Organocatalytic enantioselective synthesis of 1-vinyltetrahydroisoquinolines through allenamide activation with chiral Brønsted acids

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Electronic Supplementary Information

Table of contents:

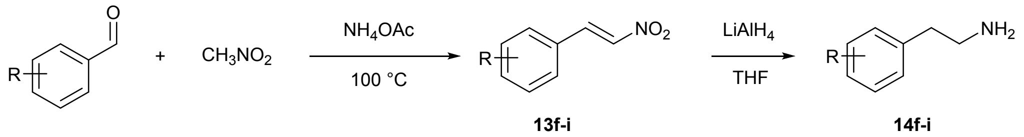
General methods. ^{1}H NMR spectra were recorded on Varian Gemini 200 and Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, pd = pseudo duplet, pt = pseudo triplet, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ = 77.0 ppm). If rotamers are present, the splitted signals are labelled as A (major rotamer) and B (minor rotamer). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 F_{254}. Determination of enantiomeric excess was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector (reference 420 nm), using Daicel Chiralpak® columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and *n*-hexane as eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 1 dm (Na_D line). Melting points (m.p.) were determined on Bibby Stuart Scientific Melting Point Apparatus SMP3 and were not corrected.

Materials. If not otherwise stated, all reactions were carried out in sealed vials in open air without nitrogen atmosphere. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification.

Reagents were purchased from Aldrich and used without further purification unless otherwise stated.

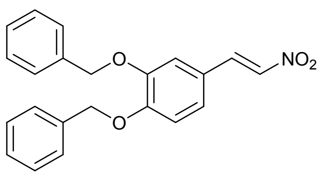
The phosphoric acids **12a-c** and **12e** were preparing according to literature procedure.[1]

General procedures for the synthesis of 2-aryl-ethylamines 14f-i.[2]

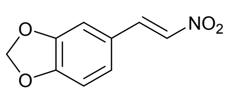


Synthesis of nitrostyrene derivatives 13f-i.

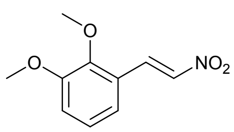
To a solution of aldehyde (15 mmol, 1 equiv.) in CH_3NO_2 (30 mL) was added NH_4OAc (3.73 mmol, 287 mg, 0.25 equiv.) in one portion. The resultant mixture was stirred at 100 °C, until complete conversion was obtained (4h, monitored by TLC), cooled at room temperature and water was added. Nitromethane was removed under reduced pressure and the residue was extracted with AcOEt (3 x 10 mL).The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (cyclohexane/ethyl acetate from 10:0 to 8:2) or by re-crystallization from ethanol (80-98% yield).



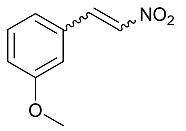
(13f): yellow solid, 4.39 g, 81% yield; m.p. 109-111°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (2H, s), 5.24 (2H, s), 6.97 (1H, d, J = 8.3 Hz), 7.08 (1H, d, J = 2.0 Hz), 7.12 (1H, dd, J = 8.3 Hz, J = 1.9 Hz), 7.33 (11H, m), 7.90 (1H, d, J = 13.6 Hz); ^{13}CNMR (101 MHz, $CDCl_3$): δ 70.9, 71.4, 114.1, 114.3, 123.1, 124.8, 127.1 (2C), 127.2 (2C), 128.1 (2C), 128.7 (4C), 135.6, 136.2, 136.45, 139.1, 149.1, 152.7; Spectroscopic data are according to those reported in literature.[2]



(13g): yellow solid, 2.46 g, 85% yield; m.p. 148-150°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.07 (2H, s), 6.88 (1H, d, J = 7.7 Hz), 7.01 (1H, d, J = 1.6 Hz), 7.09 (1H, dd, J = 8.2 Hz, J = 1.6 Hz), 7.48 (1H, d, J = 13.5 Hz), 7.94 (1H, d, J = 13.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 102.1, 107.0, 109.0, 124.2, 126.6, 135.3, 139.1, 148.7, 151.4; Spectroscopic data are according to those reported in literature.[3]



(13h): yellow solid, 2.76 g, 88% yield; m.p. 80-83°C; Spectroscopic data are according to those reported in literature.[3]



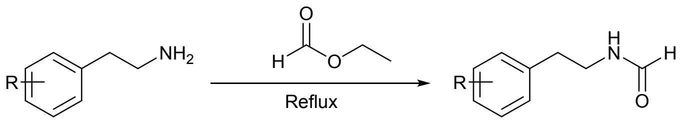
(13i): yellow sticky solid, 1.88 g, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (3H, s), 7.04-7.07 (2H, m), 7.15 (1H, d, J = 7.9 Hz), 7.36-7.40 (1H, m), 7.58 (1H, d, J = 13.7 Hz), 7.98 (1H, d, J = 13.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.4, 114.0, 117.9, 121.7, 130.4, 131.3, 137.3, 139.0, 160.1; Spectroscopic data are according to those reported in literature.[3]

Reduction of nitrostyrenes derivatives 13f-i.

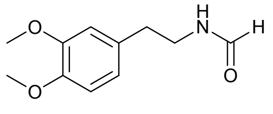
To a stirred suspension of $LiAlH_4$ (30 mmol, 1.14 g, 3 equiv.) in THF (30 mL) at 0 °C, a solution of nitrostyrene derivative **13f-i** (10 mmol, 1 equiv.) in THF (10 mL) was added dropwise. The mixture was allowed to reach room temperature and refluxed for 24 h. The mixture was cooled at 0 °C, diluted with Et_2O (5 mL) and water (1.14 mL) was slowly added. After 15 minutes, 15% (*w/w)* aqueous NaOH solution (1.14 mL) was added followed after further 15 minutes by addition of water (3.42 mL). The resultant mixture was stirred at room temperature for 30 minutes, then $MgSO_4$ was added and it was filtered through a Celite pad and it was washed with Et_2O (20 mL). The solvent was removed under reduced pressure to afford desired amine **14f-i** that was used as such in the next reaction steps.

General Procedure for the synthesis of allenamide derivatives 10a-i.

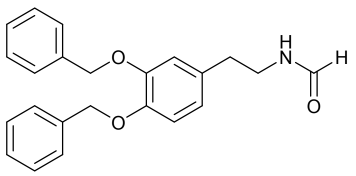
Synthesis of formamide derivatives.



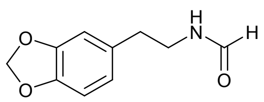
Amine **13f-i** or 3,4-dimethoxyphenethylamine (10 mmol, 1 equiv.) was dissolved in ethyl formate (20 mL) and the solution was refluxed for 24 h until complete conversion (monitored by ^{1}HNMR). The solvent was removed under reduced pressure and the crude residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate from 8:2 to 1:1) to afford formamides **8e-i**.



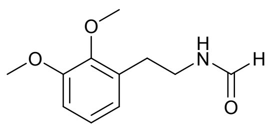
(8e): yellow oil, 1.43 g, 86% yield; Spectroscopic data are according to those reported in literature.[4]



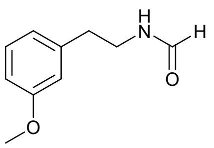
(8f): yellow oil, 1.91 g, 53% yield (two steps, from **37**); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 5.8:1): δ 2.70 ($2H_B$, t, *J* = 6.8 Hz), 2.72 ($2H_A$, t, *J* = 6.8 Hz), 3.39 ($2H_B$, q, *J* = 6.8 Hz), 3.48 ($2H_A$, q, *J* = 6.5 Hz), 5.16 ($4H_A$+$2H_B$, s), 5.18 ($2H_B$, s), 5.32 ($1H_A$, bs), 5.50 ($1H_B$, bs), 6.68-6.75 ($2H_A$+$2H_B$, m), 6.89 ($1H_A$+$1H_B$, d, *J* = 8.2 Hz), 7.30-7.46 ($10H_A$+$10H_B$, m), 7.89 ($1H_B$, d, *J* = 12Hz), 8.03 ($1H_A$, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 34.9, 39.2, 71.3, 71.4, 115.4, 115.8, 121.6, 127.4 (2C), 127.4 (2C), 127.9, 127.9, 128.5 (4C), 132.0, 137.2, 137.3, 147.7, 148.8, 161.3;



(8g): yellow oil, 888 mg, 46% yield (two steps, from **38**); ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 4.9:1): δ 2.70-2.77 ($2H_A$+$2H_B$, m), 3.38-3.45 ($2H_B$, m), 3.47-3.54 ($2H_A$, m), 5.92-5.94 ($2H_A$+$2H_B$, m), 6.60-6.76 ($3H_A$+$3H_B$, m), 7.90 ($1H_B$, t, *J* = 11.7 Hz), 8.11 ($1H_A$, d, *J* = 7.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 35.0 ($1C_A$), 37.1 ($1C_B$), 39.4 ($1C_A$), 43.3 ($1C_B$), 100.7 ($1C_A$), 100.8 ($1C_B$), 108.1 ($1C_A$), 108.2 ($1C_B$) 108.9 ($1C_A$), 109.0 ($1C_B$), 121.5 ($1C_A$), 121.7 ($1C_B$), 131.5 ($1C_B$), 132.4 ($1C_A$), 146.0 ($1C_A$), 146.2 ($1C_B$), 147.6 ($1C_A$), 147.7 ($1C_B$), 161.6 ($1C_A$), 164.8 ($1C_B$);

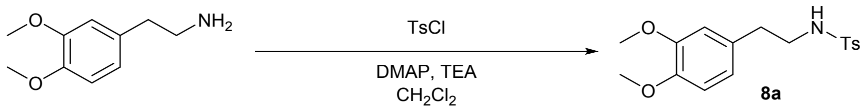


(8h): yellow oil, 1.11 g 53% yield (two steps, from **39**); ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.1:1) : δ 2.84 ($2H_B$, t, *J* = 6.7 Hz), 2.87 ($2H_A$, t, *J* = 6.7 Hz), 3.48 ($2H_A$, pq, *J* = 6.2 Hz), 3.54 ($2H_B$, pq, *J* = 6.0 Hz), 3.85 ($3H_A$, s), 3.86 ($3H_B$, s), 3.88 ($3H_A$ + $3H_B$, s), 6.77-6.80 ($1H_A$+$1H_B$, m), 6.82-6.85 ($1H_A$+$1H_B$, m), 7.00-7.05 ($1H_A$+$1H_B$, m), 8.11 ($1H_A$+$1H_B$, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ29.57 ($1C_A$), 29.63 ($1C_B$), 39.0 ($1C_A$), 40.5 ($1C_B$), 55.6 ($2C_A$), 60.5 ($2C_B$), 110.8 ($1C_B$), 110.9 ($1C_A$), 122.16 ($1C_A$), 122.17 ($1C_B$), 124.1 ($1C_B$), 124.2 ($1C_A$), 132.5 ($1C_A$), 132.8 ($1C_B$), 146.99 ($1C_B$), 147.01 ($1C_A$), 152.57 ($1C_A$), 152.58 ($1C_B$), 161.6 ($1C_A$), 170.5 ($1C_B$);

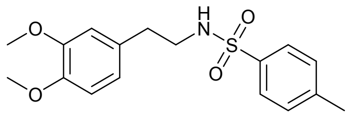


(8i): yellow oil, 1.22 g 68% yield (two steps, from **40**); Spectroscopic data are according to those reported in literature.[5]

Preparation of compound 8a.

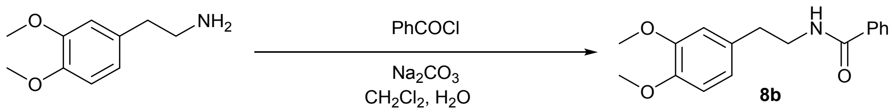


To a solution of 3,4-dimethoxyphenethylamine (3 mmol, 543 mg, 1 equiv.) in DCM (10 mL), Et_3N (4.5 mmol, 0.624 mL, 1.5 equiv.) and DMAP (0.075 mmol, 9.15 mg, 0.025 equiv.) were added. To the resulting solution at 0 °C, tosyl chloride (3.6 mmol, 688 mg, 1.2 equiv.) was slowly added in small portions. The mixture was allowed to reach room temperature and stirred for 24 h. Subsequently, water (10 mL) was added, the organic phase was separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were washed with HCl 1M (10 mL), $NaHCO_3$ sat. sln. (10 mL) and brine (10 mL). The organic layers was dried with Na_2SO_4, filtered and concentrated under reduced pressure to give pure **8a**, that was used as such, without further purification in the next steps.

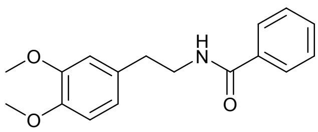


(8a): yellow solid, 894 mg, 89% yield; m.p. 133-135°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (3H, s), 2.71 (2H, t, *J* = 6.7 Hz), 3.19 (2H, q, *J* = 6.4 Hz), 3.82 (3H, s), 3.86 (3H, s), 4.37 (1H, bs), 6.57 (1H, s), 6.63 (1H, d, *J* = 8.5 Hz), 6.77 (1H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 7.6 Hz), 7.68 (2H, d, *J* = 7.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.5, 35.3, 44.30, 55.7, 55.9, 111.3, 111.7, 120.7, 127.0 (2C), 129.6 (2C), 130.1, 136.8, 144.3, 147.8, 149.0; EI-MS: *m/z* = 335 (60), 184 (14), 151 (100), 91 (84).

Preparation of compound 8b.

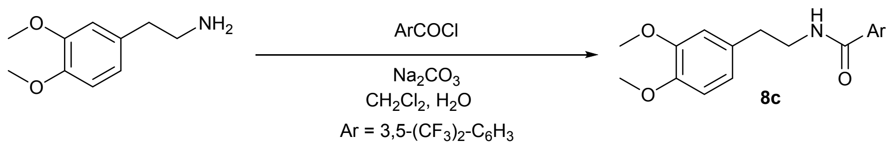


To a solution of 3,4-dimethoxyphenethylamine (3 mmol, 543 mg, 1 equiv.) and Na_2CO_3 (6 mmol, 636 mg, 2 equiv.), in H_2O/DCM (1/1, 20 mL), PhCOCl (4.5 mmol, 0.521 mL, 1.5 equiv.) was added dropwise. The mixture was stirred for 72 h, then water (10 mL) and DCM (10 mL) were added. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with HCl 1M (15 mL), $NaHCO_3$ sat. sln. (15 mL) and brine (15 mL). The organic layers was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was washed with *n*-hexane and then it was used such as, without further purification in the next steps.

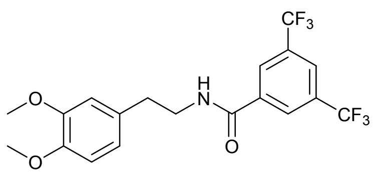


(8b): white solid, 710 mg, 83% yield; m.p. 63-65°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71-2.78 (2H, m), 3.38 (2H, m), 3.84 (3H, s), 3.85 (3H, s), 6.71-6.81 (3H, m), 7.34 (5H, s);^{13}C NMR (101 MHz, $CDCl_3$): δ 35.2 ($1C_A$+$1C_B$), 41.3 ($1C_A$+$1C_B$), 55.8 ($1C_A$+$1C_B$), 55.9 ($1C_A$+$1C_B$), 111.4 ($1C_A$+$1C_B$), 111.9 ($1C_A$+$1C_B$), 120.6 ($1C_A$+$1C_B$), 126.8 ($2C_A$+$2C_B$), 128.4 ($1C_B$), 128.5 ($2C_A$+$2C_B$), 130.1 ($1C_A$), 131.3 ($1C_B$), 131.4 ($1C_A$), 133.5 ($1C_A$), 134.5 ($1C_B$), 147.7 ($1C_A$+$1C_B$), 149.0 ($1C_A$+$1C_B$), 167.6 ($1C_A$+$1C_B$); EI-MS: *m/z* = 285 (8), 164 (100), 105 (53), 77 (48).

Preparation of compound 8c.



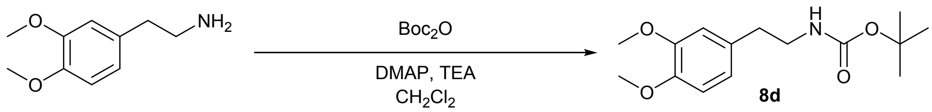
To a solution of 3,4-dimethoxyphenethylamine (3 mmol, 543 mg, 1 equiv.) and Na_2CO_3 (6 mmol, 636 mg, 2 equiv.), in H_2O/DCM (1/1, 20 mL), 3,5-$(CF_3)_2$-C_6H_3-COCl (3.6 mmol, 0.637 mL, 1.2 equiv.) was added dropwise. The mixture was stirred for 72 h and then water (10 mL) and DCM (10 mL) were added.The organic phase was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with HCl 1M (15 mL), $NaHCO_3$ sat. sln. (15 mL) and brine (15 mL). The organic layers was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was washed with *n*-hexane and then it was used such as, without further purification in the next steps.



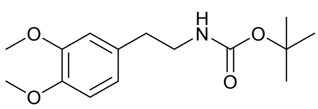
(8c): white solid, 1.23 g, 97% yield; m.p. 99-101°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (2H, t, J = 6.9 Hz), 3.75 (2H, q, J = 6.5 Hz), 3.88 (3H, s), 3.89 (3H, s), 6.18 (1H, bs), 6.77-6.80 (2H, m), 6.85 (1H, d, J = 7.8 Hz), 8.00 (1H, s), 8.14 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 35.1, 41.6, 55.8, 55.9, 111.4, 111.8, 120.7, 122.7 (2C, q, $J_{C\text{-}F}$ = 273.3 Hz), 124.9 (2C, t,

J_{C-F} = 4.1 Hz), 127.1 (2C, q, J_{C-F} = 3.4 Hz), 130.8, 132.4, 136.7, 148.0, 149.3, 164.5; EI-MS: *m/z* = 421 (25), 241 (46), 213 (36), 164 (100).

Preparation of compound 8d.[6]

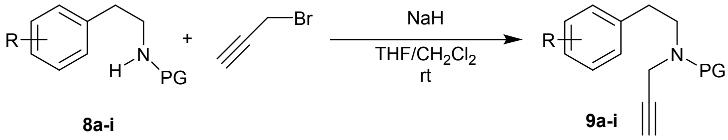


To a solution of 3,4-dimethoxyphenethylamine (3 mmol, 543 mg, 1 equiv.) in DCM (10 mL), Et_3N (4.5 mmol, 0.624 mL, 1.5 equiv.), DMAP (0.075 mmol, 9.15 mg, 0.025 equiv.) were added. To the resulting solution at 0 °C, Boc_2O (3.6 mmol, 785 mg, 1.2 equiv.) was slowly added in small portions. The mixture was allowed to reach room temperature and stirred for 24 h. Subsequently, water (10 mL) was added, the organic phase was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with HCl 1M (10 mL), $NaHCO_3$ sat. sln. (10 mL) and brine (10 mL). The organic layers was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was washed with *n*-hexane and then it was used such as, without further purification in the next steps.

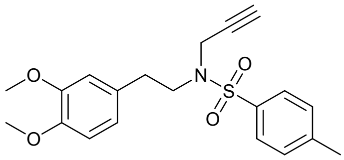


(8d): sticky yellow solid, 767 mg, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (9H, s), 2.75 (2H, t, *J* = 7.0 Hz), 3.33-3.38 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 4.54 (1H, bs), 6.72-6.75 (2H, m), 6.82 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.4 (3C), 35.7, 41.9, 55.8, 55.9, 79.2, 111.3, 111.9, 120.6, 131.5, 147.5, 148.9, 155.8; EI-MS: *m/z* =281 (129, 225 (14), 209 (13), 165 (58), 151 (100), 57 (63). Spectroscopic proprieties are according to those reported in literature.[6]

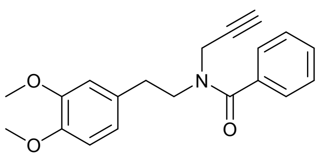
General Procedure for the propargylation of amides.



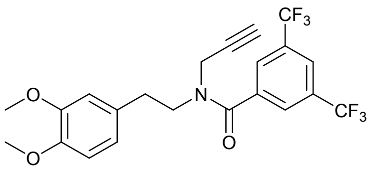
To a solution of **8a-i** (5 mmol, 1 equiv.) in anhydrous THF (15 mL) and CH_2Cl_2 (5 mL) at 0 °C, NaH (6.5 mmol, 156 mg, 1.3 equiv.) was slowly added. After 20 minutes, propargyl bromide (6 mmol, 0.539 mL, 1.2 equiv.) was added at 0°C. The reaction mixture was allow to reach room temperature and it was stirred for 24 h. Water (10 mL) was slowly added at 0 °C and organic volatiles were removed under reduced pressure. The residue was extracted with AcOEt (3 x 5mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel silica gel (cyclohexane/EtOAc 7/3) to give the desired products **9a-i**.



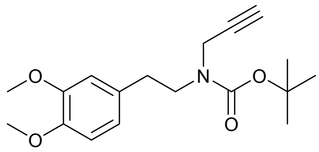
(9a): yellow solid, 1.66 g, 89% yield; m.p. 10-103°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (1H, t, *J* = 2.4 Hz), 2.42 (3H, s), 2.86 (2H, pt, *J* = 7.6 Hz), 3.42 (2H, pt, *J* = 7.6 Hz), 3.87 (3H, s), 3.88 (3H, s), 4.08 (2H, d, *J* = 2.5 Hz), 6.74 (1H, s), 6.75 (1H, d, *J* = 6.9 Hz), 6.80 (1H, d, *J* = 8.7 Hz), 7.28 (2H, d, *J* = 6.6 Hz), 7.71 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.5, 34.3, 36.8, 48.0, 55.86, 55.87, 73.7, 76.7, 111.3, 112.0, 120.7, 127.6 (2C), 129.4 (2C), 130.7, 135.9, 143.5, 147.7, 148.9; EI-MS: *m/z* = 373 (42), 222 (100), 155 (95), 151 (86), 91 (75).



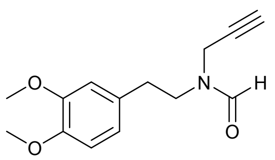
(9b): yellow oil, 291 mg, 18% yield; Although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) : δ 2.30 (2H, t, *J* = 2.5 Hz), 2.76 (1H, bs), 2.98 (1H, bs), 3.62 (1H, bs), 3.73 (1H, bs), 3.84 (6H, bs), 4.42 (2H, bs), 6.41 (1H, bs), 6.75 (2H, bs), 7.20 (1H, bs), 7.39 (4H, bs); ^{13}C NMR (101 MHz, $CDCl_3$): δ 33.0 ($1C_B$), 34.2 ($1C_A$), 40.0 ($1C_A$+$1C_B$), 47.3 ($1C_A$), 50.2 ($1C_B$), 55.8 ($2C_A$), 55.9 ($2C_A$), 72.4 ($1C_A$), 73.0 ($1C_B$), 78.8 ($1C_A$+$1C_B$), 113.3 ($1C_A$+$1C_B$), 111.8 ($1C_B$), 112.0 ($1C_A$), 120.7 ($2C_A$+$2C_B$), 126.7 ($2C_A$+$2C_B$), 128.4 ($1C_A$+$1C_B$), 129.9 ($1C_B$), 130.2 ($1C_A$), 131.3 ($1C_A$), 131.4 ($1C_A$), 135.7 ($1C_A$+$1C_B$), 147.7 ($2C_B$), 148.9 ($1C_A$), 171.1 ($1C_A$+$1C_B$); EI-MS: *m/z* = 323 (4), 164 (100), 105 (89), 77 (64).



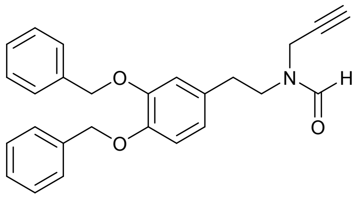
(9c): yellow oil, 291 mg, 18% yield; Although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product; ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C) (two rotamers A:B, ratio 1:1):δ 2.73 (1H$_A$+1H$_B$, t, J = 2.5 Hz), 2.80 (2H$_A$, bs), 2.99 (2H$_B$, bs),3.60 (2H$_A$, bs),3.75 (2H$_A$+2H$_B$, bs),3.84 (6H$_A$+6H$_B$, bs), 4.47 (2H$_B$, bs), 6.44 (1H$_A$, bs),6.50 (1H$_B$, bs),6.74 (2H$_A$, bs),6.80 (2H$_B$, bs), 7.51 (1H$_A$+1H$_B$, bs), 7.87 (2H$_A$, bs), 7.96 (2H$_B$, bs); ^{13}C NMR (101 MHz, CDCl$_3$): δ 33.0 (1C$_B$), 33.6 (1C$_A$), 34.2 (1C$_A$), 39.9 (1C$_B$), 47.7 (2C$_B$), 50.3 (2C$_A$), 73.2 (1C$_A$), 73.8 (1C$_B$), 77.9 (1C$_A$+1C$_B$), 112.2 (1C$_A$+1C$_B$), 111.9 (1C$_A$+1C$_B$), 120.7 (1C$_A$+1C$_B$), 122.9 (2C$_A$+2C$_B$, q, $J_{C\text{-}F}$ = 271.5 Hz), 123.3 (1C$_A$), 123.7 (1C$_B$), 124.1 (1C$_A$+1C$_B$), 127.0 (1C$_A$+1C$_B$, bs), 129.3 (1C$_B$), 130.8 (1C$_A$), 131.2 (2C$_A$+2C$_B$), 137.7 (1C$_A$+1C$_B$), 147.9 (1C$_A$), 148.0 (1C$_B$), 149.1 (1C$_A$+1C$_B$), 168.0 (1C$_B$), 168.5 (1C$_A$); EI-MS: m/z = 459 (9), 241 (88), 213 (67), 164 (100).



(9d): sticky white solid, 1.37 g, 86% yield; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.46 (9H, s), 2.22 (1H, s), 2.83 (2H, bs), 3.52 (2H, pt, J = 7.4 Hz), 3.86 (3H, s), 3.88 (3H, s), 4.03 (2H, bs), 6.74-6.82 (3H, m); ^{13}C NMR (101 MHz, CDCl$_3$): δ 28.3, 29.7, 30.9, 48.5, 55.8, 55.9, 71.5, 79.9, 80.1, 111.3, 111.0, 120.7, 131.7, 147.5, 148.9, 154.8; EI-MS: m/z = 319 (31), 246 (25), 151 (100), 57 (87).

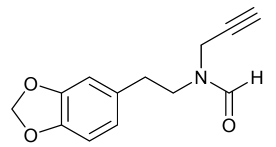


(9e): yellow oil, 469 mg, 38% yield; ^{1}H NMR (400 MHz, CDCl$_3$) (two rotamers A:B, ratio 2:1): δ 2.28 (1H$_B$, t, J = 2.3 Hz), 2.34 (1H$_A$, t, J = 2.5 Hz), 2.85 (2H$_A$, pt, J = 6.8 Hz), 2.86 (2H$_B$, pt, J = 6.4 Hz), 3.60 (2H$_A$, pt, J = 6.8 Hz), 3.63 (2H$_B$, pt, J = 6.8 Hz), 3.86 (3H$_A$, s), 3.87 (3H$_A$+3H$_B$, s), 3.88 (3H$_B$, s), 4.18 (2H$_A$+2H$_B$, d, J = 2.4 Hz), 6.67-6.83 (3H$_A$+3H$_B$, m), 7.80 (1H$_A$, bs), 8.10 (1H$_B$, bs); ^{13}C NMR (101 MHz, CDCl$_3$): δ 31.4 (1C$_A$), 32.8 (1C$_B$), 34.4 (1C$_A$), 37.5 (1C$_B$), 43.9 (1C$_B$), 48.7 (1C$_A$), 55.8 (2C$_A$+ 2C$_B$), 72.5 (1C$_A$), 73.6 (1C$_B$), 77.7 (1C$_B$), 78.0 (1C$_A$), 111.3 (1C$_B$), 111.4 (1C$_A$), 111.8 (1C$_B$), 111.9 (1C$_A$), 120.6 (1C$_B$), 120.8 (1C$_A$), 130.1 (1C$_A$), 130.9 (1C$_B$), 147.6 (1C$_B$), 147.8 (1C$_A$), 148.9 (1C$_B$), 149.0 (1C$_A$), 162.1 (1C$_A$), 162.1 (1C$_B$); ESI-MS: m/z = 248.2 [M+H]$^+$, 270.0 [M+Na]$^+$, 495.2 [2M+H]$^+$; ESI-MS: m/z = 248.0 [M+H]$^+$, 270.0 [M+Na]$^+$, 495.2 [2M+H]$^+$.

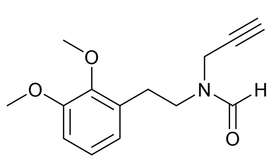


(9f): brown oil, 1.26 g, 63% yield;^{1}H NMR (400 MHz, CDCl$_3$) (two rotamers A:B, ratio 1.7:1): δ 2.23 (1H$_A$, t, J = 2.2 Hz), 2.29 (1H$_B$, t, J

= 2.0 Hz), 2.78 (2H_A, t, J = 6.8 Hz), 2.80 (2H_B, t, J = 7.02 Hz), 3.49 (2H_B, t, J = 6.9 Hz), 3.52 (2H_A, t, J = 6.8 Hz), 3.68 (2H_B, d, J = 1.6 Hz), 4.13 (2H_A, d, J = 2.2 Hz), 5.14 (2H_A+2H_B, s), 5.16 (2H_A, s), 5.18 (2H_B, s), 6.67 (1H_A, d, J =8.3 Hz), 6.73 (1H_A, s), 6.74 (1H_B, s), 6.80 (1H_B, s), 6.88 (1H_A+1H_B, d, J = 8.0 Hz), 7.30-7.45 (10H_A+10H_B, m), 7.71 (1H_A, s), 8.00 (1H_B, s); ^{13}C NMR (101 MHz, $CDCl_3$) (two rotamers A:B, ratio 6:1): δ 31.4 (1C_A), 32.9 (1C_B), 34.3 (1C_A), 37.6 (1C_B), 44.1 (1C_B), 48.5 (1CA), 71.4 (1CB), 71.4 (1CA), 71.5 (1C_A), 73.5 (1C_B), 77.8 (1C_B), 78.0 (1C_A), 115.4 (1C_A), 115.5 (1C_B), 115.8 (1C_B), 116.0 (1C_A), 121.6 (1C_B), 121.8 (1C_A), 127.3 (4C_A), 127.4 (4C_B), 127.76 (2C_B), 127.80 (1C_A), 127.82 (1C_A), 128.44 (2C_B), 128.46 (2C_A), 128.48 (2C_B), 128.5 (2C_A), 131.0 (1C_A), 132.0 (1C_B), 137.2 (1C_A+1C_B), 137.2 (1C_A +1C_B), 147.6 (1C_B), 147.9 (1C_A), 148.9 (1C_B), 149.0 (1C_A), 162.1 (1C_A), 162.1 (1C_B); ESI-MS: m/z = 400.2 $[M+H]^+$, 422.2 $[M+Na]^+$, 799.4 $[2M+H]^+$.

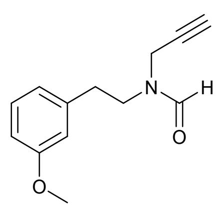


(9g): yellow oil, 658 mg, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.9:1): δ 2.28 (1H_A, t, J = 2.6 Hz), 2.34 (1H_B, t, J = 2.5 Hz), 2.83 (2H_A+2H_B, t, J = 6.7 Hz), 3.58 (2H_A, t, J =7.5 Hz), 3.62 (2H_B, pt, J = 7.4 Hz), 3.90 (2H_B, d, J = 2.1 Hz), 4.19 (2H_A, d, J = 2.2 Hz), 5.94 (2H_B, s), 5.95 (2H_A, s), 6.60-6.76 (3H_A+3H_B, m), 7.82 (1H_A, s), 8.11 (1H_B, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 31.2 (1C_A), 32.9 (1C_B), 34.4 (1C_A), 37.4 (1C_B), 44.1 (1C_B), 48.5 (1C_A),72.6 (1C_A), 73.7 (1C_B), 77.9 (1C_B), 78.0 (1C_A), 100.8 (1C_B), 100.9 (1C_A), 108.2 (1C_B), 108.3 (1C_A), 108.9 (1C_A), 109.0 (1C_B), 121.5 (1C_B), 121.7 (1C_A), 131.3 (1C_A), 132.2 (1C_B), 146.0 (1C_B), 146.3 (1C_A), 147.6 (1C_B), 147.8 (1C_A), 162.0 (1C_A), 162.1 (1C_B); ESI-MS: m/z = 232.2 $[M+H]^+$, 254.0 $[M+Na]^+$, 463.2 $[2M+H]^+$.



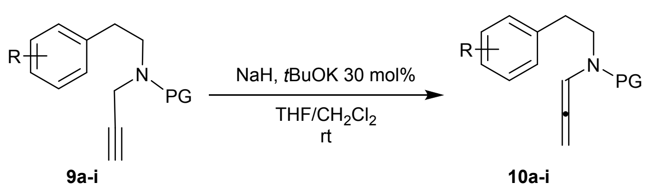
(9h): yellow oil, 630 mg, 51% yield;^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 2.2:1): δ 2.26 (1H_A, t, J = 2.6 Hz), 2.31 (1H_B, t, J = 2.5 Hz), 2.91 (2H_A, t, J = 6.9Hz), 2.92 (2H_B, t, J = 7.0 Hz), 3.61 (2H_A, t, J = 7.0 Hz), 3.67 (2H_B, t, J = 7.3 Hz), 3.85 (6H_B, s), 3.87 (6H_A, s), 3.92 (2H_B, d, J = 2.5 Hz), 4.22 (2H_A, d, J = 2.5 Hz), 6.72 (1H_A, dd, J_1 = 7.7 Hz, J_2 = 1.4 Hz), 6.81-6.84 (1H_A + 2H_B, m), 6.99 (1H_A + 1H_B, pt, J = 8.0 Hz), 7.82 (1H_A, s), 8.10 (1H_B, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ27.6 (1C_B), 29.4 (1C_A), 31.1 (1C_A), 37.3 (1C_B), 43.0 (1C_B), 47.3 (1C_A), 55.50 (1C_B), 55.51 (1C_A), 60.4 (1C_A), 60.6 (1C_B), 72.4 (1C_A), 73.5 (1C_B), 78.0 (1C_B), 78.1 (1C_A), 110.9 (1C_B), 111.3 (1C_A), 122.11 (1C_A), 122.13 (1C_B), 123.9 (1C_B), 124.0 (1C_A), 131.2 (1C_A), 132.1 (1C_B), 147.15 (1C_A), 147.23 (1C_B), 152.55

($1C_B$), 152.62 ($1C_A$), 162.0 ($1C_A$), 162.1 ($1C_B$); ESI-MS: *m/z* = 248.2 $[M+H]^+$, 270.0 $[M+Na]^+$, 494.2 $[2M+H]^+$.

