ELETTRONIC SUPPLEMENTARY INFORMATION

Si-Gly-CD-PdNPs as Hybrid Heterogeneous Catalyst for Environmentally Friendly Continuous Flow Sonogashira Cross-Coupling

*Francesco Ferlin,[a†] Daniele Sciosci,[a†] Federica Valentini,[a] Janet Menzio,[b] Giancarlo Cravotto,[b] Katia Martina,[b] Luigi Vaccaro *[a]*

[a] Laboratory of Green S.O.C. – Dipartimento di Chimica, biologia e Biotecnologie, Università degli Studi di Perugia, Via Elce di Sotto 8, 06123 – Perugia – Italy;

E-mail: luigi.vaccaro@unipg.it; web: http://greensoc.chm.unipg.it/.

[b] Dipartimento di Scienza e Tecnologia del Farmaco, University of Turin, Via P. Giuria 9, 10125, Turin, Italy.

[†] These authors contributed equally

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1. General Remarks

Unless otherwise stated, all chemicals were purchased and used without any further purification. GLC analyses were performed by using Hewlett-Packard HP 5890 SERIES II equipped with a capillary column DB-5MS (30 m, 0.32 mm), a FID detector, and helium as gas carrier. GC-EIMS analyses were carried out by using a Hewlett-Packard HP 6890N Network GC system/5975 mass selective detector equipped with an electron impact ionizer at 70 eV, or a GC Agilent 6890 (Agilent Technologies, Santa Clara, CA, USA) that was fitted with a mass detector Agilent Network 5973, using a 30 m capillary column, i.d. of 0.25 mm and film thickness 0.25 μm. GC conditions were: injection split 1:10, injector temperature 250 °C, detector temperature 280 °C. Gas carrier: helium (1.2 mL/min), temperature program: from 50 °C (5 min) to 100 °C (1 min) at 10 °C/min, to 230 °C (1 min) at 20 °C/min, to 300 °C (5 min) at 20 °C/min. Elemental Analysis (EA) were conducted on Elementar UNICUBE® elemental analyzer. Melting points were measured on a Büchi 510 apparatus. NMR spectra were recorded on a Bruker DRX-ADVANCE 400 MHz (^{1}H at 400 MHz, ^{13}C at 100.6 MHz and ^{19}F at 376.4 MHz) in $CDCl_3$. Chemical shifts are reported in ppm (δ), coupling constant (J) in hertz and multiplicity are reported as follows: *s* = singlet, *bs* = broad singlet, *d* = doublet, *dd* = double doublet, *td* = double triplet, *t* = triplet, *m* = multiplet. Metal loading was measured using MP-AES 4210 instrument. SIPERNAT 320 amorphous silica was supplied by Evonik Degussa. β-CD was provided by Wacker Chemie (München, Germany) and the synthesis of 6I-O-amino-β-CD was performed following published synthetic procedure.[1] When reactions were carried out in a combined system MW/US, the device has been designed in our laboratory by inserting a sonic horn made of pirex inside a RotoShynth (Milestone) microwave chamber. Thermogravimetric analyses were performed using a thermogravimetric analyzer TGA 4000 (PerkinElmer) at 10 °C min−1 operating with alumina crucibles that contained 10−20 mg of sample. The analyses were performed under an nitrogen atmosphere at a starting temperature of 50 °C and an end temperature of 800 °C. Fourier transform infrared spectra (FTIR) were recorded on a Bruker IFS28 equipped with a MCT detector, working at a resolution of 4 cm-1 over 64 scans. Samples were in the form of self-supporting pellets which were suitable for infrared transmission experiments and were placed in a quartz cell equipped with KBr windows and designed for in situ activation and measurements. The samples were outgassed at room temperature before measurements to remove physically adsorbed water and impurities.

Characterization data, ^{1}H, ^{13}C and ^{19}F NMR spectra are reported below.

2. General procedures

Preparation of Chlorinate Silica

To 1 g of silica SIPERNAT 320, 10.5 mL of thionyl chloride were added dropwise. The mixture was left refluxed 16 h, cooled and filtered. The powder was washed with chloroform and dried under a vacuum.

Si-Cl Titration was performed as previously described.[2]

Preparation of Si-NH-CD

To 163 mg of 6I-amino-6I-deoxy-β-CD (0.14 mmol) dissolved in 2 mL of water, 100 mg of Si-Cl and 0.332 mL of pyridine were added. The mixture was conventionally stirred at 60 °C for 12 h. In alternative the mixture was sonicated in a US bath reactor (80 kHz, 200 W) for 2 h. Si-NH-CD was filtered, washed with water, methanol, and chloroform, and dried under a vacuum at room temperature for 12 h.

Preparation of Si-Gly

To a solution of 40 µL of (3-Glycidyloxypropyl)trimethoxysilane in 1 mL toluene, 100 mg of silica SIPERNAT 320 was added. The reaction was heated at 80 °C under stirring for 5 h. In alternative it was heated in MW reactor (80 °C for 1 h) or irradiated in US bath for 2 hrs (power 200 W, frequency 80 kHz). Si-Gly was filtered, washed with toluene and chloroform, and dried under vacuum at r.t.

Preparation of Si-Gly-CD

1 g of 6I amino-6I-deoxy-β-CD (0.88 mmol) dissolved in DMF (15 mL) were reacted with 1g of Si-Gly. The suspension was heated in presence of LiBr at 80°C for 16 hrs. In alternative irradiated under combined MW/US at 100 °C for 4 h (average MW power 20 W, average US power 35 W). Si-Gly-CD was cooled, filtered, washed with water, methanol and chloroform, and dried under vacuum at r. t.

IR spectrum of Si-Gly-CD support.

Preparation of Si-Gly-Und

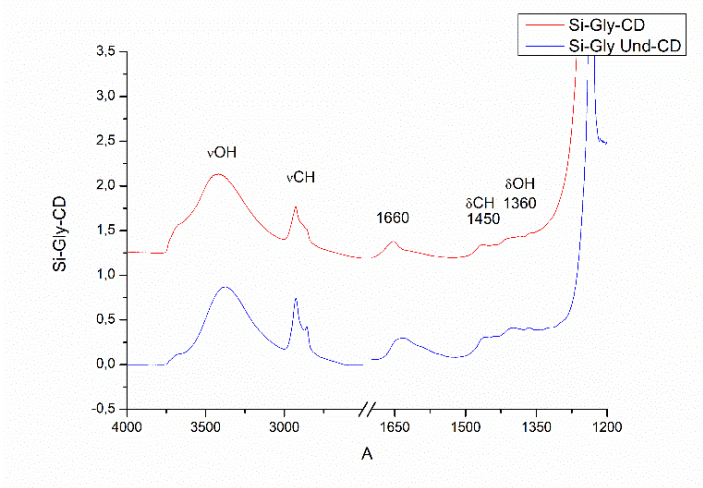
10-undecynil-1-amine (0.275 g, 1.64 mmol) were dissolved in DMF (3 mL) and 1g of Si- Gly (1 g) was added. The solution was heated to 80 °C and stirred for 24 h. The obtained Si-Gly-Und was filtered, washed with DMF, water and toluene and dried under vacuum. In alternative the procedure can be heated under MW irradiation at 100 °C for 2 h. After cooling to r.t., the modified silica was dried under vacuum.

Preparation of Si-Gly-Und-CD

1.95 g of 6-monoazido-β-CD (1.68 mmol), 100 mg of $CuSO_4 \cdot 4H_2O$ (0.4 mmol) and 148 mg of ascorbic acid (0.84 mmol) were dissolved in 30 mL of H_2O. The reaction was heated at 80°C o.n. or

in alternative in MW oven at 80 °C for 2 h. Si-Gly-Und-CD was filtered, washed with water and dried under high vacuum. Being copper salts trapped in CD cavity, the silica was purified via the addition of Na_2H_2EDTA (3.14 g,) dissolved in 5 mL of H_2O and left shaking o.n. under magnetic stirring. The silica was then filtered, washed with water and dried under high vacuum.

IR spectrum of Si-Gly-CD support.



Procedure for Characterization of hybrid organic inorganic silica supports

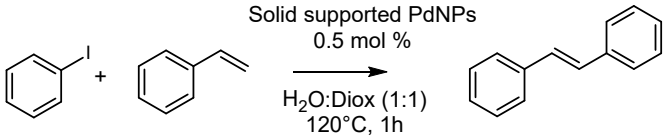
Sorption Experiments: Phenolphthalein

A buffer solution in 250 mL of ultrapure water (pH = 10.5) was prepared from 13.2 g Na_2CO_3 and 2.1 g $NaHCO_3$. Phenolphthalein (Php) powder was dissolved in ethanol to obtain a 5 mM Php stock solution and β-CD powder was dissolved in ultrapure water to obtain a 0.88 mM β-CD stock solution. The Php stock solution was diluted in the buffer solution to achieve a constant Php concentration of 0.008 mM and mixed with the β-CD stock solution to achieve β-CD concentrations of 0, 7.9, 9.6, 11.3, 13, 14.7, 16.4, 18.1 mmol l^{-1}. The absorbance of the CD calibration solutions was measured at a wavelength of 553 nm at room temperature. Si-CD hydrid supports (5 mg) were dispersed in a Php solution in buffer (0.008 mM, 5 mL). The mixture was stirred for 15 min at room temperature and filtered (0.45 µm cellulose acetate membrane filters, CPS Analitica, Italy). UV absorbance was recorded at 553 nm.

Loading of PdNPs:

Derivatized silica (0.2 g) was suspended in 4 mL of EtOH and Pd(OAc)2 (19.7 mg, 0.088 mmol) was added. The reaction was heated under reflux (80 °C) for 2 hours, silica assumed black color and was recovered by filtration and washed with EtOH.

Procedure for preliminary test of supportedPd NPs in Heck-Mizoroki reaction:



Iodobenzene (0.16 mmol), styrene (0.2 mmol) and K_2CO_3 (0.32 mmol) were dissolved in a solution of H2O: 1,4-Dioxane (1:1) and 0.5 mol% of solid supported PdNPs were added. The reaction was heated for 30 min under MW irradiation at 120 °C. The crude was filtered and washed with DCM. The desired product was extracted with DCM and injected in GC and GC-MS.

Catalyst	Conversion	Yield
Pd/Si-Gly-Und CD	>99	>99
Pd/Si-Gly-CD	>99	>99
Pd/Si-NH-CD	82	82

General procedure for screening of reaction media (Table 3)

A 2 mL screw capped vial, equipped with a magnetic stirrer, was charged with the aryl iodide (1 mmol), the terminal alkyne (1.5 equiv), DABCO (1.2 equiv), the catalyst **Si-Gly-CD-PdNPs** (1.8 wt%, 5 mol%), and 1 mL of solvent (1 M). The reaction mixture was then stirred at 85° for 16 h. The conversion was determined by GLC analysis.

General procedure for optimized conditions in batch

A 2 mL screw capped vial, equipped with a magnetic stirrer, was charged with the aryl iodide (1 mmol), the terminal alkyne (1.5 equiv), DABCO (1.2 equiv), the catalyst **Si-Gly-CD-PdNPs** (1.8 wt%, 5 mol%), and 1 mL of CPME/water azeotropic mixture 84/16 w/w (1 M). The reaction mixture was then stirred at 85° for 16 h. After reaction completion, the catalyst was separated through filtration and washed three times with 1 mL of CPME/water azeotrope, the CPME fraction was separated and after evaporation of the solvent and filtration over silica plug (eluting with heptane) the pure product was recovered.

General procedure for catalyst recycle in batch

A 2 mL screw capped vial, equipped with a magnetic stirrer, was charged with the aryl iodide (1 mmol), the terminal alkyne (1.5 equiv), DABCO (1.2 equiv), the catalyst **Si-Gly-CD-PdNPs** (1.8 wt%, 5 mol%), and 1 mL of CPME/water azeotropic mixture 84/16 w/w (1 M). The reaction mixture was then stirred at 85° for 16 h. After reaction completion, the catalyst was separated through filtration and washed three times with 1 mL of CPME/water azeotrope. The catalyst was then dried at 110 °C for 6h and reused for the subsequent reaction.

General procedure for leaching determination

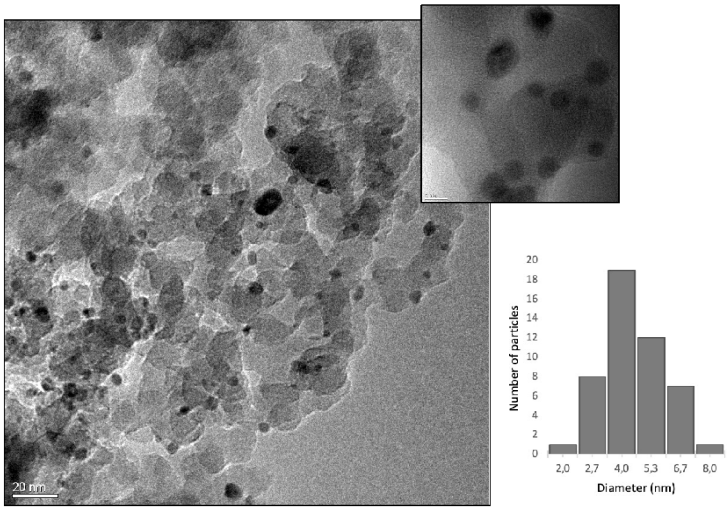
After reaction completion, the catalyst was separated through filtration and washed three times with 1 mL of CPME/water azeotrope. The reaction mixture was dried under vacuum, dissolved in 2 mL of aqua regia, and stirred for 1h at room temperature. The reaction mixture was transferred in a 10 mL graduated flask and Milli-Q water was added to reach the final volume. If present, residual solid was filtered off and the sample was analysed by MP-AES 4210 instrument.

General procedure for the continuous flow Sonogashira reaction

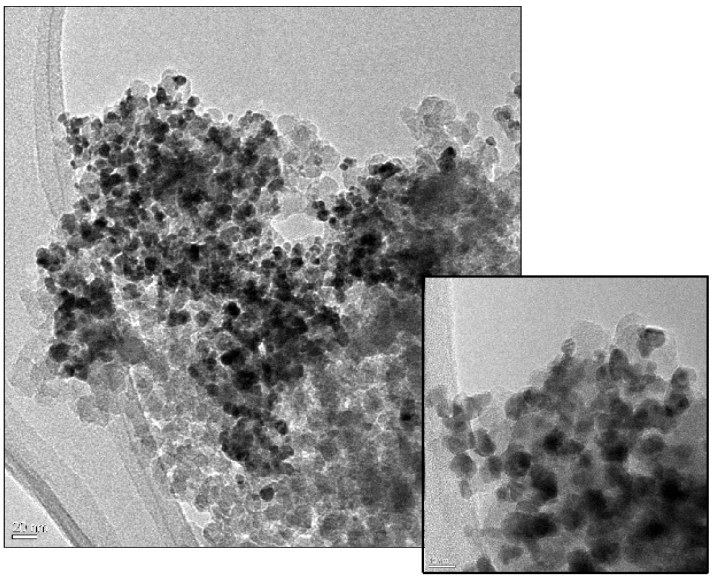
The continuous flow Sonogashira coupling was performed using two Shimadzu LC-20AD HPLC pump and a stainless-steel column (5 cm, ID: 3 mm) fitted with HPLC peek connections. The reactor column was packed with 350 mg of **Si-Gly-CD-PdNPs** (1.8 % wt) dispersed in 30 mg of quartz powder (0.2-0.8 mm particle size). The Channel A was charged with the iodoarene (1 or 2 mmol) and the acetylenic compound (1.5 or 3 mmol), in 2 or 4 mL of CPME (0.5 M and 0.75 M respectively for iodoarene and acetylenic compound). The Channel B was charged with 3.25 M solution of DABCO. The two channels were connected with a T-mixer and the flow directly inserted into the reactor column thermostated at 85 °C. The flow rate for Channel A was set at 0.084 mL min^{-1}, and the Channel B was set at 0.016 mL min^{-1}. An in-line sample collector was installed at the output of the reactor column to take the sample for the leaching analysis (MP-AES). The organic phase was separated at the end of the catalyst column using a Zaiput liquid/liquid separator. The water phase containing DABCO-I is directed to the waste disposal. The organic phase (CPME) containing the products and the unreacted acetylenic compounds was directed to a continuous distillation apparatus. The CPME was recovered at 106-108 °C and, after NMR analysis to confirm the purity, was reused continuously. The crude reaction mixture, for each compound, was evaporated to remove the unreacted acetylenic compound and then subjected to silica filtration or simply crystallized to obtain the pure products.

3. TEM images of the fresh and used catalyst

a)



b)



a) freshly prepared catalyst. b) catalyst after usage in the flow system.

3. E-factor Analysis

E-factor was calculated with the general equation:

$$E - factor = \frac{Kg\ of\ waste}{Kg\ of\ product}$$

3.1 E-factor calculation and distribution analysis for literature flow protocols[1]:

S. Voltrova, J. Srogl, **Org. Chem. Front., 2014, 1, 1067-1071:**

Reactant:

Phenylacetylene: 0.102 g
Iodobenzene: 0.061 g

Reaction Solvent:

THF: 8 g
DMA: 0.937 g

Catalyst:

Pd-Cu (consecutive reactor) : not listed

Work-up materials:

Water: 30 g
Hexane: 59.4 g

Product:

Yield 74%: 0.066 g

E-factor: $\{[0.102 + 0.061]_{[reactants]} + [8 + 0.937]_{[solvents]} + [30 + 59.4]_{[work\text{-}up]} - 0.066_{[product]}\} / 0.066 =$ **1491**

Raw E-factor profile

E-kernel	1,319151468
E-excess	0,154636411
E-rxn solvent	135,4090909
E-catalyst	0
E-work-up	1354,545455
E-purification	0
E-aux	1489,95
E-total	1491,428333

L.-M. Tan, Z.-Y. Sem, W.-Y. Chong, X. Liu, Hendra, W. L. Kwan, C.-L. Ken Lee **Org. Lett. 2013, 15, 65-67:**

Reactant:

2,5-dimethylphenylacetylene: 0.026 g
Iodobenzene: 0.051 g

Reaction Solvent:

DMF: 7.52 g
disopropylethylamine: 0.0775 g

Catalyst:

Pd-Cu (consecutive reactor) : not listed

Work-up materials:

Column Chromatography: not listed

Product:

Yield 76%: 0.039 g

E-factor: $\{[0.026 + 0.051]_{[reactants]} + [7.52 + 0.0775]_{[solvents]} - 0.039_{[product]}\} / 0.039 =$ **195**

Raw E-factor profile

E-kernel	1,142202682
E-excess	0,0000
E-rxn solvent	194,8076923
E-catalyst	0
E-work-up	0
E-purification	0
E-aux	194,81
E-total	195,7820513

D. Znidar, C. A. Hone, P. Inglesby, A. Boyd, C. O. Kappe, **Org. Process Res. Dev. 2017, 21, 878–884:**

Reactant:

Propyne: 0.379 g
3,5-dibromopyridine: 1.4 g

Reaction Solvent:

NMP: 15.45 g
Triethylamine: 0.943 g

Catalyst:

$Pd(PPh_3)_4$: 0.21 g
CuI: 0.114 g

Work-up materials:

No quantification provided

Product:

Yield 39%: 0.450 g

E-factor: $\{[0.379 + 1.4]_{[reactants]} + [15.45 + 0.943]_{[solvents]} + [0.21 + 0.114]_{[catalyst]} - 0.450_{[product]}\} / 0.450$ = **40**

Raw E-factor profile

E-kernel	2,637277499
E-excess	0,316055835
E-rxn solvent	36,42888889
E-catalyst	0,72
E-work-up	0
E-purification	0
E-aux	37,15
E-total	40,10222222

***This Work*:**

Reactant:

Phenylacetylene: 0.306 g
Iodobenzene: 0.408 g

Reaction Solvent:

CPME: 1.44 g → (recovered 98% 1.41)
water: 0.320 g
DABCO: 0.269 g

Catalyst:

Pd/β-CD: not listed

Work-up materials:

Heptane: 1.368 g → (recovered 99% 1.35)

Product:

Yield 97%: 0.346 g

E-factor: $\{[0.306 + 0.408]_{[reactants]} + [1.44 + 0.320 + 0.269]_{[solvents]} + [1.368]_{[work\text{-}up]} - 0.346_{[product]} - 1.41_{[CPME\ recovered]} - 1.35_{[heptane\ recovered]}\} / 0.346 =$ **2.12**

Raw E-factor profile

E-kernel	0,770810317
E-excess	0,295381848
E-rxn solvent	5,86813047
E-catalyst	0
E-work-up	3,933295928
E-purification	0
E-aux	9,80
E-total	10,86761856

***This Work for compound 3p (Tazarotene intermediate)*:**

E-factor: $\{[0.295 + 0.404]_{[reactants]} + [1.44 + 0.320 + 0.269]_{[solvents]} + [1.368]_{[work\text{-}up]} - 0.408_{[product]} - 1.41_{[CPME\ recovered]} - 1.35_{[heptane\ recovered]}\} / 0.408 =$ **2.27**

4. Benign Index and Safety Hazard Index Analysis

Safety Hazard and Benign index analysis

Solvent	log Kow	HLC	LC50	LD50	**BAP**	**BCP**	**INHTP**	**INGTP**	**Ω** $_{EnvImpact}$
DMF	-0,85	7,39E-08	5,82	2000	0,000263	0,001902	0,01613	53,49606	53,51435
THF	0,46	7,05E-05	180	1650	0,00537	0,018828	0,207601	27,05777	27,28957
DMA	-0,77	1,31E-08	8,81	4263	0,000316	0,002188	0,001585	7,533028	7,537118
NMP	-0,46	3,20E-09	5,1	3914	0,000646	0,003764	0,000588	20,17162	20,17662
CPME	1,59	9,30E-05	21,5	2450	0,072444	0,136019	1,373832	10,93355	12,51584
Reference									
triethylamine	1,45		3,63	730	0,052481	0,106463	8,13702	36,69478	44,99075
DABCO	-0,49			1700	0,000603	0,003571		15,75717	15,76135
diisopropylethylamine	-1,8		2,63	317	2,95E-05	0,000361	11,23094	84,50218	95,73352

Safety Hazard analysis															
Solvent	LD50 mg/k	LC50 g m3	**Risk Phrases**	**CarcinogerQEissen**	**FLP (C)**	**FLP(K)**	**FP**	**OEL (mg/m**	**OEL (mmo**	**CGP**	**CLP**	**OELP**	**RPP**	**Ω** $_{SafetyHazard}$
DMF	2000	5,82	R 61-20/21-36	11,25	57,5	330,65	0,705126	15	0,2	0,089347	0,318	20,35	1,635508	23,09798
THF	1650	180	R 11-19-40-36/37	Group2B	27	-21,2	251,95	0,925382	150	2,08	0,002889	0,385455	1,956731	2,192719	5,463175
DMA	4263	8,81	R 61-20/21		7,5	64	337,15	0,691532	36	0,4	0,059024	0,149191	10,175	1,160703	12,23545
NMP	3914	5,1	R 61-36/37/38		7,5	91	364,15	0,640258	40	0,4	0,101961	0,162494	10,175	1,160703	12,24042
CPME	2450	21,5	R 11-22-36/38		1,5	-1	272,15	0,856697		0,024186	0,259592			1,282233	2,422708
additives															
triethylamine	730	3,63			4,5		262,15	0,889376	8,4	0,083	0,143251	0,871233	49,03614	1,474854	52,41486
DABCO	1700				2		335,15	0,695659	10	0,089	#DIV/0!	0,374118	45,73034	1,332673	48,13279
diisopropylethylamine	317	2,63			3		283,15	0,823415	4,2	0,032	0,197719	2,006309	127,1875	1,403763	131,6187

references	**fractional weight**		**Benign Index**			**Safety Hazard Index**		
			EI	BI	SHZI		SHI	
Org. Lett 2013, 15, 65	0,989	0,0102	0,354616	0,006543	0,645384	0,14765	0,008677	0,85235
Org. Chem. Front. 2014, 1, 1067	0,895	0,105	0,701306	0,022724	0,298694	0,276267	0,072589	0,723733
OPRD 2017, 21, 878	0,942	0,057	0,291655	0,039352	0,708345	0,178338	0,046209	0,821662
This work	0,112	0,887	0,049573	0,494403	0,950427	0,005367	0,844493	0,994633

4.1 Equation for RME, MRP

$$RME = \frac{Mass\ of\ Product}{(Total\ Imput\ Mass - Mass\ of\ recovered\ materials)}$$

$$MRP = \frac{RME \times Stoichiometric\ factor}{\left(\frac{Atom\ economy}{100}\right) - \left(\frac{Yield}{100}\right)}$$

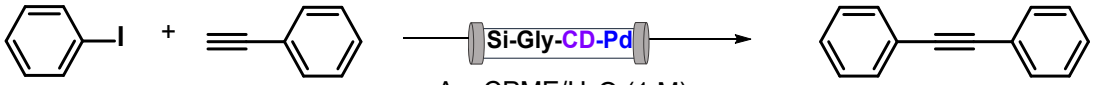
References:

1. F. Trotta, K. Martina, B. Robaldo, A. Barge, G. Cravotto, *J. Incl. Phenom. Macrocycl. Chem*. 2007, **57**, 3–7

2. K. Martina, F. Calsolaro, A. Zuliani, G. Berlier, F. Chavez-Rivas, M. J. Moran, R. Luque, G. Cravotto, *Molecules*, 2019**, 24,** 2490.

