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Supporting Information

Towards novel tacrine analogues: $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ catalyzed improved synthesis, *in Silico* docking and hepatotoxicity studies

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General information

All experiments were set-up on fume hoods and were carried out under nitrogen atmosphere in Schlenk tubes unless otherwise noted. All solvents and reagents were procured from commercially available sources like Aldrich, Combi-bolcks and Spectrochem. Commercially available neutral alumina was used for column chromatography and all the synthesized molecules were purified by using solvents such as hexane, ethyl acetate, dichloromethane or methanol. ^{1}H NMR was recorded on Bruker 400MHz AVANCE series or Bruker300 MHz DPX Spectrometer with DMSO-d_6 or CD_3OD as the solvent. All NMR chemical shifts were reported in parts per million (ppm) and all coupling constants are reported in Hertz (Hz). Tetramethylsilane (TMS) (δ = 0.00 ppm) or residual solvent peak in DMSO-d_6 (δ = 2.50 ppm) and $CDCl_3$ (δ = 7.26 ppm) served as internal standard for recording [1]. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet

(t), quartet (q), doublet-doublet (dd), multiplet (m), and broad (br). Liquid chromatography-mass spectrometry (LC-MS) was used for reaction monitoring and identification for product mass on Agilent 1100 Series LC/MSD mass spectrometer. Microanalyses were performed on PerkinElmer Series II CHNS/O 2400 elemental analyzer. Melting points were determined using a Stuart SMP 3 apparatus. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} TLC plates.

Experimental section

Synthesis of 6-bromo tacrine 1

The synthesis of 6-bromo tacrine scaffold **1** was carried out according to the previously reported procedure [2].

Procedure for the synthesis of 6-borylated tacrine derivative 3

To a solution of **1** (0.27 g, 1 mmol, 1.0 equiv) in 1,4-dioxane (2 mL) and water (1 mL), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (**2**) (0.38 g, 1.5 mmol, 1.5 equiv) and K_2CO_3 (0.35 g, 2.5 mmol, 2.5 equiv) was added. The mixture was degassed for 10 min under N_2 atmosphere and then Pd(dppf)Cl_2.DCM (0.04 g, 0.05 mmol, 0.05 equiv) was added. The reaction mixture was heated at 100^{o}C for 8h. After the specified time, the reaction mixture was filtered through celite bed,

the filtrate was diluted with water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The organic layers separated was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was washed with dichloromethane to yield *B6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroacridin-9-amine* **3** (0.24 g, 73%) as off-white solid.

Mp 117-120^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (d, J = 8.6 Hz, 1H, ArH), 7.90 (s, 1H, ArH), 7.51 (dd, J = 8.5, 1.2 Hz, 1H, ArH), 6.78 (s, 2H, NH_2), 2.85 (t, J = 5.8 Hz, 2H, CH_2), 2.55 (s, 2H, CH_2), 1.81 (m, 4H, CH_2), 1.05 (s, 12H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.7, 155.6, 151, 136.7, 131.2, 128.6, 119.9, 115.5, 114.8, 109.4, 55.7, 28.1, 23.0, 21.2.

LC-MS: 325.43 (M+H).

Anal. Calculated for $C_{19}H_{25}BN_2O_2$: C, 74.08; H, 6.09; N, 10.02; Found: C, 73.9; H, 6.45; N, 9.75%.

Procedure for Suzuki-Miyaura coupling of 3 with aryl bromides for the synthesis of 6-arylated tacrine derivatives 7a-c

To a mixture of **3** (0.32 g, 1 mmol, 1.0 equiv) in 1,4-dioxane (2 mL) and water (1 mL), different aryl bromides **4a-c** (1.2 mmol, 1.2 equiv) and K_2CO_3 (0.35 g, 2.5 mmol, 2.5 equiv) were added. The mixture was degassed for 10 min. under N_2 atmosphere and Pd(dppf)Cl_2.DCM (0.04 g, 0.05 mmol, 0.05 equiv) was then added. The reaction mixture was heated at 100^{o}C for 8-10 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was filtered through celite bed and the filtrate was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers was dried over anhydrous Na_2SO_4, filtered and distilled under reduced pressure. The crude was washed with dichloromethane (DCM) twice to afford the titled 6-arylated tacrine derivatives **7a-c** in varying yields (The products were partially soluble in DCM, however this method was convenient as column chromatography was not required).

6-(3-Fluorophenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7a**)

Yield=78% (0.23 g); off white solid.

Mp 160-164^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 14.11 (d, J = 33.5 Hz, 1H, ArH), 9.09 (s, 1H, ArH), 8.79 (s, 1H, ArH), 8.11 (d, J = 8.6 Hz, 1H, ArH), 7.97 (d, J = 8.2 Hz, 1H, ArH), 7.74 (s, 2H, NH_2), 7.48 (dt, J = 14.3, 7.1 Hz, 1H, ArH), 7.18 (t, J = 7.7 Hz, 1H, ArH), 2.93 (s, 2H, CH_2), 2.55 (s, 2H, CH_2), 1.78 (s, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3 (J = 242 Hz), 155.7, 151.3, 141.0 (J = 8 Hz), 136.9, 135.5, 131.3, 131.2 (J = 8 Hz), 123.3, 121.2, 120.1, 115.3, 114.9, 113.9, 109.5, 28.1, 23.0, 21.1.

LC-MS: 293.4 (M+H).

Anal. Calculated for $C_{19}H_{17}FN_2$: C, 78.06; H, 5.86; N, 9.58; Found: C, 78.41; H, 6.06; N, 9.20%.

6-(3,5-Difluorophenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7b**)

Yield=78% (0.24 g); off white solid.

Mp 152-155^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 14.07 (s, 1H, ArH), 9.02 (d, J = 48.9 Hz, 1H, ArH), 8.78 (d, J = 19.9 Hz, 1H, ArH), 8.14 (d, J = 8.9 Hz, 2H, ArH), 7.90 (d, J = 8.7 Hz, 1H, ArH), 7.63 (d, J = 7.6 Hz, 2H, NH_2), 7.21 (t, J = 8.8 Hz, 1H, ArH), 2.94 (s, 2H, CH_2), 2.48 (s, 2H, CH_2), 1.81 (s, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5 (J = 14 Hz, 244 Hz), 155.7, 151.5, 141.9, 137.2, 134.1, 131.2, 121.5, 120.0, 115.1, 110.4 (J = 26 Hz), 109.7, 103.6 (J = 26 Hz), 28.1, 22.9, 21.4, 20.9.

LC-MS: 311.4 (M+H).

Anal. Calculated for $C_{19}H_{16}F_2N_2$: C, 73.53; H, 5.20; N, 9.03; Found: C, 73.33; H, 4.82; N, 9.01%.

6-(4-Chlorophenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7c**)

Yield=73% (0.23 g); off white solid.

Mp 168-172^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 14.09 (s, 1H, ArH), 9.14 (s, 1H, ArH), 8.87 (s, 1H, ArH), 8.20 (d, J = 8.6 Hz, 1H, ArH), 8.03 (t, J = 8.7 Hz, 1H, ArH), 7.94 (d, J = 8.3 Hz, 2H, ArH), 7.58 (d, J = 8.3 Hz, 2H, NH_2), 3.00 (s, 2H, CH_2), 2.55 (s, 2H, CH_2), 1.85 (s, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 155.8, 151.6, 137.5, 136.9, 135.9, 133.4, 131.6, 129.2, 121.2, 120.1, 115.5, 109.7, 28.1, 23.1, 21.2.

LC-MS: 310.8 (M+2H).

Anal. Calculated for $C_{19}H_{17}ClN_2$: C, 73.90; H, 5.55; N, 9.07; Found: C, 74.03; H, 5.19; N, 9.08%.

Procedure for Suzuki-Miyaura coupling of 1 with aryl boronic acids for the synthesis of 6-arylated tacrine derivatives 7a-e

To a solution of **1** (0.27 g, 1 mmol, 1.0 equiv) in 1,4-dioxane (2 mL) and water (1 mL), various boronic acids **5a-e** (1.2 mmol, 1.2 equiv) and K_2CO_3 (0.35 g, 2.5 mmol, 2.5 equiv) was added. The mixture was degassed for 10 min. under N_2

atmosphere and Pd(dppf)Cl_2.DCM (0.04 g, 0.05 mmol, 0.05 equiv) was then added. The reaction mixture was heated at 100^{o}C for 8-10 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was filtered through celite bed and the filtrate was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers was dried over anhydrous Na_2SO_4, filtered and distilled off under reduced pressure to obtain the crude product. The crude was washed with dichloromethane to obtain the entitled 6-arylated tacrine derivatives **7a-e** in varying yields (The products were partially soluble in DCM, however this method was convenient as column chromatography was not required).

6-(3-Fluorophenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7a**)

Yield=84% (0.25 g); off white solid.

6-(3,5-Difluorophenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7b**)

Yield=80% (0.25 g); off white solid.

6-(4-Chlorophenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7c**)

Yield=87% (0.27 g); off white solid.

6-(4-Methoxyphenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7d**)

Yield=80% (0.24 g); off white solid.

Mp 170-173^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 14.02 (s, 1H, ArH), 8.91 (s, 1H, ArH), 8.55 (d, J = 8.8 Hz, 1H, ArH), 8.11 (s, 1H, ArH), 8.02 (dd, J = 18.8, 8.4 Hz, 1H, ArH), 7.84 (d, J = 8.8 Hz, 1H, ArH), 7.71 (d, J = 8.6 Hz, 2H, ArH), 7.07 (t, J = 9.9 Hz, 2H, ArH), 3.82 (s, 3H, OCH_3), 2.98 (s, 2H, CH_2), 2.52 (s, 2H, CH_2), 1.83 (s, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 160.5, 155.5, 151.7, 143.9, 138.1, 130.6, 128.7, 124.4 (d, J = 30.8 Hz), 115.2, 113.8, 109.3, 55.8, 28.2, 21.1 (d, J = 53.8 Hz).

LC-MS: 305.2 (M+H).

Anal. Calculated for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20; Found: C, 79.12; H, 6.98; N, 9.60%.

6-(3-Methoxyphenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7e**)

Yield=78% (0.23 g); off white solid.

Mp 171-174^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 14.11 (s, 1H, ArH), 9.05 (s, 1H, ArH), 8.76 (s, 1H, ArH), 8.12 (d, *J* = 8.7 Hz, 1H, ArH), 7.99 (d, *J* = 8.8 Hz, 1H, ArH), 7.85 (d, *J* = 8.4 Hz, 2H, ArH), 7.05 (d, *J* = 8.4 Hz, 2H, ArH), 3.82 (s, 3H, OCH_3), 2.97 (s, 2H, CH_2), 2.52 (d, *J* = 7.2 Hz, 2H, CH_2), 1.82 (d, *J* = 3.2 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.8, 155.7, 151.1, 136.7 (d, *J* = 74.1 Hz), 131.2 (d, *J* = 33.9 Hz), 128.6, 120.0, 115.6, 114.8, 109.4, 55.7, 28.1, 23.1, 21.2 (d, *J* = 55.8 Hz).

LC-MS: 305.2 (M+H).

Anal. Calculated for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20; Found: C, 78.84; H, 6.85; N, 9.62%.

Procedure for Stille coupling of 1 with tributyl(aryl/vinyl)stannanes for the synthesis of 6-arylated tacrine derivatives 7d-h

To a solution of **1** (0.27 g, 1 mmol, 1.0 equiv) in DMF (2 mL), different tributyl(aryl/vinyl)stannanes **6d-h** (1 mmol, 1.0 equiv) and NaCl (0.09 g, 1.5 mmol, 1.5 equiv) was added. The mixture was degassed for 10 min. under N_2 atmosphere and Pd(dppf)Cl_2.DCM (0.04 g, 0.05 mmol, 0.05 equiv) was then added. The reaction mixture was heated at 100^{o}C for 8-10 hours. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered through celite bed and the filtrate was distilled off under reduced pressure. The residue obtained was purified by column chromatography in neutral

alumina using 1-5% methanol in dichloromethane as eluent to obtain the entitled 6-arylated tacrine derivatives **7d-h** in varying yields.

6-(4-Methoxyphenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7d**)

Yield=80% (0.24 g); off white solid.

6-(3-Methoxyphenyl)-1,2,3,4-tetrahydroacridin-9-amine (**7e**)

Yield=78% (0.23 g); off white solid.

6-(1-Ethoxyvinyl)-1,2,3,4-tetrahydroacridin-9-amine (**7f**)

Yield=88% (0.24 g); off white solid.

Mp 160-163^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, J = 8.8 Hz, 1H, ArH), 7.84 (s, 1H, ArH), 7.48 (t, J = 11.4 Hz, 1H, ArH), 6.30 (s, 2H, NH_2), 4.88 (d, J = 2.0 Hz, 1H, CH_2), 4.33 (d, J = 2.0 Hz, 1H, CH_2), 3.90 (q, J = 6.8 Hz, 2H, OCH_2), 2.79 (d, J = 5.7 Hz, 2H, CH_2), 2.52 (d, J = 5.5 Hz, 2H, CH_2), 1.79 (d, J = 4.9 Hz, 4H, CH_2), 1.41 (t, J = 7.0 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 158.2, 148.2, 146.7, 135.4, 124.3, 122.2, 120.1, 117.2, 109.6, 83.9, 63.3, 34.2, 24.1, 23.1, 14.8.

LC-MS: 269.4 (M+H).

Anal. Calculated for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44; Found: C, 76.03; H, 7.72; N, 10.24%.

6-Allyl-1,2,3,4-tetrahydroacridin-9-amine ***(7g)***

Yield=73% (0.17 g); Off-white solid.

Mp 136-143^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, J = 8.6 Hz, 1H, ArH), 7.42 (d, J = 1.7 Hz, 1H, ArH), 7.14 (dd, J = 8.6 Hz, 1.8 Hz,1H, ArH), 6.4 (m, 2H, NH_2), 6.03 (m, 1H, CH), 5.19-5.06 (m, 2H, CH_2), 3.48 (d, J = 6.8 Hz, 1H, CH_2), 2.81 (t, J = 5.8 Hz, 2H, CH_2), 2.54 (t, J = 5.8 Hz, 2H, CH_2), 1.89 (p, J = 6.1, 5.7 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 157.3, 148.9, 140.3, 137.9, 126.4, 124.5, 122.5, 116.5, 115.8, 109.1, 37.7, 33.6, 25.1, 24.2, 23.9, 22.9, 22.9, 21.4.

LC-MS: 239.2 (M+H).

Anal. Calculated for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75; Found: C, 80.99; H, 7.44; N, 11.92%.

6-(3-Fluoropyridin-2-yl)-1,2,3,4-tetrahydroacridin-9-amine ***(7h)***

Yield=70% (0.205 g); Brown solid.

Mp 121-123^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 - 8.34 (m, 2H, ArH), 8.29 (d, J = 8.8 Hz, 1H, ArH), 7.91 - 7.78 (m, 2H, ArH), 7.44 (m, 1H, ArH), 6.51 (s, 2H, NH_2), 2.88 (t, J = 5.8 Hz, 2H, CH_2), 2.57 (t, J = 5.8 Hz, 2H, CH_2), 1.82 (p, J = 6.1, 5.7 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 162.1, 158.1, 148.5, 146.1, 145.8, 136.2, 134.3, 133.2, 129.4, 126.7, 125.7, 125, 119.5, 114.7, 110.9, 34.1, 24.3, 23, 22.8.

LC-MS: 294.2 (M+H).

Anal. Calculated for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.32; Found: C, 73.75; H, 5.64; N, 14.5%.

Procedure for Sonogashira coupling of 1 with alkynes for the synthesis of 6-alkynyl tacrine derivatives 9a-d

To a solution of **1** (0.27 g, 1 mmol, 1.0 equiv) in DMF (2 mL), different alkynes **8a-d** (1.2 mmol, 1.2 equiv), CuI (0.19 g, 1 mmol, 1.0 equiv) and triethylamine (0.28 mL, 2 mmol, 2.0 equiv) was added. The mixture was degassed for 10 min. under

N_2 atmosphere and Pd(dppf)Cl_2.DCM (0.04 g, 0.05 mmol, 0.05 equiv) was then added. The reaction mixture was heated at 100^{o}C for 8-10 hours. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure. The residue obtained was purified by column chromatography in neutral alumina using 1-5% methanol in dichloromethane as eluent to obtain the entitled 6-alkynyl tacrine derivatives **9a-d** in varying yields.

6-((4-Fluorophenyl)ethynyl)-1,2,3,4-tetrahydroacridin-9-amine (**9a**)

Yield=88% (0.28 g); off white solid.

Mp 132-135^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (d, J = 8.5 Hz, 1H, ArH), 7.77 (s, 1H), 7.62 (d, J = 5.6 Hz, 2H, ArH), 7.36 (d, J = 8.3 Hz, 1H, ArH), 7.26 (t, J = 8.4 Hz, 2H, ArH), 6.39 (s, 2H, NH_2), 2.81 (s, 2H, CH_2), 2.53 (s, 2H, CH_2), 1.79 (d, J = 4.7 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7 (J = 246 Hz), 158.9, 148.4, 146.4, 134.2 (J = 8 Hz), 131.5, 125.1, 123.1, 121.8, 119.2, 117.3, 116.5 (J = 21 Hz), 110.3, 89.8, 89.2, 34.1, 24.1, 23.0, 22.9.

LC-MS: 305.4 (M+H).

Anal. Calculated for $C_{21}H_{17}FN_2$: C, 79.72; H, 5.42; N, 8.85; Found: C, 79.84; H, 5.50; N, 8.47%.

6-((3-Chlorophenyl)ethynyl)-1,2,3,4-tetrahydroacridin-9-amine (**9b**)

Yield=81% (0.27 g); off white solid.

Mp 139-142^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (d, J = 8.7 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 7.65 (s, 1H, ArH), 7.54 (d, J = 7.1 Hz, 1H, ArH), 7.50 – 7.41 (m, 2H, ArH), 7.38 (dd, J = 8.6, 1.1 Hz, 1H, ArH), 6.39 (s, 2H, NH_2), 2.82 (d, J = 5.6 Hz, 2H, CH_2), 2.53 (d, J = 5.8 Hz, 2H, CH_2), 1.80 (d, J = 4.9 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 148.4, 146.4, 133.7, 131.8, 131.1, 131.1, 130.5, 129.3, 125.1, 124.7, 123.2, 121.4, 91.4, 88.7, 63.2, 34.1, 24.2, 22.9.

LC-MS: 334.4 (M+2H).

Anal. Calculated for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42; Found: C, 76.16; H, 5.28; N, 8.20%.

6-((4-Chlorophenyl)ethynyl)-1,2,3,4-tetrahydroacridin-9-amine (**9c**)

Yield=84% (0.28 g); off white solid.

Mp 141-144^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (d, J = 8.6 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 7.58 (d, J = 8.2 Hz, 2H, ArH), 7.47 (d, J = 8.3 Hz, 2H, ArH), 7.37 (d, J = 8.4 Hz, 1H, ArH), 6.41 (s, 2H, NH_2), 2.81 (d, J = 5.6 Hz, 2H, CH_2), 2.53 (d, J = 5.6 Hz, 2H, CH_2), 1.79 (d, J = 4.8 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 148.4, 146.4, 133.8, 131.8, 131.3, 131.1, 130.5, 129.3, 125.1, 124.8, 123.2, 121.4, 91.4, 88.7, 63.2, 34.1, 24.2, 22.9.

LC-MS: 334.4 (M+2H).

Anal. Calculated for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42; Found: C, 76.16; H, 5.28; N, 8.20%.

6-(Pyridin-2-ylethynyl)-1,2,3,4-tetrahydroacridin-9-amine (**9d**)

Yield=78% (0.23 g); off white solid.

Mp 130-133^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (d, J = 4.2 Hz, 1H, ArH), 8.20 (d, J = 8.6 Hz, 1H, ArH), 7.84 (t, J = 6.6 Hz, 2H, ArH), 7.66 (d, J = 7.7 Hz, 1H, ArH), 7.40 (t, J = 7.1 Hz, 2H, ArH), 6.44 (s, 2H, NH_2), 2.82 (d, J = 5.5 Hz, 2H, CH_2), 2.54 (d, J = 5.7 Hz, 2H, CH_2), 1.79 (d, J = 4.9 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 150.5, 148.4, 146.3, 142.7, 137.2, 132.1, 127.8, 125.1, 123.9, 123.3, 121.1, 117.7, 110.6, 89.8, 89.1, 34.1, 24.2, 22.9.

LC-MS: 300.4 (M+2H).

Anal. Calculated for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04; Found: C, 80.31; H, 6.01; N, 13.95%.

Procedure for Heck coupling of 1 with alkenes for the synthesis of 6-alkenyl tacrine derivatives 11a-d

A mixture of **1** (0.27 g, 1 mmol, 1.0 equiv), alkenes **10a-d** (1.2 mmol, 1.2 equiv), triethylamine (0.42 mL, 3 mmol, 3.0 equiv) and Pd(dppf)Cl_2.DCM (0.04 g, 0.05 mmol, 0.05 equiv) in DMF (2 mL) was heated at 100^{o}C for 8-10 hours. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered through celite bed and the filtrate was

concentrated under reduced pressure. The residue obtained was purified by column chromatography in neutral alumina using 1-6% methanol in dichloromethane as eluent to obtain the titled compounds **11a-d** in varying yields.

Methyl 3-(9-amino-5,6,7,8-tetrahydroacridin-3-yl)acrylate (**11a**)

Yield=77% (0.22 g); off white solid.

Mp 128 -131^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (d, J = 8.8 Hz, 1H, ArH), 7.85 (s, 1H, ArH), 7.75 (d, J = 16.0 Hz, 1H, CH), 7.64 (d, J = 8.6 Hz, 1H, ArH), 6.72 (d, J = 16.0 Hz, 1H, CH), 6.35 (s, 2H, NH_2), 3.72 (s, 3H), 2.80 (d, J = 6.1 Hz, 2H, CH_2), 2.53 (d, J = 5.7 Hz, 2H, CH_2), 1.80 (d, J = 5.1 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 158.6, 148.3, 146.7, 145.3, 133.8, 130.4, 123.2, 120.8, 118.5, 110.5, 51.8, 33.9, 24.2, 22.9.

LC-MS: 283.4 (M+H).

Anal. Calculated for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92; Found: C, 72.49; H, 6.39; N, 9.55%.

Ethyl 3-(9-amino-5,6,7,8-tetrahydroacridin-3-yl)acrylate (**11b**)

Yield=80% (0.24 g); off white solid.

Mp 131-134^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (d, J = 8.8 Hz, 1H, ArH), 7.84 (s, 1H, ArH), 7.73 (d, J = 16.0 Hz, 1H, CH), 7.65 (d, J = 8.6 Hz, 1H, ArH), 6.71 (d, J = 16.0 Hz, 1H, CH), 6.37 (s, 2H, NH_2), 4.18 (q, J = 7.0 Hz, 2H, OCH_2), 2.80 (d, J = 5.4 Hz, 2H, CH_2), 2.53 (d, J = 5.6 Hz, 2H, CH), 1.79 (d, J = 4.9 Hz, 4H, CH_2), 1.24 (t, J = 7.0 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 166.7, 158.6, 148.3, 146.8, 144.9, 133.9, 130.5, 123.2, 120.8, 118.8, 118.3, 110.5, 60.4, 34.1, 24.1, 22.9, 14.6.

LC-MS: 297.4 (M+H).

Anal. Calculated for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45; Found: C, 72.75; H, 7.08; N, 9.57%.

Tert-butyl 3-(9-amino-5,6,7,8-tetrahydroacridin-3-yl)acrylate (**11c**)

Yield=75% (0.24 g); off white solid.

Mp 133-135^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (d, J = 8.8 Hz, 1H, ArH), 7.84 (s, 1H, ArH), 7.73 (d, J = 16.0 Hz, 1H, CH), 7.65 (d, J = 8.6 Hz, 1H, ArH), 6.63 (d, J = 16.0 Hz, 1H, CH), 6.39 (s, 2H, NH_2), 2.80 (d, J = 5.4 Hz, 2H, CH_2), 2.53 (d, J = 5.6 Hz, 2H, CH_2), 1.79 (d, J = 4.9 Hz, 4H, CH_2), 1.5 (s, 9H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 158.7, 144.2, 134.1, 130.4, 120.7, 120.6, 118.3, 110.5, 80.4, 34.1, 28.4, 24.2, 23.1, 22.9.

LC-MS: 325.2 (M+H).

Anal. Calculated for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64; Found: C, 73.96; H, 7.08; N, 8.81%.

6-Styryl-1,2,3,4-tetrahydroacridin-9-amine (**11d**)

Yield=78% (0.23 g); off white solid.

Mp 135-137^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (d, J = 8.8 Hz, 1H, CH), 7.75 (s, 1H, ArH), 7.66 (d, J = 7.5 Hz, 3H, ArH), 7.44-7.37 (m, 4H, ArH), 7.29 (t, J = 7.5 Hz, 1H, CH), 6.63 (s, 2H, NH_2), 2.88 (d, J = 5.4 Hz, 2H, CH_2), 2.55 (d, J = 6.3 Hz, 2H, CH_2), 1.83 (d, J = 4.9 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 158.3, 148.4, 147.4, 137.6, 136.9, 129.4, 129.2, 129.1, 128.1, 127.1, 127.1, 122.8, 120.5, 116.9, 109.7, 34.1, 24.2, 23.3, 23.1.

LC-MS: 301.4 (M+H).

Anal. Calculated for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33; Found: C, 84.33; H, 6.92; N, 9.71%.

Procedure for Buchwald coupling of 1 with amines for the synthesis of 6-amino tacrine derivatives 13a-g

To a solution of **1** (0.27 g, 1 mmol, 1.0 equiv) in 1,4-dioxane (2 mL), amines **12a-g** (1.3 mmol, 1.3 equiv) and KO*t*-Bu (0.45 g, 4 mmol, 4.0 equiv) was added. The reaction mixture was degassed for 10 min. under N_2 atmosphere and then Pd(dppf)Cl_2.DCM (0.04 g, 0.05 mmol, 0.05 equiv) was added. The reaction mixture was heated at 100^{o}C for 8-10 hours. After completion of the reaction as indicated by TLC, the reaction mixture was filtered through celite bed and the filtrate

was concentrated under reduced pressure. The residue obtained was purified by column chromatography in neutral alumina using 5-8% methanol in dichloromethane as eluent to obtain the entitled 6-amino tacrine derivatives **13a-g** in varying yields.

N3-(4-methoxybenzyl)-5,6,7,8-tetrahydroacridine-3,9-diamine (**13a**)

Yield=72% (0.24 g); brown solid.

Mp 146-149^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H, NH), 8.10 (d, J = 9.2 Hz, 1H, ArH), 7.84 (s, 2H, ArH), 7.52 – 7.43 (m, 1H, ArH), 7.27 (d, J = 8.4 Hz, 2H, ArH), 6.92 (d, J = 9.1 Hz, 1H, ArH), 6.86 (d, J = 8.5 Hz, 2H, ArH), 6.64 (s, 2H, NH_2), 4.24 (d, J = 5.2 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 2.75 (d, J = 5.6 Hz, 2H, CH_2), 2.41 (d, J = 5.6 Hz, 2H, CH_2), 1.74 (d, J = 4.7 Hz, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 158.7, 154.7, 152.1, 149.9, 141.0, 130.9, 129.1, 124.4, 116.2, 114.2, 106.6 (d, J = 42.0 Hz), 94.8, 55.5, 45.9, 28.1, 22.7, 21.5 (d, J = 57.2 Hz).

LC-MS: 334.4 (M+H).

Anal. Calculated for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60; Found: C, 75.50; H, 6.84; N, 12.20%.

N-(4-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydroacridine-3,9-diamine (**13b**)

Yield=80% (0.30 g); off white solid.

