Tandem Palladium-catalyzed N,C-Coupling/Carbonylation Sequence for the Synthesis of 2-Carboxyindoles

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Supporting Information

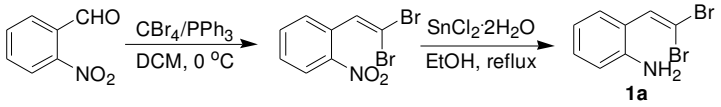
General:

The palladium catalysts were purchased from Strem Chemicals, and were used as received. All the 2-(2,2-dibromovinyl)phenylamines are known compounds, and were prepared as described in the literature.[1] Flash column chromatography was effected using silica gel (60 Å, 200–430 mesh) supplied by EMD. Mass spectra were determined using a VG 7070E spectrometer. Solution ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$, or in DMSO-d_6,containing TMS as internal standard, on a Bruker Avance 400 MHz. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are given in Hertz (Hz).

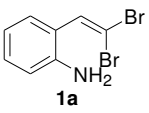
Carbon monoxide is a powerful asphyxiant and should be used with care. To use and work with carbon monoxide safely, reactions must be carried out in a proper working fumehood with carbon monoxide detectors installed nearby.

[1] Fang, Y. –Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538.

General procedure for the preparation of the gemdihalovinylanilines:[1]



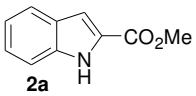
To a solution of CBr_4 (24.0 g, 72 mmol)and 2-nitrobenzaldehyde (7.26 g, 48 mmol) in DCM (200 mL) at 0 °C was added dropwise a solution of PPh_3 (37.8 g, 144 mmol) in DCM (150 mL). After addition, the mixture was stirred for another 0.5 h, and then for an additional 1 h at room temperature. The reaction mixture was filtered through a short column of silica gel, and washed with DCM until no product was found. the solvent was evaporated. The crude product was dissolved in EtOH (95%, 200 mL), and treated with $SnCl_2{\cdot}2H_2O$ (56 g, 240 mmol). The suspension was heated at 100 °C (reflux) for 45 min, and then cooled to rt. After most of the ethanol was removed under vacuum, H_2O (150 mL) and EtOAc (150 mL) were added. To the resulting mixture, solid K_2CO_3 was added carefully until pH 10. The EtOAc layer was separated from the heterogeneous mixture, and the aqueous phase was extracted several times with EtOAc. The combined organic phase were washed with brine and dried over Na_2SO_4 and K_2CO_3. The solvent was removed under vacuum and the residue was re-dissolved in Et_2O. The resulting precipitated triphenylphosphine oxide was removed by filtration. The product was further purified by flash chromatography using 10 % EtOAc in hexanes, to furnish **1a** as a yellow solid (10.8 g, 81% over 2 steps).



2-(2,2-Dibromovinyl)-phenylamine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (br, 2H), 6.70 (dd, *J* = 0.8 and 8.0 Hz, 1H), 6.77-6.81(m, 1H), 7.16 (ddd, *J*=7.7, 7.7, 1.4 Hz, 1H), 7.30 (d, *J*=7.7 Hz, 1H), 7.34(s, 1H).

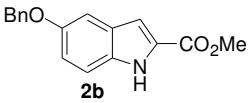
General procedure for the synthesis of the indoles:

A glass liner, equipped with a magnetic stirring bar, containing 1.0 mmol of the appropriate 2-(2,2-dibromovinyl)phenylamine **1**, $PdCl_2(PPh_3)_3$ (5.0 mol%, 35.6 mg), PPh_3 (10 mol %; 26.2 mg), DIPEA (2.0 mmol; 0.35 mL), THF (4 mL) and MeOH (4 mL) was placed in a 45 mL autoclave. The autoclave was flushed three times with carbon monoxide and pressurized to 10 atm. The autoclave was then placed in an oil bath pre-set to 110 °C on a stirring hot plate. After 20 h, the autoclave was removed from the oil bath and cooled to room temperature prior to the release of excess carbon monoxide. The residue was impregnated on silica gel, and then purified by chromatography with a mixture of hexane and ethyl acetate (85:15) as the eluant, to afford the 1*H*-indole-2-carboxylic acid methyl esters **2**.



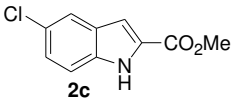
2a

1*H*-Indole-2-carboxylic acid methyl ester:[2] 70% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.15 (m, 1H), 7.23 (dd, *J*=2.1 and 1.0 Hz, 1H), 7.32 (m, 1H), 7.42 (dd, *J*=8.3 and 0.9 Hz, 1H), 7.68 (dd, *J*=8.1 and 0.9 Hz, 1H), 9.21 (bs, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 52.1, 108.8, 112.0, 120.8, 122.7, 125.4, 127.1, 127.5, 137.0, 162.7; HRMS Calcd. for $C_{10}H_9NO_2$ 175.0633, found 175.0651.



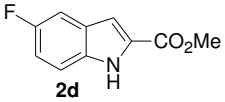
2b

5-Benzyloxy-1*H*-indole-2-carboxylic acid methyl ester:[3] 72% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 5.08 (s, 2H), 7.07 (dd, *J*=9.0 and 2.4 Hz, 1H), 7.12 (dd, *J*=2.0 and 0.8 Hz, 1H), 7.14 (d, *J*=2.4 Hz, 1H), 7.30-7.47 (m, 6H), 9.09 (bs, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 52.0, 70.7, 104.2, 108.4, 112.9, 117.7, 127.5, 127.6, 127.8, 127.9, 128.6, 132.5, 137.3, 153.9, 162.5; HRMS Calcd. for $C_{17}H_{15}NO_3$ 281.1052, found 281.1052.



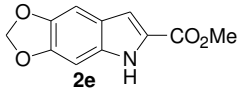
2c

5-Chloro-1*H*-indole-2-carboxylic acid methyl ester:[2] 68% yield, ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.14 (dd, *J*=2.0 and 0.7 Hz, 1H), 7.27 (dd, *J*=8.7 and 2.1 Hz, 1H), 7.46 (d, *J*=8.8 Hz, 1H), 7.73 (d, *J*=2.0 Hz, 1H), 12.14 (bs, 1H); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 52.4, 107.7, 114.7, 121.6, 125.2, 125.3, 128.2, 129.0, 136.2, 161.9; HRMS Calcd. for $C_{10}H_8ClNO_2$ 209.0244, found 209.0282.



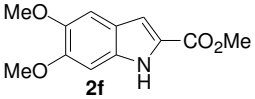
2d

5-Fluoro-1*H*-indole-2-carboxylic acid methyl ester:[4] 78% yield, ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.11-7.17 (m, 2H), 7.41-7.47 (m, 2H), 12.05 (bs, 1H); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 52.4, 106.5 (d, *J*= 23 Hz), 108.1, 108.2, 114.1 (d, *J*= 27 Hz), 114.4 (d, *J*= 10 Hz), 127.2 (d, *J*= 11 Hz), 129.2, 134.6, 157.7 (d, *J*= 232 Hz); HRMS Calcd. for $C_{10}H_8FNO_2$ 193.0539, found 193.0544.



2e

5*H*-[1,3]Dioxolo[4,5-f]indole-6-carboxylic acid methyl ester:[5] 67% yield, ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 (s, 3H), 5.99 (s, 2H), 6.88 (s, 1H), 7.01 (dd, *J*=2.2 and 0.8 Hz, 1H), 7.06 (s, 1H), 11.75 (bs, 1H); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 51.9, 92.5, 99.7, 101.2, 108.8, 121.3, 125.9, 133.7, 143.9, 147.5, 161.9; HRMS Calcd. for $C_{11}H_9NO_4$ 219.0532, found 219.0520.

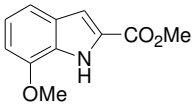


2f

5,6-Dimethoxy-1*H*-indole-2-carboxylic acid methyl ester:[2] 62% yield, ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.72 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 6.84 (s, 1H), 6.98 (d, *J*=1.6

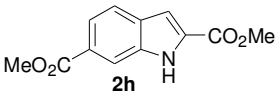
[2] Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500.
[3] Nazaré, M.; Will, D. W.; Matter, H.; Schreuder, H.; Ritter, K.; Urmann, M.; Essrich, M.; Bauer, A.; Wagner, M.; Czech, J.; Lorenz, M.; Laux, V.; Wehner, V. *J. Med. Chem.* **2005**, *48*, 4511.
[4] Barberis, C.; Gordon, T. D.; Thomas, C.; Zhang, Z.; Cusack, K. P. *Tetrahedron Lett.* **2005**, *46*, 8877.
[5] Sechi, M.; Derudas, M.; Dallocchio, R.; Dessì, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam. R.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 5298.

Hz, 1H), 7.04 (s, 1H), 11.59 (bs, 1H); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 51.9, 55.9, 56.0, 94.8, 102.9, 108.4, 120.1, 125.6, 133.1, 146.2, 149.9, 162.1; HRMS Calcd. for $C_{12}H_{13}NO_4$ 235.0845, found 235.0821.



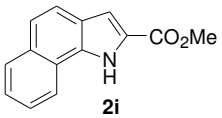
2g

7-Methoxy-1*H*-indole-2-carboxylic acid methyl ester:[6] 75% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.96 (s, 3H), 6.71 (dd, *J*=7.6 and 0.4 Hz, 1H), 7.06 (dd, *J*=8.0 and 7.7 Hz, 1H), 7.19 (d, *J*=2.3 Hz, 1H), 7.26 (dt, *J*=8.1 and 0.7 Hz, 1H), 9.09 (bs, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 51.9, 55.4, 104.1, 109.0, 114.8, 121.2, 126.9, 128.1, 128.6, 146.5, 162.2; HRMS Calcd. for $C_{11}H_{11}NO_3$ 205.0739, found 205.0748.



2h

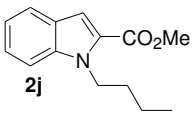
1*H*-Indole-2,6-dicarboxylic acid dimethyl ester: 73% yield, ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 3H), 3.92 (s, 3H), 7.24 (dd, *J*=2.0 and 0.8 Hz, 1H), 7.68 (dd, *J*=8.4 and 1.4 Hz, 1H) 7.77 (d, *J*=8.4 Hz, 1H), 8.14 (s, 1H), 12.36 (bs, 1H); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 52.5, 52.6, 108.0, 115.1, 120.8, 122.6, 125.9, 130.5, 130.6, 136.9, 161.9, 167.2; HRMS Calcd. for $C_{12}H_{11}NO_4$ 233.0688, found 233.0702.



2i

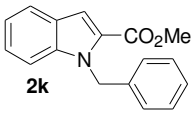
1*H*-Benzo[*g*]indole-2-carboxylic acid methyl ester:[2] 60% yield, ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 3H), 7.28 (d, *J*=2.1 Hz, 1H), 7.46 (m, 1H), 7.48 (d, *J*=0.6 Hz, 1H), 7.53 (m, 1H), 7.65 (d, *J*=8.7 Hz, 1H), 7.89 (d, *J*=7.5 Hz, 1H), 8.74 (dd, *J*=7.6 and 0.5 Hz, 1H), 12.77 (bs, 1H); ^{13}C NMR (100.1 MHz, DMSO-d_6) δ 52.2, 110.2, 121.6, 121.9, 122.6, 122.7, 123.6, 125.8, 126.2, 126.3, 128.9, 131.9, 133.7, 162.1; HRMS Calcd. for $C_{14}H_{11}NO_2$ 225.0790, found 225.0784.

[6] Coowar, D,; Bouissac, J.; Hanbali, M,; Paschaki, M.; Mohier, E.; Luu, B. *J. Med. Chem.* **2004**, *47*, 6270.



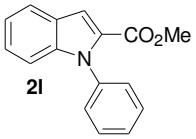
2j

1-Butyl-1*H*-indole-2-carboxylic acid methyl ester: 67% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.36 (sext, *J*=7.3 Hz, 2H), 1.77 (m, 2H), 3.89 (s, 3H), 4.55 (t, *J*=7.5 Hz, 2H), 7.10-7.15 (m, 1H), 7.28 (s, 1H), 7.29-7.34 (m, 1H), 7.38 (dd, *J*=8.4 and 0.8 Hz, 1H), 7.66 (d, *J*=8.1 Hz, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 13.8, 20.2, 32.7, 44.5, 51.6, 110.5, 120.5, 122.7, 124.9, 127.9, 126.0, 127.1, 139.1, 162.5; HRMS Calcd. for $C_{14}H_{17}NO_2$ 231.1259, found 231.1255.



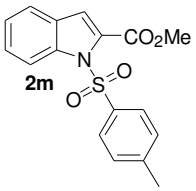
2k

1-Benzyl-1*H*-indole-2-carboxylic acid methyl ester:[7] 70% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 5.82 (s, 2H), 7.02 (d, *J*=7.4 Hz, 2H), 7.11-7.33 (m, 6H), 7.37 (s, 1H), 7.68 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 47.9, 51.7, 110.9, 111.2, 120.9, 122.8, 125.4, 126.2, 126.3, 127.2, 127.4, 128.6, 138.3, 139.6, 162.4; HRMS Calcd. for $C_{17}H_{15}NO_2$ 265.1103, found 265.1196.



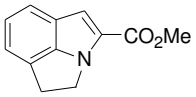
2l

1-Phenyl-1*H*-indole-2-carboxylic acid methyl ester: 72% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 7.08-7.34 (m, 5H), 7.44 (d, *J*=0.8 Hz, 1H), 7.45-7.53 (m, 3H), 7.72 (dt, *J*=7.9 and 1.0 Hz, 1H), 7.41 (d, *J*=8.3 Hz, 1H), 7.68 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 51.7, 111.5, 111.6, 121.3, 122.5, 125.5, 126.1, 128.0, 128.2, 128.6, 129.0, 138.4, 140.7, 161.7; HRMS Calcd. for $C_{16}H_{13}NO_2$ 251.0946, found 251.0957.



2m

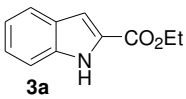
1-(Toluene-4-sulfonyl)-1*H*-indole-2-carboxylic acid methyl ester:[8] 50% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.92 (s, 3H), 7.15 (d, *J*=0.8 Hz, 1H), 7.22-7.27 (m, 3H), 7.39-7.55 (m, 2H),7.90 (d, *J*=8.4 Hz, 2H), 8.11 (dd, *J*=8.0 and .08 Hz, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 21.6, 52.8, 115.4, 116.9, 122.5, 124.1, 127.1, 127.4, 128.2, 129.6, 131.4, 135.7, 138.2, 145.0, 161.8; HRMS Calcd. for $C_{17}H_{15}NO_4S$ 329.0722, found 329.0618.



