

# Supporting Information

## **An Alternative Approach to Synthesis of 3-(4-chloro butyl)-1*H*-indole -5-carbonitrile: A key intermediate of Vilazodone hydrochloride, an antidepressant drug**

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### Materials and Instruments:

All commercially available materials and solvents were used as received without any further purification.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  at 400 and 70 MHz, respectively, on a Varian Gemini 200 MHz spectrometer. The chemical shift values were reported on  $\delta$  scale in ppm with respect to TMS ( $\delta$  0.00 ppm) as internal standard. The ESI mass spectrum was recorded on 4000-Q-trap LC/MS spectrometer. FTIR spectrum was recorded on Perkin-Elmer model spectrum series FT-IR as KBr pellet.

### Experimental Section:

#### Synthesis of 4-cyanophenyl hydrazine hydrochloride (3):

The 4-cyanophenyl hydrazine hydrochloride (**3**) was prepared similarly to the reported procedure (Jose L. Castro. 1994) Yield: 82%,  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  10.59 (2H, br s), 9.15 (1H, br s), 7.72 (2H, d,  $J=8.8\text{Hz}$ ), 7.06 (2H, d,  $J=8.8\text{Hz}$ ); MS (DIP)  $m/z$  132 ( $\text{M}^+-1$ );

IR (KBr,  $\text{cm}^{-2}$ ): 3213 (- $\text{NH}_2$ ), 2236(-CN), 1614 (-NH), 1513,1496,1416, 869 and 681 (Aromatic CH).

#### Synthesis of 6-hydroxy hexanal (4b):

The 6-hydroxy hexanal (**4a**) was prepared similarly to the reported procedure starting from  $\epsilon$ -caprolactone (**8**) (Milena et al 2000, Jalal et al 2010)

Yield: 82%,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.8 (1H, t,  $J=1.8\text{Hz}$ ), 3.65 (2H, t,  $J=6.8\text{Hz}$ ), 2.46 (2H, m), 1.83 (2H, m), 1.70 (2H, m), MS (DIP)  $m/z$  115 ( $\text{M}^+-1$ ); IR (KBr,  $\text{cm}^{-2}$ ): 3420 (-OH), 1722(-C=O).

#### Synthesis of 6-chloro hexanal (4a):

To a stirred solution of **7** (15.0 gm, 0.10 mol) in dichloromethane at 25-30 °C were added TEMPO (0.17 gm, 0.001 mol), 1.2 M  $\text{NaHCO}_3$  (aq) (140 mL, 0.16 mol) and 0.55 M. KBr (aq) (10 mL, 0.005 mol). The resulting mixture was cooled to 0-5°C and 12.0 % aqueous NaOCl solution (81.80 gm, 0.13 mol) was added in a and drop wise at such a rate as to maintain the reaction temperature of 0-5°C. The reaction mixture was stirred for 30-45 min at 0-5°C, and confirmation that the reaction was complete was achieved by TLC. The phases were separated,

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and the aqueous phase was extracted with dichloromethane (75 ml). The dichloromethane fractions were combined, the resulting solution was washed with 1 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (aq) (150 mL) and water (2 x 150 ml) and evaporated under vacuum Yield: 90 %. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.78 (1H, t, *J*=1.6Hz), 3.56 (2H, t, *J*=6.6Hz), 2.48 (2H, m), 1.83 (2H, m), 1.70 (2H, m), 1.56 (2H, m), MS (DIP) *m/z* 133 (M<sup>+</sup>-1); IR (Nujol, cm<sup>-2</sup>): 1724(-C=O), 648 (-C-Cl).

