Supplementary Materials

Novel phthalazin-1(2H)-one derivatives displaying a dithiocarbamate moiety as potential anticancer agents

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Table S1. CYP450 inhibition predicted by SwissADME for compounds **6e**, **8e**, **6g**, **9a-b**, **9d**, and **9g**.

Compound	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
6e	Yes	Yes	Yes	No	Yes
8e	Yes	Yes	Yes	No	Yes
6g	Yes	Yes	Yes	No	No
9a	Yes	Yes	Yes	No	Yes
9b	Yes	Yes	Yes	No	Yes
9d	Yes	Yes	Yes	No	Yes
9g	Yes	Yes	Yes	No	No

Table S2. Toxicity model predicted by ProTox-II for compounds **6e**, **8e**, **6g**, **9a-b**, **9d,** and **9g**.

Compound	Hepatotoxicity Probability	Carcinogenicity Probability	Immunotoxicity Probability	Mutagenicity Probability	Cytotoxicity Probability
6e	Inactive	Inactive	Inactive	Inactive	Inactive
	0.56	0.55	0.80	0.53	0.67
8e	Inactive	Inactive	Inactive	Inactive	Inactive
	0.58	0.56	0.98	0.51	0.67
6g	Inactive	Active	Inactive	Inactive	Inactive
	0.54	0.53	0.84	0.53	0.72
9a	Inactive	Active	Inactive	Inactive	Inactive
	0.57	0.53	0.98	0.51	0.71
9b	Inactive	Active	Inactive	Inactive	Inactive
	0.58	0.53	0.99	0.51	0.71
9d	Inactive	Inactive	Inactive	Inactive	Inactive
	0.58	0.57	0.93	0.52	0.6
9g	Inactive	Active	Inactive	Inactive	Inactive
	0.55	0.53	0.92	0.51	0.72

Materials and Methods

Chemical synthesis

General procedure for the preparation of 2-(2-bromoethyl)phthalazin-1(2*H*)-ones (15-17)

To a solution of phthalazinone **12-14** (2 mmol) in DMF (20 mL) was added K_2CO_3 (8 mmol) and 1,2-dibromoethane (12 mmol). The reaction mixture was stirred at 60 ºC for 1.5 h and the solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) to afford the desired compound.

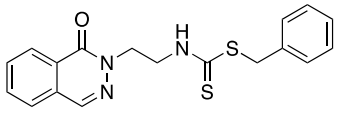
2-(2-Bromoethyl)phthalazin-1(2H)-one (**15**). White solid; yield: 50%; R_f = 0.4 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$): δ = 8.43 (d, 1H, J = 7.7 Hz, H8), 8.18 (s, 1H, H4), 7.85-7.76 (m, 2H, H6, H7), 7.71 (d, 1H, J = 7.3 Hz, H5), 4.63 (t, 2H, J = 6.8 Hz, H1´), 3.77 (t, 2H, J = 6.8 Hz, H2´); ^{13}C NMR ($CDCl_3$): δ = 159.6 (C1), 138.3, 133.5, 132.0, 129.8, 127.9, 126.9 (C8), 126.3, 52.2 (C1´), 28.6 (C2´); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{10}BrN_2O$: 252.99710, found: 252.99790.

2-(2-Bromoethyl)-4-p-tolylphthalazin-1(2H)-one (**16**). White solid; yield: 75%; R_f = 0.4 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$): δ = 8.53 (d, 1H, J = 7.1 Hz, H8), 7.82-7.75 (m, 3H, H5,

H6, H7), 7.49 (d, 2H, J = 7.9 Hz, Ar), 7.34 (d, 2H, J = 7.9 Hz, Ar), 4.69 (t, 2H, J = 7.0 Hz, H1′), 3.80 (t, 2H, J = 7.0 Hz, H2′), 2.46 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ = 159.3 (C1), 147.7, 139.5, 133.1, 132.1, 131.6, 129.5, 129.4, 129.3, 128.2, 127.4, 127.0, 52.1 (C1′), 28.5 (C2′), 21.5 (CH_3); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}BrN_2O$: 343.04405, found: 343.04401.

2-(2-Bromoethyl)-4-methylphthalazin-1(2H)-one (**17**). White solid; yield: 45%; R_f = 0.4 (hexane/EtOAc, 1:1); ^{1}H NMR ($CDCl_3$): δ = 8.45-8.41 (m, 1H, H8), 7.83-7.72 (m, 3H, H5, H6, H7), 4.56 (t, 2H, J = 7.0 Hz, H1′), 3.73 (t, 2H, J = 7.0 Hz, H2′), 2.57 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ = 159.4 (C1), 144.1 (C4), 133.2, 131.5, 129.9, 127.7, 127.2, 125.0, 51.8 (C1′), 28.5 (C2′), 19.0 (CH_3); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{12}BrN_2O$: 267.01275, found: 267.01300.

^{1}H NMR and ^{13}C NMR spectra of compounds 6-9



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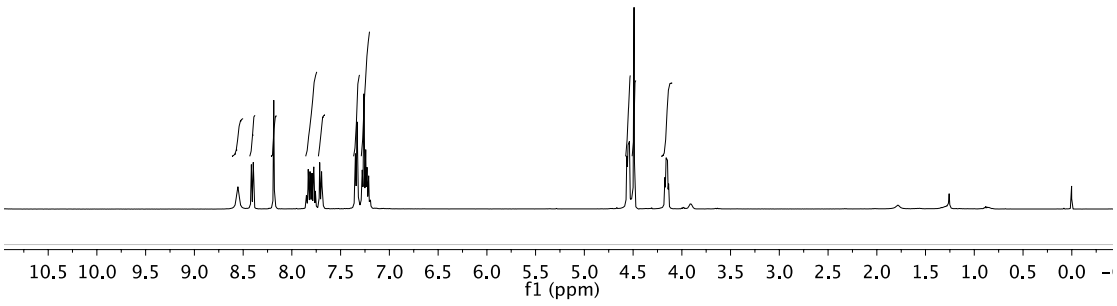

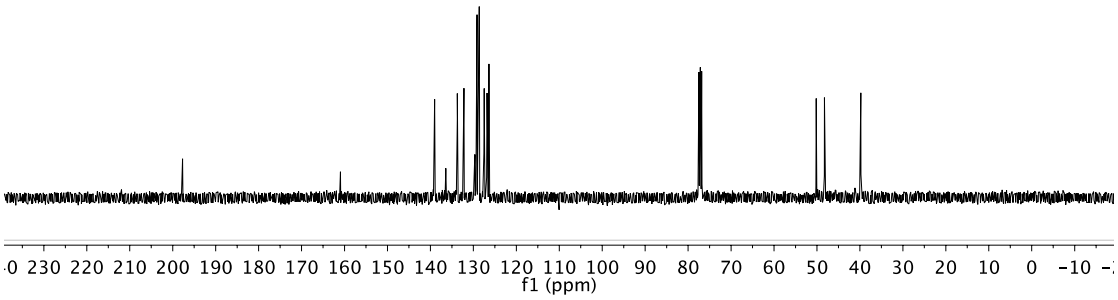

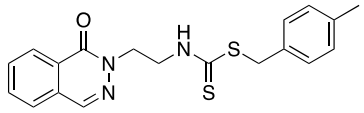

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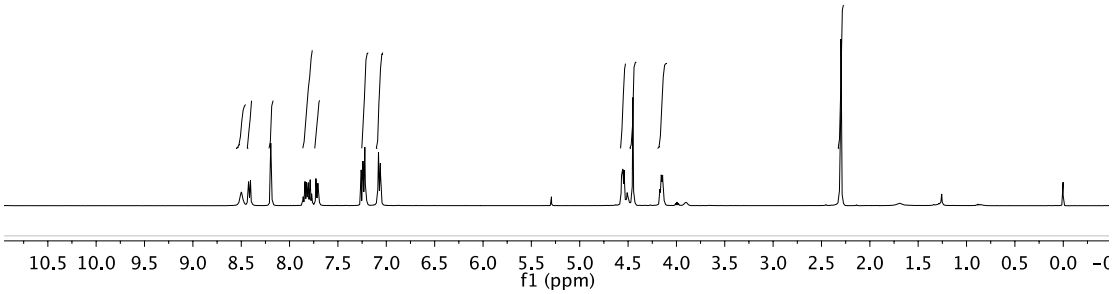
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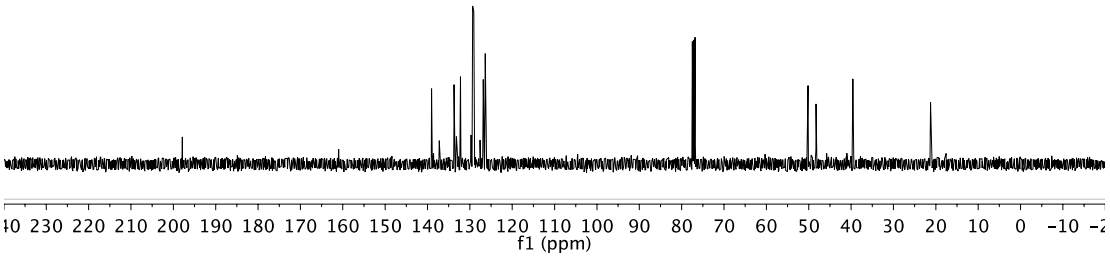
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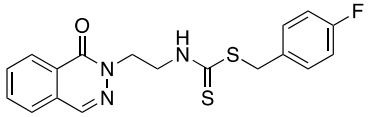

