Regioselectively Rh-catalyzed direct carbonylation of indole to synthesize indole-3-carboxylate

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1. General information

All the chemicals and solvents were used as received without further purification. Silica gel was purchased from Qing Dao Hai Lang Chemical Industry Co. NMR spectra of the products were recorded using a Bruker Avance TM □ spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C in $CDCl_3$ unless otherwise noted. High resolution mass spectra (HRMS) of the products were obtained on a Bruker Daltonics micrO TOF-Q□spectrometer. High-performance liquid chromatography (HPLC) analysis was performed by Agilent 1260 Infinity equipped with an Agilent ZORBAX SB-C18 column using aqueous methanol as eluent and 2, 3-dimethylindole as inner standard. X-ray Single Crystal Diffraction measurement was conducted at 296 K on a Bruker SMART APEX II diffractometer using Mo Kα radiation (γ = 0.71073Å). The data were corrected for Lorentz and polarization effects with the SMART suite of programs and for absorption effects with SADABS. The structure was solved by direct methods using the SHELXS program.

2. General procedures for the synthesis of *N*-substituted indoles

General procedure for the preparation of N-methyl indoles[1]

To a stirred solution of N-H indoles (1 mol) in ether (10 mL) was slowly added Potassium tert-butanolate (2 mol) and Iodomethane (2 mol) at 0 °C. after 24 h, the mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ether three times. The combined organic layers were dried over Na_2SO_4 and concerntrated in vacuo. Purification by column chromatograph on silica gel.

General procedure for the preparation of N-allyl indoles[2]

To a stirred solution of N-H indoles (1 mol) in DMF (10 mL) was slowly added Potassium hydroxide (1.2 mol) and Allyl bromide (1.2 mol). After 12 h at 50 °C, the reaction mixture was cooled to room temperature, poured into saturated aqueous $NaHCO_3$ solution and extracted with ether three times. The combined organic layers were dried over Na_2SO_4 and concerntrated in vacuo. Purification by column chromatograph on silica gel.

General procedure for the preparation of N-benzyl indoles[3]

To a stirred solution of N-H indoles (1 mol) in Tetrahedrofuran (10 mL) was slowly added Potassium hydroxide (4 mol) and Benzyl bromide (1 mol) at 0 °C. after 24 h,

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[1] Y. Naruse, Y. Ito and S. Inagaki, *J. Org. Chem.*, 1991, **56**, 2256-2258.

[2] F. Gagosz and S. Z. Zard, *Org. Lett.*, 2002, **4**, 4345-4348.

[3] H. Heaney, S. V. Ley, A. Brossi, E. E. Garcia and R. P. Schwartz, *Org. Synth., Coll.*, 1988, **6**, 104; 1974, **54**, 58.

[4] Y.-Z. Huang, H. Miao, Q.-H. Zhang, C. Chen and J. Xu, *Catal. Lett.*, 2008, **122**, 344–348.

the mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ether three times. The combined organic layers were dried over Na_2SO_4 and concerntrated in vacuo. Purification by column chromatograph on silica gel.

General procedure for the preparation of N- phenyl indoles[4]

A mixture of Iodobenzene (1 mol), Indole (1.5 mol), Cuprous oxide (0.1 mol), Potassium hydroxide (2 mol) and DMSO (2 mL) was stirred at 120 °C under N_2 atmosphere for 24 hours. Then the mixture was poured into H_2O and extracted with ether three times. The combined organic layers were dried over Na_2SO_4 and concerntrated in vacuo. Purification by column chromatograph on silica gel.

3. Experimental procedure for Rh-catalyzed direct carbonylation (Table 2)

Indole (0.5 mmol), $[Rh(COD)Cl]_2$ (0.02 mmol), $K_2S_2O_8$ (2.0 mmol), alcohol (2.5 mmol) and toluene (1.0 mL) were added to a 50 mL Schlenk tube. The glass tube was vacummed and purged with CO (99.99% purity) three times before it was finally pressurized with 1.0 atm CO gas. Then the tube was tightly screw-capped, immersed in an oil bath preheated at 110 °C, and stirred for 24 h. After cooling to room temperature, excess CO was discharged and the resultant reaction mixture was purified by flash chromatography on 200–300-mesh silica gel with petroleum ether/ethyl acetate (50:1-5:1) as eluent to afford the corresponding product.

4. Experiments on investigation of mechanism

4.1 Stoichiometric amount of $[Rh(COD)Cl]_2$ catalyzed carbonylation of 1a in the absence of $K_2S_2O_8$

N-methyl indole (**1a**, 0.5 mmol), $[Rh(COD)Cl]_2$ (0.25 mmol), *n*-butyl alcohol (2.5 mmol), and toluene (1.0 mL) were added to a 50 mL Schlenk tube. The glass tube was vacummed and purged with CO (99.99% purity) three times before it was finally pressurized with 1.0 atm CO gas. Then the tube was tightly screw-capped, immersed in an oil bath preheated at 110 °C, and stirred for 24 h. Resultant reaction mixture was analyzed by HPLC, ***BUT*** **no carbonylative reaction was observed. This controll experiment could possibly suggest that Rh(I) itself can not initiate the carbonylation.**

4.2 Stoichiometric amount of $RhCl_3$ catalyzed carbonylation of 1a in the absence of $K_2S_2O_8$

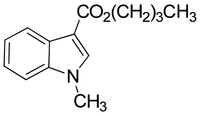
N-methyl indole (**1a**, 0.5 mmol), $RhCl_3$ (0.5 mmol), *n*-butyl alcohol (2.5 mmol) and toluene (1.0 mL) were added to a 50 mL Schlenk tube. The glass tube was vacummed and purged with CO (99.99% purity) three times before it was finally pressurized with 1.0 atm CO gas. Then the tube was tightly screw-capped, immersed in an oil bath preheated at 110 ˚C, and stirred for 24 h. Resultant reaction mixture was analyzed by HPLC, and **4% yield of the desired product 3a was obtained. This controll experiment may indicate that Rh(III) can finish the oxidative carbonylation cycle from metallation of C-H bond to the reductive elimination.**

4.3 Pre-oxidized $[Rh(COD)Cl]_2$ (2.0 mol %) catalyzed direct carbonylation of 1a

$[Rh(COD)Cl]_2$ (0.01 mmol), $K_2S_2O_8$ (2.0 mmol) and toluene (1.0 mL) were added to a 50 mL Schlenk tube with a magnetic bar. The glass tube was vacummed and purged with CO (99.99% purity) three times before it was finally pressurized with 1.0 atm CO gas. Then the tube was tightly screw-capped and immersed in an oil bath preheated at 110 ˚C for 2 h. Subsequently, *N*-methyl indole (0.5 mmol) and *n*-butyl alcohol (2.5 mmol) were introduced under CO atmosphere and the tube was sealed again to react further for 18 h. After the completion of reaction, **99% yield of the desired product 3a was achieved. This controll experiment may further prove that it is Rh(III) species, which is generated from the oxidation of Rh(I) by excess $K_2S_2O_8$, initiate the catalytic cycle.**

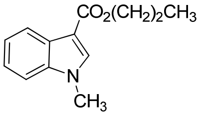
5. Characterization data for products

Butyl 1-methylindole-3-carboxylate (3a).



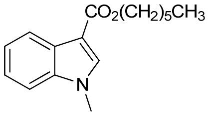
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 1H), 7.77 (s, 1H), 7.35–7.25 (m, 3H), 4.33 (t, J = 6.6 Hz, 2H), 3.81 (s, 3H), 1.78 (m, 2H), 1.51 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (C=O), 136.2, 134.1, 125.6, 121.7, 120.8, 120.7, 108.7, 106.2, 62.5, 32.4, 30.0, 18.4, 12.8. HRMS (ESI) Calcd for $C_{14}H_{17}NNaO_2$: $[M+Na]^+$, 254.1151; Found: 254.1152.

Propyl 1-methylindole-3-carboxylate (3b).



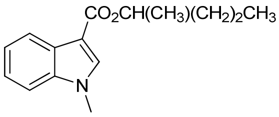
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 1H), 7.75 (s, 1H), 7.43–7.07 (m, 3H), 4.28 (t, J = 6.7 Hz, 2H), 3.77 (s, 3H), 1.81 (dd, J = 14.1, 6.8 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C=O), 137.2, 135.2, 126.6, 122.7, 121.8, 121.7, 109.8, 107.2, 65.3, 33.4, 22.4, 10.7. HRMS (ESI) Calcd for $C_{13}H_{15}NNaO_2$: $[M+Na]^+$, 240.0995; Found: 240.0985.

Hexyl 1-methylindole-3-carboxylate (3c).



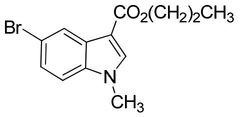
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (m, 1H), 7.77 (s, 1H), 7.36–7.26 (m, 3H), 4.32 (t, J = 6.7 Hz, 2H), 3.81 (s, 3H), 1.78 (m, 2H), 1.47 (m, 2H), 1.35 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C=O), 137.2, 135.2, 126.6, 122.7, 121.8, 121.7, 109.8, 107.3, 63.9, 33.4, 31.6, 29.0, 25.9, 22.6, 14.1. HRMS (ESI) Calcd for $C_{16}H_{21}NNaO_2$: $[M+Na]^+$, 282.1441; Found: 282.1465.

1-Methylbutyl 1-methylindole-3-carboxylate (3d).



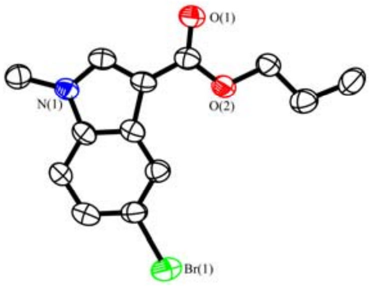
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (m, 1H), 7.76 (s, 1H), 7.34–7.24 (m, 3H), 5.20 (dd, J = 12.8, 6.2 Hz, 1H), 3.79 (s, 3H), 1.75 (m, 1H), 1.60 (m, 1H), 1.46 (m, 2H), 1.36 (d, J = 6.3 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (C=O), 137.2, 135.1, 126.7, 122.7, 121.8, 121.7, 109.8, 107.6, 69.9, 38.5, 33.4, 20.5, 18.9, 14.1. HRMS (ESI) Calcd for $C_{15}H_{19}NNaO_2$: $[M+Na]^+$, 268.1332; Found: 268.1324.

Propyl 5-bromo-1-methylindole-3-carboxylate (3e).



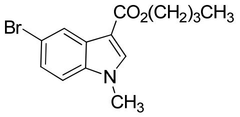
A white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 1.5 Hz, 1H), 7.66 (s, 1H), 7.28 (m, 1H), 7.10 (d, J = 8.7 Hz, 1H), 4.20 (t, J = 6.7 Hz, 2H), 3.71 (s, 3H), 1.74 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (C=O), 134.9, 134.8, 127.1, 124.7, 123.3, 114.5, 110.2, 105.9, 64.5, 32.5, 21.3, 9.6. HRMS (ESI) Calcd for $C_{13}H_{14}BrNNaO_2$: $[M+Na]^+$, 318.0100; Found: 318.0093.

Crystal data for **3e**. Formula $C_{13}H_{14}BrNO_2$, colorless crystal, monoclinic, space group *P21/c*; a = 13.696(9) Å, b = 5.641(4) Å, c = 17.155(11) Å, α = 90°, β = 101.063(8)°, γ = 90°, V = 1300.8(15) Å^3; Z = 1; crystal size 0.15 × 0.20 × 0.40 mm^3; GOF = 0.918; reflections collected 7198; independent reflections: 2305 [R_{int} = 0.1257]; R_1 = 0.0742; wR_2 = 0.2178. The crystal structure of **3e** has been deposited at the Cambridge Crystallographic Data Centre and allocated a deposition number: CCDC 838366.



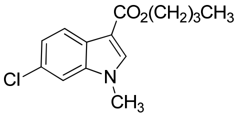
Scheme 1. Crystal structure of **3e**

Butyl 5-bromo-1-methylindole-3-carboxylate (3f).



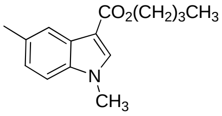
A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.29 (d, *J* = 1.7 Hz, 1H), 7.74 (s, 1H), 7.36 (m, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 4.32 (t, *J* = 6.7 Hz, 2H), 3.80 (s, 3H), 1.78 (m, 2H), 1.51 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.7 (C=O), 135.9, 128.2, 125.7, 124.3, 115.6, 111.2, 107.0, 63.8, 33.6, 31.0, 19.4, 13.8. HRMS (ESI) Calcd for $C_{14}H_{16}BrNNaO_2$: [M+Na]$^+$, 332.0257; Found: 332.0244.

Butyl 6-chloro-1-methylindole-3-carboxylate (3g).



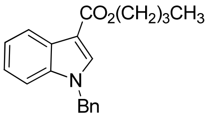
A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05(m, 1H), 7.75 (s, 1H), 7.34 (d, *J* = 1.5 Hz, 1H), 7.23 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.32 (t, *J* = 6.7 Hz, 2H), 3.79 (s, 3H), 1.87–1.68 (m, 2H), 1.56–1.43 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.8 (C=O), 137.6, 135.6, 128.8, 125.1, 122.7, 122.5, 109.9, 107.6, 63.7, 33.5, 31.0, 19.4, 13.8. HRMS (ESI) Calcd for $C_{14}H_{16}ClNNaO_2$: [M+Na]$^+$, 288.0767; Found: 288.0770.

Butyl 1,5-dimethylindole-3-carboxylate (3h).



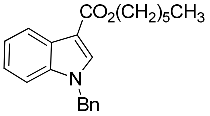
A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (s, 1H), 7.71 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.11 (m, 1H), 4.32 (t, *J* = 6.7 Hz, 2H), 3.77 (s, 3H), 2.49 (s, 3H), 1.77 (m, 2H), 1.52 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.3 (C=O), 135.6, 135.1, 131.4, 126.9, 124.3, 121.4, 109.4, 106.6, 63.5, 33.4, 31.1, 21.6, 19.4, 13.9. HRMS (ESI) Calcd for $C_{15}H_{19}NNaO_2$: [M+Na]$^+$, 268.1308; Found: 268.1297.

Butyl 1-benzylindole-3-carboxylate (3i).



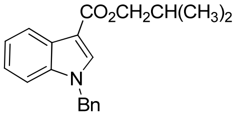
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (m, 1H), 7.86 (s, 1H), 7.35–7.26 (m, 5H), 7.23 (m, 1H), 7.15 (m, 2H), 5.34 (s, 2H), 4.34 (t, *J* = 6.7 Hz, 2H), 1.78 (m, 2H), 1.51 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C=O), 136.8, 136.0, 134.6, 129.0, 128.1, 127.0, 126.8, 122.9, 122.0, 121.8, 110.3, 108.0, 63.7, 50.7, 31.1, 19.4, 13.9. HRMS (ESI) Calcd for $C_{20}H_{21}NNaO_2$: $[M+Na]^+$, 330.1465; Found: 330.1455.

Hexyl 1-benzylindole-3-carboxylate (3j).



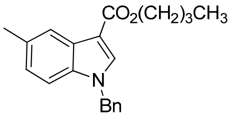
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (m, 1H), 7.84 (s, 1H), 7.33–7.18 (m, 6H), 7.15–7.09 (m, 2H), 5.29 (s, 2H), 4.32 (t, *J* = 6.7 Hz, 2H), 1.85–1.70 (m, 2H), 1.54–1.40 (m, 2H), 1.34 (m, 4H), 0.90 (t, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (C=O), 136.8, 136.0, 134.6, 128.9, 128.1, 127.0, 126.8, 122.9, 122.0, 121.8, 110.3, 107.9, 64.0, 50.7, 31.5, 28.9, 25.8, 22.6, 14.0. HRMS (ESI) Calcd for $C_{22}H_{25}NNaO_2$: $[M+Na]^+$, 358.1778; Found: 358.1766.

Isobutyl 1-benzylindole-3-carboxylate (3k).



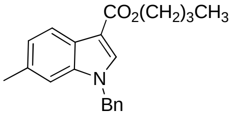
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (m, 1H), 7.85 (s, 1H), 7.30–7.26 (m, 2H), 7.26–7.18 (m, 4H), 7.12–7.08 (m, 2H), 5.26 (s, 2H), 4.12 (d, *J* = 6.6 Hz, 2H), 2.10 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C=O), 136.8, 136.1, 134.8, 129.0, 128.1, 127.0, 126.8, 123.0, 122.1, 121.9, 110.4, 108.0, 70.1, 50.7, 28.1, 19.5. HRMS (ESI) Calcd for $C_{20}H_{21}NNaO_2$: $[M+Na]^+$, 330.1465; Found: 330.1460.

Butyl 1-benzyl-5-methylindole-3-carboxylate (3l).



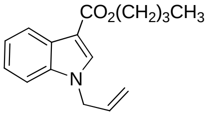
A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.99 (d, *J* = 0.7 Hz, 1H), 7.80 (s, 1H), 7.35–7.25 (m, 3H), 7.21–7.08 (m, 3H), 7.05 (m, 1H), 5.29 (s, 2H), 4.33 (t, *J* = 6.7 Hz, 2H), 2.47 (s, 3H), 1.78 (m, 2H), 1.57–1.44 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.3 (C=O), 136.1, 135.2, 134.6, 131.5, 129.0, 128.1, 127.1, 127.0, 124.5, 121.5, 110.0, 107.3, 63.6, 50.8, 31.1, 21.6, 19.4, 13.9. HRMS (ESI) Calcd for $C_{21}H_{23}NNaO_2$: [M+Na]$^+$, 344.1621; Found: 344.1619.

Butyl 1-benzyl-6-methylindole-3-carboxylate (3m).



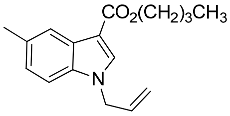
A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.68 (s, 1H), 7.25–7.18 (m, 3H), 7.05–6.98 (m, 4H), 5.17 (s, 2H), 4.24 (t, *J* = 6.7 Hz, 2H), 2.34 (s, 3H), 1.68 (m, 2H), 1.42 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.3 (C=O), 136.1, 135.1, 133.0, 131.8, 127.9, 127.0, 125.9, 123.5, 122.7, 120.4, 109.1, 106.8, 62.5, 49.4, 30.0, 20.8, 18.4, 12.8. HRMS (ESI) Calcd for $C_{21}H_{23}NNaO_2$: [M+Na]$^+$, 344.1621; Found: 344.1619.

Butyl 1-allylindole-3-carboxylate (3n).



