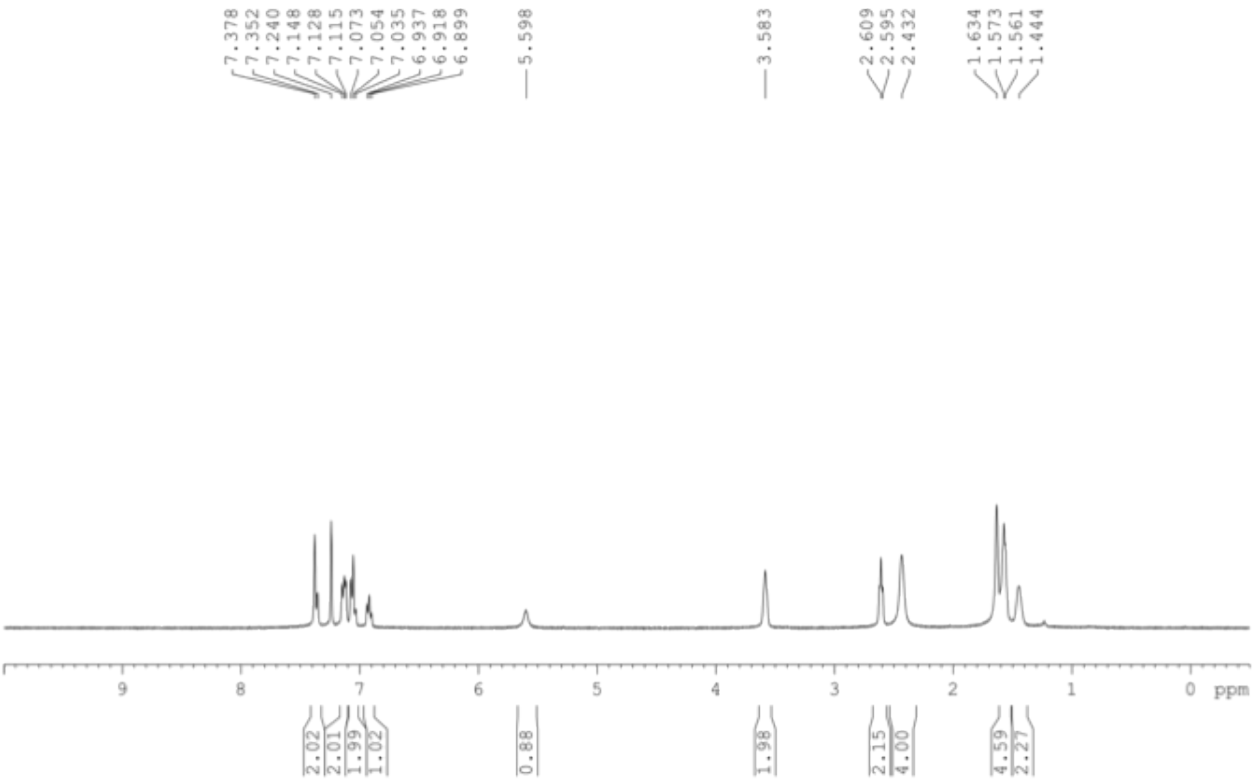


SW2 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

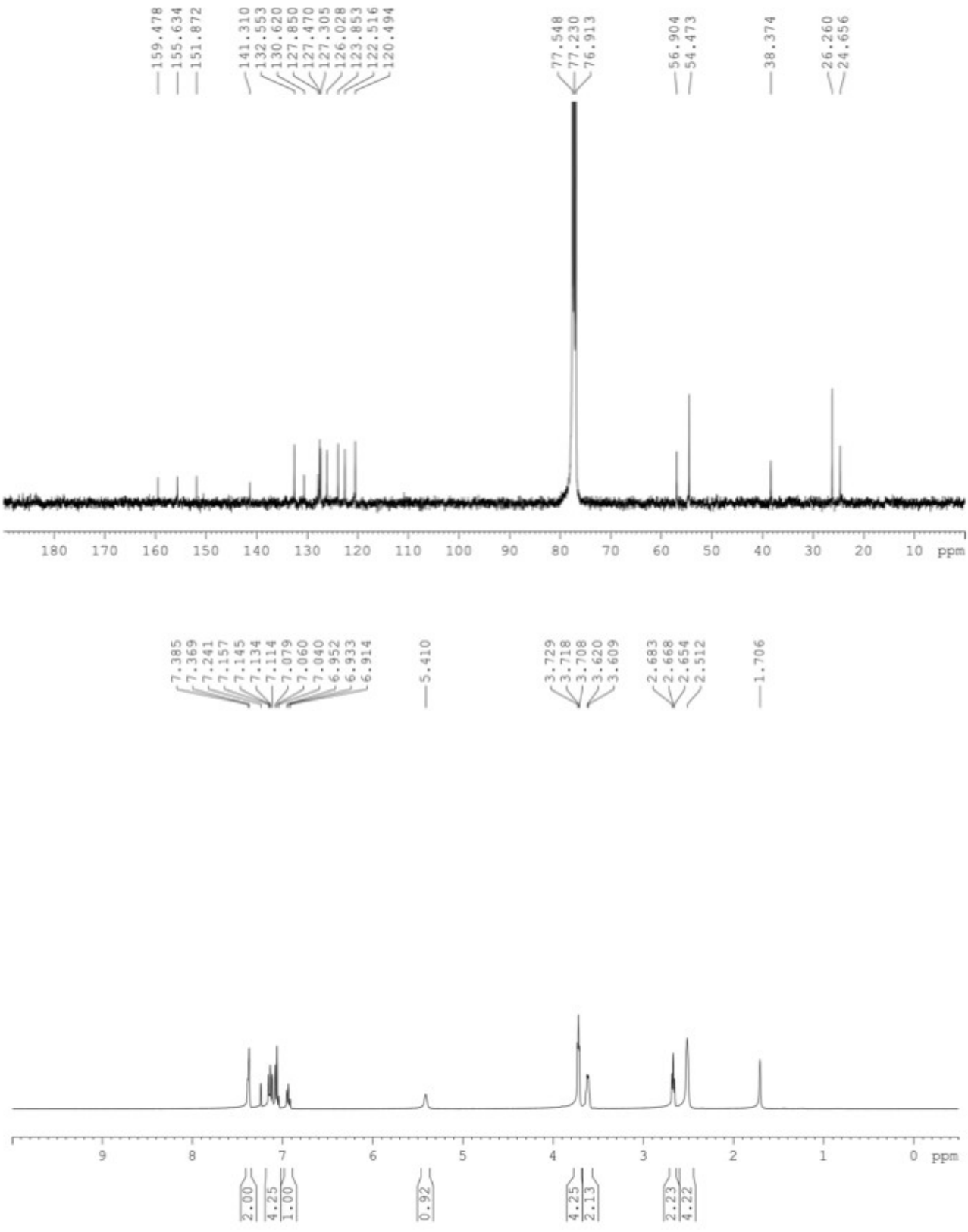
SW2 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



SW3 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

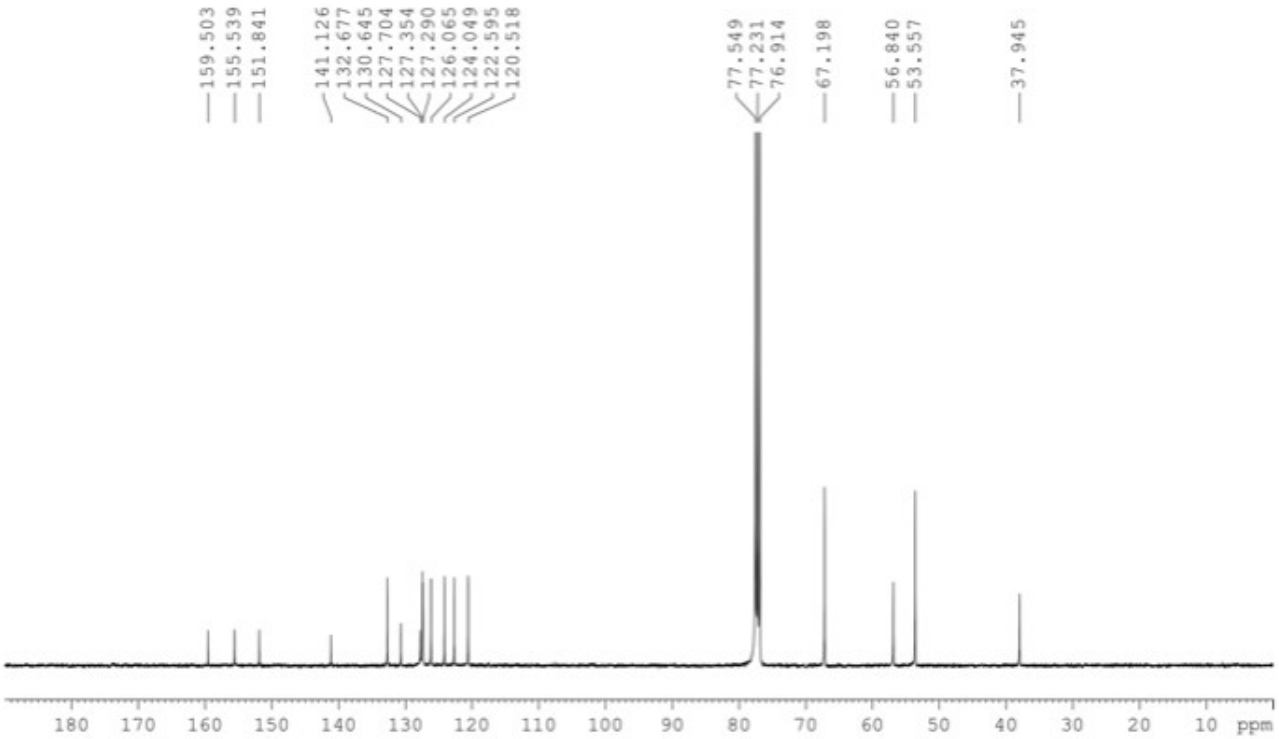


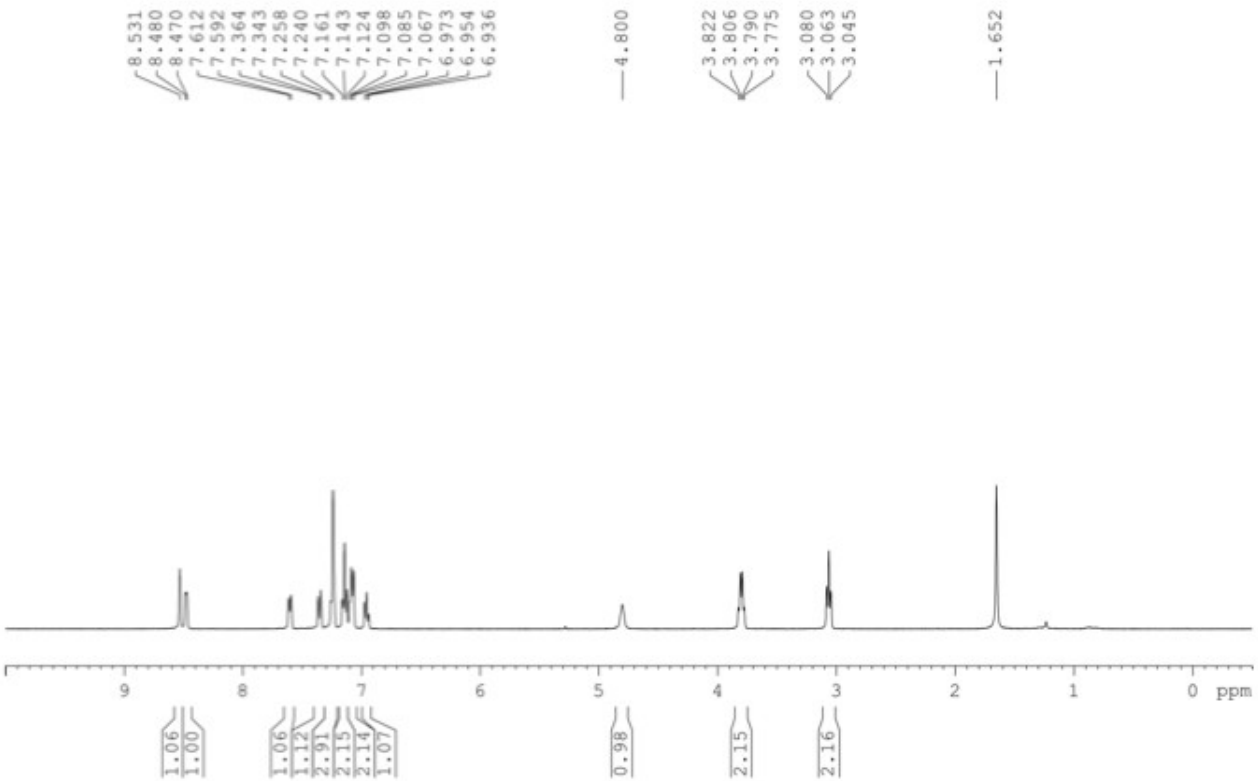
SW3 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



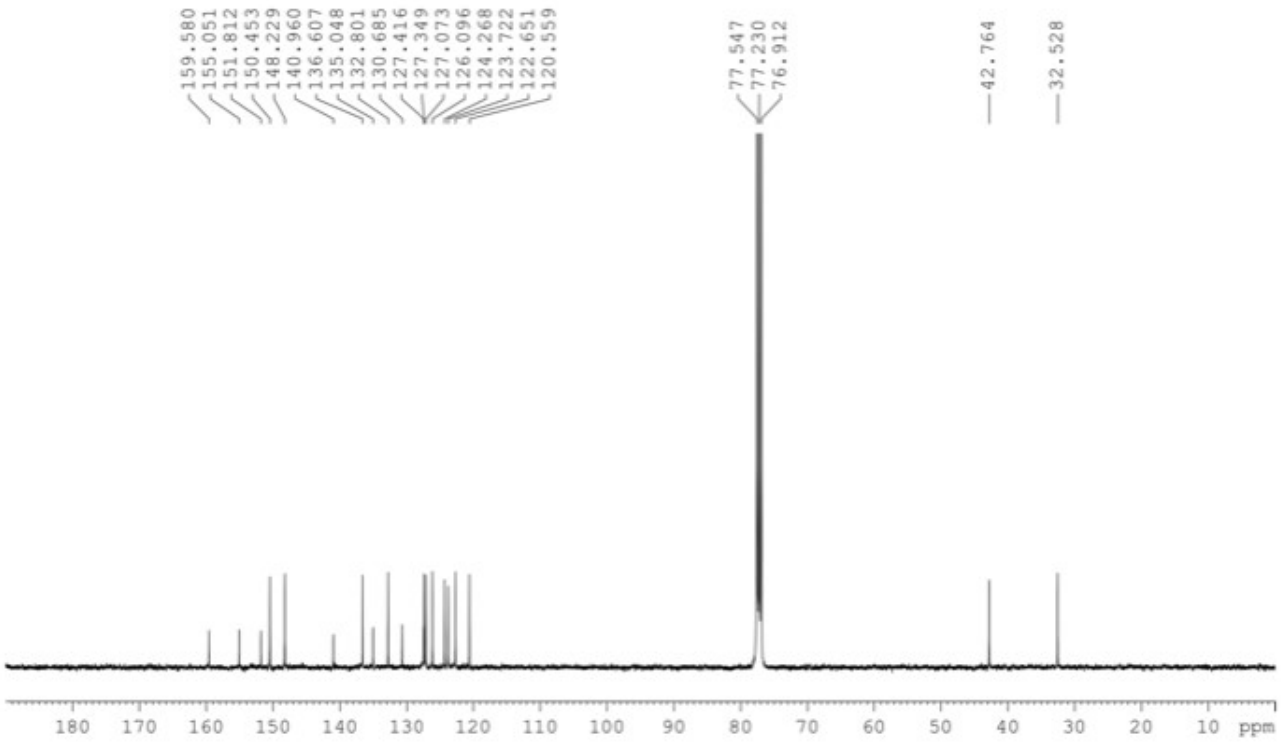
SW4 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