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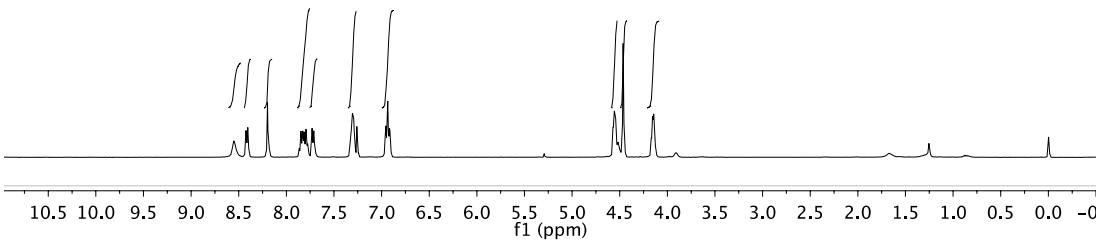
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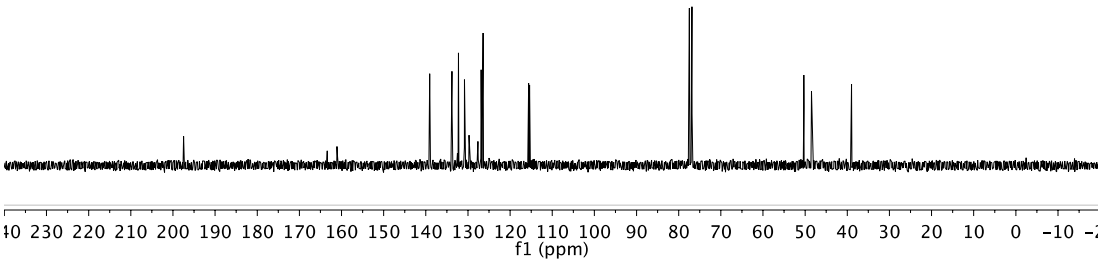
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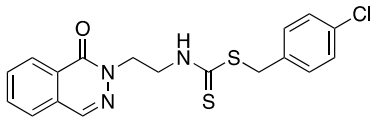
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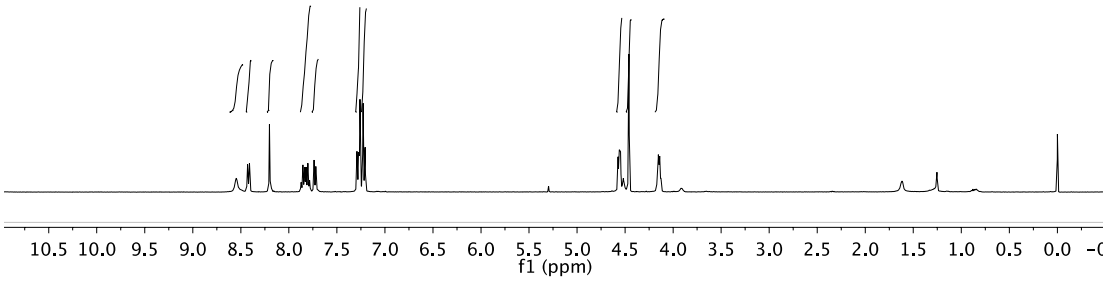
6d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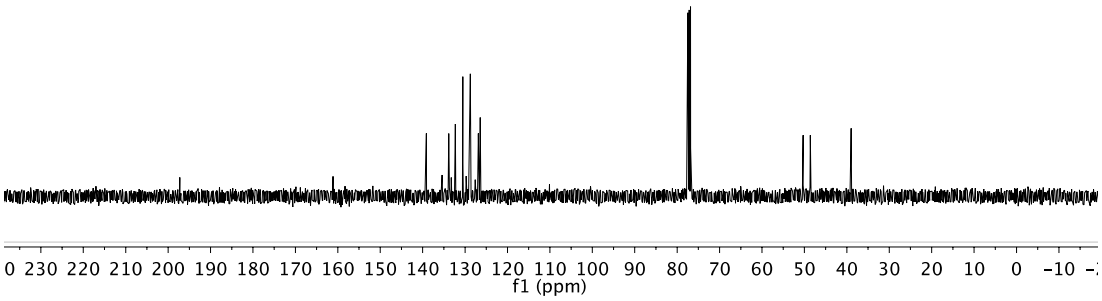
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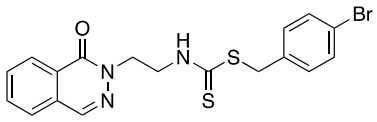
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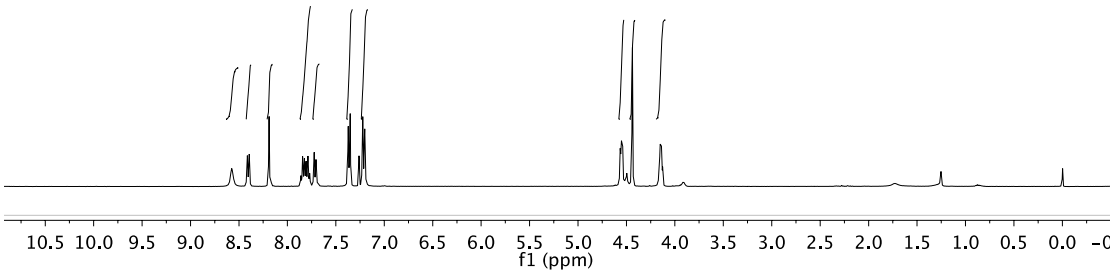
6e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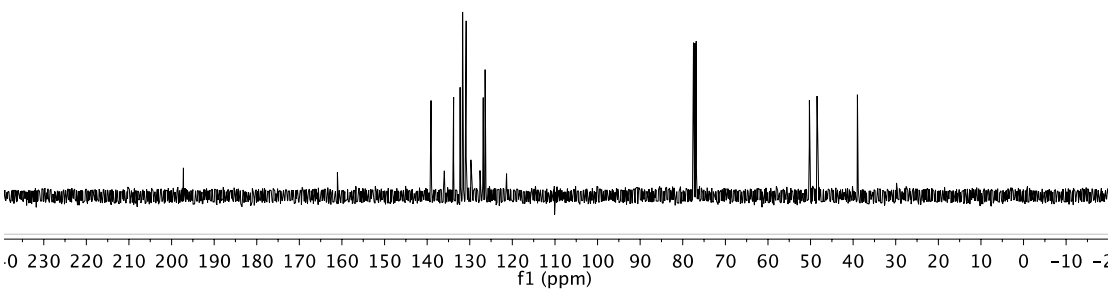
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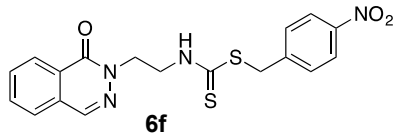
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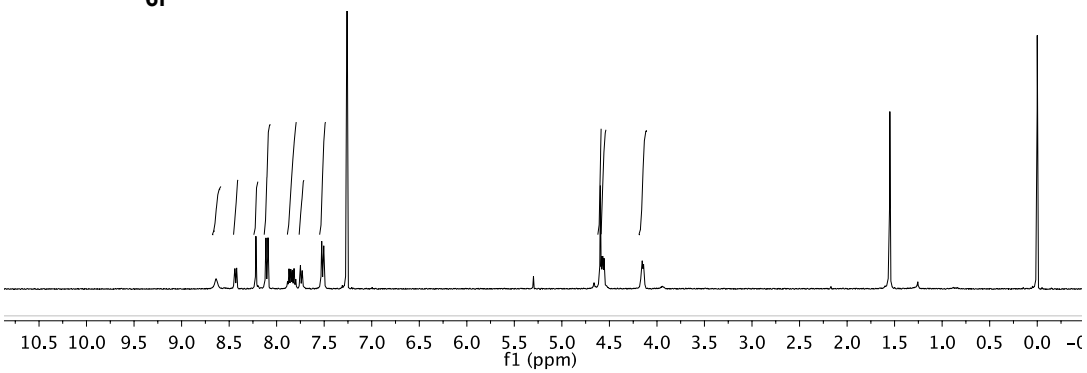
