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Improved Knoevenagel Condensation Protocol for the Synthesis of Cyanoacrylates and their Anticancer Activity

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Supplementary Information

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Experimental

Materials and methods

All the reagents and solvents used in the synthesis are laboratory grade. The purity of the compounds was checked by TLC (silica gel 60 F254), which were purchased from merck Inc and visualized under UV light. Melting points are analyzed for all synthesized analogues were determined by open tube capillary tube by using Meltemp equipment. The mass spectrums were obtained on Agilent (1100 series) instrument. The Perkin Elmer FT-IR spectrometer was used for IR spectra.

^{1}HNMR &^{13}CNMR were recorded with BRUKER-400 MHz spectrometer using $CDCl_3$/DMSO solvent. All the chemical shifts were reported in δ (ppm), using tetramethylsilane (TMS) as internal standard. Multiplicities are recorded by the following abbreviation: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs broad singlet; bd, broad doublet; J, coupling constant (hertz).

General procedure for synthesis of Cyano acrylate derivatives

Diisopropylethylammonium acetate (0.1 mmol) was added to a mixture of aromatic aldehydes **1a-1l** (1 mmol), ethylcyanoacetoacetate **2** (1 mmol) in hexane (10 ml) and heated at 65-70 °C. After 3-6 hours, the progress of reaction was monitored by TLC (hexane:Ethylacteate, 8:2). After completion of the reaction, was cooled to 40-45 °C. Separated the layers and bottom (product) layer was concentrated under vacuum, resulting material was purified by suitable solvents to give desired products are given below (**3a-3l)**.

Ethyl-2-cyano-3-phenylacrylate (3a). [1] solid (91 %) mp 48-51 °C; IR (KBr) Cm^{-1}: 2982, 2220, 1716, 1600, 1440; ^{1}HNMR (400 MHz, $CDCl_3$): δ1.41 (t, *J*= 7.4 Hz, 3H), 4.36-4.41 (q, *J* = 7.4 Hz, 2H), 7.50-7.60 (m, 3H), 8.02 (d, *J*= 7.4 Hz, 2H), 8.40 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ14.2, 62.8, 103.0, 115.5, 130.1, 131.1, 131.5, 133.4, 155.1, 162.5.Anal Calc for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96 %; found:C, 71.59; H, 5.48 ; N, 6.84 %.

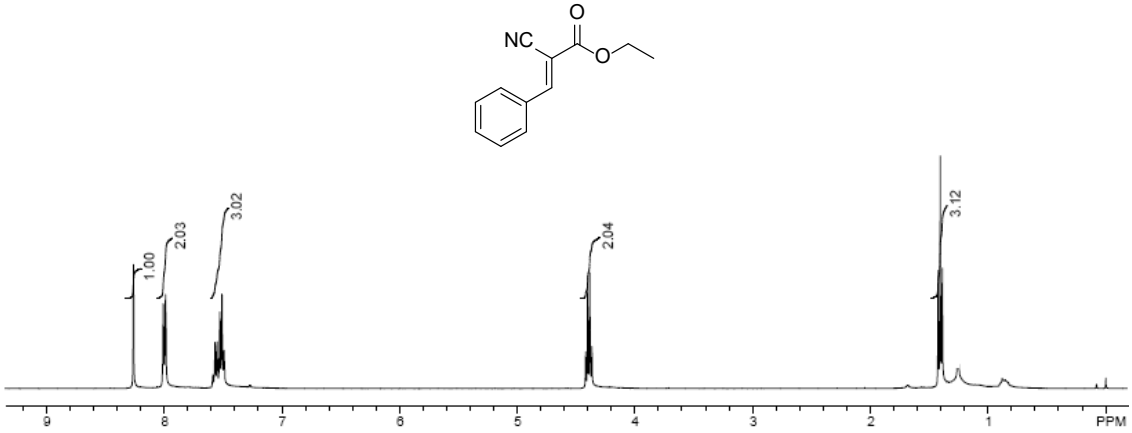

Fig. S1. ^{1}HNMR of compound **3a**.

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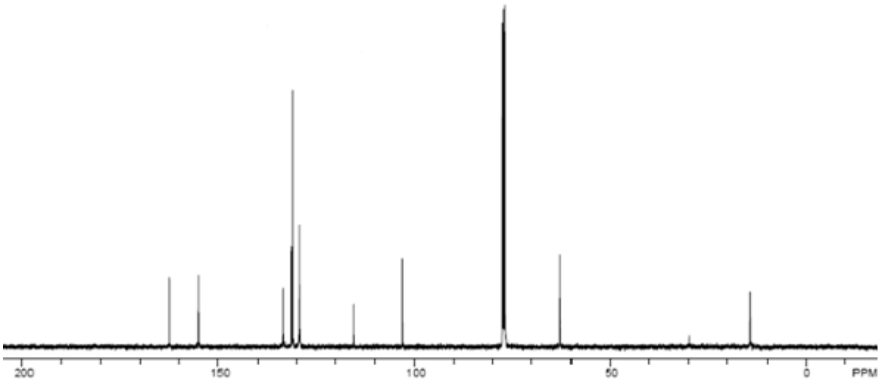

Fig. S2. ^{13}CNMR of compound **3a**.

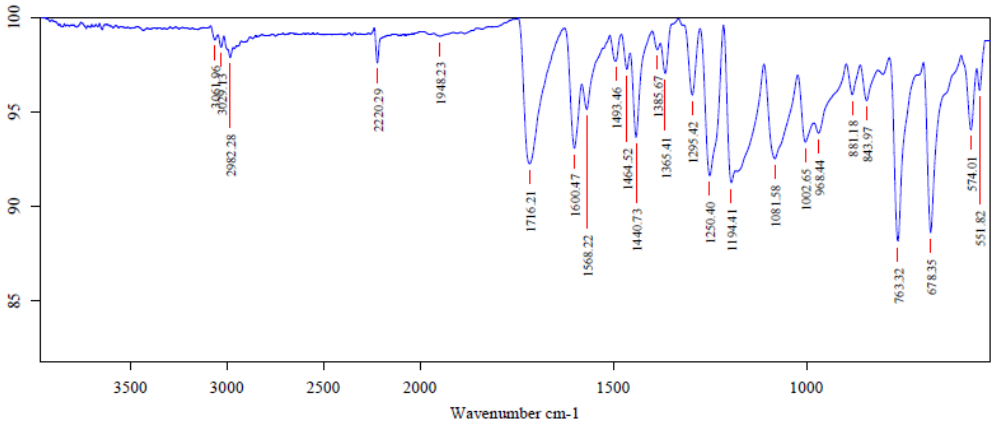

Fig. S3. IR Spectrum of compound **3a**.

Ethyl-2-cyano-3-(2-nitrophenyl)acrylate (3b). [3] solid (90 %) mp 119-123 ºC; IR (KBr) Cm^{-1}: 2986, 2218, 1718, 1582, 1485; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.42 (t, *J*= 7.4 Hz, 3H), 4.39-4.45 (q, *J* = 7.4 Hz, 2H), 7.70-7.74 (m, 1H), 7.80-7.87 (m, 2H), 8.28 (d, *J*= 7.4 Hz, 2H), 8.72 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.1, 63.1, 106.7, 113.7, 125.3, 128.1, 130.5, 132.1, 134.4, 147.3, 152.9, 161.0;Anal Calc for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38 %; found:C, 58.50; H, 3.99; N, 11.32 %.

