Supplementary Material

Gold catalysis on immobilized substrates: a heteroannulation approach to the solid-supported synthesis of indoles.

Agustina La-Venia, Sebastián A. Testero, Mirta P. Mischne* and Ernesto G. Mata*

Instituto de Química Rosario. Facultad de Ciencias Bioquímicas y Farmacéuticas - Universidad Nacional de Rosario-CONICET, Suipacha 531, S2002LRK Rosario, Argentina

Content:

General

Chemical reagents were purchased from commercial sources and were used without further purification unless noted otherwise. Solvents were analytical grade or were purified by standard procedures prior to use. Resins were purchased from Novabiochem (San Diego, CA, U.S.A.). Infrared spectra (IR) were recorded on a Shimadzu Prestige 21 spectrophotometer and only partial spectral data are listed. ^{1}H NMR spectra were recorded on a Bruker avance at 300 MHz in $CDCl_3$, in the presence of TMS (0.00 ppm) as the internal standard. Conventional and gel–phase ^{13}C NMR spectra were recorded on the same apparatus at 75 MHz with $CDCl_3$ as solvent and reference (76.9 ppm), unless otherwise stated. ^{13}C NMR assignments were made on the basis of chemical shifts and proton multiplicities (from inverse HSQC spectra). High resolution mass spectra were recorded on a Bruker micrOTOF-Q II spectrometer. Analytical thin–layer chromatography (TLC) was carried out with silica gel 60 F_{254} pre–coated aluminum sheets. Flash column chromatography was performed using silica gel 60 (230–400 mesh).

Experimental Section

Procedure for the obtention of resin 3. To a suspension of 4-bromo-3-nitro benzoic acid (**2**) (672.9 mg, 2.74 mmoles, 3 equiv.) in anhydrous CH_2Cl_2 (8 mL) was added diisopropylcarbodiimide (0.43 mL, 2.74 mmoles, 3 equiv.) and this solution was immediately transferred via cannula to a suspension of Wang resin (760.0 mg, 1.20 mmoles/g, 0.91 mmoles) and catalytic DMAP in anhydrous CH_2Cl_2 (2 mL). The reaction was magnetically stirred for 18 h under dry nitrogen atmosphere. After filtration, the resulting resin **3** was washed with MeOH (3 × 3 mL), THF (3 × 3 mL) and CH_2Cl_2 (3 × 3 mL) and dried under high vacuum.

General procedure for the solid-phase synthesis of 5: Sonogashira reaction. A suspension of resin **3** (340.0 mg, 0.94 mmoles/g, 0.32 mmoles), $PdCl_2(PPh_3)_2$ (11.0 mg, 0.016 mmoles, 5 mol%) and CuI (6 mg, 0.032 mmoles, 10 mol %) in anhydrous toluene (3 mL) was stirred for 15 minutes at room temperature. After that, anhydrous Et_3N (3 mL) and phenylacetylene (0.17 mL, 1.6 mmoles, 5 equiv.) were added. The mixture was stirred for 4 h under dry nitrogen atmosphere at room temperature, after which the resin was filtrated, washed with MeOH (3 × 3 mL), DMF (3 × 3 mL) and CH_2Cl_2 (3 × 3 mL) and finally once more with CH_2Cl_2 (3 × 3 mL). The resulting resin was dried under high vacuum.

Representative procedure for the obtention of solid–supported 2-alkynylanilines (6). To a suspension of resin **5a** (304.0 mg, 0.92 mmoles/g, 0.28 mmoles) in anhydrous DMF (5 mL) placed in a 25 mL round bottomed flask with a condenser fitted was added $SnCl_2.2H_2O$

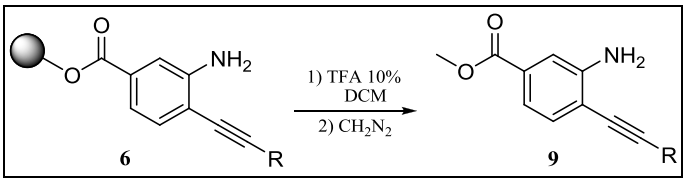
(622.7 mg, 2.76 mmoles, 10 equiv.) and reaction was refluxed for 10 minutes under dry nitrogen atmosphere, after which the resin was filtered, washed with DMF (3 mL), THF (3 mL), MeOH (3 mL) and CH_2Cl_2 (3 mL). The resulting resin was thoroughly washed with THF (9 mL) at room temperature, after which the resin was filtrated, washed again with DMF (3 × 3 mL), THF (3 × 3 mL), MeOH (3 × 3 mL) and CH_2Cl_2 (3 × 3 mL) and dried under high vacuum to obtain the solid–supported 2-alkynylaniline **6a**.

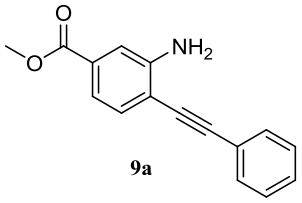
Representative procedure for the obtention of solid–supported indoles (7). Support-bound 2-alkynylaniline (**6a**) (210 mg, 0.95mmol/g, 0,20 mmol) in a 20-mL polypropylene filtration tube with polyethylene frit was suspended in anhydrous dichloromethane (3 mL), AuCl (2.5 mg, 0.01 mmol, *ca.* 5 mol %) was added under a nitrogen atmosphere, and the mixture was stirred at room temperature for 4 h. After that, the resin was filtered, washed with THF (3 x 3 mL), MeOH (3 x 3 mL), CH_2Cl_2 (4 x 3 mL), and dried under high vacuum to obtain the solid–supported indole **7a**.

General procedure for the cleavage of the solid–supported 2-alkynylanilines and solid–supported indoles using TFA. Resin **7** (0.15 mmol) was treated with 5 mL of 10% TFA in CH_2Cl_2 for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude product. This crude material was dissolved in CH_2Cl_2 and treated with etheral solution of diazomethane at 0ºC until yellowish coloration is achieved. The reaction was stirred for 30 minutes and diazomethane was quenched by the addition of AcOH until discoloration was achieved. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (hexane–AcOEt) to provide the desired product.

Spectroscopic Data

Cleavage of resins 6 to obtain 2-alkynylanilines 9:





3-Amino-4-(2-phenylethynyl)benzoic acid methyl ester (9a):

Yield: 40%

Pale yellow crystals.

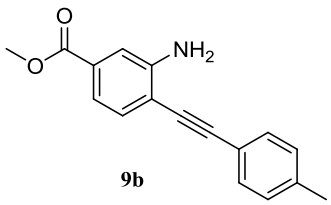
MP: 141.9-142.5 ºC.

IR (KBr): ν (cm^{-1}) 3439, 3345, 2208, 1709, 1234.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.52 (m, 2H, Ar), 7.43–7.35 (m, 6H, Ar), 4.40 (bs, 2H, -NH_2), 3.89 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7, 147.5, 131.9, 131.4 (2C), 130.7, 128.5, 128.3 (2C), 122.6, 118.7, 114.9, 112.1, 97.0, 85.1, 52.0.

HRMS m/z 252.10191 [(M + H$^+$); calcd for $C_{16}H_{14}NO_2$: 252.1025].



3-Amino-4-*p*-tolylethynyl-benzoic acid methyl ester (9b):

Yield: 15%

Pale yellow crystals.

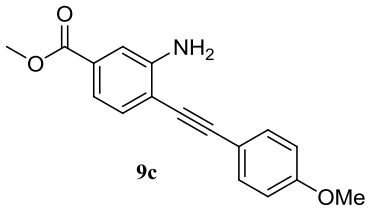
MP: 144.0-146.0 ºC.

IR (film): ν (cm^{-1}) 3481, 3384, 3024, 2919, 2209, 1717, 1559.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44–7.35 (m, 5H, Ar), 7.17 (d, *J*=8.7 Hz, 2H, Ar), 4.41 (bs, 2H, $-NH_2$), 3.90 (s, 3H, OMe), 2.38 (s, 3H, PhMe).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 147.4, 138.8, 131.8, 131.4 (2C), 131.3, 130.5, 129.1 (2C), 119.6, 118.7, 114.9, 112.4, 97.3, 84.5, 52.0, 21.4.

HRMS m/z 266.11756 [($M + H^+$); calcd for $C_{17}H_{16}NO_2$: 266.1181].



9c

3-Amino-4-(4-methoxy-phenylethynyl)-benzoic acid methyl ester (9c):

Yield: 14%

Pale yellow crystals.

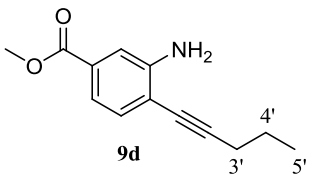
MP: 145.0-146.0 ºC.

IR (film): ν (cm^{-1}): 3456, 3358, 2916, 2201, 1703, 1622, 1439, 1251, 1240.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (dt, *J*=8.9 Hz, *J*=2.5 Hz, 2H, Ar), 7.41–7.35 (m, 3H, Ar), 6.89 (td, *J*=2.5 Hz,*J*=9.0 Hz, 2H, Ar), 4.37 (bs, 2H, $-NH_2$), 3.90 (s, 3H, OMe), 3.84 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 159.8, 147.3, 133.0 (2C), 131.8, 130.4, 118.8, 114.9, 114.7, 114.0 (2C), 112.7, 97.1, 83.8, 55.2, 52.0.

HRMS m/z 282.11247 [($M + H^+$); calcd for $C_{17}H_{16}NO_3C_{30}$: 282.1130].



9d

3-Amino-4-pent-1-ynyl-benzoic acid methyl ester (9d):

Yield: 36%

Pale yellow crystals.

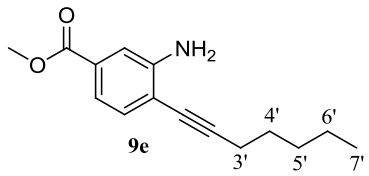
MP: 55-56 ºC.

IR (film): ν (cm^{-1}) 3482, 3383, 3022, 2916, 2218, 1719, 1508, 1209.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.29 (m, 3H, Ar), 4.27 (bs, 2H, -NH_2), 3.88 (s, 3H, OMe), 2.47 (t, *J*=7.2 Hz, 2H, H3'), 1.66 (sext, *J*=7.2 Hz, 2H, H4'), 1.06 (t, *J*=7.2 Hz, 3H, H5').