6f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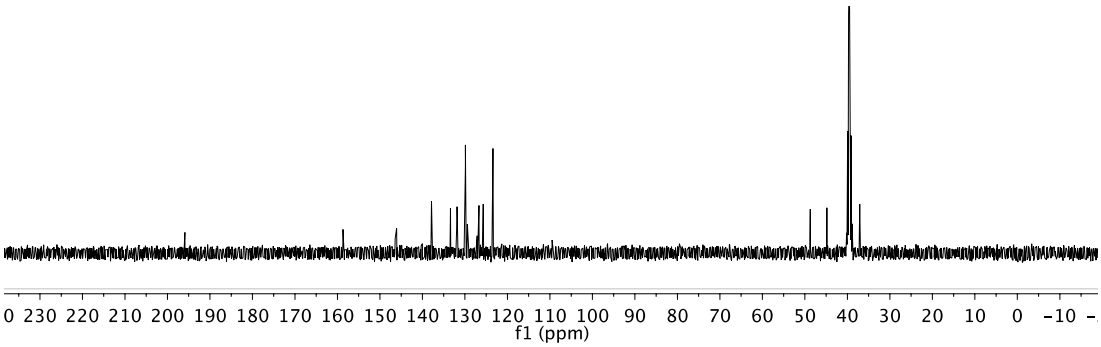
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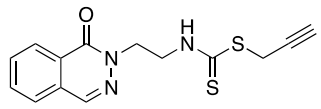
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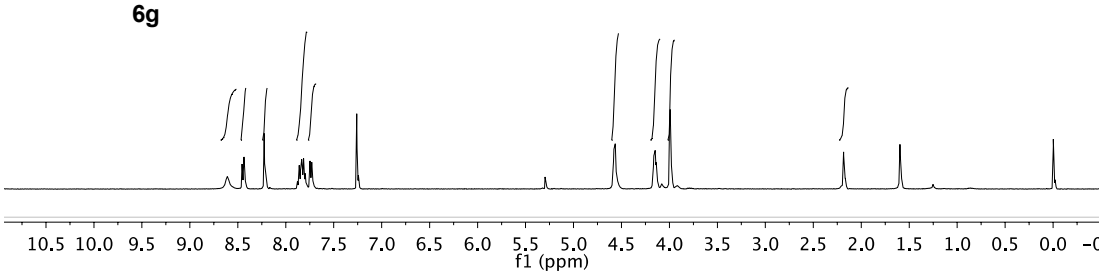
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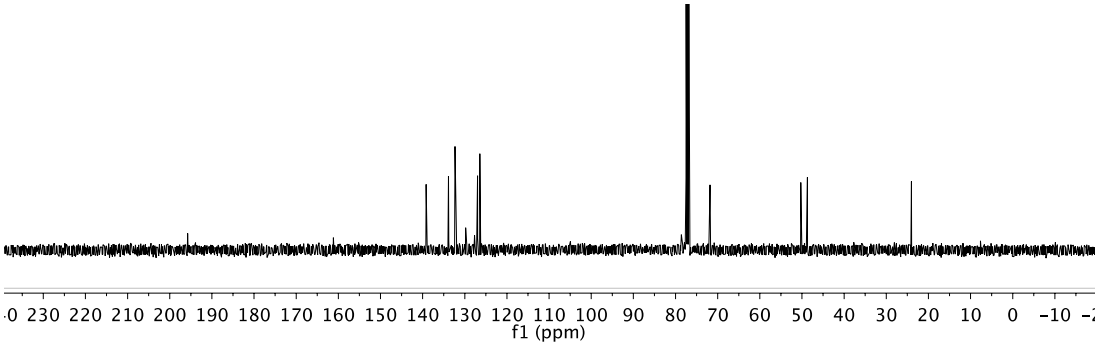
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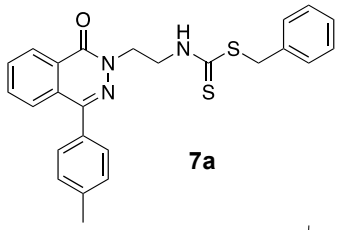
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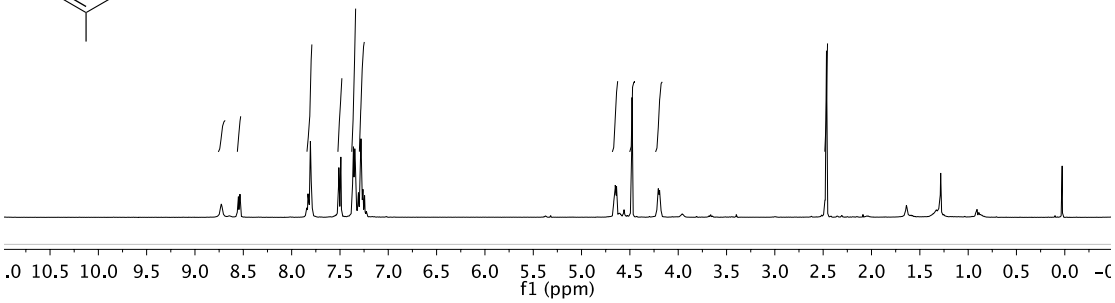
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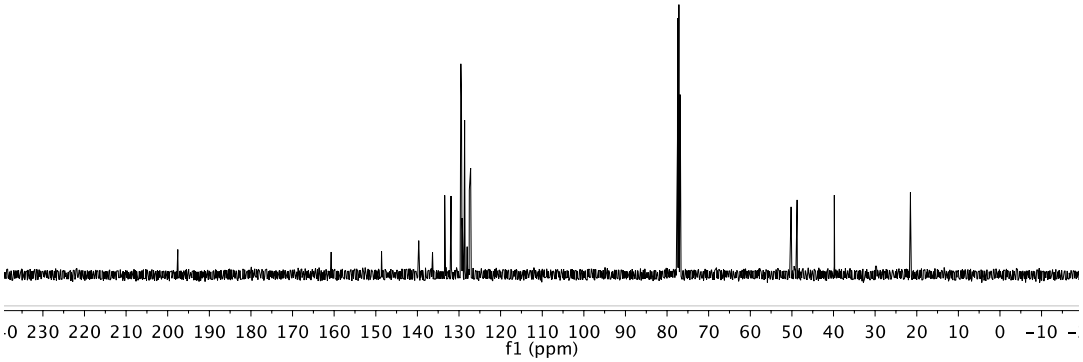
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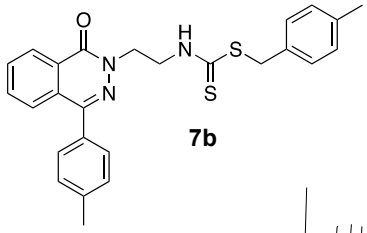
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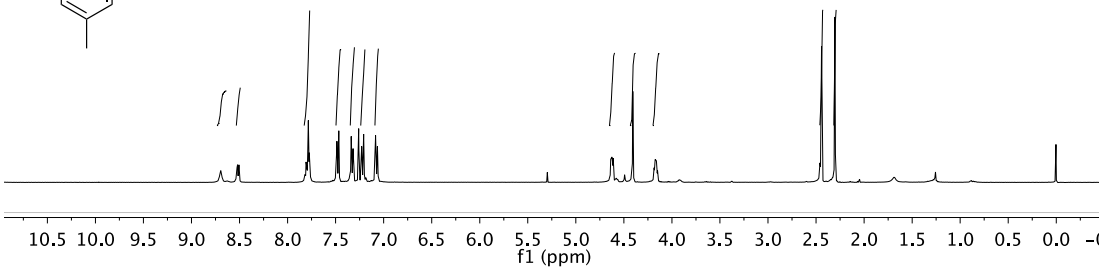
7b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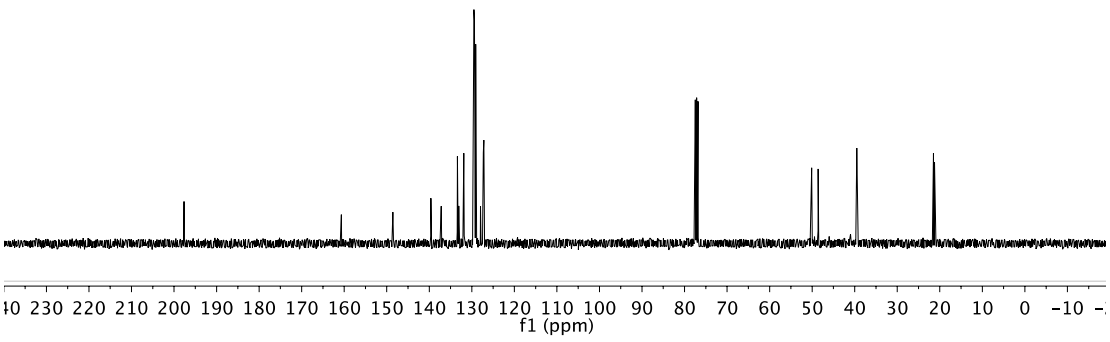
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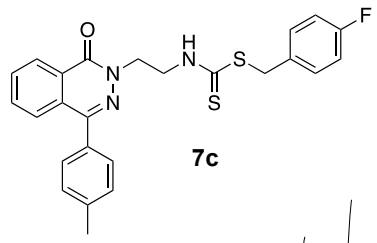

