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A simple and greener approach for the amide bond formation employing $FeCl_3$ as a catalyst

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Supporting information

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General information

All solvents were freshly distilled before use. Melting points were determined using capillary method and are uncorrected. IR spectra were recorded on Schimadzu model FT-IR spectrophotometer (KBr pellets, 3 cm^{-1} resolution). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO on a Bruker AMX spectrometer using TMS as an internal standard. The RP-HPLC experiments were carried out in Agilent 1100 series instrument having G1311A VWD at λ = 254 nm for Fmoc compound, flow 0.5 mL/min, column: Agilent Eclipse XDB-C18, pore size-5µm, diameter x length = 4.6 x 150 mm; method: gradient 0.1% TFA, water-acetonitrile system in 30 min. TLC experiments were done using MERCK TLC aluminium sheets (silica gel 60 F_{254}) and chromatograms were visualized by exposing in iodine chamber, UV-lamp or spraying with $KMnO_4$ and heating. Column chromatography was performed on neutral alumina and silica gel (100-200 mesh) using ethyl acetate and hexane mixtures as eluent.

Experimental Section

To a solution of acid (1.0 mmol) in toluene (6 mL) was added 20 mol% $FeCl_3$ and an additional 0.5 eq of AcOH and the reaction mixture was allowed stir at 50 ^oC for 10-15 min. Then an amine (1.0 mmol) in toluene (4 mL) was added to the above reaction mixture. The reaction mixture was refluxed at an elevated temperature till the completion of the reaction as monitored by TLC. Upon complete consumption of the starting materials, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The crude product was extracted into EtOAc (15 mL). The EtOAc layer was then washed with 5% Na_2CO_3 (5 mL), dil. HCl (5 mL), water (2 x 5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to afford the crude which was then purified through silica gel column chromatography (EtOAc/hexane).

Compound 3a: White solid (188 mg, 89%); mp 116-118 °C (Lit.[1] 118-119 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (br, 1H), 7.42 (d, J = 7.6 Hz, 2H), 7.40-7.21 (m, 7H), 7.07-7.04 (m, 1H), 3.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.28, 137.68, 134.50, 129.53, 129.21, 128.95, 127.65, 124.49, 119.93, 44.79; IR (KBr) 3286, 2924, 1659, 1600, 1535, 1442 cm^{-1}.

Compound 3b: White solid (180 mg, 80%); mp 147-148 °C (Lit.[2] 144-146 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8 Hz, 1H), 6.95-7.47 (m, 9H), 3.81 (s, 2H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.07, 135.36, 132.82, 129.50, 129.05, 126.20, 126.17, 124.76, 124.46, 124.42, 119.99, 44.30, 22.71; IR (KBr) 3341, 2926, 1654, 1519 cm^{-1}.

Compound 3c: White solid (189 mg, 84%); mp 132-133 °C (Lit.[3] 130-131 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H),7.40-7.34 (m, 7H), 7.08 (d, J = 8.4 Hz, 2H), 3.68 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.40, 135.22, 134.73, 134.09, 129.51, 129.41, 129.09, 127.50, 120.17, 44.60, 20.89; IR (KBr) 3332, 2926, 1649, 1601, 1514, 1461, 1410 cm^{-1}.

Compound 3d: White solid (235 mg, 81%); mp 178-179 °C (Lit.[4] 177-179 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.31 (m, 9H), 7.27 (br, 1H), 3.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.05, 136.65, 134.11, 131.91, 129.56, 129.37, 127.87, 121.33, 117.06, 44.86; IR (KBr) 3346, 2927, 1654, 1596, 1513, 1458, 1399 cm^{-1}.

Compound 3e: White solid (204 mg, 83%); mp 166-167 °C (Lit.[5] 167-168 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 8H), 7.22 (d, J = 8.8 Hz, 2H), 3.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.14, 136.18, 134.17, 129.53, 129.46, 129.33, 128.95, 127.82, 121.08, 44.78; IR (KBr) 3345, 2925, 1661, 1613, 1596, 1506, 1406, 1349, 1305 cm^{-1}.

Compound 3f: White solid (205 mg, 85%); mp 117-119 °C (Lit.[6] 118-119 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8 Hz, 2H), 7.31-7.26 (m, 4H), 7.12 (d, J = 7.6 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 3.85 (s, 3H), 3.70 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.63, 159.12, 137.65, 130.72, 128.94, 126.33, 124.43, 119.80, 114.67, 55.34, 43.96; IR (KBr) 3289, 2928, 1652, 1542, 1488, 1302 cm^{-1}.

Compound 3g: White solid (180 mg, 80%); mp 53-55 °C (Lit.[7] 52 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.44 (m, 2H), 7.04-7.31 (m, 8H), 3.71 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.42, 137.65, 137.46, 131.30, 129.97, 129.48, 128.93, 124.43, 119.83, 44.49, 21.14; IR (KBr) 3310, 2926, 1660, 1544,1441, 1389 cm^{-1}.

Compound 3h: White solid (175 mg, 83%); mp 128-129 ^{o}C (Lit.[8] 129-130 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.07 (s, 1H), 7.90 (d, J = 6.9 Hz, 2H), 7.57-7.45 (m, 3 H), 7.36-7.21 (m, 5H), 4.49 (d, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.17, 139.79, 134.32, 131.23, 128.32, 128.27, 127.23, 127.18, 126.72, 42.54; IR (KBr) 3310, 2926, 1660, 1544,1441, 1389, 1254, 1098, 1049 cm^{-1}.

Compound 3i: White solid (185 mg, 82%); mp 133-134 °C (Lit.[9] 133-135°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 7.37-7.32 (m, 4H), 7.09 (t, J = 7.2 Hz, 1H), 4.22 (d, J = 6.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.36, 141.53, 139.27, 132.09, 128.89, 128.56, 127.69, 123.52, 120.34, 42.58, 21.00; IR (KBr) 3349, 2973, 1660, 1438, 1389, 1095, 1050 cm^{-1}.

Compound 3j: White solid (209 mg, 85%); mp 167-168 °C (Lit.[9] 165-167 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 7.98 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.10 (t, J = 7.2 Hz, 1H), 4.09 (d, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.41, 138.97, 136.38, 133.64, 129.61, 128.61, 128.43, 123.80, 120.41, 42.21; IR (KBr) 3351, 2921, 2851, 1653, 1599, 1463, 1440 cm^{-1}.

Compound 3k: White solid (182 mg, 81%); mp 84-85 °C (Lit.[10] 83-84 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1 H), 7.79-7.73 (m, 4H), 7.42-7.32 (m, 4H), 7.09 (t, J = 7.5 Hz, 1H), 4.17 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.69, 139.25, 137.69, 135.02, 132.12, 128.60, 128.28, 128.15, 124.83, 123.60, 120.33, 42.28, 20.98; IR (KBr) 3289, 2923, 1651, 1600, 1535, 1499, 1441, 1325 cm^{-1}.

Compound 3l: Pale yellow solid (145 mg, 68%); mp 128-129 °C (Lit.[11] 130-131°C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.93 (s, 1 H), 7.57 (d, J = 8.1 Hz, 2 H), 7.28 (t, J = 7.5 Hz, 2 H), 7.02 (t, J = 7.2 Hz, 1 H), 4.03 (s, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.26, 139.33, 128.65, 122.94, 118.94, 40.05; IR (KBr) 3295, 2926, 1669, 1600, 1547, 1498, 1442, 1372, 1319, 1265 cm^{-1}.

Fmoc-Aib-Aib-OMe, 4: White solid (284 mg, 67%); mp 72-73 °C (Lit.[12] 70-71°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.2 Hz, 2H), 7.59 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.32(t, J = 7.2 Hz, 2H), 6.61 (br s, 1H), 5.38 (br s, 1H), 4.49 (d, J = 6.3 Hz, 2H), 4.19 (t, J = 6.3

Hz, 1H), 3.62 (s, 3H), 1.45 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.41, 154.90, 143.83, 141.34, 127.72, 127.05, 125.04, 124.91, 120.02, 65.93, 59.52, 54.81, 52.24, 47.43, 24.91; IR (KBr) 3294, 3245, 1748, 1709, 1698, 1548 cm^{-1}.

