

***N*-Acylated and *N*-Alkylated 2-Aminobenzothiazoles are Novel Agents that Suppress the Generation of Prostaglandin E₂**

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SUPPLEMENTARY MATERIALS

Contents

	Page
Table S1. Names and code numbers of tested compounds.	2
Figure S1. Effect of the inhibitor 19a on IL-1/Fk-stimulated nitrite formation in rat mesangial cells.	4
¹H NMR and ¹³C NMR spectra of the compounds synthesized.	5
HPLC traces of 5b, 11, 19a, 19b, 19c, 19d, 19e, 23a and 23c.	40

Table S1. Names and code numbers of tested compounds.

Compound chemical name	No	Code number
<i>N</i> -(Benzo[<i>d</i>]thiazol-2-yl)-4-(naphthalen-2-yl)butanamide	5a	GK509
<i>N</i> -(Benzo[<i>d</i>]thiazol-2-yl)-3-(naphthalen-2-yl)propanamide	5b	GK510
<i>N</i> -(Benzo[<i>d</i>]oxazol-2-yl)-3-(naphthalen-2-yl)propanamide	5c	GK538
<i>N</i> -(Benzo[<i>d</i>]oxazol-2-yl)-4-(naphthalen-2-yl)butanamide	5d	GK540
<i>N</i> -(1 <i>H</i> -Benzo[<i>d</i>]imidazol-2-yl)-3-(naphthalen-2-yl)propanamide	5e	GK539
<i>N</i> -(1 <i>H</i> -Benzo[<i>d</i>]imidazol-2-yl)-4-(naphthalen-2-yl)butanamide	5f	GK541
<i>N</i> -(Benzo[<i>d</i>]thiazol-2-yl)-2-(naphthalen-2-yloxy)acetamide	7	GK591
(<i>E</i>)- <i>N</i> -(Benzo[<i>d</i>]thiazol-2-yl)-3-(naphthalen-2-yl)acrylamide	9a	GK522
(<i>E</i>)- <i>N</i> -(Benzo[<i>d</i>]thiazol-2-yl)-3-(4-methoxyphenyl)acrylamide	9b	GK523
<i>N</i> -(Benzo[<i>d</i>]thiazol-2-yl)-3-(4-methoxyphenyl)propanamide	11	GK521
<i>N</i> -(3-(Naphthalen-2-yl)propyl)benzo[<i>d</i>]thiazole-2-carboxamide	14	GK508
4-Methoxybenzyl benzo[<i>d</i>]thiazol-2-ylcarbamate	16a	GK524
Naphthalen-2-ylmethyl benzo[<i>d</i>]thiazol-2-ylcarbamate	16b	GK525
<i>N</i> -(1-Methoxy-3-(naphthalen-2-yl)propyl)benzo[<i>d</i>]thiazol-2-amine	18a	GK542
<i>N</i> -(1-Methoxy-3-phenylpropyl)benzo[<i>d</i>]thiazol-2-amine	18b	GK561
<i>N</i> -(1-Methoxy-3-(4-methoxyphenyl)propyl)benzo[<i>d</i>]thiazol-2-amine	18c	GK559
<i>N</i> -(3-(Naphthalen-2-yl)propyl)benzo[<i>d</i>]thiazol-2-amine	19a	GK543
<i>N</i> -(3-Phenylpropyl)benzo[<i>d</i>]thiazol-2-amine	19b	GK562
<i>N</i> -(3-(4-Methoxyphenyl)propyl)benzo[<i>d</i>]thiazol-2-amine	19c	GK560
<i>N</i> -(3-(Naphthalen-1-yl)propyl)benzo[<i>d</i>]thiazol-2-amine	19d	GK593
<i>N</i> -(3-(Naphthalen-1-yl)propyl)thiazol-2-amine	19e	GK610
<i>N</i> -(3-Phenylpropyl)thiazol-2-amine	19f	GK643
<i>N</i> -(3-(Naphthalen-2-yl)propyl)-6-(trifluoromethoxy)benzo[<i>d</i>]thiazol-2-amine	19g	GK642
<i>N</i> -(3-(Naphthalen-1-yl)propyl)-6-(trifluoromethoxy)benzo[<i>d</i>]thiazol-2-amine	19h	GK644

<i>N</i> -(3-(Naphthalen-2-yl)propyl)benzo[<i>d</i>]oxazol-2-amine	23a	GK566
<i>N</i> -(3-(4-Methoxyphenyl)propyl)benzo[<i>d</i>]oxazol-2-amine	23b	GK567
<i>N</i> -(2-(Naphthalen-2-yloxy)ethyl)benzo[<i>d</i>]oxazol-2-amine	23c	GK592
<i>N</i> -(2-(Naphthalen-1-yloxy)ethyl)benzo[<i>d</i>]oxazol-2-amine	23d	GK604
<i>N</i> -(2-(Naphthalen-2-yloxy)ethyl)benzo[<i>d</i>]thiazol-2-amine	25a	GK606
<i>N</i> -(2-(Naphthalen-1-yloxy)ethyl)benzo[<i>d</i>]thiazol-2-amine	25b	GK607

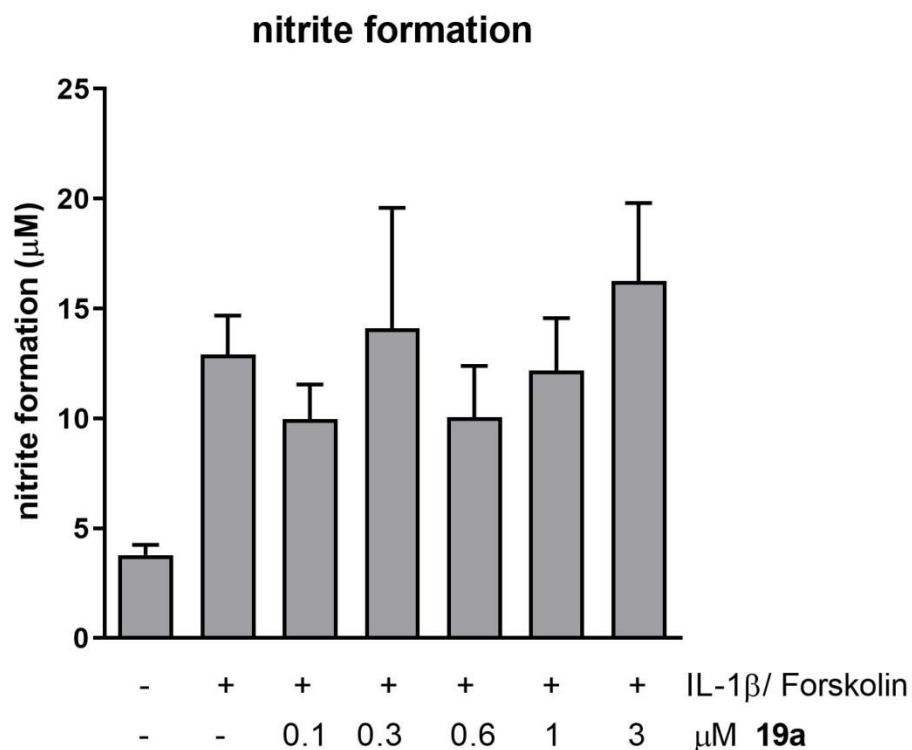


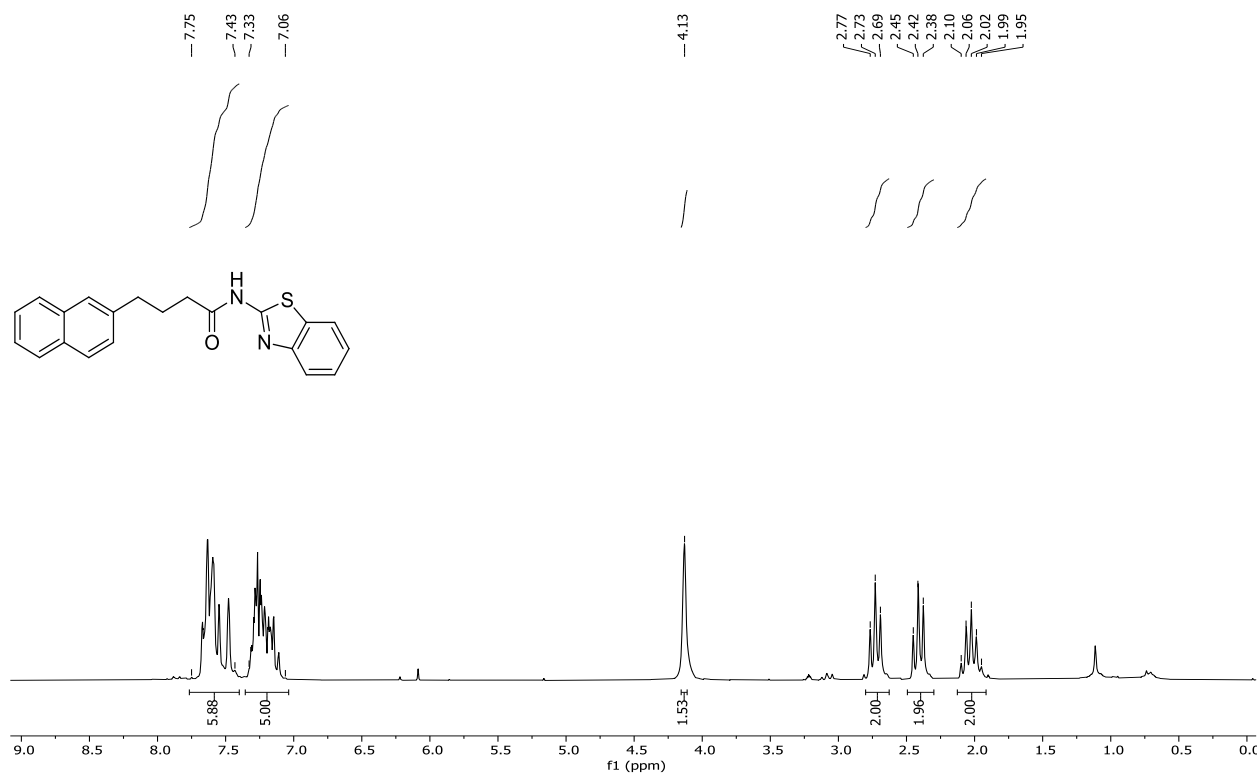
Figure S1. Effect of the inhibitor **19a** on IL-1/Fk-stimulated nitrite formation in rat mesangial cells.

Cells were pretreated for 20 min with the indicated concentrations of **19a** and then stimulated for 24 h in the absence (-) or presence (+) of 1 nM interleukin 1 β (IL-1) plus 5 μ M forskolin (Fk). Nitrite was quantified in supernatants using Griess assay as previously described.¹ Data are presented as mM of nitrite and are means \pm S.D. (n = 3).

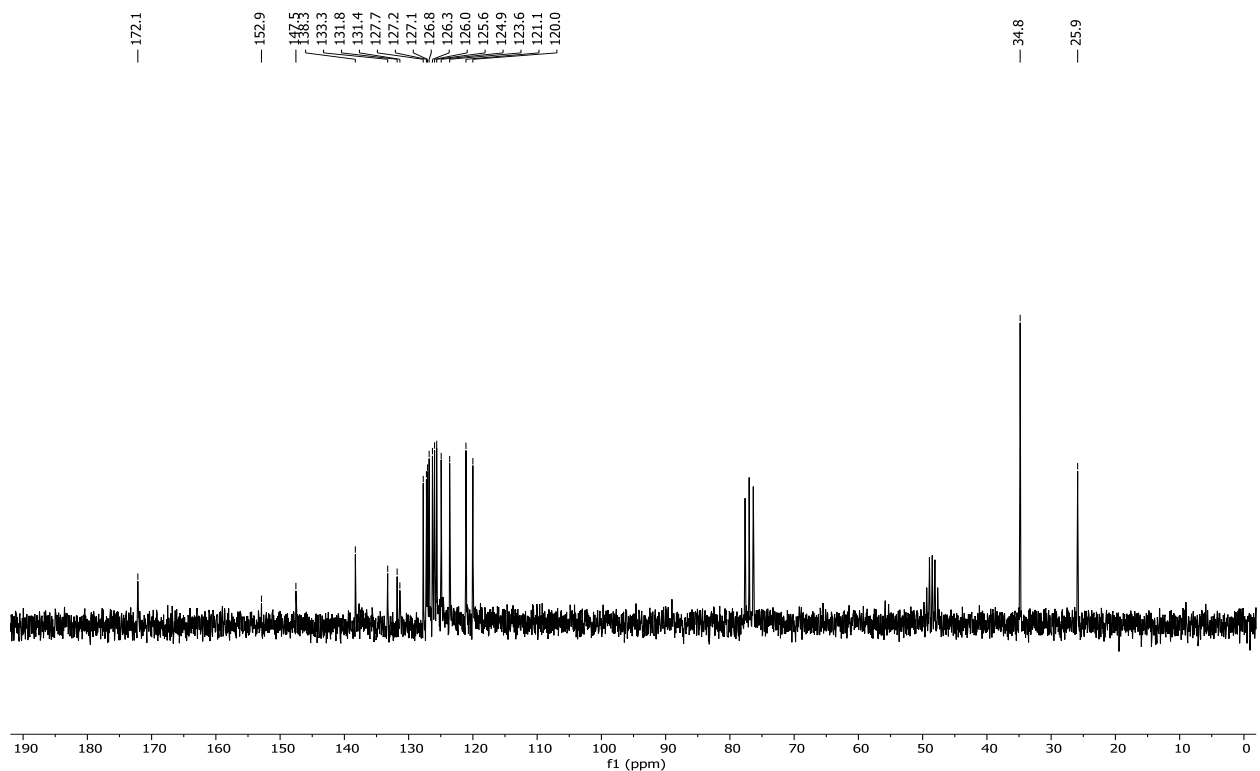
References

1. Mühl, H.; Kunz, D.; Rob, P.; Pfeilschifter, J. Cyclosporin derivatives inhibit interleukin 1 β induction of nitric oxide synthase in renal mesangial cells. *Eur. J. Pharmacol.* **1993**, 249, 95-100.

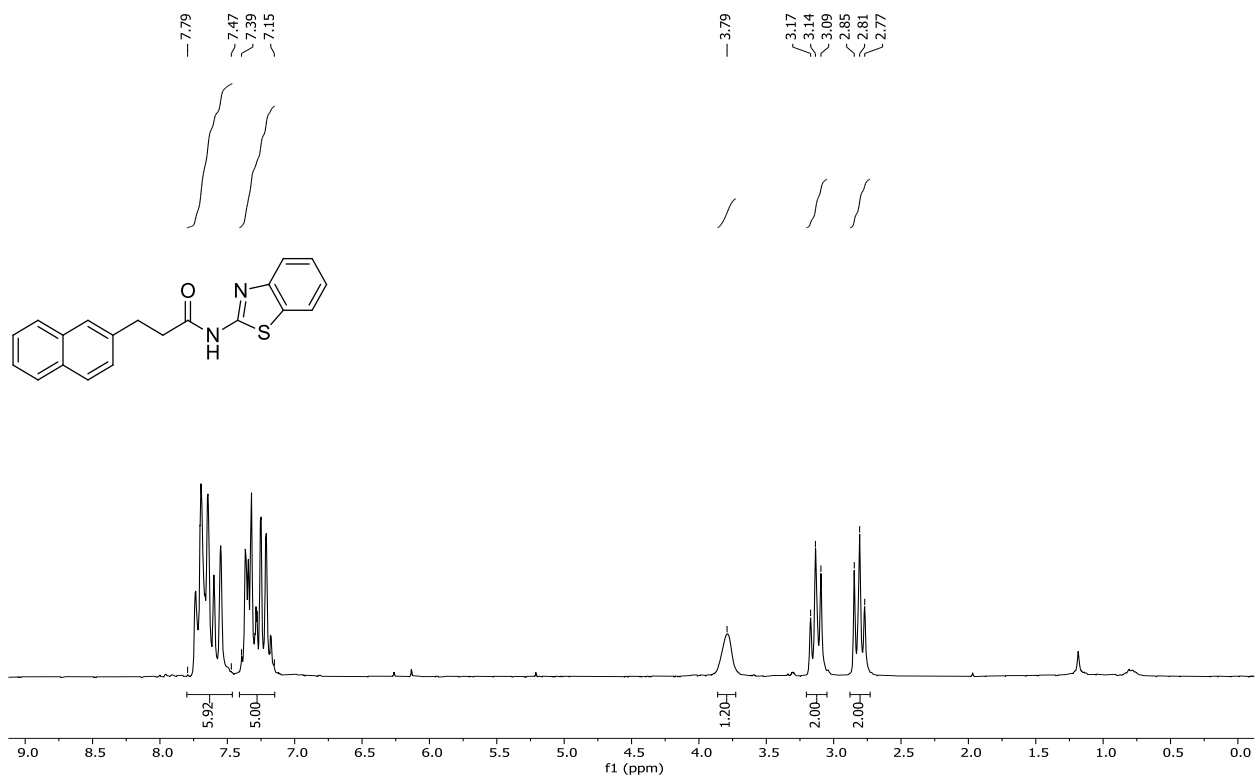
NMR Spectra



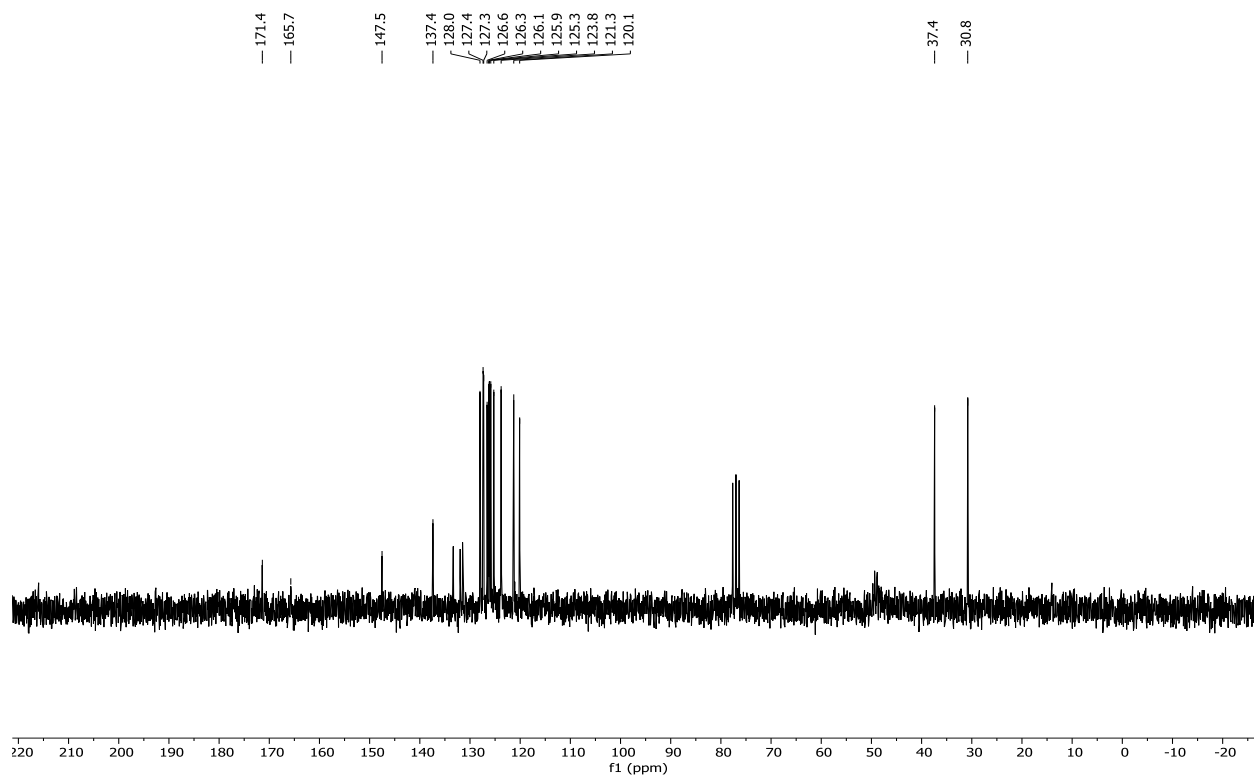
¹H NMR spectrum of 5a.



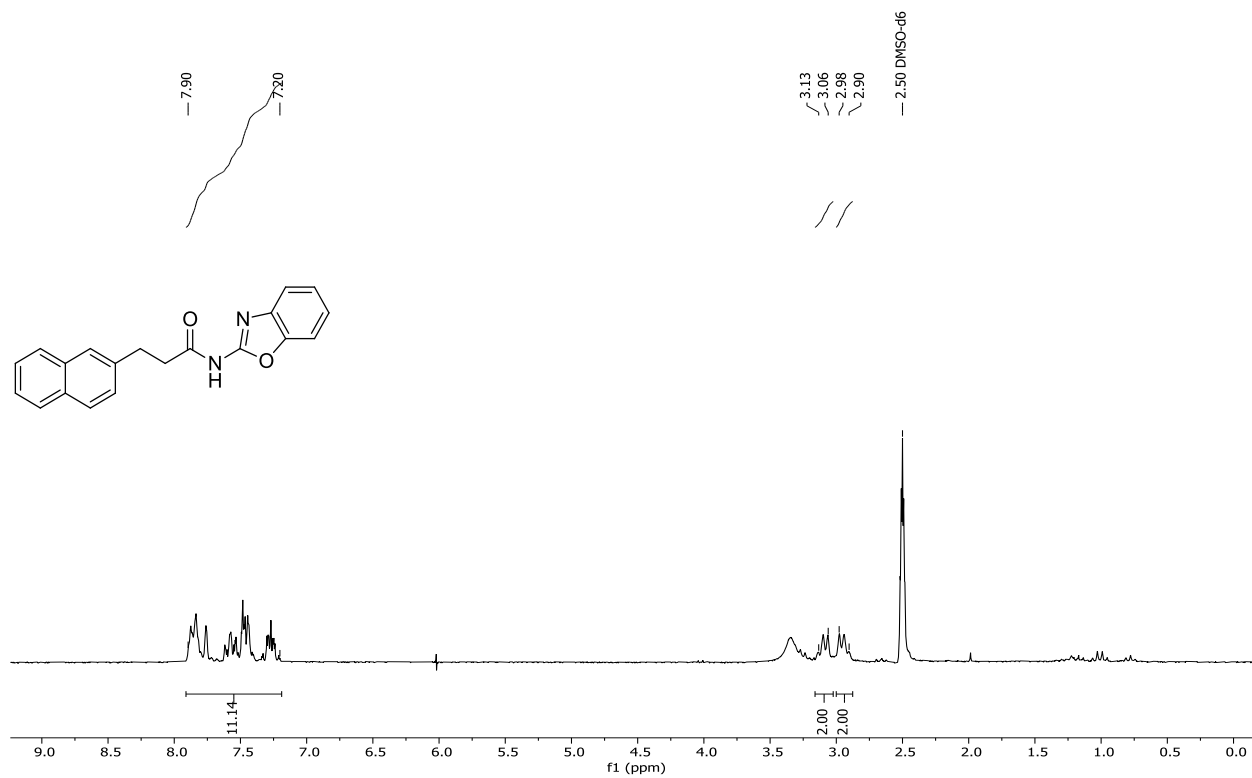
¹³C NMR spectrum of 5a.



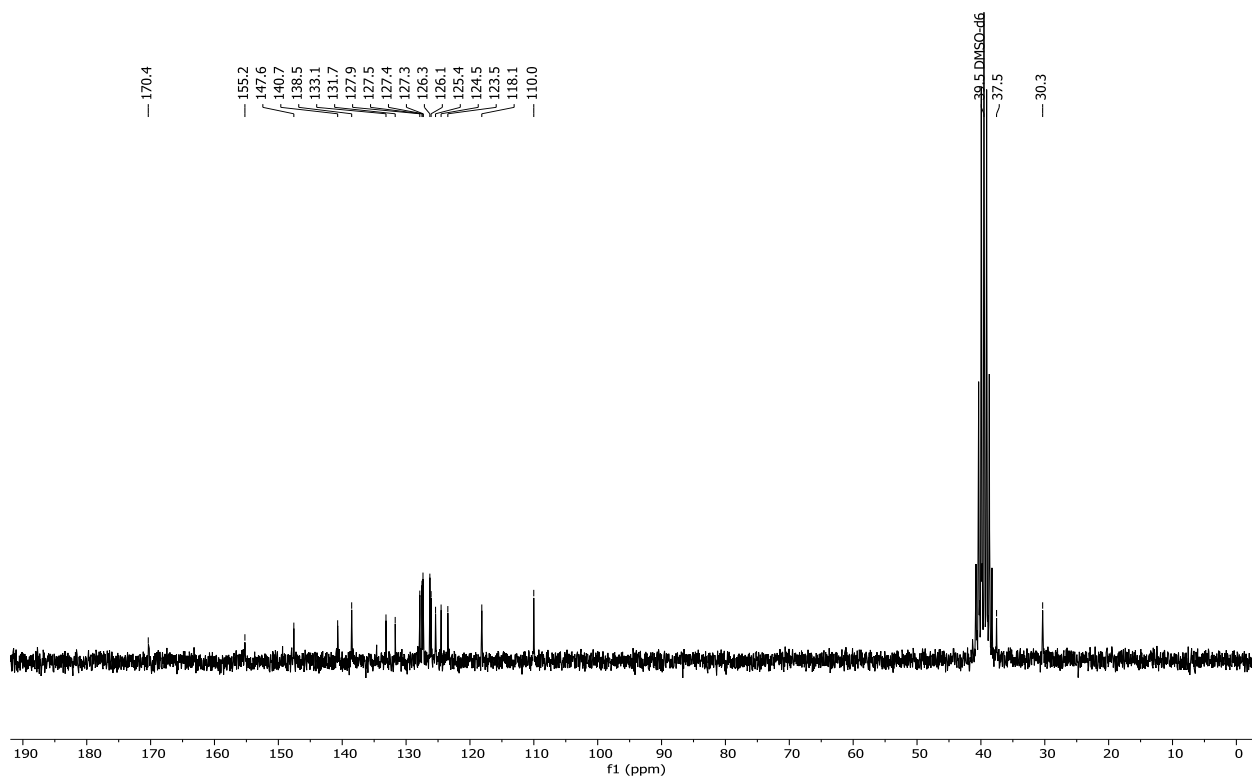
^1H NMR spectrum of **5b**.



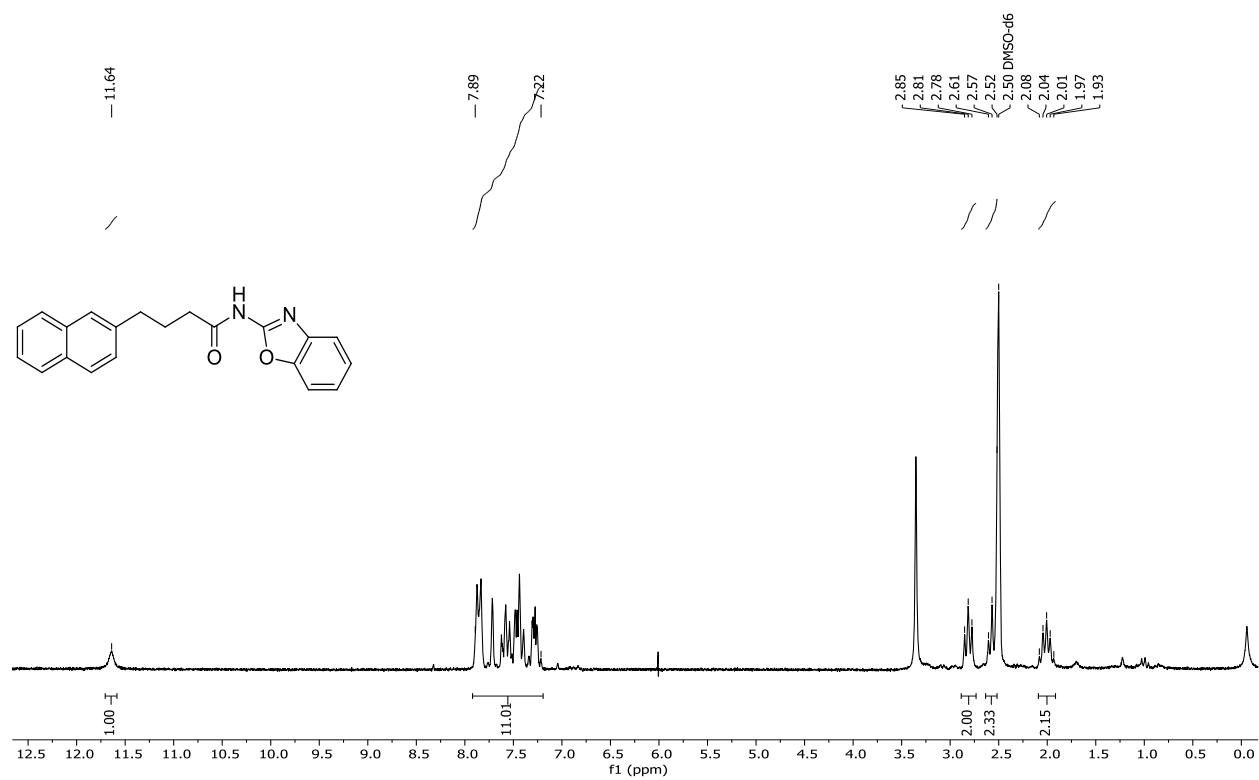
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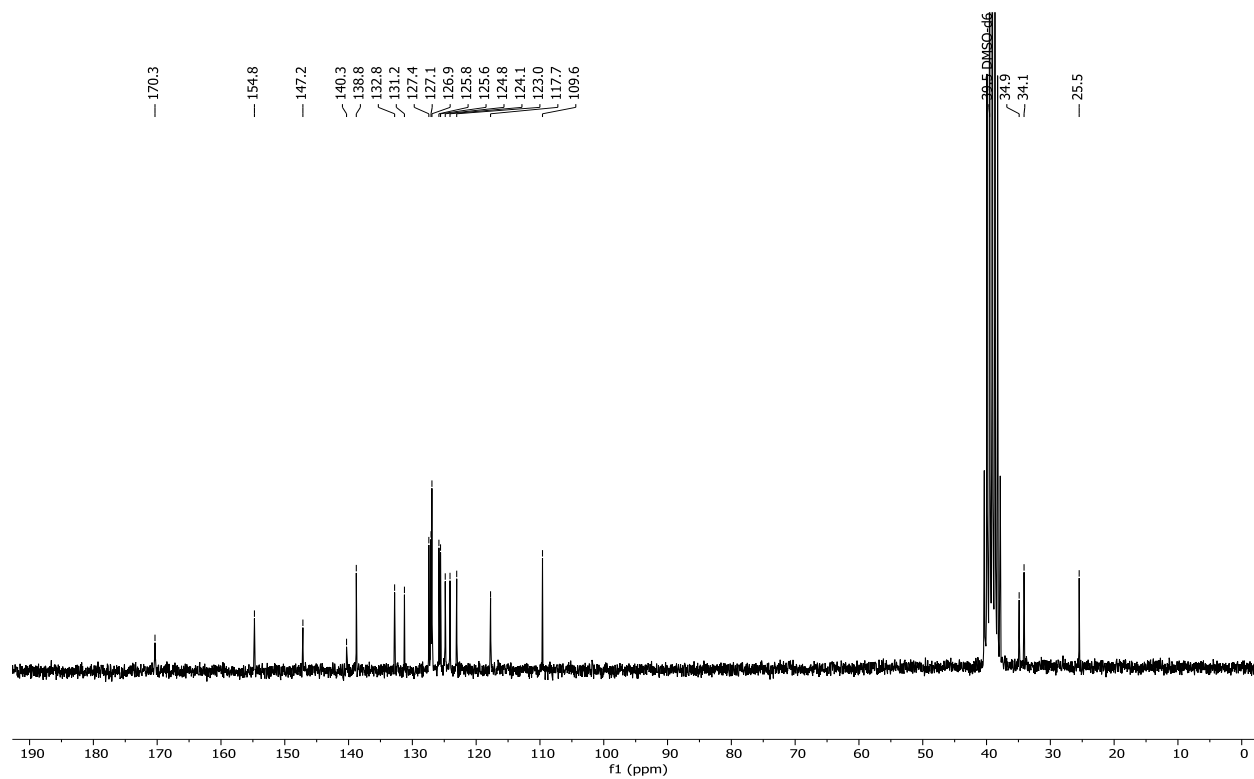
¹H NMR spectrum of **5c**.