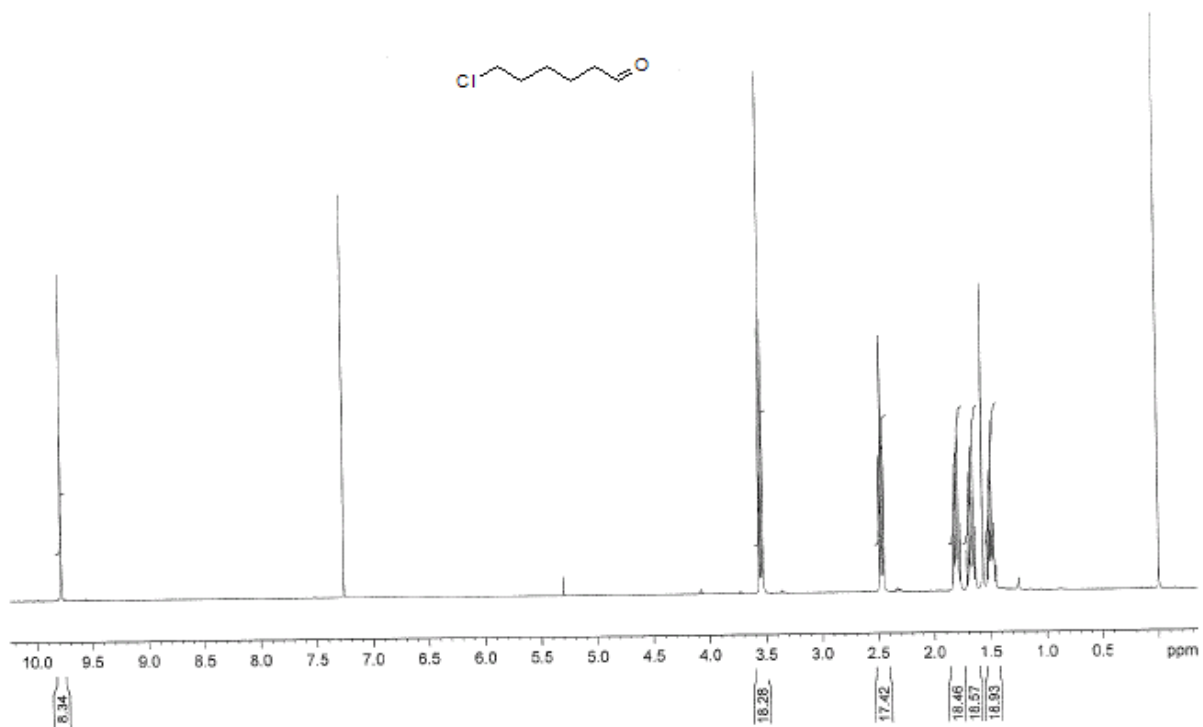
### Synthesis of 3-(4-chloro butyl)-1*H*-indole -5-carbonitrile (2a):

To a solution of 4-cyanophenyl hydrazine hydrochloride (50.0 gm, 0.29 mol) in 4% H<sub>2</sub>SO<sub>4</sub> (aq) (50 ml) and DMAc (50ml) was added aldehyde (47.6 gm, 0.35 mol), the reaction mixture was stirred for 1.0 hr at 25-35°C, product formed was extracted into toluene (100ml), 85% H<sub>3</sub>PO<sub>4</sub> (aq) (170 gm, 0.147 mol) was added to the toluene layer and refluxed for 3.0 hrs then cooled to ambient temperature. The organic phase was separated, washed with 1.2 M NaHCO<sub>3</sub> (aq) (100 ml), water (100 ml) and evaporated under vacuum. The crude obtained was recrystallized from ethyl acetate and hexane solvent system. Yield: 74.0%

