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Supporting Information

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Palladium-Catalyzed One-Pot Three-Component Coupling Reaction Approach to Promazine via Formation of one Carbon-Sulfur and two Carbon-Nitrogen Bonds

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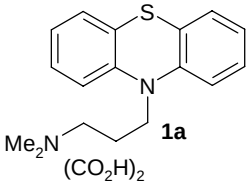
General Methods. Reactions were conducted using either 4mL screw-cap vials sealed with caps fitted with a PTFE septum (oilbath experiments) or using standard 5mL microwave-reactors from Personal Chemistry (microwave and 'alublock' experiments). Microwave experiments were performed on a Emrys Optimizer from Personal Chemistry or a Advancer Microwave Synthesizer from Biotage. Spectroscopic data and combustion analyses or high resolution MS-analyses are reported for all new compounds. Previously reported products were isolated in greater than 95% purity as determined by ^{1}H NMR. Combustion analyses or HRMS-analyses are reported for all compounds. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, C_6D_6, or d_6-DMSO on a Bruker Avance AV-500 instrument. Chemical shifts are reported in ppm relative to TMS (^{1}H) and residual solvent (^{13}C), respectively. Coupling constants are reported in Hertz (Hz). All ^{13}C NMR spectra were proton decoupled. Melting points are uncorrected. Thin layer chromatography was performed on aluminium plates precoated with silica gel (Merck; 60 F_{254}). Compounds were visualized by illumination using a UV lamp (254nm) or by charring after dipping in a solution of ammonium molybdate (6.25g) and cerium(IV)sulfate (2.5g) in 10% aq. sulphuric acid (250mL). Chromatographic purifications were performed by flash chromatography using silica gel (Machery-Nagel 60 M; 0.04-0.063 mm, 230-400 mesh). GC was performed on a Shimadzu GC-2010 instrument equipped with a Supelco Equity-1 fused silica capillary column (30mm x 0.25mm x 0.25μm) and a AOC-20i auto injector and a AOC-20s auto sampler. Elemental analyses were conducted either by dr. Johannes Theiner (Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna, Austria) or by the Analytical R&D Department, H. Lundbeck A/S. High-resolution MS was performed by Dr. Kenneth B. Nielsen (Department of Chemistry, University of Southern Denmark in Odense, Denmark) or by Dr. Henrik Pedersen (Medicinal Chemistry Research, H. Lundbeck A/S). All chemicals were purchased from Sigma-Aldrich or Strem Chemicals except 3-bromo-4-iodotoluene (purchased from ABCR) and used as received. Diphenyl sulfide (**7b**) was purchased from Aldrich. Toluene was dried over sodium wire or 4Å MS. All chemicals were weighed and handled in air, and no precautions were taken to exclude air from the reaction mixtures except when noted otherwise.

Abbreviations: DavePhos = 2'-dimethylamino-2'-dicyclohexylphosphinobiphenyl; dba=dibenzylidenacetone; BINAP=2,2'-bis(diphenylphosphino)-1,1'-binaphtyl; DPEphos=bis(2-diphenylphosphinophenl)ether; Xantphos = 9,9-dimethyl-4,5-bis(diphenyl-phosphino)xanthene; DPPF=di(bisphenylphosphino)ferrocene; X-phos = 2',4',6'-tri-*i*-propyl-2-dicyclohexylphosphinobiphenyl.



1a

Method A / Microwave Experiments (promazine 1a, Table 1, Entry 1). Pd_2dba_3 (69mg, 0.075mmol), DPPF (166mg, 0.10mmol) and NaO*t*-Bu (1.15g, 12.0mmol) were added to a 20mL microwave vial. Toluene (15.0mL) was added followed by

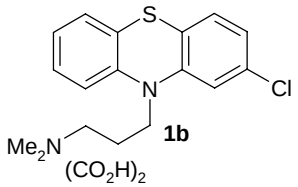
2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), 2-bromo-iodobenzene **4a** (849mg, 386μL, 3.0mmol) and 3-dimenthylamino-1-propylamine **3** (307mg, 378μL, 3.0mmol). The mixture was heated at 60°C (fixed hold-time) for 20min under microwave irradiation followed by 2h at 160°C (fixed hold-time). The crude mixture was purified by column flash chromatography (9:1 EtOAc:Et_3N) to afford 628mg (74%) of the title compound as a brown oil. The product was dissolved in acetone and crystallized as the white oxalic acid salt. mp 173°C (lit.[3] 173-175°C). R_f 0.41 (9:1 EtOAc:Et_3N). ^{1}H NMR (d_6-DMSO, 500MHz): δ 7.23 (broad dd, *J*=7.53Hz, *J*=8.00Hz, 2H) 7.19 (broad d, *J*=7.07Hz, 2H), 7.08 (broad d, *J*=8.00Hz, 2H), 6.98 (broad dd, *J*=7.07Hz, *J*=7.53Hz, 2H), 3.95 (t, *J*=6.59Hz, 2H), 3.10 (t, *J*=7.07Hz, 2H), 2.68 (s, 6H), 2.06 (broad s, 2H). ^{13}C NMR (d_6-DMSO, 125MHz): δ 164.63, 144.85 (2C), 128.05 (2C), 127.60 (2C), 124.26 (2C), 123.12 (2C), 116.28 (2C), 54.87, 44.14, 42.74 (2C), 22.07. Anal. Calc'd for $C_{17}H_{20}N_2S$-$C_2H_2O_4$-H_2O: C, 58.15; H, 6.16; N, 7.14. Found: C, 58.46; H, 5.95; N, 6.79.

Method B / Oilbath Experiments (promazine 1a, Table 1, Entry 1). Pd_2dba_3 (69mg, 0.075mmol), DPPF (166mg, 0.10mmol) and NaO*t*-Bu (1.15g, 12.0mmol) were added to a round-bottomed flask. Toluene (15.0mL) was added followed by 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), 2-bromo-iodobenzene **4a** (849mg, 386μL, 3.0mmol) and 3-dimenthylamino-1-propylamine **3** (307mg, 378μL, 3.0mmol). The flask was immersed into an oilbath preheated to 60°C. After 2h, the temperature was increased to 100°C over ~15min, and the mixture was stirred at that temperature for 12h. The crude mixture was purified by column flash chromatography (9:1 EtOAc:Et_3N) to afford 621mg (73%) of the title compound as a pale brown oil.

Method C / 'Alu-block' Experiments (promazine 1a, Table 1, Entry 1). Pd_2dba_3 (69mg, 0.075mmol), DPPF (166mg, 0.10mmol) and NaO*t*-Bu (1.15g, 12.0mmol) were added to a screw-cap vial. Toluene (15.0mL) was added followed by 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), 2-bromo-iodobenzene **4a** (849mg, 386μL, 3.0mmol) and 3-dimenthylamino-1-propylamine **3** (307mg, 378μL, 3.0mmol). The flask was sealed and placed in an aluminium block (oilbath 'replacement') and treated at rt →160°C overnight (heating to 160°C over ~0.5h; reaction times have not been minimized). The crude mixture was purified by column flash chromatography (9:1 EtOAc:Et_3N) to afford 562mg (66%) of the title compound as a pale brown oil.

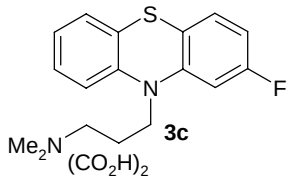
Method D / 'large-scale' Microwave Experiment (promazine 1a, Table 2, Entry 6).

Bis(dibenzylideneacetone)palladium (2.6 g, 4.5 mmol), 1,1'-bis(diphenylphosphino)ferrocene (5.0 g, 9.0 mmol) and sodium *tert*-butoxide (34.6 g, 360 mmol) were mixed in an 850 mL teflon cup. To this was added a mixture of dry toluene/*N*,*N*-dimethylformamide (95:5, 450 mL) followed by 2-bromothiophenol (10.6 mL, 90 mmol), 1-bromo-2-iodobenzene (11.6 mL, 90 mmol) and *N*,*N*-dimethyl-1,3-propanediamine (11.3 mL, 90 mmol). The teflon cup was placed in a Biotage Advancer and heated to 60°C for 20 minutes and then 160°C for 120 minutes using microwave heating. The crude mixture was concentrated *in vacuo* and purified by flash chromatography (10x17 cm silica plug) eluting with heptane/ethyl acetate/triethylamine (2:7:1) affording the title compound as a brown oil (17.4 g, 68% yield).



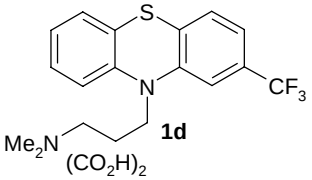
1b

Chlorpromazine (1b, Table 1, Entry 2). Using method A starting from 2-bromo-4-chloro-iodobenzene **4b** (952mg, 3.0mmol; see below for the preparation of this compound), 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), and 3-dimenthylamino-1-propylamine **3** (307mg, 378μL, 3.0mmol). 0.47g (50%) of the title compound was isolated as a brown oil after column flash chromatography (EtOAc:Et_3N 9:1). The product was dissolved in acetone and crystallized as the white oxalic acid salt. mp 164.5°C. R_f 0.45 (EtOAc:Et_3N 9:1). ^{1}H NMR (d_6-DMSO, 500MHz): δ 7.29-7.23 (m, 1H), 7.21 (d, *J*=7.53Hz, 1H), 7.20 (d, *J*=8.47Hz, 1H), 7.13 (broad s, 1H), 7.10 (broad d, *J*=7.07Hz, 1H), 7.04 (dd, *J*=1.88Hz, *J*=8.48Hz, 1H), 7.02 (app. t, *J*=7.07Hz, 1H), 4.04 (t, *J*=7.07Hz, 2H), 3.08 (t, *J*=7.53Hz, 2H), 2.67 (s, 6H), 2.03 (dt, *J*=7.07Hz, *J*=7.53Hz, 2H). ^{13}C NMR (d_6-DMSO, 125MHz): δ 161.41 (oxalic acid) 146.51, 144.12, 132.94, 128.61, 128.25, 127.74, 124.08, 123.64, 123.35, 122.80, 116.76, 116.26, 55.00, 44.23, 43.00 (2C), 22.27. Anal. Calc'd for $C_{17}H_{19}ClN_2S$-$C_2H_2O_4$: C, 55.81; H, 5.18; N, 6.85. Found: C, 55.53; H, 5.44; N, 6.48.



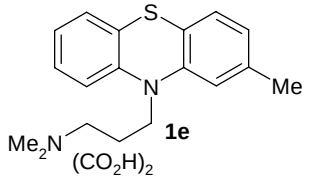
3c

Flupromazine (1c, Table 1, Entry 2). Using method A starting from 2-bromo-4-flouro-iodobenzene **4c** (903mg, 555μL, 3.0 mmol), 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), and 3-dimenthylamino-1-propylamine **3** (307mg, 378μL, 3.0mmol). 562mg (62%) of the title compound was isolated as a brown oil after column flash chromatography (EtOAc:Et_3N 9:1). This material was dissolved in acetone and crystallized as the oxalic acid salt. mp 168.4°C. R_f 0.43 (EtOAc:Et_3N 9:1). ^1H NMR (d_6-DMSO, 500MHz): δ 7.24 (dd, *J*=7.53, 1H), 7.16-7.21 (m, 2H), 7.09 (d, *J*=8.01Hz, 1H), 6.96-7.02 (m, 2H), 6.82 (ddd, *J*=2.35Hz, *J*=8.01Hz, *J*=8.48Hz, 1H), 3.97 (t, *J*=7.53Hz, 2H), 3.09 (t, J=7.06Hz, 2H), 2.67 (s, 6H), 2.07 (broad s, 2H). ^{13}C NMR (d_6-DMSO, 125MHz): δ 164.79 (oxalic acid), 162.82 (d, *J*=242.24Hz), 146.86 (d, *J*=9.48Hz), 144.16, 128.41 (d, *J*=10.34Hz), 128.17, 127.65, 124.15, 123.57, 119.32 (d, *J*=1.73Hz), 116.54, 109.58 (d, *J*=22.41Hz), 104.22 (d, *J*=25.86Hz), 54.78, 44.31, 42.78 (2C), 22.03. Anal. Calc'd for $C_{17}H_{19}FN_2S$-$C_2H_2O_4$: C, 58.15; H, 5.39; N, 7.14. Found: C, 58.20; H, 5.36; N, 7.05.



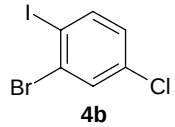
1d

Triflupromazine (1d, Table 1, Entry 2). Using method D starting from 2-bromo-1-iodo-4-trifluoromethyl-benzene **4d** (525mg, 1.5mmol), 2-bromobenzenethiol **2** (284mg, 193μL, 1.5mmol), and 3-dimenthylamino-1-propylamine **3** (154mg, 189μL, 1.5mmol). 306mg (59%) of the title compound was isolated as a brown oil after column flash chromatography (EtOAc:Et_3N 9:1). The product was dissolved in acetone and crystallized as the oxalic acid salt. mp 198.5°C (lit.[4] 196-197°C). R_f 0.51 (EtOAc:Et_3N 9:1). ^1H NMR (d_6-DMSO, 500MHz): δ 7.40 (d, *J*=7.54Hz, 1H), 7.32-7.25 (m, 3H), 7.22 (dd, *J*=0.94, *J*=7.54Hz, 1H), 7.12 (broad d, *J*=8.01Hz, 1H), 7.03 (dd, *J*=7.06Hz, *J*=7.54Hz, 1H), 3.95 (t, *J*=7.06Hz, 2H), 3.10 (t, *J*=7.54Hz, 2H), 2.68 (s, 6H), 2.06 (dt, *J*=7.06Hz, *J*=7.54Hz, 2H). ^{13}C NMR (d_6-DMSO, 125MHz): δ 164.79 (oxalic acid) 145.79, 143.89, 130.03, 128.84 (q, *J*=31.89Hz), 128.27, 127.83, 127.77, 124.52 (q, *J*=272.41Hz), 123.86, 123.47, 119.65 (q, *J*=4.31Hz), 116.93, 112.45 (q, *J*=3.45Hz), 54.75, 44.27, 42.69 (2C), 22.02. Anal. Calc'd for $C_{18}H_{19}F_3N_2S$-$C_2H_2O_4$: C, 54.29; H, 4.78; N, 6.33. Found: C, 54.23; H, 4.80; N, 6.22.



1e

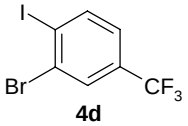
Methylpromazine (1e, Table 1, Entry 2): Using method A starting from 3-bromo-4-iodotoluene **4e** (891mg, 429μL, 3.0mmol), 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), and 3-dimenthylamino-1-propylamine **3** (307mg, 378μL, 3.0mmol). 680mg (76%) of the title compound was isolated as a brown oil after column flash chromatography (EtOAc:Et_3N 9:1). The product was dissolved in acetone and crystallized as the oxalic acid salt. mp >250°C. R_f 0.50 (EtOAc:Et_3N 9:1). ^1H NMR (d_6-DMSO, 500MHz): δ 7.20 (broad dd, *J*=7.07Hz, *J*=7.53Hz, 1H), 7.17 (broad d, *J*=7.54Hz, 1H), 7.02-7.06 (m, 2H), 6.96 (broad dd, *J*=7.07Hz, *J*=7.54Hz, 1H), 6.89 (broad s, 1H), 6.79 (broad d, *J*=7.54Hz, 1H), 3.94 (t, *J*=6.59Hz, 2H), 3.07 (t, *J*=7.07Hz, 2H), 2.66 (s, 6H), 2.25 (s, 3H), 2.04 (broad s, 2H). ^{13}C NMR (d_6-DMSO, 125MHz): δ 164.85 (oxalic acid), 144.98, 144.90, 137.65, 127.92, 127.55, 127.29, 124.67, 123.75, 122.98, 120.86, 117.06, 116.30, 54.89, 44.11, 42.76 (2C), 22.17, 21.31. Anal. Cal'd for $C_{18}H_{22}N_2S$-$C_2H_2O_4$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61,48; H, 6.36; N, 6.82.



4b

2-Bromo-4-chloro-iodobenzene (4b). Following a slightly modified literature procedure,[5] 2-bromo-4-chloroaniline (20g, 0.095mol) was dissolved in 37% HCl (150mL) and water (100mL) by heating to 80°C under stirring. The mixture was cooled to 0°C under vigorous stirring. $NaNO_2$ (7.25g, 0.105mol) was added. After stirring 1h at 0°C, a solution of KI (17.4g, 0.105mol) in water (100mL) was added at such a rate that the temperature was maintained below 10°C. Then, the mixture was allowed to warm to rt over 0.5h, after which it was briefly heated to 60°C. The mixture was extracted with 1,2-dichloroethane

(250mL). The organic layer was washed with water (200mL), 1M $Na_2S_2O_3$ (200mL), 10% NaOH (200mL), 10% HCl (200mL), sat. $NaHCO_3$ (200mL), and sat. NaCl (200mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated to afford the crude product as a solid material. Recrystallization from ethanol afforded 15.4g (50%) of title compound as pale orange needle-shaped crystals. mp 31-33°C (EtOH, lit.[6] 33°C). R_f 0.70 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.76 (d, *J*=8.4Hz, 1 H), 7.62 (d, *J*=2.2Hz, 1 H), 6.99 (dd, *J*=8.4, 2.2Hz, 1 H) ^{13}C NMR (d_6-DMSO, 125MHz) δ 141.52, 134.26, 132.25, 130.43, 129.47, 100.78. Anal. Calc'd for C_6H_3BrClI: C, 22.71; H, 0.95. Found: C, 22.47; H, 0.96.



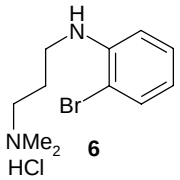
4d

2-Bromo-1-iodo-4-trifluoromethyl-benzene (4d). 3-amino-4-iodobenzotrifluoride (commercially available from Alfa Aesar; 11.06g, 46.1mmol) is suspended in water (50mL). 37% aq. HCl (250mL) and 96% aq. H_2SO_4 (100mL) is added. The resulting suspension is cooled on an ice/water-bath. $NaNO_2$ (3.34g, 48.4mmol) is added in three portions over 5min. The resulting pale yellow suspension is stirred at 0°C for 0.5h. KI (8.41g, 50.7mmol) is added over 5 min during which gas evolution is observed, and the mixture turns dark as a dark brown oil collects at bottom of the flask. The mixture is stirred overnight at 0°C→rt. Next morning, the mixture is extracted with heptane (2 x 300mL) and Et_2O (300mL). The combined organic layers are washed with water (300mL), 1 M aq. $Na_2S_2O_3$ (300mL), 10% aq. NaOH (300mL), and sat. aq. NaCl (300mL), dried over $MgSO_4$, filtered, and concentrated to afford a pale brown oil. This material was filtered through a plough of SiO2 (eluent: heptane) to yield a colorless oil, which crystallized as long white needles upon standing. Yield: 4.34g (27%). mp. 36-38.5°C (EtOH, lit.[14] 31-33°C). R_f 0.63 (heptane) ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.99 (d, *J*=8.26Hz, 1H), 7.86 (d, *J*=1.47Hz, 1H), 7.24 (dd, *J*=1.71Hz, 8.26Hz, 1H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 141.00, 130.62, 129.52 (app. q, *J*=~3.5Hz, 1C), 125.07 (app. q, *J*=~3.1Hz, 1C), 123.18 (q, *J*=273.0Hz, 1C), 106.15. Anal. Calc'd for $C_7H_3BrF_3I$: C, 23.96; H, 0.86. Found: C, 23.77; H, 0.82.

#	ligand	1a	7a	7	6b	6a	6	5a	5	PhBr	4a	SUM
A	DPPF	45.0	4.6	37.7	1.6	1.4	1.1	0.0	3.1	0.0	0.0	94.5
B	D-i-Pr-BPF	39.5	4.6	27.9	6.6	2.3	6.2	5.4	6.8	0.0	0.0	99.3
C	D-t-Bu-BPF	19.8	6.4	3.3	23.0	1.4	0.0	4.5	5.1	0.0	0.0	63.4
D	BINAP	14.0	1.8	40.0	2.0	2.8	10.0	1.0	31.0	0.0	0.0	102.6
E	DPEphos	28.0	3.3	54.0	8.0	2.9	2.0	1.0	1.8	0.0	0.0	100.9
F	XantPhos	7.8	1.4	50.0	3.0	3.9	20.2	0.0	5.2	0.0	0.0	91.6
G	IPr-DH-imidazole	0.0	0.8	0.6	2.5	0.6	0.0	15.7	1.1	32.4	2.0	55.8
H	$P(t\text{-}Bu)_3$ - BF_4	0.0	0.0	0.0	3.9	3.4	21.4	3.7	7.6	9.0	24.8	73.8
I	1-biphenyl-PCy_2	17.2	6.1	15.0	10.6	7.0	1.5	5.3	12.0	3.7	0.0	78.6
J	1-biphenyl-$P(t\text{-}Bu)_2$	0.0	0.0	1.0	0.9	1.5	46.3	0.0	1.7	5.7	6.3	63.4
K	DavePhos	31.9	1.5	6.8	3.0	2.6	9.5	0.0	30.4	3.5	0.0	89.2
L	X-Phos	3.0	0.7	2.7	5.3	1.6	2.4	21.0	35.0	16.1	0.0	87.8
M	$P(o\text{-}tol)_3$	0.0	0.0	0.9	1.8	4.1	44.0	1.3	0.5	9.7	0.0	62.2
N	PPh_3	0.0	0.0	2.2	30.3	33.6	7.9	0.0	0.0	3.6	0.0	77.7
O	No L	0.0	0.0	0.0	1.2	1.3	10.2	0.0	0.0	8.6	54.0	75.3
P	no Pd/no L	0.0	0.0	0.0	1.4	1.0	10.0	0.0	0.0	0.0	79.7	92.1

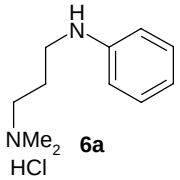
Table 1 *Ligand screening results in percentages relative to an internal standard determined by GC (cf text for details).*

Ligand Screening Experiments. Pd_2dba_3 (23mg, 0.025mmol, 5%) or $Pd(OAc)_2$ (11mg, 0.05mmol, 10%), ligand (10-20%), and NaO*t*-Bu (192 mg, 2.0mmol) were added to a 4 mL screw-cap vial followed by 2mL of a stock solution of 2-bromobenzenethiol **2** (0.79g, 16x0.26mmol), 2-iodo-bromobenzene **4a** (1.19g, 16x0.26mmol), 3-dimenthylamino-1-propylamine **3** (0.43g, ½16x0.26mmol), and *n*-dodecane (0.36g, 16x0.5x0.26mmol; internal GC-standard) in toluene (16x2mL=32mL) and a stir bar. The vials were sealed with caps fitted with PTFE septa. The vials were immersed in an oilbath preheated to 60°C and stirred for 20min, before the temperature was increased over ~15min to 100°C. The reactions were stirred at 100°C overnight. The crude product mixtures were analyzed using GC. The results are summarized in Table 1.



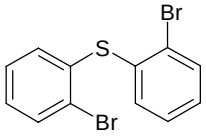
6

***N*'-(2-bromophenyl)-*N*,*N*-dimethylpropane-1,3-diamine hydrochloride (6):** Pd_2dba_3 (23 mg, 0.025mmol), BINAP (47mg, 0.075mmol), and NaO*t*-Bu (48 mg, 0.5mmol) were added to a 5mL microwave vial followed by a stir bar. Toluene (2.5mL) was added followed by 2-bromo-iodobenzene **4a** (142mg, 64μL, 0.5mmol) and 3-dimethylamino-1-propylamine **3** (51mg, 63μL, 0.5mmol). The vial was sealed, and the mixture was heated at 160°C (fixed hold-time) for 20min under microwave irradiation. The crude mixture was purified by column flash chromatography (EtOAc:Et_3N 20:1) to afford 112mg (86%) of the title compound as a brown oil. This material was dissolved in EtOH and treated with 4M HCl in Et_2O to precipitate the title compound as the hydrochloride salt as a pale beige solid. mp 131.9-132.3°C. R_f 0.55 (EtOAc:Et_3N 20:1). ^{1}H NMR (d_6-DMSO, 500MHz): δ 10.91 (broad s, 1H), 7.38, (dd, *J*=1.18Hz, *J*=8.01Hz, 1H), 7.16 (ddd, *J*=1.18Hz, *J*=7.54Hz, *J*=7.53Hz, 1H), 6.64 (broad d, *J*=7.54Hz, 1H), 6.49 (ddd, *J*=1.18Hz, *J*=7.53Hz, *J*=8.01Hz, 1H), 5.73 (t, *J*=5.65Hz, 1H), 3.15 (dt, *J*=5.65Hz, *J*=6.59Hz, 2H), 2.32 (t, *J*=6.12Hz, 2H), 2.16 (s, 6H), 1.71 (dt, *J*=6.12Hz, *J*=6.59Hz, 2H). ^{13}C NMR (d_6-DMSO, 125MHz): δ 144.64, 132.42, 128.71, 117.43, 111.61, 108.71, 54.37, 41.90, 40.10, 23.15. High-resolution MS: Calc'd for $[C_{11}H_{17}BrN_2]^+$ 257.0648. Found 257.0647.



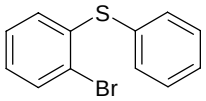
6a

***N*,*N*-Dimethyl-*N'*-phenyl-propane-1,3-diamine hydrochloride (6a):** Pd_2dba_3 (137 mg, 0.15mmol), XantPhos (347mg, 0.60mmol), and NaO*t*-Bu (1.15g, 12.0mmol) were added to a screw-cap vial followed by a stir bar. Toluene (40mL) was added followed by iodobenzene (2.04g, 10.0mmol) and 3-dimethylamino-1-propylamine **3** (1.02g, 10.0mmol). The vial was sealed, and the mixture was stirred at 100°C for 2½h. The crude mixture was filtered through a pad of Celite. The filtrate was washed with water (50ml) and extracted with 10% aqueous HCl (50mL). The acidic aqueous layer was washed woth Et_2O (2x50mL), before it was basified with 15% aqueous NaOH (50mL) and extracted with EtOAc (2x50mL). The combined organic layers were washed with water (50mL), saturated aqueous NaCl (50mL), dried over $MgSO_4$, filtered, and evaporated to afford a pale brown oil (2.1g of the title compound >80% pure by ^{1}H NMR). This material was dissolved in EtOH and treated with 4M HCl in Et_2O to precipitate the title compound as the hydrochloride salt as a pale beige solid (0.37g, 17%). mp 171-173°C (lit.[12] 174.5-178.5). R_f 0.27 (EtOAc:Et_3N 20:1). ^{1}H NMR (d_6-DMSO, 500MHz): δ 10.6 (broad s, 1H), 7.41-7.33 (m, 2H), 7.26-7.04 (m, 3H), 3.28 (app. t, *J*=7.12Hz, 2H), 3.17 (app. t, 7.53Hz, 2H), 2.73 (broad s, 6H), 2.11-2.03 (m, 2H). ^{13}C NMR (CD_3OD, 125MHz): δ 136.15, 130.84 (2C), 130.00, 122.76 (2C), 54.88, 48.74, 42.85 (2C), 21.92. High-resolution MS: Calc'd for $[C_{11}H_{19}N_2]^+$ 179.1543. Found: 179.1543.