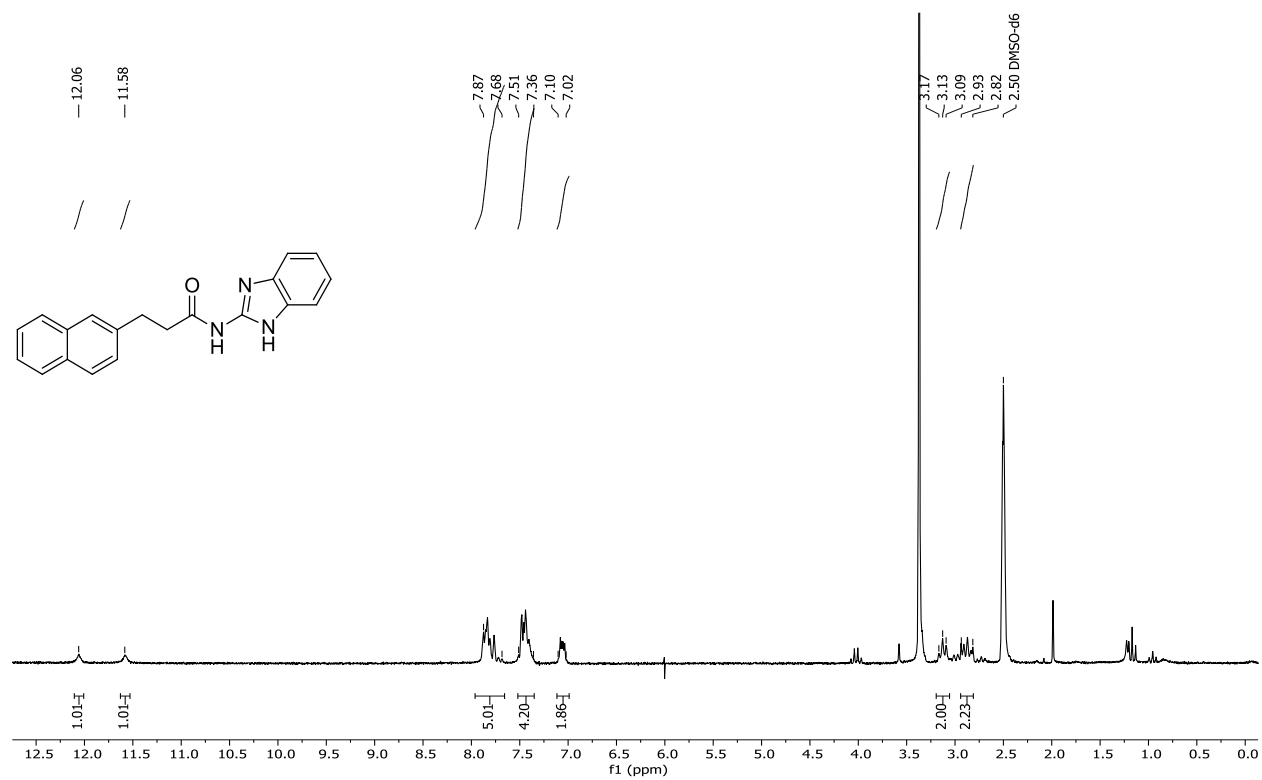
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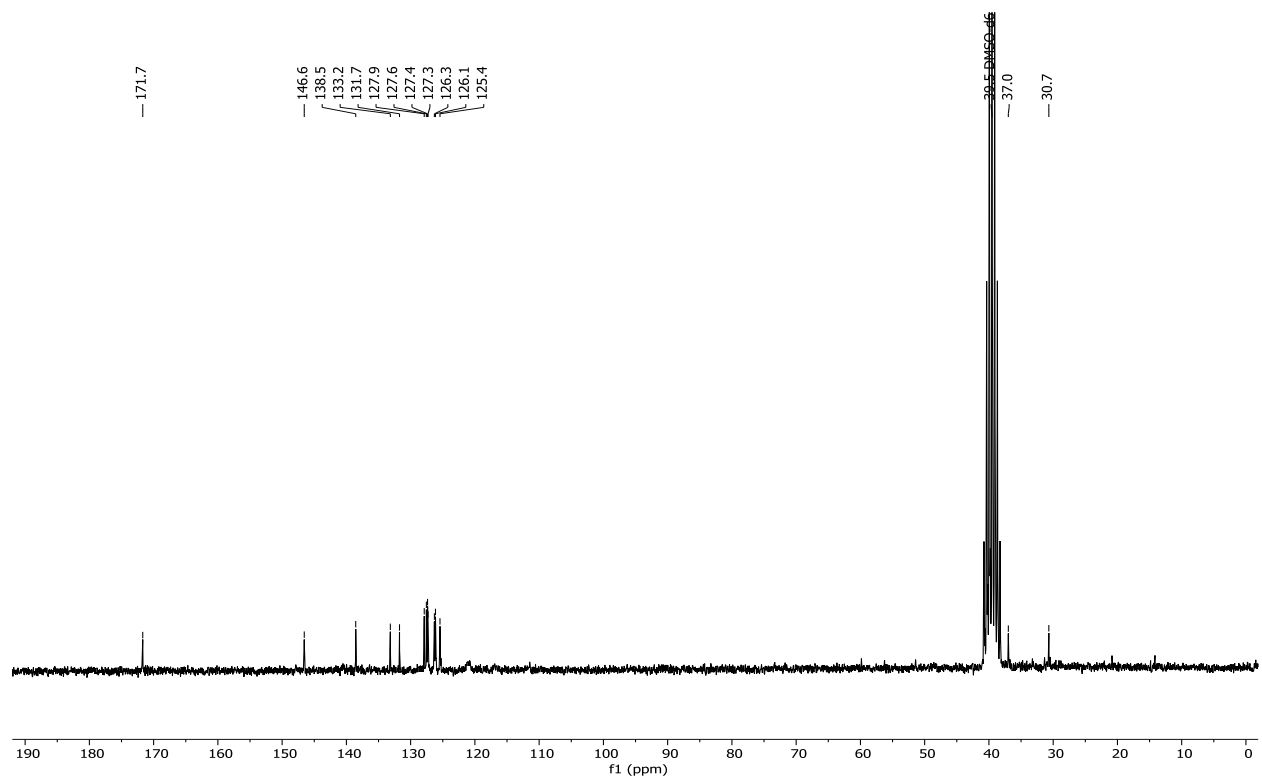
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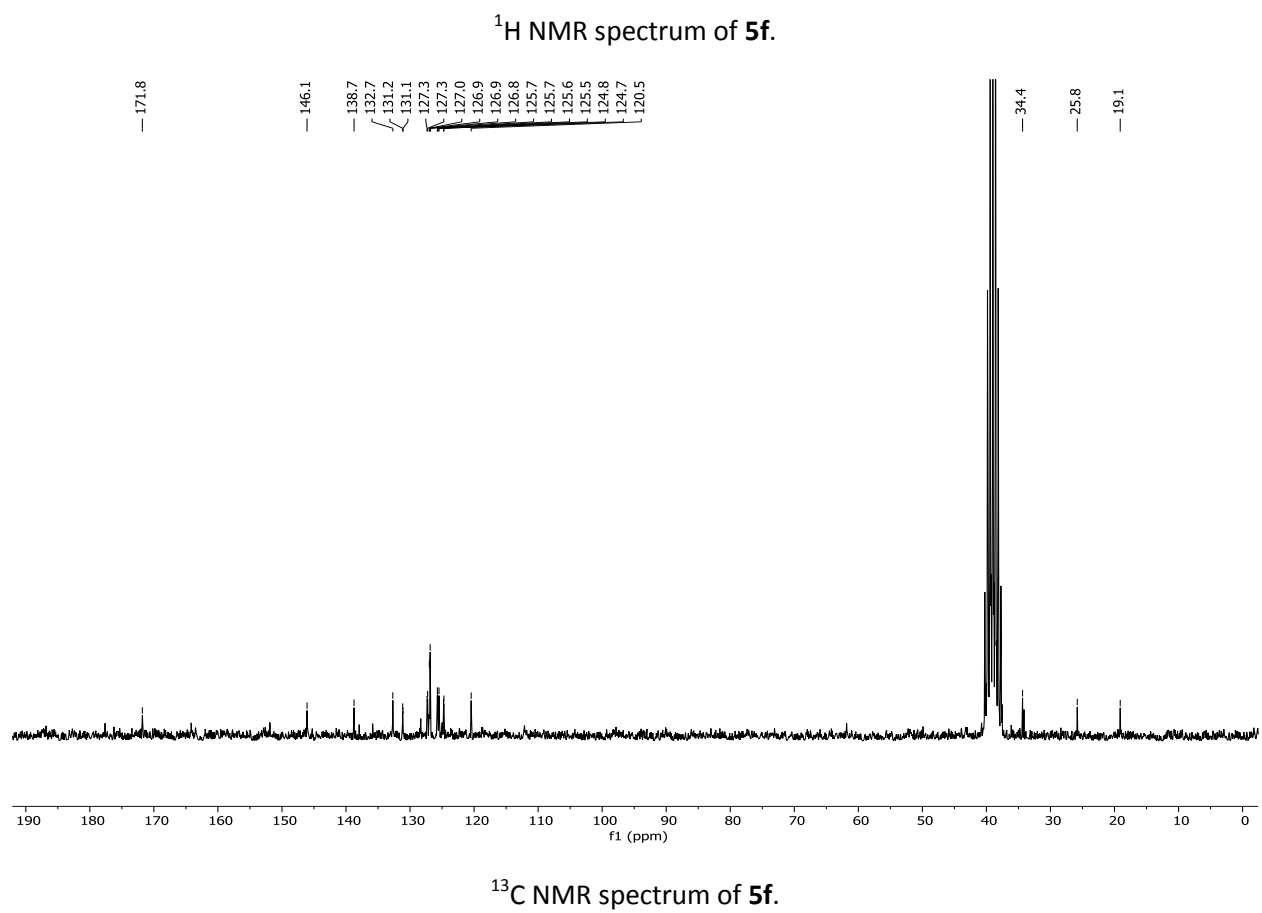
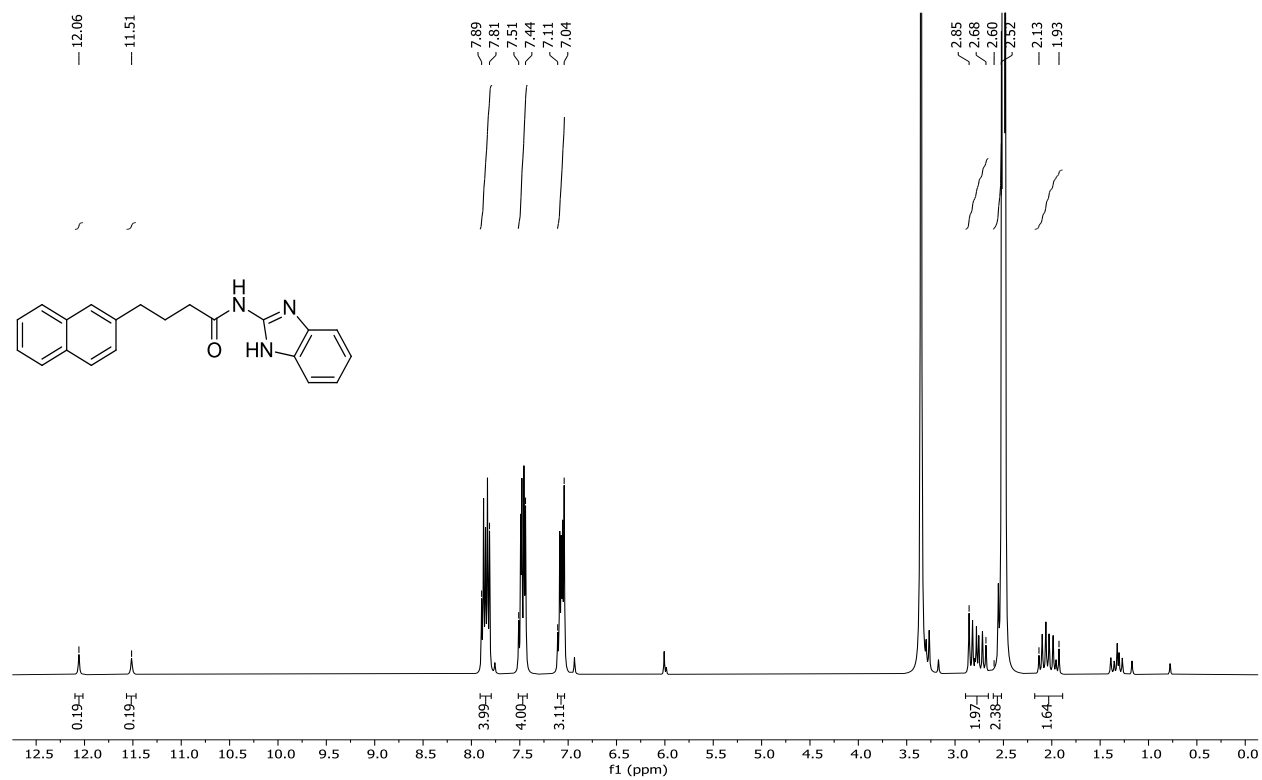
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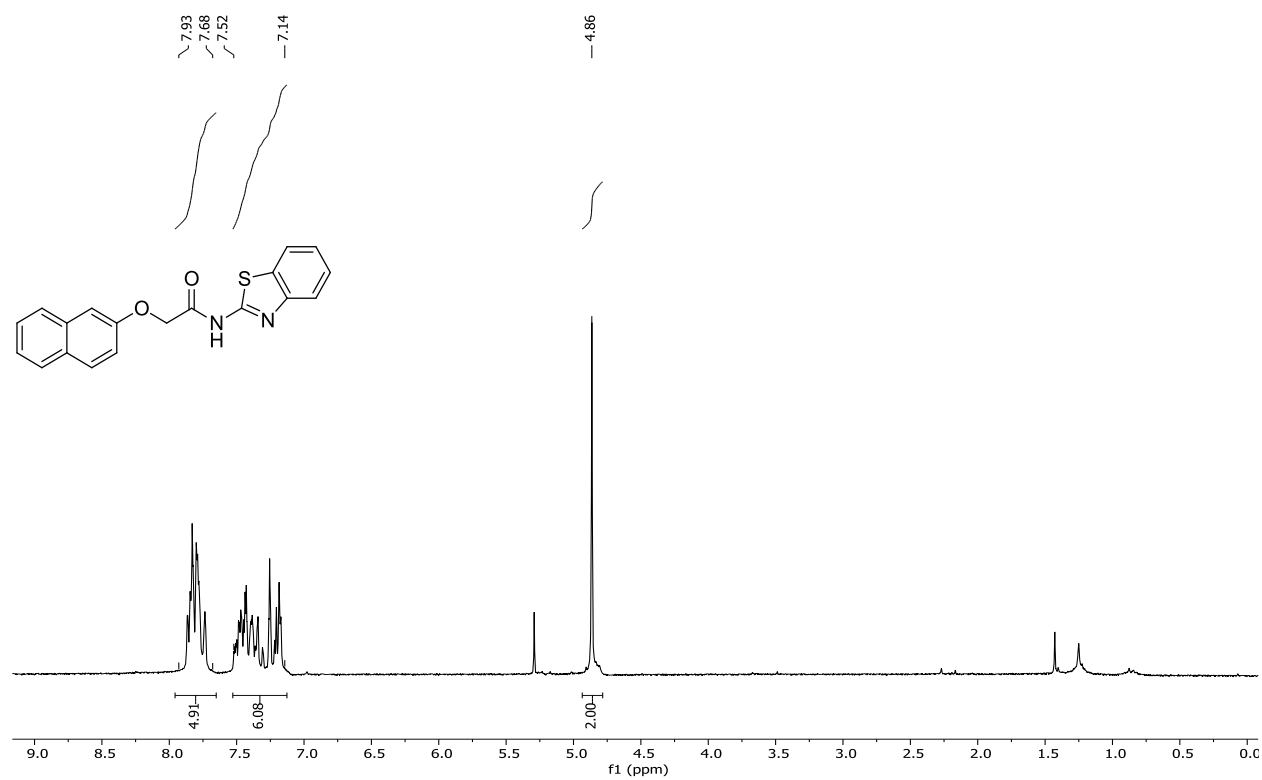


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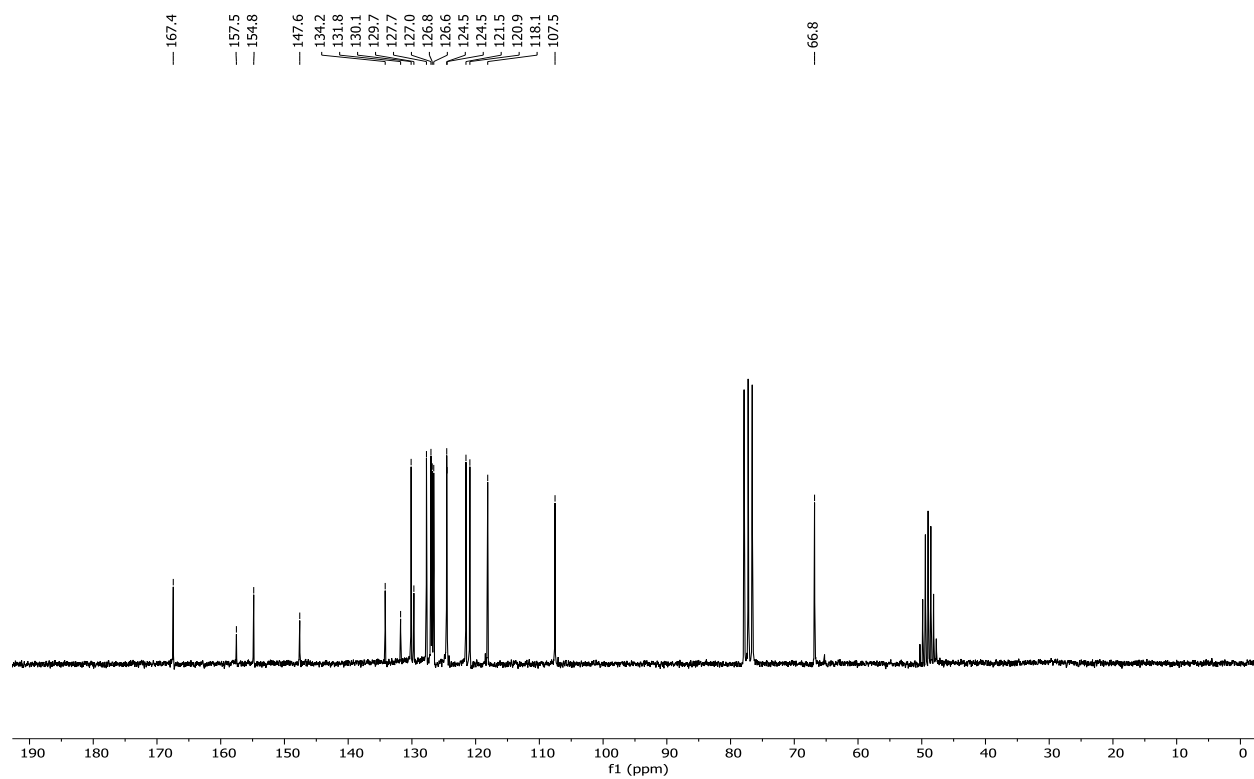


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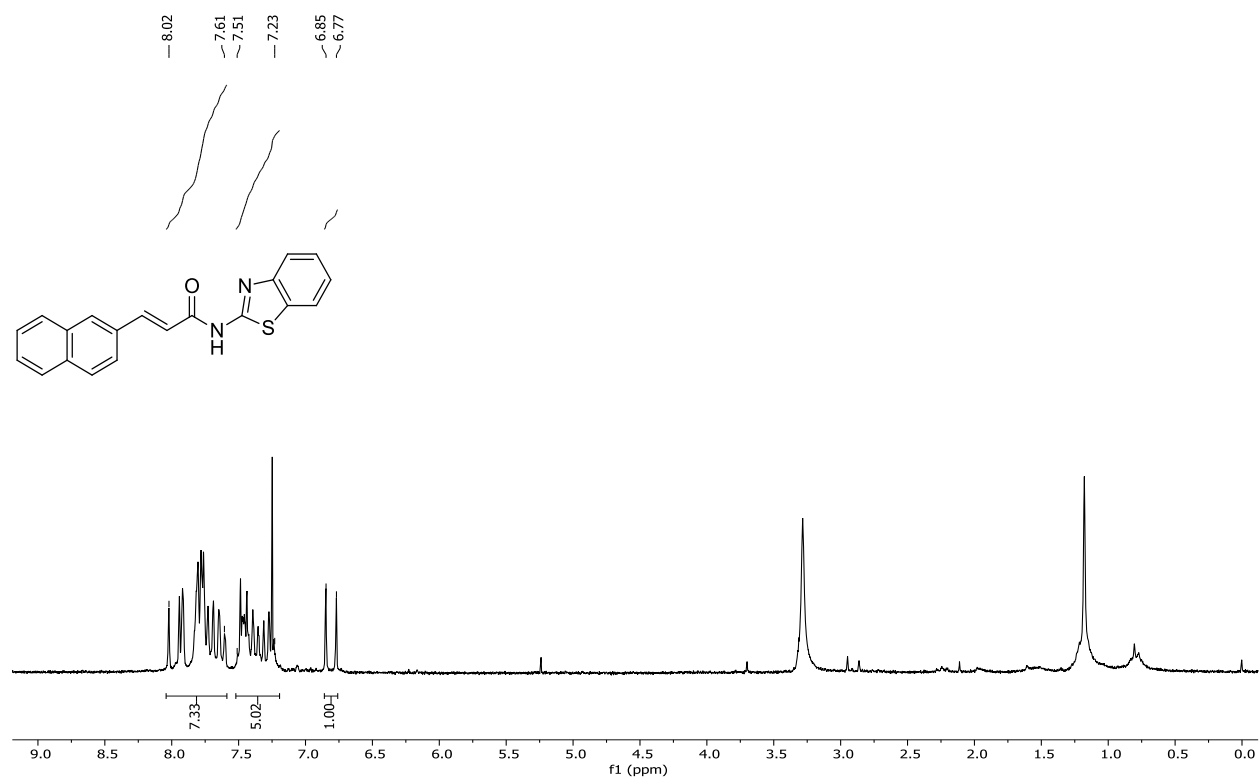




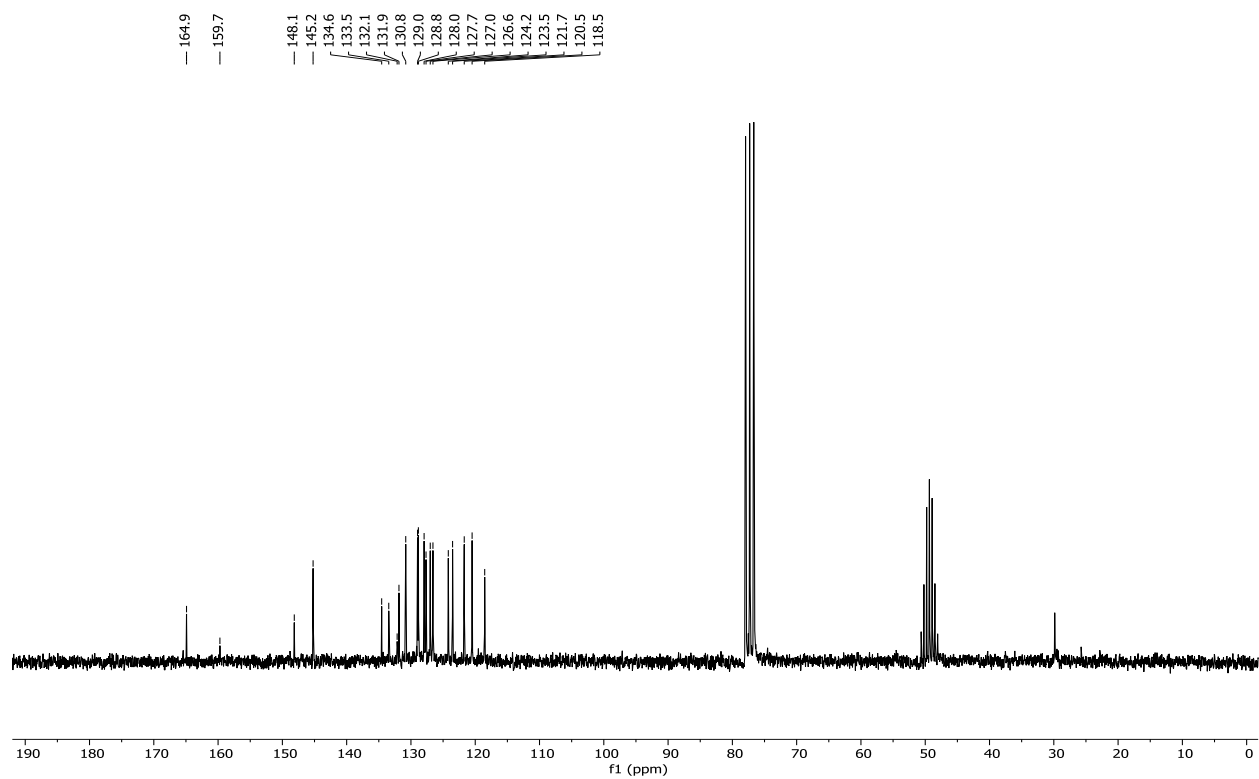
¹H NMR spectrum of 7.