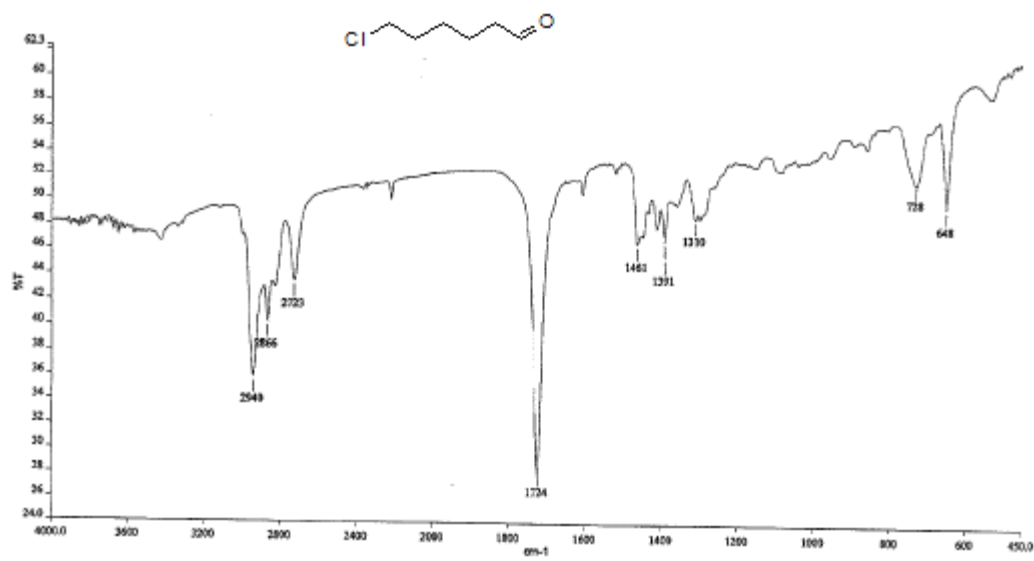
**2a:** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.46 (1H, br s), 7.94 (1H, s), 7.40 (2H, d, *J*=1.08Hz), 7.10 (1H, t, *J*=1.08Hz), 3.59 (2H, t, *J*=1.92Hz), 2.80 (2H,m), 1.87 (4H, m); <sup>13</sup>C NMR (400 MHz) (CDCl<sub>3</sub>); δ 138.1, 127.4, 124.7,124.6, 123.6,121.2, 116.9, 112.2, 101.8, 45.0,32.3, 27.3,24.1; MS (DIP) *m/z* 231 (M<sup>+</sup>-1); IR (KBr, cm<sup>-2</sup>): 3332 (-NH), 2940 (-CH), 2214(-CN), 1618 (-C=N), 1579, 1462, 1097 and 802(Aromatic CH);

**2b:** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.42 (1H, br s), 7.94 (1H, s), 7.41 (2H, d, *J* =1.08Hz), 7.12 (1H, t, *J*=1.08Hz), 3.71 (2H, t, *J* = 6.52Hz), 2.80 (2H,m), 1.82 (2H, m), 1.70 (2H, m); <sup>13</sup>C NMR (400 MHz) (CDCl<sub>3</sub>); δ 138.0, 127.4, 124.8,124.7, 123.3,121.0, 117.5, 112.0, 102.1, 62.7, 32.5, 26.3,24.6; MS (DIP) *m/z* 213 (M<sup>+</sup>-1); IR (KBr, cm<sup>-2</sup>): 3426 (-OH), 3212 (-NH), 2932 (-CH), 2228(-CN), 1618 (-C=N), 1577,1472, 1363, 1077 and 803(Aromatic CH);

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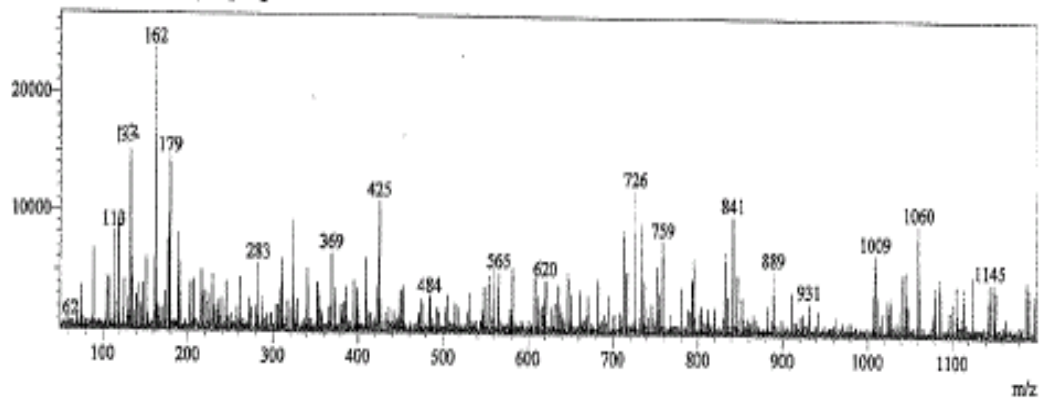
<sup>1</sup>H-NMR Spectrum of **4a** (400 MHz, CDCl<sub>3</sub>)