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 147.3, 131.8, 129.9, 118.7, 114.7, 113.3, 98.4, 76.7, 52.0, 22.1, 21.6, 13.5.

HRMS m/z 240.09950 [(M + Na^+); calcd for $C_{13}H_{15}NO_2Na$: 240.100].



9e

3-Amino-4-hept-1-ynyl-benzoic acid methyl ester (9e):

Yield: 50%

Pale yellow crystals.

MP: 44-45 ºC.

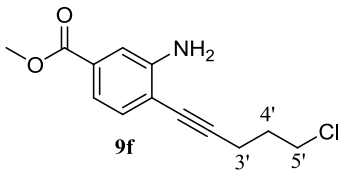
IR (film): ν (cm^{-1}) 3476, 3382, 3023, 2917, 2222, 1718, 1600, 1490, 1214.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.26 (m, 3H, Ar), 4.26 (bs, 2H, -NH_2), 3.88 (s, 3H, OMe), 2.48 (t, *J*=7.5 Hz, 2H, H3'), 1.66–1.59* (m, 2H, H4'), 1.47–1.32* (m, 4H, H5', H6'), 0.93 (t, *J*=7.3 Hz, 3H, H7').

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 147.3, 131.8, 129.9, 118.7, 114.7, 113.3, 98.7, 77.1, 52.0, 31.0, 28.4, 22.1, 19.6, 13.9.

HRMS m/z 246.14886 [(M + H^+); calcd for $C_{15}H_{19}NO_2$: 246.1494].

(*Interchangeable assignation)



9f

3-Amino-4-(5-chloro-pent-1-ynyl)-benzoic acid methyl ester (9f):

Yield: 60%

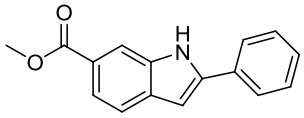
Colorless oil.

IR (film): ν (cm^{-1}) 3474, 3374, 2949, 2922, 2224, 1717, 16160, 1438, 1234.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.29 (m, 3H, Ar), 4.27 (bs, 2H, -NH_2), 3.88 (s, 3H, OMe), 3.73 (t, *J*=6.3 Hz, 2H, H5'), 2.70 (t, *J*=6.6 Hz, 2H, H3'), 1.66 (quin., *J*=6.6 Hz, 2H, H4').

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 147.5, 132.0, 130.3, 118.7, 114.8, 112.7, 96.1, 77.6, 52.0, 43.6, 31.2, 17.0.

HRMS m/z 252.07858 [(M + H^+); calcd for $C_{13}H_{15}ClNO_2$: 252.0791].



8a

Methyl 2-phenyl-1*H*-indole-6-carboxylate (8a):[1]

Overall Yield: 34%

Colorless crystals.

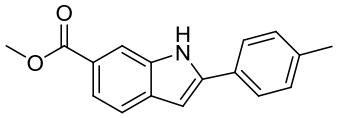
MP: 206.2-207.0 ºC.

IR (KBr): ν (cm^{-1}) 3348, 1695, 1620, 1234.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.71 (bs, 1H, NH), 8.19 (s, 1H, Ar), 7.82 (dd, *J*=1.3 Hz, *J*=8.3 Hz, 1H, Ar), 7.73–7.70 (m, 2H, Ar), 7.64 (d, *J*=8.3 Hz, 1H, Ar), 7.50–7.45 (m, 2H, Ar), 7.39 (d, *J*=7.3 Hz, 1H, Ar), 6.87 (d, *J*=1.3 Hz, 1H, Ar), 3.95 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.1, 141.2, 136.0, 132.9, 131.6, 129.0 (2C), 128.4, 125.4 (2C), 123.7, 121.3, 120.0, 113.1, 100.1, 51.9.

[1]Feng Liu and Dawei Ma, *J. Org. Chem.*, **2007**, *72*, 4844-4850.



8b

Methyl 2-*p*-tolyl-1*H*-indole-6-carboxylate (8b):

Overall Yield: 14%

Colorless crystals.

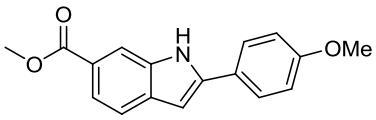
MP: 195.0-196.0 ºC.

IR (film): ν (cm^{-1}) 3352, 2916, 1692, 1620, 1504, 1223.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.58 (bs, 1H, NH), 8.15 (s, 1H, Ar), 7.81 (dd, *J*=1.4 Hz, *J*=8.3 Hz, 1H, Ar), 7.63–7.58 (m, 3H, Ar), 7.29–7.26 (overlapped with $CDCl_3$, 2H, Ar), 6.82 (d, *J*=1.3 Hz, 1H, Ar), 3.94 (s, 3H, OMe), 2.41 (s, 3H, PhMe).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.0, 141.3, 138.5, 135.8, 132.9, 129.7 (2C), 128.8, 125.3 (2C), 123.5, 121.3, 119.8, 113.0, 99.6, 51.8, 21.2.

HRMS m/z 266.11756 [(M + H^+); calcd for $C_{17}H_{16}NO_2$: 266.1181].



8c

Methyl 2-(4-Methoxy-phenyl)-1*H*-indole-6-carboxylate (8c):

Overall Yield: 13%

Colorless crystals.

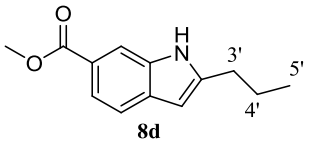
MP: 209.0-210.0 ºC.

IR (film): ν (cm^{-1}) 3354, 2916, 1686, 1607, 1504, 1287, 1250.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.54 (bs, 1H, NH), 8.14 (s, 1H, Ar), 7.80 (dd, *J*=1.3 Hz, *J*=8.4 Hz, 1H, Ar), 7.65–7.59 (m, 3H, Ar), 7.00 (d, *J*=8.8 Hz, 2H, Ar), 6.75 (d, *J*=1.5 Hz, 1H, Ar), 3.94 (s, 3H, OMe), 3.87 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.0, 159.8, 141.2, 135.8, 133.1, 126.7 (2C), 124.3, 123.2, 121.3, 119.7, 114.5 (2C), 112.9, 99.0, 55.3, 51.8.

HRMS m/z 282.11247 [(M + H^+); calcd for $C_{17}H_{16}NO_3$: 282.113].



8d

Methyl 2-propyl-1*H*-indole-6-carboxylate (8d):

Overall Yield: 5%

Pale yellow crystals.

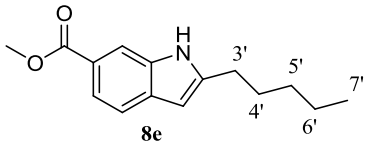
MP: 74.0-76.0 ºC

IR (film): ν (cm^{-1}) 3343, 2955, 2868, 1697, 1433, 1307, 1211.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.23 (bs, 1H, NH), 8.06 (d, *J*=0.5 Hz, 1H, Ar), 7.77 (dd, *J*=1.5 Hz, *J*=8.3 Hz, 1H, Ar), 7.52 (d, *J*=8.3 Hz, 1H, Ar), 6.29 (d, *J*=1.1 Hz, 1H, Ar), 3.92 (s, 3H, OMe), 2.76 (t, *J*=7.5 Hz, 2H, H3'), 1.77 (sext, *J*=7.5 Hz, 2H, H4'), 1.01 (t, *J*=7.4 Hz, 3H, H5').

^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.3, 143.6, 135.0, 132.6, 122.4, 120.7, 119.0, 112.5, 100.1, 51.7, 30.3, 22.2, 13.8.

HRMS m/z 218.1176 [($M + H^+$); calcd for $C_{29}H_{30}NO_4$: 218.1181].



8e

Methyl 2-pentyl-1*H*-indole-6-carboxylate (8e):

Overall Yield: 22%

Colorless crystals.

MP: 63.0-64.0 ºC

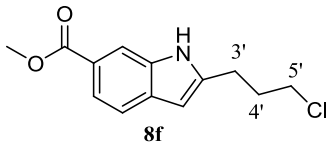
IR (film): ν (cm^{-1}) 3314, 2922, 2854, 1694, 1435, 1309, 1213.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (bs, 1H, NH), 8.05 (s, 1H, Ar), 7.77 (dd, *J*=1.4 Hz, *J*=8.4 Hz, 1H, Ar), 7.52 (d, *J*=8.3 Hz, 1H, Ar), 6.29 (d, *J*=1.1 Hz, 1H, Ar), 3.92 (s, 3H, OMe), 2.78 (t, *J*=7.5 Hz, 2H, H3'), 1.75* (quin., *J*=7.5 Hz, 2H, H4'), 1.40–1.36* (m, 4H, H5', H6'), 0.91 (t, *J*=7.0 Hz, 3H, H7').

^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.2, 143.8, 135.0, 132.6, 122.4, 120.8, 119.0, 112.4, 100.0,

51.7, 31.4, 28.6, 28.3, 22.3, 13.9.

HRMS m/z 246.14795 [(M + H^+); calcd for $C_{15}H_{19}NO_2$: 246.1416].



8f

Methyl 2-(3-Chloro-propyl)-1*H*-indole-6-carboxylate (8f):

Overall Yield: 15%

Pale yellow crystals.

MP: 66.0-68.0 ºC.

IR (film): ν (cm^{-1}) 3337, 2920, 1692, 1435, 1314, 1213.