Mp 151-154^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (s, 1H, NH), 7.69 (d, J = 8.0 Hz, 2H, ArH), 7.60 (d, J = 8.2 Hz, 2H, ArH), 6.8 (dd, J = 9.0 Hz, 1H, ArH), 6.67 (t, J = 6.1 Hz, 1H, ArH), 6.37 (d, J = 2.3 Hz, 1H, ArH), 6.08 (s, 2H, NH_2), 4.24 (d, J = 5.2 Hz, 2H, CH_2), 2.88 (d, J = 5.4 Hz, 2H, CH_2), 2.45 (d, J = 6.3 Hz, 2H, CH_2), 1.78 (m, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, 158.9, 148.4, 146.3, 145.1, 133.7, 128.4 (J = 32 Hz), 126.2, 125.6 (J = 292 Hz), 123.5, 121.2, 119.1, 110.6, 42.9, 34.1, 24.2, 23.0, 22.9.

LC-MS: 372.2 (M+H).

Anal. Calculated for $C_{21}H_{20}F_3N_3$: C, 67.91; H, 5.47; N, 11.31; Found: C, 67.93; H, 5.75; N, 11.62%.

N-(3-(trifluoromethyl)benzyl)-5,6,7,8-tetrahydroacridine-3,9-diamine (**13c**)

Yield=75% (0.28 g); off white solid.

Mp 150-152^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (s, 1H, NH), 7.73 (d, J = 8.0 Hz, 2H, ArH), 7.62-7.56 (m, 3H, ArH), 6.81 (dd, J = 9.0 Hz, 1H, ArH), 6.68-6.57 ((m, 1H, ArH), 6.41 (d, J = 2.3 Hz, 1H, ArH), 6.06 (s, 2H, NH_2), 4.45 (d, J = 6.0 Hz, 2H, CH_2), 2.66 (d, J = 5.4 Hz, 2H, CH_2), 2.45 (d, J = 6.3 Hz, 2H, CH_2), 1.78 (m, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 170.1, 160.6, 160.1, 157.4, 145.9, 142.7, 141.9, 137.0, 136.7, 134.8 (J = 28 Hz), 129.1, 128.7, 124.0 (J = 274 Hz), 115.0, 47.6, 33.0, 27.8, 26.1, 25.6, 13.5.

LC-MS: 371.9 (M+H).

Anal. Calculated for $C_{18}H_{20}N_2O_2$: C, 67.91; H, 5.43; N, 11.31; Found: C, 67.55; H, 5.91; N, 12.15%.

N-(3,5-difluorobenzyl)-5,6,7,8-tetrahydroacridine-3,9-diamine (**13d**)

Yield=84% (0.28 g); off white solid.

Mp 139-143^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (s, 1H, NH), 7.09 (m, 3H, ArH), 6.79 (dd, J = 9.0 Hz, 1H, ArH), 6.64-6.57 ((m, 1H, ArH), 6.41 (d, J = 2.4 Hz, 1H, ArH), 6.03 (s, 2H, NH_2), 4.39 (d, J = 6.0 Hz, 2H, CH_2), 2.67 (d, J = 5.4 Hz, 2H, CH_2), 2.45 (d, J = 6.3 Hz, 2H, CH_2), 1.78 (m, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6 (J = 242 Hz), 158.9, 157.0, 156.5, 148.1, 147.8, 145.6, 122.5, 114.8 (J = 37 Hz), 110.1, 109.7 (J = 32 Hz), 106.1, 103.8, 45.6, 33.3, 24.2, 23.3, 22.7.

LC-MS: 339.8 (M+H).

Anal. Calculated for $C_{20}H_{19}F_2N_3$: C, 70.78; H, 5.64; N, 12.38; Found: C, 70.52; H, 5.94; N, 12.42%.

*N3-phenyl-5,6,7,8-tetrahydroacridine-3,9-diamine (**13e**)*

Yield=70% (0.20 g); Yellow solid.

Mp 140-144^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (s, 1H, NH), 8.13 (d, J = 9.1 Hz, 1H, ArH), 7.35 (dd, J = 8.2 Hz, 7.2 Hz, 2H, ArH), 7.29-7.22 (m, 3H, ArH), 7.1 (m, 3H, ArH, NH_2), 6.99 (t, J = 7.3 Hz, 1H, ArH), 2.84 (d, J = 5.4 Hz, 2H, CH_2), 2.48 (d, J = 6.3 Hz, 2H, CH_2), 1.8 (m, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 153.8, 151.2, 146.2, 144.1, 142.3, 129.7, 124.3, 121.9, 119.3, 116.9, 109.8, 107.6, 103.2, 30.8, 23.3, 22.4, 22.1.

LC-MS: 290.2 (M+H).

Anal. Calculated for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52; Found: C, 79.18; H, 6.35; N, 14.63%.

*N3-methyl-N3-phenyl-5,6,7,8-tetrahydroacridine-3,9-diamine (**13f**)*

Yield=68% (0.21 g); Pale yellow solid.

Mp 143-146^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, J = 9.1 Hz, 1H, ArH), 7.41 (dd, J = 8.5 Hz, 7.3 Hz, 2H, ArH), 7.23-7.19 (m, 3H, ArH), 6.96-6.92 (m, 3H, ArH, NH_2), 3.36 (s, 3H, CH_3), 2.78 (d, J = 5.9 Hz, 2H, CH_2), 2.48 (d, J = 6.3 Hz, 2H, CH_2), 1.82 (m, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 150.9, 149.8, 148.2, 130.1, 124.27, 124.3, 124.1, 123.6, 116.6, 107.8, 48.1, 31.8, 24.2, 23.4, 22.6, 22.4.

LC-MS: 304.2 (M+H).

Anal. Calculated for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85; Found: 78.91; H, 7.08; N, 13.46%.

*N3-(3,5-difluoropyridin-2-yl)-5,6,7,8-tetrahydroacridine-3,9-diamine (**13g**)*

Yield=79% (0.25 g); Off-white solid.

Mp 151-154^{o}C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 1H, NH), 8.28 (d, J = 2.2 Hz, 1H, ArH), 8.17 (d, J = 2.5 Hz, 1H, ArH), 8.04 (d, J = 9.2 Hz, 1H, ArH), 7.89 (m, 1H, ArH), 7.53 (dd, J = 9.1Hz, 2.3Hz, 1H, ArH), 7.51 (t, J = 7.3 Hz, 1H, ArH), 6.45 (s, 2H, NH_2), 2.8 (d, J = 5.4 Hz, 2H, CH_2), 2.54 (d, J = 6.3 Hz, 2H, CH_2), 1.81 (m, 4H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8 (J = 283 Hz), 151.5 (2C), 149.3, 146.7, 145.1 (J = 282 Hz), 142.3 (J = 9 Hz), 141.2, 129.3 (J = 16 Hz, 5 Hz), 122.6, 117.5, 112.6, 112.3, 108.1, 33.3, 23.8, 22.9.

LC-MS: 327.2 (M+H).

Anal. Calculated for $C_{18}H_{16}F_2N_4$: C, 66.25; H, 4.94; N, 17.17; Found: C, 65.99; H, 4.58; N, 17.14%.

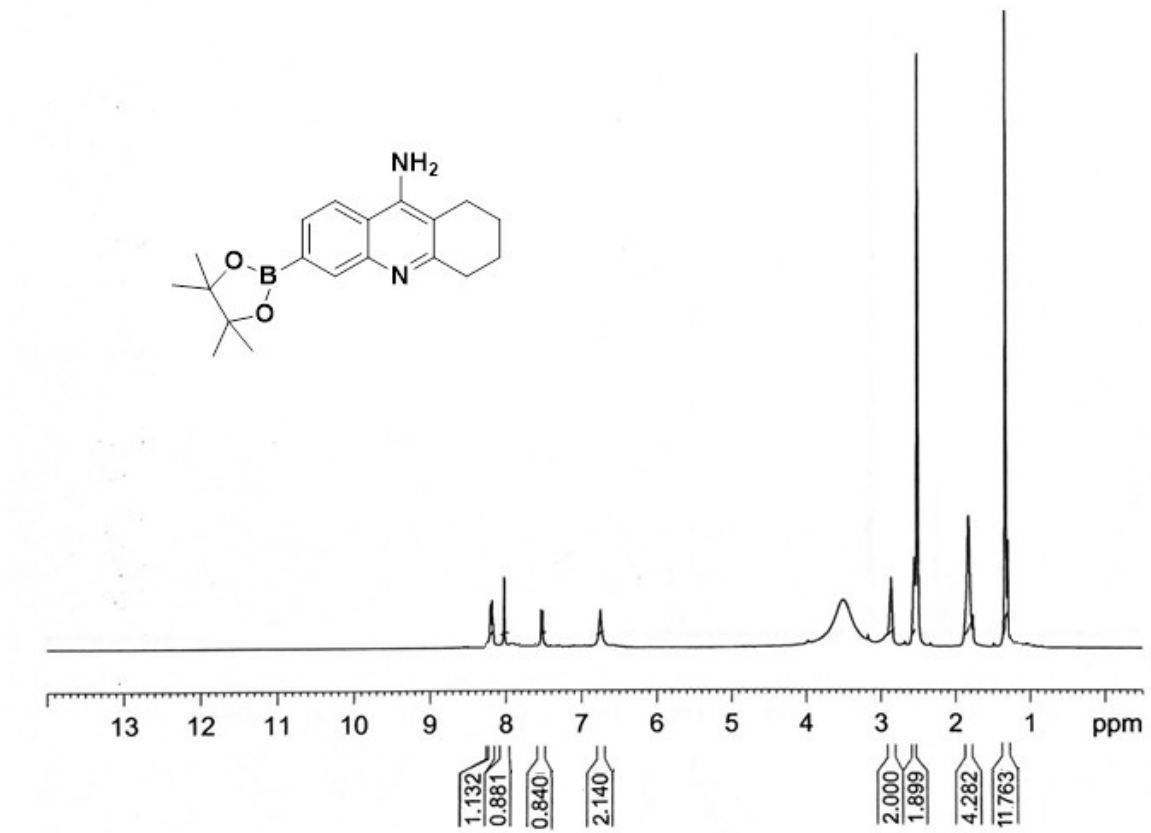
References

(1) G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw and K. I. Goldberg, *Organometallics*, 2010, **29**, 2176-2179.

(2) E. K. Reddy, C. Remya, K. Mantosh, A. M. Sajith, R. V. Omkumar, C. Sadasivan and S. Anwar, *Eur. J. Med. Chem*., 2017, **139**, 367-377.

Spectral data

^{1}H NMR of Compound **3**

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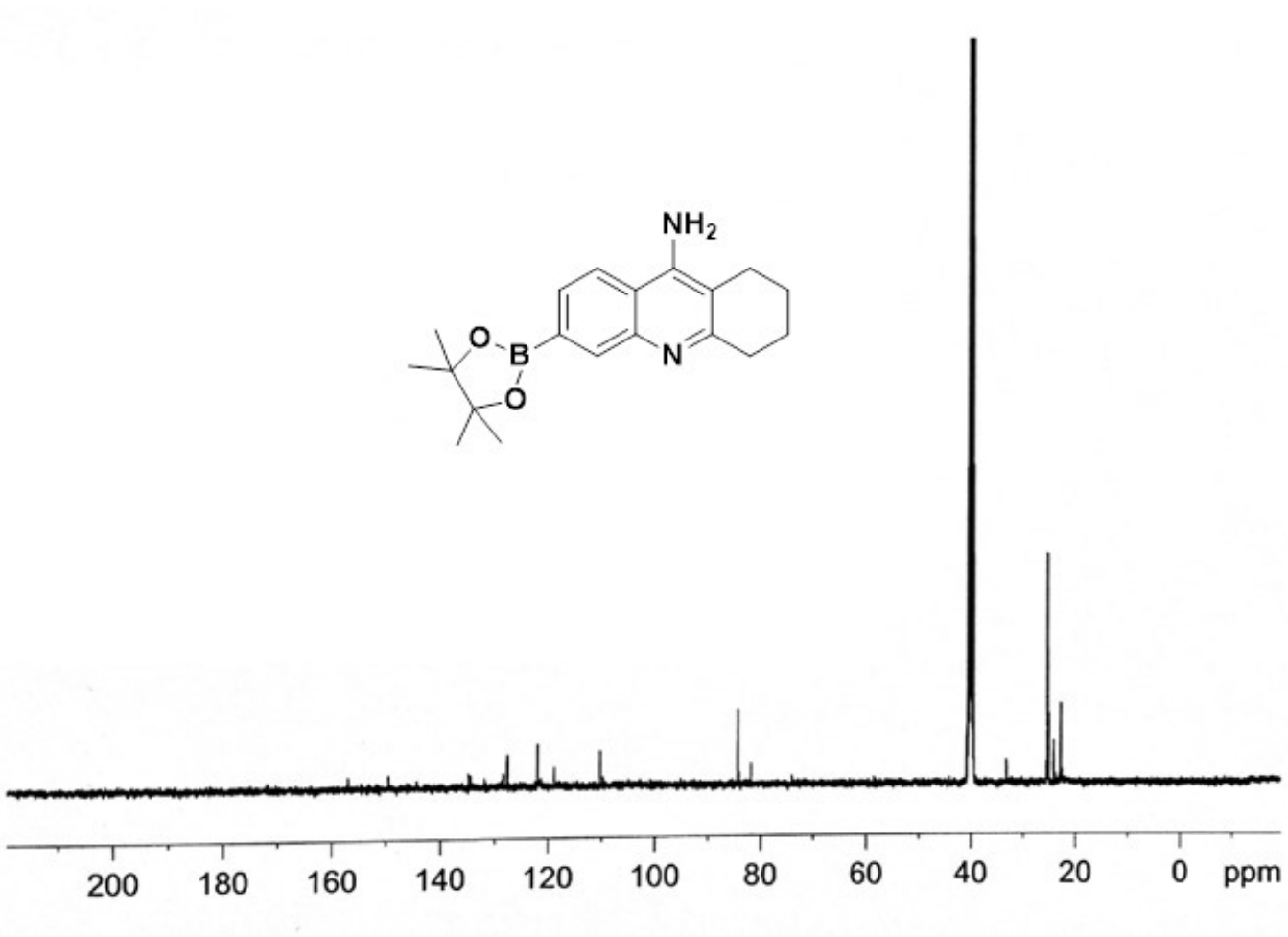
^{13}C NMR of Compound **3**

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F2 - Processing parameters
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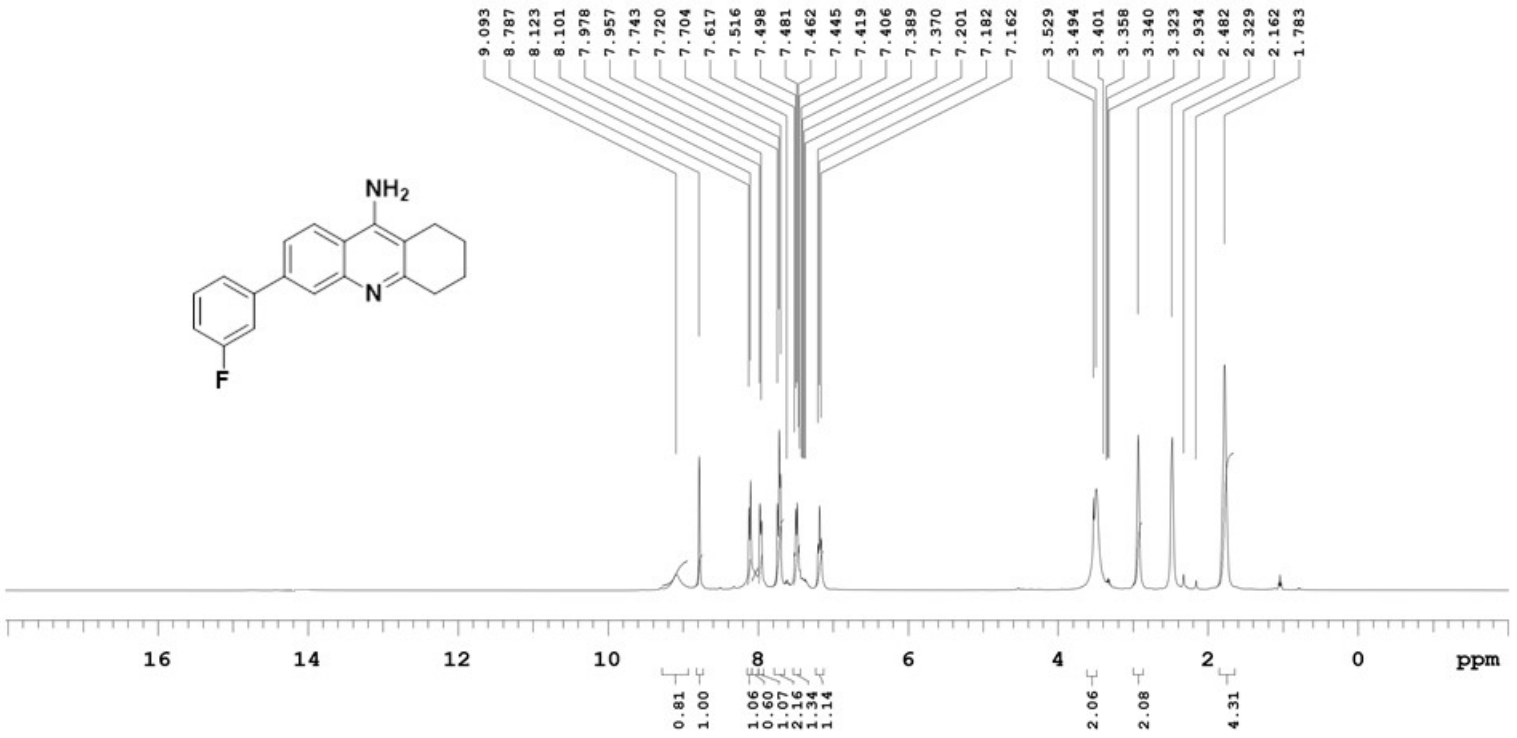
[1]H NMR of Compound **7a**



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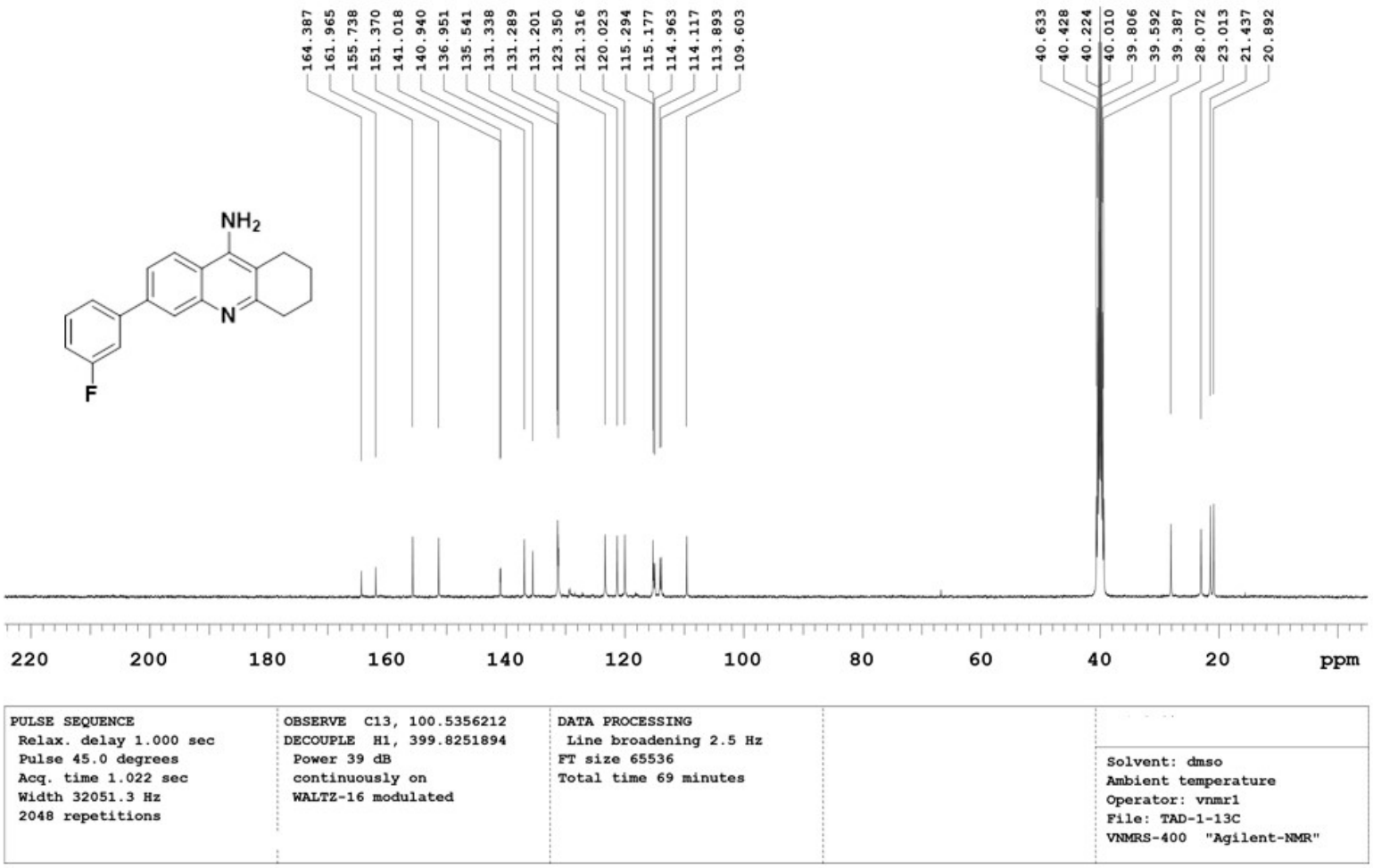
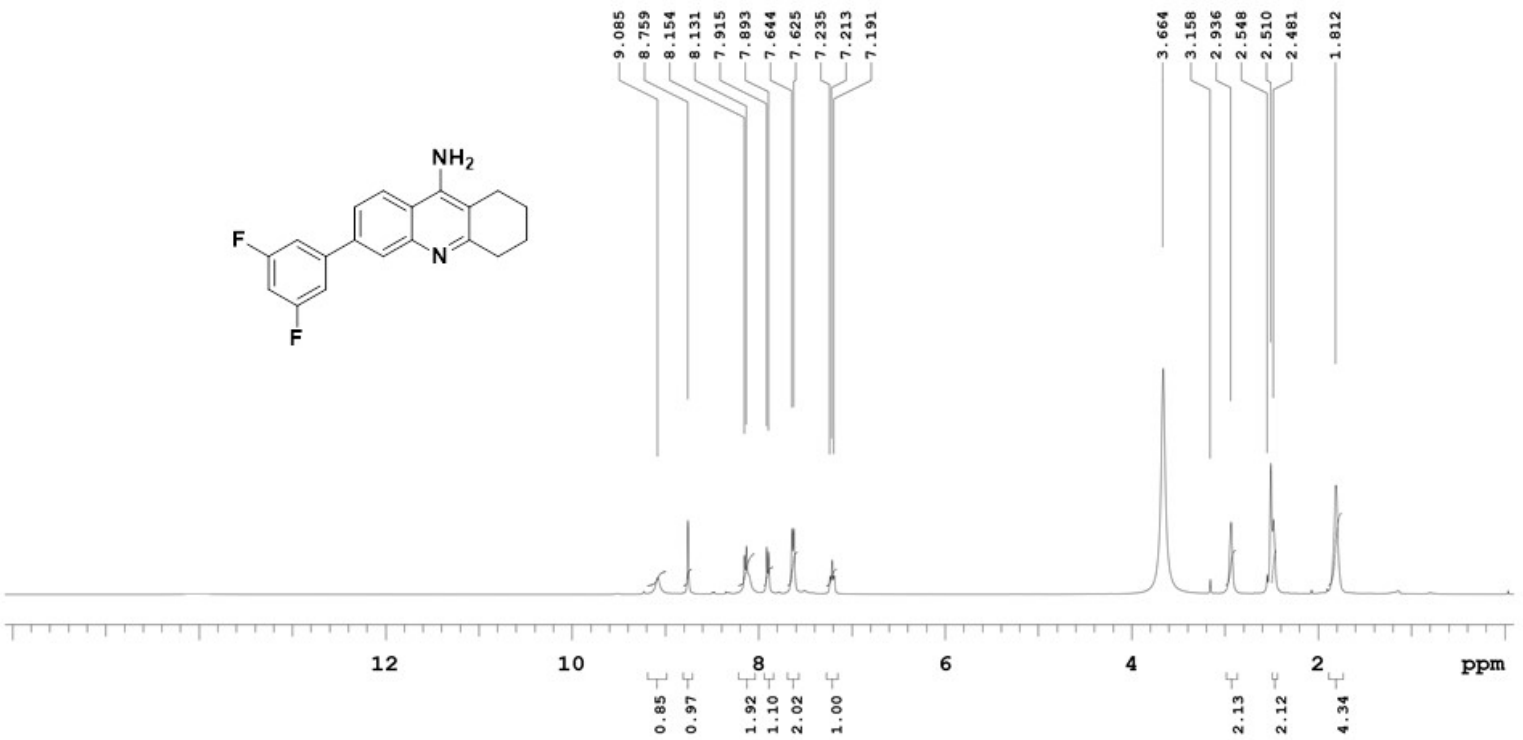
^{13}C NMR of Compound **7a**



[1]H NMR of Compound **7b**



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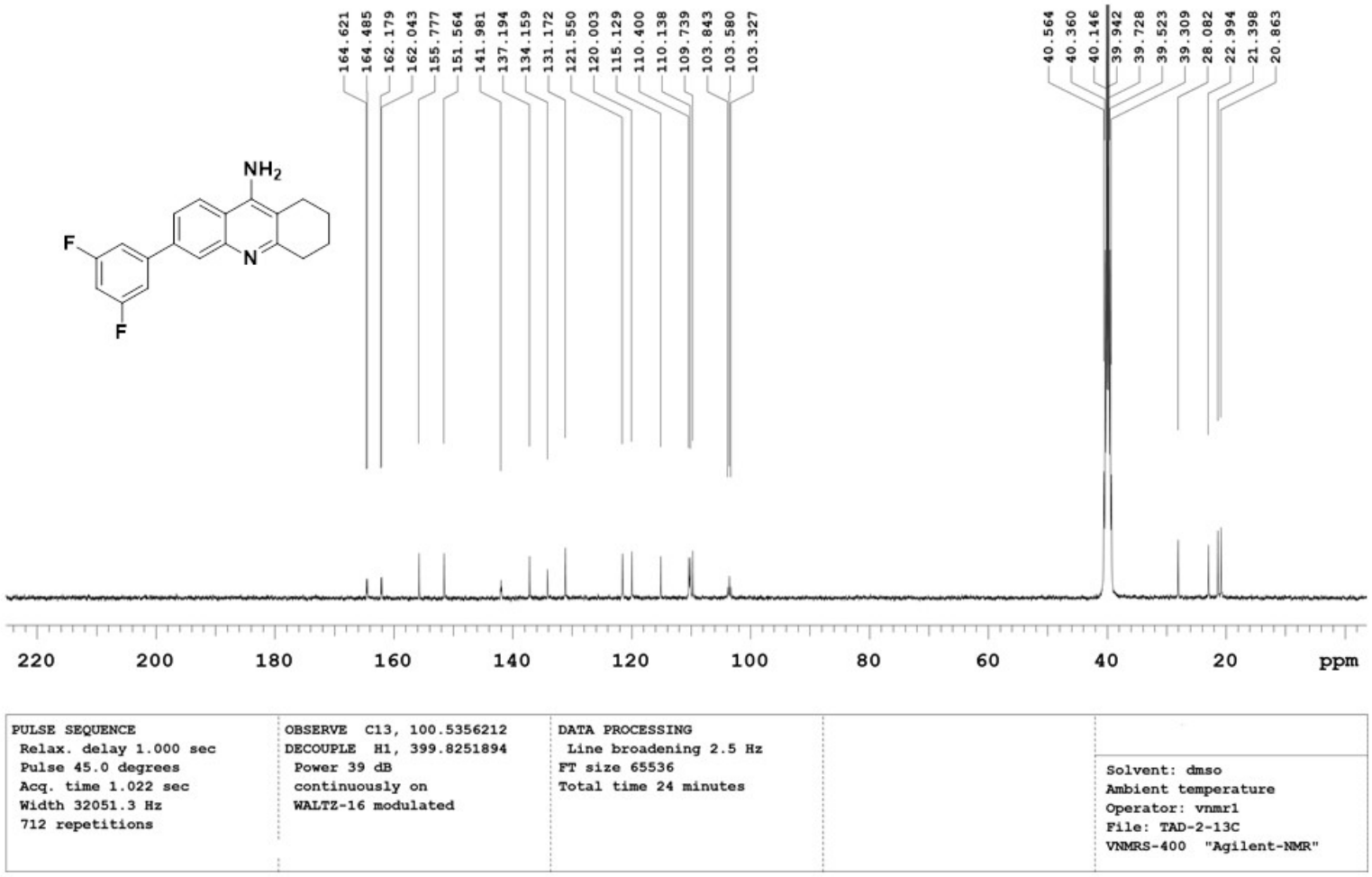
^{13}C NMR of Compound **7b**