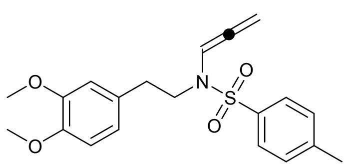


(9i): yellow oil, 521 mg, 48% yield;^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.8:1): δ 2.28 ($1H_A$, t, J = 2.5 Hz), 2.34 ($1H_B$, t, J = 2.5 Hz), 2.87-2.91 ($2H_A$+$2H_B$, m), 3.63 ($2H_A$, t, J = 7.1Hz), 3.68 ($2H_B$, t, J =7.5 Hz), 3.80 ($3H_A$, s), 3.81 ($3H_B$, s), 3.88 ($2H_B$, d, J = 2.6 Hz), 4.20 ($2H_A$, d, J = 2.6 Hz), 6.72-6.85 ($3H_A$+$3H_B$, m), 7.21-7.26 ($1H_A$+$1H_B$), 7.84 ($1H_A$, s), 8.11 ($1H_B$, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 31.3 ($1C_A$), 33.3 ($1C_B$), 34.7 ($1C_A$), 37.4 ($1C_B$), 43.8 ($1C_B$), 48.3 ($1C_A$), 55.01 ($1C_B$), 55.02 ($1C_A$), 72.6 ($1C_A$), 73.8 ($1C_B$), 77.9 ($1C_B$), 78.1 ($1C_A$), 111.88 ($1C_B$), 111.91 ($1C_A$), 114.3 ($1C_B$), 114.6 ($1C_A$), 120.96 ($1C_A$), 120.98 ($1C_B$), 129.5 ($1C_B$), 129.7 ($1C_A$), 139.3 ($1C_A$), 140.1 ($1C_B$), 159.7 ($1C_B$), 159.8 ($1C_A$), 162.0 ($1C_B$), 162.3 ($1C_A$); ESI-MS: *m/z* = 218.2 $[M+H]^+$, 240.2 $[M+Na]^+$, 435.2 $[2M+H]^+$.

General Procedure for the isomerization to allenamide compounds 10a-i.

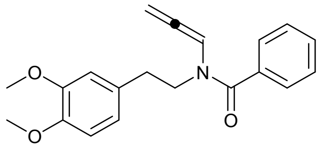


To a solution of propargylic amide **9a-i** (1.5 mmol, 1 equiv.) in THF (8 mL) at 0°C, *t*BuOK (0.3 mmol, 33.6 mg, 0.2 equiv.) and NaH (1.5 mmol, 36 mg, 1 equiv.) were added. The reaction was stirred for 24 h at room temperature, and then it was quenched with water (5 mL) at 0 °C. THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel silica gel (cyclohexane/EtOAc 7/3) to give the desired products **10a-i**.

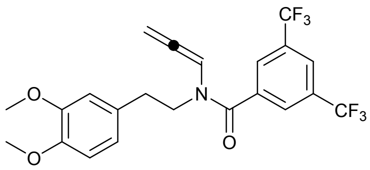


(10a): yellow oil, 509 mg, 91% yield;^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (3H, s), 2.82 (2H, pt, J = 8.0 Hz), 3.32 (2H, pt, J = 8.0 Hz), 3.85 (3H, s), 3.87 (3H, s), 5.39 (2H, d, J = 6.4 Hz), 6.70 (2H, bs), 6.77-6.79

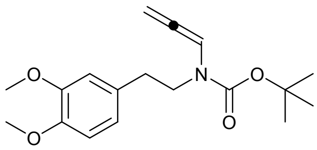
(1H, m), 6.88 (1H, t, J = 6.2 Hz), 7.30 (2H, d, J = 7.8 Hz), 7.68 (2H, d, J =7.80 Hz);^{13}C NMR (101 MHz, $CDCl_3$): δ 21.4, 34.0, 48.1, 55.6, 55.7, 87.6, 100.0, 111.1, 112.0, 120.6, 126.9 (2C), 129.6 (2C), 130.8, 135.3, 143.6, 147.5, 148.7, 201.4; ESI-MS: *m/z* = 374.0 $[M+H]^+$, 396.0 $[M+Na]^+$, 769.0 $[2M+H]^+$.



(10b): brown oil, 49 mg, 64% yield; although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 2:1): δ2.78 ($2H_B$, bs), 2.94 ($2H_A$, bs), 3.64 ($2H_B$, bs),3.77 ($2H_A$, bs), 3.89 ($6H_A$+$6H_B$, bs), 5.40 ($2H_A$, bs), 5.53 ($2H_B$, bs), 6.68 ($3H_b$, bs), 6.83 ($3H_A$, bs), 7.18 ($1H_A$+$1H_B$, m), 7.46 ($5H_A$+$5H_B$, bs); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.4 ($1C_A$+$1C_B$), 41.3 ($1C_A$+$1C_B$), 55.9 ($1C_A$+$1C_B$), 56.0 ($1C_A$+$1C_B$), 111.4 ($1C_B$), 111.5 ($1C_B$), 111.6 ($1C_A$), 112.1 ($1C_A$), 120.8 ($1C_A$), 120.9 ($1C_A$), 121.0 ($2C_B$), 126.9 ($2C_A$+$2C_B$), 128.5 ($1C_A$+$1C_B$), 128.7 ($2C_A$+$2C_B$), 131.5 ($1C_A$+$1C_B$), 134.7 ($1C_A$+$1C_B$), 147.9 ($1C_A$), 149.0 ($1C_B$), 149.1 ($1C_B$), 149.2 ($1C_A$), 151.1 ($1C_B$), ($1C_A$+$1C_B$), 167.5 ($1C_A$+$1C_B$), 198.1 ($1C_A$+$1C_B$); ESI-MS: *m/z* = 324.2 $[M+H]^+$.

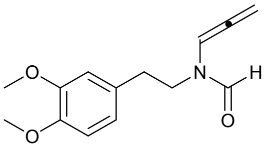


(10c): yellow oil, 185 mg, 27% yield; although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 3:1):δ 2.77 ($2H_B$, bs), 2.93 ($2H_B$, t, J = 7.2 Hz), 2.80 ($2H_A$, bs),3.59 ($2H_B$, bs),3.75 ($2H_A$, bs), 3.84 ($6H_A$+$6H_B$, bs), 5.40 ($2H_A$, d, J = 5.9 Hz),5.57 ($2H_B$, bs), 6.36-6.45 ($1H_A$+$1H_B$, bs),6.71-6.80 ($2H_A$+$2H_B$, bs), 7.40 ($2H_A$, bs),7.62 ($2H_B$, bs), 7.86 ($2H_A$, bs),7.94 ($2H_B$, bs); ^{13}C NMR (101 MHz, $CDCl_3$): δ 33.1, 46.4, 55.9 (2C), 87.5, 101.4, 112.3, 113.2, 121.0 (2C), 122.3 (2C, q, $J_{C\text{-}F}$ = 272.4 Hz), 123.9 (1C, m), 128.3 (2C, bs), 131.9 (2C), 137.4, 149.1, 151.1, 168.3, 198.1; ESI-MS: *m/z* = 460.2 $[M+H]^+$, 492.0 $[M+Na]^+$.

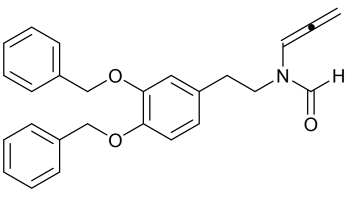


(10d): yellow oil, 325 mg, 80% yield; Although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 1:1): δ1.38 ($9H_A$, bs), 1.47($9H_B$, bs), 2.73 ($2H_A$+$2H_B$, bs),3.52

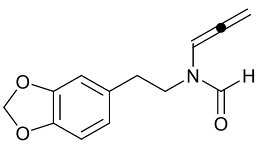
(2H$_A$+2H$_B$, bs),3.83 (3H$_A$+3H$_B$, bs),3.84 (3H$_A$+3H$_B$, bs), 5.37 (2H$_A$+2H$_B$, bs), 6.65-6.78 (3H$_A$+3H$_B$, m), 6.98 (1H$_A$, m),7.16 (1H$_A$, m); ESI-MS: *m/z* = 319.1 [M+H]$^+$, 342.0 [M+Na]$^+$, 639.2 [2M+H]$^+$.



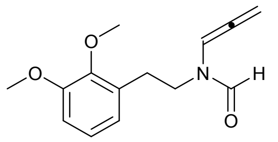
(10e): brown oil, 133 mg, 36% yield;^{1}H NMR (400 MHz, CDCl$_3$) (two rotamers A:B, ratio 1.2:1): δ 2.77-2.83 (2H$_A$ + 2H$_B$, m), 3.56 (2H$_A$, t, *J* = 6.6 Hz), 3.63-3.67 (2H$_B$, m), 3.86 (6H$_B$,s), 3.87 (3H$_A$, s), 3.88 (3H$_A$, s), 5.48 (2H$_B$, d, *J* = 6.3 Hz), 5.51 (2H$_A$, d, *J* = 6.6 Hz), 6.58 (1H$_A$, t, *J* = 6.3 Hz), 6.64-6.82 (3H$_A$ + 3H$_B$, m), 7.30 (1H$_B$, t, *J* = 6.4 Hz), 7.76 (1H$_B$, s), 8.20 (1H$_A$, s);^{13}C NMR (101 MHz, CDCl$_3$): δ 32.8 (1C$_B$), 34.0 (1C$_A$), 43.5 (1C$_B$), 48.2 (1C$_A$), 55.8 (2C$_B$), 55.9 (2C$_A$), 87.3 (1C$_A$), 87.9 (1C$_B$), 97.4 (1C$_A$), 100.4 (1C$_B$), 111.2 (1C$_B$), 111.4 (1C$_A$), 112.0 (1C$_B$), 112.0 (1C$_A$), 120.7 (1C$_B$), 120.9 (1C$_A$), 130.4 (1C$_A$), 131.0 (1C$_B$), 147.6 (1C$_A$), 147.9 (1C$_B$), 148.8 (1C$_B$), 149.0 (1C$_A$), 160.3 (1C$_B$), 160.5 (1C$_A$), 200.4 (1C$_A$), 202.2 (1C$_B$); ESI-MS: *m/z* = 248.0 [M+H]$^+$, 270.0 [M+Na]$^+$, 495.2 [2M+H]$^+$.



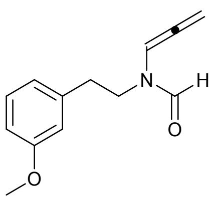
(10f): yellow oil, 479 mg, 80% yield; ^{1}H NMR (400 MHz, CDCl$_3$) (two rotamers A:B, ratio 1.7:1): δ 2.71-2.75 (2H$_A$+2H$_B$, m), 3.46-3.52 (2H$_A$, m), 3.59 (2H$_B$, t, *J* = 7.7 Hz), 5.14 (4H$_A$, s), 5.15 (2H$_B$, s), 5.17 (2H$_B$, s), 5.38 (2H$_B$, d, *J* = 6.2 Hz), 5.45 (2H$_A$, d, *J* = 6.4 Hz), 6.45 (1H$_A$, t, *J* = 6.3 Hz), 6.64 (1H$_A$, d, *J* = 8.3 Hz), 6.69 (1H$_B$, s), 6.72 (1H$_B$, d, *J* = 8.3 Hz), 6.79 (1H$_A$, s), 6.87 (1H$_A$+1H$_B$, d, *J* = 8.0 Hz), 7.25 (1H$_A$, t, *J* = 6.6 Hz), 7.30-7.47 (10H$_A$+10H$_B$, m), 7.67 (1H$_A$, s), 8.10 (1H$_B$, s); ^{13}C NMR (101 MHz, CDCl$_3$): δ 32.7 (1C$_B$), 33.4 (1C$_A$), 43.4 (1C$_B$), 48.1 (1C$_A$), 71.2 (1C$_A$), 71.35 (1C$_B$), 71.40 (1C$_B$), 71.5 (1C$_A$), 87.2 (1C$_A$), 87.9 (1C$_B$), 95.4 (1C$_A$), 100.4 (1C$_B$), 115.27 (1C$_B$), 115.31 (1C$_A$), 115.9 (1C$_A$), 116.1 (1C$_B$), 121.7 (1C$_B$), 121.9 (1C$_A$), 127.27 (2C$_B$), 127.31 (2C$_B$+2C$_A$), 127.3 (2C$_A$), 127.7 (1C$_A$+1C$_B$), 127.7 (1C$_A$), 127.9 (1C$_B$), 128.44 (2C$_B$), 128.46 (2C$_A$+2C$_B$), 128.49 (2C$_A$), 131.2 (1C$_B$), 131.9 (1C$_A$), 137.3 (1C$_A$+1C$_B$), 137.4 (1C$_A$+1C$_B$), 147.6 (1C$_B$), 148.0 (1C$_A$), 148.8 (1C$_A$), 149.0 (1C$_B$), 160.3 (1C$_A$), 160.5 (1C$_B$), 200.3 (1C$_A$), 202.2 (1C$_B$); ESI-MS: *m/z* = 400.0 [M+H]$^+$, 422.0 [M+Na]$^+$, 799.0 [2M+H]$^+$.



(10g): yellow oil, 208 mg, 60% yield; ^{1}H NMR (400 MHz, CDCl$_3$) (two rotamers A:B, ratio 1.1:1): δ 2.74-2.80 (2H$_A$+2H$_B$, m), 3.54 (2H$_A$, t, *J* = 6.8 Hz), 3.62 (2H$_B$, pt, *J* = 7.8 Hz), 5.48 (2H$_B$, d, *J* = 6.2 Hz), 5.50 (2H$_A$, d, *J* = 6.2 Hz), 5.93 (2H$_B$, s), 5.95 (2H$_A$, s), 6.56-6.76 (3H$_A$+4H$_B$, m), 7.30 (1H$_A$, t, *J* = 6.3 Hz), 7.79 (1H$_A$, s), 8.10 (1H$_B$, s);^{13}C NMR (101 MHz, CDCl$_3$): δ 32.9 (1C$_B$), 34.1 (1C$_A$), 43.5 (1C$_B$), 48.2 (1C$_A$), 87.3 ($1C_A$), 88.0 ($1C_B$), 95.4 ($1C_A$), 100.4 ($1C_B$), 100.8 ($1C_B$), 100.9 ($1C_A$), 108.2 ($1C_B$), 108.4 ($1C_A$), 109.0 ($1C_A$), 109.2 ($1C_B$), 121.7 ($1C_B$), 121.9 ($1C_A$), 131.5 ($1C_A$), 132.1 ($1C_B$), 146.1 ($1C_A$), 146.4 ($1C_B$), 147.5 ($1C_B$), 147.8 ($1C_A$), 160.3 ($1C_B$), 160.5 ($1C_A$), 200.24 ($1C_B$), 202.18 ($1C_A$); ESI-MS: *m/z* = 270.0 $[M+Na]^+$.



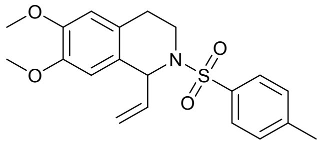
(10h): yellow oil, 256 mg, 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.3:1): δ 2.86-2.90 ($2H_A$+$2H_B$, m), 3.59 ($2H_A$, t, J = 7.2 Hz), 3.67 ($2H_B$, t, J = 7.7 Hz, 3.84-3.87 ($6H_A$+$6H_B$, m), 5.43 ($2H_B$, d, J = 6.2 Hz), 5.50 ($2H_A$, d, J = 6.5 Hz), 6.56 ($1H_B$, t, J = 6.6 Hz), 6.68 ($1H_A$, d, J = 7.5 Hz), 6.82 ($1H_A$+$2H_B$, pt, J = 7.9 Hz), 6.98 ($1H_A$+$1H_B$, pt, J = 7.5 Hz), 7.26-7.29 ($1H_A$, m), 7.83 ($1H_A$, s), 8.20 ($1H_B$, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 27.8 ($1C_B$), 29.6 ($1C_A$), 42.5 ($1C_B$), 46.9 ($1C_A$), 55.6 ($1C_A$ + $1C_B$), 60.6 ($1C_A$), 60.7 ($1C_B$), 87.2 ($1C_A$), 87.9 ($1C_B$), 95.5 ($1C_A$), 100.4 ($1C_B$), 110.9 ($1C_B$), 111.3 ($1C_A$), 122.4 ($1C_B$), 122.4 ($1C_A$), 123.8 ($1C_B$), 124.1 ($1C_A$), 131.5 ($1C_A$), 132.3 ($1C_B$), 147.2 ($1C_A$), 147.5 ($1C_B$), 152.7 ($1C_B$), 152.8 ($1C_A$), 160.4 ($1C_B$), 160.6 ($1C_A$), 200.1 ($1C_B$), 200.2 ($1C_A$); ESI-MS: *m/z* = 248.0 $[M+H]^+$, 270.0 $[M+Na]^+$, 495.2 $[2M+H]^+$.



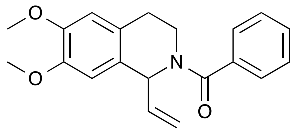
(10i): brown oil, 208 mg, 64% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.1:1): δ 2.80-2.86 ($2H_A$+$2H_B$, m), 3.58 ($2H_A$, t, J = 7.2 Hz), 3.67 ($2H_B$, pt, J = 7.8 Hz), 3.80 ($3H_A$, s), 3.81 ($3H_B$, s), 5.48 ($2H_B$, d, J = 6.5 Hz), 5.51 ($2H_A$, d, J =6.6 Hz), 6.58 ($1H_B$, t, J = 6.1 Hz) 6.68-6.83 ($3H_A$+$3H_B$, m), 7.20-7.25 ($1H_A$+$1H_B$, m), 7.30 ($1H_A$, t, J = 6.5 Hz), 7.80 ($1H_A$, s), 8.20 ($1H_B$, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 33.3 ($1C_B$), 34.5 ($1C_A$), 43.2 ($1C_B$), 47.9 ($1C_A$), 55.1 ($1C_B$), 55.1 ($1C_A$), 87.3 ($1C_A$), 87.9 ($1C_B$), 95.4 ($1C_A$), 100.4 ($1C_B$), 111.8 ($1C_B$), 111.9 ($1C_A$), 114.5 ($1C_A$), 114.7 ($1C_B$), 121.10 ($1C_B$), 121.13 ($1C_A$), 129.4 ($1C_B$), 129.7 ($1C_A$), 139.5 ($1C_B$), 140.0 ($1C_A$), 159.6 ($1C_B$), 159.8 ($1C_A$), 160.3 ($1C_B$), 160.5 ($1C_A$), 200.3 ($1C_B$), 202.2 ($1C_A$); ESI-MS: *m/z* = 218.0 $[M+H]^+$, 240 $[M+Na]^+$.

General Procedure for the organocatalytic enantioselective cyclization of compounds 10a-i.

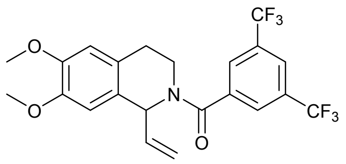
To a solution of allenammide (0.1 mmol, 1 equiv.) in trifluorotoluene (1 mL), Brønsted acid (0.01 mmol, 0.1 equiv.) and MS 4Å (0.05 g) were added and the reaction was stirred for 24h. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 3/7) to obtain the desired products.



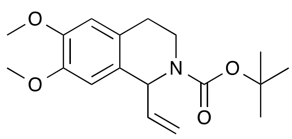
(11a): sticky white solid, 23.5 mg, 63% yield, 21% *ee*; the *ee* was determined by HPLC analysis, Daicel Chiralpak® ia column: hexane/*i*-PrOH from 70:30, flow rate 1.0 mL/min, 40°C, λ = 280 nm: τ_{major} = 8.18 min., τ_{minor} = 6.98 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s), 2.48-2.54 (1H, m), 2.65-2.74 (1H, m), 3.27-3.34 (1H, m), 3.82 (3H, s), 3.84 (3H, s), 3.85-3.89 (1H, m), 5.05 (1H, d, *J* = 17.14 Hz), 5.18 (1H, d, *J* = 10.20 Hz), 5.46 (1H, d, *J* = 5.98 Hz), 5.91 (1H, ddd, *J* = 5.72 Hz, *J* = 10.12 Hz, *J* = 16.98 Hz), 6.47 (1H, s), 6.53 (1H, s), 7.20 (2H, d, *J* = 8.08 Hz), 7.67 (2H, d, *J* = 8.33 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.5, 27.2, 39.1, 55.8, 55.9, 57.7, 110.4, 111.3, 117.7, 125.4, 125.6, 127.1 (2C), 129.4 (2C), 137.3, 137.9, 143.9, 147.4, 148.0; EI-MS: *m/z* = 373 (12), 346 (84), 308 (75), 217 (82), 198 (87), 91 (100); ESI-MS: *m/z* = 374.0 $[M+H]^+$, 396.0 $[M+Na]^+$, 769.0 $[2M+Na]^+$; HMRS calcd for $C_{18}H_{19}N$: 373.13478; found 373.13486.



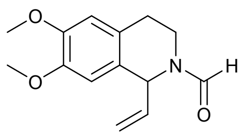
(11b): sticky white solid, 21.0 mg, 65% yield, 14% *ee*; the *ee* was determined by HPLC analysis, Daicel Chiralpak® IA column: hexane/*i*-PrOH from 60:40 , flow rate 0.50 mL/min, 40°C, λ = 280 nm: τ_{major} = 11.62 min., τ_{minor} = 16.86 min; Although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 2:1): δ 2.61 ($1H_A$, bs), 2.89 ($1H_A$, bs), 3.22 ($1H_B$, bs), 3.40 ($1H_B$, bs), 3.75 ($2H_A$+$2H_B$, bs), 3.85 ($6H_A$+$6H_B$, bs), 4.72-5.11 ($2H_A$+$2H_B$, m), 5.26 ($1H_A$+$1H_B$, bs), 6.07 ($1H_A$+$1H_B$, bs), 6.17 ($1H_A$, bs), 6.36 ($1H_B$, bs), 6.61 ($2H_A$, bs), 6.67 ($2H_B$, bs),7.38 ($5H_A$+$5H_B$, bs); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.9 ($1C_B$), 29.7 ($1C_A$), 41.2 ($1C_A$+$1C_B$), 54.2 ($1C_A$+$1C_B$), 55.8 ($1C_A$+$1C_B$), 56.0 ($1C_A$+$1C_B$), 111.4 ($1C_A$+$1C_B$), 117.4 ($1C_A$+$1C_B$), 120.6 ($1C_A$+$1C_B$), 126.0 ($1C_A$+$1C_B$), 126.7 ($2C_A$+$2C_B$), 128.5 ($2C_A$+$2C_B$), 129.2 ($2C_A$+$2C_B$), 131.4 ($1C_A$+$1C_B$), 136.3 ($1C_A$), 137.1 ($1C_B$), 147.6 ($1C_A$+$1C_B$), 148.1 ($1C_A$+$1C_B$), 170.4 ($1C_A$+$1C_B$); ESI-MS: *m/z* = 323 (25), 308 (20), 280 (6), 264 (11), 218 (34), 105 (100), 77 (85); ESI-MS: *m/z* = 324.2 $[M+H]^+$, 346.0 $[M+Na]^+$, 669.2 $[2M+Na]^+$;



(11c): sticky yellow solid, 28.9 mg, 63% yield, 0% *ee*; the *ee* was determined by HPLC analysis, Daicel Chiralpak® IA colum hexane/*i*-PrOH from 90:10, flow rate 0.5 mL/min, 40°C, λ = 285 nm: τ_{major} = 14.66 min., τ_{minor} = 16.76 min; Although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 2:1): δ2.60 ($1H_A$+$1H_B$, bs), 2.89 ($1H_A$+$1H_B$, bs), 3.00 ($2H_A$, bs), 3.28 ($1H_B$, bs),3.53 ($1H_A$, bs),3.85 ($6H_A$+$6H_B$, bs), 4.72-5.16 ($2H_A$+$2H_B$, m),5.34 ($1H_A$+$1H_B$, d, J = 9.4 Hz),6.09 ($1H_A$, bs),6.37 ($1H_B$, bs),6.67 ($2H_A$+$2H_B$, bs),7.45 ($1H_A$+$1H_B$, bs),7.89 ($2H_A$+$2H_B$, bs); The presence of rotamers avoids the detection of some signals, that result too broad to be identified from the noise; ^{13}C NMR (101 MHz, $CDCl_3$): δ 34.2 ($1C_A$), 35.1 ($1C_B$), 41.6 ($1C_A$), 41.7 ($1C_B$), 55.9 ($2C_A$), 56.0 ($1C_B$), 77.2 ($1C_A$+$1C_B$), 110.9 ($1C_A$+$1C_B$), 111.4 ($1C_A$+$1C_B$), 117.2 ($1C_A$), 118.3 ($1C_B$), 119.8 ($2C_B$, q, $J_{C\text{-}F}$ = 274.2 Hz), 122.8 ($2C_A$, q, $J_{C\text{-}F}$ = 272.4 Hz), 123.6 ($2C_A$+$2C_B$), 124.9 ($1C_B$), 125.1 ($1C_A$), 125.4 ($1C_B$), 125.6 ($1C_A$), 127.2 ($1C_A$+$1C_B$, bs), 136.5 ($1C_A$), 136.8 ($1C_B$), 138.1 ($1C_A$+$1C_B$), 147.9 ($1C_A$+$1C_B$), 148.4 ($1C_A$+$1C_B$); EI-MS: *m/z* = 459 (22), 430 (76), 241 (100), 213 (84); ESI-MS: *m/z* = 460.0 $[M+H]^+$, 482.0 $[M+Na]^+$, 941.0 $[2M+Na]^+$;



(11d): yellowish oil, 10.0 mg, 30% yield, 32% *ee*; the *ee* was determined by HPLC analysis, Daicel Chiralpak® ia column: hexane/*i*-PrOH from 90:10, flow rate 0.70 mL/min, 40°C, λ = 280 nm: τ_{major} = 11.80 min., τ_{minor} = 18.4 min; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.47 (9H, s), 2.60 (1H, dt,J = 3.4 Hz, J = 15.5 Hz), 2.71-2.77 (1H, m), 2.80-2.88 (1H, m), 3.13 (1H, bs), 3.83 (3H, s), 3.84 (3H, s), 3.85 (1H, dJ = 4.0 Hz), 5.05 (1H, d,J = 17.0 Hz), 5.14 (1H, dt,J = 1.4 Hz, J = 10.2 Hz), 5.89-5.97 (1H, m), 6.58 (s, 1H), 6.59 (s, 1H); Due to the presence of rotamers, it was not possible to obtain suitable spectra performing a ^{13}C NMR experiment; the signals have been determined from gHSQC and gHMBC experiments; ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.9 ($1C_A$+$1C_B$), 29.6 ($3C_A$), 32.5 ($3C_B$), 42.3 ($1C_A$+$1C_B$), 56.0 ($1C_A$+$1C_B$), 56.5 ($1C_A$+$1C_B$), 57.3 ($1C_A$+$1C_B$), 80.4 ($1C_A$), 85.6 ($1C_B$), 111.4 ($1C_A$), 111.3 ($1C_A$), 111.6 ($1C_B$), 112.4 ($1C_B$), 116.8 ($1C_A$+$1C_B$), 127.3 ($1C_A$), 128.7 ($1C_B$), 129.2 ($1C_A$+$1C_B$), 148.3 ($1C_A$+$1C_B$), 148.8 ($1C_A$+$1C_B$), 149.5 ($1C_A$+$1C_B$), 181.6 ($1C_A$+$1C_B$); ESI-MS: *m/z* = 342.2 $[M+Na]^+$, 661.2 $[2M+Na]^+$;



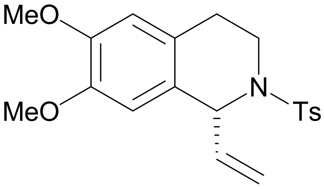
(11e): sticky white solid, 9.9 mg, 40% yield, 81% *ee*; to perform the HPLC analysis of product **11e**, it was necessary to reduce the amide moiety to methyl group $LiAlH_4$ (1.5 equiv.) was added to **11e**. After 2h, a few drops of water were added, followed by $MgSO_4$. The mixture was filtered and directly subjected to HPLC analysis; Daicel Chiralpak® OD-H column: hexane/*i*-PrOH from 90:10, flow rate 0.70 mL/min, 40°C, λ = 285 nm: τ_{major} = 7.87 min., τ_{minor} = 14.93 min; ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1:1): δ 2.62-2.72 ($2H_B$, m), 2.78-2.91 ($2H_A$, m), 3.13 ($1H_B$, ddd, *J* = 4.7 Hz, *J* = 11.0 Hz, *J* = 15.6 Hz), 3.45 ($1H_A$, ddd, *J* = 4.2 Hz, *J* = 13.0 Hz, *J* = 13.0 Hz), 3.65 ($1H_A$, dd, *J* = 5.8 Hz, *J* = 13.2 Hz), 3.80 ($3H_A$, s), 3.81 ($3H_A$ + $3H_B$, bs), 3.82 ($3H_B$, s), 4.29 ($1H_B$, m), 5.02 ($1H_B$, d, *J* = 5.7 Hz), 5.09 ($1H_A$, d, *J* = 17 Hz), 5.11 ($1H_B$, d, *J* = 17.0 Hz), 5.19 ($1H_A$, d, *J* = 10.1 Hz), 5.20 ($1H_B$, d, *J* = 10.1 Hz), 5.78 ($1H_A$, d, *J* = 5.6 Hz), 5.86-5.99 ($1H_A$ +$1H_B$, m), 6.55 ($1H_A$, s), 6.56 ($1H_A$ +$1H_B$, bs), 6.59 ($1H_B$, s), 8.15 ($1H_A$, s), 8.25 ($1H_B$, s);^{13}C NMR (101 MHz, $CDCl_3$): δ 27.6 ($1C_B$), 29.2 ($1C_A$), 35.1 ($1C_B$), 40.2 ($1C_A$), 52.7 ($1C_A$), 55.8 ($1C_A$), 55.8 ($1C_A$), 55.9 ($1C_A$), 56.0 ($1C_B$), 58.7 ($1C_B$), 110.1 ($1C_B$), 110.6 ($1C_A$),111.3 ($1C_A$), 111.5 ($1C_B$), 117.0 ($1C_B$), 117.3 ($1C_A$), 125.2 ($1C_A$ + $1C_B$), 125.4 ($1C_A$), 126.5 ($1C_B$), 136.4 ($1C_A$), 138.0 ($1C_B$), 147.6 ($1C_B$), 147.7 ($1C_A$), 148.0 ($1C_A$), 148.3 ($1C_B$), 161.1 ($1C_A$), 161.6 ($1C_B$); ESI-MS: *m/z* = 248.2 $[M+H]^+$, 270.0 $[M+Na]^+$, 495.2 $[2M+H]^+$; HMRS calcd for $C_{18}H_{19}N$: 247.12084; found 247.12075.

References

1. F. Romanov-Michailidis, L. Guénée and A. Alexakis, *Angew. Chem. Int. Ed.*, 2013, **52**, 9266-9270; F. Romanov-Michailidis, L. Guénée and A. Alexakis, *Org. Lett.*, 2013, **15**, 5890-5893; V. Rauniyar, A. D. Lackner, G. L. Hamilton and F. D. Toste, *Science*, 2011, **334**, 1681-1684; Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar and F. D. Toste, *J. Am. Chem. Soc.*, 2012, **134**, 12928-12931; V. Rauniyar, Z. J. Wang, H. E. Burks and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 8486-8489; T. Akiyama, H. Morita and K. Fuchibe, *J. Am. Chem. Soc.*, 2006, **128**, 13070-13071.
2. J. Párraga, N. Cabedo, S. Andujar, L. Piqueras, L. Moreno, A. Galán, E. Angelina, R. D. Enriz, M. D. Ivorra, M. J. Sanz and D. Cortes, *Eur. J. Med. Chem.*, 2013, **68**, 150-166.
3. S. H. Yang, C.-H. Song, H. T. M. Van, E. Park, D. B. Khadka, E.-Y. Gong, K. Lee and W.-J. Cho, *J. Med. Chem.*, 2013, **56**, 3414-3418.

