Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry


**Supporting Information**

# Synthesis and anti-toxoplasmosis activity of 4-arylquinoline-2-carboxylate derivatives.

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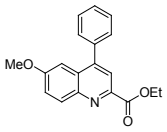
**General Information:**

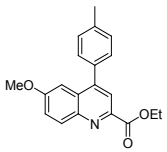
All fine chemicals were obtained from Sigma-Aldrich and used as obtained. Dichloromethane was distilled over calcium hydride. All reactions were performed under nitrogen atmosphere in oven dried glassware. Toluene (dry) was distilled over sodium/benzophenone. DMSO (dry) was obtained from Sigma Aldrich. Phenyl acetylenes were obtained from Sigma-Aldrich or Alfa Aesar. Melting points were recorded in open capillary using a calibrated Büchi melting point B540 apparatus and are corrected. Thin layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel $60F_{254}$ (Merck) and was visualized under 254 nm UV light. $^{1}H$, $^{13}C$ spectra were recorded on a AV 600 spectrometer in $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) are reported in ppm downfield of TMS and coupling constants (*J*) are expressed in hertz (Hz).

**General Procedure** : A mixture of phenylacetylene (0.010 g, 0.090 mmol), ethylglyoxalate (50 % in toluene, 0.039 g, 0.19 mmol), amine (0.024 g, 0.19 mmol) and AgOTf (0.005 g, 0.01 mmol) were dissolved in $CH_2Cl_2$ (0.5 mL) and then stirred at 50 $^{0}C$ for 48h in a screw capped, teflon sealed vial. After completion of the reaction the crude reaction mixture was concentrated and purified by flash column chromatography (hexane and ethyl acetate, 9:1) to afford the desired compound.

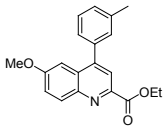
**Ethyl-6-methoxy-4-phenylquinoline-2-carboxylate (4)**[1]; Yellow solid (89 %); $^{1}H$ NMR (600 MHz, $CDCl_3$) : δ 1.48 (t, *J* = 7.2 Hz, 3H), 3.81 (s, 3H), 4.55 (q, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 2.8 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.49 – 7.58 (m, 5H), 8.09 (s, 1H), 8.30 (d, *J* = 9.3 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 14.55, 55.66, 62.24, 103.45, 121.95, 122.95, 128.78, 128.92, 129.34, 129.46, 132.84, 138.06, 144.25, 145.47, 148.05, 159.64, 165.75.



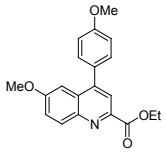

**Ethyl-6-methoxy-4-p-tolylquinoline-2-carboxylate (4a)**[2]; Yellow solid (97 %); $^{1}H$ NMR (600 MHz, $CDCl_3$): δ 1.39 (t, *J* = 7.2 Hz, 3H), 2.38 (s, 3H), 3.72 (s, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 7.25 (d, *J* = 2.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.41-7.50 (m, 3H) 8.09 (s, 1H), 8.30 (d, *J* = 9.3 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 14.55, 21.47, 55.68, 62.25, 103.52, 121.93, 122.97, 129.38, 129.46, 129.64, 132.75, 138.77, 140.23, 144.33, 145.23, 148.42, 159.51, 165.92.



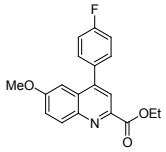

**Ethyl-6-methoxy-4-m-tolylquinoline-2-carboxylate (4b)**[3]; Yellow solid (97 %); $^{1}H$ NMR (600 MHz, $CDCl_3$): δ 1.48 (t, *J* = 7.2 Hz, 3H), 2.47 (s, 3H), 3.81 (s, 3H), 4.55 (q, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 2.8 Hz, 1H), 7.31-7.37 (m, 3H), 7.42-7.45 (m, 2H) 8.08 (s, 1H), 8.29 (d, *J* = 9.3 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 14.56, 21.62, 55.67, 62.25, 103.59, 121.90, 122.93, 126.52, 128.72, 129.41, 129.51 130.16, 132.76, 137.99, 138.76, 144.38, 145.44, 148.50, 159.62, 165.75.



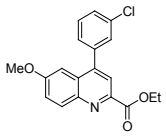

**Ethyl-6-methoxy-4-(4-methoxyphenyl)quinoline-2-carboxylate (4c)**[3]; Yellow solid (82 %); $^{1}H$ NMR (600 MHz, $CDCl_3$): δ 1.48 (t, *J* = 7.1 Hz, 3H), 3.83 (s, 3H), 3.91 (s, 3H), 4.55 (q, *J* = 7.1 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 2.8 Hz, 1H), 7.43 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.49 (d, *J* = 8.7, 2H), 8.07 (s, 1H), 8.28 (d, *J* = 9.3 Hz, 1H); $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 14.56, 55.56, 55..68, 62.24, 103.51, 114.40, 121.88, 122.89, 129.53, 130.32, 130.76 132.82, 144.45, 145.49, 148.03, 159.62, 160.13, 165.81.



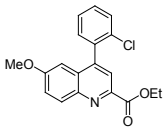

**Ethyl-4-(4-fluorophenyl)-6-methoxyquinoline-2-carboxylate (4d)**[3]; Yellow solid (97 %); $^{1}$H NMR (600 MHz, $CDCl_3$): δ 1.51 (t, *J* = 7.1 Hz, 3H), 3.84 (s, 3H), 4.58 (q, *J* = 7.1 Hz, 2H), 7.17 (d, *J* = 2.8 Hz, 1H), 7.27- 7.30 (m, 2H), 7.47 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.53-7.55 (m, 2H), 8.09 (s, 1H), 8.32 (d, *J* = 9.3 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.55, 55.69, 62.32, 103.22, 116.13 (d, $J_{C\text{-}F}$ = 22.6 Hz), 121.98, 123.05, 129.35, 131.20 (d, $J_{C\text{-}F}$ = 7.5 Hz), 132.91, 134.01, 144.38, 145.46, 147.18, 159.82, 163.96 (d, $J_{C\text{-}F}$ = 247.6 Hz), 165.65.



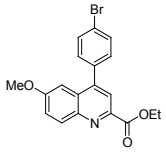

**Ethyl-4-(3-chlorophenyl)-6-methoxyquinoline-2-carboxylate (4e)**[4]; Yellow solid (90 %); $^{1}$H NMR (600 MHz, $CDCl_3$): δ 1.49 (t, *J* = 7.1 Hz, 3H), 3.83 (s, 3H), 4.56 (q, *J* = 7.1 Hz, 2H), 7.14 (d, *J* = 2.8 Hz, 1H), 7.41-7.52 (m, 4H), 7.54-7.55 (m, 1H), 8.07 (s, 1H), 8.30 (d, *J* = 9.3 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.56, 55.74, 62.36, 103.11, 121.88, 123.17, 127.64, 128.97, 129.05, 129.54, 130.21, 132.94, 139.78, 144.38, 145.45, 146.64, 159.93, 165.41.



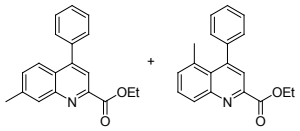

**Ethyl-4-(2-chlorophenyl)-6-methoxyquinoline-2-carboxylate (4f)**[4]; Yellow solid (91 %); $^{1}$H NMR (600 MHz, $CDCl_3$): δ 1.48 (t, *J* = 7.1 Hz, 3H), 3.77 (s, 3H), 4.55 (dtt, *J* = 10.8, 7.3 and 3.7 Hz, 2H), 6.76 (d, *J* = 2.7 Hz, 1H), 7.37 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.42-7.49 (m, 3H), 7.59 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.06 (s, 1H), 8.30 (d, *J* = 9.3 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.56, 55.69, 62.30, 103.41, 122.46, 123.21, 127.18, 129.48, 130.13, 130.22, 131.43, 132.79, 136.67, 144.12, 145.37, 145.67, 159.78, 165.58.



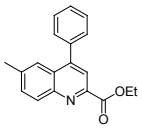

**Ethyl-4-(4-bromophenyl)-6-methoxyquinoline-2-carboxylate (4g)**[4]; Yellow solid (83 %); $^{1}$H NMR (600 MHz, $CDCl_3$): δ 1.49 (t, *J* = 7.1 Hz, 3H), 3.82 (s, 3H), 4.56 (q, *J* = 7.1 Hz, 2H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.39-7.47 (m, 3H), 7.70 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H), 8.30 (d, *J* = 9.3 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.55, 55.75, 62.37, 103.07, 121.82, 123.22, 129.08, 131.07, 132.21, 132.91, 136.92, 144.34, 145.41, 146.99, 159.92, 165.56.



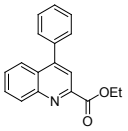
**Ethyl-7-methyl-4-phenylquinoline-2-carboxylate and Ethyl-5-methyl-4-phenylquinoline-2-carboxylate (4h)**[4,5]; Mixture of regioisomers in the ratio of 75:25; white solid (23 %); $^1$H NMR (600 MHz, $CDCl_3$): δ 1.47 (t, *J* = 7.1 Hz, 3H, minor), 1.48 (t, *J* = 7.1 Hz, 3H, major), 2.04 (s, 3H, minor), 2.59 (s, 3H, major), 4.56 (q, *J* = 7.1 Hz, 2H, minor), 4.56 (q, *J* = 7.1 Hz, 2H, major), 7.42-7.46 (m, 3H, major and 3H minor), 7.51-7.55 (m, 3H, major and 3H minor), 7.66 (dd, *J* = 8.4, 7.1 Hz, 1H, minor), 7.86 (d, *J* = 8.6 Hz, 1H, major), 7.99 (s, 1H, minor), 8.07 (s, 1H, major), 8.18 (s, 1H, major), 8.27 (d, *J* = 8.5 Hz, 1H, minor); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.55, 21.85, 62.36, 120.74, 123.47, 125.49, 126.02, 121.89, 128.81, 128.91, 129.71, 130.17, 130.23, 131.09, 131.96, 137.87, 140.37, 147.85, 148.63, 165.62.



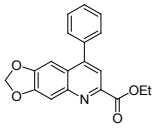

**Ethyl-6-methyl-4-phenylquinoline-2-carboxylate (4i)**[4,5]; White solid (66 %); $^1$H NMR (600 MHz, $CDCl_3$): δ 1.49 (t, *J* = 7.1 Hz, 3H), 2.50 (s, 3H), 4.56 (q, *J* = 7.1 Hz, 2H), 7.49-7.59 (m, 5H), 7.62 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.71 (s, 1H), 8.10 (s, 1H), 8.29 (d, *J* = 8.6 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.55, 22.18, 62.35, 121.57, 124.55, 127.98, 128.76, 128.81, 129.70, 130.99, 132.54, 137.93, 139.16, 146.89, 147.00, 149.08, 165.42.




**Ethyl-4-phenyl-2-quinoline-2-carboxylate (4j)**[6]; Yellow solid (18 %); $^1$H NMR (600 MHz, $CDCl_3$): δ 1.50 (t, *J* = 7.1 Hz, 3H), 4.58 (q, *J* = 7.1 Hz, 2H), 7.50-7.58 (m, 5H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 8.40 (d, *J* = 8.4 Hz, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.55, 62.47, 121.43, 125.88, 127.96, 128.77, 128.85, 128.91, 129.74, 130.20, 131.31, 137.67, 147.91, 148.28, 165.66.

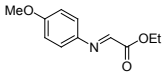



**Ethyl- 4-phenyl-[1,3]dioxolo-6,7-quinoline-2-carboxylate (4k)**; White solid (55 %); $^1$H NMR (600 MHz, $CDCl_3$): δ 1.48 (t, *J* = 7.1 Hz, 3H), 4.54 (q, *J* = 7.1 Hz, 2H), 6.13 (s, 2H), 7.19 (s, 1H), 7.45-7.57 (m, 5H), 7.69 (s, 1H), 8.00 (s, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.55, 62.27, 101.08, 102.32, 107.01, 120.58, 125.51, 128.80, 128.90, 129.48, 137.94, 142.69, 146.99, 150.10, 159.60, 169.15; HRMS calcd. For $C_{19}H_{15}NO_4$ [$M^+$] 322.1079; found 322.1088.

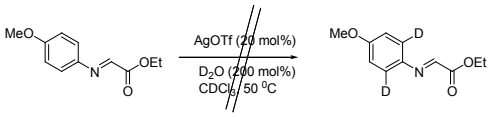



**General Procedure for the synthesis of Imine 5**

**Ethyl-2-(4-methoxy-phenylimino) acetate (5)**[7]; To p-Anisidine (0.500 g, 4.05 mmol) dissolved in toluene (4.0 mL), was added solid $Na_2SO_4$ (1.441 g, 10.1 mmol) and ethyl glyoxalate (50 % in toluene, 0.828 g, 4.05 mmol) added slowly. The reaction mixture was stirred at room temperature and was completed in 30 mins. The $Na_2SO_4$ was filtered off through a thin pad of celite and toluene then removed under vacuum and the crude compound purified by flash column chromatography (hexane and ethyl acetate, 9:1) to afford the imine **5** as a brown oil in 72% yield. $^1$H NMR (600 MHz, $CDCl_3$): δ 1.39 (t, *J* = 7.1 Hz, 3H), 3.83 (s, 3H), 4.40 (q, *J* = 7.1 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.93 (s, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.35, 55.63, 62.02, 114.65, 123.74, 141.53, 148.14, 160.65, 163.74.

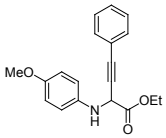


**General procedure for attempted deuteration of Imine 5:** To the imine (0.0280 g, 0.135 mmol) dissolved in $CDCl_3$ (0.50 mL), $D_2O$ (0.005 g, 0.270 mmol), AgOTf (0.006 g, 0.027 mmol) were added and stirred at 50 $^0$C for 48 h. Analysis by $^1$H NMR (600 mHz) showed no detectable trace of deuterium incorporation.

