One-Pot Synthesis of Substituted Indoles via Titanium (IV) Alkoxide Mediated Imine Formation – Copper-Catalyzed N-Arylation

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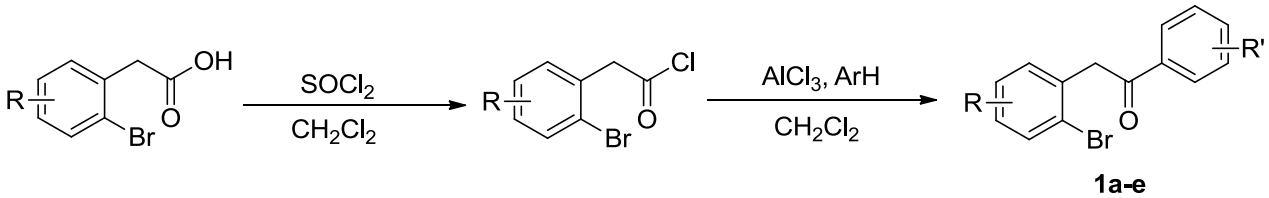
Supporting information

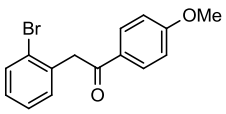
1. Synthesis of Starting Materials

General Procedure for the Synthesis of Ketones 1a–e.

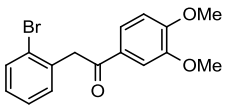


1a-e

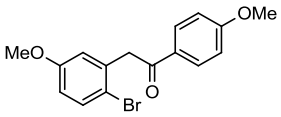
To a solution of an appropriate phenylacetic acid (50 mmol) in 100 mL of DCM a few drops of DMF were added, and then $SOCl_2$ (7.2 g, 4.41 mL, 60 mmol) was added dropwise at 0 °C under stirring. The reaction mixture was refluxed for 2 h and then was allowed to cool to room temperature; the volatile materials were removed under reduced pressure. The residue was dried under vacuum and redissolved in DCM (150 mL). An arene (93 mmol) or benzene (39g, 500 mmol) was added to the solution. The resulting mixture was cooled to 0 °C and $AlCl_3$ (7.2 g, 56 mmol) was gradually added keeping the internal temperature below 10 °C. The resulting mixture was stirred at room temperature for 2 h and was quenched with cold 3N HCl (200 mL). The organic layer was separated; the aqueous layer was extracted with DCM (50 mL). The combined extracts were washed with water, 5% sodium bicarbonate, and brine; dried over sodium sulfate. The solvent was removed under reduced pressure and residue was recrystallized from ethanol to afford a pure material.



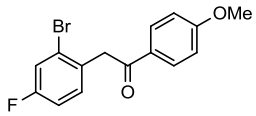
2-(2-Bromophenyl)-1-(4-methoxyphenyl)ethanone (1a):[1] synthesized from 2-bromophenylacetic acid (10.75 g) and anisole (10.04 g); white solid; 81% (12.35 g); mp 93–95 °C (lit.[1] mp 90–92 °C). ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H), 4.42 (s, 2H), 6.97 (d, J=8.6 Hz, 2H), 7.13–7.18 (m, 1H), 7.25–7.31 (m, 2H), 7.60 (d, J=8.0 Hz, 1H), 8.05 (d, J=8.6 Hz, 2H).



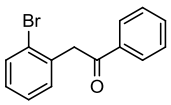
2-(2-Bromophenyl)-1-(3,4-dimethoxyphenyl)ethanone (1b):[2] synthesized from 2-bromophenylacetic acid (10.75 g) and veratrole (12.83 g); white solid; yield 84 % (14.05 g); mp 134–136 °C. (lit.[2] mp 137–138 °C). ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3H), 3.97 (s, 3H), 4.43 (s, 2H), 6.93 (d, J=8.4 Hz, 1H), 7.13–7.18 (m, 1H), 7.25–7.31 (m, 2H), 7.59 (d, J=2.0 Hz, 1H), 7.61 (dd, J=7.9, 1.0 Hz, 1H), 7.72 (dd, J=2.1, J=8.4 Hz, 1H).



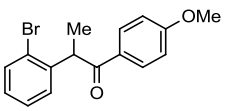
2-(2-Bromo-5-methoxyphenyl)-1-(4-methoxyphenyl)ethanone (1c):[3] synthesized from 2-bromo5-methoxyphenylacetic acid (12.25 g) and anisole (13.40 g); white solid; 80% (12.35 g); mp 133–115 °C (lit.[3] mp 117–118 °C). ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 3.90 (s, 3H), 4.38 (s, 2H), 6.73 (dd, *J*=8.8, 3.1 Hz, 1H), 6.83 (d, *J*=3.1 Hz, 1H), 6.98 (d, *J*=9.0 Hz, 2H), 7.48 (d, *J*=8.6 Hz, 1H), 8.05 (d, *J*=8.8 Hz, 2H).



2-(2-Bromo-4-fluorophenyl)-1-(4-methoxyphenyl)ethanone (1d):[2] synthesized from 2-bromo-4-fluorophenylacetic acid (11.65 g) and anisole (10.05 g); white solid; yield 78% (12.60 g); mp 80–82 °C (lit.[2] mp 79–83 °C). ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H), 4.36 (s, 2H), 6.96 (d, *J*=9.0 Hz, 2H), 7.00 (m, 1H), 7.21 (m, 1H), 7.33 (m, 1H), 8.01 (d, *J*=9.0 Hz, 2H).

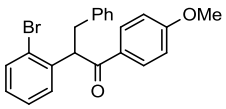


2-(2-Bromophenyl)-1-phenylethanone (1e):[4] synthesized from 2-bromophenylacetic acid (10.75 g) and benzene (39 g, 0.5 mol); white solid; 80% (11.0 g); mp 70–72 °C (lit.[4] mp 66–67 °C). ^{1}H NMR ($CDCl_3$): δ 4.58 (s, 2H), 7.21–7.27(m, 1H), 7.34-7.43(m, 2H), 7.53–7.66(m, 3H), 7.69 (t, *J*=7.2 Hz, 1H), 8.09(d, *J*=7.4 Hz, 2H).



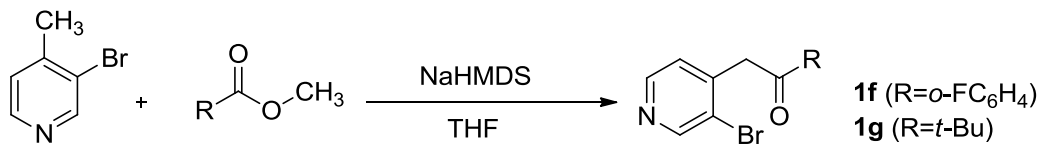
2-(2-Bromophenyl)-1-(4-methoxyphenyl)propan-1-one (1f) was obtained starting from ketone **1a** by adapting a procedure described early.[27] To a solution of ketone **1a** (460 mg, 1.5 mmol) in 1,2-dimethoxyethane (8 mL) powdered potassium hydroxide (170 mg, 3 mmol, 2 equiv) was added. Iodomethane (280 µL, 4.5 mmol) was then added via syringe and the resulting reaction mixture was stirred vigorously at room temperature for 48 h, after which time the solvent was removed under vacuum. The residue was dissolved in a mixture of DCM (10 mL) and 3N HCl (15 mL). The organic layer was separated and the aqueous fraction was further extracted with DCM (10 mL). The combined organic fractions were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The

crude residue was purified by flash chromatography (EtOAc/hexane, 1:10) to afford the title compound as a clear colorless oil; yield 95 % (454 mg). ^{1}H NMR ($CDCl_3$): δ 1.49 (d, J=6.9 Hz, 3H), 3.82 (s, 3H), 6.88 (d, J=9.1 Hz, 2H), 7.02–7.11 (m, 1H), 7.13–7.23 (m, 2H), 7.58–7.63 (m, 1H), 7.94 (d, J=9.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 20.9, 49.6, 58.3, 116.7, 126.8, 131.1, 131.3, 131.6, 132.0, 133.9, 136.1, 144.3, 166.3, 201.4. MS, *m/z* (I, %): 320, 318 (M^+, 3, 3), 135 (100). Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.21; H, 4.74. Found: C, 60.29; H, 4.67.



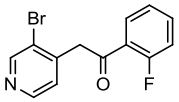
2-(2-Bromophenyl)-1-(4-methoxyphenyl)-3-phenylpropan-1-one (1g). To a suspension of NaH (60% in mineral oil) (160 mg, 4 mmol) in dry THF (15 mL) a solution of ketone **1a** (1000 mg, 3.2 mmol) in THF (30 mL) was gradually added at room temperature for 1 h. The resulting mixture was added dropwise to a solution of benzylchloride (810 mg, 6.4 mmol) in THF (10 mL). The resulted mixture was warmed to 60 °C and stirred at this temperature for 4 h or until the starting ketone **1a** was consumed (monitored by TLC). The mixture was cooled to room temperature, quenched with 3N HCl (100 mL) and extracted with DCM. Organic layer washed with 5% sodium bicarbonate, brine and dried over sodium sulfate and evaporated under reduced pressure, the residue purified by column chromatography on silica gel (EtOAc/hexanes, 1:10) to afford the title compound as a colorless viscous oil; yield 90 % (1130 mg). ^{1}H NMR ($CDCl_3$): δ 2.98 (dd, J=13.7, 5.1 Hz, 1H), 3.51 (dd, J=13.7, 8.9 Hz, 1H), 3.80 (s, 3H), 5.34 (dd, J=8.9, 5.2 Hz, 1H), 6.84 (d, J=9.0 Hz, 2H), 7.07–7.11 (m, 1H), 7.15–7.19 (m, 2H), 7.21–7.27 (m, 4H), 7.32 (dd, J=7.8, 1.6 Hz, 1H), 7.59 (dd, J=7.8, 1.2 Hz, 1H), 7.91(d, J=9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 42.2, 56.8, 58.3, 116.7, 127.5, 129.1, 131.0, 131.1, 131.6, 131.9, 132.2, 132.4, 133.9, 136.2, 142.2, 142.6, 166.4, 200.0. Anal. Calcd. for $C_{22}H_{19}BrO_2$: C, 66.85; H, 4.84. Found: C, 66.79; H, 4.79.

General Procedure for the Synthesis of Ketones 1h, i.

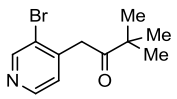


To a solution of 3-bromo-4-methylpyridine (0.86 g, 5 mmol) in THF (5 mL) at –20° C a solution of NaHMDS (6 mL, 1 M in THF, 6 mmol) was added, keeping the internal temperature below –5 °C. The mixture was stirred at –20 °C for 30 min and then an appropriate methyl ester (7.5 mmol) in THF (5 mL) was added dropwise over 5 min. Then mixture was stirred at –20 °C for 30 min, warmed to room temperature and left to stir for another 1 h and was then quenched with 1 M citric acid (10 mL). The

organic layer was separated and the aqueous layer was extracted with DCM (30 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuum; the residue was purified by column chromatography (EtOAc/hexanes, 1:1).



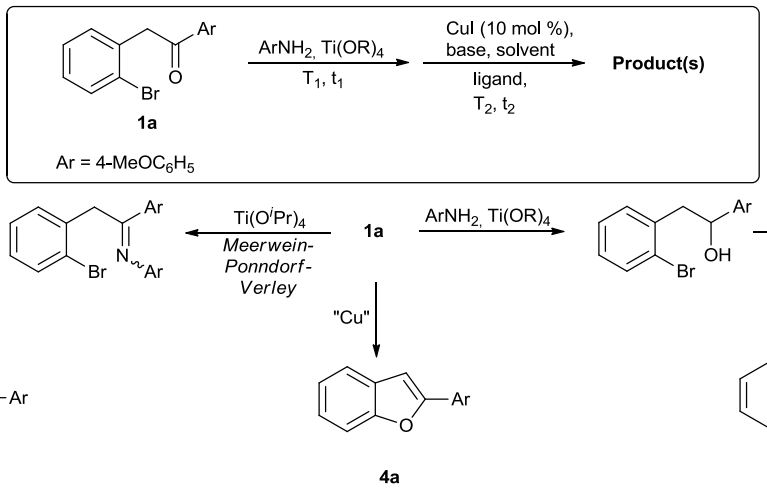
2-(4-Bromopyridin-3-yl)-1-(2-fluorophenyl)ethanone (1h)*:* synthesized from methyl 2-fluorobenzoate (1.15 g); yellow amorphous solid; yield 62 % (911 mg); mp 126 – 129 °C. NMR ^{1}H ($CDCl_3$): δ 4.47 (d, J=2.2 Hz, 2H), 7.19–7.26 (m, 2H), 7.29–7.34 (m, 1H), 7.61 (m, 1H), 7.95 (td, J=7.5, 1.76 Hz, 1H), 8.51 (d, J=4.9 Hz, 1H), 8.76 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 49.7 ($J_{C\text{-}F}$=9.1 Hz), 116.8 ($J_{C\text{-}F}$=23.8 Hz), 123.9, 124.8 ($J_{C\text{-}F}$=3.3 Hz), 124.9 ($J_{C\text{-}F}$=12.8 Hz), 126.7, 130.9 ($J_{C\text{-}F}$=1.8 Hz), 135.4 ($J_{C\text{-}F}$=9.2 Hz), 143.7 ($J_{C\text{-}F}$=2.2 Hz), 148.3, 151.9, 162.0 ($J_{C\text{-}F}$=254.7 Hz), 192.7 ($J_{C\text{-}F}$=4.4 Hz). MS, *m/z* (I, %): 294, 296 (M+1, 2, 2), 295, 293 (M^+, 2, 2), 214 (25), 123 (100), 95 (55). Anal. Calcd for $C_{13}H_9BrFNO$: C, 53.09; H, 3.08; N, 4.76. Found: C, 53.15; H, 3.01; N, 4.70.



1-(4-Bromopyridin-3-yl)-3,3-dimethylbutan-2-one (1i): synthesized from methyl pivalate (870 mg) yellow viscous oil; yield 71 % (910 mg). ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 9H), 4.01 (s, 2H), 7.14 (d, J=4.9 Hz, 1H), 8.47 (d, J=4.9 Hz, 1H), 8.71 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 26.6, 43.3, 44.8, 123.6, 126.8, 144.1, 148.1, 151.7, 210.0. MS, *m/z* (I, %): 255, 257 (M^+, 2, 2), 85 (15), 57 (100). Anal. Calcd for $C_{11}H_{14}BrNO$: C, 51.58; H, 5.51; N, 5.47. Found: C, 51.62; H, 5.46; N, 5.41.

Titanium (IV) *tert*-Butoxide[5]. The following literature procedure was used for the synthesis. A 500 ml three necked flask equipped with magnetic stirrer, condenser and argon inlet was charged with 48 g (169 mmol) of Ti(OPr-*i*)$_4$ and 86 g (740 mmol) of *tert*-butyl acetate. The mixture was slowly heated under stirring. Isopropyl acetate formed during the reaction was removed by distillation at 95 °C. After all isopropyl acetate was distilled off, the mixture was cooled to room temperature and 43 g (370 mmol) of *tert*-butyl acetate was added. The solution was heated to remove isopropyl acetate formed and an excess of *tert*-butyl acetate at 95-100 °C. The residue was fractionally distilled in vacuo to collect fraction with boiling point 82-85 °C (0.5 mm/Hg). Yield 96 %. Colorless liquid. NMR ^{1}H ($CDCl_3$): δ, ppm, 1.32 (s, 36H).

2. Additional optimization data



Entry	$Ti(OR)_4$; equiv	T_1, °C	t_1, h	Base; equiv	Solvent	Ligand	T_2, °C	t_2, h	Yields, %[b]		
									2b	**3a**	**4a**
1	$Ti(O^iPr)_4$; 5	75	5	Cs_2CO_3; 2	DMF		125	10		75	
2	$Ti(O^iPr)_4$; 5	140	5	Cs_2CO_3; 2	DMF		125	10	45		15
3[c]	$Ti(O^iPr)_4$; 10	140	10	Cs_2CO_3; 2	DMF		125	10			70[d]
4	$Ti(O^tBu)_4$; 5	60	5	Cs_2CO_3; 2	DMF		125	10		98	
5	$Ti(O^tBu)_4$; 5	100	5	Cs_2CO_3; 2	DMF		125	10	60	29	
6	$Ti(O^tBu)_4$; 5	140	5	Cs_2CO_3; 2	DMF		125	10	70	10	
7	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMF		125	10	77		
8	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMA		125	10	85[d]		
9	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMA		125	5	65		
10	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMA		125	18	78		
11[e]	$Ti(O^tBu)_4$; 2	140	10	Cs_2CO_3; 2	DMA		125	10	93[d]		
12	$Ti(O^tBu)_4$; 2	140	10	Cs_2CO_3; 3	DMA		125	10	91[d]		
13	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	none		125	10			
14	$Ti(O^tBu)_4$; 2	140	10	Cs_2CO_3; 2	*o*-xylene[f]		125	10			
15	$Ti(O^tBu)_4$; 2	140	10	Cs_2CO_3; 2	DMA[f]		125	10		50	
16	$Ti(OEt)_4$; 5	140	10	Cs_2CO_3; 2	DMA		125	10	70		
17	$Ti(O^tBu)_4$; 5	140	10	K_2CO_3; 2	DMA		125	10	67		
18	$Ti(O^tBu)_4$; 5	140	10	K_3PO_4; 2	DMA		125	10	73		
19	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMA		90	10	11		
20	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMA	*L*-proline	90	10	75[d]		
21	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMA	ethylene glycol	90	10	20		
22	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMA	DMEDA	90	10	26		
23	$Ti(O^tBu)_4$; 5	140	10	Cs_2CO_3; 2	DMA	1,10-phenantroline	90	10	43		

[a] Reaction scale: **1a** (0.5 mmol, 0.25 M); *p*-anisidine (0.65 mmol), under argon. [b]NMR yields determined using CH_2Br_2 as internal standard. [c]Without $ArNH_2$. [d]Isolated yield. [e]Reaction scale: **1a** (2 mmol, 0.25 M); *p*-anisidine (2.6 mmol). [f]Added at the beginning of the two-step reaction. DMEDA=*N*,*N*′-dimethylethylenediamine.

3. References

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2. J. Ichikawa, H. Miyazaki, K. Sakoda, Y. Wada, *J. Fluorine Chem*., 2004, **125**, 585.
3. J. Bonnamour, M. Piedrafita and C. Bolm, *Adv. Synth. Catal*., 2010, **352**, 1577.
4. M. C. Willis, D. Taylor and A. T. Gillmore, *Tetrahedron*, 2006, **62**, 11513
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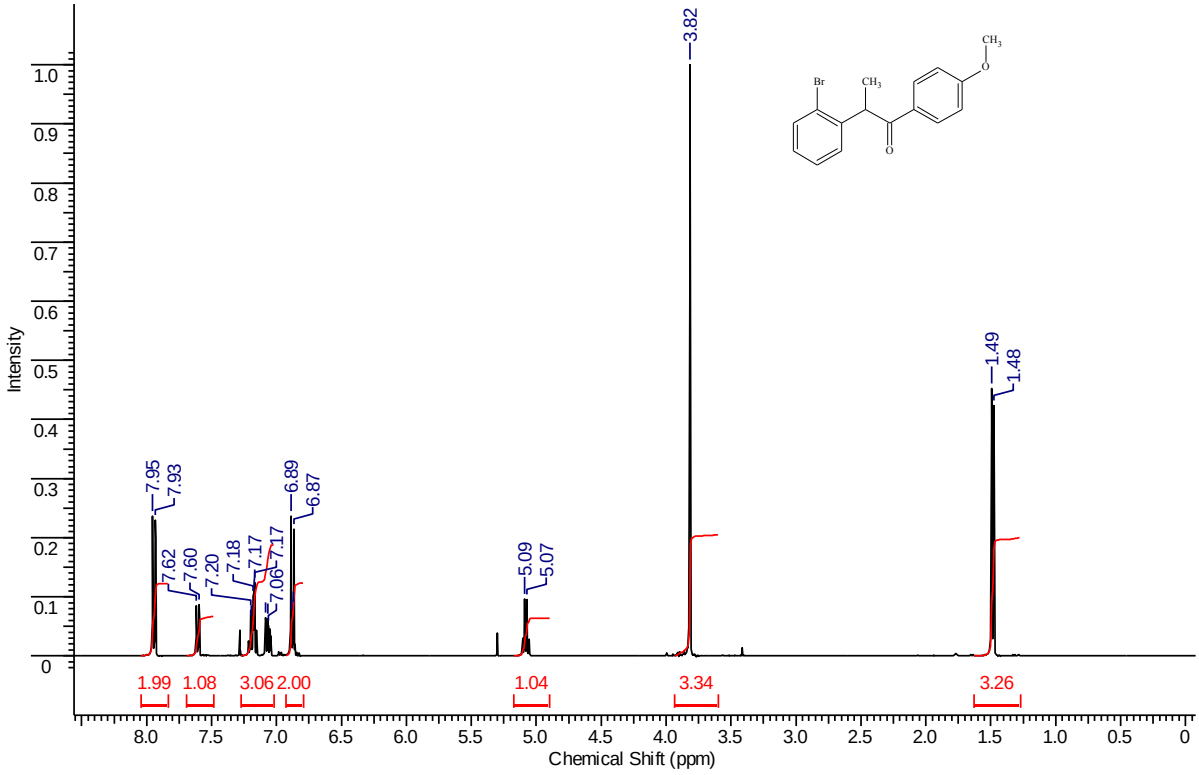
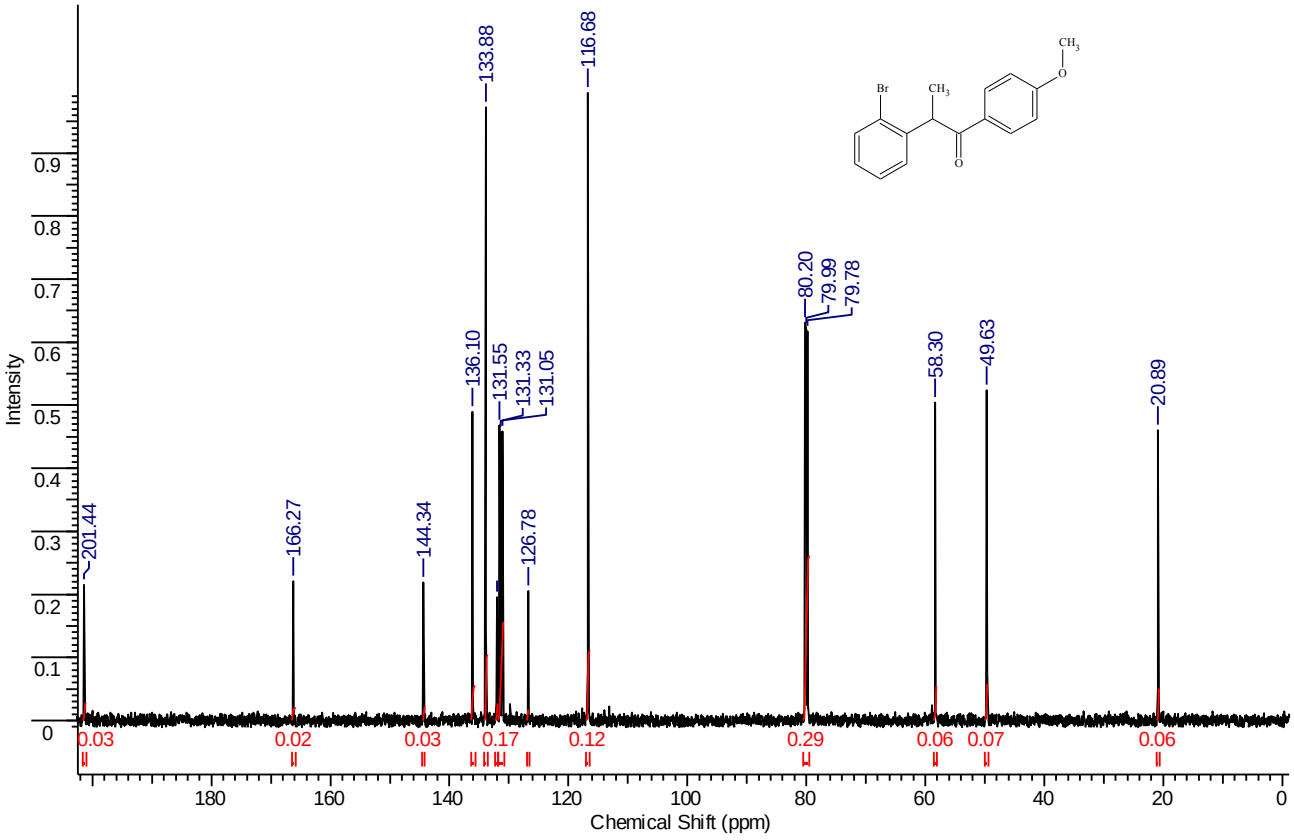
4. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds

