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Supporting information

A facile access to 1-substituted and unsubstituted isoquinolin-3-ones via Mannich or Sn2 initiated cascade reactions under catalyst-free conditions.

Lorenzo Serusi, Antonia Di Mola* and Antonio Massa*

Dipartimento di Chimica e Biologia "A. Zambelli", Università degli Studi di Salerno, Via Giovanni Paolo II, 84084-Fisciano (SA), Italy.

*Corresponding Authors email: amassa@unisa.it, adimola@unisa.it

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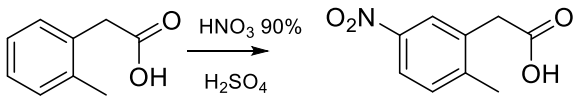
Experimental section

General information

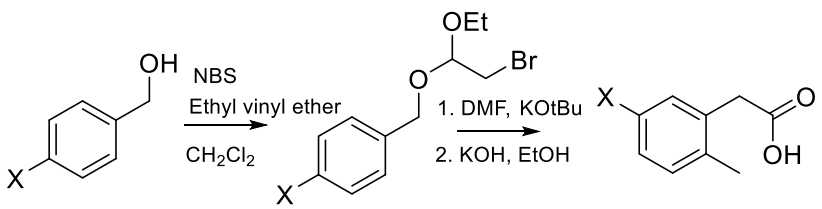
Unless otherwise noted, all chemicals, reagents and solvents for the performed reactions are commercially available. 2-tolyl acetic acid was purchased from Fluorochem, substituted 2-tolyl acetic acids were prepared according to literature procedures.[1-2] Methyl 2-(2-(bromomethyl)phenyl)acetate[3a,b] and methyl-2-(2-formylphenyl) acetate were prepared according to a modified literature procedure.[3b] All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel plates (0.25 mm) and visualized by fluorescence quenching at 254 nm. Flash chromatography was carried out using silica gel 60 (70–230 mesh, Merck, Darmstadt, Germany). Yields are given for isolated products showing one spot on a TLC plate. The NMR spectra were recorded on Bruker DRX 600, 400, and 300 MHz spectrometers (600 MHz, ^{1}H, 150 MHz, ^{13}C; 400 MHz, ^{1}H, 100.6 MHz; ^{13}C, 300 MHz, ^{1}H, 75.5 MHz, ^{13}C, 250 MHz, ^{1}H, 62.5 MHz, ^{13}C). Internal reference was set to the residual solvent signals (δ_H 7.26 ppm, δ_C 77.16 ppm for $CDCl_3$). The ^{13}C NMR spectra were recorded under broad-band proton-decoupling. ^{1}HNMR data and HRMS are reported for all compounds. IR and ^{13}CNMR data are given only for unknown compounds. The following abbreviations are used to indicate the multiplicity in NMR spectra: s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, m-multiplet, brs-broad signal. High resolution mass spectra (HRMS) were acquired using a Bruker SolariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7T refrigerated actively-shielded superconducting magnet. For ionization of the samples electrospray ionization (ESI) or MALDI was applied. IR spectra were recorded on a IR Bruker Vertex 70v spectrometer. Polarimeter Jasco P-2000 (Tokio, Japan).

Synthesis of 2-(2-methyl-5-nitrophenyl)acetic acid



Prepared from 2-tolyl acetic acid as reported in reference 1. White solid. Yield: 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (br s, 1H), 8.13 (d, *J*= 2.5 Hz, 1H), 8.04 (d, *J*= 8.3 Hz, 1H), 7.47 (d, *J*= 8.5 Hz, 1H), 3.80 (s, 2H), 2.34 (s, 3H). HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_9H_9NO_4 + H]^+$: 196.0604; found: 196.0613. IR and spectral data were found in agreement with reported in the literature.[1]

Synthesis of 2-(2-methyl-5-methoxyphenyl)acetic acid and 2-(2-methyl-5-chlorophenyl)acetic acid



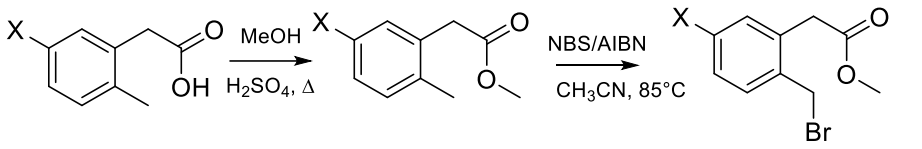
X= OCH_3, Cl

Prepared from corresponding benzyl alcohols as reported in reference 2.

(2-methyl-5-methoxyphenyl)acetic acid. White solid. Yield: 58%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.23 (br s, 1H), 7.10 (d, *J*= 7.8 Hz, 1H), 6.76 (m, 2H), 3.79 (s, 3H), 3.64 (s, 2H), 2.26 (s, 3H). HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{12}O_3 + H]^+$: 182.0859; found: 181.0878. IR and spectral data were found in agreement with reported in the literature.[2]

2-(2-methyl-5-chlorophenyl)acetic acid. White solid. Yield: 50%. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 9.45 (br s, 1H), 6.97 (m, 3H), 3.62 (s, 2H), 2.27 (s, 3H). HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_9H_9ClO_2 + H]^+$: 185.0364; found: 185.0371.-IR and spectral data were found in agreement with reported in the literature.[2]

General Procedure for the synthesis of bromides 2a-d



1a X= H
1b X= OCH_3
1c X= Cl
1d X= NO_2

Step 1. Esterification

To a solution of o-tolylacetic acid (5.00 g, 33.29 mmol) in MeOH (60 mL) were added concentrated H_2SO_4 (1.0 mL) and the mixture was refluxed for 5h. The solvent was removed under reduced pressure, the crude rinsed up with Ethyl Acetate and washed twice with $NaHCO_3$ saturated solution and brine.

Methyl 2-(o-tolyl)acetate. Pale oil (5.35 g, yield: 98%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.15 (m, 4H), 3.69 (s, 3H), 3.64 (s, 2H), 2.31 (s, 3H). HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{12}O_2 + H]^+$: 165.0910; found: 165.0913. Spectral data were found in agreement with reported in the literature.[4]

Methyl 2-(2-methyl-5-methoxyphenyl)acetate. The mixture was refluxed for 3h. Evaporation of the solvent gave a pale oil (650 mg, yield: 98% starting from 600 mg of acid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J*= 7.6 *Hz*, 1H), 6.77 -6.73 (m, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.61 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 157.9, 133.8, 131.2, 128.8, 115.9, 112.7, 55.3, 52.1, 39.3, 18.7. IR (neat): 2950, 1652, 758, 732 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{11}H_{14}O_3 + H]^+$: 195.1016; found: 195.1038.

Methyl 2-(2-methyl-5-chlorophenyl)acetate. The mixture was refluxed for 7h. Evaporation of the solvent gave a pale oil (550 mg, yield: 95% starting from 500 mg of acid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.09 (m 3H), 3.71 (s, 3H), 3.61 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 135.4, 134.5, 131.6, 130.1, 128.7, 127.5, 52.3, 38.9, 19.1. IR (neat): 1665, 747, 731 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{11}ClO_2 + H]^+$: 199.0520; found: 199.0534.

Methyl 2-(2-methyl-5-nitrophenyl)acetate. The mixture was refluxed for 18h. Evaporation of the solvent gave a pale oil (1.2 g, yield: 98% starting from 1 g of acid). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-7.93 (m, 2H), 7.33 (d, *J*= 7.*9* Hz, 1H), 3.71 (s, 3H), 3.69 (s, 2H), 2.36 (s, 3H). HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{11}N_2O_4 + H]^+$: 210.0761; found: 210.0756. IR and spectral data were found in agreement with reported in the literature.[5]

Step 2. Benzylic bromination

Esters (3.0 g, mmol, 18 mmol, 1.0 equiv.) was dissolved in CH_3CN (18 mL) and treated with *N*-Bromosuccinimide (NBS, 2.4 g, 1.2 equiv.) and azaisobutyrronitrile (AIBN, 200 mg, 0.1 equiv.) at 80 °C for 2h. Then, the mixture was concentrated and purified by flash chromatography on silica gel (Petroleum ether/Ethyl acetate, 20:1) to give brominated compound.

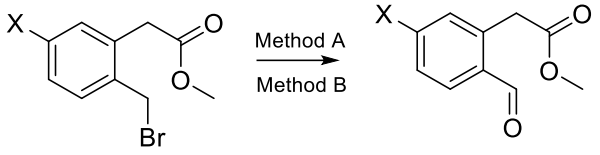
Methyl 2-(2-(bromomethyl)phenyl)acetate 1a. Pale oil (4.0 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.36 (s, 1H), 7.30-7.20 (m, 3H), 4.58 (s, 2H), 3.81 (s, 2H), 3.71 (s, 3H). HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{11}BrO_2 + H]^+$: 243.0015; found: 243.0020. IR and spectral data were found in agreement with reported in the literature.[3a]

Methyl 2-(2-(bromomethyl)-5-methoxyphenyl)acetate 1b. 1,2-Dichloroethane was used instead of CH_3CN. Pale oil (350 mg, 86% starting from 1.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.10 (m, 1H), 6.80 -6.75 (m, 2H), 4.59 (s, 2H), 3.81 (s, 3H), 3.73 (s, 2H), 3.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 160.2, 133.8, 131.2, 128.8, 115.9, 113.2, 55.5, 52.7, 39.3, 28.2. IR (neat): 2952, 1653, 758, 682 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{11}H_{13}BrO_3 + H]^+$: 273.0121; found: 273.0128.

Methyl 2-(2-(bromomethyl)-5-chlorophenyl)acetate 1c. Refluxed for 8h. Pale oil (530 mg, 78% starting from 2.5 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 3H), 4.58 (ms, 2H), 3.82 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 135.1, 135.0, 134.8, 131.9, 131.3, 128.2, 52.4, 37.9, 30.7. IR (neat): 1656, 1356, 750, 710 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{10}BrClO_2 + H]^+$: 276.9625; found: 276.9648.

Methyl 2-(2-(bromomethyl)-5-nitrophenyl)acetate 1d. Refluxed overnight**.** Pale oil (600 mg, 83% starting from 2.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.09 (m, 2H), 7.54 (d, *J*= 7.9 Hz, 1H), 4.56 (s, 2H), 3.89 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 147.9, 143.6, 135.0, 131.7, 126.4, 123.1, 52.7, 38.1, 29.3. IR (neat): 2952, 1658, 1550, 1451, 756, 722 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{10}BrNO_4 + H]^+$: 287.9866; found: 287.9860.

Step 3. Oxidation



1a X= H
1b X= OCH_3

2a X= H
2b X= OCH_3

Method A[6]

To a solution of bromide **1** (3.20 g, 13.2 mmol) in CH_3CN (25 mL) was added *N*-methylmorphline *N*-oxide (NMO, 4.60 g, 3 equiv.) and the mixture was stirred at room temperature for 3h. The solvent was removed under reduced pressure and a solution of $Na_2S_2O_3$ was added to destroy excess of oxidant. The aqueous layer was extracted with ethyl acetate and the resulting product was purified by chromatography (Petroleum ether/Ethyl acetate, 5:1).

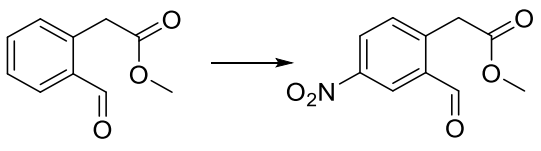
Method B[7]

A solution of bromide **1** (200 mg, 0.82 mmol) in DMSO (4.0 mL) and $NaHCO_3$ (8 eq, 550 mg) was stirred at 100 °C for 1h. The mixture was cooled down, extracted with ethyl acetate twice and washed with brine. the resulting product was purified by chromatography (Petroleum ether/Ethyl acetate, 5:1).

Methyl-2-(2-formylphenyl)acetate 2a. Pale oil. By method A, yield: 98%. By method B yield: 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.85-7.82 (m, 1H), 7.58-7.45 (m, 2H), 7.31-7.27 (m, 1H), 4.05 (s, 2H), 3.69 (s, 3H). HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{10}O_3 + H]^+$: 179.0703; found: 179.0712. IR and spectral data were found in agreement with reported in the literature.[8]

Methyl 2-(2-formyl-5-methoxyphenyl)acetate 2b. Obtained by method A. Pale oil (115 mg, 99% starting from 0.55 mmol).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.83 (d, *J*= 8.65 Hz, 1H), 7.01 (dd, *J*= 8.65, 2.63 Hz, 1H), 6.85 (d, *J*= 2.63 Hz, 1H), 4.08 (s, 2H), 3.94 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 171.4, 163.6, 137.9, 137.2, 128.0, 118.4, 112.4, 55.6, 52.1, 39.1. IR (neat): 2950, 1670, 1650, 759, 738 cm-^{1}HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_{12}O_4 + Na]^+$: 231.0628; found: 231.0634.

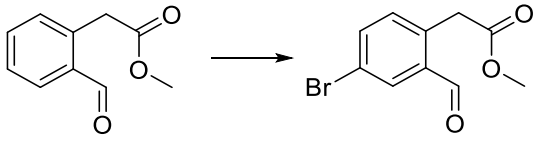
Synthesis of methyl 2-(2-formyl-4-nitrophenyl)acetate 2c



2a **2c**

A solution of concentrated H_2SO_4 (300 µL) and fuming nitric acid (150 µL) was stirred for 1h. Then, keeping the mixture at 0°C (ice bath), a solution of aldehyde **2a** (100 mg, 0.56 mmol) in anhydrous dichloromethane (150 µL) and stirring was continued at room temperature for 1h. Ice was added and the aqueous phase was extracted twice with dichloromethane affording a yellow thick oil. Purification by chromatography (Hexane/ Ethyl acetate, 7:3) gave a pale oil. Yield: 71% (89 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.72 (d, *J*= 2.3 Hz, 1H), 8.41 (dd, *J*= 8.3 Hz, 2.3 Hz, 1H), 7.57 (d, *J*= 8.3 Hz, 1H), 4.20 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 170.2, 147.6, 142.18, 135.3, 133.7, 128.1, 127.7, 52.5, 38.6. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_9O_5 + H]^+$: 224.0553; found: 224.0567.

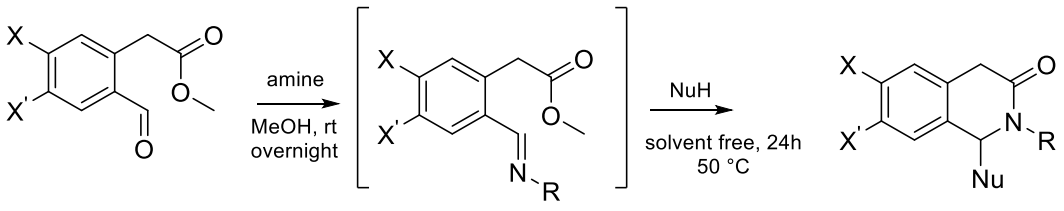
Synthesis of methyl 2-(2-formyl-4-bromophenyl)acetate 2d



2a **2d**

To a solution of aldehyde **2a** (150 mg, 0.84 mmol) in concentrated H_2SO_4 (1.5 mL), silver sulphate (400 mg, 1.5 equiv.) and bromine (48 µL, 1 equiv.) were added and stirring was continued at room temperature for 2h. Ice was added and the aqueous phase was extracted twice with dichloromethane affording a yellow thick oil. Purification by chromatography (Hexane/ Ethyl acetate, 9:1) gave a pale oil. Yield: 68% (146 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (s, 1H), 7.98 (d, *J*= 1.8 Hz, 1H), 7.70 (dd, *J*= 8.1 Hz, 1.8 Hz, 1H), 7.22 (d, *J*= 8.1 Hz, 1H), 4.03 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 170.9, 136.6, 136.4, 135.8, 134.4, 133.9, 121.9, 52.2, 38.2. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{10}H_9BrO_3 + H]^+$: 255.9735; found: 255.8745.

General procedure for Mannich/lactamization reaction



2 **3** **6, 7**

Methyl 2-(2-formylphenyl)acetate **2a** (X and X′= H, 0.15 mmol, 1.0 eq.) was treated with the amine (0.15 mmol, 1.0 eq.) at rt in MeOH (0.3 mL) for 18h. After solvent evaporation, the crude product imine **3** was reacted without further purification with the pronucleophile NuH (1.5 mmol, 10.0 eq.) at 50°C (oil bath) for 24h. Then the product was directly purified by chromatography on silica gel (Hexane/Ethyl acetate, 7:3) affording the corresponding products **6** and **7**.

2-benzyl-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one 6a.[9] Compound was obtained as a yellow oil in 99% yield (44 mg).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 8H), 7.04 (d, *J= 7.5 Hz*, 1H), 5.27 (d, *J*= 15.1 *Hz*, 1H), 5.10 (t, *J*= 6.7 Hz, 1H), 4.50-4.43 (m, 2H), 4.32 (d, *J*= 15.1 Hz, 1H), 3.75 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 136.1, 132.2, 130.9, 129.3, 129.2, 128.3, 128.2, 127.6, 125.9, 77.7, 58.9, 49.1, 37.4. IR (neat): 2923, 1652, 1553, 1451, 1379, 1260, 758, 732 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{16}N_2O_3 + H]^+$: 297.1233; found: 297.1226. Reaction was scaled up to 1 mmol of aldehyde **2a** and product was isolated in 90% yield.

2-(3,4-Dichlorobenzyl)-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one 6b. Compound was obtained as a yellow solid in 73% yield (40 mg). Mp 121−123 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 7.09-7.01 (m, 3H), 5.31 (d, *J*= 15.8 Hz, 1H), 5.09 (t, *J*= 6.5 Hz, 1H), 4.61-4.47 (m, 2H), 4.11 (d, *J*= 15.8 Hz, 1H), 3.75 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 136.5, 133.2, 132.3, 132.0, 131.1, 130.5, 130.1, 129.6, 128.4, 127.8, 127.3, 125.8, 77.9, 59.2, 48.1, 37.3. IR (KBr disc): 2918, 2360, 1663, 1471, 1421, 1380, 1264, 1029, 761 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{14}Cl_2N_2O_3 + H]^+$: 365.0454; found: 365.0478.

2-(2-Methoxybenzyl)-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one 6c. Compound was obtained as a red solid in 70% yield (34 mg). Mp 115−1117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.23 (m, 1H), 7.21-7.19 (m, 3H), 7.07 (d, *J*= 7.6 Hz, 1H), 6.89-6.86 (m, 3H), 5.26 (dd, J_1= 5.2 Hz, J_2= *2*.9 Hz, 1H), 5.10 (d, *J*= 14.8 Hz, 1H), 4.59 (dd, J_1= 7.1 Hz, J_2= 5.2 Hz, 1H), 4.52-4.44 (m, 2H), 3.84 (s, 3H), 3.70 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 157.7, 132.3, 131.3, 130.6, 129.5, 129.2, 128.2, 127.4, 126.0, 124.2, 121.1, 110.6, 59.3, 55.5, 44.1, 37.4. IR (KBr disc): 2923, 2360, 1661, 1642, 1549, 1455, 1252, 1025, 759 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{18}H_{18}N_2O_4 + H]^+$: 327.1339; found: 327.1318.

2-(3,5-Bis(trifluoromethyl)benzyl)-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one 6d. Compound was obtained as a yellow oil in 73% yield (46 mg).^{1}H NMR(300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.60 (s, 2H), 7.38 (t, *J*= 7.7 Hz, 1H), 7.28 (t, *J*= 6.3 Hz, 2H), 7.11 (d, *J*= 7.7 Hz, 1H), 5.47 (d, *J*= 15.3 Hz, 1H), 5.12 (t, *J*= 6.8 Hz, 1H), 4.68-4.50 (m, 2H), 4.28 (d, *J*= 15.3 Hz, 1H), 3.79 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 139.0, 132.3 (q, J_{CF}= *34.4 Hz),* 131.9, 130.3, 129.7, 128.5, 127.9, 125.7, 124.9, 122.1, 121.3, 77.9, 59.8, 48.8, 37.3. ^{19}F (376 MHz): -62.8. IR (KBr disc): 2925, 2853, 1687, 1682, 1558, 1455, 1382, 1173, 1126, 758, 739 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{19}H_{14}F_6N_2O_3 + H]^+$: 433.0981; found: 433.1017.

2-(4-Nitrobenzyl)-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one 6e. Compound was obtained as a orange solid in 98% yield (50 mg). Mp 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J*= 8.8 Hz, 2H), 7.39-7.25 (m, 5H), 7.09 (d, *J*= 7.6 Hz, 1H), 5.47 (d, *J*=15.8 Hz, 1H), 5.10 (t, *J*= 6.7 Hz, 1H), 4.66-4.50 /m, 2H), 4.24 (d, *J*=15.8 Hz, 1H), 3.78 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 147.8, 143.7, 132.0, 130.4, 129.7, 128.6. 128.5,

127.9, 125.8, 124.3, 78.0, 59.6, 48.7, 37.3. IR (KBr disc): 2361, 1654, 1601, 1552, 1516, 1453, 1344, 732 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{15}N_3O_5 + H]^+$: 342.1084; found: 342.1097.

1-(Nitromethyl)-2-(prop-2-yn-1-yl)-1,2-dihydroisoquinolin-3(4H)-one 6f. Compound was obtained as a orange oil in 78% yield (28 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.20 (m, 4H), 5.46 (t, *J*= 6.7 Hz, 1H), 4.87 (dd, J_1= 6.7 Hz, J_2= 5.9 Hz, 1H), 4.63-4.55 (m, 2H), 4.28 (dd, J_1= 15.6 Hz, J_2= 2.2 Hz, 1H), 3.69 (s, 2H), 2.35 (t, *J*= 2.2 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 131.9, 130.6, 129.4, 128.3, 127.6, 126.1, 77.7, 74.0, 59.1, 37.1, 35.3. IR (KBr neat): 1652, 1553, 1451, 1265 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{13}H_{12}N_2O_3 + H]^+$: 245.0920; found: 245.0913.

2-Methyl-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one 6g. Compound was obtained as a yellow oil in 80% yield (26 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (m, 4H), 5.14 (t, *J*= 6.4 Hz, 1H), 4.69-4,50 (m, 2H), 3.65 (s, 2H), 3.13 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 132.3, 130.3, 129.3, 128.3, 127.5, 125.9, 78.0, 62.3, 36.8, 34.4. IR (KBr neat): 2361, 2342, 1654, 1555, 1449, 1400, 1379, 758 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{11}H_{12}N_2O_3 + H]^+$: 221.0920; found: 221.0924.

2-Butyl-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one 6h. Compound was obtained as a orange oil in 60% yield (23 mg).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.18 (m, 4H), 5.14 (t, *J*= 6.3 Hz, 1H), 4.66-4.61 (m, 1H), 4.51-4.46 (m, 1H), 4.11-4.03 (m, 1H), 3.65 (s, 2H), 2.97-2.90 (m, 1H), 1.60-1.51 (m, 2H), 1.30-1.25 (m, 2H), 0.92-0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 132.5, 131.0, 129.3, 128.3, 127.5, 125.9, 78.0, 59.9, 46.4, 37.4, 30.0, 20.2, 13.9. IR (KBr neat): 2958, 2928, 2360, 1652, 1635, 1562 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{14}H_{18}N_2O_3 + H]^+$: 263.1390; found: 263.1382.

2-Benzyl-6-methoxy-1-(nitromethyl)-1,2-dihydroisoquinolin-3(4H)-one 6aa. Prepared from compound **2b** (X= OCH_3 and X_1= H) following the same procedure reported above. Compound was obtained as a orange oil in 83% yield (41 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 6.96 (d, *J*= 9.1 Hz, 1H), 6.75-6.74 (m, 2H), 5.28 (d, *J*= 14.7 Hz, 1H), 4.48-4.38 (m, 2H), 4.56 (d, *J*= 14.7 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 160.2, 136.1, 133.7, 129.1, 128.0, 127.1, 122.8, 113.2, 78.6, 58.4, 55.5, 49.0, 37.6. IR (neat): 2920, 2362, 1666, 1640, 1458, 1252, 758 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{18}H_{18}N_2O_4 + H]^+$: 327.1339; found: 327.1352.

2-Benzyl-7-nitro-1-(nitromethyl)-1,4-dihydroisoquinolin-3(2H)-one 6ab. Prepared from compound **2c** (X= H and, X'= NO_2, 0.15 mmol) following the same procedure reported above. Compound was obtained as a orange oil in 62% yield (31 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, *J*= 8.2 Hz, 1H), 7.90 (s, 1H), 7.36 (d, *J*= 8.2 Hz, 1H), 7.27-7.25 (m, 3H), 7.16-7.14 (m, 2H), 5.22 (d, *J*= 15.1 Hz, 1H), 5.14-5.12 (m, 1H), 4.48 (s, 2H), 4.27 (d, *J*=

15.1 Hz, 1H), 3.81 (d, *J*= 18.2 Hz, 1H), 3.77 (d, *J*= 18.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 148.5, 141.1, 136.7, 133.6, 130.7, 130.6, 129.9, 129.5, 125.7, 122.6, 78.1, 59.3, 50.3, 38.7. IR (neat): 2362, 1670, 1552, 1457, 1251, 782 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{15}N_3O_5 + H]^+$: 342.1084; found: 342.1094.

2-Benzyl-7-bromo-1-(nitromethyl)-1,4-dihydroisoquinolin-3(2H)-one 6ac. Prepared from compound **2d** (X= H and, X′= Br, 0.15 mmol) following the same procedure reported above. Compound was obtained as an orange oil in 74% yield (41 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J*= 8.2 Hz, 1H), 7.34-7.32 (m, 3H), 7.27-7.21 (m, 3H), 7.12 (d, *J*= 8.2 Hz, 1H), 5.28 (d, *J*= 15.1 Hz, 1H), 5.06 (m, 1H), 4.50-4.45 (m, 2H), 4.28 (d, *J*= 15.1 Hz, 1H), 3.74 (d, *J*= 15.9 Hz, 1H), 3.65 *(d, J*= 15.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 135.7, 132.8, 132.4, 131.3, 129.8, 129.2, 128.8, 128.3, 128.1, 121.2, 77.9, 58.1, 48.9, 36.9. IR (neat): 2370, 1672, 1550, 1455, 1278, 742 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{15}BrN_2O_3 + H]^+$: 375.0339; found: 375.0367.

Dimethyl 2-(2-benzyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate 7a. Compound was obtained as a yellow oil in 65% yield (36 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.02 (m, 9H), 5.44 (d, *J*= 14.7 Hz, 1H), 5.19 (d, *J*= 8.8 Hz, 1H), 4.07 (d, *J*= 14.7 Hz, 1H), 3.81-3.73 (m, 6H), 3.50 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 168.9, 168.2, 137.7, 134.9, 134.1, 130.1, 130.0, 129.9, 129.1, 129.0, 128.8, 128.1, 127.3, 61.1, 58.2, 54.6, 54.1, 50.7, 39.5. IR (KBr neat): 2954, 2924, 2361, 1739, 1652, 1452, 1437 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{21}H_{21}NO_5 + H]^+$: 368.1492; found: 368.1468. Reaction was scaled up to 1 mmol of aldehyde **2a** and product was isolated in 84% yield.

Dimethyl 2-(2-(3,4-dichlorobenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate 7b. Compound was obtained as a yellow solid in 55% yield (36 mg). Mp 119−121 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.14 (m, 6H), 7.06 (d, *J= 7.3 Hz*, 1H), 6.93-6.91 (m, 1H), 5.33 (d, *J*= 15.4 *Hz*, 1H), 5.14 (d, *J*= 8.1 Hz, 1H), 4.07 (d, *J*= 15.4 Hz, 1H), 3.80-3.71 (m, 6H), 3.51 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 167.6, 166.8, 137.0, 133.3, 132.8, 132.5, 131.6, 130.7, 129.9, 128.8, 128.0, 127.1, 127.1, 126.0, 60.1, 57.0, 53.4, 52.9, 38.1. IR (KBr disc): 1748, 1661, 1473, 1433, 1399, 1147 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{21}H_{19}Cl_2NO_5 + H]^+$: 436.0713; found: 436.0725.

Dimethyl 2-(3-oxo-2-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate 7c. Compound was obtained as a yellow oil in 74% yield (35 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.16 (m, 4H), 5.51 (d, *J*= 7.9 Hz, 1H), 4.76 (dd, J_1= 14.9 Hz, J_2= 2.4 Hz, 1H), 3.97 (dd, J_1= 14.9 Hz, J_2= 2.4 Hz, 1H), 3.84-3.65 (m, 6H), 3.52 (s, 3H), 2.20 (t, *J*= 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 167.5, 166.9, 133.1, 132.6, 128.7, 127.9, 126.9, 126.2, 78.3, 72.6, 60.1, 57.1, 53.4, 52.9, 37.9, 36.2. IR (KBr neat): 2361, 2237, 1734, 1662, 1449, 1437, 1157 cm^{-1}. HRMS (MALDI-FT ICR)**:** *m/z* calcd. for $[C_{17}H_{17}NO_5 + H]^+$: 316.1179; found: 316.1181.

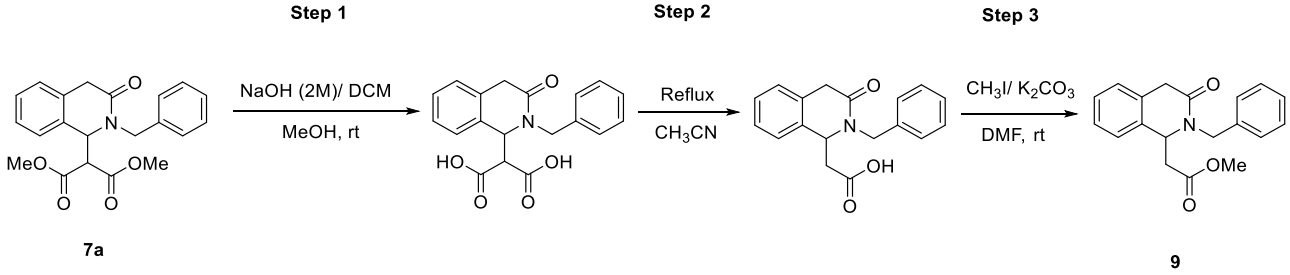
Dimethyl 2-(3-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate 7d. Compound was obtained as a yellow oil in 73% yield (34 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.16 (m, 4H), 5.19 (d, *J*= 9.1 Hz, 1H), 4.08-3.99 (m, 1H), 3.78-3.62 (m, 6H), 3.54 (s, 3H), 2.87-2.77 (m, 1H), 1.56-144 (m, 2H), 0.77 (t, *J*= 7.2 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 167.5, 167.0, 133.9, 133.2, 128.6, 127.9, 126.8, 126.0, 61.0, 56.8, 53.4, 52.8, 48.9, 38.3, 21.0, 11.3. IR (KBr neat): 2960, 1733, 1658, 1652, 1436, 1280, 757 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{21}NO_5 + H]^+$: 320.1492; found: 320.1495.