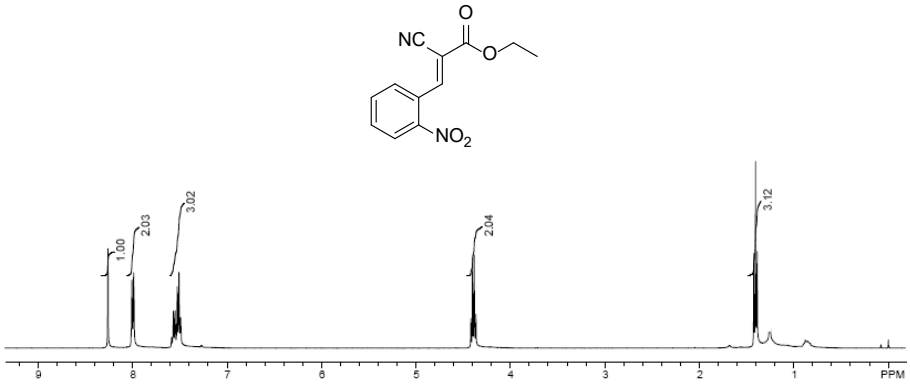

Fig. S4. ^{1}HNMR of compound **3b**.

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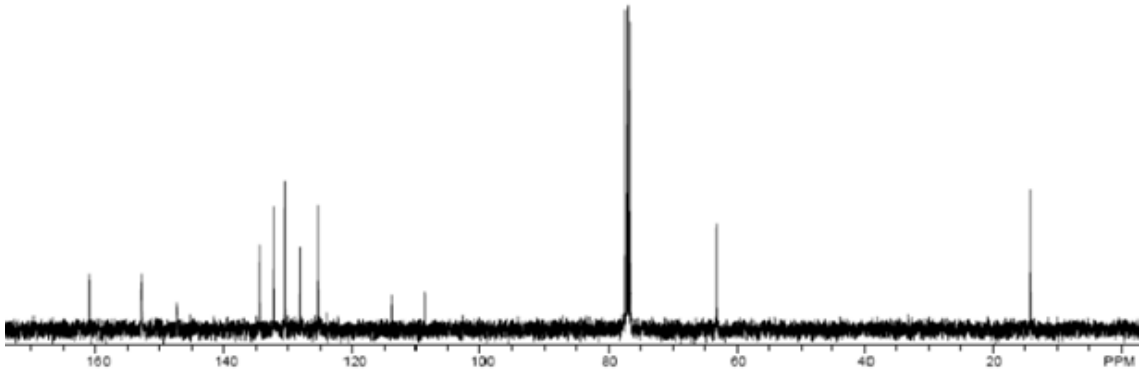

Fig. S5. ^{13}CNMR of compound **3b**.

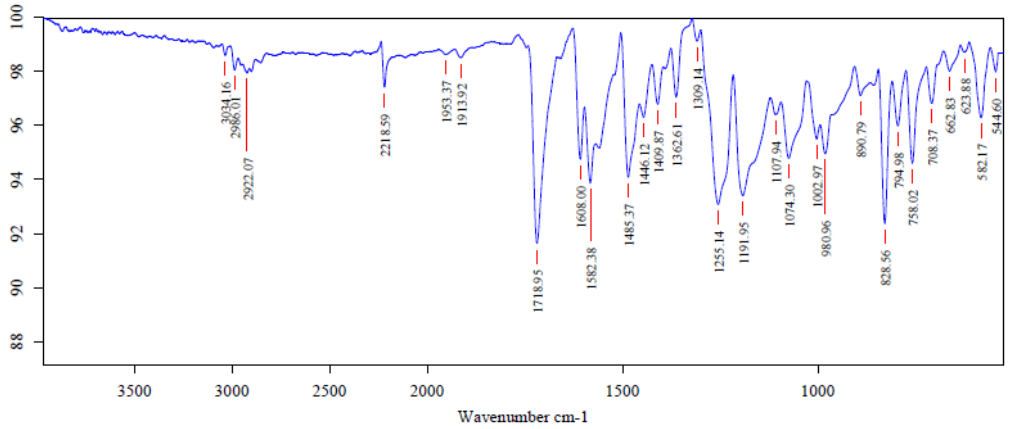

Fig. S6. IR Spectrum of compound **3b**.

Ethyl-2-cyano-3-(3-nitrophenyl)acrylate (3c). [3] solid (91 %) mp 129-132 ºC; IR (KBr) Cm^{-1}: 2929, 2252, 1738, 1600, 727; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.42 (t, *J*= 7.4 Hz, 3H), 4.40-4.45 (m, 2H), 7.72-7.76 (m, 1H), 8.32 (s, 1H), 8.39-8.42 (m, 2H), 8.70 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ= 13.5, 62.7, 106.3, 113.9, 125.3, 126.4, 130.0, 132.5, 134.6, 148.2, 151.2, 160.9;Anal Calc for $C_{12}H_{10}N_2O_4$: C,58.54; H,4.09; N,11.38 %; found:C, 58.51 ; H, 4.01; N, 11.29 %.

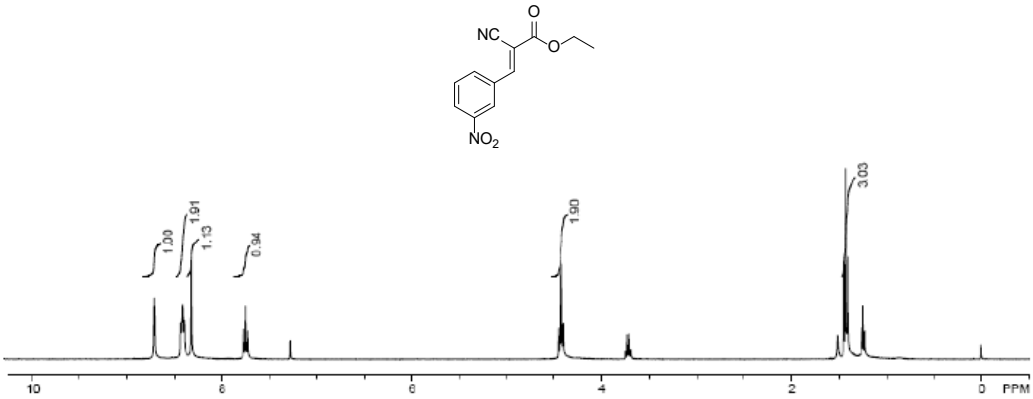

Fig. S7. ^{1}HNMR of compound **3c**.

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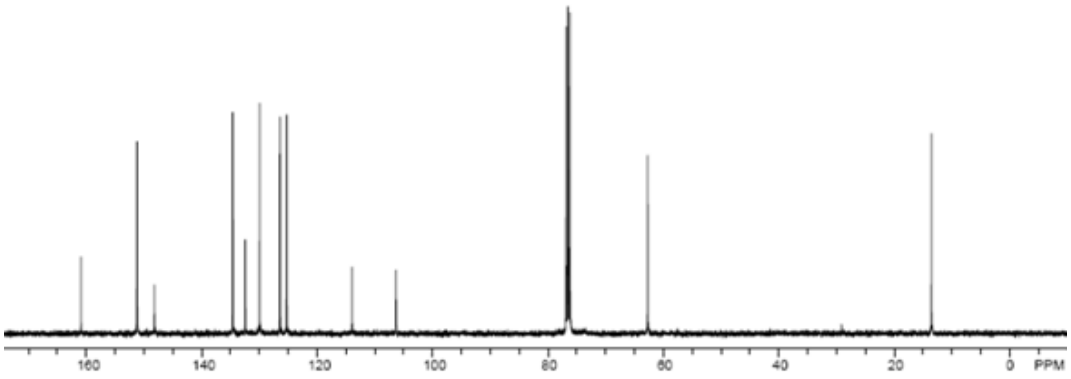


Fig. S8. ^{13}CNMR of compound **3c**.

