Synthesis of Novel Xanthone and Acridone Carboxamides with Potent Antiproliferative Activities

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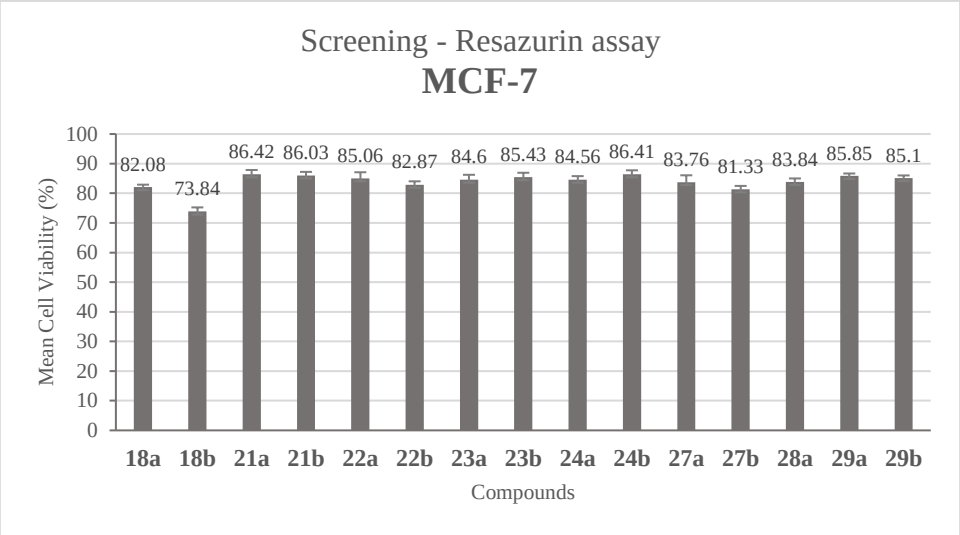
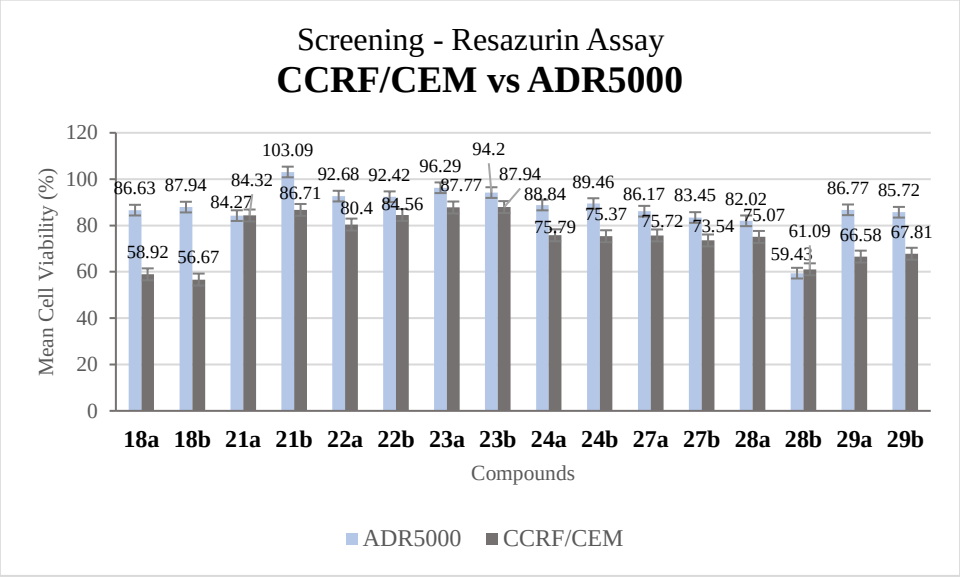


Figure S1: Bar-chart of the mean cell viability of target compounds against the MCF-7 cell line at 30 µM applied dose. Bars denote SEM values.



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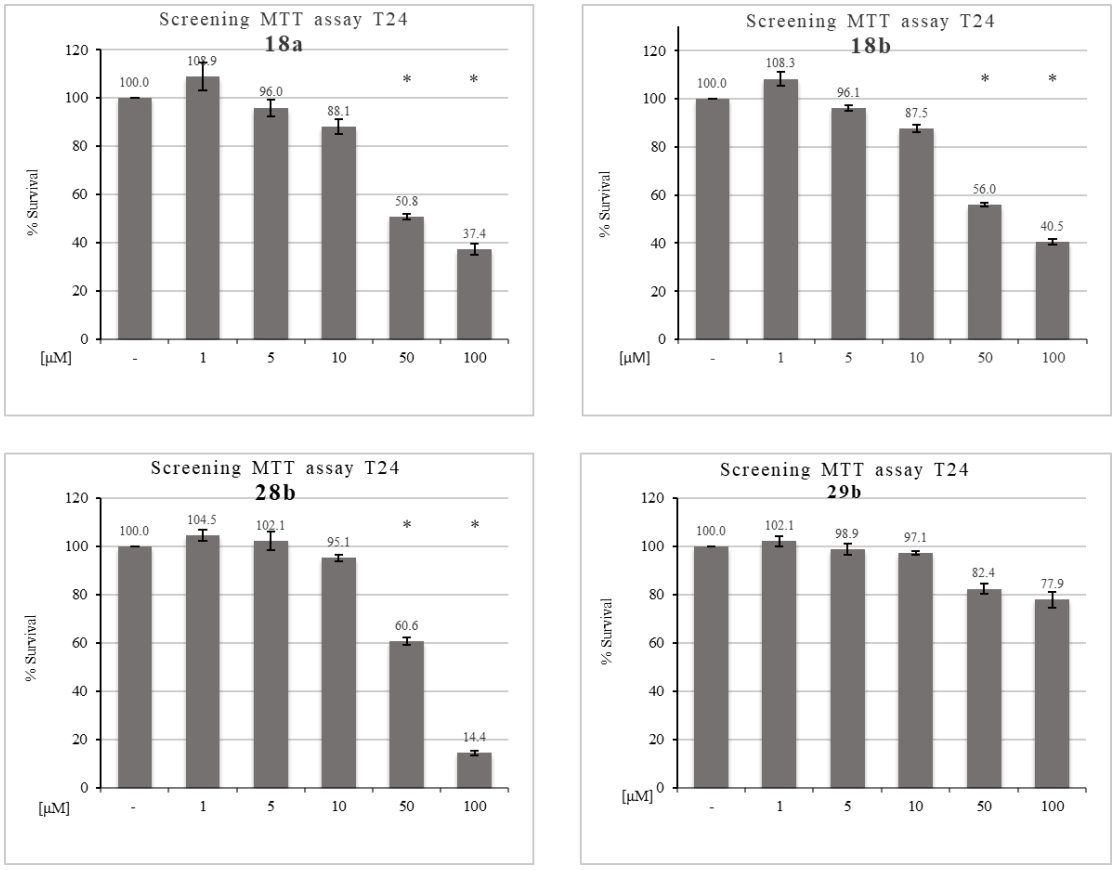


Figure S3: MTT cytotoxicity assays, demonstrating the dose-dependent cell death of T24 human cancer cells, in response to **18a**, **18b, 28b** and **29b** (in µM) for 24 h. Bars denote SD values.

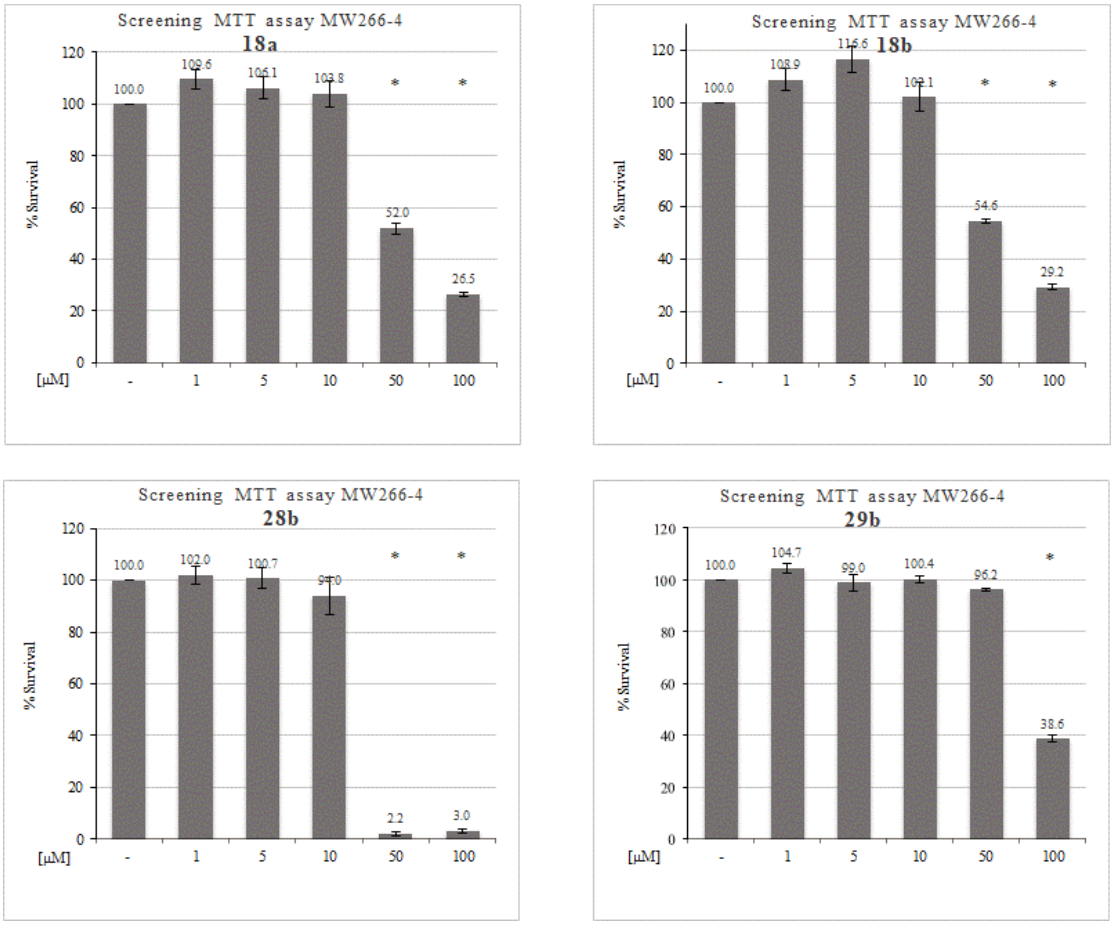


Figure S4: MTT cytotoxicity assays, demonstrating the dose-dependent cell death of MW266-4 human cancer cells, in response to **18a**, **18b**, **28b** and **29b** (in µM) for 24 h. Bars denote SD values.

^{1}H NMR and ^{13}C NMR spectrum

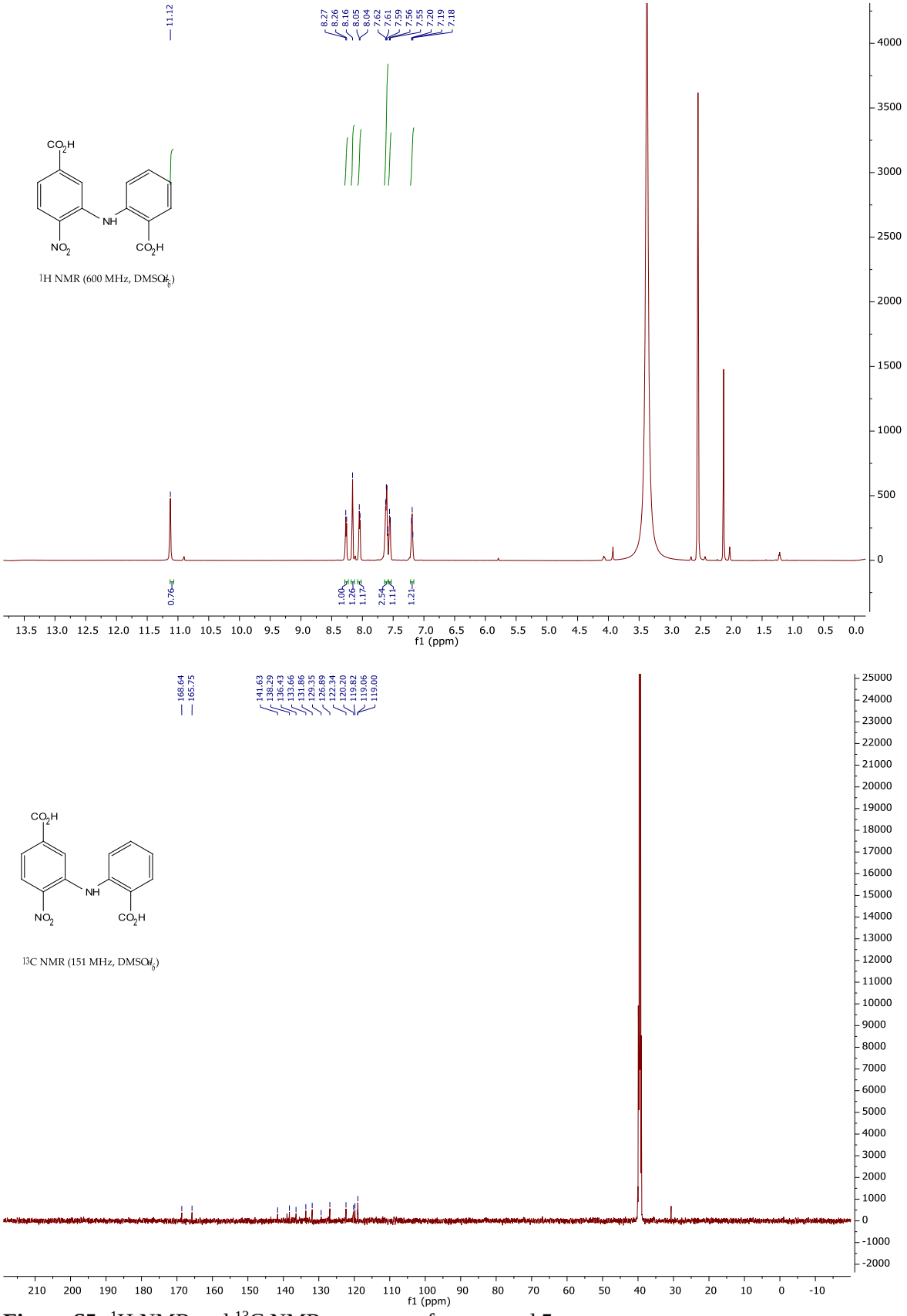


Figure S5: ^{1}H NMR and ^{13}C NMR spectrum of compound **5**.

