Electronic Supplementary Information

The Knoevenagel condensation using quinine as organocatalyst under solvent-free condition

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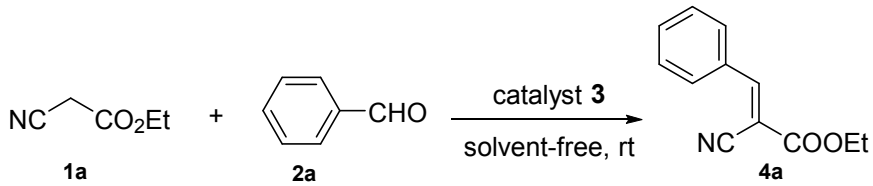
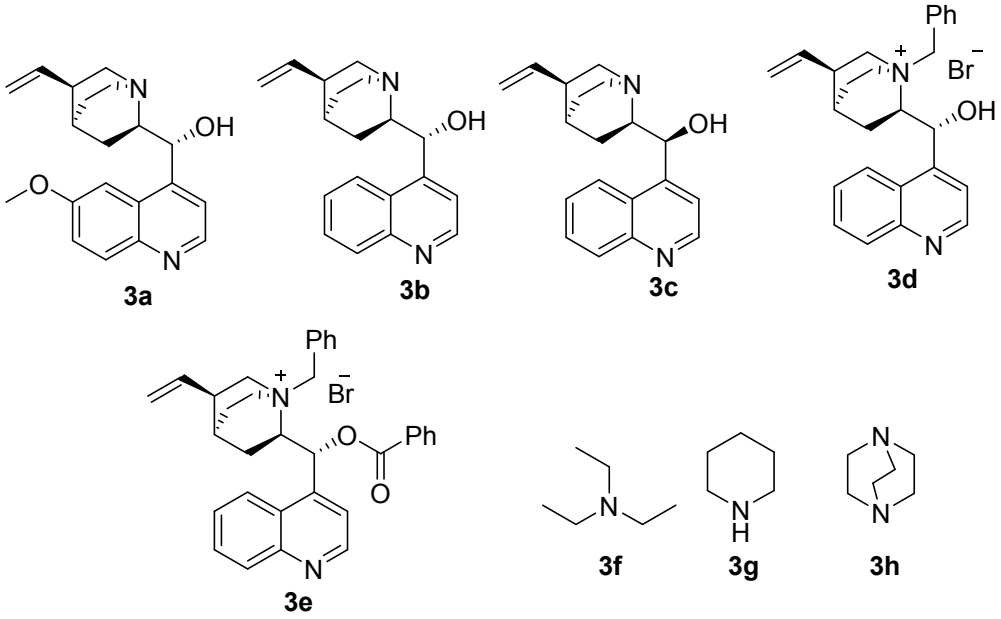
1. General experimental

Unless otherwise noted, all reactions were performed at room temperature reactions using oven-dried glassware and normal atmosphere. Where appropriate, solvents and all reagents were purified prior to use according to the handbook *Purification of Laboratory Chemicals*.[1] Commercially available reagents were used as received. Quinine (Alfa-Aesar), cinchonine and cinchonidine, *N*-benzylcinchonidinium bromide (Sigma-Aldrich) were employed as organocatalyst. Thin layer chromatography (TLC) of each reaction was performed using silica gel 60 F_{254} pre-coated plates (Merck). Visualization was accomplished with UV lamp or iodine stain or exposure to $KMnO_4$ stain. For column chromatography, 230-400 mesh silica gel (Spectrochem, India) was employed for the isolation of pure compounds using the combination of ethyl acetate and hexane as an eluent. ^{1}H NMR spectra were recorded on Bruker 400 MHz/ JEOL 500 MHz spectrometers and chemical shifts were reported in parts per million (ppm, δ) relative to tetramethyl silane (TMS) at δ 0.00 ppm, and coupling constants (*J*) were in Hertz (Hz). ^{1}H NMR splitting patterns are designated as singlet (s), broad singlet (br. s), doublet (d), triplet (t), quartet (q) or multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz or 125 MHz and are referenced relative to $CDCl_3$ at δ 77.16 ppm. The IR spectra were recorded using a FTIR-84005 Shimadzu and were reported in terms of frequency of absorption (cm^{-1}). High resolution ESI and EI mass spectra were recorded on MicrOTOF-Q-II and AccuTOF-GCv 4G, respectively.

2. General experimental procedure for the optimization of Knoevenagel condensation

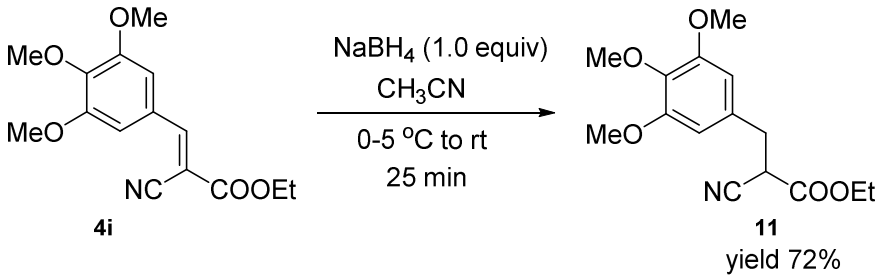




A mixture of ethyl cyanoacetate **1a** (113 mg, 1.0 mmol) and benzaldehyde **2a** (106 mg, 1.0 mmol) were placed into an oven dried 10 mL round bottomed flask equipped with a magnetic stir bar. Then, quinine **3a** (48.6 mg, 0.15 mmol) was added and the reaction mixture was stirred at room temperature under solvent free condition for appropriate time as indicated in Table 1. The crude reaction mixture was directly analyzed by ^{1}H NMR using phenanthrene as an internal standard and yield of the product **4a** was determined.

*Note: Unless otherwise noted all reactions of **Table 1** were performed according to this reaction procedure.*

3. Experimental procedure for the reduction of alkene (4i)



An oven dried 10 mL round bottomed flask equipped with a magnetic stir bar was charged with ethyl (*E*)-2-cyano-3-(3,4,5-trimethoxyphenyl)acrylate **4i** (100 mg, 0.343 mmol) in dry acetonitrile. Then sodium borohydride (12.9 mg, 0.343 mmol) was added portionwise at 0-5 ^{o}C and resulting reaction mixtures was allow to warm up to room temperature and stirred until the complete consumption of substrate as indicated by TLC. After the reaction was quenched with 10% HCl solution and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography over silica gel using ethyl acetate in hexane as eluent to afford the pure product **11** in 72% yield (73 mg) as light yellow solid, TLC R_f = 0.12 (Hexane: EtOAc = 4:1).

4. Experimental for the determination of the pK_a values of catalysts (3a-d)

An exact 10 mL of 0.01 M solution of each catalyst (**3a-d)** was prepared in anhydrous dimethyl sulfoxide (DMSO) and titrated against 0.01 M solution of trifluoroacetic acid (TFAA) in anhydrous DMSO. During each titration pH of the solution was measured using pH Tutor Bench meter (Eutech Instruments). After the titration, a graph of pH vs volume of TFAA added was plotted in each case (**Fig**. **5-8**). A first derivative plot (**Fig**. **9-12)** of the original titration curve was obtained to determine the volume of TFAA at the end point, the pH value at the endpoint

and pH at ½ end points. The results are summarized in **Table 4-5**. In this experiment, the pK_b value of the catalyst was determined according to the Henderson-Hasselbalch equation (See eq. 1),[2] and finally pK_a value was calculated from eq. 4.

$pOH = pK_b + \log \{[\text{Conj Acid/Base}]\}$ eq. 1

Since $pH + pOH = 14$ eq. 2

So $pOH = 14 - pH = pK_b$ at half end point eq. 3

$pK_a + pK_b = 14$ eq. 4

The pK_b of the catalyst (**3a-d**) can be obtained from the experimental pH at half endpoint and subsequently, the pK_a values were obtained and are given in **Table 6**.

Preparation of the 0.01 M CF_3COOH solution

100 mL of stock solution of exact 0.1 M trifluoroacetic acid in anhydrous DMSO was prepared by measuring 765 µl of trifluoroacetic acid in 100 mL DMSO in a volumetric flask. From this stock solution we prepared 100 mL of 0.01 M solution of trifluoroacetic acid by following the algebraic equation given below:

$N_1V_1 = N_2V_2$ eq. 5

N_1 = Concentration of Stock Solution
V_1 = Volume of Stock Solution (unknown)
N_2 = the new Concentration
V_2 = Total volume needed

By algebraic arrangement
$V_1 = N_2V_2/N_1$
$V_1 = 0.01 \times 100/0.1$
$V_1 = 10$ mL

So, we taken 10 mL of stock solution of trifluoroacetic acid and diluted it with 90 mL of anhydrous DMSO to get the 100 mL of 0.01 M solution of trifluoroacetic acid.

Preparation of the 0.01 M solution of catalysts (3a-d)

1. An exact 10 mL of 0.01 M solution of quinine (**3a**) was prepared by weighing 32.4 mg of quinine in 10 mL anhydrous DMSO in a volumetric flask.

2. An exact 10 mL of 0.01 M solution of cinchonidine (**3b**) was prepared by weighing 29.4 mg of cinchonidine in 10 mL anhydrous DMSO in a volumetric flask.
3. An exact 10 mL of 0.01 M solution of cinchonine (**3c**) was prepared by weighing 29.4 mg of cinchonine in 10 mL anhydrous DMSO in a volumetric flask.
4. An exact 10 mL of 0.01 M solution of *N*-benzylcinchonidinium bromide (**3d**) was prepared by weighing 46 mg of *N*-benzylcinchonidinium bromide in 10 mL anhydrous DMSO in a volumetric flask.

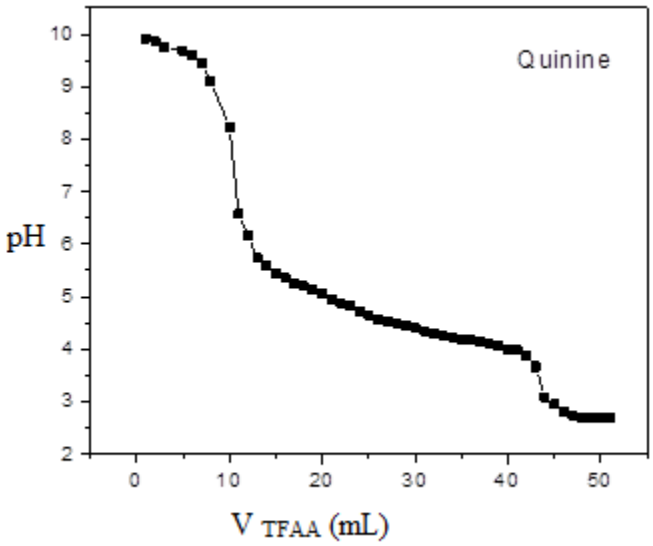


Figure 5. The titration of 10 mL quinine (**3a**) solution (0.01 M) with 0.01 M solution of trifluoroacetic acid (TFAA) is shown. The pH at the first end point was 8.23. The volume at the first endpoint was determined to be 9.98 mL. The pH at the second end point was 3.70. The volume at the second endpoint was determined to be 42.9 mL.

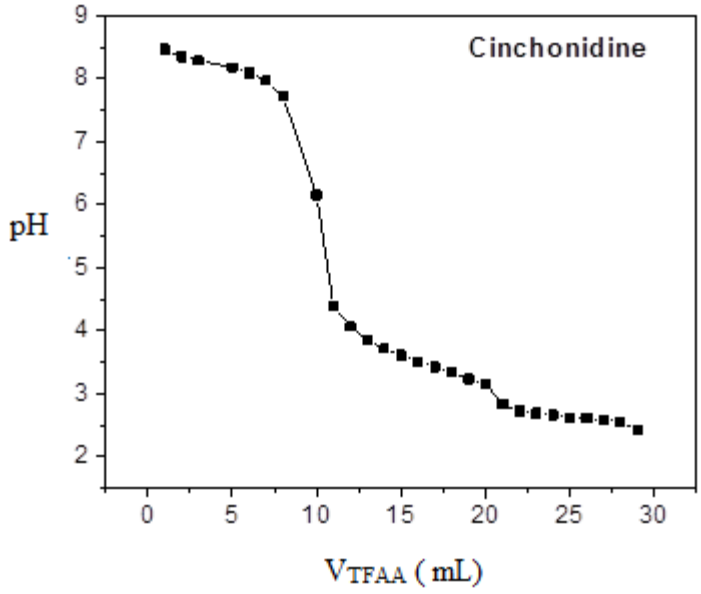


Figure 6. The titration of 10 mL Cinchonidine (**3b**) solution (0.01 M) with 0.01 M solution of trifluoroacetic acid (TFAA) is shown. The pH at the first end point was 6.1. The volume at the first endpoint was determined to be 9.9 mL. The pH at the second end point was 2.83. The volume at the second endpoint was determined to be 21.0 mL.

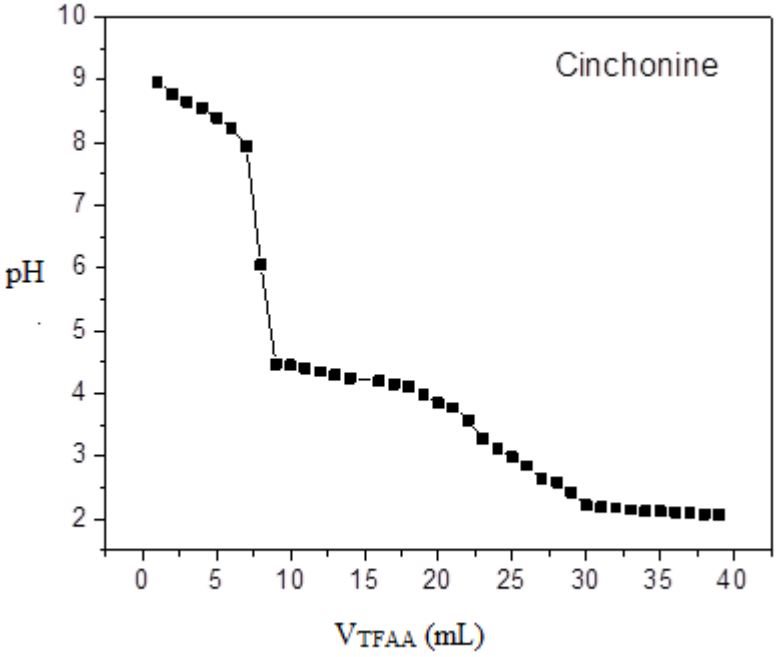


Figure 7. The titration of 10 mL Cinchonine (**3c**) solution (0.01 M) with 0.01 M solution of trifluoroacetic acid (TFAA) is shown. The pH at the first end point was 8.51. The volume at the first endpoint was determined to be 7.86 mL. The pH at the second end point was 2.48. The volume at the second endpoint was determined to be 28.9 mL.

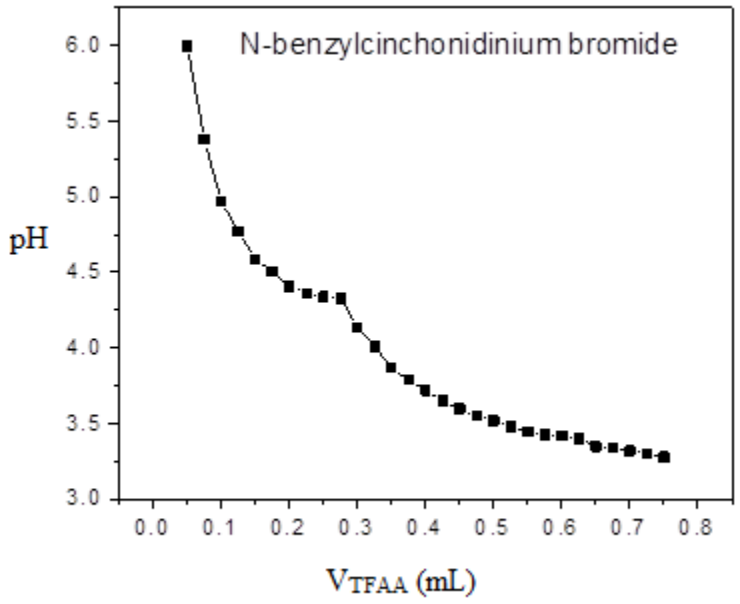


Figure 8. The titration of 10 mL *N*-benzylcinchonidinium bromide (**3d**) solution (0.01 M) with 0.01 M solution of trifluoroacetic acid is shown. The pH at the first end point was 4.08. The volume at the first endpoint was determined to be 0.3 mL.

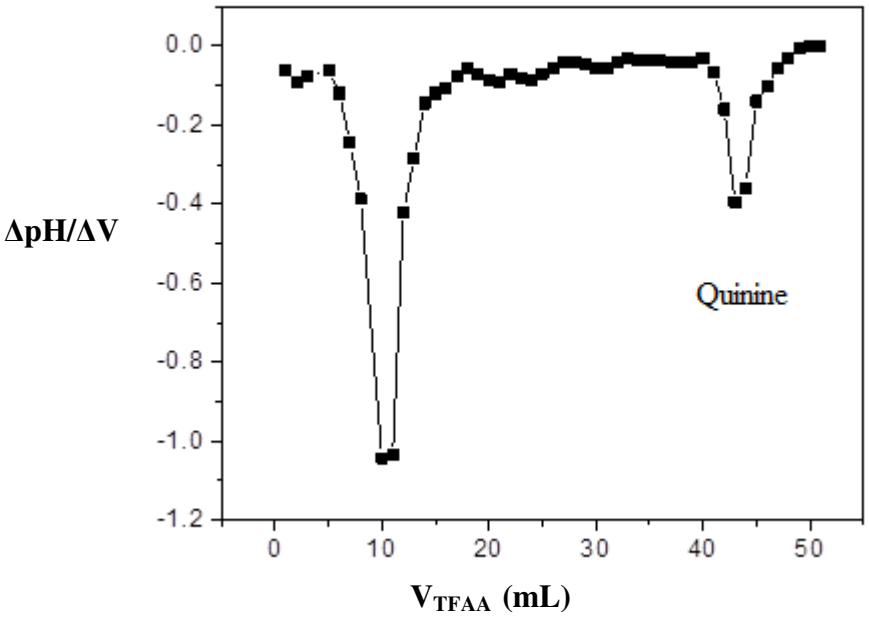


Figure 9. First Derivative plot for quinine (**3a**)

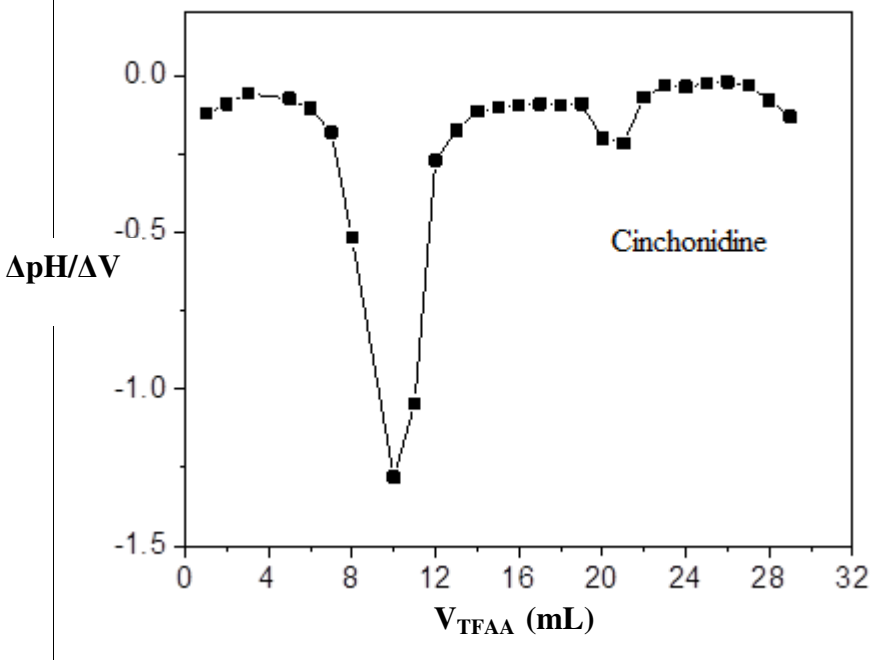


Figure 10. First Derivative plot for cinchonidine (**3b)**

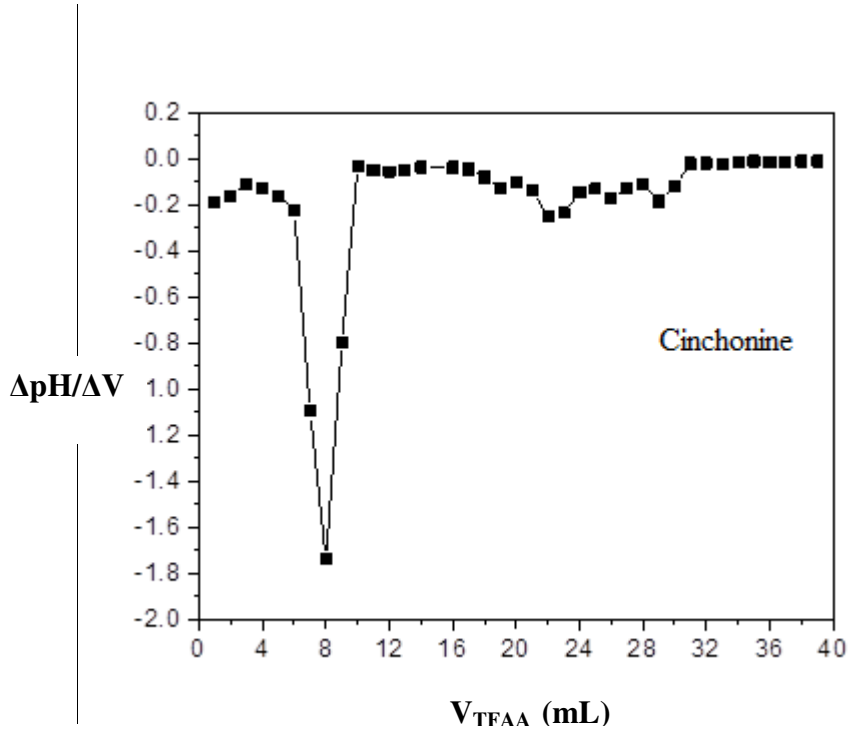


Figure 11. First Derivative plot for cinchonine (**3c**)