7

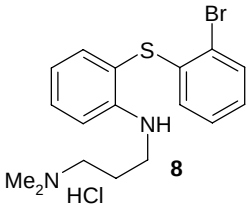
1-bromo-2-[(2-bromophenyl)thio]benzene (7). Following a slightly modified literature procedure,[1] Pd_2dba_3 (46mg, 0.05mmol), DPEphos (54mg, 0.10mmol), and NaO*t*-Bu (575mg, 6mmol) were added to a round-bottomed flask followed by toluene (30mL). 2-Bromo-iodobenzene **4a** (1.42g / 645μL, 5mmol) and 2-bromobenzenethiol **2** (945mg / 945μL, 5mmol) were added. The mixture was degassed three times with argon using a vac-line, and flask was closed with a stopper. The mixture was stirred at 60°C for 2h in an oil bath. The crude mixture was purified by column flash chromatography (heptane) to afford 1.76g (97%) of the title compound as a white solid. mp 65.5-66°C (heptane; lit.[2] 67.5-68°C). R_f 0.38 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz)**:** δ 7.64 (dd, *J*=1.06Hz, *J*=7.95Hz, 2H), 7.24 (ddd, *J*=1.53Hz, *J*=7.94Hz, *J*=8.78Hz, 2H), 7.17-7.11 (m, 4H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 136.11 (2C), 133.91 (2C), 132.84 (2C), 129.17 (2C), 128.55 (2C), 126.23 (2C). High-resolution MS: Calc'd for $[C_{12}H_8Br_2S]^+$ 341.8708. Found: 341.8704.



7a

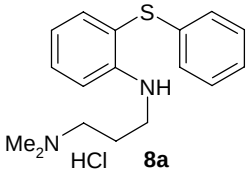
1-Bromo-2-phenylsulfanyl-benzene (7a). Following a slightly modified literature procedure,[1] Pd_2dba_3 (46mg, 0.05mmol), DPEphos (54mg, 0.10mmol), and NaO*t*-Bu (1.23g, 11.0mmol) were added to a screw-cap vial followed by toluene (30mL) and a stir bar. Iodobenzene (2.04g, 10.0mmol) and 2-bromobenzenethiol **2** (1.89g, 10.5mmol) were added. The vial was sealed and the mixture stirred at 100°C for 1h. The crude mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by filtration through a short column of silica gel and eluted with heptane to afford 2.50g of a

colourless oil (94%). R_f 0.31 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz):[13] δ 7.56 (dd, *J*=1.35Hz, *J*=7.95Hz, 1H), 7.47-7.43 (m, 2H), 7.41-7.36 (m, 3H), 7.14 (ddd, *J*=1.35Hz, *J*=7.89Hz, *J*=8.90Hz, 1H), 7.03 (ddd, *J*=1.53Hz, *J*=7.95Hz, *J*=8.90Hz, 1H), 6.93 (dd, *J*=1.53Hz, 7.89Hz, 1H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 139.54, 134.23 (2C), 133.81, 133.70, 130.61, 130.40 (2C), 129.21, 128.58, 128.03, 123.89. High-resolution MS: Calc'd for $[C_{12}H_9BrS]^+$ 263.9603. Found: 263.9603.



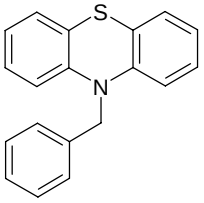
8

***N'*-{2-[(2-bromophenyl)thio]phenyl}-*N*,*N*-dimethylpropane-1,3-diamine (8).** Pd_2dba_3 (46mg, 0.05mmol), BINAP (93mg, 0.15mmol), and NaO*t*-Bu (115 mg, 1.2mmol) were added to a round-bottomed flask followed by toluene (5mL). 1-Bromo-2-[(2-bromophenyl)thio]benzene **7** (344mg, 1.0mmol) and 3-dimenthylamino-1-propylamine **3** (102mg, 126μL, 1.0mmol) were added. The mixture was degassed three times with argon using a vac-line, and flask was closed with a stopper. The flask was immersed in an oilbath preheated to 100°C and stirred for 12h. The crude mixture was purified by column flash chromatography (9:1 EtOAc:Et_3N) to afford 231mg (63%) of the title compound as a pale brown oil. This material was dissolved in EtOH (1mL) and treated with 4M HCl in Et_2O to precipitate the title compound as its hydrochloride salt. mp 173.4-173.9 (EtOH/Et_2O). R_f 0.59 (9:1 EtOAc:Et_3N). ^{1}H NMR (d_6-DMSO, 500MHz): δ 9.95 (broad s, 1H), 7.62 (dd, *J*=1.06Hz, *J*=7.89Hz, 1H), 7.41-7.36 (m, 2H), 7.26-7.21 (m, 1H), 7.07 (ddd, *J*=1.47Hz, *J*=7.54Hz, *J*=7.71Hz, 1H), 6.83 (broad d, *J*=8.01Hz, 1H), 6.69 (app. t, *J*=7.36Hz, 1H), 6.49 (dd, *J*=1.29Hz, *J*=8.01Hz, 1H), 3.22 (app. t, *J*=6.71Hz, 2H), 3.0-2.89 (m, 2H), 2.68 (s, 6H), 1.9-1.8 (m, 2H). ^{13}C NMR (d_6-DMSO, 125MHz): δ 149.30, 137.68, 137.61, 132.66, 132.16, 128.13, 126.50, 125.76, 119.93, 116.69, 111.43, 110.73, 54.27, 41.79 (2C); one signal 'hidden' by the DMSO-signal, 23.01. High-resolution MS: Calc'd for $[C_{17}H_{21}BrN_2S\text{-}Na^+]$ 387.0501. Found 387.0483.



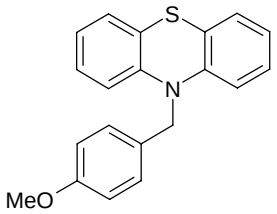
8a

***N*,*N*-Dimethyl-*N'*-(2-phenylsulfanyl-phenyl)-propane-1,3-diamine (8a)**. Pd_2dba_3 (115mg, 0.13mmol), BINAP (234mg, 0.38mmmol), NaO*t*-Bu (0.58g, 6.0mmol), 1-bromo-2-phenylsulfanyl-benzene **7a** (1.33g), and 3-dimenthylamino-1-propylamine **3** (0.56g, 5.5mmol) were added to a screw-cap vial followed by a stir bar and toluene (25mL). The vial was sealed and stirred at 100°C overnight. Next morning, the crude mixture was filtered through a pad of Celite, and the filtrate was washed with water (25mL). The organic layer was extracted with 10% aqueous HCl (25mL), and the aqueous layer was washed with Et_2O (2x25mL) before it was basified with 15% aqueous NaOH (25mL) and extracted with EtOAc (2x25mL). The combined organic extracts were washed with water (25mL) followed by saturated aqueous NaCl (25mL) before they were dried over $MgSO_4$. Evaporation afforded 0.37g (27%) of the free base of the target molecule as brown sticky oil after repeated attempts to obtain the hydrochloride salt from EtOH. R_f 0.70 (9:1 EtOAc:Et_3N) ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.46 (dd, *J*= 1.53Hz, *J*=7.95Hz, 1H), 7.30 (ddd, *J*=1.59Hz, *J*=8.07Hz, *J*=9.31Hz, 1H), 7.22-7.16 (m, 2H), 7.10-7.03 (m, 3H), 6.70-6.64 (m, 2H), 5.3 (broad s, 1H), 3.18 (app. t, *J*=6.77Hz, 2H), 2.24 (app. t, *J*=6.77Hz, 2H), 2.14 (s, 6H), 1.71 (app. quintet, *J*=6.77Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 150.03, 138.09, 137.55, 131.80, 129.29 (2C), 126.65 (2C), 125.59, 116.97, 114.05, 110.76, 57.77, 45.57 (2C), 42.35, 26.91. High-resolution MS: Calc'd for $[C_{17}H_{22}N_2S+H]^+$ 287.1577. Found: 287.1581.

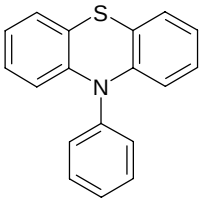


***N*-Benzyl-phenothiazine (Table 1, Entry 3)**. Using method A starting from benzylamine (321mg, 328μL, 3.0mmol), 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), and 2-bromo-iodobenzene **4a** (849mg, 386μL, 3.0mmol) using 10% catalyst loading: Pd_2dba_3 (103mg, 0.113mmol) and DPPF (249mg, 0.15mmol). 659mg (76%) of the title compound was isolated as a pale brown solid after chromatography (heptane:EtOAc 20:1). Applying Method C using benzylamine (161mg, 164μL, 1.5mmol), 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), and 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol) gave 395mg (91%) of the title compound as an off-white solid after chromatography (heptane:EtOAc 20:1). mp 90-91°C (heptane; lit.[7] 90-91°C). R_f 0.38 (heptane:EtOAc 20:1). ^{1}H NMR ($CDCl_3$, 500MHz):[7] δ 7.33-7.24 (m, 5H), 7.08 (dd, *J*=1.53Hz, 7.56Hz,

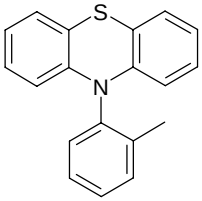
2H), 6.97 (ddd, *J*=1.53Hz, 7.48Hz, 8.01Hz, 2H), 6.86 (ddd, *J*=1.12, 7.47Hz, 7.48Hz, 2H), 6.63 (dd, *J*=0.88, 8.14Hz, 2H), 5.05 (s, 2H), 5.09 (s, 2H). ^{13}C NMR ($CDCl_3$, 125MHz):[11] δ 144.86 (2C), 137.05, 129.12 (2C), 127.61 (2C), 127.40, 127.22 (2C), 127.00 (2C), 123.52, 122.89 (2C), 115.83 (2C), 53.09. Anal. Cal'd for $C_{19}H_{15}NS$: C, 78.86; H, 5.22; N, 4.84. Found: C, 78.77; H, 5.36; N, 4.78.



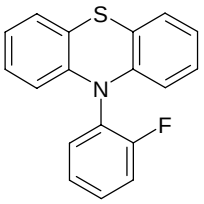
***N*-(4-Methoxy-benzyl)-phenothiazine (Table 1, Entry 3)**. Using method A starting from 4-methoxy-benzylamine (412mg, 3.0mmol), 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), and 2-bromo-iodobenzene **4a** (849mg, 386μL, 3.0mmol). 585mg (61%) of the title compound was isolated as a pale brown oil which crystallized on standing after column flash chromatography (heptane:EtOAc 20:1). Using Method C, 4-methoxy-benzylamine (206mg, 1.5mmol), 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), and 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol) gave 326mg (68%) of the title compound as a yellow/brown oil that crystallized on standing after column flash chromatography (heptane:EtOAc 20:1). mp 99-100°C (heptane) (lit. 101.5-103°C[9]). R_f 0.21 (heptane:EtOAc 20:1). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.19 (d, *J*=8.94Hz, 2H), 7.06 (dd, *J*=1.41Hz, 7.53Hz, 2H), 6.95 (ddd, *J*=1.41Hz, 7.53Hz, 8.01Hz, 2H), 6.84-6.81 (m, 4H), 6.63 (dd, *J*=0.94Hz, 8.48Hz, 2H), 4.99 (s, 2H) 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 125MHz): 159.00, 144.97 (2C), 128.83, 128.18 (2C), 127.65 (2C), 127.26 (2C), 123.63 (2C), 122.89 (2C), 115.94 (2C), 114.56 (2C), 55.67, 52.49. High-res. MS: Calc'd for $[C_{20}H_{17}NOS\text{-}H]^+$ 318.0947. Found 318.0946.



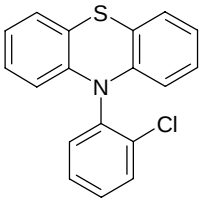
***N*-Phenyl-phenothiazine (Table 1, Entry 4)**. Using method A starting from 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), 2-bromo-iodobenzene **4a** (849mg, 386μL, 3.0mmol) and aniline (279mg, 274μL, 3.0mmol) using 10% catalyst loading: Pd_2dba_3 (103mg, 0.113mmol) and DPPF (249mg, 0.15mmol). 754mg (91%) of the title compound was isolated as an off-white solid after column flash chromatography (heptane:EtOAc 9:1). mp 82°C (lit.[7] 89-90°C). R_f 0.62 (heptane:EtOAc 9:1). ^{1}H NMR (d_6-DMSO, 500MHz): δ 7.67 (dd, *J*=7.54Hz, *J*=7.53Hz, 2H), 7.54 (broad t, *J*=7.53Hz, 2H), 7.41 (d, *J*=7.54Hz, 2H), 7.07 (dd, *J*=7.07Hz, *J*=1.42Hz, 2H), 6.93 (ddd, *J*=1.42Hz, *J*=8.00Hz, *J*=8.01Hz, 2H), 6.86 (ddd, *J*=0.94Hz, *J*=7.07Hz, *J*=8.00Hz, 2H), 6.17 (dd, *J*=8.00Hz, *J*=0.94Hz, 2H). ^{13}C NMR (d_6-DMSO, 125MHz):[11] 143.96 (2C), 140.74, 131.39 (2C), 130.60 (2C), 128.75, 127.62 (2C), 127.03 (2C), 123.09 (2C), 119.79, 116.45 (2C). High-res. MS: Calc'd for $[C_{18}H_{13}BrNS]^+$ 275.0763. Found 275.0766.



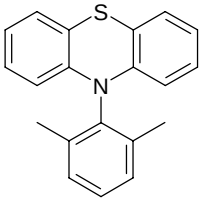
***N*-(2-Methyl-phenyl)-phenothiazine (Table 1, Entry 4)**. Using method C starting from 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol) and *o*-toluidine (161mg, 160μL, 1.5mmol). 340mg (78%) of the title compound was isolated as a an off-white solid after column flash chromatography (heptane:EtOAc 20:1). mp 99-7-100.2°C (MeOH). R_f 0.49 (heptane:EtOAc 20:1). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.53-7.29 (m, 4H), 6.95 (app. d, *J*=6.81Hz, 2H), 6.87-6.57 (m, 4H), 5.99 (app. d, *J*=5.94Hz, 2H), 2.23 (broad s, 3H). ^{13}C NMR ($CDCl_3$, 125MHz) δ: 143.80 (2C), 139.85, 139.23, 132.91, 132.37, 129.06, 128.72, 127.63 (2C), 127.38 (2C), 123.07 (2C), 120.15 (2C), 115.68 (2C), 17.91.High-res. MS: Calc'd for $[C_{18}H_{13}BrNS]^+$ 289.09197. Found: 289.09193.



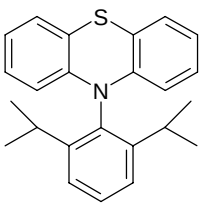
***N*-(2-Fluoro-phenyl)-phenothiazine (Table 1, Entry 4)**. Using method C starting from 2-bromobenzenethiol **6** (284mg, 177μL, 1.5mmol), 2-bromo-iodobenzene **7** (425mg, 193μL, 1.5mmol) and 2-fluoro-aniline (167mg, 145μL, 1.5mmol) using 10% catalyst loading: Pd_2dba_3 (52mg, 0.057mmol) and DPPF (125mg, 0.075mmol). 405mg (92%) of the title compound was isolated as a pale brown oil after column flash chromatography (heptane→heptane:EtOAc 20:1). This material was crystallized from methanol to afford the title compound as an off-white solid. mp. 98.7-98.9°C (MeOH). R_f 0.20 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.55-7.43 (m, 2H), 7.41-7.32 (m, 2H), 7.03 (dd, *J*=1.42, 7.44Hz, 2H), 6.88 (app. dt, *J*=1.49, 7.30Hz, 2H), 6.83 (app. dt, *J*=1.07, 7.31Hz, 2H), 6.15 (app. d, *J*=8.08Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 161.28 (d, *J*=252.61Hz, 1C), 143.66 (2C), 133.43 (2C), 131.08 (d, *J*=7.76Hz, 1C), 128.71 (d, *J*=31.92Hz, 1C), 127.47 (2C), 127.18 (2C), 126.67 (d, *J*=3.44Hz, 1C), 123.17, 120.67 (2C), 117.82 (d, *J*=19.83Hz, 1C), 115.58 (2C). High-resolution MS: Calc'd for $[C_{18}H_{13}FNS]^+$ 294.0747. Found: 294.0772.



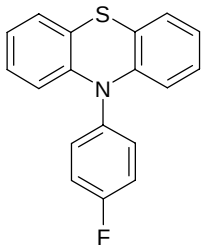
***N*-(2-Chloro-phenyl)-phenothiazine (Table 1, Entry 4)**. Using method C starting from 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol) and 2-chloro-aniline (192mg, 158μL, 1.5mmol) using 10% catalyst loading: Pd_2dba_3 (52mg, 0.057mmol) and DPPF (125mg, 0.075mmol). 415mg (89%) of the title compound was isolated as a pale brown semisolid after column flash chromatography (heptane→heptane:EtOAc 10:1). This material was crystallized from methanol to provide the title compound as a cream-coloured solid. mp 95.1-95.3°C (MeOH). R_f 0.17 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.66 (broad d, *J*=8.02Hz, 1H), 7.52-7.43 (m, 3H), 6.98 (dd, *J*=1.72, 7.39, 2H), 6.83 (ddd, *J*=1.72, 7.42, 8.02Hz, 2H), 6.79 (ddd, *J*=1.42, 7.42, 8.78Hz, 2H), 6.01 (dd, *J*=1.33, 8.02Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 142.63 (2C), 138.29, 136.50, 133.78, 131.97, 130.40, 129.58, 127.34 (2C), 127.01 (2C), 123.01 (2C), 119.85 (2C), 115.44 (2C). Anal. Cal'd for $C_{18}H_{12}ClNS$: C, 69.78; H, 3.90; N, 4.52. Found: C, 69.44; H, 4.03; N, 4.47.



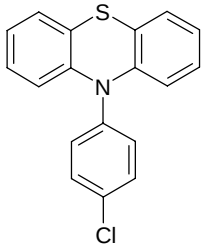
***N*-(2,6-dimethyl-phenyl)-phenothiazine (Table 1, Entry 5)**. Using method C starting from 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol) and 2,6-dimethyl-aniline (182mg, 185μL, 1.5mmol) using 10% catalyst loading: Pd_2dba_3 (52mg, 0.057mmol) and DPPF (125mg, 0.075mmol). Column flash chromatography (heptane→heptane:EtOAc 20:1) gave a pale yellow oil, which was crystallized from heptane to afford 257mg (56%) of the title compound as a pale brown solid. This material was recrystallized from methanol to provide the title compound as an analytically pure white crystalline material. mp 147.2-147.5°C (MeOH). R_f 0.15 (heptane). ^{1}H NMR (C_6D_6, 500MHz): δ 7.05-7.00 (m, 1H), 6.98-6.95 (m, 2H), 6.83 (dd, *J*=2.17, 6.89Hz, 2H), 6.55-6-48 (m, 4H), 5.91 (dd, *J*=1.88, 7.83Hz, 2H), 2.06 (s, 6H). ^{13}C NMR (C_6D_6, 125MHz): δ 142.06 (2C), 139.26 (2C), 138.40, 130.23 (2C), 129.02 (2C), 127.87 (2C), 127.25 (2C), 122.97 (2C), 119.42, 114.58 (2C), 18.26 (2C). Anal. Cal'd for $C_{20}H_{17}NS$: C, 79.17; H, 5.65; N, 4.62. Found: C, 78.79; H, 5.83; N, 4.54.



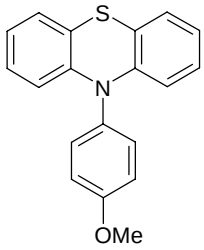
***N*-(2,6-di-*i*-propyl-phenyl)-phenothiazine (Table 1, Entry 5)**. Using method C starting from 2-bromobenzenethiol **2** (584mg, 177μL, 1.5mmol), 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol) and 2,6-di-*i*-propyl-aniline (266mg, 283μL, 1.5mmol) using 10% catalyst loading: Pd_2dba_3 (52mg, 0.057mmol) and DPPF (125mg, 0.075mmol). The crude mixture was purified by column flash chromatography (heptane→heptane:EtOAc 20:1) to afford a pale yellow oil. The title compound was crystallized from heptane to afford 113mg (21%) as a white solid, which was recrystallized from heptane to afford the title compound as white needle-shaped crystals. mp 195.9-196.3°C (heptane). R_f 0.48 (heptane:EtOAc 20:1). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.47 (t, *J*=7.71Hz, 1H), 7.36 (d, *J*=7.72Hz, 2H), 6.82 (dd, *J*=1.83, 7.13Hz, 2H), 6.73-6.62 (m, 4H), 5.77 (d, *J*=7.89Hz, 2H), 3.21 (septet, *J*=6.89Hz, 2H), 1.08 (d, *J*=6.89Hz, 12H). ^{13}C NMR ($CDCl_3$, 125MHz – very broad signals are observed due to hindered rotation): δ 148.34 (2C), 141.86 (2C), 134.72, 129.29 (2C), 126.60-125.60 (m, 6C), 121.94 (2C), 117.14 (2C), 115.06, 28.10 (2C), 24.16 (4C). Anal. Cal'd for $C_{24}H_{25}NS$: C, 80.18; H, 7.01; N, 3.90. Found: C, 80.07; H, 6.97; N, 3.82.



***N*-(4-Fluoro-phenyl)-phenothiazine (Table 1, Entry 6)**. Using method C starting from 4-fluoro-aniline (167mg, 142μL, 1.5mmol), 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), and 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol). 387mg (88%) of the title compound was isolated by column flash chromatography (heptane→heptane:EtOAc 20:1) as a pale yellow oil that crystallized on standing. The material was recrystallized from methanol to afford a white solid. mp 106-106°C (MeOH; lit.[10] 104-105°C). R_f 0.17 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.37 (m, 2H). 7.29 (m 2H), 7.01 (dd, *J*=1.41Hz, 7.06Hz, 2H), 6.90 – 6.75 (m, 4H), 6.15 (d, *J*=8.01Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 162.06 (d, *J*=249.1Hz, 1C), 144.21 (2C), 136.72, 132.64 (d, *J*=8.6Hz, 2C), 126.86 (2C), 126.77 (2C), 122.56 (2C), 120.08 (2C), 117.74 (d, *J*=22.4Hz, 2C), 115.70 (2C). Anal. Cal'd for $C_{18}H_{12}FNS$: C, 73.70; H, 4.12; N, 4.77. Found: C, 73.10; H, 4.44; N, 4.69.

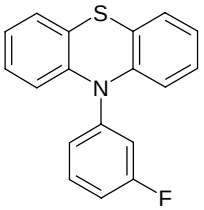


***N*-(4-Chloro-phenyl)-phenothiazine (Table 1, Entry 6)**. Using Method C starting from 4-chloro-anline (191mg, 1.5mmol), 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), and 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol). 385mg (83%) of the title compound was isolated as a yellow sticky pale brown oil which crystallized on standing after column flash chromatography (heptane→heptane:EtOAc 20:1). This material was recrystallized from methanol to provide the title compound as a off-white solid. mp 113.9-114.7°C (MeOH; lit.[10] 121-122°C). R_f 0.15 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.56 (d, *J*=8.60Hz, 2H), 7.33 (d, *J*=8.60Hz, 2H), 7.04 (dd, *J*=1.58Hz, 7.42Hz, 2H), 6.88 (ddd, *J*=1.58Hz, 7.39Hz, 8.13Hz, 2H), 6.83 (ddd, *J*=1.18Hz, 7.39Hz, 7.42Hz, 2H), 6.22 (dd, *J*=1.18Hz, 8.13Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz):[11] δ 144.29 (2C), 140.10, 134.15, 132.26 (2C), 131.38 (2C), 127.31 (2C), 126.89 (2C), 123.23 (2C), 121.26 (2C), 116.71 (2C). Anal. Cal'd for $C_{18}H_{12}ClNS$: C, 69.78; H, 3.90; N, 4.52. Found: C, 69.66; H, 4.09; N, 4.44.

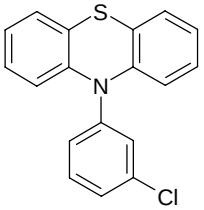


***N*-(4-Methoxyphenyl)-phenothiazine (Table 1, Entry 6)**. Using method A starting from *p*-anisidine (370mg, 3.0mmol), 2-bromobenzenethiol **2** (567mg, 353μL, 3.0mmol), and 2-bromo-iodobenzene **4a** (849mg, 386μL, 3.0mmol). 596mg (65%) of the title compound was isolated as a pale brown solid after column flash chromatography (heptane:EtOAc 9:1). mp 165.2°C (lit.[8] 173-174°C). R_f 0.43 (heptane:EtOAc 9:1). ^{1}H NMR (d_6-DMSO, 500MHz): δ 7.36-7.32 (m, 2H), 7.23-7.18 (m, 2H), 7.04

(dd, *J*=1.59, 7.52Hz, 2H), 6.94-6.88 (m, 2H), 6.83 (app. dt, *J*=1.21, 7.42Hz, 2H), 6.14 (dd, *J*=1.18, 8.26Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (d_6-DMSO, 125MHz):[11] δ 158.92, 143.99 (2C), 132.45, 131.90 (2C), 127.20 (2C), 126.48 (2C), 122.42 (2C), 118.68 (2C), 116.14 (2C), 115.53 (2C), 55.40. High-resolution MS: Calc'd for $[C_{19}H_{15}BrNOS]^+$ 305.0869. Found 305.0862.