2n

4,5-Dihydro-pyrrolo[3,2,1-*hi*]indole-2-carboxylic acid methyl ester: 69% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (t, *J*=6.9 Hz, 2H), 3.88 (s, 3H), 4.63 (t, *J*=6.8 Hz, 2H), 6.95-7.01 (m, 2H), 7.08 (s, 1H), 7.32 (dd, *J*=7.6 and 0.8 Hz, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 33.6, 51.0, 51.7, 110.7, 118.0, 118.5, 119.1, 123.1, 126.2, 127.0, 149.6, 162.5; HRMS Calcd. for $C_{12}H_{11}NO_2$ 201.0790, found 201.0776.

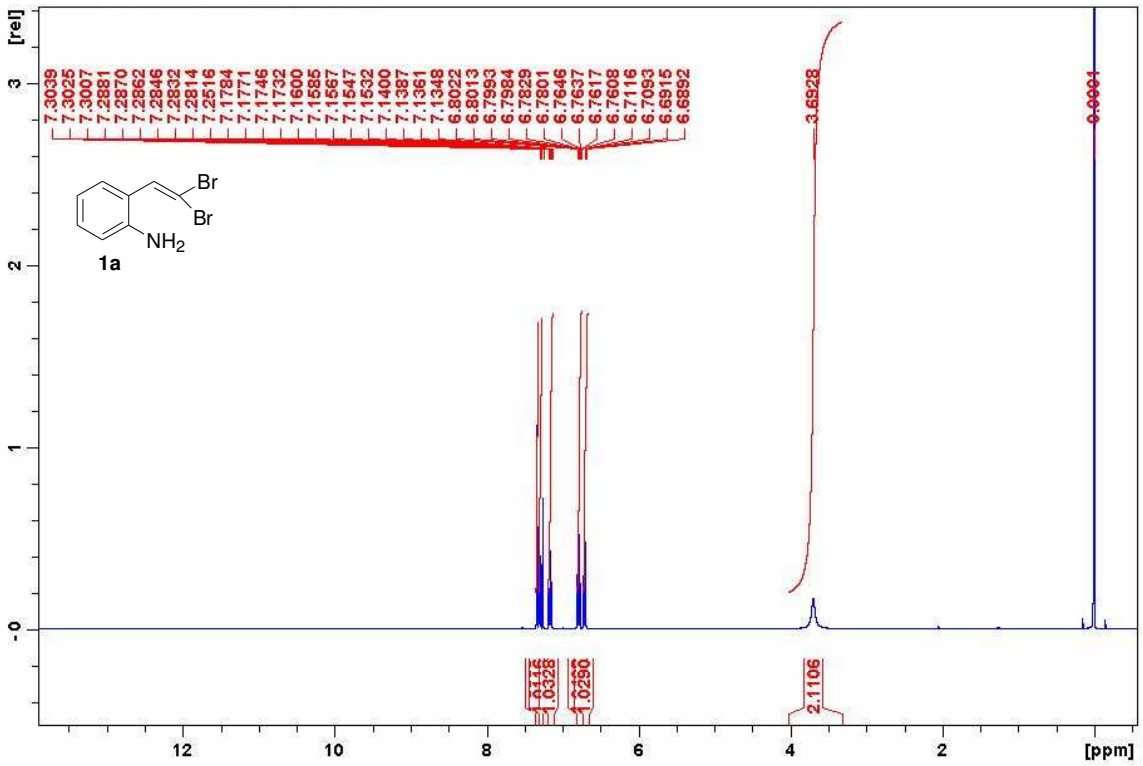
[7] Reed, G. W. B.; Cheng, P. T. W.; McLean, S. *Can. J. Chem.* **1982**, *60*, 419.
[8] Rosa, C. D.; Kneeteman, M.; Mancini, P. **2007**, *48*, 1435.



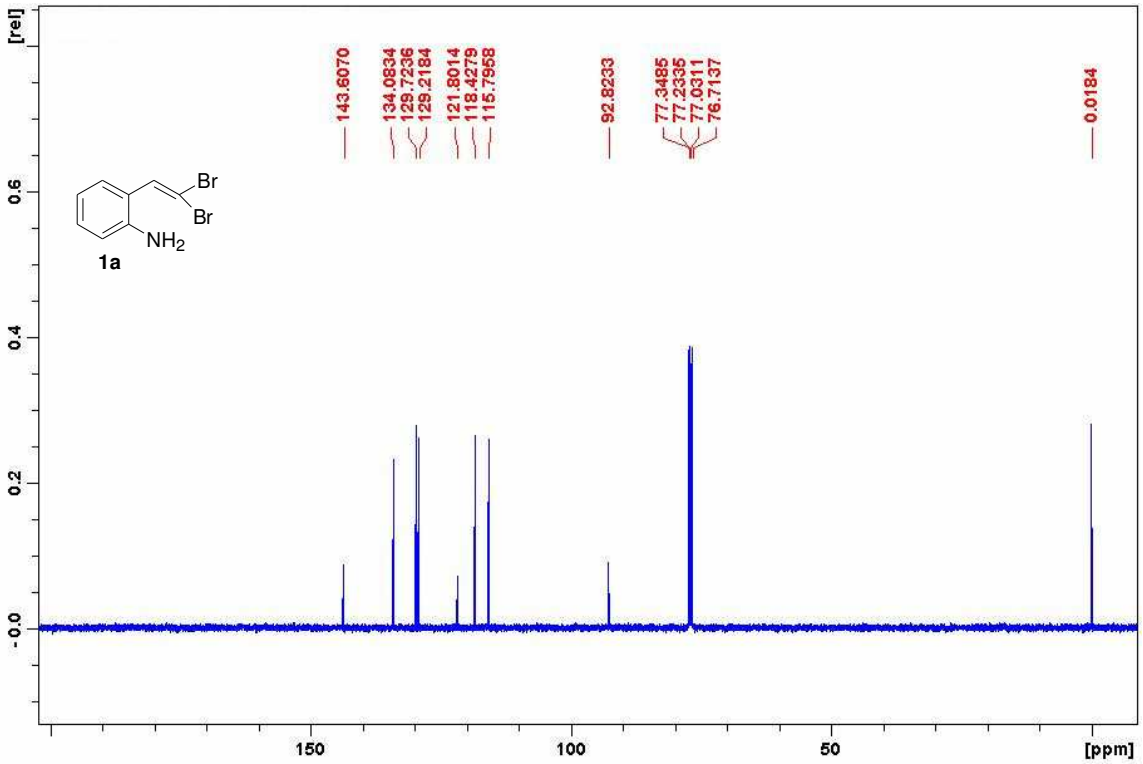
3a

1*H*-Indole-2-carboxylic acid ethyl ester:[9] 61% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, *J*=7.1 Hz, 3H), 4.42 (q, *J*=7.1 Hz, 2H), 7.14 (t, *J*=7.2 Hz, 1H), 7.23 (d, *J*=1.2 Hz, 1H), 7.30 (t, *J*=7.2 Hz, 1H), 7.41 (d, *J*=8.3 Hz, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 9.33 (bs, 1H); ^{13}C NMR (100.1 MHz, $CDCl_3$) δ 14.4, 61.1, 108.7, 112.0, 120.8, 122.6, 125.7, 127.5, 129.3, 137.0, 162.3; HRMS Calcd. for $C_{11}H_{11}NO_2$ 189.0790, found 189.0774.

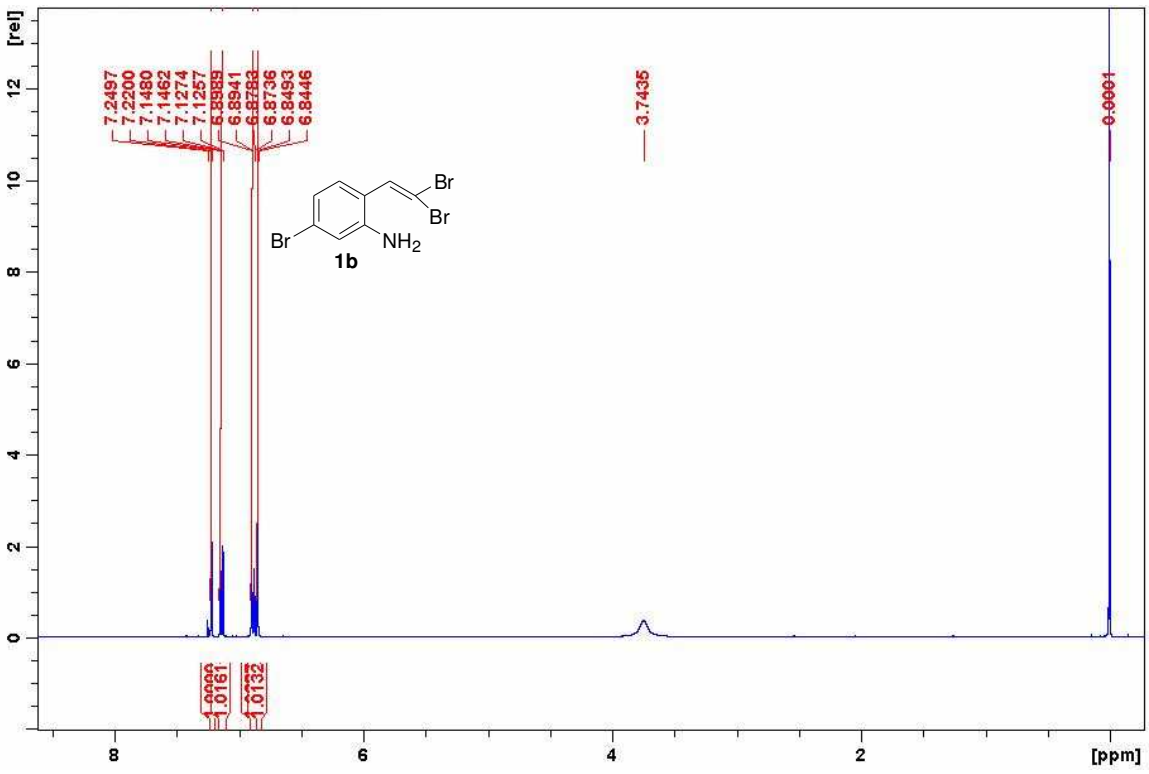
[9] Csomós, P.; Fodor, L.; Mándity, I.; Bernáth, G. *Tetrahedron* **2007**, *63*, 4983.



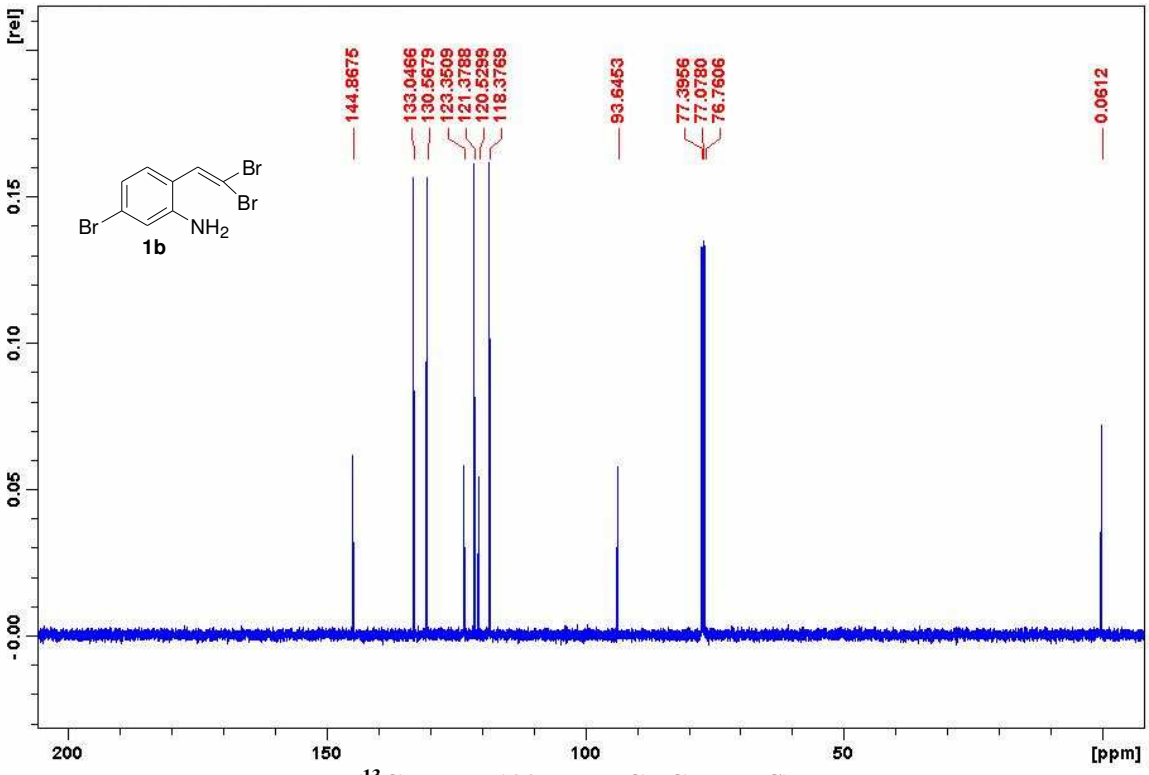
(¹H NMR, 400 MHz, $CDCl_3$, TMS)