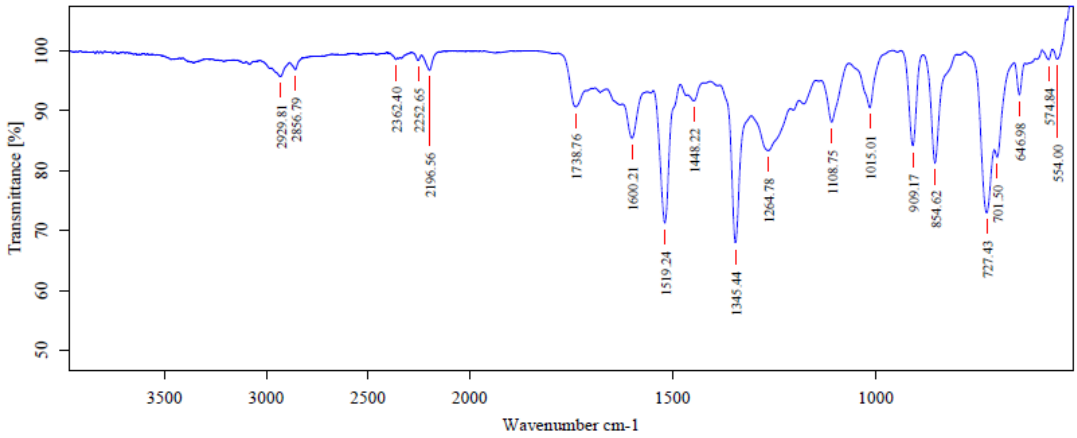
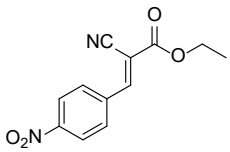


Fig. S9. IR Spectrum of compound **3c**.

Ethyl-2-cyano-3-(4-nitrophenyl)acrylate (3d). [3] solid (93 %) mp 161-165 ºC; IR (KBr) Cm^{-1}: 2856, 2196, 1738, 1519, 854; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.32 (t, *J*= 7.2 Hz, 3H), 4.32-4.38 (m, 2H), 8.23-8.26 (m, 2H), 8.42-8.40 (m, 2H), 8.56 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.4, 63.2, 107.1, 115.4, 124.6, 132.1, 137.7, 149.7, 153.1, 161.6; Anal Calc for $C_{12}H_{10}N_2O_4$: C,58.54; H,4.09, ; N,11.38 %; found:C, 58.48; H, 4.03; N, 11.35 %.



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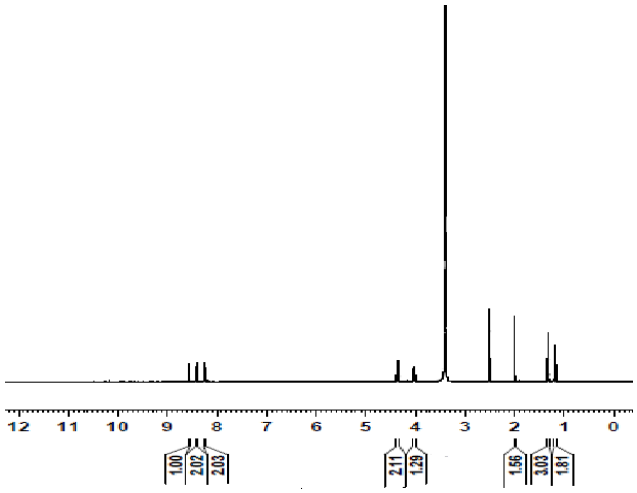

Fig. S10. [1]HNMR of compound **3d**.

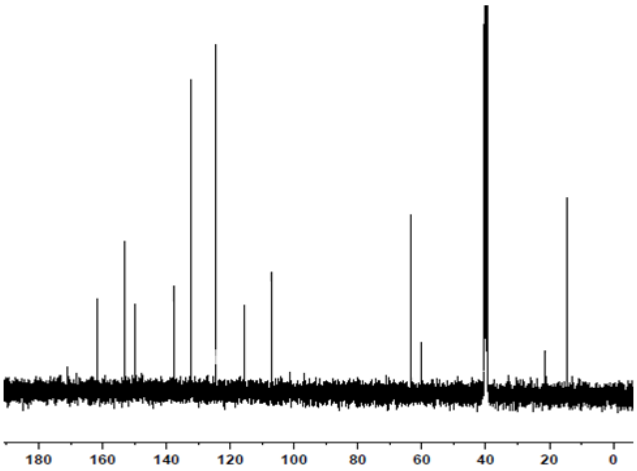

Fig. S11. [13]CNMR of compound **3d**.

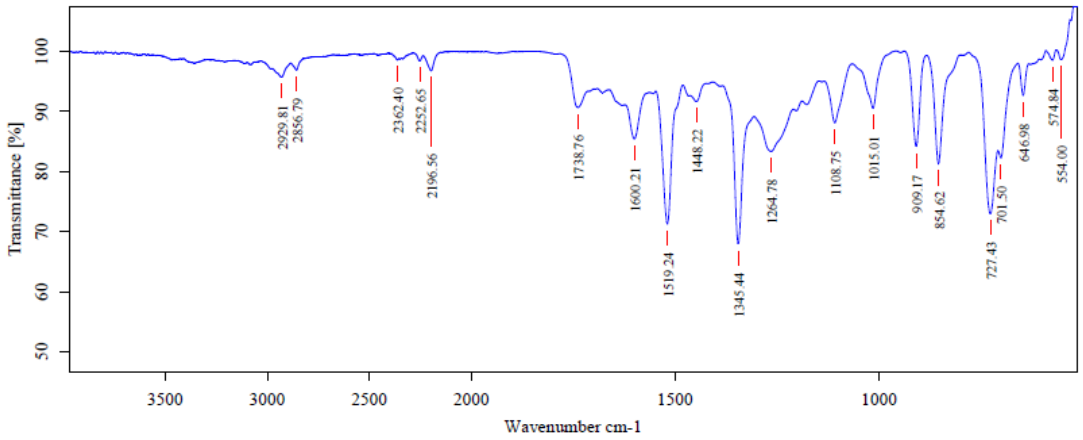

Fig. S12. IR Spectrum of compound **3d**.

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Ethyl-2-cyano-3-(2-Chlorophenyl)acrylate (3e). [1,2] solid (88 %) mp 45-48 °C; IR (KBr) Cm^{-1}: 2981, 1716, 1688, 1441, 755; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.41 (t, *J*= 7.2 Hz, 3H), 4.38-4.43 (m, 2H), 7.41-7.51 (m, 3H), 8.22-8.24 (m, 1H), 8.68 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.0, 62.9, 106.1, 114.8, 127.4, 129.8, 130.3, 136.4, 151.2, 161.8; Anal Calc for $C_{12}H_{10}ClNO_2$: C,61.16; H,4.28, ; N,5.94 %; found:C, 61.09 ; H, 4.23; N, 5.89 %.

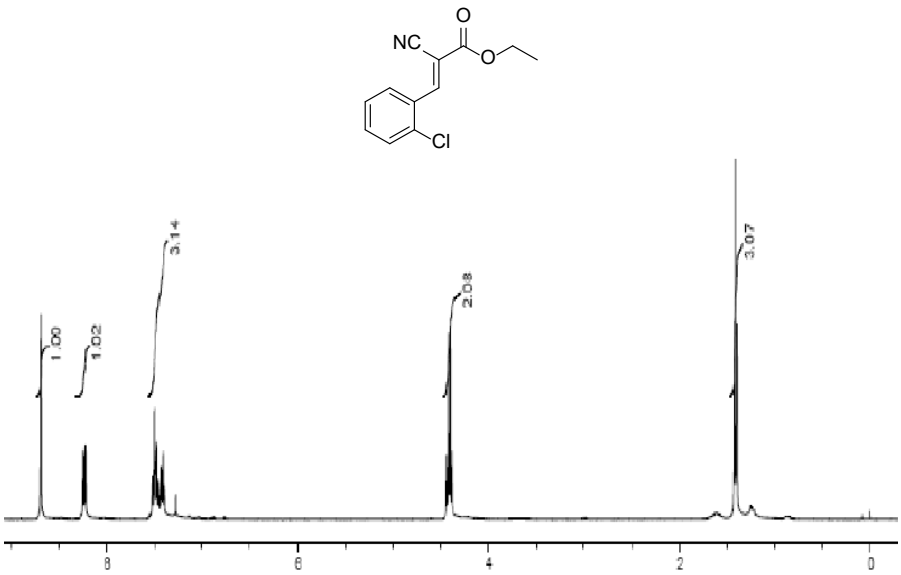

Fig. S13. ^{1}HNMR of compound **3e**.