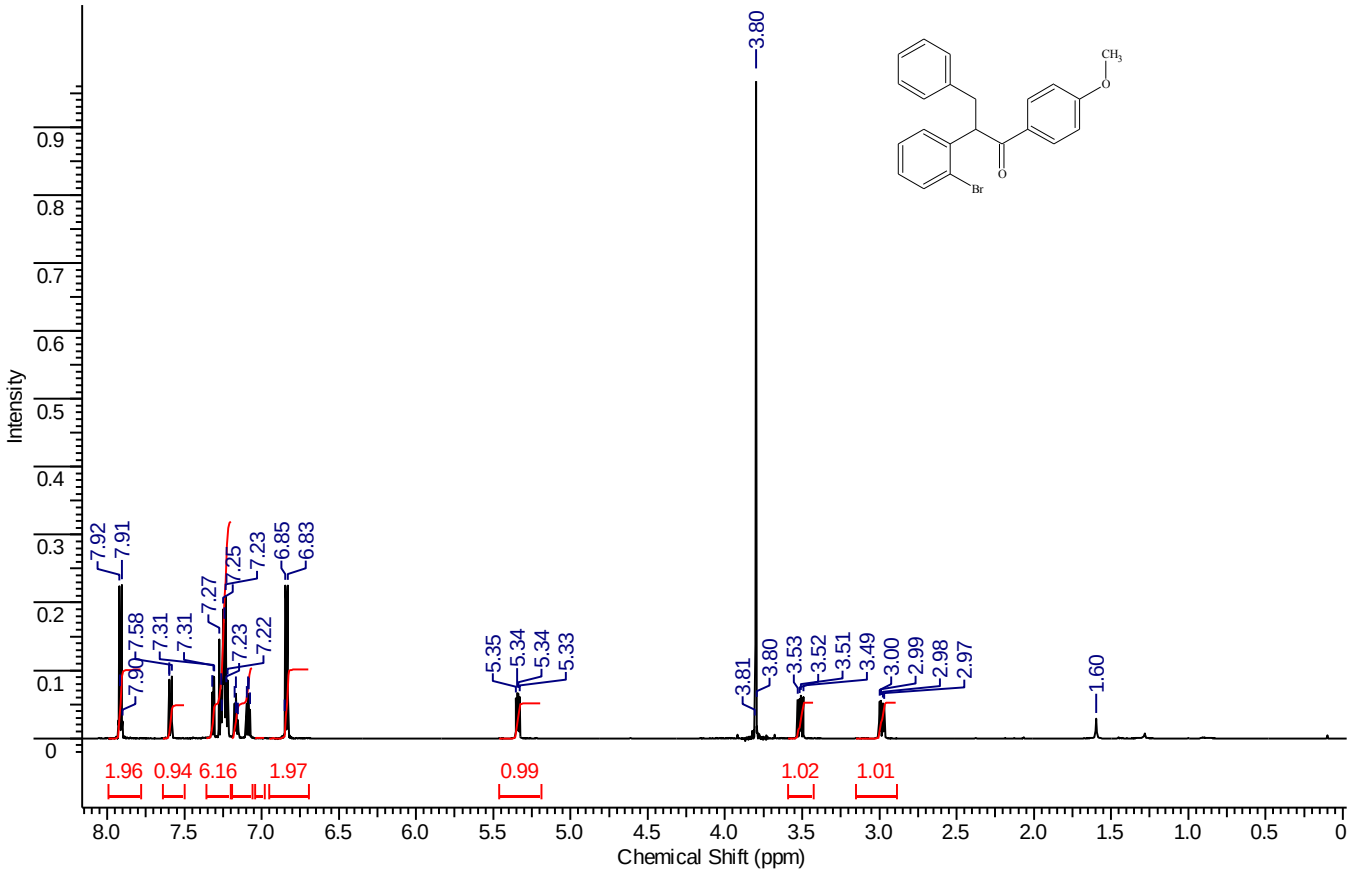
1f ($CDCl_3$) ^{1}H



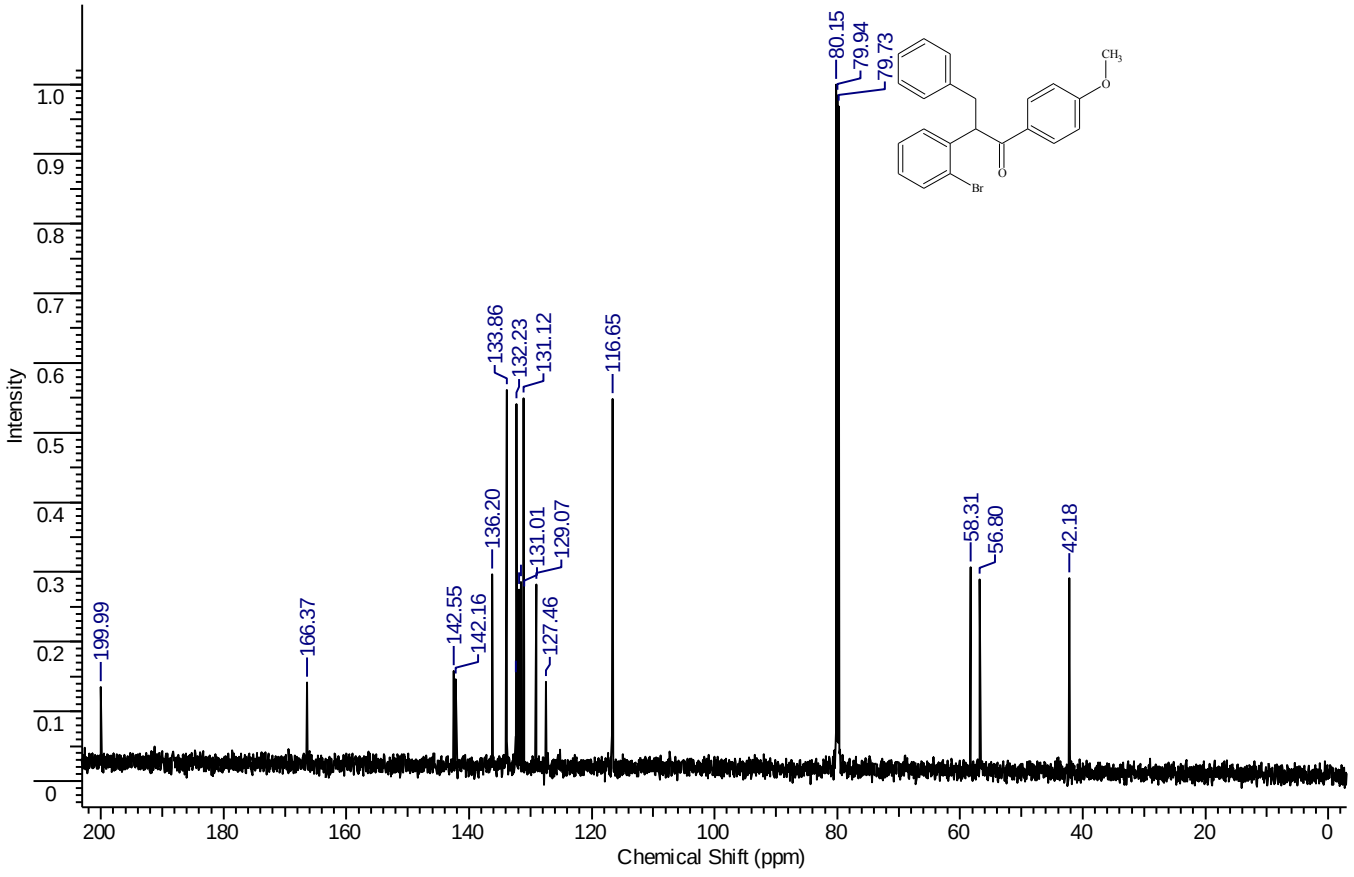
1f ($CDCl_3$) ^{13}C



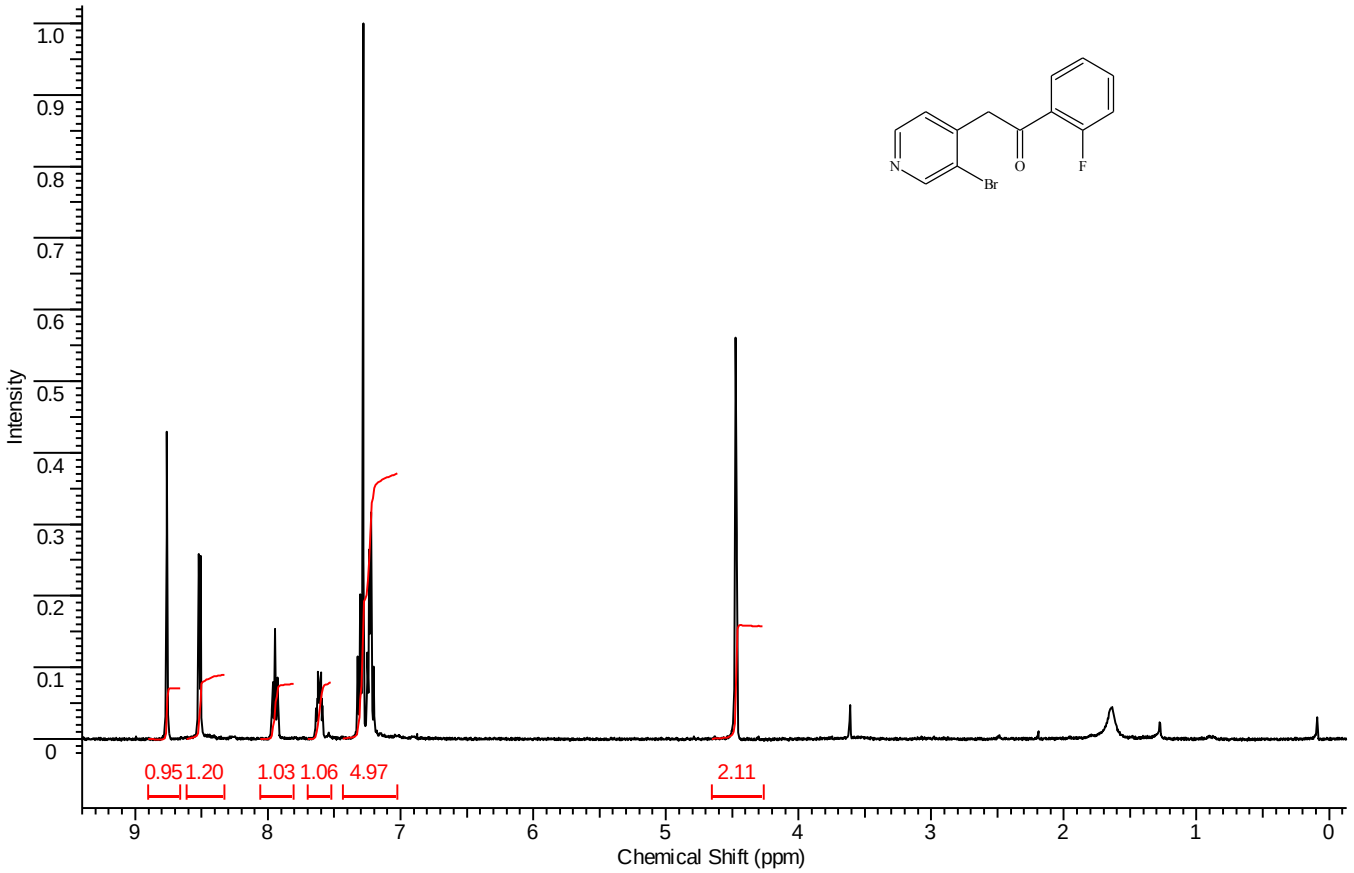
1g ($CDCl_3$) ^1H



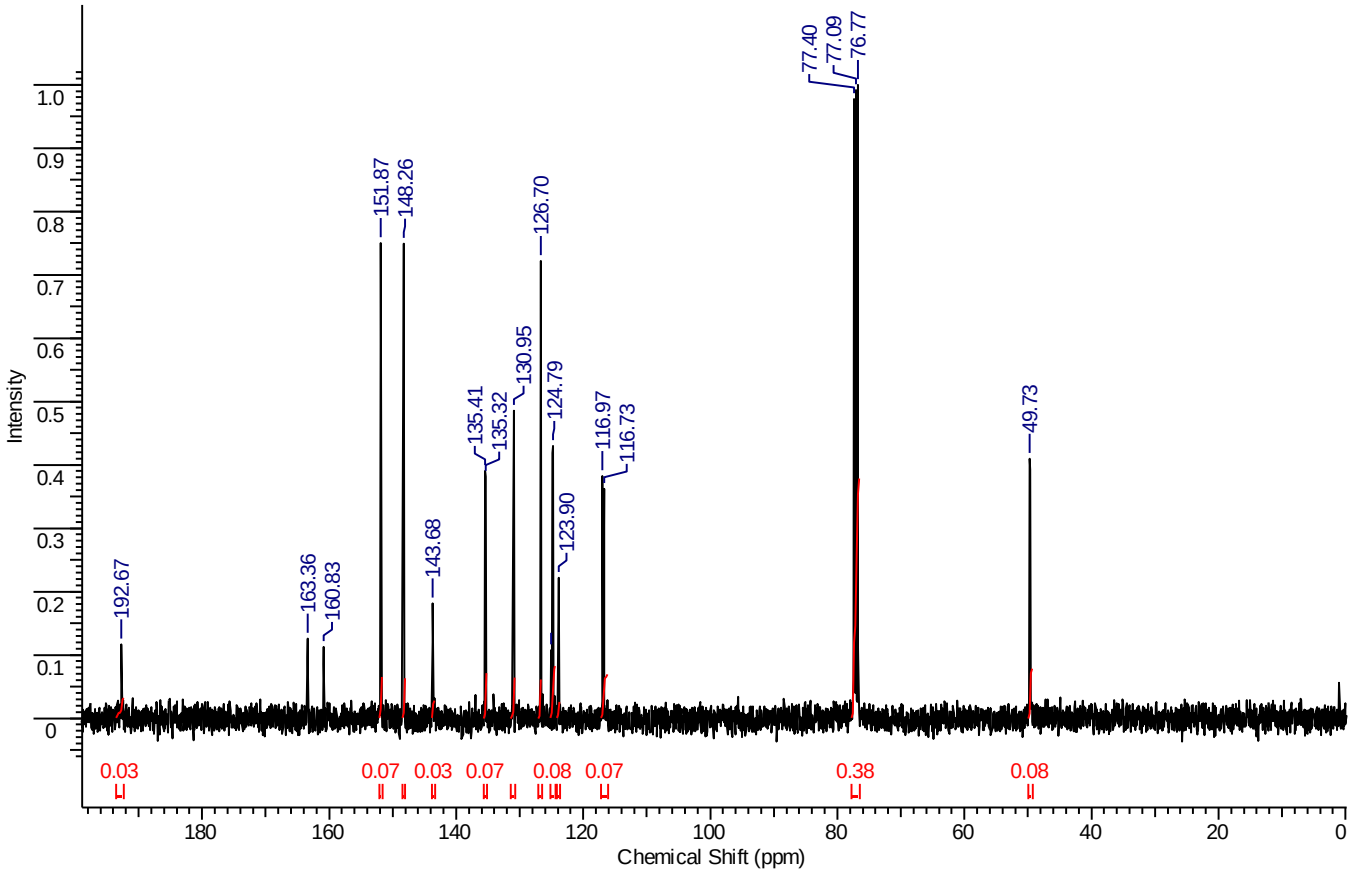
1g ($CDCl_3$) ^{13}C



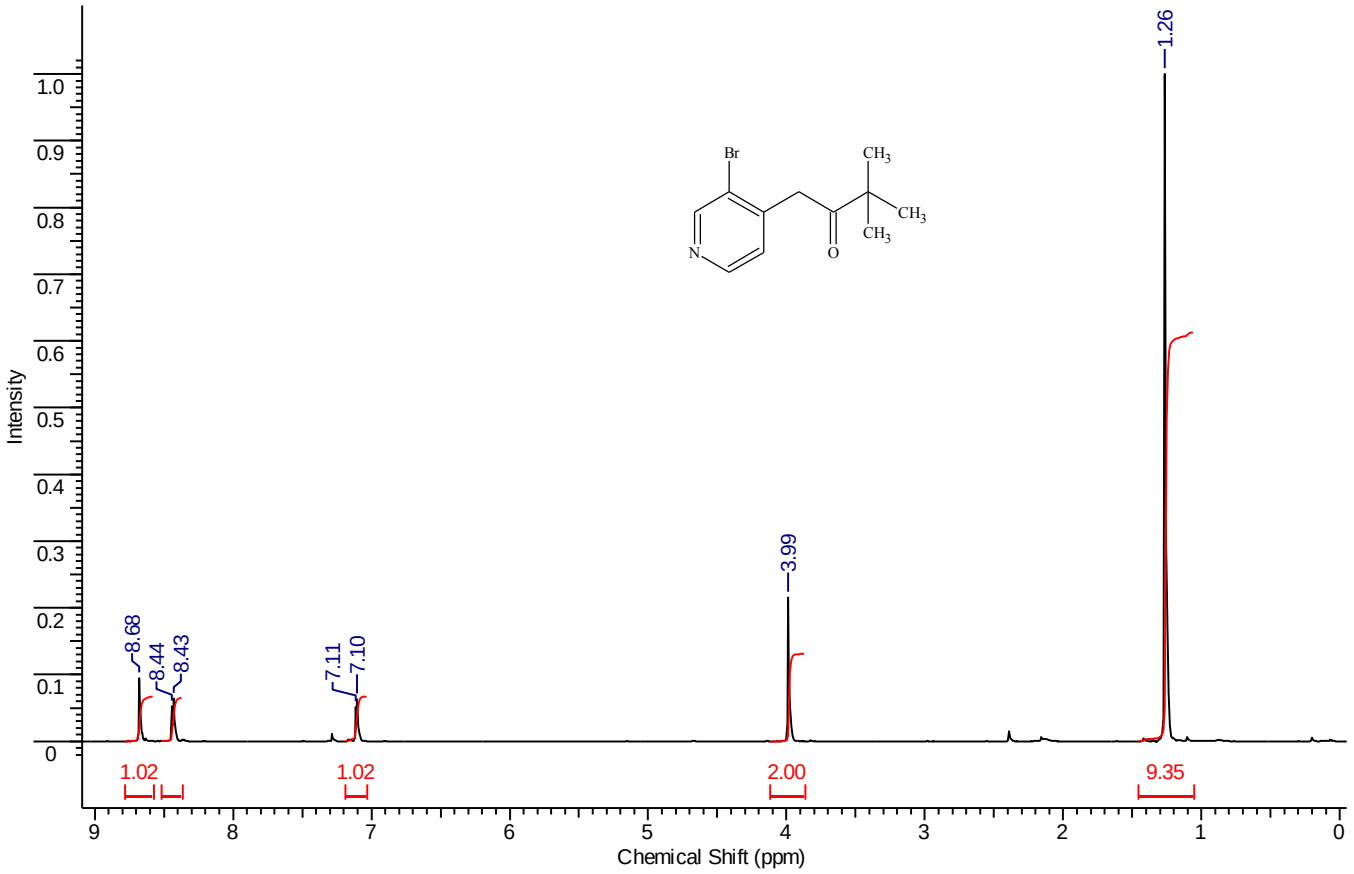
1h ($CDCl_3$) ^{1}H



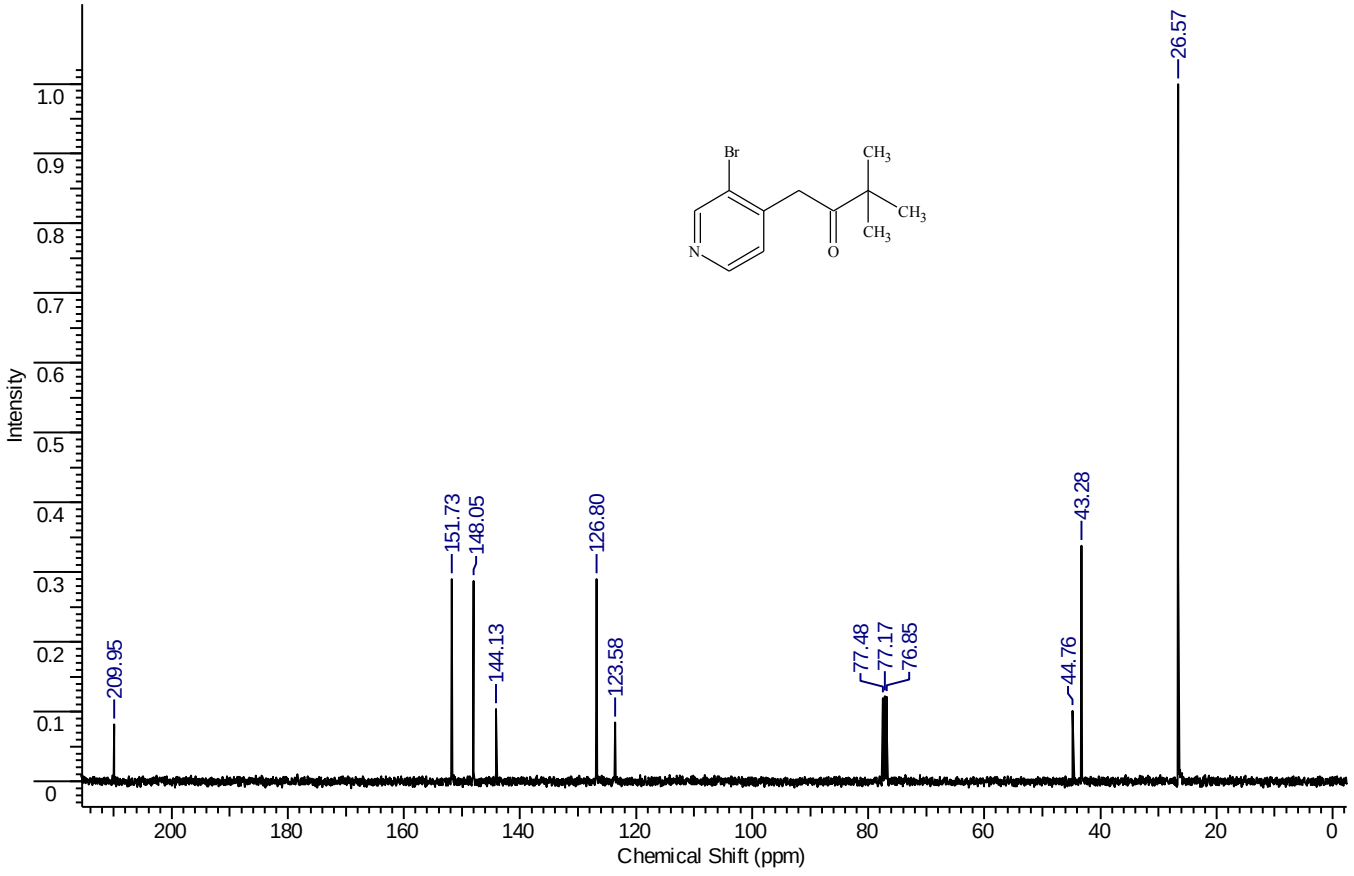
1h ($CDCl_3$) ^{13}C



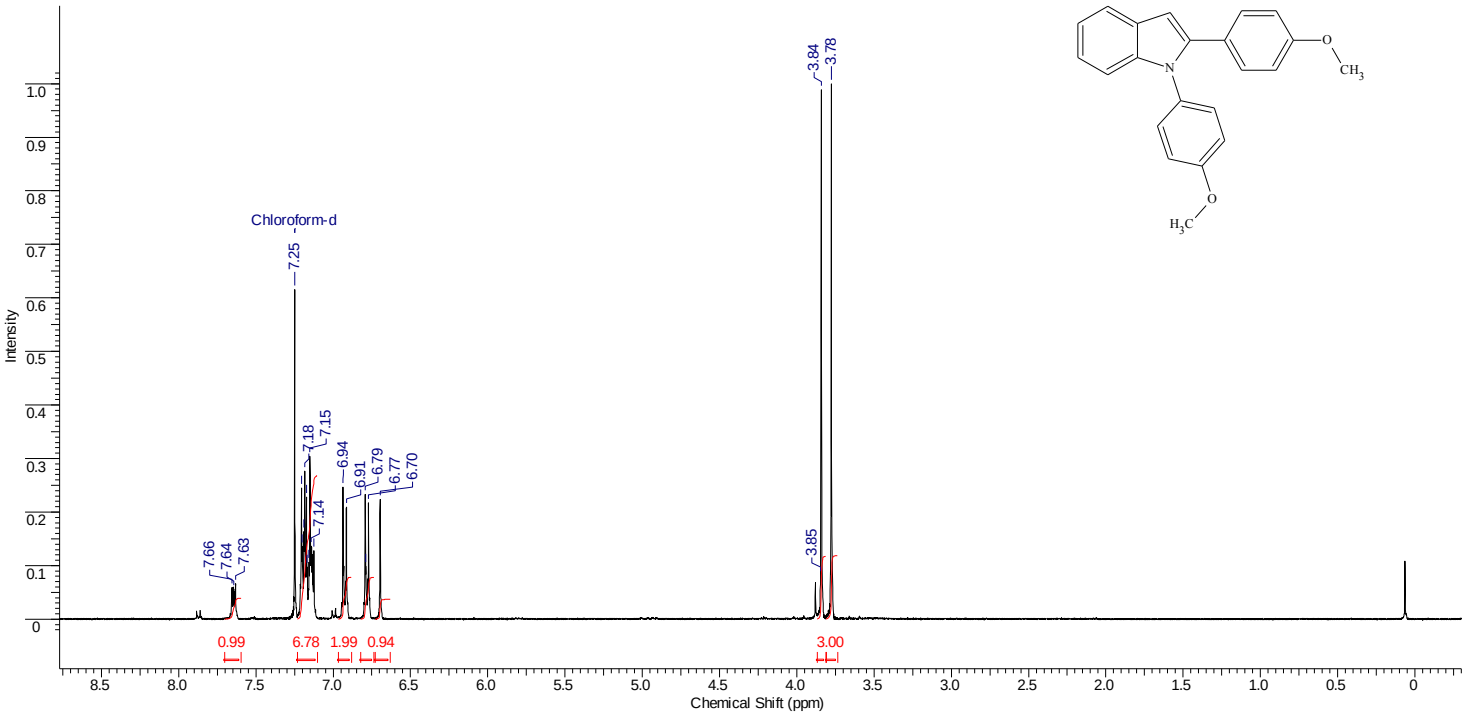
1i ($CDCl_3$) ^1H