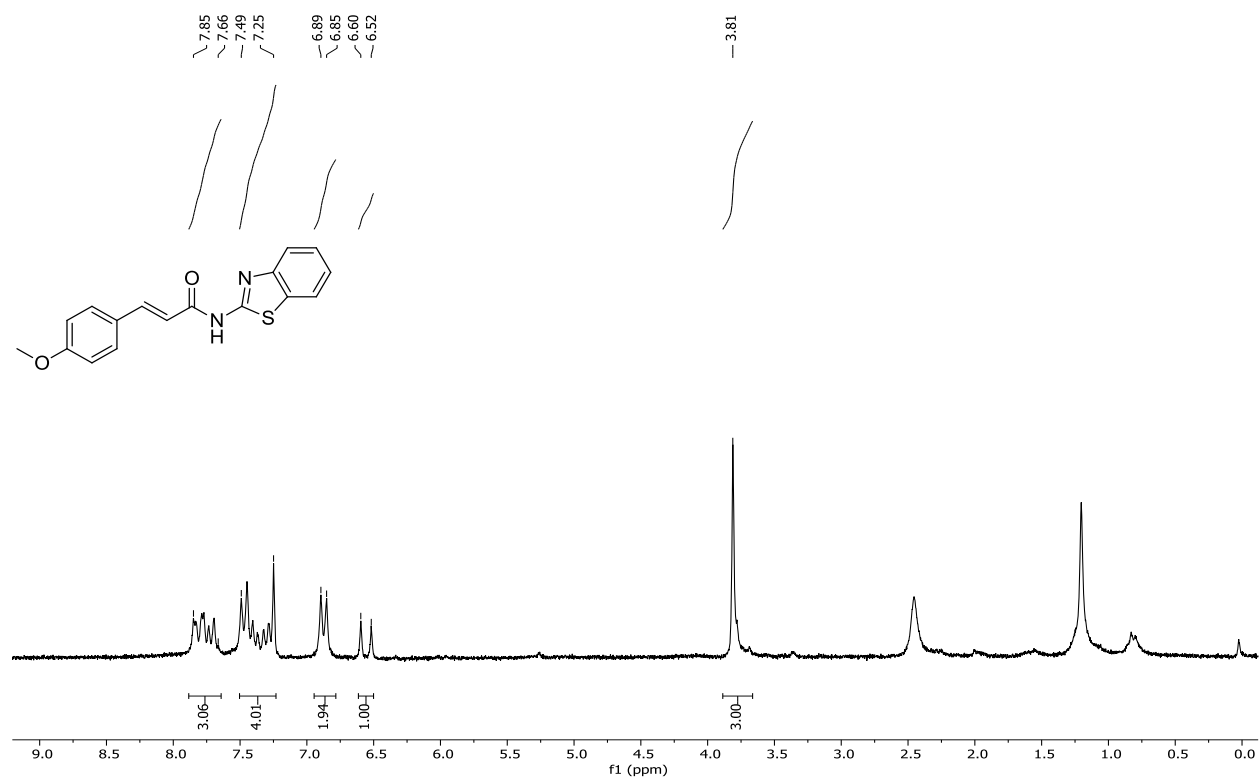
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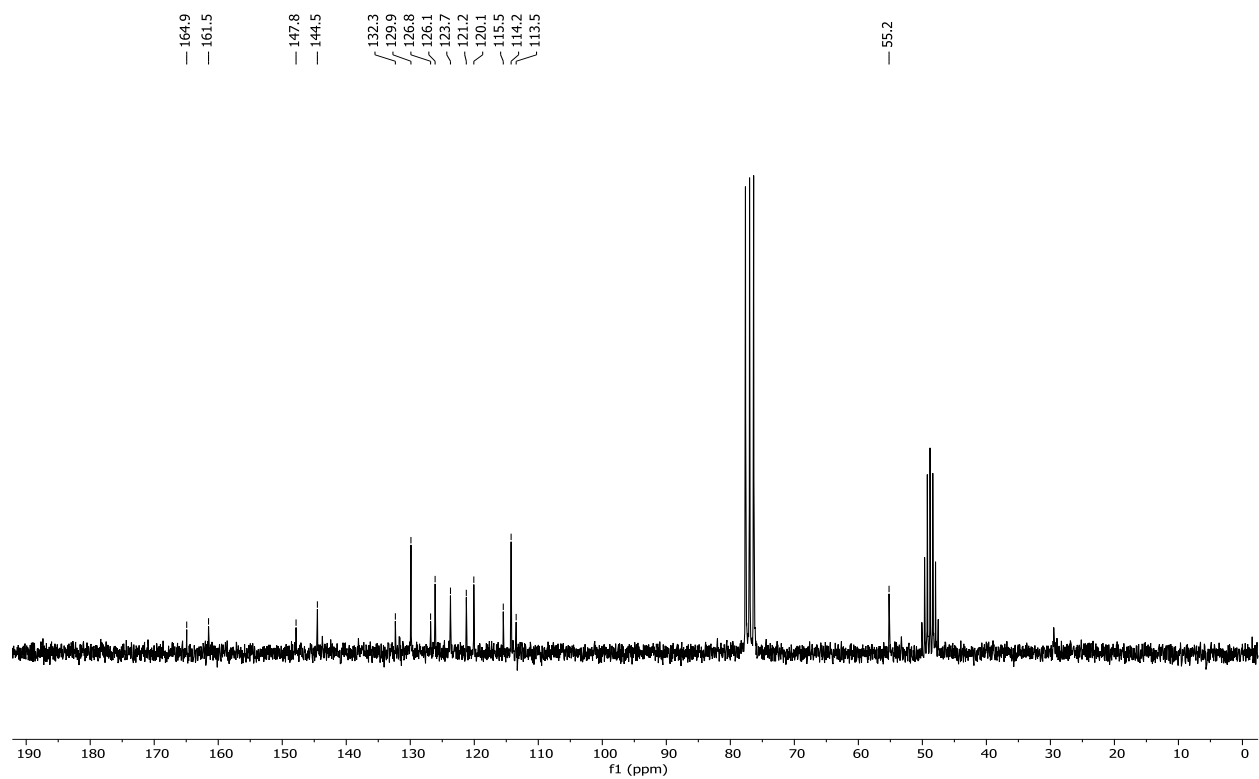
^1H NMR spectrum of **9a**.



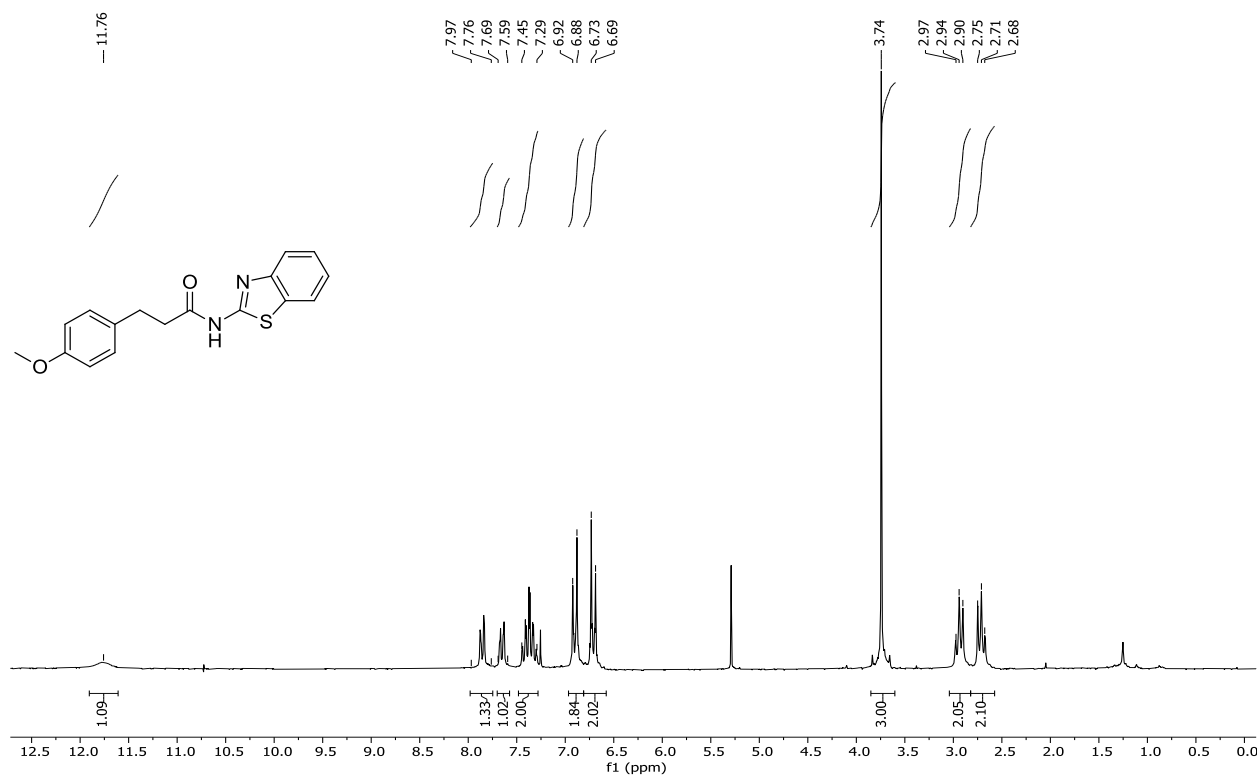
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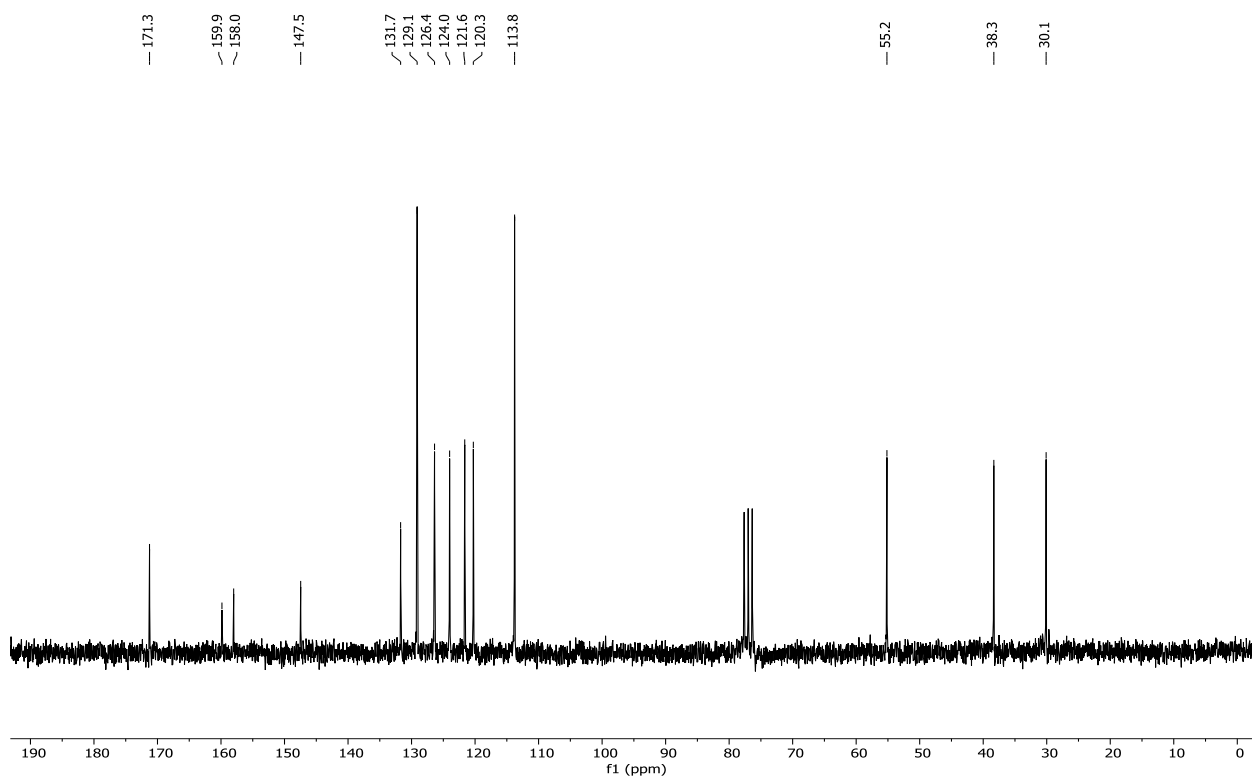
¹H NMR spectrum of **9b**.



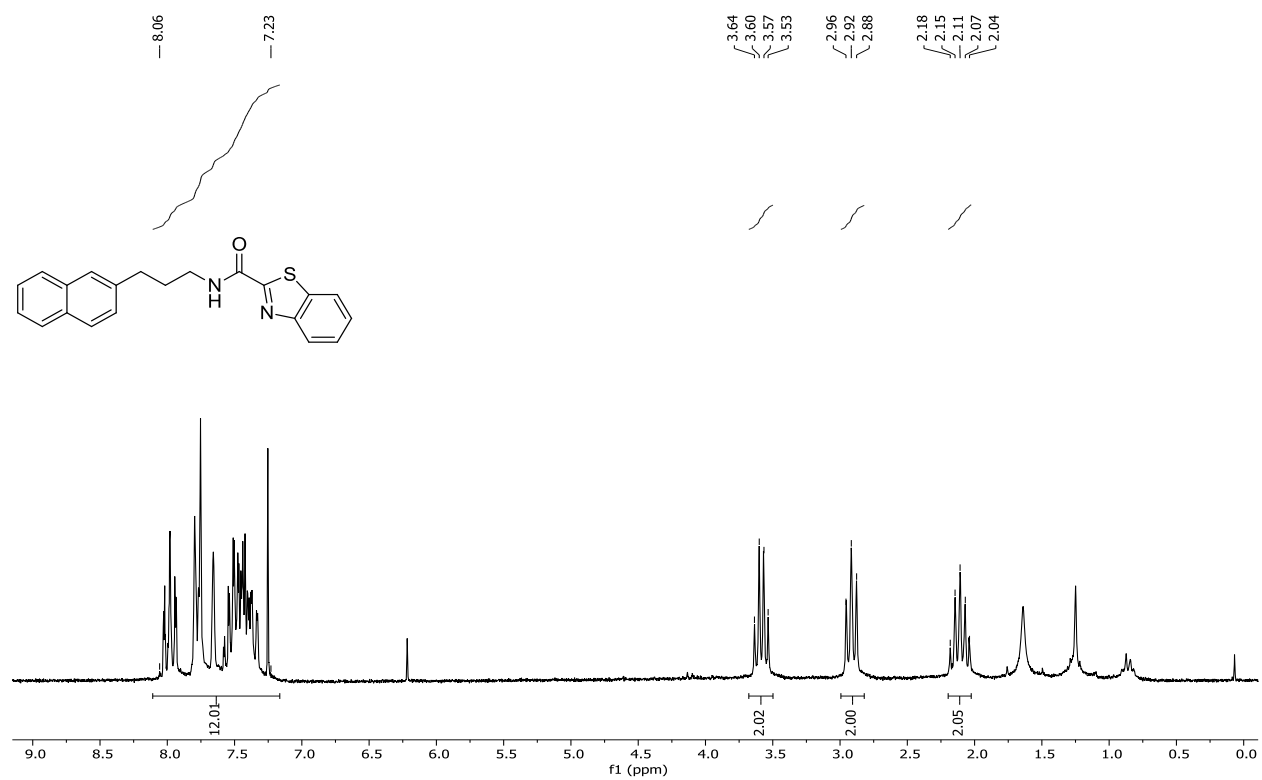
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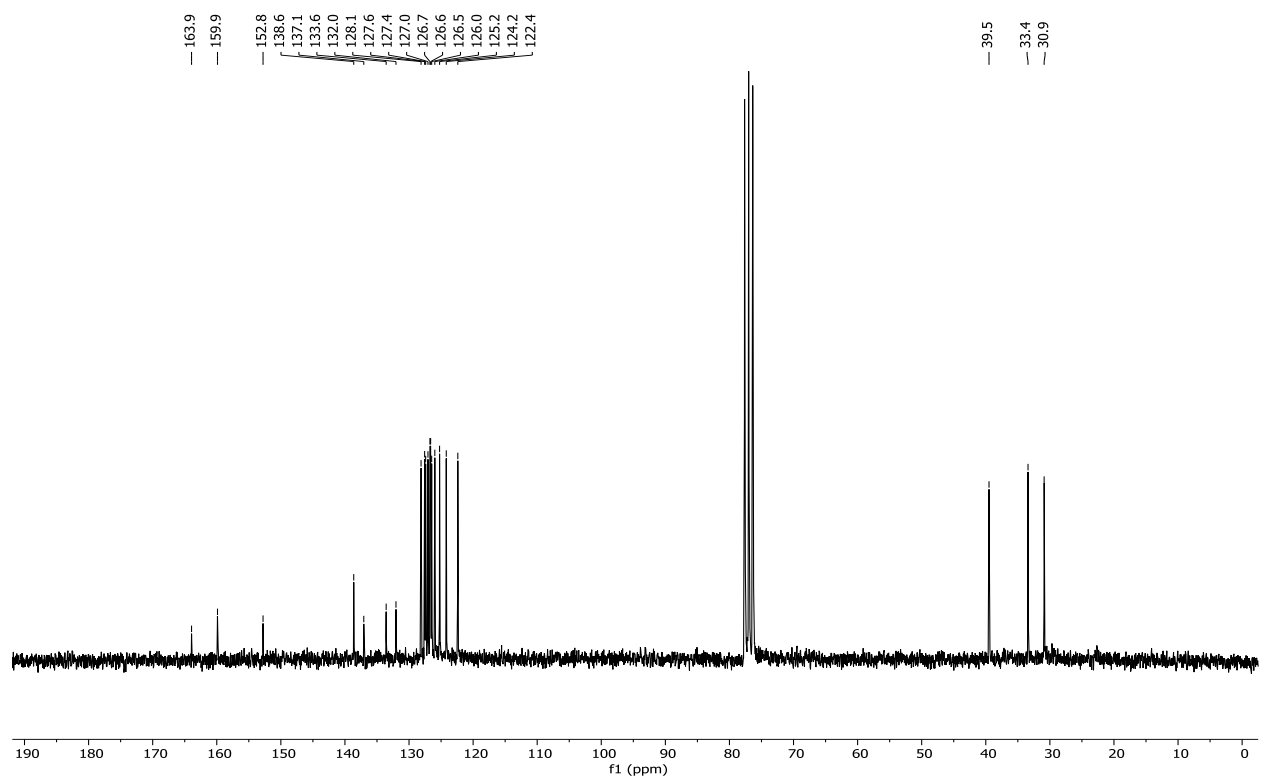
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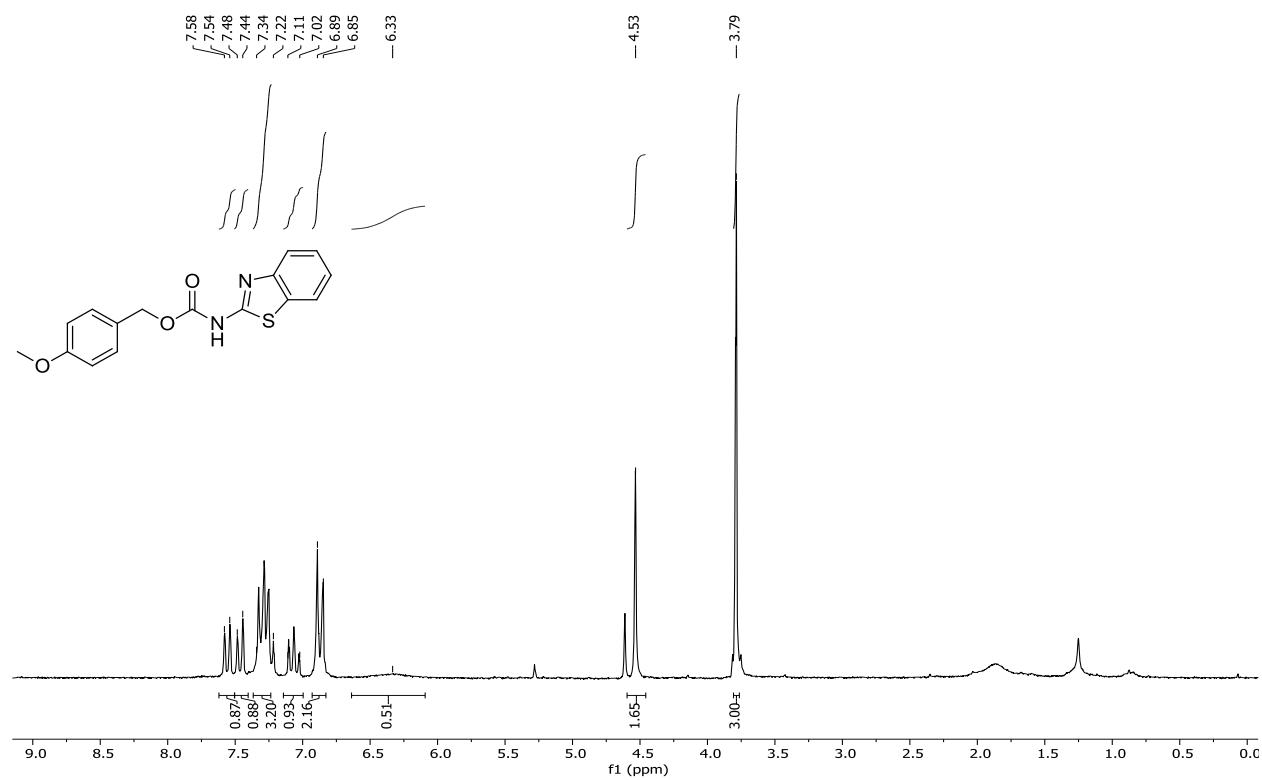
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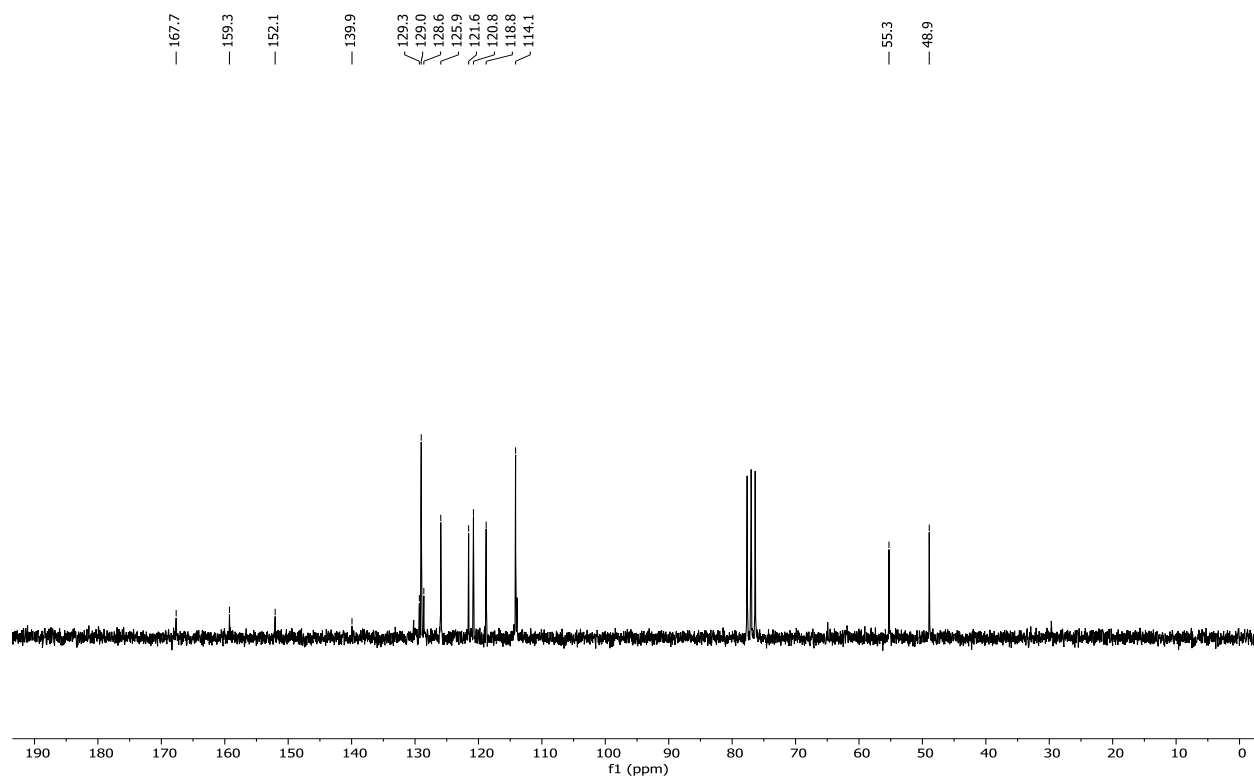
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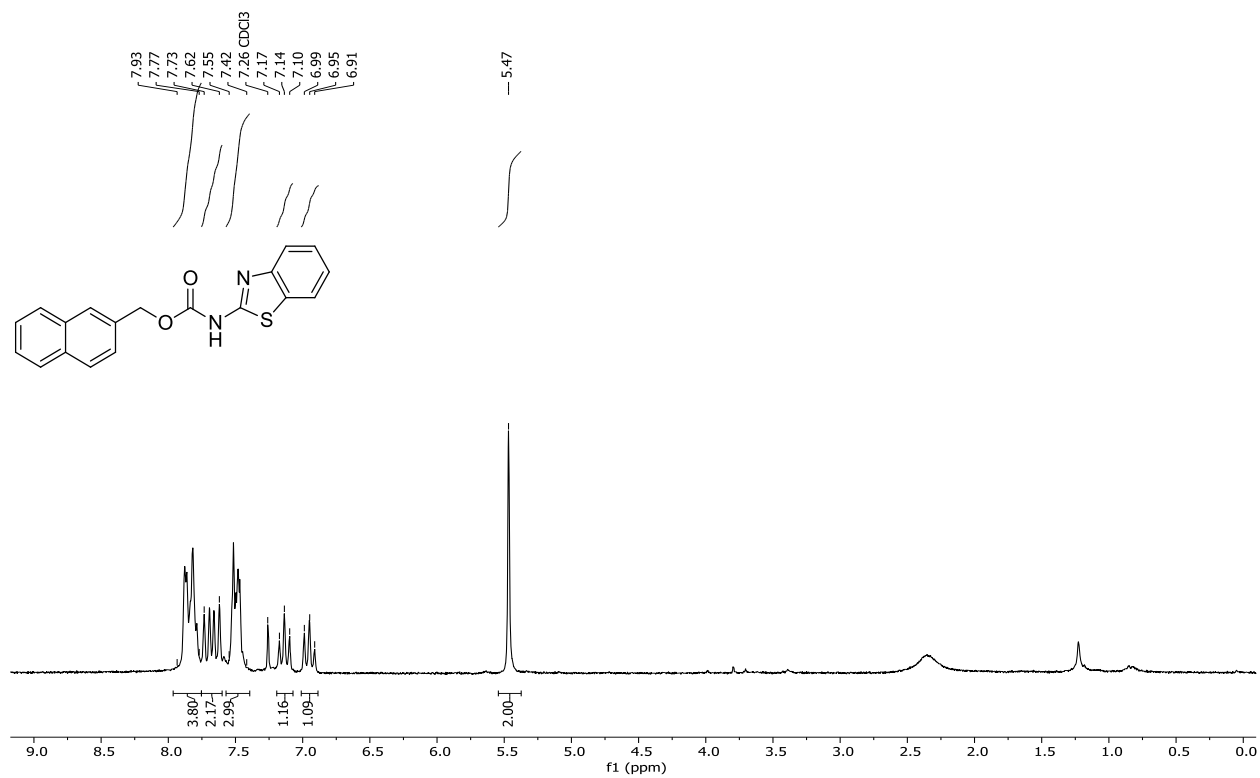
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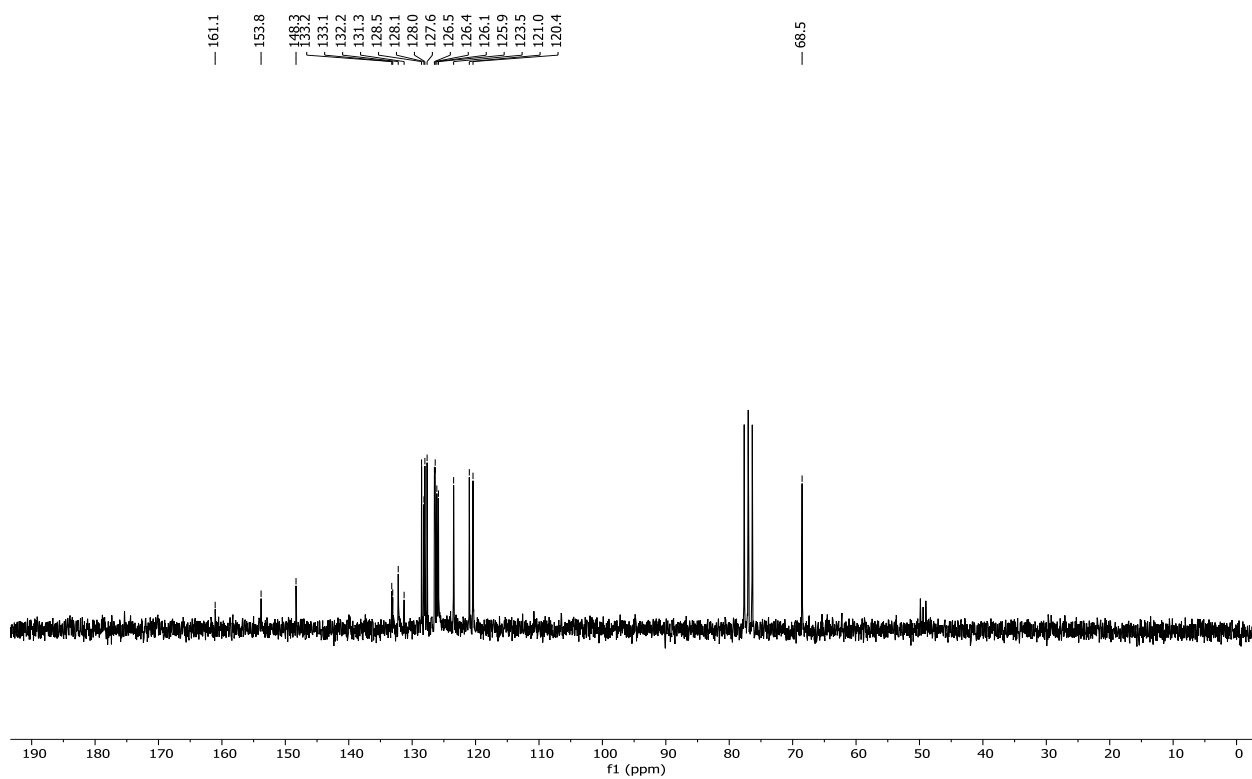
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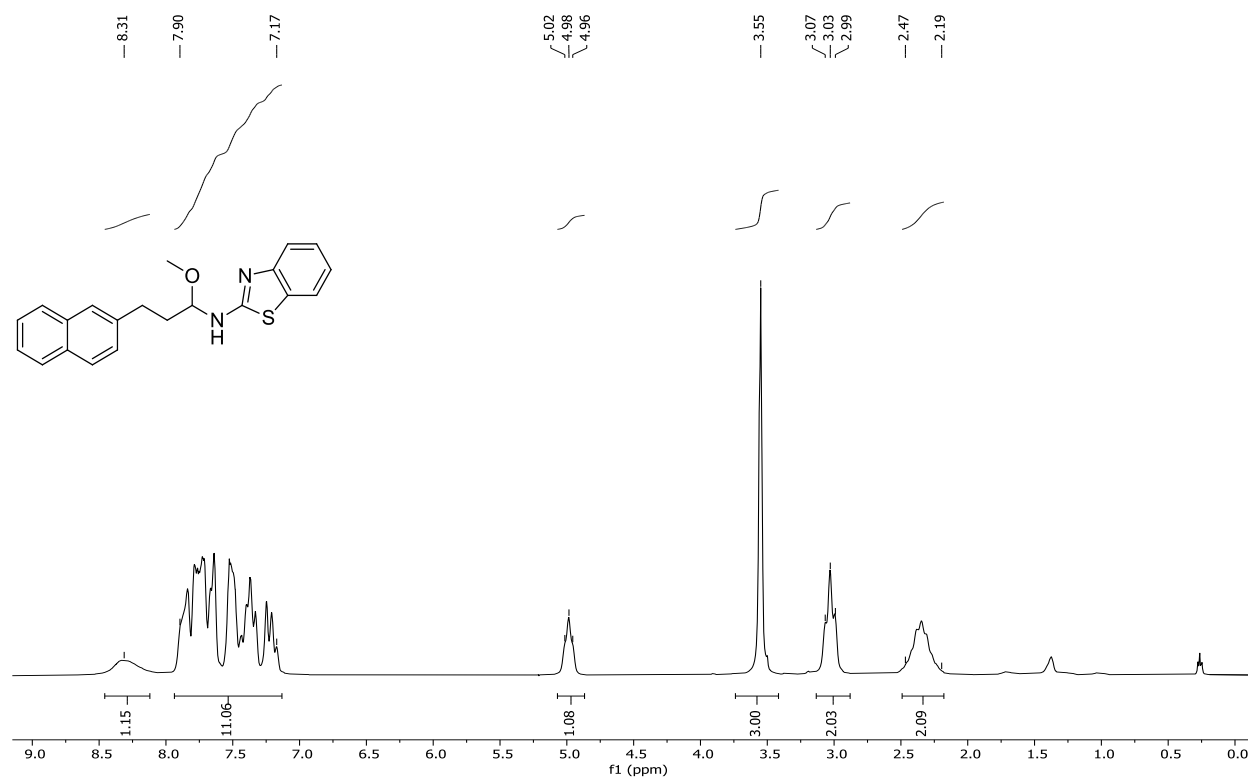
¹³C NMR spectrum of 16a.