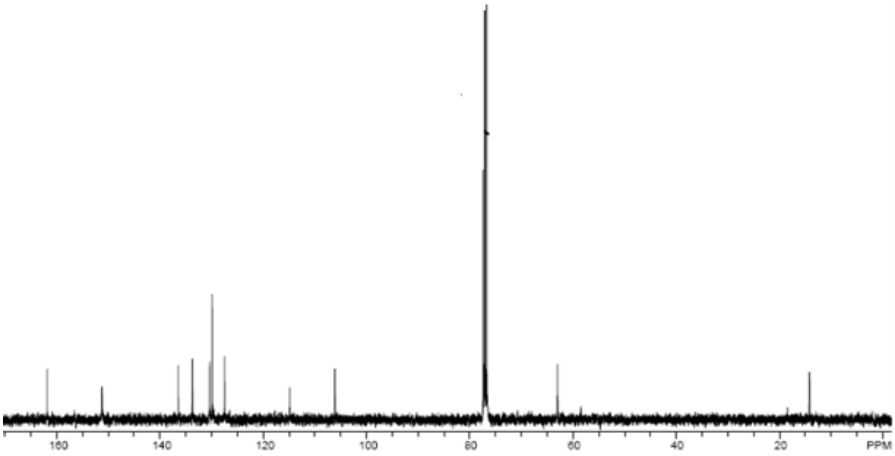

Fig. S14. ^{13}CNMR of compound **3e**.

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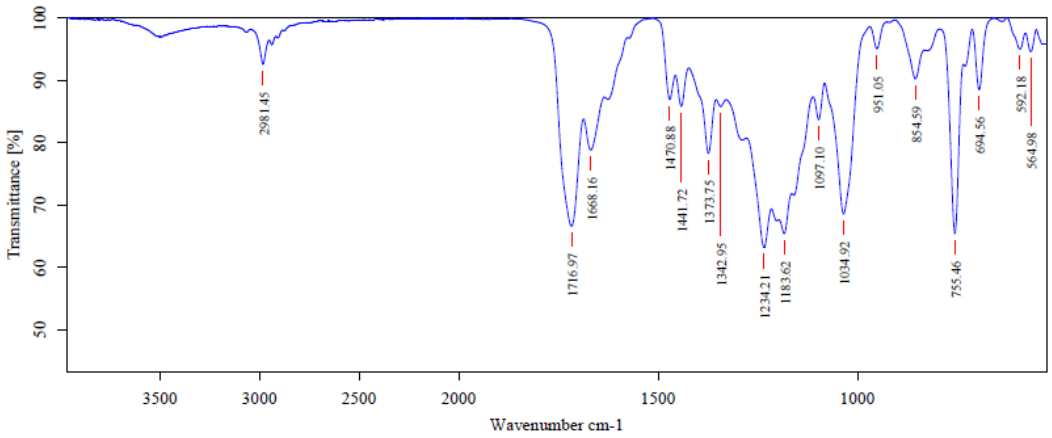

Fig. S15. IR Spectrum of compound **3e**.

Ethyl-2-cyano-3-(4-Chlorophenyl)acrylate (3f). [1] solid (94 %) mp 88-90 ºC; IR (KBr) Cm^{-1}: 2986, 2218, 1718, 1582, 1485, 828; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.40 (t, *J*= 7.2 Hz, 3H), 4.36-4.41 (m, 2H), 7.48(d, *J*= 7.2 Hz, 2H), 7.93 (d, *J*= 7.2 Hz, 2H), 8.19 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.1, 62.8, 103.5, 115.2, 129.6, 129.9, 139.5, 153.3, 162.1; Anal Calc for $C_{12}H_{10}ClNO_2$: C,61.16; H,4.28, ; N,5.94 %; found:C, 61.08; H, 4.19; N, 5.87 %.

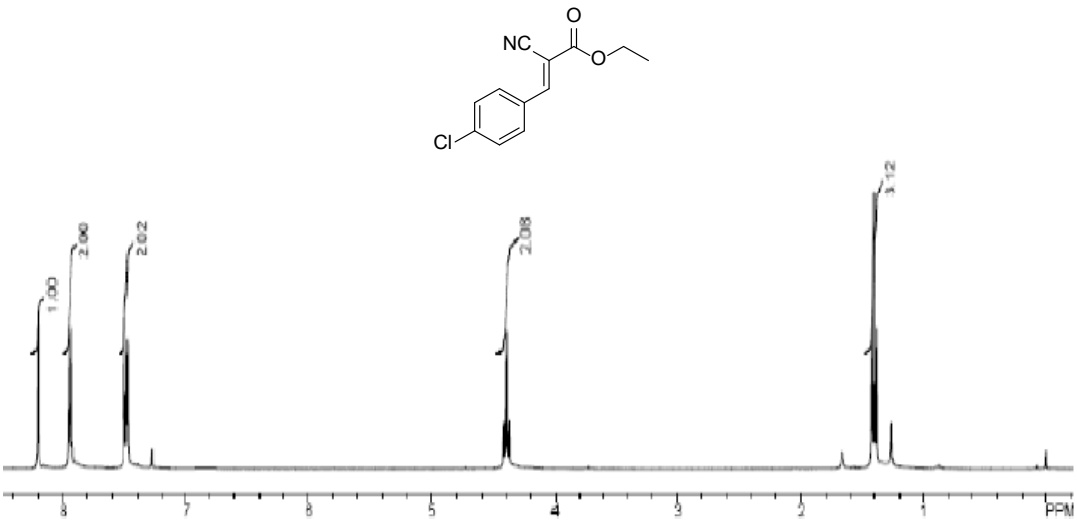

Fig. S16. ^{1}HNMR of compound **3f**.

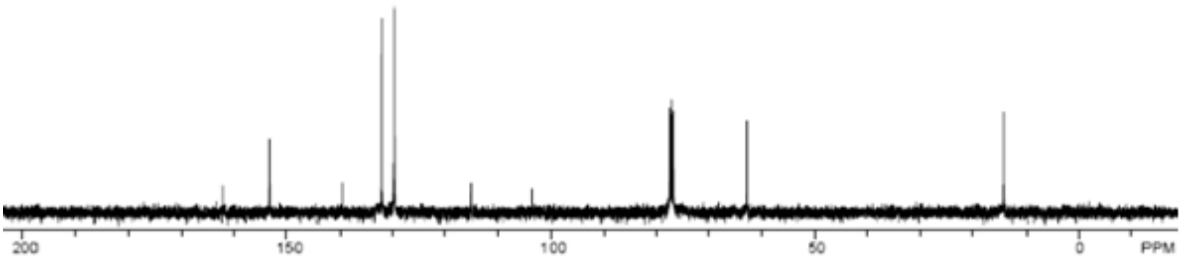

Fig. S17. ^{13}CNMR of compound **3f**.

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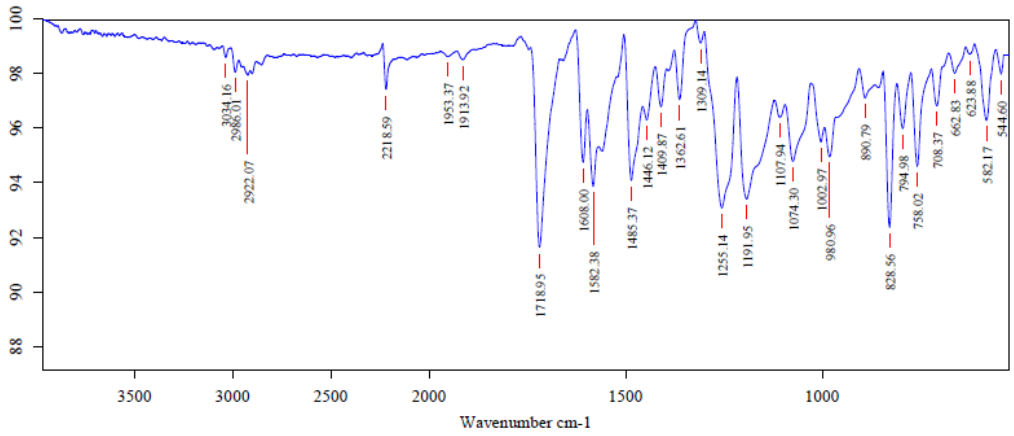

Fig. S18. IR Spectrum of compound **3f**.