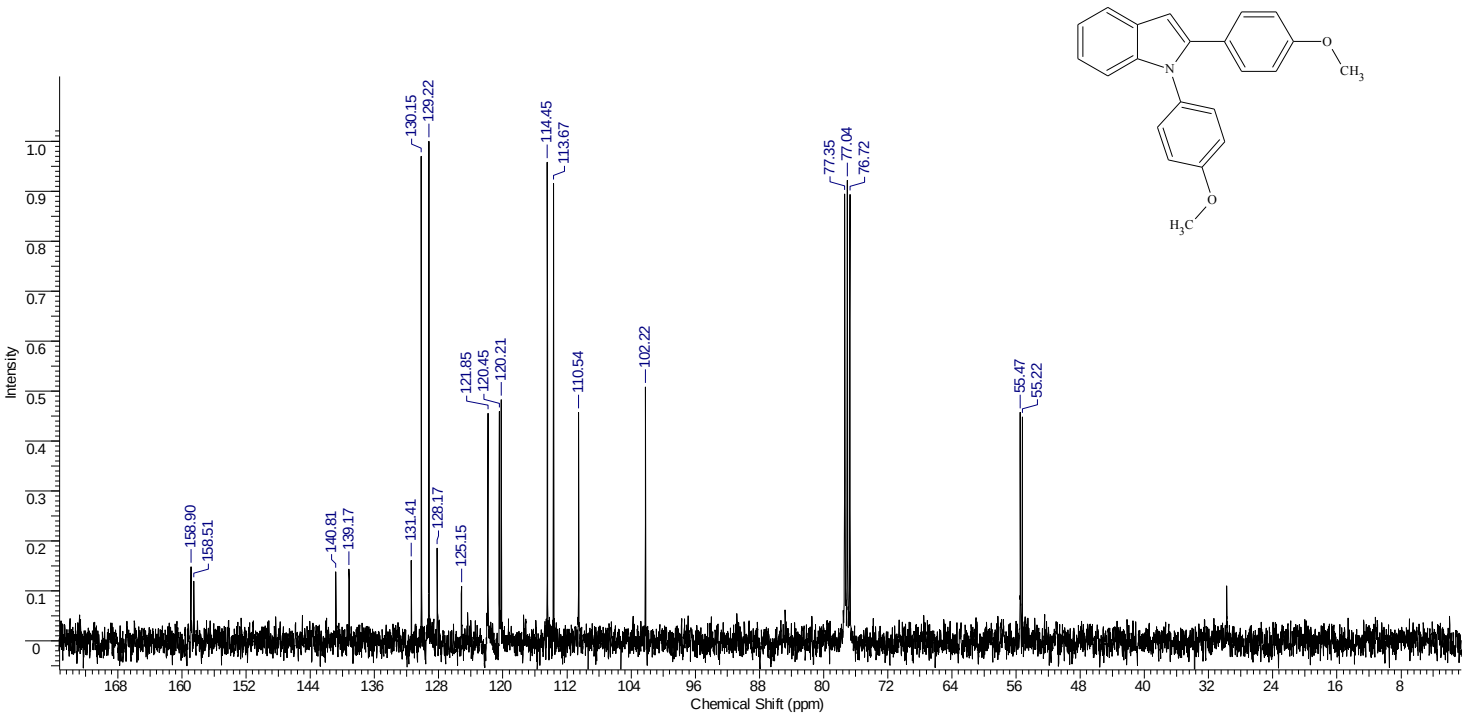
1i ($CDCl_3$) ^{13}C



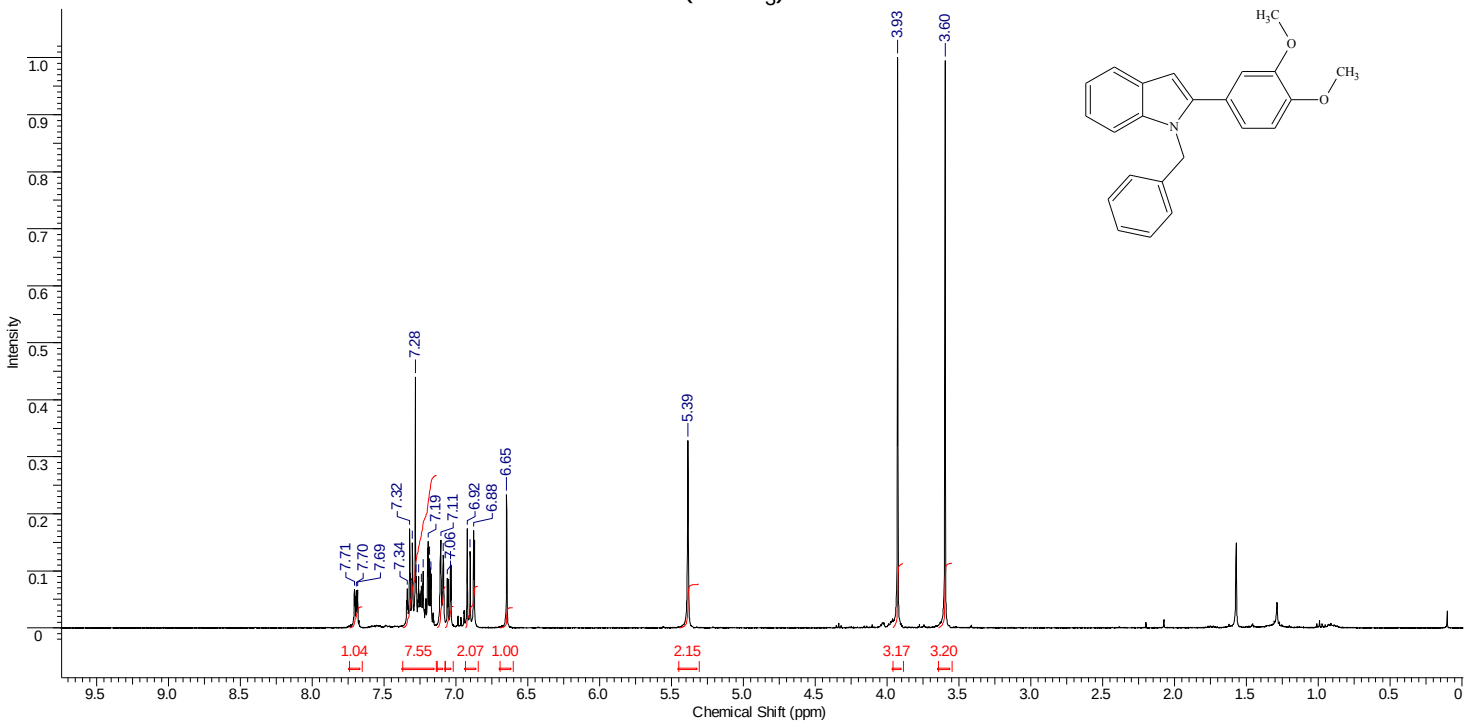
2a ($CDCl_3$) ^1H



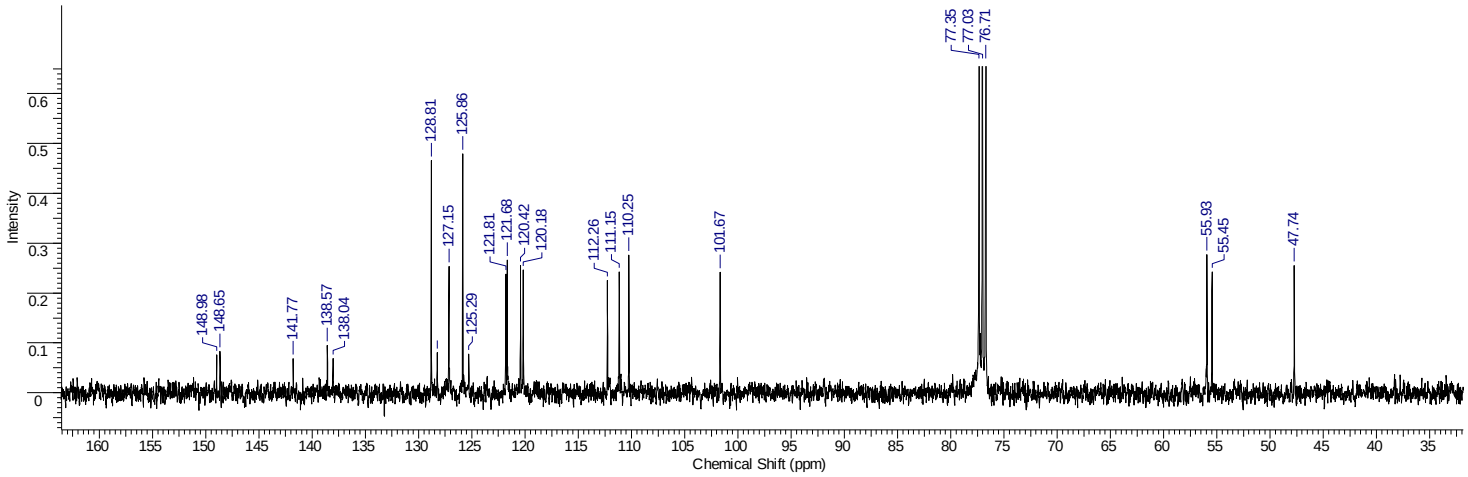
2a ($CDCl_3$) ^{13}C



2b ($CDCl_3$) ^1H



2b ($CDCl_3$) ^{13}C



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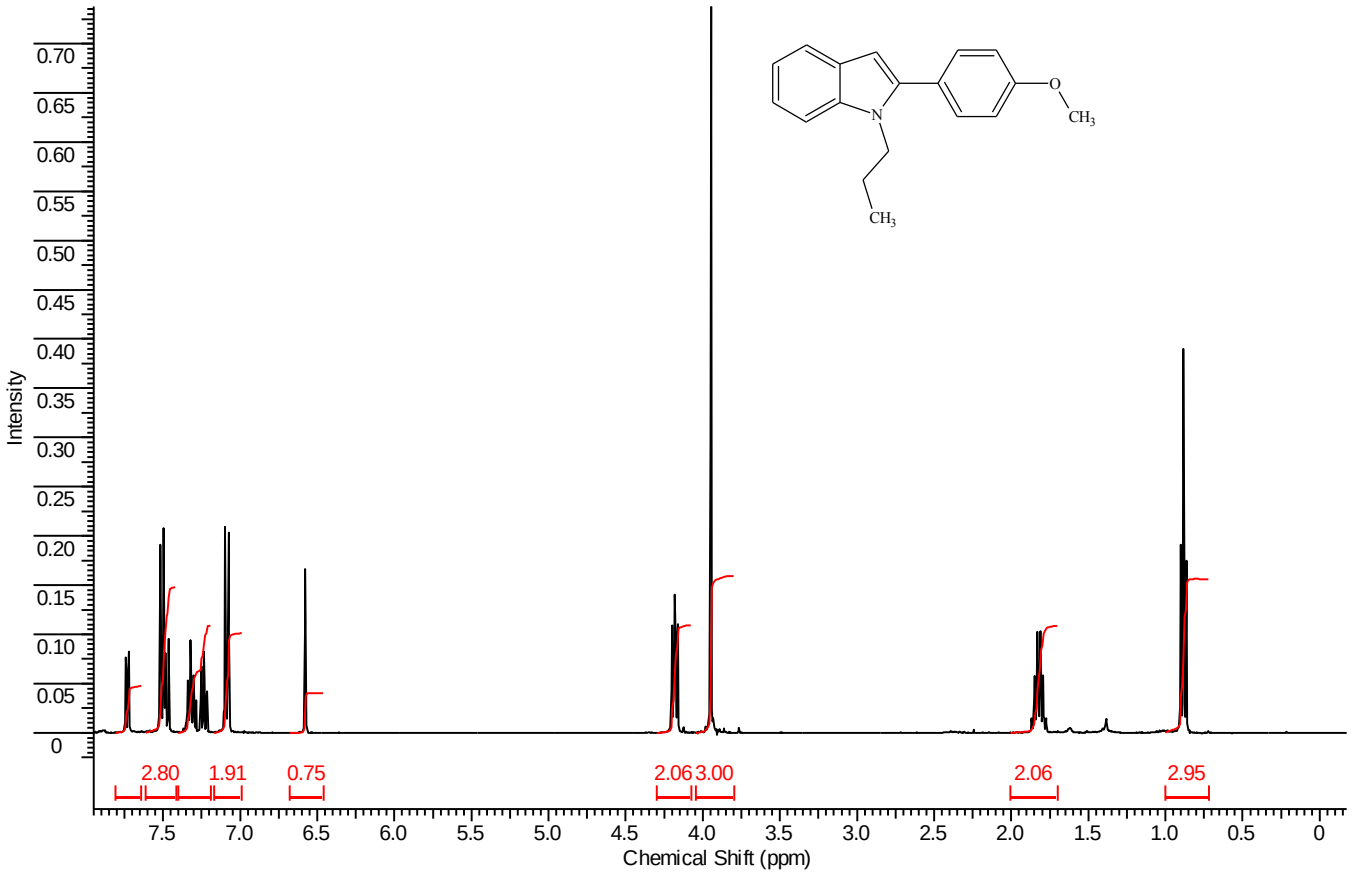

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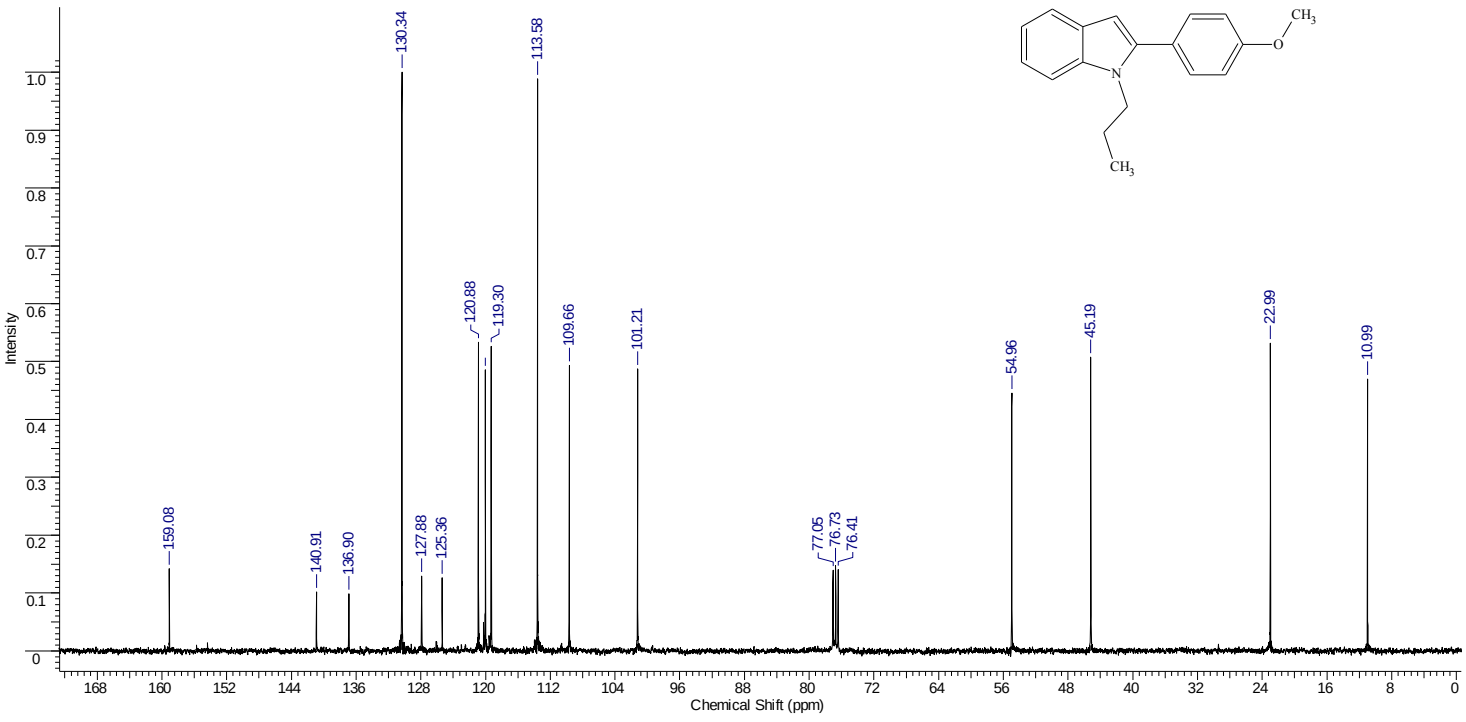