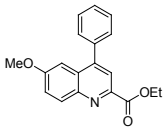



**General procedure for the synthesis of A$^3$ adduct 6**

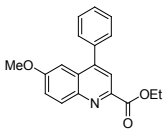
**Ethyl-2-(*p*-Methoxyphenylamino)-4-phenyl-3-butynoate (6)**[8]: Yellow oil (40%); To a stirred solution of phenylacetylene (0.0980 g, 0.965 mmol) and AgOTf (0.0120 g, 0.0480 mmol) in dichloromethane (5 mL) was added *N*-PMP protected iminoglyoxalate (0.100 g, 0.482 mmol). The reaction mixture was stirred at room temperature for 0.5 hrs and then diluted with ethyl acetate to give a brown solution. The solution was concentrated under reduced pressure and purified by column chromatography using 9:1 hexane-ethyl acetate to yield the product as a yellow oil. $^1$H NMR (600 MHz, $CDCl_3$): δ 1.33 (t, $J$ = 7.2 Hz, 3H), 3.75 (s, 3H), 4.31 (q, $J$ = 7.0 Hz, 2H), 4.96 (s, 1H), 6.73-6.75 (m, 2H), 6.80-6.82 (m, 2H), 7.28-7.31(m, 2H), 7.39-7.41 (m, 2H) ; $^{13}$C NMR (151 MHz, $CDCl_3$) δ 14.22, 50.79, 55.79, 62.54, 84.30, 84.48, 114.93, 116.21, 122.29, 128.37, 128.79, 132.04, 139.57, 153.53, 169.11.

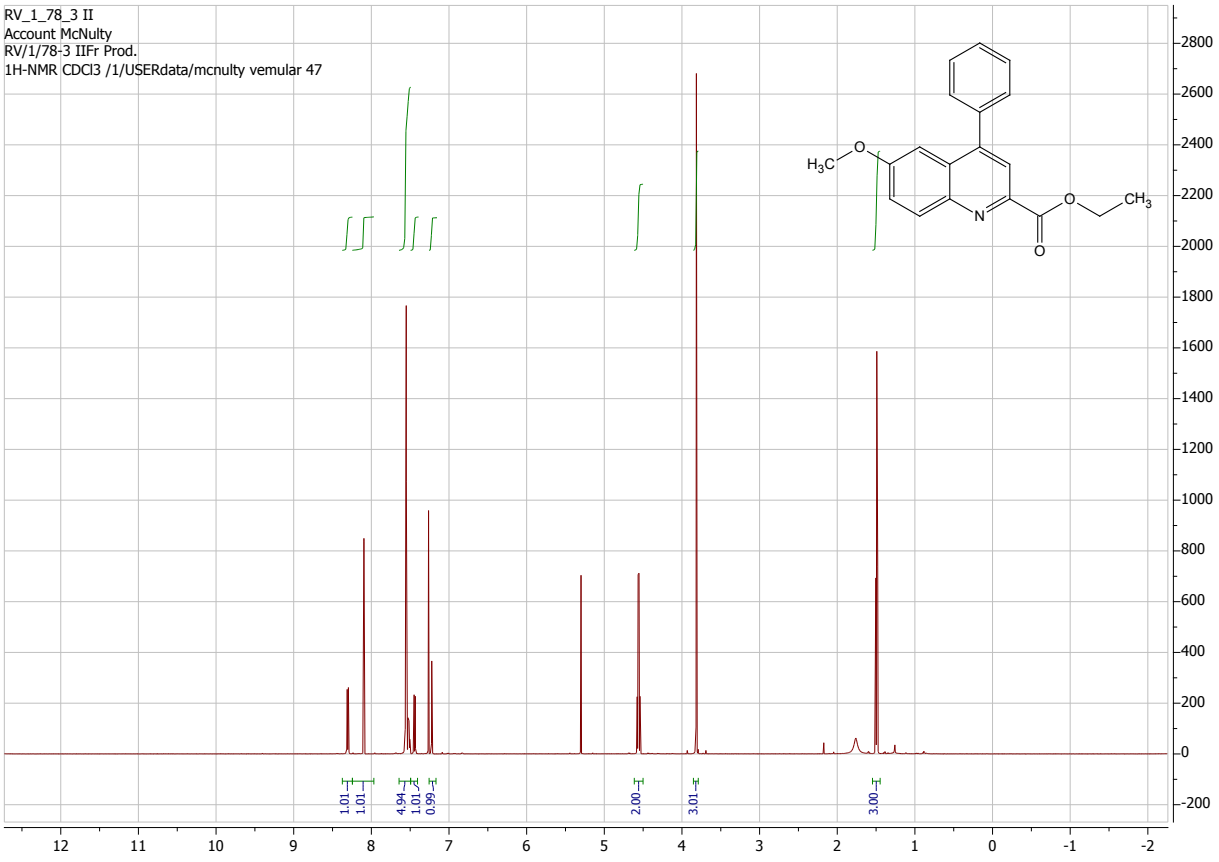


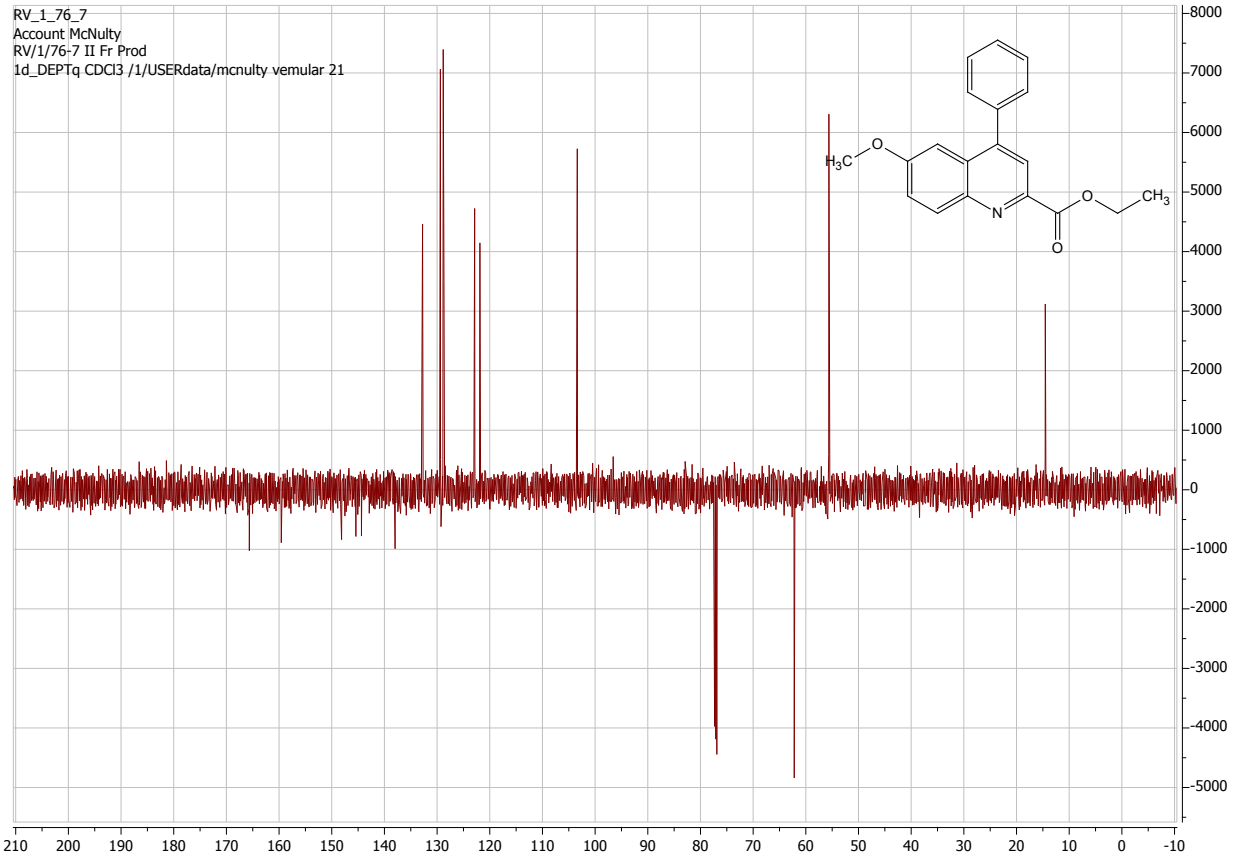
**General procedure to synthesise Quinoline-2-carboxylate using TfOH** : A mixture of phenylacetylene (0.010 g, 0.090 mmol), ethyl glyoxalate (50 % in toluene, 0.039 g, 0.19 mmol), amine (0.024 g, 0.19 mmol) and triflic acid (0.86 µL, 0.0090 mmol) were dissolved in $CH_2Cl_2$ (0.5 mL) and then stirred at room temperature for 24h in a screw capped teflon vial. After completion of the reaction the crude reaction mixture was concentrated and purified by flash column chromatography (hexane and ethyl acetate, 9:1) to afford the desired compound. $^1$H NMR data identical to compound **4**.

