A practical synthesis of 2,3-dihydro-1,5-benzothiazepines

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1. Materials and Methods

Reagents and solvents were purchased from commercial suppliers and used as received, without further purification. Melting points were determined with a BÜCHI 535 melting point apparatus (BÜCHI, Flawil, Switzerland) and are corrected. NMR spectra were recorded with a Bruker Fourier 300 spectrometer (Bruker Billerica, Massachusetts, MA, USA). Chemical shifts are reported by using $CHCl_3$ as an external standard (δ = 7.24 ppm for ^{1}H NMR and 77.0 for ^{13}C NMR). APT experiments were used in the assignment of carbon spectra. Infrared spectra were recorded as thin films between NaCl plates using a Jasco FT-IR 4100 (Jasco, Easton, Maryland, MD, USA) spectrometer and absorptions are reported in wavenumbers (cm^{-1}) and only selected peaks are reported.

Mass spectra were measured with a LCQ Advantage Thermo-Finnigan LLC spectrometer (Thermo-Finnigan LLC San Jose, California, CA, USA). Column chromatography on silica gel (230–400 mesh) was performed by the flash technique. Petroleum ether (PE) refers to the fraction boiling in the range of 40–60 °C.

2. General procedure for the optimization of the synthesis of 2,3-dihydro-1,5-benzothiazepine 4a

To a stirred solution of chalcone **1a** (26 mg, 0.125 mmol) in the appropriate solvent (0.150 mL) at 28 °C, 2-aminothiophenol (**2a**) (19-31 mg, 0.15-0.250 mmol) was added. After completion of the reaction (monitored by TLC) the solvent was removed by flushing with nitrogen at room temperature. A weighed amount of the solid residue (~ 5 mg) was added with β-methoxynaphthalene (5 mg) as internal standard and dissolved in $CDCl_3$. The ^1H NMR spectra allowed us to determine the yield of **3a** and **4a** reported in Table 1 of the manuscript.

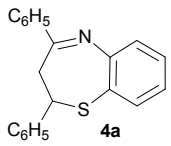
As suggested by a referee, a control experiment has been carried out by adding the internal standard without removing HFIP before ^1H NMR analysis. The calculated yields was found to be 84%, very close to 86% (Table 1, entry 4) within experimental reproducibility.

3. General procedure for the synthesis of 2,3-dihydro-1,5-benzothiazepine 4a-p

To a stirred solution of chalcone **1a-p** (1.25 mmol) in HFIP (1.50 mL) at 28 °C, **2a** (313 mg, 2.50 mmol) was added. After completion of the reaction (monitored by TLC) the solvent was removed by distillation and the product was purified by column chromatography on silica gel (hexane/ethyl acetate 80:20 unless otherwise noted).

The starting chalcone, physical, spectroscopic and analytical data of compounds **4a-p** are as follows.

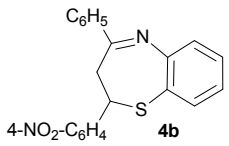
2,4-Diphenyl-2,3-dihydro-1,5-benzothiazepine (4a)



4a

1,3-Diphenyl-2-propen-1-one (**1a**). Yellow solid; mp 114-116 °C [lit.[1], 114-115 °C], AcOEt/PE 1:9. ^1H NMR (300 MHz, $CDCl_3$,): 3.07 (t, J = 12.6 Hz, 1 H), 3.32 (dd, J = 4.7, 13.1 Hz, 1 H), 4.99 (dd, J = 4.5, 12.0 Hz, 1 H), 7.12-7.17 (m, 1 H), 7.25-7.30 (m, 5 H), 7.44-7.51 (m, 4 H), 7.62 (d, J = 6.1 Hz, 2 H), 8.06 (d, J = 7.5 Hz, 2 H). Isolated Yield: 339 mg, 86%.

2-(4-Nitrophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine (4b)

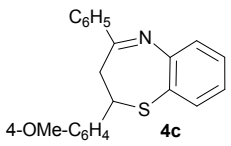


4b

3-(4-Nitrophenyl)-1-phenyl-2-propen-1-one (**1b**). Pale yellow solid; mp 183-184 °C. [lit.[2], 185 °C] AcOEt/PE 15:85. ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.09 (t, J = 12.7 Hz, 1 H), 3.40 (dd, J = 4.9, 12.8 Hz, 1 H), 5.04 (dd, J = 4.8,

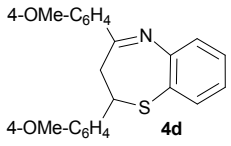
12.5 Hz, 1 H), 7.20–7.26 (m, 1 H), 7.45–7.62 (m, 8 H), 8.18 (d, *J* = 8.7 Hz, 2 H). Isolated Yield: 442 mg, 98%.

2-(4-Methoxyphenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine (4c)



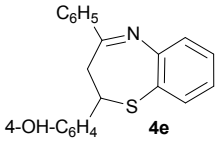
3-(4-Methoxyphenyl)-1-phenyl-2-propen-1-one (**1c**). Pale yellow solid; mp 127-128 °C [lit.[3], 128-130 °C]. AcOEt/PE 30:70. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.05 (t, *J* = 12.7 Hz, 1 H), 3.30 (dd, *J* = 4.7, 12.9 Hz, 1 H), 3.80 (s, 3 H), 4.98 (dd, *J* = 4.7, 12.5 Hz, 1 H), 6.84 (d, *J* = 11.15 Hz, 2 H), 7.15 (t, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 8.6 Hz, 2 H), 7.31 (d, *J* = 7.9 Hz, 1 H), 7.46–7.53 (m, 4 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 8.06 (d, *J* = 7.15 Hz, 2 H). Isolated Yield: 351 mg, 81%.

2-(4-Methoxyphenyl)-4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine (4d)



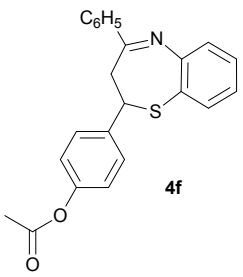
(E)-1,3-bis(4-methoxyphenyl)-2-propen-1-one (**1d**). Yellow solid; mp 107-108 °C [lit.[1], 107-108 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.01 (t, *J* = 12.8 Hz, 1 H), 3.24 (dd, *J* = 4.5, 13.0 Hz, 1 H), 3.79 (s, 3 H), 4.01 (s, 3 H), 4.94 (dd, *J* = 4.3, 12.1 Hz, 1 H), 6.82 (d, *J* = 8.3 Hz, 2 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.20-7.29 (m, 3 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.58 (d, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 7.6 Hz, 2 H). Isolated Yield: 338 mg, 72%.

2-(4-Hydroxyphenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine (4e)



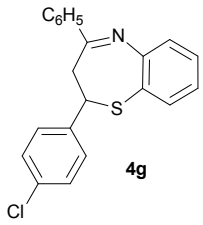
3-(4-Hydroxyphenyl)-1-phenyl-2-propen-1-one (**1e**). Light brown solid; mp 131-134 °C. AcOEt/PE 40:60. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.01 (t, *J* = 12.7 Hz, 1 H), 3.28 (dd, *J* = 4.8, 12.9 Hz, 1 H), 4.95 (dd, *J* = 4.7, 12.5 Hz, 1 H), 5.10 (bs, 1 H), 6.76 (d, *J* = 8.5 Hz, 2 H), 7.18-7.21 (m, 3 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.46-7.55 (m, 4 H), 7.63 (dd, *J* =1.5, 7.7 Hz, 1 H), 8.06 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 37.99 (CH_2), 60.07 (CH), 115.53 (CH), 123.08 (C), 127.40 (CH), 128.79 (CH), 131.17 (CH), 136.54 (C), 141.59 (C), 155.24 (C). IR (KBr): 1599, 2921, 3350 cm^{-1}. MS (ESI): *m/z*= 332.24 $(MH)^+$. Anal. Calcd. for $C_{21}H_{17}NOS$: C, 76.10; H, 5.17; N, 4.23, found: C, 76.21; H, 5.15; N, 4.24. Isolated Yield: 360 mg, 87%.

2-(4-acetoxyphenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine (4f)



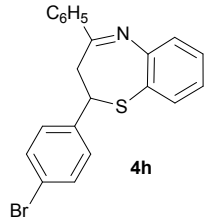
(*E*)-3-[4-(acetyloxy)phenyl]-1-phenyl-2-propen-1-one (**1f**).[4] Yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.32 (s, 3 H), 3.02 (t, *J* = 12.8 Hz, 1 H), 3.32 (dd, *J* = 4.7, 12.9 Hz, 1 H), 4.98 (dd, *J* = 4.7, 12.6 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 7.33-7.39 (m, 3 H), 7.48-7.66 (m, 5 H), 8.07 (d, *J* = 8.19 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 21.17 (CH_3), 37.77 (CH_2), 59.79 (CH), 121.89 (CH), 122.79 (C), 125.52 (CH), 127.20 (CH), 127.58 (CH), 128.87 (CH), 129.92 (CH), 131.40 (CH), 134.97 (CH), 137.26 (C), 141.59 (C), 150.06 (C), 151.95 (C), 169.25 (C), 169.47 (C). IR (KBr): 1604, 1747, 2918 cm^{-1}. MS (ESI): *m/z*= 373.7. Anal. Calcd. for $C_{23}H_{19}NO_2S$: C, 73.97; H, 5.13; N, 3.75, found: C, 74.11; H, 5.14; N, 3.74. Isolated Yield: 421 mg, 90.0%.

2-(4-Chlorophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine (4g)



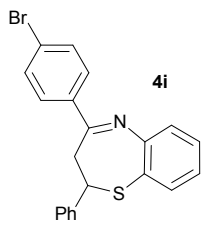
3-(4-Chlorophenyl)-1-phenyl-2-propen-1-one (**1g**). White solid; mp 126-128 °C. [lit.[5], 127-129°C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.03 (t, *J* = 12.8 Hz, 1 H), 3.30 (dd, *J* = 4.8, 12.8 Hz, 1 H), 4.96 (dd, *J* = 4.8, 12.8 Hz, 1 H), 7.16 (t, *J* = 7.4 Hz 1 H), 7.24-7.33 (m, 5 H), 7.47-7.54 (m, 3 H), 7.60 (d, *J* = 7.6 Hz, 2 H), 8.58 (d, *J* = 7.6 Hz, 2 H). Isolated Yield: 319 mg, 73.0%.

2-(4-Bromophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine (4h)



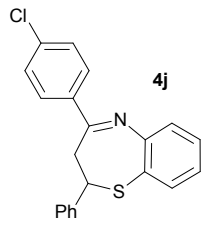
3-(4-Bromoophenyl)-1-phenyl-2-propen-1-one (**1h**). Pale yellow solid; mp 119-121 °C. [lit.[6], 131 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.00 (t, *J* = 12.8 Hz, 1 H), 3.28 (dd, *J* = 4.8, 12.9 Hz, 1 H), 4.93 (dd, *J* = 4.8, 12.5 Hz, 1 H), 7.15-7.22 (m, 3 H), 7.32 (dd, *J* = 1.2, 7.9 Hz, 1 H), 7.44-7.56 (m, 6 H), 7.60 (dd, *J* = 1.3, 7.7 Hz, 1 H), 8.05 (d, *J* = 8.0 Hz, 2 H).[12] TLC**:** R_f = 0.36 (Hexane/Ethyl acetate 8:2). Isolated Yield: 365 mg, 74.0%.