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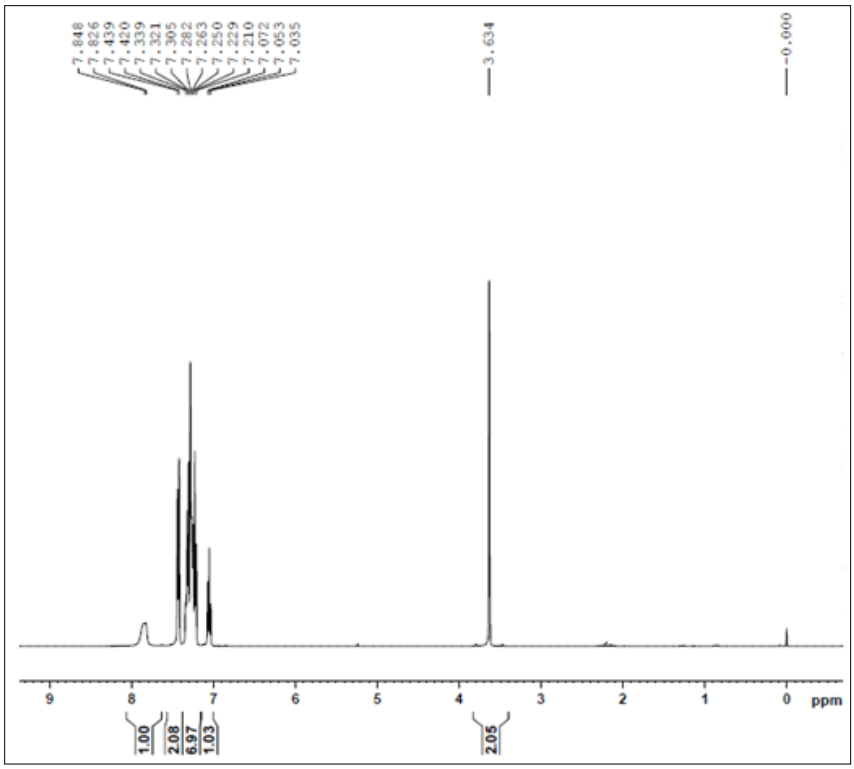
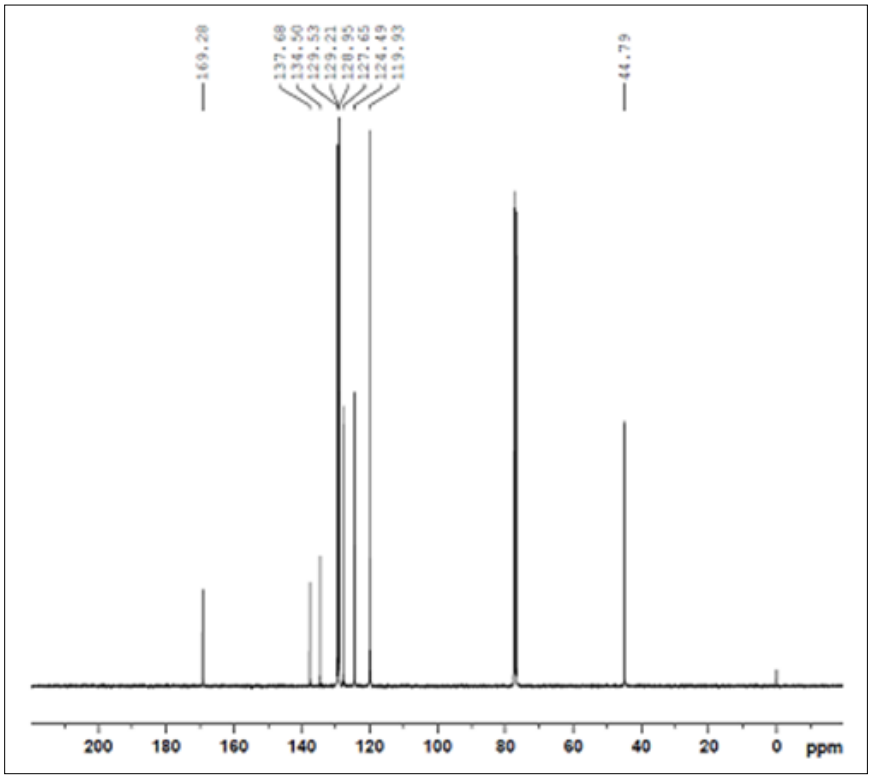


^{1}H NMR spectrum of compound **3a**



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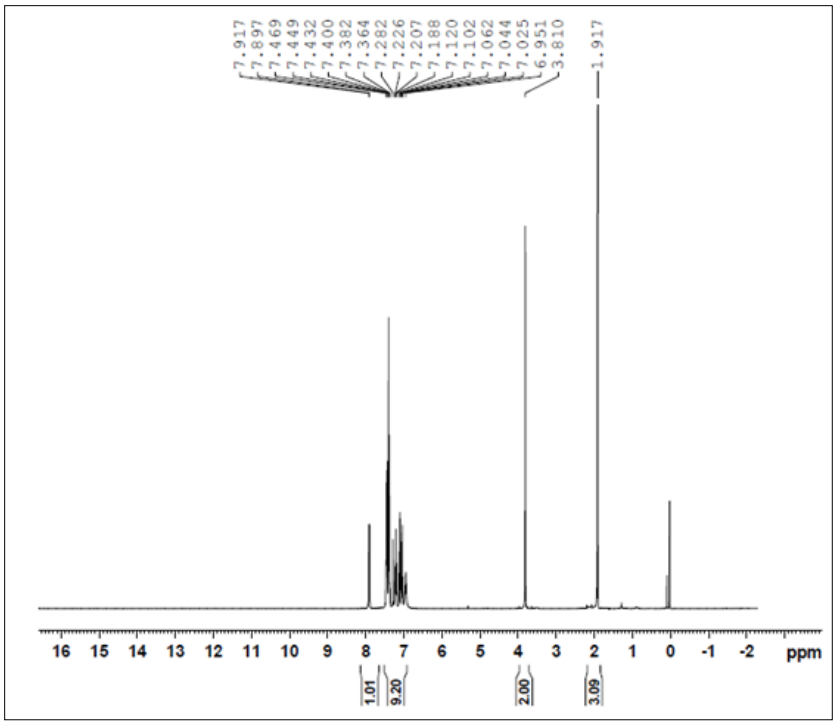

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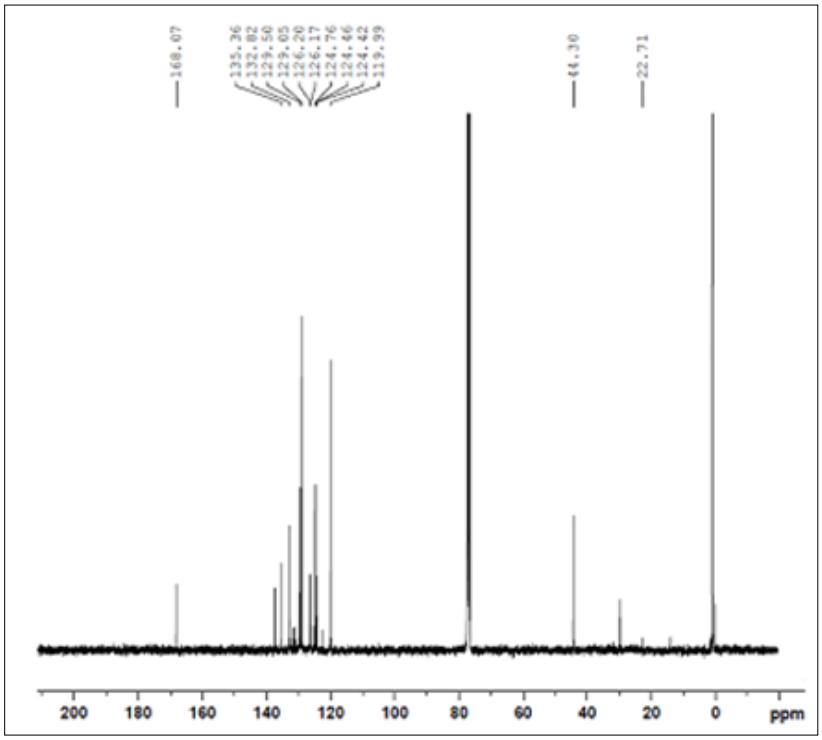