5. Charcterization Data

Chem.Name	1,2-diphenylethyne (**3a**)
Lit.Ref	Kozell, V.; McLaughlin, M.; Strappaveccia, G.; Santoro, S.; Bivona, L. A.; Aprile, C.; Gruttadauria, M.; Vaccaro L. *ACS Sustainable Chem. Eng*. 2016, **4,** 7209−7216



1 a **2 a** **3a**

MW: 178.23 g/mol

Method:

The general flow procedure was followed using **1a** (2mmol) and **2a** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3a** in 97% Yield (346 mg)

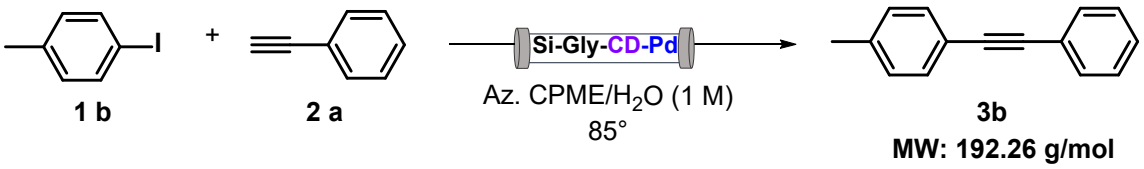
Elemental Analysis: Calc: C, 94.34; H, 5.66. Found: C, 94.32; H, 5.66.

Mol Formula	$C_{14}H_{10}$	**m.p.**	61-63°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.57-7.56	4	*m*	
	7.37-7.36	6	*m*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 131.8, 128.5, 128.4, 123.4, 89.5.

GC-EIMS (m/z, %): 179 (M^++1, 15), 178 (M^+, 100), 177 (11), 176 (20), 152 (13).

Chem.Name	1-methyl-4-(phenylethynyl)benzene (**3b**)
Lit.Ref	Kozell, V.; McLaughlin, M.; Strappaveccia, G.; Santoro, S.; Bivona, L. A.; Aprile, C.; Gruttadauria, M.; Vaccaro L. *ACS Sustainable Chem. Eng*. 2016, **4**, 7209−7216



1 b **2 a** **3b**
MW: 192.26 g/mol

Method:

The general flow procedure was followed using **1b** (2mmol) and **2a** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3b** in 95% Yield (365 mg)

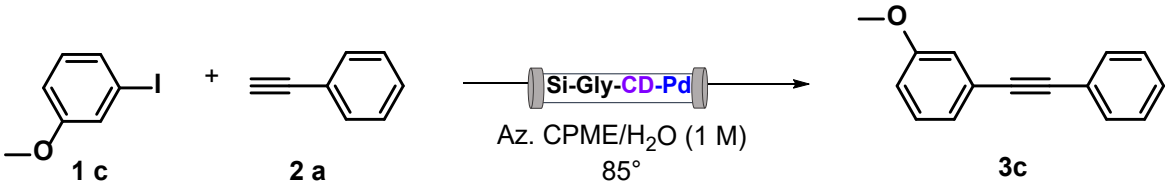
Elemental Analysis: Calc: C, 93.71; H, 6.29. Found: C, 93.71; H, 6.32.

Mol Formula	$C_{15}H_{12}$	**m.p.**	67-70°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.54-7.52	2	*m*	-
	7.43	2	*d*	7.8
	7.35-7.33	3	*m*	-
	7.16	2	*d*	7.8
	2.38	3	*s*	-

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 138.5, 131.7, 131.6, 129.3, 128.5, 128.2, 123.6, 120.3, 89.7, 88.9, 21.7.

GC-EIMS (m/z, %): 193 (M^++1, 16), 192 (M^+1, 100), 191 (50), 189 (23), 165 (14).

Chem.Name	1-methoxy-3-(phenylethynyl)benzene (**3c**)
Lit.Ref	Kozell, V.; McLaughlin, M.; Strappaveccia, G.; Santoro, S.; Bivona, L. A.; Aprile, C.; Gruttadauria, M.; Vaccaro L. *ACS Sustainable Chem. Eng*. 2016, **4**, 7209−7216



MW: 208.26 g/mol

Method:

The general flow procedure was followed using **1c** (2 mmol) and **2a** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3c** in 97% Yield (404 mg)

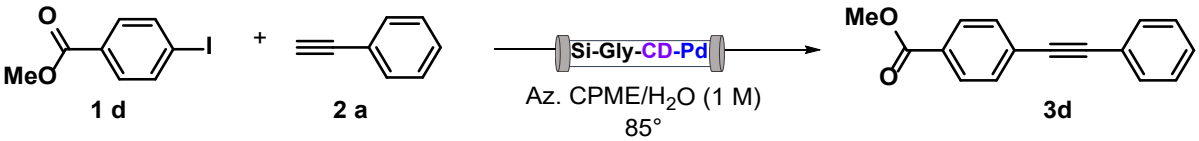
Elemental Analysis: Calc: C, 86.51; H, 5.81. Found: C, 86.49; H, 5.82.

Mol Formula	$C_{15}H_{12}O$	**m.p.**	74-75°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.55-7.53	2	*m*	
	7.35-7.34	3	*m*	
	7.26	1	*t*	7.7
	7.13	1	*d*	7.8
	7.07	1	*s*	
	6.91-6.87	1	*m*	-
	3.83	3	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 159.5, 131.8, 129.6, 128.5, 128.5, 124.4, 124.3, 123.3, 116.5, 115.1, 89.4, 89.3, 55.4.

GC-EIMS (m/z, %): 209 (M^++1, 17), 208 (M^+, 100), 178 (28), 165 (30), 164 (13), 163 (13).

Chem.Name	Methyl 4-(phenylethynyl)benzoate (**3d**)
Lit.Ref	Kozell, V.; McLaughlin, M.; Strappaveccia, G.; Santoro, S.; Bivona, L. A.; Aprile, C.; Gruttadauria, M.; Vaccaro L. *ACS Sustainable Chem. Eng*. 2016, **4**, 7209−7216



MW: 236.27 g/mol

Method:

The general flow procedure was followed using **1d** (1 mmol) and **2a** (1.5 mmol). Evaporation of CPME and filtration over silica plug afforded **3d** in 94% Yield (222 mg)

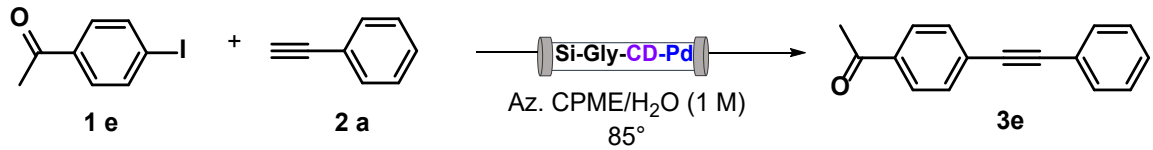
Elemental Analysis: Calc: C, 81.34; H, 5.12. Found: C, 81.33; H, 5.14.

Mol Formula	$C_{16}H_{12}O_2$	**m.p.**	120-121°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	8.02	2	*d*	7.7
	7.59	2	*d*	7.7
	7.56-7.54	2	*m*	
	7.37-7.36	3	*m*	
	3.93	3	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 166.7, 131.9, 131.6, 129.6, 129.6, 128.9, 128.6, 128.1, 122.8, 92.5, 88.8, 52.3.

GC-EIMS (m/z, %): 237 (M^++1, 17), 236 (M^{+1}, 100), 206 (15), 205 (92), 176 (45), 151 (17).

Chem.Name	1-(4-(phenylethynyl)phenyl)ethan-1-one (**3e**)
Lit.Ref	Kozell, V.; McLaughlin, M.; Strappaveccia, G.; Santoro, S.; Bivona, L. A.; Aprile, C.; Gruttadauria, M.; Vaccaro L. *ACS Sustainable Chem. Eng*. 2016, **4**, 7209−7216



1 e **2 a** **3e**

MW: 220.27 g/mol

Method:

The general flow procedure was followed using **1e** (1 mmol) and **2a** (1.5 mmol). Evaporation of CPME and filtration over silica plug afforded **3e** in 96% Yield (211 mg)

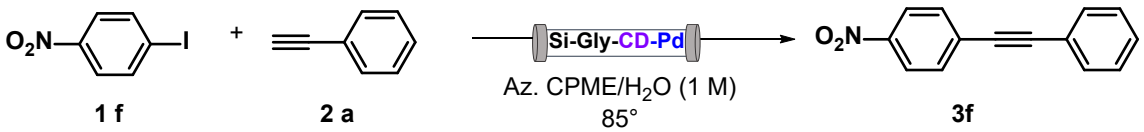
Elemental Analysis: Calc: C, 87.25; H, 5.49. Found: C, 87.24; H, 5.48.

Mol Formula	$C_{16}H_{12}O$	**m.p.**	98-99 °C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.94	2	*d*	7.8
	7.61	2	*d*	7.8
	7.57-7.54	2	*m*	
	7.38-7.36	3	*m*	
	2.62	3	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 197.5, 136.3, 131.9, 131.8, 129.0, 128.6, 128.4, 128.4, 122.8, 92.9, 88.7, 26.8.

GC-EIMS (m/z, %): 221 (M^++1, 11), 220 (M^+, 66), 206 (15), 176 (48), 151 (16).

Chem.Name	1-nitro-4-(phenylethynyl)benzene (**3f**)
Lit.Ref	Kozell, V.; McLaughlin, M.; Strappaveccia, G.; Santoro, S.; Bivona, L. A.; Aprile, C.; Gruttadauria, M.; Vaccaro L. *ACS Sustainable Chem. Eng.* 2016, **4**, 7209−7216



1 f **2 a** **3f**

MW: 223.23 g/mol

Method:

The general flow procedure was followed using **1f** (2mmol) and **2a** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3f** in 98% Yield (438 mg)

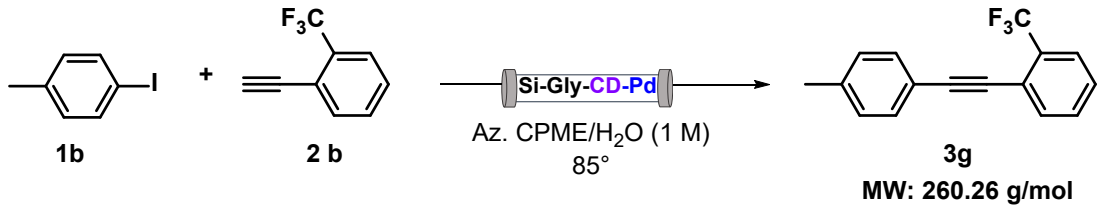
Elemental Analysis: Calc: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.32; H, 4.07; N, 6.26.

Mol Formula	$C_{14}H_9NO_2$	**m.p.**	116-118°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	8.22	2	*d*	7.6
	7.67	2	*d*	7.7
	7.57-7.55	2	*m*	
	7.39-7.40	3	*m*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 147.1, 132.4, 132.0, 130.4, 129.4, 128.7, 123.8, 122.2, 94.9, 87.7.

GC-EIMS (m/z, %): 224 (16), 223 (100), 177 (20), 176 (67), 165 (49), 151 (24), 150 (23).

Chem.Name	1-(p-tolylethynyl)-2-(trifluoromethyl)benzene (**3g**)
Lit.Ref	W. Xu, B. Yu, H. Sun, G. Zhang, W. Zhang, Z. Gao*, Appl. Organometal. Chem.* 2015*,* **29***, 301–304*



1b **2 b** **3g**

MW: 260.26 g/mol

Method:

The general flow procedure was followed using **1b** (2mmol) and **2b** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3g** in 95% Yield (494 mg)

Elemental Analysis: Calc: C, 73.84; H, 4.26. Found: C, 73.82; H, 4.28

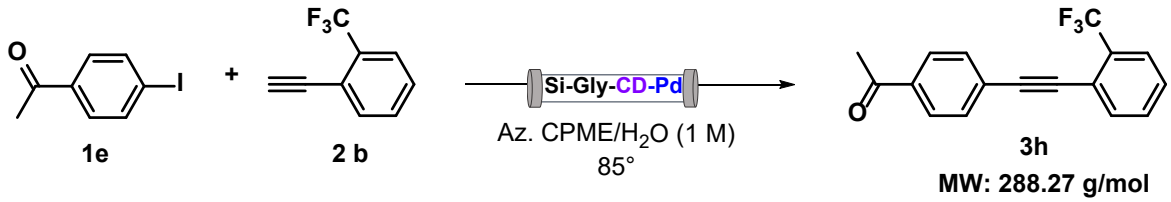
Mol Formula	$C_{16}H_{11}F_3$	**m.p.**	90–92°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.67	2	*t*	7.8
	7.53 – 7.49	1	*m*	-
	7.47 – 7.45	2	*m*	-
	7.42 – 7.38	1	*m*	-
	7.18	2	*d*	7.8
	2.40	3	*s*	-

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 139.22, 133.76, 131.75, 131.53, 131.50, 129.31, 127.84, 125.99, 123.82, 121.93, 119.83, 95.38, 84.94, 21.70.

^{19}F NMR (376 MHz, $CDCl_3$) δ : -62.4

GC-EIMS (m/z, %): 260 (M^+), 239 (24), 238 (17), 220 (15).

Chem.Name	1-(4-((2-(trifluoromethyl)phenyl)ethynyl)phenyl)ethan-1-one (**3h**)
Lit.Ref	*Zhang, G. Synlett* 2005, **4**, 0619–0622



1e **2 b** **3h**

MW: 288.27 g/mol

Method:

The general flow procedure was followed using **1e** (1 mmol) and **2b** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3h** in 93% Yield (268 mg)

Elemental Analysis: Calc: C, 70.83; H, 3.85. Found: C, 70.85; H, 3.86.

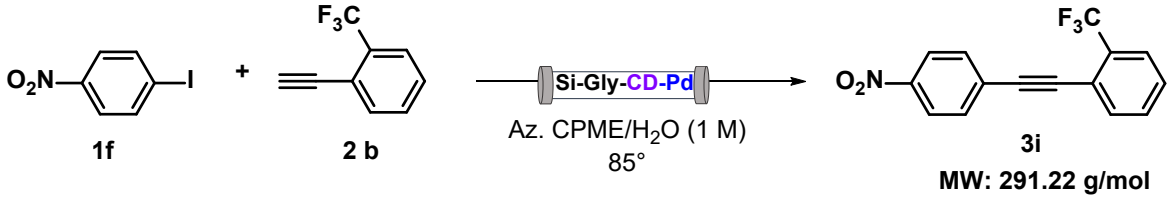
Mol Formula	$C_{16}H_{12}O$	**p.f.**	83–85°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.95	2	*dd*	7.7, 2.1
	7.69	2	*t*	7.5
	7.63 – 7.61	2	*m*	
	7.54	1	*t*	7.7
	7.45	1	*t*	7.8
	2.62	3	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 197.4, 136.8, 134.0, 132.0, 131.6, 128.7, 128.4, 127.7, 126.2 (*q*, $J_{C\text{-}F}$= 5), 125.0, 122.3, 121.1, 94.0, 88.5, 26.8

^{19}F NMR (376 MHz, $CDCl_3$) δ : -62.2

GC-EIMS (m/z, %): 288 (M^+), 273 (36), 245 (18), 225 (15).

Chem.Name	1-((4-nitrophenyl)ethynyl)-2-(trifluoromethyl)benzene (**3i**)
Lit.Ref	S. Mori, T. Yanase, S. Aoyagi, Y. Monguchi, T. Maegawa, H. Sagiki *Chem. Eur. J.* 2008, **14**, *6994 – 6999*



1f **2 b** **3i**

MW: 291.22 g/mol

Method:

The general flow procedure was followed using **1f** (1 mmol) and **2b** (1.5 mmol). Evaporation of CPME and filtration over silica plug afforded **3i** in 97% Yield (282 mg)

Elemental Analysis: Calc: C, 61.86; H, 2.77; N, 4.81. Found: C, 61.87; H, 2.75; N, 4.83.

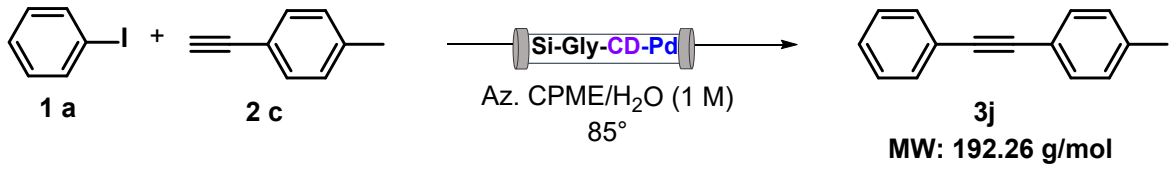
Mol Formula	$C_{15}H_8F_3NO_2$	**m.p.**	105–108°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	8.22	2	*dd*	7.8, 2.1
	7.71 – 7.67	4	*m*	-
	7.57	1	*t*	7.5
	7.49	1	*t*	7.5

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 147.50, 134.08, 132.54, 132.02, 131.73, 129.66, 129.15, 126.27, 123.80, 123.59, 120.43, 92.72, 90.35.

^{19}F NMR (376 MHz, $CDCl_3$) δ : -62.2.

GC-EIMS (m/z, %): 291 (M^+), 261(34), 245 (22), 233 (18), 225 (15).

Chem.Name	1-methyl-4-(phenylethynyl)benzene (**3j**)
Lit.Ref	Kozell, V.; McLaughlin, M.; Strappaveccia, G.; Santoro, S.; Bivona, L. A.; Aprile, C.; Gruttadauria, M.; Vaccaro L. *ACS Sustainable Chem. Eng*. 2016, **4**, 7209−7216



1 a **2 c** **3j**

MW: 192.26 g/mol

Method:

The general flow procedure was followed using **1a** (2mmol) and **2c** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3j** in 90% Yield (346 mg)

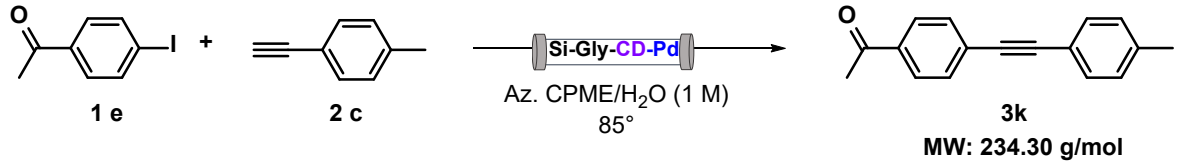
Elemental Analysis: Calc: C, 93.71; H, 6.29. Found: C, 93.73; H, 6.26.

Mol Formula	$C_{15}H_{12}$	**m.p.**	67-70°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.55-7.53	2	*m*	
	7.44	2	*d*	7.6
	7.37-7.34	3	*m*	
	7.16	2	*d*	7.5
	2.38	3	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 138.5, 131.7, 131.6, 129.3, 128.5, 128.2, 123.6, 120.3, 89.7, 88.9, 21.7.

GC-EIMS (m/z, %): 193 (M^++1, 16), 192 (M^+1, 100), 191 (50), 189 (23), 165 (14).

Chem.Name	1-(4-(p-tolylethynyl)phenyl)ethan-1-one (**3k**)
Lit.Ref	Shi, Y.; Li, X.; Liu, J.; Jiang, W.; Sun, L. *Tetrahedron Letters*. 2010, **51**, 28, 3626-3628



1 e **2 c** **3k**

MW: 234.30 g/mol

Method:

The general flow procedure was followed using **1e** (1 mmol) and **2c** (1.5 mmol). Evaporation of CPME and filtration over silica plug afforded **3k** in 92% Yield (216 mg)

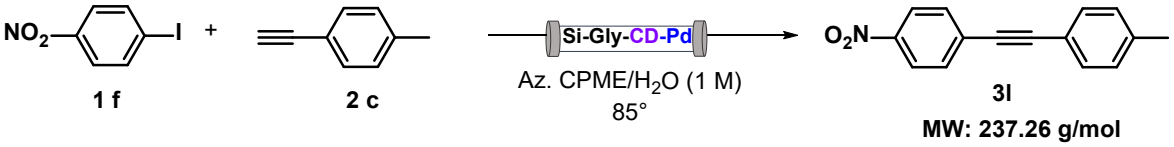
Elemental Analysis: Calc: C, 87.15; H, 6.02. Found: C, 87.17; H, 6.01.

Mol Formula	$C_{17}H_{14}O_2$	**m.p.**	130-132℃	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.93	*2*	*d*	7.5
	7.60	*2*	*d*	7.7
	7.45	*2*	*d*	7.5
	7.18	*2*	*d*	7.6
	2.61	*3*	*s*	
	2.38	*3*	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 197.5, 139.2, 136.2, 131.8, 131.8, 129.4, 128.6, 128.4, 119.7, 93.2, 88.2, 26.8, 21.7.