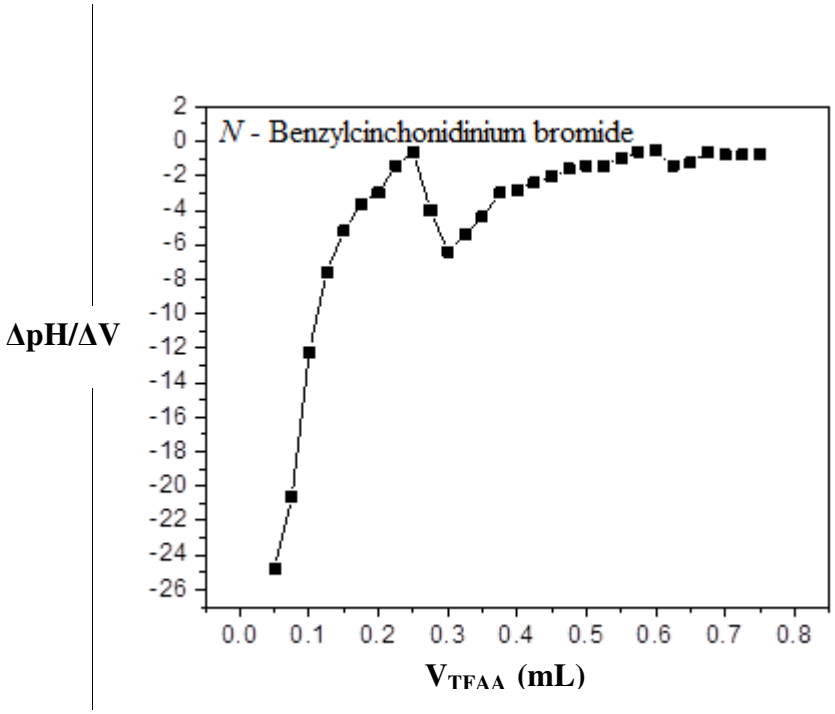


Figure 12. First Derivative plot for *N*-benzylcinchonidinium bromide (**3d**)

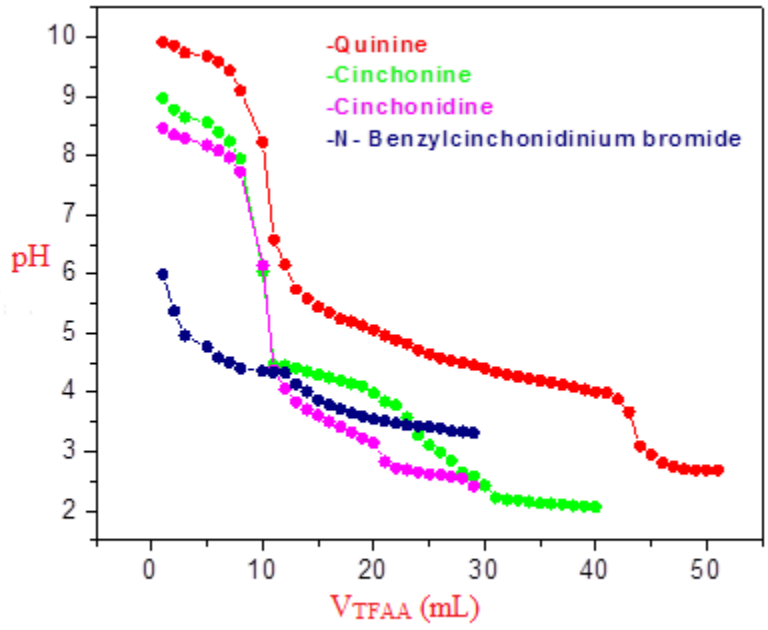


Figure 13. The titrations of 10.0 mls of 0.01 M solution of quinine, cinchonine, cinchonidine and *N*-benzylcinchonidinium bromide with 0.01 M trifluoroacetic acid (TFAA) solution are shown. The pH at the first endpoint for each titration was 8.23, 8.51, 6.1 and 4.08, respectively. The volume of TFAA at the first endpoint for the titration of quinine was 9.98 mL, for the titration with cinchonine was 7.86 mL, for the titration with cinchonidine was 9.9 mL and 0.3 mL for the titrations with *N*-benzylcinchonidinium bromide. The pH at the second endpoint was 3.70, 2.48, 2.83 for quinine, cinchonine, cinchonidine, respectively.

Table 4: Summary of the experimental pH at End Point (EP) of 0.01 M solution of quinine (**3a**), cinchonidine (**3b**), cinchonine (**3c**) and *N*-benzylcinchonidinium bromide (**3d**) titrated with 0.01 M trifluoroacetic acid (TFAA) solution.

S. No.	Base	Volume at first EP (ml)	pH at first EP	Volume at second EP (ml)	pH at second EP
1.	Quinine **(3a)**	9.98	8.23	42.9	3.70
2.	Cinchonidine **(3b)**	9.9	6.1	21.0	2.83
3.	Cinchonine **(3c)**	7.86	8.51	28.9	2.48
4.	*N*-benzylcinchonidinium bromide **(3d)**	0.3	4.08	–	–

Note: The pH of the end point of each base was calculated from the minima of the first derivative plot (**Figure 9-12**.) of the original graph **(Figure 5-8).**

Table 5: Summary of the experimental pH at half endpoint of quinine, cinchonidine, cinchonine and *N*-benzylcinchonidinium bromide.

S. No.	Base	pH at1/2 endpoint Experimental	
		first EP	second EP
1.	Quinine **(3a)**	9.67	4.91
2.	Cinchonidine **(3b)**	8.19	5.0
3.	Cinchonine **(3c)**	8.54	4.26
4.	*N*-benzylcinchonidinium bromide **(3d)**	4.58	–

Note: The pH of the half end point of each base was calculated from the half of the minima of the first derivative plot (**Figure 9-12**.) of the original graph **(Figure 5-8).**

Table 6: Summary of the experimental pK_b and pK_a value of quinine, cinchonidine, cinchonine, and *N*-benzylcinchonidinium bromide.

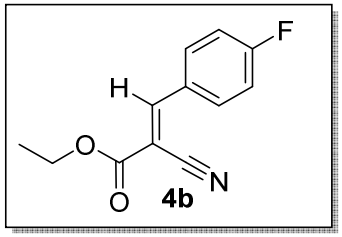
S. No.	Base	pH at1/2 endpoint Experimental first EP	pK_b Experimental	pK_a Experimental
1.	Quinine **(3a)**	9.67	4.33*	9.67*
2.	Cinchonidine **(3b)**	8.19	5.81*	8.19*
3.	Cinchonine **(3c)**	8.54	5.46*	8.54*
4.	*N*-benzylcinchonidinium bromide **(3d)**	4.58	9.42	4.58

*Note: pK_{a1} and pK_{b1}values of the corresponding bases are shown.

5. Experimental for Crystal structure determination of 4a

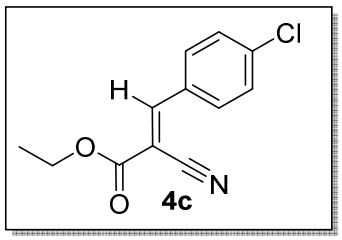
A single crystal of $C_{12}H_{11}NO_2$ (**4a)** was glued to a glass fiber and mounted on a Bruker**'Bruker APEX-II CCD'** diffractometer and data were collected using graphite-mono-chromated Mo-Kαradiation (λ = 0.71069 Å) at low temperature (100 K). An empirical absorption correction was applied using the SADABS program. Cell constants were obtained from the least-squares refinement of three-dimensional centroids by recording narrow ω rotation frames until completion of almost all reciprocal space in the stated θ range. The data were integrated with the Bruker SAINT program. The space group of this compound was determined based on the lack of systematic absences and intensity statistics. The structure was solved using SIR97[3] and refined using SHELXL-97[4]. Full-matrix least-squares/difference Fourier cycles were performed to locate the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. The crystal structure was produced with ORTEP.[5] Selected crystallographic data parameters for **4a** are listed in Table 7-12.

6. Characterization data for products (Table 2 and 3)



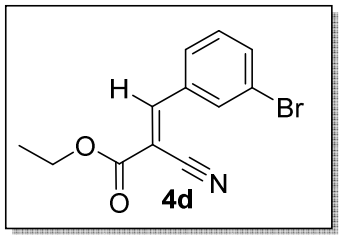
ethyl (*E*)-2-cyano-3-(4-fluorophenyl)acrylate (4b)

White solid, yield: 87 %; IR ν_{max} (KBr, cm^{-1}): 2997, 2226, 1718, 1598, 1512, 1272, 1165, 840, 763, 509; ^{1}H NMR (500 MHz, $CDCl_3$)[6]: δ 8.21 (s, 1H), 8.05-8.02 (m, 2H), 7.22-7.18 (m, 2H), 4.39 (q, *J* = 10.0 Hz, 2H), 1.40 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ165.5 (d, *J* = 256.0 Hz), 162.5, 153.6, 133.7 (d, *J* = 9.0 Hz), 127.9 (d, *J* = 4.0 Hz), 116.8 (d, *J* = 21.0 Hz), 115.6, 102.7, 62.9, 14.3; ^{19}F NMR (470 MHz, $CDCl_3$): δ -103.9 to -104.0 (m, 1F); HRMS (EI+): m/z calcd for $C_{12}H_{10}FNO_2$ (M^+): 219.0696; found: 219.0694.



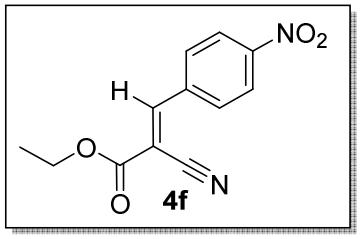
ethyl (*E*)-3-(4-chlorophenyl)-2-cyanoacrylate (4c)

White solid, yield: 84 %; IR ν_{max} (KBr, cm^{-1}): 2990, 2224, 1724, 1611, 1589, 1264, 832, 738, 499; ^{1}H NMR (500 MHz, $CDCl_3$)[7]: δ 8.20 (s, 1H), 7.94 (d, *J* = 10.0 Hz, 2H), 7.48 (d, *J* = 10.0 Hz, 2H), 4.39 (q, *J* = 10.0 Hz, 2H), 1.40 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ162.4, 153.5, 139.7, 132.3, 130.0, 129.8, 115.4, 103.6, 63.0, 14.3; HRMS (ESI+): m/z calcd for $C_{12}H_{10}ClNO_2Na$ (M+Na): 258.0298; found : 258.0292.



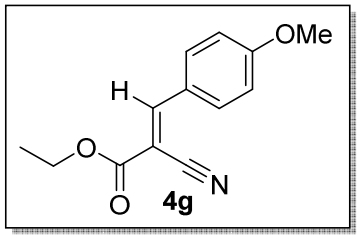
ethyl (*E*)-3-(3-bromophenyl)-2-cyanoacrylate (4d)

Yellowish solid, yield: 80 %; IR ν_{max} (KBr, cm^{-1}): 2981, 2223, 1715, 1606, 1273, 1202, 794, 681; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.04 (s, 1H), 7.99 (d, *J* = 10.0 Hz, 1H), 7.68 (d, *J* = 5.0 Hz, 1H), 7.39 (t, *J* = 10.0 Hz, 1H), 4.40 (q, *J* = 10.0 Hz, 2H), 1.41 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 153.2, 136.1, 133.9, 133.4, 130.9, 129.0, 123.4, 115.0, 104.8, 63.1, 14.3; HRMS (ESI+): m/z calcd for $C_{12}H_{10}BrNO_2Na$ (M+Na): 301.9793 ; found : 301.9789.



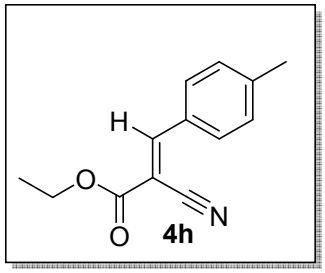
ethyl (*E*)-2-cyano-3-(4-nitrophenyl)acrylate (4f)

Yellow solid, yield: 87 %; IR ν_{max} (KBr, cm^{-1}): 2924, 2226, 1720, 1515, 1347, 1286, 858, 765, 666; ^{1}H NMR (500 MHz, $CDCl_3$)[7]: δ 8.35 (d, *J* = 10.0 Hz, 2H), 8.30 (s, 1H), 8.13 (d, , *J* = 10.0 Hz, 2H), 4.43 (q, *J* = 5.0 Hz, 2H), 1.42 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 151.8, 149.9, 137.0, 131.6, 124.5, 114.6, 107.5, 63.5, 14.2; HRMS (EI+): m/z calcd for $C_{12}H_{10}N_2O_4$ (M^+): 246.0641; found : 246.0565.



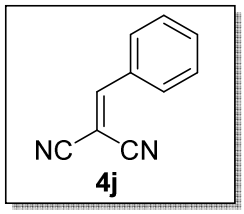
ethyl (*E*)-2-cyano-3-(4-methoxyphenyl)acrylate (4g)

Yellowish solid, yield: 88%; IR ν_{max} (KBr, cm^{-1}): 2993, 2216, 1720, 1587, 1563, 1433, 1264, 1187, 1021, 838, 555; ^{1}H NMR (500 MHz, $CDCl_3$)[6]: δ 8.17 (s, 1H), 8.0 (d, *J* = 5.0 Hz, 2H), 6.99 (d, *J* = 5.0 Hz, 2H), 4.37 (q, *J* = 10.0 Hz, 2H), 3.89 (s, 3H), 1.39 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 163.2, 154.5, 133.7, 124.5, 116.3, 114.9, 99.5, 62.5, 55.7, 14.3; HRMS (EI+): m/z calcd for $C_{13}H_{13}NO_3$ (M^+): 231.0895; found : 231.0900.



ethyl (*E*)-2-cyano-3-(p-tolyl)acrylate (4h)

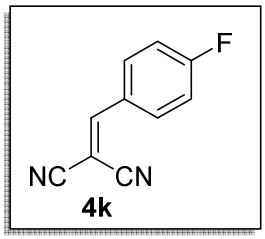
White solid, yield: 86 %; IR ν_{max} (KBr, cm^{-1}): 2995, 2218, 1724, 1600, 1269, 1208, 1192, 1094, 818, 762; ^{1}H NMR (500 MHz, $CDCl_3$)[6]: δ 8.22 (s, 1H), 7.90 (d, *J* = 5.0 Hz, 2H), 7.31 (d, *J* = 5.0 Hz, 2H), 4.38 (q, *J* = 10.0 Hz, 2H), 2.44 (s, 3H), 1.40 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9, 155.1, 144.8, 131.4, 130.1, 129.0, 115.9, 101.0, 62.7, 22.0, 14.3; HRMS (ESI+): m/z calcd for $C_{13}H_{13}NNaO_2$ (M+Na): 238.0844; found : 238.0838.



4j

2-benzylidenemalononitrile (4j)

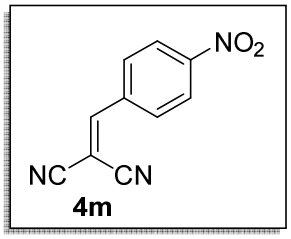
White solid, yield: 89 %; IR ν_{max} (KBr, cm^{-1}): 2223, 1593, 1450, 957, 755, 678, 616; ^1H NMR (500 MHz, $CDCl_3$)[8]: 7.91(d, *J* = 10.0 Hz, 2H), 7.79 (s, 1H), 7.65-7.62 (m, 1H), 7.56-7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 134.8, 131.0, 130.8, 129.7, 113.8, 112.6, 83.0 HRMS: (ESI-): m/z calcd for $C_{10}H_5N_2$ (M-H): 153.0531; found: 153.0451.



4k

2-(4-fluorobenzylidene)malononitrile (4k)

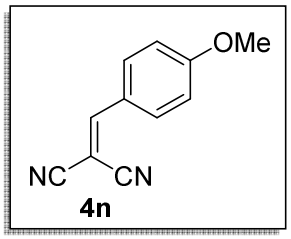
White solid, yield: 87 %; IR ν_{max} (KBr, cm^{-1}): 2232,1597, 1507, 1417, 1245, 1166, 840; ^1H NMR (400 MHz, $CDCl_3$): 7.98-7.95 (m, 2H), 7.74 (s, 1H), 7.24-7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ166.2 (d, *J* = 259.0 Hz), 158.4, 133.5 (d, *J* = 9.0 Hz), 127.5(d, *J* = 3.0 Hz), 117.3 (d, *J* = 22.0 Hz), 113.7, 112.6, 82.6 (d, *J* = 3.0 Hz); HRMS (EI+): m/z calcd for $C_{10}H_5FN_2$ (M^+): 172.0435; found: 172.0377.



4m

2-(4-nitrobenzylidene)malononitrile (4m)

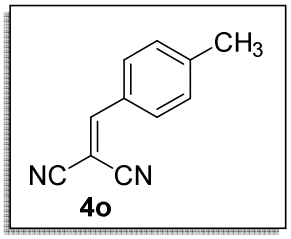
Deep yellow solid, yield: 76 %; IR ν_{max} (KBr, cm^{-1}): 2232, 1521, 1345, 935, 851; ^{1}H NMR (500 MHz, $CDCl_3$)[8]: 8.39 (d, *J* = 10.0 Hz, 2H), 8.07 (d, *J* = 10.0 Hz, 2H), 7.89 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 157.0, 150.5, 135.9, 131.4, 124.7, 112.7, 111.7, 87.7 ; HRMS (EI+): m/z calcd for $C_{10}H_5N_3O_2$ (M^+): 199.0382; found : 198.9823.



4n

2-(4-methoxybenzylidene)malononitrile (4n)

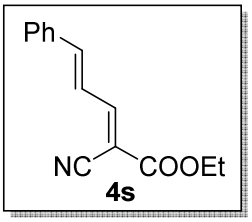
Yellow solid, yield: 72 %; IR ν_{max} (KBr, cm^{-1}): 2224, 1604, 1571, 1320, 1279, 1186, 1022, 834; ^{1}H NMR (500 MHz, $CDCl_3$)[8]: 7.91 (d, *J* = 10.0 Hz, 2H), 7.65 (s, 1H), 7.02 (d, *J* = 10.0 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ164.9, 159.0, 133.6, 124.2, 115.3, 114.6, 113.5, 78.7, 55.9; HRMS (EI+): m/z calcd for $C_{11}H_8N_2O$ (M^+): 184.0637; found: 184.0687.



4o

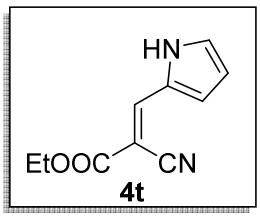
2-(4-methylbenzylidene)malononitrile (4o)

Yellow solid, yield: 77 %; IR ν_{max} (KBr, cm^{-1}): 2361, 2225, 1589, 1222, 1193, 841; ^{1}H NMR (400 MHz, $CDCl_3$): 7.81 (d, *J* = 8.0 Hz, 2H), 7.72 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.9, 146.5, 131.0, 130.5, 128.6, 114.1, 113.0, 81.4, 22.1.



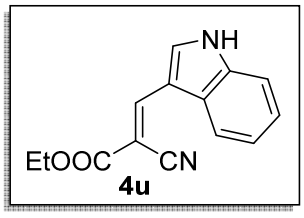
Ethyl (2*E*,4*E*)-2-cyano-5-phenylpenta-2,4-dienoate (4s)

Yellow solid, yield: 85 %; ^{1}H NMR (500 MHz, $CDCl_3$)[7]: 8.05-7.98 (m, 1H), 7.61-7.58 (m, 2H), 7.45-7.42 (m, 3H), 7.33.7.27 (m, 2H) 4.35 (q, *J* = 10.0 Hz, 2H), 1.39 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 162.4, 155.5, 148.9, 134.8, 131.3, 129.3, 128.6, 123.2, 114.7, 104.7, 62.5 14.3; HRMS (ESI+): m/z calcd for $C_{14}H_{13}NO_2$ (M^+): 227.0946; found: 227.1743.



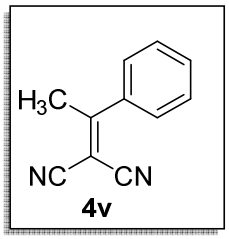
Ethyl (*E*)-2-cyano-3-(1H-pyrrol-2-yl)acrylate (4t)

Light yellow solid, yield: 81 %; ^{1}H NMR (500 MHz, $CDCl_3$)[7]: 9.91 (br. s, 1H), 8.01 (s, 1H), 7.23 (s, 1H), 6.94 (s, 1H), 6.43-6.42 (m, 1H), 4.33 (q, *J* = 10.0 Hz, 2H), 1.37 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)[5]: 163.5, 142.6, 128.5, 126.9, 124.6, 118.7, 112.5, 92.0, 62.2, 14.4; HRMS (EI+): m/z calcd for $C_{10}H_{10}N_2O_2$ (M^+) : 190.0742; found : 190.0617.



