Supporting information

Electrochemical Hofmann rearrangement mediated by NaBr: a practical access to bioactive carbamates

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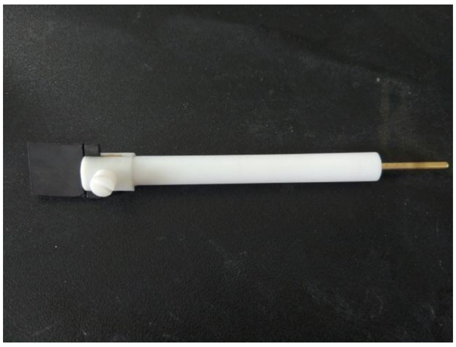
Table of Contents

Part I Experimental Section

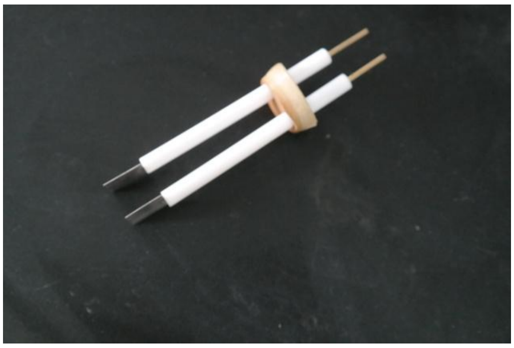
1.1 General information

^{1}H NMR and ^{13}C NMR were recorded on a Bruker-400MHz Spectrometer (^{1}H NMR: 400MHz, ^{13}C NMR: 100MHz) using TMS as internal reference. All the ^{13}C NMR spectra are obtained in ^{13}C{H} experiments. The chemical shifts (δ) and coupling constants (*J*) were expressed in ppm and Hz respectively. The abbreviations used for explaining the multiplicities were as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and the time-of-flight (TOF) mass analyzer. Commercially available compounds were used without further purification. Substrate **1b**-**1ad**[1] and **^{15}N-1d**[2] were prepared according to the literature procedures.

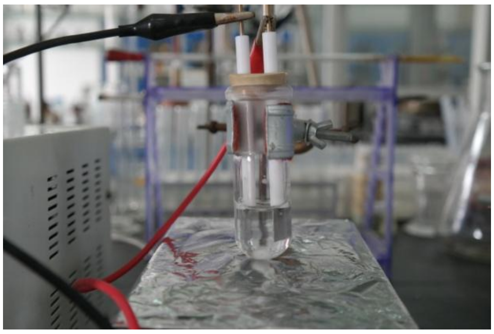
1.2 General procedure for electrochemical Hofmann rearrangement



graphite plate electrode



platinum plate electrode



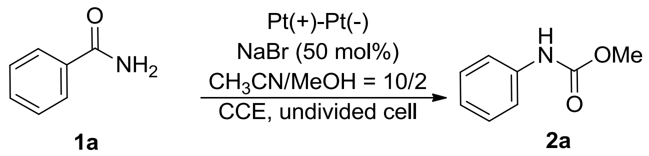
undivided cell

divided cell

Figure S1. Electrolysis setup

1.2.1 General procedure

Condition A (1a as example)

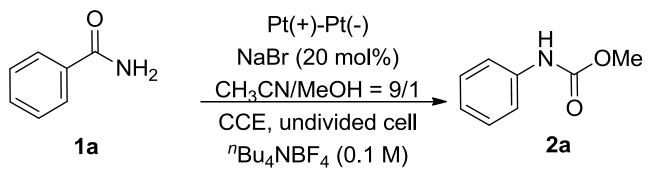


An undivided cell was equipped with a magnet stirrer, platinum plate (1.5×1.5 cm^2) electrode, as the working electrode and counter electrode. The substrate benzamide **1a** (121 mg, 1 mmol) and mediator NaBr (50 mg, 0.5 mmol) was added to the mixture solvent CH_3CN/MeOH (10/2 mL). The resulting mixture was allowed to stir and electrolyze at constant current conditions (6.7 mA/cm^2) at 50 ºC for 6 hours. Then the solvent was removed with a rotary evaporator and the residue was purified by column chromatography (EA/PE = 15/1) on silica gel to afford the desired product **2a** with 88 % yield.

In the cases of **2t, 2v, 2w, 2x, 2aa** and **2ab**, Higher temperature 60 ºC is required.

In the cases of **2ag-2ah**, ^{n}Bu$_4$NBr (161mg, 0.5 mmol) was used as the mediator.

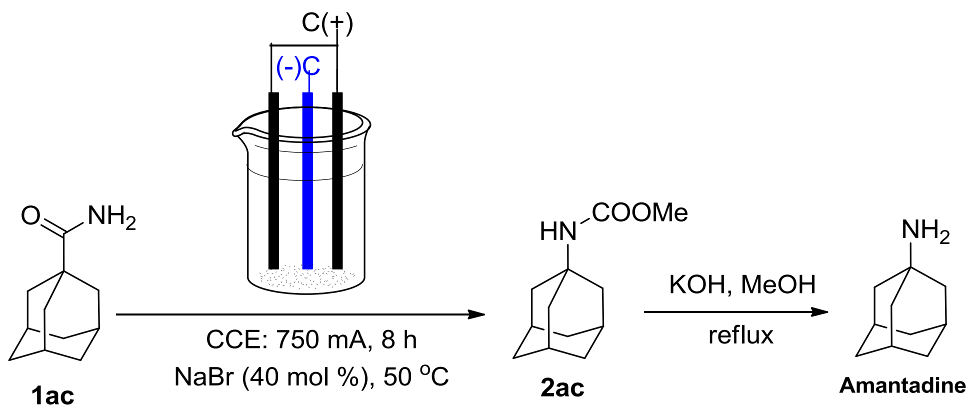
Condition B (1a as example)



An undivided cell was equipped with a magnet stirrer, platinum plate (1.5×1.5 cm^2) electrode, as the working electrode and counter electrode. The substrate benzamide **1a** (121 mg, 1 mmol) and mediator NaBr (20 mg, 0.2 mmol), supporting electrolyte ^{n}Bu$_4$NBF$_4$ (329mg, 1mmol) was added to the mixture solvent CH_3CN/MeOH (9/1 mL). The resulting mixture was allowed to stir and electrolyze at constant current conditions (6.7 mA/cm^2) at 50 ºC for 8 hours. Then the solvent was removed with a rotary evaporator and the residue was purified by column chromatography (EA/PE = 15/1) on silica gel to afford the desired product **2a** with 80 % yield.

In the cases of **2t, 2v, 2w, 2x, 2aa** and **2ab**, Higher temperature 60 ºC is required

1.2.2 Gram-scale reaction and synthesis of Amantadine (2ac)



An undivided cell was equipped with a magnet stirrer, three pieces of graphite plates as anodes and cathodes (4×7 cm^2 per piece, total area for anode: (4×7)×2 cm^2). The substrate

(3r,5r,7r)-adamantane-1-carboxamide **1e** (9.0 g, 50 mmol) and electrolyte NaBr (2.0 g, 20 mmol) was added to the mixture solvent CH_3CN/H_2O (162/18 mL). The resulting mixture was allowed to stir and electrolyze at constant current conditions (13.3 mA/cm^2, 750 mA) at 50 ºC for 8 hours. Then the solvent was removed with a rotary evaporator and the residue was extracted with EtOAc 3 times. The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography (EA/PE = 15/1) on silica gel to afford the desired product **2ac** with 73% yield (7.7 g).

According to a reported procedure,[3] to a solution of **2ac** (7.7 g, 36.7 mmol) in methanol (100 mL) was added 40% KOH solution (50 mL), and the mixture was refluxed overnight. After being cooled to room temperature, the mixture was diluted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual was recrystallized to obtain **Amantadine** (4.8 g, 86%).

1.3 Cyclic voltammetric experiments

The electrochemical analysis was demonstrated with Ag wire as a reference electrode, which is not a stable reference electrode. CVs can be calibrated using ferrocene as an external reference. (Figure S2) $E_0(Fc/Fc^+)$ = (0.088-0.058)/2 = 0.015V.

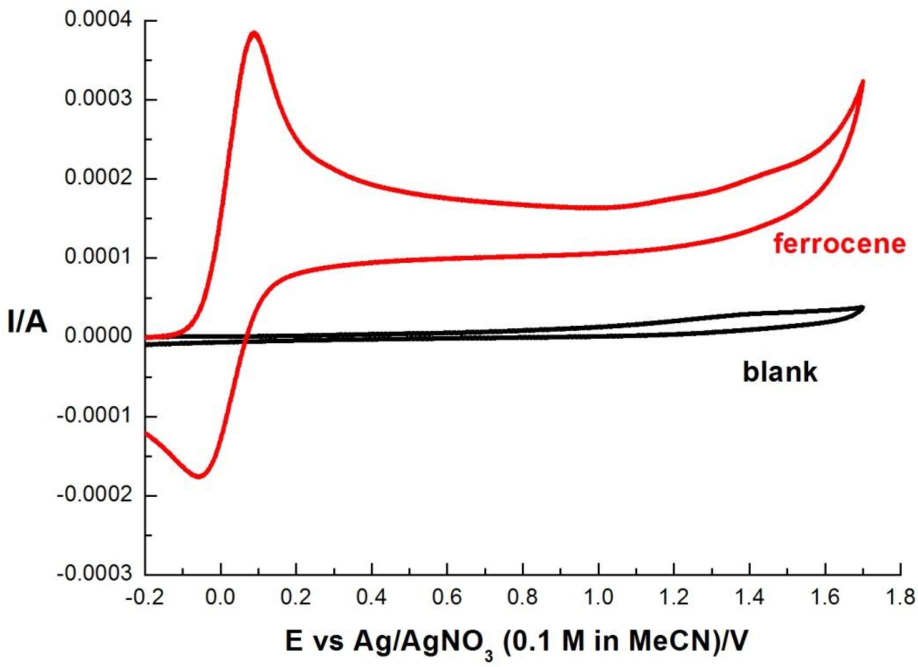


Figure S2. Cyclic voltammograms of ferrocene in 0.1 M LiClO4/CH3CN/MeOH (9/1, v/v), using Pt wire working electrode, glassy carbon, and $Ag/AgNO_3$ (0.1 M in CH_3CN) as counter and reference electrodes at 100 mV/s scan rate.

The cyclic voltammetric experiments were performed as shown below (Figure S3). All potentials reported here vs. Fc/Fc^+ were obtained by comparing the potentials measured vs. the Ag/Ag^+ electrode with $E_0(Fc/Fc^+)$ (Figure S4).

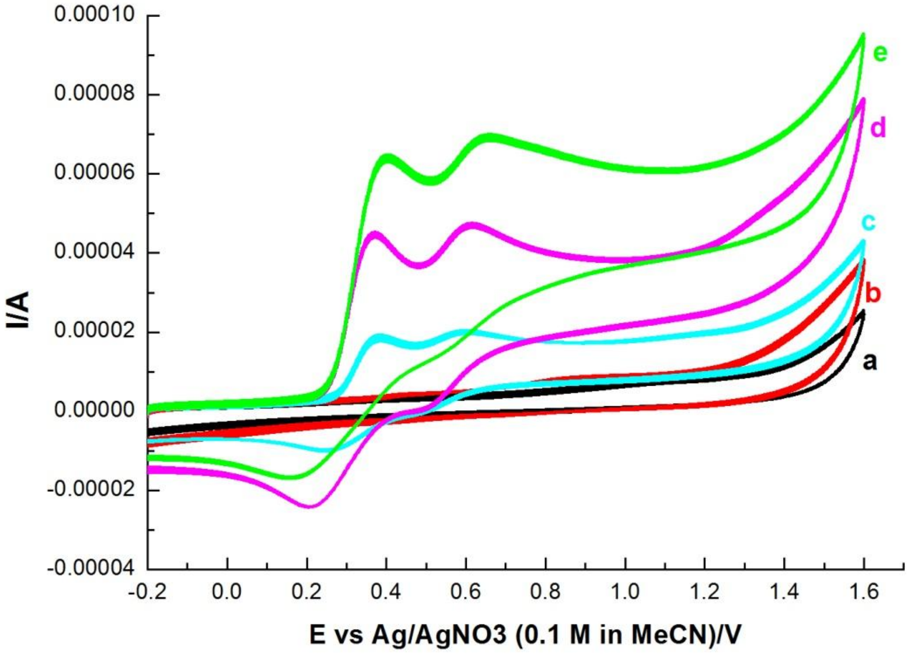


Figure S3. Cyclic voltammograms of NaBr and related compounds in 0.1 M $LiClO_4/CH_3CN/MeOH$ (9/1, v/v) using Pt wire working electrode, Pt disk, and Ag/Ag NO_3 (0.1 M in CH3CN) as counter and reference electrodes at 100 mV/s scan rate: (a) background, (b) **1a** (5 mmol/L), (c) NaBr (5 mmol/L), (d) NaBr (5 mmol/L) and **1a** (10 mmol/L), (e) NaBr (5 mmol/L), **1a** (10 mmol/L) and MeONa (10 mmol/L).

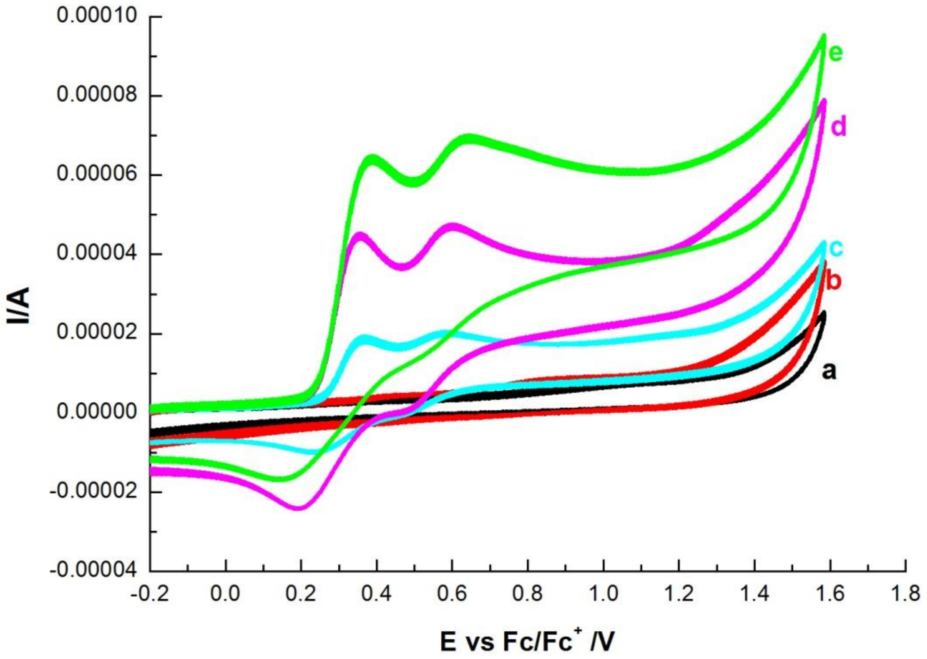
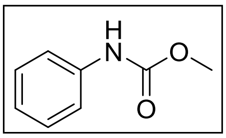
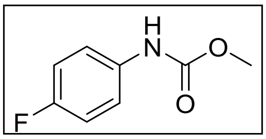


Figure S4. Cyclic voltammograms of NaBr and related compounds (vs Fc/Fc^{+}).

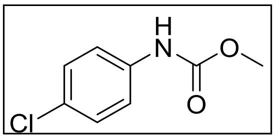
1.4 Experimental data of products



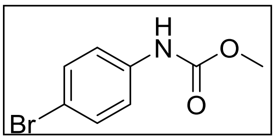
Methyl phenylcarbamate (2a): White solid in 88% yield, 132 mg; m.p. 46-47 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.75 (br, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 137.8, 129.0, 123.4, 118.8, 52.3; The spectroscopic data correspond to those previously reported in the literature.[4]



Methyl (4-fluorophenyl)carbamate (2b): White solid in 67% yield, 113 mg; m.p. 90-91 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 2H), 7.00 (t, J = 8.5 Hz, 2H), 6.75 (br, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9 (d, $J_{F\text{-}C}$ = 242.2 Hz), 154.2, 133.8, 120.3, 115.6 (d, $J_{F\text{-}C}$ = 22.5 Hz), 52.4; The spectroscopic data correspond to those previously reported in the literature.[4]

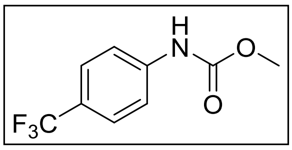


Methyl (4-chlorophenyl)carbamate (2c): White solid in 92% yield, 170 mg; m.p. 113-115 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 (d, J = 7.3 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.80 (br, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 136.4, 129.0, 128.4, 119.8, 52.4; The spectroscopic data correspond to those previously reported in the literature.[4]

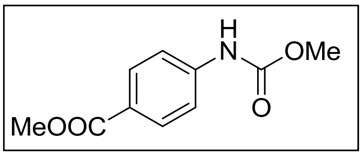


Methyl (4-bromophenyl)carbamate (2d): White solid in 76% yield, 174 mg; m.p. 118-120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 6.74 (br, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 136.9, 131.9, 120.1, 115.9, 52.5; The spectroscopic data correspond to those previously reported in the literature.[4]

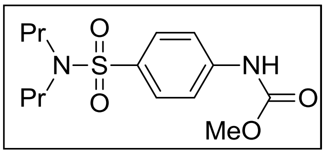
^{15}N-2d: ^{1}H NMR (400 MHz, $CDCl_3$): 7.41 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 7.6 Hz, 2H), 6.76 (d, $J_{N\text{-}H}$ = 90.8 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 153.7, 136.9 (d, $J_{N\text{-}C}$ = 16.8 Hz), 131.9 (d, $J_{N\text{-}C}$ = 1.9 Hz), 120.1, 115.9, 52.5; HRMS (ESI) m/z calcd for $C_8H_8Br^{15}NO_2$ $[M+H]^+$ 230.9782, found 230.9783.



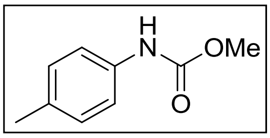
Methyl (4-(trifluoromethyl)phenyl)carbamate (2e): White solid in 80% yield, 175 mg; m.p. 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 4H), 6.97 (br, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 140.9, 126.29 (q, $J_{F\text{-}C}$ = 3.5 Hz), 125.4 (q, $J_{F\text{-}C}$ = 12.9 Hz), 123.9 (q, $J_{F\text{-}C}$ = 224.4 Hz), 118.0, 52.6; The spectroscopic data correspond to those previously reported in the literature.[5]



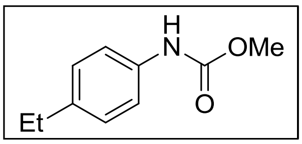
methyl 4-((methoxycarbonyl)amino)benzoate (2f): White solid in 84% yield, 176 mg; m.p. 169-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.92 (br, 1H), 3.90 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 153.5, 142.1, 130.9, 124.8, 117.5, 52.6, 52.0; The spectroscopic data correspond to those previously reported in the literature.[6]



Methyl (4-(N,N-dipropylsulfamoyl)phenyl)carbamate (2g): White solid in 68% yield, 214 mg; m.p. 103-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.46 (br, 1H), 3.78 (s, 3H), 3.06 (t, *J* = 7.4 Hz, 4H), 1.55 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 141.8, 133.6, 128.2, 118.0, 52.5, 49.9, 21.9, 11.1; HRMS (ESI) m/z calcd for $C_{14}H_{22}N_2O_4S$ $[M+Na]^+$ 337.1193, found 337.1188.

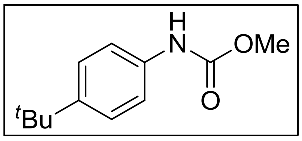


Methyl p-tolylcarbamate (2h): White solid in 71% yield, 117 mg; m.p. 98-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 6.4 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.71 (br, 1H), 3.76 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 135.2, 133.0, 129.5, 118.7, 52.2, 20.7; The spectroscopic data correspond to those previously reported in the literature.[7]

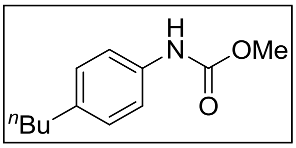


Methyl (4-ethylphenyl)carbamate (2i): Colorless oil in 75% yield, 134 mg; ^{1}H NMR (400 MHz,

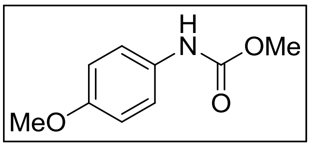
$CDCl_3$): δ 7.29 (d, *J* = 5.6 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.72 (br, 1H), 3.76 (s, 3H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 139.4, 135.3, 128.3, 118.8, 52.2, 28.1, 15.7; The spectroscopic data correspond to those previously reported in the literature.[8]



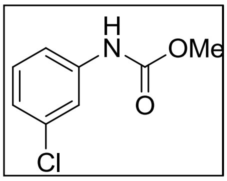
Methyl (4-(tert-butyl)phenyl)carbamate (2j): white solid in 92% yield, 191 mg; m.p. 77-78 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 4H), 6.6 (br, 1H), 3.77 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 146.4, 135.1, 125.8, 118.5, 52.3, 34.2, 31.3; The spectroscopic data correspond to those previously reported in the literature.[4]



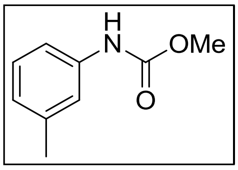
Methyl (4-butylphenyl)carbamate (2k): white solid in 82% yield, 170 mg; m.p. 60-61 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 6.0 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.67 (br, 1H), 3.76 (s, 3H), 2.56 (t, *J* = 7.8 Hz, 2H), 1.56 (m, 2H), 1.34 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 138.1, 135.3, 128.9, 118.7, 52.3, 34.9, 33.7, 22.2, 13.9; The spectroscopic data correspond to those previously reported in the literature.[9]



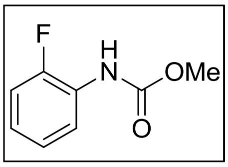
Methyl (4-methoxyphenyl)carbamate (2l): white solid in 87% yield, 158 mg; m.p. 87-88 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.72 (br, 1H), 3.78 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 154.4, 130.9, 120.6, 114.1, 55.4, 52.2; The spectroscopic data correspond to those previously reported in the literature.[10]



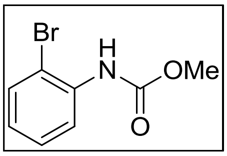
Methyl (3-chlorophenyl)carbamate (2m): white solid in 92% yield, 170 mg; m.p. 74-76 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.22 (d, *J* = 5.0 Hz, 2H), 7.04-7.03 (m, 1H), 6.79 (br, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 139.0, 134.7, 130.0, 123.4, 118.6, 116.5, 52.5; The spectroscopic data correspond to those previously reported in the literature.[4]



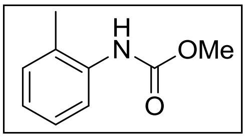
Methyl *m*-tolylcarbamate (2n): white solid in 93% yield, 153 mg; m.p. 61-63 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (br, 1H), 7.18 (d, *J* = 4.3 Hz, 2H), 6.87 (m, 2H), 3.75 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 138.8, 137.7, 128.7, 124.1, 119.2, 115.6, 52.2, 21.4; The spectroscopic data correspond to those previously reported in the literature.[4]



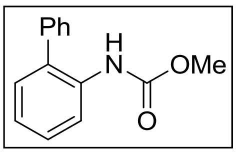
Methyl (2-fluorophenyl)carbamate (2o): colorless oil in 92% yield, 156 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.14-6.93 (m, 4H), 3.80 (d, *J* = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 152.1 (d, J_{F-C} = 241.7 Hz), 126.4 (d, J_{F-C} = 9.8 Hz), 124.5, 123.4 (d, J_{F-C} = 7.3 Hz), 120.1, 114.8 (d, J_{F-C} = 18.9 Hz), 52.5; The spectroscopic data correspond to those previously reported in the literature.[8]



Methyl (2-bromophenyl)carbamate (2p): colorless oil in 87% yield, 200 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.15 (br, 1H), 6.93(t, *J* = 7.6 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 135.7, 132.2, 128.4, 124.2, 120.1, 52.5; The spectroscopic data correspond to those previously reported in the literature.[11]

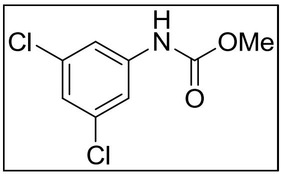


Methyl o-tolylcarbamate (2q): white solid in 93% yield, 154 mg; m.p. 51-53 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (br, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.46 (s, 1H), 3.77 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 135.7, 130.3, 126.8, 124.1 121.0, 52.3, 17.6; The spectroscopic data correspond to those previously reported in the literature.[8]

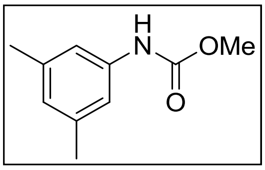


Methyl [1,1'-biphenyl]-2-ylcarbamate (2r): white solid in 82% yield, 186 mg; m.p. 48-50 ℃; ^{1}H

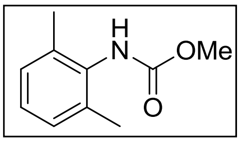
NMR (400 MHz, $CDCl_3$): δ 8.14 (br, 1H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.41-7.34 (m, 4H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.68 (br, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 137.9, 134.7, 131.3, 130.1, 129.2, 129.0, 128.4, 127.8, 123.3, 119.4, 52.2; The spectroscopic data correspond to those previously reported in the literature.[12]



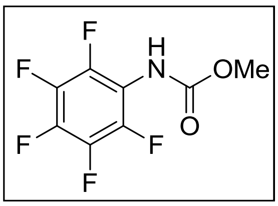
Methyl (3,5-dichlorophenyl)carbamate (2s): white solid in 60% yield, 132 mg; m.p. 114-116 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 2H), 7.05 (s, 1H), 6.8 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 139.7, 135.3, 123.4, 116.7, 52.7; The spectroscopic data correspond to those previously reported in the literature.[13]



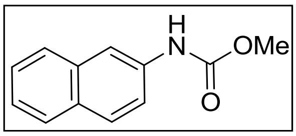
Methyl (3,5-dimethylphenyl)carbamate (2t): white solid in 42% yield, 75 mg; m.p. 54-56 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (s, 2H), 6.70 (s, 2H), 3.76 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 138.7, 137.6, 125.1, 116.3, 52.2, 21.3; The spectroscopic data correspond to those previously reported in the literature.[14]



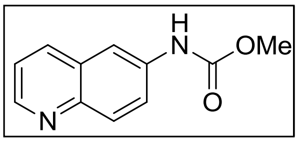
Methyl (2,6-dimethylphenyl)carbamate (2u): white solid in 93% yield, 167 mg; m.p. 91-93 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 7.09 (m, 3H), 6.05 (br, 1H), 3.77 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 135.8, 131.0, 128.2, 127.2, 52.5, 18.3; The spectroscopic data correspond to those previously reported in the literature.[15]



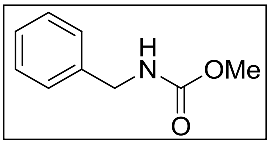
Methyl (perfluorophenyl)carbamate (2v): white solid in 75% yield, 181 mg; m.p. 68-70 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 6.60 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 144.4-144.3 (m), 142.0 (m), 141.2 (m), 139.0 (m), 136.5 (m), 112.2 (m), 53.5; HRMS (ESI) m/z calcd for $C_8H_4F_5NO_2$ $[M+H]^+$ 242.0235, found 242.0232.