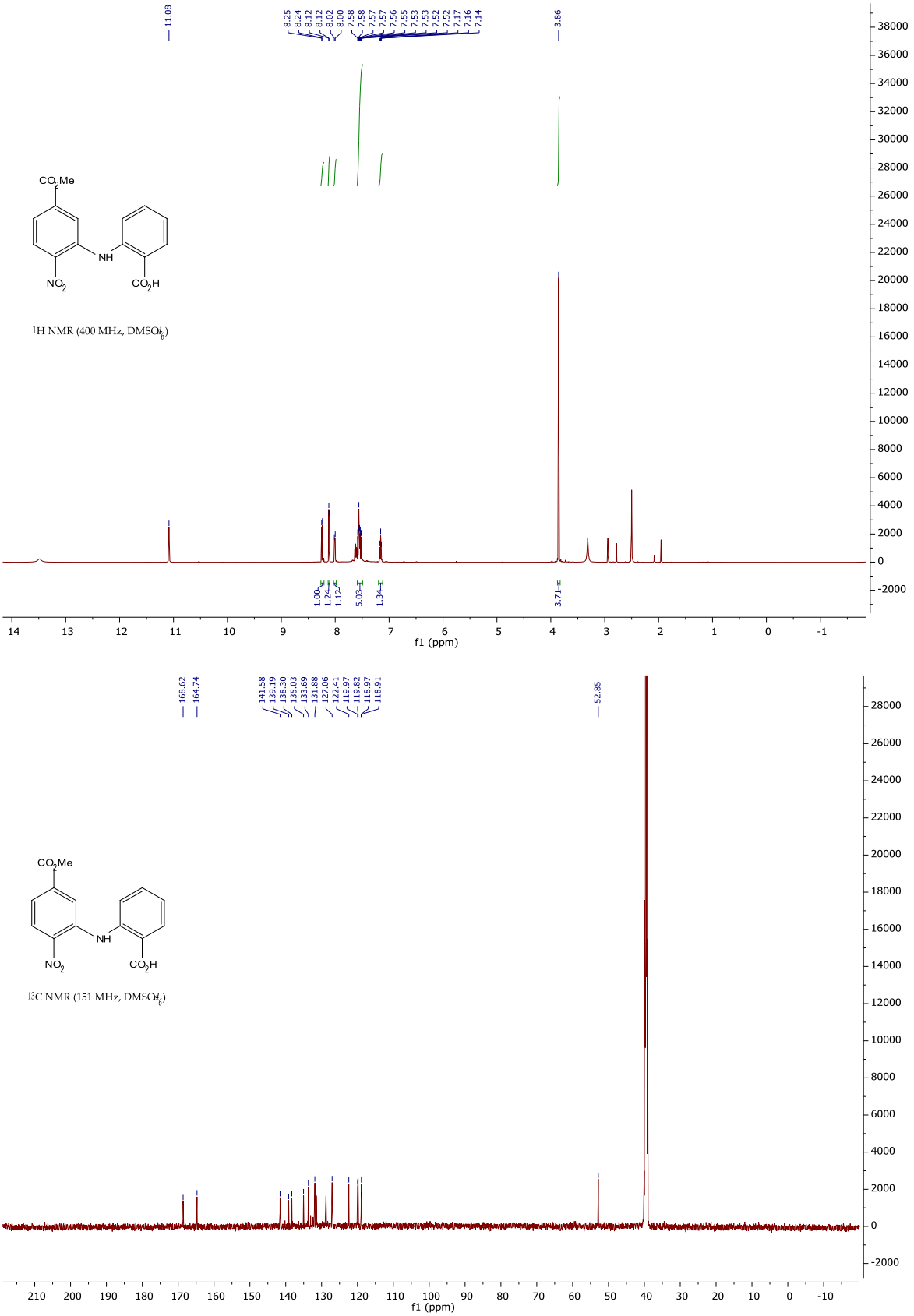


Figure S6: ^{1}H NMR and ^{13}C NMR spectrum of compound **6**.

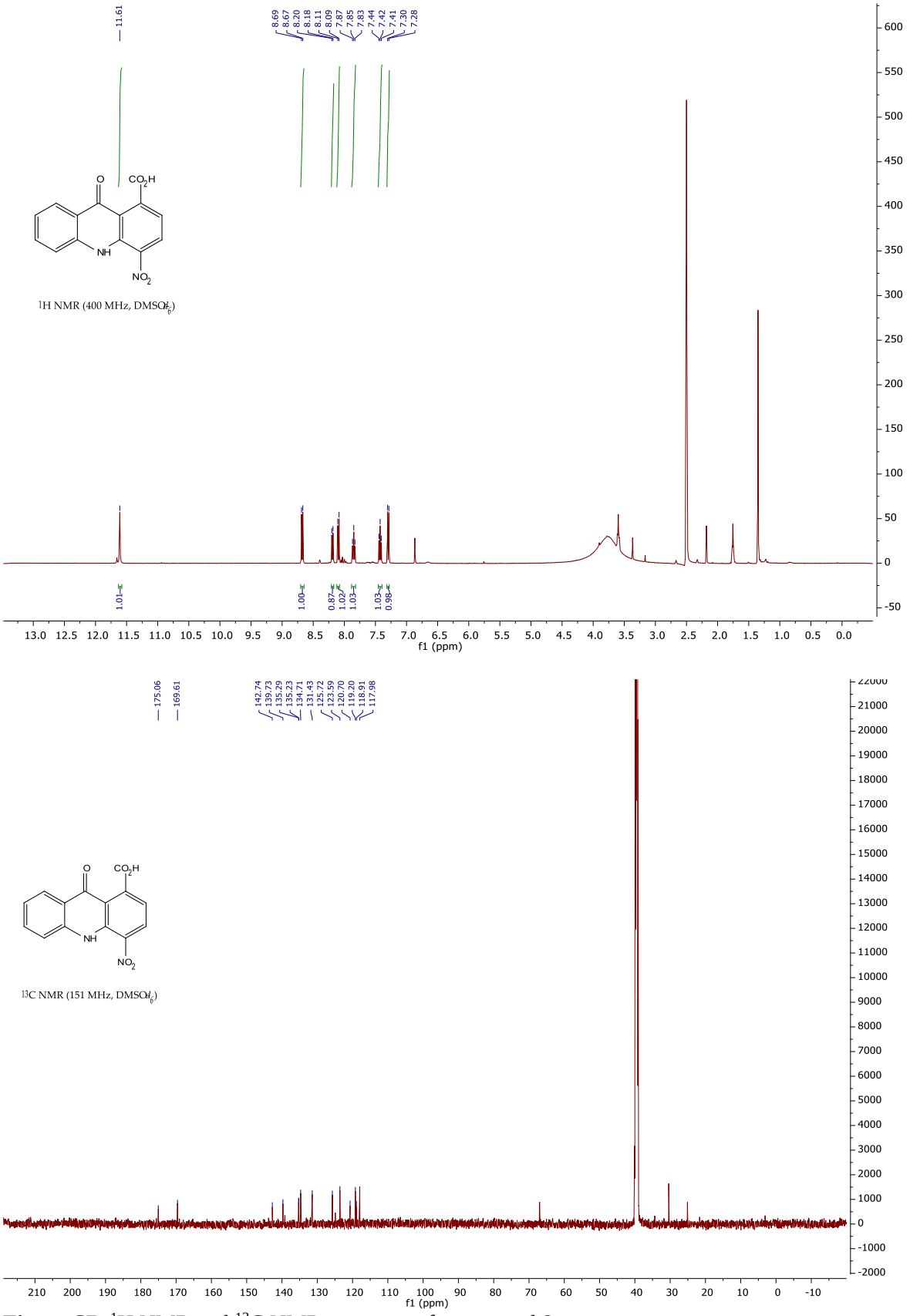
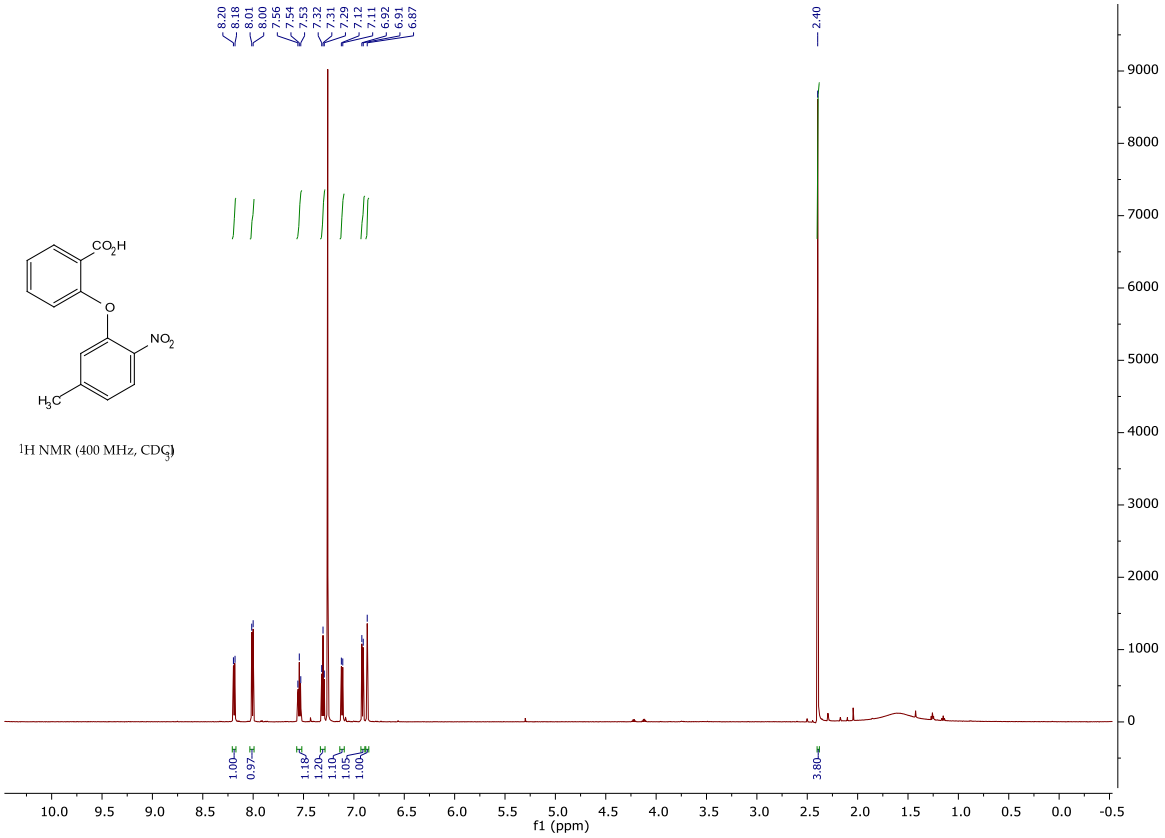


Figure S7: ^{1}H NMR and ^{13}C NMR spectrum of compound **8**.



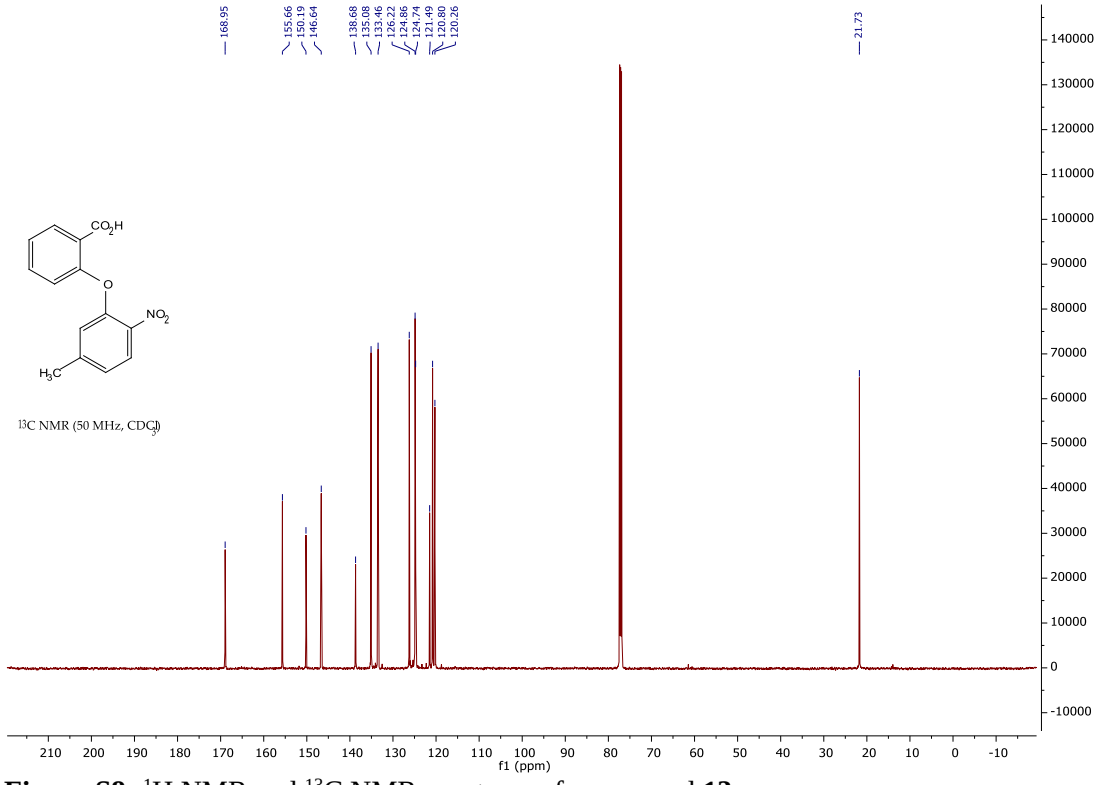


Figure S8: ^{1}H NMR and ^{13}C NMR spectrum of compound **13**.