GC-EIMS (m/z, %): 234 (M^+, 100), 245 (22), 222 (18)

Chem.Name	1-methyl-4-((4-nitrophenyl)ethynyl)benzene (**3l**)
Lit.Ref	Pan, D.; Zhang, C.; Ding, S. N. Jiao, *Eur. J. Org. Chem.* 2011, **25**, 4751-4755



1 f **2 c** **3l**

MW: 237.26 g/mol

Method:

The general flow procedure was followed using **1f** (1 mmol) and **2c** (1.5 mmol). Evaporation of CPME and filtration over silica plug afforded **3l** in 95% Yield (225 mg)

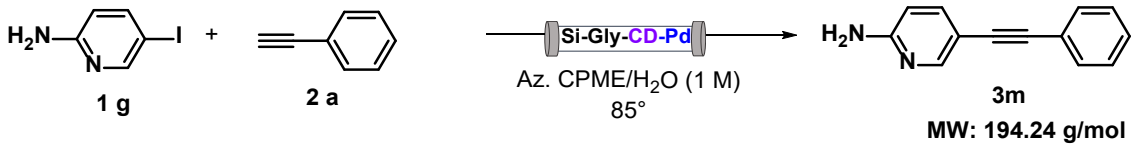
Elemental Analysis: Calc: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.92; H, 4.68; N, 5.91

Mol Formula	$C_{15}H_{11}NO_2$	**m.p.**	220 °C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	8.21	2	*d*	7.5
	7.65	2	*d*	7.5
	7.45	2	*d*	7.5
	7.20	2	*d*	7.5
	2.39	3	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 147.0, 139.8, 132.3, 131.9, 130.7, 129.5, 123.8, 119.2, 95.2, 87.2, 21.8.

GC-EIMS (m/z, %): 237 (M^+, 100), 207 (32), 190 (21), 189 (61).

Chem.Name	5-(phenylethynyl)pyridin-2-amine (**3m**)
Lit.Ref	*Fleckenstein, C. A.; Plenio, H. Green Chem.* 2008, **10**, 563-570



1 g **2 a** **3m**

MW: 194.24 g/mol

Method:

The general flow procedure was followed using **1g** (1 mmol) and **2a** (1.5 mmol). Evaporation of CPME and filtration over silica plug afforded **3m** in 65% Yield (126 mg)

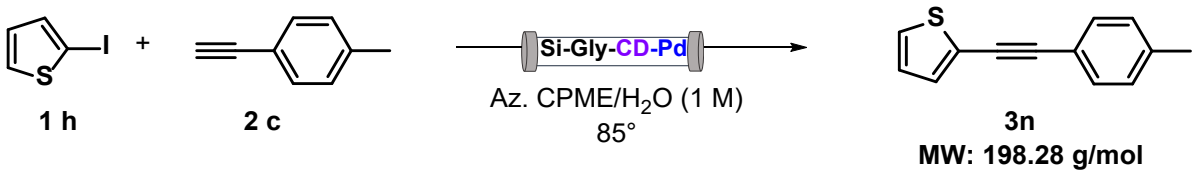
Elemental Analysis: Calc: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.40; H, 5.17; N, 14.44.

Mol Formula	$C_{13}H_{10}N_2$	**m.p.**		
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	8.26	1	*s*	
	7.58-7.51	1	*m*	-
	7.51-7.49	2	*m*	
	7.35-7.31	3	*m*	
	6.49	1	*d*	7.7
	4.66	2	*bs*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 157.5, 151.1, 140.9, 131.6, 128.6, 128.3, 123.5, 110.2, 108.4, 90.2, 87.0.

GC-EIMS (m/z, %): 195 (M^++1, 11), 194 (M^+, 100), 193 (25), 166 (19), 139 (20).

Chem.Name	2-(p-tolylethynyl)thiophene (**3n**)
Lit.Ref	Pan, C., Luo, F., Wang, W., Ye, Z., & Liu, M. *Journal of Chemical Research*, 2009, **8**, 478-481



1 h **2 c** **3n**

MW: 198.28 g/mol

Method:

The general flow procedure was followed using **1h** (1 mmol) and **2c** (1.5 mmol). Evaporation of CPME and filtration over silica plug afforded **3n** in 64% Yield (127 mg)

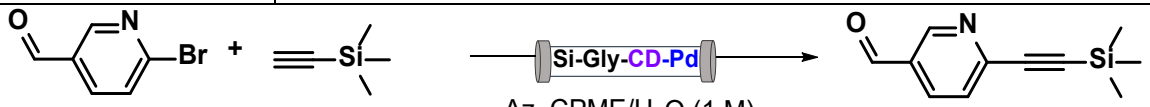
Elemental Analysis: Calc: C, 78.85; H, 5.08; S, 16.17. Found: C, 78.83; H, 5.10; S, 16.15

Mol Formula	$C_{13}H_{10}S$	**m.p.**	68-70 °C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	7.42	2	*d*	7.7
	7.29-7.27	2	*m*	
	7.16	2	*d*	7.6
	7.02-7.01	1	*m*	-
	2.38	3	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 138.8, 131.9, 131.6, 129.4, 127.3, 127.2, 123.8, 120.1, 93.5, 82.2, 21.8.

GC-EIMS (m/z, %): 199 (M^++1, 16), 198 (M^+, 100), 197 (48)

Chem.Name	6-((trimethylsilyl)ethynyl)nicotinaldehyde (**3o**)
Lit.Ref	H. Xie, L. Ming, J. Wu, Y. Zhang, Y. Cheng, patent number: WO 2020/114494 A1 (2020)



4 c **2 d** **3o**

MW: 203.316 g/mol

Method:

The general flow procedure was followed using **4c** (2mmol) and **2d** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3o** in 95% Yield (386 mg)

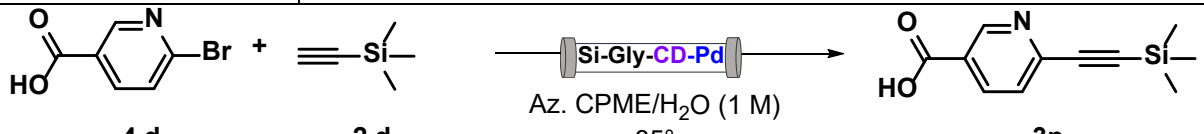
Elemental Analysis: Calc: C, 64.98; H, 6.45; N, 6.89. Found: C, 64.97; H, 6.41; N, 6.90.

Mol Formula	$C_{14}H_{10}$	**m.p.**	118-119°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	10.09	1	*s*	
	9.01	1	*d*	1.4
	8.11	1	*dd*	8.0, 2.0
	7.59	1	*d*	8.0
	0.28	9	*s*	

^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 190.0, 152.3, 147.9, 135.9, 130.1, 127.6, 130.0, 100.0, -0.3

GC-EIMS (m/z, %): 203 (M^+, 100), 175 (15), 174 (24), 130 (42), 117 (15), 73 (42).

Chem.Name	6-((trimethylsilyl)ethynyl)nicotinic acid (**3p**)
Lit.Ref	H. Xie, L. Ming, J. Wu, Y. Zhang, Y. Cheng, patent number: WO 2020/114494 A1 (2020)



4 d **2 d** **3p**

MW: 219.315 g/mol

Method:

The general flow procedure was followed using **4d** (2mmol) and **2d** (3 mmol). Evaporation of CPME and filtration over silica plug afforded **3p** in 93% Yield (408 mg)

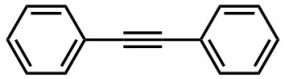
Elemental Analysis: Calc: C, 60.24; H, 5.97; N, 6.39. Found: C, 60.26; H, 5.98; N, 6.37.

Mol Formula	$C_{14}H_{10}$	**m.p.**	135-137°C	
^{1}H NMR (400 MHz, $CDCl_3$)	δ value:	No. H	Mult	J value/Hz
	10.80	1	*s(br)*	
	9.28	1	*s*	
	8.36	1	*dd*	8.1, 1.5
	7.57	1	*d*	8.1
	0.28	9	*s*	

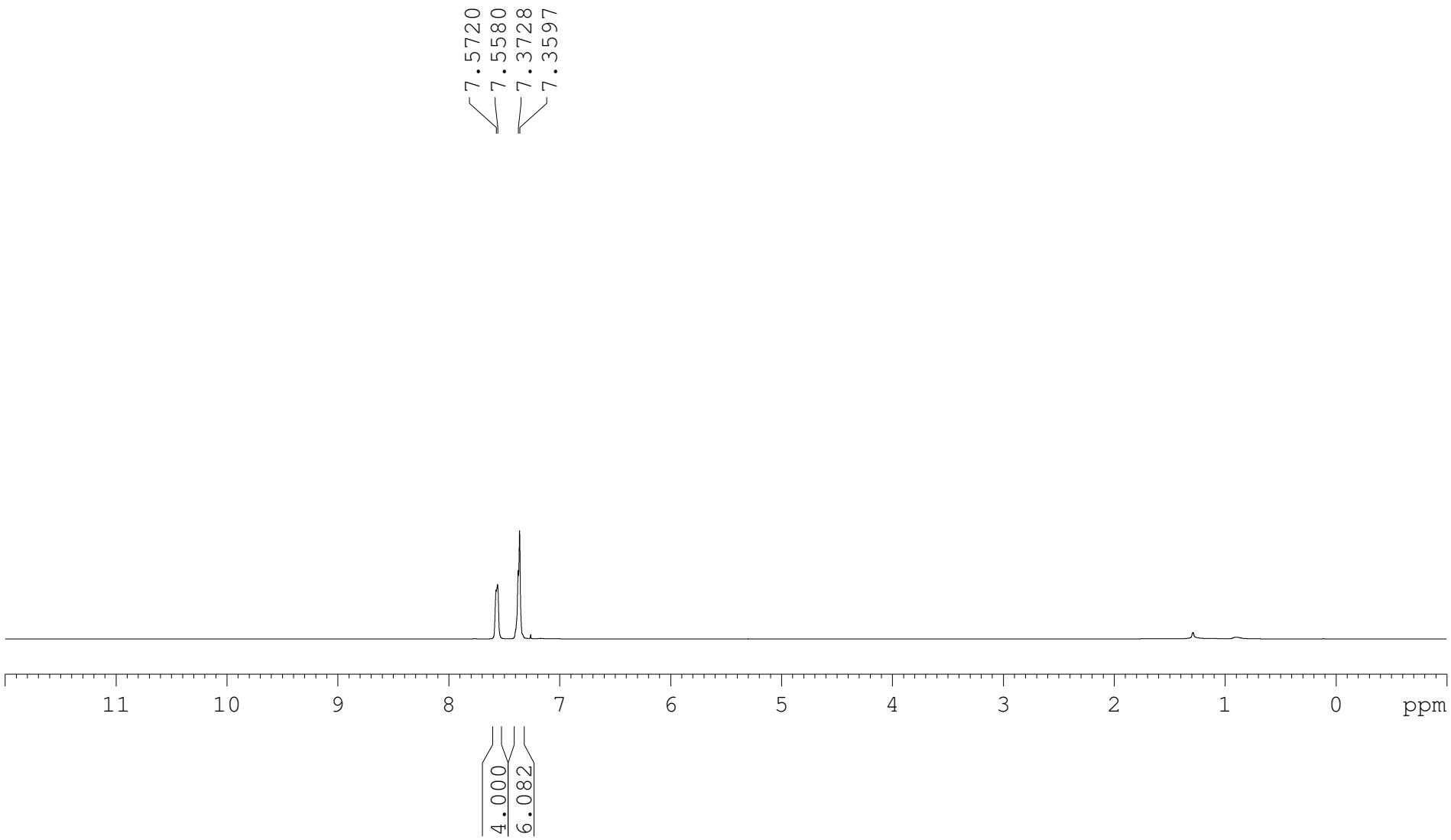
^{13}C NMR (100.6 Hz, $CDCl_3$) δ: 168.9, 151.3, 146.6, 138.3, 127.1, 125.1, 102.6, 100.0, -0.3

GC-EIMS (m/z, %): 219 (M^+, 100), 205 (15), 204 (22), 174 (27), 117 (21), 73 (35)

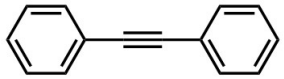
1,2-diphenylethyne (**3a**)



3a



1,2-diphenylethyne (**3a**)



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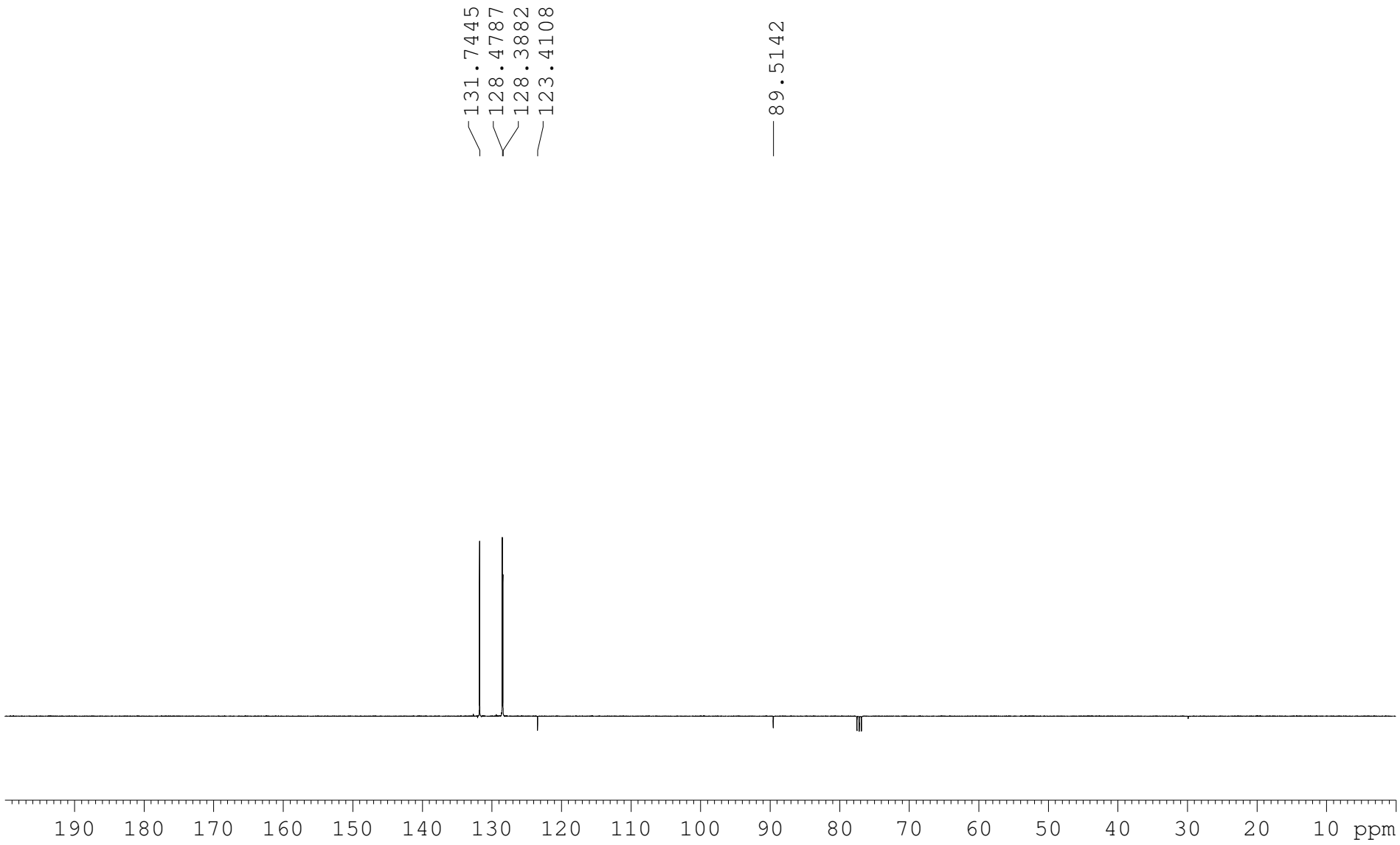
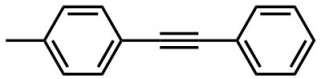


1-methyl-4-(phenylethynyl)benzene (**3b**)



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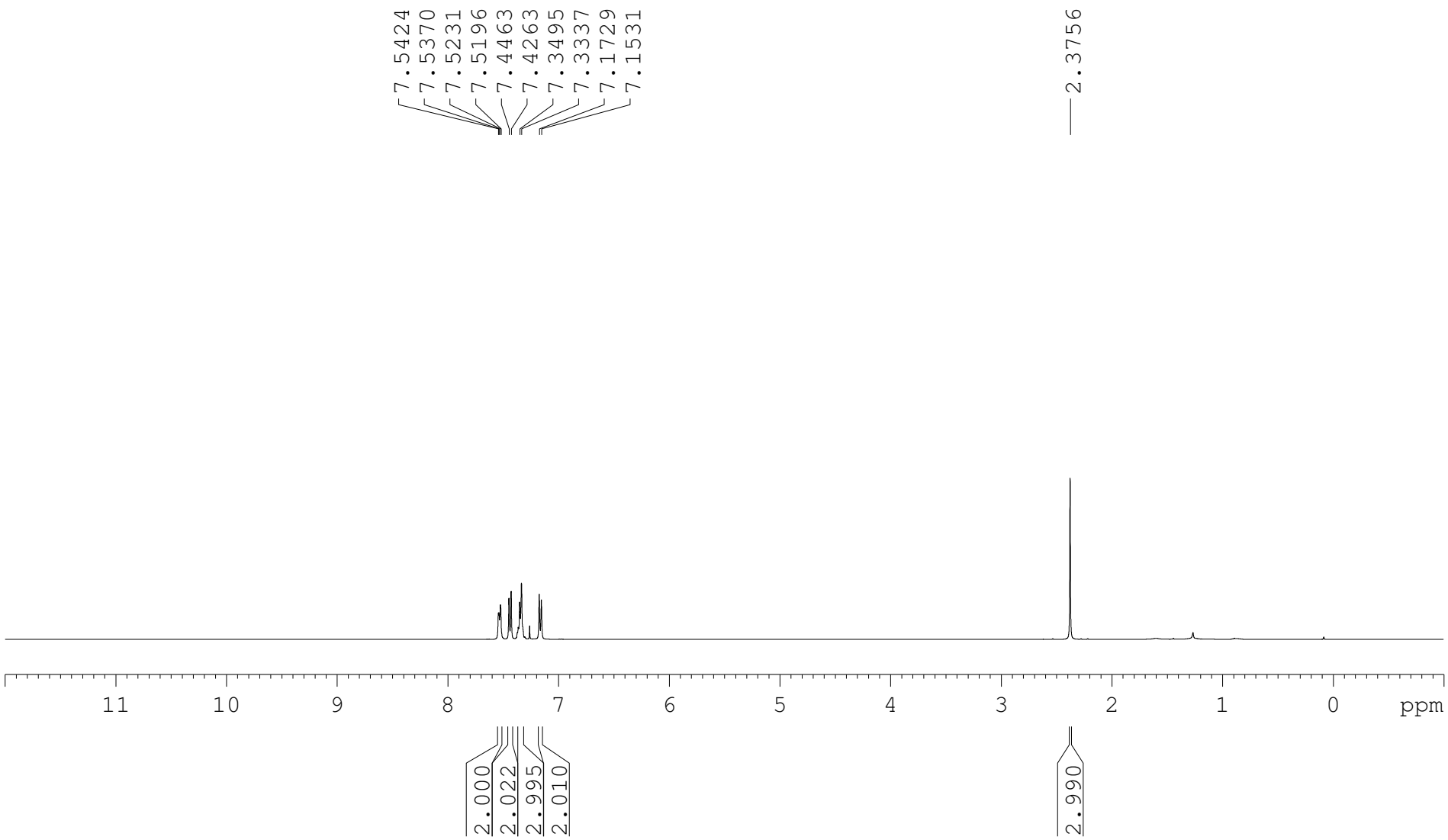
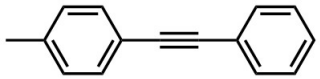


1-methyl-4-(phenylethynyl)benzene (**3b**)



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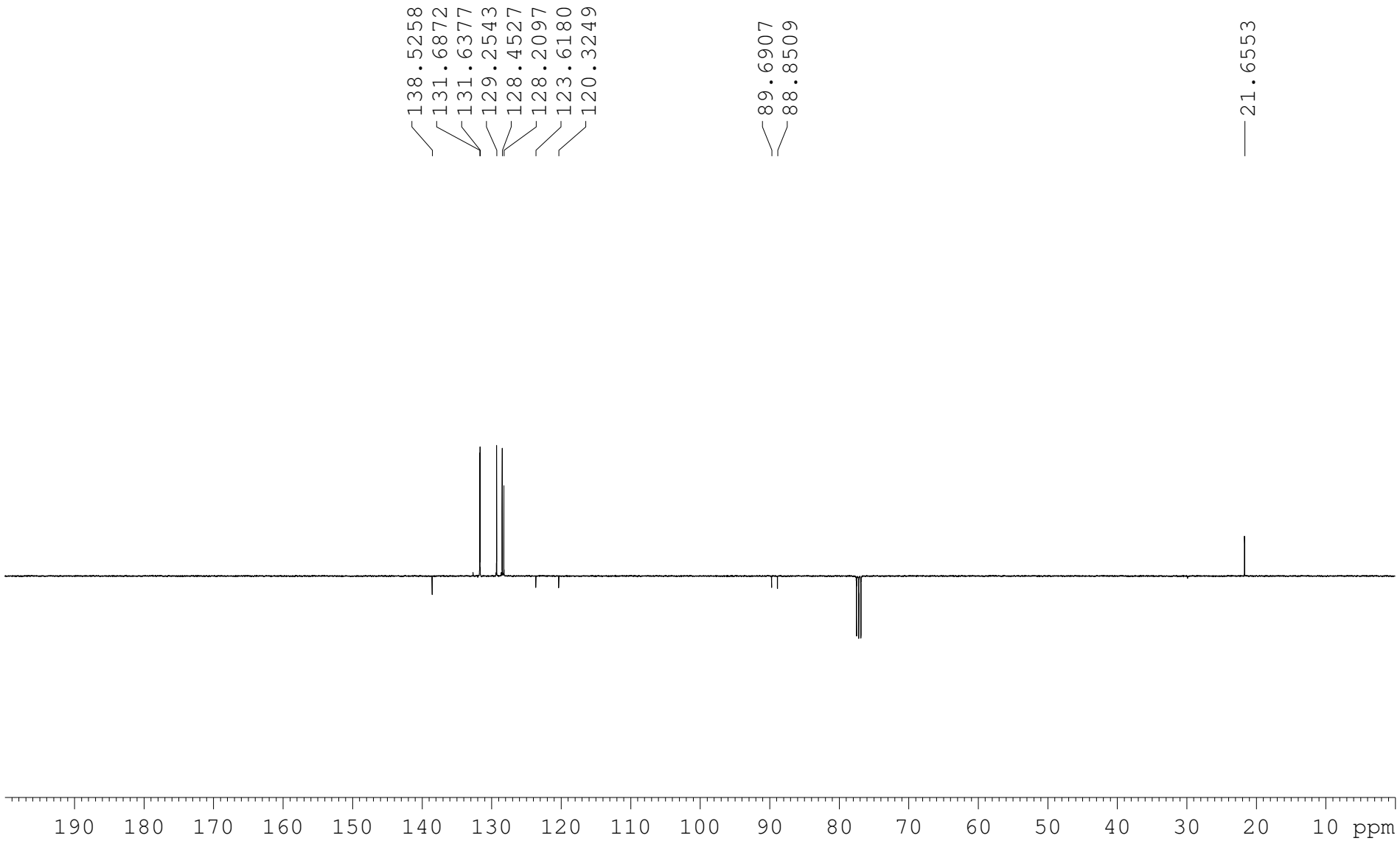
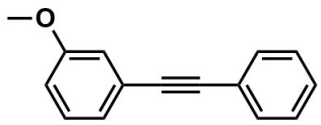


1-methoxy-3-(phenylethynyl)benzene (**3c**)