4. C. Zhang , Z. Xu, T. Shen, G. Wu, L. Zhang and N. Jiao *Org. Lett.* 2012, **14***,* 2362–2365.
5. T. M. Böhme, C. E. Augelli-Szafran, H. Hallak, T. Pugsley, K. Serpa and R. D. Schwarz, *J. Med. Chem.*, 2002, **45**, 3094-3102.
6. D. S. Ermolat'ev, J. B. Bariwal, H. P. L. Steenackers, S. C. J. De Keersmaeckerand E. V. Van der Eycken, *Angew. Chem. Int. Ed.*, 2010, **49**, 9465-9468**.**

Copies of HPLC traces



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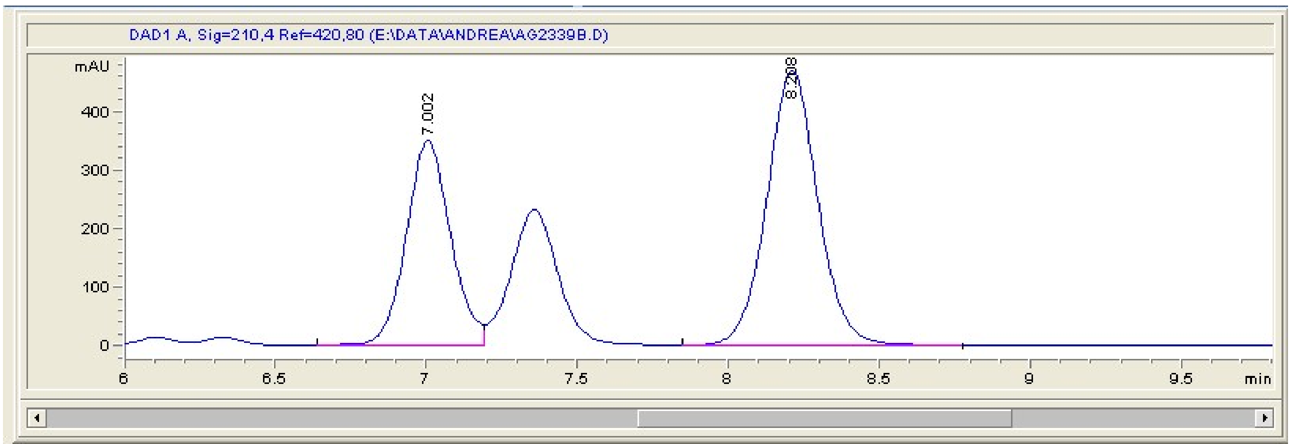
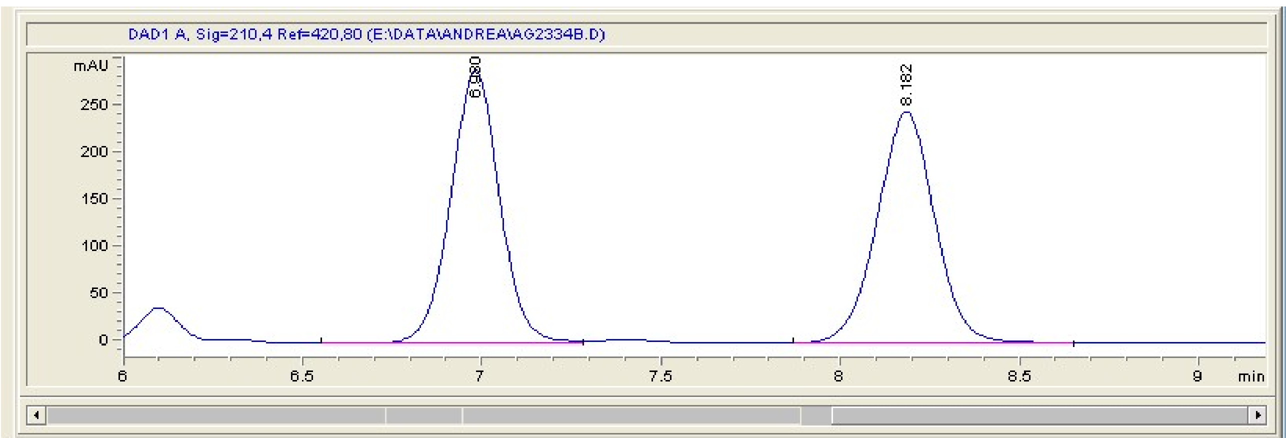


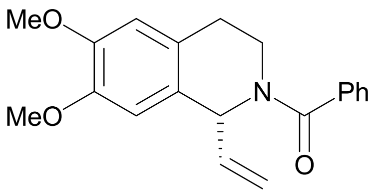
#	Time	Area	Height	Width	Area%	Symmetry
1	7.002	3599.4	350.3	0.1559	39.352	0.92
2	8.208	5547.4	469.9	0.1797	60.648	0.934

Active



#	Time	Area	Height	Width	Area%	Symmetry
1	6.98	2759.6	291.4	0.1445	49.953	0.988
2	8.182	2764.7	246.7	0.1707	50.047	0.995

Racemic



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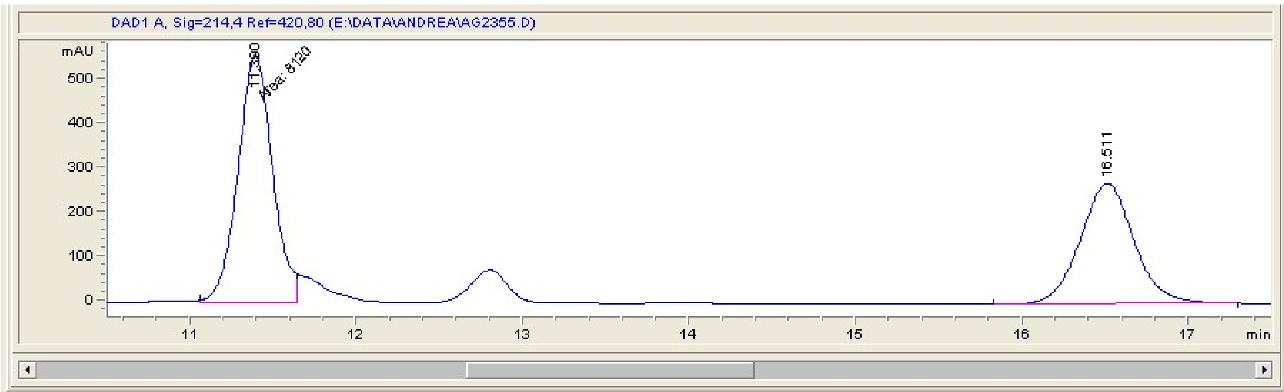
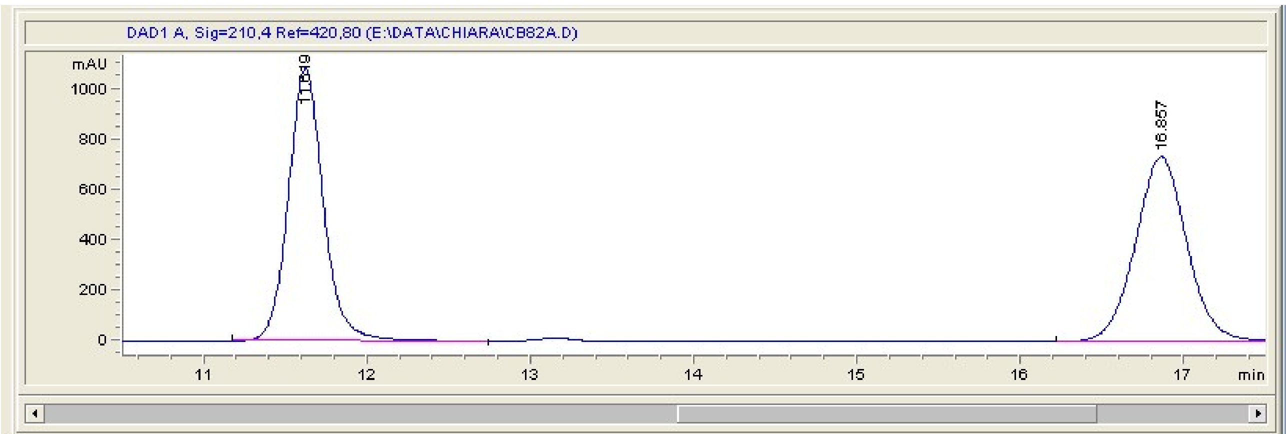


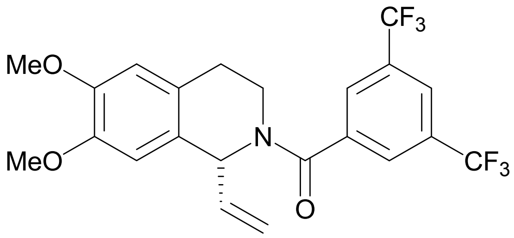
#	Time	Area	Height	Width	Area%	Symmetry
1	11.39	8120	558.7	0.2422	56.970	0.975
2	16.511	6133	272.2	0.3389	43.030	0.959

Active



#	Time	Area	Height	Width	Area%	Symmetry
1	11.619	16248.5	1086.7	0.2264	50.131	0.876
2	16.857	16163.2	734.2	0.3389	49.869	0.959

Racemic



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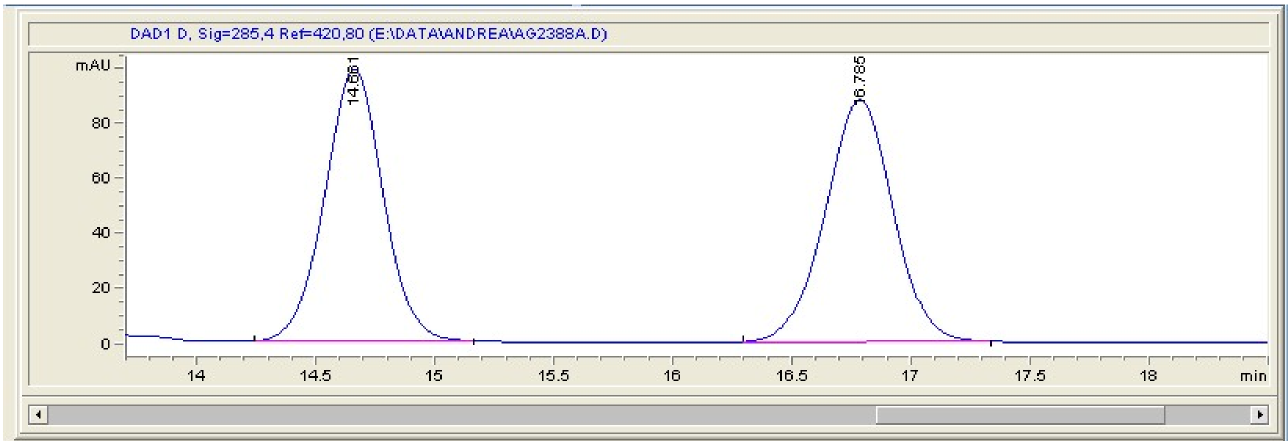

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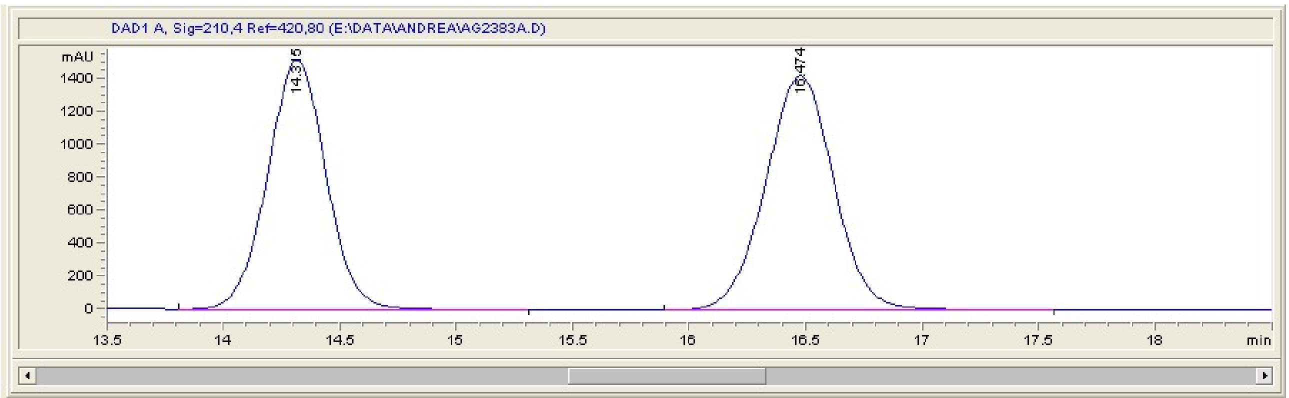
1	14.661	1718.7	99.3	0.2659	49.242	1.006
2	16.785	1771.7	88.4	0.3099	50.758	1.025

Active



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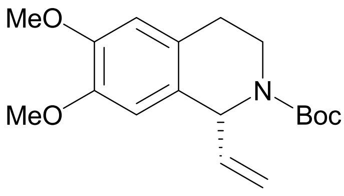
1	14.315	26740.2	1516	0.2738	47.877	0.989
2	16.474	29112.2	1423.3	0.3166	52.123	1

Racemic



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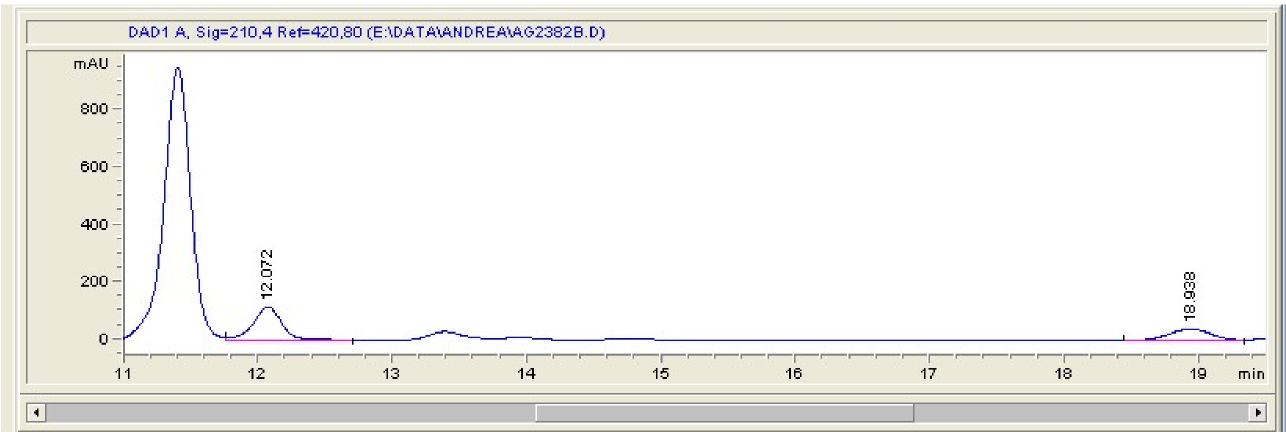

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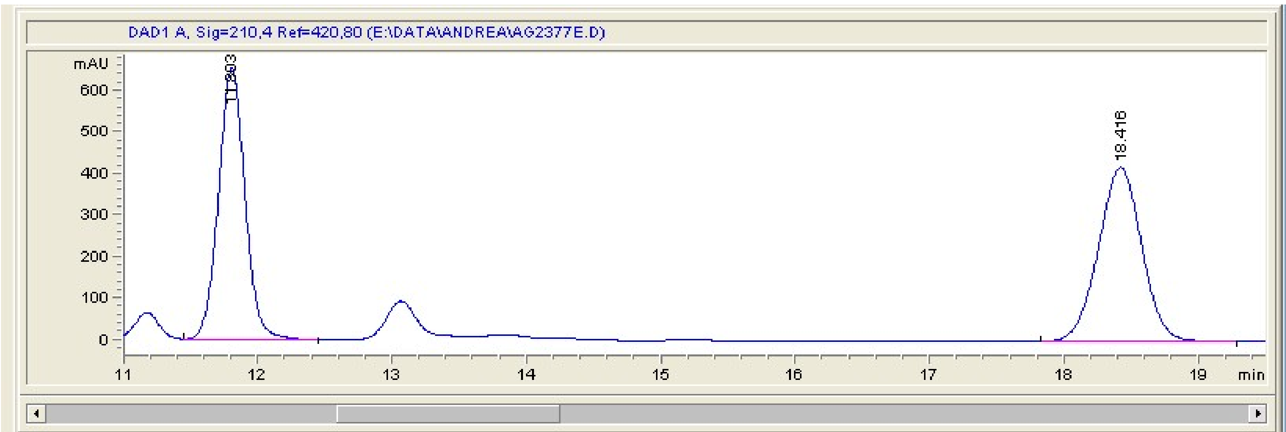
2	18.938	938.5	40.8	0.3561	33.757	1.045

Active



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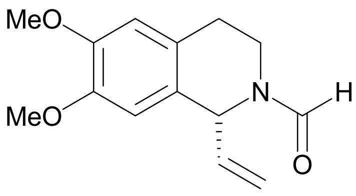
1	11.803	9100.9	656.8	0.2116	49.105	0.941
2	18.416	9432.8	419.3	0.3485	50.895	1.012

Racemic



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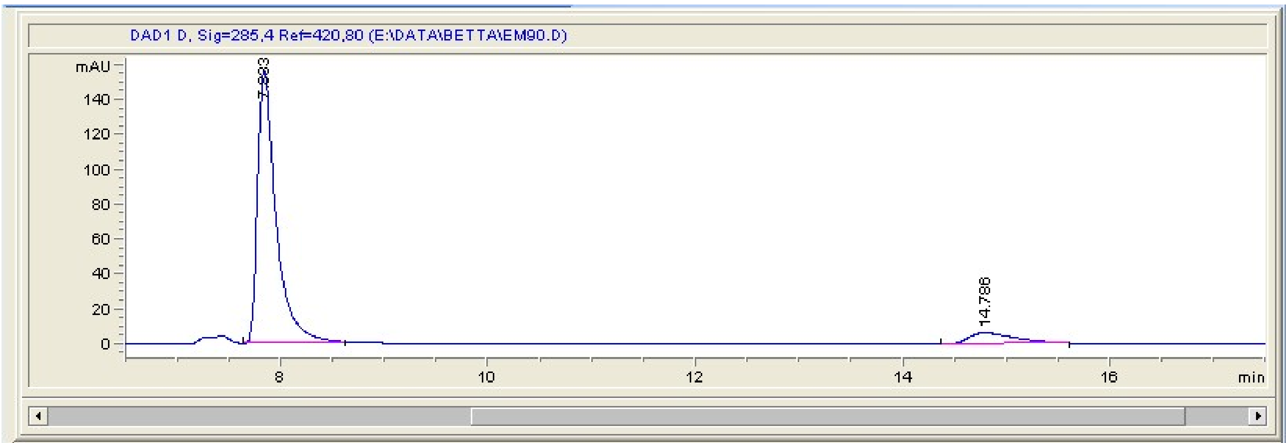

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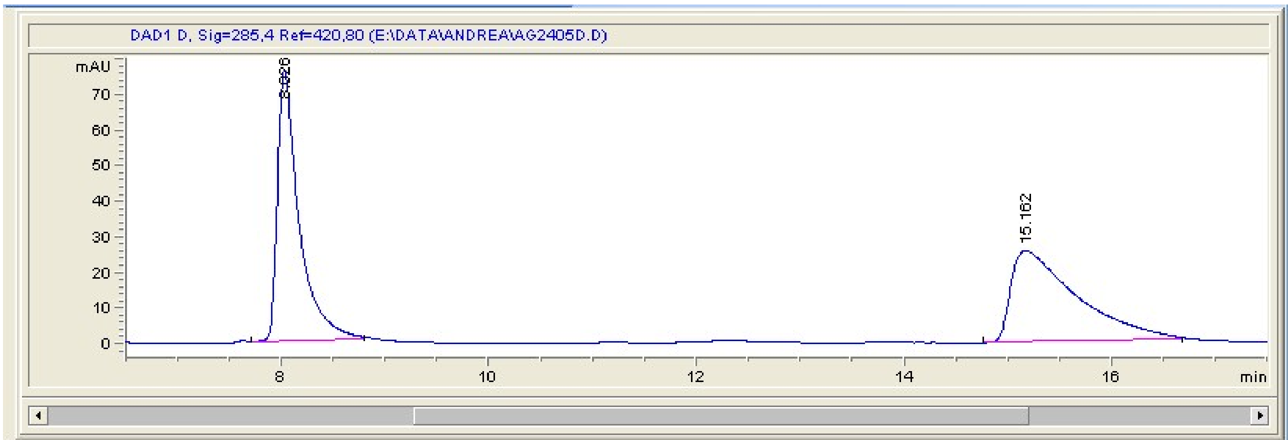
Active



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1	8.026	1121.6	76.3	0.2116	49.588	0.424
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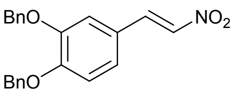
Racemic

Copies of NMR spectrum



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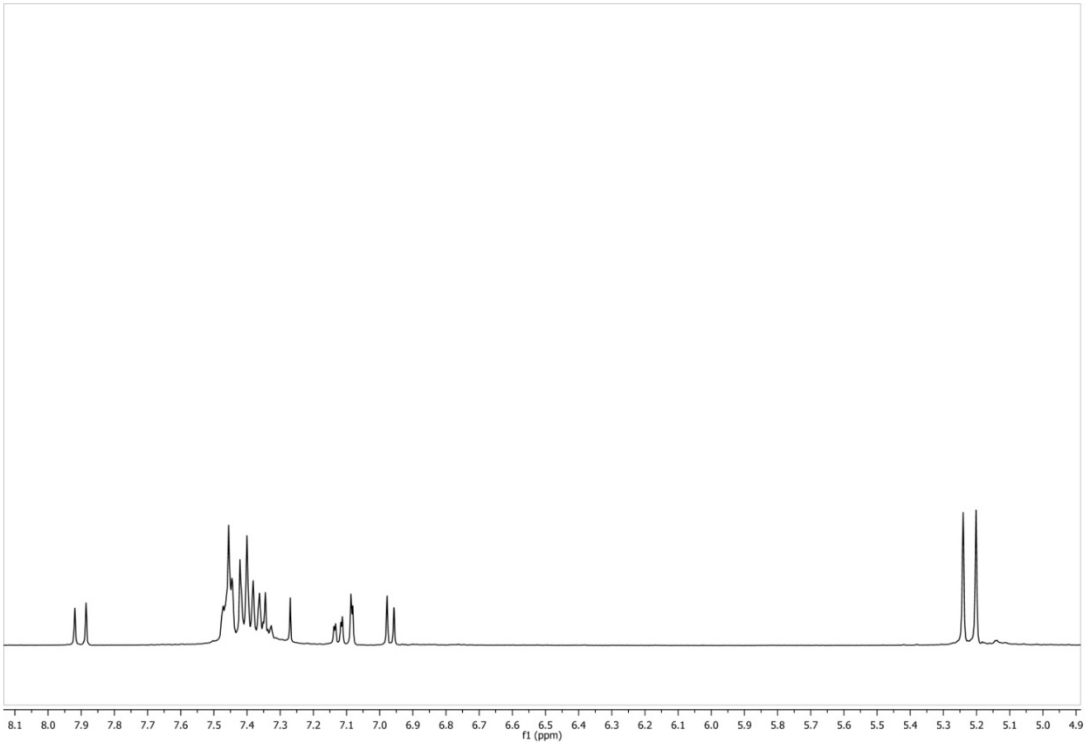

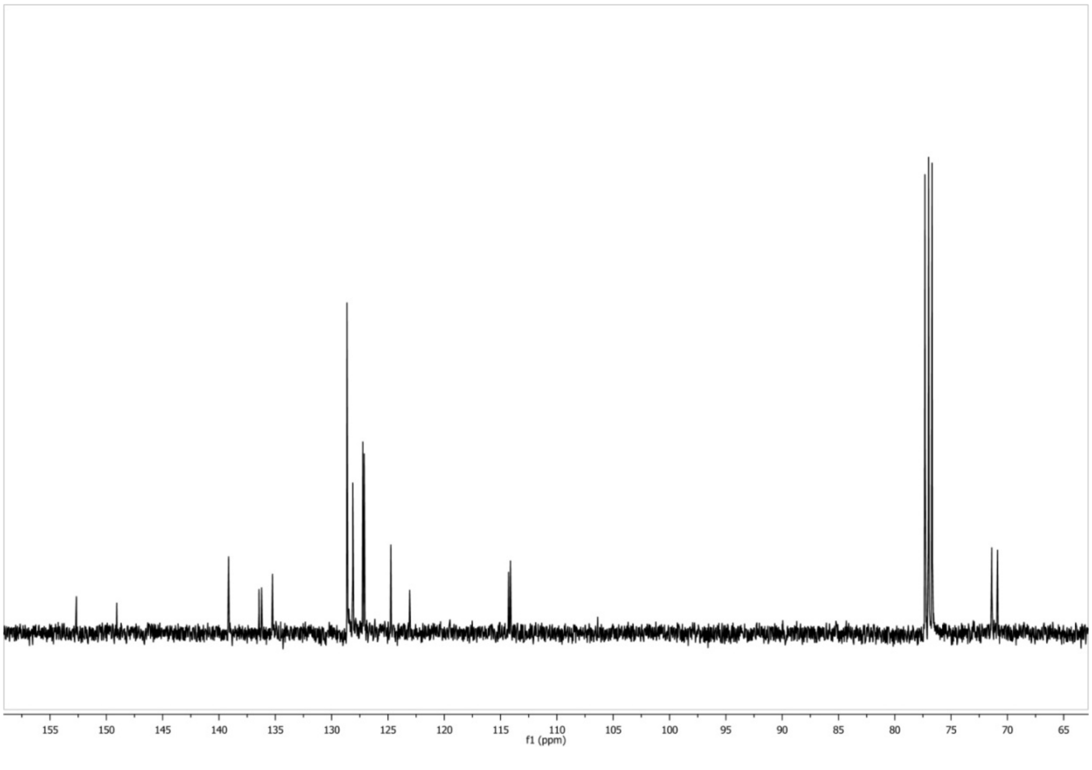

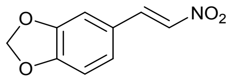

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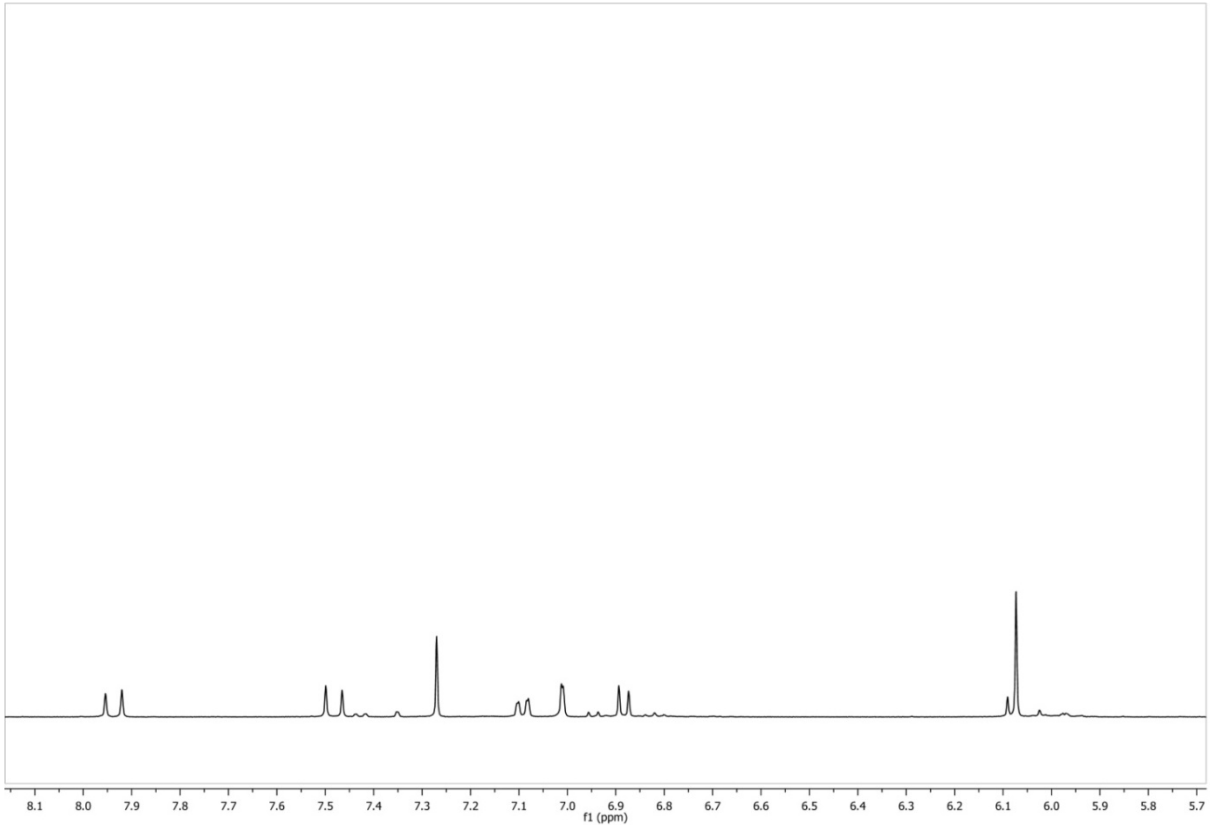

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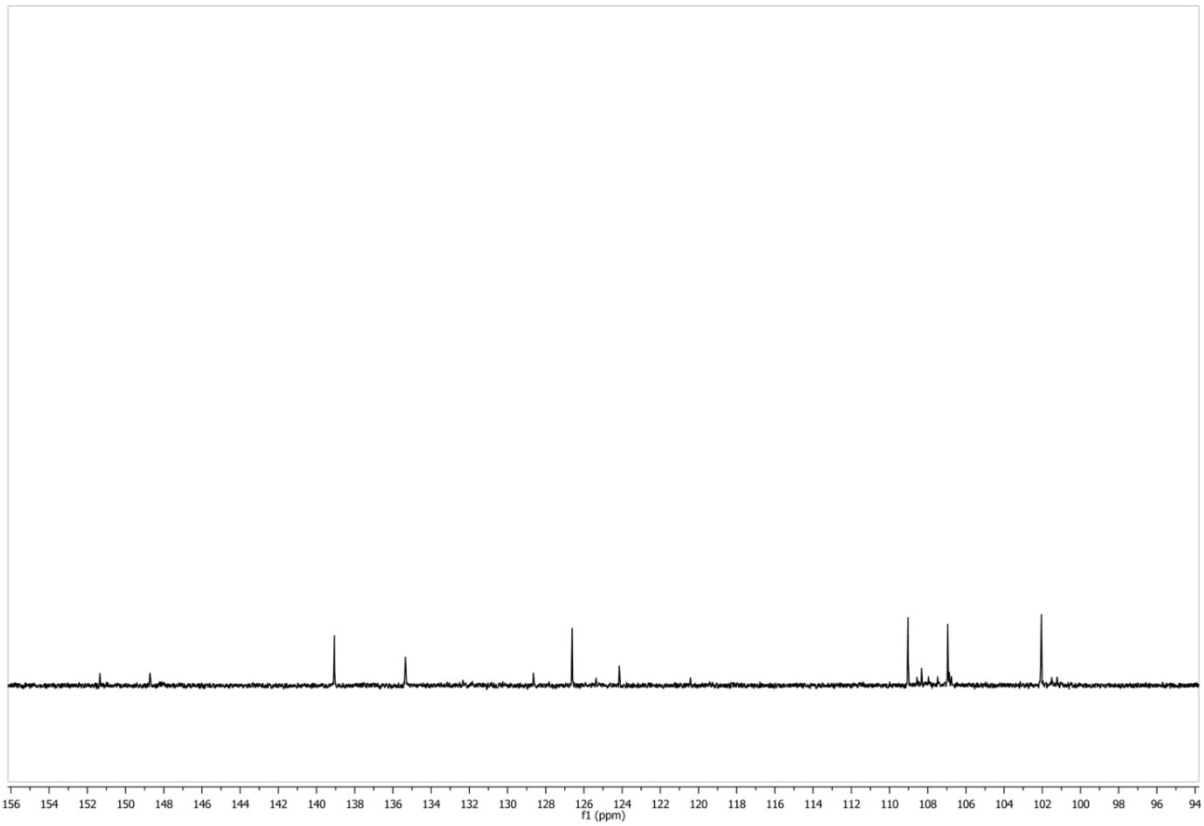
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
5.9
5.8
5.7
f1 (ppm)



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152
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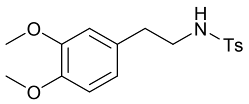
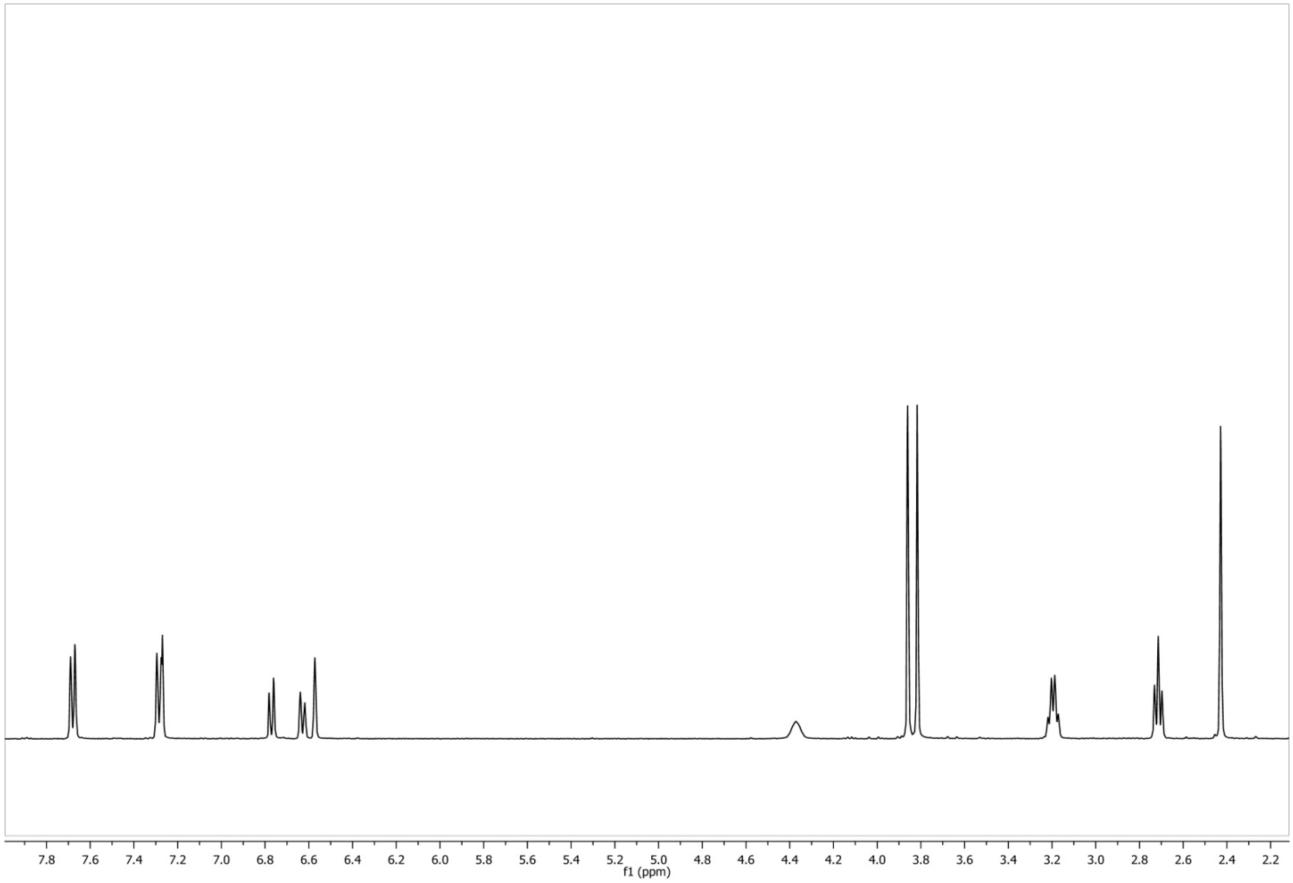
98
96
94
f1 (ppm)