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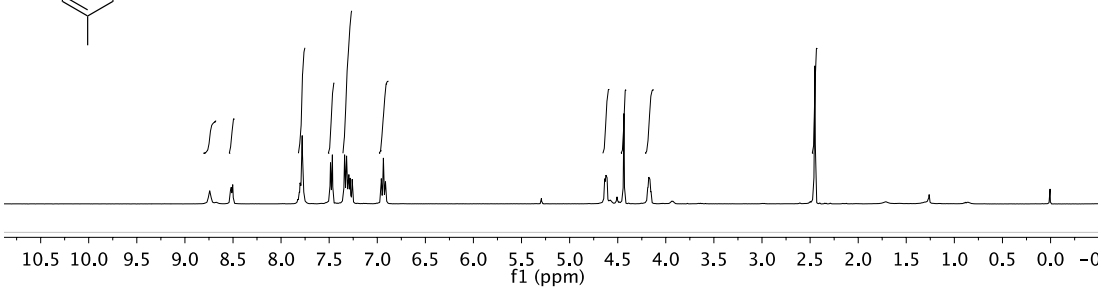

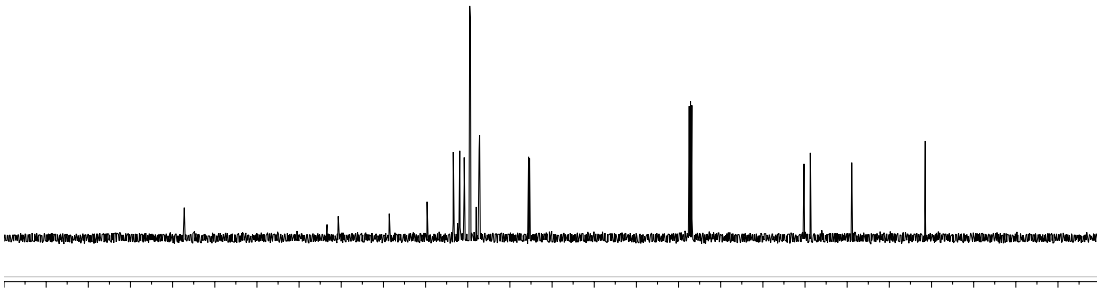

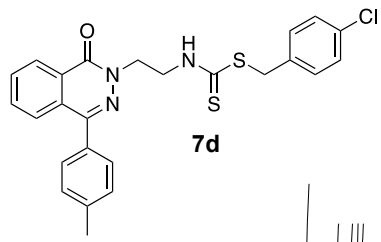

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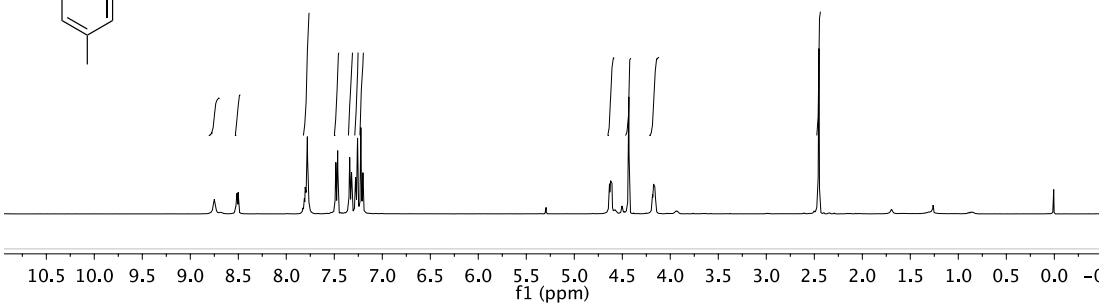

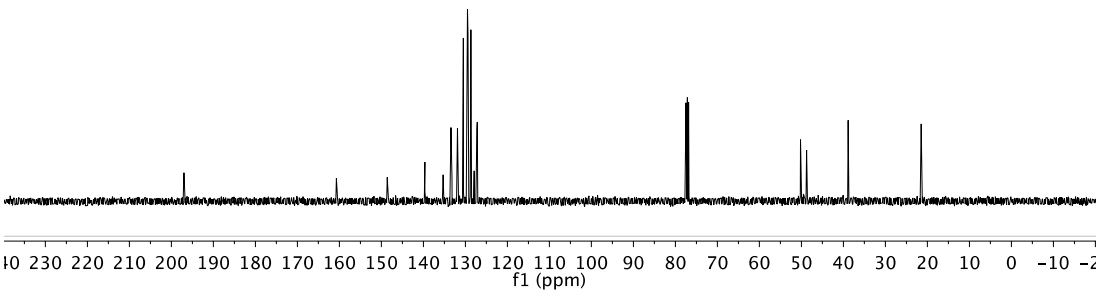

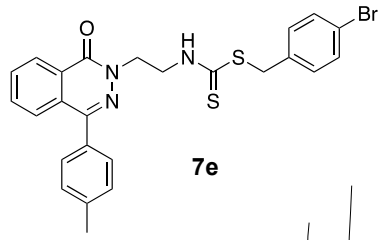
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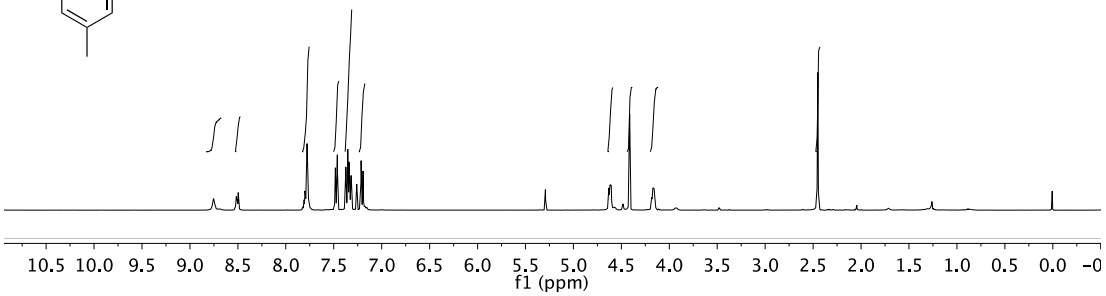
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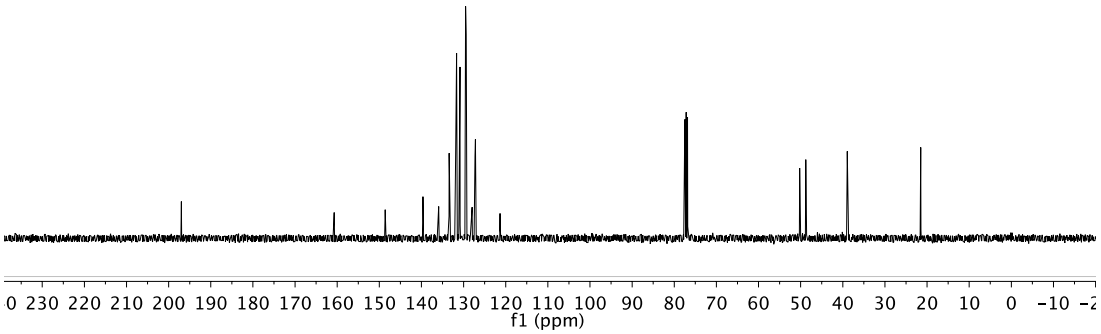
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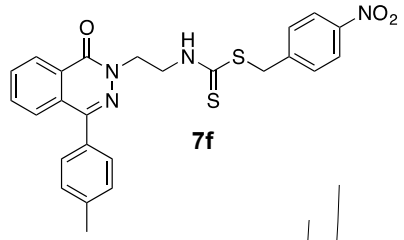
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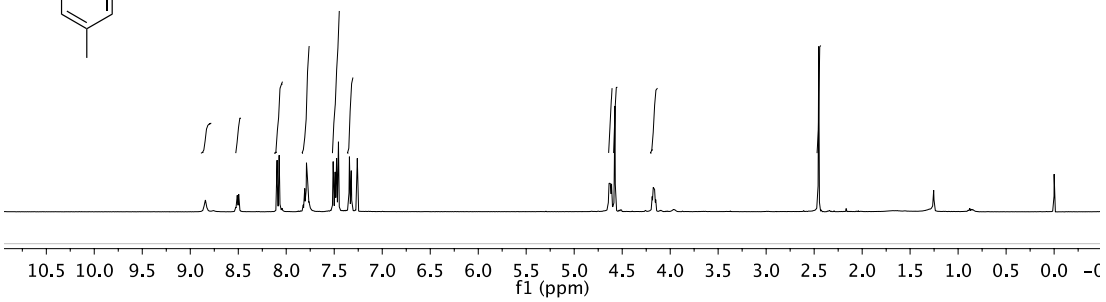
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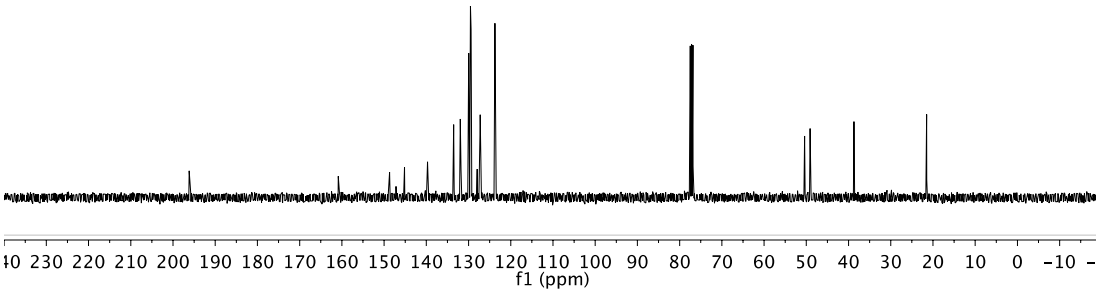
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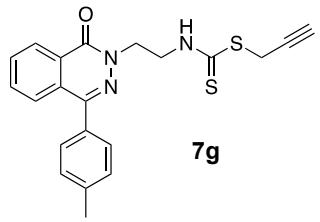
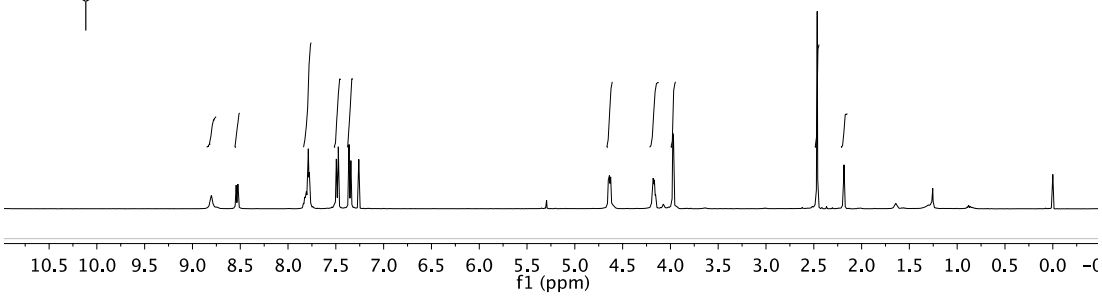