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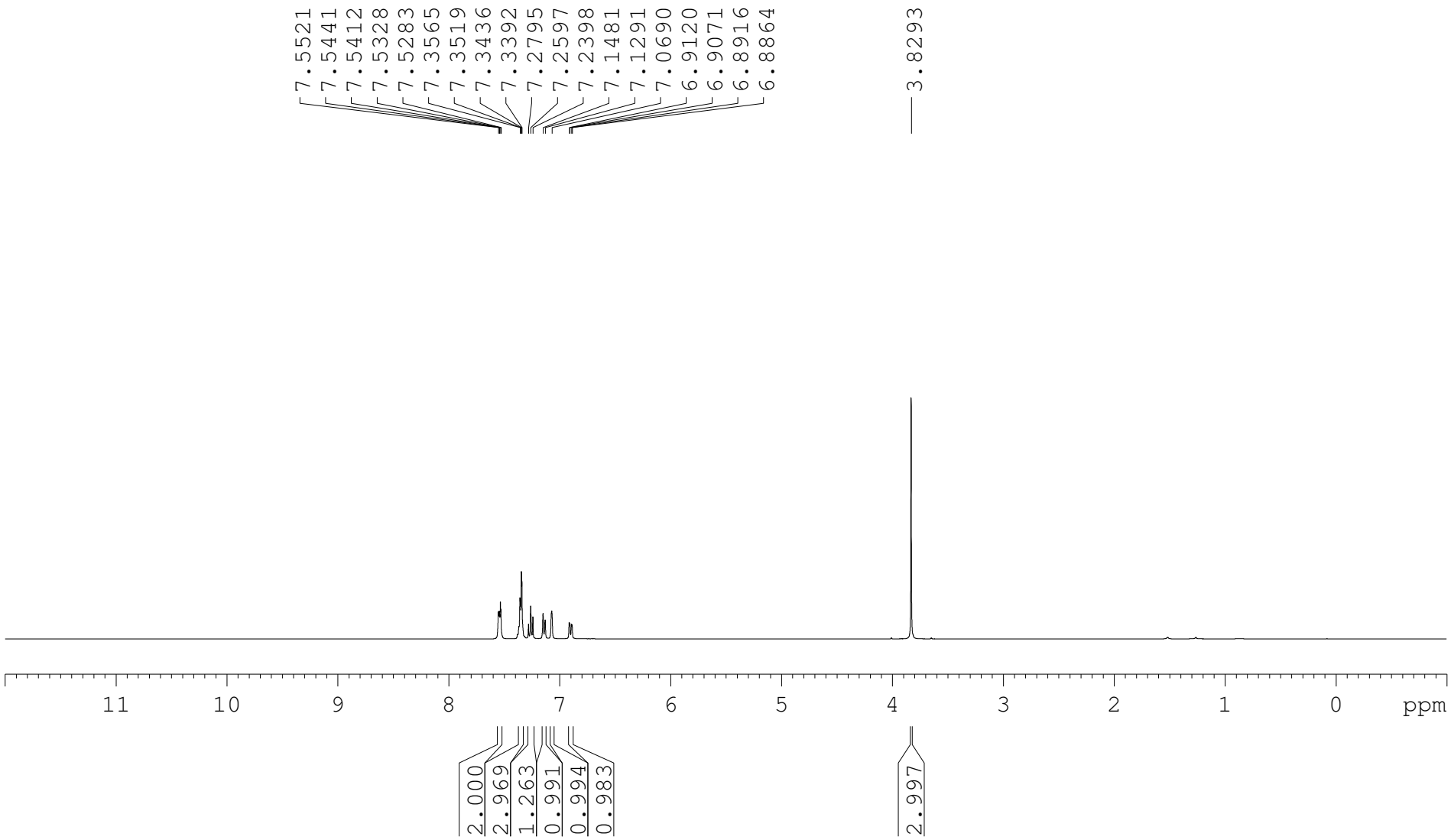
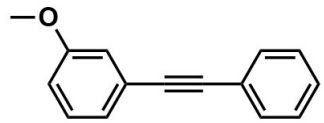


1-methoxy-3-(phenylethynyl)benzene (**3c**)



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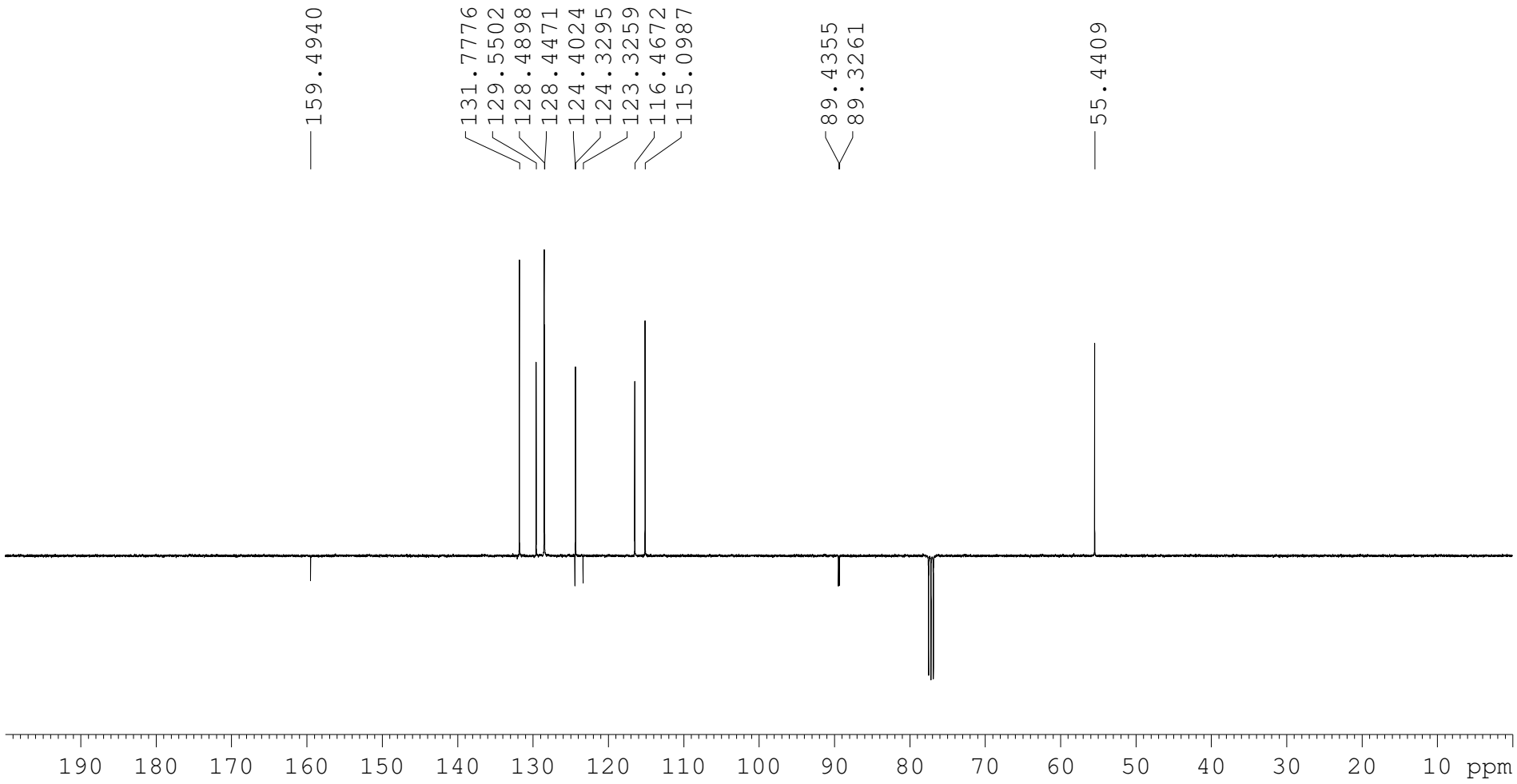
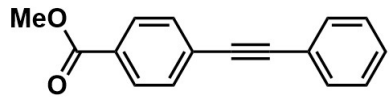


Methyl 4-(phenylethynyl)benzoate (**3d**)



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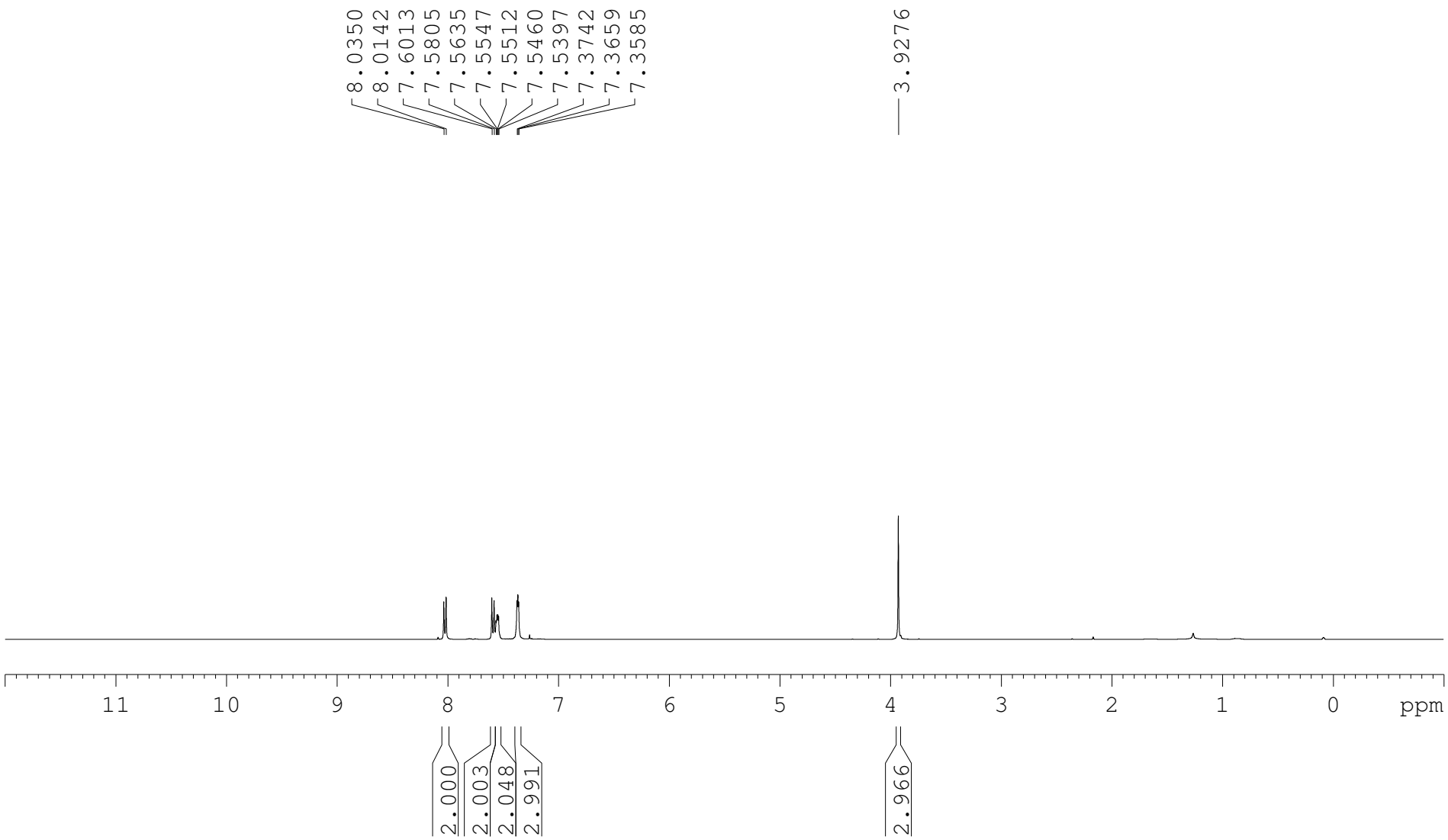
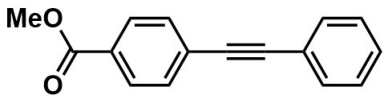


Methyl 4-(phenylethynyl)benzoate (**3d**)



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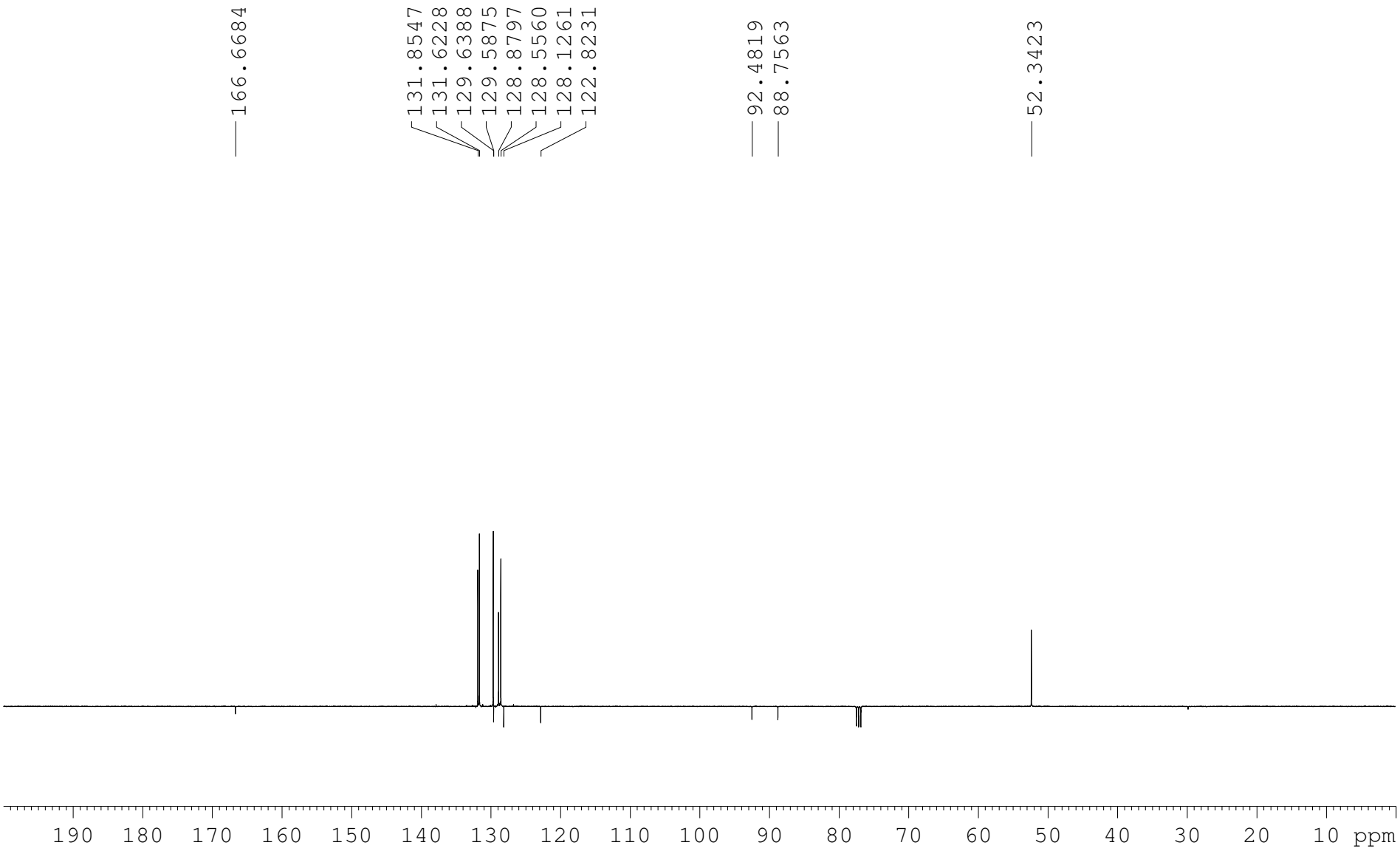
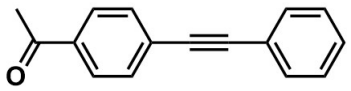


1-(4-(phenylethynyl)phenyl)ethan-1-one (**3e**)



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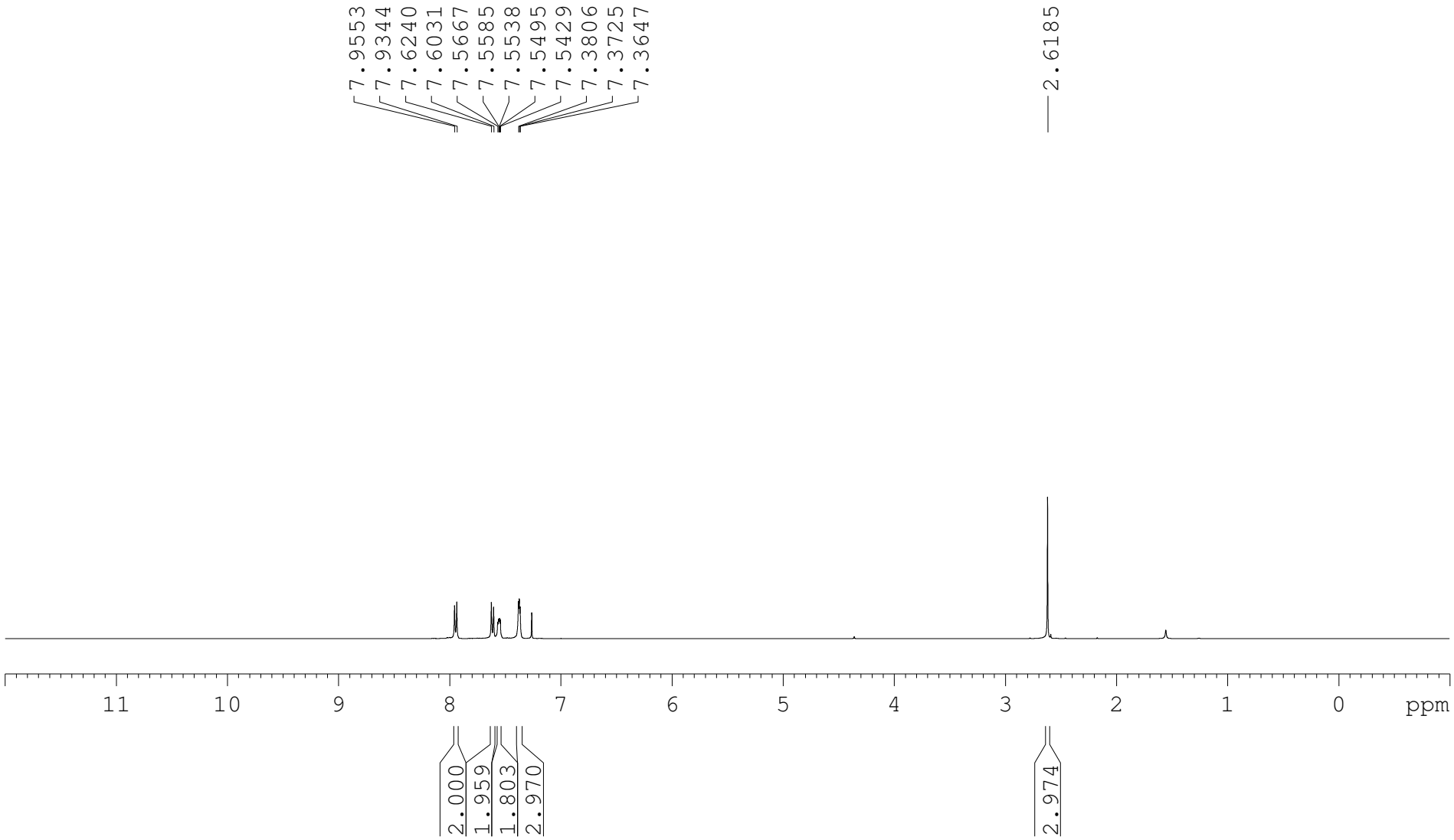
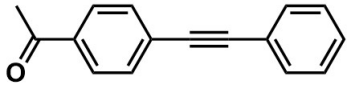


1-(4-(phenylethynyl)phenyl)ethan-1-one (**3e**)



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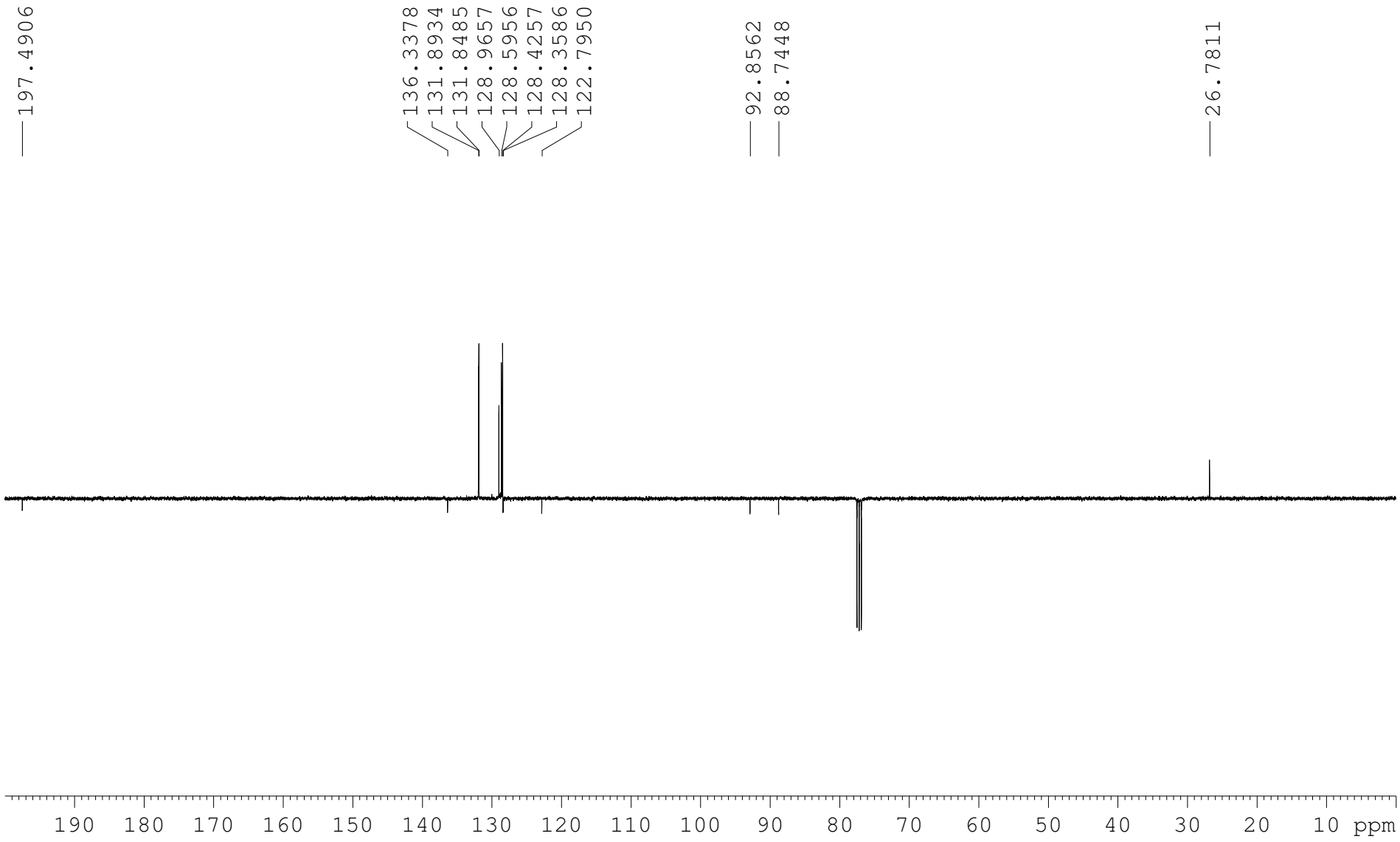
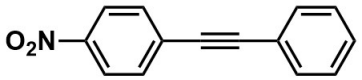


