Structure-activity relationships of CNS penetration by fatty acid amide hydrolase (FAAH) targeted thyromimetic prodrugs

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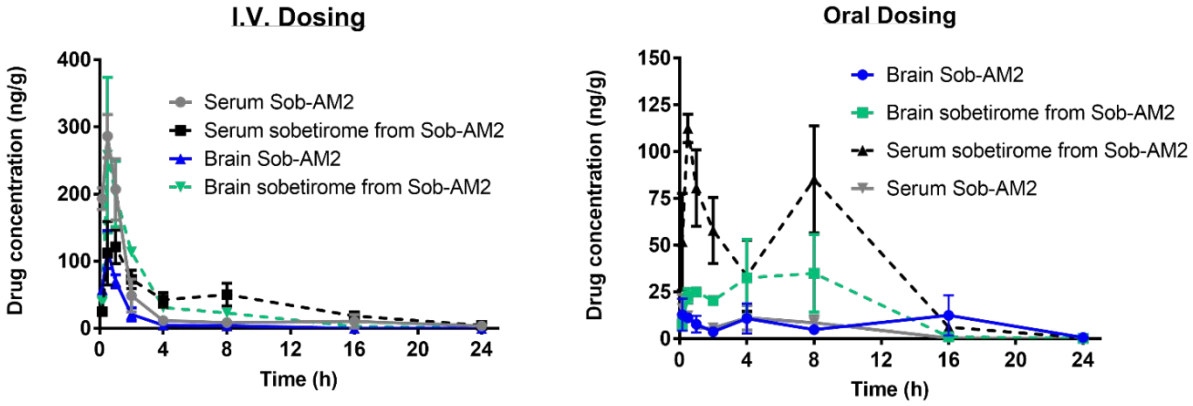


Figure S1. Distribution of Sob-AM2 and sobetirome from mice dosed with Sob-AM2. The additional curves for Sob-AM2 quantification are overlaid with the curves shown in Figure 3C and 3D. AUC data can be found in Table S1.

Table S1. Additional pharmacokinetic parameters from 24-hour experiments

Properties[a]	Sobetirome[b]	Sob-AM2
serum AUC [sobetirome]$_{0 \rightarrow 24h}$ (iv, ng·h·g^{-1})	6516 (dose corrected)	849
serum AUC [sobetirome]$_{0 \rightarrow 24h}$ (po, ng·h·g^{-1})	5986 (dose corrected)	867
brain AUC [Sob-AM2]$_{0 \rightarrow 24h}$ (iv, ng·h·g^{-1})	−	182
brain AUC [Sob-AM2]$_{0 \rightarrow 24h}$ (po, ng·h·g^{-1})	−	184
serum AUC [Sob-AM2]$_{0 \rightarrow 24h}$ (iv, ng·h·g^{-1})	−	567
serum AUC [Sob-AM2]$_{0 \rightarrow 24h}$ (po, ng·h·g^{-1})	−	110
$K_p^{0\text{-}24h}$ [Sob-AM2] (iv)	−	0.32
$K_p^{0\text{-}24h}$ [Sob-AM2] (po)	−	1.67

[a]AUCs were quantified for either [sobetirome] from dosed sobetirome or for [Sob-AM2] as the uncleaved prodrug [b]From S.I. Ref 1, exposure is dosed corrected to match the 9.15 μmol/kg of Sob-AM2

Table S2: Calculated EC_{50} for T3 and sobetirome[a,b]

Plate assay	T3 EC_{50} (nM)	Sobetirome EC_{50} (nM)
TRβ	2.9	18
TRα	1.1	86

[a]Calculated in GraphPad Prism 7 (four-parameter fit) [b]EC_{50} values for T3 and sobetirome resemble those which were previously reported in S.I. Ref 3,4

Animal Studies

Experimental protocols were in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Oregon Health & Science University Institutional Animal Care & Use Committee. Wild-type C57BL/6 male mice, aged 8−10 weeks, were purchased from Jackson Laboratory. All mice were housed in climate-controlled rooms with a 12 h/12 h light−dark cycle with ad libitum access to food and water.

LC-MS/MS analysis for pharmacokinetics. Tissue processing for distribution studies were performed as previously described.[1,2] Doses in the 1 h initial screen (Table 1) were 3.05 μmol/kg (equivalent to 1 mg/kg sobetirome) delivered i.p. AUCs for both the i.v.-dosed and orally-dosed experiments over a 24 h time period were generated and oral bioavailability was calculated using the equation: %oral bioavailability (%F) = ($AUC_{p.o.}$ / $AUC_{i.v.}$)·($dose_{i.v.}$ / $dose_{p.o.}$)·100. In these experiments, the dose for both oral and i.v. administration was equimolar (9.15 μmol/kg). The half-life of Sob-AM2 was determined from the i.v.-administered serum AUC described above. Data from the five latest time points, which approximate the elimination phase of the pharmacokinetic profile, was plotted as log (concentration ng/g) vs time (h). The $t_{½}$ value for Sob-AM2 was calculated from the slope of this plot. Clearance values were calculated from the

AUC of the drug concentration vs. time plots. LC-MS/MS parameters have been previously described.[2]

Biology

FAAH hydrolysis assay. The assay for quantifying sobetirome cleavage from sobetiramides using COS-7 cell homogenate with overexpressed human FAAH has been previously described.[2] The compound library was screened at 100 μM with a final concentration of 0.1% DMSO. Observed rates are expressed as nanomoles of sobetirome produced per milligram of homogenate protein per minute.

Cell-based TR α/β agonist assays. Indigo Biosciences 96-well human thyroid hormone receptor alpha (NR1A1, cat. #IB01001) and thyroid hormone receptor beta (NR1A2, cat. #IB01101) reporter assay system plates were used to examine activity by T3, sobetirome, and lead prodrug Sob-AM2 at each receptor isoform. Assays were run according to the manufacturer's instructions. Compound stock solutions were created in DMSO and diluted to working concentrations with Indigo Bioscience compound screening medium as suggested to final concentrations containing <0.4% DMSO. Before the addition of test compound solutions, all wells were incubated with 2 μM fatty acid amide hydrolase (FAAH) inhibitor PF-3845 for 1 h, then diluted 2-fold with test compound media (at 2x concentration) or DMSO control to working concentrations, maintaining co-incubation with 1 μM PF-3845 for the duration of the 24 h incubation period. Addition of PF-3845 suppresses activity-based signal derived from cellular endogenous FAAH cleavage of the prodrug Sob-AM2 into full agonist sobetirome. Final test compound concentrations were in the following ranges: T3 (150 nM – 68.7 pM), sobetirome (3.33 μM – 1.52 nM), and Sob-AM2 (50 μM – 68.6 nM) with n = 3 per dose. Chemiluminescence resulting from TR-induced luciferase expression was measured in a SpectraMax i3 (Molecular Devices) using SoftMax Pro 6.5.1 software. EC_{50} values (calculated from GraphPad Prism 7) for T3 and sobetirome resemble those which were previously reported.[3,4]

Chemistry

General Chemistry. ^{1}H and ^{13}C NMR were taken on a Bruker 400®. All ^{1}H NMR were calibrated to the NMR solvent reference peak (DMSO-d_6, chloroform-d, methanol-d_4). High-resolution mass spectrometry (HRMS) with electrospray ionization was performed by the Bioanalytical MS Facility at Portland State University. Inert atmosphere reactions were performed under argon gas passed through a small column of drierite and were conducted in flame-dried rbfs. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM), and dimethylformamide (DMF) were obtained from a Seca Solvent System. All other solvents used were purchased from Sigma-Aldrich or Fisher. Sobetirome (2),[5,6] Sob-AM1, and Sob-AM2[2] were synthesized as previously reported. All other reagents were purchased from Fisher, Sigma, or TCI and used as received. Purity analysis of final compounds was determined to be >95% by HPLC. Analytical HPLC analysis was performed on a Varian ProStar HPLC with a Grace Alltima C18, 5 μm column (4.6 x 250 mm) with a gradient (Solvent A: 95:5 Water:MeCN, 0.2% $Et_3NH_3PO_4$, pH 2.5; Solvent B:

MeCN) for B of 40% to 100% over 20 minutes with a flowrate of 1 mL/min. Preparative HPLC was performed on a Varian Dynamax Microscrob 100-5 µm C18, 21.4x250mm (Solvent A: Water +0.1% formic acid; Solvent B: MeCN +0.1% formic acid) using a gradient of B 20-100% over 20 minutes with a flowrate of 25 mL/min. Physicochemical properties for each prodrug were calculated and organized using Schrödinger's cheminformatics software Canvas.

Synthetic Methods

General Method A:

Sobetirome (**2**, 0.76 mmol, 1 eq) is treated with MeOH (3 mL) in a sealed tube. Sulfuric acid (1 drop, ~10 µL) is added and the flask is sealed. The reaction is heated to 65 ^{o}C for 1 hour with stirring. After cooling to room temperature, a solution of the amine in methanol (7 eq) is added. The reaction is resealed and reheated to 65 ^{o}C for 1 hour. Upon reaction completion, the reaction flask is cooled to room temperature and transferred to a separatory funnel. Following treatment with a solution of 0.5 N NaOH (20 mL), the reaction is extracted with DCM. The organic layers are dried and concentrated. Product is purified by flash chromatography.

General Method B:

A stirring solution of **32** (0.36 mmol, 1 eq) in dry THF (5 mL) is treated with 1,1'-carbonyldiimidazole (2.4 eq) followed by heating to 45 ^{o}C for 2 h. The reaction is concentrated under reduced pressure and redissolved into dry THF (2.5 mL). Amine is added (3 eq) and stirred for 1 h. Following dilution with diethyl ether (20 mL), the solution is washed with 0.5N HCl (2x 20 mL) followed by brine. The organic layer is dried and concentrated. The crude intermediate is taken up in DCM (3 mL) and placed under argon. Pentamethylbenzene (2 eq) is added and the reaction is cooled to -78 ^{o}C. A solution of BCl_3 (1 M DCM, 2 eq) is added slowly and the reaction stirs for 15 min. The reaction is quenched with addition of a saturated $NaHCO_3$ solution (2 mL) and the flask is warmed to room temperature. The reaction mixture is extracted with DCM (2 x 20 mL). The organic layers are dried and concentrated. Product is purified by flash chromatography.

General Method C:

A stirring solution of **32** (0.31 mmol, 1 eq) in DCM (2 mL) at 0 ^{o}C is treated with oxalyl chloride (4 eq). DMF is added (1 drop) and the reaction stirs for 3 h while warming to room temperature. The solvent is removed under reduced pressure and the crude intermediate is treated with DCM (5 mL), which is subsequently removed under reduced pressure. The crude intermediate is treated with 1.5 mL of DCM followed by dropwise addition of amine (1.87 mmol, 6 eq) and the reaction stirs for 1 h. The reaction mixture is purified by flash chromatography to give the intermediate product. The benzyl protected intermediate is treated with 1:1 MeOH:EtOAc (1 mL) under argon. Palladium on carbon (10 wt%, 22 mg) and triethylsilane (8 eq) are added and the reaction stirs

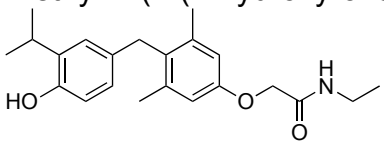
overnight. The reaction mixture is filtered over a plug of celite. Product is purified by flash chromatography.

General Method D:

A solution of compound **32** (0.6 mmol, 1 eq) in dry DMF (6mL) was stirred with 1-Ethyl-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) (1.2mmol, 2eq), 1-Hydroxybenzotriazole (HOBt) (1.2mmol, 2eq) and diisopropyl amine (DIEA) (2.4mmol, 4eq) at room temperature for 1h.The aminophenol (1.2mmol, 2eq) was then added to it and the reaction mixture was stirred overnight at room temperature. It was then diluted with EtOAc (15 mL) and washed with 0.5N HCl (2x5 mL) followed by saturated $NaHCO_3$ solution (2x5 mL) and brine (1x10mL). The organic layer was dried and concentrated. The crude product was purified by flash chromatography to give the benzyl protected intermediate which was then suspended in MeOH (5 mL) and treated under argon with palladium on carbon (wetted with ca. 55% water, 10 wt%, 60mg) and triethylsilane (10 eq). The reaction mixture was stirred at room temperature for 2 hours while monitored by TLC. Upon completion, it was filtered on a plug of celite and purified by flash chromatography.

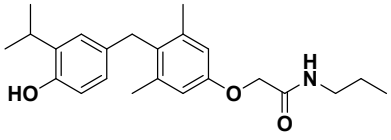
Methods & Characterization

N-ethyl-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide (**5**)



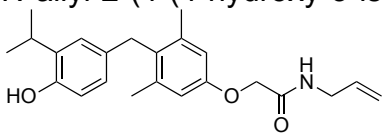
General method A was followed (0.304 mmol scale) using ethyl amine (33% in water, 0.25 mL, 1.84 mmol, 6 eq) to give the product as a white solid (82 mg, 76%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.94 (d, *J* = 2.2 Hz, 1H), 6.72 – 6.61 (m, 4H), 6.55 (dd, *J* = 8.1, 2.2 Hz, 1H), 5.77 (d, *J* = 17.7 Hz, 1H), 4.50 (s, 2H), 3.92 (s, 2H), 3.43 (qd, *J* = 7.3, 5.8 Hz, 2H), 3.22 (hept, *J* = 6.8 Hz, 1H), 2.24 (s, 6H), 1.32 – 1.15 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.76, 155.11, 151.29, 138.85, 134.46, 131.45, 131.41, 126.07, 125.20, 115.14, 114.09, 67.25, 34.02, 33.75, 27.06, 22.61, 20.51, 14.78. HRMS **(**ESI-MS): calculated for $C_{22}H_{30}NO_3$ $(M+Na)^+$: 356.2220, found 356.2220.

2-(4-(4-hydroxy-3-isopropylbenzyl)-3, 5-dimethylphenoxy)-*N*-propylacetamide (**6**)



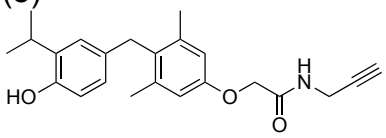
Following the general method A, compound **2** afforded compound **6** as white solid (115 mg, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (s, 1H), 6.63-6.53 (m, 5H), 4.48 (s, 2H), 3.90 (s, 2H), 3.31 (m, 2H), 3.15 (m, 1H), 2.22 (s, 6H), 1.59 (m, 2H), 1.21 (d, J= 6.94 Hz, 6H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 155.1, 150.9, 138.9, 134.4, 131.6, 125.9, 124.8, 115.2, 113.9, 67.5, 40.3, 33.5, 27.2, 22.6, 22.4, 20.3 and 10.9. HRMS **(**ESI-MS): calculated for $C_{23}H_{31}NO_3Na$ $[M+Na]^+$: 392.2196, found 392.2203.

N-allyl-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide (**7**)



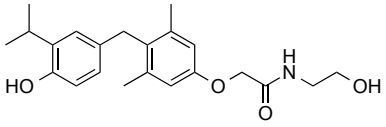
General method B was followed (0.36 mmol scale) using allylamine hydrochloride (90 mg, 1.075 mmol, 3 eq) to give the product as a white solid (70 mg, 0.2 mmol, 55%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.94 (d, *J* = 2.1 Hz, 1H), 6.75 (s, 1H), 6.68 – 6.52 (m, 4H), 5.96 – 5.81 (m, 1H), 5.27 – 5.14 (m, 2H), 4.96 (s, 1H), 4.54 (s, 2H), 4.02 (tt, *J* = 5.8, 1.6 Hz, 2H), 3.93 (s, 2H), 3.19 (hept, *J* = 6.9 Hz, 1H), 2.24 (s, 6H), 1.23 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.77, 155.08, 151.17, 138.88, 134.42, 133.60, 131.55, 131.43, 126.08, 125.22, 116.68, 115.16, 114.08, 67.23, 41.35, 33.75, 27.08, 22.60, 20.50. HRMS (ESI) m/z [M+H+] $C_{23}H_{30}NO_3$+ requires 368.2220, found 368.2220

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*-(prop-2-yn-1-yl)acetamide (**8**)



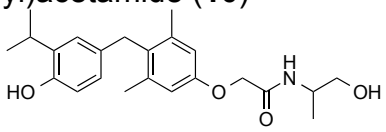
General method B was followed (0.36 mmol scale) using propargylamine (90 mg, 1.075 mmol, 3 eq) give the product as an off-white solid (88 mg, 0.24 mmol, 67%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.92 (t, *J* = 3.5 Hz, 2H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.63 (s, 2H), 6.53 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.69 (s, 1H), 4.51 (s, 2H), 4.16 (dd, *J* = 5.5, 2.6 Hz, 2H), 3.90 (s, 2H), 3.20 (hept, *J* = 6.9 Hz, 1H), 2.22 (s, 6H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.71, 155.00, 151.16, 138.89, 134.43, 131.56, 131.53, 126.09, 125.24, 115.18, 114.13, 78.92, 71.96, 67.17, 33.75, 28.80, 27.08, 22.61, 20.51. HRMS (ESI) m/z [M-H] $C_{23}H_{26}NO_3^-$ requires 364.1918, found 364.1914.

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*-(2-hydroxyethyl)acetamide (**9**)



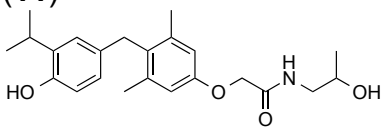
General method C was used with ethanolamine (114 mg, 1.87 mmol, 6 eq) to give to give the product as a white solid (29 mg, 0.076 mmol, 73%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.11 (b, 1H), 6.93 (d, *J* = 2 Hz, 1H), 6.64-6.55 (m, 4H), 5.36 (b, 1H), 4.52 (s, 2H), 3.91 (s, 2H), 3.79 (t, *J* = 4.8 Hz, 2H), 3.55 (q, *J* = 5.5 Hz, 2H), 3.19 (sept, *J* = 6.9, 1H), 2.22 (s, 6H), 1.25 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, 20:1 $CDCl_3$:methanol-d_4) δ 173.82, 158.97, 155.62, 142.67, 138.63, 135.44, 134.67, 129.76, 128.94, 118.71, 117.96, 70.98, 64.76, 45.37, 37.58, 30.66, 26.42, 24.25. HRMS (ESI) m/z [M+H+] $C_{22}H_{30}NO_4$+ requires 372.2169, found 372.2182

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*-(1-hydroxypropan-2-yl)acetamide (**10**)



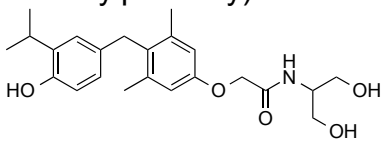
General method C was used (scale of 0.207 mmol) with (+/-)-alaninol (93 mg, 1.24 mmol, 6 eq) to give the product as a white solid (21 mg, 0.055 mmol, 64%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (b, 1H), 6.93 (d, *J* = 2 Hz, 1H), 6.73-6.53 (m, 4H), 5.04 (b, 1H), 4.50 (s, 2H), 4.19 (m, 1H), 3.92 (s, 2H), 3.72-3.61 (m 2H), 3.19 (s, *J* = 6.9 Hz, 1H), 2.65 (s, 1H), 2.24 (s, 6H), 1.23 (m, 9H). ^{13}C NMR (101 MHz, 20:1 $CDCl_3$:methanol-d_4) δ 169.81, 155.06, 151.07, 138.87, 134.37, 131.64, 131.41, 126.10, 125.22, 115.14, 114.10, 67.37, 67.20, 46.52, 33.73, 27.08, 22.58, 20.88, 20.49. HRMS (ESI) m/z [M+H+] $C_{23}H_{32}NO_4^+$requires 386.2326, found 386.2335

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*-(2-hydroxypropyl)acetamide (**11**)



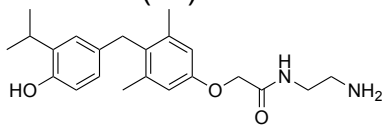
General method C was used (scale of 0.207 mmol) with 1-amino-2-propanol (93 mg, 1.24 mmol, 6 eq) to give the product as a white solid (43 mg, 0.11 mmol, 73%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.11 (b, 1H), 6.93 (d, *J* = 2 Hz, 1H), 6.61-6.51 (m, 4H), 5.84 (b, 1H), 4.49 (s, 2H), 3.96 (m, 1H), 3.91 (s, 2H), 3.51 (m, 1H), 3.19 (m, 2H), 2.27 (s, 6H), 1.20 (m, 9H). HRMS (ESI) m/z. 33-3 ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.81, 155.06, 151.07, 138.87, 134.37, 131.64, 131.41, 126.10, 125.22, 115.14, 114.10, 67.37, 67.20, 46.52, 33.73, 27.08, 22.58, 20.88, 20.49. [M+H+] $C_{23}H_{32}NO_4^+$requires 386.2326, found 386.2335

N-(1,3-dihydroxypropan-2-yl)-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide (**12**)