Ethyl-2-cyano-3-(4-methoxyphenyl)acrylate (3g). [1,2] solid (96 %) mp 77-80 ºC; IR (KBr) Cm^{-1}: 2988, 2213, 1712, 1583, 1177; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.37 (t, *J*= 7.2 Hz, 3H), 3.87 (s, 3H), 4.32-4.37 (m, 2H), 6.97 (d, *J*= 7.2 Hz, 2H), 7.98 (d, *J*= 7.2 Hz, 2H), 8.15 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.1, 55.8, 62.4, 99.4, 114.7, 116.2, 124.3, 133.6, 154.3, 163.1, 163.7; Anal Calc for $C_{13}H_{13}NO_3$: C,67.52; H,5.67 ; N,6.06 %; found:C, 67.49; H, 5.61; N, 6.03 %.

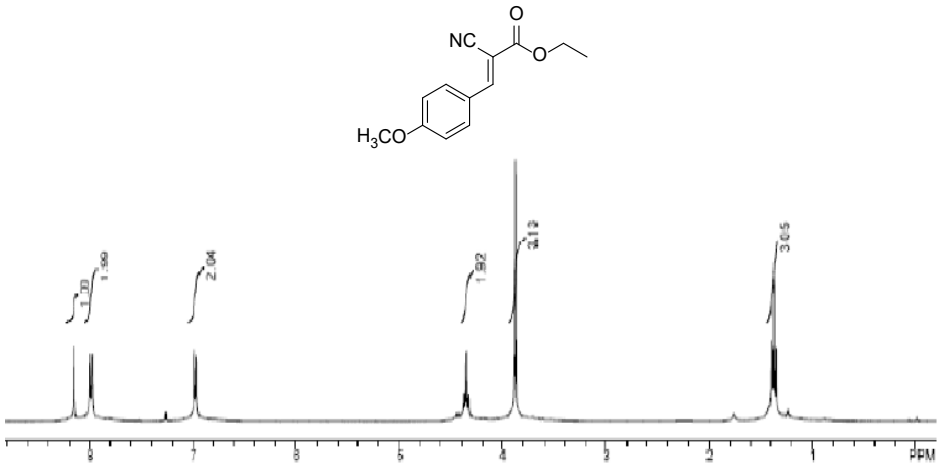

Fig. S19. ^{1}HNMR of compound **3g**.

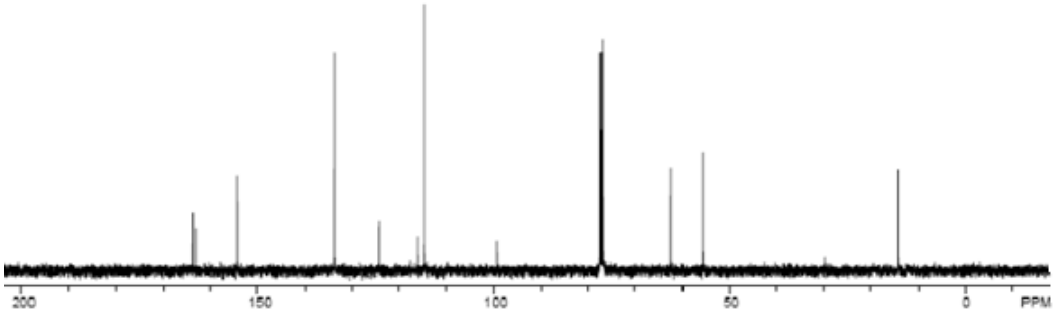

Fig. S20. ^{13}CNMR of compound **3g**.

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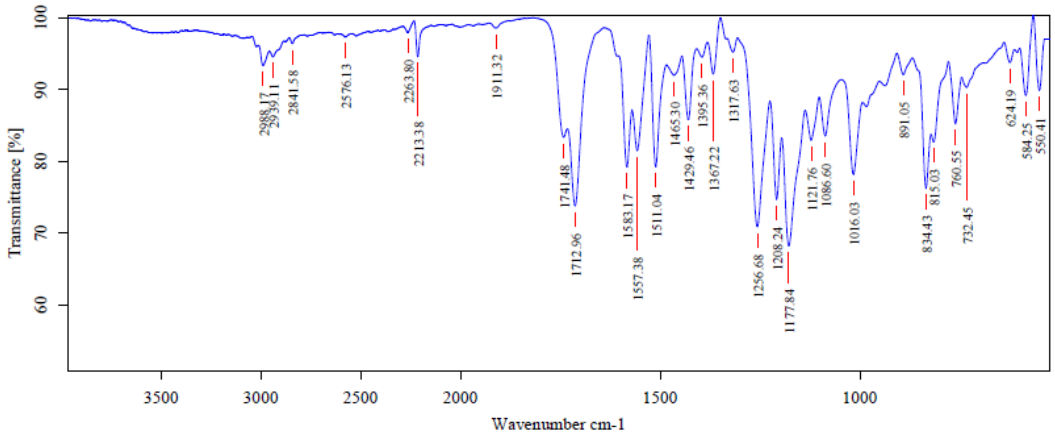

Fig. S21. IR Spectrum of compound **3g**.

Ethyl-2-cyano-3-(4-benzyloxyphenyl)acrylate (3h). [5] solid (93 %) mp 146-149 ºC; IR (KBr) Cm^{-1}: 2922, 2218, 1714, 1586, 1177, 903; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.33 (t, *J*= 8.0 Hz, 3H), 4.34-4.39 (m, 2H), 5.15 (s, 2H), 7.04-7.08 (m, 2H), 7.34-7.45 (m, 5H), 8.01 (d, *J*= 4.0 Hz, 2H), 8.17 (s, 1H);^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.1, 62.4, 70.3, 99.4, 115.5, 116.1, 124.5, 127.4, 128.3, 128.7, 133.6, 135.7, 154.3, 162.8; Anal Calc for $C_{19}H_{17}NO_3$: C,74.25; H,5.58 ; N,4.56 %; found:C, 74.18; H, 5.51; N, 4.53 %.

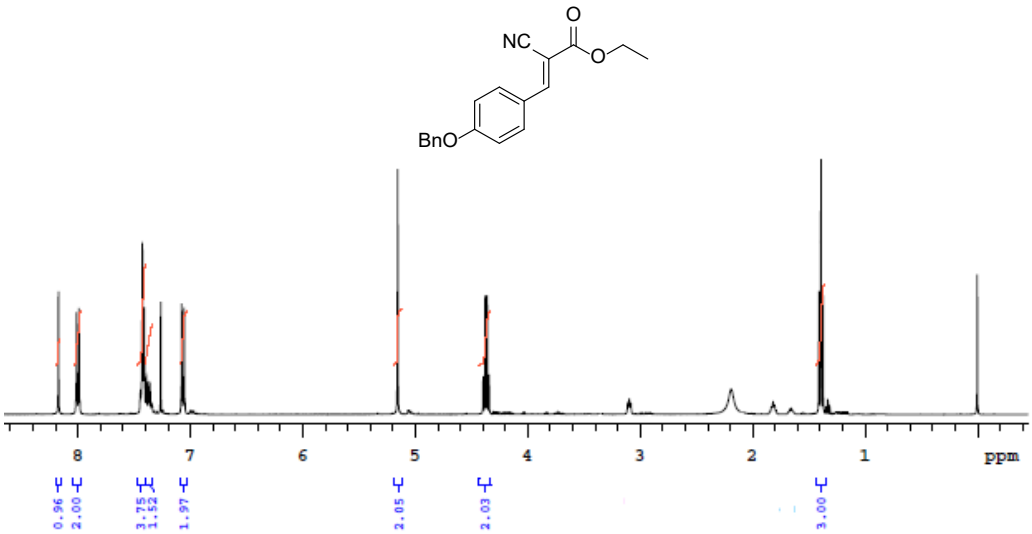

Fig. S22. ^{1}HNMR of compound **3h**.