1-nitro-4-(phenylethynyl)benzene (**3f**)



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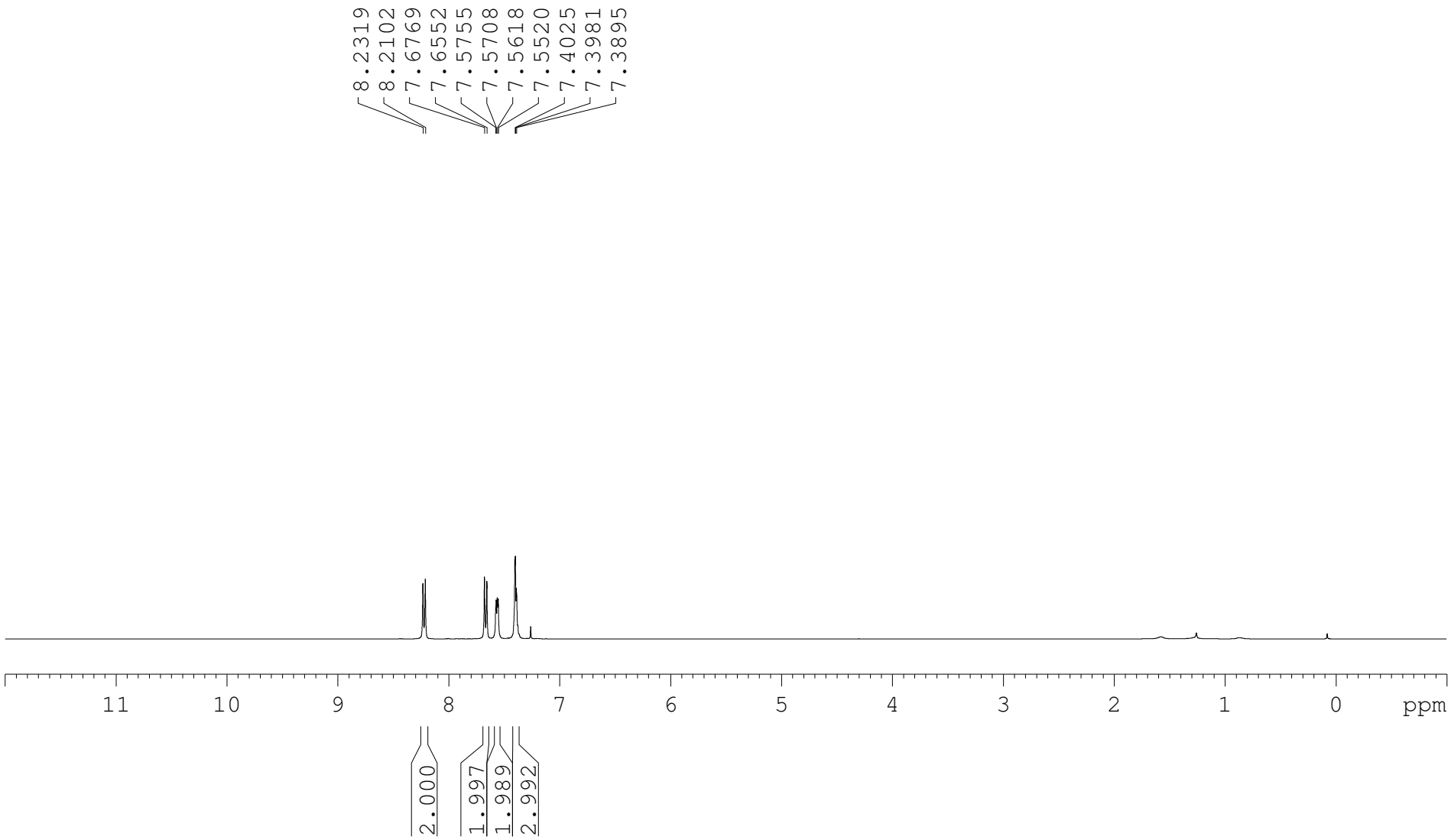
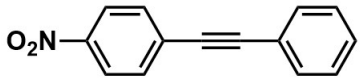


1-nitro-4-(phenylethynyl)benzene (**3f**)



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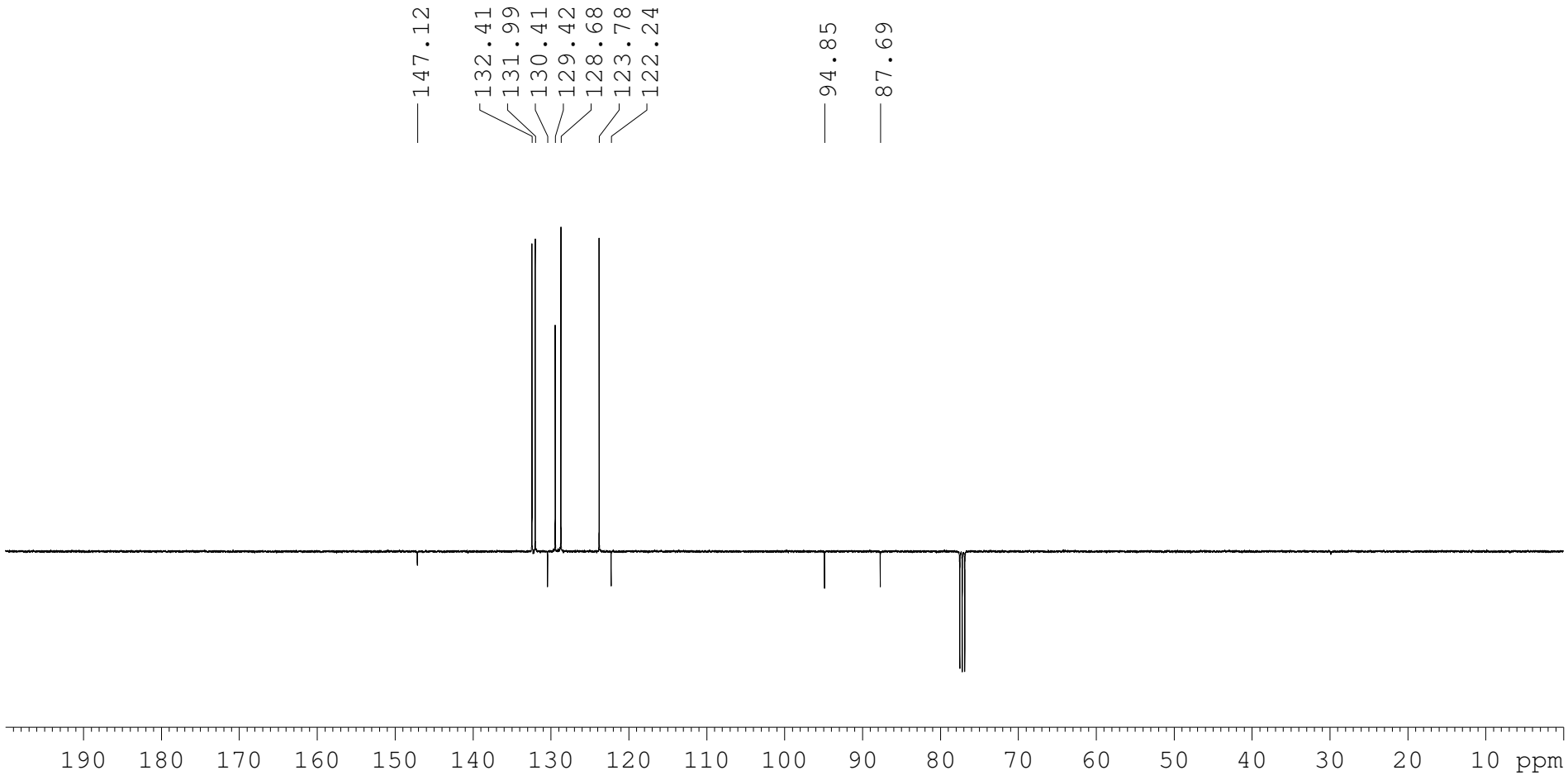
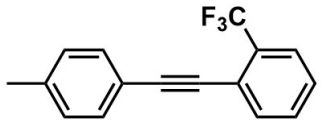


1-(p-tolylethynyl)-2-(trifluoromethyl)benzene (**3g**)



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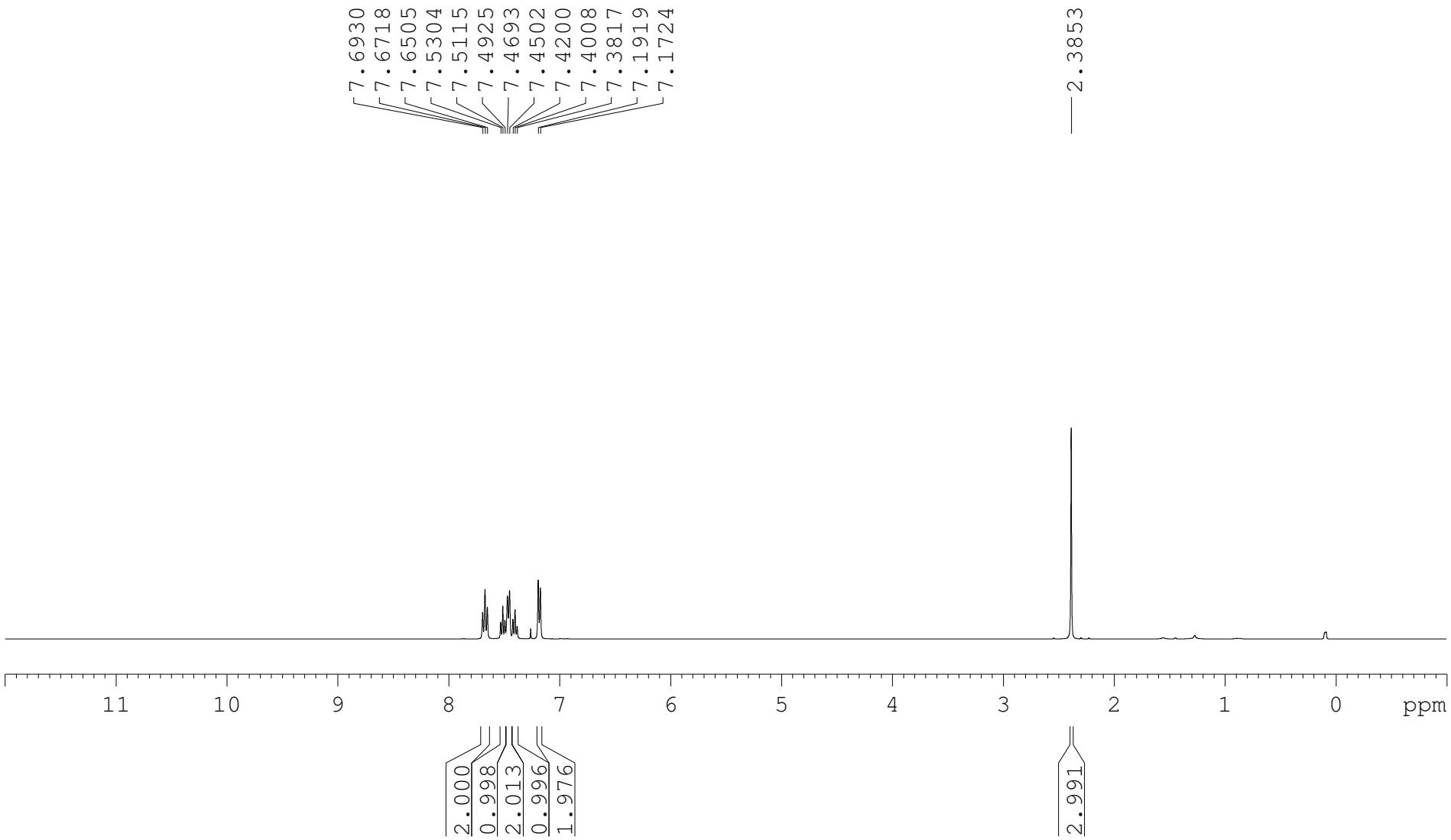
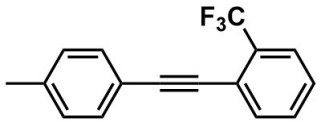


1-(p-tolylethynyl)-2-(trifluoromethyl)benzene (**3g**)



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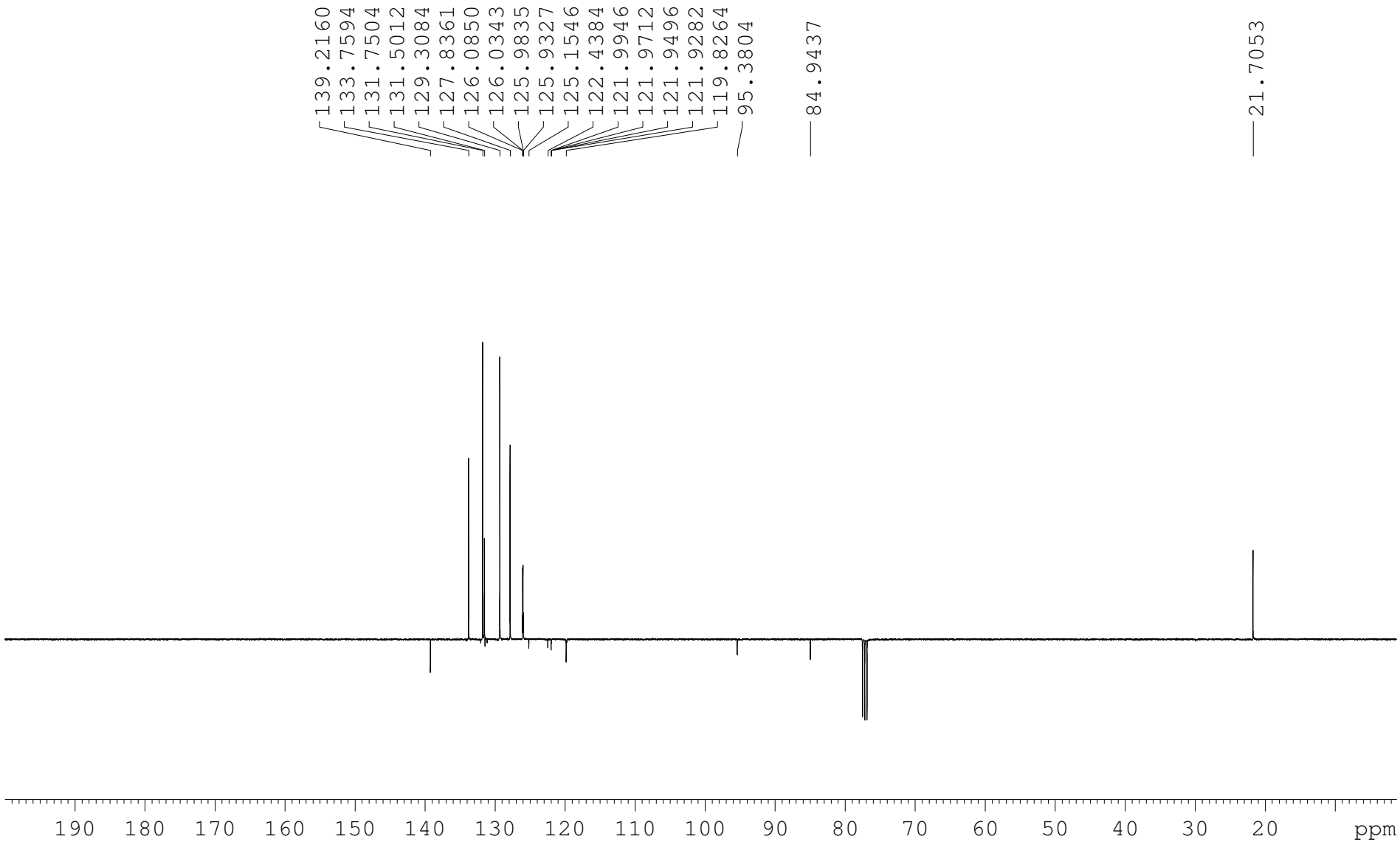
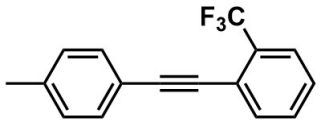


1-(p-tolylethynyl)-2-(trifluoromethyl)benzene (**3g**)



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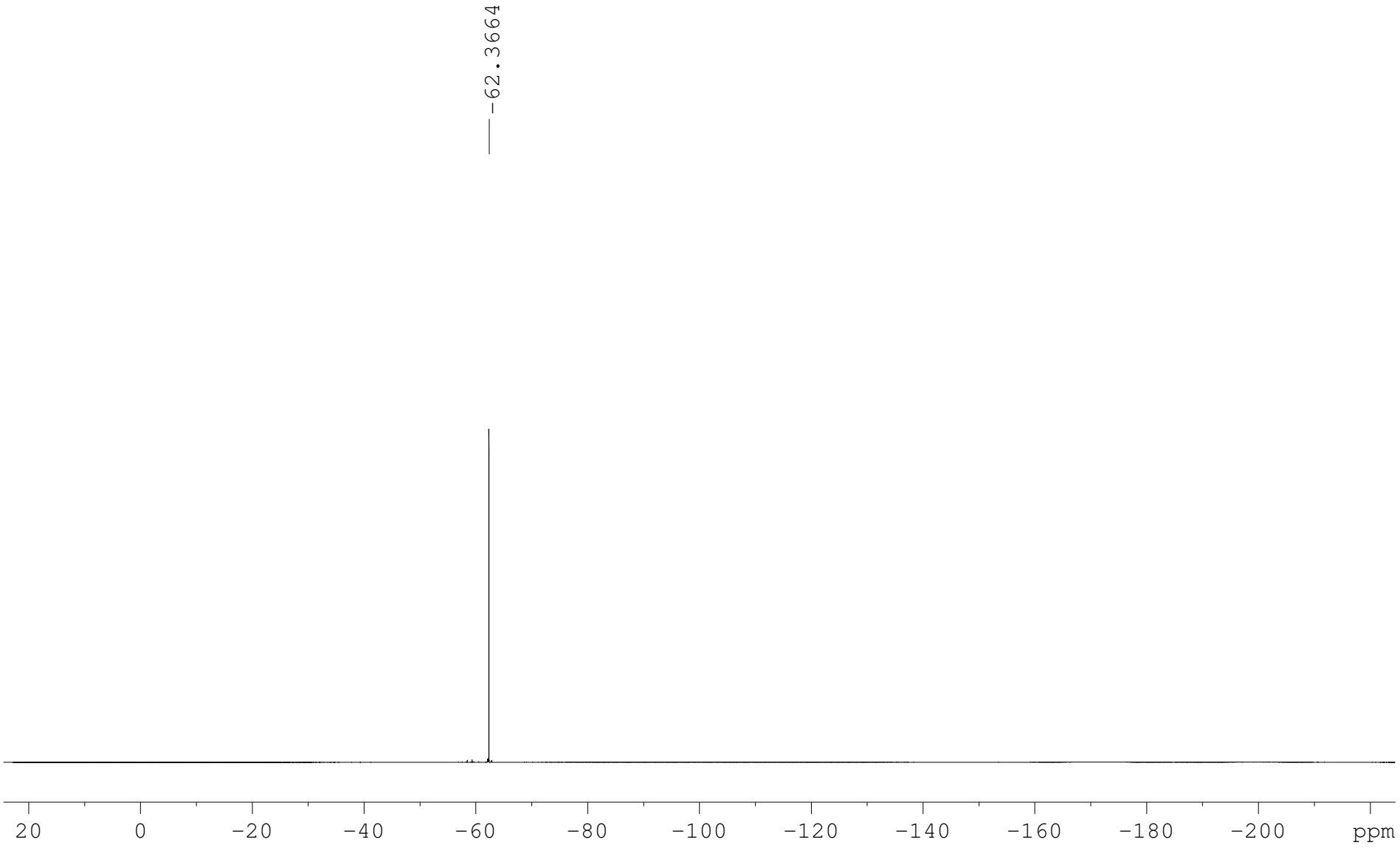
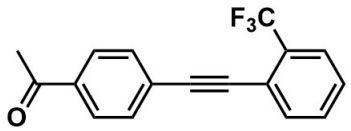


1-(4-((2-(trifluoromethyl)phenyl)ethynyl)phenyl)ethan-1-one (**3h**)



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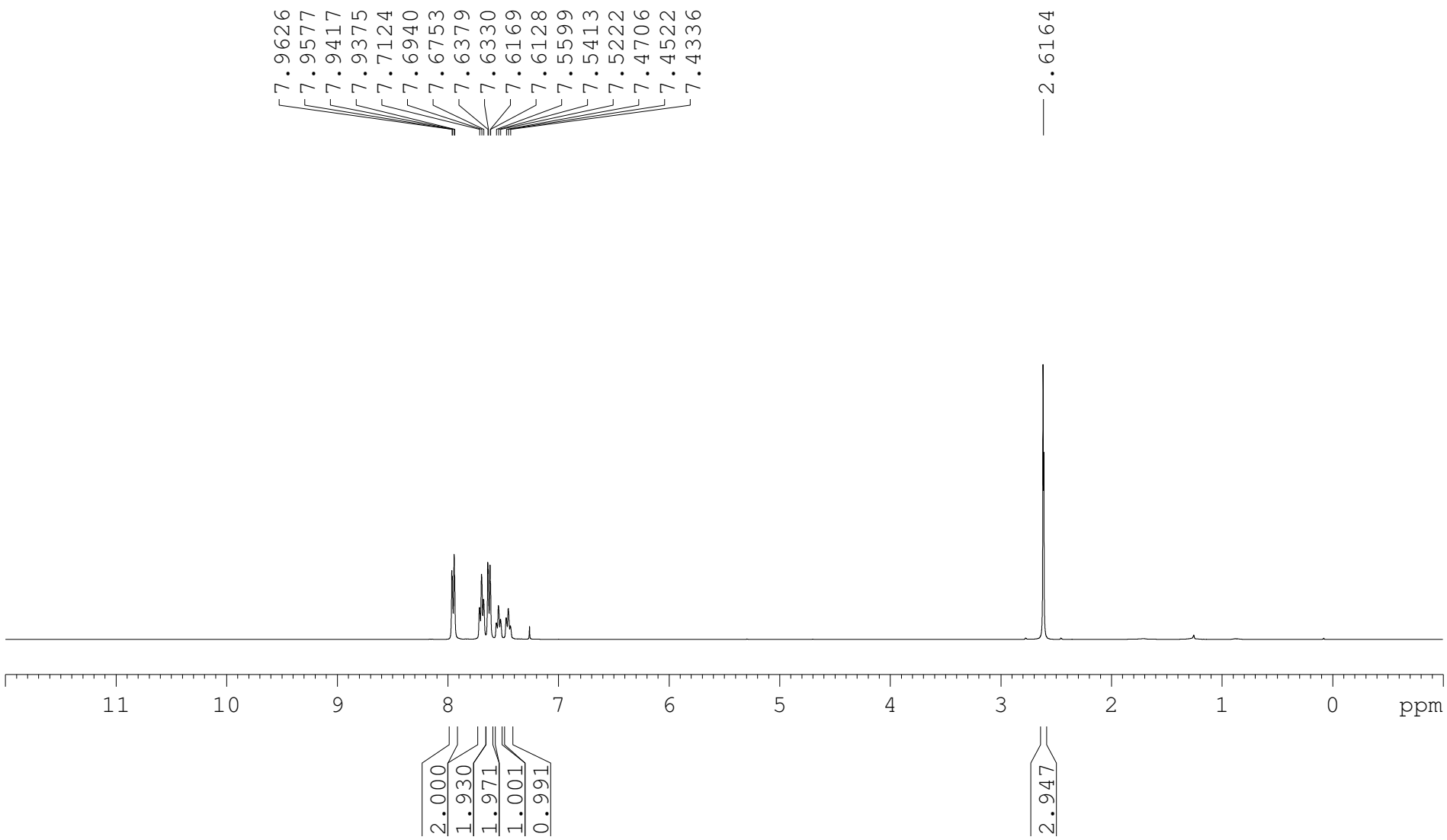
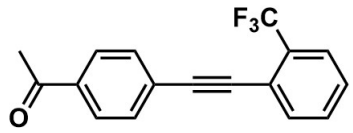