***N*-(3-Fluoro-phenyl)-phenothiazine (Table 1, Entry 7)**. Using method C starting from 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol) and 3-fluoro-aniline (167mg, 144μL, 1.5mmol) using 10% catalyst loading: Pd_2dba_3 (52mg, 0.057mmol) and DPPF (125mg, 0.075mmol). 390mg (89%) of the title compound was isolated as an yellow-brown oil after column flash chromatography (heptane→heptane:EtOAc 20:1). A melting point of 60-64 °C has been reported in the literature,[10] but we were unable to obtain a solid material. R_f 0.19 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.50 (dd, *J*=8.01Hz, 7.96Hz, 1H), 7.15 – 7.06 (m, 5H), 6.95 (ddd, *J*=1.41Hz, 7.53Hz, 8.01Hz, 2H), 6.89 (dd, *J*=6.60Hz, 7.53Hz, 2H), 6.41 (d, *J*=8.00Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz): 163.48 (d, *J*=249.1Hz, 1C), 142.92 (2C), 130.99 (d, *J*=9.48Hz, 1C), 127.95 (d, *J*=6.9Hz, 1C), 126.59 (2C), 126.40 (2C), 123.69 (d, *J*=3.45Hz, 1C), 122.73 (2C), 122.02 (2C), 117.15 (2C), 115.24 (d, *J*=21.55Hz, 1C), 113.68 (d, *J*=20.69Hz, 1C). High-resolution MS: Calc'd for $[C_{18}H_{12}FNS]^+$ 293.0669. Found: 293.0664.



***N*-(3-Chloro-phenyl)-phenothiazine (Table 1, Entry 7)**. Using method C starting from 2-bromobenzenethiol **2** (284mg, 177μL, 1.5mmol), 2-bromo-iodobenzene **4a** (425mg, 193μL, 1.5mmol) and 3-chloro-aniline (192mg, 159μL, 1.5mmol). The crude mixture was purified by column flash chromatography (heptane→heptane:EtOAc 20:1) to afford 380mg (82%) of the title compound was isolated as a pale yellow/orange oil. R_f 0.19 (heptane). ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.49 (app. t, *J*=8.01Hz, 1H), 7.42 – 7.35 (m, 2H), 7.28 – 7.24 (m, 1H), 7.08 (dd, *J*=1.42Hz, 7.54Hz, 2H), 6.93 (ddd, *J*=1.42Hz, 7.07Hz, 8.01Hz, 2H), 6.87 (ddd, *J*=1.41Hz, 7.54Hz, 8.47Hz, 2H), 6.35 (dd, *J*=1.41Hz, 8.47Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz):[11] δ 143.92 (2C), 143.26, 136.37, 131.83, 129.70, 128.05, 127.79, 127.50 (2C), 127.37 (2C), 123.60 (2C), 122.58 (2C), 117.79 (2C). Anal. Cal'd for $C_{18}H_{12}ClNS$: C, 69.78; H, 3.90; N, 4.52. Found: C, 69.88; H, 4.21; N, 4.33.

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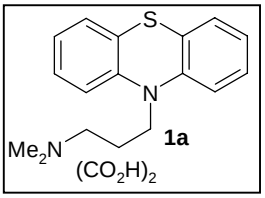
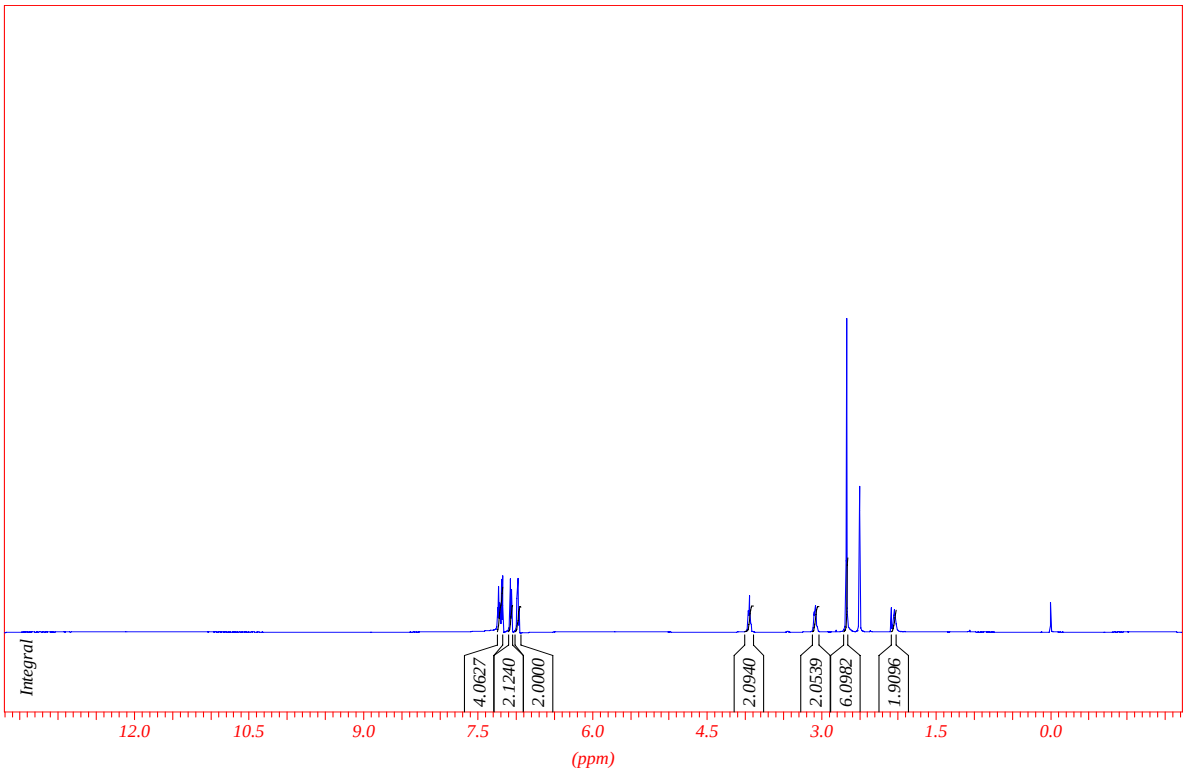
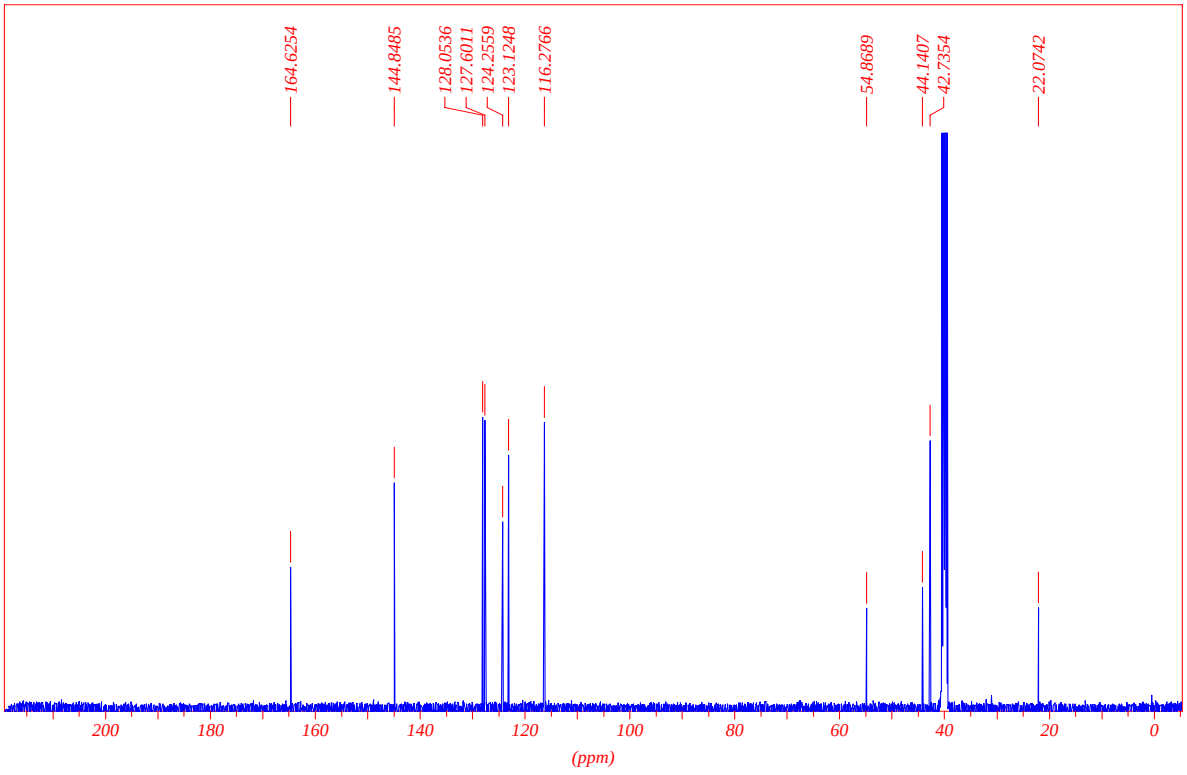
Promazine (1a, Table 1, Entry 1).

^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)

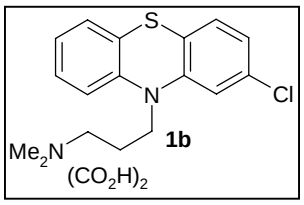


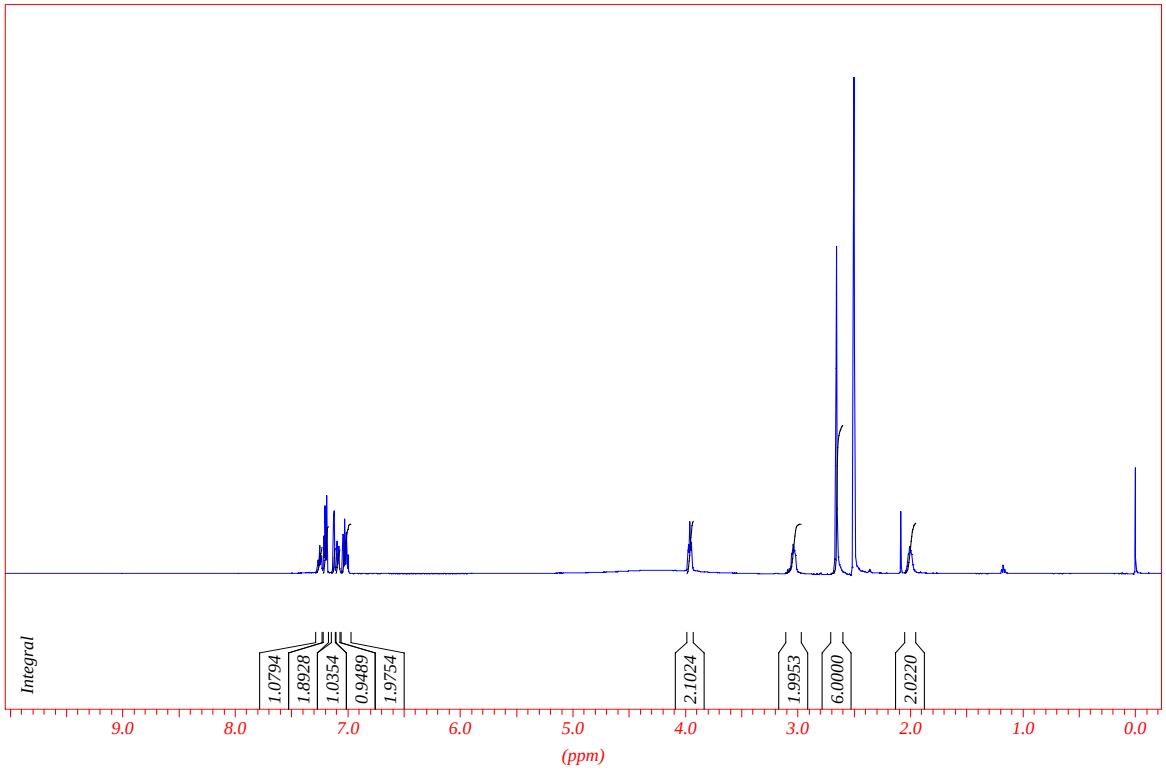


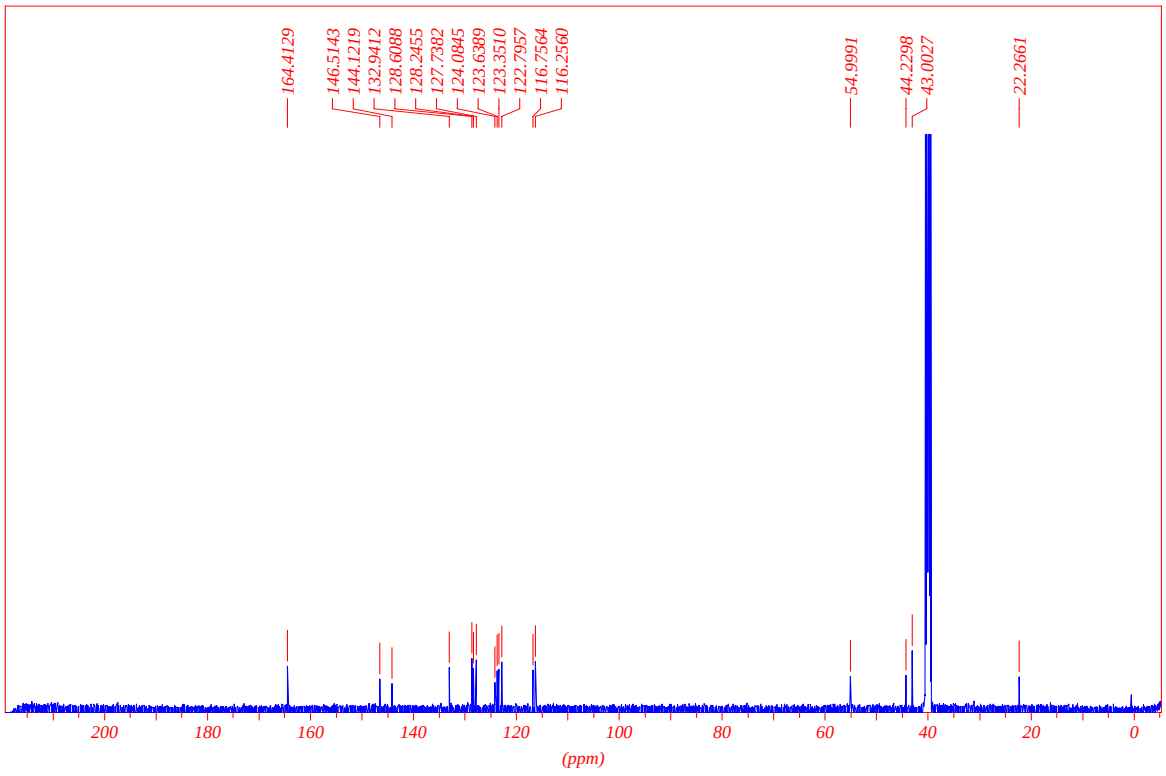


Chlorpromazine (1b, Table 1, Entry 2).

^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)

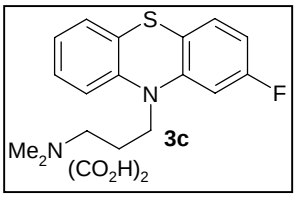


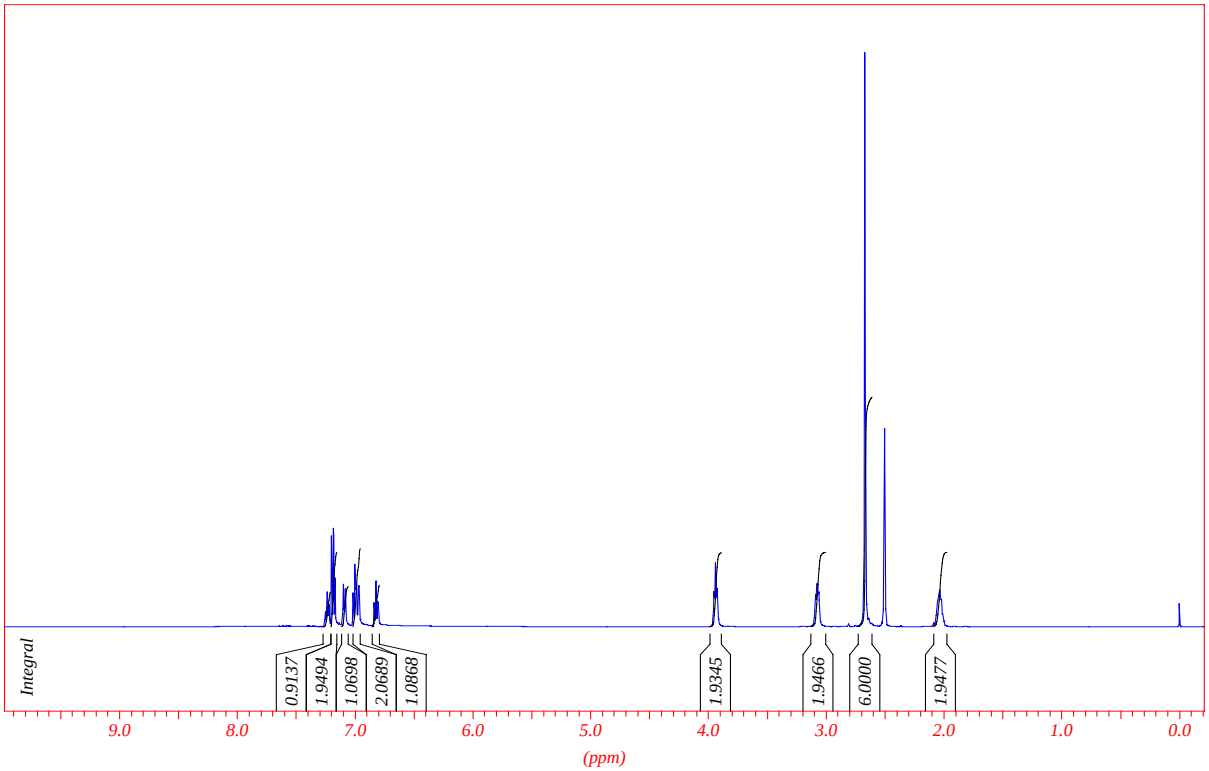


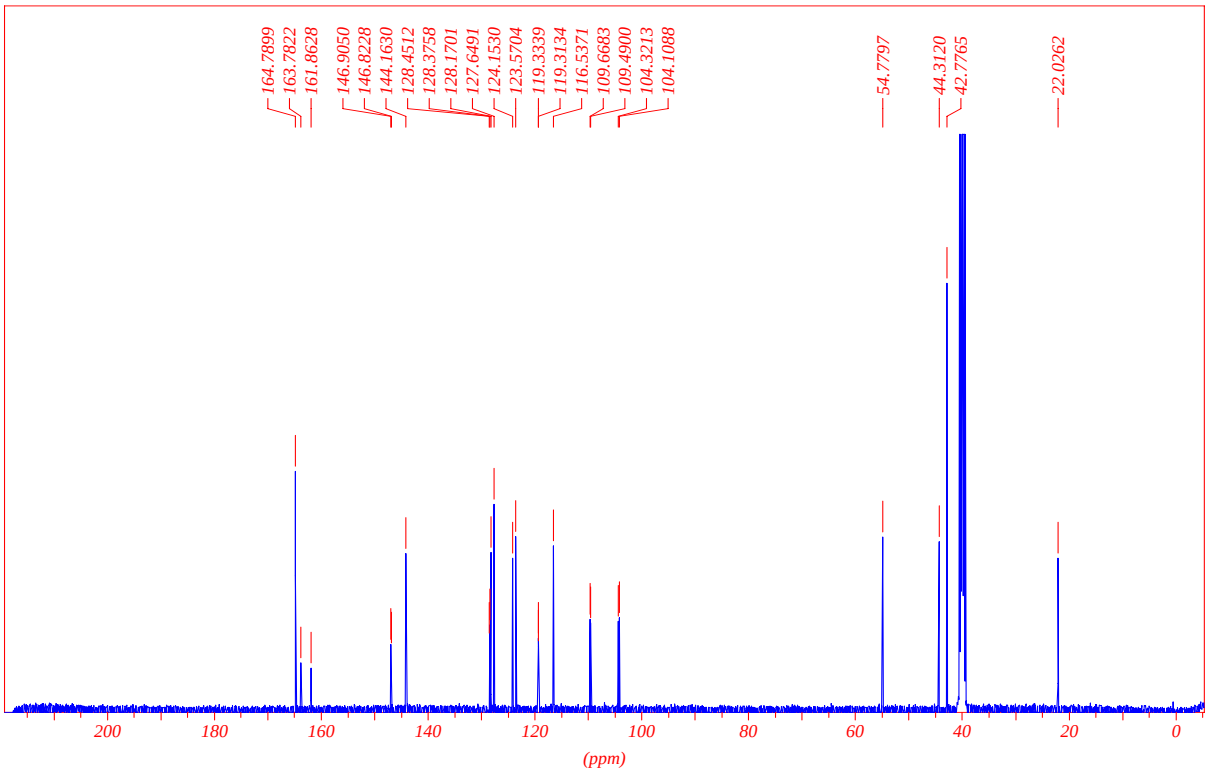


Flupromazine (1c, Table 1, Entry 2).

^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)

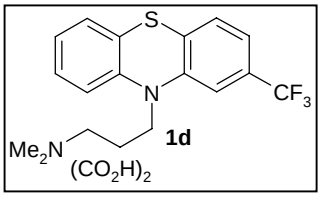


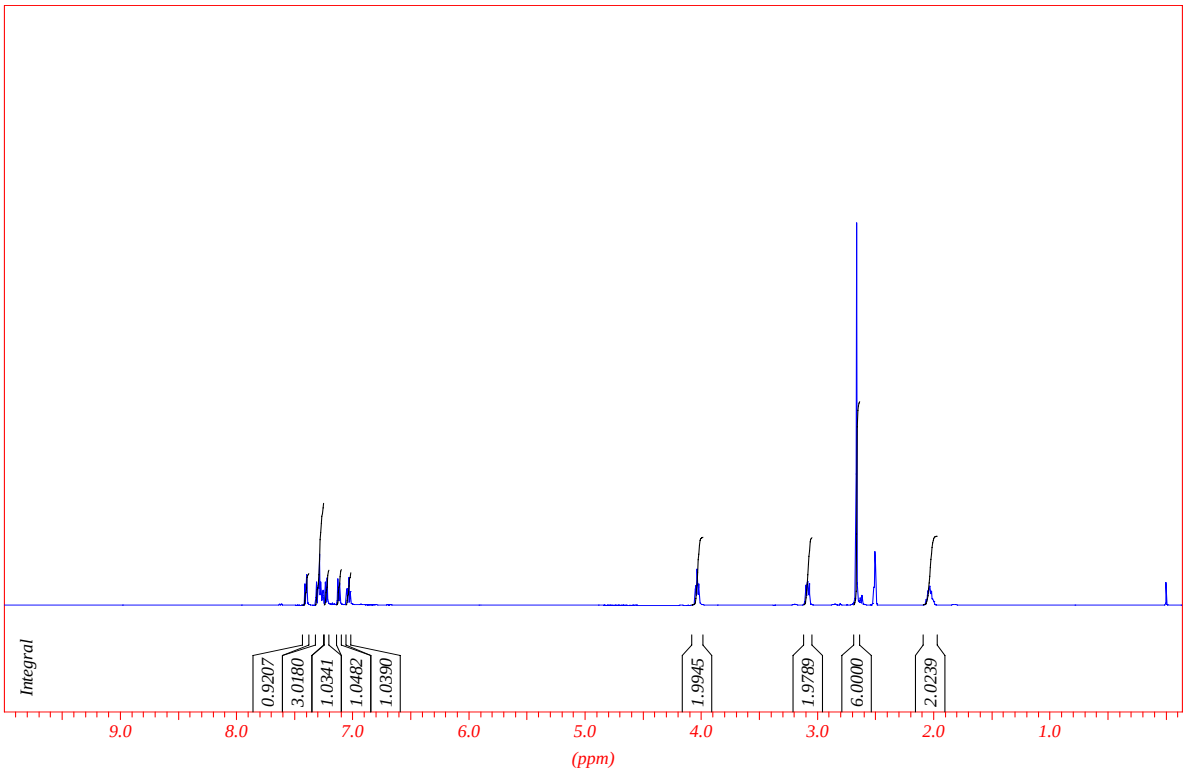


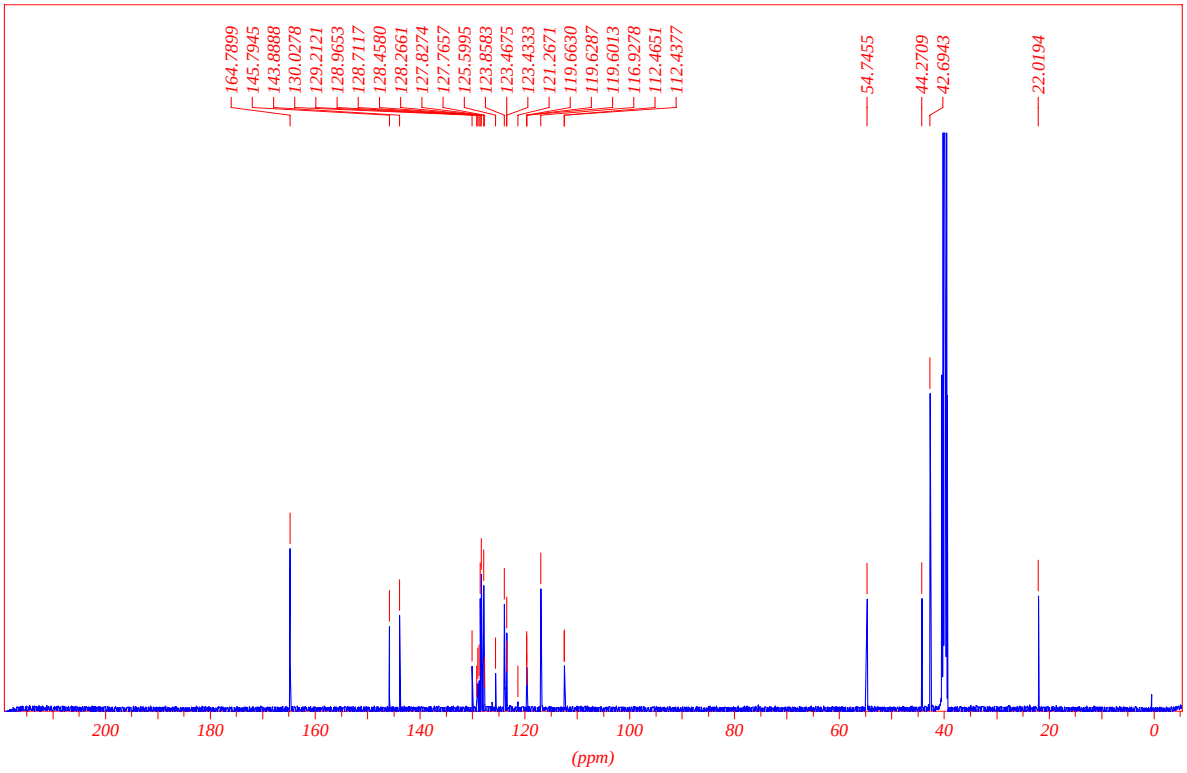


Triflupromazine (1d, Table 1, Entry 2).