Dimethyl 2-(2-benzyl-7-nitro-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate 7aa. Prepared from compound **2c** (X= H and, X'= NO_2, 0.15 mmol). Compound was obtained as a yellow oil in 48% yield (29 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J_1= 8.4, J_2= 2.2 Hz, 1H), 8.01 (d, *J*= 1.9 Hz, 1H), 7.43 (d, *J*= 8.4 Hz, 1H), 7.40-7.31 (m, 3H), 7.20-7.18 (m, 2H), 5.50 (d, *J*= 15.0 Hz, 1H), 5.36 (*J*= 7.6 Hz, 1H), 4.16 (d, *J*= 15.0 Hz, 1H), 3.92-3.86 (m, 6H), 3.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 167.1, 166.5, 146.8, 140.4, 135.8, 134.7, 128.9, 128.8, 127.9, 127.8, 123.7, 121.3, 58.9, 56.3, 53.6, 53.1, 49.3, 39.1. IR (KBr neat): 2954, 2924, 2361, 1739, 1652,1545, 1452, 1437, 757 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{21}H_{20}N_2O_7 + H]^+$: 413.1343; found: 413.1367.

Synthesis of 1-(aminomethyl)-2-benzyl-1,2-dihydroisoquinolin-3(4H)-one 8

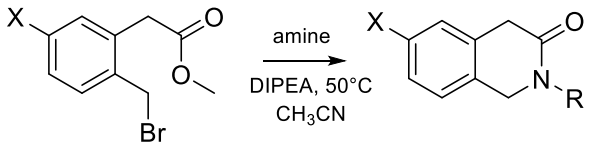
To a solution of nitro compound **6a** (0.18 mmol) in MeOH (1.20 mL), Zinc (0.72 mmol) and 37% hydrochloric acid (227 µL) were added at 0°C (ice bath). The mixture was stirred for 25 min and then basified with 2N NaOH, filtered and extracted with ethyl acetate. The organic layers were dried, the solvent removed under reduced pressure and purified by chromatography on silica (Chloroform/MeOH, 9:1) affording the corresponding reduction product 8. Compound was obtained as a yellow oil in 56% yield (27 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.19 (m, 8H), 7.07 (d, *J= 6.8 Hz*, 1H), 5.39 (d, *J= 15.1 Hz*, 1H), 4.33-4.25 (m, 2H), 3.77 (d, *J= 19.5 Hz*, 1H), 3.67 (d, *J= 19.5 Hz*, 1H), 2.98 (d, *J= 4.3 Hz*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 137.0, 133.5, 132.6, 128.8, 128.0, 127.8, 127.6, 126.7, 126.2, 77.4, 63.2, 48.6, 45.7, 37.4. IR (KBr neat): 2926, 1652, 1634, 1452, 750 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{17}H_{18}N_2O + H]^+$: 267.1491; found: 267.1519.

Synthesis of methyl 2-(2-benzyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl) acetate 9.



Step 1. In a round bottom flask, the dimethyl ester **7a** (0.21 mmol) was dissolved in DCM (1.0 mL) and a a solution of 2M NaOH in methanol (1.0 mL) wad added dropwise. The mixture was stirred overnight, then the solvent was removed and the residue was taken up with ethyl acetate and acidified with 6M HCl The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The resulting organic layer was dried with Na_2SO_4 and the solvent removed under reduced pressure affording the crude starting material for the next step. **Step 2**. Compound obtained from Step 1 (0.21 mmol) was solubilized in CH_3CN (1.0 mL) and the mixture was refluxed (oil bath) overnight. The solvent was removed under reduced pressure and the resulting decarboxylated compound was used for the next step without further purification. **Step 3.** Compound obtained from Step 2 (0.11 mmol), was stirred in DMF (1.0 mL) with K_2CO_3 (0.07 mmol) and methyl iodide (0.12 mmol) for 2h. Then the mixture was diluted with ethyl acetate and washed with water and with brine. The organic layer was dried with Na_2SO_4 and the solvent removed under reduced pressure; purification of the crude by chromatography on silica gel (Hexane/Ethyl acetate, 1:1) affording the final product **9.** Compound was obtained as a yellow oil in 52% yield (33 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.18 (m, 8H), 7.06 (d, *J*= 7.*7 Hz*, 1H), 5.30 (d, *J*= 14.7 *Hz*, 1H), 4.84 (dd, J_1= 5.34 *Hz*, J_2= 2.5 *Hz* 1H), 4.24 (d, *J*= 14.7 *Hz*, 1H), 3.74 (d, *J*= 3.3 *Hz,* 2H), 3.61 (s, 3H), 2.79-2.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.7, 136.7, 134.8, 132.0, 128.9, 128.2, 127.9, 127.8, 127.7, 126.9, 125.6, 57.8, 52.1, 48.6, 40.1, 37.5. IR (KBr neat): 2954, 2926, 1734, 1642, 1452, 1437 cm^{-1}. HRMS (MALDI-FT ICR): *m/z* calcd. for $[C_{19}H_{19}NO_3 + H]^+$: 310.1437; found: 310.1466.

General procedure for Sn2/lactamization reaction



1 **5**

To a solution of methyl 2-(2-(bromomethyl)phenyl)acetate **1a** (X= H, 30 mg, 0.125 mmol) in acetonitrile (0.6 mL) was added an equimolar amount of DIPEA (22 µl) and RNH_2 (0.125 mmol) and the mixture was stirred for 24h at 50°C (oil bath) in the dark and under nitrogen atmosphere. The solvent was removed in vacuo and the resulting product **5** was purified by silica gel chromatography (Ethyl acetate/Hexane, from 1:9 to 4:6).

2-Benzyl-1,4-dihydroisoquinolin-3(2H)-one 5a. Compound was isolated as a yellow oil in 80% yield (24 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.14 (m, 8H), 7.07 (d, *J*= 6.9 Hz, 1H), 4.76 (s, 2H), 4.38 (s, 2H), 3.71 (s, 2H). HRMS (ESI) *m/z*: calcd. for $[C_{16}H_{15}NO + H]^+$: 238.1226; found: 238.1228. Mp, IR and the spectral data were found in agreement with reported in the literature.[10] Reaction was scaled up to 1 mmol of bromide **1a** and product was isolated in 78% yield.

2-(2-Methoxybenzyl)-1,4-dihydroisoquinolin-3(2H)-one 5b. Compound was isolated as a yellow oil in 76% yield (25 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.12 (m, 5H), 7.10 (d, *J*=7.3 Hz, 1H), 6.89 (d, *J*=7.3 Hz, 2H), 4.79 (s, 2H), 4.45 (s, 2H), 3.85 (s, 3H), 3.69 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 157.5, 132.4, 131.6, 129.0, 128.5, 127.4, 127.2, 126.5, 125.1, 124.6, 120.7, 110.3, 55.3, 50.7, 44.8, 37.5. IR (neat): 1651, 1610, 1513, 1485, 1458, 1440 cm-^{1}. HRMS (MALDI-FT ICR) *m/z*: calcd. for $[C_{17}H_{17}NO_2 +H]^+$: 268.1339; found: 268.1332.

2-(3,5-(Trifluoromethyl)benzyl)-1,4-dihydroisoquinolin-3(2H)-one 5c. Compound was isolated as a yellow solid in 75% yield (35 mg). M.p. 104-106 °C.^{1}H NMR (400 MHz, $CDCl_3$): δ7.80 (s, 1H), 7.72 (s, 2H), 7.28-7.19 (m, 3H), 7.11 (d, *J*= 6.9 Hz, 1H), 4.86 (s, 2H), 4.44 (s, 2H), 3.74 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 139.5, 132.1 (q, J_{CF} = 32.8 Hz), 131.8, 130.5, 128.1, 128.0, 127.8, 127.4, 126.8, 125.1, 124.5, 121.7 (q, J_{CF} = 3.6 Hz), 50.8, 49.5, 37.3. ^{19}F (376 MHz): -62.8. IR (KBr disc): 1649, 1638, 1619, 1485, 1461, 1438, 1420, 1411 cm-^{1}. HRMS (MALDI-FT ICR) *m/z*: calcd. for $[C_{18}H_{13}F_6NO +H]^+$: 374.0974; found: 374.0980.

2-(4-Nitrobenzyl)-1,4-dihydroisoquinolin-3(2H)-one 5d. Purification by silica gel chromatography (Ethyl acetate/Hexane 3/7). Compound was isolated as a yellow solid in 85% yield (30 mg). M.p. 154-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J*= 8.1 Hz, 2H), 7.43 (d, *J*= 8.1 Hz, 2H), 7.33-7.1 (m, 3H), 7.10 (d, *J*= 7.8 Hz, 1H), 4.85 (s, 2H), 4.44 (s, 2H), 3.74 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 147.5, 144.4, 132.0, 130.8, 128.6, 127.7, 127.5, 126.9, 125.2, 124.1, 50.8, 49.7, 37.4. IR (KBr disc): 1648, 1635, 1620, 1550, 1487, 1460, 1411, 1350 cm^{-1}. HRMS (MALDI-FT ICR) *m/z*: calcd. for $[C_{16}H_{14}N_2O_3 +H]^+$: 283.1077; found: 283.1076.

2-(3,4-Dichlorobenzyl)-1,4-dihydroisoquinolin-3(2H)-one 5e. Compound was isolated as a yellow oil in 72% yield (27 mg). M.p. 91-93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.29-7.14 (m, 3H), 7.10 (t, *J*=6.7 Hz, 2H), 4.68 (s, 2H), 4.38 (s, 2H), 3.70 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 137.0, 132.8, 131.9, 131.7, 130.7, 129.9, 127.7, 127.3, 126.7, 125.2, 50.4, 49.0, 37.3. IR (KBr disc): 1650, 1472, 1447, 1380, 1090 cm^{-1}. HRMS (MALDI-FT ICR) *m/z*: calcd. for $[C_{16}H_{16}Cl_2NO +H]^+$: 306.0447; found: 306.0462.

(*S*)-2-(1-Phenylethyl)-1,4-dihydroisoquinolin-3(2H)-one 5f. Reaction was performed at 80°C. Compound was isolated as a white solid in 70% yield (22 mg). $[\alpha]^{D}_{20}$: -99. 8 (c 1, $CHCl_3$). M.p. 79-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.07 (m, 8H), 7.01 (d, *J*= 7.2 Hz, 1H), 6.15 (q, *J*= 7.0 Hz, 1H), 4.25 (d, *J*= 15.4 Hz, 1H), 3.98 (d, *J* = 15.4 Hz, 1H), 3.68 (s, 2H), 1.56 (d, *J*= 7.0 Hz). HRMS (ESI) *m/z*: calcd. for $[C_{17}H_{17}NO +H]^+$: 252.1383; found: 252.1383. IR and the spectral data were in agreement with those reported in the literature for racemate.[10b]

(*S*)-Methyl 2-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)propanoate 5g. Reaction was performed at 80°C. *L*-alanine methyl ester hydrochloride was used and 2 equivalents of DIPEA (44 µl). Purification by chromatography (Ethyl acetate/Hexane 3/7). Compound was isolated as an oil in 72% yield (21 mg). $[\alpha]^{D}_{20}$: -24.2 (c 1.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.14 (m, 4H), 5.37 (q, *J*= 7.3 Hz, 1H), 4.46 (m, 2H), 3.71

(s, 3H), 3.66 (s, 2H), 1.48 (d, *J*= 7.3 Hz, 3H). HRMS (ESI) *m/z*: calcd. for $[C_{13}H_{15}NO_3 + H]^+$: 234.1125; found, 234.1124. IR and the spectral data were found in agreement with those reported in the literature.[10b]

***Tert*-butyl 2-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate 5h.** Glycine tert-butyl ester hydrochloride was used and 2 equivalents of DIPEA (44 µl). Purification by column chromatography (Ethyl acetate/Hexane 3/7). Compound was isolated as awhite solid in 85% yield (27 mg). M.p. 87-89 °C.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.12 (m, 4H), 4.55 (m, 2H), 4.21 (s, 3H), 3.68 (br s, 2H), 1.49 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 168.2, 132.2, 131.4, 131.7, 127.7, 127.4, 126.7, 125.2, 82.2, 52.1, 49.2, 37.3, 28.2. IR (KBr disc): 1748, 1650, 1487, 1460, 1418, 1411 cm^{-1}. HRMS (MALDI-FT ICR) *m/z*: calcd. for $[C_{15}H_{19}NO_3$ +Na]: 284.1274; found: 284.1257.

2-(Propyl)-1,4-dihydroisoquinolin-3(2H)-one 5i.[10c] Compound was isolated as a liquid in 84% yield (20 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.10 (m, 4H), 4.46 (s, 2H), 3.60 (s, 2H), 3.48 (t, *J*= 7.3 Hz, 2H), 1.63 (q, *J*= 7.3 Hz, 2H), 0.92 (t, *J*= 7.3 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ168.9, 132.7, 131.7, 127.6, 127.3, 126.6, 125.1, 50.9, 48.6, 37.7, 20.7, 11.4. IR (neat): 1712, 1664, 1605, 1355, 1247, 740, 685 cm^{-1}. HRMS (ESI) *m/z*: calcd. for $[C_{12}H_{15}NO$ +H$]^+$: 190.1226; found: 190.1227.

2-(Butyl)-1,4-dihydroisoquinolin-3(2H)-one 5j. Compound was isolated as a liquid in 70% yield (18 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.17 (m, 4H), 4.47 (s, 2H), 3.61 (s, 2H), 3.52 (t, *J*= 7.5 Hz, 2H), 1.59 (quin, *J*= 7.5 Hz, 2H), 1.34 (sext, *J*= 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). HRMS (ESI) *m/z*: calcd. for $[C_{13}H_{17}NO + H]^+$: 204.1383; found: 204.13834. IR and the spectral data were found in agreement with those reported in the literature.[10d]

2-(Methyl)-1,4-dihydroisoquinolin-3(2H)-one 5k. Compound was isolated as a white solid in 72% yield (15 mg).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.12 (m, 4H), 4.48 (s, 2H) 3.63 (s, 2H), 3.12 (s, 3H). IR (KBr disc): 1714, 1661, 1350, 1246, 742, 685 cm^{-1}. HRMS (ESI) *m/z*: calcd. for $[C_{10}H_{11}NO$ +H$]^+$: 162.0913; found: 162.0914. Mp, IR and the spectral data were found in agreement with those reported in the literature.[11]

2-(Prop-2-yn-1-yl)-1,4-dihydroisoquinolin-3(2H)-one 5l. Compound was isolated as an oil in 86% yield (19 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.14 (m, 4H), 4.61 (s, 2H), 4.39 (s, 2H), 3.64 (s, 2H), 2.26 (s, 1H). HRMS (ESI) *m/z*: calcd. for $[C_{12}H_{11}NO$+ Na$]^+$: 208.0733; found, 208.0732. IR and the spectral data were found in agreement with those reported in the literature.[10b]

2-Benzyl-6-nitro-1,4-dihydroisoquinolin-3(2H)-one 5aa. Prepared from compound **1d** (X= NO_2) following the same procedure reported above. Compound was isolated as an oil in 76% yield (28 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 2H), 7.34-7.24 (m, 6H), 4.77 (s, 2H), 4.47 (s, 2H), 3.81 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 147.5, 138.4, 136.2, 134.2, 128.9, 128.2, 127.9, 126.5, 122.5, 122.0, 50.1, 49.9, 37.2. IR (neat): 1656, 1553, 1451, 1379, 1260, 758, 732 cm-^{1}. HRMS (MALDI-FT ICR) *m/z*: calcd. for $[C_{16}H_{14}N_2O_3$ +H$]^+$: 283.1077; found: 283.1069.

2-Benzyl-6-chloro-1,4-dihydroisoquinolin-3(2H)-one 5ab. Prepared from compound **1c** (X= Cl) following the same procedure reported above. Compound was isolated as an oil in 86% yield (29 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 7.19-7.16 (m, 2H), 7.01 (d, *J*= 8.3 Hz, 1H), 4.75 (s, 2H), 4.35 (s, 2H), 3.68 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 136.5, 134.1, 133.4, 129.7, 128.8, 128.0, 127.8, 127.3, 126.9, 126.6, 50.1, 49.7, 37.2. IR (KBr neat): 1671, 1367, 789, 711 cm-^{1}. HRMS (MALDI-FT ICR) *m/z*: calcd. for $[C_{16}H_{14}ClNO + H]^+$: 272.0837; found: 272.0856.

2-Propyl-6-nitro-1,4-dihydroisoquinolin-3(2H)-one 5ia. Prepared from compound **1d** (X= NO_2) following the same procedure reported above. Compound was isolated as an oil in 90% yield (25 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J*= 7.6 Hz, 1H), 8.05 (s, 1H), 7.37 (d, *J*= 7.6 Hz, 1H), 4.56 (s, 2H), 3.71 (s, 2H), 3.50 (t, (t, *J*= 7.8 Hz, 2H), 1.64 (q, *J*= 7.8 Hz, 2H), 0.93 (t, *J*= 7.8 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 147.5, 138.6, 134.6, 126.4, 122.4, 121.8, 50.6, 48.6, 37.4, 20.6, 11.2. IR (KBr neat): 1674, 1550, 1452, 1381, 750, 713 cm-^{1}. HRMS (MALDI-FT ICR) *m/z*: calcd. for $[C_{12}H_{14}N_2O_3 + H]^+$: 235.1077; found: 235.1069.

References

1. Fink, Brian; Cheng Libing et al. Imidazopyridazine useful as kinase inhibithors. WO **2010**/042699 Al.

2. Jed M Burns, Elizabeth H Krenske and Ross Peter McGeary. Aromatic Claisen Rearrangements of Benzyl Ketene Acetals: Conversion of Benzylic Alcohols to (ortho-Tolyl) Acetates. *Eur. J. Org. Chem*. **2017**, *2*, 252-256.

3. a. Sébastien, Albrechta; Albert, Defoina; Emmanuel, Salomona; Céline, Tarnusa; Anders, Wetterholmb; Jasper Z. Haeggströmb. Synthesis and structure activity relationships of novel non-peptidic metallo-aminopeptidase inhibitors. Bioorganic Medicinal Chemistry **2006**, *14*, 7241-7257. b) Wen Zhou, Yan-Xue Zhang, Xiao-Di Nie, Chang-Mei Si, Xun Sun, and Bang-Guo Wei. Approach to Chiral 1-Substituted Isoquinolone and 3-Substituted Isoindolin-1-one by Addition−Cyclization Process. *J. Org. Chem.* **2018**, *83*, 9879−9889.

4. Natsuko Kagawa, Antoinette E. Nibbs, and Viresh H. Rawal. One-Carbon Homologation of Primary Alcohols to Carboxylic Acids, Esters, and Amides via Mitsunobu Reactions with MAC Reagents. *Org. Lett*. **2016,** *1*8, 10, 2363–2366.

5. Chianelli, Donatella; Cow, Christopher; He, Yun et at. Compositions and methods for modulating C-KIT and PDGFR receptors. WO **2008**/051757 Al.

6. William P. Griffith, Jenny M. Jolliffe, Steven V. Ley, Karsten F. Springhorn, Peter D. Tiffin. Oxidation of Activated Halides to Aldehydes and Ketones by *N*-Methylmorpholine-N-oxide. *Synthetic Communications* **1992**, 22, 1967-1971.

7. Nathan Kornblum, Willard J. Jones, and George J. Anderson. A new and selective method of oxidation. The conversion of alkyl halide and alkyl tosylate to aldehydes. *J. Am. Chem. Soc*. **1959**, *81*, 4113–4114.

8. Anna Kowalkowska, Andrzej Jończyk. Sigmatropic Rearrangement of Ammonium Ylides—Key Step in the Synthesis of Methyl 2-Formylphenyl Acetate. *Synthetic Communications* **2011**, *41*, 3308-3317.

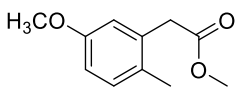
9. Jianyi Shi, Xia Chen, Jingyun Huang, a Yantong Lu, Zhendong Yang, Mingli Zhong, Zhongzhi Zhu and Xiuwen Chen. Direct Synthesis of Disubstituted 3-Isoquinolinone Derivatives through the Construction of C–N, C=O, and C(sp2)–C(sp3) Bonds under Transition-Metal-Free Conditions. *Eur. J. Org. Chem*. **2022**, e202201231.

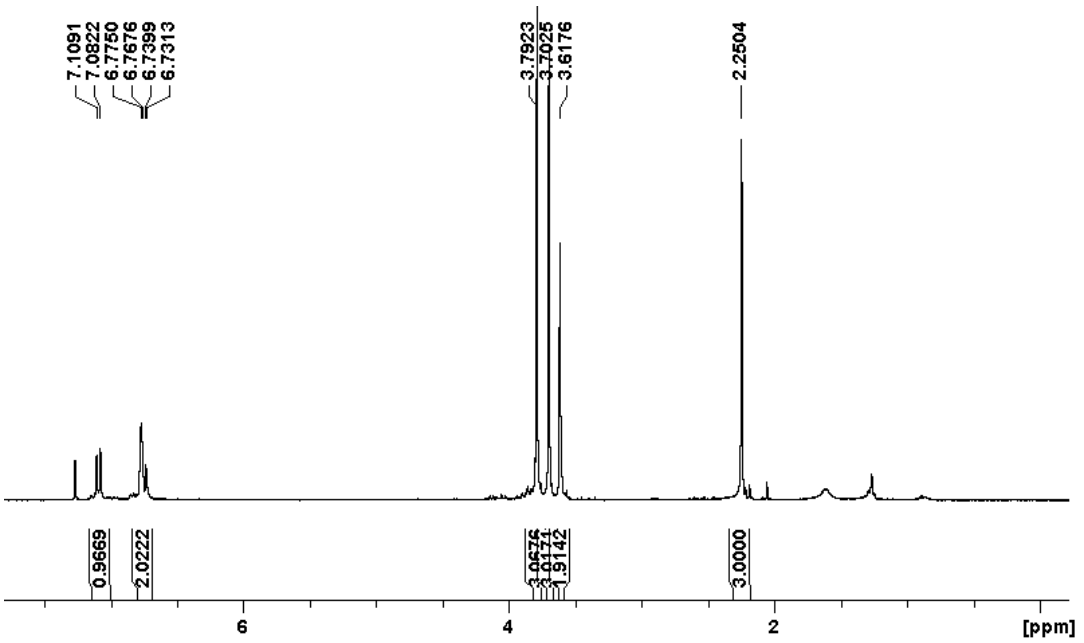
10. a) Bouaucheau, C.; Parlier, A.; Rudler, H. Aminocarbene Complexes of Chromium. 8. Access to the Pyrroloindole and Pyrrolochinoline Frameworks and Synthesis of Substituted Lycoranes. *J. Org. Chem*. **1997**, *62*, 7247−7259. b) Michael J. O' Sullivan, Richard J.D. Hatley, Christopher R. Wellaway, Sean P. Bew, Christopher J. Richards. Synthetic approaches to N- and 4-substituted 1,4-

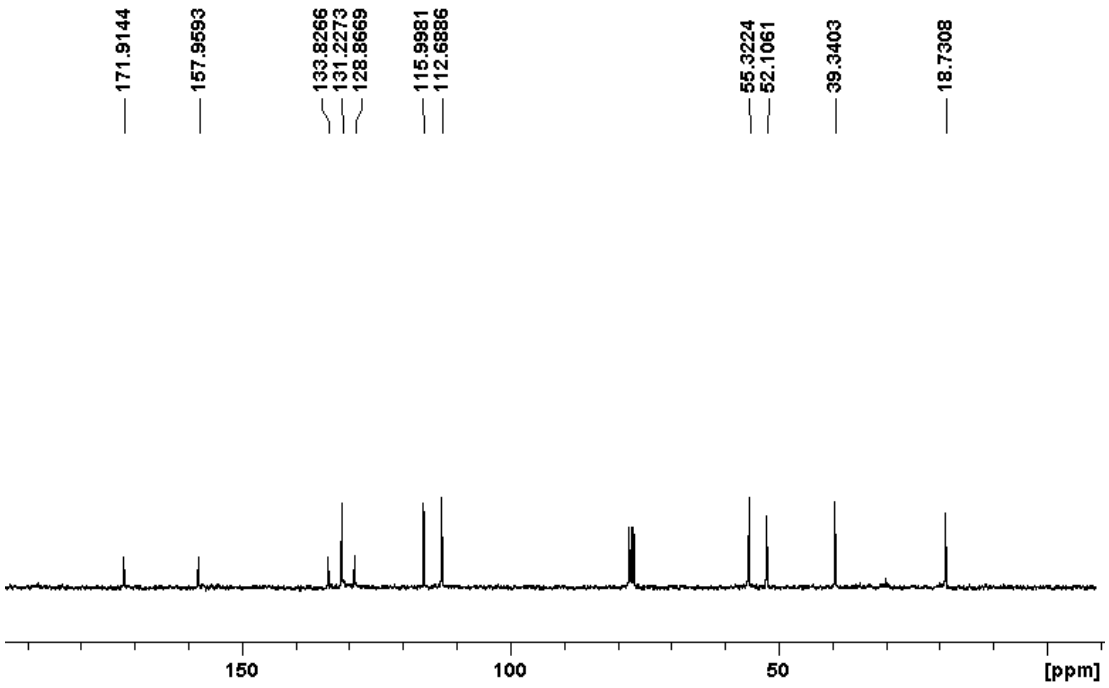
dihydro-3(2H)-isoquinolinone derivatives. *Tetrahedron* **2021**, 100, 132455. c). Chen-Yu Cheng, Hui-Bing Tsai, Mei Shan Lin. Synthetic approaches to 2-substituted 1-oxo- and 3-oxotetrahydroisoquinolines. *J. Heterocyclic chemistry* **1995**, *32*, 73-77. d) Kicheol Kim and Soon Hyeok Hong. Iridium-Catalyzed Single-Step N-Substituted Lactam Synthesis from Lactones and Amines. *J. Org. Chem*. **2015**, *80*, 4152−4156.

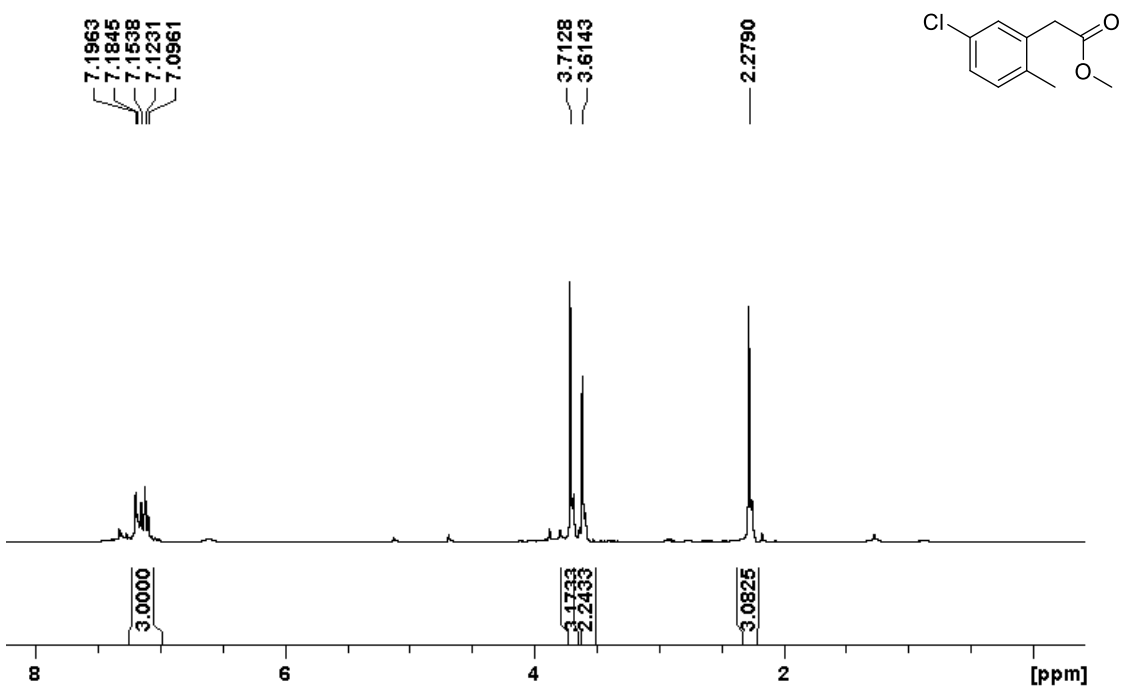
11. Li Yingxian, Chen Wei, Zhao Linchun, Zhang Ji-Quan, Zhao Yonglong, Li Chun, Guo Bing, Tang Lei, Yang Yuan-Yong. Catalytic N-methyl Amidation of Carboxylic Acids under Cooperative Conditions. *RSC Adv*. **2022**, 12, 20550-20554.

