SUPPORTING INFORMATION

$SnCl_2$-Catalyzed Kabachnik-Fields Synthesis of α-Aminophosphonates with Potent Antioxidant Activity

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1) General information

All chemicals were purchased from commercial sources and were used without further purification. The reactions were monitored by Thin Layer Chromatography (TLC) on commercial silica gel 60 GF254 plates and the reactional mixture were examined under UV light (λ=254 nm). Column chromatography was carried out using silica gel 60 Merck 0.063e0.200 mm. The reaction solvents used are of analytical quality, except that the solvents used in the column chromatography (hexane and ethyl acetate) are distilled before use. All compounds were characterized in solution by ^{1}H and ^{13}C NMR and when appropriated by using deuterated solvent ($CDCl_3$). The NMR spectra were recorded using Gemuning Bruker, 400 and 500 spectrometers operating at 400 MHz and 500.13 MHz for ^{1}H, and 100.6 MHz and 125.76 MHz for ^{13}C, respectively, with tetramethylsilane (TMS) as the internal standard. Melting points (PF in °C), uncorrected, were determined using a Gallenkamp model MFB.595.010M with an internal thermometer, and were adjusted using an external thermometer.

2) 6-Nitro-2*H*-chromen-2-one (3)

Nitro-coumarin was prepared according to a reported procedure using KNO_3 in acidic medium. Coumarin **1** (1.00 g, 6.84 mmol, 1 equiv) and KNO_3 (0.692 g, 6.84 mmol, 1 equiv) were added in a single portion to concentrated H_2SO_4 (60 mL) in a 100 mL round-bottom flask equipped with a magnetic stirrer. The mixture was stirred at room temperature for 24 h. After completion of the reaction, as confirmed by TLC, the mixture was slowly poured dropwise into ice-cold water (1000 mL) with constant stirring. The resulting white precipitate was filtered, washed thoroughly with cold water, and dried in an oven. The final product was obtained as a solid of sufficient purity to be used directly in the subsequent step without additional purification, as confirmed by TLC and NMR analyses.

White powder, yield: 92%; m.p: 200-202 ºC. **^{1}H NMR (300 MHz, DMSO-d$_6$)**: δ (ppm) 8.73 (d, J = 2.8 Hz, 1H, H-5), 8.42 (dd, J = 9.1, 2.8 Hz, 1H, H-7), 8.23 (d, J = 9.1 Hz, 1H, H-4), 7.62 (d, J = 9.7 Hz, 1H, H-8), 6.70 (d, J = 9.7 Hz, 1H, H-3). **^{13}C NMR (75 MHz, DMSO-d$_6$)**: δ (ppm) 158.9 (C=O), 157.2 (C8a), 143.5 (C6), 143.3 (C4), 126.5 (C7), 124.3 (C5), 119.1 (C4a), 118.1 (C8), 117.8 (C3).

3) 6-Amino-2H-chromen-2-one (4)

In a 100 mL round-bottom flask, nitro-coumarin **3** (0.50 g, 2.61 mmol, 1 equiv) was dissolved in ethanol (10 mL). Iron powder (26.1 mmol, 10 equiv) was added under vigorous stirring, followed by concentrated HCl (26.1 mmol, 10 equiv). The reaction mixture was heated to reflux under constant stirring for 5 min. After completion of the reaction, the hot mixture was cooled to room temperature, filtered under pressure, and washed with ethanol. The filtrate was basified with 10% aqueous NaOH and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel using a mixture of ethyl acetate/hexane (4:6, v/v) as eluent.

White powder, yield: 92%; m.p: 200-202 ºC. **^{1}H NMR (300 MHz, DMSO-d$_6$)**: δ (ppm): 7.90 (d, J = 9.5 Hz, 1H, H-4), 7.12 (d, J = 8.8 Hz, 1H, H-8), 6.87 (dd, J = 8.8, 2.7 Hz, 1H, H-7), 6.77 (d, J = 2.7 Hz, 1H, H-5), 6.37 (d, J = 9.5 Hz, 1H, H-3), 5.33 (s, 2H, NH_2). **^{13}C NMR (75 MHz, DMSO-d$_6$)**: δ (ppm) 160.5 (C=O), 145.4 (C8a), 145.2 (C6), 144.4 (C4), 119.1 (C4a), 118.78 (C7), 116.6 (C8), 115.9 (C3), 110.3 (C5).

4) General procedure for the synthesis of α-aminophosphonates coumarine derivatives 1a-l

A solution of 6-amino-2*H*-chromen-2-one (**4**) (1 mmol; 1 equiv) in ethanol (5 mL), the appropriate aldehyde (1 mmol; 1 equiv), triethyl phosphite (1.1 mmol; 1.1 equiv), and tin(II) chloride ($SnCl_2$) (10 mol%) was added, and the reaction mixture was stirred under reflux in ethanol for 24 hours. Once the reaction was deemed complete, ethanol was evaporated under reduced pressure. Then, 15 mL of water was added to the reaction mixture, and the product was extracted using ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered under reduced pressure, and the solvent was evaporated under vacuum. The crude product obtained was purified by silica gel column chromatography using a mixture of ethyl acetate/hexane (4:6).

4.1. Diethyl (((2-oxo-2*H*-chromen-6-yl)amino)(*p*-tolyl)methyl)phosphonate (**1a**)
Yellow powder, yield: 92%; m.p: 155-156 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.49 (d, *J* = 9.6 Hz, 1H, H-4), 7.33 (dd, *J* = 8.0, 2.1 Hz, 2H, H-2', H-6'), 7.15 (d, *J* = 8.0 Hz, 2H, H-3', H-5'), 7.11 (d, *J* = 8.9 Hz, 1H, H- 8), 6.83 (dd, *J* = 8.9, 2.8 Hz, 1H, H-7), 6.53 (d, *J* = 2.7 Hz, 1H, H-5), 6.32 (d, *J* = 9.5 Hz, 1H, H-3), 4.88 (t, *J* = 8.6 Hz, 1H, N-H), 4.69 (d, *J* = 7.3 Hz, 1H, CH-N), 4.65 (d, *J* = 7.3 Hz, 1H, CH-N(rotamer)) 4.12 (q, *J* = 7.1 Hz, 2H, CH_2), 3.94 (cs, 1H, CH_2), 3.68 (cs, 1H, CH_2), 2.33 (s, 3H, CH_3), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3), 1.13 (t, *J* = 7.1 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 161.3 (C=O), 147.3 (C8a), 143.3 (C4), 143.2 (C6), 138.1 (C4'), 132.1 (C1'), 129.6 (C3', C5'), 127.7 (C2', C6'), 119.3 (C4a), 119.0 (C8), 117.6 (C7), 116.9 (C3), 110.1 (C5), 63.4 (CH-N), 57.0 (CH_2-O), 55.5 (CH_2-O), 21.2 (CH_3), -16.5 (CH_3), 16.3 (CH_3).

4.2. Diethyl ((4-fluorophenyl)((2-oxo-2*H*-chromen-6-yl)amino)methyl)phosphonate (**1b**)

Yellow powder; yield: 90%; m.p: 138-139 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.49 (d, *J* = 9.5 Hz, 1H, H-4), 7.43 (ddd, *J* = 8.5, 5.1, 2.4 Hz, 2H, H-3', H-5'), 7.12 (d, *J* = 8.9 Hz, 1H, H-8), 7.04 (t, *J* = 8.5 Hz, 2H, H-2', H-6'), 6.82 (dd, *J* = 8.9, 2.8 Hz, 1H, H-7), 6.50 (d, *J* = 2.8 Hz, 1H, H-5), 6.33 (d, *J* = 9.5 Hz, 1H, H-3), 4.91 (dd, *J* = 10.0, 7.5 Hz, 1H, N-H), 4.65 (d, *J* = 7.3 Hz, 1H, CH-N), 4.71 (d, *J* = 7.3 Hz, 1H, CH-N(rotamer)), 4.18 – 4.06 (q, *J* = 7.1, 2H, CH_2-O), 3.97 (cs, 1H, CH_2-O), 3.74 (cs, 1H, CH_2-O), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3), 1.15 (t, *J* = 7.1 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 162.2 (d, *J* = 251.5 Hz, C4'), 161.1 (C=O), 147.3 (C8a), 143.3 (C4), 143.1 (C6), 131.1 (d, *J* = 11.5 Hz, C1'), 129.4 (d, *J* = 10 Hz, C2', C6'), 119.3 (C8), 118.9 (C7), 117.7 (C4a), 116.9

(C3), 115.7 (d, *J* = 21.5 Hz, C3', C5'), 110.0 (C5), 63.4 (CH-N), 56.6 (CH_2-O), 55.1 (CH_2-O), 16.5 (CH_3), 16.3 (CH_3).

4.3. Diethyl ((4-chlorophenyl)((2-oxo-2*H*-chromen-6-yl)amino)methyl)phosphonate (**1c**)

Yellow powder; yield: 86%; m.p: 166-167 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.51 (d, *J* = 9.4 Hz, 1H, H-4), 7.43 (dd, *J* = 8.5, 2.3 Hz, 2H, H3', H5'), 7.35 (d, *J* = 8.5 Hz, 2H, H2', H6'), 7.15 (d, *J* = 8.9 Hz, 1H, H-8), 6.84 (dd, *J* = 8.9, 2.8 Hz, 1H, H-7), 6.51 (d, *J* = 2.8 Hz, 1H, H-5), 6.36 (d, *J* = 9.5 Hz, 1H, H-3), 4.91 (dd, *J* = 10.2, 7.3 Hz, 1H, N-H), 4.72 (d, *J* = 7.2 Hz, 1H, CH-N), 4.62 (d, *J* = 7.2 Hz, 1H, CH-N (rotamer)), 4.23 – 4.09 (q, *J* = 7.1 Hz, 2H, CH_2-O), 4.01 (sc, 1H, CH_2-O), 3.80 (cs, 1H, CH_2-O), 1.35 – 1.30 (m, 3H, CH_3), 1.19 (td, *J* = 7.1, 0.5 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 161.0 (C=O), 147.4 (C8a), 143.1 (C4), 142.8 (C6), 134.1 (C1'), 133.8 (C4'), 129.1 (C3', C5'), 129.0 (C2', C6'), 119.3 (C4a), 118.8 (C8), 117.7 (C7), 117.0 (C3), 110.0 (C5), 63.5 (CH-N), 56.7 (CH_2-O), 55.2 (CH_2-O), 16.4 (CH_3), 16.2 (CH_3).

4.4. Diethyl ((4-methoxyphenyl)((2-oxo-2*H*-chromen-6-yl)amino)methyl)phosphonate (**1d**)

Yellow powder; yield: 96%; m.p: 152-153 ºC**. ^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.49 (dd, *J* = 9.6, 1H, H-4), 7.39 – 7.34 (m, 2H, H2', H6'), 7.10 (d, *J* = 9.0 Hz, 1H, H-8), 6.89 – 6.86 (m, 2H, H3', H5'), 6.83 (dd, *J* = 8.9, 2.8 Hz, 1H, H-7), 6.52 (d, *J* = 2.8 Hz, 1H, H-5), 6.32 (d, *J* = 9.5 Hz, 1H, H-3), 4.89 (wide signal, 1H, N-H), 4.67 (cs, 1H, CH-N), 4.18 – 4.04 (q, *J* = 7.1 Hz, 2H, CH_2-O), 3.80 (cs, 1H, CH_2-O), 3.78 (s, 3H, O-CH_3), 3.68 (cs, 1H, CH_2-O), 1.29 (td, *J* = 7.1, 0.5 Hz, 3H, CH_3), 1.13 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 161.1 (C=O), 159.5 (C4'), 159.4 (C8a), 147.1 (C6), 143.4 (C4), 128.4 (C1'), 119.0 (C4a), 117.4 (C8), 116.7 (C3), 114.2 (C3', C5'), 113.7 (C7), 110.0 (C5), 69.6 (CH-N), 63.4 (CH_2-O), 63.2 (CH_2-O), 55.2 (O-CH_3), 16.4 (CH_3), 16.2 (CH_3).

4.5. Diethyl (((2-oxo-2*H*-chromen-6-yl)amino)(phenyl)methyl)phosphonate (**1e**)

Yellow powder; yield: 88%; m.p: 143-144 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.48 (d, *J* = 9.6 Hz, 1H, H-4), 7.47 – 7.42 (m, 2H, H2', H6'), 7.37 – 7.32 (m, 2H, H3', H5'), 7.31 – 7.27 (m, 1H, H4'), 7.10 (d, *J* = 8.9 Hz, 1H, H-8), 6.84 (dd, *J* = 8.9, 2.8 Hz, 1H, H-7), 6.52 (d, *J* = 2.8 Hz, 1H, H-5), 6.31 (d, *J* = 9.6 Hz, 1H, H-3), 4.96 (dd, *J* = 10.0, 7.6 Hz, 1H, N-H), 4.73 (d, *J* = 7.5 Hz, 1H, CH-N), 4.70 (d, *J* = 7.5 Hz, 1H, CH-N (rotamer)), 4.20 – 4.02 (q, *J* = 7.1 Hz, 2H, CH_2-O), 3.93 (cs, 1H, CH_2-O), 3.66 (cs, 1H, CH_2-O), 1.29 (td, *J* = 7.0, 0.7 Hz, 3H, CH_3), 1.11 (td, *J* = 7.1, 0.7 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz,**

$CDCl_3$): δ (ppm) 161.1 (C=O), 147.2 (C8a), 143.3 (C4), 143.2 (C6), 135.2 (C1'), 128.8 (C3', C5'), 127.8 (C4'), 127.7 (C2', C6'), 119.2 (C4a), 118.9 (C8), 117.5 (C7), 116.8 (C3), 110.0 (C5), 63.5 (CH_2-O), 63.3 (CH_2-O), 57.1 (CH-N), 16.4 (CH_3), 16.1 (CH_3).

4.6. Diethyl ((3-hydroxyphenyl)((2-oxo-2*H*-chromen-6-yl)amino)methyl)phosphonate (**1f**)

Off-white powder; yield: 82%; m.p: 171-172 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.46 (d, J = 9.5 Hz, 1H, H-4), 7.23 (t, J = 7.7 Hz, 1H, H-5'), 7.08 (s, large, 2H, H-2', H-6'), 6.96 (d, J = 7.7 Hz, 1H, H-4'), 6.84 – 6.80 (m, 1H, H-8), 6.78 (d, J = 2.9 Hz, 1H, H-7), 6.50 (d, J = 2.8 Hz, 1H, H-5), 6.32 (d, J = 9.5 Hz, 1H, H-3), 4.90 (t, J = 8.9 Hz, 1H, N-H), 4.70 (d, J = 7.4 Hz, 1H, CH-N), 4.66 (d, J = 7.4 Hz, 1H, CH-N (rotamer)), 4.12 (q, J = 7.0 Hz, 2H, CH_2-O), 3.94 (cs, 1H, CH_2-O), 3.62 (cs, 1H, CH_2-O), 1.29 (t, J = 7.1 Hz, 3H, CH_3), 1.10 (t, J = 7.0 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 161.2 (C=O), 157.1 (C3'), 147.3 (C8a), 143.3 (C4), 142.9 (C6), 136.6 (C1'), 130.0 (C5'), 120.0 (C6'), 119.9 (C8), 119.2 (C4a), 118.9 (C7), 117.6 (C3), 116.9 (C4'), 115.8 (C2'), 110.0 (C5), 63.9 (CH_2-O), 63.6 (CH_2-O), 57.1 (CH-N), 16.4 (CH_3), 16.1 (CH_3).

4.7. Diethyl ((2-hydroxyphenyl)((2-oxo-2*H*-chromen-6-yl)amino)methyl)phosphonate (**1g**)

Orange powder; yield: 73%; m.p: 180-181 ºC. **1H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.49 (d, J = 9.5 Hz, 1H, H-4), 7.23 (dt, J = 7.7, 2.0 Hz, 1H, H-5'), 7.20 – 7.14 (m, 1H, H-3'), 7.11 (dd, J = 9.0, 1.2 Hz, 1H, H-8), 6.95 (dd, J = 8.2, 3.5 Hz, 1H, H-5), 6.90 – 6.85 (m, 2H, H-4', H-6'), 6.62 (d, J = 2.8 Hz, 1H, H-7), 6.32 (dd, J = 9.5, 0.8 Hz, 1H, H-3), 5.01 (d, J = 2.4 Hz, 1H, CH-N), 4.94 (d, J = 2.4 Hz, 1H, CH-N (rotamer)), 4.2 (q, J = 7.1, 2H, CH_2-O), 4.06 (cs, 1H, CH_2-O), 3.95 (cs, 1H, CH_2-O), 1.27 (t, J = 7.1 Hz, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 161.2 (C=O), 155.5 (C2'), 147.6 (C8a), 143.3 (C4), 142.9 (C6), 129.8 (C6'), 128.8 (C4'), 121.2 (C1'), 120.9 (C5'), 119.3 (C4a), 118.6 (C8), 117.6 (C7), 116.8 (C3), 110.6 (C5), 64.2 (CH_2-O), 63.8 (CH_2-O), 54.5 (CH-N), 16.4 (CH_3), 16.2 (CH_3).

4.8. Diethyl ((3-nitrophenyl)((2-oxo-2*H*-chromen-6-yl)amino)methyl)phosphonate (**1h**)

Orange powder; yield: 71%; m.p: 70-71 ºC. **1H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.39 (d, J = 2.3 Hz, 1H, H2'), 8.16 (d, J = 8.2 Hz, 1H, H4'), 7.81 (d, J = 8.2 Hz, 1H, H6'), 7.56 (t, J = 8.2 Hz, 1H, H5'), 7.50 (d, J = 9.5 Hz, 1H, H4), 7.13 (d, J = 9.0 Hz, 1H, H8), 6.83 (dd, J = 9.0, 2.8 Hz, 1H, H7), 6.49 (d, J = =2.8 Hz, 1H, H5), 5.12 (d, J = 7.1 Hz, 1H, N-H), 4.88 (d, J = 7.1 Hz, 1H, CH-N), 4.80 (d, J = 7.1 Hz, 1H, CH-N (rotamer)), 4.29 (s large,

2H, CH_2-O), 4.12 – 4.08 (m, 4H, CH_2-O), 3.85 (cs, 1H, CH_2-O (rotamer)), 1.31 – 1.25 (m, 6H, CH_3 x 2), 1.23 (t, *J* = 7.1 Hz, 3H, CH_3 (rotamer)).

4.9. Diethyl (furan-2-yl((2-oxo-2*H*-chromen-6-yl)amino)methyl)phosphonate (**1i**)
Yellow powder; yield: 82%; m.p: 112-113 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.55 (dd, *J* = 9.6, 0.6 Hz, 1H, H-4), 7.39 (td, *J* = 1.9, 0.8 Hz, 1H, H-5'), 7.14 (d, *J* = 9.0 Hz, 1H, H-8), 6.88 (dd, *J* = 9.0, 2.8 Hz, 1H, H-7), 6.64 (d, *J* = 2.7 Hz, 1H, H-5), 6.39 (tt, *J* = 3.2, 0.7 Hz, 1H, H-2'), 6.35 – 6.32 (m, 1H, H- 4'), 4.87 (d, *J* = 8.0 Hz, 1H, CH-N), 4.83 (d, *J* = 8.0 Hz, 1H, CH-N (rotamer)), 4.68 (t, *J* = 8.0 Hz, 1H, N-H), 4.18 (q, *J* = 7.1 Hz, 2H, CH_2-O), 4.06 (cs, 1H, CH_2-O), 3.87 (cs, 1H, CH_2-O), 1.30 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3), 1.20 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 161.1 (C=O), 148.7 (C8a), 147.6 (C6), 143.2 (C4), 142.9 (C5'), 142.8 (C2'), 119.3 (C4a), 117.6 (C8), 116.9 (C7), 111.0 (C3), 110.3 (C4'), 109.0 (C5), 63.6 (CH-N), 51.4 (CH_2-O), 49.8 (CH_2-O), 16.4 (CH_3), 16.2 (CH_3).

4.10. Diethyl ((2-chloroquinolin-3-yl)((2-oxo-2*H*-chromen-6-yl)amino)methyl)phosphonate (**1j**)
Yellow powder; yield: 71%; m.p: 128-129 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.37 (dd, *J* = 3.3, 0.7 Hz, 1H, H-4'), 8.01 (dd, *J* = 8.5, 1.0 Hz, 1H, H-8'), 7.80 – 7.76 (m, 1H, H-7'), 7.73 (dddd, *J* = 8.5, 6.9, 1.5, 0.8 Hz, 1H, H-5'), 7.54 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, H-6'), 7.50 (dd, *J* = 9.6, 0.6 Hz, 1H, H-4), 7.14 (d, *J* = 8.9 Hz, 1H, H-8), 6.89 (dd, *J* = 8.9, 2.8 Hz, 1H, H-7), 6.55 (d, *J* = 2.8 Hz, 1H, H-5), 6.33 (d, *J* = 9.6 Hz, 1H, H-3), 5.46 (d, *J* = 8.2 Hz, 1H, CH-N), 5.40 (d, *J* = 8.2 Hz, 1H, CH-N (rotamer)), 5.20 (dd, *J* = 10.0, 8.2 Hz, 1H, N-H), 4.30 (t, *J* = 7.1 Hz, 2H, CH_2), 3.96 (cs, 1H, CH_2-O), 3.75 (cs, 1H, CH_2-O), 1.38 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3), 1.07 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 160.9 (C=O), 150.0 (C2'), 147.6 (C8a), 147.2 (C6), 143.1 (C4), 142.5 (C8'a), 137.5 (C4'), 131.1 (C3'), 128.3 (C7'), 128.2 (C5'), 127.8 (C8'), 127.5 (C6'), 127.2 (C4'a), 119.4 (C4a), 118.7 (C8), 117.9 (C7), 117.1 (C3), 109.5 (C5), 64.0 (CH_2-O), 63.7 (CH_2-O), 52.1 (CH-N), 16.5 (CH_3), 16.1(CH_3).

4.11. Diethyl ((2-chloro-6-fluoroquinolin-3-yl)((2-oxo-2*H*-chromen-6-yl)amino)methyl) phosphonate (*1k*)
Yellow powder; yield: 75%; m.p: 187-188 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.34 (d, *J* = 2 Hz, 1H, H-4'), 8.01 (dd, *J* = 9.2, 5.1 Hz, 1H, H-8'), 7.51 (d, *J* = 9.0 1H, H-4), 7.50 – 7.48 (m, 1H, H-5'),7 .39 (dd, *J* = 8.6, 2.8 Hz, 1H, H-7'), 7.14 (d, *J* = 8.9 Hz, 1H, H-8), 6.87 (dd, *J* = 9.0, 2.8 Hz, 1H, H-7), 6.54 (d, *J* = 2.8 Hz, 1H, H-5), 6.33 (d, *J* = 9.5 Hz, 1H, H-3), 5.47 (d, *J* = 7.4 Hz, 1H, CH-N), 5.38 (d, *J* = 7.4 Hz, 1H CH-N (rotamer)), 5.23 (t, *J* =

9.1 Hz, 1H, N-H), 4.28 (t, *J* = 7.1, , 2H, CH_2-O), 3.98 (cs, 1H, CH_2-O), 3.78 (cs, 1H, CH_2), 1.38 (td, *J* = 7.0, 0.6 Hz, 3H, CH_3), 1.08 (td, *J* = 7.0, 0.6 Hz, 3H, CH_3). **^{13}C NMR(100.6 MHz, $CDCl_3$)**: δ (ppm) 161.0 (d, *J* = 250 Hz, C6'), 160.9 (C=O), 149.4 (d, *J* = 6 Hz, C2') 147.6 (C8a), 143.1 (C4), 142.4 (C8'a), 136.9 (C6), 130.8 (d, *J* = 9 Hz, C3'), 130.7 (C4'a), 128.2 (d, *J* = 10 Hz, C8'), 122.2 (d, *J* = 25 Hz, C7'), 119.4 (C4a), 118.6 (C8), 117.9 (C7), 117.1 (C3), 111.1 (d, *J* = 27 Hz, C5'), 109.5 (C5), 63.8 (CH_2-O), 63.7 (CH_2-O), 52.9 (CH-N), 51.4 (CH-N (rotamer)), 16.5 (CH_3), 16.16 (CH_3).

4.12. Diethyl ((6-bromo-2-chloroquinolin-3-yl)((2-oxo-2*H*-chromen-6-yl)amino)methyl) phosphonate (**1l**)

Off-white powder; yield: 88%; m.p: 201-202 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.27 (dd, *J* = 3.3, 0.7 Hz, 1H, H-4'), 7.94 (d, *J* = 2.1 Hz, 1H, H-5'), 7.88 (d, *J* = 9.0 Hz, 1H, H-8'), 7.79 (ddd, *J* = 9.0, 2.2, 0.8 Hz, 1H, H- 7'), 7.50 (dd, *J* = 9.6, 0.7 Hz, 1H, H-4), 7.14 (d, *J* = 8.9 Hz, 1H, H-8), 6.86 (dd, *J* = 8.9, 2.8 Hz, 1H, H-7), 6.52 (d, *J* = 2.8 Hz, 1H, H-5), 6.33 (d, *J* = 9.5 Hz, 1H, H-3), 5.45 (d, *J* = 8.1 Hz, 1H, CH-N), 5.39 (d, *J* = 8.1 Hz, 1H, CH-N (rotamer)), 5.20 (dd, *J* = 10.1, 8.1 Hz, 1H, N-H), 4.28 (t, *J* = 7.1, 1.0 Hz, 2H, CH_2-O), 3.98 (cs, 1H, CH_2-O), 3.78 (cs, 1H, CH_2-O), 1.38 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3), 1.09 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 160.9 (C=O), 147.6 (C8a), 143.1 (C4), 136.3 (C6), 134.5 (C4'), 129.9 (C3'), 129.8 (C8'), 119.4 (C4a), 118.6 (C8), 118.0 (C7), 117.1 (C3), 109.5 (C5), 63.8 (CH-N), 53.0 (CH_2-O), 51.4 (CH_2-O), 16.5 (CH_3), 16.18 (CH_3).

5) General procedure for the synthesis of α-aminophosphonates benzodioxane derivatives 6a-m

To a solution of 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (**5**) (1 mmol; 1 equiv) in ethanol (5 mL), the appropriate aldehyde (1 mmol; 1 equiv), triethyl phosphite (1 mmol; 1 equiv), and tin(II) chloride ($SnCl_2$) (10 mol%) were added. The reaction mixture was stirred under reflux in ethanol for 24 hours. Once the reaction was deemed complete, ethanol was evaporated under reduced pressure. Then, 15 mL of water was added to the reaction mixture, and the product was extracted using ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, filtered under reduced pressure, and the solvent was evaporated under reduced pressure. The crude reaction product was purified by silica gel column chromatography using an ethyl acetate/hexane (5:5) mixture.

