Palladium-Catalyzed Synthesis of 5-Amino-1,2,4-oxadiazoles via Isocyanide Insertion

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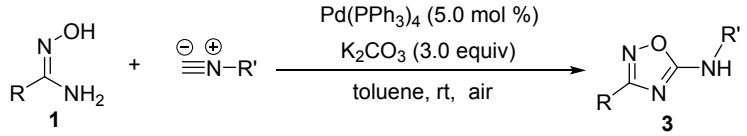
1. General Information

NMR spectra were obtained using a Bruker Avance 400 spectrometer (^{1}H at 400 MHz, and ^{13}C at 101 MHz). Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: δ 77.0 ppm). HRMS was obtained with a LCMS-IT-TOF mass spectrometer.

Materials. Unless stated otherwise, commercial reagents were used without further purification. All reagents were weighed and handled in air at room temperature.

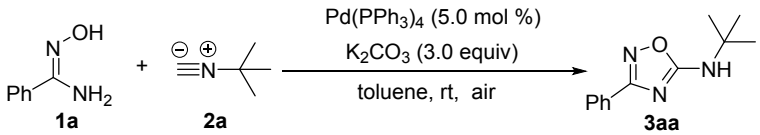
2. General Experimental Procedure

General Procedure: Synthesis of 5-Amino-1,2,4-oxadiazoles 3



The reaction mixture of **1** (0.2 mmol), **2** (0.3 mmol), $Pd(PPh_3)_4$ (5.0 mol %), K_2CO_3 (3.0 equiv), and 1.0 mL of toluene in an air atmosphere for 4 h, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography to afford 5-amino-1,2,4-oxadiazoles **3**.

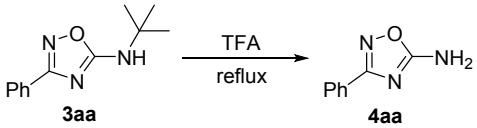
General Procedure: Procedure for Gram Scale Experiment



The reaction mixture of **1a** (8 mmol), **2a** (12 mmol), $Pd(PPh_3)_4$ (5.0 mol %), K_2CO_3 (3.0 equiv), and 10 mL of toluene in an air atmosphere for 8 h, and monitored periodically by TLC. Upon

completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography to afford *N*-(*tert*-butyl)-3-phenyl-1,2,4-oxadiazol-5-amine **3aa**.

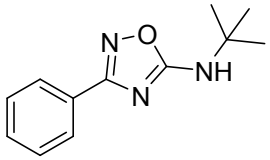
General Procedure: Deprotection of 3aa



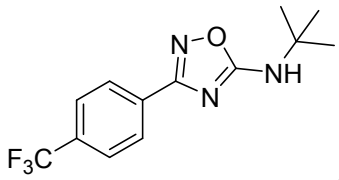
3aa **4aa**

Compound **3aa** (0.2 mmol) was dissolved in 2 mL neat trifluoroacetic acid and was transferred to a 5 mL, side-necked sealable tube equipped with stir bar. The reaction was sealed and heated at reflux for 12 hours, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography to afford 3-phenyl-1,2,4-oxadiazol-5-amine **4aa**.

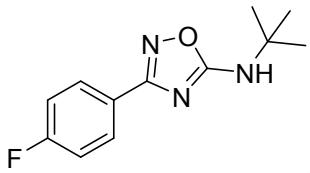
3. Characterization of the Compounds



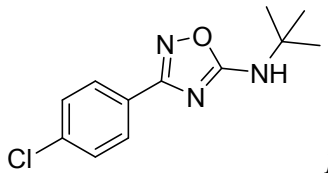
N-(*tert*-butyl)-3-phenyl-1,2,4-oxadiazol-5-amine (**3aa**)[1]: Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 91% (39.5 mg) as a yellow solid: 87-88 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 8.04-7.96 (m, 2H), 7.47-7.41 (m, 3H), 5.33 (s, 1H), 1.48 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.2, 168.2, 130.6, 128.6, 127.8, 127.2, 52.7, 29.0. **HRMS** (ESI) m/z: calcd for $C_{12}H_{16}N_3O$ $[M + H]^+$ 218.1288; found 218.1289.