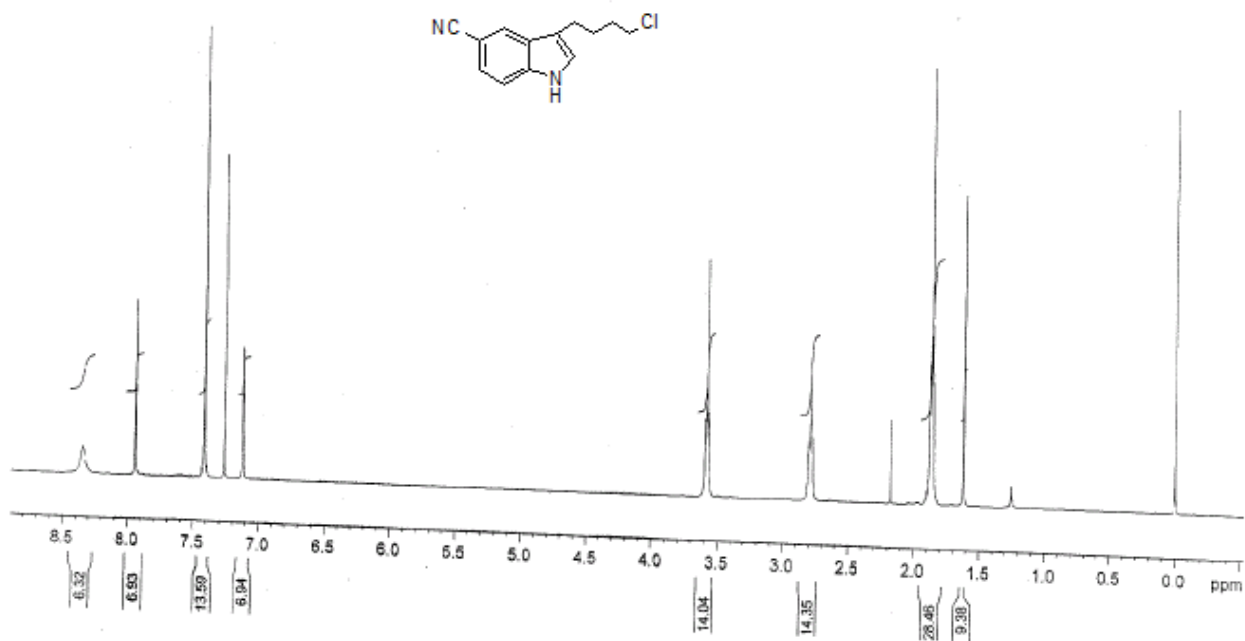
IR Spectrum of **4a**

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Retention Time: 0.193 (Scan: 12)  
Max Peak: 368 Base Peak: 162.02 (23700)  
Spectrum: Single 0.193 (12)  
Background: PkStart Polarity: Neg Segment: 1 - Event: 1