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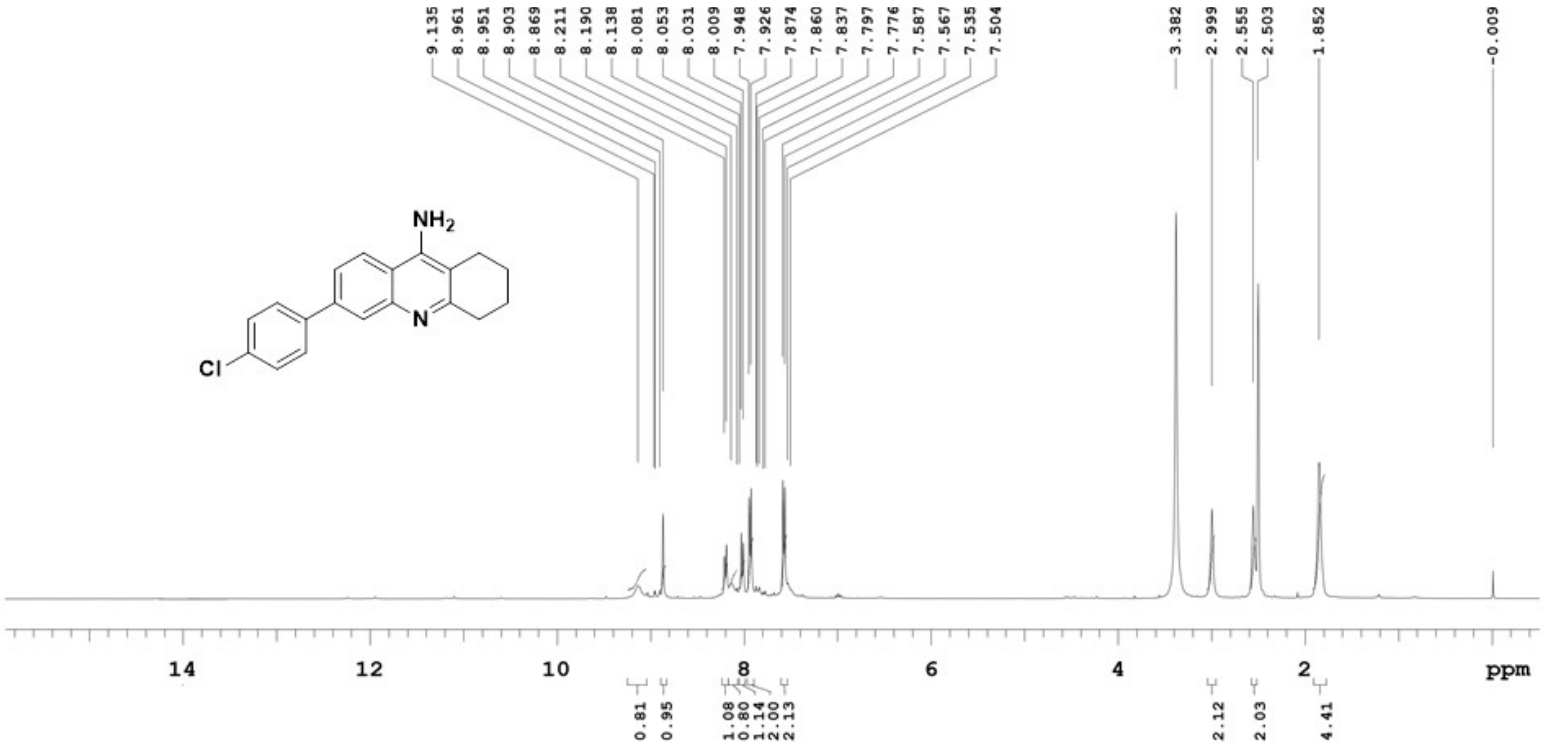
[1]H NMR of Compound **7c**



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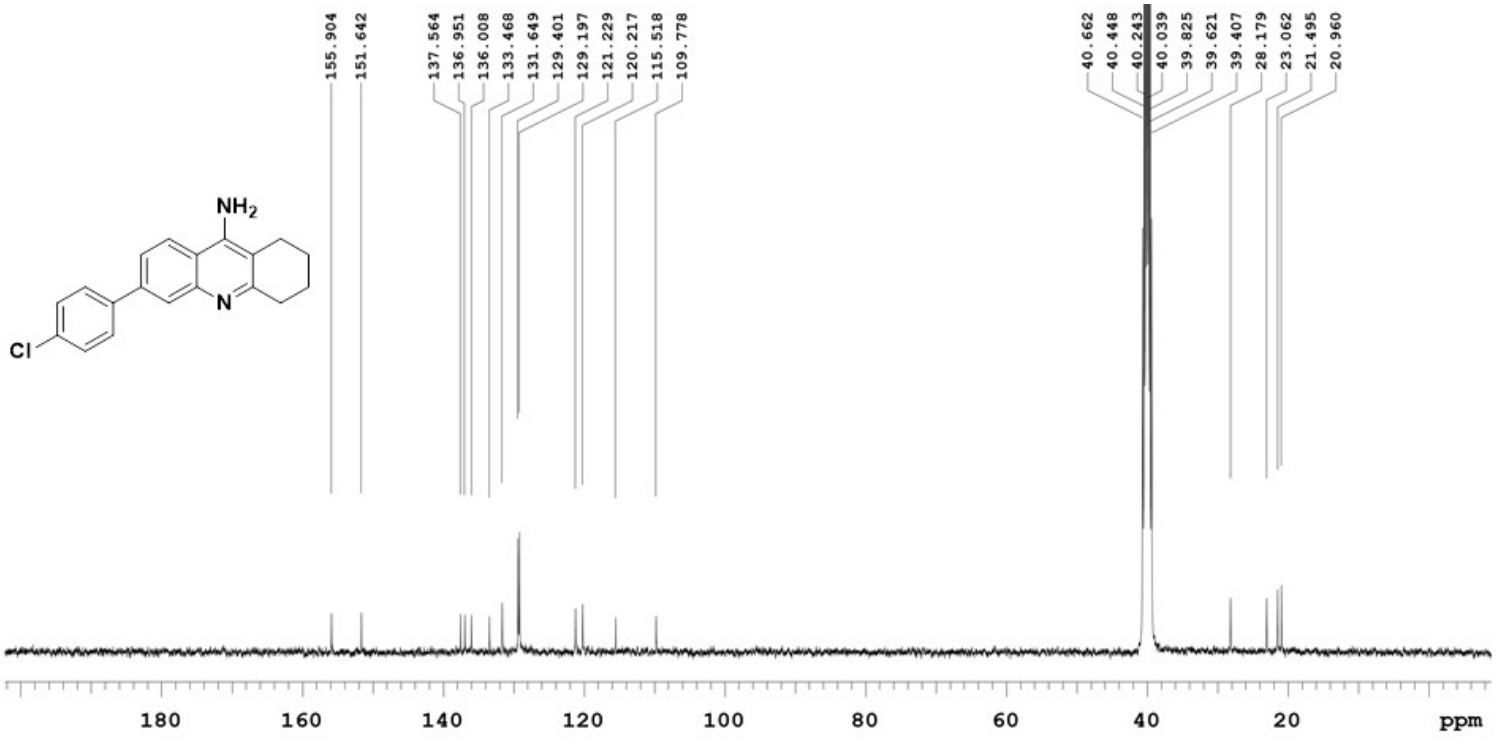
^{13}C NMR of Compound **7c**



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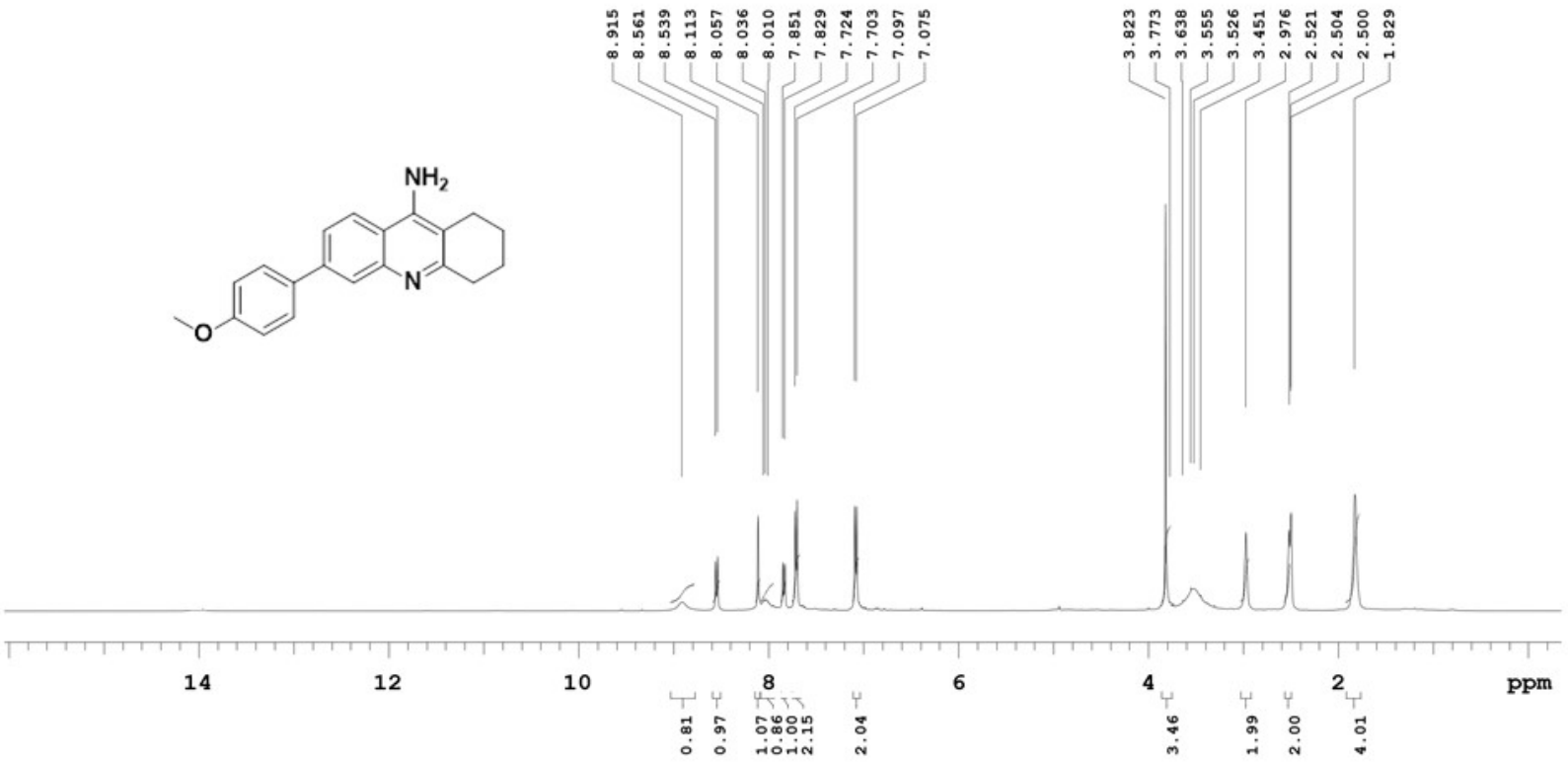
[1]H NMR of Compound **7d**



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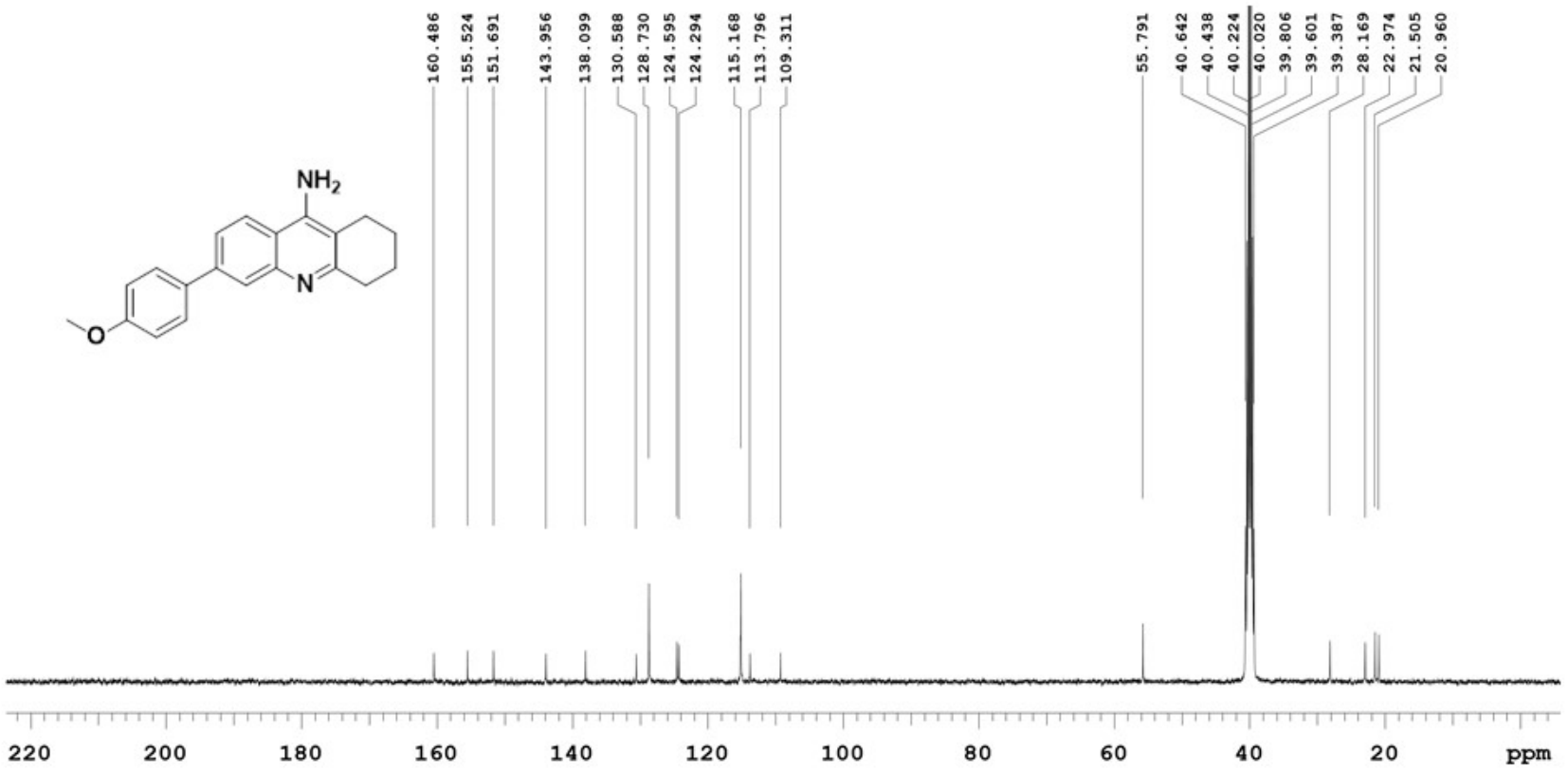
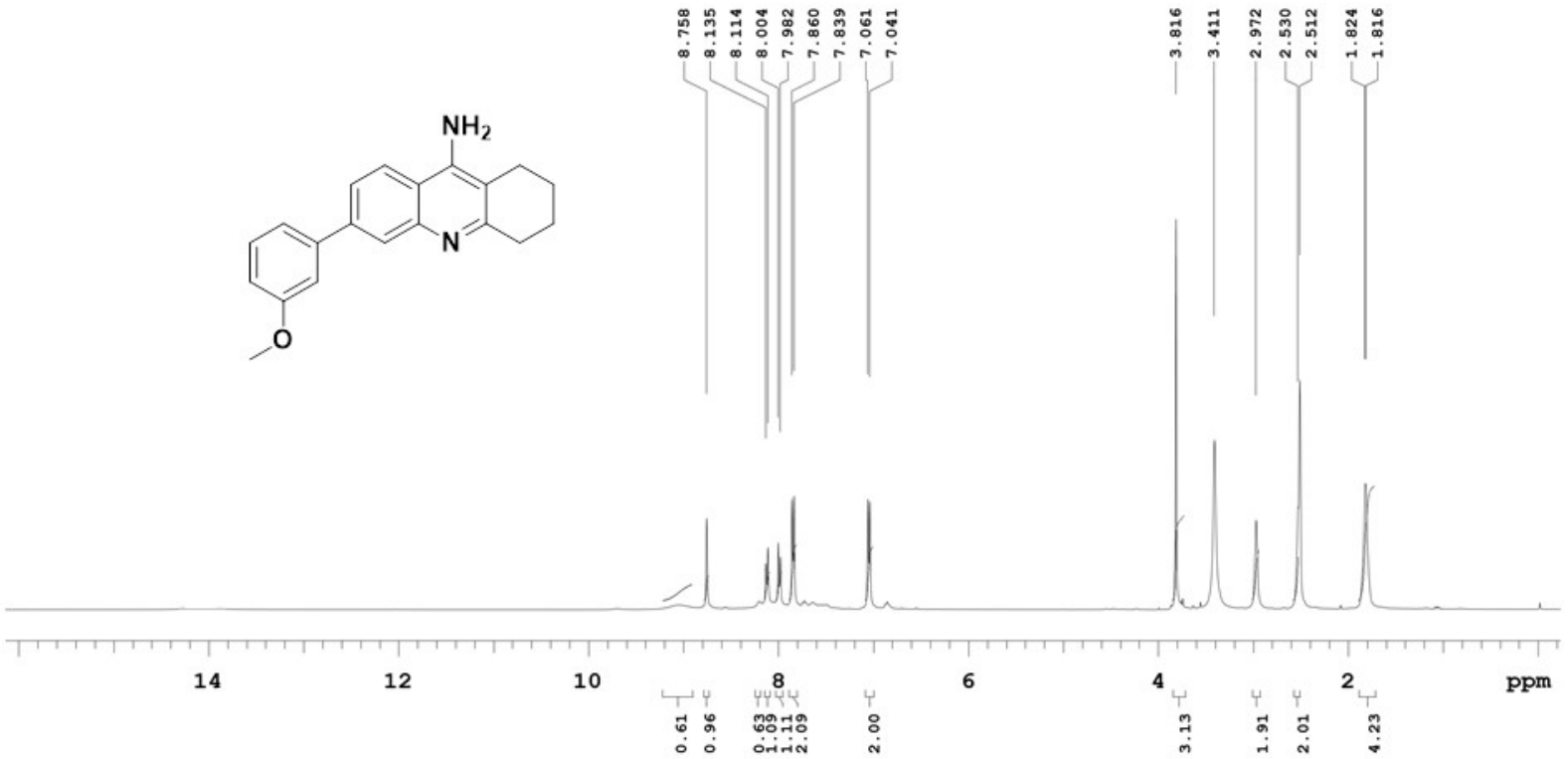
^{13}C NMR of Compound **7d**



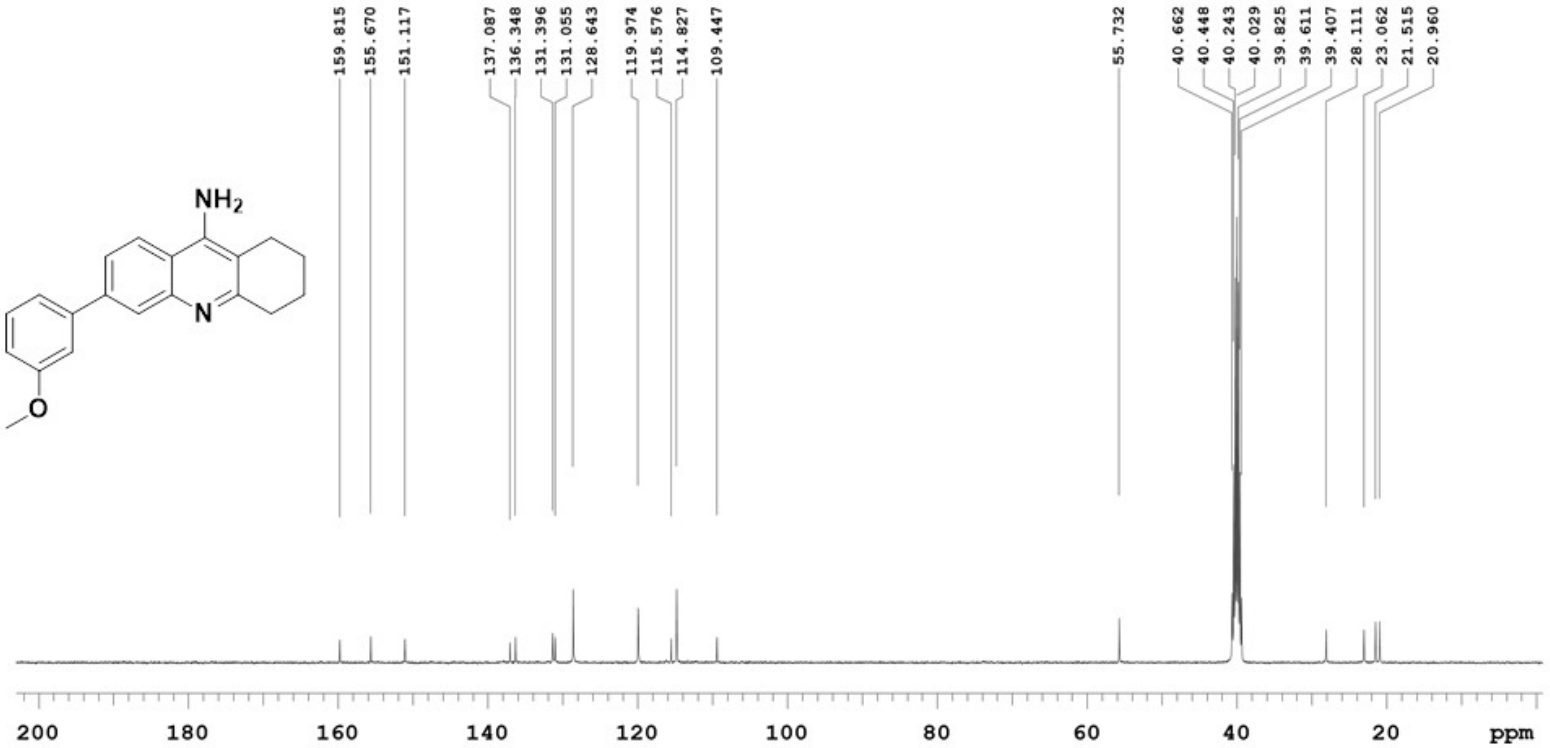
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.022 sec Width 32051.3 Hz 1024 repetitions	OBSERVE C13, 100.5356212 DECOUPLE H1, 399.8251894 Power 39 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 2.5 Hz FT size 65536 Total time 34 minutes		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-4-13C VNMRS-400 "Agilent-NMR"

[1]H NMR of Compound **7e**



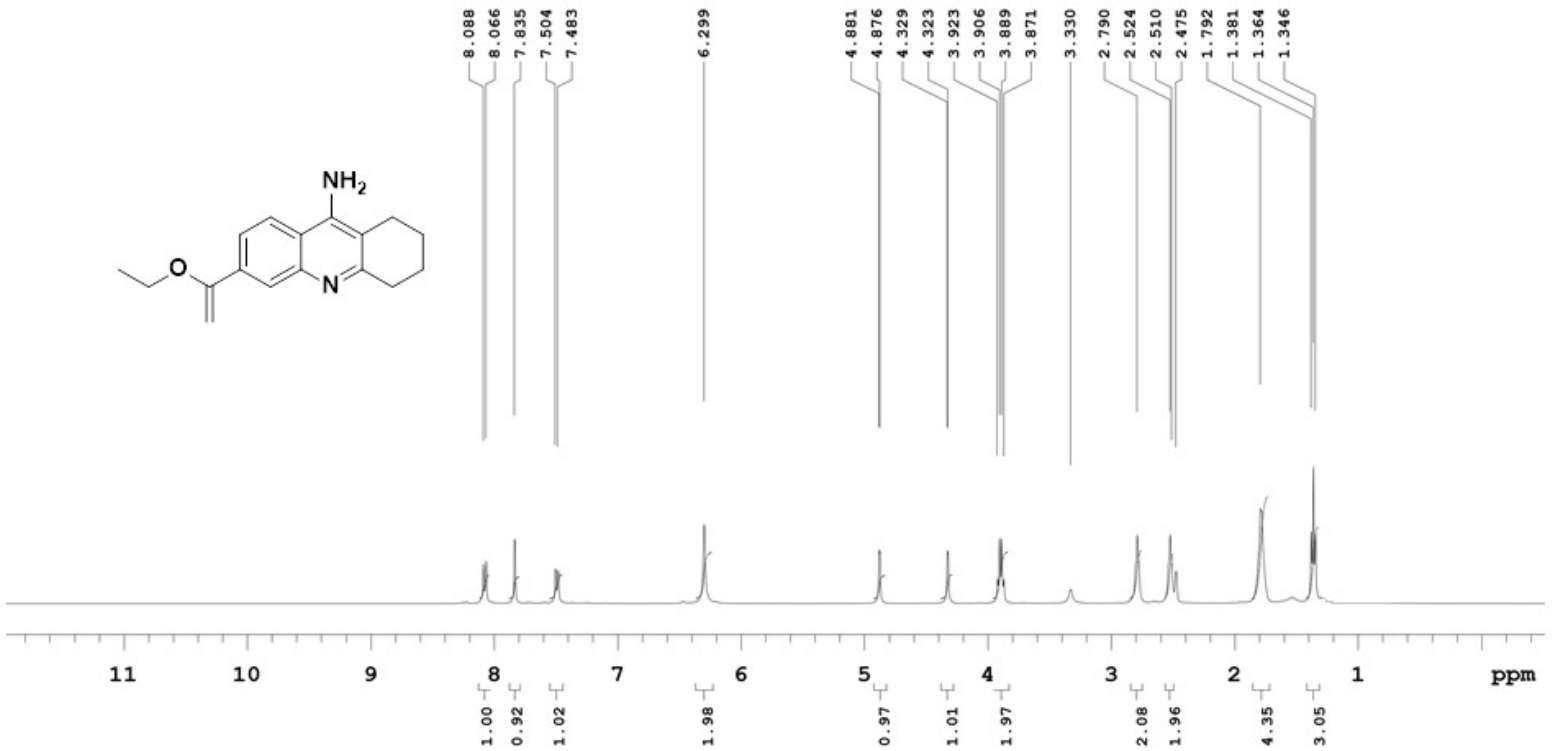
PULSE SEQUENCE Relax. delay 2.000 sec Pulse 45.0 degrees Acq. time 3.408 sec Width 9615.4 Hz 16 repetitions	OBSERVE H1, 399.8231781	DATA PROCESSING Line broadening 0.5 Hz FT size 65536 Total time 1 minute		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-05-1H VNMRS-400 "Agilent-NMR"

