Supplementary Material

Pd-catalyzed one-pot approach for installation of 9-aminoacridines via Buchwald-Hartwig amination and cycloaromatization

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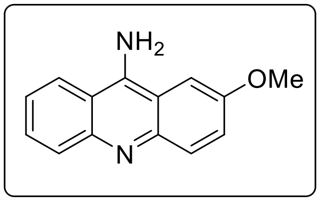
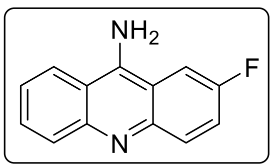
2-Methoxy-9-acridinamine (4a)[1]



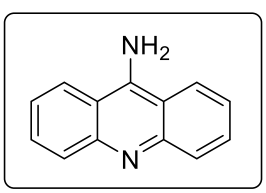
Yield: 89%, yellow solid, m.p.: 232-233 °C (Lit.: 231-233 °C)[1]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 9.6 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.68-7.64 (m, 1H), 7.43-7.39 (m, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.42 (brs, 2H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.4, 165.2, 164.7, 162.8, 143.3, 137.7, 130.6, 130.1, 129.2, 126.0, 119.8, 117.2, 113.0, 56.3; HRMS (ESI, m/z): calcd for $C_{14}H_{12}N_2O$ $[M + H]^+$ 225.1022, found 225.1025.

2-Fluoro-9-acridinamine (4g)[1]



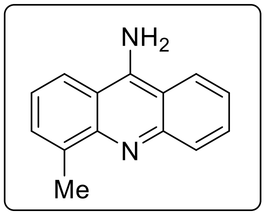
Yield: 80%, yellow brown solid, m.p.: 281-283 °C (Lit.: 279-281 °C)[1]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (brs, 2H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 10.0 Hz, 1H), 8.05-7.90 (m, 3H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.8 (d, $^1J_{CF}$ = 241.5 Hz), 157.4, 139.3, 136.6, 135.8, 125.5 (d, $^2J_{CF}$ = 26.8 Hz), 124.4, 122.0 (d, $^3J_{CF}$ = 8.6 Hz), 119.1, 112.1, 112.0, 111.2, 108.6 (d, $^2J_{CF}$ = 25.0 Hz); HRMS (ESI, m/z): calcd for $C_{13}H_9FN_2$ $[M + H]^+$ 213.0822, found 213.0823.

9-Acridinamine (5a)[2]



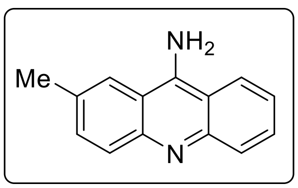
Yield: 84%, yellow solid, m.p.: 233-234 °C (Lit.: 232-233 °C)[2]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (brs, 2H), 8.71 (d, *J* = 8.8 Hz, 2H), 8.03-7.99 (m, 2H), 7.95-7.93 (m, 2H), 7.60-7.56 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, 139.6, 135.7, 124.9, 124.0, 118.9, 111.7; HRMS (ESI, m/z): calcd for $C_{13}H_{10}N_2$ $[M + H]^+$ 195.0917, found 195.0924.

4-Methyl-9-acridinamine (5e)[1]



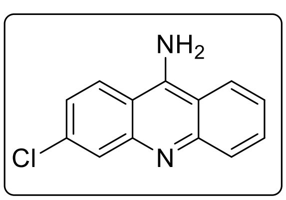
Yield: 81%, yellow brown solid, m.p.: 194-196 °C (Lit.: 193-195 °C)[1]; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.87 (brs, 2H), 8.62 (d, *J* = 8.8 Hz, 1H), 8.49 (d, *J* = 8.8 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 8.02 (t, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 6.8 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.53-7.49 (m, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 158.4, 139.7, 138.4, 136.3, 135.6, 127.4, 124.5, 124.3, 123.7, 122.5, 119.7, 111.8, 111.6, 18.2; HRMS (ESI, m/z): calcd for $C_{14}H_{12}N_2$ [M + H]$^+$ 209.1073, found 209.1079.

2-Methyl-9-acridinamine (5f)[1]



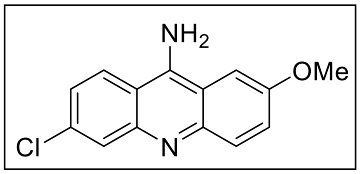
Yield: 85%, light yellow solid, m.p.: 250-252 °C (Lit.: 252-254 °C)[1]; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.84 (m, 2H), 8.62 (d, *J* = 8.8 Hz, 1H), 8.45 (s, 1H), 8.03-7.99 (m, 1H), 7.90-7.87 (m, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.61-7.57 (m, 1H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 157.4, 139.2, 137.8, 135.6, 133.8, 124.6, 123.9, 123.3, 118.9, 118.8, 111.6, 111.5, 21.1; HRMS (ESI, m/z): calcd for $C_{14}H_{12}N_2$ [M + H]$^+$ 209.1073, found 209.1068.

3-Chloro-9-acridinamine (5i)[3]



Yield: 89%, yellow solid, m.p.: 268-269 °C (Lit.: 267 °C)[3]; ^{1}H NMR (400 MHz, CD_3OD) δ 8.52-8.49 (m, 2H), 8.02 (t, *J* = 7.6 Hz, 1H), 7.85-7.81 (m, 2H), 7.63-7.59 (m, 1H), 7.56 (dd, *J* = 9.2, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.9, 143.2, 141.5, 141.1, 137.4, 127.5, 126.1, 125.9, 125.4, 119.7, 118.8, 113.3, 111.6; HRMS (ESI, m/z): calcd for $C_{13}H_9ClN_2$ [M + H]$^+$ 229.0527, found 229.0530.

9-Amino-6-chloro-2-methoxy acridine (6)[3]



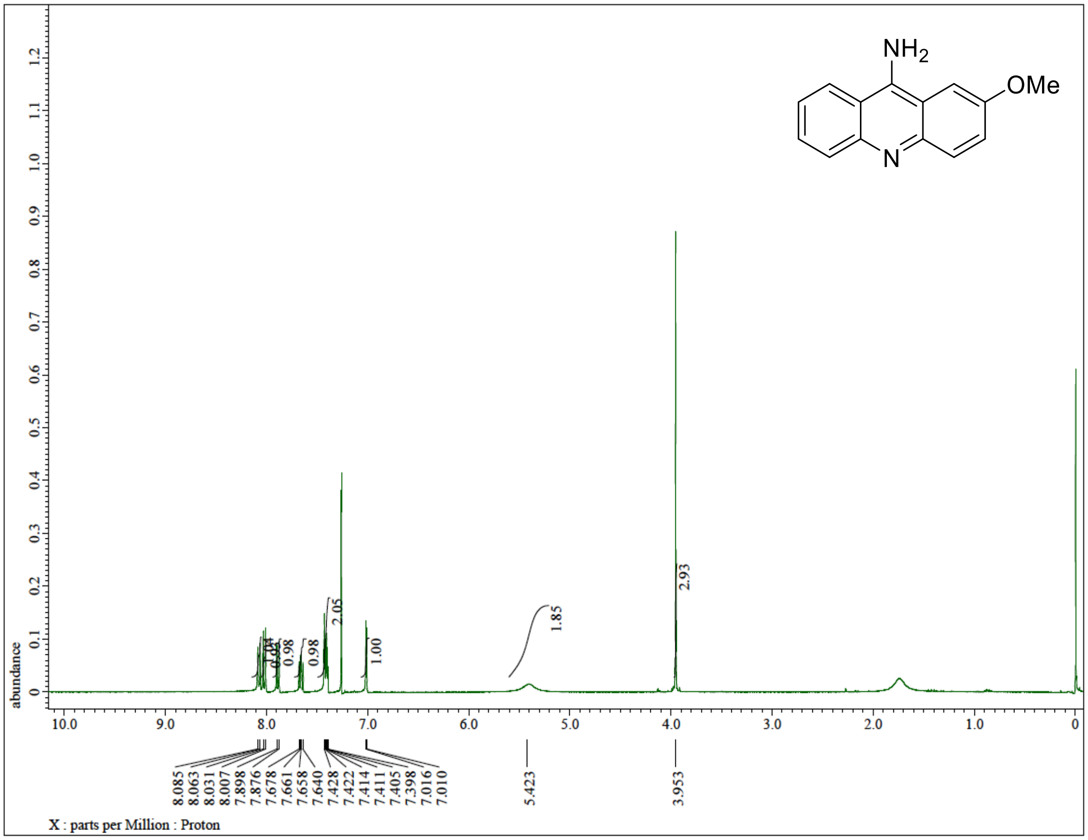
Yield: 86%, pale white solid, m.p.: 272-275 °C (Lit.: 274 °C)[3]; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.77 (br s, 2H), 8.54 (d, *J* = 9.2 Hz, 1H), 7.86 (s, 1H), 7.76-7.72 (m, 2H), 7.63 (dd, *J* = 9.2, 1.6 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 157.1, 156.3, 156.1, 139.7, 138.9, 134.8, 128.3, 126.8, 124.4, 122.9, 120.7, 112.6, 102.9, 56.4; HRMS (ESI, m/z): calcd for $C_{14}H_{11}ClN_2O$ $[M + H]^+$ 259.0632, found 259.0637.

Synthesis of 2-((4-Methoxyphenyl)amino)benzonitrile (3a).[4] To a flame dried Schlenk tube equipped with nitrogen balloon, 2-bromobenzonitrile (**1a**) (1.0 mmol), *p*-anisidine (**2a**) (1.1 mmol), palladium(II) acetate (5 mol %), rac-BINAP (10 mol %), cesium carbonate (2.0 equiv) and toluene (1 mL) were added. The tube was immersed in silicon oil bath placed over magnetic stirrer and heated at 100 °C with constant stirring for 15h. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography using hexane and ethylacetate (70 : 30) as eluents to afford the product **3a** in 92% yield as pale white solid. Melting point 119-121 °C (Lit.: 118-120 °C)[4]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.32-7.28 (m, 1H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.93-6.89 (m, 3H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.22 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 148.9, 133.9, 132.8, 132.2, 125.6, 118.1, 117.8, 114.8, 112.8, 96.8, 55.5; HRMS (ESI, m/z): calcd for $C_{14}H_{12}N_2O$ $[M + H]^+$ 225.1022, found 225.1021. Crystals of compound **3a** were grown by vapor diffusion of hexane into ethyl acetate solution. CCDC 2183508 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table S1. Crystal data and structure refinement for compound **2-[(4-Methoxyphenyl)amino] benzonitrile (3a)**

	2-[(4-Methoxyphenyl)amino]benzonitrile (3a)
Empirical formula	$C_{14}H_{12}N_2O$
Formula weight	224.26
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 5.8345(4) Å, α = 90°
	b = 20.2448(14) Å, β = 103.311 (7)°
	c = 10.2007 (7) Å, γ = 90°
Volume	1172.52 (14) $Å^3$
Z	4
Density (calculated)	1.270 Mg/m^3
Absorption coefficient	0.082 mm^{-1}
F(000)	472
Crystal size	0.200 x 0.180 x 0.120 mm^3
ϑ range for data collection	3.588 to 24.997°
Index ranges	-6<=*h*<=6, -24<=*k*<=24, -12<=*l*<=*12*

Reflections collected	14319
Independent reflections	2054 [R(int) = 0.0277]
Completeness to ϑ = 24.997°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.992 and 0.983
Refinement method	Full-matrix least-squares on F^2
Data / restraints / Parameters	2054 / 0 / 160
Goodness-of-fit on F^2	1.063
Final R indices [I>2σ(I)]	R1 = 0.0365, wR2 = 0.0880
R indices (all data)	R1 = 0.0447, wR2 = 0.0918
Extinction coefficient	0.059 (4)
Largest diff. peak and hole	0.124 and -0.134 e.Å^{-3}



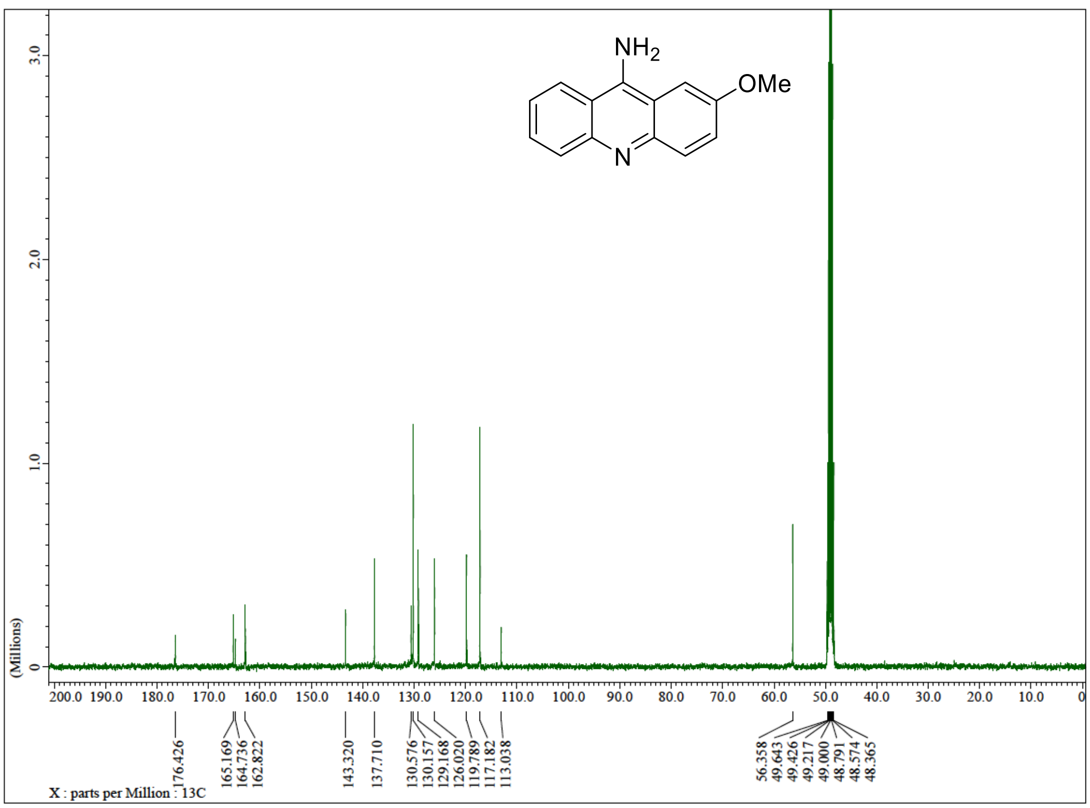
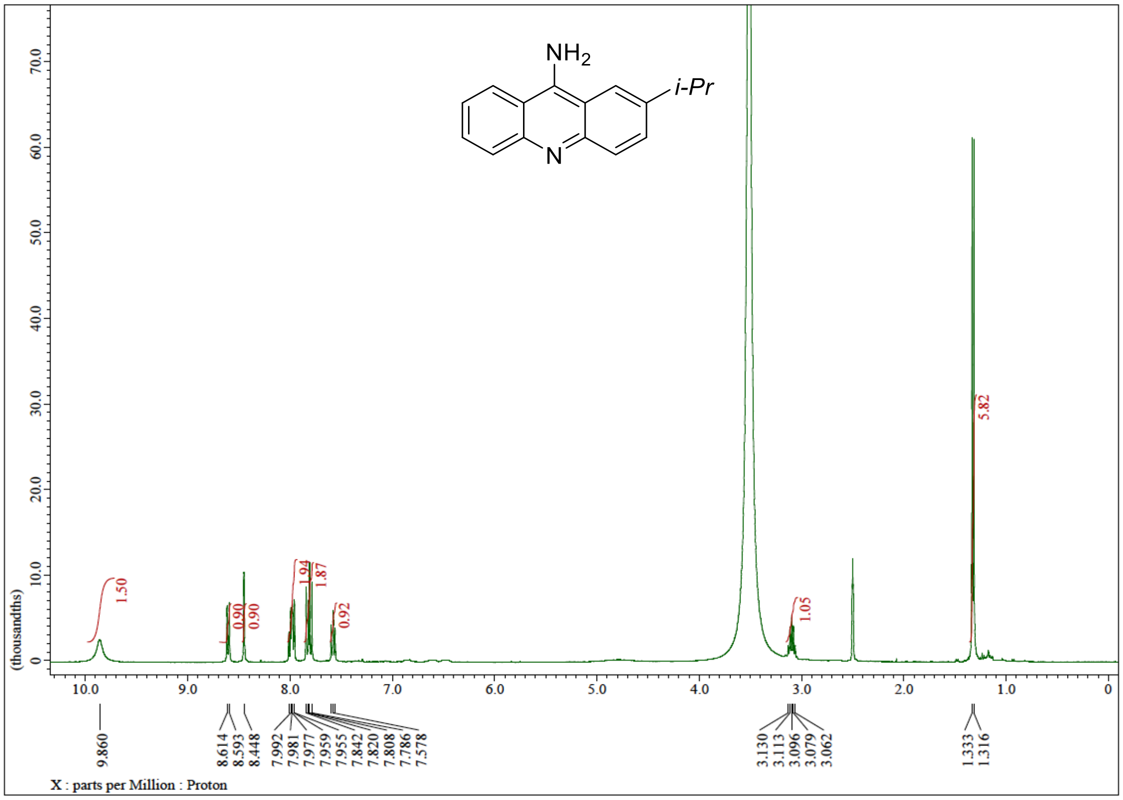


Figure S1: ^{1}H NMR of **4a** (400 MHz, CD_3OD) and ^{13}C NMR of **4a** (100 MHz, CD_3OD).



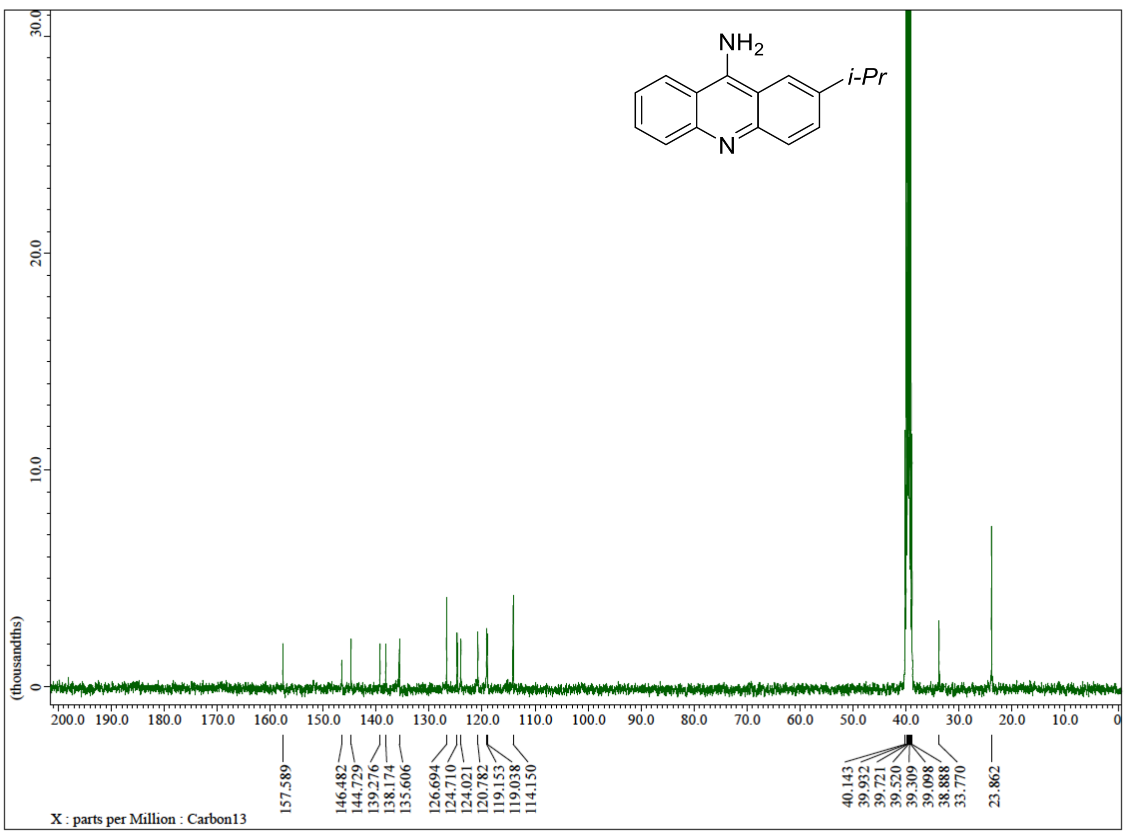
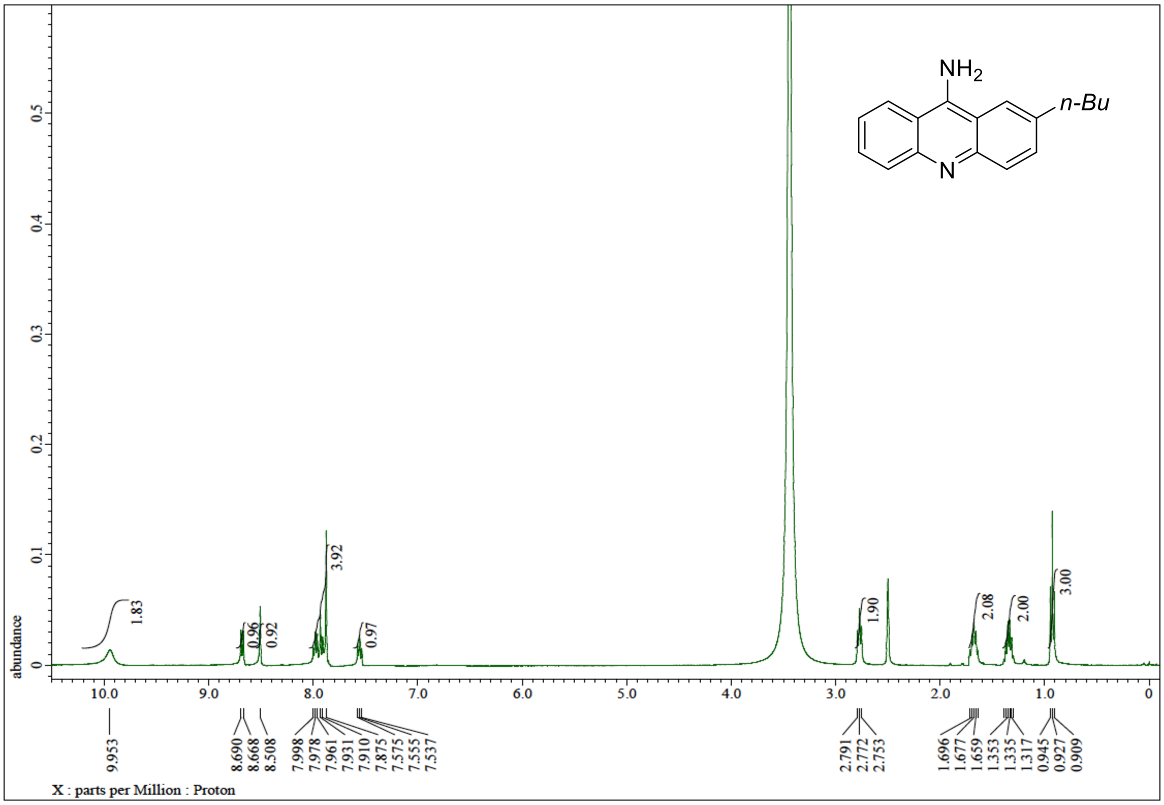


Figure S2: ^{1}H NMR of **4b** (400 MHz, DMSO-d$_6$) and ^{13}C NMR of **4b** (100 MHz, DMSO-d$_6$).