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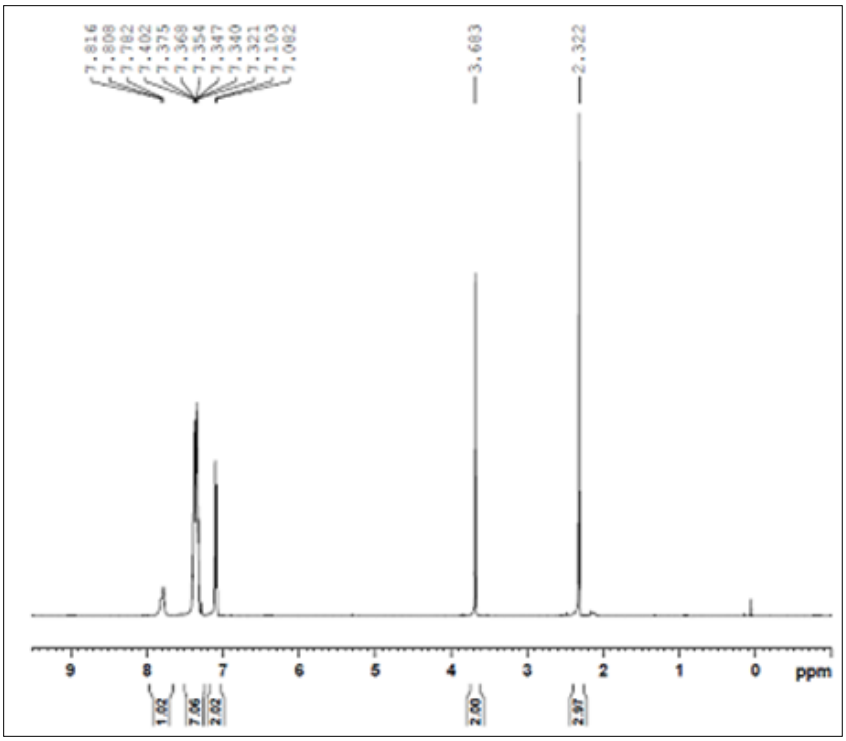

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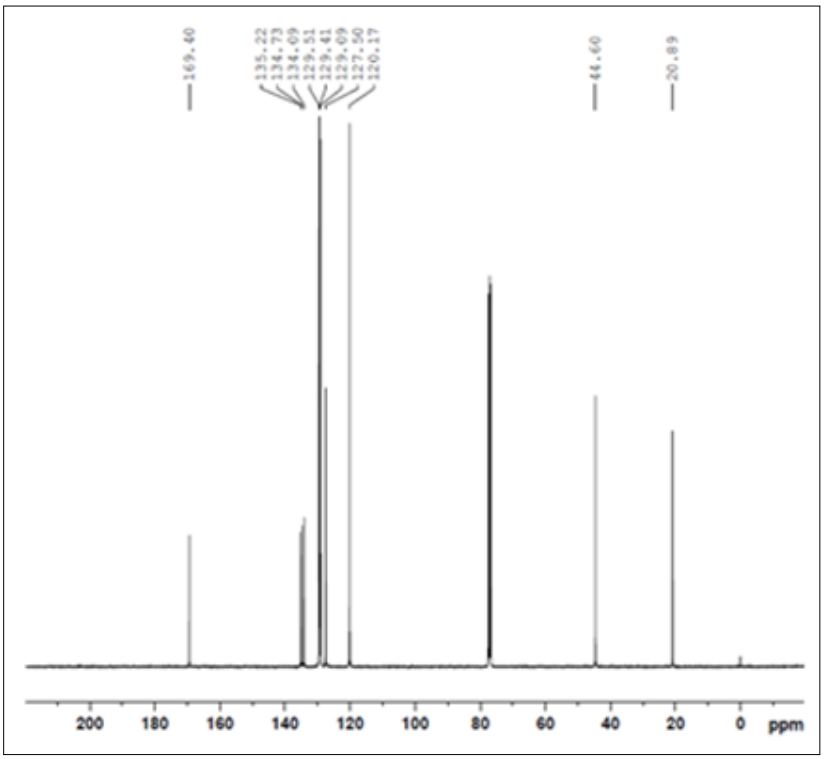
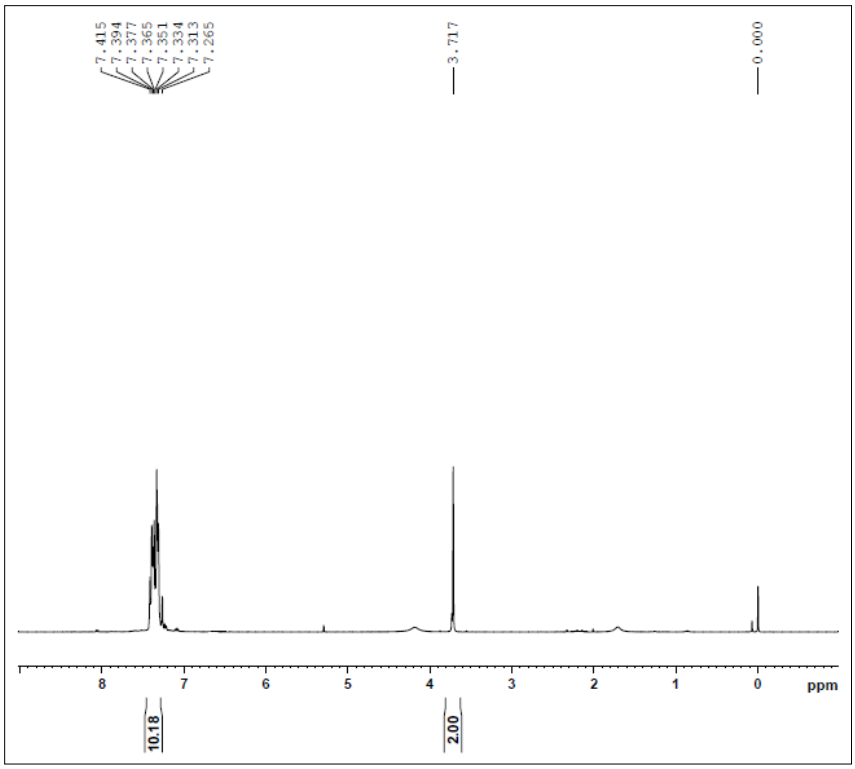


^{13}C NMR spectrum of compound **3c**



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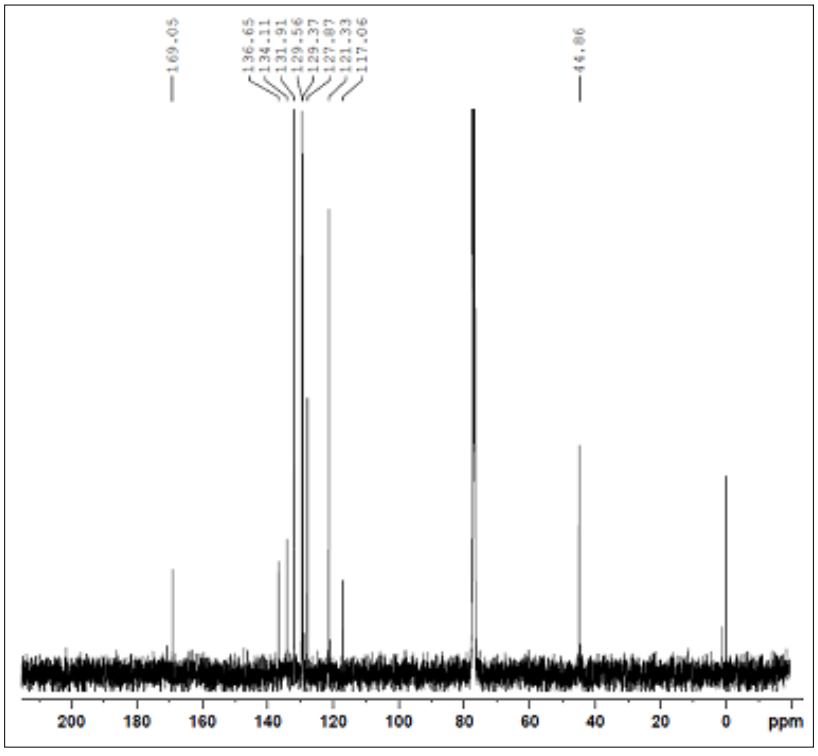