1-(4-((2-(trifluoromethyl)phenyl)ethynyl)phenyl)ethan-1-one (**3h**)



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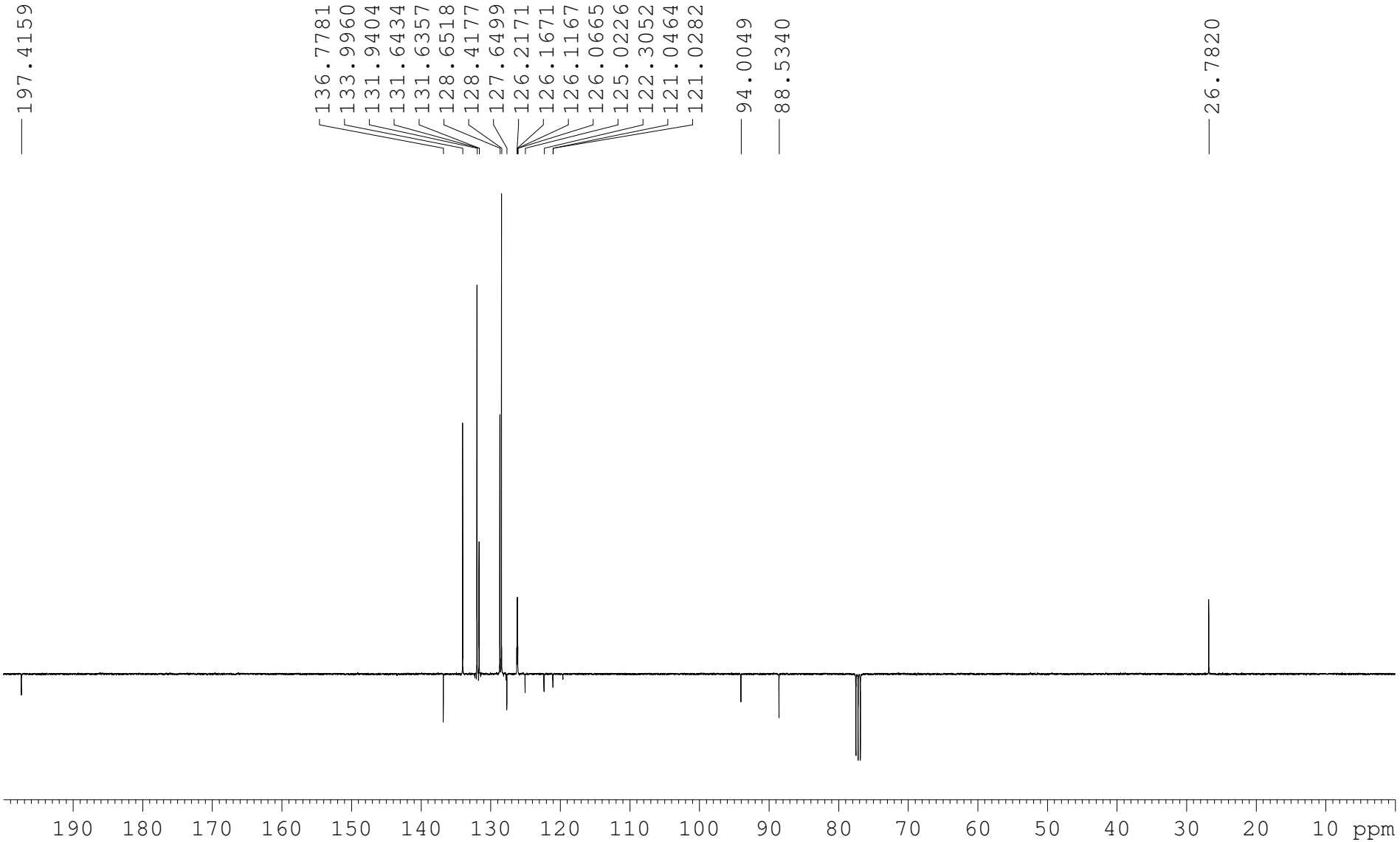
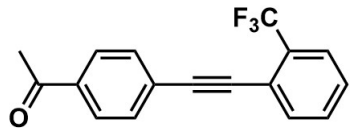


1-(4-((2-(trifluoromethyl)phenyl)ethynyl)phenyl)ethan-1-one (**3h**)



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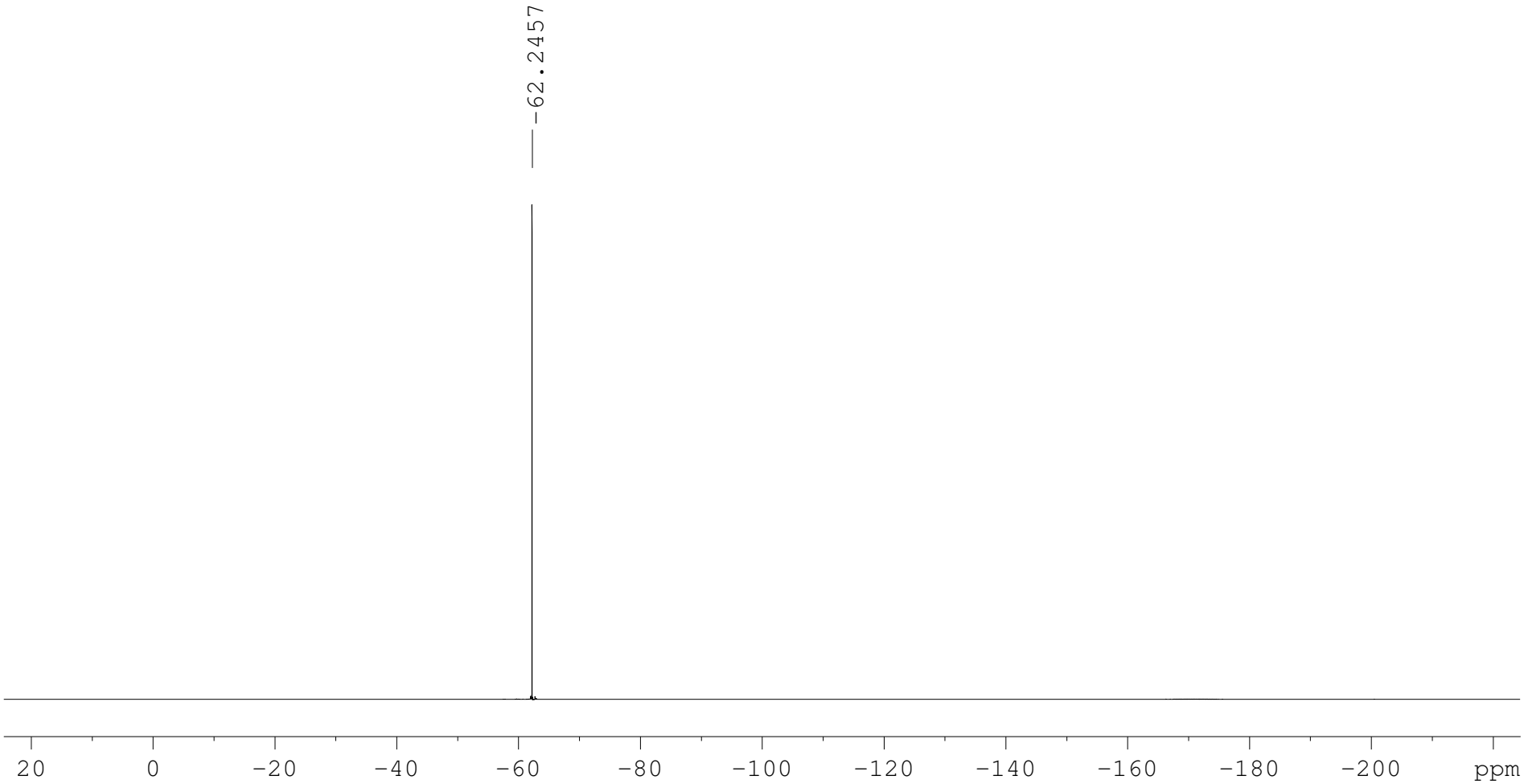
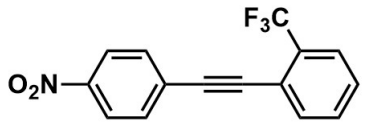


1-((4-nitrophenyl)ethynyl)-2-(trifluoromethyl)benzene (**3i**)



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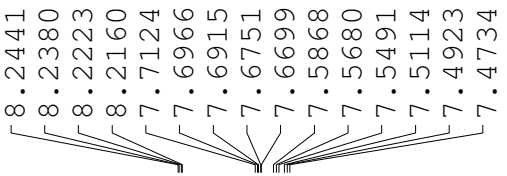
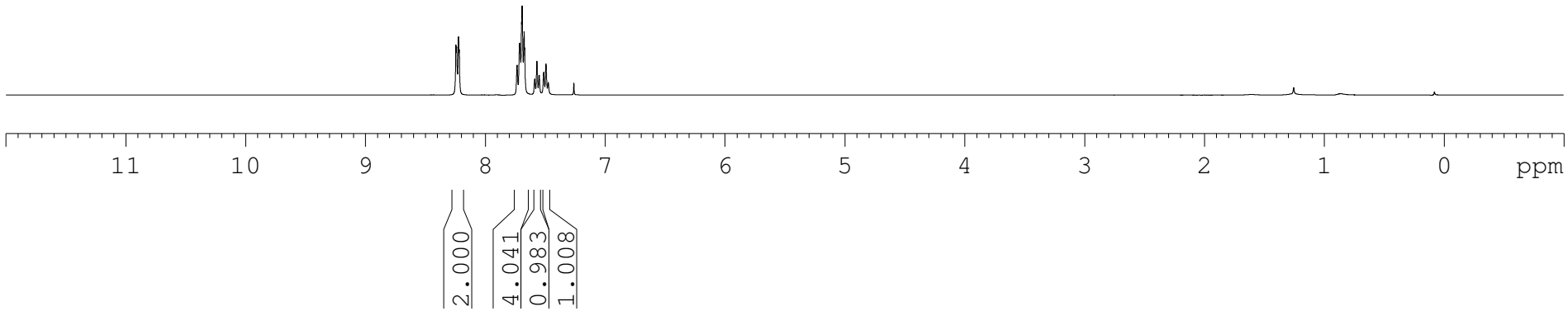
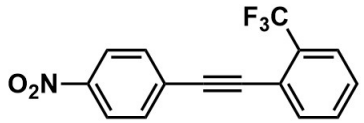




1-((4-nitrophenyl)ethynyl)-2-(trifluoromethyl)benzene (**3i**)



3i

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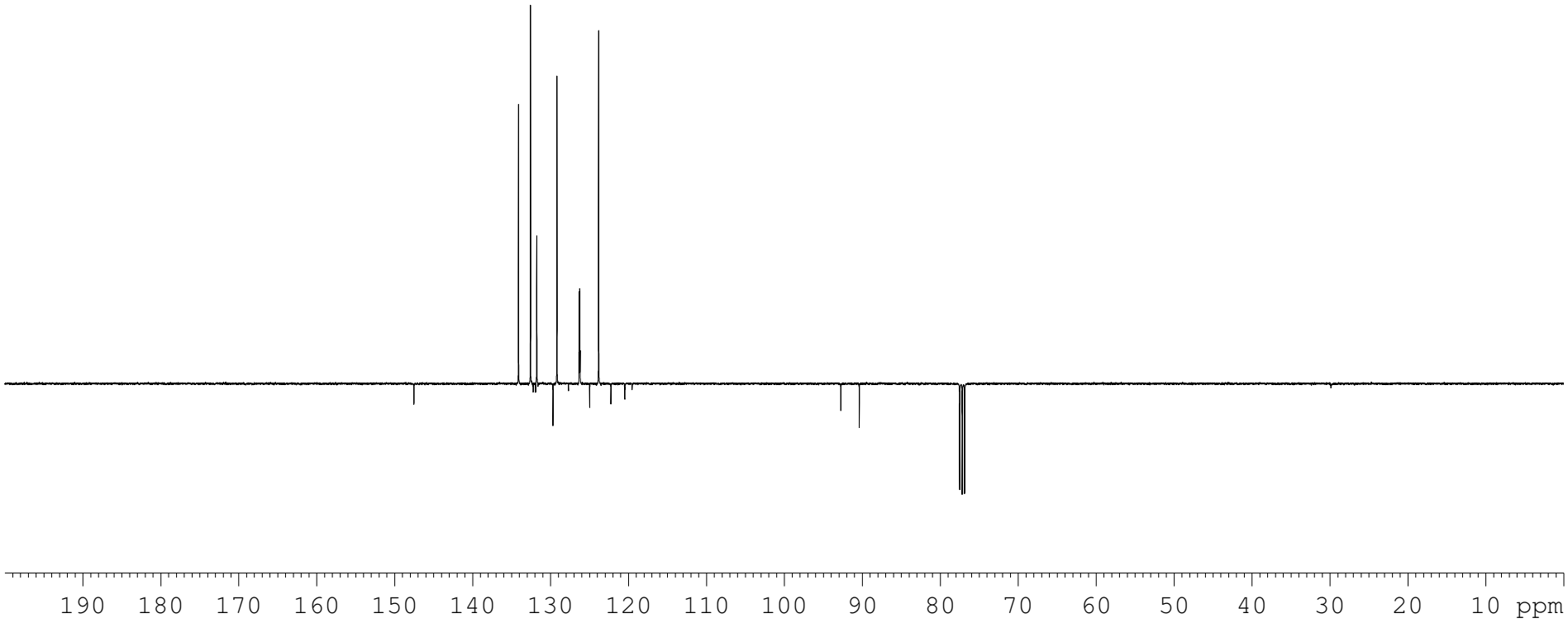
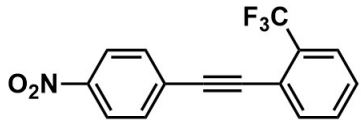
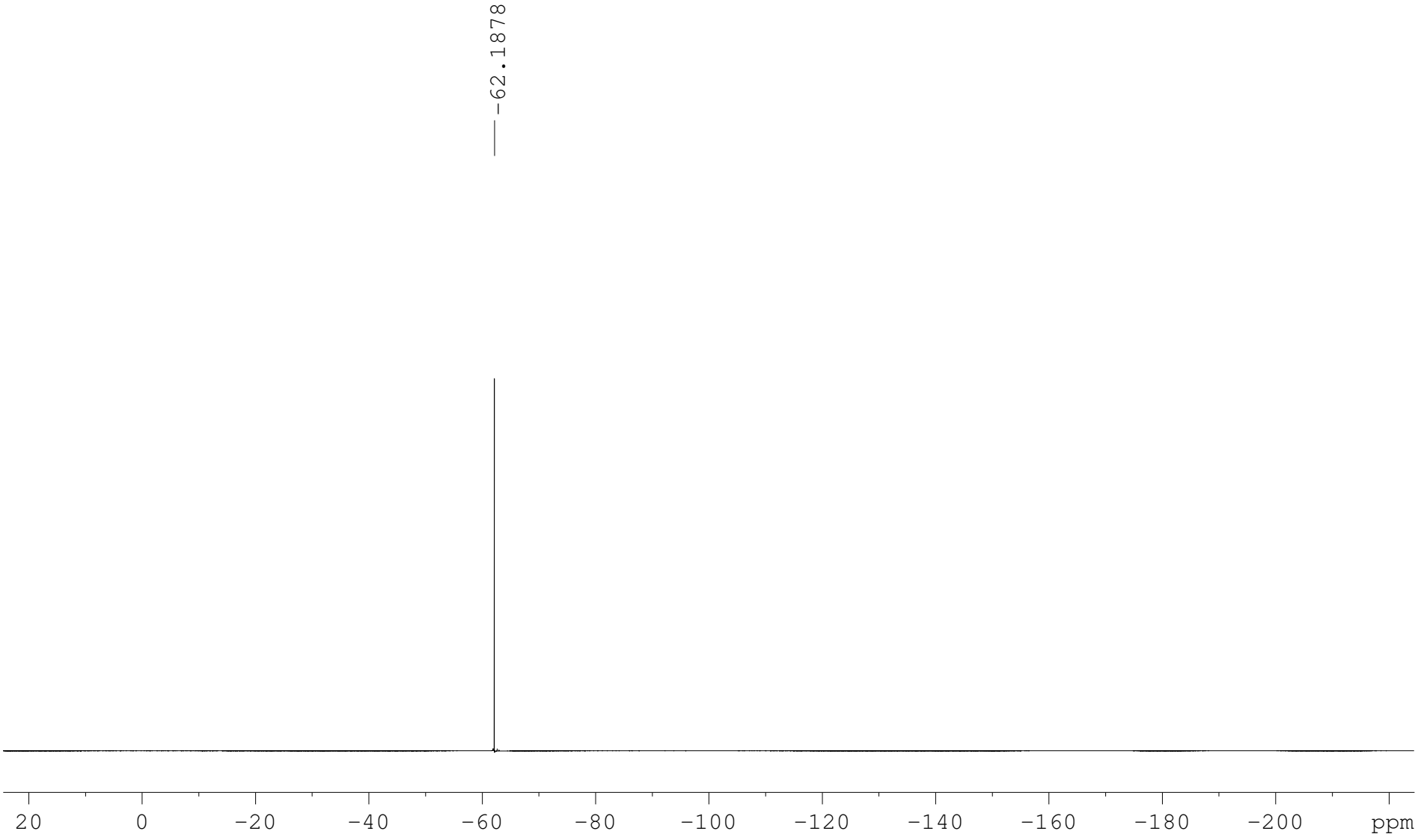


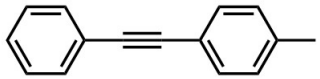
1-((4-nitrophenyl)ethynyl)-2-(trifluoromethyl)benzene (**3i**)



3i



1-methyl-4-(phenylethynyl)benzene (**3j**)



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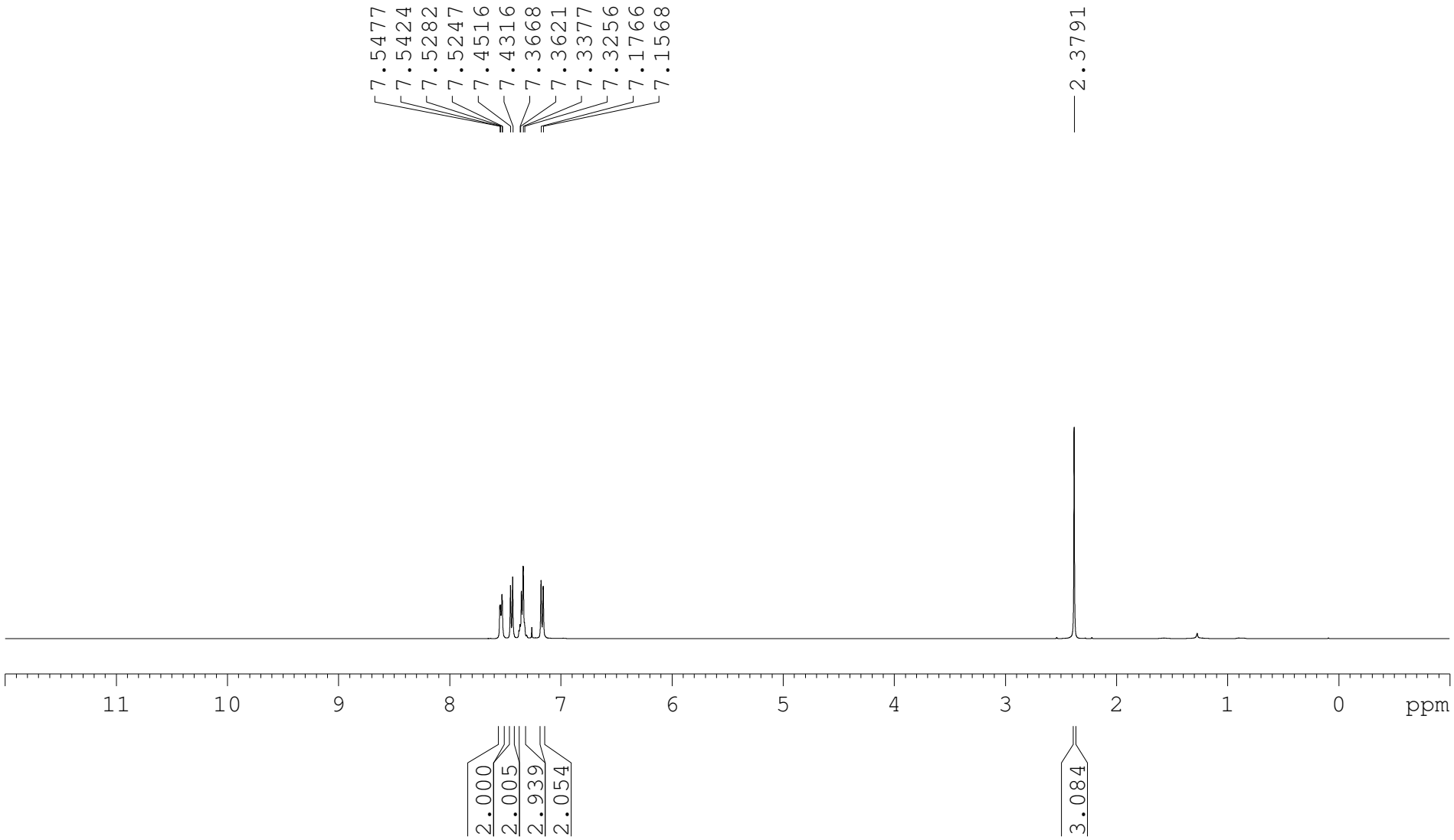
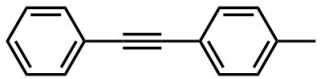


1-methyl-4-(phenylethynyl)benzene (**3j**)