2-Phenyl-4-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepine (4i)



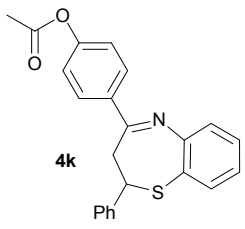
(2*E*)-1-(4-Bromophenyl)-3-phenyl-2-propen-1-one (**1i**). Pale yellow solid; mp 136 °C. [lit.[6], 136 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.05 (t, *J* = 12.7 Hz, 1 H), 3.23 (dd, *J* = 4.9, 13.0 Hz, 1 H), 4.96 (dd, *J* = 4.8, 12.4 Hz, 1 H), 7.14 (td, *J* = 1.5, 7.5 Hz 1 H), 7.28-7.35 (m, 6 H), 7.47 (td, *J* = 1.5, 7.6 Hz 1 H), 7.62 (d, *J* = 8.6 Hz, 3 H), 7.93 (d, *J* = 8.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 37.74 (C), 60.50 (CH_2), 123.34 (C), 125.62 (CH), 126.07 (CH), 128.07 (CH), 128.89 (CH), 129.35 (CH), 129.98 (CH), 132.11 (CH), 135.21 (CH), 143.61 (C), 151.09 (C), 168.90 (C). Isolated Yield: 370 mg, 75.0%.

4-(4-Chlorophenyl)-2-phenyl-2,3-dihydro-1,5-benzothiazepine (4j)



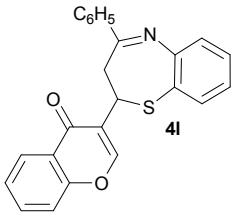
(2*E*)-1-(4-Chlorophenyl)-3-phenyl-2-propen-1-one (**1j**). White solid; mp 132-133 °C. [lit.[6], 132 °C]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.05 (t, *J* = 12.8 Hz, 1 H), 3.25 (dd, *J* = 4.8, 13.1 Hz, 1 H), 4.97 (dd, *J* = 4.8, 12.4 Hz, 1 H), 7.16 (td, *J* = 1.2, 15.1 Hz 1 H), 7.28-7.34 (m, 6 H), 7.46-7.50 (m, 3 H), 7.62 (dd, *J* = 1.1, 7.65 Hz, 1 H), 7.99 (d, *J* = 8.6 Hz, 2 H).[12] Isolated Yield: 398 mg, 91.0%.

4-(4-acetoxyphenyl)-2-phenyl-2,3-dihydro-1,5-benzothiazepine (4k)



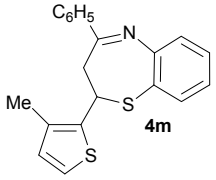
1-[4-(Acetyloxy)phenyl]-3-phenyl-2-propen-1-one (**1k**).[7] Yellow solid; mp 141-144 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.32 (s, 3 H), 3.05 (t, *J* = 12.8 Hz, 1 H), 3.28 (dd, *J* = 4.8, 13.0 Hz, 1 H), 4.98 (dd, *J* = 4.8, 13.0 Hz, 1 H), 7.14 (td, *J* = 1.4, 7.5 Hz, 1 H), 7.23-7.31 (m, 8 H), 7.48-7.52 (m, 1 H), 7.63 (dd, *J* = 1.4, 7.7 Hz, 1 H), 8.10 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 21.213 (CH_3), 37.6 (CH_2), 60.4 (CH), 121.9 (CH), 125.4 (CH), 126.0 (CH), 127.9 (CH), 128.8 (CH), 129.8 (CH), 135.1 (CH), 144.0 (C), 152.3 (C), 153.0 (C), 168.0 (C), 169.2 (C). IR (KBr): 1596, 1751, 2919 cm^{-1}. MS (ESI): *m/z*= 374.43 $(MH)^+$. Anal. Calcd. for $C_{23}H_{19}NO_2S$: C, 73.97; H, 5.13; N, 3.75, found: C, 74.09; H, 5.14; N, 3.76. Isolated Yield: 327 mg, 70%.

3-(2,3-Dihydro-4-phenyl-1,5-benzothiazepin-2-yl)-4*H*-1-benzopyran-4-one (4l)



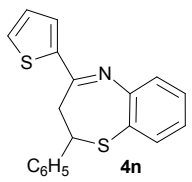
3-[(*1E*)-3-Oxo-3-phenyl-1-propen-1-yl]-*4H*-1-benzopyran-4-one (**1l**). Pale yellow solid; mp 123-125 °C. AcOEt/hexane 30:70. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.49 (t, *J* = 12.5 Hz, 1 H), 3.60 (dd, *J* = 4.6, 12.6 Hz, 1 H), 5.22 (dd, *J* = 4.5, 12.3 Hz, 1 H), 7.06 (t, *J* = 7.6 Hz 1 H), 7.27-7.48 (m, 7 H), 7.59-7.65 (m, 2 H), 8.17-8.32 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 35.32 (CH_2), 51.58 (CH), 118.21 (CH), 122.53 (C), 123.55 (C), 125.45 (CH), 126.05 (C), 128.25 (CH), 129.03 (CH), 129.87 (CH), 130.15 (CH), 132.03 (CH), 133.98 (CH), 135.07 (CH), 136.17 (CH), 136.18 (C), 154.25 (CH), 154.32 (C), 156.33 (C), 170.55 (C), 176.50 (C). IR (KBr): 1596, 1753, 2918 cm^{-1}. MS (ESI): *m/z*= 384.19 $(MH)^+$. Anal. Calcd for $C_{24}H_{17}NO_2S$: C, 75.17; H, 4.47; N, 3.65, found: C, 75.01; H, 4.45; N, 3.66, Isolated Yield: 197 mg, 41%.

2-(3-Methylthiophen-2-yl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine (4m)



(2*E*)-3-(3-methyl-2-thienyl)-1-phenyl-2-propen-1-one (**1m**). Yellow solid; mp 120-124 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.26 (s, 3 H), 2.95 (t, *J* = 12.8 Hz, 1 H), 3.37 (dd, *J* = 4.9, 12.9 Hz, 1 H), 5.32 (dd, *J* = 4.8, 12.5 Hz, 1 H), 6.81 (d, *J* = 5.1 Hz, 1 H), 7.07 (d, *J* = 5.0 Hz, 1 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.31 (d, *J* = 8.9 Hz, 1 H), 7.47-7.63 (m, 5 H), 8.06 (d, *J* = 7.9 Hz, 2 H) ^{13}C NMR ($CDCl_3$, 75 MHz): 14.04 (CH_3), 38.18 (CH_2), 53.78 (CH), 122.91 (CH), 125.73 (CH), 126.59 (CH), 128.34 (CH), 128.65 (CH), 129.12 (CH), 129.89 (CH), 130.30 (CH), 132.54 (CH), 135.85 (CH). MS (ESI): *m/z*= 336.36 $(MH)^+$. IR (KBr): 1608, 2918 cm^{-1}. Anal. Calcd for $C_{20}H_{17}NS_2$: C, 71.60; H, 5.11; N, 4.18, found: C, 71.65; H, 5.10; N, 4.19. Isolated Yield: 252 mg, 60%.

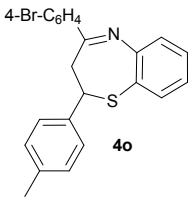
2-Phenyl-4-(Thiophen-2-yl)-2,3-dihydro-1,5-benzothiazepine (4n)



(2*E*)-3-(2-thienyl)-1-phenyl-2-propen-1-one (**1n**). Pale yellow solid. mp 123-125 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.06 (t, *J* = 12.6 Hz, 1 H), 3.23 (dd, *J* = 4.7, 12.8 Hz, 1 H), 5.03 (dd, *J* = 4.7, 12.0 Hz, 1 H), 7.08-7.14 (m, 2 H), 7.19-7.31 (m, 6 H), 7.37-7.42 (m, 1 H), 7.50-7.57 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 38.9 (CH_2), 60.3 (CH), 123.8 (C), 125.8 (CH), 126.1 (CH), 128.0 (CH), 128.8 (CH),

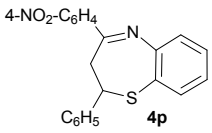
129.9 (CH), 132.1 (CH), 135.1 (CH), 143.6 (C), 164.1 (C). IR (KBr): 1600, 2920 cm^{-1}. Anal. Calcd for $C_{19}H_{15}NS_2$: C, 70.99; H, 4.70; N, 4.36, found: C, 71.15; H, 4.70; N, 4.37. Isolated Yield: 253 mg, 63%.

2-(4-Methylphenyl)-4-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepine (4o)



(2*E*)-1-(4-Bromophenyl)-3-(4-methylphenyl)-2-propen-1-one (**1o**). Pale yellow solid; mp 128-130 °C. AcOEt/PE 5/95. ^{1}H NMR ($CDCl_3$, 300MHz): δ = 2.37 (s, 3 H), 3.03 (t, *J* = 12.8 Hz, 1 H), 3.21 (dd, *J* = 4.9, 13.0 Hz, 1 H), 4.94 (dd, *J* = 4.9, 12.3 Hz, 1 H), 7.12-7.22 (m, 5 H), 7.29 (dd, *J* = 1.5, 7.9 Hz, 1 H), 7.46 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.61-7.66 (m, 3 H), 7.91-7.96 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 21.16 (CH_3), 38.08 (CH_2), 60.24 (CH), 123.96 (C), 125.72 (CH), 125.91 (CH), 126.03 (CH), 126.69 (CH), 129.56 (CH), 129.64 (CH), 129.68 (CH), 129.77 (CH), 129.95 (CH), 130.09 (CH), 132.26 (CH), 135.31 (CH), 138.05 (C), 140.48(C). MS (ESI): *m/z*= 408.26 $(MH)^+$. IR (KBr): 1606, 2920 cm^{-1}. Anal. Calcd for $C_{22}H_{18}BrNS$: C, 64.71; H, 4.44; N, 3.43, found: C, 64.85; H, 4.45; N, 3.44. Isolated Yield: 332 mg, 65%.

4-(4-Nitrophenyl)-2-phenyl-2,3-dihydro-1,5-benzothiazepine (4p)



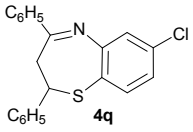
(2*E*)-1-(4-Nitrophenyl)-3-phenyl-2-propen-1-one (**1p**). Yellow solid; mp 123-125 °C. [lit.[1], 116-118 °C]. AcOEt/PE 10/90. ^{1}H NMR ($CDCl_3$, 300MHz): δ = 3.10 (t, *J* = 13.1 Hz, 1 H), 3.29 (dd, *J* = 5.0, 13.2 Hz, 1 H), 5.03 (dd, *J* = 5.0, 12.0 Hz, 1 H), 7.19 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.25-7.37 (m, 6 H), 7.50 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.66 (dd, *J* = 1.5, 7.7 Hz, 1 H), 8.19-8.24 (m, 2 H), 8.32-8.37 (m 2 H). Isolated Yield: 311 mg, 69%.

4. General procedure for the synthesis of 2,3-dihydro-1,5-benzothiazepine 4q-r

To a stirred solution of chalcone **1a** (260 mg, 1.25 mmol) in HFIP (1.50 mL) at 28 °C, **2b**[8] (399 mg, 2.50 mmol) or **2c**[8] (348 mg, 2.50 mmol) was added. After completion of the reaction (monitored by TLC) the solvent was removed by distillation and the product was purified by column chromatography on silica gel (hexane/ethyl acetate 80:20 unless otherwise noted).

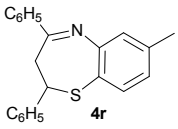
The starting chalcone, aminothiol, physical, spectroscopic and analytical data of compounds **4q-r** are as follows.