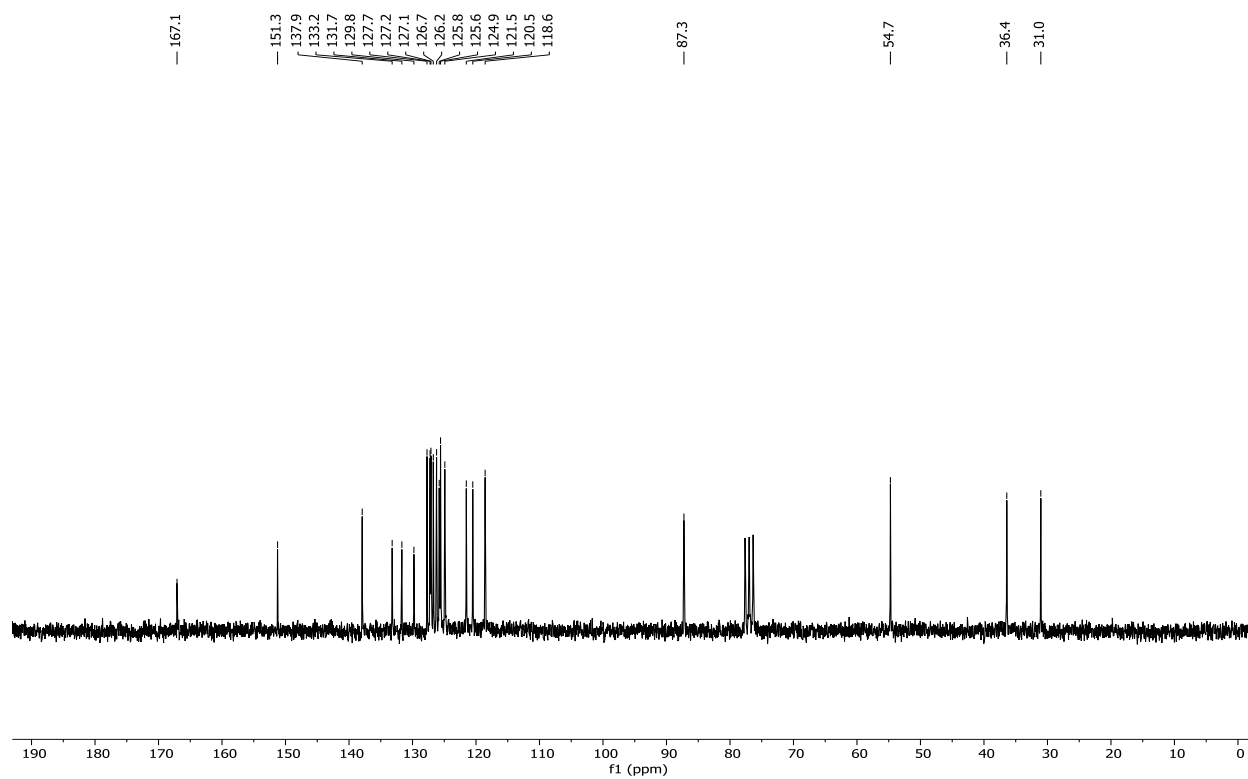
¹H NMR spectrum of **16b**.



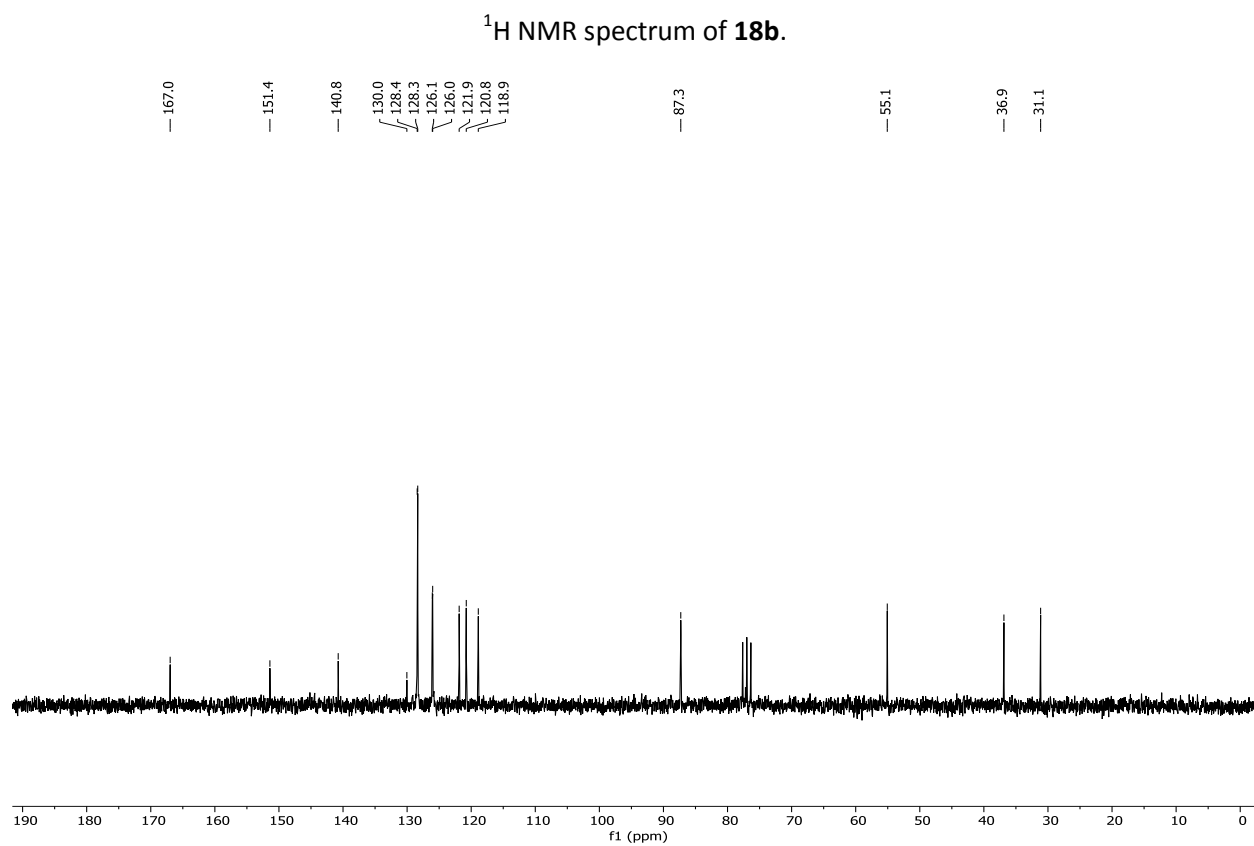
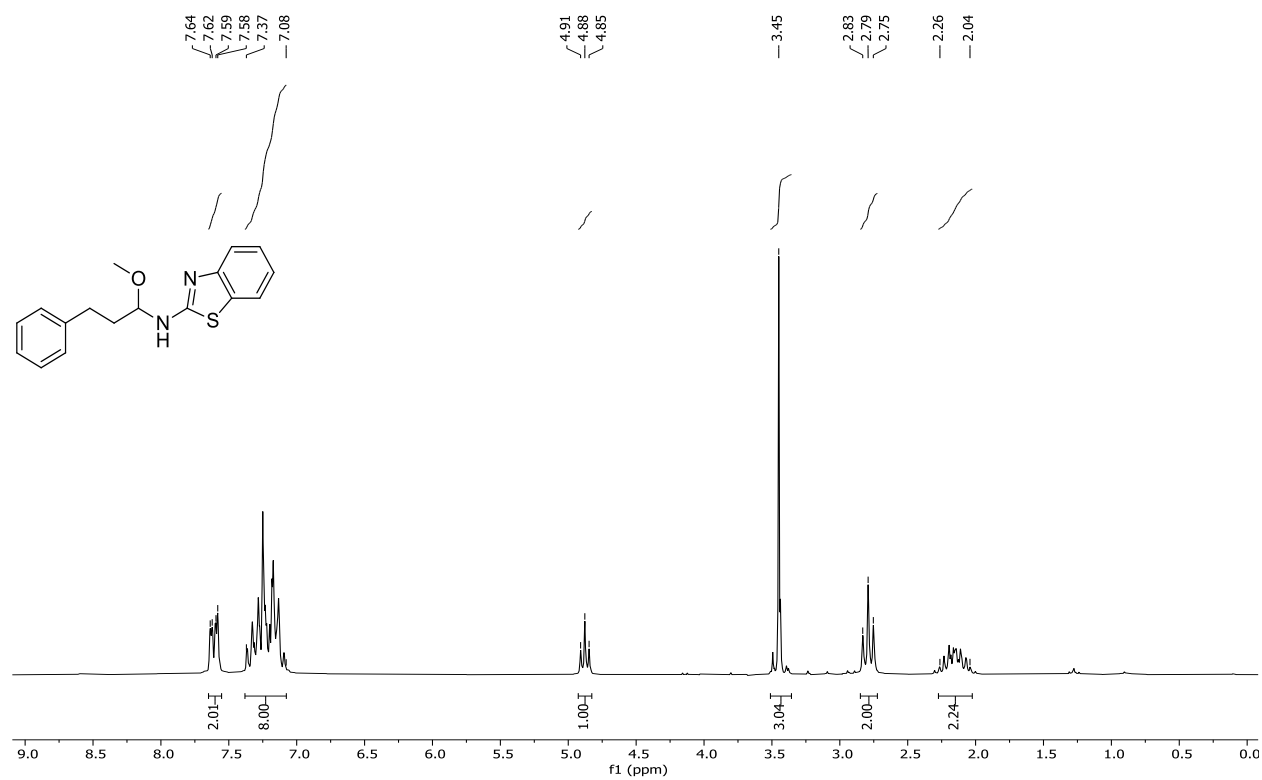
¹³C NMR spectrum of **16b**.

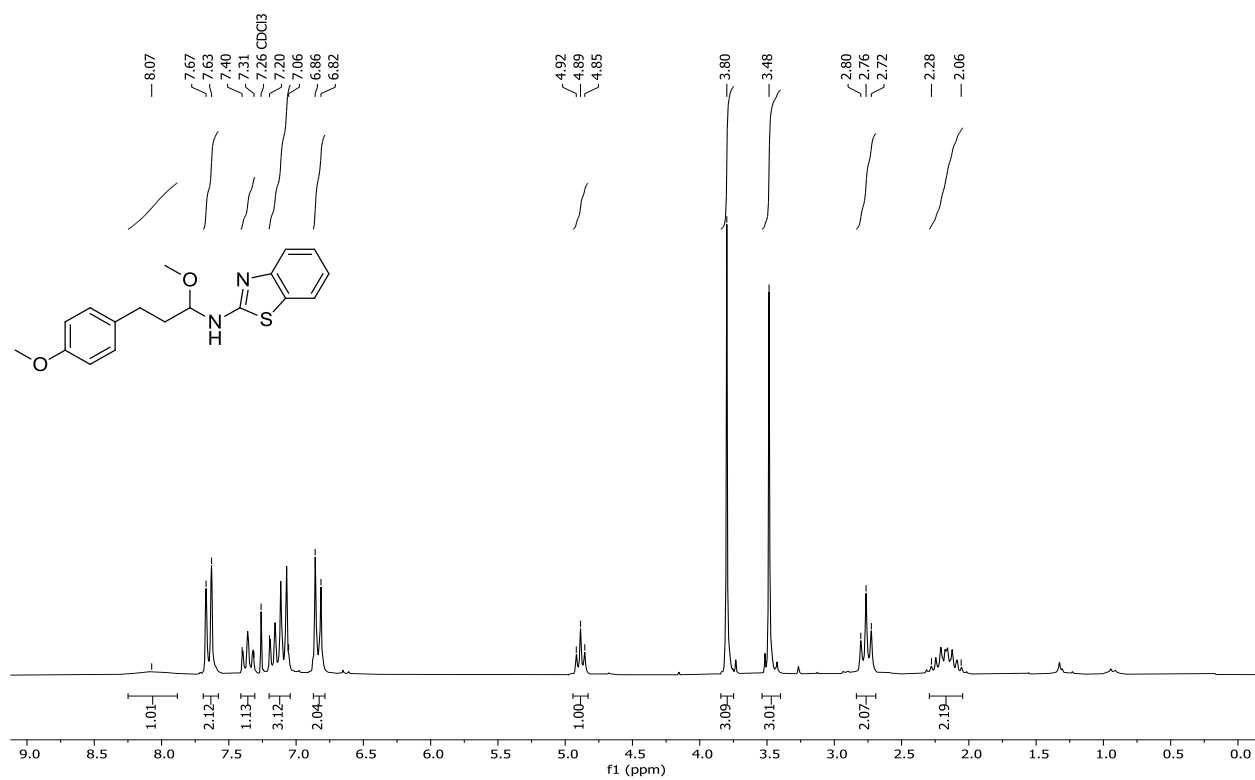


¹H NMR spectrum of **18a**.

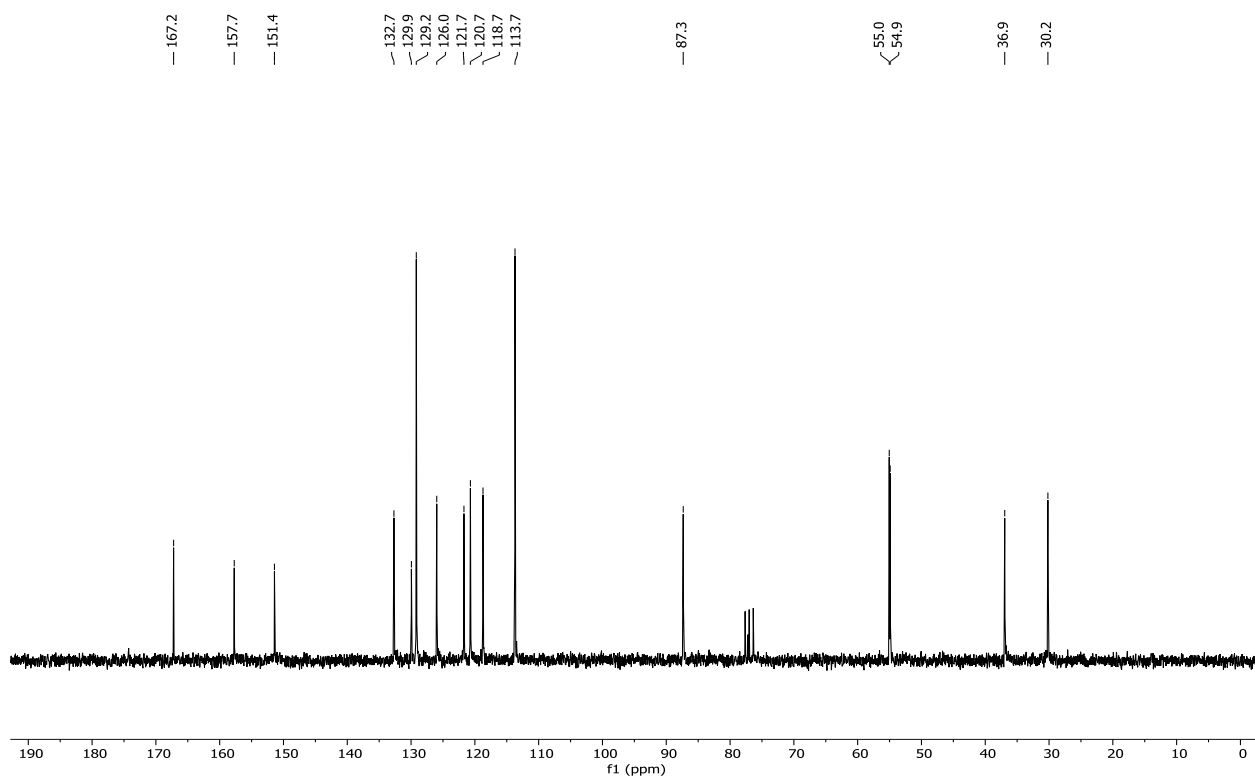


¹³C NMR spectrum of **18a**.