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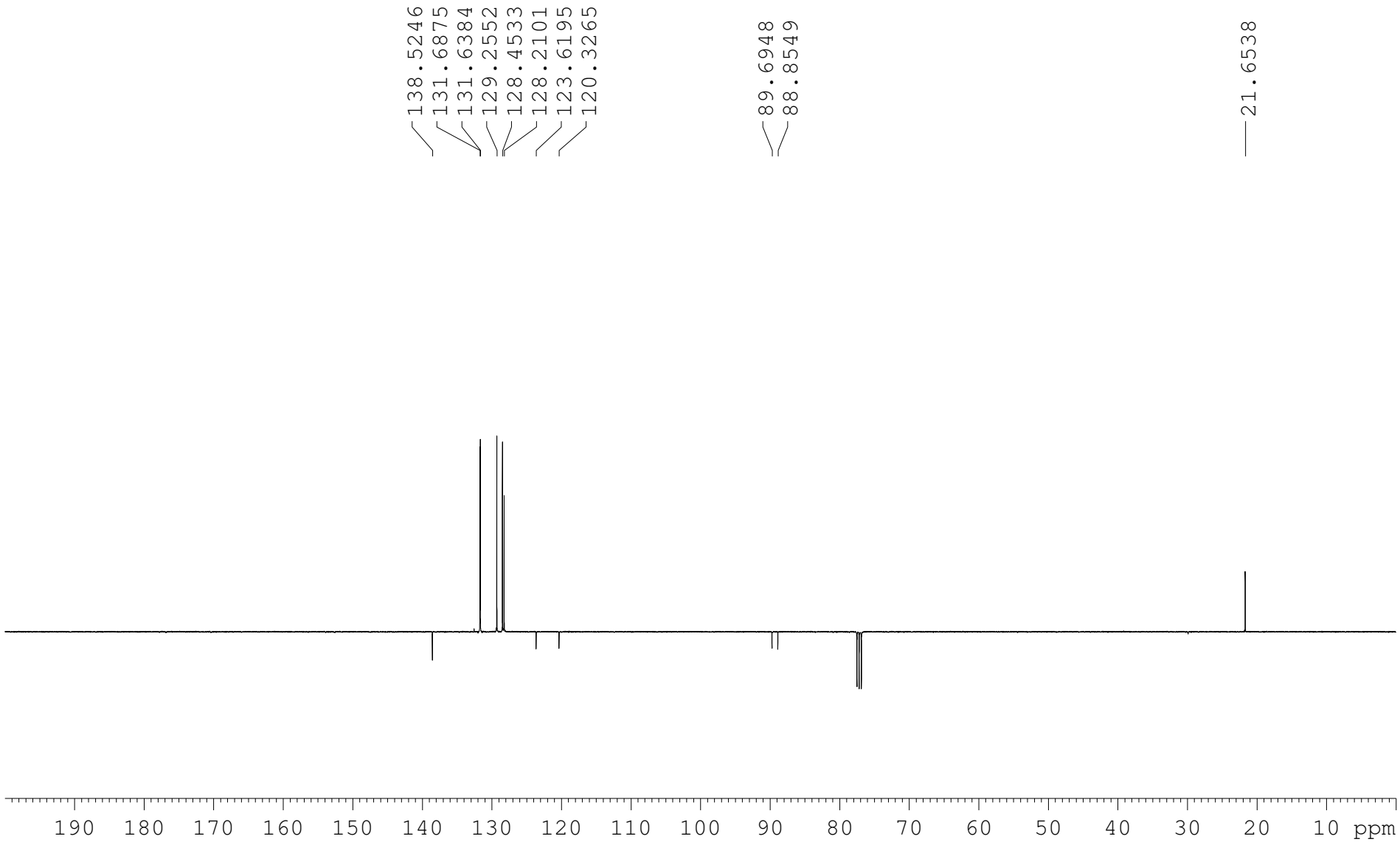
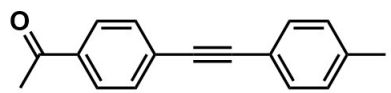


1-(4-(p-tolylethynyl)phenyl)ethan-1-one (**3k**)



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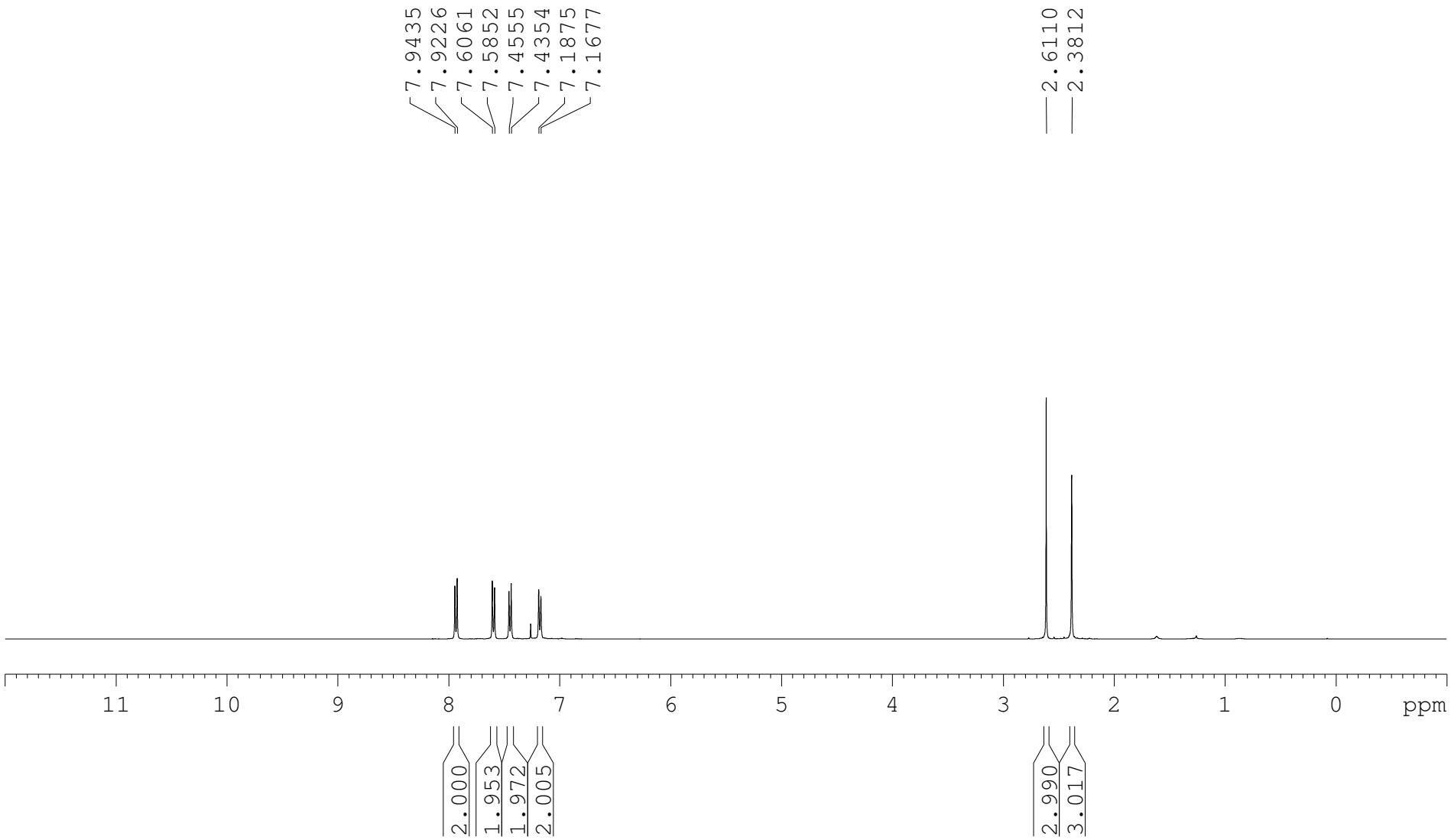
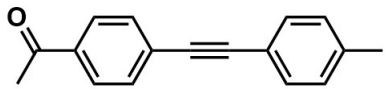


1-(4-(p-tolylethynyl)phenyl)ethan-1-one (**3k**)



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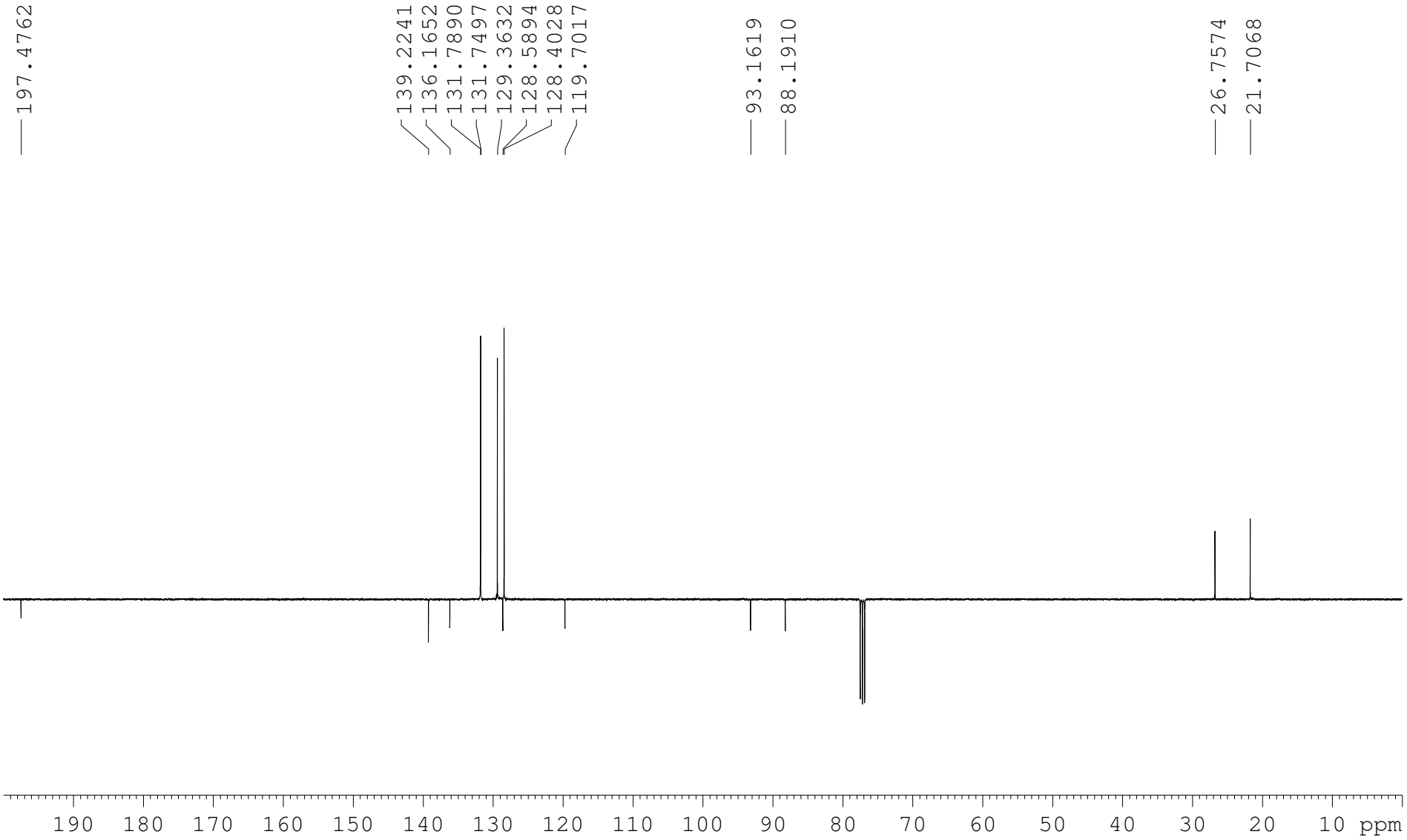
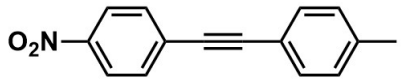


1-methyl-4-((4-nitrophenyl)ethynyl)benzene (**3l**)



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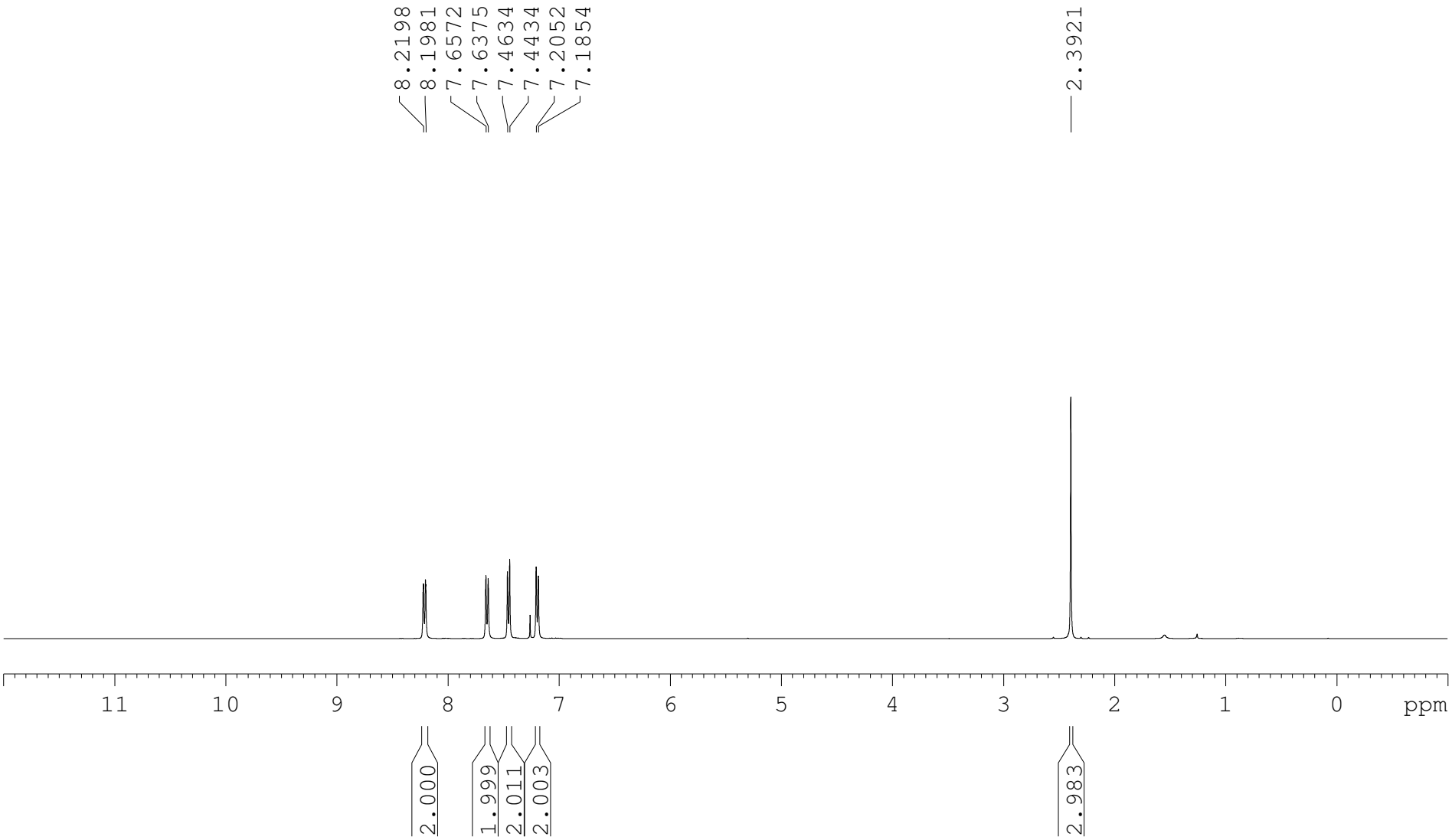
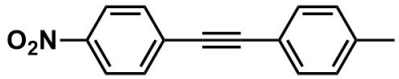


1-methyl-4-((4-nitrophenyl)ethynyl)benzene (**3l**)



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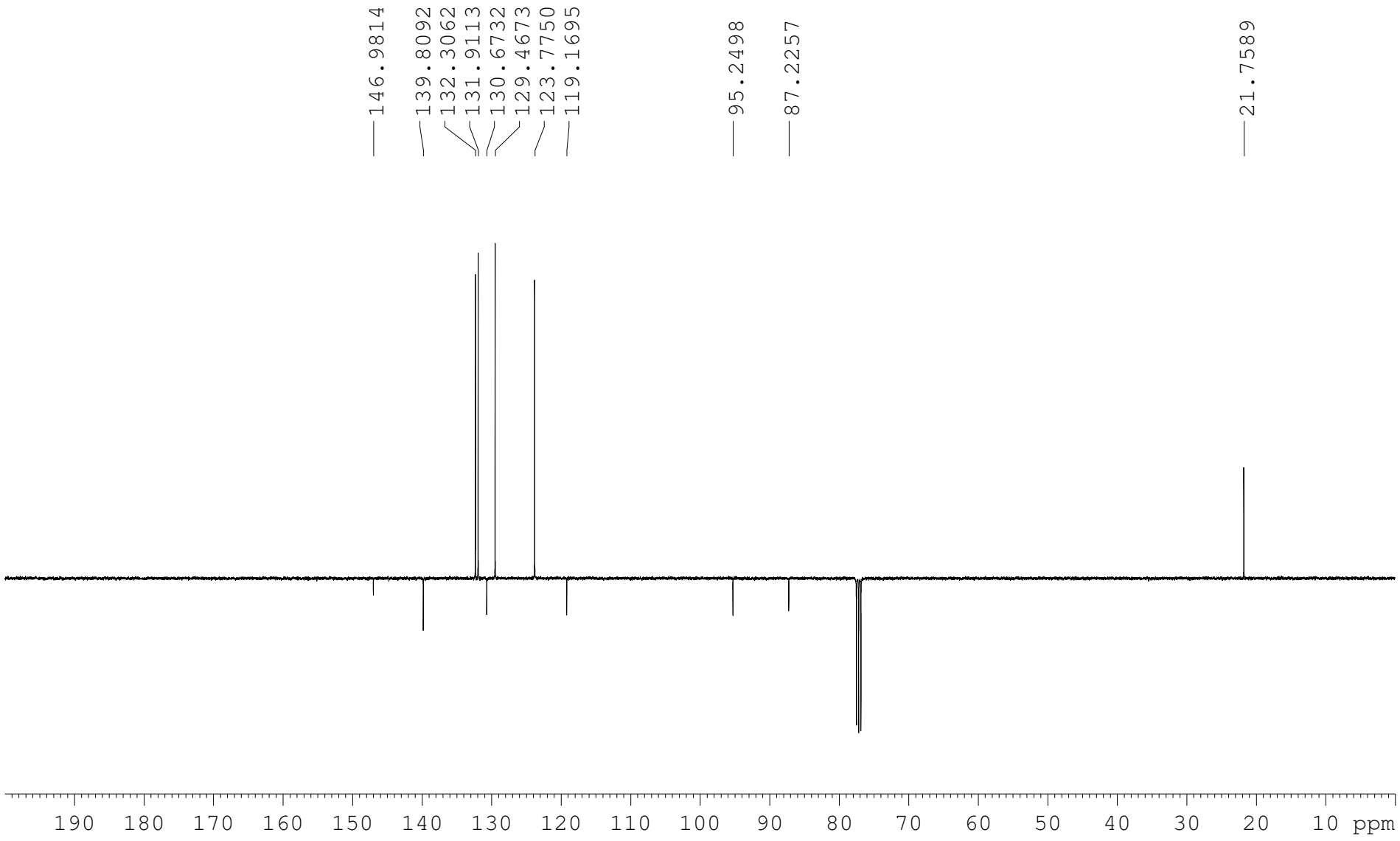
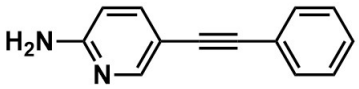


5-(phenylethynyl)pyridin-2-amine (**3m**)



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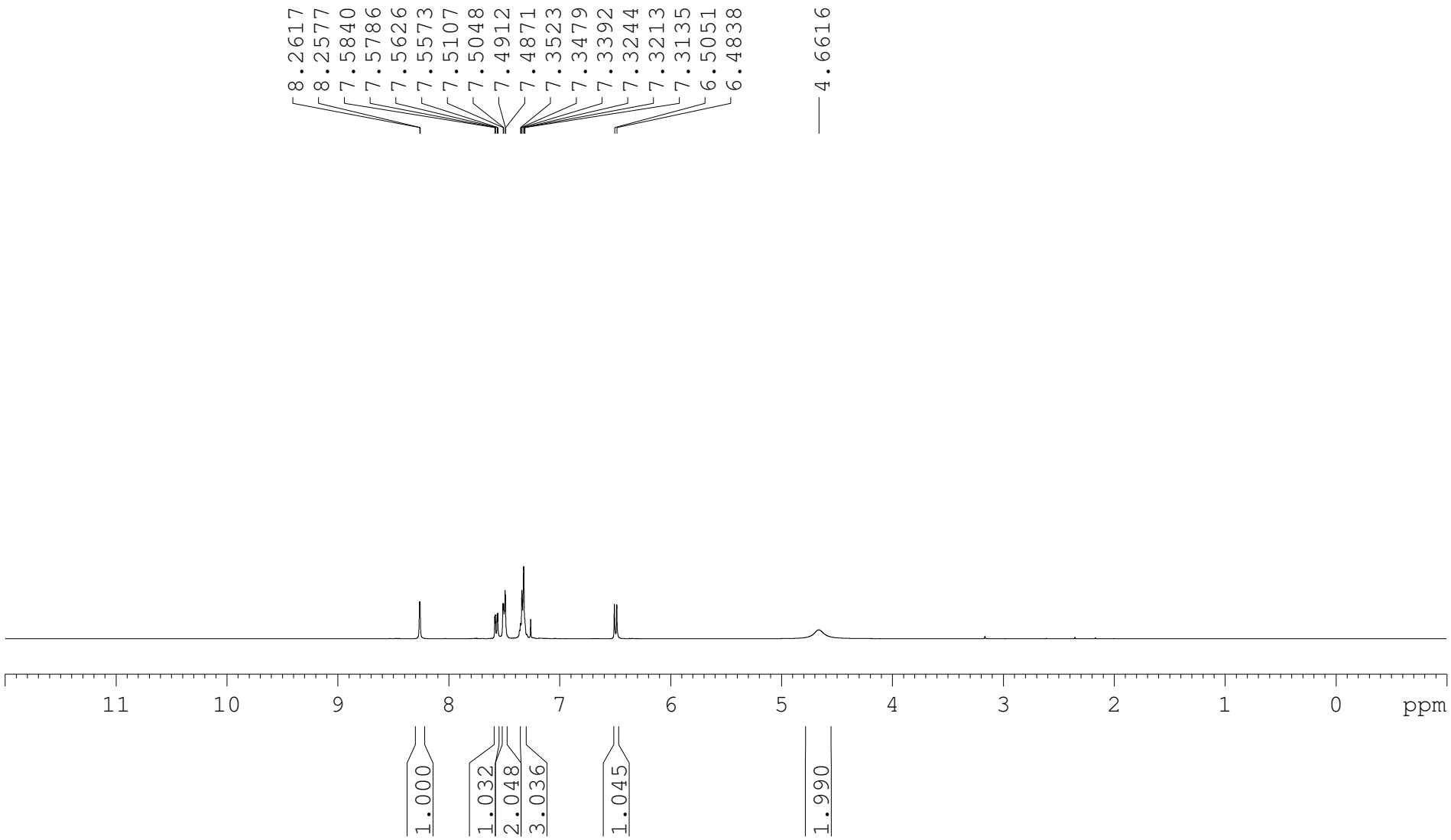
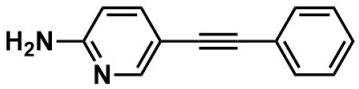
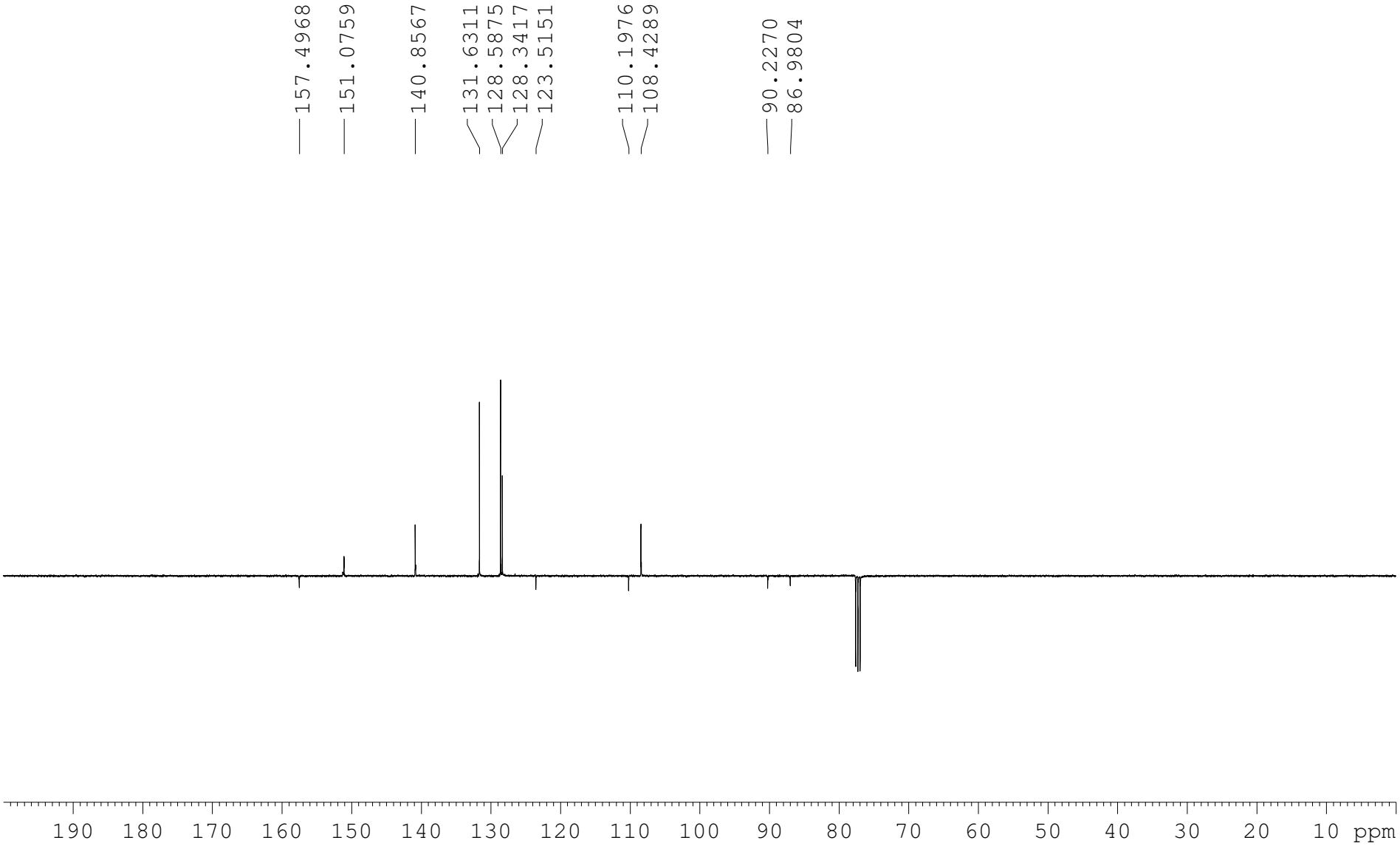