5.1. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(phenyl)methyl)phosphonate (**6a**)

White powder; yield: 96%; m.p.: 110-111 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.47 – 7.41 (m, 2H, H-2', H-6'), 7.35 – 7.29 (m, 2H, H-3', H-5'), 7.28 – 7.23 (m, 1H, H-4'), 6.62 (d, J = 8.5 Hz, 1H, H-8), 6.12 (d, J = 8.5 Hz, 1H, H-7), 6.10 (d, J = 2.0 Hz, 1H, H-5), 4.67 (s, 1H, CH-N (rotamer)) 4.61 (s, 1H, CH-N), 4.18 – 4.14 (m, 2H, O- CH_2), 4.14 – 4.11 (m, 2H- O- CH_2), 4.11 – 4.03 (m, 2H, CH_2), 3.92 (cs, 1H, CH_2), 3.67 (cs, 1H, CH_2), 1.28 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.10 (td, J = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 143.9 (C4a), 141.3 (C6), 136.3 (C1'), 136.0 (C8a), 128.6 (C3', C5'), 127.9 (C2', C6'), 127.8 (C4'), 117.6 (C7), 107.7 (C5), 102.74 (C8), 64.6 (CH_2-O (dioxane)), 64.1 (CH_2-O (dioxane)), 63.3 (CH_2-O), 63.2 (CH_2-O), 57.5 (CH-N), 56.0 (CH-N (rotamer)), 16.5 (CH_3), 16.2 (CH_3).

5.2. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(p-tolyl)methyl)phosphonate (**6b**)

White powder; yield: 91%; m.p: 102-103 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.31 (dd, J = 8.2, 2.3 Hz, 2H, H-2', H-6'), 7.12 (dd, J = 8.2, 0.6 Hz, 2H, H-3', H-5'), 6.61 (dd, J = 8.4, 0.6 Hz, 1H, H-8), 6.16 – 6.09 (m, 2H, H-5, H-7), 4.64 (s, 1H, CH-N), 4.61 (s, 1H, CH-N (rotamer)), 4.50 (s. large, 1H, N-H), 4.18 – 4.14 (m, 2H, O- CH_2), 4.12 (td, J = 2.5, 1.3 Hz, 2H, O- CH_2), 4.11 – 4.04 (m, 2H, CH_2), 3.93 (cs, 1H, CH_2), 3.69 (cs, 1H, CH_2), 2.30 (s, 3H, CH_3), 1.28 (td, J = 7.1, 0.5 Hz, 3H, CH_3), 1.12 (td, J = 7.0, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 143.9 (C4a), 141.3 (C6), 137.6 (C4'), 136.3 (C8a), 132.9 (C1'), 129.3 (C3', C5'), 127.8 (C2', C6'), 117.6 (C8), 107.7 (C7), 102.8 (C5), 64.6 (CH_2-O (dioxane)), 64.1 (CH_2-O (dioxane)), 63.3 (CH_2-O), 63.1 (CH_2-O), 57.2 (CH-N (rotamer)), 55.7 (CH-N (rotamer)), 21.2 (CH_3-Ar), 16.4 (CH_3), 16.21 (CH_3).

5.3. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(4-methoxyphenyl)methyl) phosphonate (**6c**)

White powder; yield: 96%; m.p: 99-100 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.37 (d, J = 7 Hz, 2H, H-3', H-5'), 6.86 (d, J = 7 Hz,, 2H, H-2', H-6'), 6.62 (d, J = 8.5 Hz, 1H, H-8), 6.12 (dd, J = 8.5, 2 Hz, 1H, H-7) 6.10 (d, J = 2 Hz, 1H, H-5), 4.62 (s, 1H, CH-N), 4.56 (s, 1H, CH-N (rotamer)), 4.48 (s, 1H, N-H), 4.18 – 4.14 (m, 2H, O-CH_2), 4.14 – 4.11 (m, 2H, O-CH_2), 4.11 – 4.04 (m, 2H, CH_2), 3.93 (cs, 1H, CH_2), 3.77 (s, 3H, O-CH_3), 3.69 (cs, 1H, CH_2), 1.28 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.13 (td, J = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 159.3 (C4'), 143.9 (C4a), 141.3 (C6), 136.3 (C8a), 128.9 (C2', C6'), 127.8 (C1'), 117.6 (C3', C5'), 114.1 (C8), 107.8 (C7), 102.8 (C5), 64.6

(CH_2-O (dioxane)), 63.3 (CH_2-O (dioxane)), 63.2 (CH-N), 63.1 (CH-N(rotamer)), 56.8 (CH_2-O), 55.3 (CH_2-O), 55.2 (O-CH_3), 16.5 (CH_3), 16.31(CH_3).

5.4. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(4-fluorophenyl)methyl) phosphonate (**6d**)

White powder; yield: 88%; m.p: 120-121 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.42 (ddd, *J* = 8.9, 5.2, 2.4 Hz, 2H, H-3', H-5'), 7.06 – 6.98 (m, 2H, H-2', H-6'), 6.63 (d, *J* = 8.6 Hz, 1H, H-8), 6.12 (dd, *J* = 8.6, 2.8 Hz, 1H, H-7), 6.08 (d, *J* = 2.7 Hz, 1H, H-5), 4.65 (s, 1H, CH-N), 4.59 (s, 1H, CH-N (rotamer)), 4.17 (dq, *J* = 5.8, 1.8 Hz, 2H, O-CH_2), 4.15 – 4.12 (m, 2H, O-CH_2), 4.12 – 4.03 (m, 2H, CH_2), 3.96 (cs, 1H, CH_2), 3.75 (cs, 1H, CH_2), 1.28 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3), 1.14 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 162.1 (d, *J* = 246 Hz, C4'), 143.9 (C4a), 141.0 (d, *J* = 15 Hz, C1'), 136.4 (C6), 137.7 (C8a), 129.4 (d, *J* = 8 Hz, C2', C6'), 117.6 (C8), 115.5 (d, *J* = 21 Hz, C3', C5'), 107.7 (C7), 102.7 (C5), 64.1 (CH_2-O (dioxane)), 63.4 (CH_2-O (dioxane)), 63.2 (CH-N), 63.1 (CH-N (rotamer)), 56.8 (O-CH_2), 55.3 (O-CH_2), 16.5 (CH_3), 16.3 (CH_3).

5.5. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(3-hydroxyphenyl)methyl) phosphonate (**6e**)

Brown powder; yield: 92%; m.p: 131-132 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.93 (s, 1H, OH), 7.18 (td, *J* = 7.9, 1.0 Hz, 1H, H- 5'), 7.12 (q, *J* = 2.2 Hz, 1H, H-2'), 6.90 (ddt, *J* = 7.7, 2.6, 1.2 Hz, 1H, H-4'), 6.78 (dtd, *J* = 8.2, 2.3, 1.0 Hz, 1H, H-6'), 6.63 – 6.56 (m, 1H, H-8), 6.12 (d, *J* = 1.1 Hz, 1H, H-5), 6.11 – 6.09 (m, 1H, H-7), 4.60 (d, *J* = 6.4 Hz, 1H, CH-N), 4.58 (d, *J* = 6.4 Hz, CH-N (rotamer)) 4.51 (d, *J* = 8.9 Hz, 1H, N-H), 4.18 – 4.14 (m, 2H, O-CH_2), 4.13 (td, *J* = 3.0, 1.5 Hz, 2H, O-CH_2), 4.11 – 4.03 (m, 2H, CH_2), 3.92 (cs, 1H, CH_2), 3.63 (cs, 1H, CH_2), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3), 1.08 (td, *J* = 7.1, 0.7 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 157.5 (C3'), 143.9 (C4a), 141.2 (C6), 137.0 (C1'), 136.3 (C8a), 129.7 (C5'), 119.8 (C6'), 117.5 (C8), 115.7 (C4'), 114.4 (C2'), 108.4 (C8), 102.8 (C5), 63.9 (CH_2-O (dioxane)), 63.8 (CH_2-O (dioxane)), 63.7 (CH-N), 57.4 (CH_2-O), 55.9 (CH_2-O), 16.4 (CH_3), 16.2 (CH_3).

5.6. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(2-hydroxyphenyl)methyl) phosphonate (**6f**)

Brown powder; yield: 82%; m.p: 148-149 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.19 (dt, *J* = 5.7, 1.8 Hz, 1H, H-6'), 7.18 – 7.13 (m, 1H, H-4'), 6.90 (d, *J* = 9.2, 1H, H-3'), 6.86 (tt, *J* = 7.5, 1.1 Hz, 1H, H-5'), 6.64 (d, *J* = 8.6 Hz, 1H, H-8), 6.24 (d, *J* = 2 Hz, 1H, H-5),

6.22 (d, *J* = 8.6 Hz, 1H, H-7) 4.80 (s, 1H, CH-N), 4.77 (s, 1H, CH-N (rotamer)), 4.18 – 4.15 (m, 2H, O-CH_2), 4.15 – 4.12 (m, 2H, O-CH_2), 4.12 – 4.06 (m, 2H, CH_2), 4.05 – 3.91 (m, 2H, CH_2), 1.26 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3), 1.22 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 156.0 (C2'), 143.9 (C4a), 140.9 (C6), 137.3 (C8a), 129.5 (C6'), 129.1 (C4'), 121.0 (C1'), 120.5 (C5'), 118.2 (C3'), 117.6 (C8), 108.7 (C7), 104.0 (C5), 64.6 (CH_2-O (dioxane)), 64.1 (CH_2-O (dioxane)), 63.7 (CH_2-O), 63.6 (CH_2-O), 56.3 (CH-N), 54.83 (CH-N (rotamer)), 16.4 (CH_3), 16.3 (CH_3).

5.7. Diethyl ((4-chlorophenyl)((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)methyl) phosphonate (**6g**)

White powder; yield: 91%; m.p: 106-107 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.38 (dq, *J* = 9.0, 2.5 Hz, 2H, H-3', H-5'), 7.33 – 7.27 (m, 2H, H-2', H-6'), 6.63 (d, *J* = 8.6 Hz, 1H, H-8), 6.11 (dd, *J* = 8.6, 2.8 Hz, 1H, H-7), 6.06 (d, *J* = 2.7 Hz, 1H, H-5), 4.64 (s, 1H, CH-N), 4.58 (s, 1H, CH-N (rotamer)), 4.19 – 4.15 (m, 2H, O-CH2), 4.13 (td, *J* = 3.3, 2.0 Hz, 2H, O-CH_2), 4.12 – 4.05 (m, 2H, O-CH_2), 3.97 (cs, 1H, CH_2), 3.77 (cs, 1H, CH_2), 1.29 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3), 1.15 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 143.9 (C4a), 140.9 (C6), 136.5 (C8a), 134.7 (C1'), 133.7 (C4'), 129.2 (C3', C5'), 128.8 (C2', C6'), 117.7 (C8), 107.7 (C7), 102.7 (C5), 64.7 (CH_2-O (dioxane)), 64.1 (CH_2-O (dioxane)), 63.4 (CH_2-O), 63.3 (CH_2-O), 57.0 (CH-N), 55.5 (CH-N (rotamer)), 16.5 (CH_3), 16.3 (CH_3).

5.8. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(4-(dimethylamino)phenyl) methyl)phosphonate (**6h**)

Orange powder; yield: 84%; m.p: 150-151 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.25 (dd, *J* = 7 Hz, 2H, H-2', H-6'), 6.66 (d, *J* = 7 Hz, 2H, H-3', H-5'), 6.61 (dt, *J* = 8.7, 1.2 Hz, 1H, H-8), 6.13 (d, *J* = 8.6 Hz, 1H, H-7), 6.11 (d, *J* = 1.2 Hz, 1H, H-5), 4.55 (s, 1H, CH-N), 4.49 (s, 1H, CH-N (rotamer)), 4.18 – 4.14 (m, 2H, O-CH_2), 4.12 (td, *J* = 3.3, 1.9 Hz, 2H, O-CH_2), 4.11 – 4.07 (m, 2H, CH_2), 3.92 (cs, 1H, CH_2), 3.67 (sc, 1H, CH_2), 2.95 (s, 1H, N-H), 2.91 (s, 6H, 2 x N-CH_3), 1.30 – 1.26 (m, 3H, CH_3), 1.13 (td, *J* = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 150.1 (C4'), 143.8 (C4a), 141.5 (C6), 136.1 (C8a), 128.5 (C2', C6'), 123.0 (C1'), 117.4 (C8), 112.5 (C3', C5'), 107.7 (C7), 102.7 (C5), 64.6 (CH_2-O (dioxane)), 63.1 (CH_2-O (dioxane)), 63.0 (CH_2-O), 56.7 (CH_2-O), 40.5 (CH-N), 40.4 (CH-N (rotamer)), 16.4 (CH_3), 16.27 (CH_3).

5.9. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(3-nitrophenyl)methyl) phosphonate (**6i**)

Red powder; yield: 45%; m.p: 104-105 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.30 (q, J = 2.2 Hz, 1H, H-2'), 8.12 (dtd, J = 8.2, 2.1, 1.0 Hz, 1H, H-4'), 7.83 – 7.77 (m, 1H, H-6'), 7.50 (td, J = 8.0, 0.8 Hz, 1H, H-5'), 6.62 (d, J = 8.6 Hz, 1H, H-8), 6.11 (dd, J = 8.7, 2.8 Hz, 1H, H-7), 6.05 (d, J = 2.7 Hz, 1H, H-5), 4.77 (s, 1H, CH-N), 4.71 (s, 1H, CH-N (rotamer)), 4.62 (s, large, 1H, N-H), 4.25 – 4.16 (m, 2H, O-CH_2), 4.16 – 4.14 (m, 2H, O-CH_2), 4.13 – 4.11 (m, 2H, CH_2), 4.11 – 4.06 (m, 2H, CH_2), 4.02 (sc, 1H, CH_2), 3.88 (cs, 1H, CH_2), 1.31 – 1.28 (m, 3H, CH_3), 1.17 (td, J = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 148.4 (C3'), 143.9 (C4a), 140.4 (C6), 139.0 (C1'), 138.8 (C1' (rotamère)), 136.6 (C6'), 133.7 (C8a), 129.4 (C5'), 122.8 (C2'), 122.7 (C4'), 117.7 (C8), 107.5 (C7), 102.6 (C5), 64.5 (CH_2-O (dioxane)), 64.1 (CH_2-O (dioxane)), 64.0 (CH_2-O), 63.2 (CH_2-O), 56.9 (CH-N), 55.5 (CH-N (rotamer)), 16.3 (CH_3), 16.2 (CH_3).

5.10. Diethyl (hydroxy(3-nitrophenyl)methyl)phosphonate (**6i'**)

Orange powder; yield: 32%; m.p: 97-98 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.40 (d, J = 1.8 Hz, 1H, H-2), 8.17 (dtd, J = 8.2, 2.1, 1.0 Hz, 1H, H-4), 7.82 (dddt, J = 7.7, 2.4, 1.8, 0.9 Hz, 1H, H-6), 7.54 (td, J = 8.0, 0.9 Hz, 1H, H-5), 5.16 (d, J = 4.9 Hz, 1H, CH-N), 5.13 (d, J = 4.9 Hz, 1H, CH-N(rotamer)), 4.77 – 4.71 (m, 1H, N-H), 4.20 – 4.04 (m, 4H, O-CH_2), 1.33 – 1.28 (m, 3H, CH_3), 1.28 – 1.24 (m, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 148.2 (C3), 139.1 (C1), 133.0 (C6), 129.1 (C5), 122.9 (C2), 122.0 (C4), 70.7 (CH_2-O), 69.1 (CH_2-O), 64.0 (CH_2-O), 63.4 (CH_2-O), 16.4 (CH_3), 16.3 (CH_3).

5.11. Diethyl (((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)(furan-2-yl)methyl) phosphonate (**6j**)

Off-white powder; yield: 96%; m.p: 132-133 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 7.38 (td, J = 1.9, 0.9 Hz, 1H, H-5'), 6.69 – 6.63 (m, 1H, H-8), 6.36 (tt, J = 3.3, 0.8 Hz, 1H, H-2'), 6.34 – 6.30 (m, 1H, H-4'), 6.21 (d, J = 9 Hz, 1H, H-7), 6.18 (d, J = 2 Hz, 1H, H-5), 4.76 (d, J = 7.5 Hz, 1H, CH-N), 4.72 (d, J = 7.5 Hz, 1H, CH-N(rotamer)), 4.23 – 4.19 (m, 2H, O-CH_2), 4.19 – 4.16 (m, 2H, O-CH_2), 4.16 – 4.13 (m, 2H, CH_2), 4.05 (cs, 1H, CH_2), 3.87 (cs, 1H, CH_2), 1.31 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.20 (td, J = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm), 143.2 (C4a), 142.5 (C5'), 140.9 (C6), 140.8 (C2'), 136.7 (C8a), 117.6 (C8), 110.8 (C3'), 108.8 (C4'), 107.9 (C7), 103.1 (C5), 64.6

(CH_2-O (dioxane)), 63.6 (CH_2-O (dioxane)), 63.5 (CH_2-O), 63.2 (CH_2-O), 51.9 (CH-N), 50.3 (CH-N (rotamer)), 16.5 (CH_3), 16.3 (CH_3).

5.12. Diethyl ((2-chloroquinolin-3-yl)((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)methyl) phosphonate (**6k**)

Yellow powder; yield: 82%; m.p: 165-166 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.35 (dd, J = 3.4, 0.7 Hz, 1H, H-6'), 8.00 (dd, J = 8.5, 1.0 Hz, 1H, H-2'), 7.82 – 7.76 (m, 1H, H-3'), 7.71 (dddd, J = 8.5, 6.9, 1.5, 0.8 Hz, 1H, H-5'), 7.53 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H, H-4'), 6.66 – 6.59 (m, 1H, H-8), 6.18 – 6.14 (m, 2H, H-5, H-7), 5.36 (d, J = 8.5 Hz, 1H, CH-N), 5.33 (d, J = 8.5 Hz, 1H, CH-N (rotamer)), 4.82 (dd, J = 9.9, 8.6 Hz, 1H, N-H), 4.26 (dq, J = 8.1, 7.1 Hz, 2H, O-CH_2), 4.18 – 4.12 (m, 2H, O-CH_2), 4.11 – 4.04 (m, 2H, CH_2), 3.99 – 3.87 (sc, 1H, CH_2), 3.74 (sc, 1H, CH_2), 1.36 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.06 (td, J = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 150.3 (C2'), 147.1 (C4a), 144.1 (C8'a), 140.1 (C6), 139.9 (C6 (rotamer)), 137.6 (C8a), 136.7 (C4'), 130.7 (C3'), 129.1 (C7'), 128.2 (C5'), 127.9 (C8'), 127.3 (C4'a), 127.2 (C6'), 117.8 (C8), 107.2 (C7), 102.6 (C5), 64.6 (CH_2-O (dioxane)), 64.1 (CH_2-O (dioxane)), 63.9 (CH_2-O), 63.4 (CH_2-O), 53.2 8 (CH-N), 51.7 (CH-N (rotamer)), 16.5 (CH_3), 16.1 (CH_3).

5.13. Diethyl ((2-chloro-6-fluoroquinolin-3-yl)((2,3-dihydrobenzo[**b**][1,4]dioxin-6-yl)amino)methyl)phosphonate (**6l**)

Orange powder; yield: 71%; m.p: 161-162 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.29 (d, J = 3.3 Hz, 1H, H-4'), 8.00 (dd, J = 9.2, 5.2 Hz, 1H, H-8'), 7.71 (dd, J = 5.7, 3.3 Hz, 1H, H-5'), 7.53 (dd, J = 5.7, 3.3 Hz, 1H, H- 7'), , 6.66 – 6.60 (m, 1H, H-8), 6.17 – 6.13 (m, 1H, H-7), 6.13 (d, J = 1.0 Hz, 1H, H-5), 5.37 (d, J = 7.9 Hz, 1H, CH-N), 5.32 (d, J = 7.9 Hz, 1H, CH-N(rotamer)), 4.80 (t, J = 9.3 Hz, 1H, N-H), 4.31 – 4.24 (m, 2H, O-CH_2), 4.24 – 4.19 (m, 2H, O-CH_2), 4.18 – 4.13 (m, 2H, CH_2), 3.96 (sc, 1H, CH_2), 3.77 (sc, 1H, CH_2), 1.36 (td, J = 7.1, 0.6 Hz, 3H, CH_3), 1.07 (td, J = 7.1, 0.6 Hz, 3H, CH_3).

5.14. Diethyl ((6-bromo-2-chloroquinolin-3-yl)((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)methyl)phosphonate (**6m**)

Yellow powder; yield: 82%; m.p: 213-214 ºC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ (ppm) 8.25 (d, J = 3.4 Hz, 1H, H-5'), 7.94 (d, J = 2.1 Hz, 1H, H-4'), 7.86 (d, J = 9.0 Hz, 1H, H-8'), 7.76 (ddd, J = 9.0, 2.2, 0.8 Hz, 1H, H-7'), 6.63 (dt, J = 9.0, 1.3 Hz, 1H, H-8), 6.15 (d , J = 9 Hz, 1H, H-7), 6.12 (d , J = 2 Hz, 1H, H-5) 5.38 (d, J = 8.3 Hz, 1H, CH-N), 5.32 (d, J = 8.3 Hz, 1H, CH-N(rotamer)), 4.81 (t, J = 9.2 Hz, 1H, N-H), 4.26 (dq, J = 8.1, 7.1 Hz, 2H,

O-CH_2), 4.18 – 4.15 (m, 2H, O-CH_2), 4.12 – 4.06 (m, 2H, CH_2), 3.96 (cs, 1H, CH_2), 3.77 (cs, 1H, CH_2), 1.36 (td, J = 7.0, 0.6 Hz, 3H, CH_3), 1.08 (td, J = 7.1, 0.6 Hz, 3H, CH_3). **^{13}C NMR (100.6 MHz, $CDCl_3$)**: δ (ppm) 150.8 (C2'), 150.7 (C8'a), 145.6 (C4a), 139.9 (C6), 136.8 (C4'), 136.5 (C8a), 134.2 (C7'), 130.4 (C3'), 129.9 (C8'), 128.4 (C4'a), 121.2 (C6'), 117.9 (C8), 107.2 (C7), 102.6 (C5), 64.6 (CH_2-O (dioxane)), 64.0 (CH_2-O (dioxane)), 63.5 (CH_2-O), 63.5 (CH_2-O), 53.3 (CH-N (rotamer)), 51.8 (CH-N (rotamer)), 16.5 (CH_3), 16.2 (CH_3).

6) ^{1}H NMR, ^{13}C NMR spectrum of compounds **3**, **4** and **1a-l** and **6a-m**