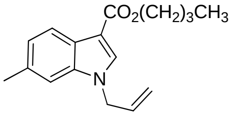
A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.18 (m, 1H), 7.82 (s, 1H), 7.33 (m, 1H), 7.29–7.24 (m, 2H), 5.99 (m, 1H), 5.26 (m, 1H), 5.14 (m, 1H), 4.81–4.67 (m, 2H), 4.34 (t, *J* = 6.7 Hz, 2H), 1.78 (m, 2H), 1.51 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.3 (C=O), 136.6, 134.3, 132.2, 126.8, 122.8, 121.9, 121.8, 118.5, 110.2, 107.7, 63.6, 49.3, 31.1, 19.4, 13.9. HRMS (ESI) Calcd for $C_{16}H_{19}NNaO_2$: [M+Na]$^+$, 280.1308; Found: 280.1306.

Butyl 1-allyl-5-methylindole-3-carboxylate (3o).



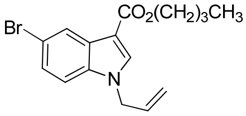
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.96 (m, 1H), 7.77 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.09 (m, 1H), 5.98 (m, 1H), 5.25 (m, 1H), 5.13 (m, 1H), 4.72 (m, 2H), 4.33 (t, *J* = 6.7 Hz, 2H), 2.49 (s, 3H), 1.86–1.72 (m, 2H), 1.58–1.45 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3 (C=O), 135.0, 134.2, 132.3, 131.4, 127.0, 124.3, 121.5, 118.4, 109.8, 107.1, 63.5, 49.4, 31.1, 21.6, 19.4, 13.9. HRMS (ESI) Calcd for $C_{17}H_{21}NNaO_2$: $[M+Na]^+$, 294.1465; Found: 294.1470.

Butyl 1-allyl-6-methylindole-3-carboxylate (3p).



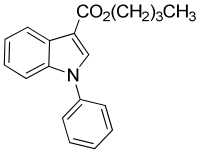
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.90 (m, 1H), 5.17 (m, 1H), 5.04 (m, 1H), 4.65–4.57 (m, 2H), 4.24 (t, *J* = 6.7 Hz, 2H), 2.40 (s, 3H), 1.68 (m, 2H), 1.42 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (C=O), 137.0, 133.8, 132.7, 132.3, 124.6, 123.7, 121.4, 118.3, 110.1, 107.6, 63.6, 49.2, 31.1, 21.9, 19.4, 13.9. HRMS (ESI) Calcd for $C_{17}H_{21}NNaO_2$: $[M+Na]^+$, 294.1465; Found: 294.1470.

Butyl 1-allyl-5-bromoindole-3-carboxylate (3q).



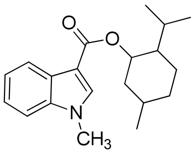
A pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 1.9 Hz, 1H), 7.78 (s, 1H), 7.33 (m, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 5.95 (m, 1H), 5.27 (m, 1H), 5.10 (m, 1H), 4.70 (m, 2H), 4.32 (t, *J* = 6.7 Hz, 2H), 1.83–1.73 (m, 2H), 1.56–1.44 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (C=O), 135.3, 135.0, 131.8, 128.3, 125.7, 124.4, 118.7, 115.6, 111.7, 107.3, 63.8, 49.5, 31.0, 19.4, 13.8. HRMS (ESI) Calcd for $C_{16}H_{18}BrNNaO_2$: $[M+Na]^+$, 358.0413; Found: 358.0412.

Butyl 1-phenylindole-3-carboxylate (3r).



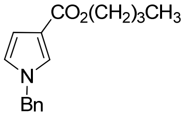
A yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.25 (m, 1H), 8.03 (s, 1H), 7.57–7.42 (m, 5H), 7.43 (m, 1H), 7.35–7.25 (m, 2H), 4.37 (t, *J* = 6.6 Hz, 2H), 1.84–1.77 (m, 2H), 1.61–1.43 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.2 (C=O), 138.6, 136.7, 134.1, 129.8, 127.8, 127.0, 124.9, 123.4, 122.5, 121.9, 111.0, 109.5, 63.8, 31.1, 19.4, 13.9. HRMS (ESI) Calcd for $C_{19}H_{20}NO_2$: [M+H]$^+$, 294.1465; Found: 294.1475.

Menthyl 1-methylindole-3-carboxylate (3u).



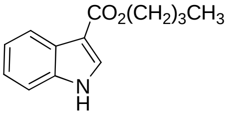
A white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.17 (m, 1H), 7.79 (s, 1H), 7.39–7.27 (m, 3H), 4.96 (m, 1H), 3.84 (s, 3H), 2.18 (d, *J* = 12.1 Hz, 1H), 2.03 (m, 1H), 1.74 (d, *J* = 11.5 Hz, 2H), 1.68–1.52 (m, 3H), 1.20–1.07 (m, 2H), 0.93 (dd, *J* = 6.8, 2.8 Hz, 6H), 0.81 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.8 (C=O), 137.2, 135.1, 126.7, 122.7, 121.8, 109.7, 107.6, 73.3, 47.5, 41.5, 34.5, 33.4, 31.5, 26.5, 23.7, 22.1, 20.9, 16.6. HRMS (ESI) Calcd for $C_{20}H_{27}NNaO_2$: [M+Na]$^+$, 336.1934; Found: 336.1933.

Butyl 1-benzylpyrrole-3-carboxylate (3v).



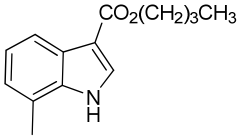
A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34–7.32 (m, 4H), 7.19–7.09 (m, 2H), 6.61 (d, *J* = 1.9 Hz, 2H), 5.05 (s, 2H), 4.21 (t, *J* = 6.7 Hz, 2H), 1.68 (m, 2H), 1.50–1.37 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.9 (C=O), 136.7, 128.9, 128.1, 127.2, 126.3, 122.0, 116.6, 110.5, 63.6, 53.8, 31.0, 19.3, 13.8. HRMS (ESI) Calcd for $C_{16}H_{19}NNaO_2$: [M+Na]$^+$, 280.1308; Found: 280.1316.

Butyl indole-3-carboxylate (3w).



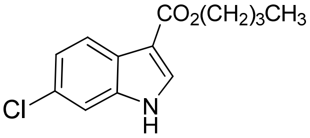
A white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.56 (s, 1H), 8.19 (m, 1H), 7.94 (d, *J* = 3.0 Hz, 1H), 7.42 (m, 1H), 7.31–7.26 (m, 2H), 4.35 (t, *J* = 6.6 Hz, 2H), 1.80 (m, 2H), 1.53 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.3 (C=O), 136.1, 131.0, 125.8, 123.2, 122.0, 121.6, 111.4,109.3, 63.7, 31.0, 19.4, 13.8. HRMS (ESI) Calcd for $C_{13}H_{15}NNaO_2$: [M+Na]$^+$, 240.0995; Found: 240.0996.

Butyl 7-methylindole-3-carboxylate (3x).



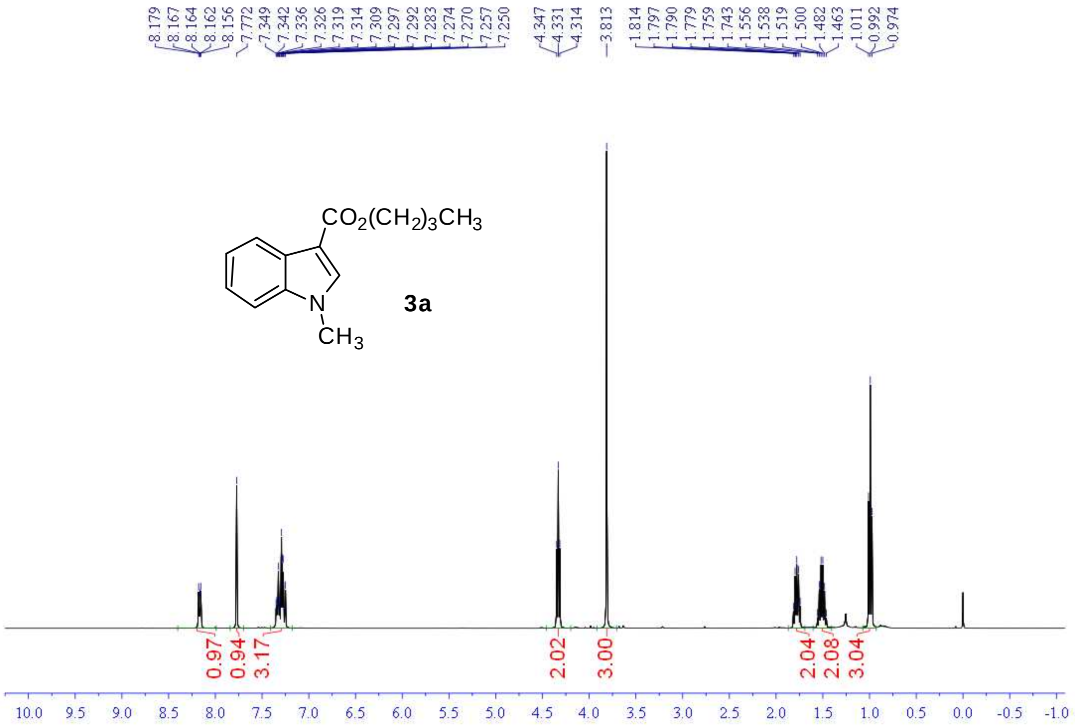
A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.75 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 3.0 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 4.27 (t, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 1.72 (m, 2H), 1.44 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.6 (C=O), 134.7, 129.8, 124.4, 122.6, 121.1, 119.7, 118.2, 108.4, 62.7, 30.0, 18.4, 15.5, 12.8. HRMS (ESI) Calcd for $C_{14}H_{18}NO_2$: [M+H]$^+$, 232.1259; Found: 232.1284.

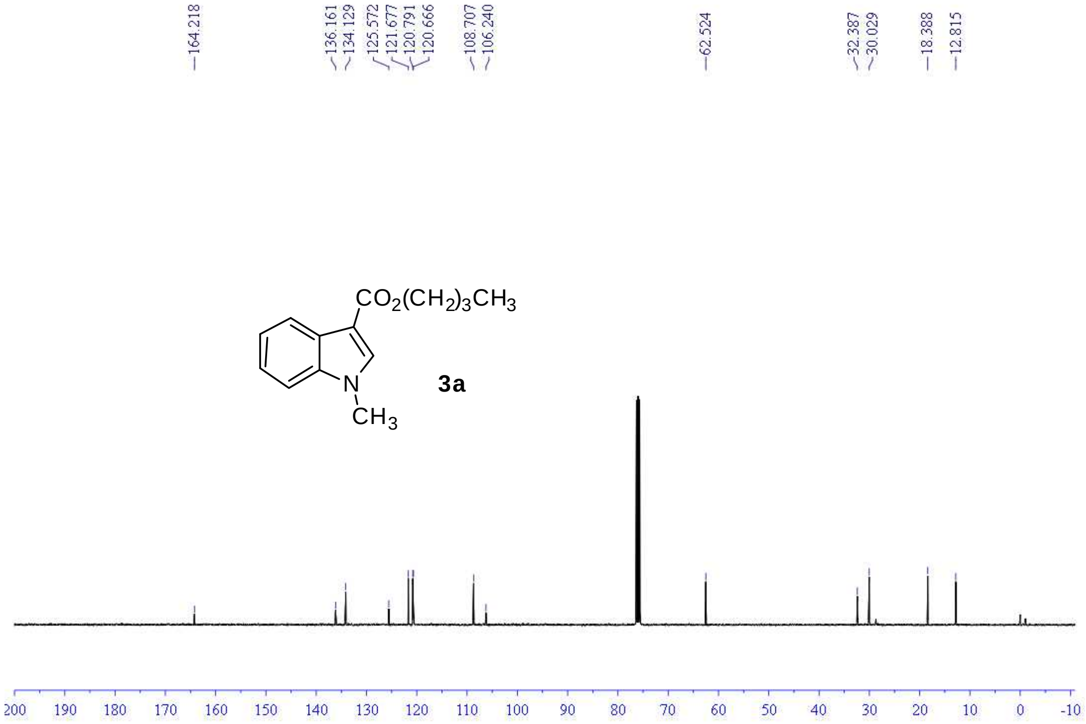
Butyl 6-chloro-indole-3-carboxylate (3y).

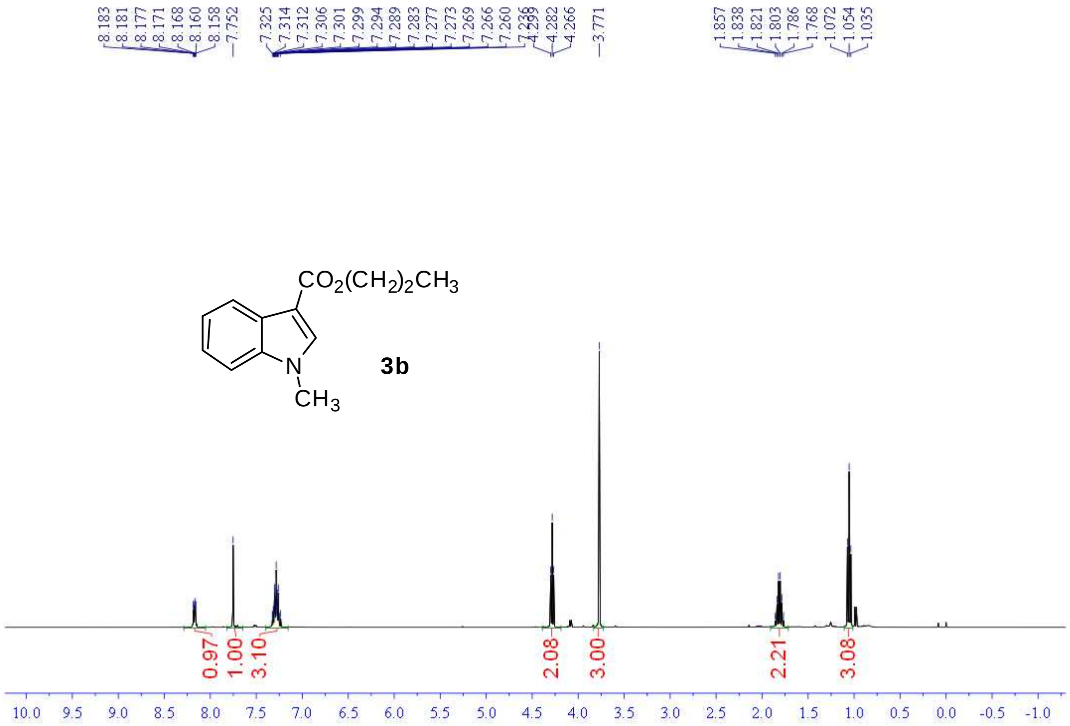


A pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.89 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 2.9 Hz, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.15 (dd, *J* = 8.6, 1.8 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 1.71 (m, 2H), 1.42 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.2（C=O）, 136.5, 131.6, 129.1, 124.4, 122.7, 122.5, 111.6, 109.2, 64.0, 31.0, 19.4, 13.8. HRMS (ESI) Calcd for $C_{13}H_{14}ClNNaO_2$: [M+Na]$^+$, 274.0605; Found: 274.2704.