7-Chloro-2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine (4q)



(2*E*)-1,3-Diphenyl-2-propen-1-one (**1a**) and 2-amino-4-chlorobenzenethiol (**2b**). Pale yellow solid; mp 144-146 °C. [lit.[9], 132-134 °C]. AcOEt/PE 5/95. ^{1}H NMR ($CDCl_3$, 300MHz): δ = 3.08 (t, *J* = 12.8 Hz, 1 H), 3.35 (dd, *J* = 4.8, 13.0 Hz, 1 H), 5.01 (dd, *J* = 4.8, 12.6 Hz, 1 H), 7.14 (dd, *J* = 2.3, 8.3 Hz, 1 H), 7.29-7.34 (m, 6 H), 7.48-7.58 (m, 4 H), 8.09-8.05 (m, 2 H). Isolated Yield: 149 mg, 34%.

7-Methyl-2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine (4r)



(2*E*)-1,3-Diphenyl-2-propen-1-one (**1a**) and 2-amino-4-methylbenzenethiol (**2c**). Pale yellow solid; mp 149-153 °C. AcOEt/PE 5/95. ^{1}H NMR ($CDCl_3$, 300MHz): δ = 2.46 (s, 3 H), 3.09 (t, *J* = 12.8 Hz, 1 H), 3.33 (dd, *J* = 4.8, 12.9 Hz, 1 H), 4.99 (dd, *J* = 4.8, 12.6 Hz, 1 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 7.19 (s, 1 H), 7.28-7.35 (m, 5 H), 7.48-7.58 (m, 4 H), 8.08-8.11 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 21.38 (CH_3), 37.90 (CH_2), 60.35 (CH), 119.79 (C), 127.80 (CH), 128.00 (CH), 128.04 (CH), 128.25 (CH), 128.37 (CH), 128.57 (CH), 131.38 (CH), 134.95 (CH), 137.36 (C), 140.20 (C), 144.17 (C), 151.68 (C), 169.46 (C). IR (KBr): 1591, 2899 cm^{-1}. MS (ESI): *m/z*= 330.39 $(MH)^+$. Anal. Calcd for $C_{22}H_{19}NS$: C, 80.20; H, 5.81; N, 4.25, found: C, 80.25; H, 5.84; N, 4.26. Isolated Yield: 383 mg, 93%.

5. Reaction scale-up and solvent reuse

To a stirred solution of chalcone **1a** (2.50 g, 12 mmol) in HFIP (15.0 mL, 12 eq) at 28 °C, **2** (3.00 g, 24 mmol) was added. After completion of the reaction (monitored by TLC) the solvent was recovered by distillation at atmospheric pressure (13.5 mL, 90%). The residue was purified by column chromatography on silica gel to give **4a** (3.44 g, 91%) as white solid (Table 1, entry 1). The recovered solvent was added with HFIP (1.5 mL) to restore initial conditions. Reagents **1a** and **2** were also added to carry out the second run (Table 1, entry 2). The same procedure was followed for a third run (Table 1, entry 3).

Table 1

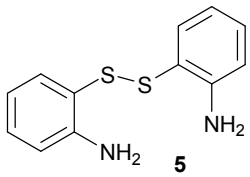
	1a (mmol)	HFIP (mL)	Yield (%)	HFIP recovered (%)	Fresh added HFIP (mL)	HFIP used (mL/mmol **4a**)
1	12	15	91	90	–	1.37
2	12	15	90	92	1.5	0.14
3	12	15	92	93	1.2	0.11

E-factor

1a (12 mmol, 2.50 g) +
2a (24 mmol, 3.00 g) +
HFIP (15 mL, 23.94 g)

⟶

4a (10.92 mmol, 3.44 g)
5 (11.5 mmol, 2.86 g)



5

E_1 = amount of waste/amount of product = [(2.50 + 3.00 + 23.94) – 3.44]/3.44 = 7.6

E_2 (with 90% HFIP recovery) = amount of waste/amount of product = [(2.50 + 3.00 + 23.94) – 23.94 x 0.9 + 3.44]/3.44 = (29.44 - 24.99)/3.44 = 1.3