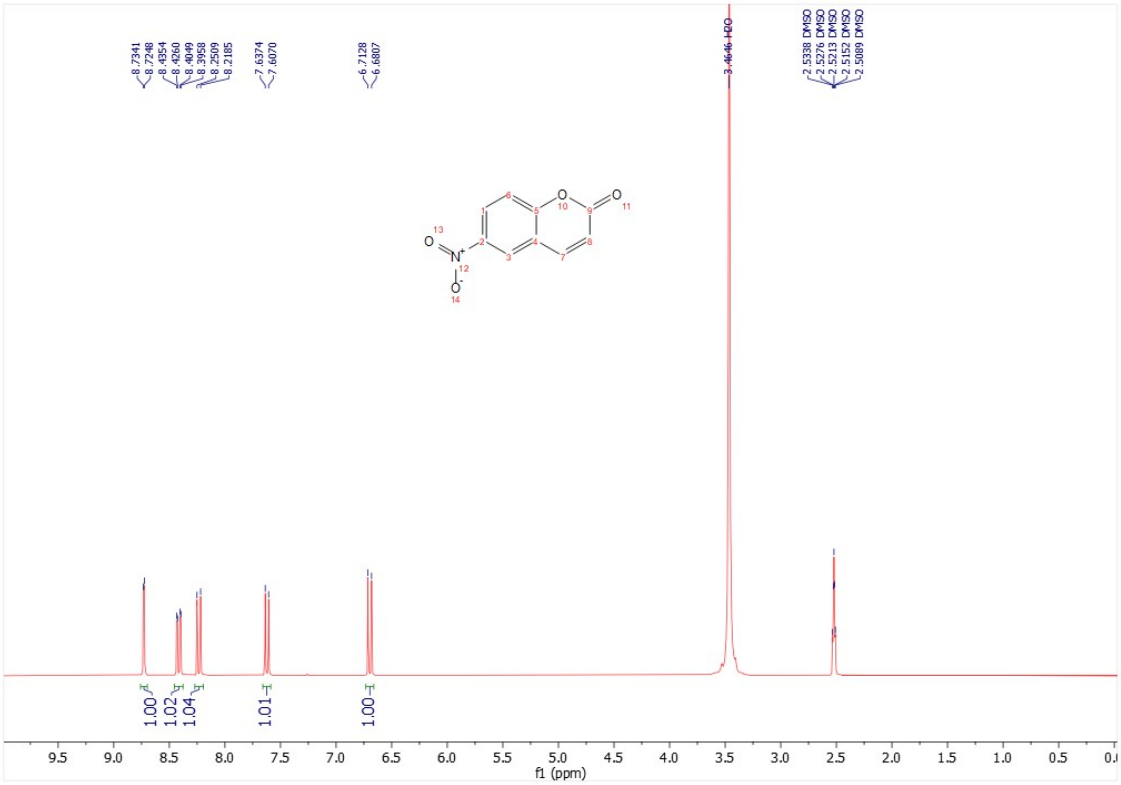

Figure 1. ^{1}H NMR spectrum of compound **3** in DMSO-d_6

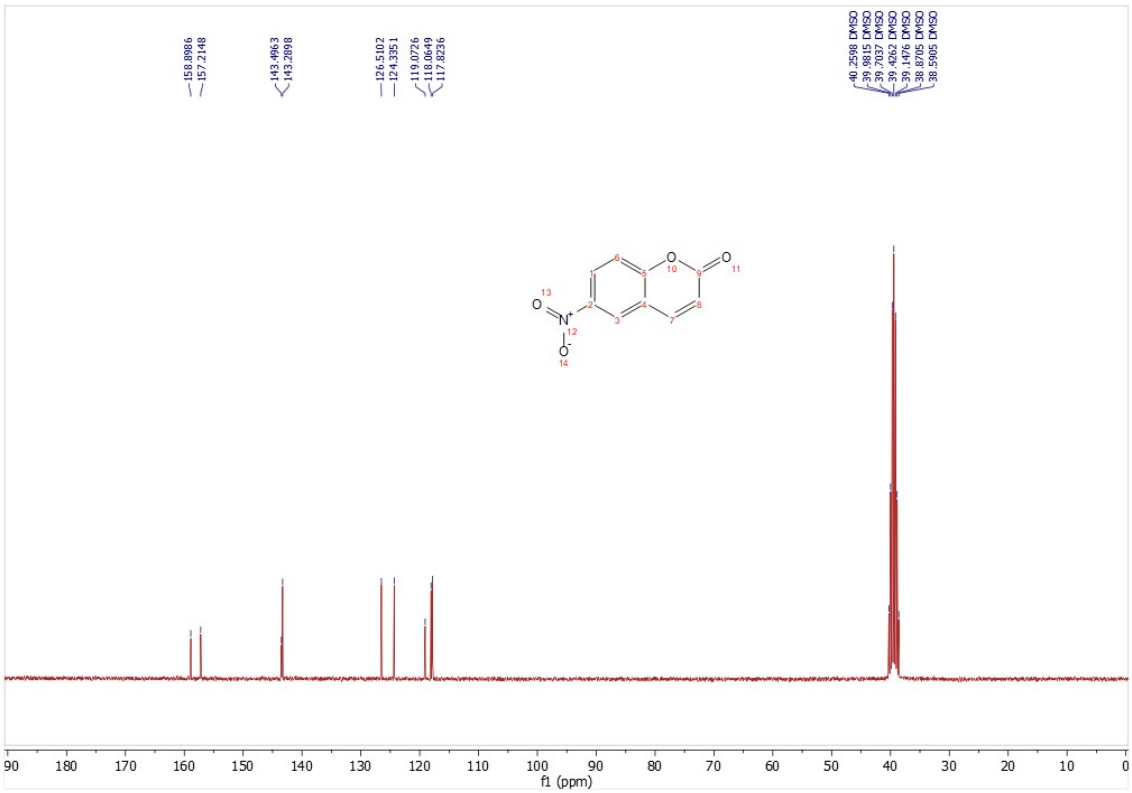

Figure 2. ^{13}C NMR spectrum of compound **3** in DMSO-d_6

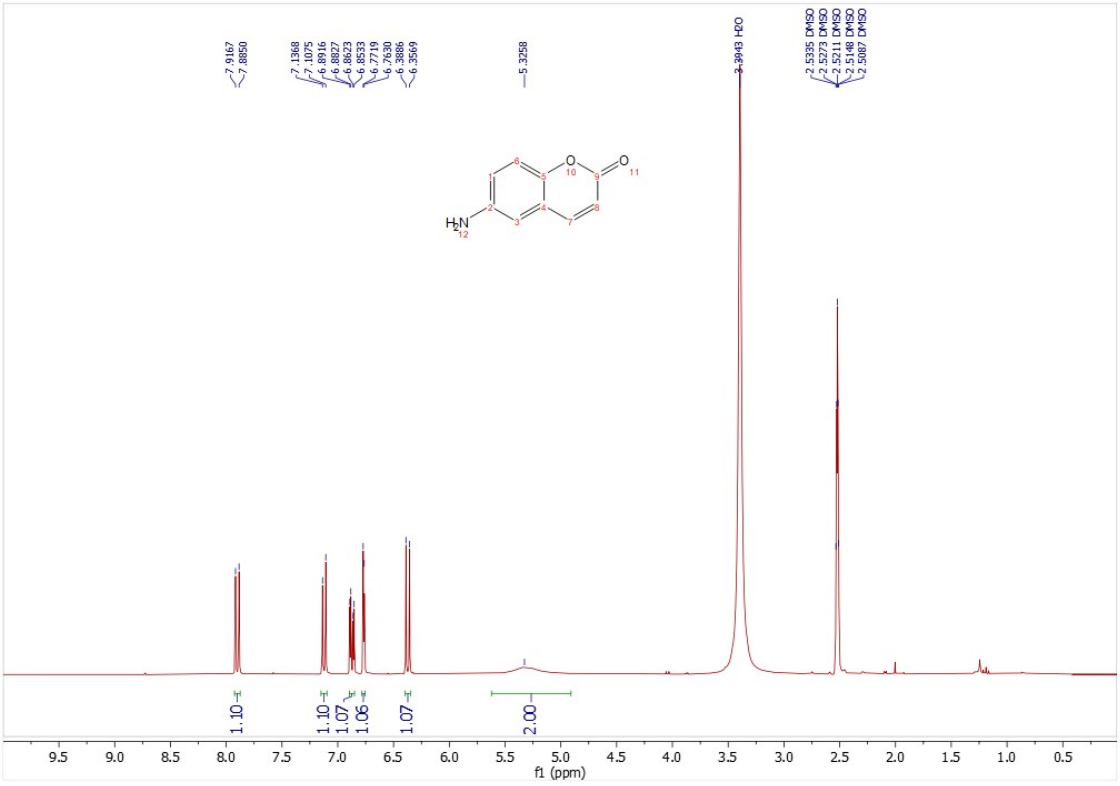

Figure 3. ^{1}H NMR spectrum of compound **3** in DMSO-d_6

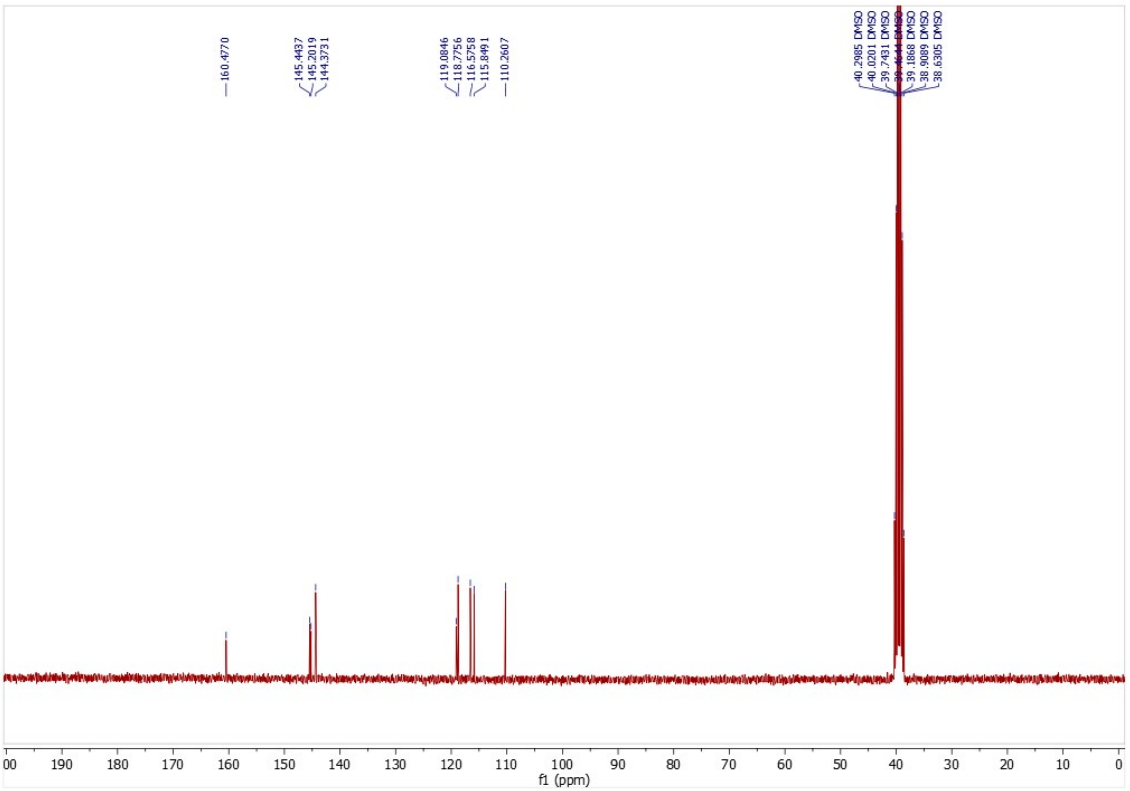

Figure 4. ^{13}C NMR spectrum of compound **3** in DMSO-d_6

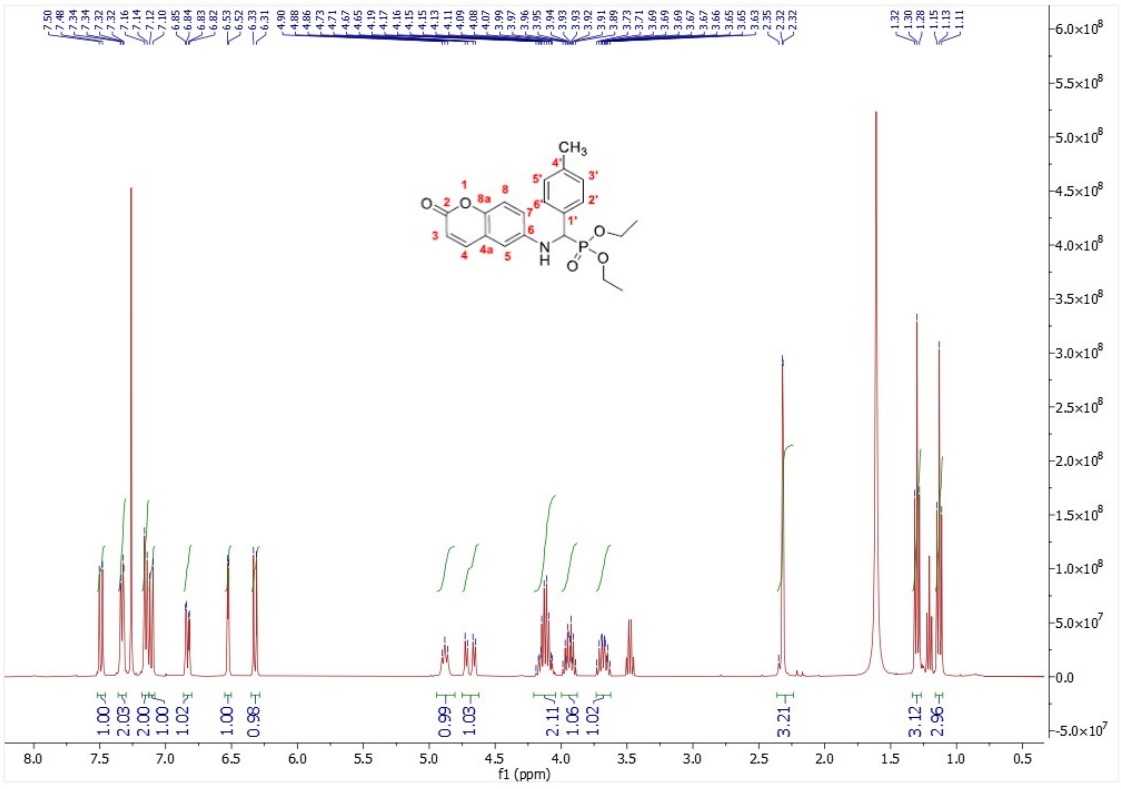

Figure 5. ^{1}H NMR spectrum of compound **1a** in $CDCl_3$

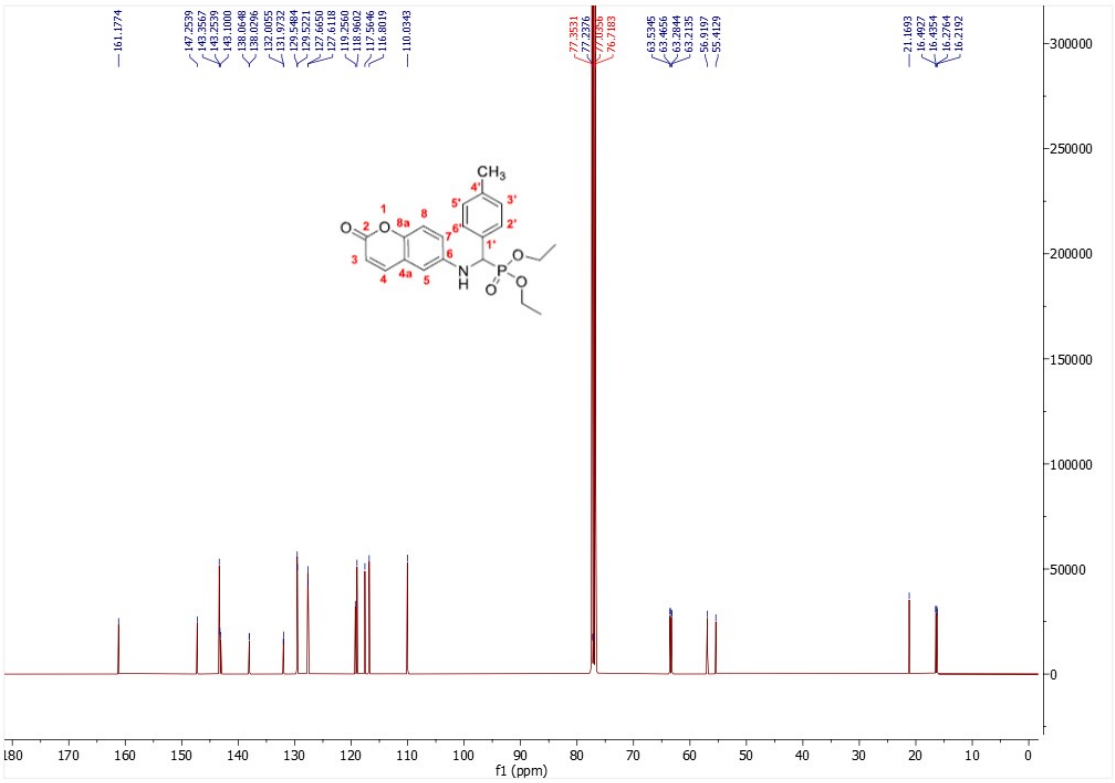

Figure 6. ^{13}C NMR spectrum of compound **1a** in $CDCl_3$

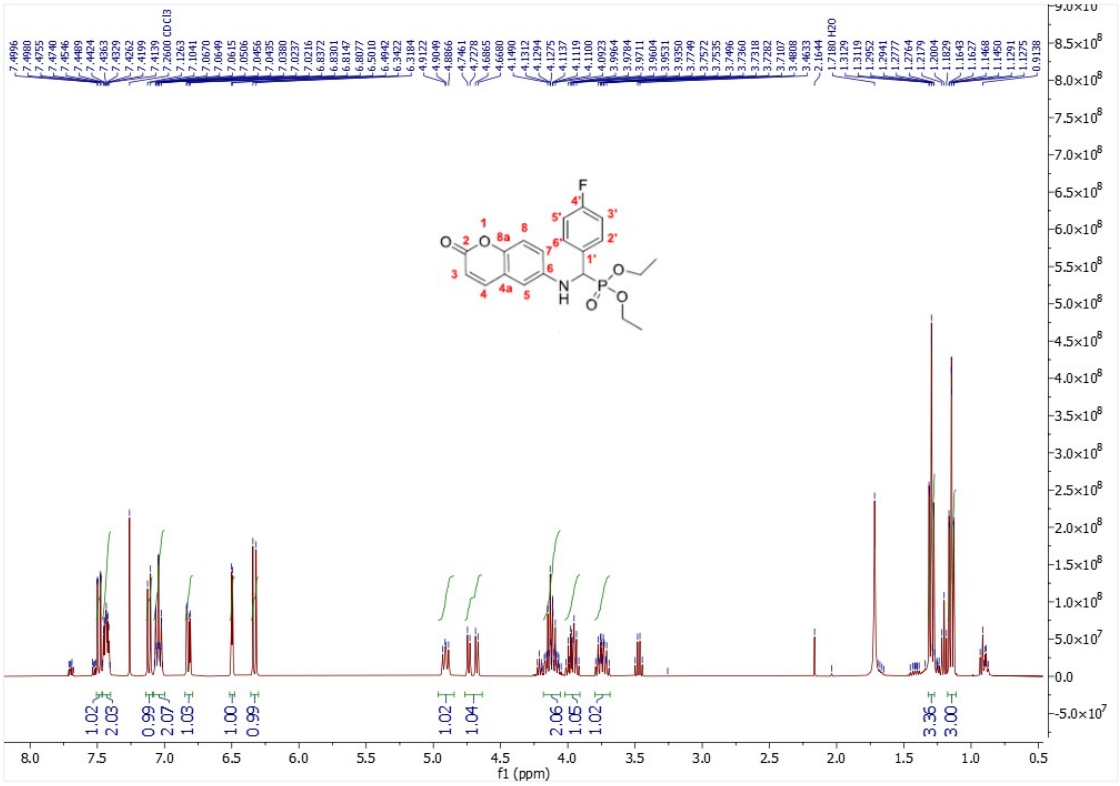

Figure 7. ^{1}H NMR spectrum of compound **1b** in $CDCl_3$

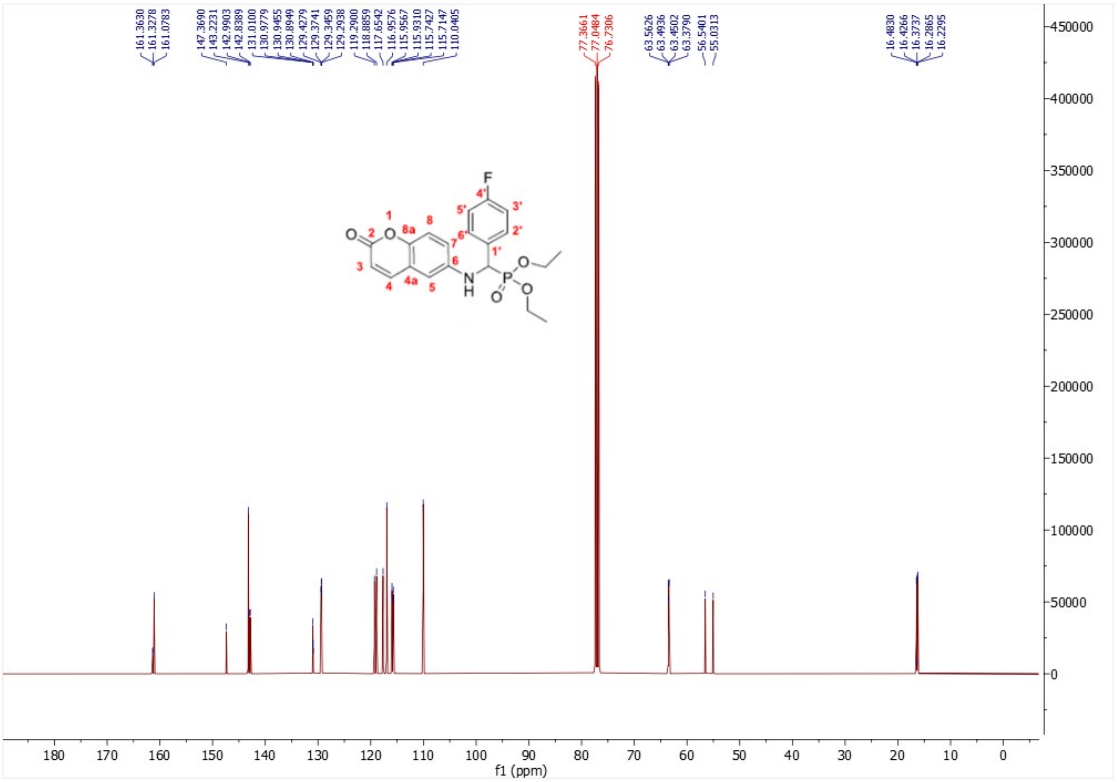

Figure 8. ^{13}C NMR spectrum of compound **1b** in $CDCl_3$

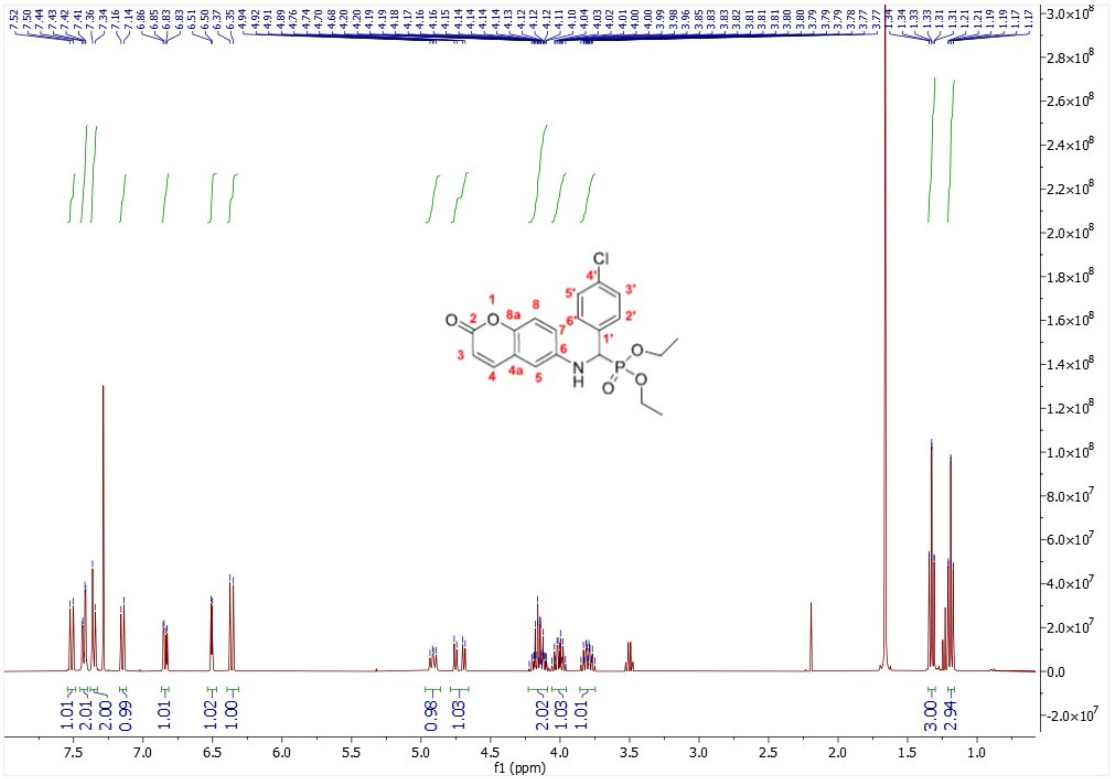

Figure 9. ^{1}H NMR spectrum of compound **1c** in $CDCl_3$

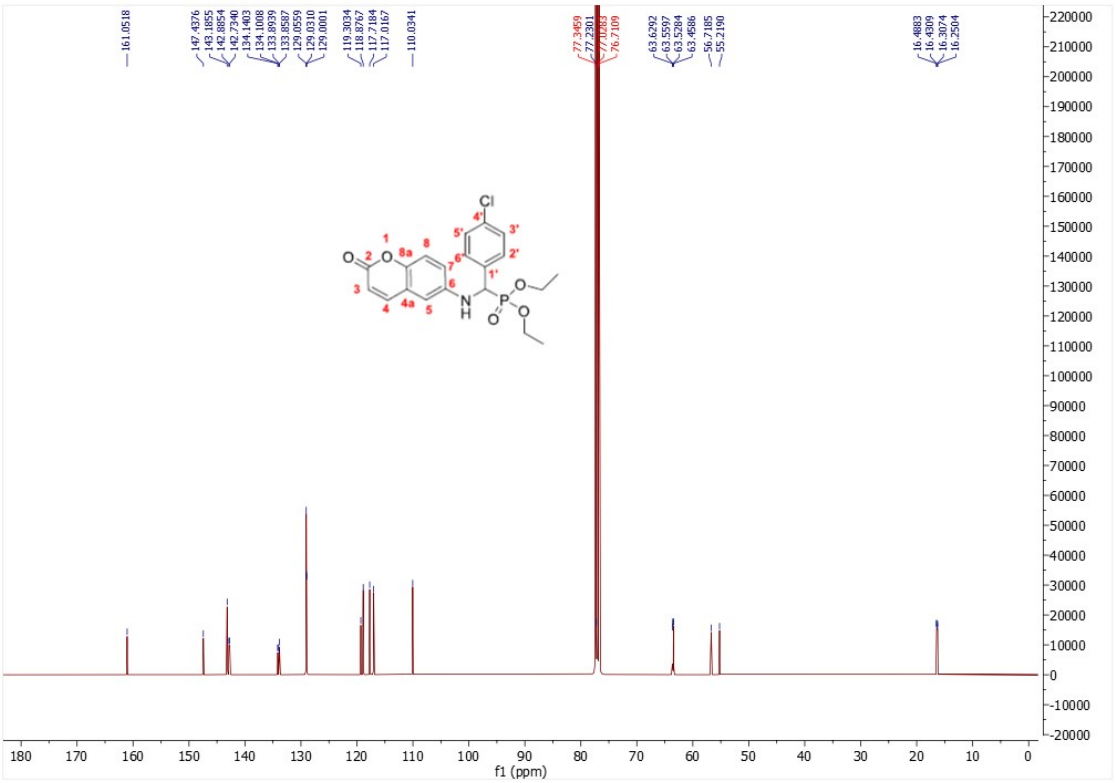

Figure 10. ^{13}C NMR spectrum of compound **1c** in $CDCl_3$

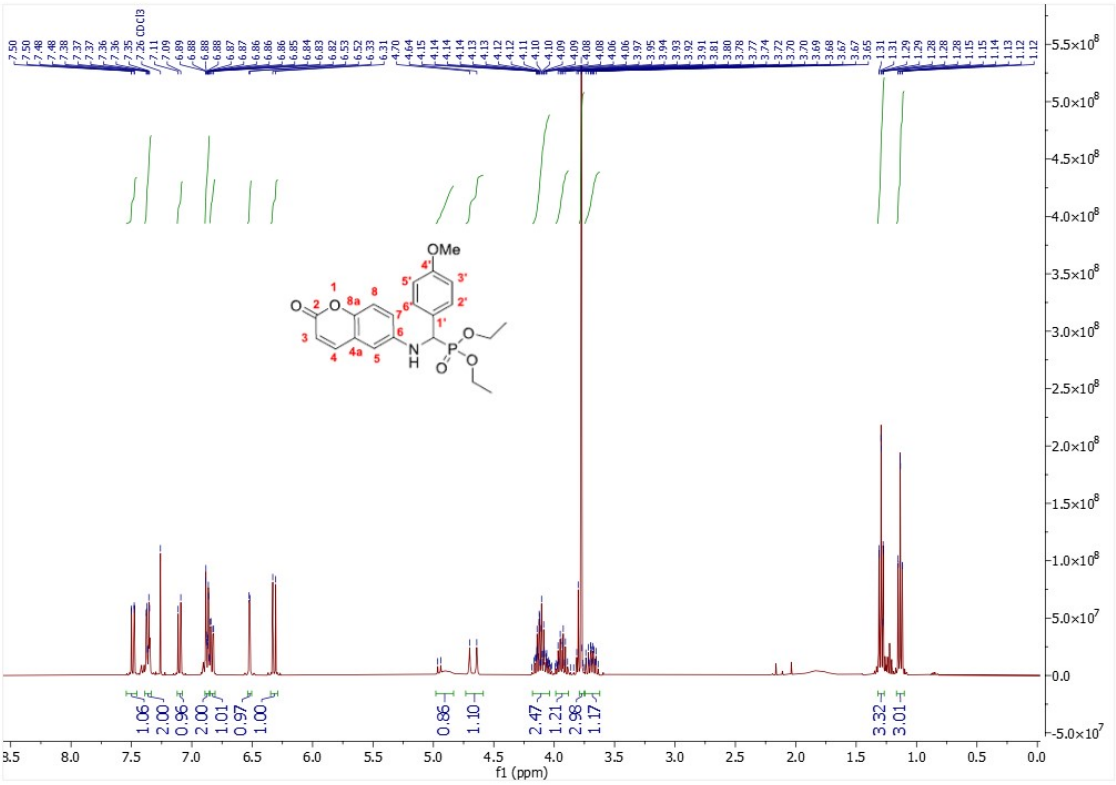

Figure 11. ^{1}H NMR spectrum of compound **1d** in $CDCl_3$

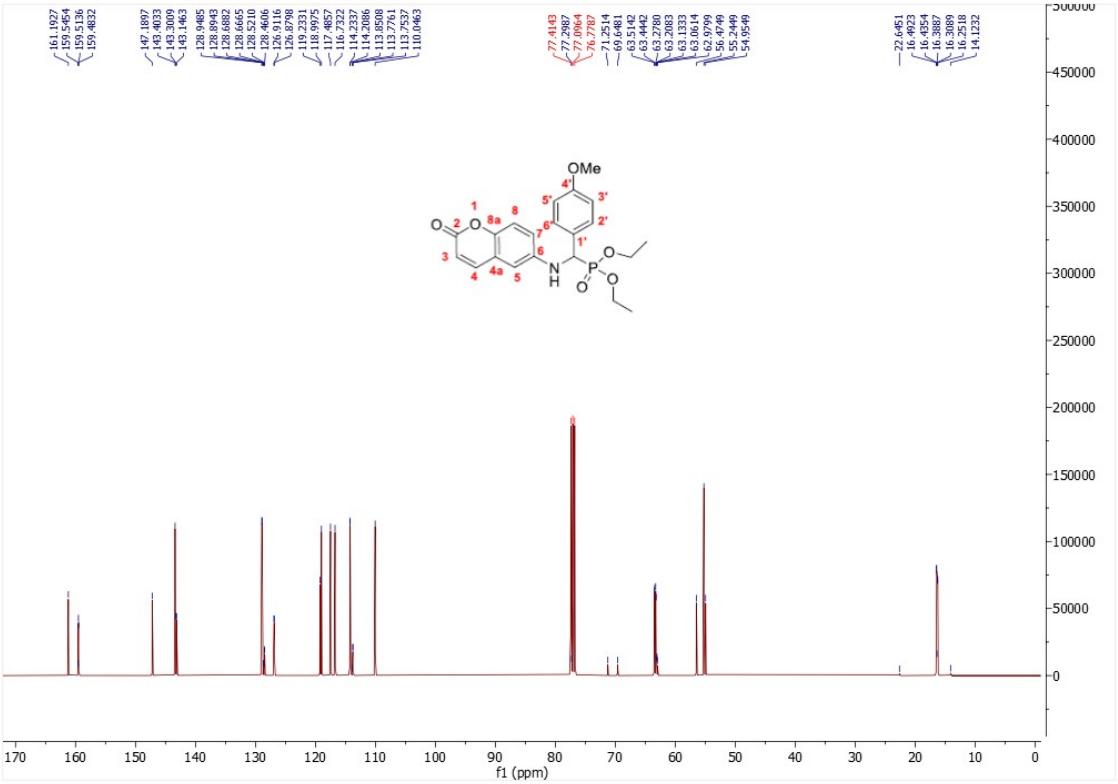

Figure 12. ^{13}C NMR spectrum of compound **1d** in $CDCl_3$

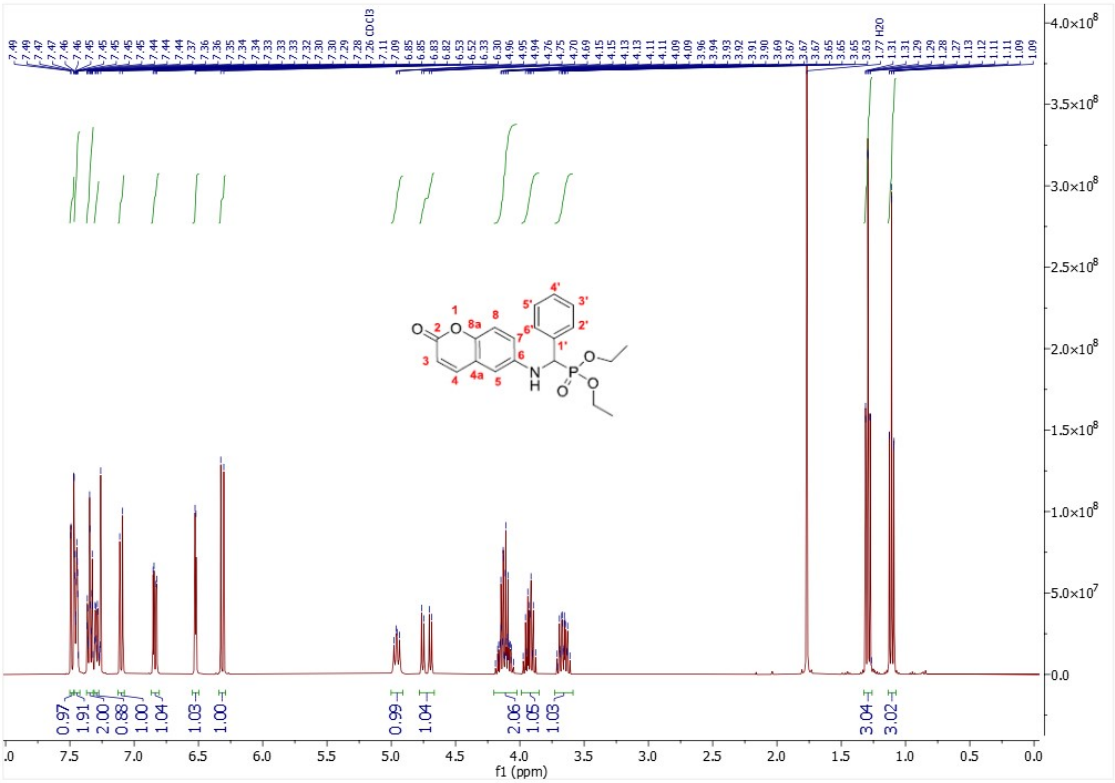

Figure 13. ^{1}H NMR spectrum of compound **1e** in $CDCl_3$