7g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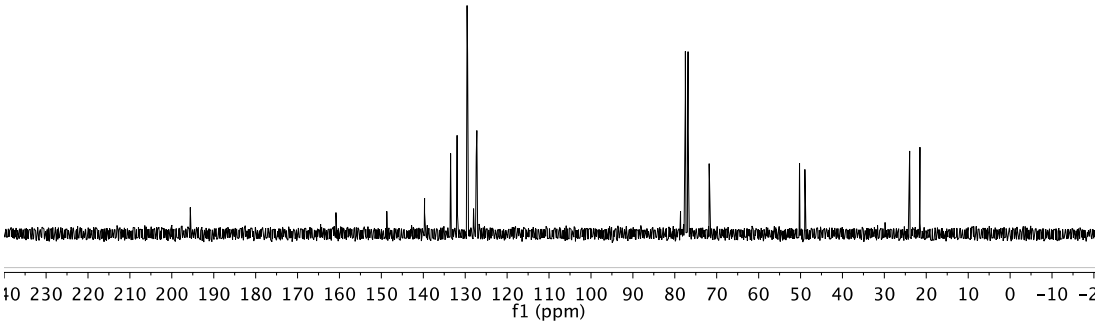
f1 (ppm)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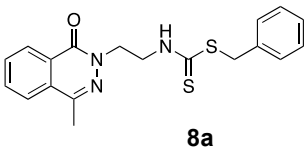

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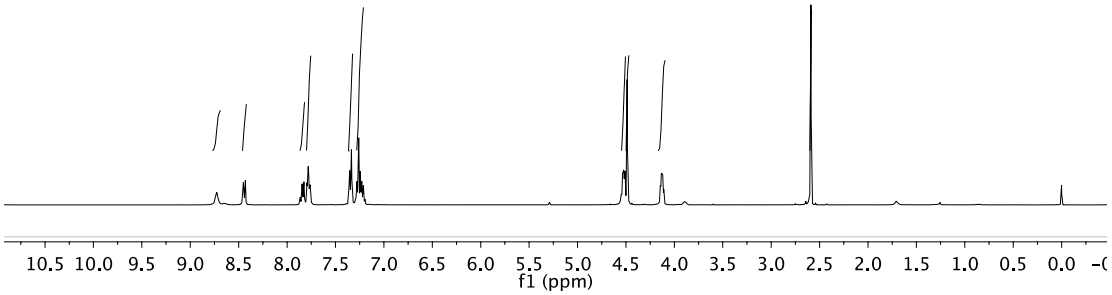
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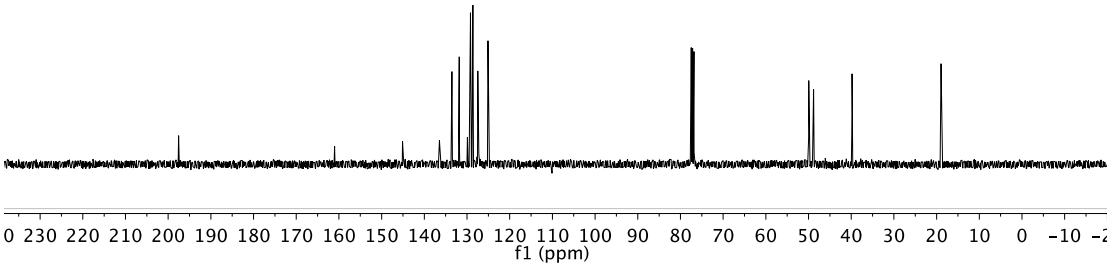
f1 (ppm)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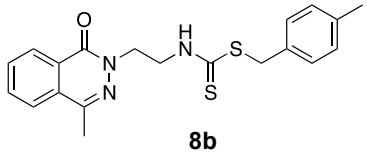
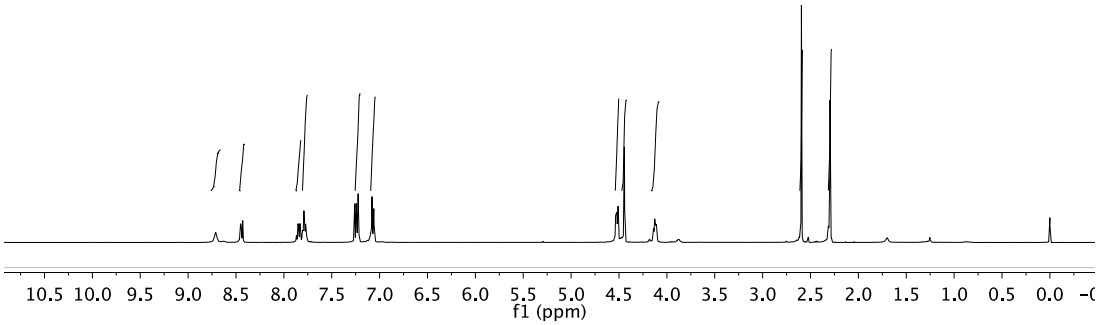


8b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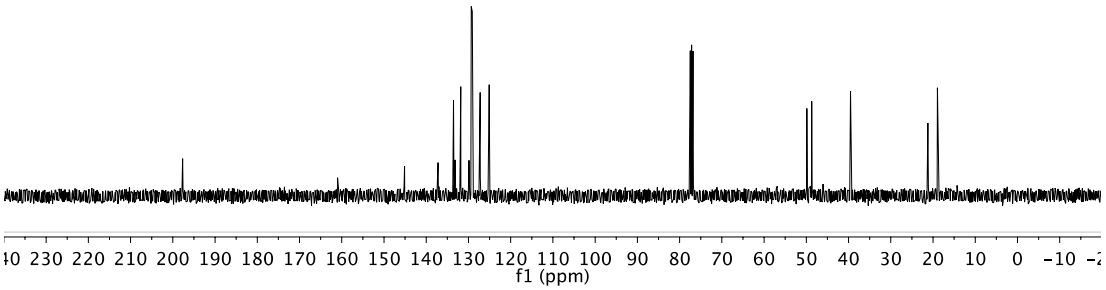
f1 (ppm)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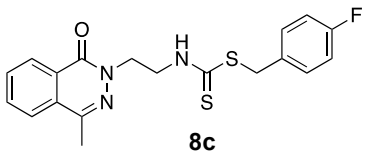
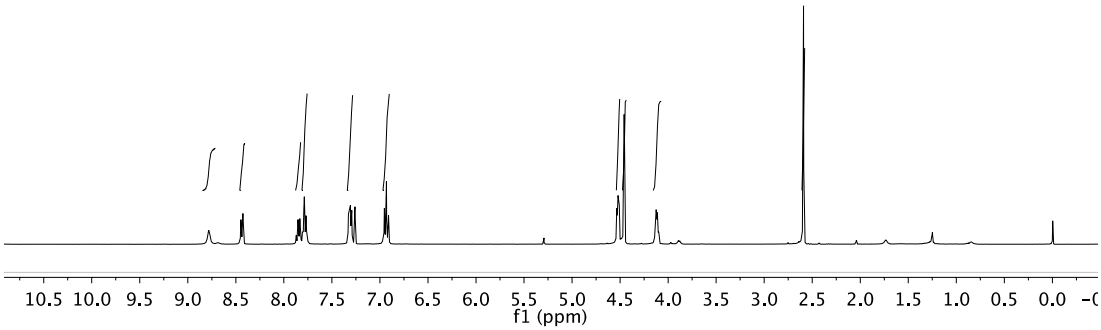
f1 (ppm)