6. ^{1}H NMR and ^{13}C NMR copies of products



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8.158
7.752
7.325
7.314
7.312
7.306
7.301
7.299
7.294
7.289
7.283
7.277
7.273
7.269
7.266
7.260
7.236
4.299
4.282
4.266
3.771
1.857
1.838
1.821
1.803
1.786
1.768
1.072
1.054
1.035
CO2(CH2)2CH3
N
CH3
3b
0.97
1.00
3.10
2.08
3.00
2.21
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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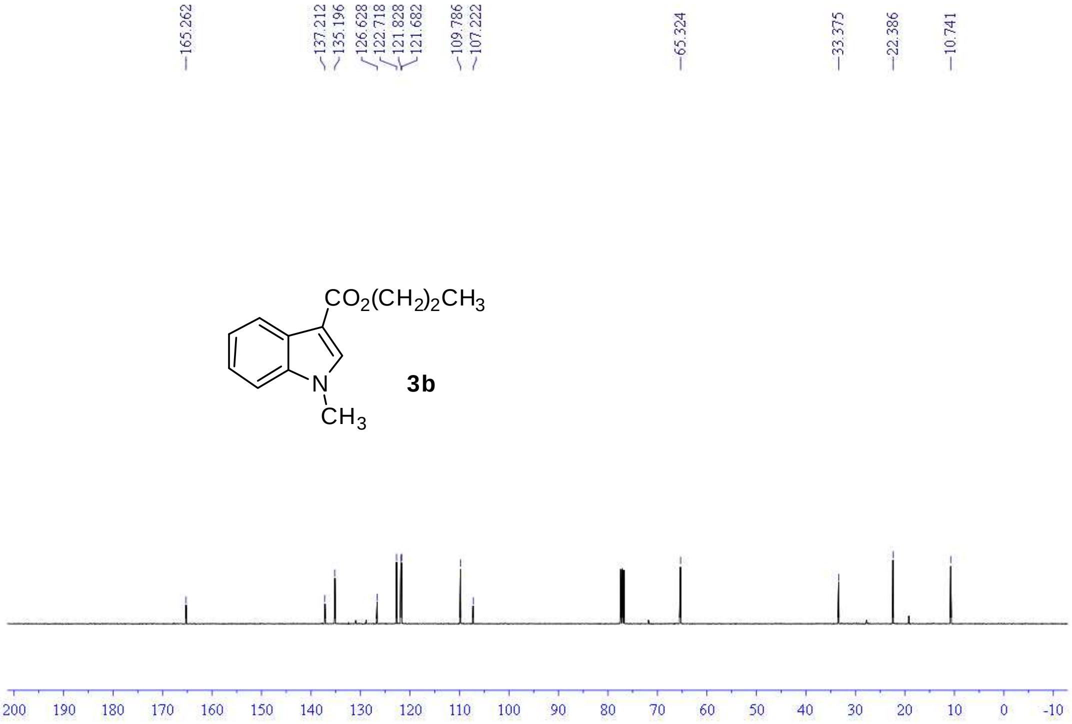
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0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109.786
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22.386
10.741
CO2(CH2)2CH3
N
CH3
3b
200
190
180
170
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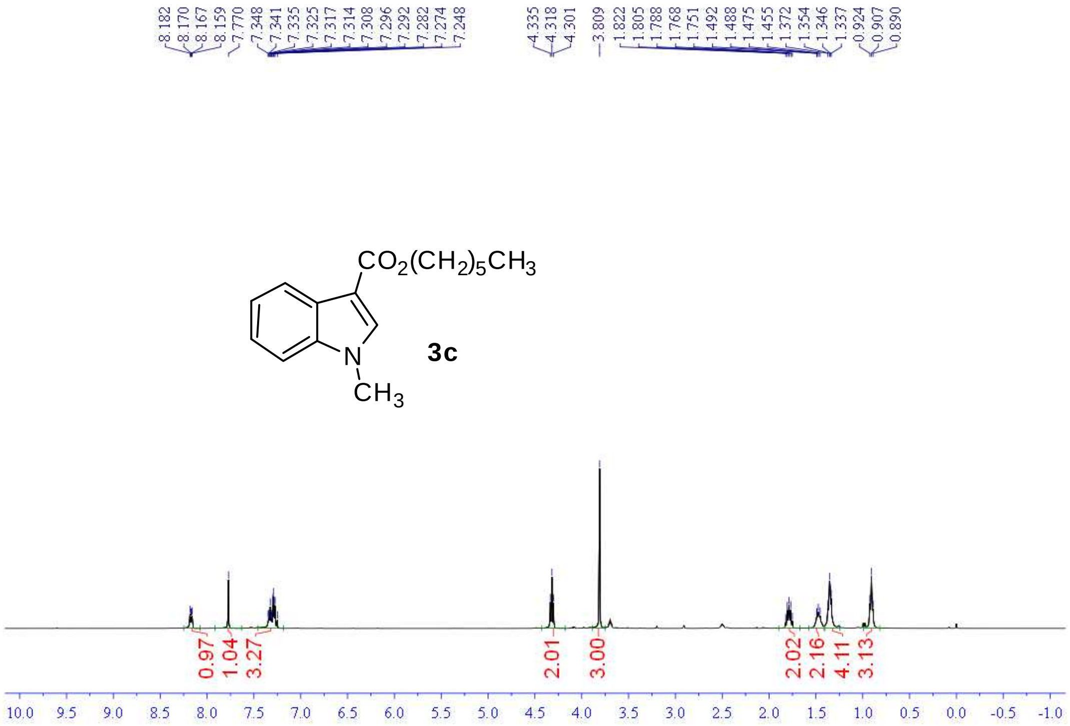
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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7.296
7.292
7.282
7.274
7.248
4.335
4.318
4.301
3.809
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1.805
1.788
1.768
1.751
1.492
1.488
1.475
1.455
1.372
1.354
1.346
1.337
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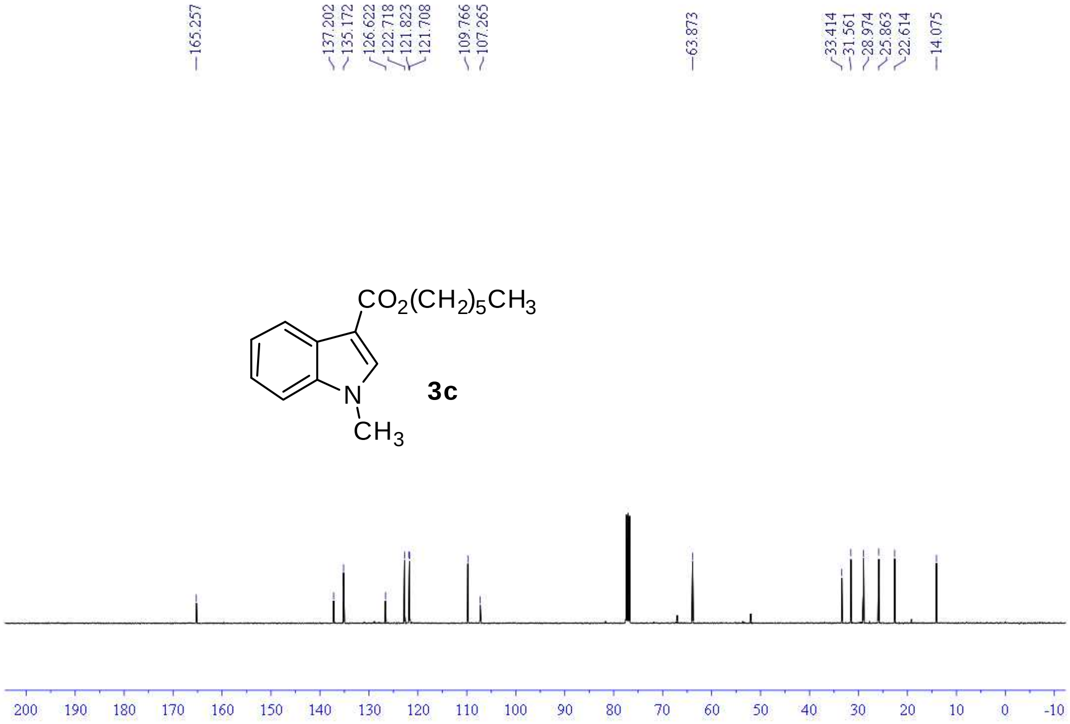
0.907
0.890
$CO_2(CH_2)_5CH_3$
N
CH_3
3c
0.97
1.04
3.27
2.01
3.00
2.02
2.16
4.11
3.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0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122.718
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109.766
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31.561
28.974
25.863
22.614
14.075
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N
CH_3
3c
200
190
180
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140
130
120
110
100
90
80
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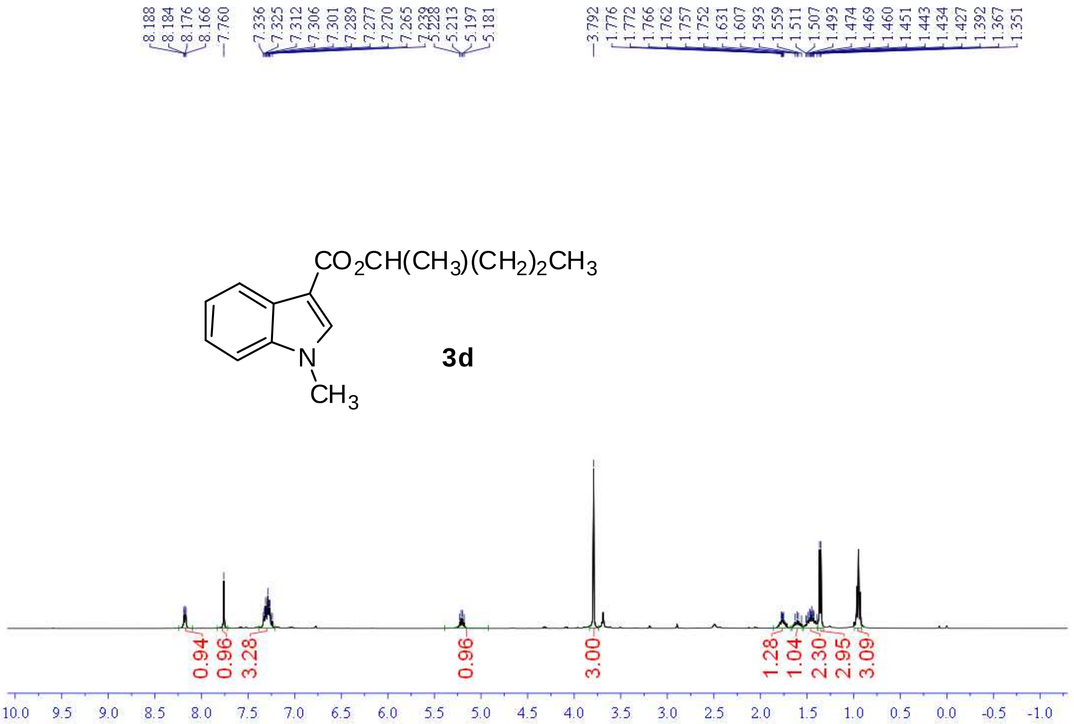
60
50
40
30
20
10
0
-10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7.270
7.265
7.239
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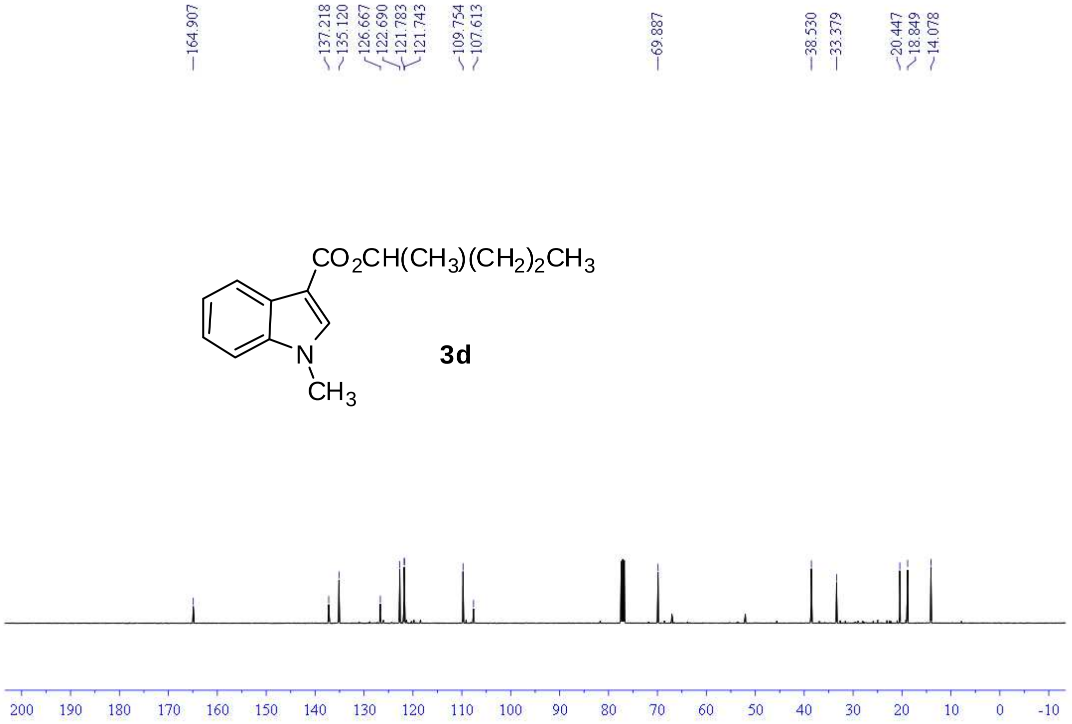
5.213
5.197
5.181
3.792
1.776
1.772
1.766
1.762
1.757
1.752
1.631
1.607
1.593
1.559
1.511
1.507
1.493
1.474
1.469
1.460
1.451
1.443
1.434
1.427
1.392
1.367
1.351
CO2CH(CH3)(CH2)2CH3
N
CH3
0.94
0.96
3.28
0.96
3.00
1.28
1.04
2.30
2.95
3.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