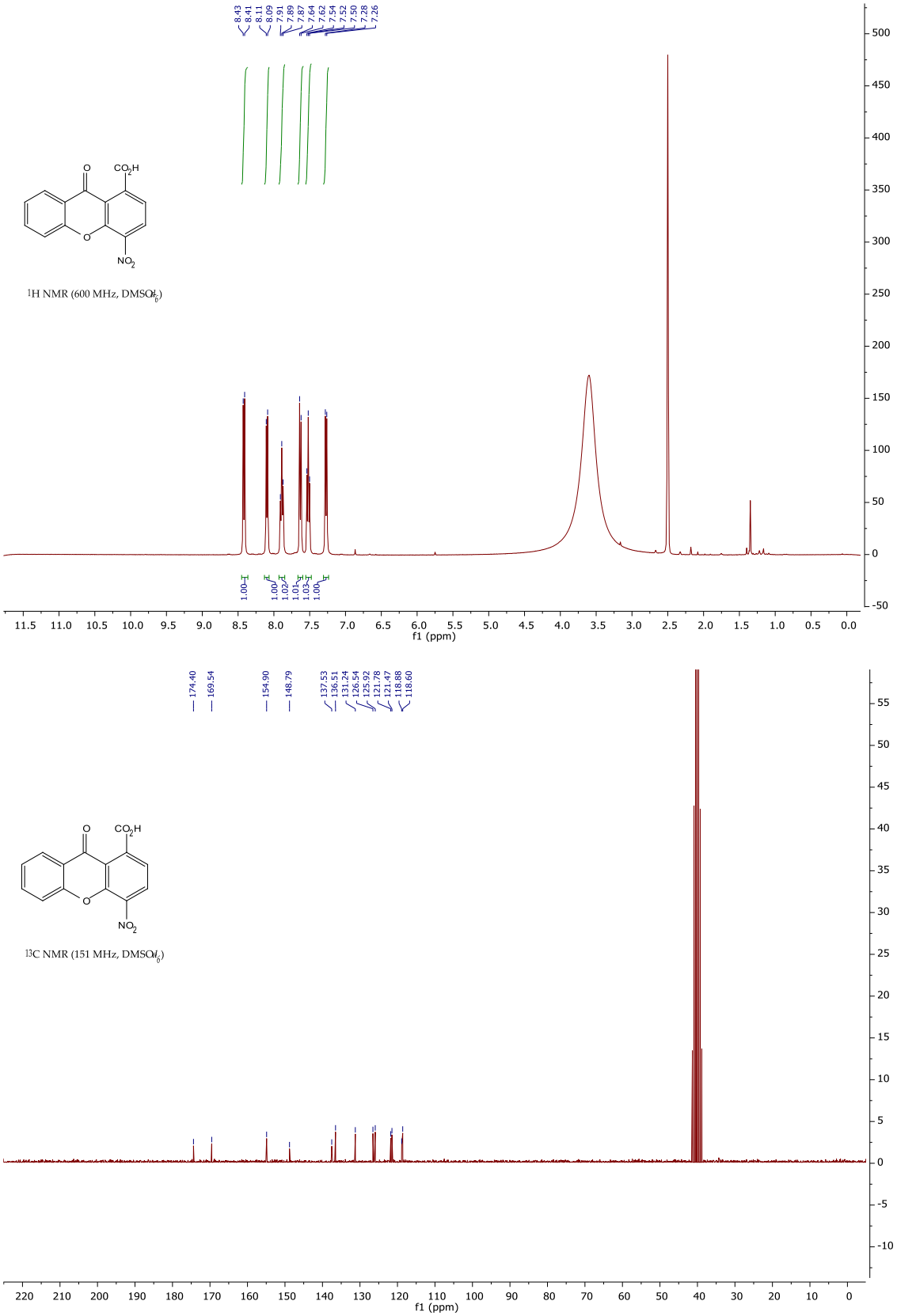
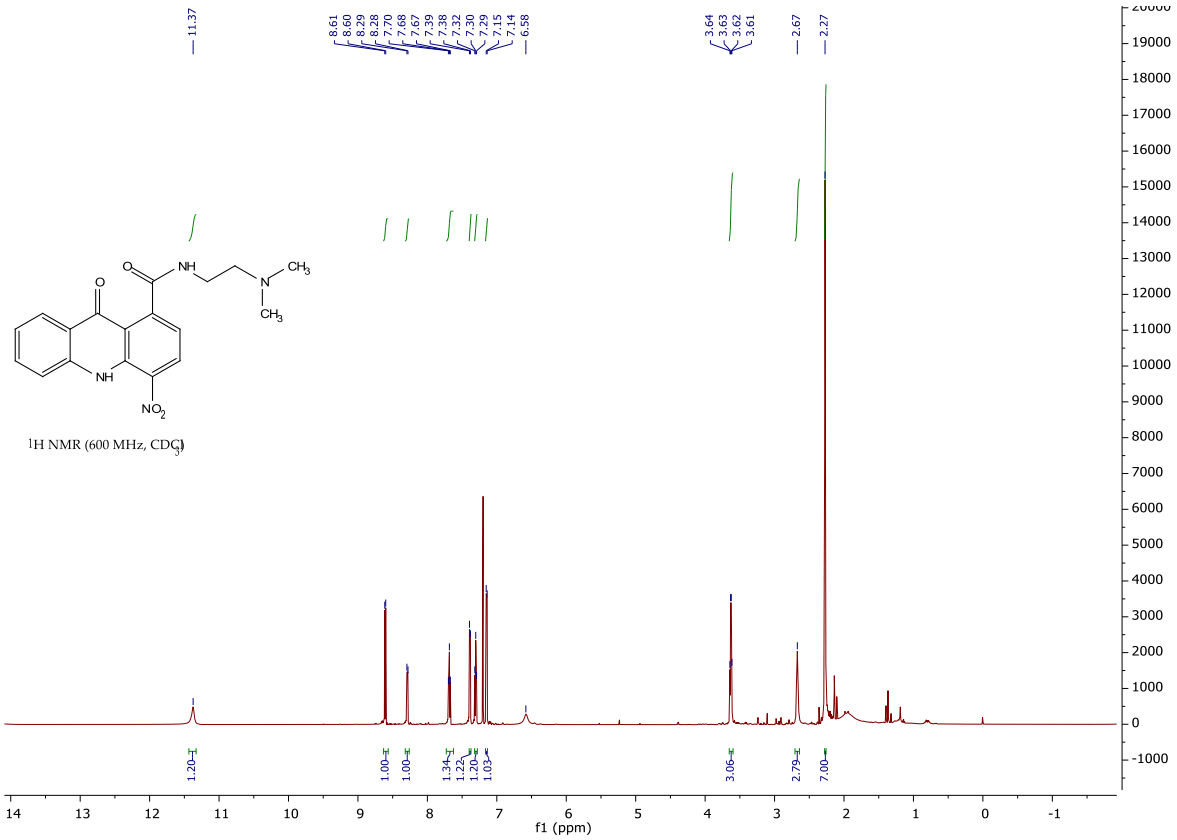
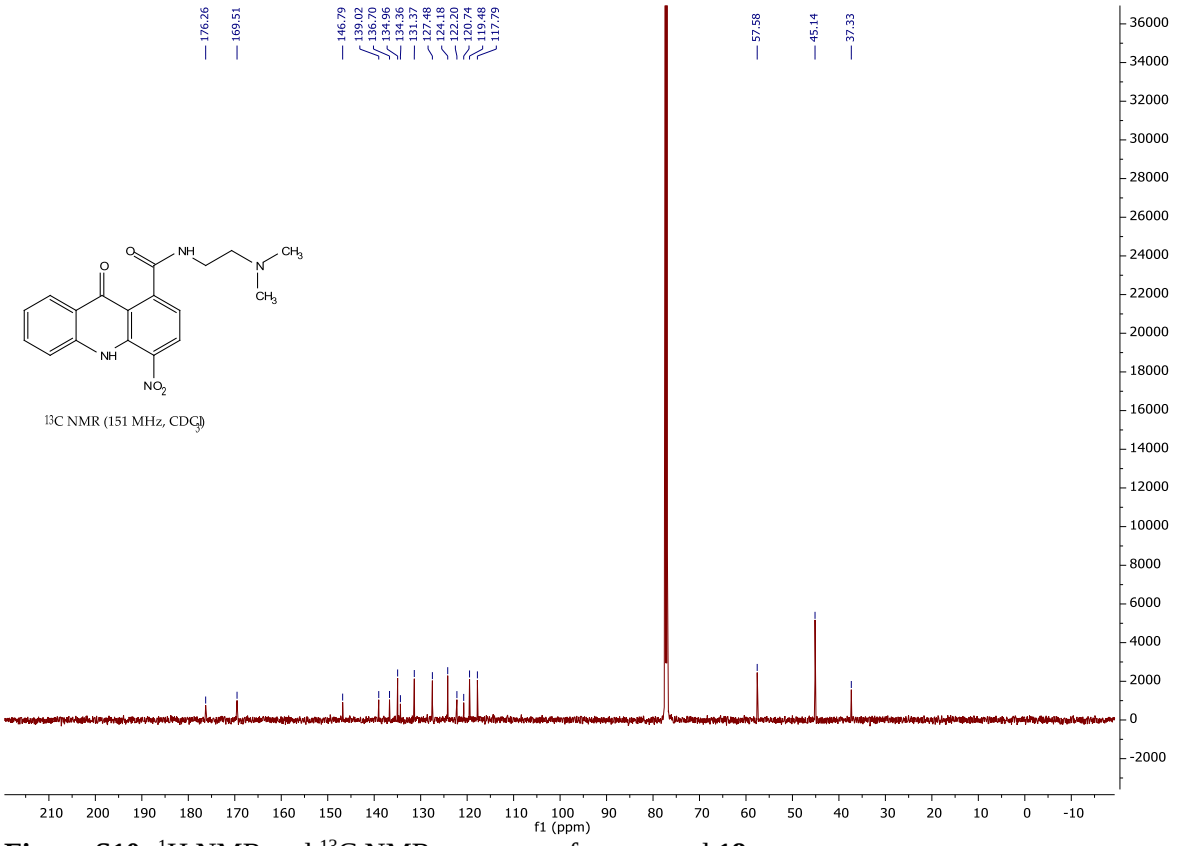


Figure S9: ^{1}H NMR and ^{13}C NMR spectrum of compound **17**.

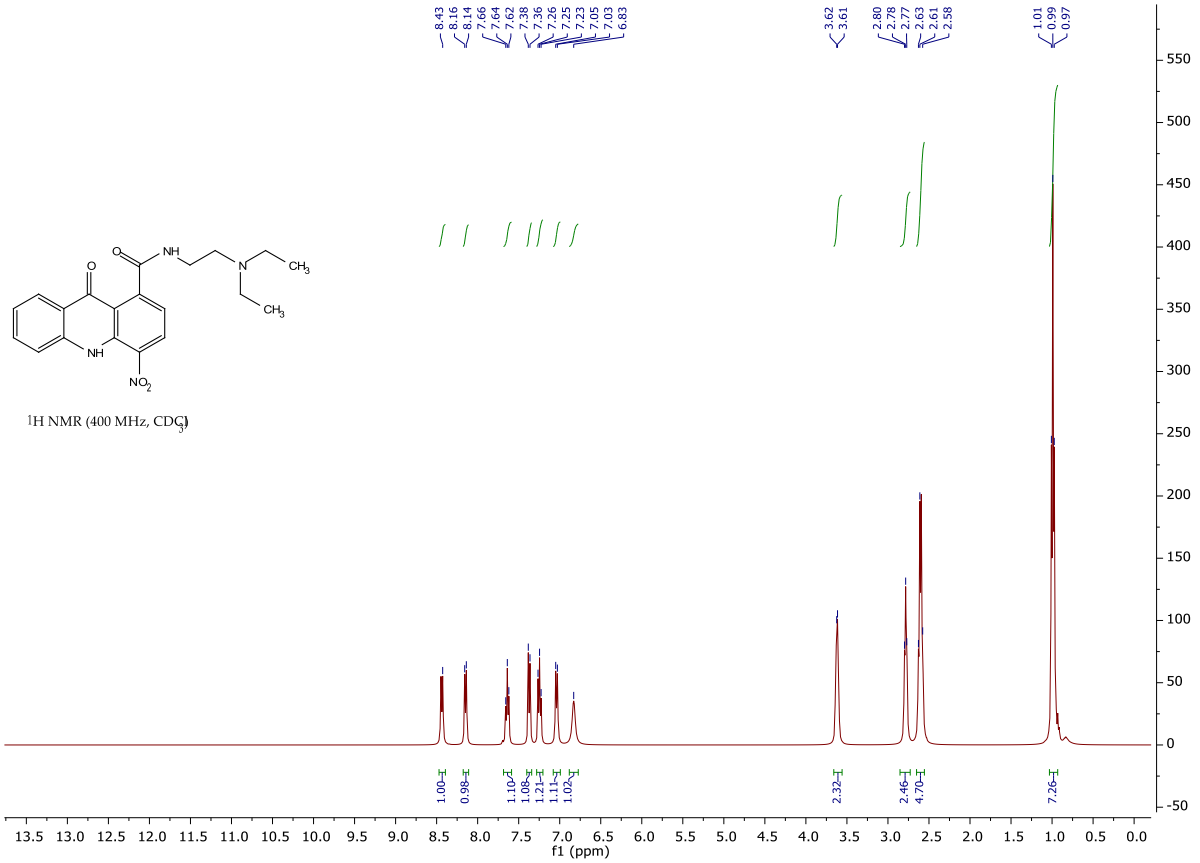


^{1}H NMR (600 MHz, $CDCl_3$)

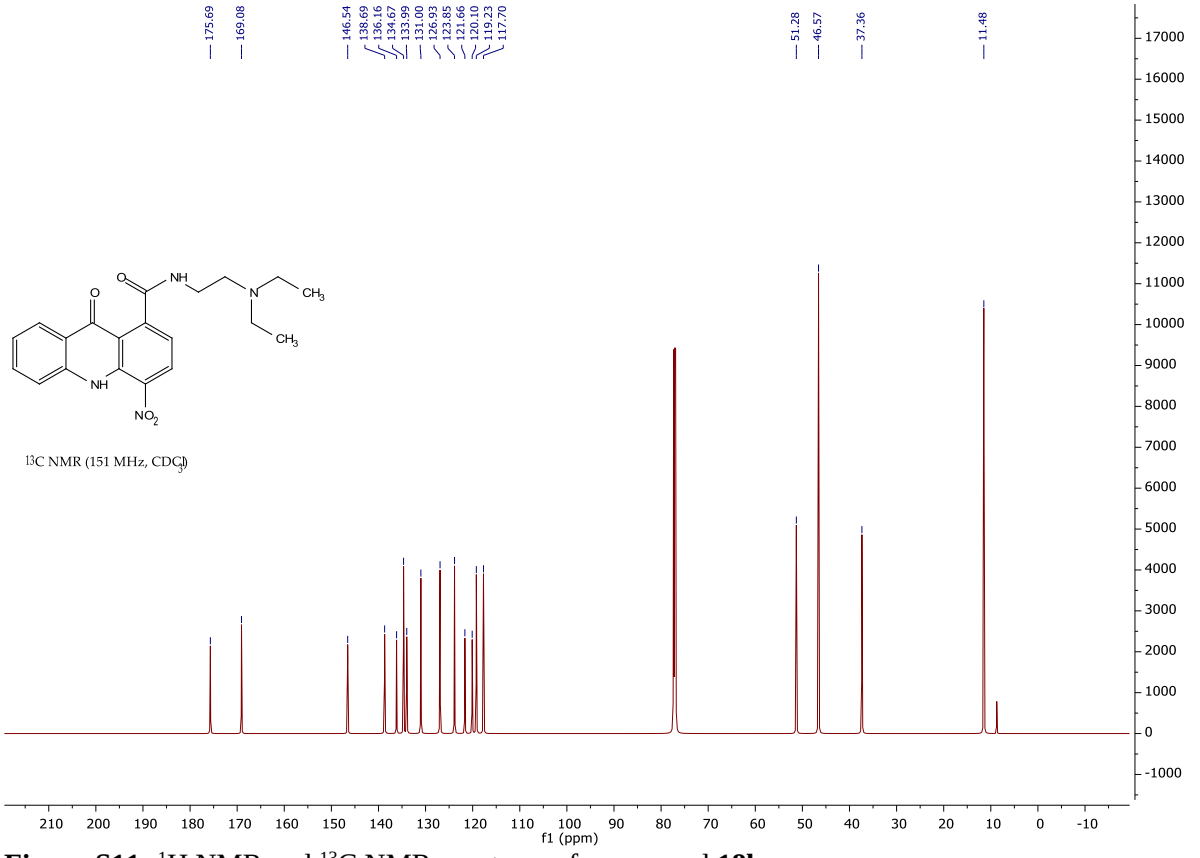


^{13}C NMR (151 MHz, $CDCl_3$)

Figure S10: ^{1}H NMR and ^{13}C NMR spectrum of compound **18a**.

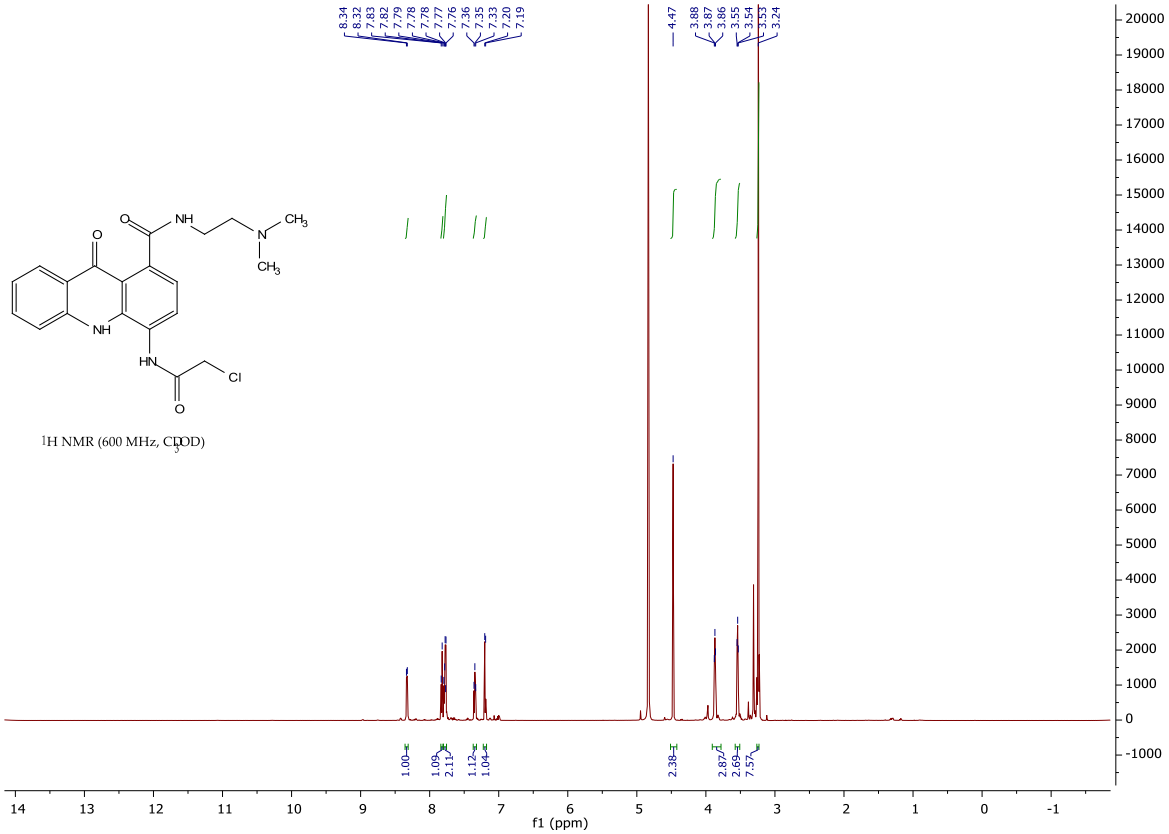


^{1}H NMR (400 MHz, $CDCl_3$)