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





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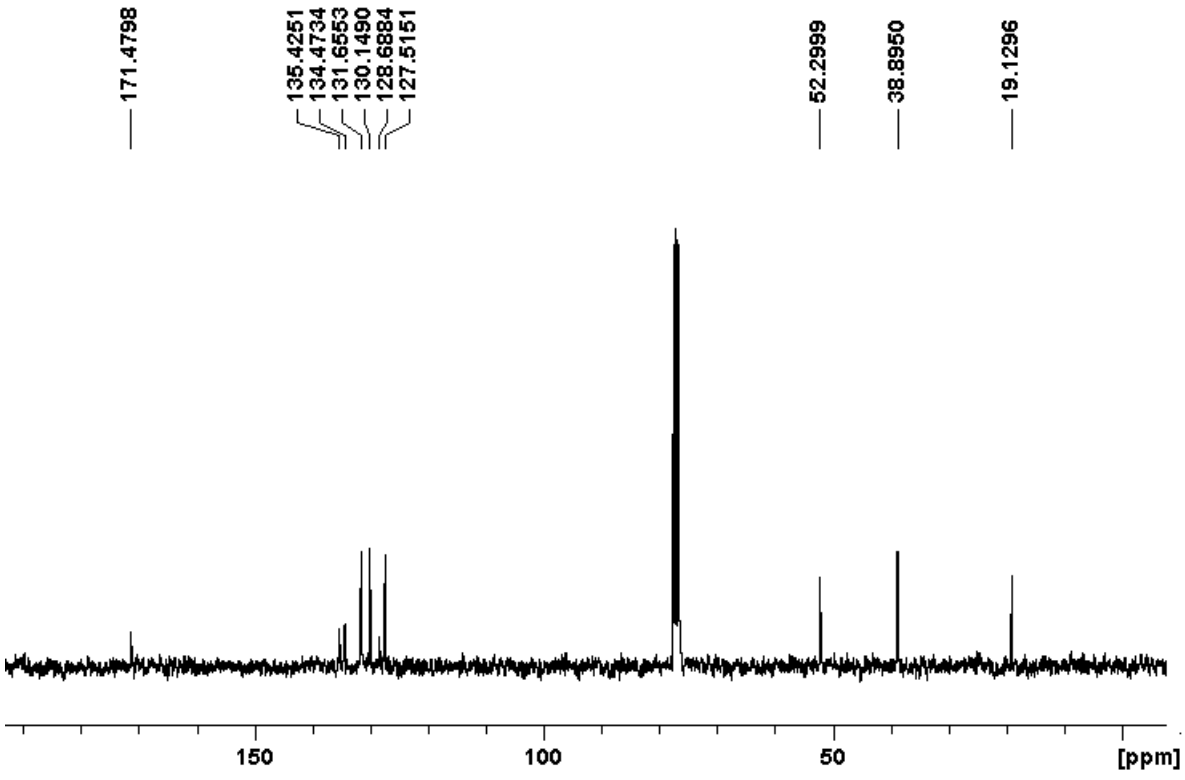
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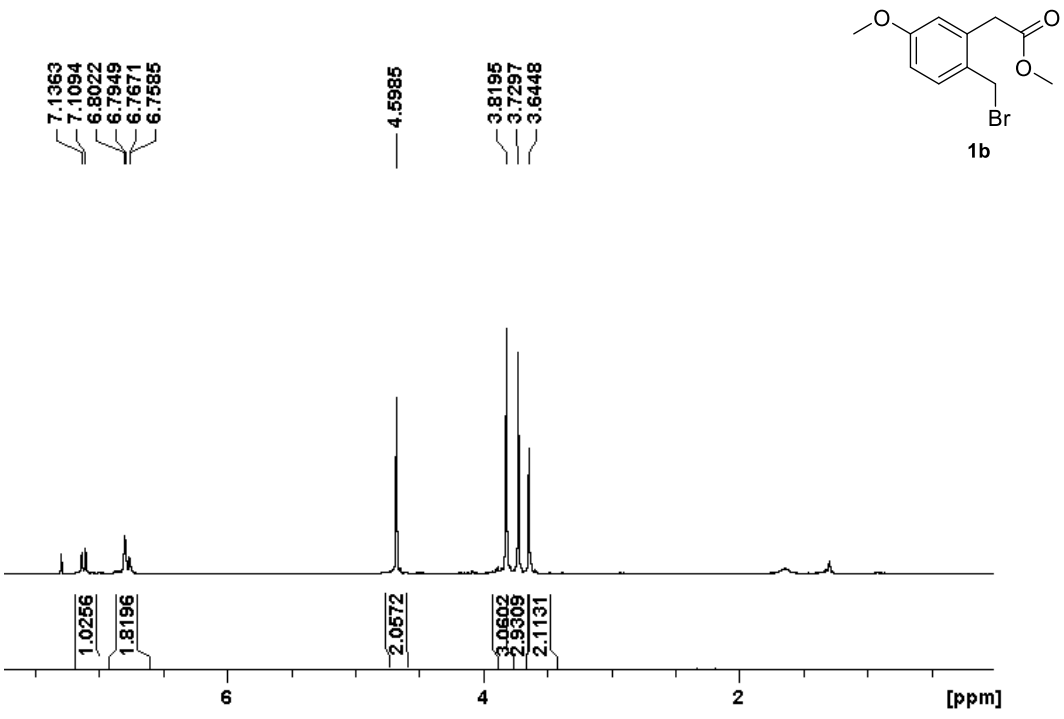
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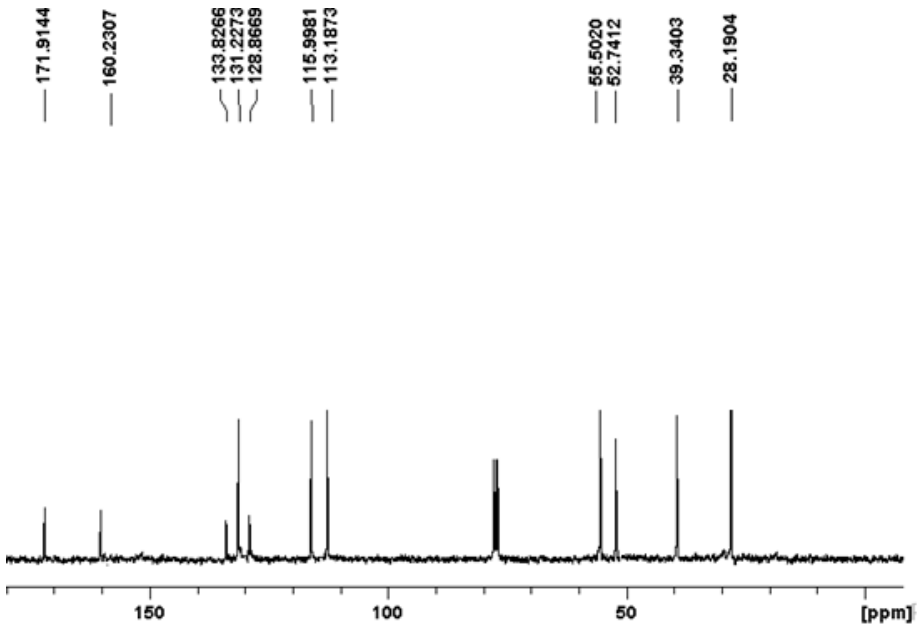
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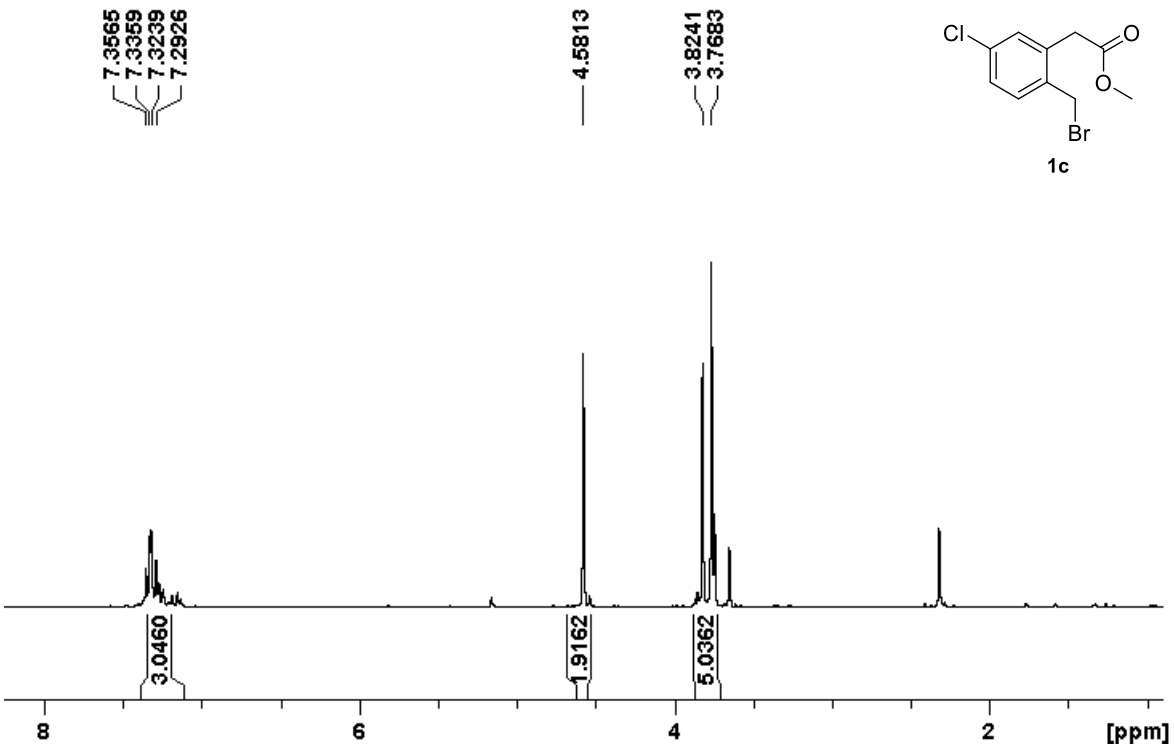
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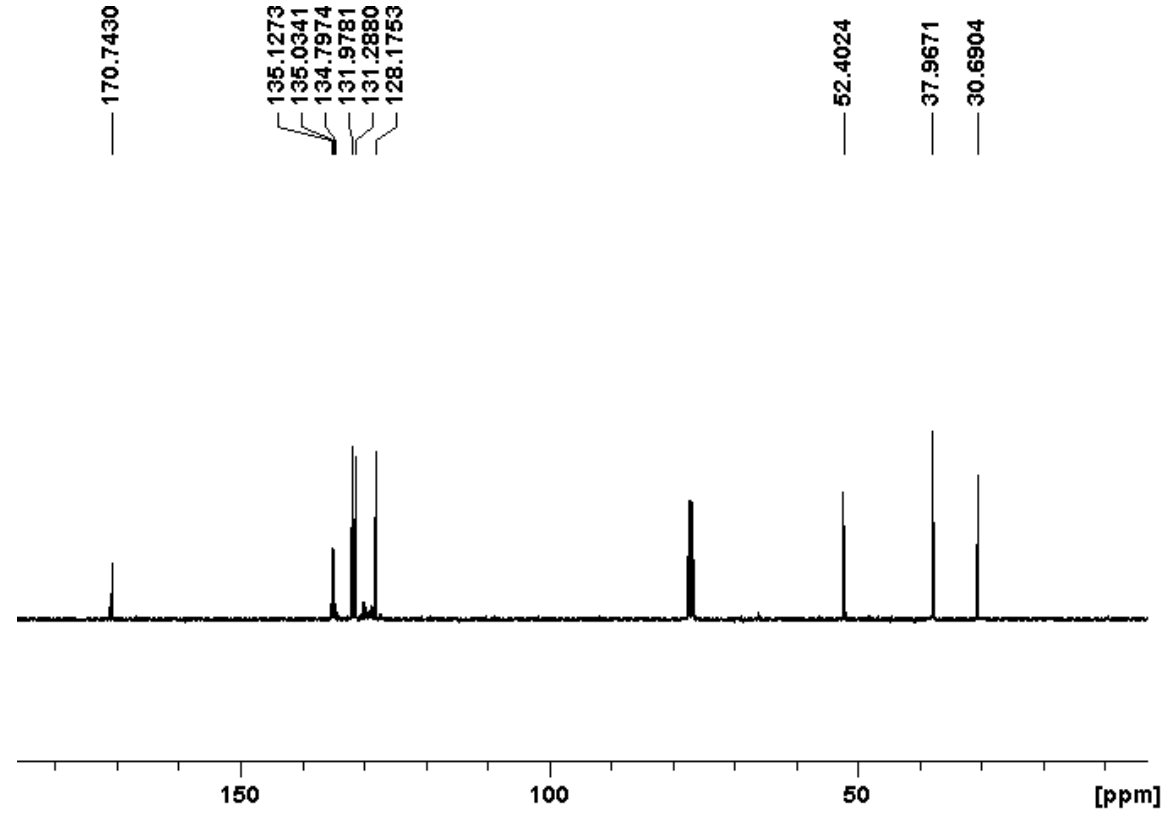
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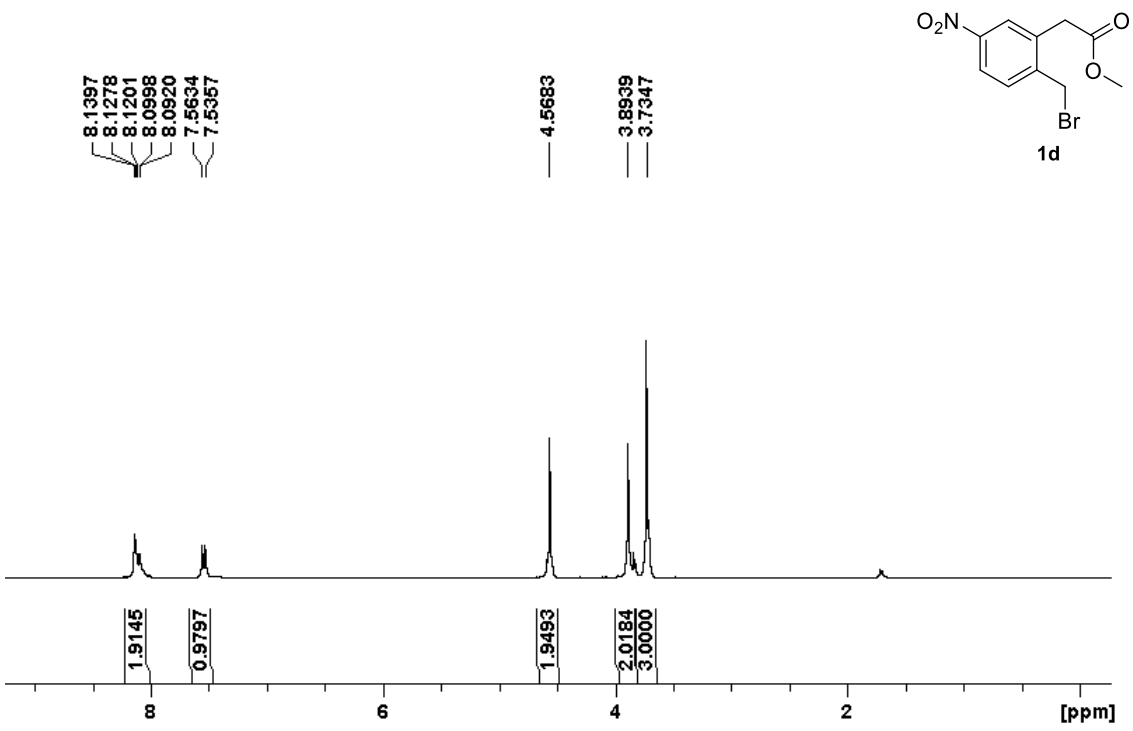
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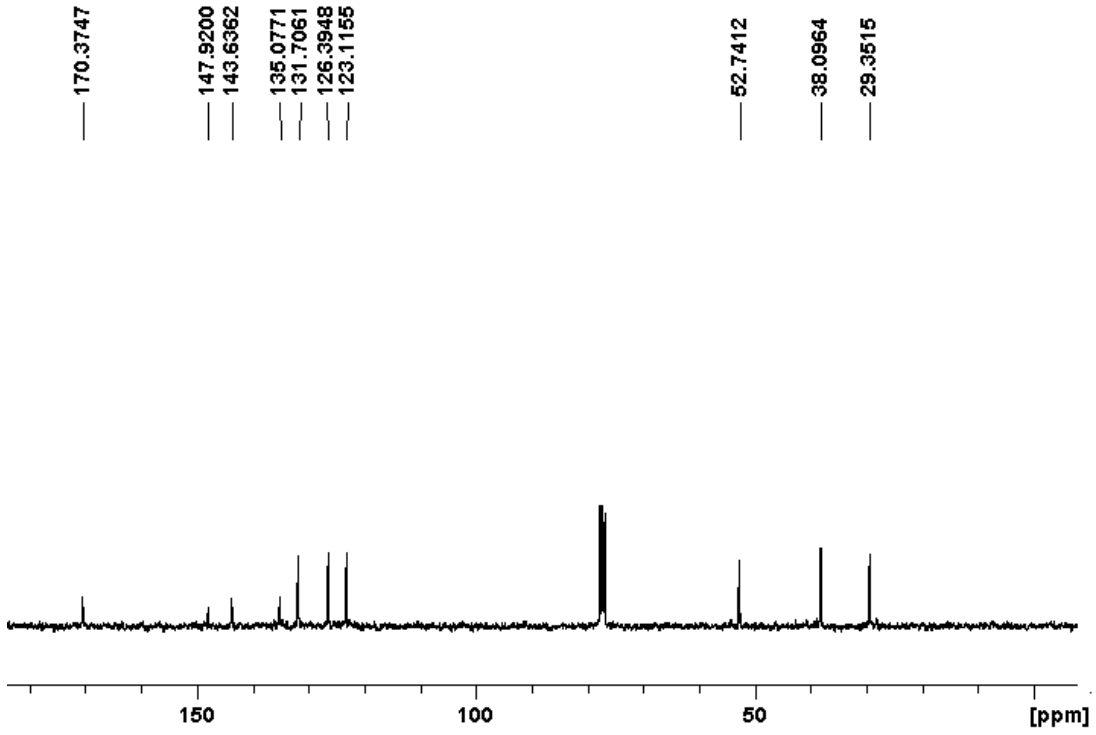
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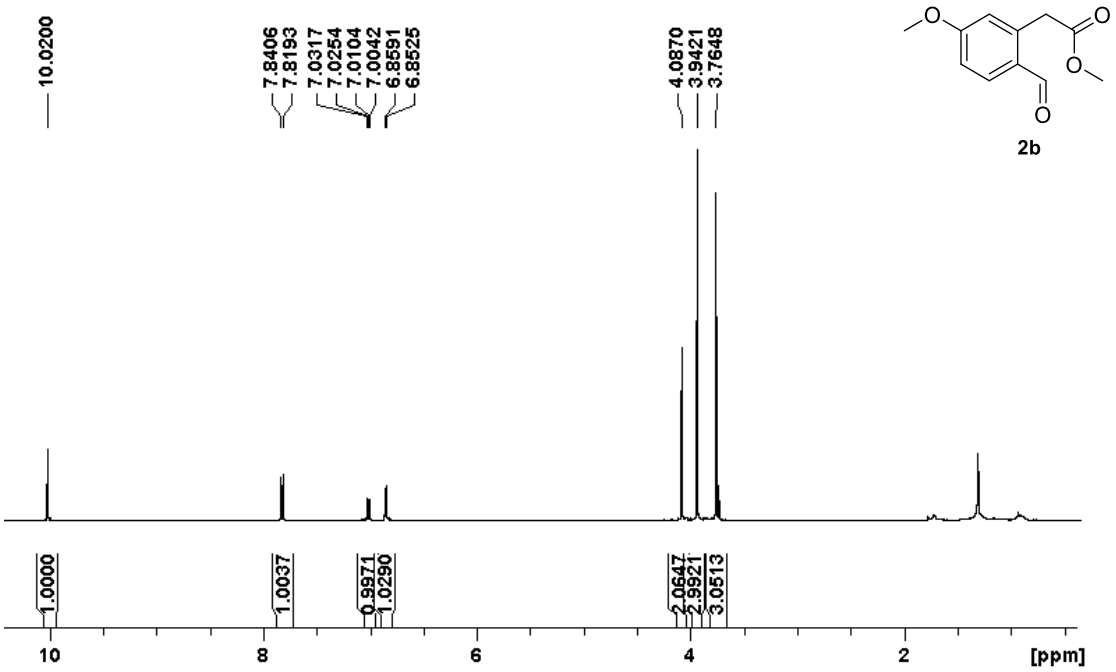
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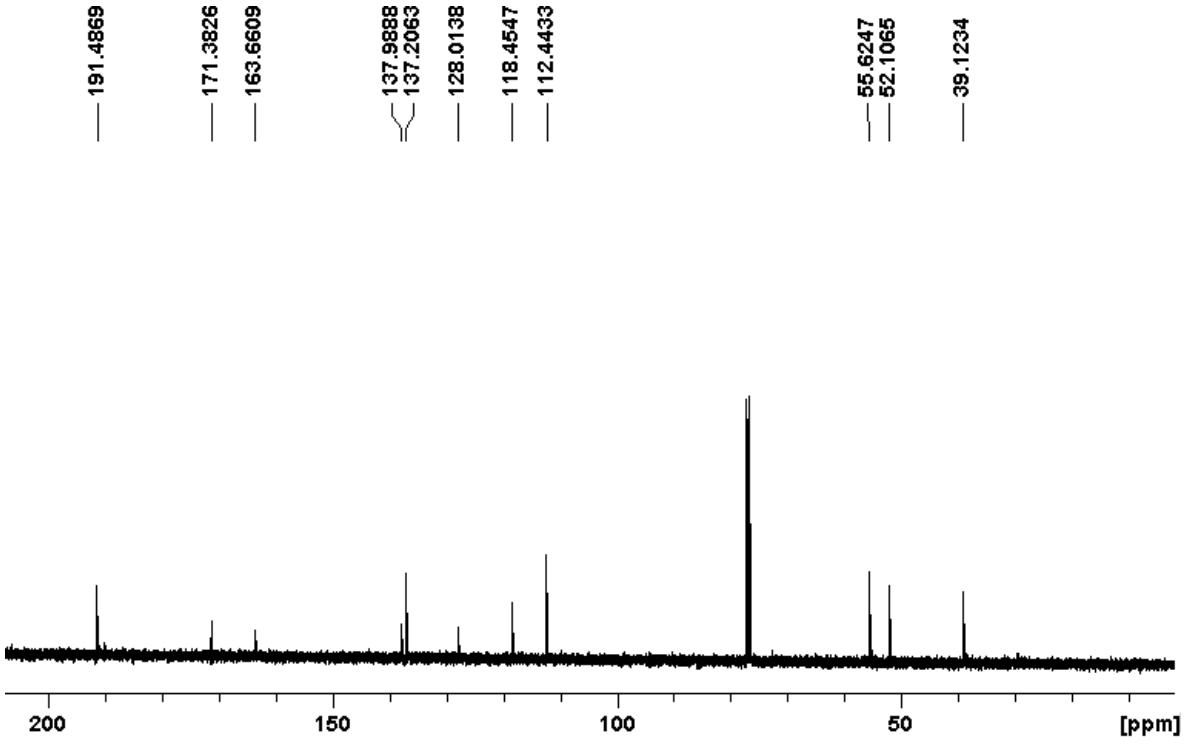
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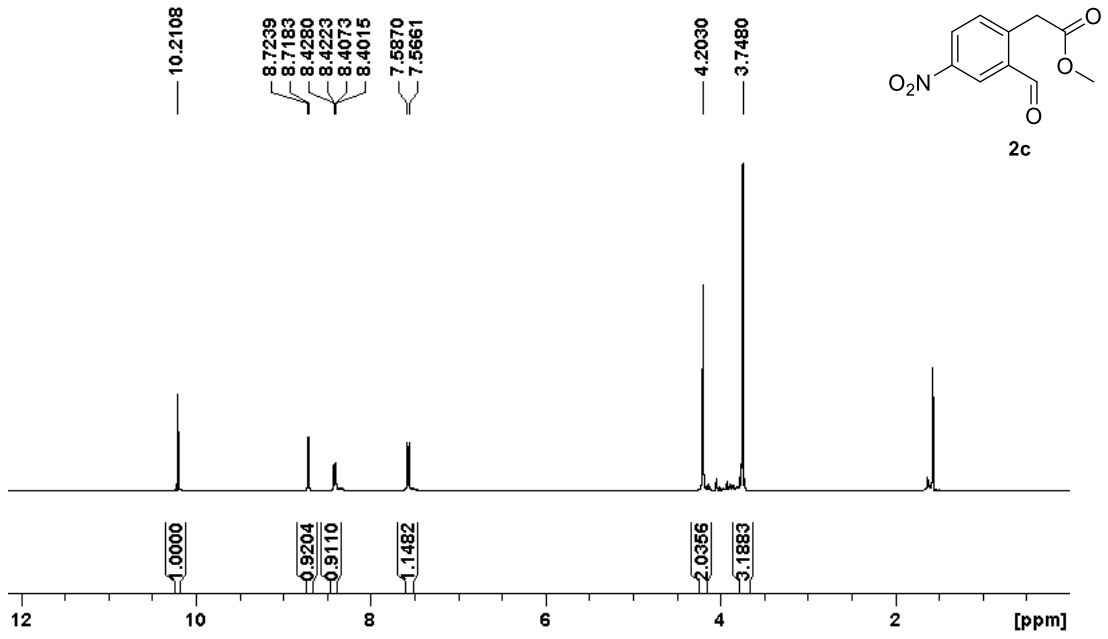
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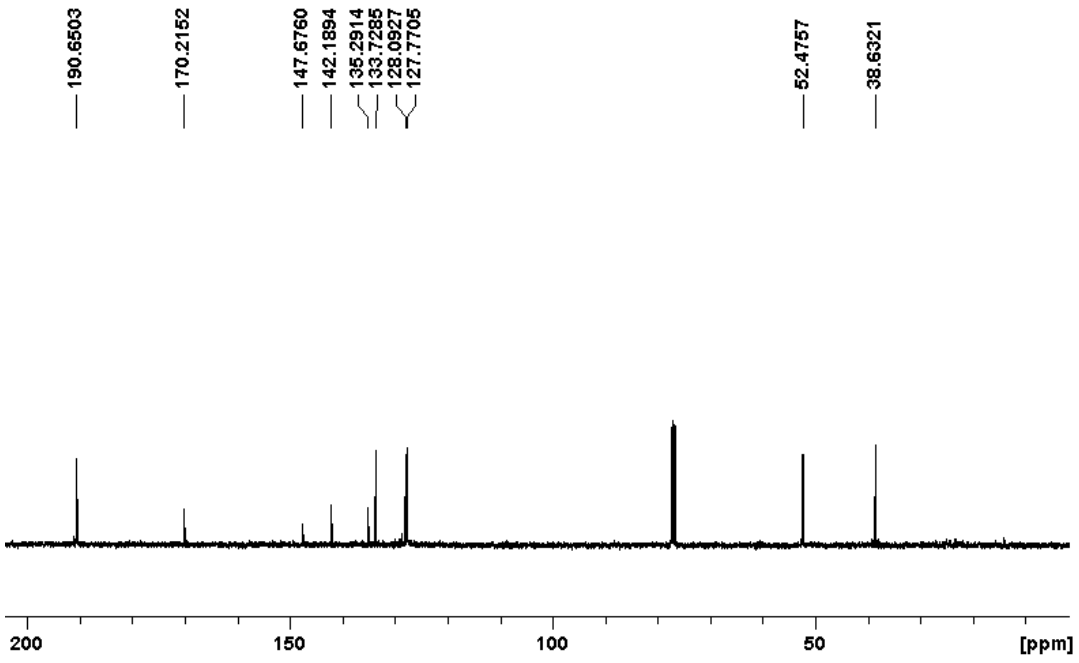
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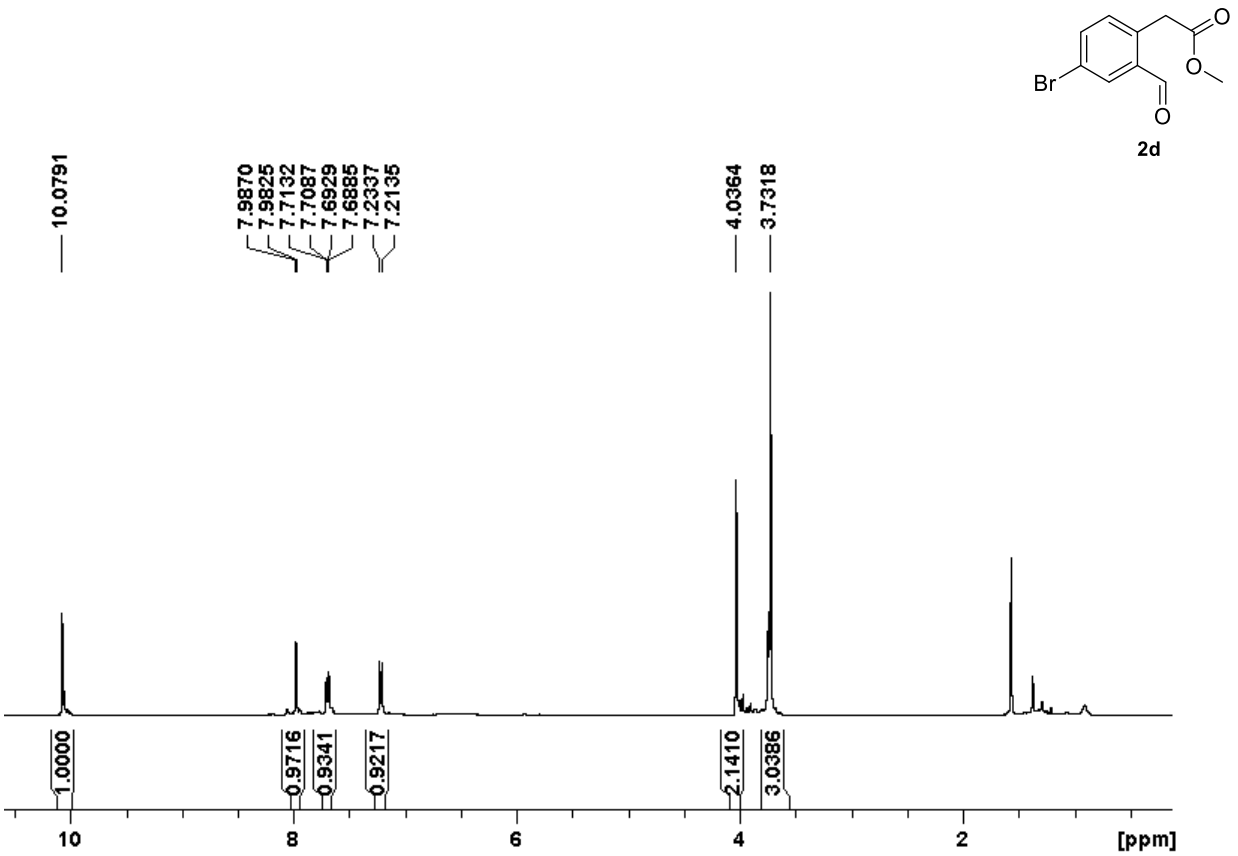
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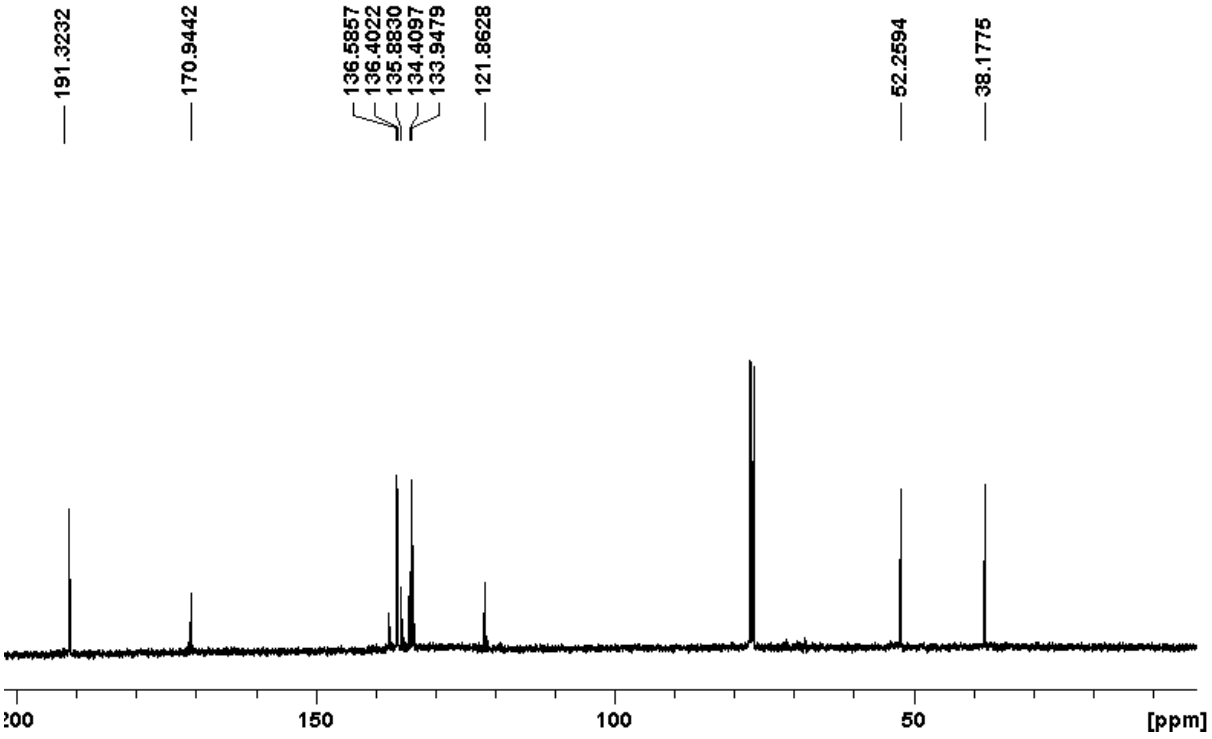
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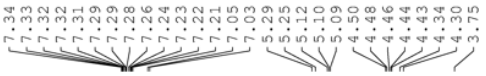
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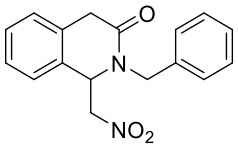
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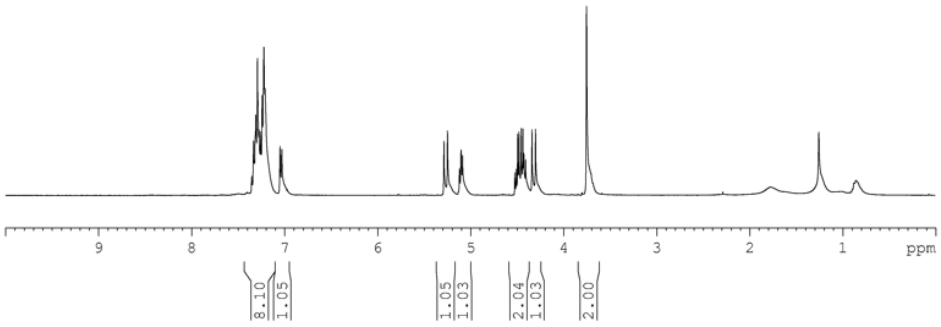
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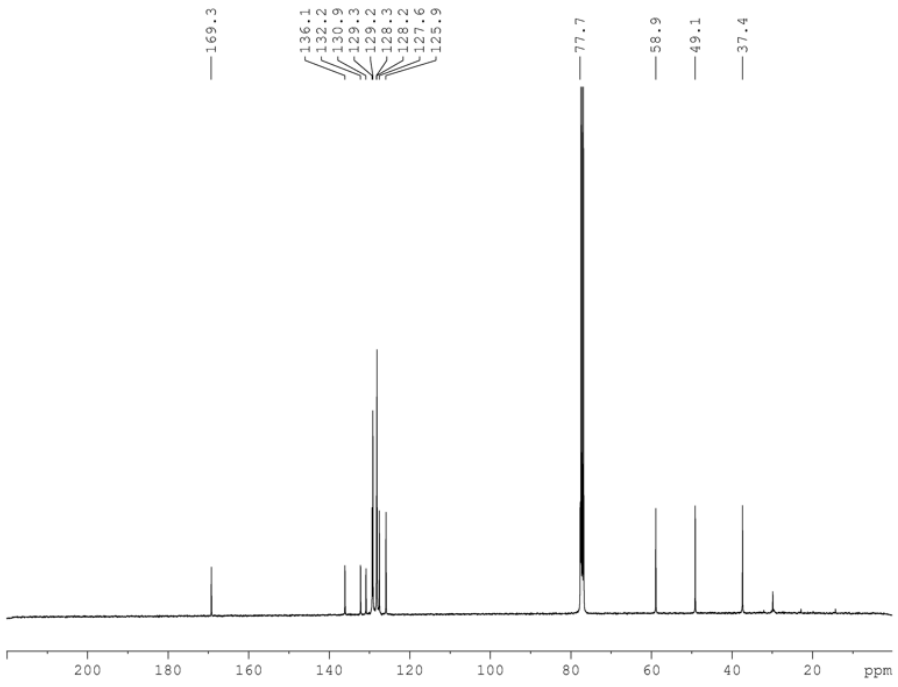
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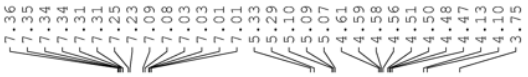
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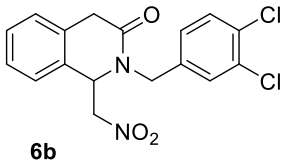
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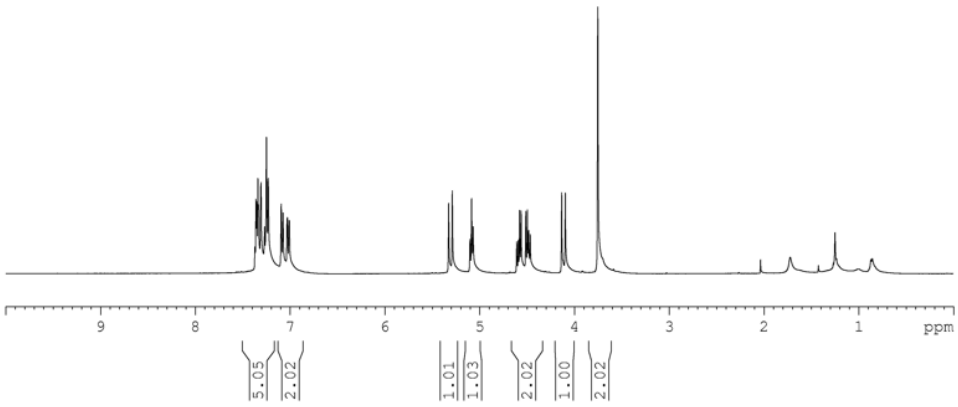
N
Cl
Cl
NO2