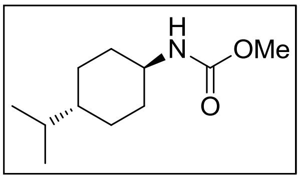
Methyl naphthalen-2-ylcarbamate (2w): white solid in 43% yield, 87 mg; m.p. 104-106 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.77-7.75 (m, 3H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.39-7.36 (m, 2H), 6.89 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 135.2, 133.8, 130.1, 128.8, 127.5, 127.4, 126.5, 124.7, 119.1, 114.8, 52.4; The spectroscopic data correspond to those previously reported in the literature.[8]



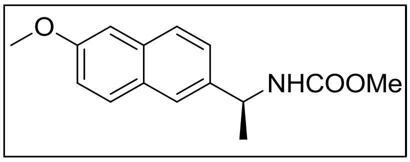
Methyl quinolin-6-ylcarbamate (2x): white solid in 58% yield, 117 mg; m.p. 105-107 ℃; ^1H NMR (400 MHz, d^6-DMSO): δ 10.0 (s, 1H), 8.76 (d, *J* = 2 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.48-7.45 (m, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, d^6-DMSO): δ 154.5, 149.1, 144.8, 137.6, 135.6, 130.0, 128.8, 123.1, 122.2, 113.8, 52.2; HRMS (ESI) m/z calcd for $C_{11}H_{10}N_2O_2$ $[M+H]^+$ 203.0815, found 203.0817.



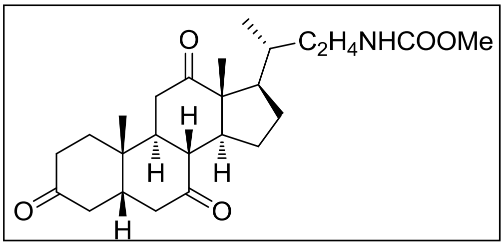
Methyl benzylcarbamate (2y): white solid in 94% yield, 155 mg; m.p. 60-62 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 5.16 (br, 1H), 4.36 (d, *J* = 6.0 Hz, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 138.5, 128.6, 127.41, 127.38, 52.2, 45.0; The spectroscopic data correspond to those previously reported in the literature.[16]



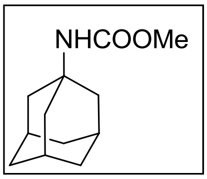
Methyl (trans-4-isopropylcyclohexyl)carbamate (2y): white solid in 81% yield, 161 mg; m.p. 65-66 ℃; ^1H NMR (400 MHz, $CDCl_3$): δ 4.56 (s, 1H), 3.65 (s, 3H), 3.40 (m, 1H), 2.02 (m, 2H), 1.74-1.72 (m, 2H), 1.45-1.40 (m, 1H), 1.10-1.07 (m, 4H), 1.02-1.00 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 51.8, 50.4, 43.1, 33.6, 32.5, 28.3, 19.8; HRMS (ESI) m/z calcd for $C_{11}H_{21}NO_2$ $[M+H]^+$ 200.1645, found 200.1641.



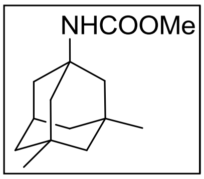
(S)-Methyl (1-(6-methoxynaphthalen-2-yl)ethyl)carbamate (2z): white solid in 68% yield, 176 mg; m.p. 107-108 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.67 (s, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.15-7.11 (m, 2H), 5.03 (m, 2H), 3.91 (s, 3H), 3.67 (s, 3H), 1.55 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 133.8, 129.3, 128.7, 127.3, 125.0, 124.2, 119.0, 105.5, 55.3, 52.1, 50.5, 22.2; HRMS (ESI) m/z calcd for $C_{15}H_{17}NO_3$ $[M+H]^+$ 260.1281, found 260.1287.



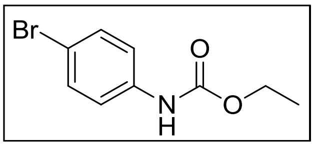
Methyl ((*R*)-3-((5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)butyl)carbamate (2aa): white solid in 63% yield, 272 mg; m.p. 194-196 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (br, 1H), 3.66 (s, 3H), 3.26 (m, 1H), 3.18-3.16 (m, 1H), 2.95-2.82 (m, 3H), 2.34-2.21 (m, 6H), 2.16-2.13 (m, 2H), 2.09-1.95 (m, 4H), 1.89-1.84 (m, 1H), 1.66-1.58 (m, 3H), 1.41 (s, 3H), 1.29-1.27 (m, 3H), 1.08 (s, 3H), 0.88 (d, *J* = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.9, 209.2, 208.7, 156.8, 56.6, 51.7, 51.5, 48.6, 46.5, 45.5, 45.2, 44.7, 42.5, 38.7, 38.4, 36.2, 35.7, 35.3, 34.9, 33.7, 27.5, 24.8, 21.6, 18.7, 11.5; HRMS (ESI) m/z calcd for $C_{25}H_{37}NO_5$ $[M+H]^+$ 432.2750, found 432.2753.



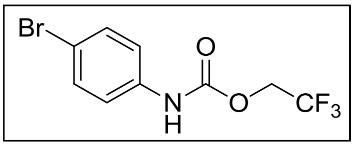
Methyl (3*s*,5*s*,7*s*)-adamantan-1-ylcarbamate (2ab): white solid in 85% yield, 178 mg; m.p. 119-120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (s, 1H), 3.60 (s, 3H), 2.08 (s, 3H), 1.93 (s, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 51.3, 50.6, 41.8, 36.2, 29.4; The spectroscopic data correspond to those previously reported in the literature.[17]



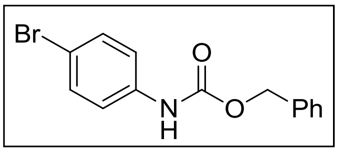
Methyl ((1*r*,3*R*,5*S*,7*r*)-3,5-dimethyladamantan-1-yl)carbamate (2ac): white solid in 87% yield, 206 mg; m.p. 34-36 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (s, 1H), 3.60 (s, 3H), 2.16-2.13 (m, 1H), 1.76 (s, 2H), 1.57 (s, 4H), 1.37 (d, J = 12.0 Hz, 2H), 1.29 (d, J = 12.4 Hz, 2H), 1.15 (dd, J = 13.2 Hz, 16.4 Hz, 2H), 0.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 52.1, 51.2, 50.4, 47.7, 42.5, 40.3, 32.3, 30.0; HRMS (ESI) m/z calcd for $C_{14}H_{23}NO_2$ $[M+H]^+$ 238.1807, found 238.1802.



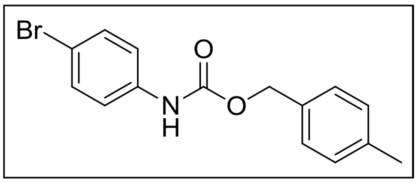
Ethyl (4-bromophenyl)carbamate (2ad): white solid in 64% yield, 156 mg; m.p. 68-70 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 6.69 (br, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 137.0, 131.9, 120.1, 115.7, 61.4, 14.5; The spectroscopic data correspond to those previously reported in the literature.[4]



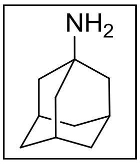
2,2,2-Trifluoroethyl (4-bromophenyl)carbamate (2ae): white solid in 71% yield, 200 mg; m.p. 71-73 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.89 (br, 1H), 4.56 (q, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 135.9, 132.1, 122.8 (q, $J_{F\text{-}C}$ = 275.6 Hz), 120.4, 116.9, 61.0 (q, $J_{F\text{-}C}$ = 36.2 Hz); HRMS (ESI) m/z calcd for $C_9H_7BrF_3NO_2$ $[M+H]^+$ 297.9685, found 297.9681.



Benzyl (4-bromophenyl)carbamate (2af): white solid in 49% yield, 150 mg; m.p. 106-109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.35 (m, 7H), 7.28 (d, J = 7.8 Hz, 2H), 6.73 (s, 1H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, CDCl3): δ 153.1, 136.8, 135.7, 132.0, 128.6, 128.4, 128.3, 120.1, 116.0, 67.2; The spectroscopic data correspond to those previously reported in the literature.[18]



4-Methylbenzyl (4-bromophenyl)carbamate (2ag): white solid in 42% yield, 134 mg; m.p. 135-137 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.7 Hz, 2H), 7.28 (t, J = 8.1 Hz, 4H), 7.19 (d, J = 7.7 Hz, 2H), 6.69 (s, 1H), 5.14 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 153.1, 138.4, 136.9, 132.7, 131.9, 129.3, 128.5, 120.0, 115.9, 67.1, 21.2; HRMS (ESI) m/z calcd for $C_{15}H_{14}BrNO_2$ $[M+H]^+$ 320.0286, found 320.0289.



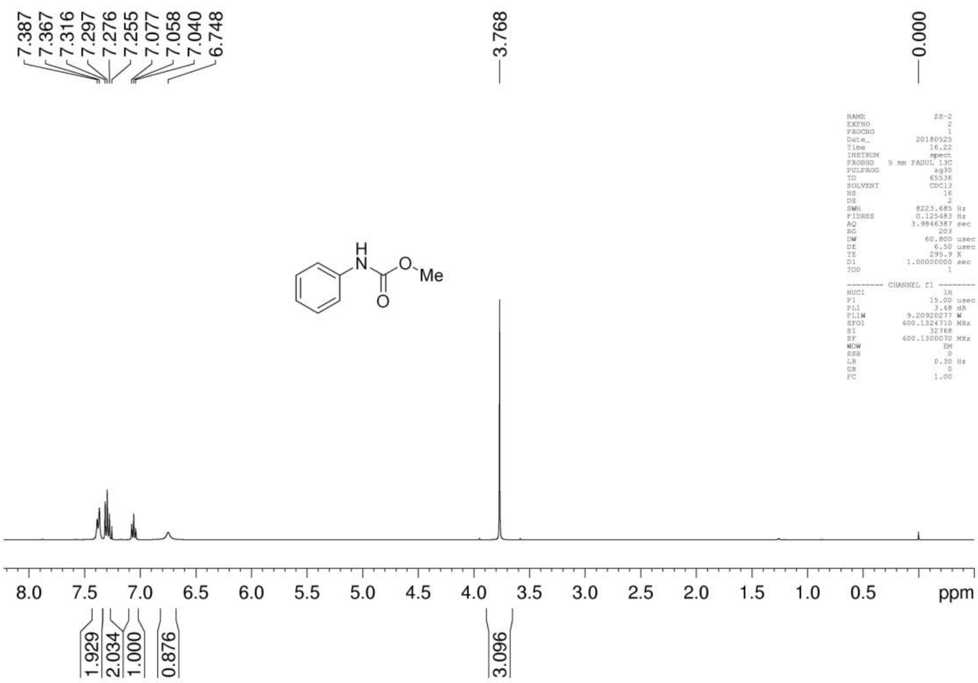
(3s,5s,7s)-Adamantan-1-amine (**3**): white solid in 89% yield, 5.6 g; m.p. 109-110 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 1.77 (s, 3H), 1.67 (s, 1H), 1.64 (s, 2H), 1.59-1.58 (m, 8H) ; ^{13}C NMR (100 MHz, CDCl3): δ 47.3, 46.0, 36.1, 29.6;

Reference:

1. Y.-Z. Wu, P. Sun, K.-F. Zhang, T. Yang, H.-Q. Yao and A.-J. Lin, *J. Org. Chem.,* 2016, **81**, 2166.
2. Y. Ma, C. E. Stivala, A. M. Wright, T. Hayton, J. Liang, I. Keresztes, E. Lobkovsky, D. B. Collum and A. Zakarian, *J. Am. Chem. Soc.,* 2013, **135**, 16853.
3. D.-D. Li, T.-T. Yuan and G.-W. Wang, *J. Org. Chem.,* 2012, **77**, 3341.
4. E. Kianmehr and M. H. Baghersad, *Adv. Syn. Catal.,* 2011, **353**, 2598.
5. A. Yoshimura, M.W. Luedtke and V. V. Zhdankin, *J. Org. Chem.*, 2012, **77,** 2087.
6. D. I. Patel and R. K. Smalley, *J. Chem. Soc., Perkin Trans. 1*, 1984, **11**, 2587.
7. Z. D. Crane, P. J. Nichols, T. Sammakia and P. J. Stengel, *J. Org. Chem.,* 2011, **76**, 277.
8. Q. Yang, A. Robertson and H. Alper, *Org. Lett.*, 2008, **10**, 5079.
9. J.Takahashi, O. Kirino, C. Takayama, S. Nakamura, H. Noguchi, T. Kato and K. Kamoshita, *Pestic. Biochem. Phys.*, 1988, **30**, 262.
10. Z.-H. Guan, H. Lei, M. Chen, Z.-H. Ren, Y. Bai and Y.-Y. Wang, *Adv. Synth. Catal.*, 2012, **354**, 489.
11. P. Mampuys, H. Neumann, S. Sergeyev, R. V. A. Orru, H. Jiao, A. Spannenberg, B. U. W. Maes, and M. Beller, *ACS Catal.*, 2017, **7**, 5549.
12. D.-D. Li, T.-T. Yuan and G.-W. Wang, *J. Org. Chem.,* 2012, **77**, 3341.
13. B. Schick, P. N Moza, K. Hustert and A. Kettrup, *Pestic. Sci.*, 1999, **55**, 1116.
14. M. Han, X. Jin, H. Yang, X. Liu, Y. Liu and S. Ji, *Carbohydrate Polymers*, 2017, **172**, 223.
15. S. Kumar and S. L. Jain, *New J. Chem.*, 2013,**37**, 2935.
16. M. Selva, P. Tundo, A. Perosa, and F. Dall'Acqua, *J. Org. Chem.*, 2005, **70**, 2771.
17. A. A. Zagulyaeva, C. T. Banek, M. S. Yusubov, and V. V. Zhdankin, *Org. Lett.*, 2010, **12**, 4644.
18. Y. Yang, and J. K. Coward, *J. Org. Chem.,* 2007, **72**, 5748.

Part II NMR Spectra

2a ^{1}H NMR:



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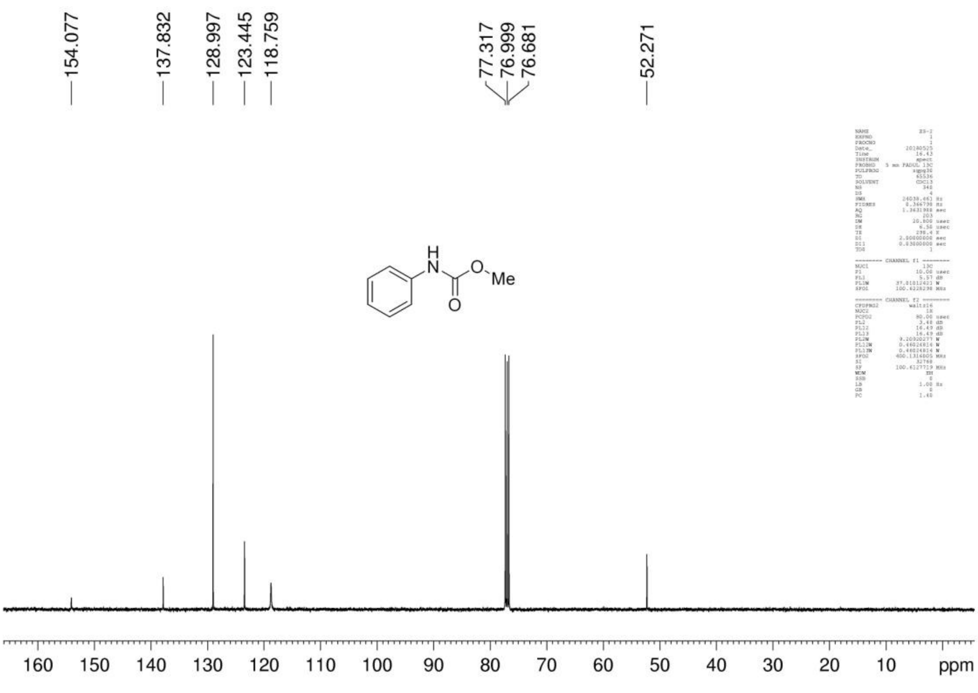

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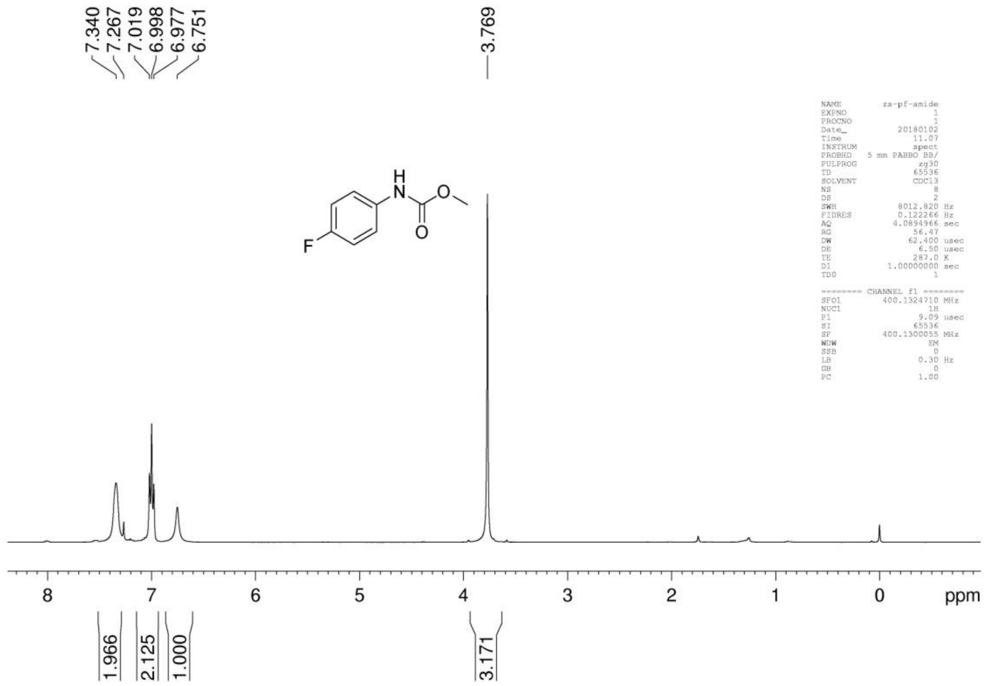

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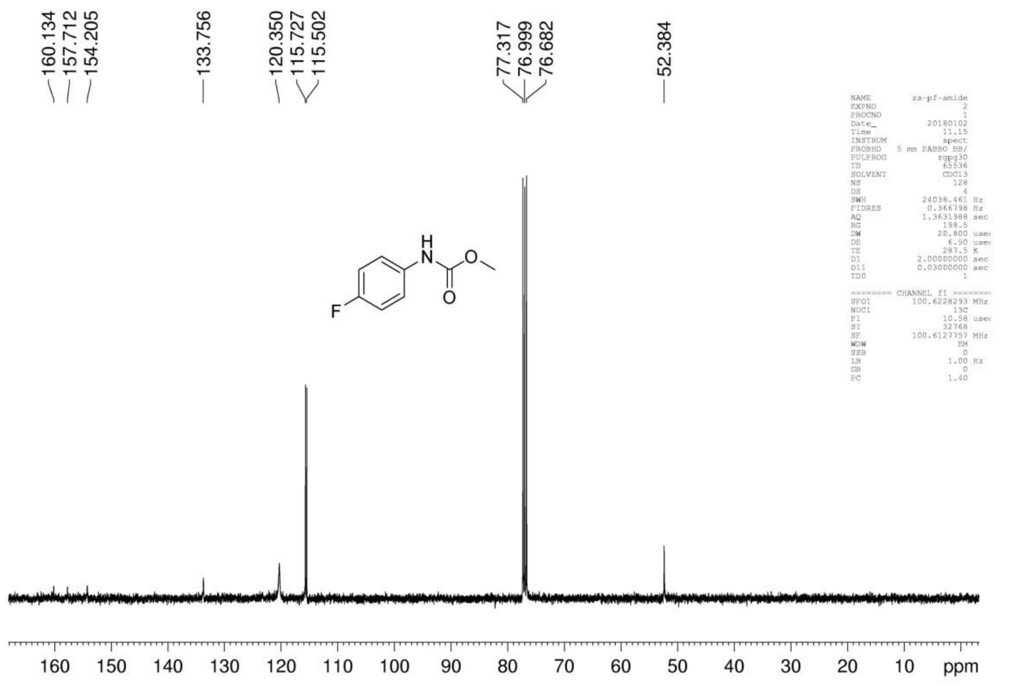

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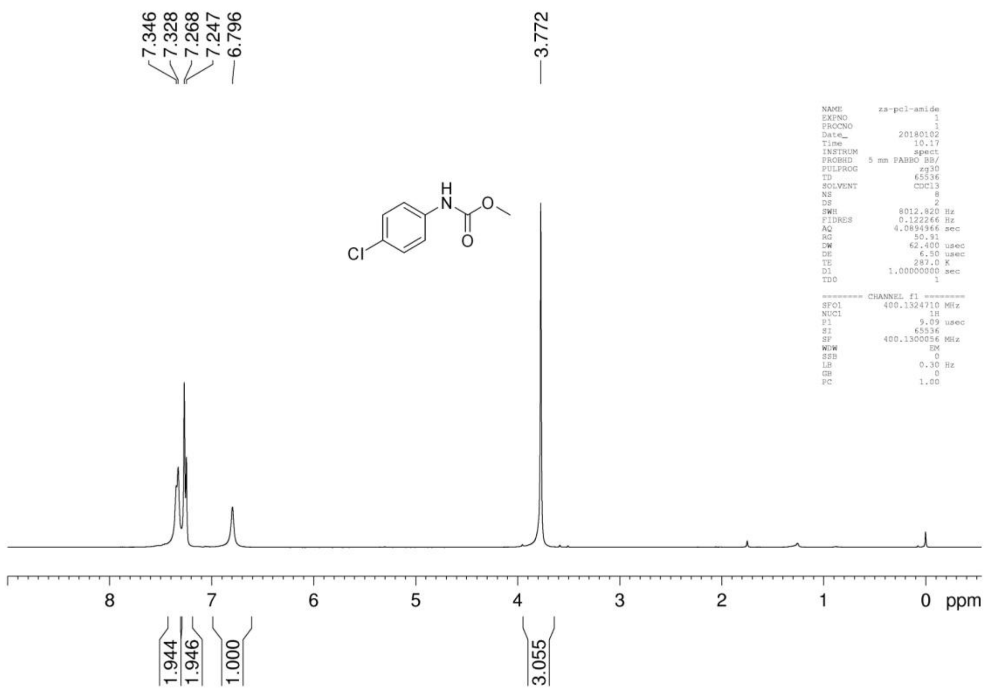