SW4 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

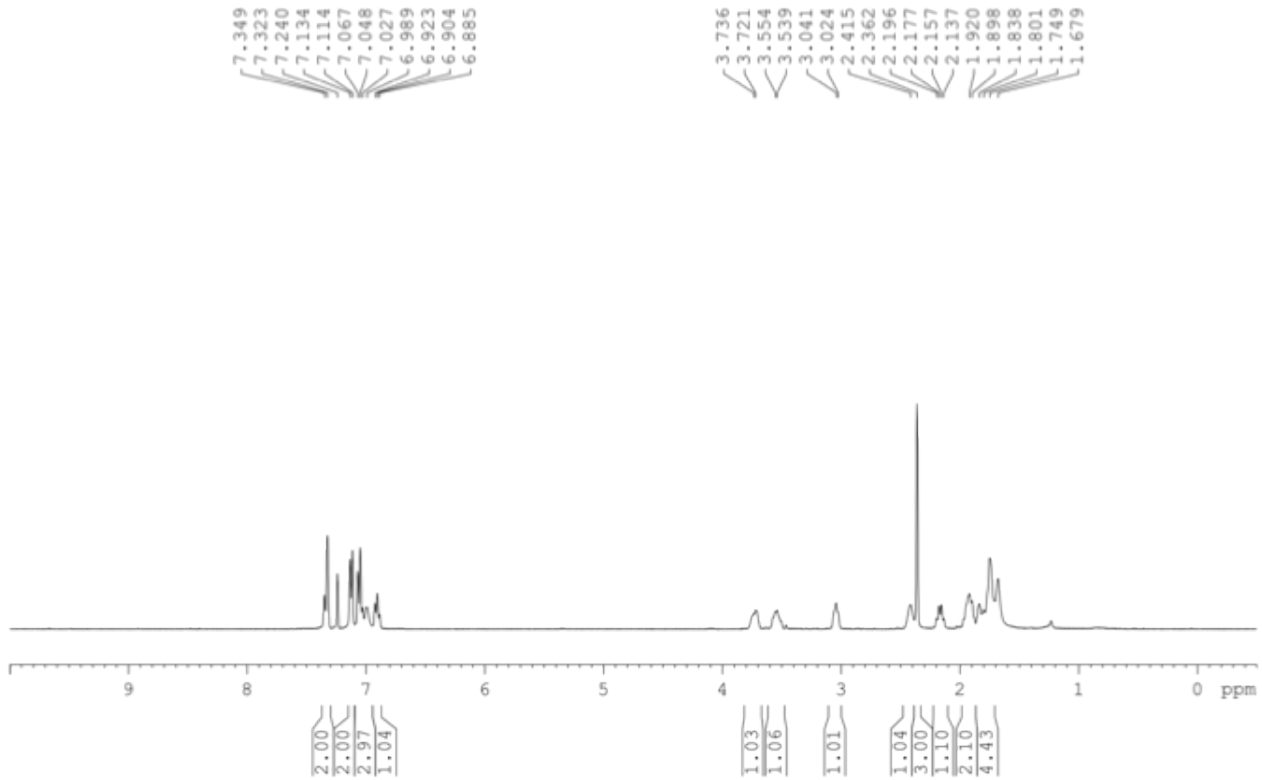




SW5 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

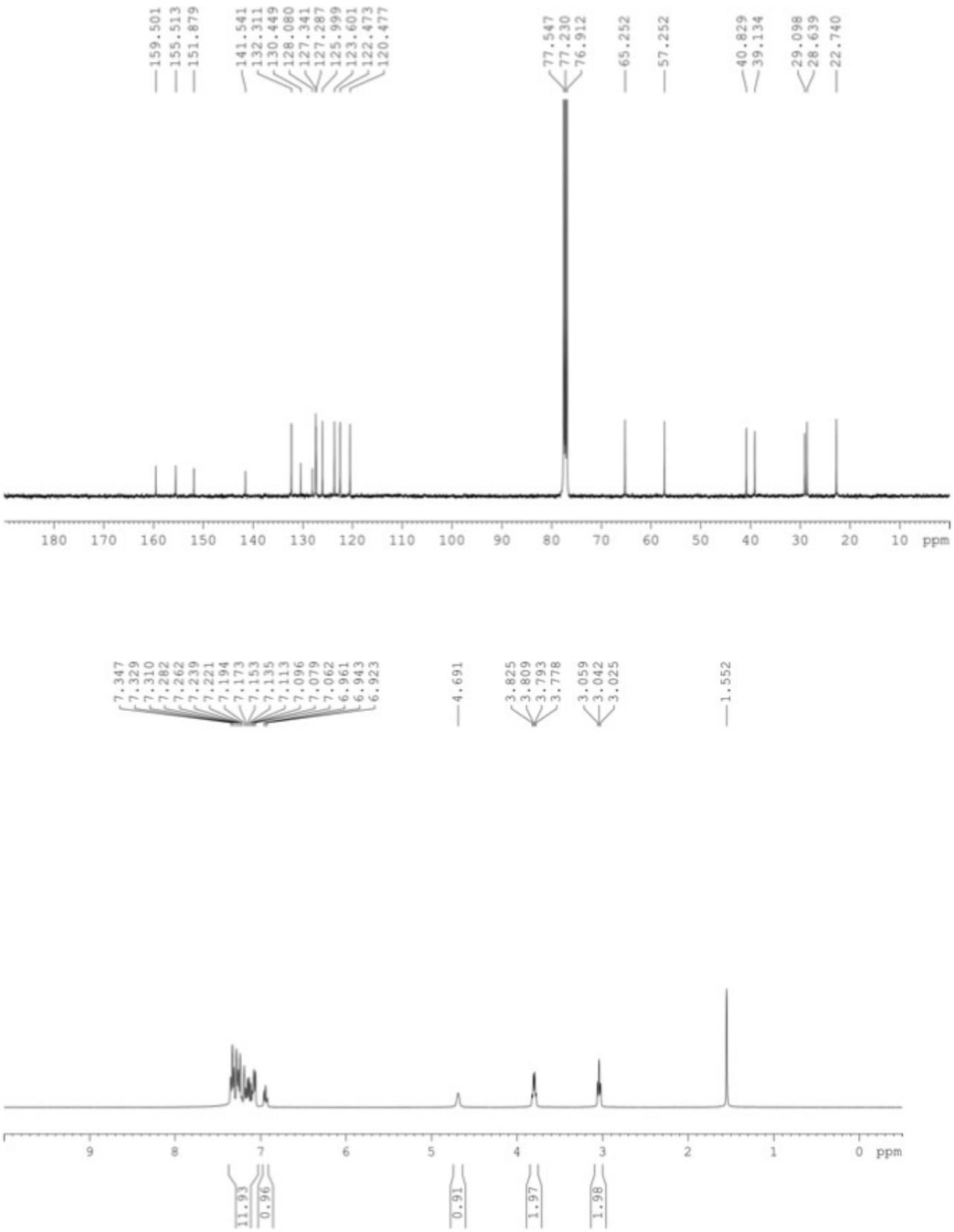


SW5 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



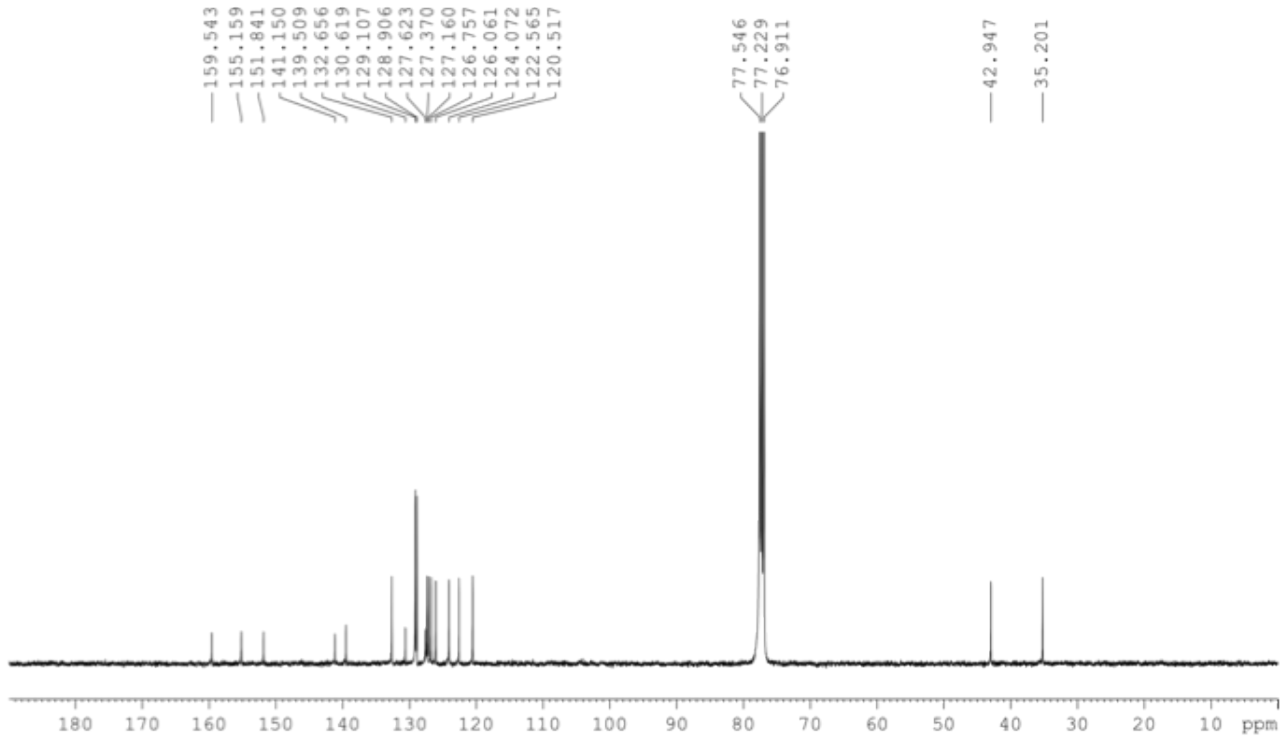
SW6 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