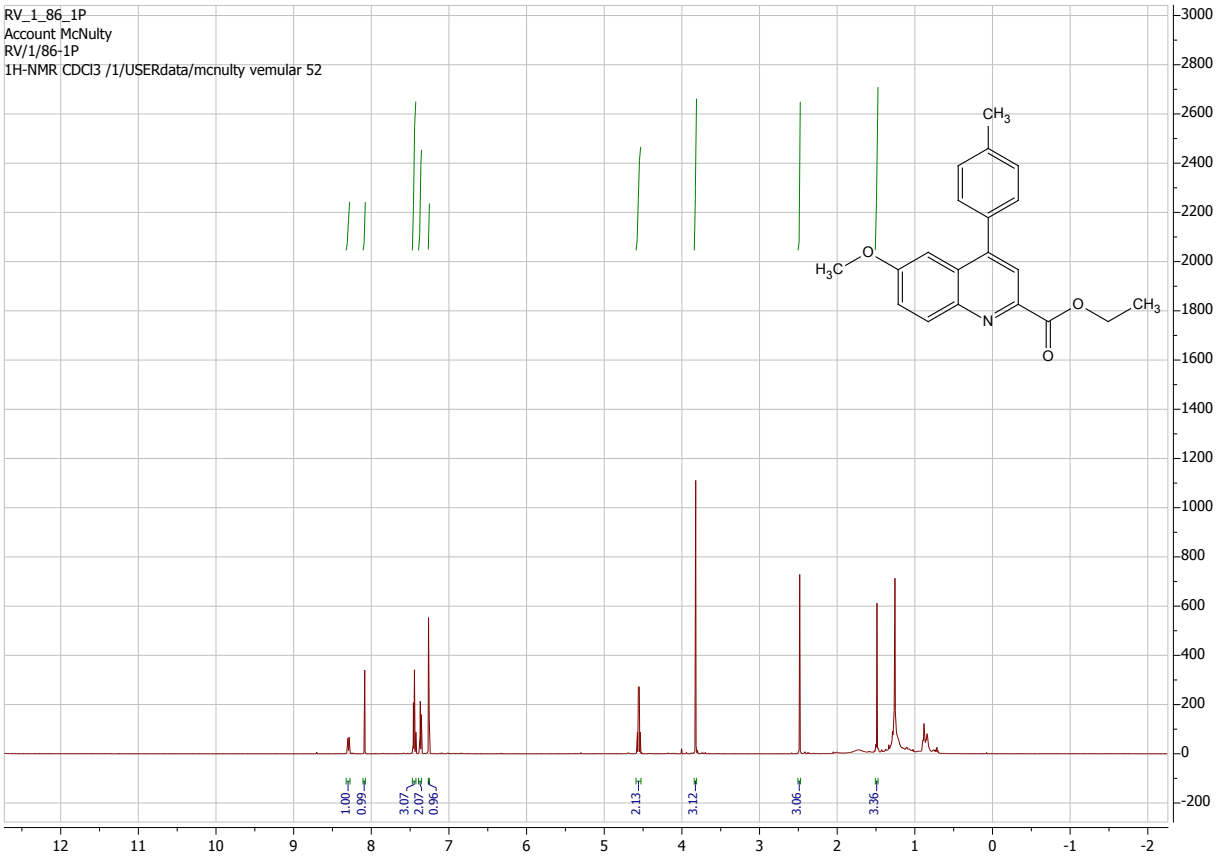


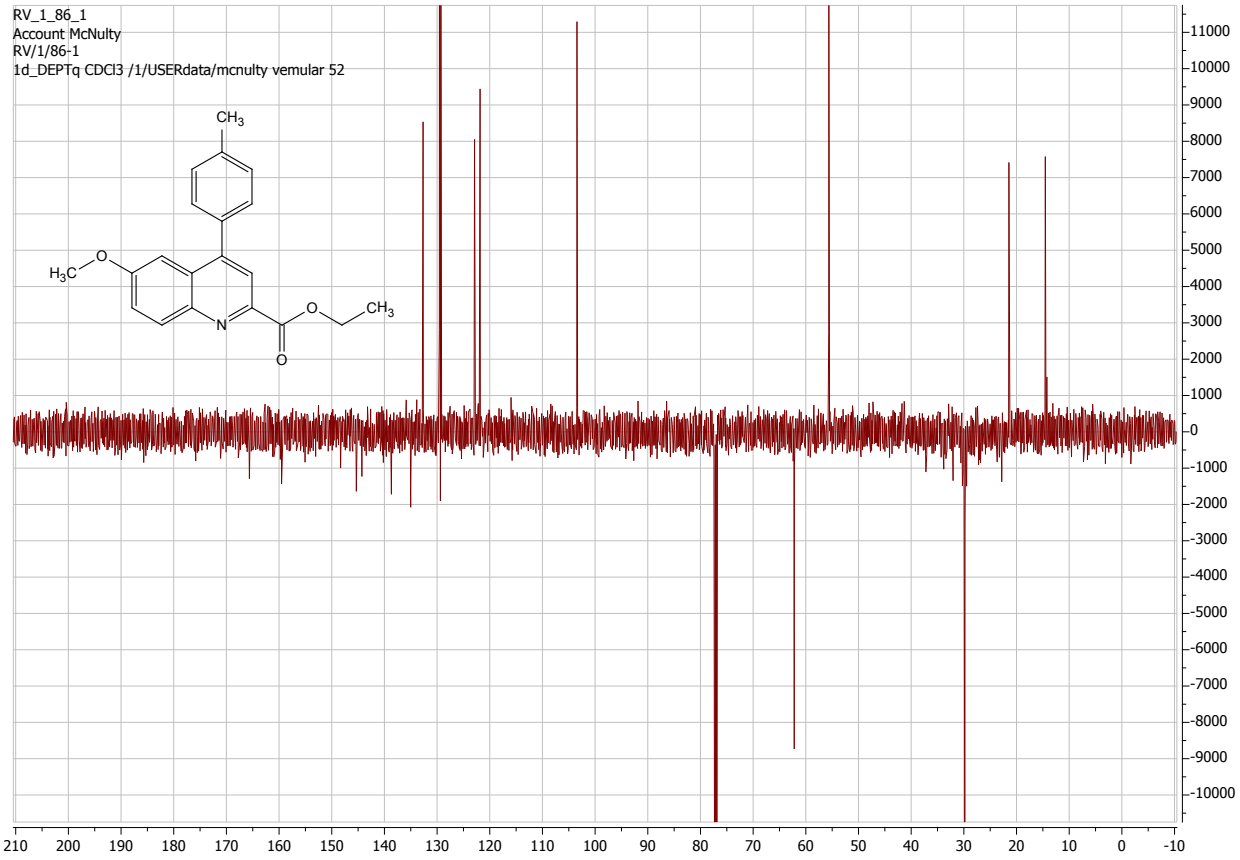
**General Procedure to form Quinoline-2-carboxylate from imine 5 and phenylacetylene using TfOH** : A mixture of imine **5** (0.010 g, 0.040 mmol), phenylacetylene (0.009 g, 0.09 mmol) and triflic acid (0.73 µL, 0.004 mmol) were dissolved in $CH_2Cl_2$ (0.5 mL) and then stirred at room temperature for 24h in a screw capped teflon vial. After completion of the reaction the crude reaction mixture was concentrated and purified by flash column chromatography (hexane and ethyl acetate, 9:1) to afford the desired compound. $^1$H NMR data identical to compound **4**.