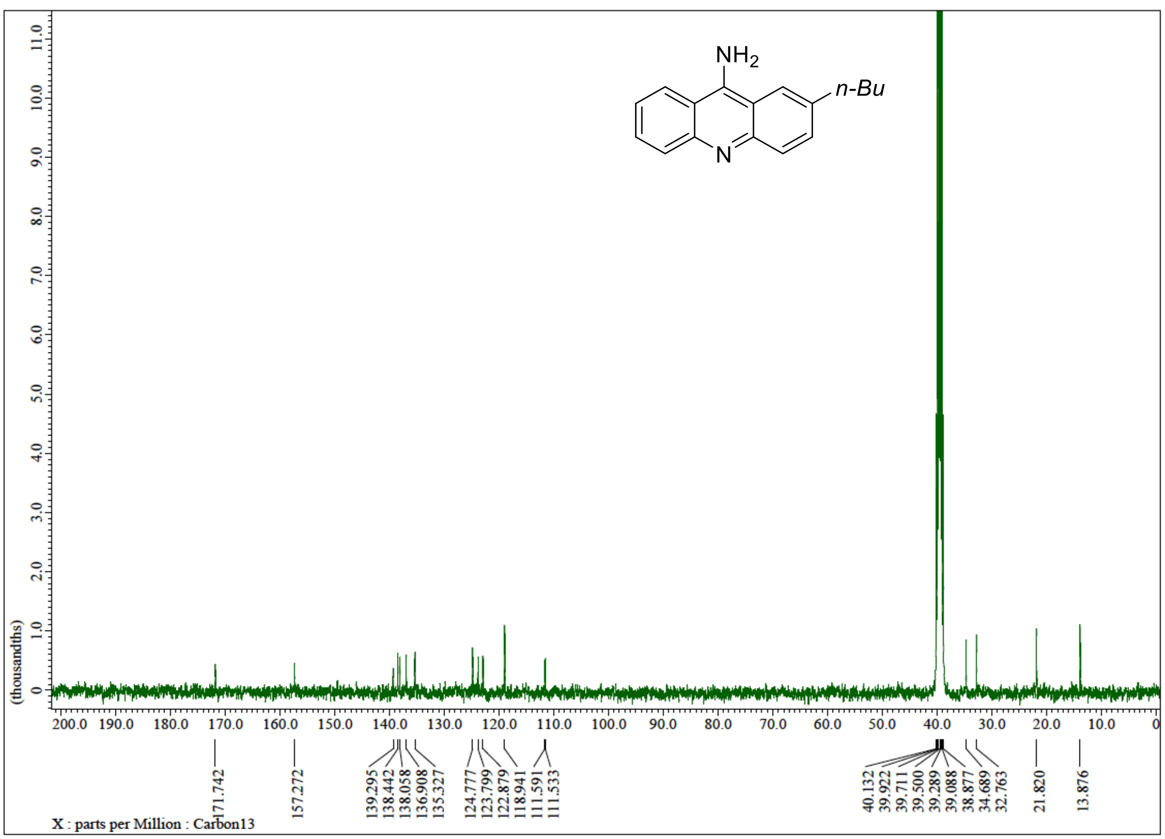
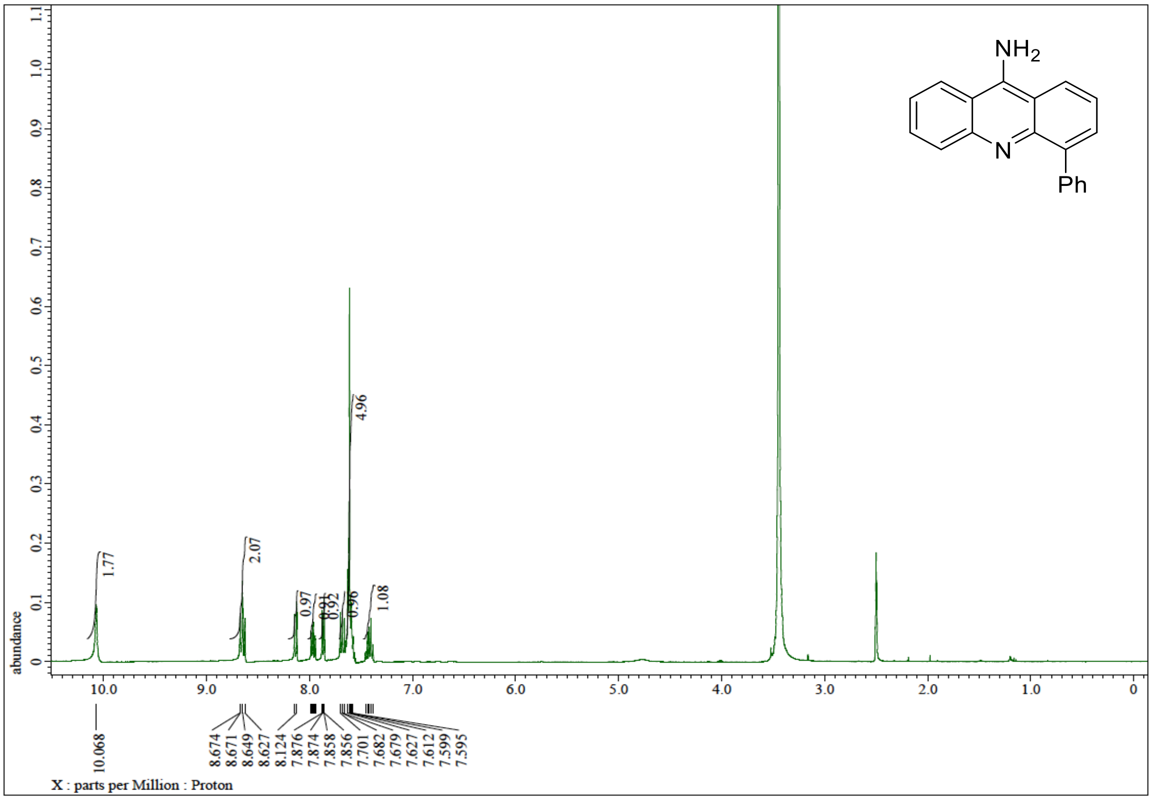


Figure S3: ^{1}H NMR of **4c** (400 MHz, DMSO-d_6) and ^{13}C NMR of **4c** (100 MHz, DMSO-d_6).



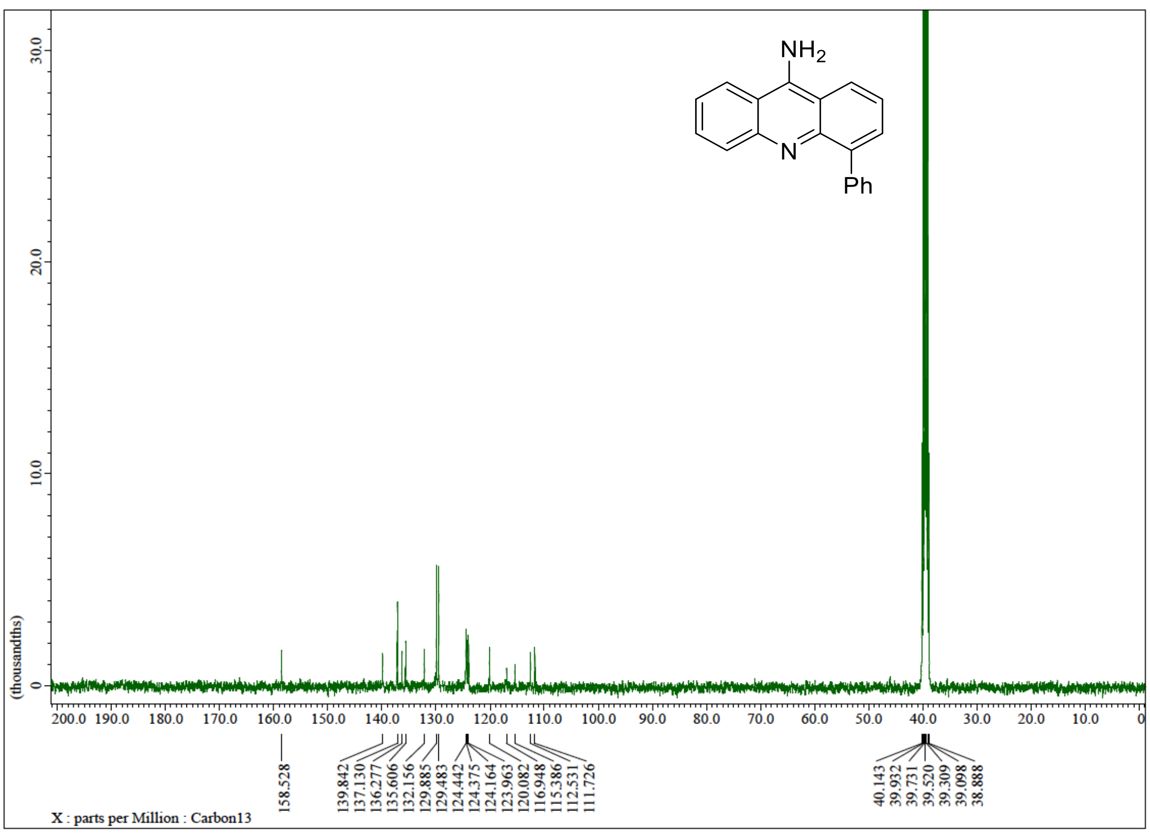
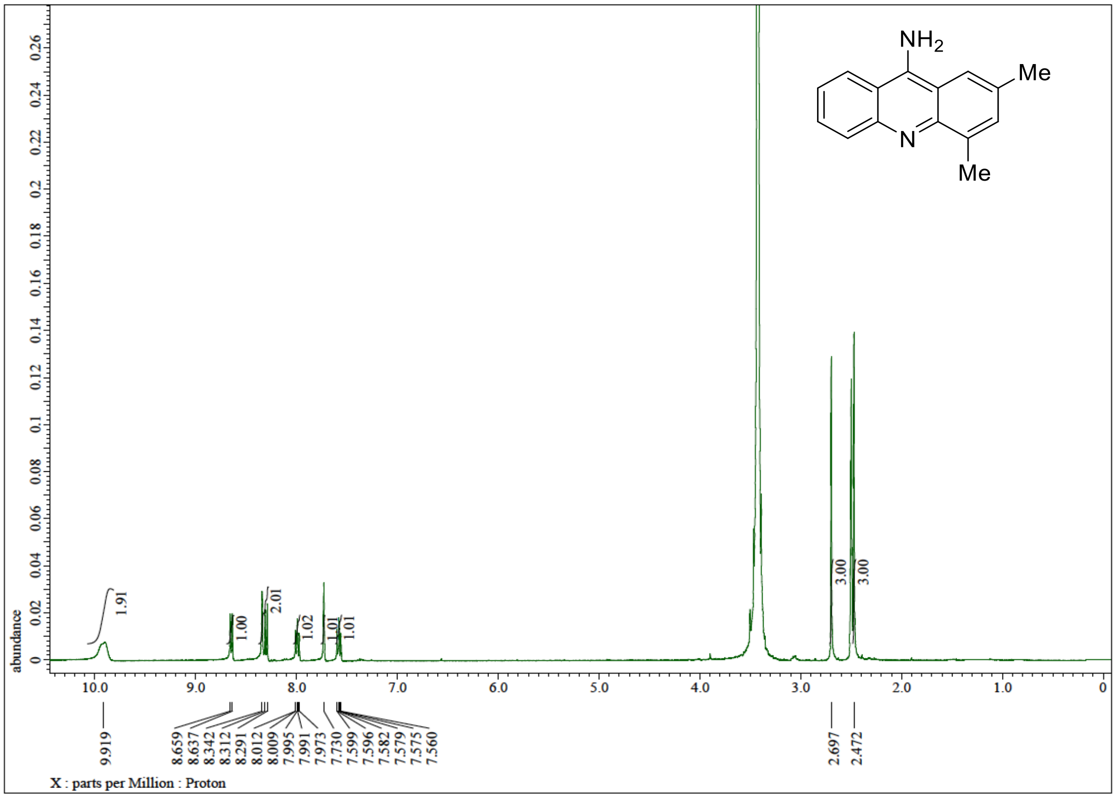


Figure S4: ^{1}H NMR of **4d** (400 MHz, DMSO-d_6) and ^{13}C NMR of **4d** (100 MHz, DMSO-d_6).



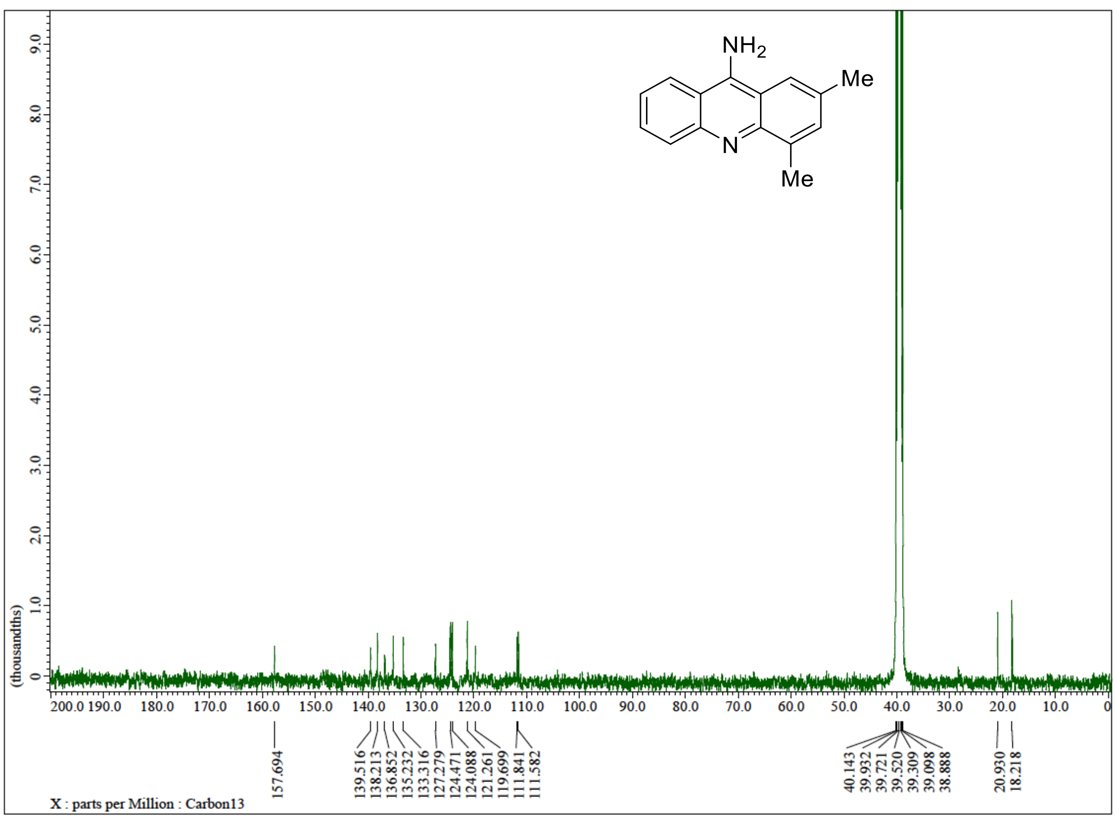
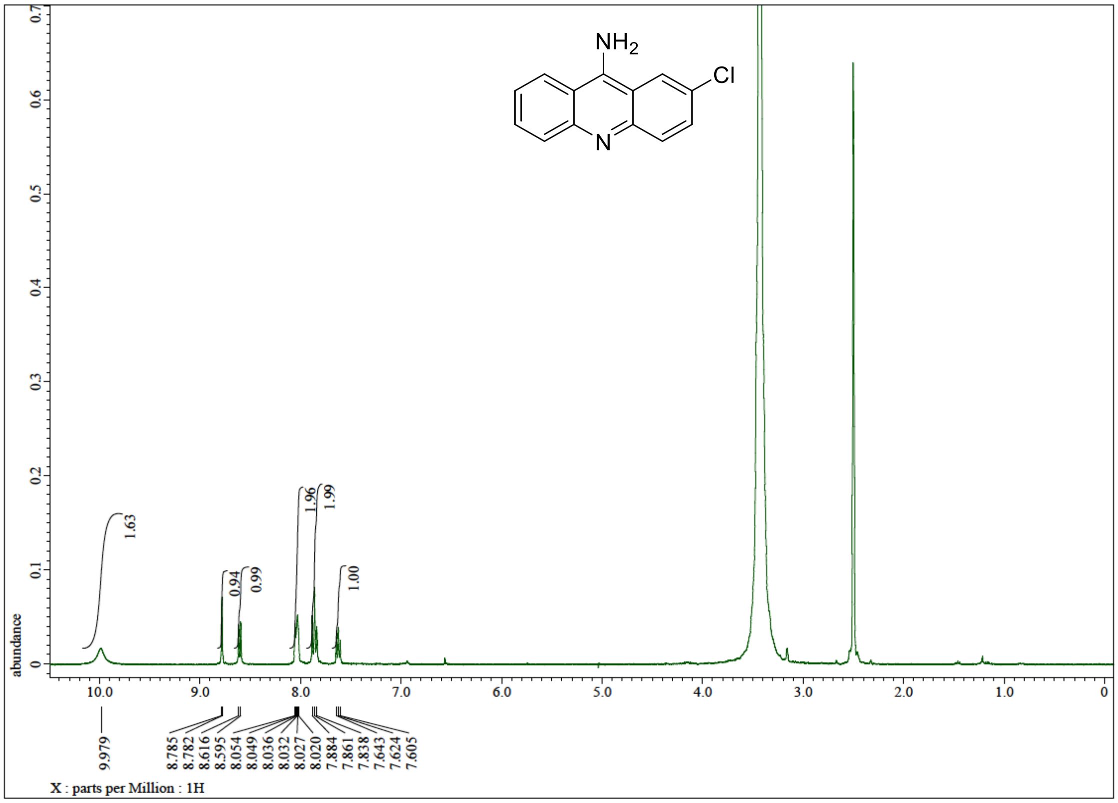


Figure S5: ^{1}H NMR of **4e** (400 MHz, DMSO-d_6) and ^{13}C NMR of **4e** (100 MHz, DMSO-d_6).



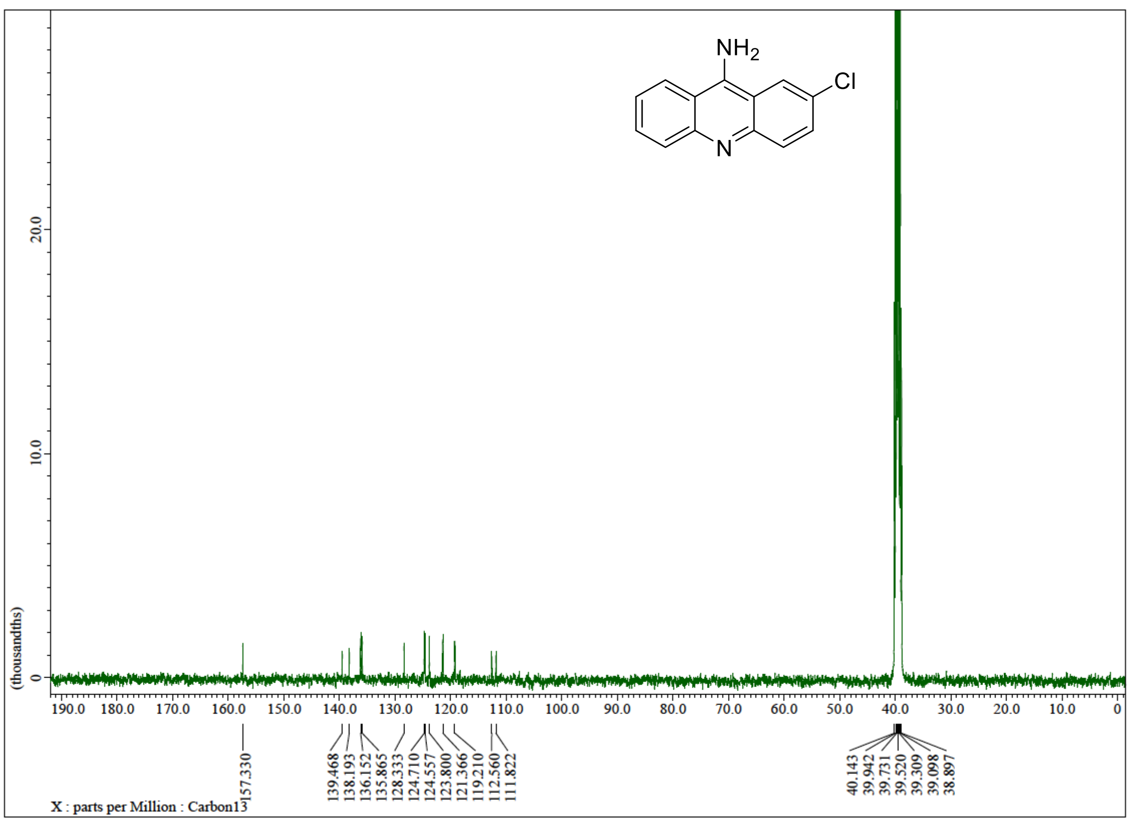
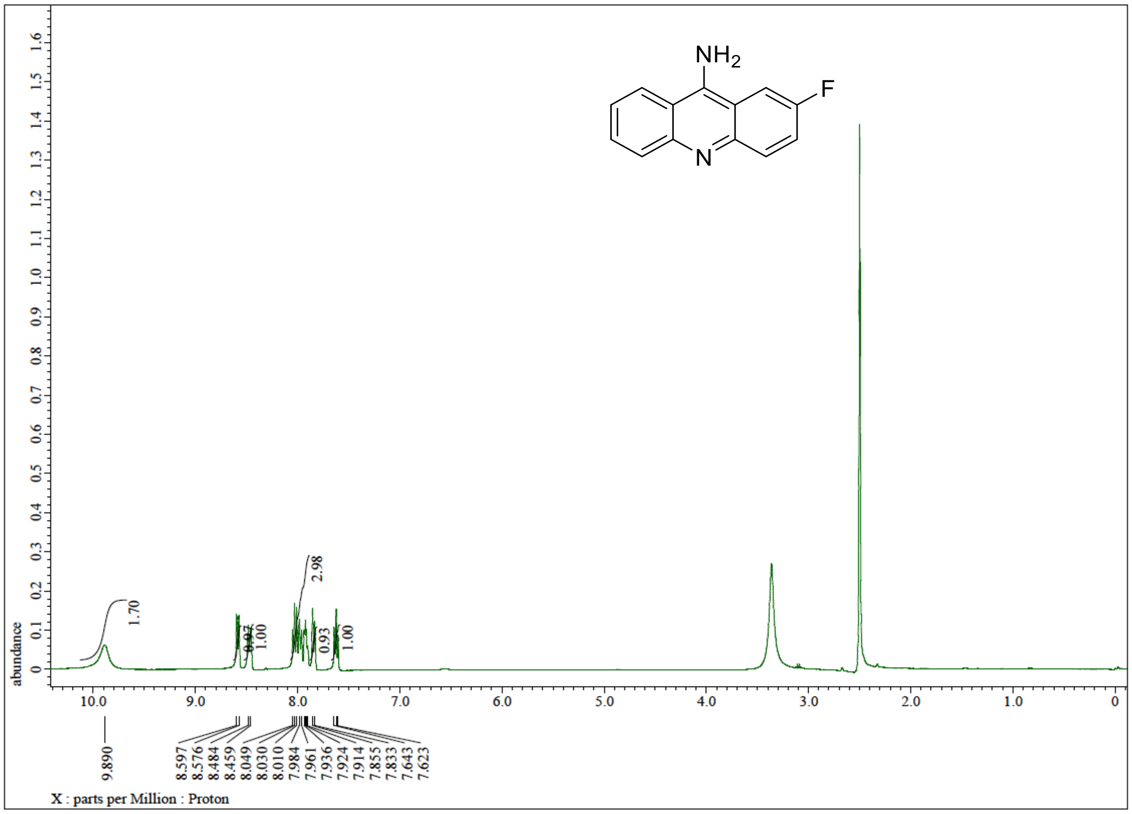


Figure S6: ^{1}H NMR of **4f** (400 MHz, DMSO-d_6) and ^{13}C NMR of **4f** (100 MHz, DMSO-d_6).