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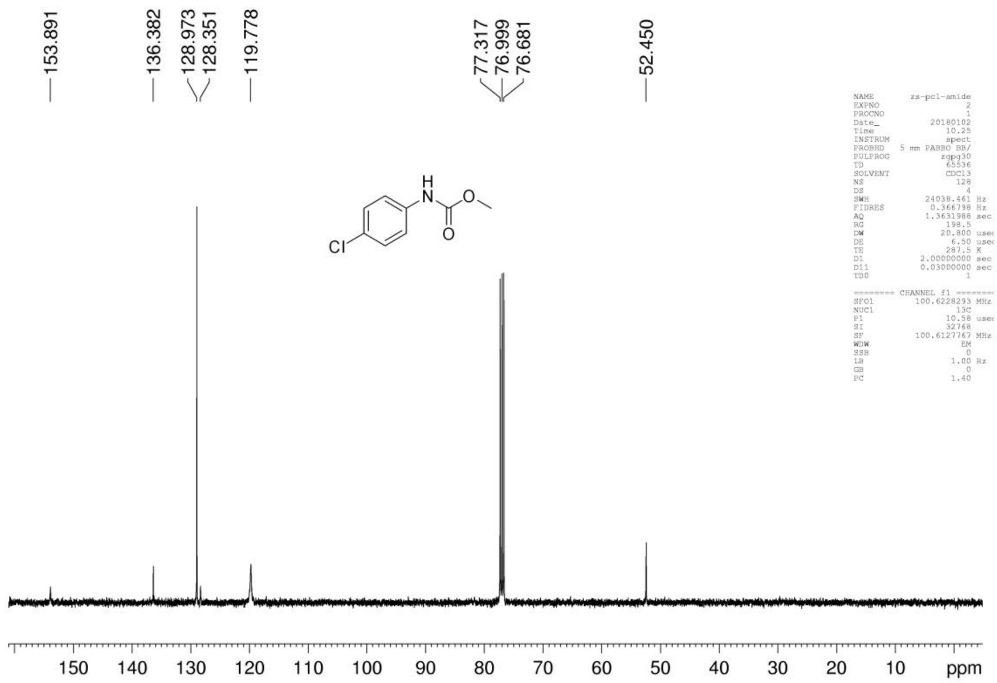

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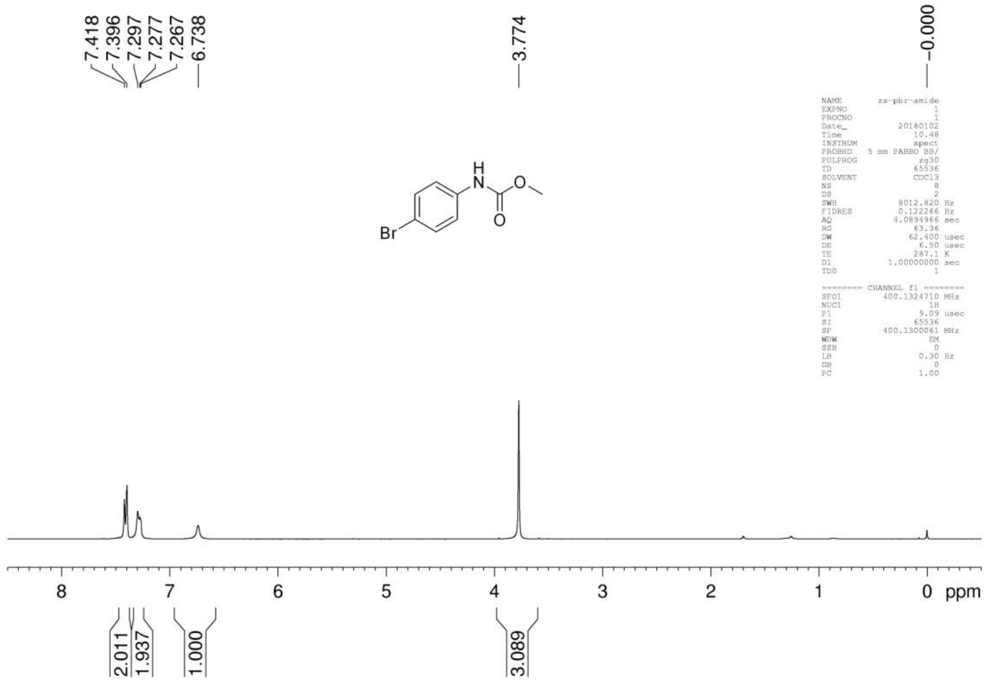

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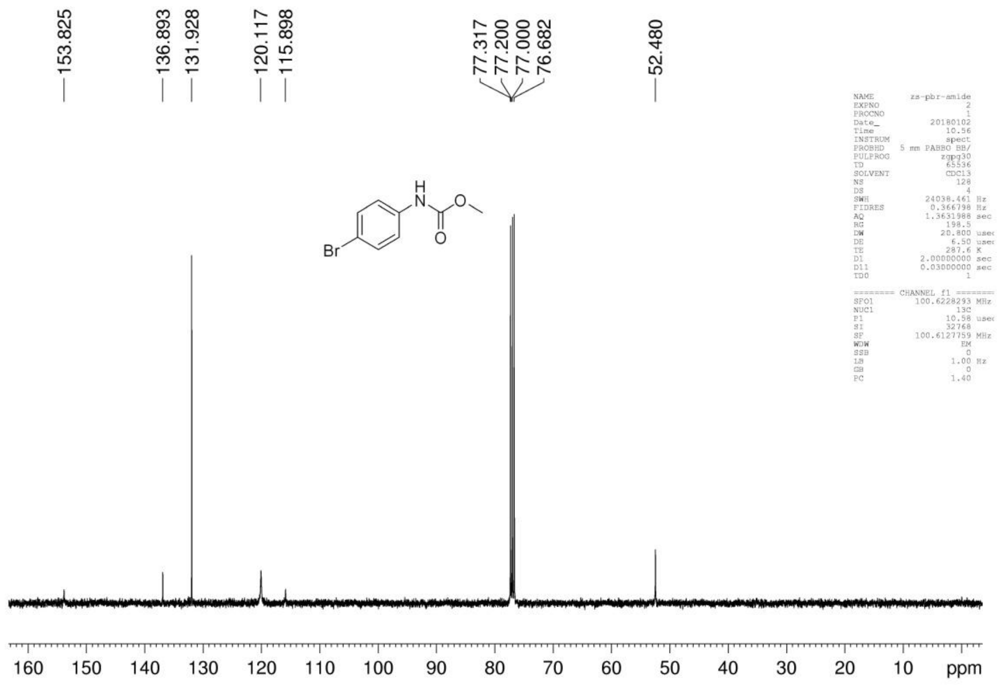

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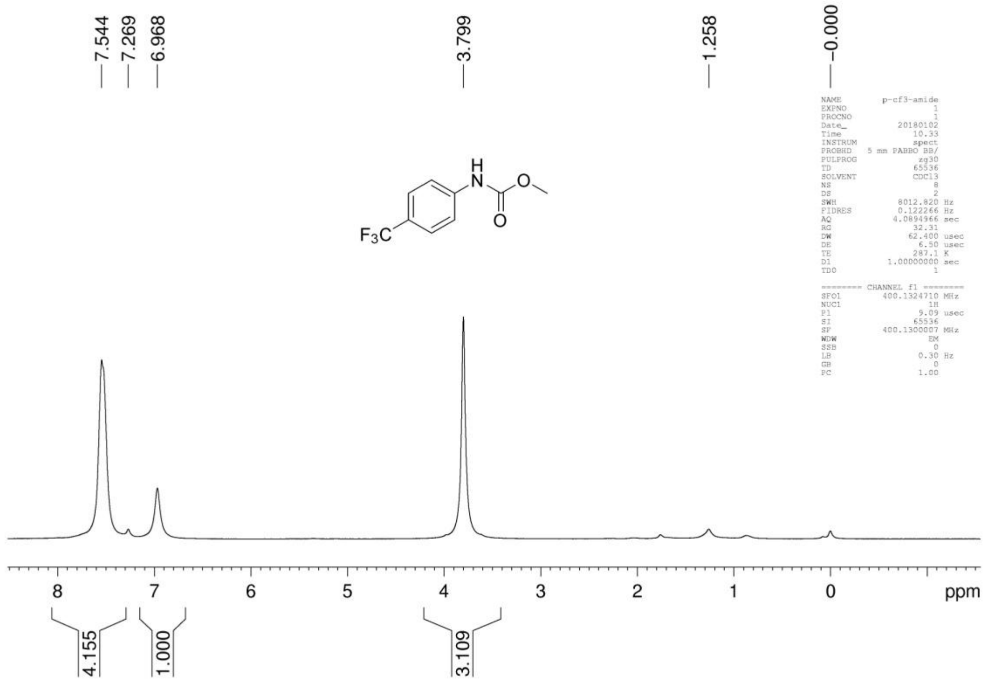

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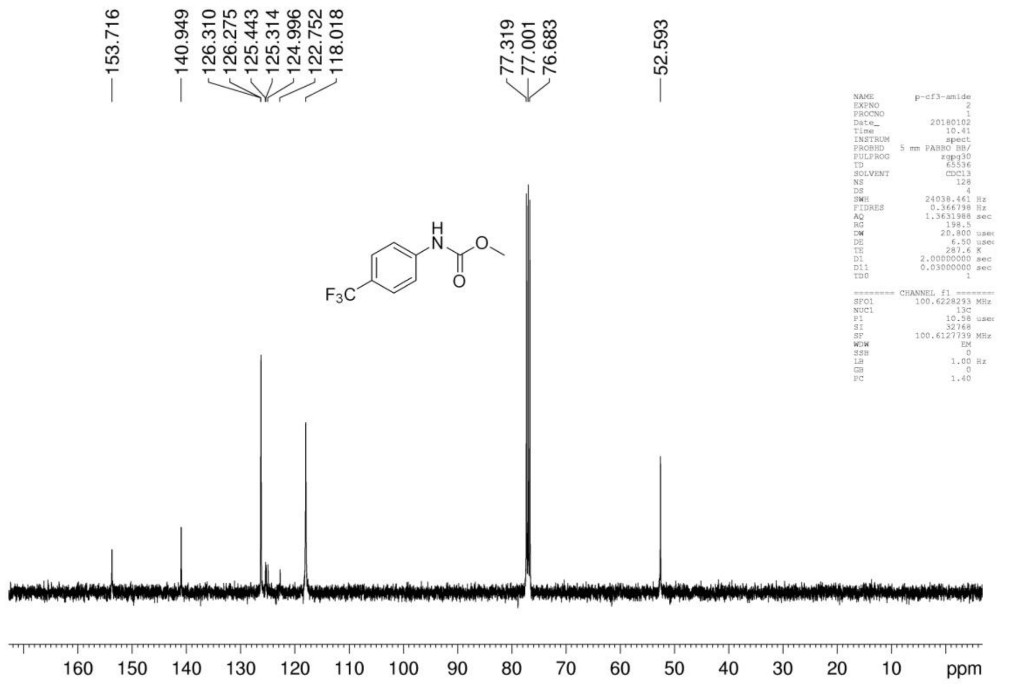
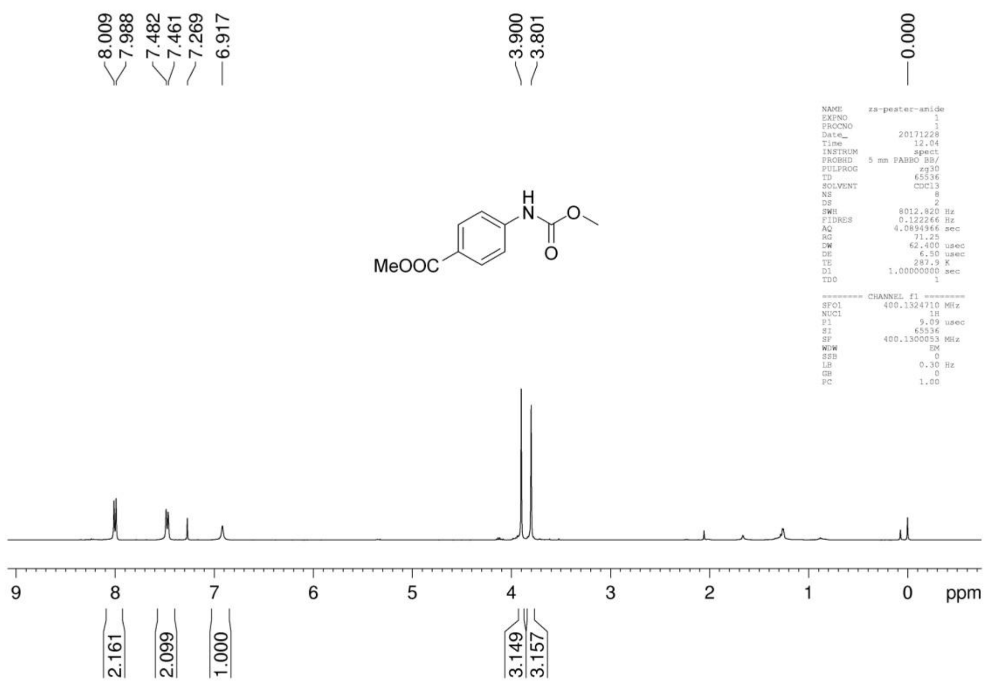


2f ¹H NMR:



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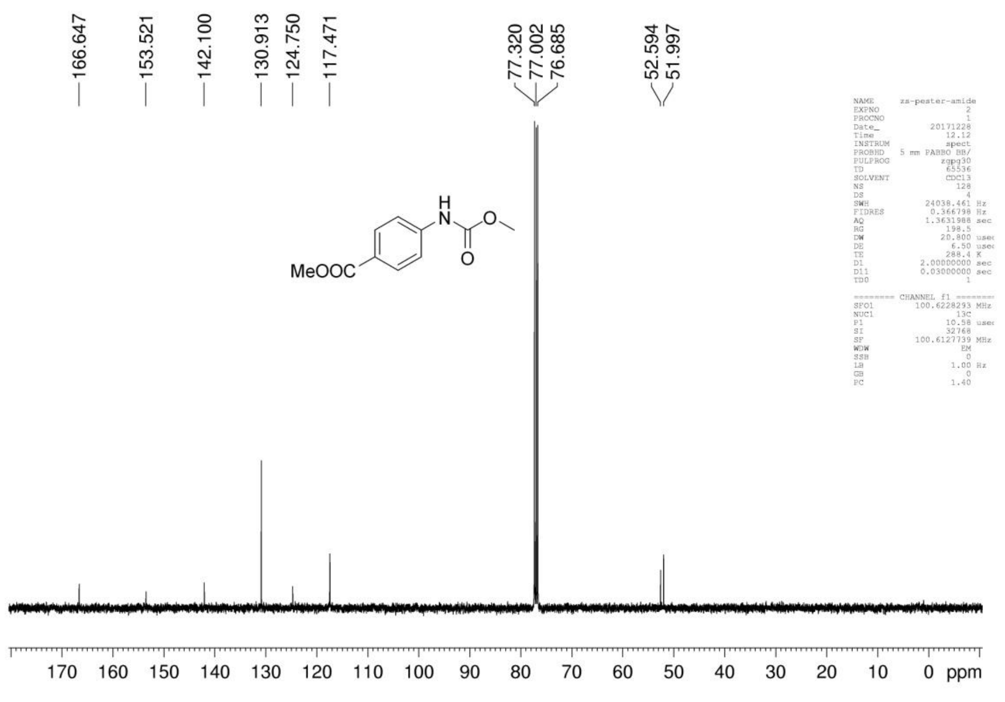

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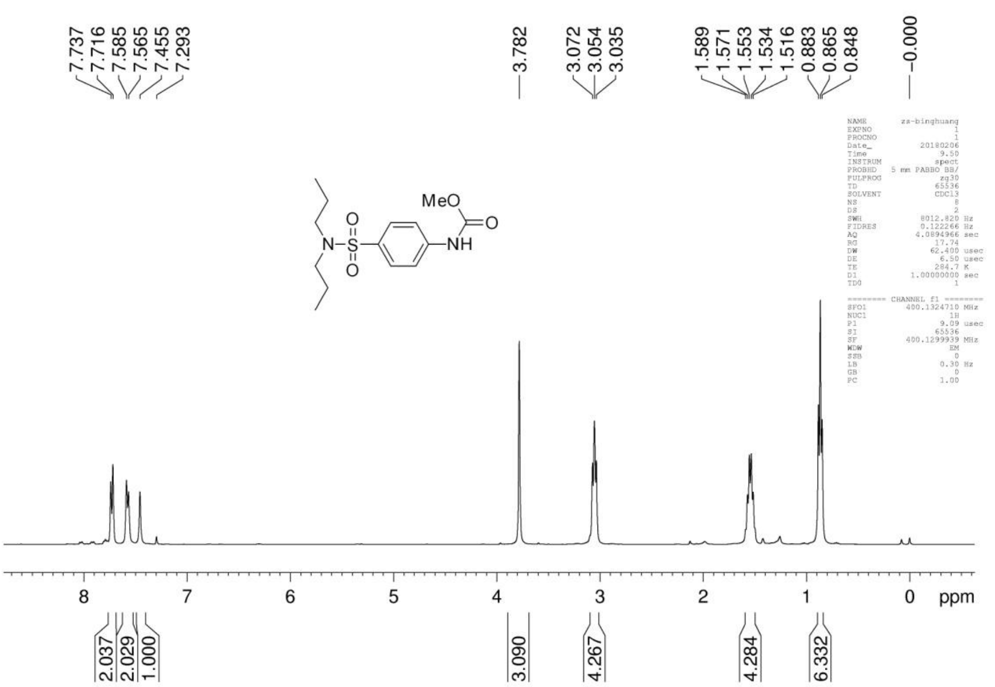

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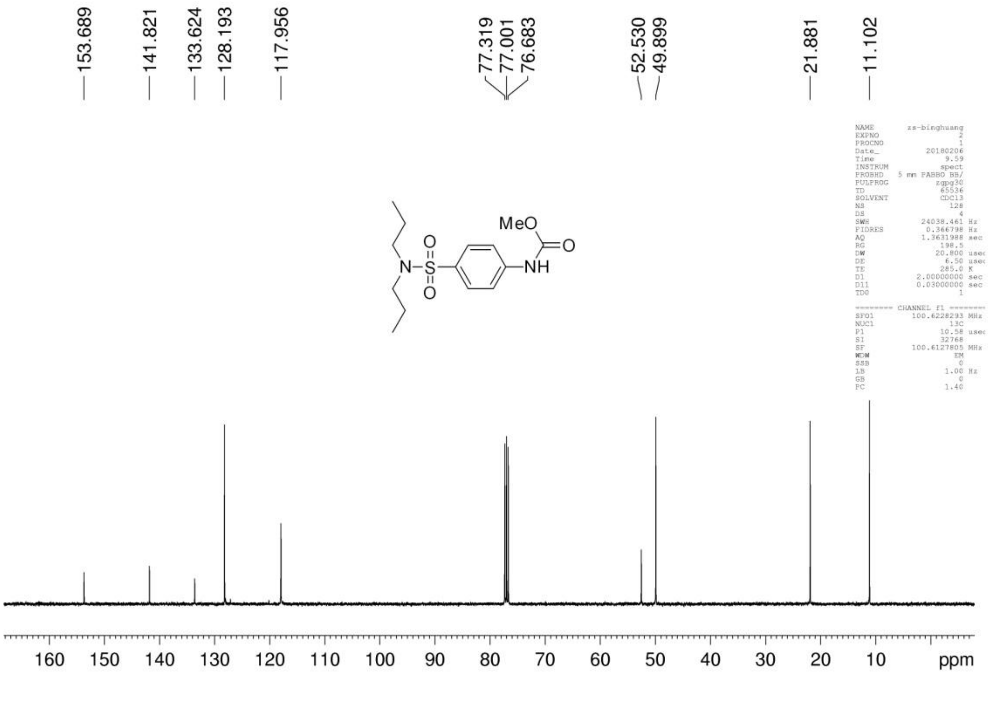
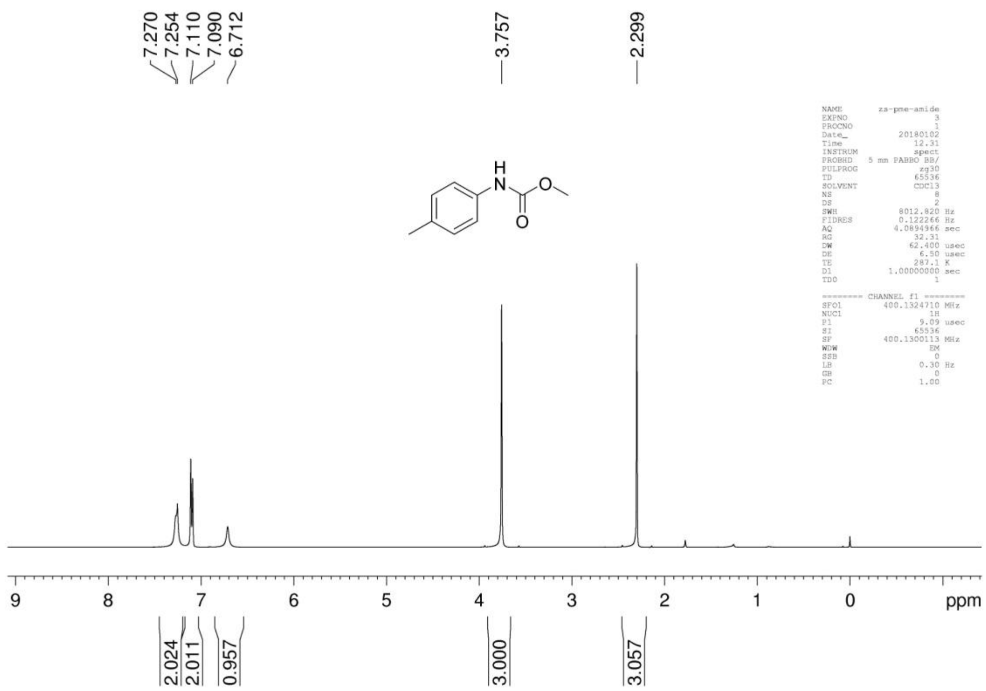


2h ¹H NMR:



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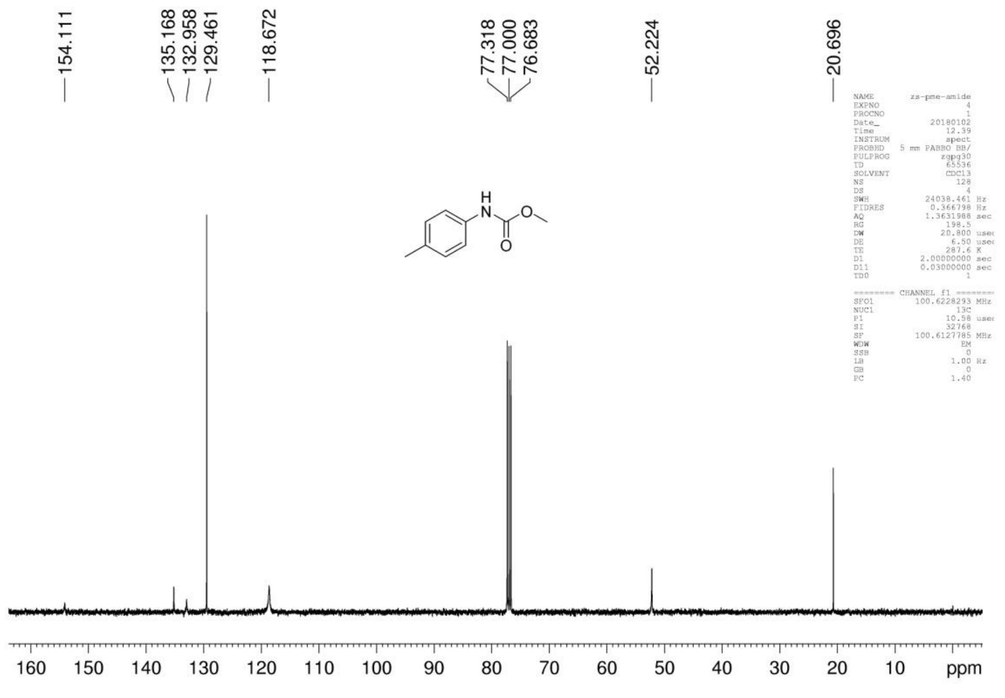