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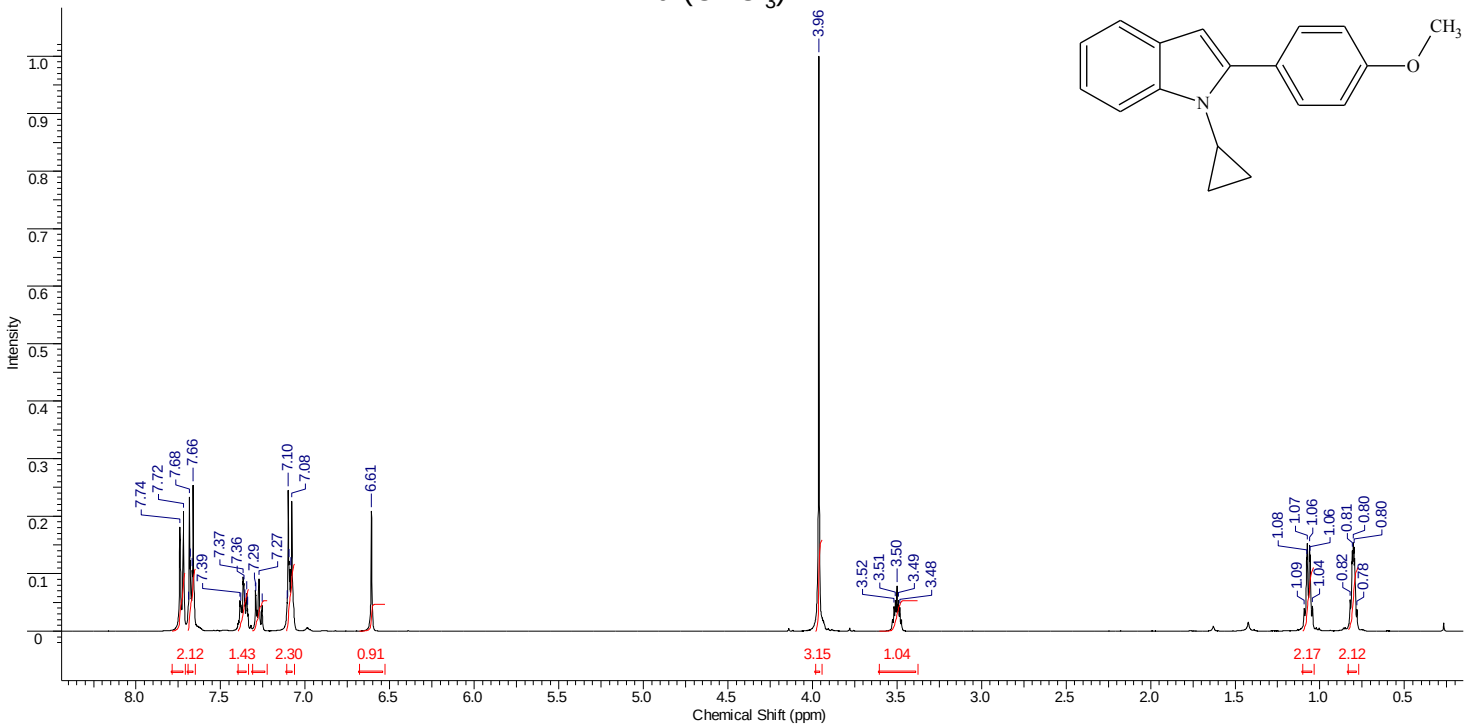

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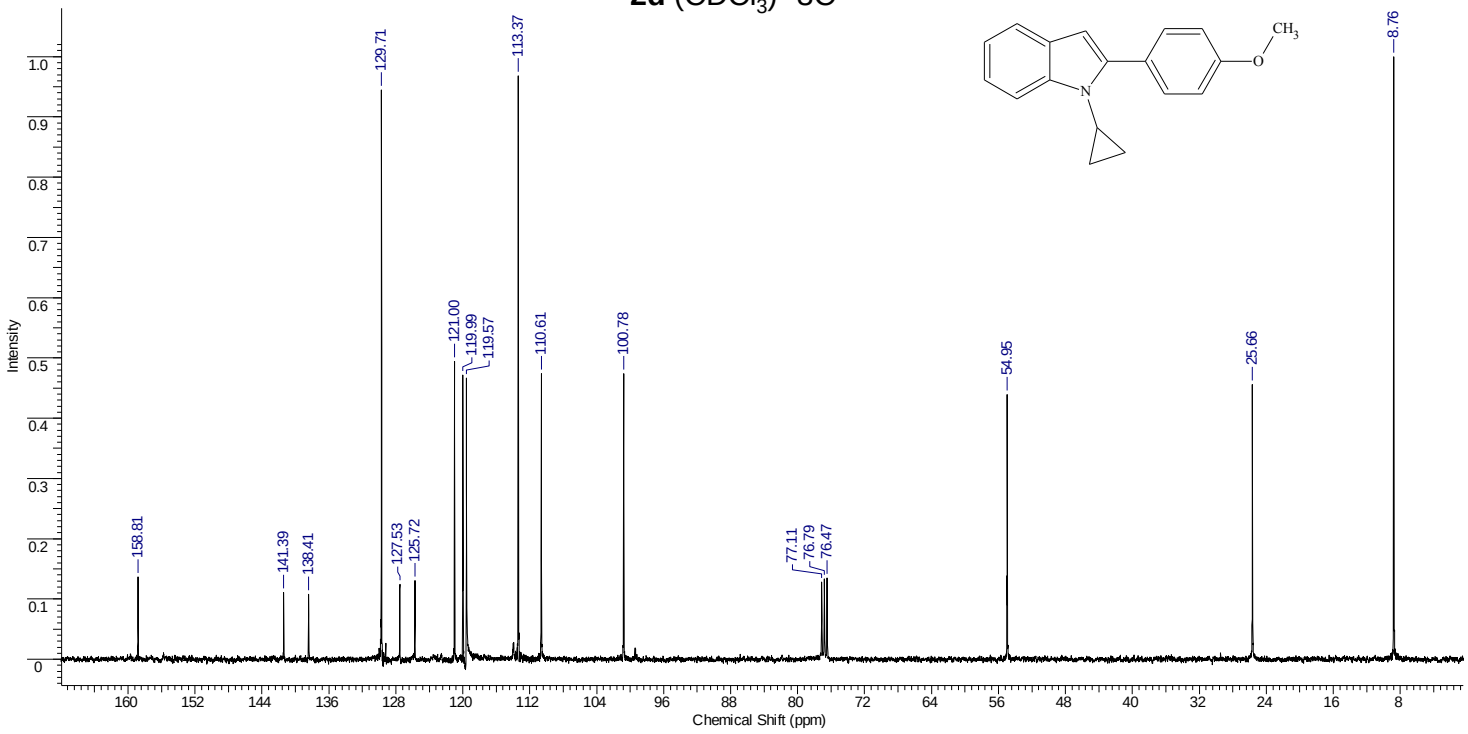

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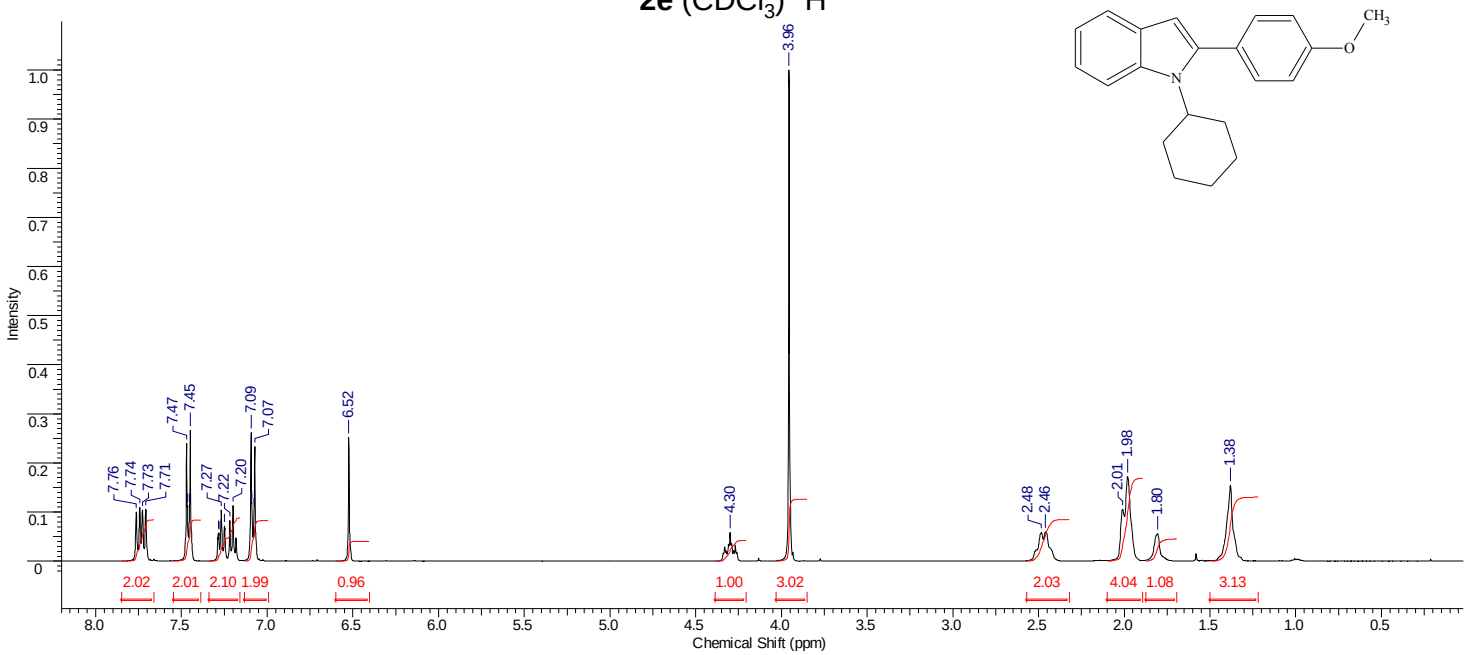

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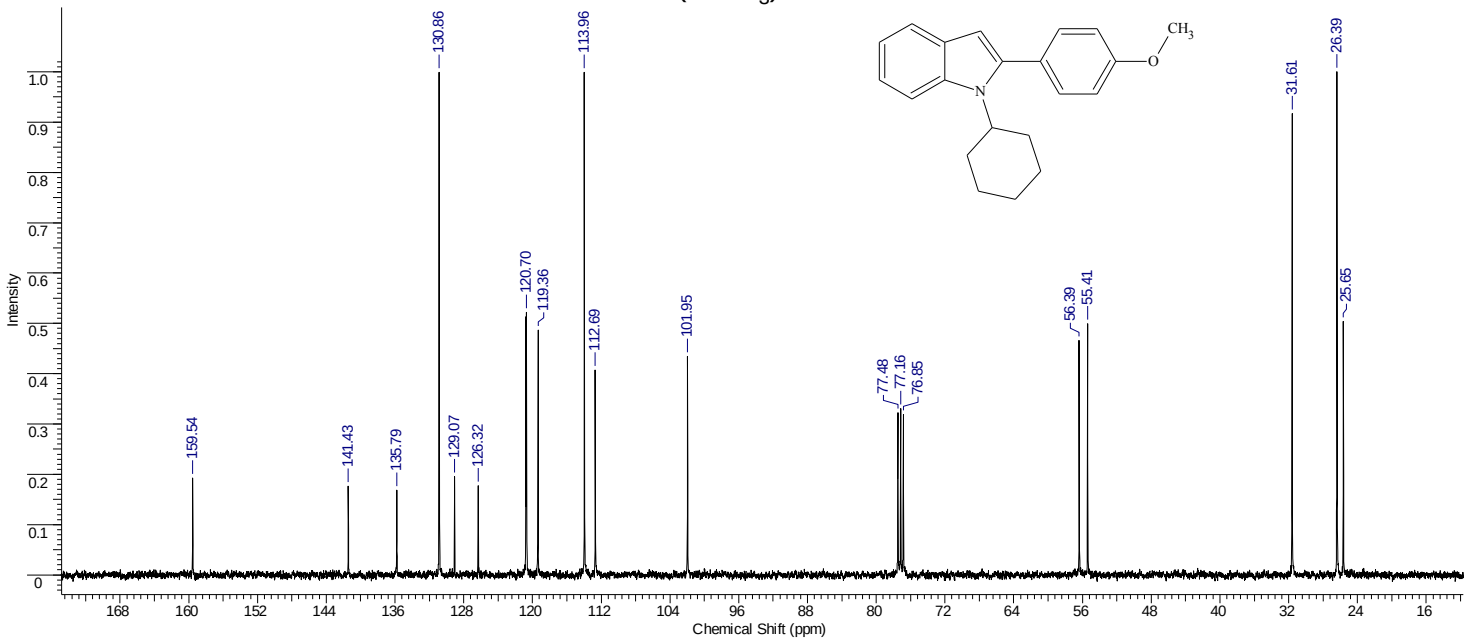

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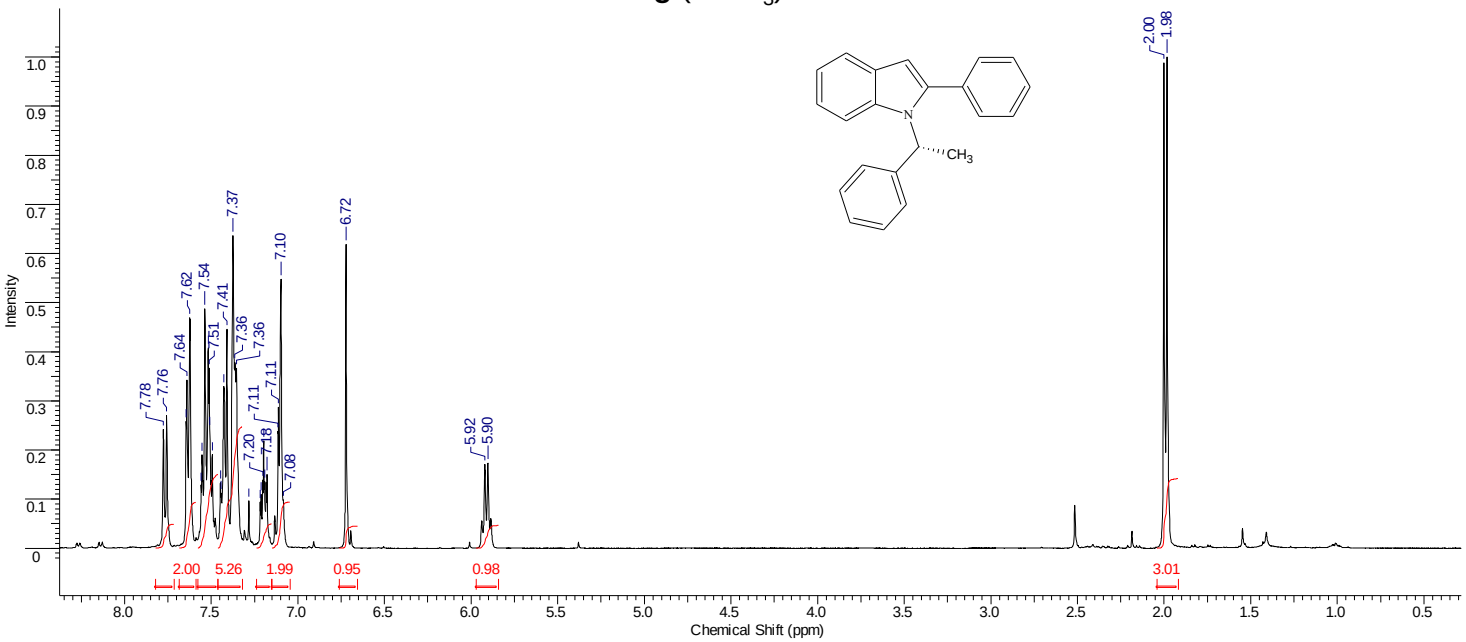

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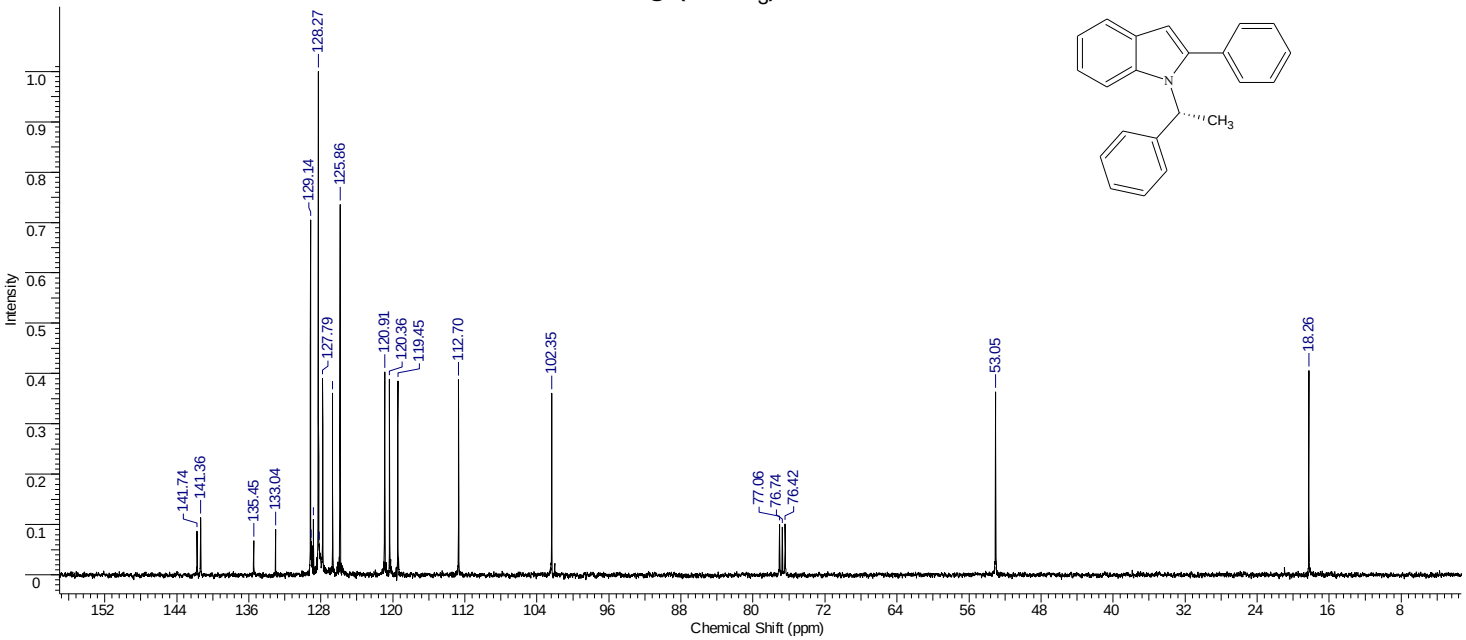

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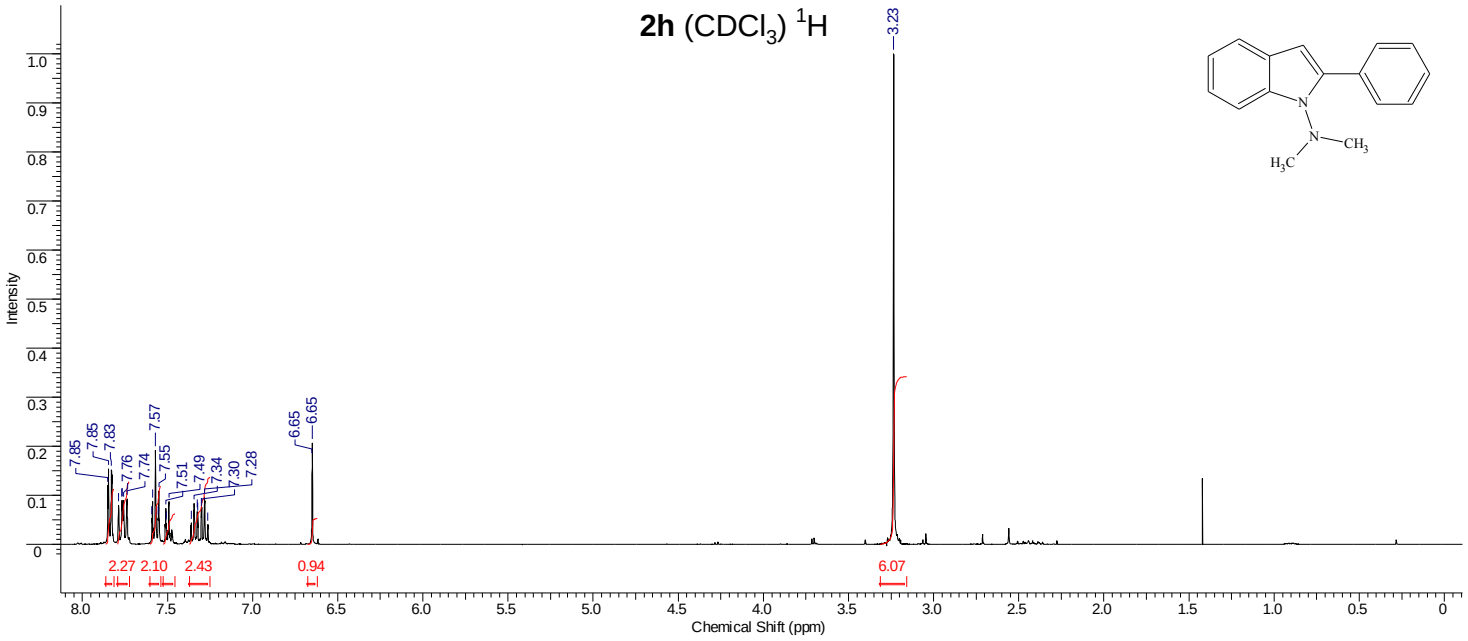

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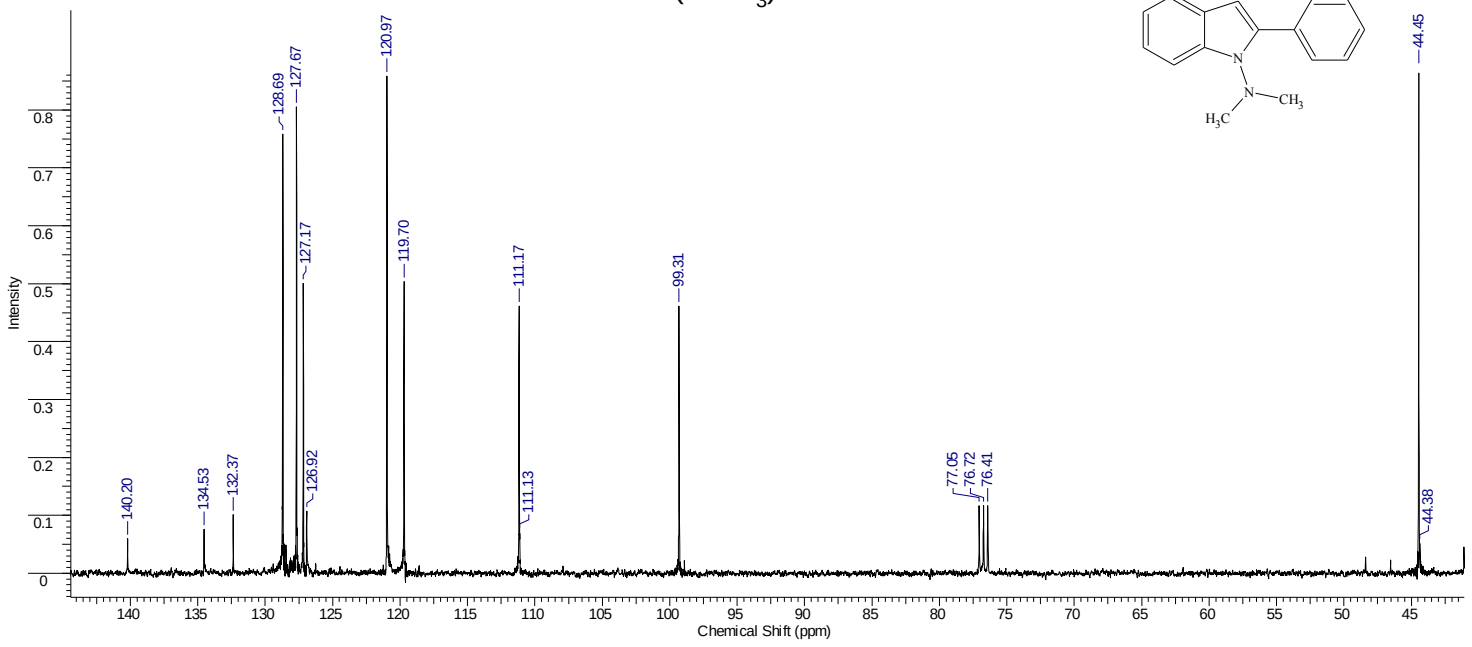