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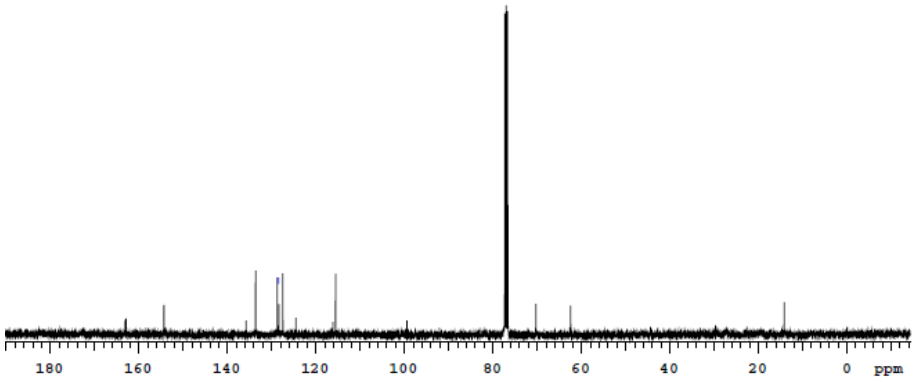


Fig. S23. ^{13}CNMR of compound **3h**.

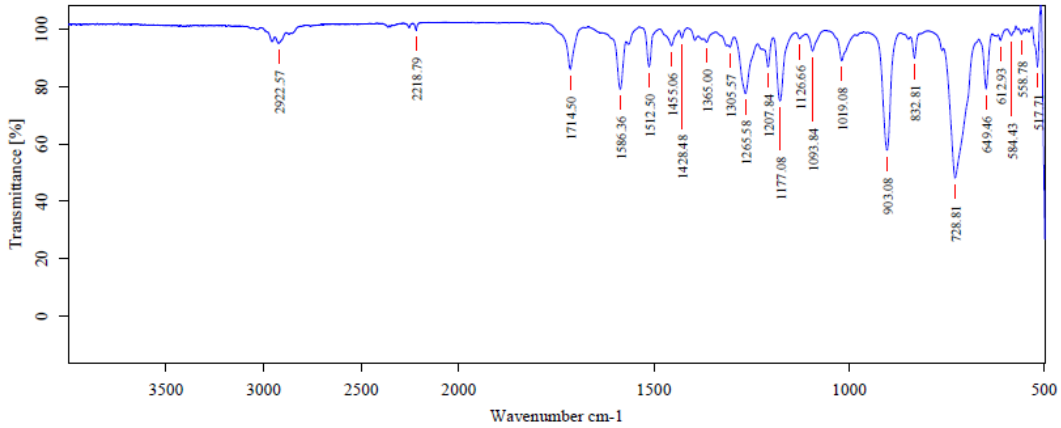
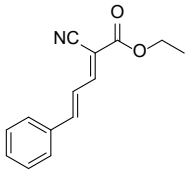


Fig. S24. IR Spectrum of compound **3h**.

(4*E*)-Ethyl-2-cyano-5-phenylpenta-2,4-dienoate (3i). [6] solid (96 %) mp 113-115 ºC; IR (KBr) Cm^{-1}: 2981, 2248, 1737, 1580, 1449, 1236; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.28 (t, *J*= 7.2 Hz, 3H), 4.24-4.30 (m, 2H), 7.18-7.25 (m, 1H), 7.46-7.48 (m, 3H), 7.69-7.72 (m, 3H), 8.17 (d, *J*= 7.2 Hz, 1H);^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.4, 62.4, 103.7, 115.0, 123.0, 129.1, 129.6, 131.7, 135.0, 150.5, 156.3, 162.2; Anal Calc for $C_{14}H_{13}NO_2$: C,73.99; H,5.77 ; N,6.16 %; found:C, 73.91; H, 5.63; N, 6.09 %.



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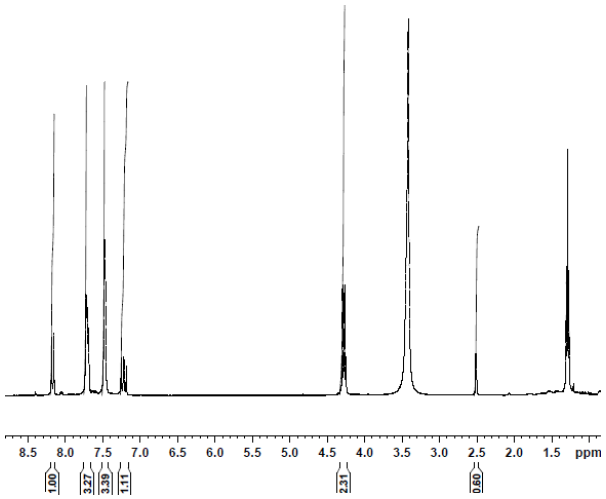

Fig. S25. [1]HNMR of compound **3i**.

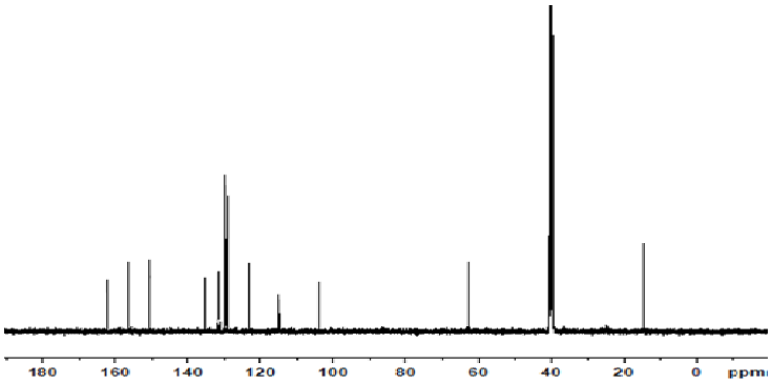

Fig. S26. [13]CNMR of compound **3i**.

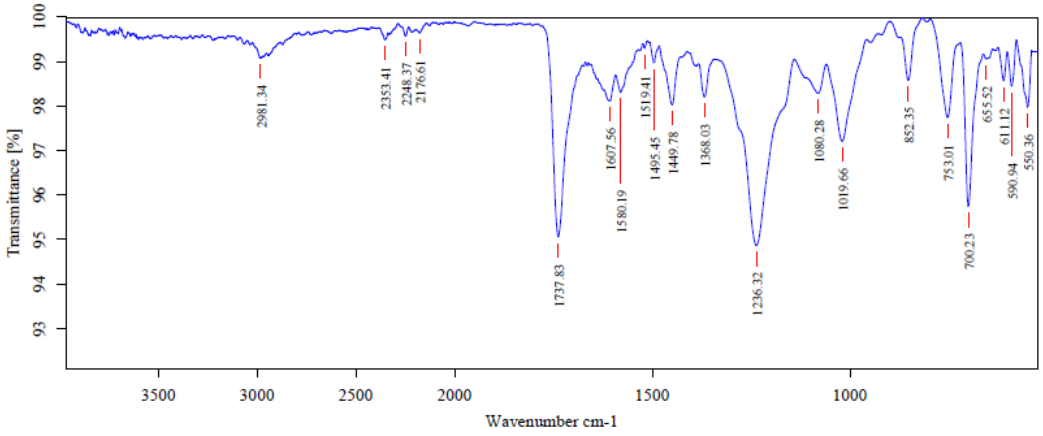

Fig. S27. IR Spectrum of compound **3i**.