6b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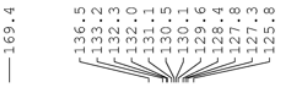
1.01
1.03
2.02
1.00
2.02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133.2
132.3
132.0
131.1
130.5
130.1
129.6
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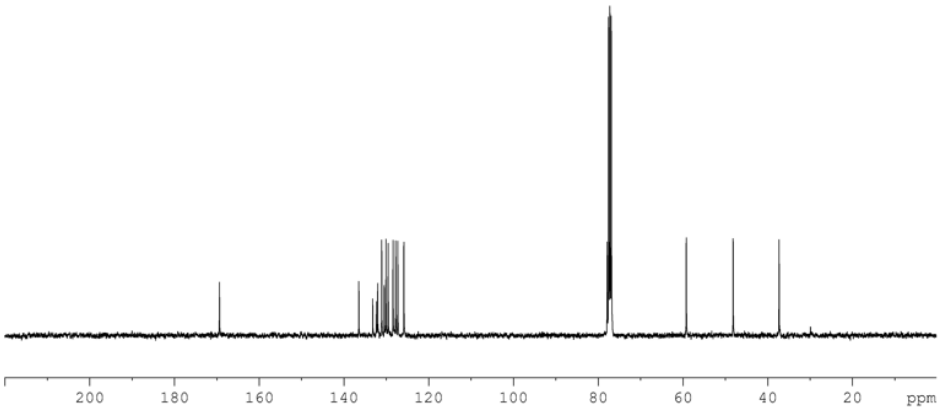
127.8
127.3
125.8
77.9
59.2
48.1
37.3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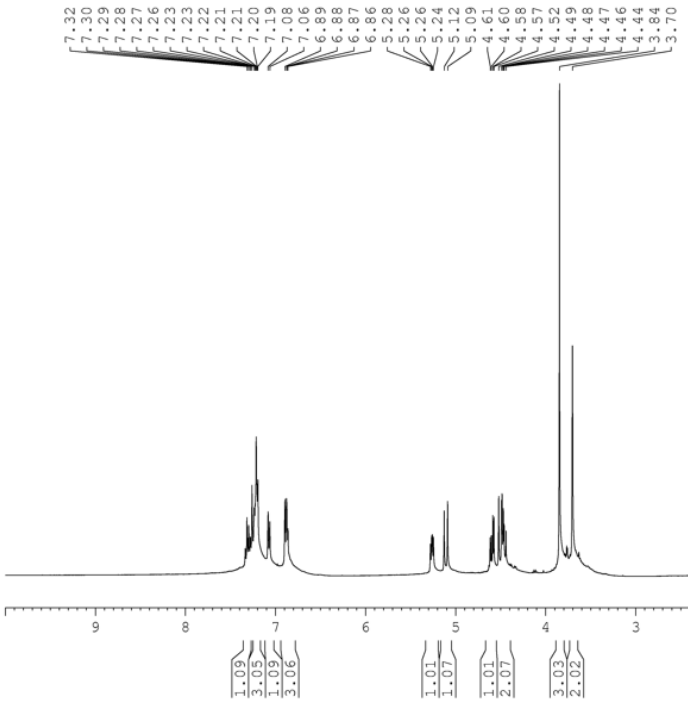
160
140
120
100
80
60
40
20
ppm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7.29
7.28
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7.26
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7.23
7.22
7.21
7.21
7.20
7.19
7.08
7.06
6.89
6.88
6.87
6.86
5.28
5.26
5.26
5.24
5.12
5.09
4.61
4.60
4.58
4.57
4.52
4.49
4.48
4.47
4.46
4.44
3.84
3.70
O
N
OMe
NO2
9
8
7
6
5
4
3
2
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ppm
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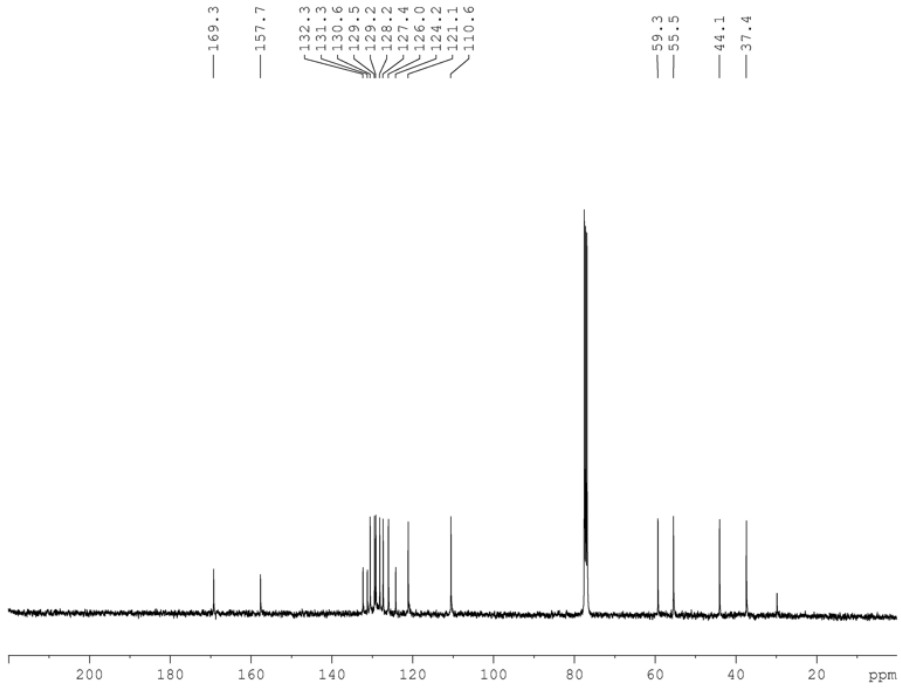
1.09
3.06
1.01
1.07
1.01
2.07
3.03
2.02

6c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132.3
131.3
130.6
129.5
129.2
128.2
127.4
126.0
124.2
121.1
110.6
59.3
55.5
44.1
37.4
200
180
160
140
120
100
80
60
40
20
ppm


7.78
7.60
7.40
7.38
7.36
7.30
7.28
7.26
7.13
7.10
5.50
5.44
5.14
5.12
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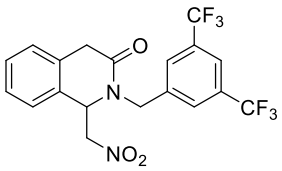
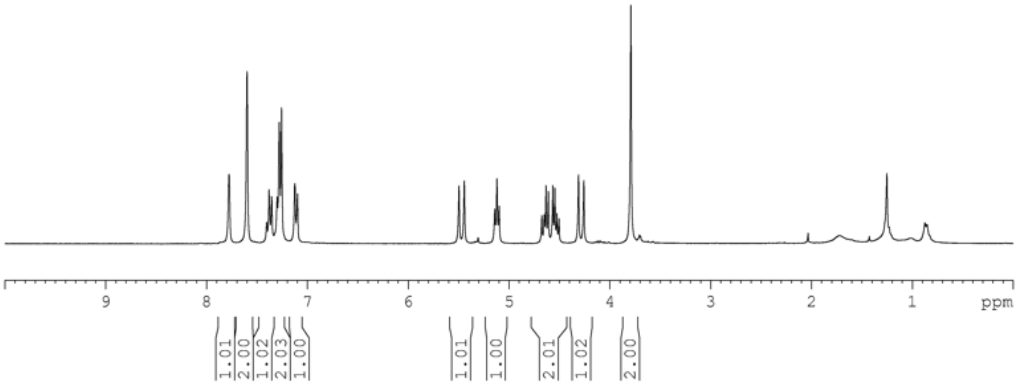
4.55
4.53
4.50
4.31
4.26
3.79


CF3
O
N
CF3
NO2

6d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8
7
6
5
4
3
2
1
ppm
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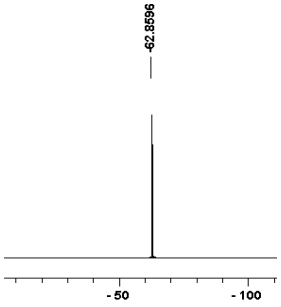
2.00
1.02
2.03
1.00
1.01
1.00
2.01
1.02
2.00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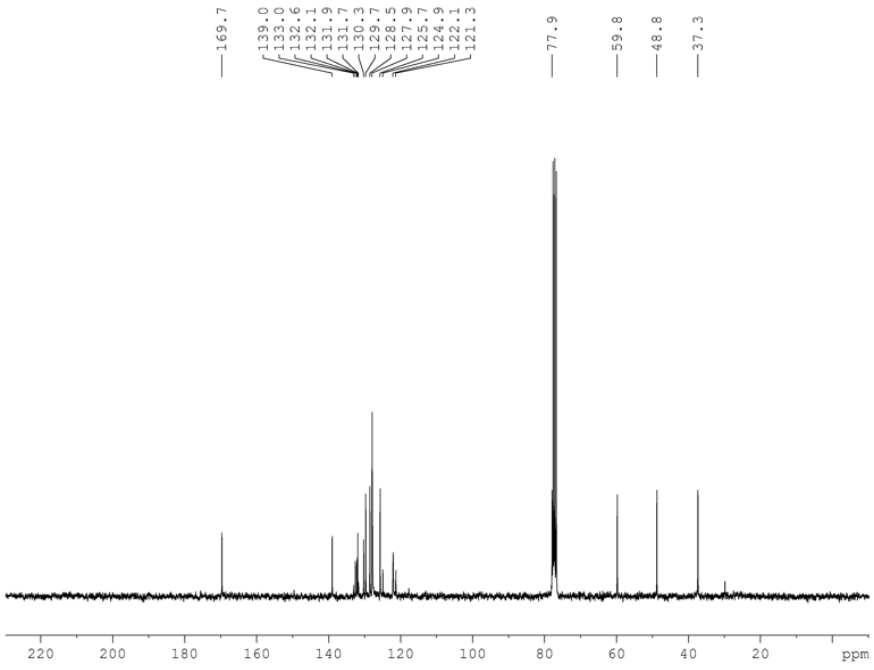
-50
-100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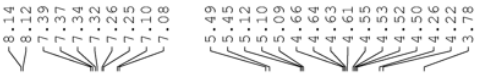
133.0
132.6
132.1
131.9
131.7
130.3
129.7
128.5
127.9
125.7
124.9
122.1
121.3
77.9
59.8
48.8
37.3
220
200
180
160
140
120
100
80
60
40
20
ppm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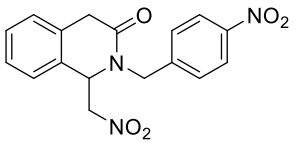
8.12
7.39
7.37
7.34
7.32
7.26
7.25
7.10
7.08
5.49
5.45
5.12
5.10
5.09
4.66
4.64
4.63
4.61
4.55
4.53
4.52
4.50
4.26
4.22
3.78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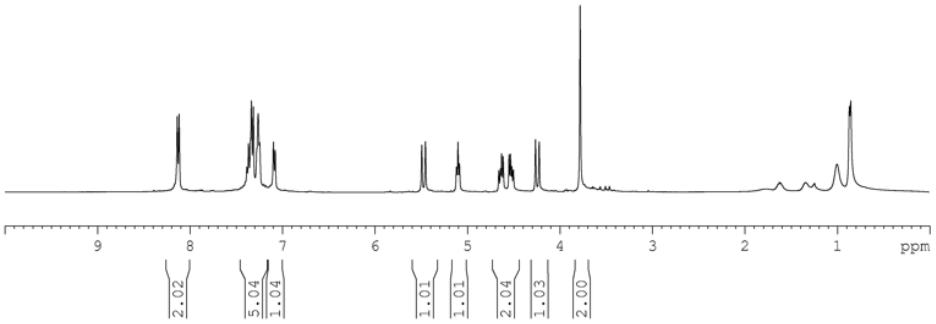
N
NO2
NO2

6e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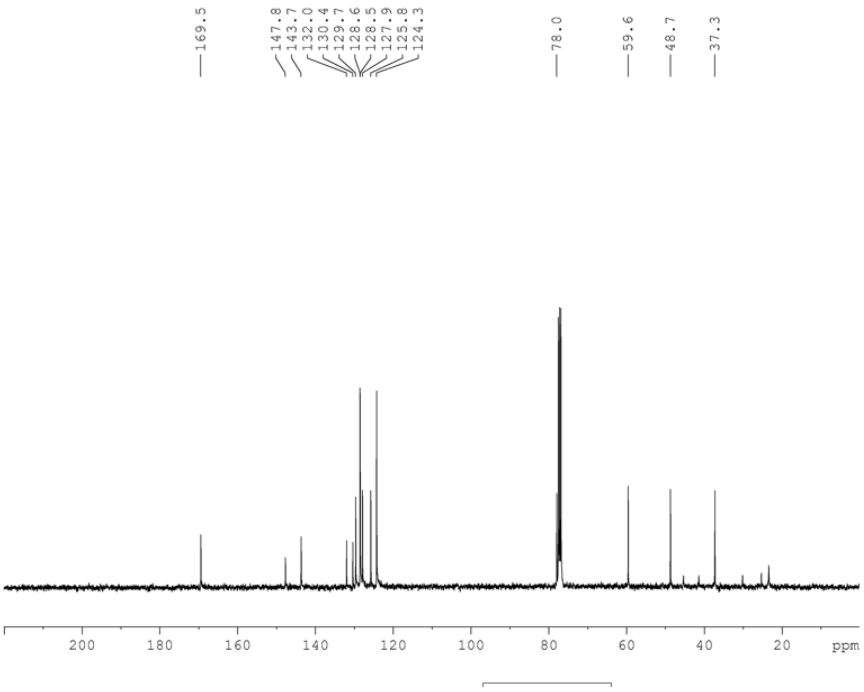
8
7
6
5
4
3
2
1
ppm
2.02
5.04
1.04
1.01
1.01
2.04
1.03
2.00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147.8
143.7
132.0
130.4
129.7
128.6
128.5
127.9
125.8
124.3
78.0
59.6
48.7
37.3
200
180
160
140
120
100
80
60
40
20
ppm


7.37
7.35
7.32
7.31
7.29
7.26
7.24
7.22
7.20
5.48
5.46
5.44
4.91
4.89
4.87
4.85
4.63
4.62
4.61
4.59
4.57
4.57
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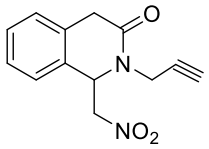
4.25
4.25
3.69
2.35
2.35
2.34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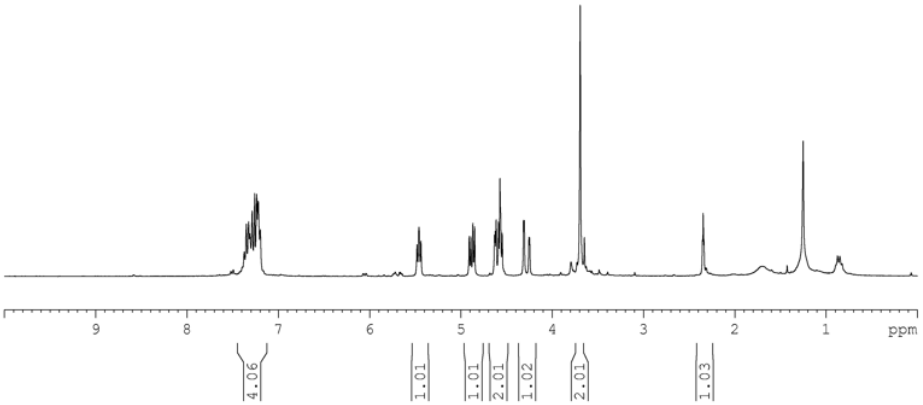
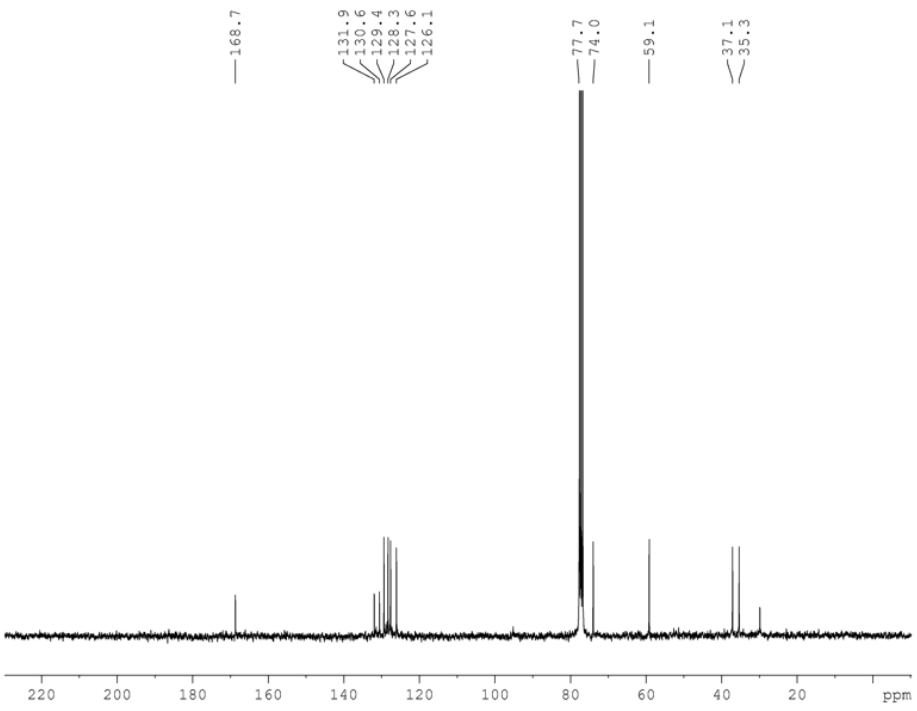
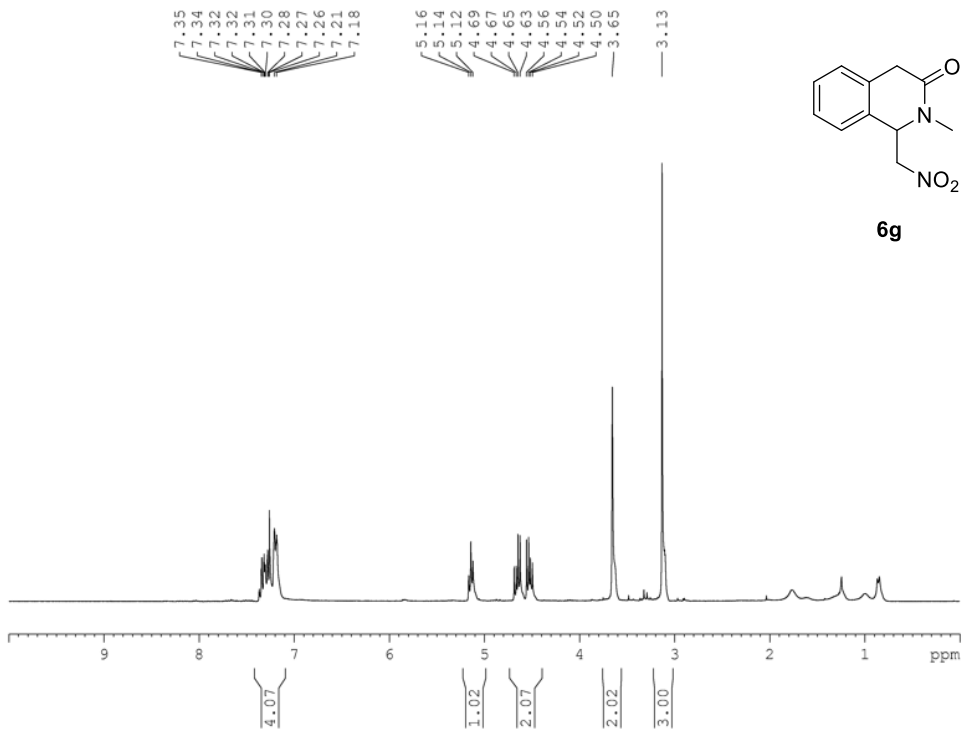
NO2

6f


9
8
7
6
5
4
3
2
1
ppm
4.06
1.01
1.01
2.01
1.02
2.01
1.03


168.7
131.9
130.6
129.4
128.3
127.6
126.1
77.7
74.0
59.1
37.1
35.3
220
200
180
160
140
120
100
80
60
40
20
ppm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7.27
7.26
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7.18
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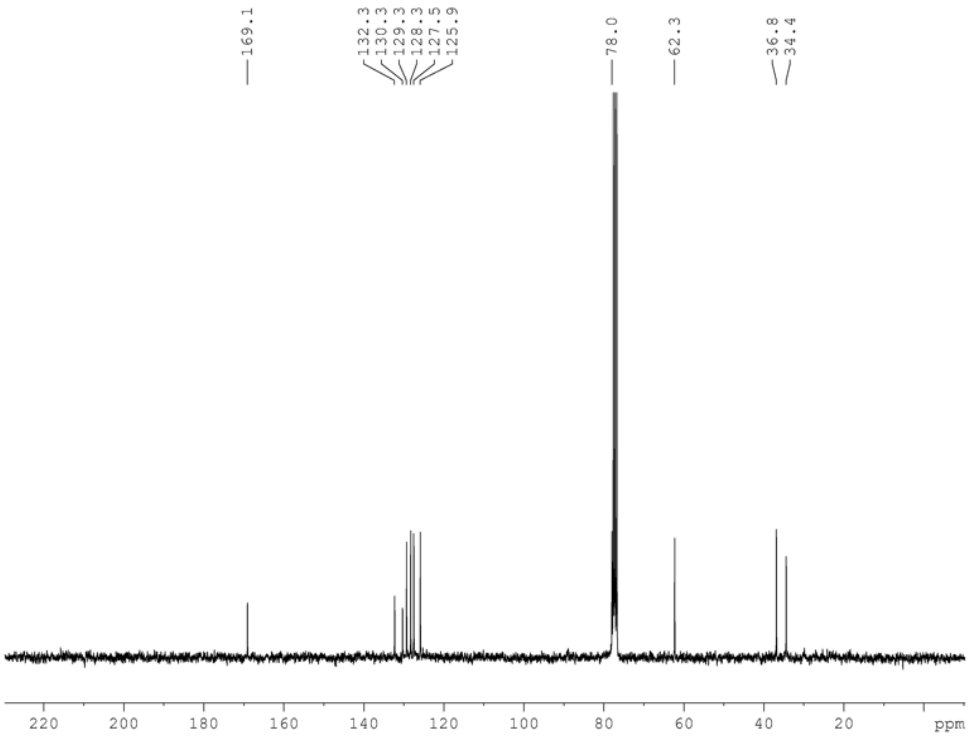
5.14
5.12
4.69
4.67
4.65
4.63
4.56
4.54
4.52
4.50
3.65
3.13
O
N
NO2
9
8
7
6
5
4
3
2
1
ppm
4.07
1.02
2.07
2.02
3.00