8c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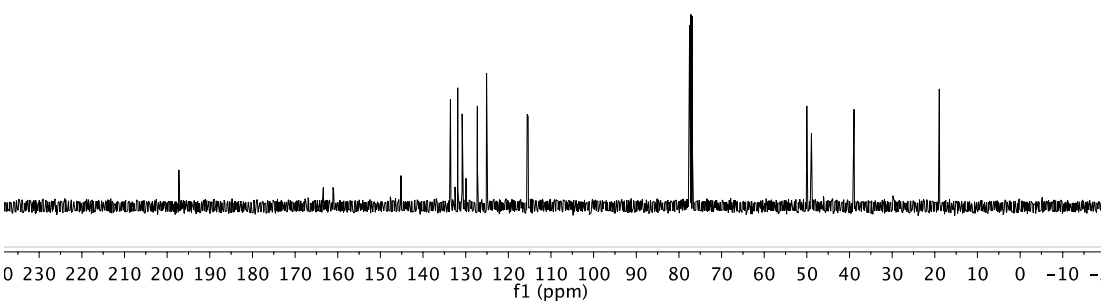
f1 (ppm)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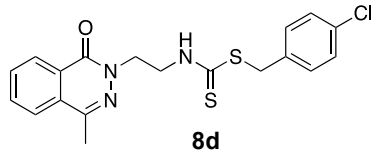
f1 (ppm)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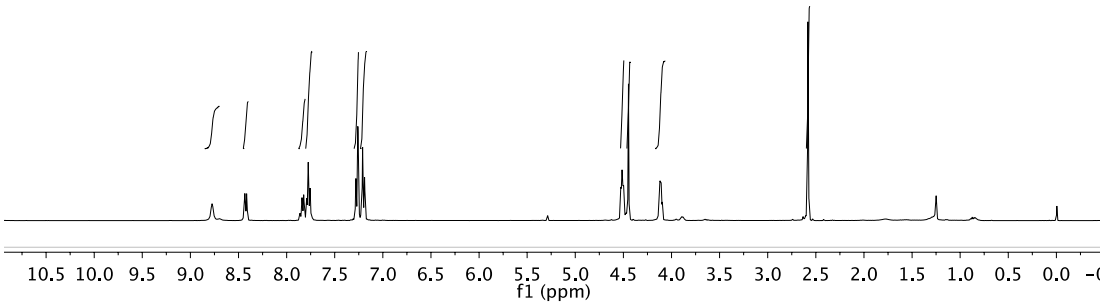
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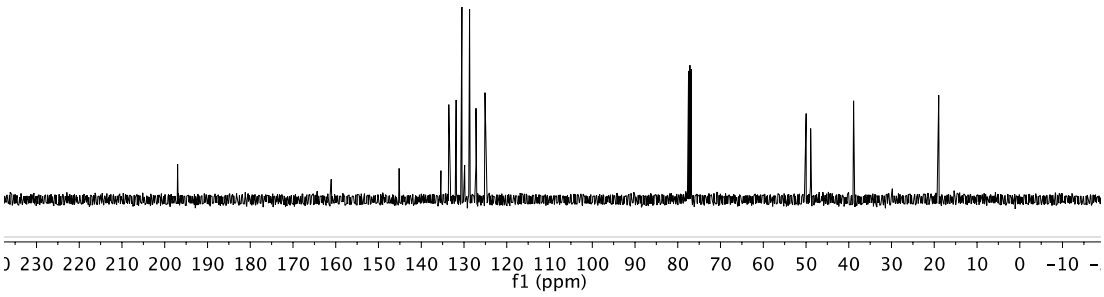
f1 (ppm)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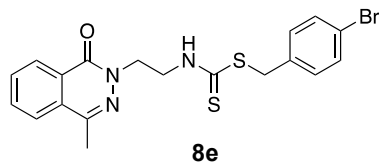
f1 (ppm)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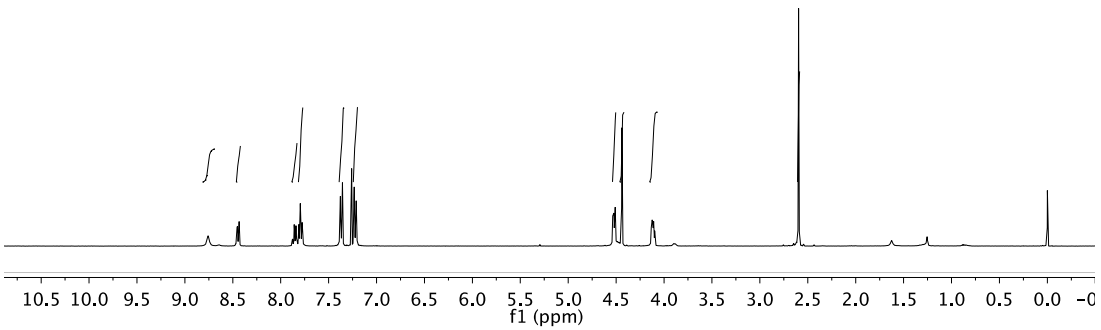
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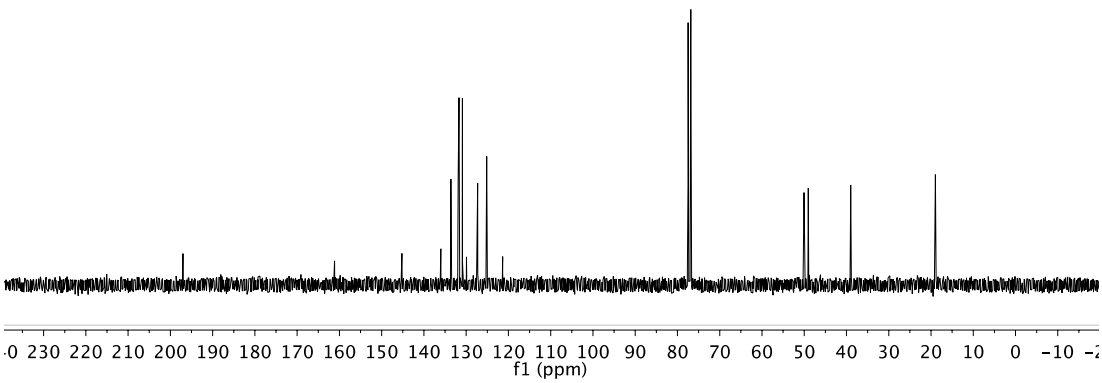
f1 (ppm)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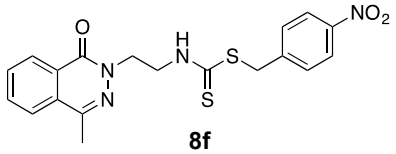
f1 (ppm)



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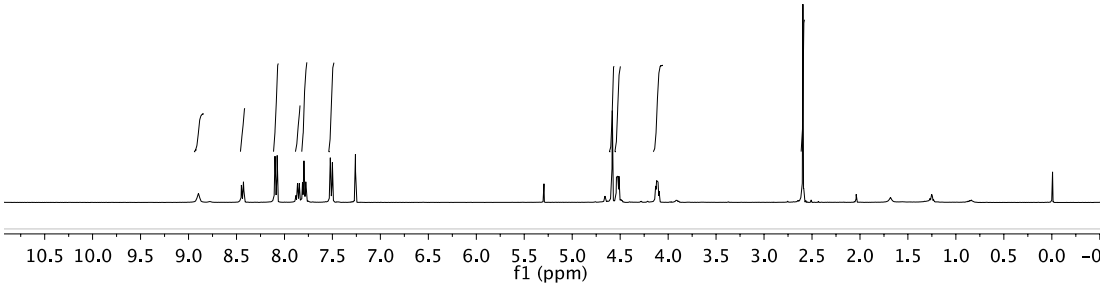
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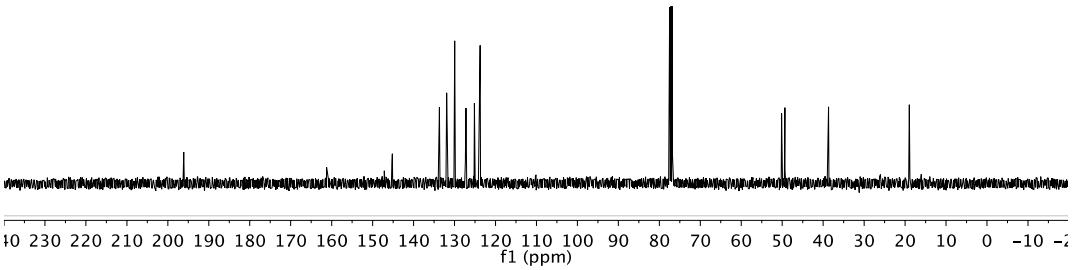
f1 (ppm)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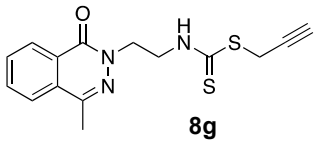
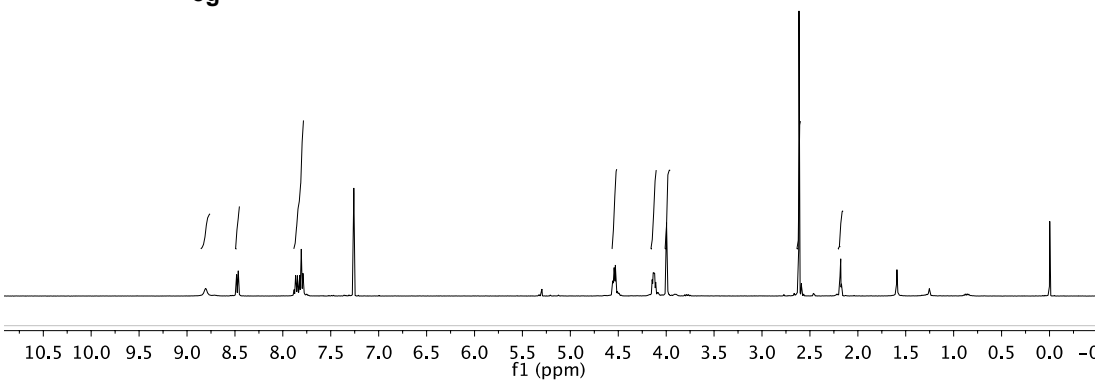
f1 (ppm)