O
O
H
N
Ts

8a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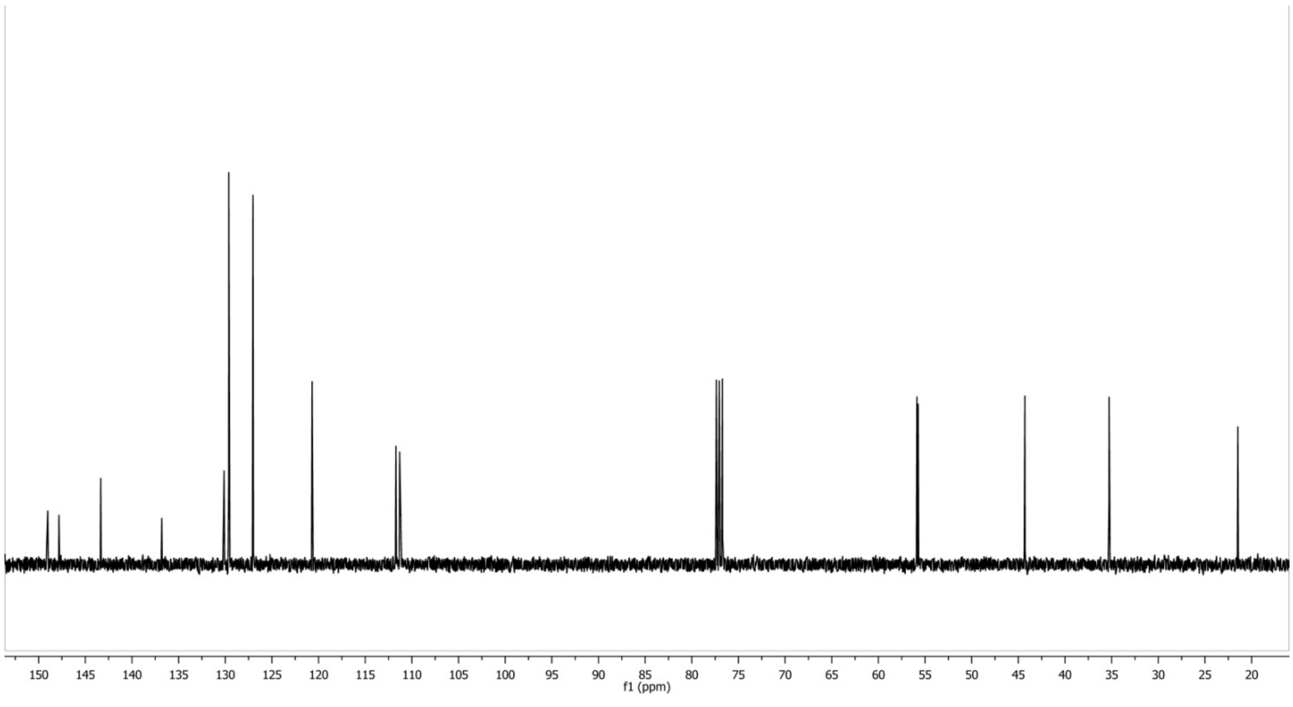
f1 (ppm)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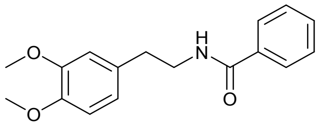

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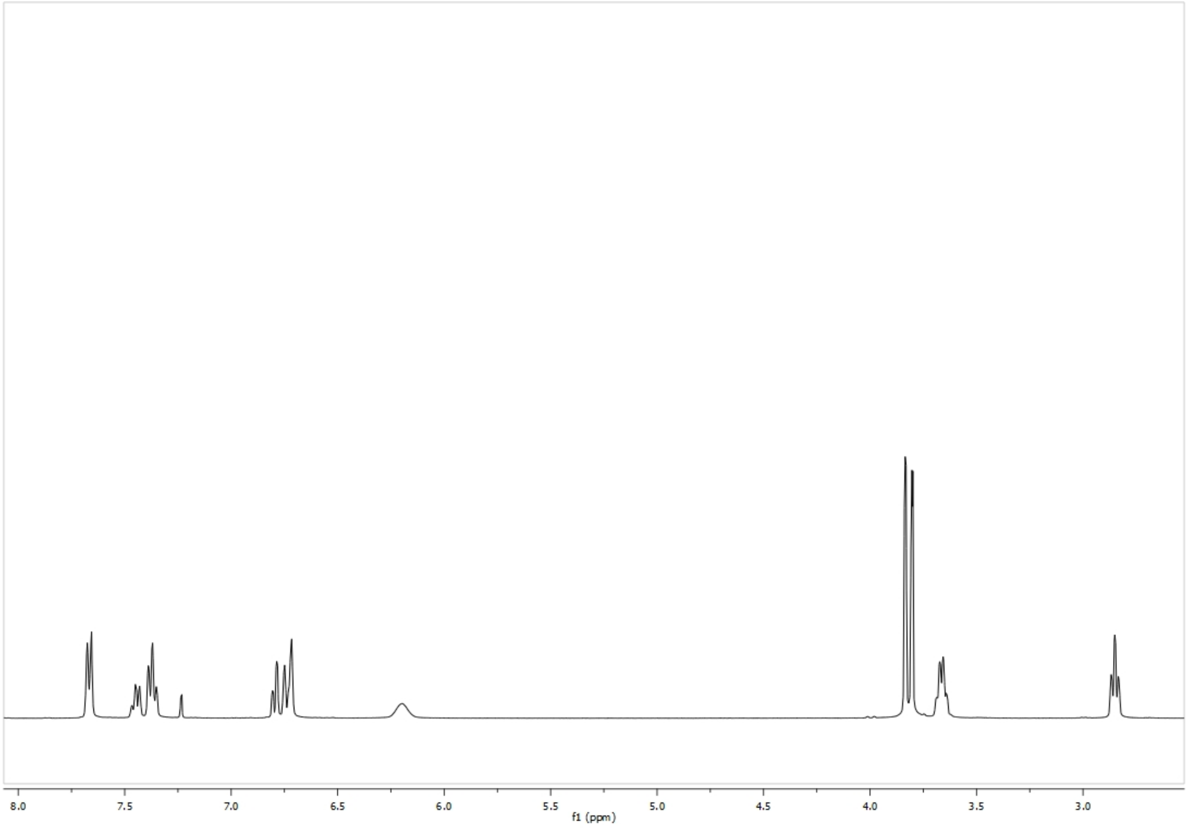

8.0
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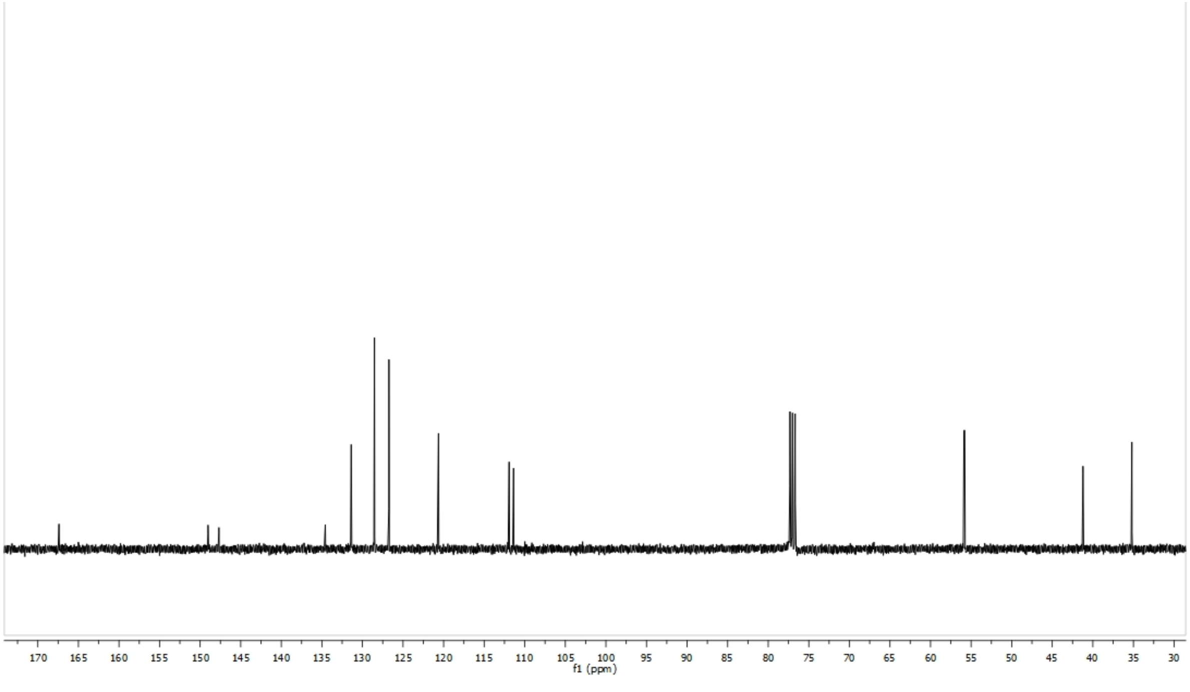
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
f1 (ppm)



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120
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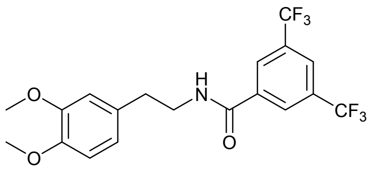
35
30
f1 (ppm)



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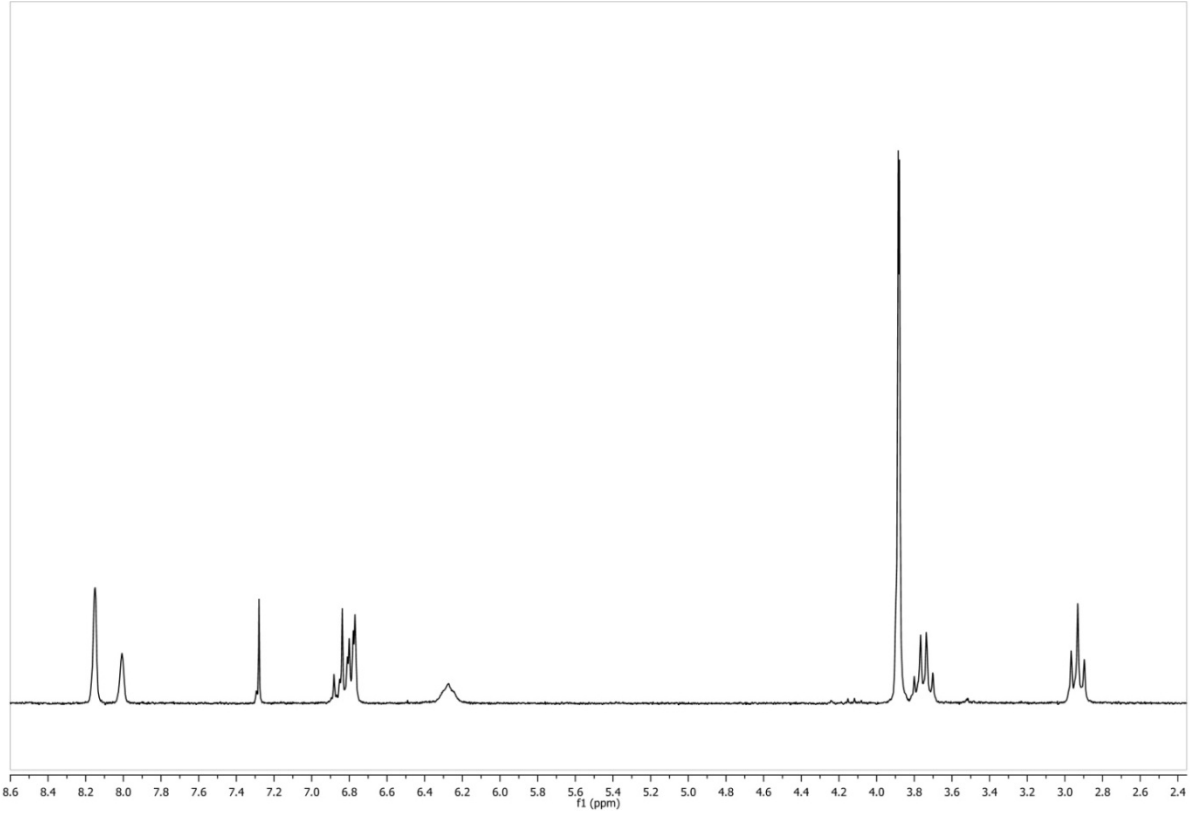
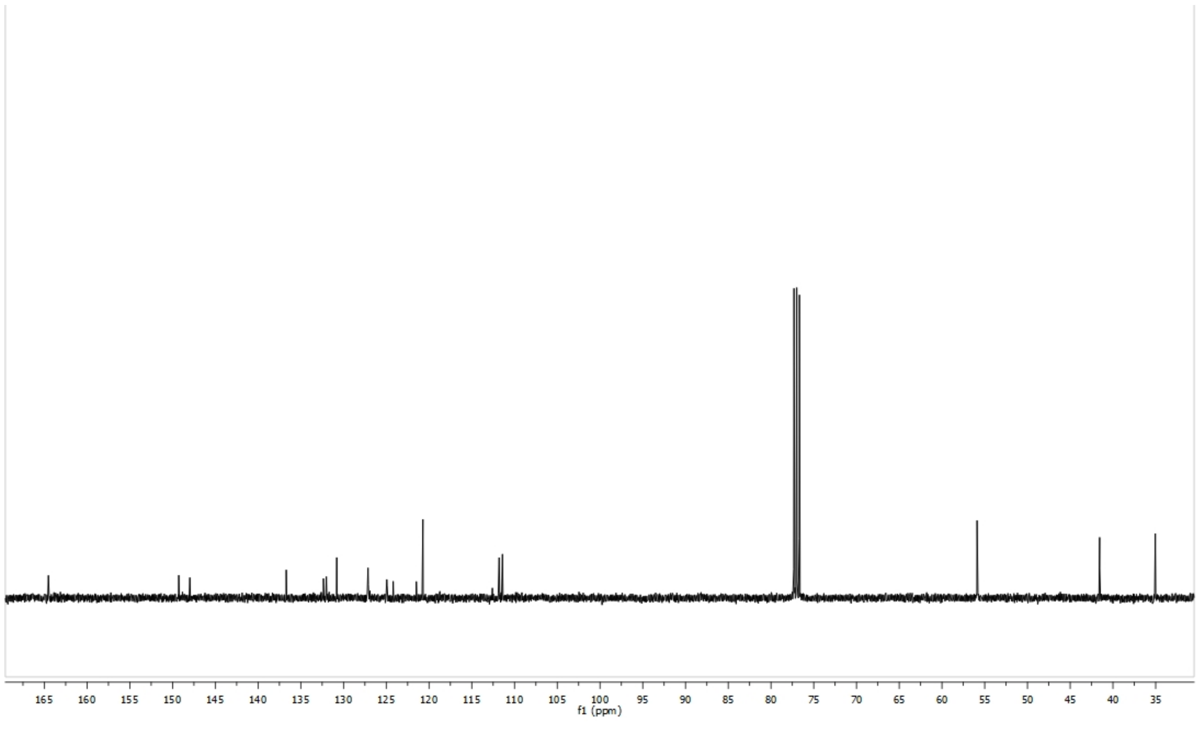
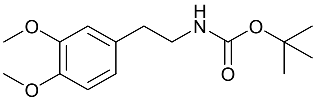
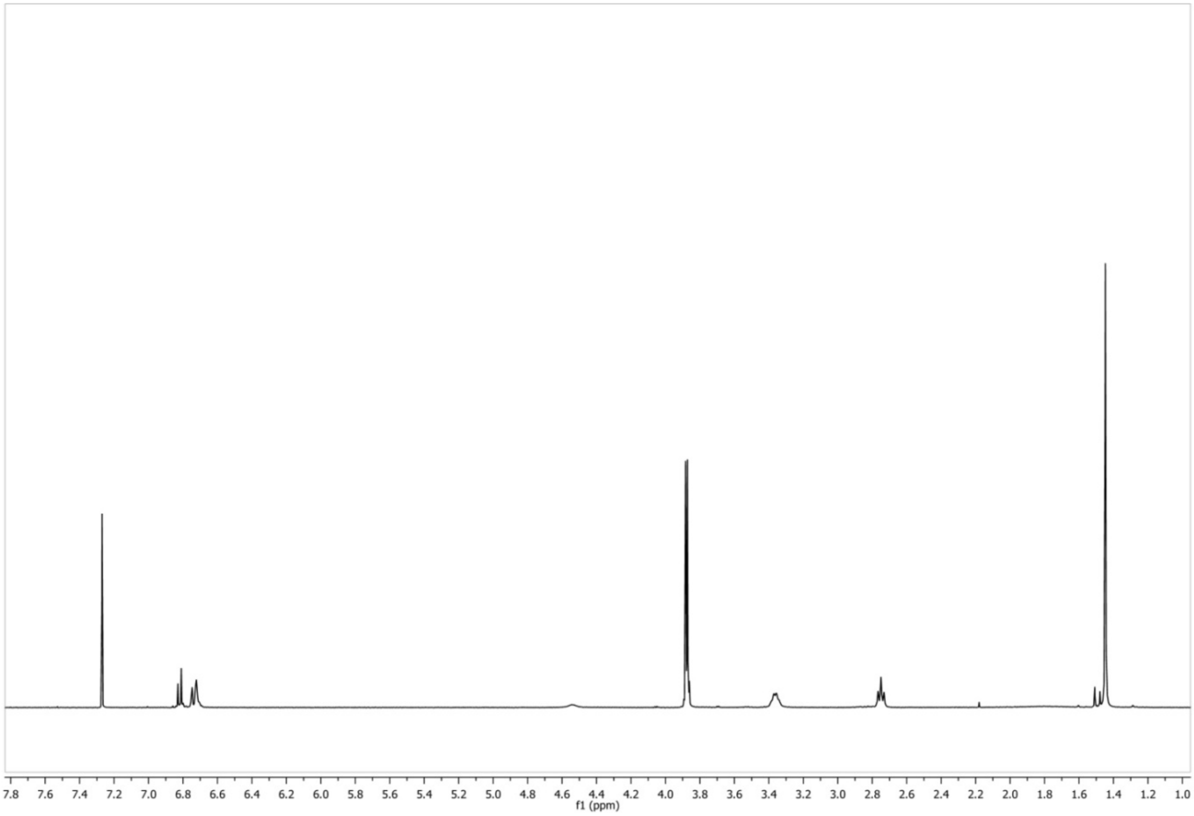





H
N
O
O
O
O

8d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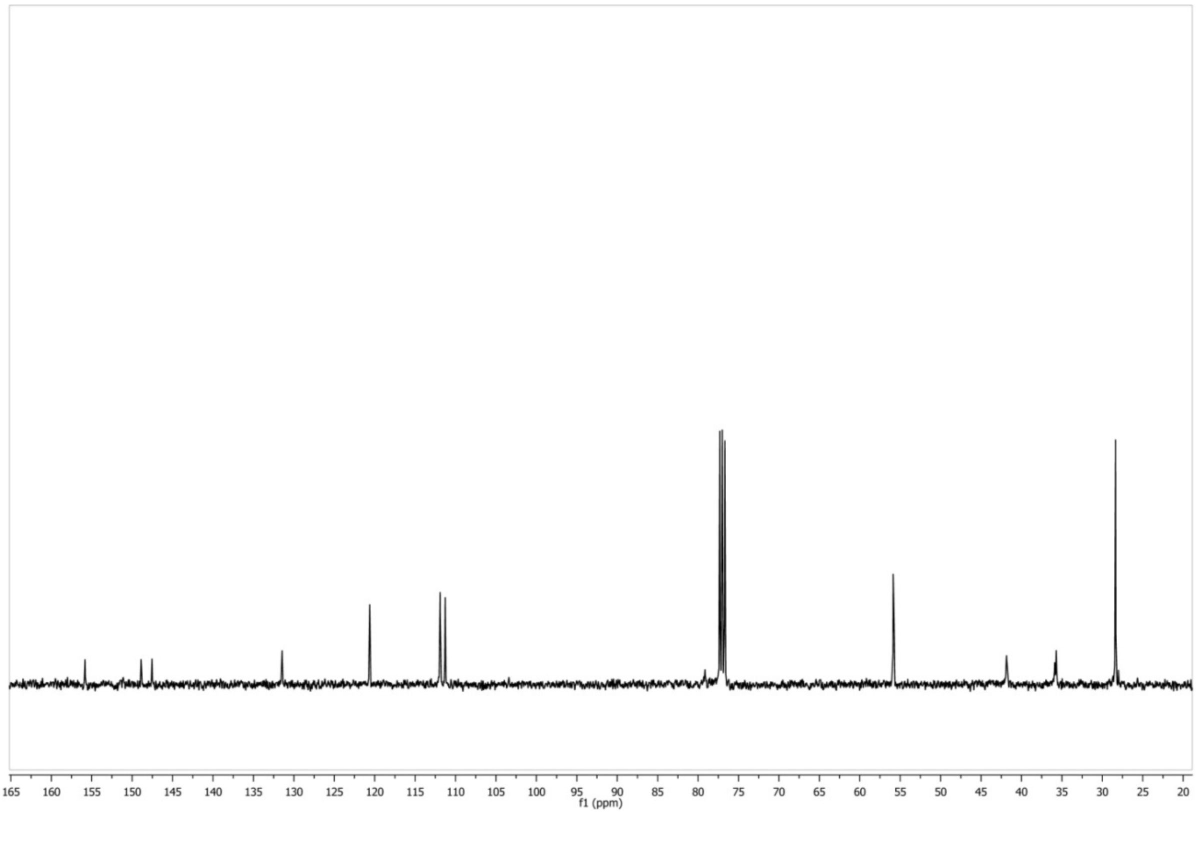
f1 (ppm)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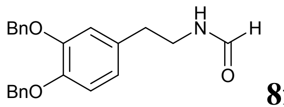

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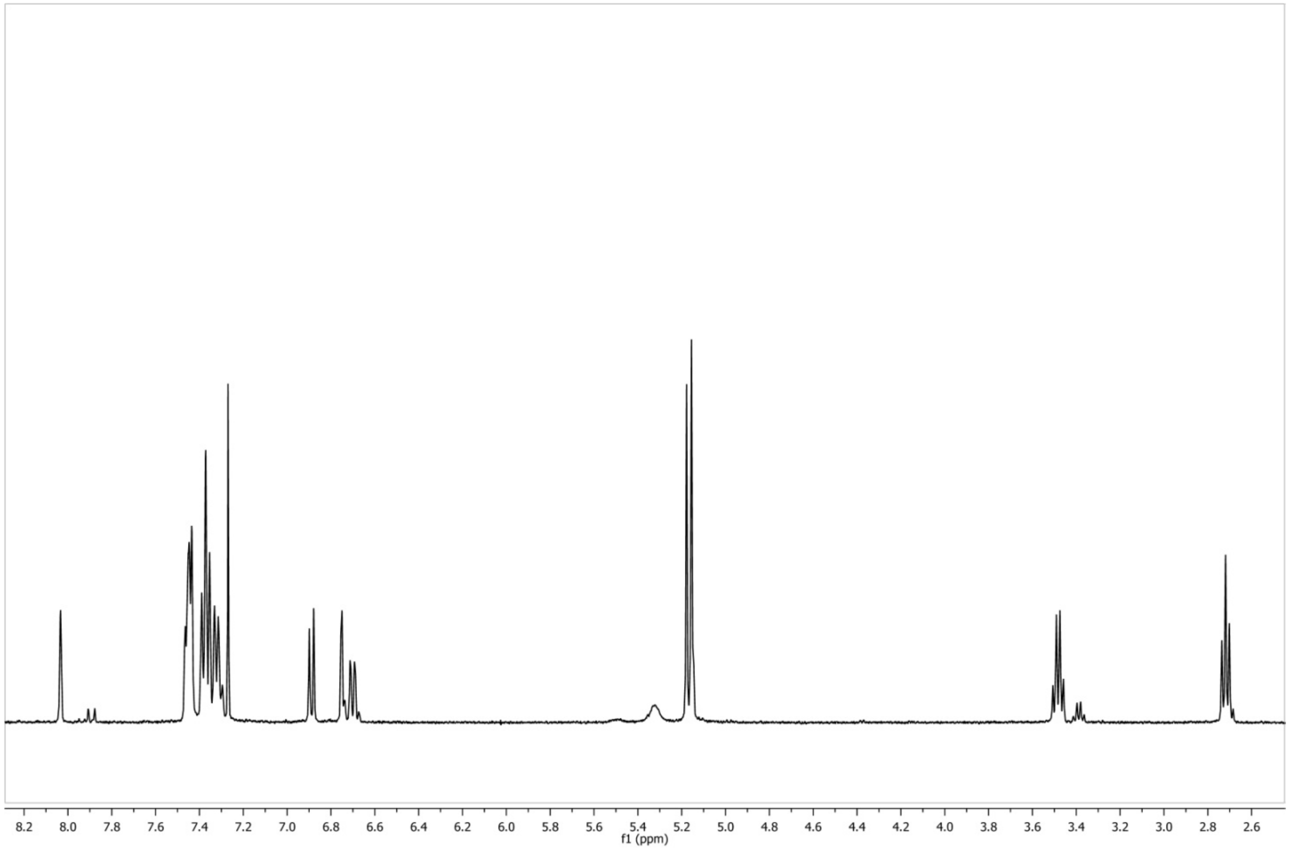
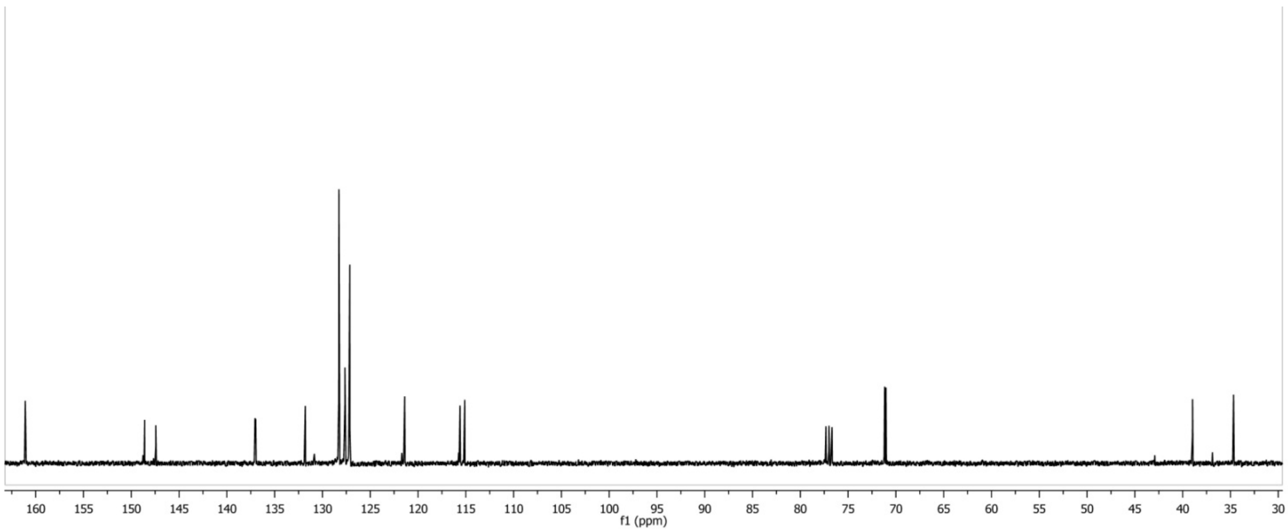
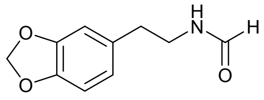
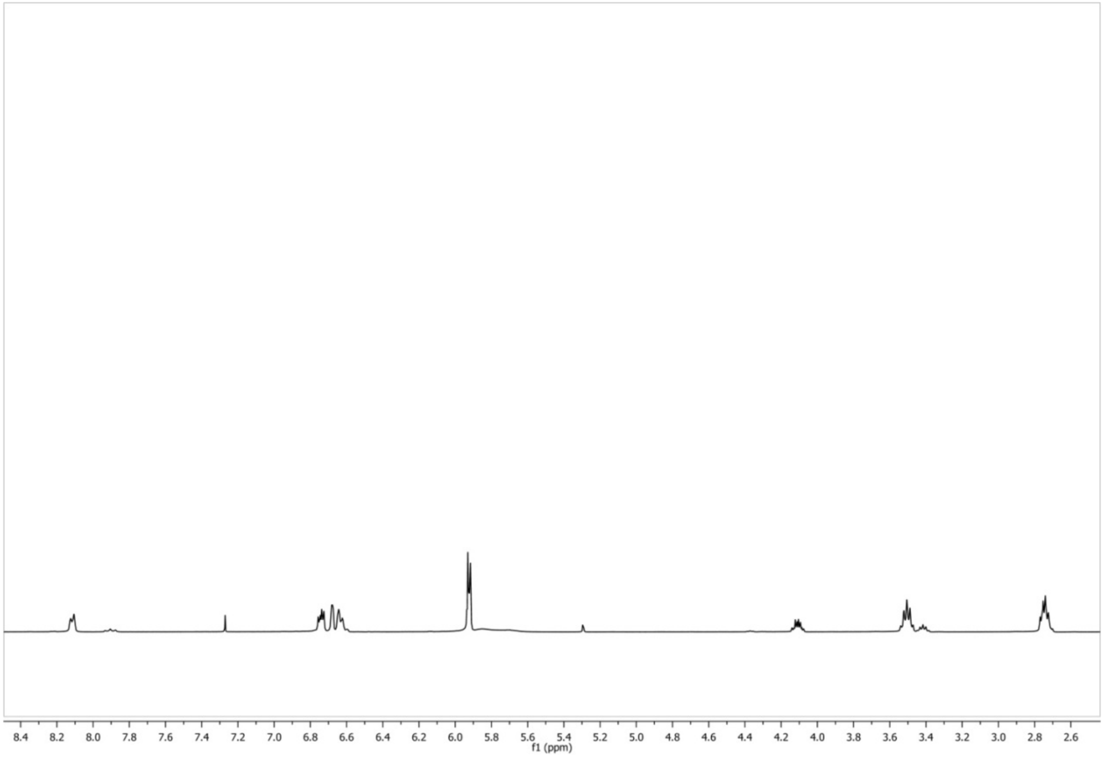






O
O
H
N
H
O

8g



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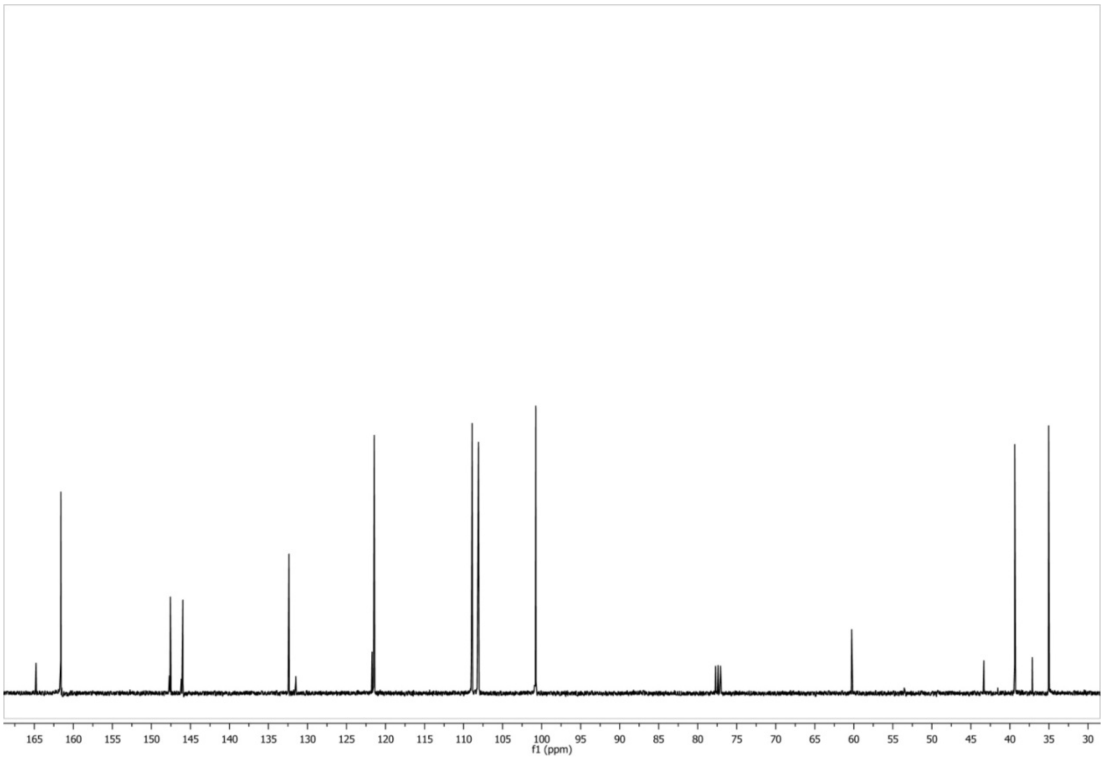
f1 (ppm)



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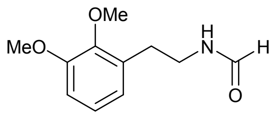
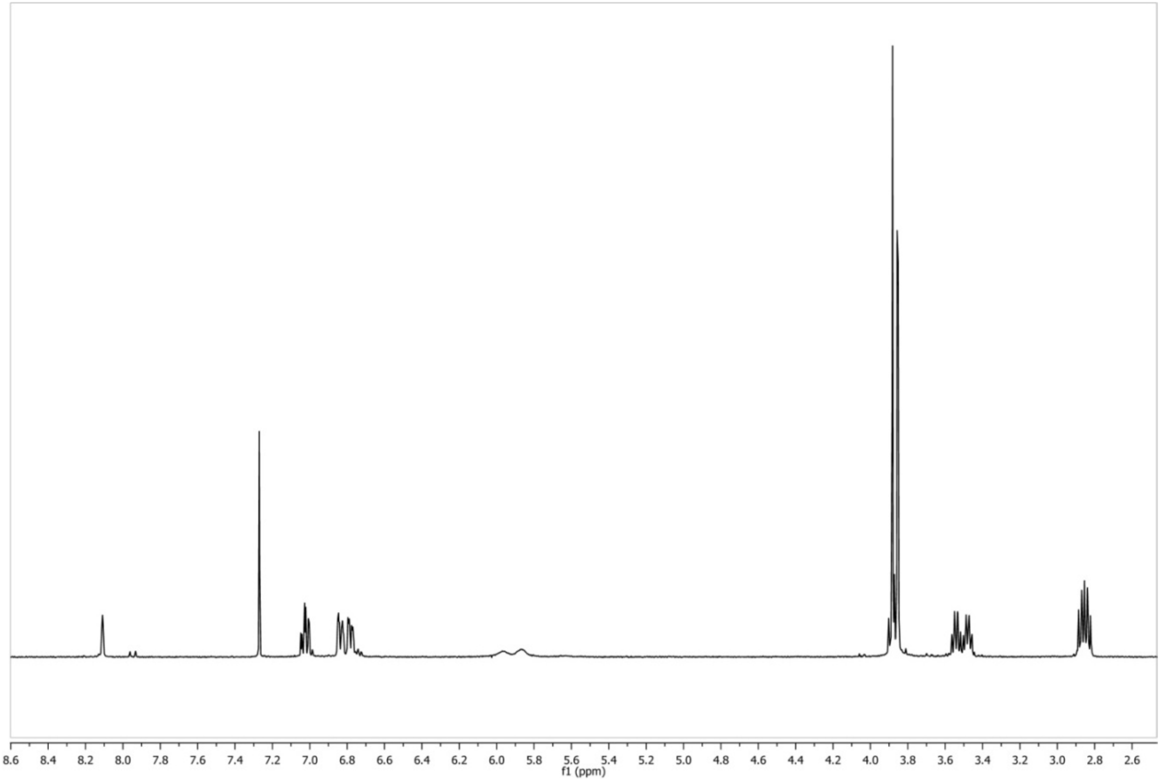