6g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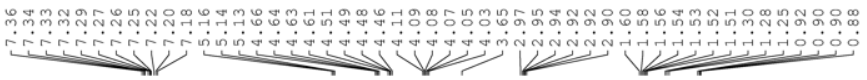
132.3
130.3
129.3
128.3
127.5
125.9
78.0
62.3
36.8
34.4
220
200
180
160
140
120
100
80
60
40
20
ppm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7.22
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7.18
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5.14
5.13
4.66
4.64
4.63
4.61
4.51
4.49
4.48
4.46
4.11
4.09
4.08
4.07
4.05
4.03
3.65
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2.92
2.90
1.60
1.58
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1.53
1.52
1.51
1.30
1.28
1.25
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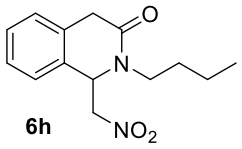
0.90
0.88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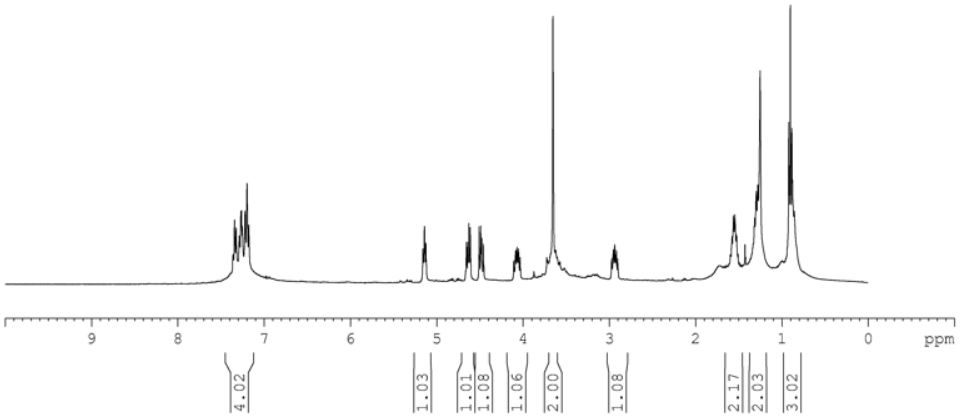
N
NO2

6h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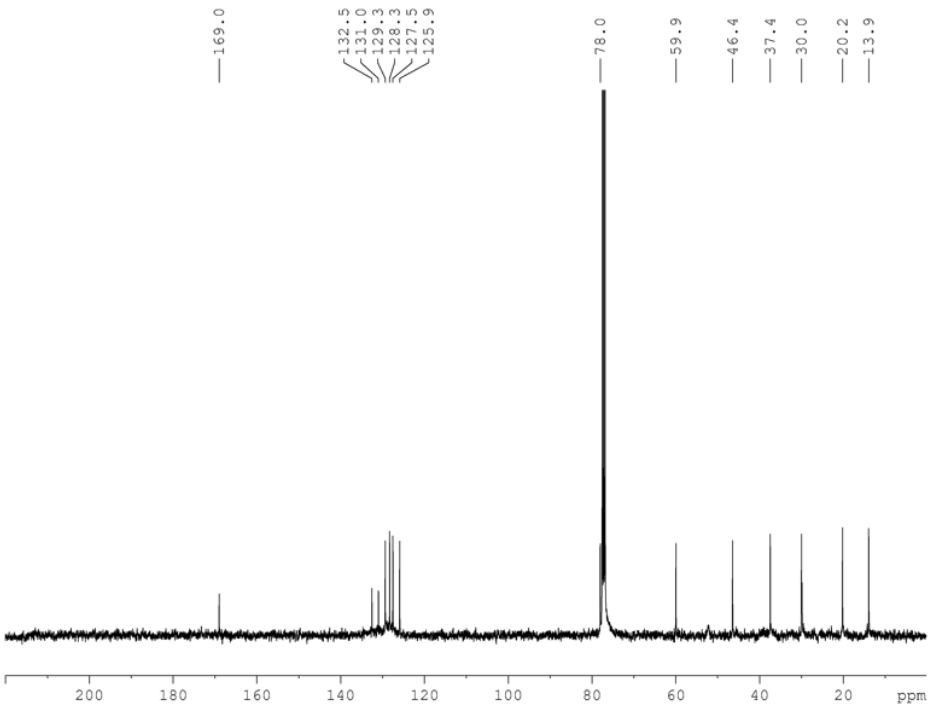
8
7
6
5
4
3
2
1
0
ppm
4.02
1.03
1.01
1.08
1.06
2.00
1.08
2.17
2.03
3.02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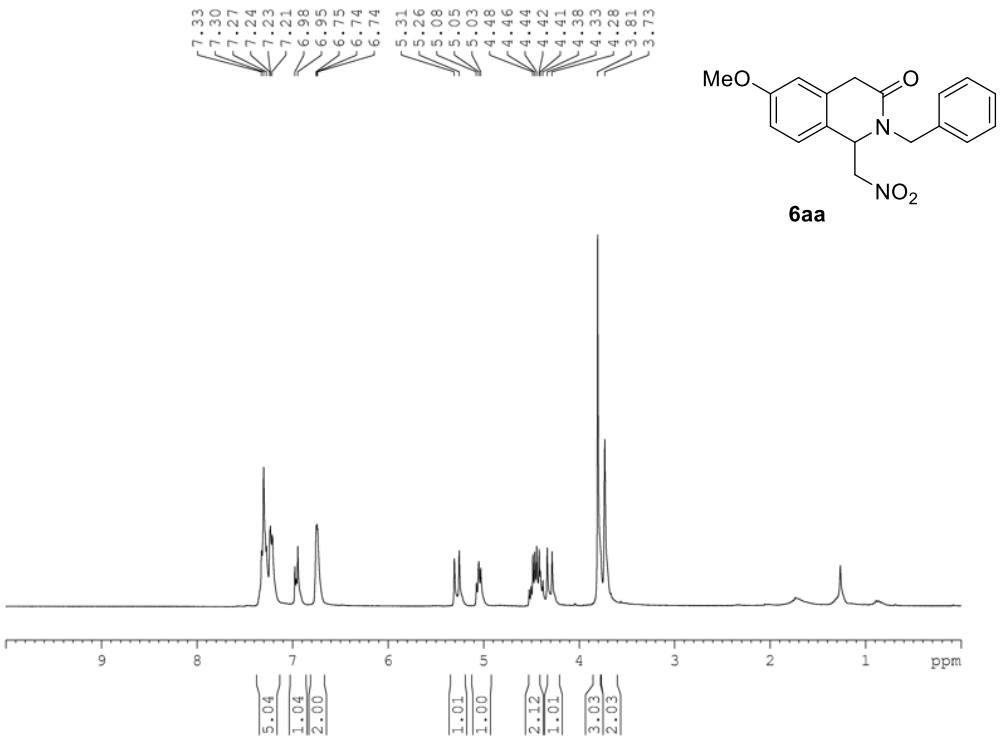
132.5
131.0
129.3
128.3
127.5
125.9
78.0
59.9
46.4
37.4
30.0
20.2
13.9
200
180
160
140
120
100
80
60
40
20
ppm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7.21
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6.95
6.75
6.74
6.74
5.31
5.26
5.08
5.05
5.03
4.48
4.46
4.44
4.42
4.41
4.38
4.33
4.28
3.81
3.73
MeO
O
N
NO2
9
8
7
6
5
4
3
2
1
ppm
5.04
1.04
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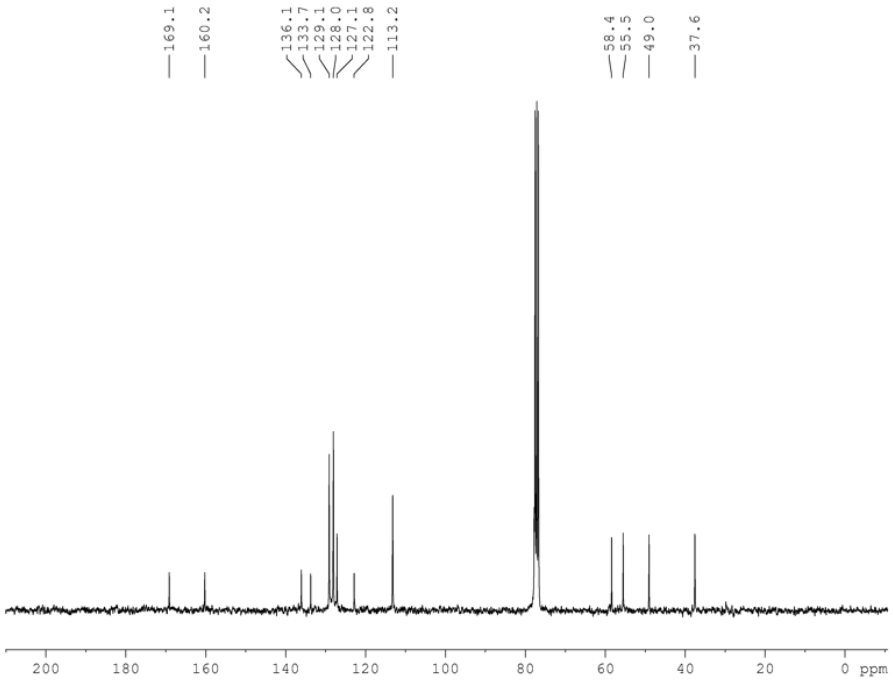
1.01
1.00
2.12
1.01
3.03
2.03

6aa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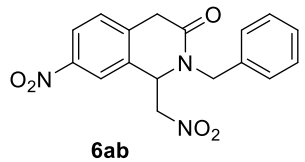
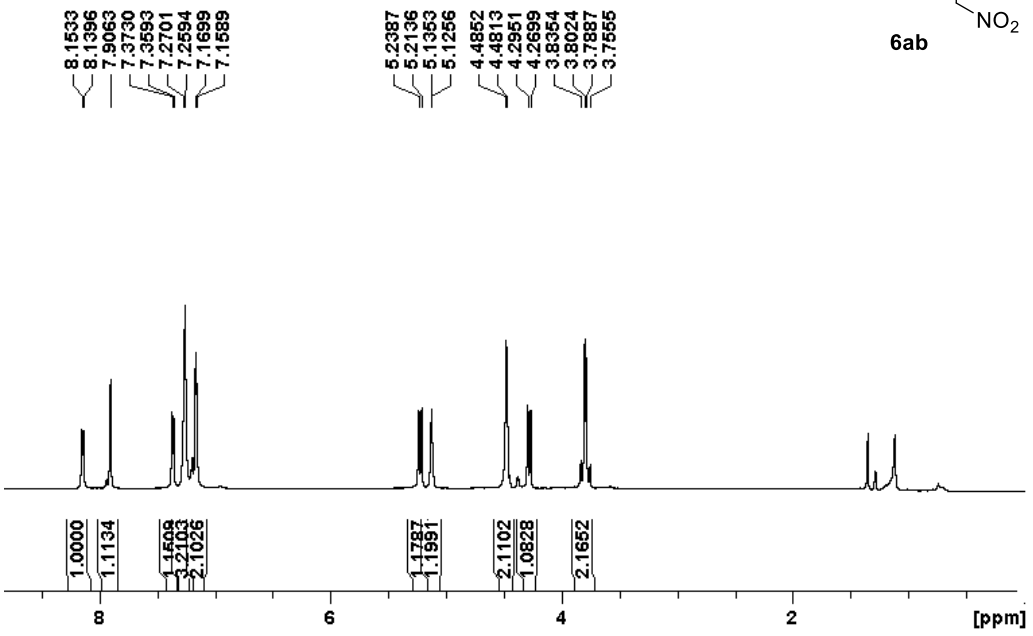
160.2
136.1
133.7
129.1
128.0
127.1
122.8
113.2
58.4
55.5
49.0
37.6
200
180
160
140
120
100
80
60
40
20
0 ppm


O
N
O_2N
NO_2

6ab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7.3730
7.3593
7.2701
7.2594
7.1699
7.1589
5.2387
5.2136
5.1353
5.1256
4.4852
4.4813
4.2951
4.2699
3.8354
3.8024
3.7887
3.7555
1.0000
1.1134
1.1509
3.2103
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1.1787
1.1991
2.1102
1.0828
2.1652
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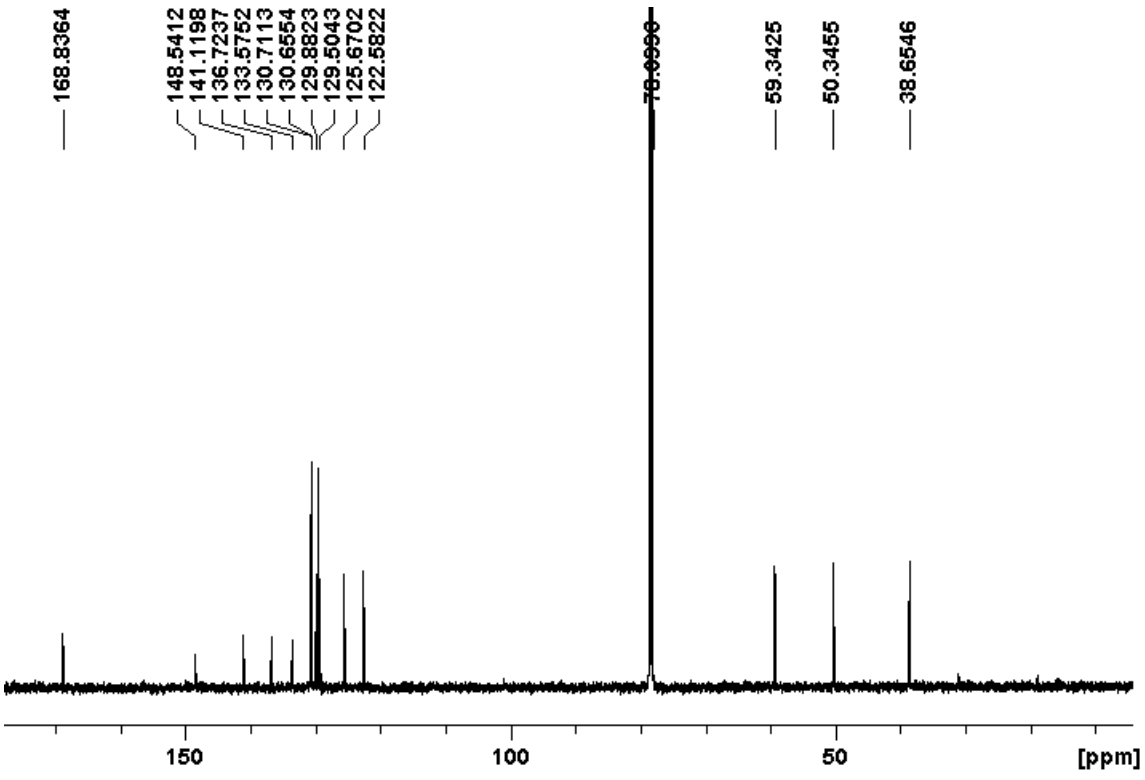
6
4
2
[ppm]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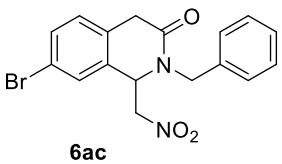
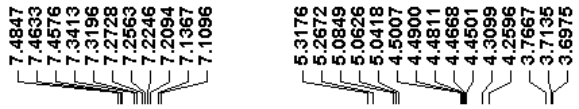
136.7237
133.5752
130.7113
130.6554
129.8823
129.5043
125.6702
122.5822
59.3425
50.3455
38.6546
150
100
50
[ppm]


O
N
Br
NO2

6ac


7.4847
7.4633
7.4576
7.3413
7.3196
7.2728
7.2563
7.2246
7.2094
7.1367
7.1096
5.3176
5.2672
5.0849
5.0626
5.0418
4.5007
4.4900
4.4811
4.4668
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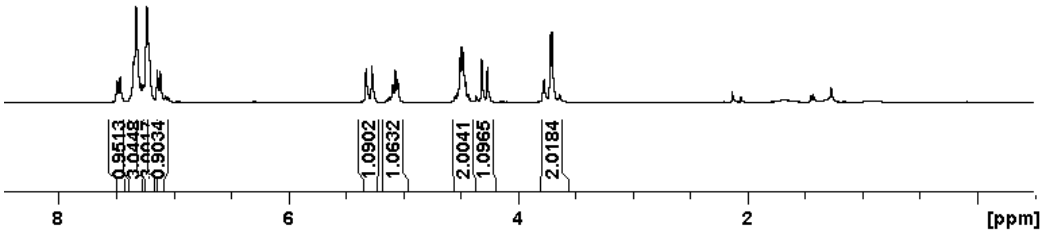
4.3099
4.2596
3.7667
3.7135
3.6975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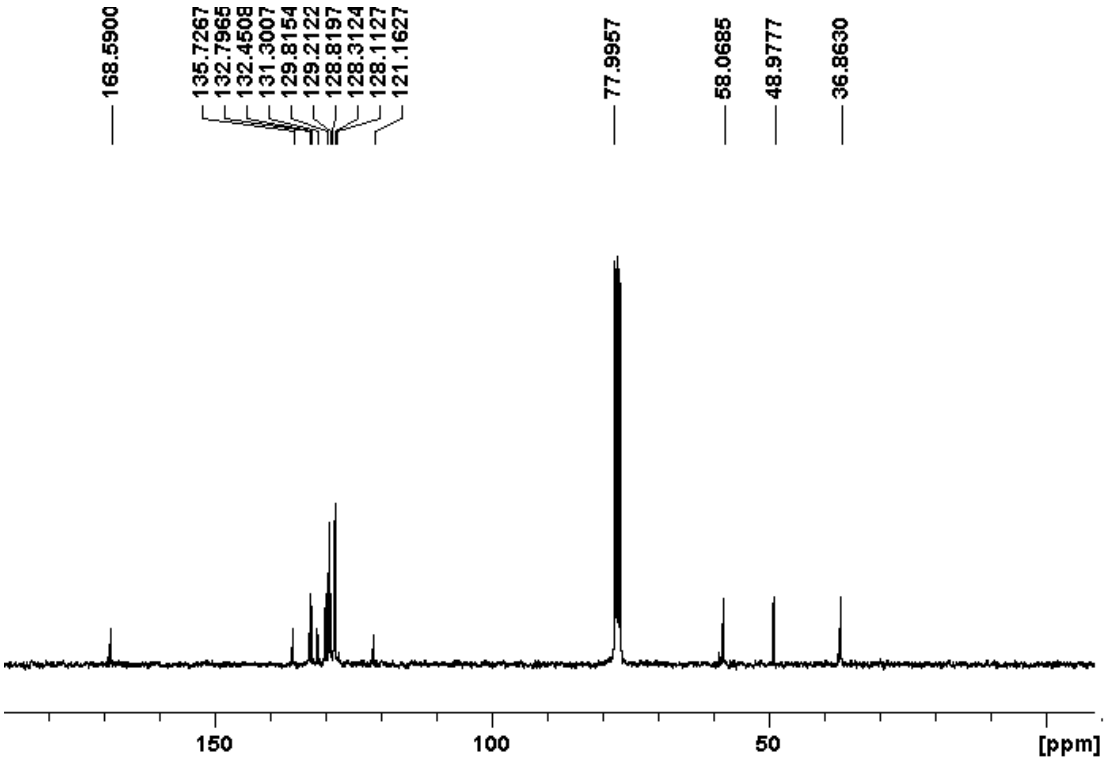
1.0902
1.0632
2.0041
1.0965
2.0184
8
6
4
2
[ppm]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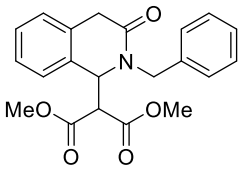
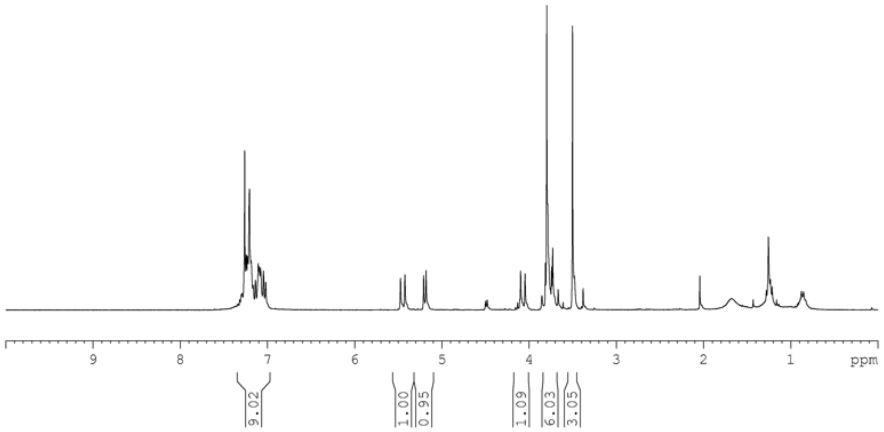
132.4508
131.3007
129.8154
129.2122
128.8197
128.3124
128.1127
121.1627
77.9957
58.0685
48.9777
36.8630
150
100
50
[ppm]


7.23
7.21
7.20
7.19
7.17
7.14
7.10
7.10
7.08
7.04
7.02
5.47
5.42
5.21
5.18
4.10
4.05
3.81
3.80
3.79
3.78
3.74
3.73
3.50


O
N
MeO
OMe
O
O

7a


9
8
7
6
5
4
3
2
1
ppm
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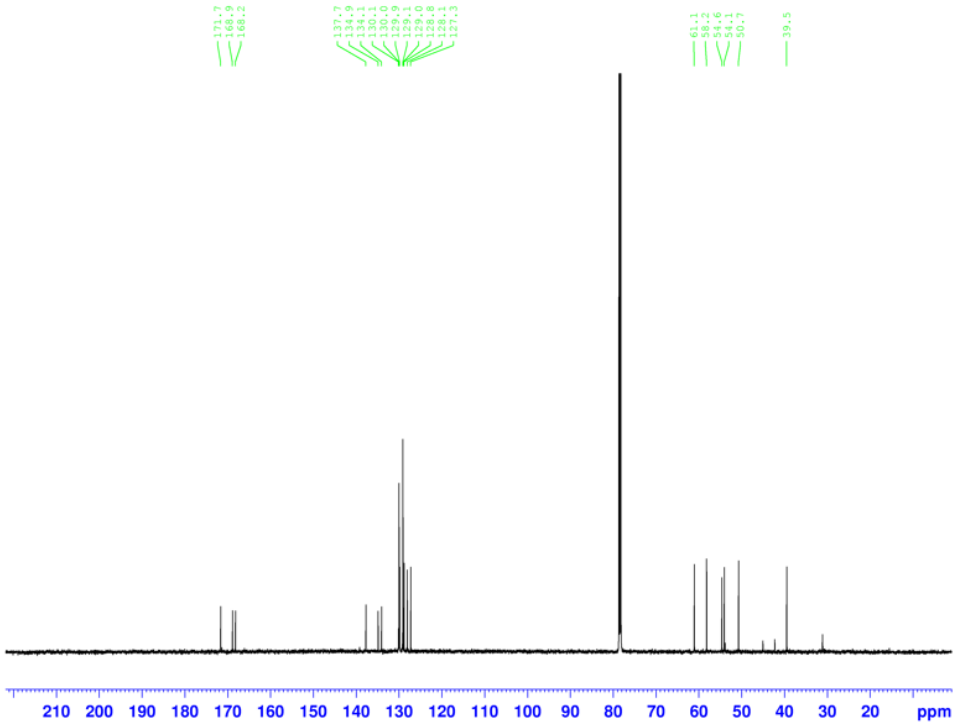
1.00
0.95
1.09
6.03
3.05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129.0
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58.2
54.6
54.1
50.7
39.5
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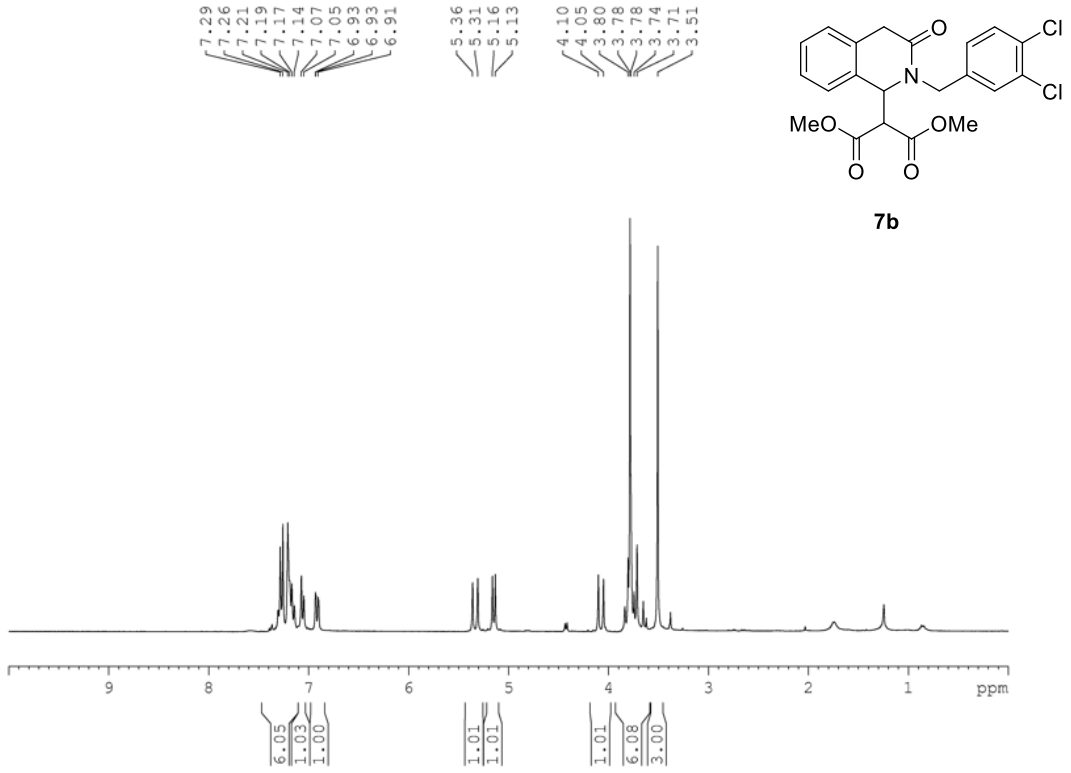
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7.14
7.07
7.05
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6.93
6.91
5.36
5.31
5.16
5.13
4.10
4.05
3.80
3.78
3.78
3.74
3.71
3.51
Cl
Cl
O
N
MeO
OMe
O
O
9
8
7
6
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ppm
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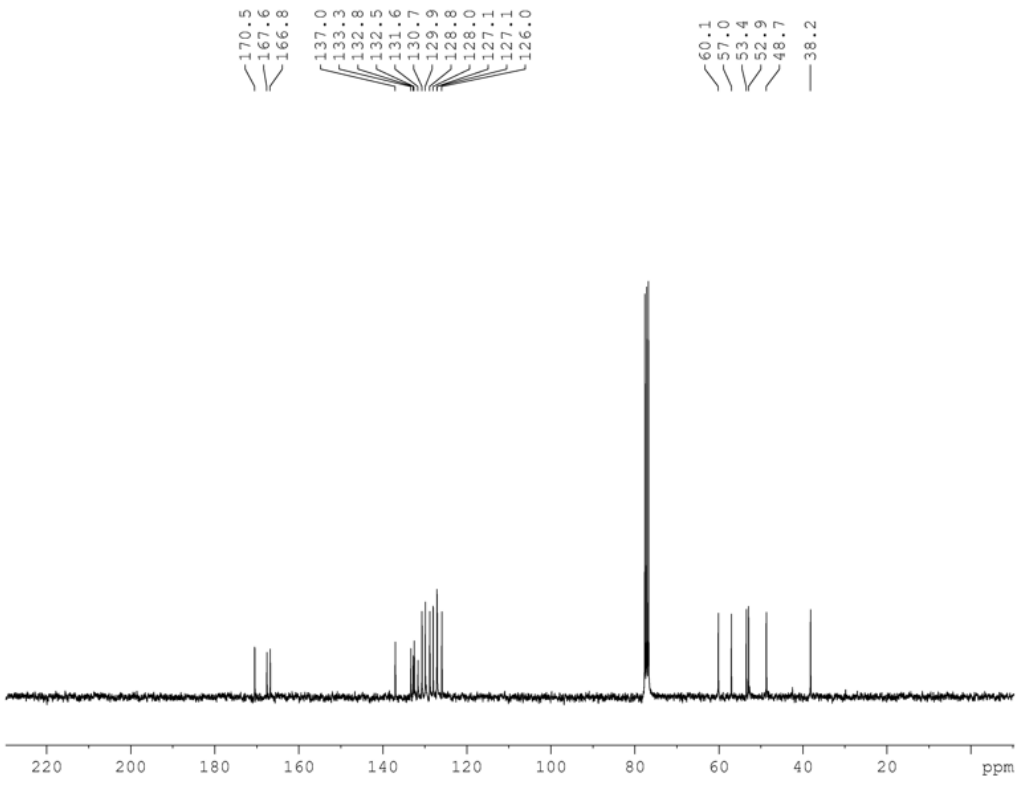
1.00
1.01
1.01
1.01
6.08
3.00