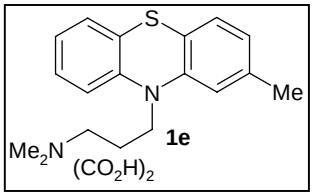
^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)

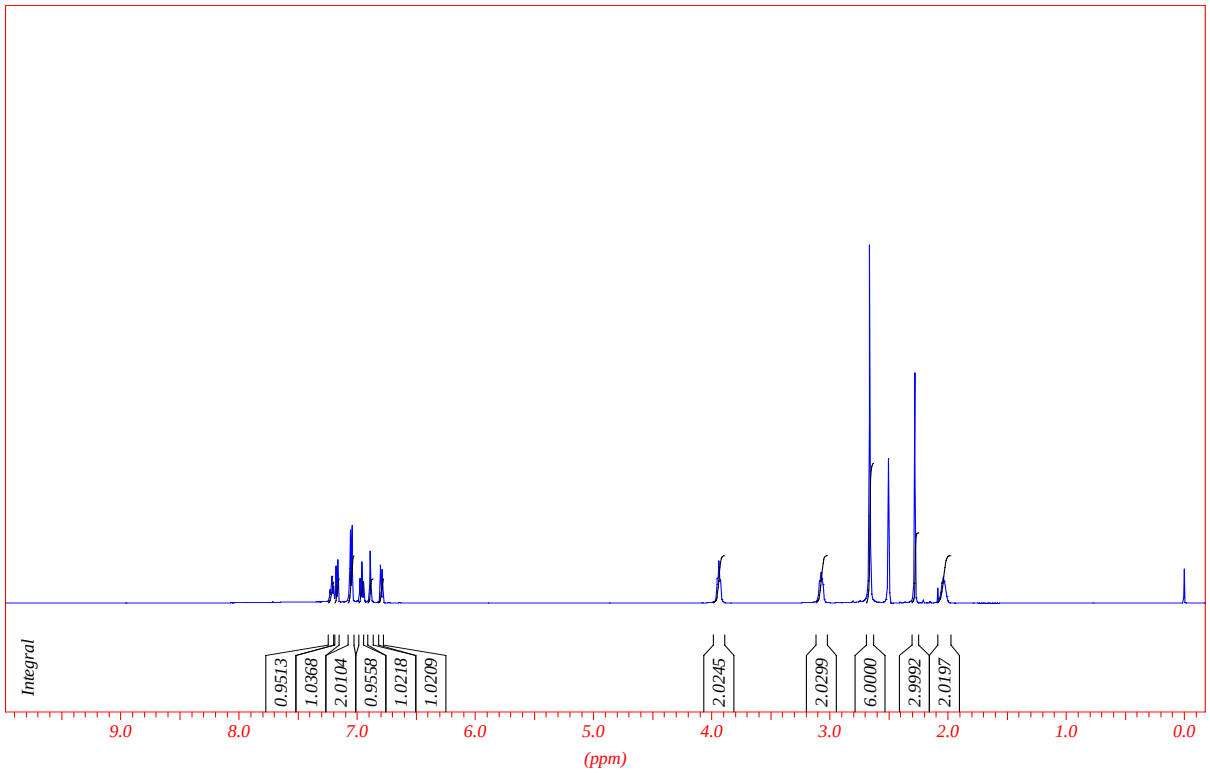


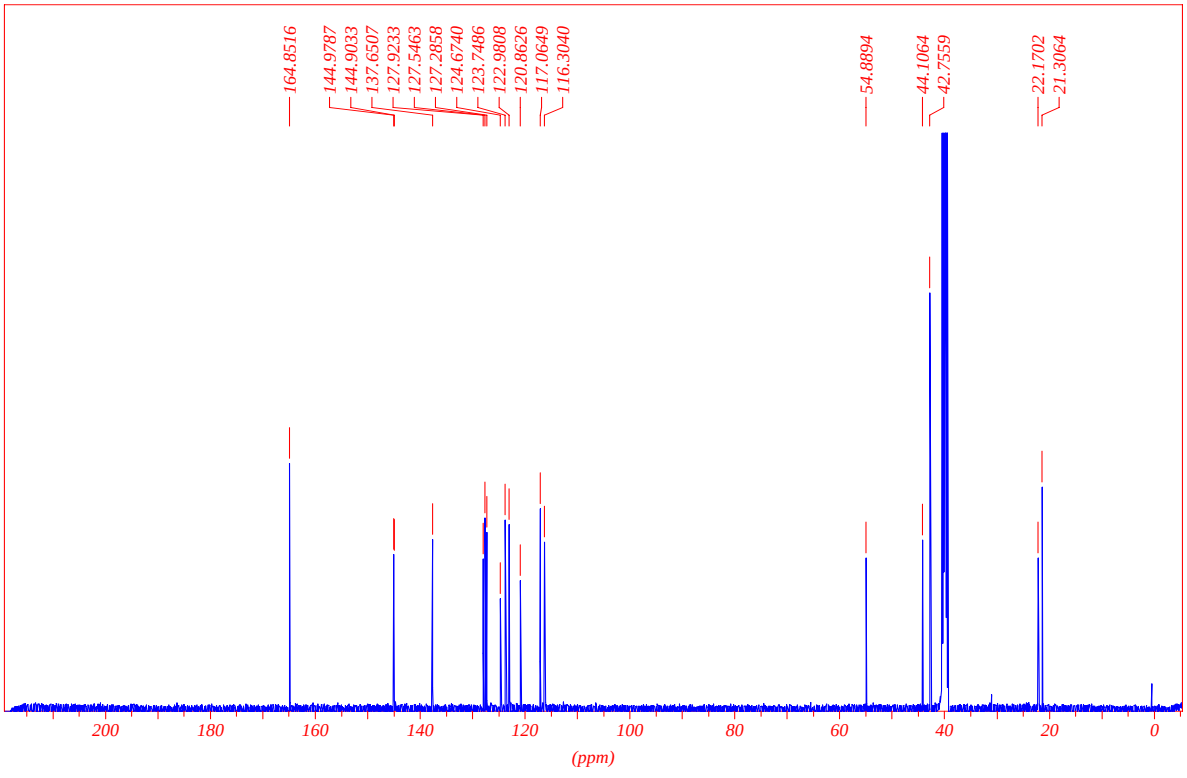




Methylpromazine (1e, Table 1, Entry 2).
^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)

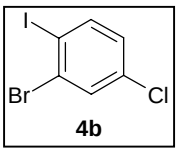




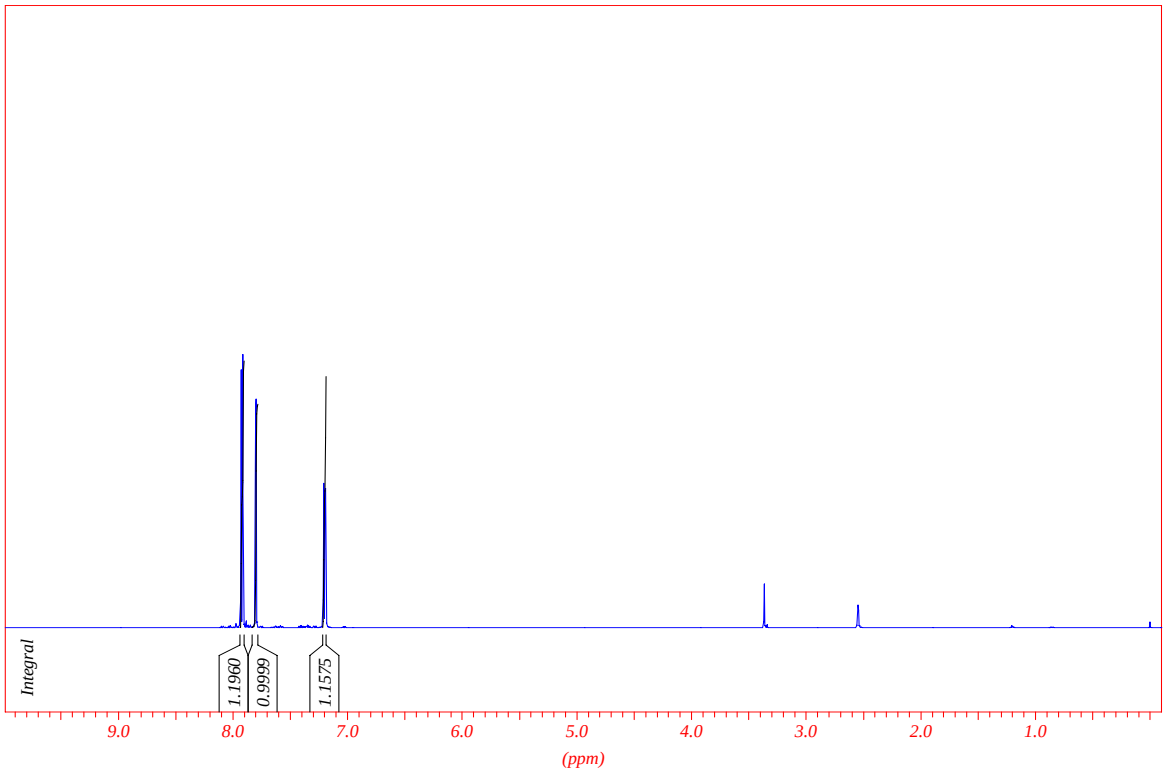


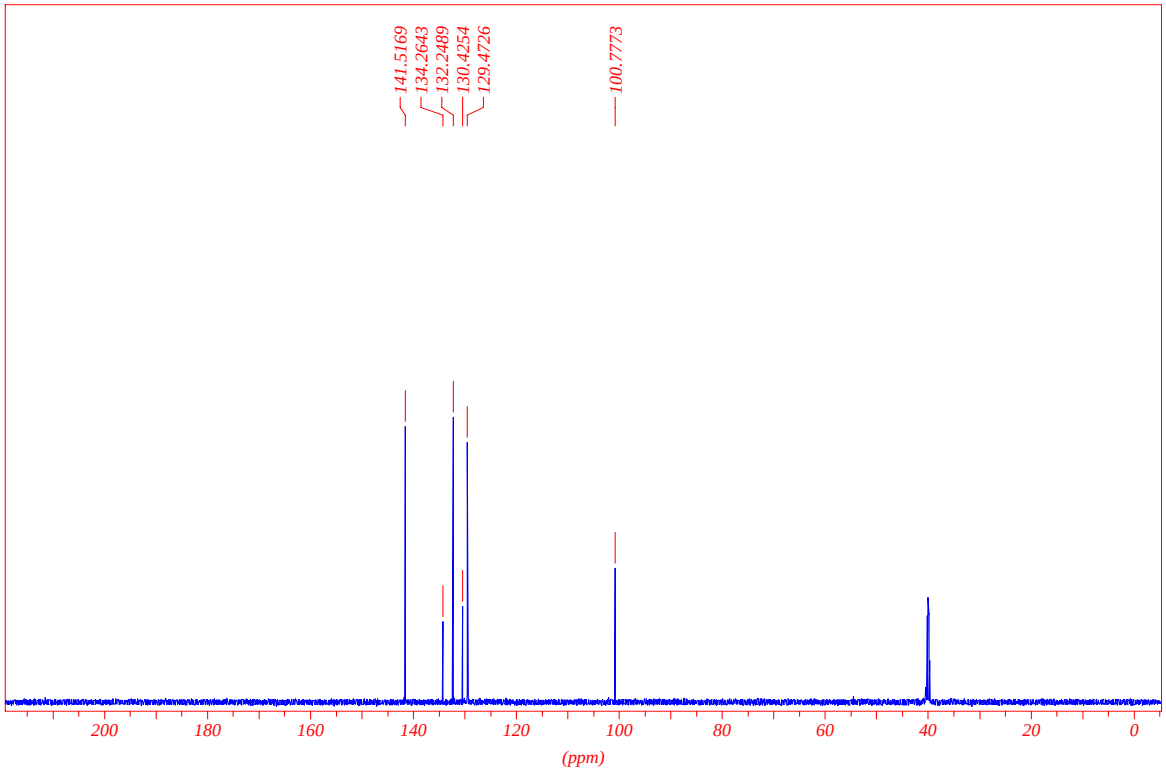
2-Bromo-4-chloro-iodobenzene (4b).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)



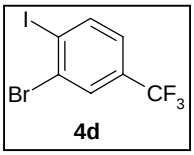
4b



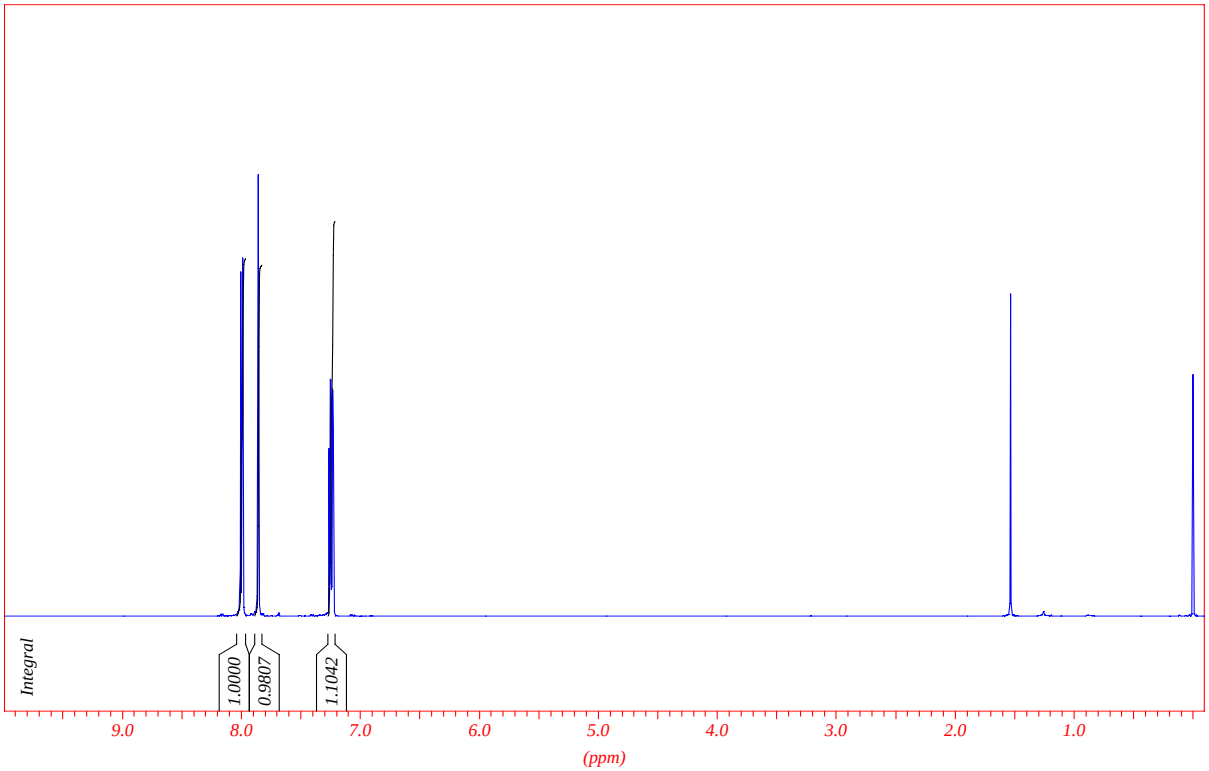


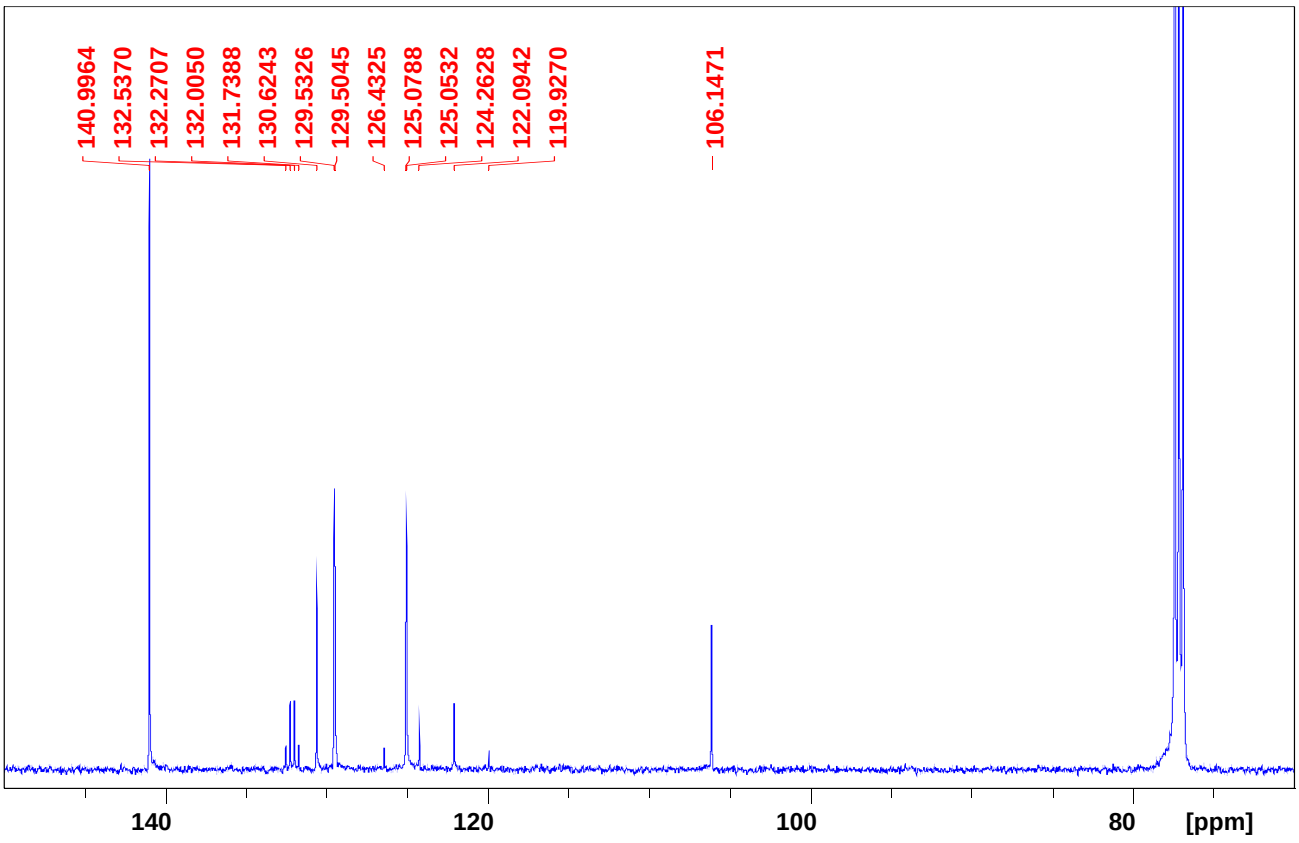
2-Bromo-1-iodo-4-trifluoromethyl-benzene (4d).

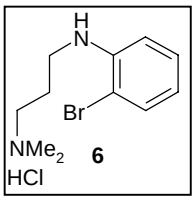
^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)



4d

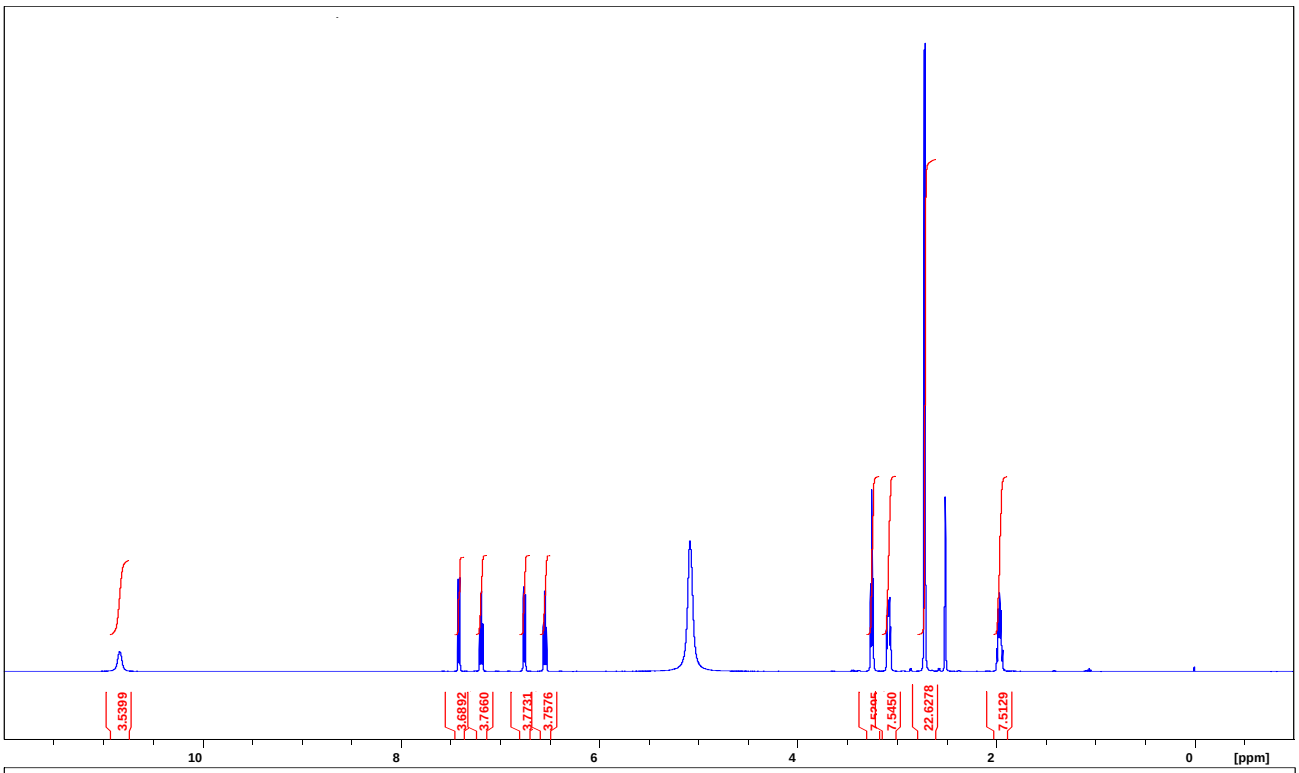


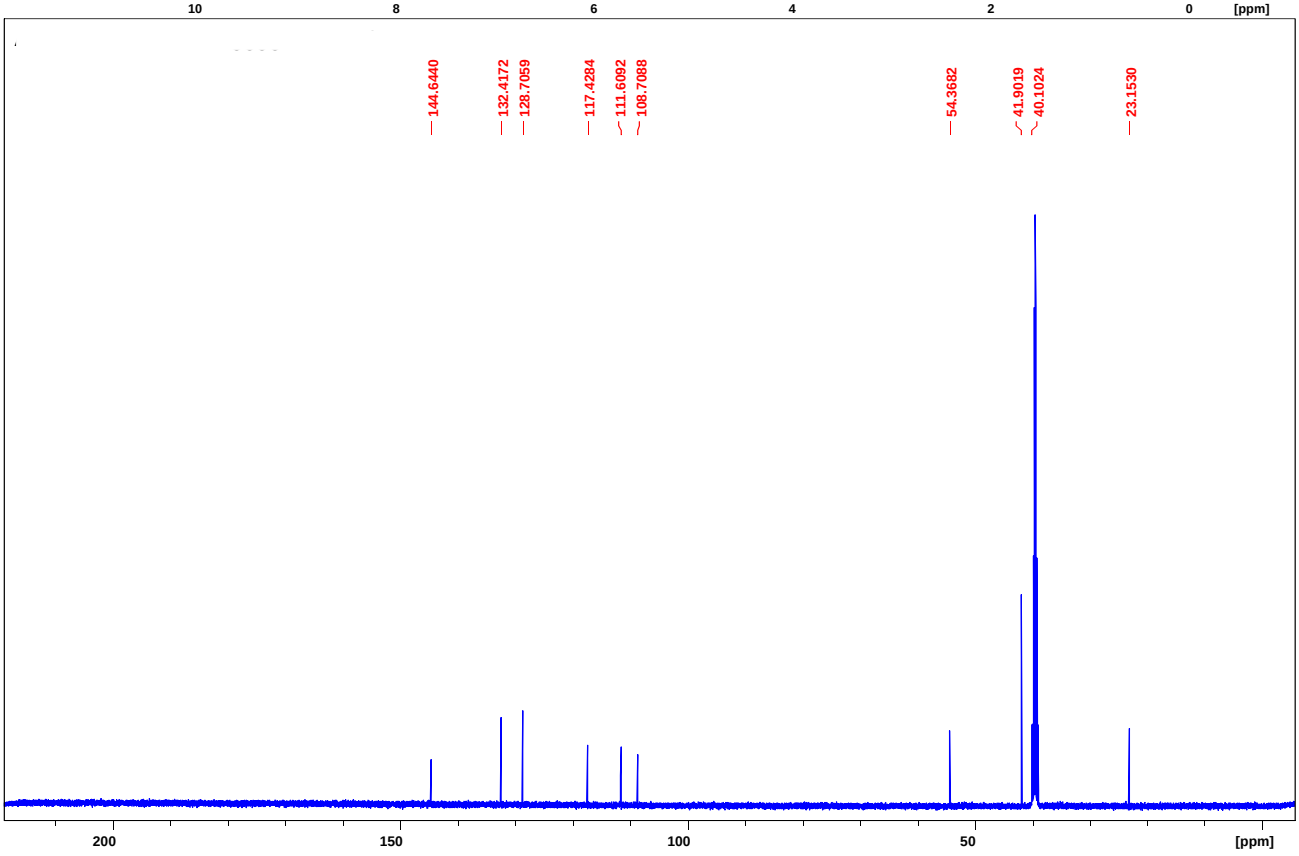




_N'_-(2-bromophenyl)-_N_,_N_-dimethylpropane-1,3-diamine hydrochloride (6).