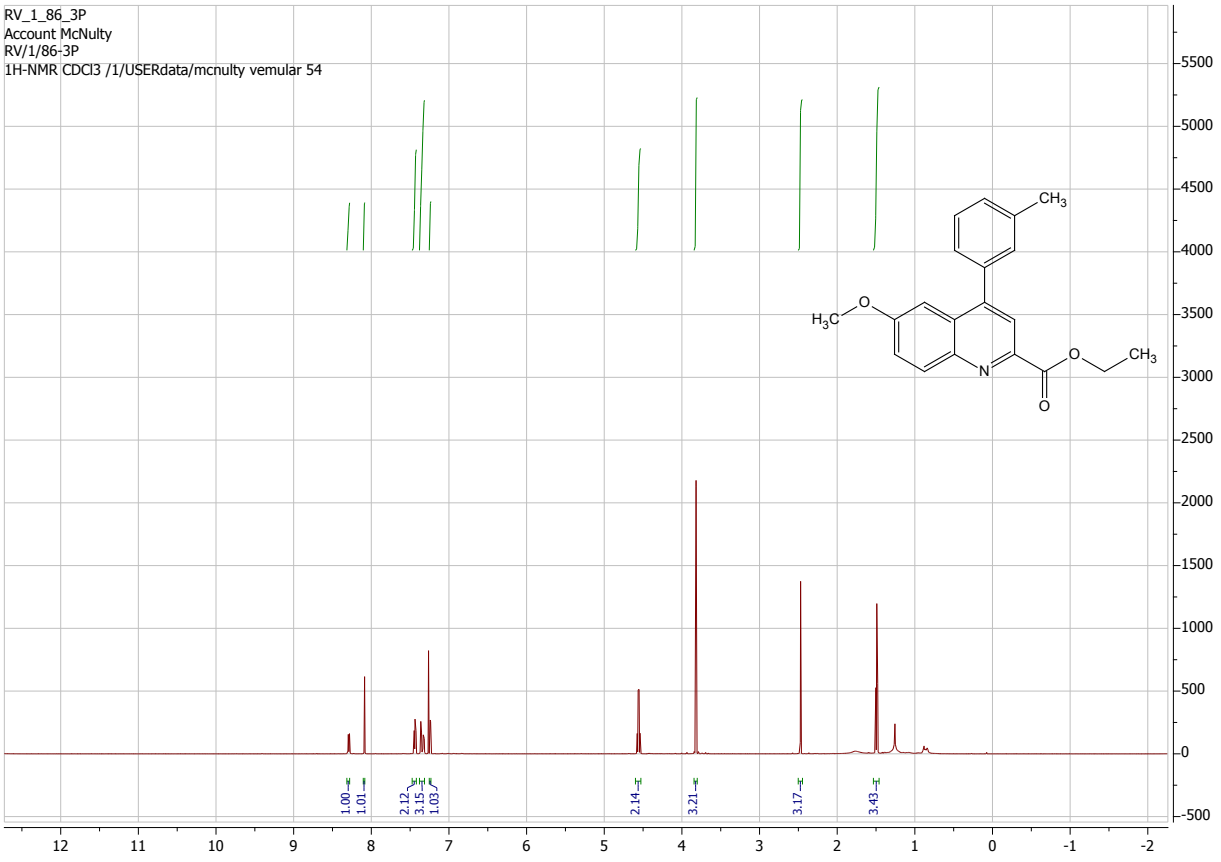


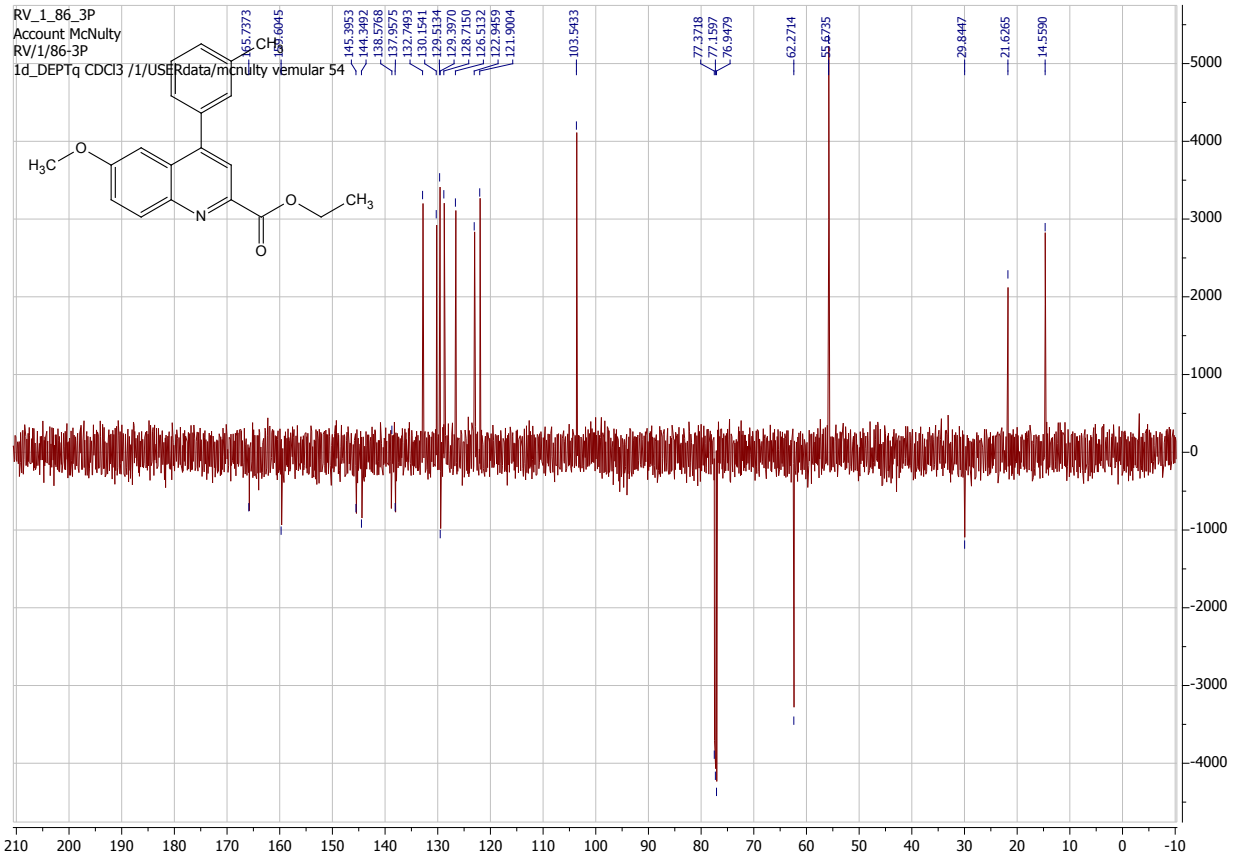


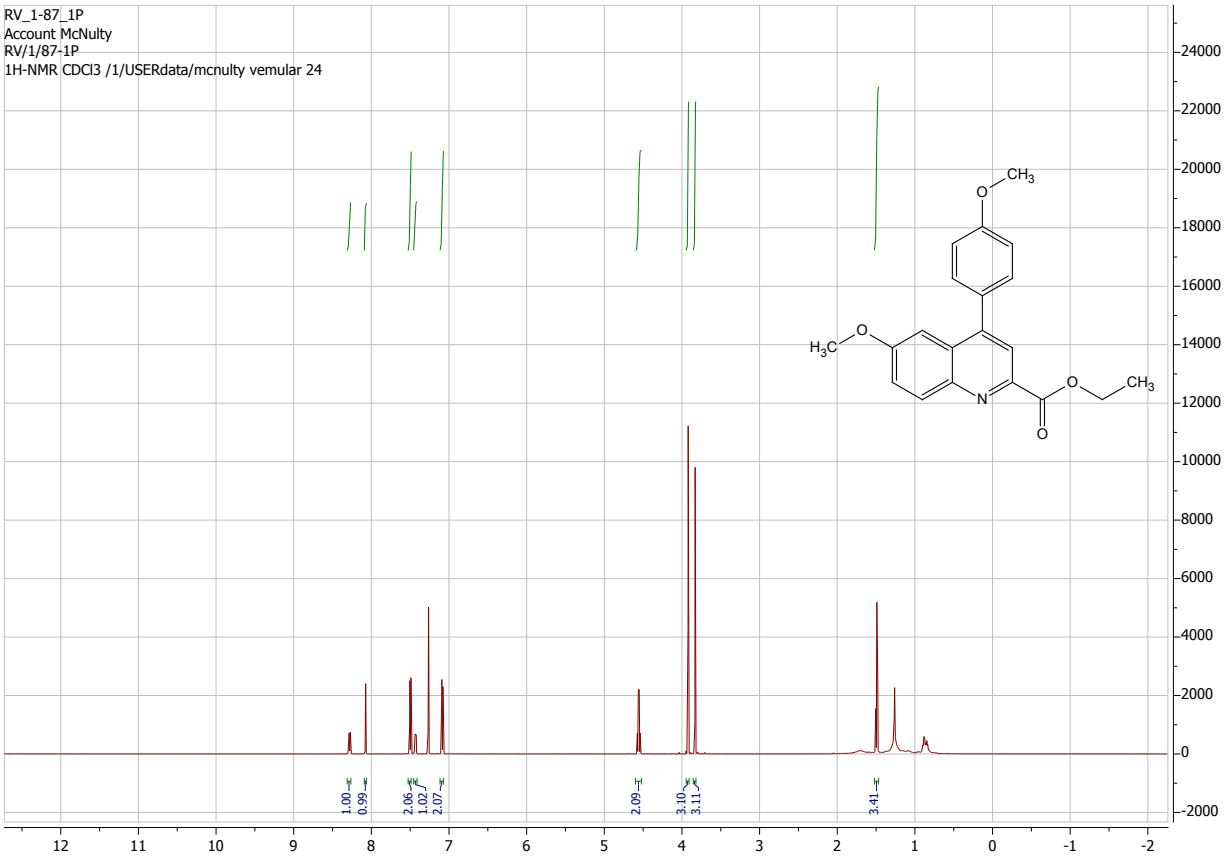


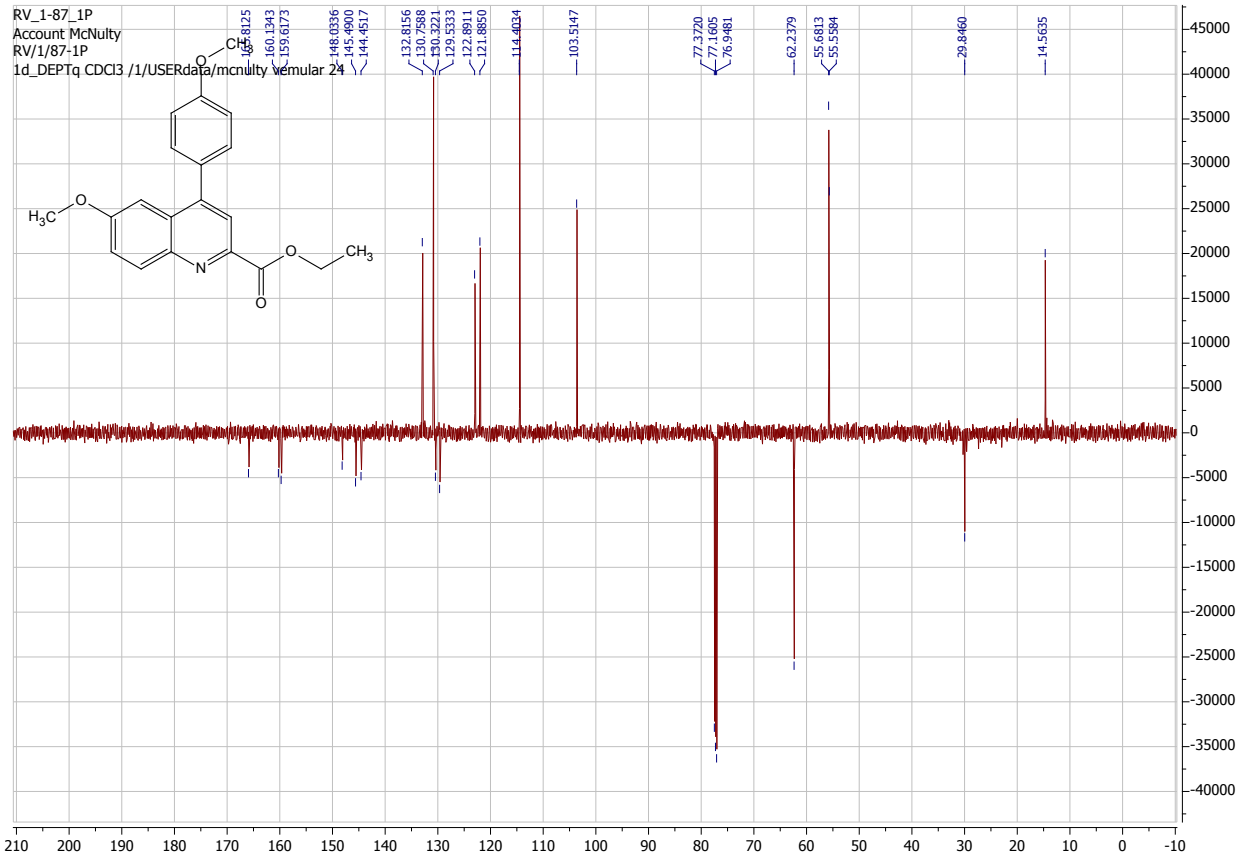


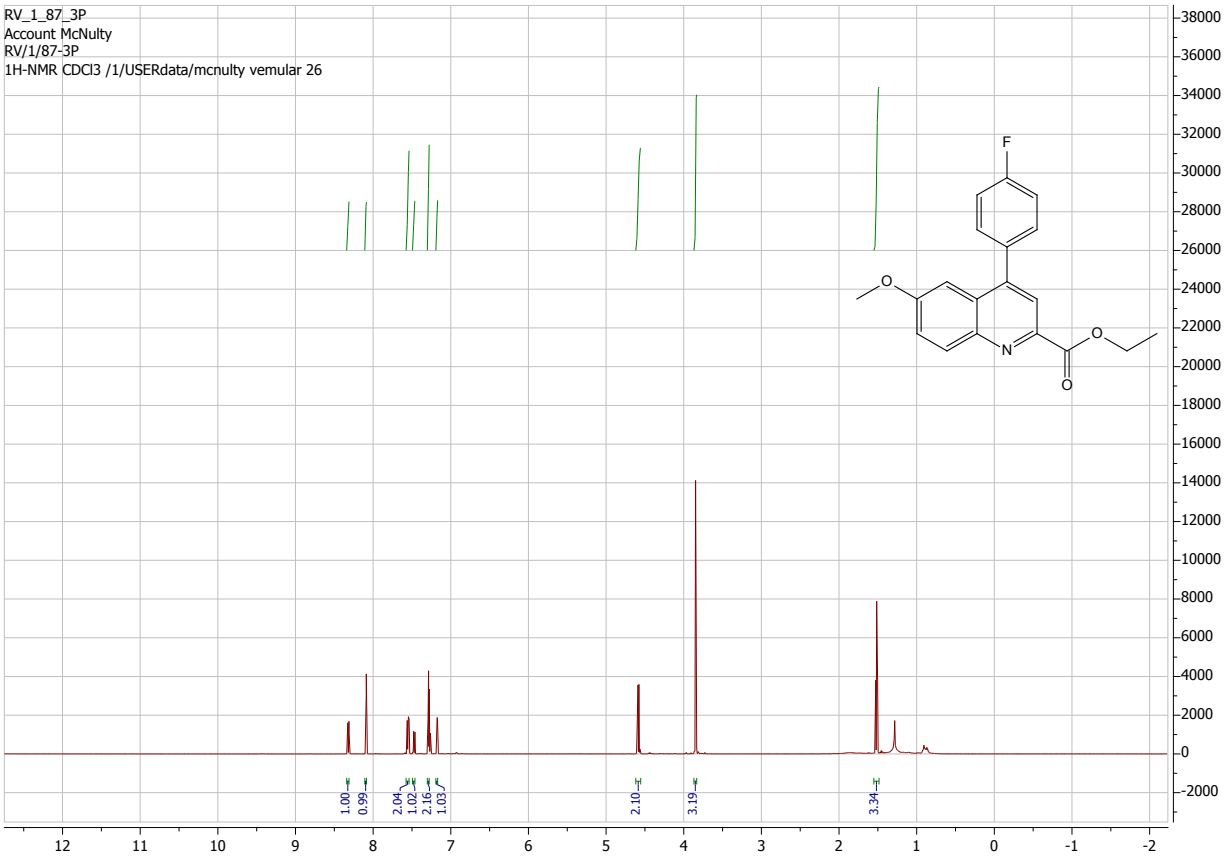


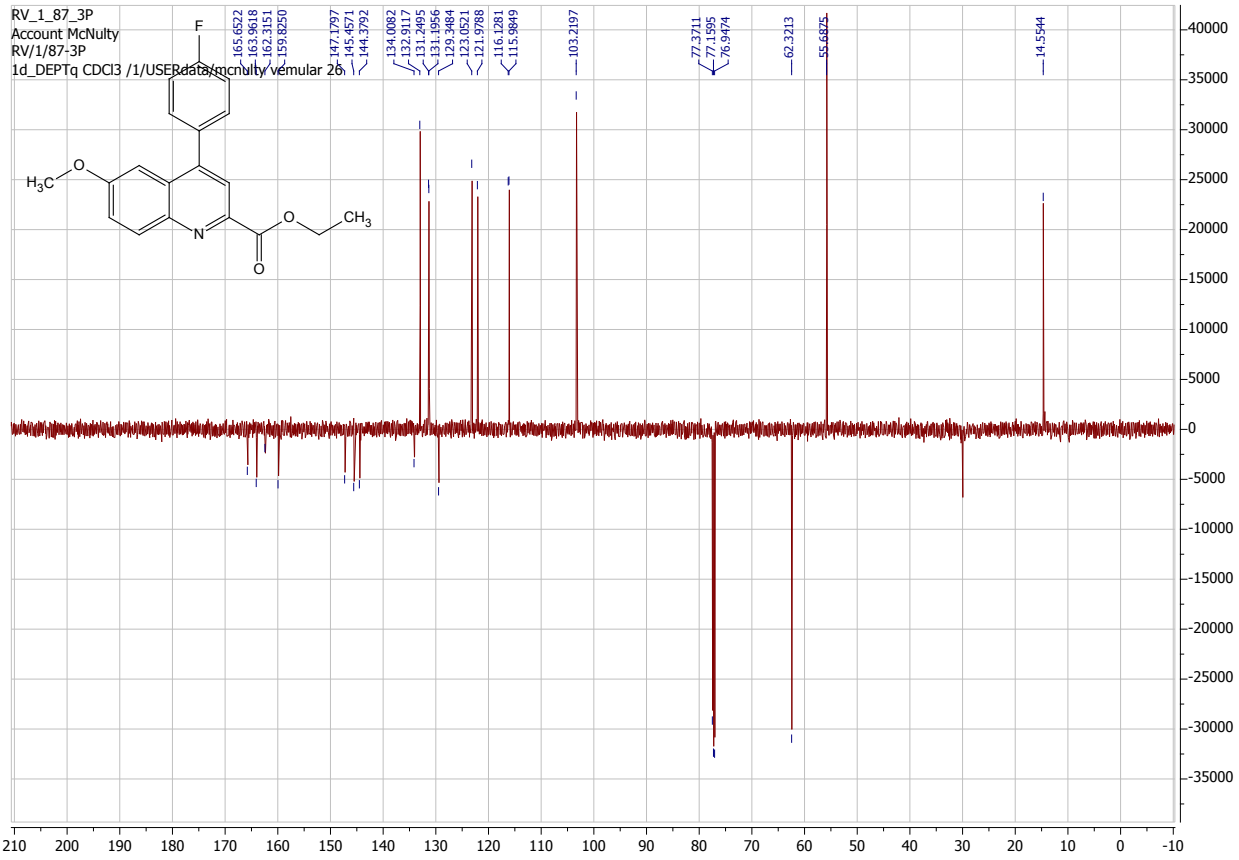


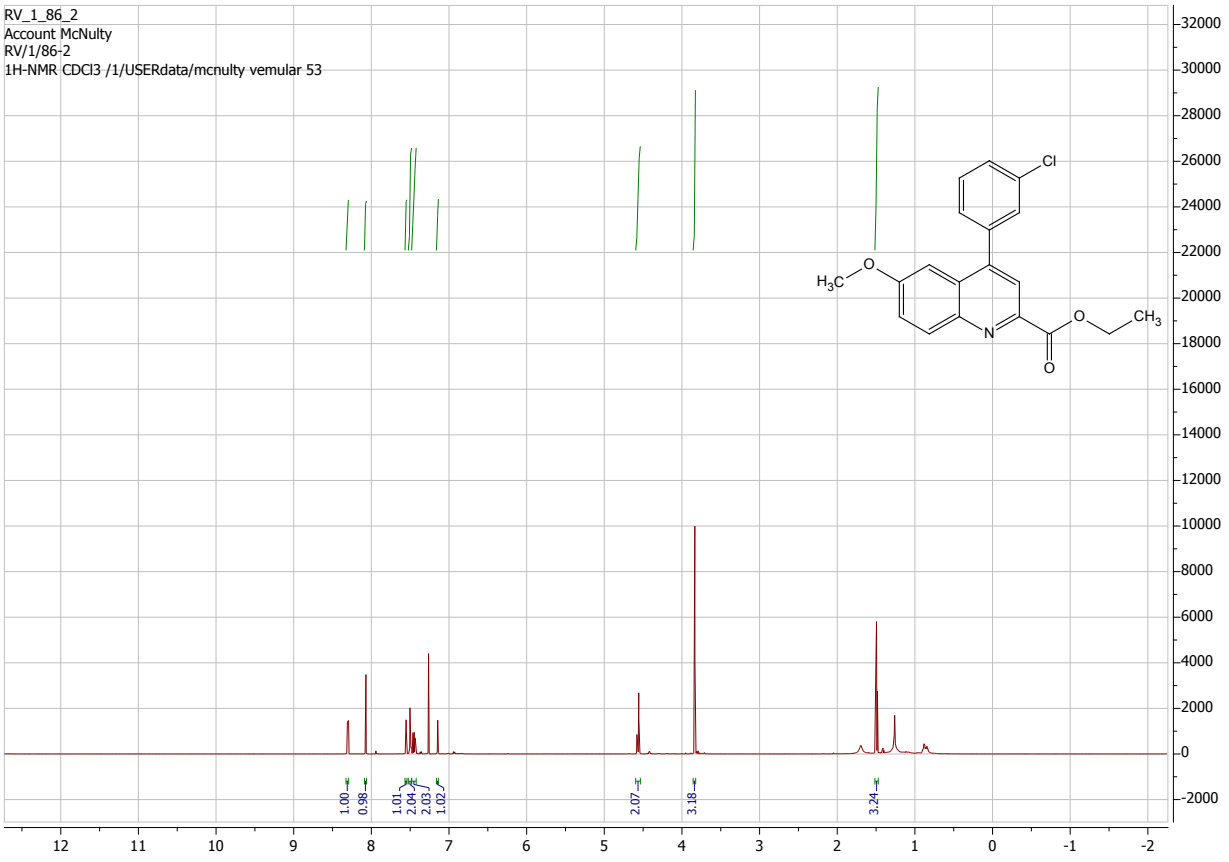