Ethyl (*E*)-2-cyano-3-(1H-indol-3-yl)acrylate (4u)

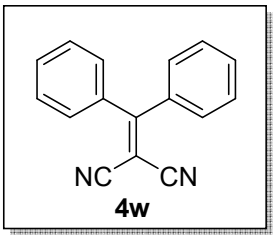
Yellow solid, yield: 85%; ^{1}H NMR (500 MHz, $CDCl_3$)[7]: 9.4 (br. s, 1H), 8.65 (d, *J* = 5.0 Hz, 1H), 8.63 (s, 1H) 7.83-7.82 (m, 1H), 7.51-7.49 (m, 1H), 7.35-7.30 (m, 2H), 4.39 (q, *J* = 10.0 Hz, 2H), 1.41 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)[5]: 164.0, 146.8, 135.8, 130.9, 127.5, 124.3, 122.8, 118.4, 118.3, 112.4, 111.3, 94.9, 62.2, 14.5; HRMS (EI+): m/z calcd for $C_{14}H_{12}N_2O_2$ (M^+) : 240.0899; found : 240.0776.



4v

2-(1-phenylethylidene)malononitrile (4v)

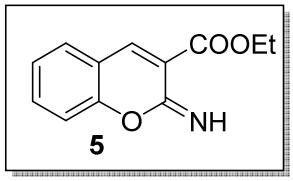
White solid, yield: 70 %; IR ν_{max} (KBr, cm^{-1}): 2357, 2228, 1566, 770; ^{1}H NMR (500 MHz, $CDCl_3$)[8]: 7.57-7.49 (m, 5H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 175.6, 136.0, 132.4, 129.3, 127.5, 112.9, 112.8, 84.9, 24.4; HRMS (EI+) m/z calcd for $C_{11}H_8N_2$ (M^+) : 168.0687; found : 168.0028.



4w

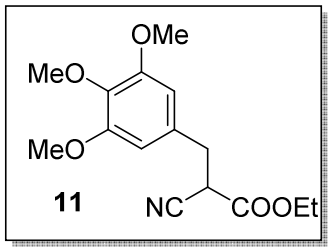
2-(diphenylmethylene)malononitrile (4w)

White solid, yield: 71 %; IR ν_{max} (KBr, cm^{-1}): 2361, 2223, 1531, 702 ; ^{1}H NMR (500 MHz, $CDCl_3$): 7.60-7.57 (m, 2H), 7.50-7.47 (m, 4H), 7.45-7.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 175.1, 136.2, 132.8, 130.5, 129.0, 114.0, 81.9; HRMS (EI^+): m/z calcd for $C_{16}H_{10}N_2$ (M^+) 230.0844; found: 230.0923.



Ethyl 2-imino-2H-chromene-3-carboxylate (5)

Light yellow solid, yield: 90 %; IR ν_{max} (KBr, cm^{-1}): 3064, 2979, 1776, 1507, 1565, 1451, 1374, 1209, 1033, 775; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.65-7.61 (m, 2H), 7.37-7.32 (m, 2H), 4.43 (q, *J* = 10.0 Hz, 2H), 1.42 (t, *J* = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 156.8, 155.3, 148.7, 134.4, 129.6, 124.9, 118.5, 118.0, 116.9, 62.1, 14.3; HRMS (ESI+): m/z calcd for $C_{12}H_{12}NNaO_3$ (M+Na): 241.0715 ; found : 241.0503.



Ethyl 2-cyano-3-(3,4,5-trimethoxyphenyl)propanoate (11)

Light yellow solid, yield: 72%; IR ν_{max} (KBr, cm^{-1}): 2251, 1740, 1591, 1465, 1345, 1250, 1127, 843; ^{1}H NMR (400 MHz, $CDCl_3$): 6.50 (s, 2H), 4.26 (q, *J* = 8.0 Hz, 2H), 3.86 (s, 6H), 3.83(s, 3H), 3.72-3.70 (m, 1H), 3.24-3.11 (m, 2H), 1.40 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.6, 153.5, 137.7, 131.0, 116.4, 106.2, 63.1, 60.9, 56.3, 39.9, 36.3, 14.0; HRMS (EI+): m/z calcd for $C_{15}H_{19}NO_5$ (M^+) : 293.1263; found : 293.1203.

7. X-ray Crystallographic data of 4a [CCDC 1854216]

Table 7 Crystal data and structure refinement for 4a.	
Identification code	KJ_5KN_0m_a
Empirical formula	$C_{12}H_{11}NO_2$
Formula weight	201.22
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	7.4403(5)
b/Å	7.5372(5)
c/Å	10.8823(7)
α/°	100.819(2)
β/°	96.705(2)
γ/°	113.4590(10)
Volume/Å^3	537.32(6)
Z	2
ρ_{calc}g/cm^3	1.2437
μ/mm^{-1}	0.085
F(000)	212.1
Crystal size/mm^3	0.2 × 0.1 × 0.08
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	6.1 to 56.7
Index ranges	$-9 \le h \le 9$, $-10 \le k \le 10$, $-14 \le l \le 14$
Reflections collected	16679
Independent reflections	2669 [R_{int} = 0.0610, R_{sigma} = 0.0356]
Data/restraints/parameters	2669/0/138
Goodness-of-fit on F^2	1.103
Final R indexes [I>=2σ (I)]	R_1 = 0.0635, wR_2 = 0.1668
Final R indexes [all data]	R_1 = 0.0970, wR_2 = 0.2003
Largest diff. peak/hole / e Å^{-3}	0.45/-0.32

Table 8 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 4a. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O(1)	2030(3)	938(2)	6494.2(17)	79.0(6)
O(2)	3966(3)	3506(2)	8164.6(16)	73.5(5)
N(1)	5341(4)	7888(3)	7517(2)	89.0(8)
C(1)	698(4)	3790(4)	2962(2)	67.4(6)
C(2)	472(5)	4765(5)	2046(2)	82.3(8)
C(3)	1374(4)	6812(5)	2338(3)	77.7(8)

C(4)	2440(4)	7888(4)	3542(3)	77.9(8)
C(5)	2675(3)	6925(3)	4465(2)	66.3(6)
C(6)	1831(3)	4849(3)	4183.5(19)	49.8(5)
C(7)	2002(3)	3688(3)	5079(2)	50.4(5)
C(8)	3054(3)	4253(3)	6276(2)	49.2(5)
C(9)	4314(3)	6279(3)	6964(2)	58.5(6)
C(10)	2940(3)	2696(3)	6967(2)	56.9(5)
C(11)	4066(5)	2130(4)	8935(3)	83.5(8)
C(12)	2322(5)	1543(5)	9502(3)	97.7(10)

Table 9 Anisotropic Displacement Parameters ($Å^2×10^3$) for 4a. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	103.5(13)	37.9(8)	77.2(11)	18.0(8)	−1.1(9)	13.7(7)
O(2)	91.6(12)	46.3(8)	68.0(10)	20.0(8)	−5.1(9)	17.5(7)
N(1)	113.3(18)	42.6(11)	79.7(14)	13.4(11)	−14.7(13)	12.3(10)
C(1)	83.0(16)	60.9(14)	59.0(13)	34.4(12)	13.6(11)	9.9(11)
C(2)	102(2)	102(2)	54.4(14)	55.3(18)	15.4(13)	19.9(14)
C(3)	80.3(17)	99(2)	80.3(18)	47.8(16)	32.9(14)	51.0(16)
C(4)	66.5(15)	66.4(15)	103(2)	19.8(12)	16.2(14)	47.0(15)
C(5)	57.2(13)	50.9(12)	77.4(15)	9.8(10)	2.7(11)	24.0(11)
C(6)	46.0(10)	48.5(10)	57.4(11)	20.4(8)	16.3(9)	16.2(9)
C(7)	50.4(10)	37.7(9)	60.4(12)	16.6(8)	14.0(9)	10.8(8)
C(8)	50.2(10)	36.8(9)	60.1(12)	17.5(8)	13.1(9)	13.4(8)
C(9)	67.5(13)	40.9(10)	61.2(12)	18.7(10)	5.0(10)	15.6(9)
C(10)	62.1(12)	40.1(10)	63.6(13)	18.4(9)	7.6(10)	13.6(9)
C(11)	95.4(19)	66.5(16)	78.1(17)	25.7(14)	4.9(15)	23.8(13)
C(12)	113(2)	101(2)	77.9(19)	47(2)	14.7(17)	21.0(17)

Table 10 Bond Lengths for 4a.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O(1)	C(10)	1.195(2)	C(4)	C(5)	1.379(3)
O(2)	C(10)	1.324(3)	C(5)	C(6)	1.389(3)
O(2)	C(11)	1.469(3)	C(6)	C(7)	1.453(3)
N(1)	C(9)	1.139(3)	C(7)	C(8)	1.334(3)
C(1)	C(2)	1.378(4)	C(8)	C(9)	1.428(3)
C(1)	C(6)	1.385(3)	C(8)	C(10)	1.489(3)
C(2)	C(3)	1.369(4)	C(11)	C(12)	1.447(4)
C(3)	C(4)	1.359(4)			

Table 11 Bond Angles for 4a.							
Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C(11)	O(2)	C(10)	117.07(18)	C(8)	C(7)	C(6)	131.14(18)
C(6)	C(1)	C(2)	121.0(2)	C(9)	C(8)	C(7)	124.54(18)
C(3)	C(2)	C(1)	119.9(2)	C(10)	C(8)	C(7)	119.07(17)
C(4)	C(3)	C(2)	120.2(2)	C(10)	C(8)	C(9)	116.39(18)
C(5)	C(4)	C(3)	120.3(2)	C(8)	C(9)	N(1)	179.0(3)
C(6)	C(5)	C(4)	120.7(2)	O(2)	C(10)	O(1)	124.6(2)
C(5)	C(6)	C(1)	117.8(2)	C(8)	C(10)	O(1)	123.9(2)
C(7)	C(6)	C(1)	116.98(19)	C(8)	C(10)	O(2)	111.52(17)
C(7)	C(6)	C(5)	125.19(19)	C(12)	C(11)	O(2)	108.3(3)

Table 12Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 4a.				
Atom	*x*	*y*	*z*	U(eq)
H(1)	80(4)	2399(4)	2758(2)	80.9(8)
H(2)	−292(5)	4034(5)	1230(2)	98.8(10)
H(3)	1257(4)	7469(5)	1712(3)	93.2(9)
H(4)	3014(4)	9278(4)	3743(3)	93.5(9)
H(5)	3405(3)	7674(3)	5286(2)	79.6(7)
H(7)	1248(3)	2313(3)	4762(2)	60.4(6)
H(11a)	4088(5)	959(4)	8398(3)	100.2(10)
H(11b)	5279(5)	2786(4)	9601(3)	100.2(10)
H(12a)	2306(19)	2711(6)	10026(18)	146.6(15)
H(12b)	1130(5)	870(30)	8837(3)	146.6(15)
H(12c)	2372(18)	660(30)	10020(18)	146.6(15)

8. References

1. W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals;* 4th Edition, Butterworth Heinemann, 1997.
2. R. P. D'Amelia, S. Chiang, S. Pollut, W. F. Nirode, *J. Chem. Educ.*, 2014, **91**, 1070.
3. A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C.Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R.Spagna, *J. Appl. Crystallogr*. 1999, **32**, 115.
4. G. M. Sheldrick, SHELX97: A Program for Crystal StructureAnalysis (release 97-2), University of Göttingen, Germany, 1997.
5. L. J. Farrugia, *J. Appl. Crystallogr.* 1997, **30**, 565.
6. F. Pandolfi, M. Feroci, I. Chiarotto, *ChemistrySelect* 2018, **3**, 4745.
7. J. S. Yadav, B. V. S. Reddy, A. K. Basak, B. Visali, A. V. Narsaiah and K. Nagaiah, *Eur. J. Org. Chem*., 2004, 546.
8. G. R. Krishnan, K. Sreekumar, *Eur. J. Org. Chem.* 2008, 4763.

9. ^{1}H and ^{13}C Spectra

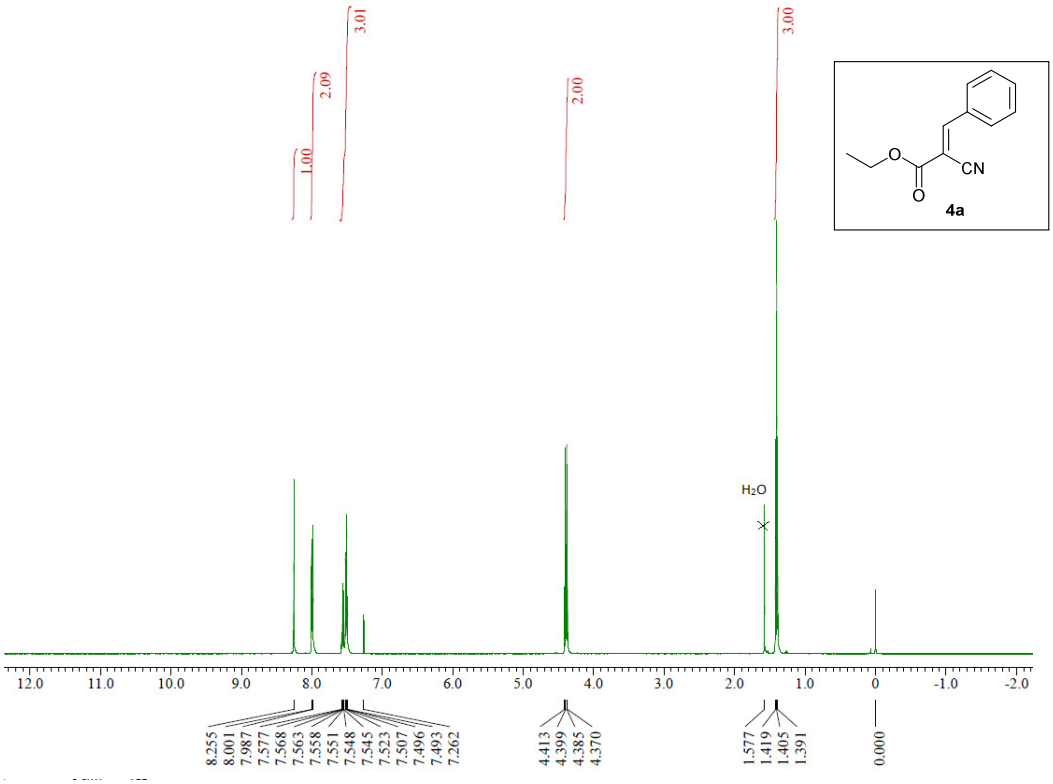


Figure 14: ^{1}H NMR spectrum of **4a** ($CDCl_3$, 500 MHz)

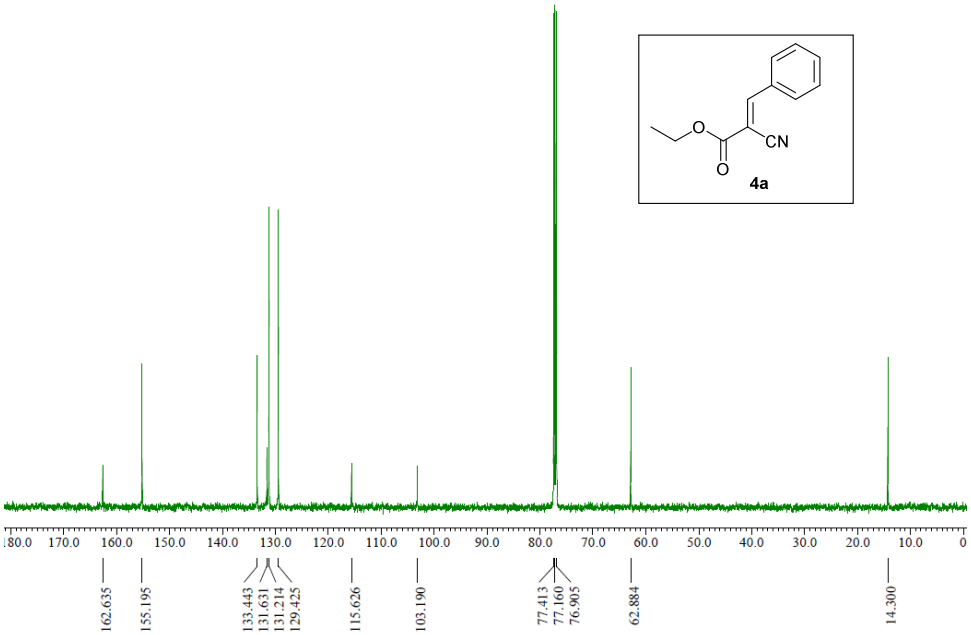


Figure 15: ^{13}C NMR spectrum of **4a** ($CDCl_3$, 125 MHz)

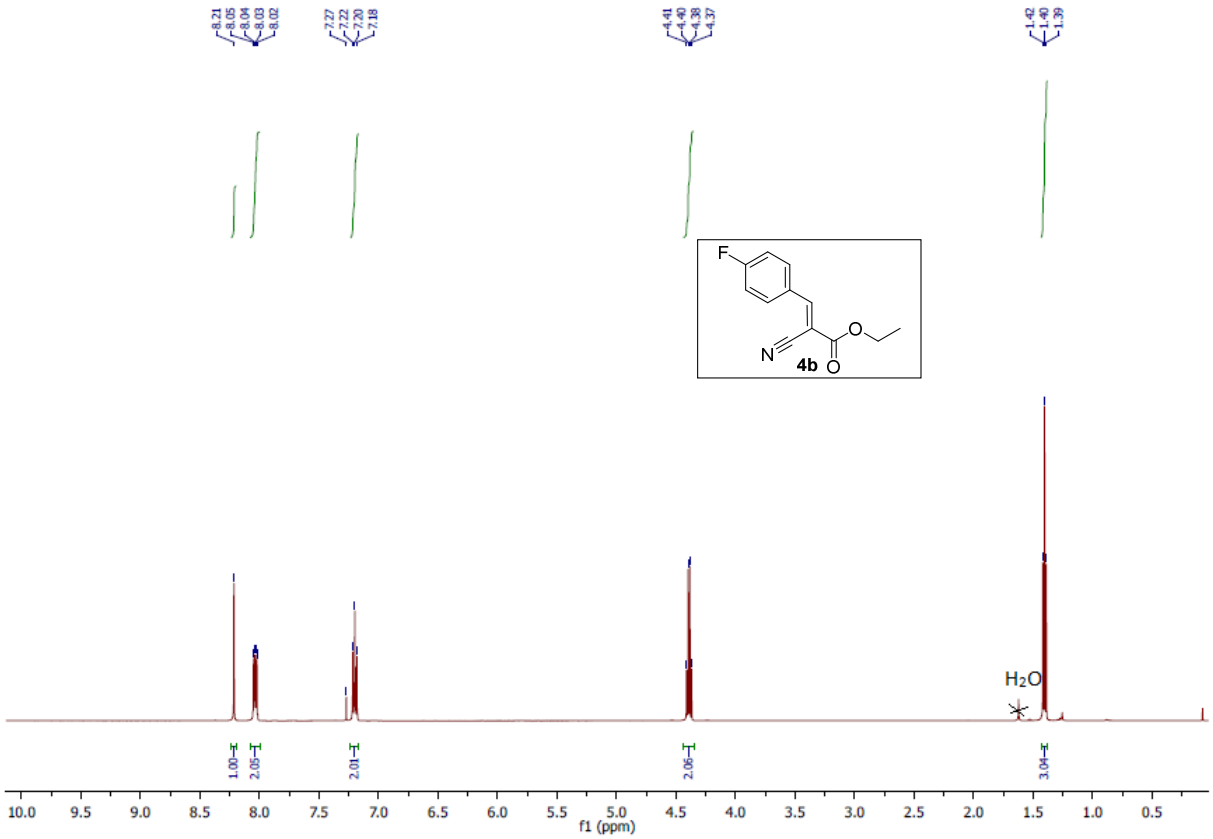


Figure 16: ^{1}H NMR spectrum of **4b** ($CDCl_3$, 500 MHz)

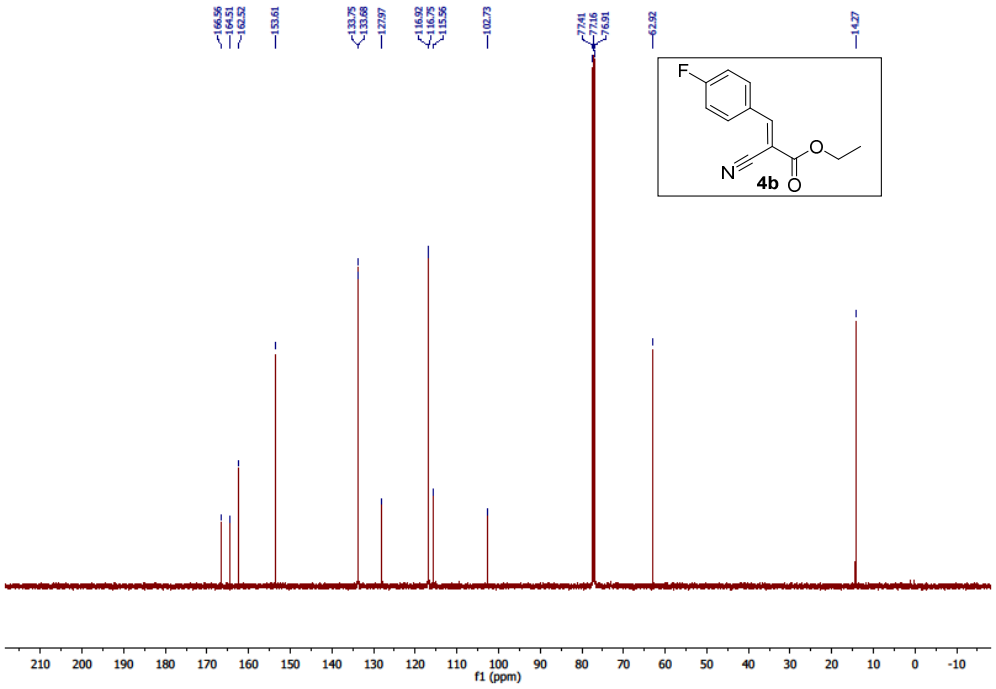


Figure 17. ^{13}C NMR spectrum of **4b** ($CDCl_3$, 125 MHz)