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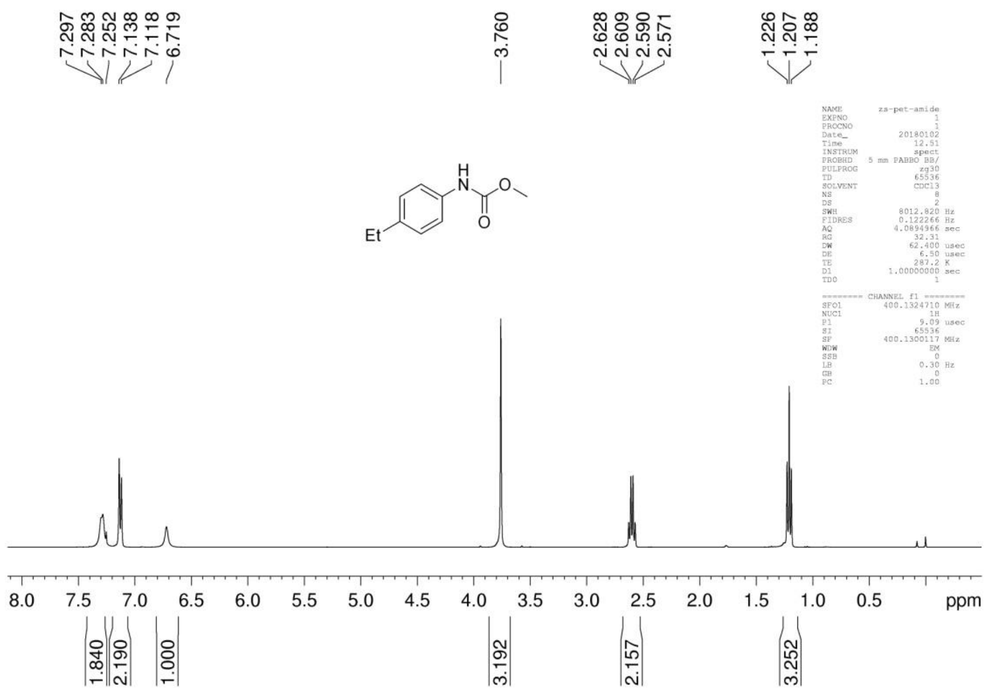

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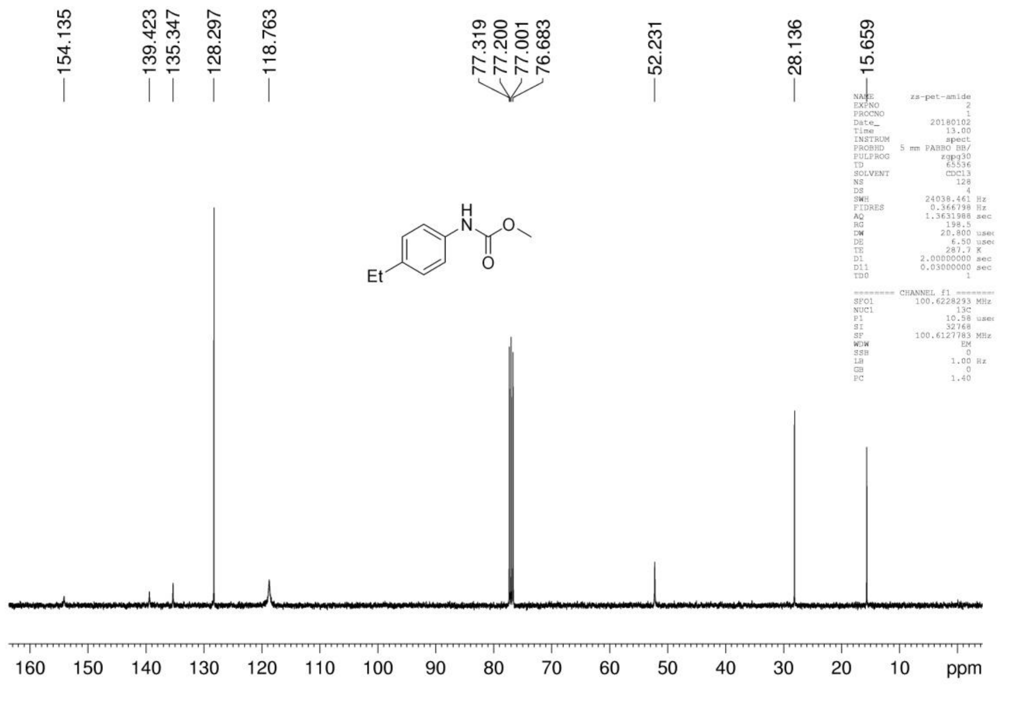

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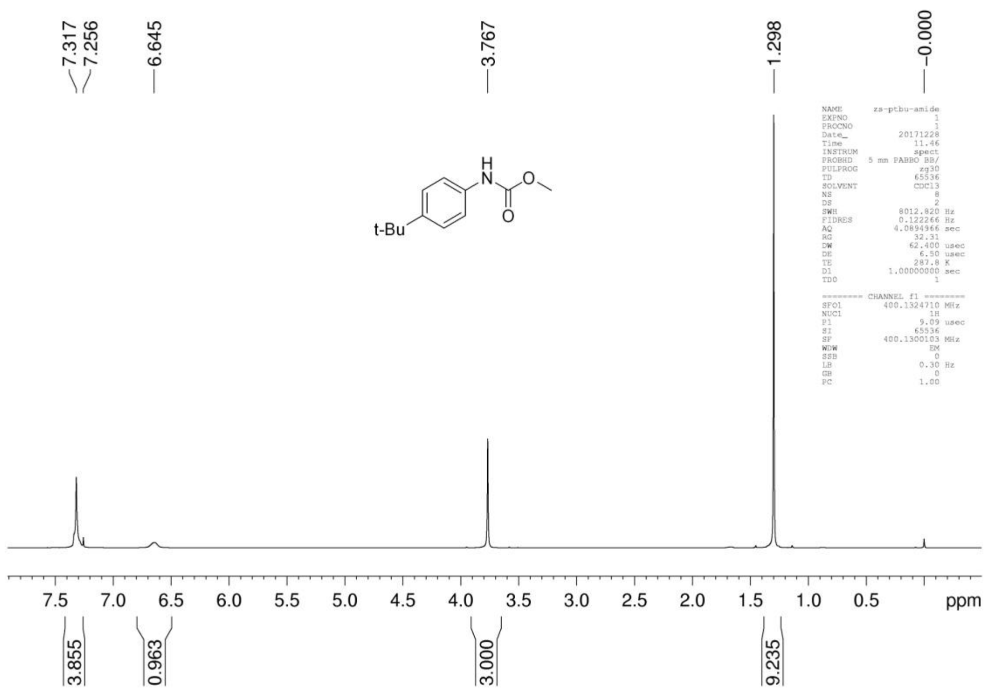

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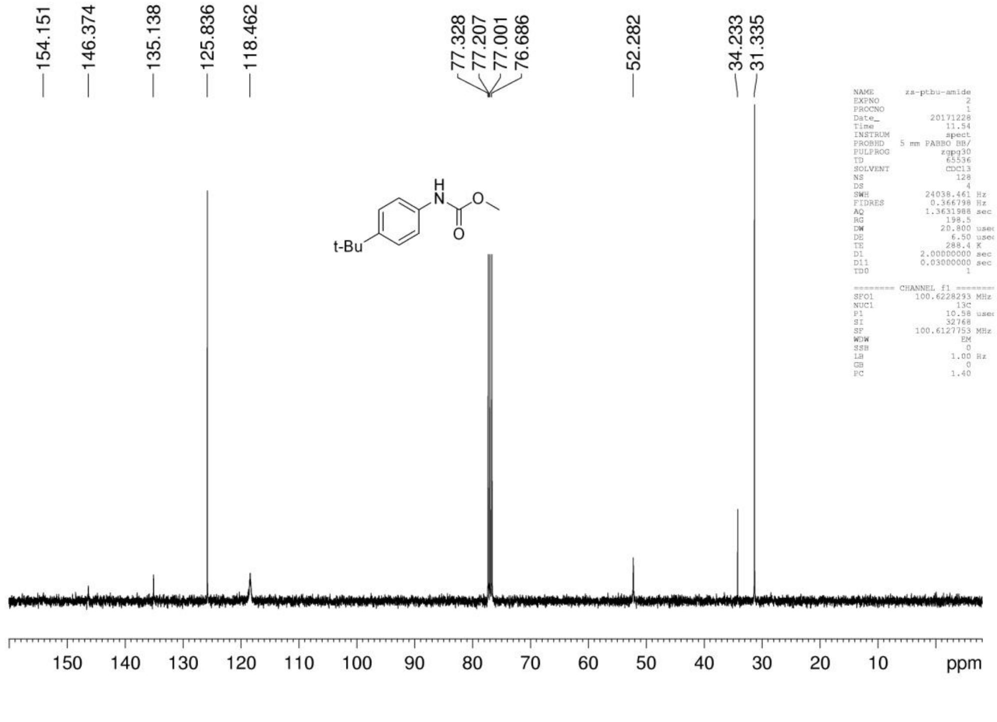

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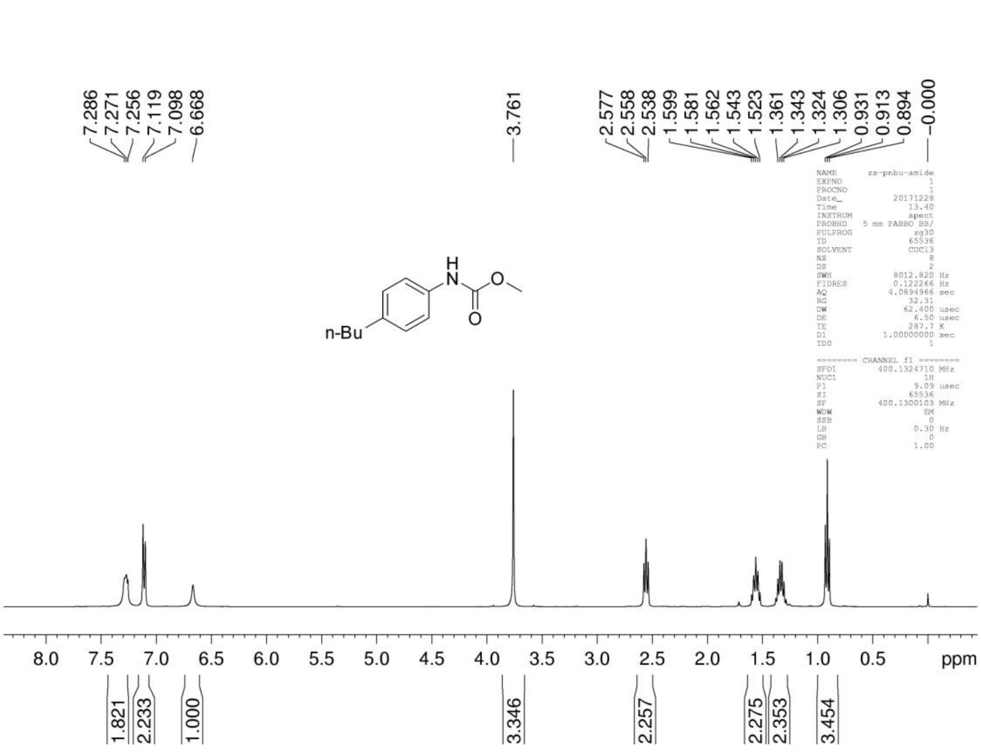

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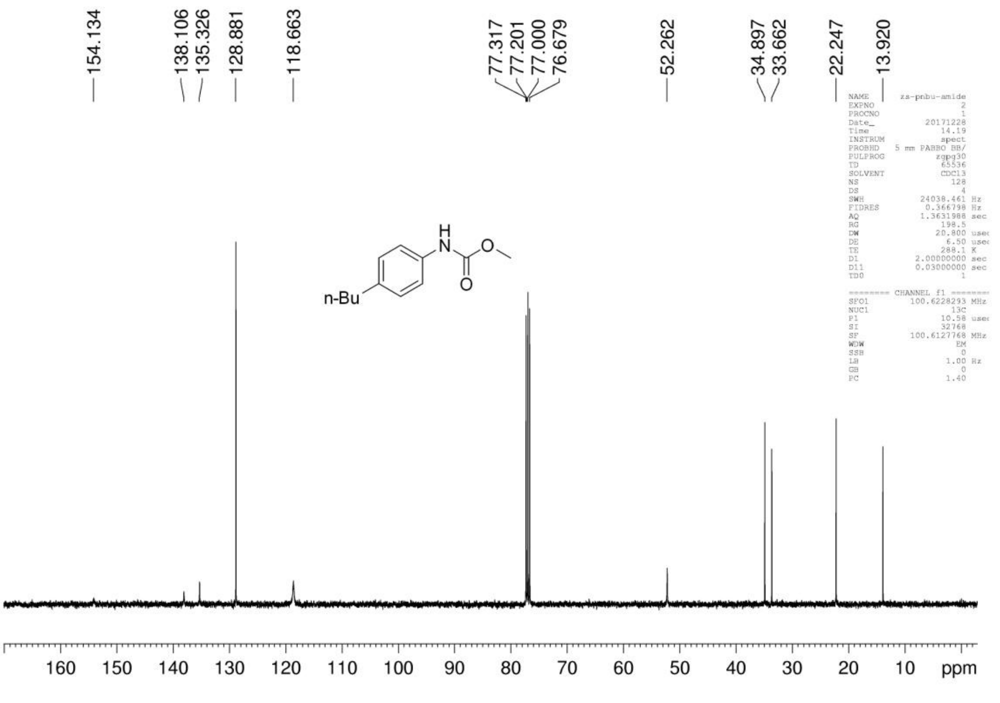

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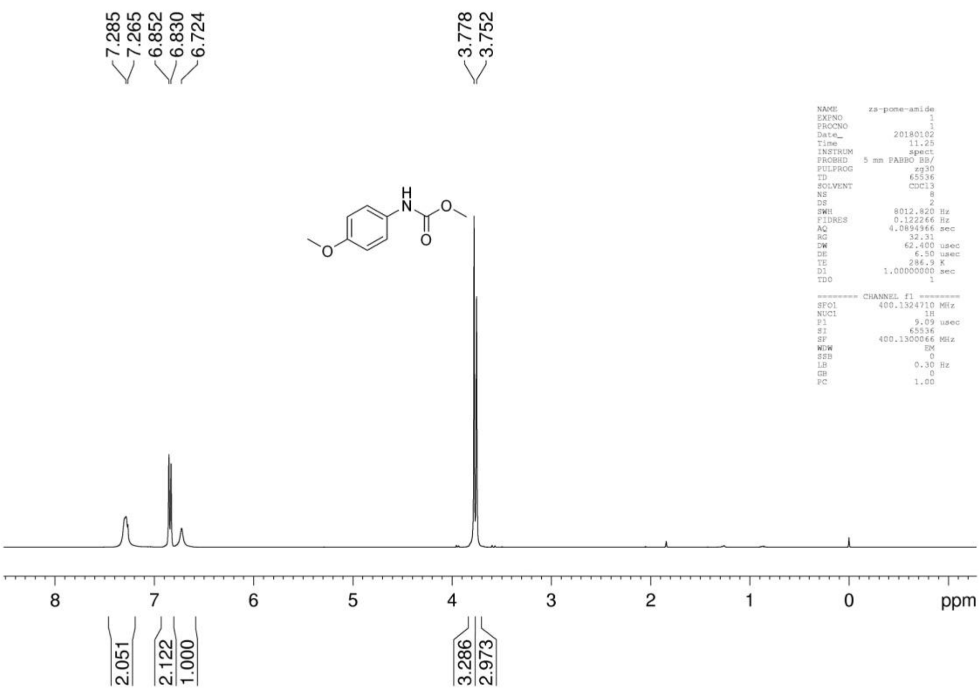

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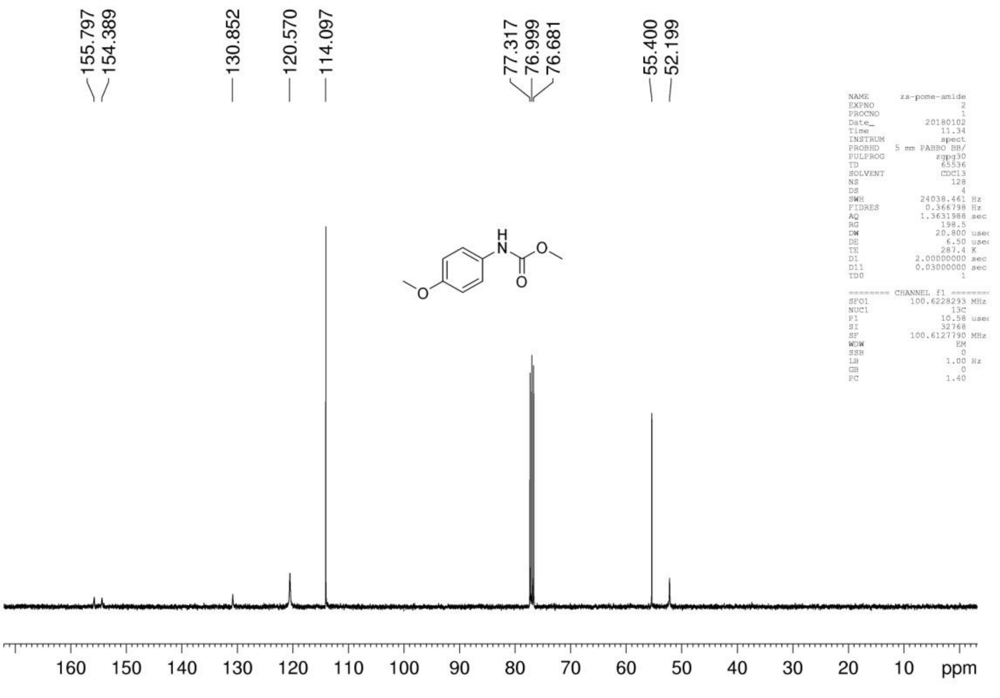

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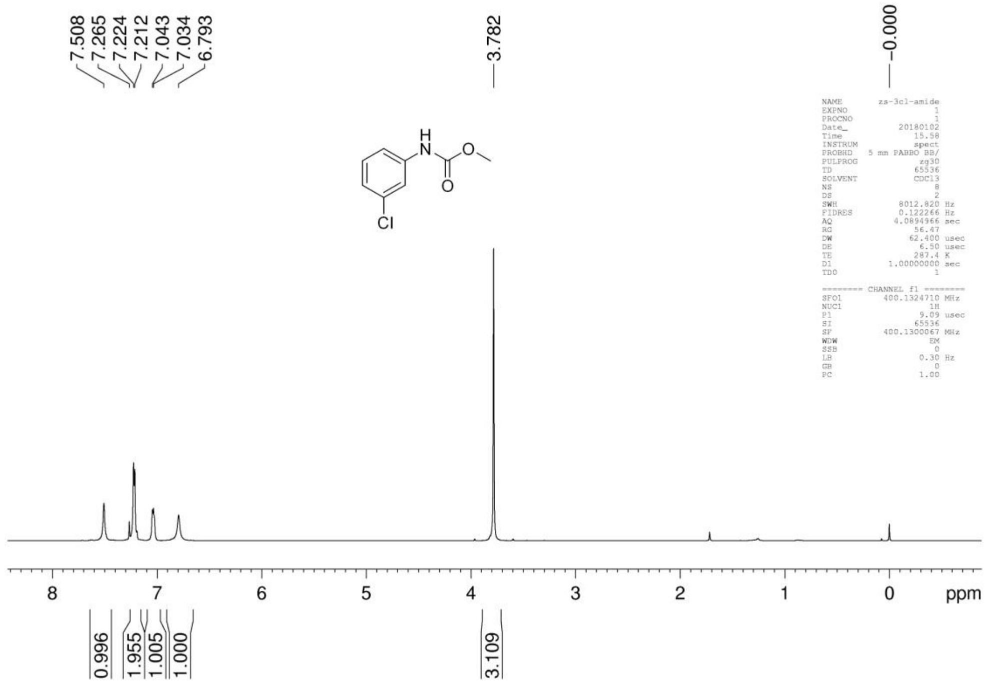

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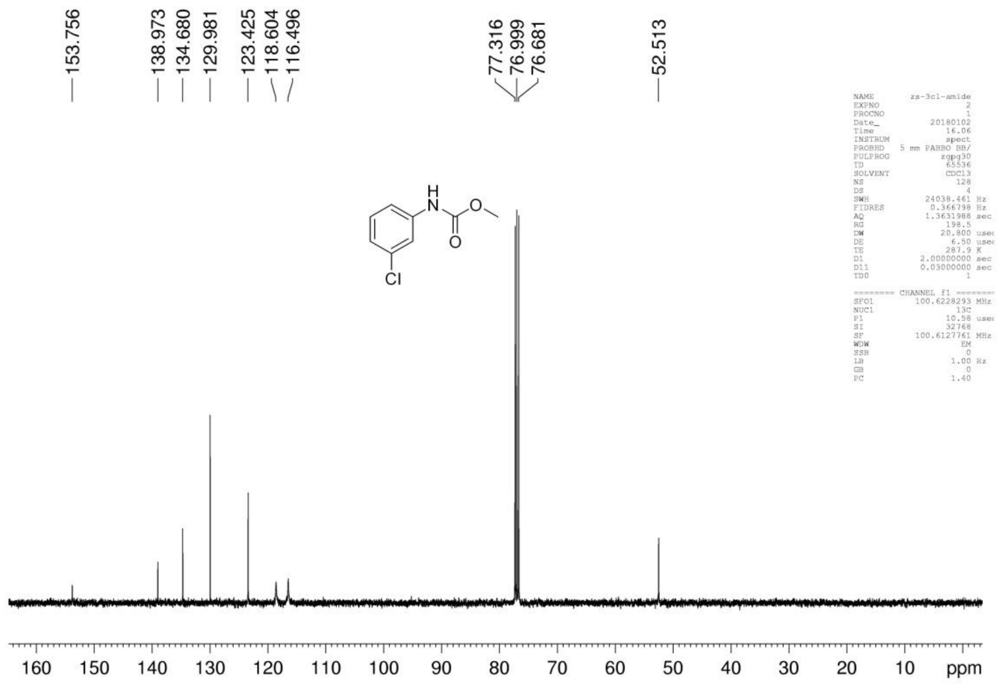

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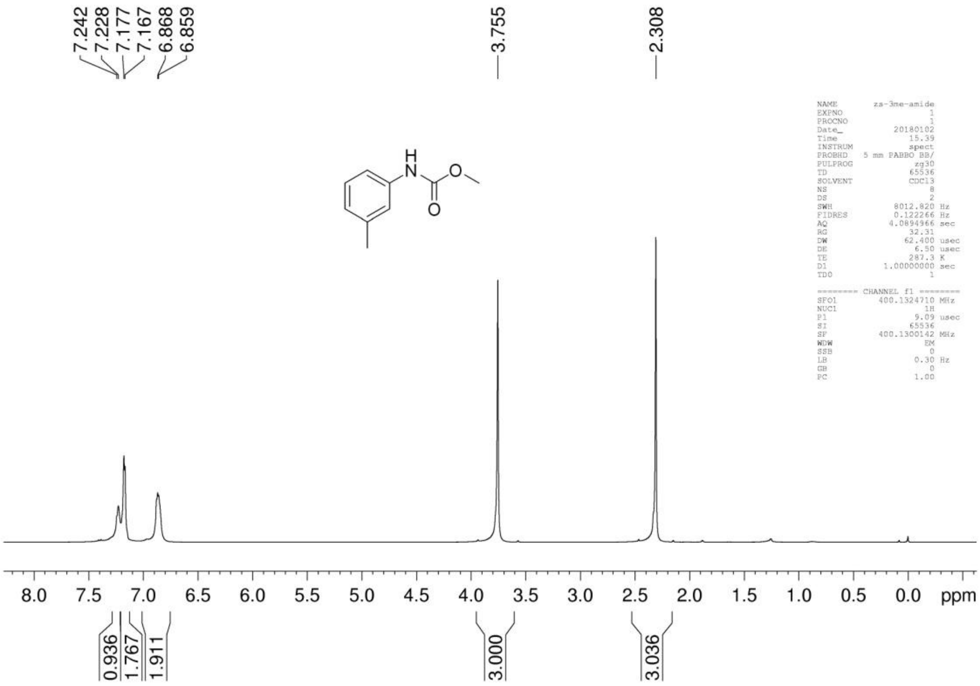