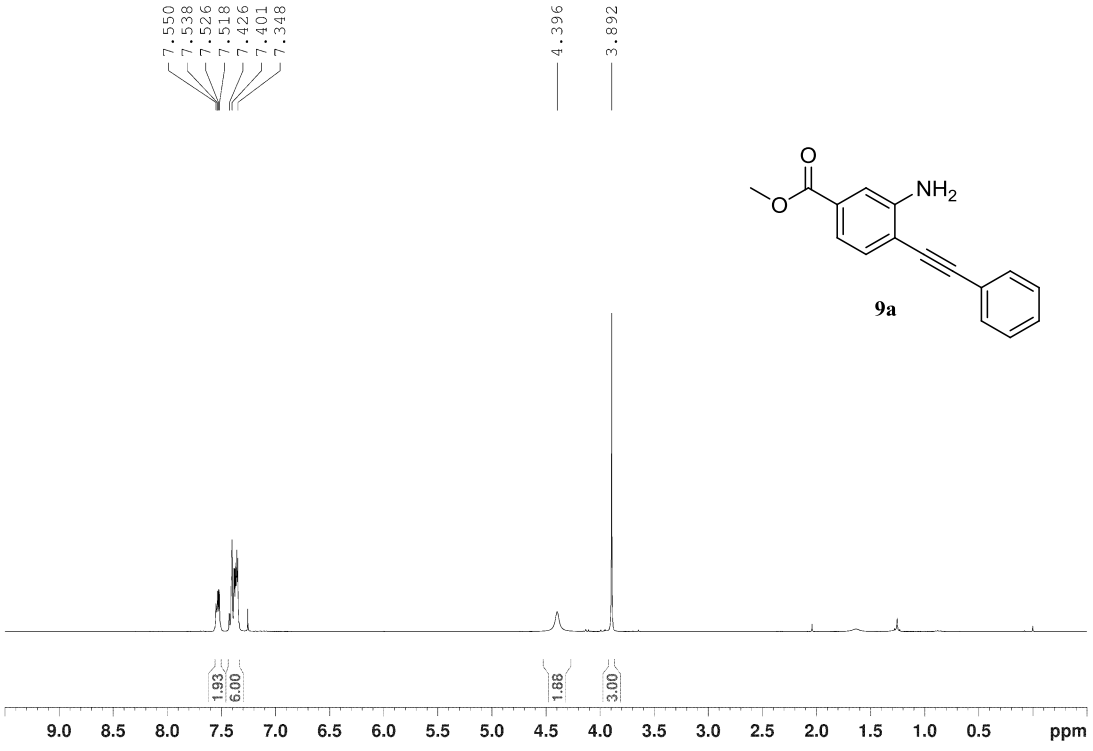
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.32 (bs, 1H, NH), 8.08 (s, 1H, Ar), 7.78 (dd, *J*=1.5 Hz, *J*=8.4 Hz, 1H, Ar), 7.54 (d, *J*=8.1 Hz, 1H, Ar), 6.33 (d, *J*=1.2 Hz, 1H, Ar), 3.93 (s, 3H, OMe), 3.60 (t, *J*=6.3 Hz, 2H, H5'), 2.99 (t, *J*=7.2 Hz, 2H, H3'), 2.21 (quin., *J*=6.6 Hz, 2H, H4').

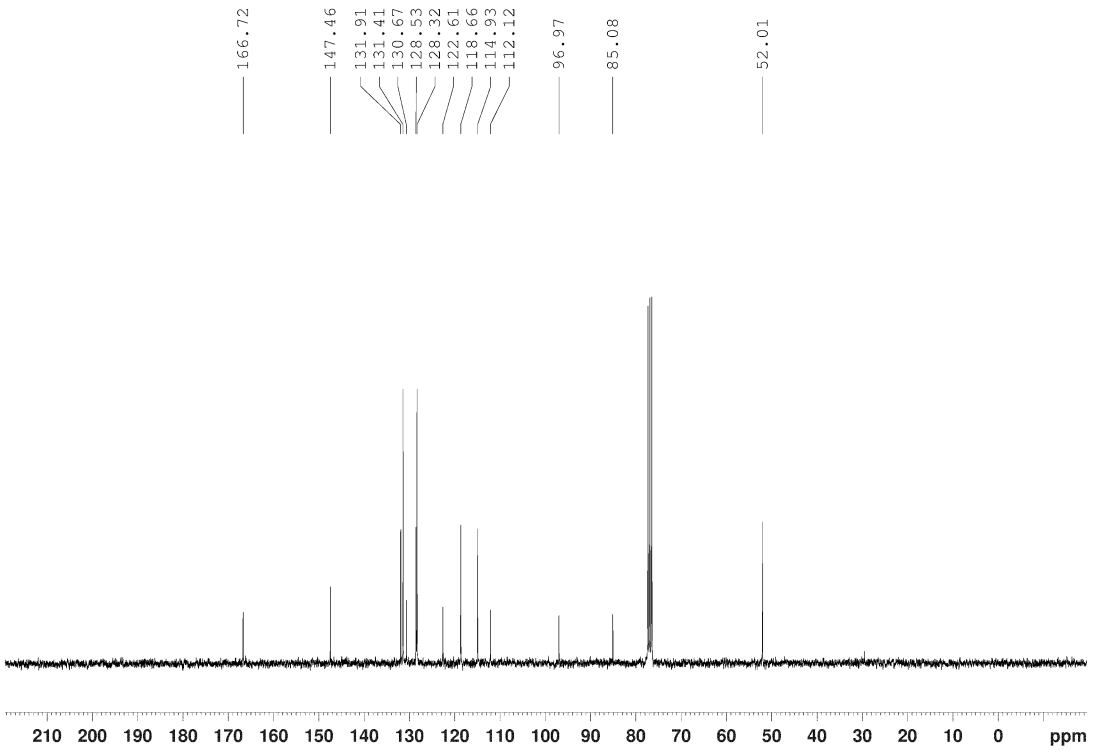
^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.2, 141.5, 135.1, 132.5, 122.8, 120.9, 119.2, 112.6, 100.6, 51.8, 43.9, 31.6, 25.2.

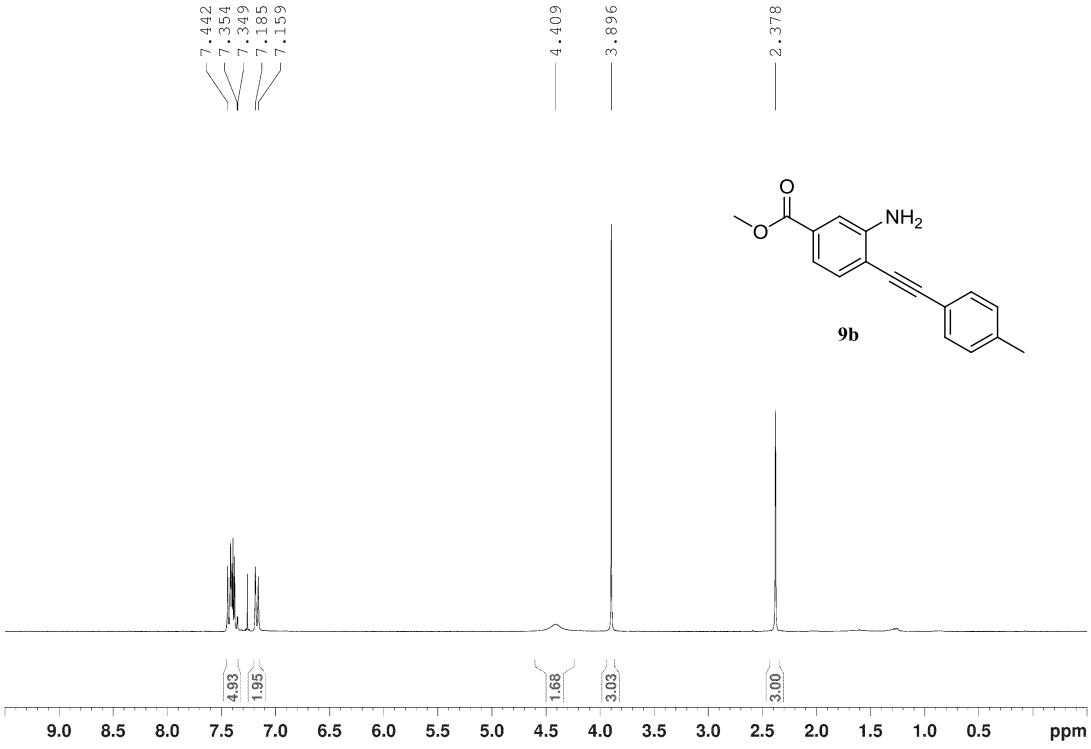
HRMS m/z 252.07858 [(M + H^+); calcd for $C_{13}H_{14}ClNO_2$: 252.0791].

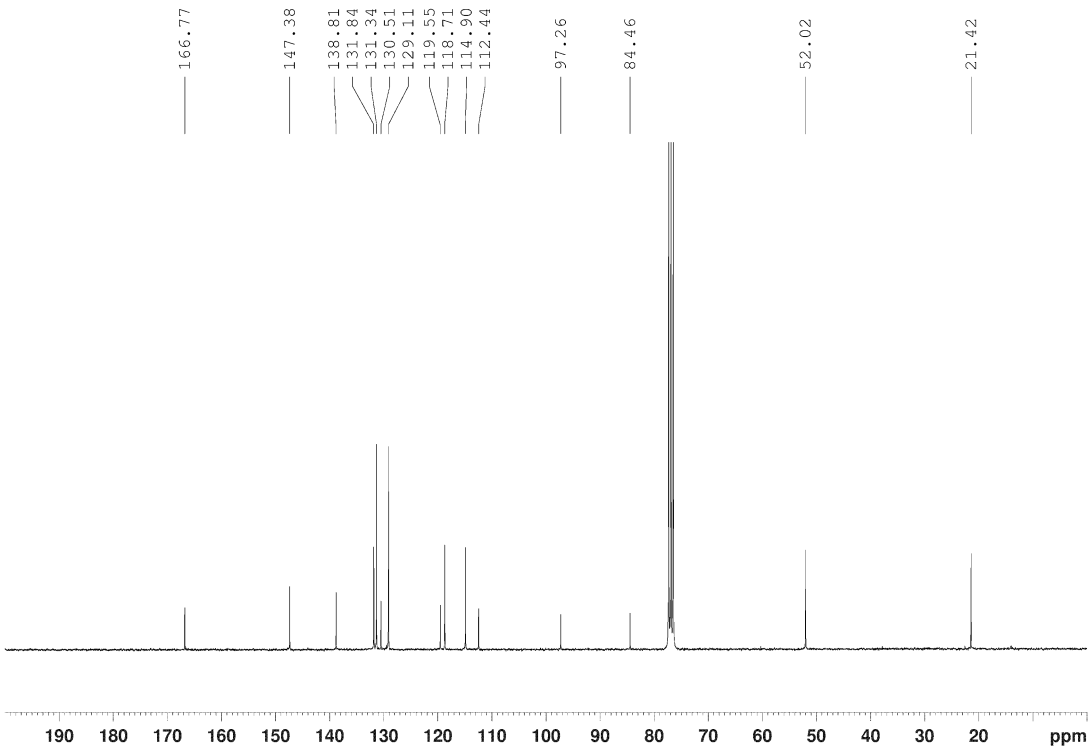
(*Interchangeable assignation)