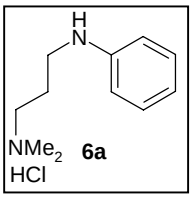
^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)

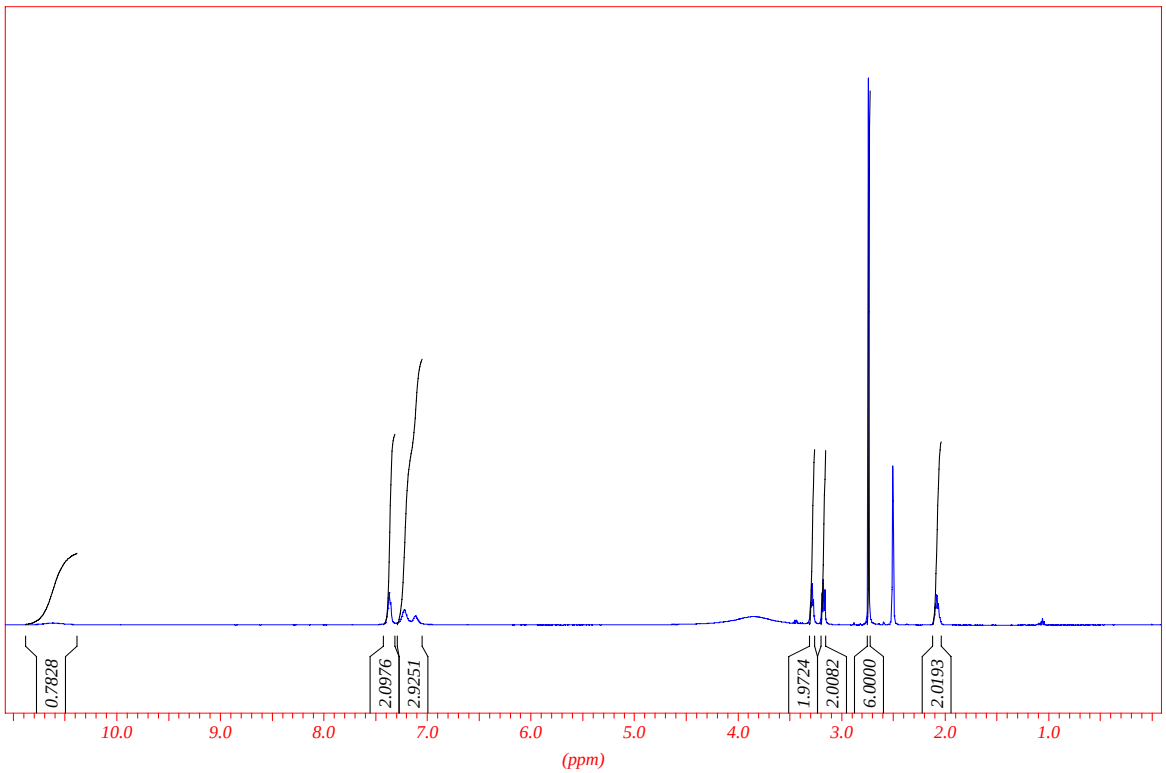


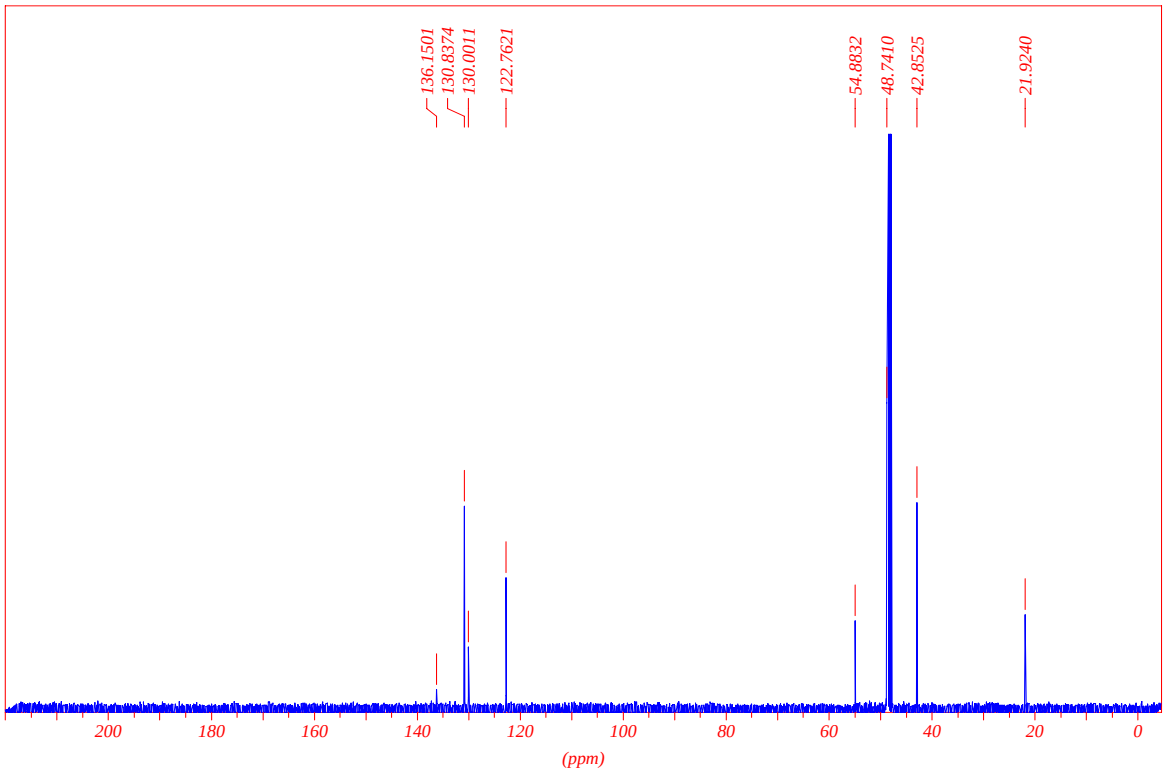


_N_,_N_-Dimethyl-_N'_-phenyl-propane-1,3-diamine hydrochloride (6a).

^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (CD_3OD, 125MHz)

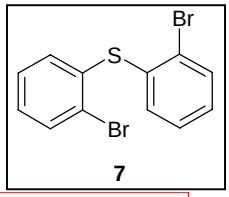






1-bromo-2-[(2-bromophenyl)thio]benzene (7).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)



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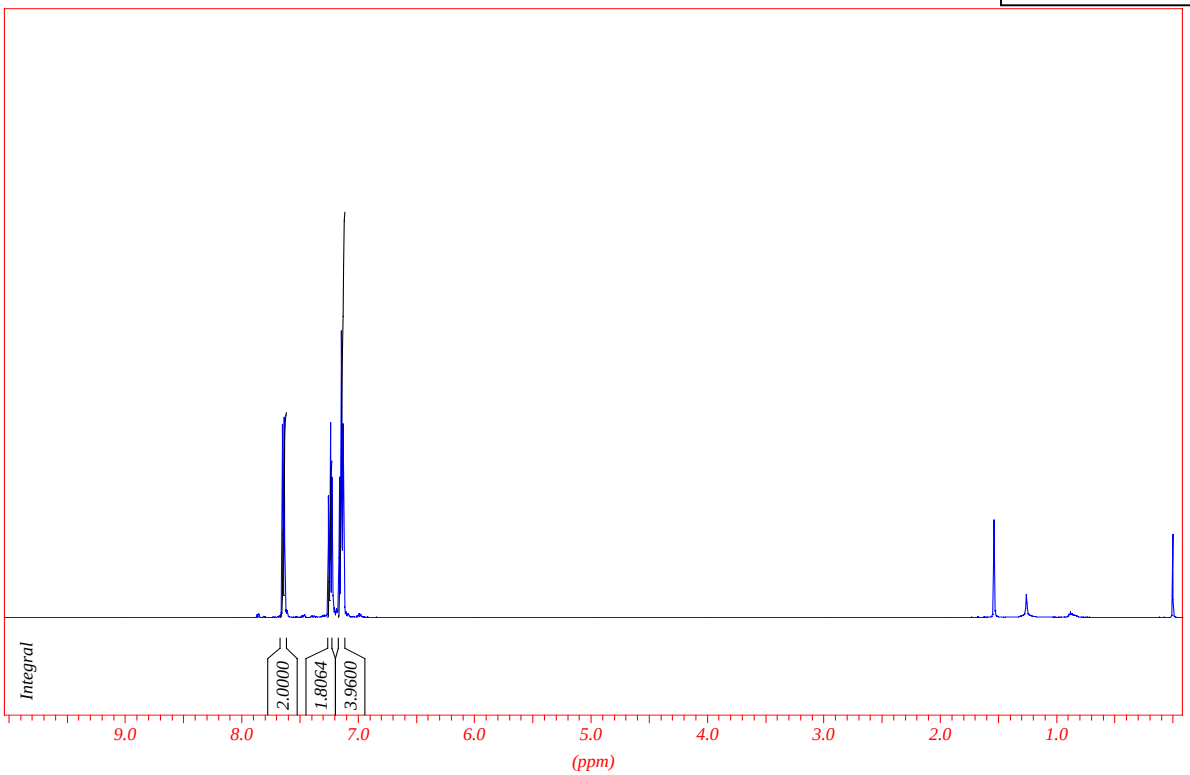
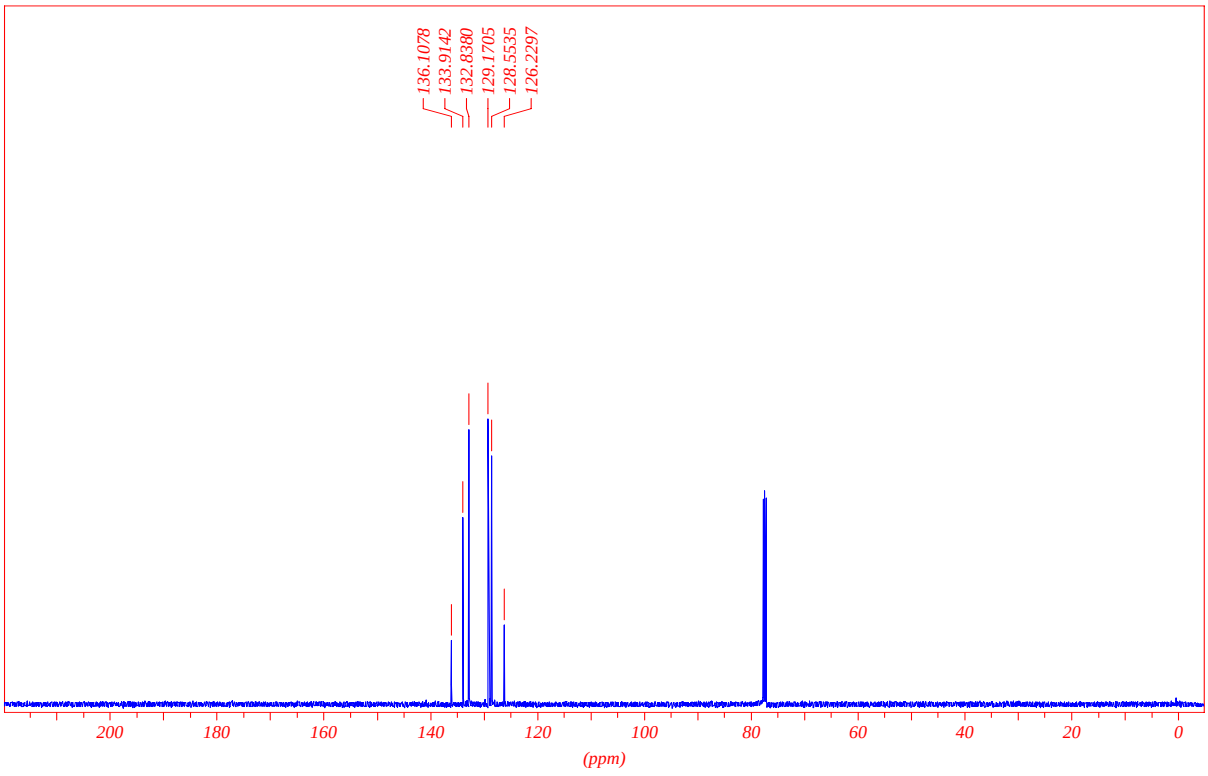
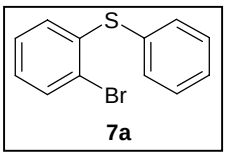


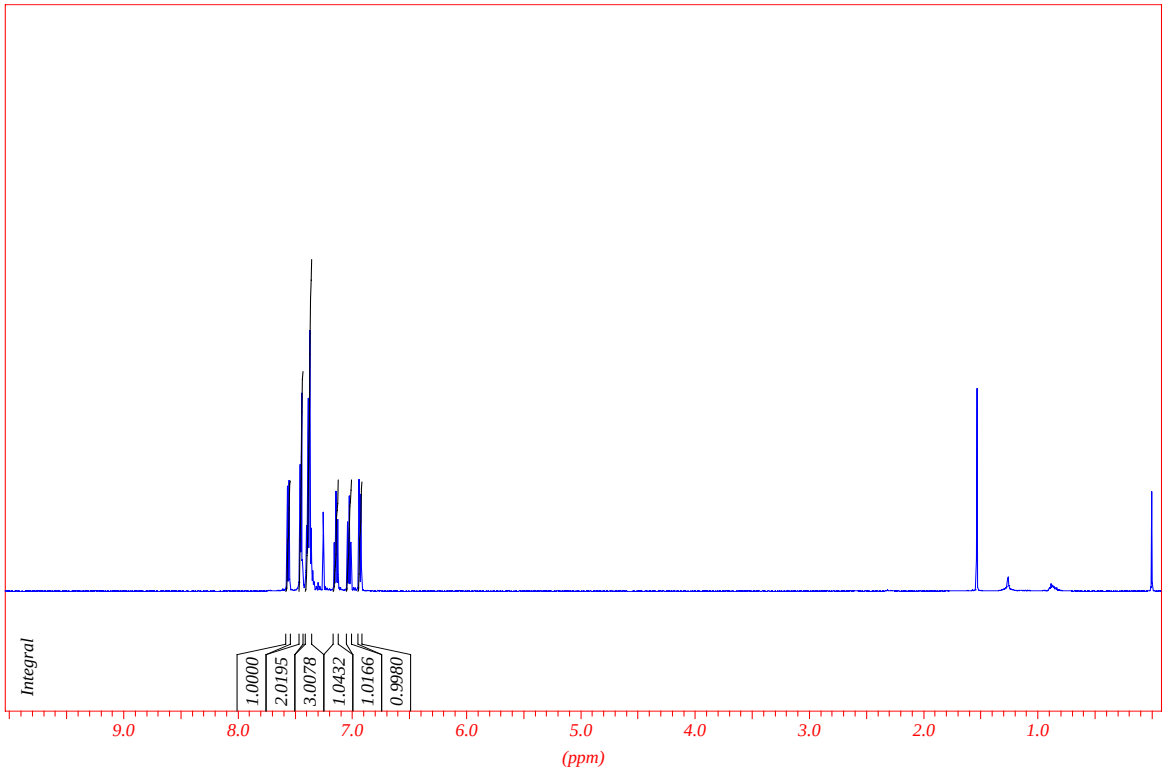


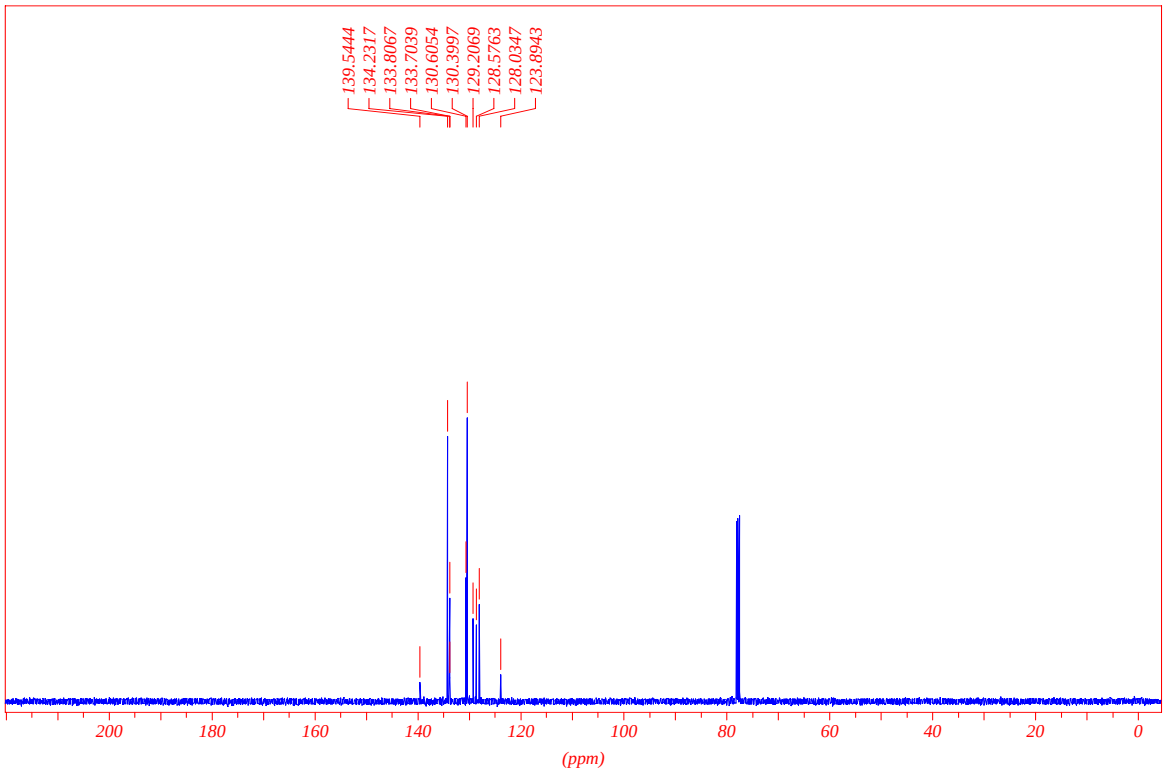
1-Bromo-2-phenylsulfanyl-benzene (7a).

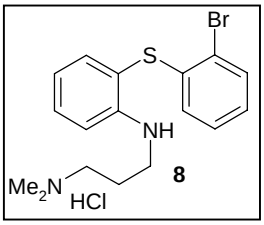
^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)



7a

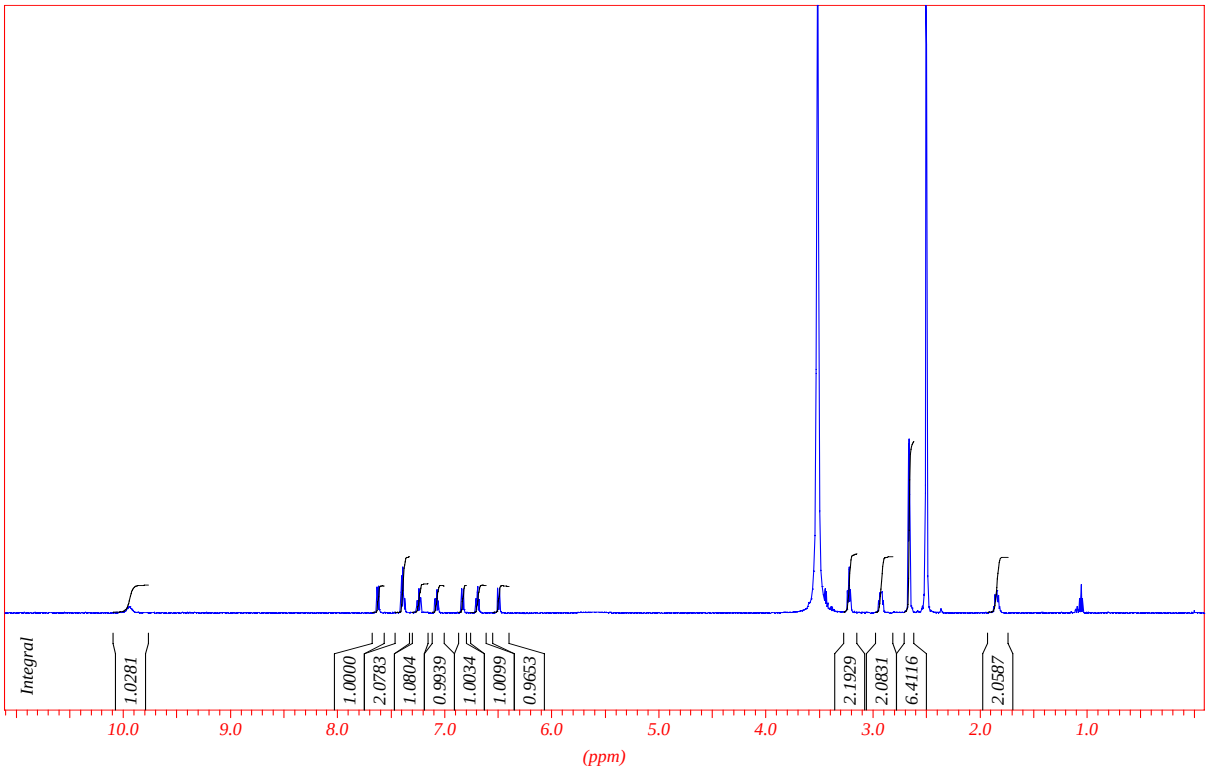


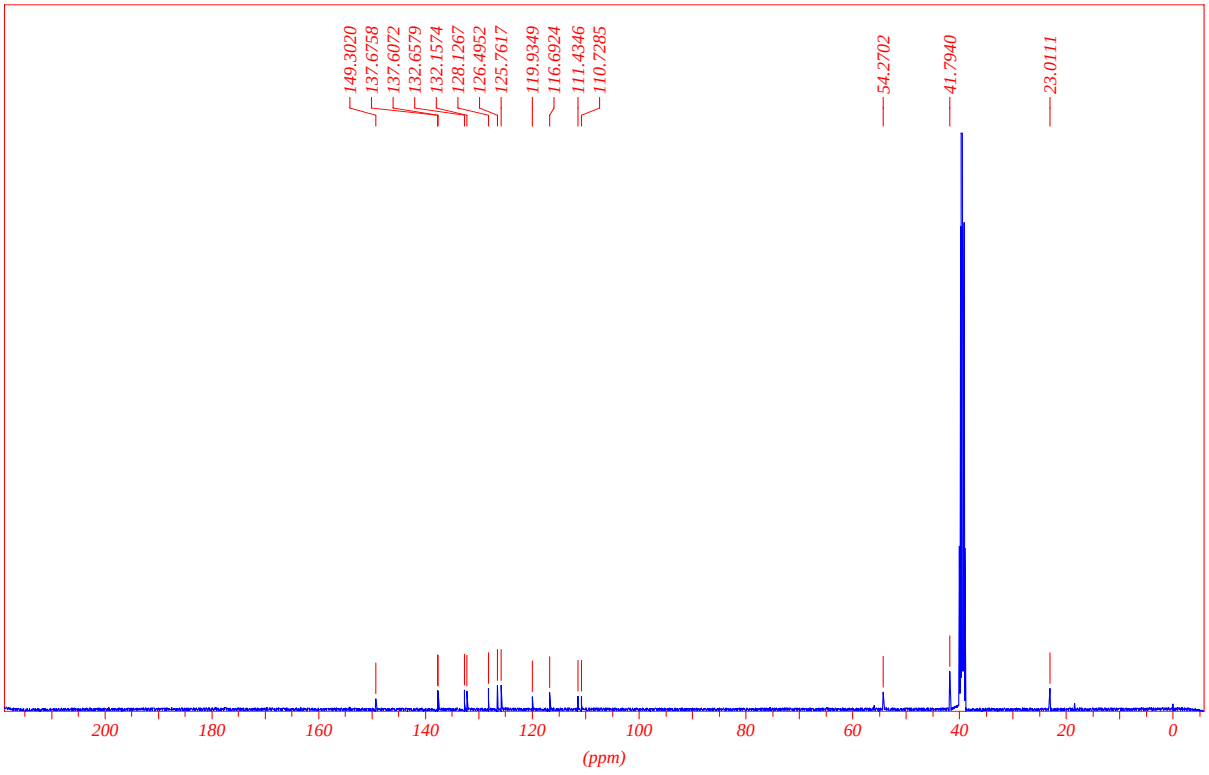




_N_'-{2-[(2-bromophenyl)thio]phenyl}-_N_,_N_-dimethylpropane-1,3-diamine hydrochloride (8).