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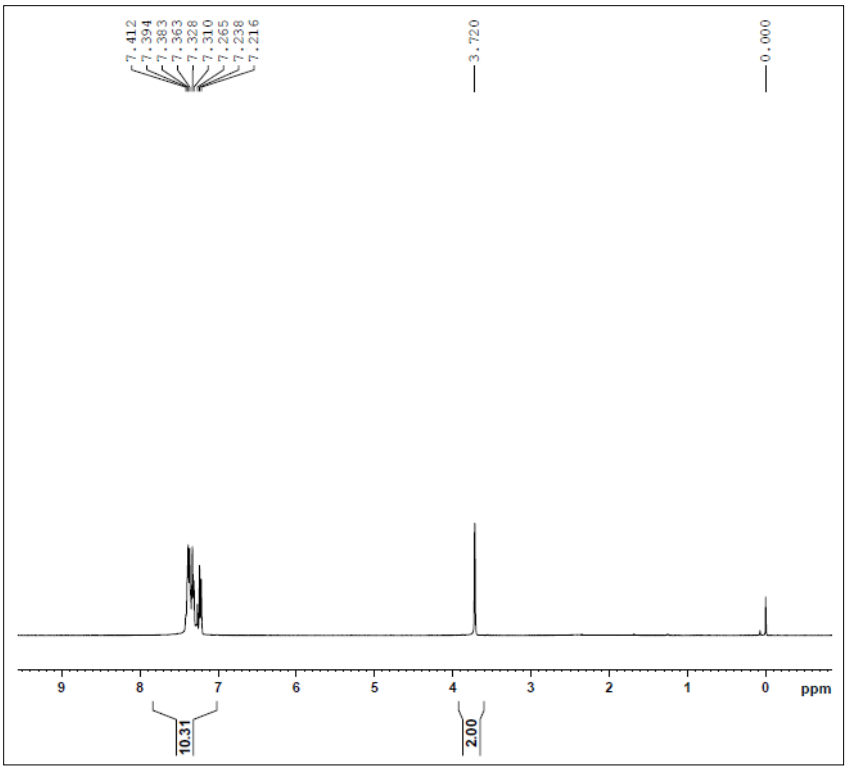

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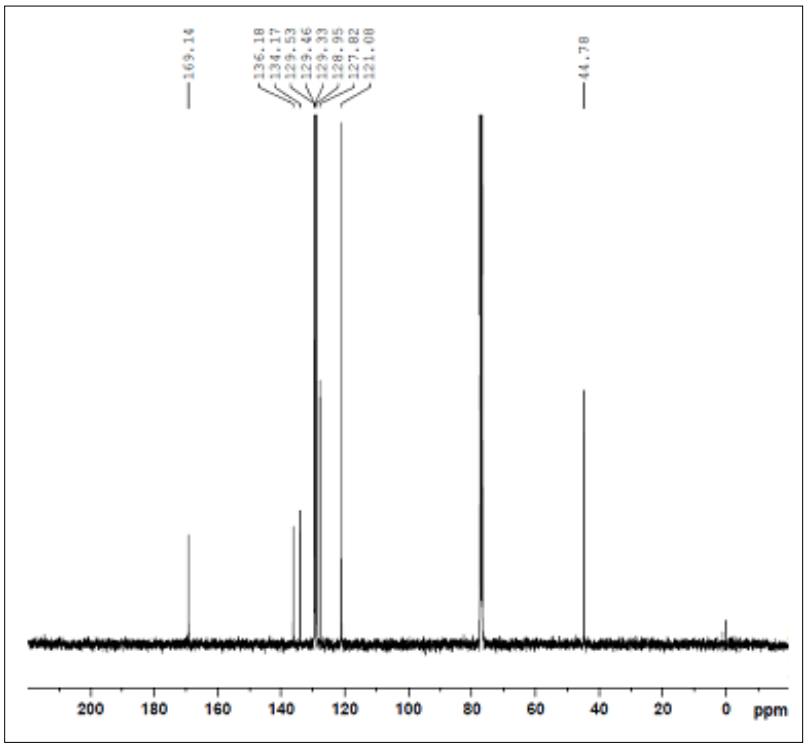

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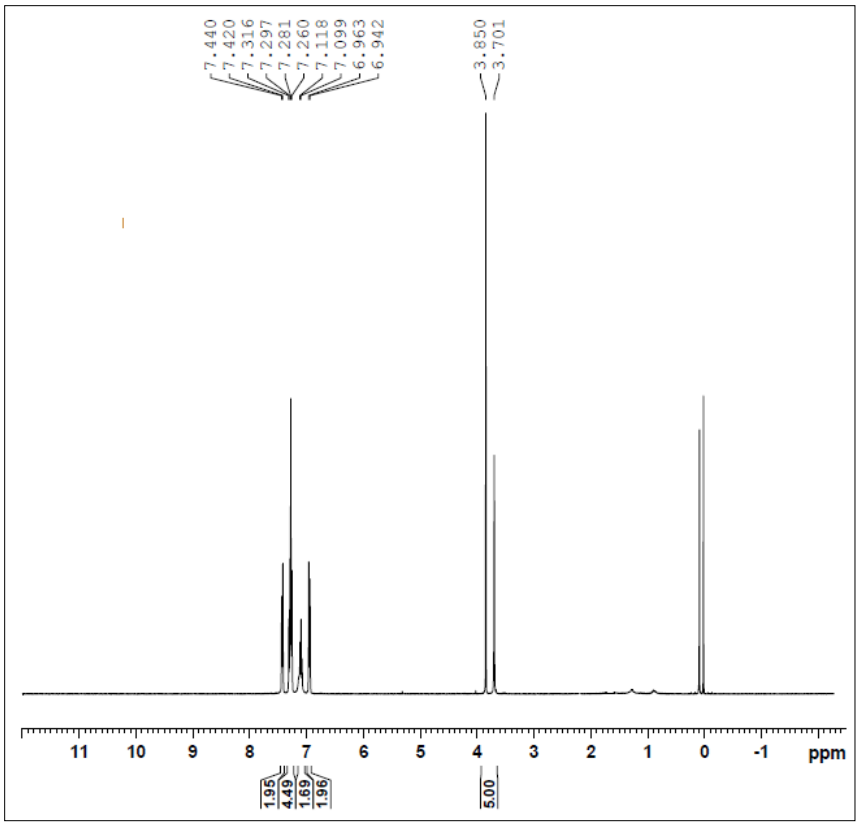

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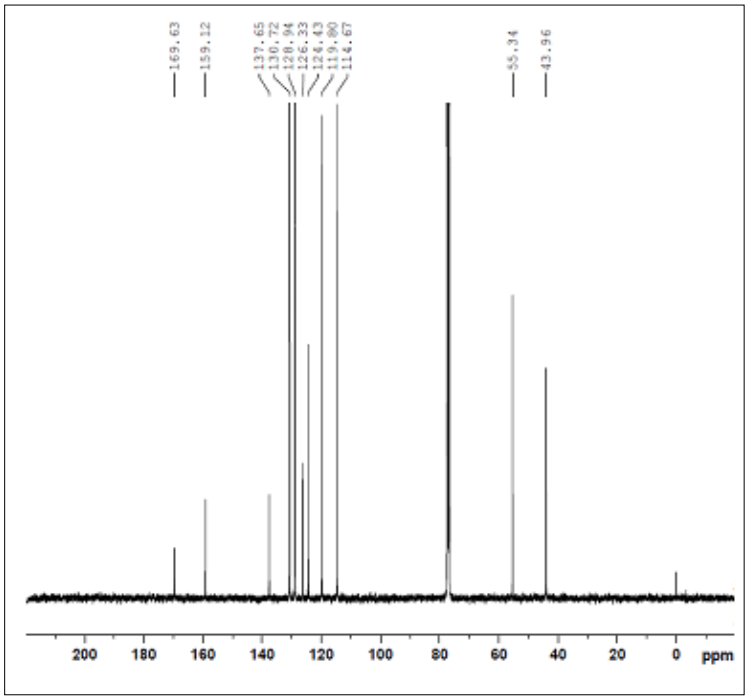

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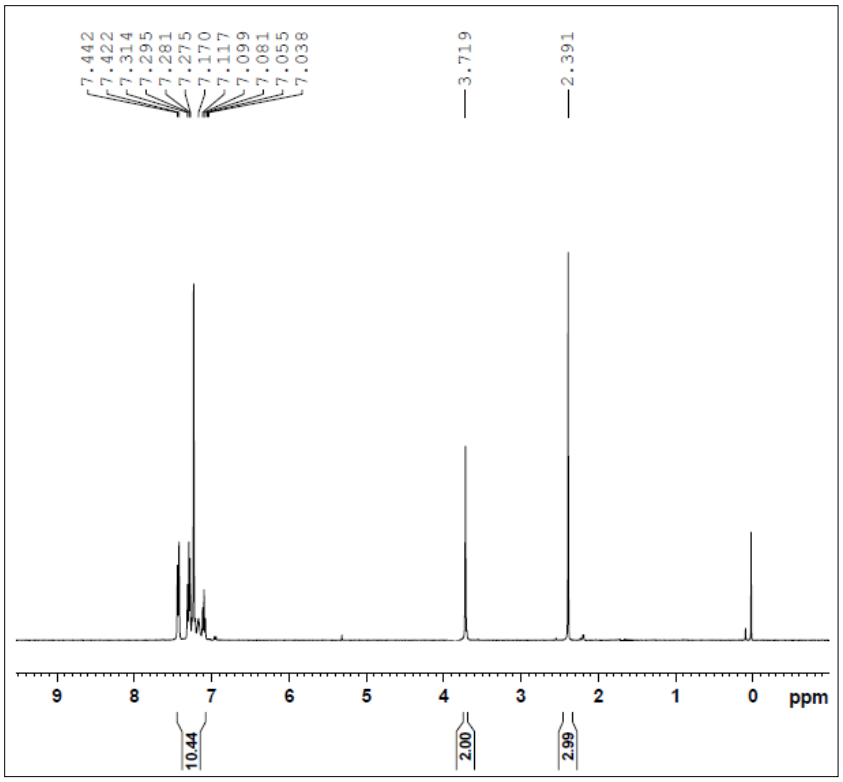