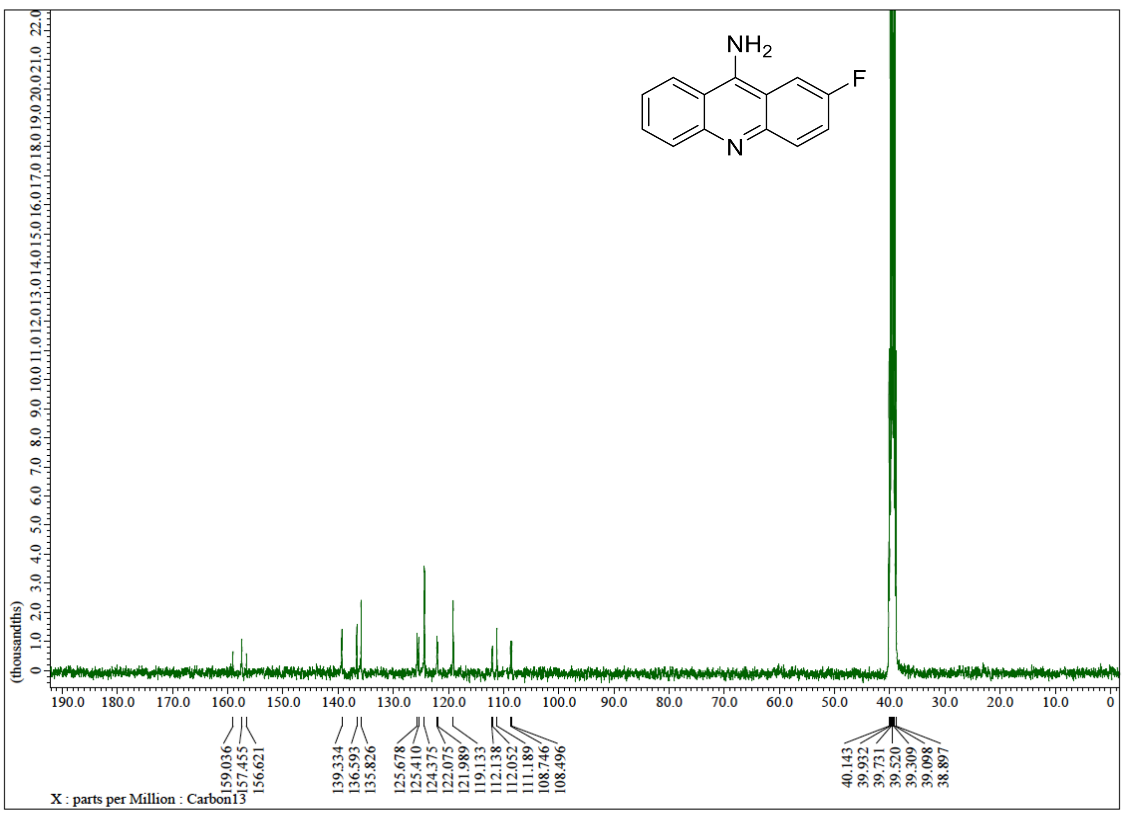
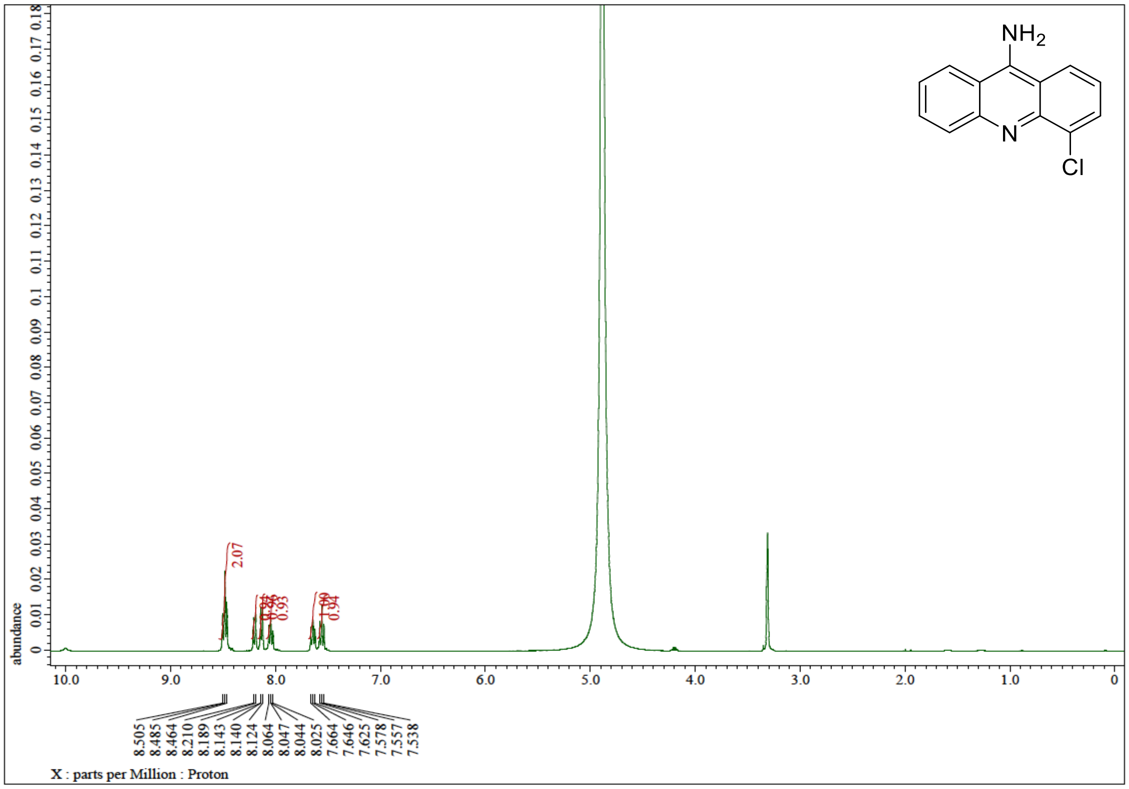


Figure S7: ^{1}H NMR of **4g** (400 MHz, DMSO-d$_6$) and ^{13}C NMR of **4g** (100 MHz, DMSO-d$_6$).



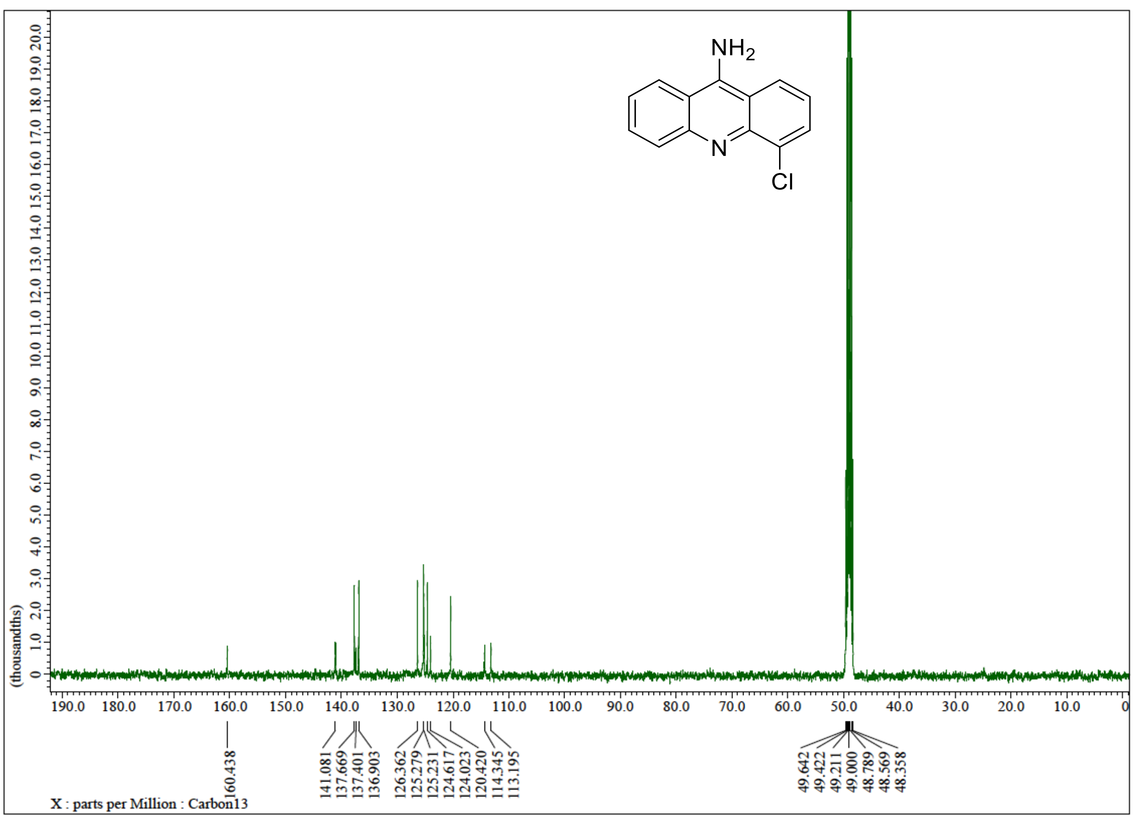
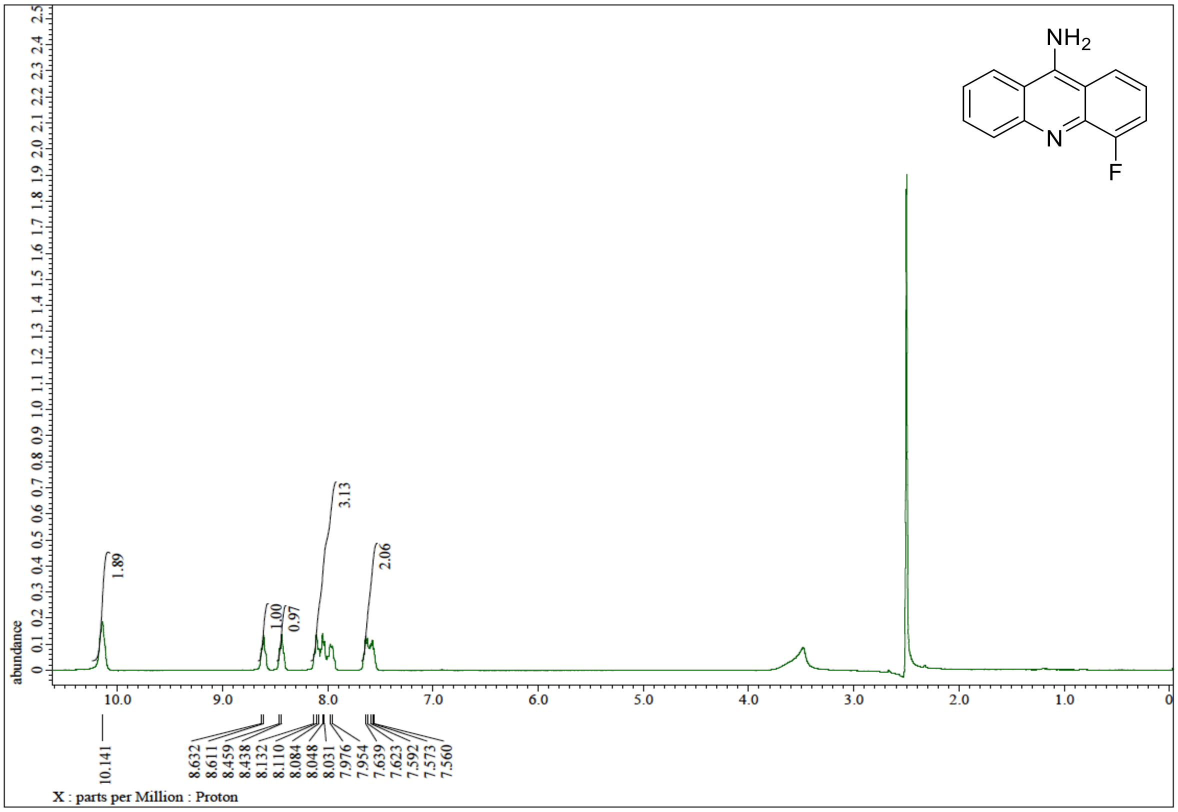


Figure S8: ^{1}H NMR of **4h** (400 MHz, CD_3OD) and ^{13}C NMR of **4h** (100 MHz, CD_3OD).



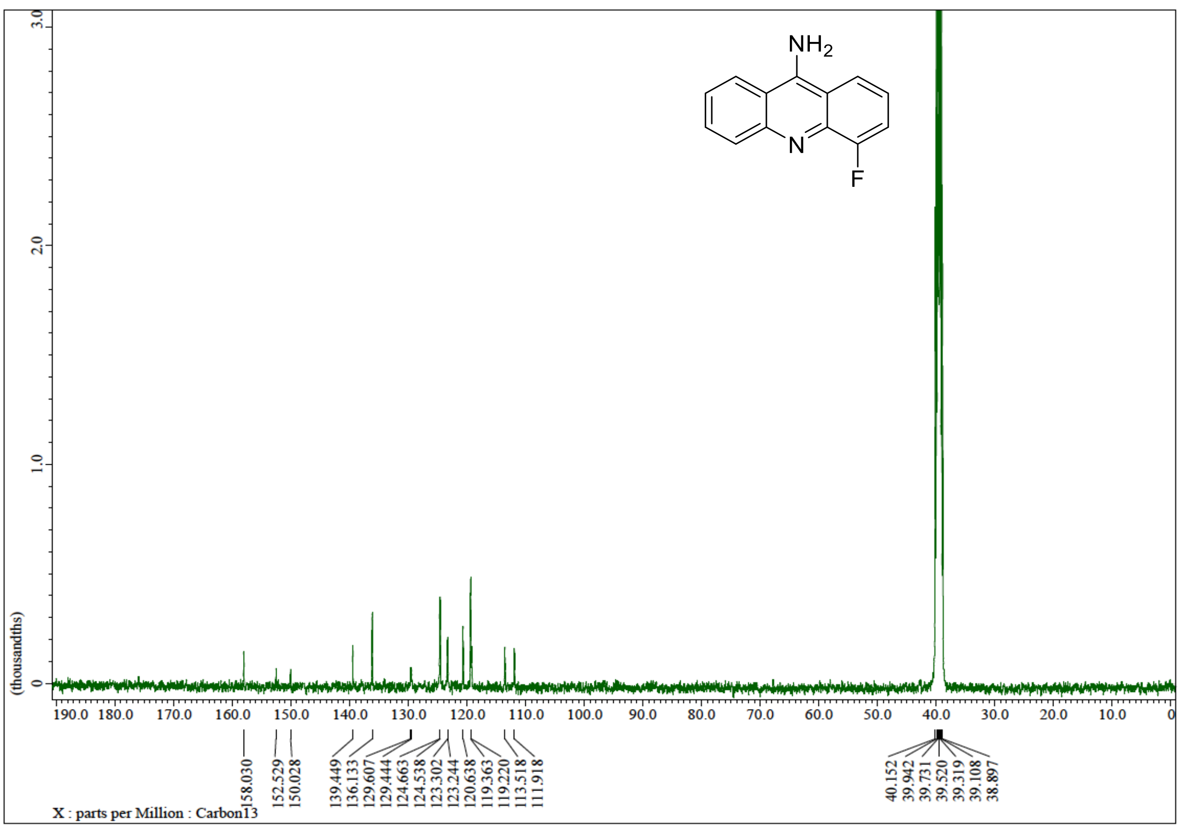
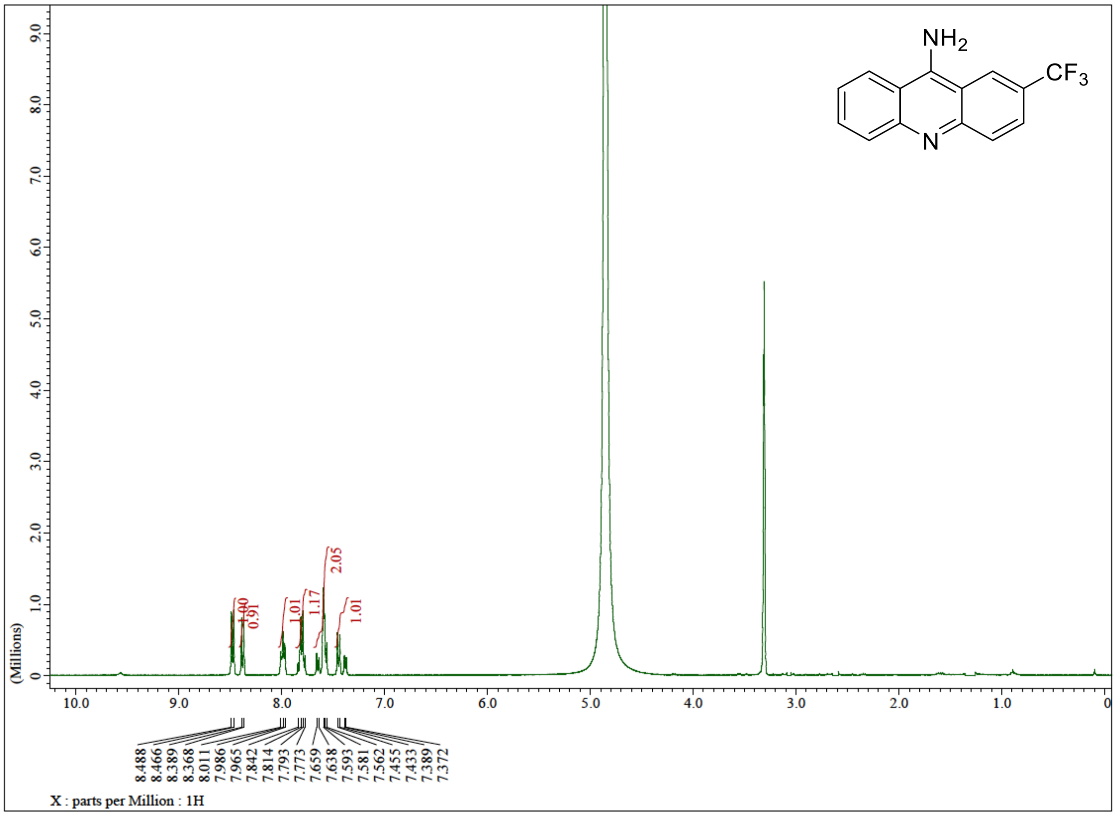


Figure S9: ^{1}H NMR of **4i** (400 MHz, DMSO-d_6) and ^{13}C NMR of **4i** (100 MHz, DMSO-d_6).