A stirring solution of GC-1 (411 mg, 1.25 mmol, 1 eq) is treated with DCM (6 mL) followed by addition of DCC (283 mg, 1.34 mmol, 1.1 eq) and N-hydroxysuccinimide (158 mg, 1.34 mmol, 1.1 eq). The reactions stirs for 4 h during which time a white precipitate forms. The urea byproduct is filtered off and the intermediate NHS ester is purified by flash chromatography (0-80% EtOAc in hexanes) to give a white product (323 mg, 0.76 mol, 60%). The intermediate NHS ester (55 mg, 0.129 mmol, 1 eq) is treated with THF (1 mL) and triethylamine (27 µL, 0.19 mmol, 1.5 eq). The reaction is treated with (+/-)-serinol (17 mg, 0.19 mmol, 1.5 eq) and stirred for 30 min. The reaction mixture is purified directly by flash chromatography to give the product as a white solid (14 mg, 0.035 mmol, 27%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.87 (d, *J* = 2.2 Hz, 1H), 6.63 – 6.52 (m, 3H), 6.46 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.45 (s, 2H), 3.95 (p, *J* = 4.9 Hz, 1H), 3.85 (s, 2H), 3.78 (dd, *J* = 11.4, 4.3 Hz, 2H), 3.67 (dd, *J* = 11.4, 5.1 Hz, 2H), 3.17 (sept, *J* = 6.9 Hz, 1H), 2.18 (s, 6H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, 9:1 $CDCl_3$:methanol-d_4) δ 173.61, 158.91, 155.57, 142.64, 138.60, 135.44, 134.71, 129.77, 128.93, 118.70, 118.03, 71.03, 65.13, 56.04, 37.56, 30.67, 26.43, 24.24. HRMS (ESI) m/z [M+Na+] $C_{23}H_{31}NNaO_5^+$ requires = 424.2094, found 424.2099

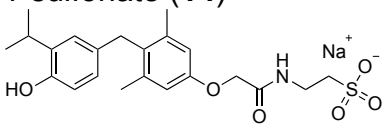
N-(2-aminoethyl)-2-(4-([4-hydroxy-3-(propan-2-yl)phenyl]methyl)-3,5-dimethylphenoxy)acetamide (**13**)



General method C was used (scale of 1.05 mmol) with 2-aminoethyl benzyl carbamate (408 mg, 2.1 mmol, 2 eq) with the noted modification. The deprotection step was done with 0.2 mL acetic acid as cosolvent. Following celite filtration, the solution is concentrated and then taken up in a minimal amount of DCM and MeOH and reconcentrated under reduced pressure. The crude product is retreated with DCM (0.25 mL) with several drops of MeOH. Hexanes (3 mL) is slowly added to the solution, which leads to precipitation of the product. The hexane supernatant is removed by pipette and the white product is washed with hexanes and extensively dried under reduced pressure to give a white, viscous solid product to give a white, viscous solid product (57 mg, 0.132 mmol, 21%). ^{1}H NMR (400 MHz, *d*6-DMSO) δ 8.40 (b, 1H), 6.83 (d, *J* = 2 Hz, 1H), 6.82-6.44 (m, 4H), 4.42 (s, 2H), 3.71 (s, 2H), 3.31 (t, *J* = 6 Hz, 2H), 3.19 (sept, *J* = 6.9 Hz, 1H), 2.79 (m, 2H), 2.16 (s, 6H), 1.83 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, 9:1 $CDCl_3$:methanol-d_4) δ 177.20, 170.68, 154.92, 151.56, 138.38, 134.48,

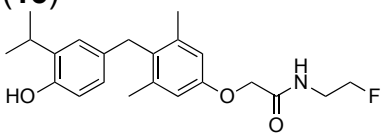
131.20, 130.39, 125.49, 124.76, 114.55, 113.76, 66.73, 39.00, 36.83, 33.37, 31.24, 26.43, 22.28, 22.19, 19.99, 13.62, 6.06, 5.30. HRMS (ESI) m/z [M+H+] $C_{22}H_{31}N_2O_3^+$ requires 371.2335, found 371.2329

Sodium 2-(2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamido)ethane-1-sulfonate (**14**)



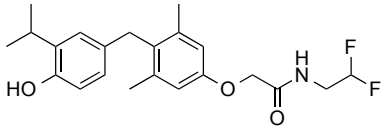
General method A was used (0.3 mmol scale) with modifications. Taurine (229 mg, 1.83 mmol in 2 mL of 0.9N NaOH in water) was used in the aminolysis step. A portion of the solvent is removed under reduced pressure and the total volume of the solution is adjusted to ~5 mL with additional water. The solution is filtered through a 0.22 µm filter and purified by preparative HPLC. The combined product fractions were combined and concentrated by a steady stream of air followed by reduced pressure to give a white solid (7.8 mg, 0.02 mmol, 5%). ^{1}H NMR (400 MHz, 9:1 Chloroform-*d*: Methanol-d_4) δ 6.85 (d, *J* = 2.2 Hz, 1H), 6.61 – 6.52 (m, 3H), 6.43 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.40 (s, 2H), 3.83 (s, 2H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.37 (s, 6H), 3.17 (hept, *J* = 6.9 Hz, 1H), 3.02 (t, *J* = 6.0 Hz, 2H), 2.15 (s, 6H), 1.13 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, 9:1 $CDCl_3$:methanol-d_4) δ 173.43, 159.12, 155.69, 142.49, 138.64, 135.25, 134.65, 129.68, 128.93, 118.70, 118.02, 77.20, 49.33, 38.68, 37.53, 30.61, 26.36, 24.08. HRMS (ESI) m/z [M-H-] $C_{22}H_{28}NO_6S^-$ requires 434.1643, found 434.1637.

N-(2-fluoroethyl)-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide (**15**)



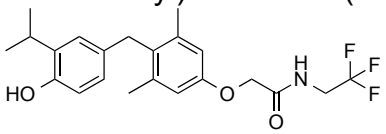
General method B was used (scale of 0.36 mmol) with 2-fluoroethylamine hydrochloride (87 mg, 1.075 mmol, 3 eq) to give the product as a white solid (70 mg, 0.19 mmol, 52%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 (s, 1H), 6.94 (d, *J* = 2.1 Hz, 1H), 6.68 – 6.52 (m, 4H), 4.76 (s, 1H), 4.62 (dt, *J* = 47.4, 4.8 Hz, 1H), 4.53 (s, 2H), 3.93 (s, 2H), 3.71 (dq, *J* = 27.8, 5.0 Hz, 2H), 3.17 (hept, *J* = 7.0 Hz, 1H), 2.24 (s, 6H), 1.23 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.19, 155.03, 151.07, 138.87, 134.38, 131.66, 131.44, 126.10, 125.25, 115.14, 114.12, 82.3 (d, *J* = 167 Hz), 67,20, 39.51 (d, *J* = 20 Hz), 33.74, 27.09, 22.58, 20.50. HRMS (ESI) m/z [M+H+] $C_{22}H_{29}FNO_3^+$requires 374.2126, found 374.2145

N-(2,2-difluoroethyl)-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide (**16**)



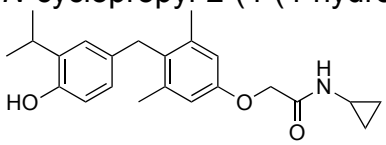
General method B was used (scale of 0.36 mmol) with difluoroethylamine (87 mg, 1.075 mmol, 3 eq) to give the product as a clear, crystalline solid (79 mg, 0.2 mmol, 56%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.94 (m, 2H), 6.65-6.55 (m, 4H), 5.91 (tt, *J* = 55.8, 4.1 Hz, 1H), 5.19 (s, 1H), 4.55 (s, 2H), 3.93 (s, 2H), 3.77 (m, 2H), 3.20 (sept, *J* = 6.9, 1H), 2.24 (s, 6H), 1.23 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.70, 154.89, 151.09, 138.94, 134.43, 131.63, 131.61, 126.10, 125.25, 115.16, 114.11, 113.35 (t, *J* = 242 Hz), 67.13, 41.26 (t, *J* = 26 Hz), 33.75, 27.08, 22.58, 20.50. HRMS (ESI) m/z [M+H+] $C_{22}H_{28}F_2NO_3^+$ requires = 392.2032, found 392.2040

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*-(2,2,2-trifluoroethyl)acetamide (**17**)



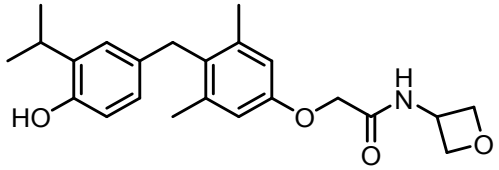
General method C was used (scale of 0.36 mmol) with trifluoroethylamine hydrochloride (87 mg, 1.075 mmol, 3 eq) and DMAP (13 mg, 0.11 mmol, 0.3 eq) are added as a solution in THF (0.2 mL) to give the product as a white solid (89 mg, 0.22 mmol, 61%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.93 (m, 2H), 6.65-6.57 (m, 4H), 4.80 (s, 1H), 4.58 (s, 2H), 4.05 (m, 2H), 3.93 (s, 2H), 3.18 (sept, *J* = 6.8, 1H), 2.24 (s, 6H), 1.23 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.36, 154.83, 151.00, 138.98, 134.37, 131.69, 131.68, 126.08, 125.27, 125.85 (q, *J* = 280 Hz),115.17, 114.12, 77.35, 77.04, 76.72, 67.15, 40.21 (q, *J* = 35 Hz), 33.74, 27.09, 22.56, 20.48. HRMS (ESI) m/z [M+Na+] $C_{22}H_{26}F_3NNaO_3^+$ requires = 432.1757, found 432.1762

N-cyclopropyl-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide (**18**)



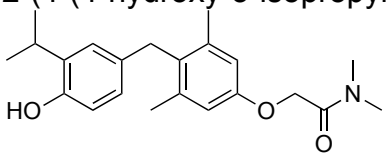
General method B was used (scale of 0.36 mmol) with cyclopropylamine (60 mg, 1.075 mmol, 3 eq) to give the product as a white solid (63 mg, 0.17 mmol, 48%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.93 (d, *J* = 2.1 Hz, 1H), 6.76 (s, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.62 (s, 2H), 6.54 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.94 (s, 1H), 4.48 (s, 2H), 3.92 (s, 2H), 3.23 (hept, *J* = 6.9 Hz, 1H), 2.82 (tq, *J* = 7.2, 3.7 Hz, 1H), 2.23 (s, 6H), 1.23 (d, *J* = 6.9 Hz, 6H), 0.95 – 0.80 (m, 2H), 0.71 – 0.56 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.28, 155.05, 151.17, 138.85, 134.39, 131.54, 131.41, 126.06, 125.22, 115.16, 114.05, 67.28, 33.74, 27.08, 22.59, 22.16, 20.50, 6.54. HRMS (ESI) m/z [M+H+] $C_{23}H_{30}NO_3^+$ requires 368.2220, found 368.2234

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*-(oxetan-3-yl)acetamide (**19**)



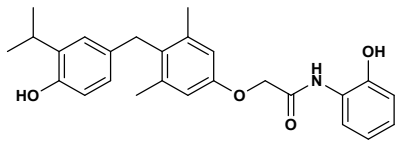
General method B was followed using 3-oxetanamine, product was isolated as a white solid (106 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.0 Hz, 1 H), 6.92 (s, 1 H), 6.65 (s, 2 H), 6.60 (d, J = 8.2 Hz, 1 H), 6.54 (dd, J = 8.1, 2.2 Hz, 1 H), 5.18 (sext, J = 7.6 Hz. 1 H), 4.97 (t, J = 7.2 Hz, 2 H), 4.68 (s, 1H), 4.57 (t, J = 7.0 Hz, 2 H), 4.49 (s, 2 H), 3.91 (s, 2 H), 3.15 (sept., J = 6.9 Hz, 1 H), 2.23 (s, 6 H), 1.21 (d, J = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 167.7, 155.8, 152.3, 138.2, 134.3, 131.0, 130.7, 125.7, 125.2, 114.8, 114.2, 77.3, 67.0, 44.2, 33.3, 26.9, 22.0, 19.6. HRMS (ESI) m/z [M+H+] $C_{23}H_{30}NO_4^+$ requires 384.2169, found 384.2182

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*,*N*-dimethylacetamide (**20**)



General method B was used (scale of 0.36 mmol) with dimethylamine hydrochloride (88 mg, 1.075 mmol, 3 eq) to give the product as a white solid (38 mg, 0.11 mmol, 30%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.95 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 9.9 Hz, 3H), 6.53 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.58 (s, 1H), 4.68 (s, 2H), 3.90 (s, 2H), 3.21 (h, *J* = 6.9 Hz, 1H), 3.13 (s, 3H), 3.02 (s, 3H), 2.20 (s, 6H), 1.23 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.28, 155.89, 150.95, 138.53, 134.20, 131.93, 130.72, 126.14, 125.30, 115.15, 114.07, 67.53, 36.73, 35.79, 33.74, 27.10, 22.58, 20.50. HRMS (ESI) m/z [M+H+] $C_{22}H_{30}NO_3^+$ requires 356.2220, found 356.2233

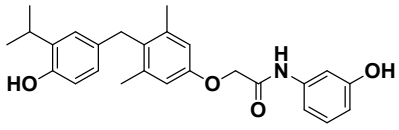
2-(4-(4-hydroxy-3-isopropyl benzyl)-3, 5-dimethylphenoxyl)-*N*-(2-hydroxyphenyl) acetamide (**21**)



Following the general method D, compound **32** afforded compound **21** as white solid (158mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.57 (s, 1H), 7.16 (m,

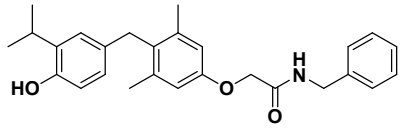
1H), 7.08 (m, 1H), 6.92 (m, 2H), 6.72 (s, 2H), 6.59 (m, 2H), 4.68 (s, 2H), 3.93 (s, 2H), 3.13 (m, 1H), 2.26 (s, 6H), 1.22 (d, *J* = 6.98 Hz, 6H). ^{13}C NMR (100 MHz, acetone-d_6) δ 168.5, 154.8, 150.9, 148.9, 139.2, 134.4, 132.1, 131.9, 127.8, 126.2, 125.5, 124.7, 122.5, 120.7, 120.1, 115.3, 114.5, 67.3, 33.9, 27.3, 22.7 and 20.7. HRMS (ESI-MS): calculated for $C_{26}H_{29}NO_4Na$+ $[M+Na]^+$: 442.1988, found 442.1993.

2-(4-(4-hydroxy-3-isopropyl benzyl)-N-(3-hydroxyphenyl) acetamide (**22**)



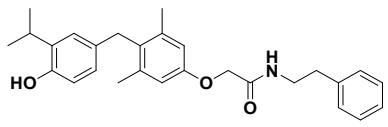
Following the general method D, compound **32** provided compound **22** as white solid (163mg, 61% yield). ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.28(m, 1H), 7.16 (t, *J* =7.89 Hz, 1H), 6.88 (m, 1H), 6.83 (m, 1H), 6.67 (s, 1H), 6.63 (m, 1H), 6.59 (d, *J* = 7.89Hz, 1H), 6.49 (m, 1H), 4.56 (s, 2H), 3.88 (s, 2H), 3.12 (m, 1H), 2.22 (s, 6H), 1.16 (d, *J* = 6.85 Hz, 6H). ^{13}CNMR (100 MHz, CDCl3): δ 166.1, 155.5, 152.2, 139.4, 137.9, 134.2, 130.9, 129, 125.5, 125, 114.8, 114.1, 110.6, 67.3, 33.3, 26.8, 21.9, and 19.7. HRMS (ESI-MS): calculated for $C_{26}H_{29}NO_4$ $[M+Na]^+$: 442.1988, found 442.1994.

N-benzyl-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide (**23**)



Following the general method B, compound **32** afforded compound **23** (129 mg, 87% yield) as colorless, sticky liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H), 6.90 (d, 2H), 6.57 (m, 4H), 4.55 (m, 4H), 3.88 (s, 2H), 3.14 (hept, *J* = 6.8Hz, 1H), 2.20 (s, 6H), 1.20 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, Methanol-d_4): δ 170.1, 156.2, 152.5, 138.7, 138.3, 135, 131.8, 130.5, 128.3, 127.4, 127.1, 125.5, 125.3, 115, 114.1, 67.3, 42.9, 33.5, 27.2, 22 and 19.6. HRMS (ESI-MS): calculated for $C_{27}H_{32}NO_3^+$ $[M+H]^+$: 418.2377, found 418.2387.

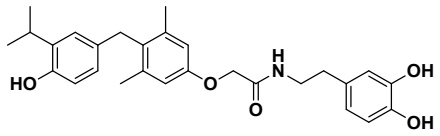
2-(4-(4-hydroxy-3-isopropylbenzyl)-3, 5-dimethylphenoxy)-*N*-phenethylacetamide (**24**)



Following the general method B, compound **32** afforded compound **24** as white solid (112mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 - 7.12 (m, 5H), 6.92 (d, *J* = 2.1 Hz, 1 H), 6.67 (s, 1H), 6.62-6.50 (m, 4H), 4.67 (s, 1H), 4.46 (s, 2H), 3.90 (s, 2H), 3.61

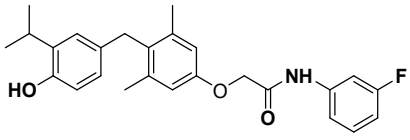
(q, *J* = 6.8 Hz, 2H), 3.15 (hept, *J*= 6.9 Hz, I H), 2.84 (t, *J* = 7.0 Hz, 2H), 2.22 (s, 6H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 155.2, 151.8, 138.9, 138.5, 134.8, 131.5, 131.2, 128.8, 128.7, 126.7, 126.1, 125.2, 115.4, 114, 67.4, 40.6, 35.7, 33.9, 27.2, 22.9 and 20.5. HRMS (ESI-MS): calculated for $C_{28}H_{34}NO_3^+$ $[M+H]^+$: 432.2533, found 432.2541

N-(3,4-dihydroxyphenethyl)-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide **(25)**



Following the general method B, compound **32** was first converted to the benzyl protected sobetirome acetamide which was crystallized from chloroform. ^{1}H NMR (400 MHz, Methanol-d4): δ 7.48-7.26 (m, 3H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.82 (dd, *J* = 8.5, 1.3 Hz, 1H), 6.71-6.62 (m, 3H), 6.51 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.03 (s, 1H), 4.47 (d, *J* = 1.4 Hz, 1H), 3.95 (s, 1H), 3.45 (dd, *J* = 8.1, 6.7 Hz, 1H), 3.38-3.26 (m, 1H), 2.67 (t, *J* = 7.4 Hz, 1H), 2.22 (s, 3H), 1.16 (dd, *J* = 6.9, 1.3 Hz, 3H). To a stirred solution of this protected acetamide (0.17 mmol) in MeOH (5 mL) under argon, 10% Pd-C wetted with ca. 55% water (36 mg) and triethylsilane (198 µL, 1.3mmol) were added. The reaction mixture was stirred at room temperature for 3 hours. It was then filtered through a bed of celite and the crude product was purified by flash chromatography. Compound **25** (111mg, 67%) was thus obtained as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, *J* = 2.1 Hz, 1 H), 6.69 (d, *J* = 6.8 Hz, 4H), 6.63 -6.49 (m, 3H), 4.48 (s, 2H), 3.92 (s, 2H), 3.47 (t, *J* = 7.4 Hz, 2H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.23 (s, 6H), 1.32 (s, 1H), 1.15 (d, *J* = 6.9 Hz, 6H), 0.93 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, methanol-d_4): δ 170.3, 155.9, 152.4, 145.3, 143.8, 138.6, 138.5, 134.8, 131.5, 130.8, 130.7, 130.6, 125.6, 125.3, 120, 115.8, 115.4, 114.8, 114.2, 114.1, 67.5, 40.9, 35.1, 33.3, 27.2, 22.2, 19.4. HRMS (ESI-MS): calculated for $C_{28}H_{34}NO_5^+$ $[M+H]^+$: 464.2431, found 464.2436

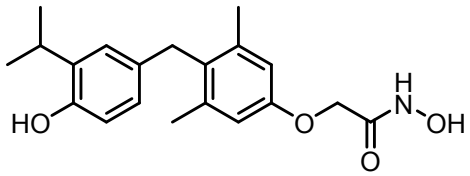
N-(3-fluorophenyl)-2-(4-(4-hydroxy-3-isopropylbenzyl)-3, 5-dimethylphenoxy) acetamide (**26**)



Following the general method B, compound **32** yielded compound **26**(139mg, 91% yield) as white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1 H), 7.34 -7.17 (m, 2H), 6.92 -6.79 (m, 2H), 6.68 (s, 2H), 6.61-6.49 (m, 2H), 4.58 (s, 3H), 3.90 (s, 2H), 3.13 (hept, *J* = 6.8Hz, 1H), 2.22 (s, 6H), 1.19 (d, *J* = 6.9Hz, 6H). ^{13}C NMR (100 MHz,

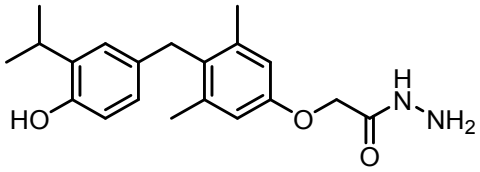
$CDCl_3$): δ 167.2, 164.4, 162.1, 155.1, 151.3, 139.3, 138.5, 138.3, 134.5, 131.9, 131.8, 130.4, 126.4, 125.4, 115.4, 115.3, 114.6, 111.8, 111.5, 108.1, 107.5, 67.7, 34.2, 27.2, 23 and 20.6. HRMS (ESI-MS): calculated for $C_{26}H_{29}FNO_3^+$ $[M+H]^+$: 422.2126, found 422.2132

N-hydroxy-2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetamide (**27**)



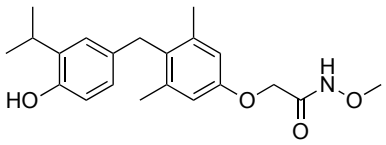
General method B was followed using hydroxylamine hydrochloride, product was isolated as an off-white solid (63 mg, 46%). The product tests positive (red-orange stain) with iron (III) chloride on TLC. ^{1}H NMR (400 MHz, CD_3CN): δ 6.91 (s, 1 H), 6.68 (s, 2 H), 6.62 (d, J = 8.3 Hz, 1 H), 6.54 (dd, J = 8.3, 2 Hz, 1 H), 4.48 (s, 2 H), 3.88 (s, 2 H), 3.15 (sept. 1 H), 2.20 (s, 6 H), 1.12 (d, J = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 154.9, 151.0, 138.9, 134.5, 131.7, 131.6, 126.1, 125.3, 115.3, 114.1, 66.4, 33.7, 27.1, 22.6, 20.5. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 154.9, 151.0, 138.9, 134.5, 131.7, 131.6, 126.1, 125.3, 115.3, 114.1, 66.4, 33.7, 27.1, 22.6, 20.5. HRMS (ESI-MS): calculated for $C_{20}H_{26}NO_4^+$ $[M+H]^+$: 344.1856, found 344.1864