7b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127.1
127.1
126.0
60.1
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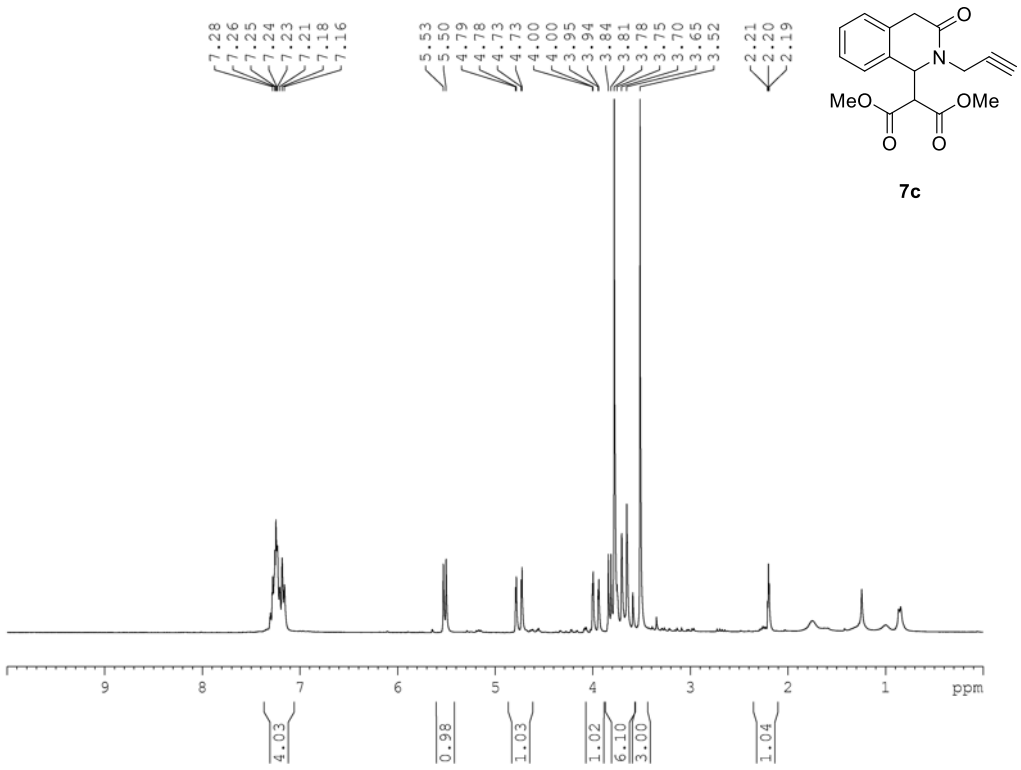
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7.18
7.16
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5.50
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4.78
4.73
4.73
4.00
4.00
3.95
3.94
3.84
3.81
3.78
3.75
3.70
3.65
3.52
2.21
2.20
2.19
MeO
OMe
O
O
O
N
9
8
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1.02
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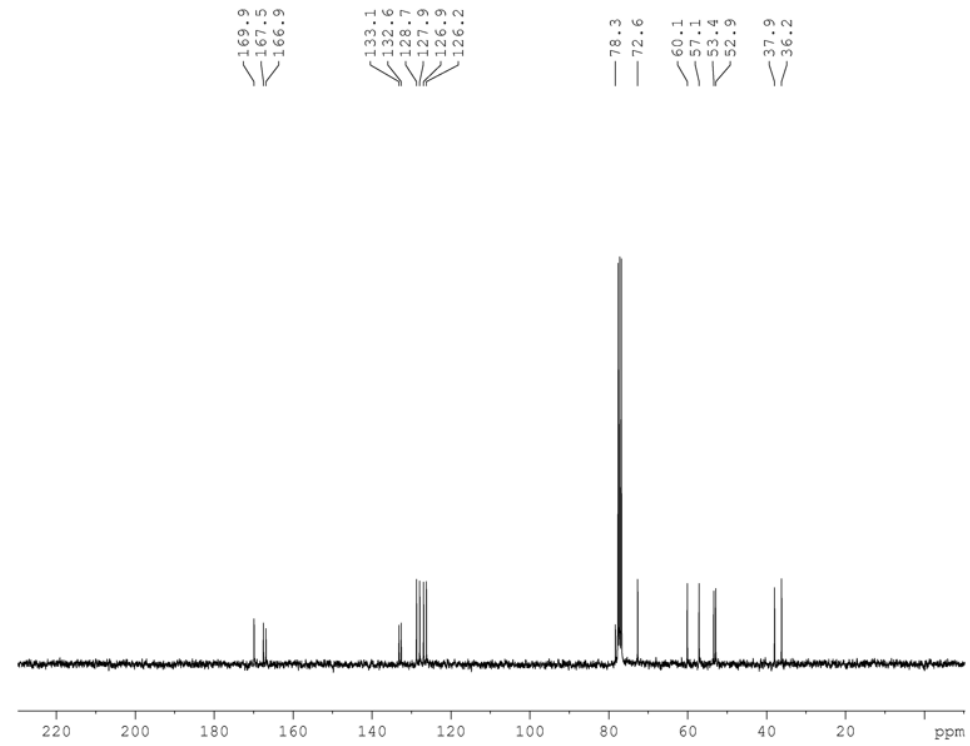
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126.9
126.2
78.3
72.6
60.1
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37.9
36.2
220
200
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140
120
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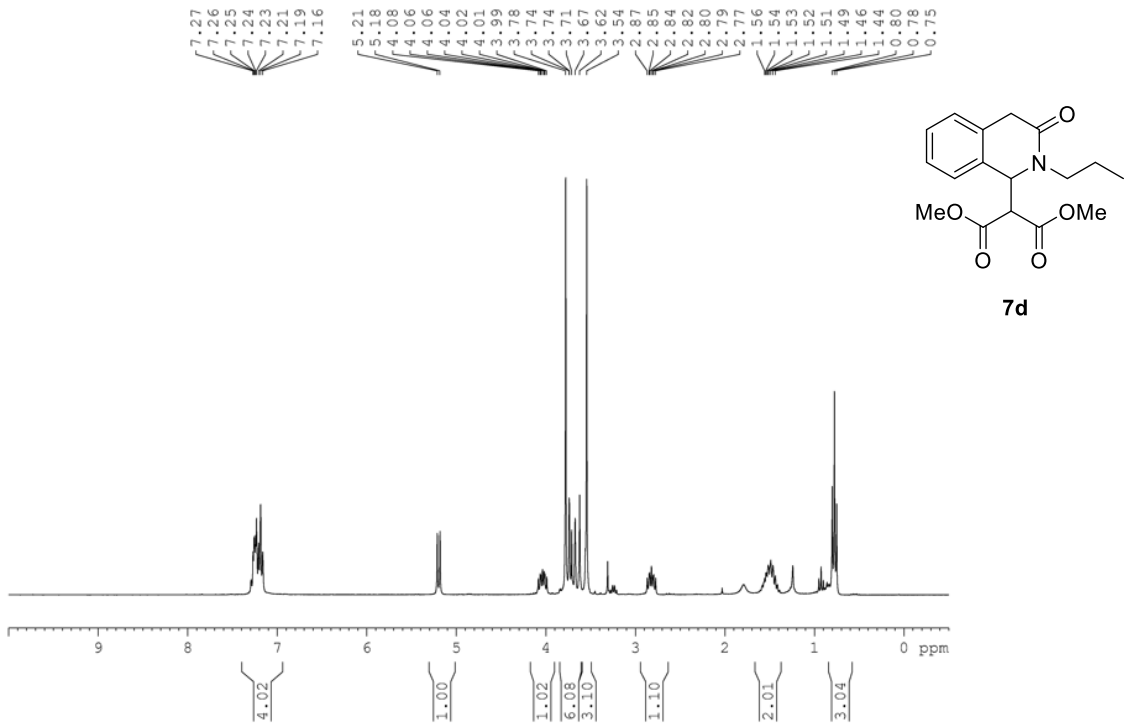
80
60
40
20
ppm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7.16
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5.18
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4.06
4.06
4.04
4.02
4.01
3.99
3.78
3.74
3.74
3.71
3.67
3.62
3.54
2.87
2.85
2.84
2.82
2.80
2.79
2.77
1.56
1.54
1.53
1.52
1.51
1.49
1.46
1.44
0.80
0.78
0.75
O
N
MeO
OMe
O
O
9
8
7
6
5
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3
2
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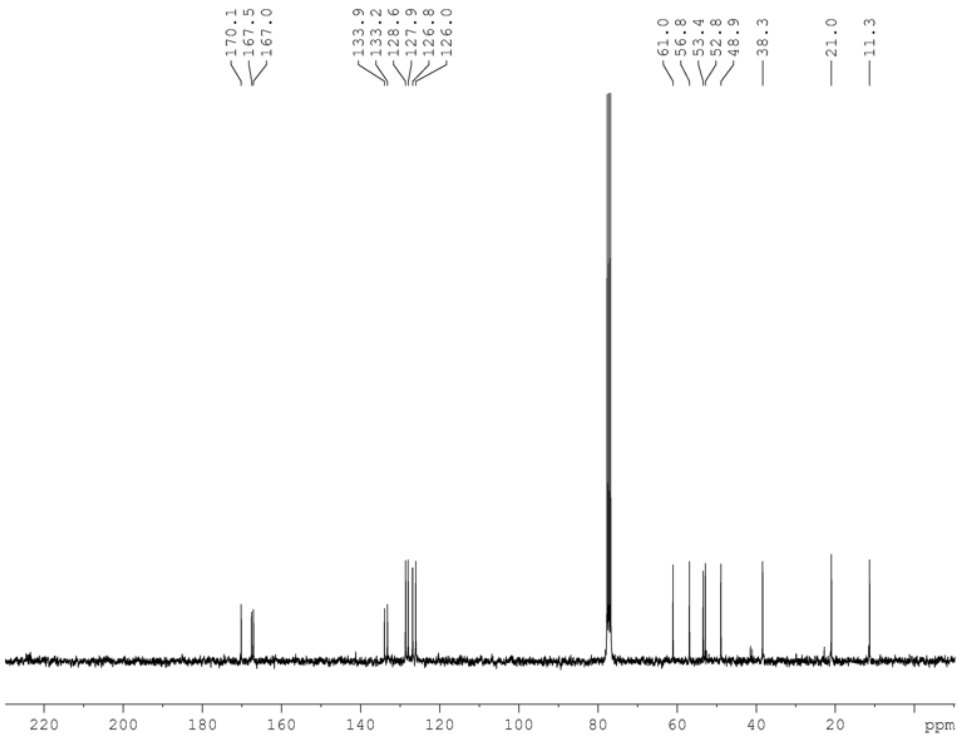
0 ppm
4.02
1.00
1.02
6.08
3.10
1.10
2.01
3.04

7d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167.5
167.0
133.9
133.2
128.6
127.9
126.8
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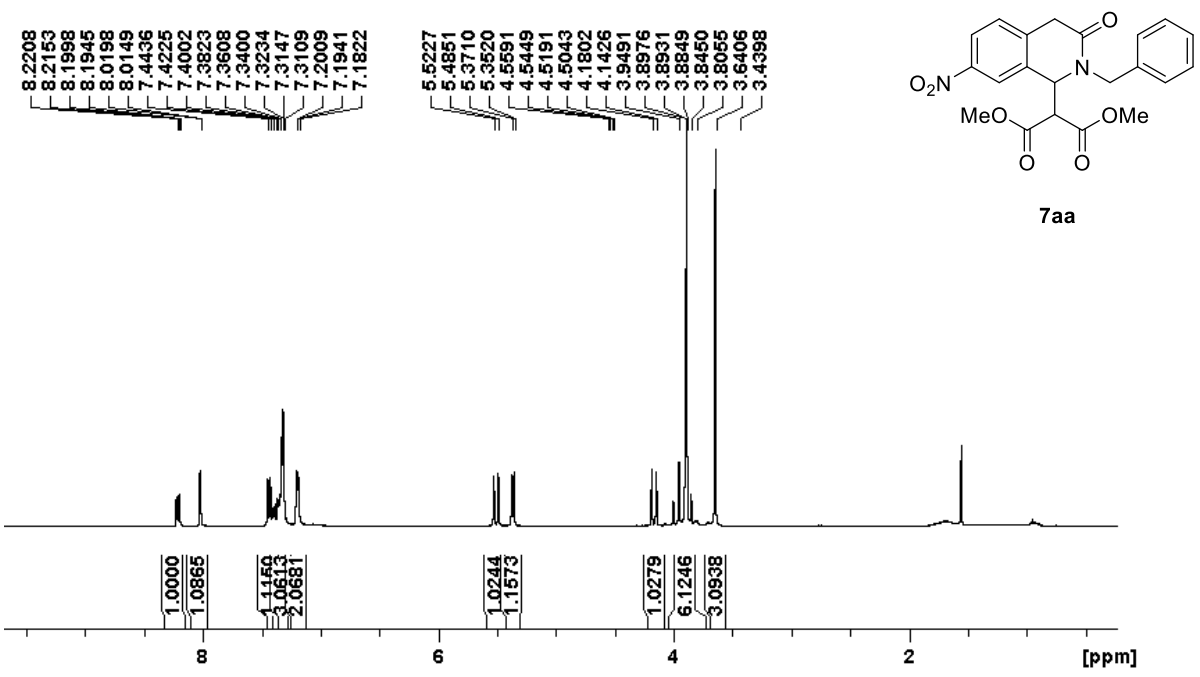
61.0
56.8
53.4
52.8
48.9
38.3
21.0
11.3
220
200
180
160
140
120
100
80
60
40
20
ppm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8.1998
8.1945
8.0198
8.0149
7.4436
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7.4002
7.3823
7.3608
7.3400
7.3234
7.3147
7.3109
7.2009
7.1941
7.1822
5.5227
5.4851
5.3710
5.3520
4.5591
4.5449
4.5191
4.5043
4.1802
4.1426
3.9491
3.8976
3.8931
3.8849
3.8450
3.8055
3.6406
3.4398
1.0000
1.0865
1.1150
3.0613
2.0681
1.0244
1.1573
1.0279
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8
6
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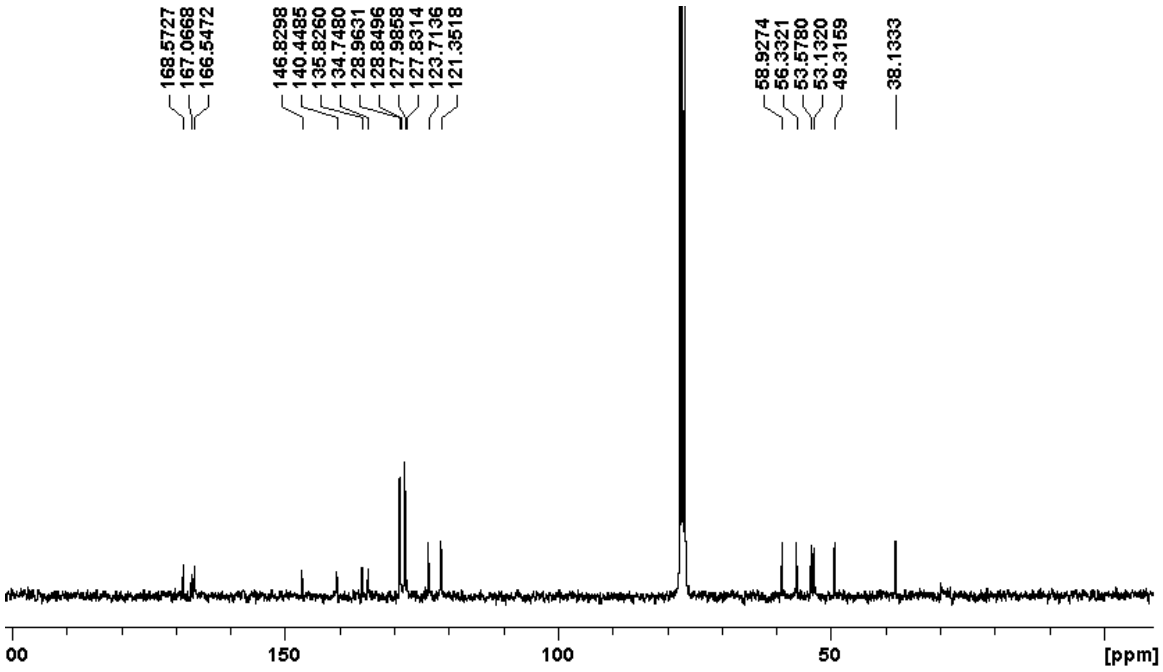
MeO
OMe
O
O
O
N

7aa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166.5472
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128.8496
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123.7136
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56.3321
53.5780
53.1320
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38.1333
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100
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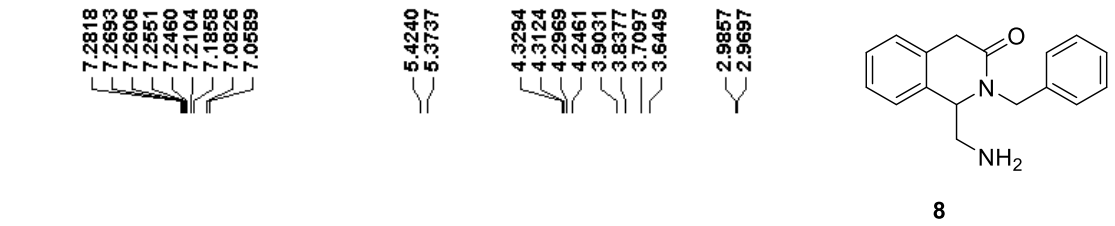
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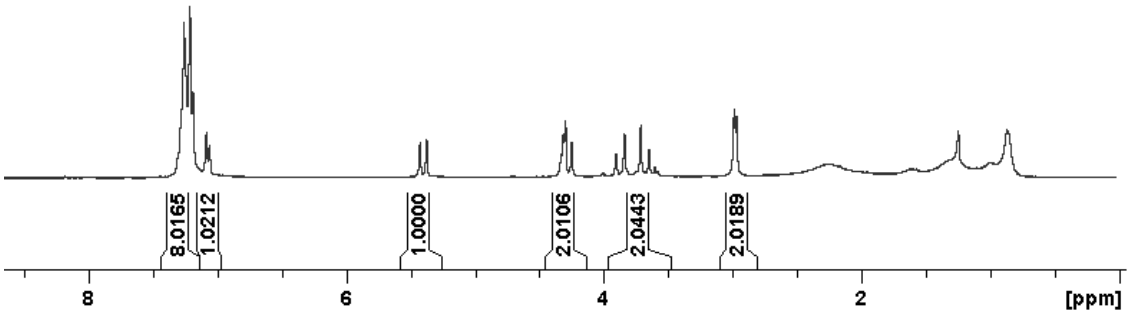
7.2606
7.2551
7.2460
7.2104
7.1858
7.0826
7.0589
5.4240
5.3737
4.3294
4.3124
4.2969
4.2461
3.9031
3.8377
3.7097
3.6449
2.9857
2.9697
O
N
NH2

8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2.0189
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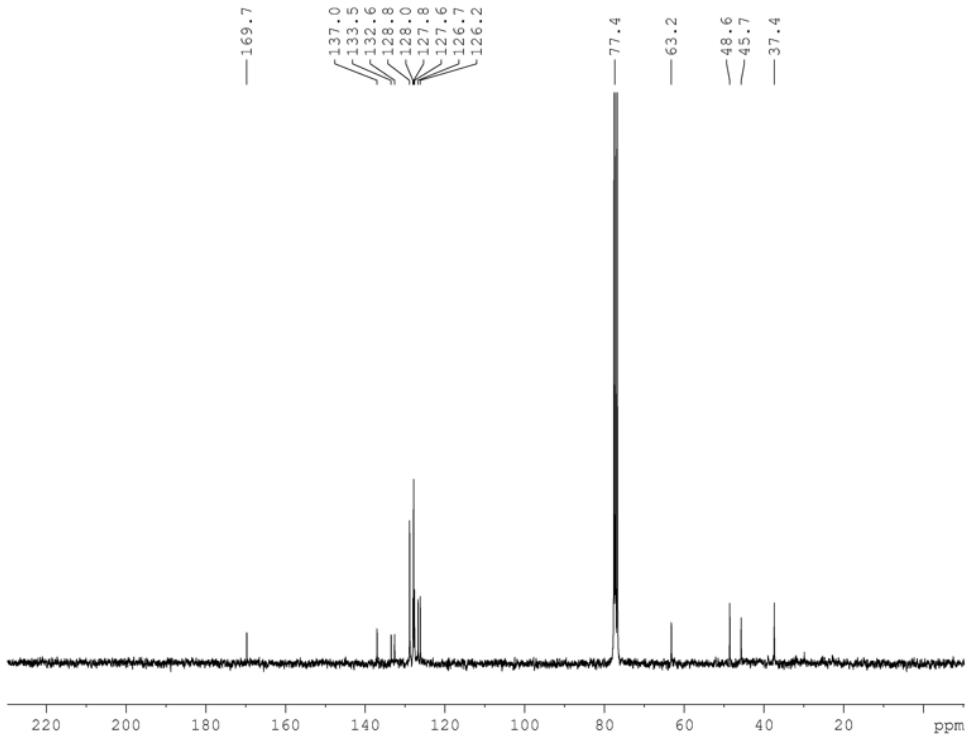
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133.5
132.6
128.8
128.0
127.8
127.6
126.7
126.2
77.4
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45.7
37.4
220
200
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140
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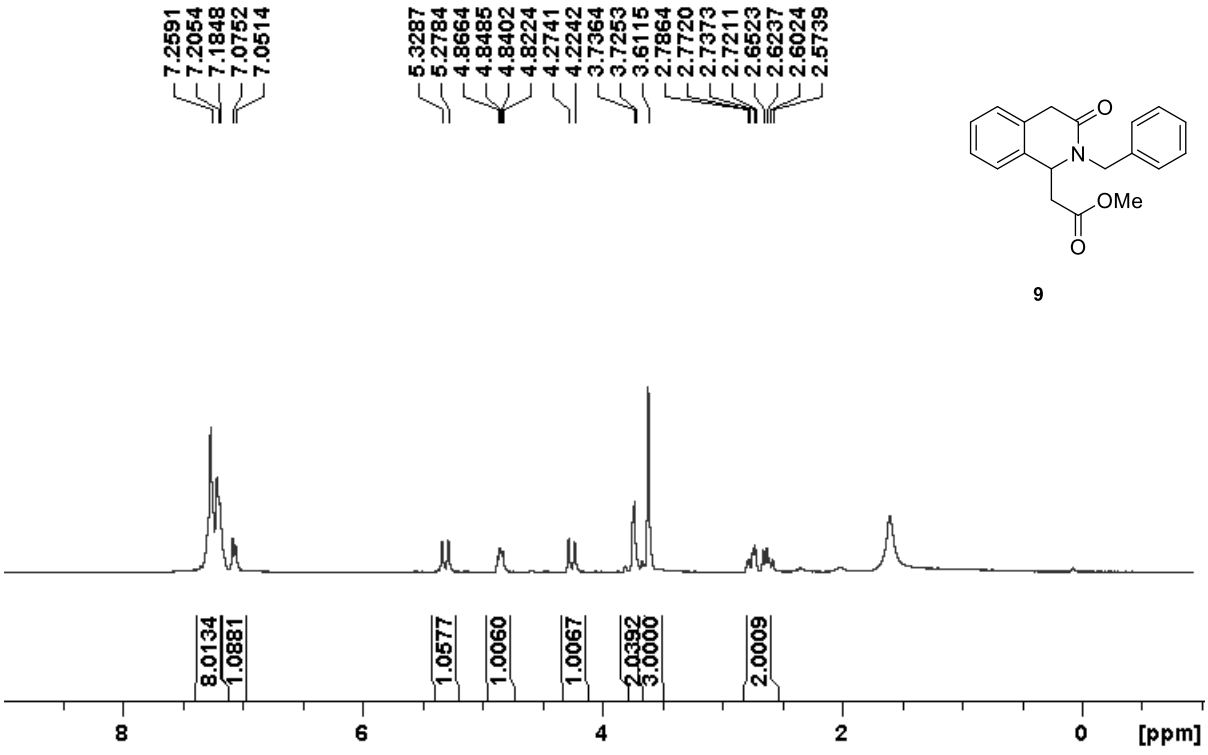
60
40
20
ppm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7.0752
7.0514
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5.2784
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4.8485
4.8402
4.8224
4.2741
4.2242
3.7364
3.7253
3.6115
2.7864
2.7720
2.7373
2.7211
2.6523
2.6237
2.6024
2.5739
O
N
OMe
O
9
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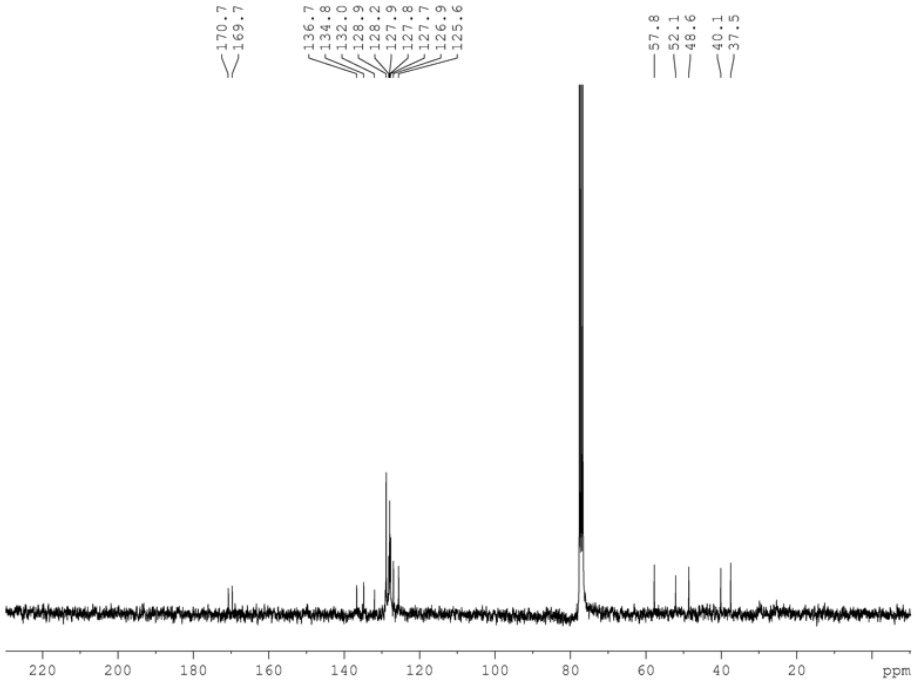
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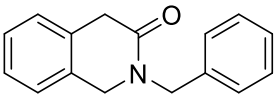
169.7
136.7
134.8
132.0
128.9
128.2
127.9
127.8
127.7
126.9
125.6
57.8
52.1
48.6
40.1
37.5
220
200
180
160
140
120
100
80
60
40
20
ppm



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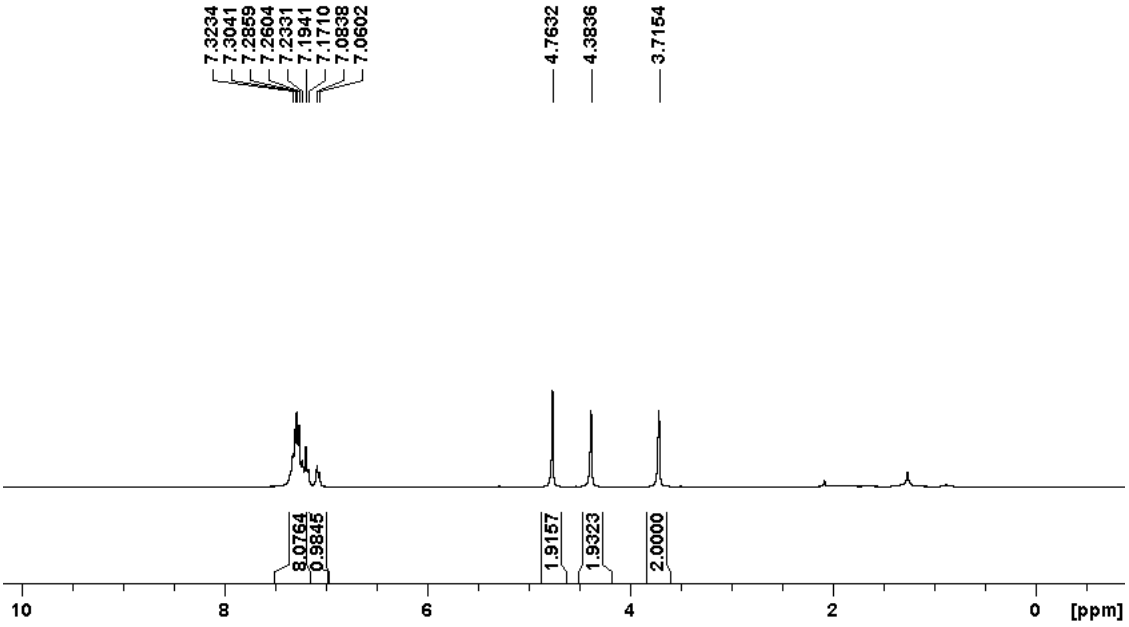
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7.2331
7.1941
7.1710
7.0838
7.0602
4.7632
4.3836
3.7154
8.0764
0.9845
1.9157
1.9323
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10
8
6
4
2
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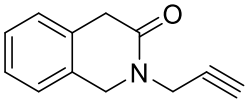