SW6 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

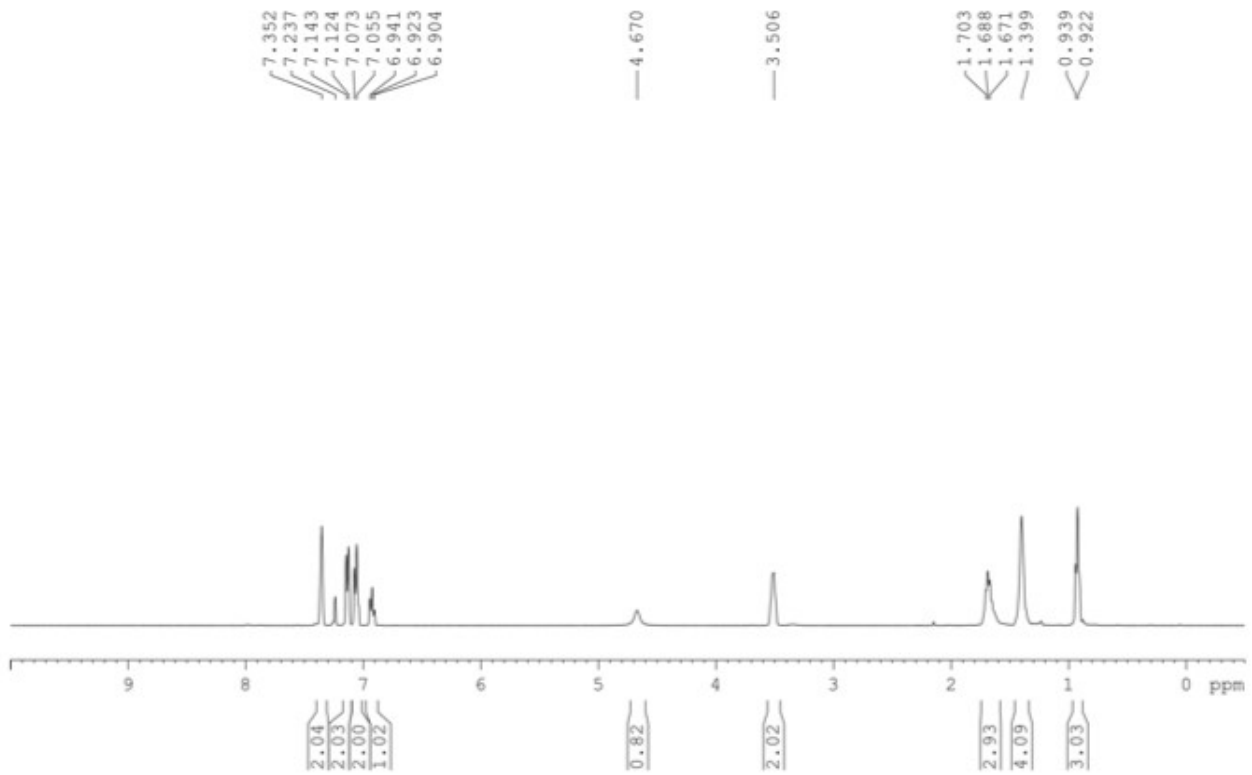


SW7 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

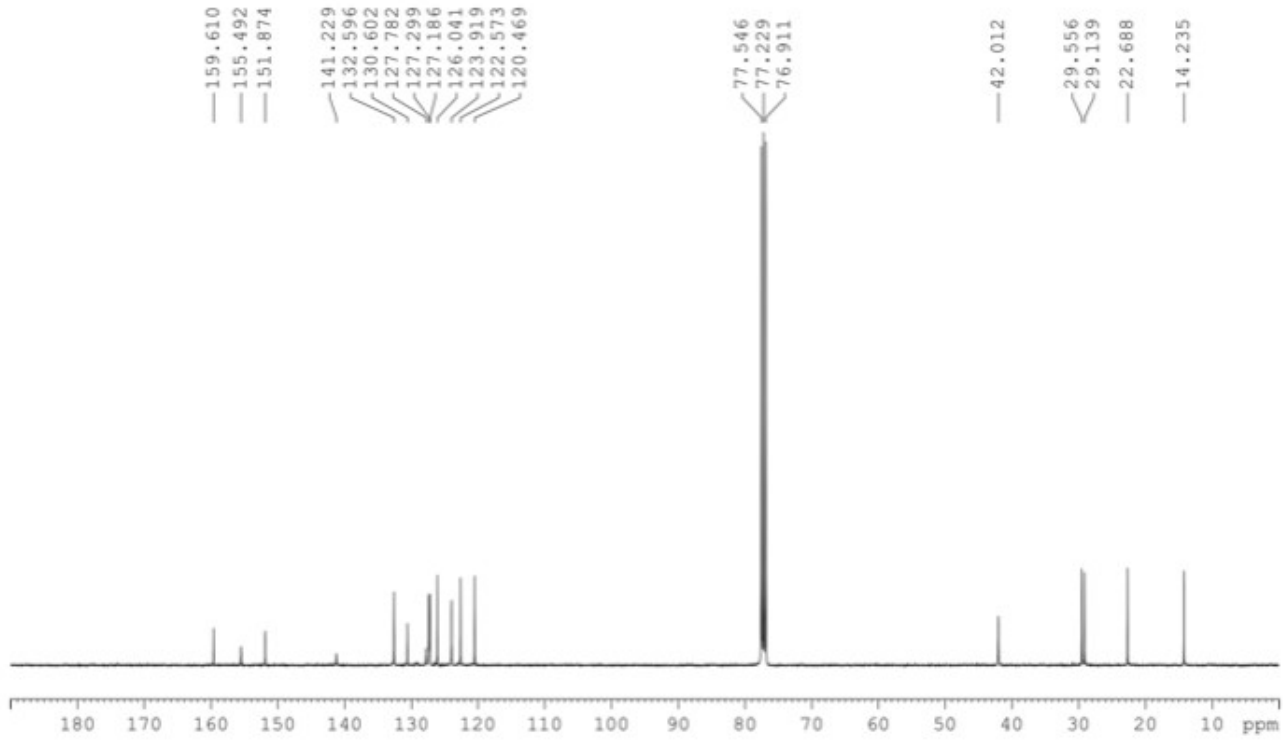
SW7 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



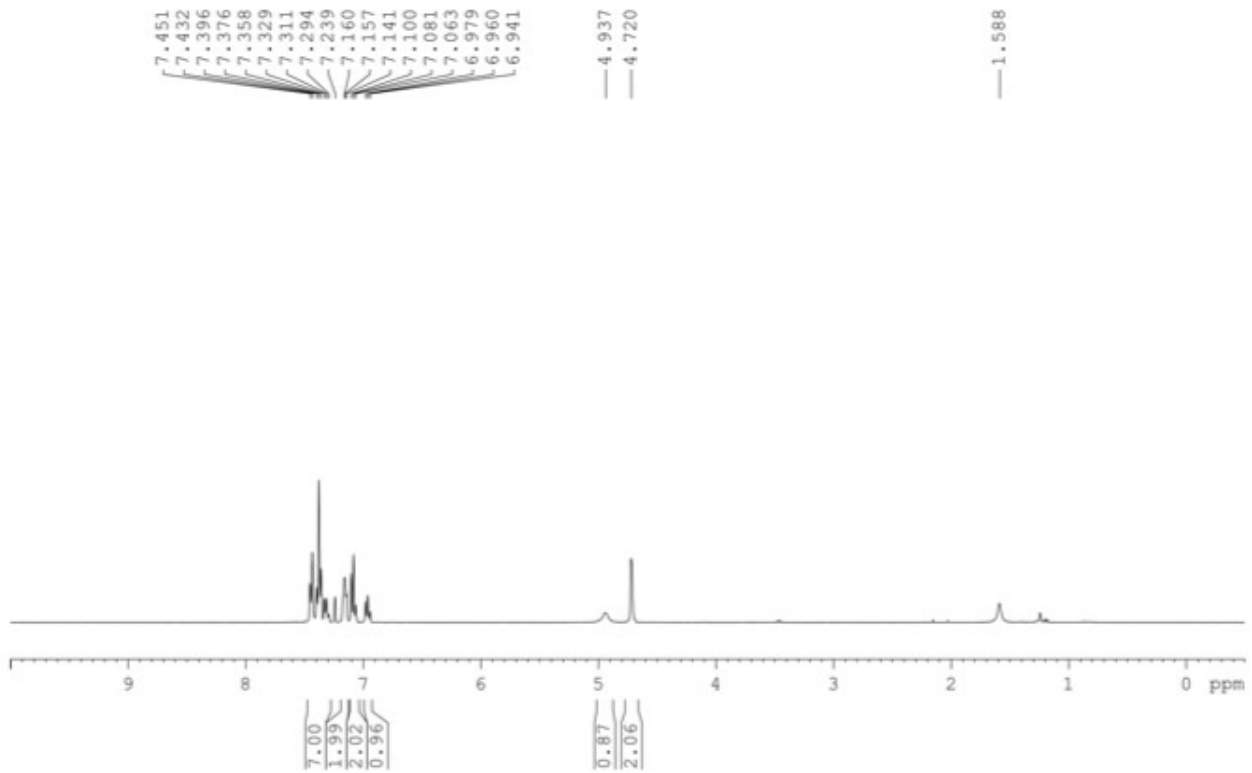
SW8 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)



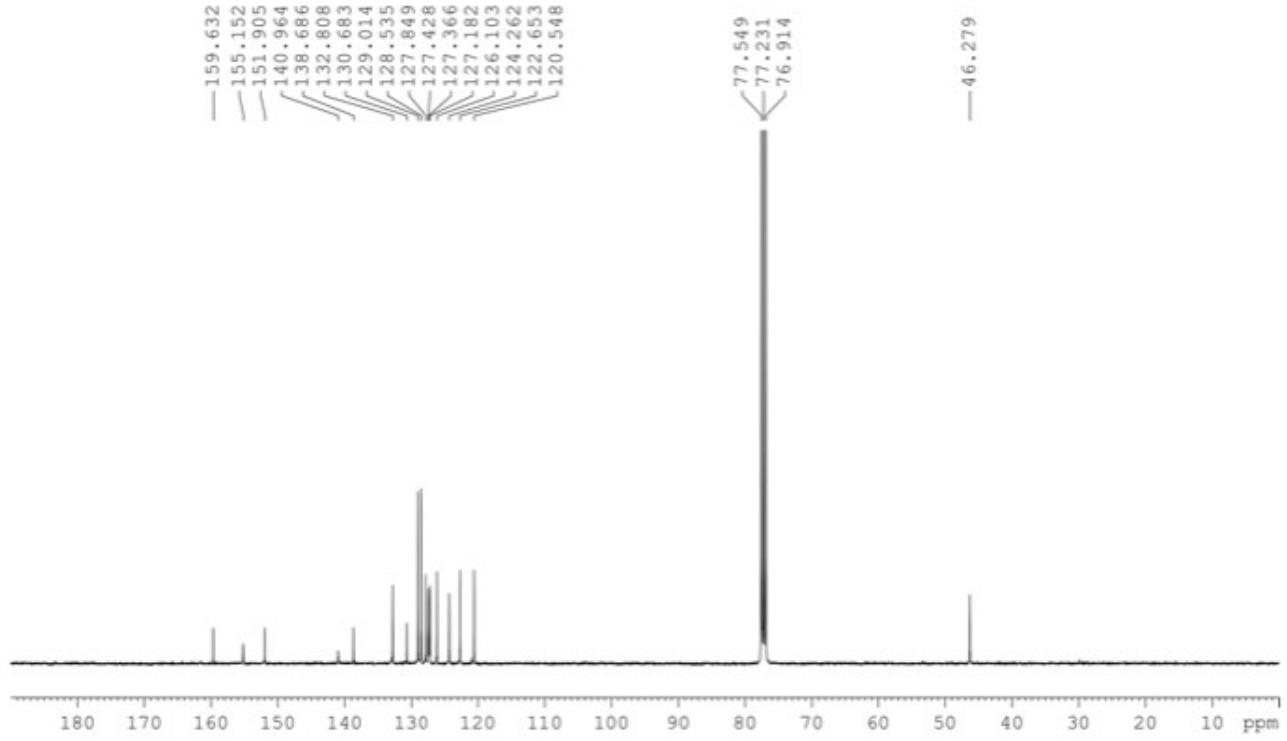
SW8 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



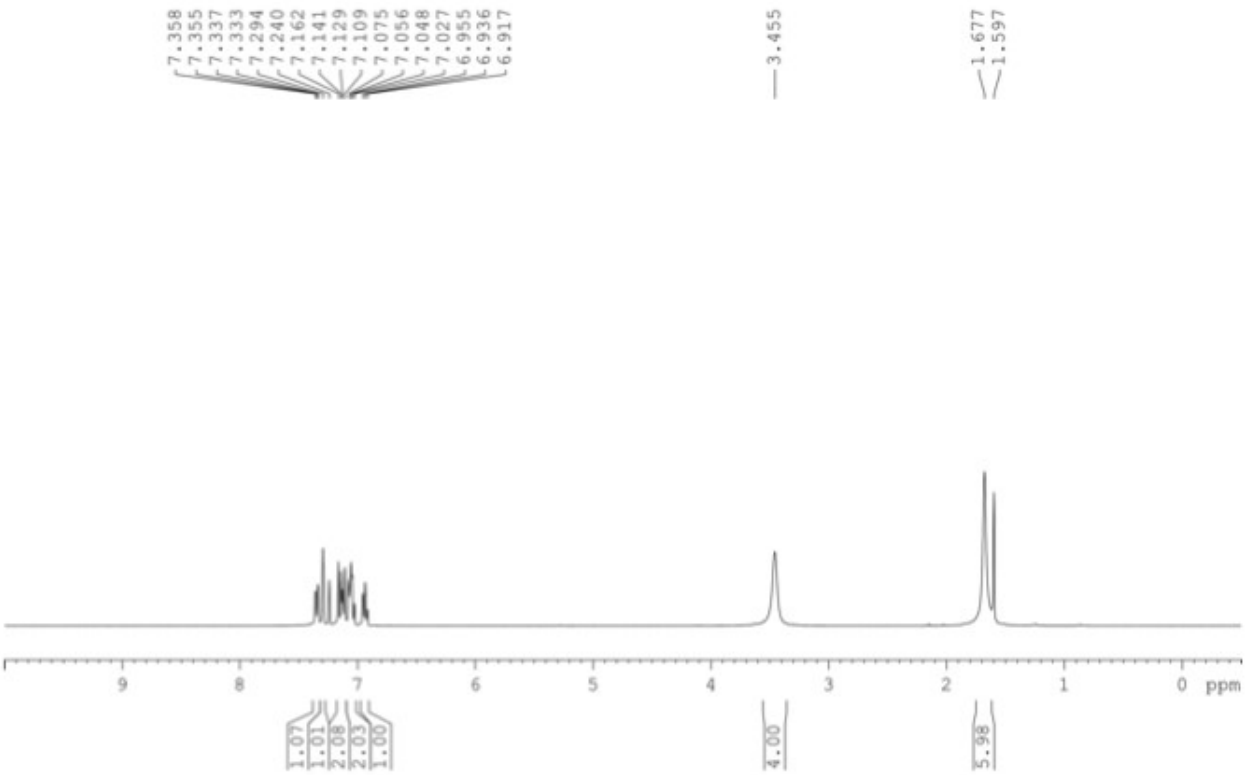
SW9 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)



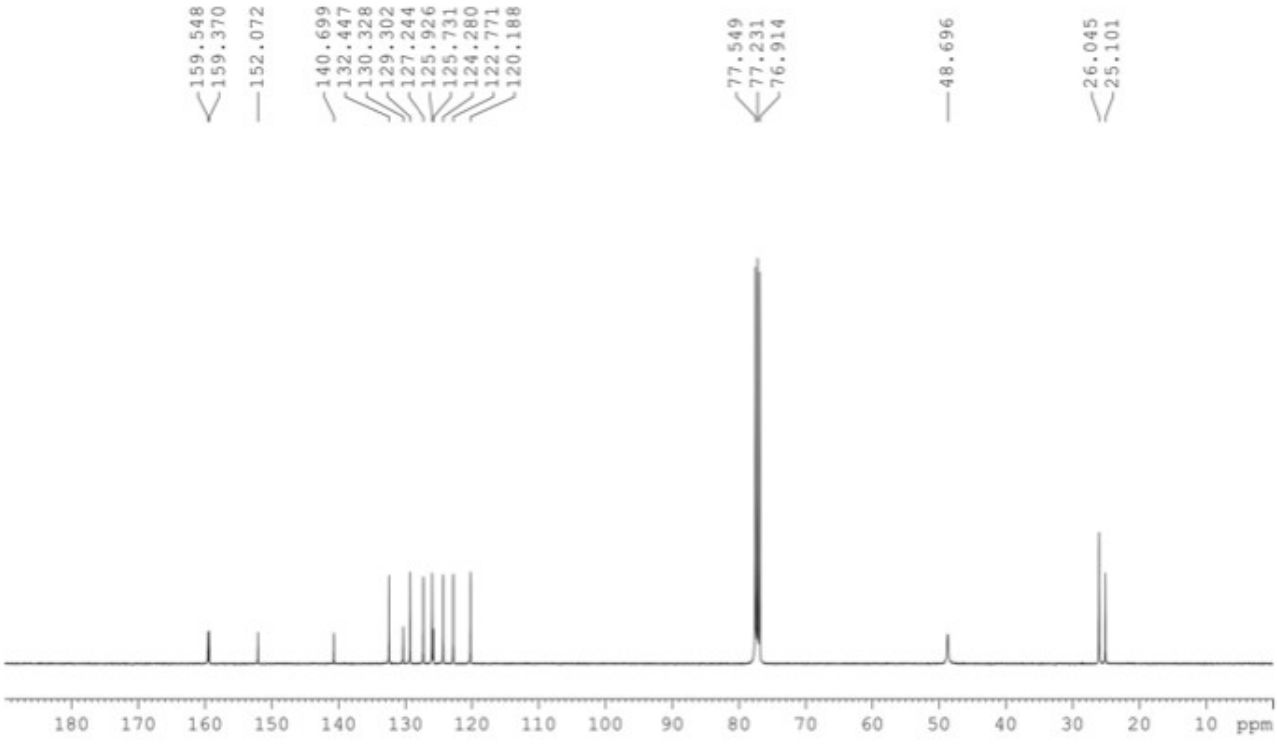
SW9 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