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)acetohydrazide (**28**)



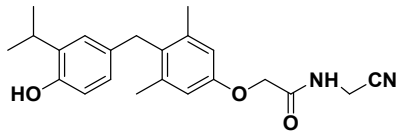
General method A was followed using hydrazine hydrate, product was isolated as a white solid (224 mg, 86%). The product tests positive with ninhydrin on TLC. ^{1}H NMR (400 MHz, CD_3OD): δ 6.77 (s, 1 H), 6.64 (s, 2 H), 6.53 (d, J = 8.2 Hz, 1 H), 6.46 (dd, J = 8.3, 2 Hz, 1 H), 4.48 (s, 2 H), 3.83 (s, 2 H), 3.16 (sept. 1 H), 2.16 (s, 6 H), 1.08 (d, J = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, CD_3OD): δ 168.9, 155.7, 152.0, 138.2, 134.5, 131.0, 130.5, 125.2, 124.9, 114.4, 113.8, 66.2, 33.1, 26.6, 21.6, 19.1. HRMS (ESI-MS): calculated for $C_{20}H_{27}N_2O_3^+$ $[M+H]^+$: 343.2016, found 343.2034

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*-methoxyacetamide (**29**)



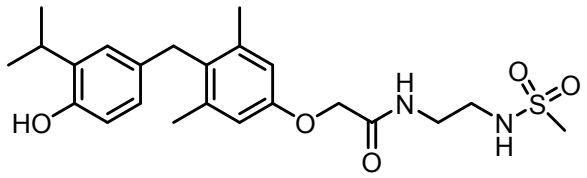
General method B was used (scale 0.36 mmol) with methoxyamine hydrochloride (83 mg, 1.075 mmol, 3 eq) to give the product as a white solid (94.5 mg, 0.26 mmol, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.06 (s, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.66 – 6.52 (m, 4H), 4.74 (s, 1H), 4.59 (s, 2H), 3.92 (s, 2H), 3.86 (s, 3H), 3.18 (hept, *J* = 6.9 Hz, 1H), 2.24 (s, 6H), 1.23 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.77, 155.08, 151.17, 138.88, 134.42, 133.60, 131.55, 131.43, 126.08, 125.22, 116.68, 115.16, 114.08, 67.23, 41.35, 33.75, 27.08, 22.60, 20.50. HRMS (ESI-MS): calculated for $C_{21}H_{28}NO_4^+$ $[M+H]^+$: 358.2013, found 358.2014

N-(cyanomethyl)-2-(4-(4-hydroxy-3-isopropylbenzyl)-3, 5-dimethylphenoxy) acetamide (**30**)



Following the general method B, compound **32** yielded compound **30** (84mg, 64% yield) as white amorphous solid. ^{1}H NMR (400MHz, Methanol-d_4): δ 6.83 (d, *J*= 2.2 Hz, 1H), 6.72 (s, 2H), 6.62 -6.49 (m, 2H), 4.57 (d, *J* = 1.6 Hz, 2H), 4.25 (d, *J*= 1.6 Hz, 2H), 3.90 (s, 2H), 3.21 (hept, *J* = 6.9Hz, 1H), 2.22 (d, *J* = 1.5 Hz, 6H), 1.14 (dd, J = 7.0,1.7 Hz, 6H). ^{13}C NMR (100 MHz, Methanol-d_4): δ 170.8, 155.6, 152.2, 138.5, 134.7, 131.4, 130.6, 125.4, 125.1, 116.1, 114.6, 114.0, 66.8, 33.3, 26.9, 26.5, 21.9 and 19.4. HRMS (ESI-MS): calculated for $C_{22}H_{25}N_2O_3^-$ (M-H): 365.1871, found 365.1861.

2-(4-(4-hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy)-*N*-(2-(methylsulfonamido)ethyl)acetamide (**31**)

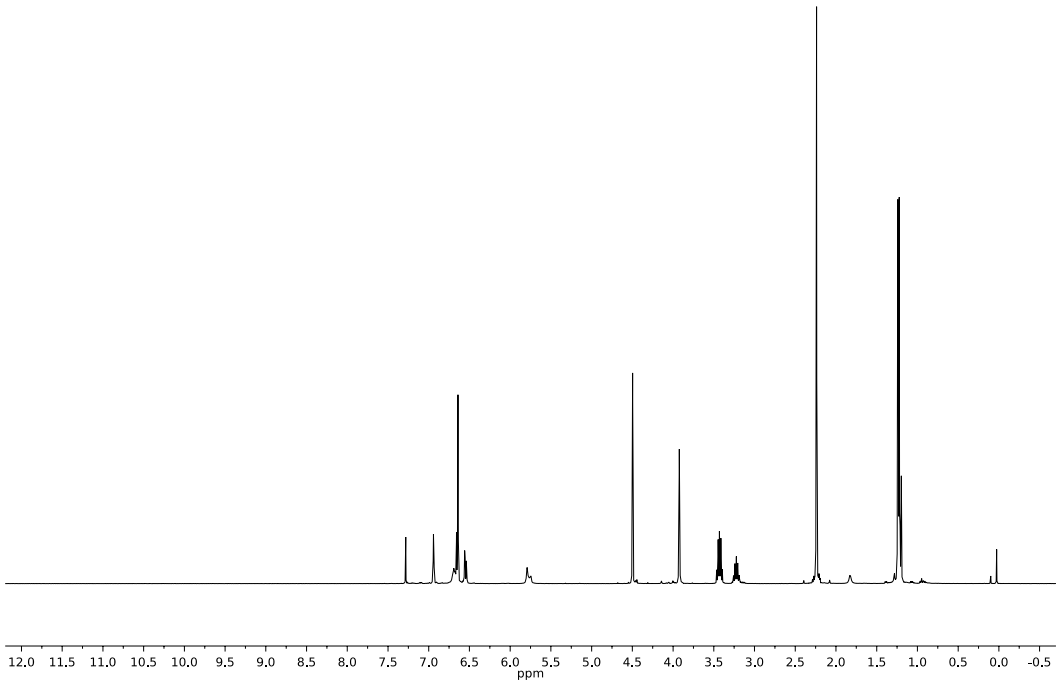


General method B was followed using *N*-(2-aminoethyl)-methanesulfonamide, product isolated as an off-white solid (149 mg, 92%). ^{1}H NMR (400 MHz, CD_3CN): δ 7.29 (br, 1 H), 6.89 (s, 1 H), 6.69 (s, 2 H), 6.62 (d, J = 8.2 Hz, 1 H), 6.54 (d, J = 8.4, 2.0 Hz, 1 H), 4.43 (s, 2 H), 3.88 (s, 2 H), 3.39 (m, 2 H), 3.16 (m, 3 H), 2.88 (s, 3 H), 2.20 (s, 6 H), 1.12 (d, J = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, CD_3CN): δ 164.8, 155.6, 151.9, 138.5, 134.5, 131.3, 131.2, 126.0, 125.4, 115.0, 114.1, 67.1, 42.6, 39.3, 38.9, 33.2, 26.7, 21.9, 19.7. HRMS exact mass calcd for $C_{23}H_{32}N_2O_5SNa+$ $[M + Na]^+$: m/z 471.19241. Found m/z 471.19335.

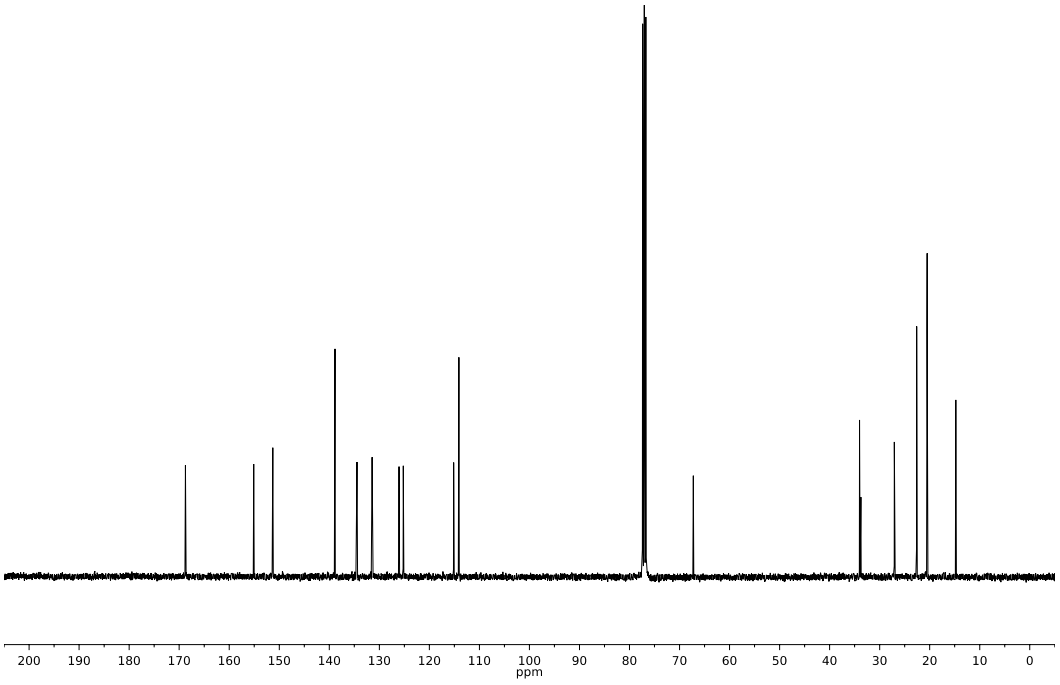
1. Ferrara, S.J., *et al.* Ester-to-amide rearrangement of ethanolamine-derived prodrugs of sobetirome with increased blood-brain barrier penetration. *Bioorg Med Chem* **25**, 2743-2753 (2017).
2. Meinig, J.M., *et al.* Targeting Fatty-Acid Amide Hydrolase with Prodrugs for CNS-Selective Therapy. *ACS Chem Neurosci* **8**, 2468-2476 (2017).
3. Chiellini, G., *et al.* A high-affinity subtype-selective agonist ligand for the thyroid hormone receptor. *Chem Biol* **5**, 299-306 (1998).
4. Devereaux, J., Ferrara, S.J., Banerji, T., Placzek, A.T. & Scanlan, T.S. Increasing Thyromimetic Potency through Halogen Substitution. *ChemMedChem* (2016).
5. Chiellini, G., Nguyen, N.-H., Yoshihara, H.A.I. & Scanlan, T.S. Improved synthesis of the iodine-free thyromimetic GC-1. *Bioorg. Med. Chem. Lett.* **10**, 2607-2611 (2000).
6. Placzek, A.T. & Scanlan, T.S. New synthetic routes to thyroid hormone analogs: d6-sobetirome, 3H-sobetirome, and the antagonist NH-3. *Tetrahedron* **71**, 5946-5951 (2015).

NMR Spectra of Novel Compounds

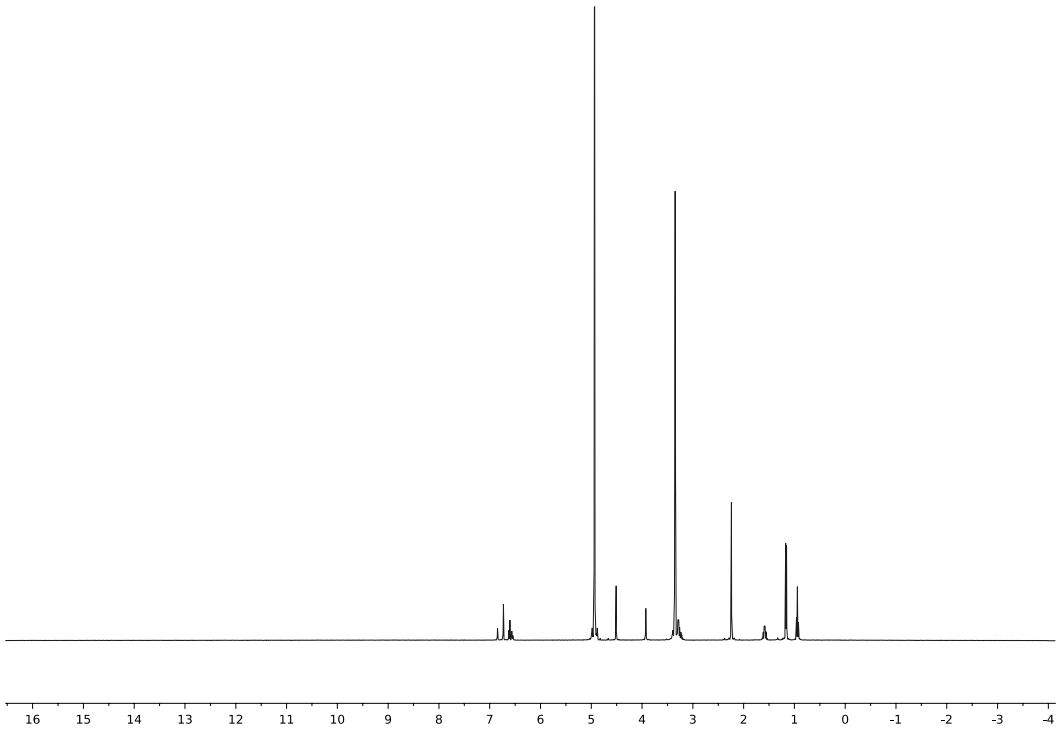
^{1}H NMR of Compound 5 (400 MHz, Chloroform-*d*)



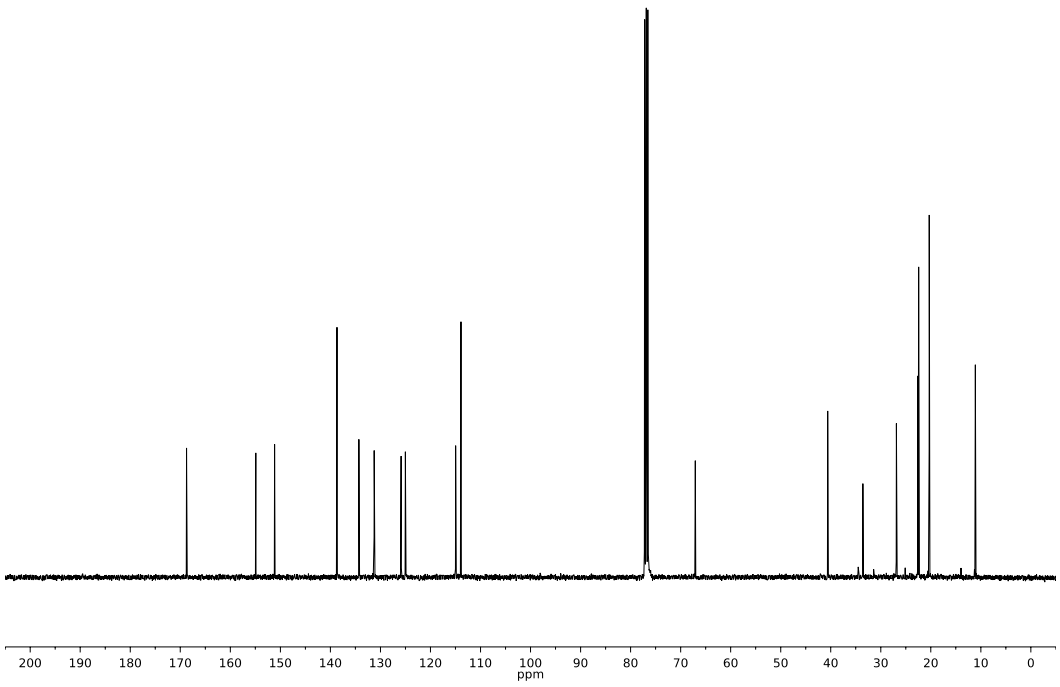
^{13}C NMR of Compound 5 (101 MHz, Chloroform-*d*)



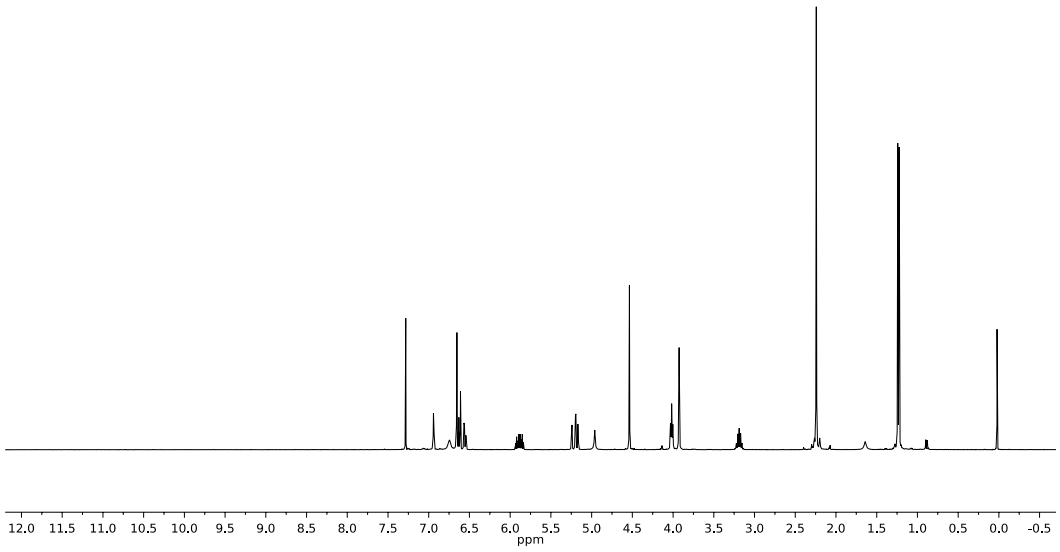
^{1}H NMR of Compound 6 (400 MHz, Chloroform-*d*)



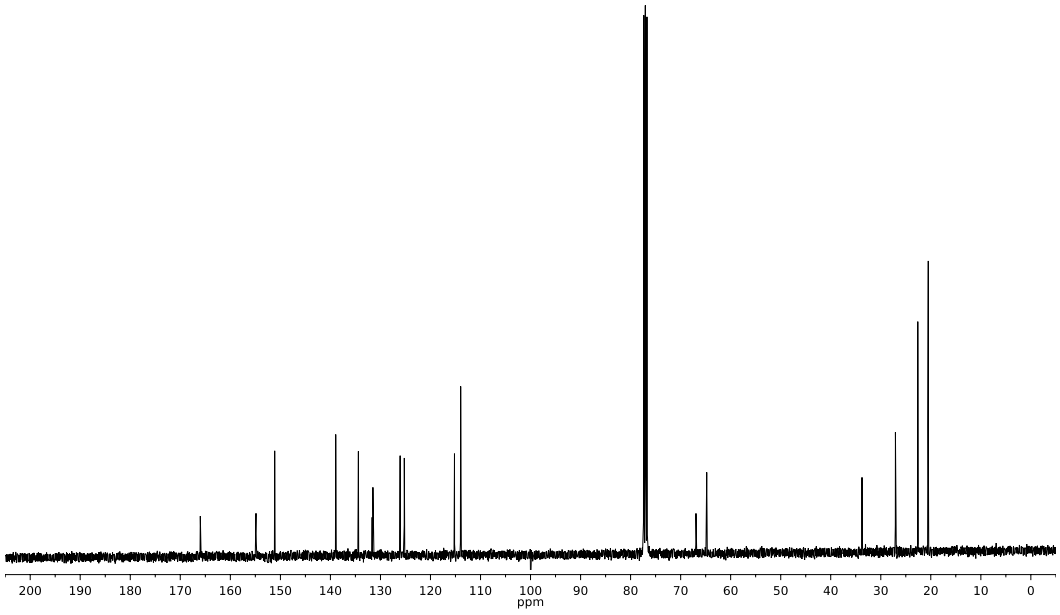
^{13}C NMR of Compound 6 (101 MHz Chloroform-*d*)



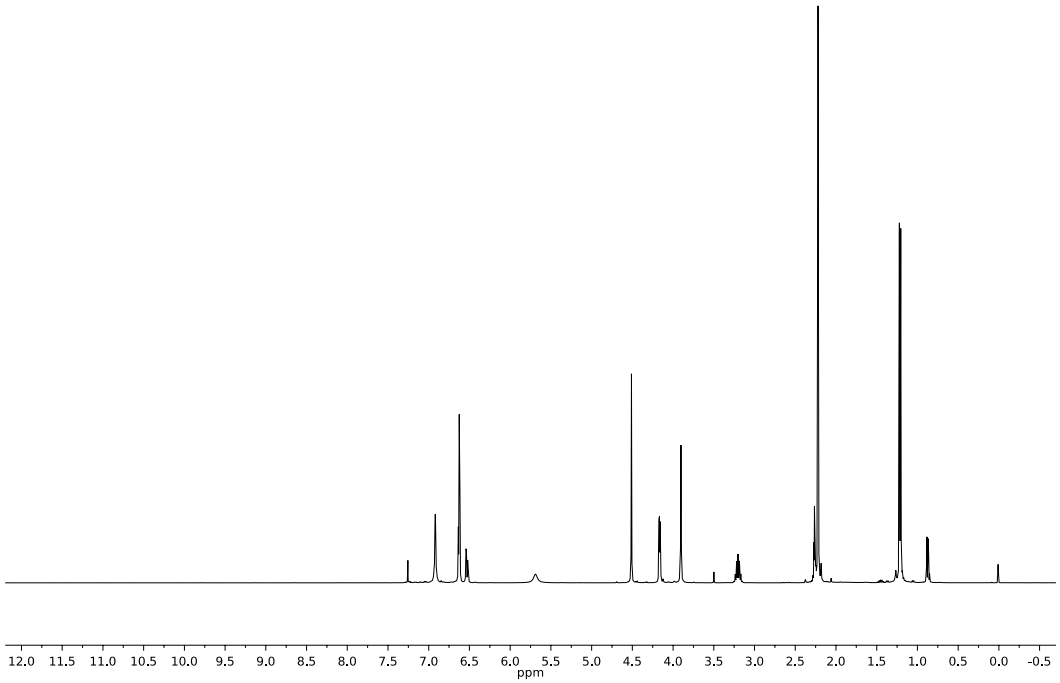
^{1}H NMR of Compound 7 (400 MHz, Chloroform-*d*)