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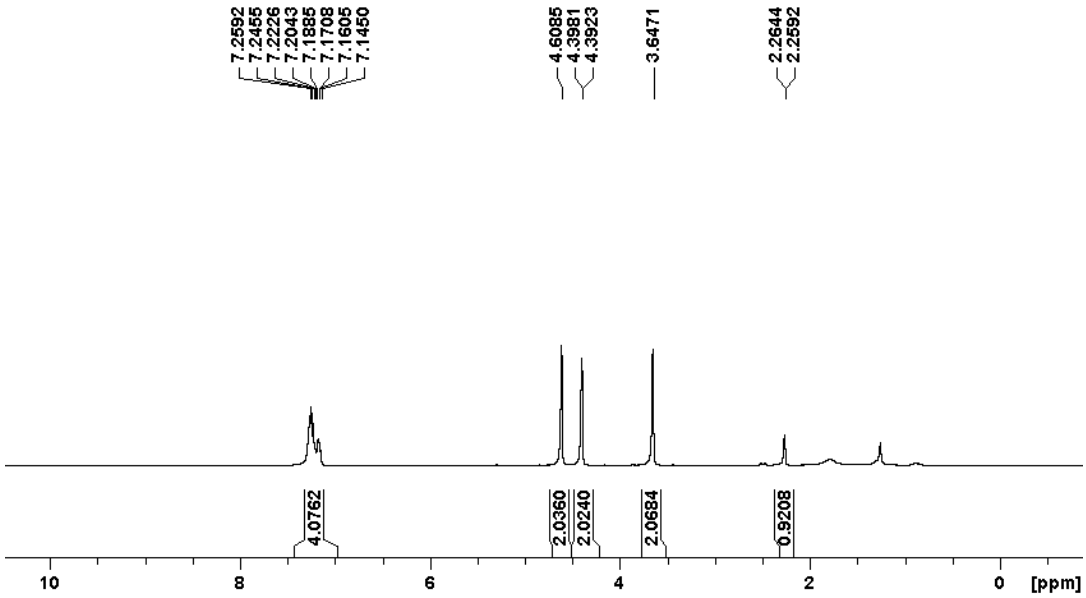
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7.1885
7.1708
7.1605
7.1450
4.6085
4.3981
4.3923
3.6471
2.2644
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2.0360
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2.0684
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10
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0
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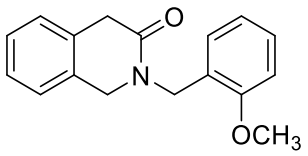
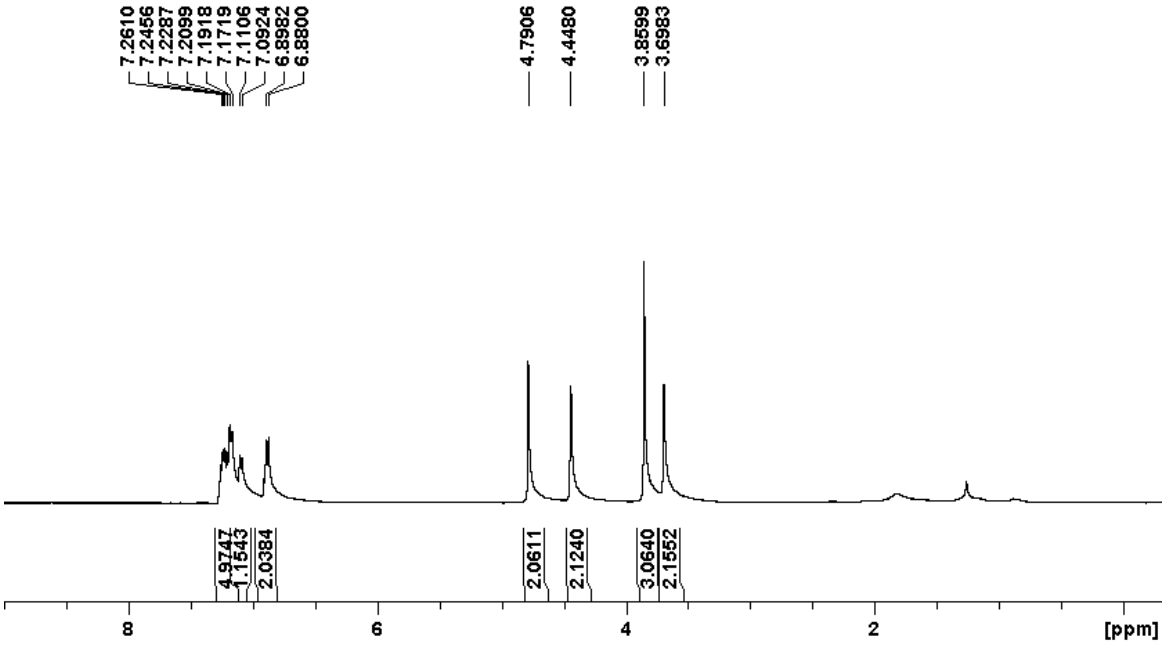

O
N
OCH3

5b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7.1719
7.1106
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6.8982
6.8800
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3.6983
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3.0640
2.1552
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4
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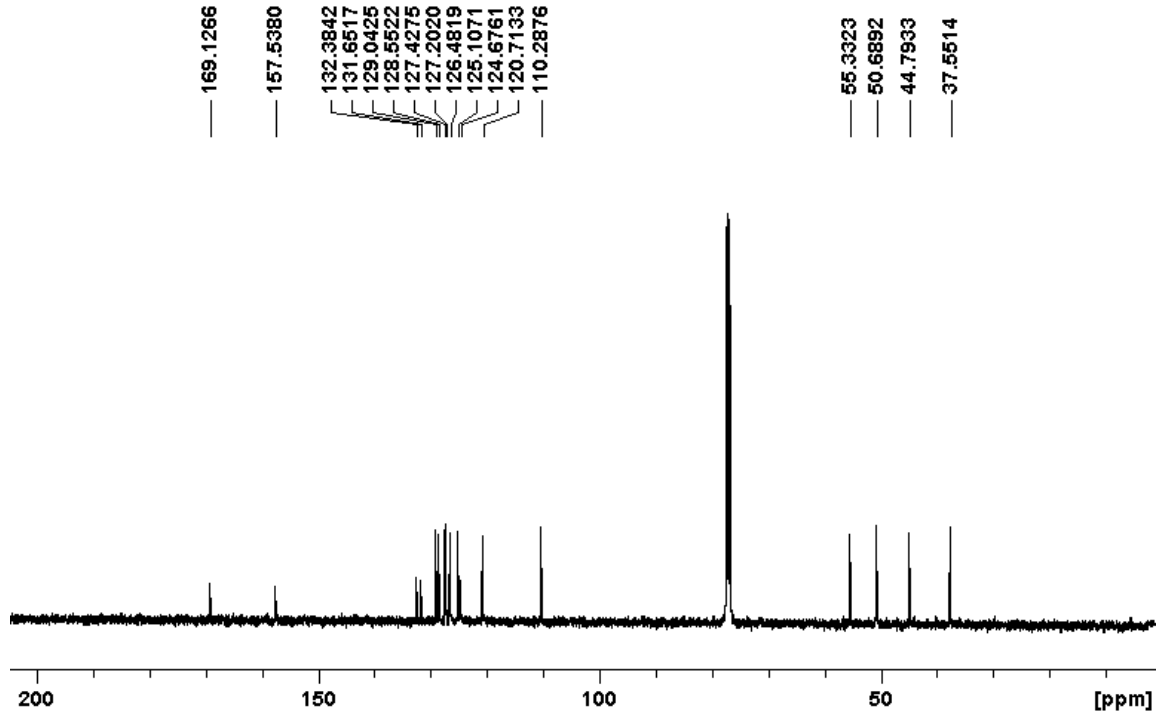
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127.4275
127.2020
126.4819
125.1071
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37.5514
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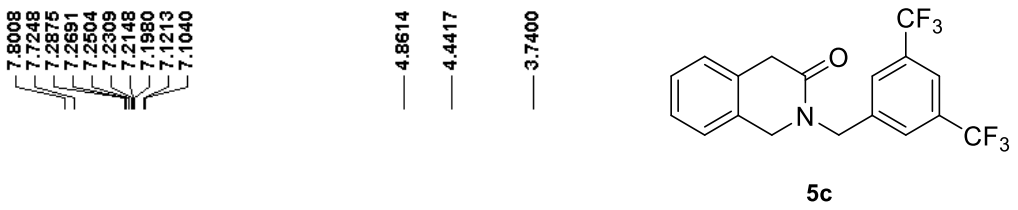
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7.2309
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7.1213
7.1040
4.8614
4.4417
3.7400
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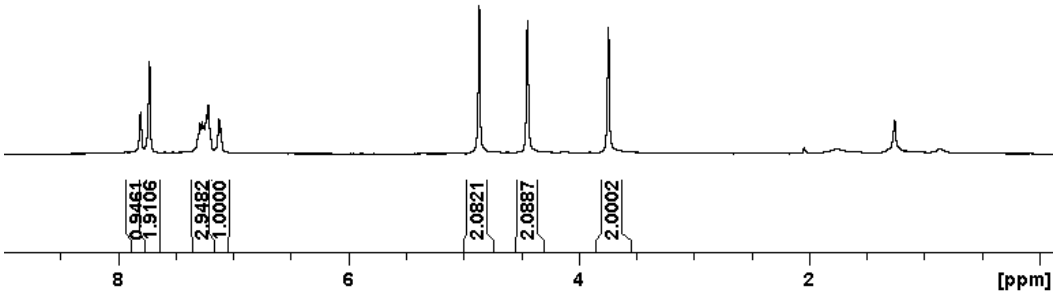
N
CF3
CF3

5c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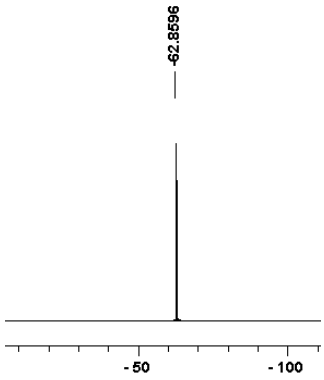
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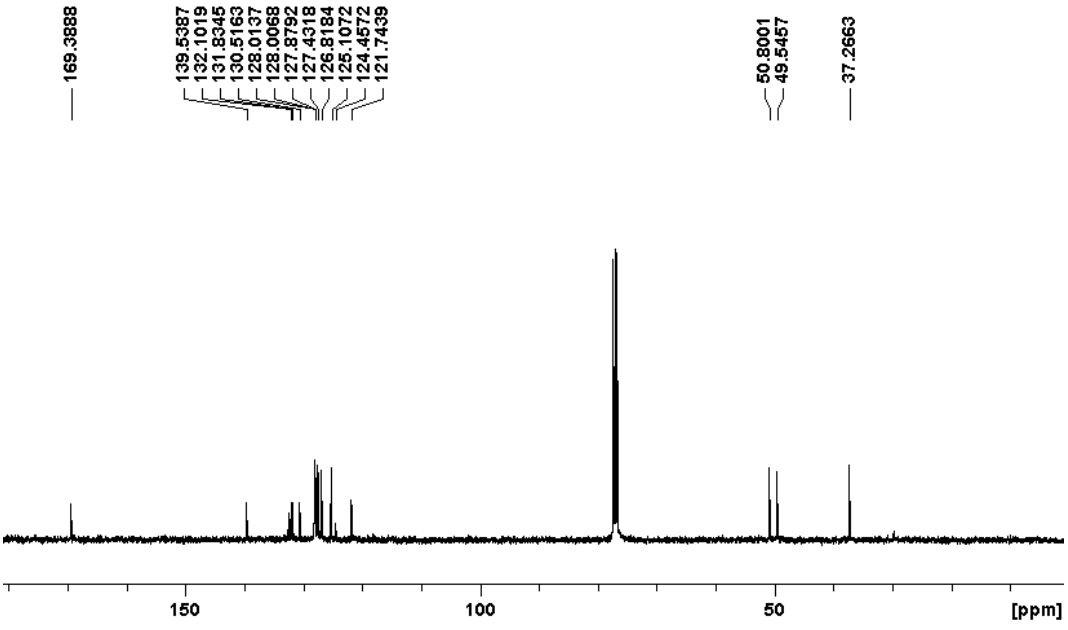
-100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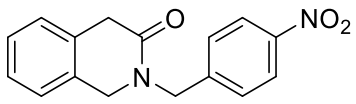
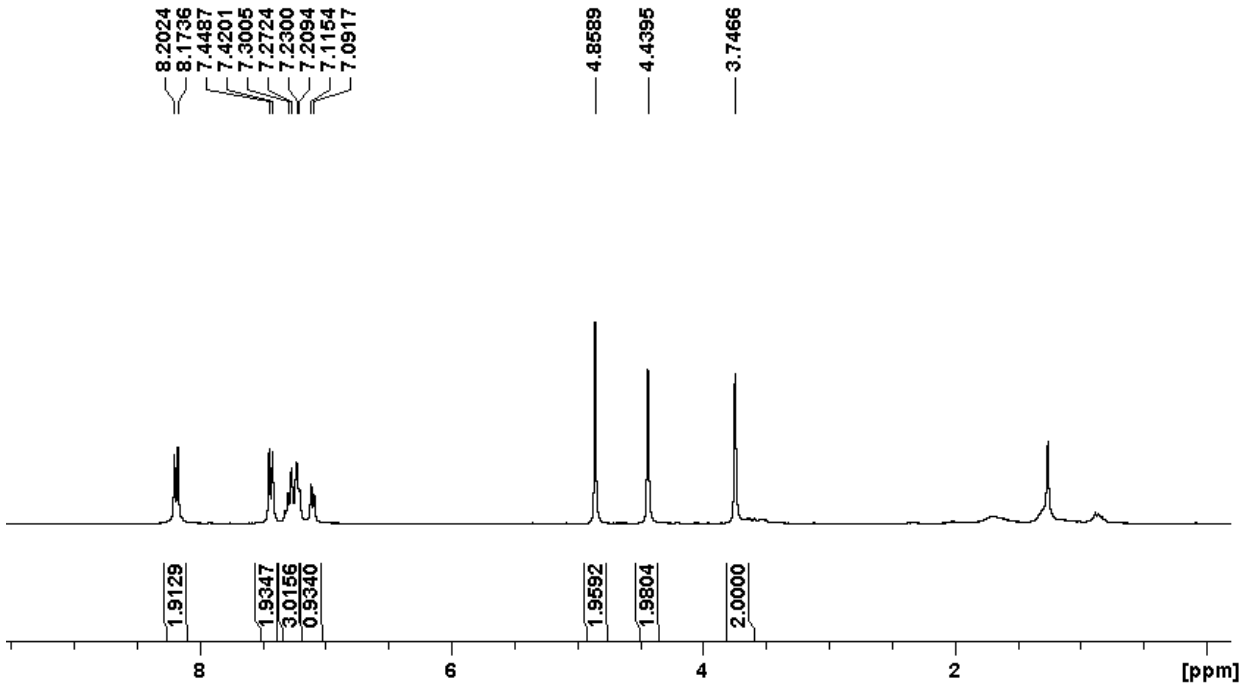

O
NO2
N

5d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7.3005
7.2724
7.2300
7.2094
7.1154
7.0917
4.8589
4.4395
3.7466
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3.0156
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1.9592
1.9804
2.0000
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4
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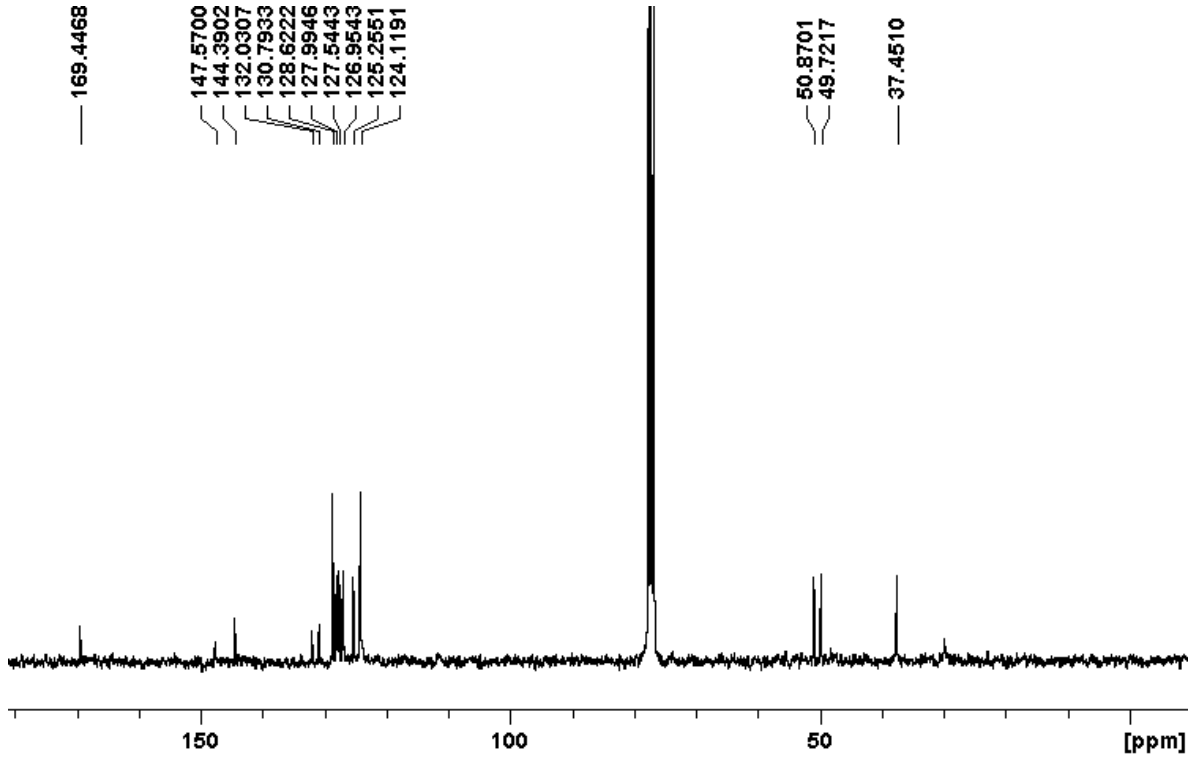
[ppm]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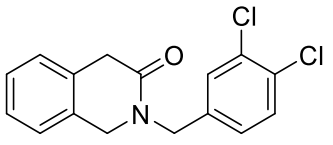
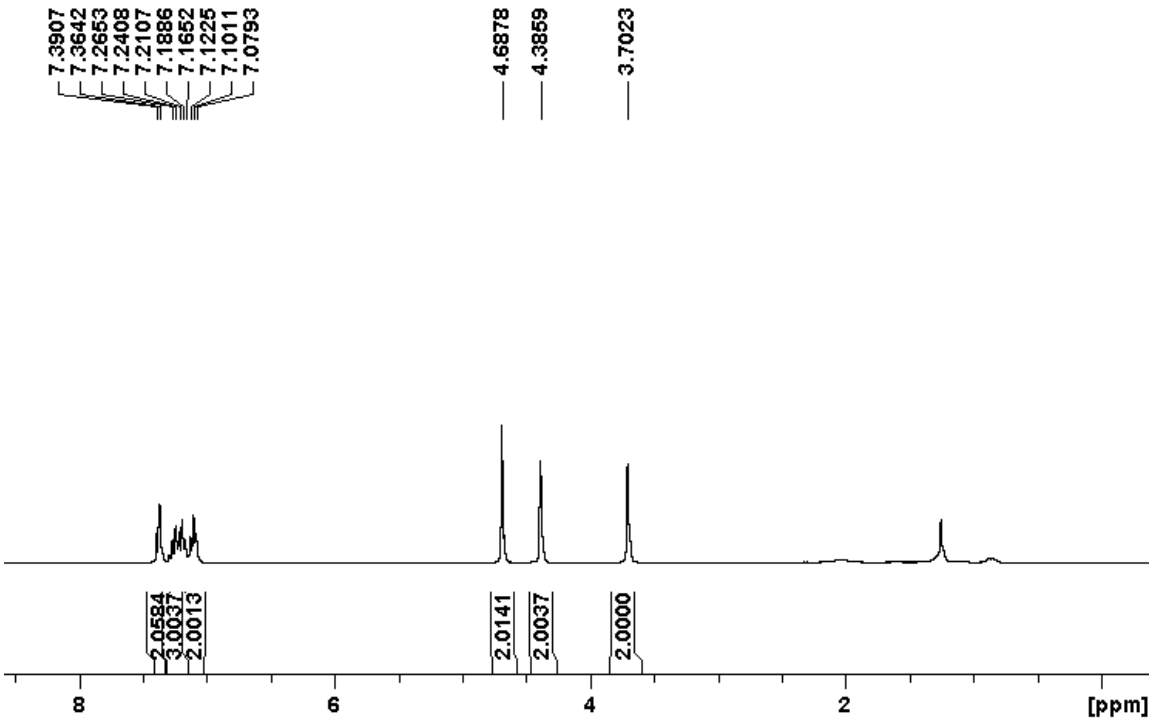

Cl
Cl
O
N

5e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7.2107
7.1886
7.1652
7.1225
7.1011
7.0793
4.6878
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2.0584
3.0037
2.0013
2.0141
2.0037
2.0000
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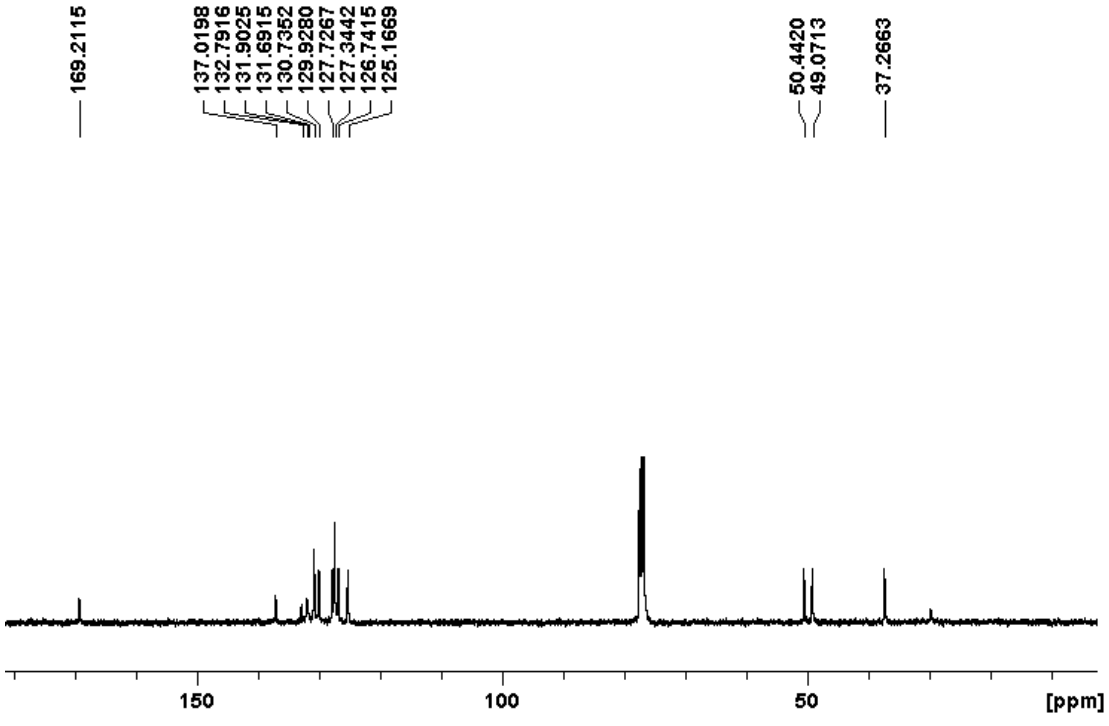
6
4
2
[ppm]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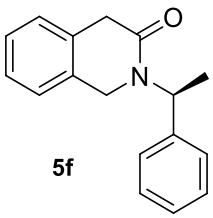

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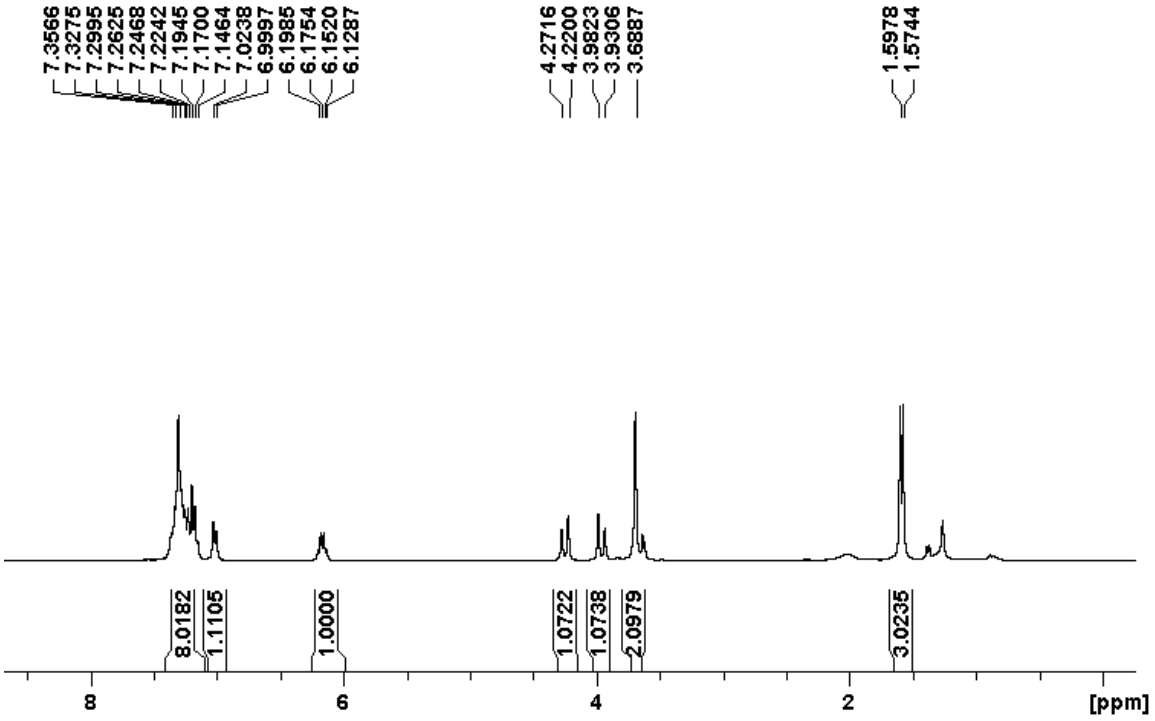
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7.1945
7.1700
7.1464
7.0238
6.9997
6.1985
6.1754
6.1520
6.1287
4.2716
4.2200
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3.9306
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1.0738
2.0979
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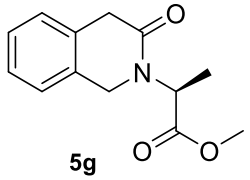

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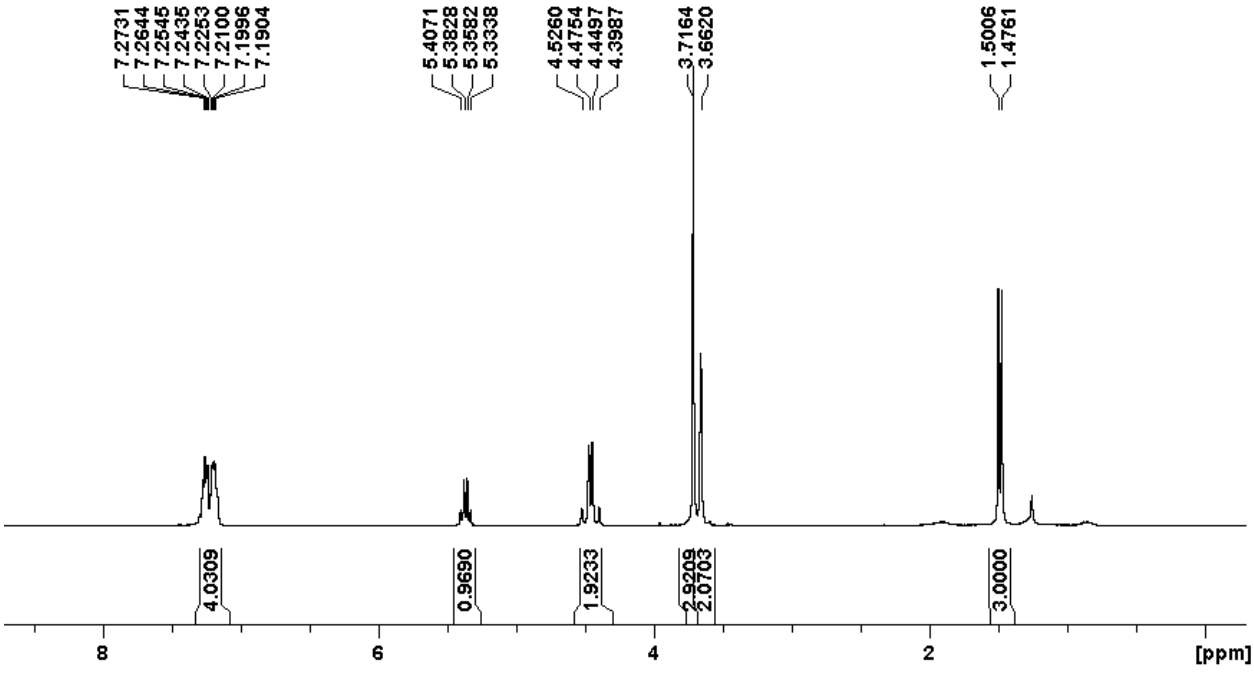
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4.4497
4.3987
3.7164
3.6620
1.5006
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4
2
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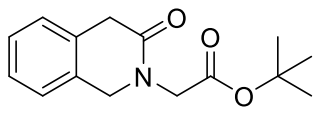