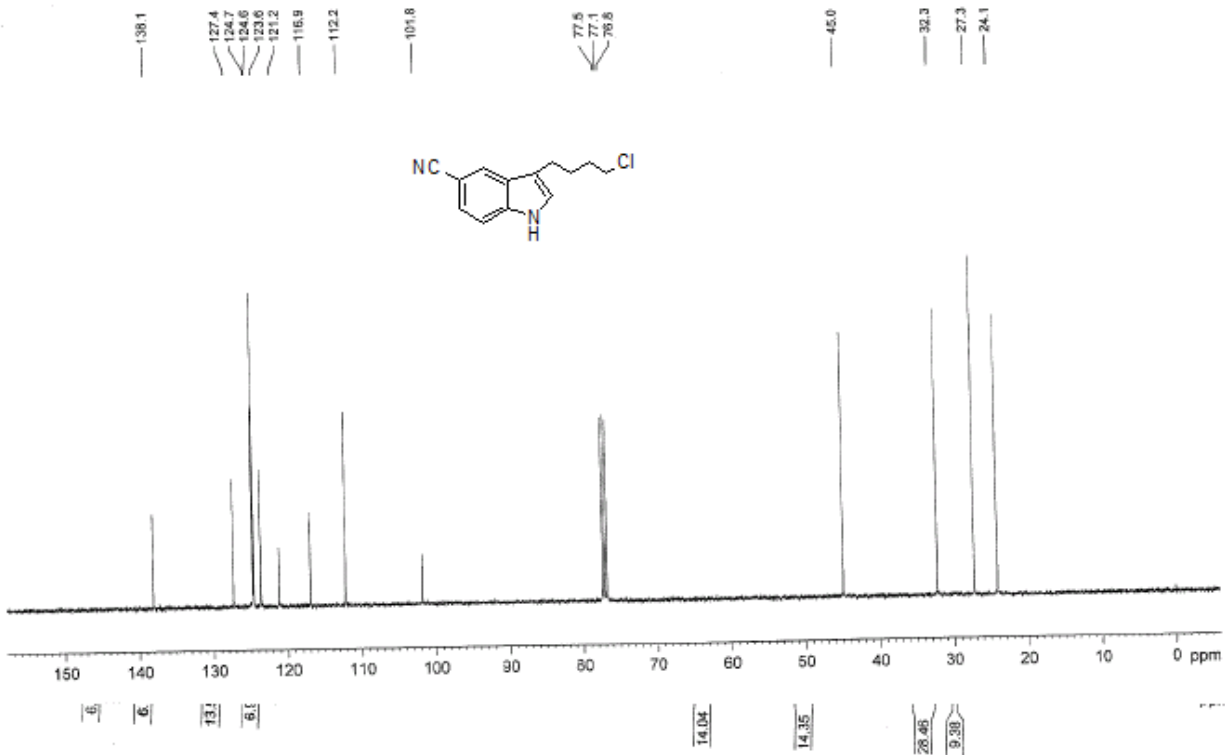


Mass Spectrum of **4a**

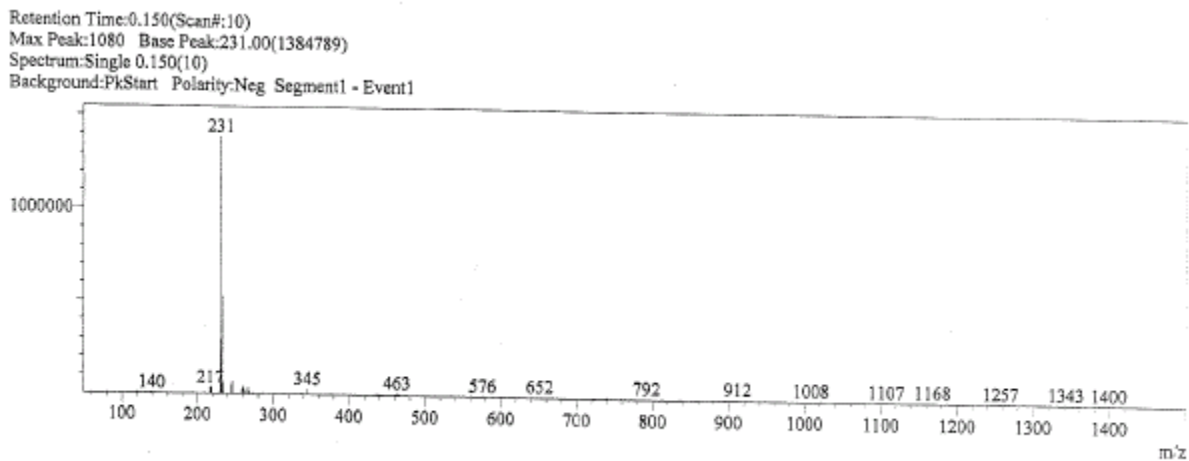


<sup>1</sup>H-NMR Spectrum of **2a** (400 MHz, CDCl<sub>3</sub>)