3d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135.120
126.667
122.690
121.783
121.743
109.754
107.613
69.887
38.530
33.379
20.447
18.849
14.078
CO2CH(CH3)(CH2)2CH3
N
CH3
200
190
180
170
160
150
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120
110
100
90
80
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50
40
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0
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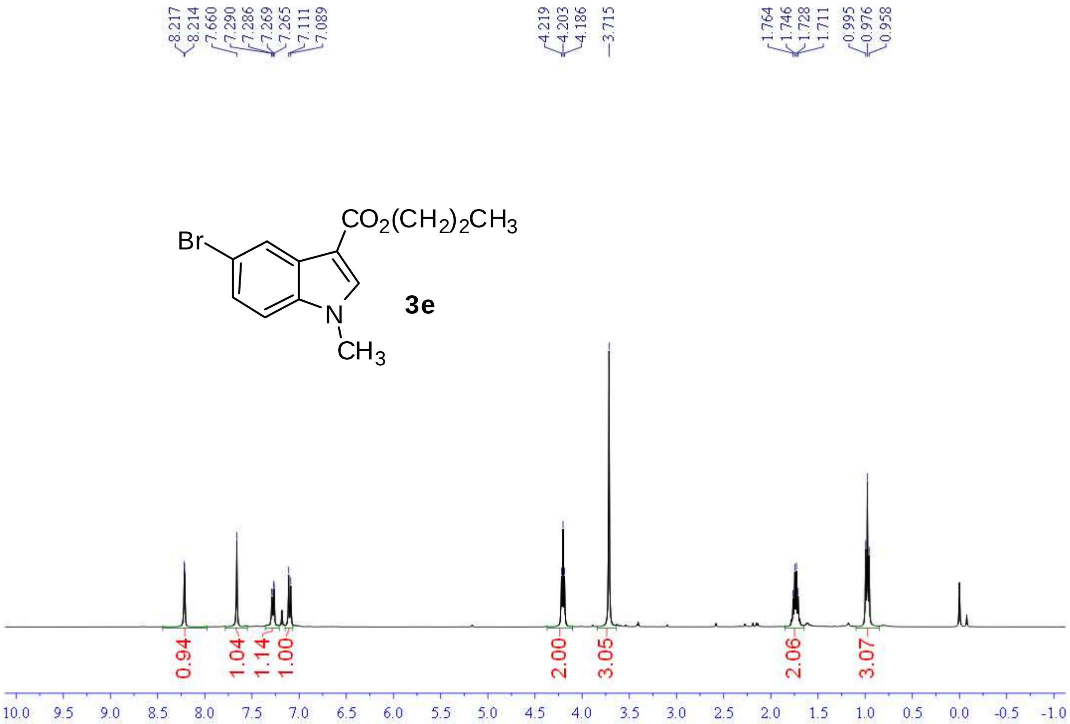
3d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7.265
7.111
7.089
4.219
4.203
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3.715
1.764
1.746
1.728
1.711
0.995
0.976
0.958
Br
$CO_2(CH_2)_2CH_3$
N
CH_3
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1.14
1.00
2.00
3.05
2.06
3.07
10.0
9.5
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
5.0
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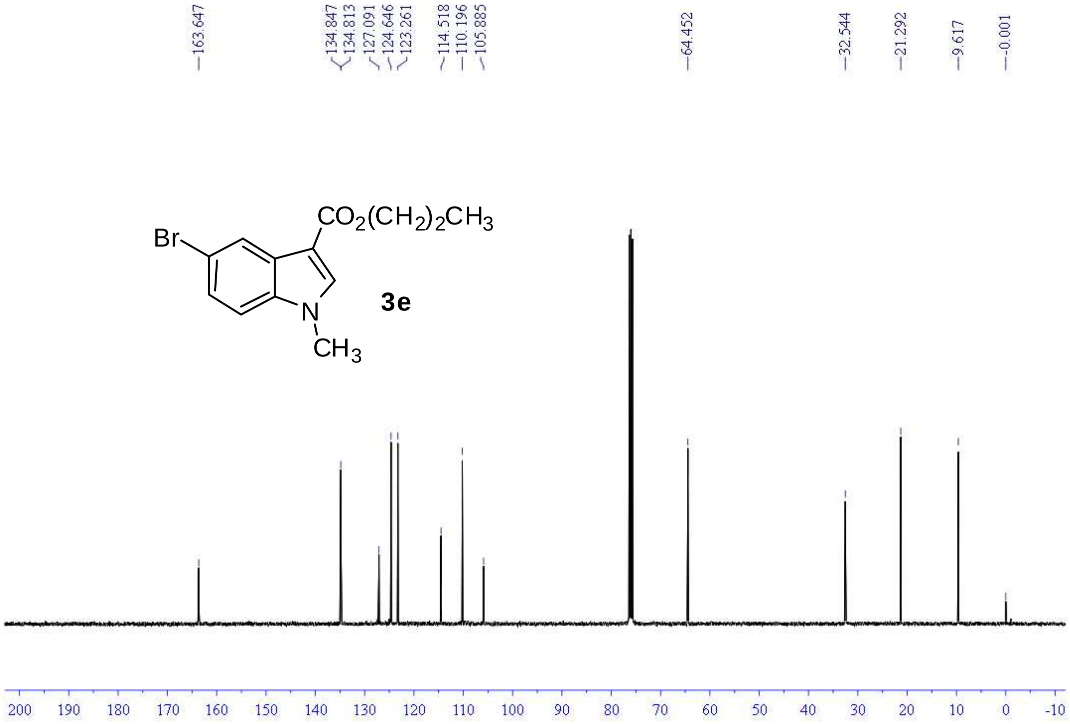
-1.0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134.813
127.091
124.646
123.261
114.518
110.196
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64.452
32.544
21.292
9.617
-0.001
Br
$CO_2(CH_2)_2CH_3$
N
CH_3
3e
200
190
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140
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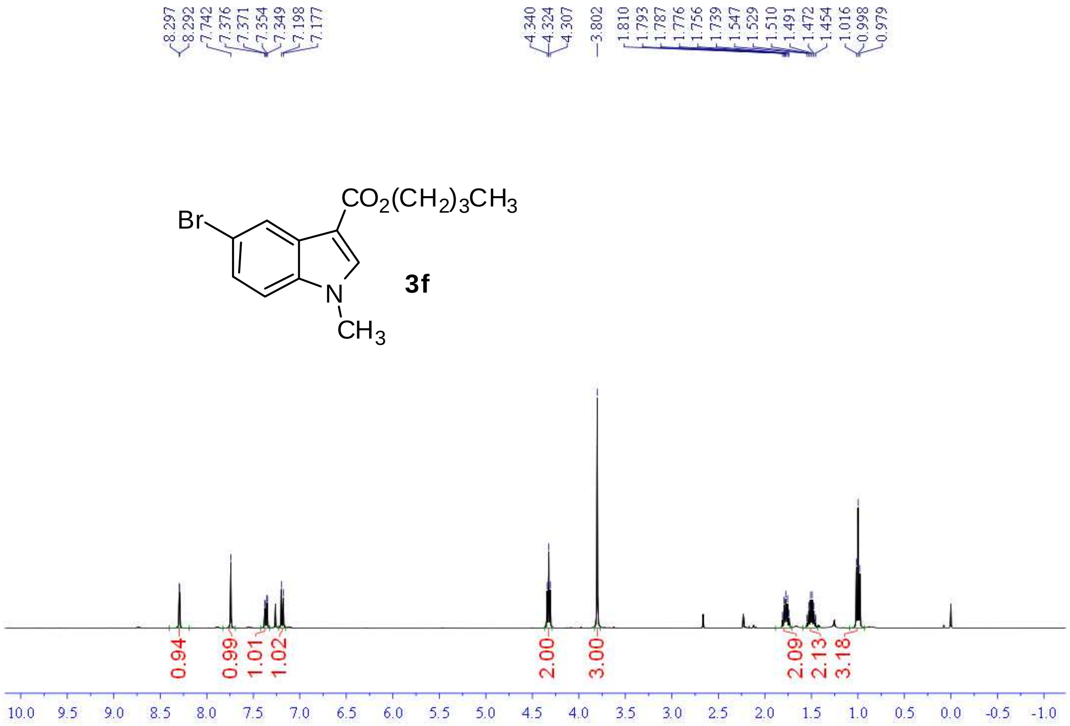
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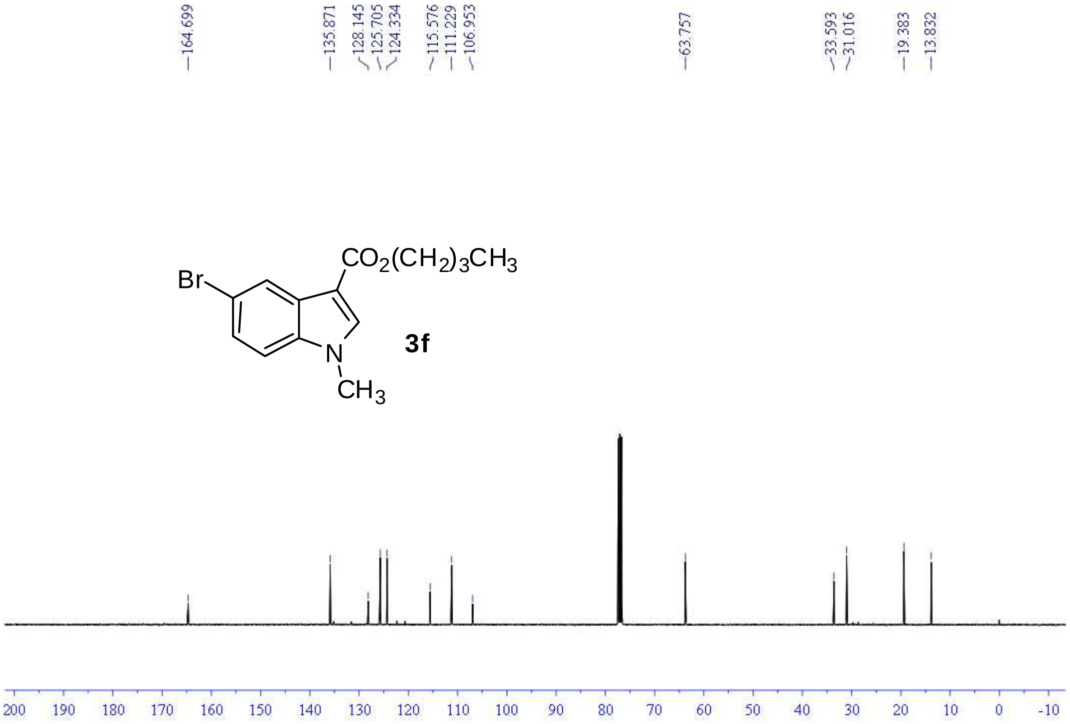
3.802
1.810
1.793
1.787
1.776
1.756
1.739
1.547
1.529
1.510
1.491
1.472
1.454
1.016
0.998
0.979
Br
$CO_2(CH_2)_3CH_3$
N
CH_3
3f
0.94
0.99
1.01
1.02
2.00
3.00
2.09
2.13
3.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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111.229
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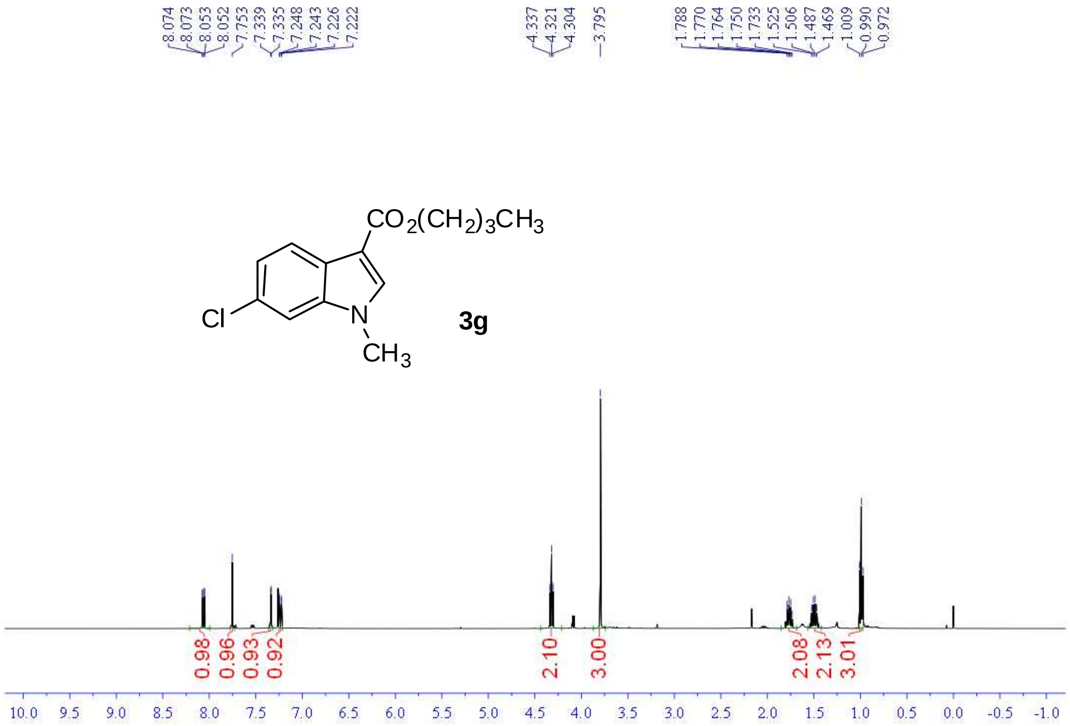
63.757
33.593
31.016
19.383
13.832
Br
$CO_2(CH_2)_3CH_3$
N
CH_3
3f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10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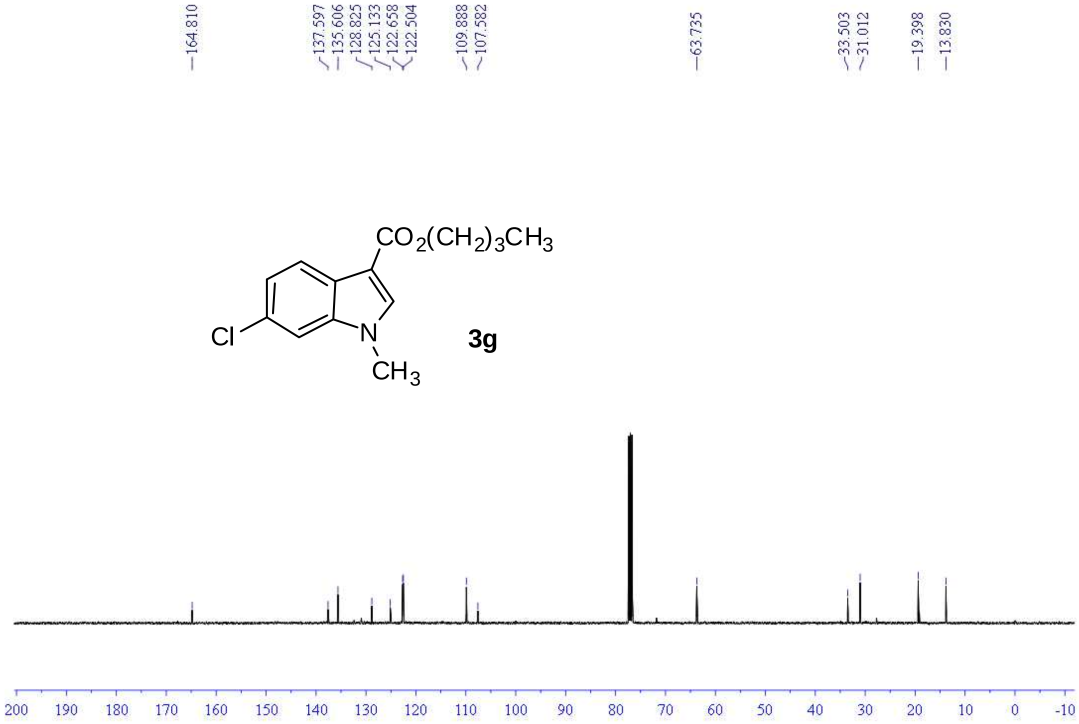
4.321
4.304
3.795
1.788
1.770
1.764
1.750
1.733
1.525
1.506
1.487
1.469
1.009
0.990
0.972
$CO_2(CH_2)_3CH_3$
Cl
N
CH_3
3g
0.98
0.96
0.93
0.92
2.10
3.00
2.08
2.13
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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122.504
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63.735
33.503
31.012
19.398
13.830
$CO_2(CH_2)_3CH_3$
Cl
N
CH_3
3g
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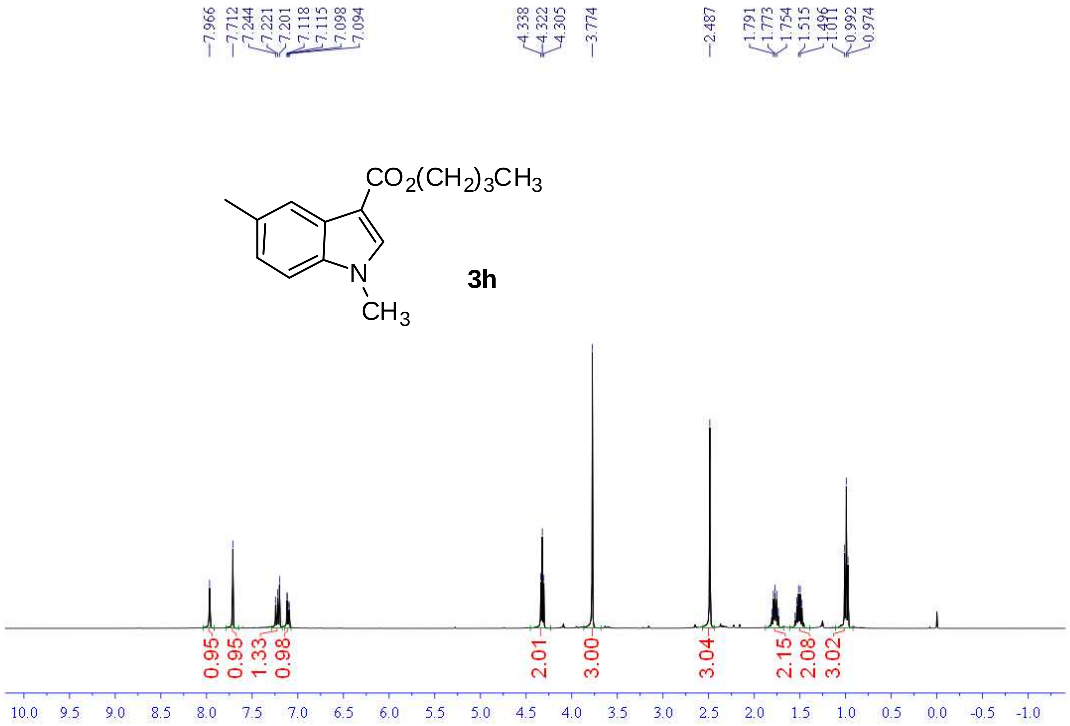
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2.487
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1.754
1.515
1.496
1.011
0.992
0.974
CO2(CH2)3CH3
N
CH3
3h
0.95
0.95
1.33
0.98
2.01
3.00
3.04
2.15
2.08
3.02
10.0
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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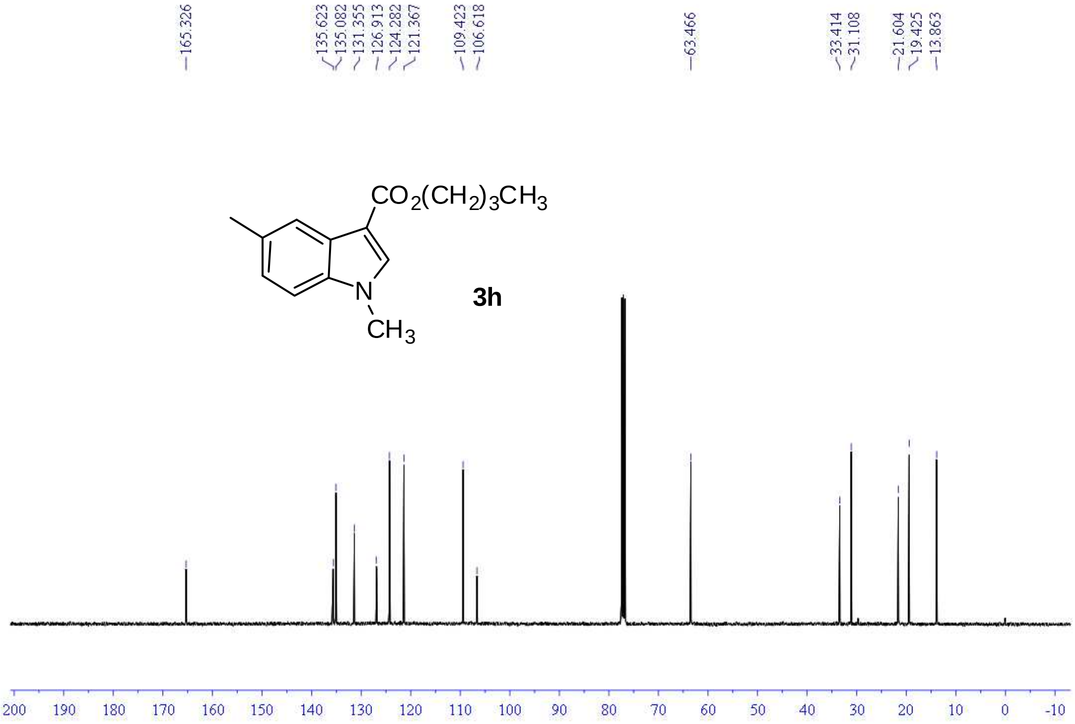
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19.425
13.863
CO2(CH2)3CH3
N
CH3
3h
200
190
180
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120
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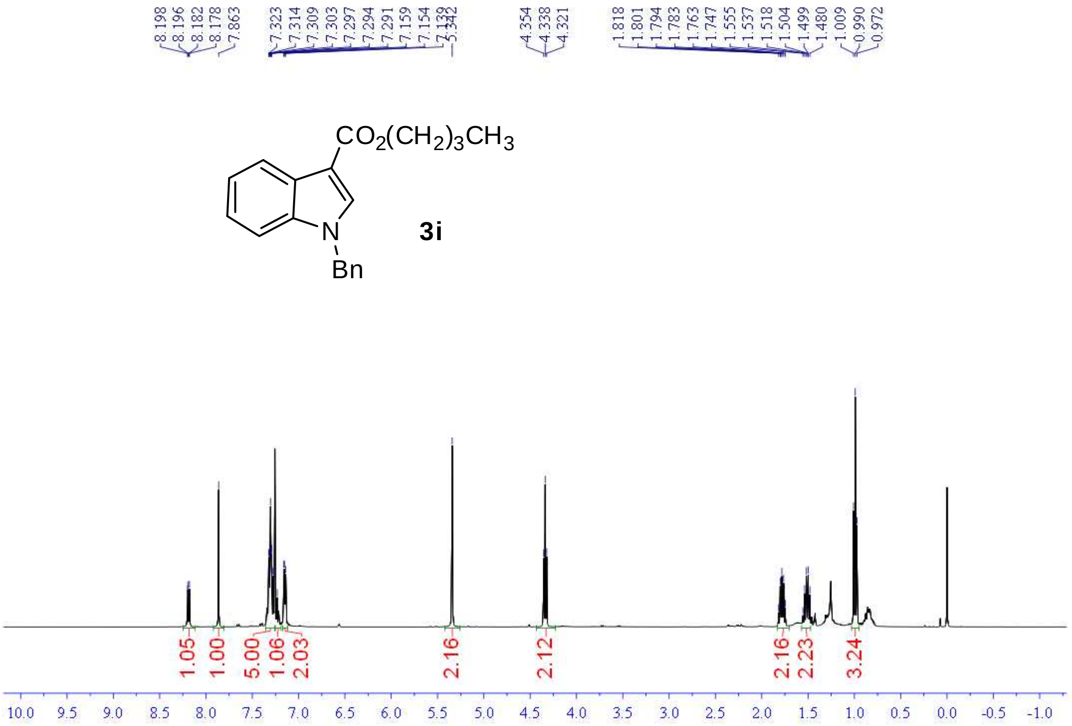
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7.139
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4.354
4.338
4.321
1.818
1.801
1.794
1.783
1.763
1.747
1.555
1.537
1.518
1.504
1.499
1.480
1.009
0.990
0.972
CO2(CH2)3CH3
N
Bn
3i
1.05
1.00
5.00
1.06
2.03
2.16
2.12
2.16
2.23
3.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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6.0
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5.0
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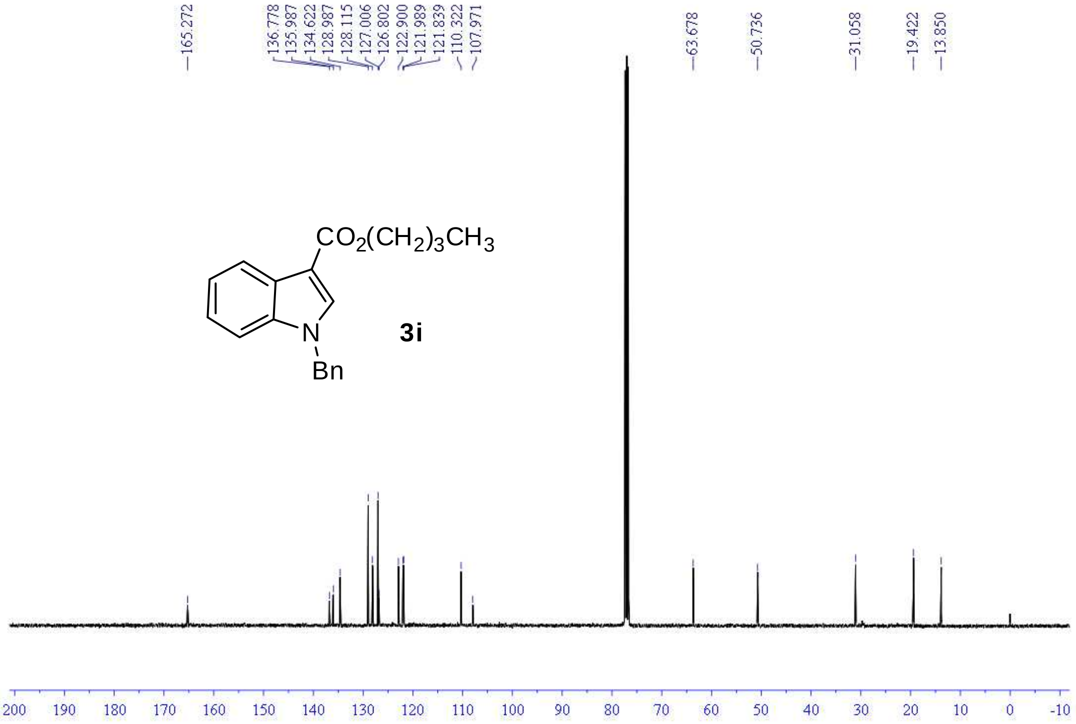
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31.058
19.422
13.850
CO2(CH2)3CH3
N
Bn
3i
200
190
180
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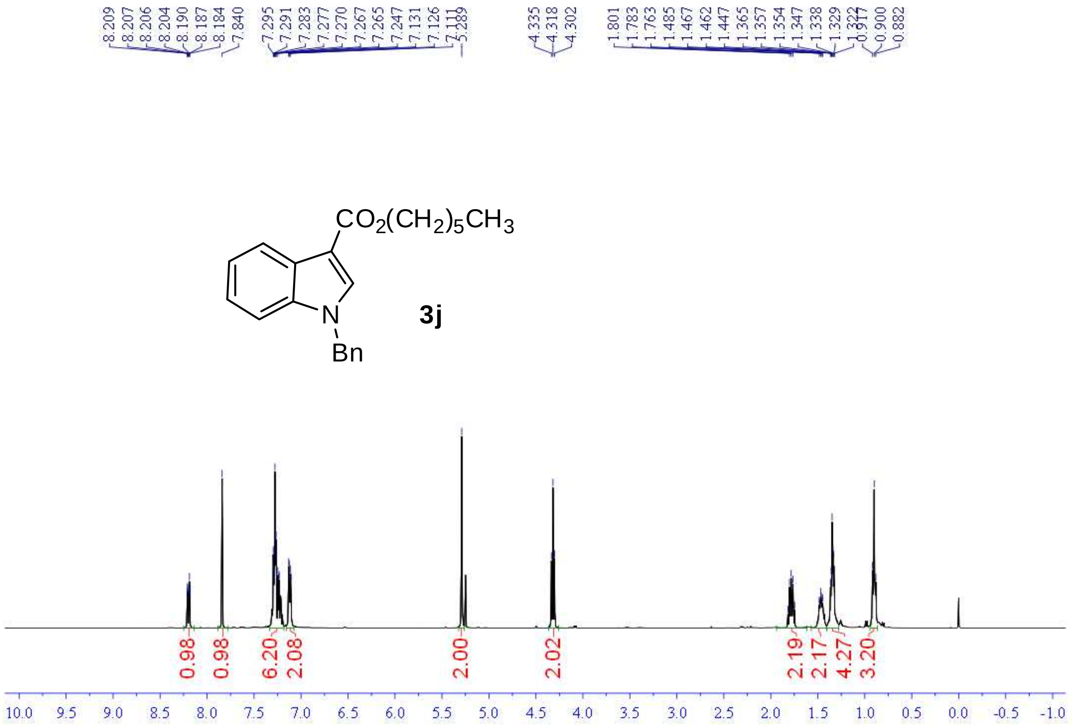
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7.265
7.247
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4.302
1.801
1.783
1.763
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1.322
0.917
0.900
0.882
CO2(CH2)5CH3
N
Bn
3j
0.98
0.98
6.20
2.08
2.00
2.02
2.19
2.17
4.27
3.20
10.0
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9.0
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5.0
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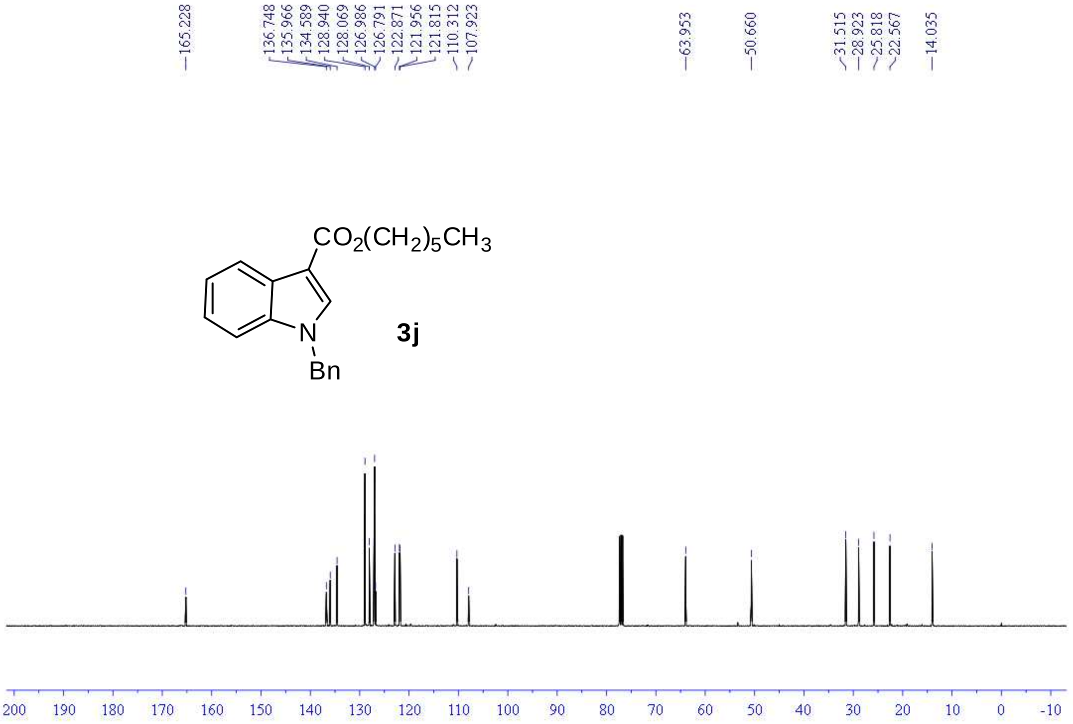
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31.515
28.923
25.818
22.567
14.035
CO2(CH2)5CH3
N
Bn
3j
200
190
180
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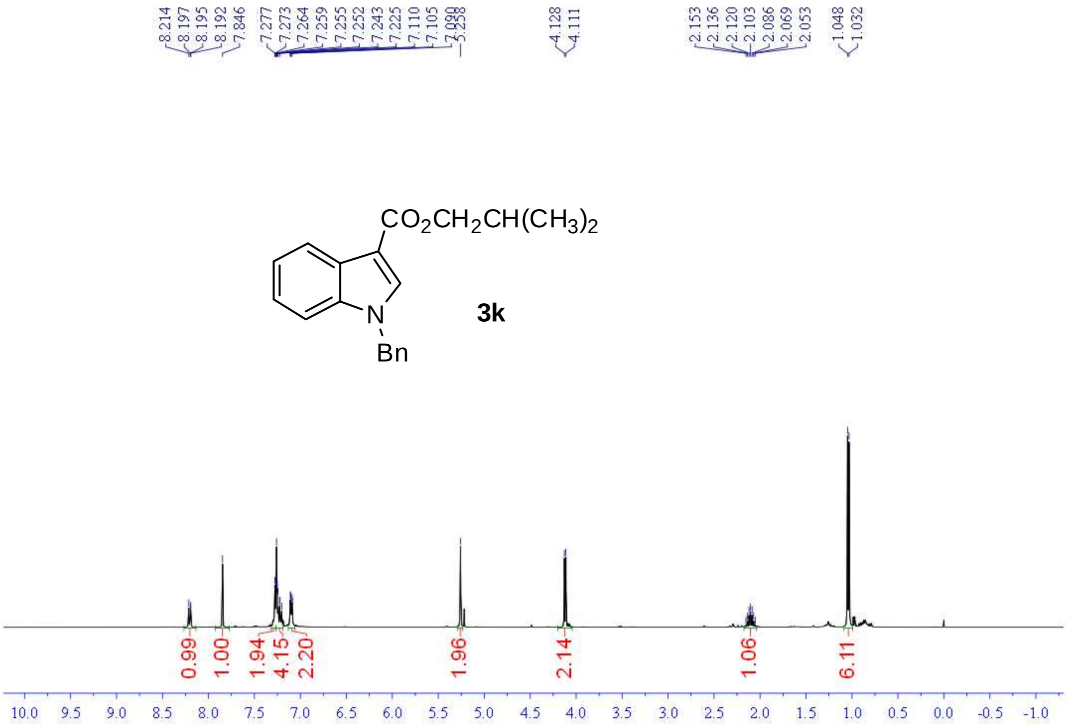
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7.225
7.110
7.105
7.090
5.258
4.128
4.111
2.153
2.136
2.120
2.103
2.086
2.069
2.053
1.048
1.032
$CO_2CH_2CH(CH_3)_2$
N
Bn
3k
0.99
1.00
1.94
4.15
2.20
1.96
2.14
1.06
6.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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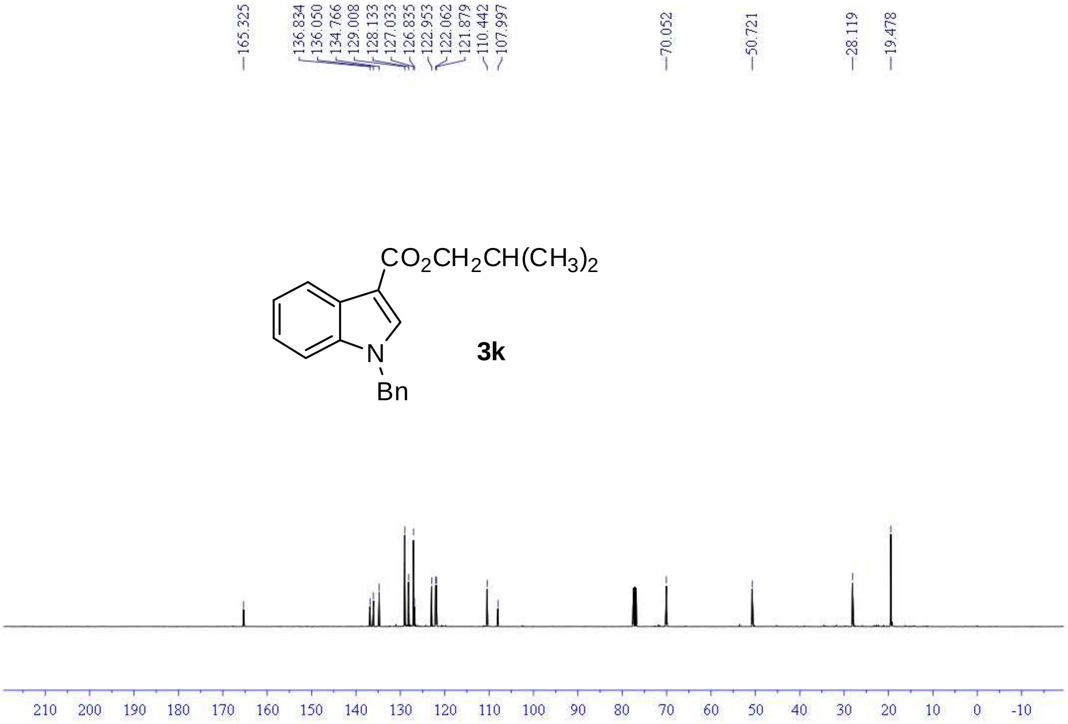
-1.0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107.997
70.052
50.721
28.119
19.478
$CO_2CH_2CH(CH_3)_2$
N
Bn
3k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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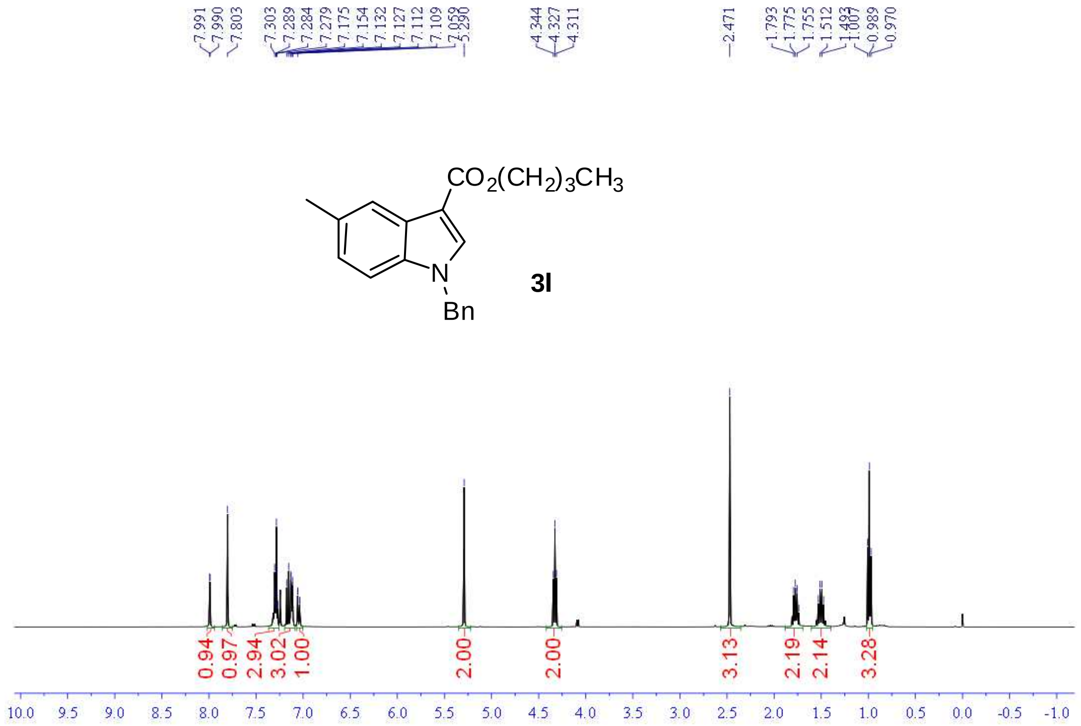
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7.059
5.290
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4.327
4.311
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1.755
1.512
1.493
1.007
0.989
0.970
CO2(CH2)3CH3
N
Bn
3l
0.94
0.97
2.94
3.02
1.00
2.00
2.00
3.13
2.19
2.14
3.28
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9.0
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8.0
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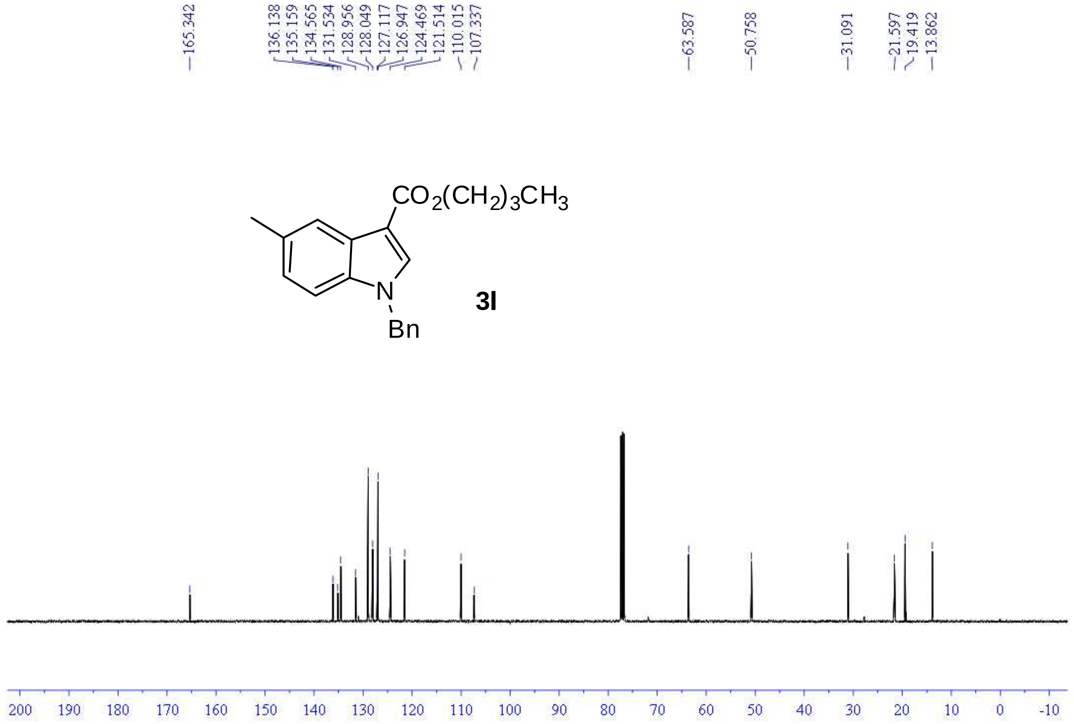
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CO2(CH2)3CH3
N
Bn
3l
200
190
180
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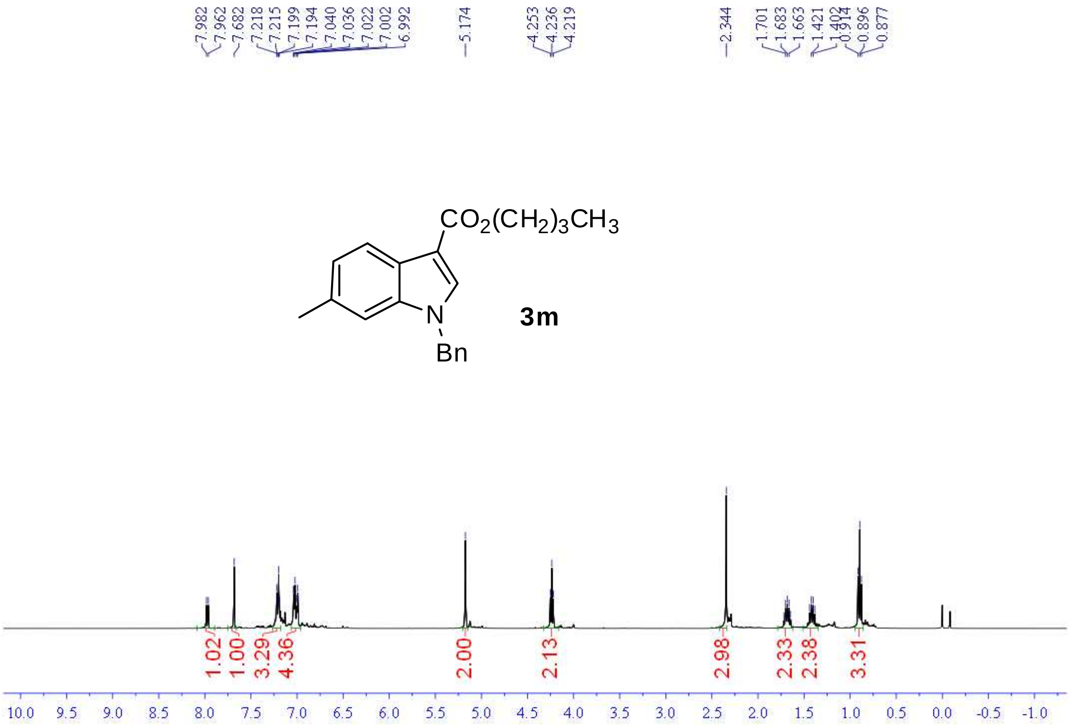
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1.683
1.663
1.421
1.402
0.914
0.896
0.877
CO2(CH2)3CH3
N
Bn
3m
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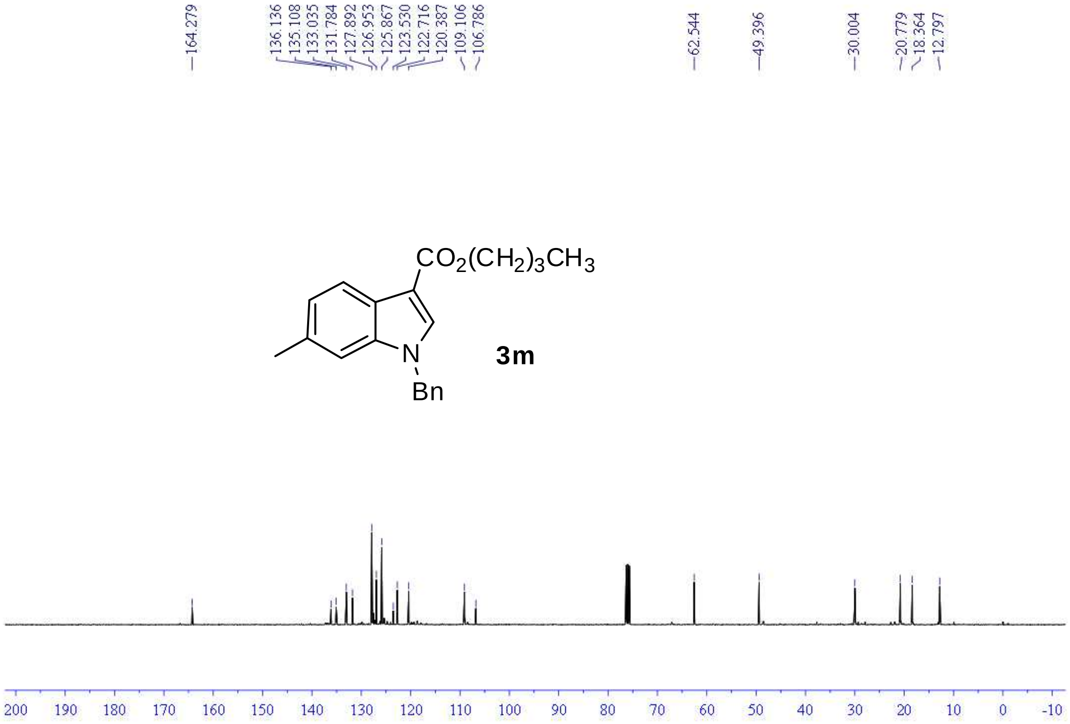
1.00
3.29
4.36
2.00
2.13
2.98
2.33
2.38
3.31
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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106.786
62.544
49.396
30.004
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CO2(CH2)3CH3
N
Bn
3m
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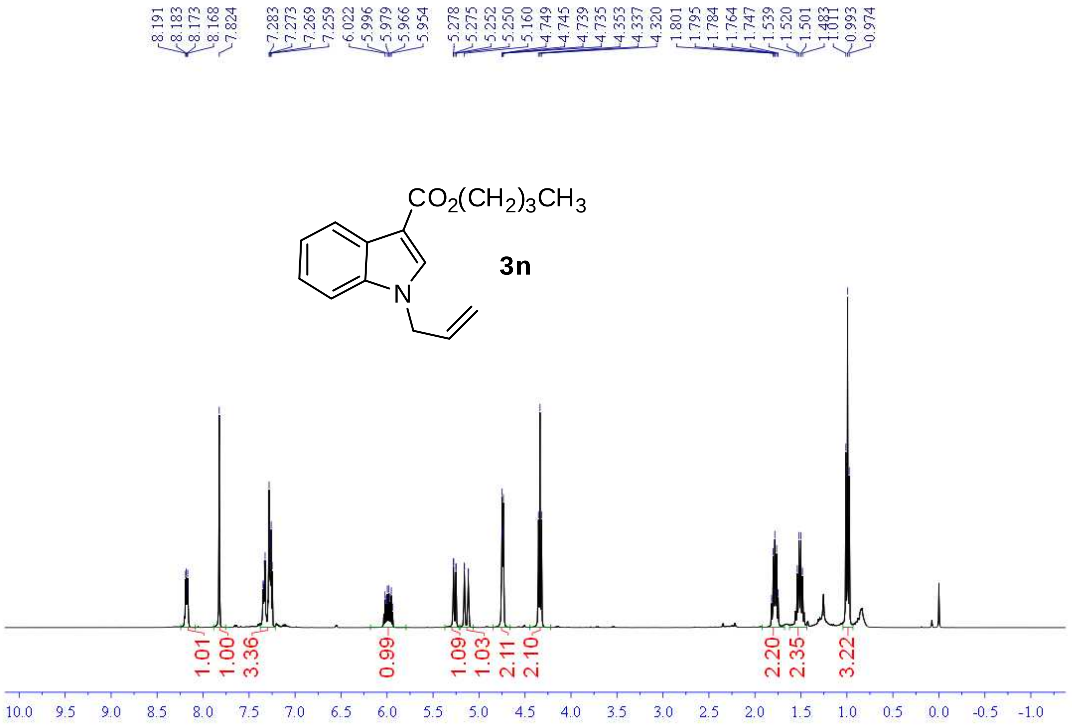
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5.278
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5.250
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4.745
4.739
4.735
4.353
4.337
4.320
1.801
1.795
1.784
1.764
1.747
1.539
1.520
1.501
1.483
1.011
0.993
0.974
CO2(CH2)3CH3
N
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1.00
3.36
0.99
1.09
1.03
2.11
2.10
2.20
2.35
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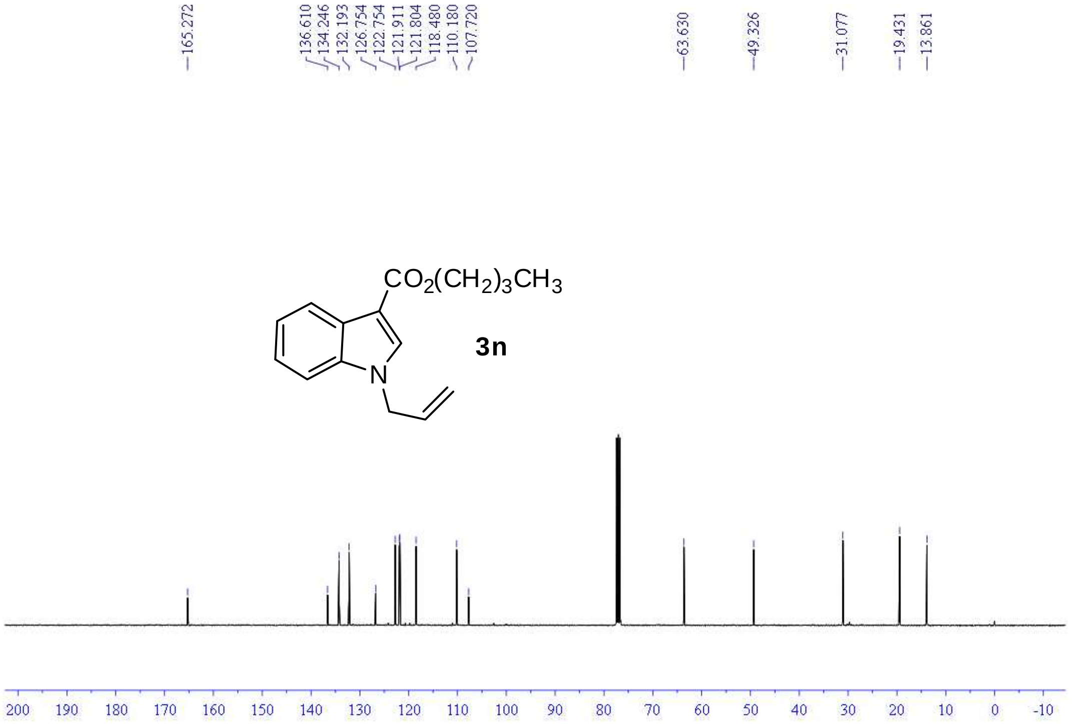
3n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CO2(CH2)3CH3
N
200
190
180
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40
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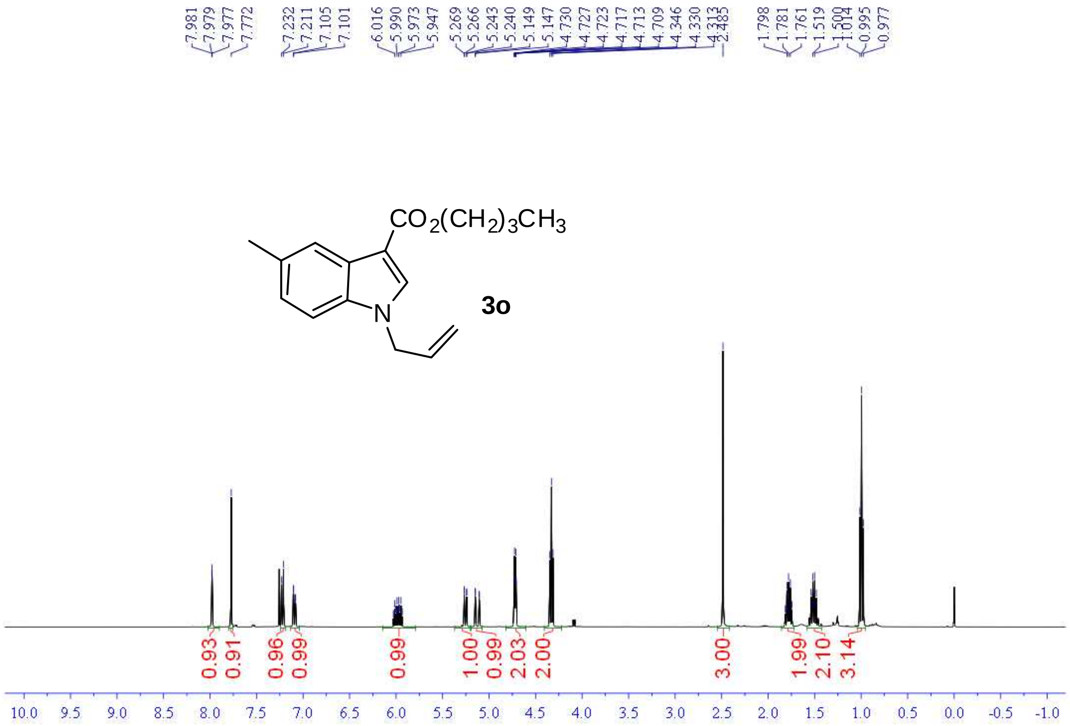
0
-10