^{13}C NMR of Compound **7e**



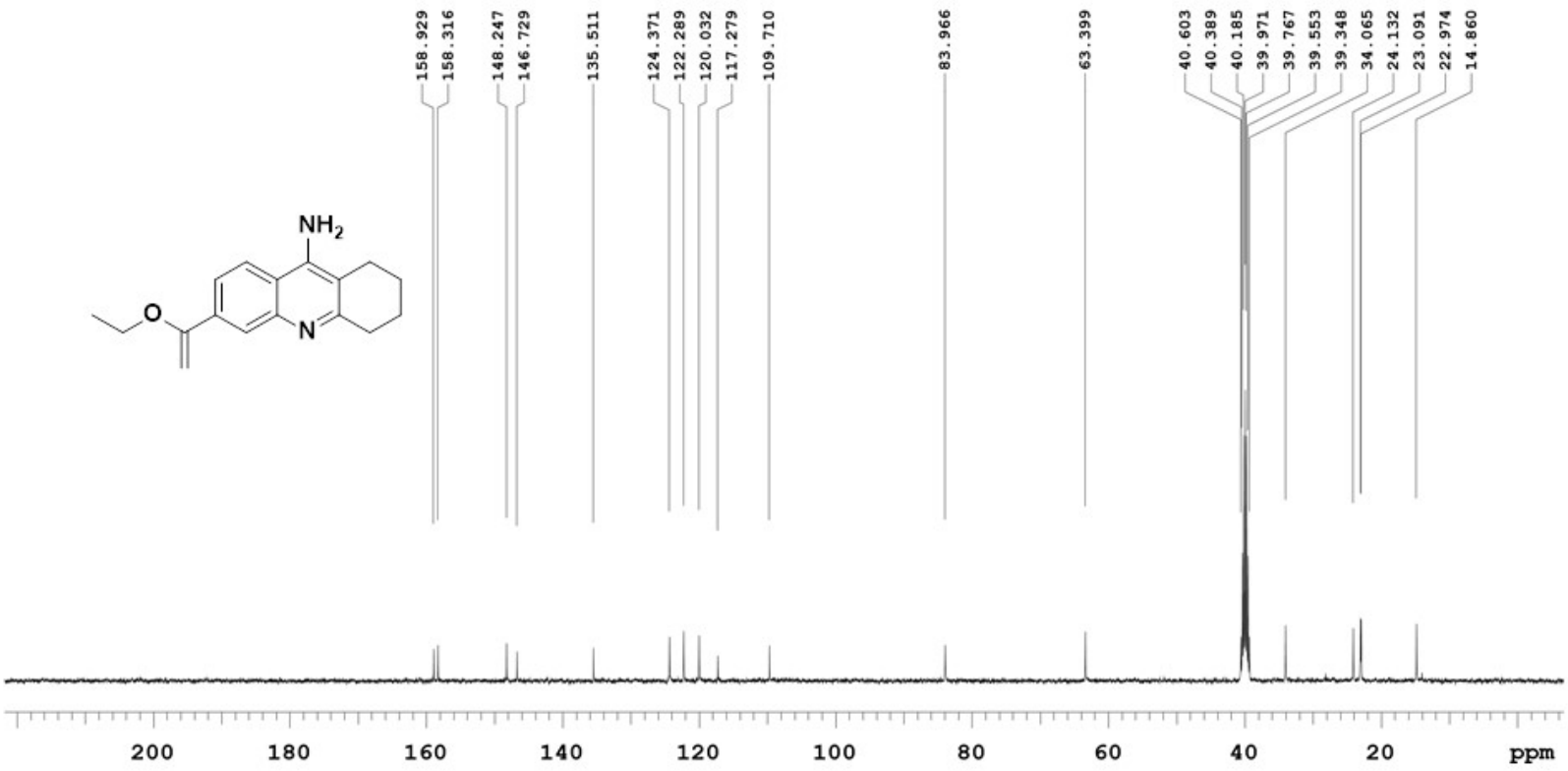
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.022 sec Width 32051.3 Hz 2048 repetitions	OBSERVE C13, 100.5356212 DECOUPLE H1, 399.8251894 Power 39 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 2.5 Hz FT size 65536 Total time 69 minutes		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-05-13C VNMRS-400 "Agilent-NMR"

[1]H NMR of Compound **7f**



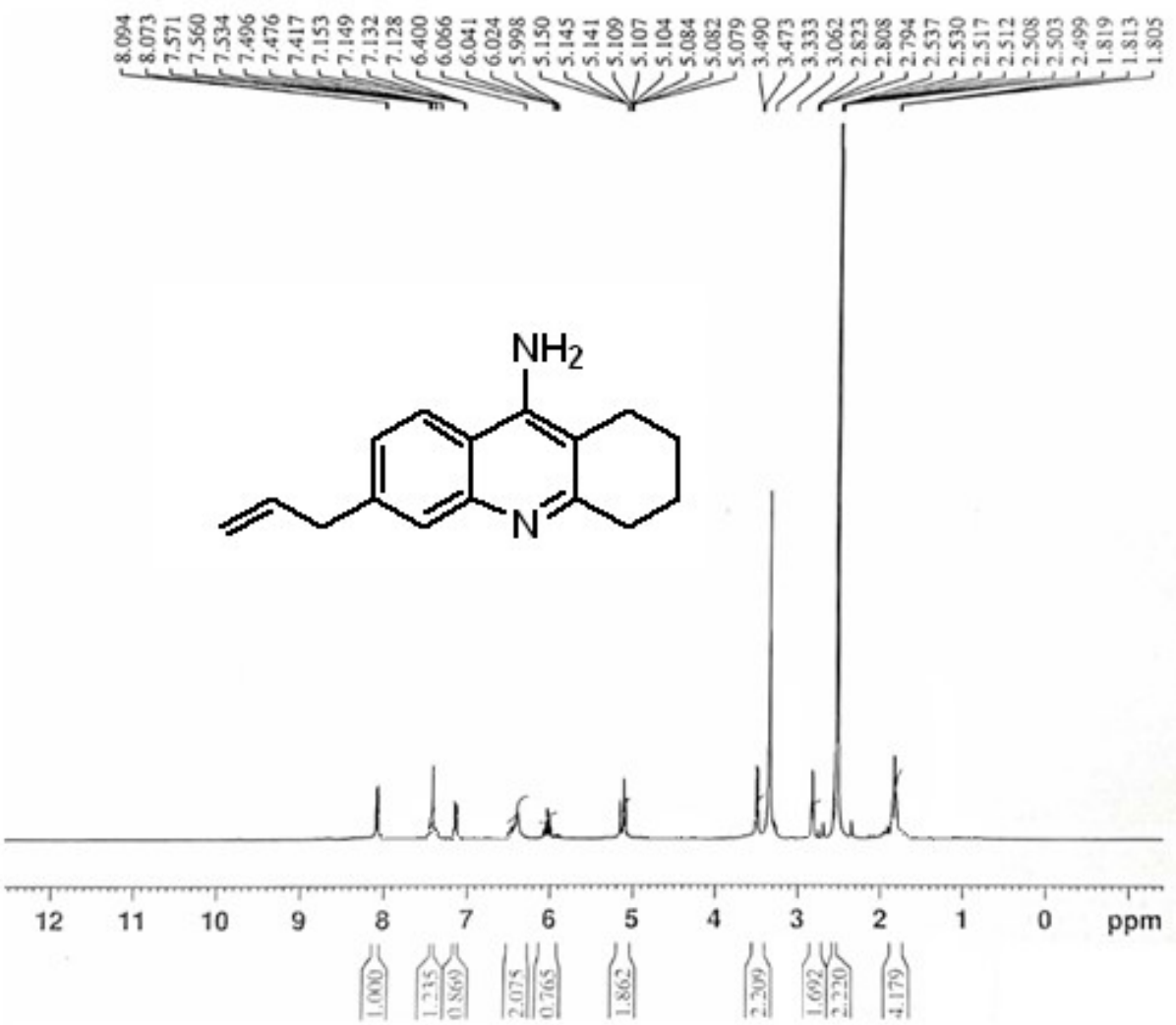
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 3.146 sec Width 10416.7 Hz 8 repetitions	OBSERVE H1, 399.8231903	DATA PROCESSING Line broadening 1.0 Hz FT size 65536 Total time 1 minute		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-57-1H VNMRS-400 "Agilent-NMR"

^{13}C NMR of Compound **7f**



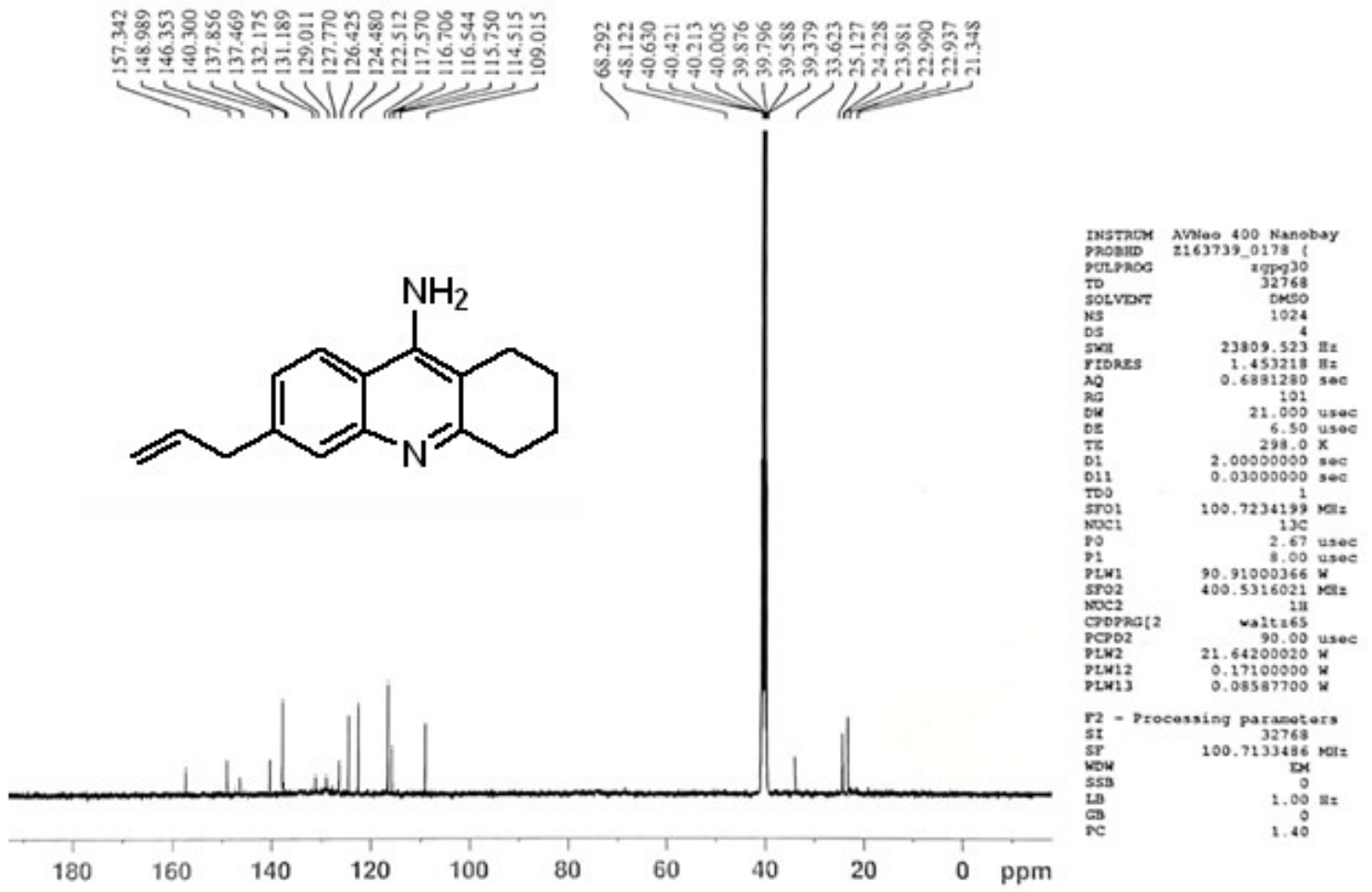
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.022 sec Width 32051.3 Hz 334 repetitions	OBSERVE C13, 100.5356212 DECOUPLE H1, 399.8251894 Power 39 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 2.5 Hz FT size 65536 Total time 11 minutes		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-57-13C VNMRS-400 "Agilent-NMR"

[1]H NMR of Compound **7g**



INSTRUM	AVNeo 400 Nanobay	
PROBHD	Z163739_0178 (	
PULPROG	zg30	
TD	32768	
SOLVENT	DMSO	
NS	16	
DS	2	
SWH	8196.722	Hz
FIDRES	0.500288	Hz
AQ	1.9988480	sec
RG	101	
DW	61.000	usec
DE	13.89	usec
TE	298.0	K
D1	2.00000000	sec
TD0	1	
SFO1	400.5324733	MHz
NUC1	1H	
P0	2.67	usec
P1	8.00	usec
PLW1	21.64200020	W
F2 - Processing parameters		
SI	65536	
SF	400.5300000	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
P(	1.00	

^{13}C NMR of Compound **7g**



INSTRUM	AVNeo 400 Nanobay	
PROBHD	Z163739_0178 (	
PULPROG	zgpg30	
TD	32768	
SOLVENT	DMSO	
NS	1024	
DS	4	
SWH	23809.523	Hz
FIDRES	1.453218	Hz
AQ	0.6881280	sec
RG	101	
DW	21.000	usec
DE	6.50	usec
TE	298.0	K
D1	2.00000000	sec
D11	0.03000000	sec
TD0	1	
SFO1	100.7234199	MHz
NUC1	13C	
P0	2.67	usec
P1	8.00	usec
PLW1	90.91000366	W
SFO2	400.5316021	MHz
NUC2	1H	
CPDPRG[2	waltz65	
PCPD2	90.00	usec
PLW2	21.64200020	W
PLW12	0.17100000	W
PLW13	0.08587700	W
F2 - Processing parameters		
SI	32768	
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WDW	EM	
SSB	0	
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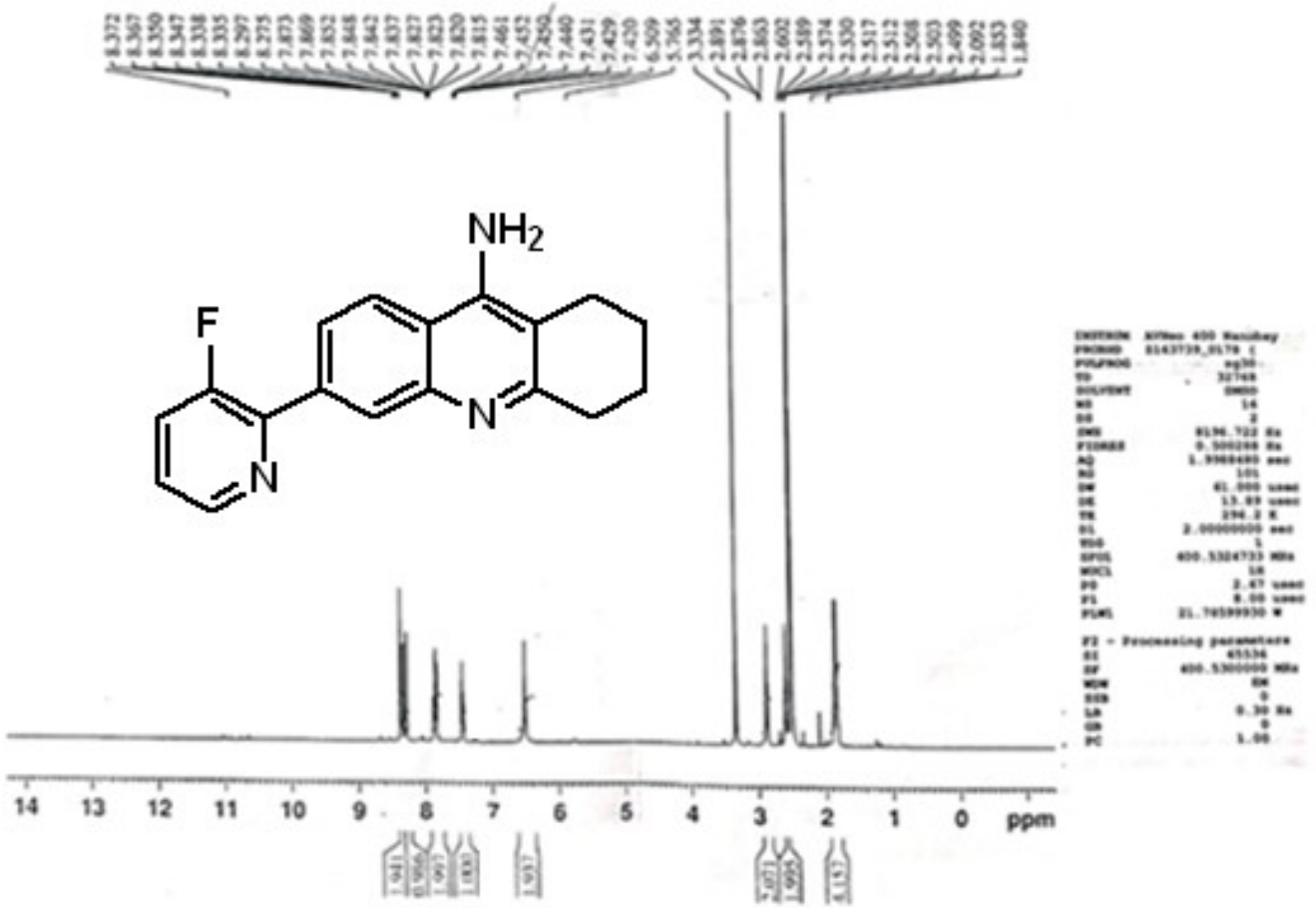
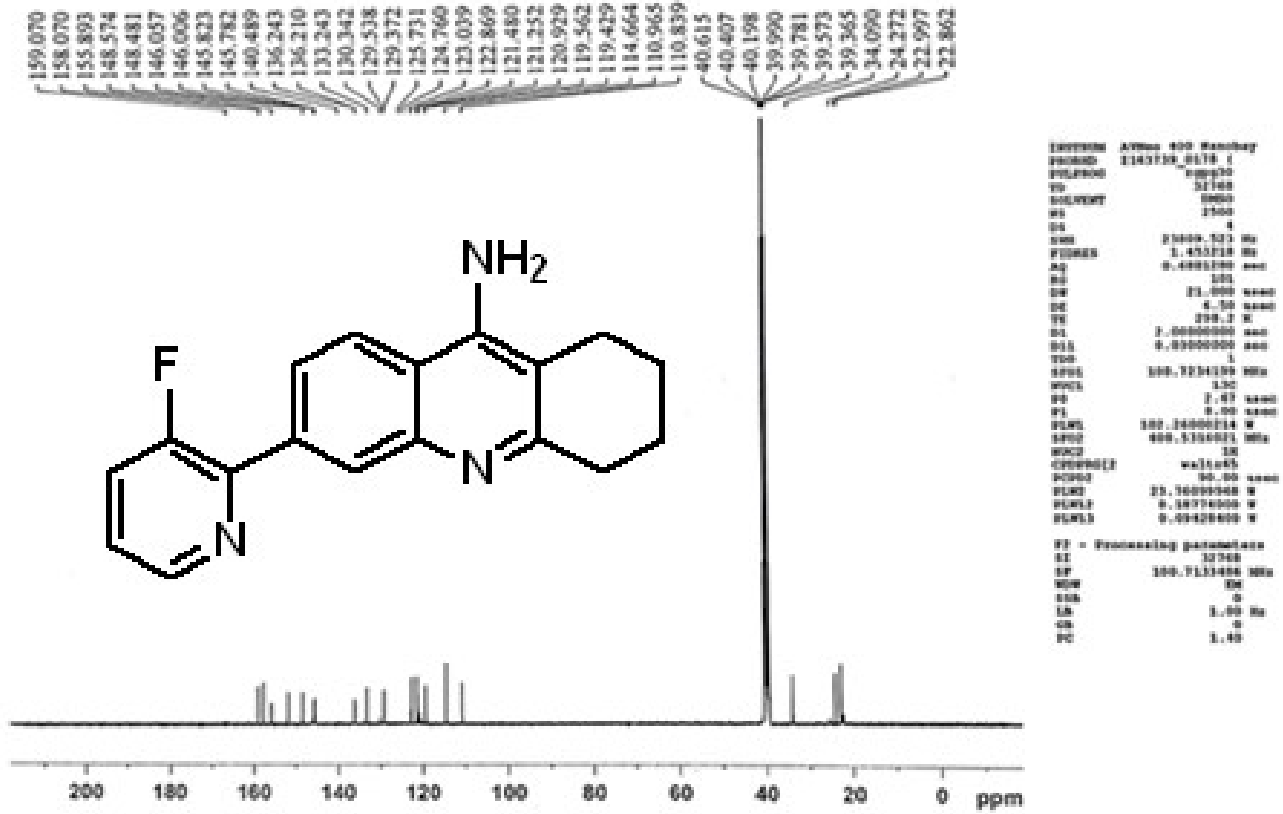
PC	1.40	