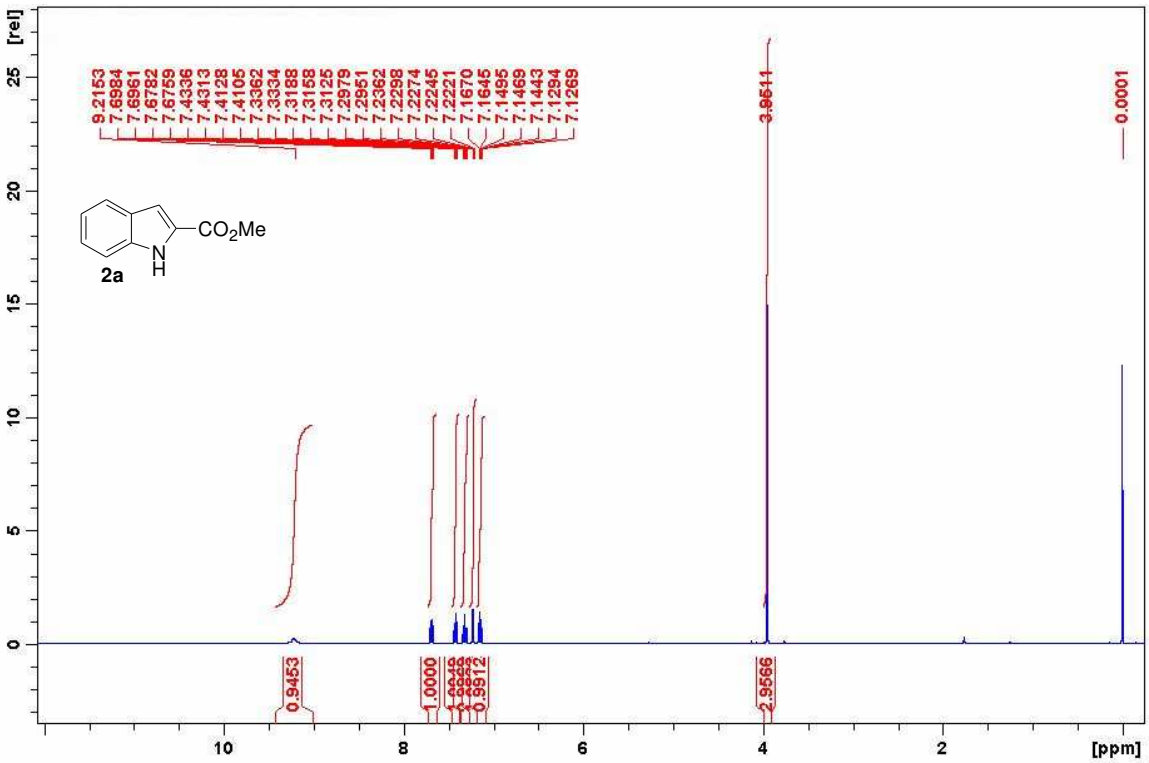
(¹³C NMR, 100 MHz, $CDCl_3$, TMS)



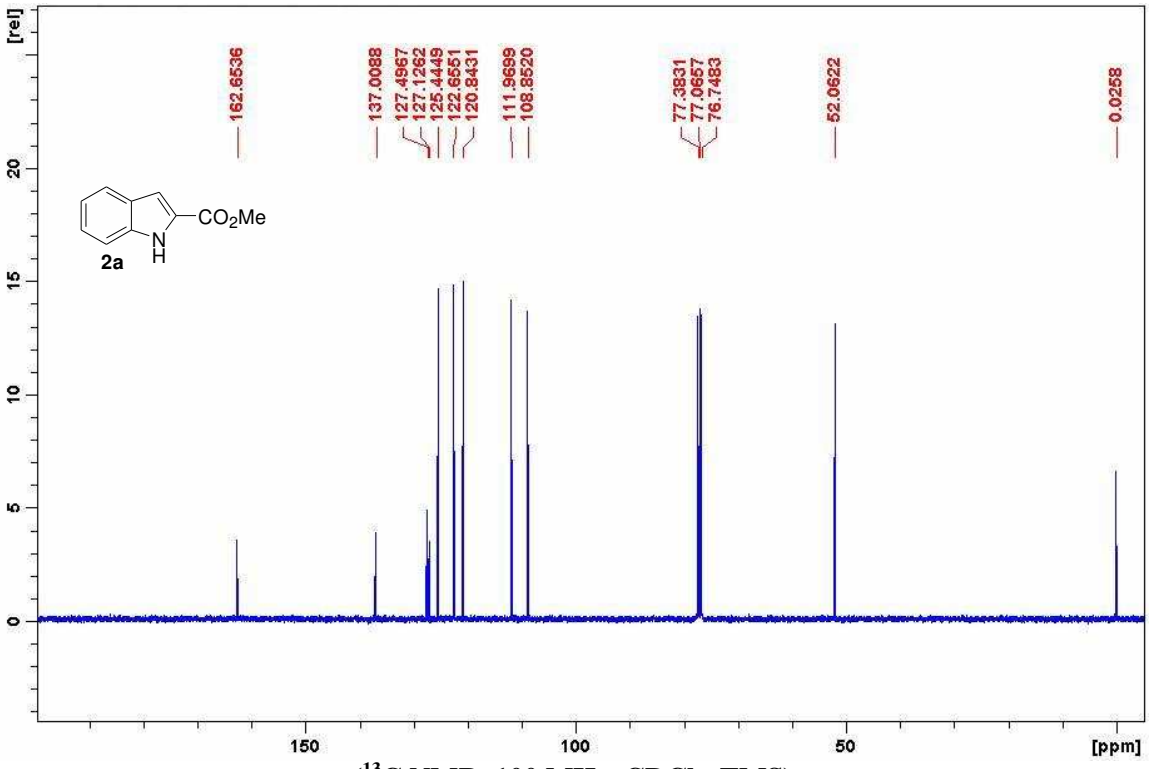
(**^{1}H NMR, 400 MHz, $CDCl_3$, TMS**)



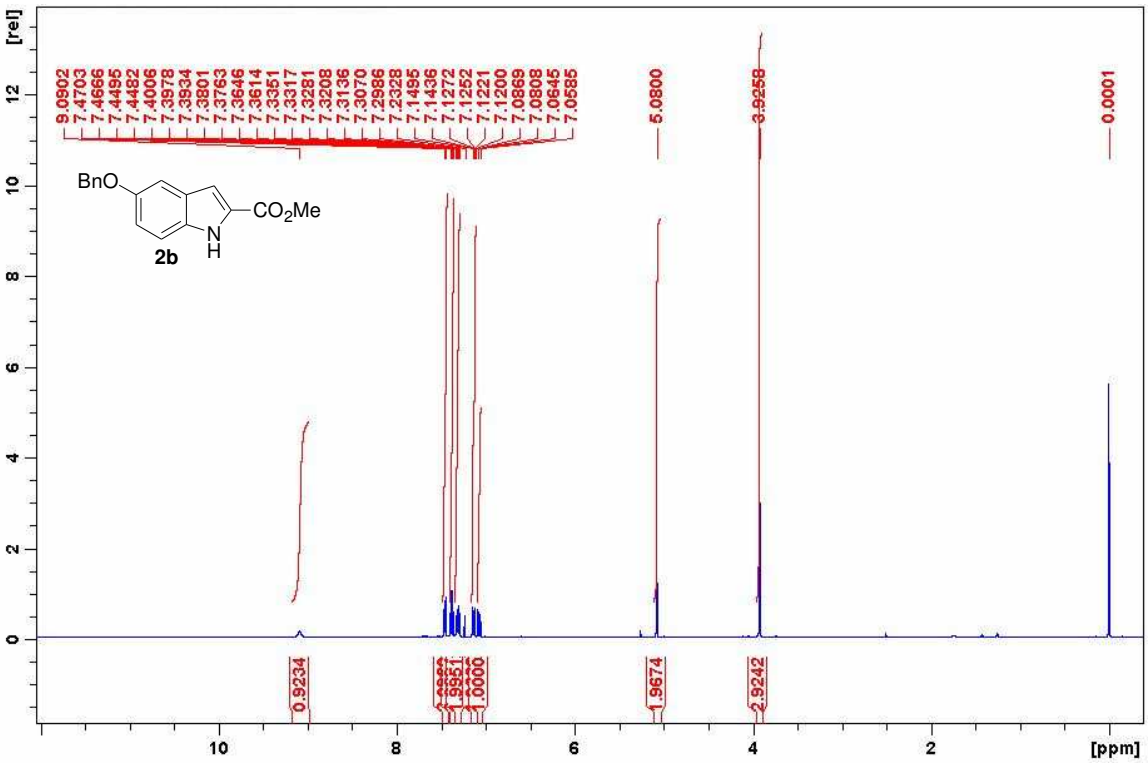
(**^{13}C NMR, 100 MHz, $CDCl_3$, TMS**)



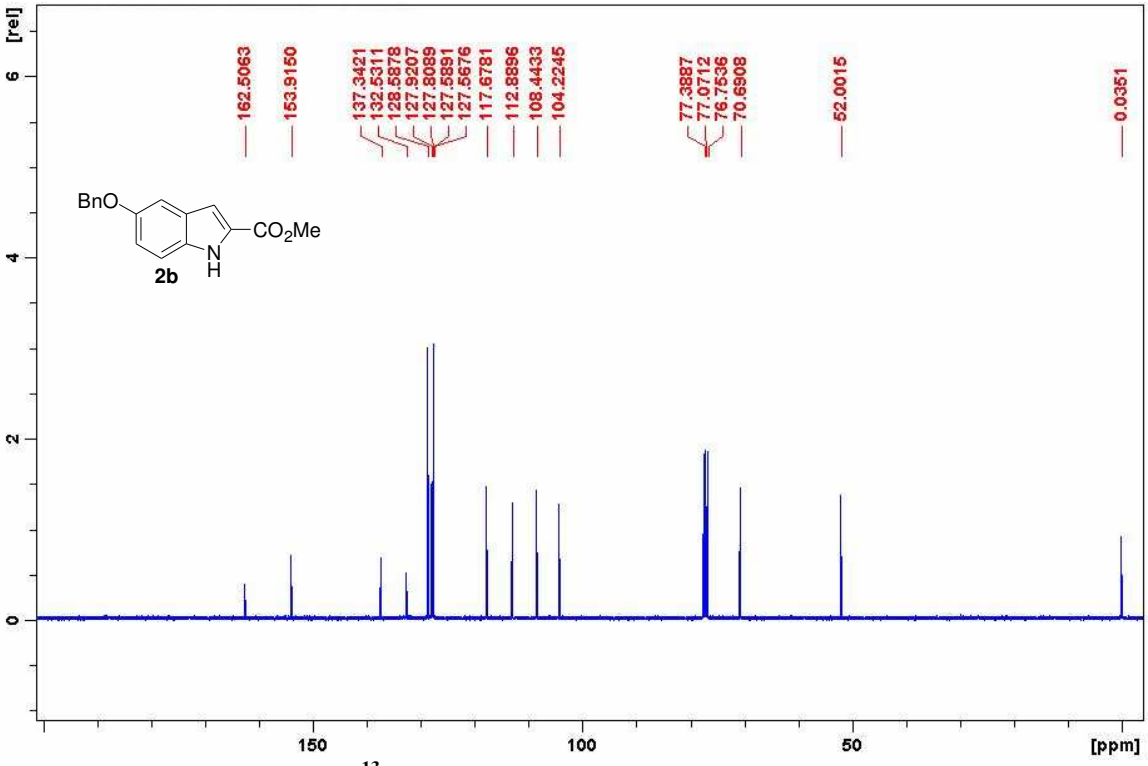
(¹H NMR, 400 MHz, $CDCl_3$, TMS)



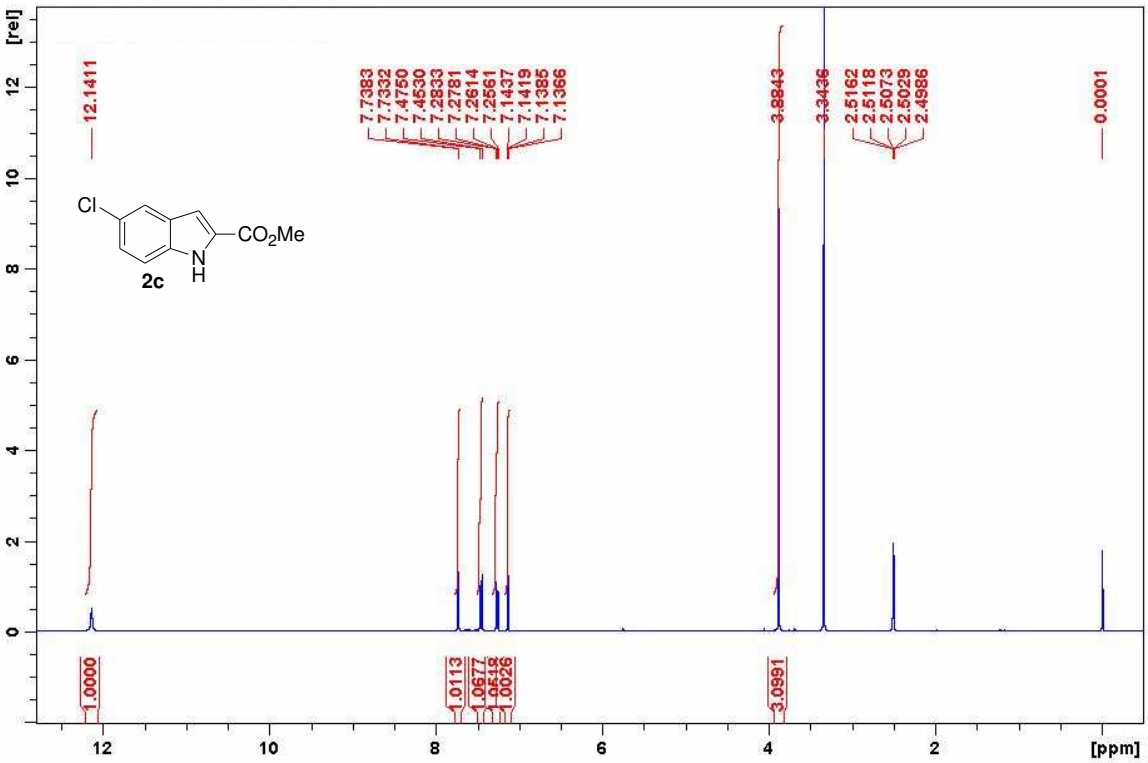
(¹³C NMR, 100 MHz, $CDCl_3$, TMS)