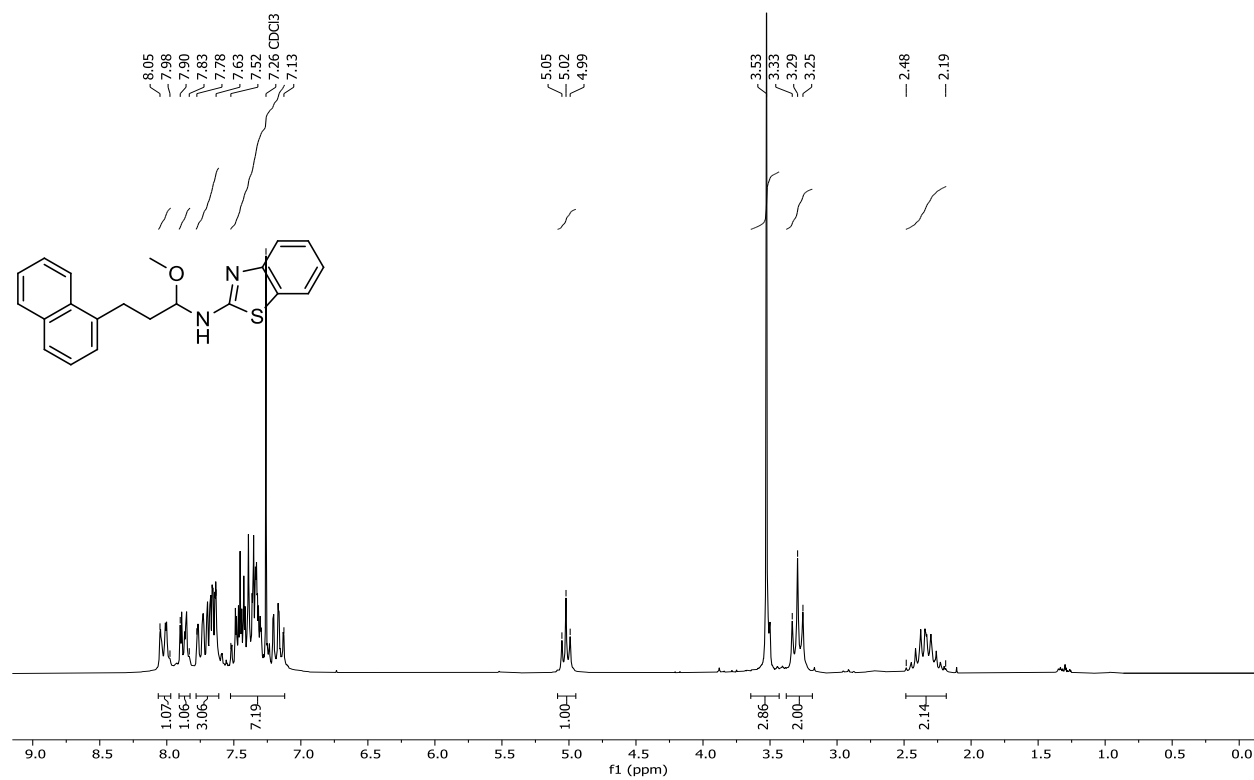




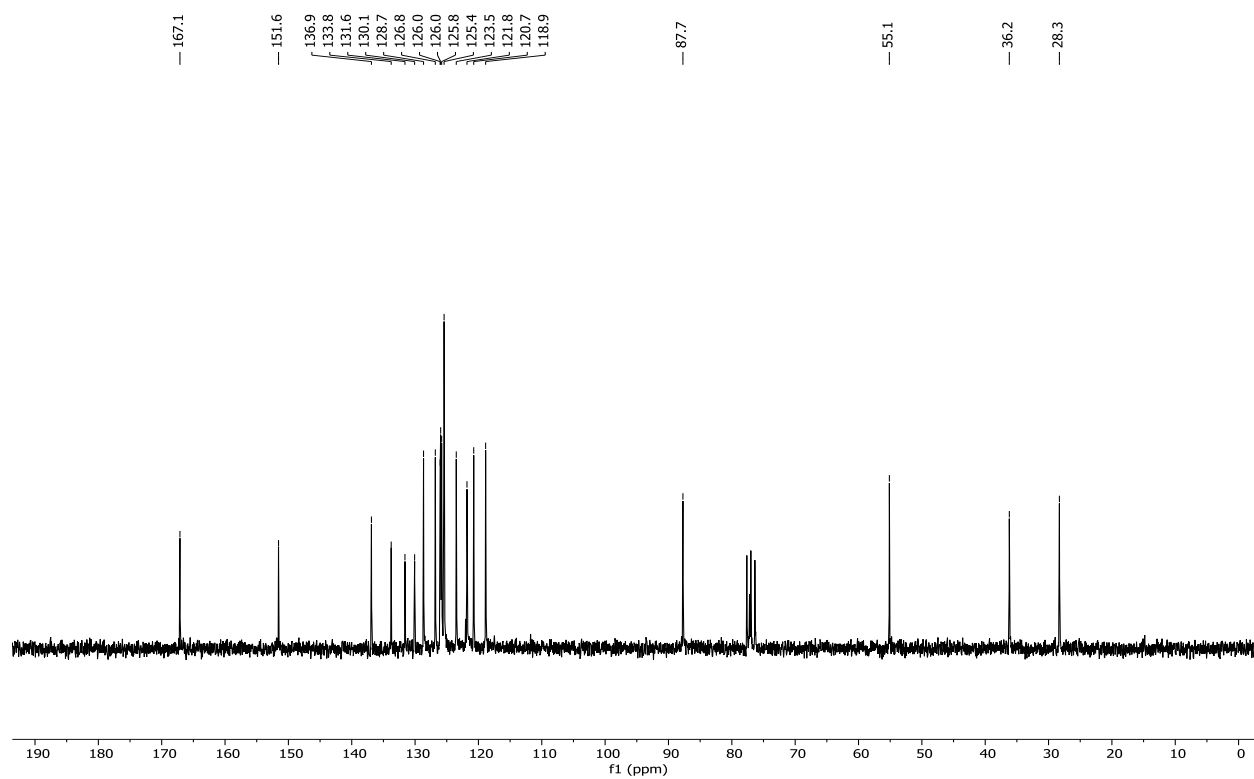
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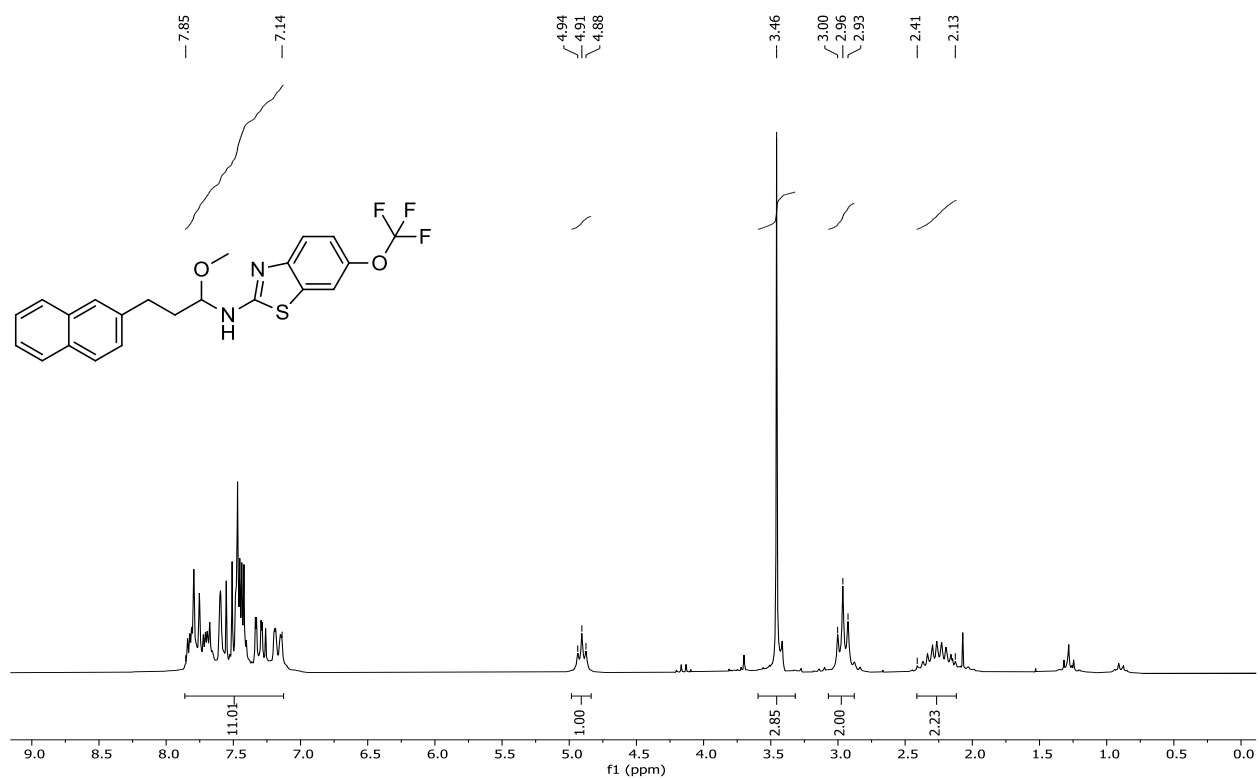
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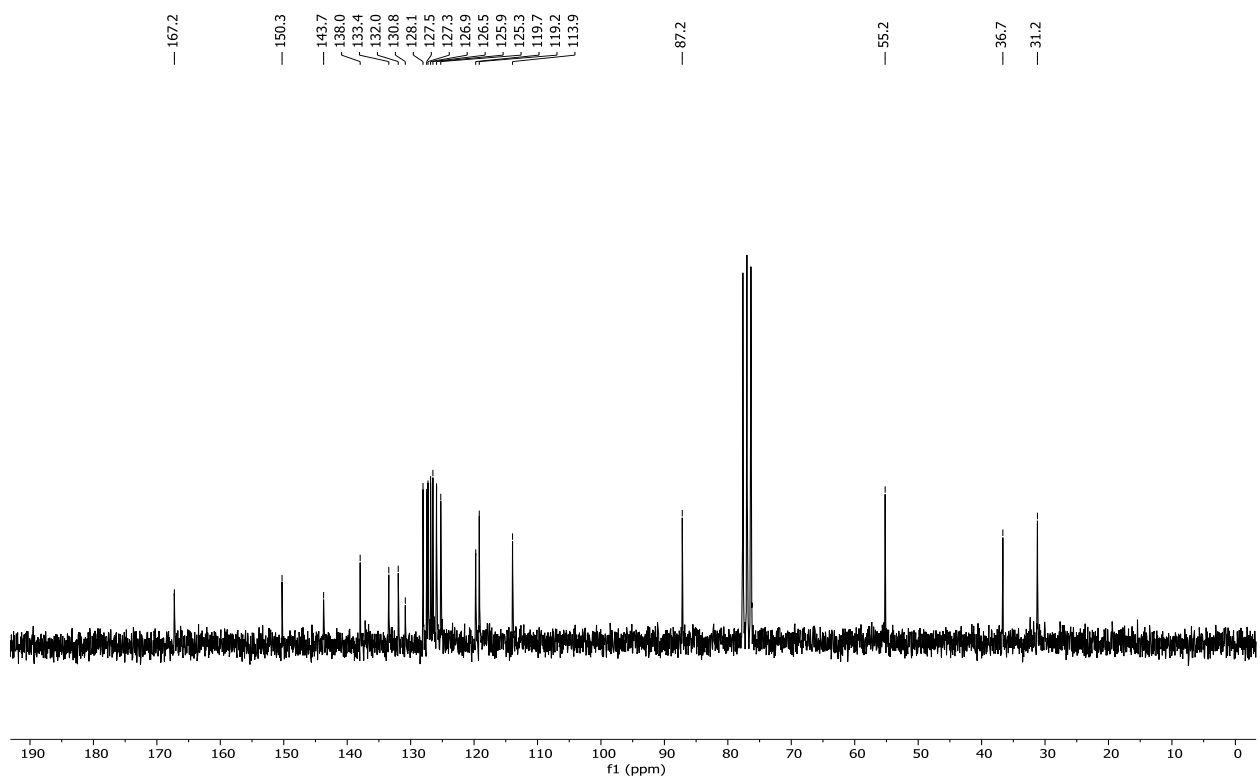
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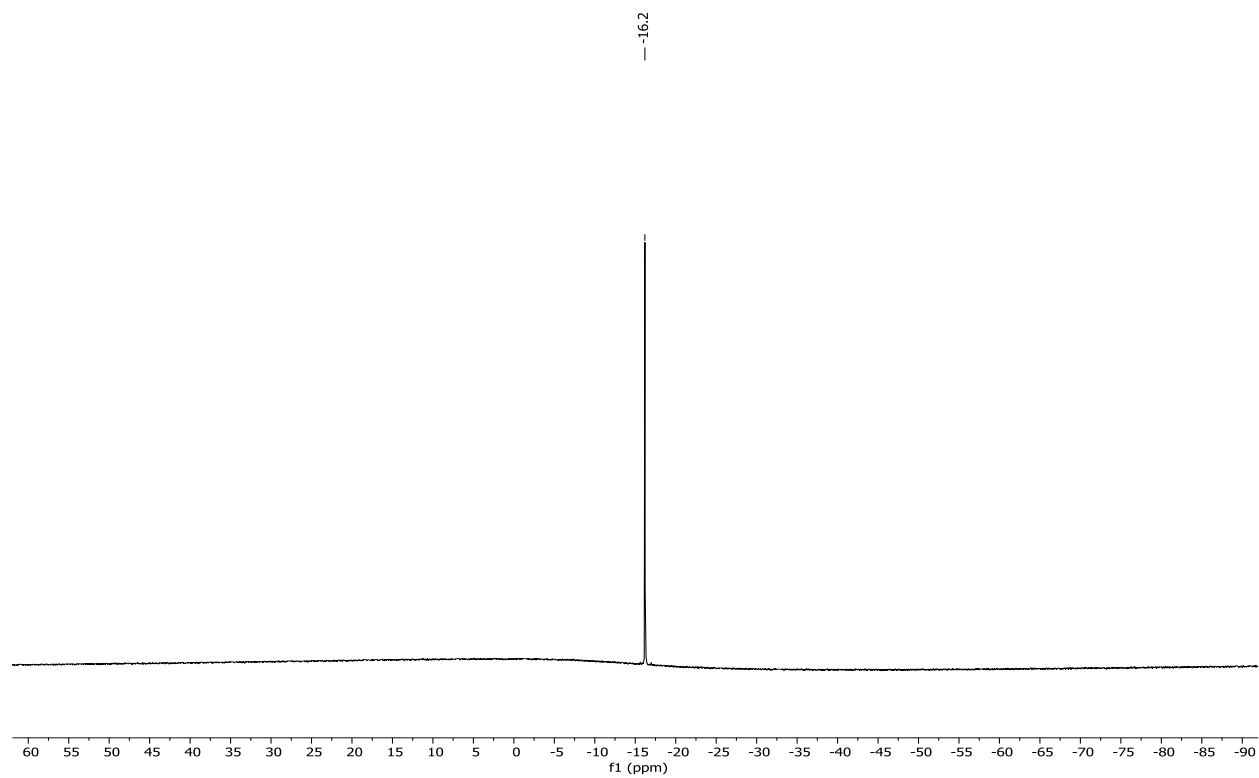
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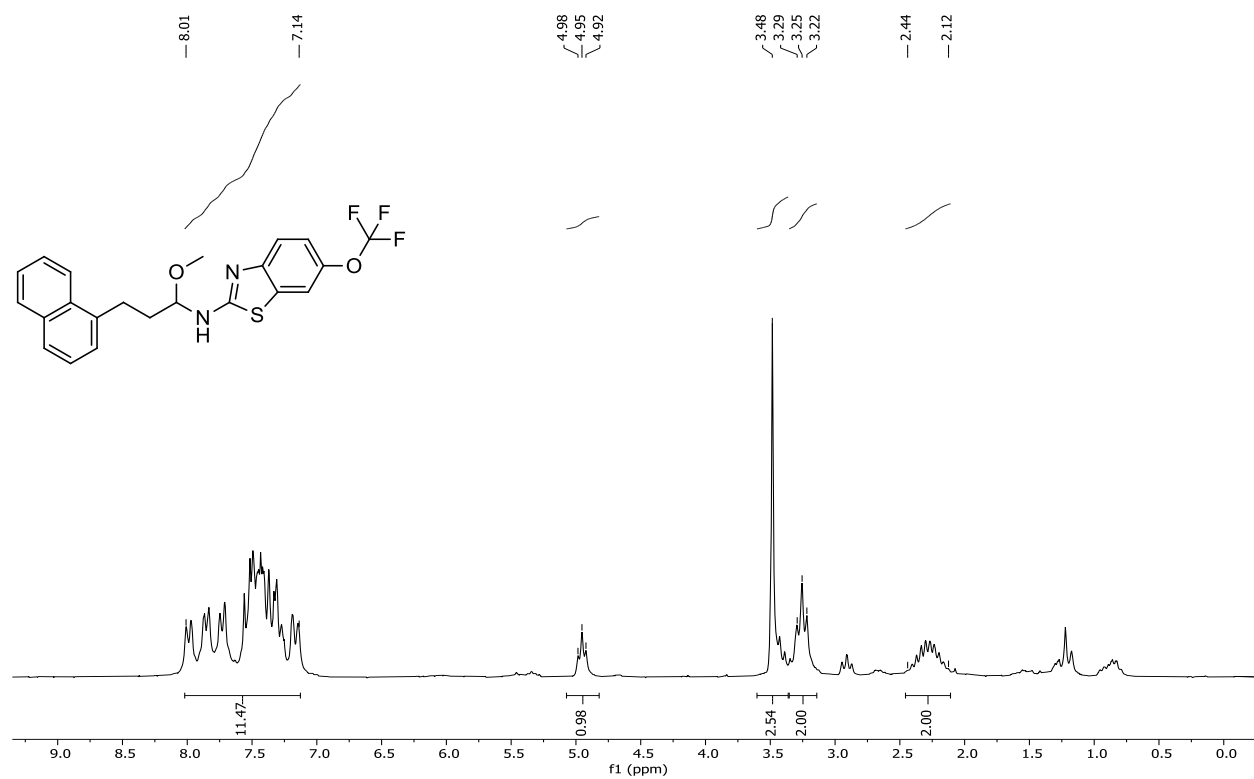
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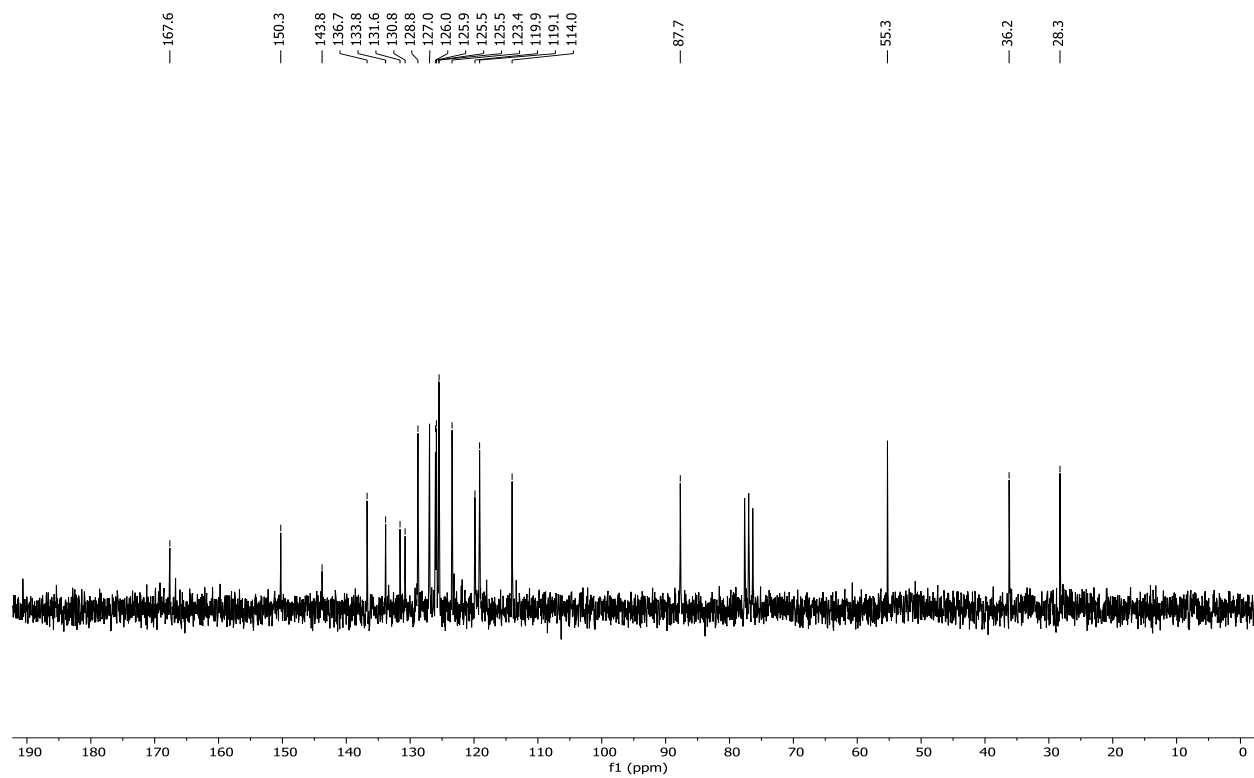
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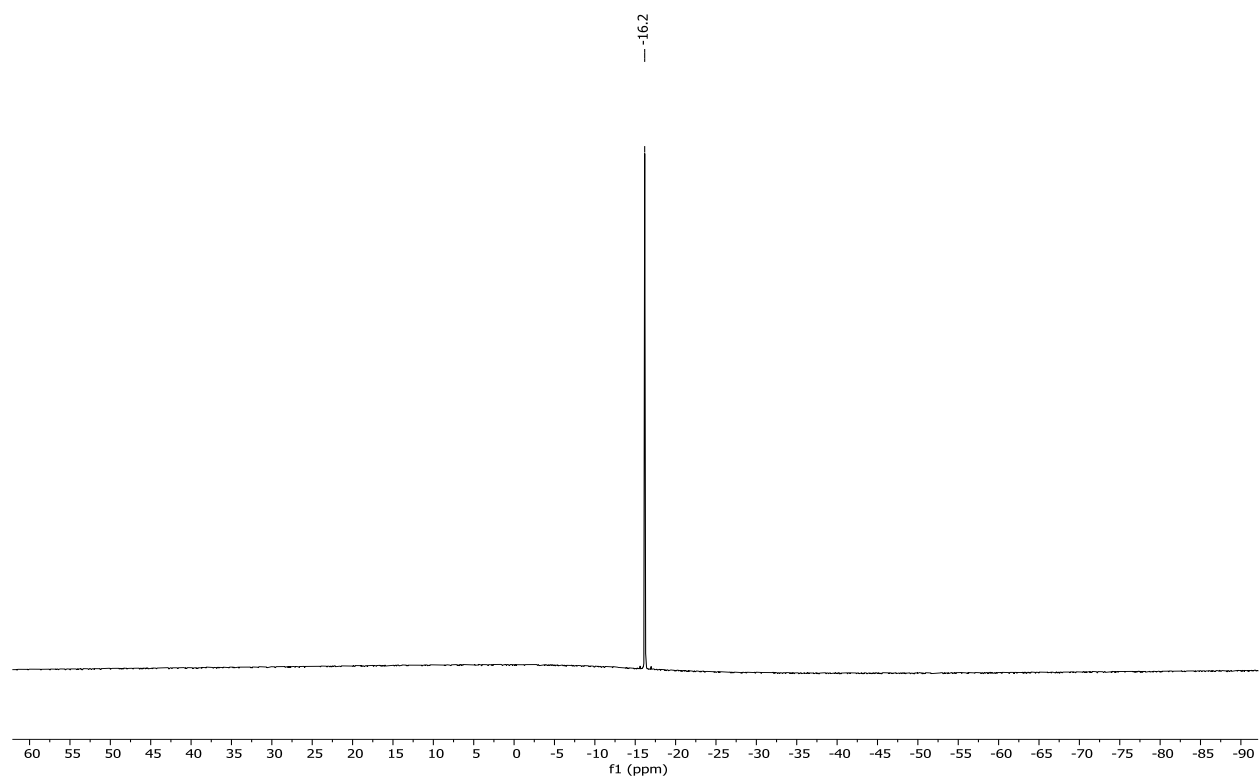
^{19}F NMR spectrum of **18g**.



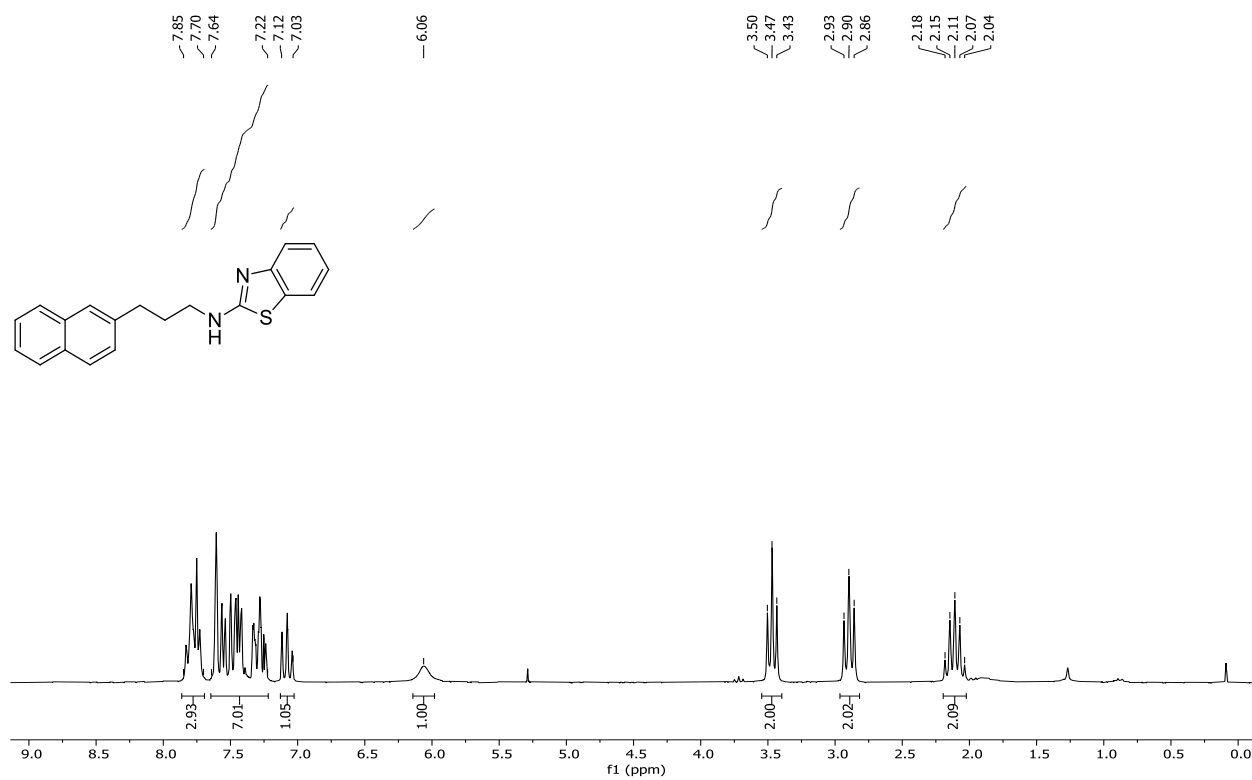
^1H NMR spectrum of **18h**.



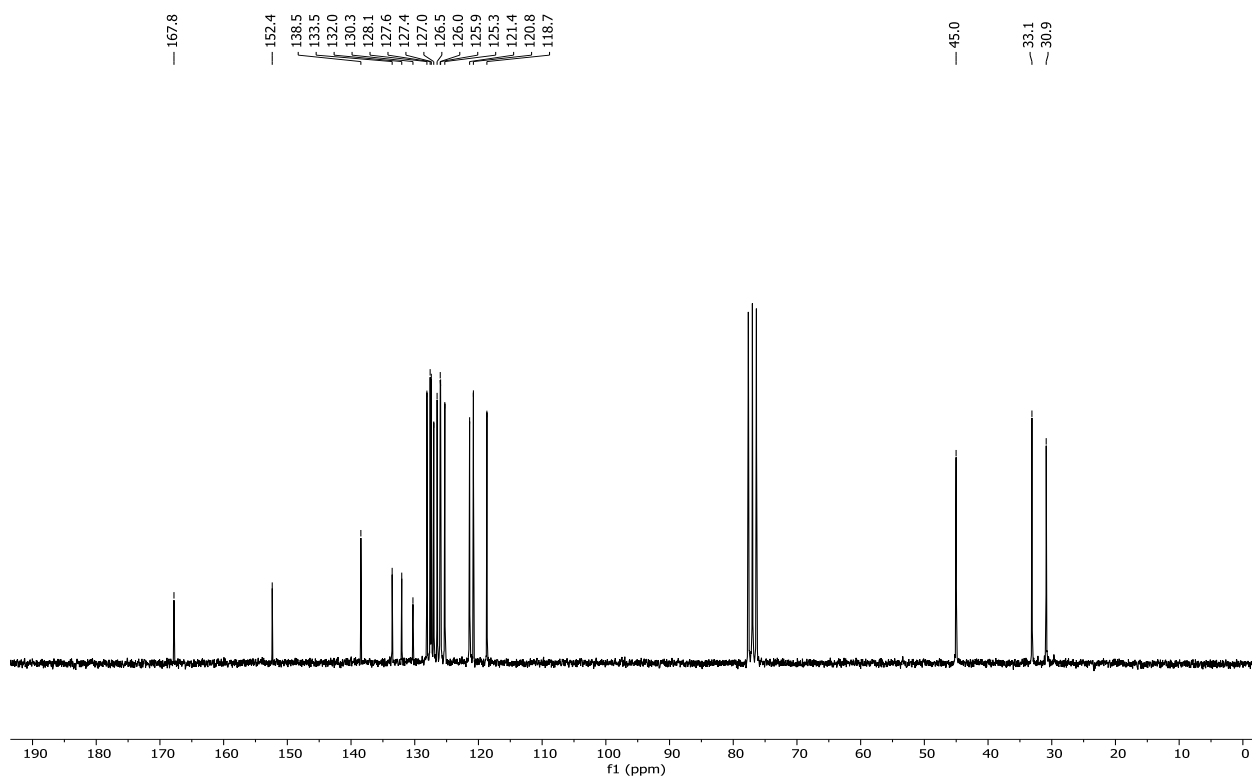
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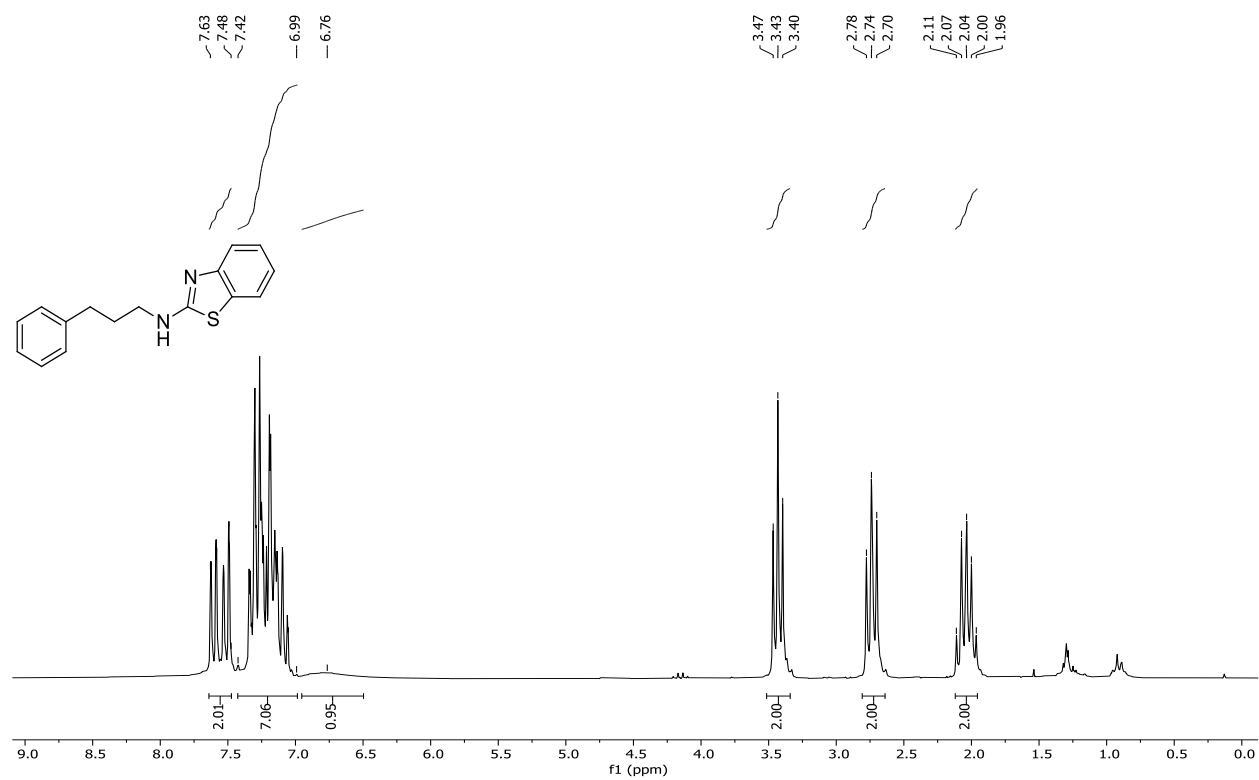
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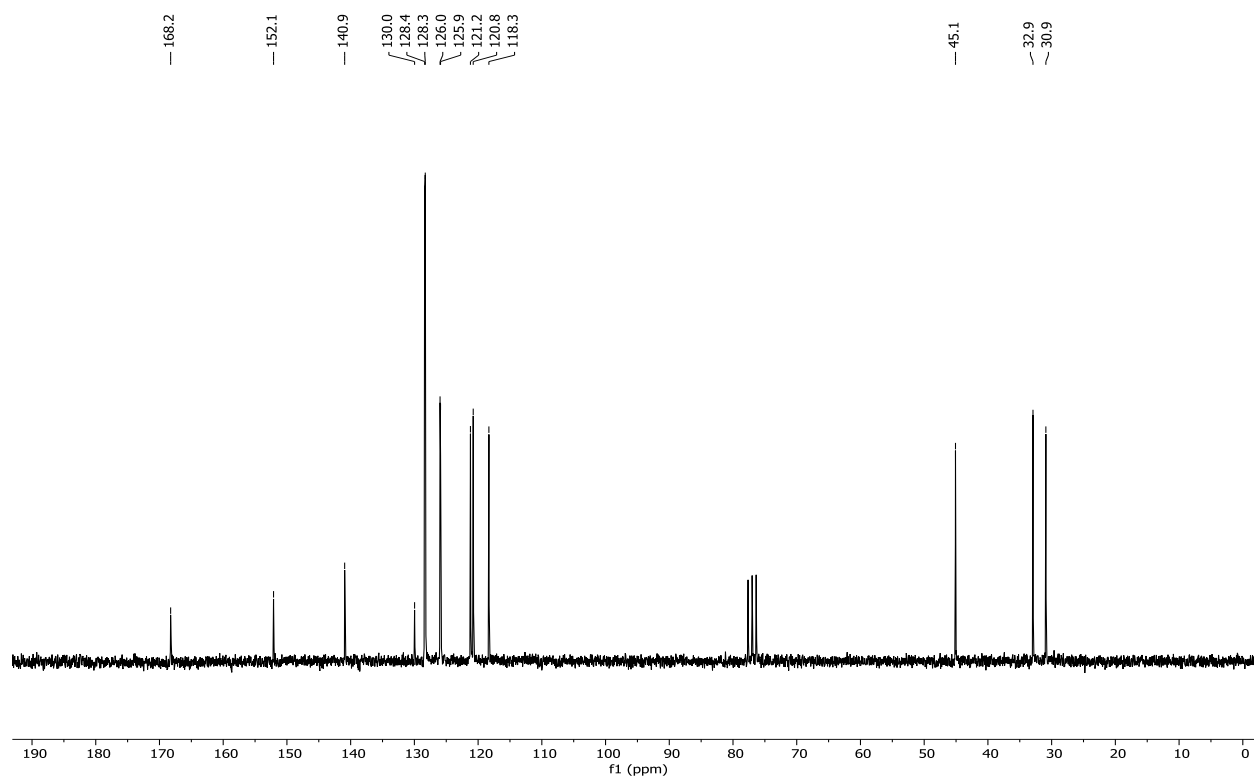
^1H NMR spectrum of 19a.