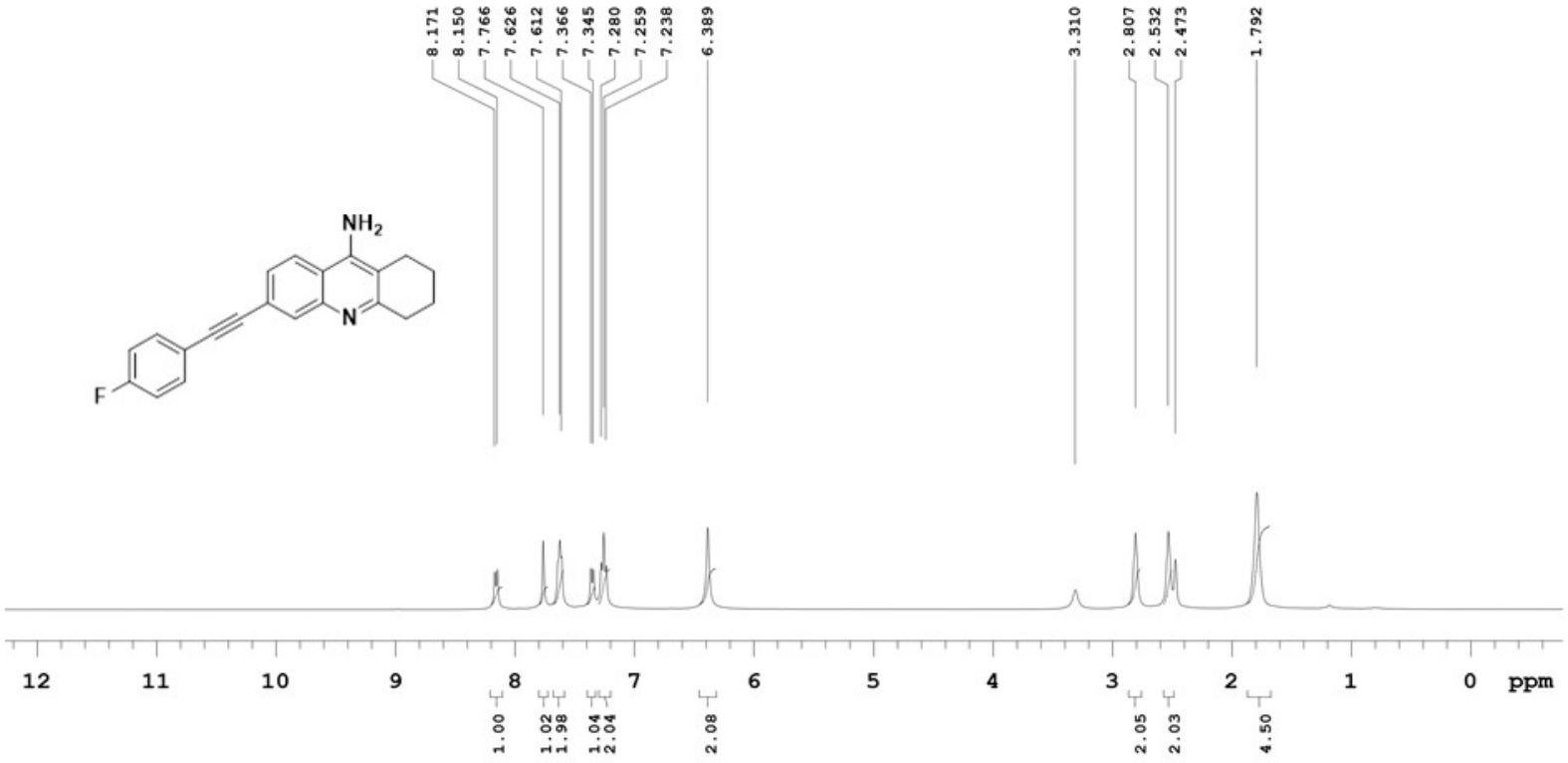
^{1}H NMR of Compound **7h**



^{13}C NMR of Compound **7h**

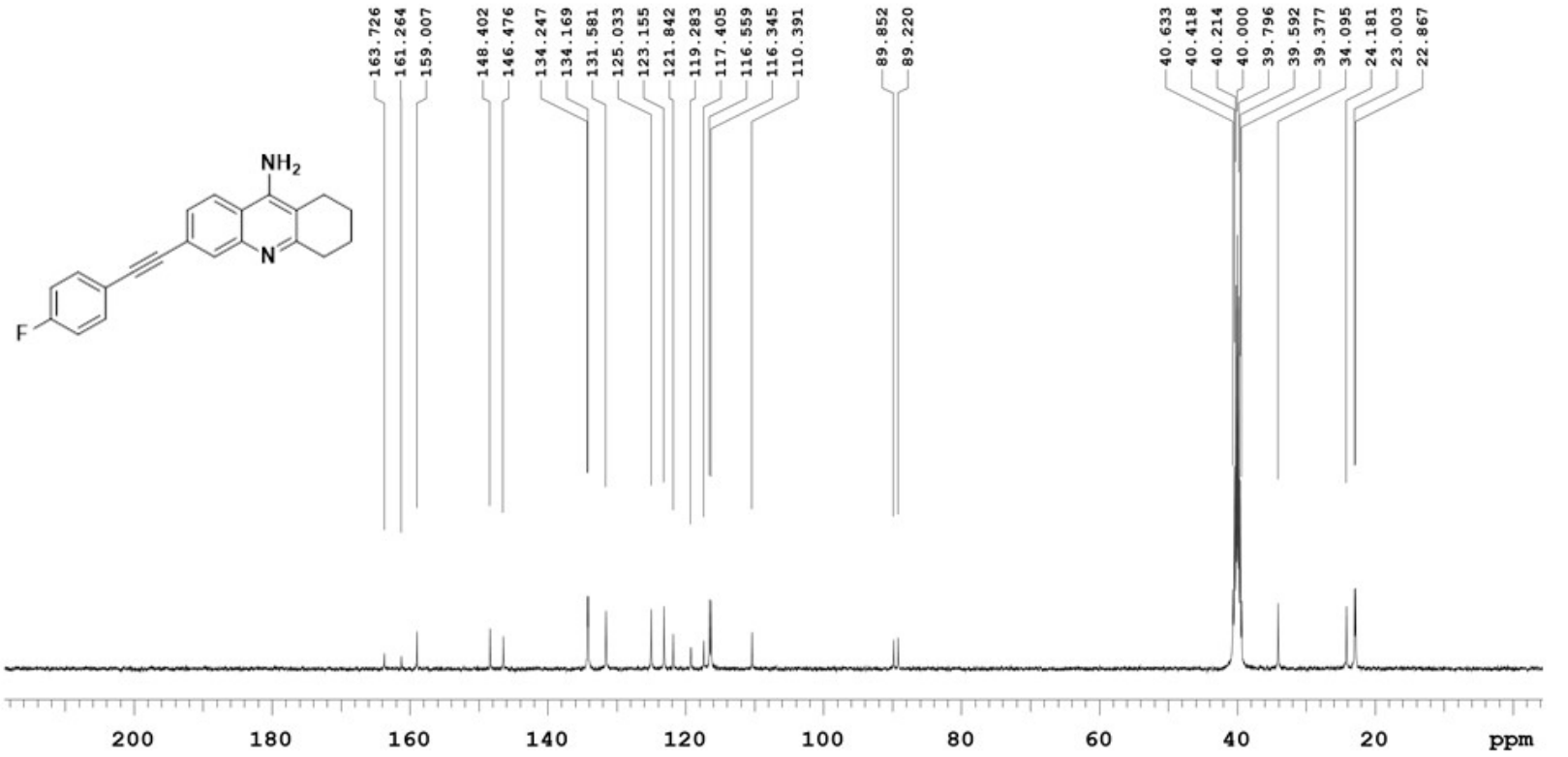


[1]H NMR of Compound **9a**



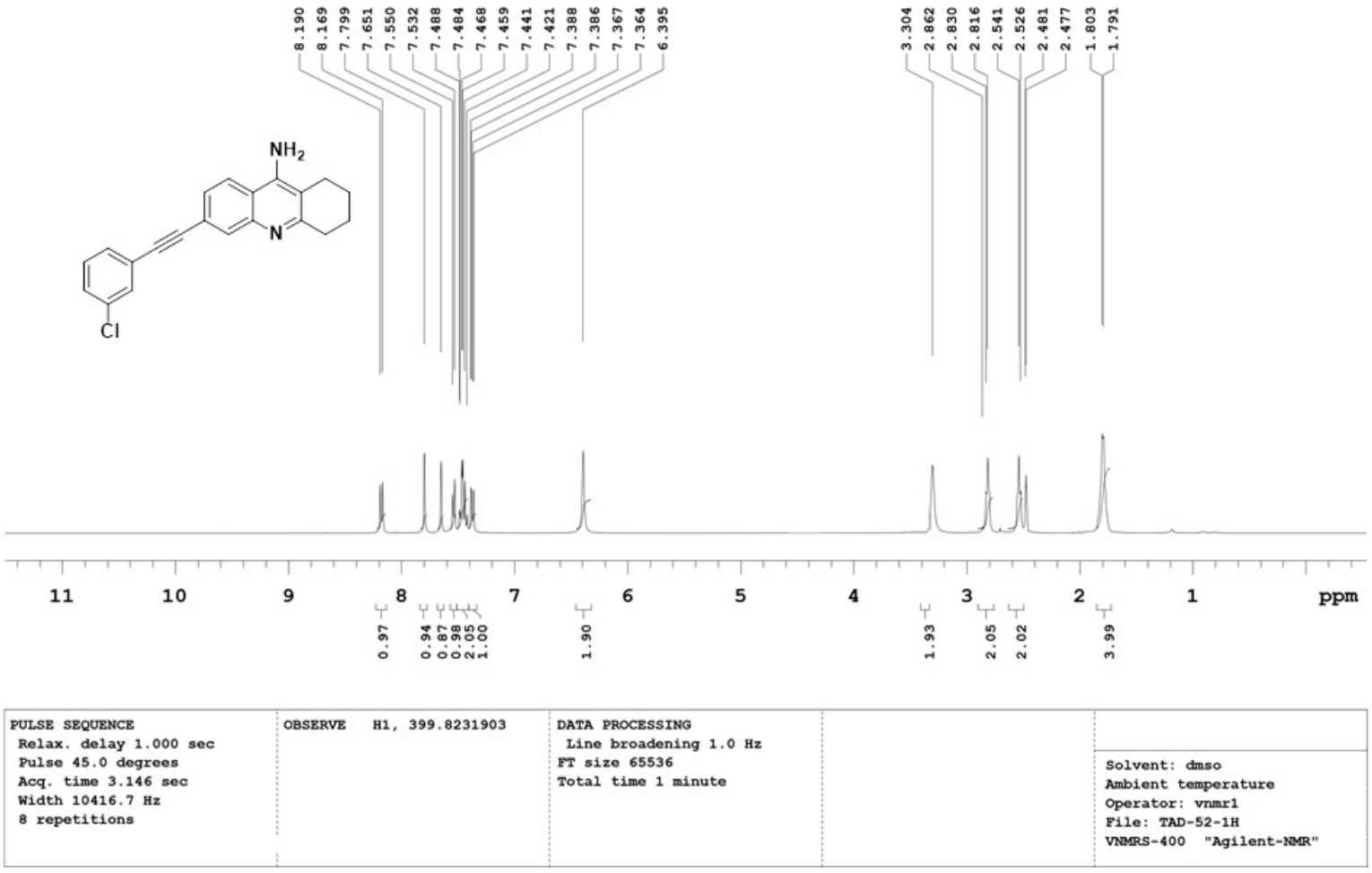
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 3.146 sec Width 10416.7 Hz 8 repetitions	OBSERVE H1, 399.8231903	DATA PROCESSING Line broadening 1.0 Hz FT size 65536 Total time 1 minute		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-51-1H VNMRS-400 "Agilent-NMR"

^{13}C NMR of Compound **9a**

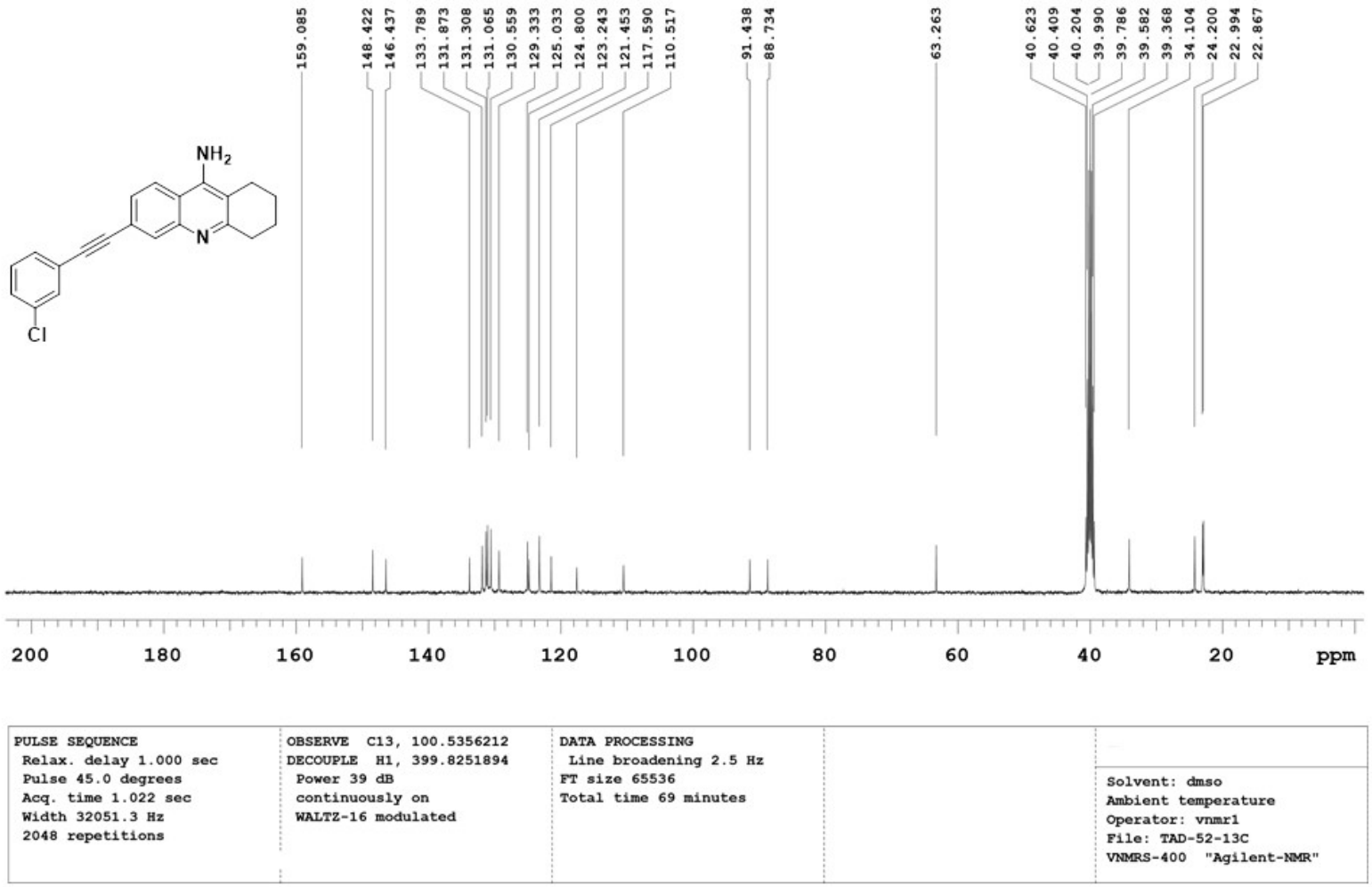


PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.022 sec Width 32051.3 Hz 3000 repetitions	OBSERVE C13, 100.5356212 DECOUPLE H1, 399.8251894 Power 39 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 2.5 Hz FT size 65536 Total time 101 minutes		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-51-13C VNMRS-400 "Agilent-NMR"

^{1}H NMR of Compound **9b**

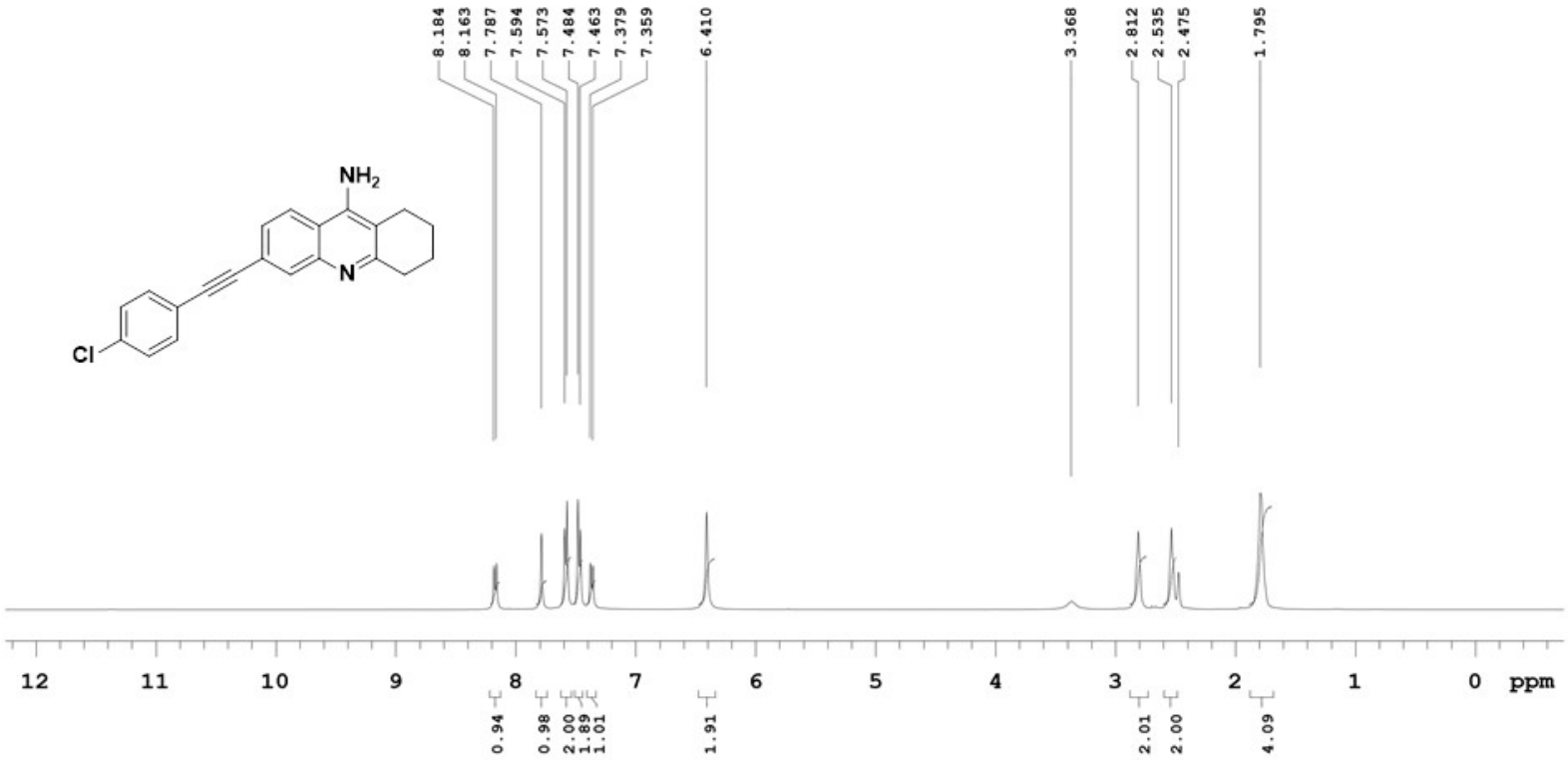


^{13}C NMR of Compound **9b**



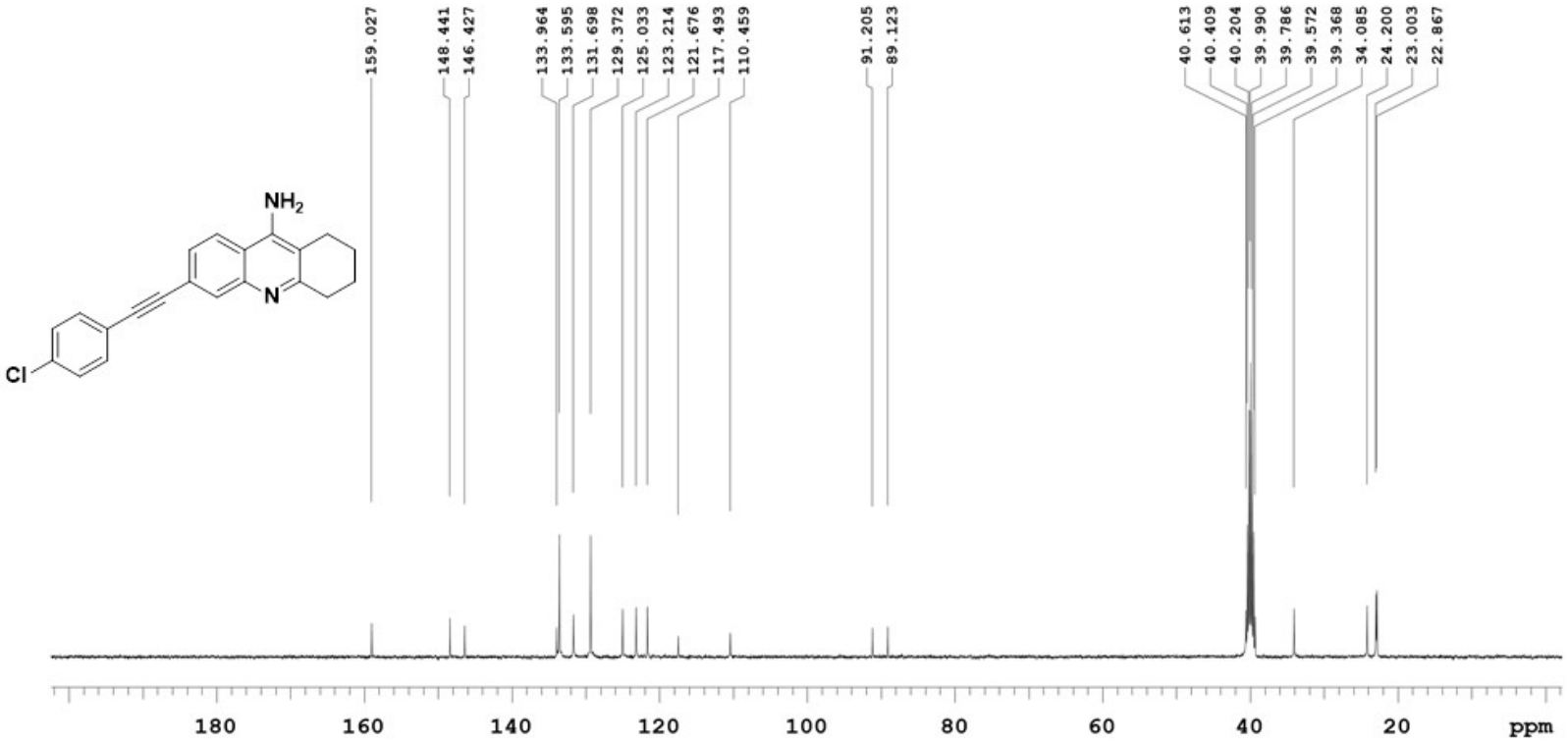
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.022 sec Width 32051.3 Hz 2048 repetitions	OBSERVE C13, 100.5356212 DECOUPLE H1, 399.8251894 Power 39 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 2.5 Hz FT size 65536 Total time 69 minutes		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-52-13C VNMRS-400 "Agilent-NMR"

[1]H NMR of Compound **9c**



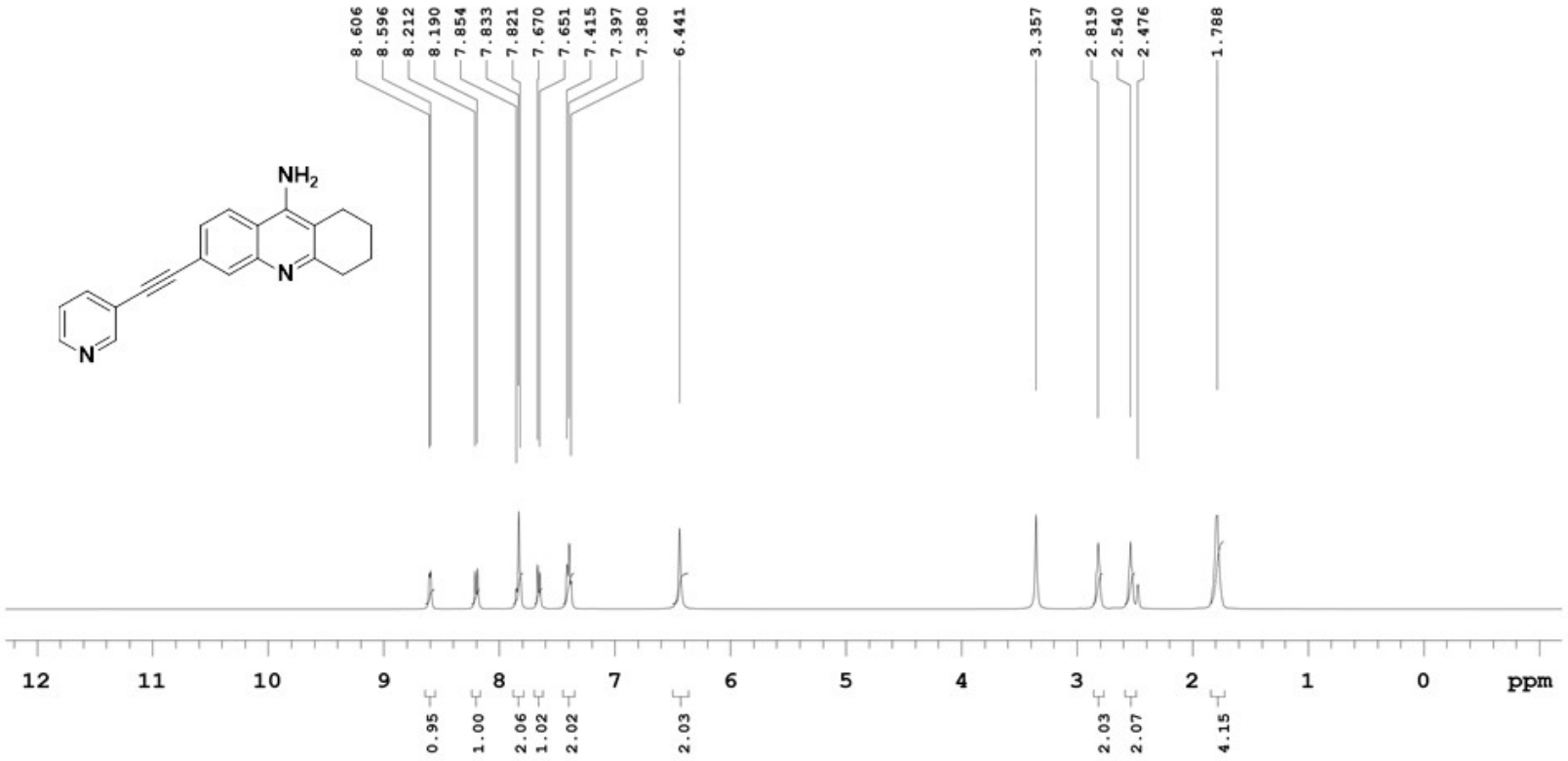
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 3.146 sec Width 10416.7 Hz 8 repetitions	OBSERVE H1, 399.8231903	DATA PROCESSING Line broadening 1.0 Hz FT size 65536 Total time 1 minute		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-53-1H VNMRS-400 "Agilent-NMR"

^{13}C NMR of Compound **9c**



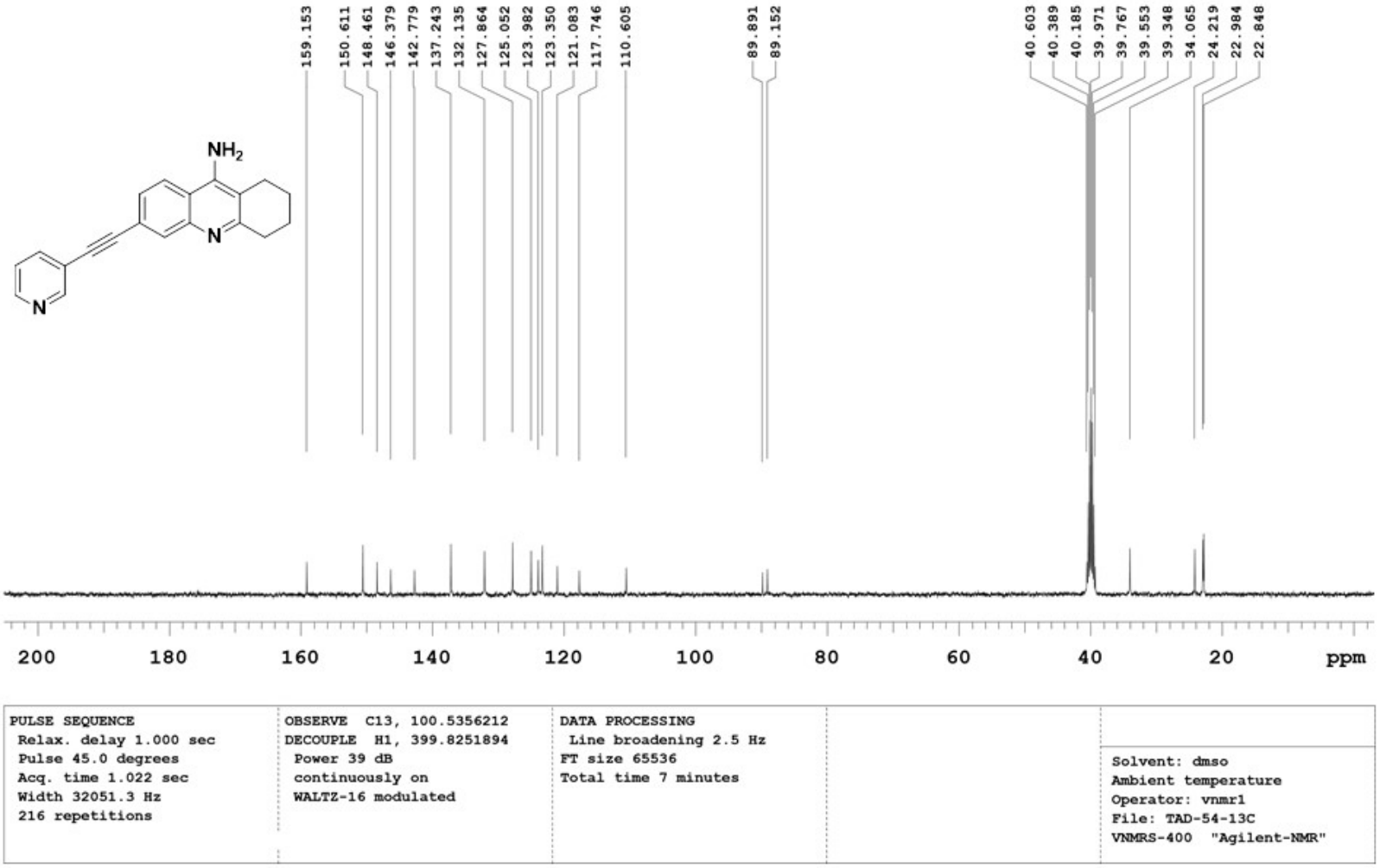
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.022 sec Width 32051.3 Hz 854 repetitions	OBSERVE C13, 100.5356212 DECOUPLE H1, 399.8251894 Power 39 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 2.5 Hz FT size 65536 Total time 28 minutes		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-53-13C VNMRS-400 "Agilent-NMR"