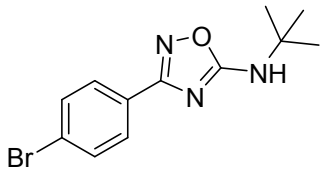
N-(*tert*-butyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-amine (**3ba**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 78% (44.5 mg) as a yellow solid: 117-118 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 8.12 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 5.41 (s, 1H), 1.48 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.4, 167.2, 132.5 (q, J = 33 Hz), 131.3, 127.5, 125.57 (q, *J* = 3.8 Hz), 123.3(q, J = 272 Hz), 52.9, 28.9; **^{19}F NMR** (376 MHz, $CDCl_3$, δ ppm) -63.62. **HRMS** (ESI) m/z: calcd for $C_{13}H_{15}N_3OF_3$ $[M + H]^+$ 286.1162; found 286.1161.



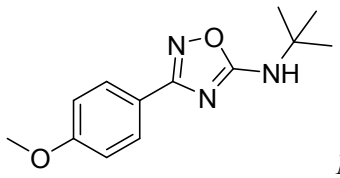
N-(*tert*-butyl)-3-(4-fluorophenyl)-1,2,4-oxadiazol-5-amine (**3ca**)[1]: Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 84% (39.5 mg) as a yellow solid: 108-109 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 8.04-7.93 (m, 2H), 7.17-7.05 (m, 2H), 5.45 (s, 1H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.2, 167.4, 164.8 (d, *J* = 251.4 Hz), 129.30 (d, *J* = 8.6 Hz), 124.01 (d, *J* = 3.2 Hz), 115.7(d, *J* = 22.0 Hz), 52.7, 29.0; **^{19}F NMR** (376 MHz, $CDCl_3$, δ ppm) -102.55. **HRMS** (ESI) m/z: calcd for $C_{12}H_{15}N_3OF$ $[M + H]^+$ 236.1194; found 236.1191.



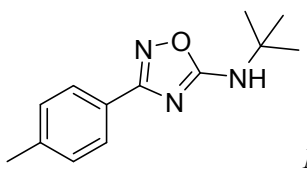
N-(*tert*-butyl)-3-(4-chlorophenyl)-1,2,4-oxadiazol-5-amine (**3da**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 81% (44.7 mg) as a yellow solid: 131-132 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.94-7.88 (m, 2H), 7.40-7.35 (m, 2H), 5.46 (s, 1H), 1.43 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.3, 167.4, 136.7, 128.9, 128.5, 126.3, 52.8, 29.0. **HRMS** (ESI) m/z: calcd for $C_{12}H_{15}N_3O_2Cl$ $[M + H]^+$ 252.0898; found 252.0896.



3-(4-bromophenyl)-*N*-(*tert*-butyl)-1,2,4-oxadiazol-5-amine (**3ea**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 86% (50.7 mg) as a yellow solid: 129-130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.90-7.84 (m, 2H), 7.59-7.53 (m, 2H), 5.47 (s, 1H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.3, 167.5, 131.9, 128.8, 126.8, 125.1, 52.8, 29.0. **HRMS** (ESI) m/z: calcd for $C_{12}H_{14}N_3OBrNa$ $[M + Na]^+$ 318.0212; found 318.0217.

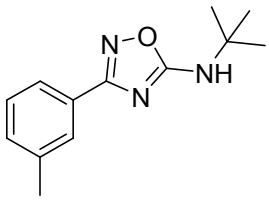


N-(*tert*-butyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-amine (**3fa**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 92% (45.4 mg) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.96-7.89 (m, 2H), 6.96-6.89 (m, 2H), 5.44 (s, 1H), 3.84 (s, 3H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.0, 167.8, 161.5, 128.7, 120.2, 113.9, 55.3, 52.6, 29.0. **HRMS** (ESI) m/z: calcd for $C_{13}H_{18}N_3O_2$ $[M + H]^+$ 248.1394; found 248.1398.