6. References

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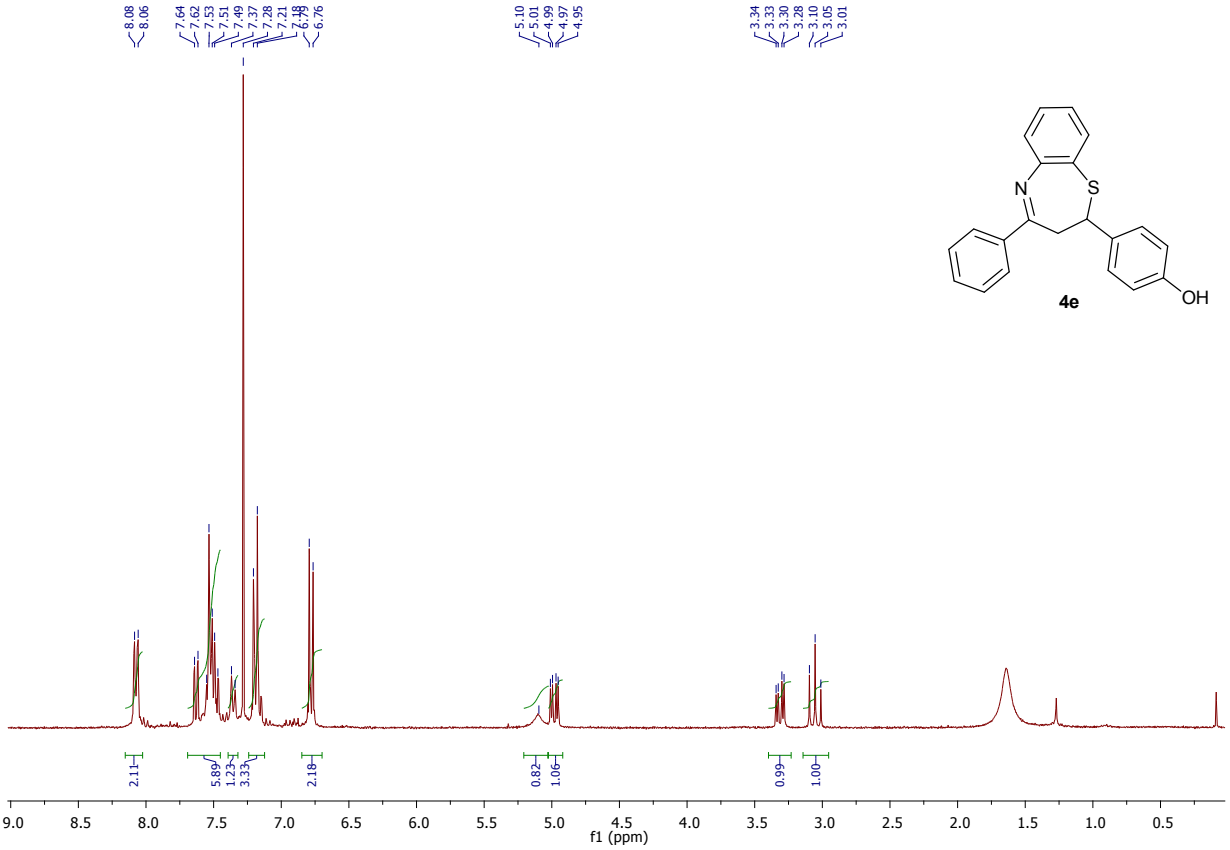
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7.62
7.53
7.51
7.49
7.37
7.28
7.21
6.76
5.10
5.01
4.99
4.97
4.95
3.34
3.33
3.30
3.28
3.10
3.05
3.01
N
S
OH
4e
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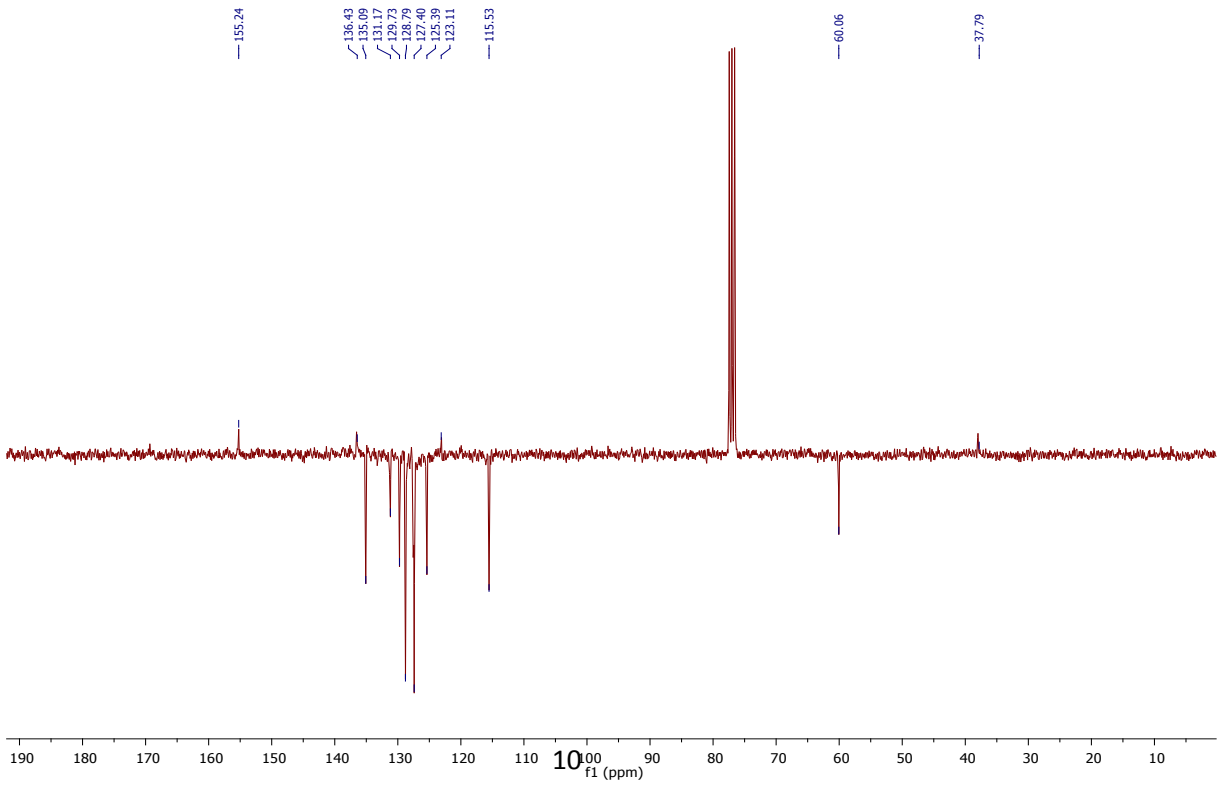
5.89
1.23
3.33
2.18
0.82
1.06
0.99
1.00
f1 (ppm)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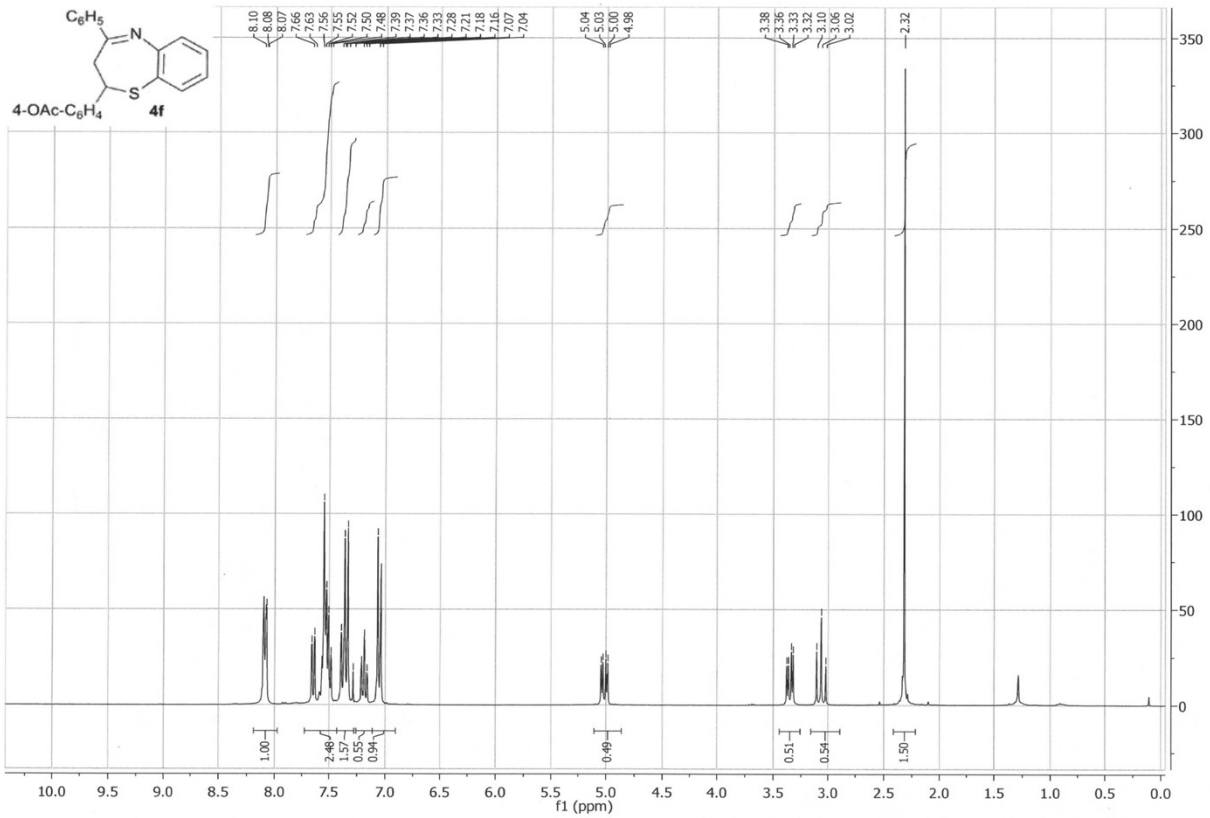
115.53
60.06
37.79
f1 (ppm)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S
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8.08
8.07
7.66
7.63
7.56
7.55
7.52
7.50
7.48
7.39
7.37
7.36
7.33
7.28
7.21
7.18
7.16
7.07
7.04
5.04
5.03
5.00
4.98
3.38
3.36
3.33
3.32
3.10
3.06