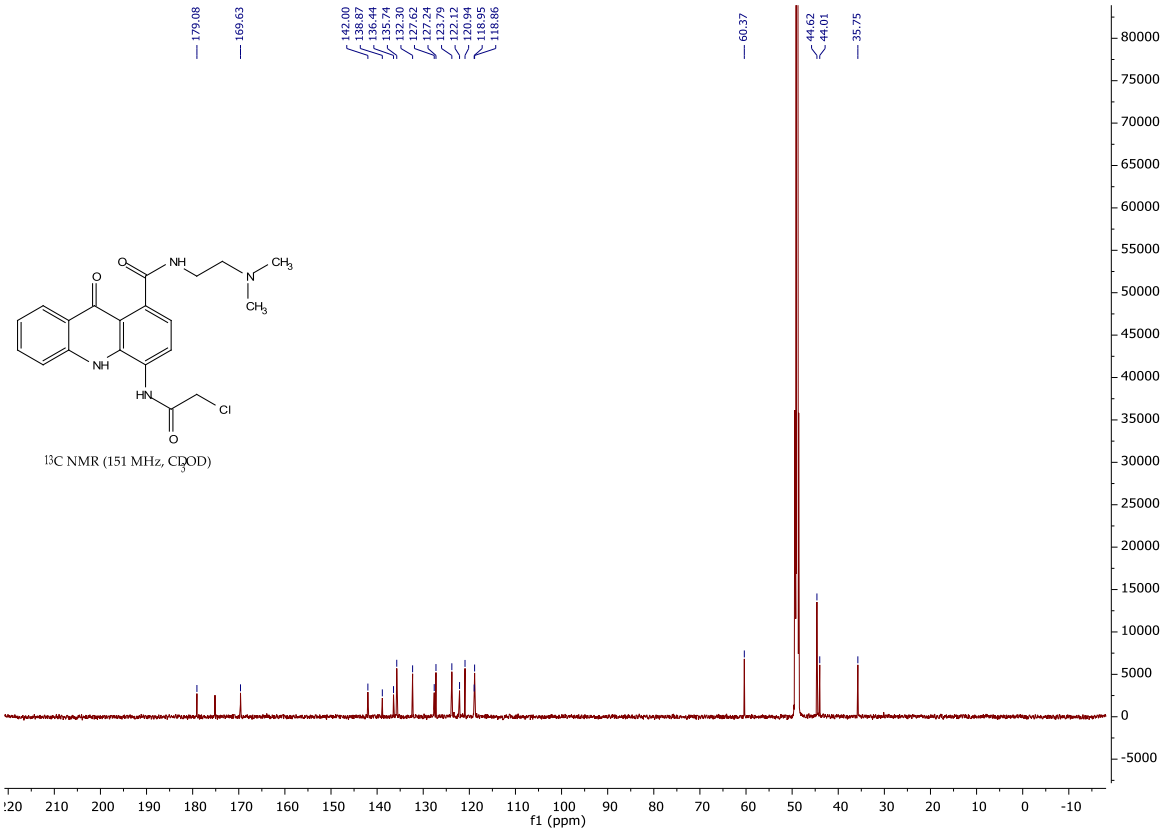


^{13}C NMR (151 MHz, $CDCl_3$)

Figure S11: ^{1}H NMR and ^{13}C NMR spectrum of compound **18b**.



^{1}H NMR (600 MHz, CD_3OD)



^{13}C NMR (151 MHz, CD_3OD)

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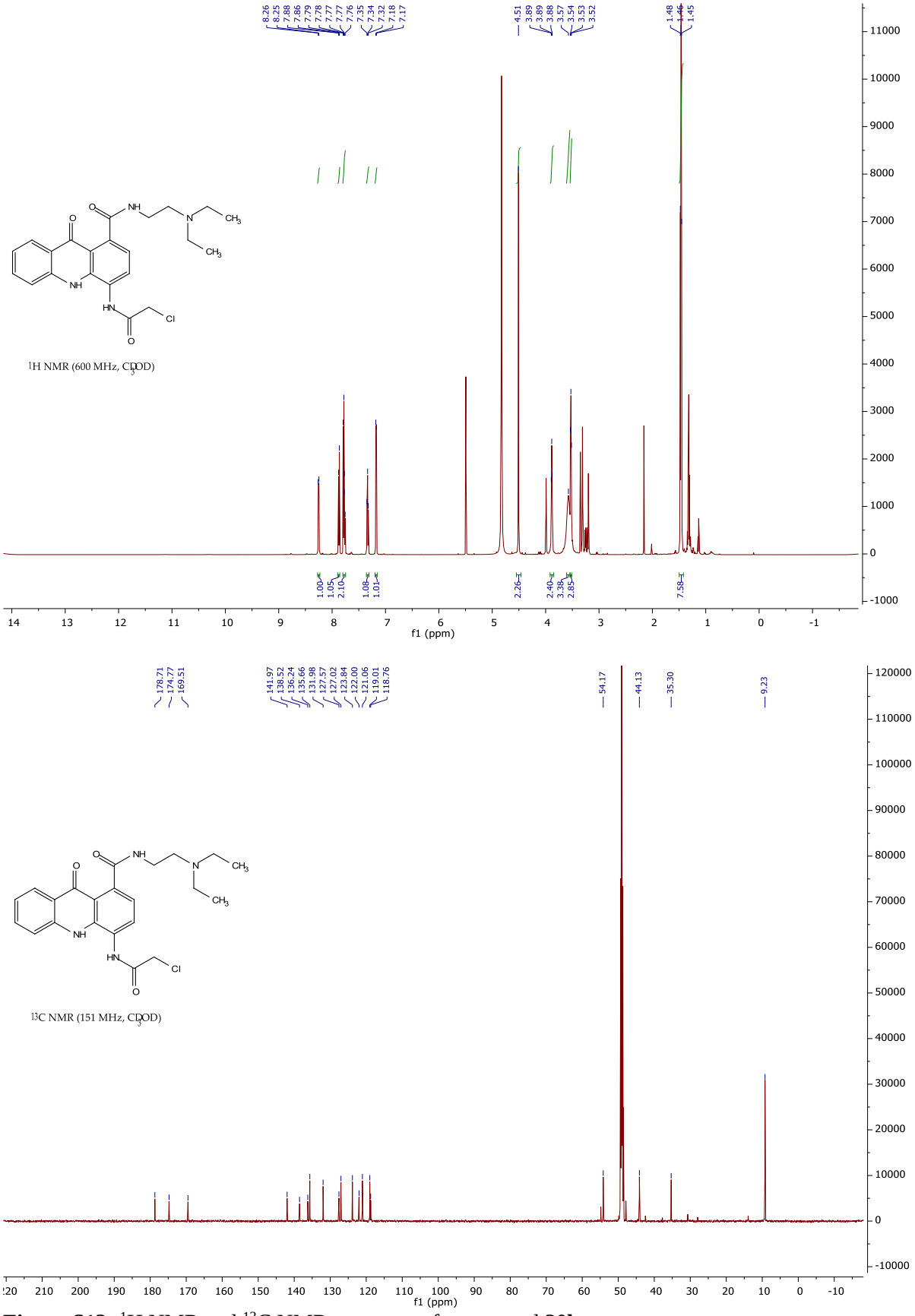
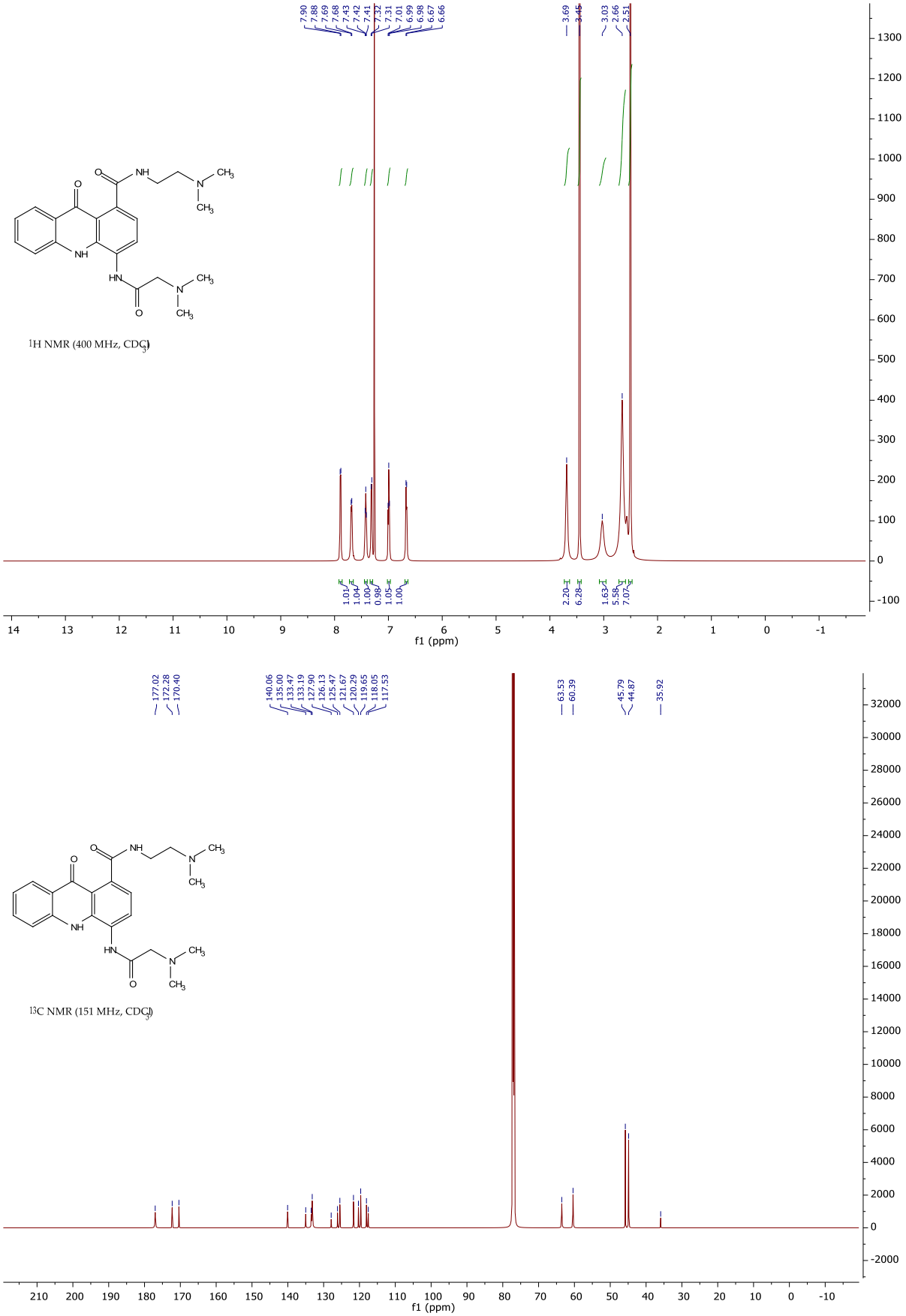


Figure S13: ^{1}H NMR and ^{13}C NMR spectrum of compound **20b**.



^{1}H NMR (400 MHz, $CDCl_3$)

^{13}C NMR (151 MHz, $CDCl_3$)

Figure S14: ^{1}H NMR and ^{13}C NMR spectrum of compound **21a**.

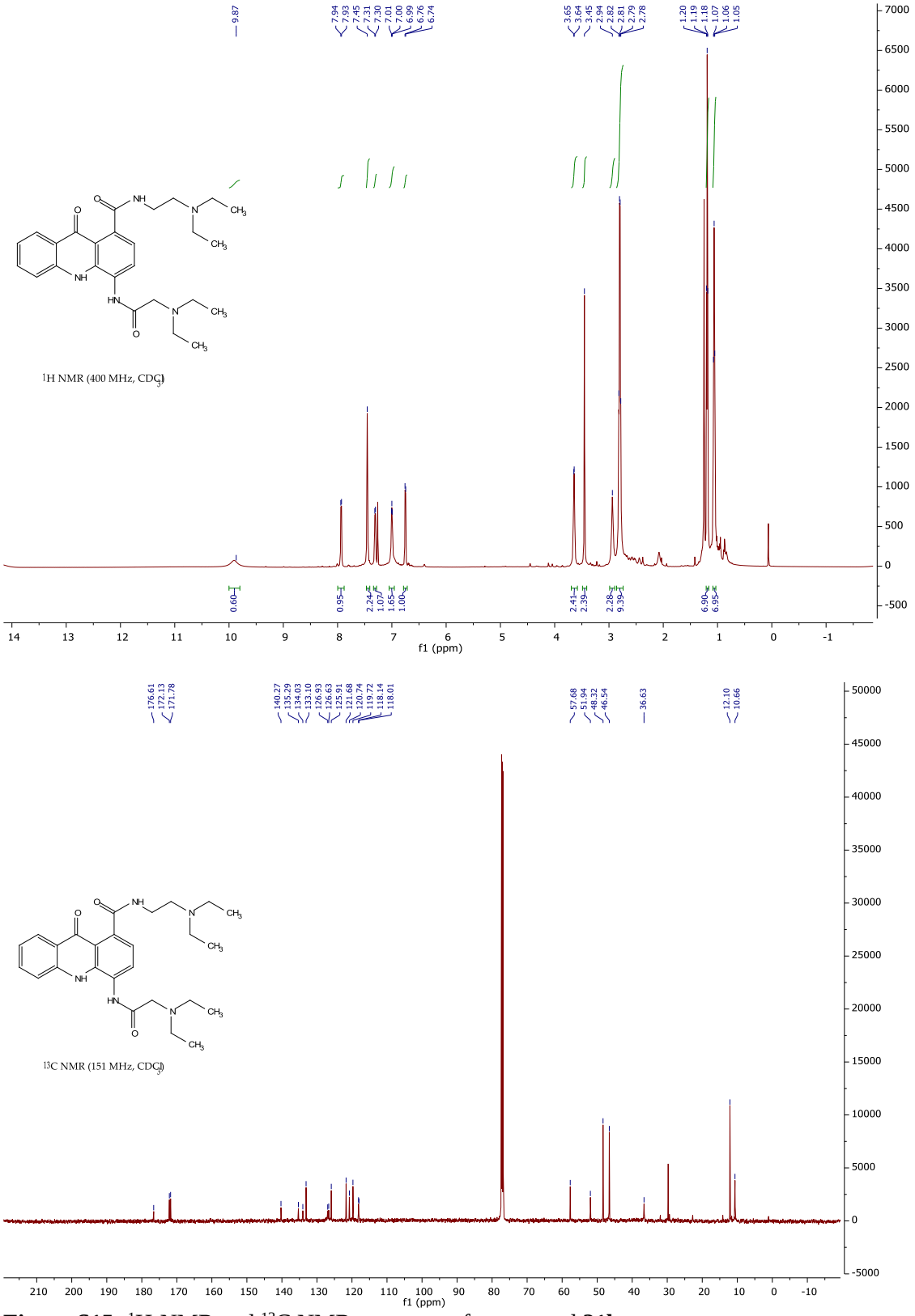
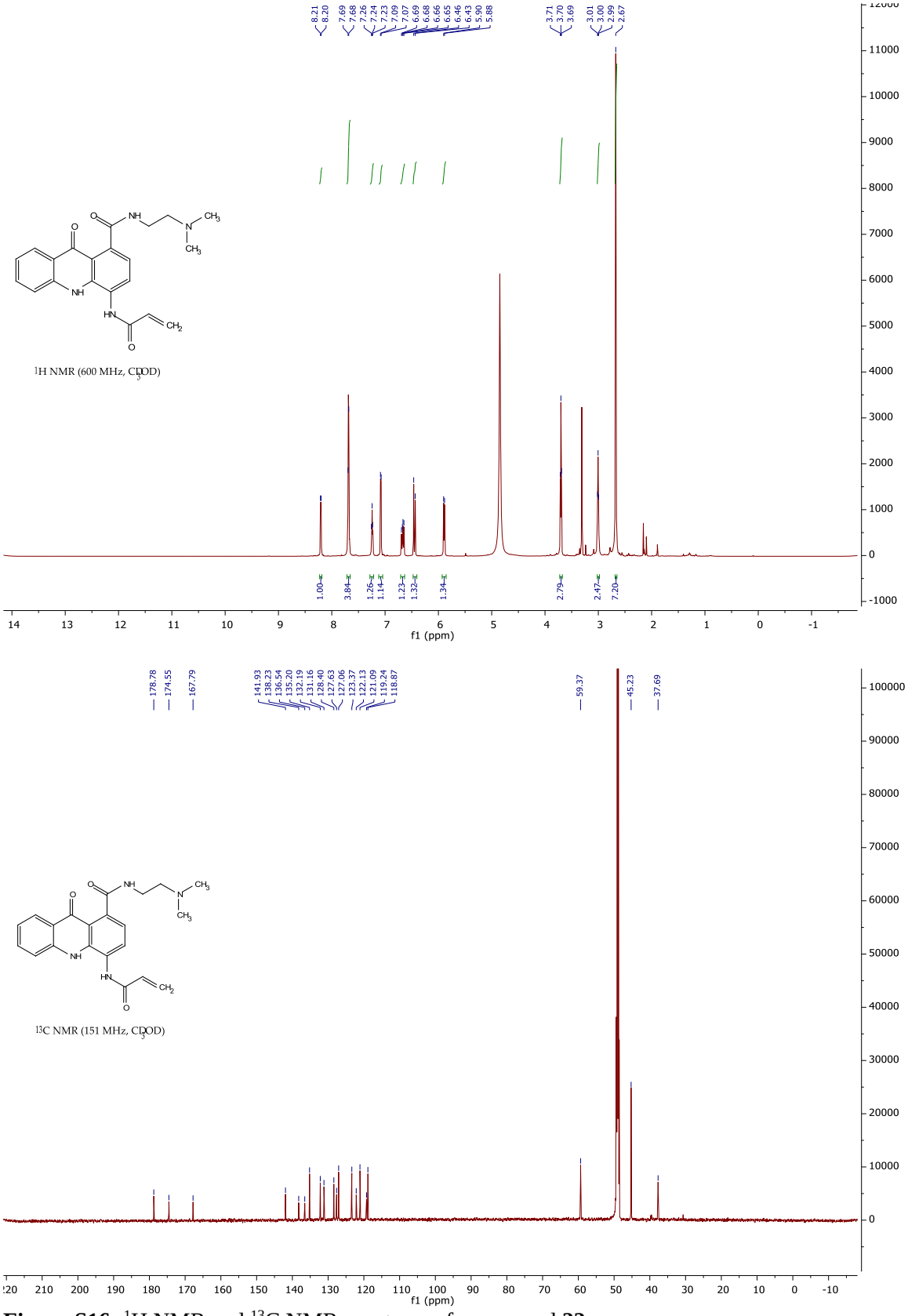