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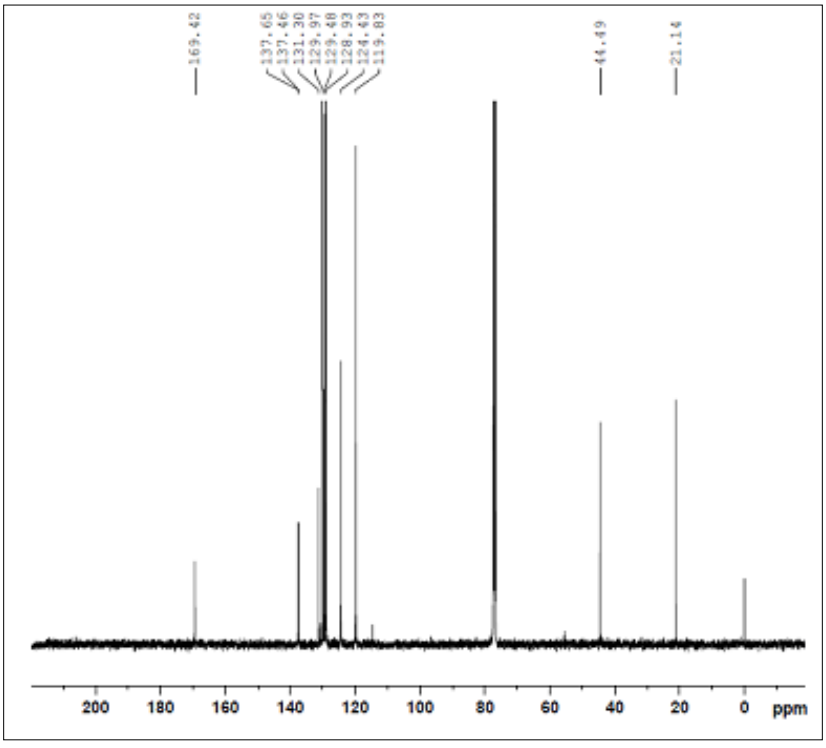

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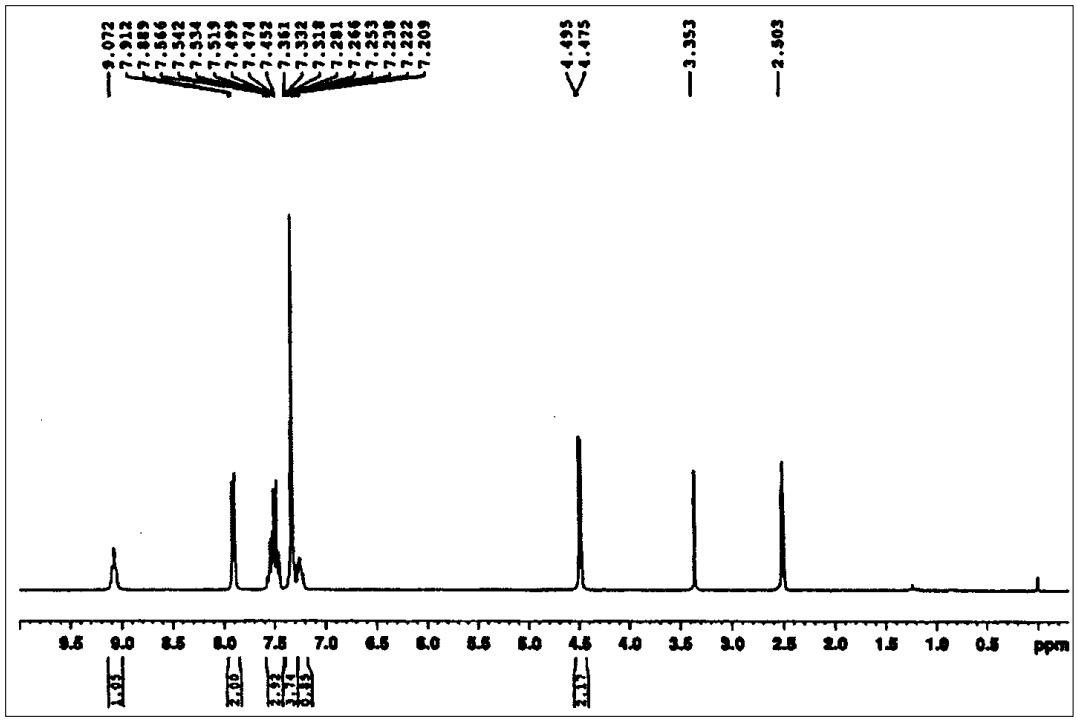

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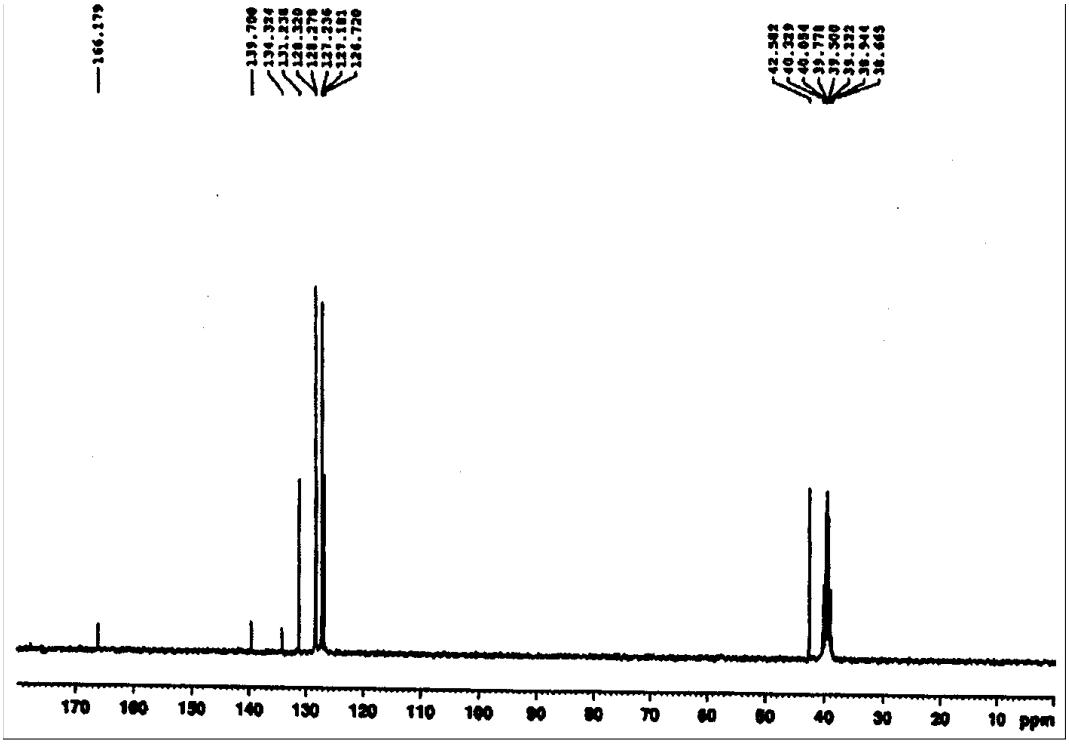