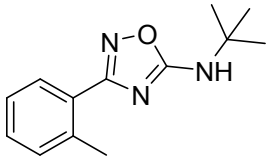


N-(*tert*-butyl)-3-(p-tolyl)-1,2,4-oxadiazol-5-amine (**3ga**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 89% (41.1 mg) as

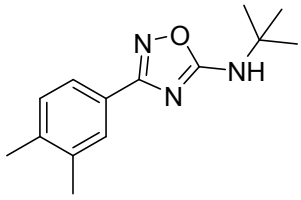
a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.89 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.58 (s, 1H), 2.39 (s, 3H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.2, 168.1, 140.9, 129.3, 127.1, 124.9, 52.6, 29.0, 21.5. **HRMS** (ESI) m/z: calcd for $C_{13}H_{17}N_3ONa$ $[M + Na]^+$ 254.1264; found 254.1265.



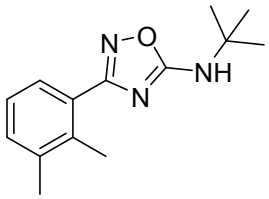
N-(*tert*-butyl)-3-(m-tolyl)-1,2,4-oxadiazol-5-amine (**3ha**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 85% (39.3 mg) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.88-7.71 (m, 2H), 7.33-7.24 (m, 2H), 5.58 (s, 1H), 2.38 (s, 3H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.3, 168.3, 138.3, 131.5, 128.5, 127.7, 127.6, 124.3, 52.7, 29.0, 21.4. **HRMS** (ESI) m/z: calcd for $C_{13}H_{18}N_3O$ $[M + H]^+$ 232.1444; found 232.1438.



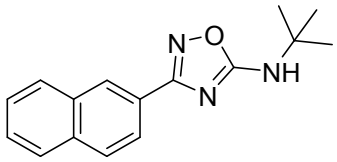
N-(*tert*-butyl)-3-(o-tolyl)-1,2,4-oxadiazol-5-amine (**3ia**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 67% (30.9 mg) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.90 (d, *J* = 7.6 Hz, 1H), 7.36-7.31 (m, 1H), 7.28-7.24 (m, 2H), 5.40 (s, 1H), 2.60 (s, 3H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 169.4, 169.0, 138.0, 131.2, 130.1, 129.9, 127.0, 125.8, 52.6, 29.0, 22.0. **HRMS** (ESI) m/z: calcd for $C_{13}H_{18}N_3O$ $[M + H]^+$ 232.1444; found 232.1449.



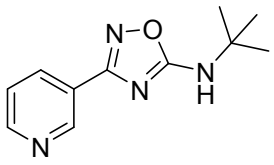
N-(*tert*-butyl)-3-(3,4-dimethylphenyl)-1,2,4-oxadiazol-5-amine (**3ja**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 83% (40.7 mg) as a yellow solid: 79-80 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.76 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 5.60 (s, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.2, 168.2, 139.6, 136.9, 129.9, 128.2, 125.2, 124.7, 52.6, 29.0, 19.8, 19.7. **HRMS** (ESI) m/z: calcd for $C_{14}H_{20}N_3O$ $[M + H]^+$ 246.1601; found 246.1604.



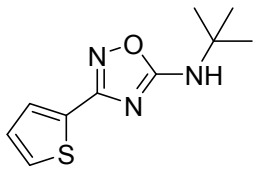
N-(*tert*-butyl)-3-(2,3-dimethylphenyl)-1,2,4-oxadiazol-5-amine (**3ka**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 69% (33.8 mg) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.61 (d, *J* = 7.6 Hz, 1H), 7.27-7.23 (m, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 5.48 (s, 1H), 2.47 (s, 3H), 2.34 (s, 3H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 169.6, 169.5, 137.7, 136.4, 131.7, 127.9, 127.6, 125.4, 52.6, 29.0, 20.7, 17.1. **HRMS** (ESI) m/z: calcd for $C_{14}H_{20}N_3O$ $[M + H]^+$ 246.1601; found 246.1603.



N-(*tert*-butyl)-3-(naphthalen-2-yl)-1,2,4-oxadiazol-5-amine (**3la**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 81% (43.3 mg) as a yellow solid: 106-108 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 8.54 (s, 1H), 8.09 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.96 -7.84 (m, 3H), 7.57-7.47 (m, 2H), 5.56 (s, 1H), 1.50 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.3, 168.3, 134.5, 133.1, 128.8, 128.4, 127.8, 127.6, 127.2, 126.5, 125.1, 123.9, 52.8, 29.1. **HRMS** (ESI) m/z: calcd for $C_{16}H_{18}N_3O$ $[M + H]^+$ 268.1444; found 268.1442.