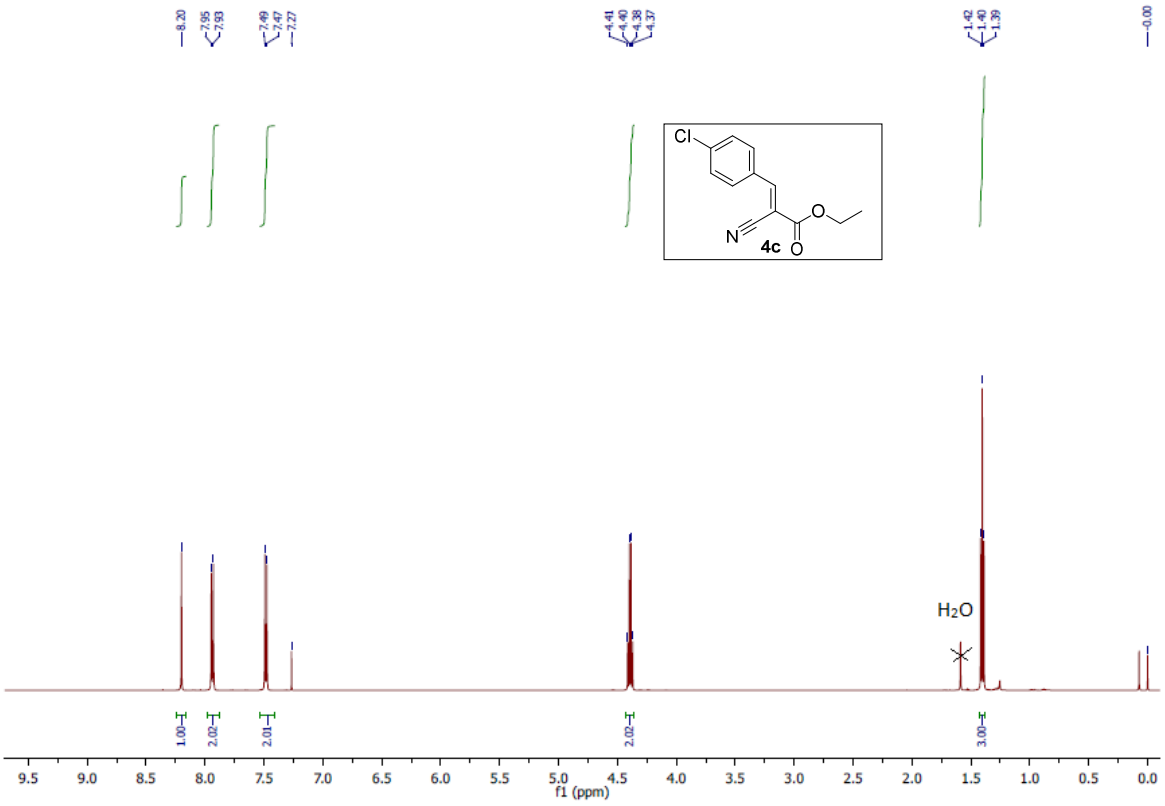


Figure 18: ^{1}H NMR spectrum of **4c** ($CDCl_3$, 500 MHz)

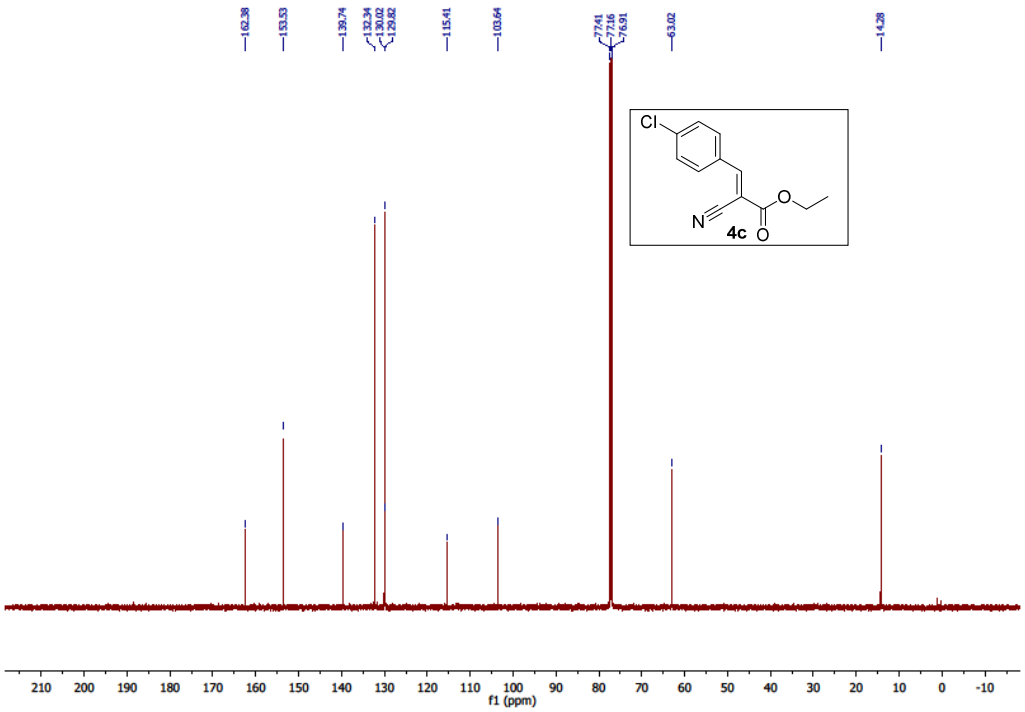


Figure 19: ^{13}C NMR spectrum of **4c** ($CDCl_3$, 125 MHz)

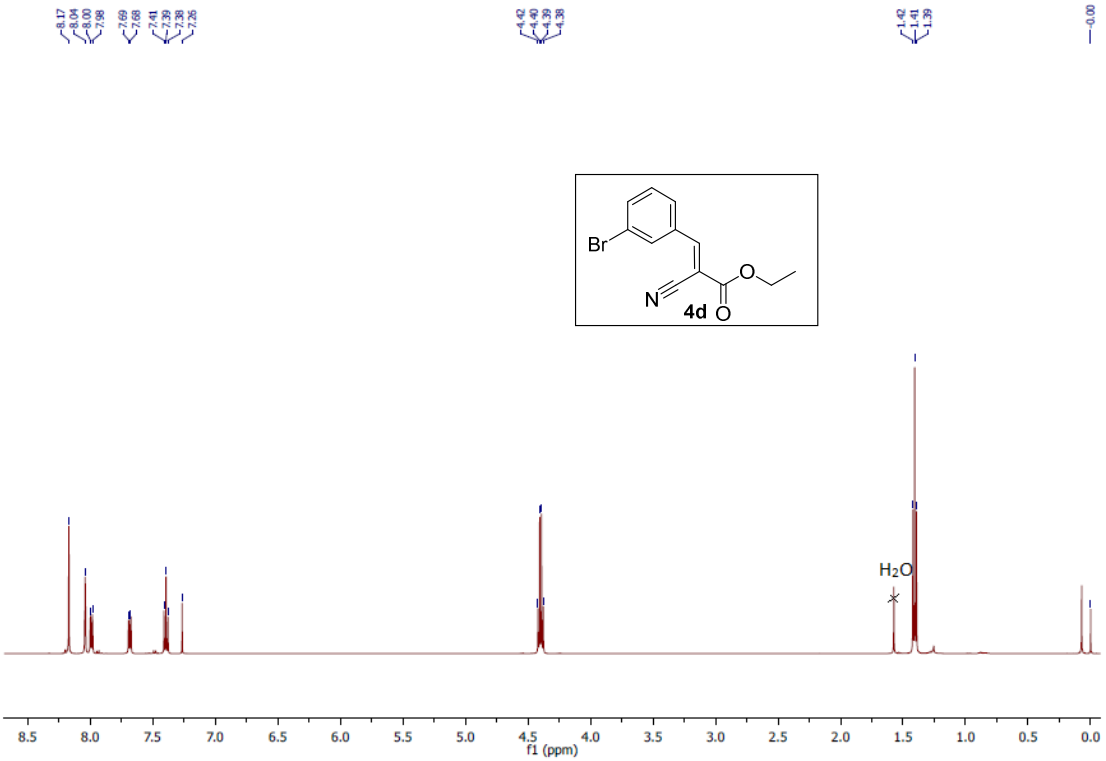


Figure 20: ^{1}H NMR spectrum of **4d** ($CDCl_3$, 500 MHz)

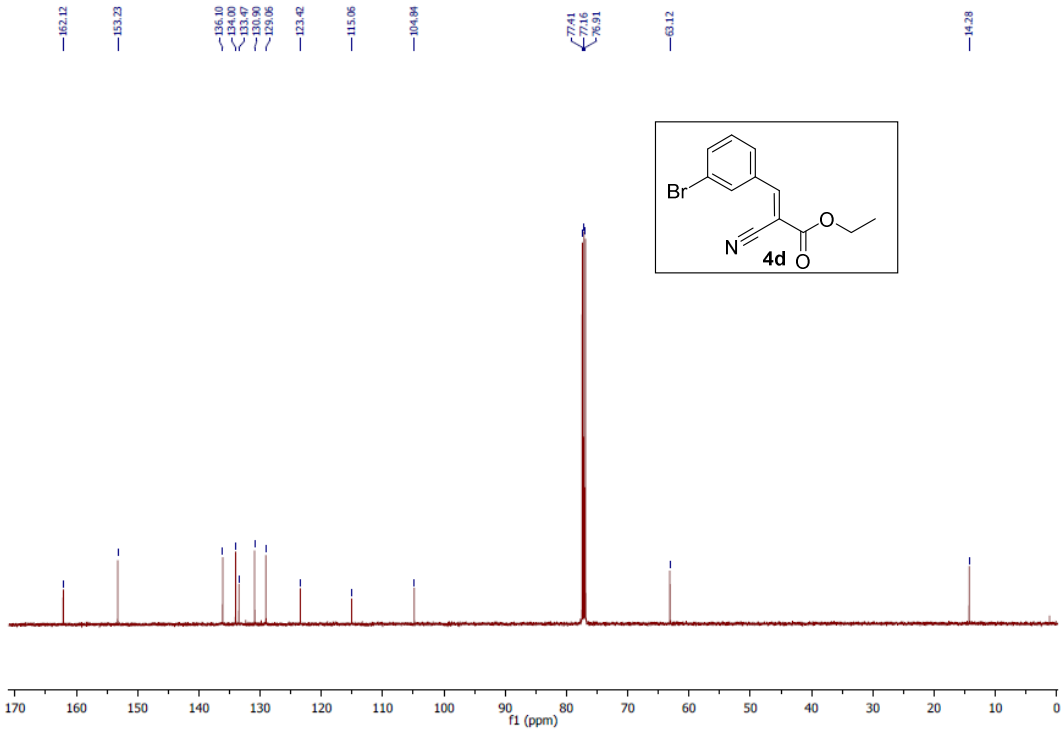


Figure 21: ^{13}C NMR spectrum of **4d** ($CDCl_3$, 125 MHz)

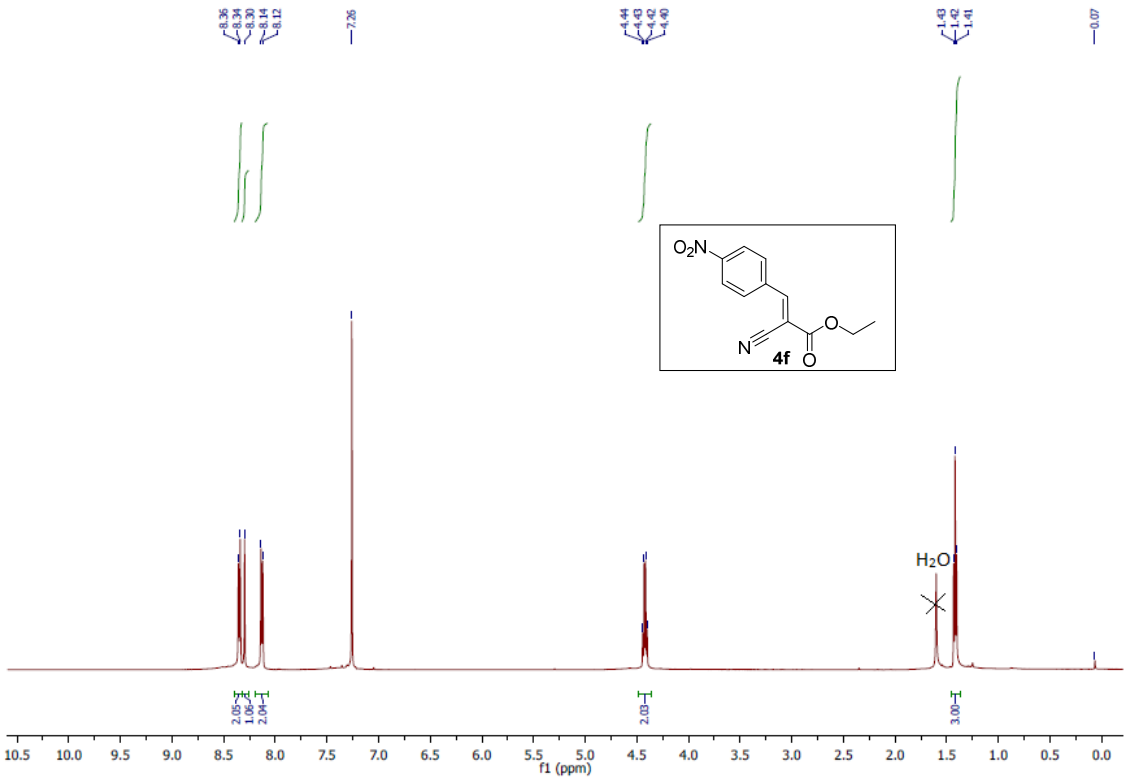


Figure 22: ^{1}HNMR spectrum of **4f** ($CDCl_3$, 500 MHz)

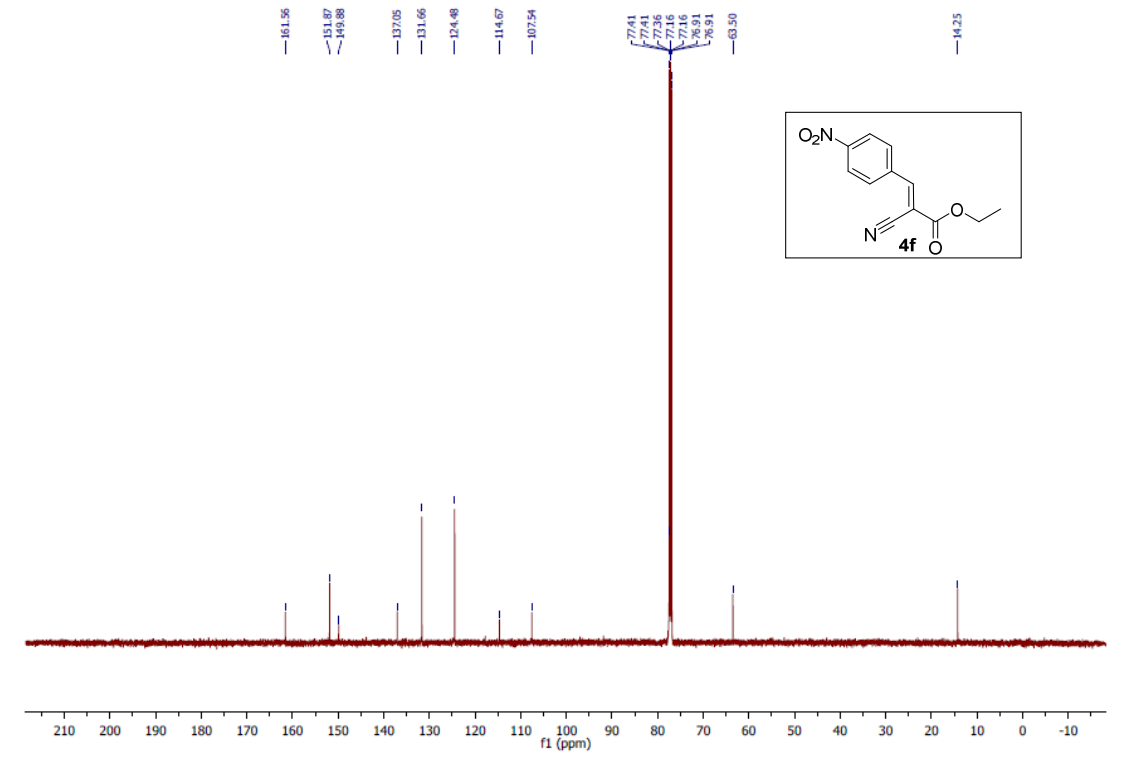


Figure 23: ^{13}C NMR spectrum of **4f** ($CDCl_3$, 125 MHz)

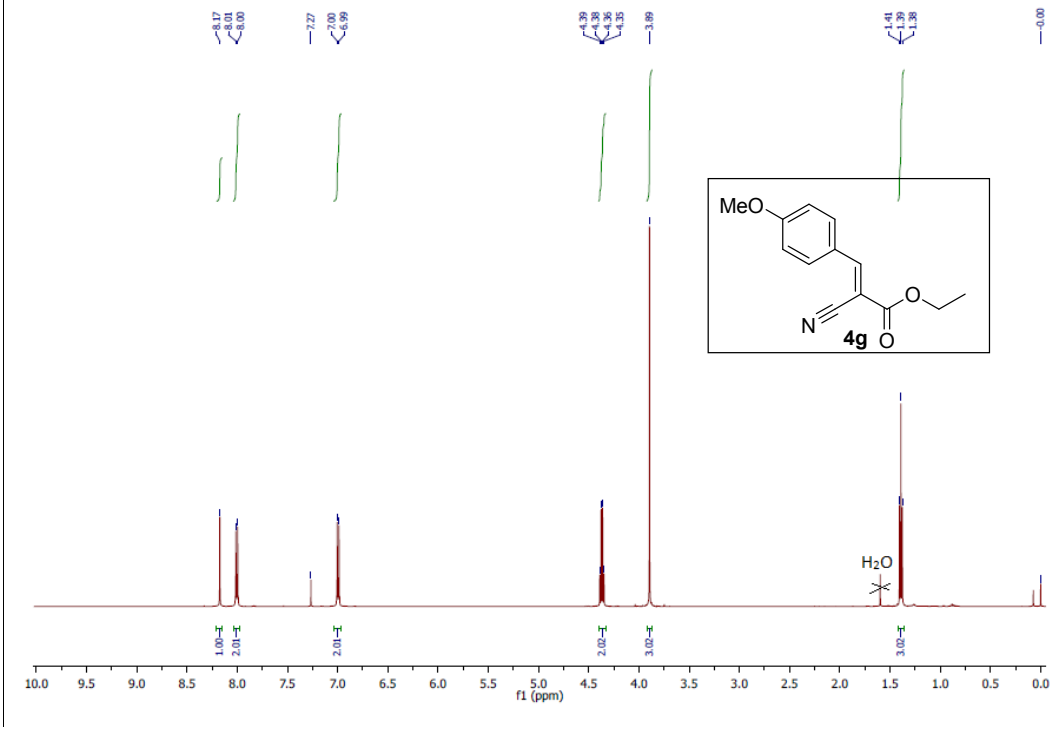


Figure 24: ^{1}H NMR spectrum of **4g** ($CDCl_3$, 500 MHz)

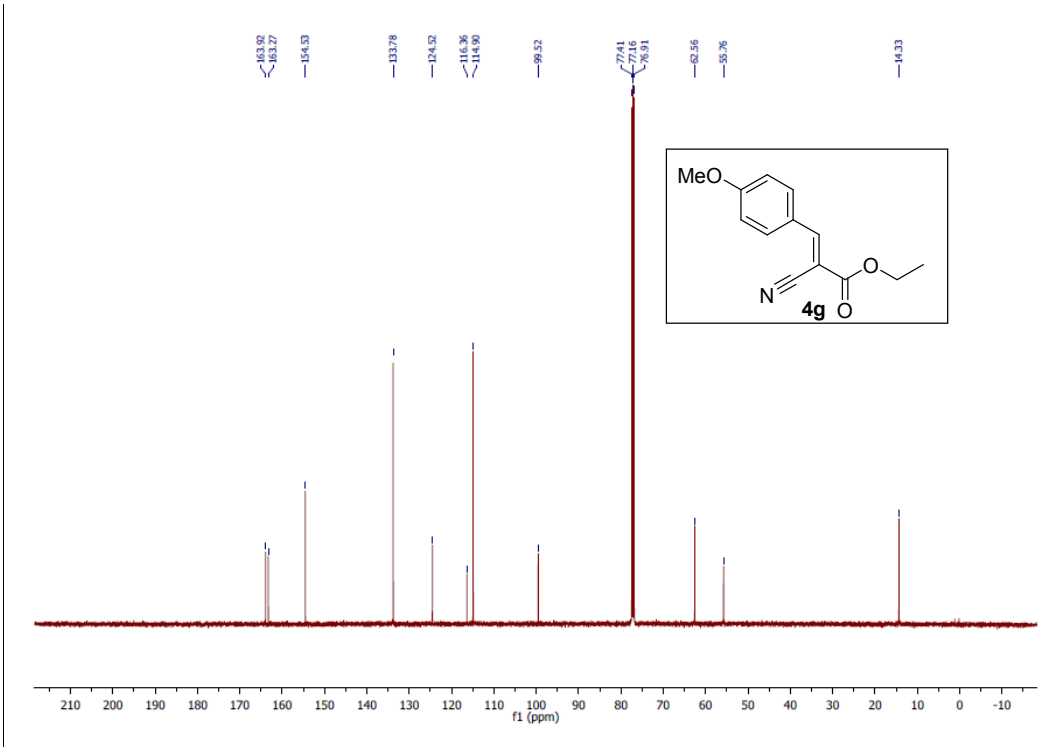


Figure 25: ^{13}C NMR spectrum of **4g** ($CDCl_3$, 125MHz)