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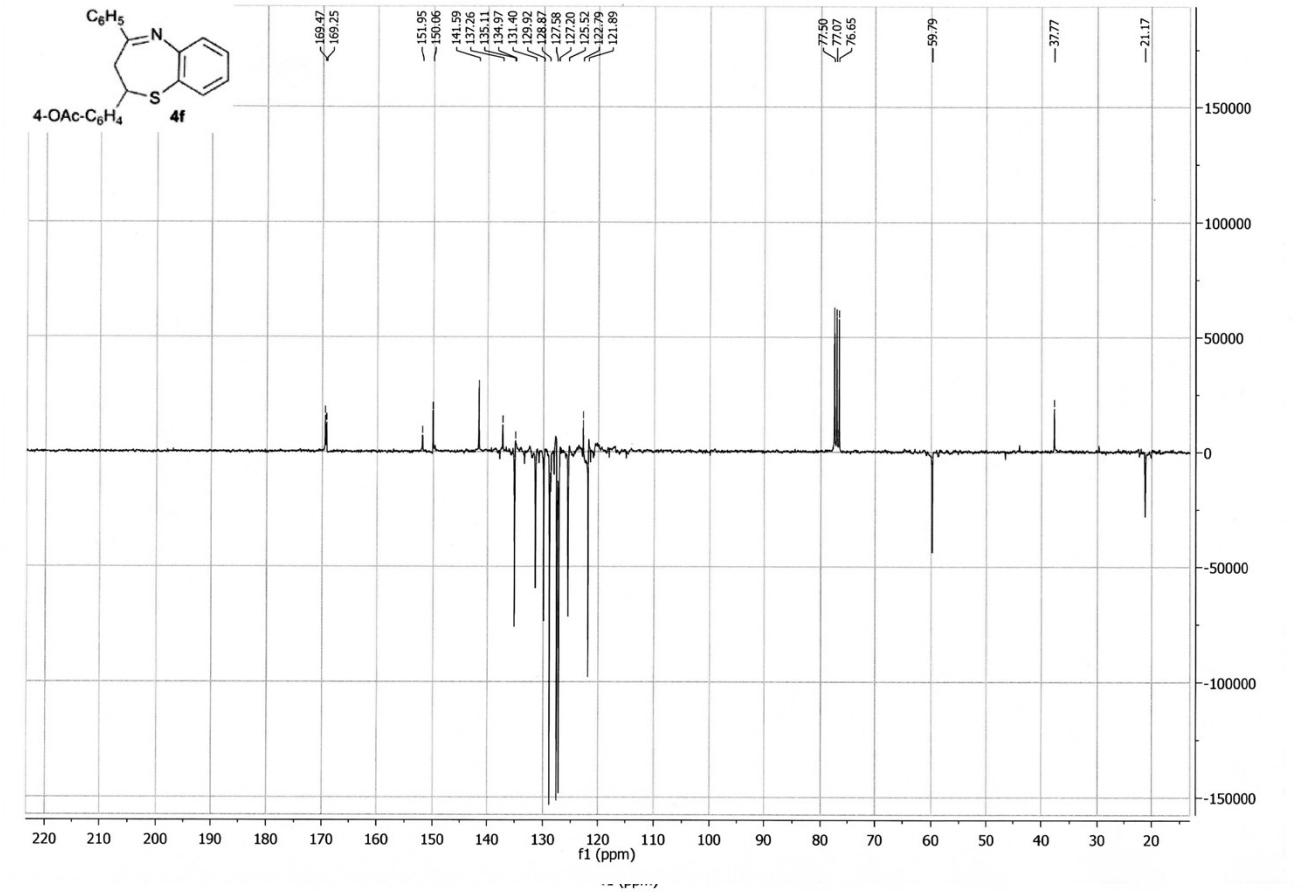
f1 (ppm)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4-OAc-C6H4
4f
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169.25
151.95
150.06
141.59
137.26
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134.97
131.40
129.92
128.87
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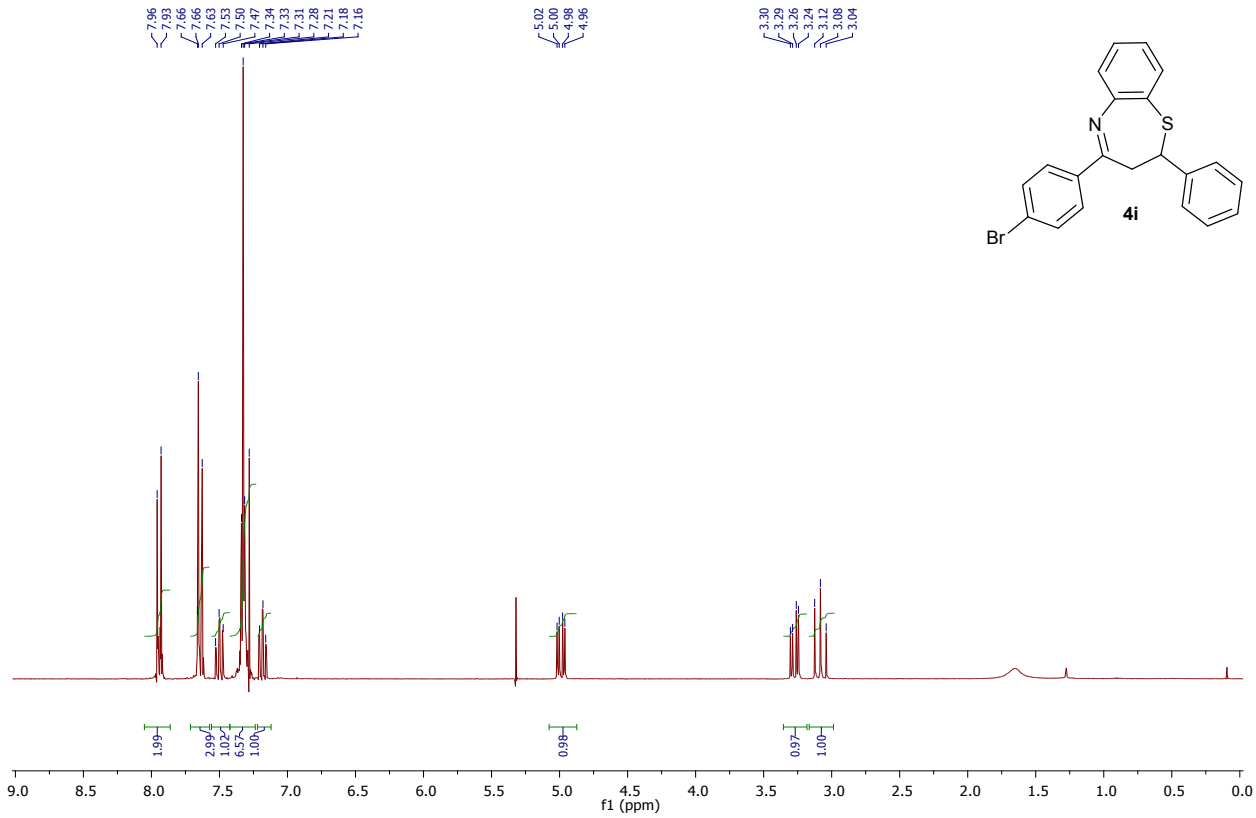
122.79
121.89
77.50
77.07
76.65
59.79
37.77
21.17
f1 (ppm)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7.33
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5.00
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3.29
3.26
3.24
3.12
3.08
3.04
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1.02
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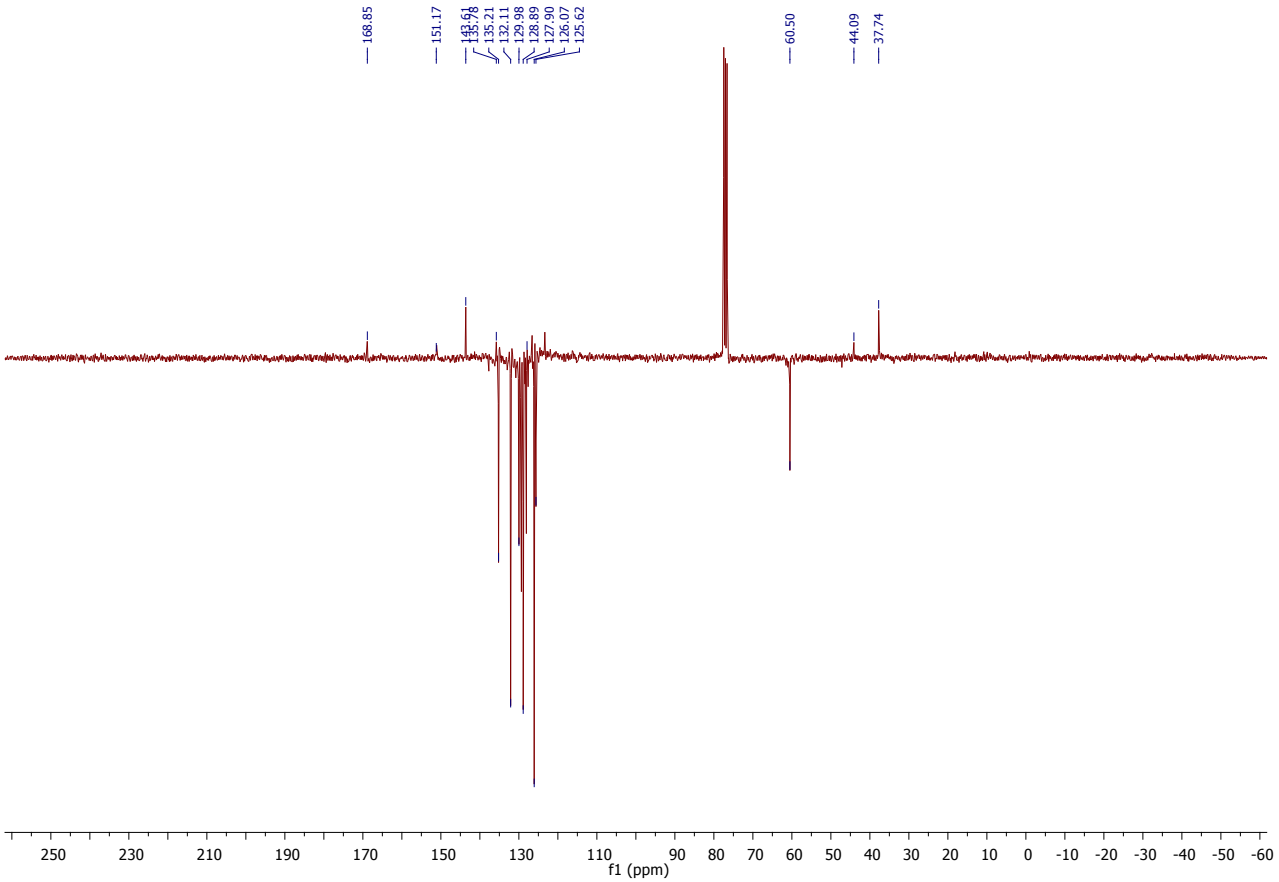
0.97
1.00
f1 (ppm)