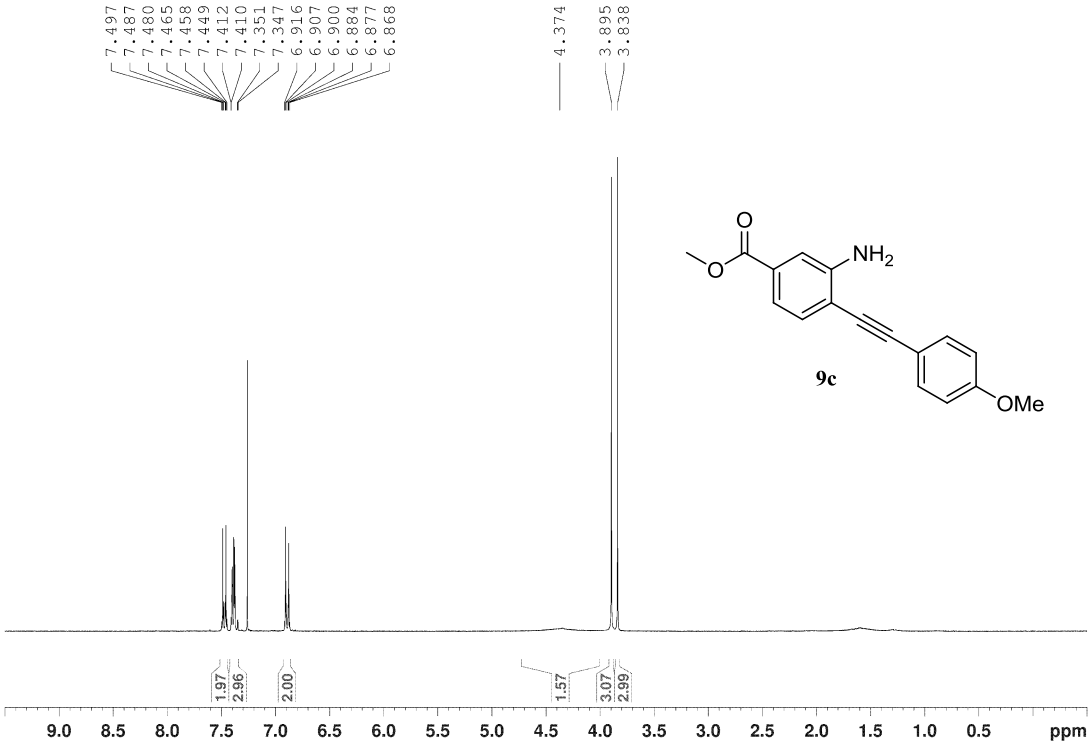
^{1}H and ^{13}C NMR Spectra

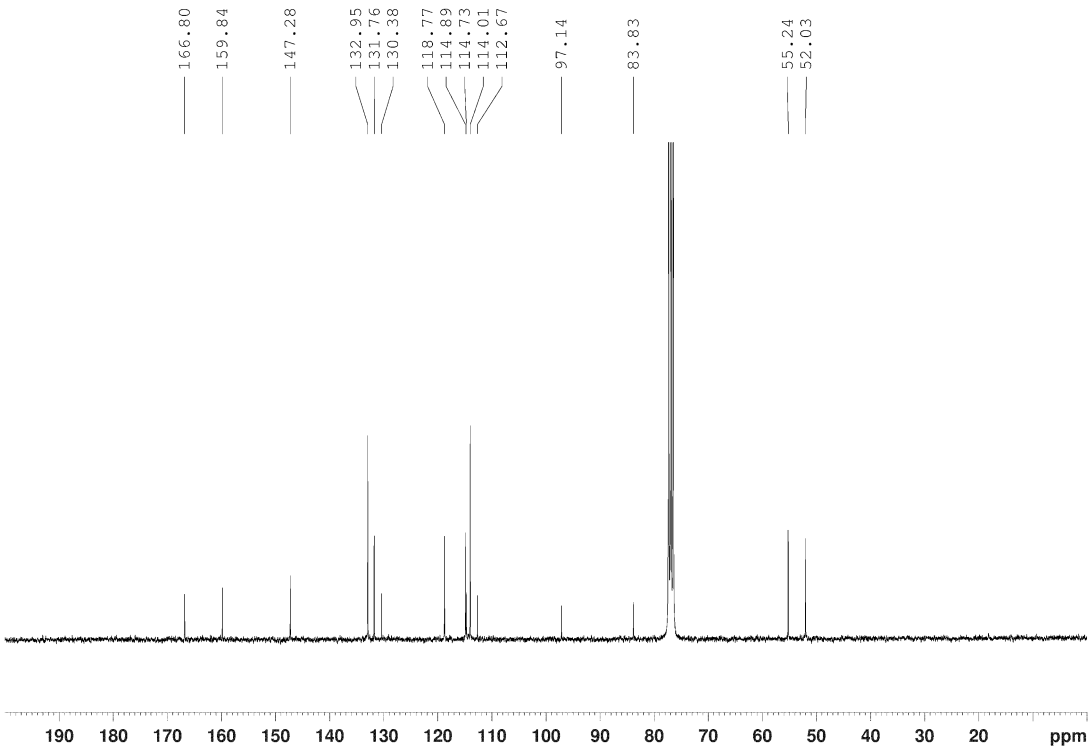


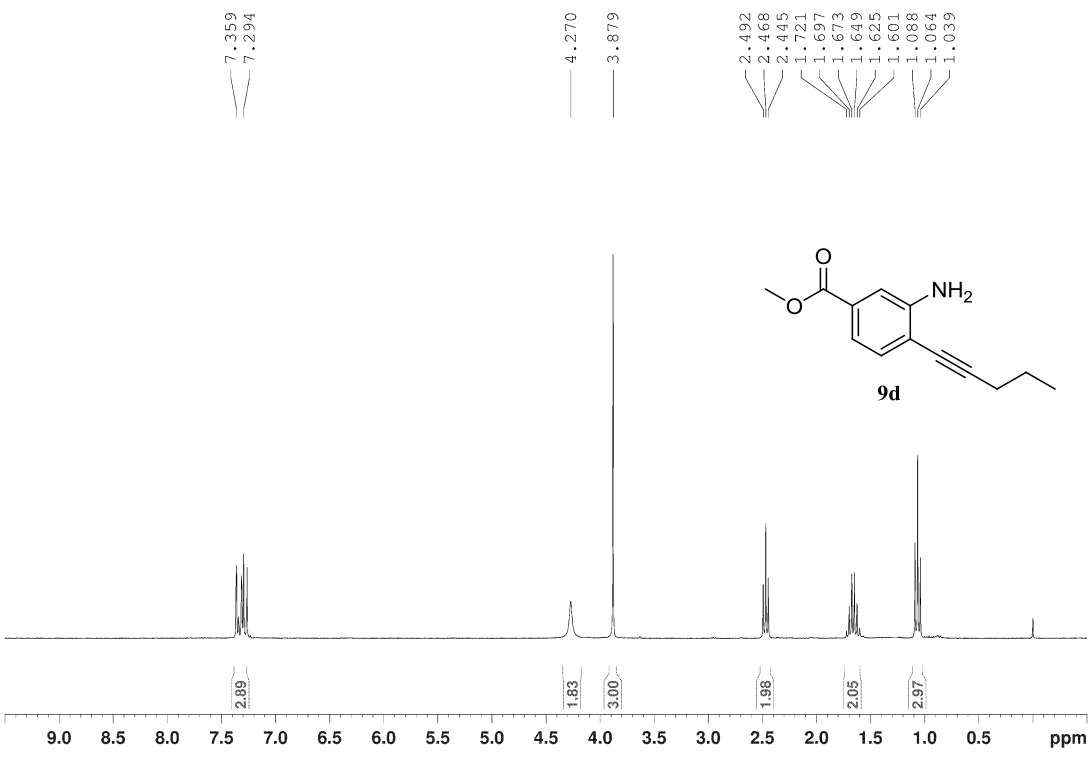