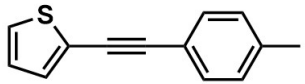
5-(phenylethynyl)pyridin-2-amine (**3m**)



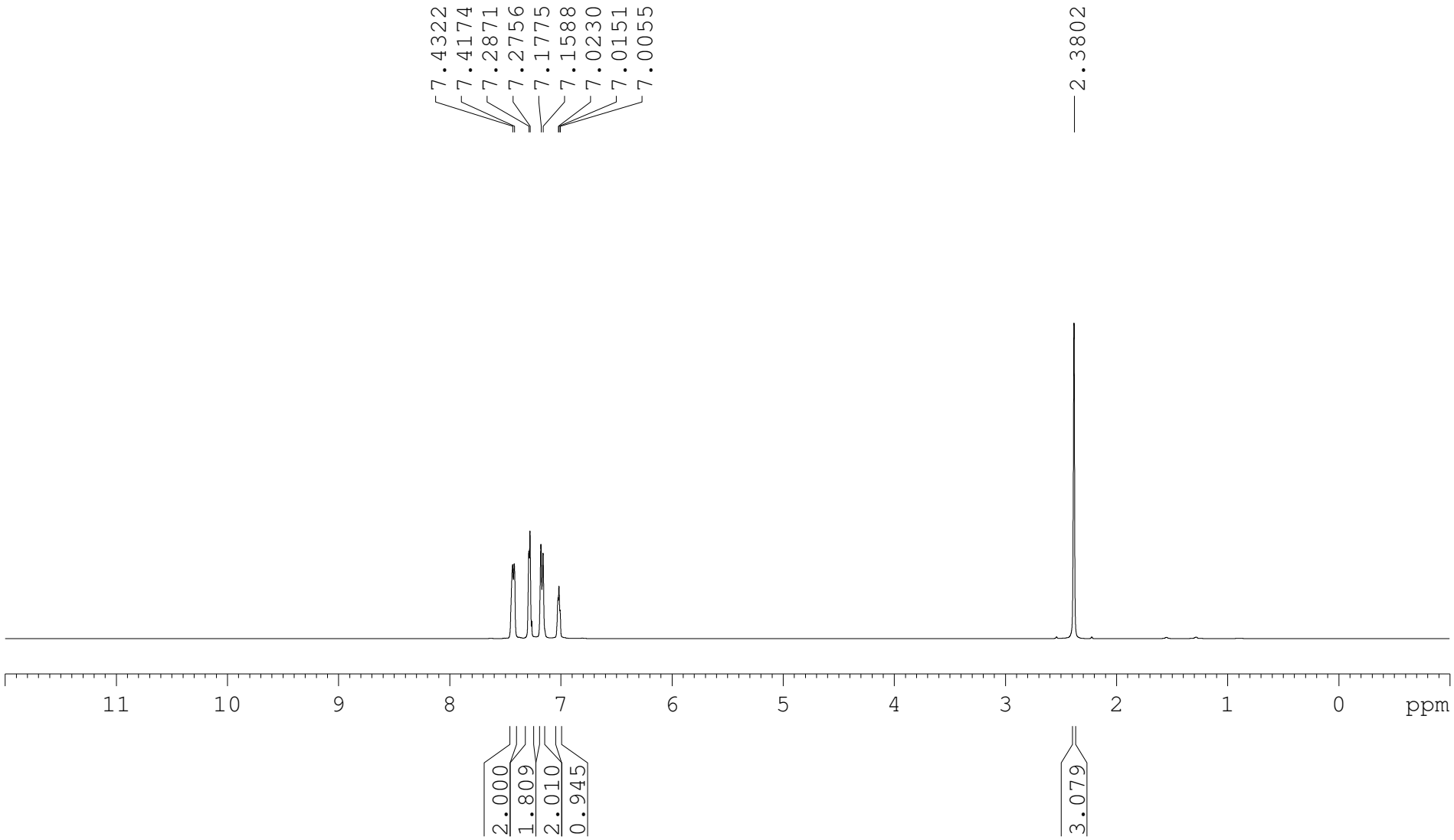
3m



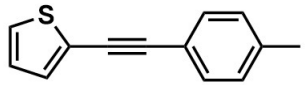
2-(p-tolylethynyl)thiophene (**3n**)



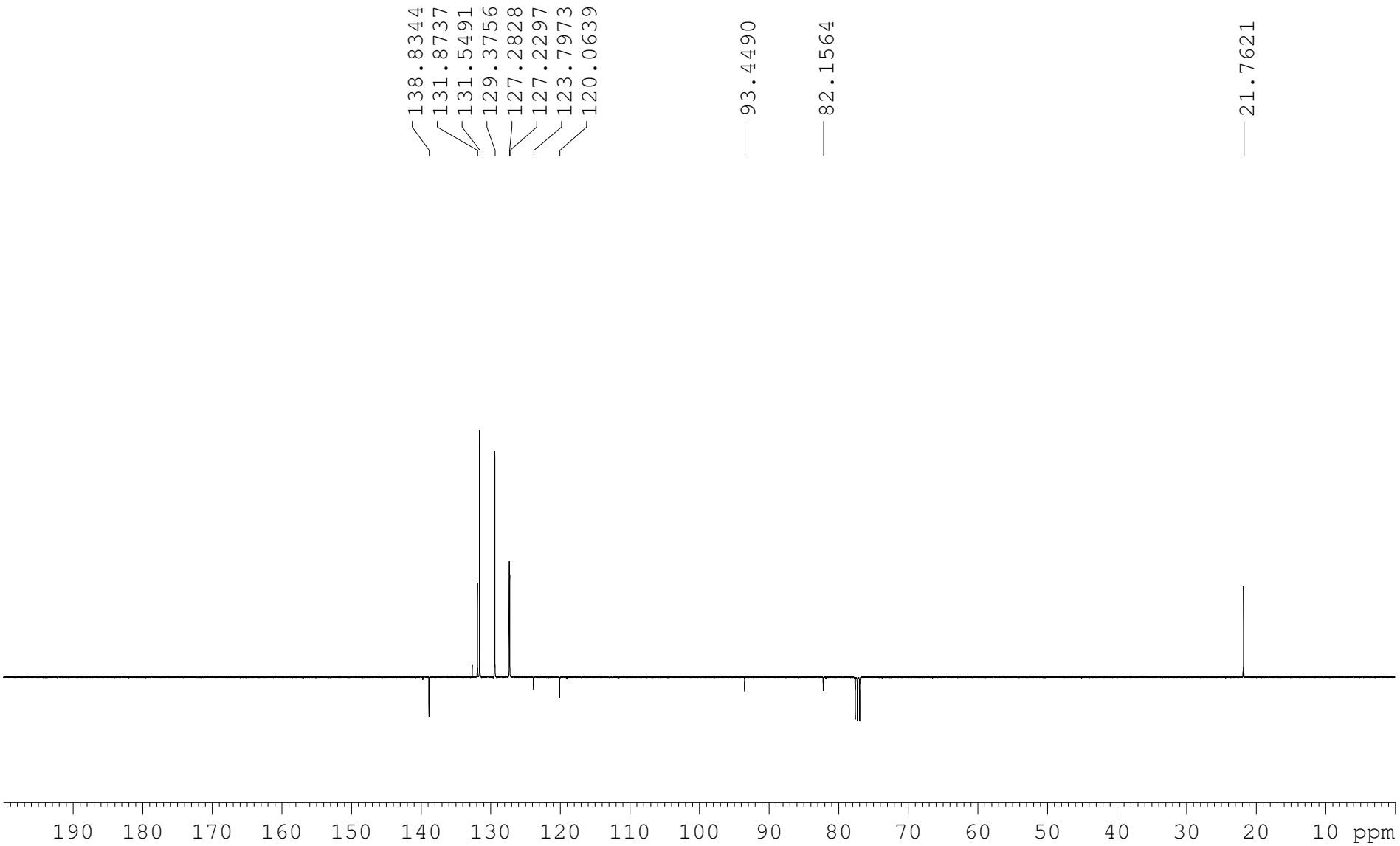
3n



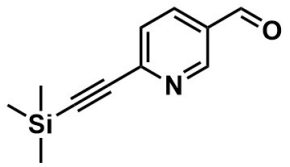
2-(p-tolylethynyl)thiophene (**3n**)



3n



6-((trimethylsilyl)ethynyl)nicotinaldehyde (**3o**)



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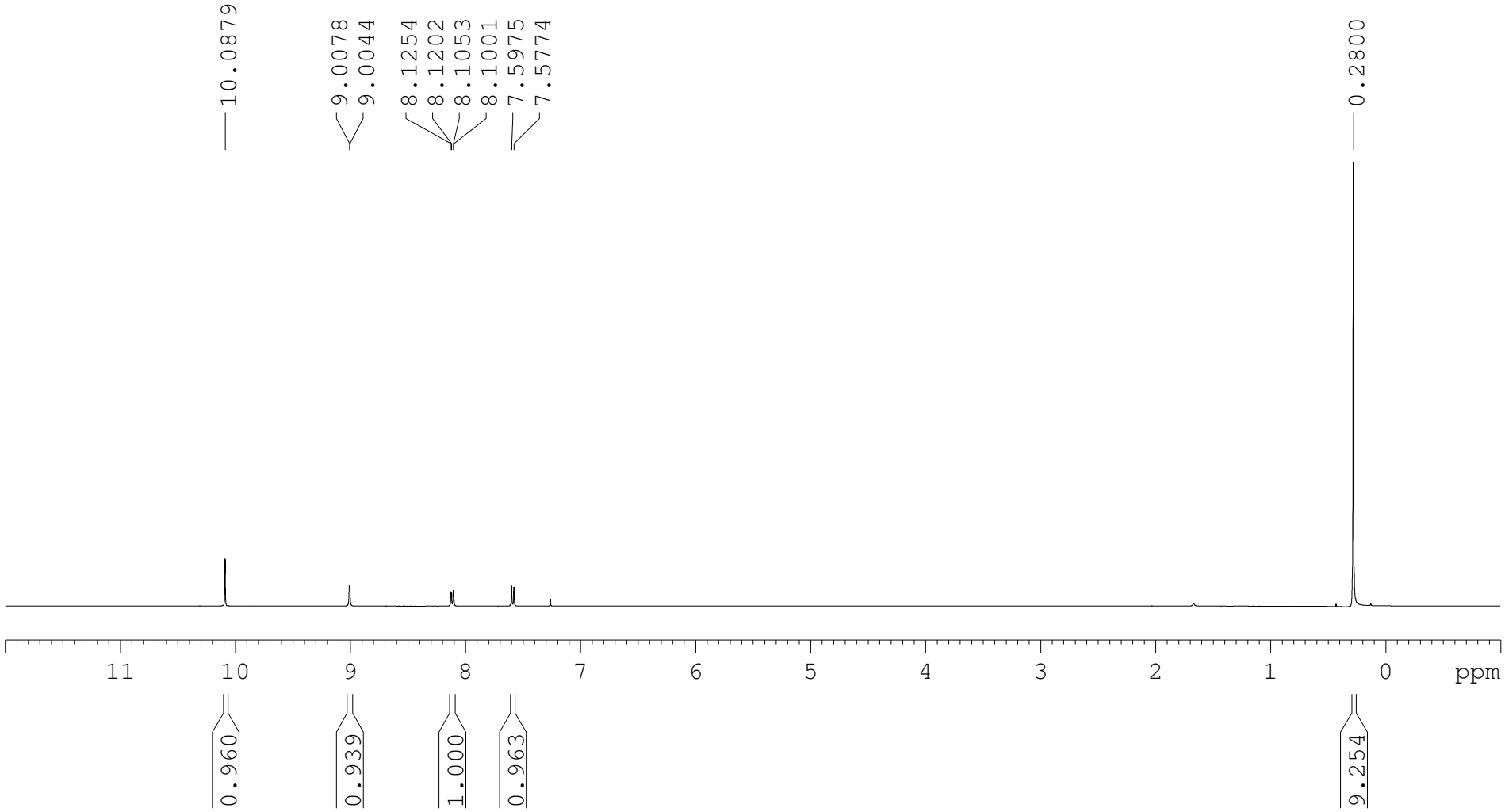
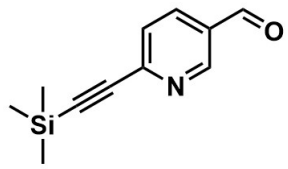


6-((trimethylsilyl)ethynyl)nicotinaldehyde (**3o**)



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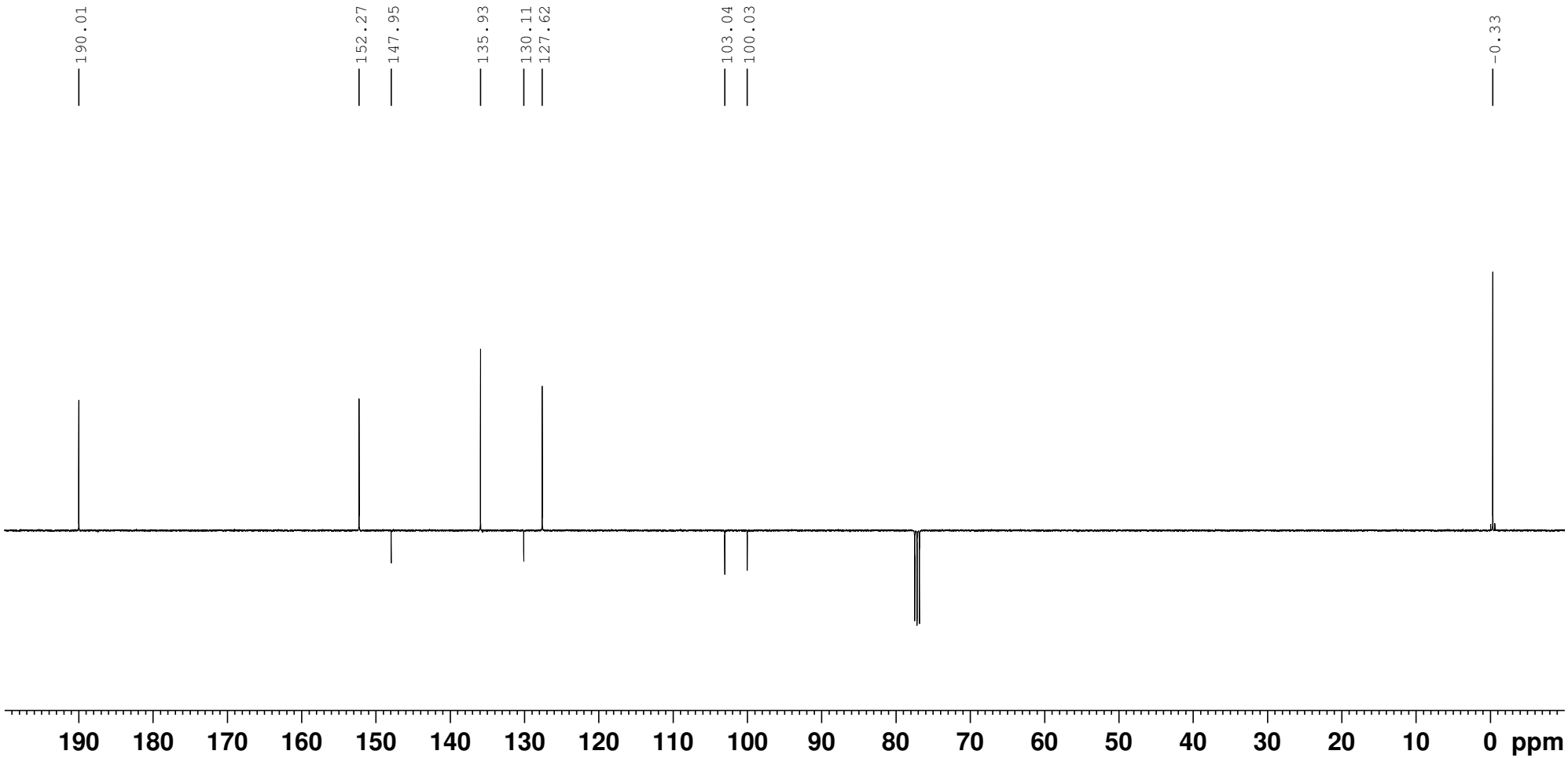
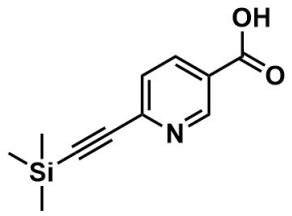


6-((trimethylsilyl)ethynyl)nicotinic acid (**3p**)



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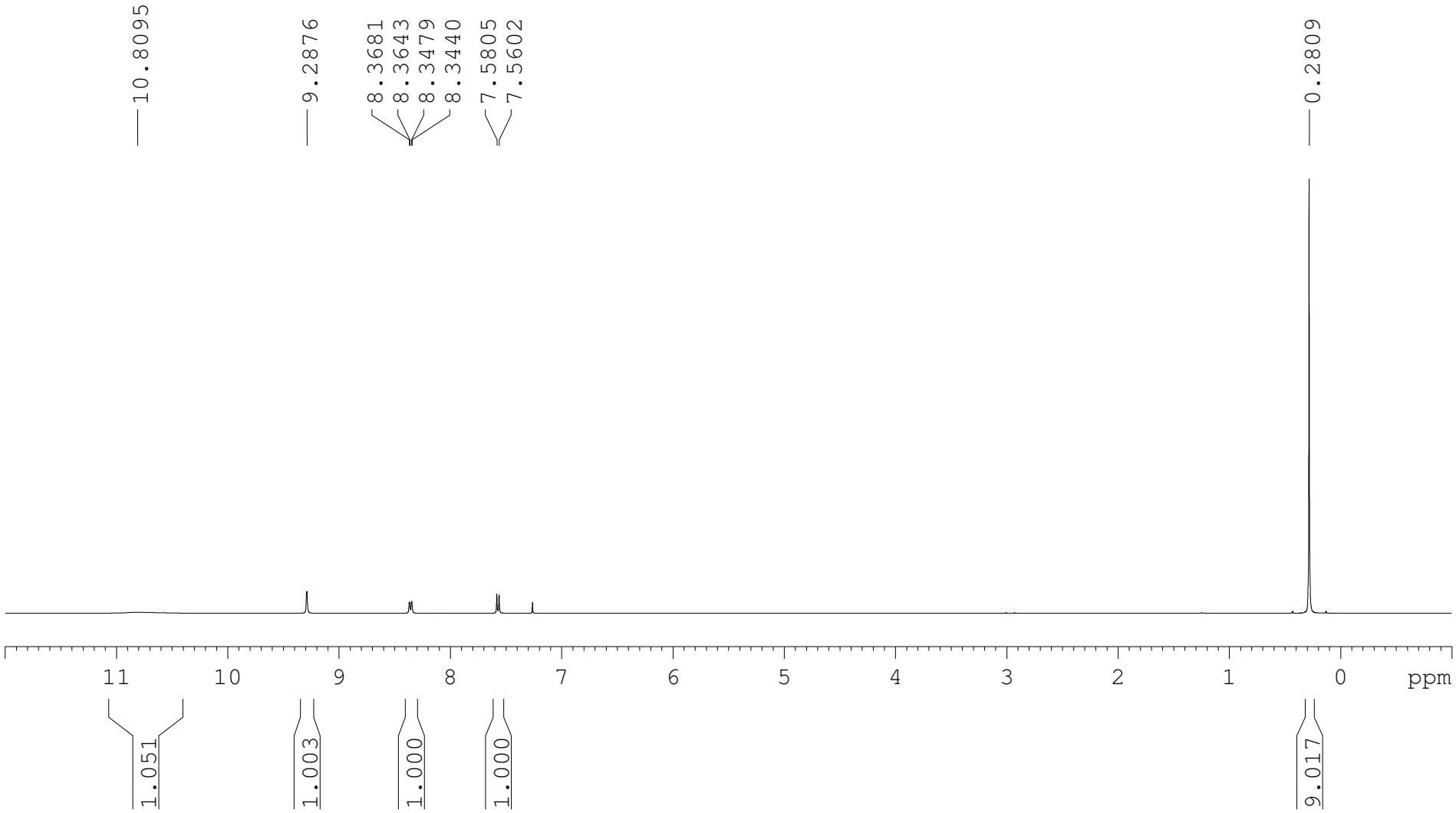
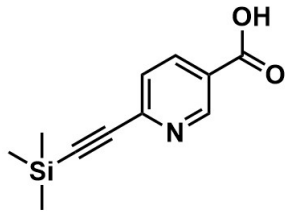


6-((trimethylsilyl)ethynyl)nicotinic acid (**3p**)



3p