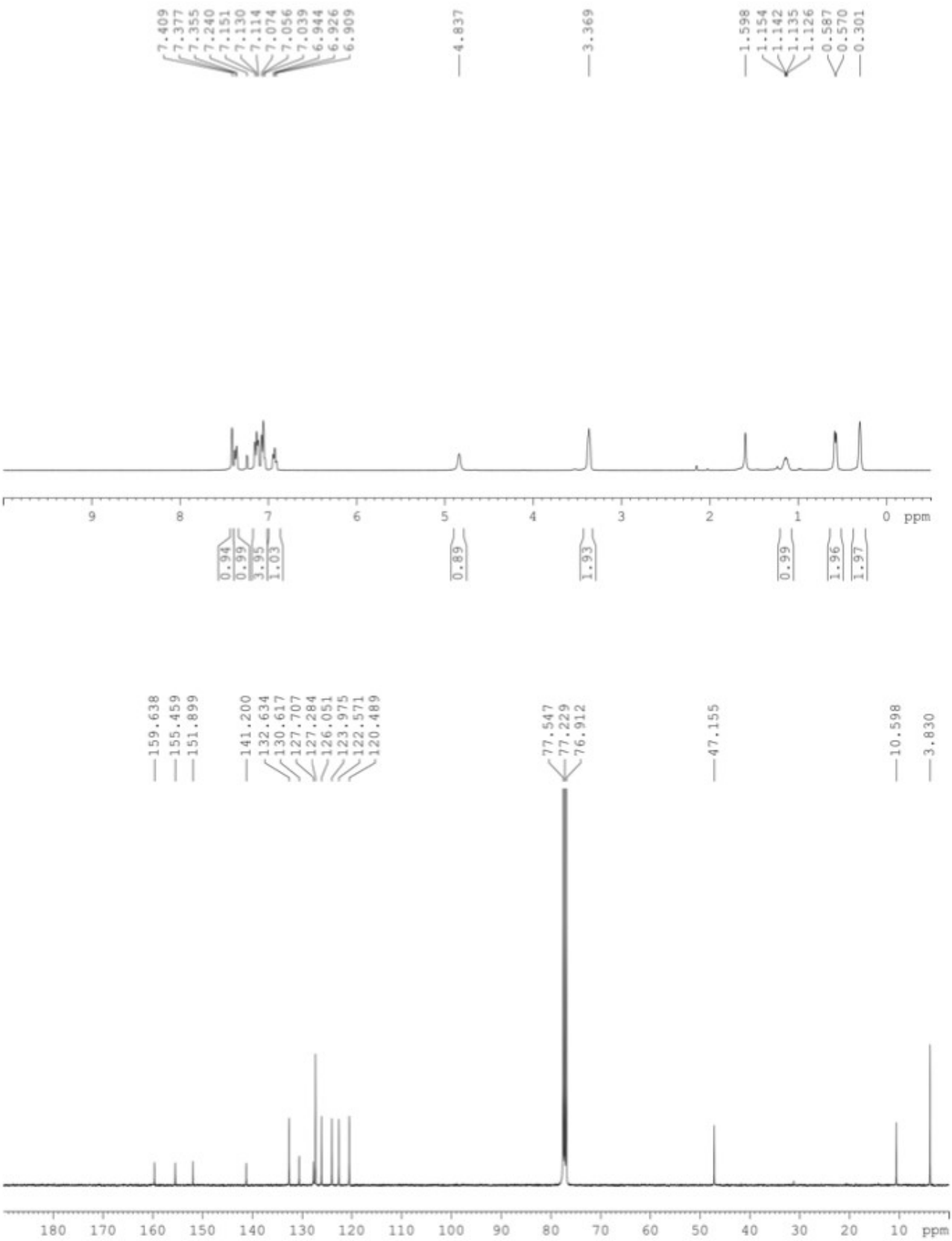
SW10 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)



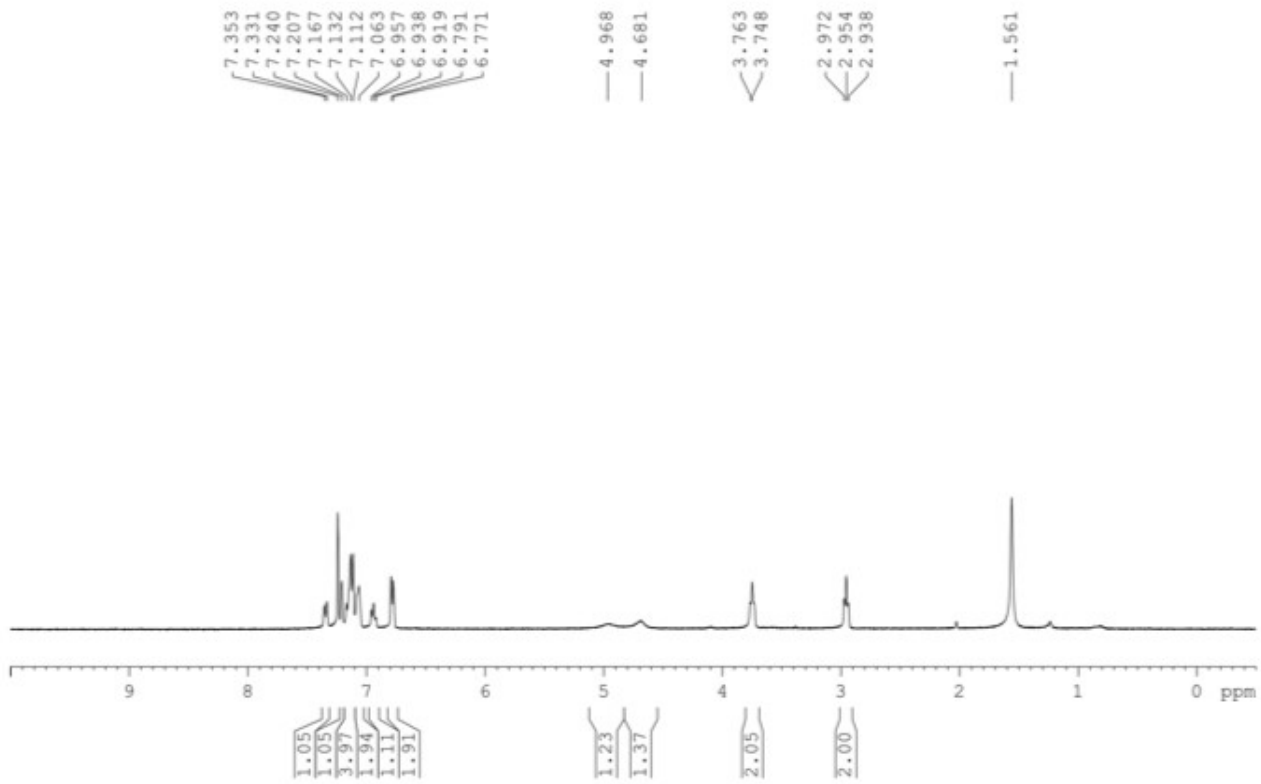
SW10 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