OMe
MeO
H
N
H
O

8h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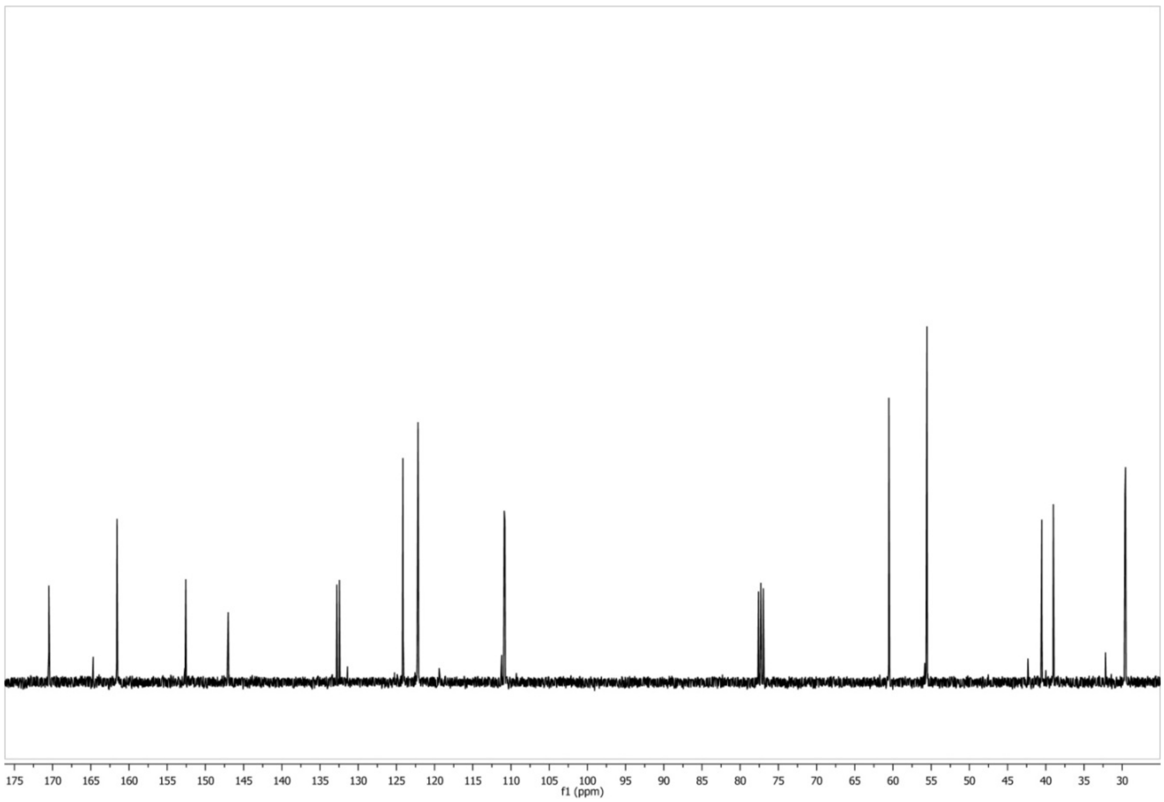
f1 (ppm)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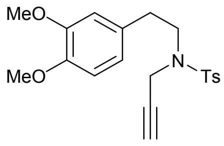
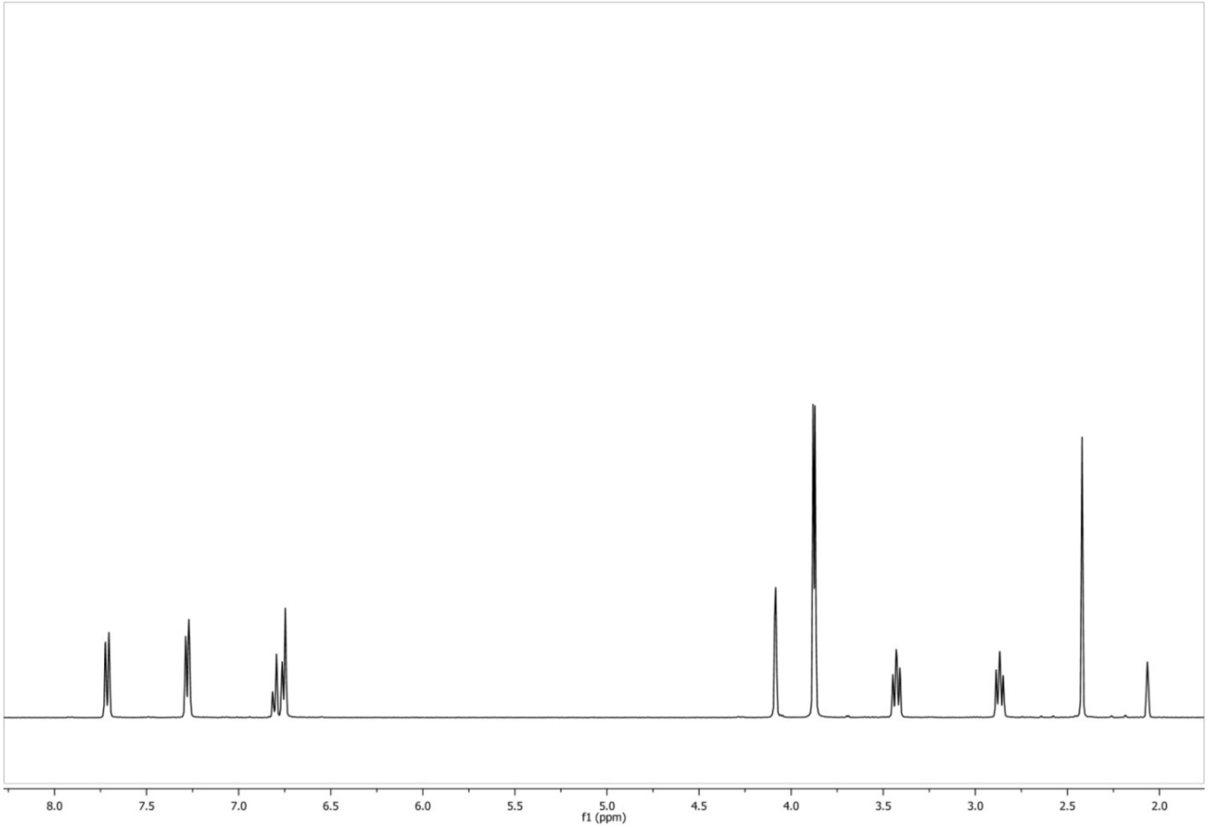

MeO
MeO
N
Ts

9a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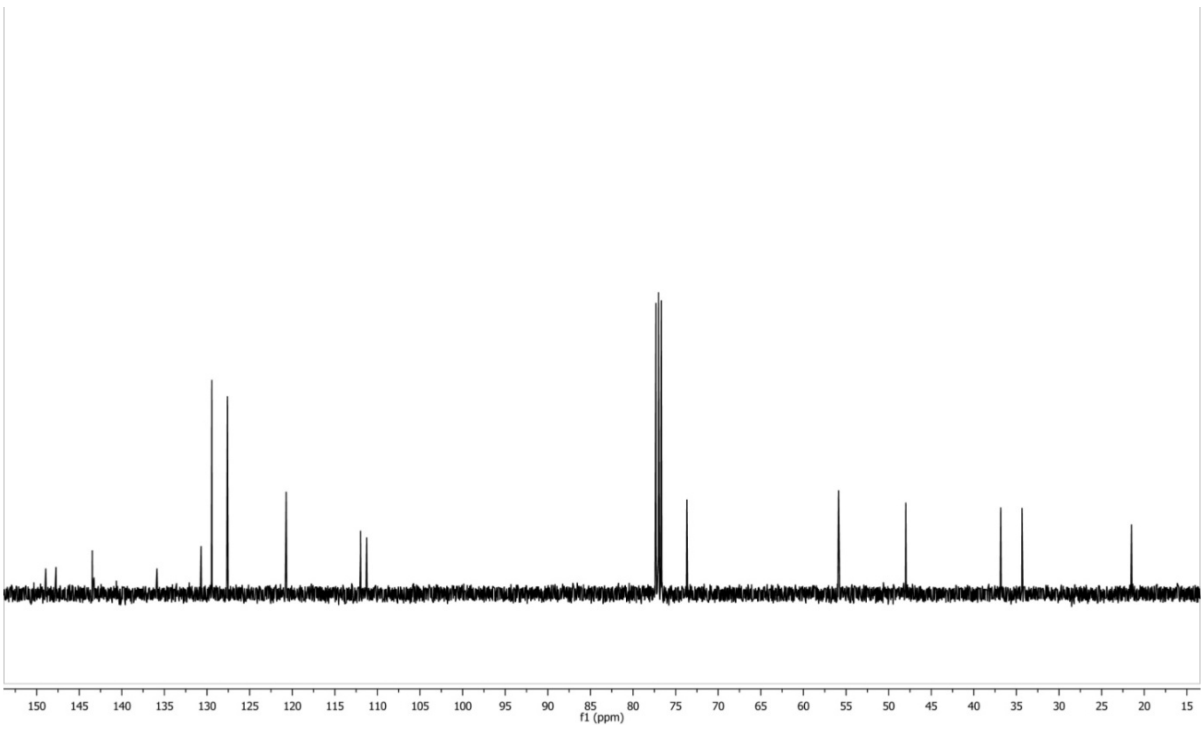
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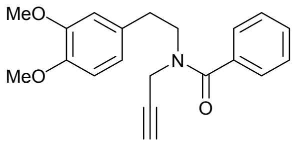
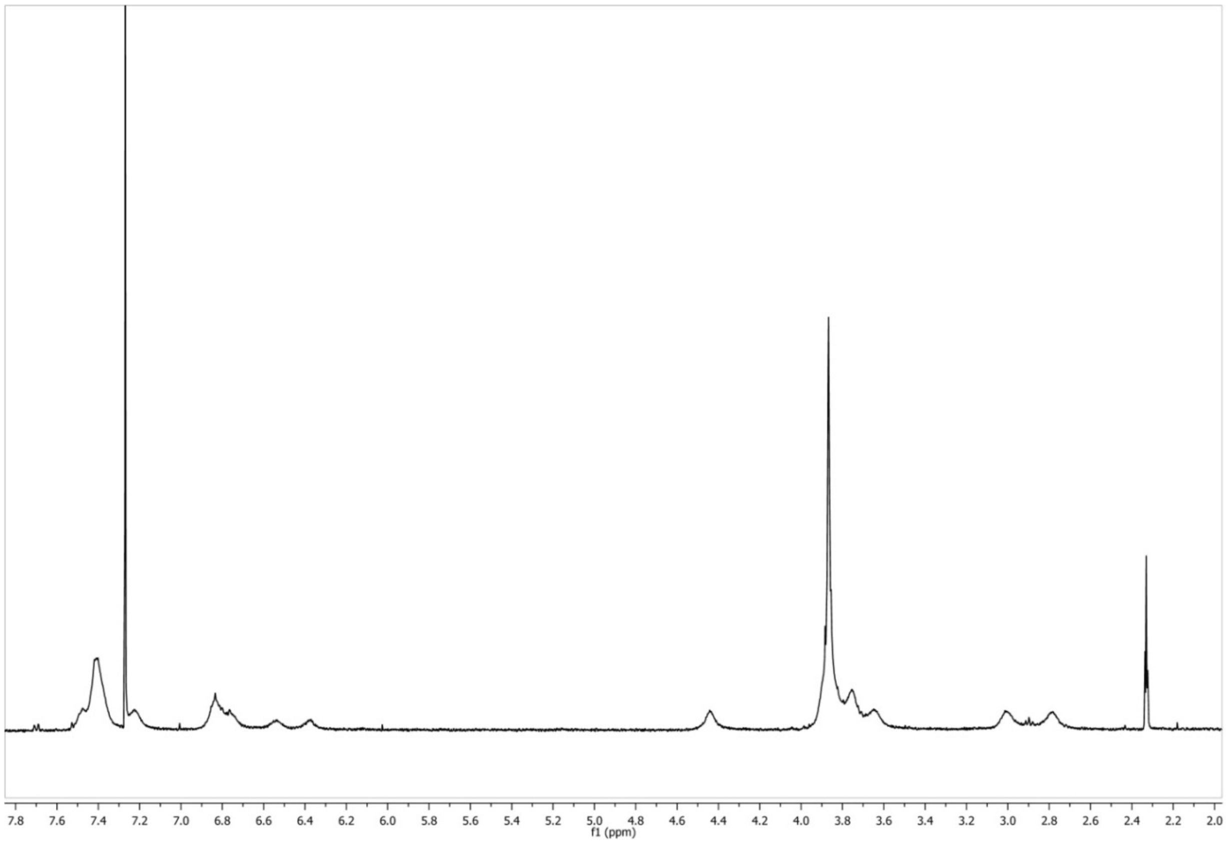

MeO
MeO
N
O

9b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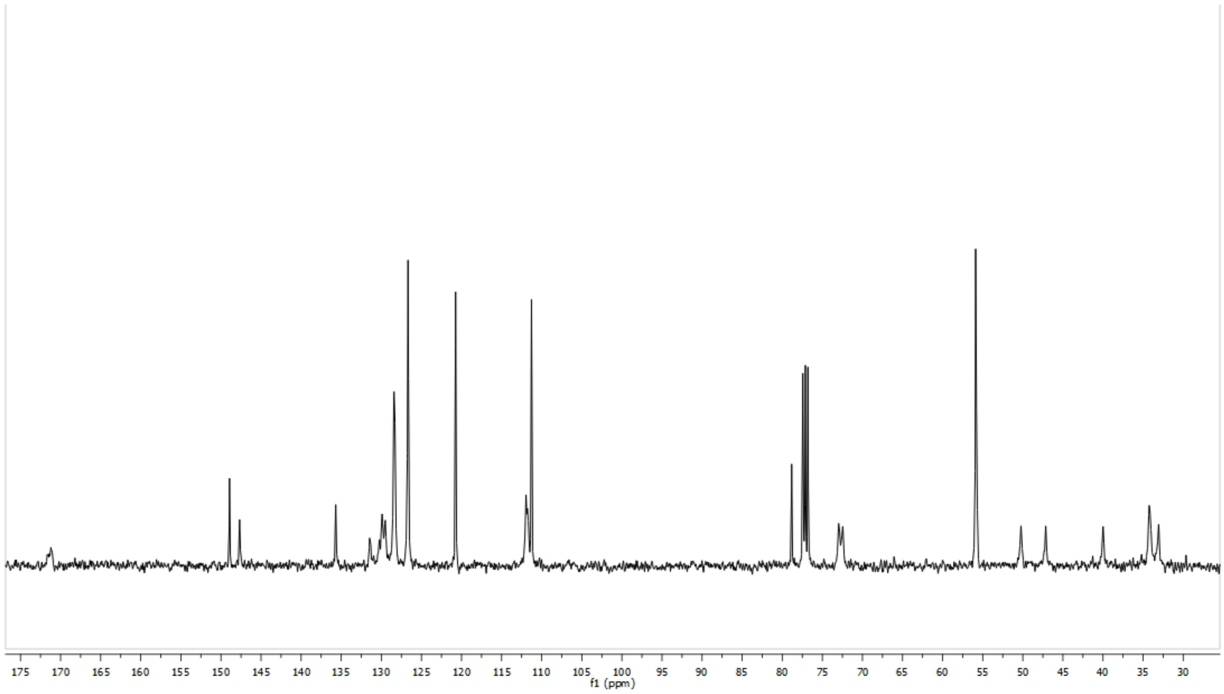
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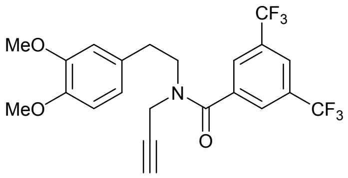

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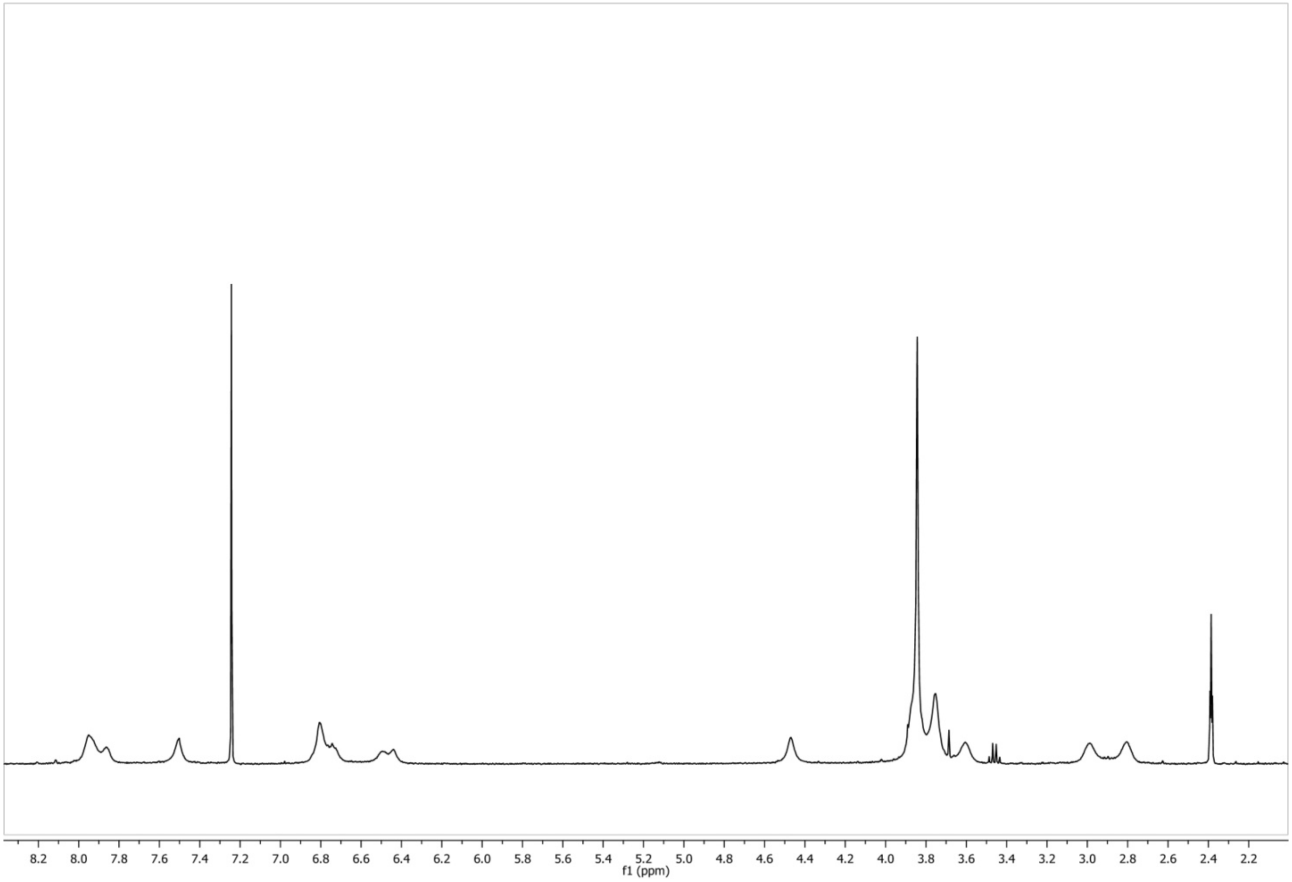

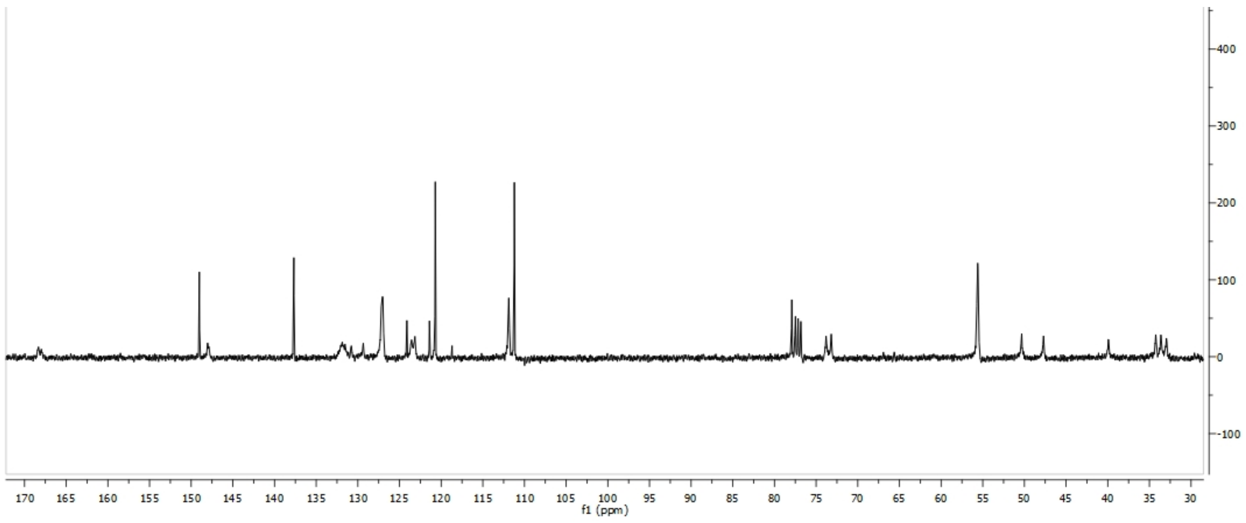

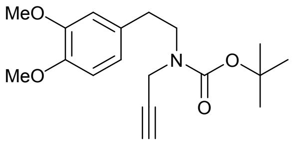

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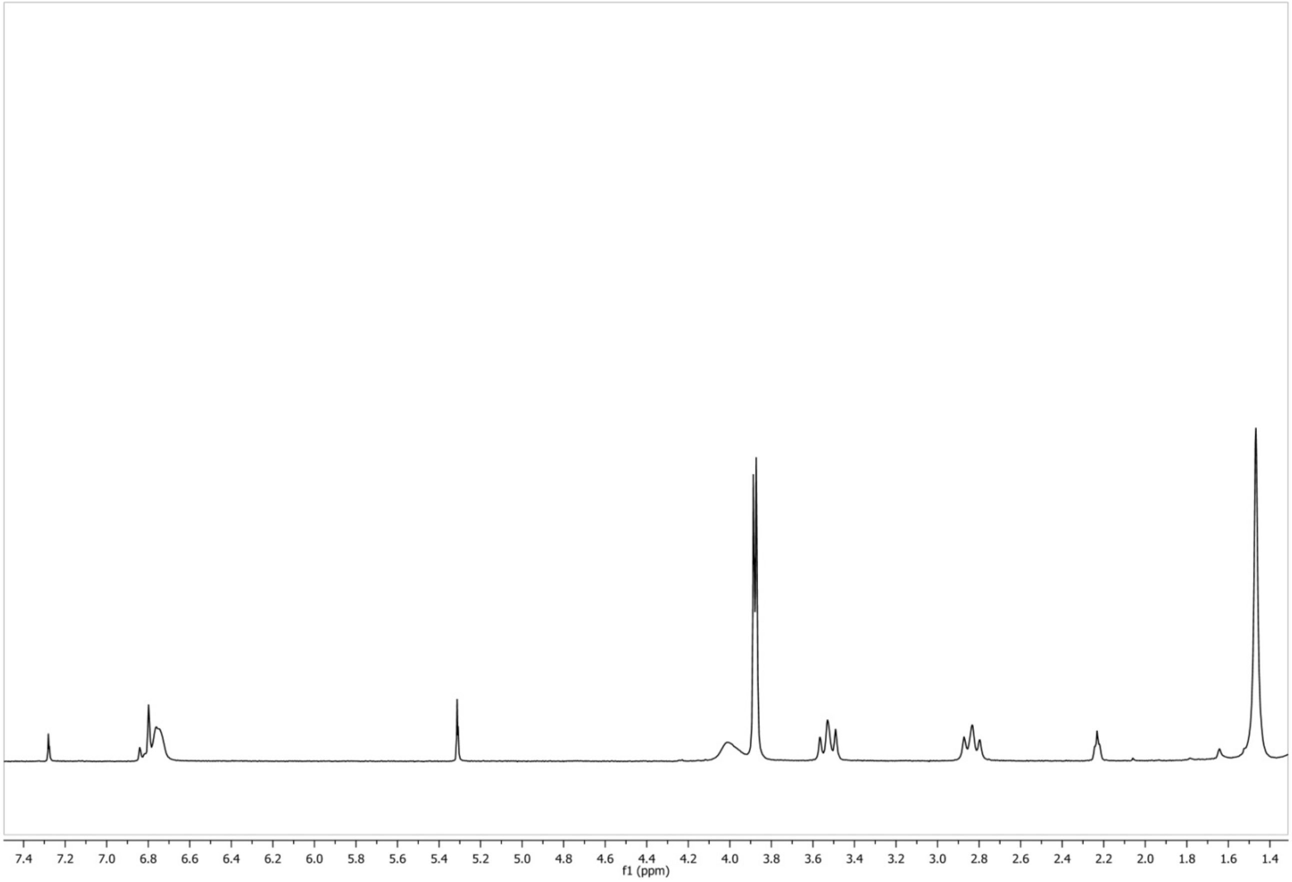
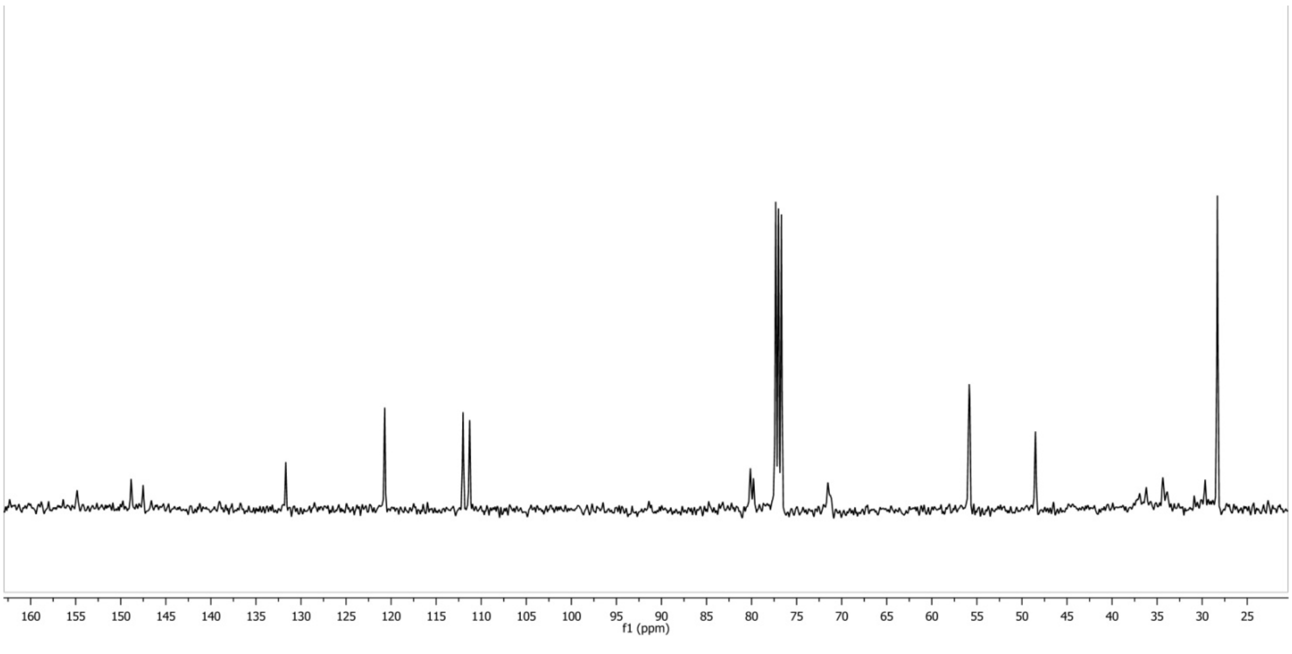
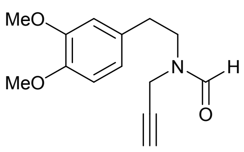
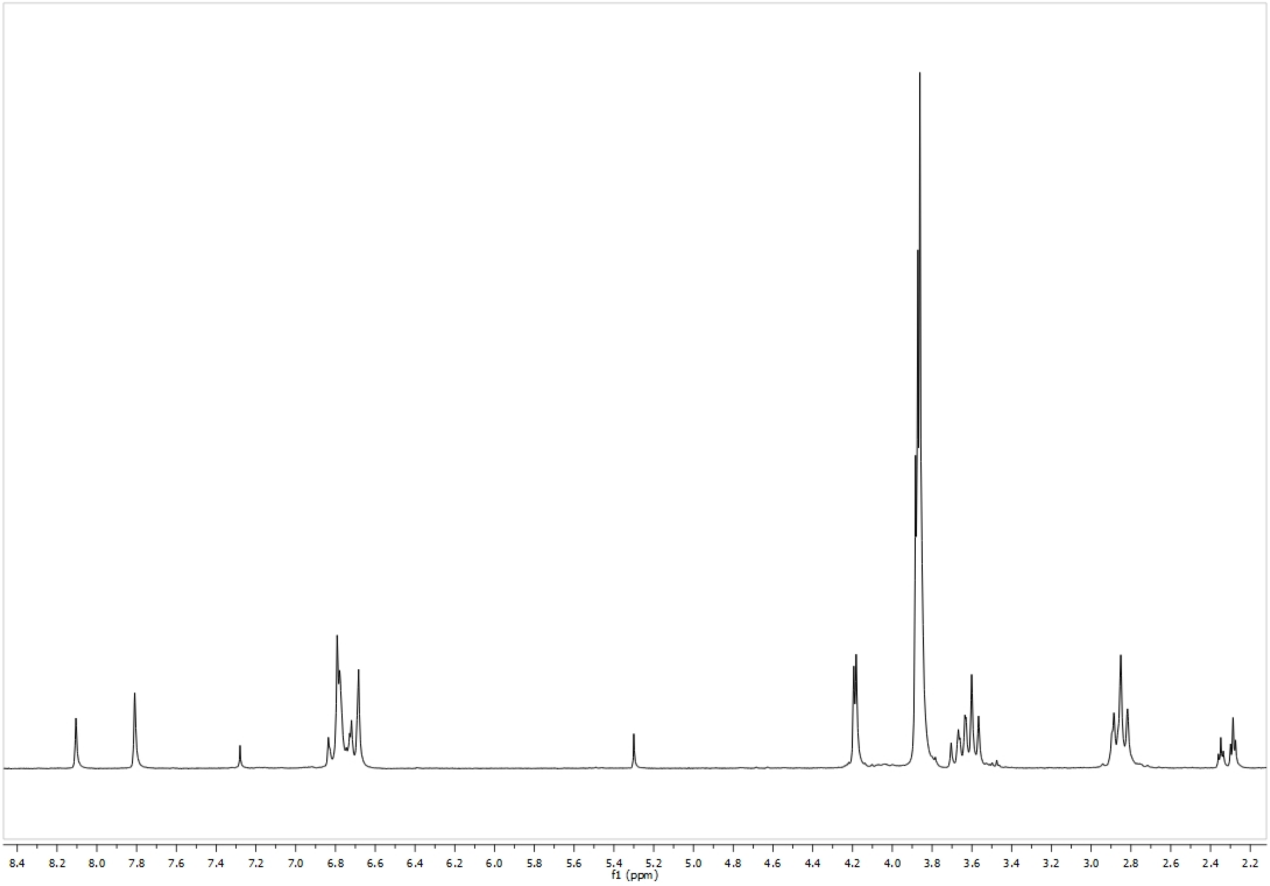
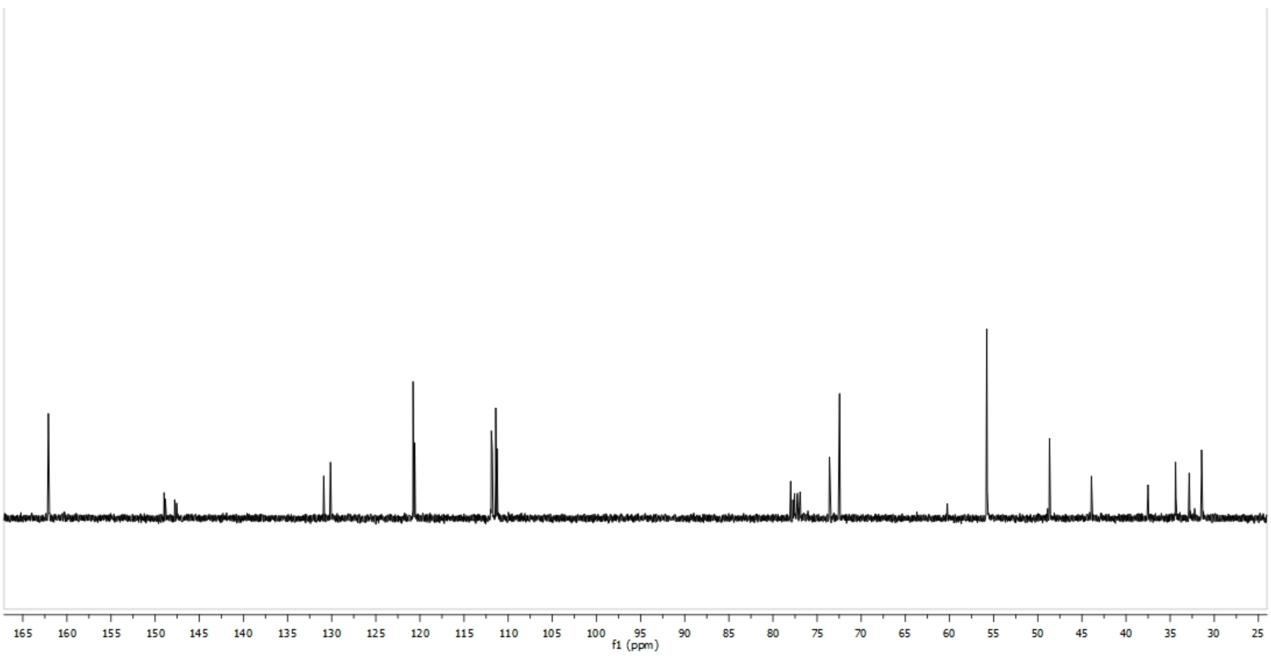