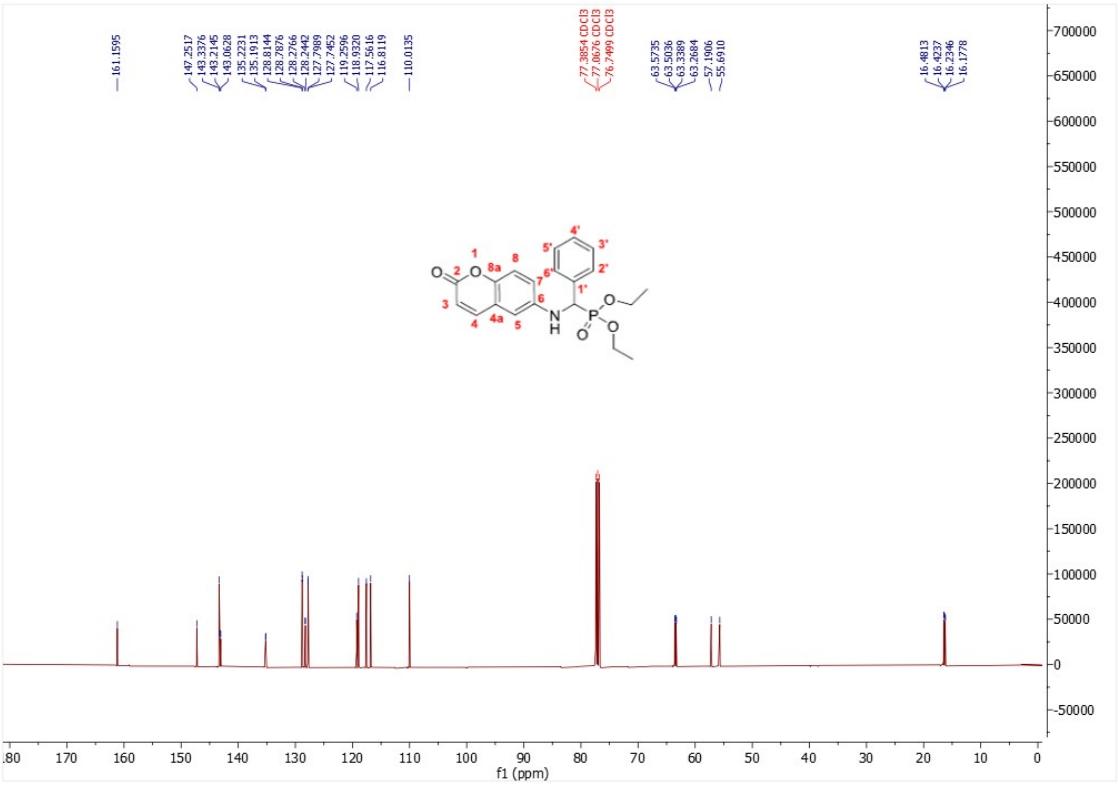

Figure 14. ^{13}C NMR spectrum of compound **1e** in $CDCl_3$

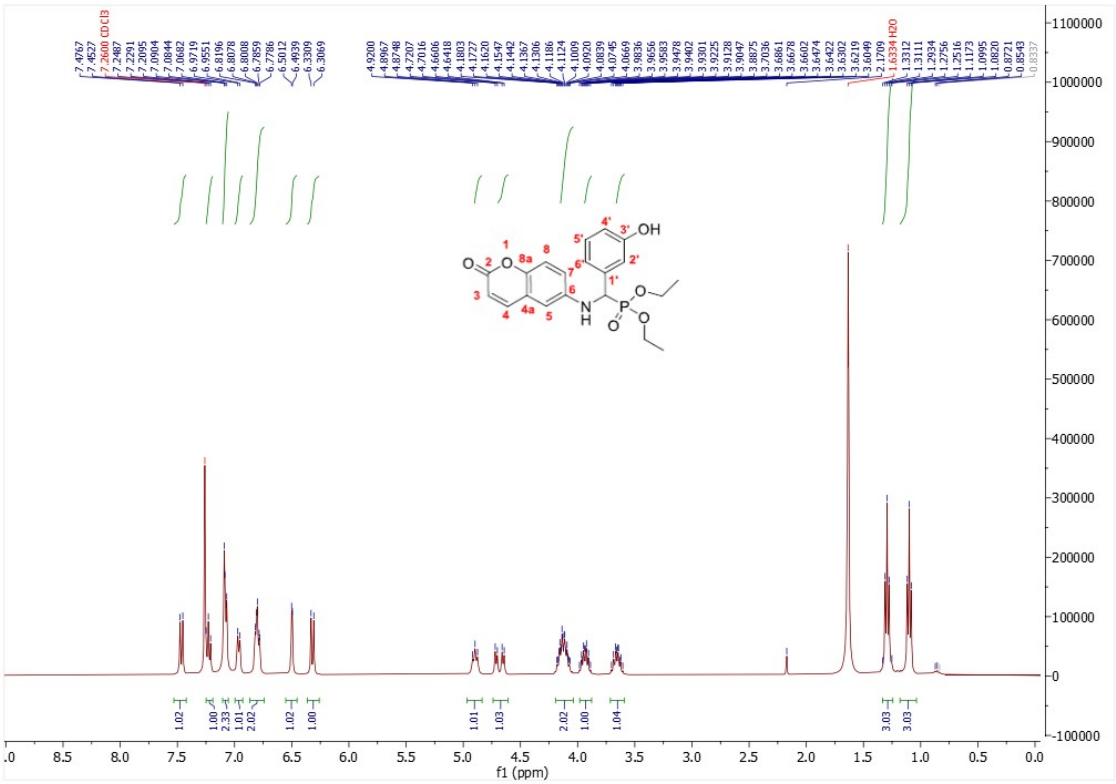

Figure 15. ^{1}H NMR spectrum of compound **1f** in $CDCl_3$

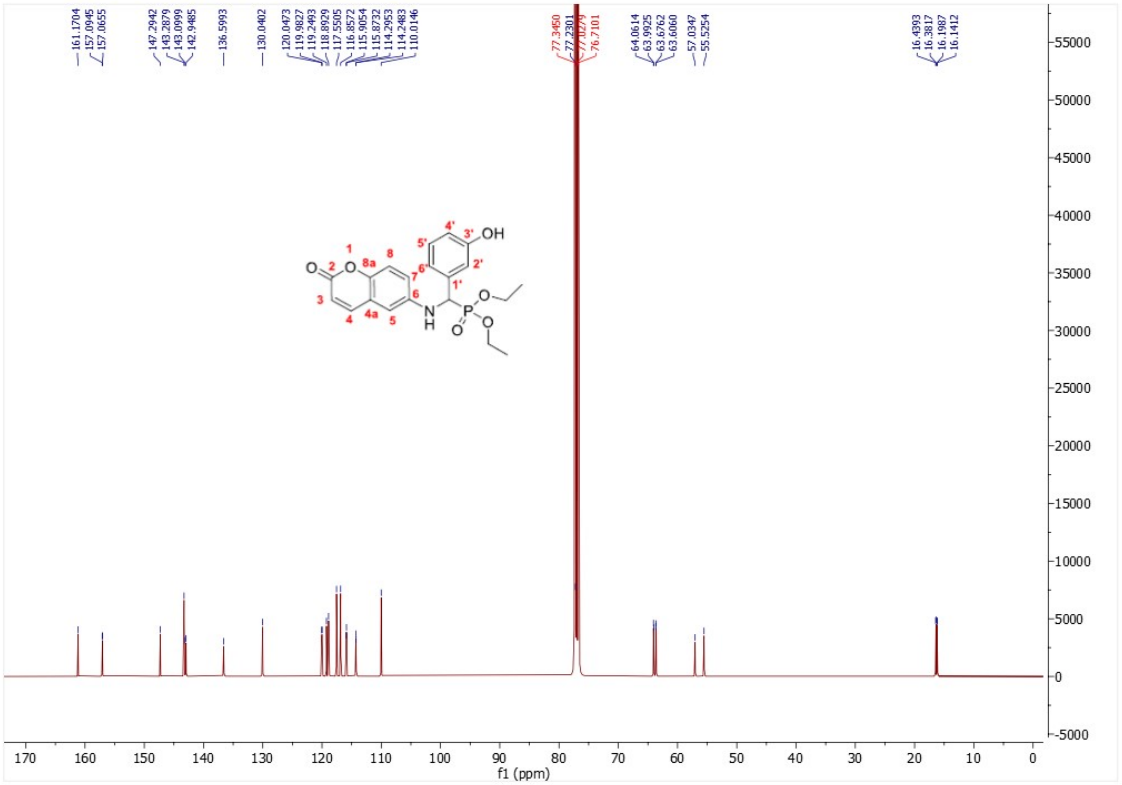

Figure 16. ^{13}C NMR spectrum of compound **1f** in $CDCl_3$

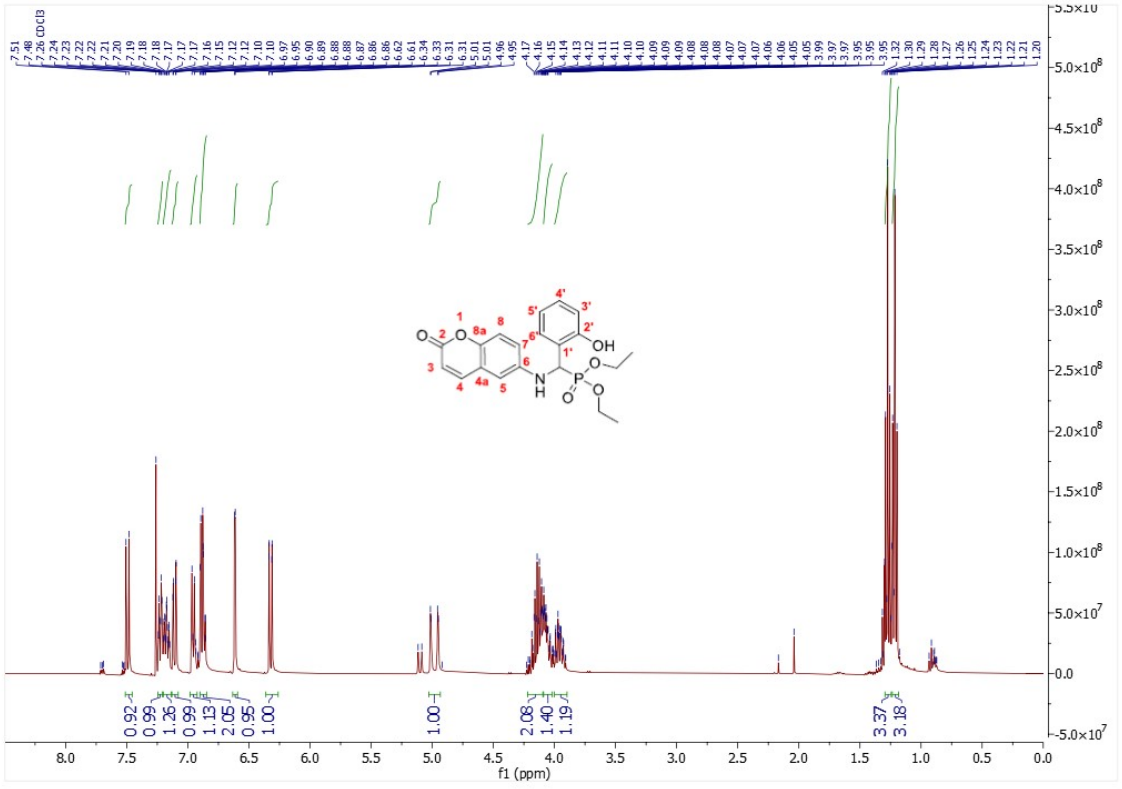

Figure 17. ^{1}H NMR spectrum of compound **1g** in $CDCl_3$

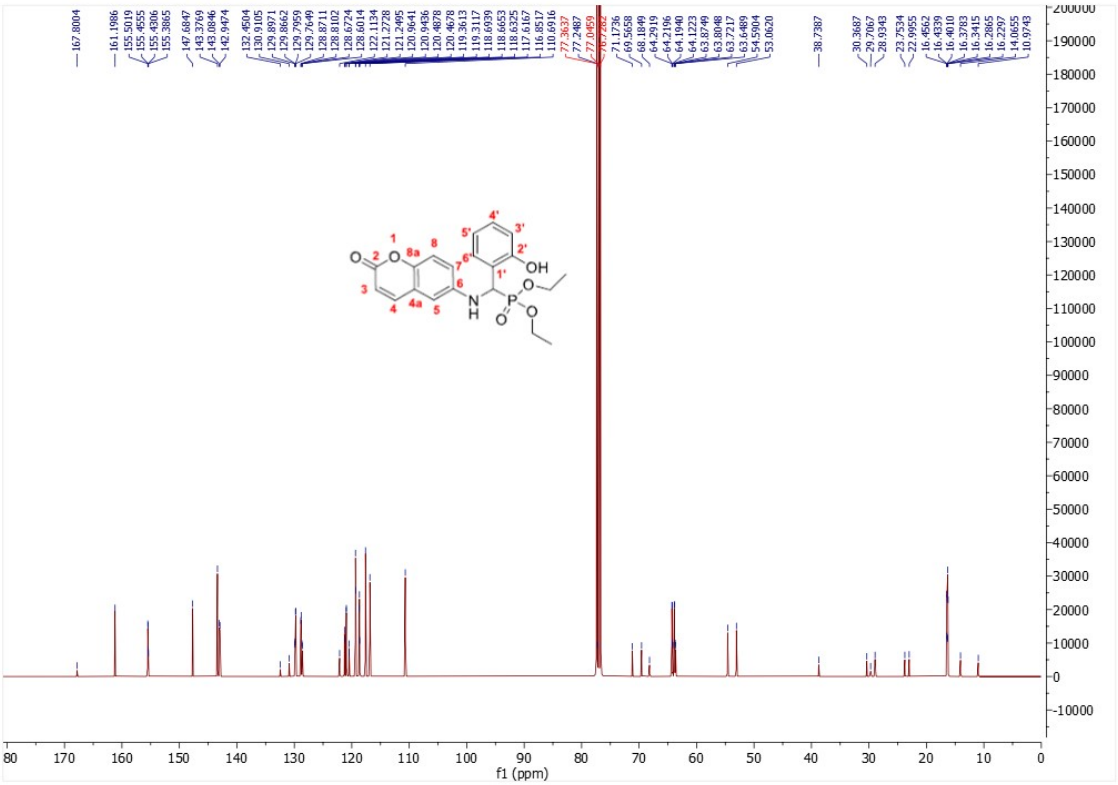

Figure 18. ^{13}C NMR spectrum of compound **1g** in $CDCl_3$

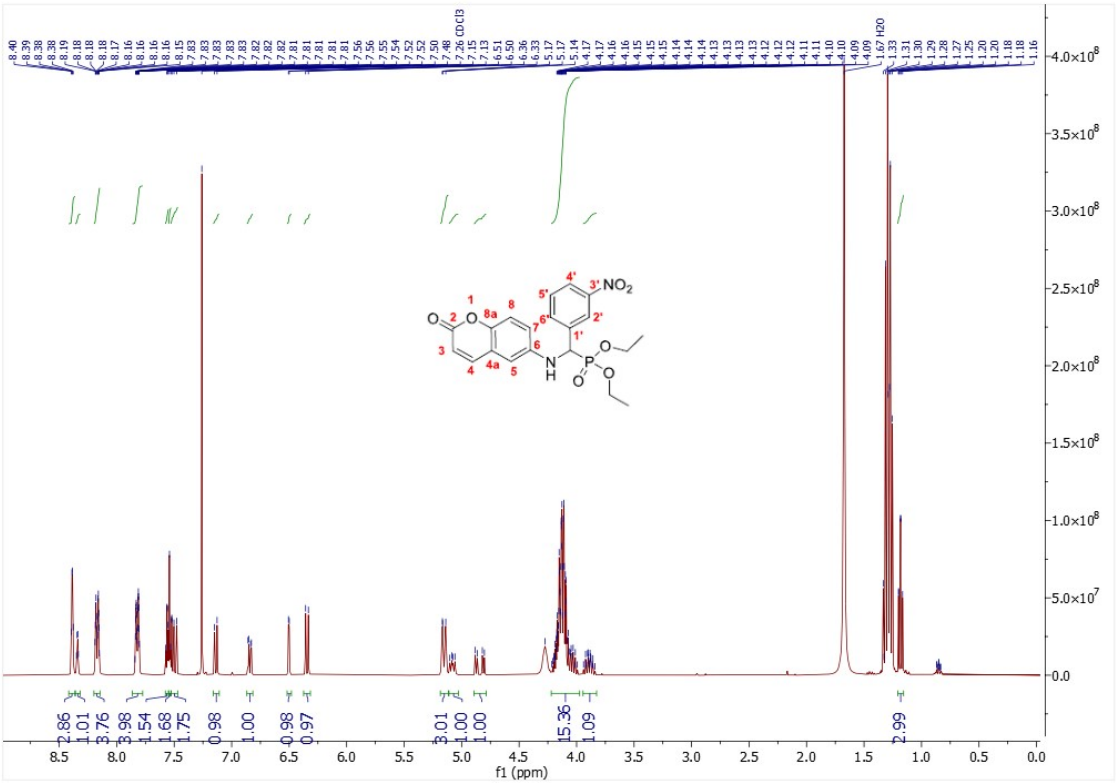

Figure 19. ^{1}H NMR spectrum of compound **1h** in $CDCl_3$

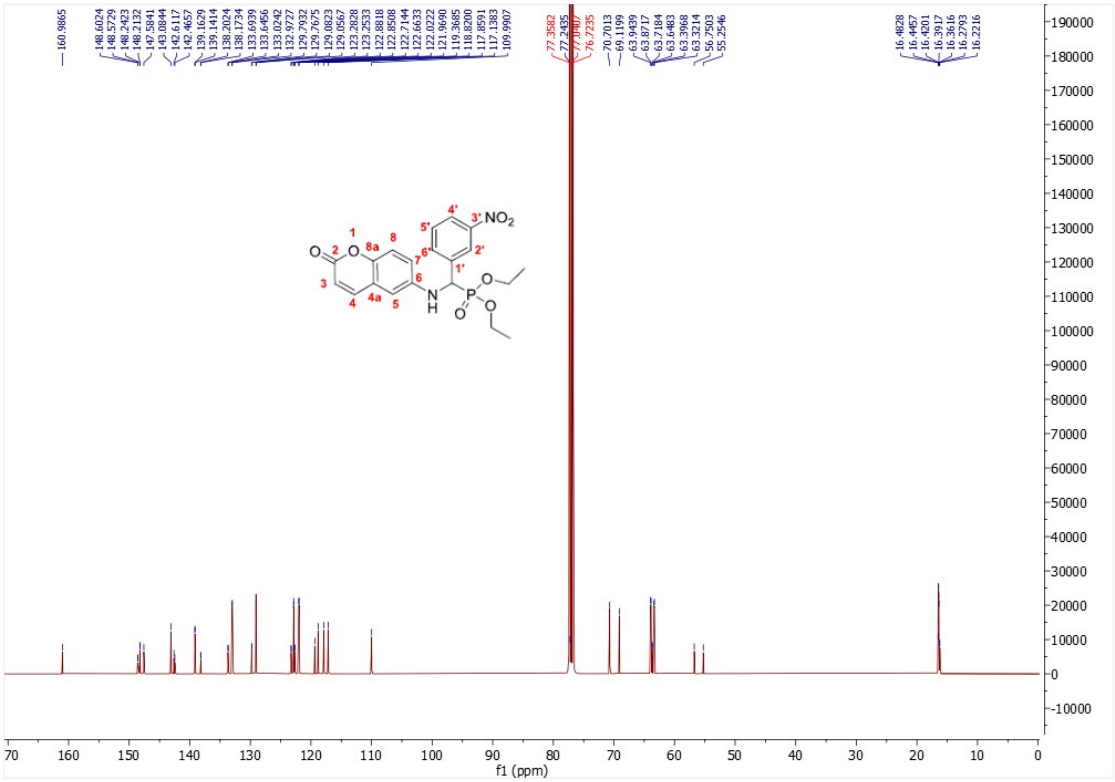

Figure 20. ^{13}C NMR spectrum of compound **1h** in $CDCl_3$

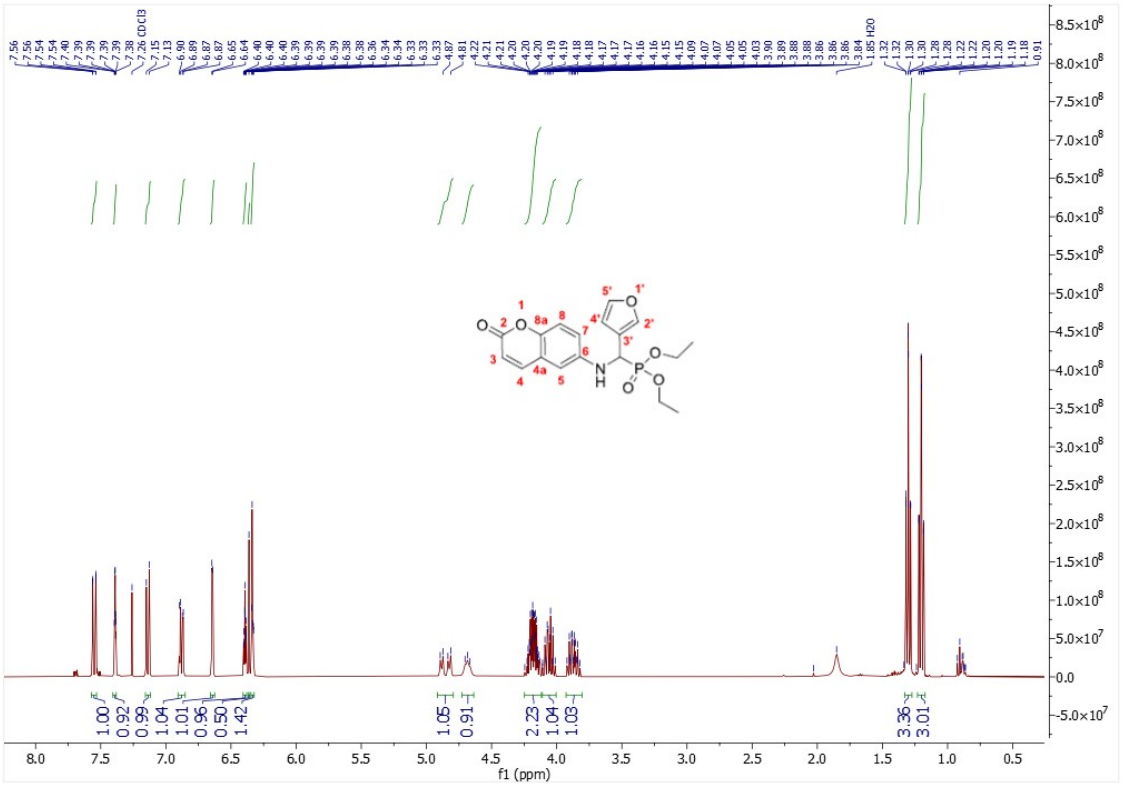

Figure 21. ^{1}H NMR spectrum of compound **1i** in $CDCl_3$

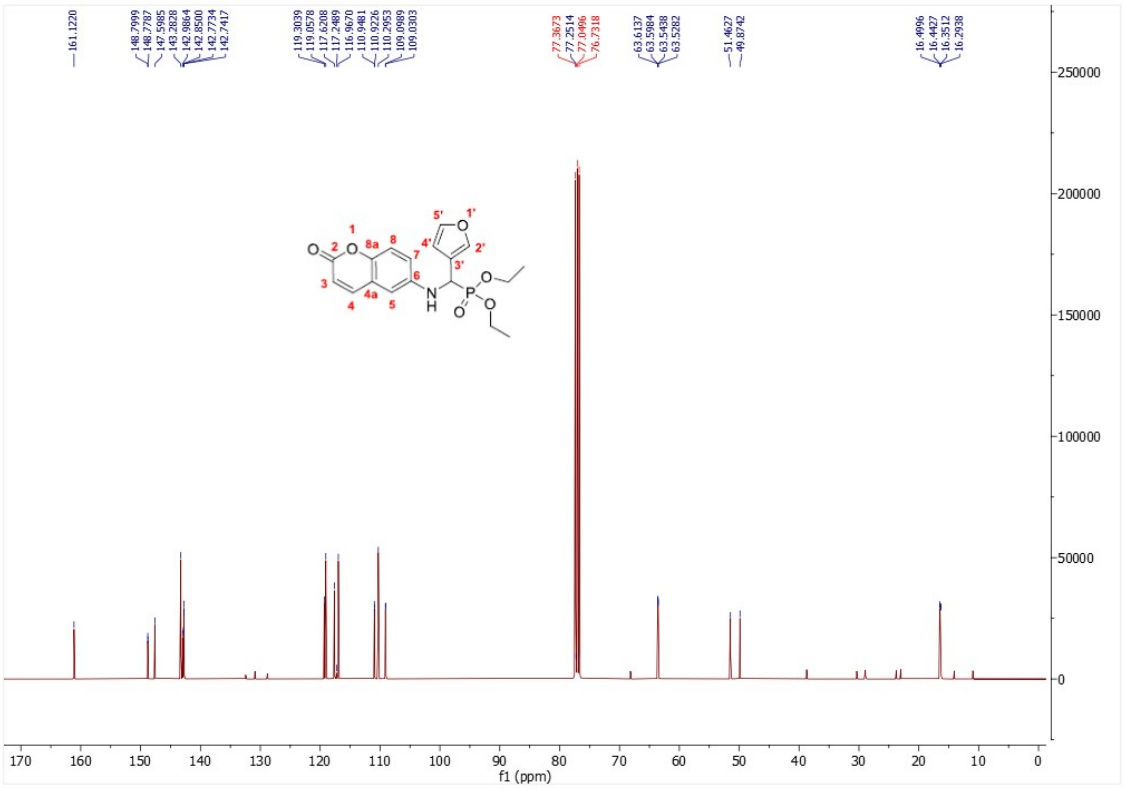

Figure 22. ^{13}C NMR spectrum of compound **1i** in $CDCl_3$

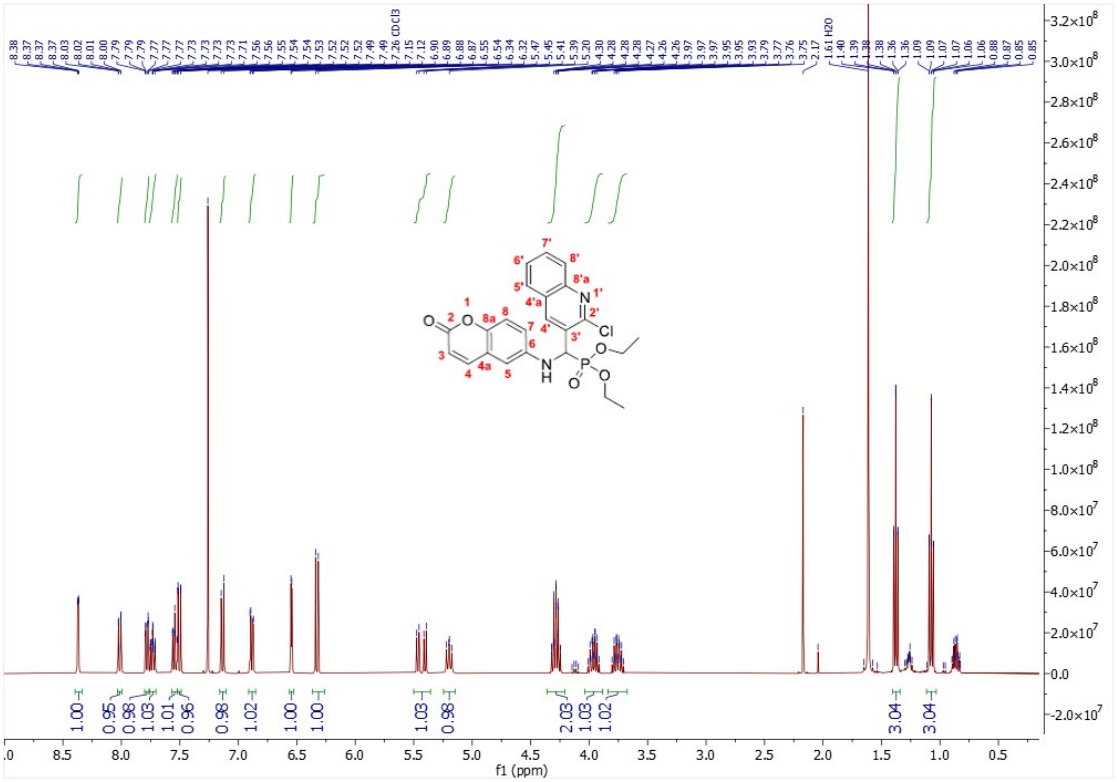

Figure 23. ^{1}H NMR spectrum of compound **1j** in $CDCl_3$

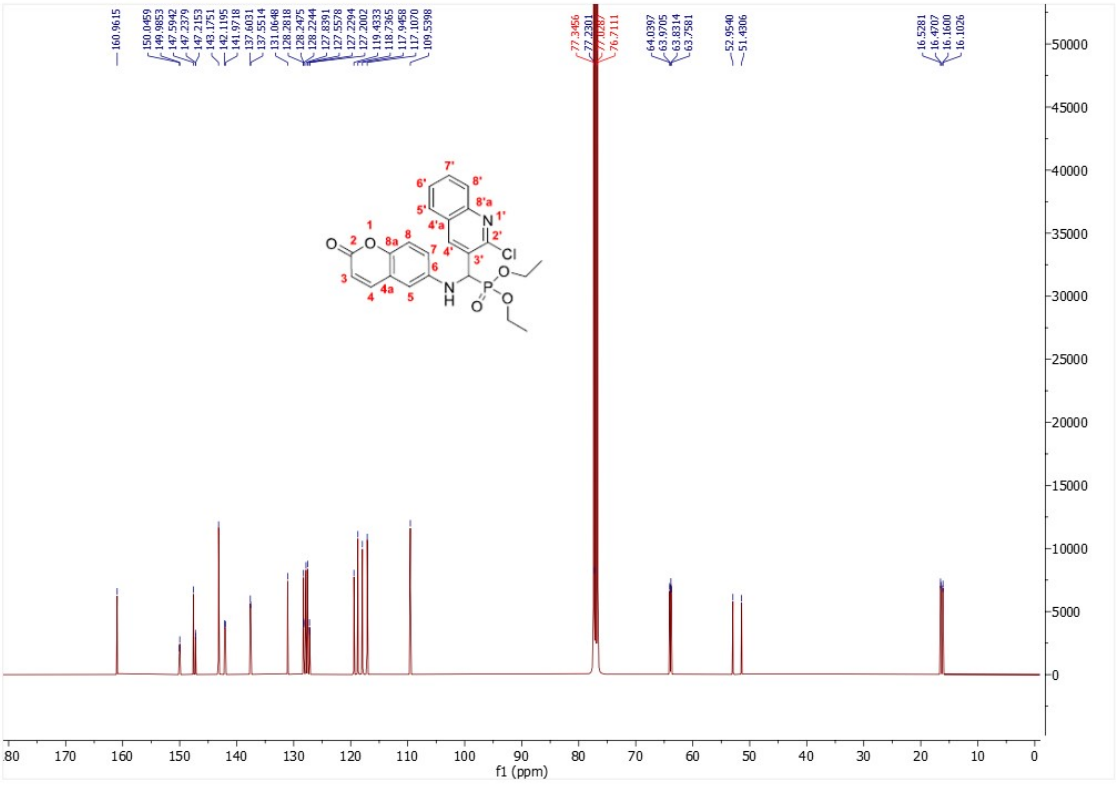

Figure 24. ^{13}C NMR spectrum of compound **1j** in $CDCl_3$

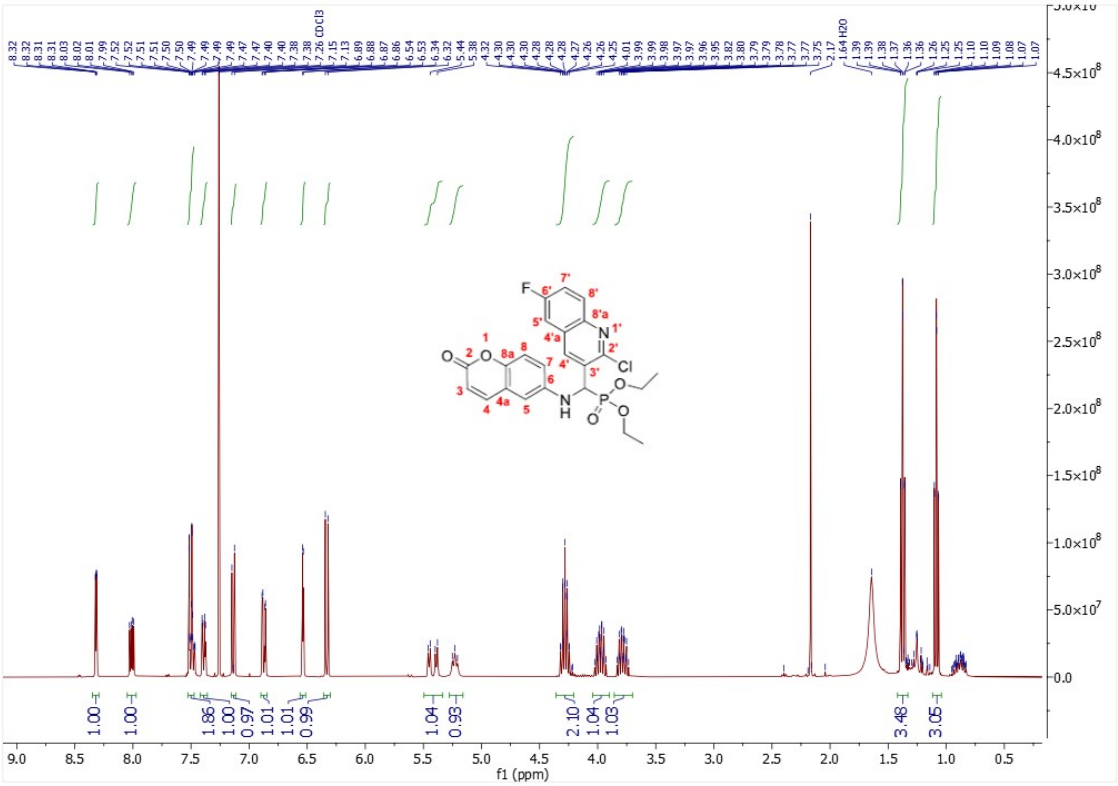

Figure 25. ^{1}H NMR spectrum of compound **1k** in $CDCl_3$

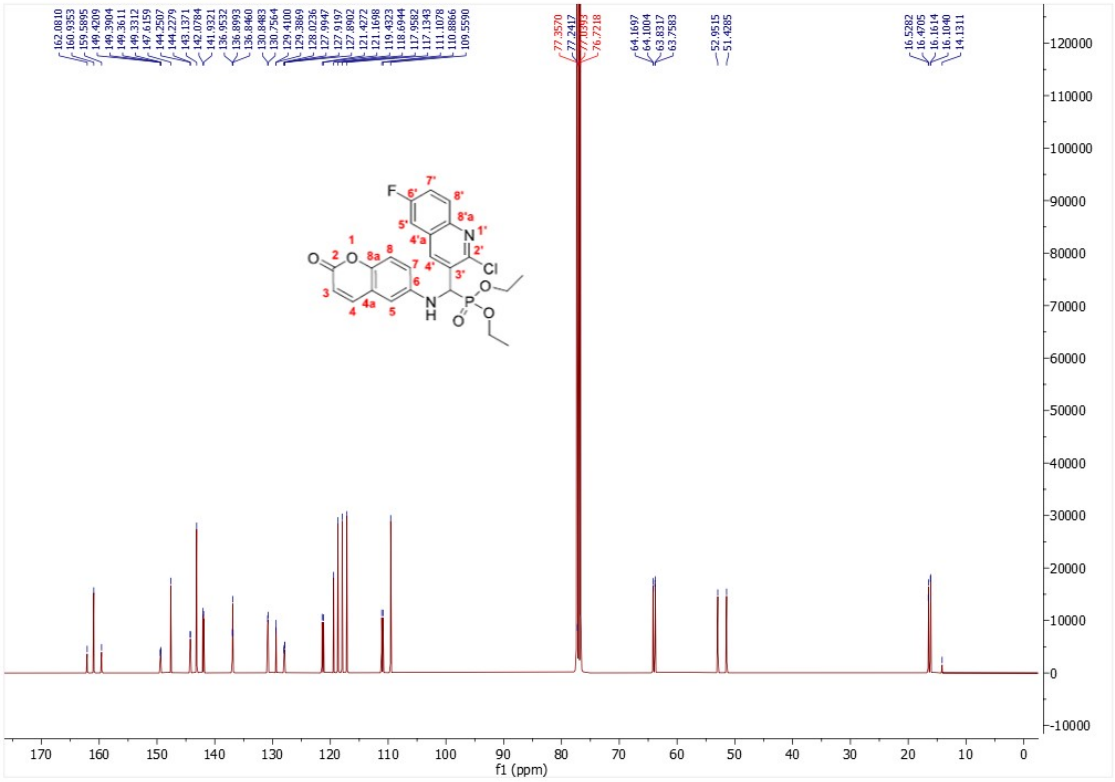

Figure 26. ^{13}C NMR spectrum of compound **1k** in $CDCl_3$