Figure S15: ^{1}H-NMR and ^{13}C NMR spectrum of compound **21b**.



^{1}H NMR (600 MHz, CD_3OD)

^{13}C NMR (151 MHz, CD_3OD)

Figure S16: ^{1}H NMR and ^{13}C NMR spectrum of compound **22a**.

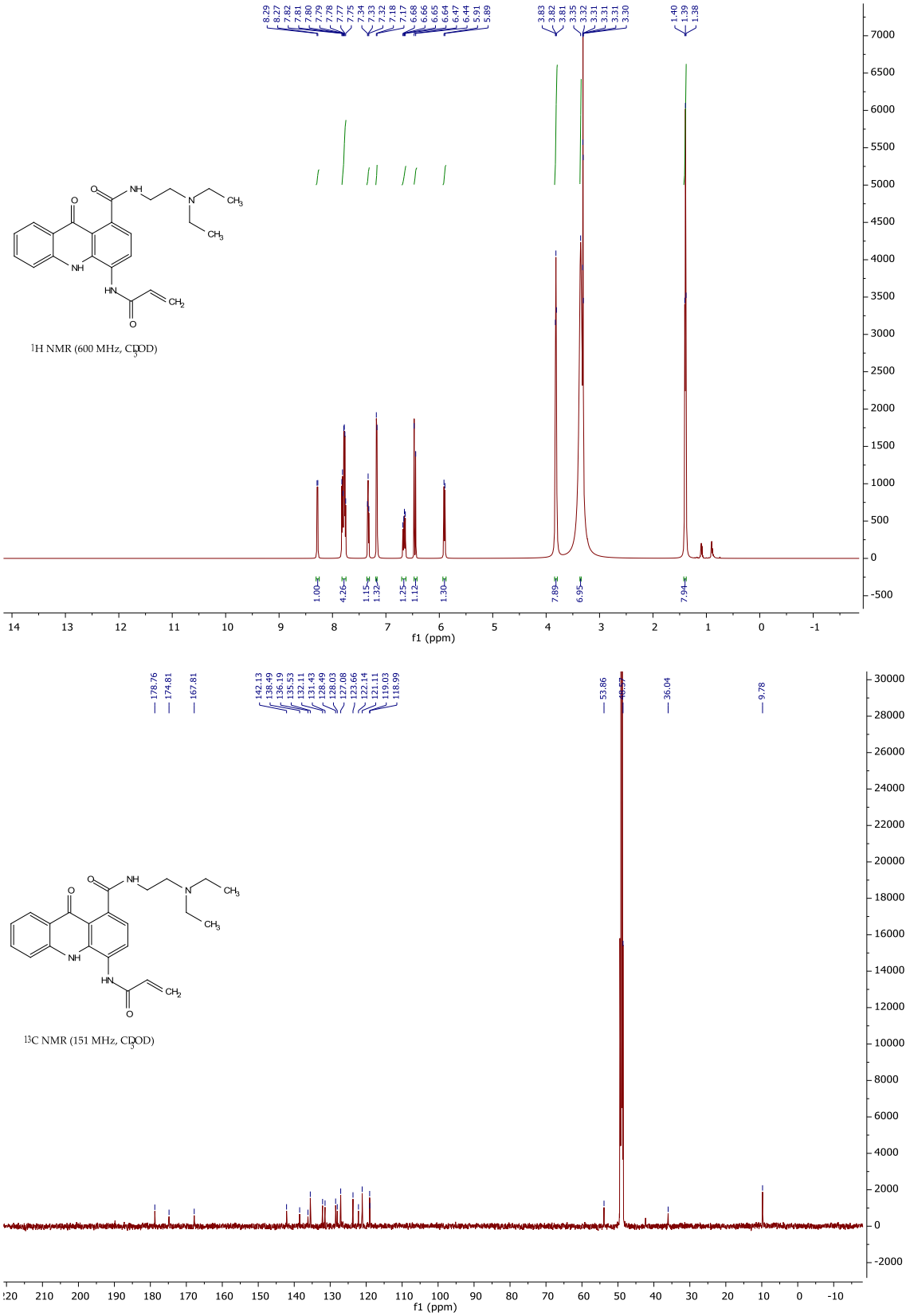


Figure S17: ^{1}H NMR and ^{13}C NMR spectrum of compound **22b**.

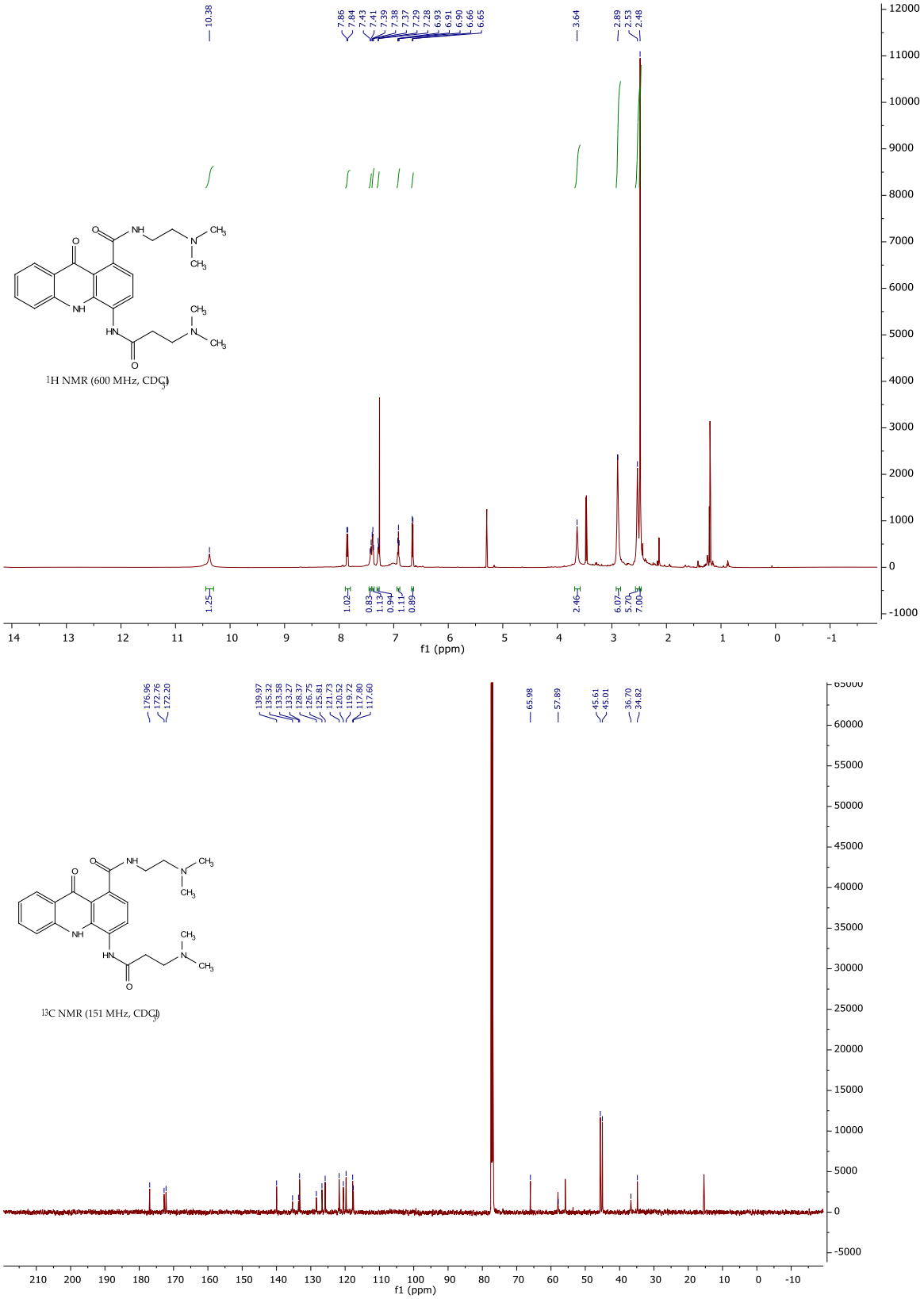


Figure S18: ^{1}H NMR and ^{13}C NMR spectrum of compound **23a**.

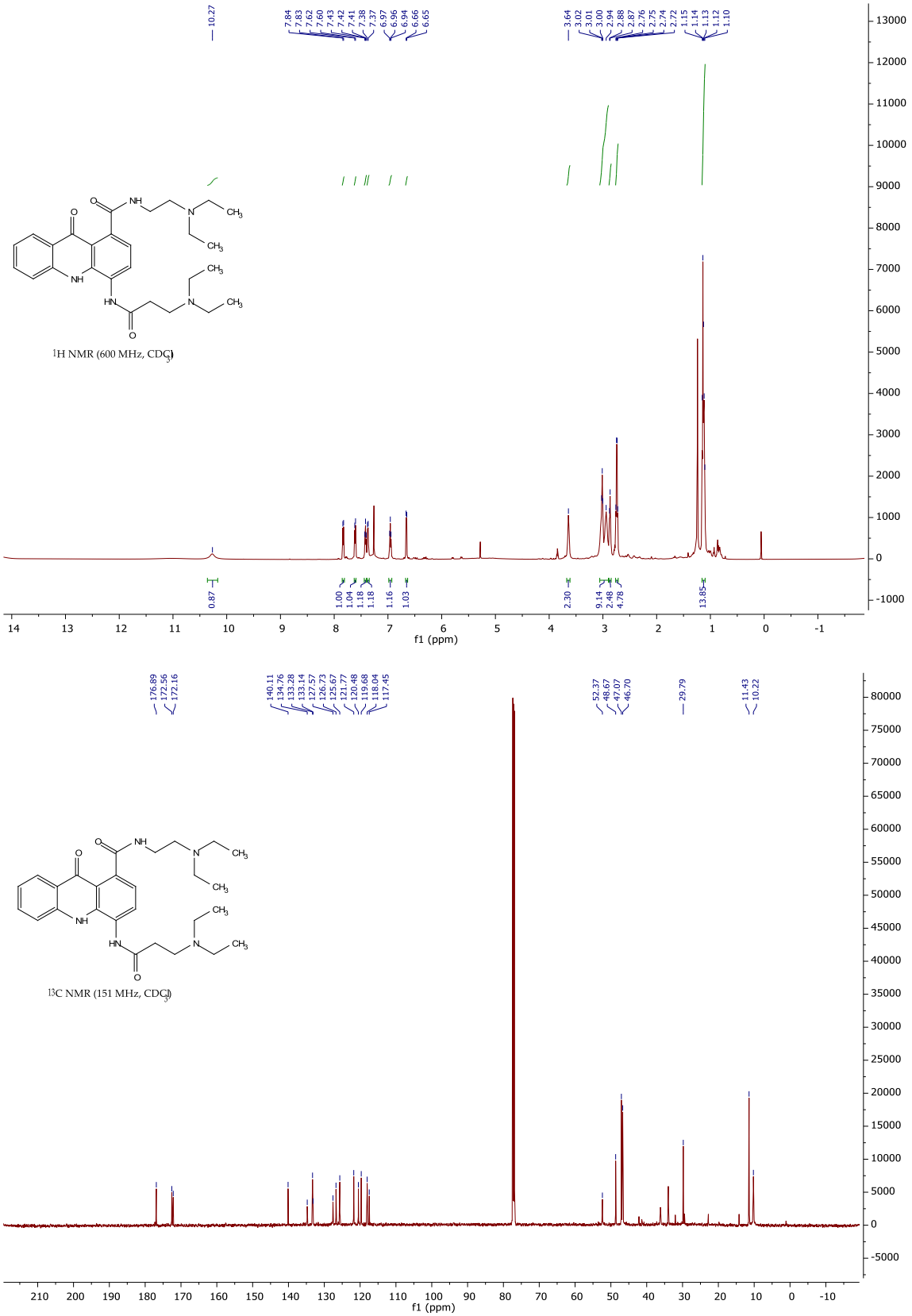


Figure S19: ^{1}H NMR and ^{13}C NMR spectrum of compound **23b**.