8g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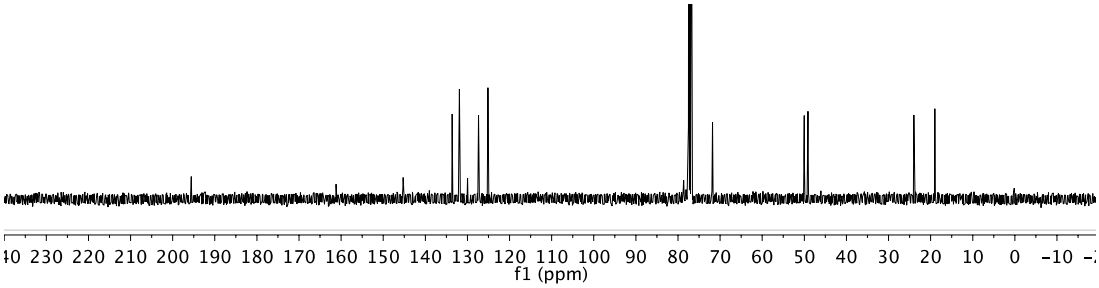
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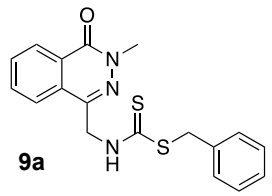
f1 (ppm)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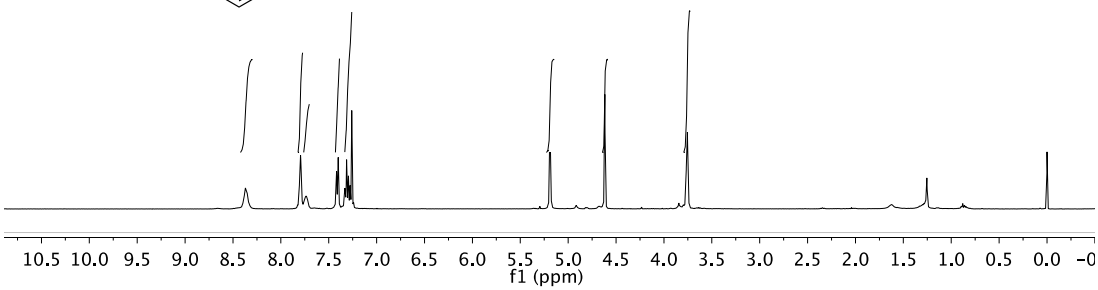
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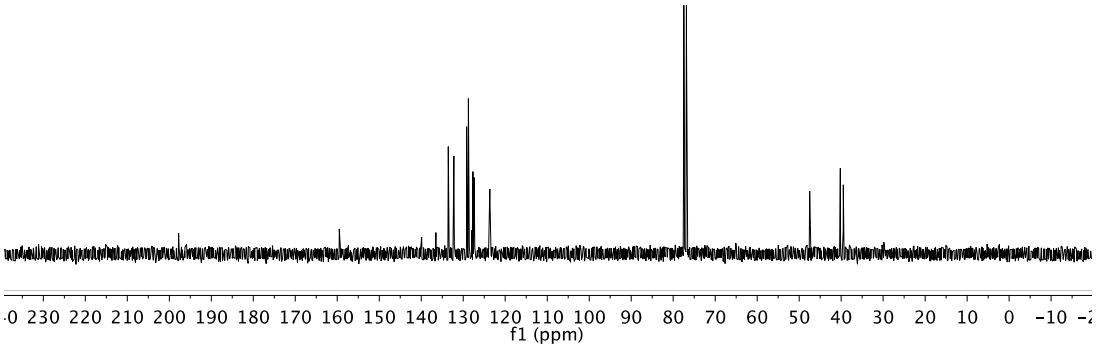
f1 (ppm)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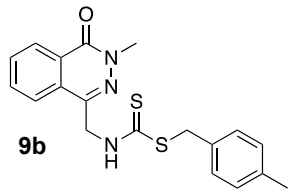
f1 (ppm)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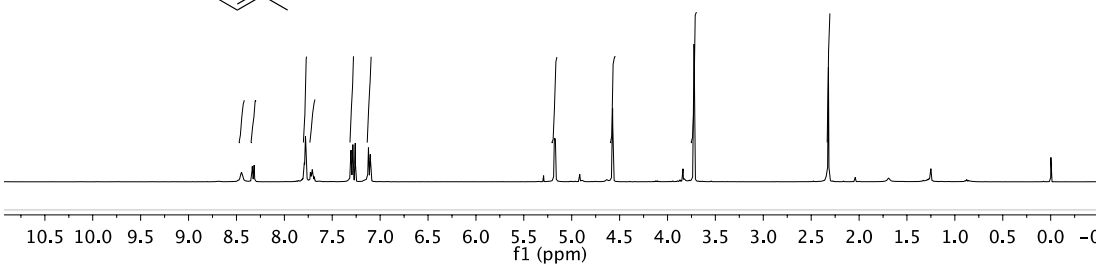
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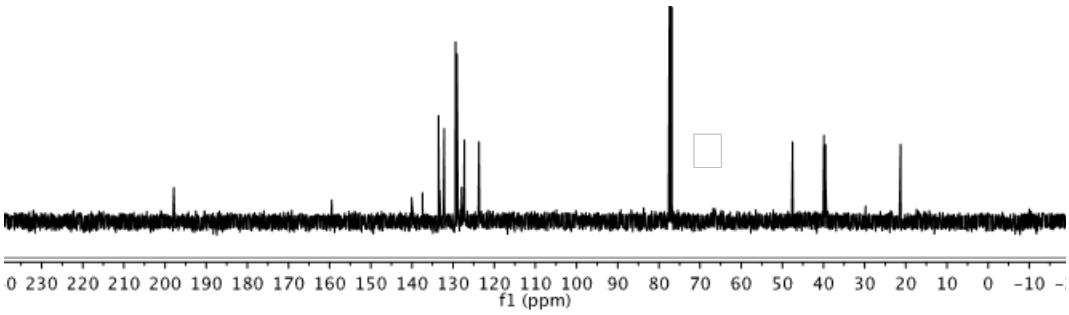
f1 (ppm)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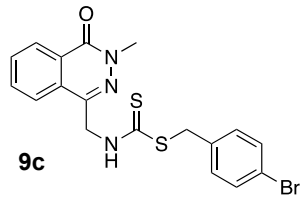
f1 (ppm)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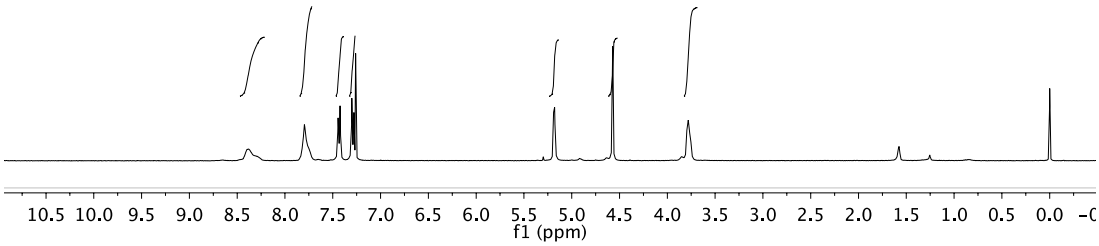
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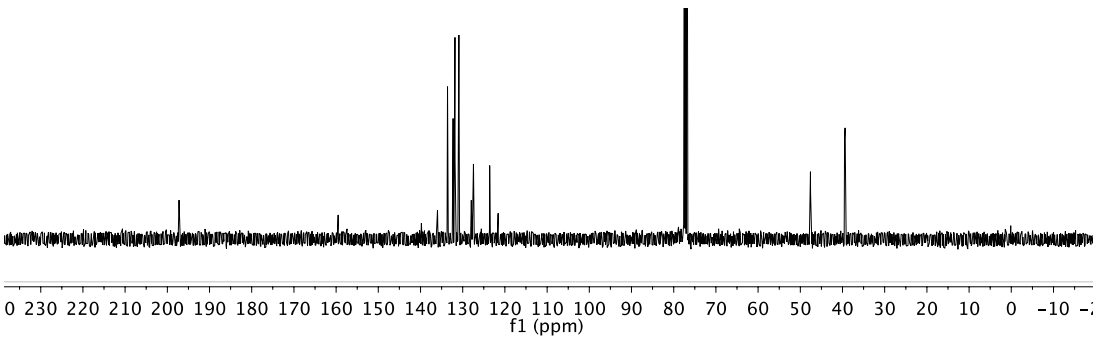