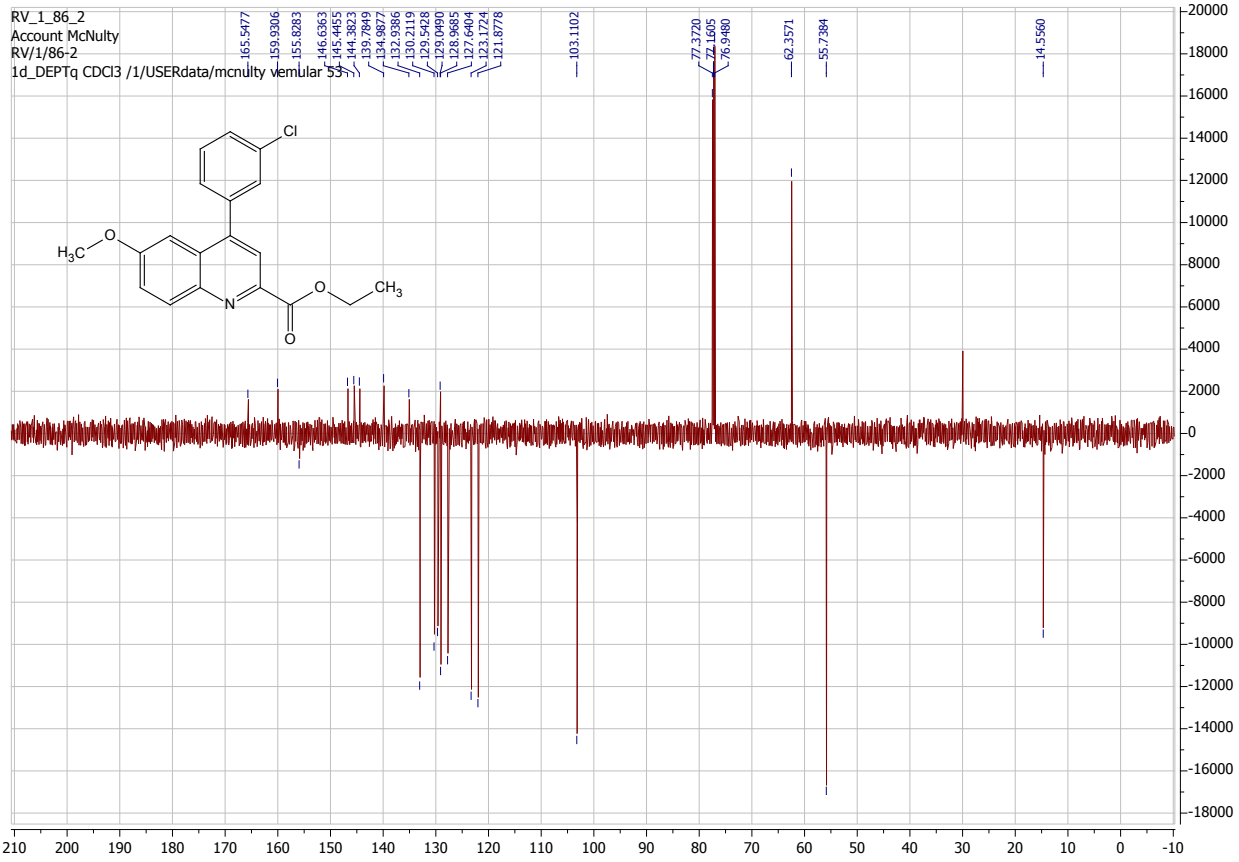


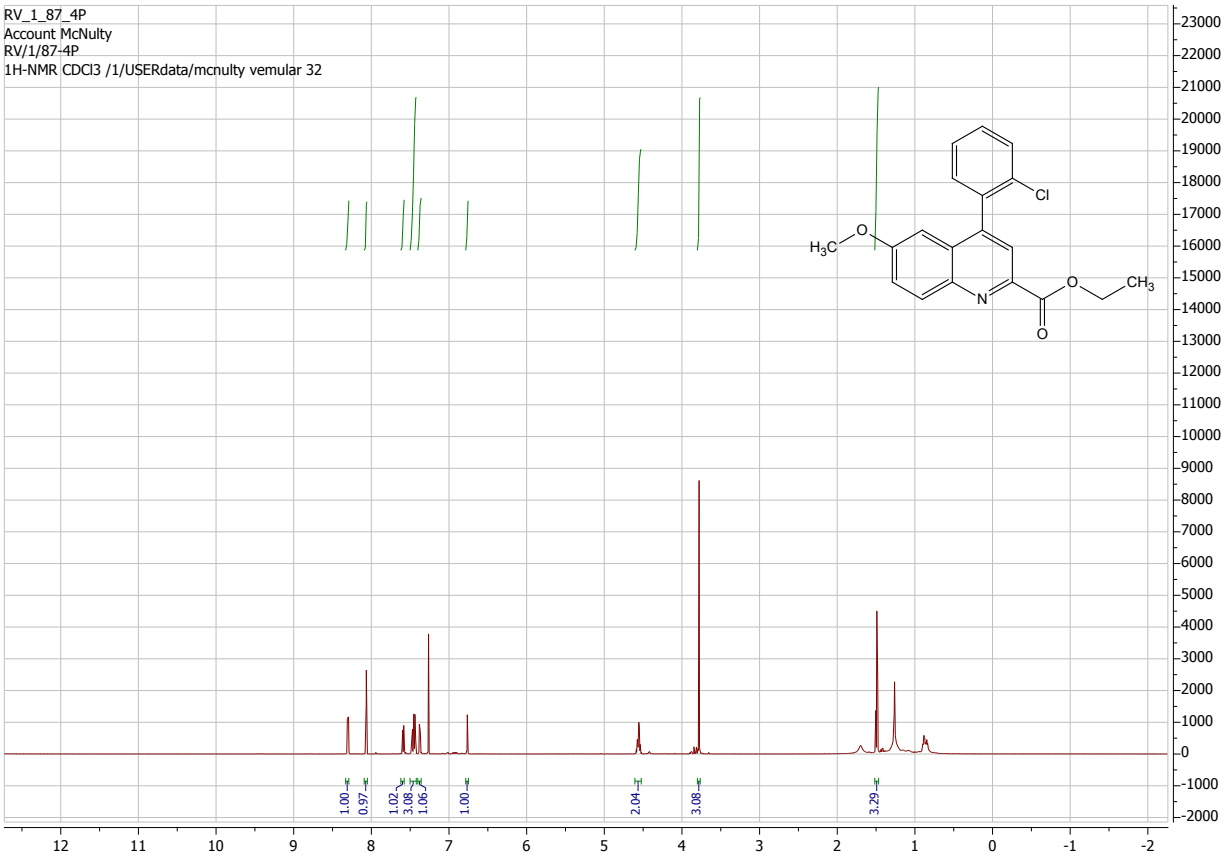


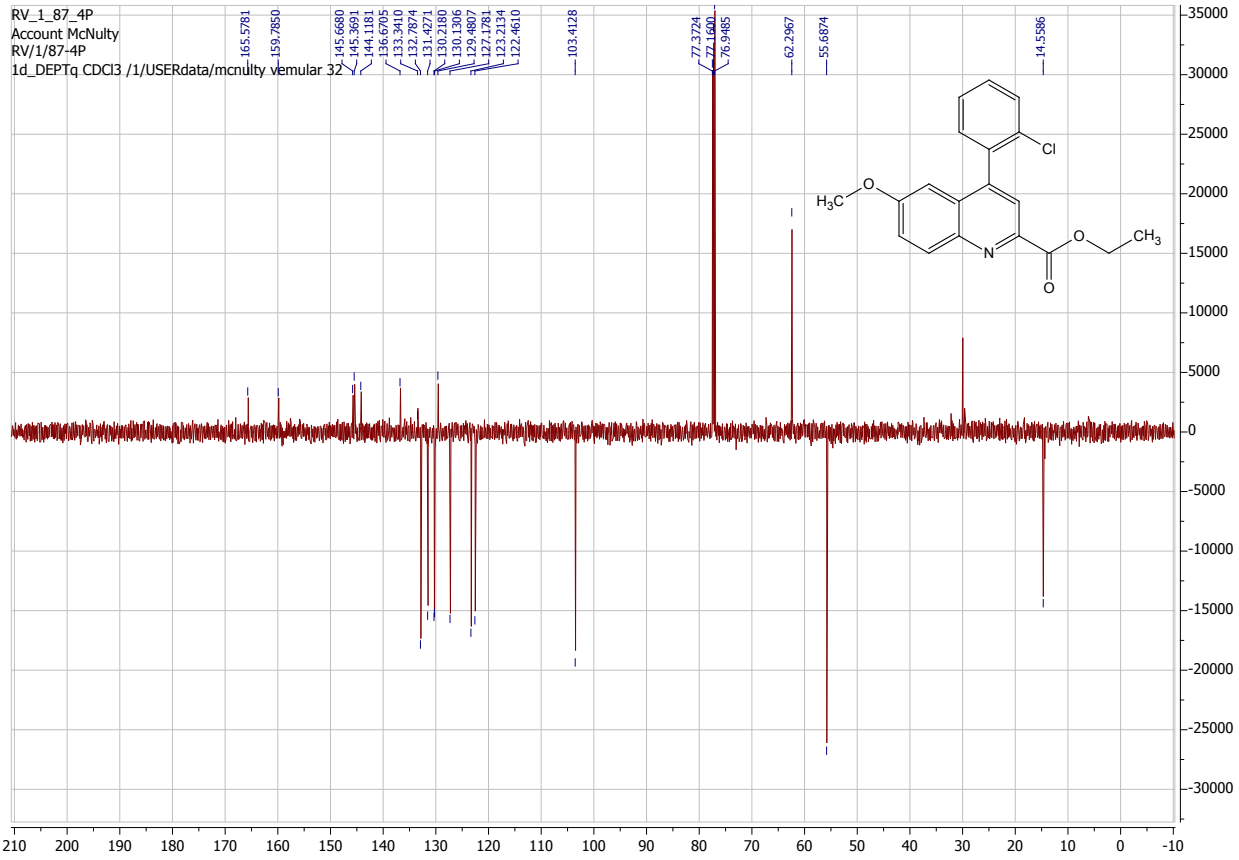


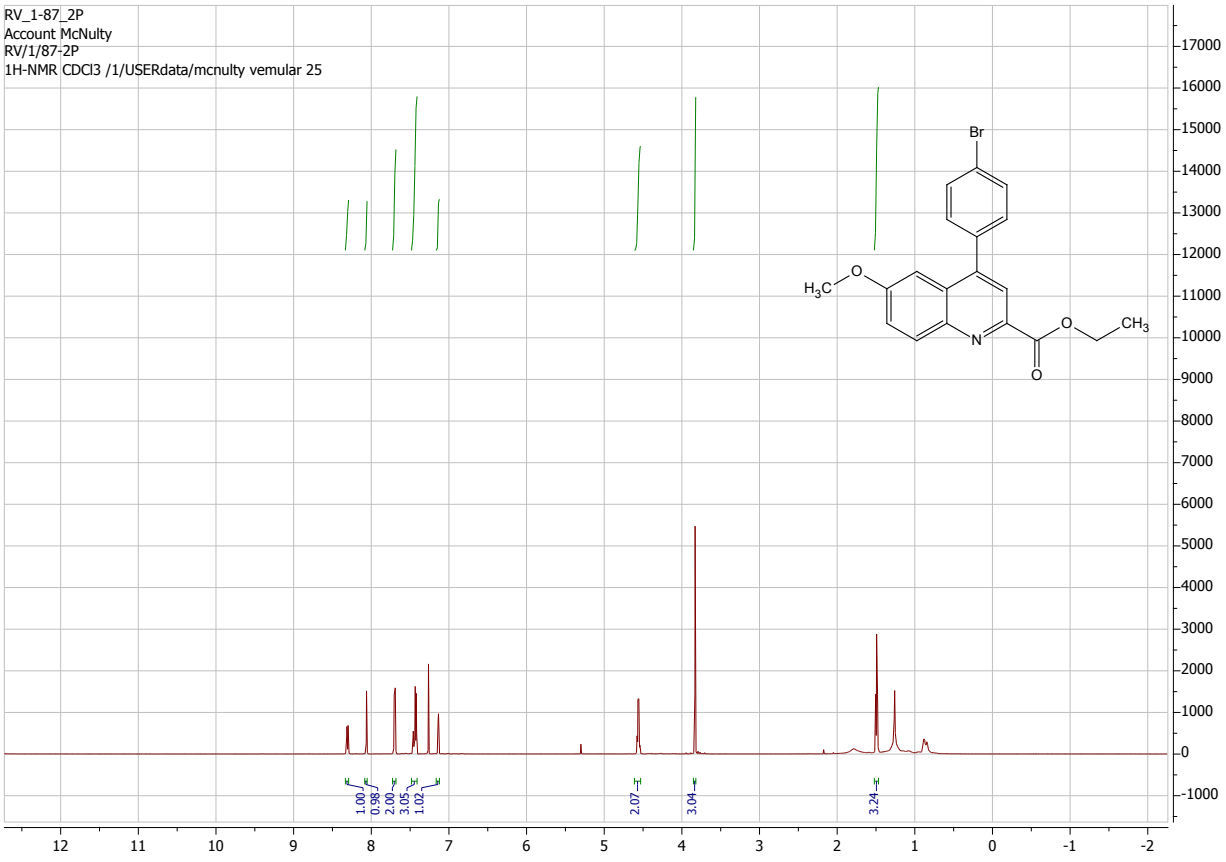








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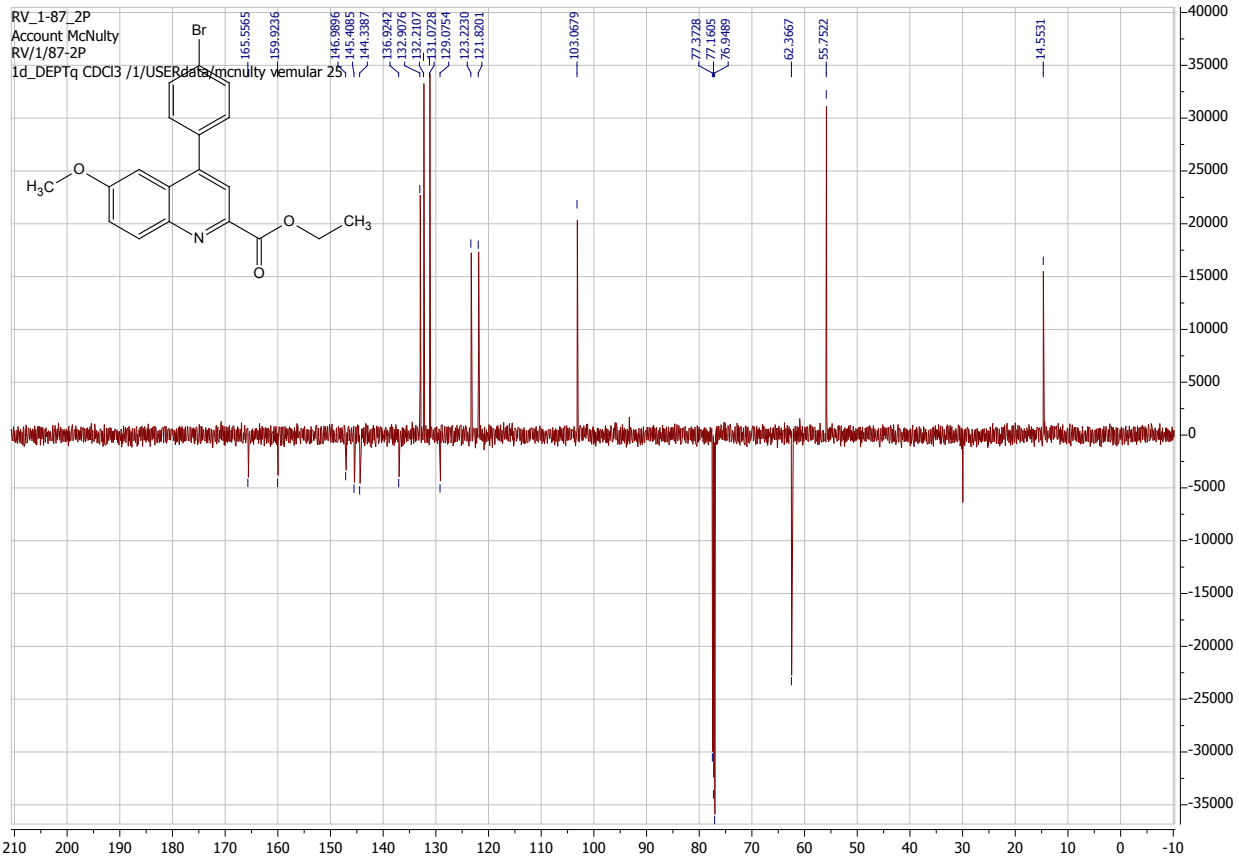