SW11 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

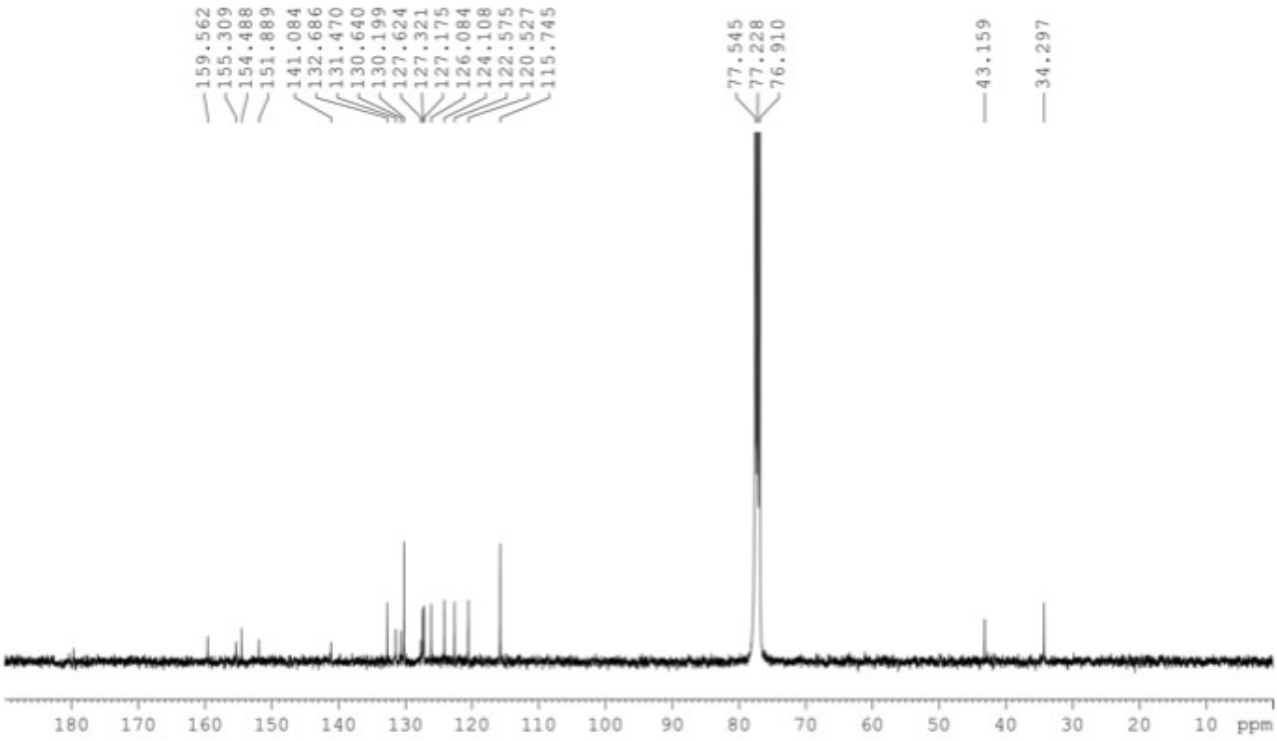


SW11 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

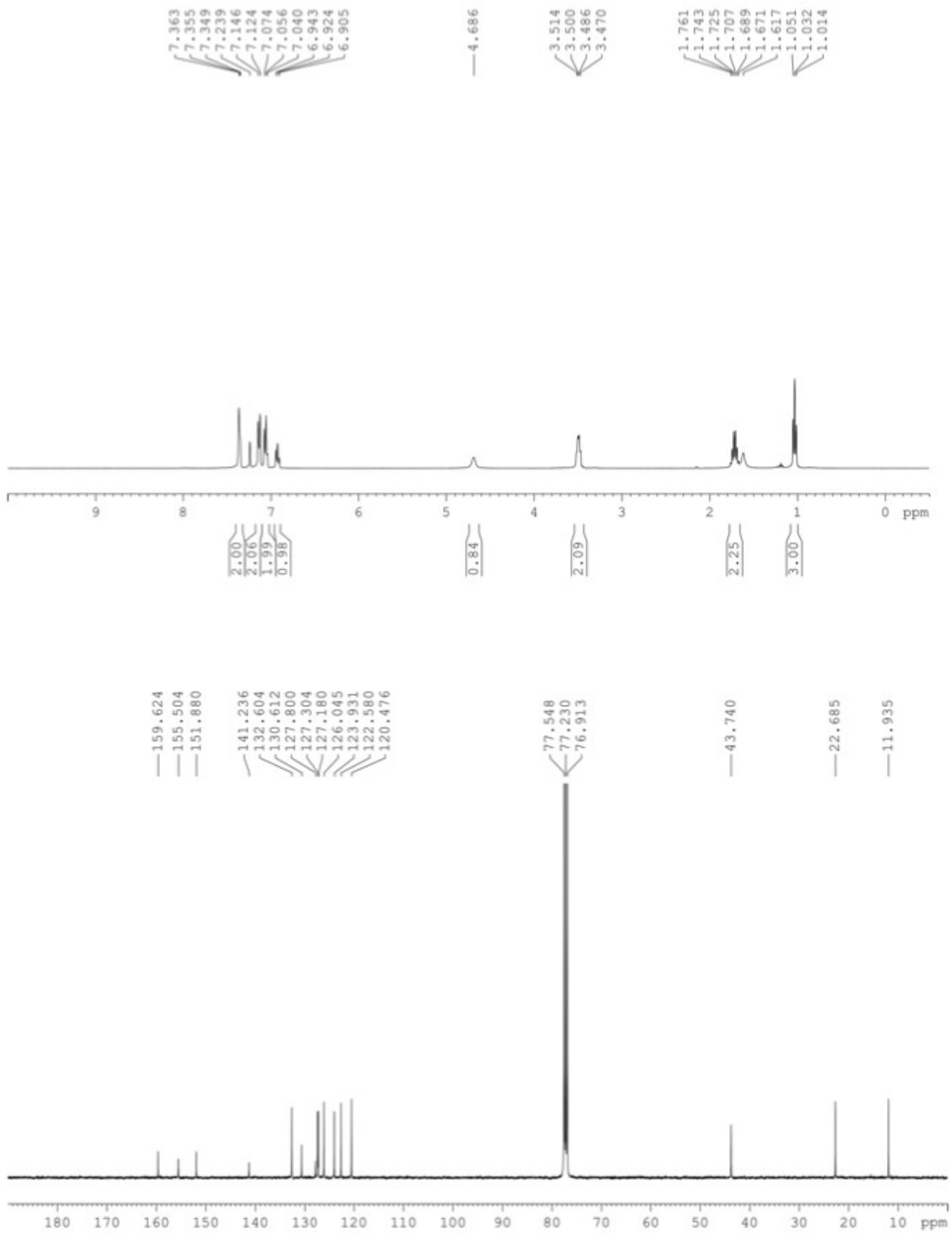


SW12 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

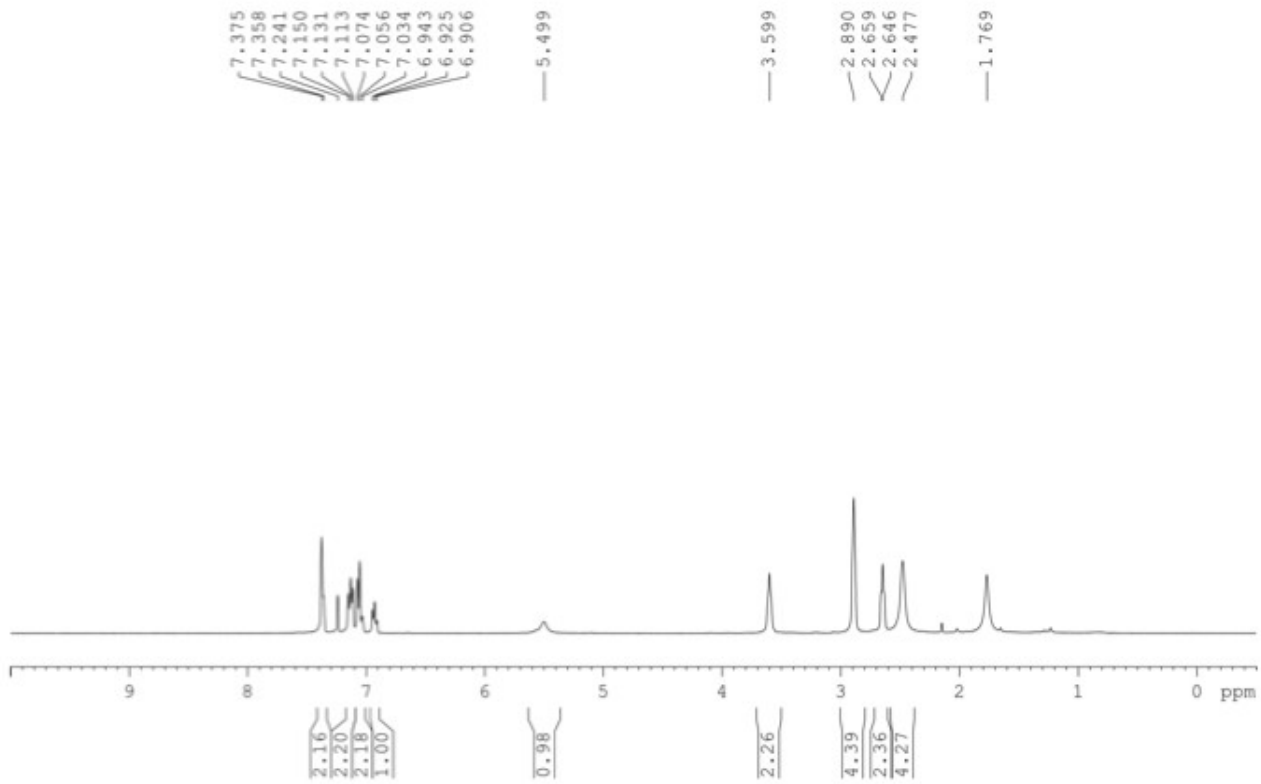
SW12 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



SW13 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

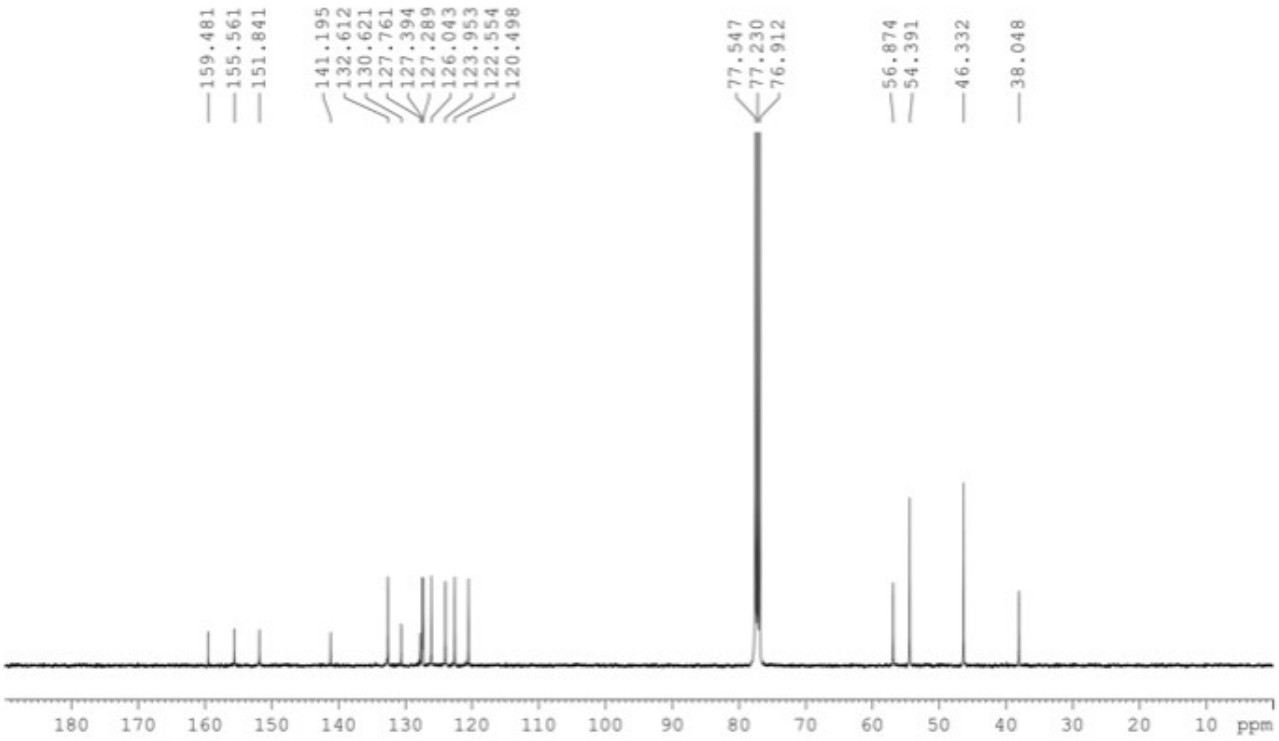


SW13 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

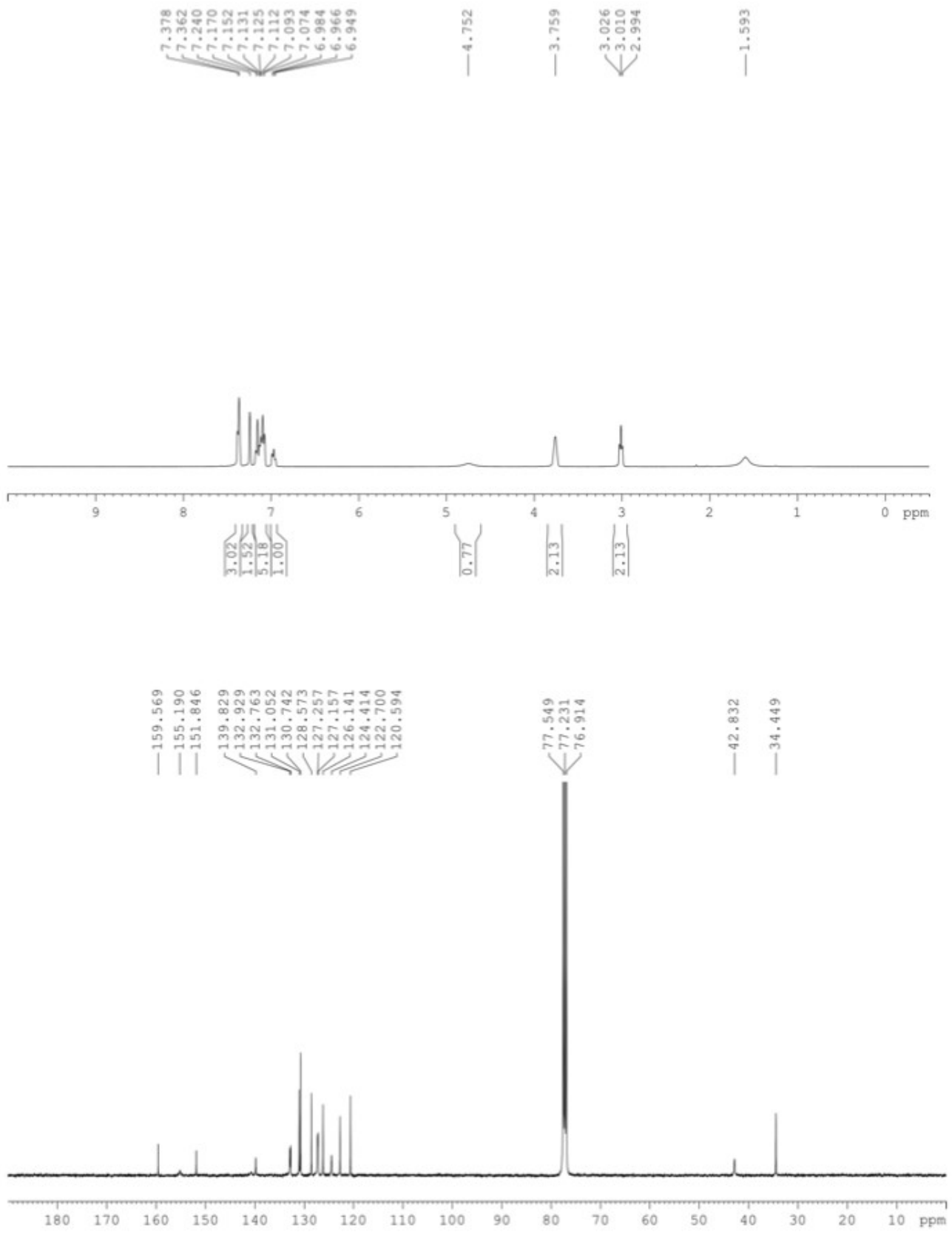


SW14 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

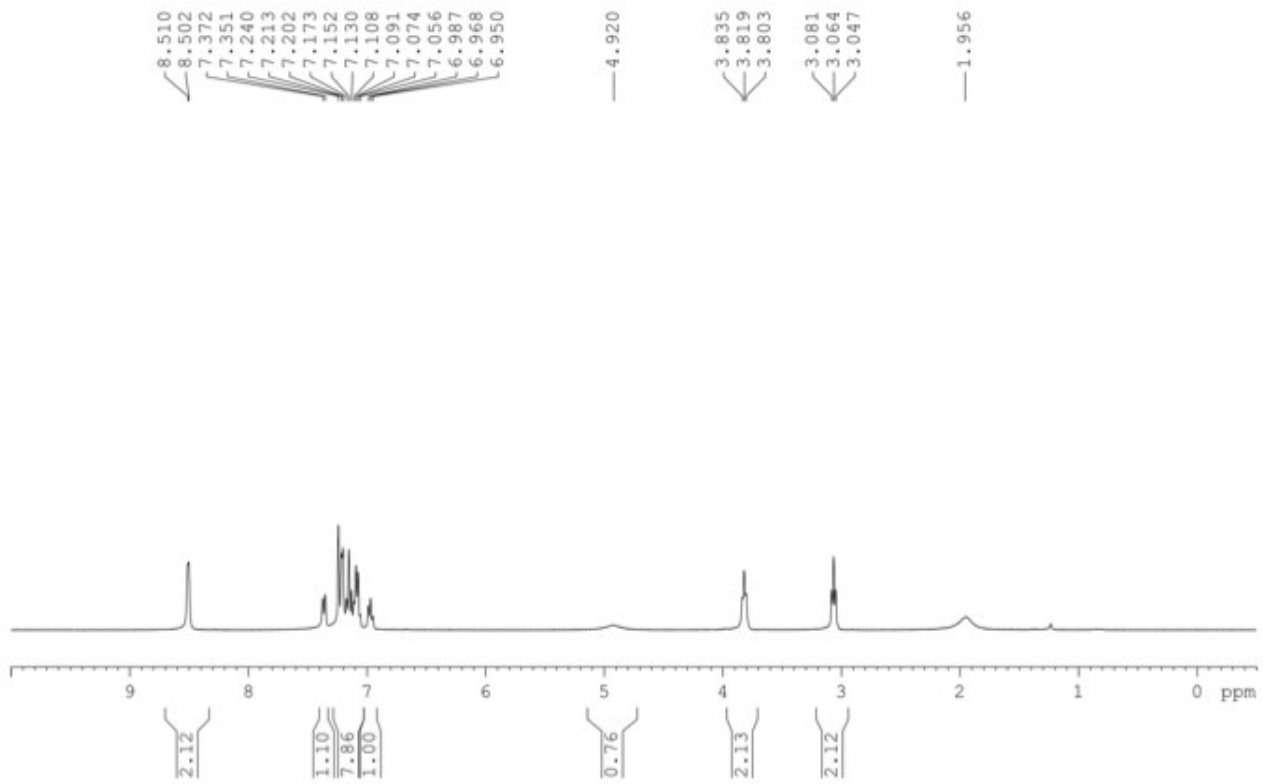
SW14 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