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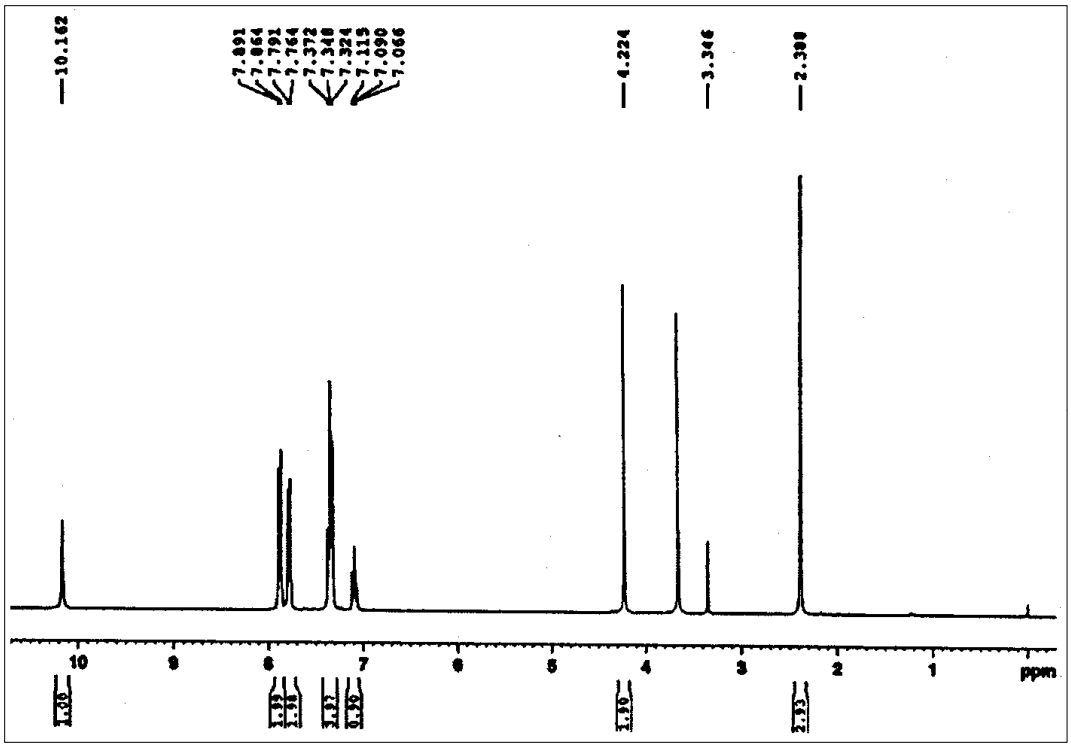

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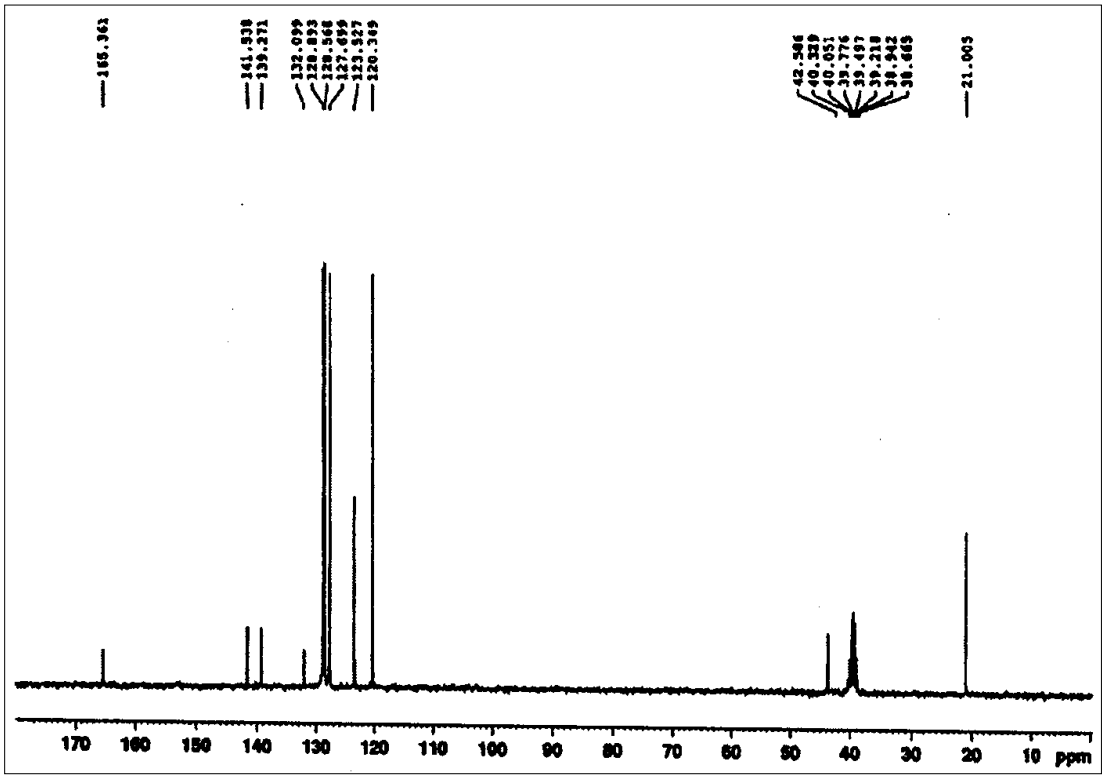
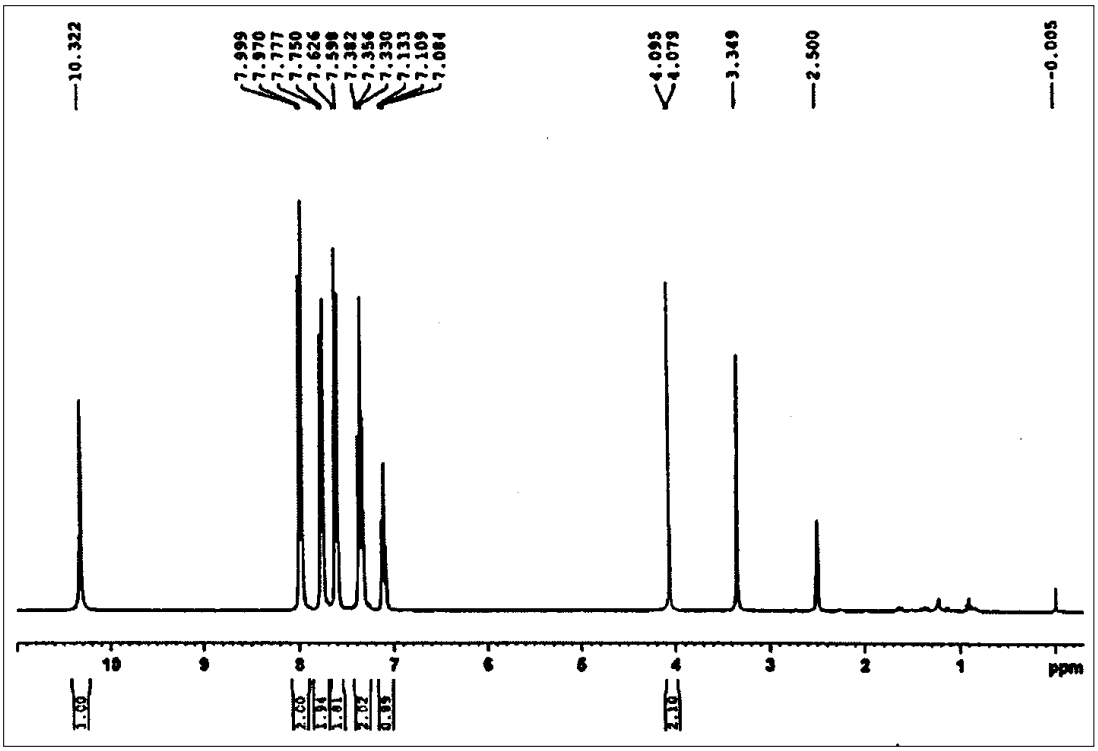