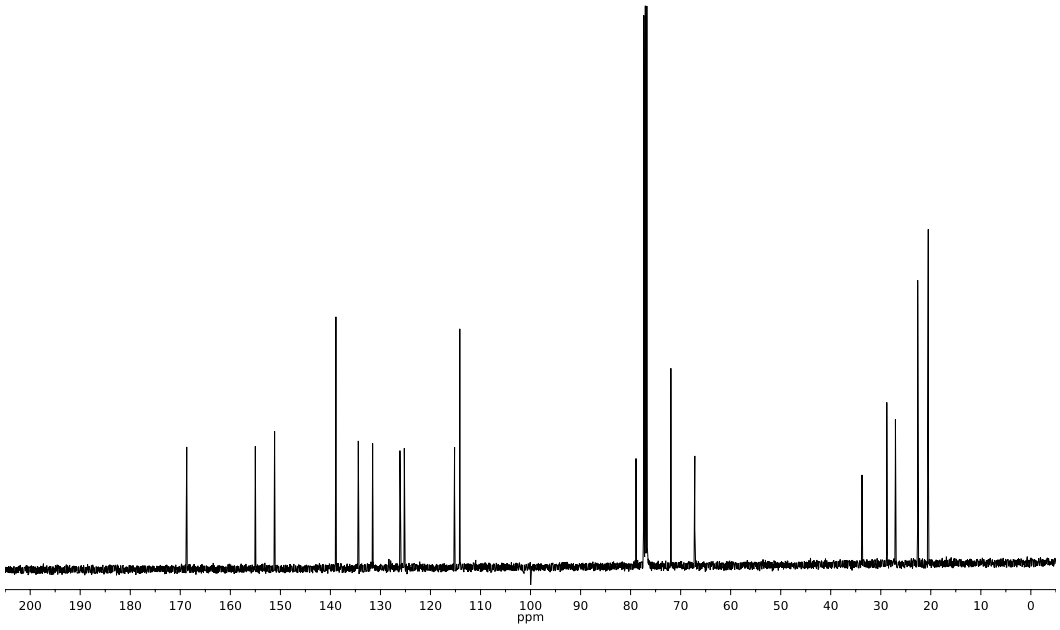
^{13}C NMR of Compound 7 (101 MHz Chloroform-*d*)



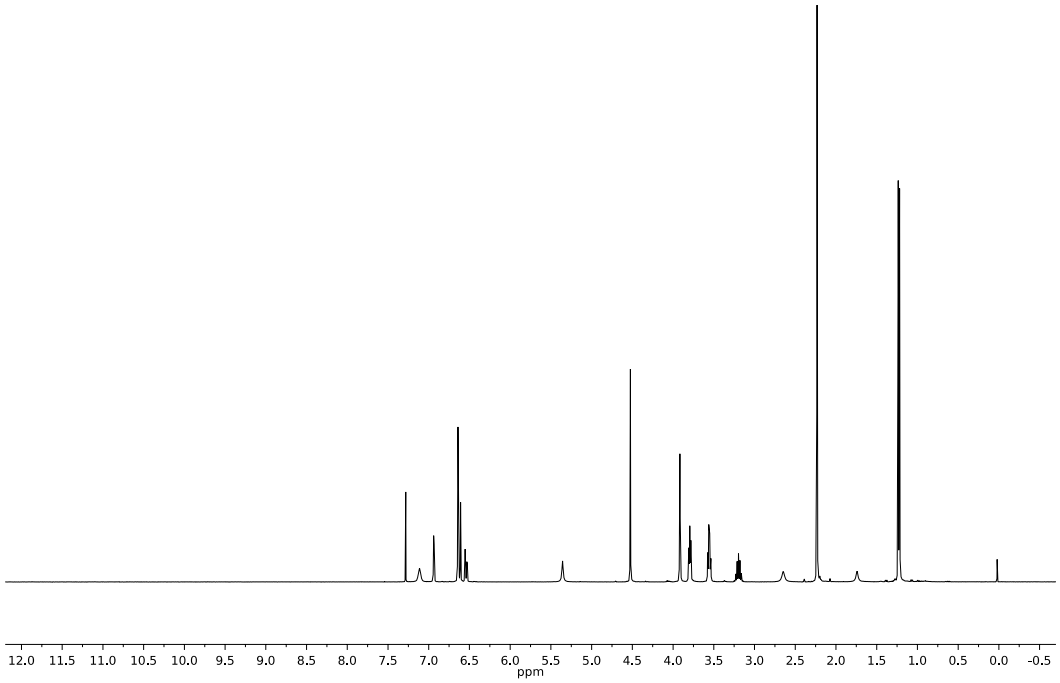
^{1}H NMR of Compound 8 (400 MHz, Chloroform-*d*)



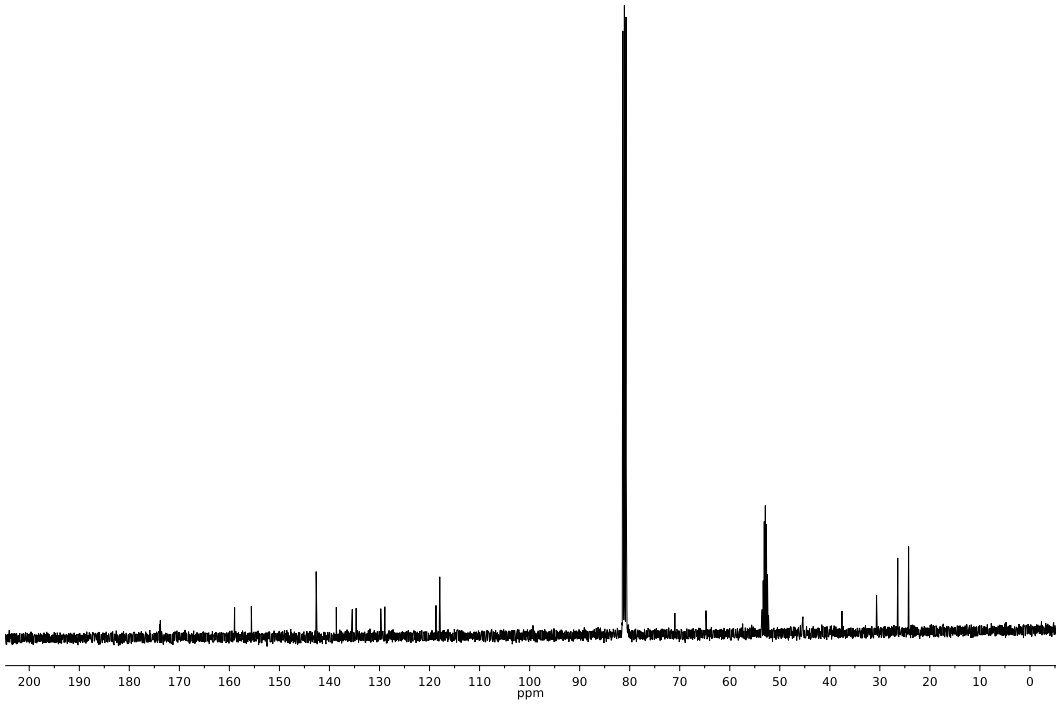
^{13}C NMR of Compound 8 (101 MHz, Chloroform-*d*)



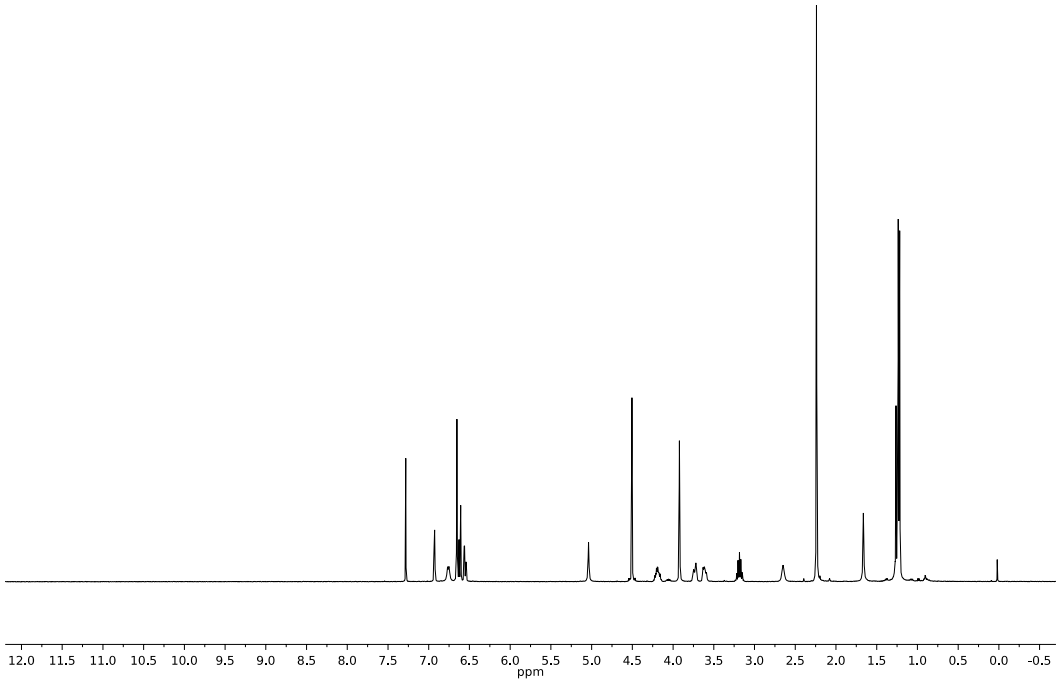
^{1}H NMR of Compound 9 (400 MHz, Chloroform-*d*)



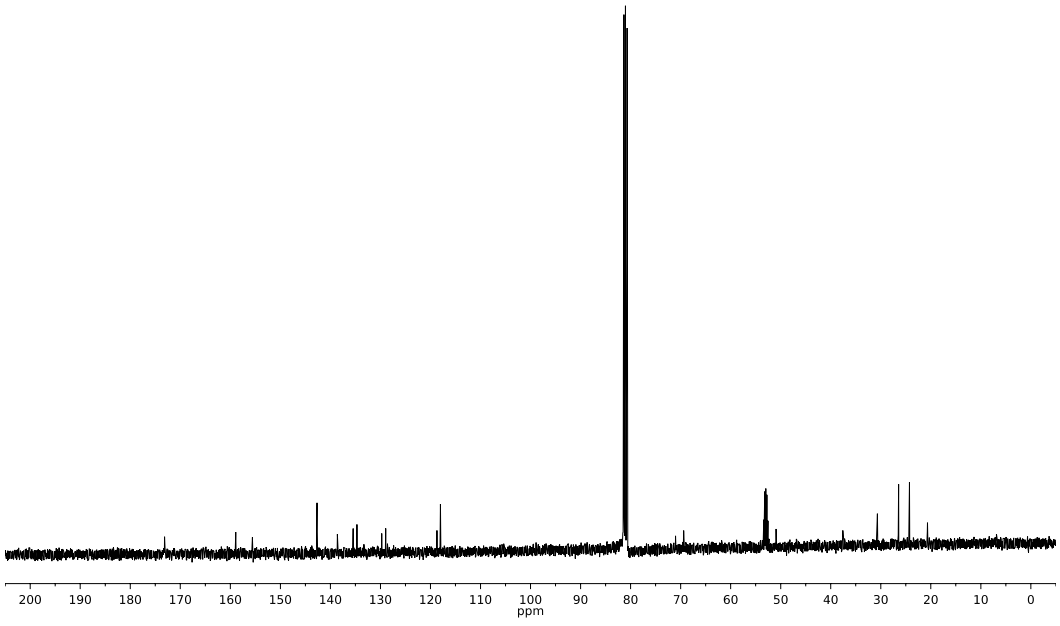
^{13}C NMR of Compound 9 (101 MHz, 20:1 Chloroform-*d*:methanol-d_4)



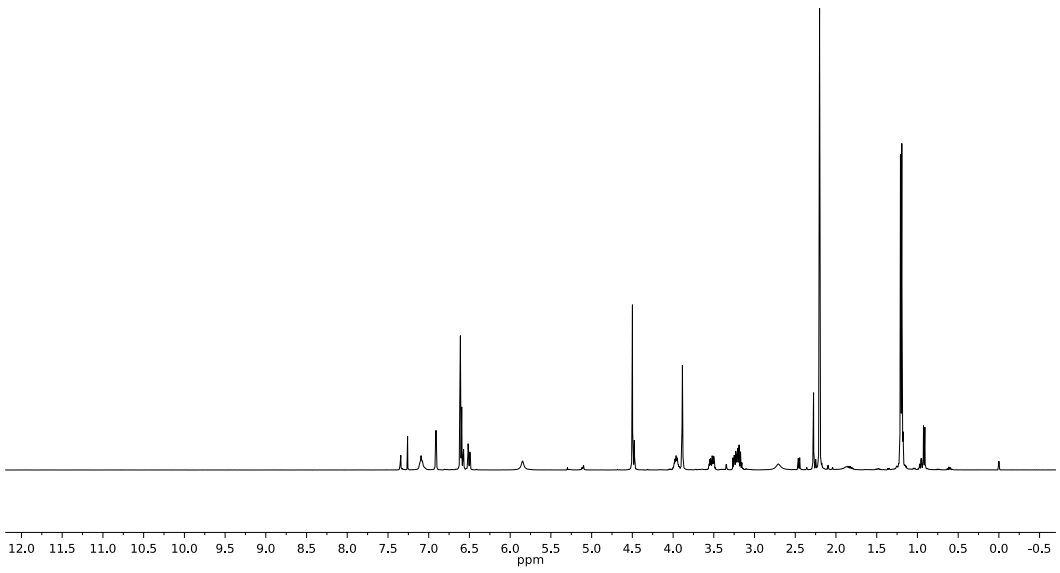
^{1}H NMR of Compound 10 (400 MHz, Chloroform-*d*)



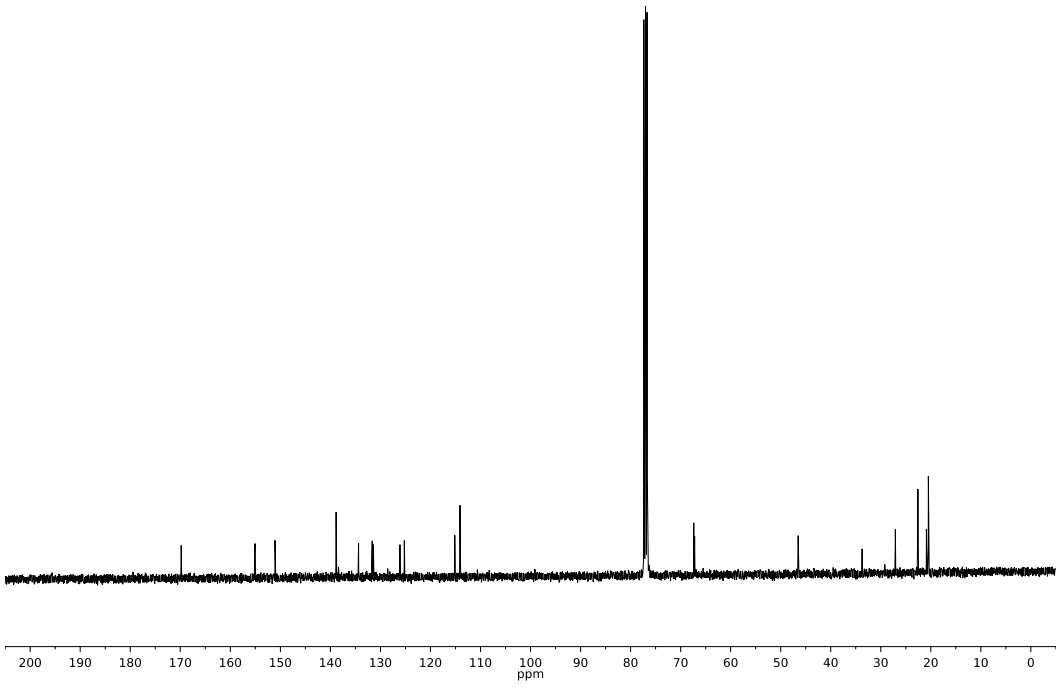
^{13}C NMR of Compound 10 (101 MHz, 20:1 Chloroform-*d*:methanol-d_4)



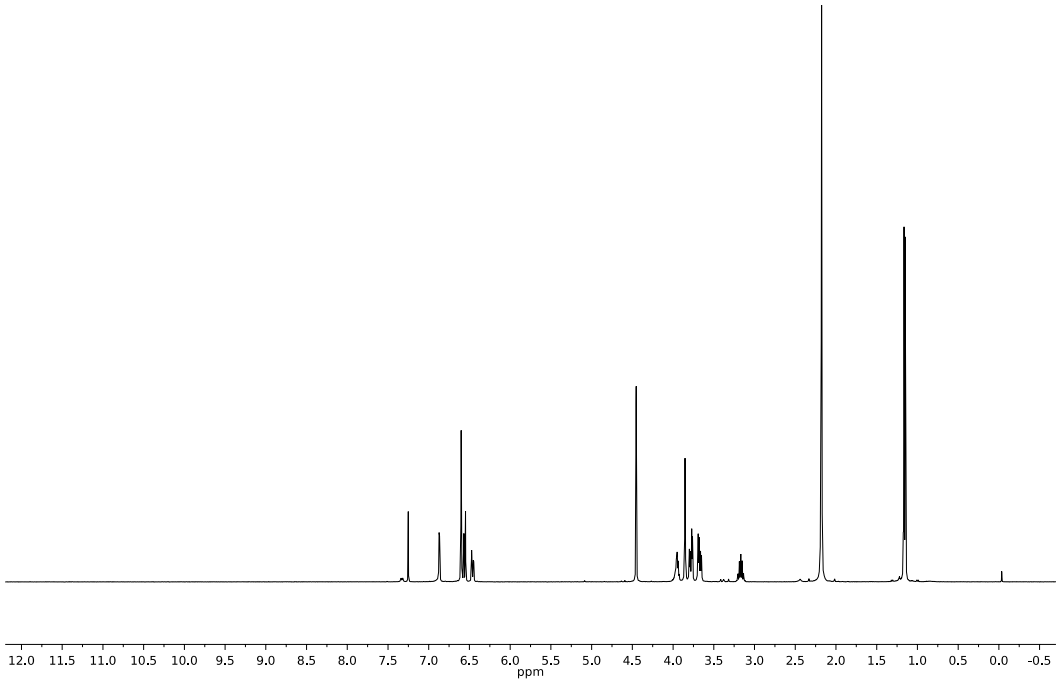
^{1}H NMR of Compound 11 (400 MHz, Chloroform-*d*)



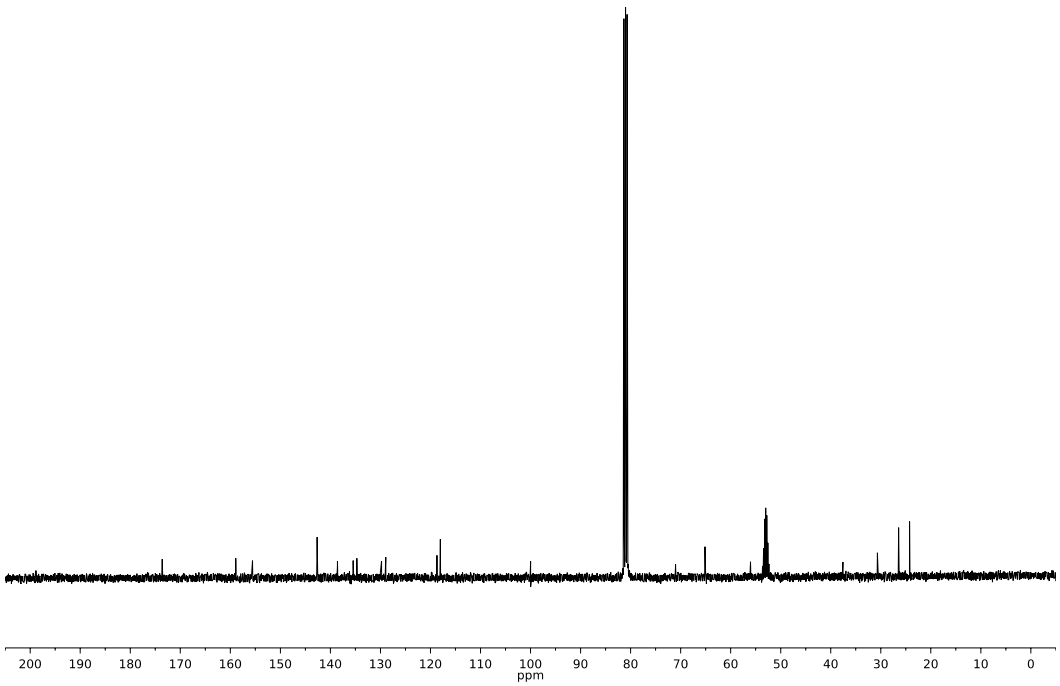
^{13}C NMR of Compound 11 (101 MHz, 20:1 Chloroform-*d*:methanol-d_4)