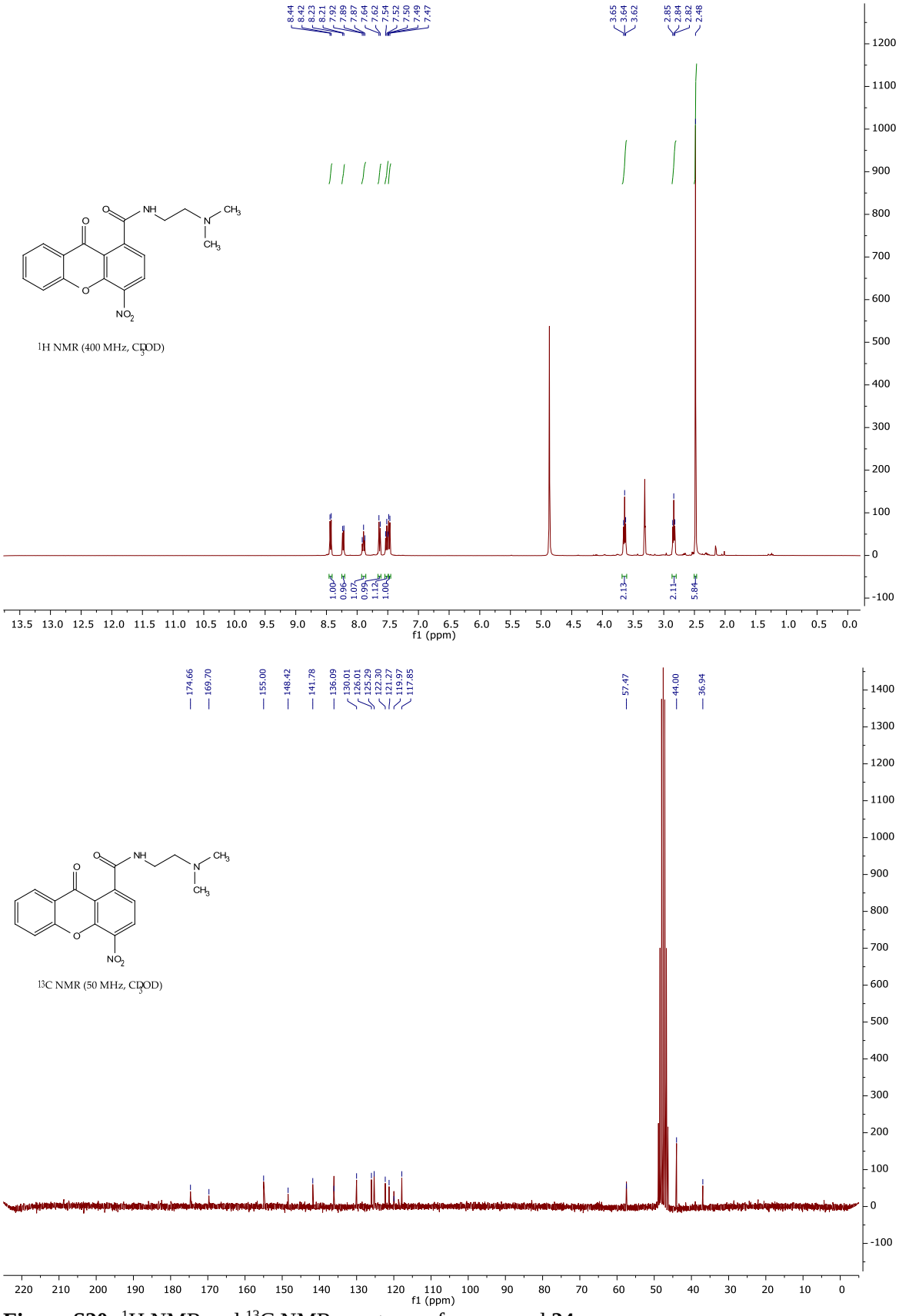


Figure S20: ^{1}H NMR and ^{13}C NMR spectrum of compound **24a**.

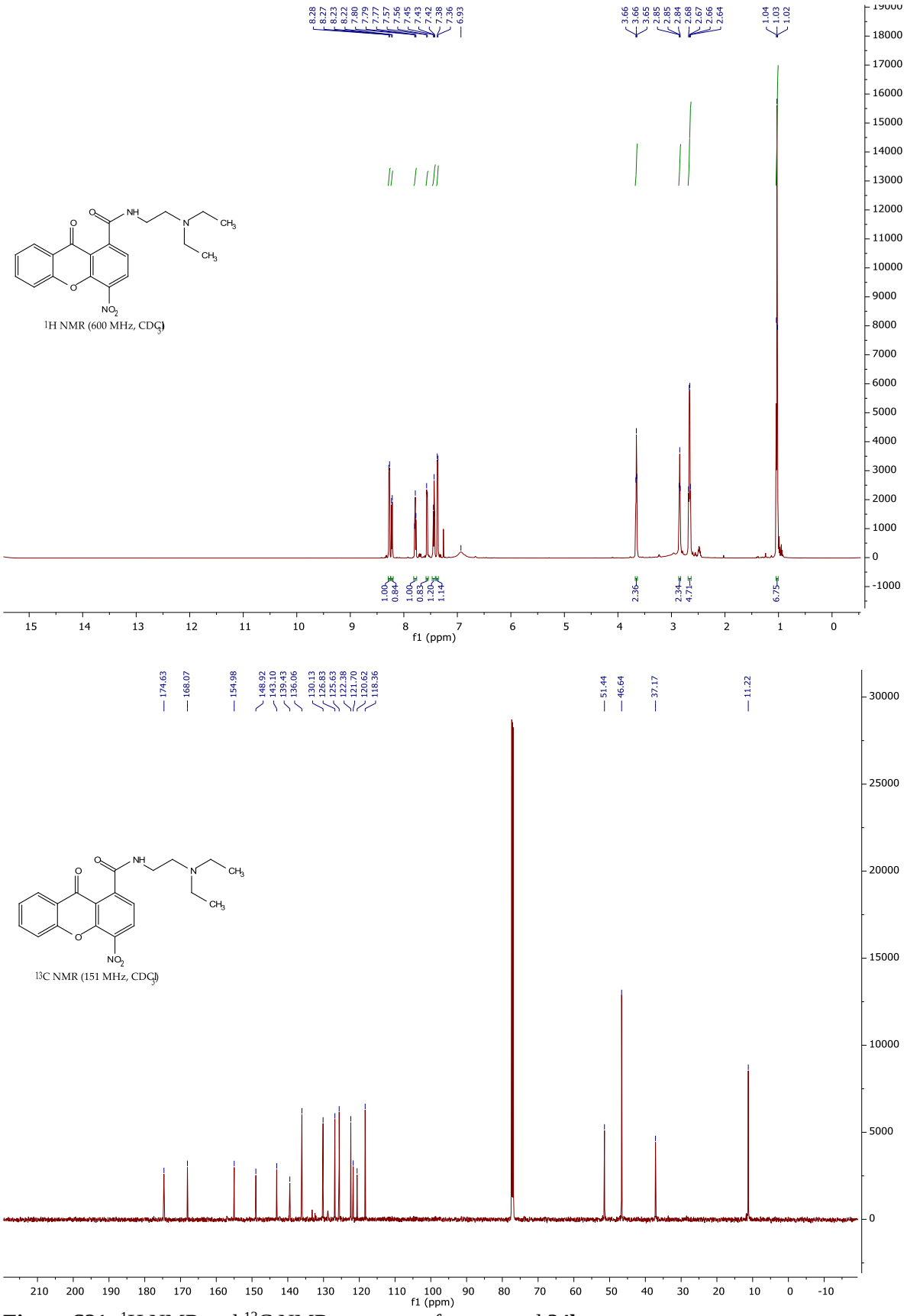
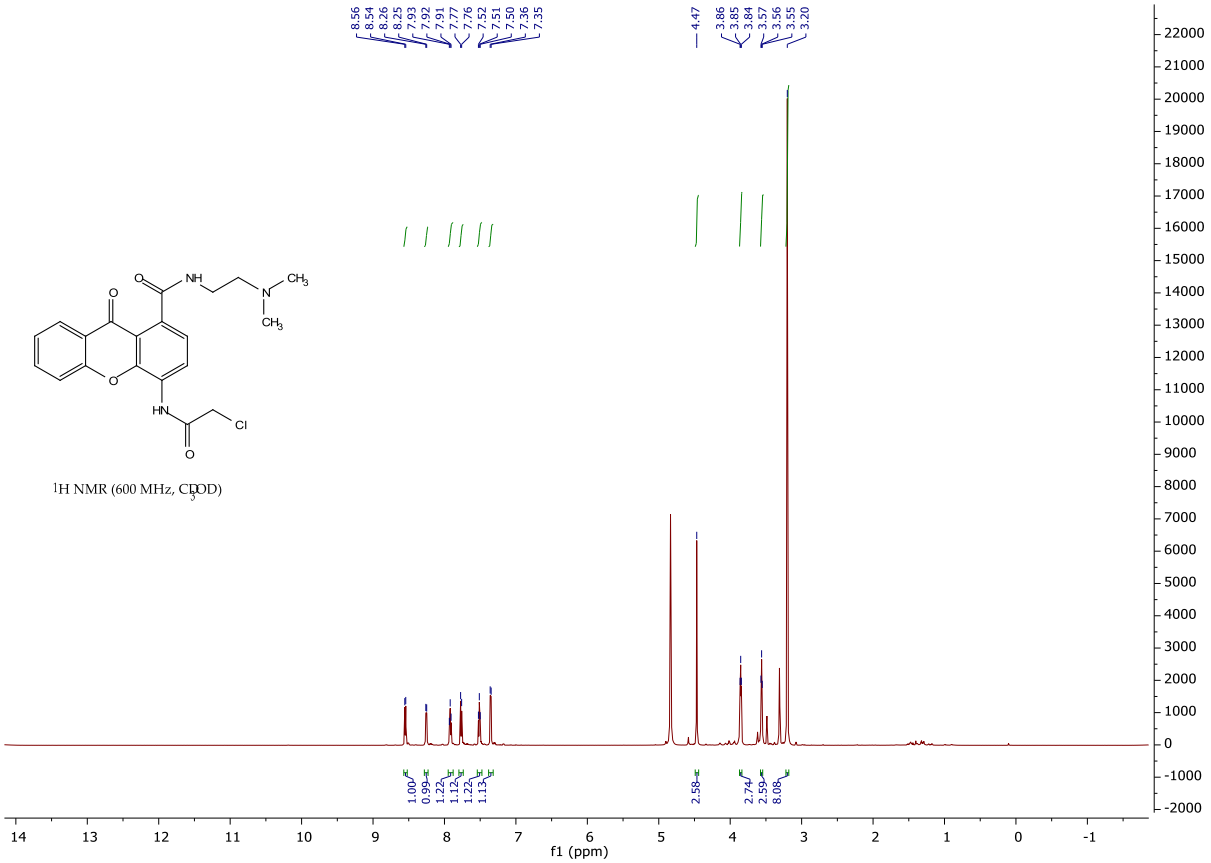
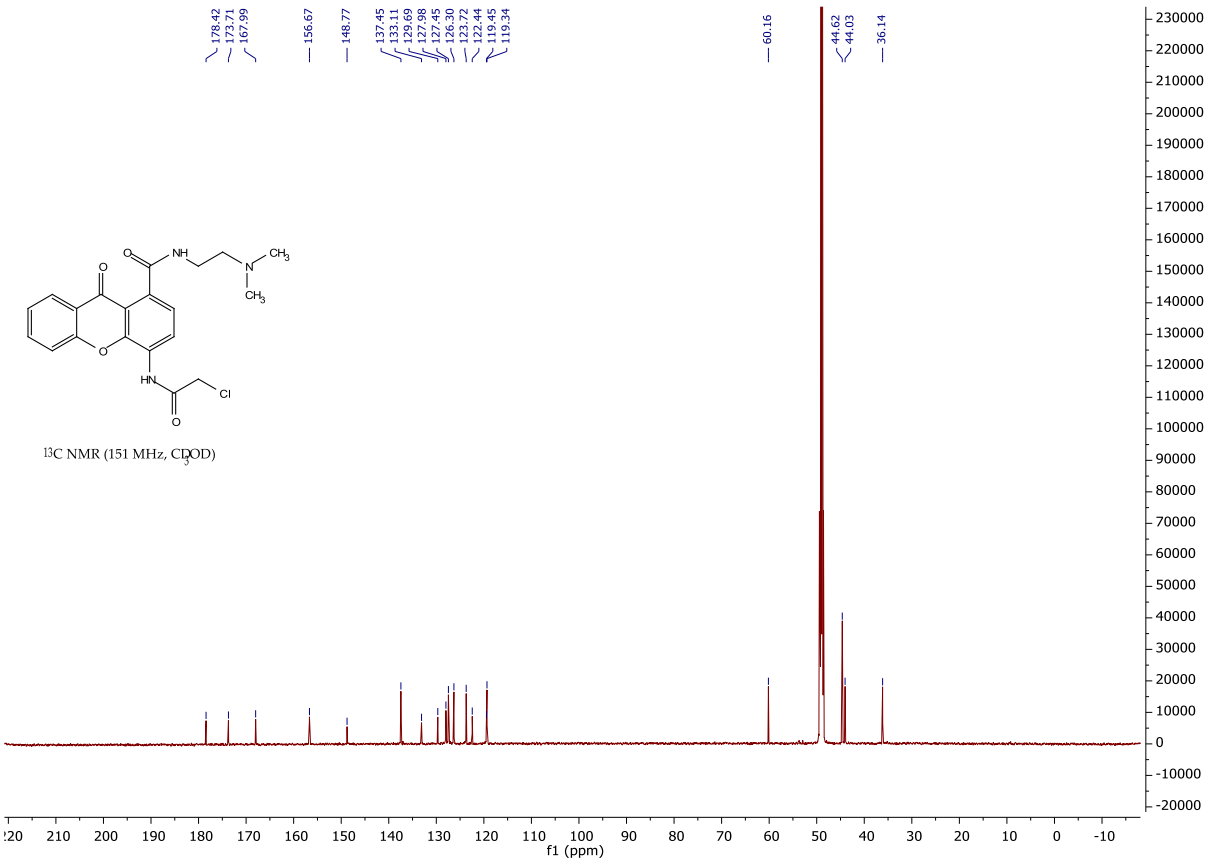


Figure S21: ^{1}H NMR and ^{13}C NMR spectrum of compound **24b**.



^{1}H NMR (600 MHz, CD_3OD)



^{13}C NMR (151 MHz, CD_3OD)

Figure S22: ^{1}H NMR and ^{13}C NMR spectrum of compound **26a**.