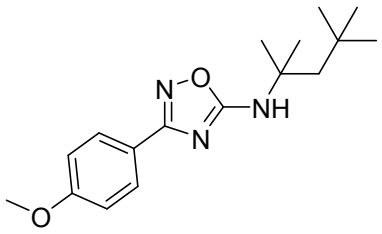


N-(*tert*-butyl)-3-(pyridin-3-yl)-1,2,4-oxadiazol-5-amine (**3ma**)[1]: Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 60% (26.1 mg) as a yellow solid: 140-142 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 9.38 (d, *J* = 1.1 Hz, 1H), 8.68 (dd, *J* = 4.8, 1.3 Hz, 1H), 8.28 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.38 (dd, *J* = 7.9, 4.9 Hz, 1H), 6.10 (s, 1H), 1.48 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.5, 166.2, 151.3, 148.8, 134.5, 124.2, 123.5, 52.8, 29.0. **HRMS** (ESI) m/z: calcd for $C_{11}H_{15}N_4O$ $[M + H]^+$ 219.1240; found 219.1245.

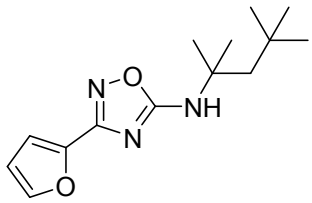


N-(*tert*-butyl)-3-(thiophen-2-yl)-1,2,4-oxadiazol-5-amine (**3na**): Purified

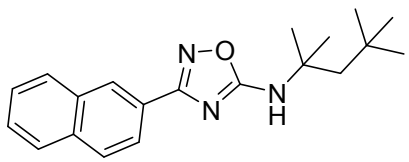
via flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 77% (34.3 mg) as a yellow solid: 92-94 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.69 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.42 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.53 (s, 1H), 1.44 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.1, 164.2, 129.5, 128.7, 128.5, 127.7, 52.8, 29.0. **HRMS** (ESI) m/z: calcd for $C_{10}H_{13}N_3OSNa$ $[M + Na]^+$ 246.0672; found 246.0675.



3-(4-methoxyphenyl)-*N*-(2,4,4-trimethylpentan-2-yl)-1,2,4-oxadiazol-5-amine (**3fb**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 86% (52.1 mg) as a yellow solid: 107-108 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.99-7.88 (m, 2H), 7.00- 6.87 (m, 2H), 5.44 (d, *J* = 6.9 Hz, 1H), 3.84 (s, 3H), 1.81 (s, 2H), 1.49 (s, 6H), 1.00 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 169.9, 167.8, 161.6, 128.8, 120.3, 114.0, 56.3, 55.3, 51.8, 31.6, 31.4, 29.5. **HRMS** (ESI) m/z: calcd for $C_{17}H_{26}N_3O_2$ $[M + H]^+$ 304.2020; found 304.2017.

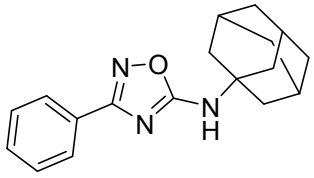


3-(furan-2-yl)-*N*-(2,4,4-trimethylpentan-2-yl)-1,2,4-oxadiazol-5-amine (**3ob**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 72% (37.9 mg) as a yellow solid: 112-114 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.54 (d, *J* = 1.0 Hz, 1H), 7.00 (d, *J* = 3.4 Hz, 1H), 6.50 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.55 (s, 1H), 1.78 (s, 2H), 1.48 (s, 6H), 0.99 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.0, 161.2, 144.5, 143.1, 112.7, 111.5, 56.5, 51.9, 31.6, 31.4, 29.4. **HRMS** (ESI) m/z: calcd for $C_{14}H_{22}N_3O_2$ $[M + H]^+$ 264.1707; found 264.1702.