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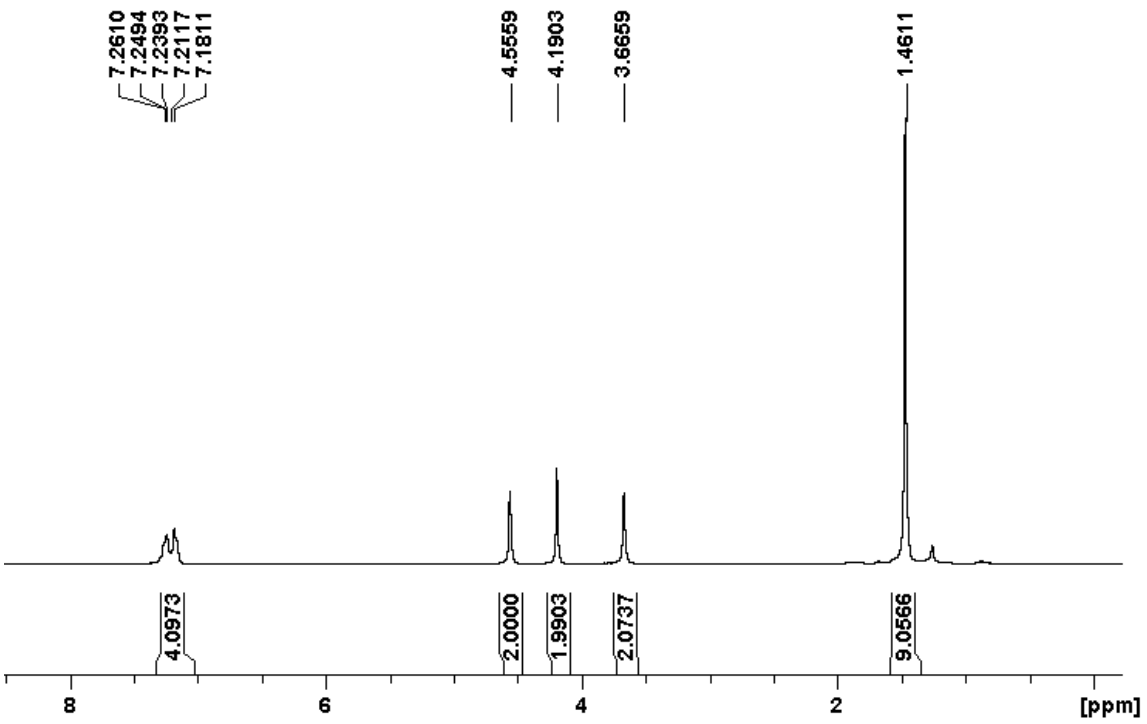
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7.2393
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7.1811
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2.0000
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9.0566
8
6
4
2
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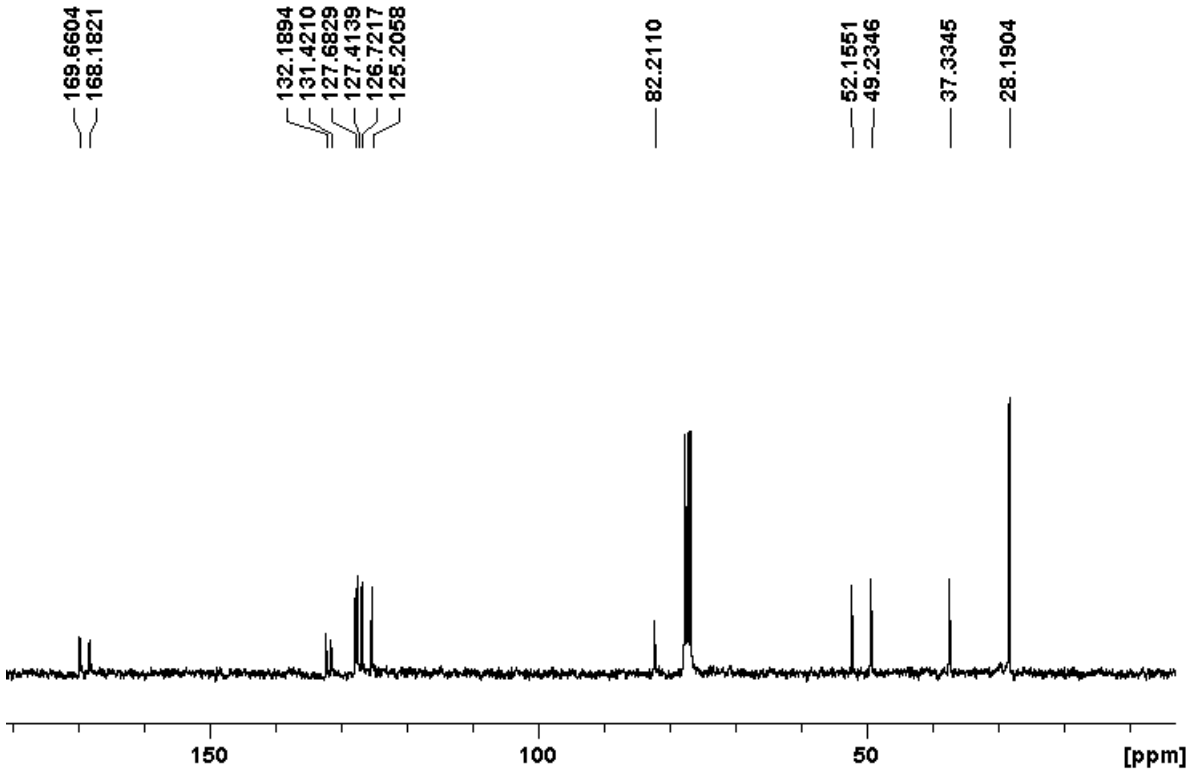
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132.1894
131.4210
127.6829
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126.7217
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82.2110
52.1551
49.2346
37.3345
28.1904
150
100
50
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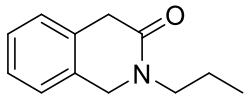
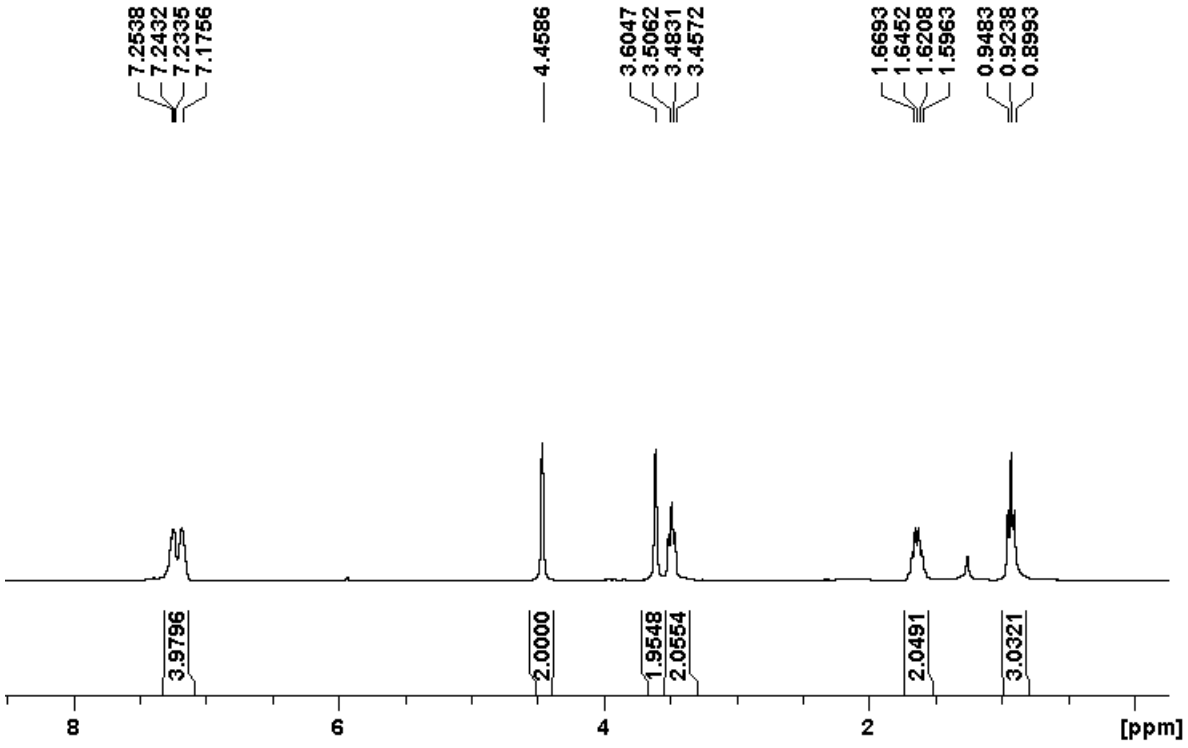

O
N

5i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4.4586
3.6047
3.5062
3.4831
3.4572
1.6693
1.6452
1.6208
1.5963
0.9483
0.9238
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2.0000
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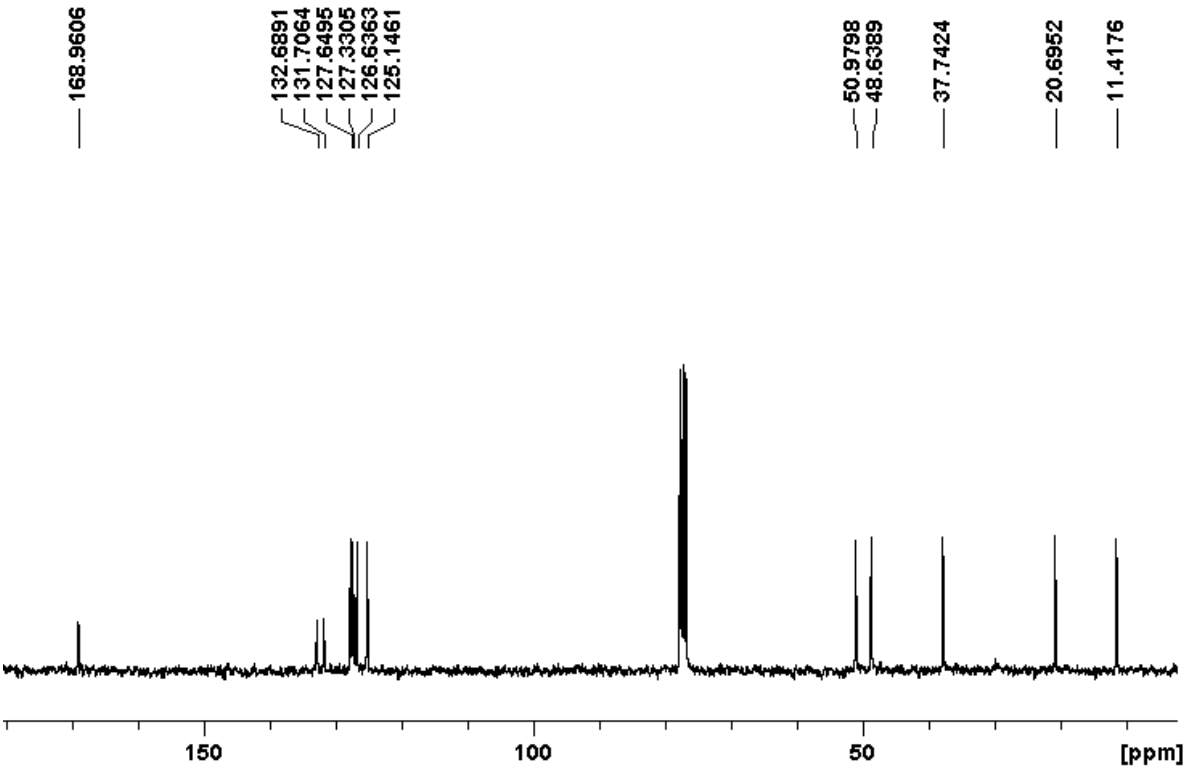
2.0554
2.0491
3.0321
8
6
4
2
[ppm]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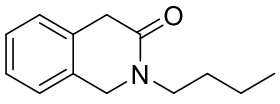

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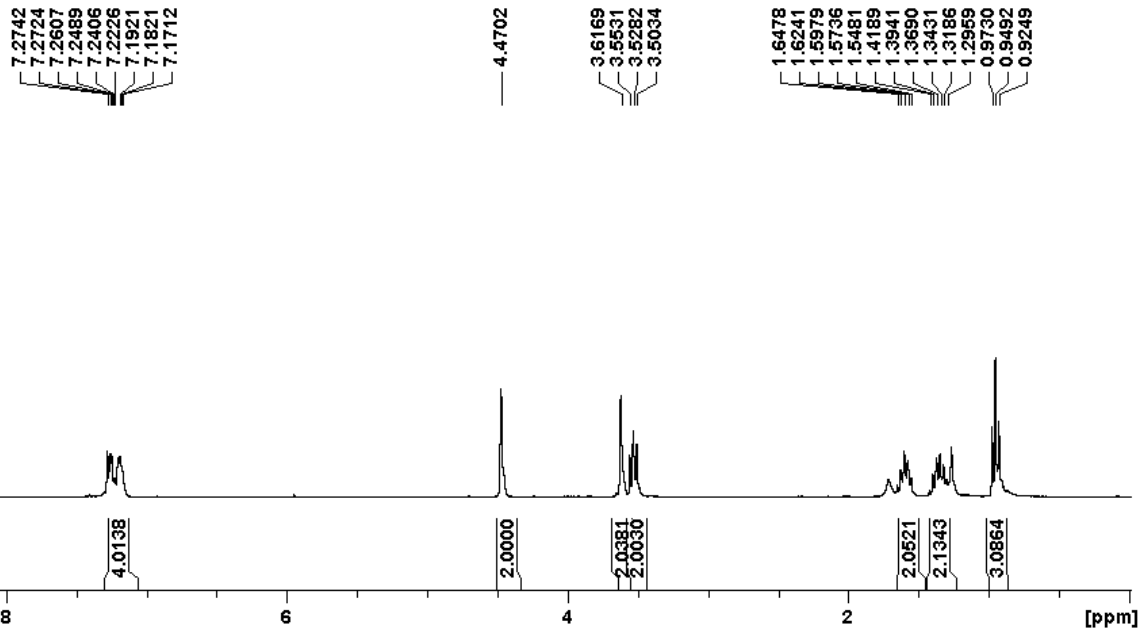
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7.1921
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7.1712
4.4702
3.6169
3.5531
3.5282
3.5034
1.6478
1.6241
1.5979
1.5736
1.5481
1.4189
1.3941
1.3690
1.3431
1.3186
1.2959
0.9730
0.9492
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4
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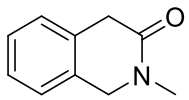

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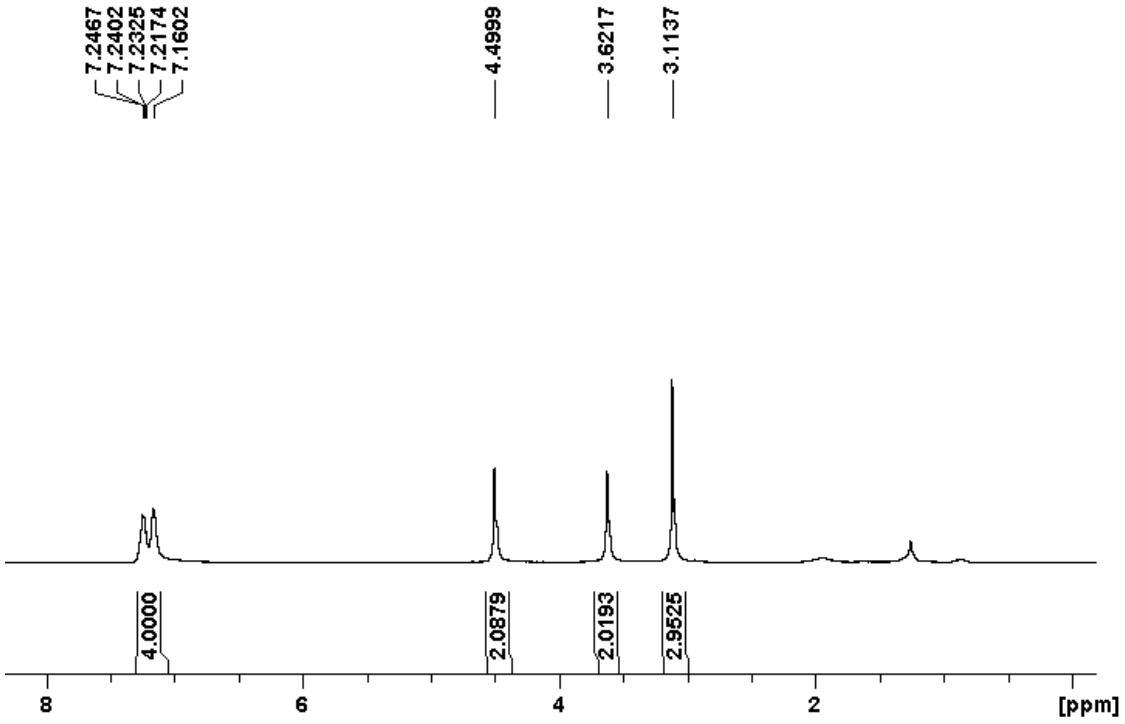
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7.1602
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2.0193
2.9525
8
6
4
2
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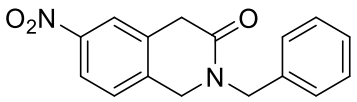
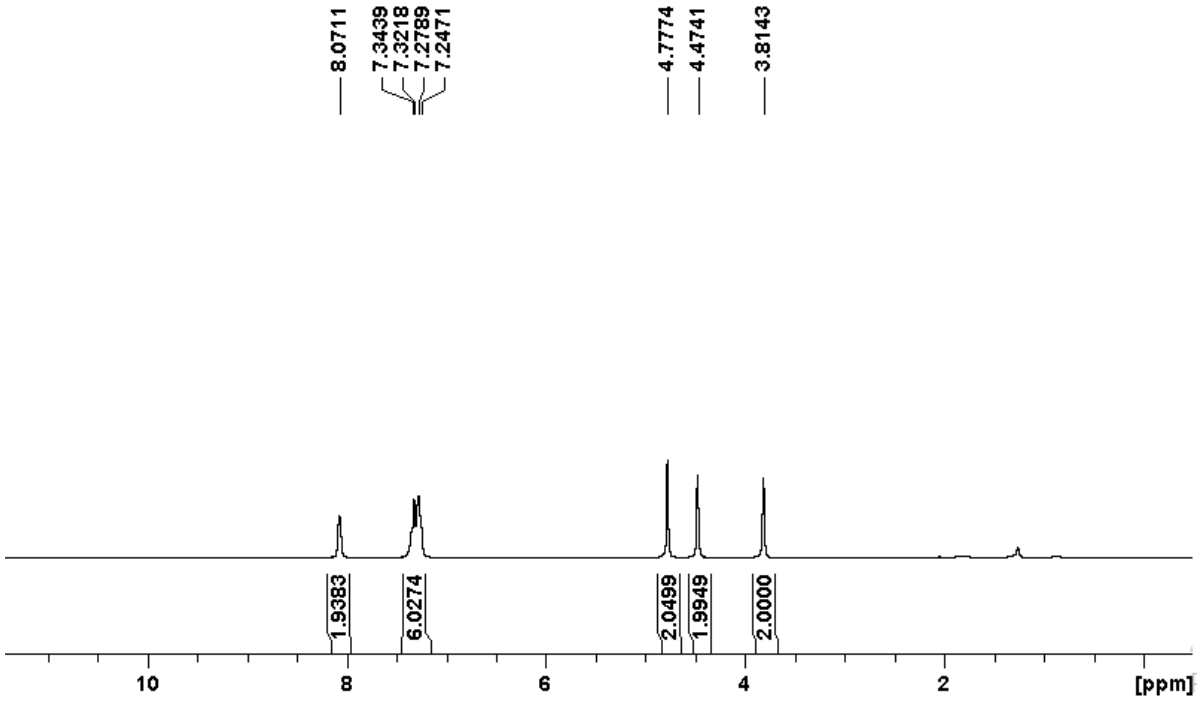

O2N
O
N

5aa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7.2471
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1.9949
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10
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6
4
2
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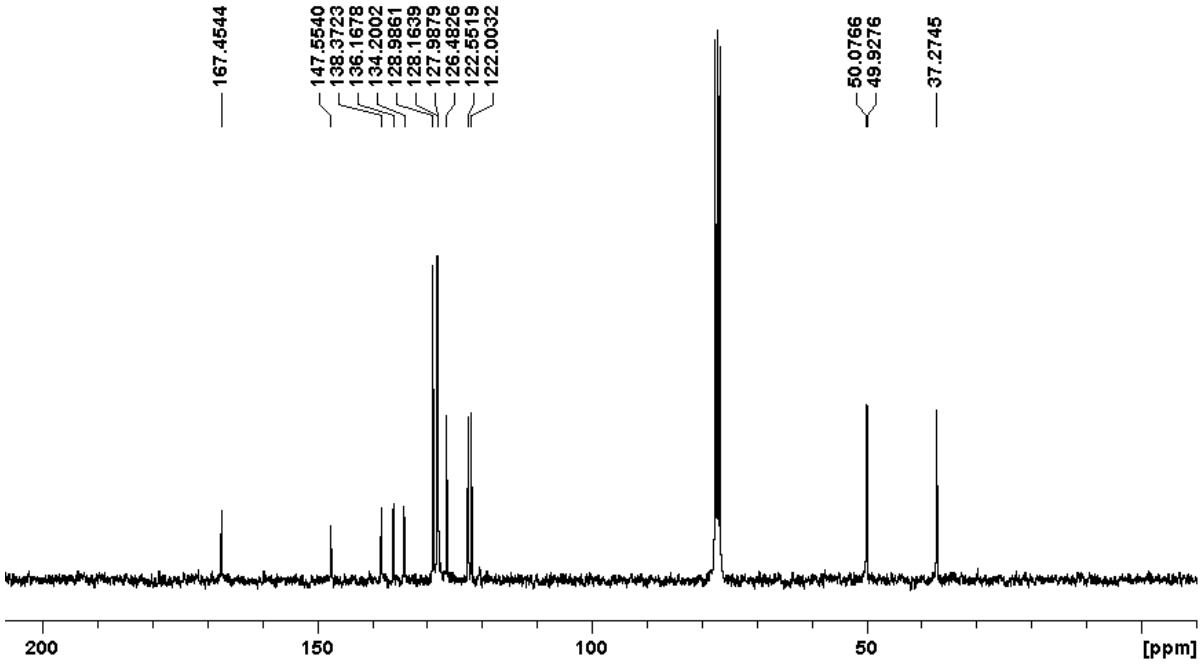
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136.1678
134.2002
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37.2745
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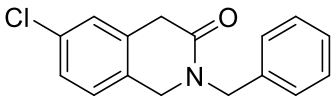
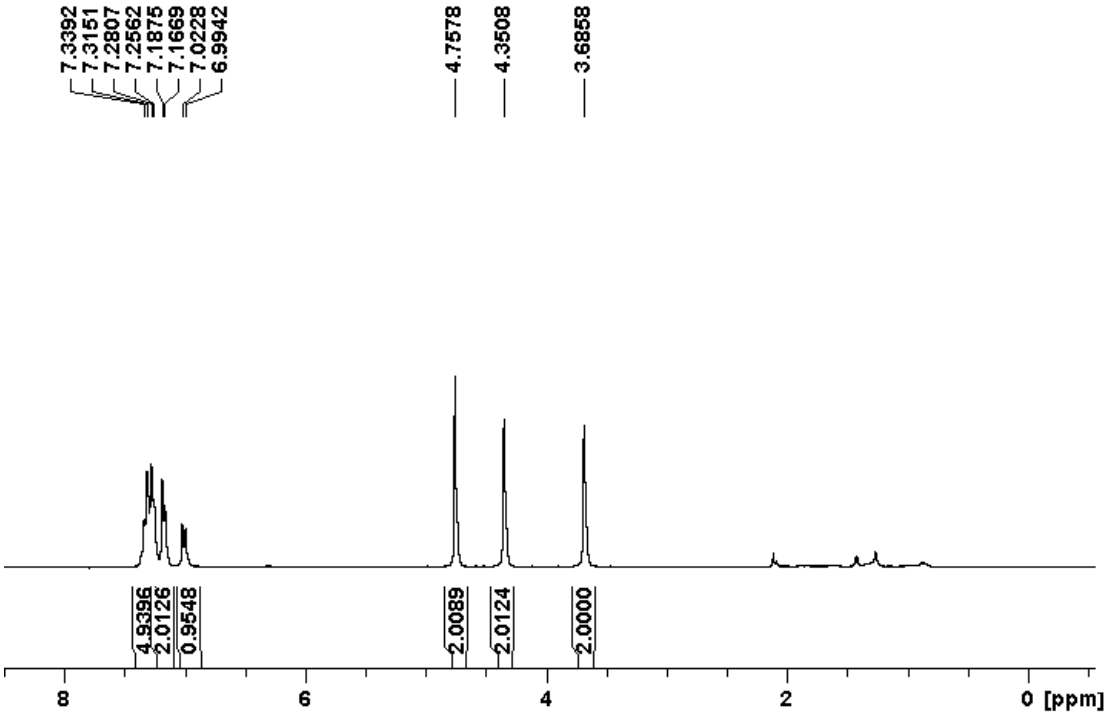

Cl
O
N

5ab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4
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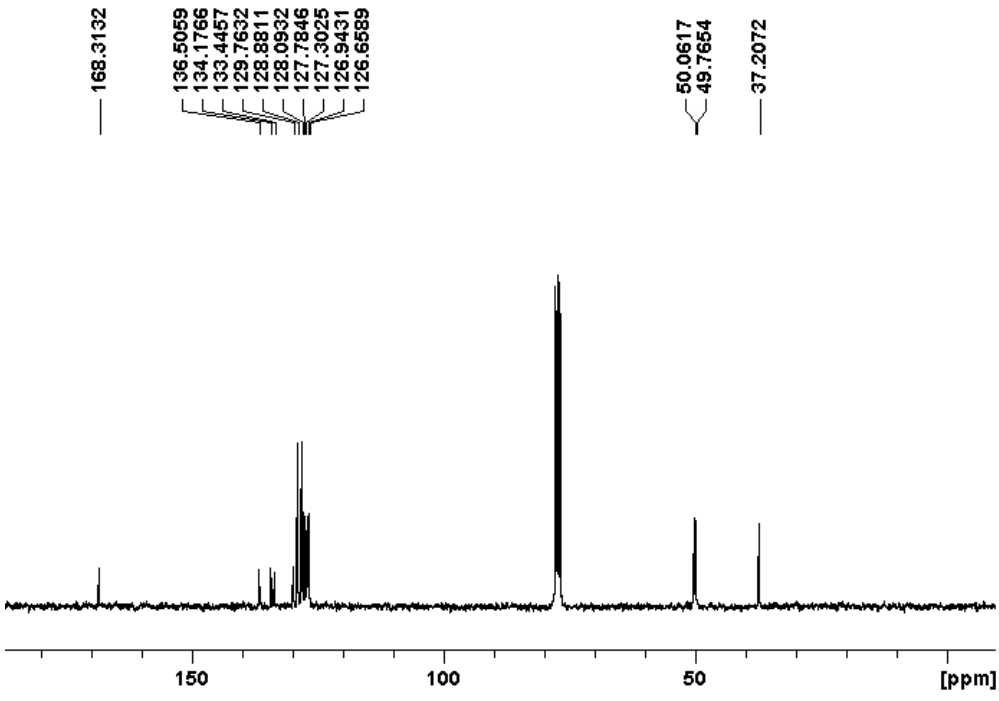
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126.6589
50.0617
49.7654
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150
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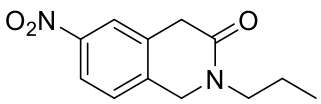

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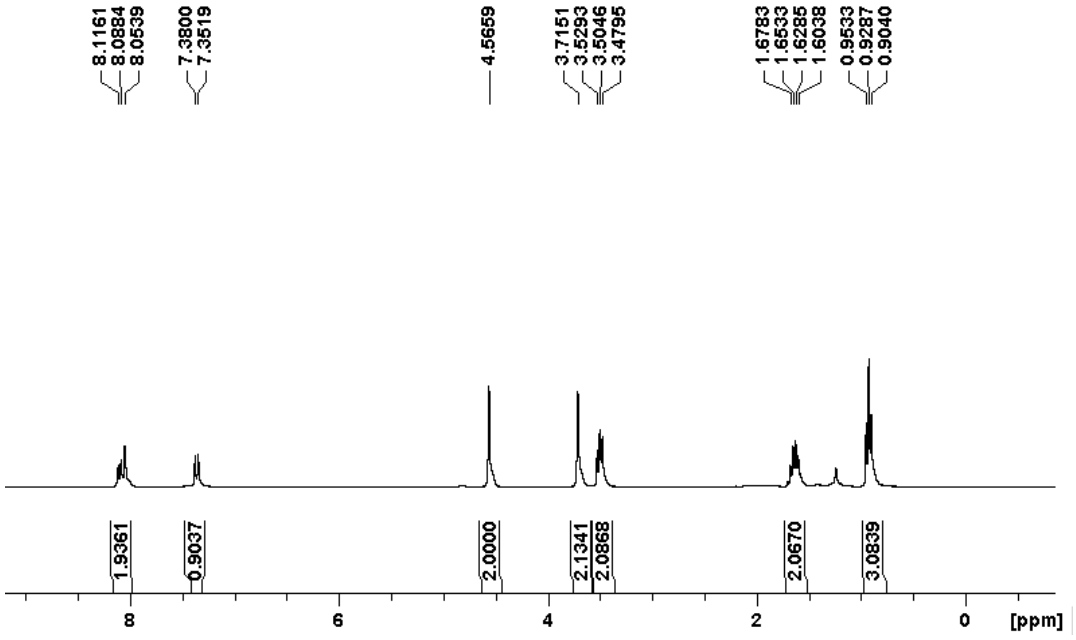
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3.5046
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1.6783
1.6533
1.6285
1.6038
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0.9040
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2.0868
2.0670
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4
2
0
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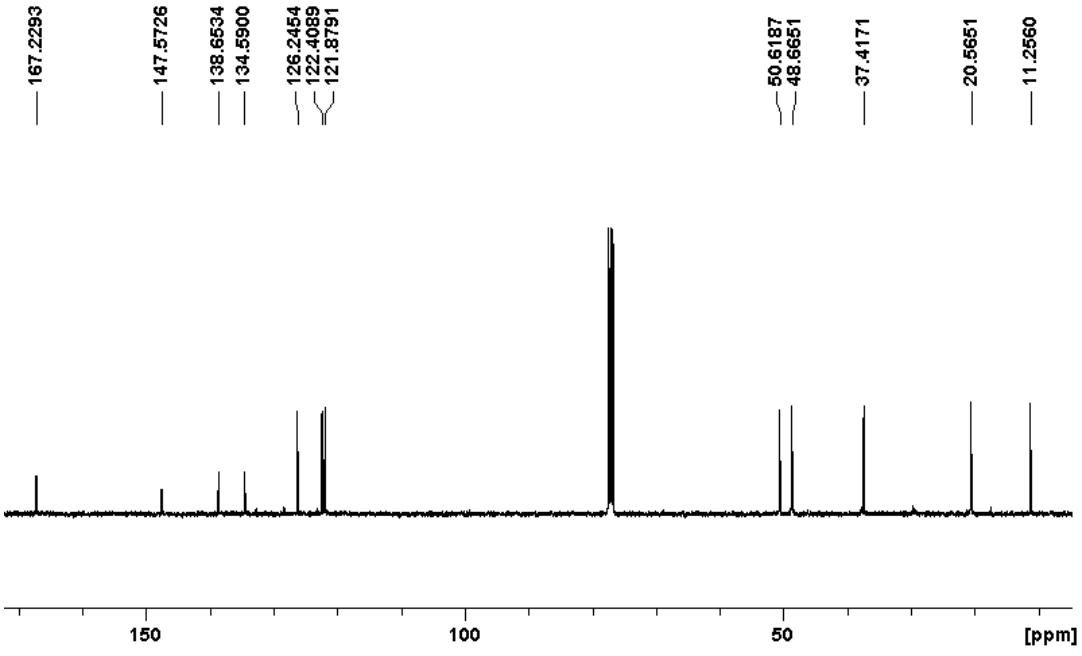
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11.2560
150
100
50
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