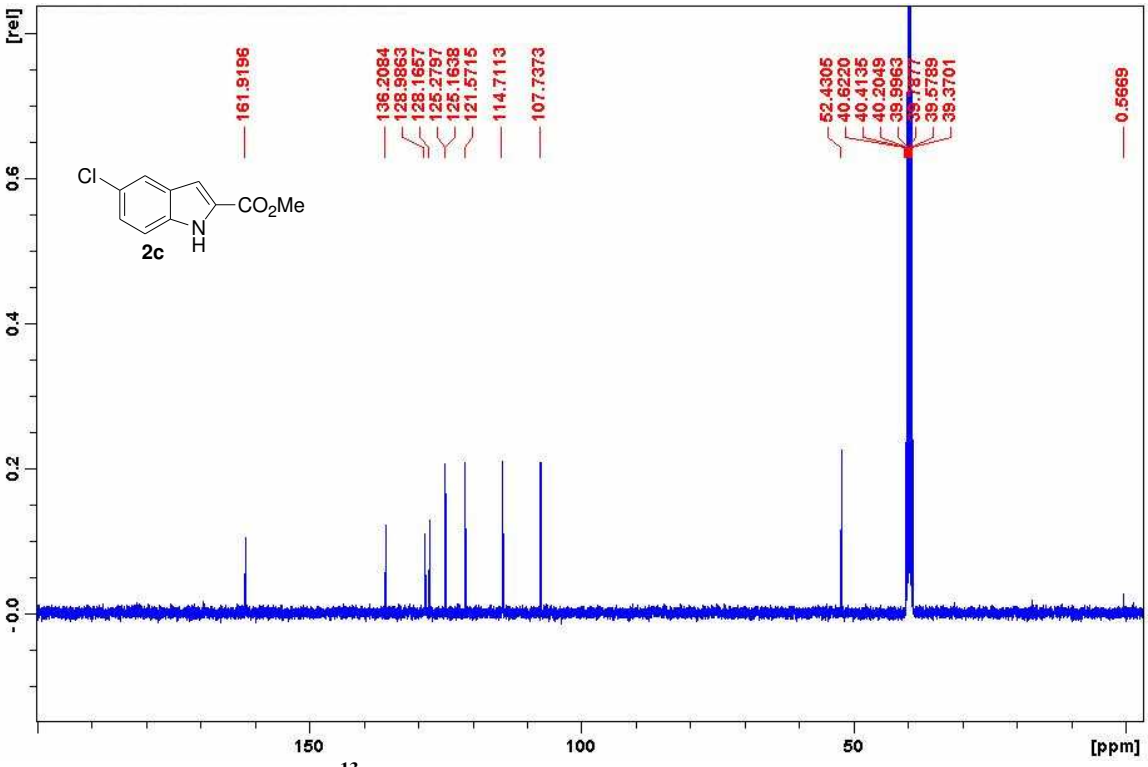
(¹H NMR, 400 MHz, $CDCl_3$, TMS)



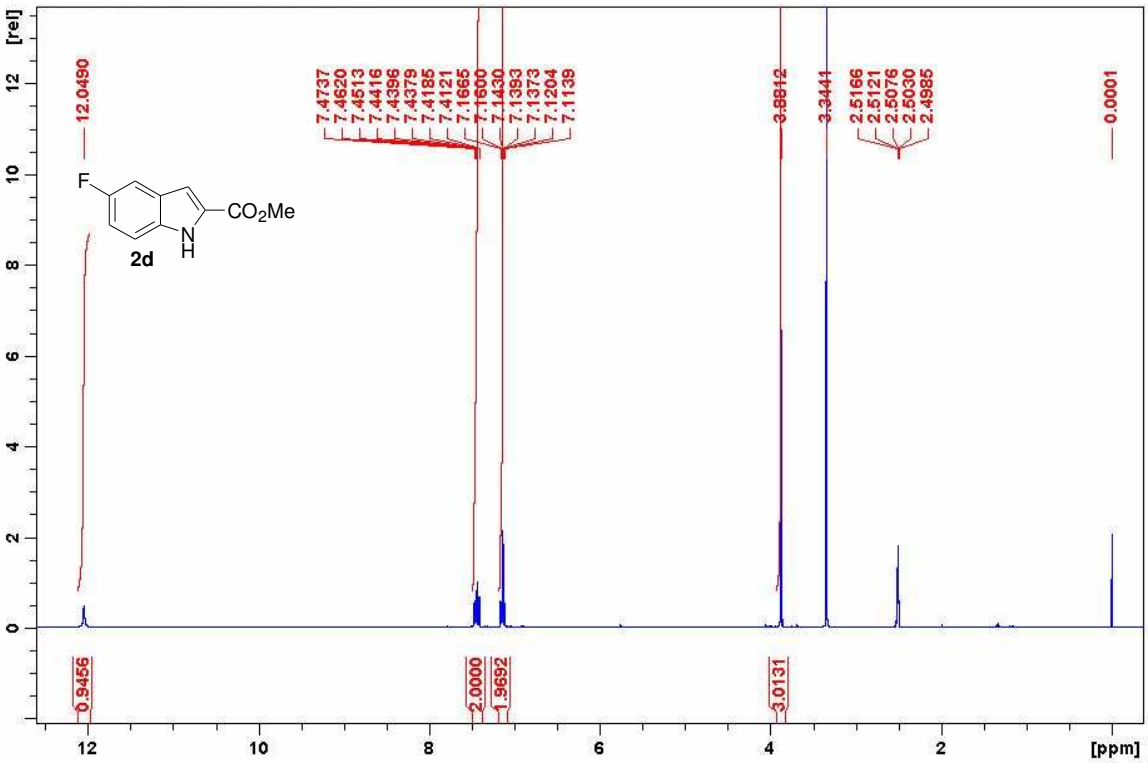
(¹³C NMR, 100 MHz, $CDCl_3$, TMS)



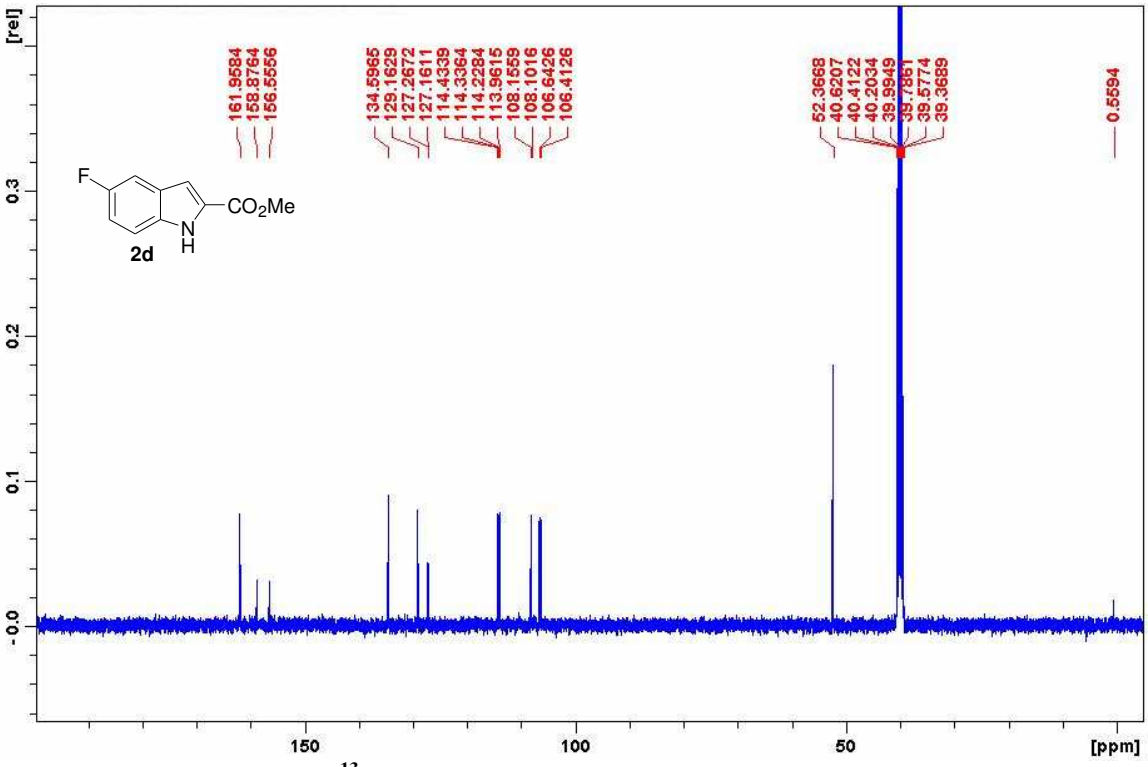
(**^{1}H NMR, 400 MHz, DMSO-d$_6$, TMS**)



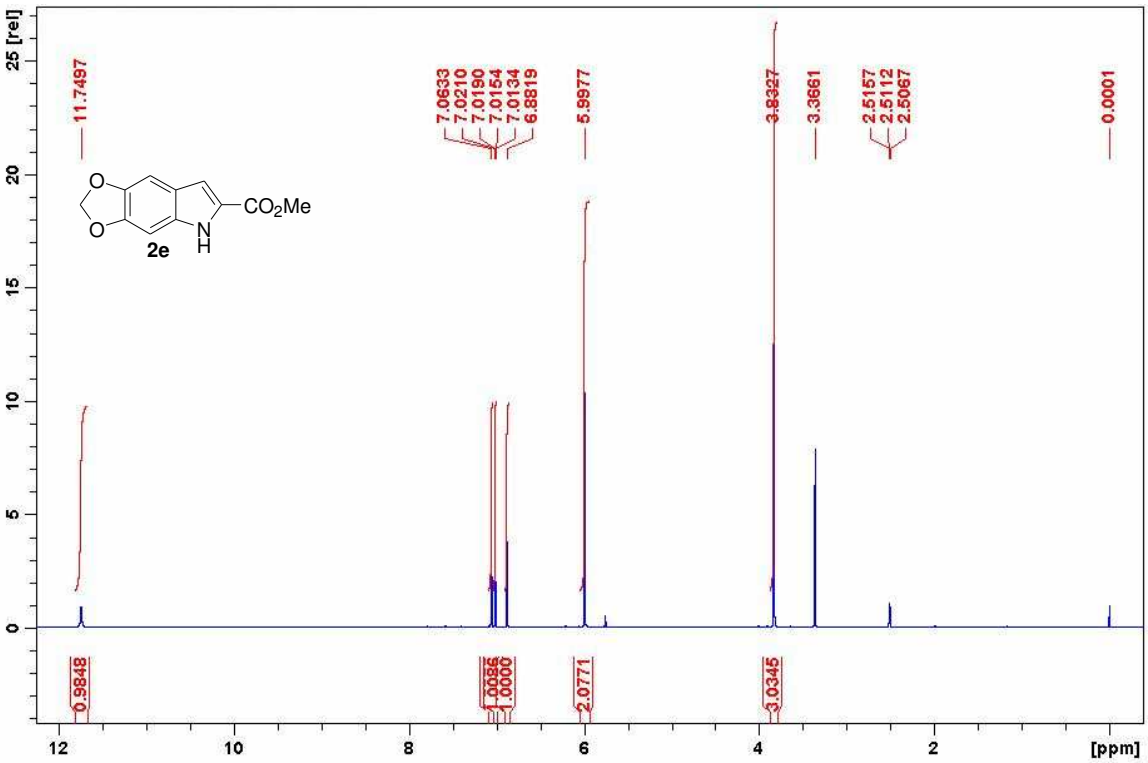
(**^{13}C NMR, 100 MHz, DMSO-d$_6$, TMS**)



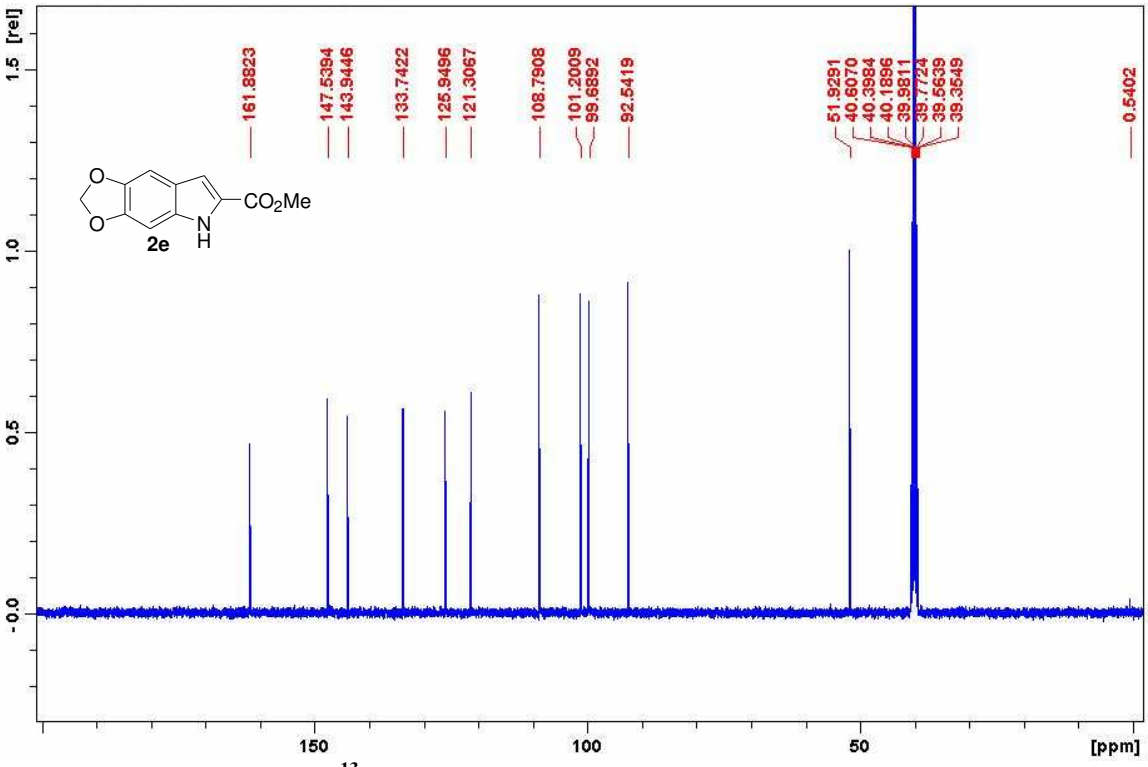
(**^{1}H NMR, 400 MHz, DMSO-d$_6$, TMS**)