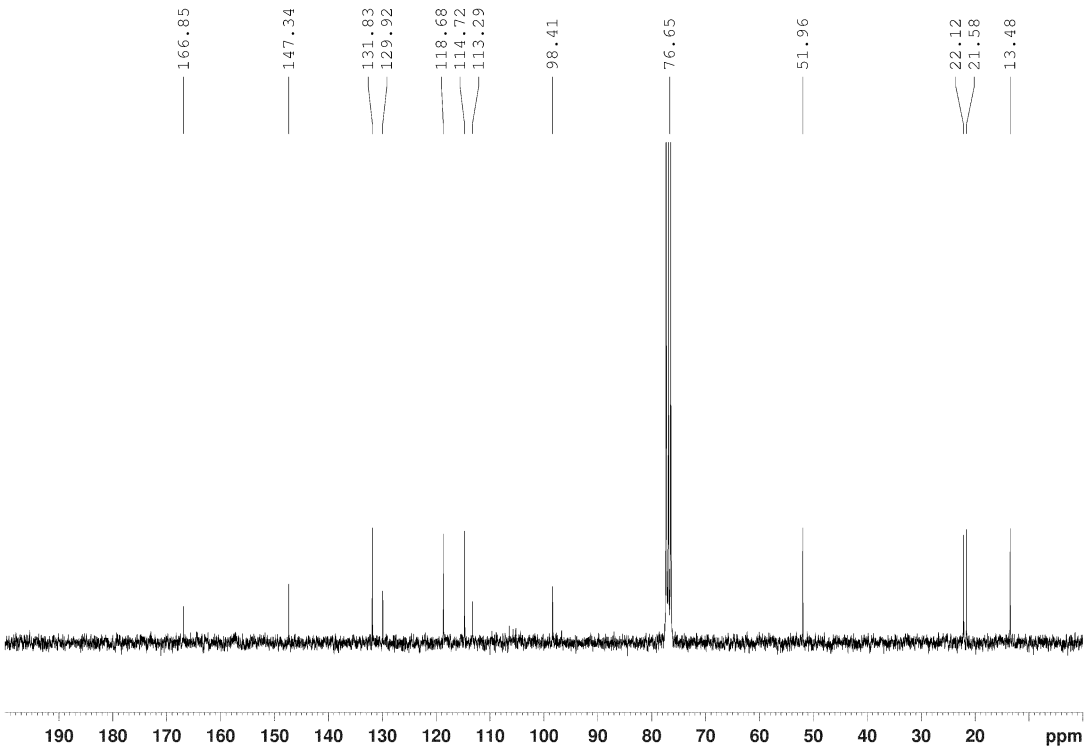


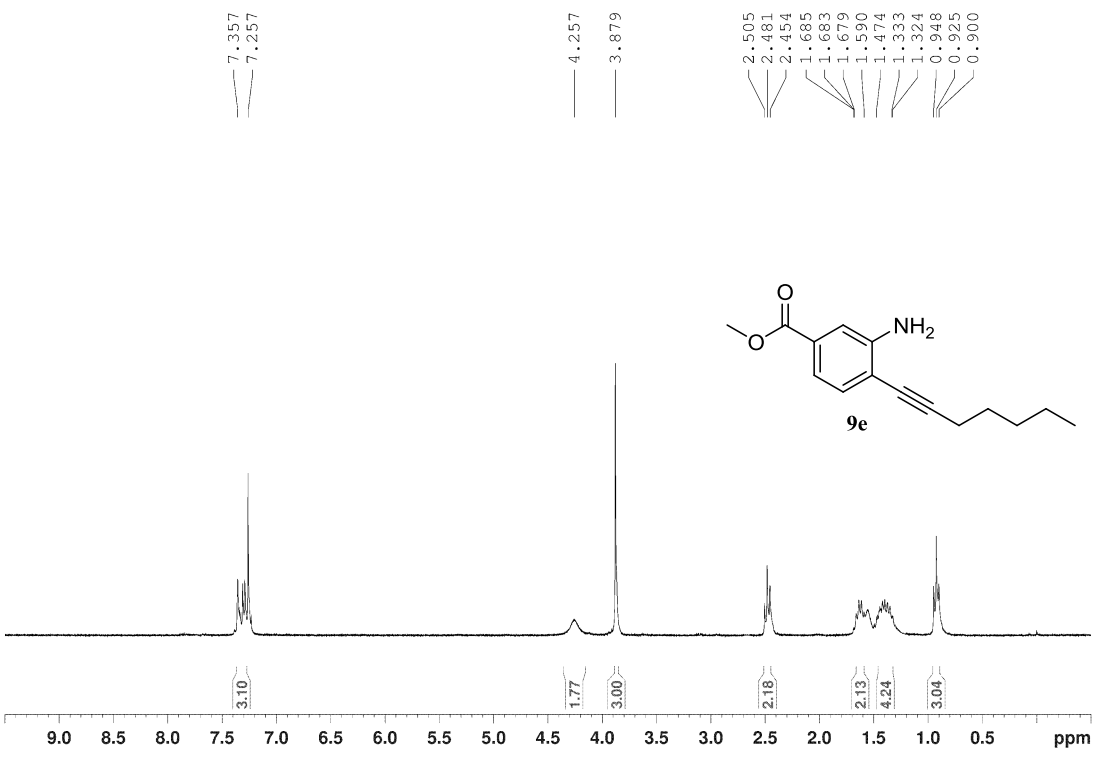


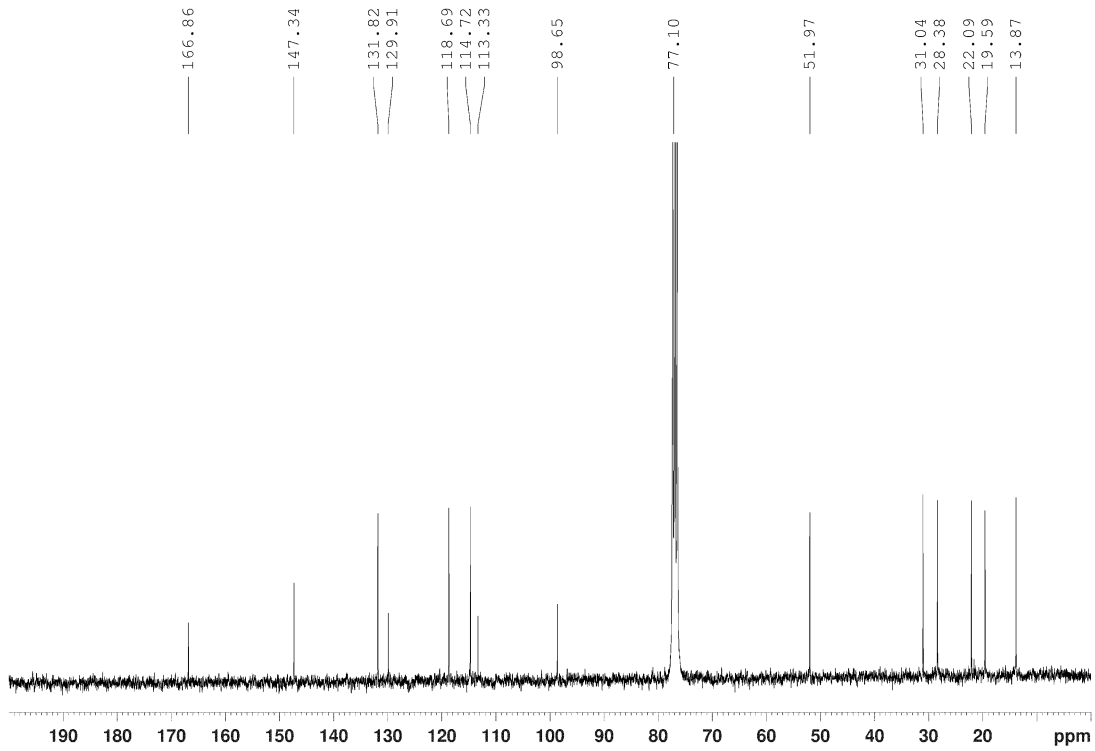


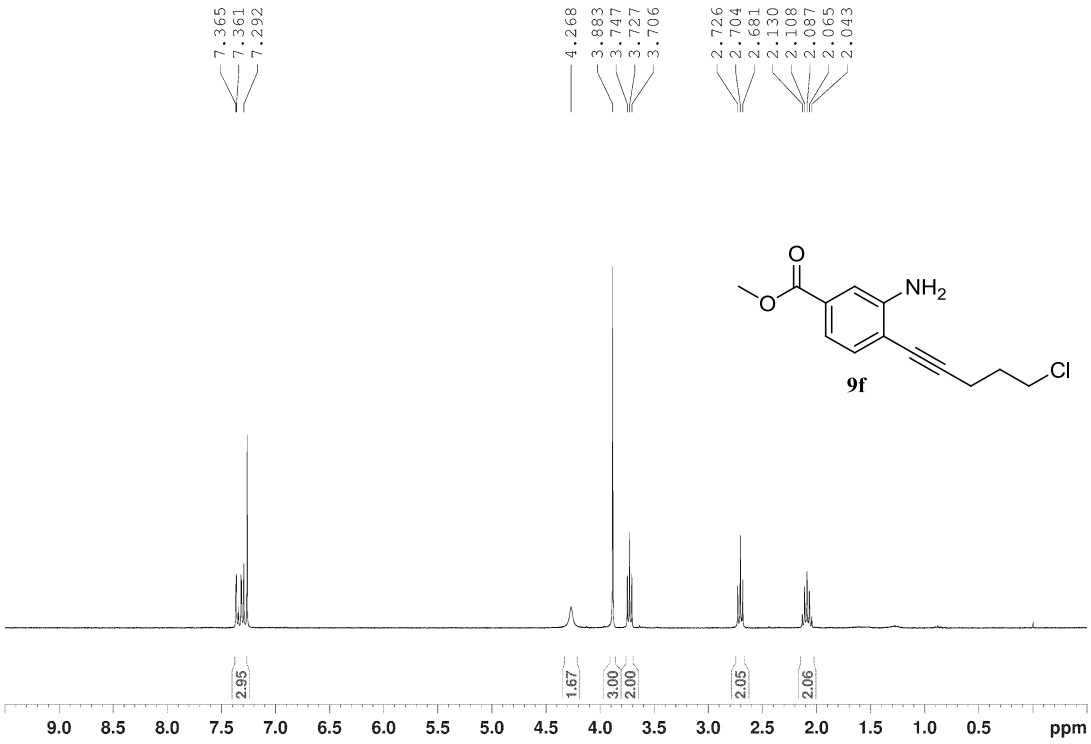


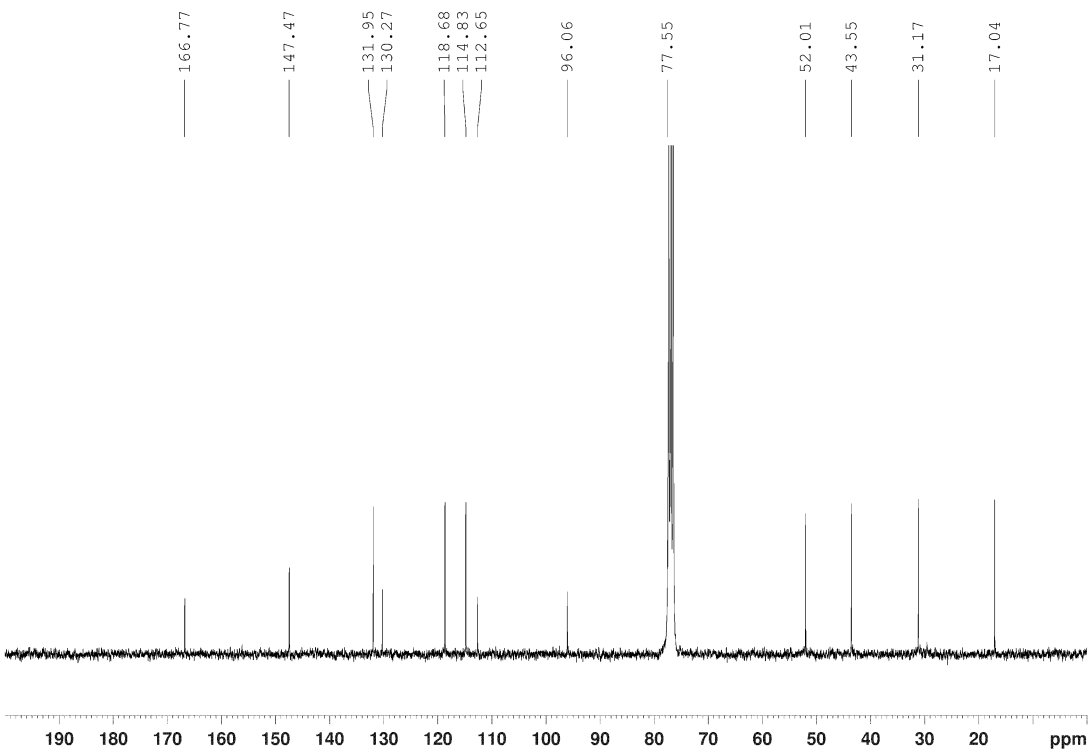