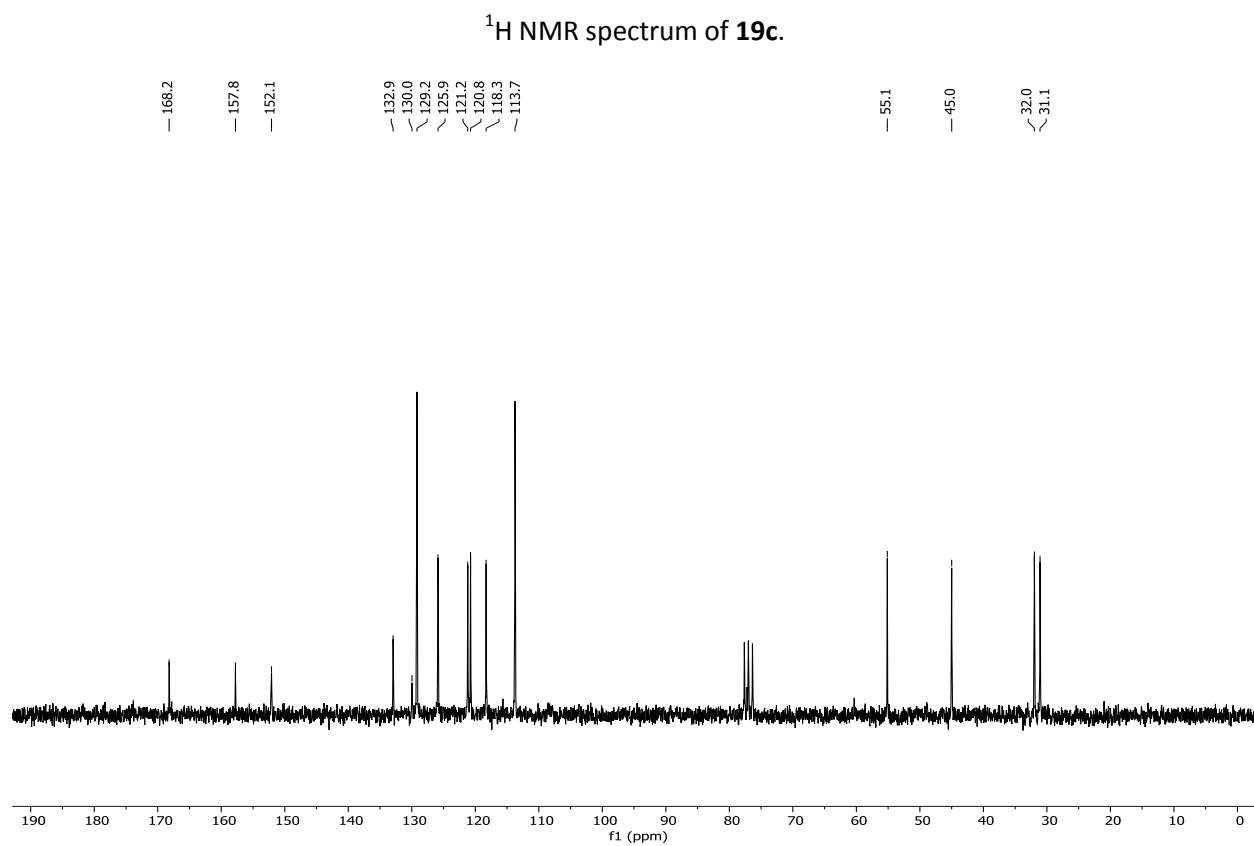
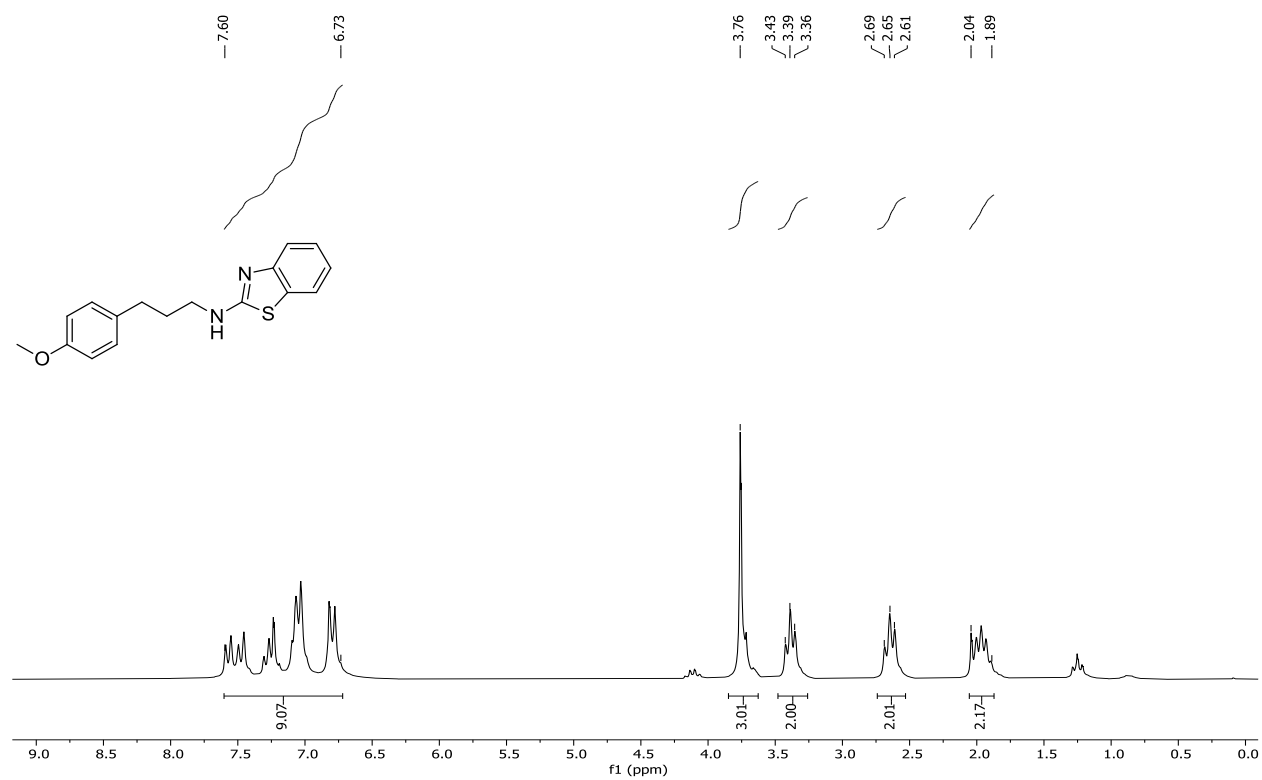
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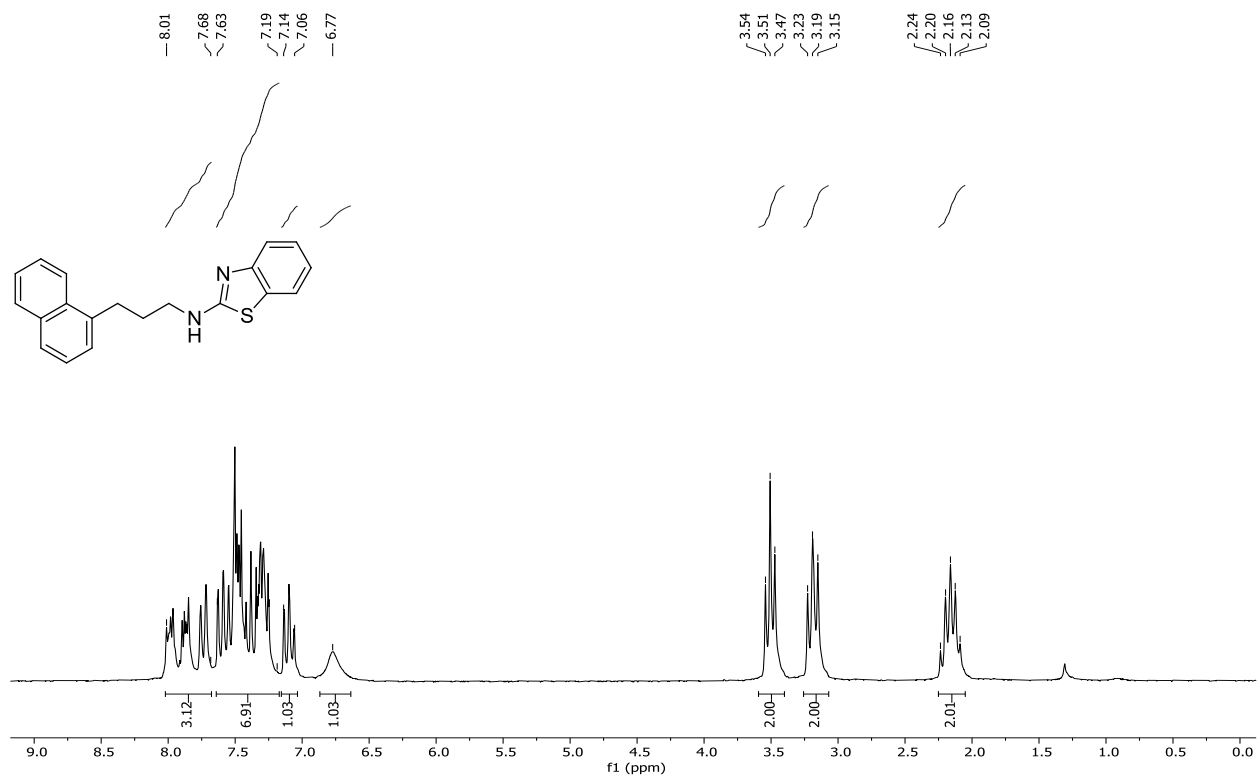


¹H NMR spectrum of **19b**.

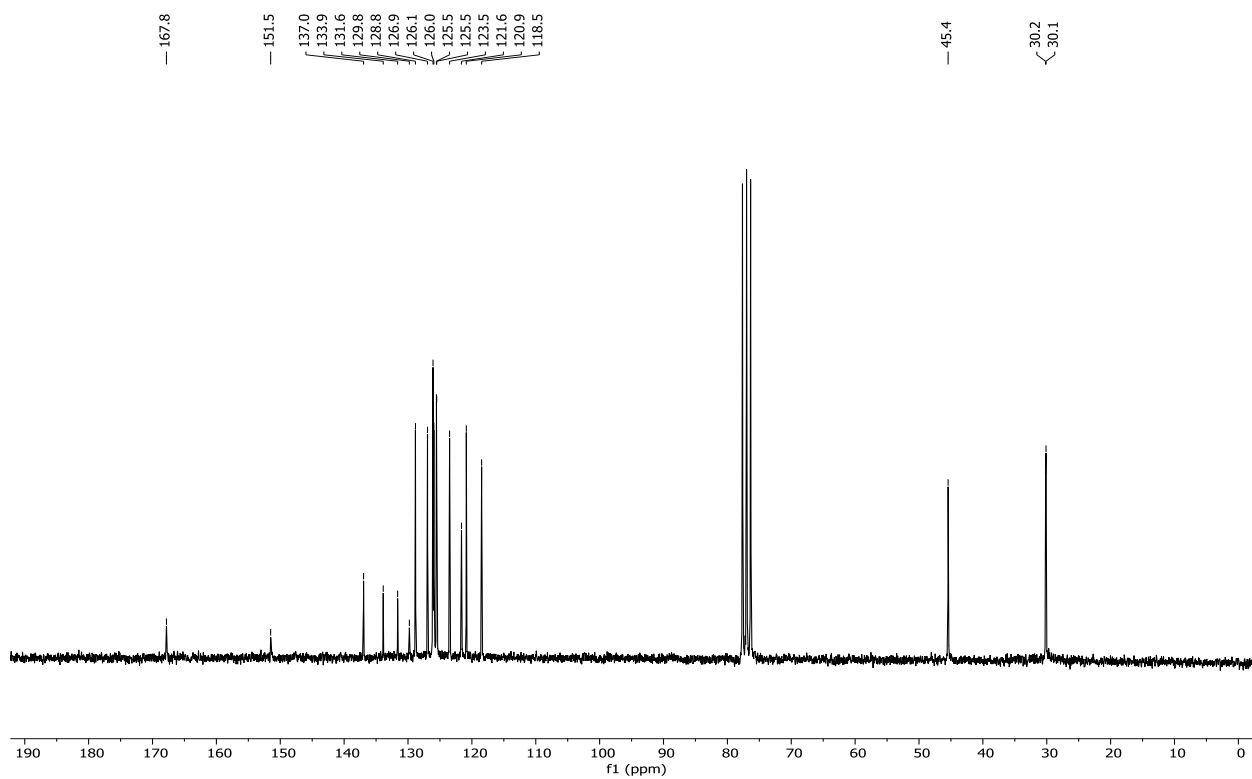


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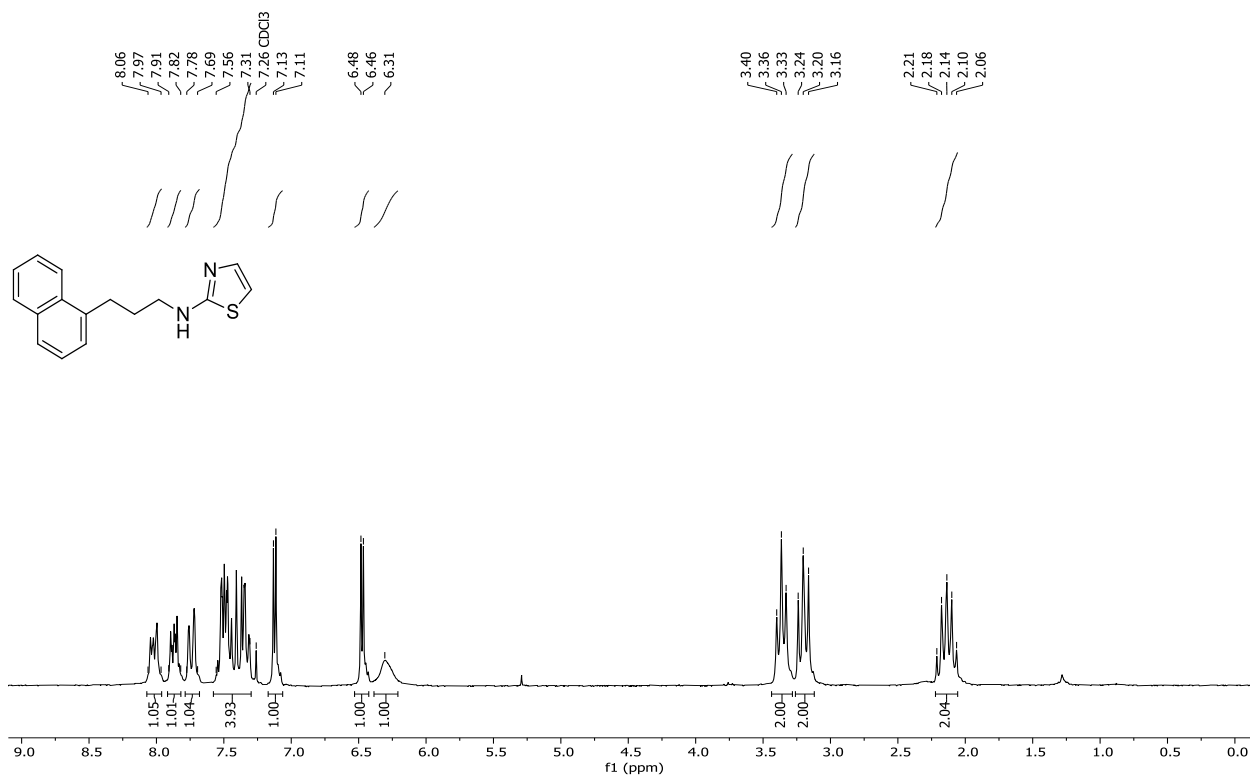




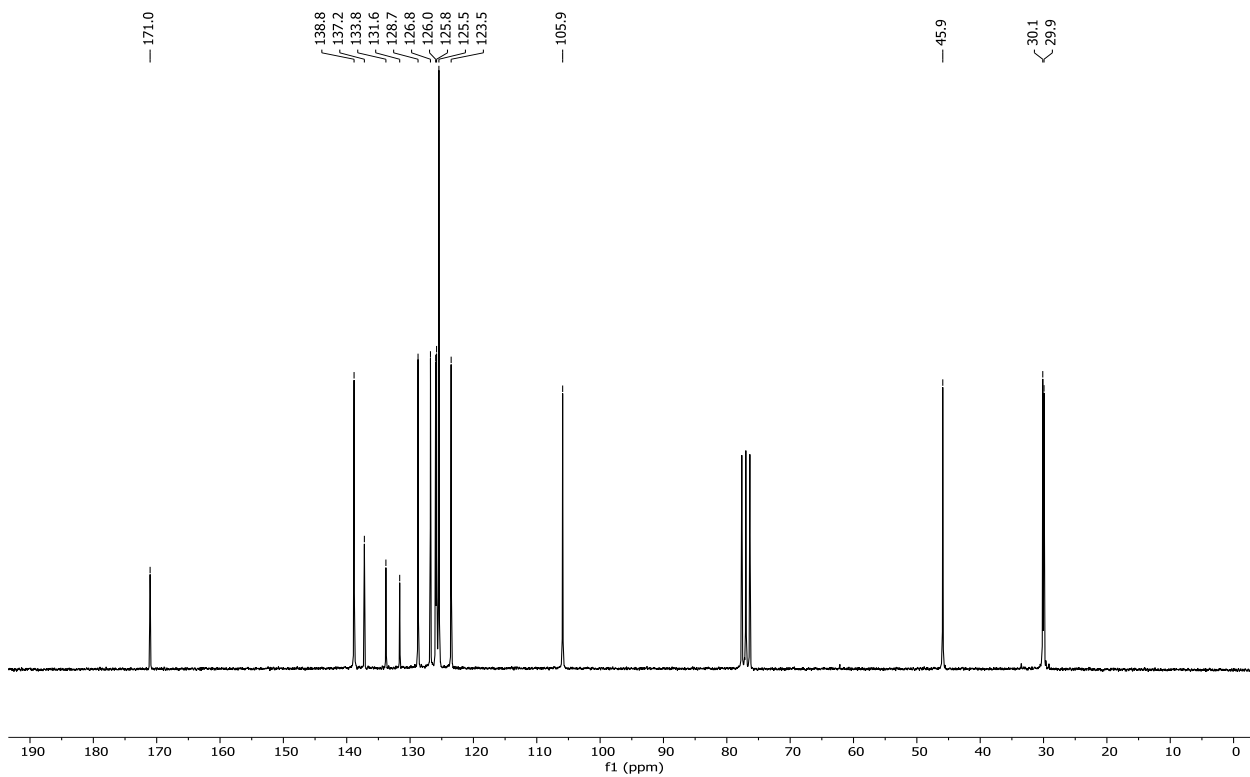
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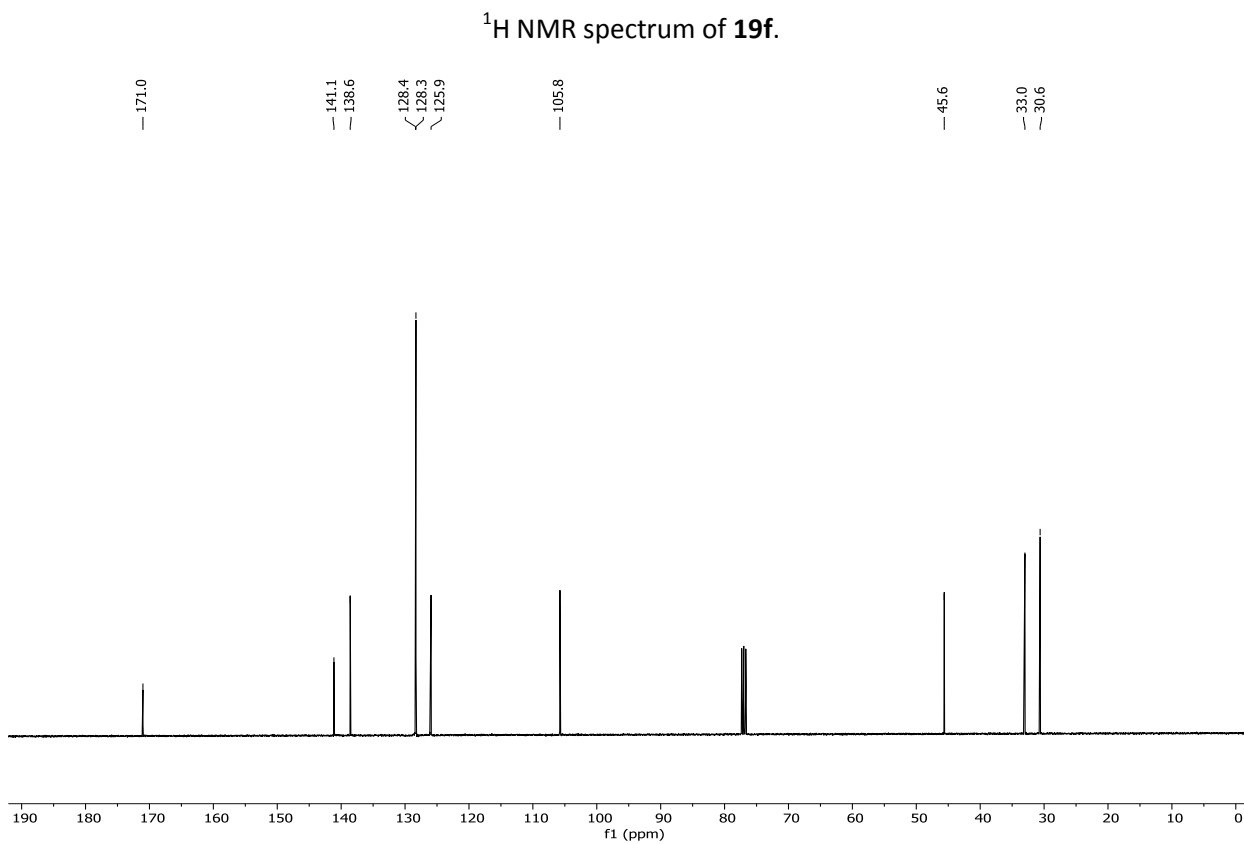
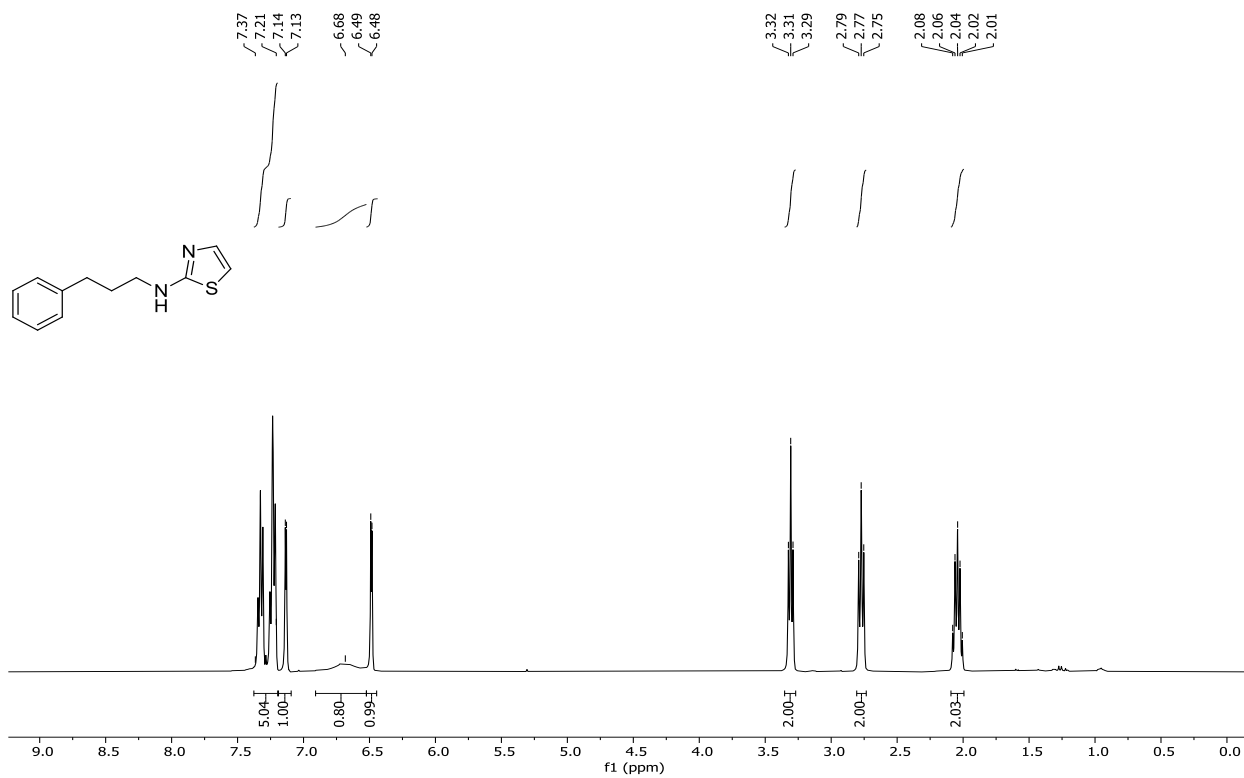
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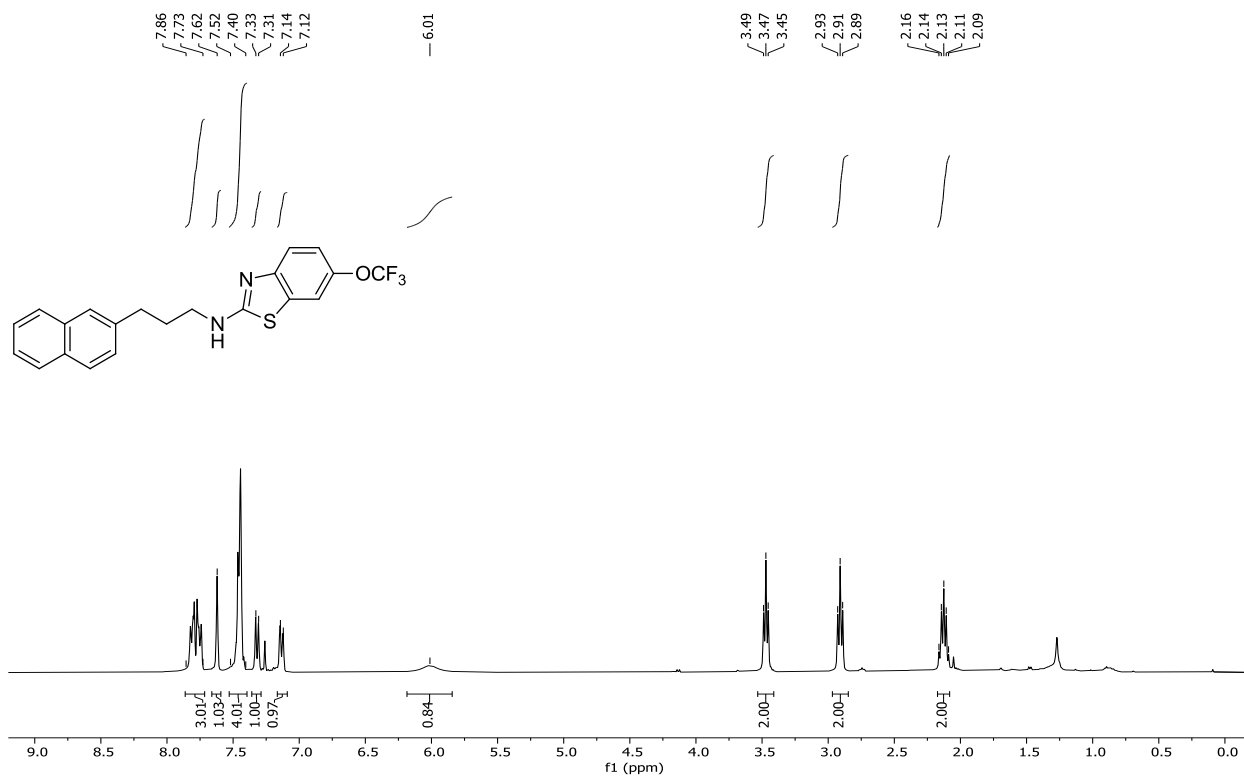


¹H NMR spectrum of **19e**.

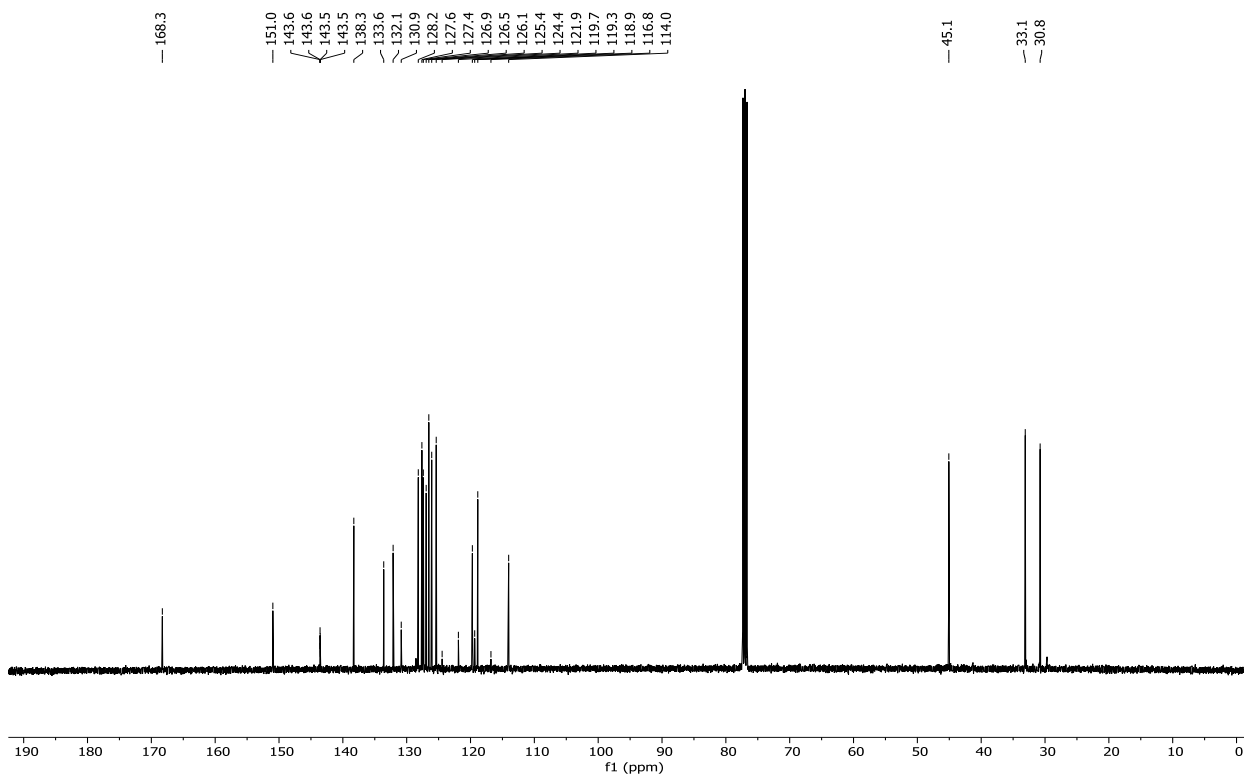


¹³C NMR spectrum of **19e**.