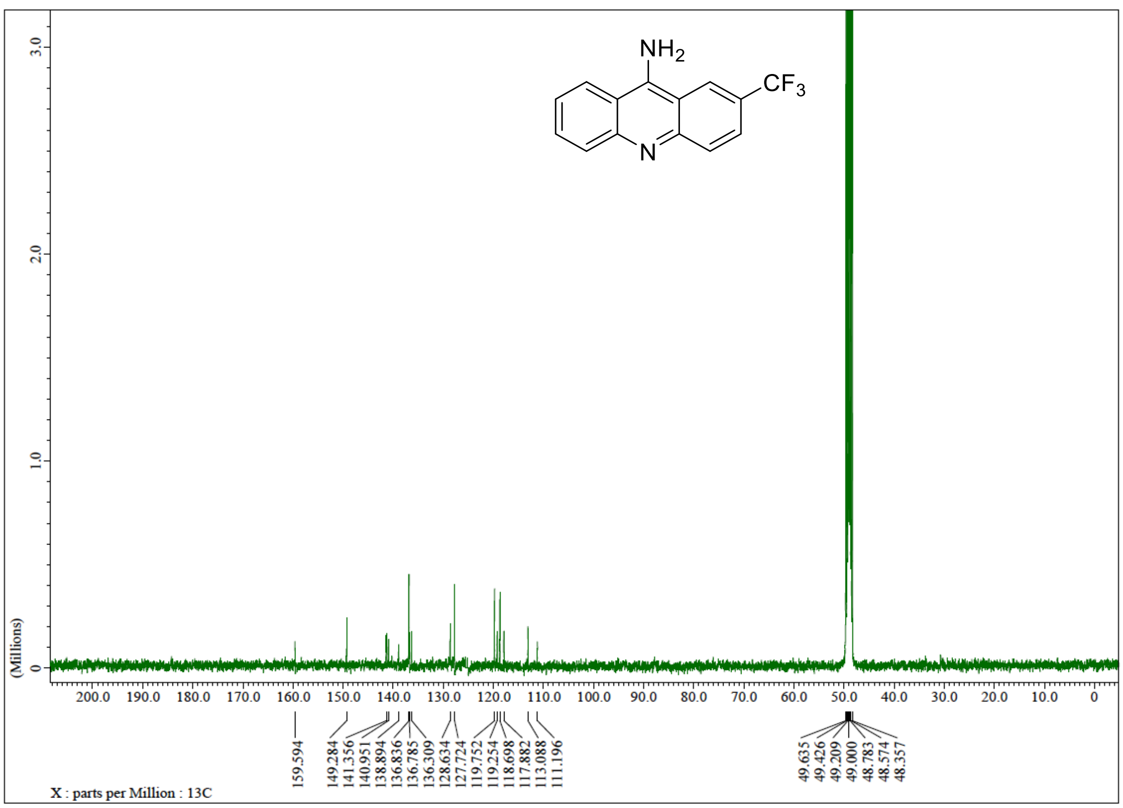
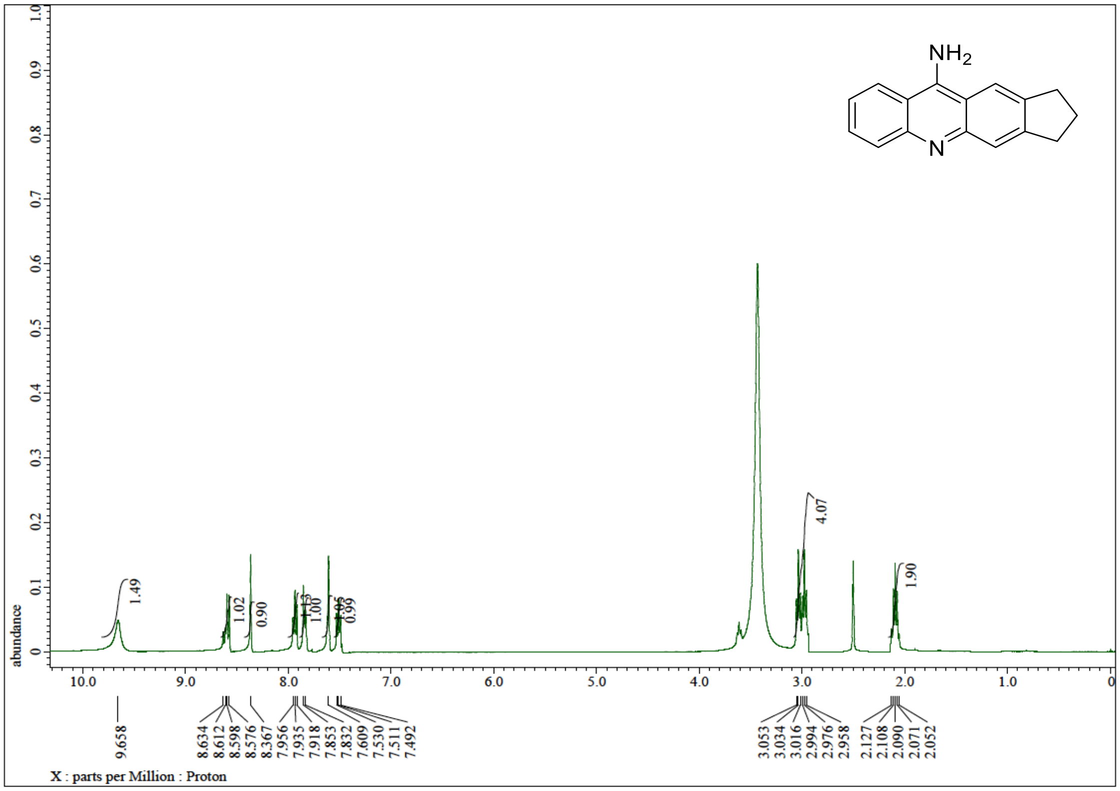


Figure S10: ^{1}H NMR of **4j** (400 MHz, CD_3OD) and ^{13}C NMR of **4j** (100 MHz, CD_3OD).



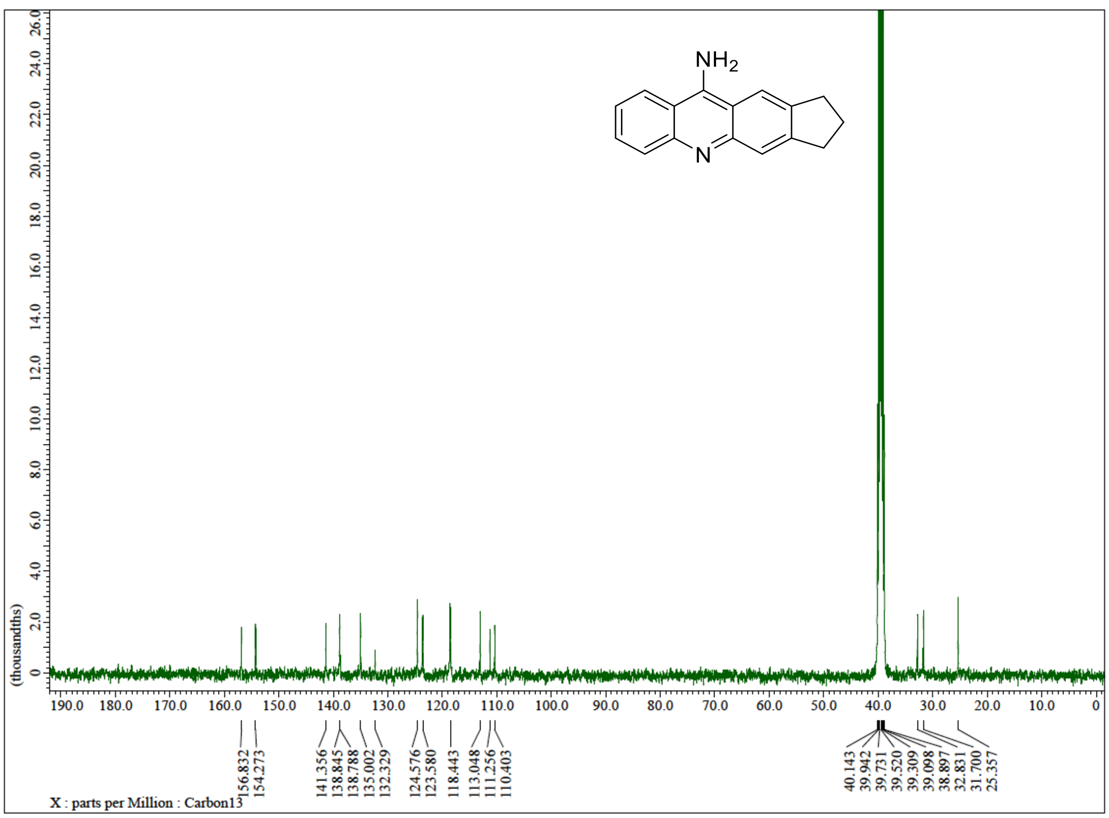


Figure S11: ^{1}H NMR of **4k** (400 MHz, DMSO-d_6) and ^{13}C NMR of **4k** (100 MHz, DMSO-d_6).

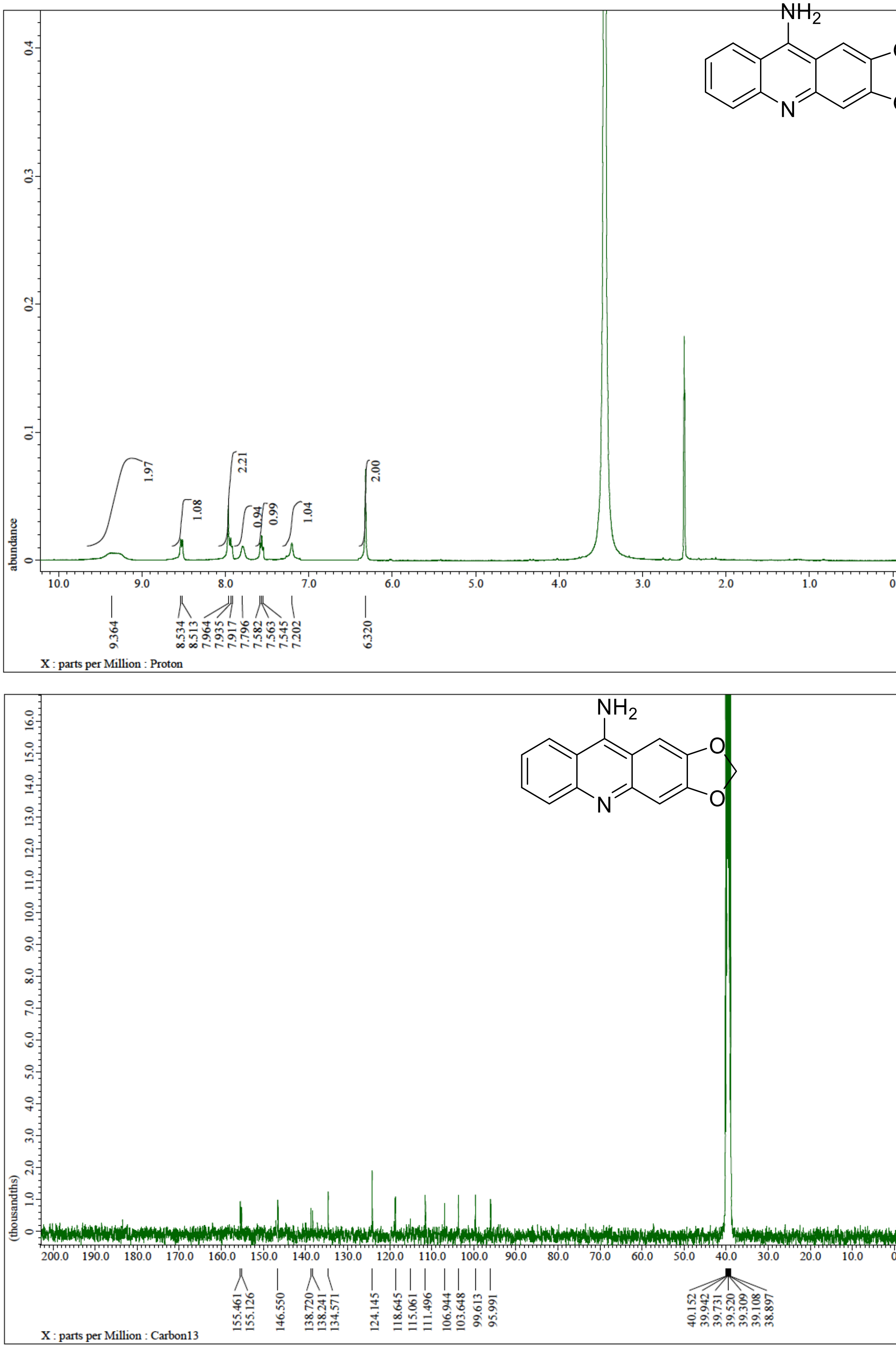
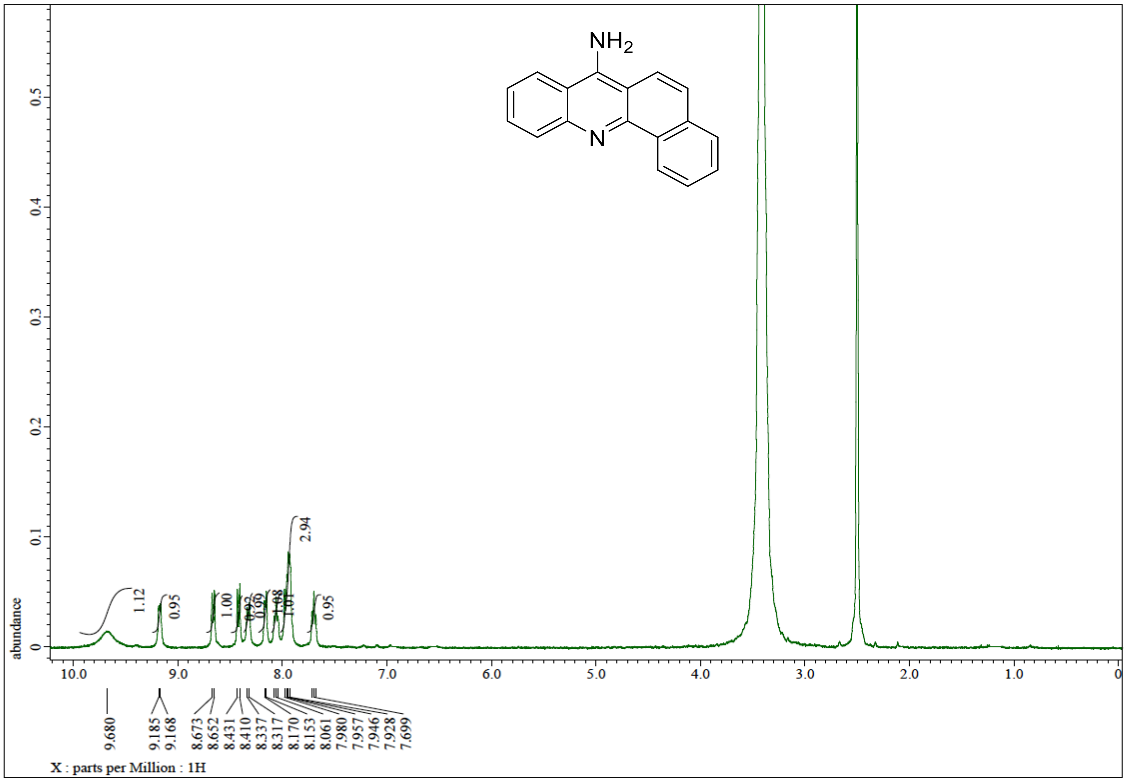


Figure S12: ^{1}H NMR of **4l** (400 MHz, DMSO-d$_6$) and ^{13}C NMR of **4l** (100 MHz, DMSO-d$_6$).



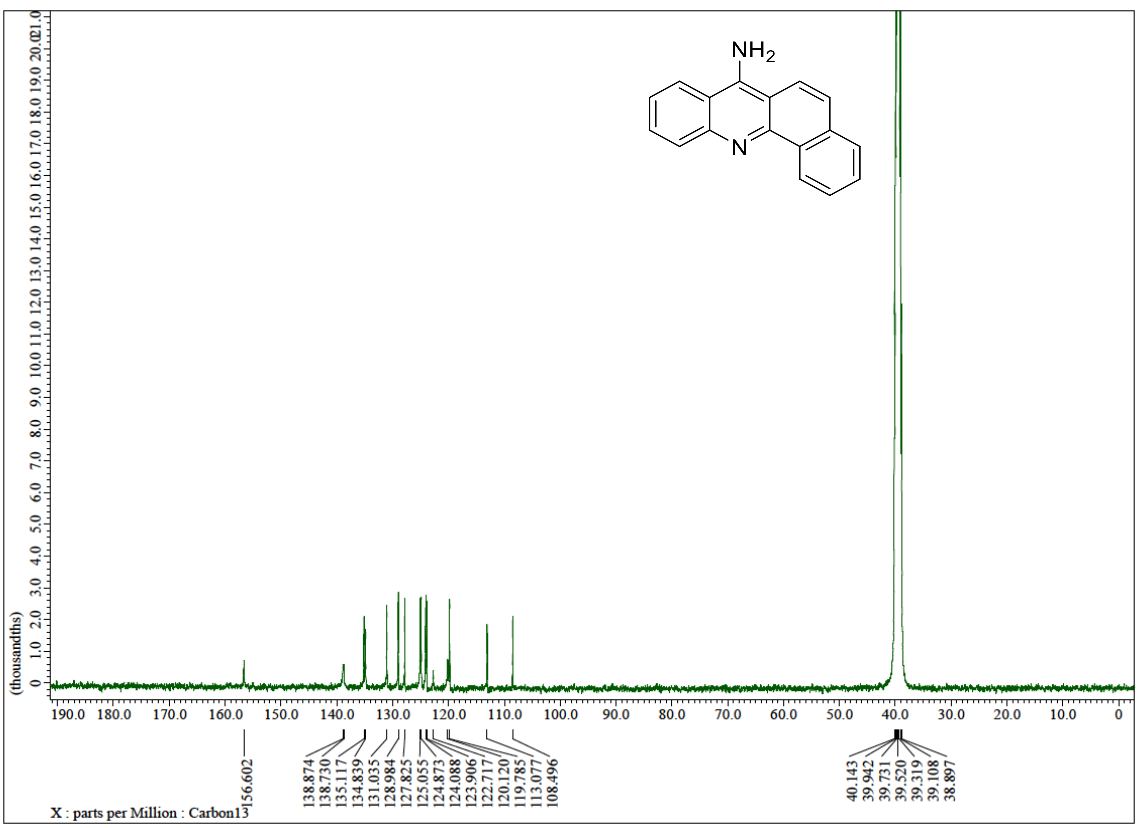
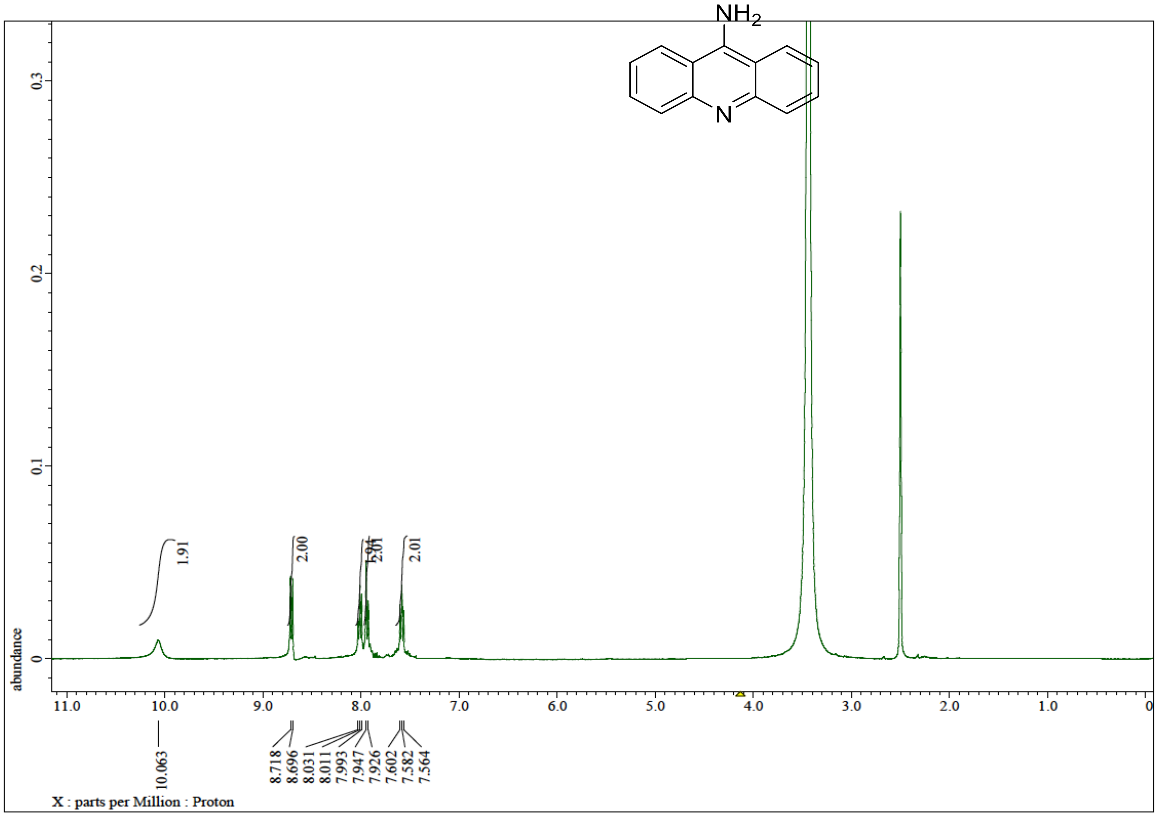


Figure S13: ^{1}H NMR of **4m** (400 MHz, DMSO-d_6) and ^{13}C NMR **4m** (100 MHz, DMSO-d_6).