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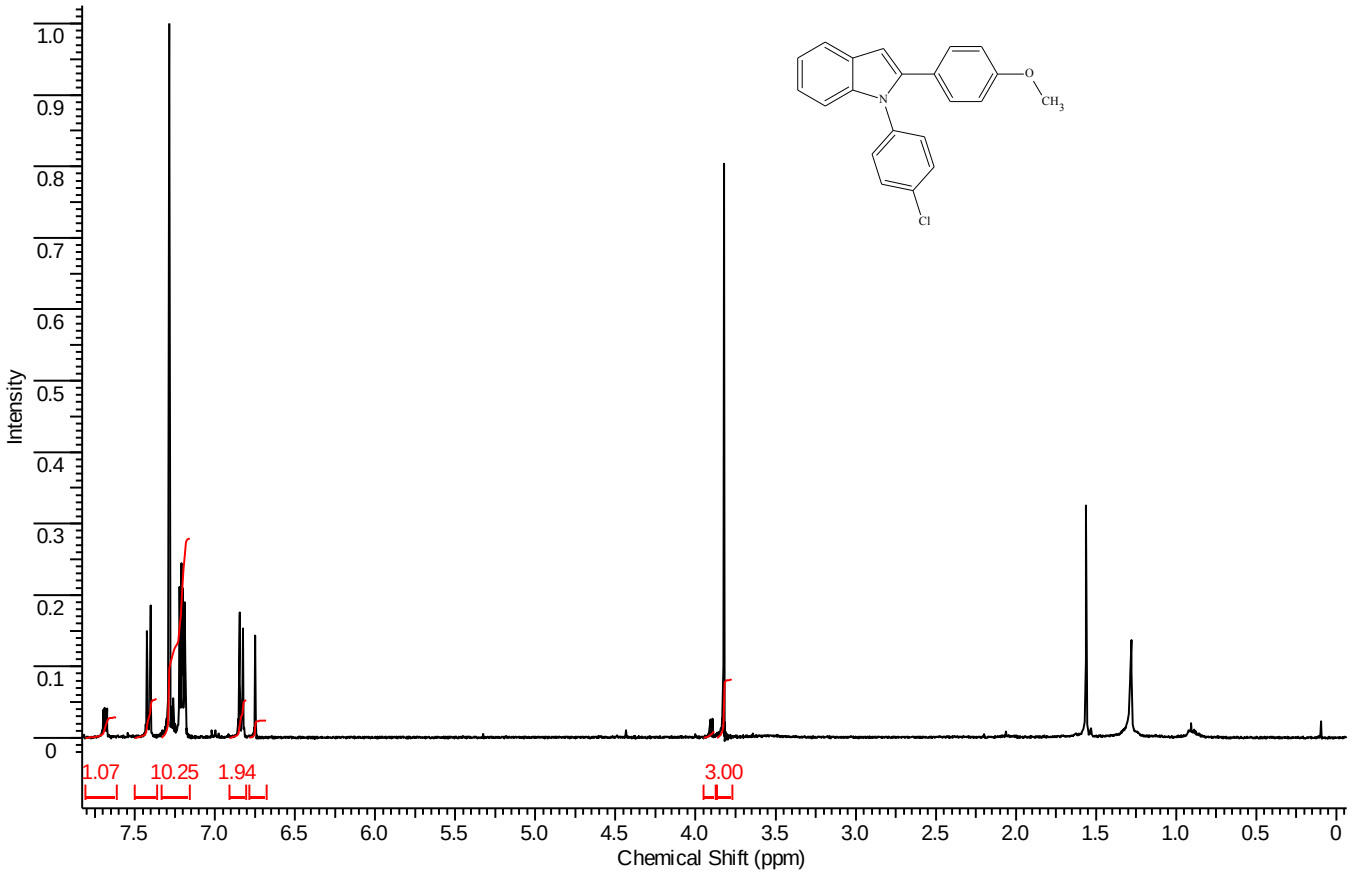

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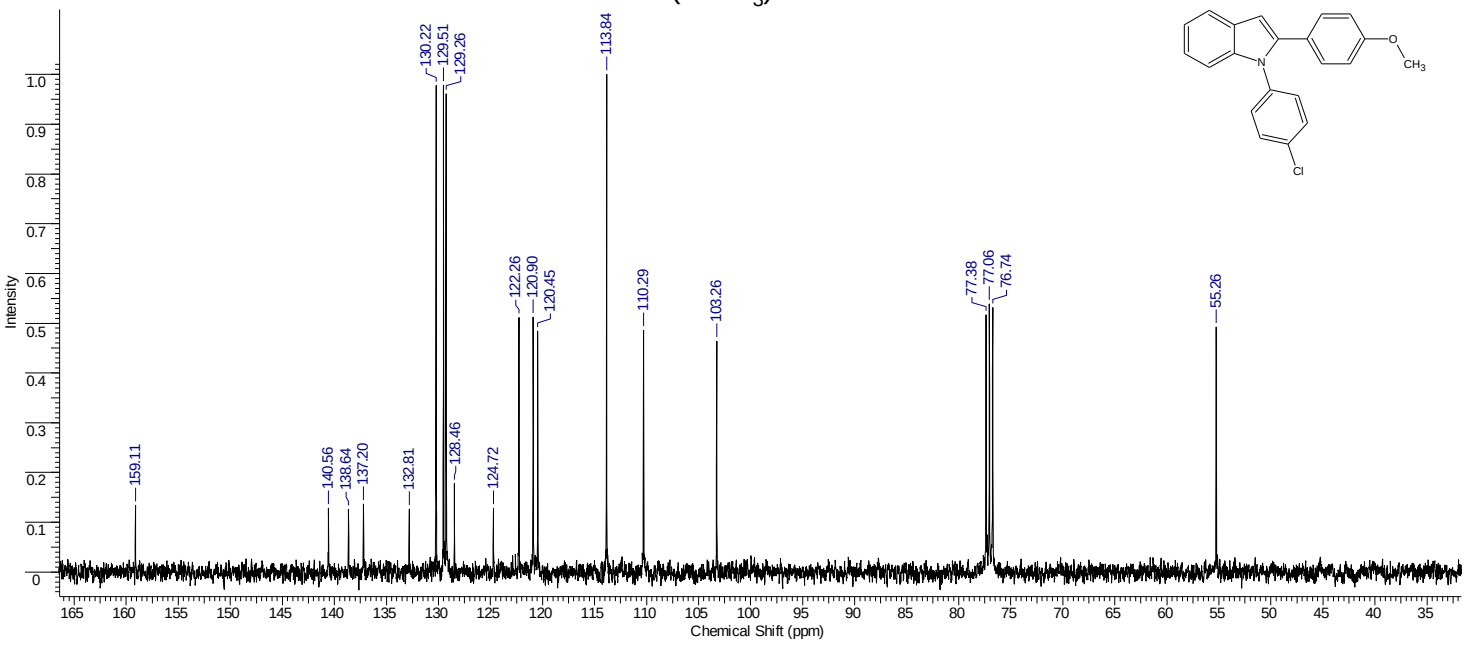

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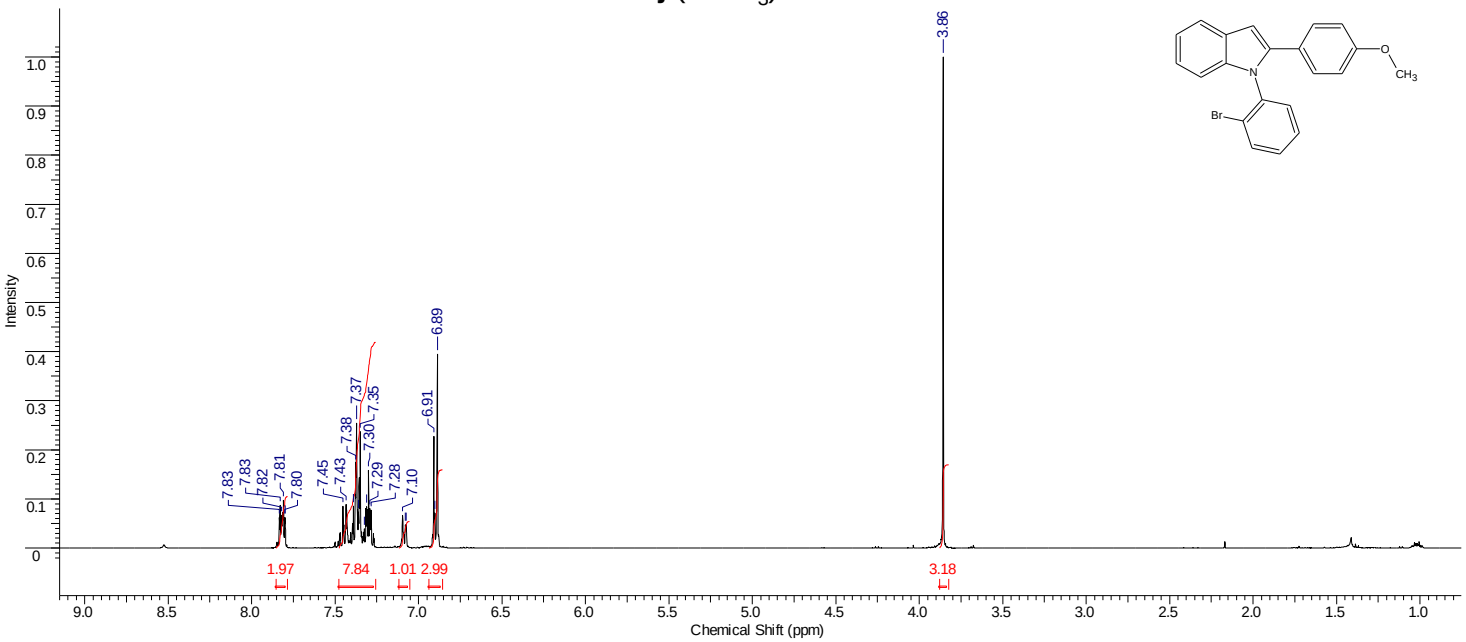

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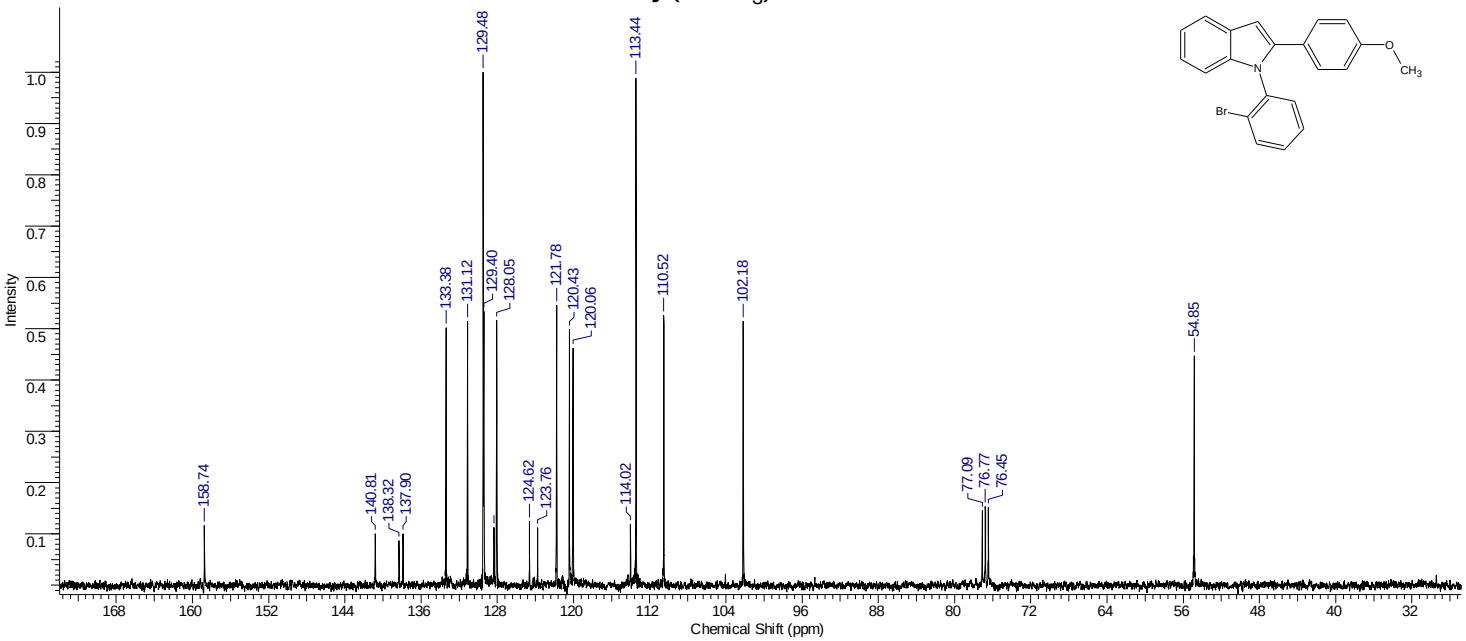

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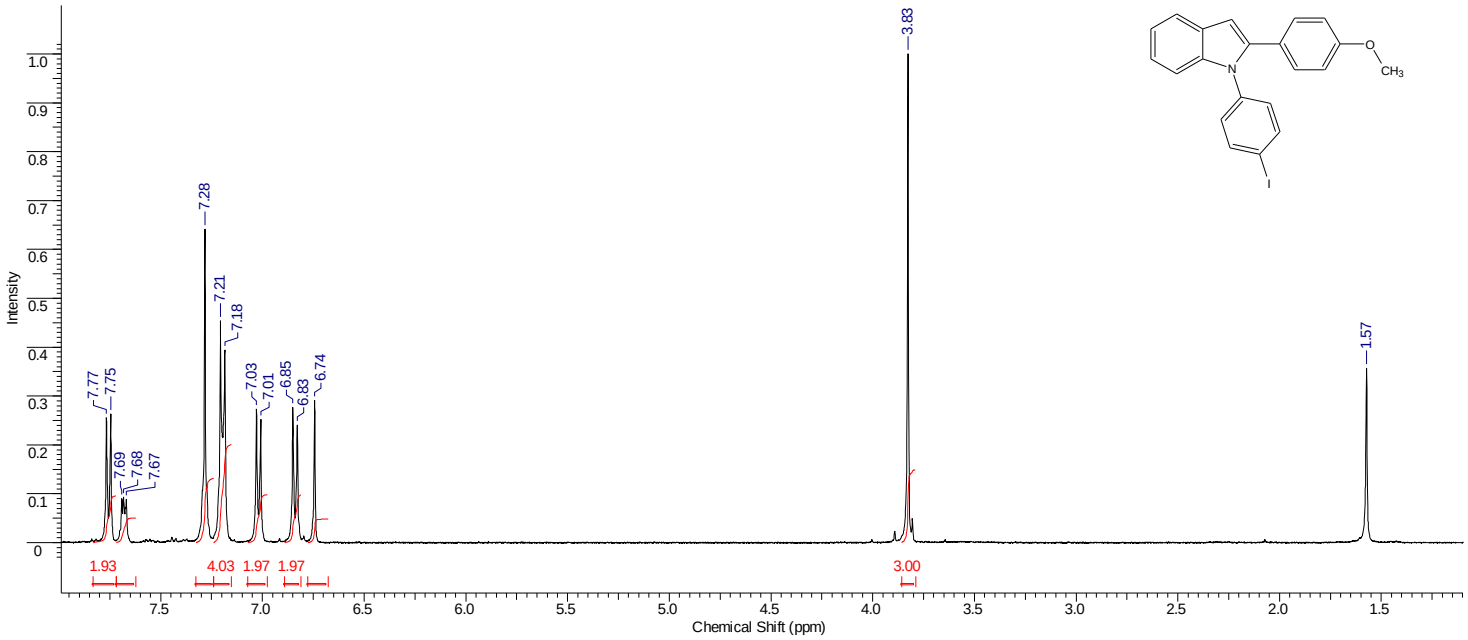

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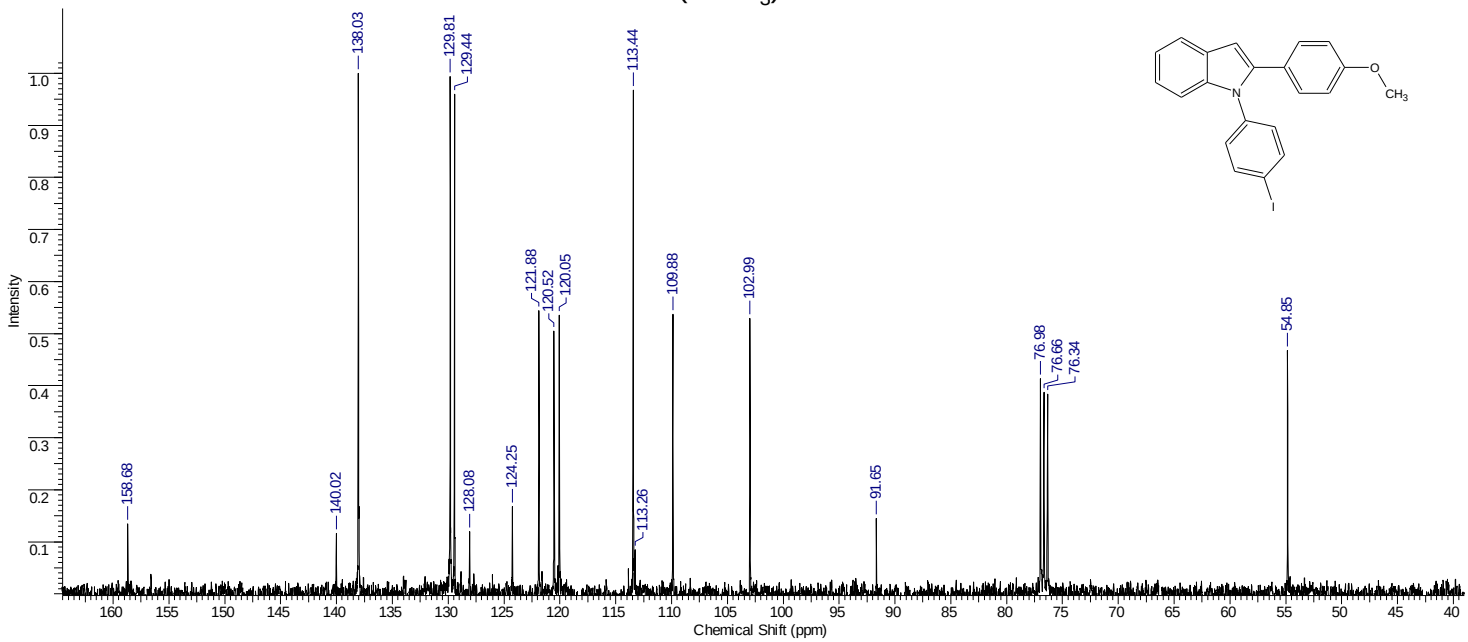

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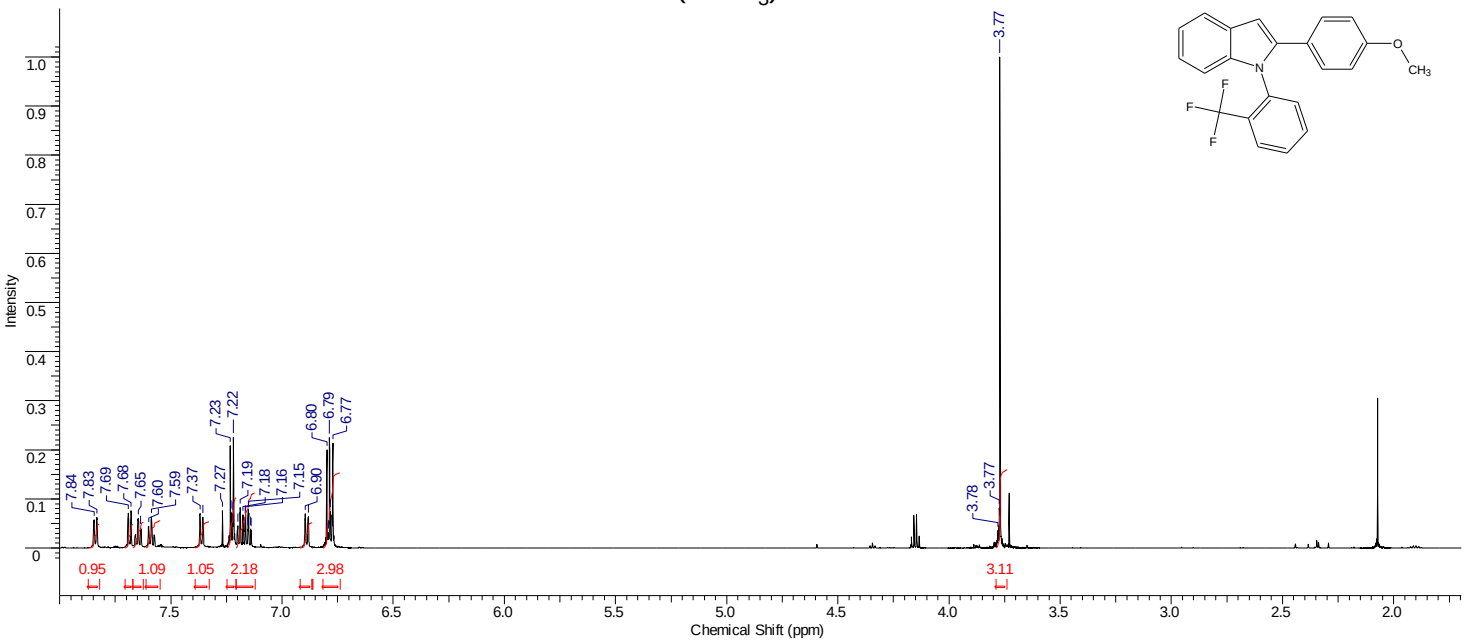