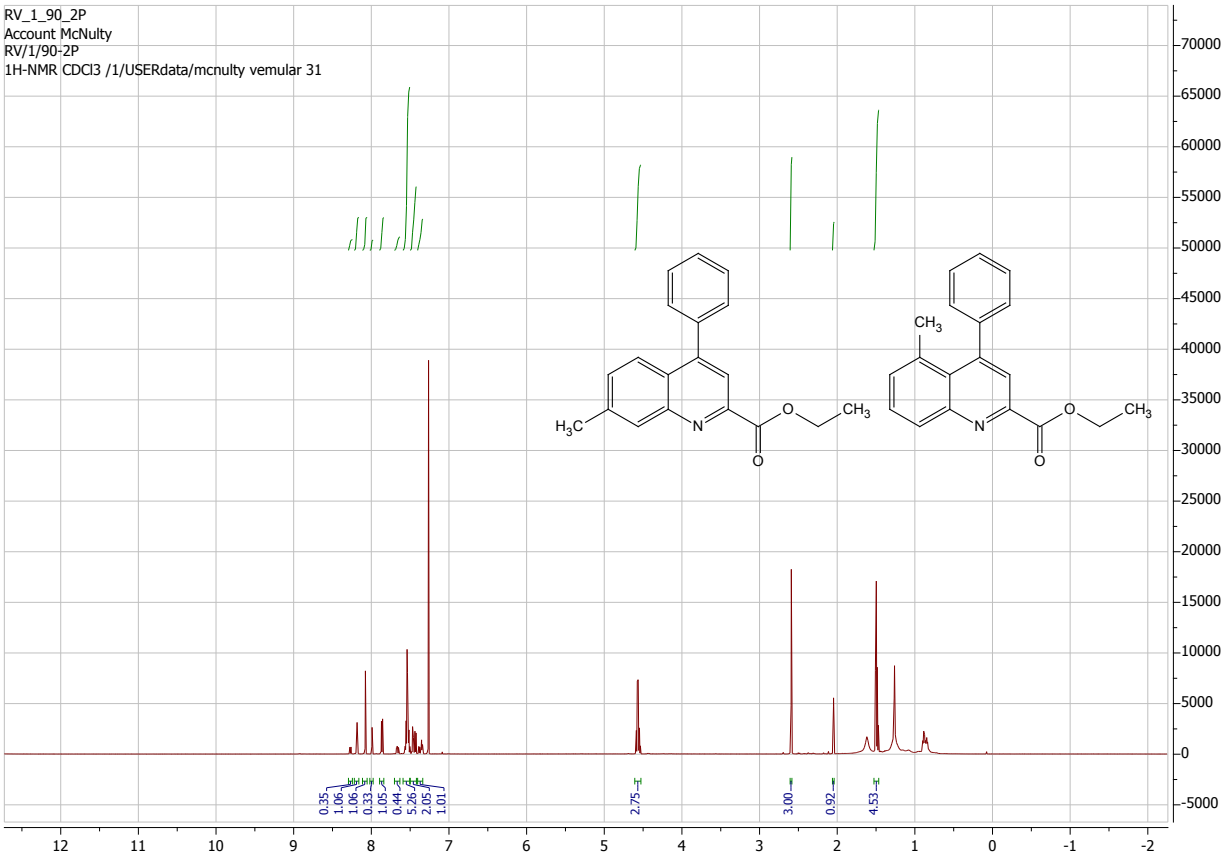

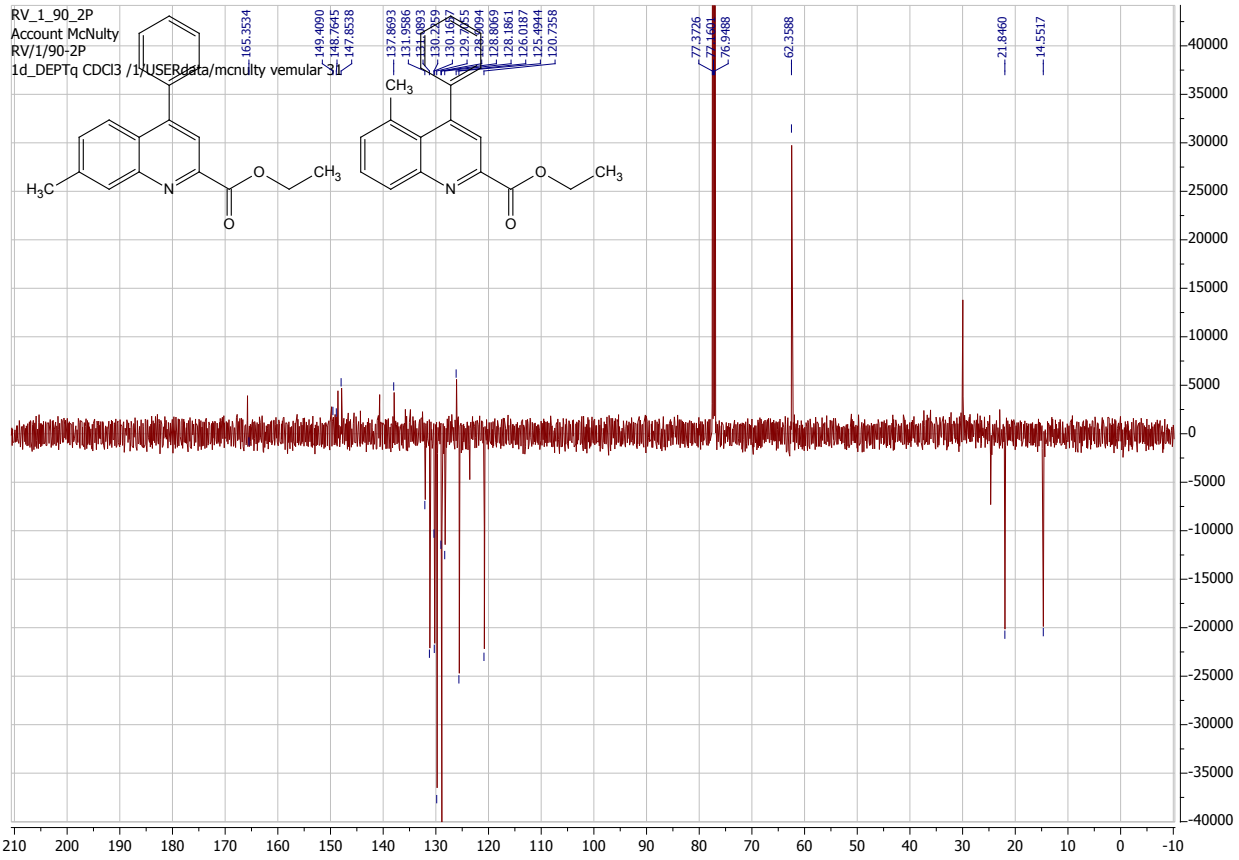

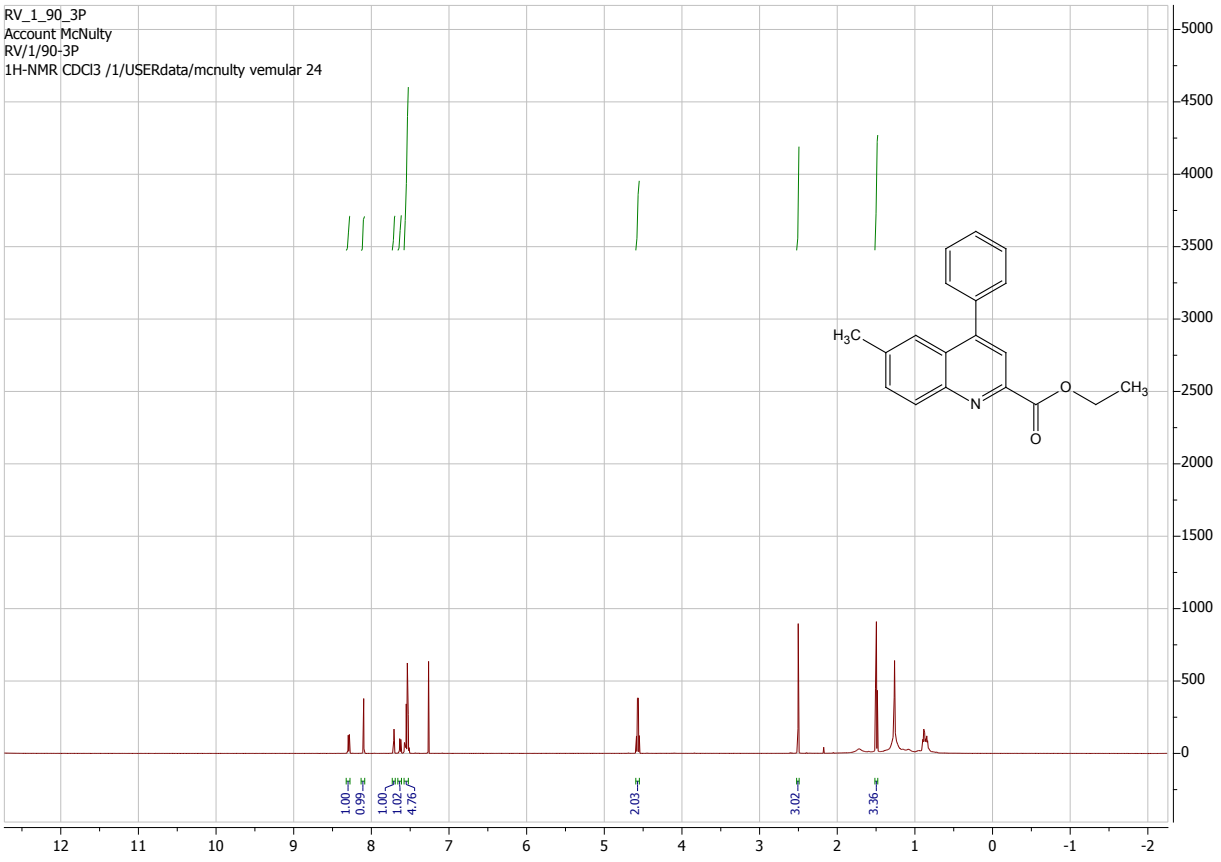

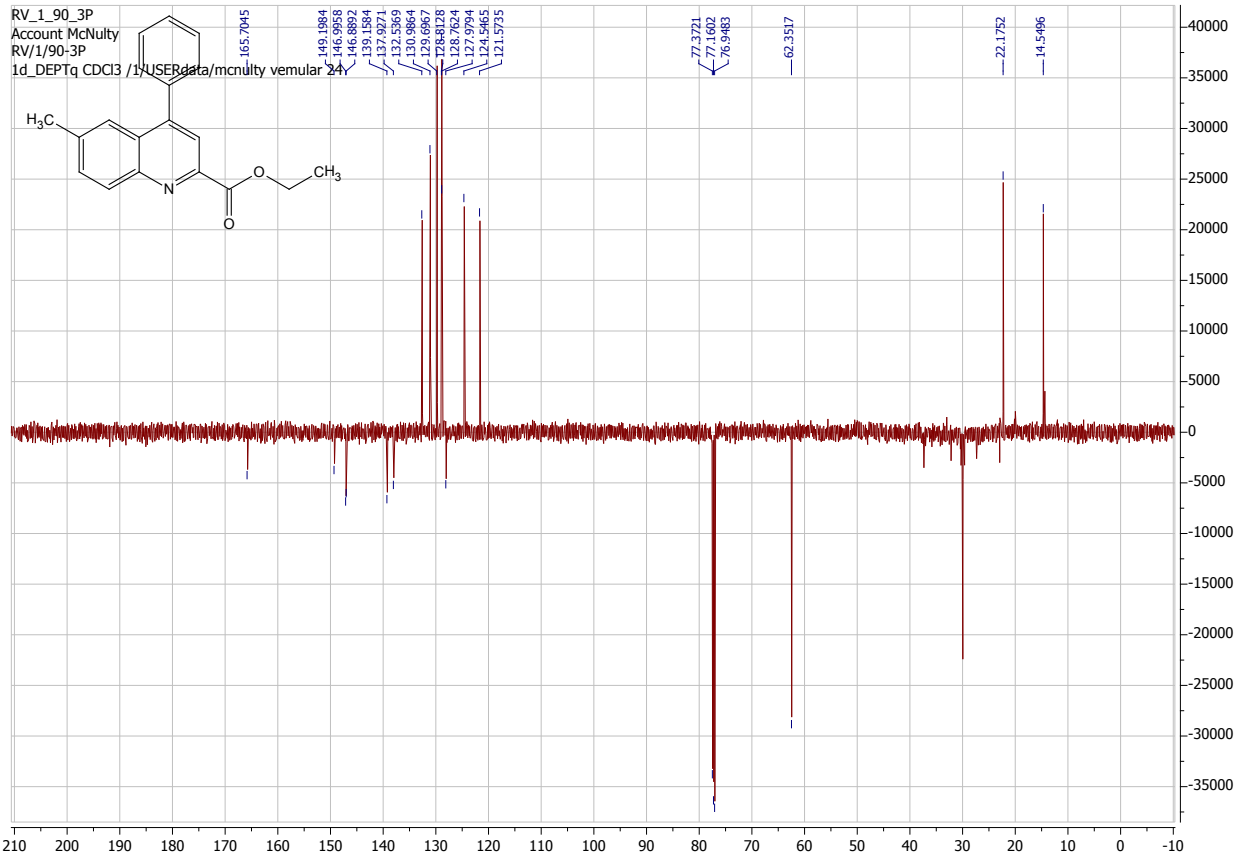

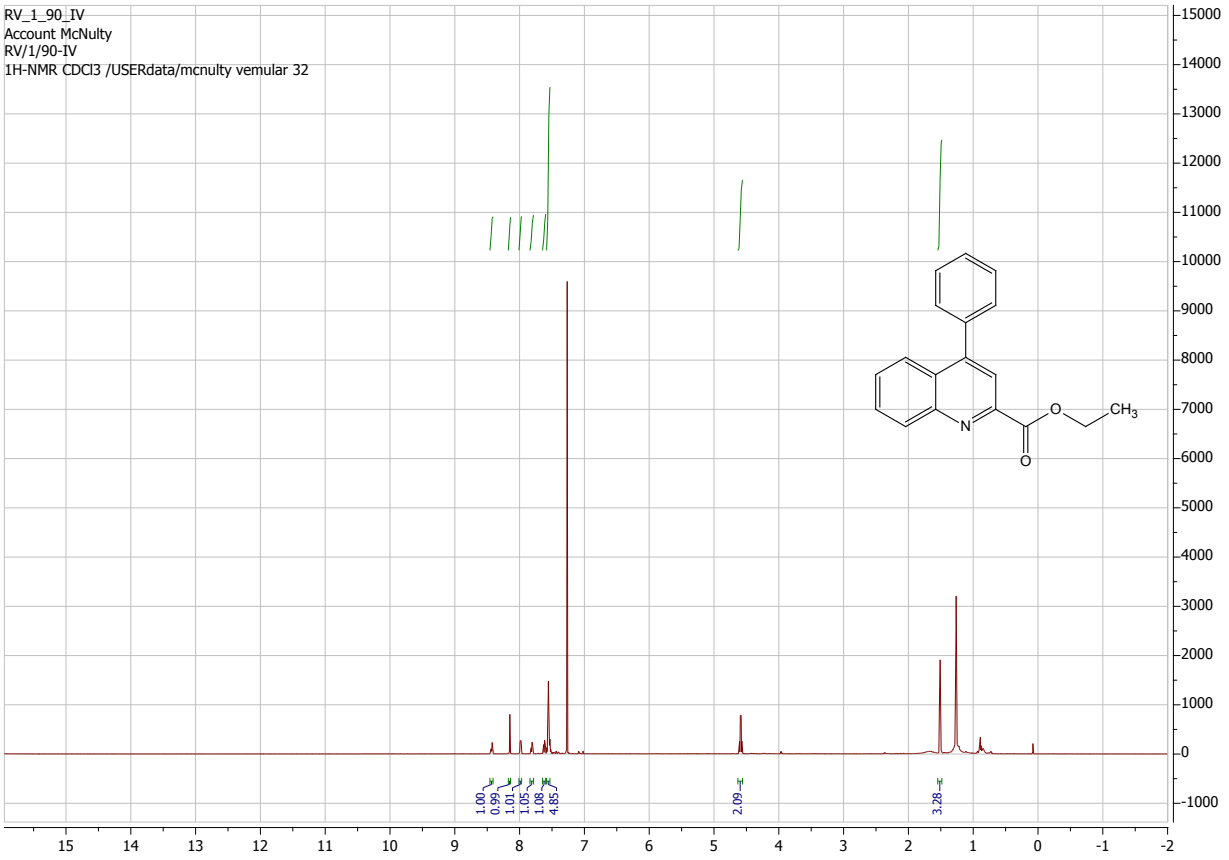

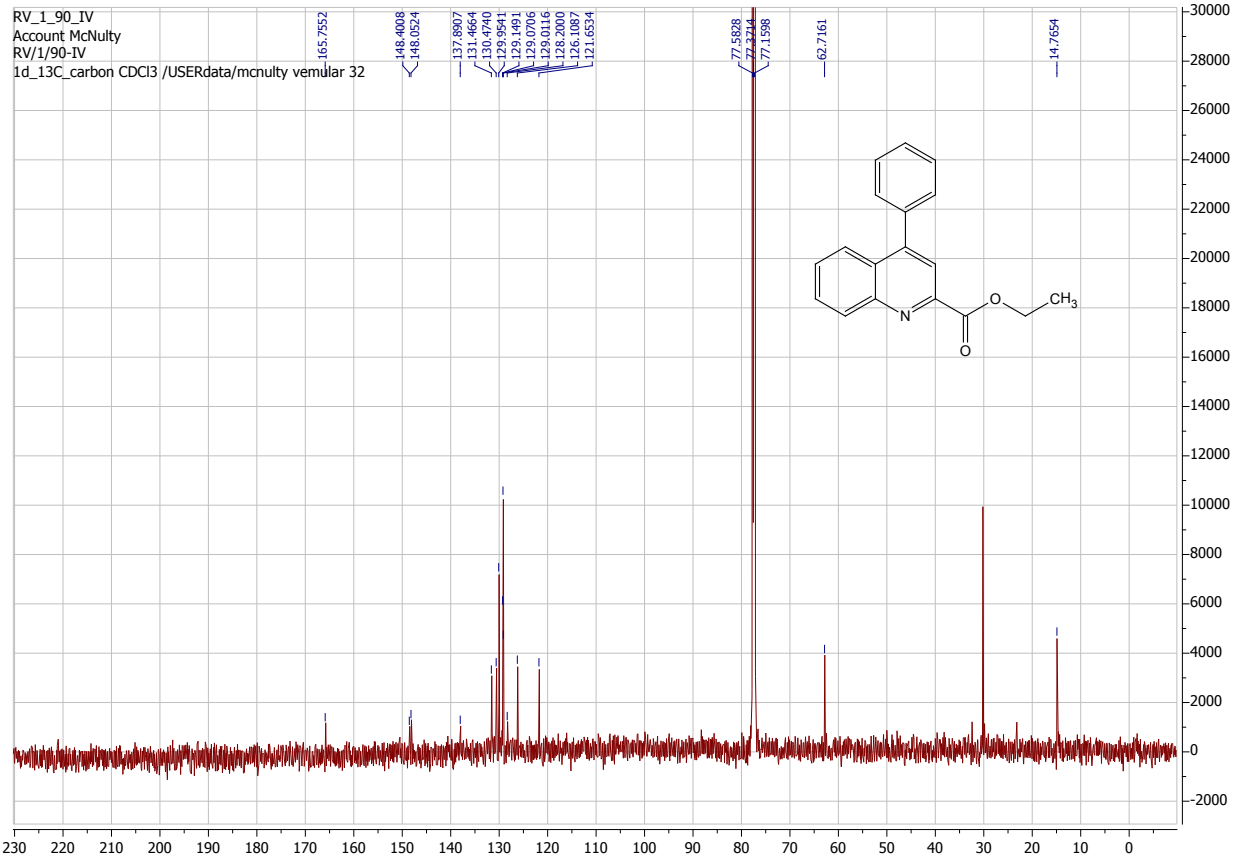