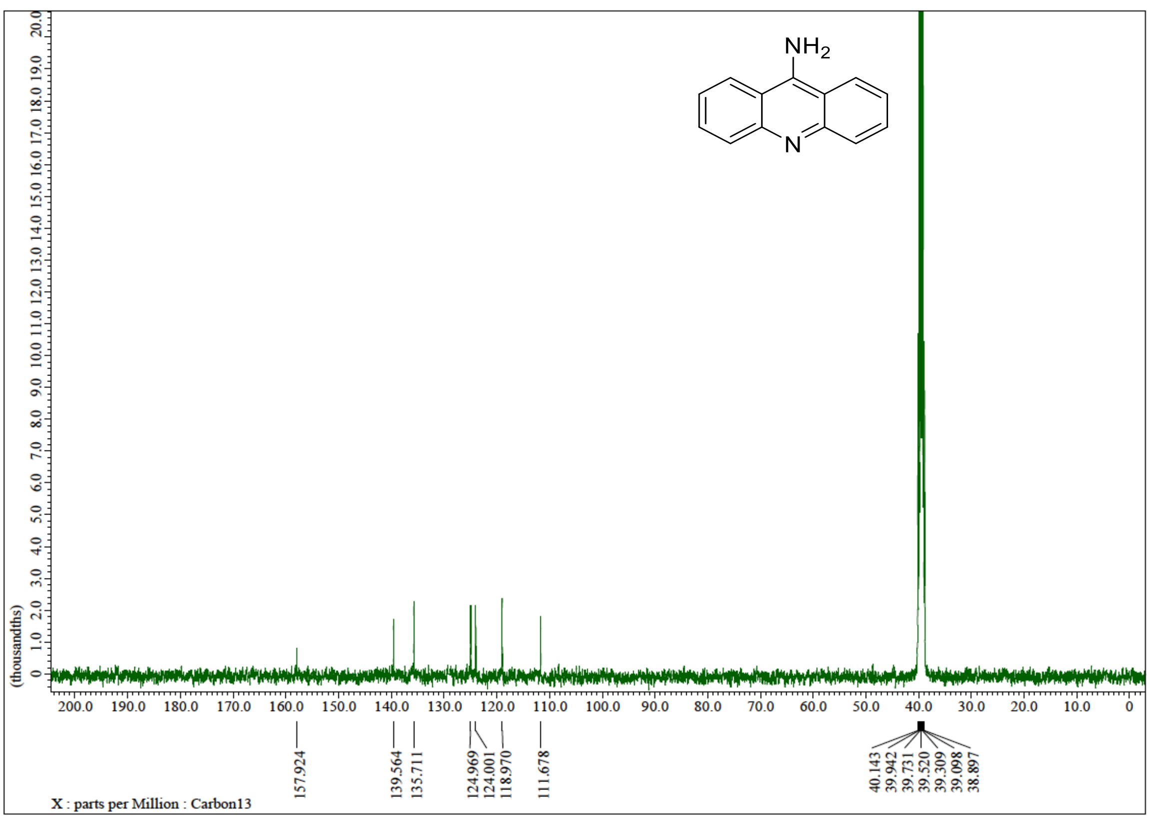
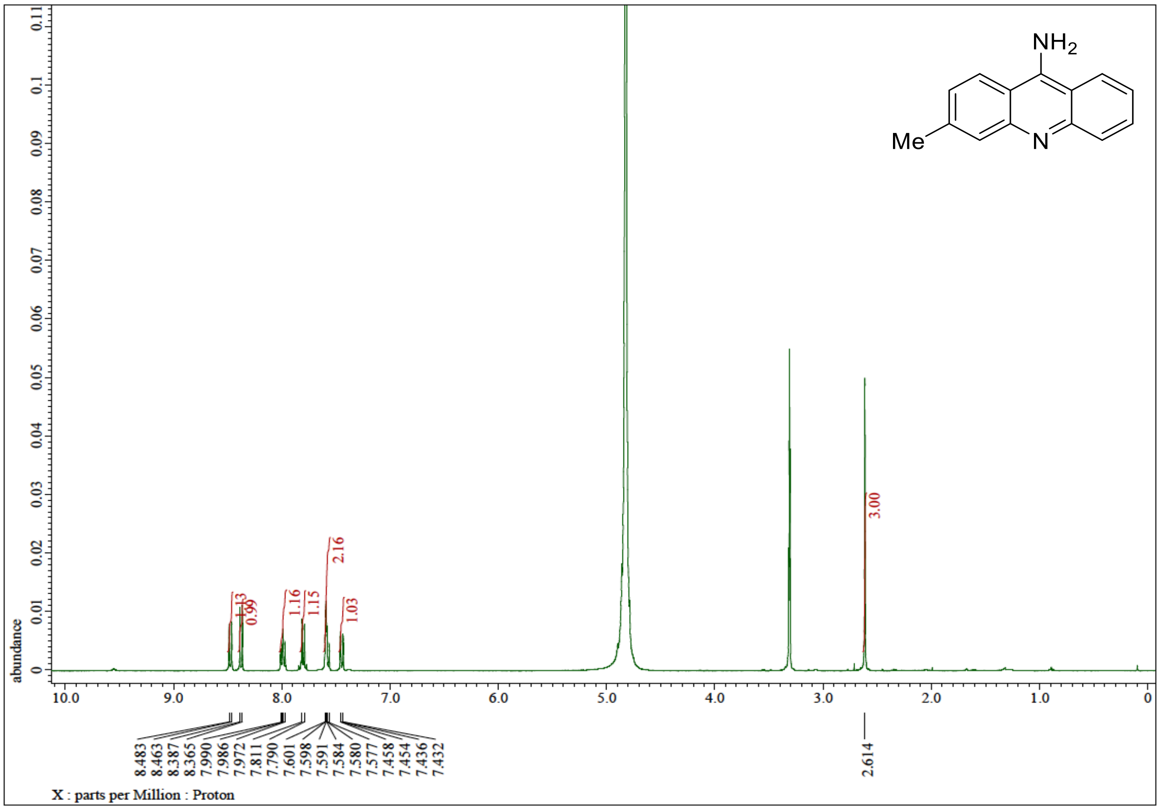


Figure S14: ^{1}H NMR of **5a** (400 MHz, DMSO-d_6) and ^{13}C NMR of **5a** (100 MHz, DMSO-d_6).



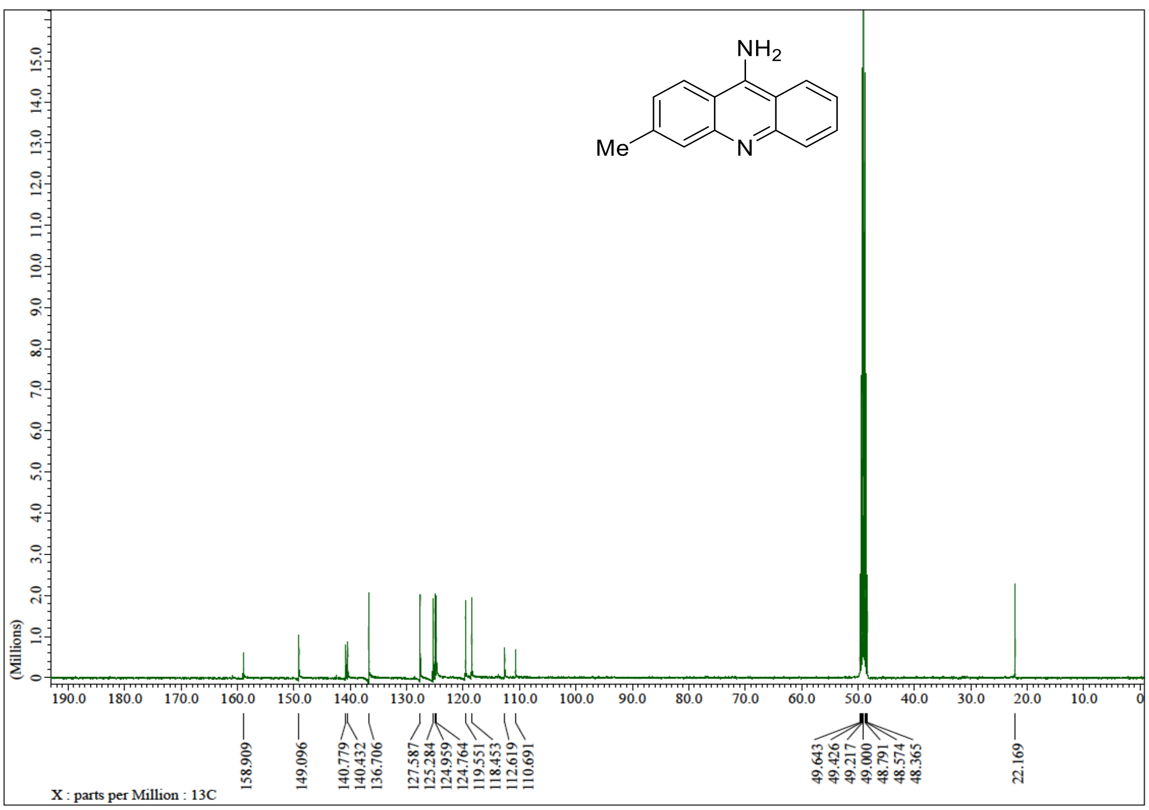
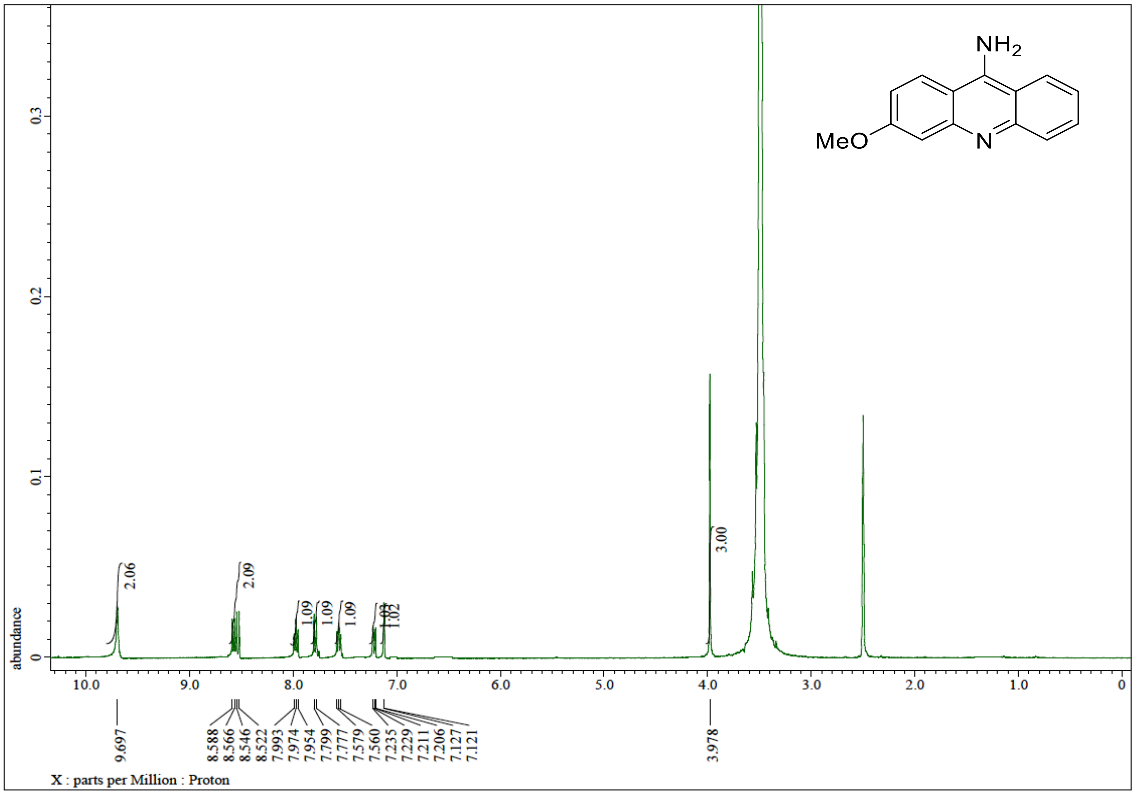


Figure S15: ^{1}H NMR of **5b** (400 MHz, CD_3OD) and ^{13}C NMR of **5b** (100 MHz, CD_3OD).



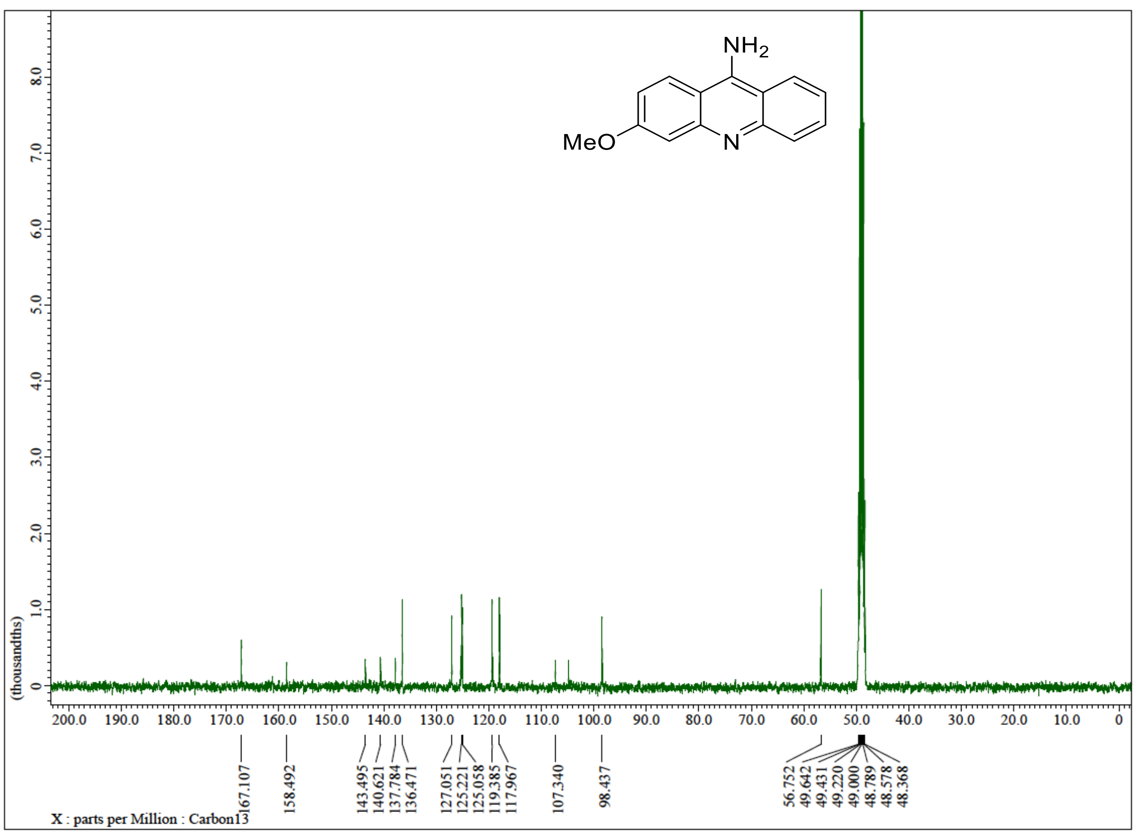
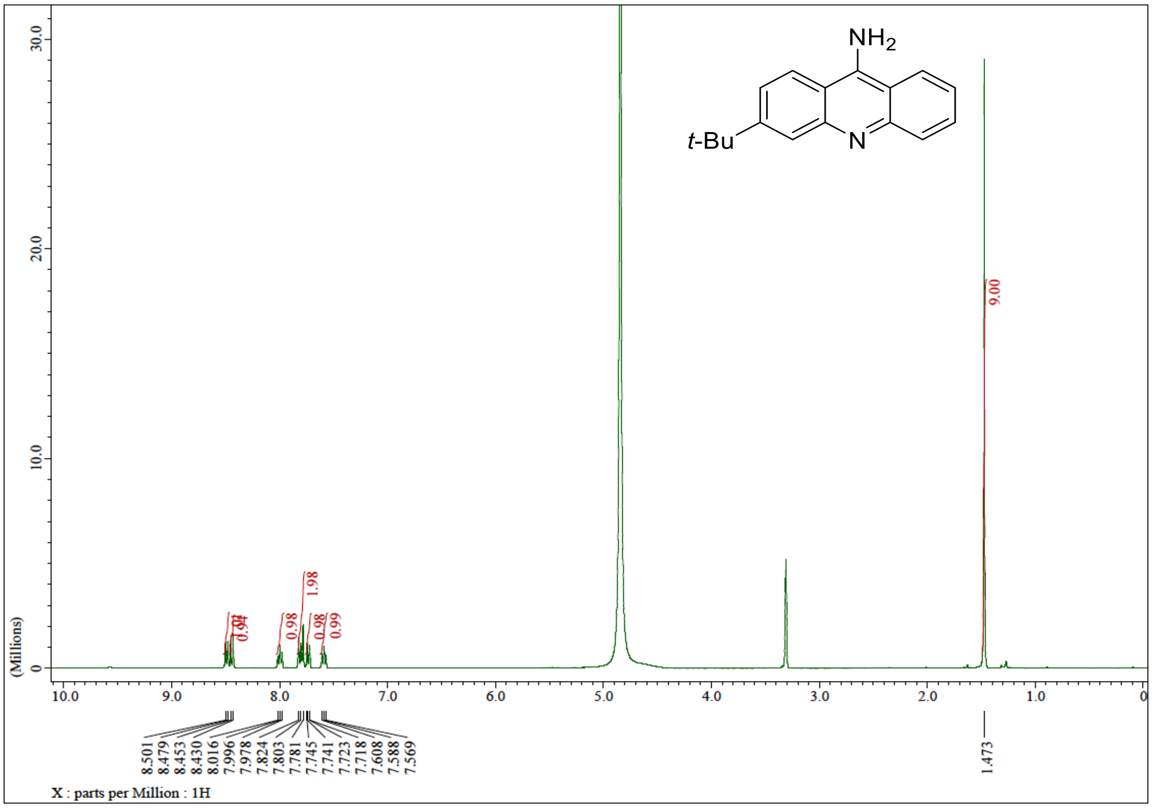


Figure S16: ^{1}H NMR of **5c** (400 MHz, DMSO-d_6) and ^{13}C NMR of **5c** (100 MHz, CD_3OD).



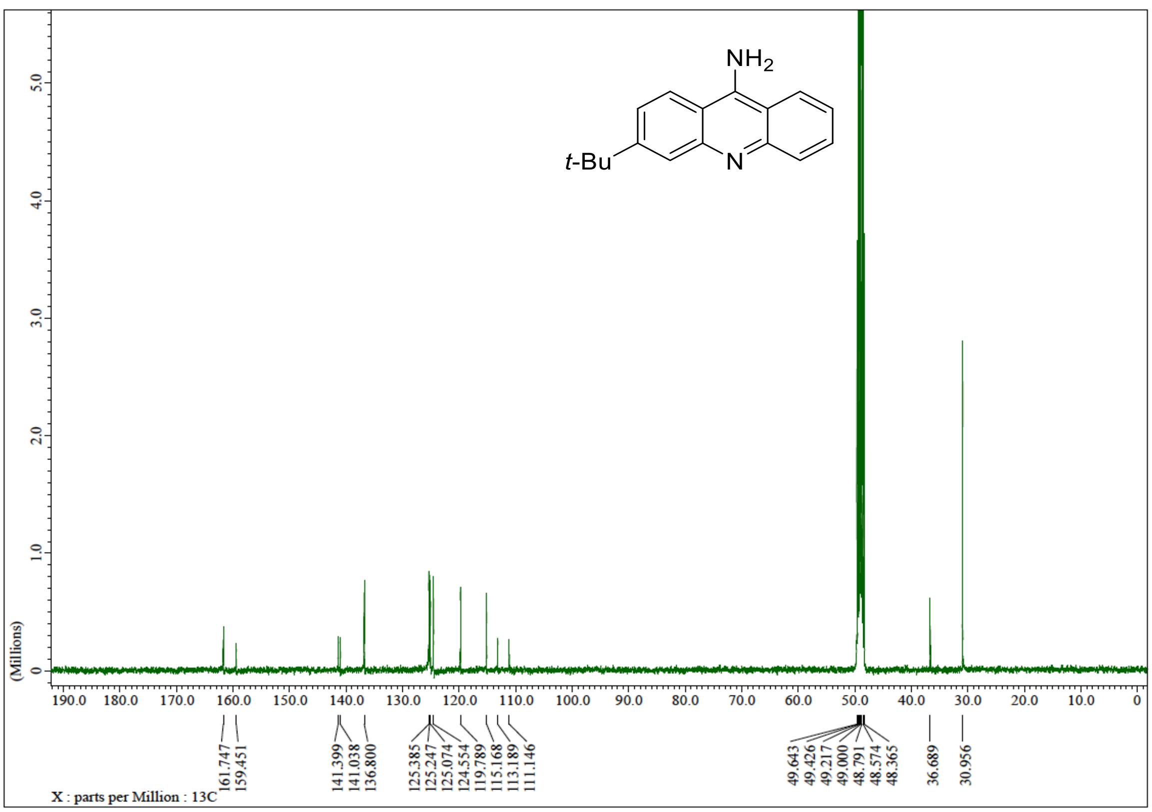
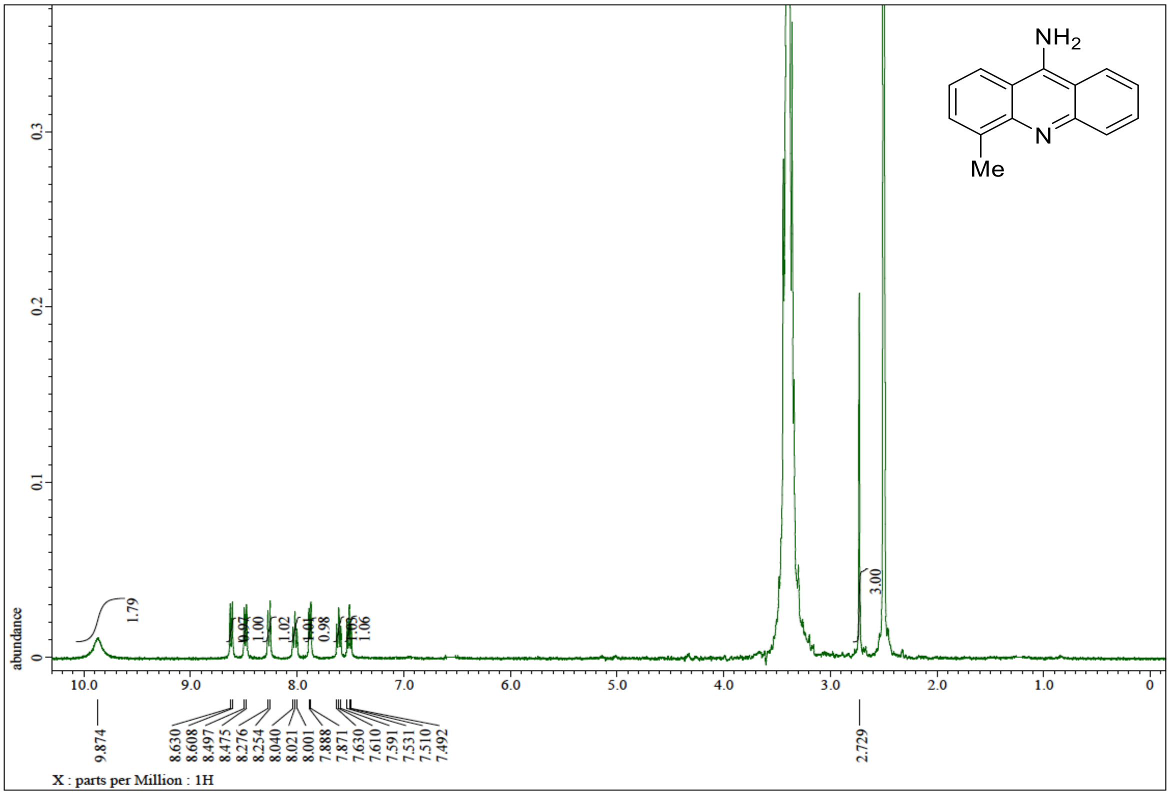


Figure S17: ^{1}H NMR of **5d** (400 MHz, CD_3OD) and ^{13}C NMR of **5d** (100 MHz, CD_3OD).