^{1}H NMR of Compound **9d**

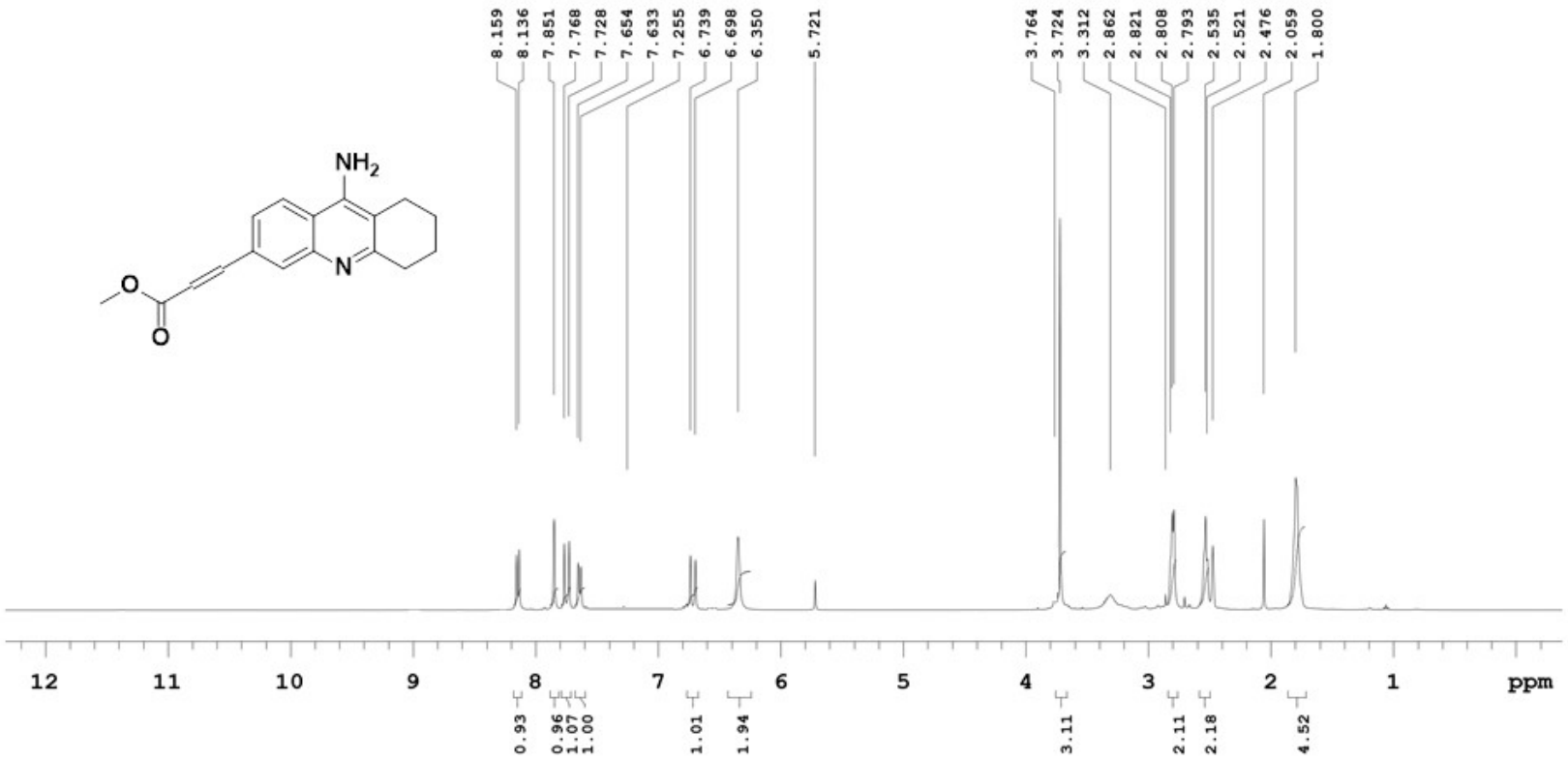


PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 3.146 sec Width 10416.7 Hz 8 repetitions	OBSERVE H1, 399.8231903	DATA PROCESSING Line broadening 1.0 Hz FT size 65536 Total time 1 minute		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-54-1H VNMRS-400 "Agilent-NMR"

^{13}C NMR of Compound **9d**

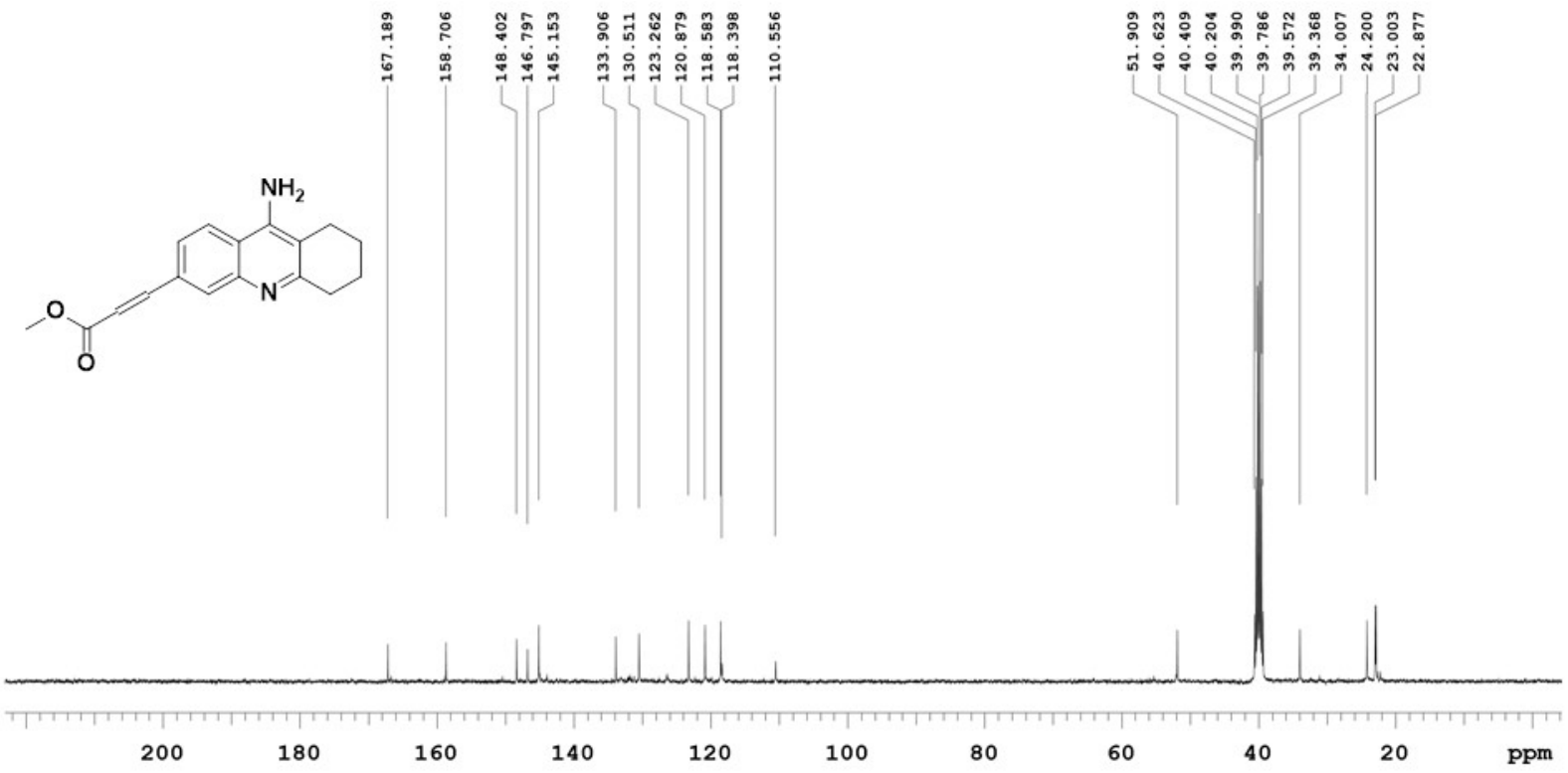


[1]H NMR of Compound **11a**



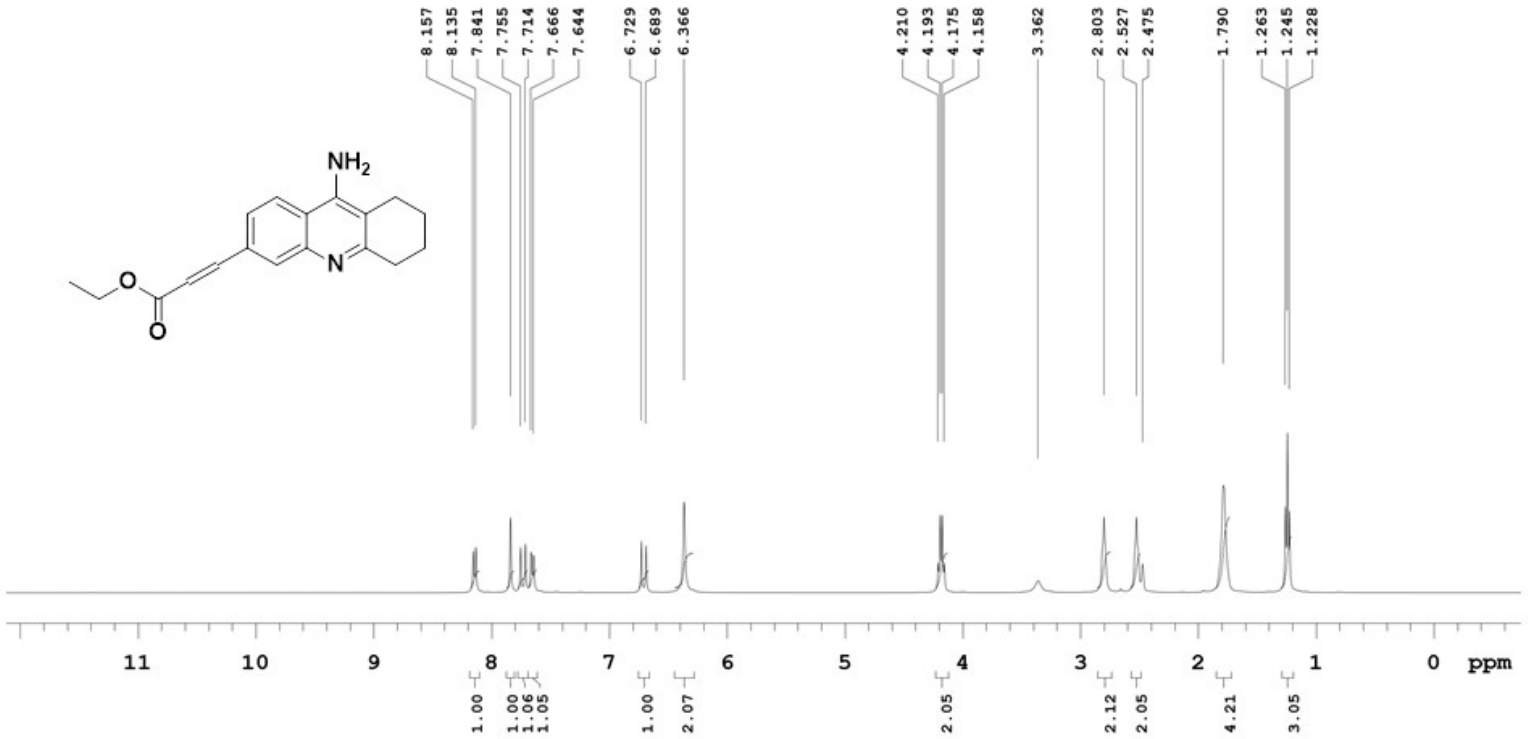
PULSE SEQUENCE Relax. delay 2.000 sec Pulse 45.0 degrees Acq. time 3.146 sec Width 10416.7 Hz 16 repetitions	OBSERVE H1, 399.8231903	DATA PROCESSING Line broadening 1.0 Hz FT size 65536 Total time 1 minute		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-55-1H VNMRS-400 "Agilent-NMR"

^{13}C NMR of Compound **11a**



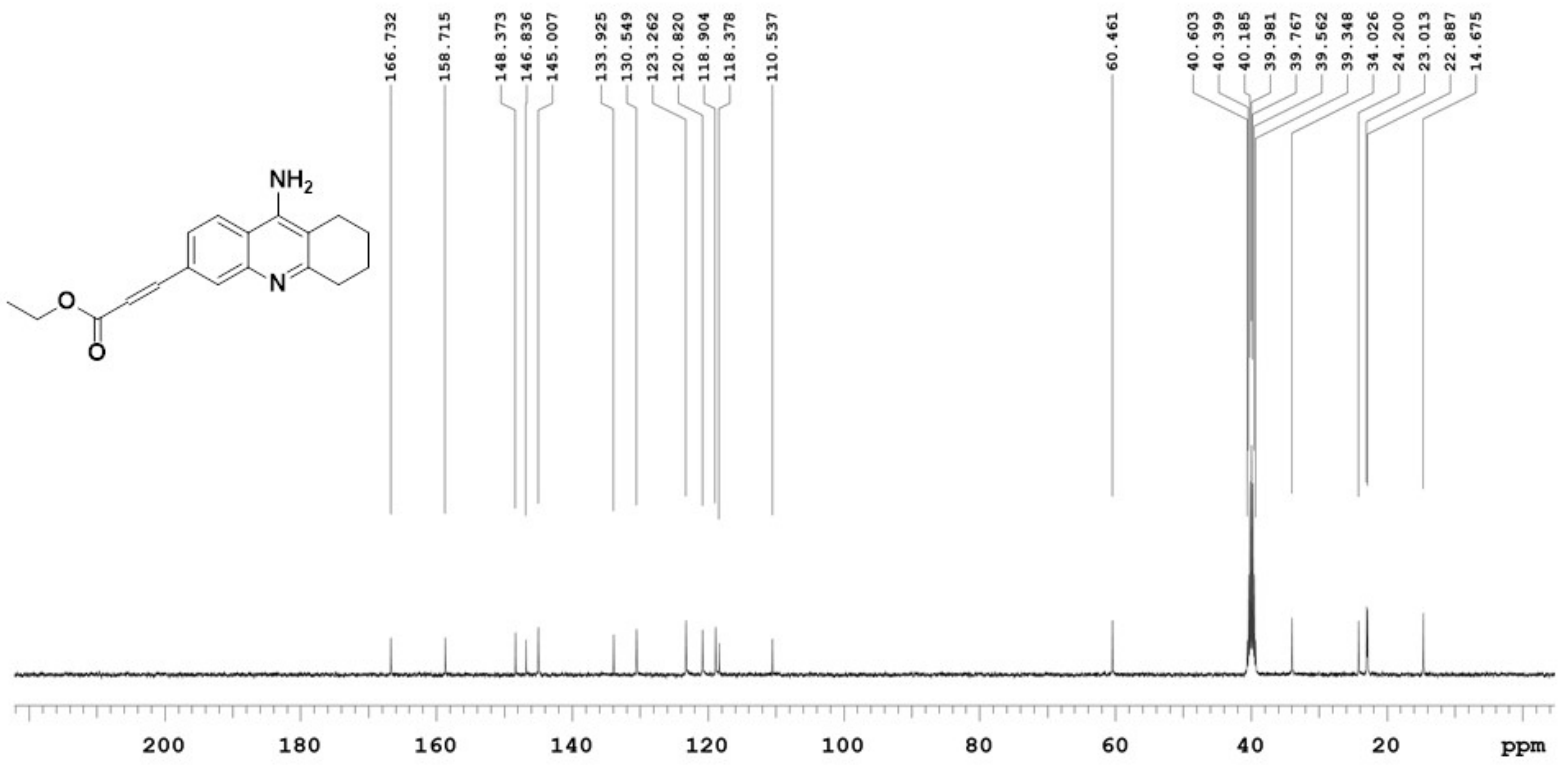
PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.022 sec Width 32051.3 Hz 1520 repetitions	OBSERVE C13, 100.5356212 DECOUPLE H1, 399.8251894 Power 39 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 2.5 Hz FT size 65536 Total time 51 minutes		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-55-13C

[1]H NMR of Compound **11b**



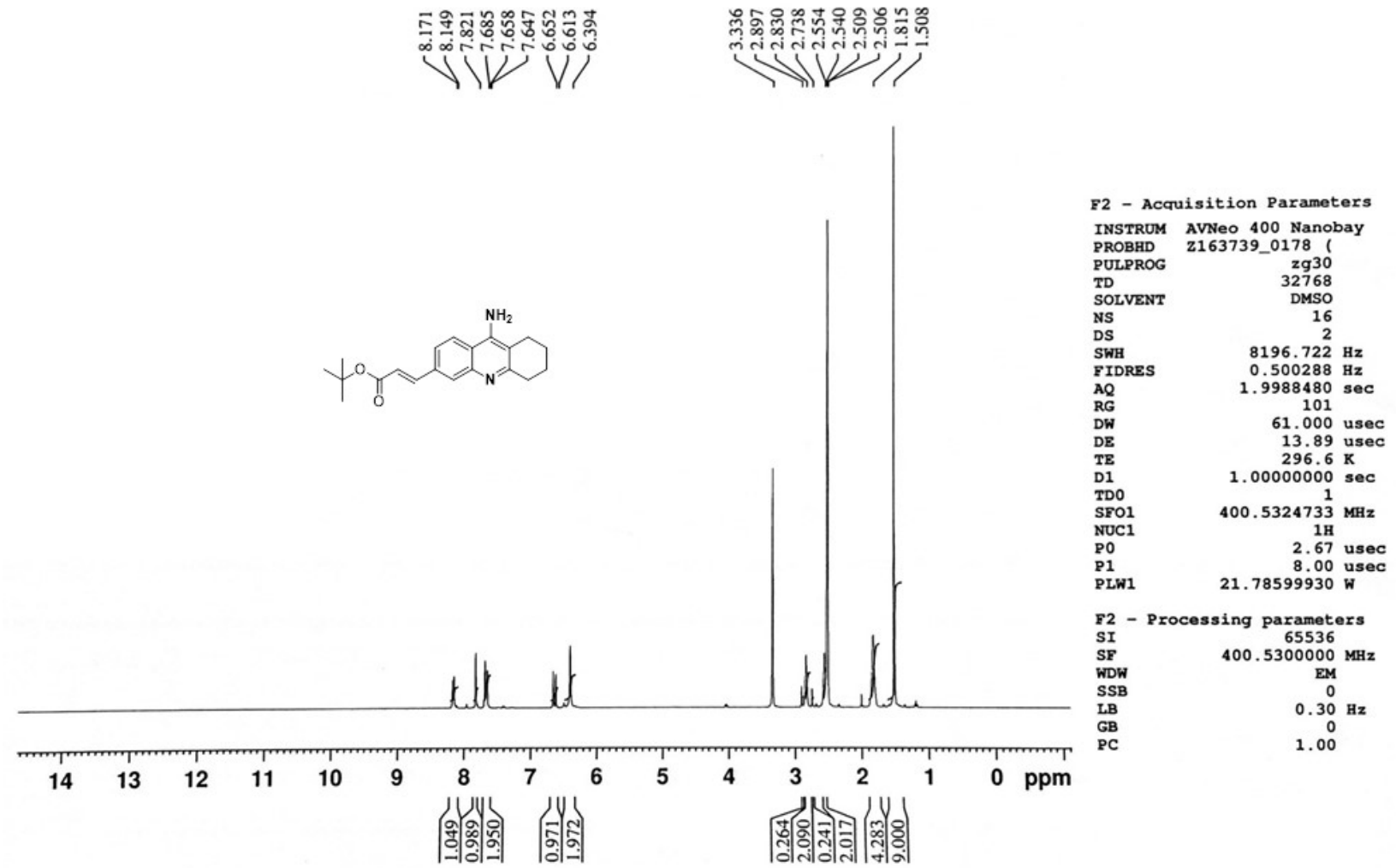
PULSE SEQUENCE	OBSERVE H1, 399.8231903	DATA PROCESSING		
Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 3.146 sec Width 10416.7 Hz 8 repetitions		Line broadening 1.0 Hz FT size 65536 Total time 1 minute		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-56-1H VNMRS-400 "Agilent-NMR"

^{13}C NMR of Compound **11b**



PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 1.022 sec Width 32051.3 Hz 320 repetitions	OBSERVE C13, 100.5356212 DECOUPLE H1, 399.8251894 Power 39 dB continuously on WALTZ-16 modulated	DATA PROCESSING Line broadening 2.5 Hz FT size 65536 Total time 10 minutes		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-56-13C VNMRS-400 "Agilent-NMR"

[1]H NMR of Compound **11c**



F2 - Acquisition Parameters

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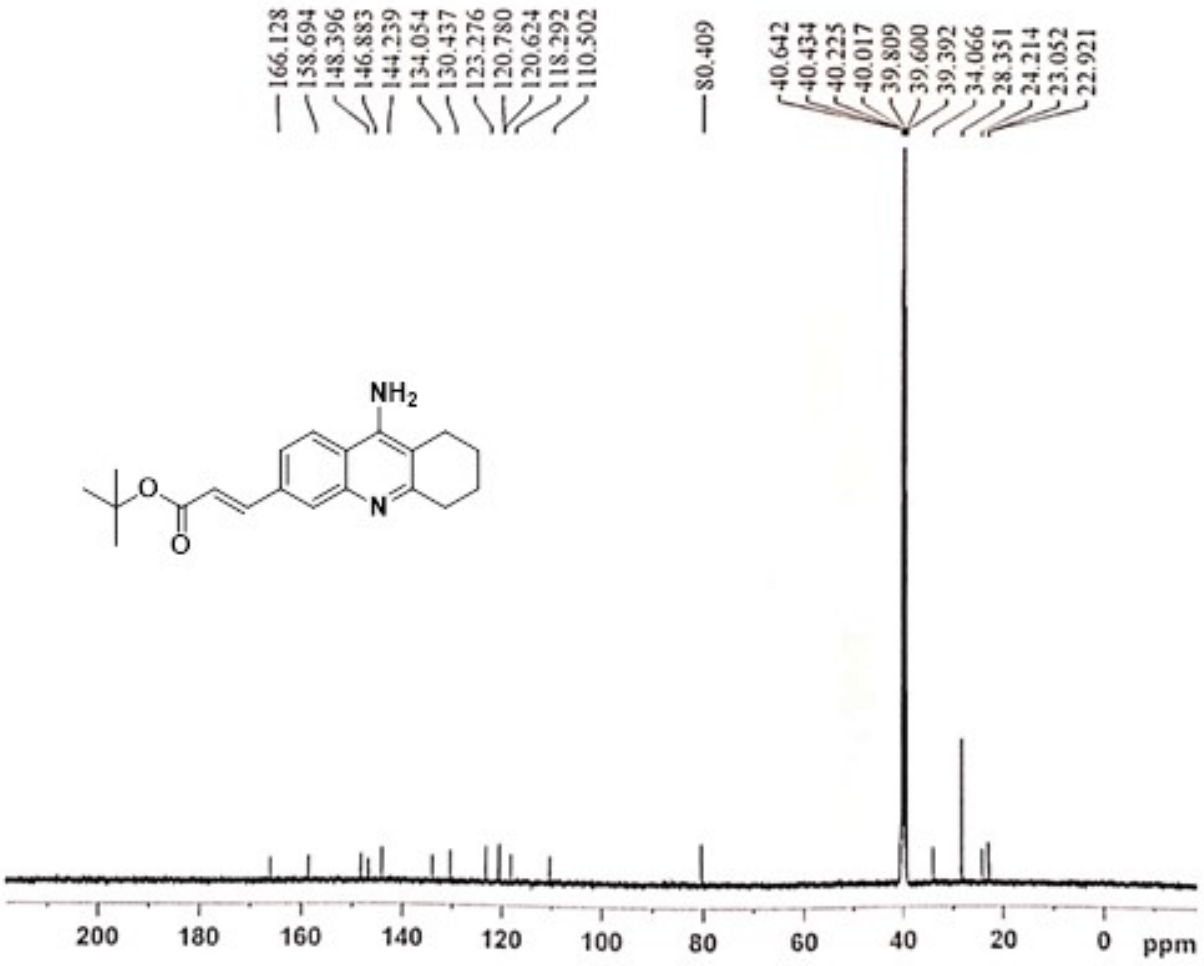
PROBHD	Z163739_0178 (
PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	16
DS	2
SWH	8196.722 Hz
FIDRES	0.500288 Hz
AQ	1.9988480 sec
RG	101
DW	61.000 usec
DE	13.89 usec
TE	296.6 K
D1	1.00000000 sec
TD0	1
SFO1	400.5324733 MHz
NUC1	1H
P0	2.67 usec
P1	8.00 usec
PLW1	21.78599930 W

F2 - Processing parameters

SI	65536
SF	400.5300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

^{13}C NMR of Compound **11c**

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TD                32768
SOLVENT            DMSO
NS                  1300
DS                     4
SWH          23809.523 Hz
FIDRES        1.453218 Hz
AQ            0.6881280 sec
RG                   101
DW              21.000 usec
DE               6.50 usec
TE              300.3 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1
SFO1       100.7234139 MHz
NUC1               13C
P0                2.67 usec
P1                8.00 usec
PLW1       91.51399994 W
SFO2       400.5316021 MHz
NUC2               1H
CPDPRG[2        waltz65
PCPD2             90.00 usec
PLW2       21.78599930 W
PLW12       0.17214000 W
PLW13       0.08644800 W

F2 - Processing parameters
SI                32768
SF         100.7133484 MHz
WDW                EM
SSB                0
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GB                 0
PC              1.40
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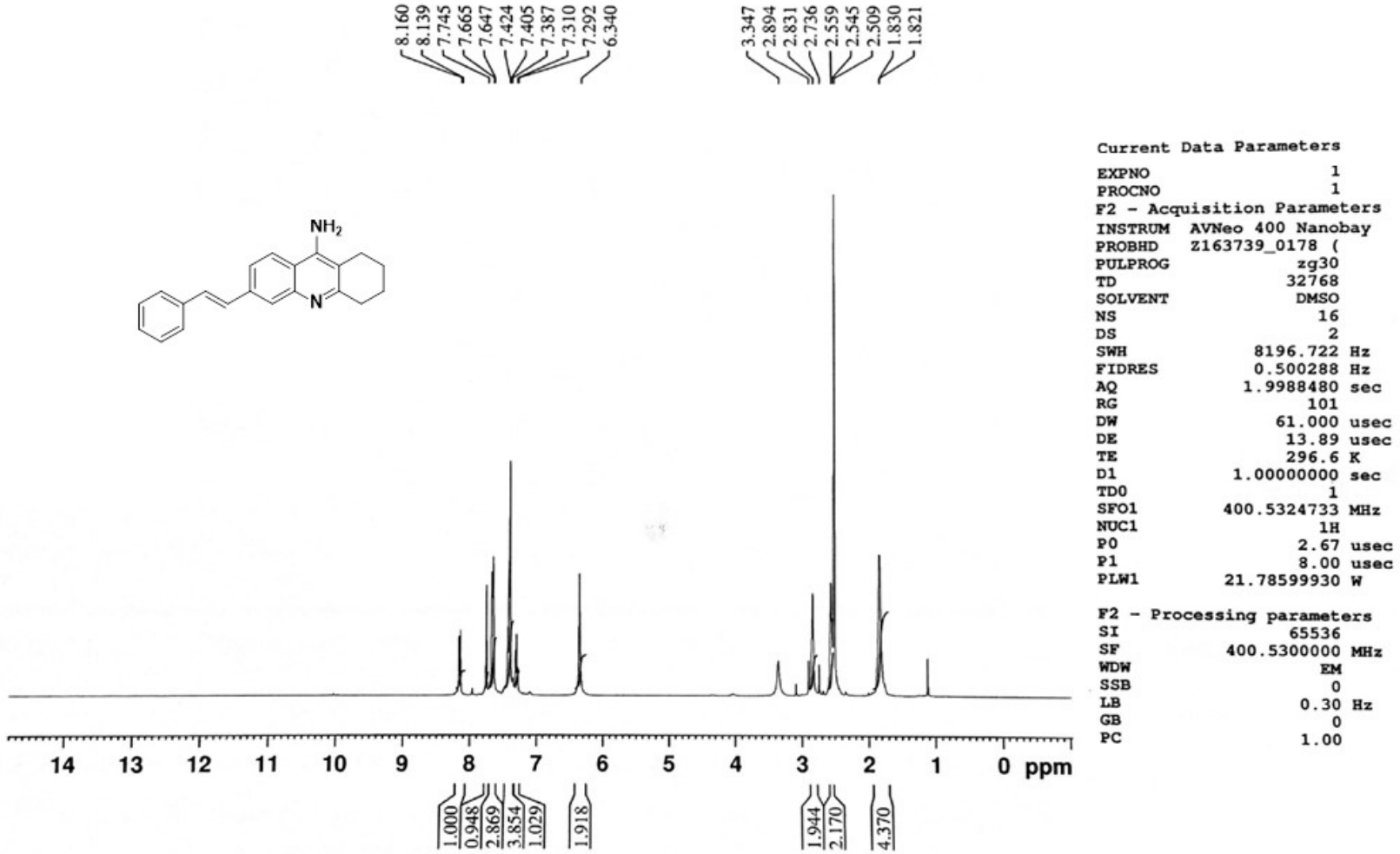
[1]H NMR of Compound **11d**