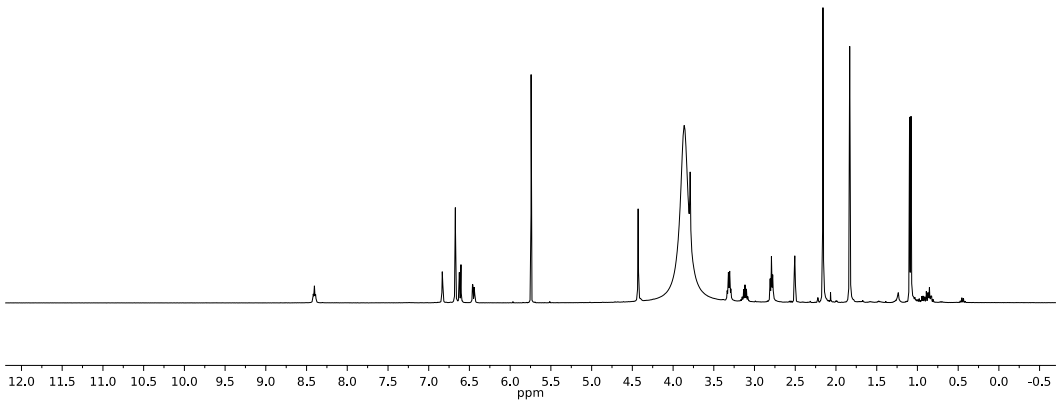
^{1}H NMR of Compound 12 (400 MHz, Chloroform-*d*)



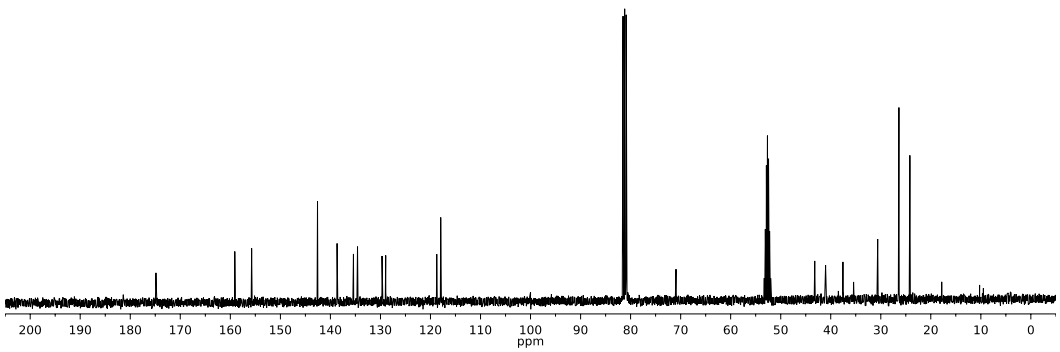
^{13}C NMR of Compound 12 (101 MHz, 20:1 Chloroform-*d*:methanol-d_4)



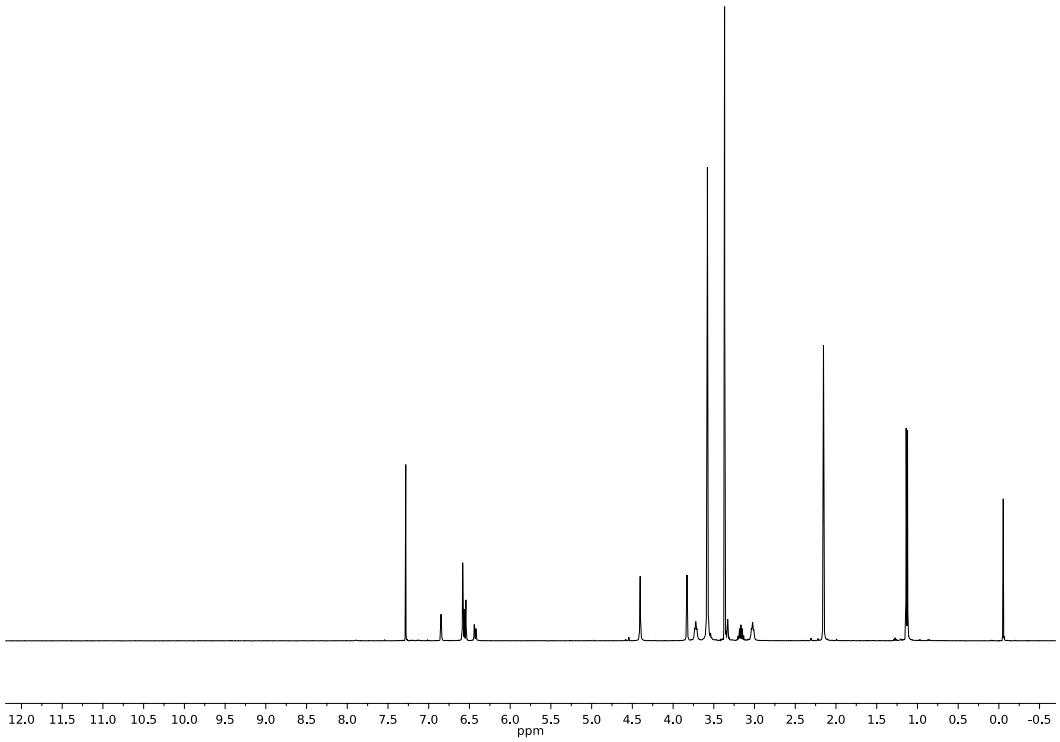
^{1}H NMR of Compound 13 (400 MHz, DMSO-d_6)



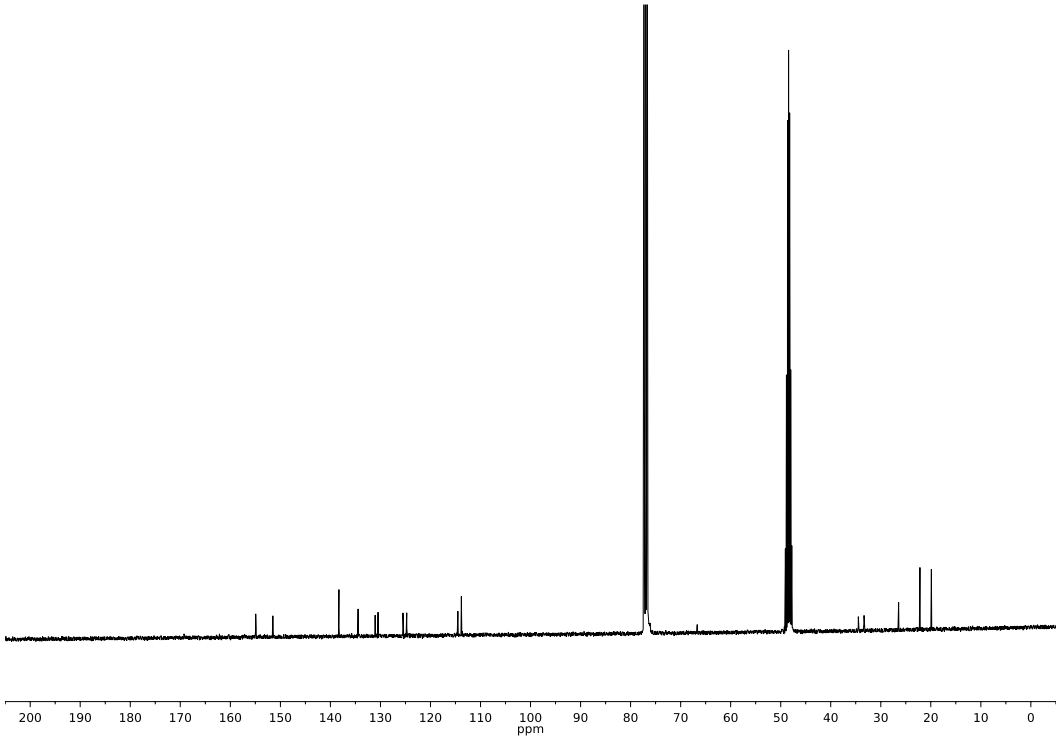
^{13}C NMR of Compound 13 (101 MHz, 9:1 $CDCl_3$:methanol-d_4)



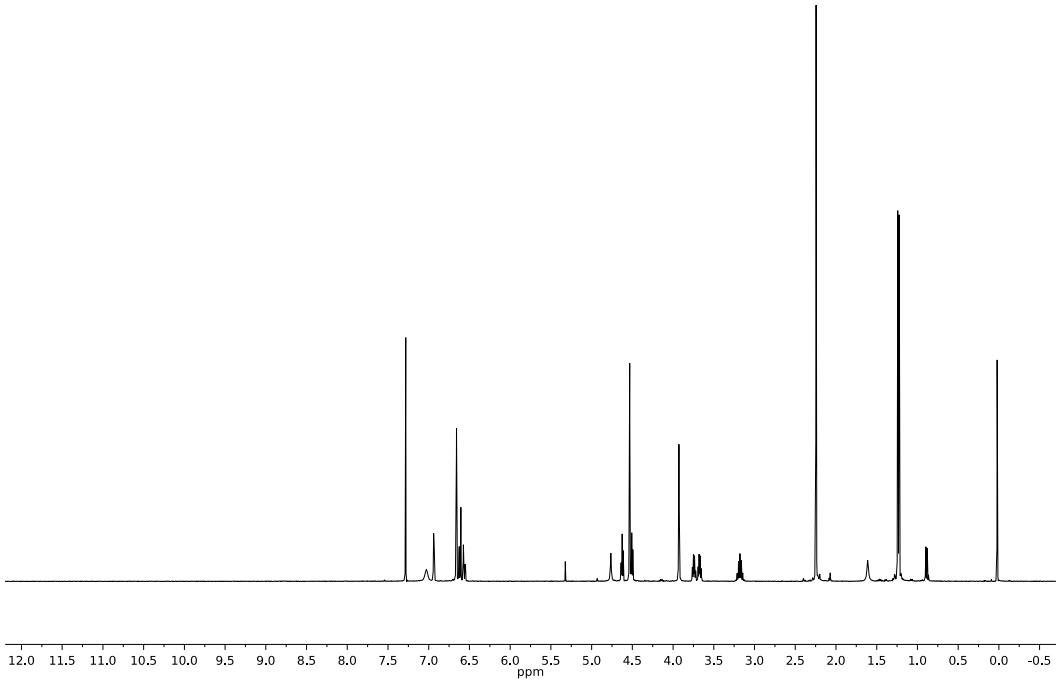
^{1}H NMR of Compound 14 (9:1 Chloroform-*d*: methanol-d_4)



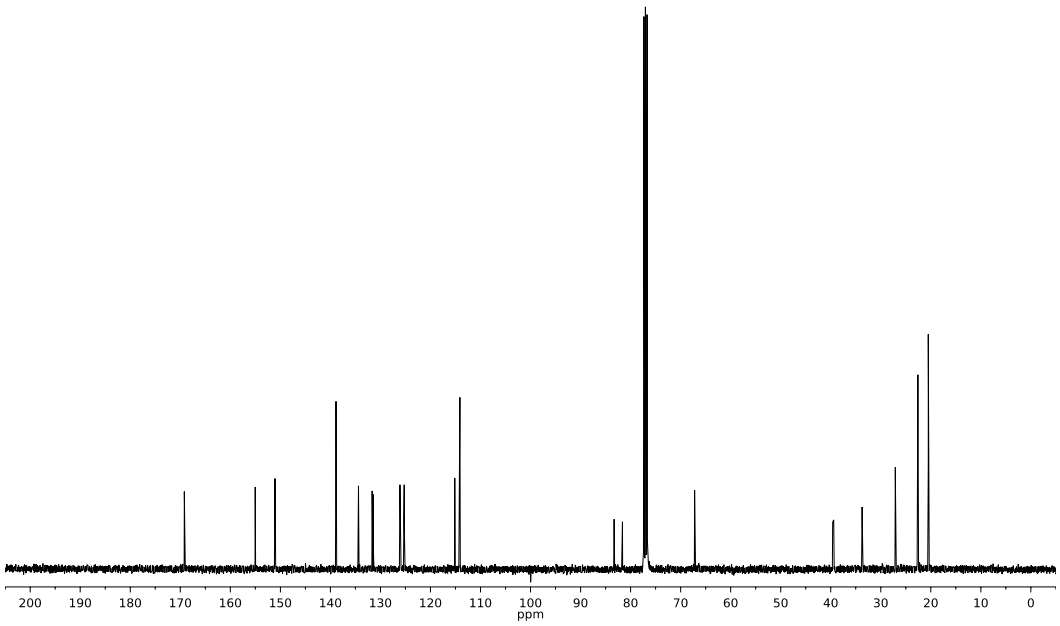
^{13}C NMR of Compound 14 (101 MHz, 9:1 Chloroform-*d*:methanol-d_4)



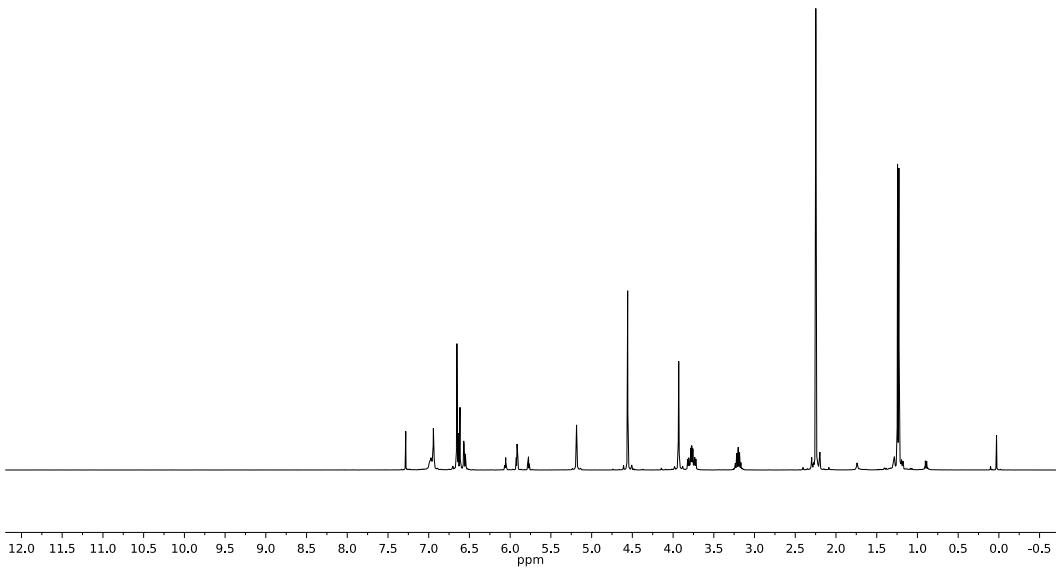
^{1}H NMR of Compound 15 (400 MHz, Chloroform-*d*)



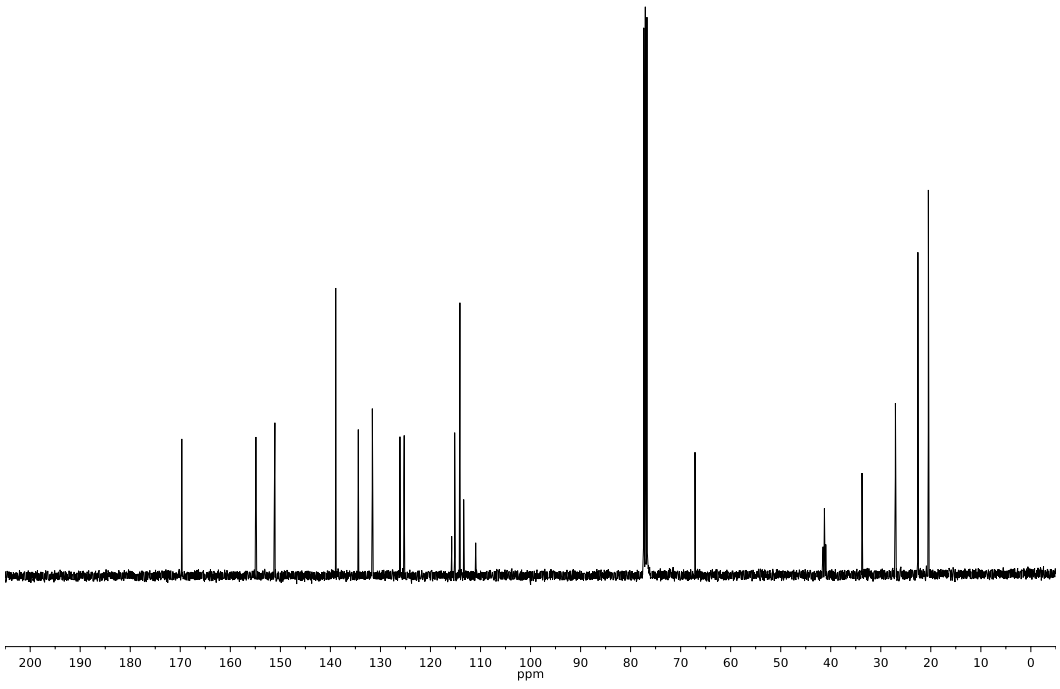
^{13}C NMR of Compound 15 (101 MHz, Chloroform-*d*)



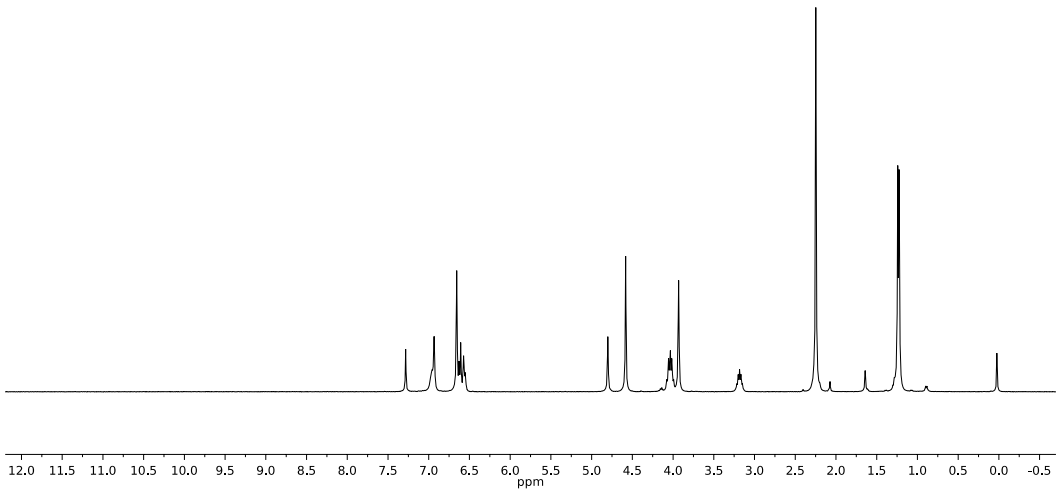
^{1}H NMR of Compound 16 (400 MHz, Chloroform-*d*)



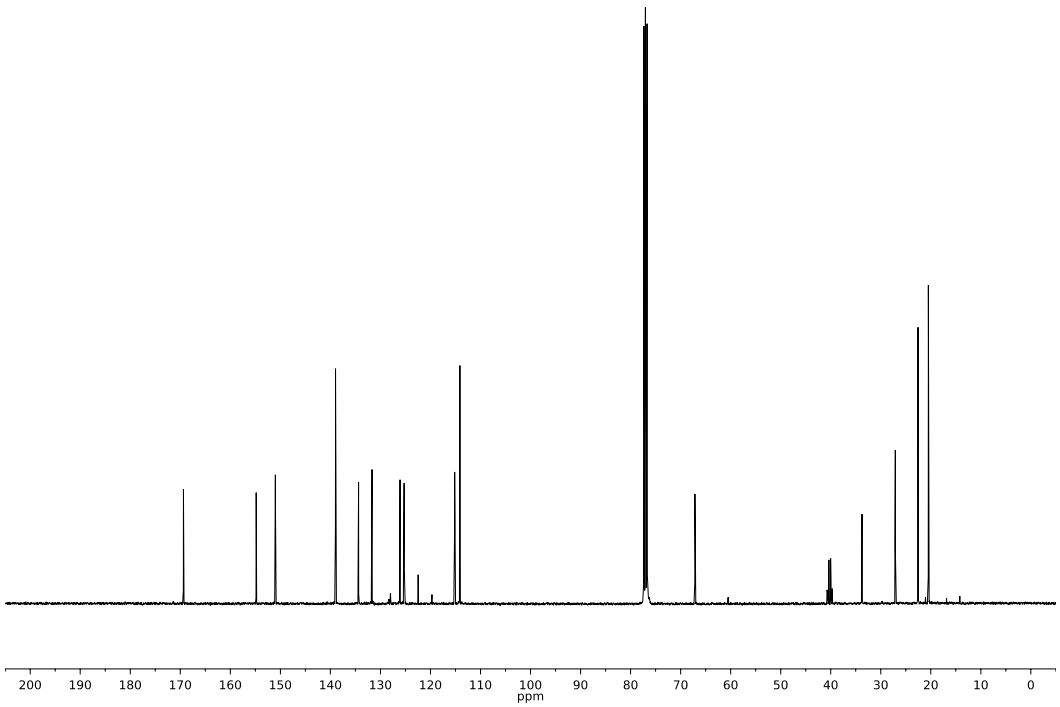
^{13}C NMR of Compound 16 (101 MHz, Chloroform-*d*)