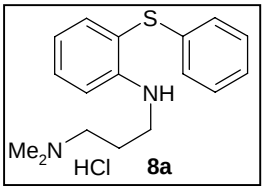
^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)

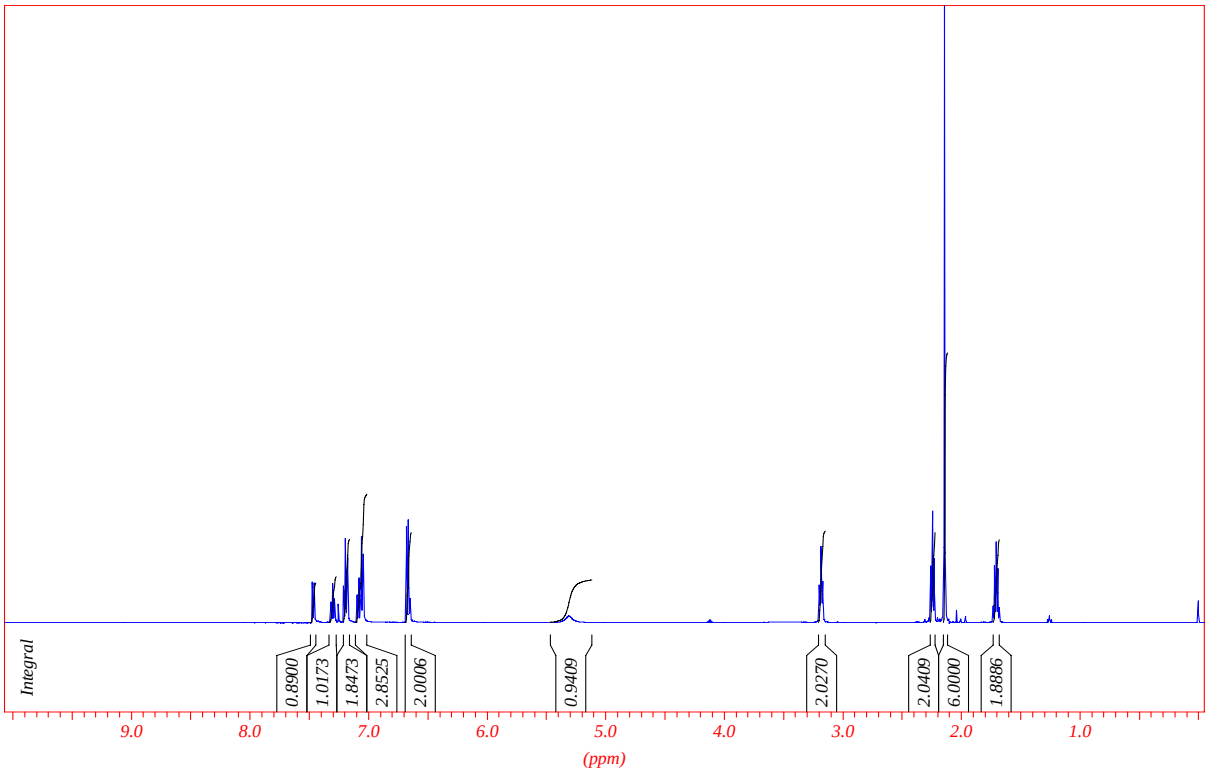


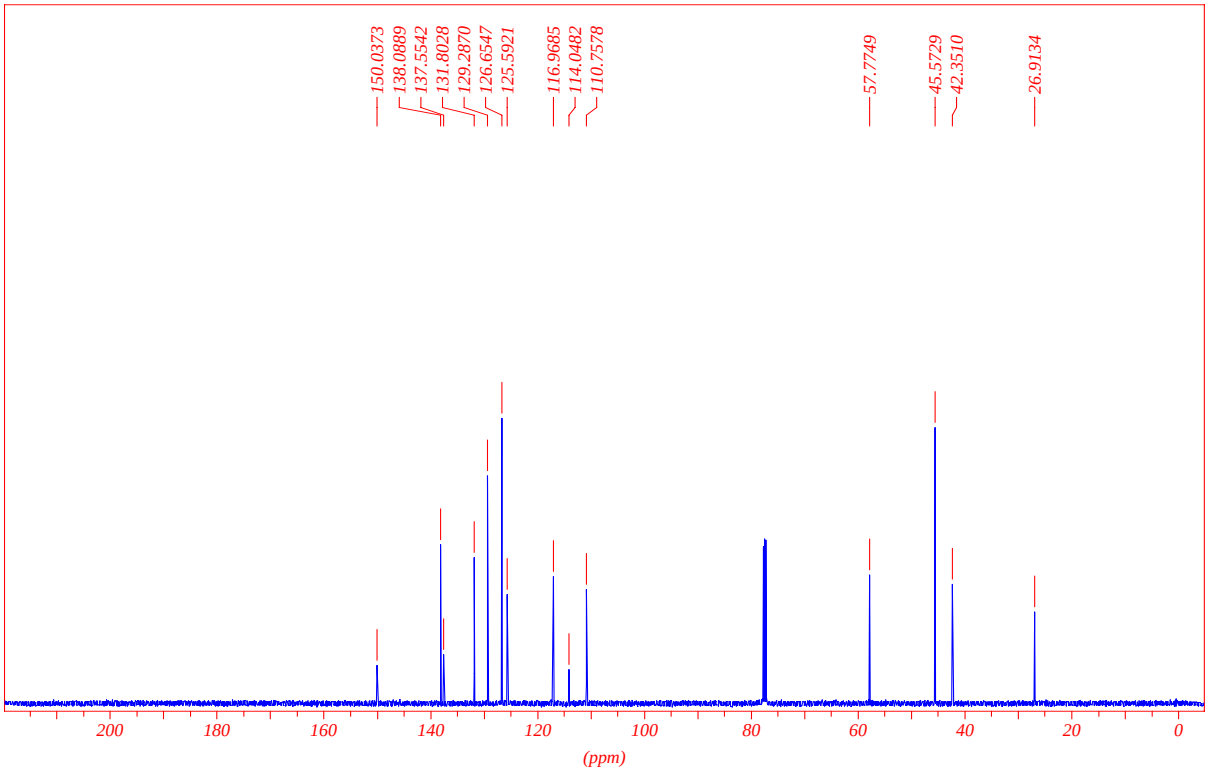


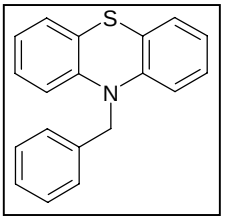
_N_,_N_-Dimethyl-_N'_-(2-phenylsulfanyl-phenyl)-propane-1,3-diamine hydrochloride (8a).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)



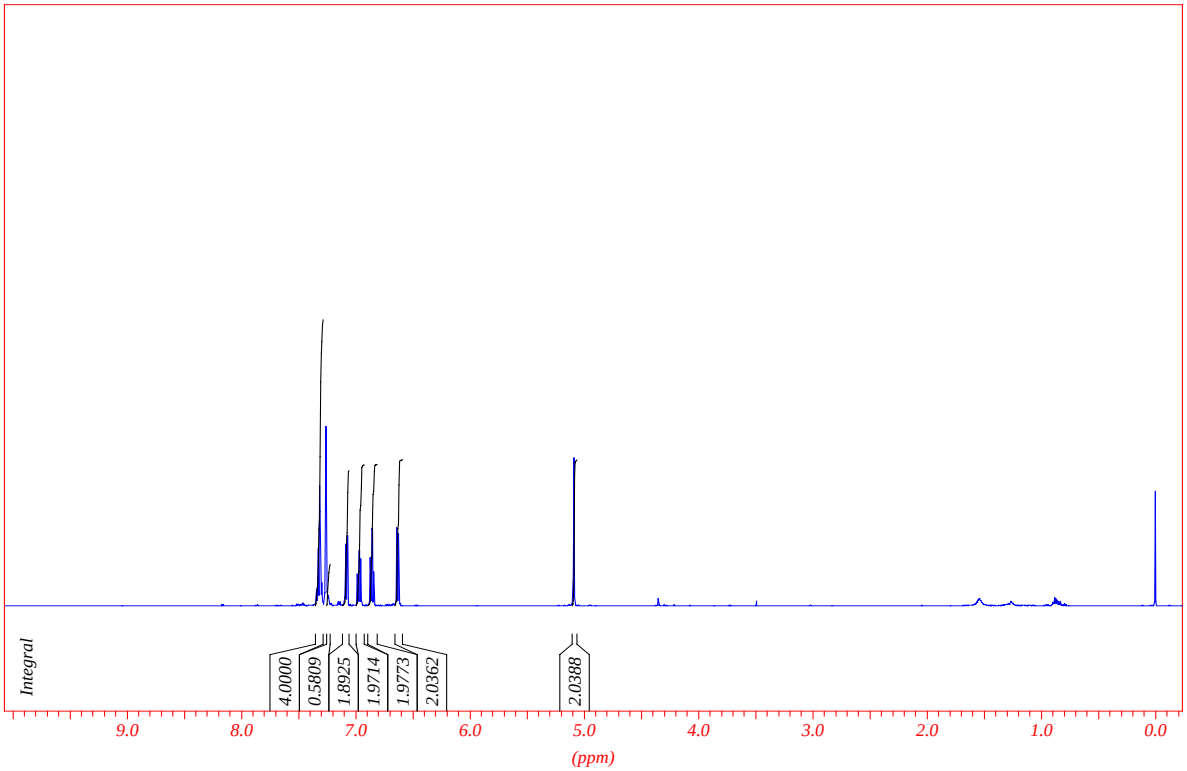


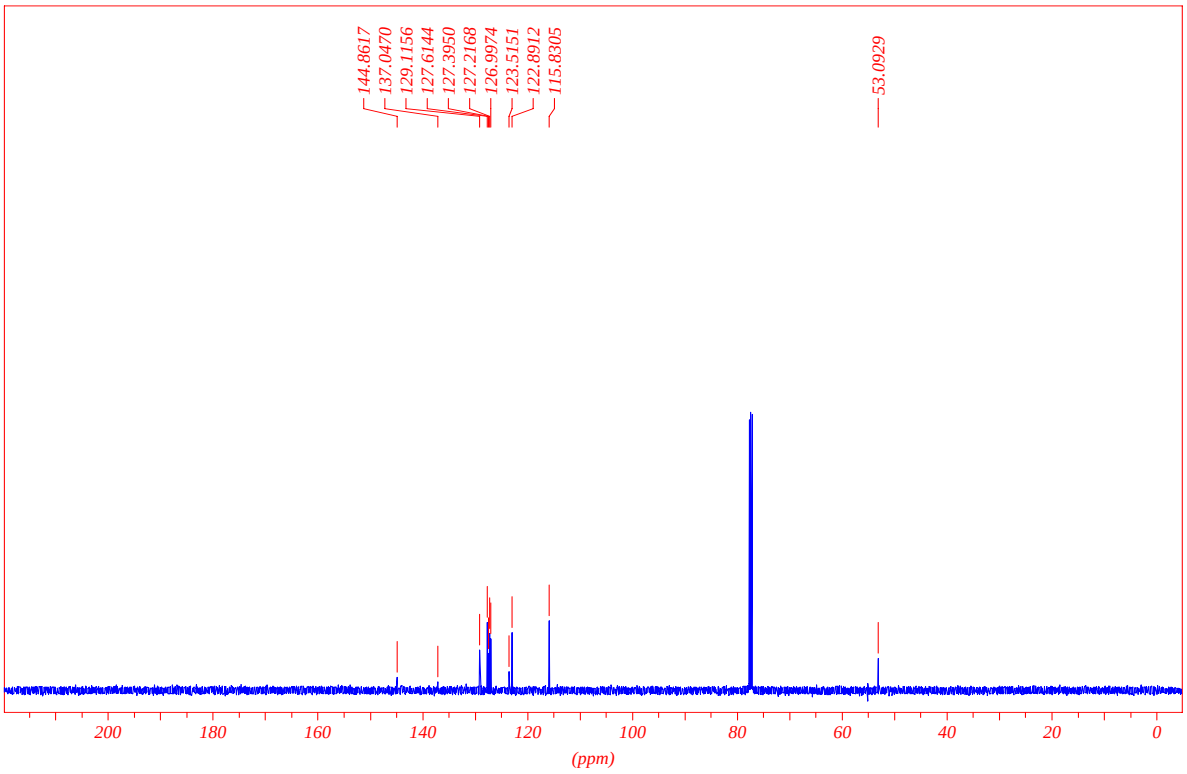


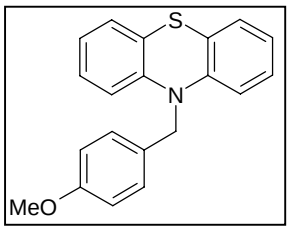


N-Benzyl-phenothiazine (Table 1, Entry 3).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)

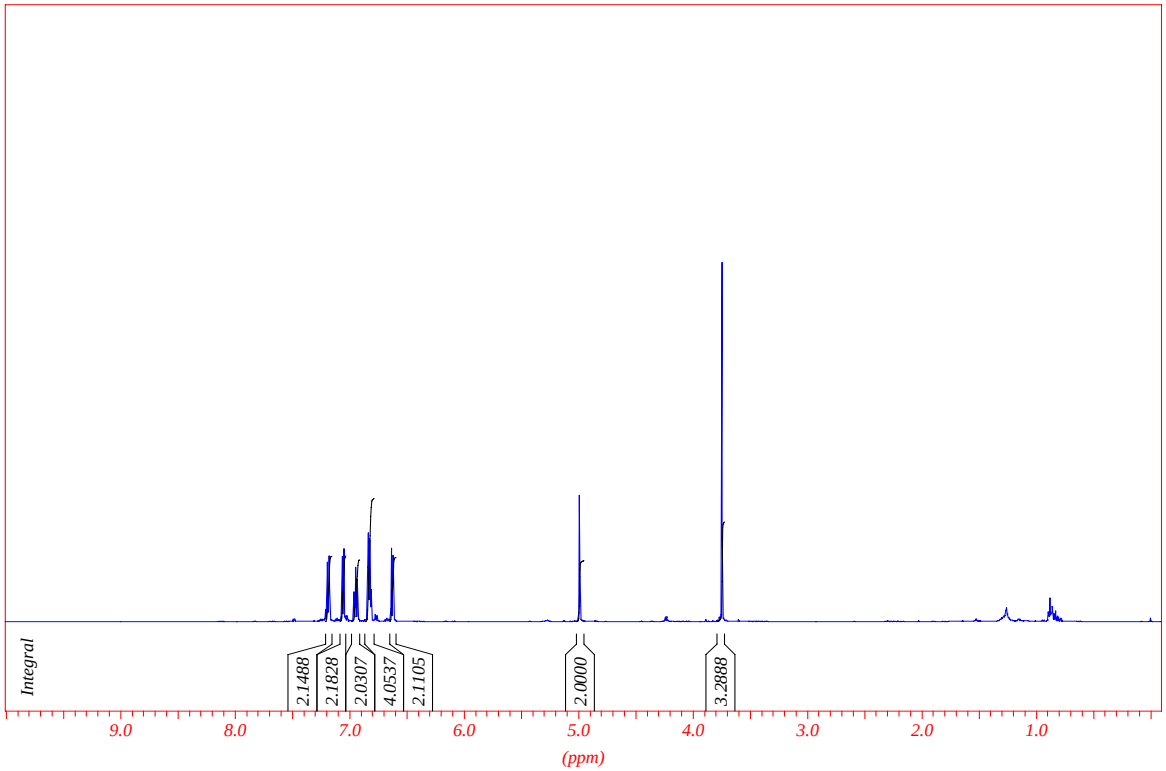


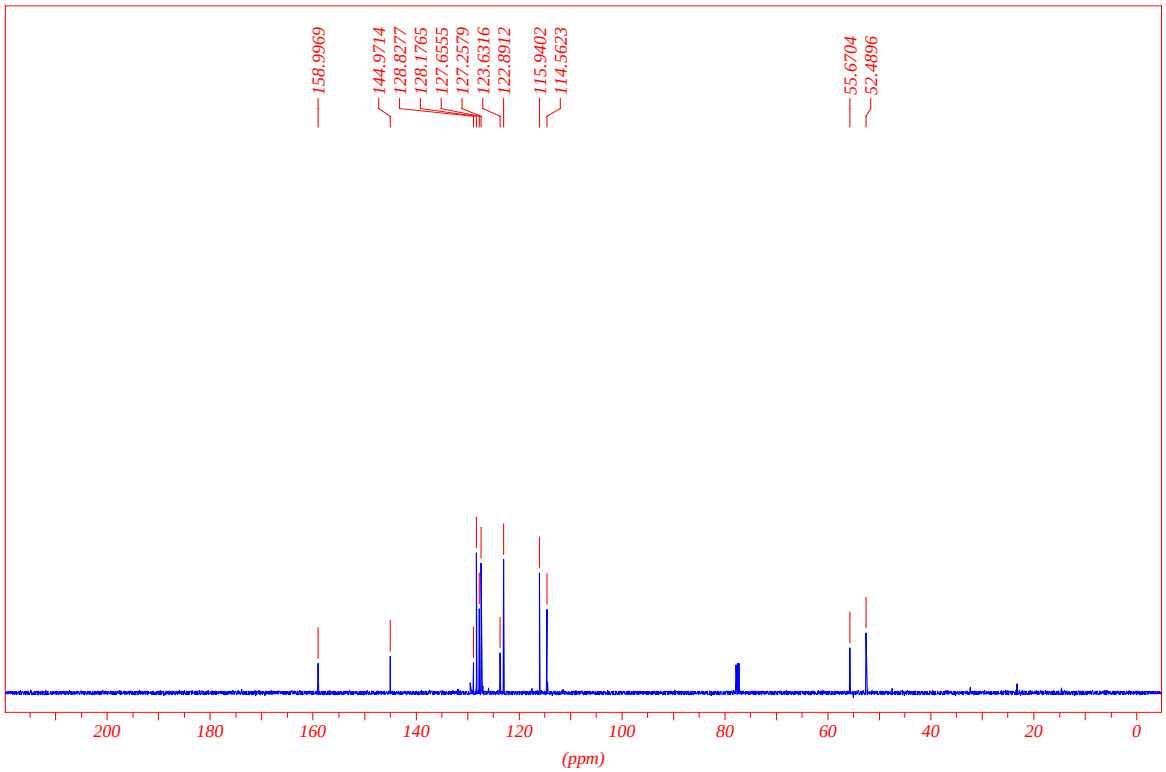


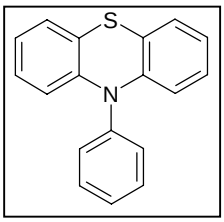


10-(4-Methoxy-benzyl)-10H-phenothiazine (Table 1, Entry 3).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)

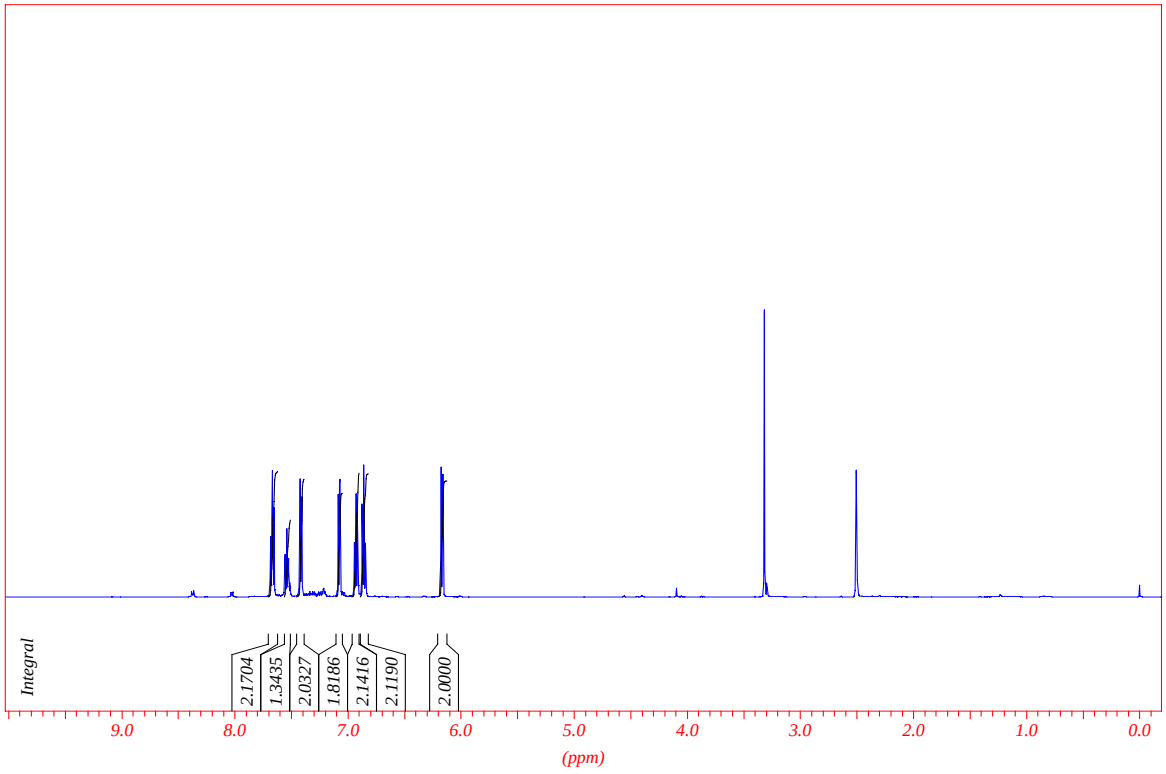


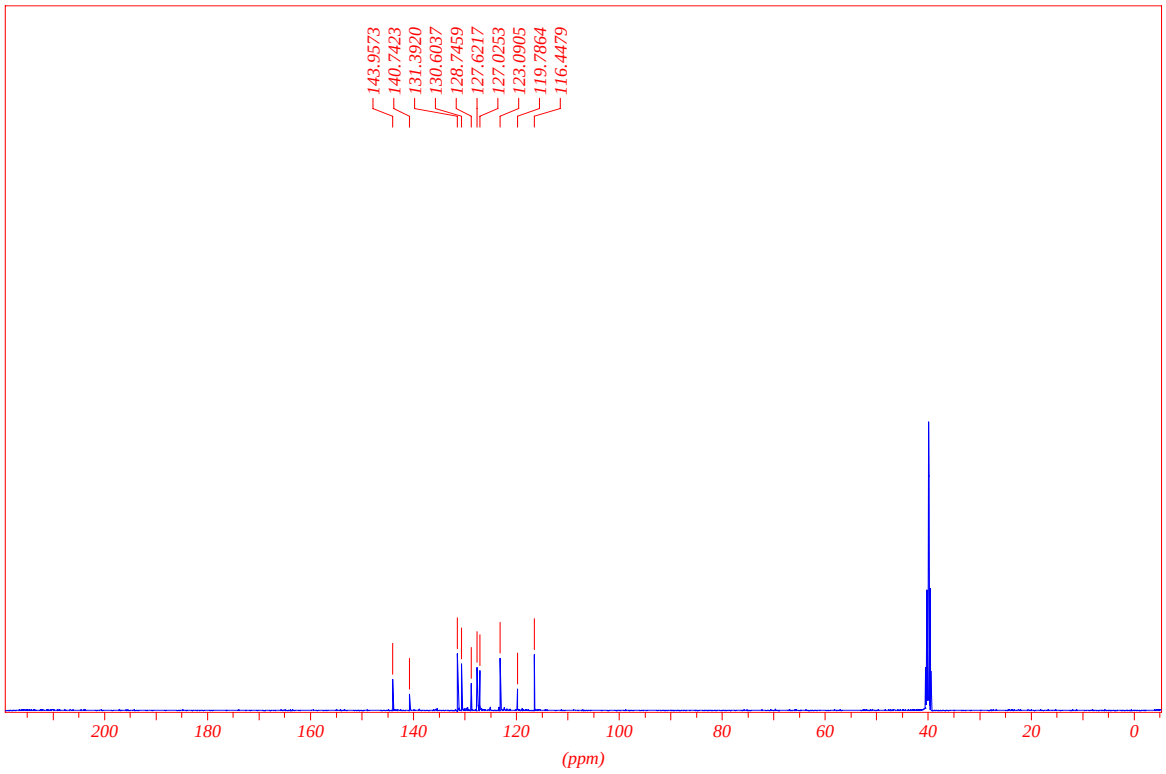


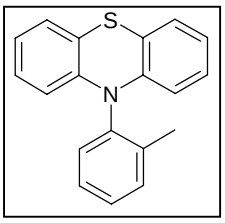


N-Phenyl-phenothiazine (Table 1, Entry 4).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)

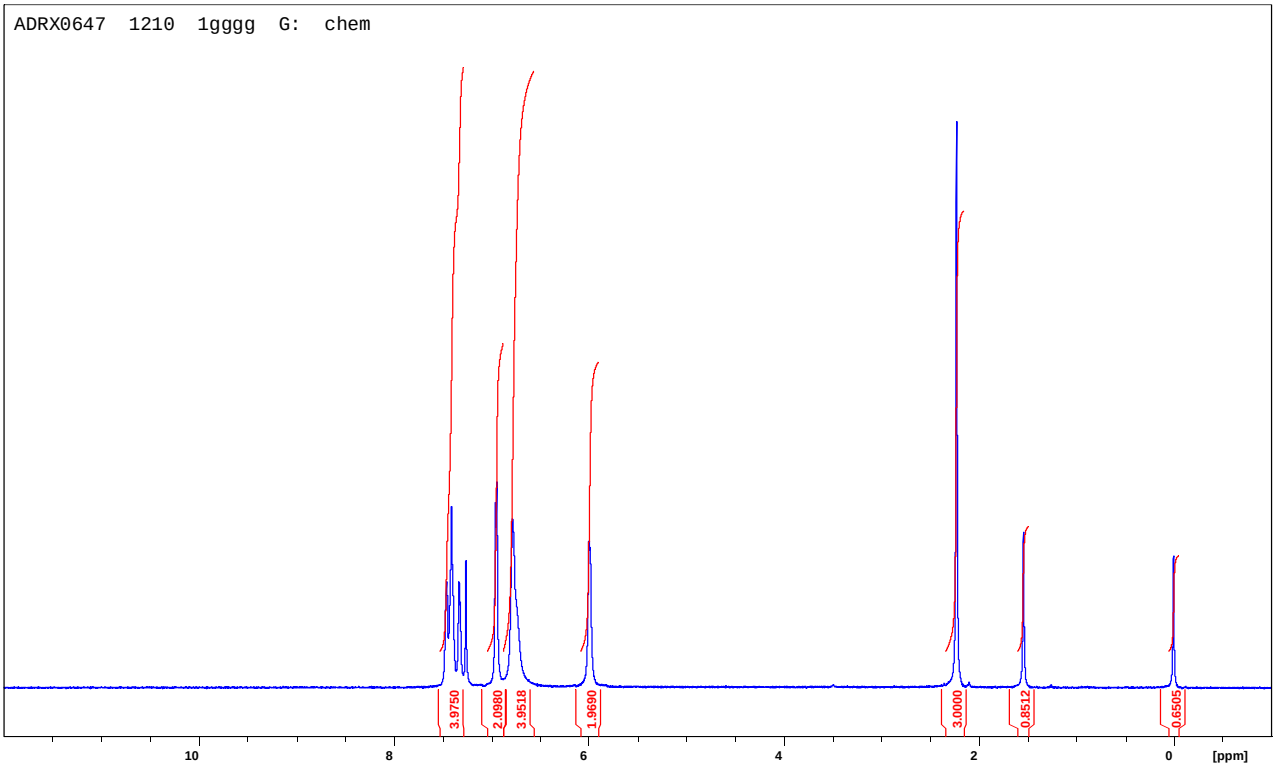


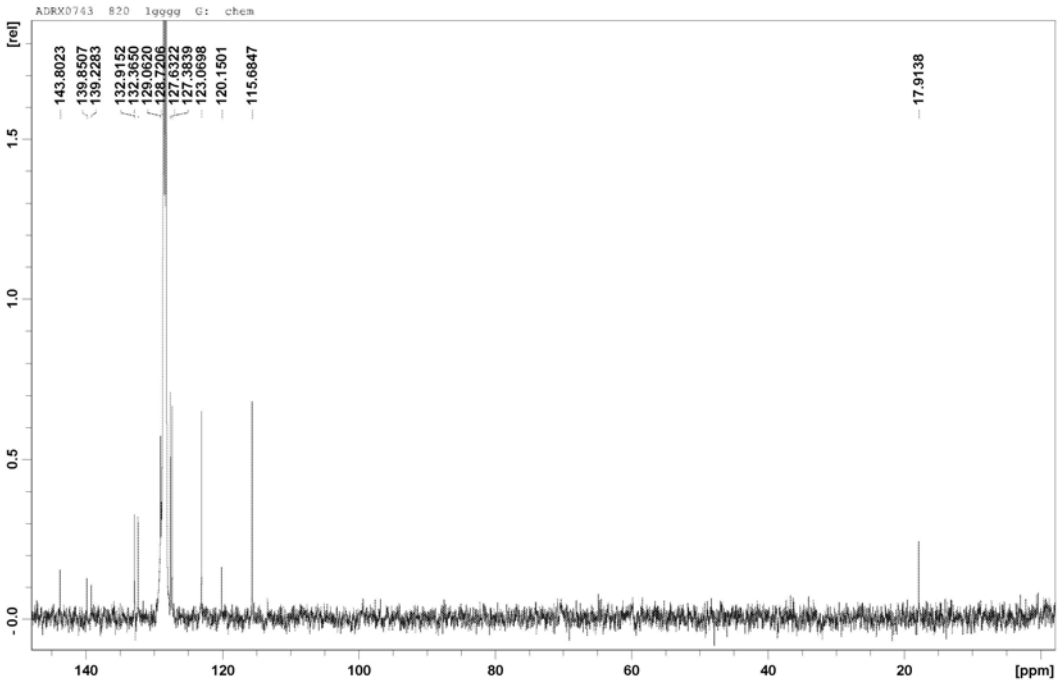


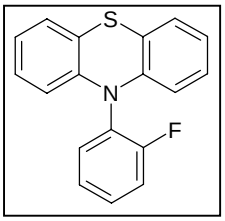


N-(2-Methyl-phenyl)-phenothiazine (Table 1, Entry 4).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)