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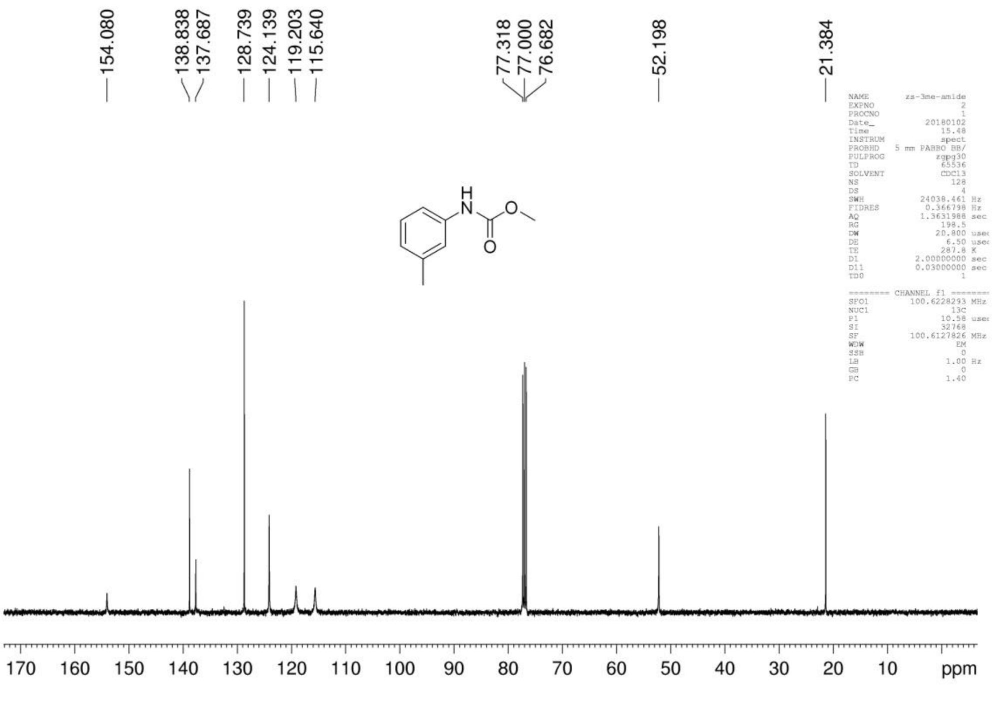

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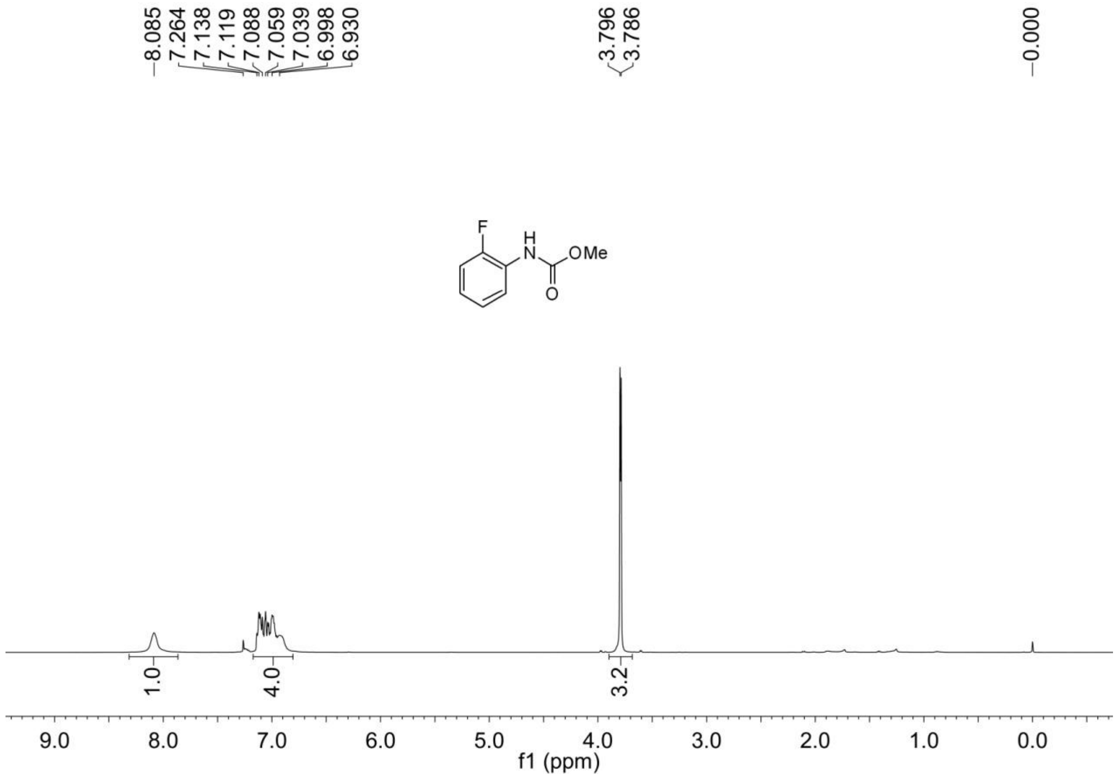

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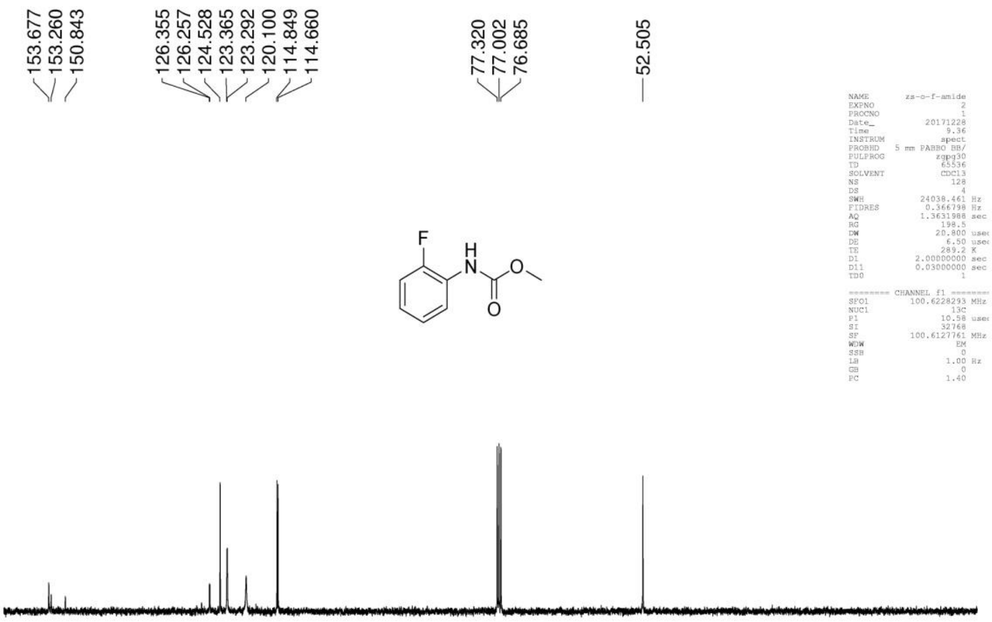

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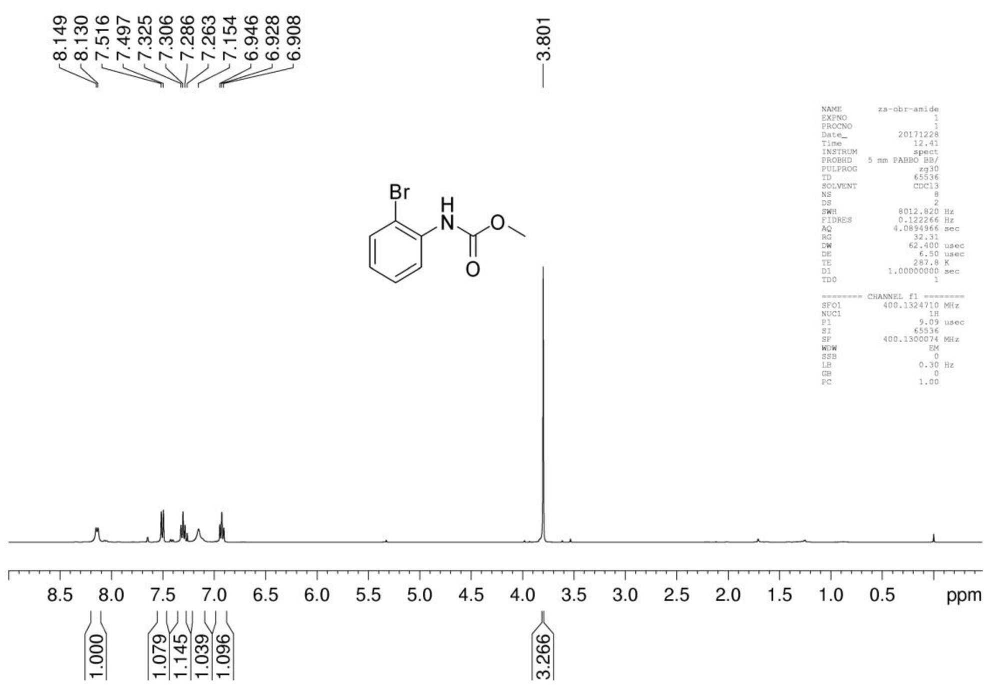

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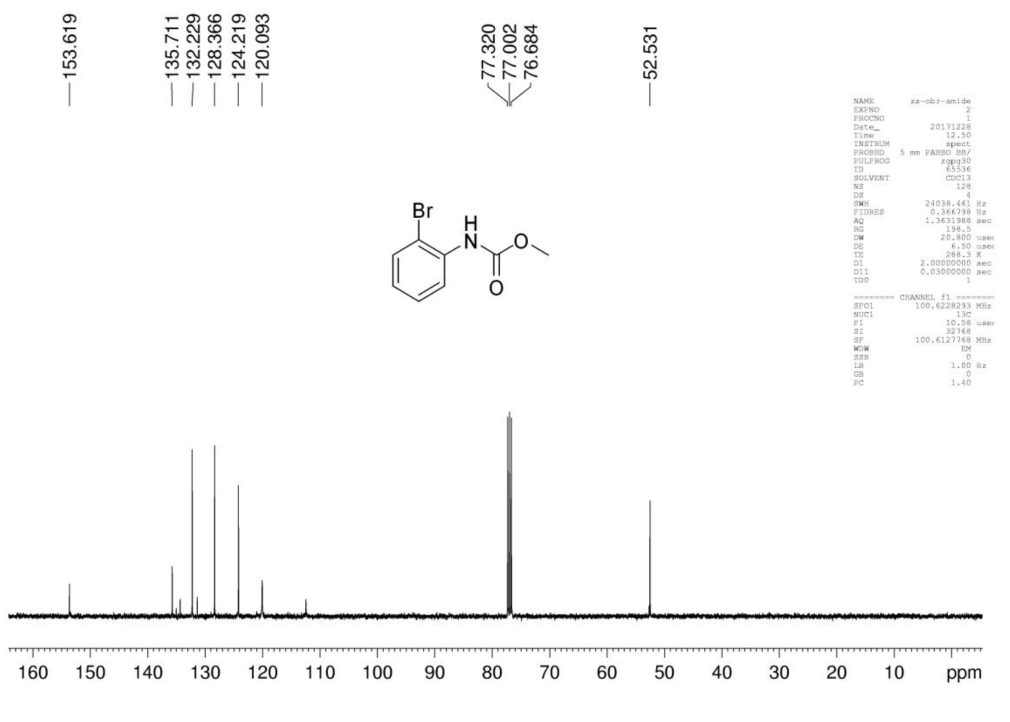

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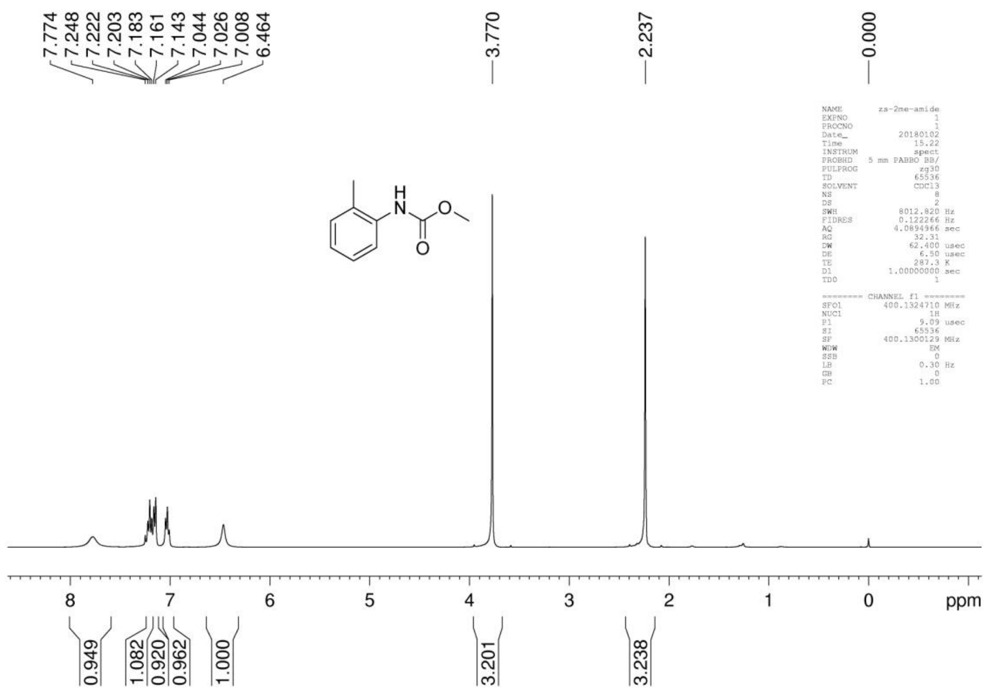

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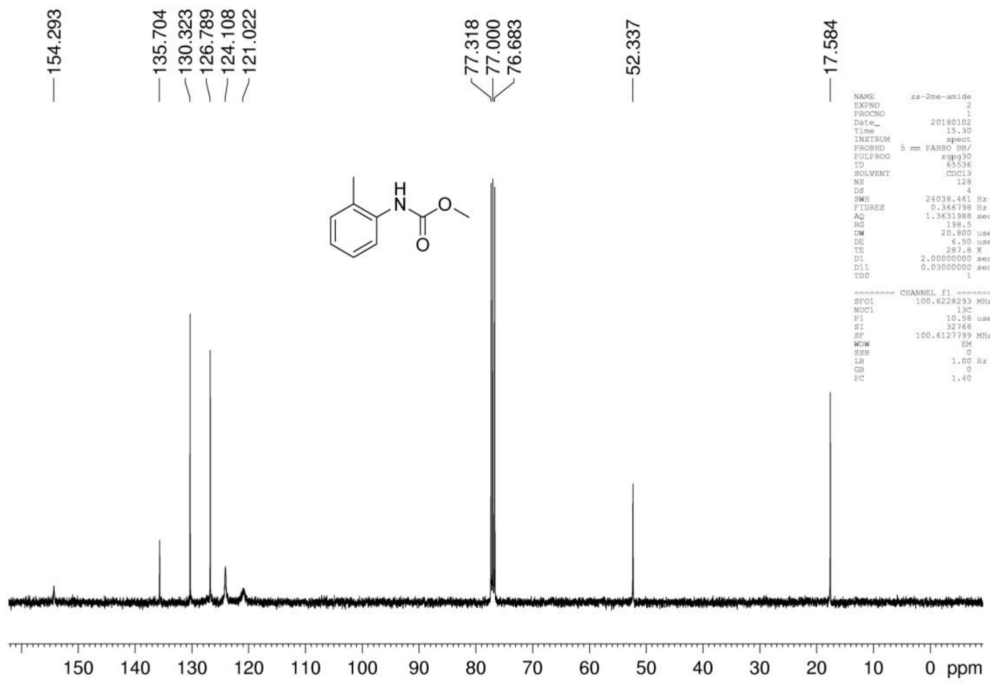

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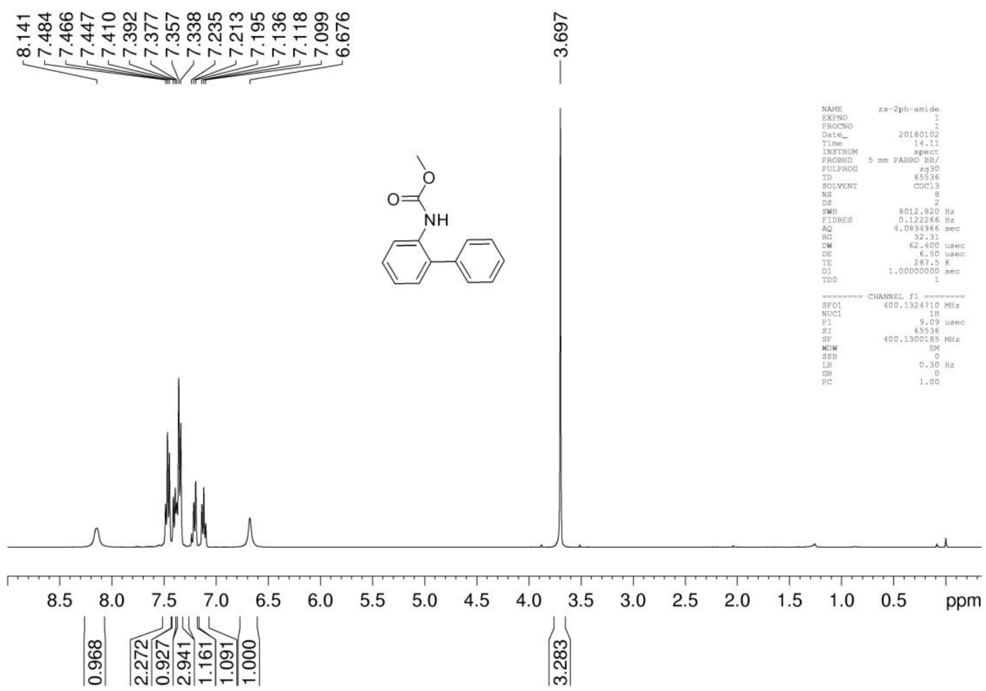

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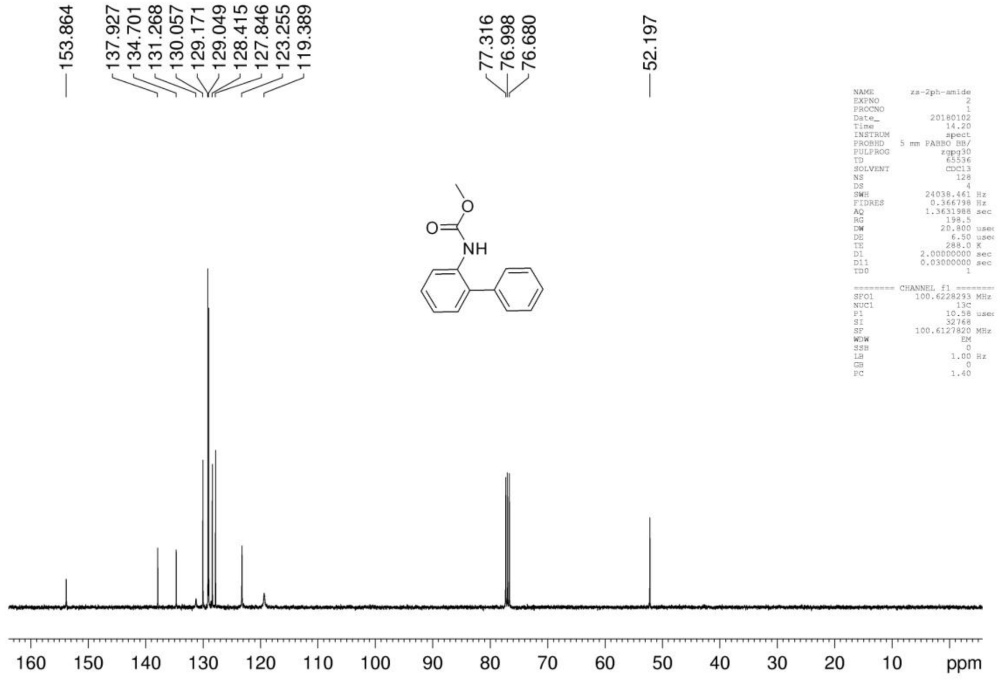

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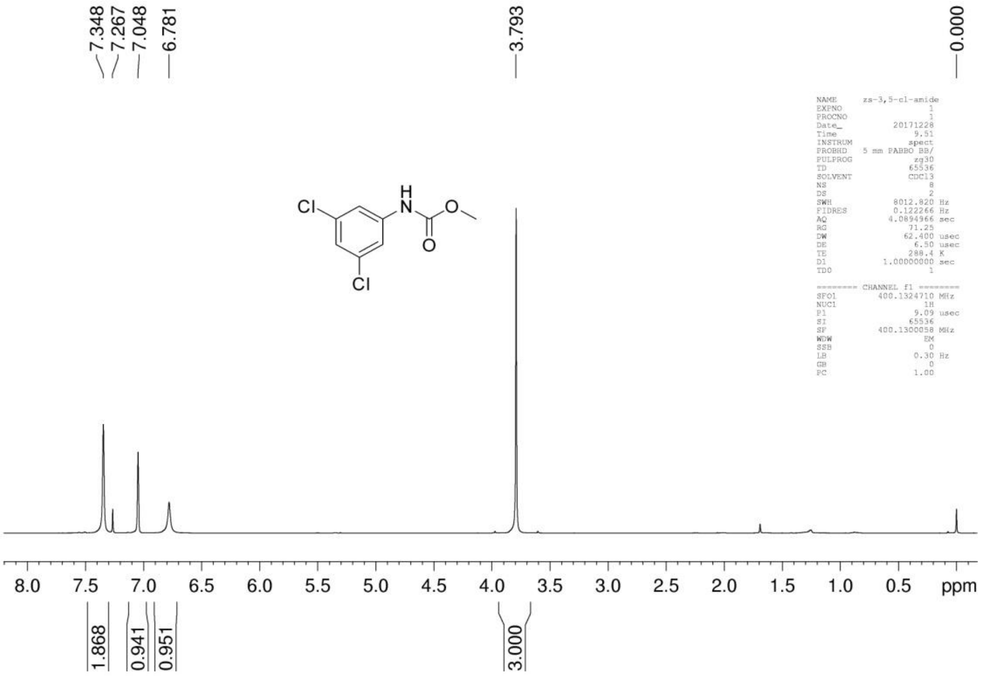

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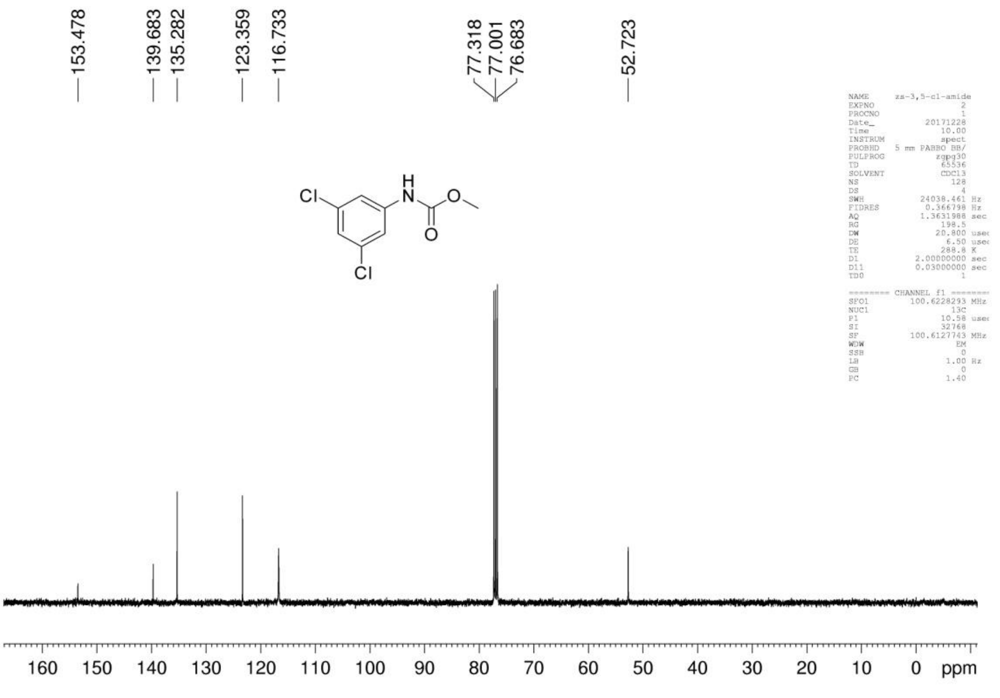