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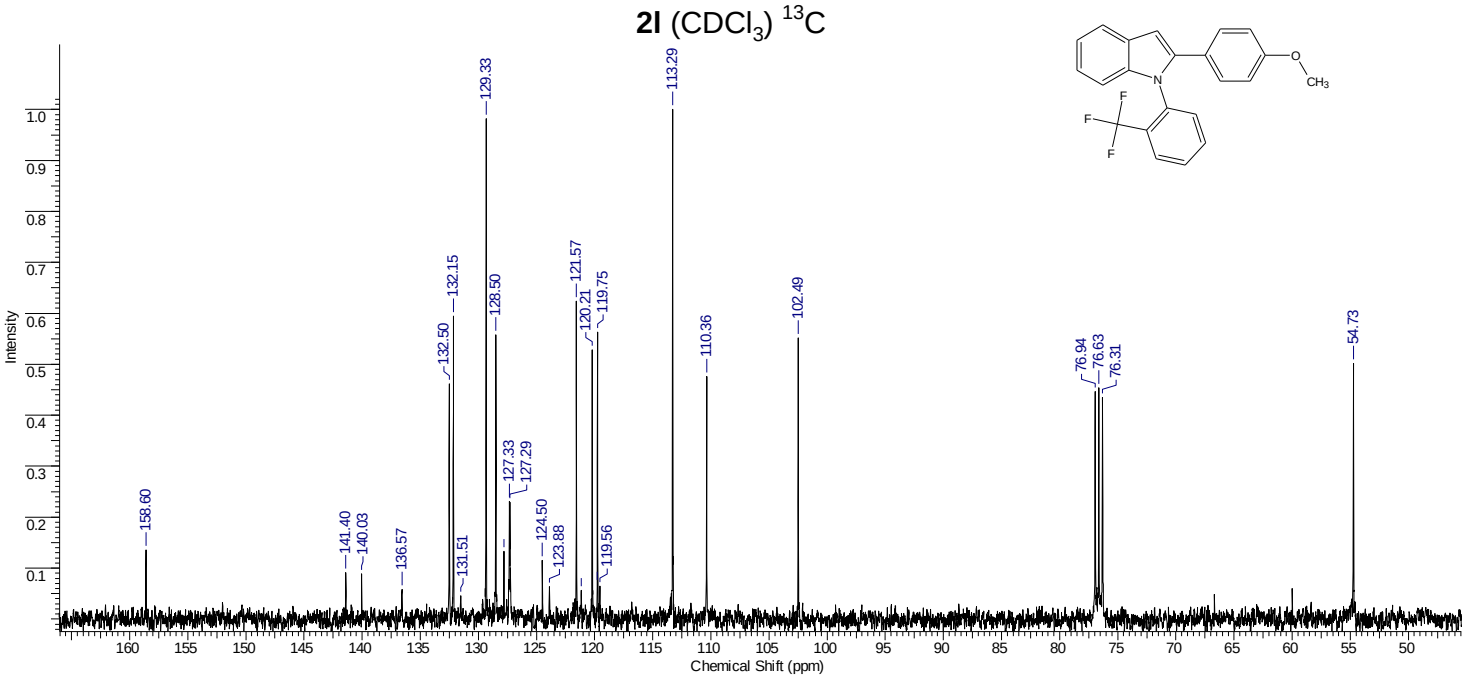

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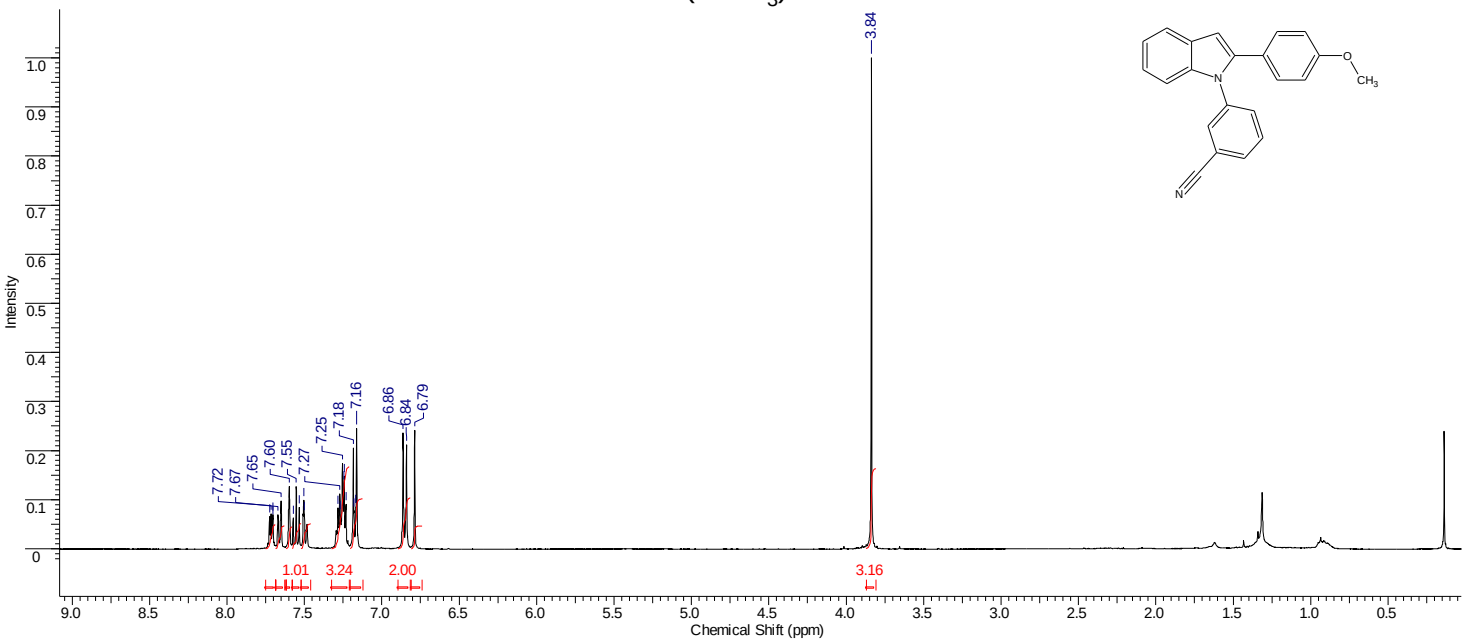

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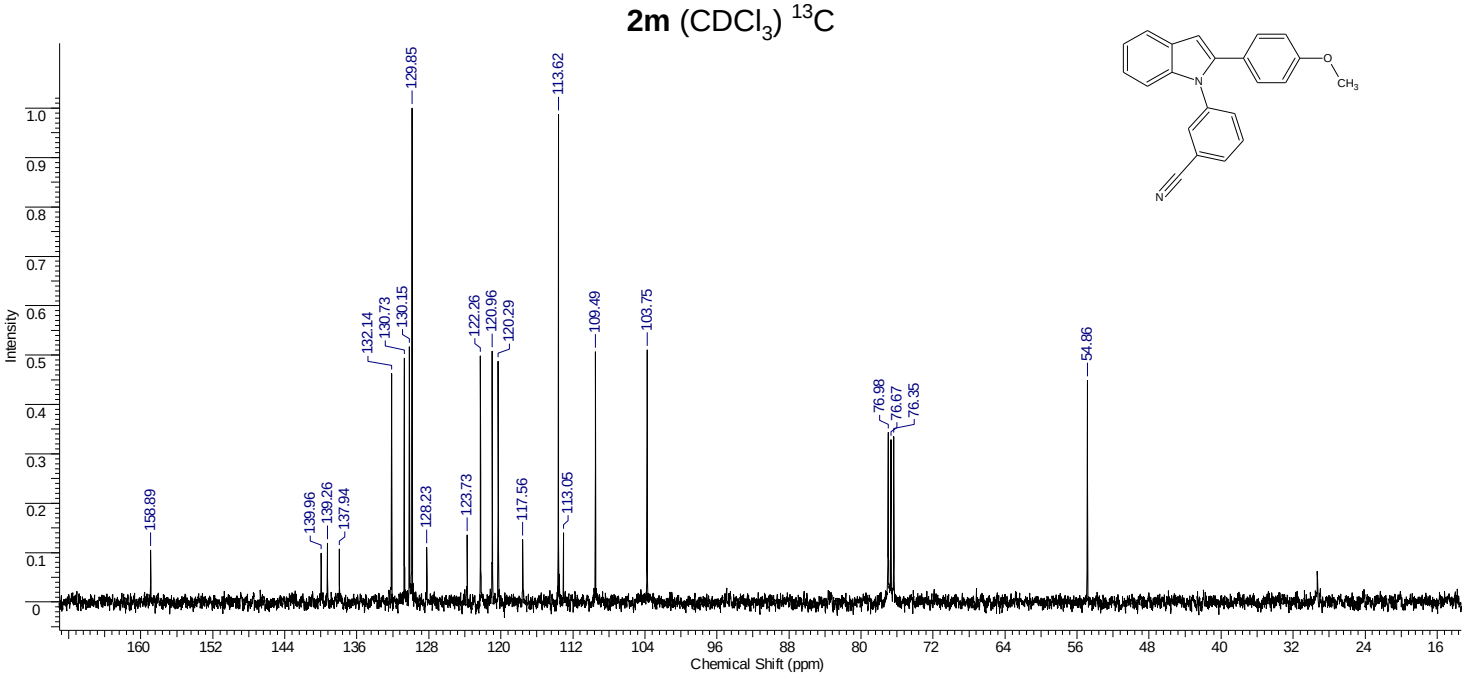

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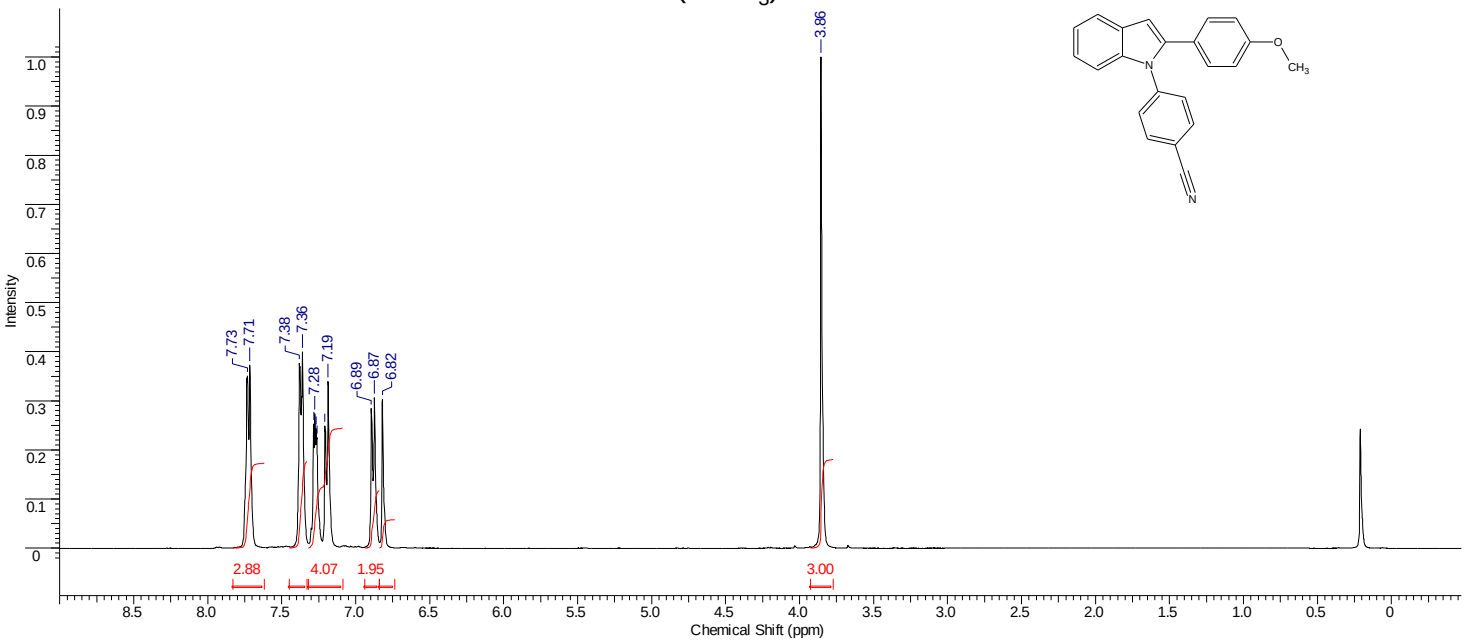

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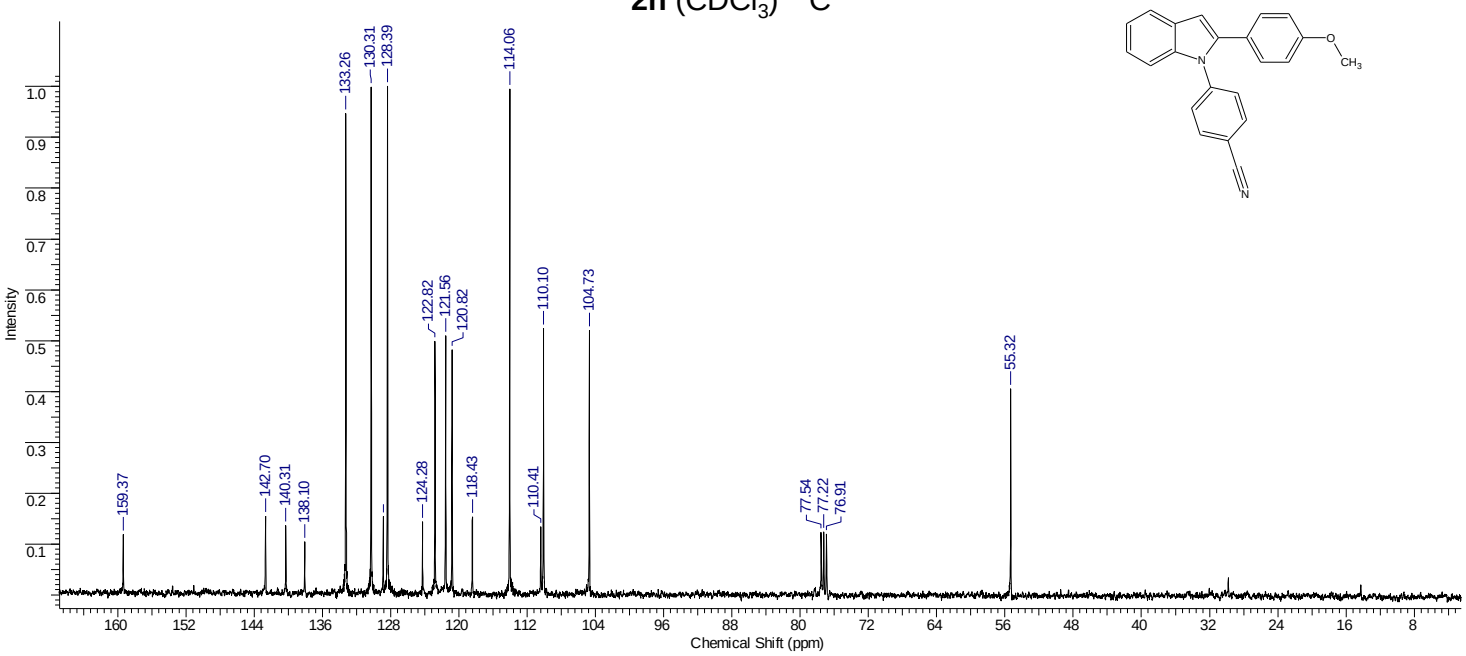

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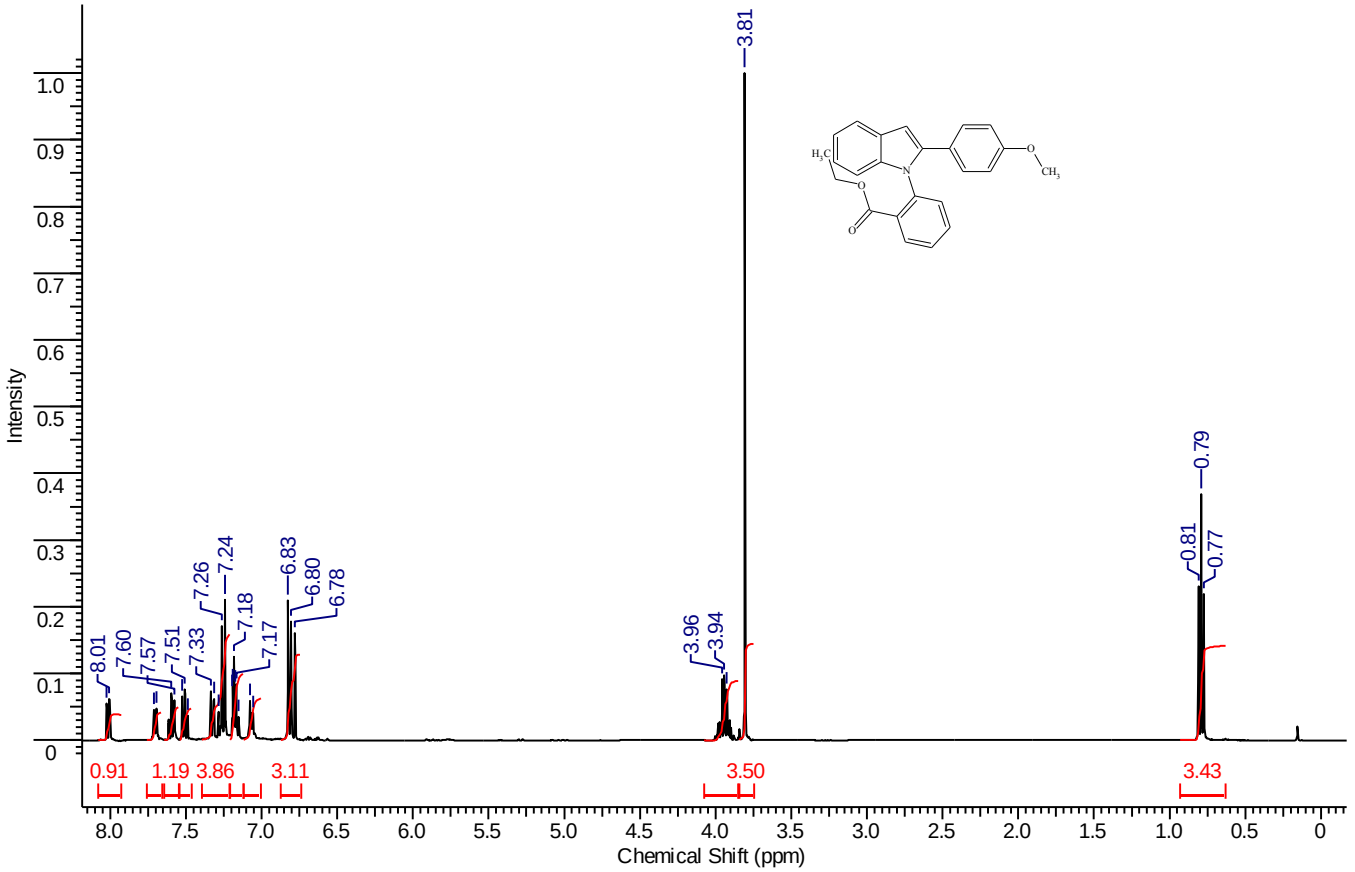

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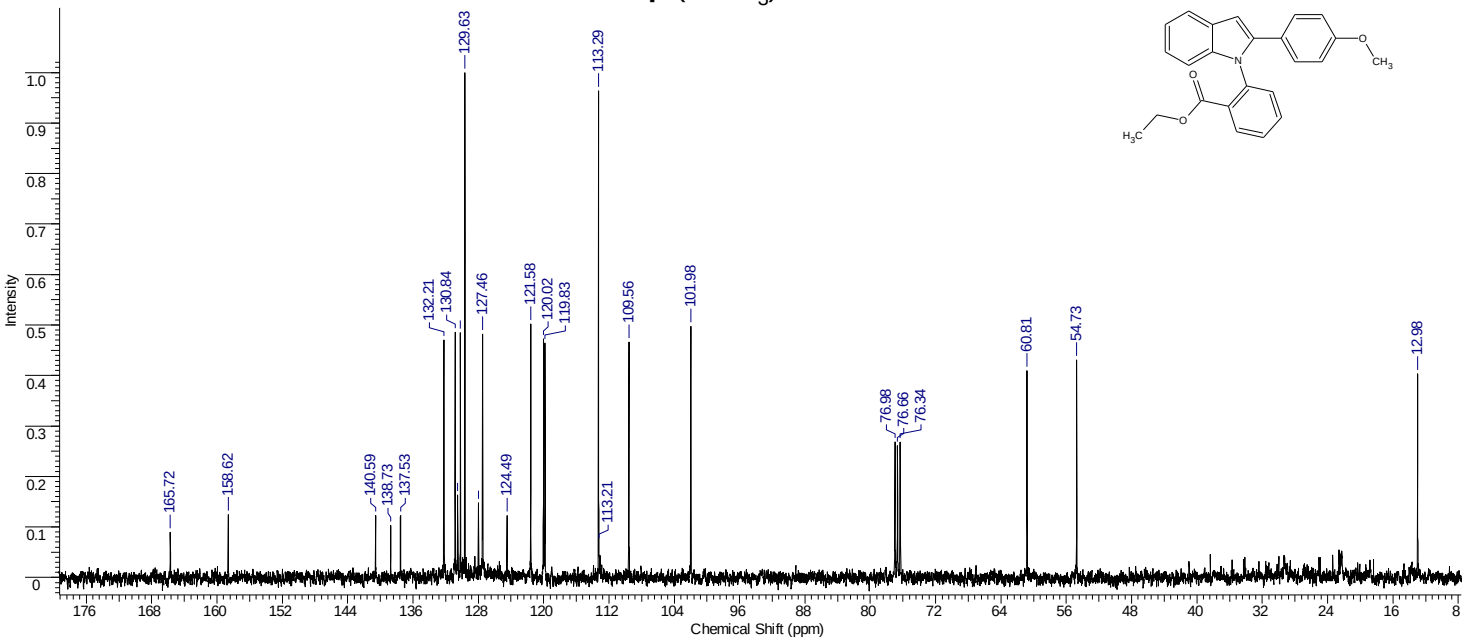