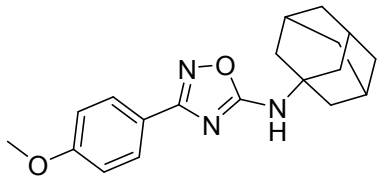


3-(naphthalen-2-yl)-*N*-(2,4,4-trimethylpentan-2-yl)-1,2,4-oxadiazol-5-amine (**3lb**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 80% (51.7 mg) as a yellow solid: 147-149 °C. **^{1}H NMR** (400

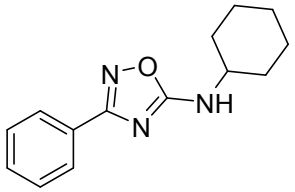
MHz, $CDCl_3$, δ ppm) 8.53 (s, 1H), 8.08 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.98-7.81 (m, 3H), 7.59-7.46 (m, 2H), 5.45 (s, 1H), 1.85 (s, 2H), 1.55 (s, 6H), 1.04 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.1, 168.2, 134.5, 133.1, 128.8, 128.4, 127.8, 127.5, 127.2, 126.5, 125.1, 123.9, 56.5, 52.0, 31.7, 31.5, 29.5. **HRMS** (ESI) m/z: calcd for $C_{20}H_{26}N_3O$ $[M + H]^+$ 324.2070; found 324.2074.



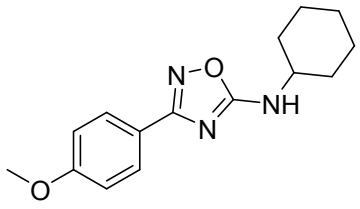
N-(adamantan-1-yl)-3-phenyl-1,2,4-oxadiazol-5-amine (**3ac**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 85% (50.2 mg) as a yellow solid: 165-166 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 8.05-7.92 (m, 2H), 7.53-7.37 (m, 3H), 5.30 (s, 1H), 2.15 (s, 3H), 2.06 (d, *J* = 2.7 Hz, 6H), 1.72 (d, *J* = 2.8 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.0, 168.1, 130.7, 128.6, 127.8, 127.2, 53.0, 41.8, 36.1, 29.5. **HRMS** (ESI) m/z: calcd for $C_{18}H_{22}N_3O$ $[M + H]^+$ 296.1757; found 296.1761.



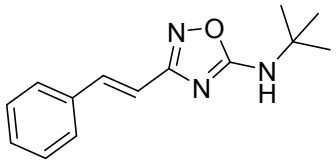
N-(adamantan-1-yl)-3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-amine (**3fc**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 82% (53.3 mg) as a yellow solid: 173-174 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.95-7.90 (m, 2H), 6.97-6.91 (m, 2H), 5.25 (s, 1H), 3.84 (s, 3H), 2.15 (d, *J* = 7.1 Hz, 3H), 2.05 (d, *J* = 2.8 Hz, 6H), 1.71 (d, *J* = 2.8 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 169.9, 167.8, 161.5, 128.8, 120.3, 114.0, 55.3, 52.9, 41.8, 36.1, 29.5. **HRMS** (ESI) m/z: calcd for $C_{19}H_{24}N_3O_2$ $[M + H]^+$ 326.1863; found 326.1861.



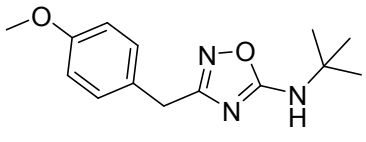
N-cyclohexyl-3-phenyl-1,2,4-oxadiazol-5-amine (**3ad**)[1]: Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 78% (37.9 mg) as a white solid: 126-128 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.99 (d, *J* = 5.6 Hz, 2H), 7.43-7.41 (m, 3H), 6.14 (d, *J* = 6.7 Hz, 1H), 3.73-3.56 (m, 1H), 2.05-1.87 (m, 2H), 1.73-1.56 (m, 3H), 1.36-1.08 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.6, 168.1, 130.6, 128.4, 127.5, 127.1, 52.7, 32.9, 25.1, 24.5. **HRMS** (ESI) m/z: calcd for $C_{14}H_{18}N_3O$ $[M + H]^+$ 244.1444; found 244.1443.