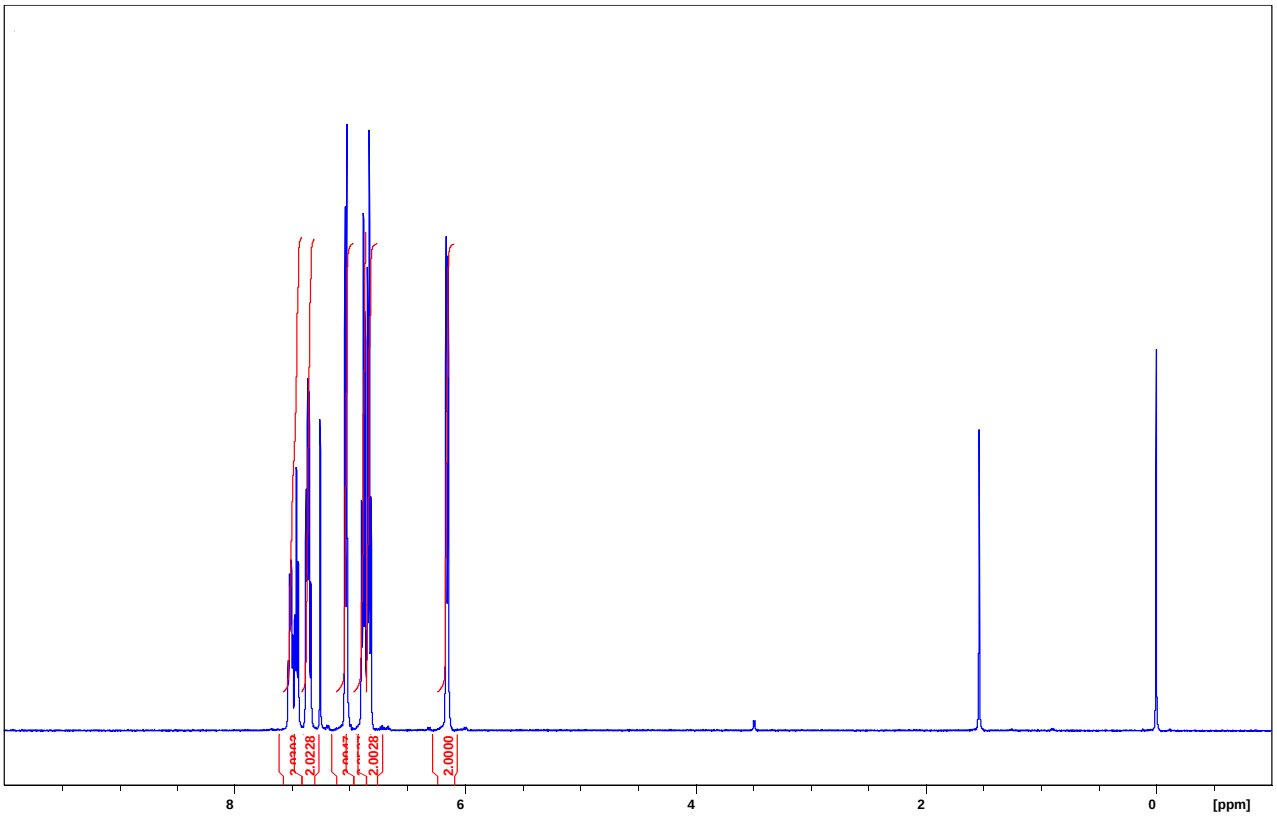


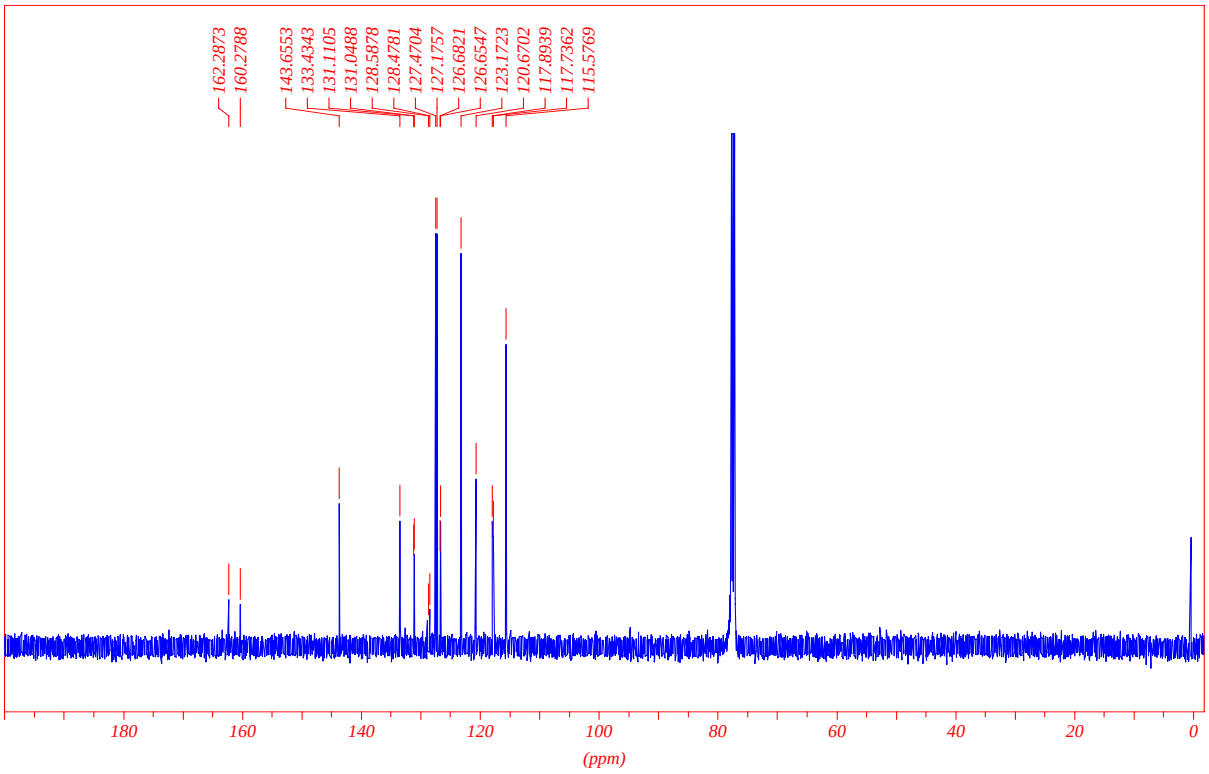




N-(2-Fluoro-phenyl)-phenothiazine (Table 1, Entry 4).

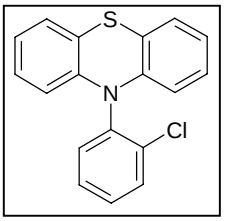
^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)

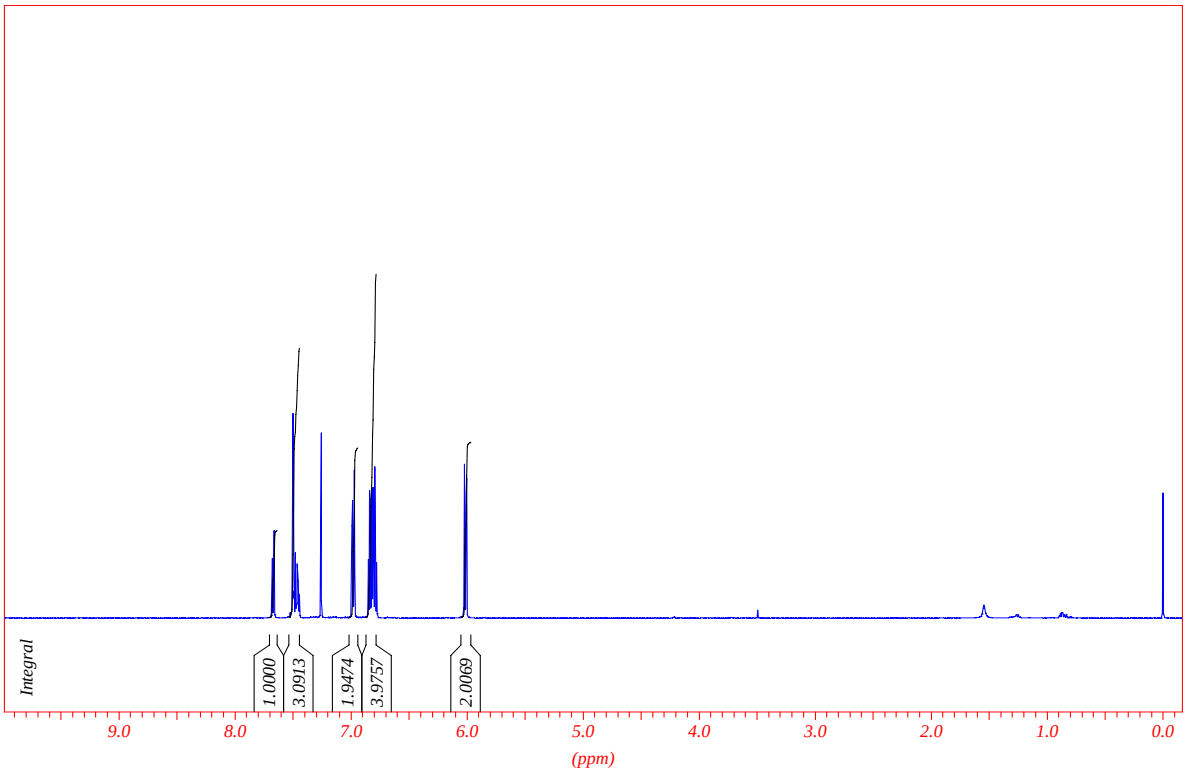


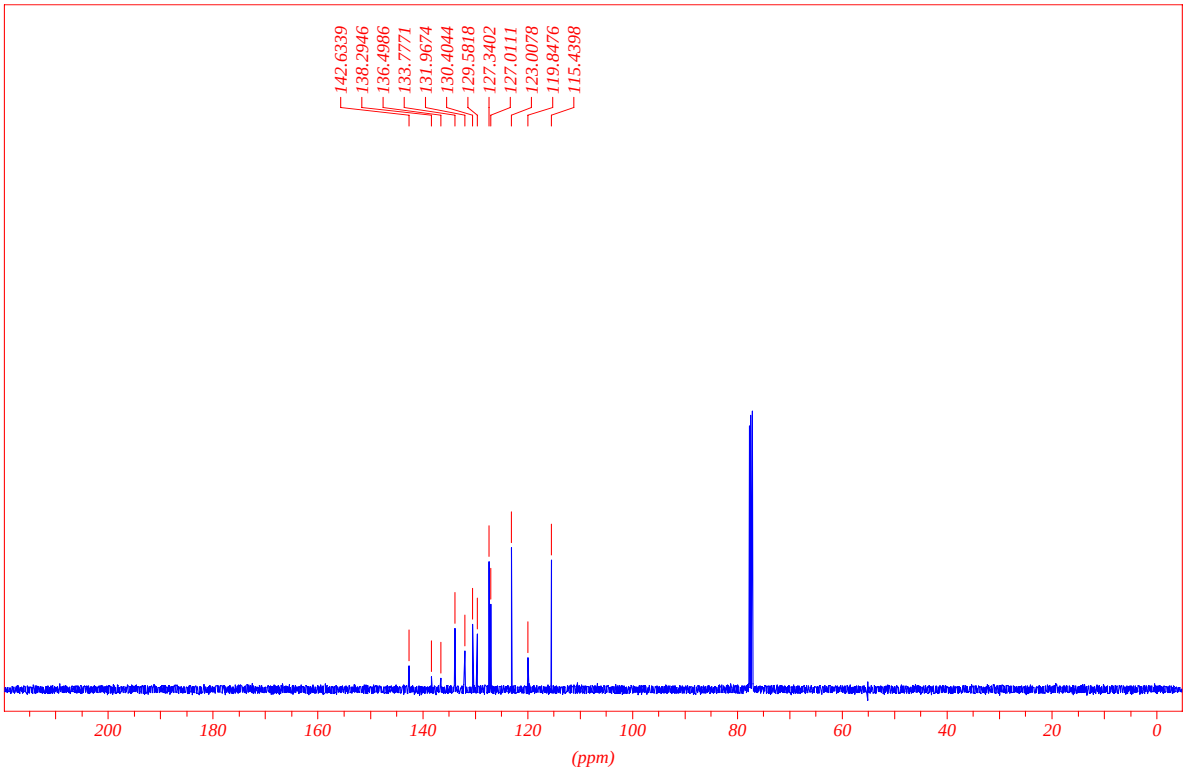


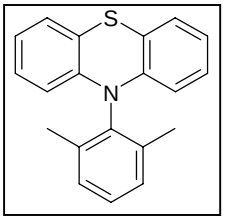
N-(2-Chloro-phenyl)-phenothiazine (Table 1, Entry 4).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)



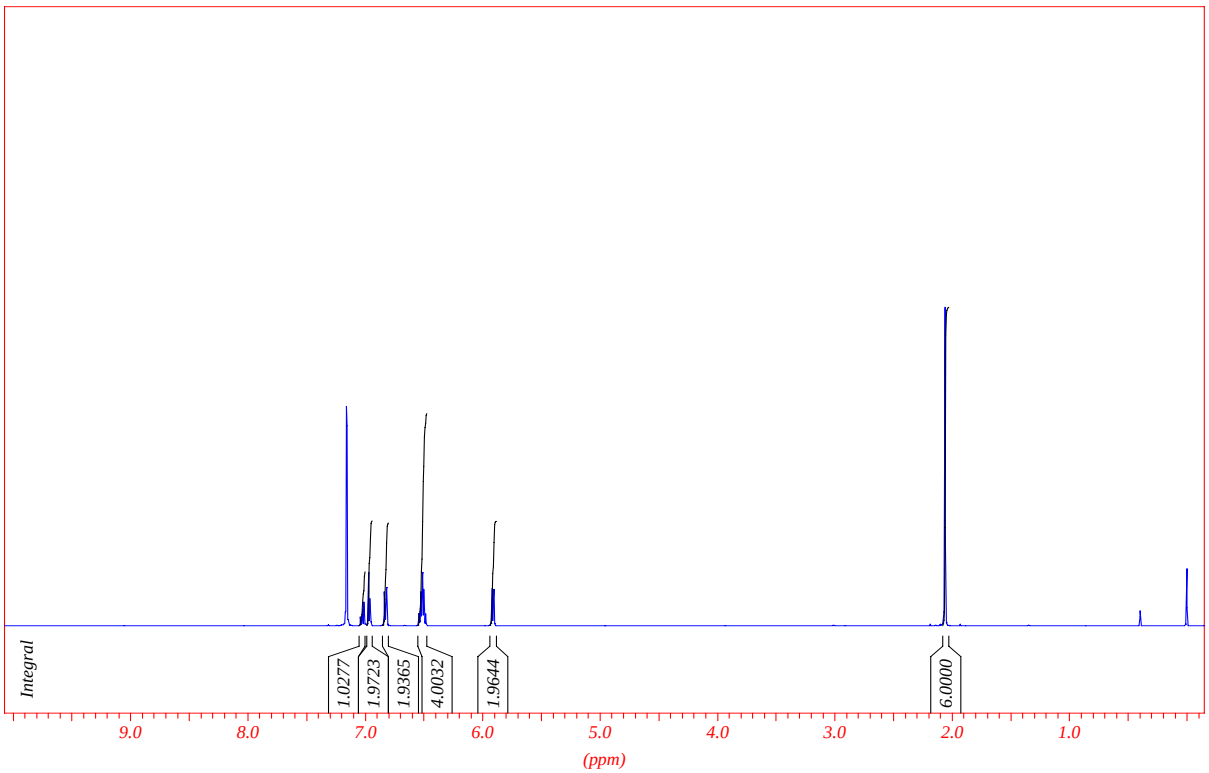


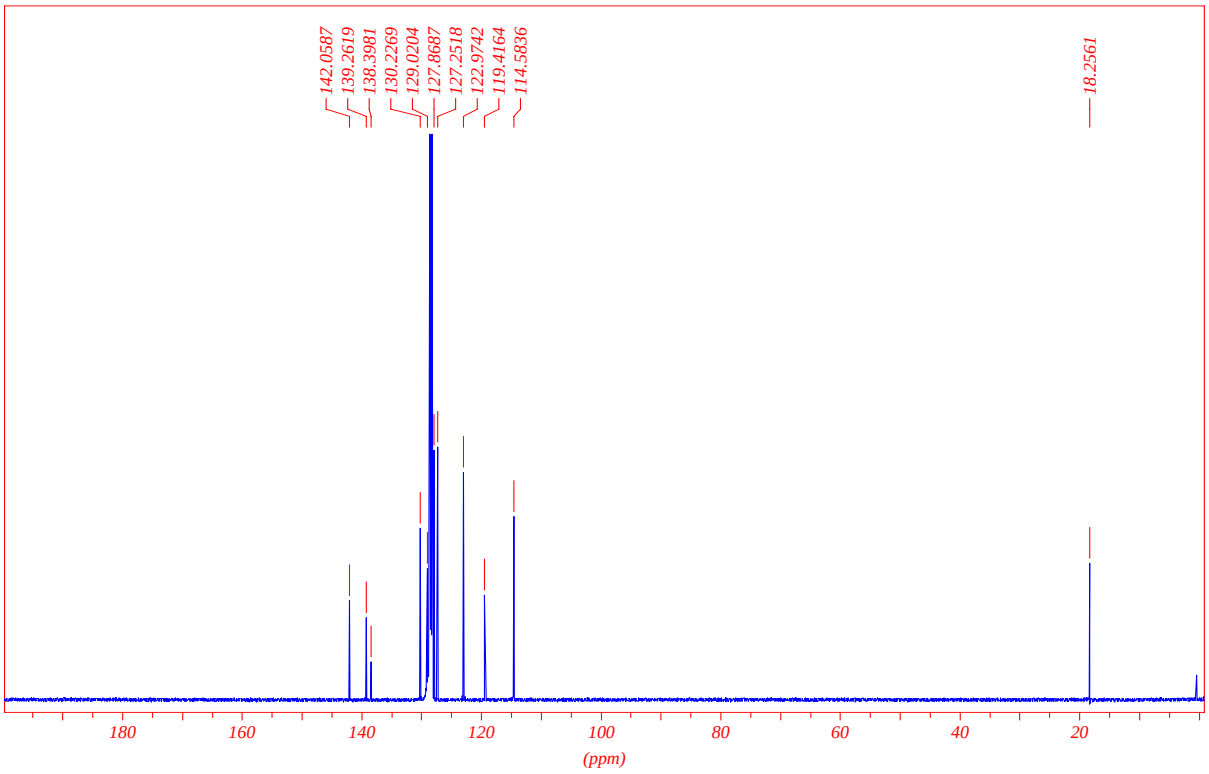


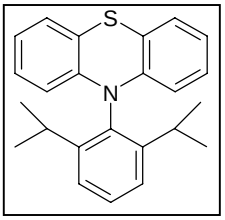


N-(2,6-dimethyl-phenyl)-phenothiazine (Table 1, Entry 5).

^{1}H NMR (C_6D_6, 500MHz) & ^{13}C NMR (C_6D_6, 125MHz)

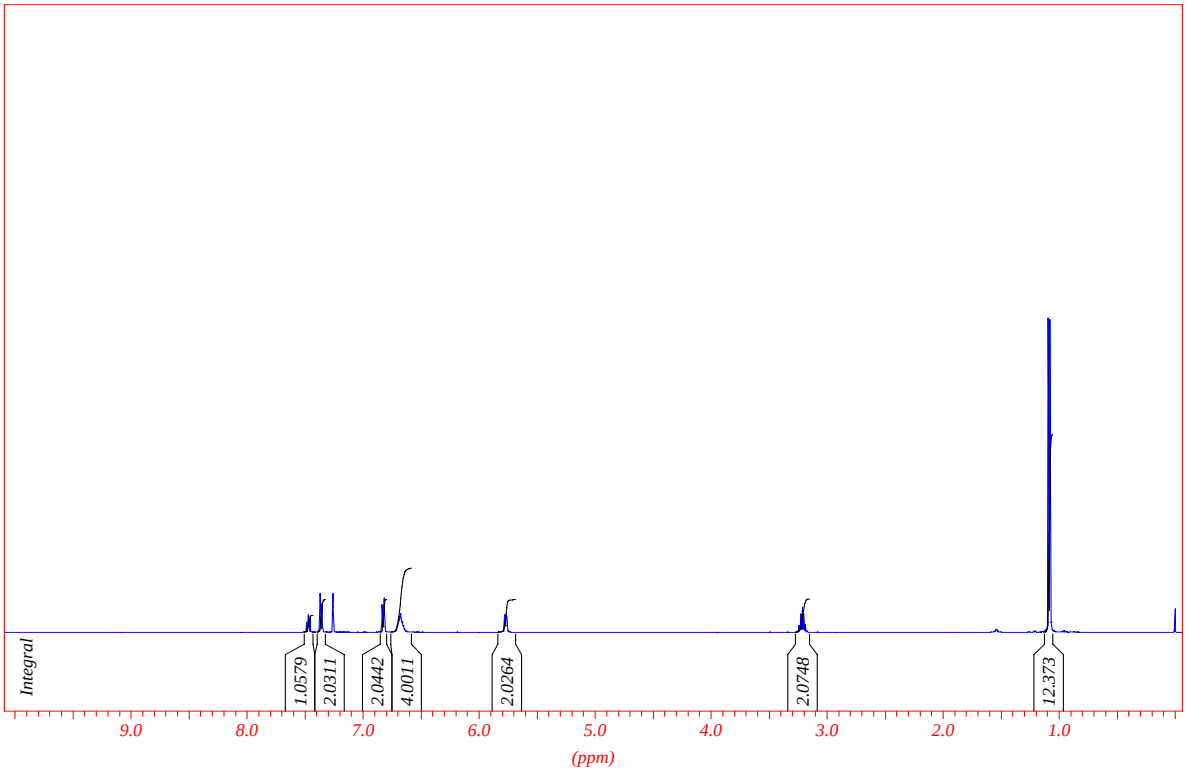


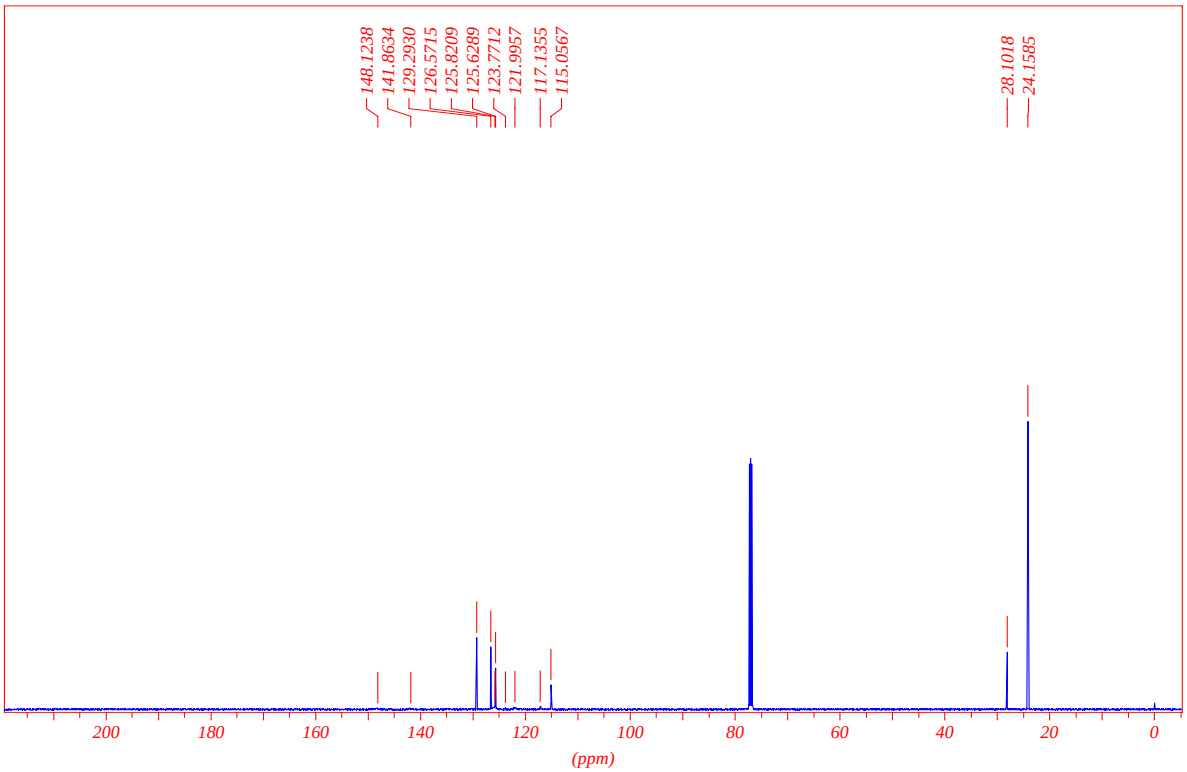


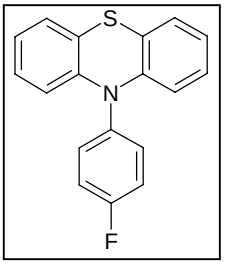


_N_-(2,6-di-_i_-propyl-phenyl)-phenothiazine (Table 1, Entry 5).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)