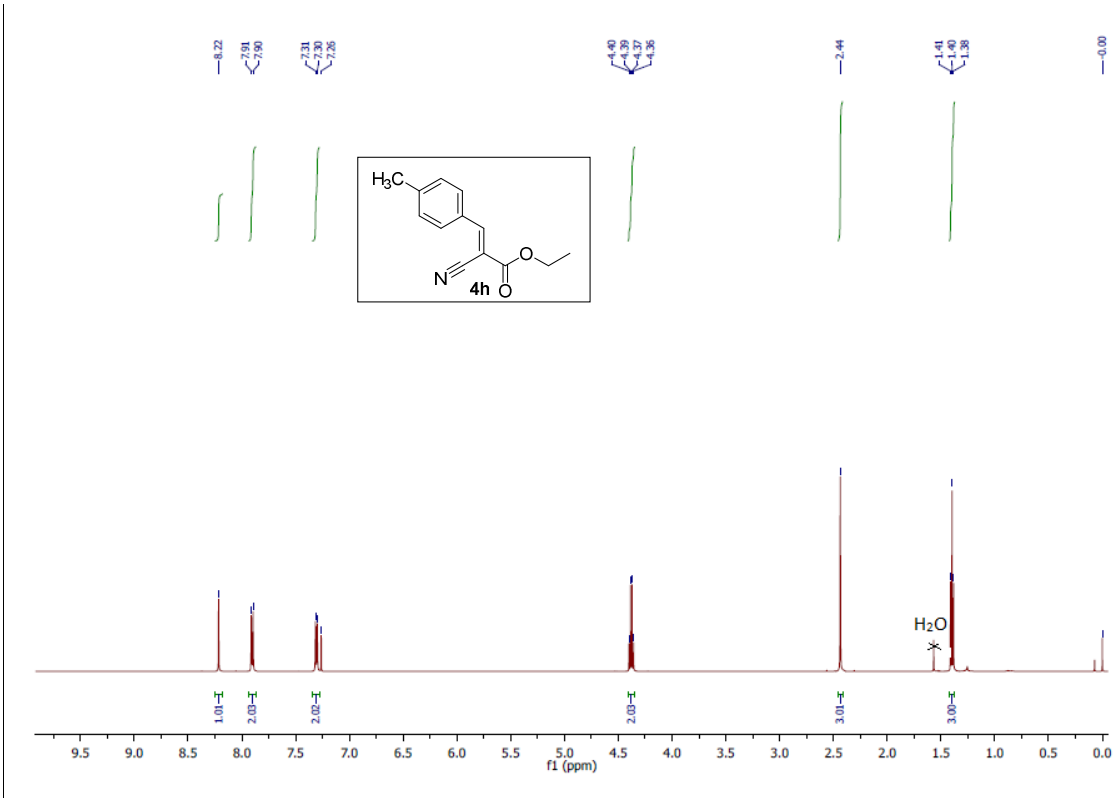


Figure 26: ^{1}H NMR spectrum of **4h** ($CDCl_3$, 400 MHz)

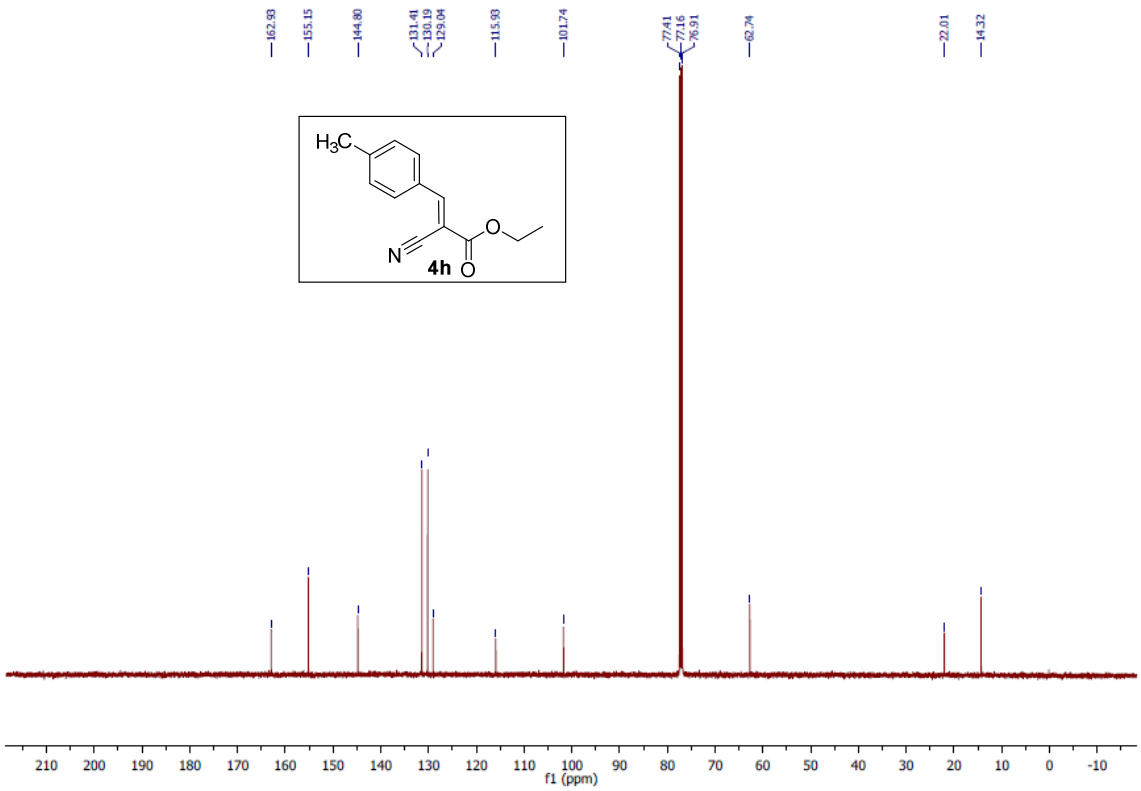


Figure 27: ^{13}C NMR spectrum of **4h** ($CDCl_3$, 100 MHz)

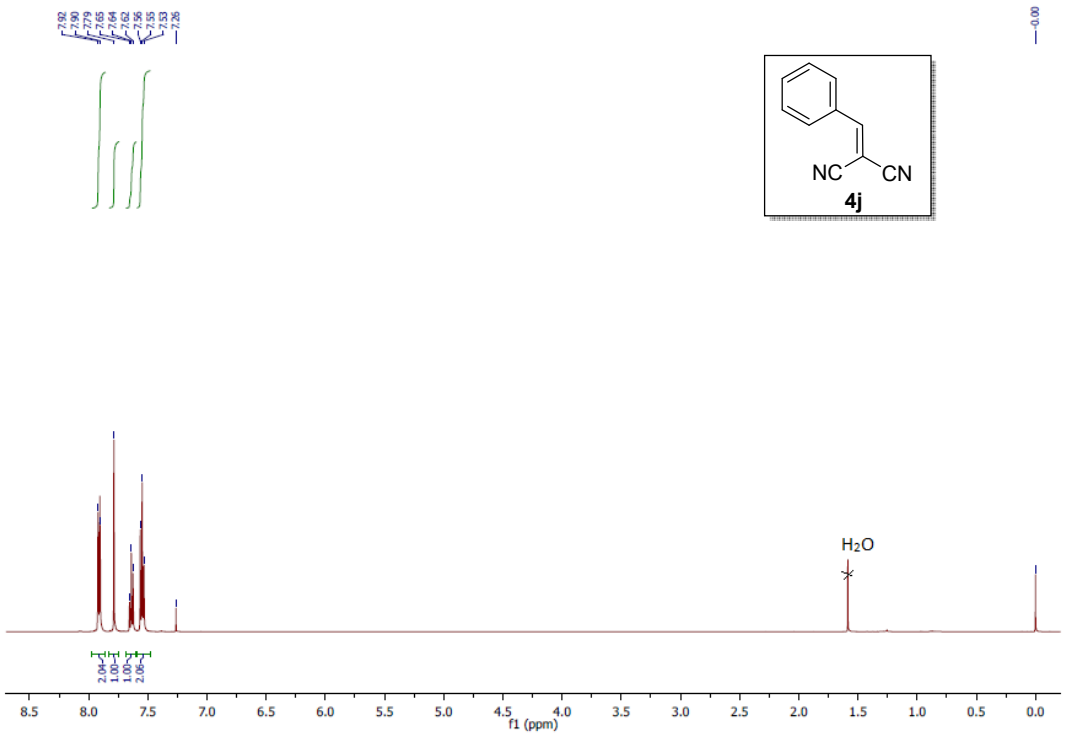


Figure 28: ^{1}H NMR spectrum of **4j** ($CDCl_3$, 500 MHz)

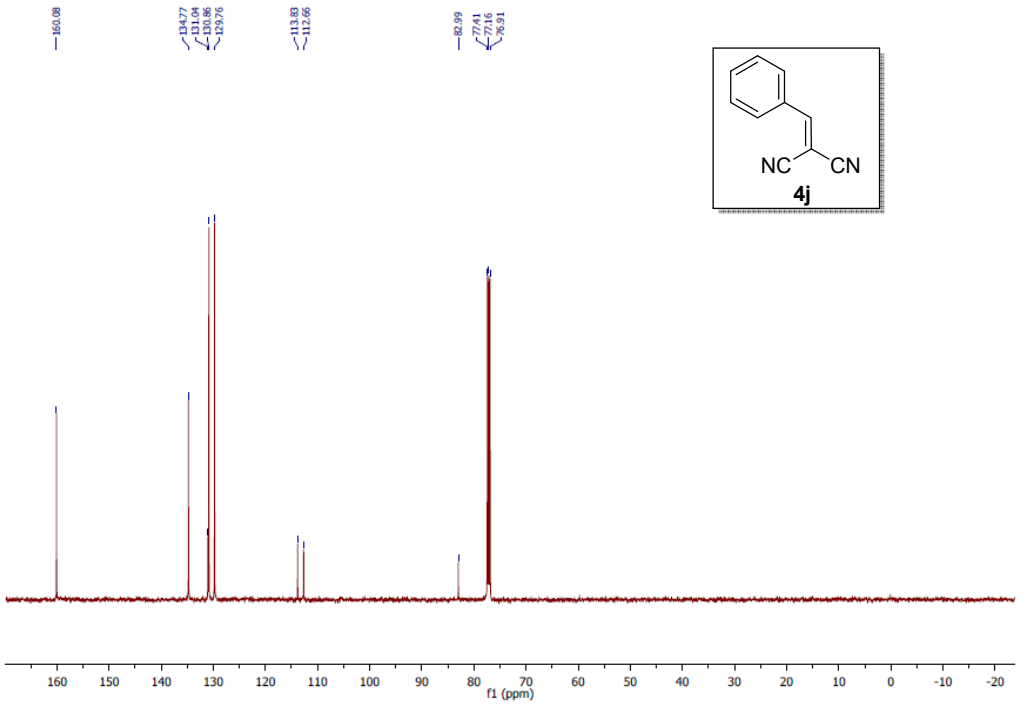


Figure 29: ^{13}C NMR spectrum of **4j** ($CDCl_3$, 125 MHz)

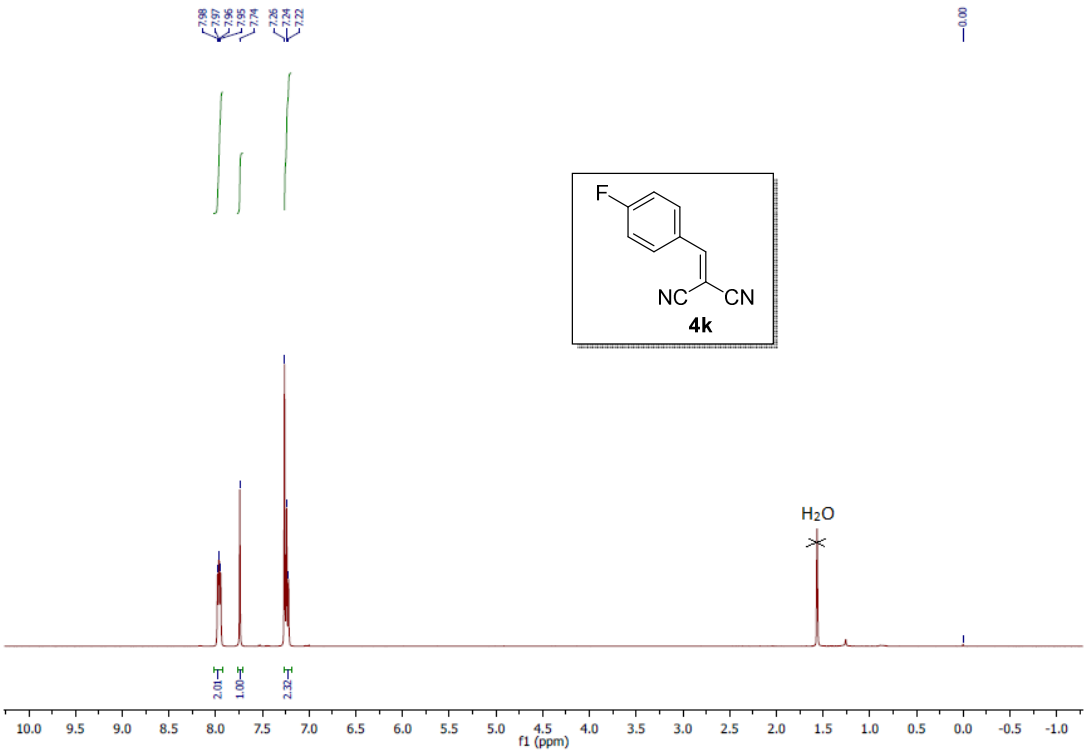


Figure 30: ^{1}H NMR spectrum of **4k** ($CDCl_3$, 400 MHz)

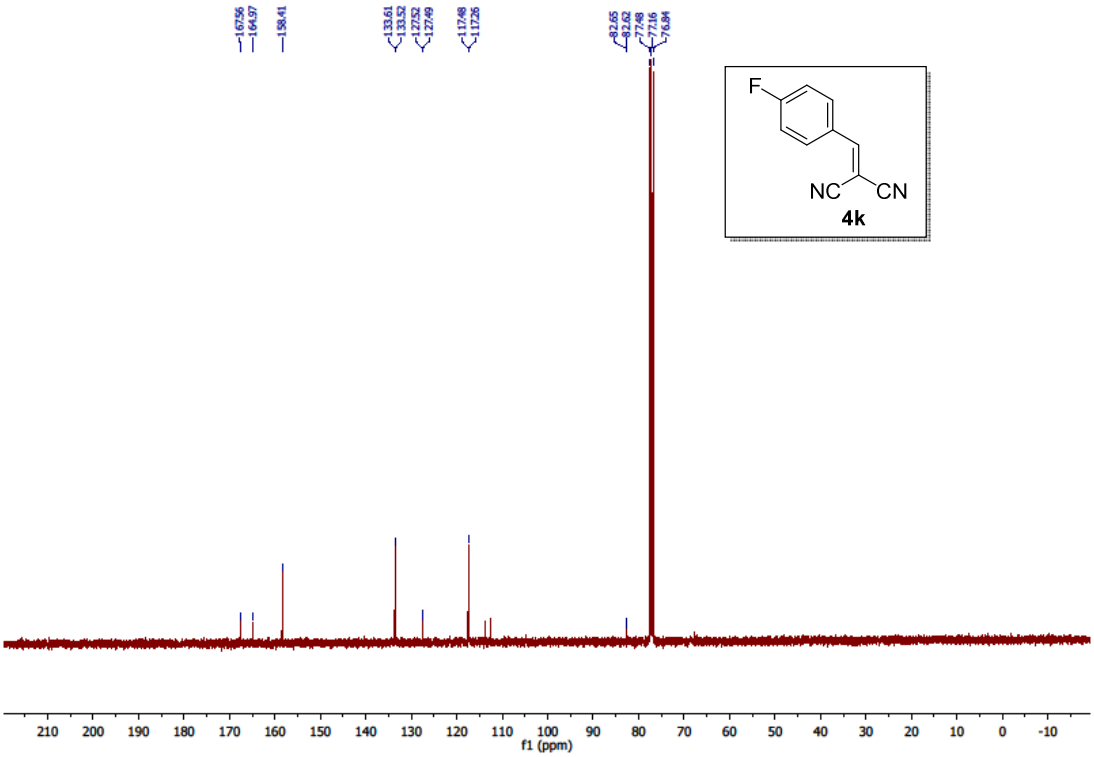


Figure 31: ^{13}C NMR spectrum of **4k** ($CDCl_3$, 100 MHz)

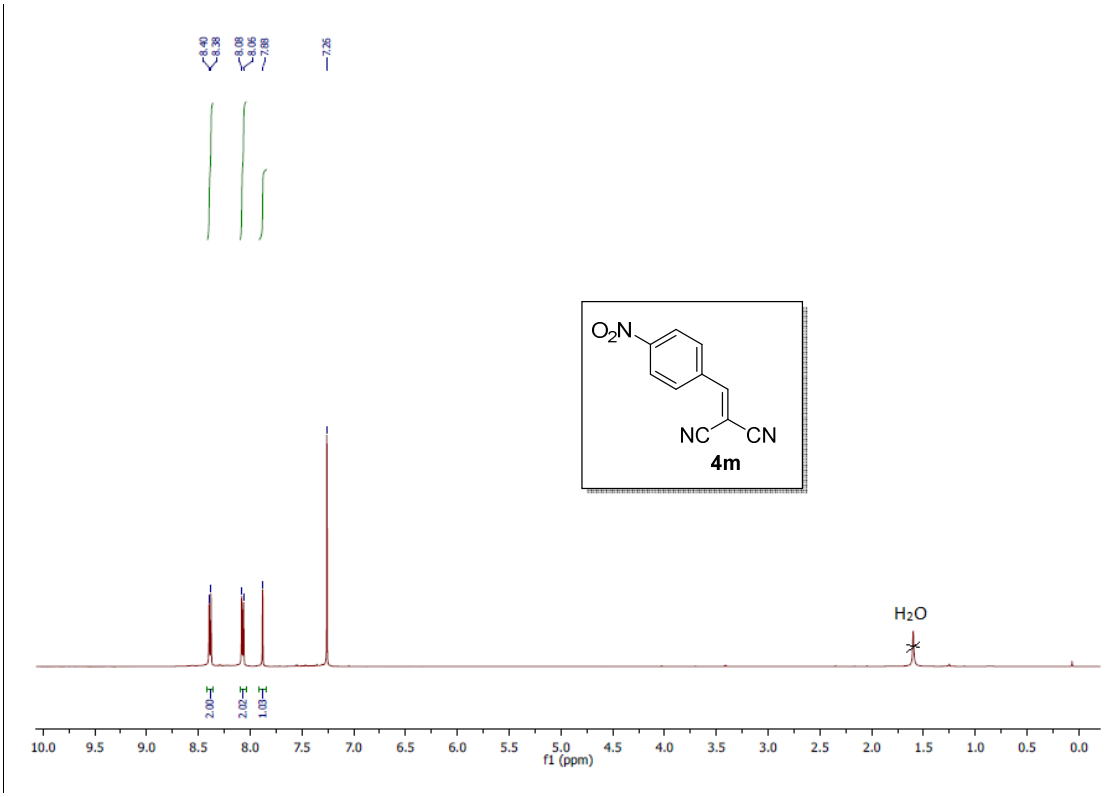


Figure 32: ^{1}H NMR spectrum of **4m** ($CDCl_3$, 500 MHz)