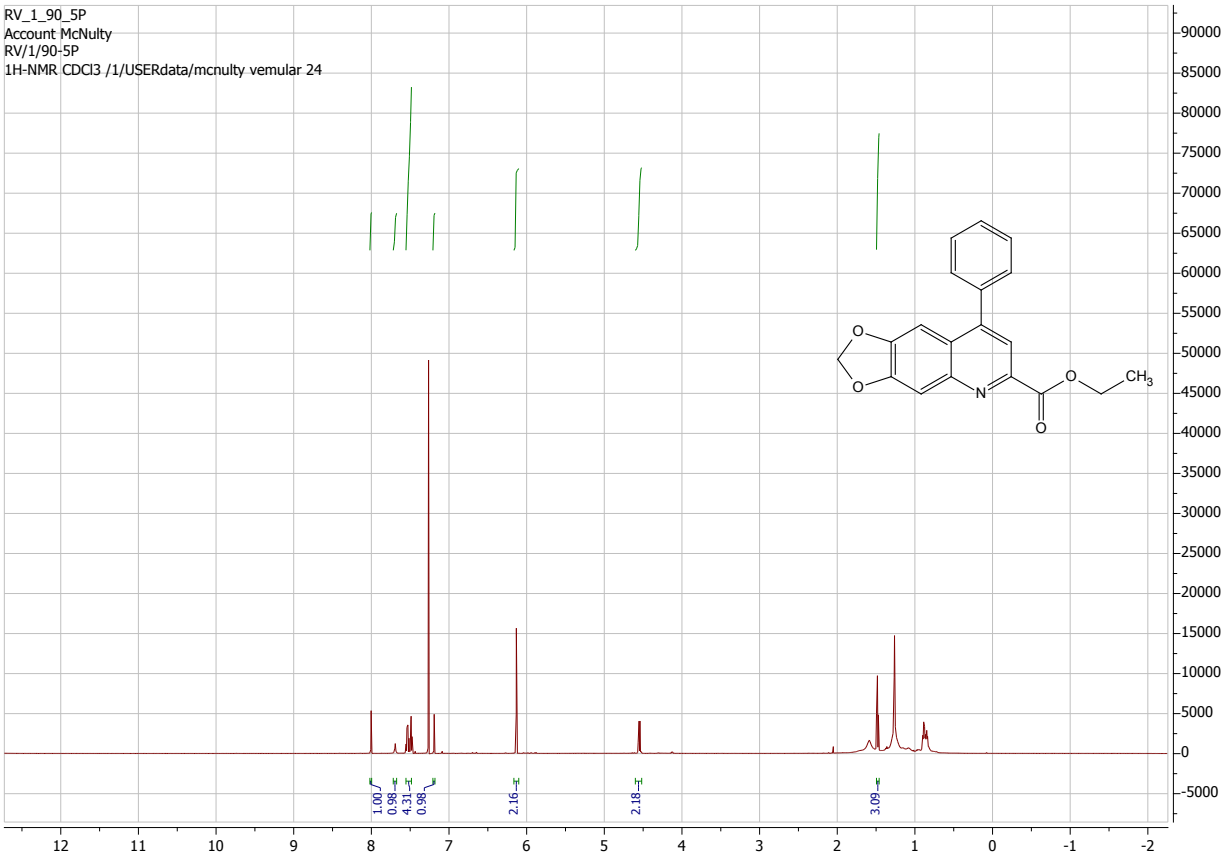

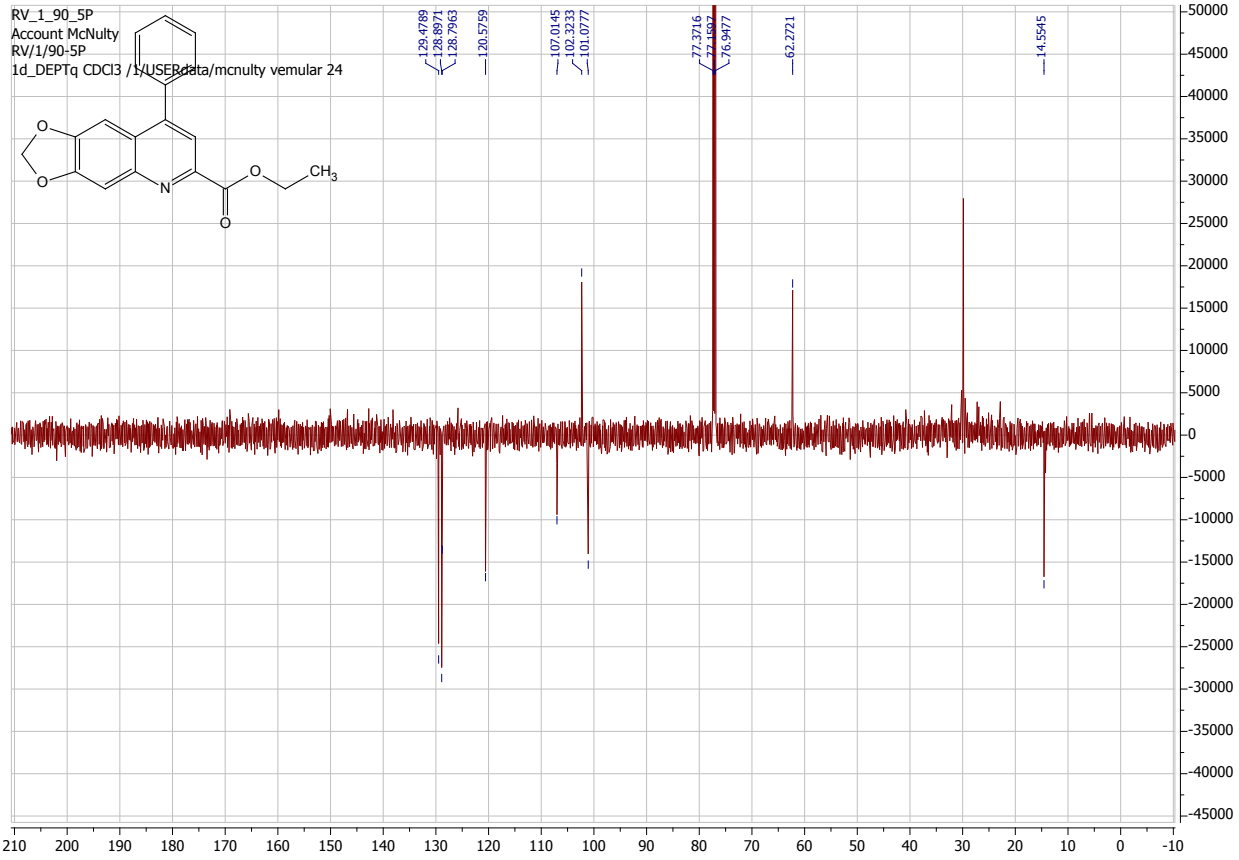

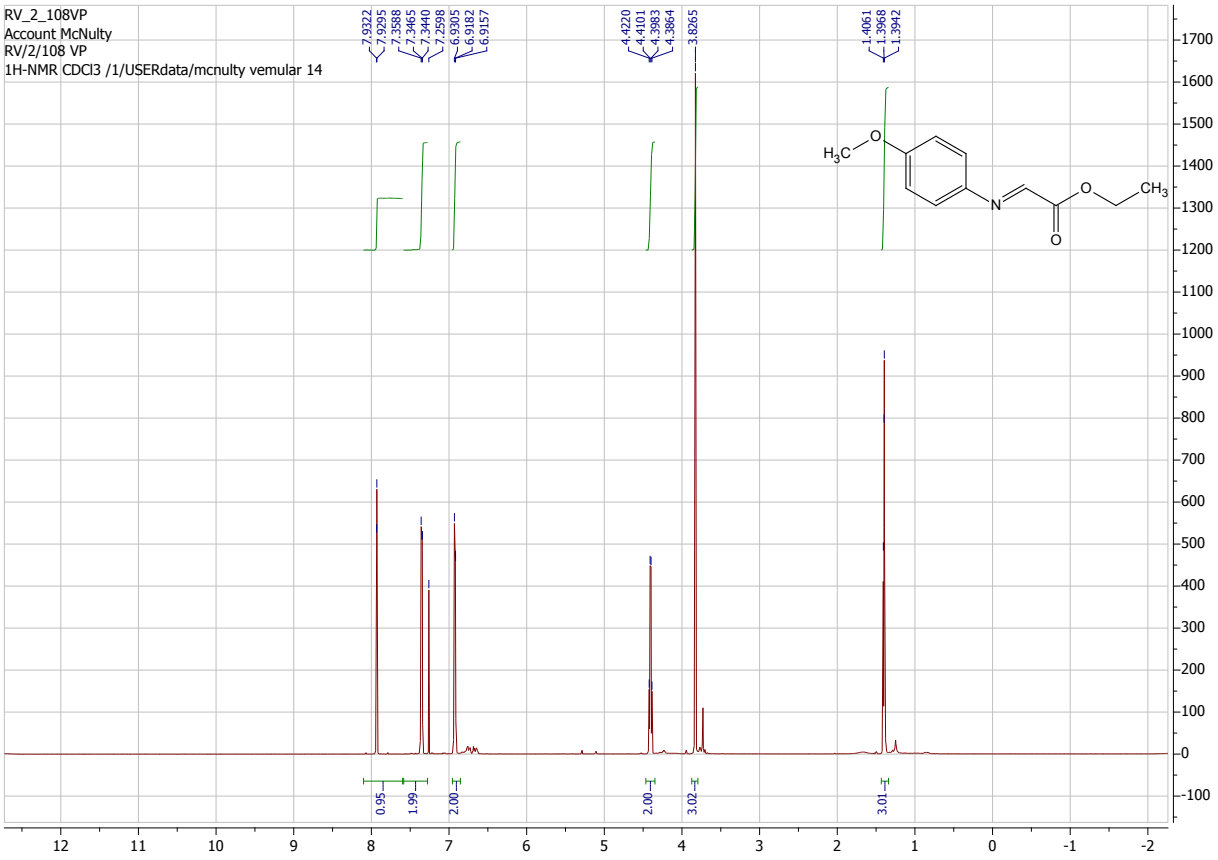

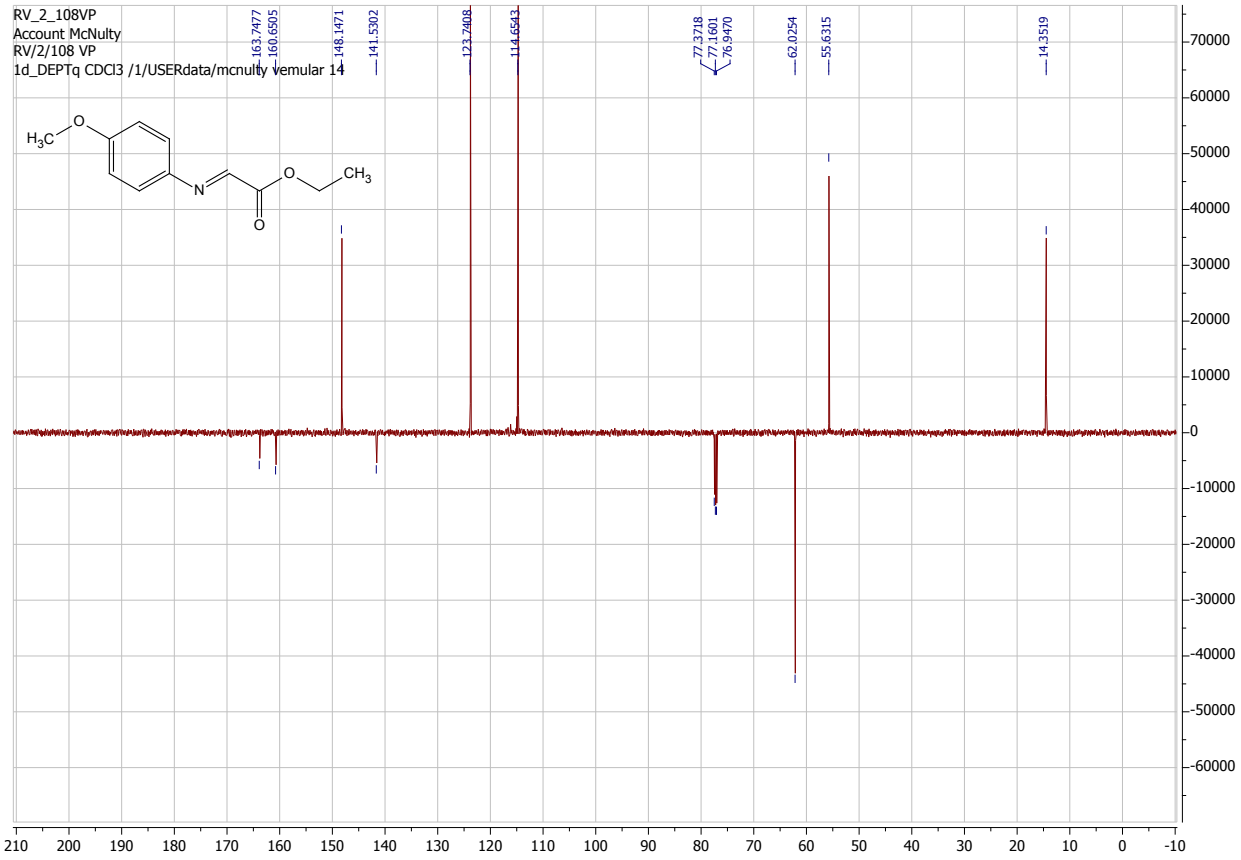

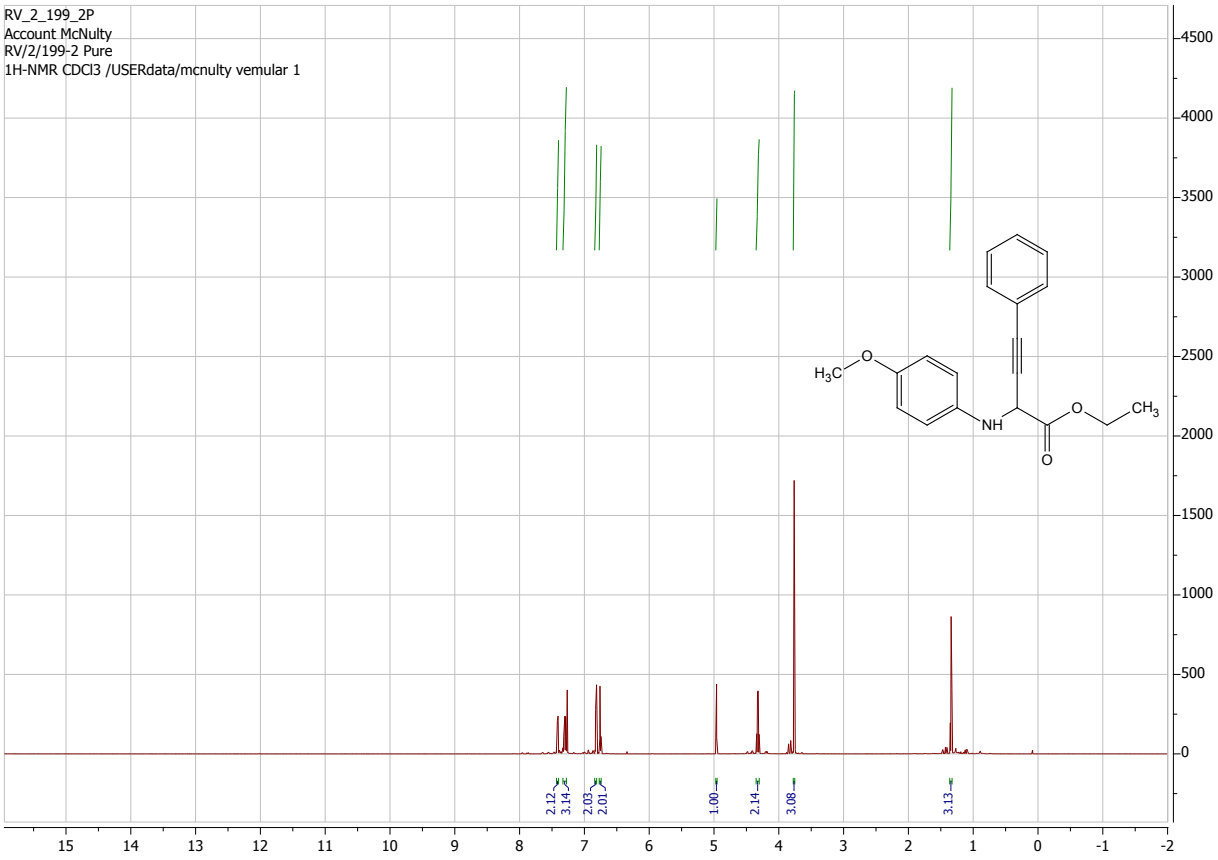

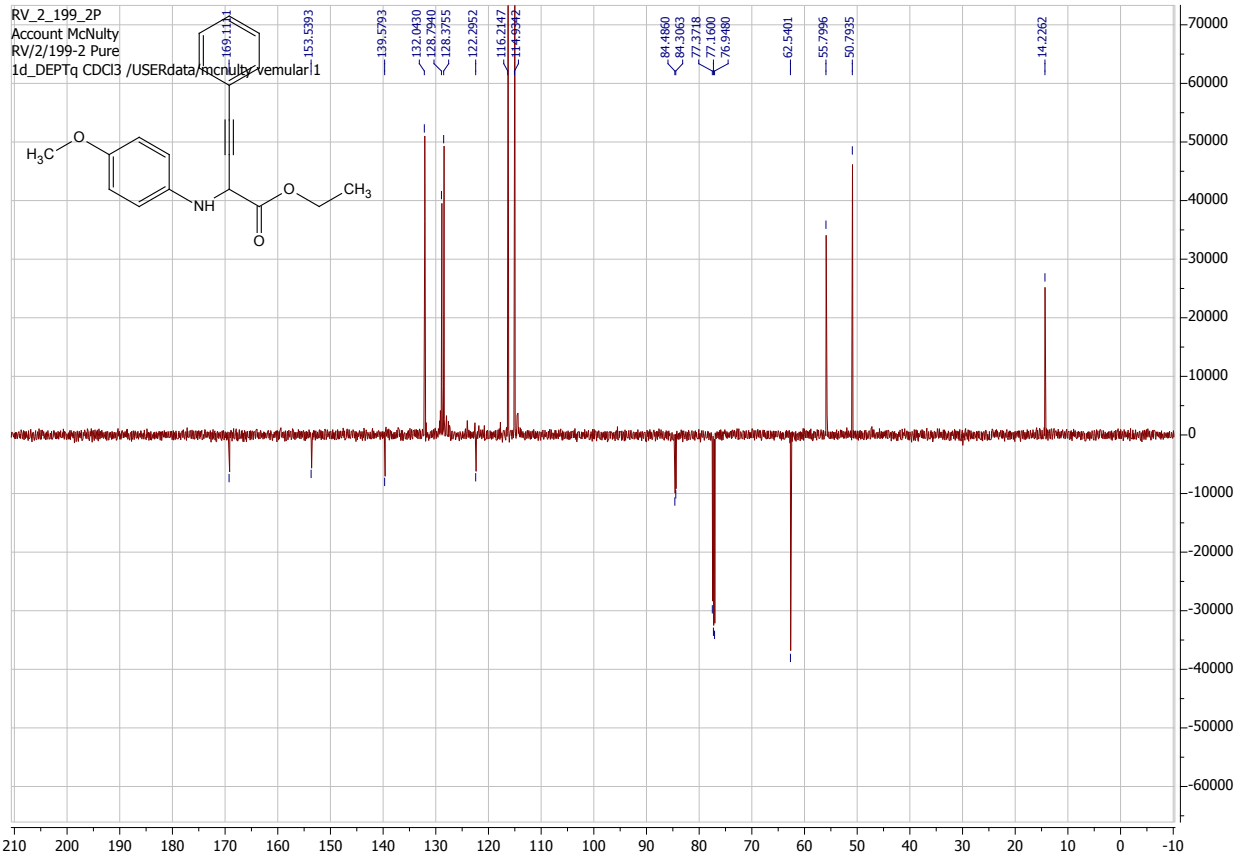



1. (a) Li, X.; Mao, Z.; Wang, Y.; Chen, W.; Lin, X. *Tetrahedron*., **2011**, 67, 3858-3862; Richter, H.; Mancheno, O.G. (b) *Org. Lett*., **2011**, 13, 6066-6069; Huang, H.; Jiang, H.; Chen, K.; Liu, H. (c) *J. Org. Chem*., **2009**, 74, 4576-5480.
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