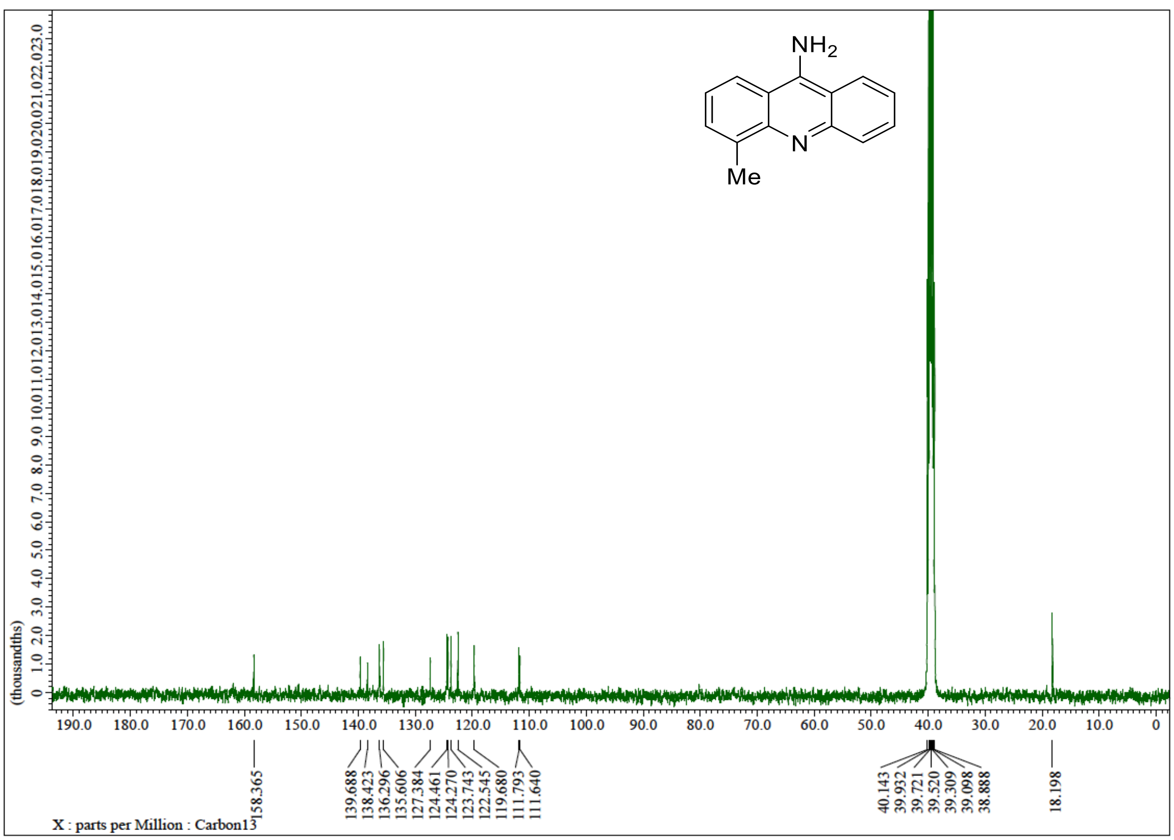
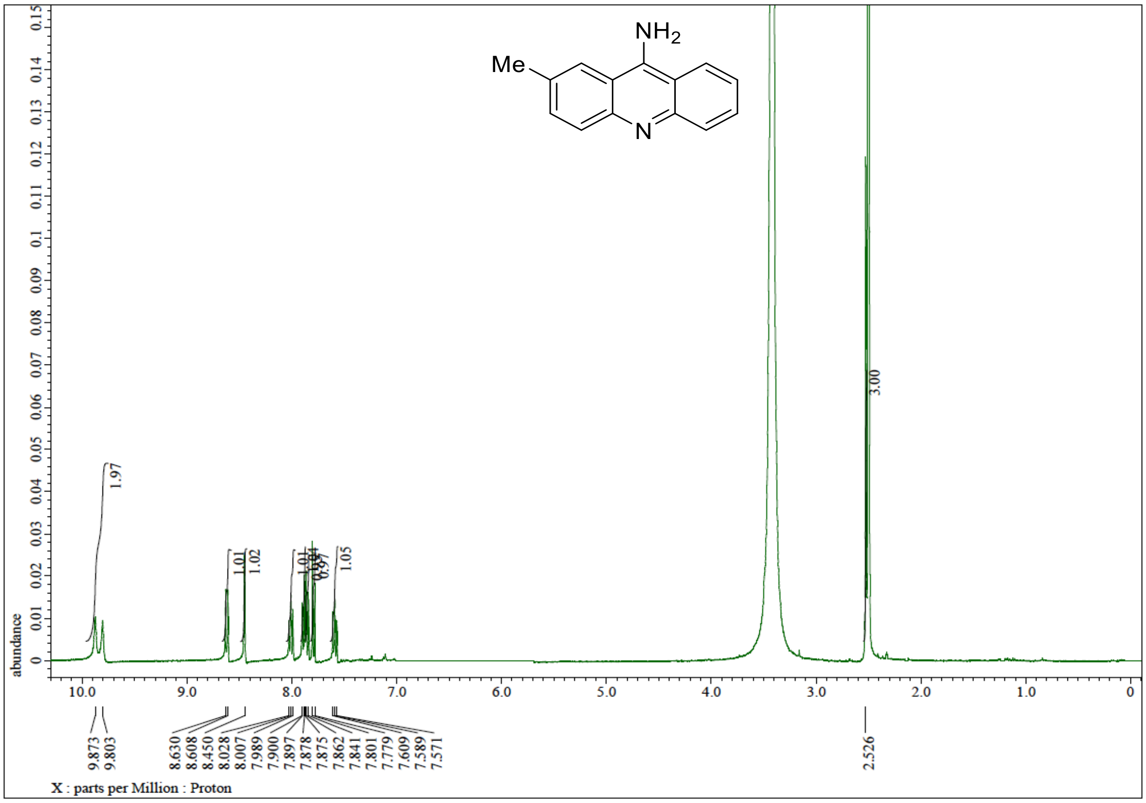


Figure S18: ^{1}H NMR of **5e** (400 MHz, DMSO-d_6) and ^{13}C NMR of **5e** (100 MHz, DMSO-d_6).



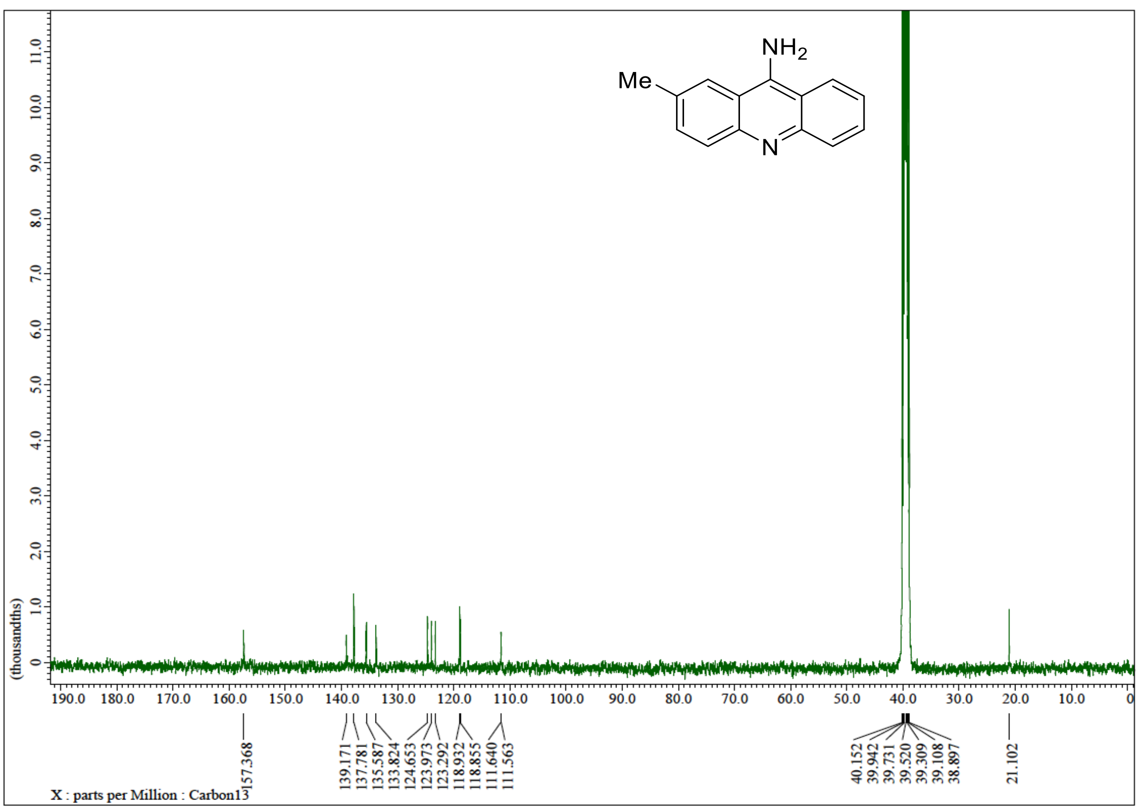
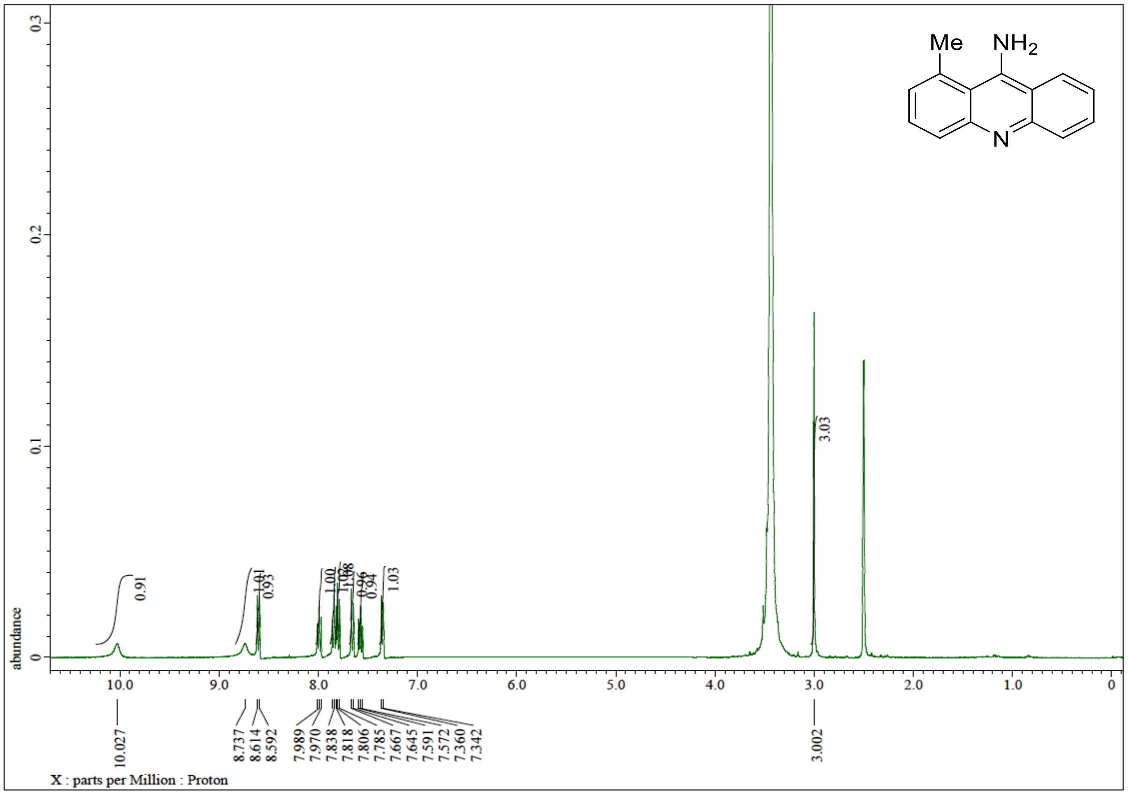


Figure S19: ^{1}H NMR of **5f** (400 MHz, DMSO-d_6) and ^{13}C NMR of **5f** (100 MHz, DMSO-d_6).



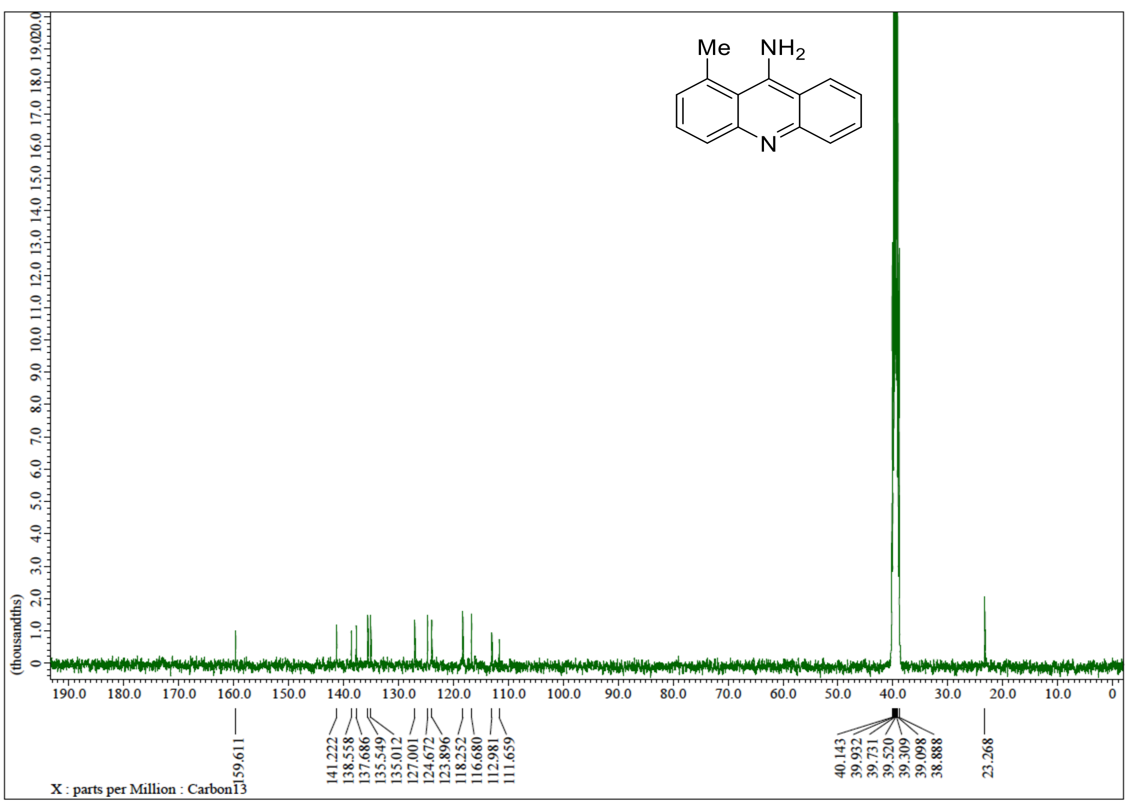
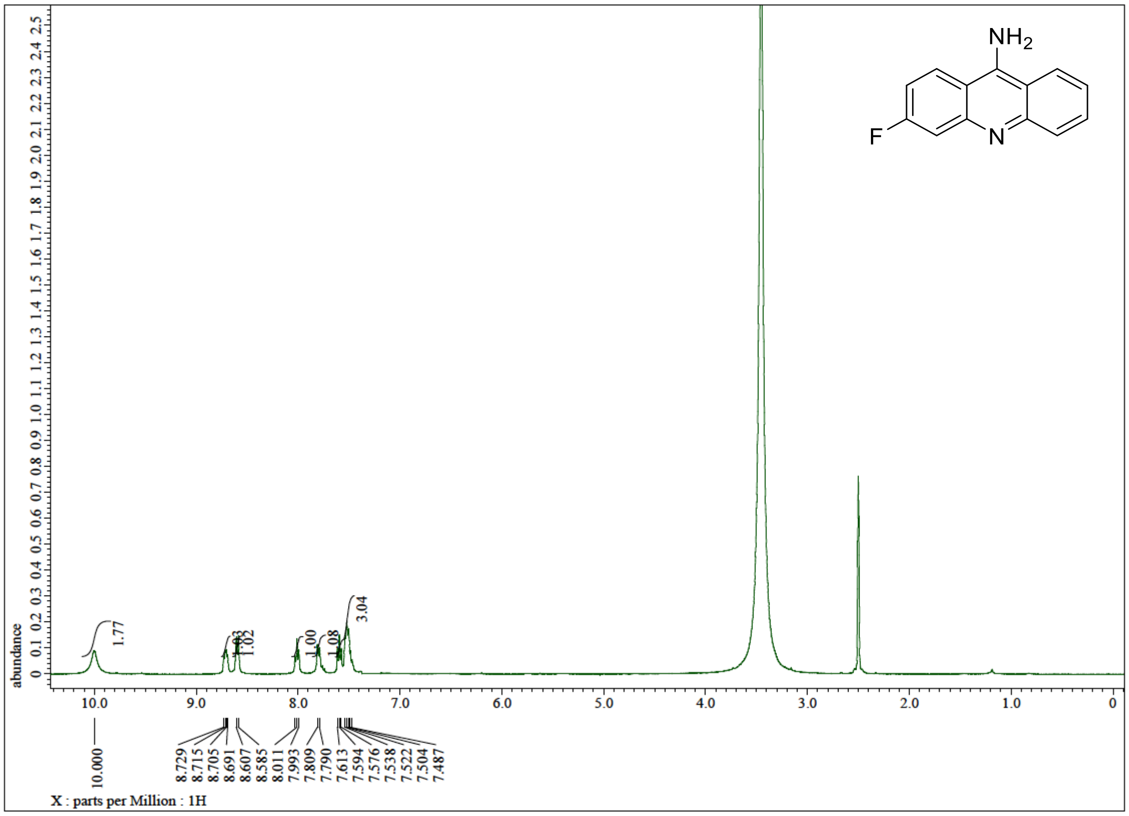


Figure S20: ^{1}H NMR of **5g** (400 MHz, DMSO-d$_6$) and ^{13}C NMR of **5g** (100 MHz, DMSO-d$_6$).



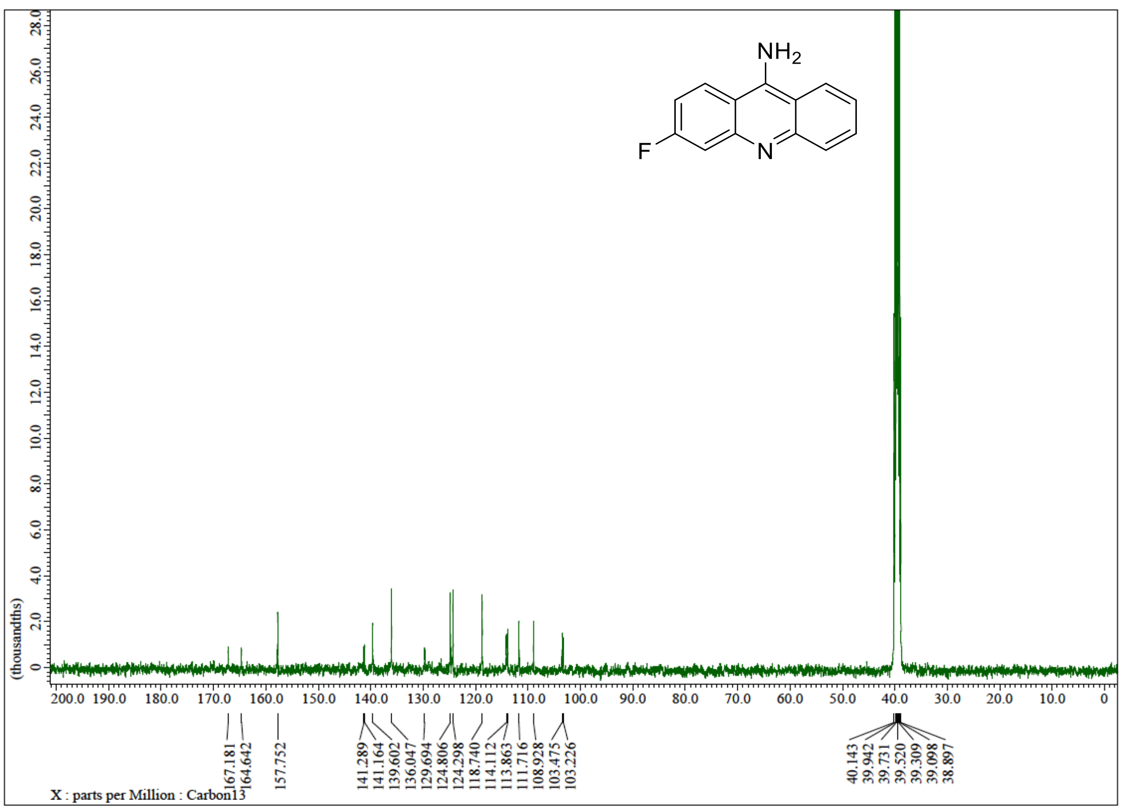
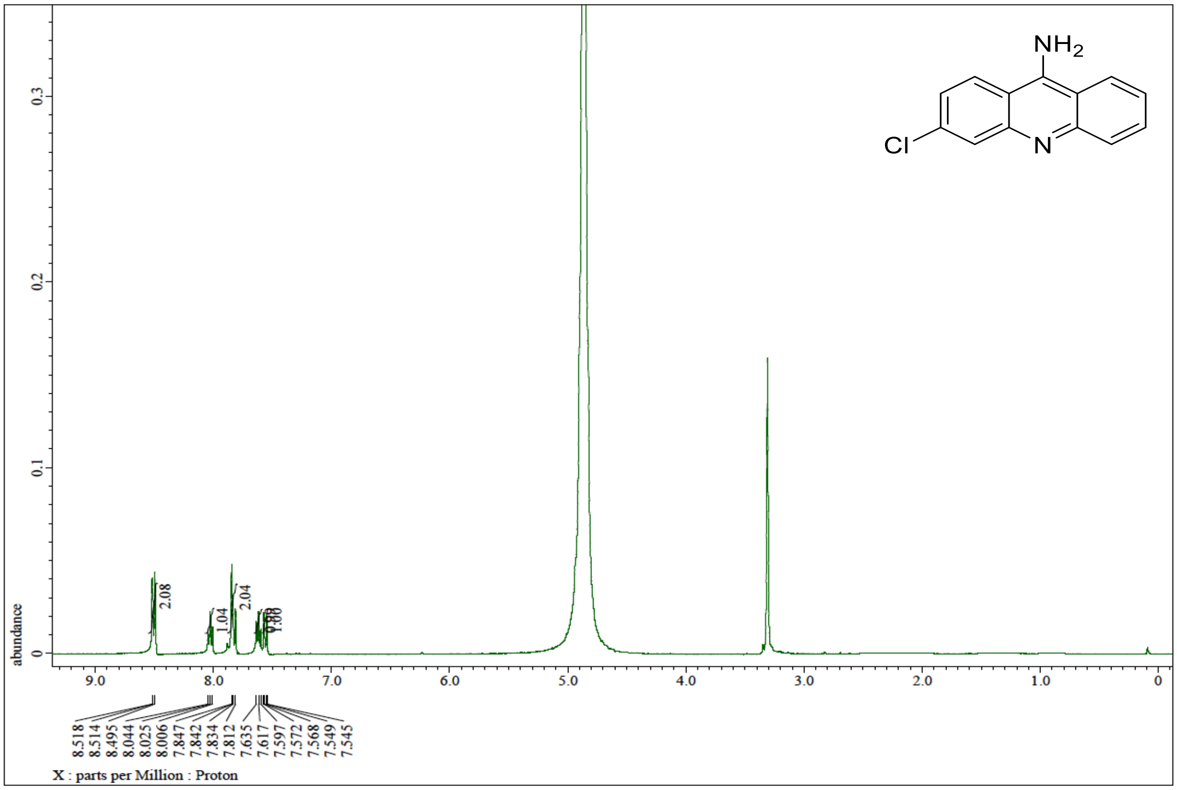


Figure S21: ^{1}H NMR of **5h** (400 MHz, DMSO-d$_6$) and ^{13}C NMR of **5h** (100 MHz, DMSO-d$_6$).