SW15 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

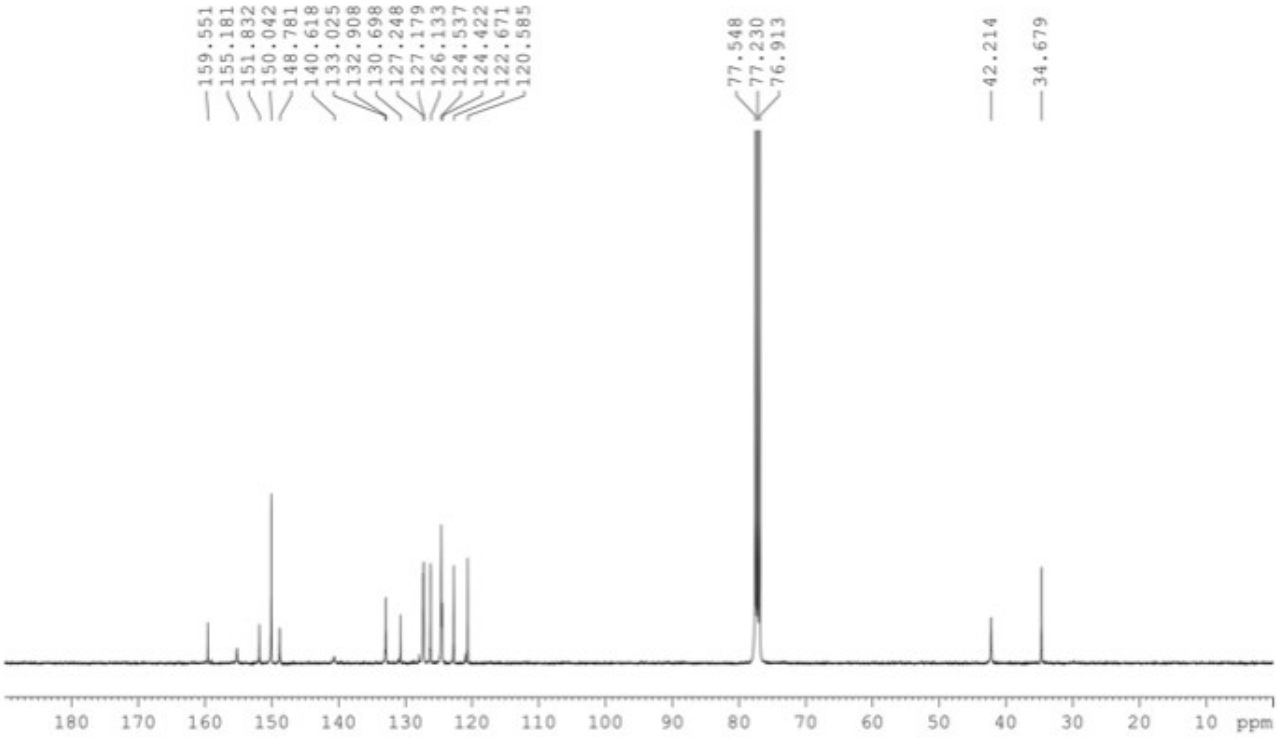


SW15 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

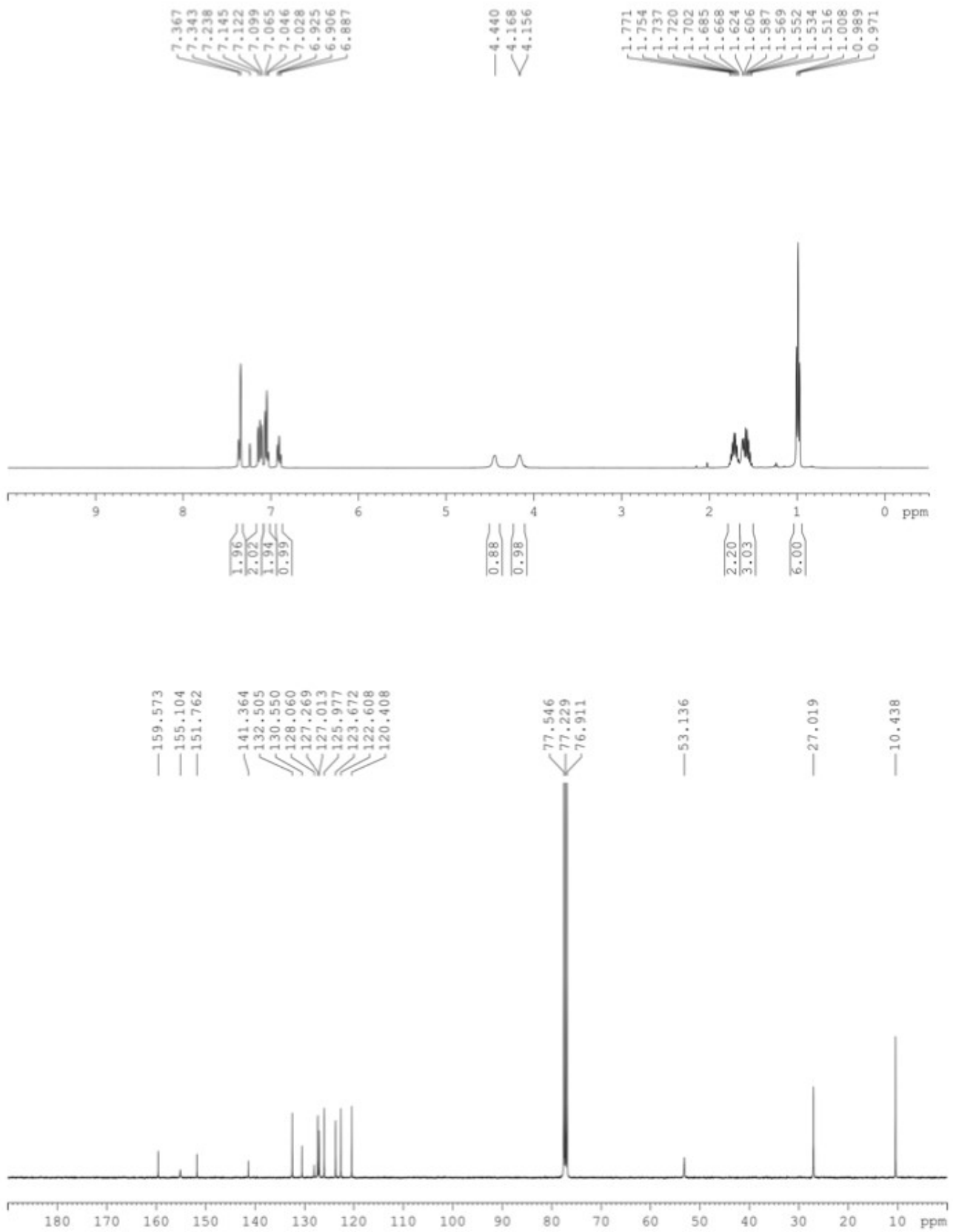


SW16 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

SW16 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

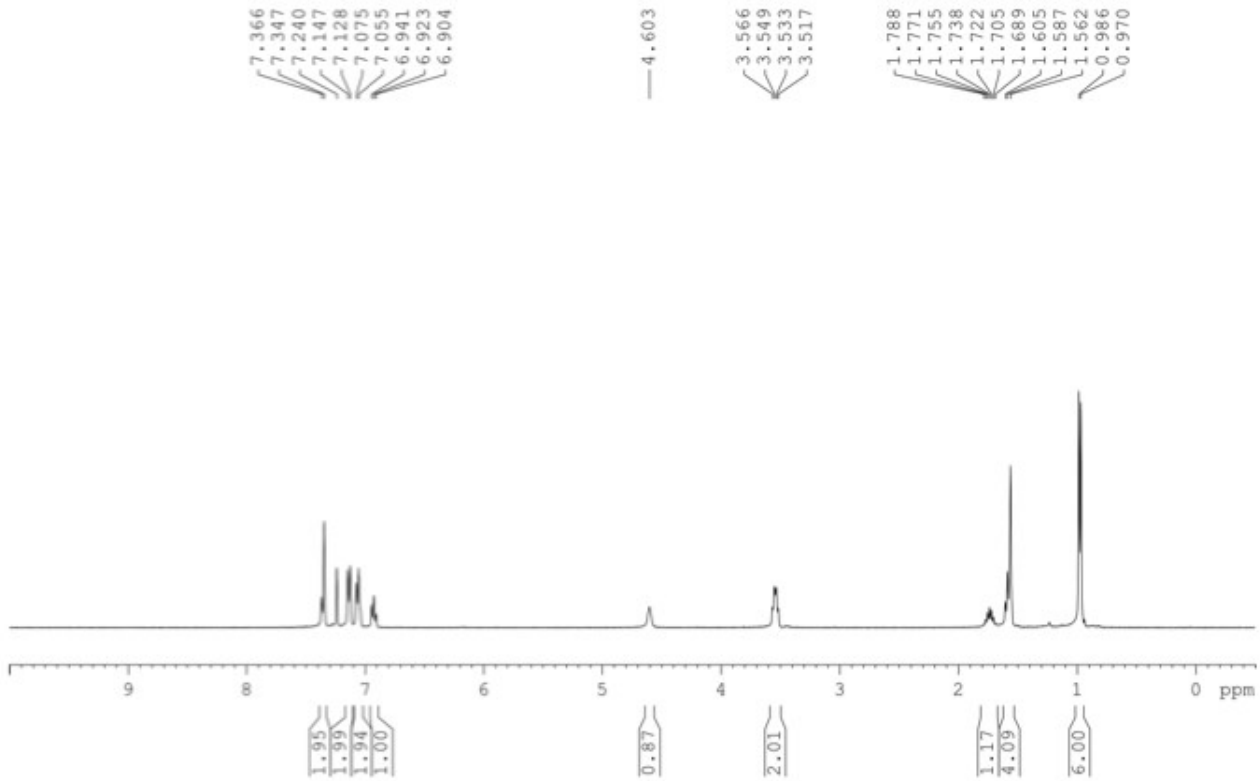


SW17 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

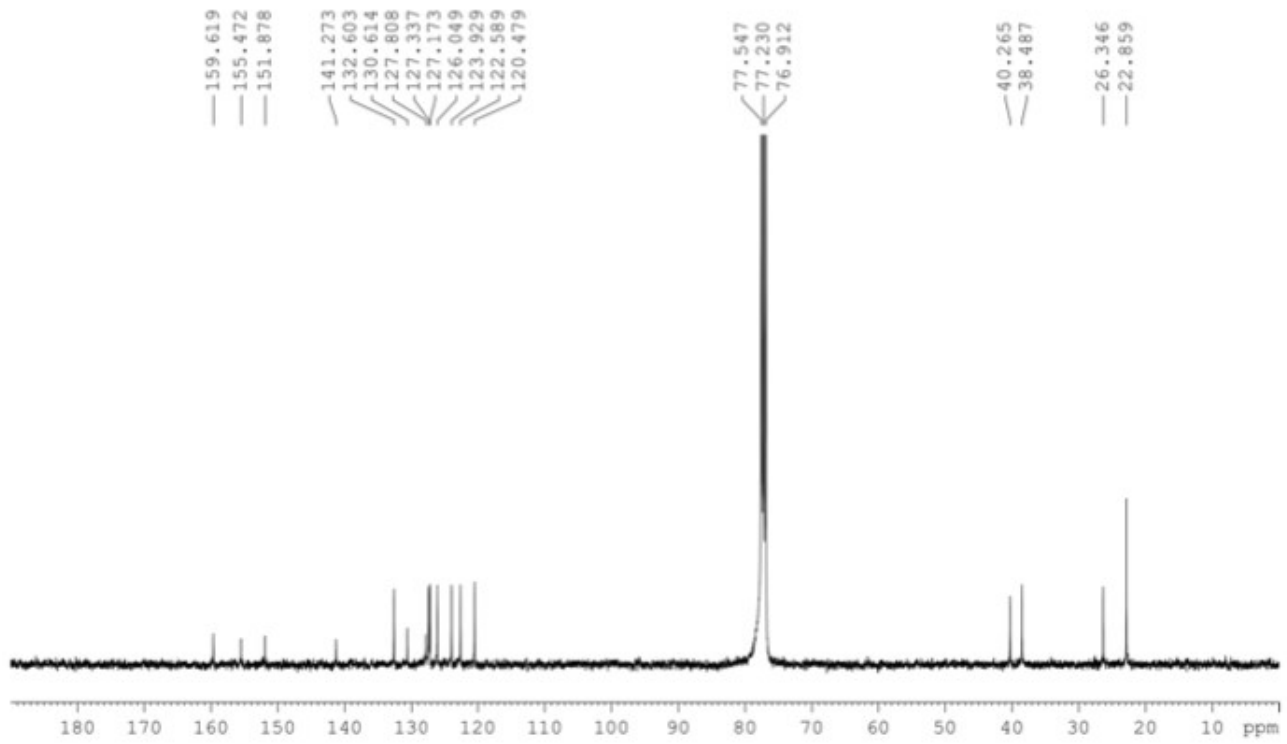


SW17 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

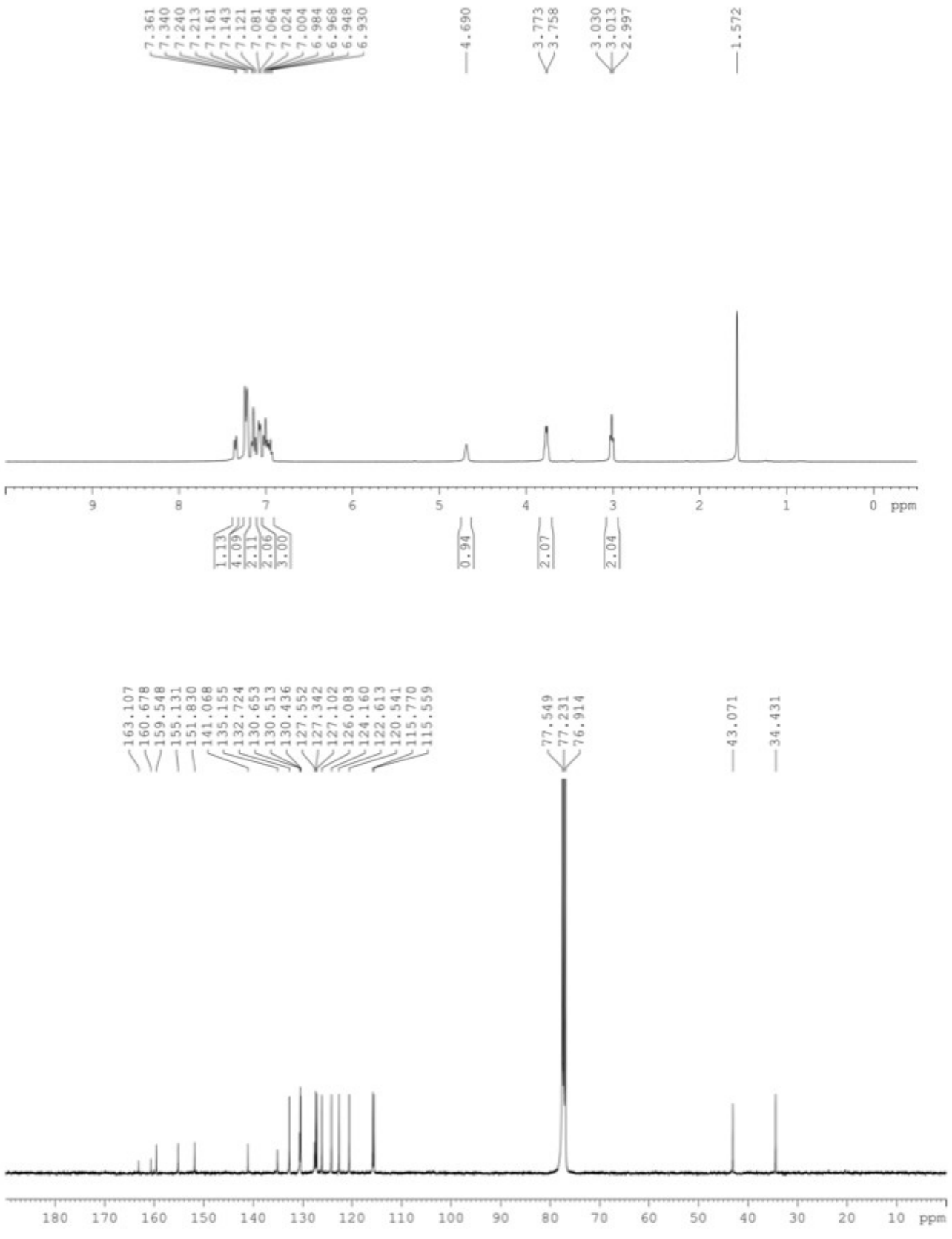
SW18 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)