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PROCNO                 1
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PULPROG              zg30
TD                  32768
SOLVENT              DMSO
NS                     16
DS                      2
SWH              8196.722 Hz
FIDRES           0.500288 Hz
AQ               1.9988480 sec
RG                    101
DW                 61.000 usec
DE                 13.89 usec
TE                 296.6 K
D1              1.00000000 sec
TD0                     1
SFO1           400.5324733 MHz
NUC1                   1H
P0                  2.67 usec
P1                  8.00 usec
PLW1           21.78599930 W

F2 - Processing parameters
SI                  65536
SF             400.5300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
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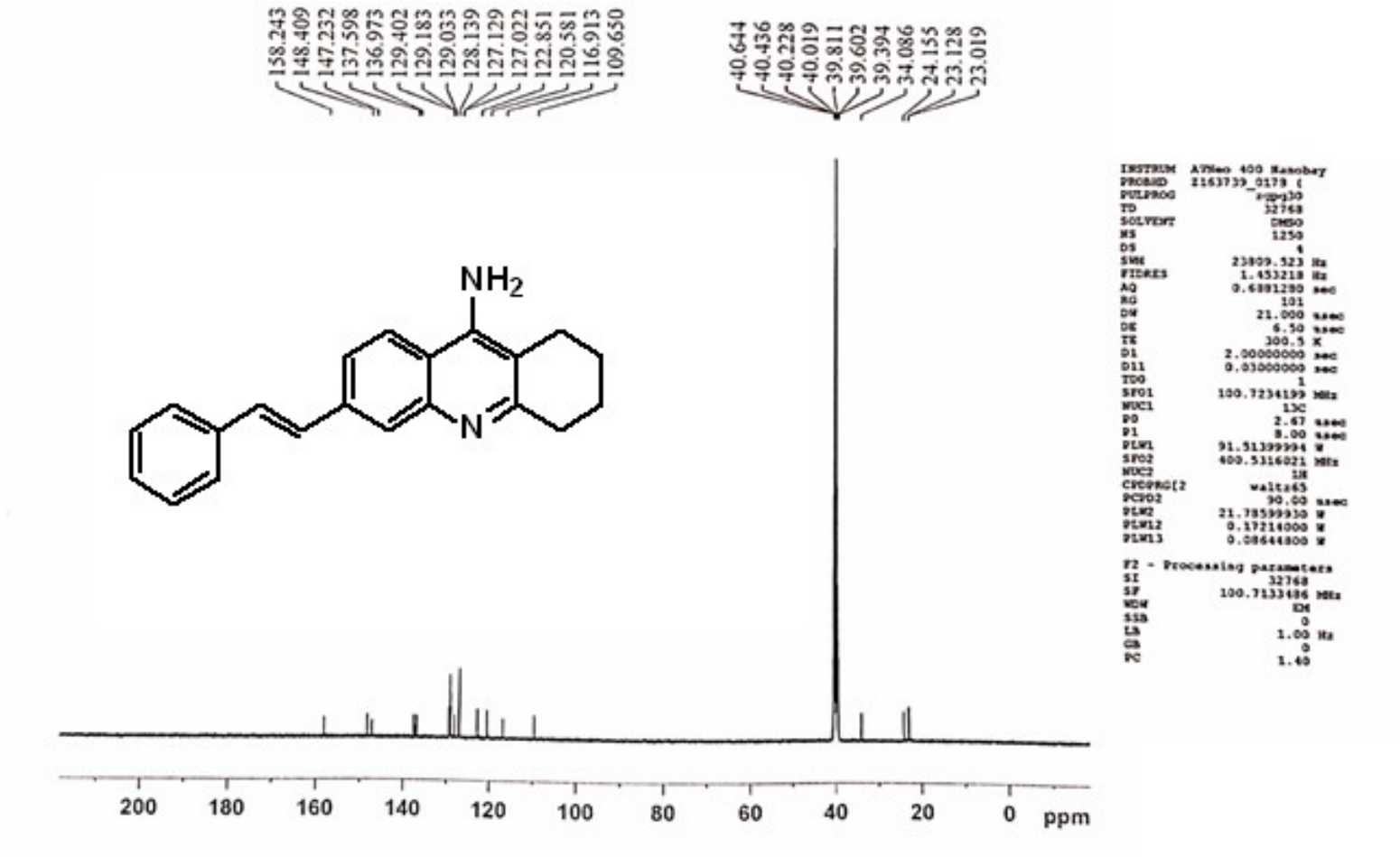
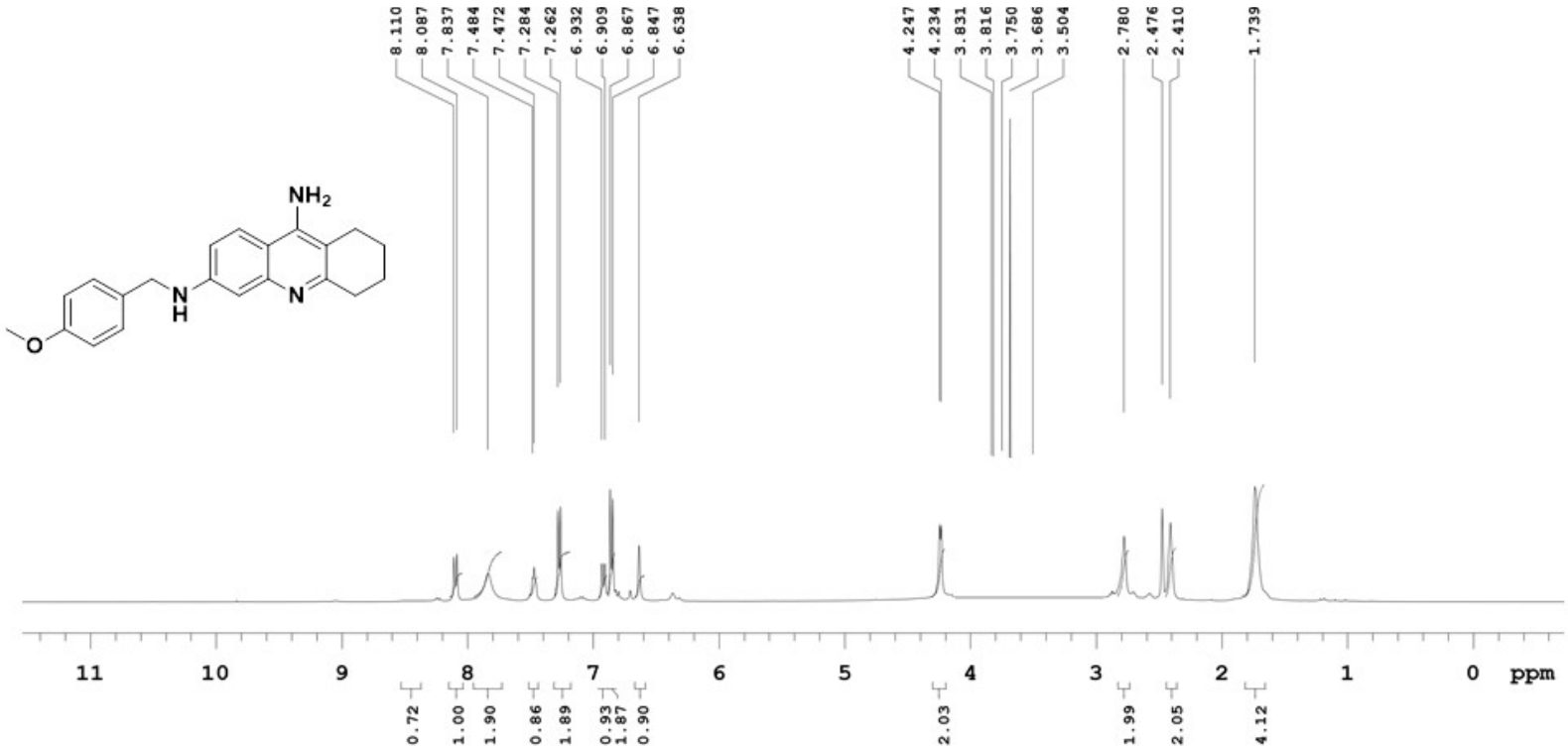
^{13}C NMR of Compound **11d**

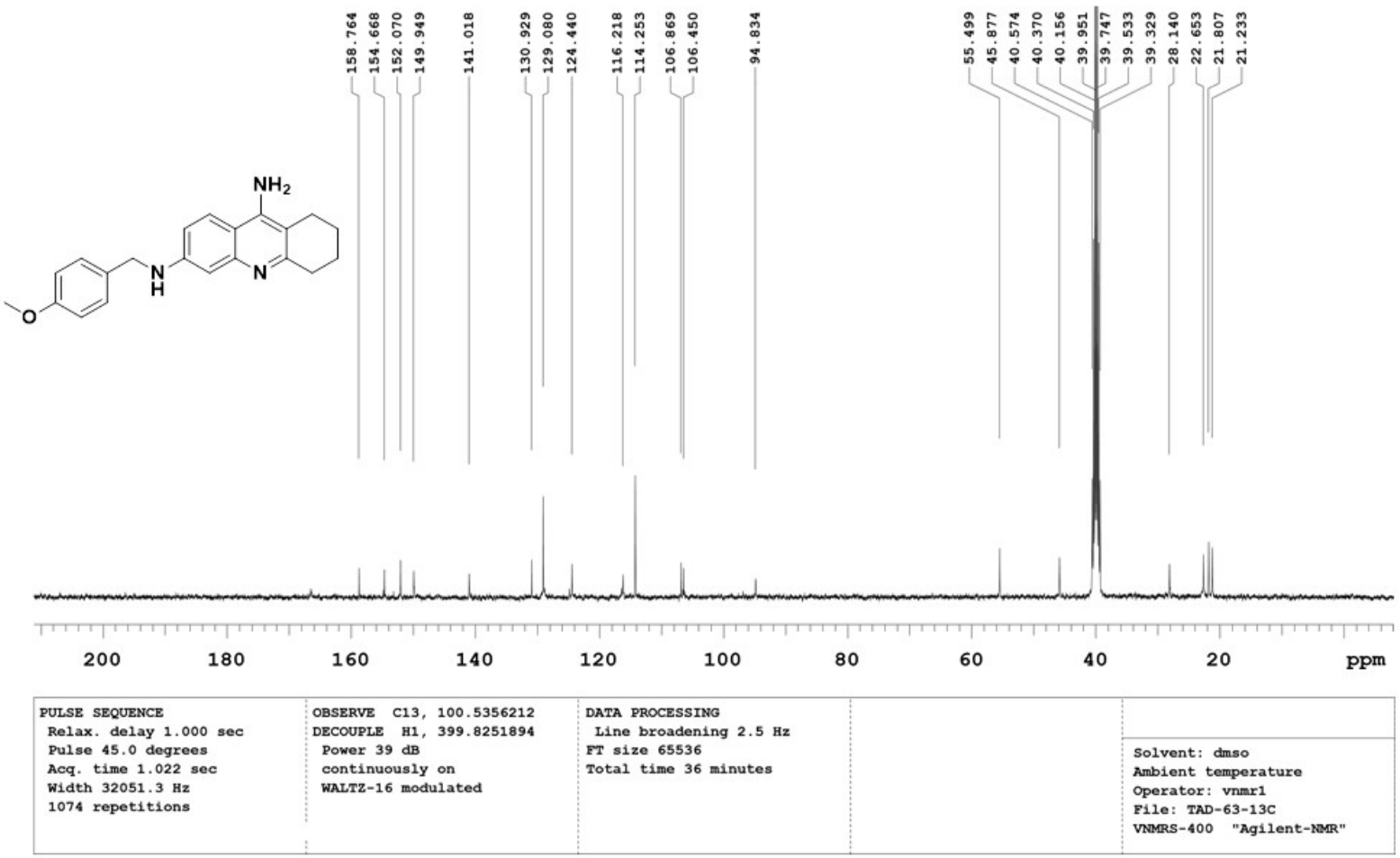


[1]H NMR of Compound **13a**

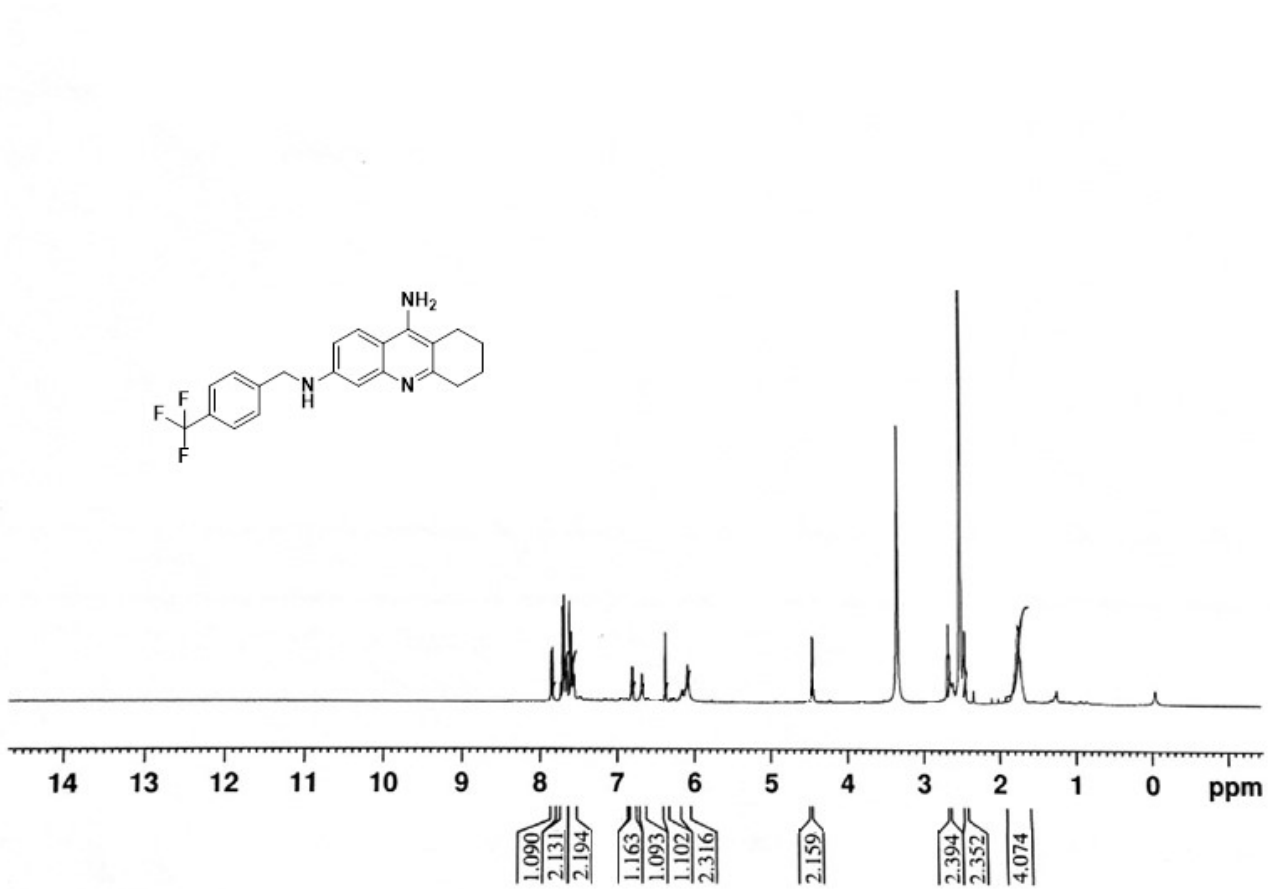


PULSE SEQUENCE Relax. delay 1.000 sec Pulse 45.0 degrees Acq. time 3.146 sec Width 10416.7 Hz 8 repetitions	OBSERVE H1, 399.8231903	DATA PROCESSING Line broadening 1.0 Hz FT size 65536 Total time 1 minute		Solvent: dmso Ambient temperature Operator: vnmr1 File: TAD-63-1H VNMRS-400 "Agilent-NMR"

^{13}C NMR of Compound **13a**



[1]H NMR of Compound **13b**

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PROCNO                 1
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PULPROG              zg30
TD                  32768
SOLVENT              DMSO
NS                     16
DS                      2
SWH             8196.722 Hz
FIDRES             0.500288 Hz
AQ              1.9988480 sec
RG                    101
DW                 61.000 usec
DE                 13.89 usec
TE                 295.8 K
D1              1.00000000 sec
TD0                     1
SFO1           400.5324733 MHz
NUC1                   1H
P0                  2.67 usec
P1                  8.00 usec
PLW1           21.78599930 W

F2 - Processing parameters
SI                  65536
SF             400.5300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
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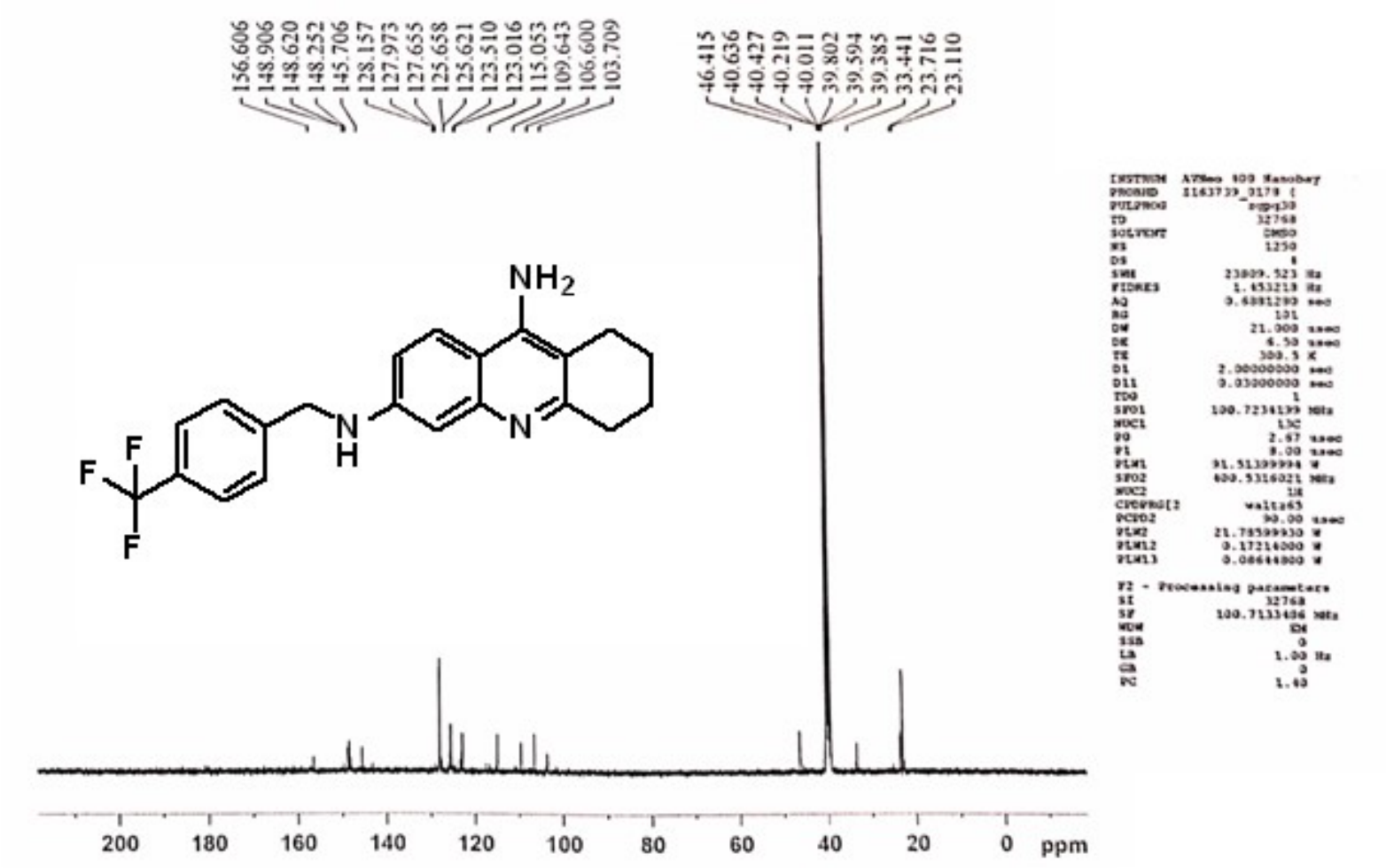
^{13}C NMR of Compound **13b**



INSTRUM	AVNeo 400 Nanobay
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TD	32768
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FIDRES	1.453219 Hz
AQ	0.6881280 sec
RG	101
DW	21.000 usec
DE	6.50 usec
TE	300.5 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
SFO1	100.7234139 MHz
NUC1	13C
P0	2.67 usec
P1	8.00 usec
PLW1	91.51399994 W
SFO2	400.5316021 MHz
NUC2	1H
CPDPRG[2	waltz65
PCPD2	90.00 usec
PLW2	21.78599930 W
PLW12	0.17216000 W
PLW13	0.08644800 W

F2 - Processing parameters

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SF	100.7133406 MHz
WDW	EM
SSB	0
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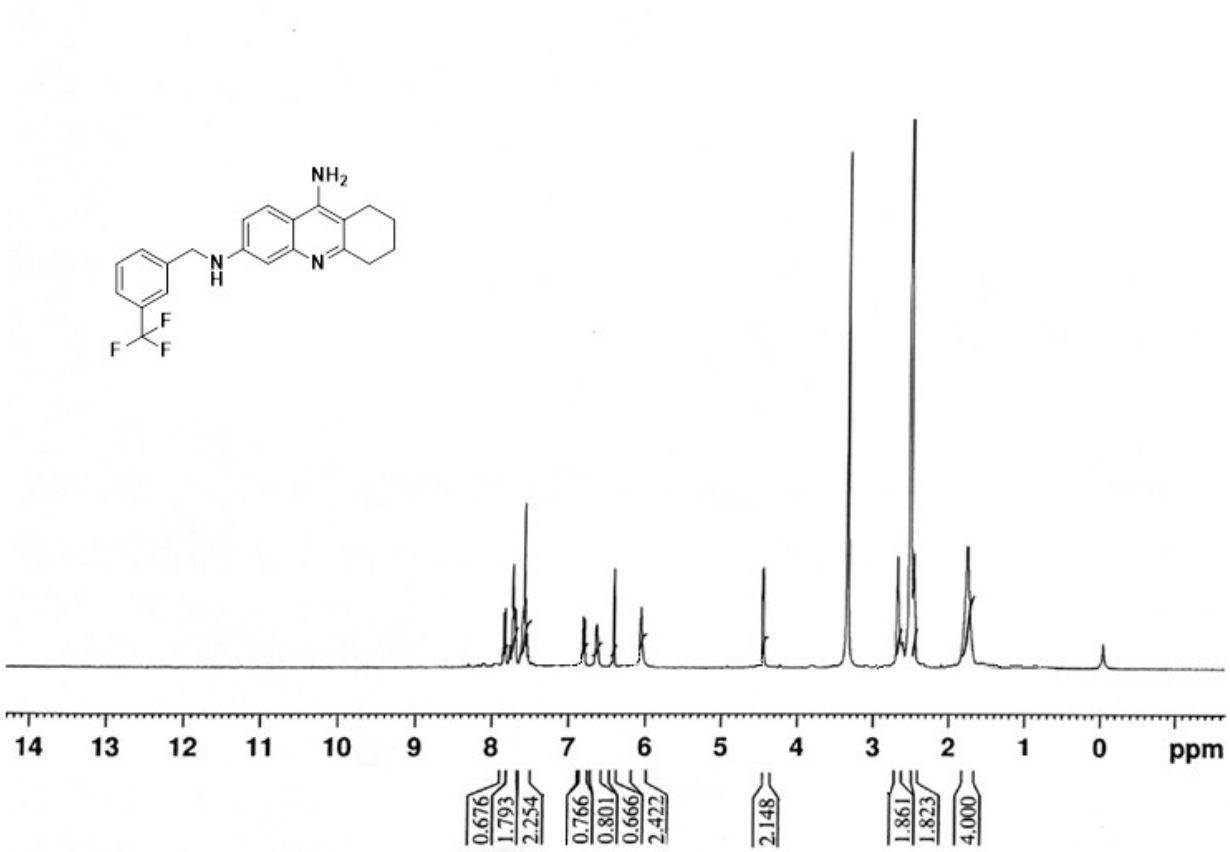
PC	1.40

[1]H NMR of Compound **13c**

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Current Data Parameters
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PROCNO                 1
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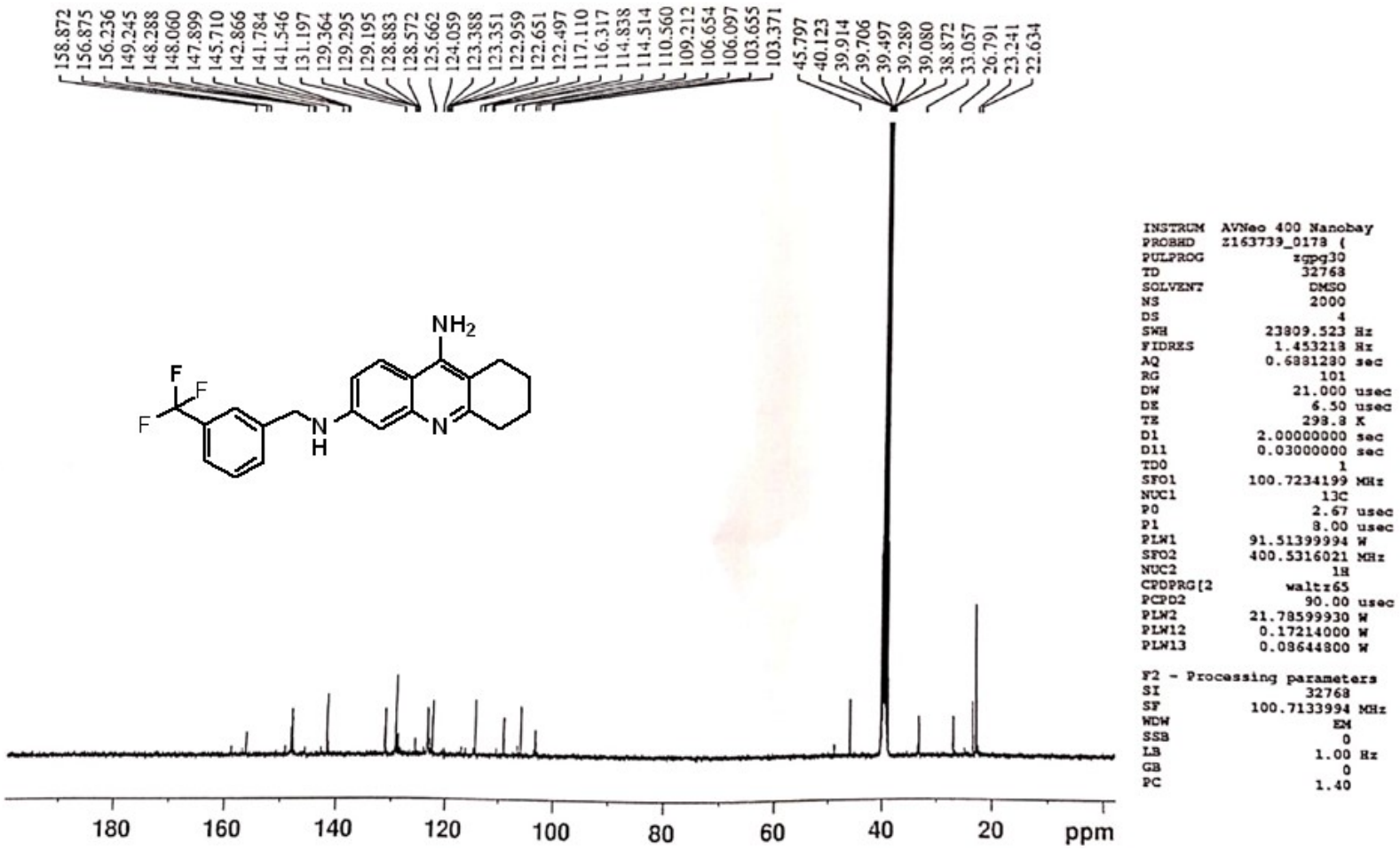
TD                  32768
SOLVENT              DMSO
NS                     16
DS                      2
SWH              8196.722 Hz
FIDRES           0.500288 Hz
AQ               1.9988480 sec
RG                    101
DW                 61.000 usec
DE                 13.89 usec
TE                 296.5 K
D1              2.00000000 sec
TD0                     1
SFO1           400.5324733 MHz
NUC1                   1H
P0                 2.67 usec
P1                 8.00 usec
PLW1           21.78599930 W