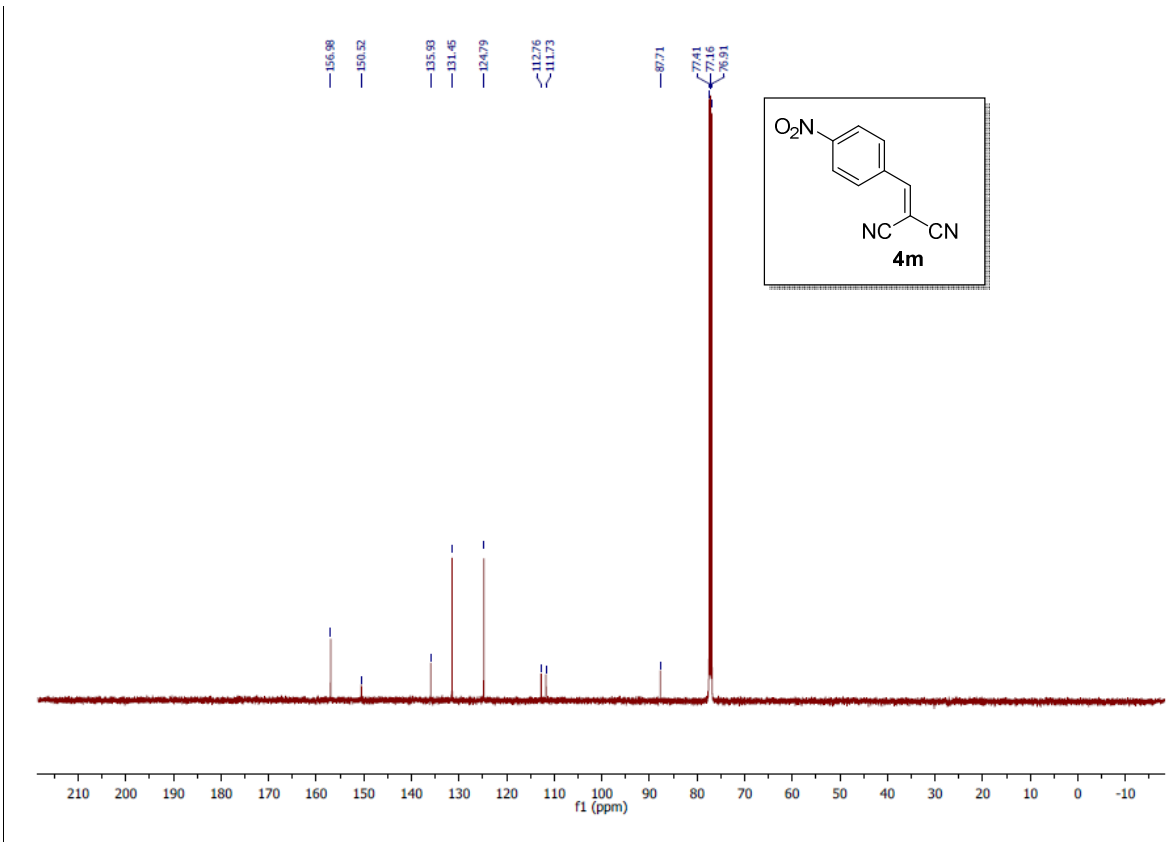


Figure 33: ^{13}C NMR spectrum of **4m** ($CDCl_3$, 125 MHz)

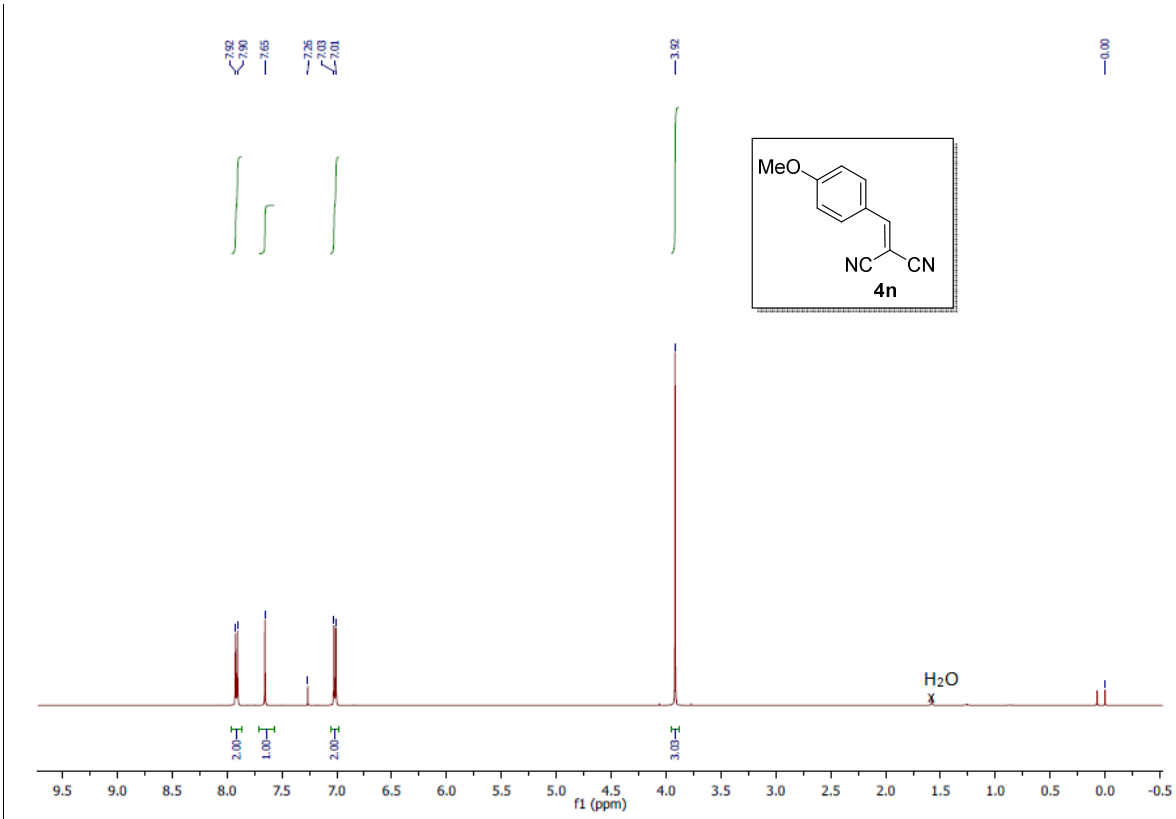


Figure 34: ^{1}H NMR spectrum of **4n** ($CDCl_3$, 500 MHz)

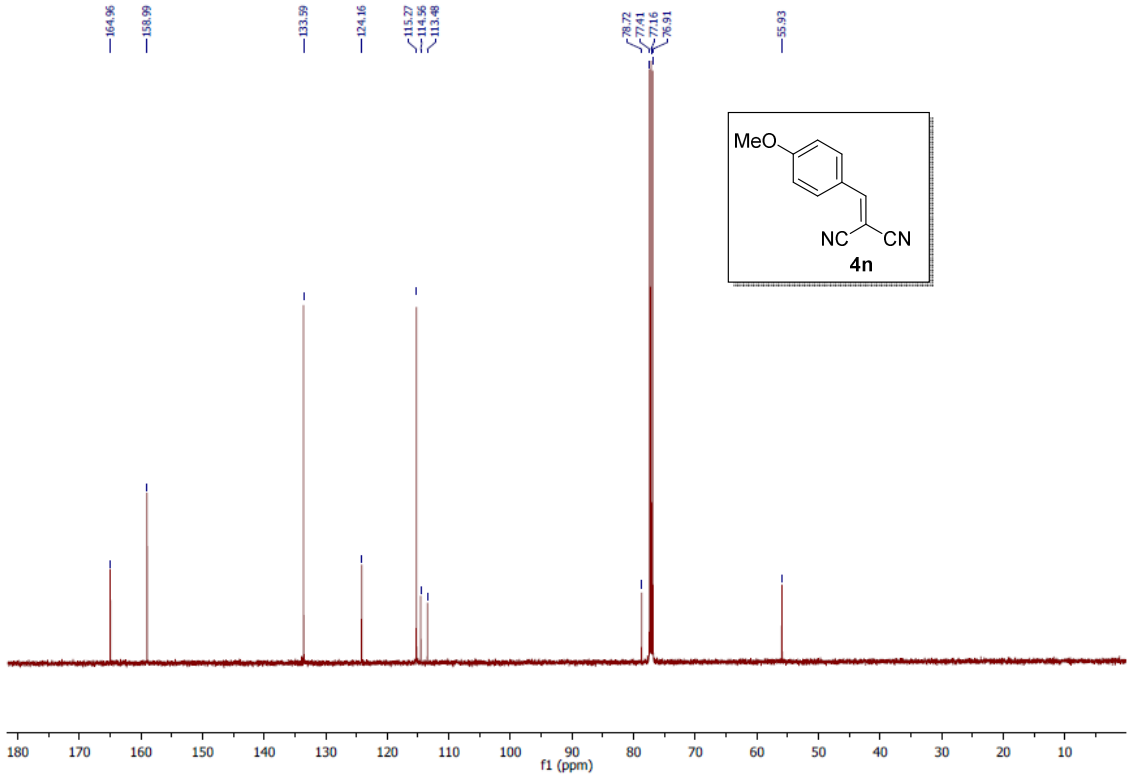


Figure 35: ^{13}C NMR spectrum of **4n** ($CDCl_3$, 125 MHz)

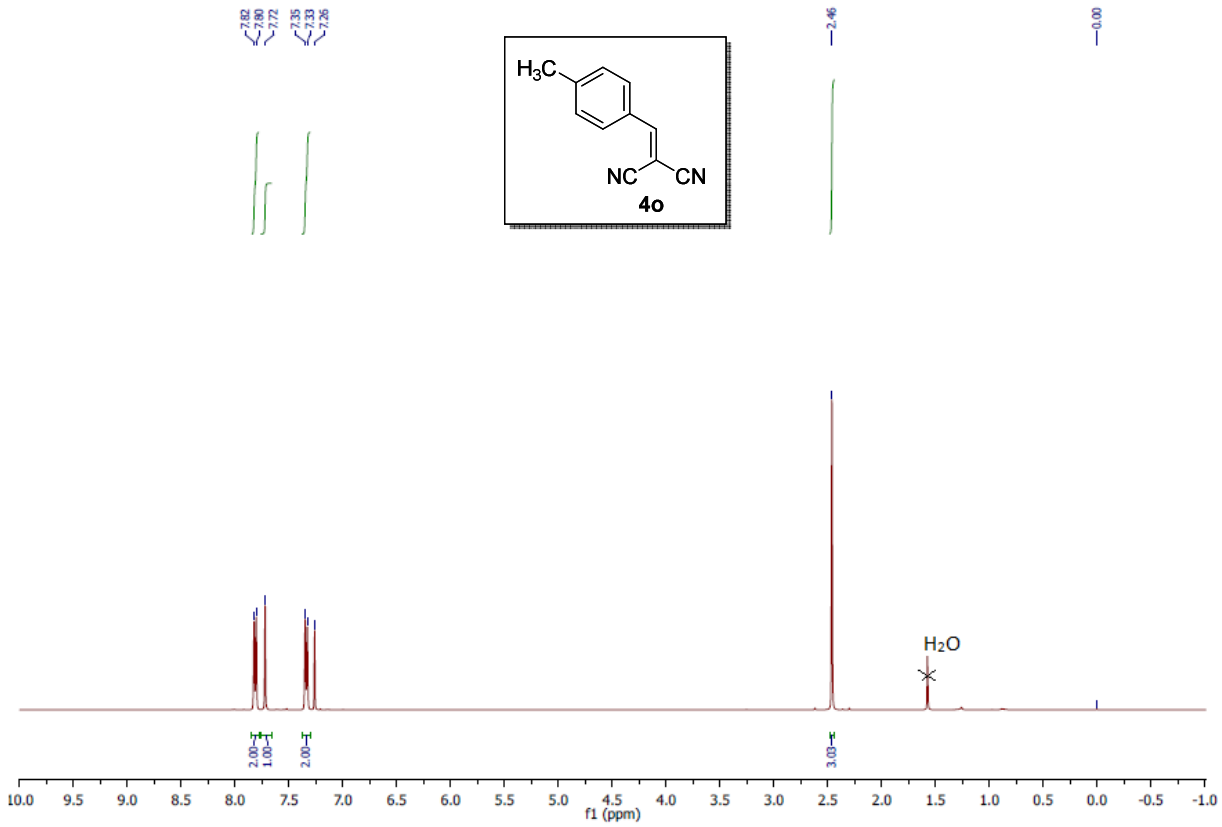


Figure 36: ^{1}H NMR spectrum of **4o** ($CDCl_3$, 400 MHz)

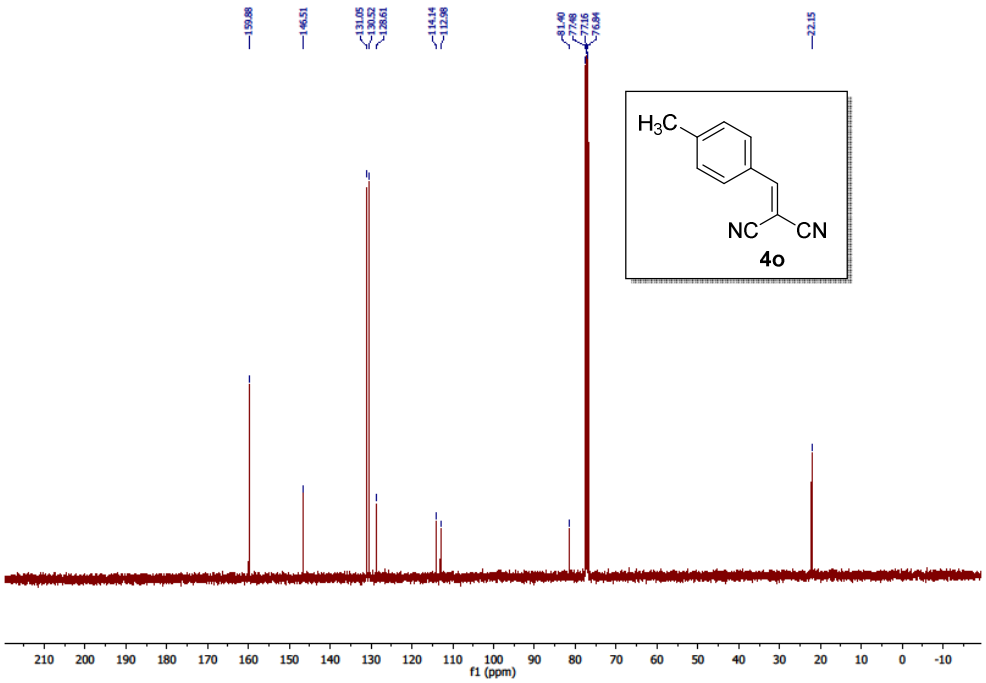


Figure 37: ^{13}C NMR spectrum of **4o** ($CDCl_3$, 100 MHz)

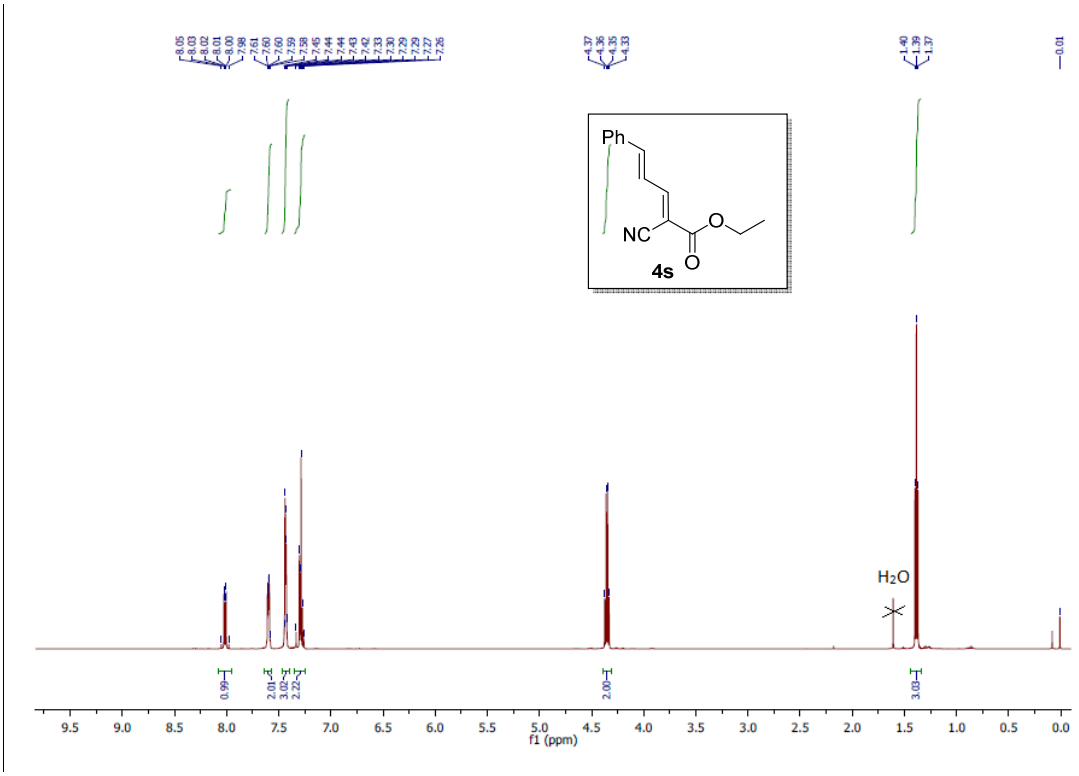


Figure 38: ^{1}HNMR spectrum of **4s** ($CDCl_3$, 500 MHz)

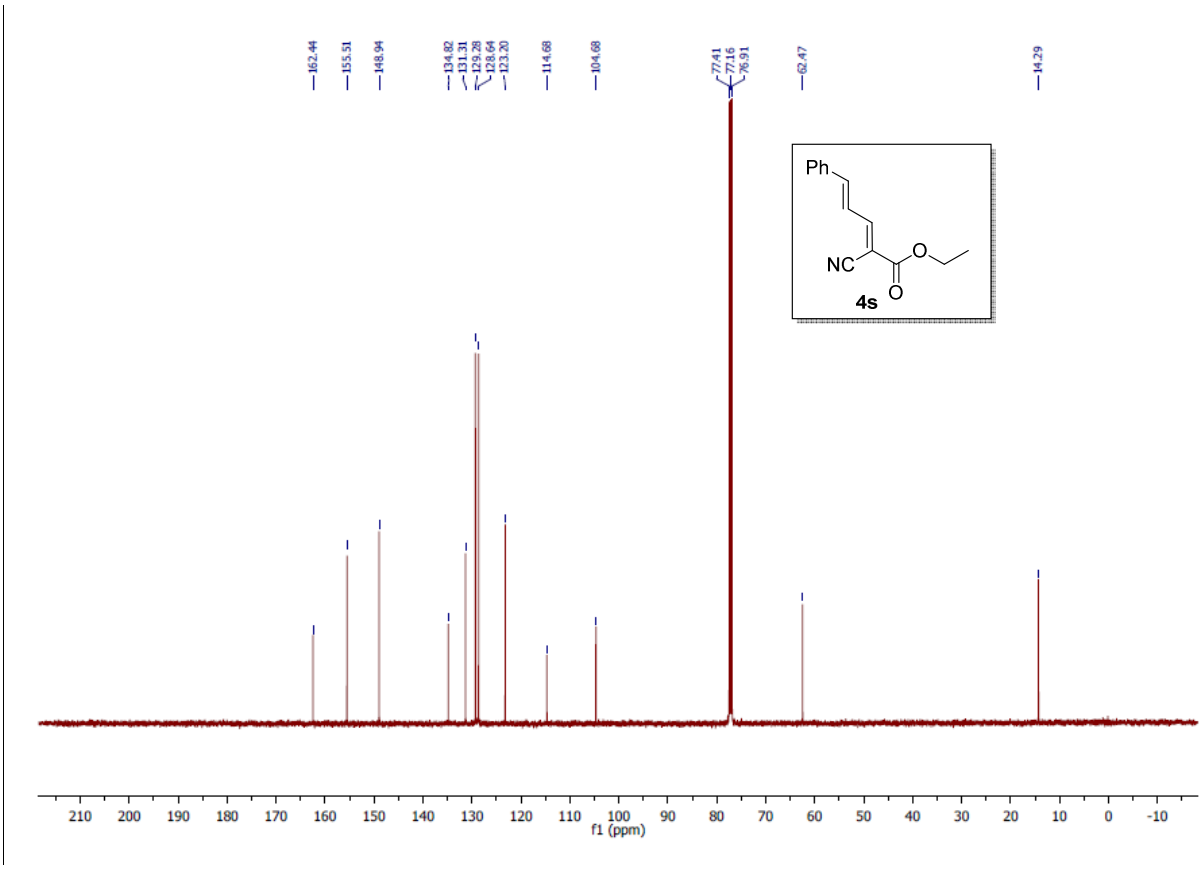


Figure 39: ^{13}C NMR spectrum of **4s** ($CDCl_3$, 125 MHz)