SW18 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

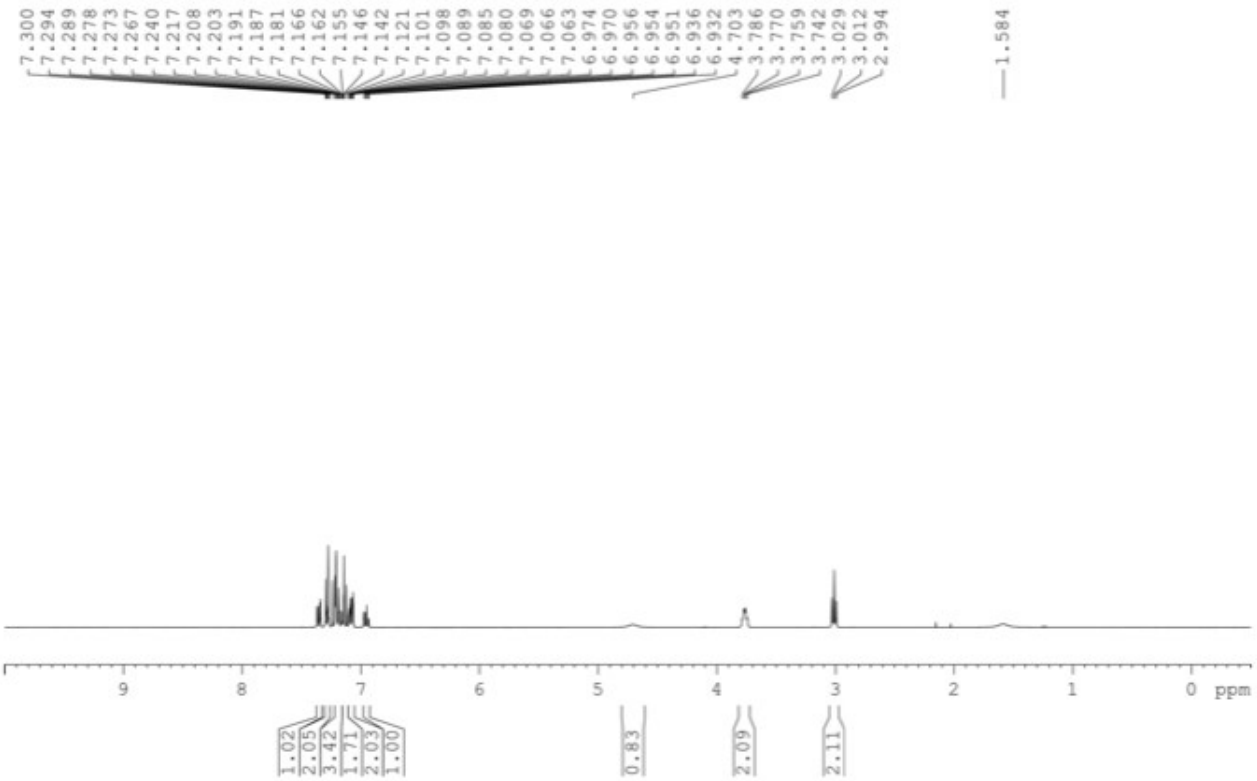


SW19 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

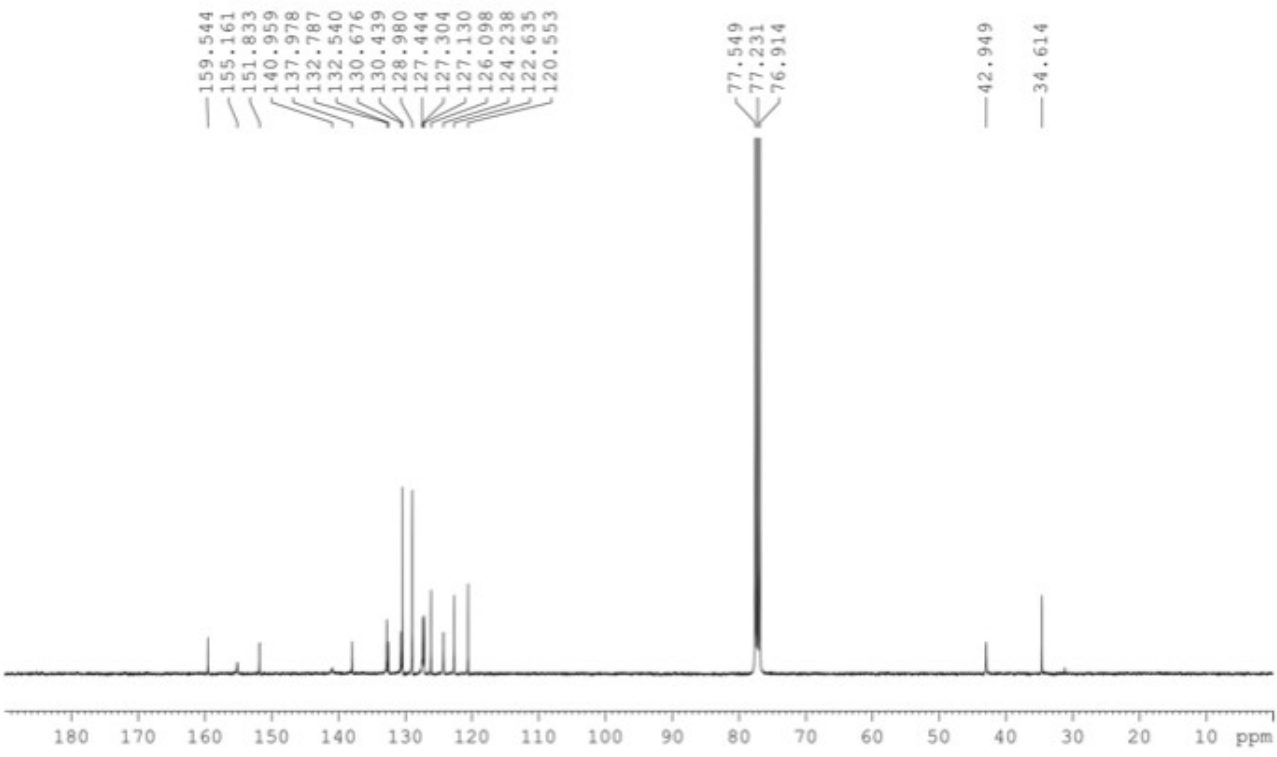


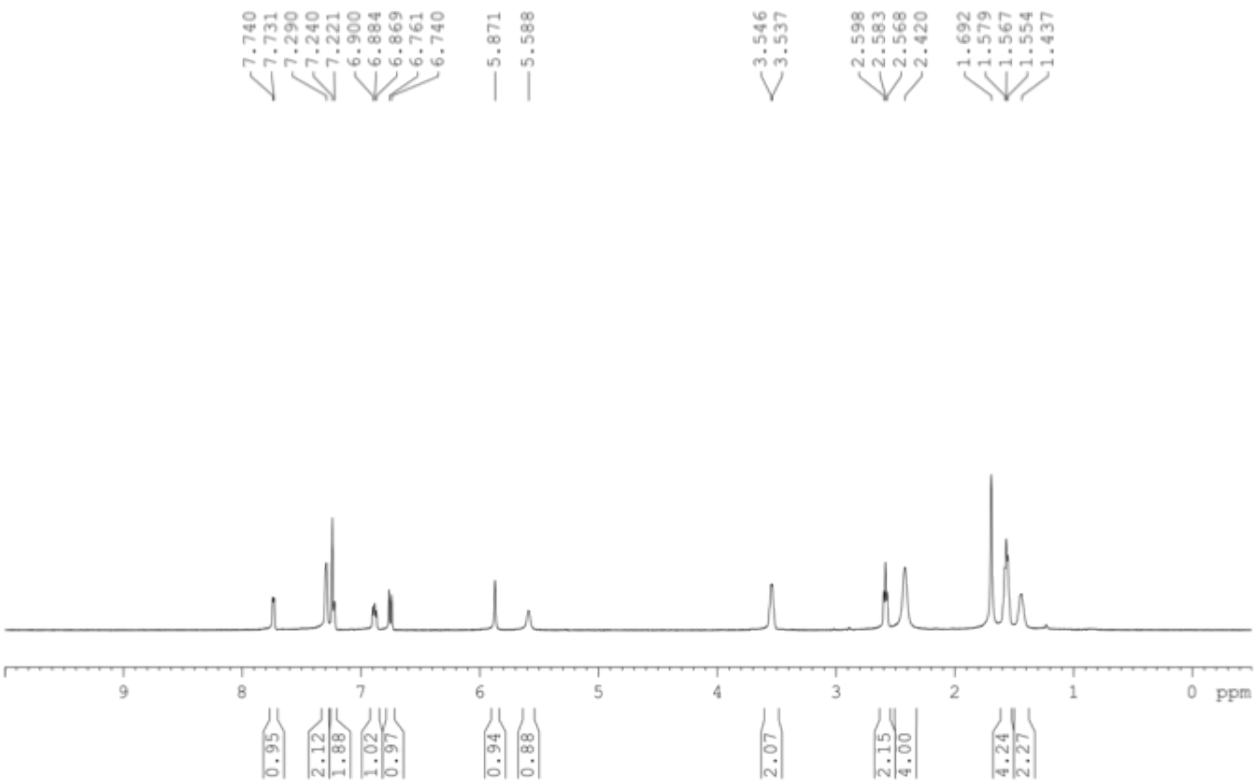
SW19 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)

SW20 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)



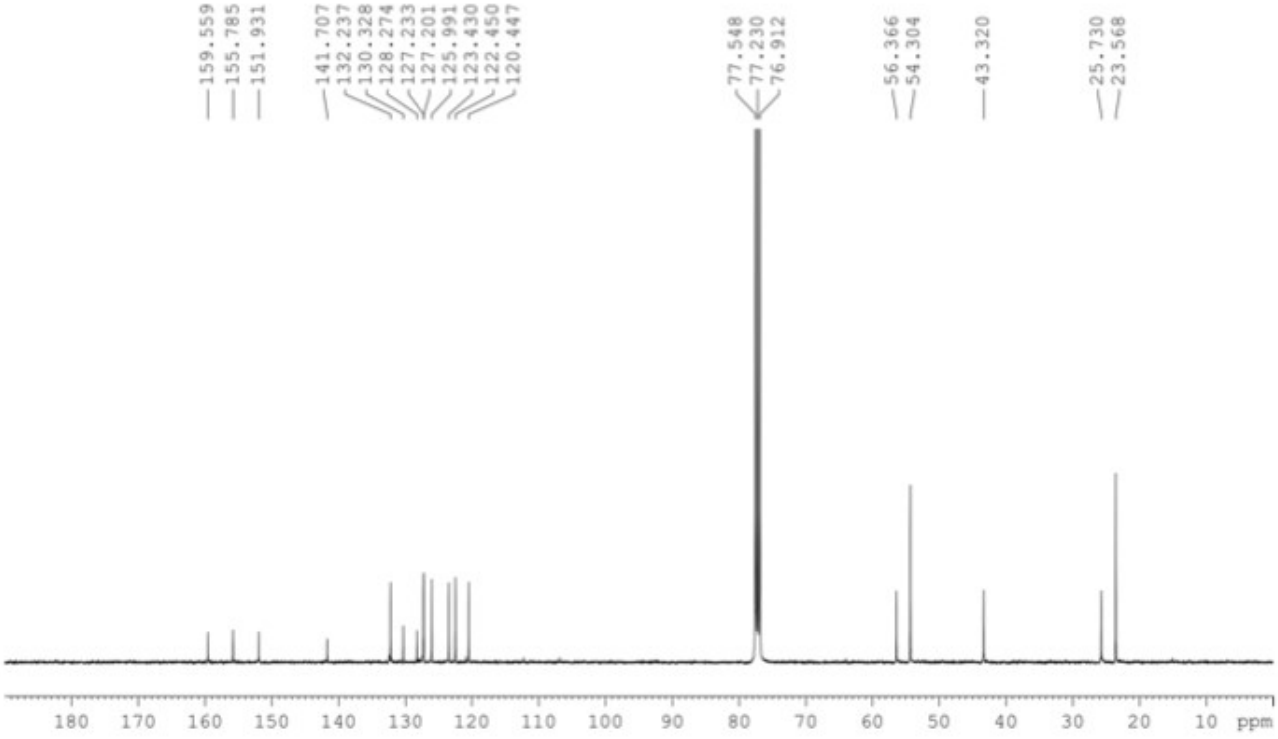
SW20 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1) .