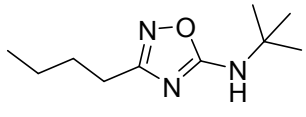
N-cyclohexyl-3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-amine (**3fd**)[1]: Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 84% (45.9 mg) as a white solid: 110-112 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.91 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.90 (s, 1H), 3.81 (s, 3H), 3.64-3.61 (m, 1H), 2.04-1.89 (m, 2H), 1.72-1.57 (m, 3H), 1.37-1.10 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.4, 167.9, 161.4, 128.7, 120.0, 113.8, 55.2, 52.7, 33.0, 25.6, 24.5. **HRMS** (ESI) m/z: calcd for $C_{15}H_{20}N_3O_2$ $[M + H]^+$ 274.1550; found 274.1548.



(*E*)-*N*-(*tert*-butyl)-3-styryl-1,2,4-oxadiazol-5-amine (**3pa**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 78% (37.9 mg) as a yellow solid: 87-89 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.57-7.52 (m, 3H), 7.39-7.30 (m, 3H), 6.91 (d, *J* = 16.1 Hz, 1H), 5.46 (s, 1H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 169.7, 167.8, 138.0, 135.7, 129.1, 128.8, 127.3, 113.8, 52.6, 29.0. **HRMS** (ESI) m/z: calcd for $C_{14}H_{18}N_3O$ $[M + H]^+$ 244.1444; found 244.1442.

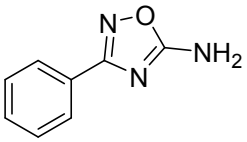


N-(*tert*-butyl)-3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-amine (**3qa**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 78% (37.9 mg) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.25 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.30 (s, 1H), 3.81 (s, 2H), 3.78 (s, 3H), 1.39 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.3, 169.8, 158.5, 130.0, 128.1, 114.0, 55.3, 52.5, 31.8, 29.0. **HRMS** (ESI) m/z: calcd for $C_{14}H_{20}N_3O_2$ $[M + H]^+$ 262.1550; found 262.1556.



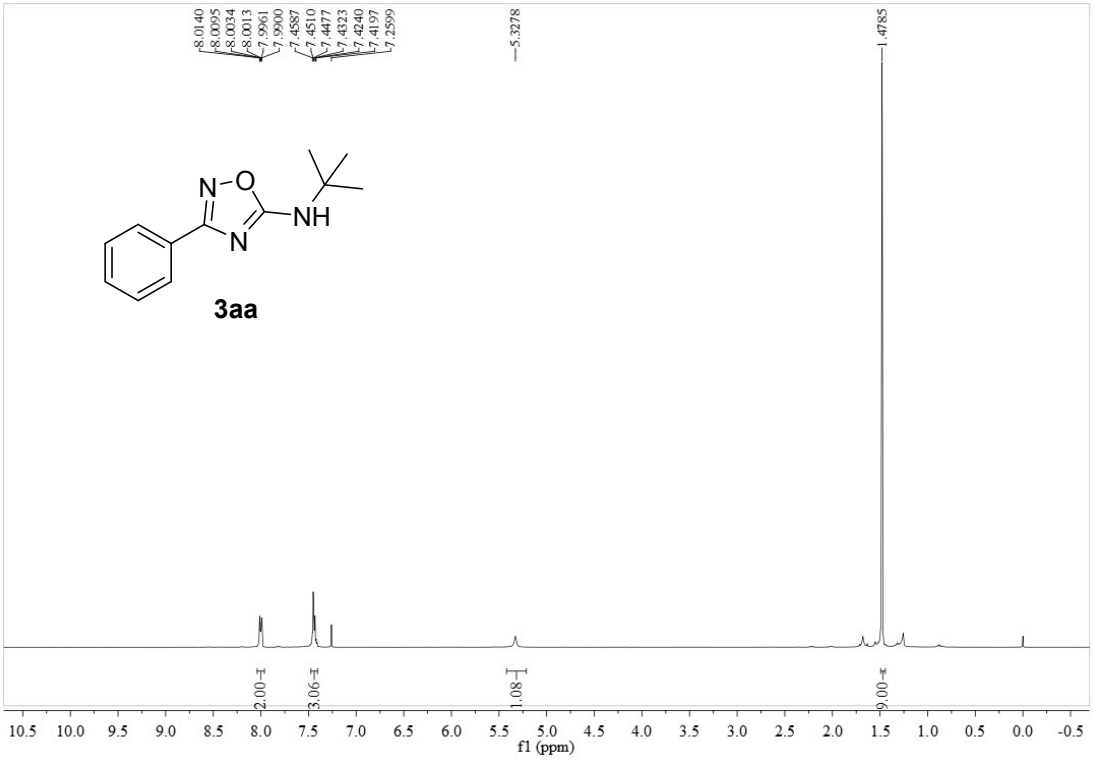
N-(*tert*-butyl)-3-butyl-1,2,4-oxadiazol-5-amine (**3ra**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 74% (38.6 mg) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 5.24 (s, 1H), 2.60-2.48 (m, 2H), 1.67 (dt, *J* =