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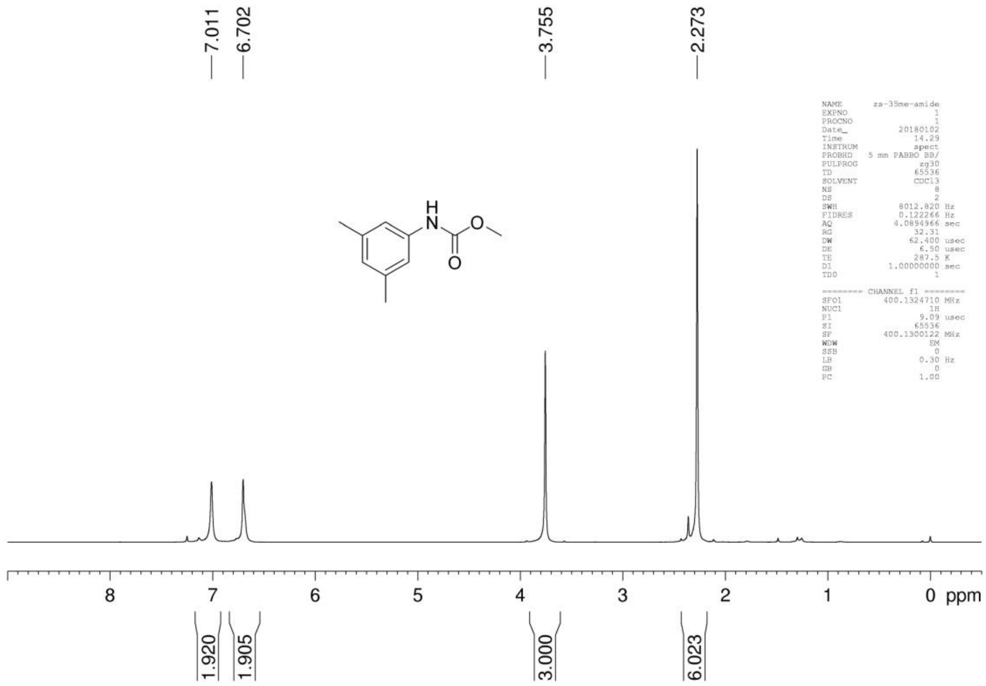

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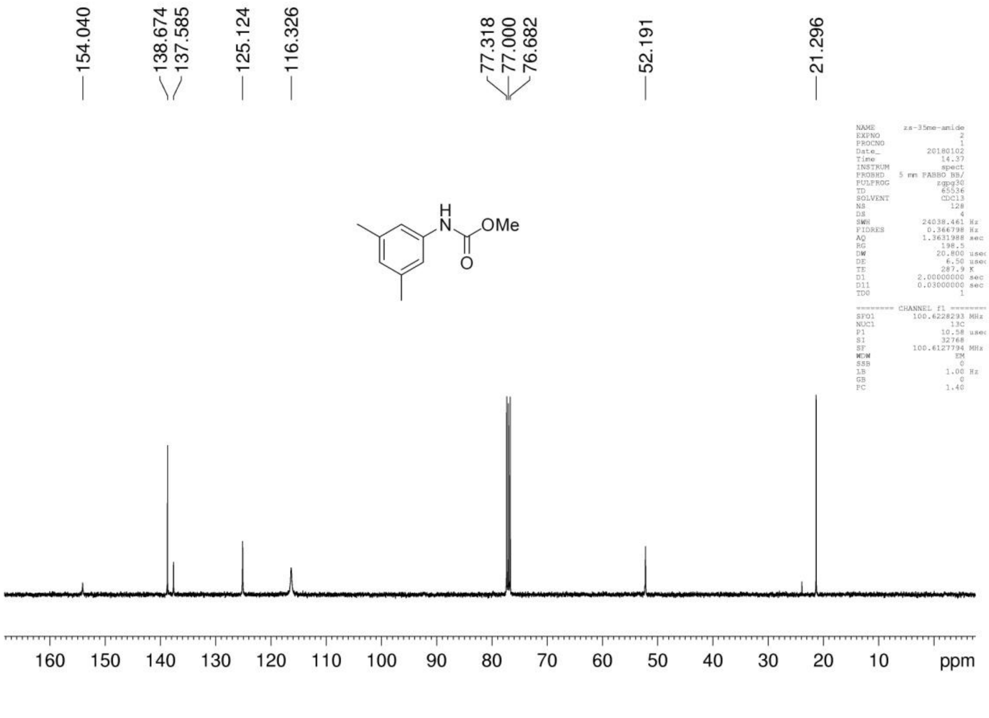

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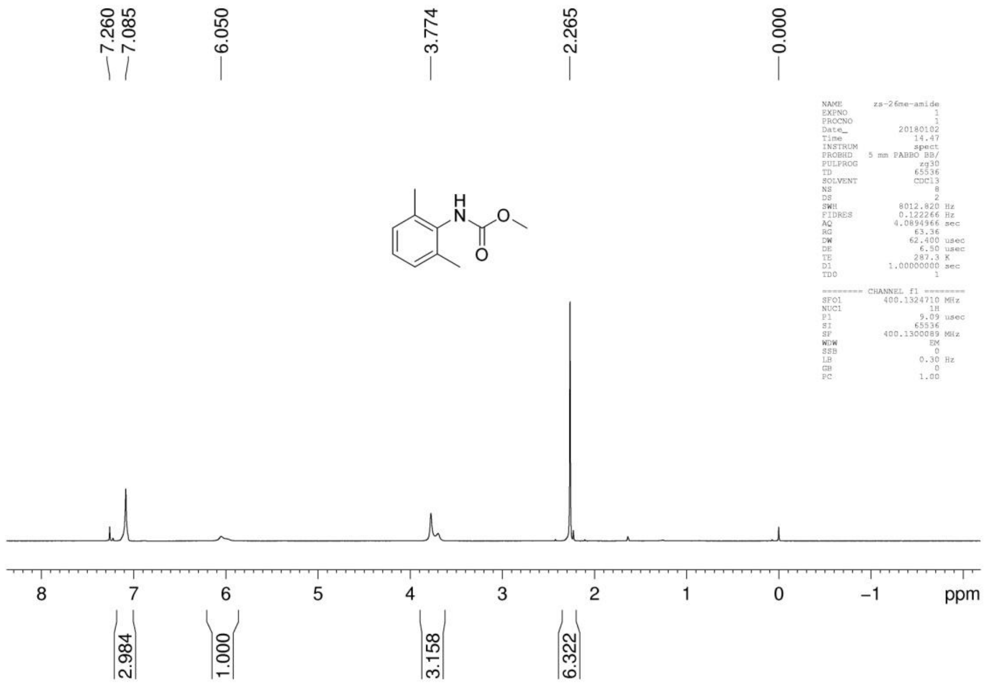

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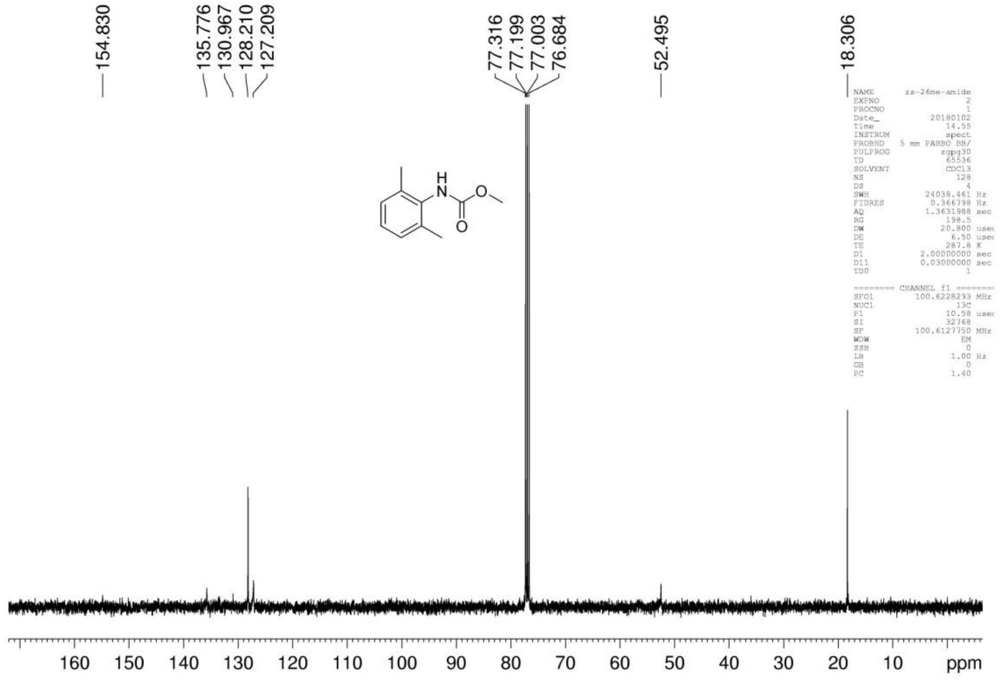

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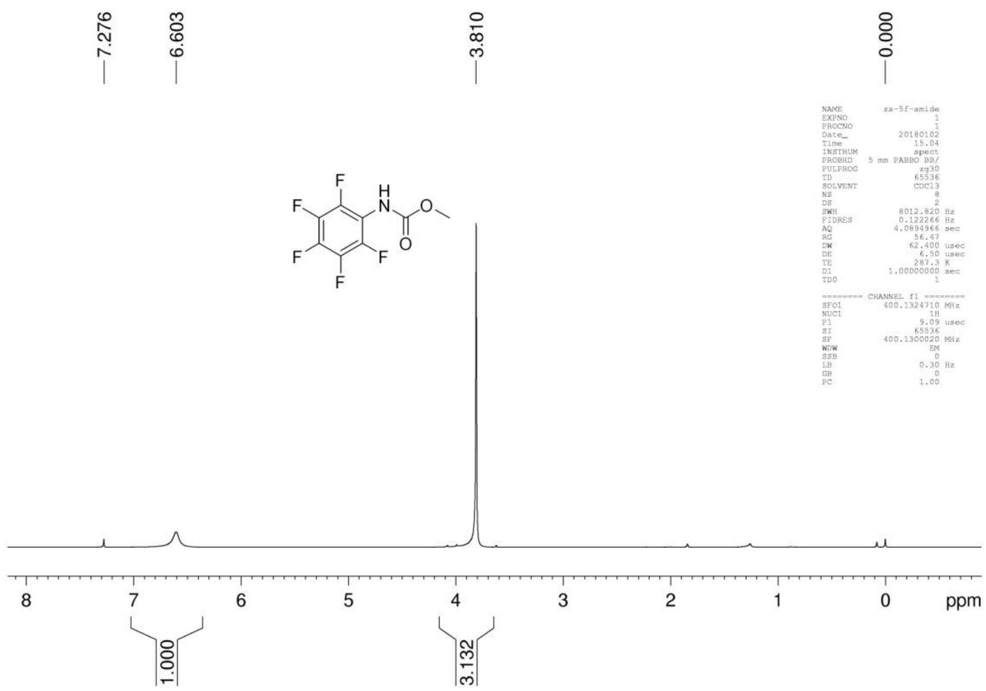

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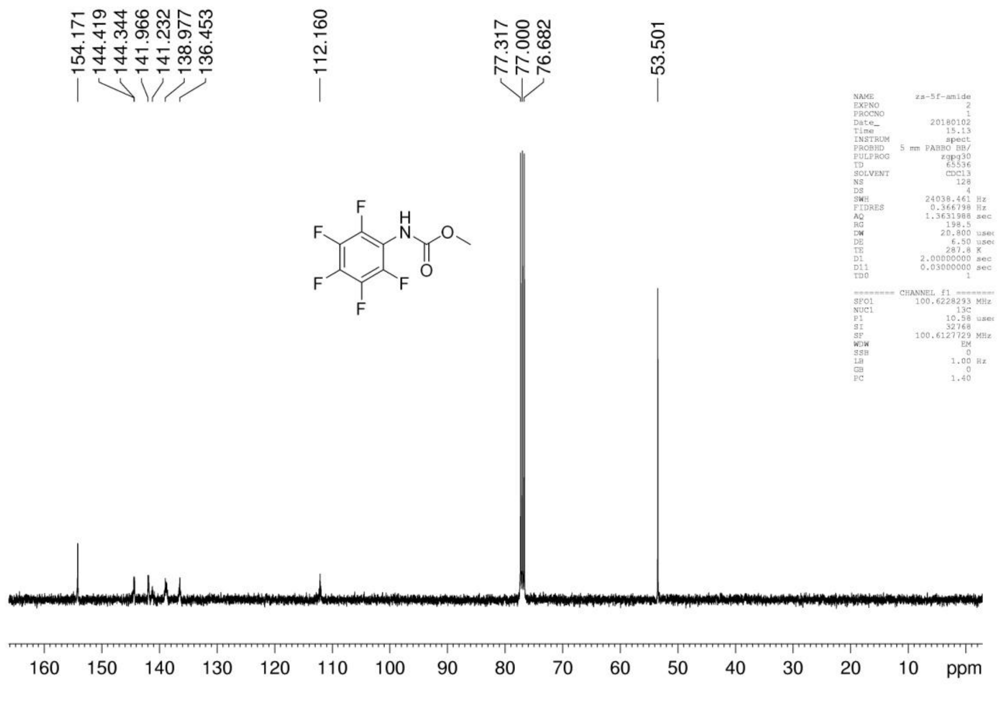

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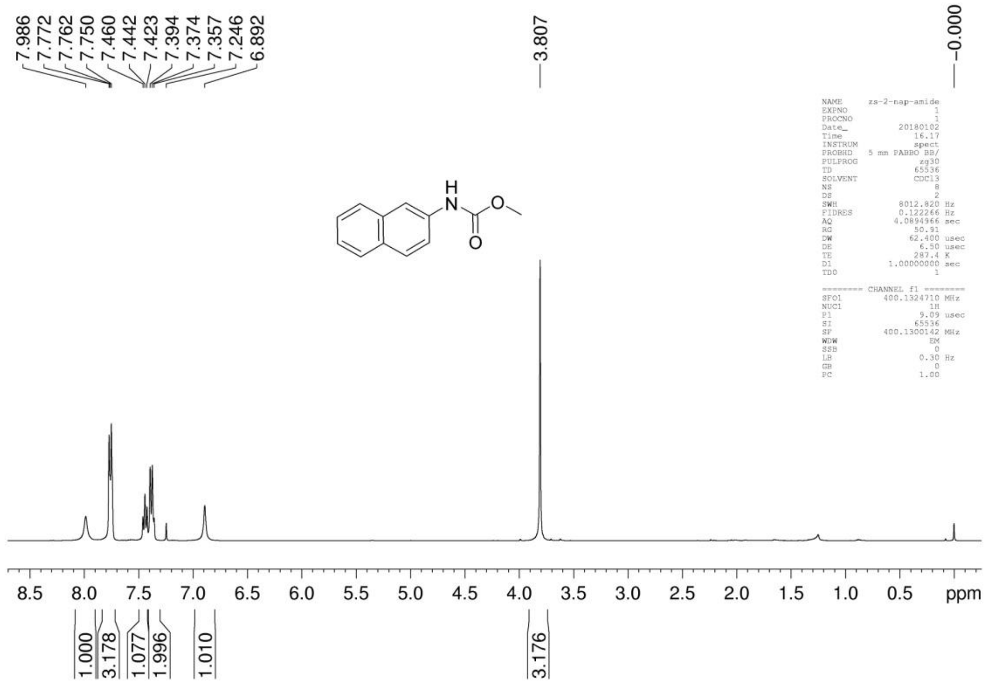

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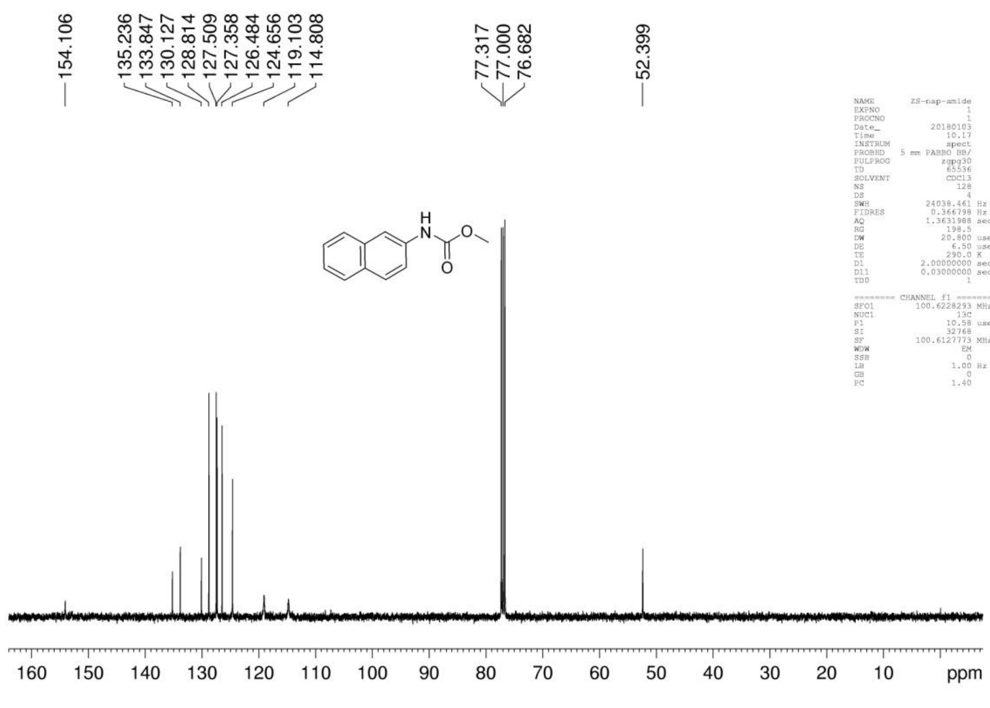

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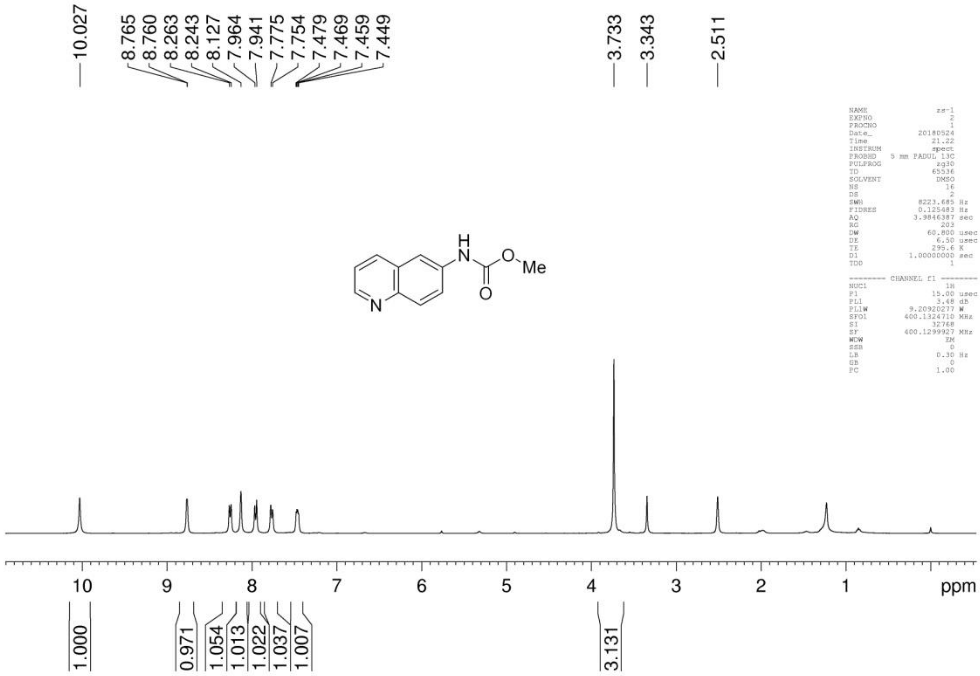

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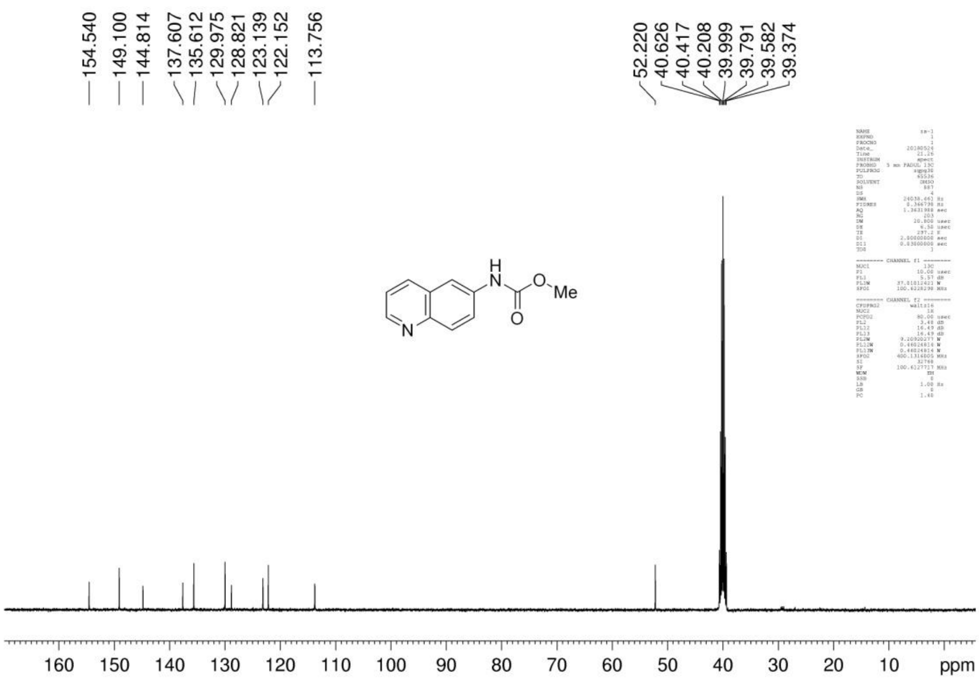

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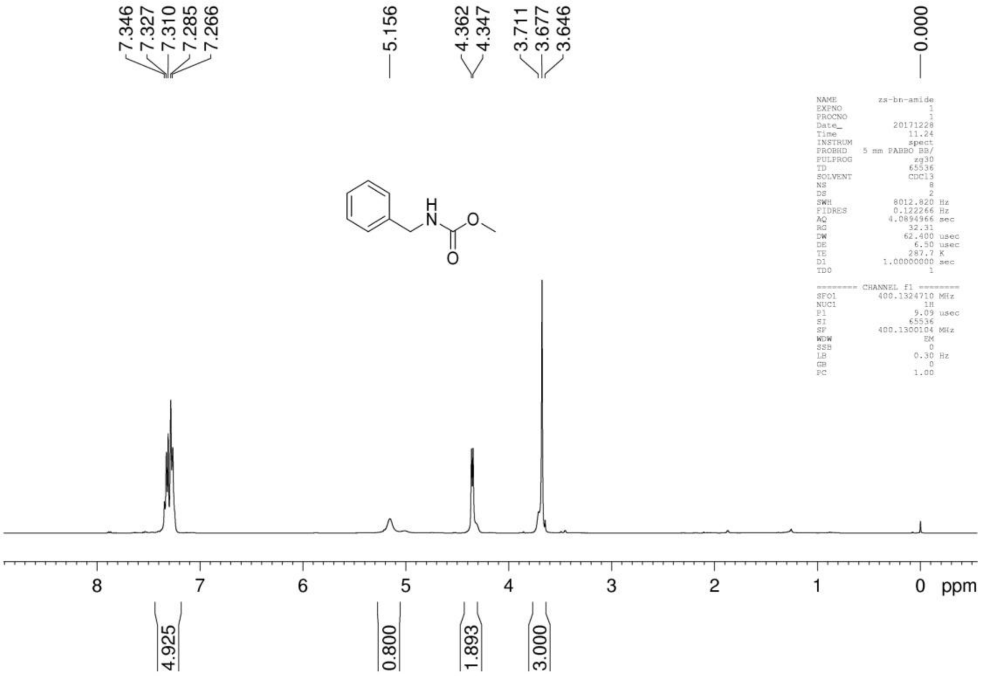