N
S
Br

4i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126.07
125.62
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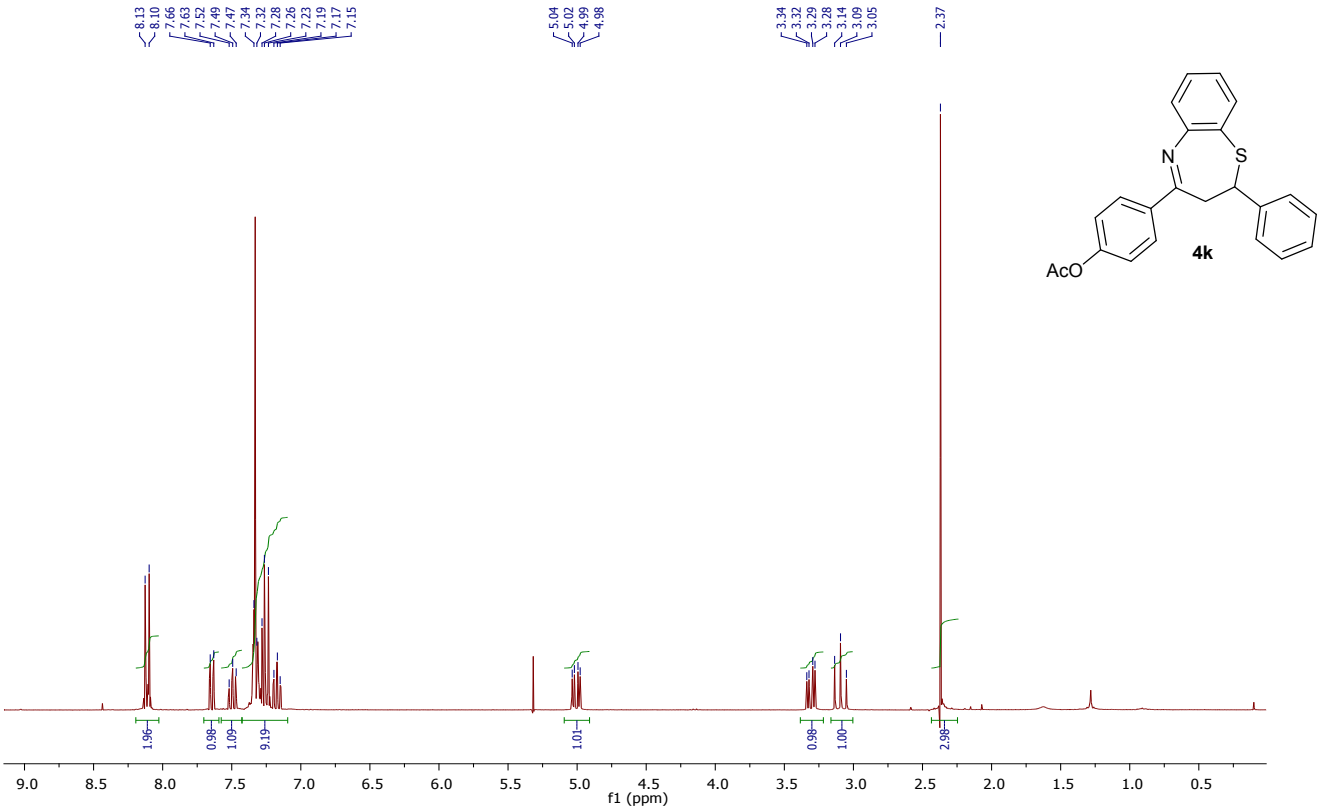
44.09
37.74
f1 (ppm)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7.66
7.63
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7.47
7.34
7.32
7.28
7.26
7.23
7.19
7.17
7.15
5.04
5.02
4.99
4.98
3.34
3.32
3.29
3.28
3.14
3.09
3.05
2.37
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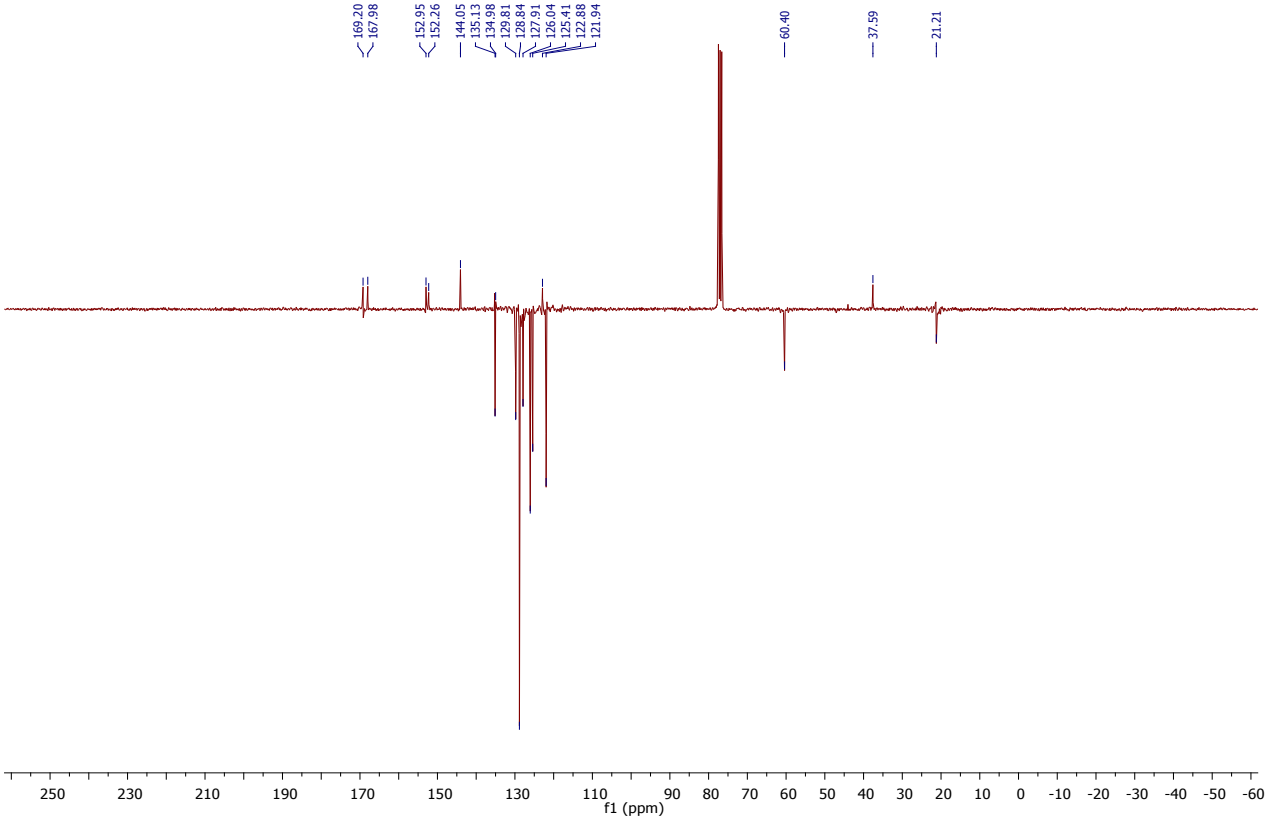
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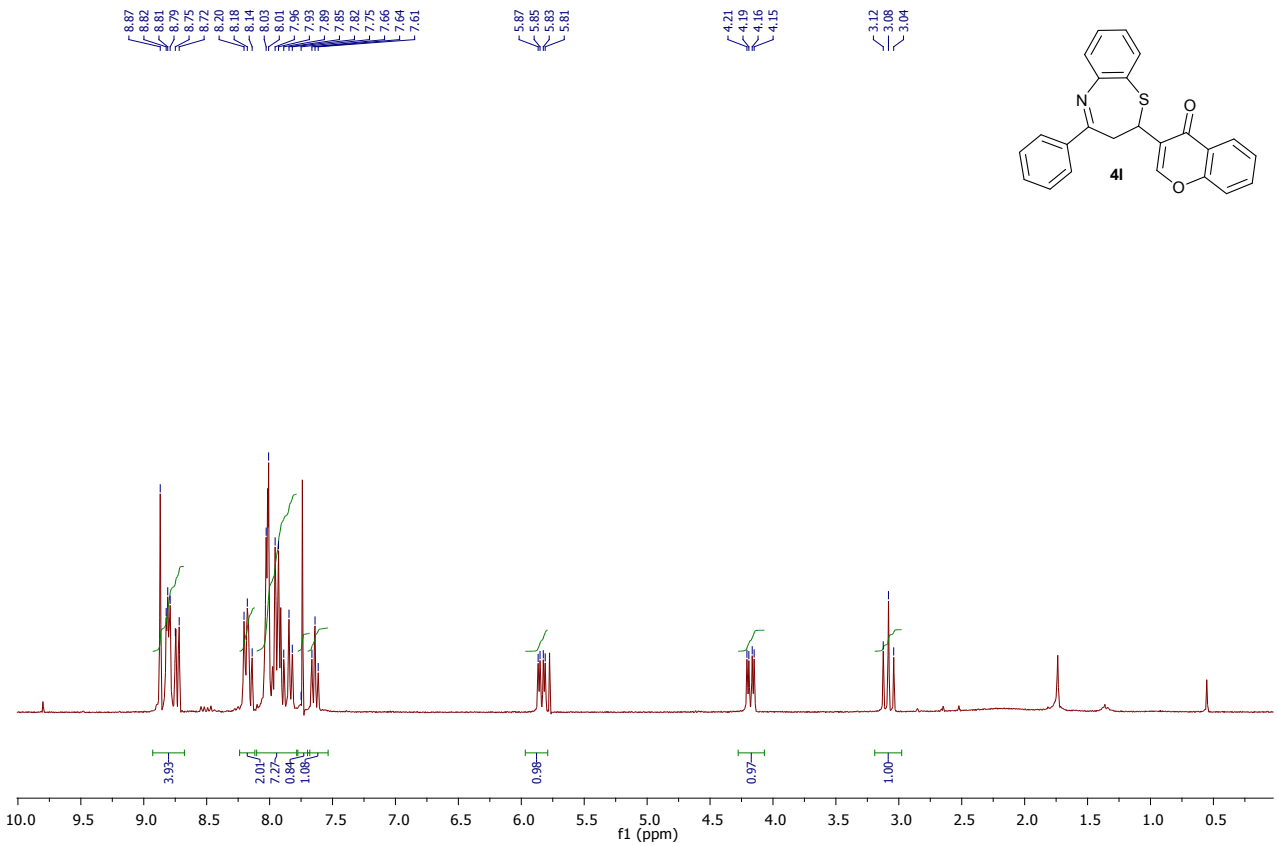
f1 (ppm)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8.03