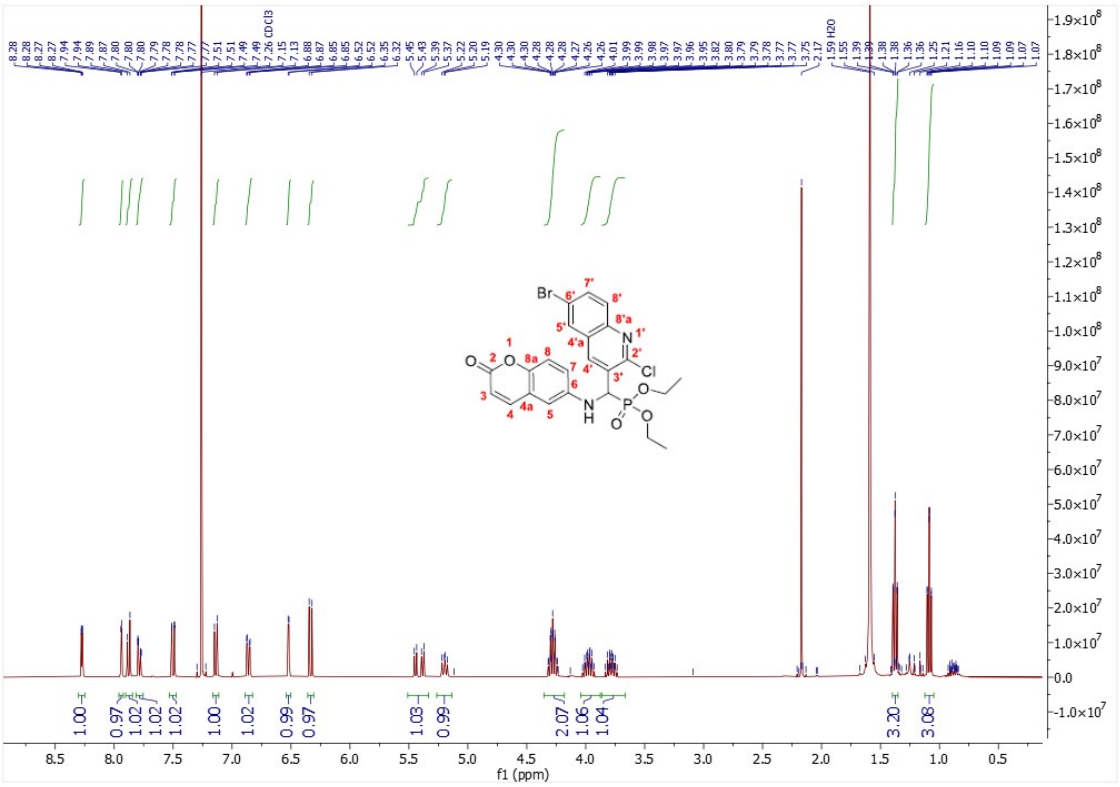

Figure 27. ^{1}H NMR spectrum of compound **1l** in $CDCl_3$

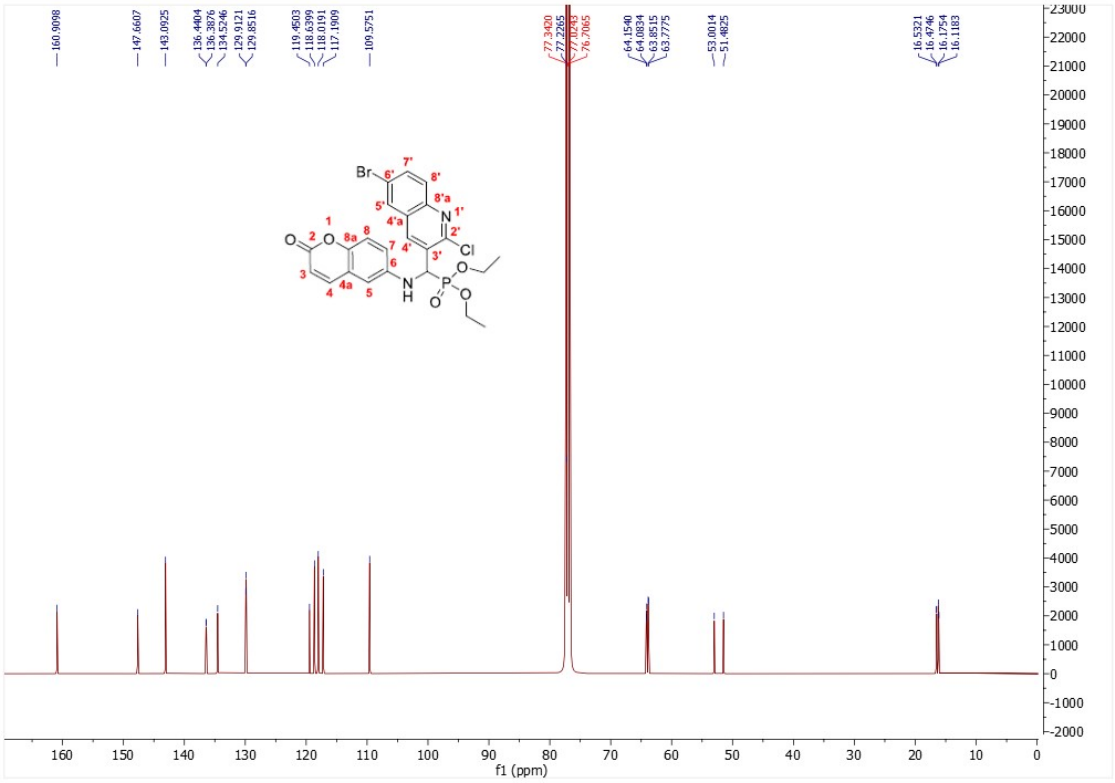

Figure 28. ^{13}C NMR spectrum of compound **1l** in $CDCl_3$

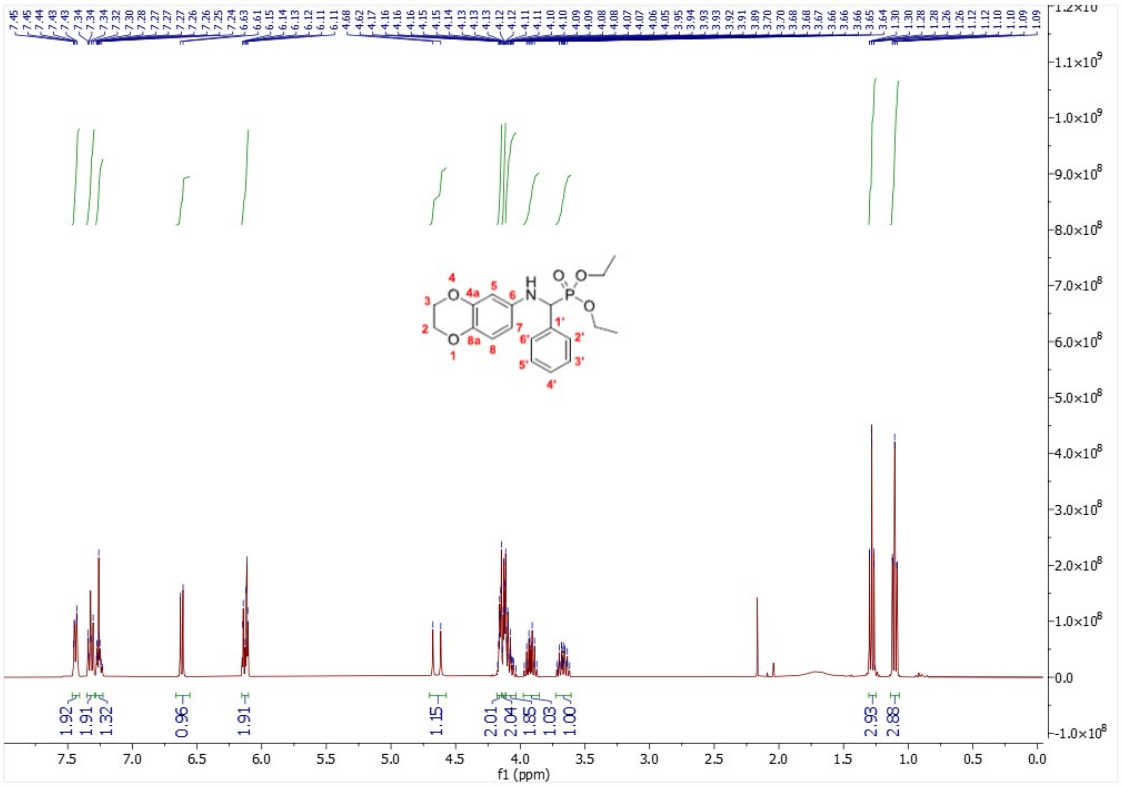

Figure 29. ^{1}H NMR spectrum of compound **6a** in $CDCl_3$

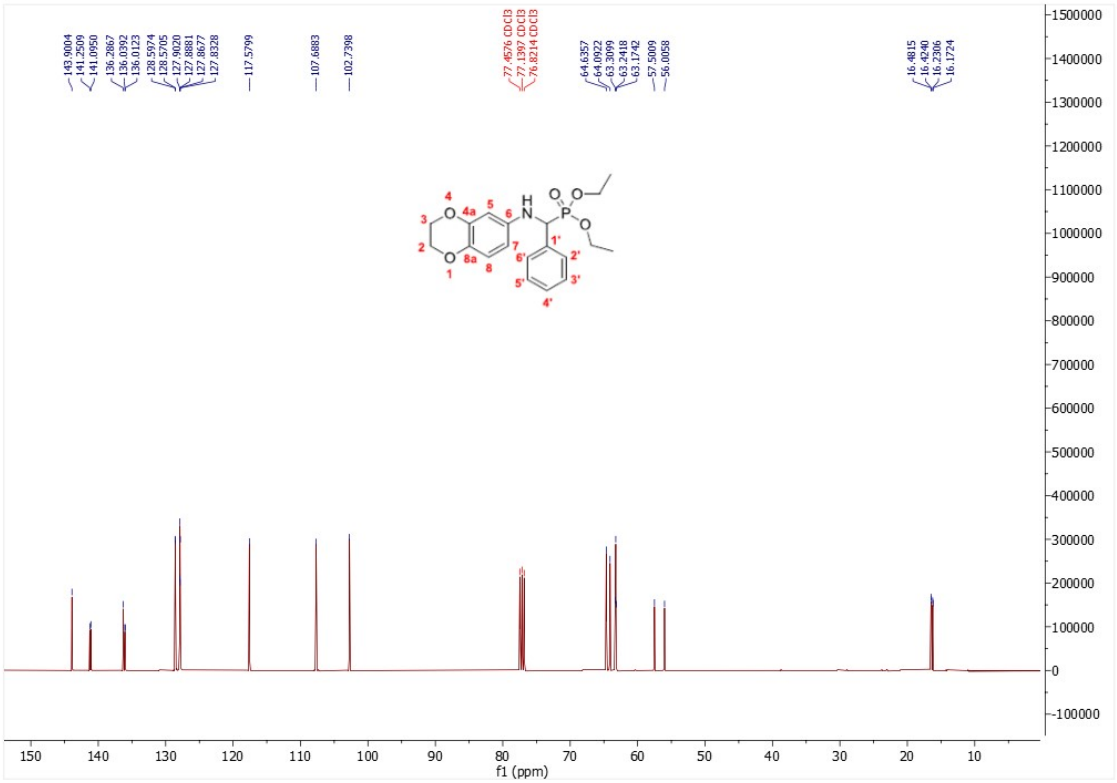

Figure 30. ^{13}C NMR spectrum of compound **6a** in $CDCl_3$

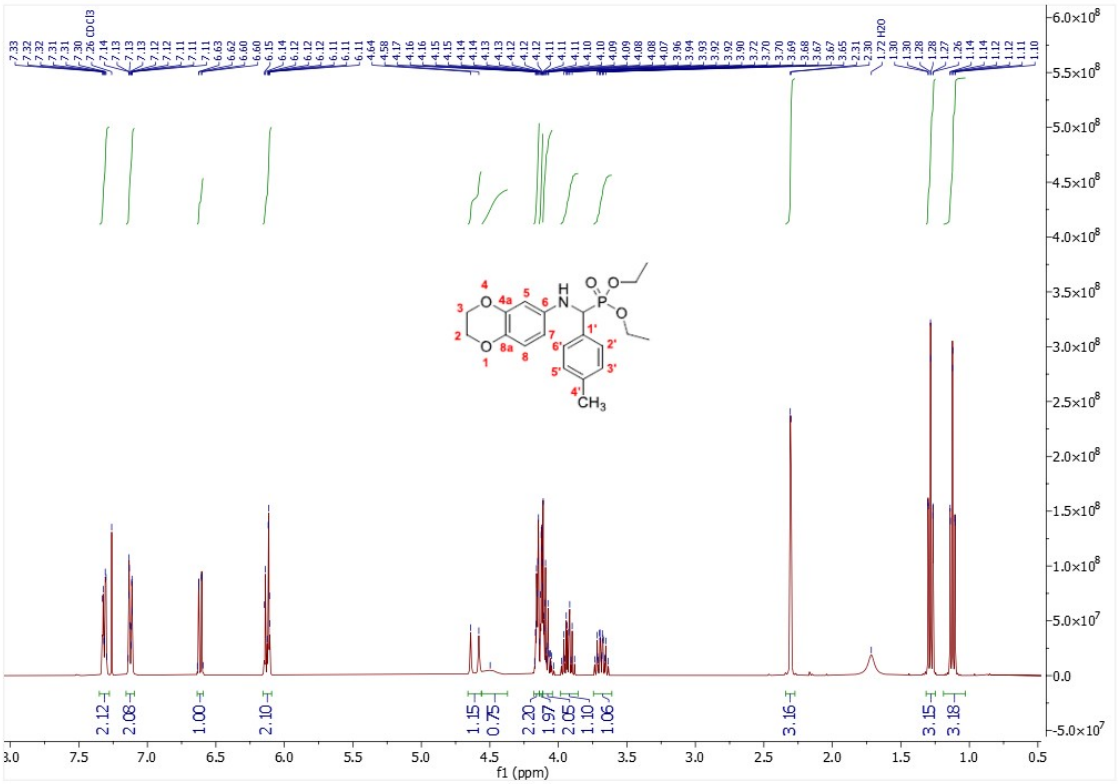

Figure 31. ^{1}H NMR spectrum of compound **6b** in $CDCl_3$

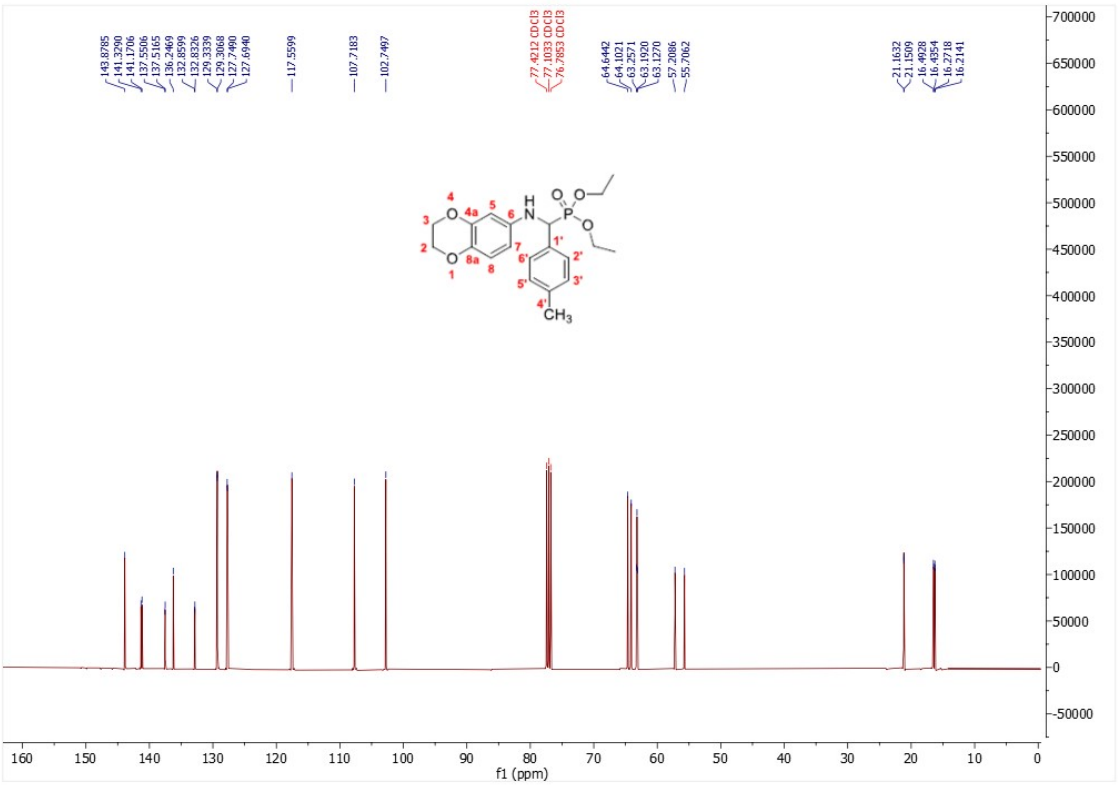

Figure 32. ^{13}C NMR spectrum of compound **6b** in $CDCl_3$

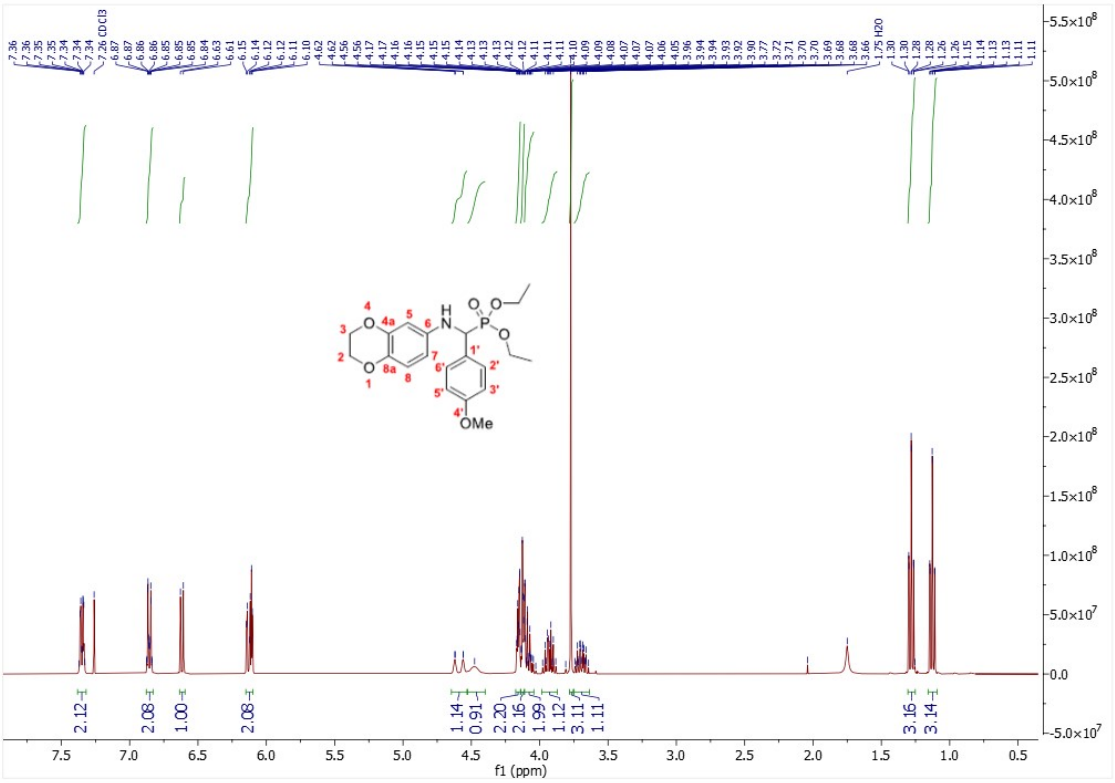

Figure 33. ^{1}H NMR spectrum of compound **6c** in $CDCl_3$

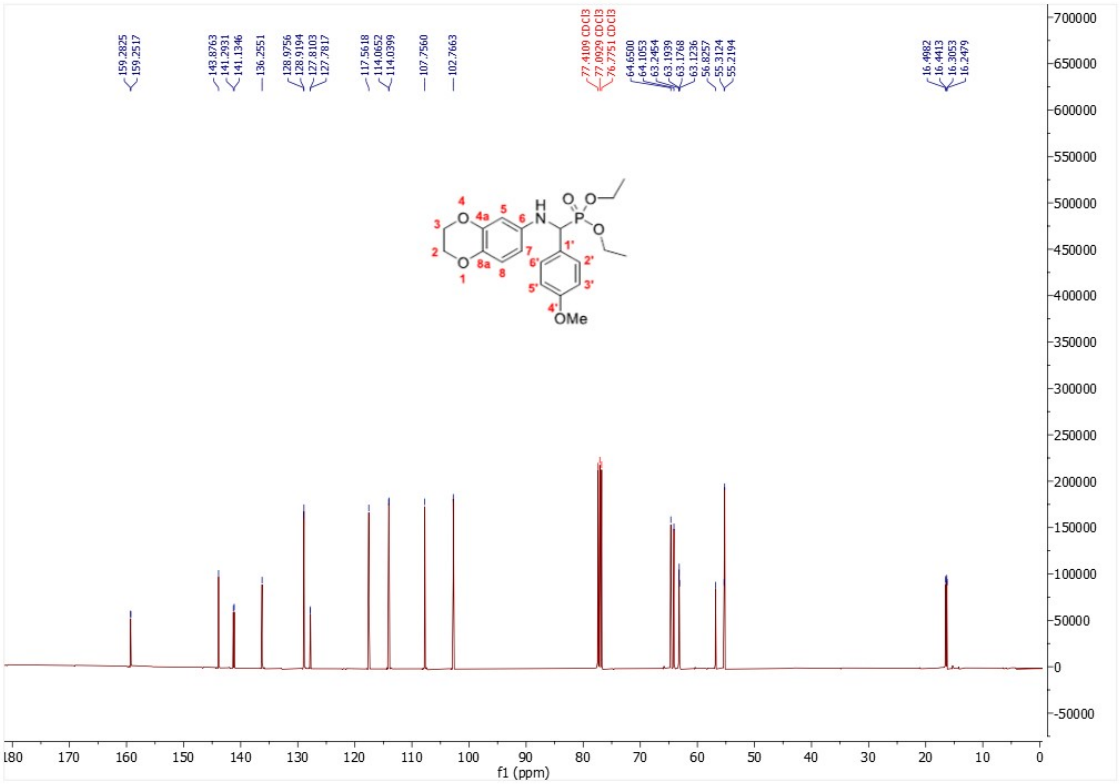

Figure 34. ^{13}C NMR spectrum of compound **6c** in $CDCl_3$

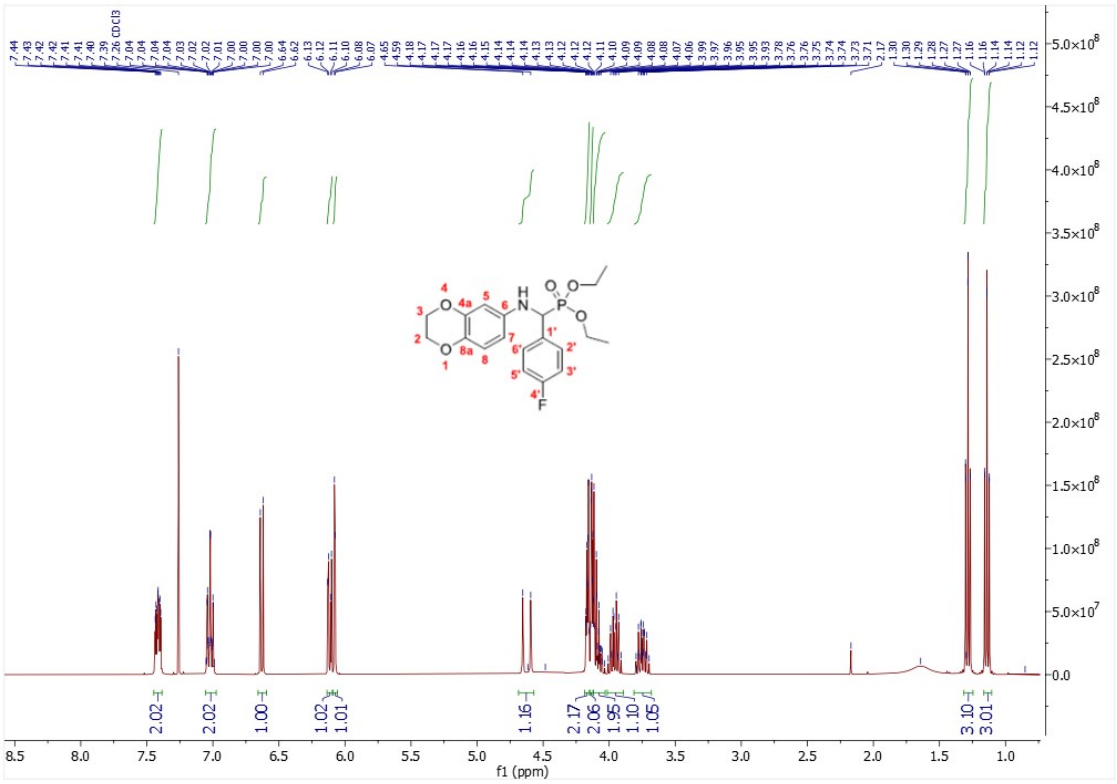

Figure 35. ^{1}H NMR spectrum of compound **6d** in $CDCl_3$

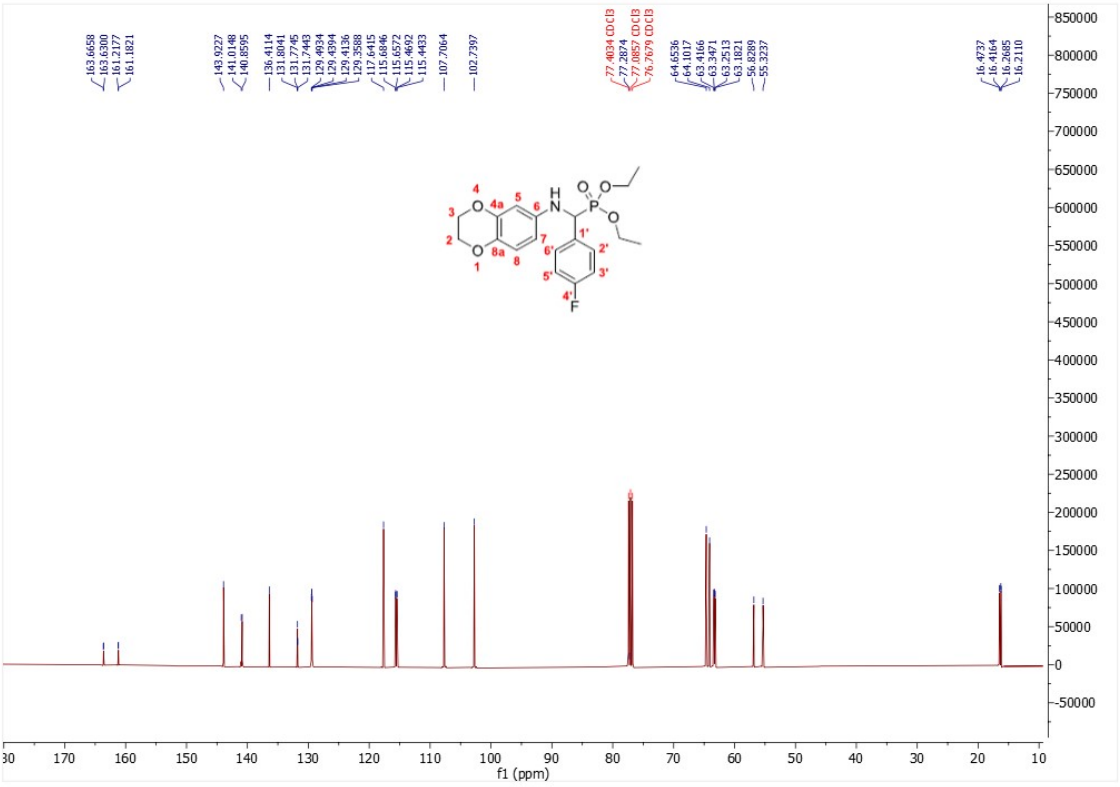

Figure 36. ^{13}C NMR spectrum of compound **6d** in $CDCl_3$

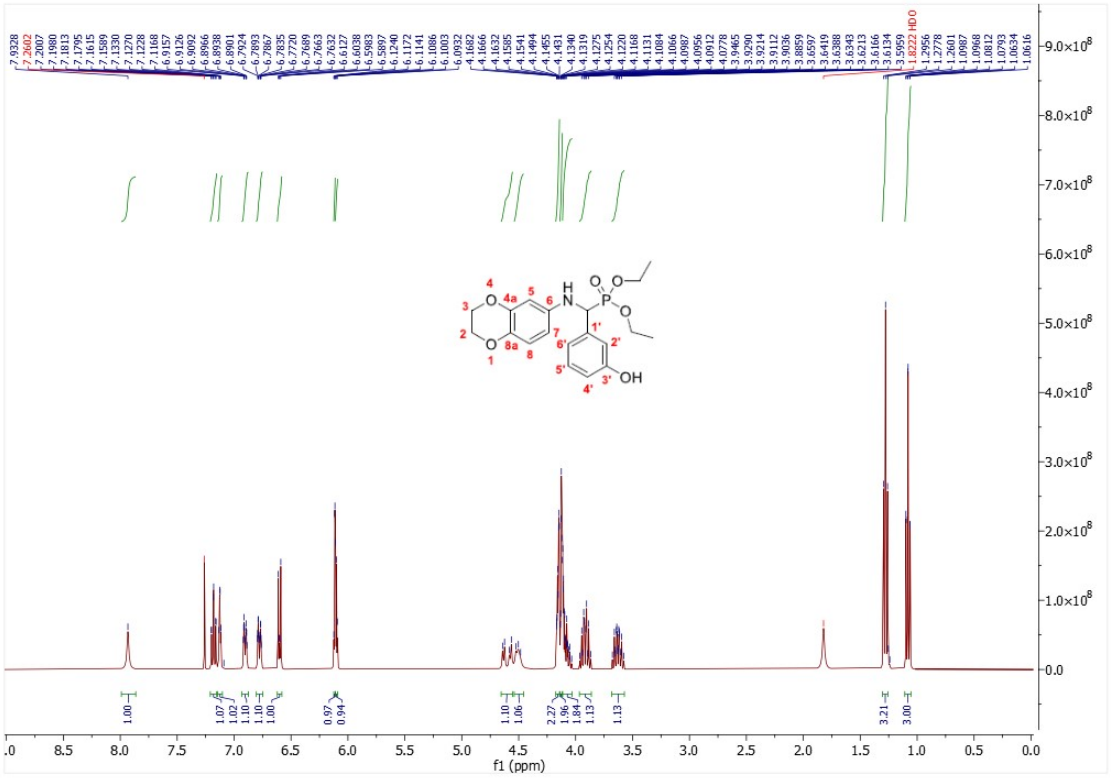

Figure 37. ^{1}H NMR spectrum of compound **6e** in $CDCl_3$

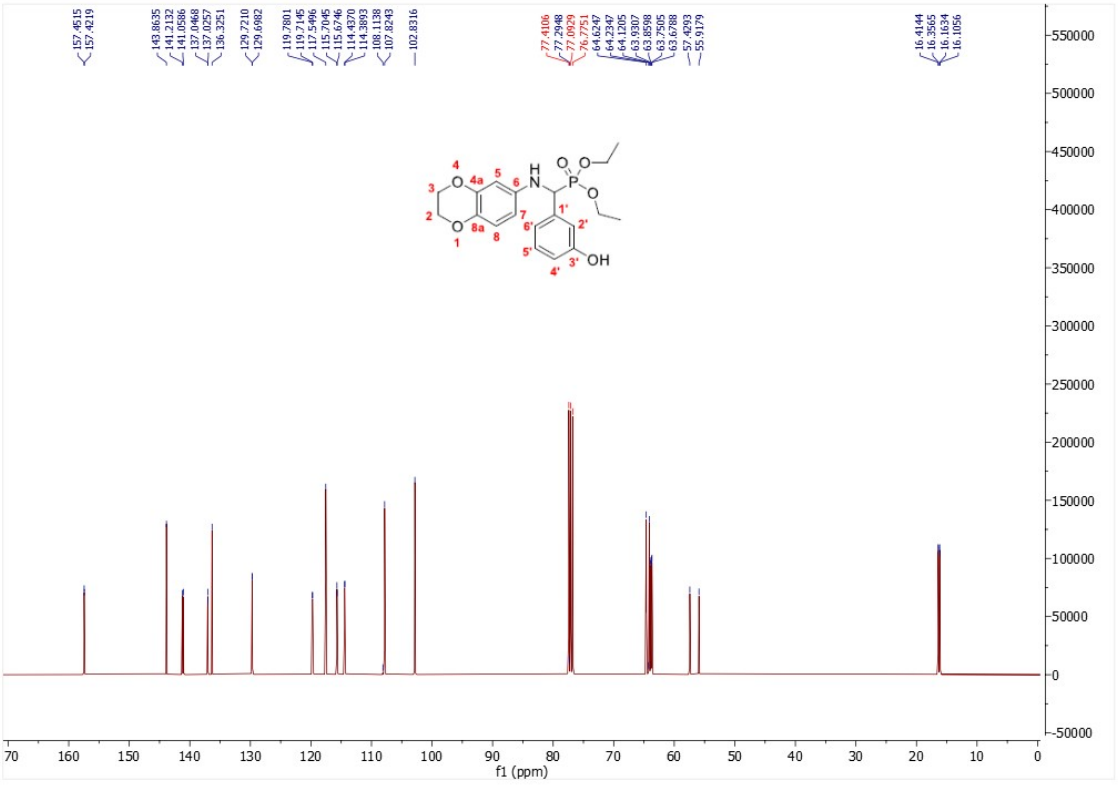

Figure 38. ^{13}C NMR spectrum of compound **6e** in $CDCl_3$

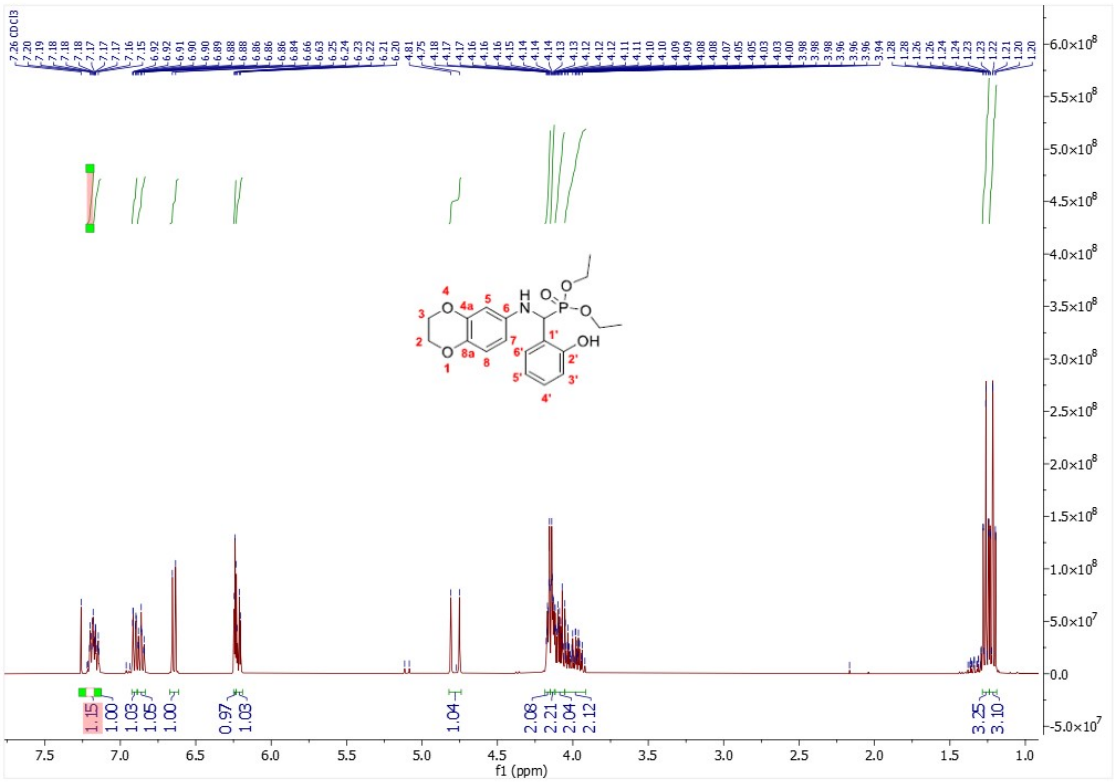

Figure 39. ^{1}H NMR spectrum of compound **6f** in $CDCl_3$