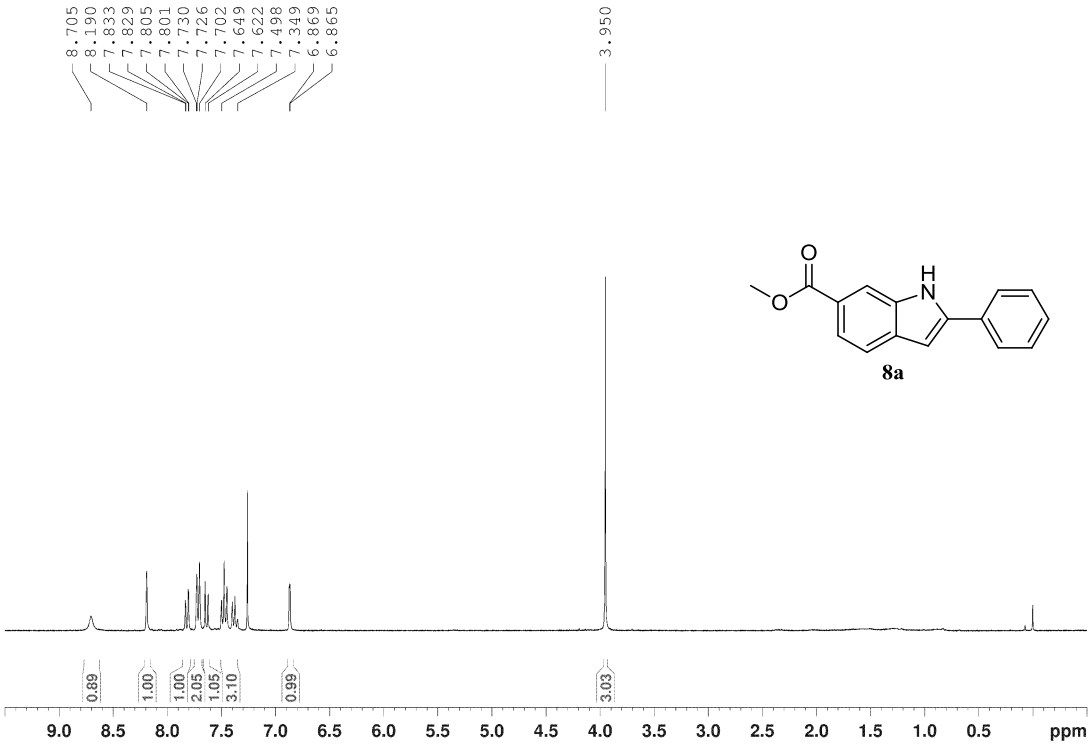




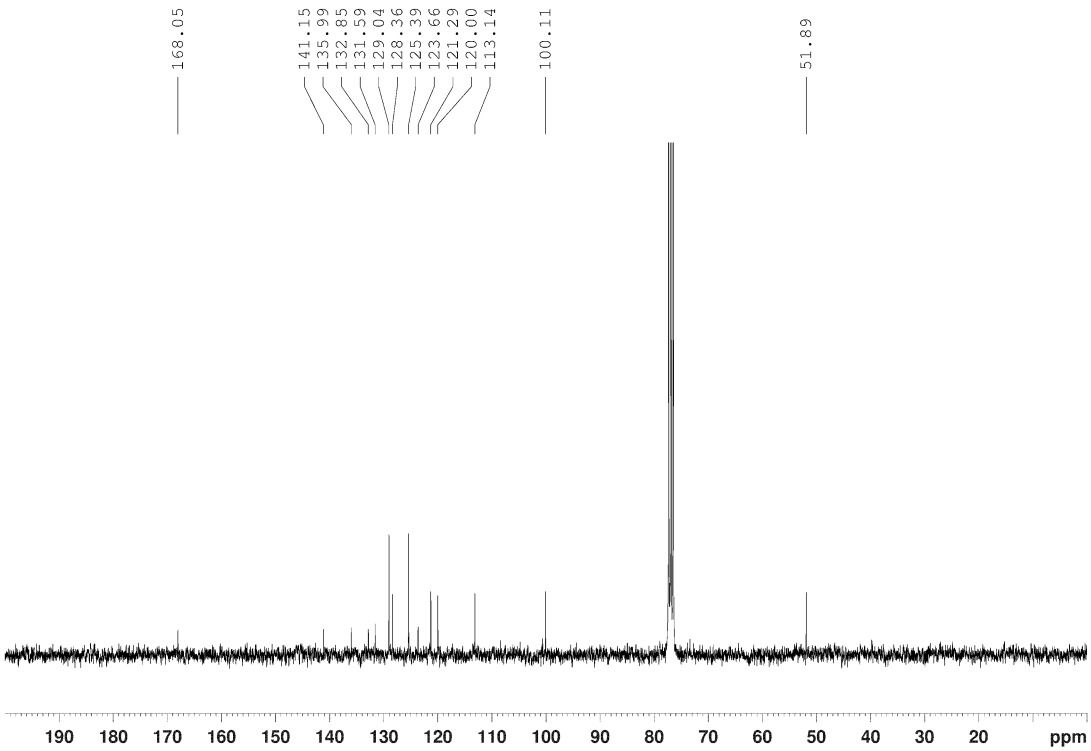


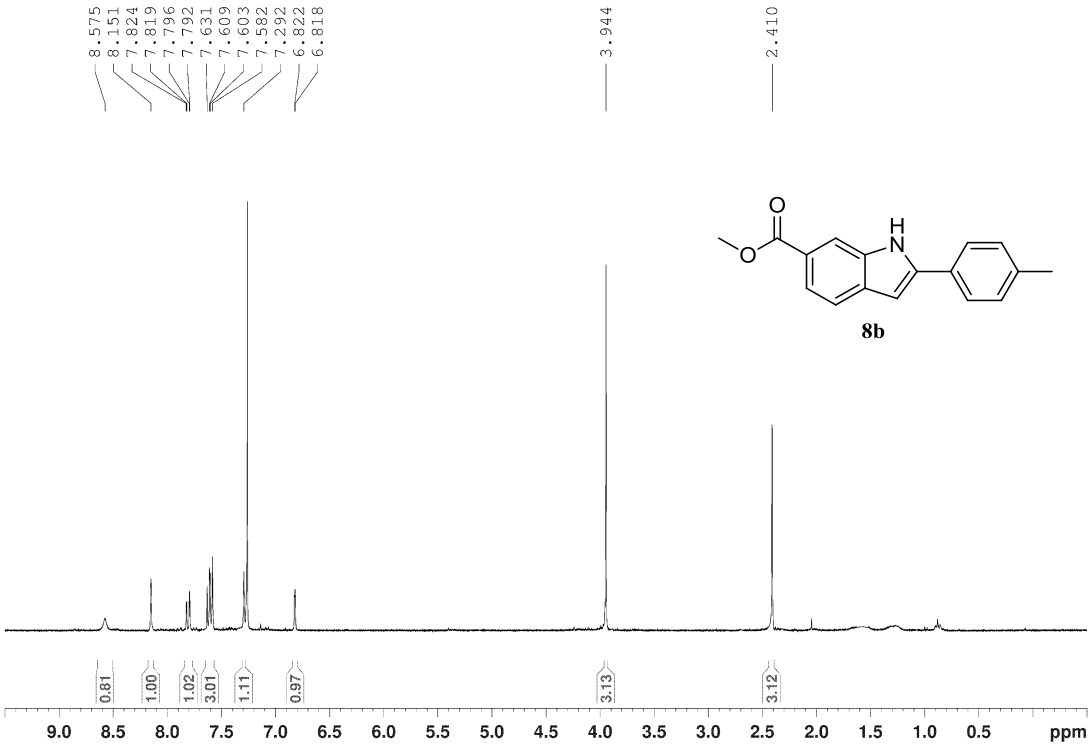