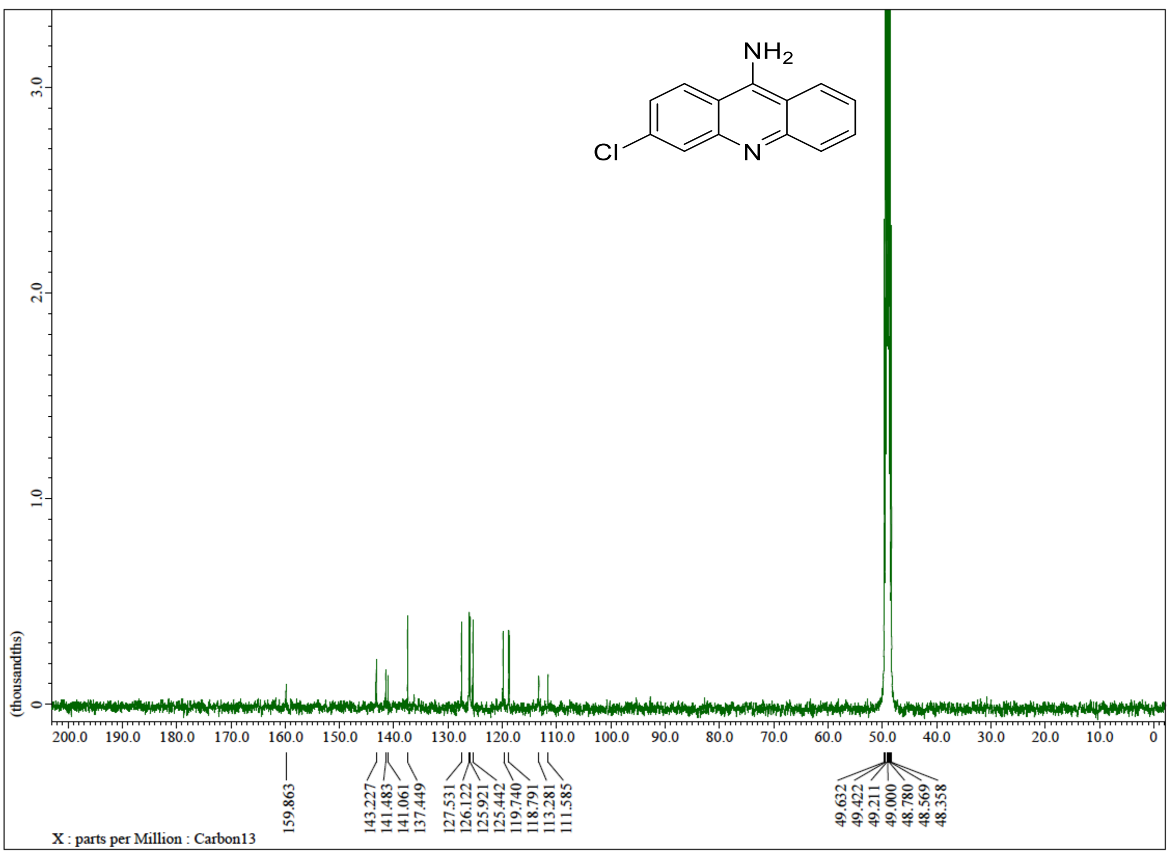
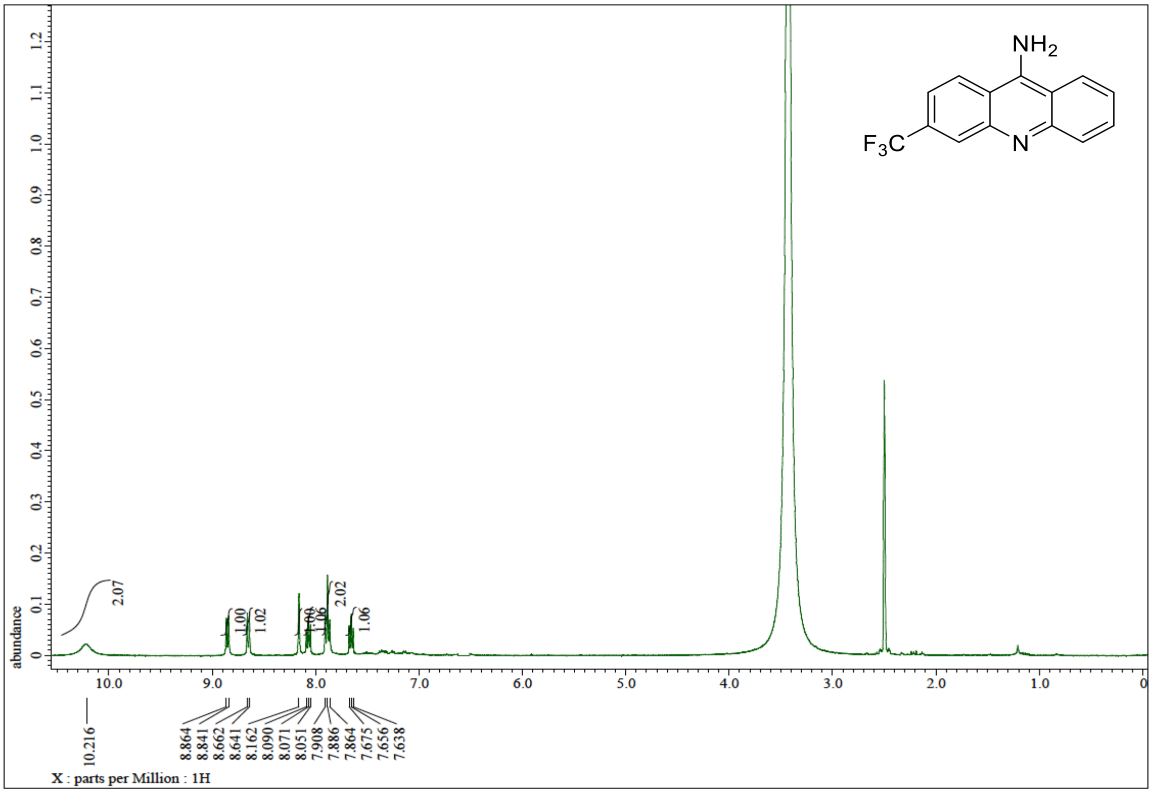


Figure S22: ^{1}H NMR of **5i** (400 MHz, CD_3OD) and ^{13}C NMR of **5i** (100 MHz, CD_3OD).



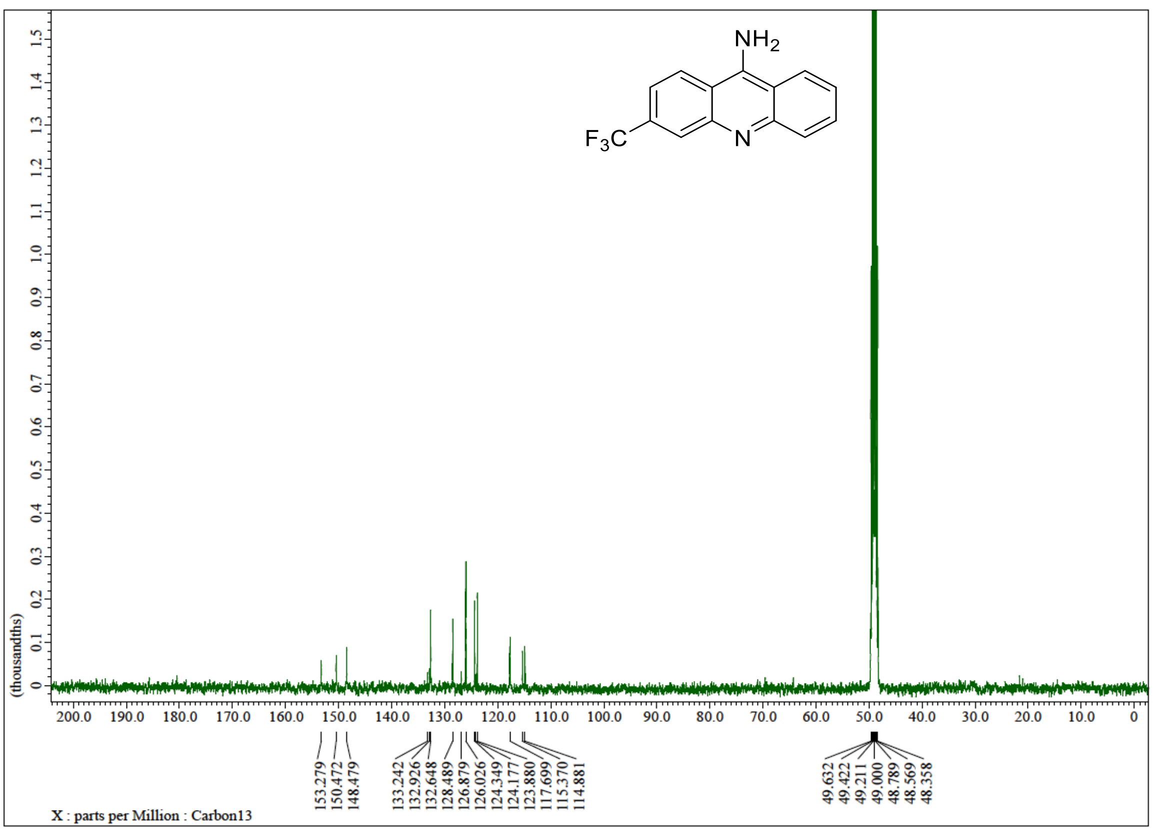
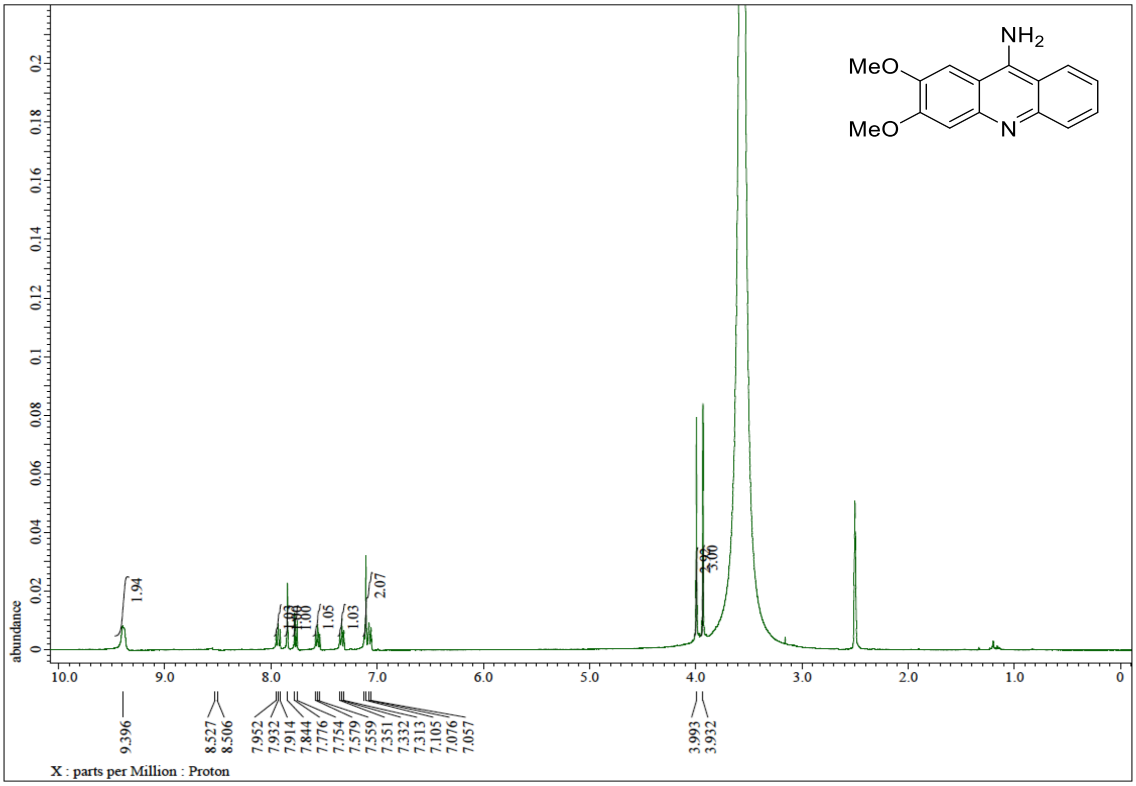


Figure S23: ^{1}H NMR of **5j** (400 MHz, DMSO-d_6) and ^{13}C NMR of **5j** (100 MHz, CD_3OD).



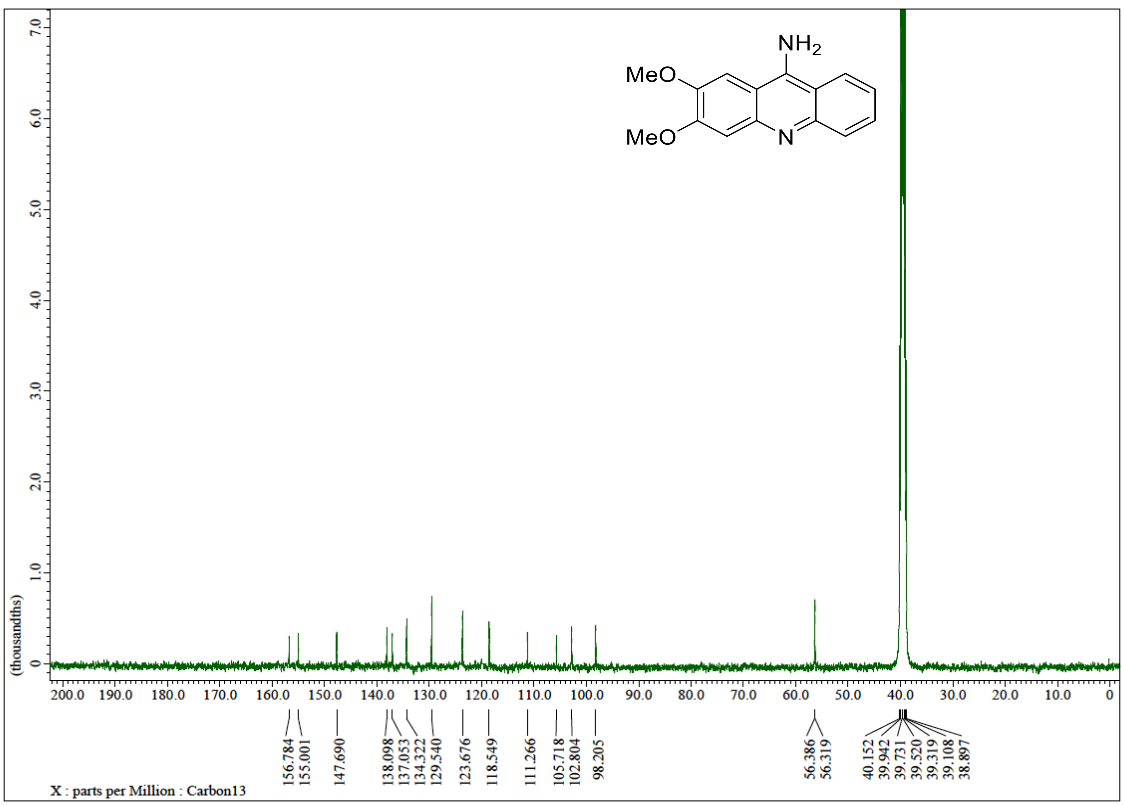
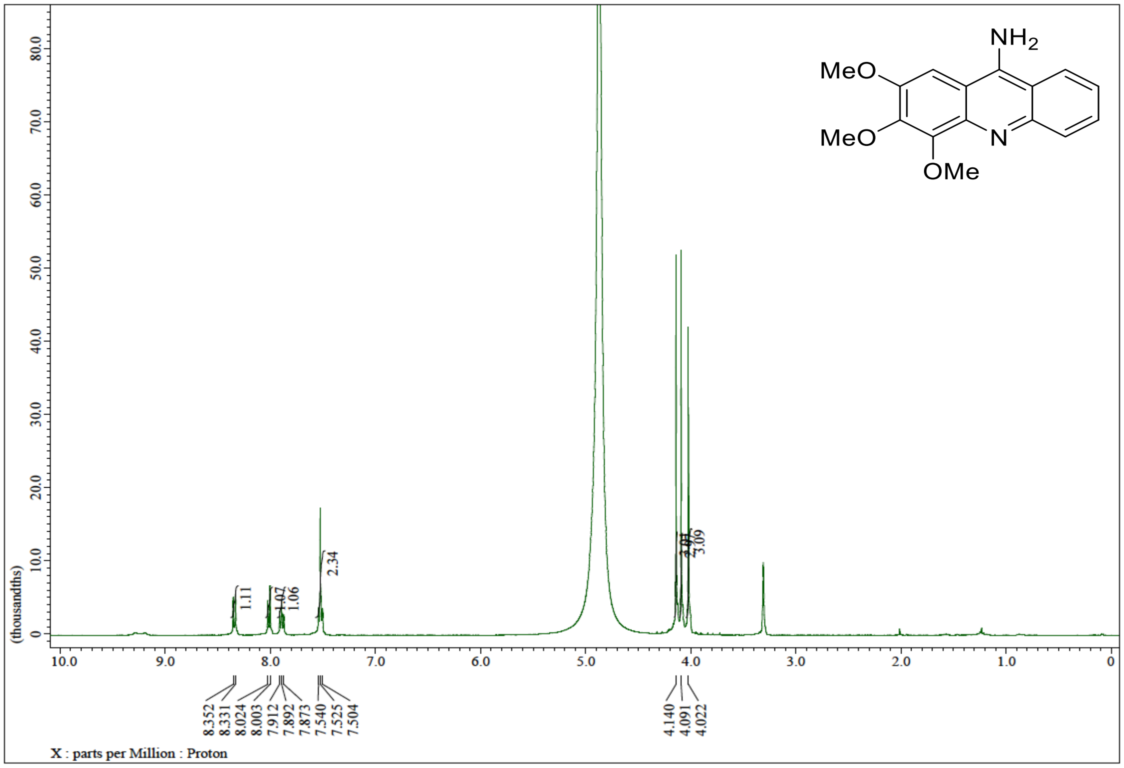


Figure S24: ^{1}H NMR of **5k** (400 MHz, DMSO-d_6) and ^{13}C NMR of **5k** (100 MHz, DMSO-d_6).



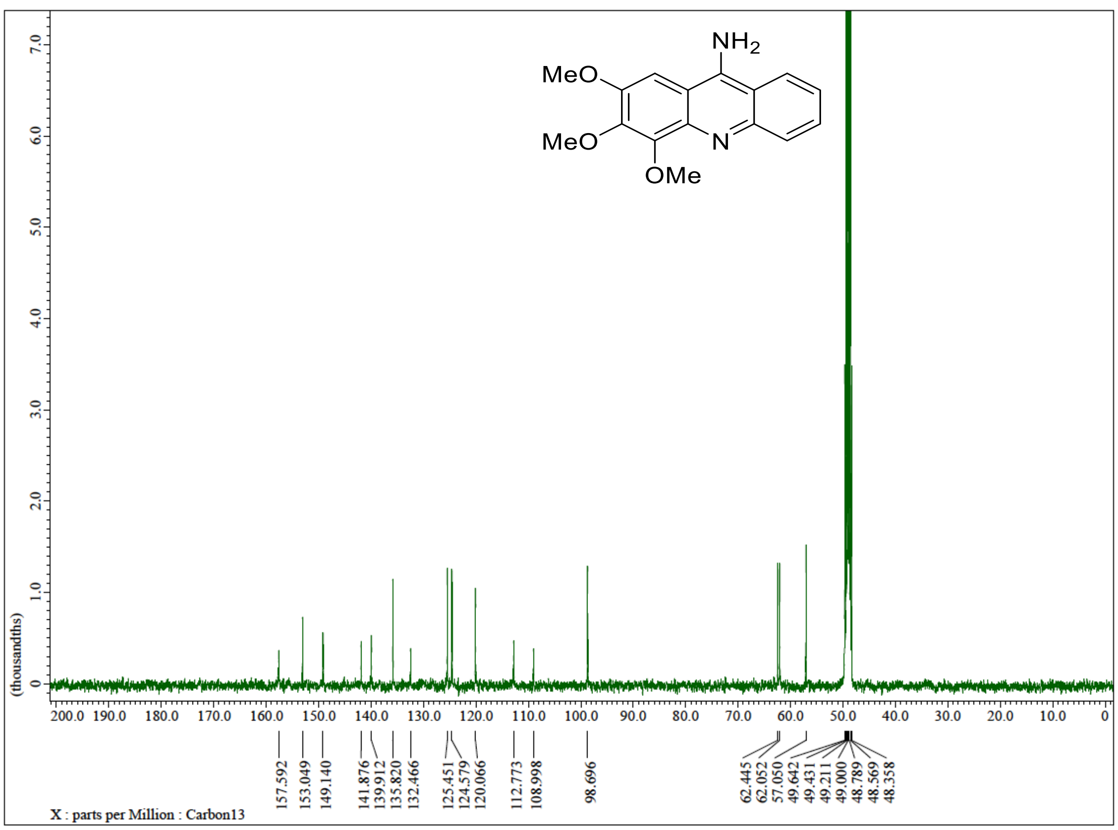
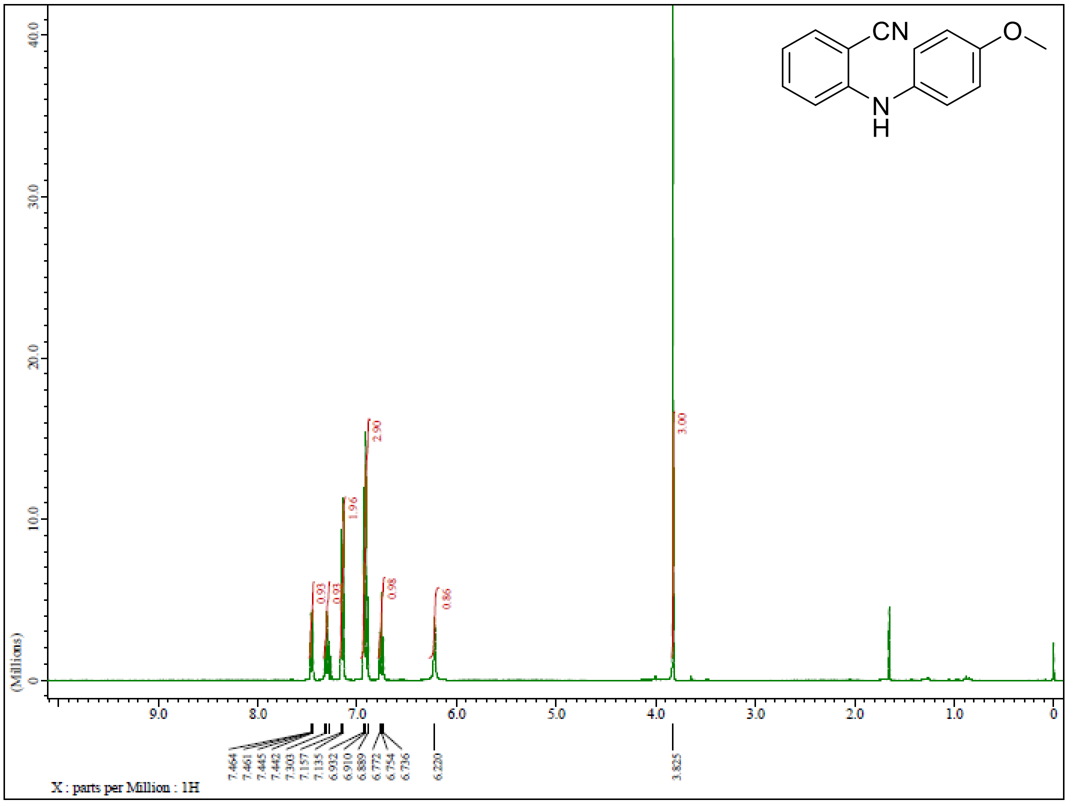


Figure S25: ^{1}H NMR of **5l** (400 MHz, CD_3OD) and ^{13}C NMR of **5l** (100 MHz, CD_3OD).