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Ethyl-2-cyano-3-p-tolylacrylate (3j). [1, 2] solid (92 %) mp 88-92 ºC; IR (KBr) Cm^{-1}: 2983, 2251, 1742, 1600, 1445; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.39 (t, *J*= 7.4 Hz, 3H), 2.46 (s, 3H), 4.34-4.40 (m, 2H), 7.18-7.30 (d, *J*= 8.0 Hz, 1H), 7.86 (d, *J*= 8.0 Hz, 1H), 8.22 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$): δ= 13.8, 21.4, 62.0, 101.1, 115.3, 128.5, 129.5, 130.8, 144.2, 154.5, 162.3. Anal Calc for $C_{13}H_{13}NO_2$: C,72.54; H,6.09 ; N,6.51 %; found:C, 72.38; H, 6.04; N, 6.39 %.

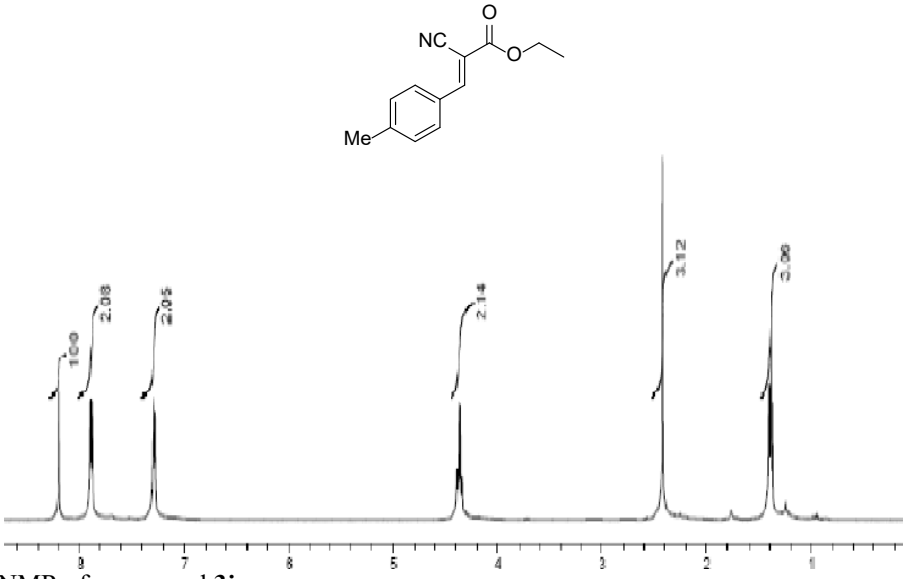

Fig. S28. ^{1}HNMR of compound **3j**.

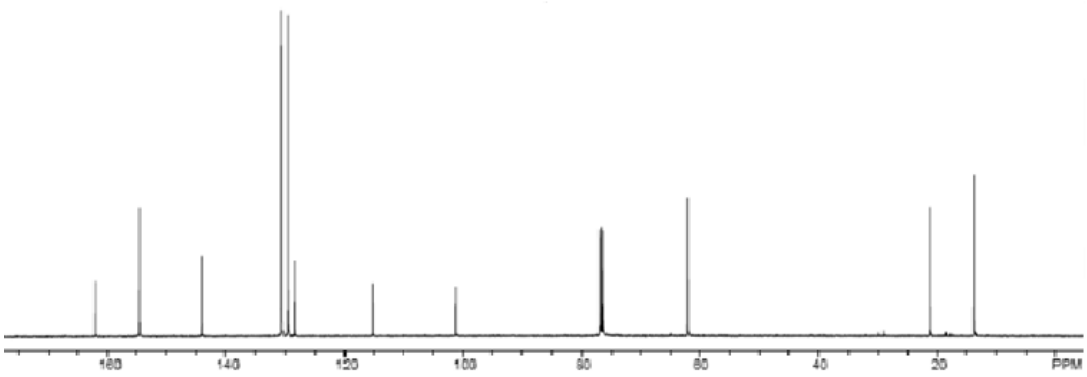

Fig. S29. ^{13}CNMR of compound **3j**.

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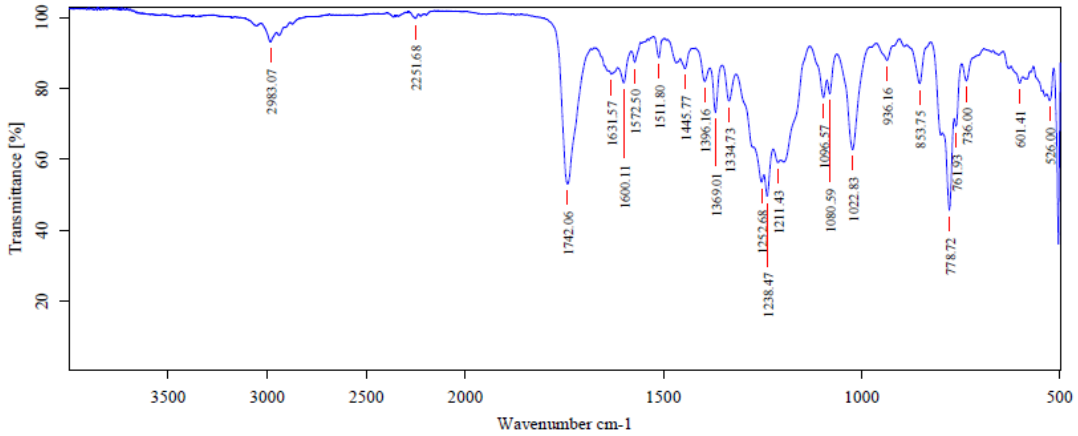

Fig. S30. IR Spectrum of compound **3j**.

Ethyl-2-cyano-3-(furan-2-yl)acrylate (3k). [3] solid (90 %) mp 83-85 ºC; IR (KBr) Cm^{-1}: 2984, 2252, 1741, 1613, 1462; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.38 (t, *J*= 7.2 Hz, 3H), 4.33-4.38 (m, 2H), 6.66-6.67 (m, 1H), 7.39-7.40 (m, 1H), 7.75-7.76 (m, 1H), 8.01 (s, 1H) ;^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.1, 62.5, 98.7, 113.8, 115.2, 121.5, 139.4, 148.1, 148.7, 162.5; Anal Calc for $C_{10}H_9NO_3$: C,62.82; H,4.74 ; N,7.33 %; found:C, 62.63; H, 4.56; N, 7.09 %.

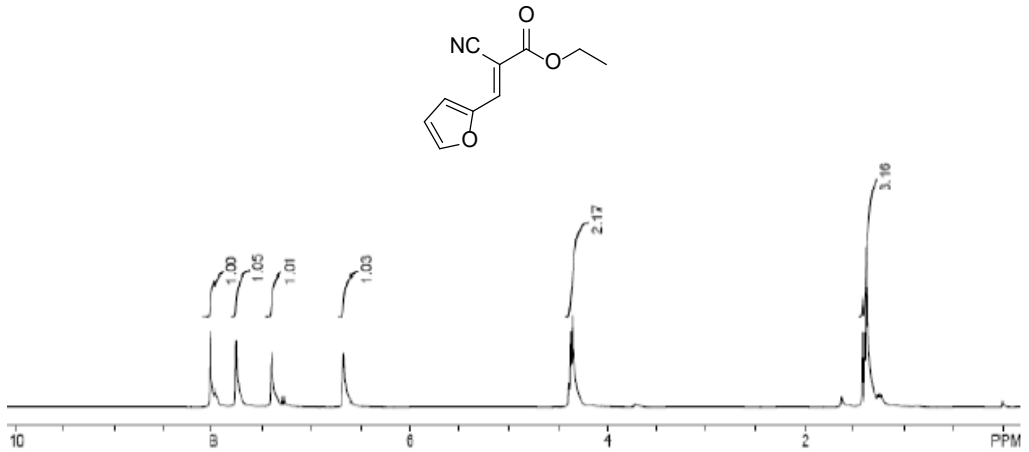

Fig. S31. ^{1}HNMR of compound **3k**.