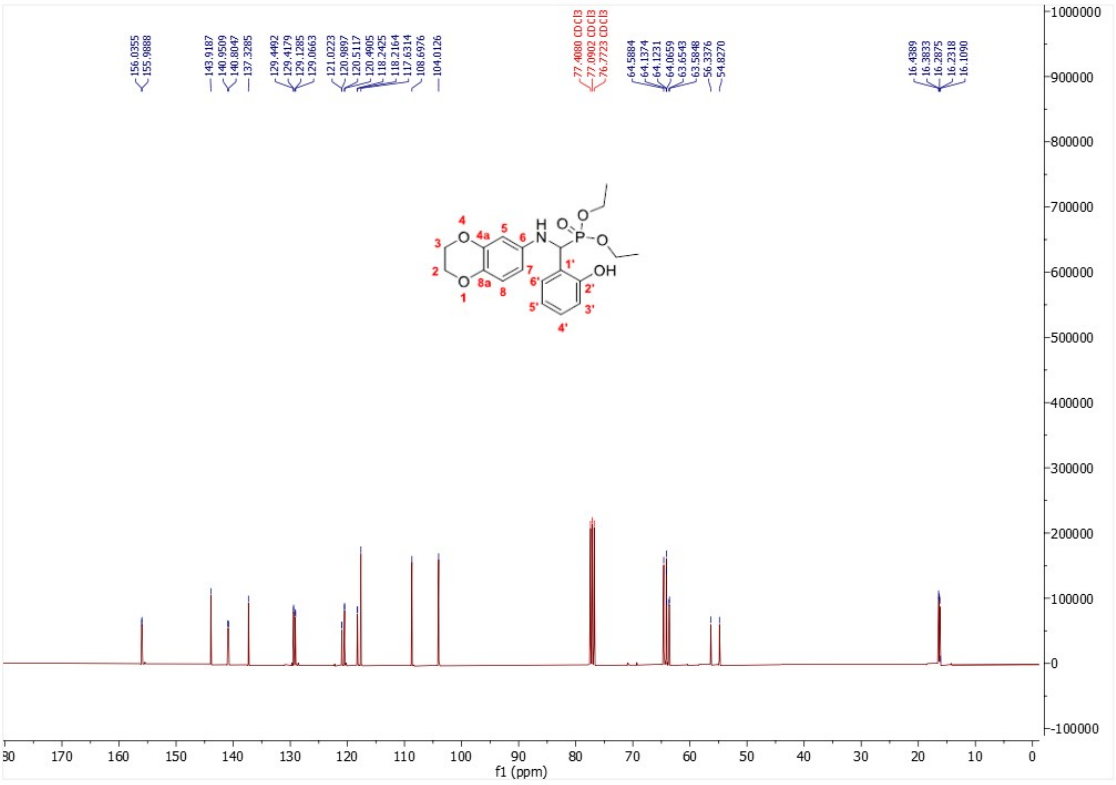

Figure 40. ^{13}C NMR spectrum of compound **6f** in $CDCl_3$

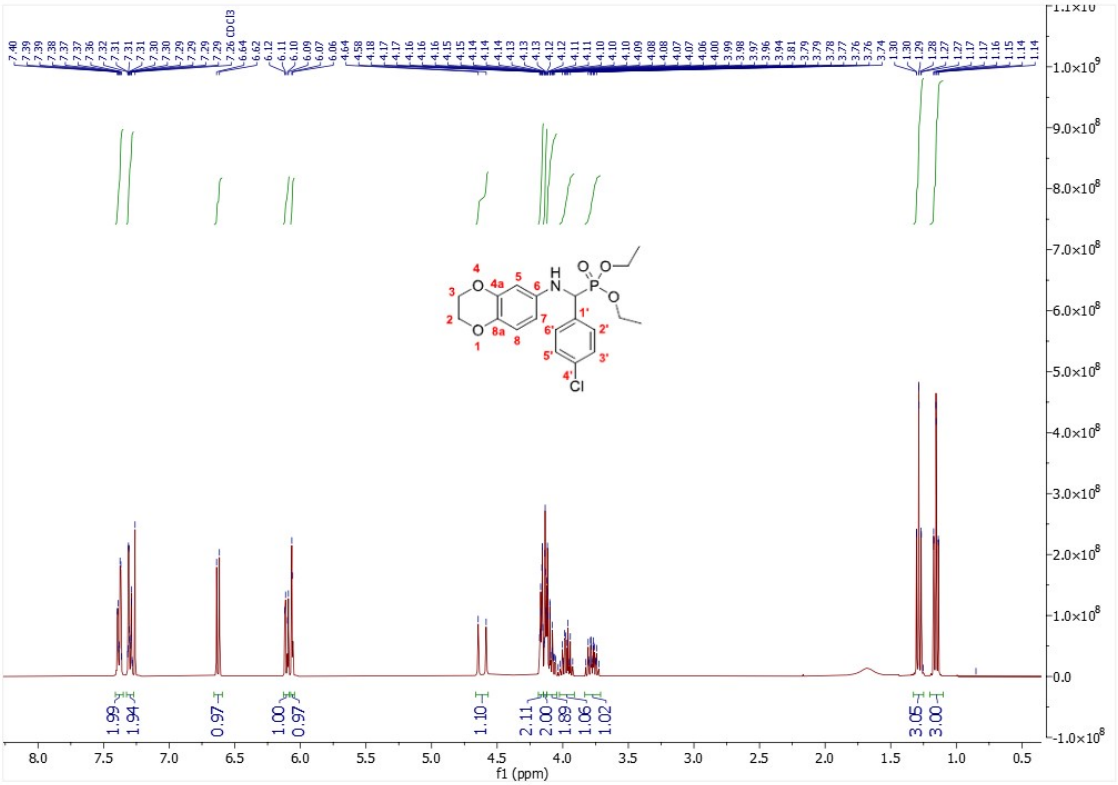

Figure 41. ^{1}H NMR spectrum of compound **6g** in $CDCl_3$

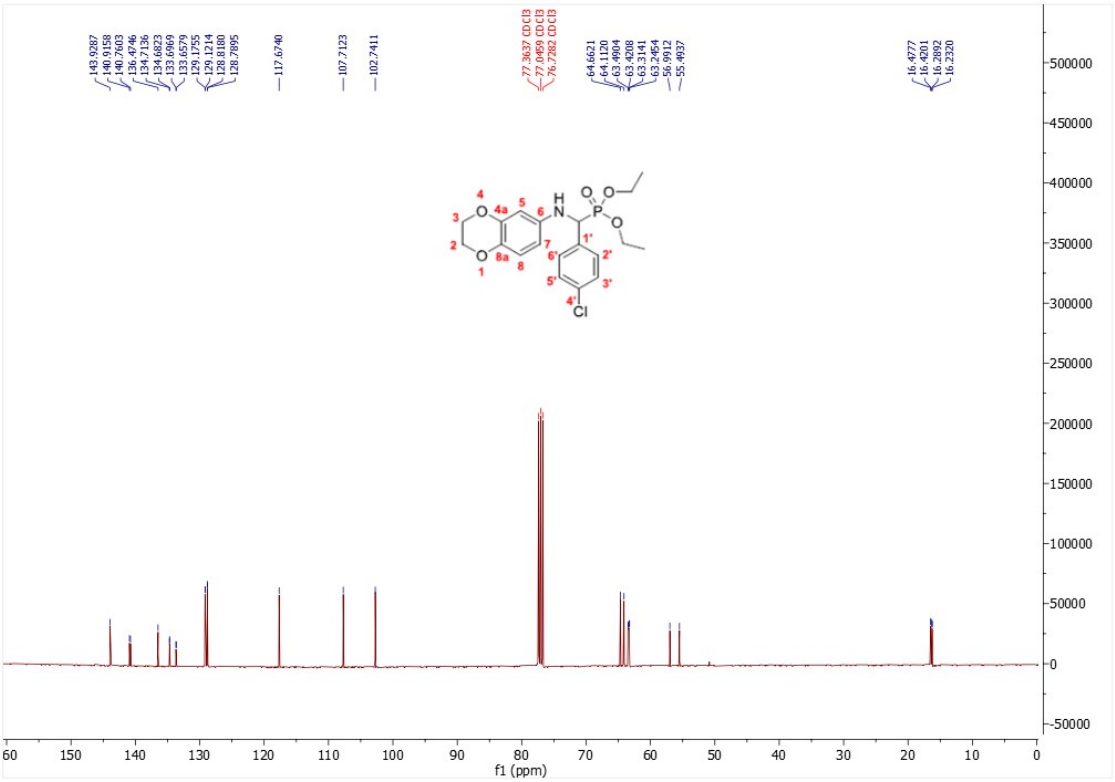

Figure 42. ^{13}C NMR spectrum of compound **6g** in $CDCl_3$

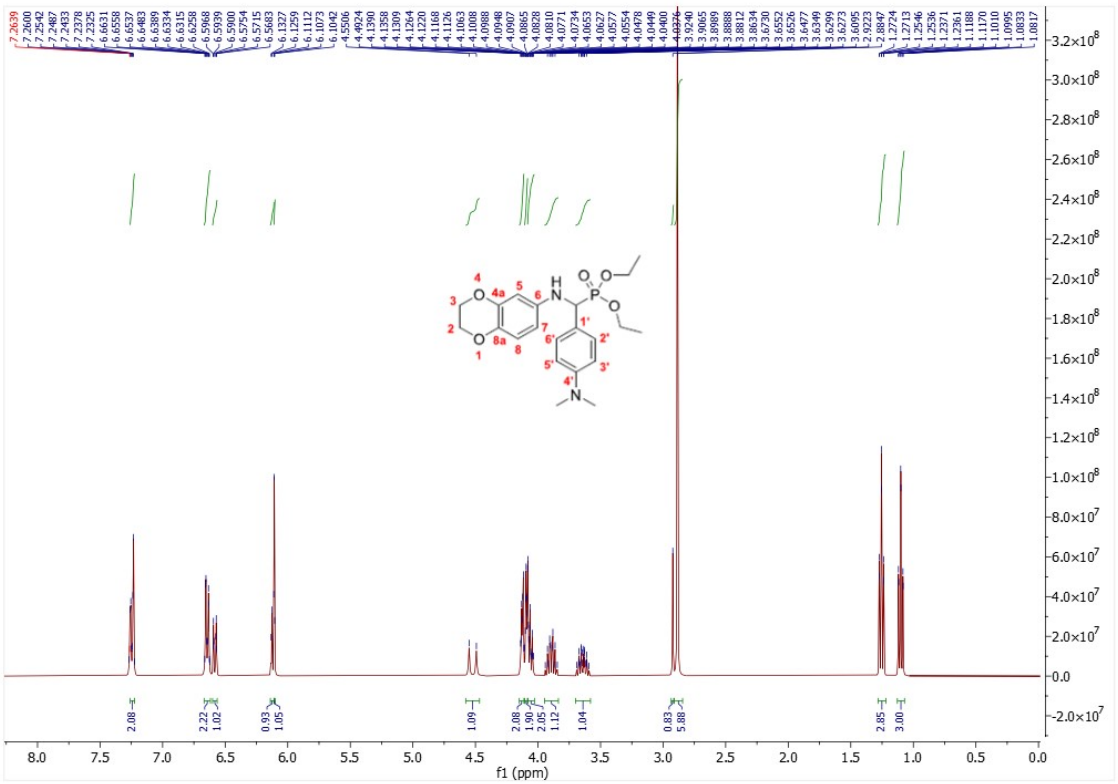

Figure 43. ^{1}H NMR spectrum of compound **6h** in $CDCl_3$

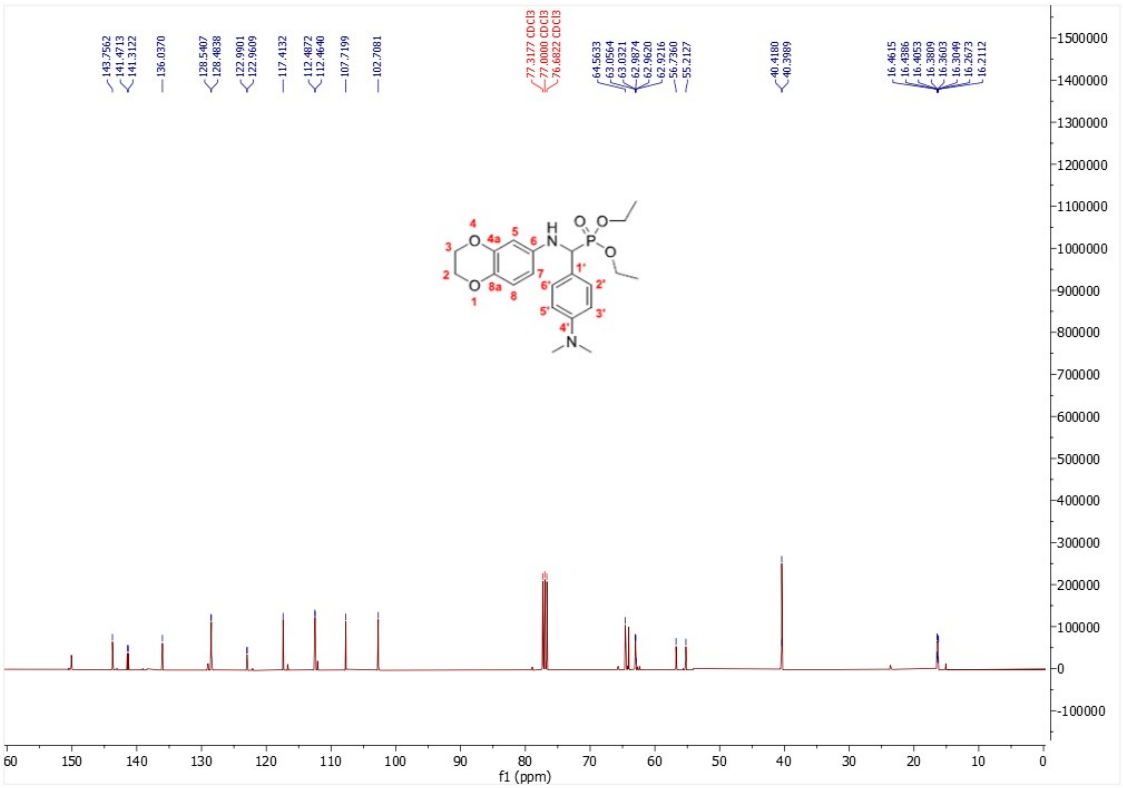

Figure 44. ^{13}C NMR spectrum of compound **6h** in $CDCl_3$

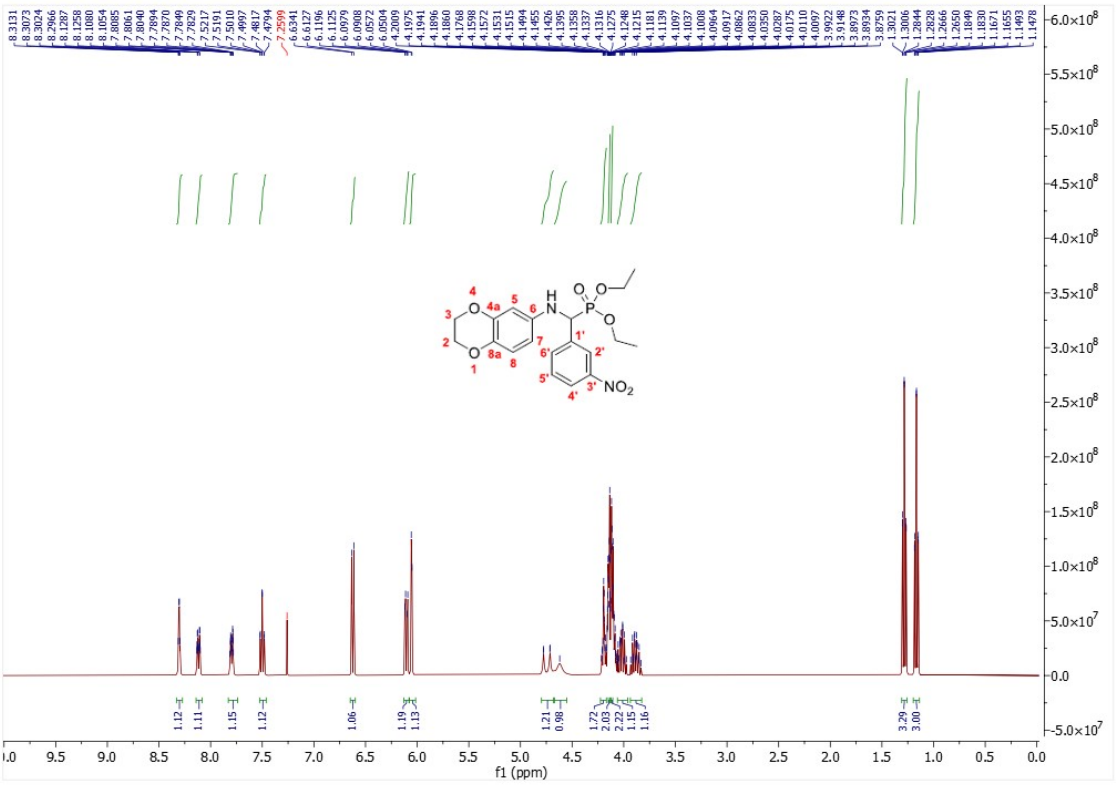

Figure 45. ^{1}H NMR spectrum of compound **6i** in $CDCl_3$

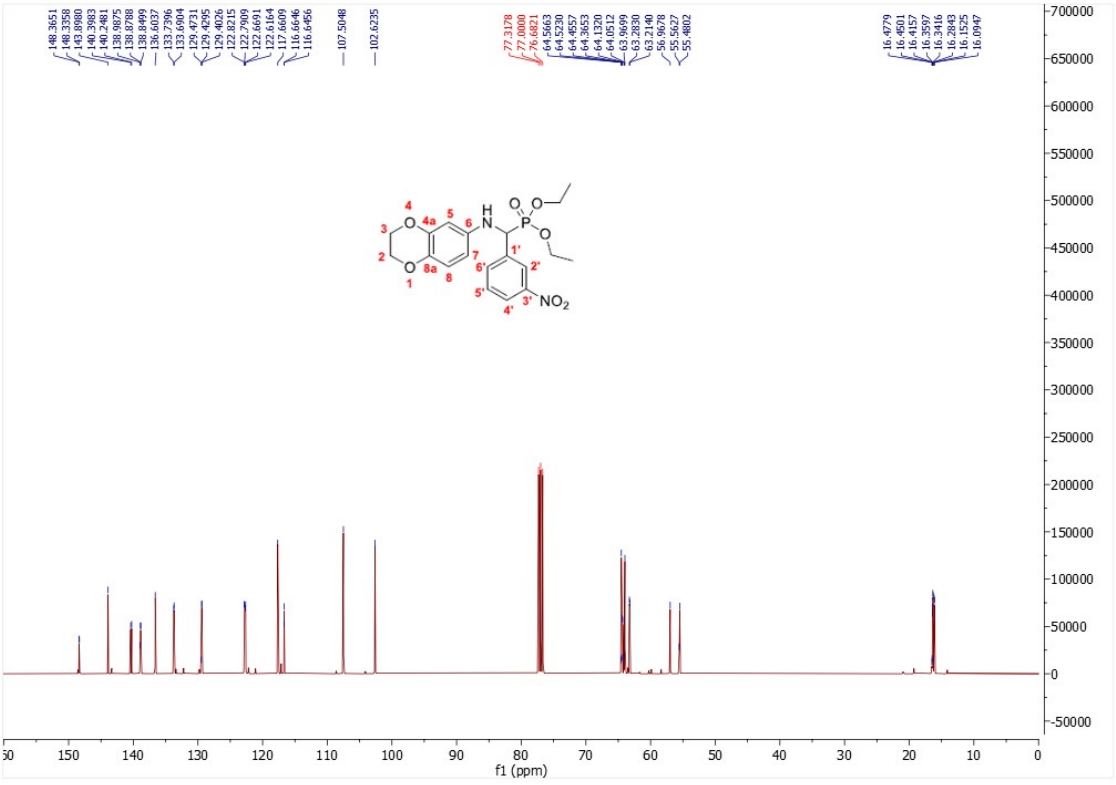

Figure 46. ^{13}C NMR spectrum of compound **6i** in $CDCl_3$

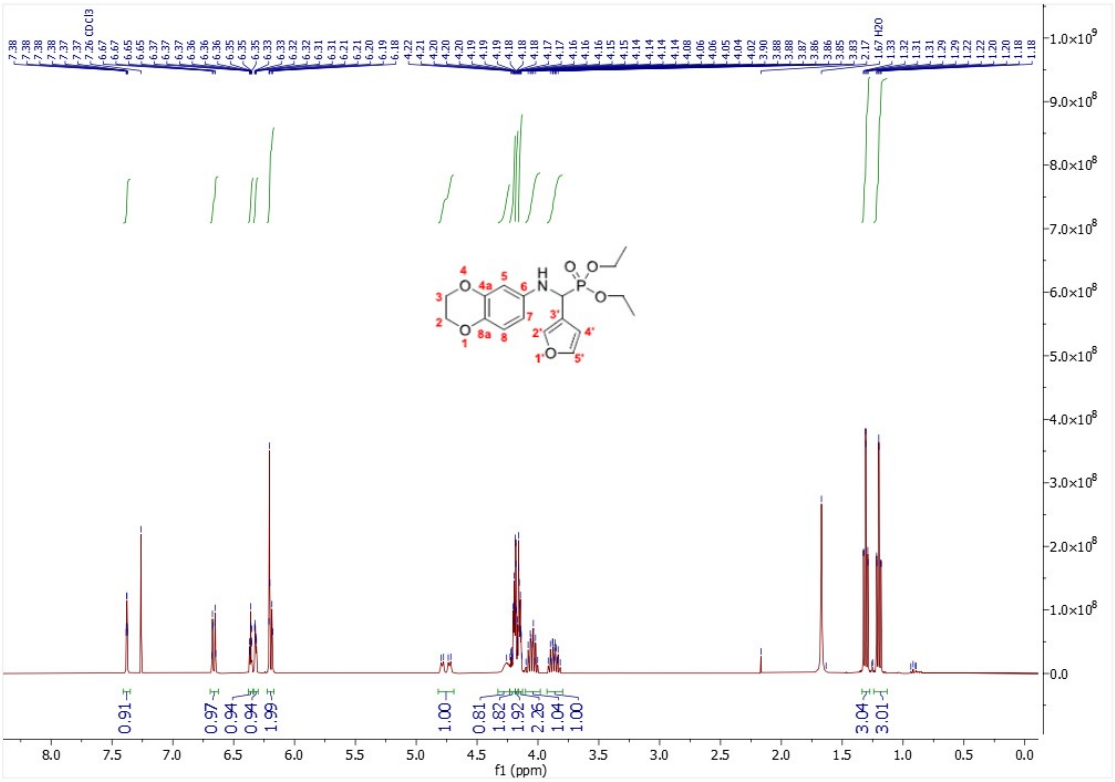

Figure 47. ^{1}H NMR spectrum of compound **6j** in $CDCl_3$

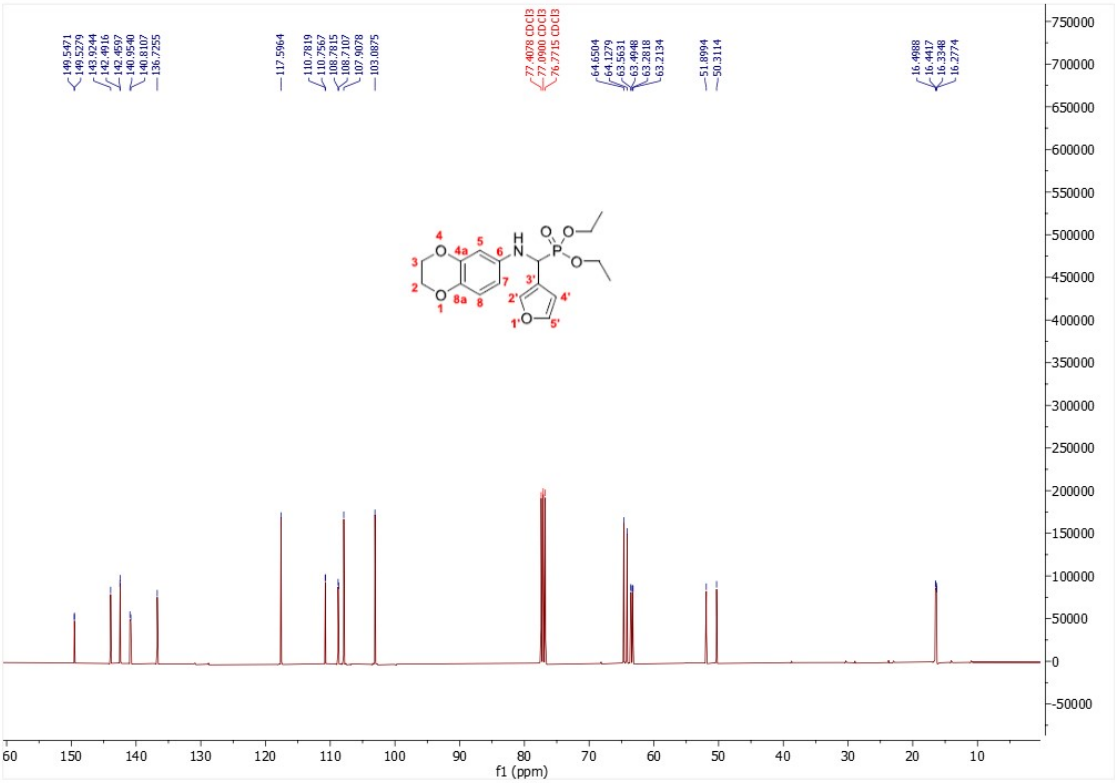

Figure 48. ^{13}C NMR spectrum of compound **6j** in $CDCl_3$

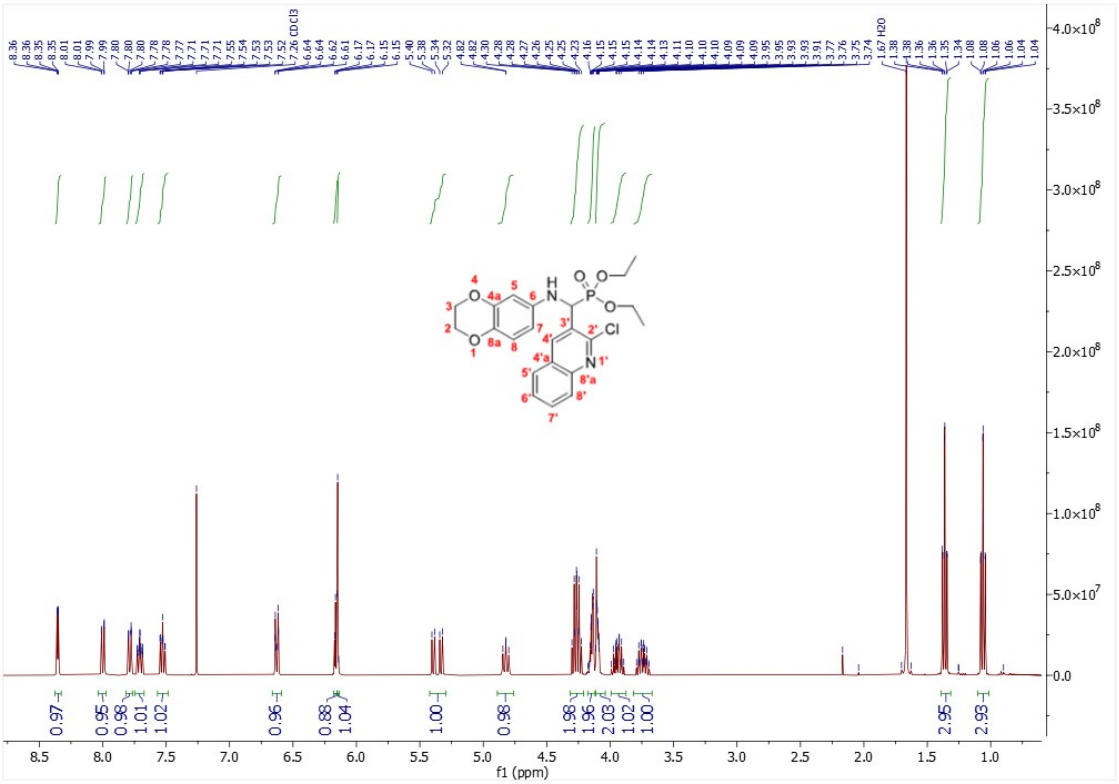

Figure 49. ^{1}H NMR spectrum of compound **6k** in $CDCl_3$

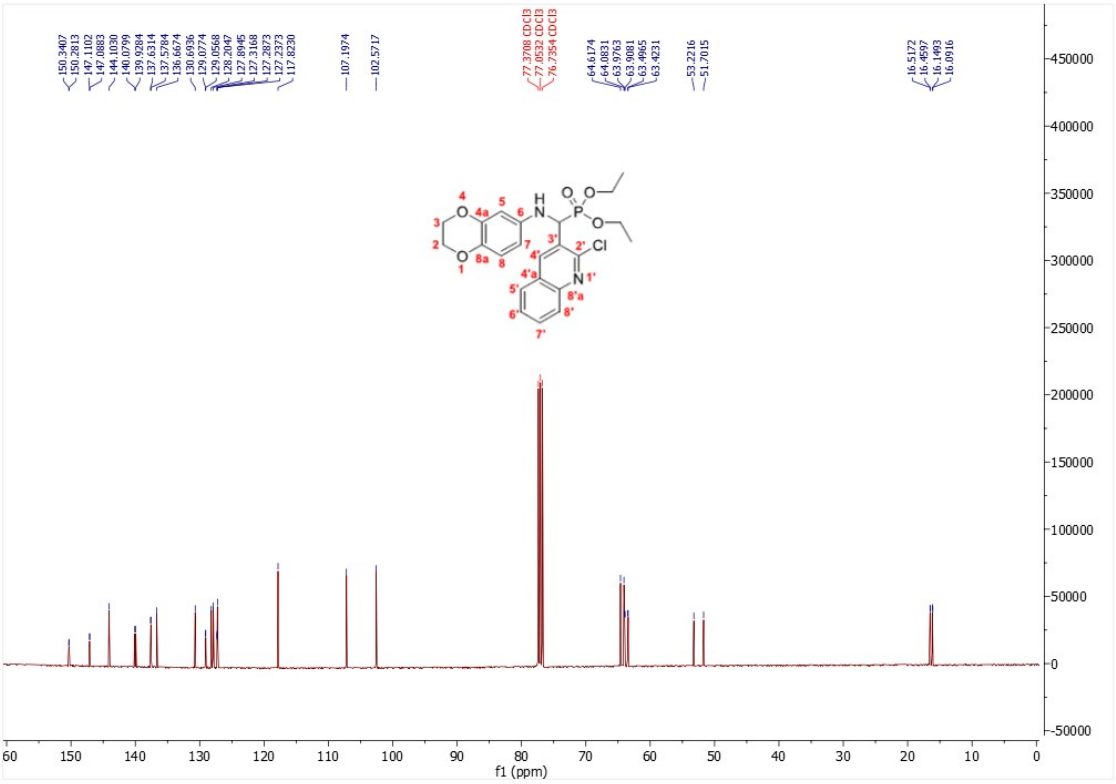

Figure 50. ^{13}C NMR spectrum of compound **6k** in $CDCl_3$

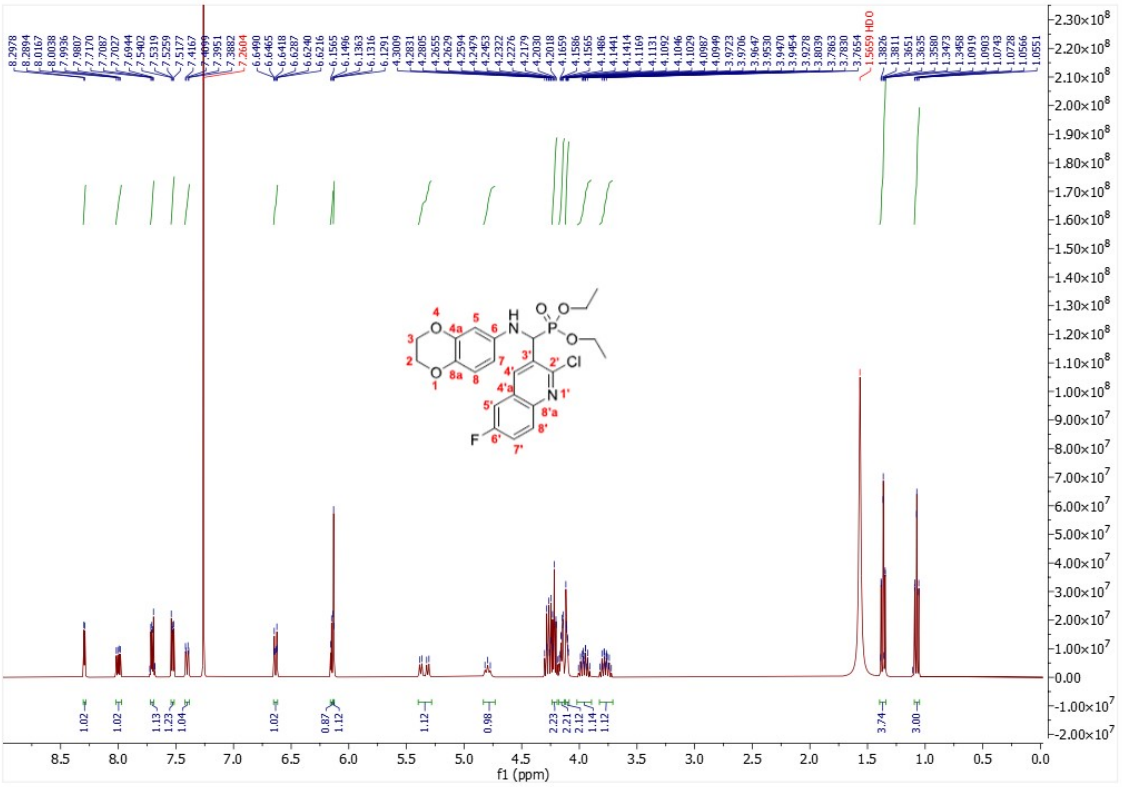

Figure 51. ^{1}H NMR spectrum of compound **6l** in $CDCl_3$

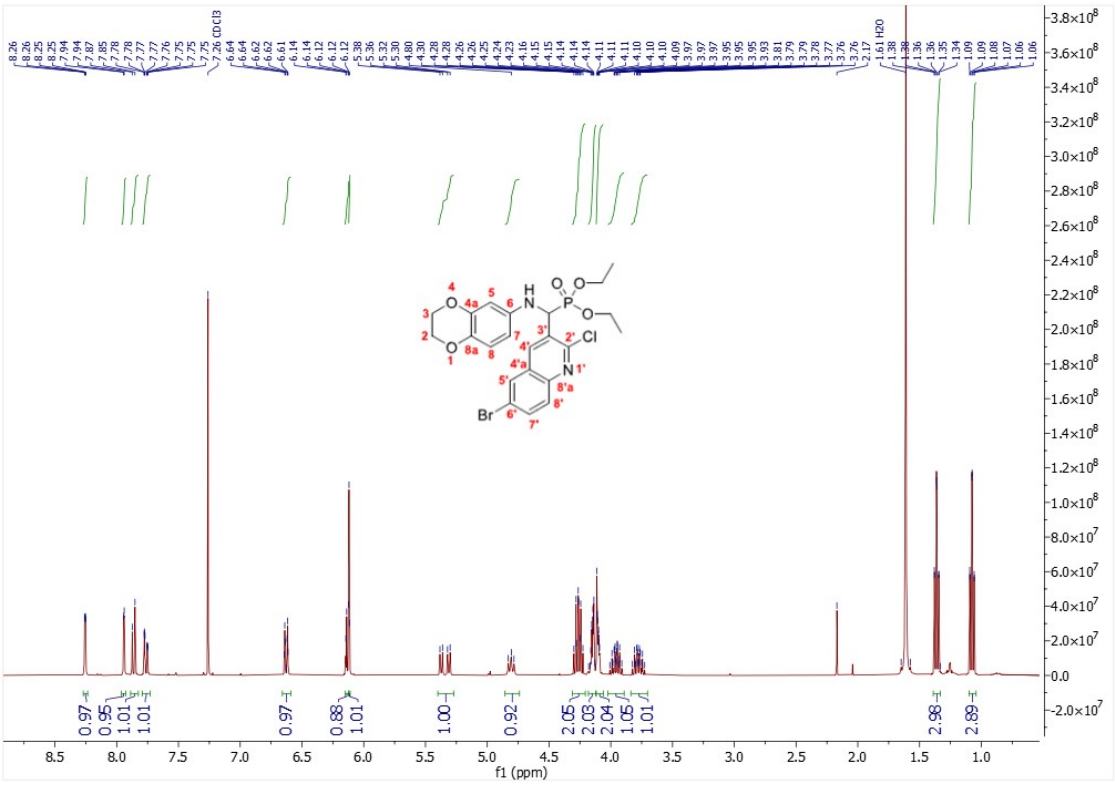

Figure 52. ^{1}H NMR spectrum of compound **6m** in $CDCl_3$