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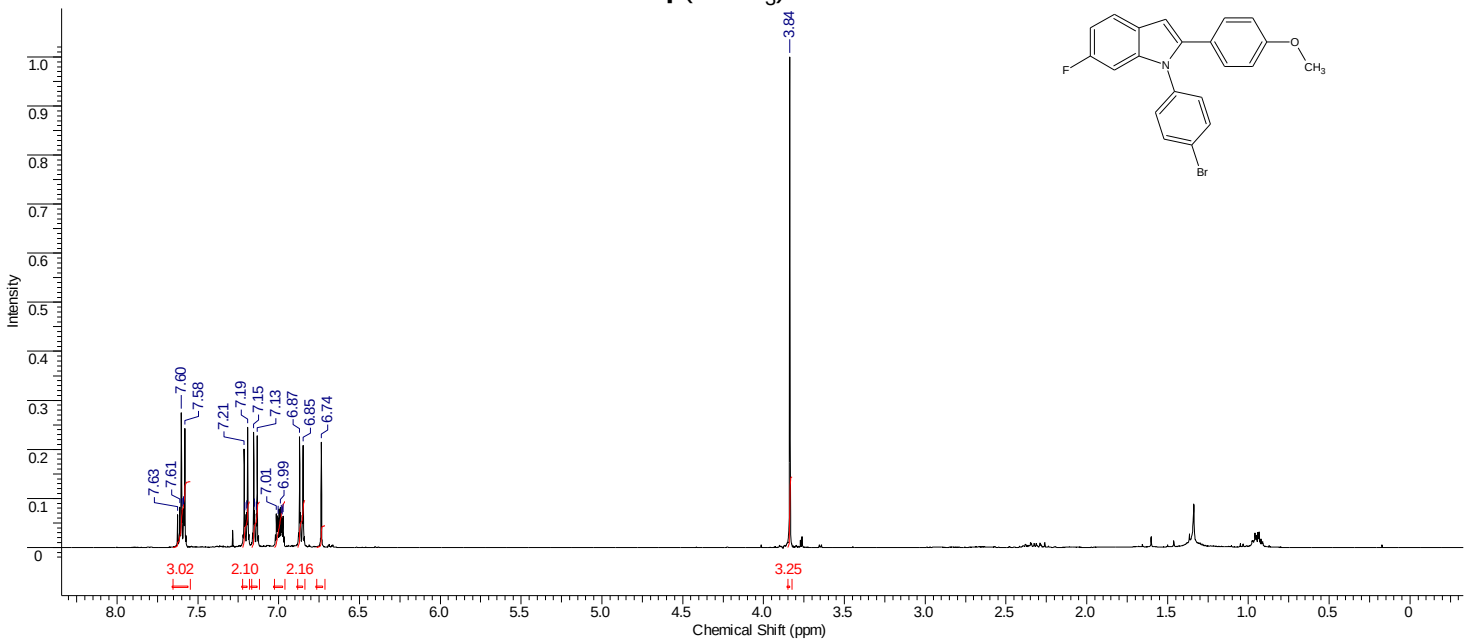

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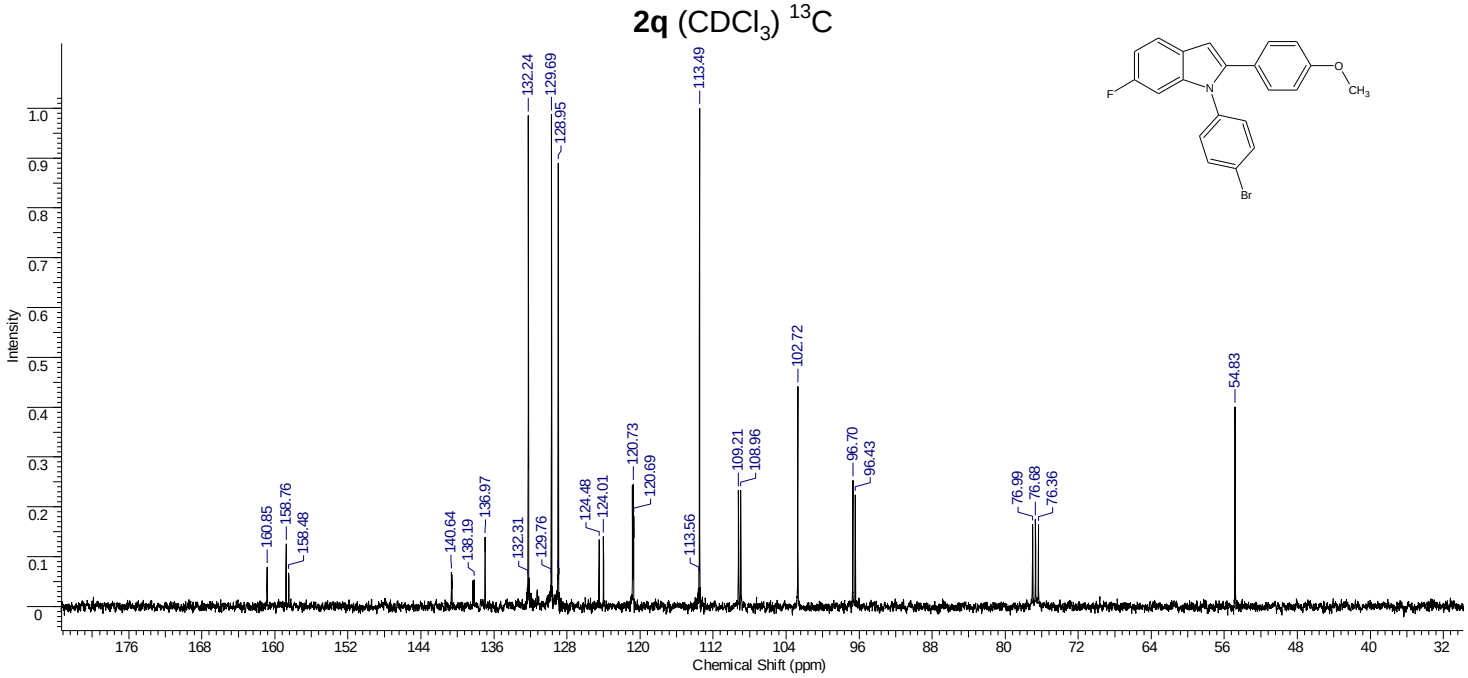

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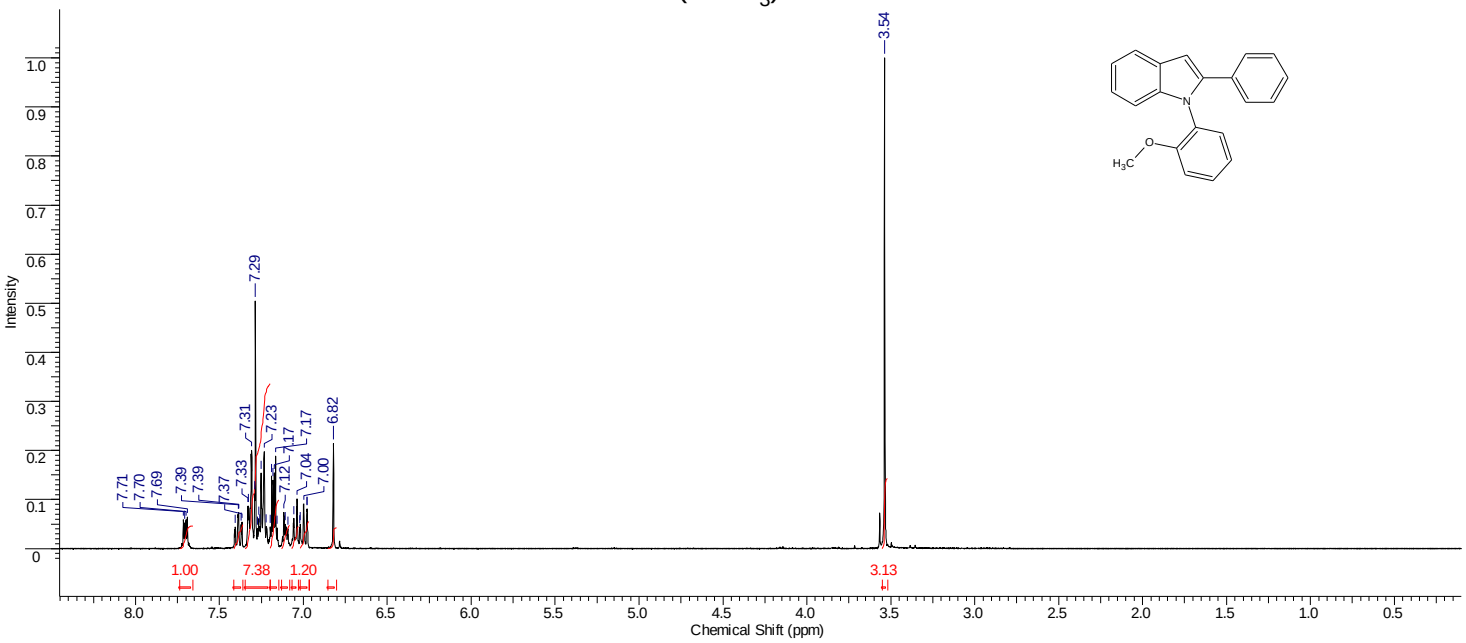

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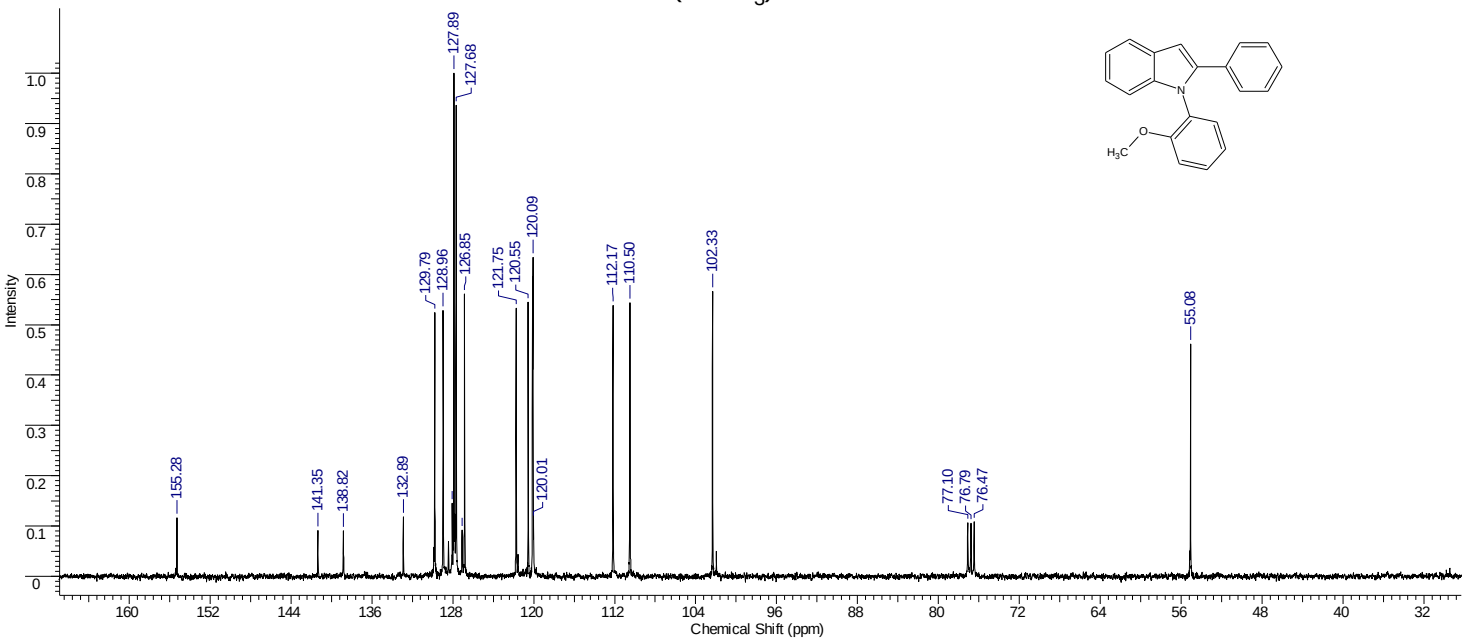

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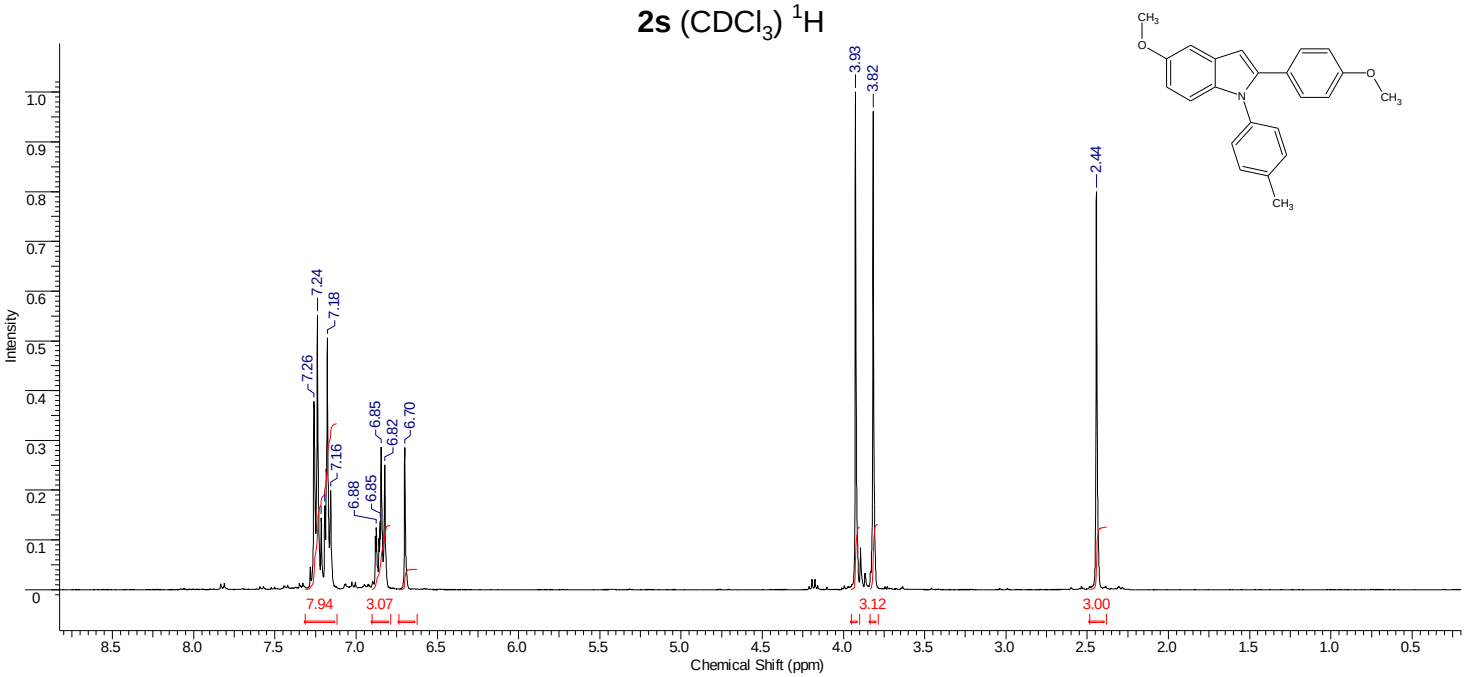

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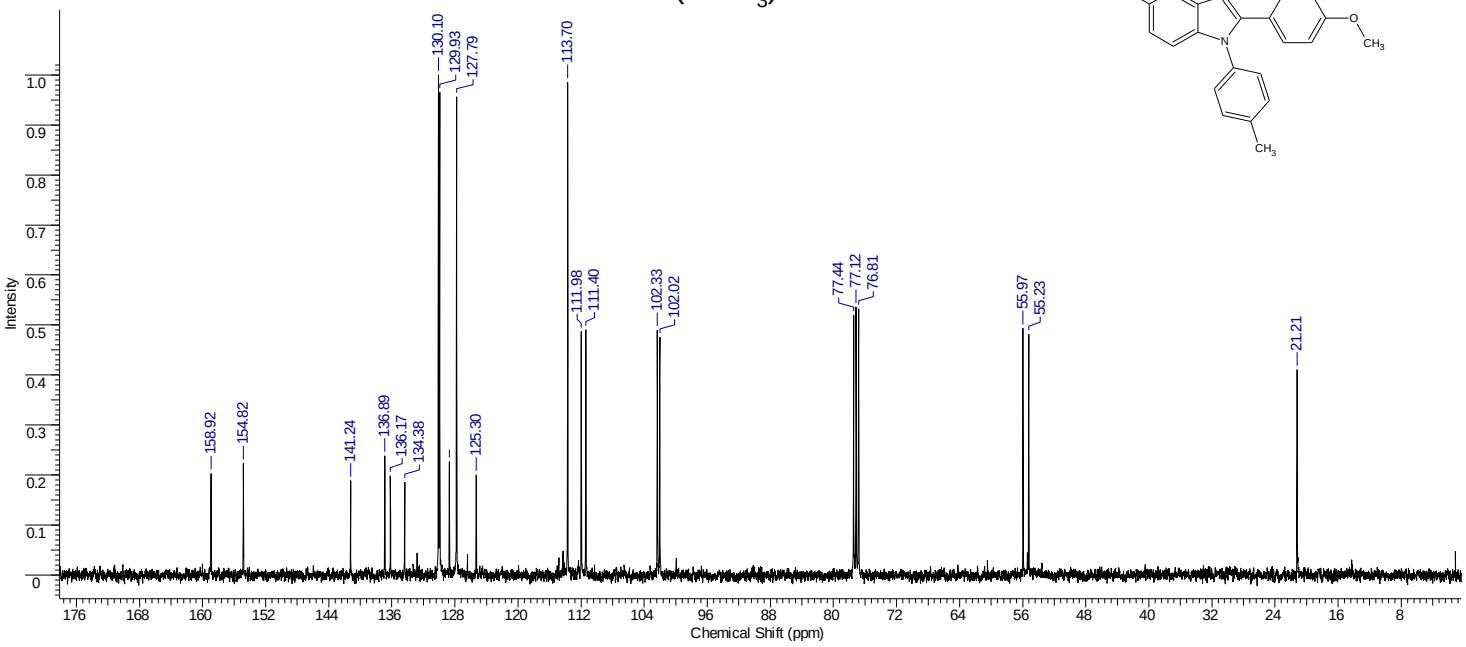

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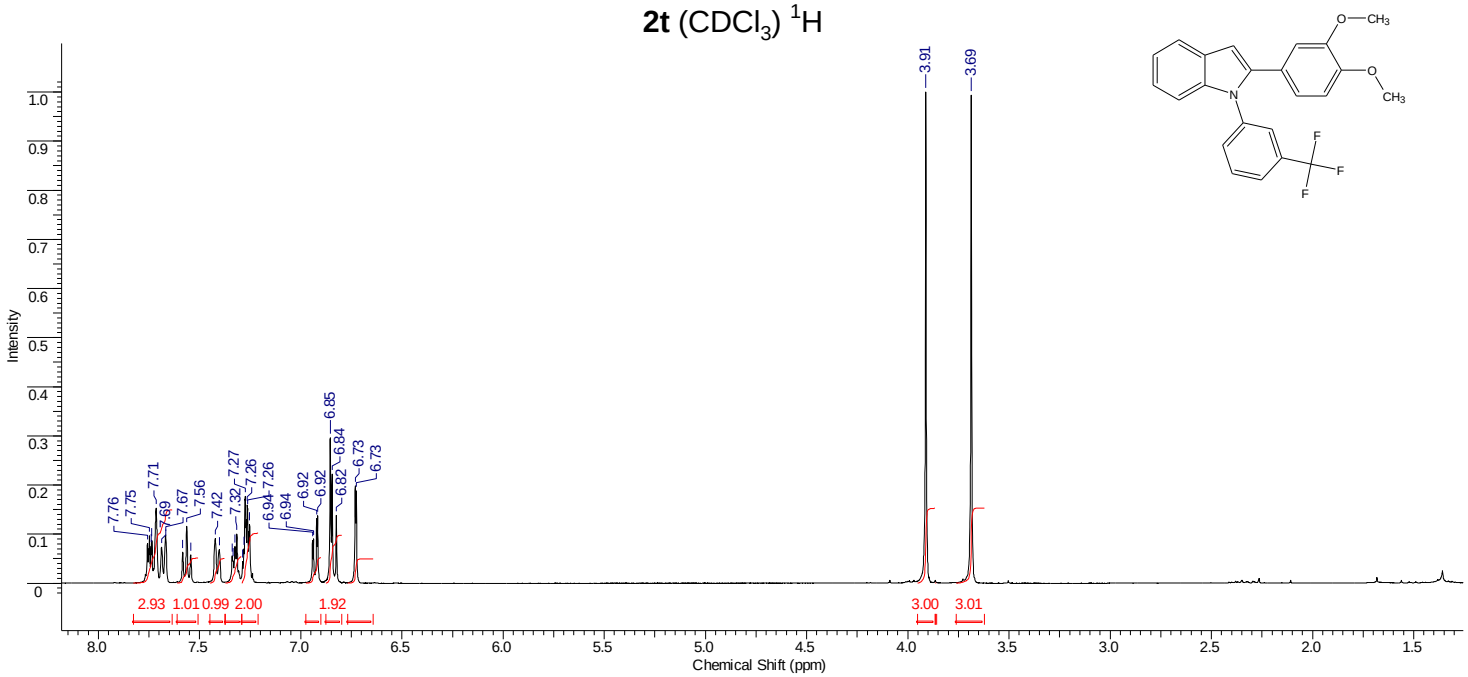

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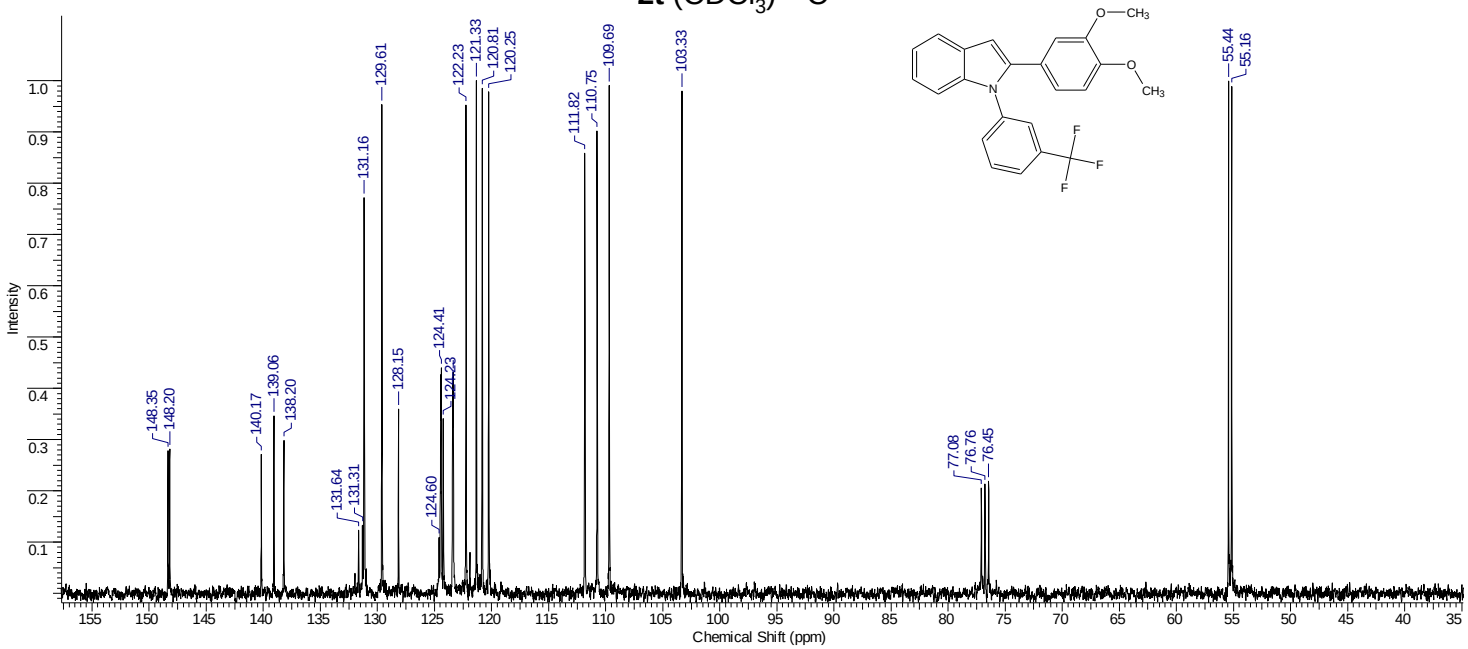