^{13}C NMR spectrum of compound **3i**



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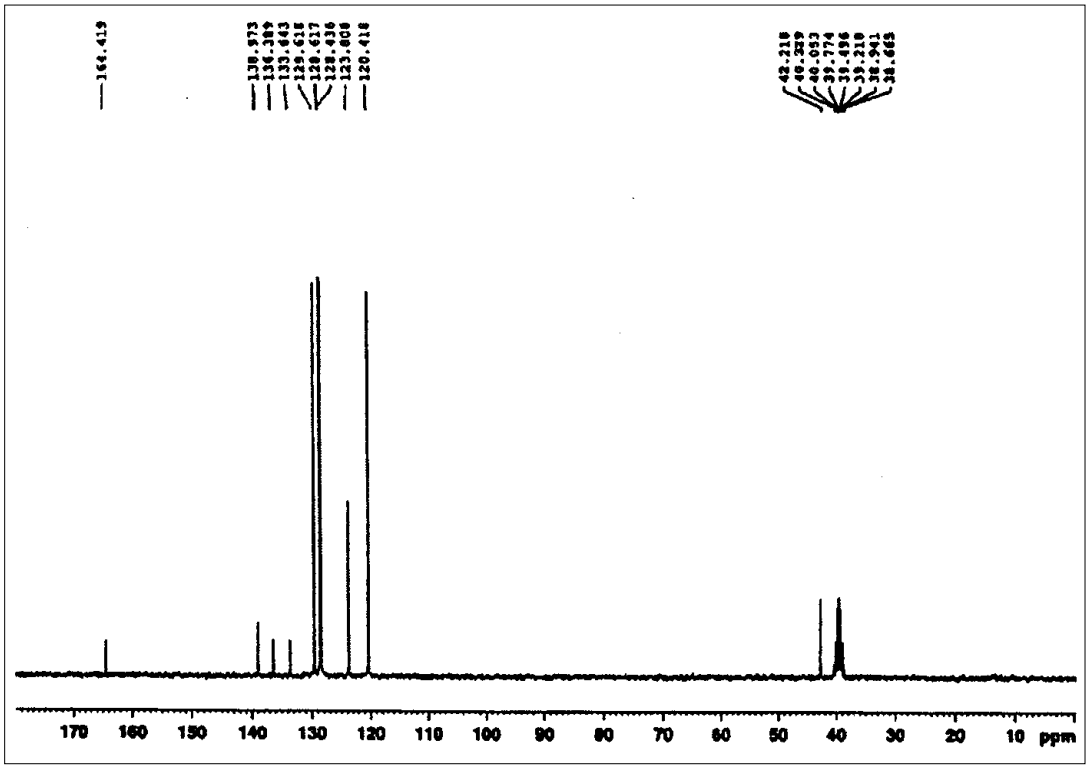
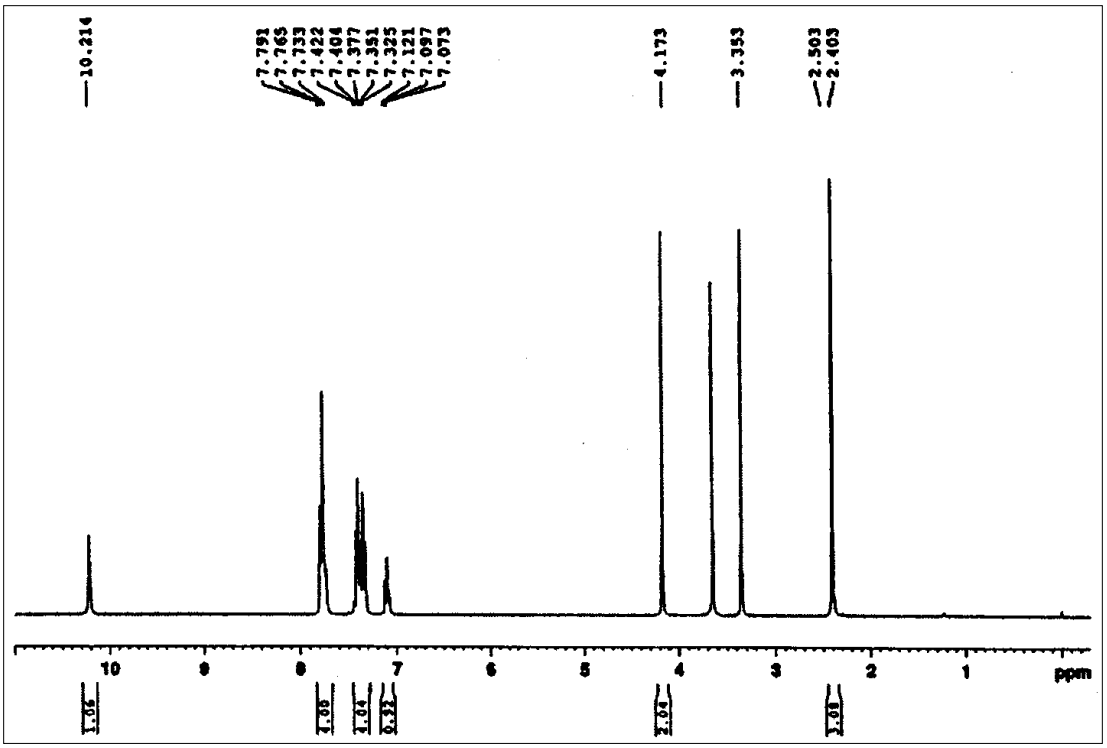


^{13}C NMR spectrum compound **3j**



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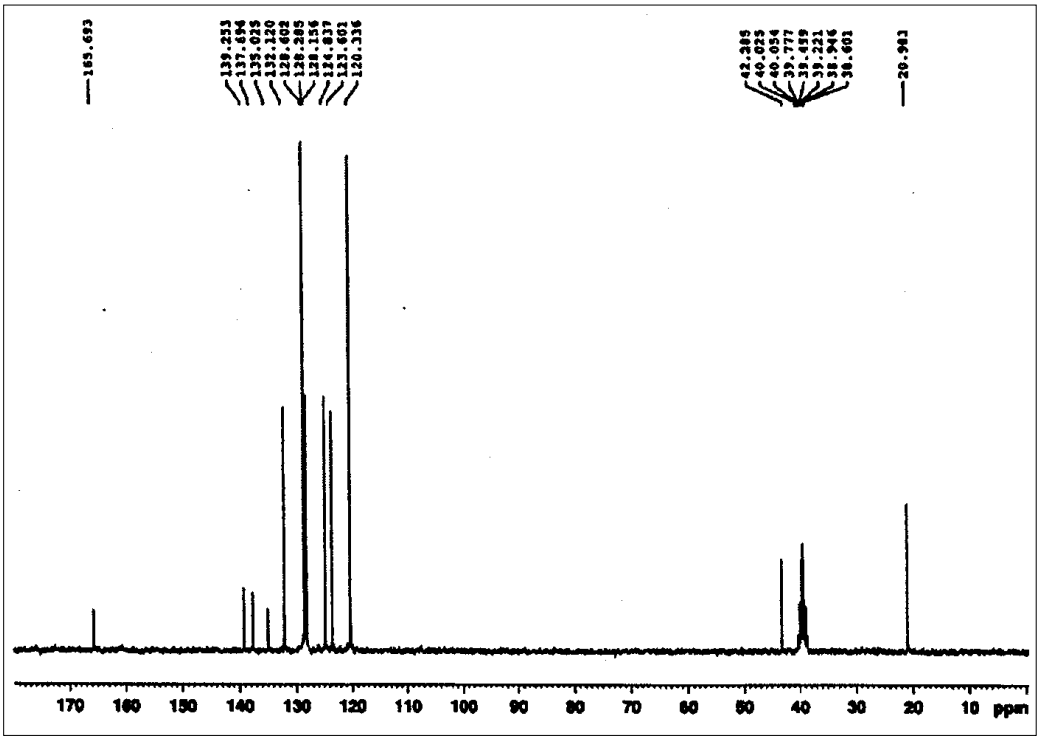

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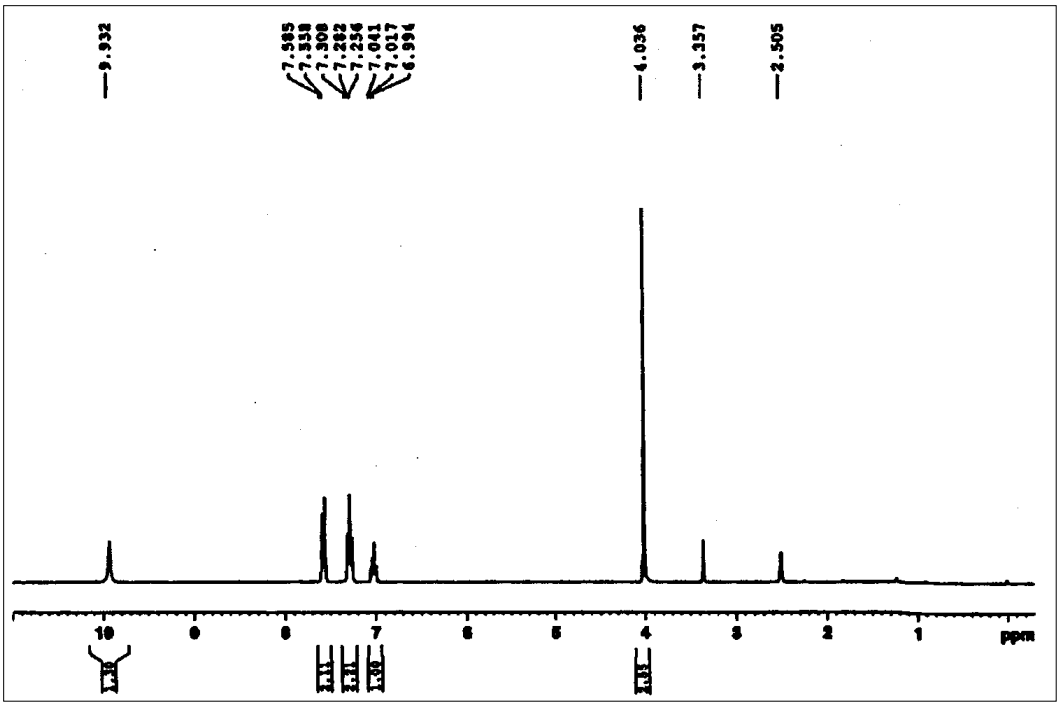