3n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4.330
4.313
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1.014
0.995
0.977
CO2(CH2)3CH3
N
3o
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0.96
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0.99
1.00
0.99
2.03
2.00
3.00
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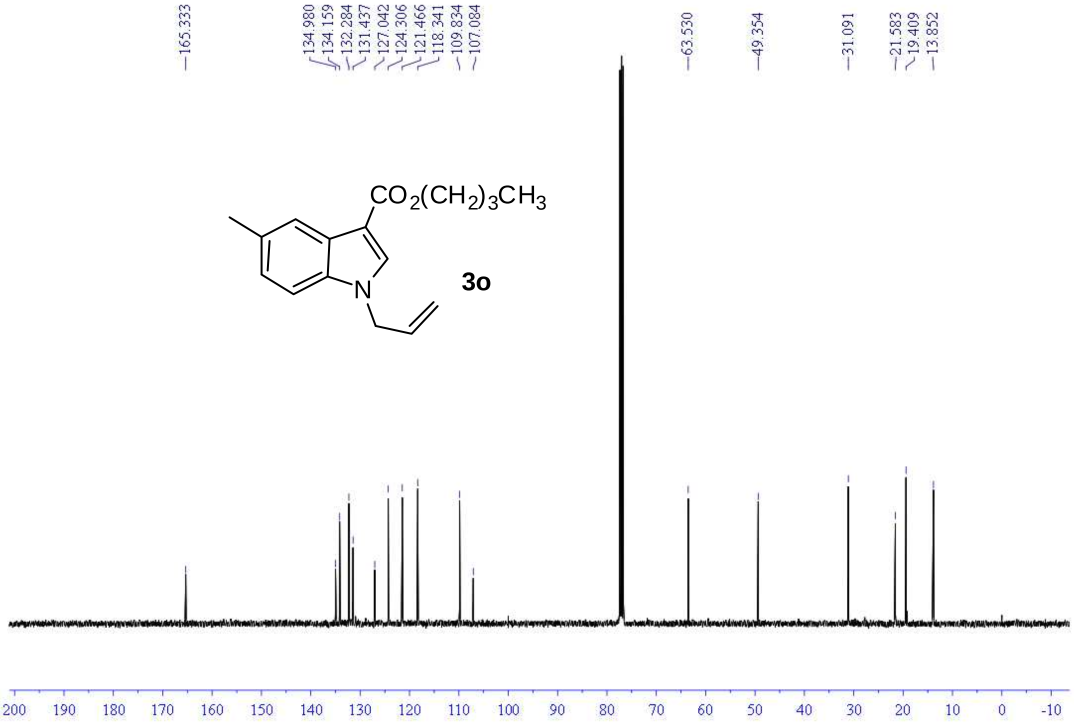
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49.354
31.091
21.583
19.409
13.852
CO2(CH2)3CH3
N
3o
200
190
180
170
160
150
140
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120
110
100
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80
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60
50
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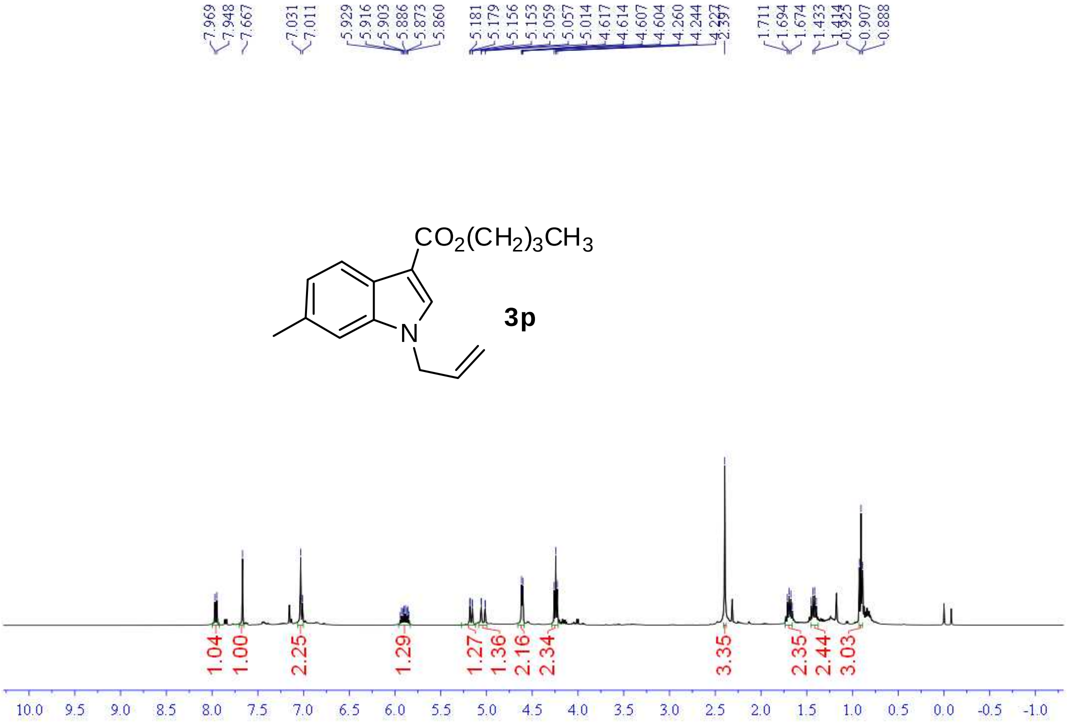