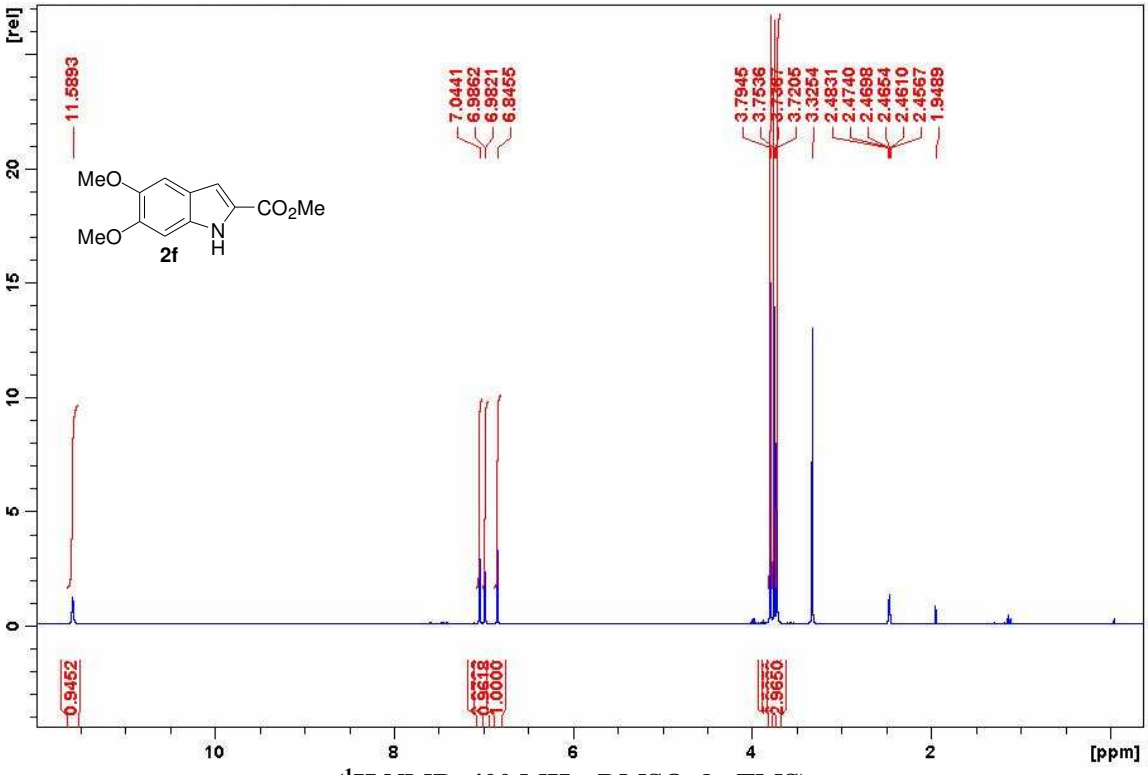
(**^{13}C NMR, 100 MHz, DMSO-d$_6$, TMS**)



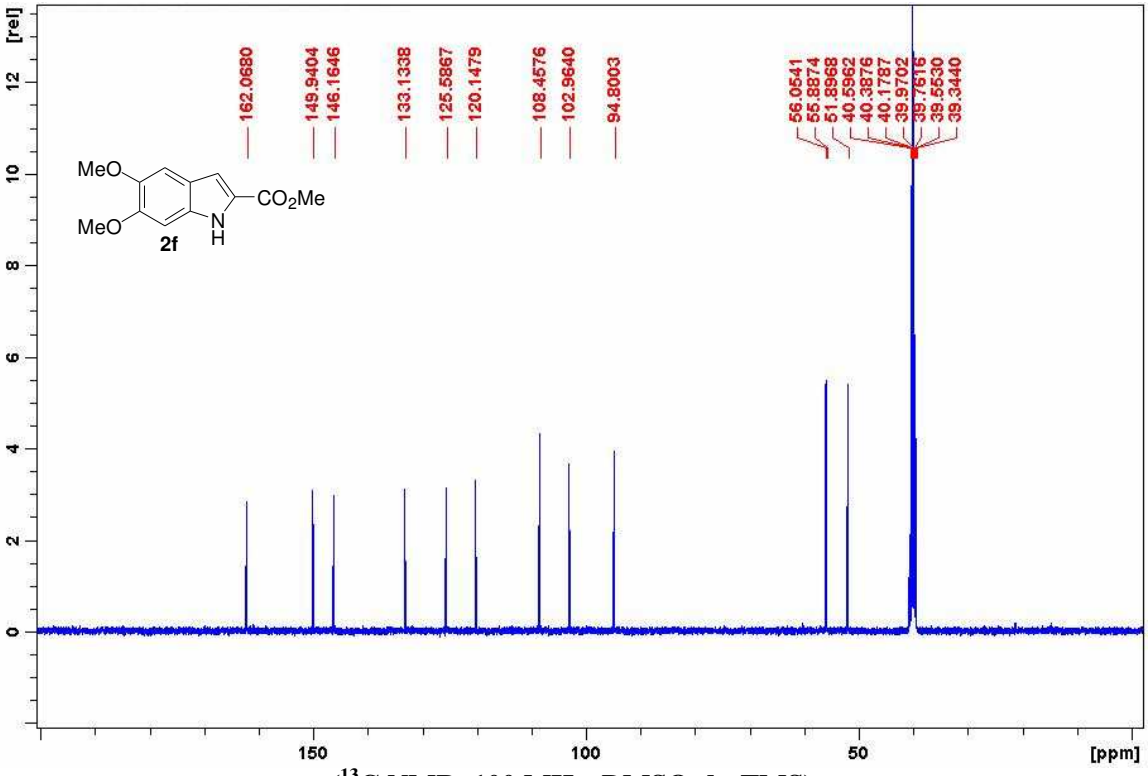
(^{1}H NMR, 400 MHz, DMSO-d_6, TMS)



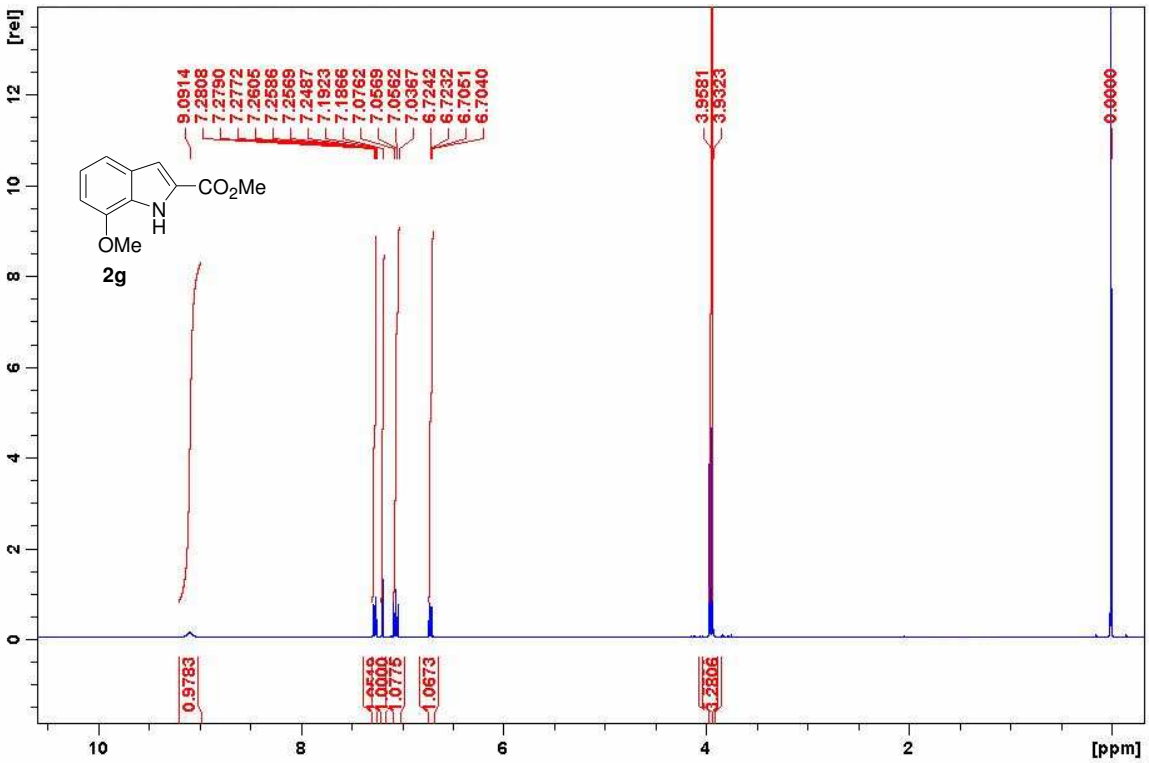
(^{13}C NMR, 100 MHz, DMSO-d_6, TMS)



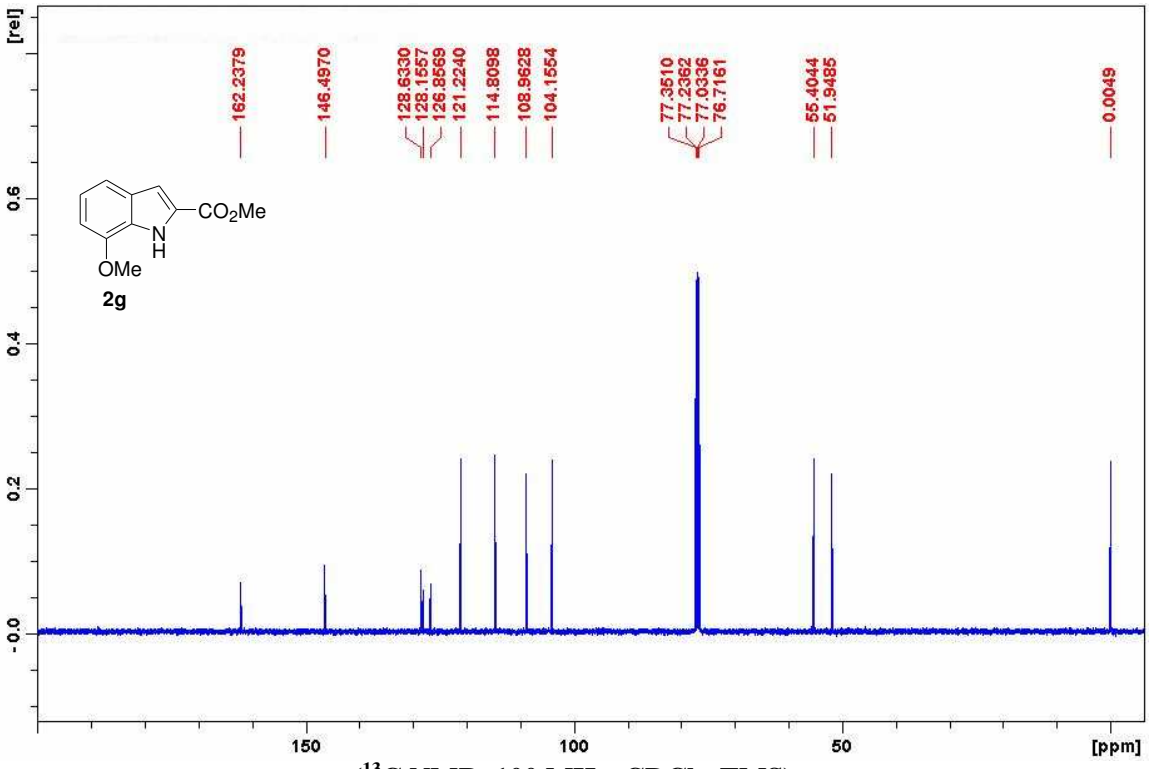
(**^{1}H NMR, 400 MHz, DMSO-d$_6$, TMS**)



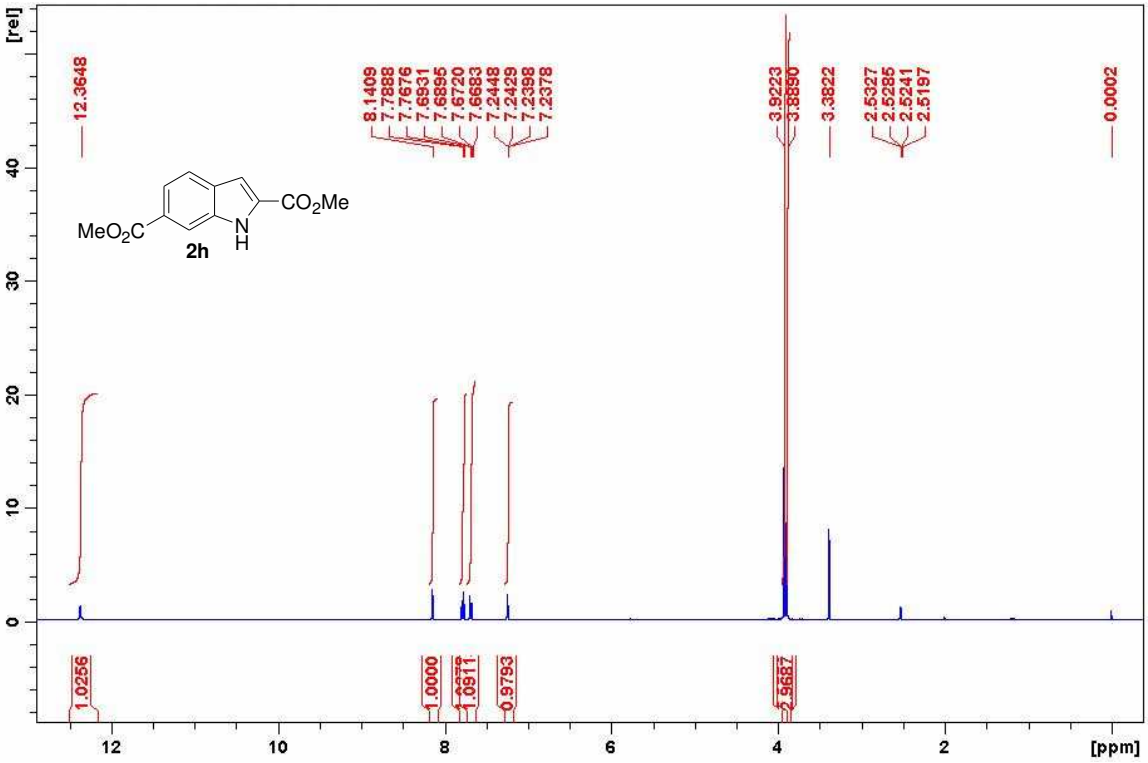
(**^{13}C NMR, 100 MHz, DMSO-d$_6$, TMS**)