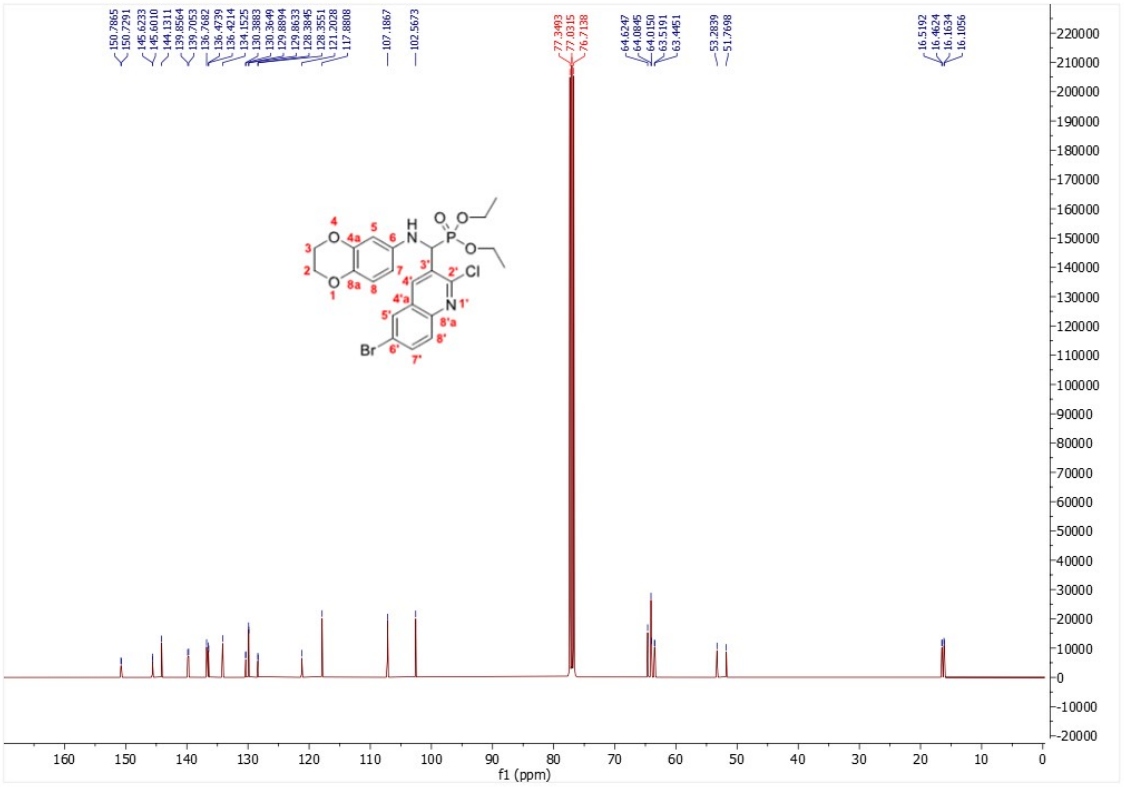

Figure 53. ^{13}C NMR spectrum of compound **6m** in $CDCl_3$

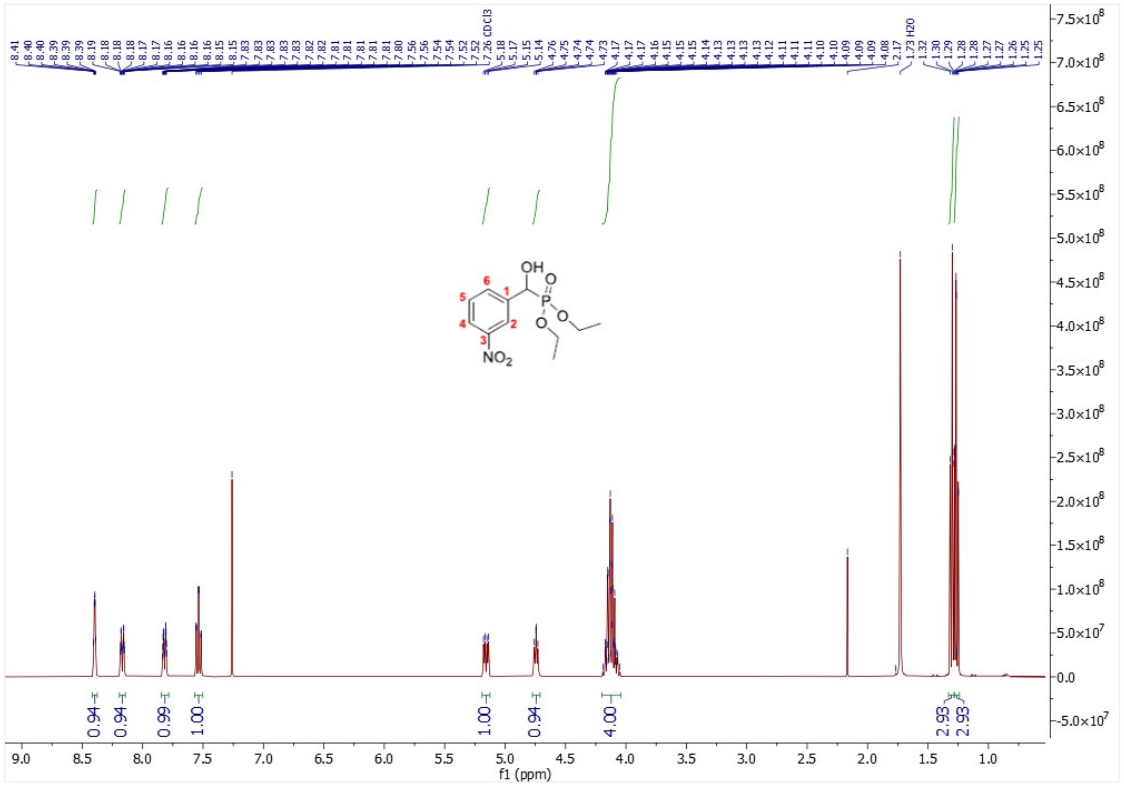

Figure 54. ^{1}H NMR spectrum of compound **6i'** in $CDCl_3$

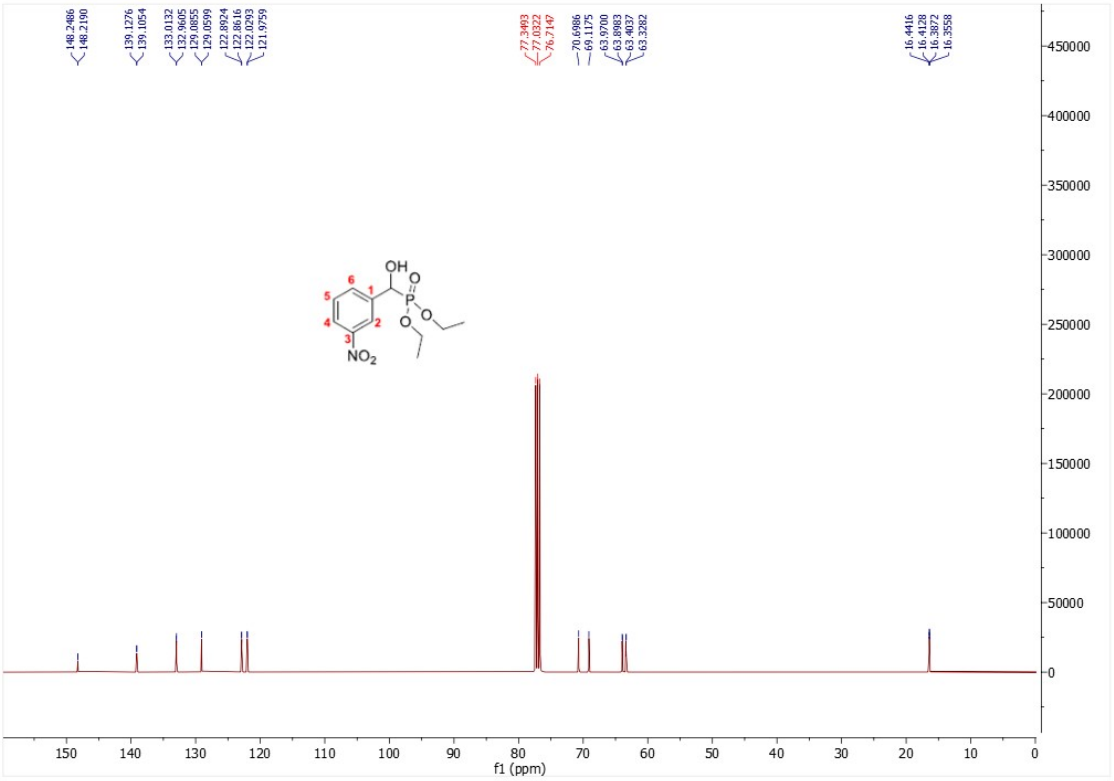

Figure 55. ^{13}C NMR spectrum of compound **6i'** in $CDCl_3$

7) Antioxidant activity

7.1. FRAP method

The method used followed the procedure established by Benzie and Strain.[1] This assay operates on the principle that antioxidants can reduce a ferric–tripyridyltriazine (Fe^{3+}–TPTZ) complex to its ferrous (Fe^{2+}) form, resulting in a blue-colored compound. In brief, the FRAP reagent was freshly prepared by mixing 2.5 mL of 10 mmol/L TPTZ (2,4,6-tripyridyl-s-triazine, Sigma) dissolved in 40 mmol/L HCl with 2.5 mL of 20 mmol/L $FeCl_3$ and 25 mL of 0.3 mol/L acetate buffer (p*H* 3.6), then warmed to 37 °C. Various concentrations of each sample (0.5 mL) were combined with 9 mL of the working FRAP solution and 0.5 mL of distilled water. After incubation at 37 °C for 30 minutes, absorbance was recorded at 593 nm using a spectrophotometer. A 1 mmol/L $FeSO_4$ solution served as the calibration standard. Results were expressed as the antioxidant capacity equivalent to 1 mmol/L $FeSO_4$. Samples with FRAP values exceeding the standard curve's linear range were appropriately diluted before analysis.