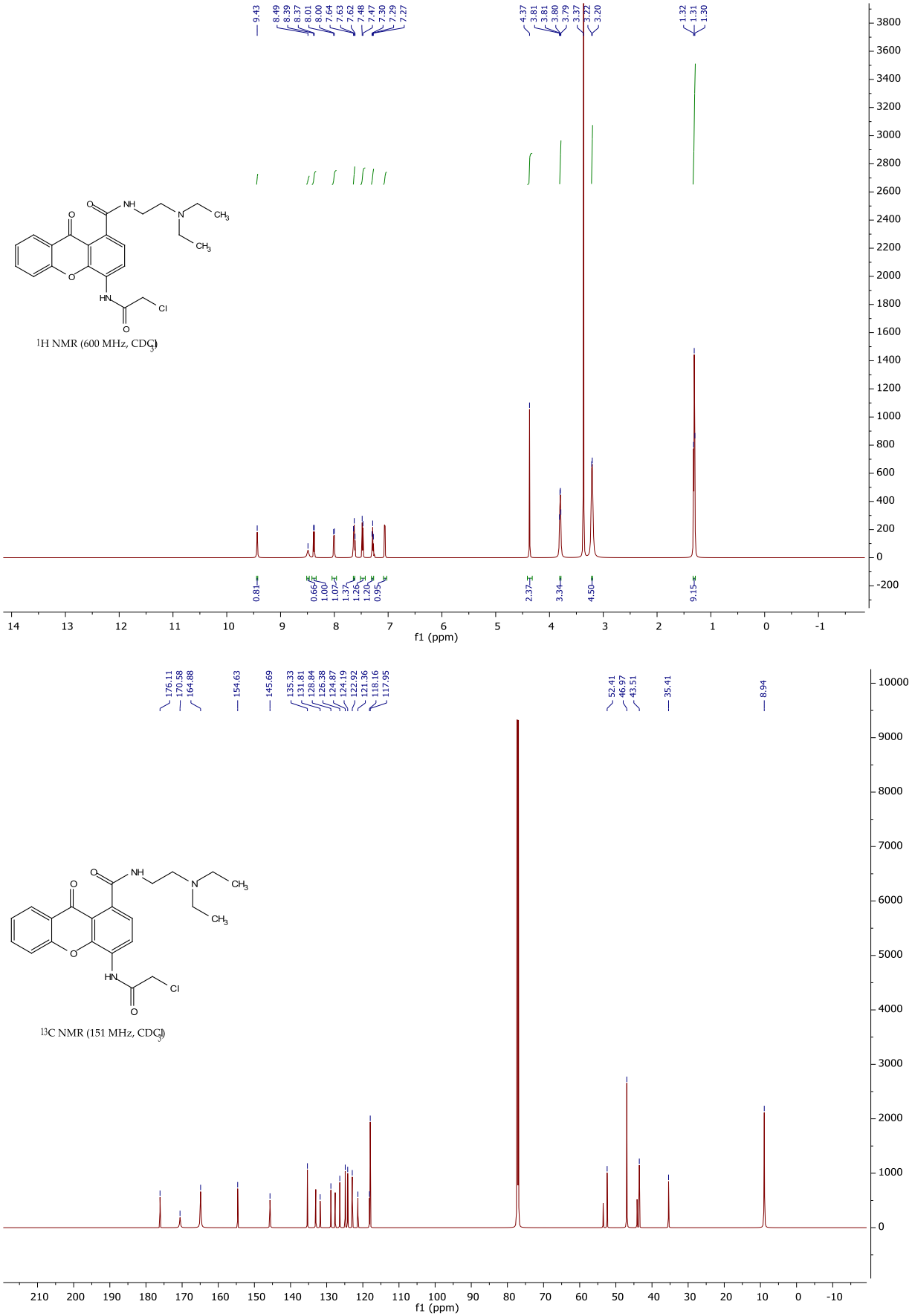
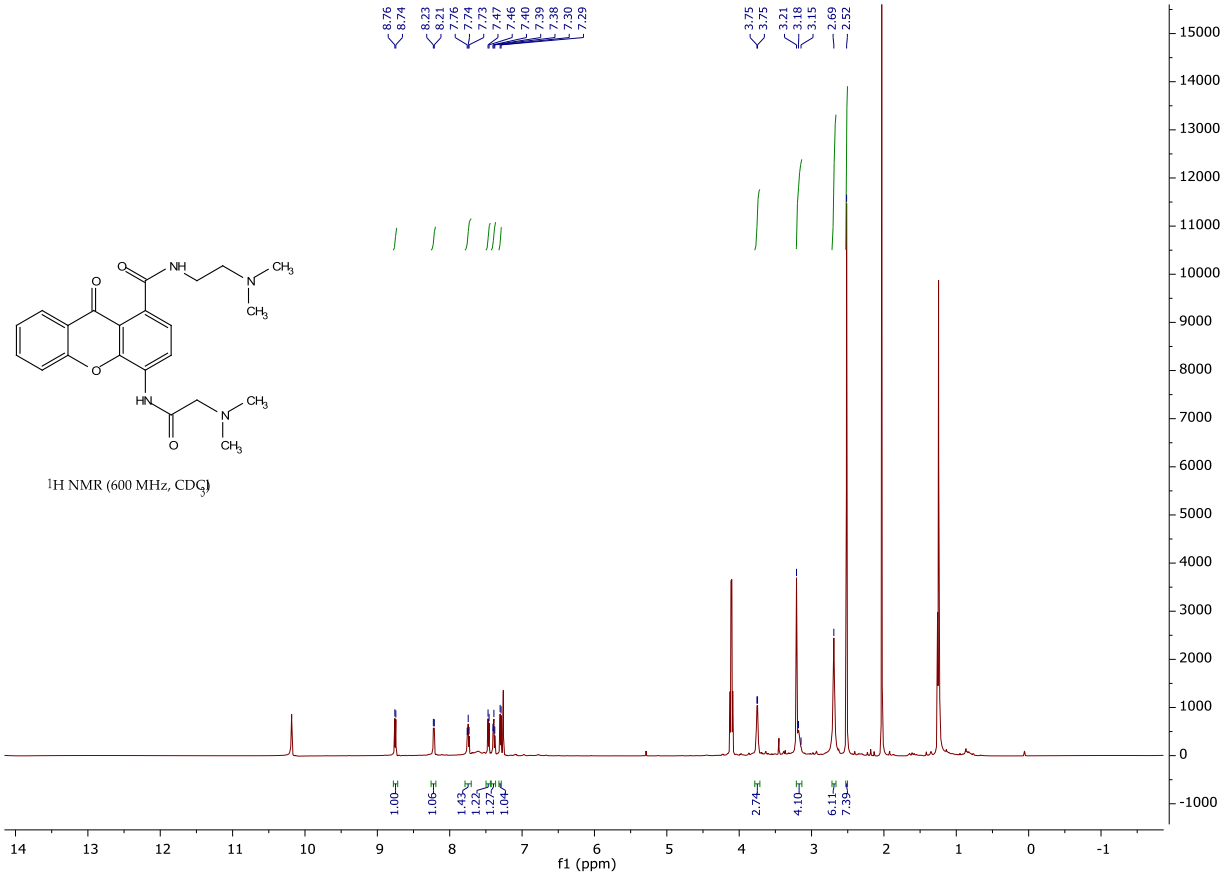
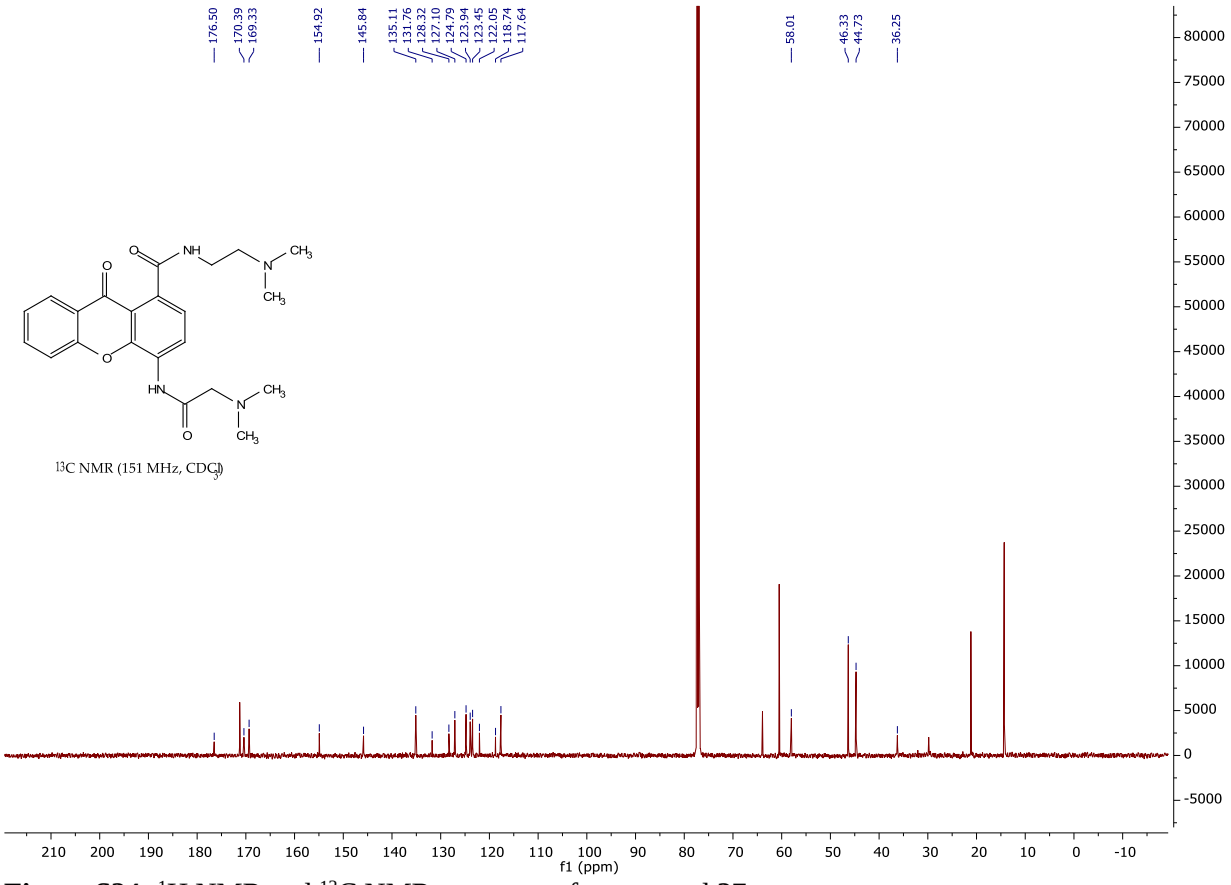


Figure S23: ^{1}H NMR and ^{13}C NMR spectrum of compound **26b**.



^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (151 MHz, $CDCl_3$)

Figure S24: ^{1}H NMR and ^{13}C NMR spectrum of compound **27a**.

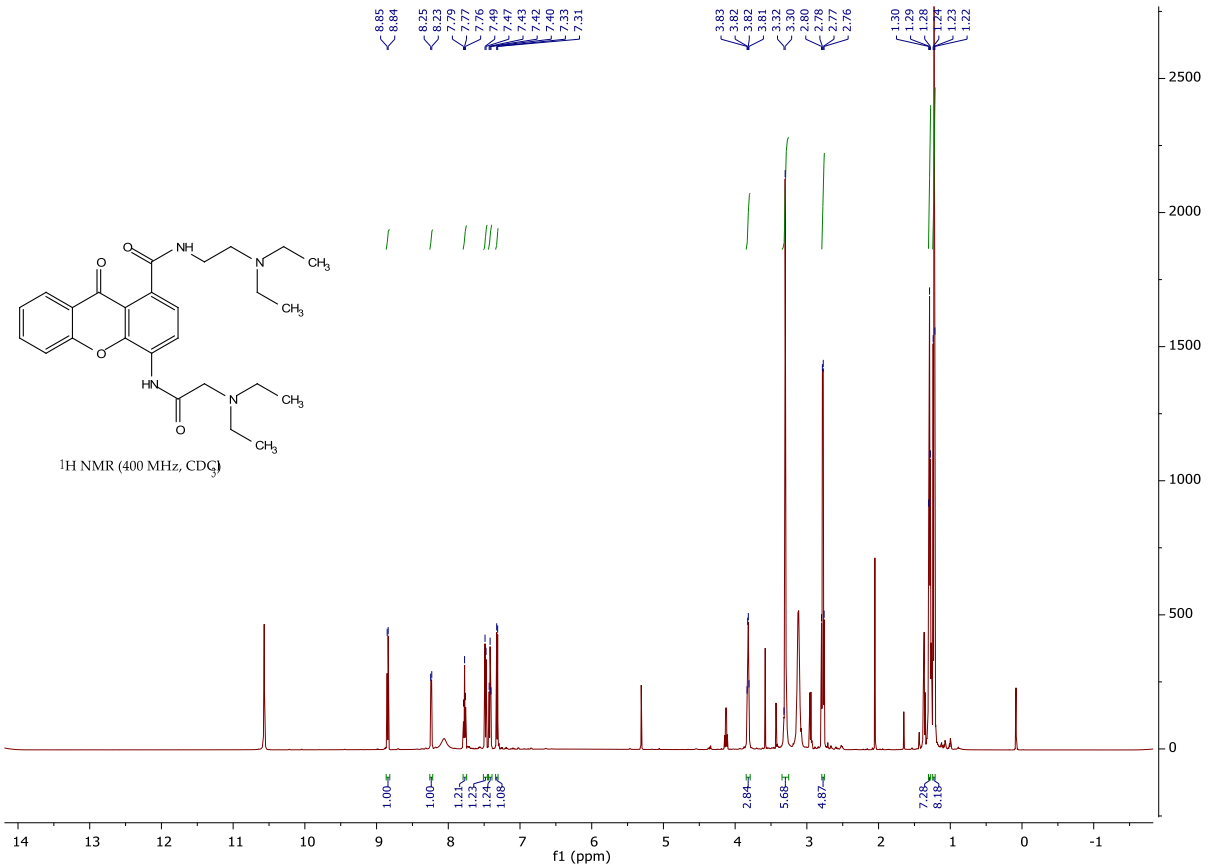


Figure S25: ^{1}H NMR spectrum of compound **27b**.

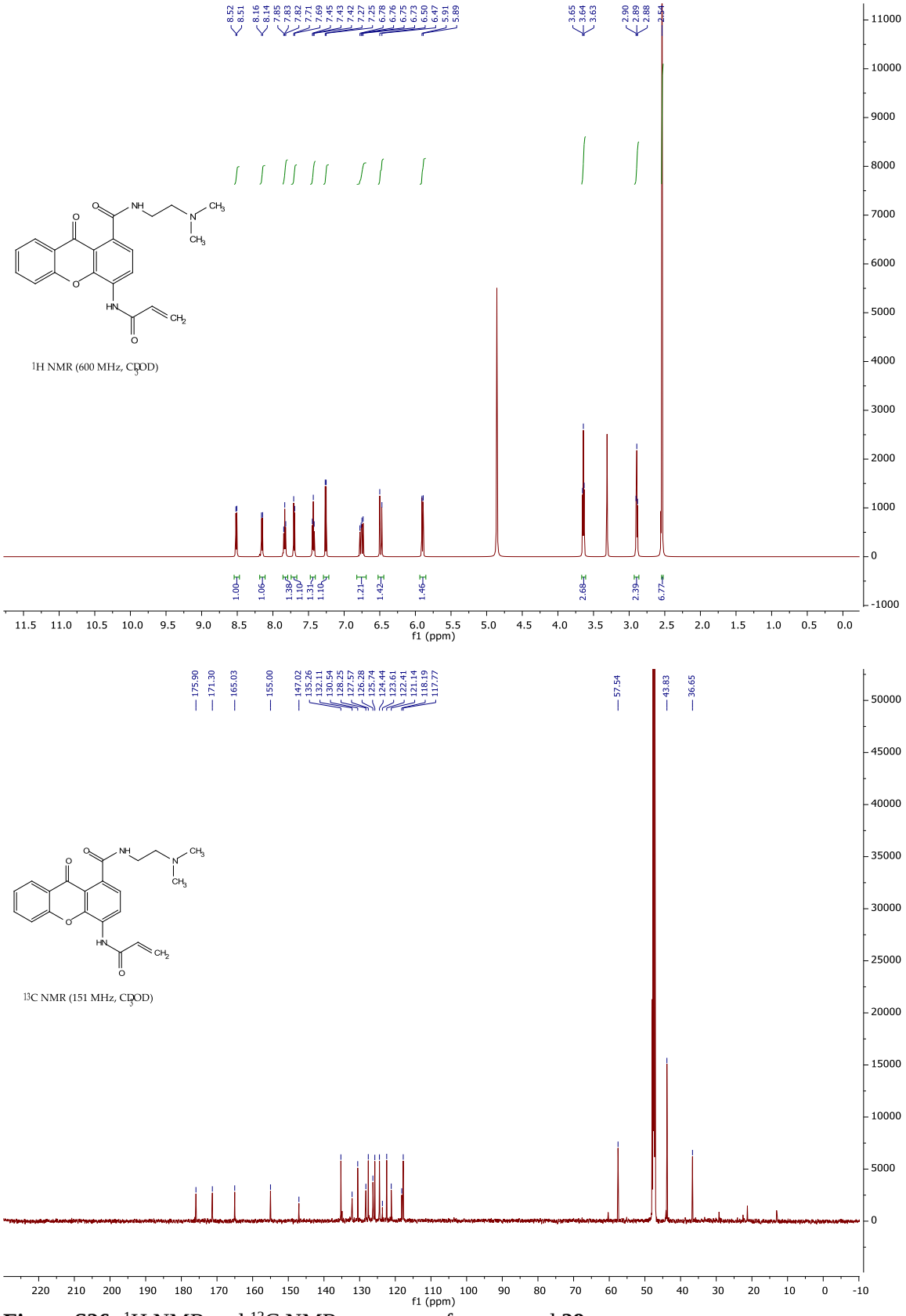


Figure S26: ^{1}H NMR and ^{13}C NMR spectrum of compound **28a**.