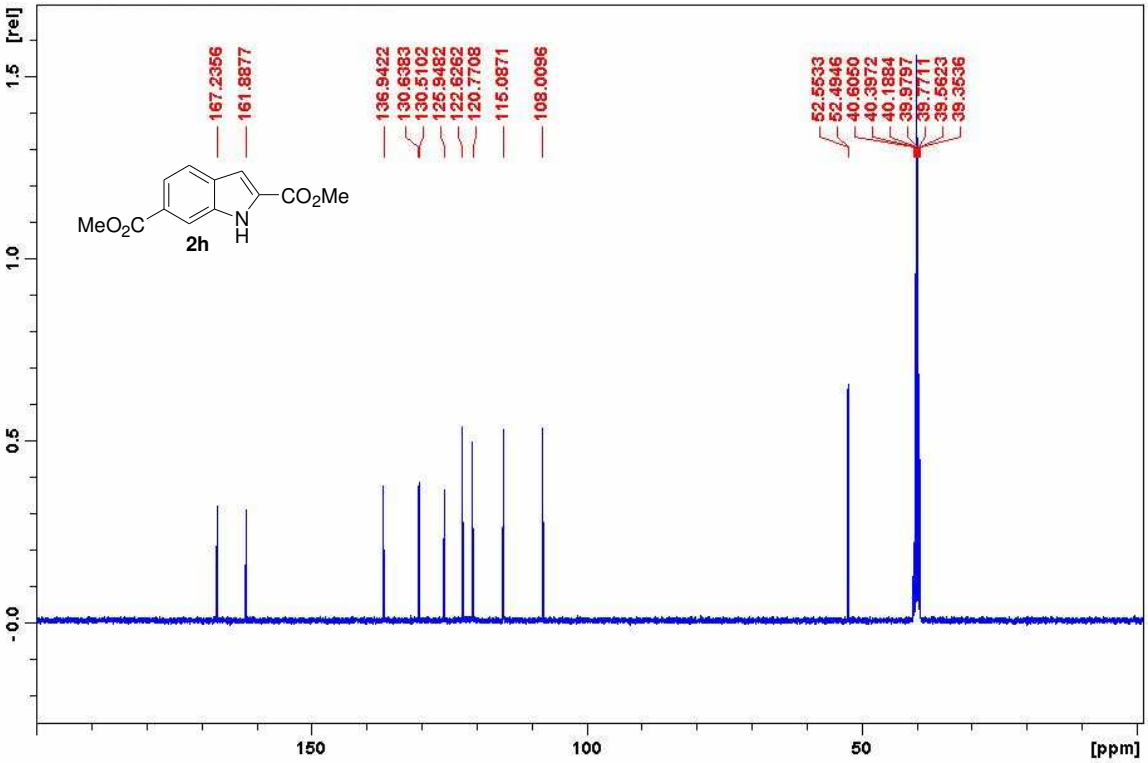
(¹H NMR, 400 MHz, $CDCl_3$, TMS)



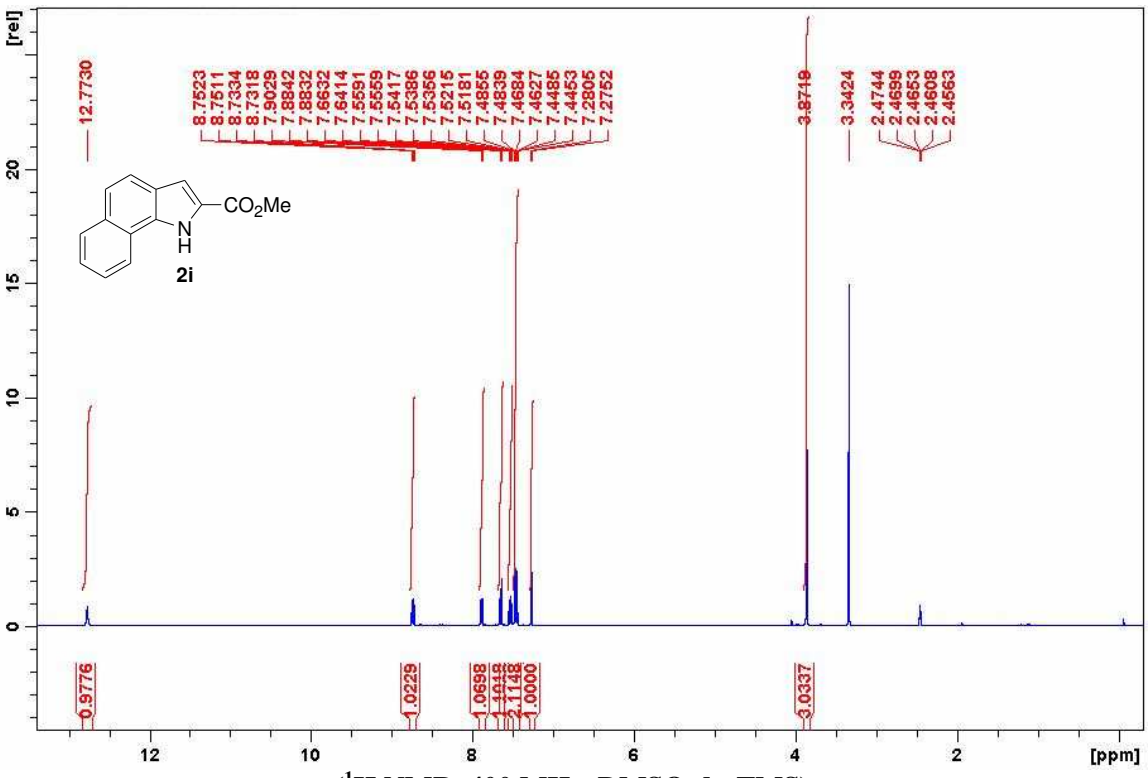
(¹³C NMR, 100 MHz, $CDCl_3$, TMS)



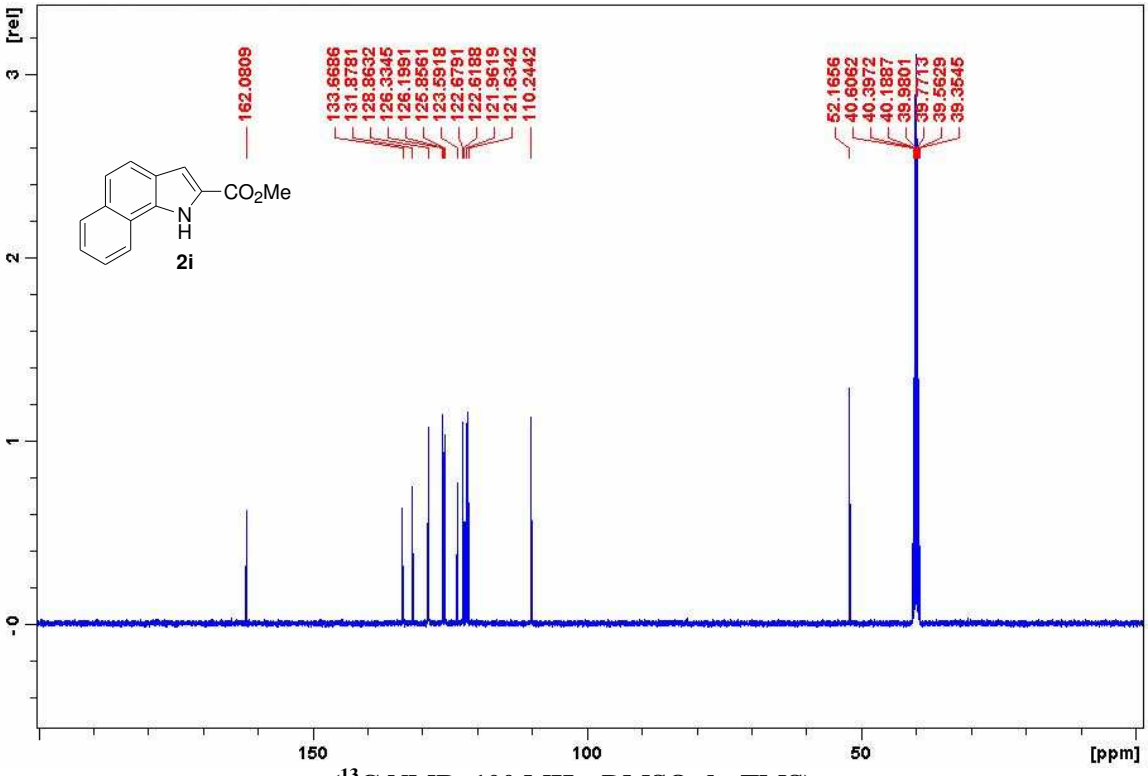
(¹H NMR, 400 MHz, DMSO-d$_6$, TMS)



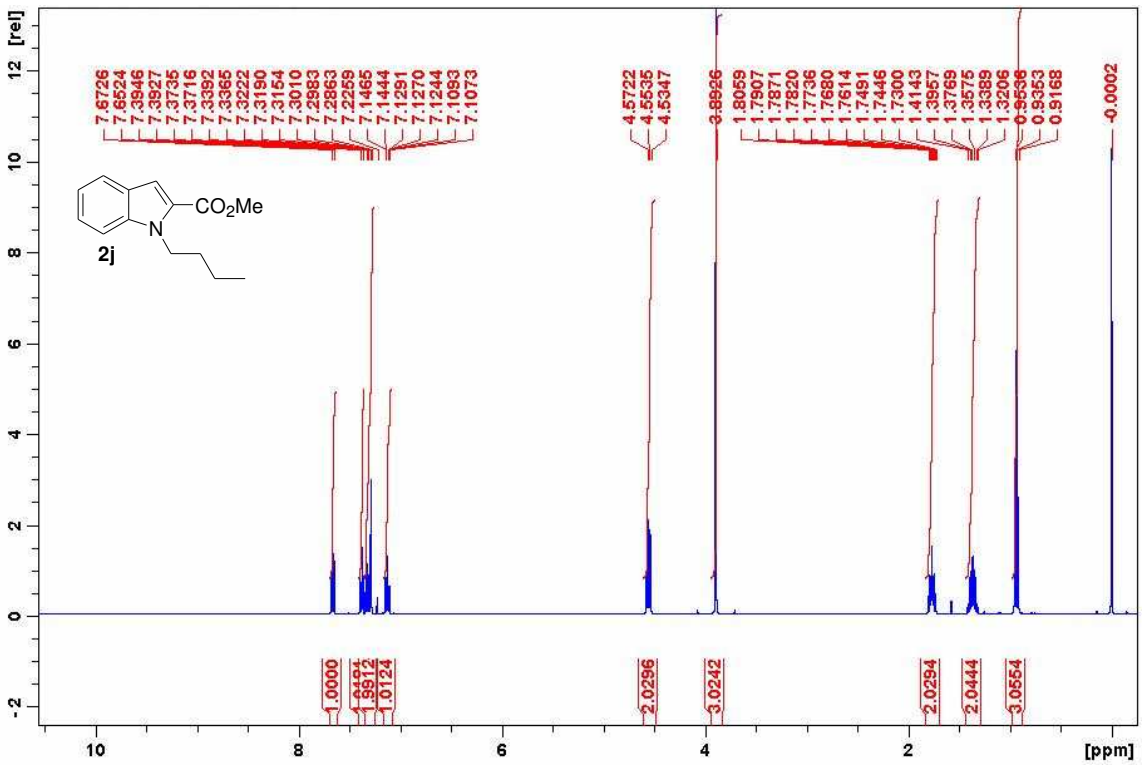
(¹³C NMR, 100 MHz, DMSO-d$_6$, TMS)



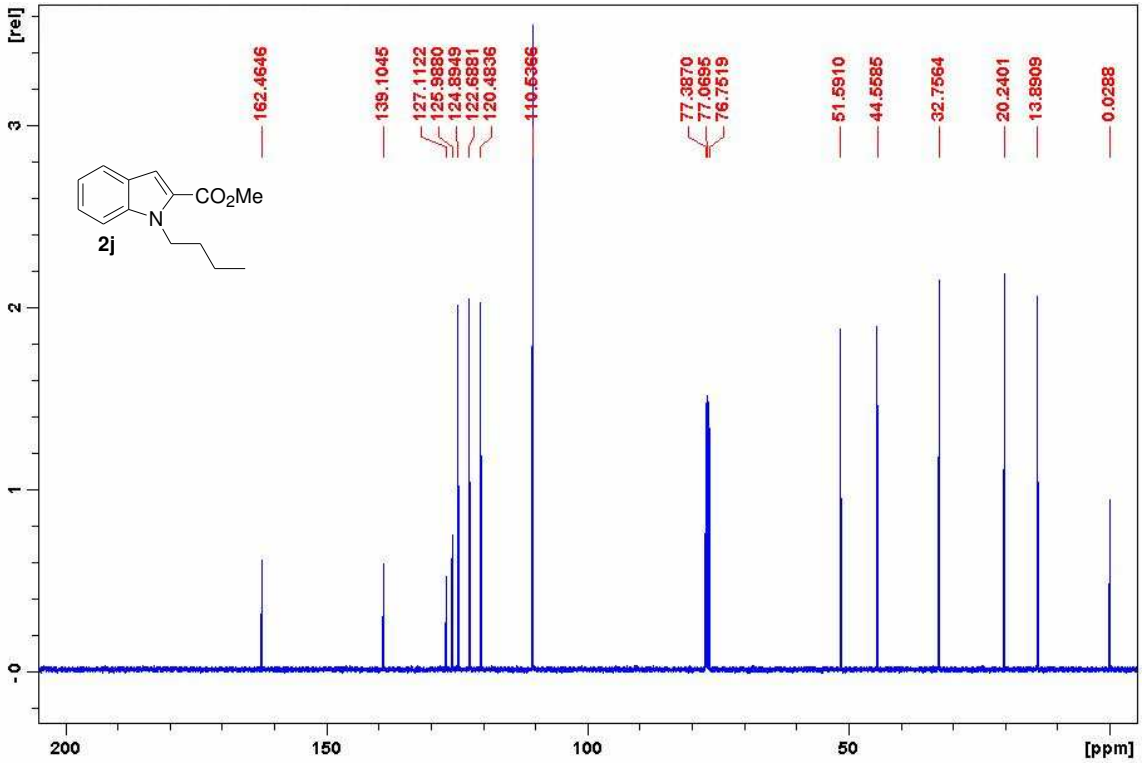
(^{1}H NMR, 400 MHz, DMSO-d_6, TMS)