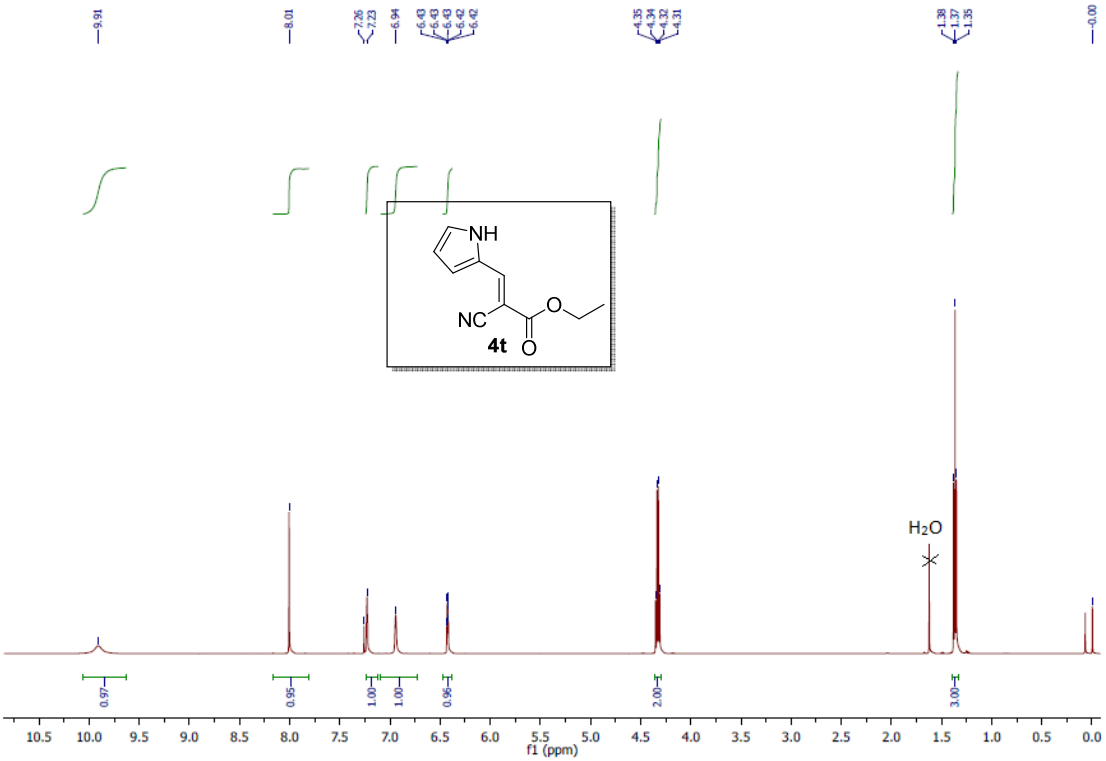


Figure 40: ^{1}H NMR spectrum of **4t** ($CDCl_3$, 500 MHz)

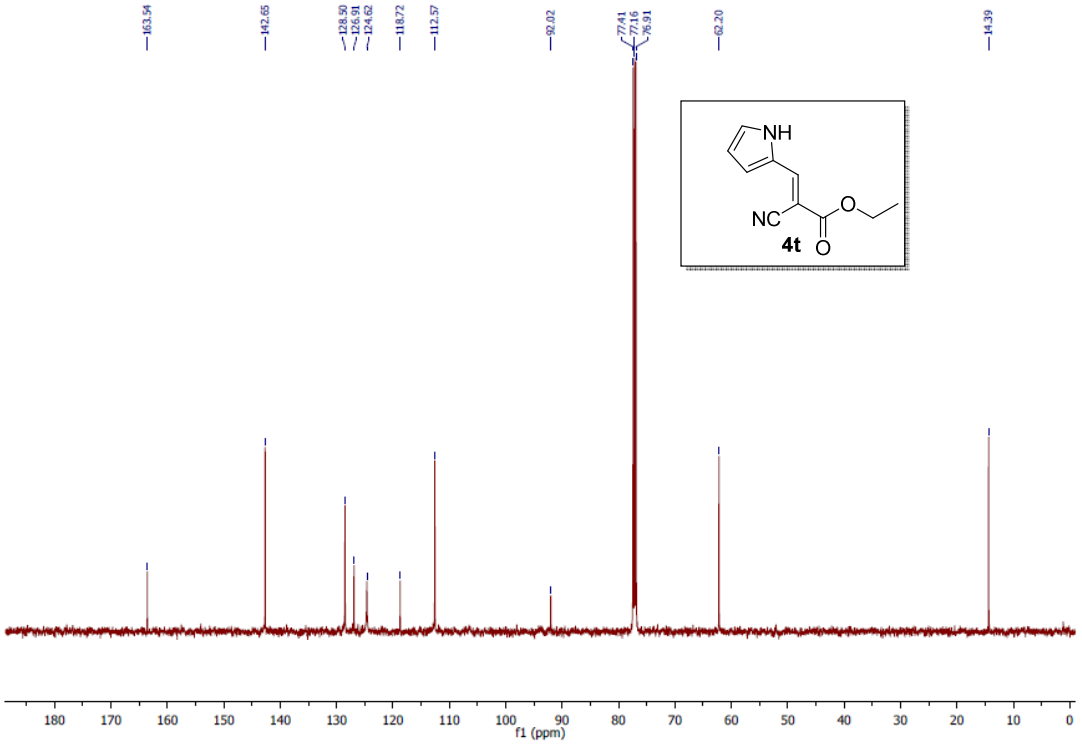


Figure 41: ^{13}C NMR spectrum of **4t** ($CDCl_3$, 125 MHz)

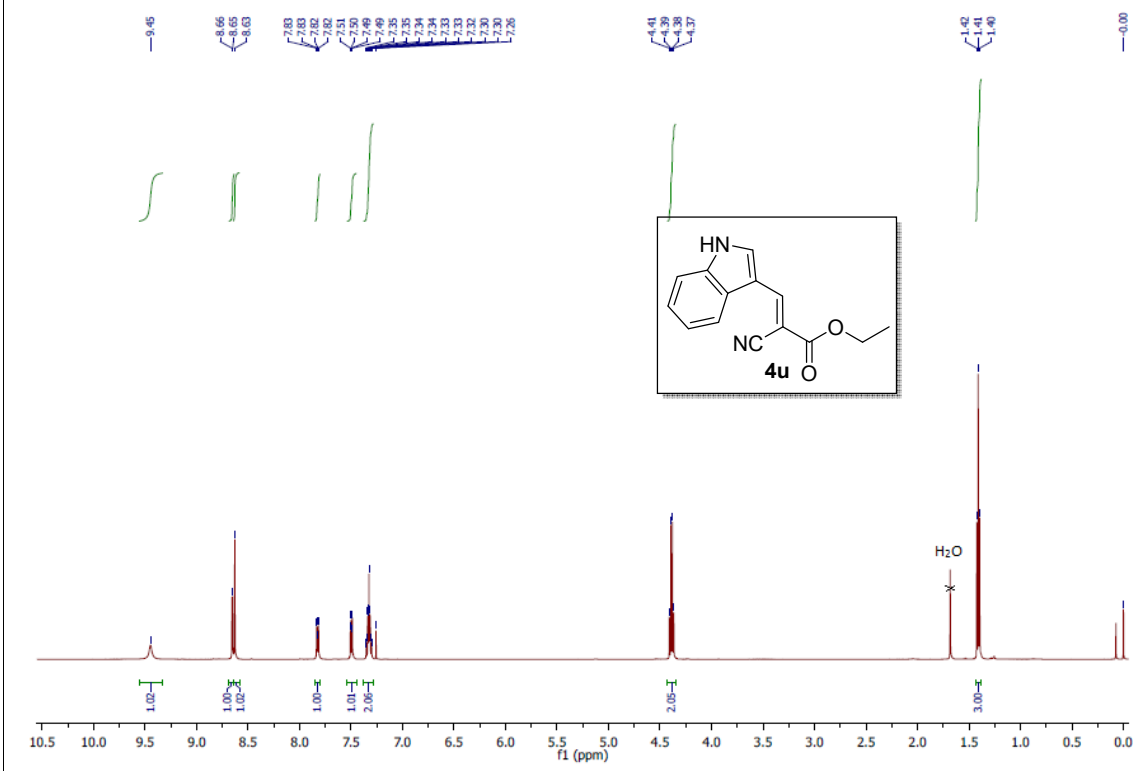


Figure 42: ^{1}H NMR spectrum of **4u** ($CDCl_3$, 500 MHz)

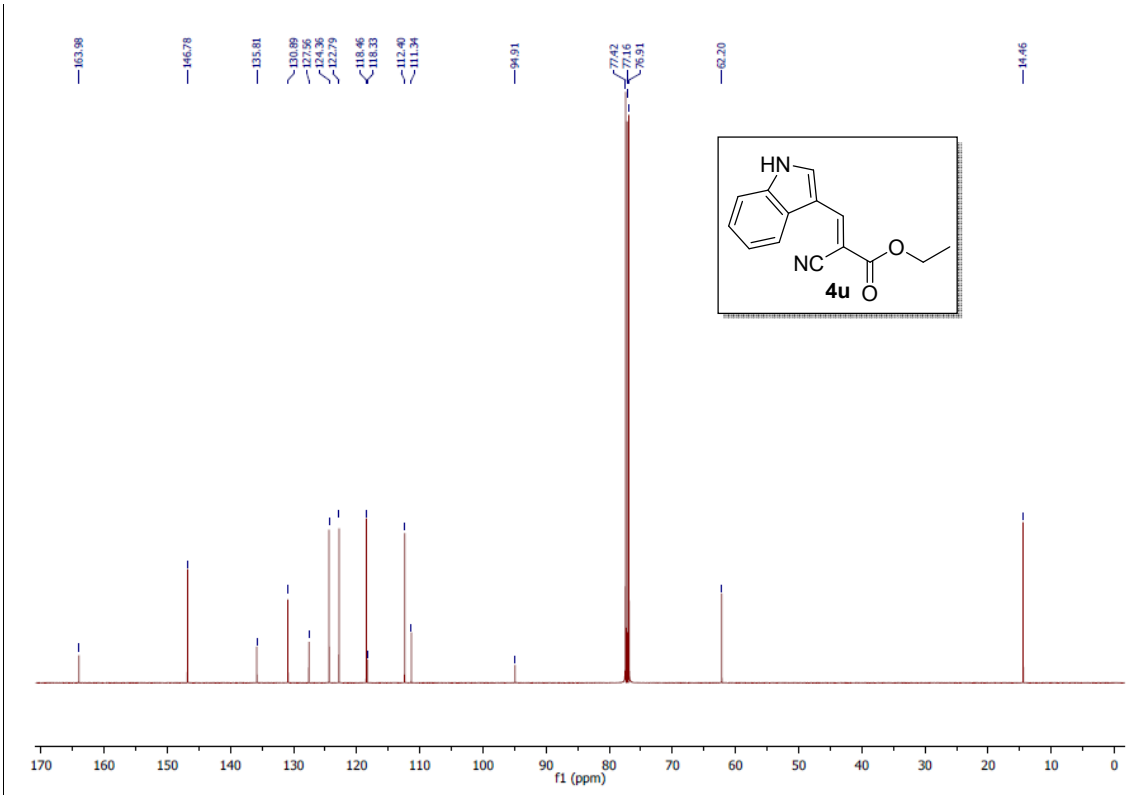


Figure 43: ^{13}CNMR spectrum of **4u** ($CDCl_3$, 125 MHz)

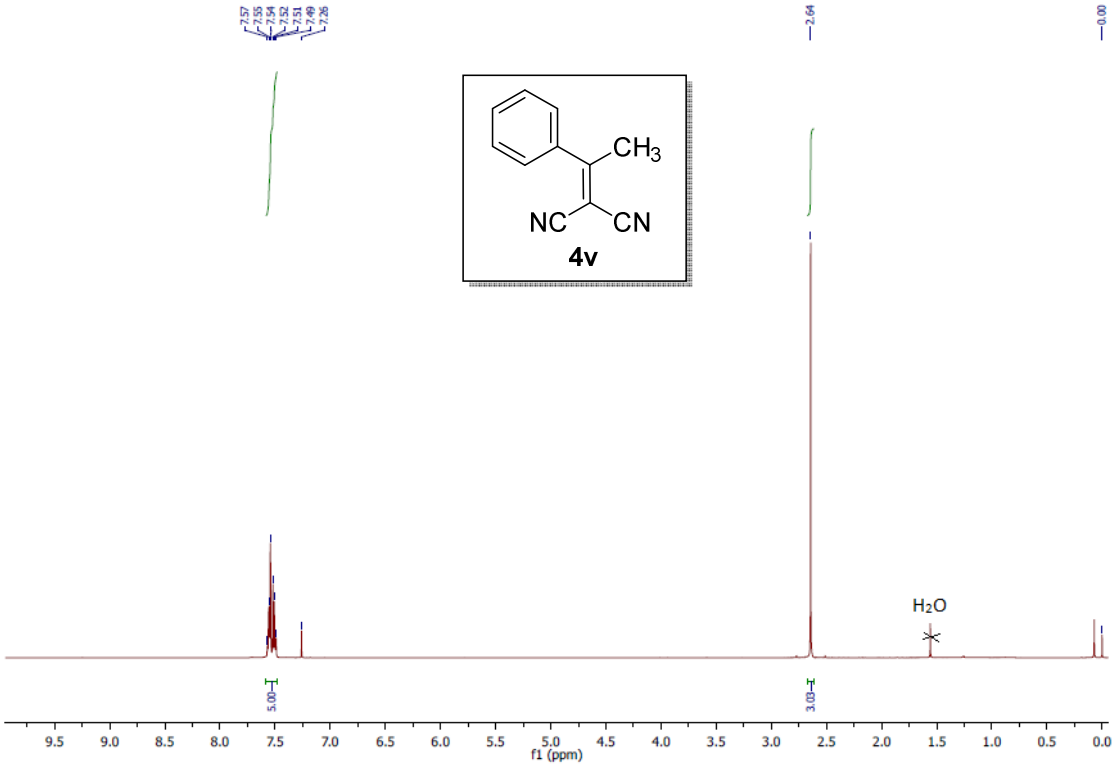


Figure 44: ^{1}H NMR spectrum of **4v** ($CDCl_3$, 500 MHz)

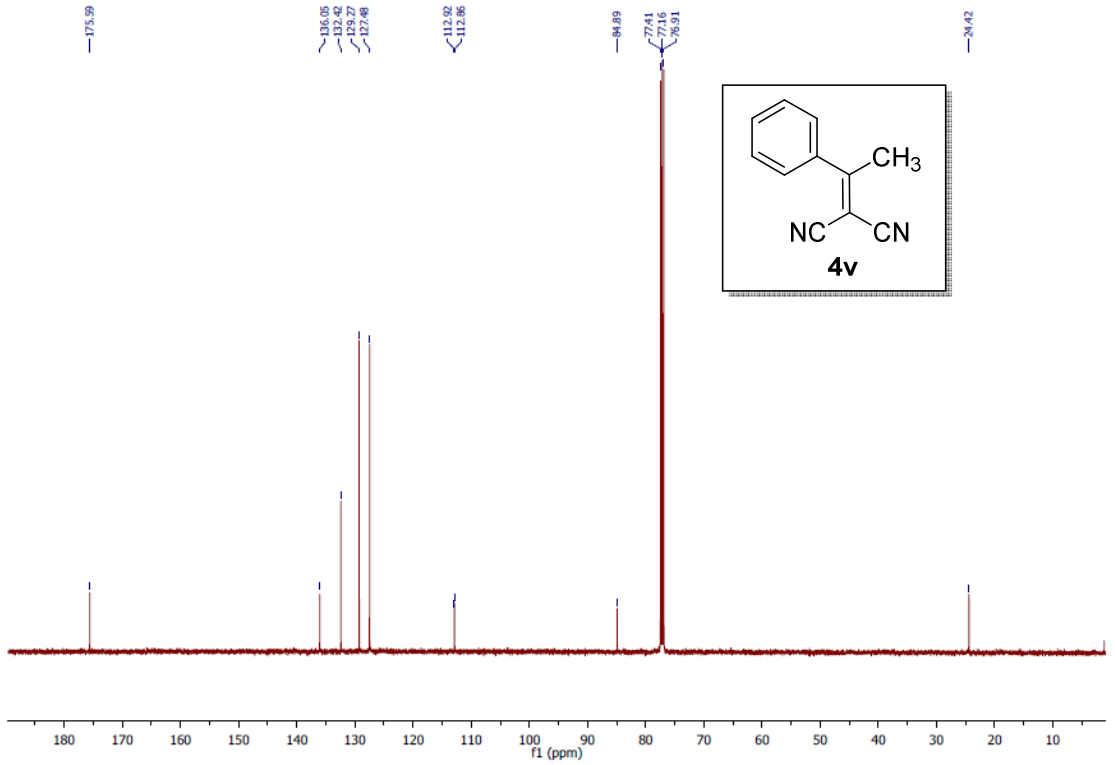


Figure 45: ^{13}C NMR spectrum of **4v** ($CDCl_3$, 125 MHz)

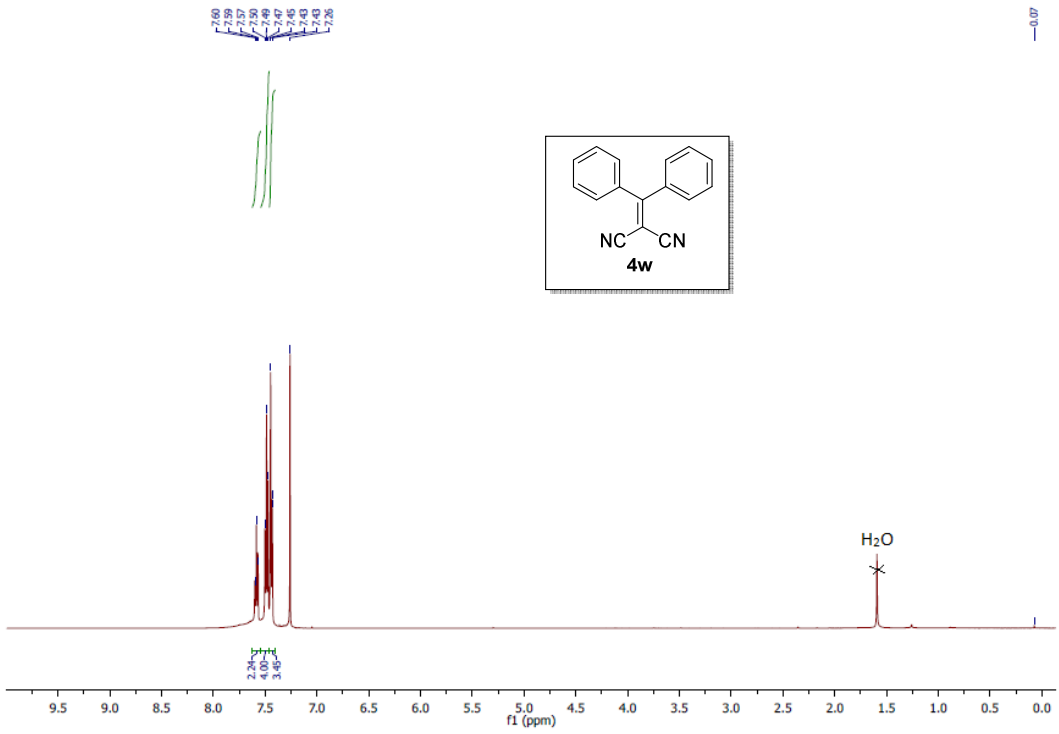


Figure 46: ^{1}H NMR spectrum of **4w** ($CDCl_3$, 500 MHz)

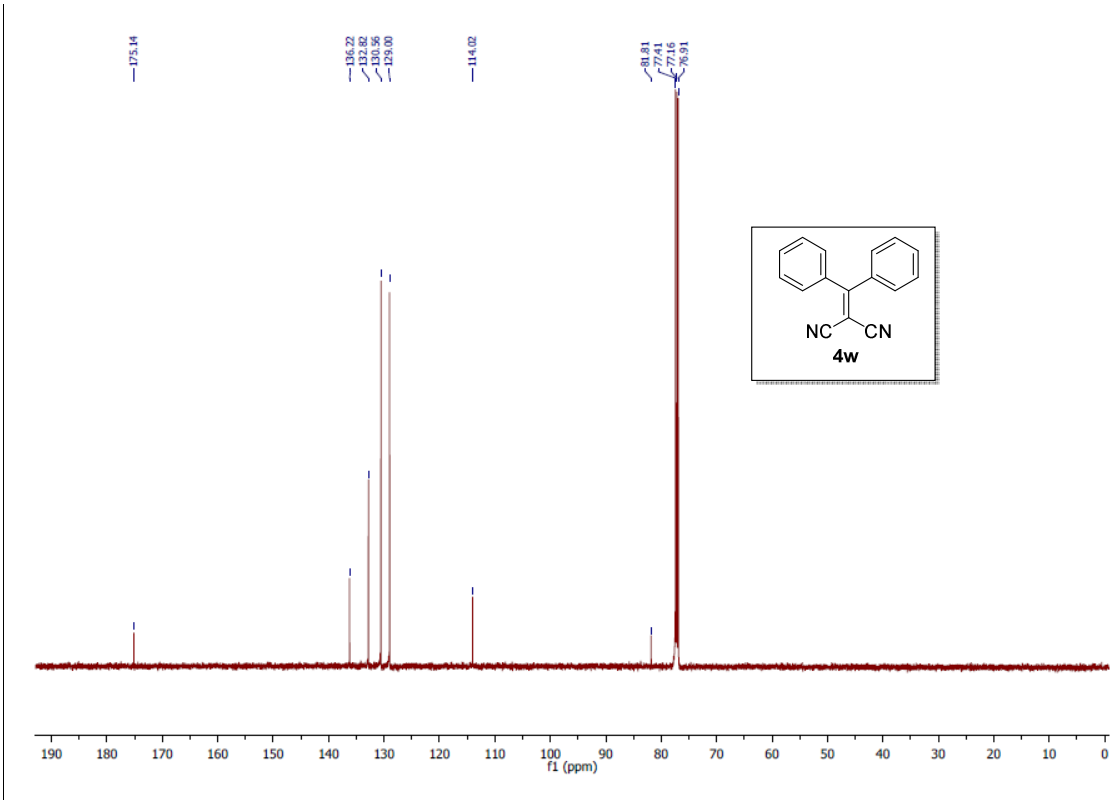


Figure 47: ^{13}C NMR spectrum of **4w** ($CDCl_3$, 125 MHz)