3p

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0.888
CO2(CH2)3CH3
N
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1.29
1.27
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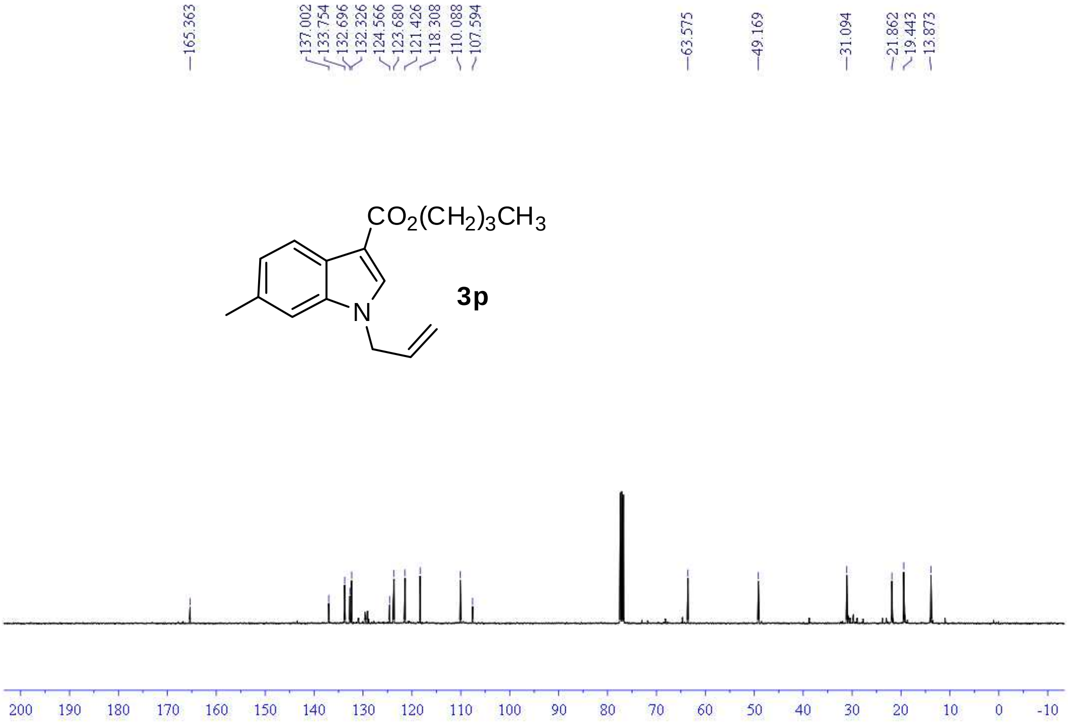