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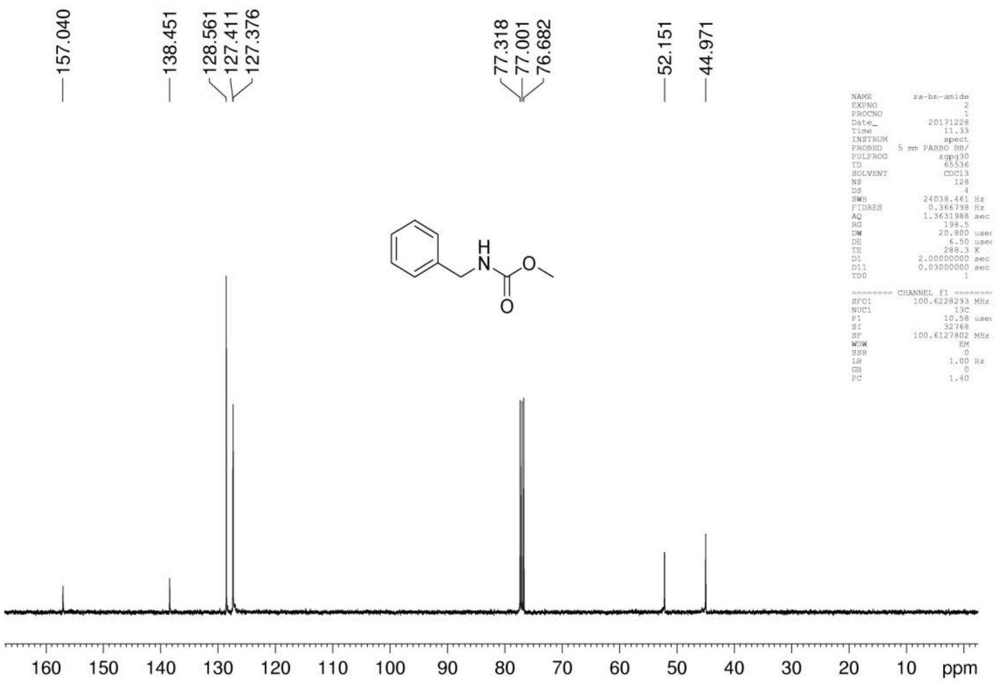

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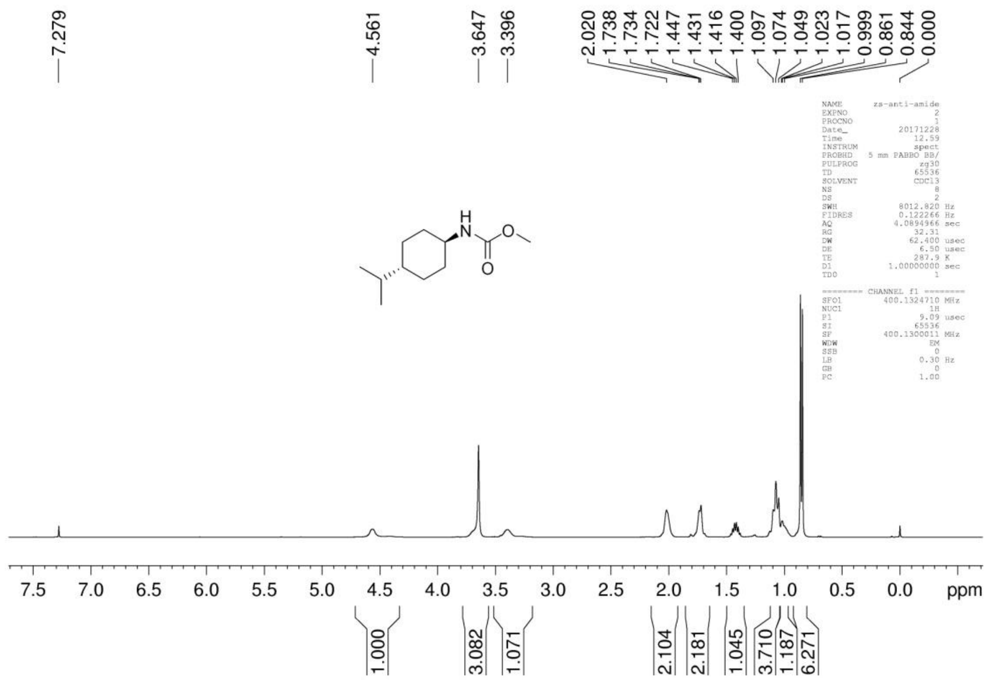

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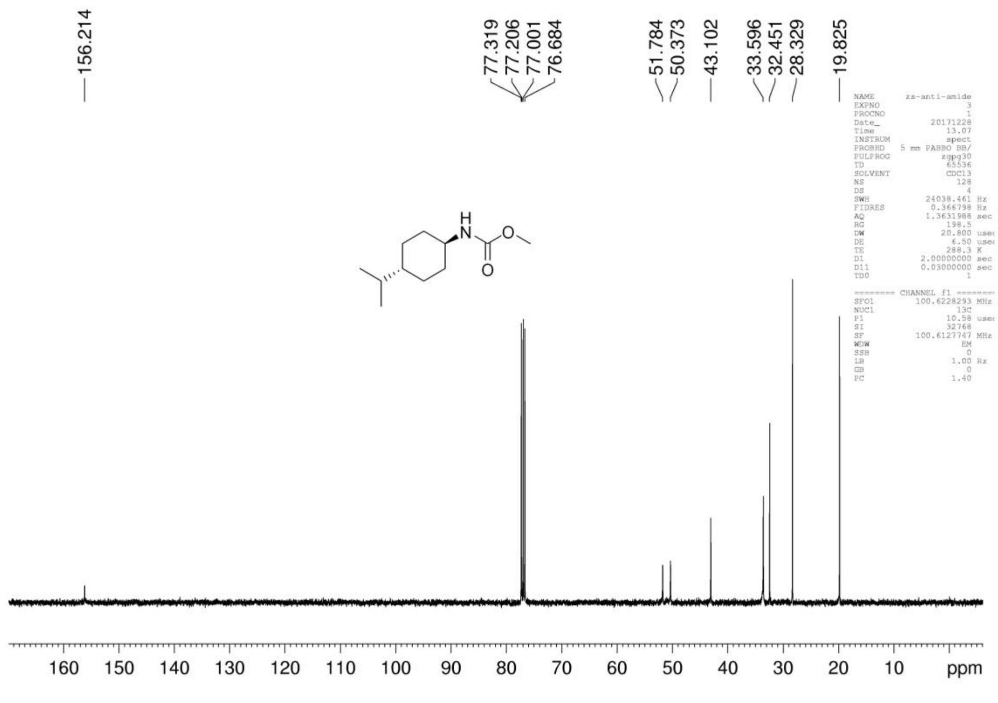

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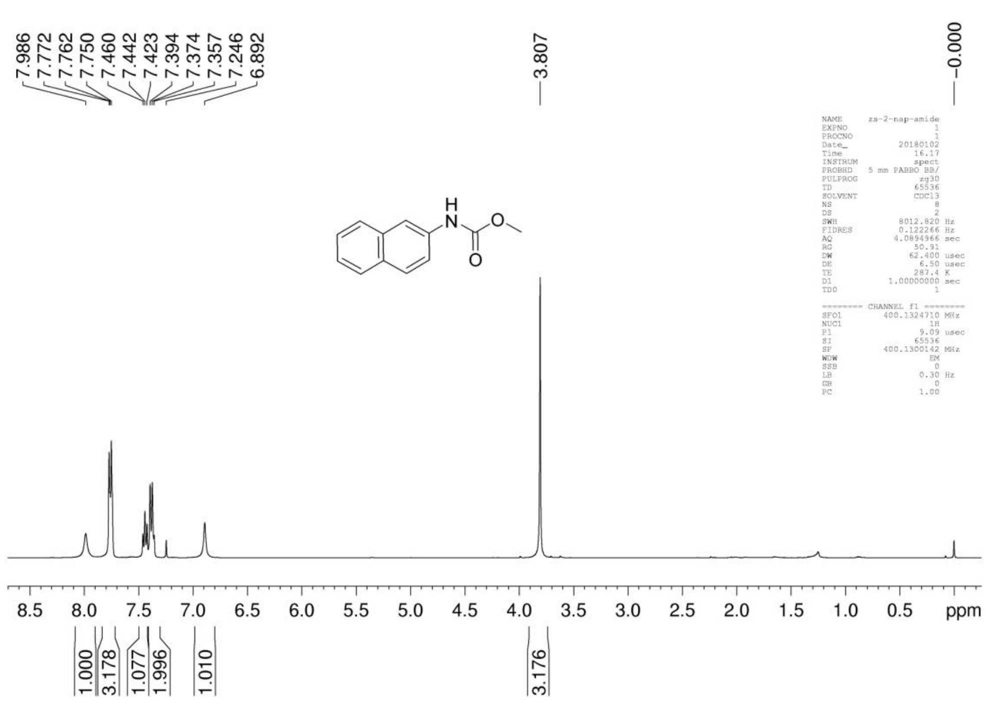

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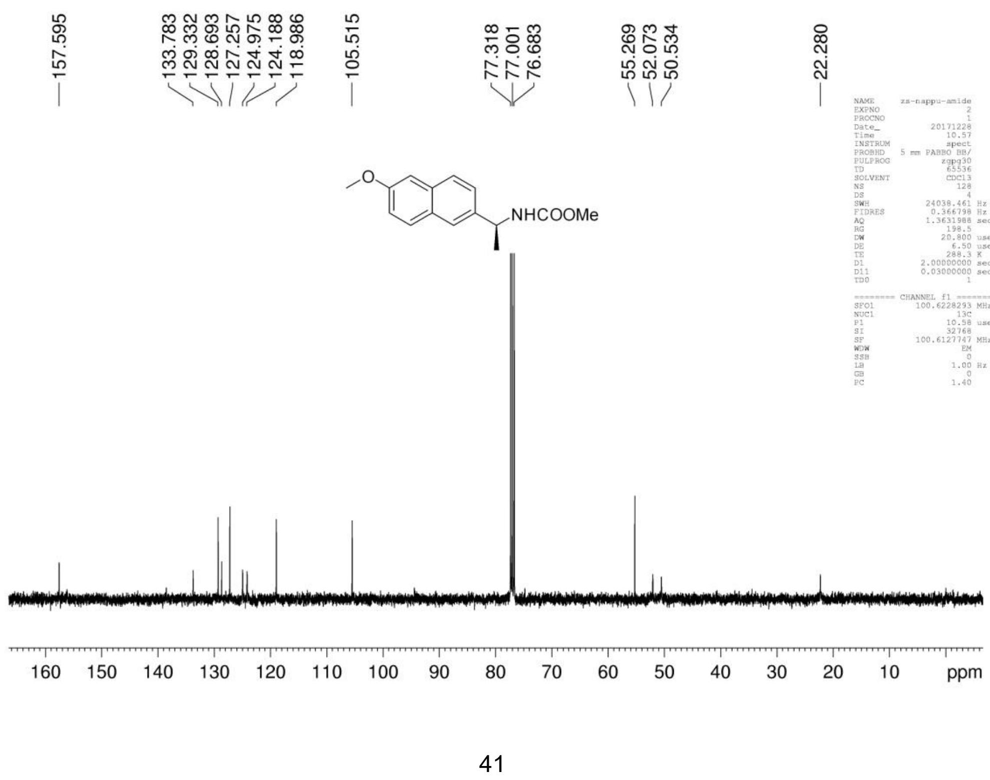

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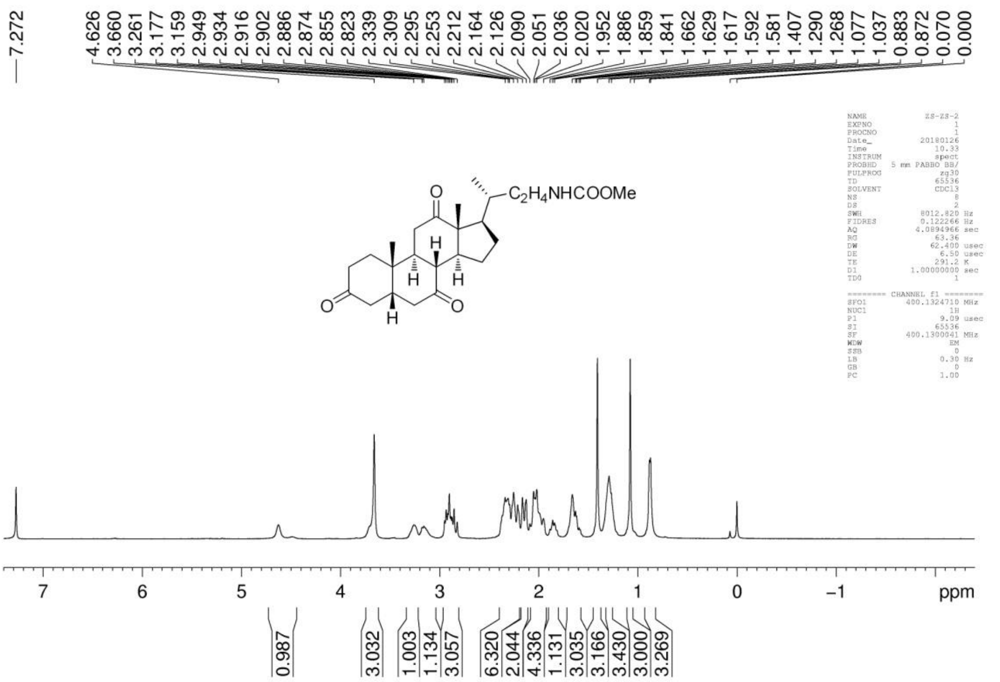

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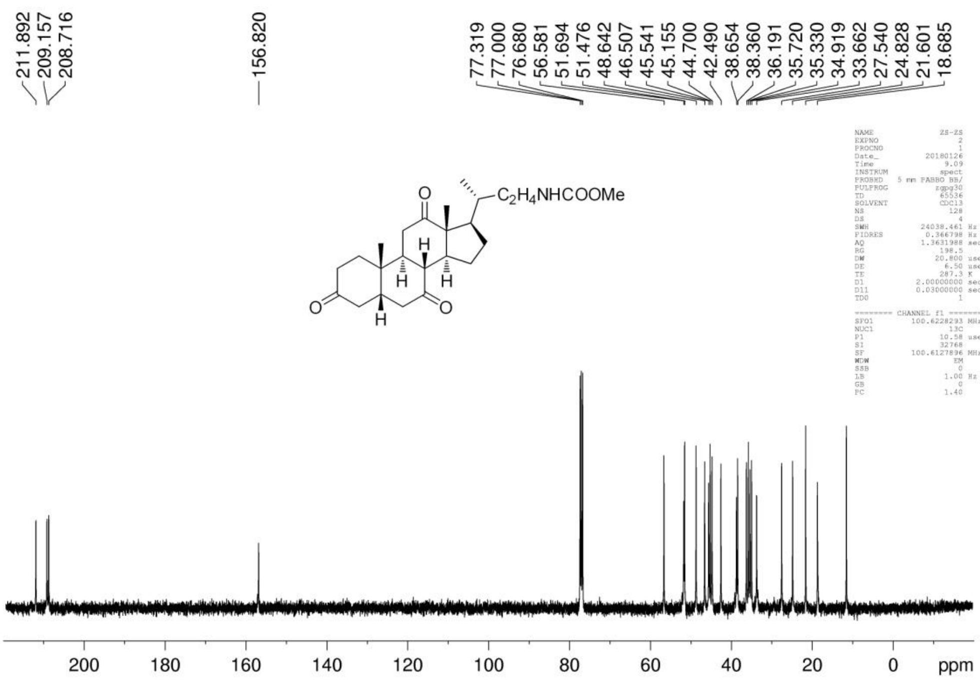

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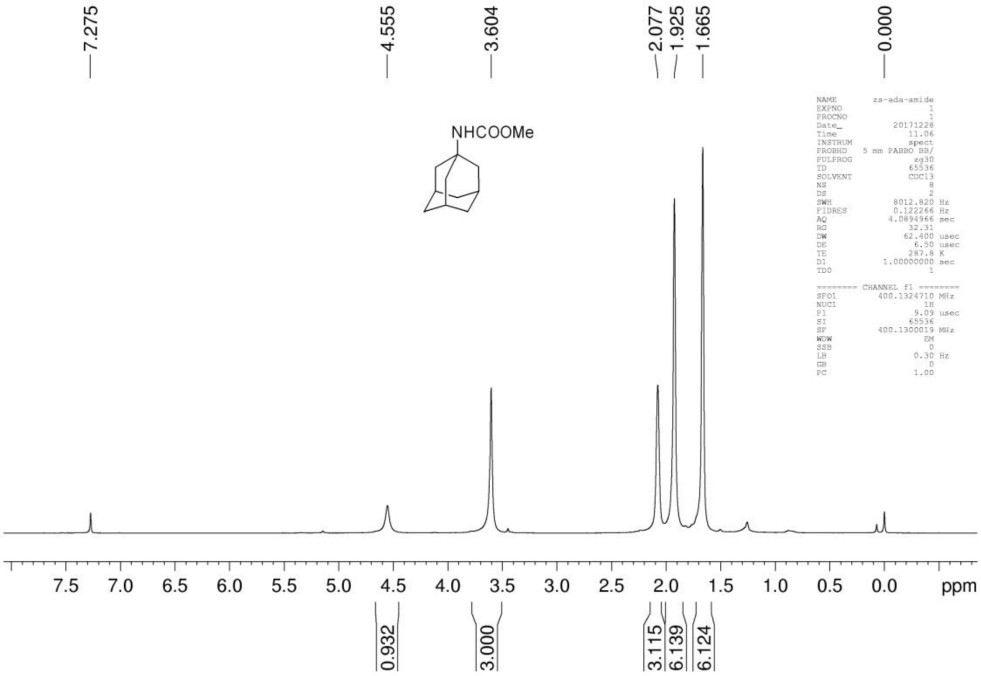

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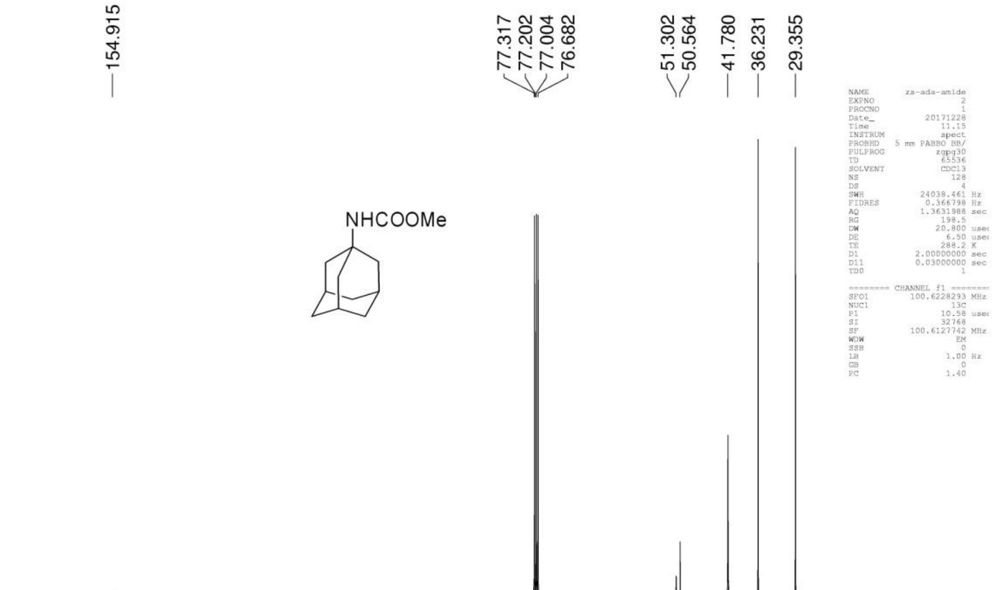

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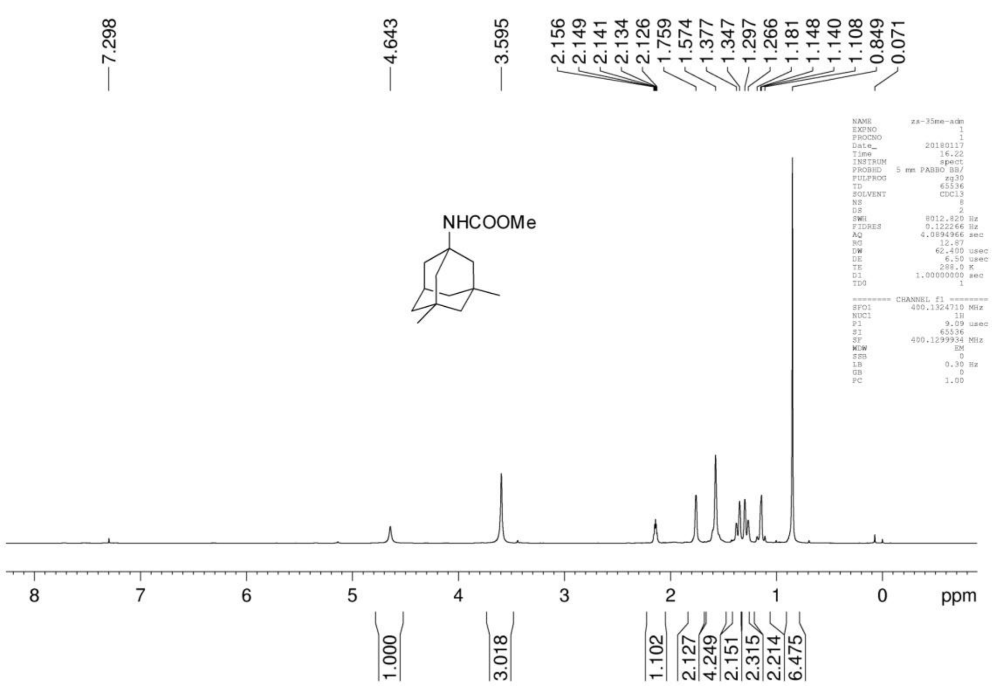

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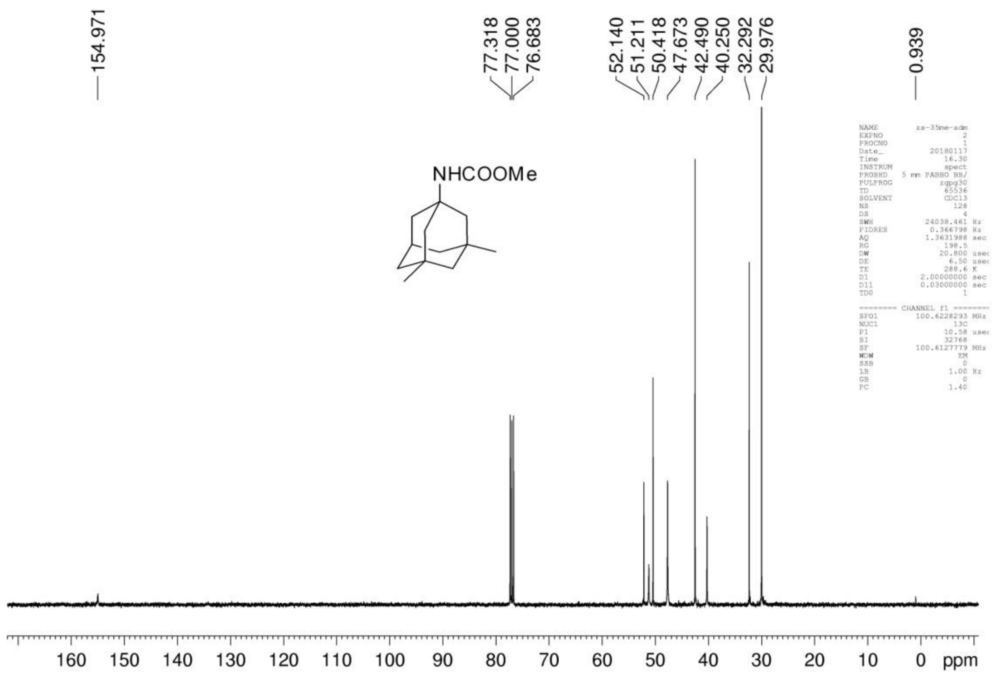