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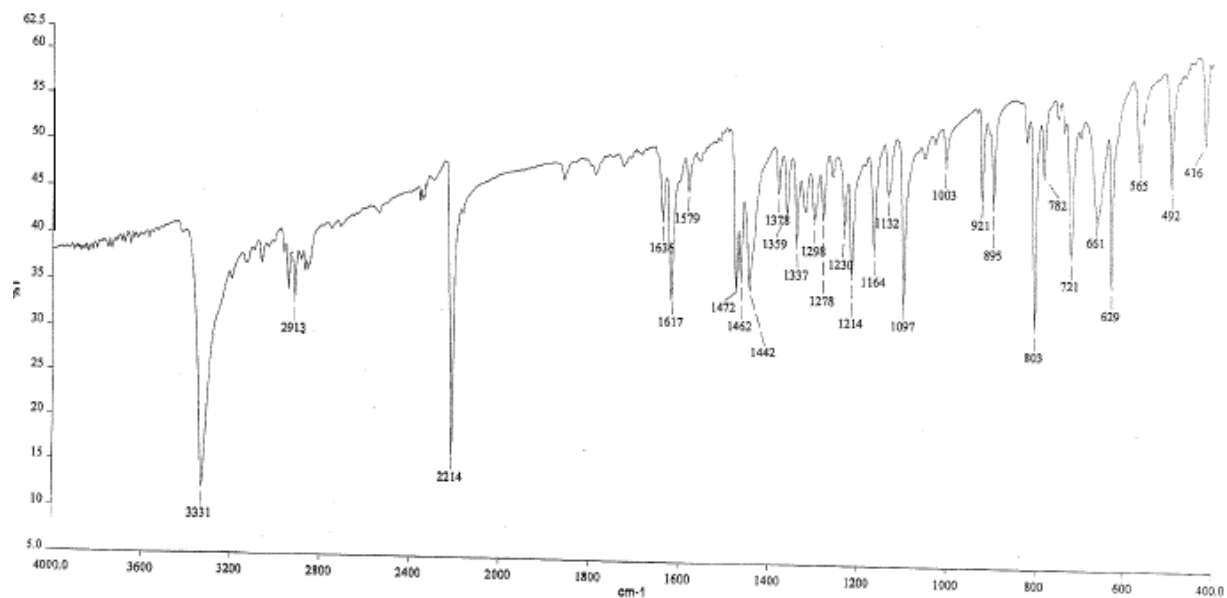


<sup>13</sup>C-NMR Spectrum of **2a** (100 MHz, CDCl<sub>3</sub>)