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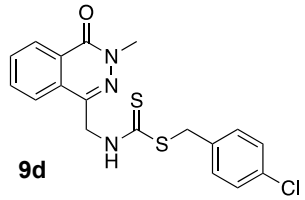
f1 (ppm)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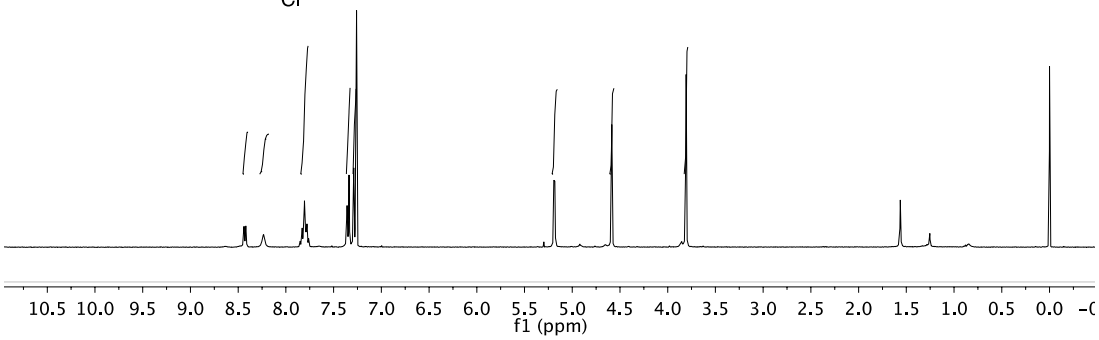
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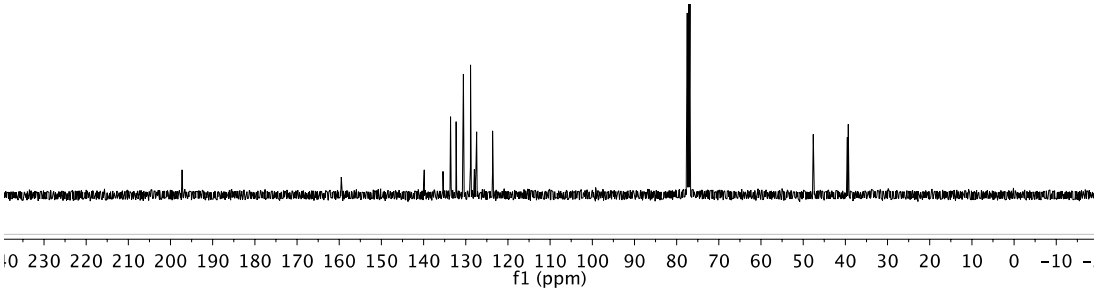
f1 (ppm)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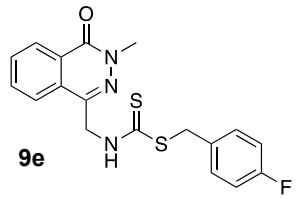
f1 (ppm)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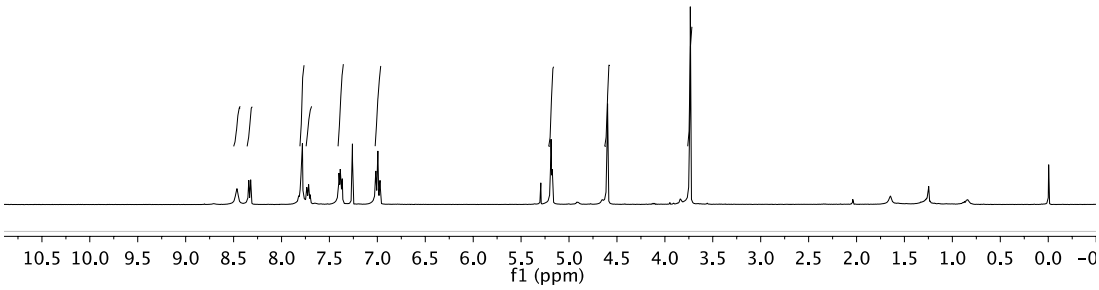
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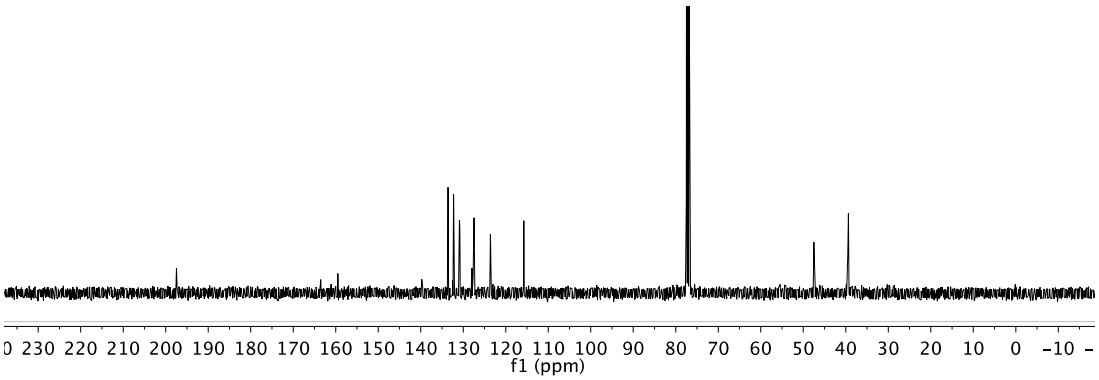
f1 (ppm)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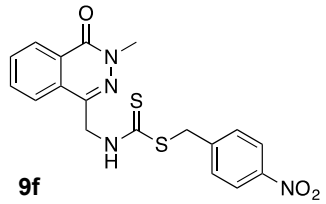
f1 (ppm)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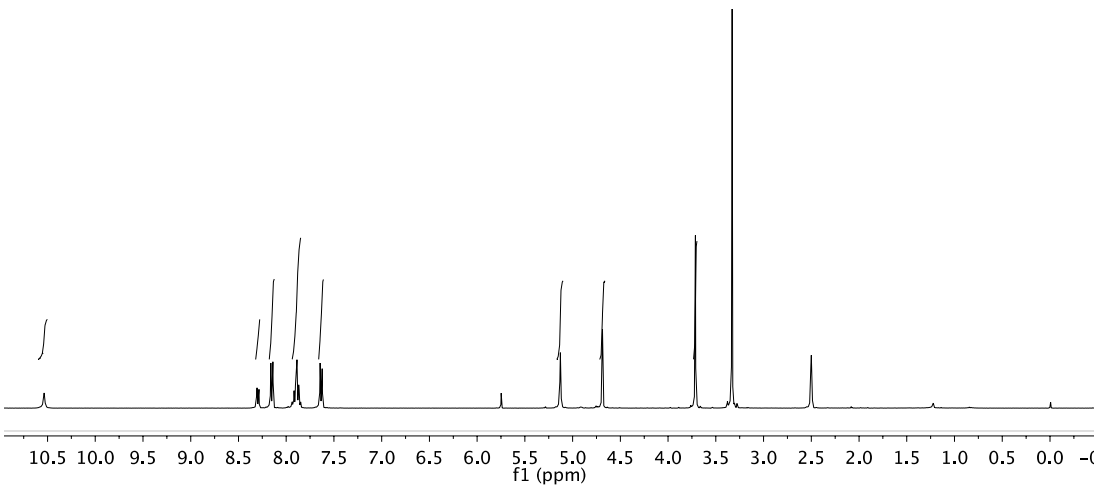
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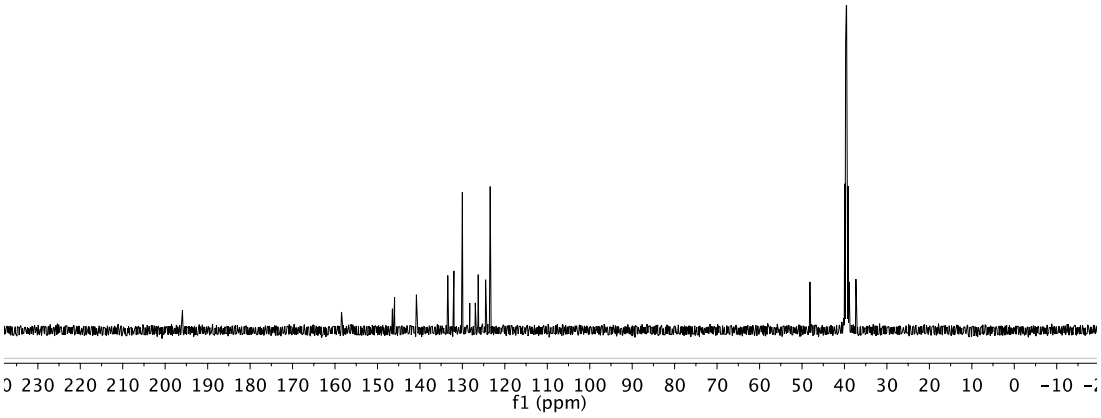
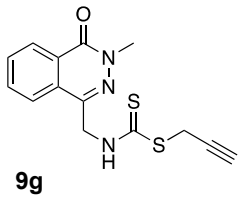
f1 (ppm)





9g