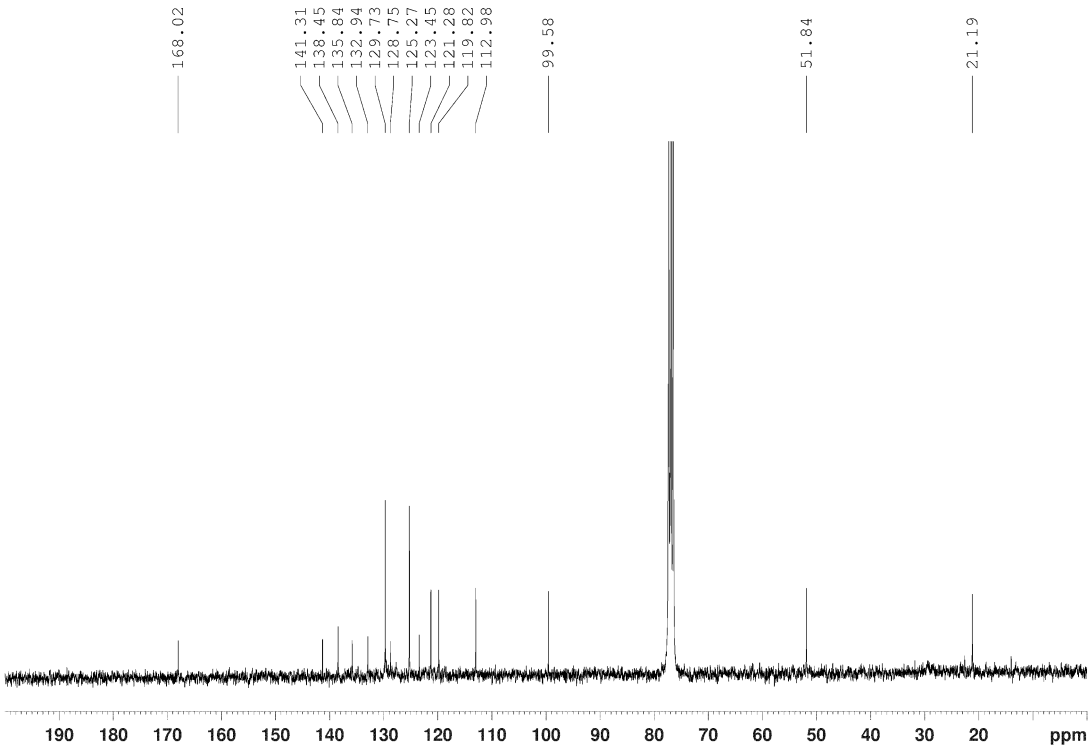


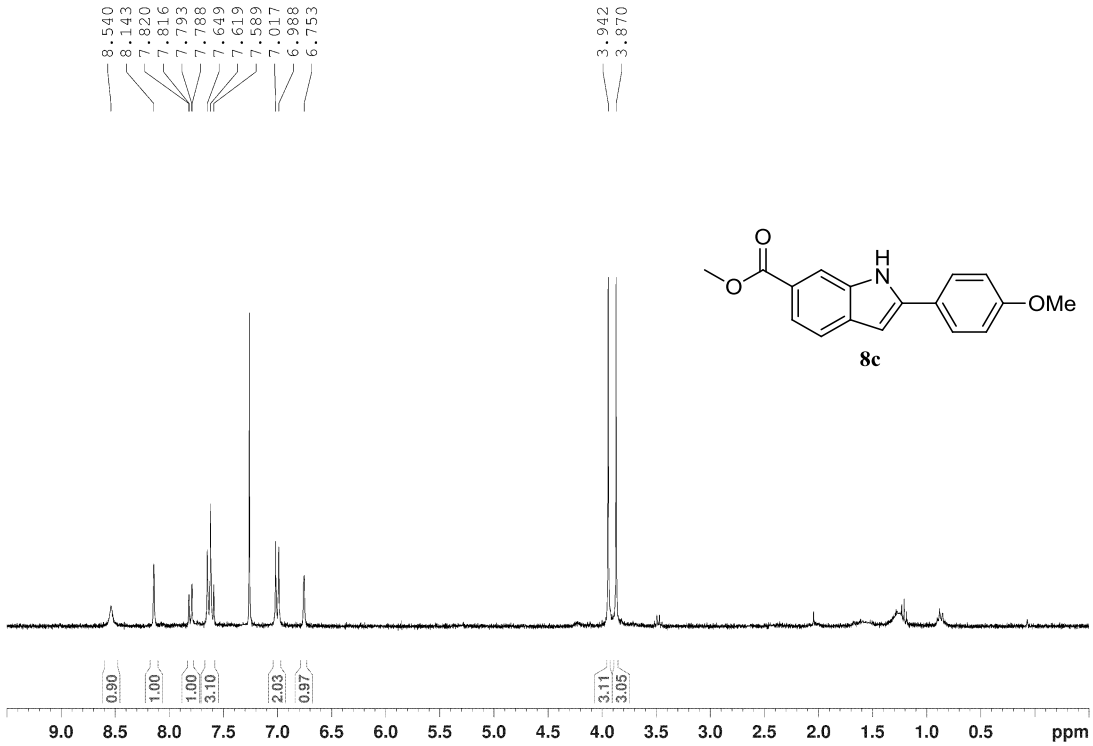
8a



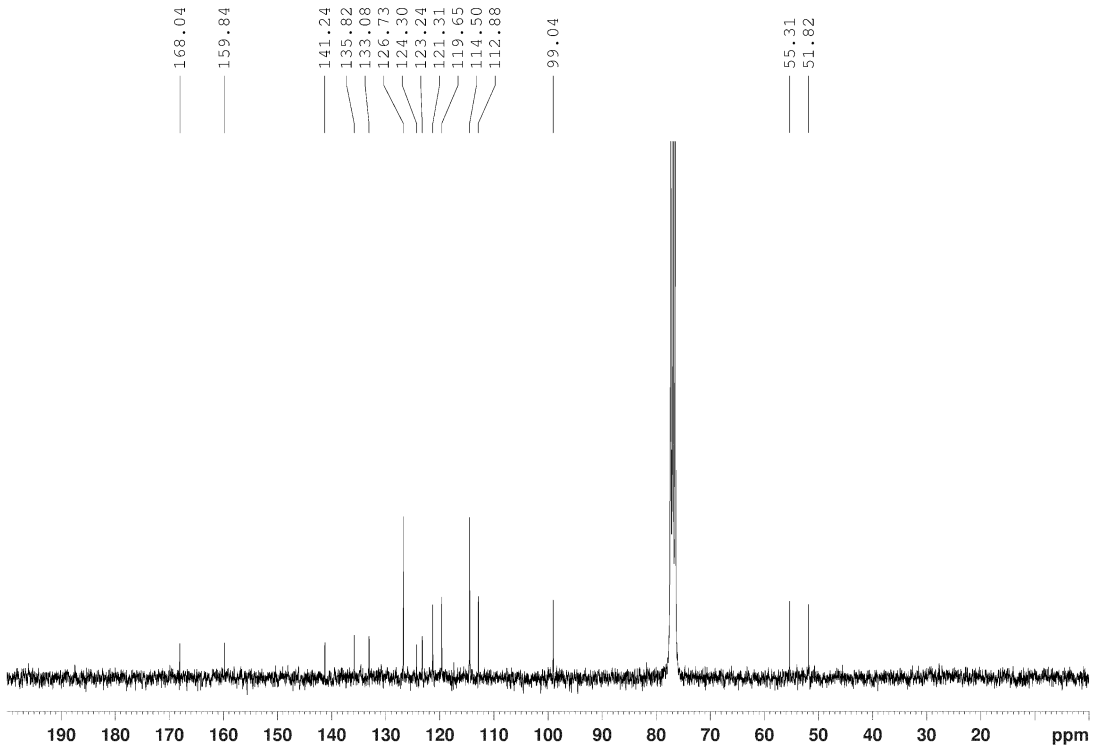


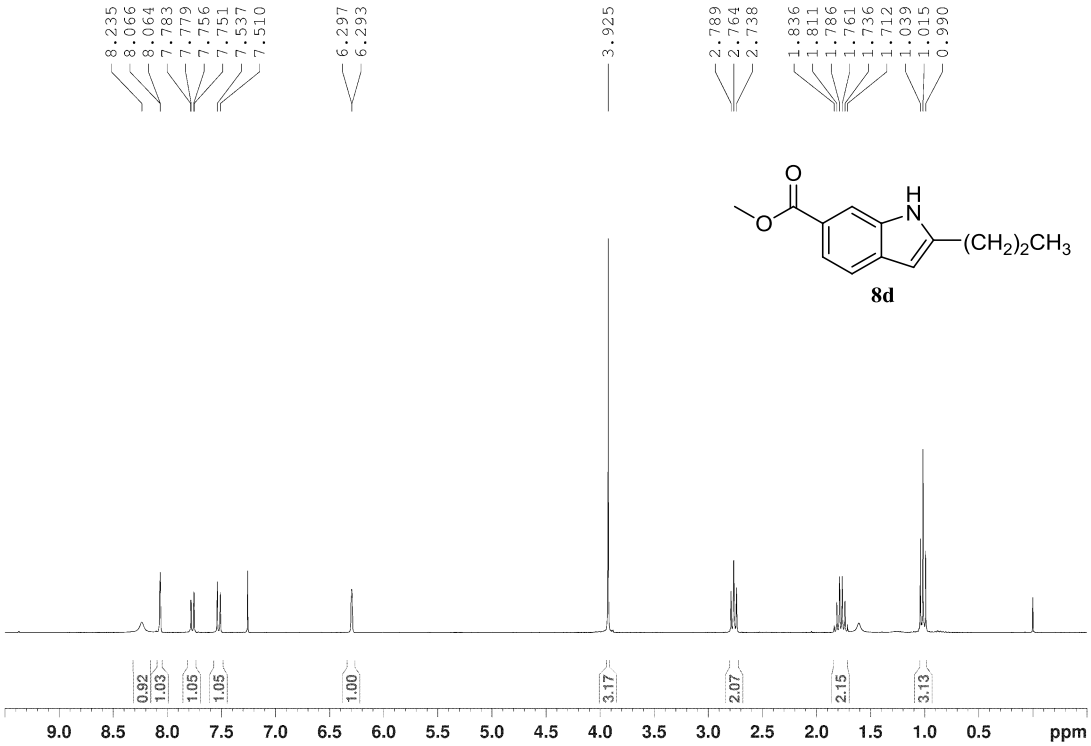
8b