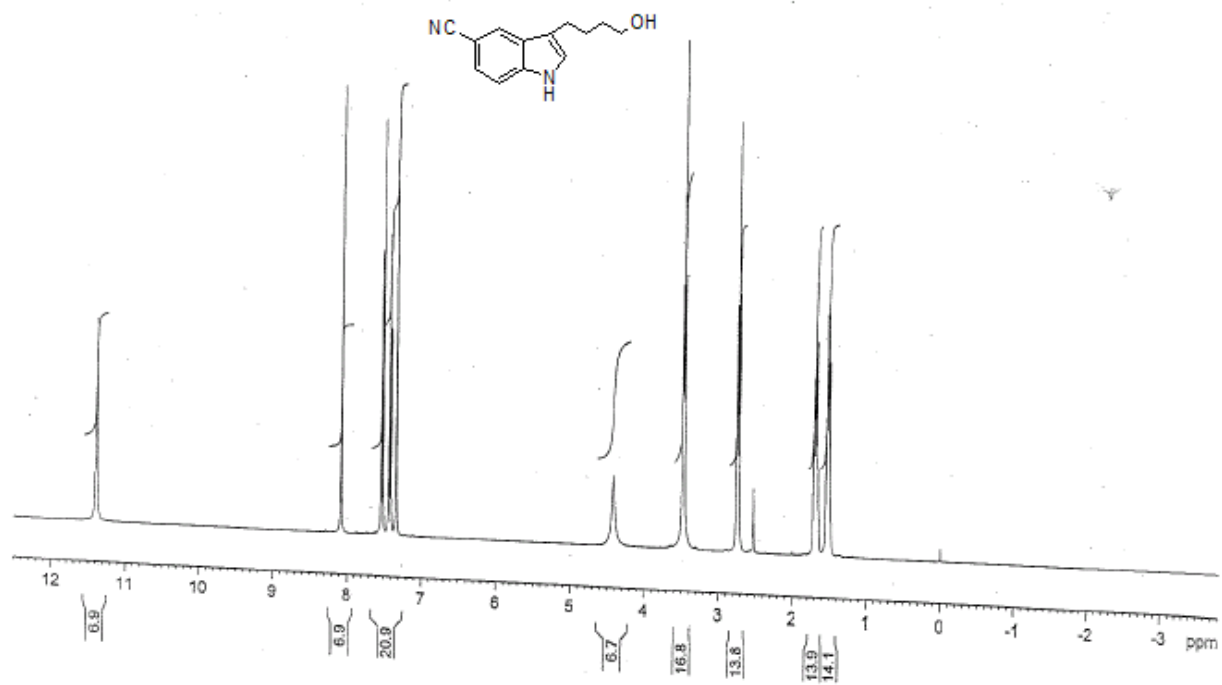


Mass Spectrum of **2a**

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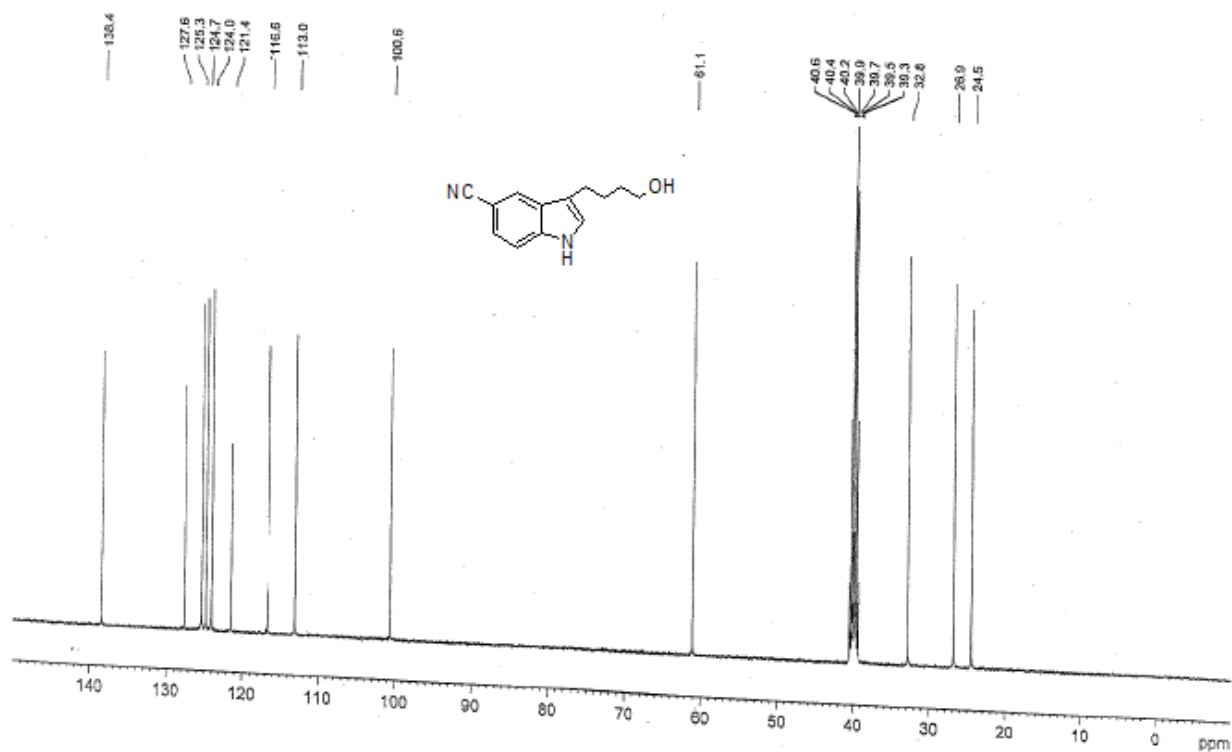