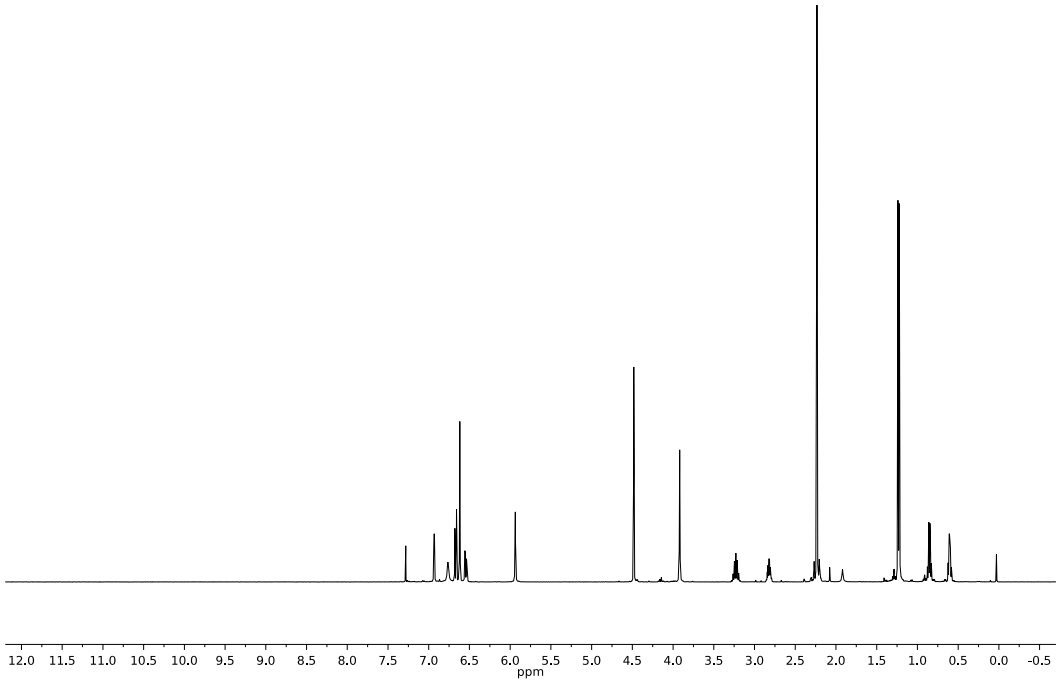
^{1}H NMR of Compound 17 (400 MHz, Chloroform-*d*)



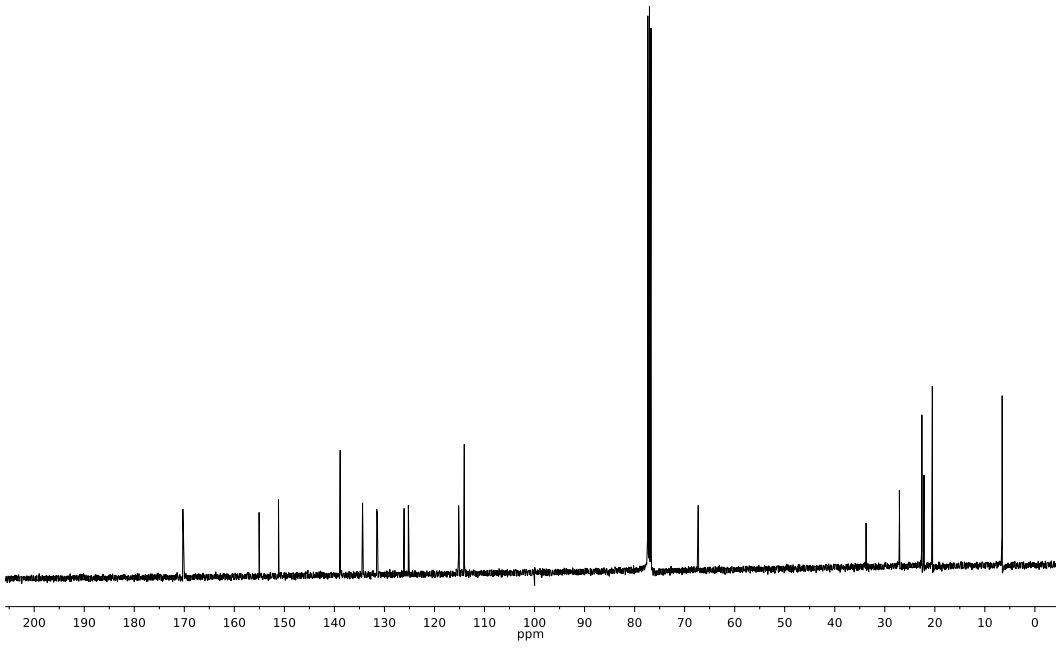
^{13}C NMR of Compound 17 (101 MHz, Chloroform-*d*)



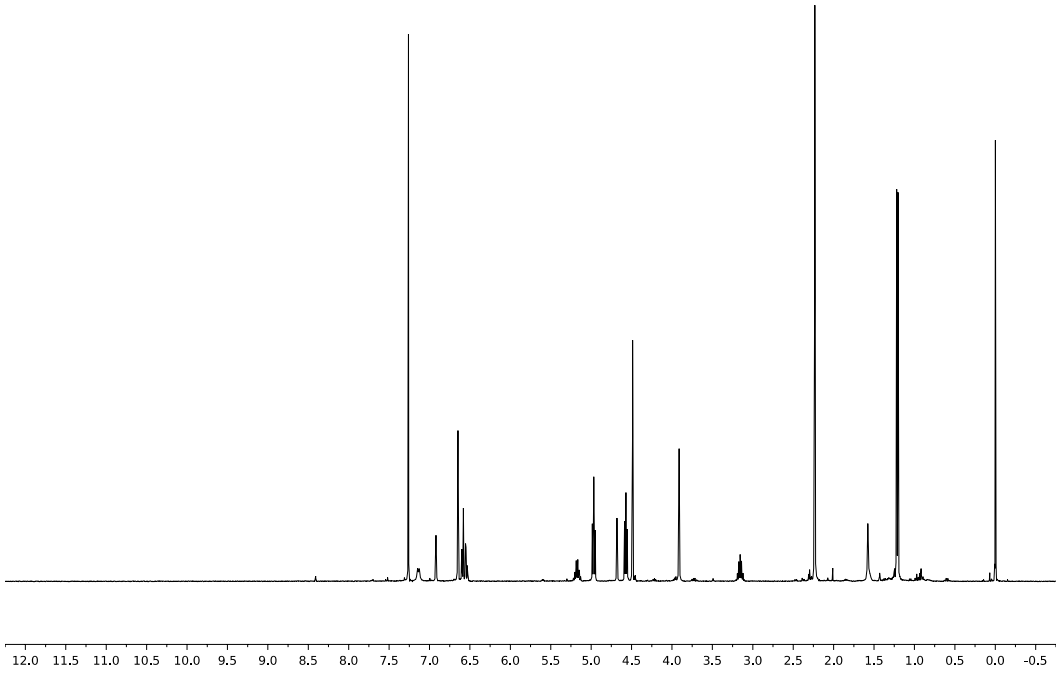
^{1}H NMR of Compound 18 (400 MHz, Chloroform-*d*)



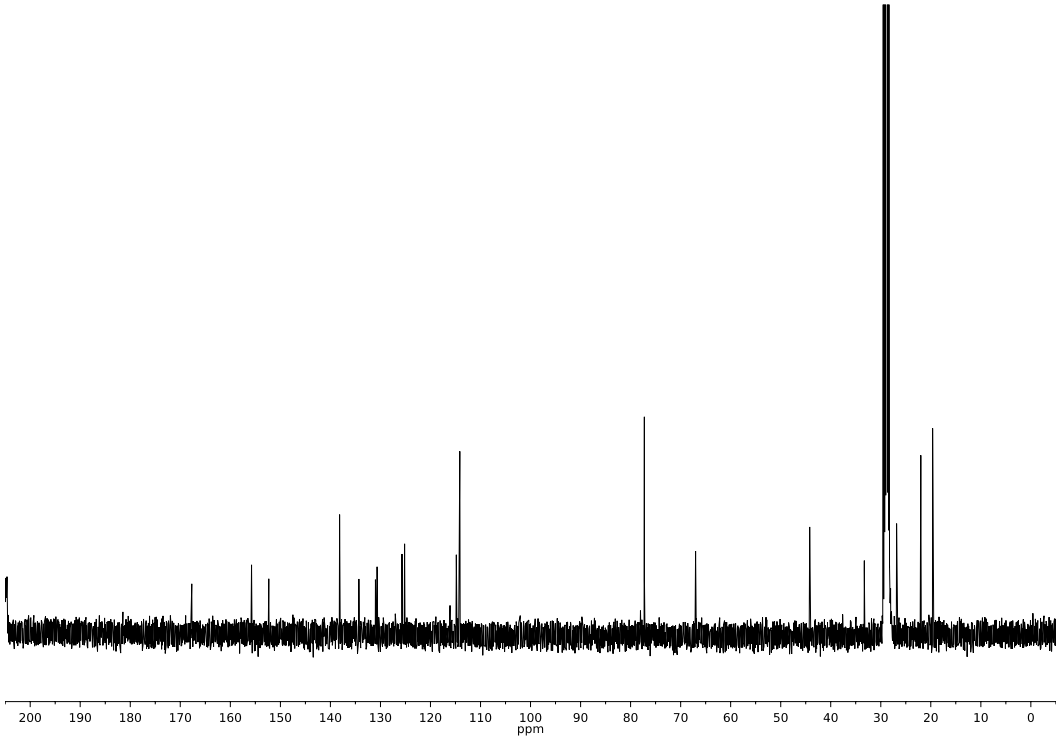
^{13}C NMR of Compound 18 (101 MHz, Chloroform-*d*)



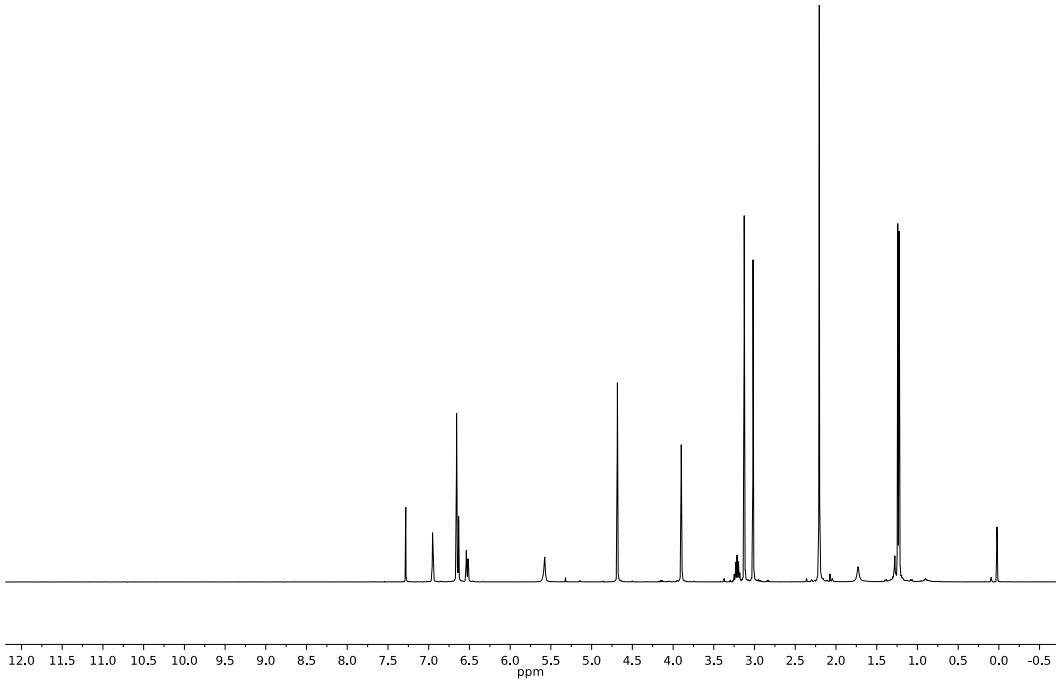
^{1}H NMR of Compound 19 (400 MHz, Chloroform-*d*)



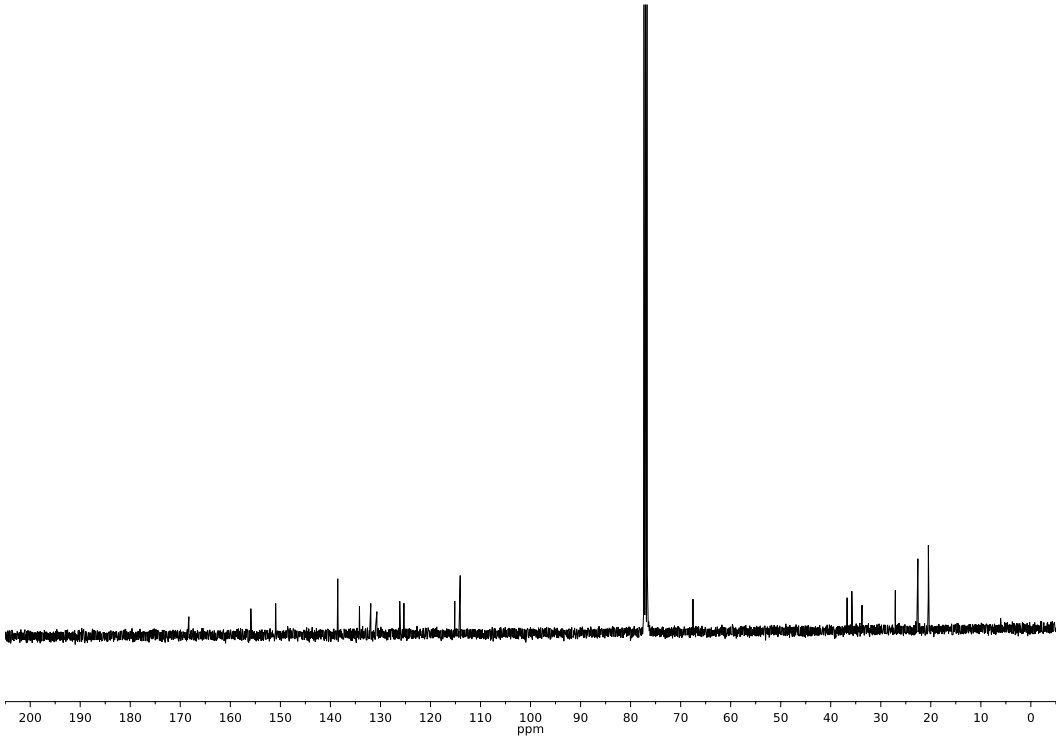
^{13}C NMR of Compound 19 (101 MHz, Acetone-d_6)



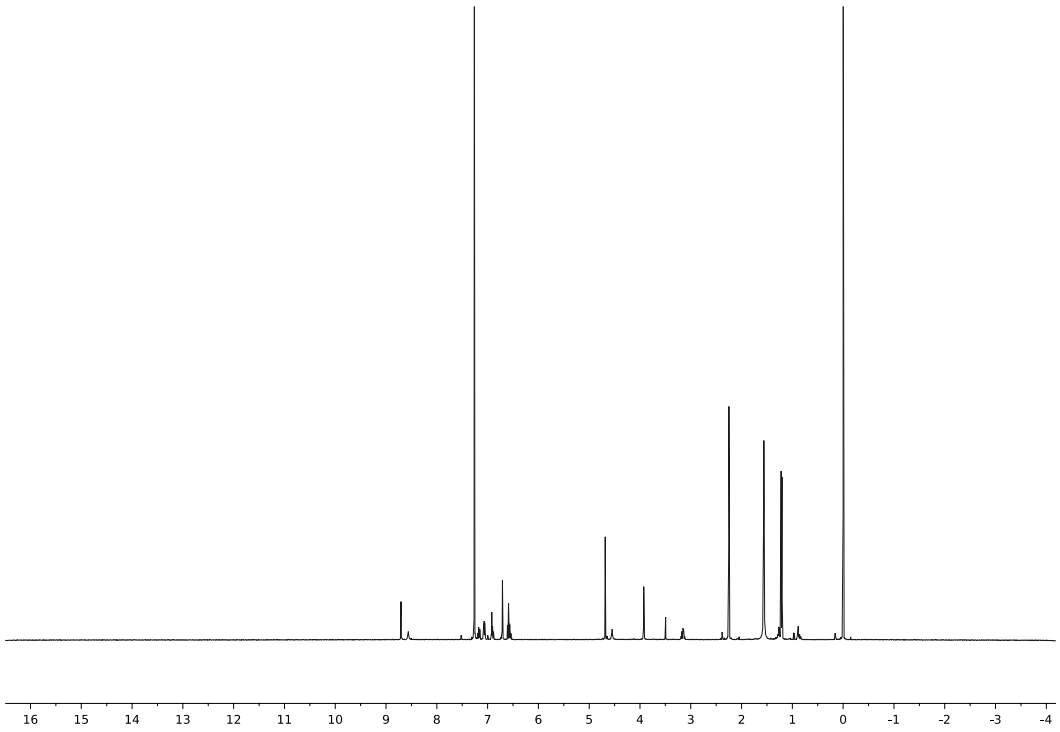
^{1}H NMR of Compound 20 (400 MHz, Chloroform-*d*)



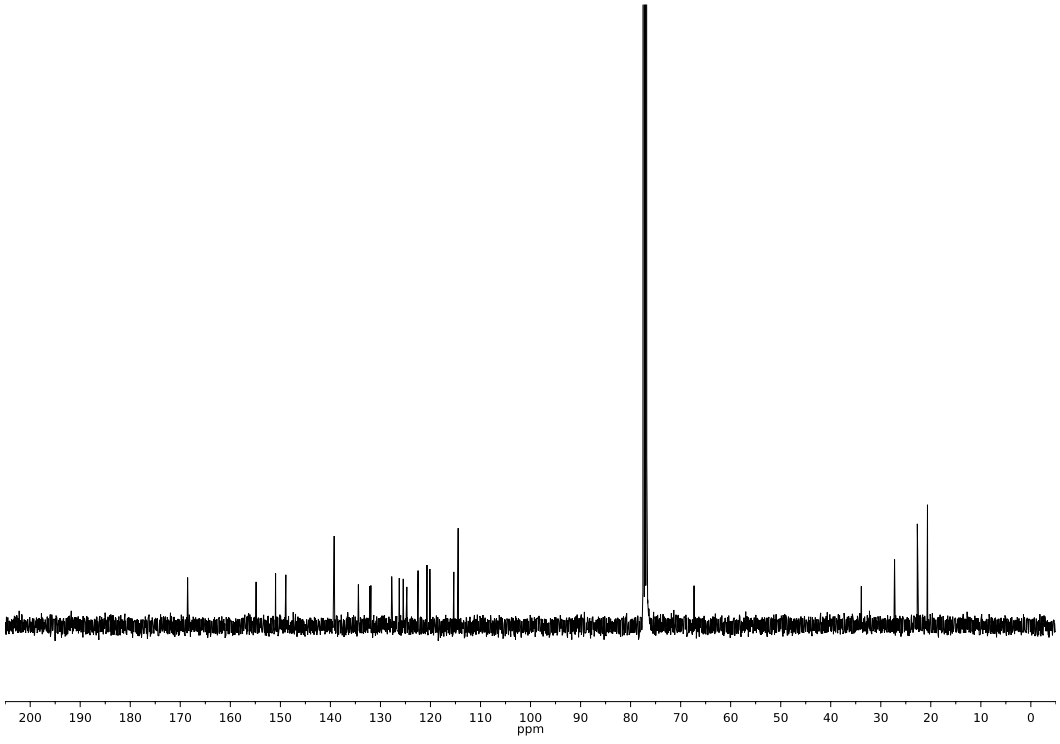
^{13}C NMR of Compound 20 (101 MHz, Chloroform-*d*)



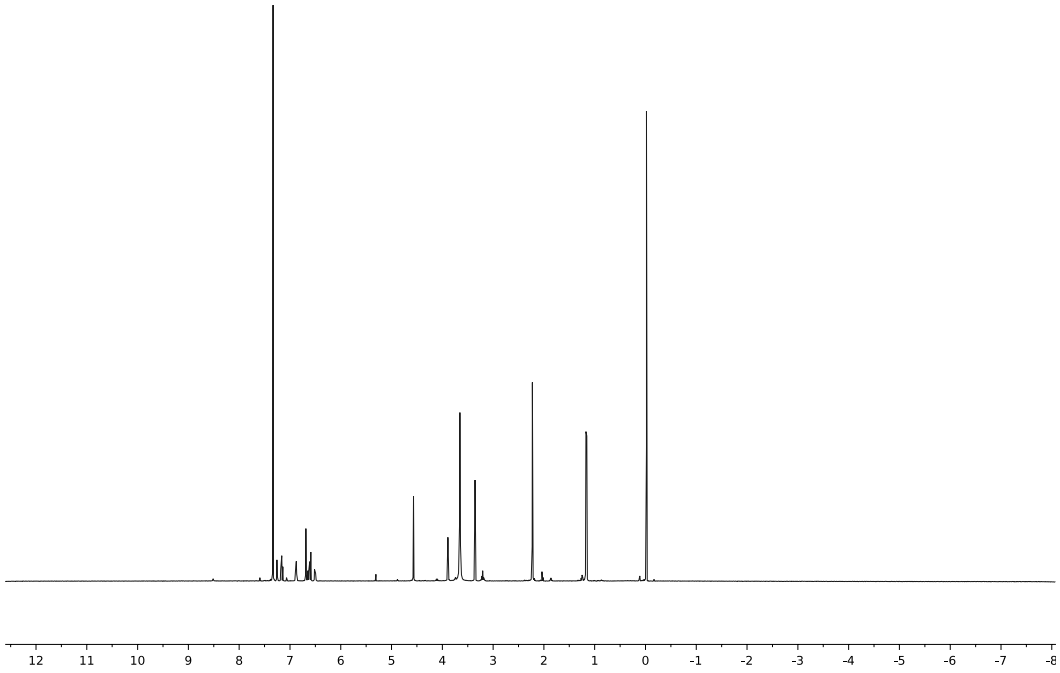
^{1}H NMR of Compound 21 (400 MHz, Chloroform-*d*)