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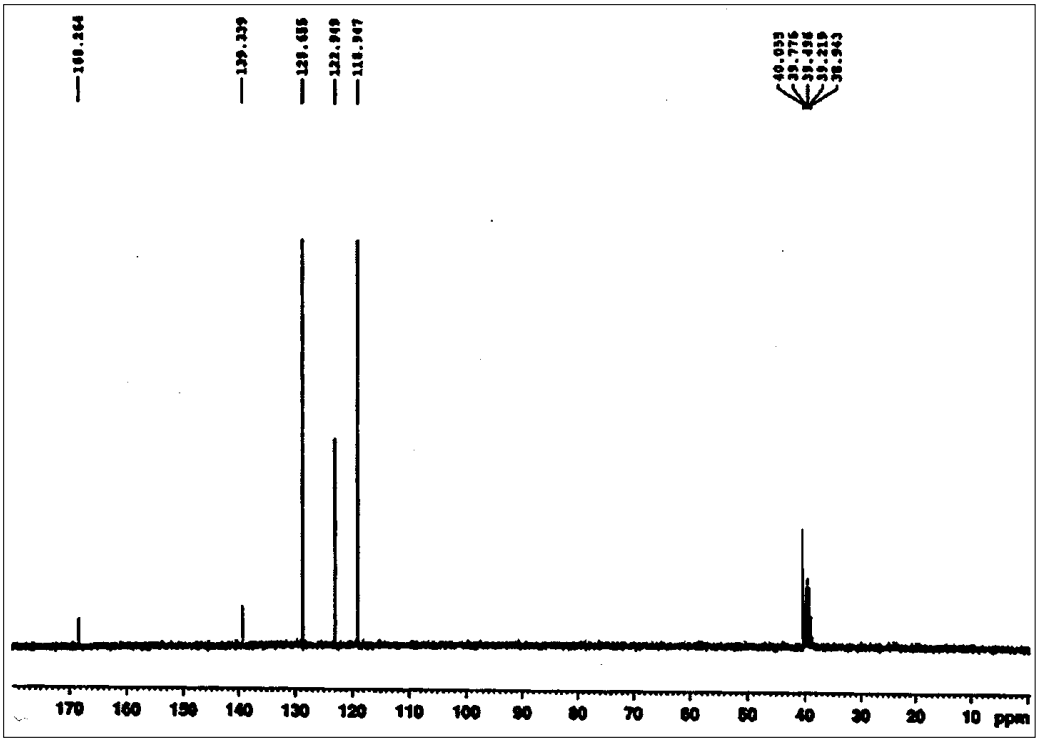

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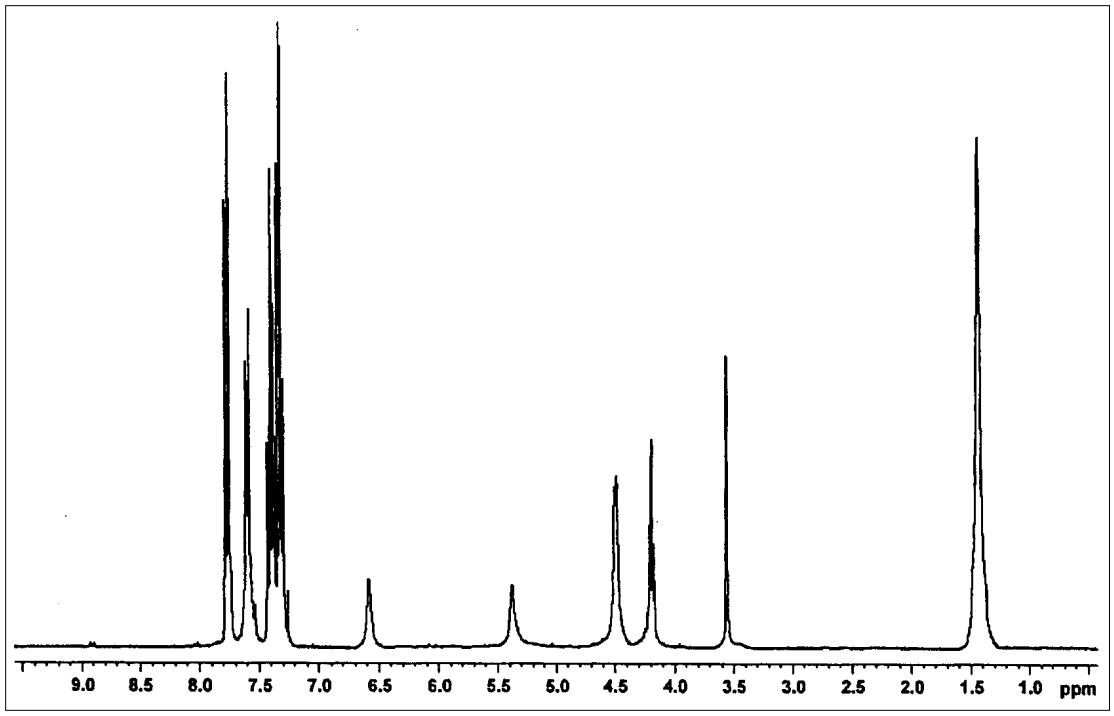

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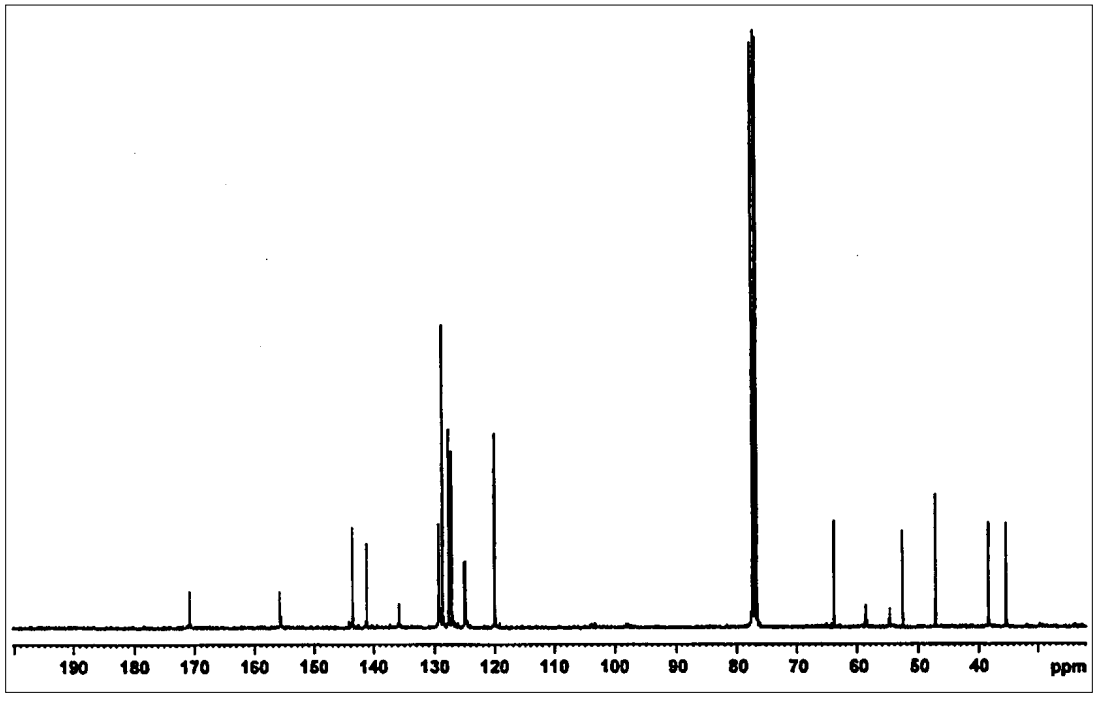

^{13}C NMR spectrum of compound **4**