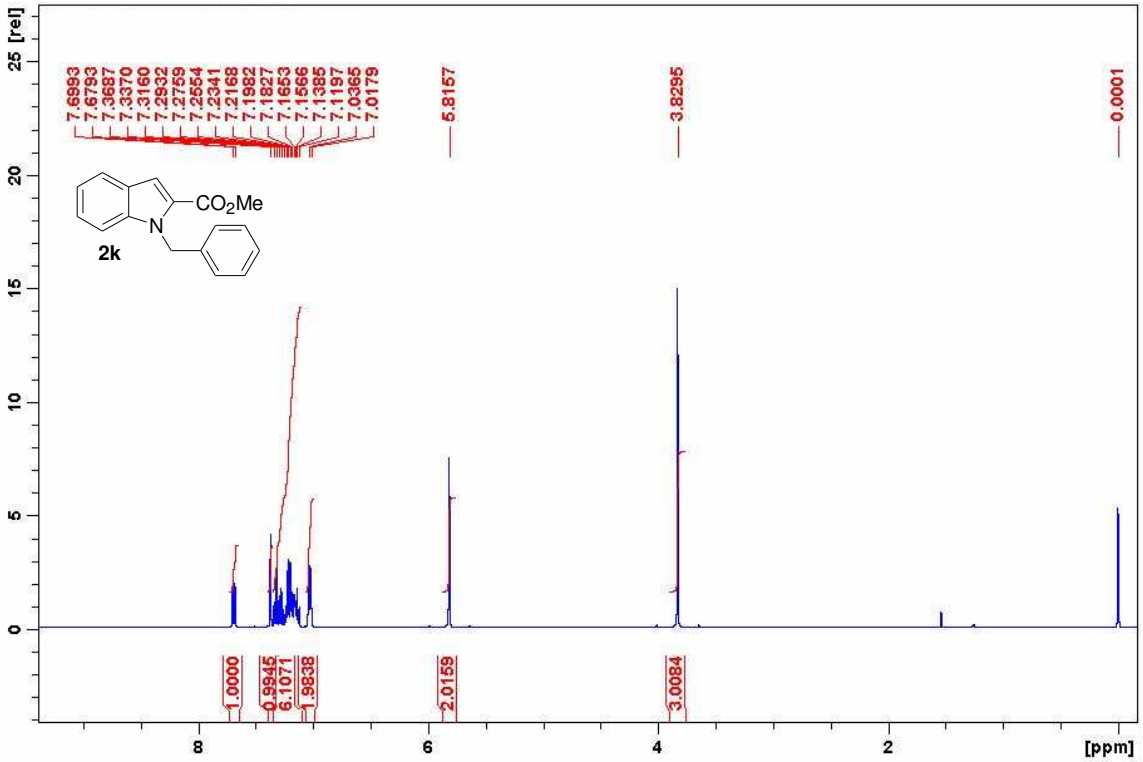
(^{13}C NMR, 100 MHz, DMSO-d_6, TMS)



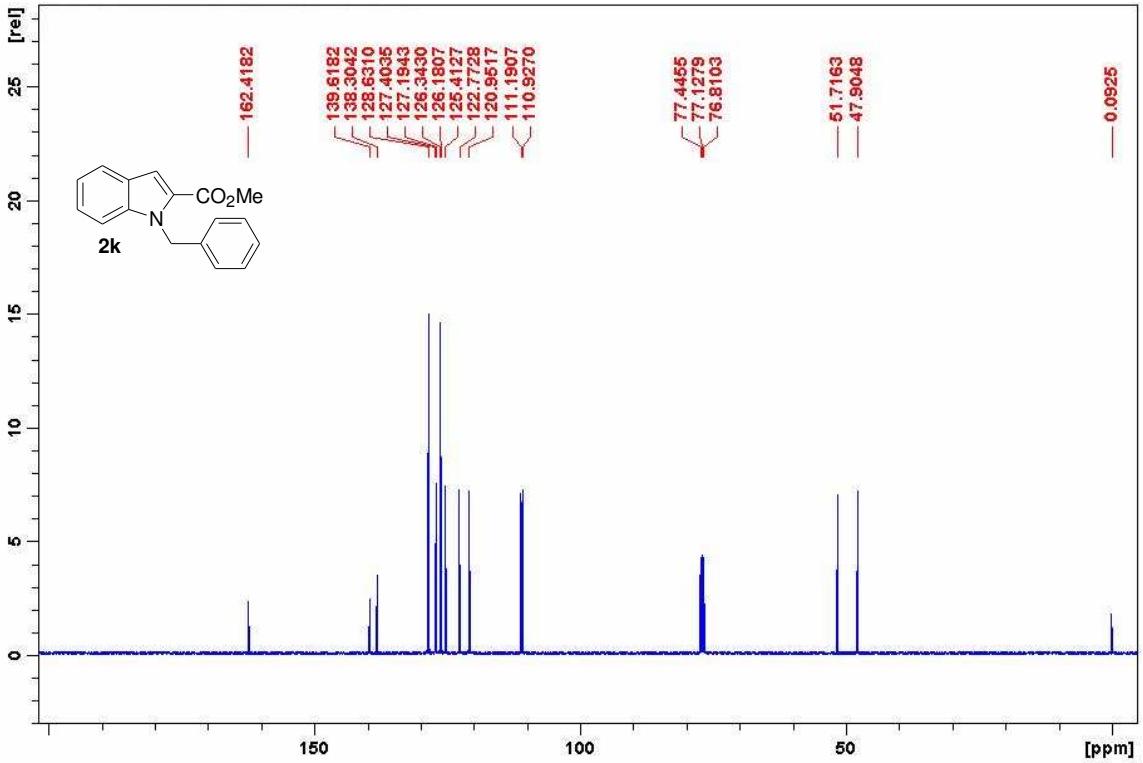
(^{1}H NMR, 400 MHz, $CDCl_3$, TMS)



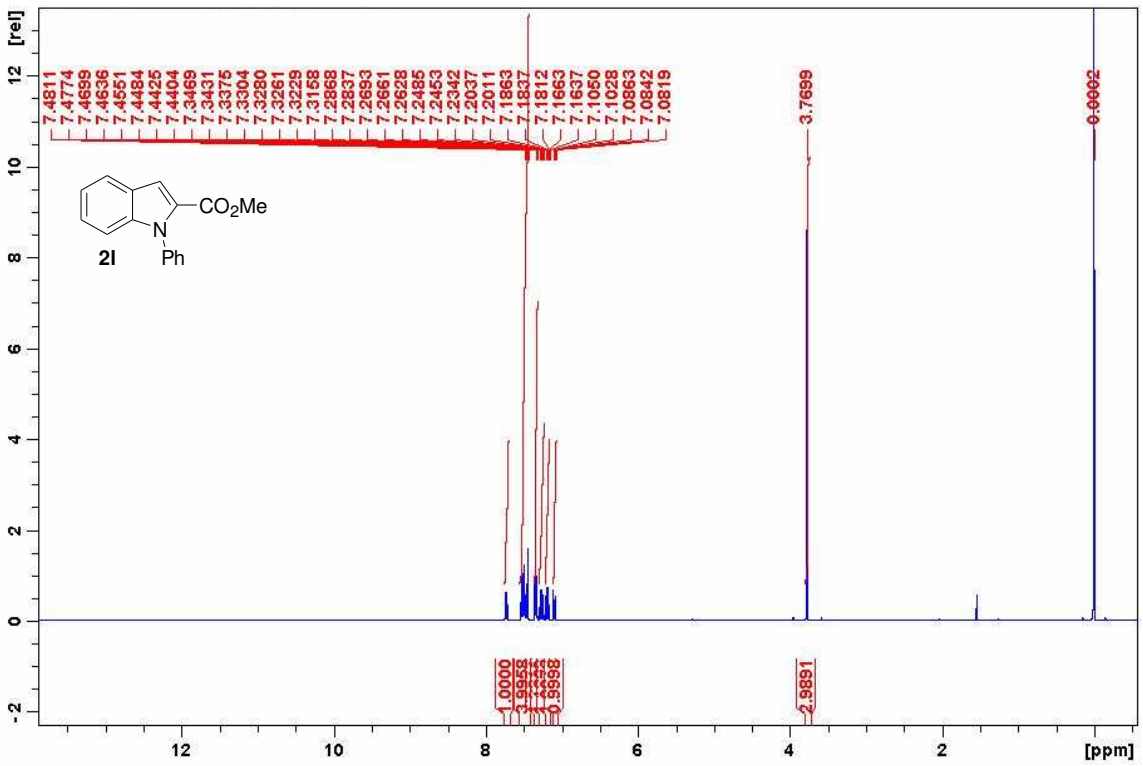
(^{13}C NMR, 100 MHz, $CDCl_3$, TMS)



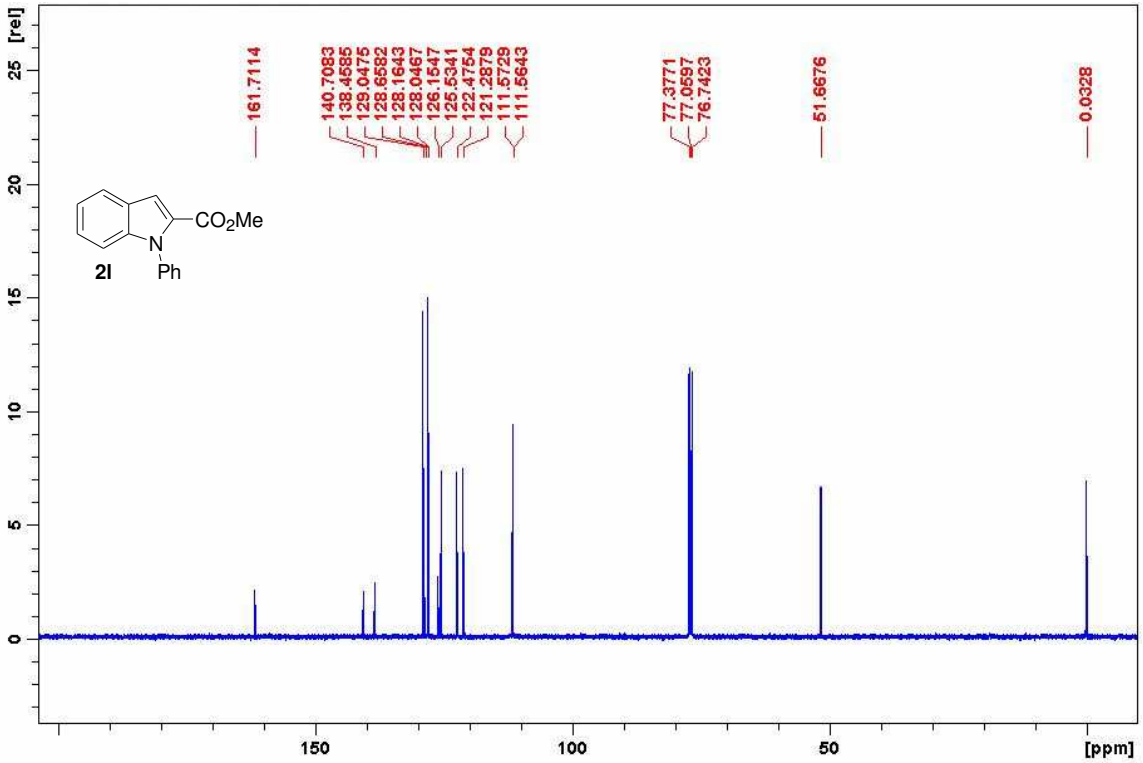
(¹H NMR, 400 MHz, $CDCl_3$, TMS)



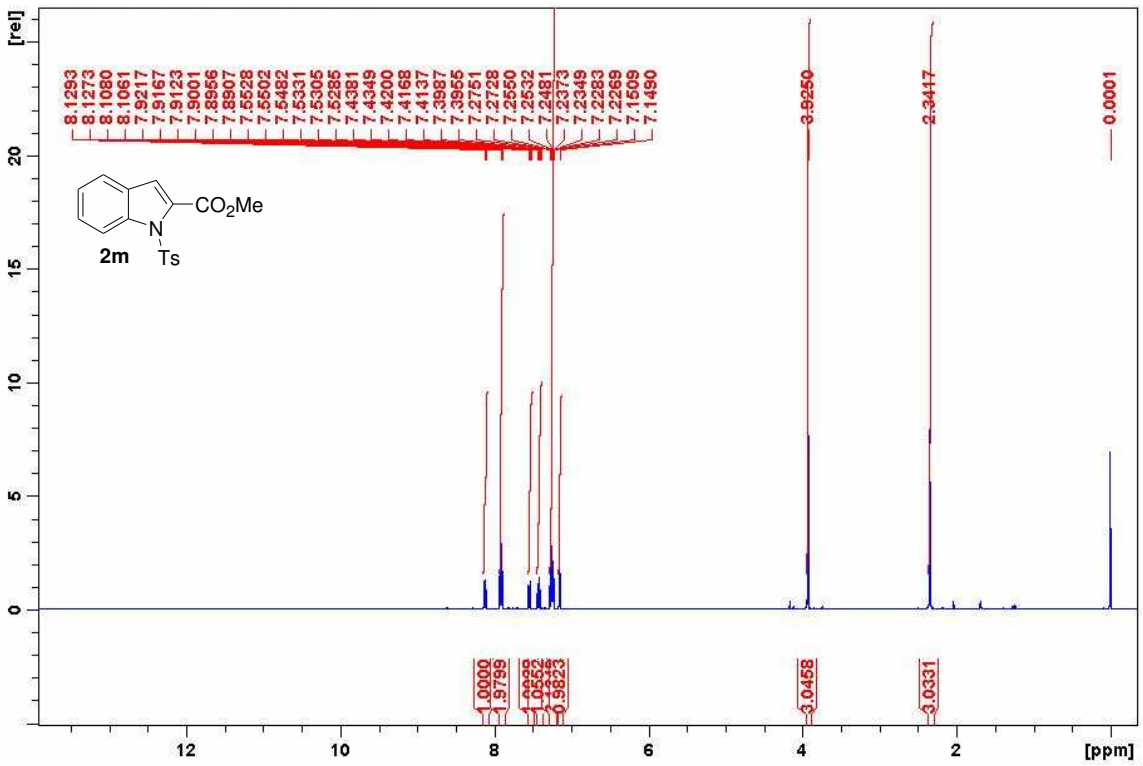
(¹³C NMR, 100 MHz, $CDCl_3$, TMS)