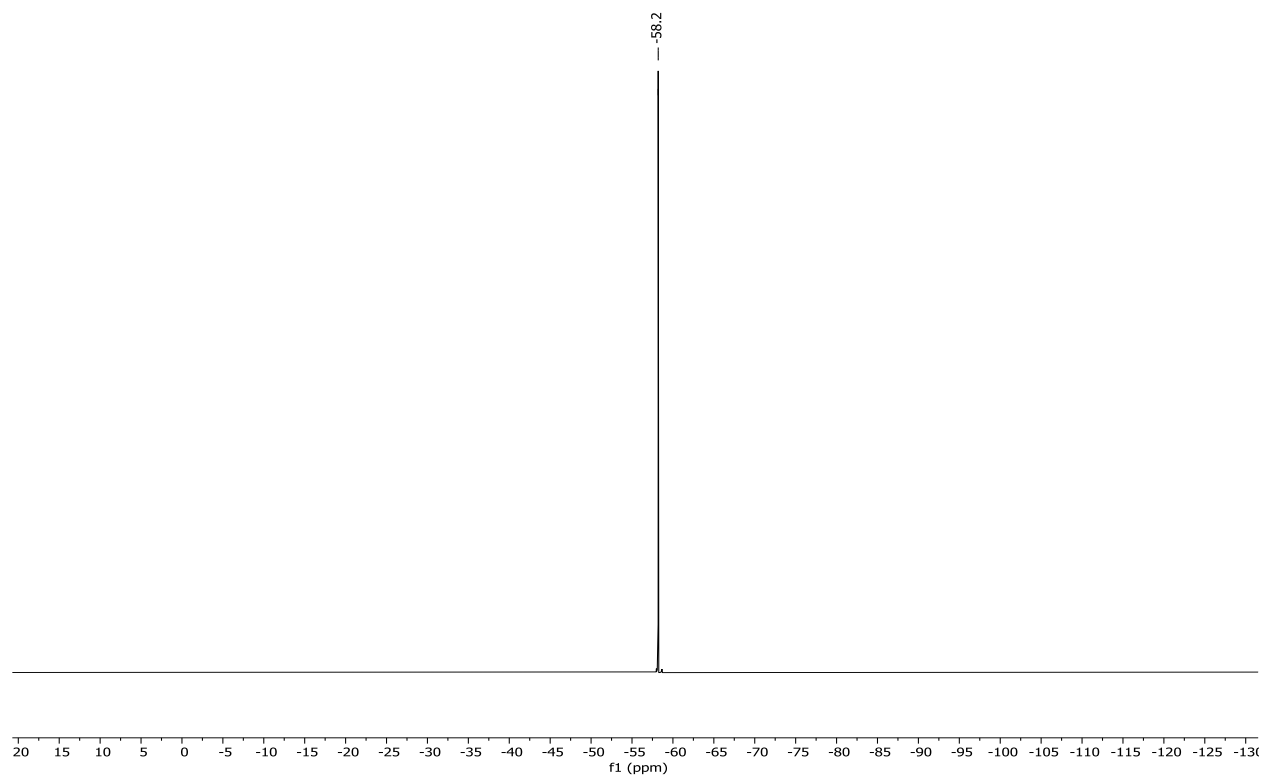




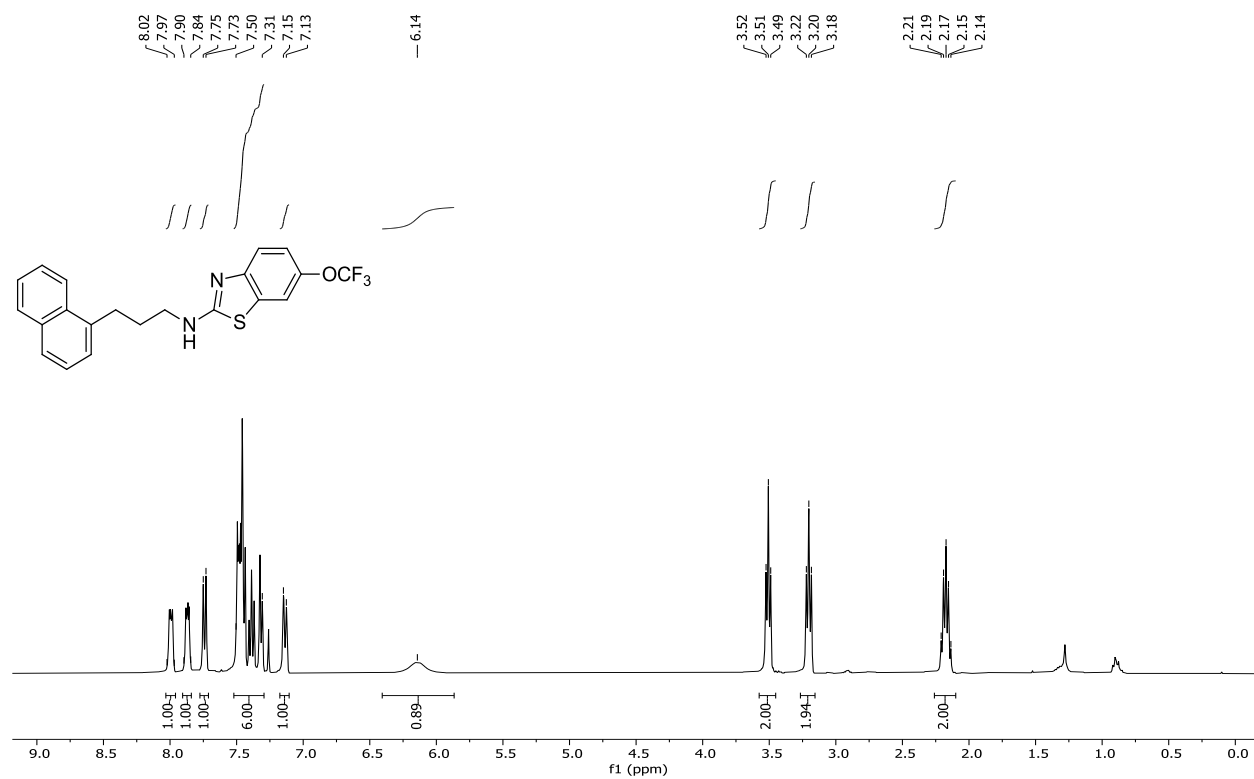
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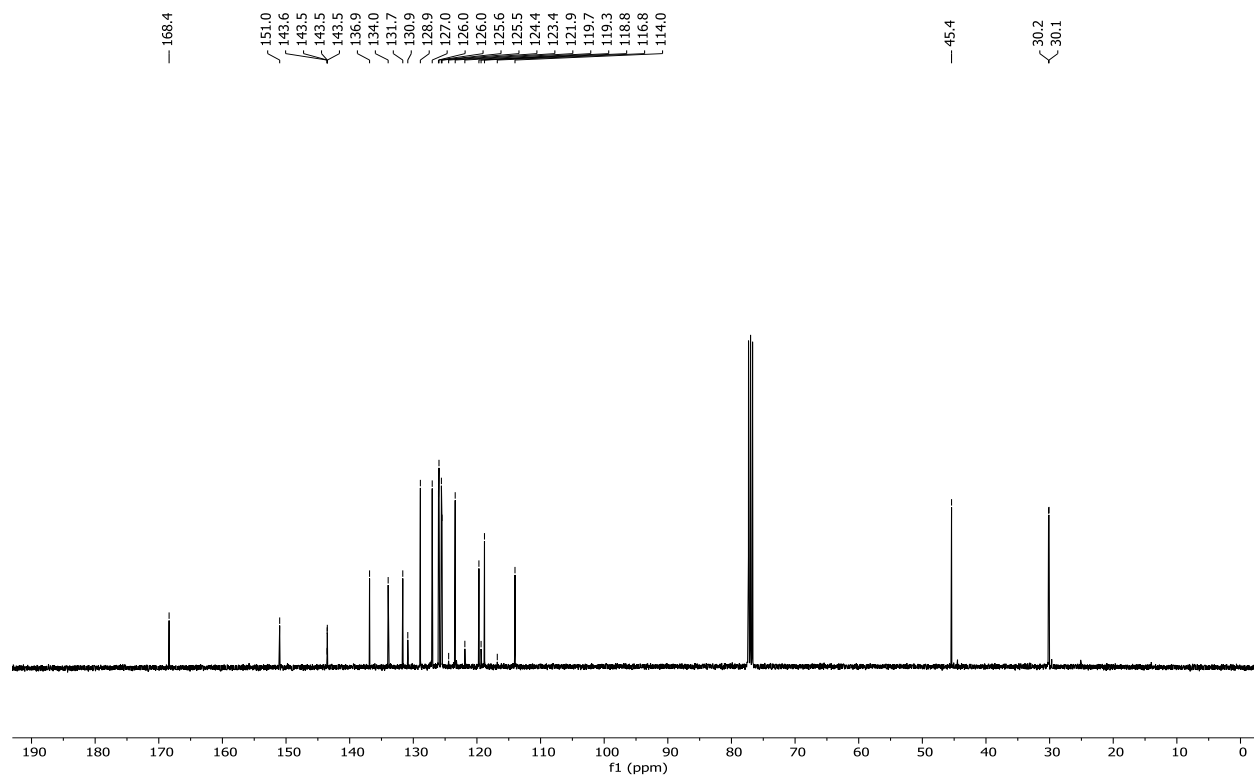
^{13}C NMR spectrum of **19g**.



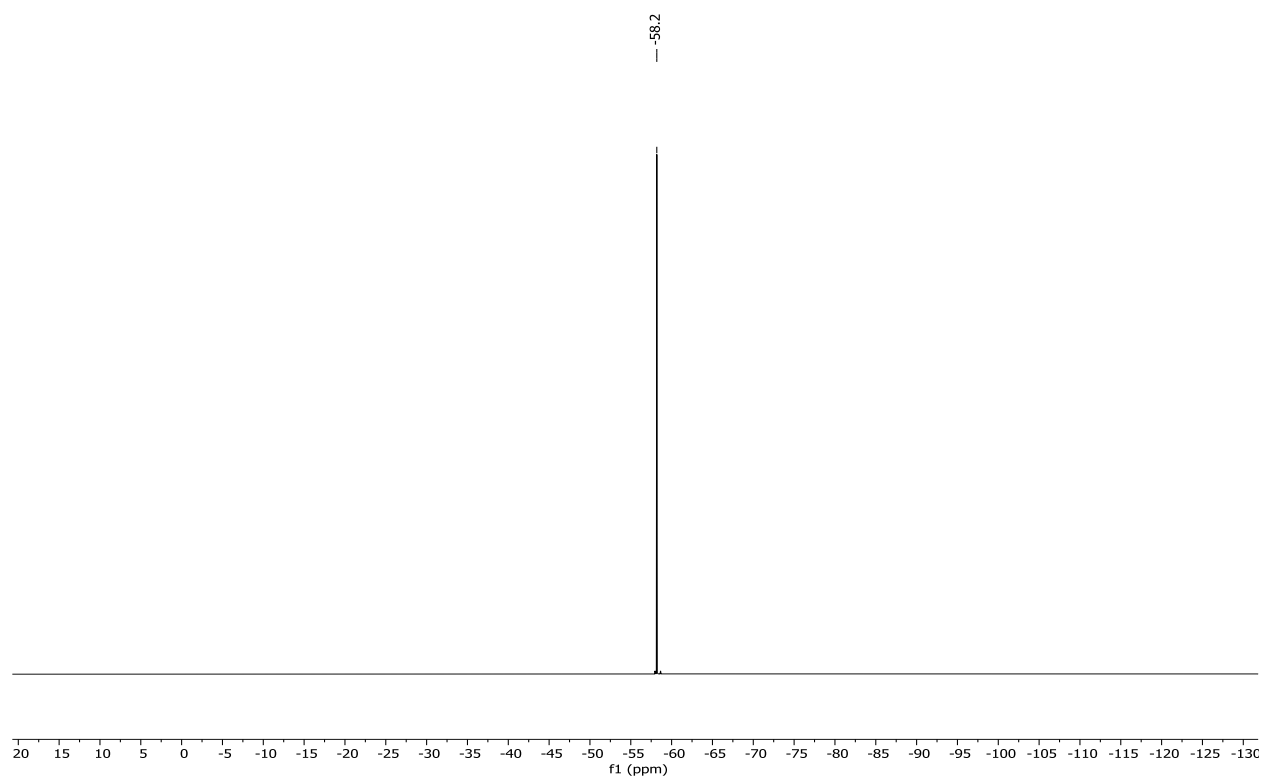
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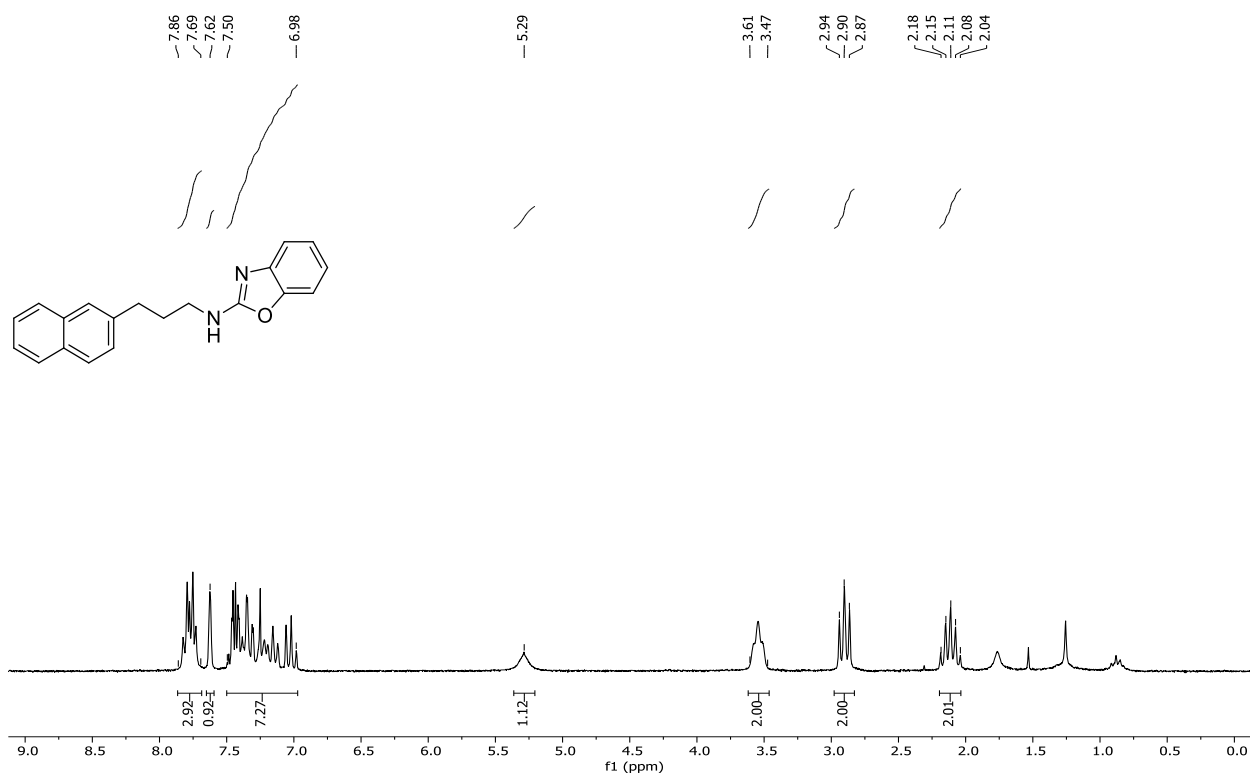
^1H NMR spectrum of **19h**.



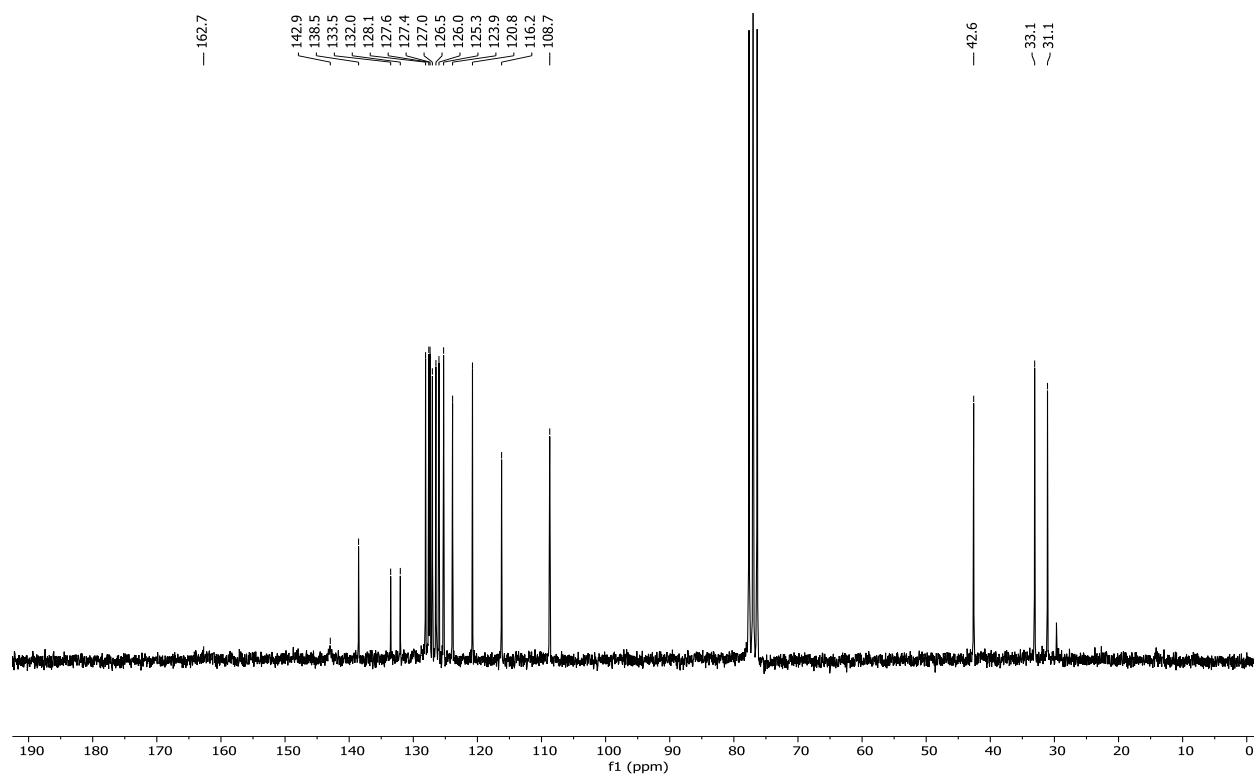
¹³C NMR spectrum of **19h**.



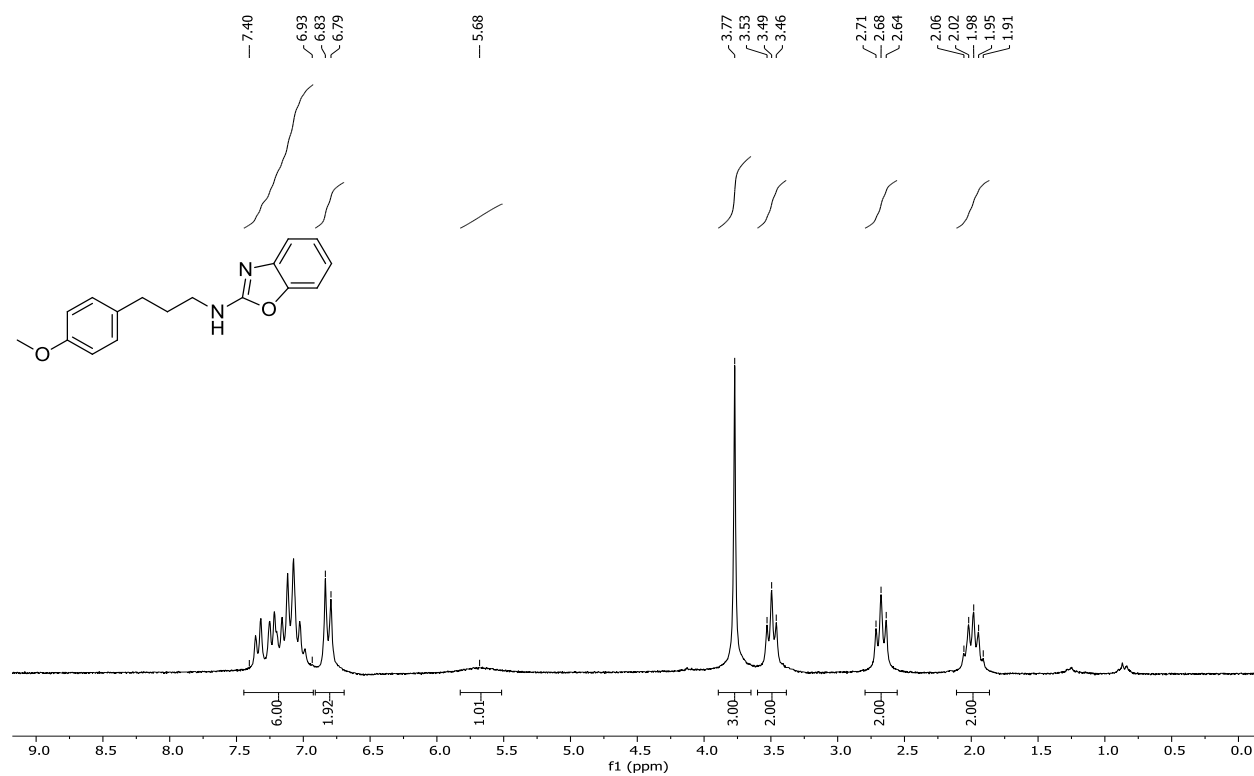
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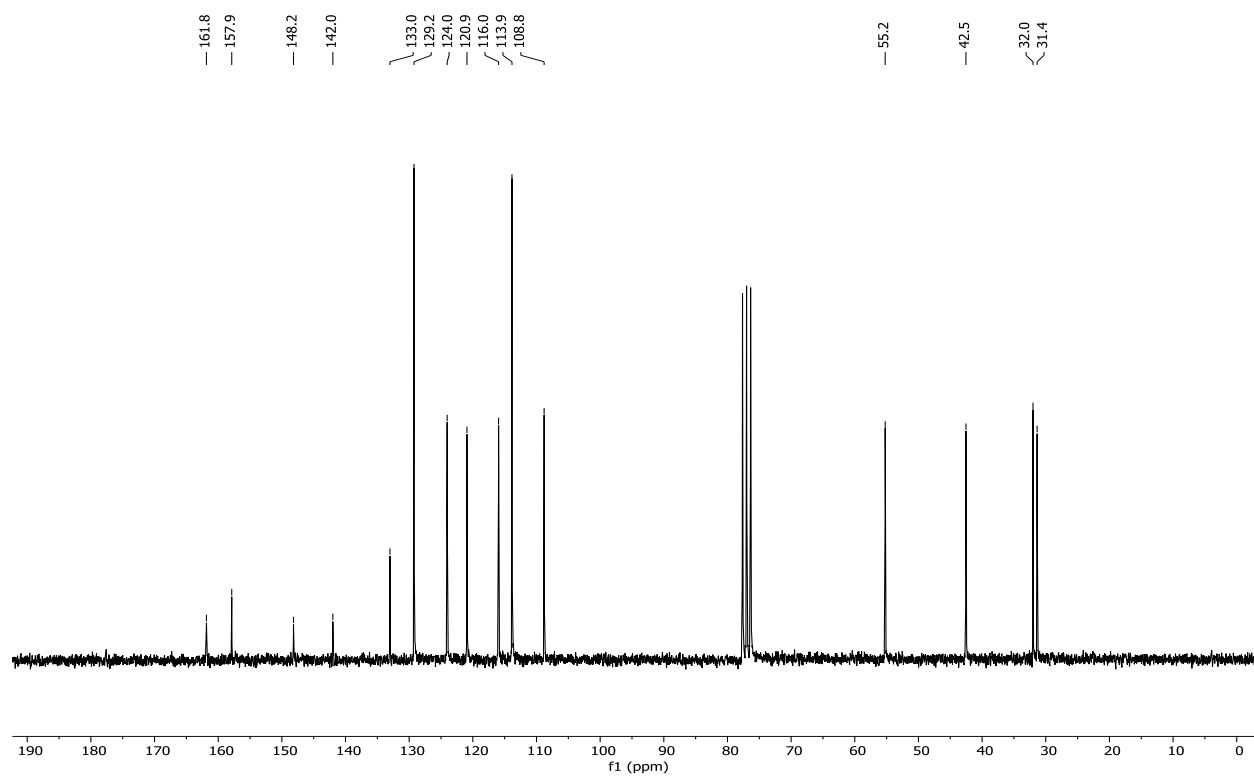
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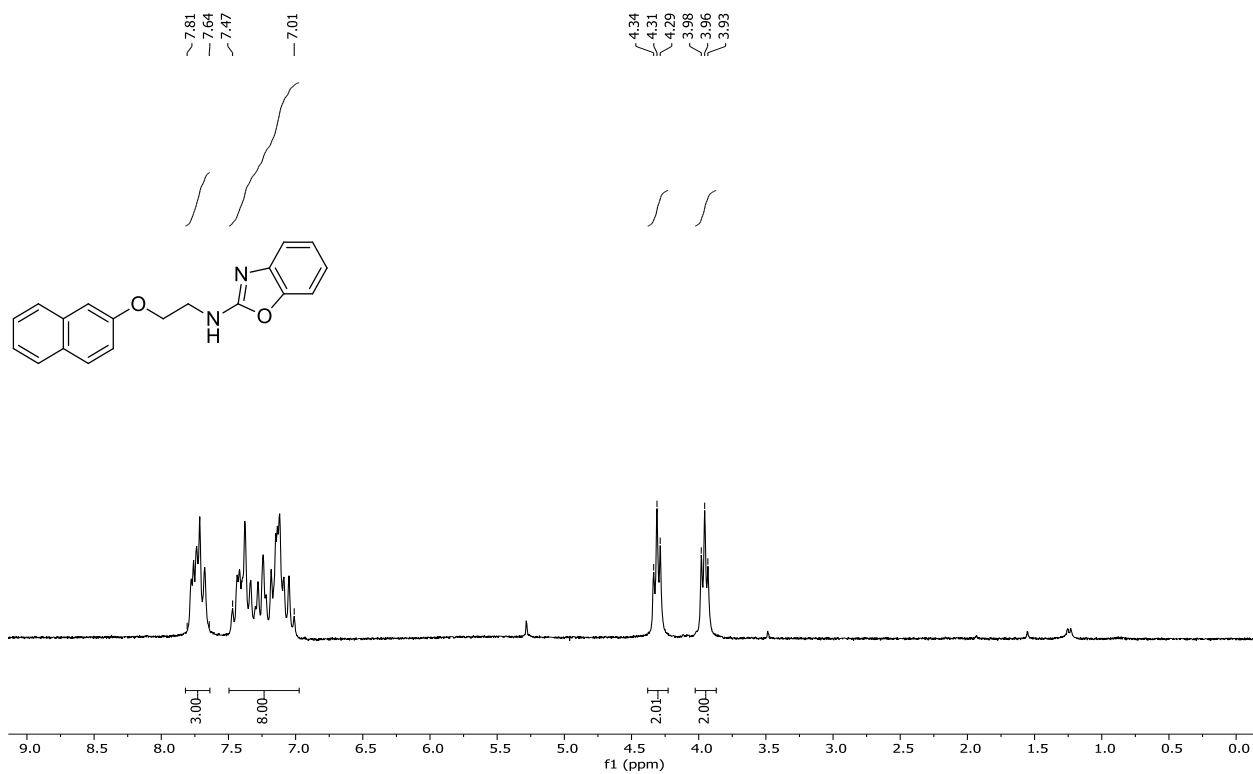
¹³C NMR spectrum of **23a**.