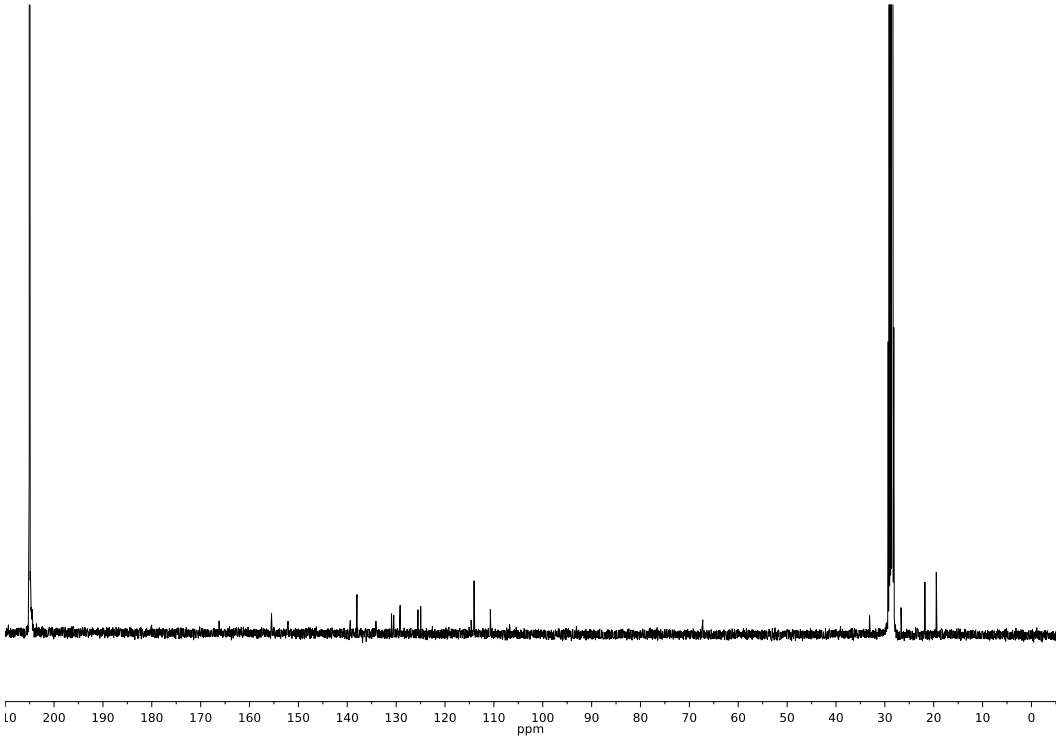
^{13}C NMR of Compound 21 (101 MHz, Acetone-d_6)



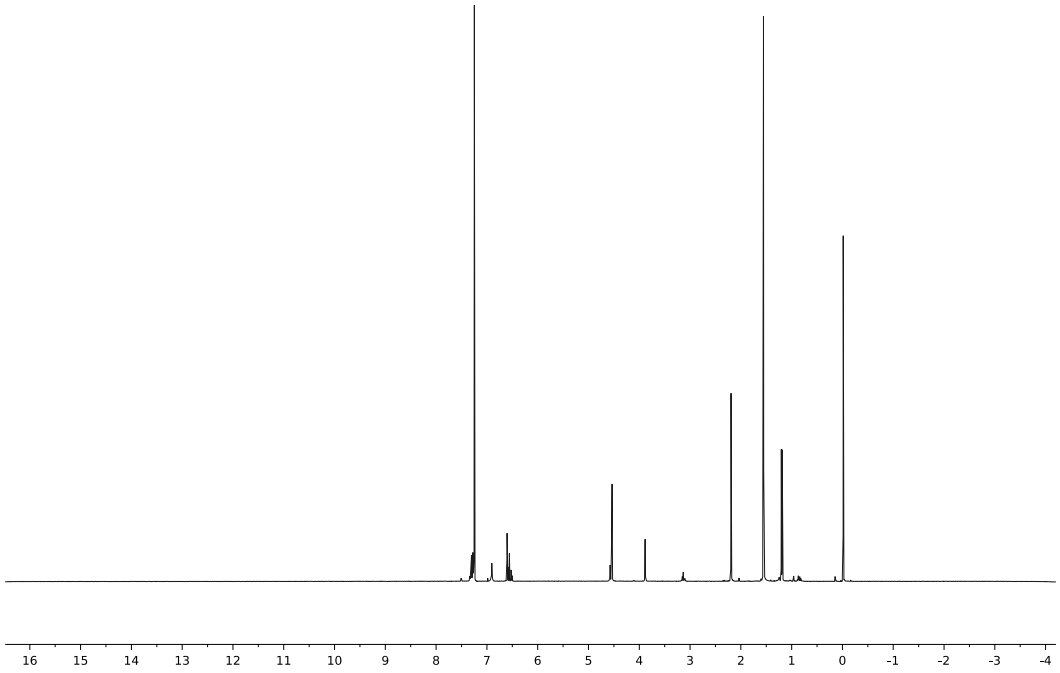
^{1}H NMR of Compound 22 (400 MHz, Chloroform-*d*)



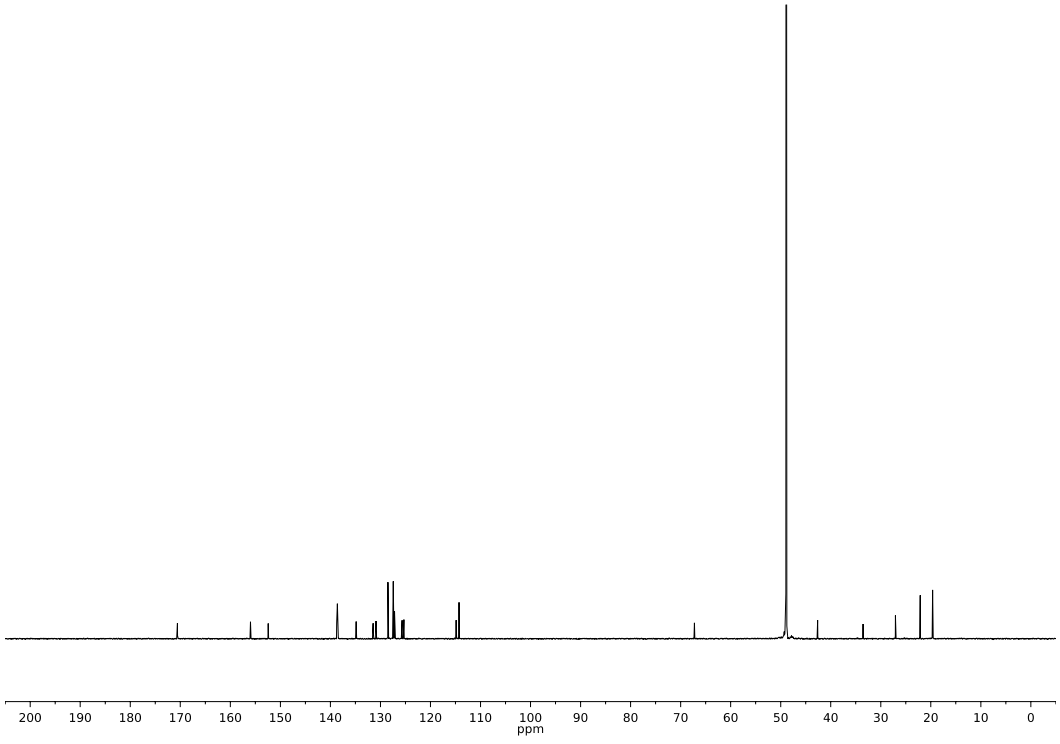
^{13}C NMR of Compound 22 (101 MHz, Chloroform-*d*)



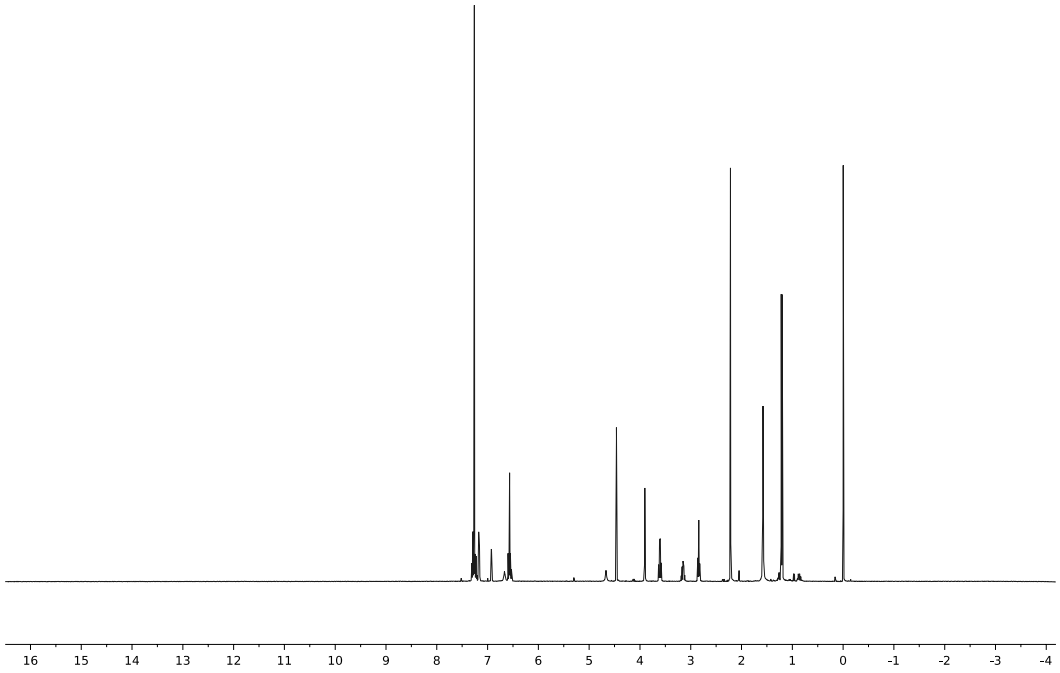
^{1}H NMR of Compound 23 (400 MHz, Chloroform-*d*)



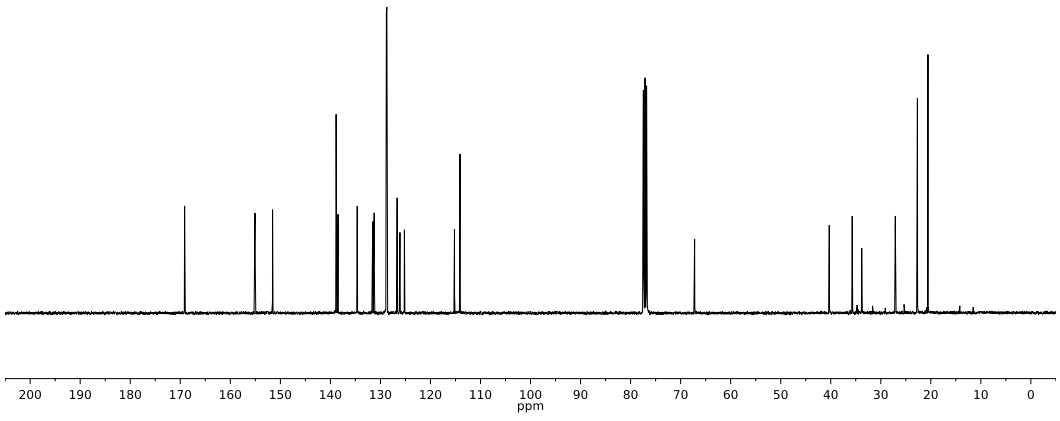
^{13}C NMR of Compound 23 (101 MHz, Methanol-d_4)



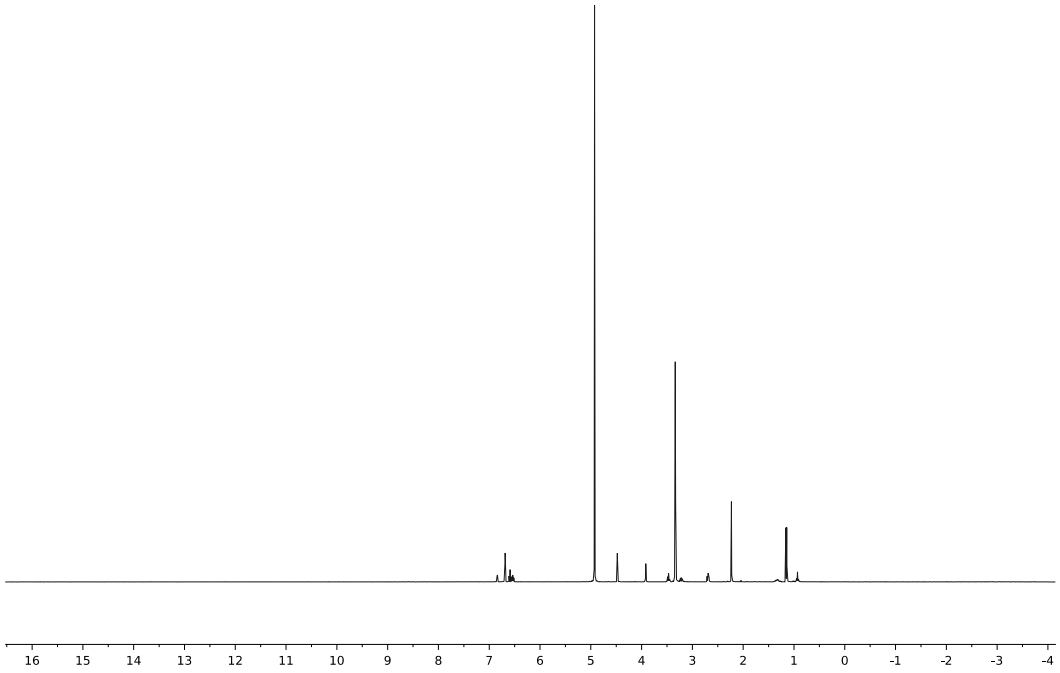
^{1}H NMR of Compound 24 (400 MHz, Chloroform-*d*)



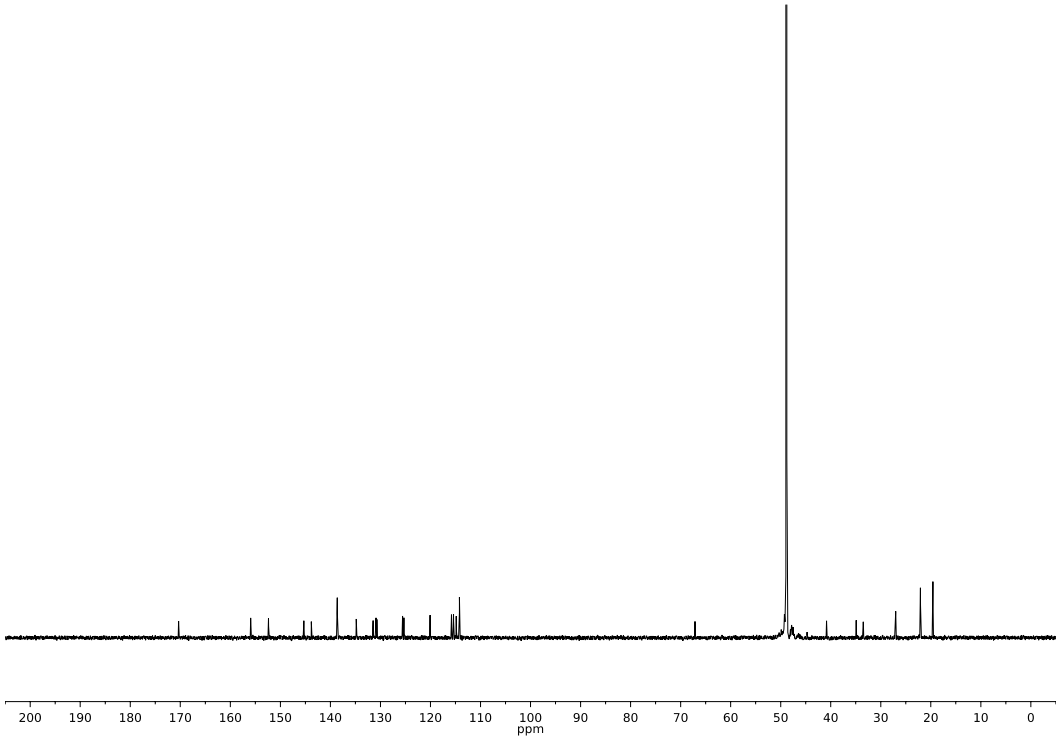
^{13}C NMR of Compound 24 (101 MHz, Chloroform-*d*)



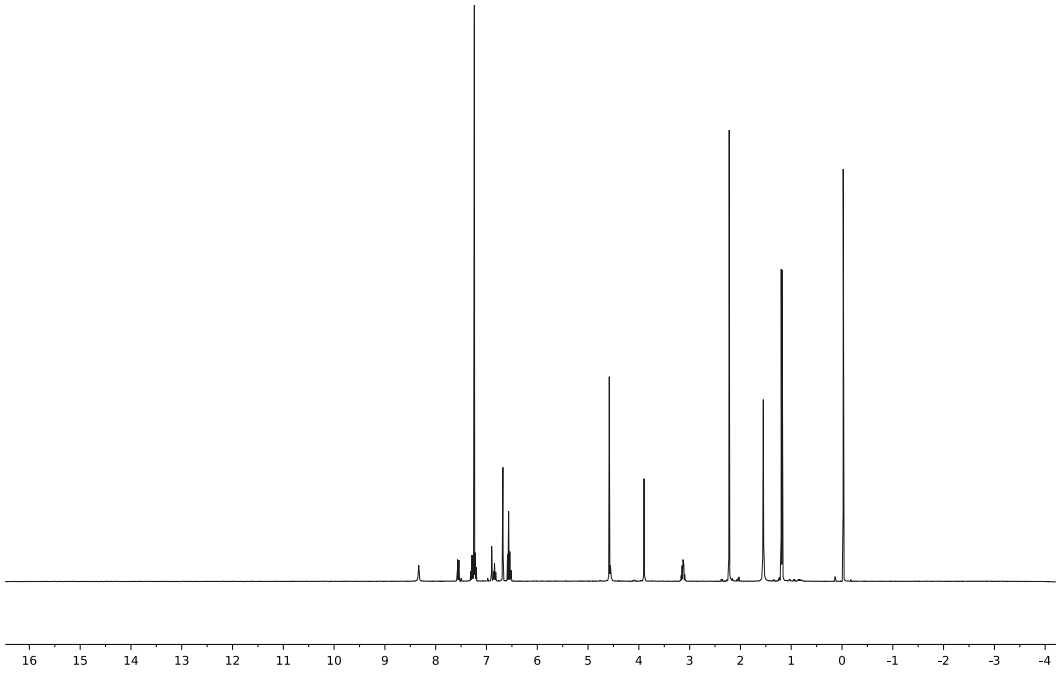
^{1}H NMR of Compound 25 (400 MHz, Chloroform-*d*)



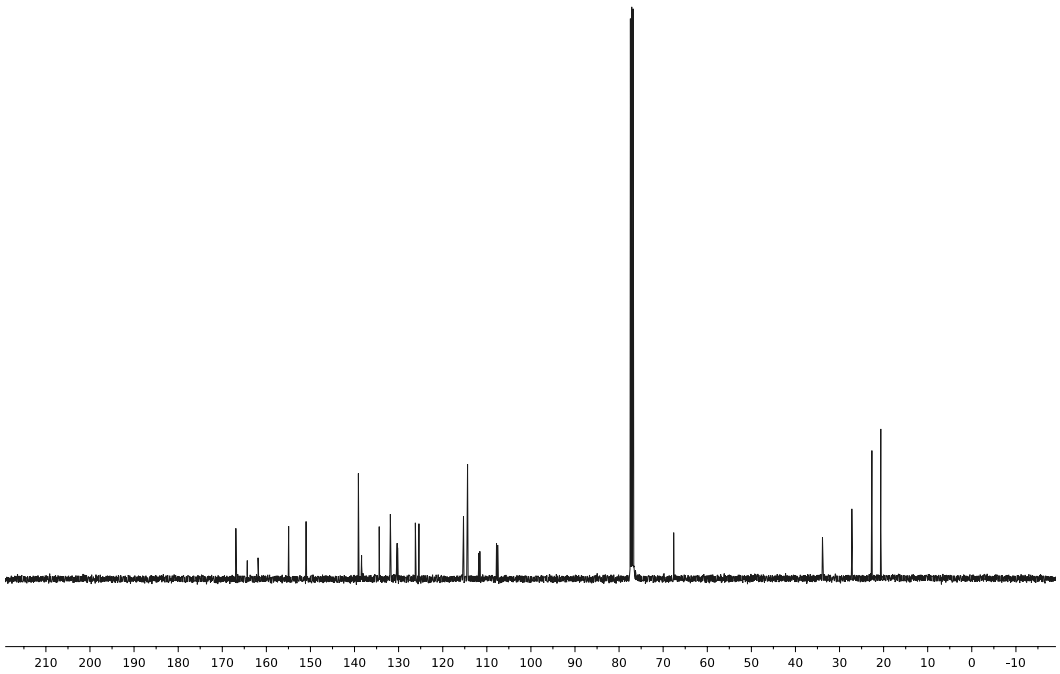
^{13}C NMR of Compound 25 (101 MHz, Methanol-d_4)