F2 - Processing parameters
SI                  65536
SF             400.5300000 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                 1.00
```

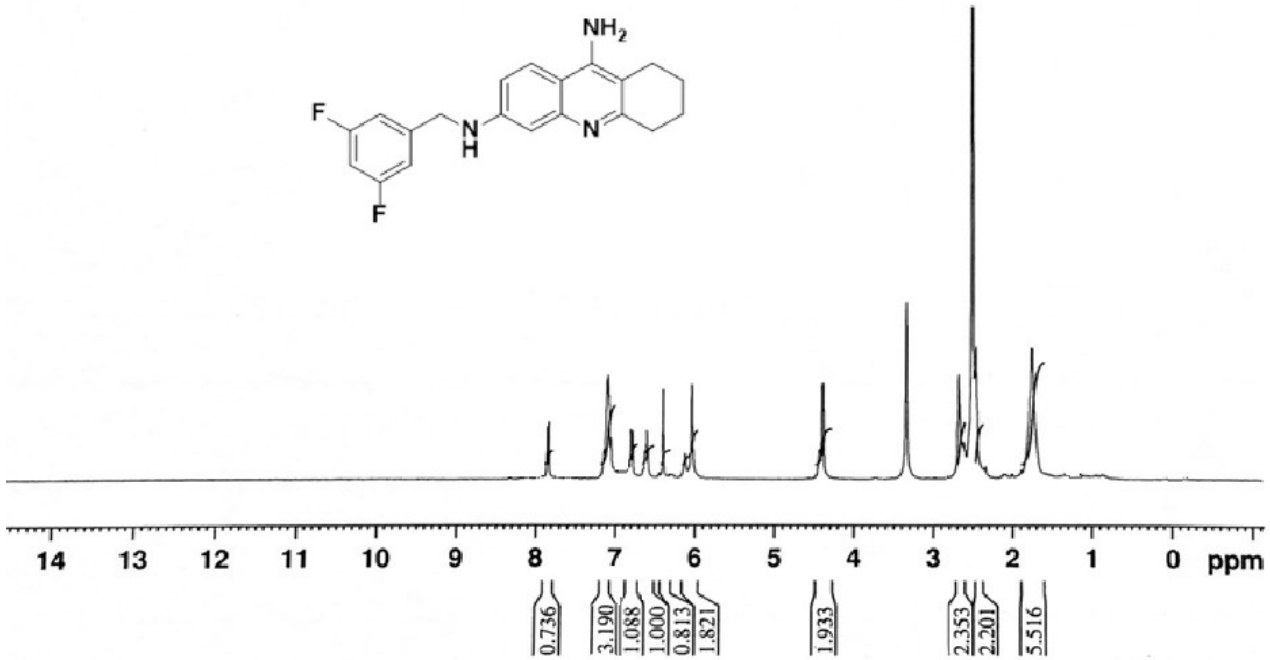
^{13}C NMR of Compound **13c**



INSTRUM	AVNeo 400 Nanobay
PROBHD	Z163739_0178 (
PULPROG	zgpg30
TD	32768
SOLVENT	DMSO
NS	2000
DS	4
SWH	23809.523 Hz
FIDRES	1.453218 Hz
AQ	0.6881280 sec
RG	101
DW	21.000 usec
DE	6.50 usec
TE	298.8 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
SFO1	100.7234199 MHz
NUC1	13C
P0	2.67 usec
P1	8.00 usec
PLW1	91.51399994 W
SFO2	400.5316021 MHz
NUC2	1H
CPDPRG[2	waltz65
PCPD2	90.00 usec
PLW2	21.78599930 W
PLW12	0.17214000 W
PLW13	0.08644800 W

F2 - Processing parameters	
SI	32768
SF	100.7133994 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

[1]H NMR of Compound **13d**

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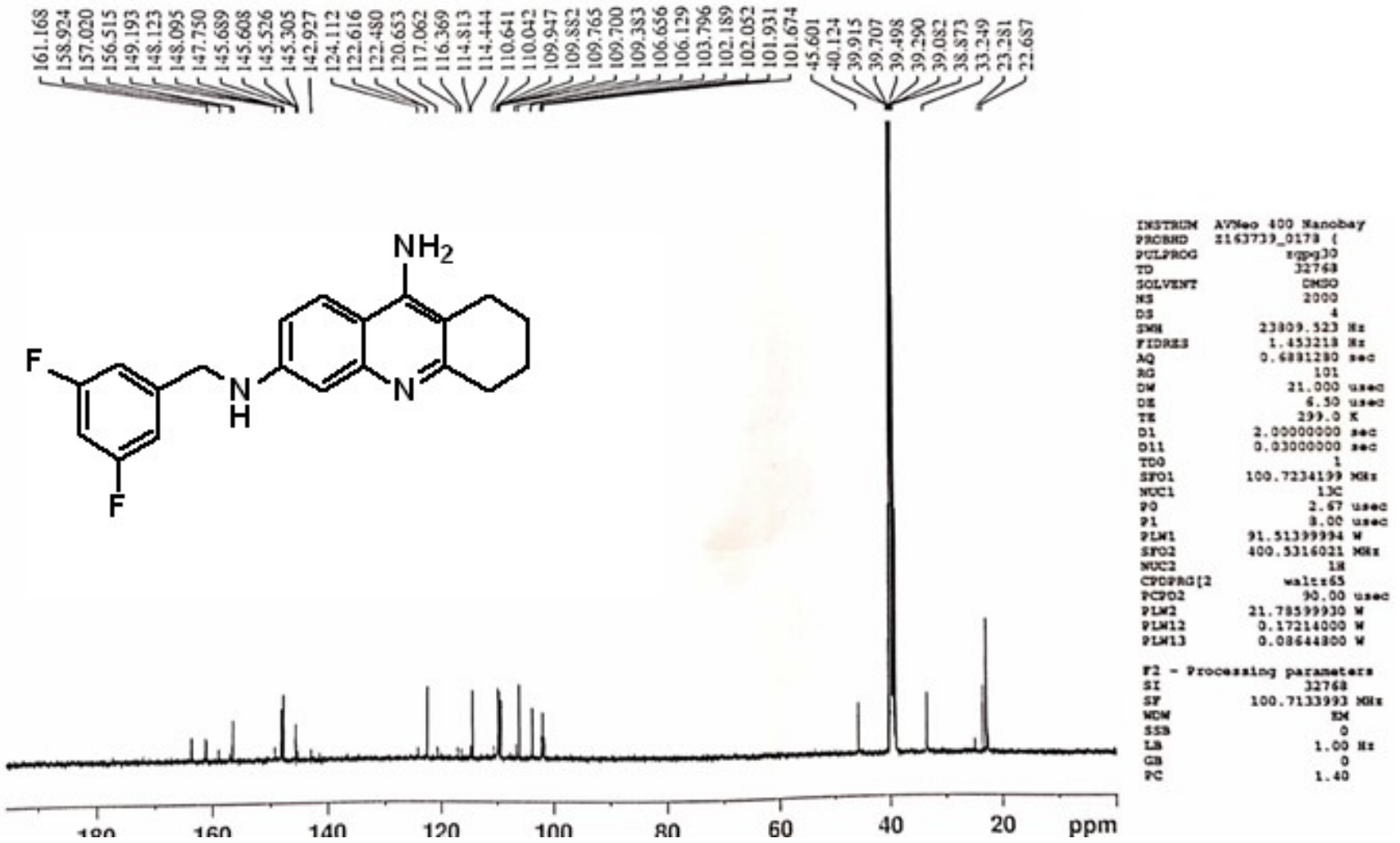
F2 - Acquisition Parameters
INSTRUM   AVNeo 400 Nanobay
PROBHD    Z163739_0178 (
PULPROG             zg30
TD                 32768
SOLVENT             DMSO
NS                    16
DS                     2
SWH             8196.722 Hz
FIDRES          0.500288 Hz
AQ             1.9988480 sec
RG                   101
DW                61.000 usec
DE                13.89 usec
TE                296.7 K
D1             2.00000000 sec
TD0                    1
SFO1          400.5324733 MHz
NUC1                  1H
P0                 2.67 usec
P1                 8.00 usec
PLW1          21.78599930 W

F2 - Processing parameters
SI                 65536
SF            400.5300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

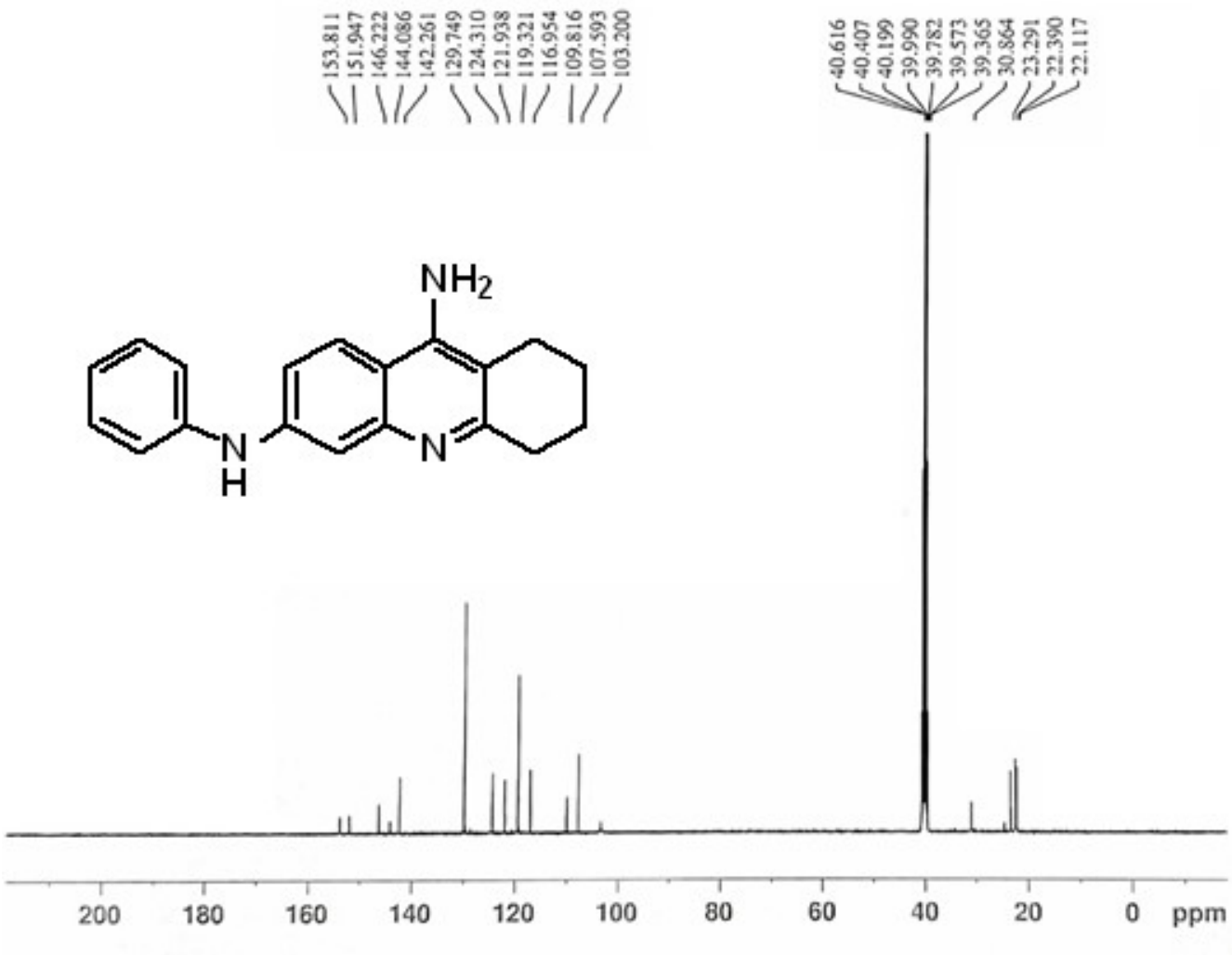
^{13}C NMR of Compound **13d**



[1]H NMR of Compound **13e**

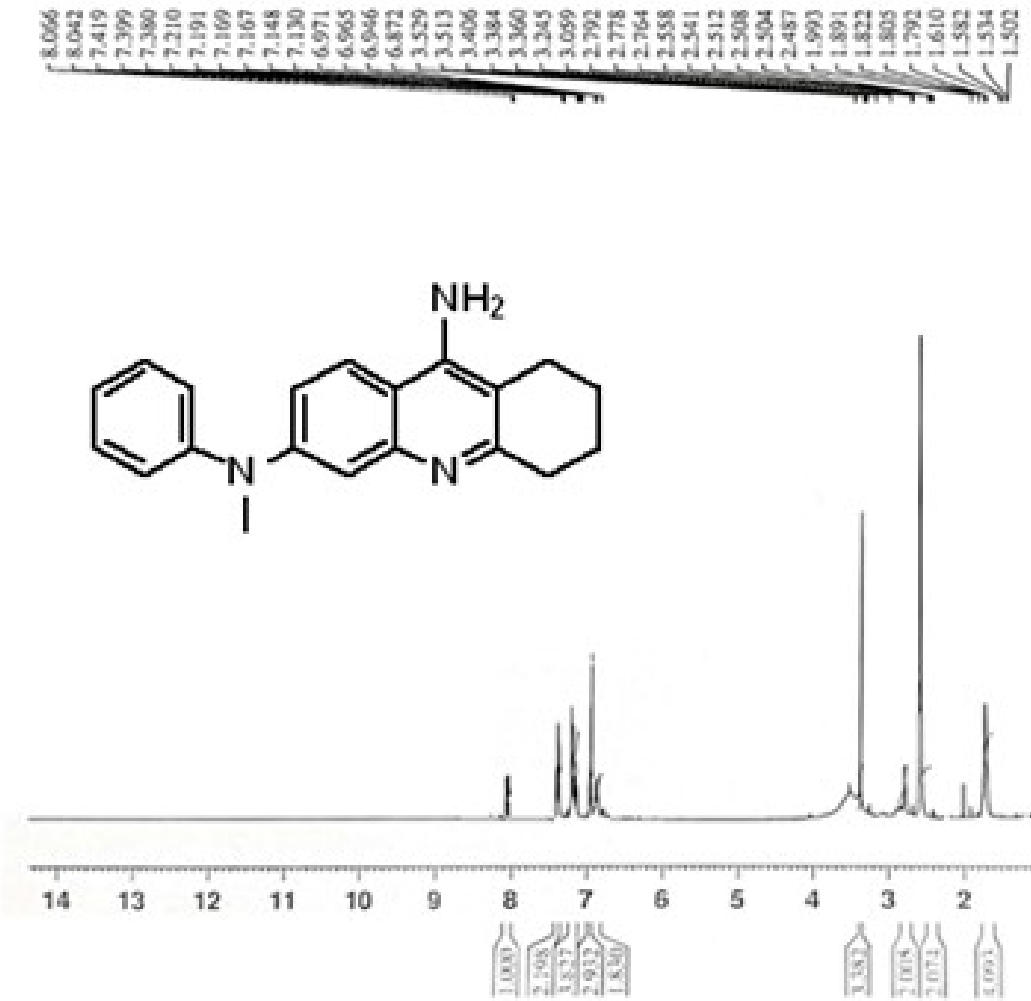
INSTRUM	AVNeo 400 Nanobay	
PROBHD	Z163739_0178 (	
PULPROG	zg30	
TD	32768	
SOLVENT	DMSO	
NS	16	
DS	2	
SWH	8196.722	Hz
FIDRES	0.500288	Hz
AQ	1.9988480	sec
RG	101	
DW	61.000	usec
DE	13.89	usec
TE	298.0	K
D1	2.00000000	sec
TD0	1	
SFO1	400.5324733	MHz
NUC1	1H	
P0	2.67	usec
P1	8.00	usec
PLW1	21.64200020	W
F2 - Processing parameters		
SI	65536	
SF	400.5300000	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	

^{13}C NMR of Compound **13e**



INSTRUM	AVNeo 400 Nanobay	
PROBHD	Z163739_0178 (	
PULPROG	zgpg30	
TD	32768	
SOLVENT	DMSO	
NS	2000	
DS	4	
SWH	23809.523	Hz
FIDRES	1.453218	Hz
AQ	0.6881280	sec
RG	101	
DW	21.000	usec
DE	6.50	usec
TE	298.0	K
D1	2.00000000	sec
D11	0.03000000	sec
TD0	1	
SFO1	100.7234199	MHz
NUC1	13C	
P0	2.67	usec
P1	8.00	usec
PLW1	90.91000366	W
SFO2	400.5316021	MHz
NUC2	1H	
CPDPRG[2	waltz65	
PCPD2	90.00	usec
PLW2	21.64200020	W
PLW12	0.17100000	W
PLW13	0.08587700	W
F2 - Processing parameters		
SI	32768	
SF	100.7133486	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

[1]H NMR of Compound **13f**

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Current Data Parameters
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EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
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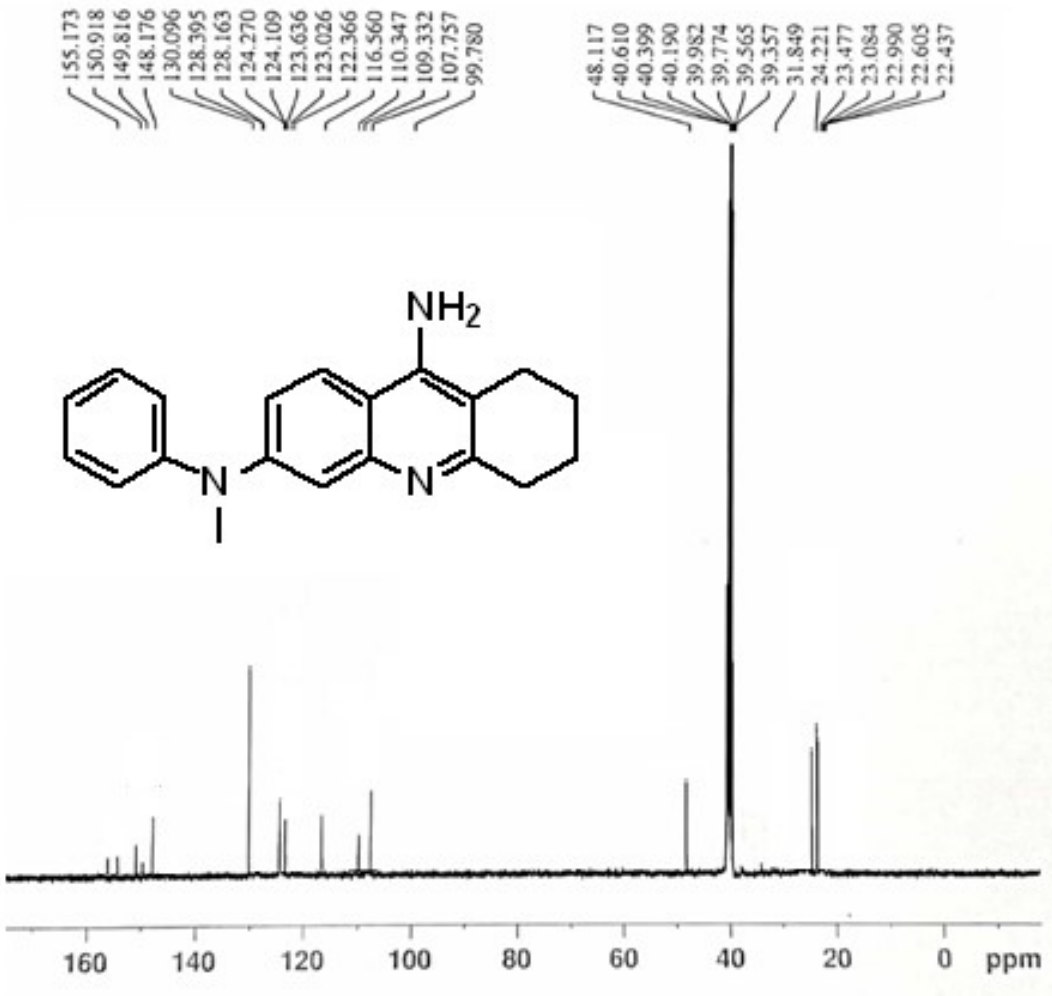
Time                 20.05 h
INSTRUM  AVNeo 400 Nanobay
PROBHD   2163739_0178 (
PULPROG                 zg30
TD                     32768
SOLVENT                 DMSO
NS                        16
DS                         2
SWH                8196.722 Hz
FIDRES             0.500288 Hz
AQ                 1.9988480 sec
RG                    91.8478
DW                   61.000 usec
DE                   13.89 usec
TE                   298.0 K
D1                2.00000000 sec
TD0                        1
SFO1            400.5324733 MHz
NUC1                      1H
P0                    2.67 usec
P1                    8.00 usec
PLW1           21.64200020 W

F2 - Processing parameters
SI                     65536
SF              400.5300000 MHz
WDW                       EM
SSB                        0
LB                    0.30 Hz
GB                         0
PC                      1.00
```

^{13}C NMR of Compound **13f**




```
INSTRUM  AVNeo 400 Nanobay
PROBHD   Z163739_0178 (
PULPROG          zgpg30
TD                32768
SOLVENT            DMSO
NS                  1024
DS                     4
SWH            23809.523 Hz
FIDRES          1.453218 Hz
AQ              0.6881280 sec
RG                   101
DW                21.000 usec
DE                 6.50 usec
TE                298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1
SFO1         100.7234199 MHz
NUC1                13C
P0                 2.67 usec
P1                 8.00 usec
PLW1          90.91000366 W
SFO2         400.5316021 MHz
NUC2                 1H
CPDPRG[2          waltz65
PCPD2             90.00 usec
PLW2          21.64200020 W
PLW12          0.17100000 W
PLW13          0.08587700 W

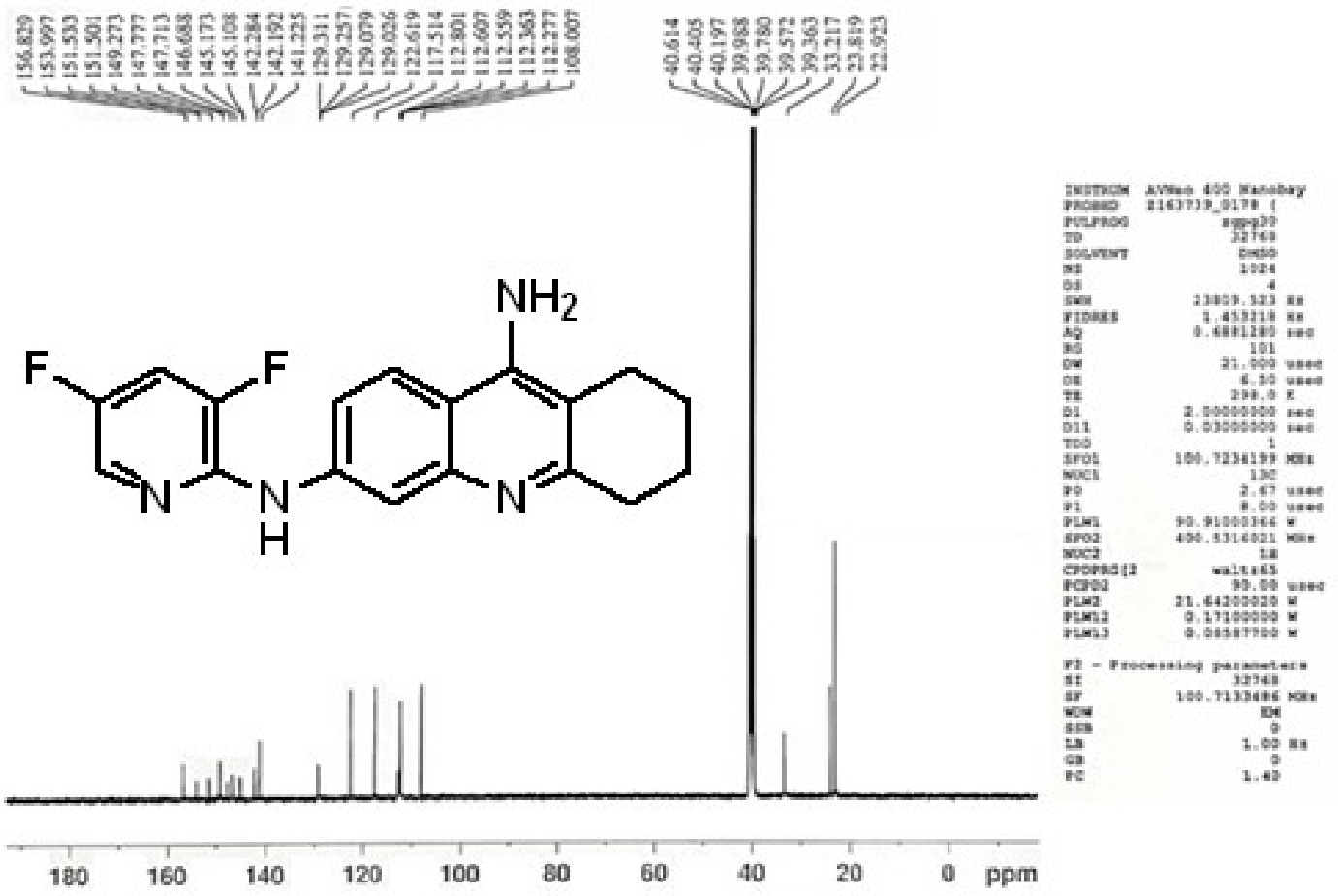
F2 - Processing parameters
SI                  32768
SF           100.7133486 MHz
WDW                    EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

^{1}H NMR of Compound **13g**


```
INSTRUM  AVNeo 400 Nanobay
PROBHD   I163739_0178 (
PULPROG          zg30
TD              32768
SOLVENT          DMSO
NS                 16
DS                  2
SWH          8196.722 Hz
FIDRES       0.500288 Hz
AQ           1.9968480 sec
RG                101
DW             61.000 usec
DE             13.89 usec
TE             298.0 K
D1          2.00000000 sec
TD0                 1
SFO1       400.5324733 MHz
NUC1               1H
P0              2.67 usec
P1              8.00 usec
PLW1       21.64200020 W

F2 - Processing parameters
SI              65536
SF         400.5300000 MHz
WDW                EM
SSB                 0
LB              0.30 Hz
GB                  0
PC              1.00
```

^{13}C NMR of Compound **13g**



INSTRUM	AVNeo 400 Nanobay
PROBHD	2163719_0178 (
PULPROG	zgpg30
TD	32768
SOLVENT	DMSO
NS	1024
DS	4
SWH	23809.523 Hz
FIDRES	1.453218 Hz
AQ	0.6881280 sec
RG	101
DW	21.000 usec
DE	6.50 usec
TE	298.0 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
SFO1	100.7234199 MHz
NUC1	13C
P0	2.67 usec
P1	8.00 usec
PLW1	90.91000366 W
SFO2	400.5316021 MHz
NUC2	1H
CPDPRG[2	waltz65
PCPD2	90.00 usec
PLW2	21.64200020 W
PLW12	0.17100000 W
PLW13	0.08387700 W

F2 - Processing parameters

SI	32768
SF	100.7133486 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40