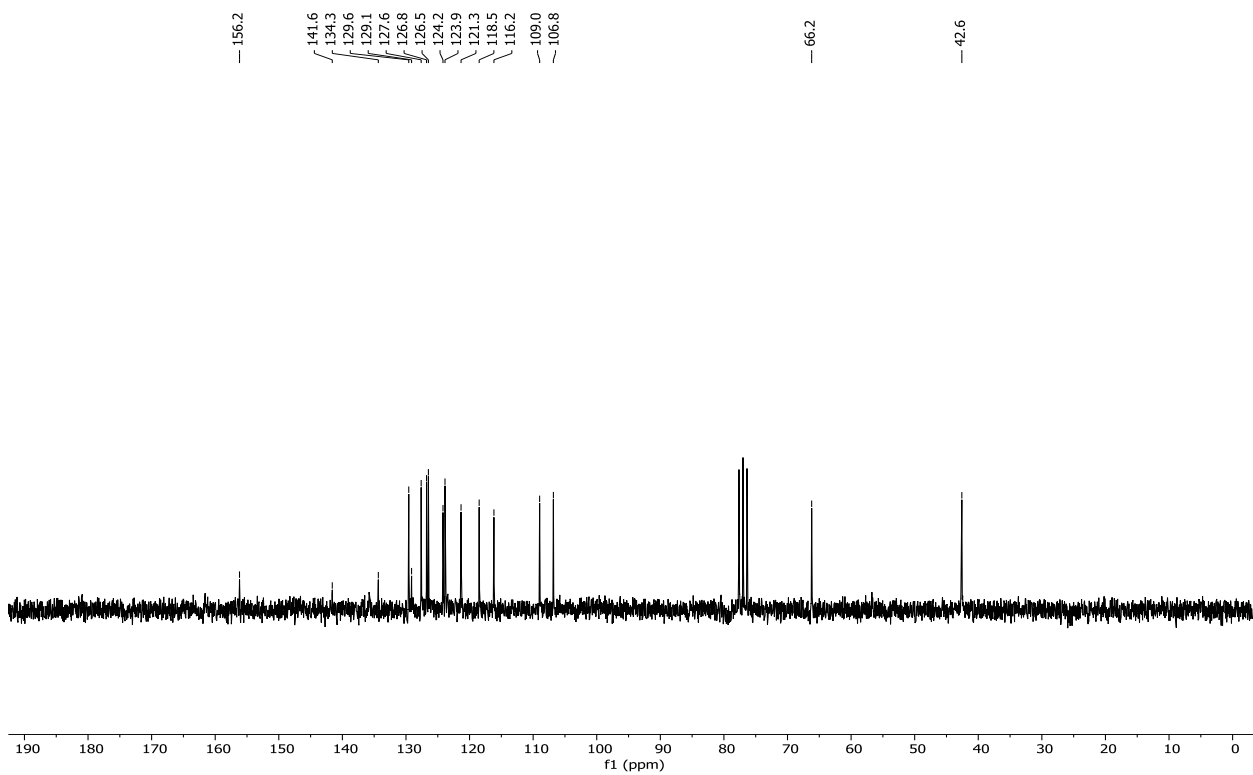
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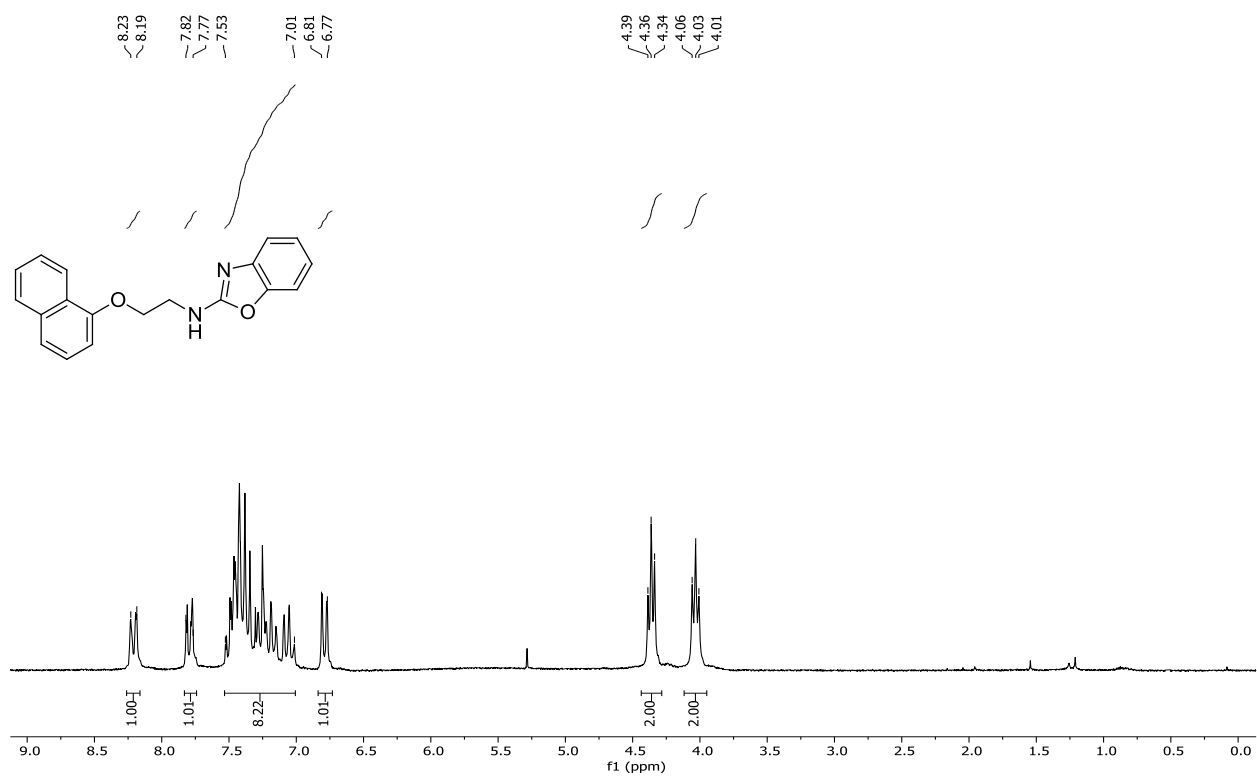
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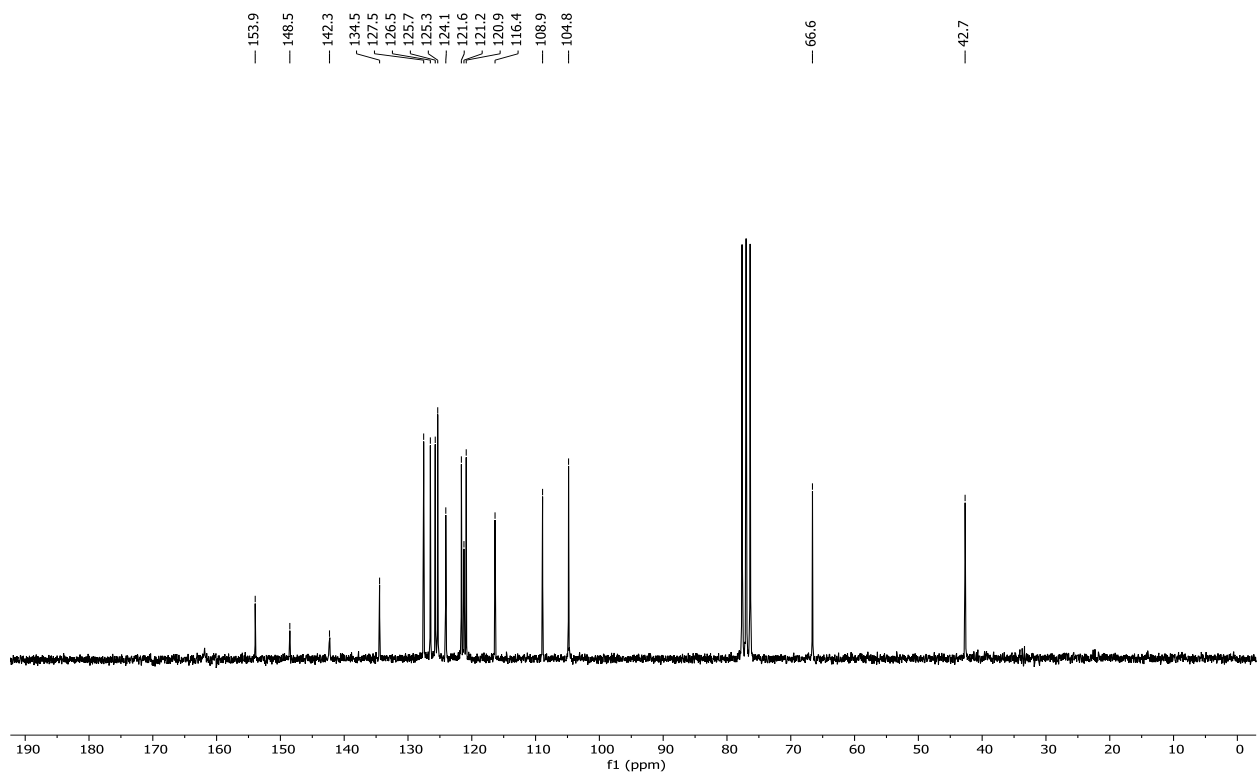
¹H NMR spectrum of **23c**.



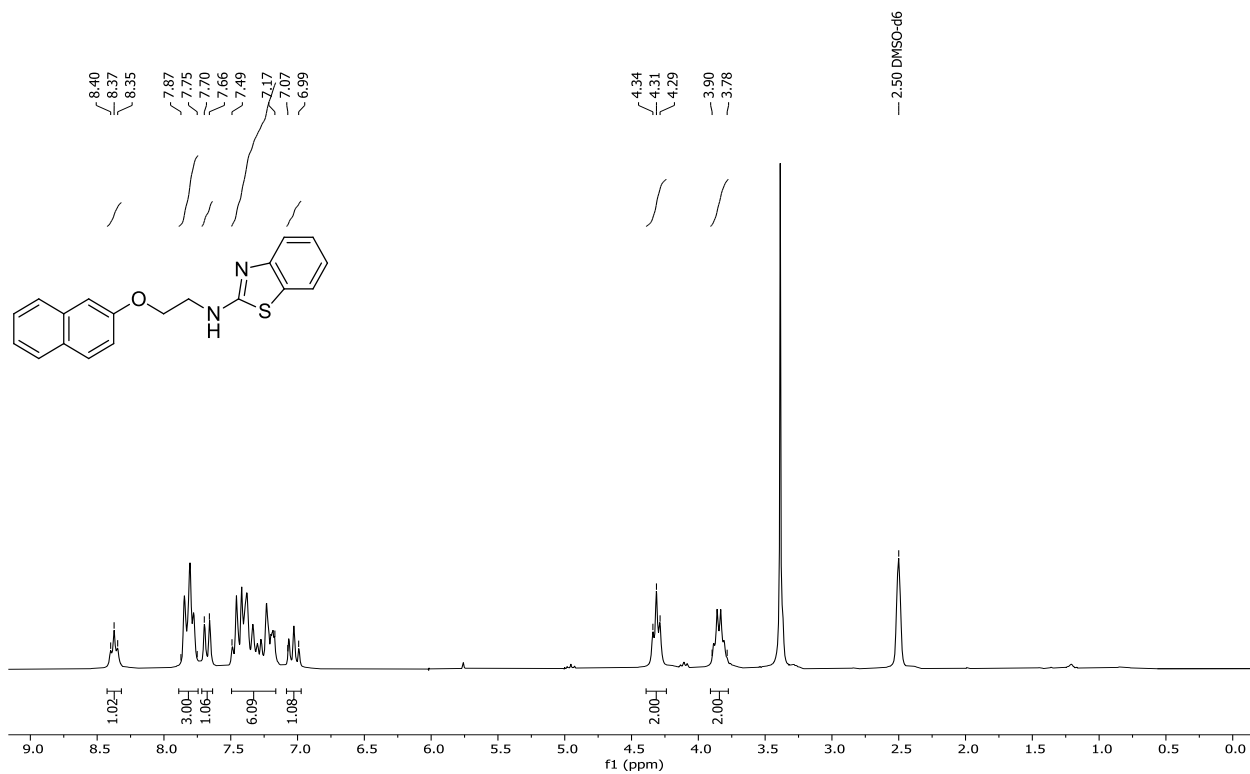
¹³C NMR spectrum of **23c**.



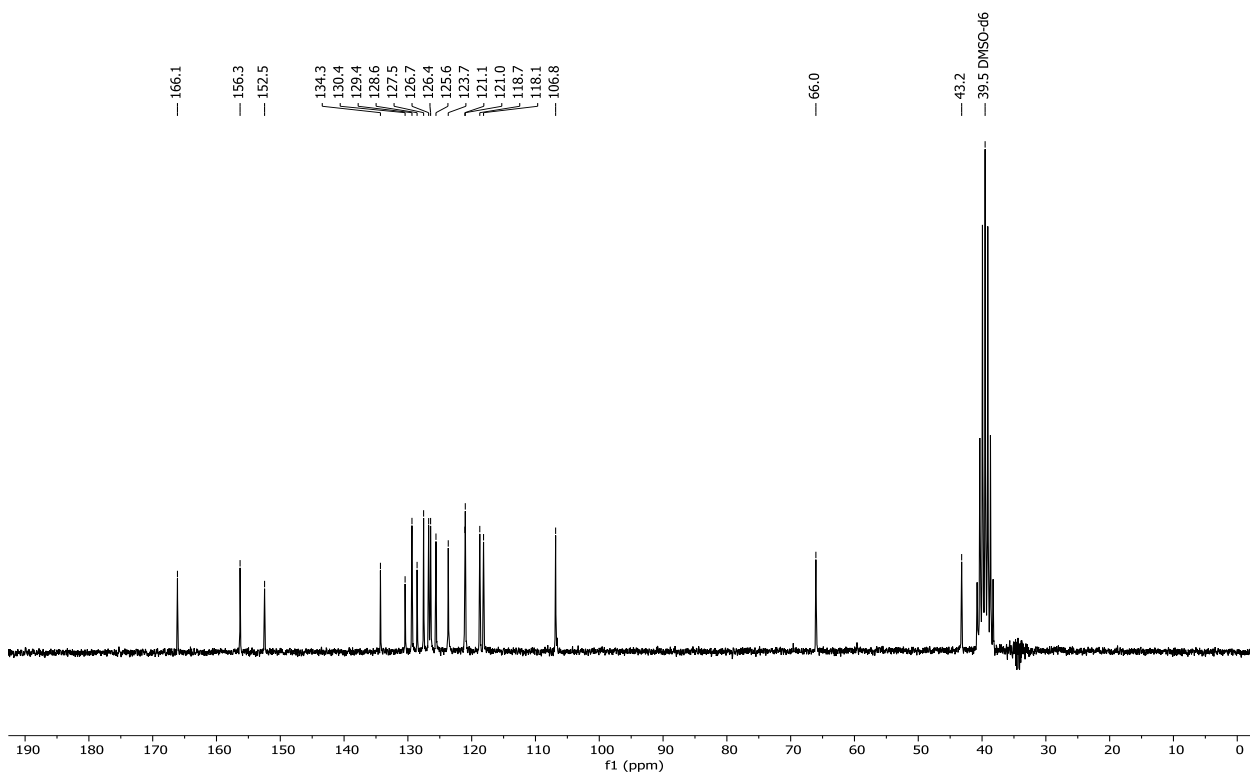
¹H NMR spectrum of **23d**.



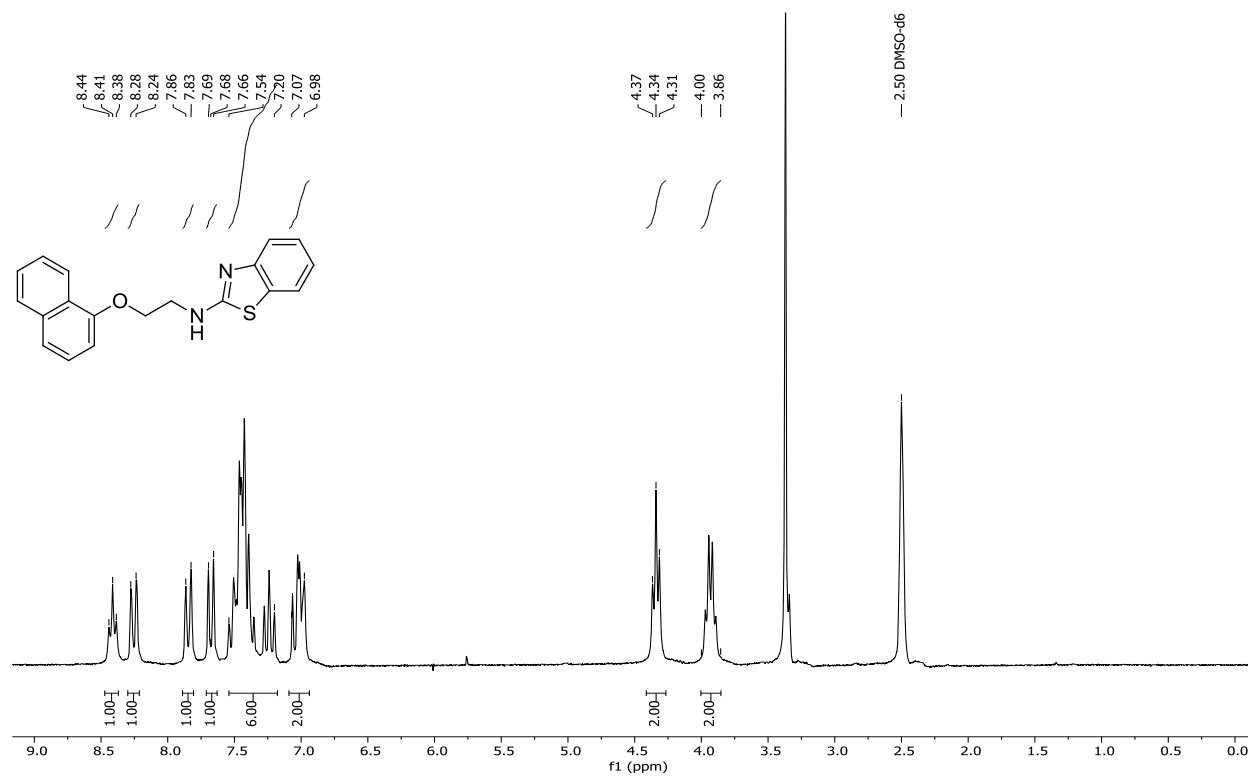
¹³C NMR spectrum of **23d**.



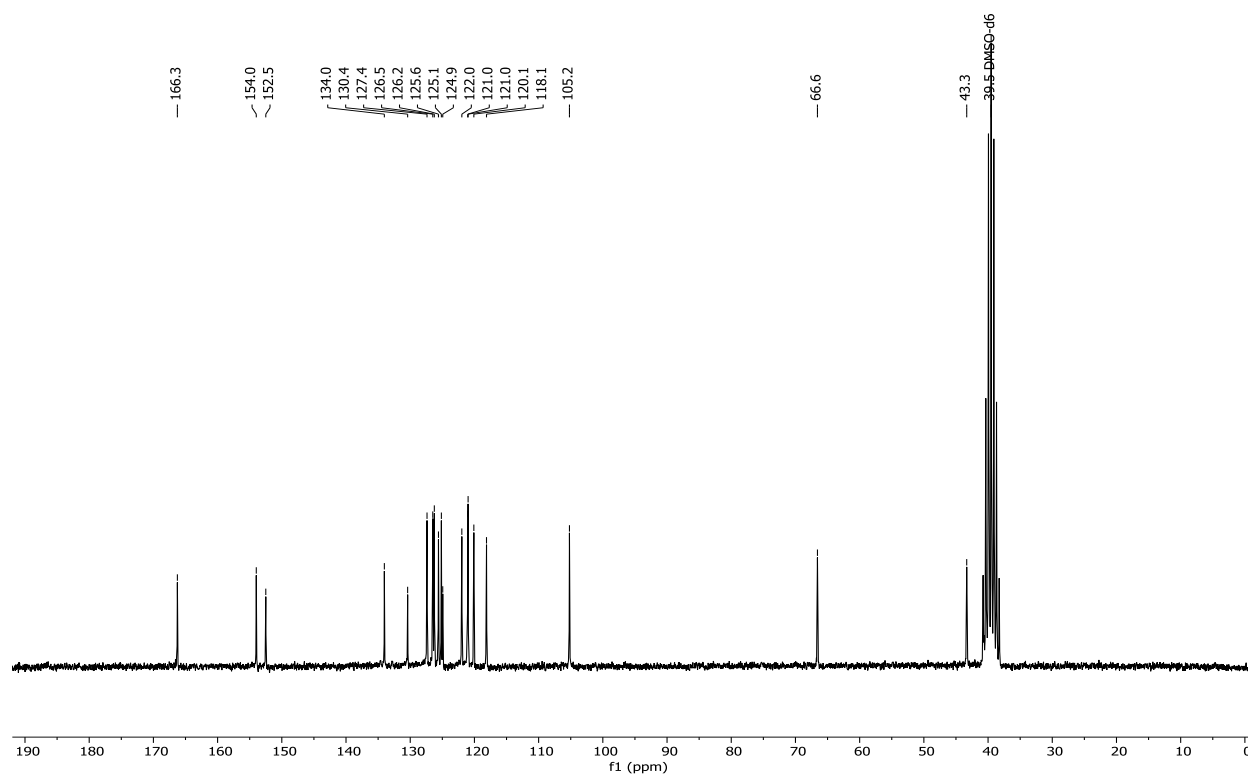
¹H NMR spectrum of **25a**.



¹³C NMR spectrum of **25a**.

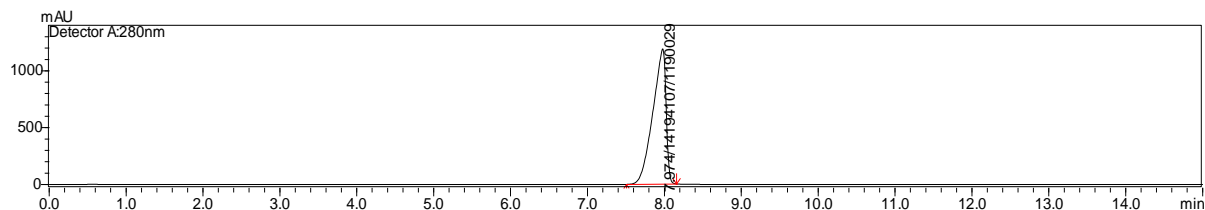


¹H NMR spectrum of **25b**.



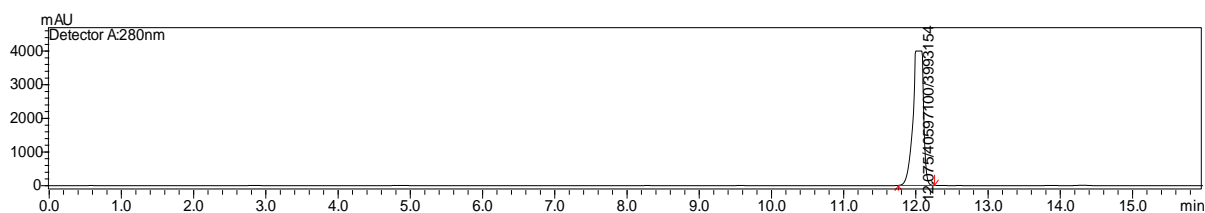
¹³C NMR spectrum of **25b**.

HPLC traces



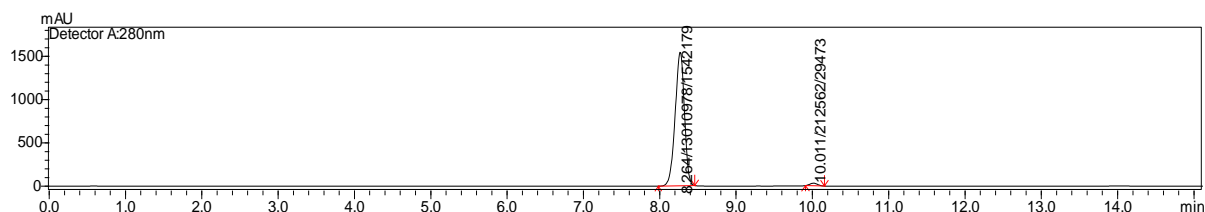
Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	7.974	0.00000	14194107	1190029	7.508	8.158	100.0000	--	0.674

Figure S2: HPLC chromatogram of inhibitor **19d** (GK593) [500 ppm, H₂O/acetonitrile 65/35 v/v, gradient to 40:60 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].



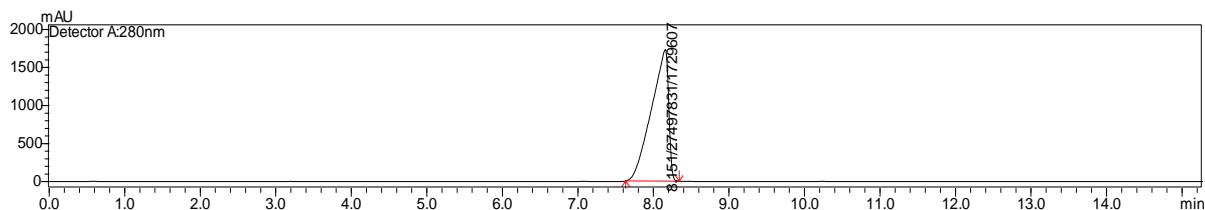
Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	12.075	0.00000	40597100	3993154	11.758	12.258	100.0000	--	0.699

Figure S3: HPLC chromatogram of inhibitor **5b** (GK510) [500 ppm, H₂O/acetonitrile 70/30 v/v, gradient to 40:60 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].



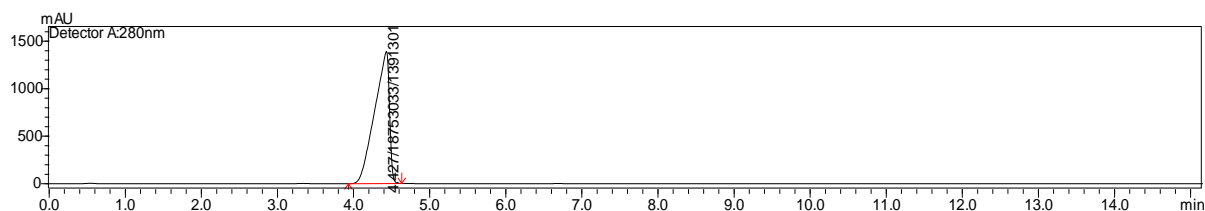
Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	8.264	0.00000	13010978	1542179	7.983	8.458	98.3925	--	0.941
2	10.011	0.00000	212562	29473	9.908	10.158	1.6075	7.955	1.149

Figure S4: HPLC chromatogram of inhibitor **11** (GK521) [500 ppm, H₂O/acetonitrile 70/30 v/v, gradient to 40:60 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].



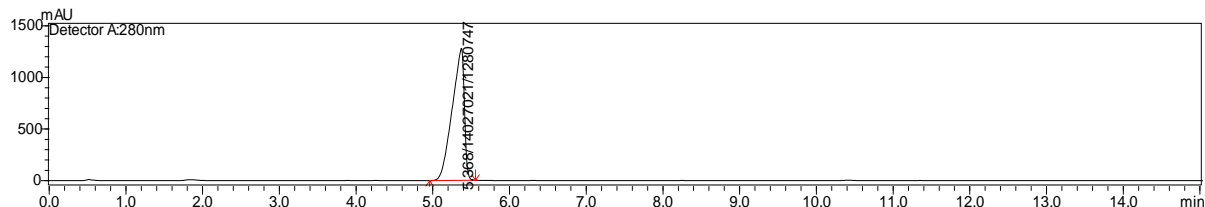
Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	8.151	0.00000	27497831	1729607	7.633	8.342	100.0000	--	0.628

Figure S5: HPLC chromatogram of inhibitor **19a** (GK543) [500 ppm, H₂O/acetonitrile 65/35 v/v, gradient to 40:60 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].



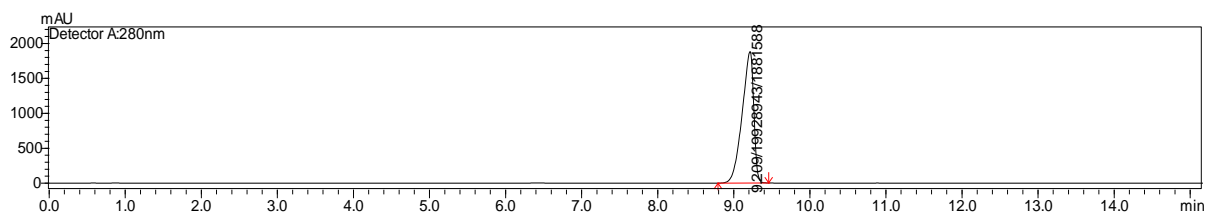
Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	4.427	0.00000	18753033	1391301	3.933	4.633	100.0000	--	0.641

Figure S6: HPLC chromatogram of inhibitor **19c** (GK560) [500 ppm, H₂O/acetonitrile 65/35 v/v, gradient to 40:60 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].



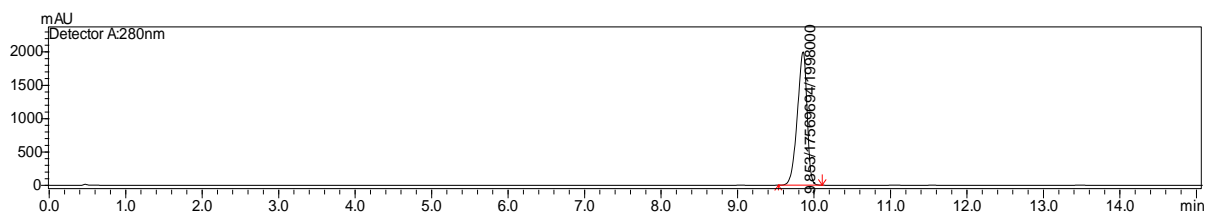
Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	5.368	0.00000	14027021	1280747	4.958	5.558	100.0000	--	0.679

Figure S7: HPLC chromatogram of inhibitor **19b** (GK562) [500 ppm, H₂O/acetonitrile 70/30 v/v, gradient to 40:60 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].



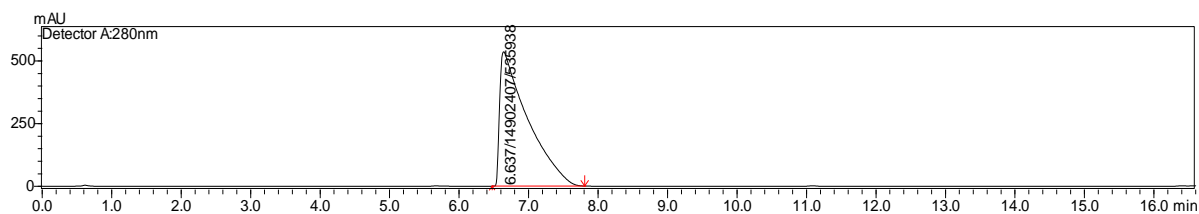
Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	9.209	0.00000	19928943	1881588	8.792	9.458	100.0000	--	0.741

Figure S8: HPLC chromatogram of inhibitor **23a** (GK566) [500 ppm, H₂O/acetonitrile 65/35 v/v, gradient to 40:60 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].



Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	9.853	0.00000	17569694	1998000	9.533	10.108	100.0000	--	0.854

Figure S9: HPLC chromatogram of inhibitor **23c** (GK592) [500 ppm, H₂O/acetonitrile 70/30 v/v, gradient to 40:60 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].



Peak#	Ret. Time	Conc.	Area	Height	Peak Start	Peak End	Area%	Resolution	Tailing F.
1	6.637	0.00000	14902407	535938	6.475	7.808	100.0000	--	5.189

Figure S10: HPLC chromatogram of inhibitor **19e** (GK610) [500 ppm, H₂O/acetonitrile 85/15 v/v, gradient to 55:45 v/v for 15 min, 35 °C, 1 mL/min, Detector: 280 nm, Column: Thermo Scientific, Hypersil Silica (250 × 4.6 mm, 5 μm)].