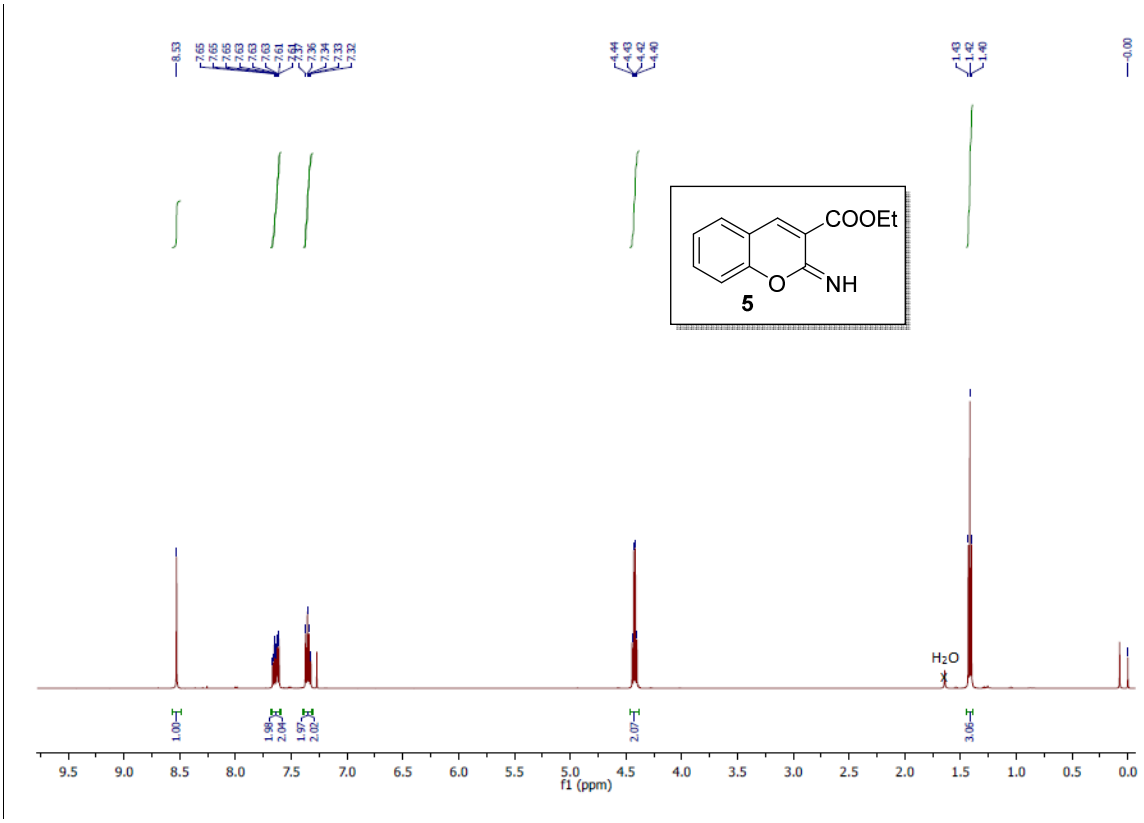


Figure 48: ^{1}H NMR spectrum of **5** ($CDCl_3$, 500 MHz)

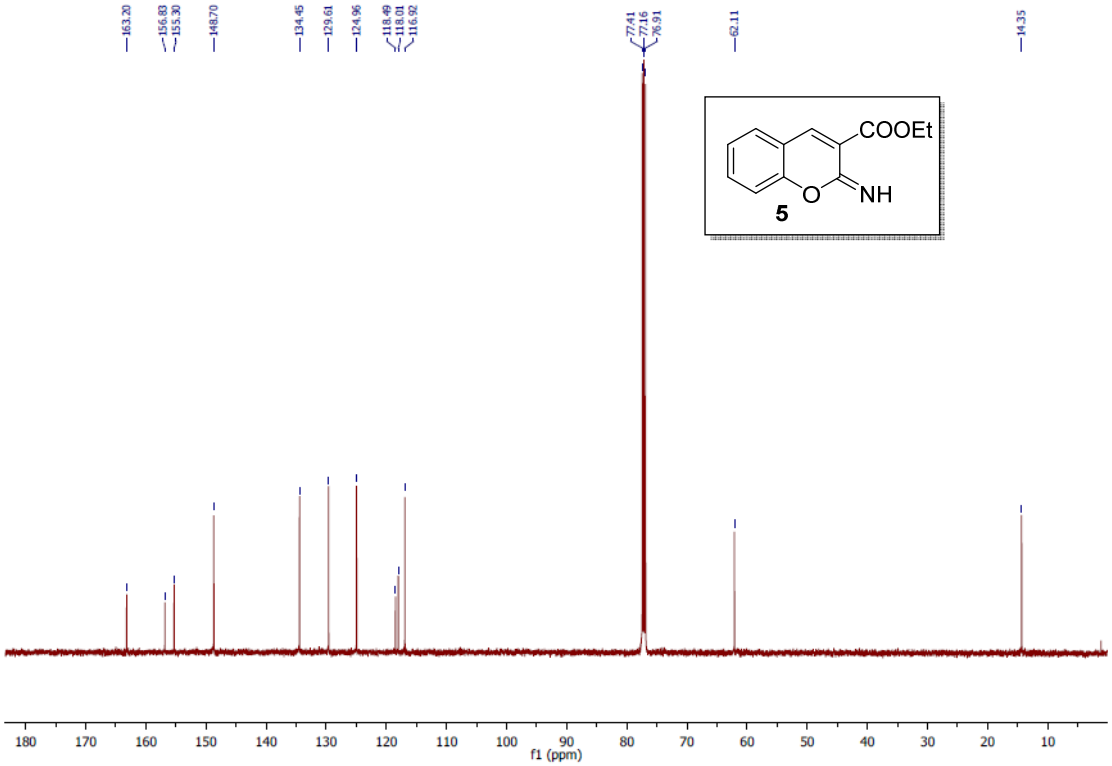


Figure 49: ^{13}C NMR spectrum of **5** ($CDCl_3$, 125 MHz)

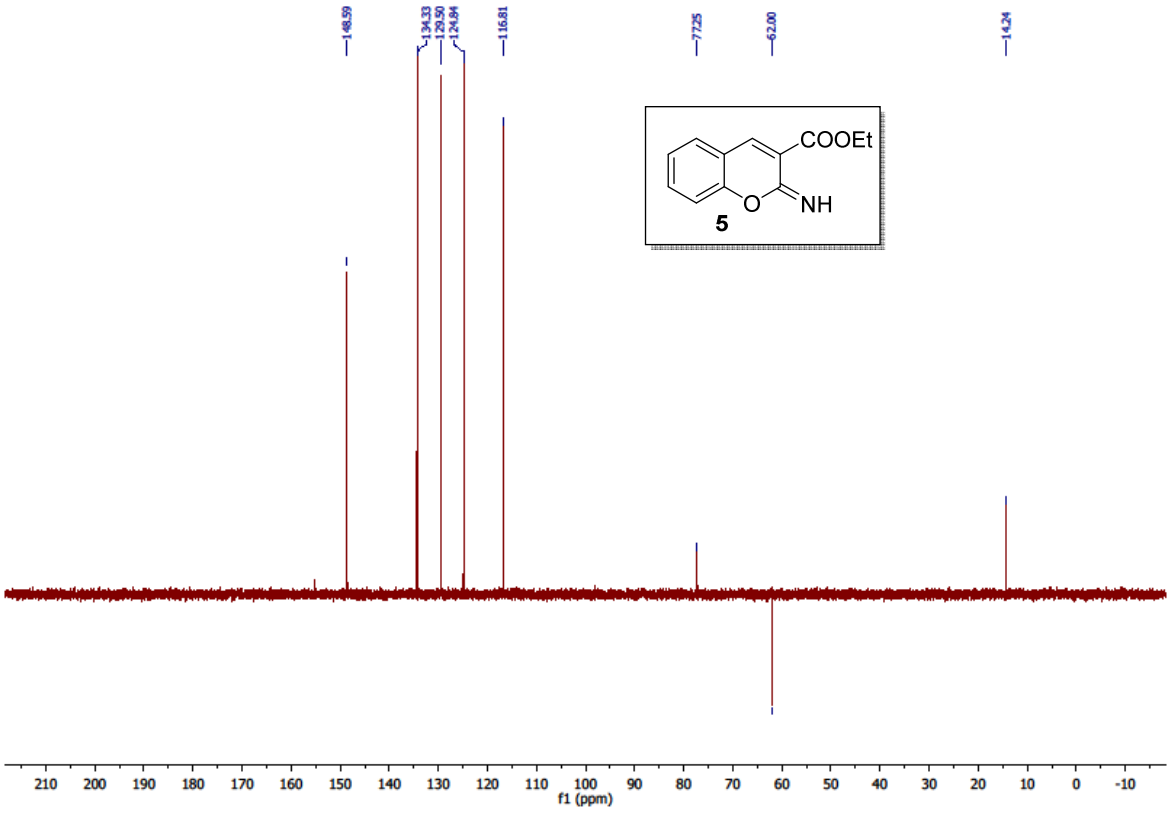


Figure 50: DEPT-135 spectrum of **5** ($CDCl_3$, 125 MHz)

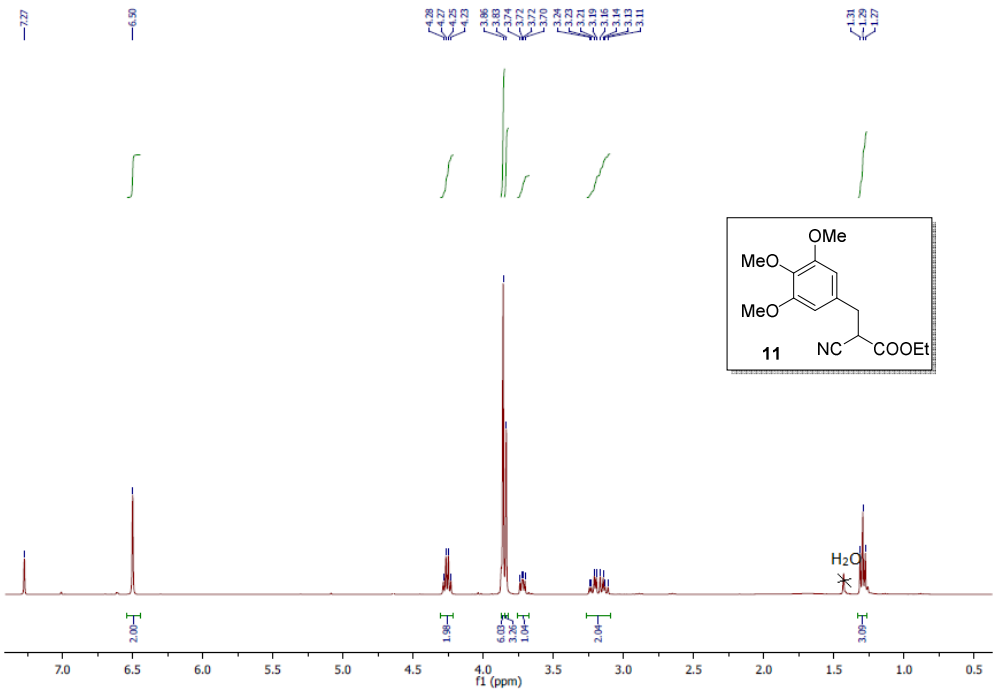


Figure 51: ^{1}H NMR spectrum of **11** ($CDCl_3$, 400 MHz)

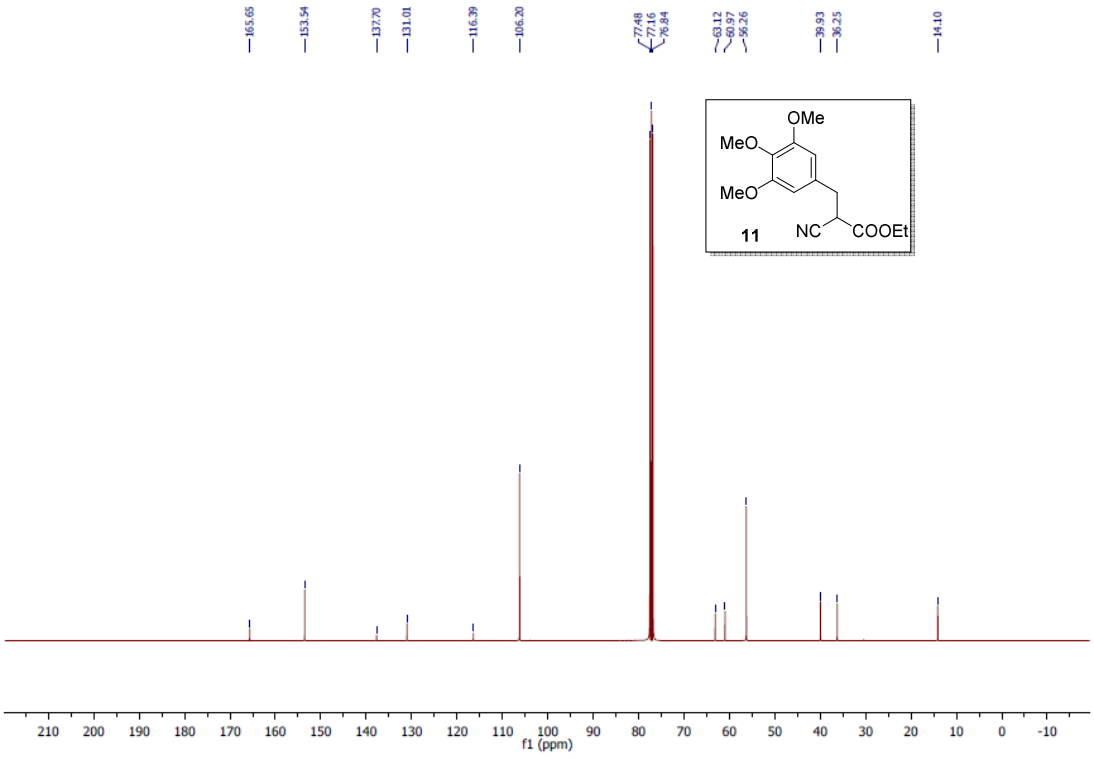


Figure 52: ^{13}C NMR spectrum of **11** ($CDCl_3$, 100 MHz)

10. GC-MS Spectra

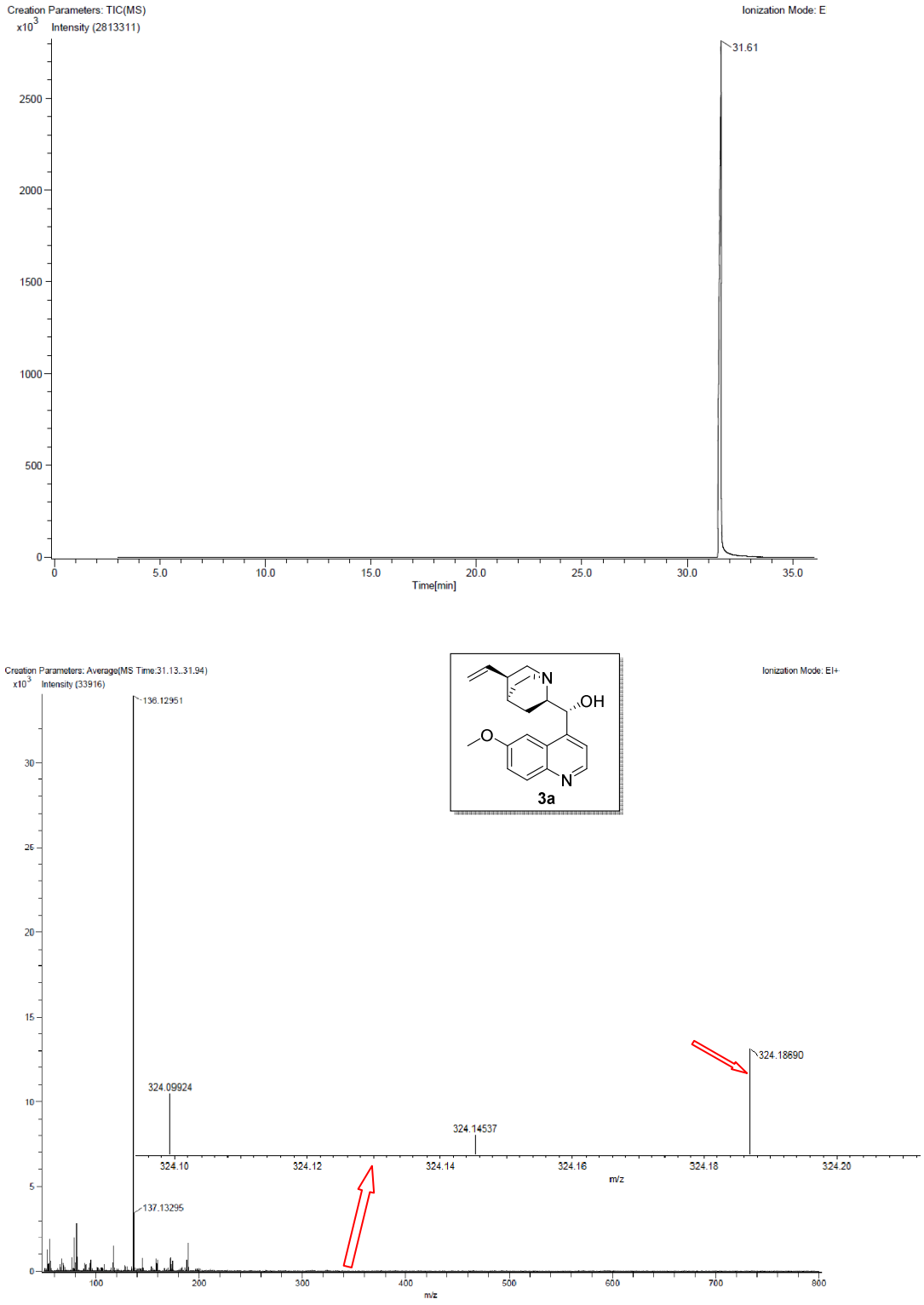


Figure 53. GC-MS spectrum of pure quinine **3a**

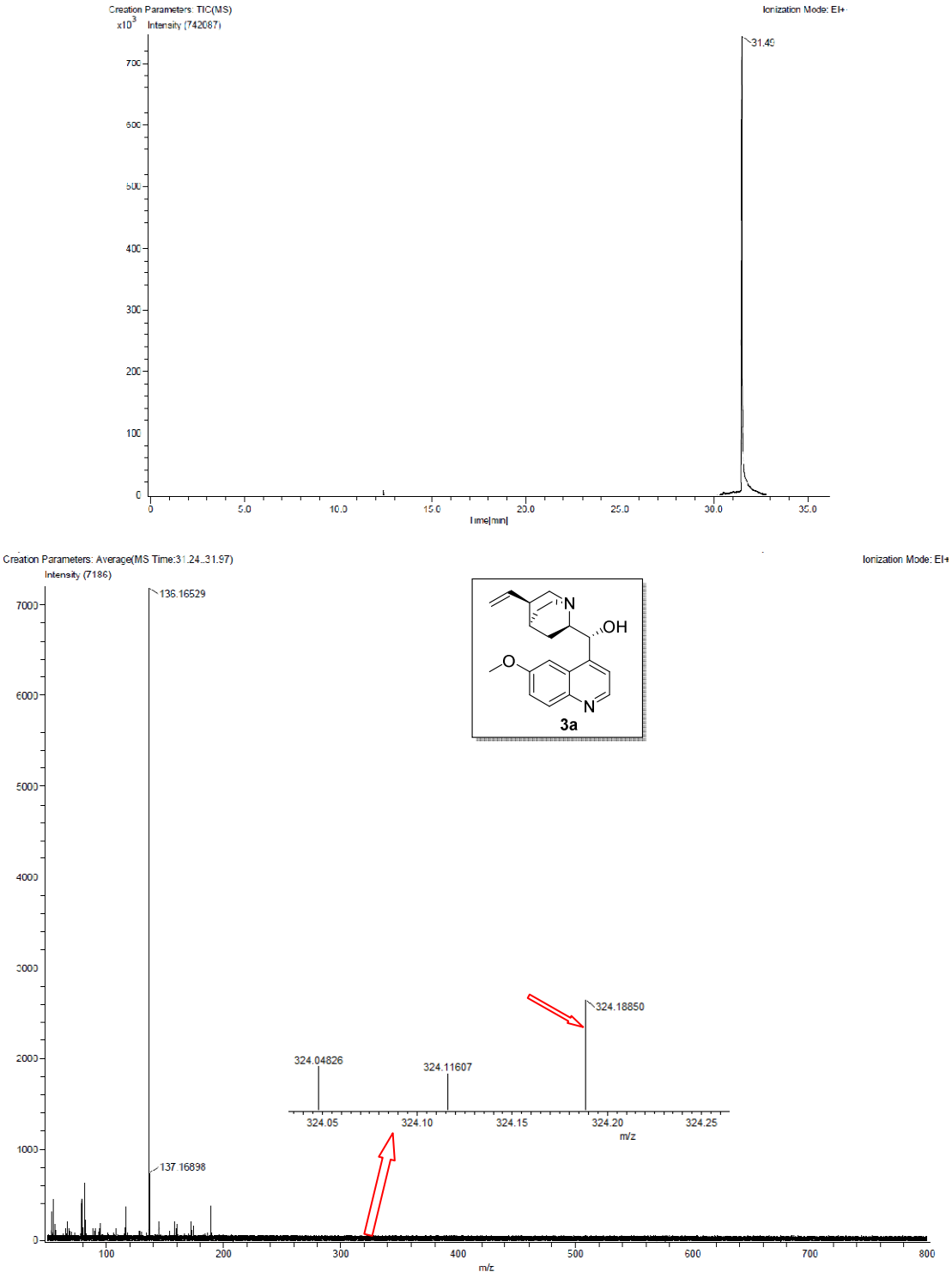


Figure 54. GC-MS spectrum of recovered quinine **3a**