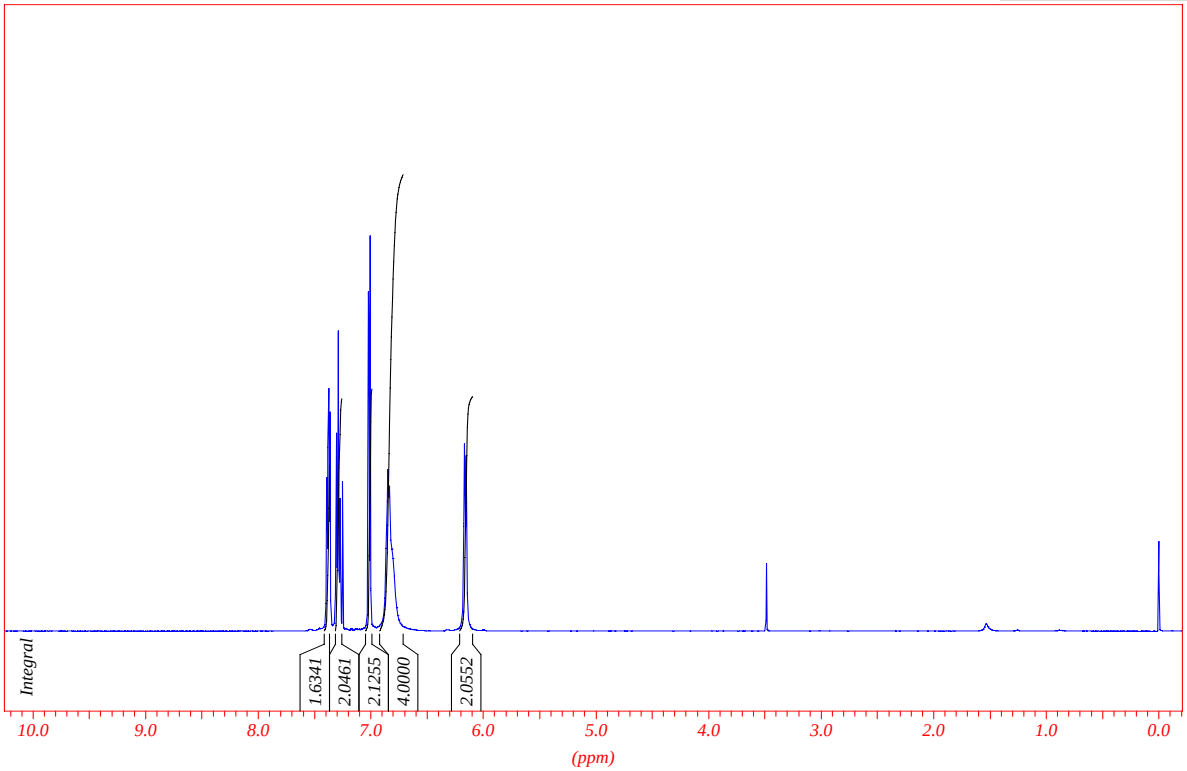


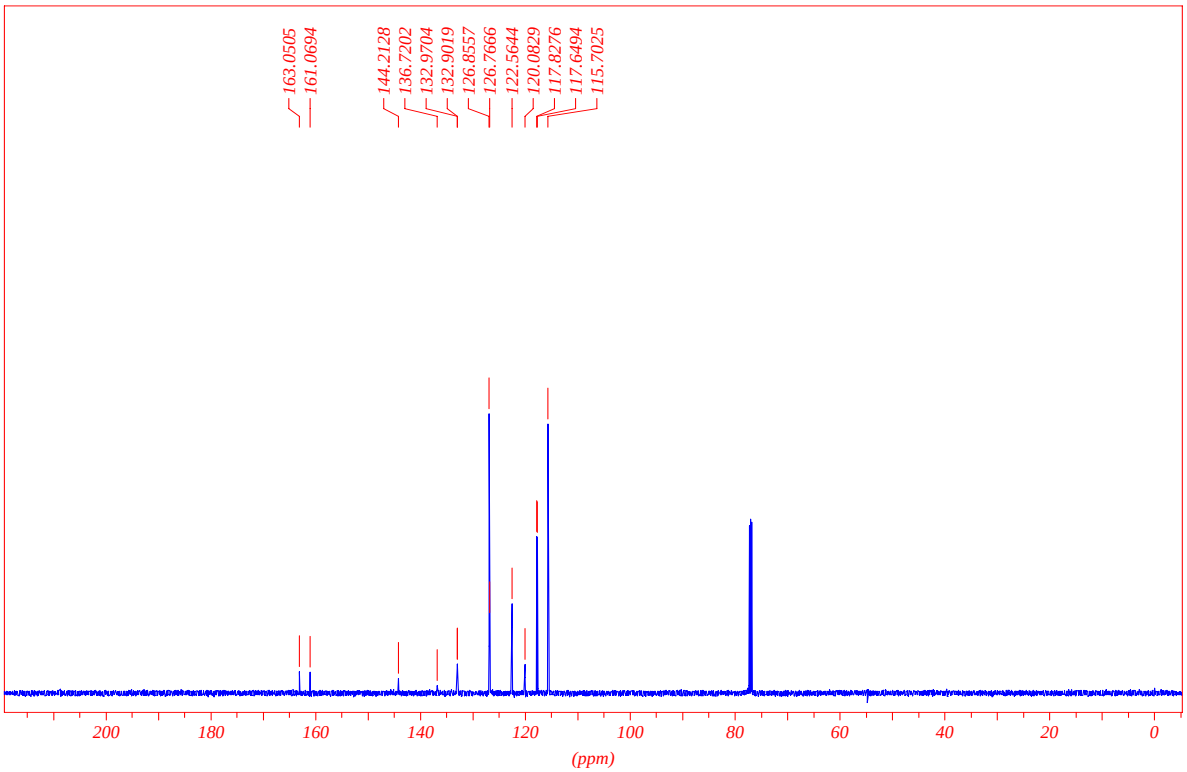


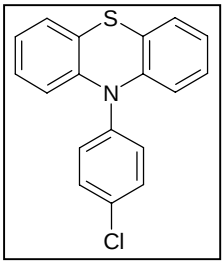


N-(4-Fluoro-phenyl)-phenothiazine (Table 1, Entry 6).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)

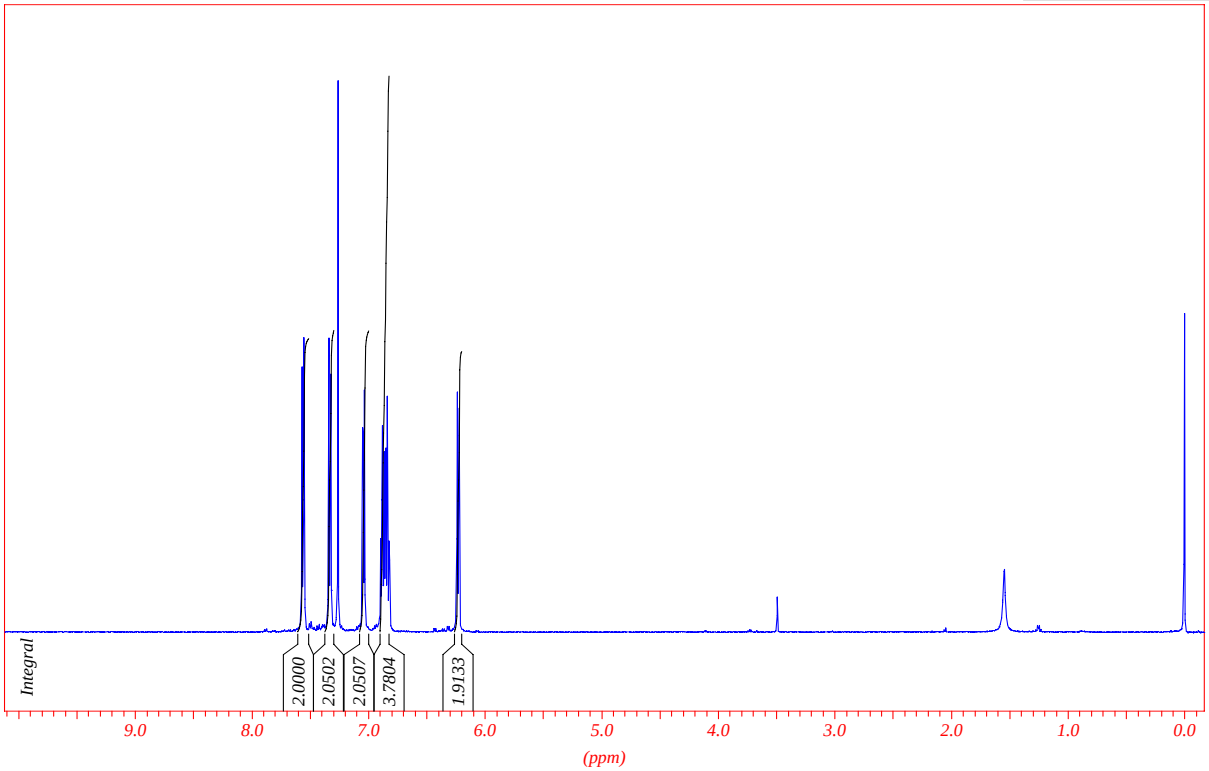


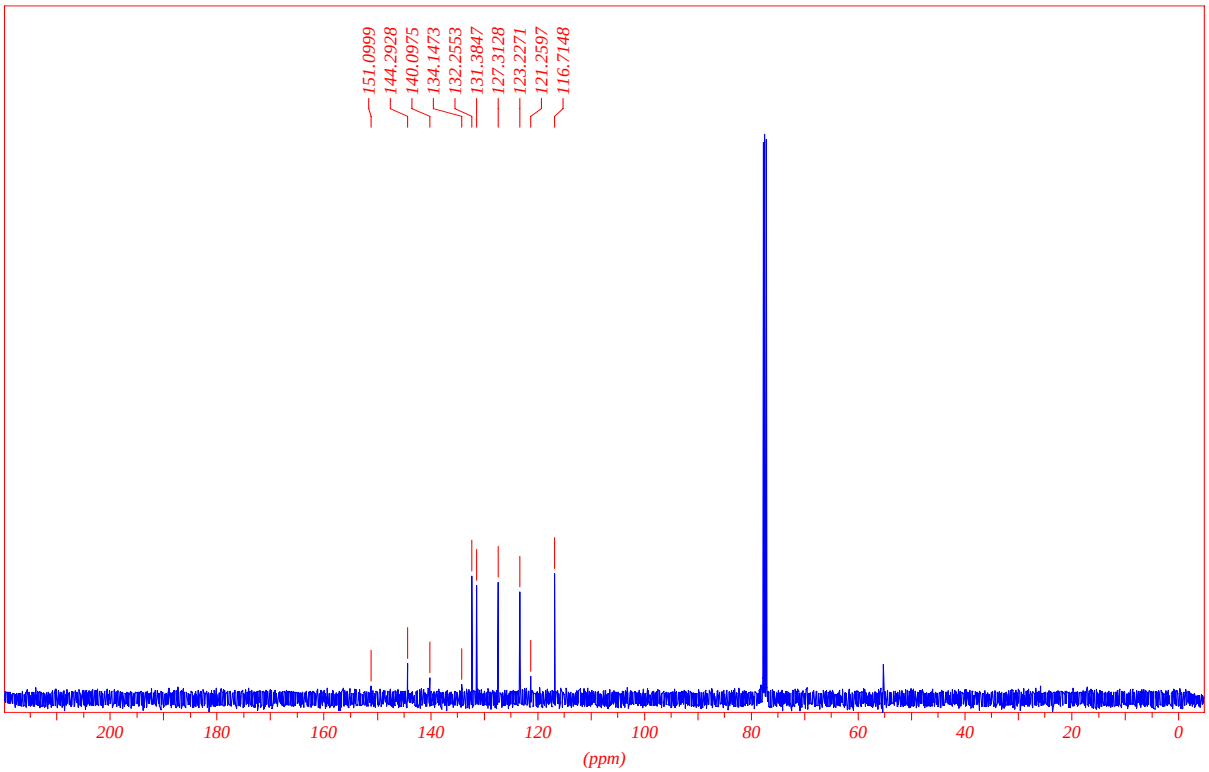




N-(4-Chloro-phenyl)-phenothiazine (Table 1, Entry 6).

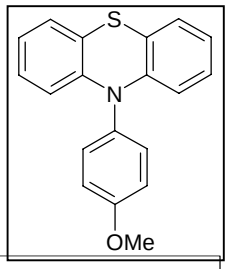
^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)

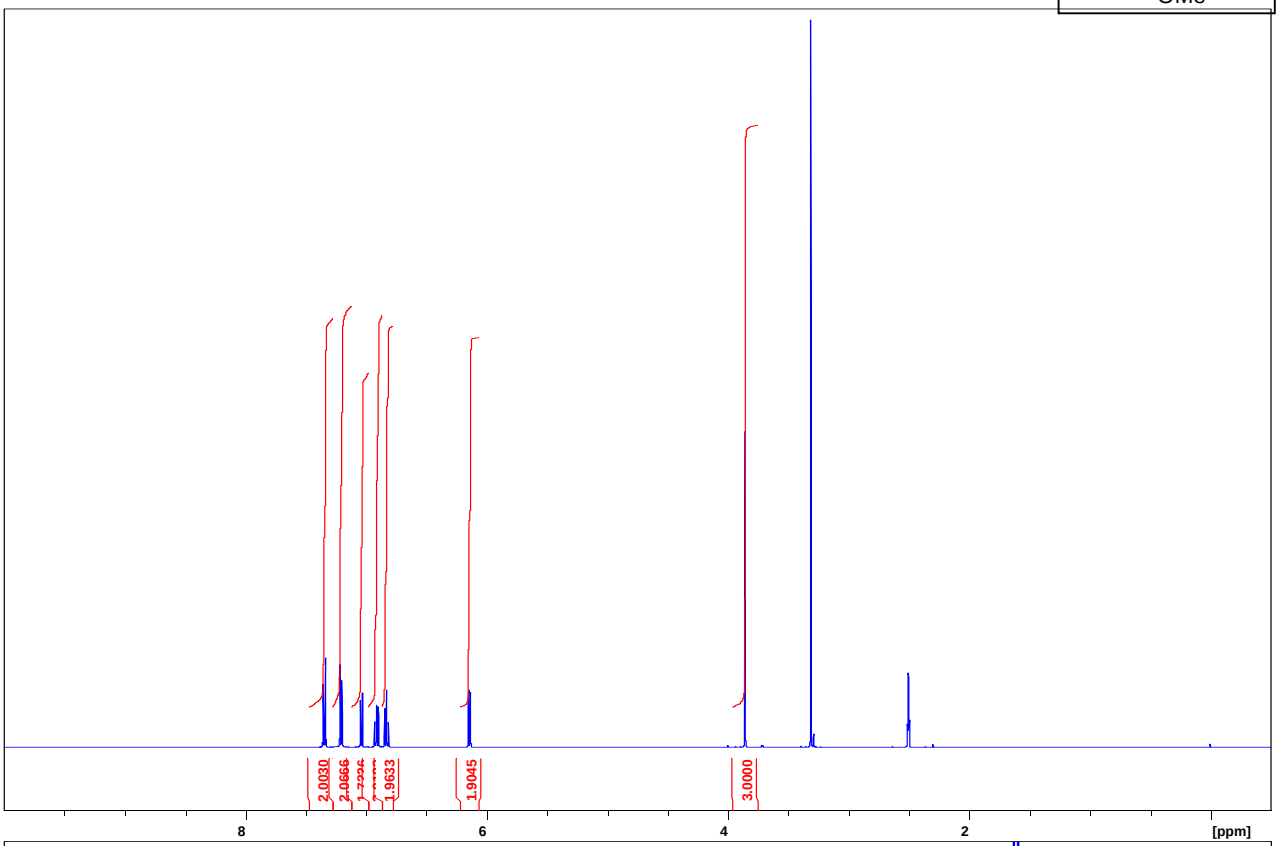


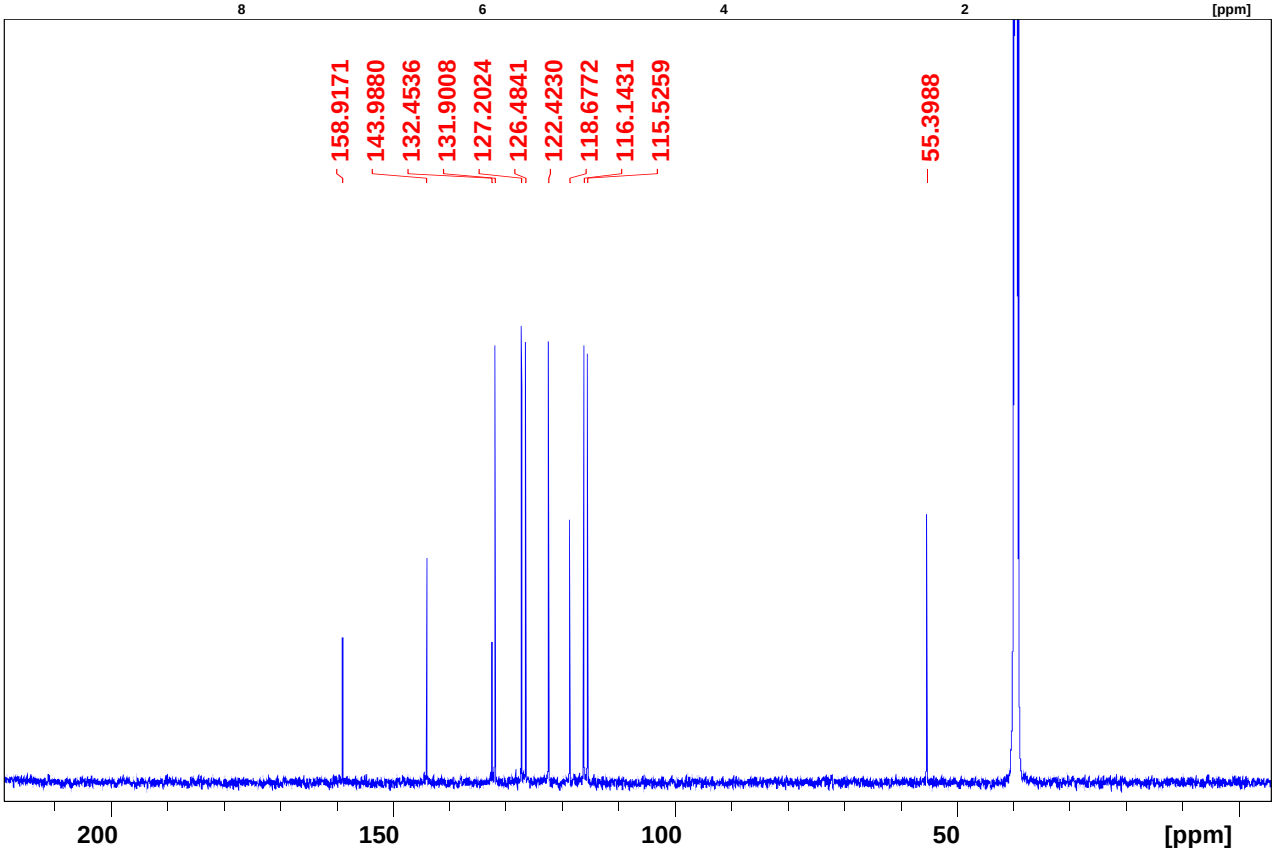


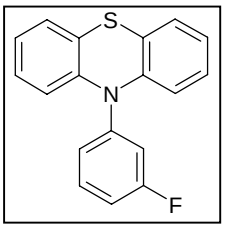
N-(4-Methoxy-phenyl)-phenothiazine (Table 1, Entry 6).

^{1}H NMR (d_6-DMSO, 500MHz) & ^{13}C NMR (d_6-DMSO, 125MHz)



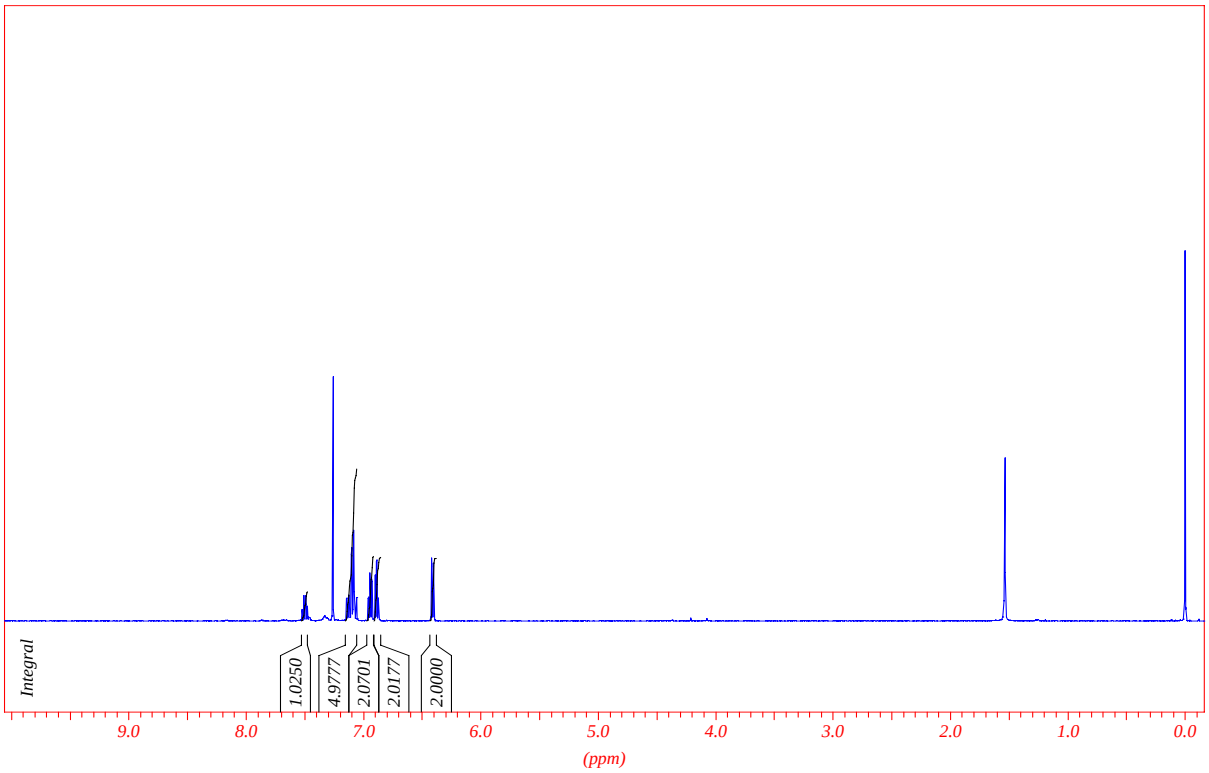


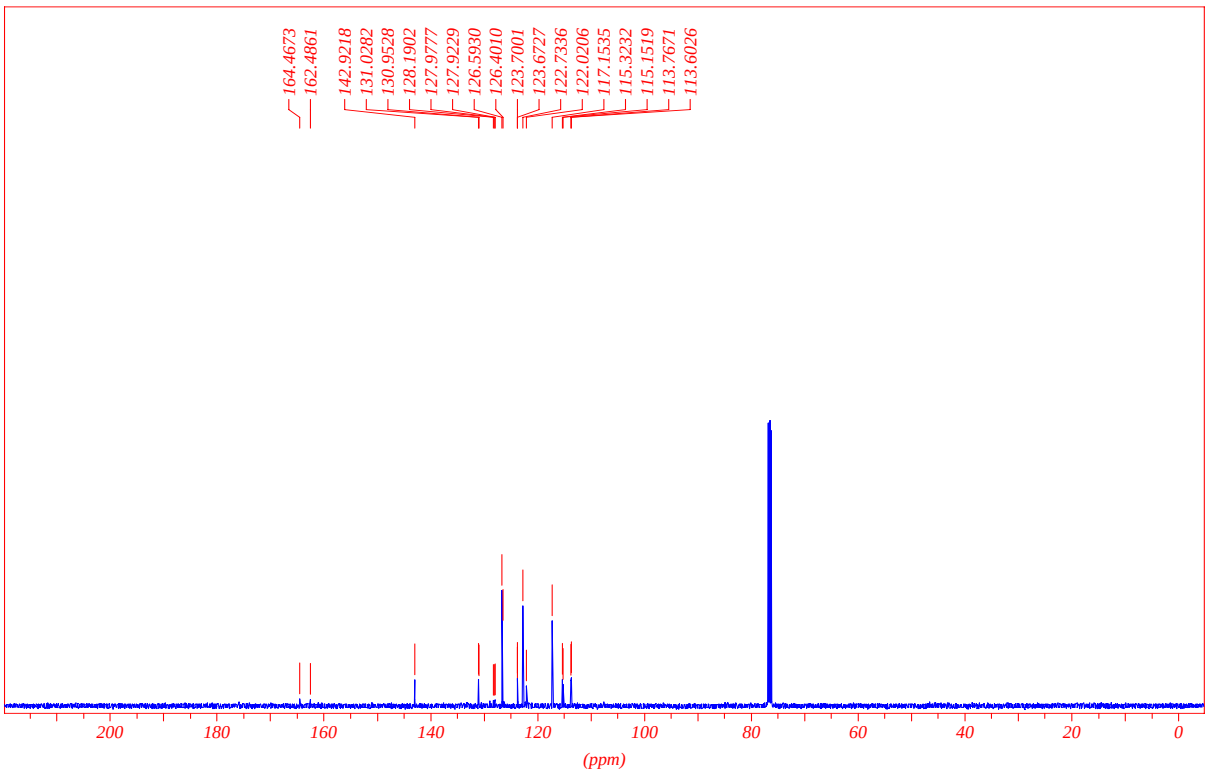


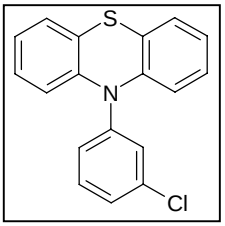


_N_-(3-Fluoro-phenyl)-phenothiazine (Table 1, Entry 7).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)







_N_-(3-Chloro-phenyl)-phenothiazine (Table 1, Entry 7).

^{1}H NMR ($CDCl_3$, 500MHz) & ^{13}C NMR ($CDCl_3$, 125MHz)