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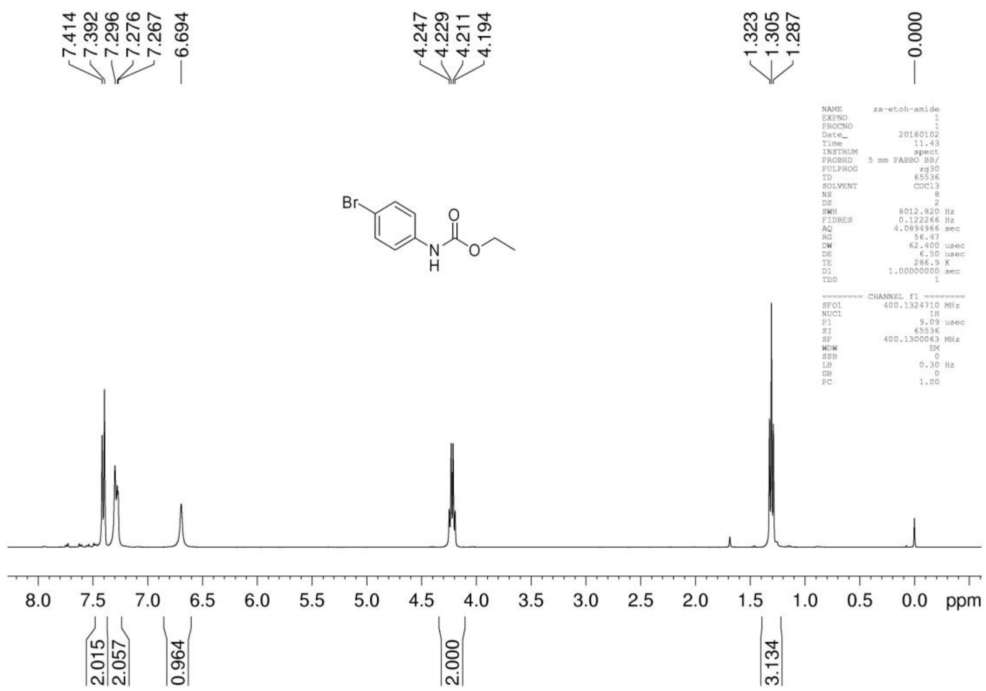

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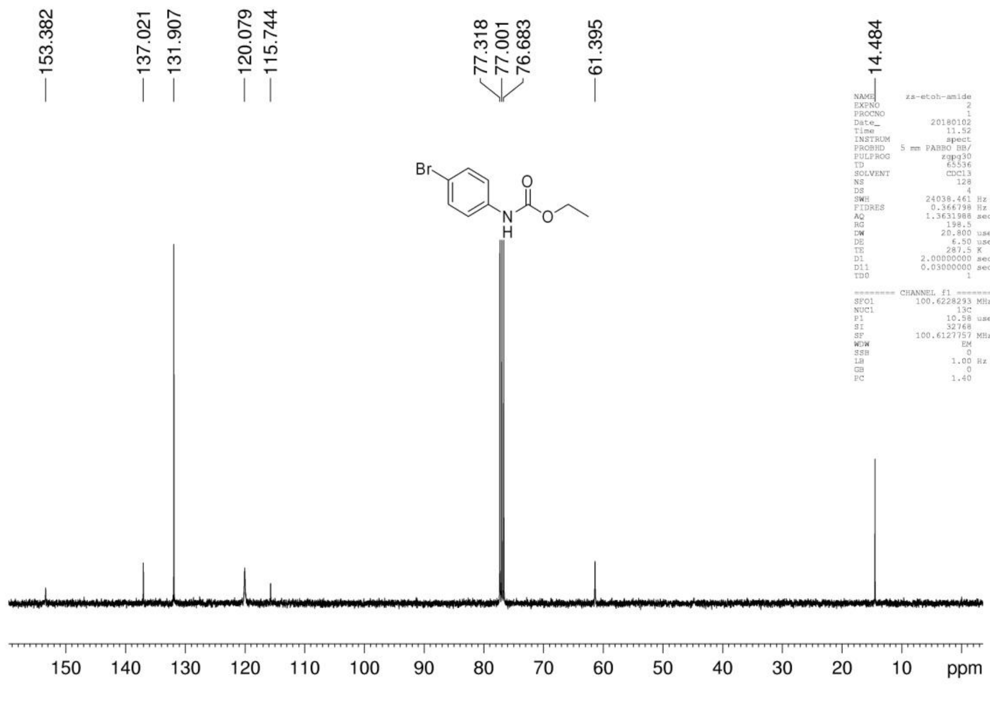

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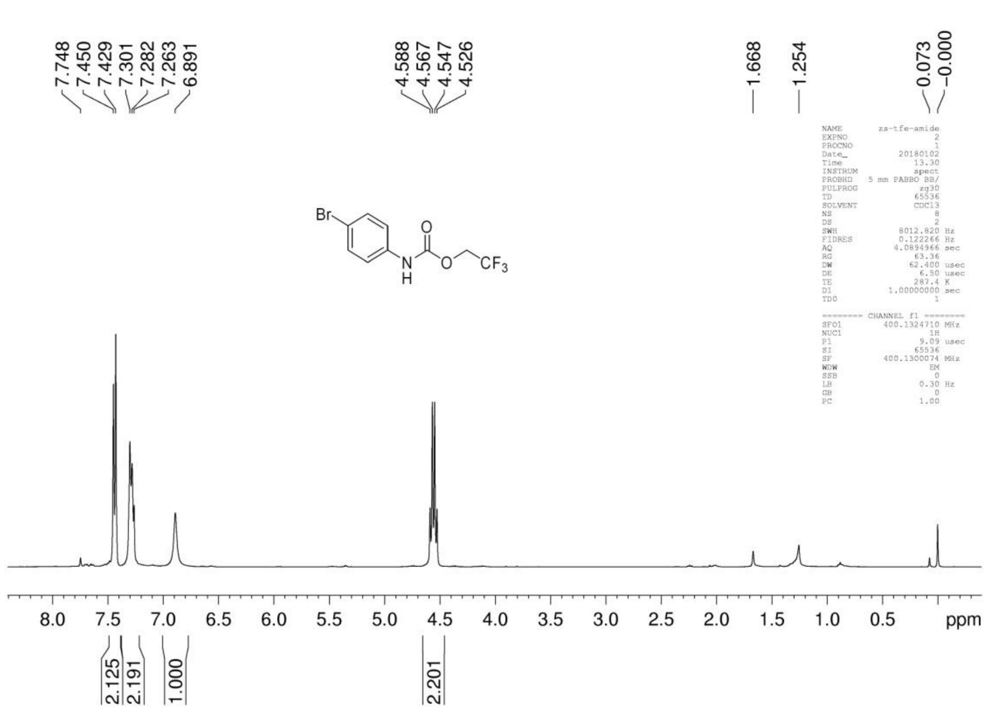

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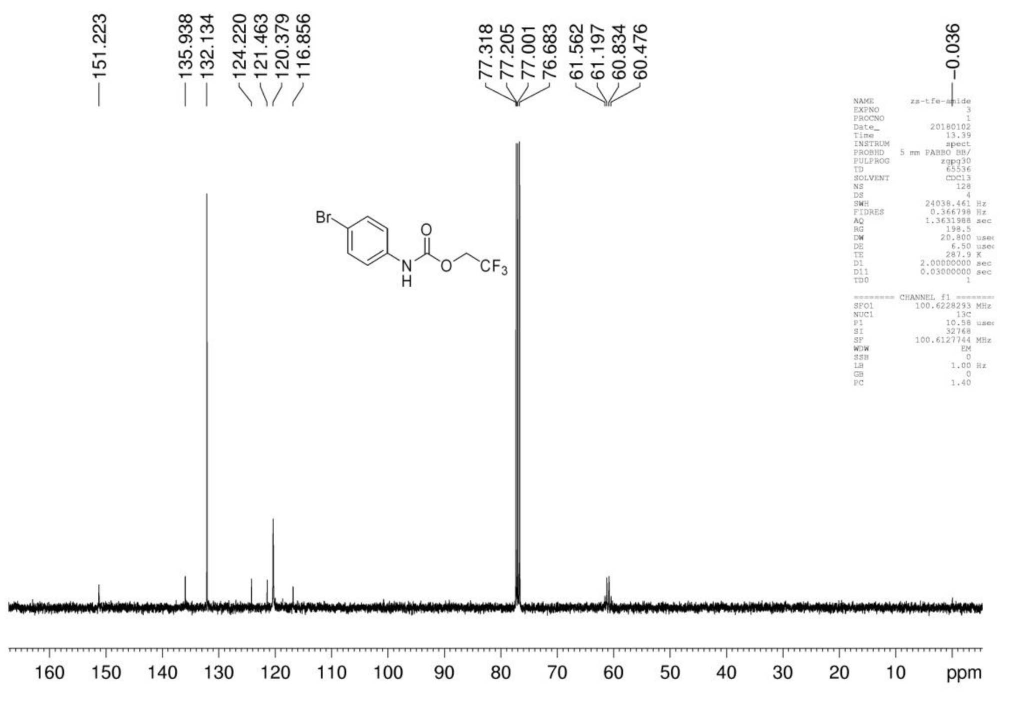

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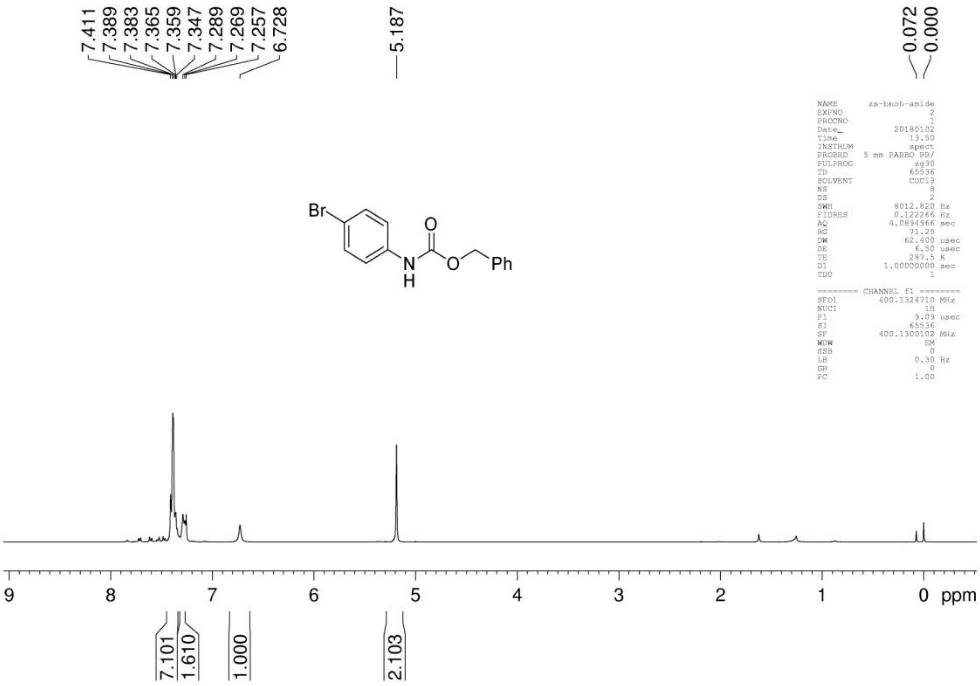

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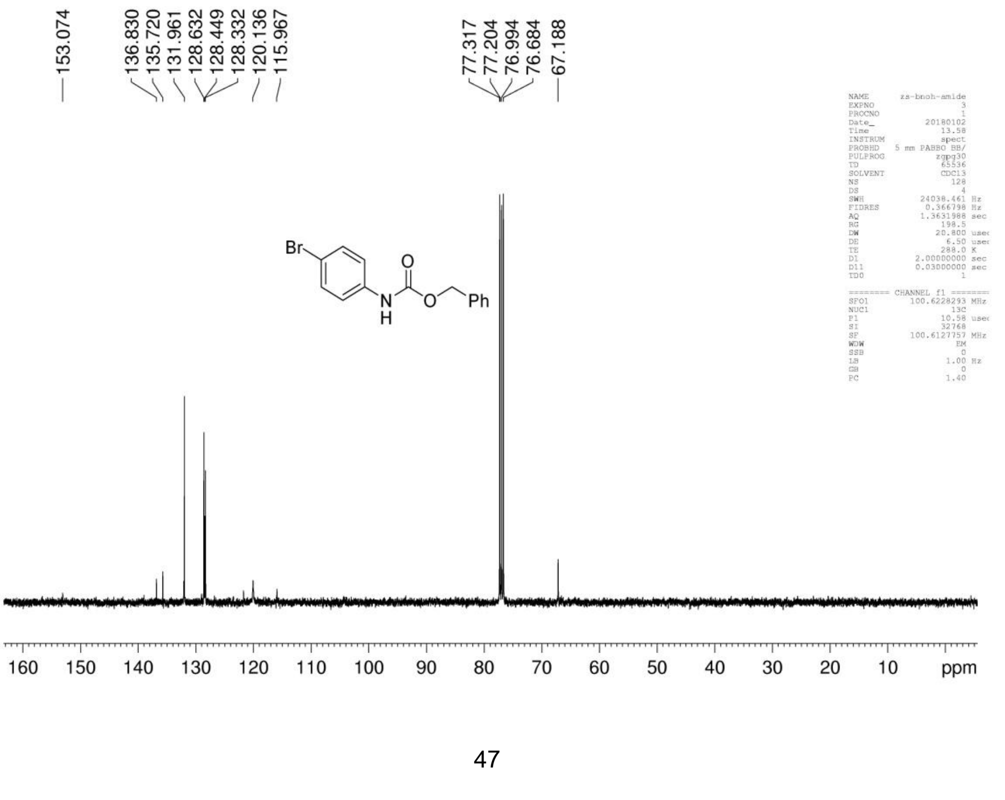

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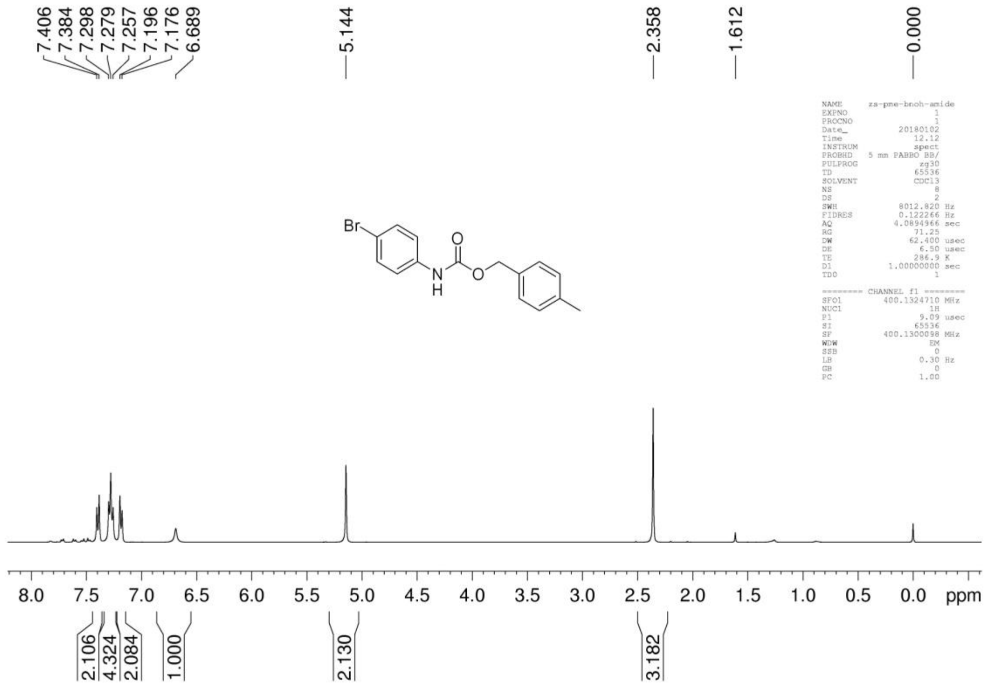

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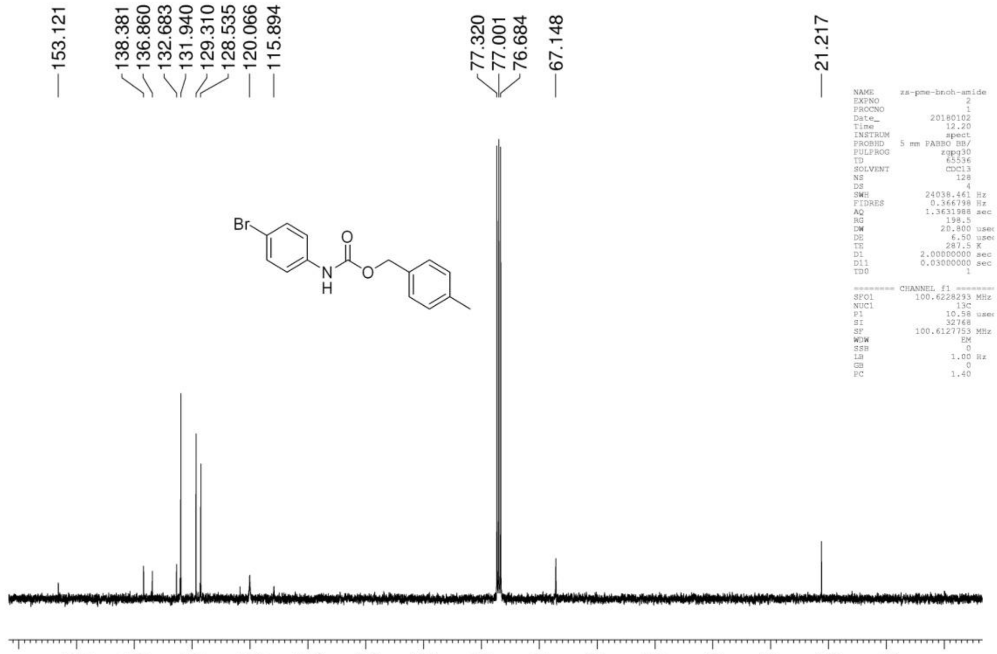
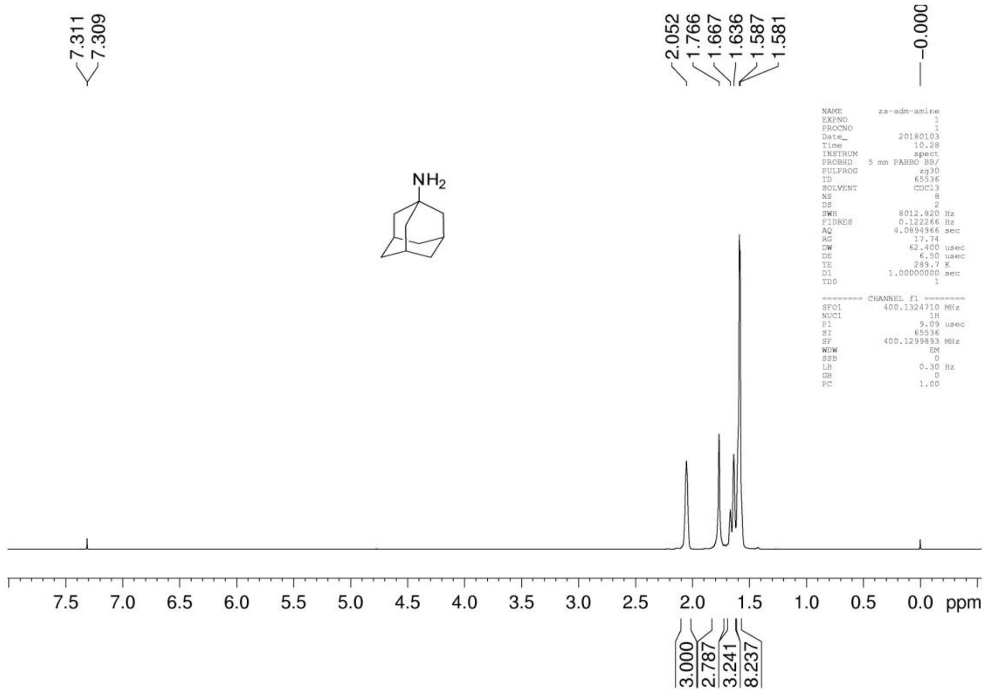


Amantadine ^{1}H NMR:



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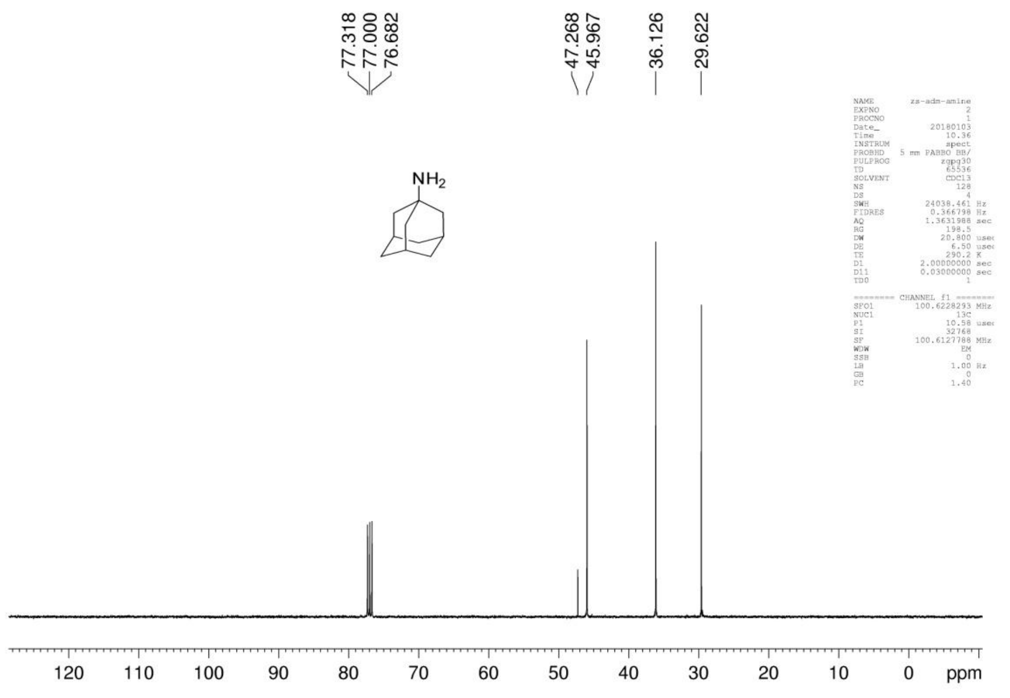
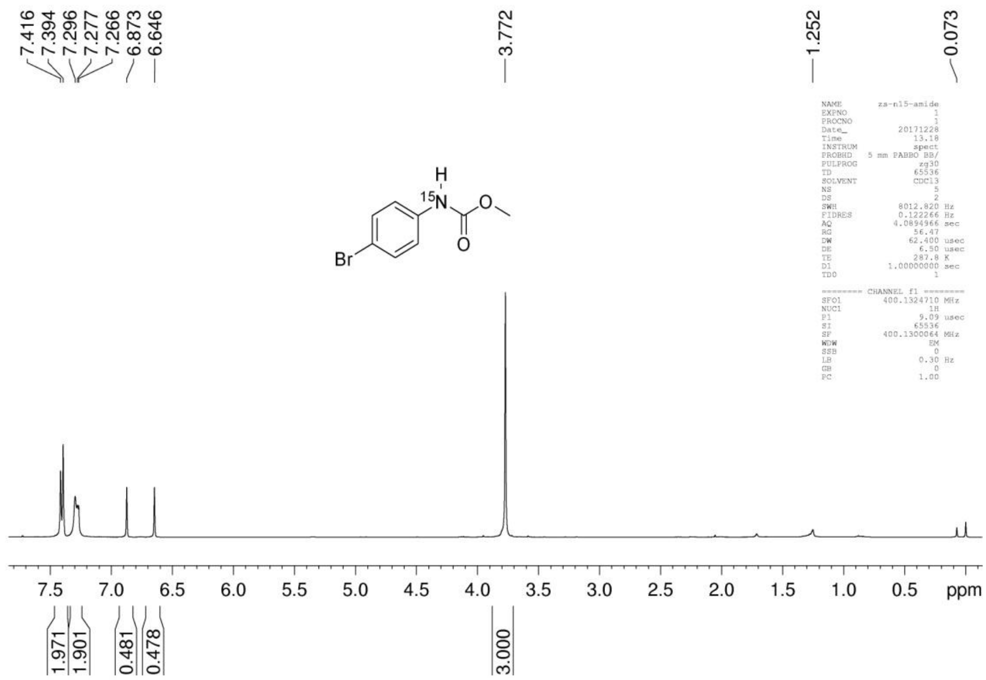


N15-2d 1H NMR:



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