MeO
MeO
N
H
O

9e


8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2
f1 (ppm)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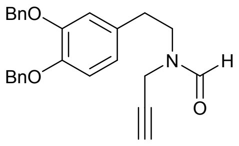
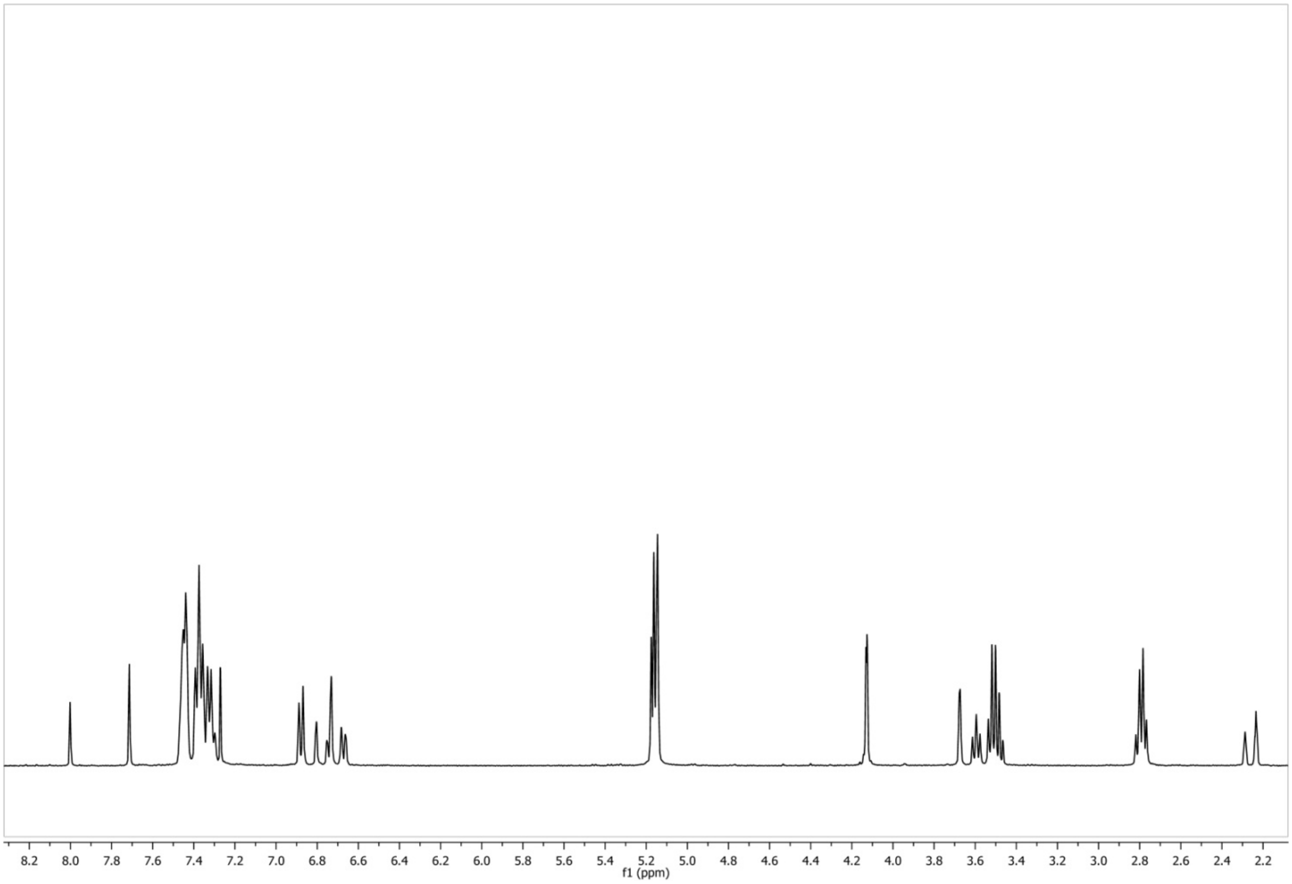
f1 (ppm)


BnO
BnO
N
H
O

9f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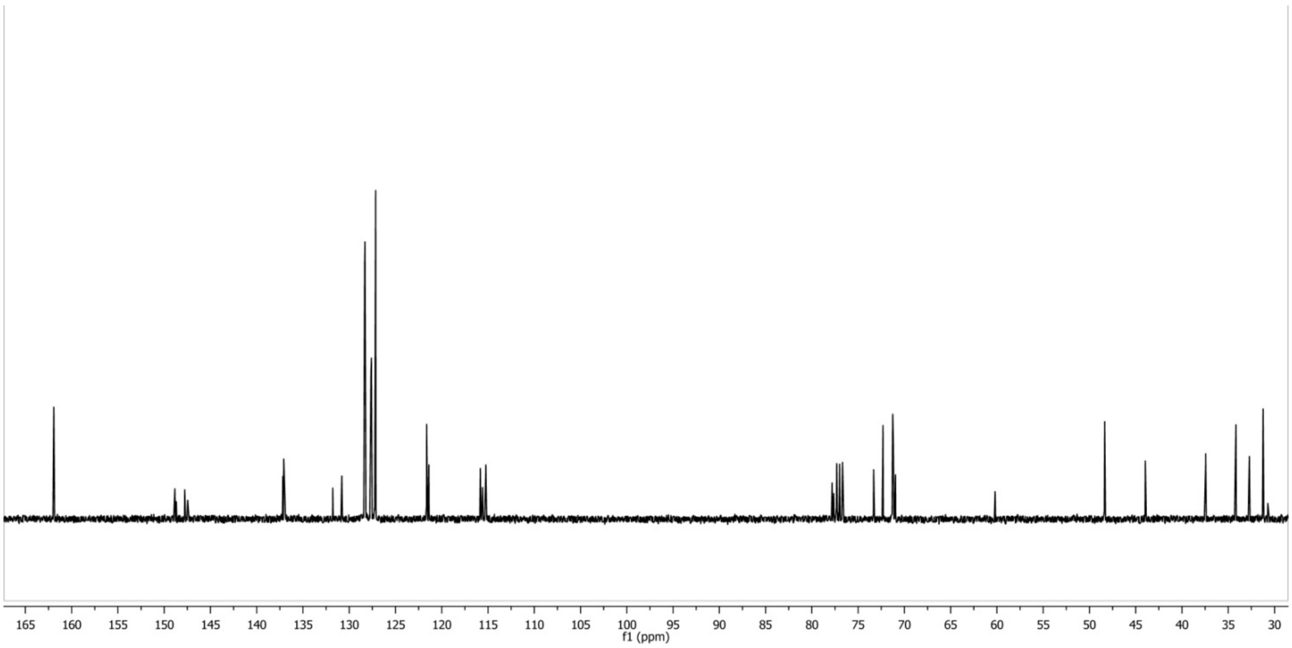
f1 (ppm)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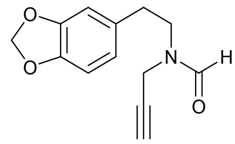
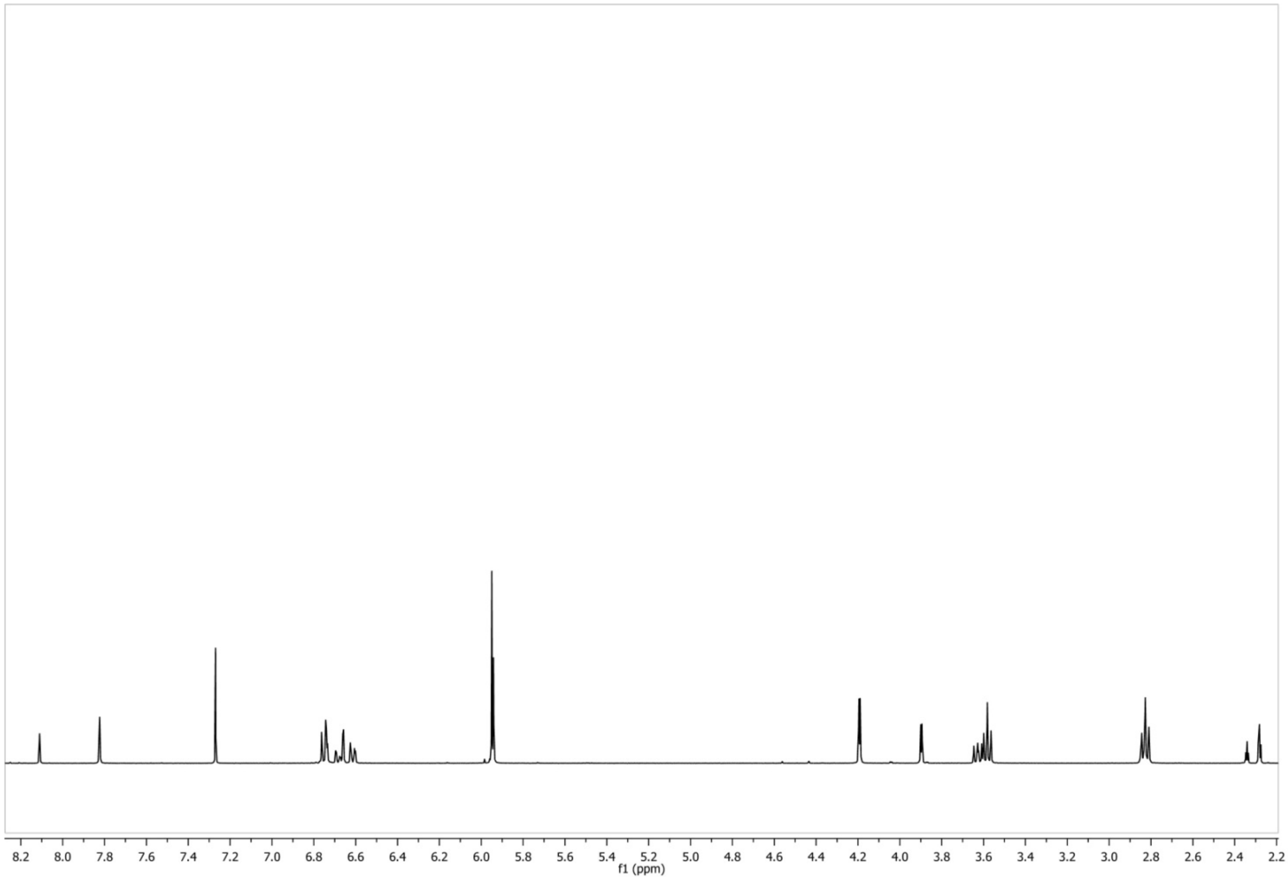
f1 (ppm)



O
O
N
H
O

9g



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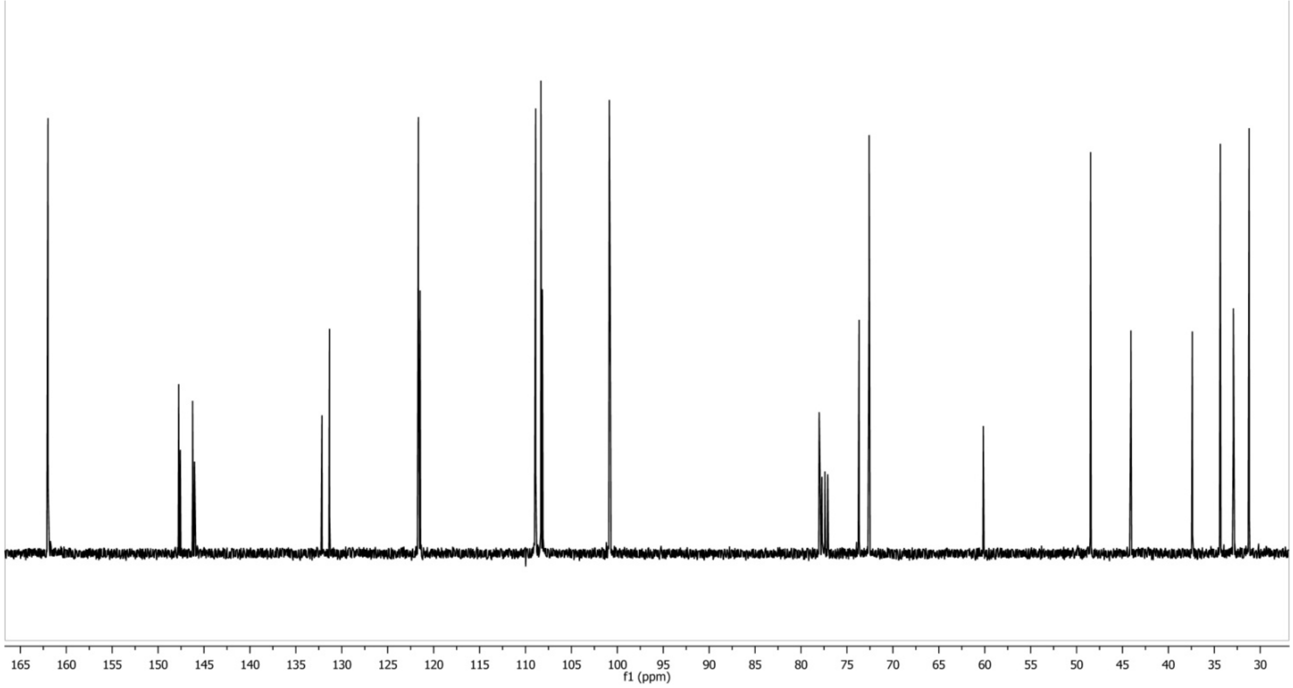
f1 (ppm)



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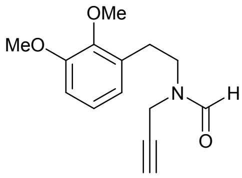
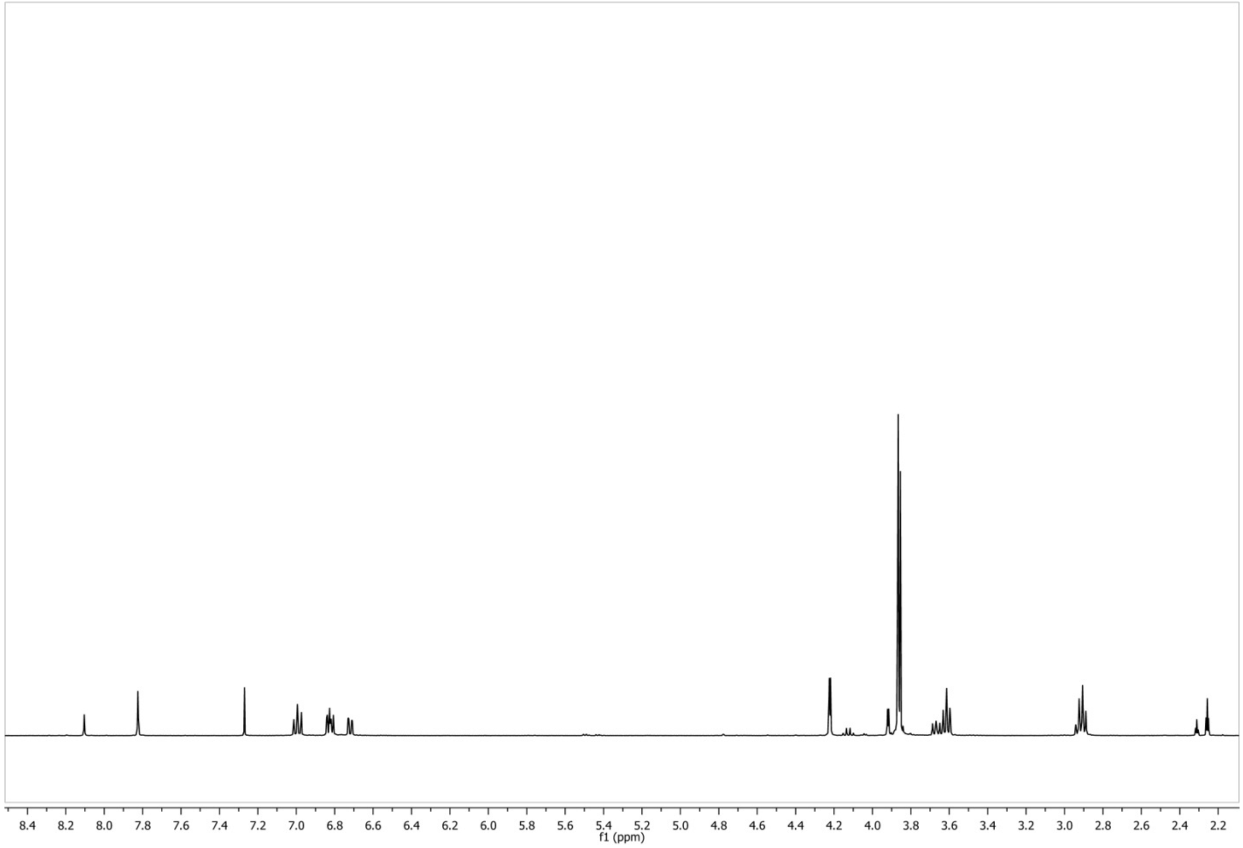
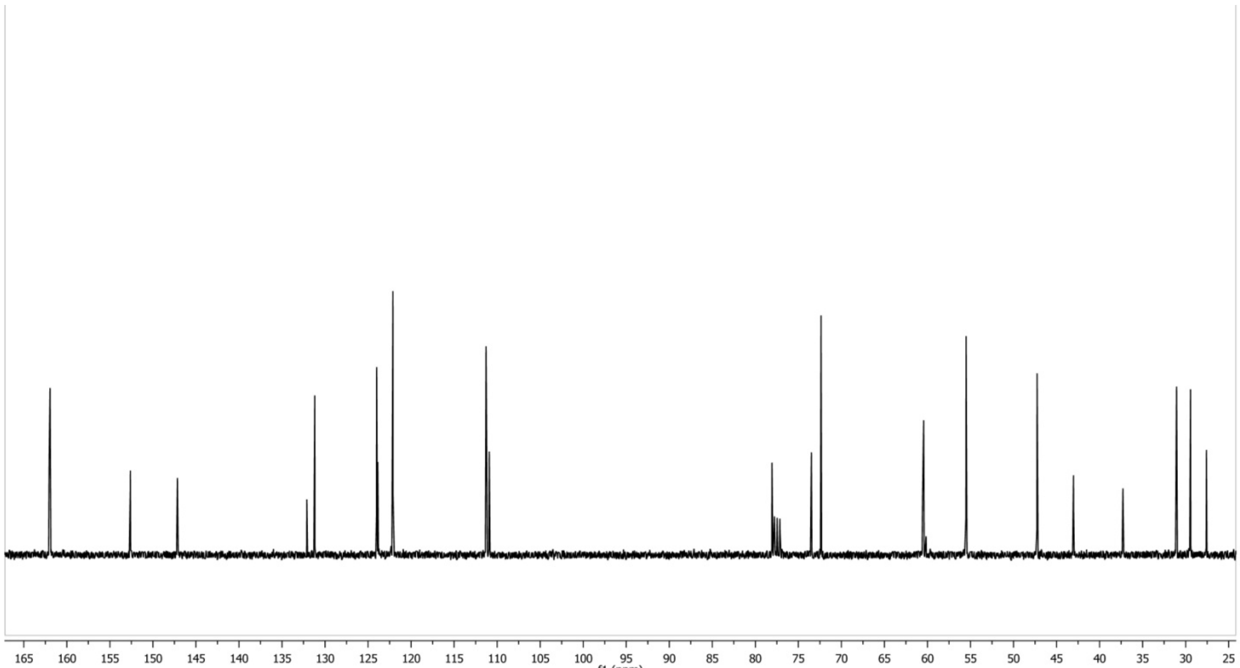
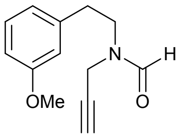
f1 (ppm)



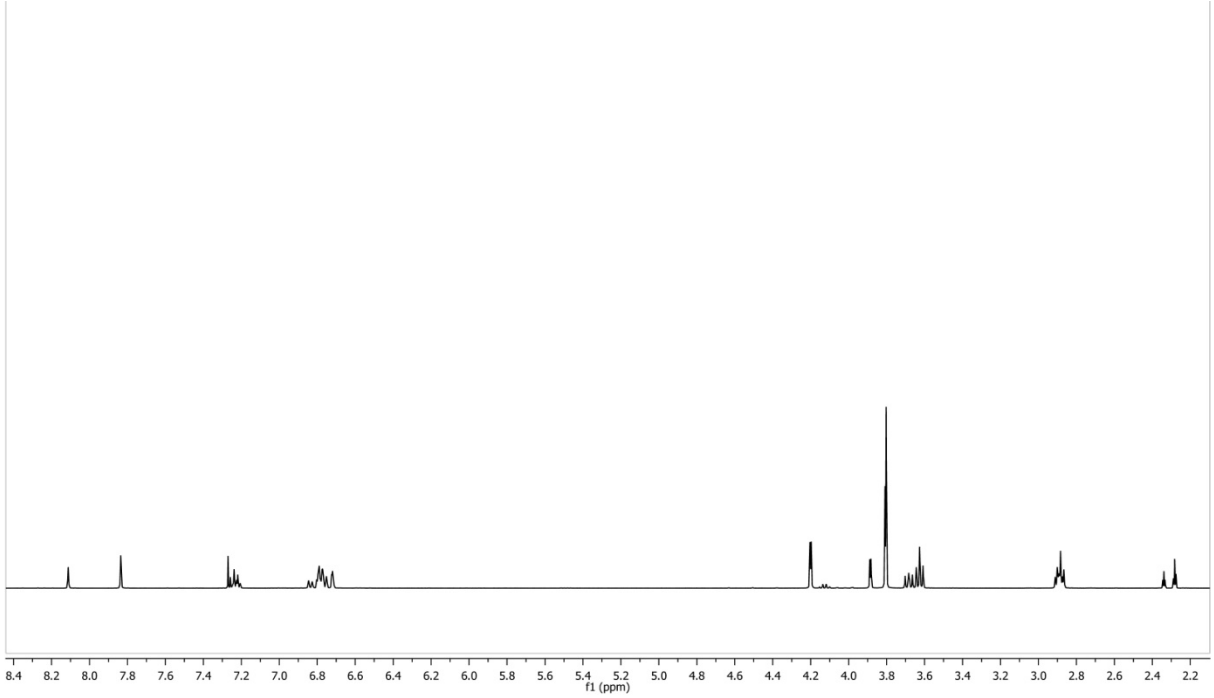
9h







9i



8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
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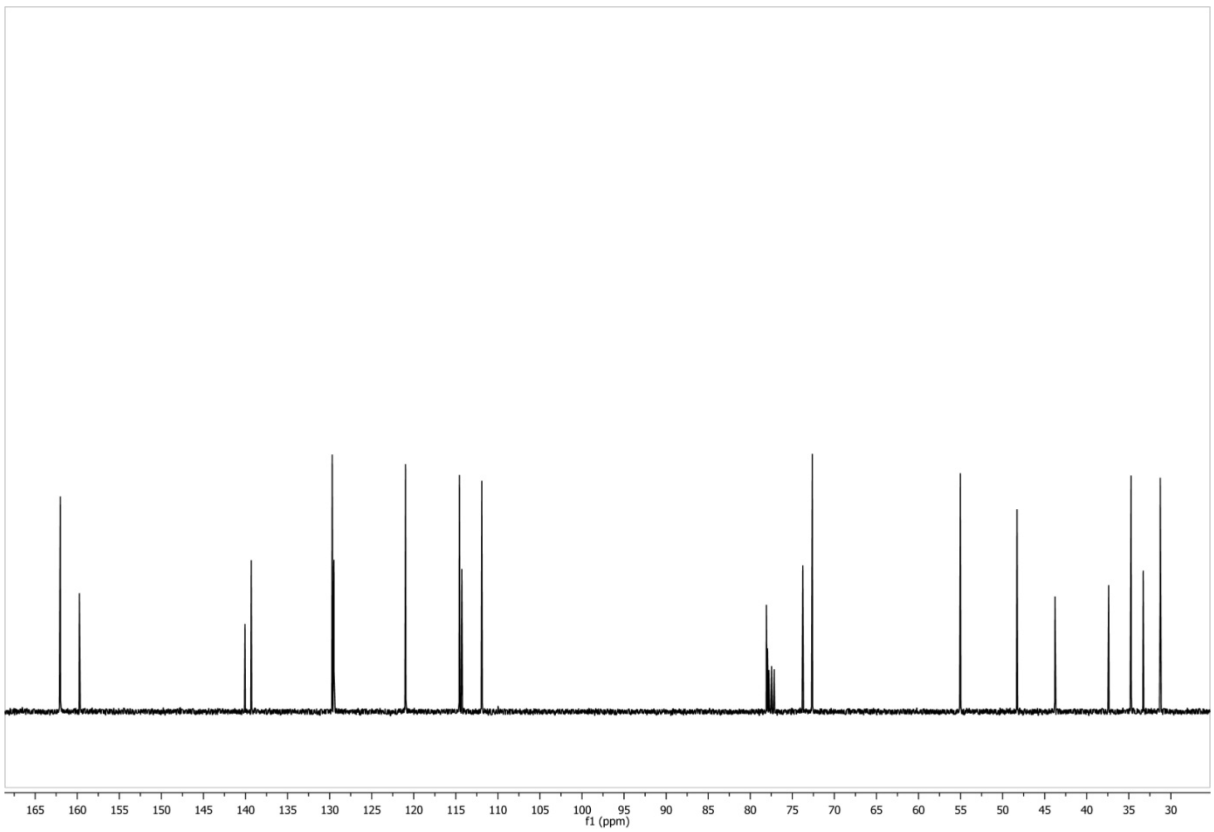
3.4
3.2
3.0
2.8
2.6
2.4
2.2
f1 (ppm)



165
160
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125
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95
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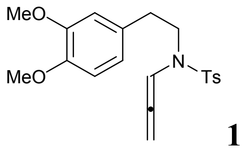
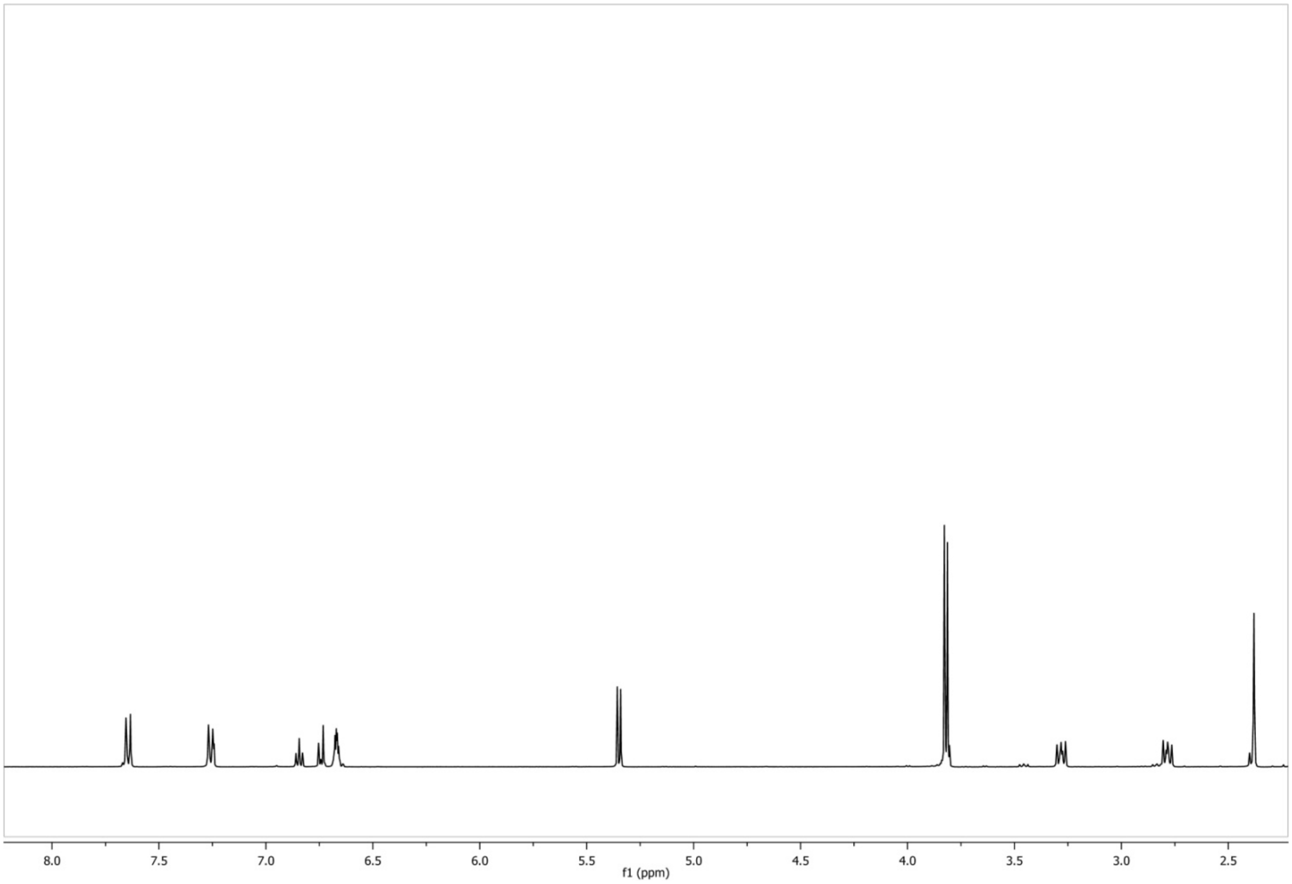
40
35
30
f1 (ppm)


MeO
MeO
N
Ts

10a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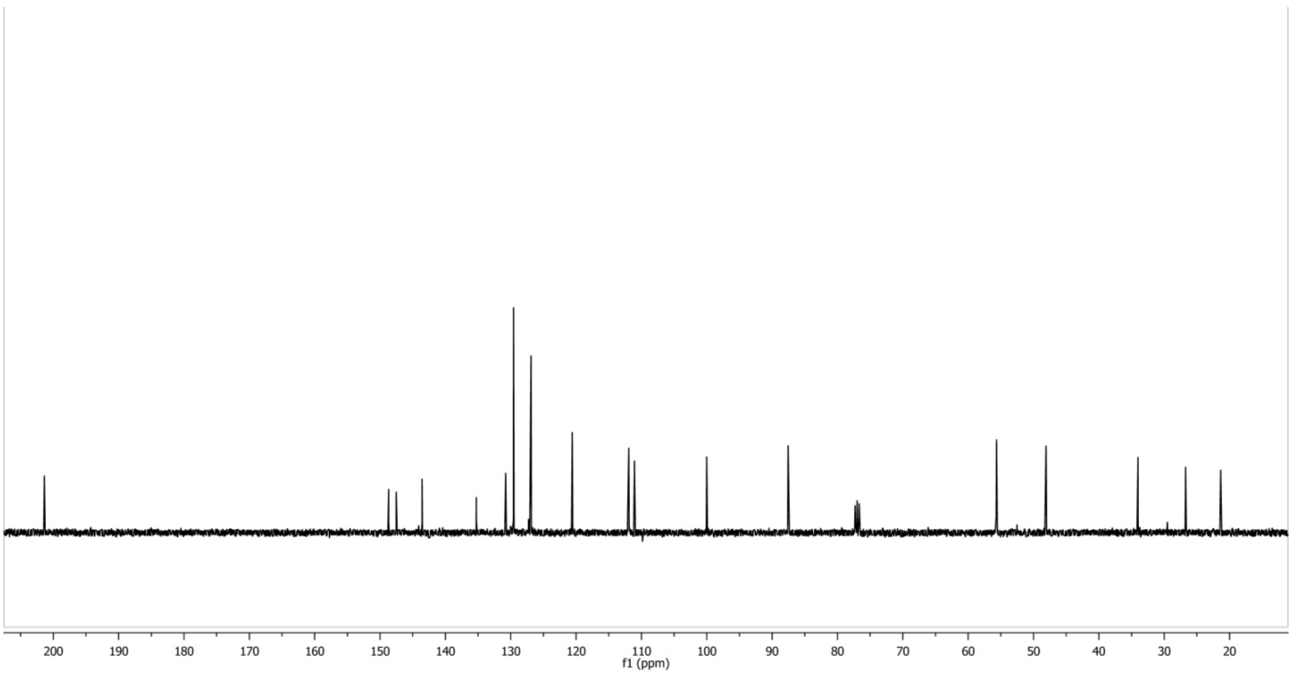
f1 (ppm)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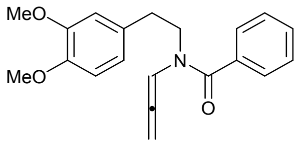
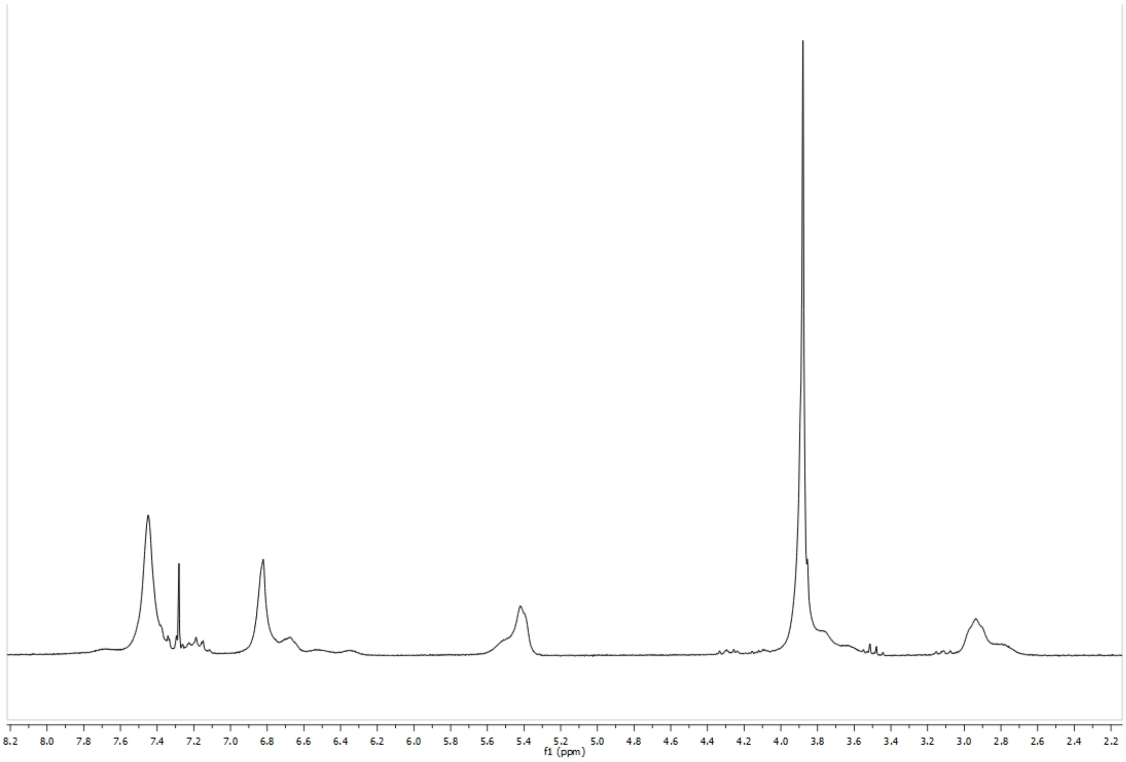
f1 (ppm)