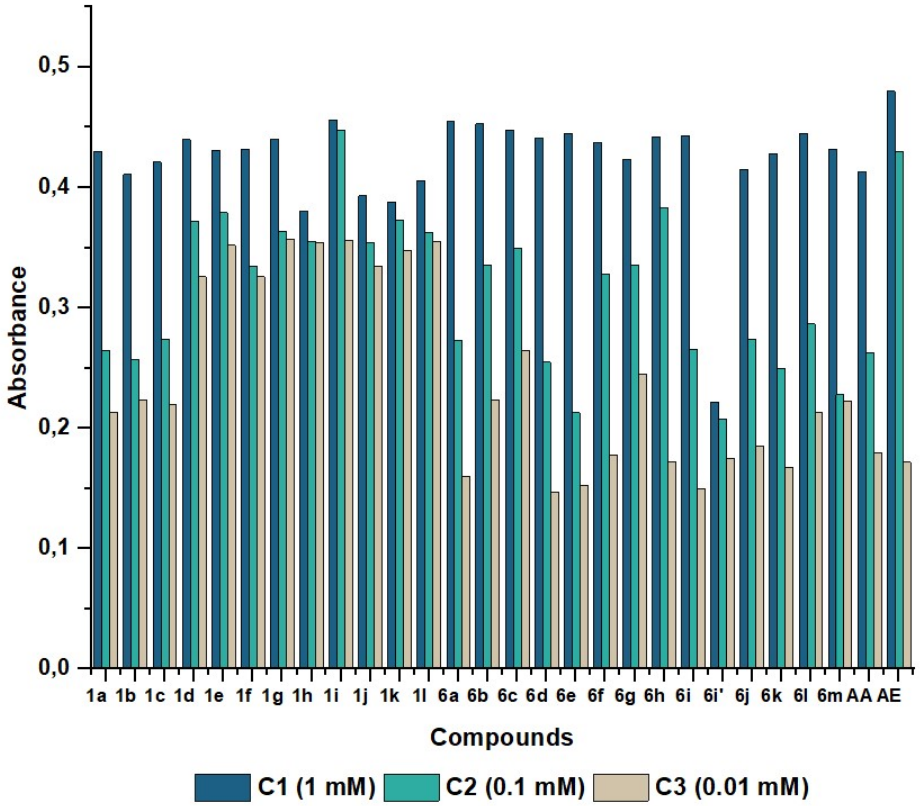

Figure 56. Absorbance of compounds **1a-l** and **6a-m** at different concentrations by FRAP method

7.2. CUPRAP method[2]

The total antioxidant capacity of compounds **1a-l** and **6a-m** was evaluated using the antioxidant assay kit (MAK334, Sigma-Aldrich, St. Louis, MO, USA) following the manufacturer's instructions. In this method, copper(II) ions (Cu^{2+}) are reduced by antioxidant molecules to copper(I) ions (Cu^{+}), which subsequently react with a chromogenic reagent to generate a colored complex. The absorbance of this complex is measured at 570 nm, and the resulting color intensity is directly correlated with the antioxidant capacity of the sample. The outcomes were expressed as micromolar (µM) Trolox equivalents.[3]

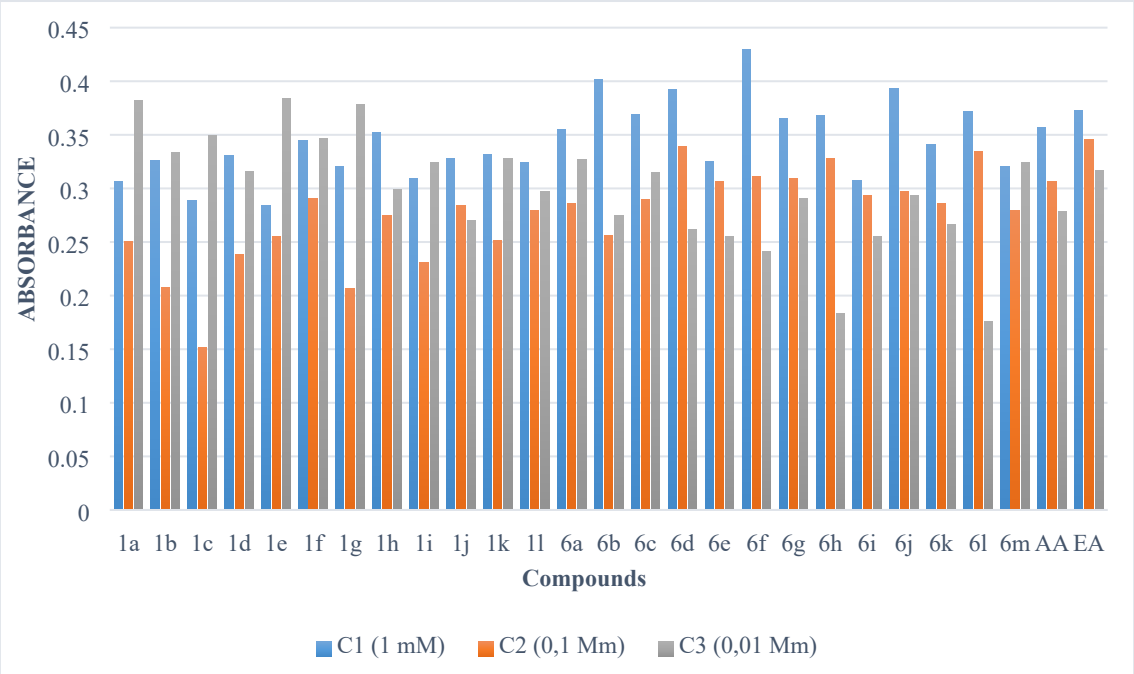

Figure 57. Absorbance of compounds **1a-l** and **6a-m** by CUPRAC method

References:

1. I. F. Benzie, J. J. Strain, The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay, *Anal. Biochem*. *239* (**1996**) 70-76.
2. Antioxidant assay kit (MAK334, Sigma-Aldrich, St. Louis, MO, USA) (https://www.sigmaaldrich.com/ES/es/product/sigma/mak334).
3. R. Amorati, L. Valgimigli, Advantages and limitations of common testing methods for antioxidants. *Free radic. Res. 49* (**2015**) 633-649, doi: 10.3109/10715762.2014.996146