IR Spectrum of **2a**

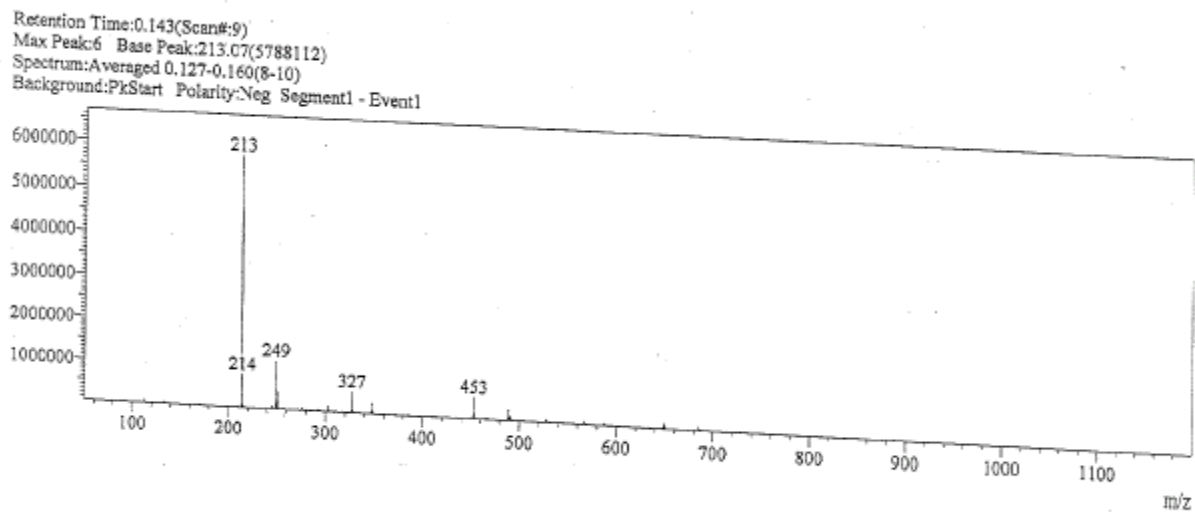


<sup>1</sup>H-NMR Spectrum of **2b** (400 MHz, CDCl<sub>3</sub>)

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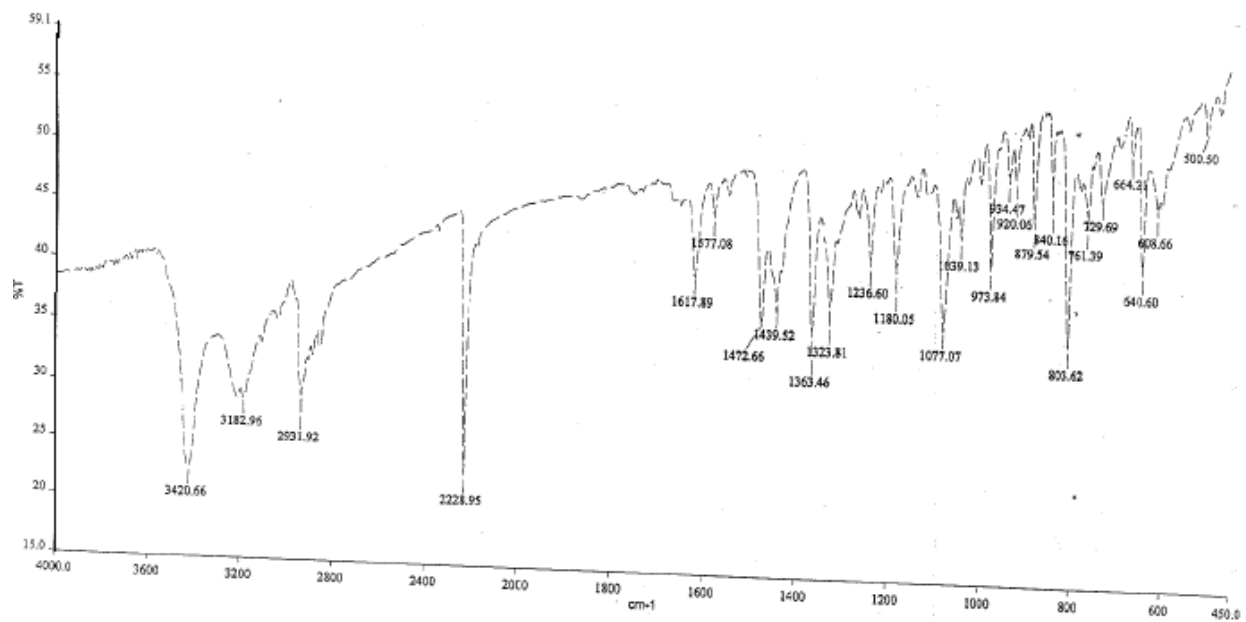
$^{13}\text{C}$ -NMR Spectrum of **2b** (100 MHz,  $\text{CDCl}_3$ )



Mass Spectrum of **2b**



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IR Spectrum of **2b**