10b



8.2
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7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
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4.0
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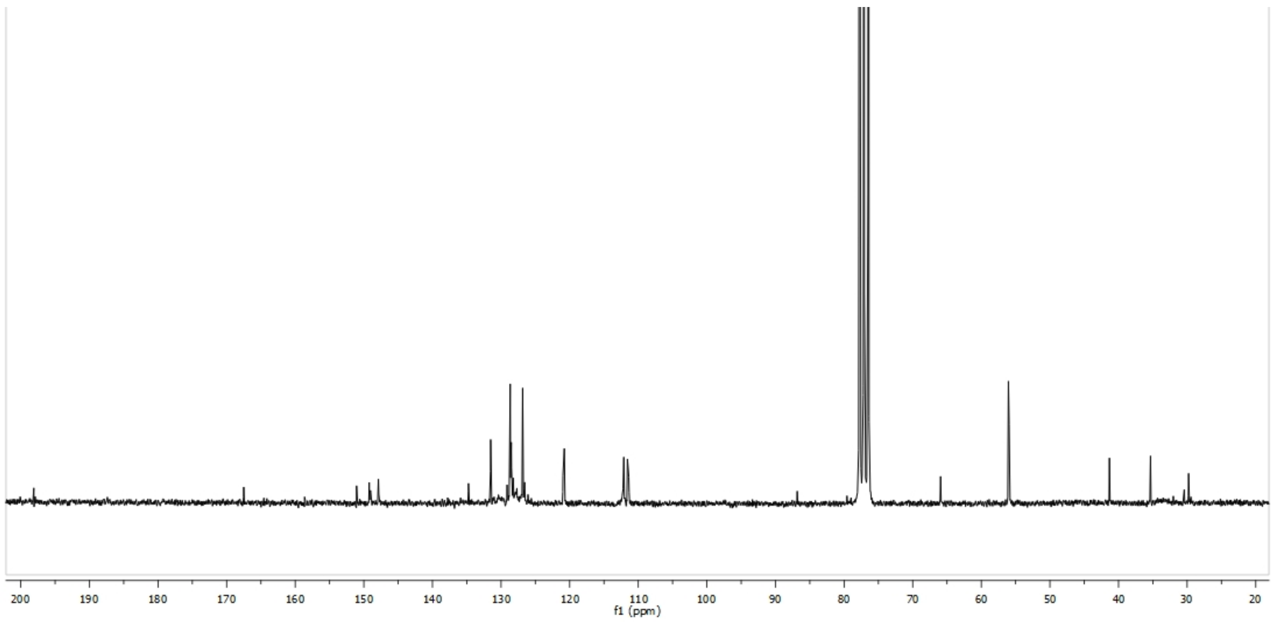
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
f1 (ppm)



200
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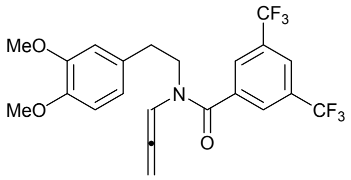
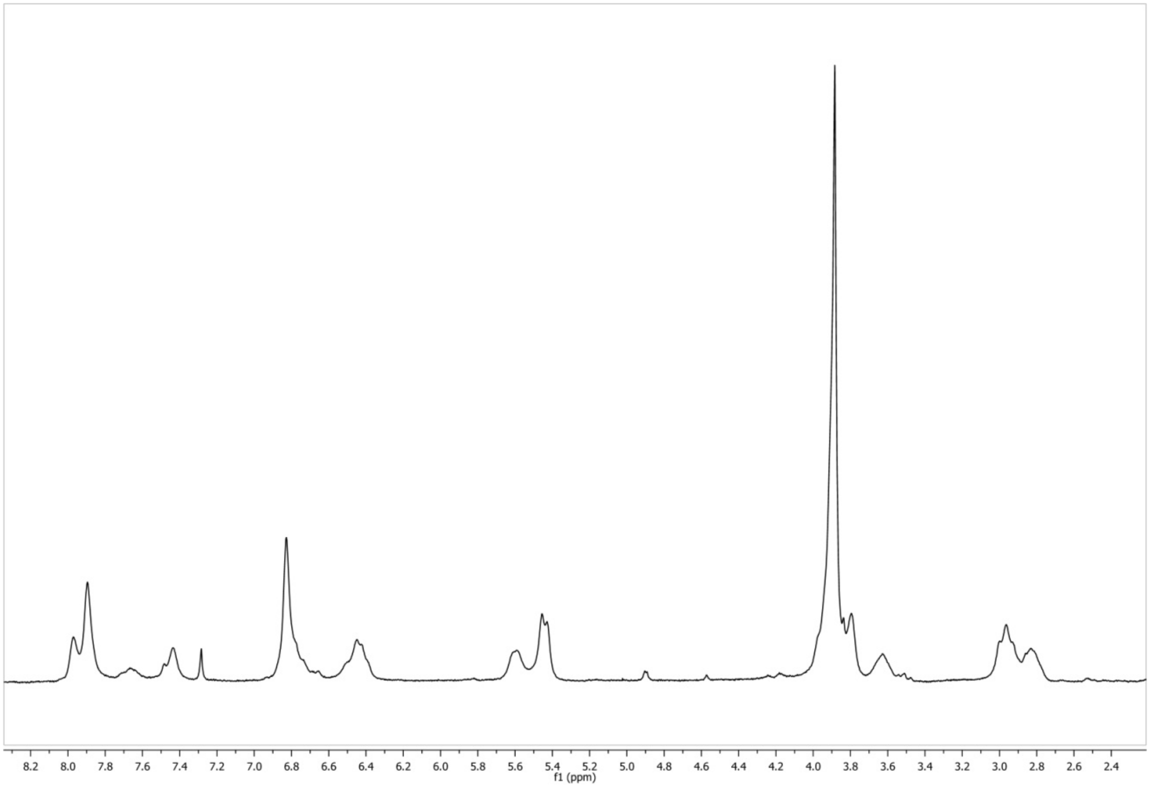
70
60
50
40
30
20
f1 (ppm)

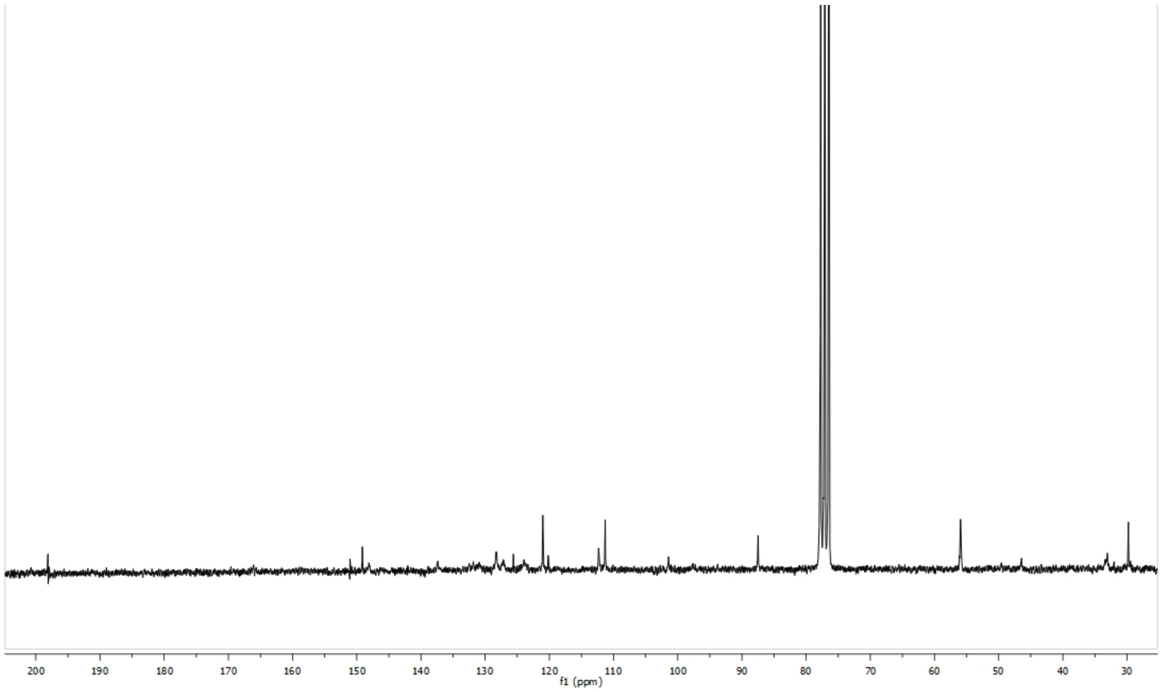


MeO
MeO
N
O
CF3
CF3

10c



8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4
f1 (ppm)



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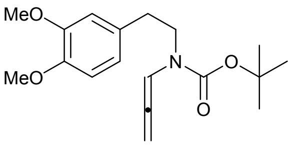
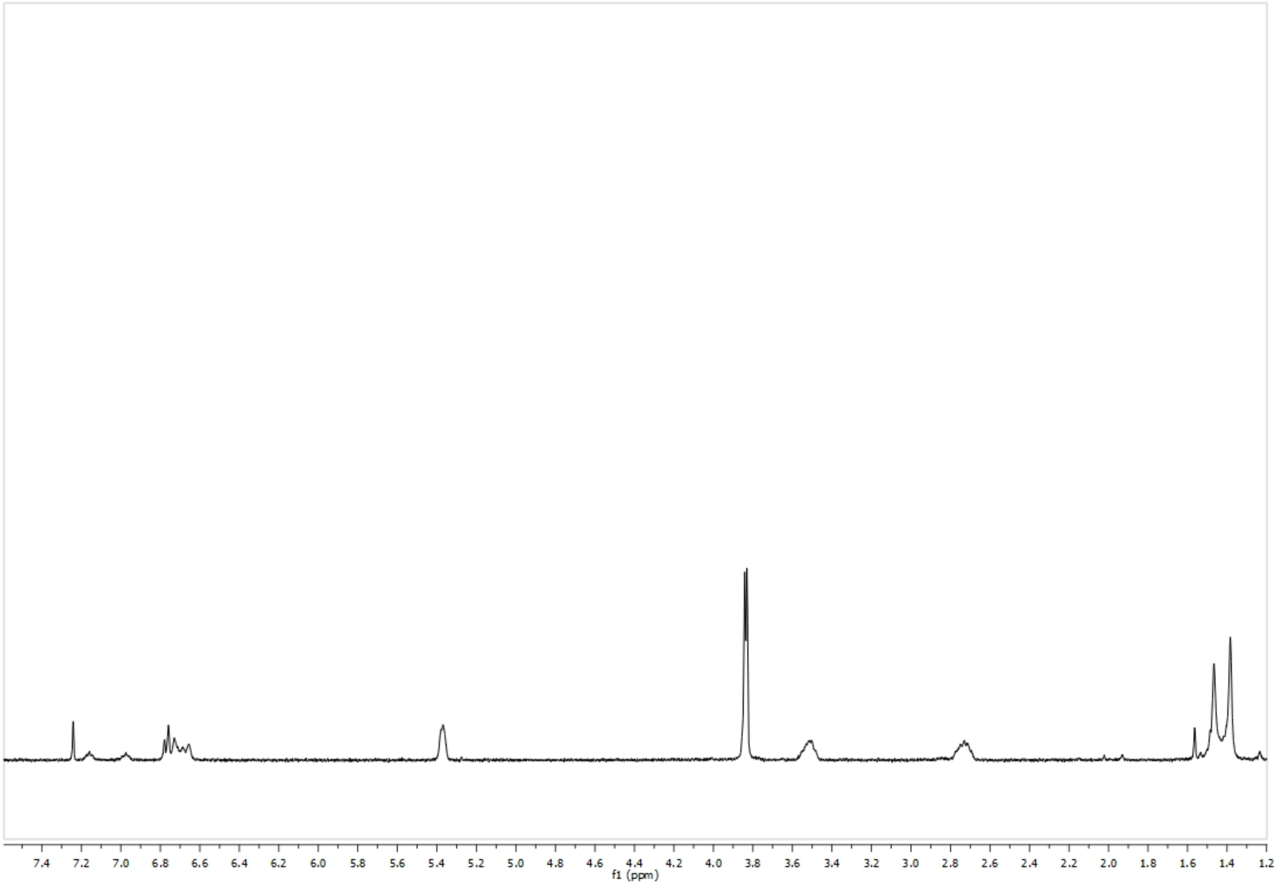
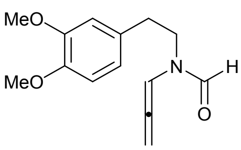
f1 (ppm)

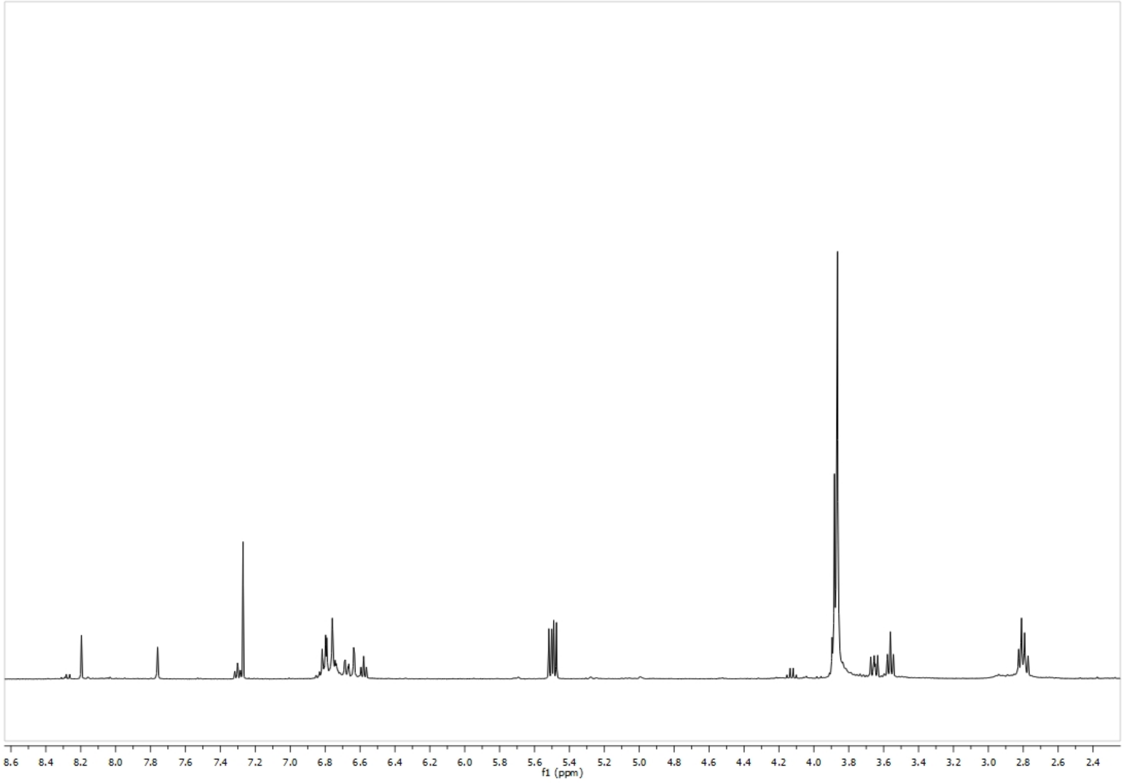

MeO
MeO
N
O
O

10d


7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)


MeO
MeO
N
H
O

10e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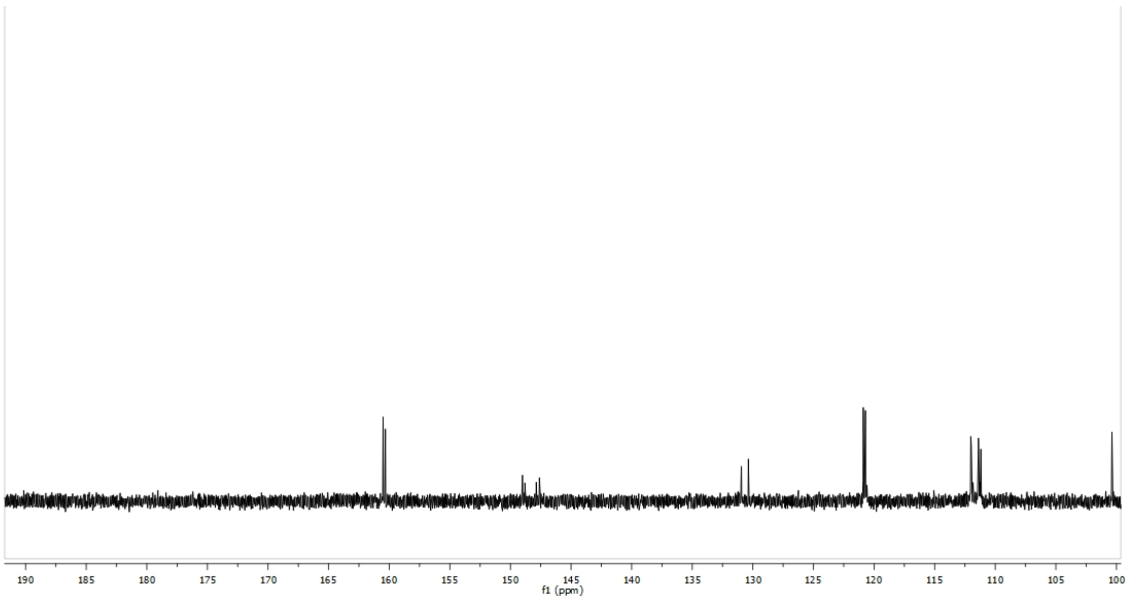
f1 (ppm)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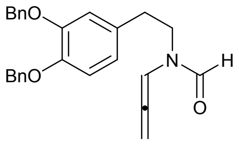
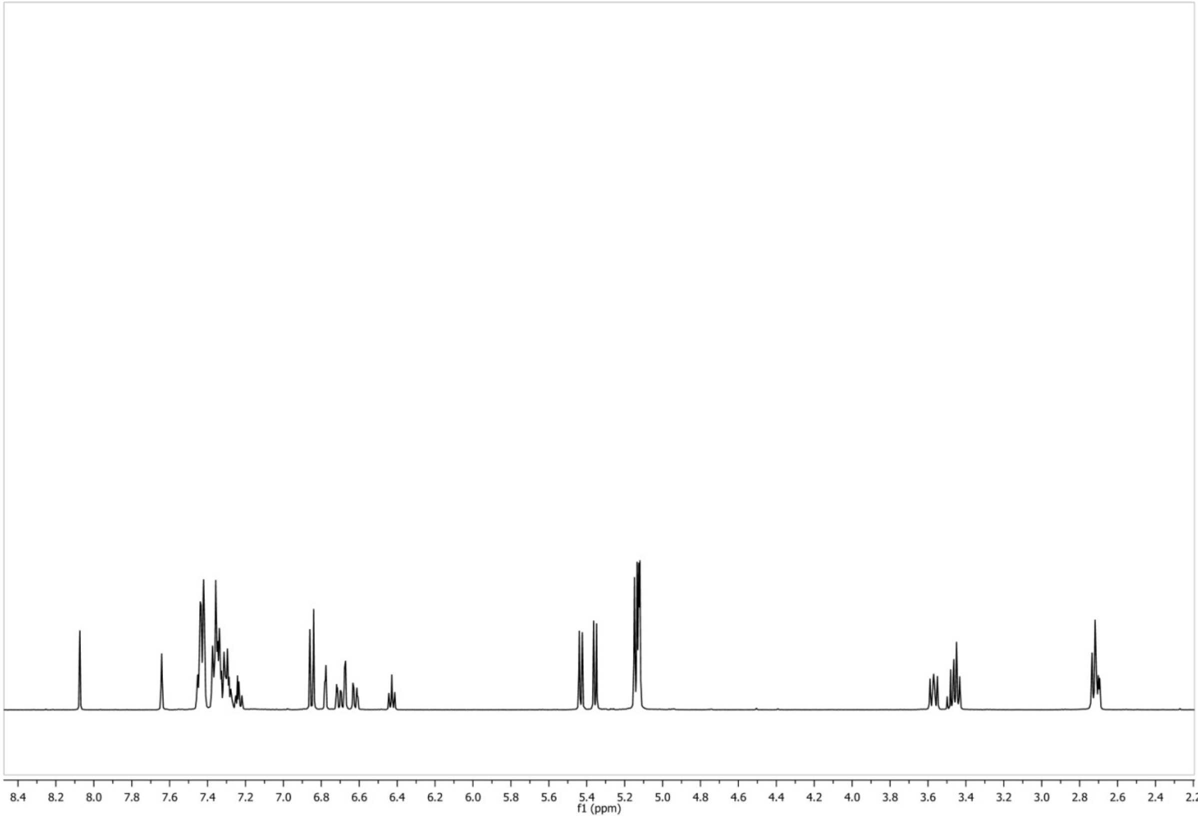
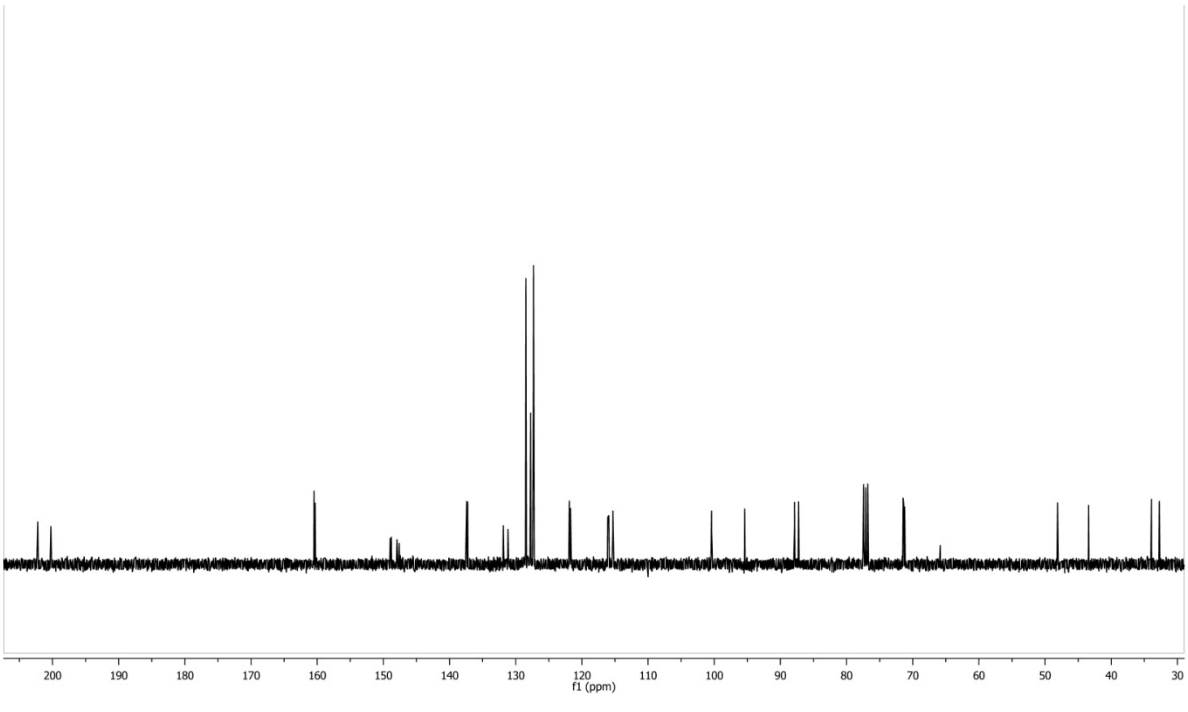
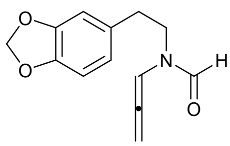
f1 (ppm)