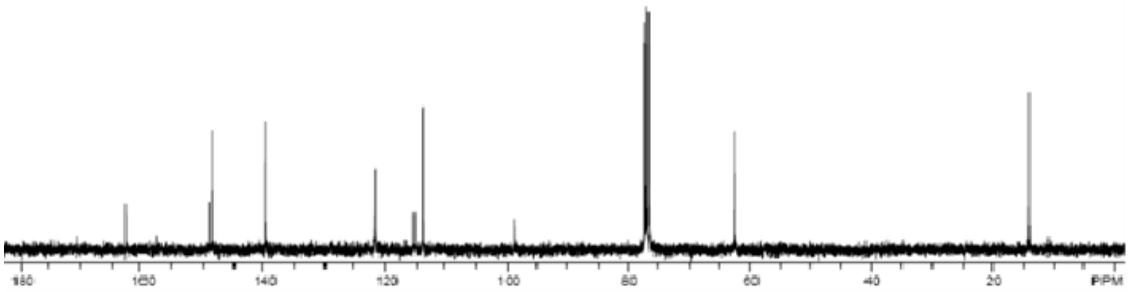

Fig. S32. ^{13}CNMR of compound **3k**.

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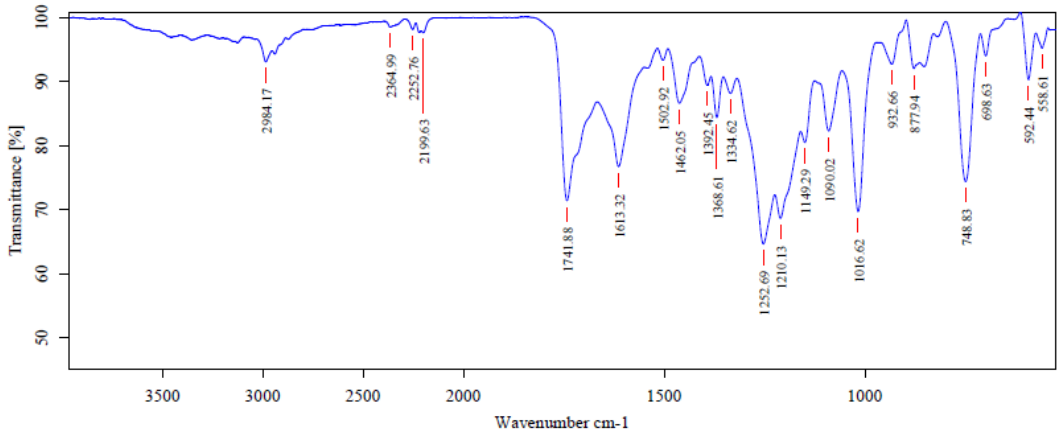

Fig. S33. IR Spectrum of compound **3k**.

Ethyl-2-cyano-3-(thiophen-2-yl)acrylate (3l)- [4] solid (91 %) mp 93-96 ºC; IR (KBr) Cm^{-1}: 3085, 2919, 2217, 1715, 1596, 1216; ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.39 (t, *J*= 7.2 Hz, 3H), 4.39-4.34(m, 2H), 7.22-7.26 (m, 1H), 7.78-7.84 (m, 2H), 8.35 (s, 1H) ;^{13}CNMR (100 MHz, $CDCl_3$): δ= 14.1, 62.5, 99.3, 115.7, 128.5, 135.1, 137.1, 146.6, 162.6; Anal Calc for $C_{10}H_9NO_2S$: C,57.95; H,4.38 ; N,6.76; S, 15.47 %; found:C, 57.88; H, 4.31; N, 6.59; S 15.36 %.

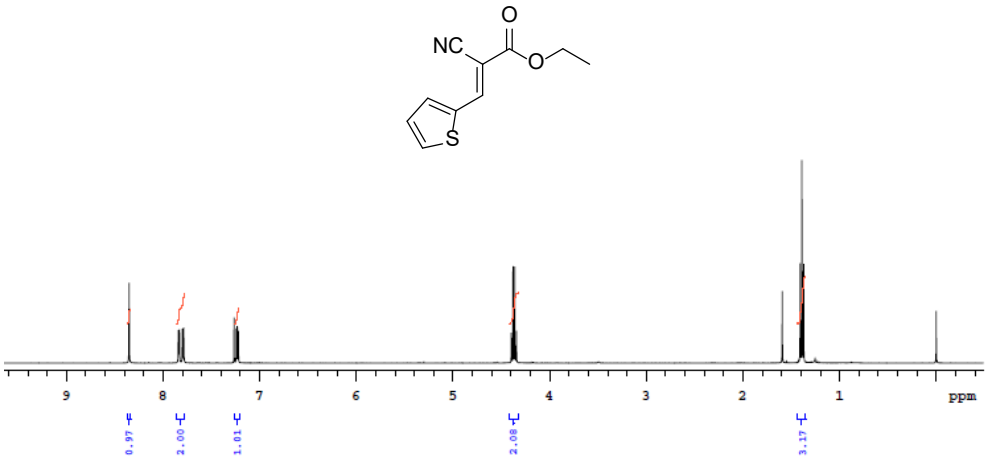

Fig. S34. ^{1}HNMR of compound **3l**.

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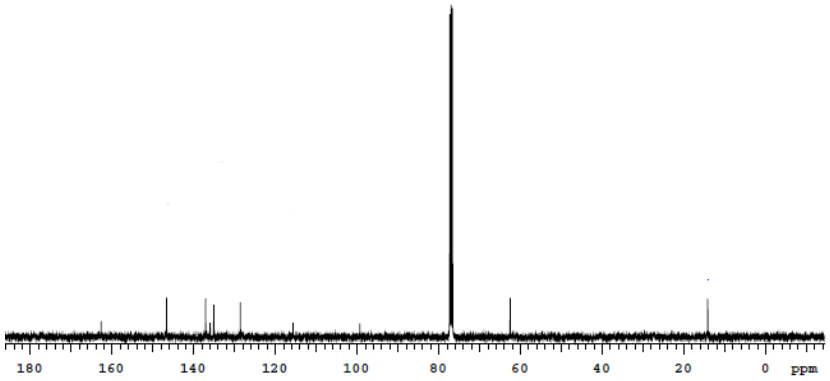

Fig. S35. ^{13}CNMR of compound **3l**.

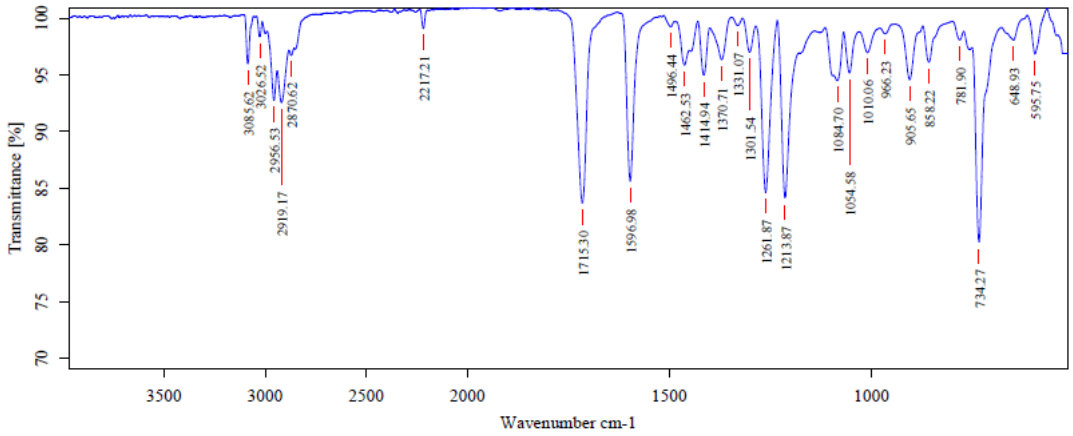

Fig. S36. IR Spectrum of compound **3l**.

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