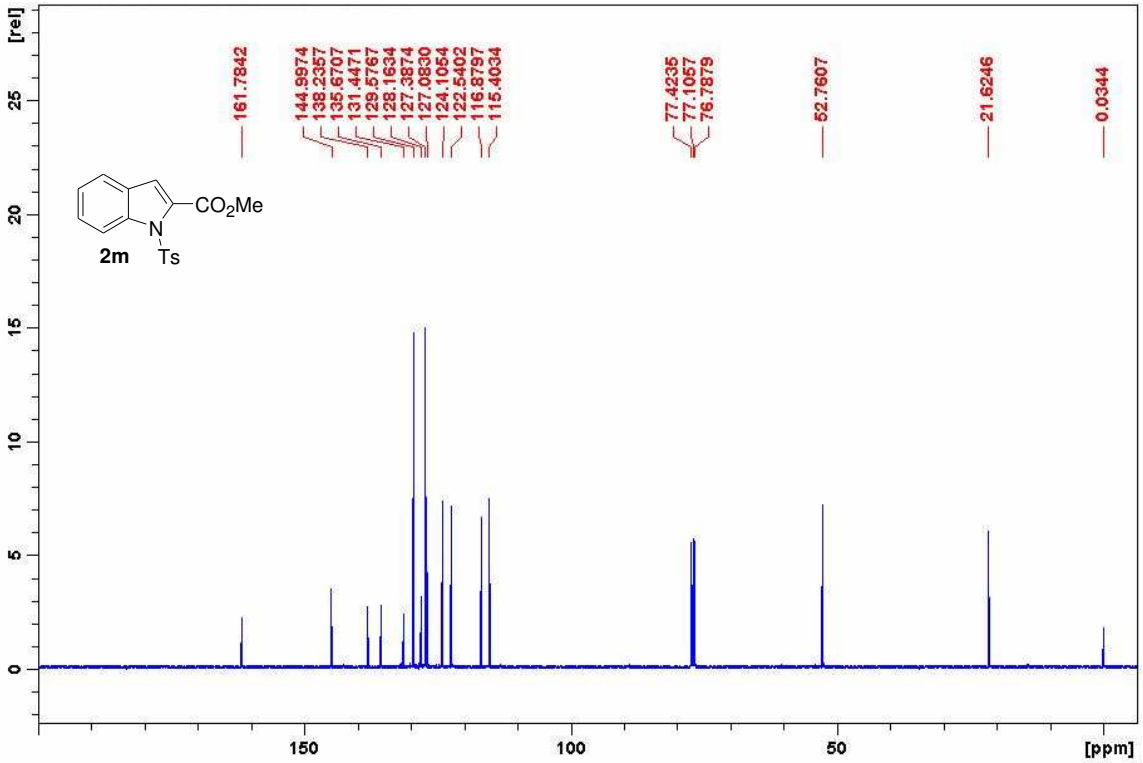
(¹H NMR, 400 MHz, $CDCl_3$, TMS)



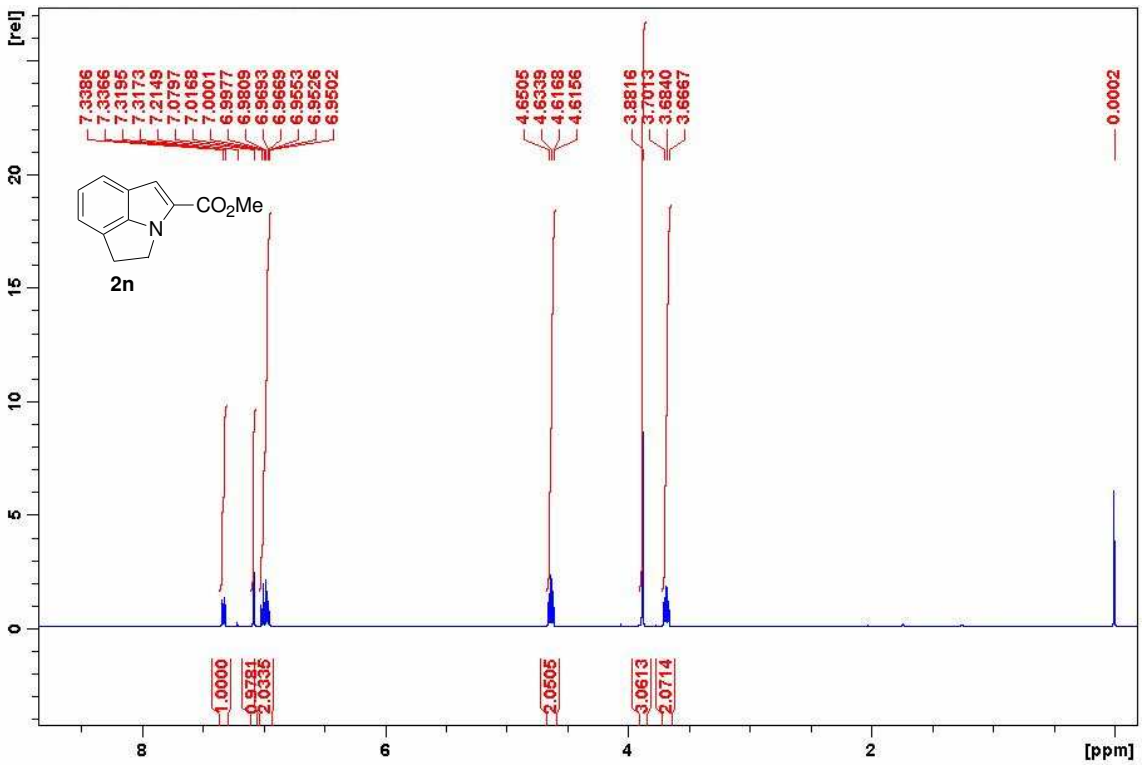
(¹³C NMR, 100 MHz, $CDCl_3$, TMS)



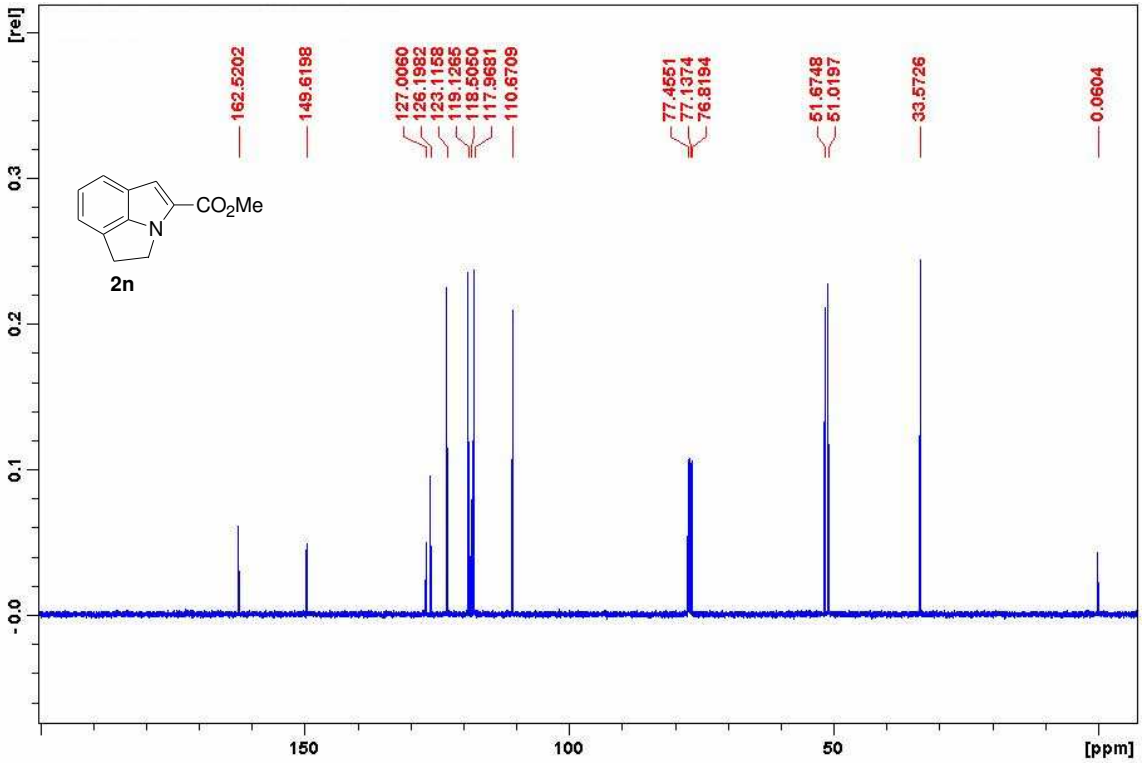
(¹H NMR, 400 MHz, $CDCl_3$, TMS)



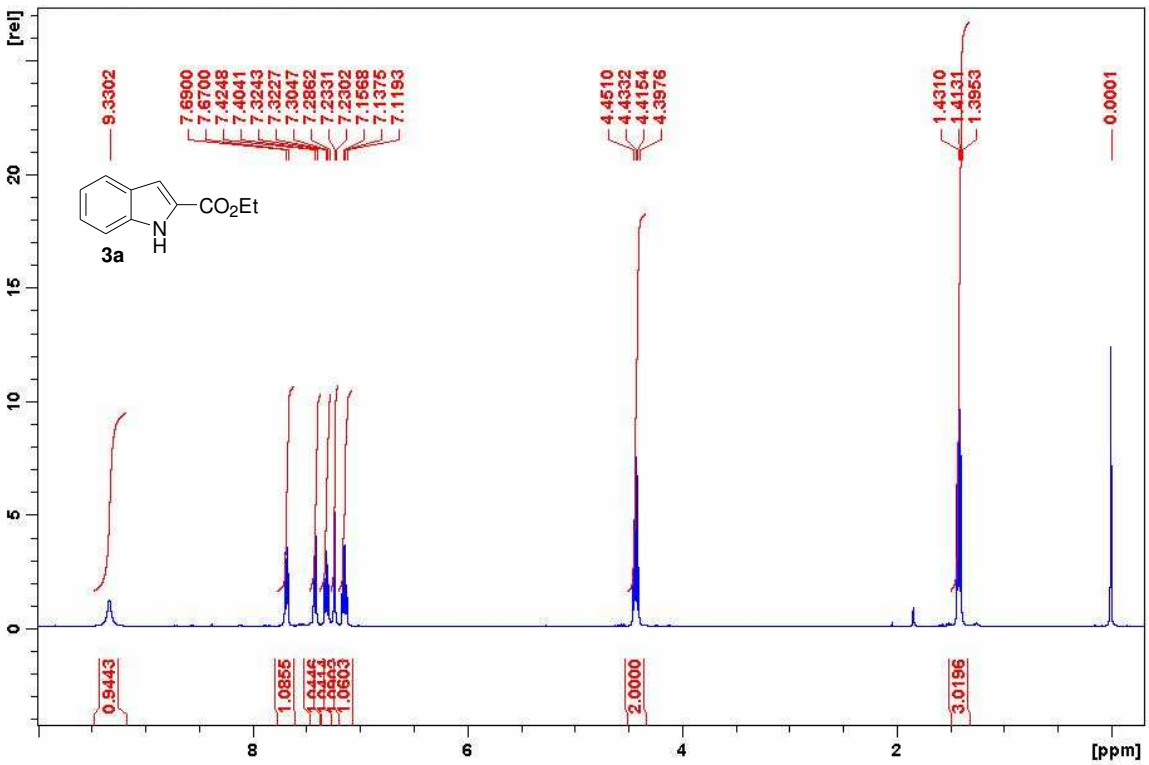
(¹³C NMR, 100 MHz, $CDCl_3$, TMS)



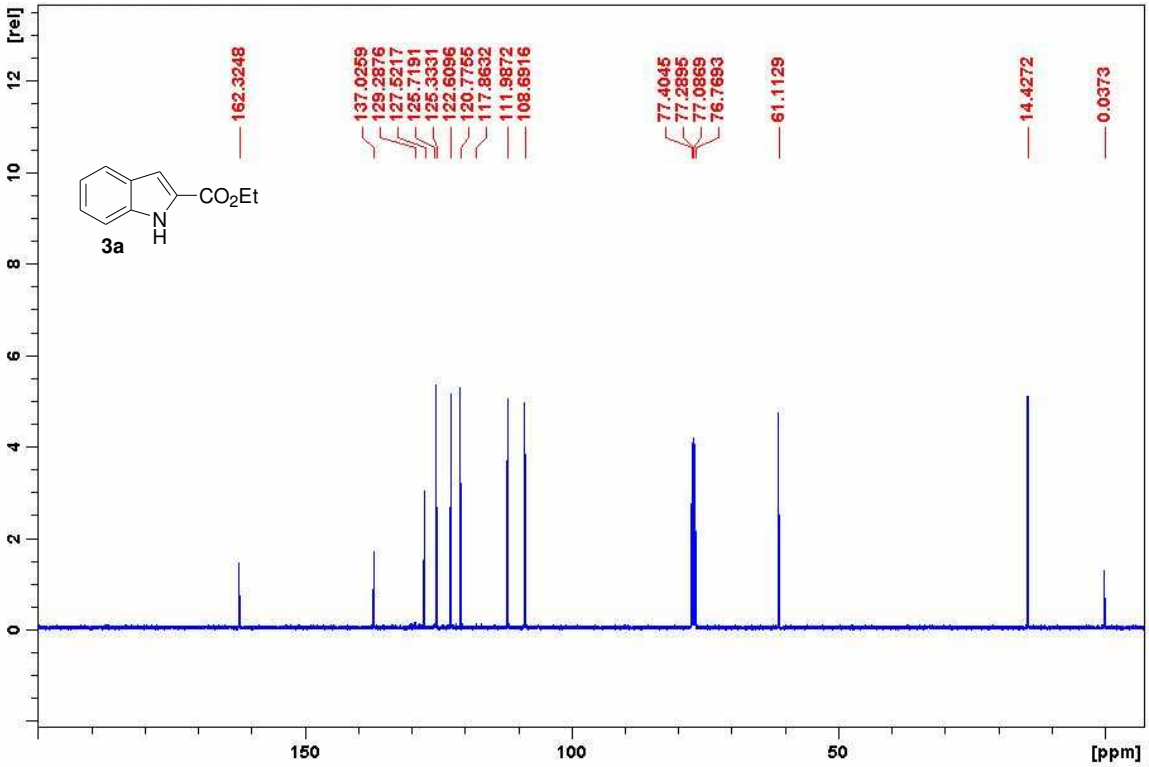
(¹H NMR, 400 MHz, $CDCl_3$, TMS)



(¹³C NMR, 100 MHz, $CDCl_3$, TMS)



(**^{1}H NMR, 400 MHz, $CDCl_3$, TMS**)



(**^{13}C NMR, 100 MHz, $CDCl_3$, TMS**)