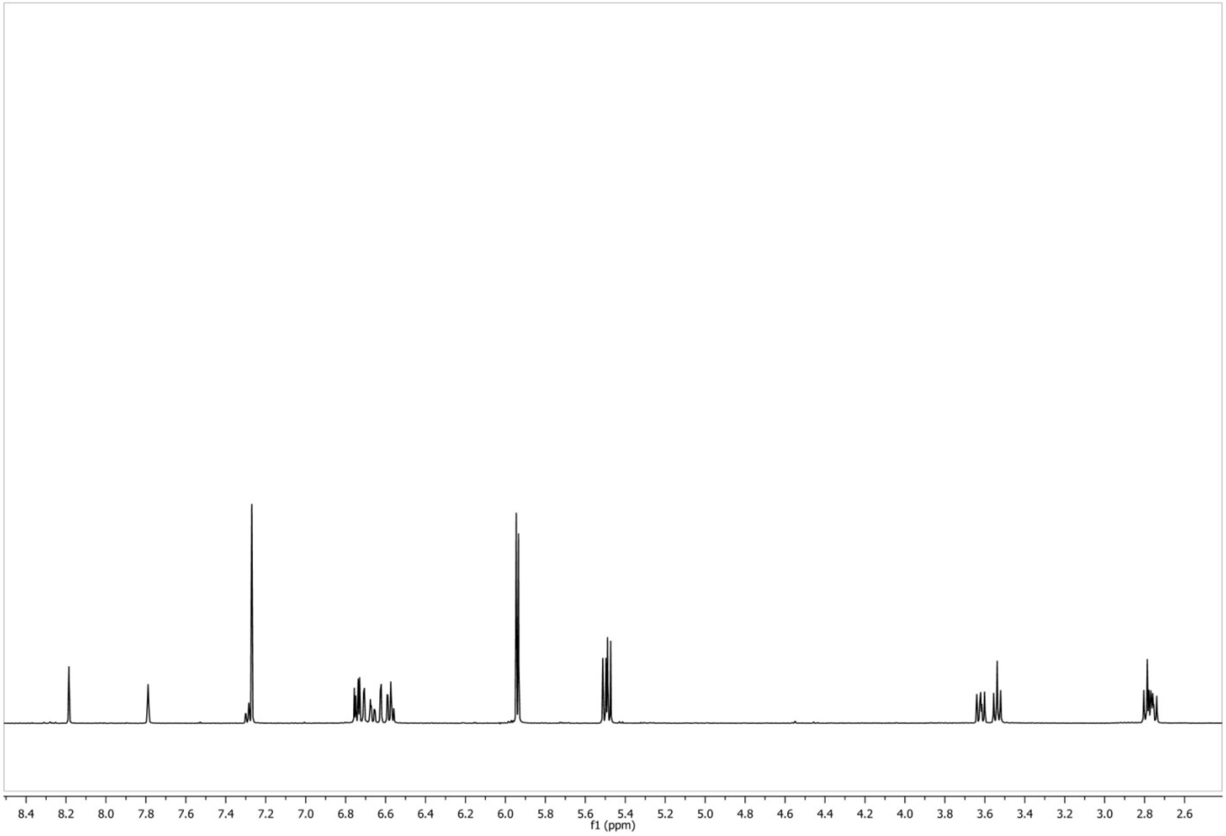
10f

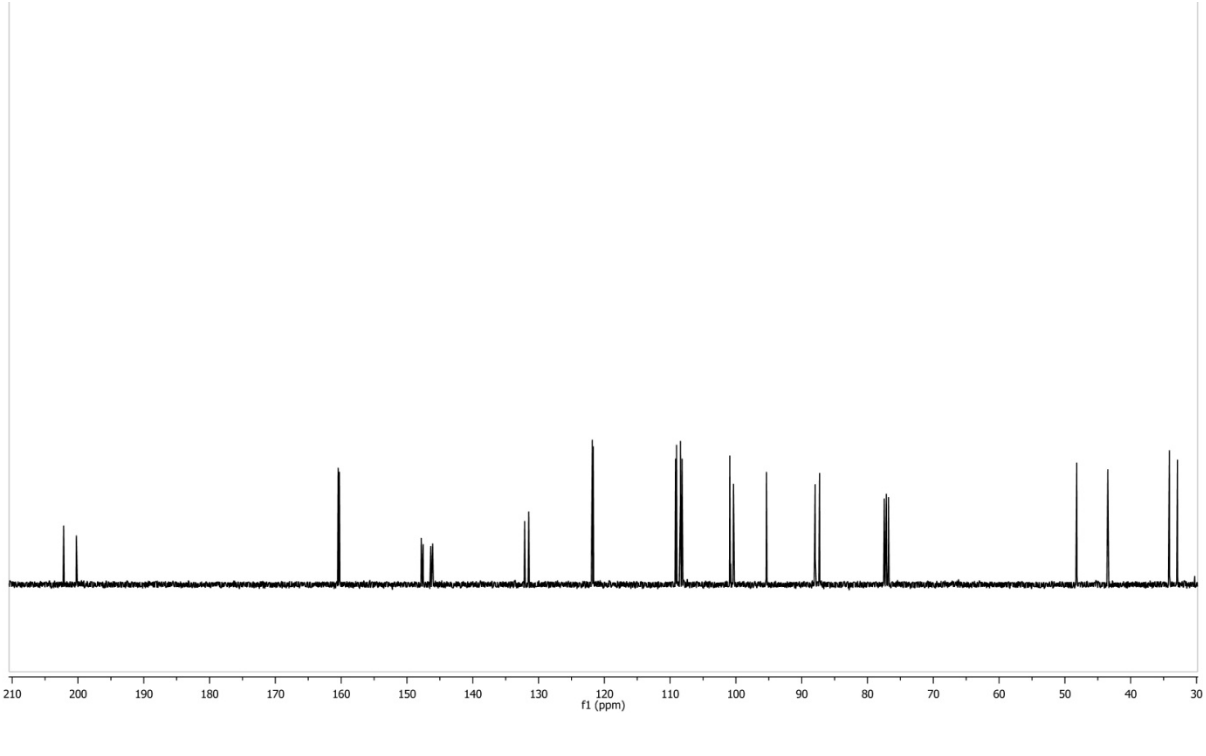


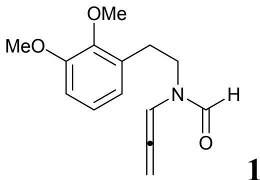




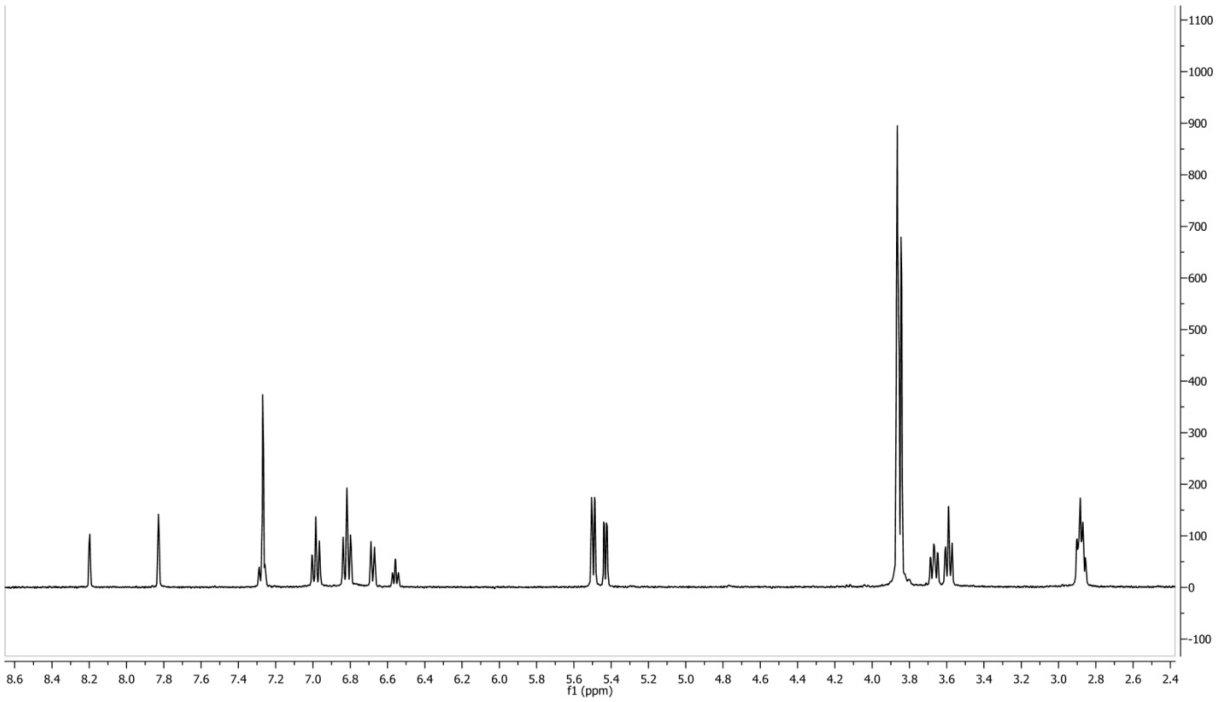
10g

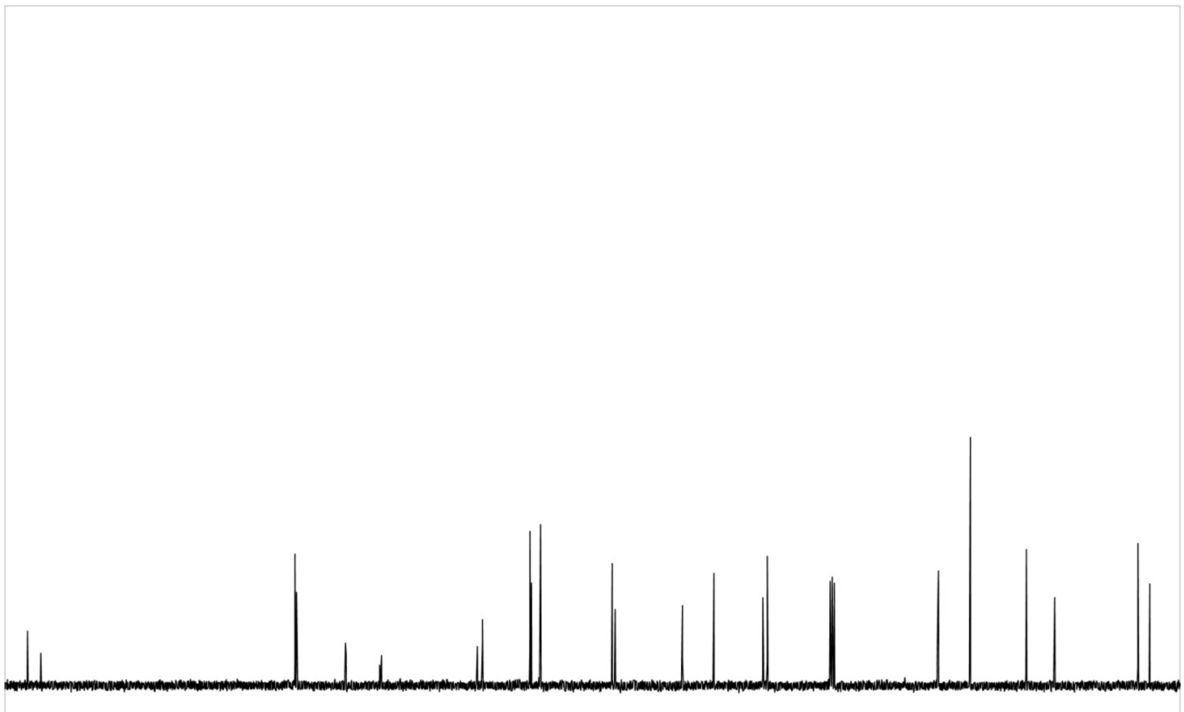


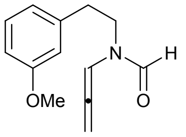




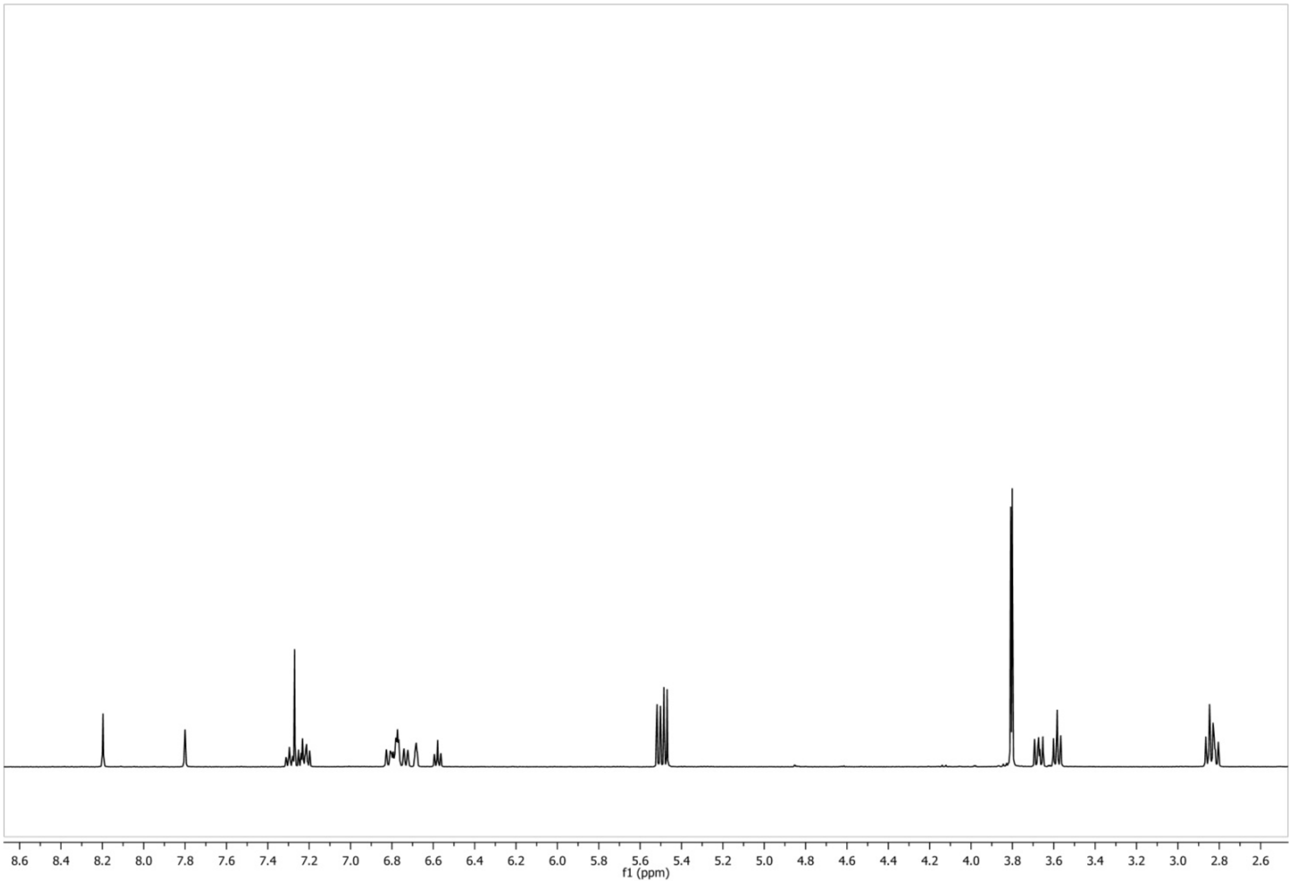
10h






OMe
N
H
O

10i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6.4
6.2
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5.4
5.2
5.0
4.8
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3.8
3.6
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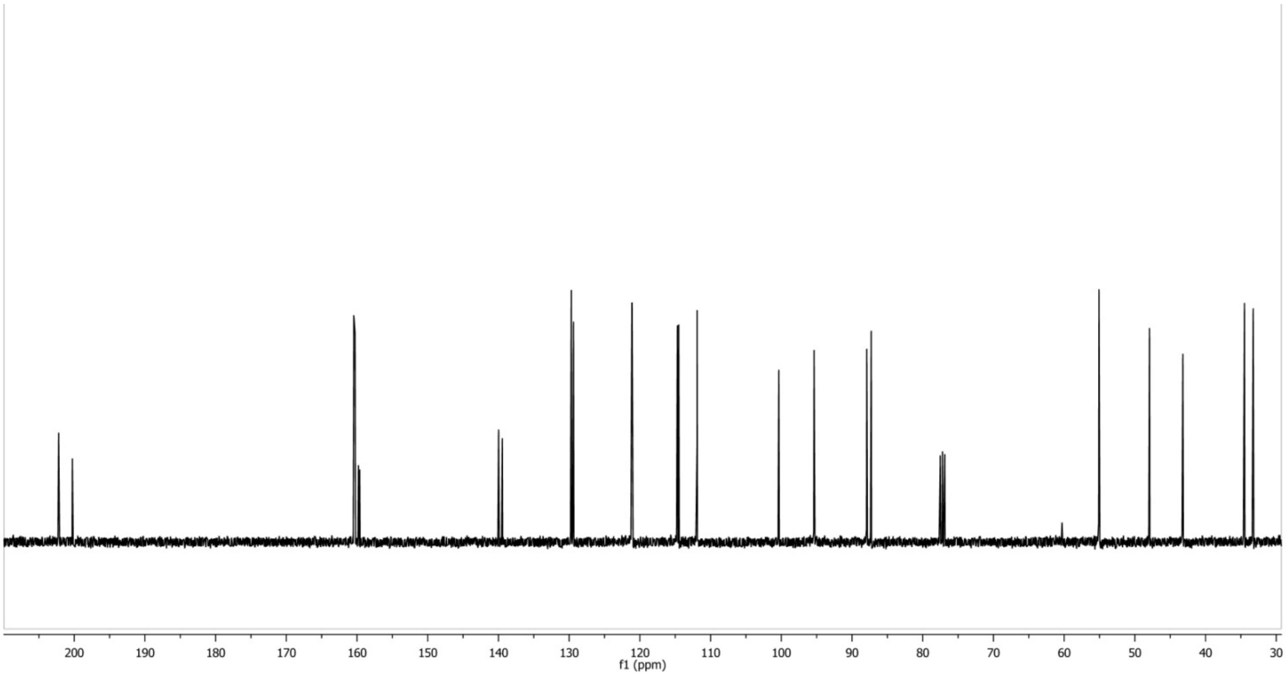
3.0
2.8
2.6
f1 (ppm)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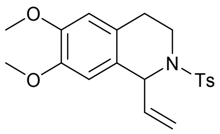
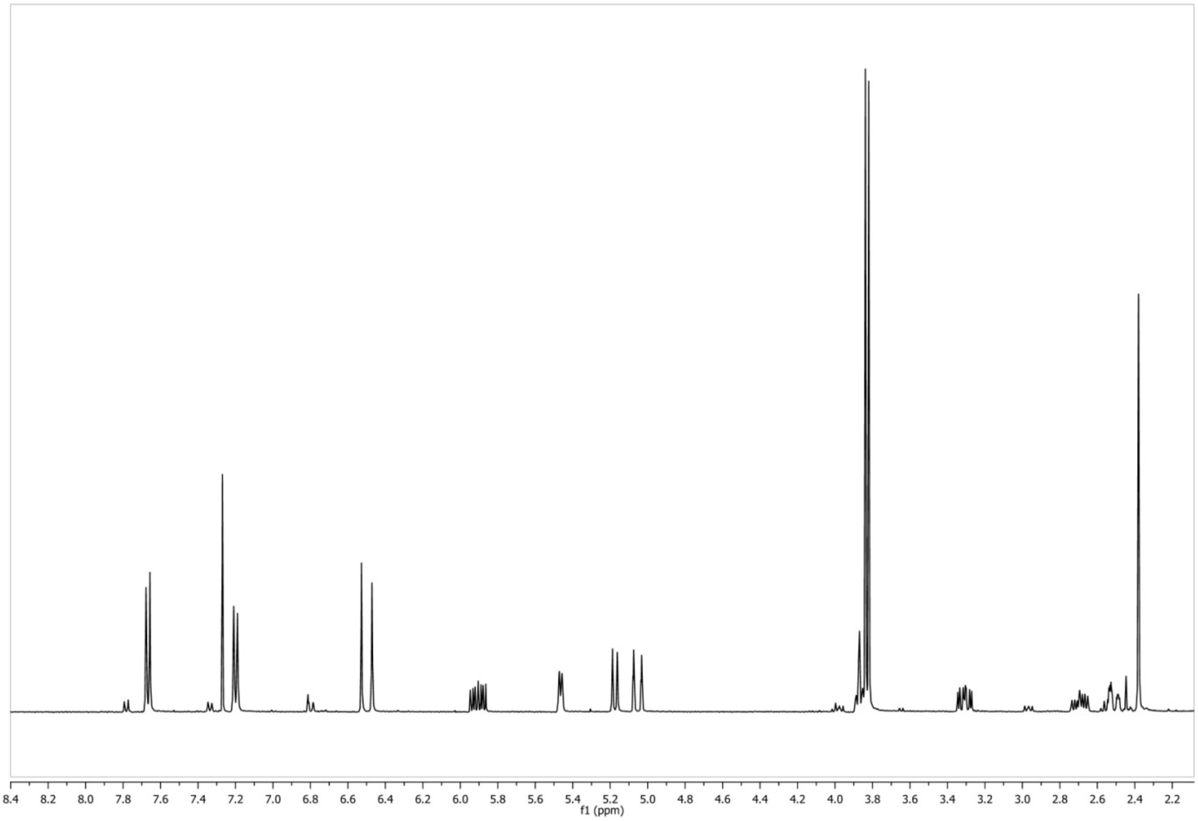
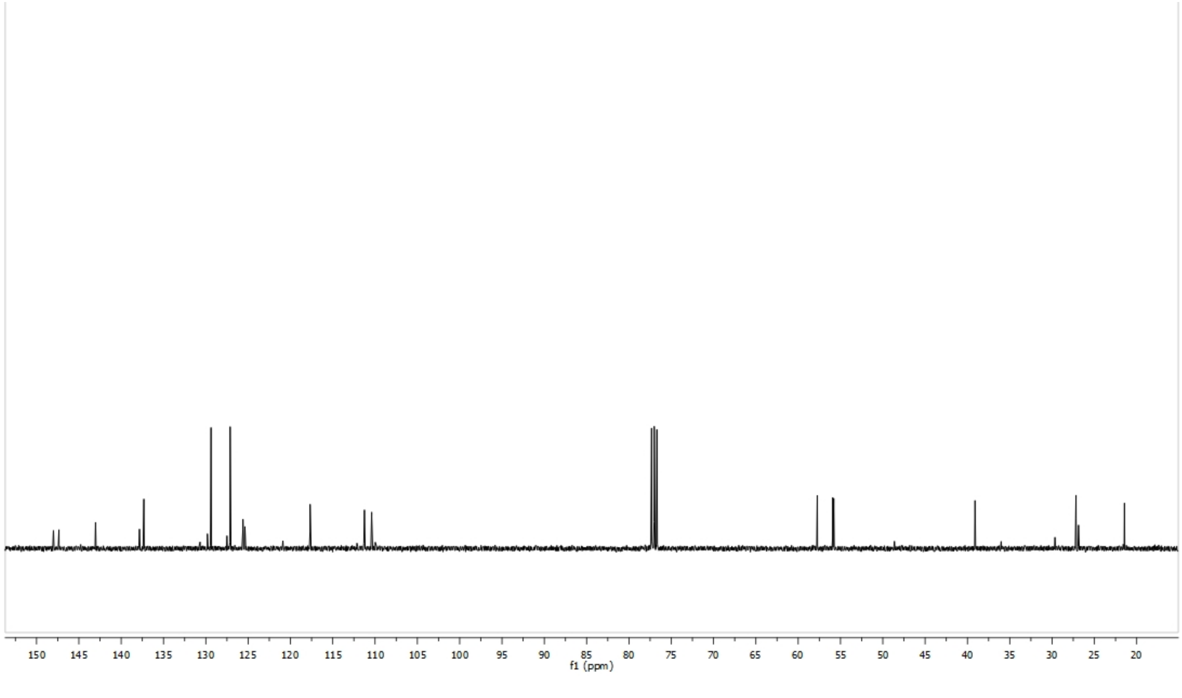
40
30
f1 (ppm)



11a



8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2
f1 (ppm)



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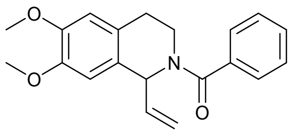
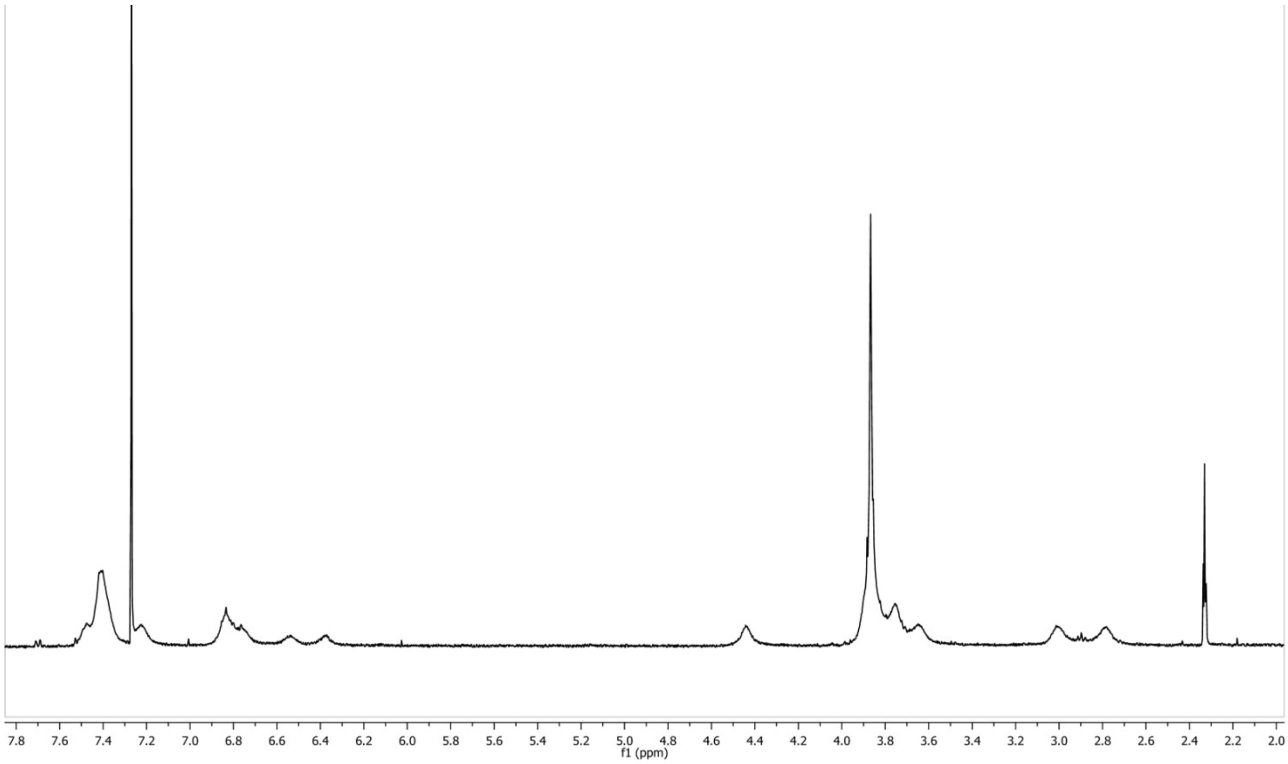
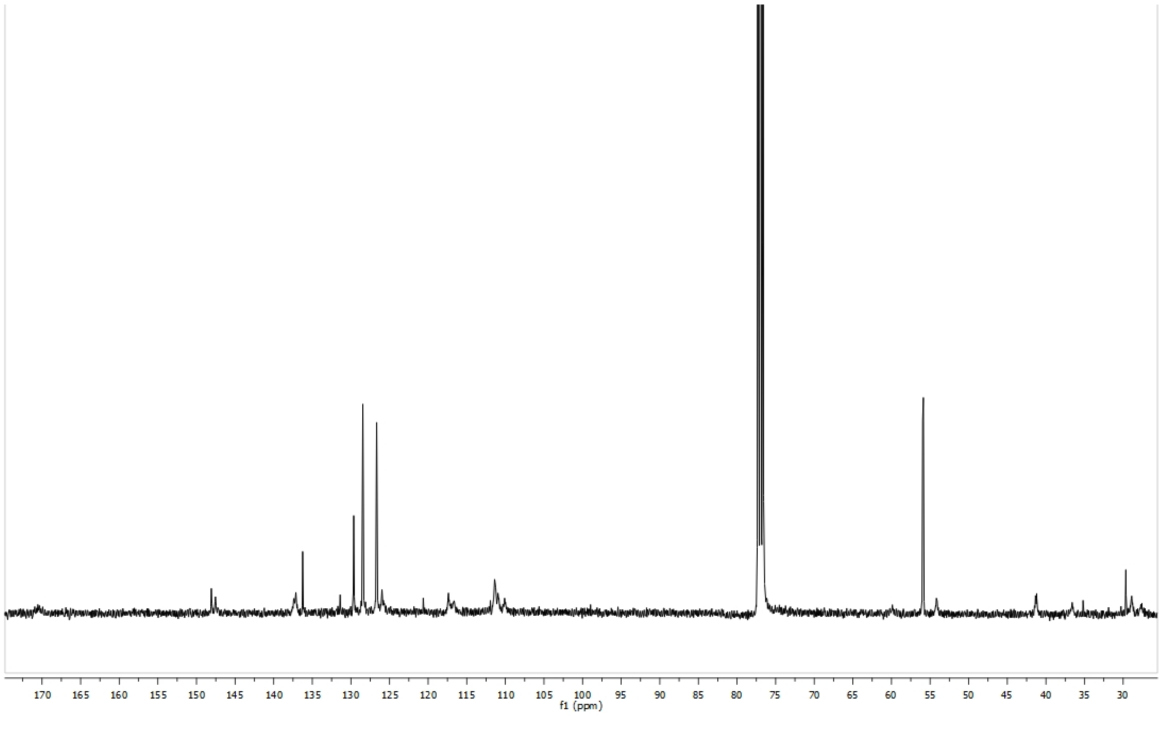
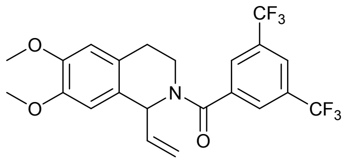
f1 (ppm)



11b







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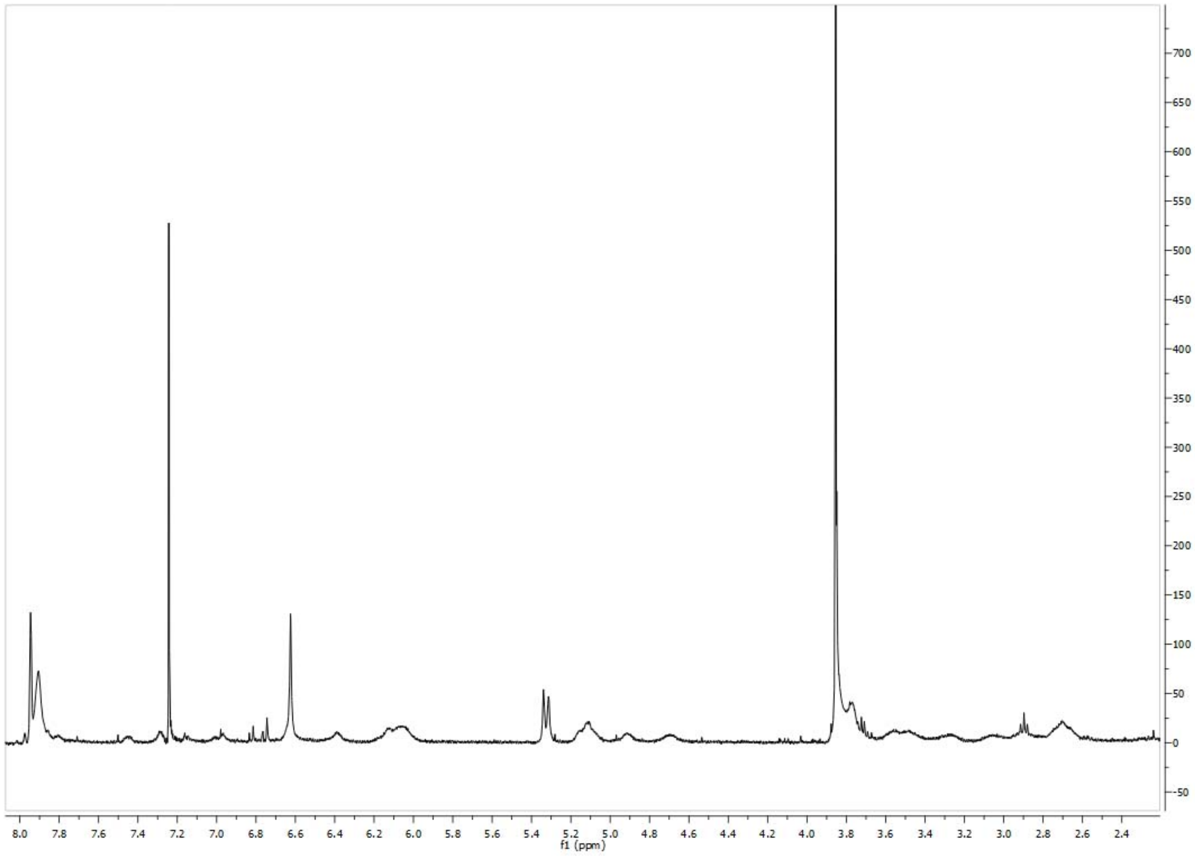
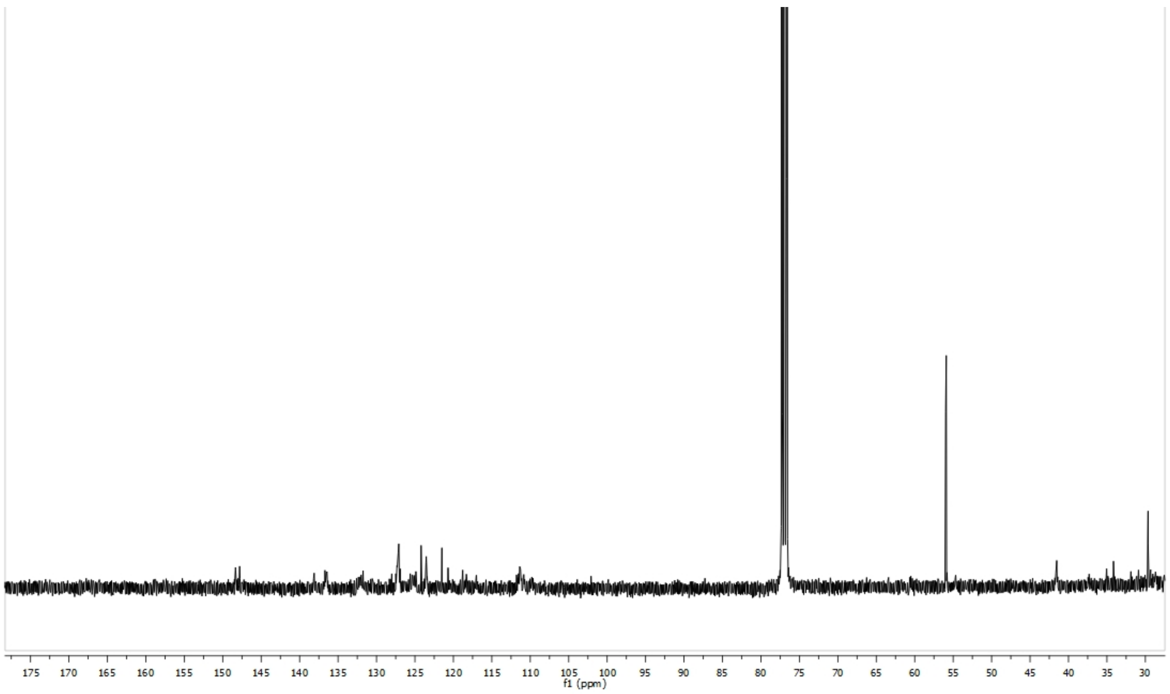
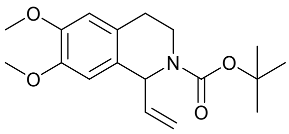
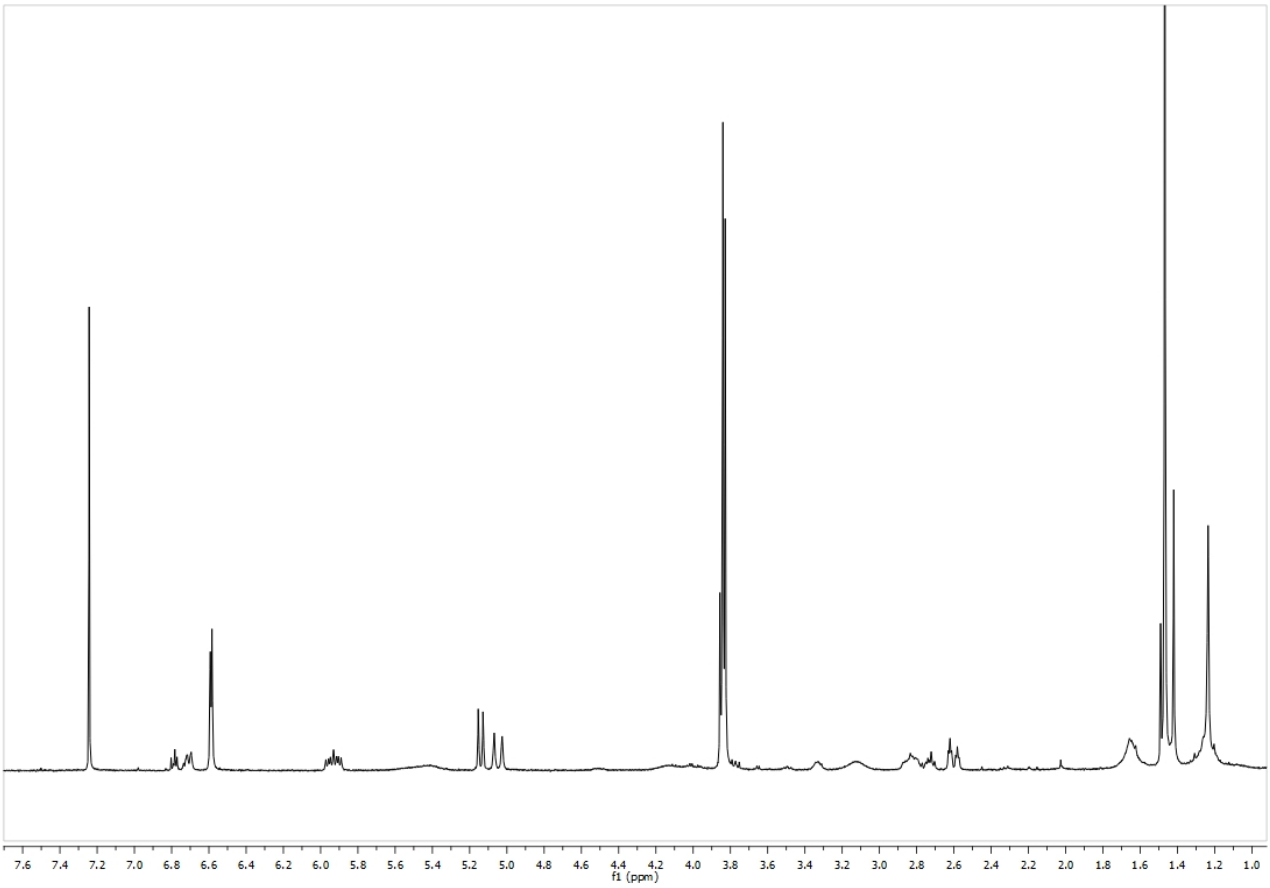






11d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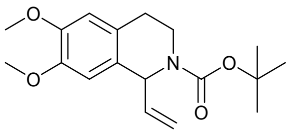
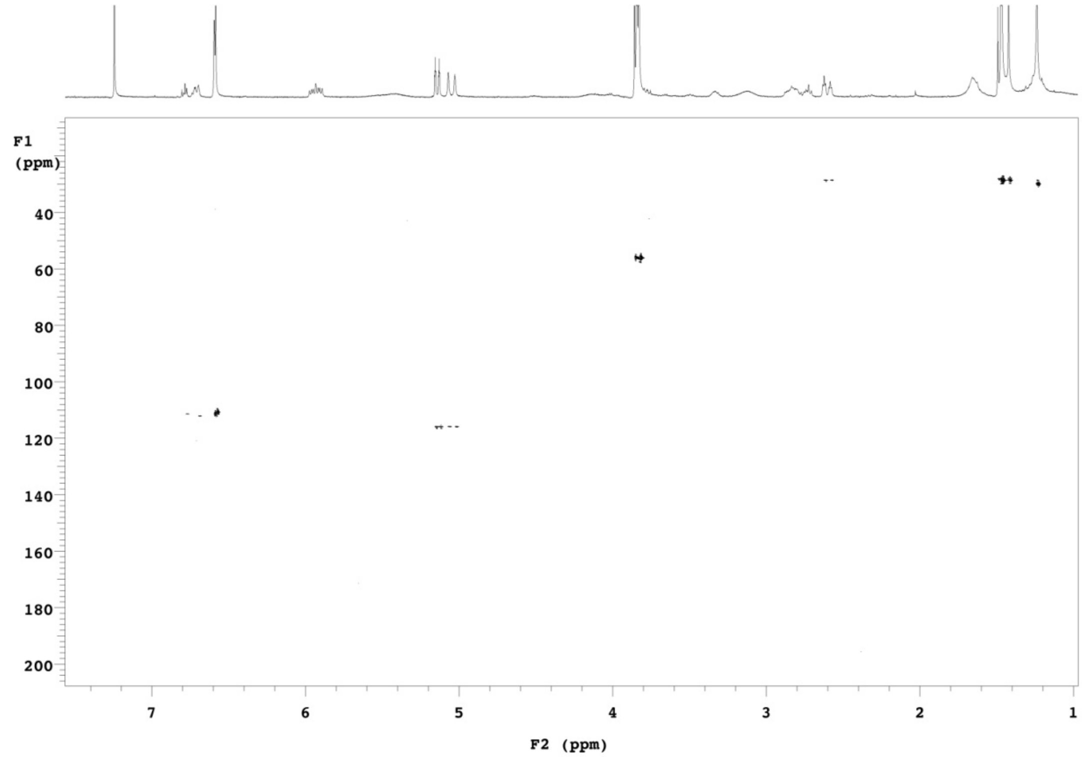
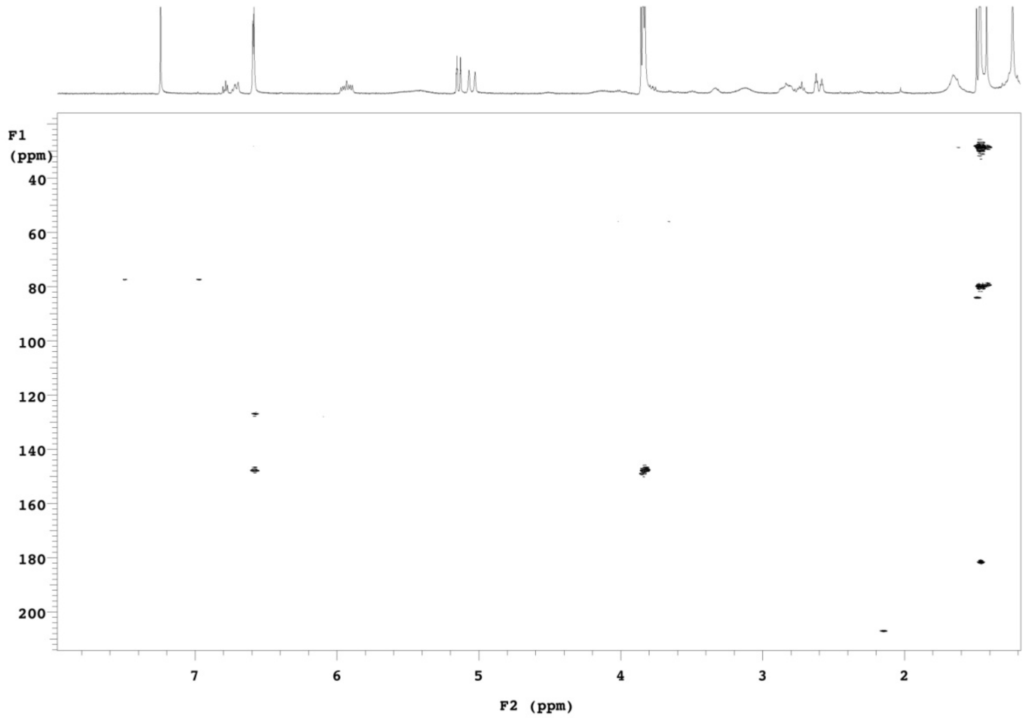
2.0
1.8
1.6
1.4
1.2
1.0
f1 (ppm)

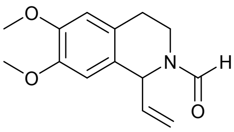


11d HSQC



HMBC





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