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4.15
3.12
3.08
3.04
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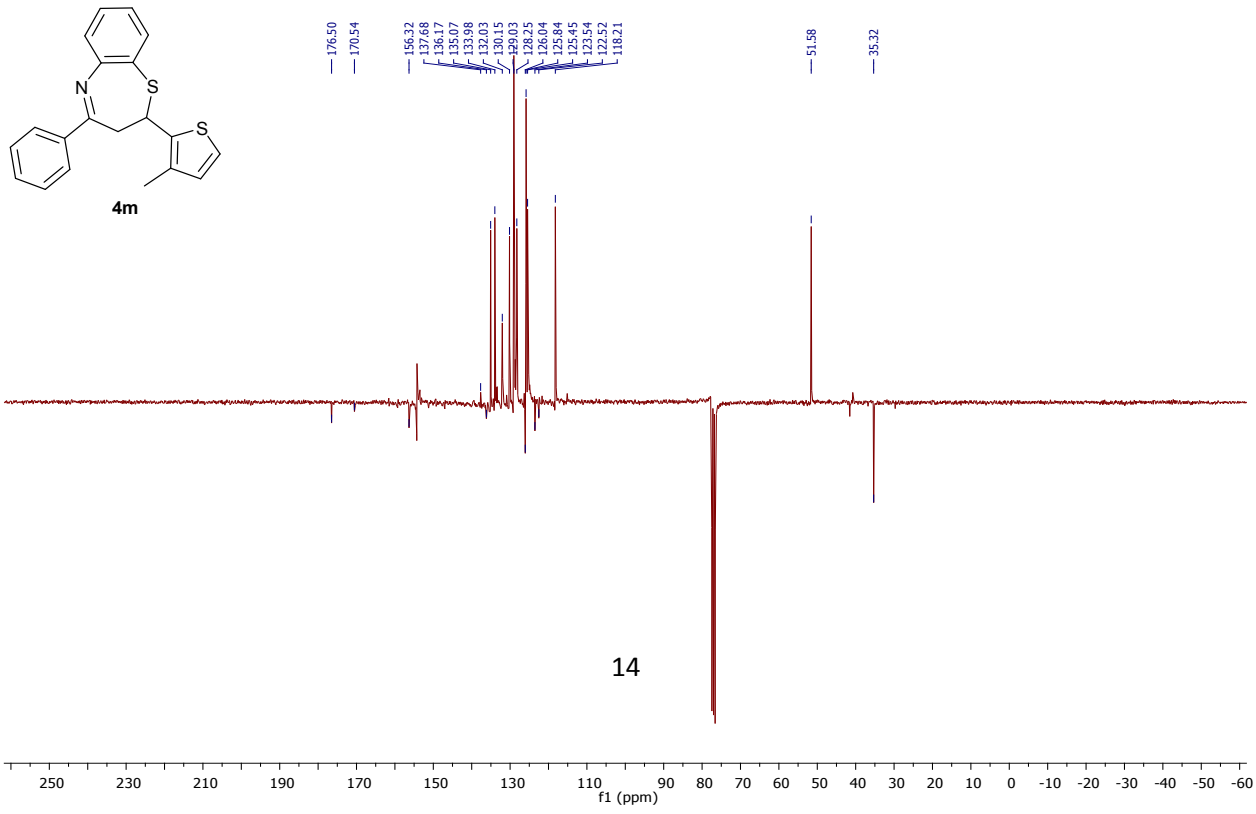
S
O
O
4l
3.93
2.01
7.27
0.84
1.08
0.98
0.97
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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128.25
126.04
125.84
125.45
123.54
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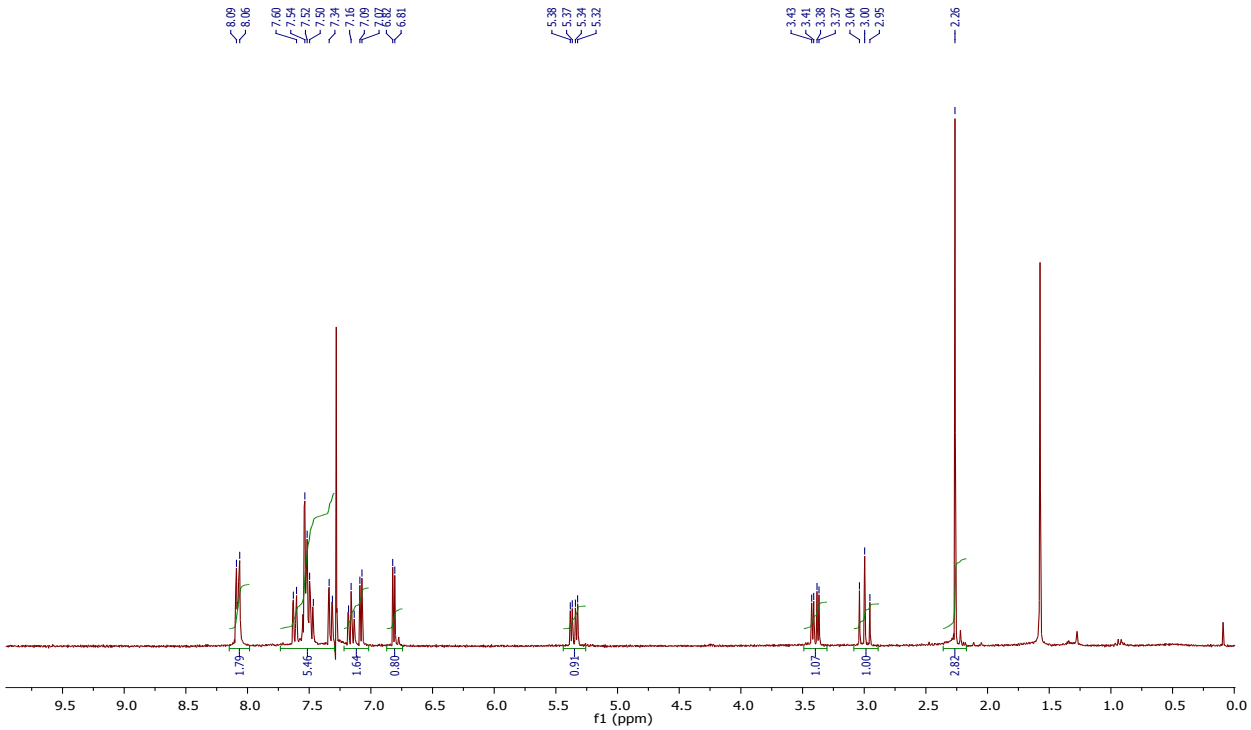
51.58
35.32
250 230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60
f1 (ppm)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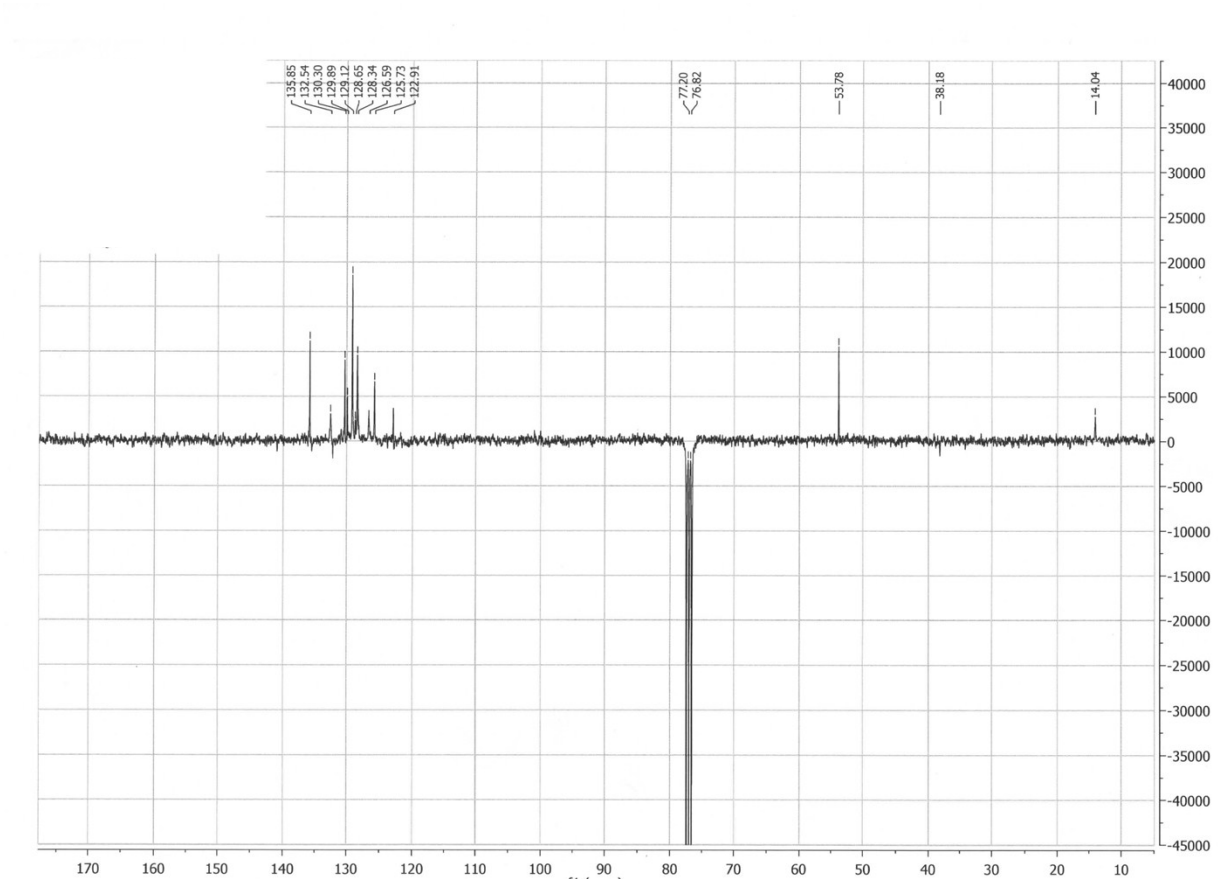