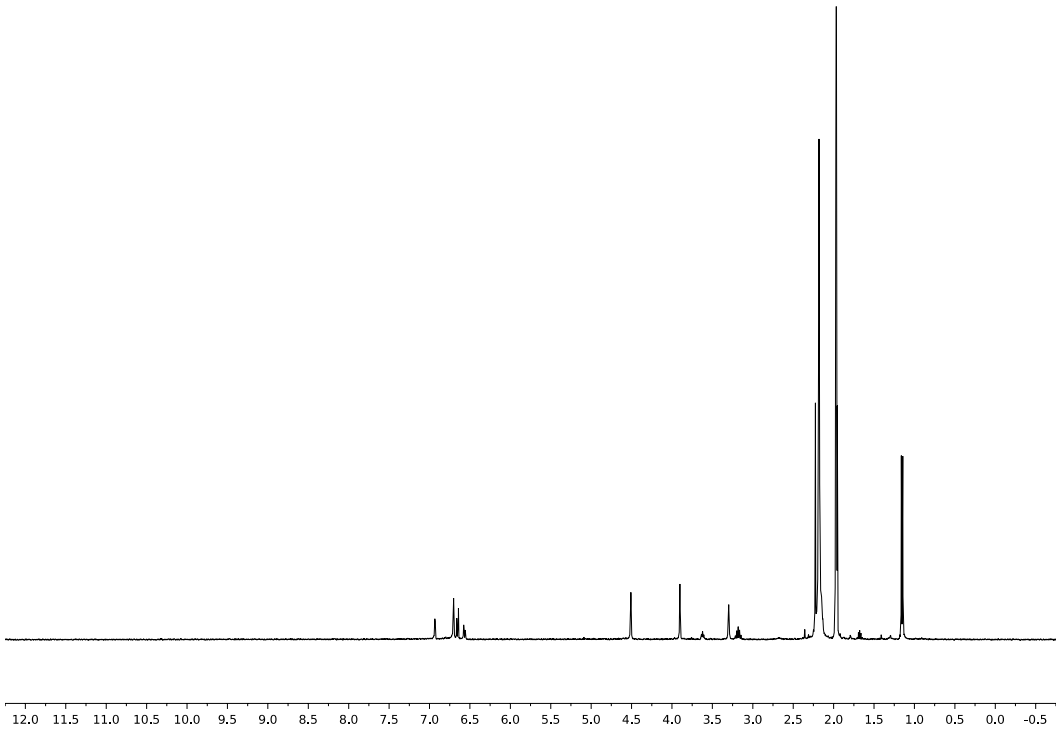
^{1}H NMR of Compound 26 (400 MHz, Chloroform-*d*)



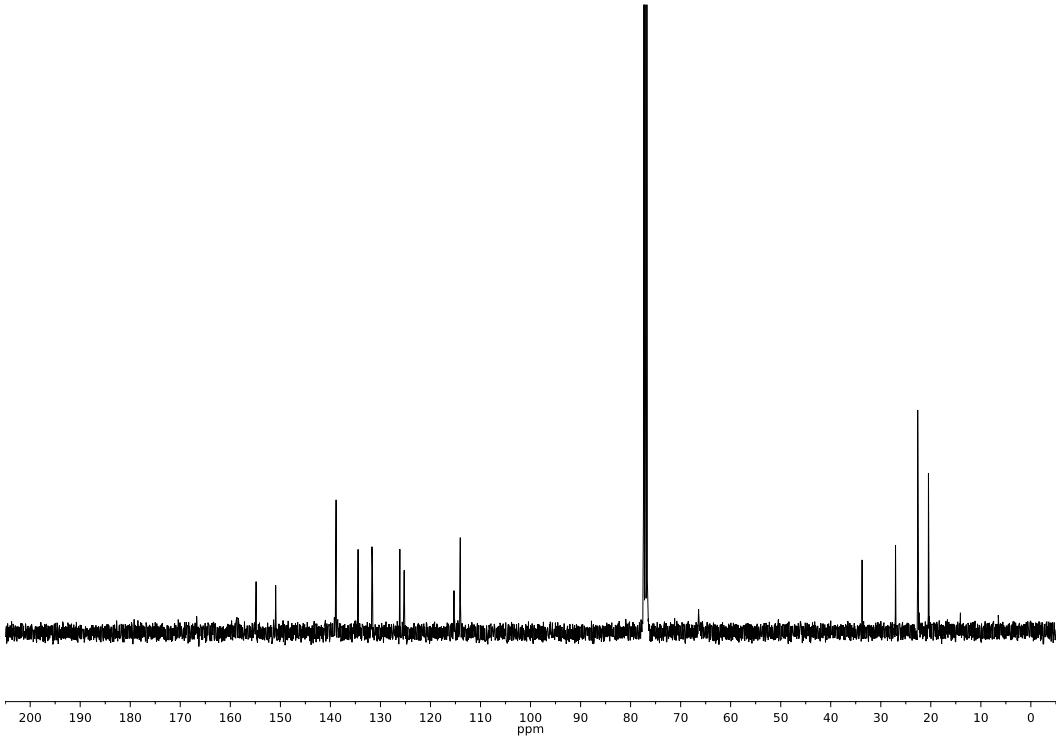
^{13}C NMR of Compound 26 (101 MHz, Chloroform-*d*)



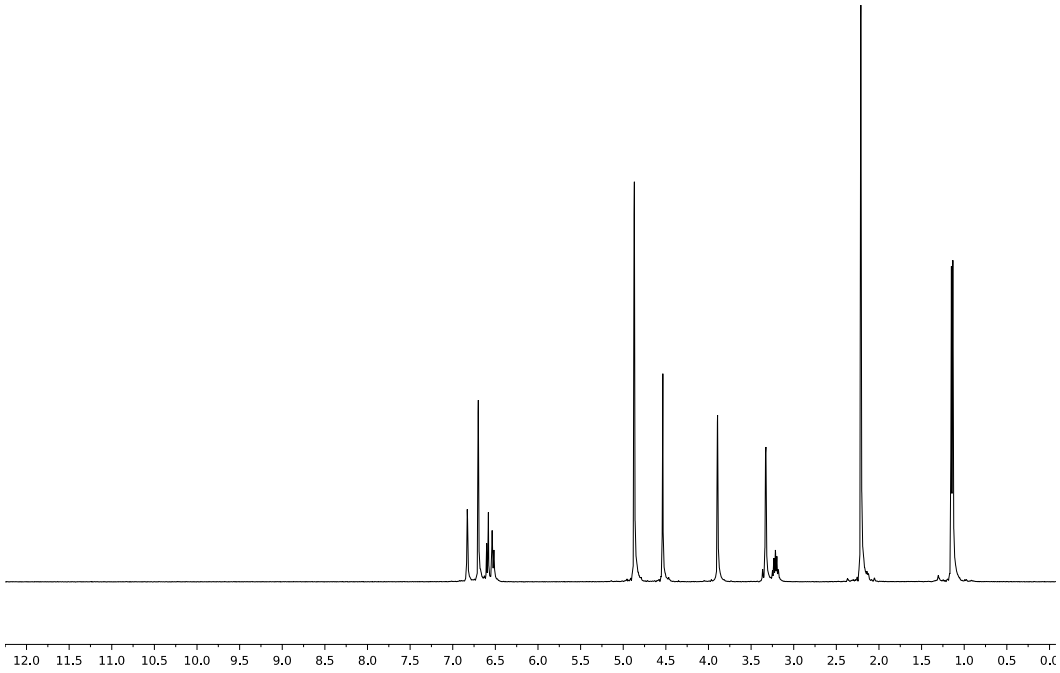
^{1}H NMR of Compound 27 (400 MHz, Chloroform-*d*)



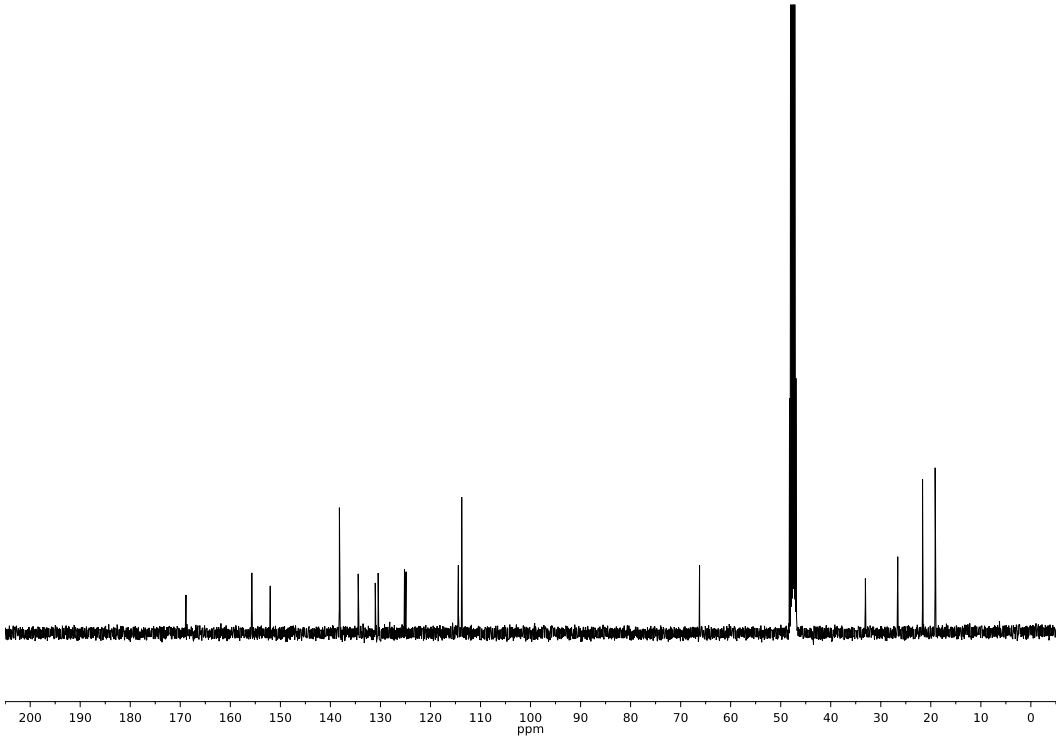
^{13}C NMR of Compound 27 (101 MHz, Chloroform-*d*)



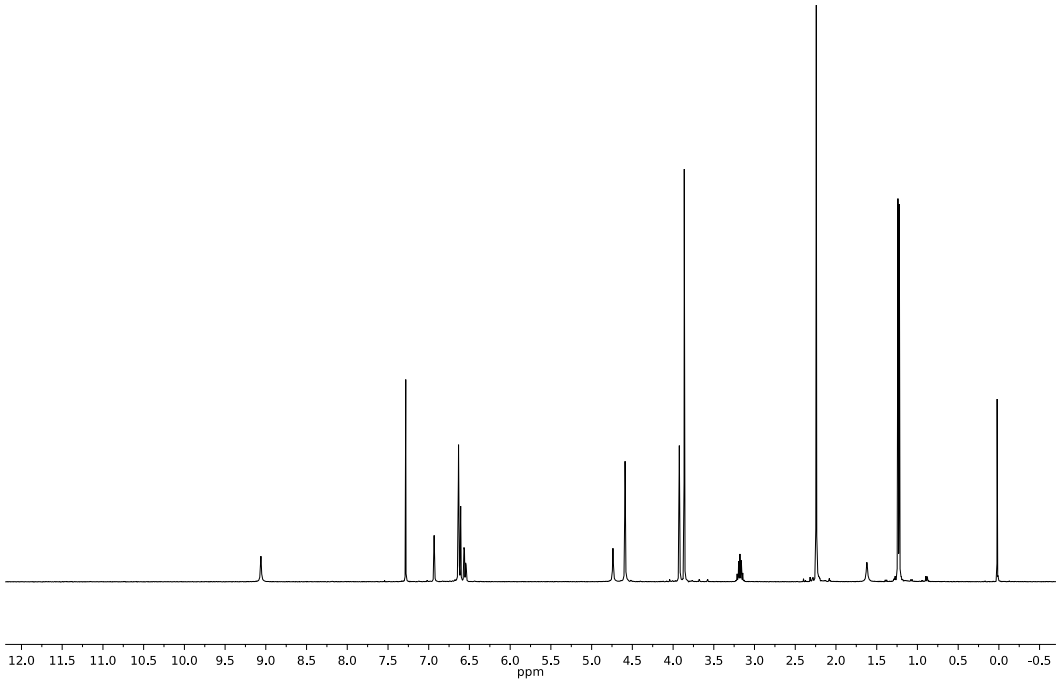
^{1}H NMR of Compound 28 (400 MHz, Methanol-d_4)



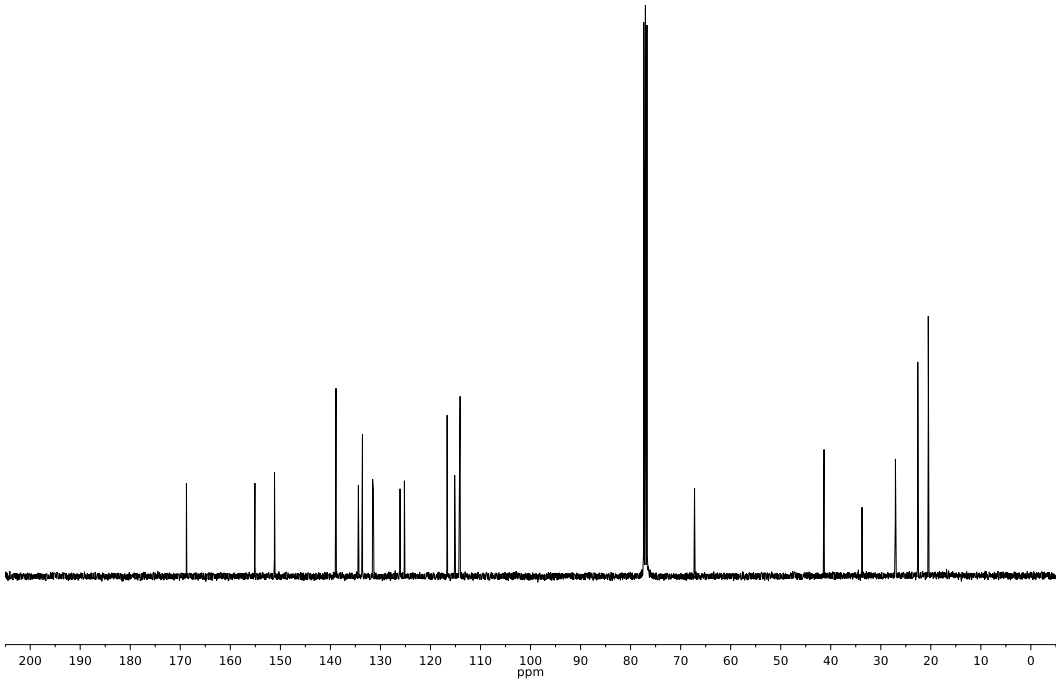
^{13}C NMR of Compound 28 (101 MHz, Methanol-d_4)



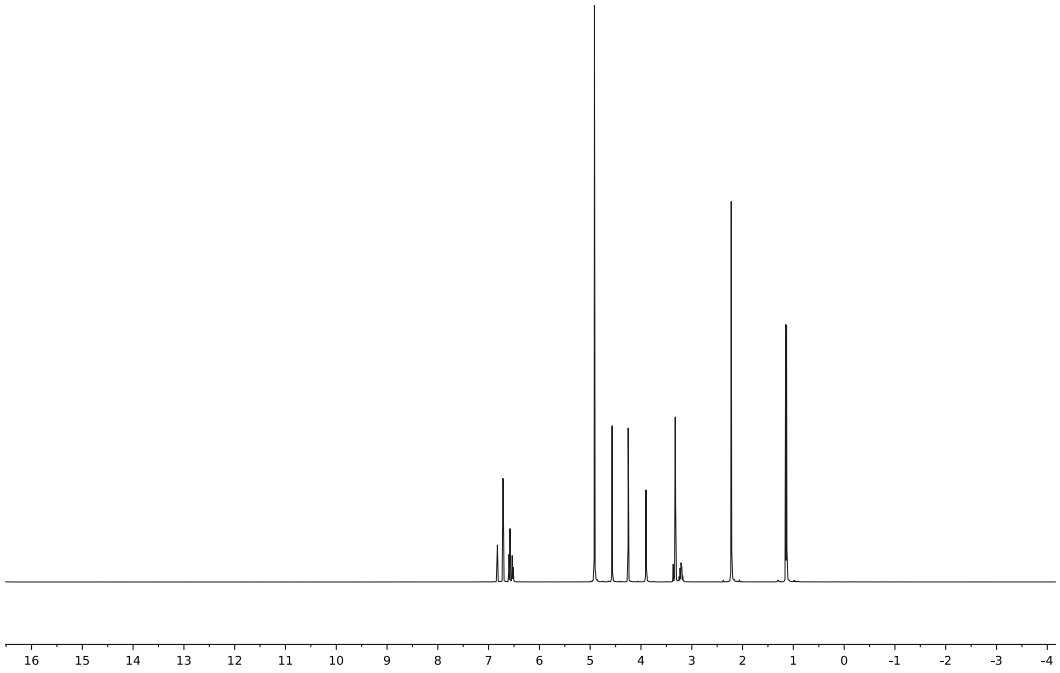
^{1}H NMR of Compound 29 (400 MHz, Chloroform-*d*)



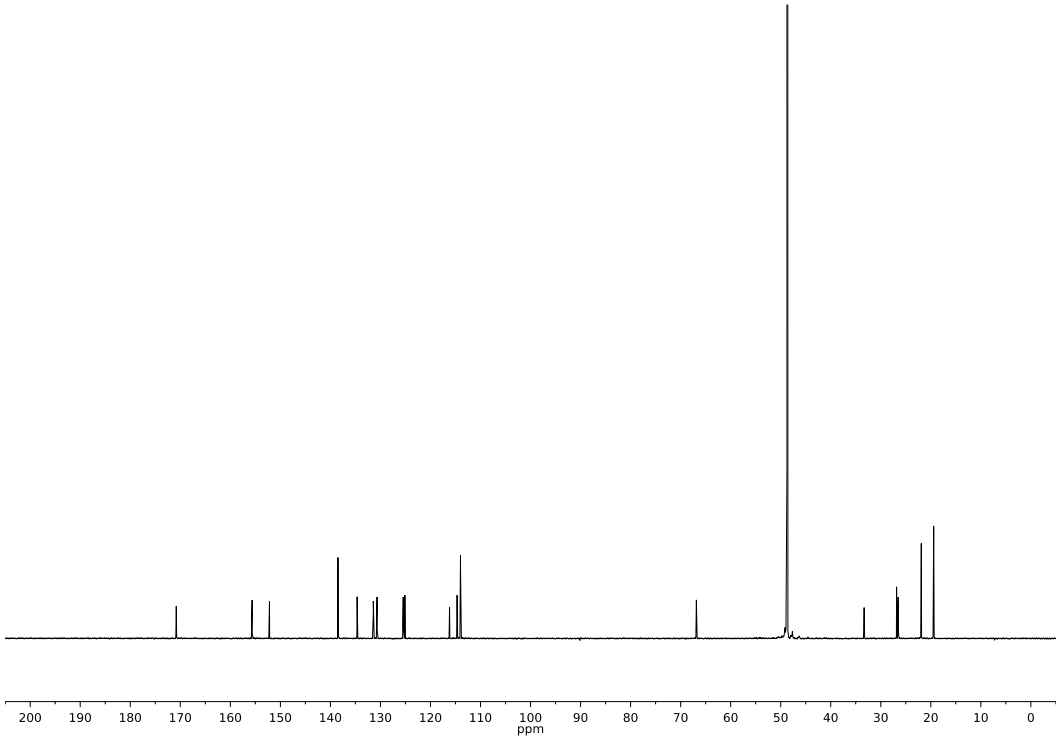
^{13}C NMR of Compound 29 (101 MHz, Chloroform-*d*)



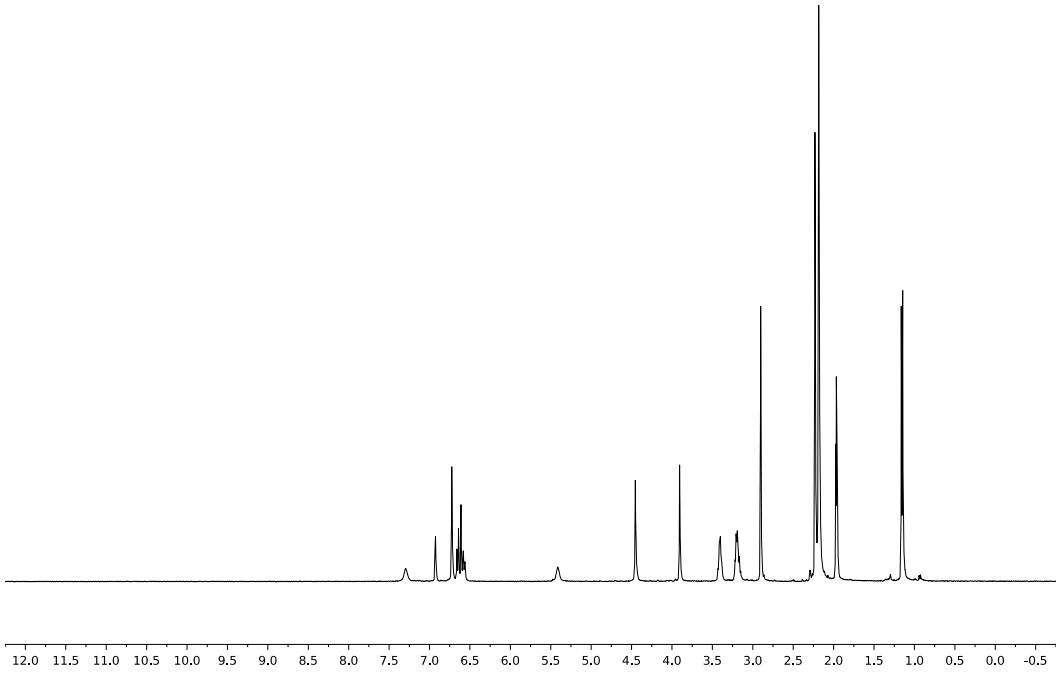
^{1}H NMR of Compound 30 (400 MHz, Methanol-d_4)



^{13}C NMR of Compound 30 (101 MHz, Methanol-d_4)



^{1}H NMR of Compound 28 (400 MHz, Acetonitrile-d_4)



^{13}C NMR of Compound 28 (101 MHz, Acetonitrile-d_4)