3p

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CO2(CH2)3CH3
N
200
190
180
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100
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80
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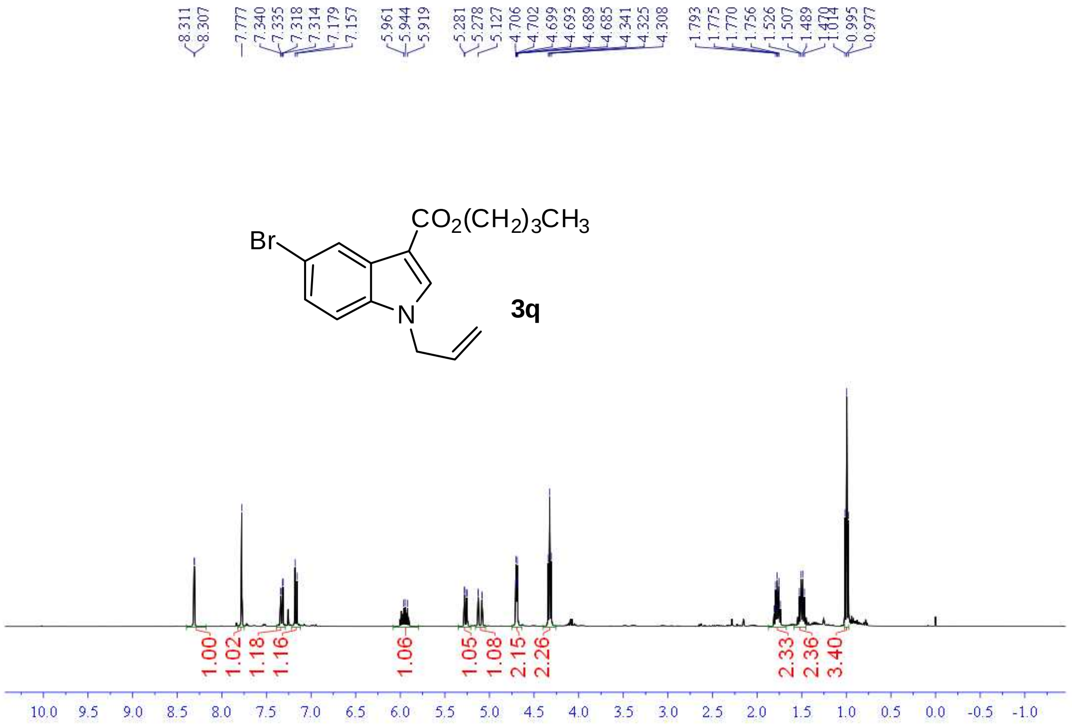
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1.793
1.775
1.770
1.756
1.526
1.507
1.489
1.470
1.014
0.995
0.977
CO2(CH2)3CH3
Br
N
3q
1.00
1.02
1.18
1.16
1.06
1.05
1.08
2.15
2.26
2.33
2.36
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9.0
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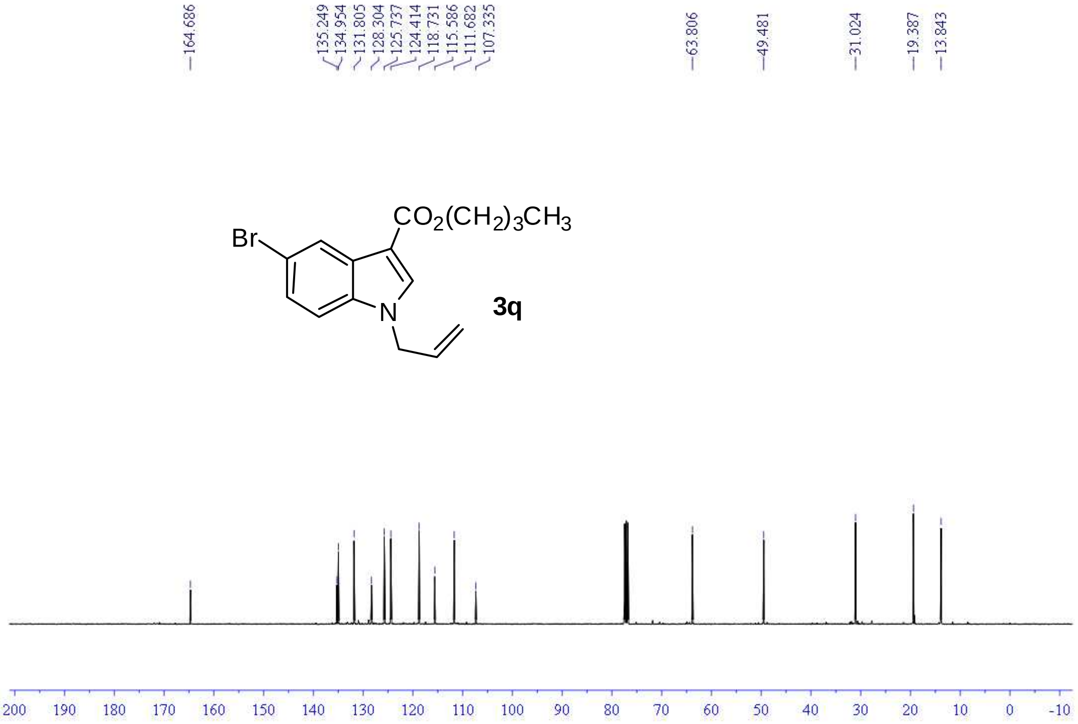
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31.024
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13.843
CO2(CH2)3CH3
Br
N
3q
200
190
180
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100
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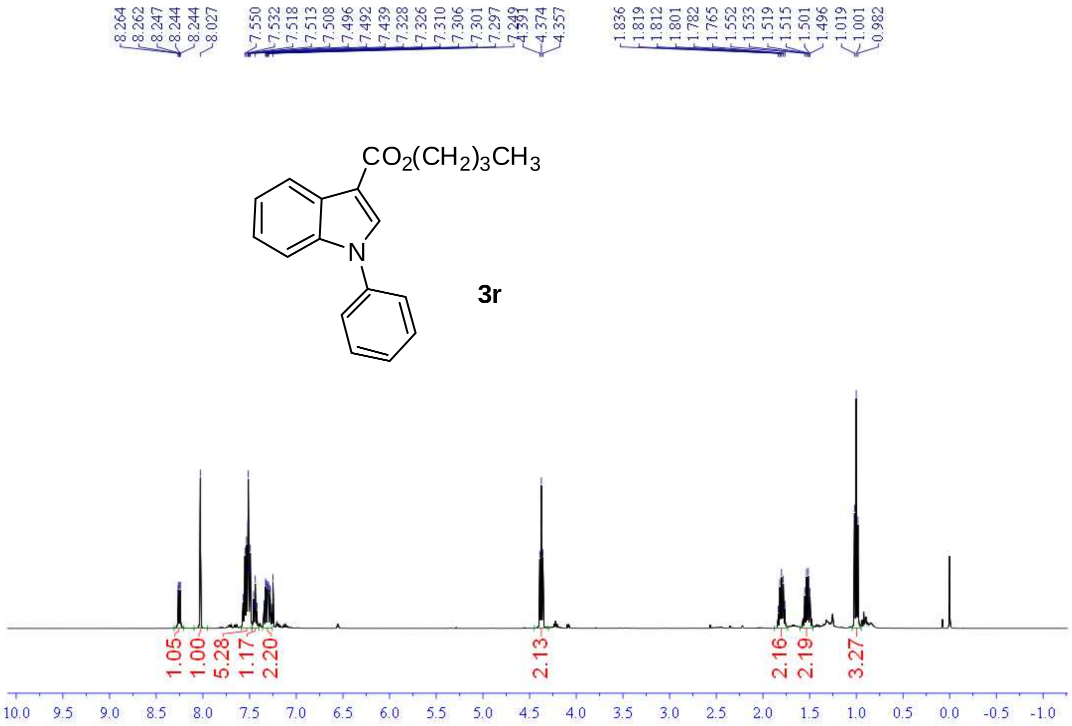
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1.819
1.812
1.801
1.782
1.765
1.552
1.533
1.519
1.515
1.501
1.496
1.019
1.001
0.982
$CO_2(CH_2)_3CH_3$
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1.00
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1.17
2.20
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2.16
2.19
3.27
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9.5
9.0
8.5
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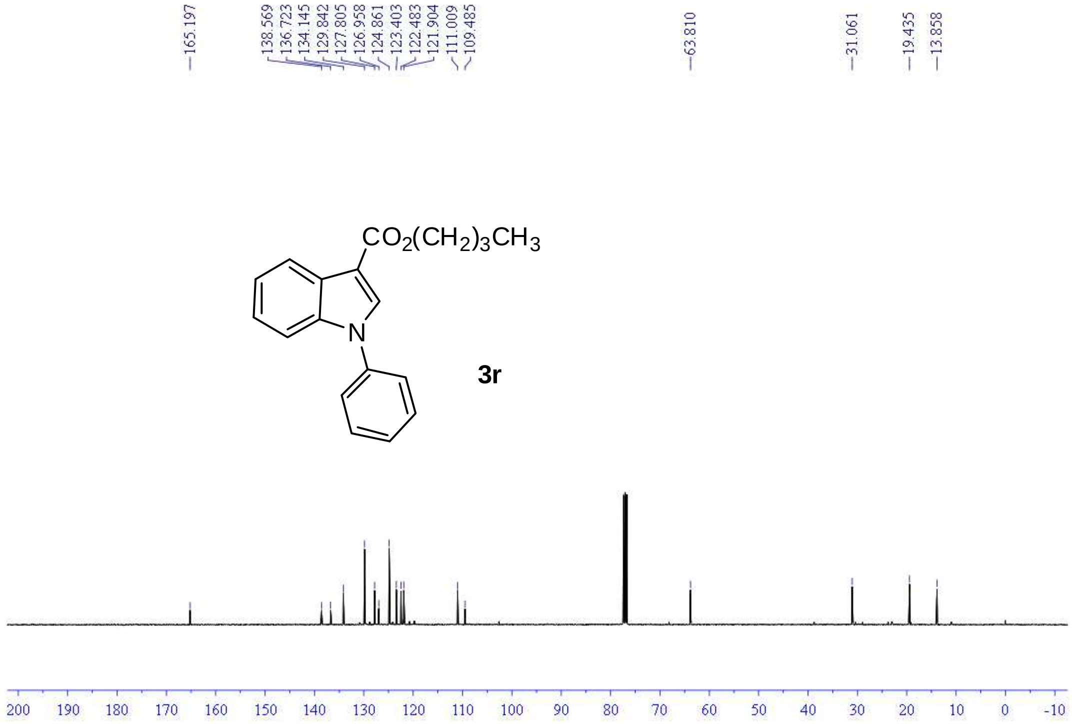
3r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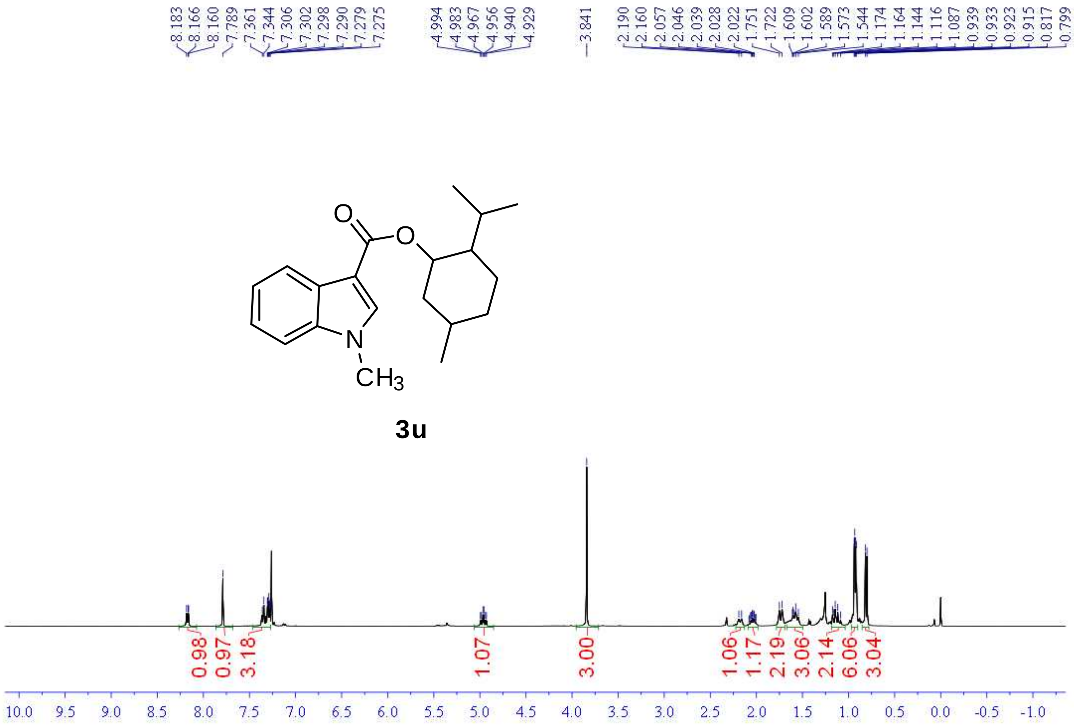
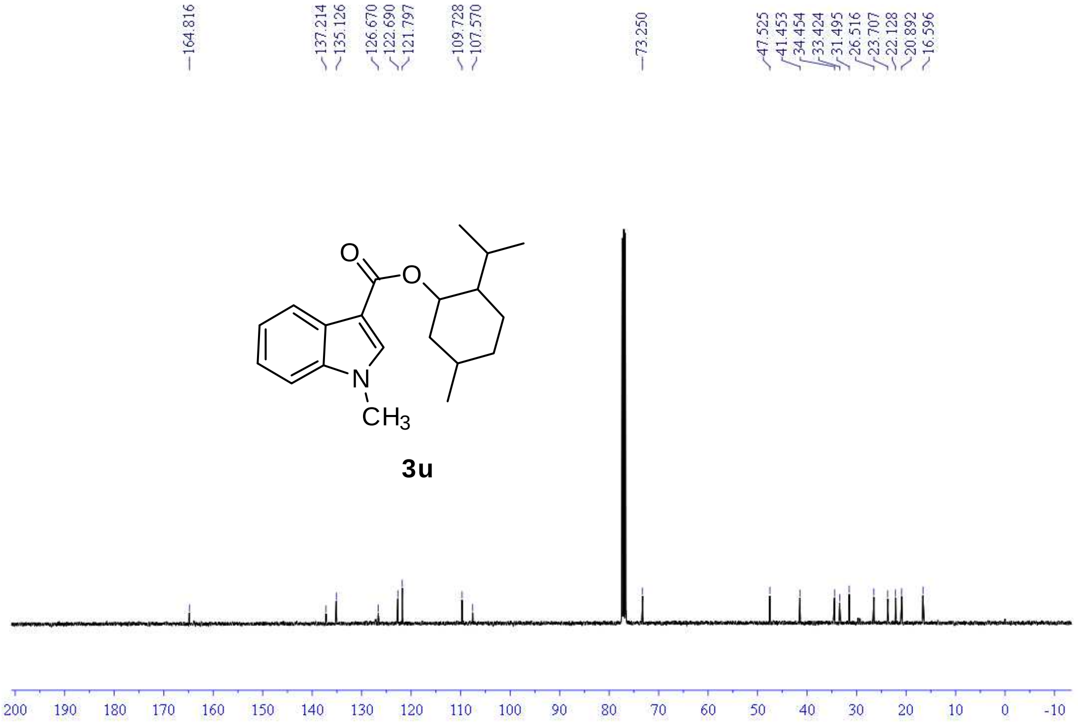
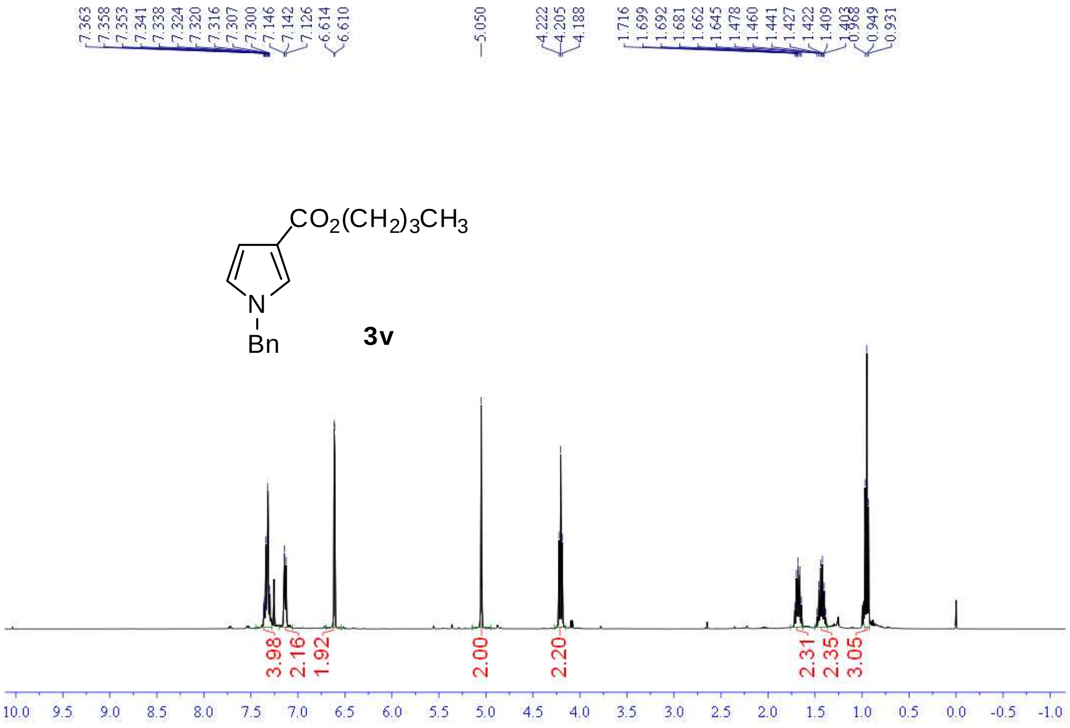
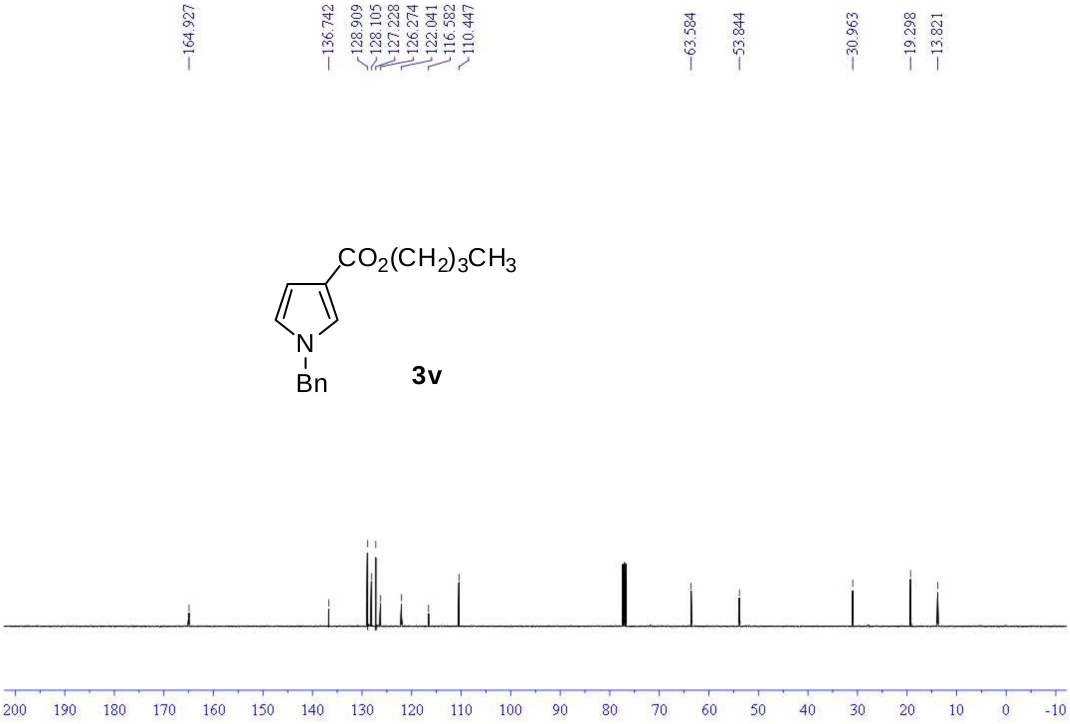
122.483
121.904
111.009
109.485
63.810
31.061
19.435
13.858
$CO_2(CH_2)_3CH_3$
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