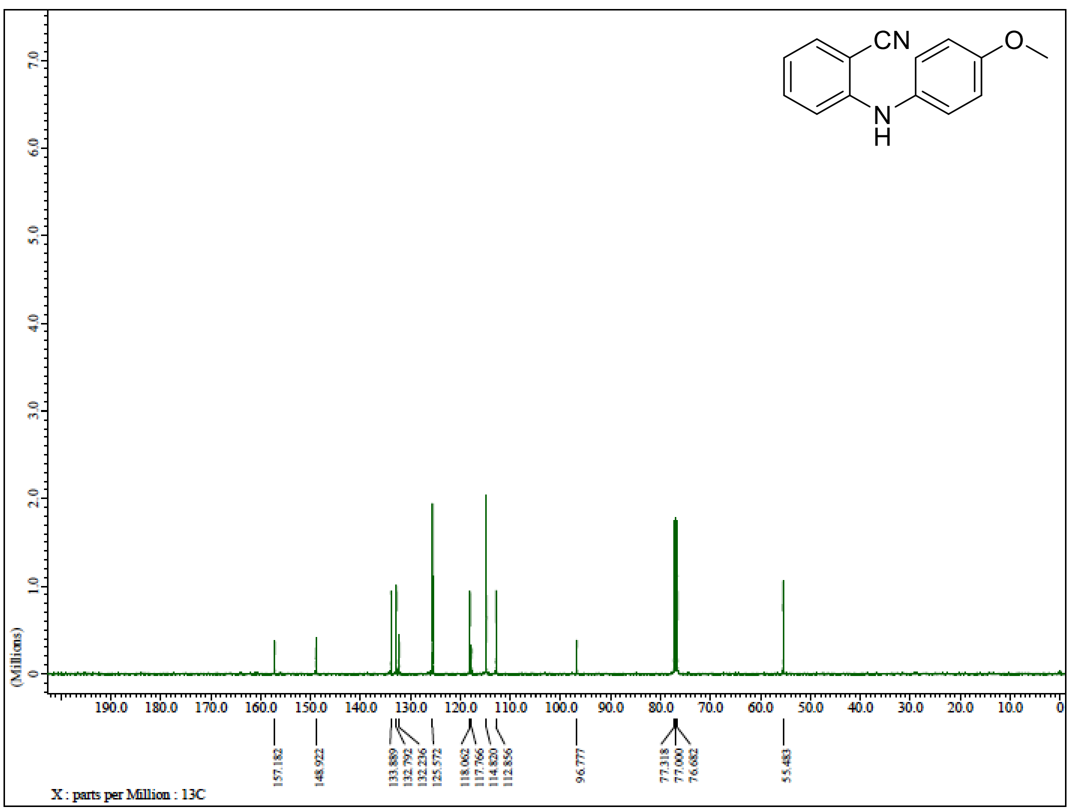
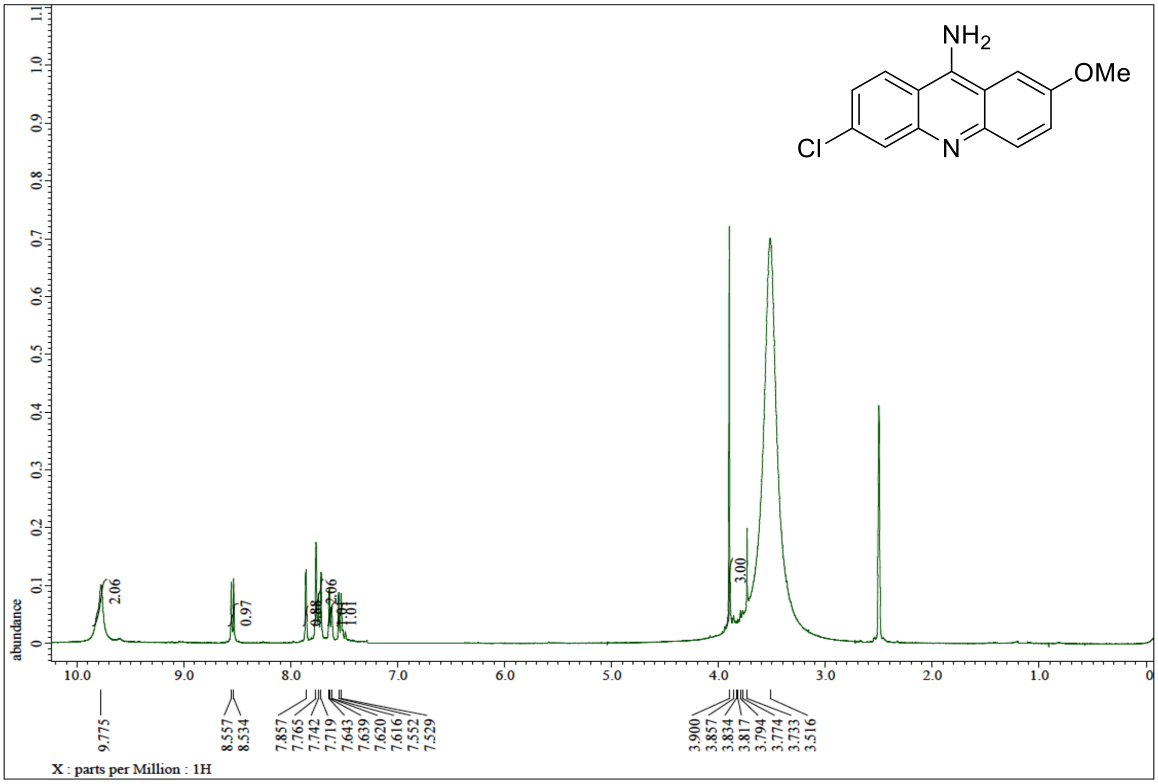


Figure S26: [1]H NMR of **3a** (400 MHz, $CDCl_3$) and [13]C NMR of **3a** (100 MHz, $CDCl_3$).



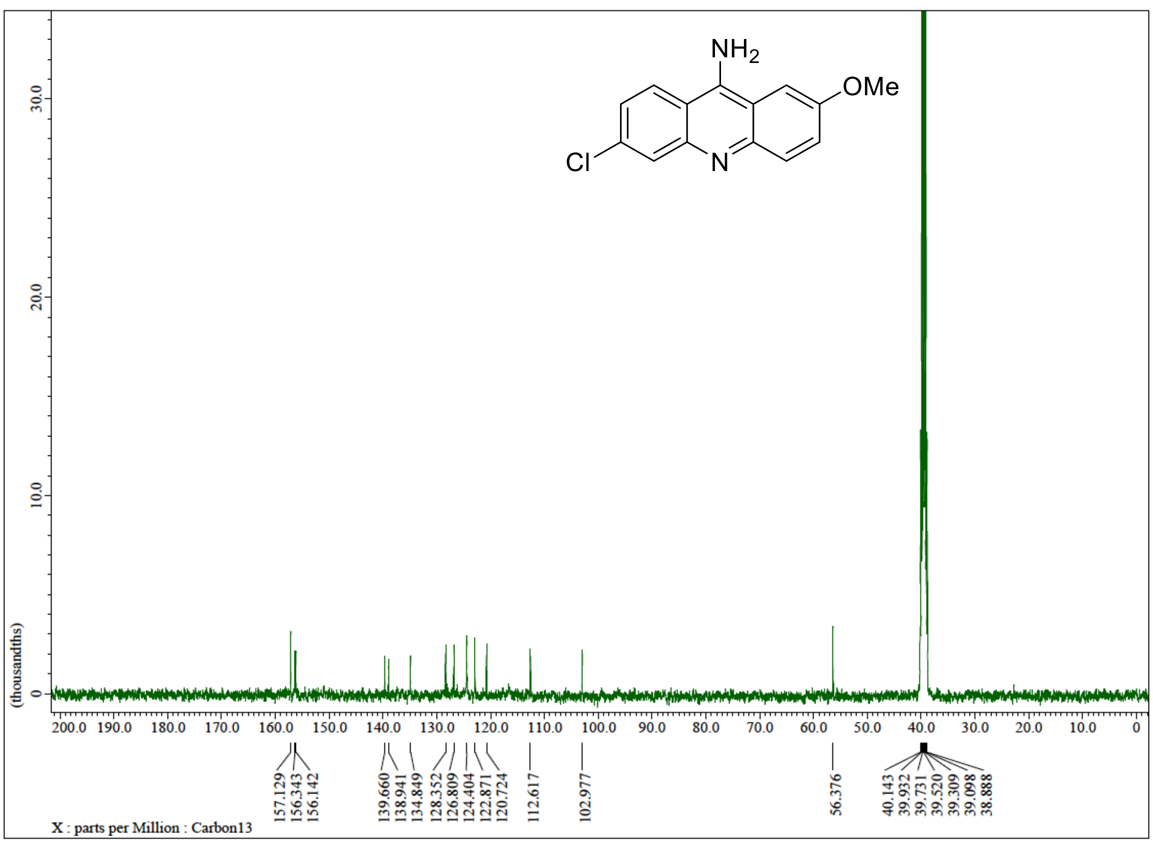
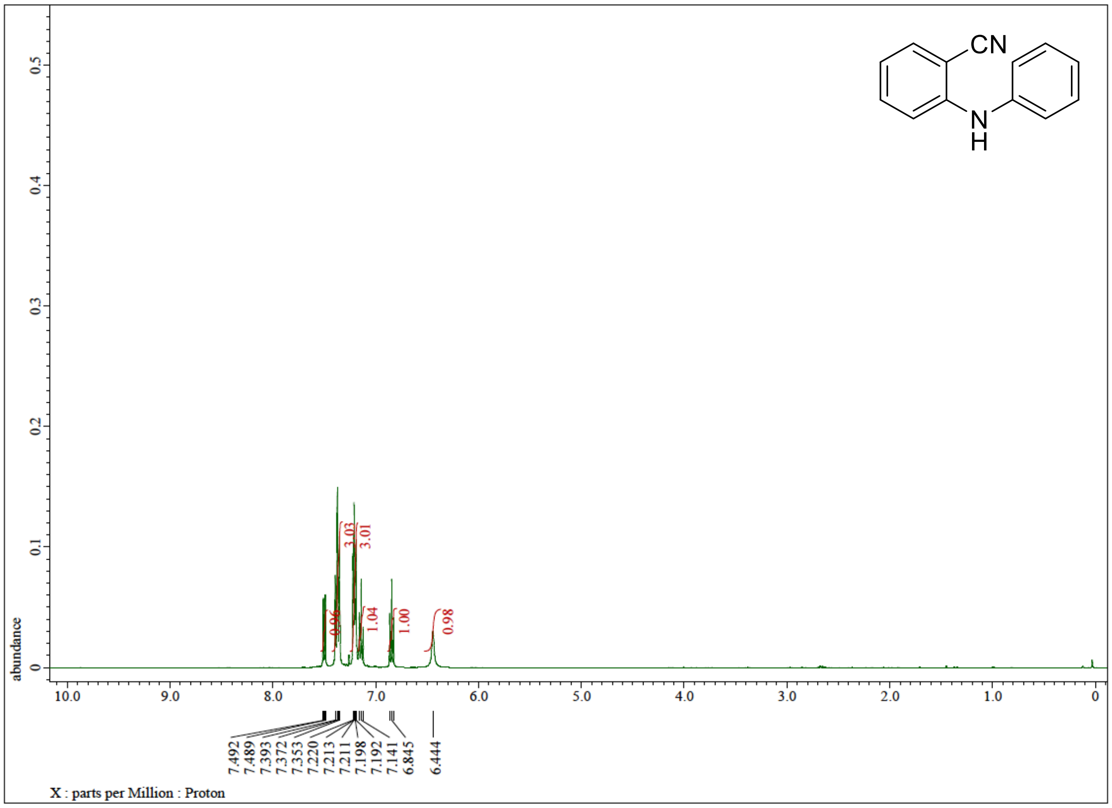


Figure S27: ^{1}H NMR of **6** (400 MHz, DMSO-d_6) and ^{13}C NMR of **6** (100 MHz, DMSO-d_6).



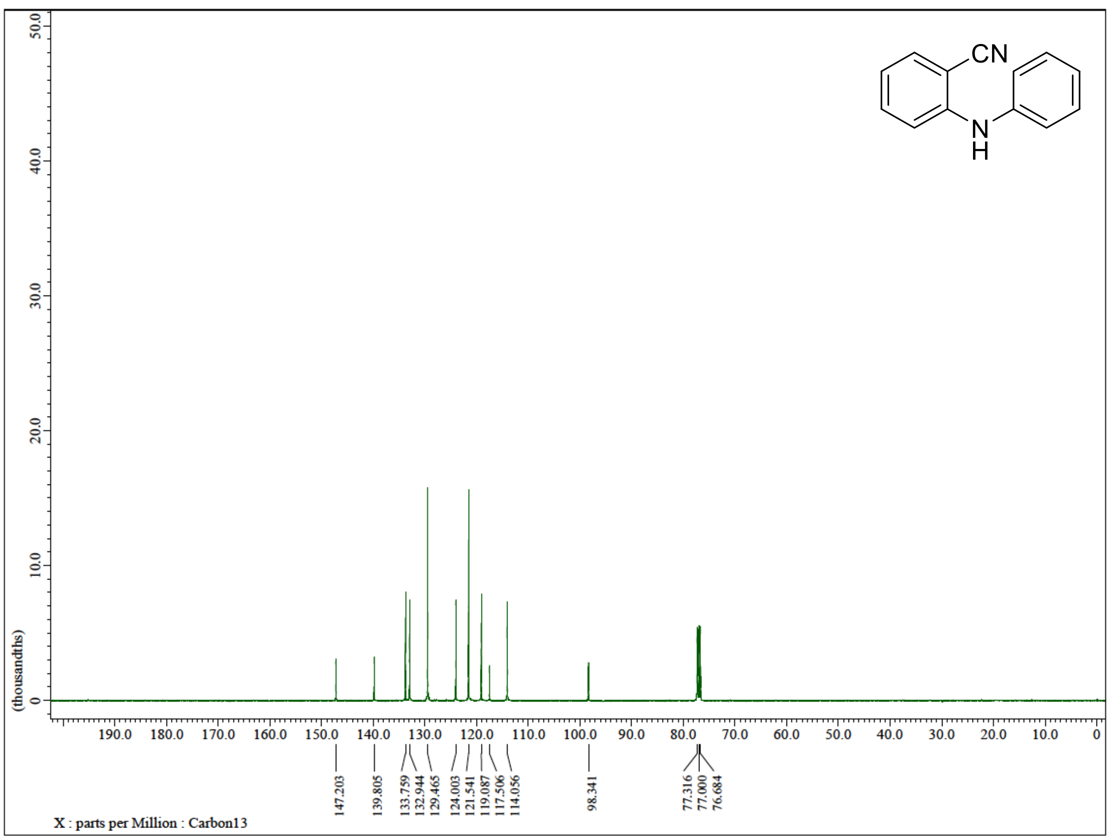
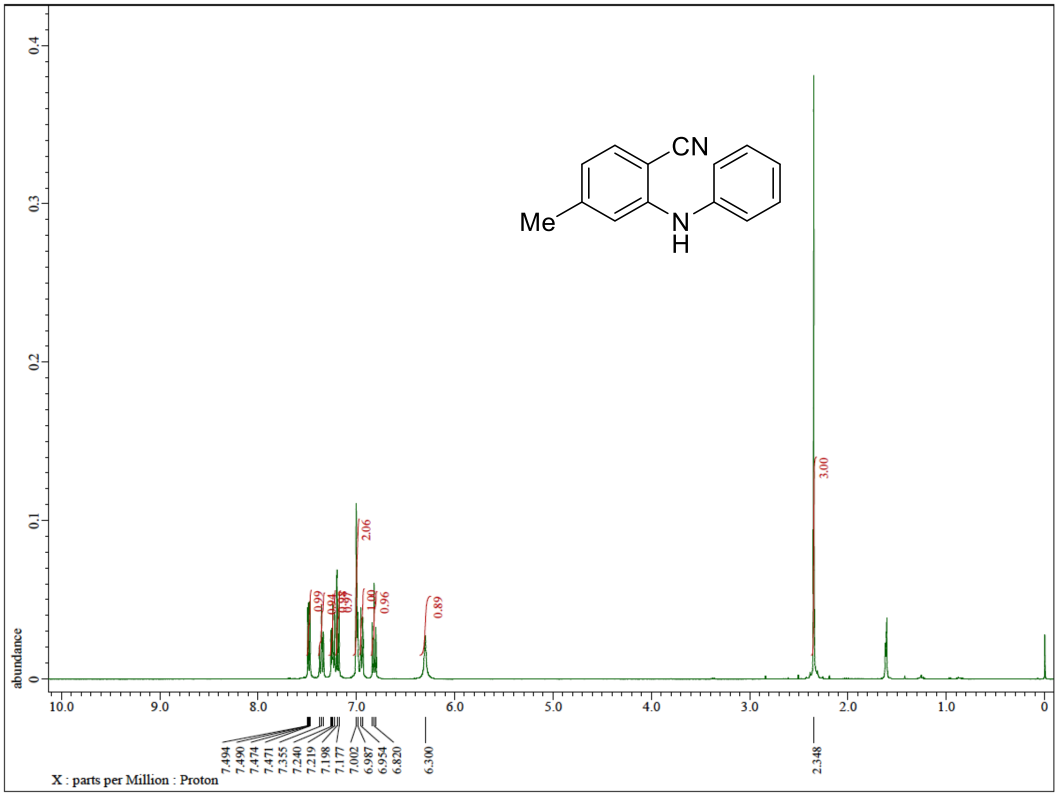


Figure S28: ^{1}H NMR of **7a** (400 MHz, $CDCl_3$) and ^{13}C NMR of **7a** (100 MHz, $CDCl_3$).



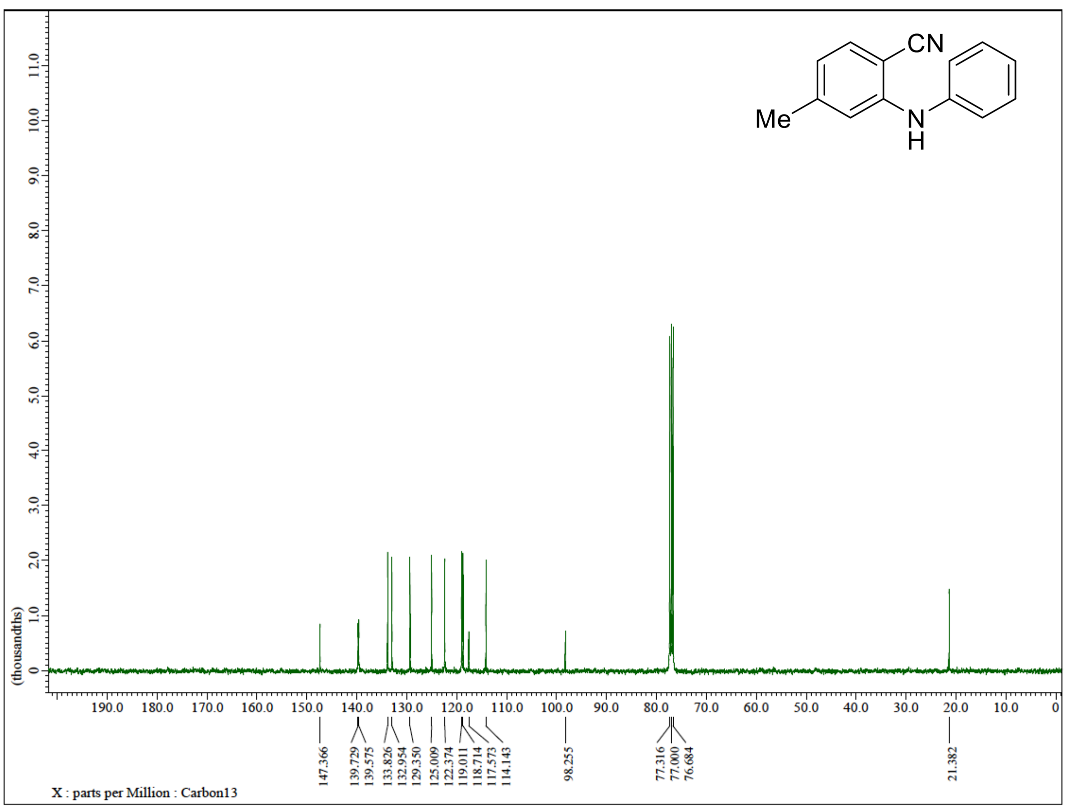


Figure S29: ^{1}H NMR of **7b** (400 MHz, $CDCl_3$) and ^{13}C NMR of **7b** (100 MHz, $CDCl_3$).

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