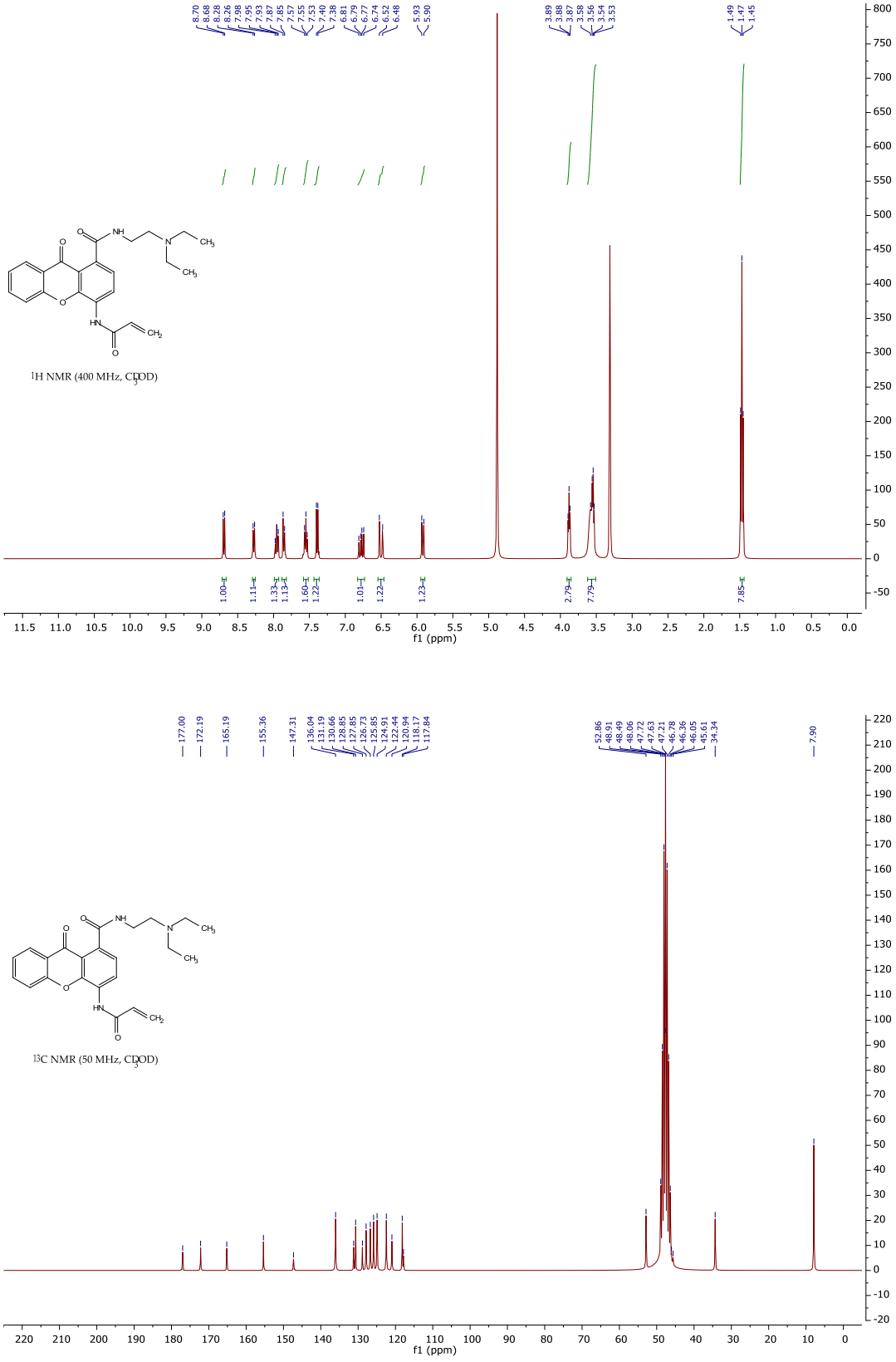
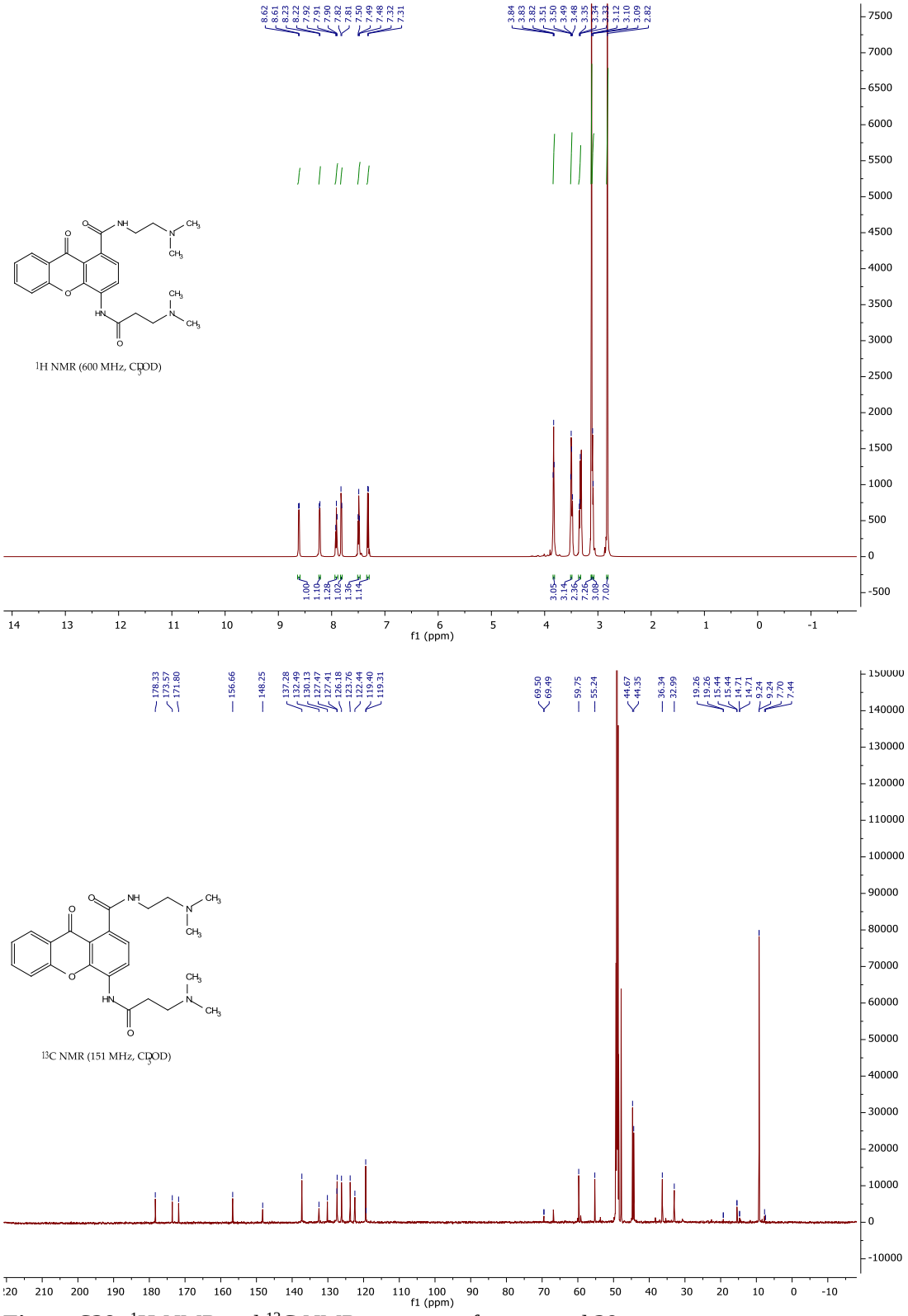


Figure S27: ^{1}H NMR and ^{13}C NMR spectrum of compound **28b**.



^{1}H NMR (600 MHz, CD_3OD)

^{13}C NMR (151 MHz, CD_3OD)

Figure S28: ^{1}H-NMR and ^{13}C NMR spectrum of compound **29a**.

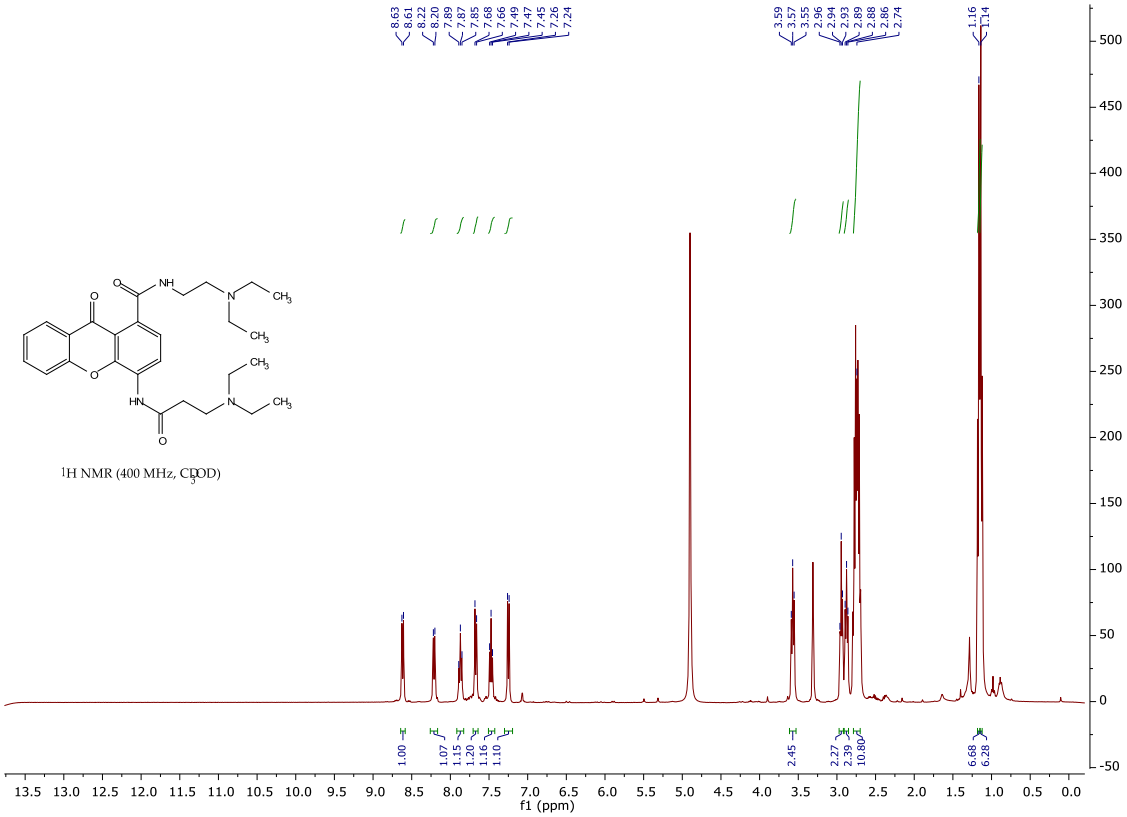


Figure S29: ^{1}H NMR spectrum of compound **29b**.

Materials and Methods

*Methyl 3-bromo-4-nitrobenzoate (**1**).* To a solution of methyl 4-aminobenzoate (5 g, 33 mmol) in $CHCl_3$ (50 mL) was added dropwise N-bromosuccinimide (5.87 g, 33 mmol) at 0 °C and the mixture was stirred at room temperature for 10 hours. After completion of the reaction, the solvent was vacuum evaporated and the residue was dissolved in CH_2Cl_2, washed with a 10% Na_2CO_3 solution, dried over Na_2SO_4, and concentrated to dryness. Flash chromatography on silica gel, using a mixture of cyclohexane / EtOAc 20 / 1, as the eluent, afforded methyl 4-amino-3-bromobenzoate (7 g, 92.6%). H_2O_2 30% (17.5 mL, 58 mmol) was added dropwise to a mixture of methyl 4-amino-3-bromobenzoate (3.5 g, 15 mmol) in glacial acetic acid (56 mL) and conc. sulfuric acid (35 µL, 0.65 mmol) was added in small portions and the resulting suspension was heated at 80 °C for 3 hours. After completion of the reaction, the mixture was poured into ice - water (200 mL), the precipitate was collected by filtration and dried over P_2O_5. The crude solid was purified by column chromatography (silica gel) using a mixture of cyclohexane / EtOAc 20 / 1, as the eluent, to afford the title compound (2 g, 92%). M.p. 70 - 71 °C (EtOAc - *n*-Pentane), 75 - 76 °C (Methanol).

*4-Nitro-9-oxo-9,10-dihydroacridine-1-carboxylic acid (**8**).* M.p. >270 °C (THF - *n*-Pentane); ^{1}H NMR (400 MHz, DMSO-d_6,) δ 11.58 (s, D_2O exch., 1H, NH), 8,66 (d, J = 8.7 Hz, 1H, H-3), 8.17 (d, J = 8.7 Hz, 1H, H-8), 8.07 (d, J = 8.7 Hz, 1H, H-5), 7.83 (td, J = 8.7 Hz, 2.1 Hz, 1H, H-6), 7.41 (td, J = 8.7 Hz, 2.1 Hz, 1H, H-7), 7.28 (d, J = 8.7 Hz, 1H, H-2); ^{13}C NMR (151 MHz, DMSO-d_6) δ 175.0 (C-9), 169.5 (*C*OOH), 142.7 (C-1), 139.8 (C-10a), 135.2 (C-4), 135.1 (C-4a), 134.7 (C-6), 131.3 (C-3), 125.6 (C-8), 123.6 (C-7), 120.6 (C-8a), 119.1 (C-5), 118.8 (C-9a), 117.8 (C-2).

*Ethyl 2-iodobenzoate (**10**).* To a suspension of 2-iodobenzoic acid (4.94 g, 20 mmol, **9**) in abs. ethanol (200 mL) was added dropwise conc. sulfuric acid (4.5 mL) and the resulting mixture was stirred under reflux for 24 hours. After completion of the reaction, most of the volatiles were removed under reduced pressure and the oily product was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with 10% $NaHCO_3$ solution, brine, dried over anh. Na_2SO_4 and evaporated to dryness, to afford 5.19 g (94%) of the title ester **10**, which was used without any further purification for the next step.

*Ethyl 2-(3-methylphenoxy)benzoate (**11**).* A mixture of *m*-cresol (1.08 g, 10 mmol), ethyl 2-iodobenzoate (1.42 g, 5.15 mol, **10**), K_2CO_3 (1.38 g, 10 mmol) and Cu(I)Cl (84.9 mg, 0.86 mmol) in dry pyridine (12 mL) was heated at 120 °C for 17 hours. After completion of the reaction, most of the volatiles were removed under reduced pressure and the oily residue was poured into water, acidified with 18% HCl solution (pH ~ 2) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness. Flash chromatography on silica gel, using a mixture of cyclohexane / EtOAc 20 / 1, as the eluent, afforded 1.19 g (90%) of the title compound **11**.

*1-Methyl-4-nitro-9H-xanthen-9-one (**14**).* A suspension of acid **13** (2.73 g, 10 mmol) in polyphosphoric acid (30 mL) was stirred at 110 °C for 3 hours. After completion of the reaction, the mixture was poured into ice - water and the resulting solid was filtered, washed with water and vacuum dried over P_2O_5. The residue was purified by column chromatography (silica gel), using a mixture of cyclohexane / EtOAc (12 / 1) as the eluent, to afford 2.37 g (93%) of the title compound **14**. M.p. 176 - 177 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 7.6 Hz, 1H, H-3), 8.18 (d, J = 8.0 Hz, 1H, H-8), 7.79 (t, J = 8.0 Hz, 1H, H-6), 7.57 (d, J = 8.0 Hz, 1H, H-5), 7.46 (t, J = 8.0 Hz, 1H, H-7), 7.24 (d, J = 7.6 Hz, 1H, H-2), 3.05 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.3 (C-9), 154.4 (C-10a), 149.8 (C-4a), 149.1 (C-1), 137.5 (C-4), 135.3 (C-6), 129.1 (C-3), 126.6(C-8), 125.7 (C-2), 125.0 (C-7), 122.4 (C-8a), 121.4 (C-9a), 117.9 (C-5), 23.9 (*C*H_3).

*1-(Bromomethyl)-4-nitro-9H-xanthen-9-one (**15**).* To a suspension of xanthone **14** (4.4 g, 17 mmol) in CCl_4 (300 mL) was added NBS (3.39 g, 19 mmol) and dibenzoyl peroxide (0.44 g, 0.17 mmol) and the resulting mixture was stirred under reflux for 5 hours (a readily available household compact fluorescent lamp (CFL) 150 Watt was used as a radical activator and a heating source). After completion of the reaction, the mixture was washed successively with 10% sodium hydrogen sulfite solution, 5% sodium bicarbonate solution and water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Flash chromatography on silica gel, using a mixture of cyclohexane / EtOAc (8 / 1) as the eluent, afforded 4.08 g (73%) of the title compound **15**. M.p. 198 - 199 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H, H-3), 8.17 (d, J = 8.0 Hz, 1H, H-8), 7.90 (t, J = 8.0 Hz, 1H, H-6), 7.69 (d, J = 8.0 Hz, 1H, H-2), 7.62 (d, J = 8.0 Hz, 1H, H-5), 7.53 (t, J = 8.0 Hz, 1H, H-7), 5.39 (s, 2H, CH_2Br); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.2 (C-9), 154.3 (C-10a), 149.3(C-4a), 145.5 (C-1), 139.5 (C-4), 136.6 (C-6), 130.4 (C-3), 127.0 (C-2), 126.6 (C-8), 125.9 (C-7), 122.1 (C-8a), 119.9 (C-9a), 118.3 (C-5), 31.9 (CH_2Br).