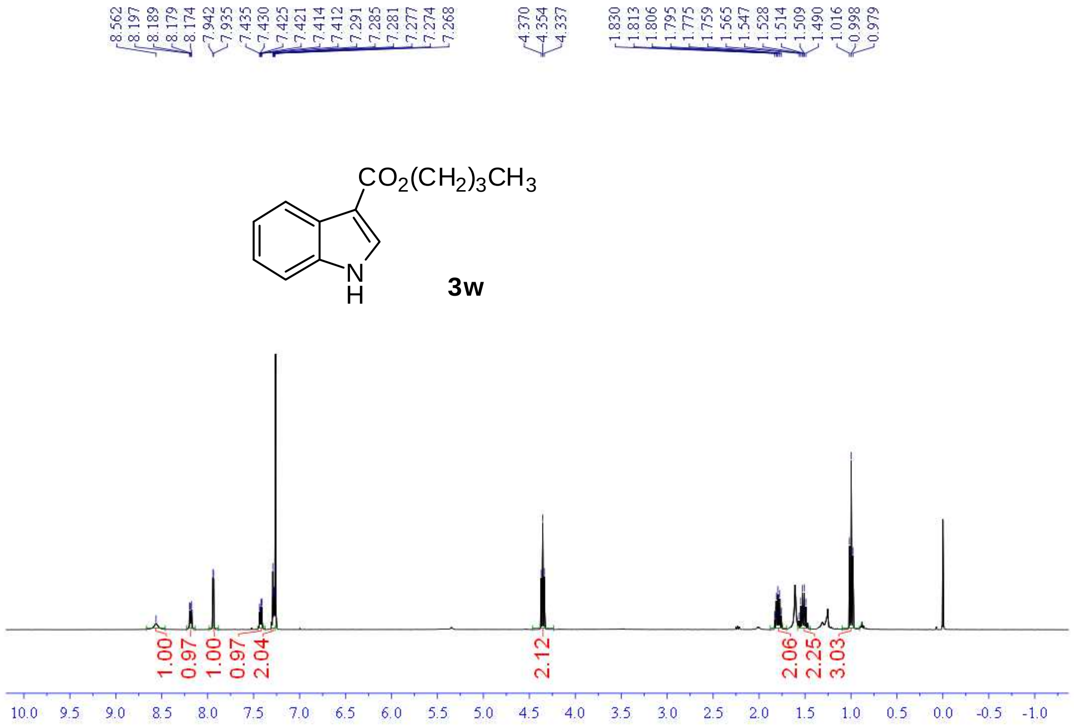
3r

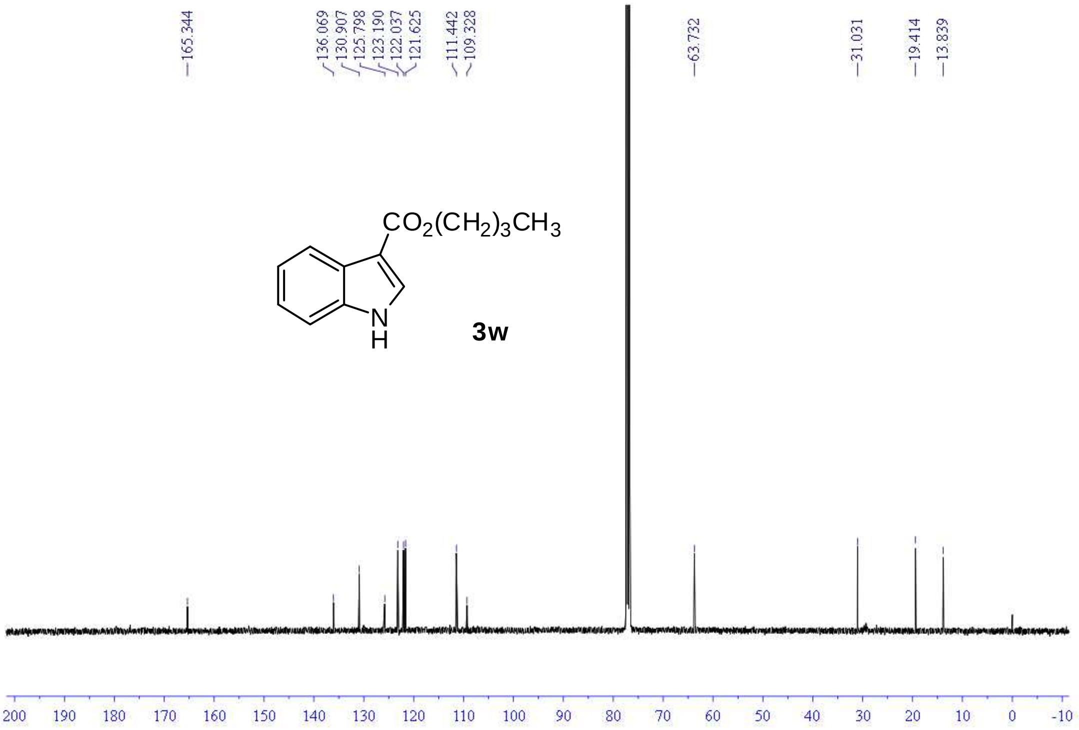

8.183
8.166
8.160
7.789
7.361
7.344
7.306
7.302
7.298
7.290
7.279
7.275
4.994
4.983
4.967
4.956
4.940
4.929
3.841
2.190
2.160
2.057
2.046
2.039
2.028
2.022
1.751
1.722
1.609
1.602
1.589
1.573
1.544
1.174
1.164
1.144
1.116
1.087
0.939
0.933
0.923
0.915
0.817
0.799
O
O
N
CH3
3u
0.98
0.97
3.18
1.07
3.00
1.06
1.17
2.19
3.06
2.14
6.06
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

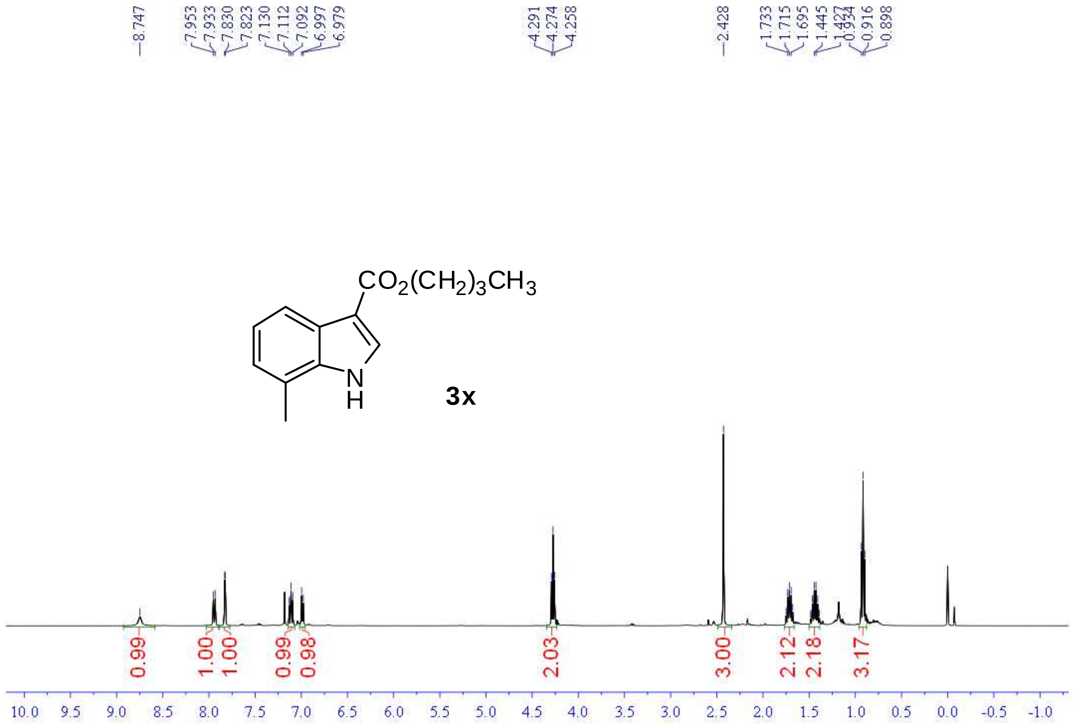

164.816
137.214
135.126
126.670
122.690
121.797
109.728
107.570
73.250
47.525
41.453
34.454
33.424
31.495
26.516
23.707
22.128
20.892
16.596
O
O
N
CH3
3u
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

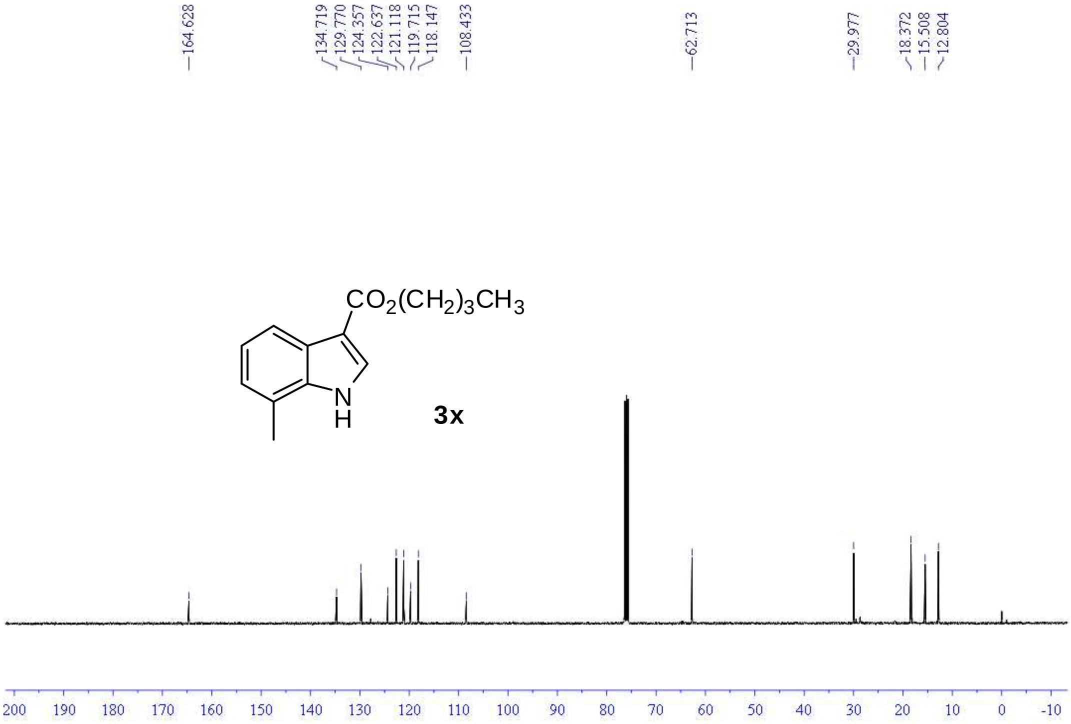

7.363
7.358
7.353
7.341
7.338
7.324
7.320
7.316
7.307
7.300
7.146
7.142
7.126
6.614
6.610
5.050
4.222
4.205
4.188
1.716
1.699
1.692
1.681
1.662
1.645
1.478
1.460
1.441
1.427
1.422
1.409
1.403
0.968
0.949
0.931
CO2(CH2)3CH3
N
Bn
3v
3.98
2.16
1.92
2.00
2.20
2.31
2.35
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0

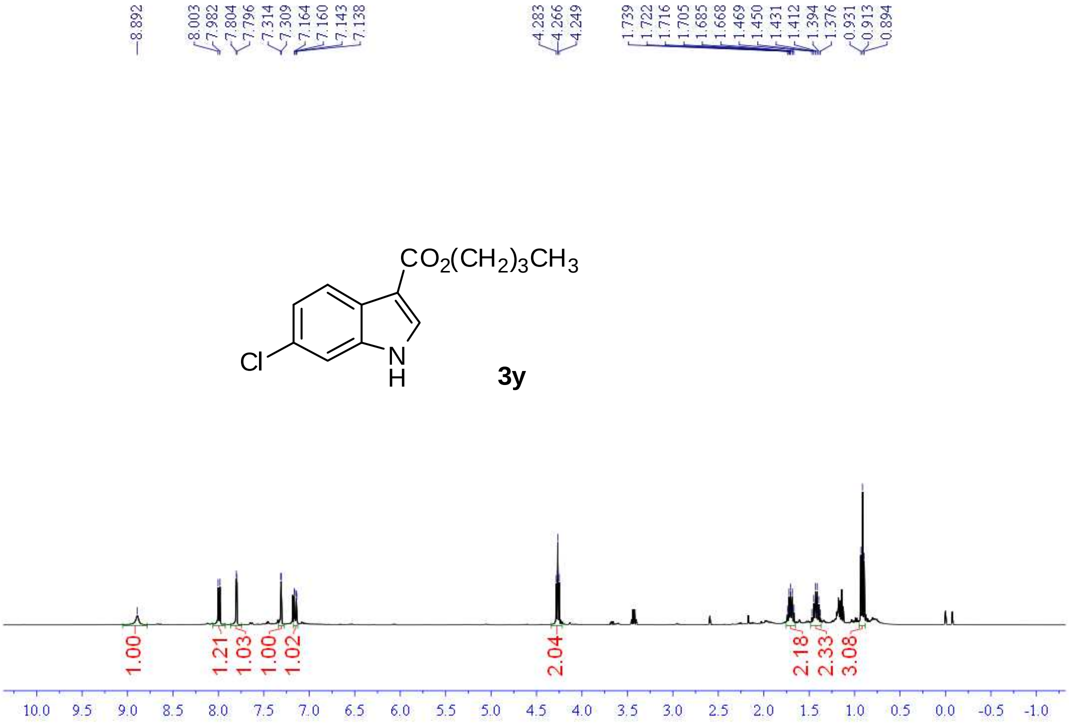

164.927
136.742
128.909
128.105
127.228
126.274
122.041
116.582
110.447
63.584
53.844
30.963
19.298
13.821
CO2(CH2)3CH3
N
Bn
3v
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

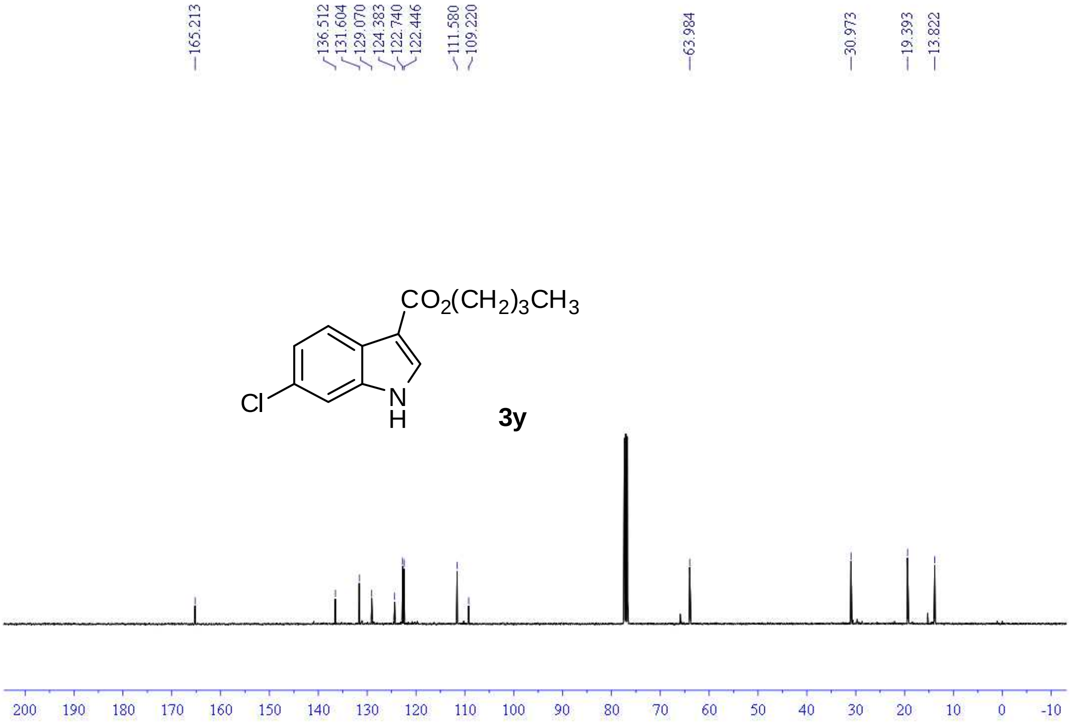

8.562
8.197
8.189
8.179
8.174
7.942
7.935
7.435
7.430
7.425
7.421
7.414
7.412
7.291
7.285
7.281
7.277
7.274
7.268
4.370
4.354
4.337
1.830
1.813
1.806
1.795
1.775
1.759
1.565
1.547
1.528
1.514
1.509
1.490
1.016
0.998
0.979
$CO_2(CH_2)_3CH_3$
N
H
3w
1.00
0.97
1.00
0.97
2.04
2.12
2.06
2.25
3.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0


165.344
136.069
130.907
125.798
123.190
122.037
121.625
111.442
109.328
63.732
31.031
19.414
13.839
$CO_2(CH_2)_3CH_3$
N
H
3w
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


8.747
7.953
7.933
7.830
7.823
7.130
7.112
7.092
6.997
6.979
4.291
4.274
4.258
2.428
1.733
1.715
1.695
1.445
1.427
0.934
0.916
0.898
$CO_2(CH_2)_3CH_3$
N
H
3x
0.99
1.00
1.00
0.99
0.98
2.03
3.00
2.12
2.18
3.17
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0


164.628
134.719
129.770
124.357
122.637
121.118
119.715
118.147
108.433
62.713
29.977
18.372
15.508
12.804
$CO_2(CH_2)_3CH_3$
N
H
3x
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


8.892
8.003
7.982
7.804
7.796
7.314
7.309
7.164
7.160
7.143
7.138
4.283
4.266
4.249
1.739
1.722
1.716
1.705
1.685
1.668
1.469
1.450
1.431
1.412
1.394
1.376
0.931
0.913
0.894
CO2(CH2)3CH3
Cl
N
H
3y
1.00
1.21
1.03
1.00
1.02
2.04
2.18
2.33
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0


165.213
136.512
131.604
129.070
124.383
122.740
122.446
111.580
109.220
63.984
30.973
19.393
13.822
CO2(CH2)3CH3
Cl
N
H
3y
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

7. Heteronuclear multiple bond coherence (HMBC) spectrum of 3a