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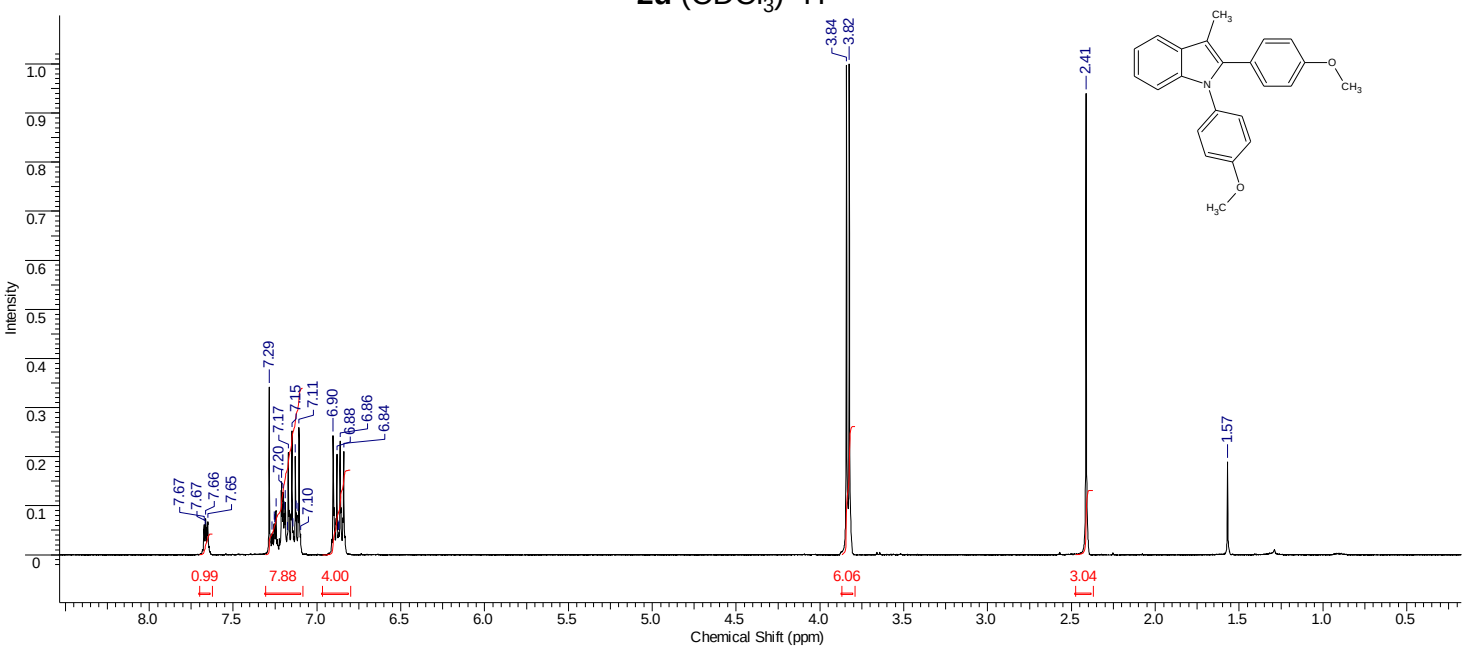

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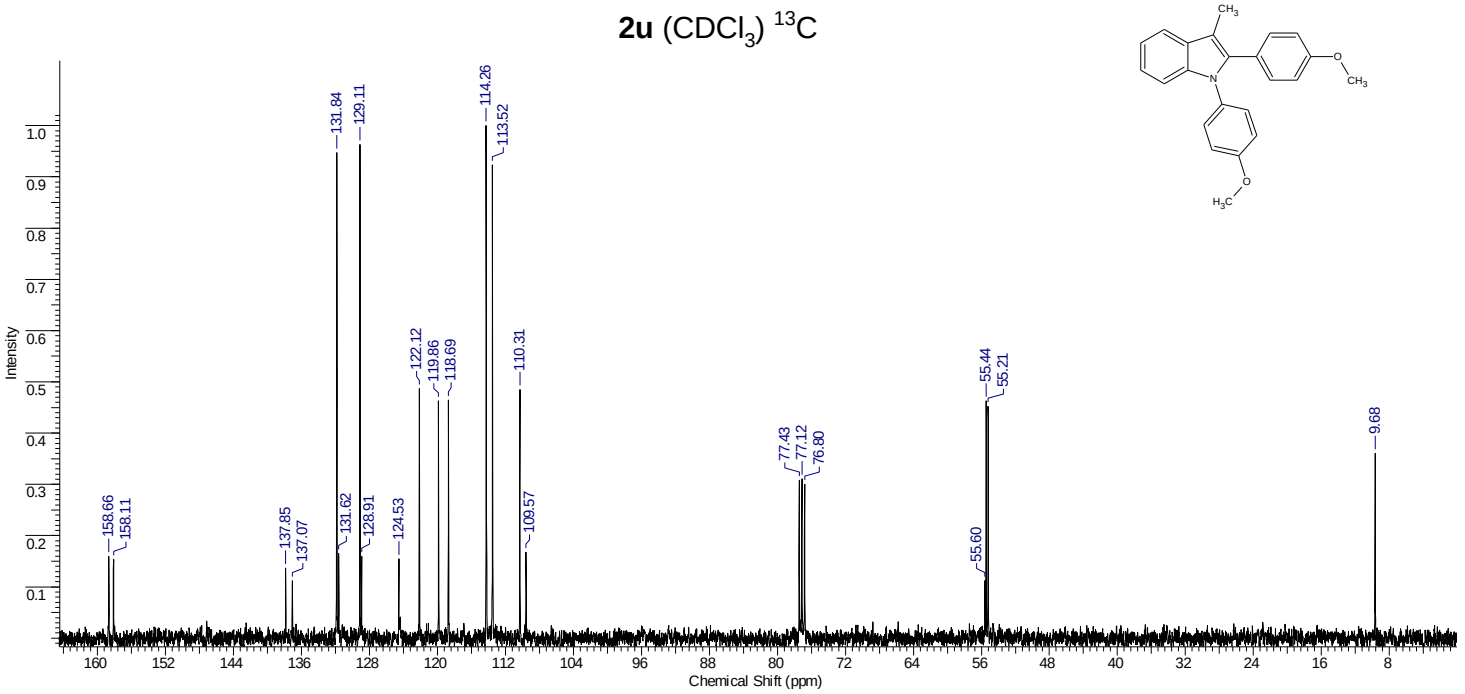

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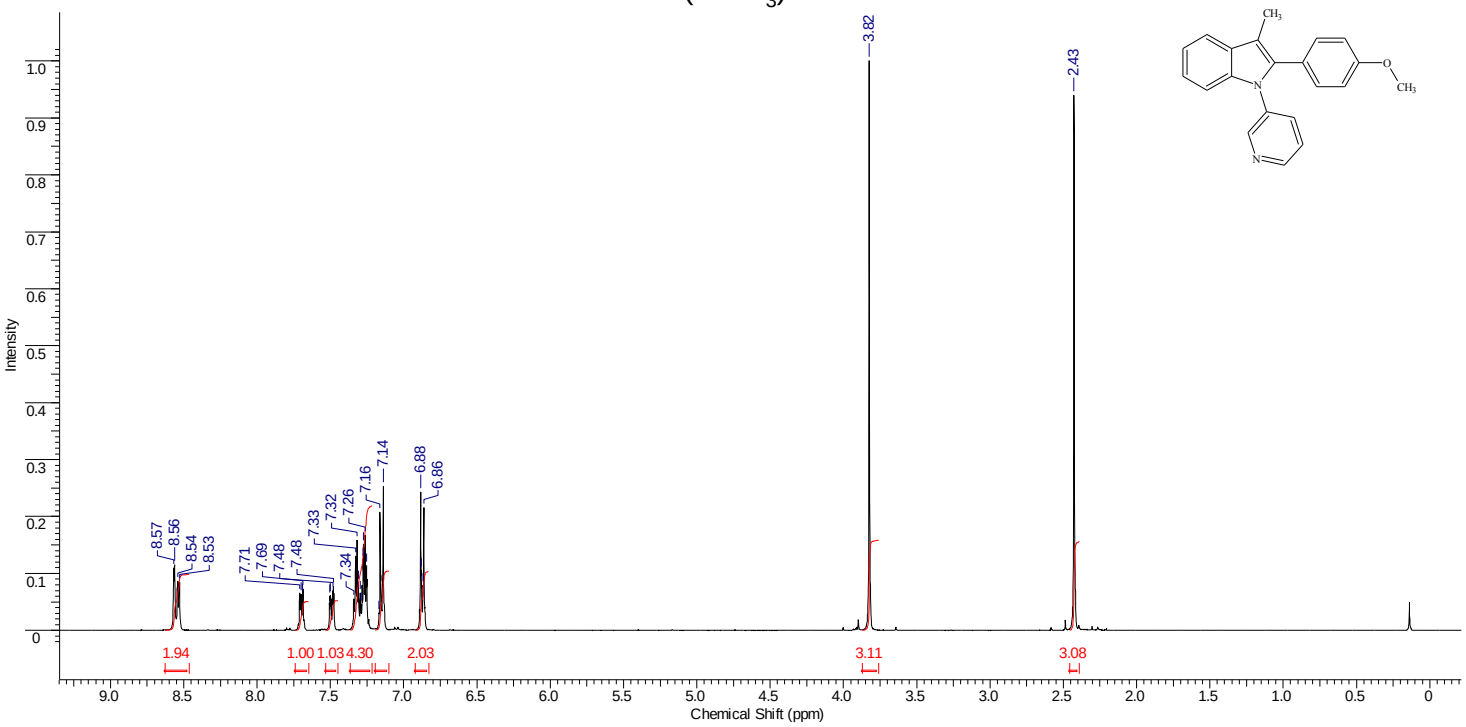

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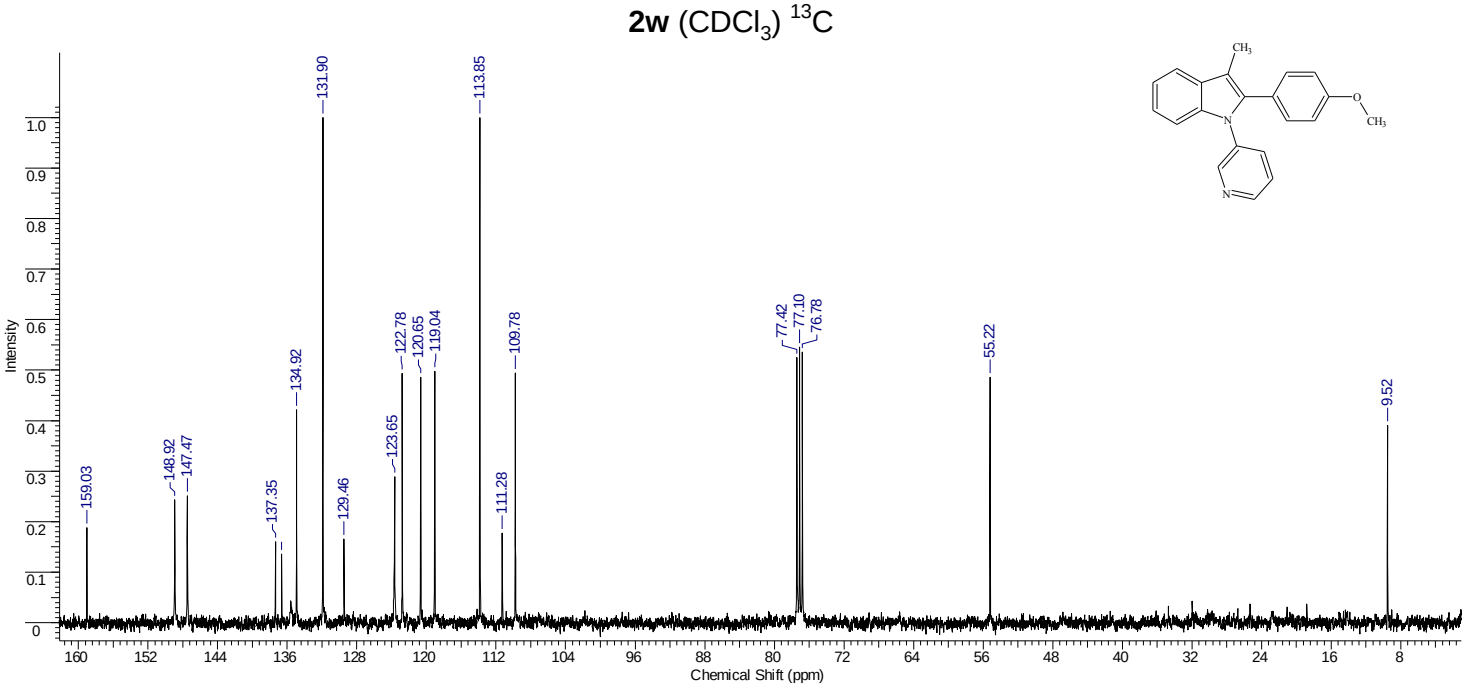

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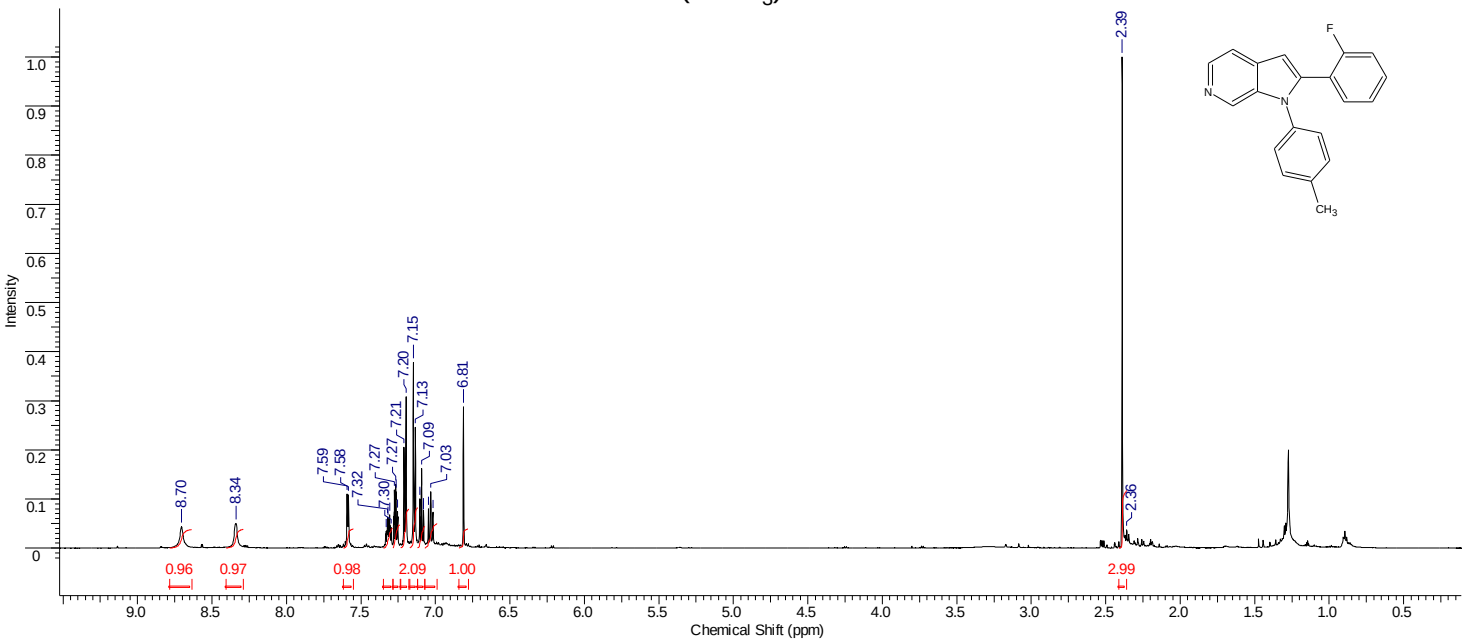

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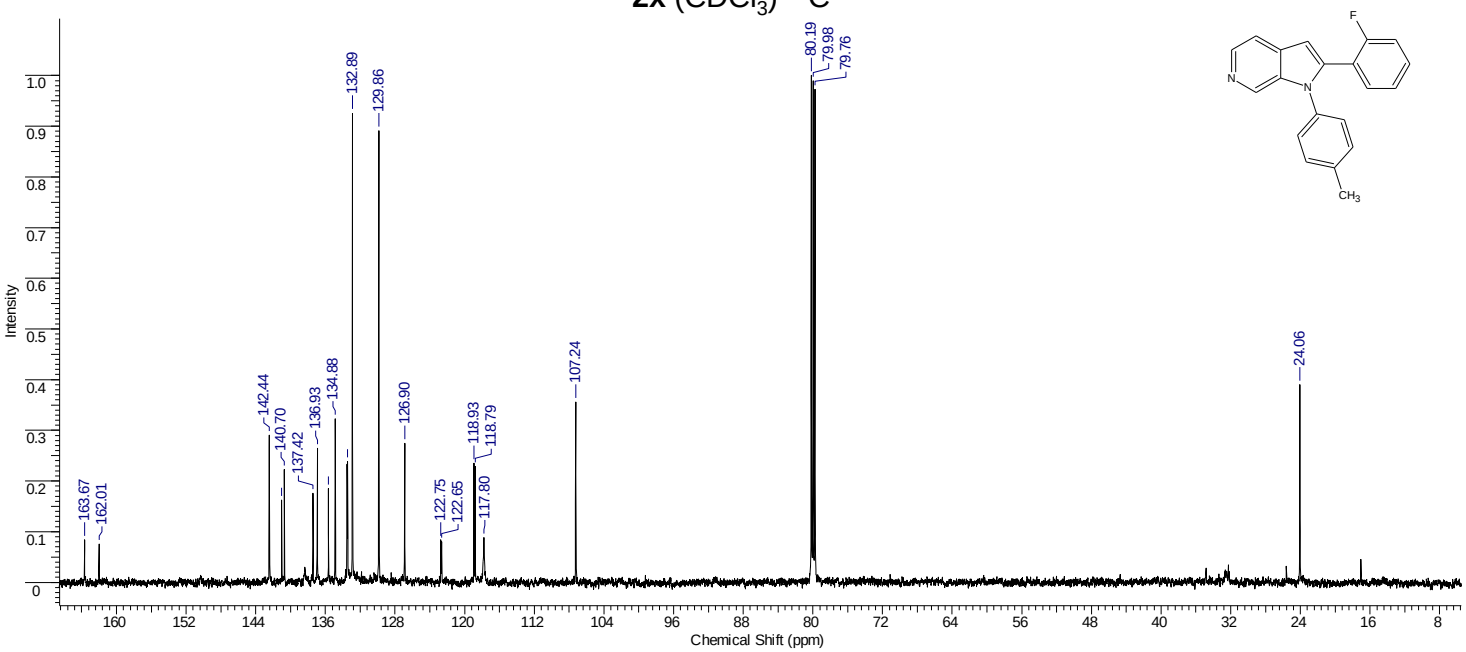

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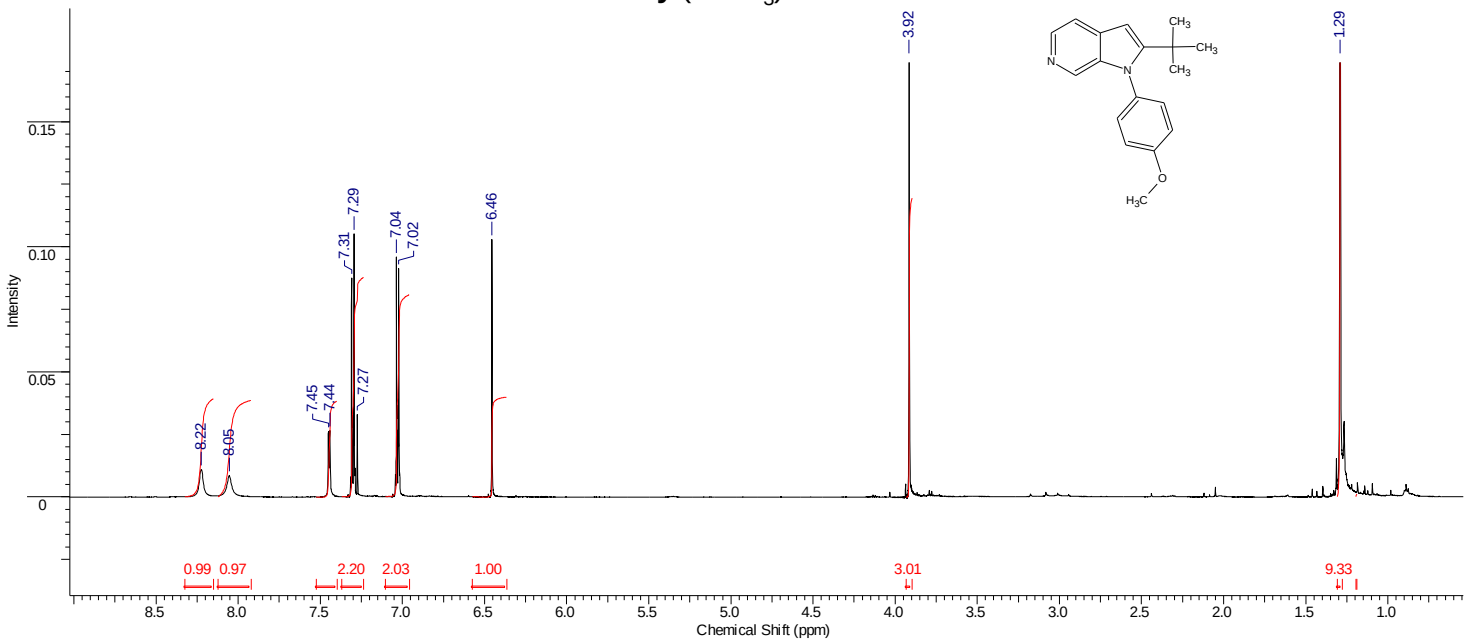

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