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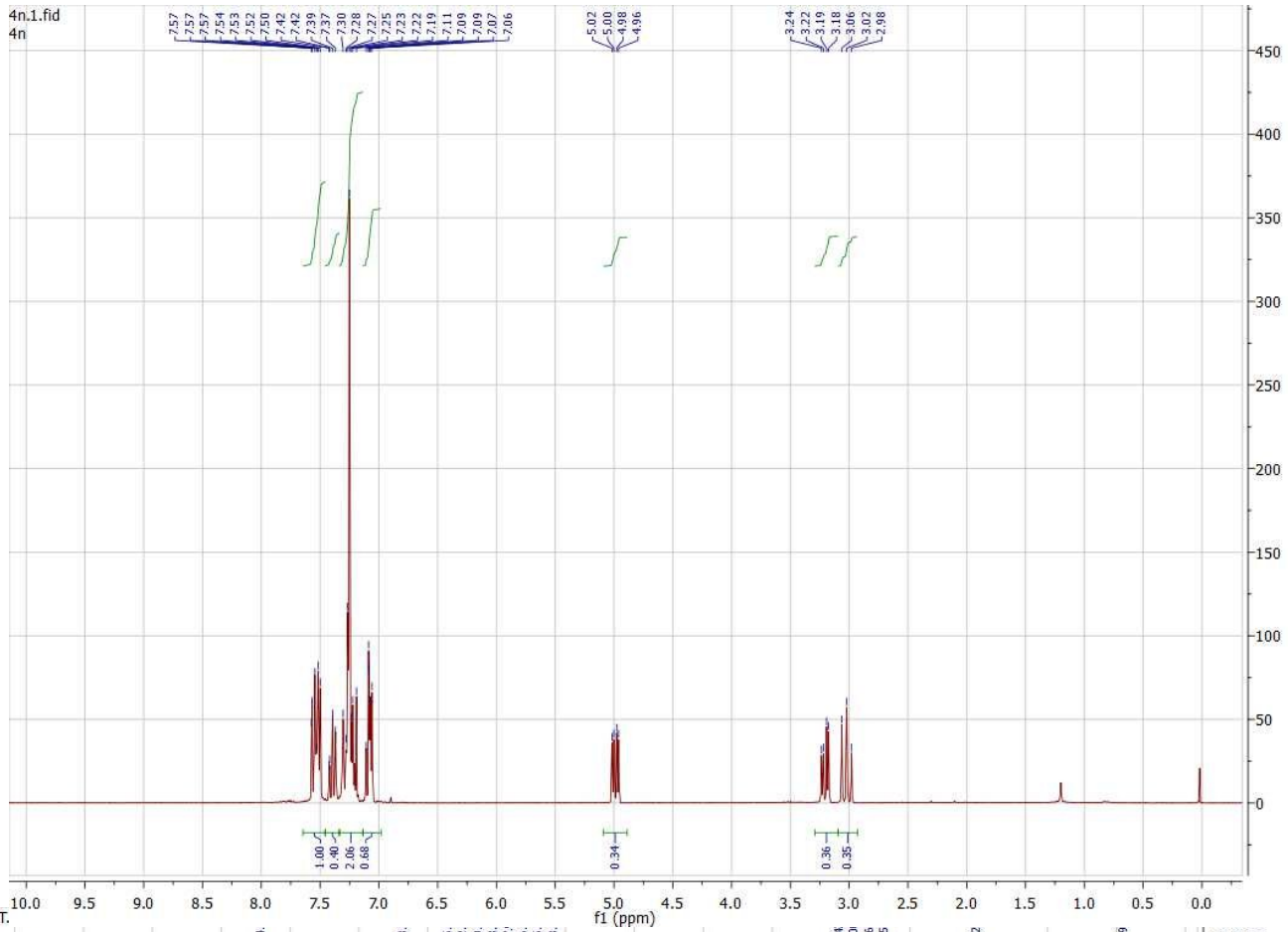
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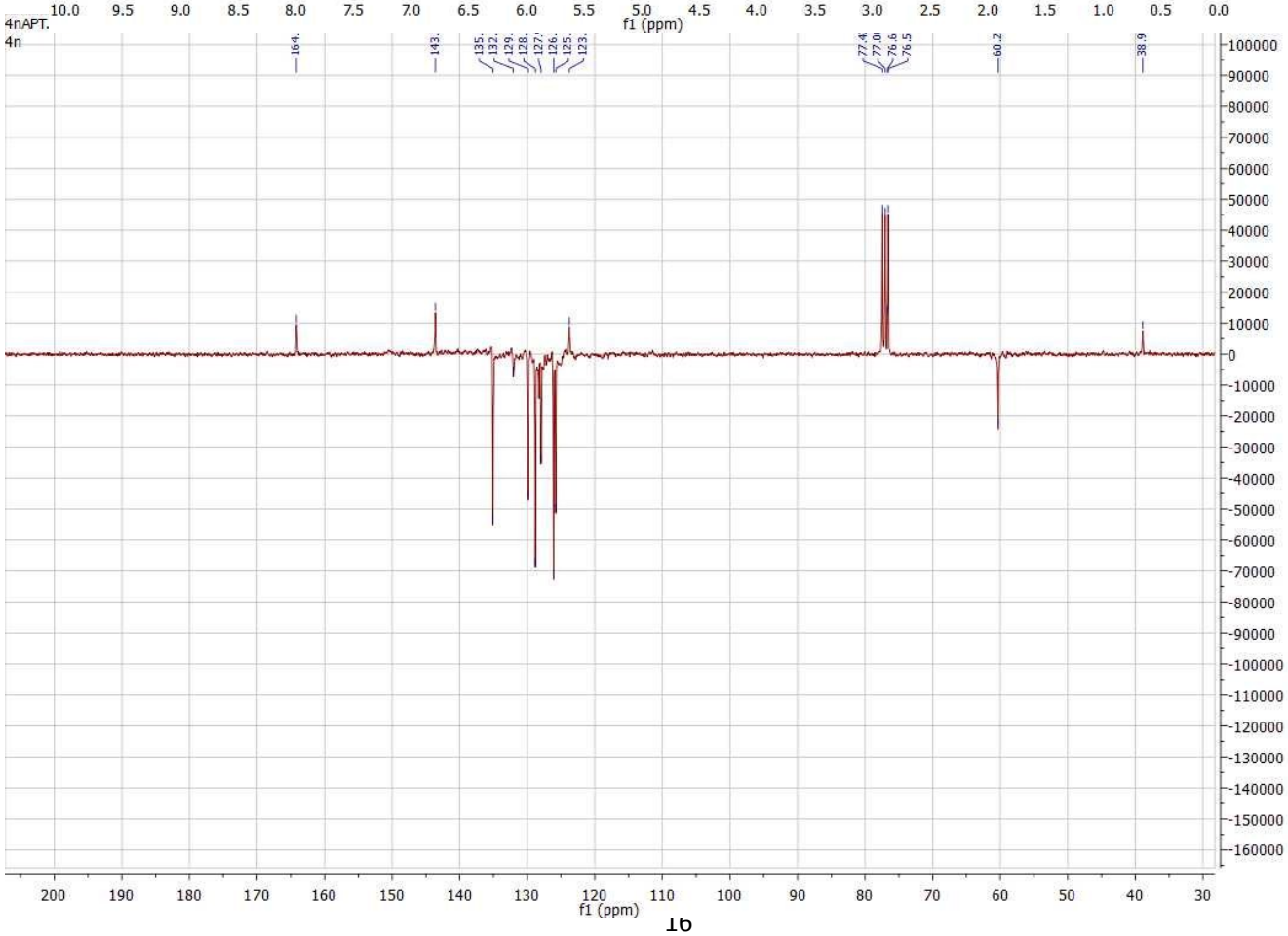
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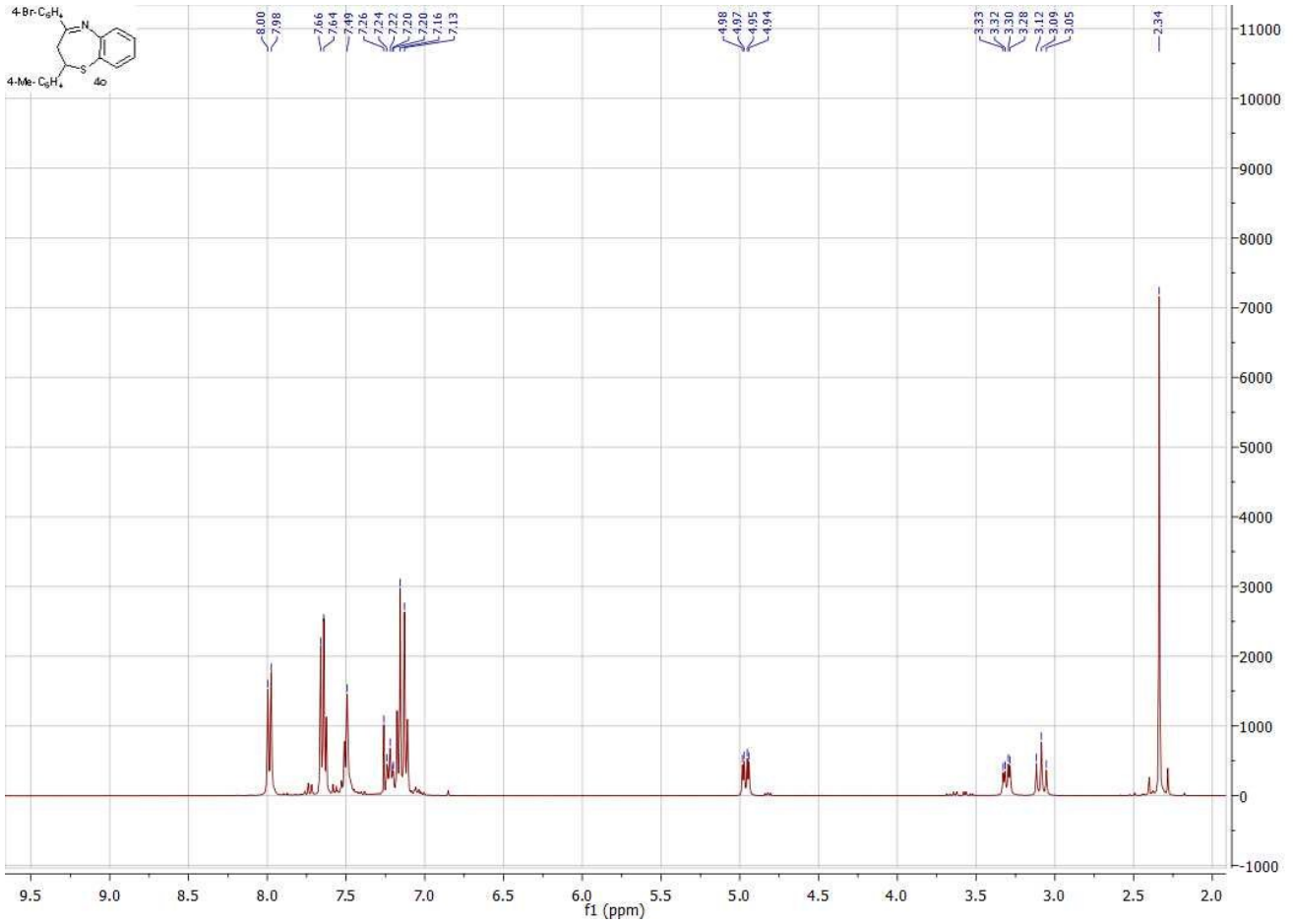
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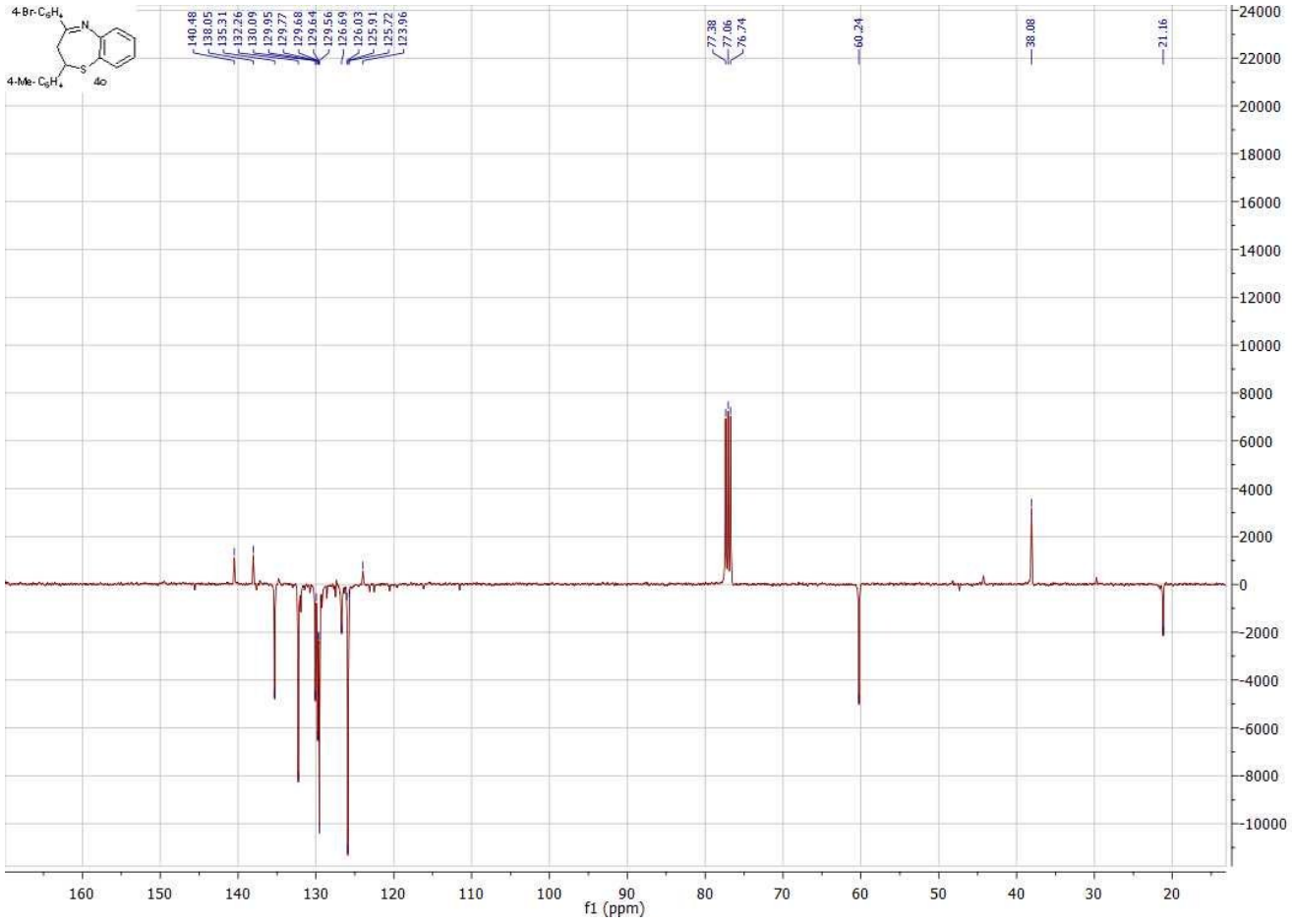
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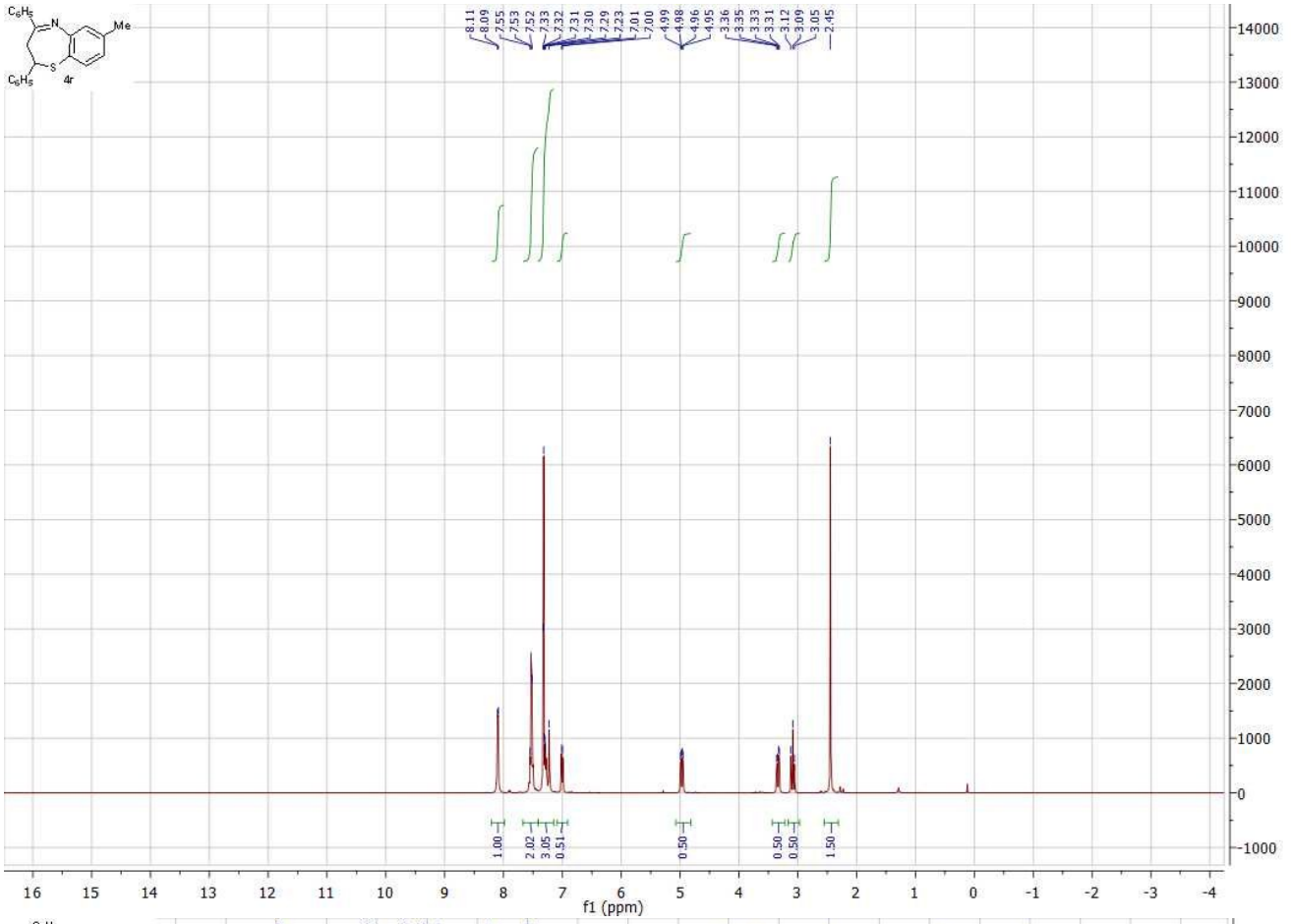
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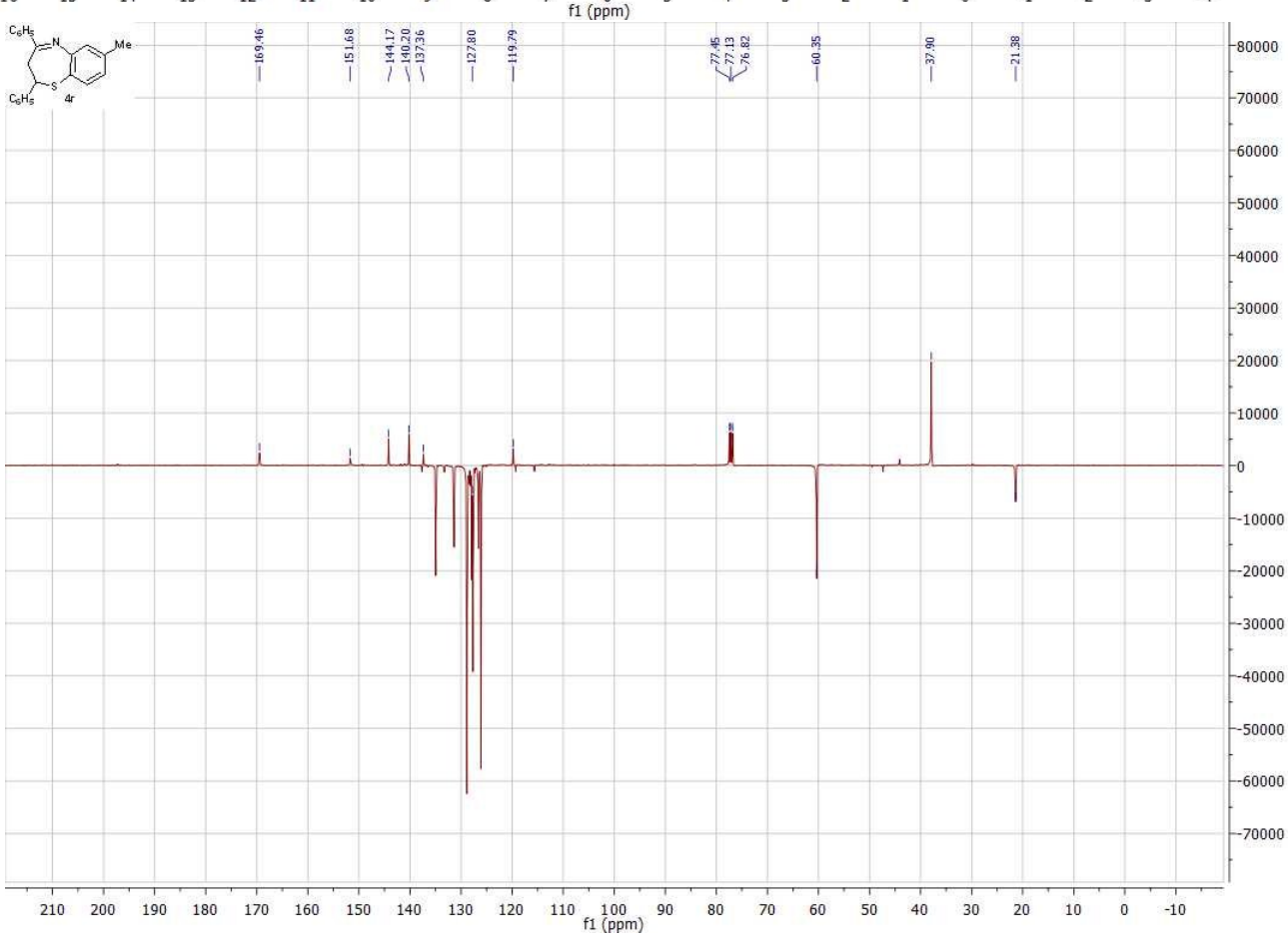
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