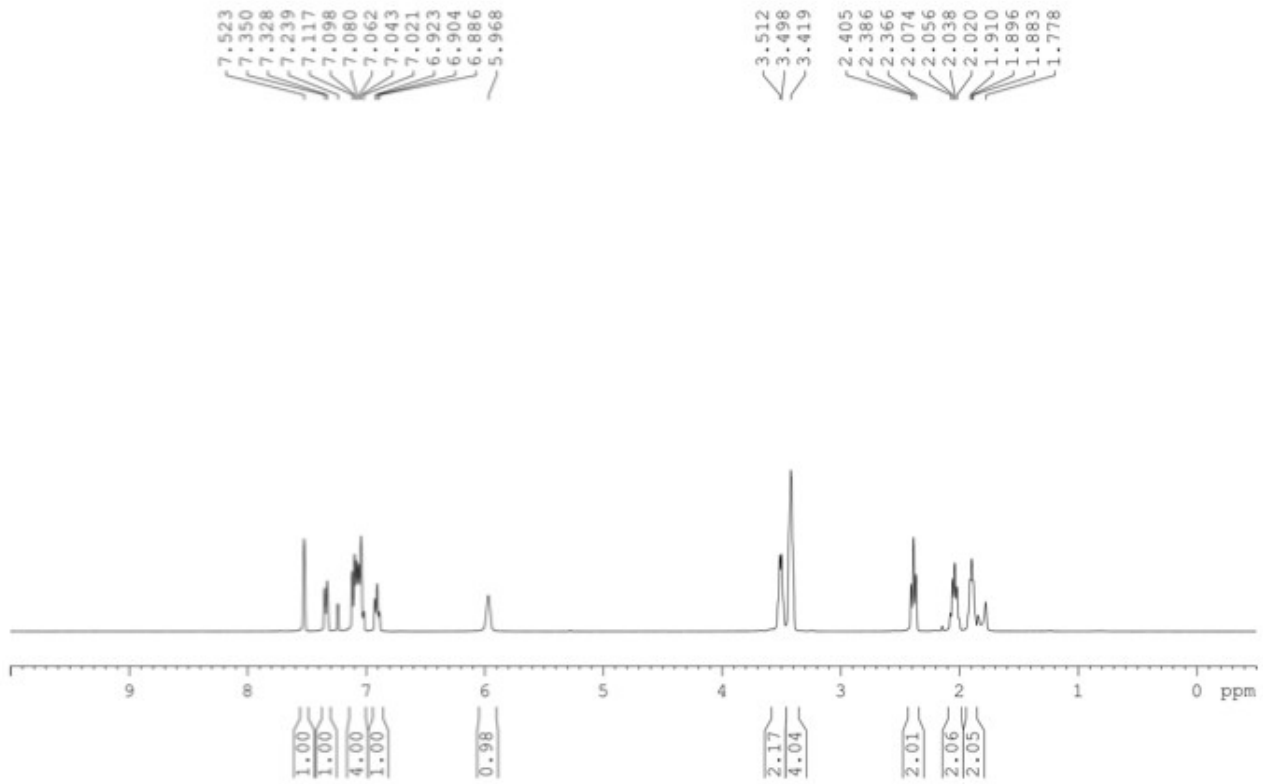


SW21 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)

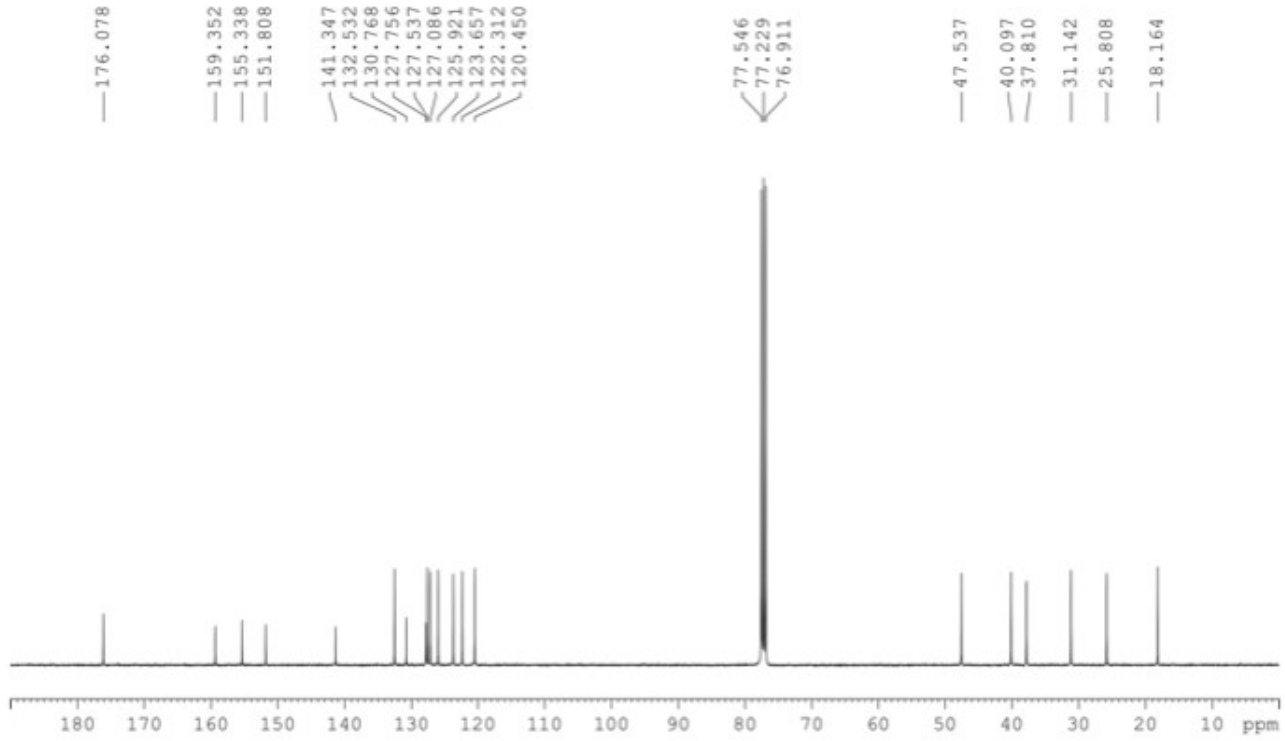
SW22 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



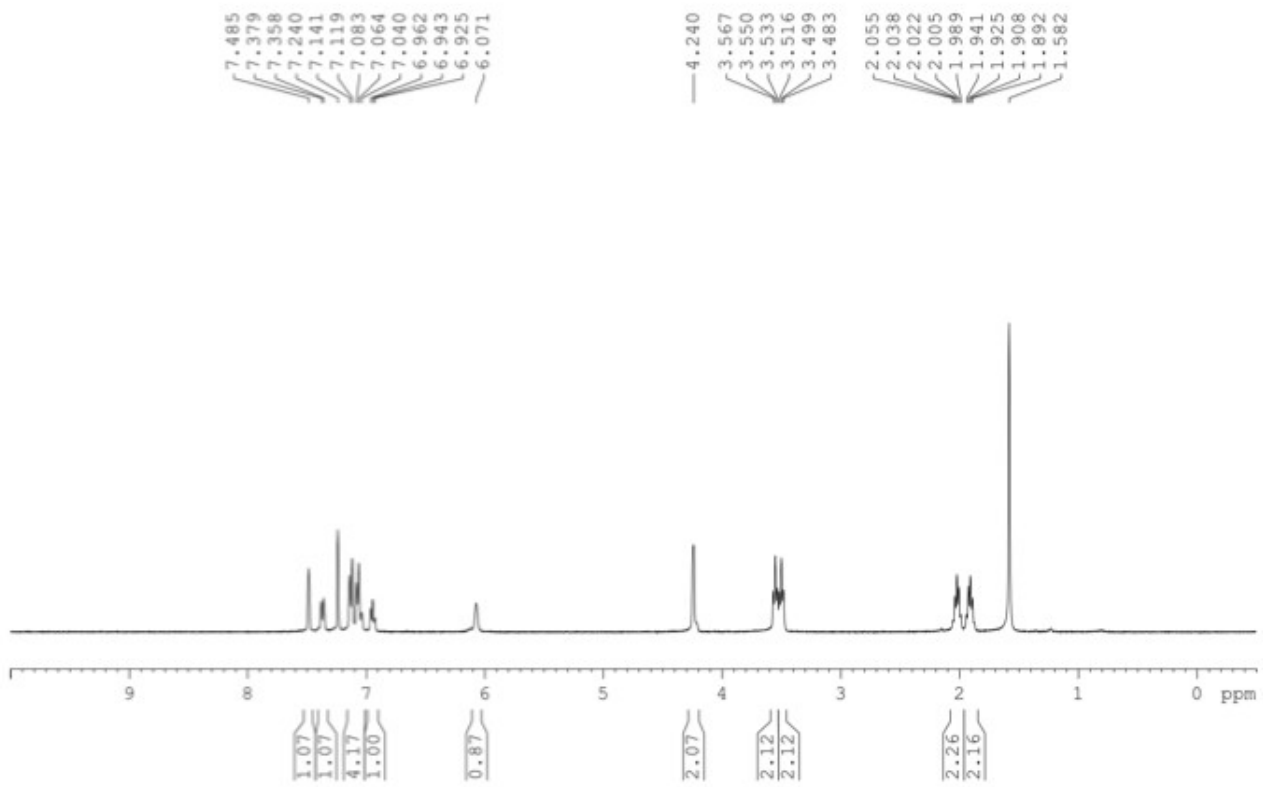
SW23 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)



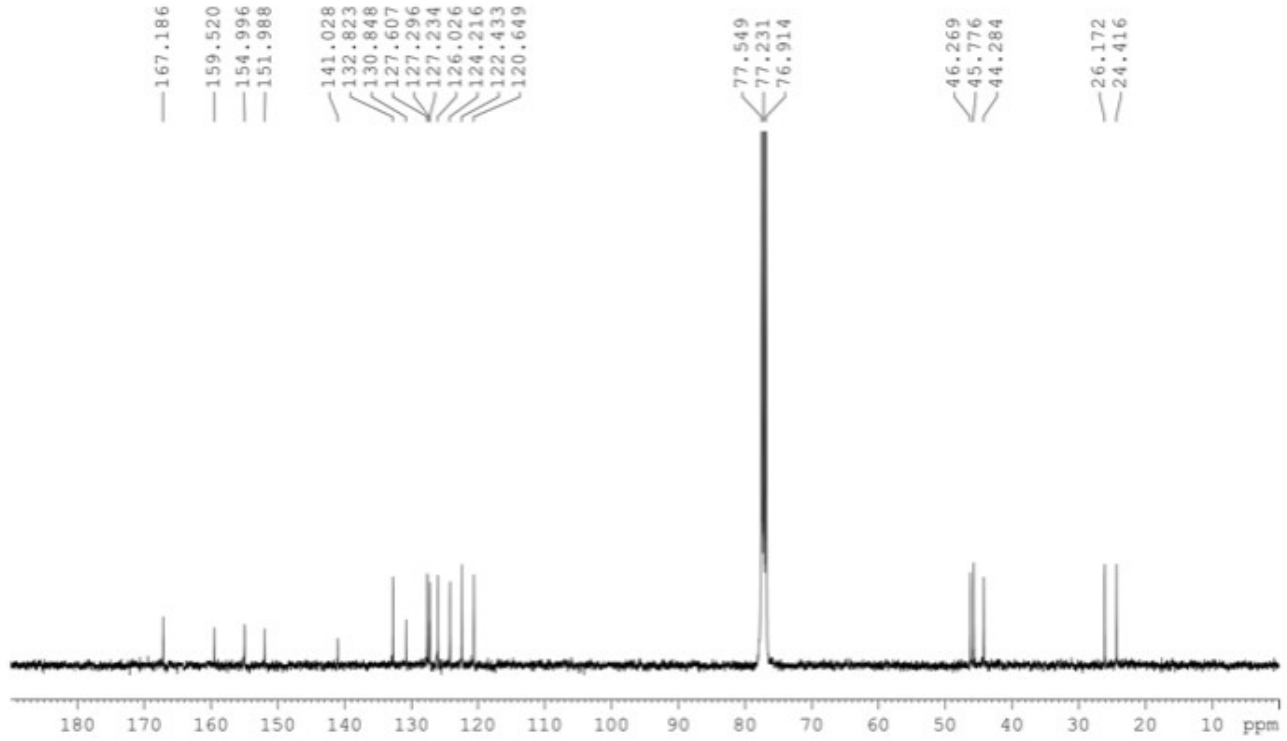
SW23 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



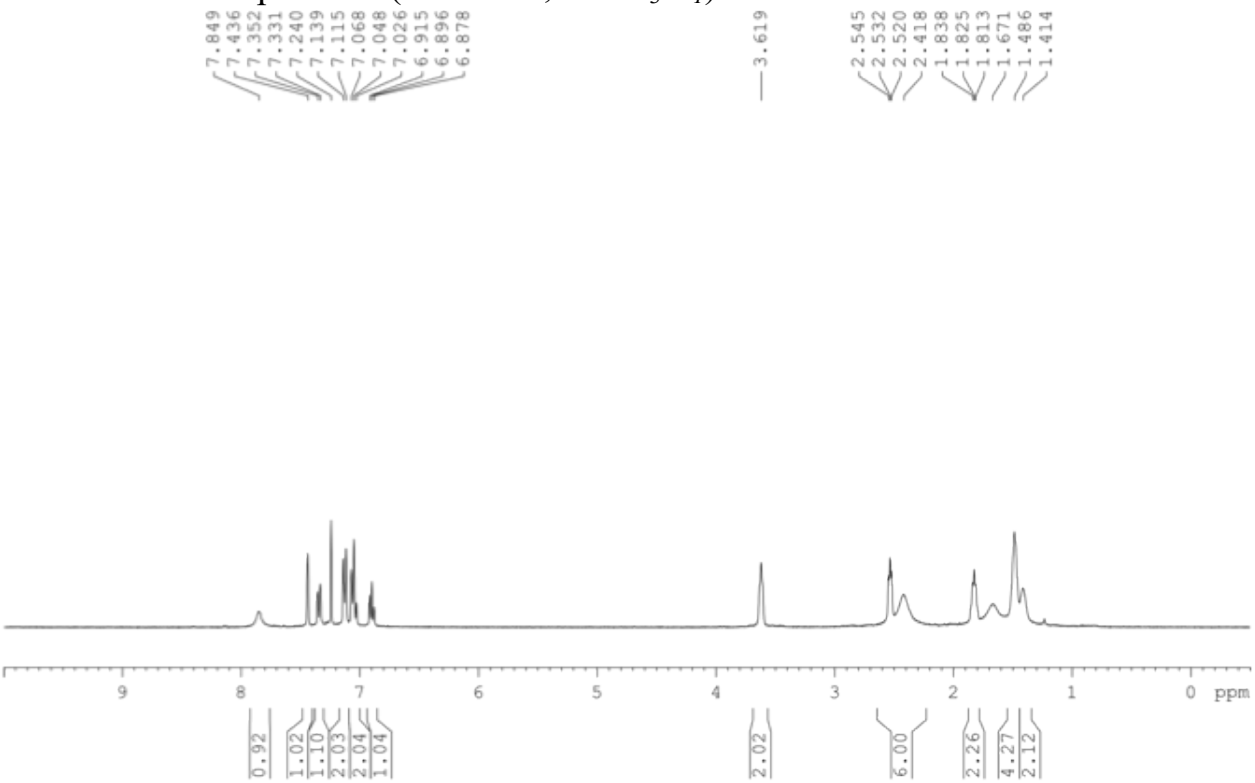
SW24 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)



SW24 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)



SW26 ^{1}H NMR Spectrum (400 MHz, $CDCl_3$-d_1)



SW26 ^{13}C NMR Spectrum (100 MHz, $CDCl_3$-d_1)