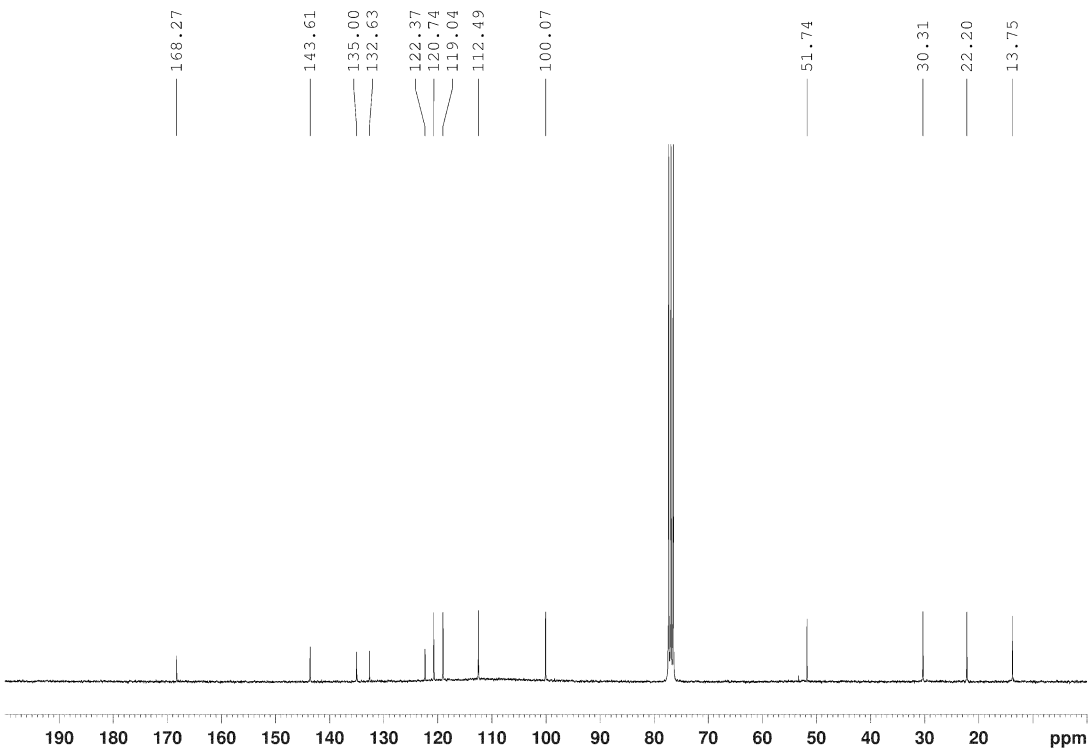


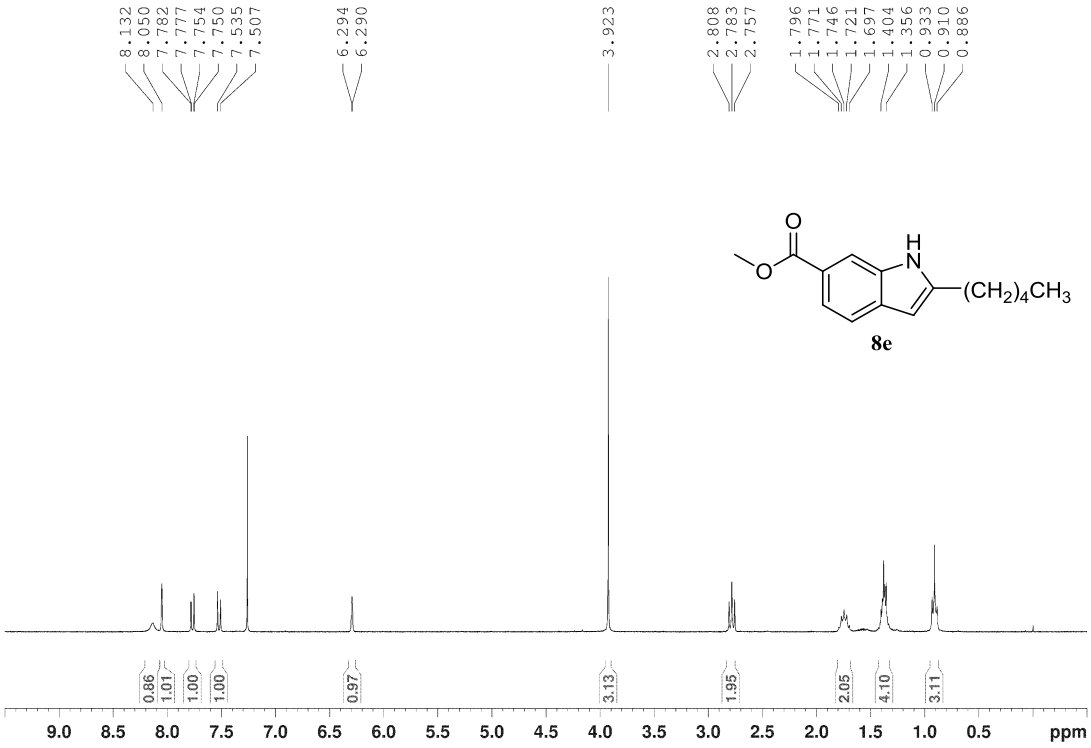
8c



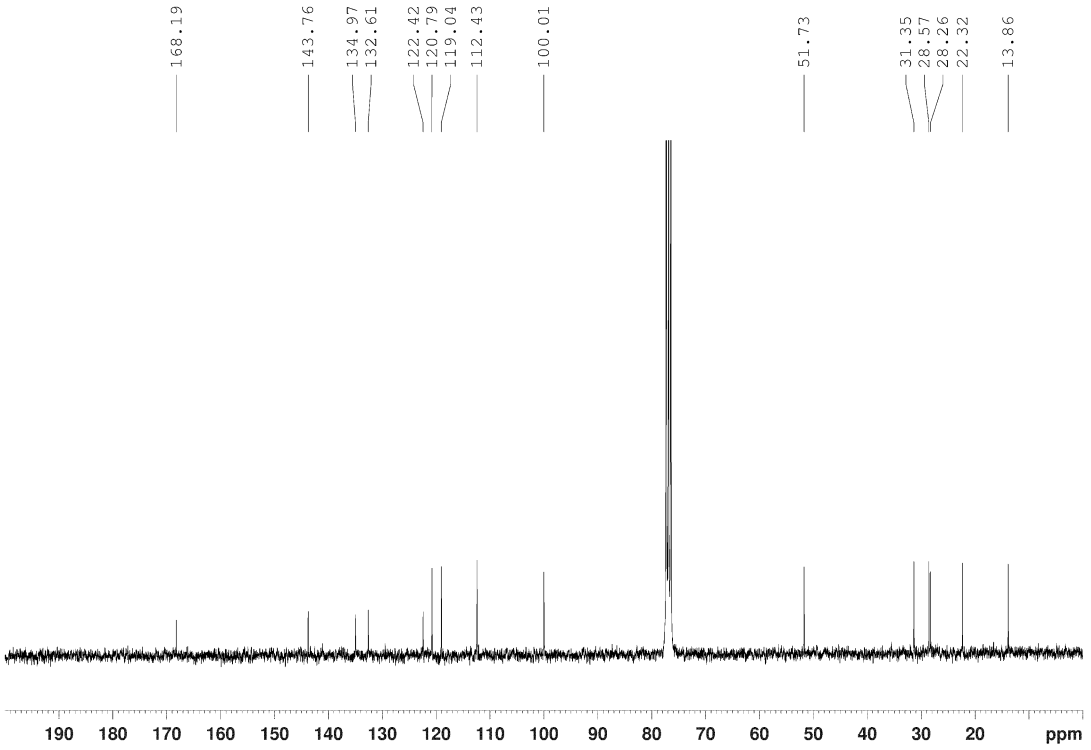


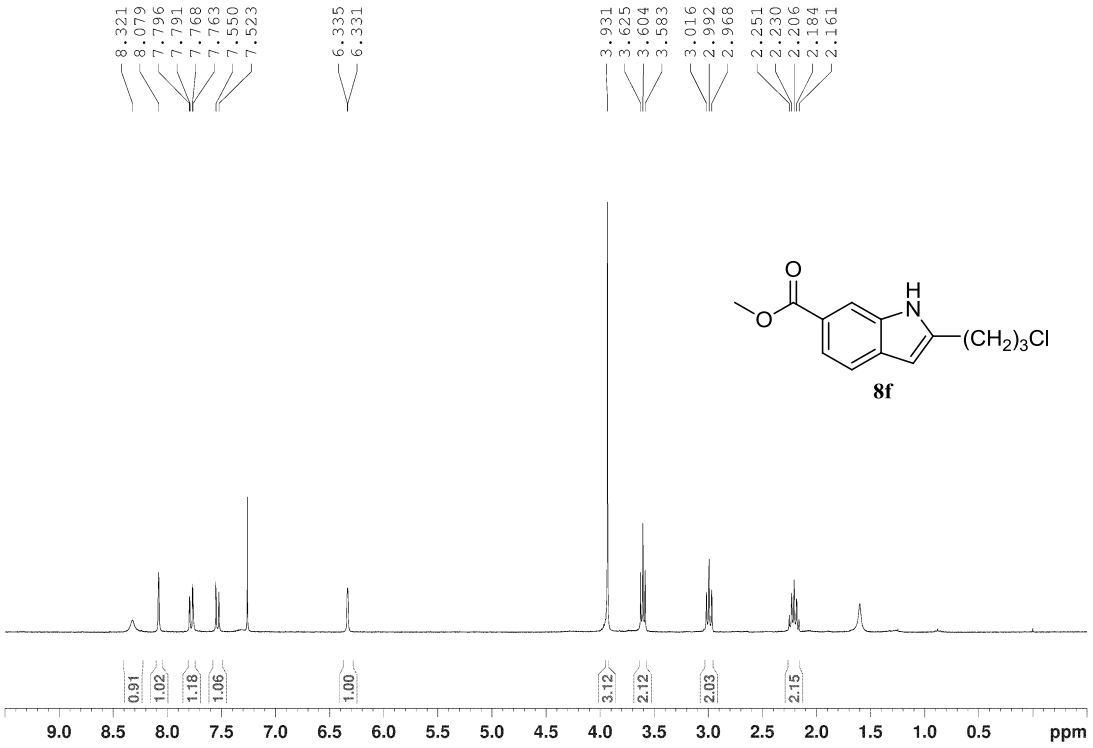
8d





8e





8f