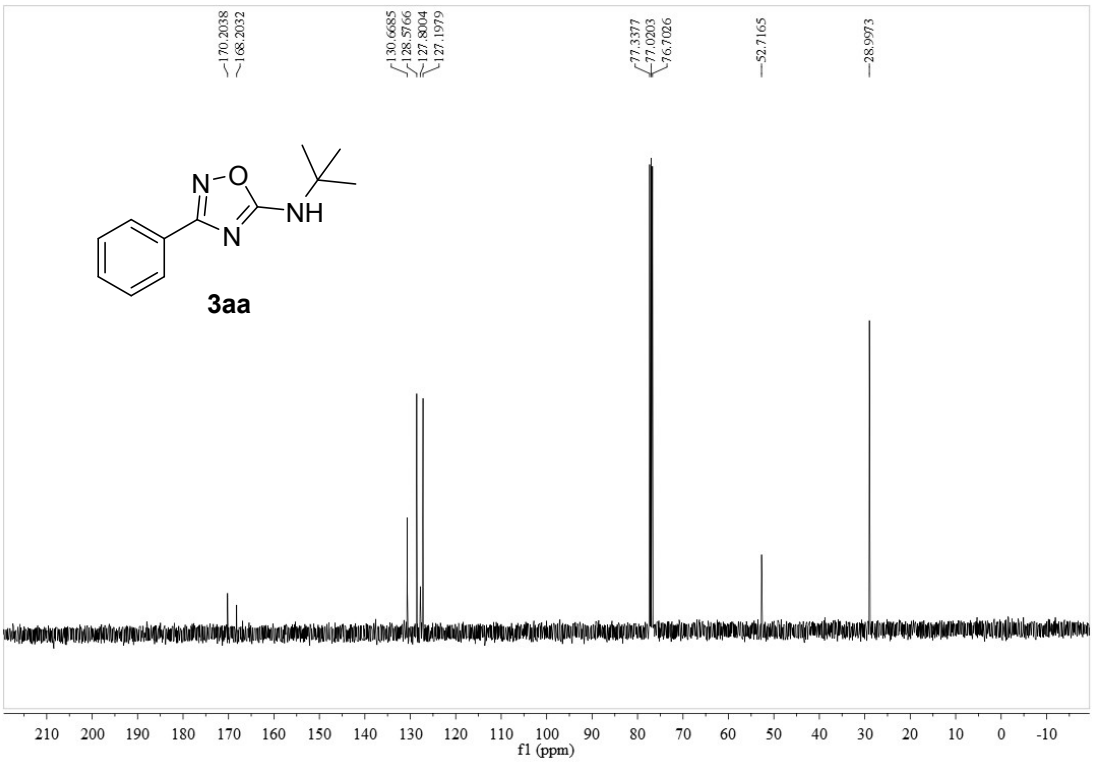
15.2, 7.6 Hz, 2H), 1.45-1.33 (m, 11H), 0.93 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 170.8, 170.0, 52.5, 29.0, 28.9, 25.9, 22.3, 13.7. **HRMS** (ESI) m/z: calcd for $C_{10}H_{20}N_3O$ $[M + H]^+$ 198.1601; found 198.1598.

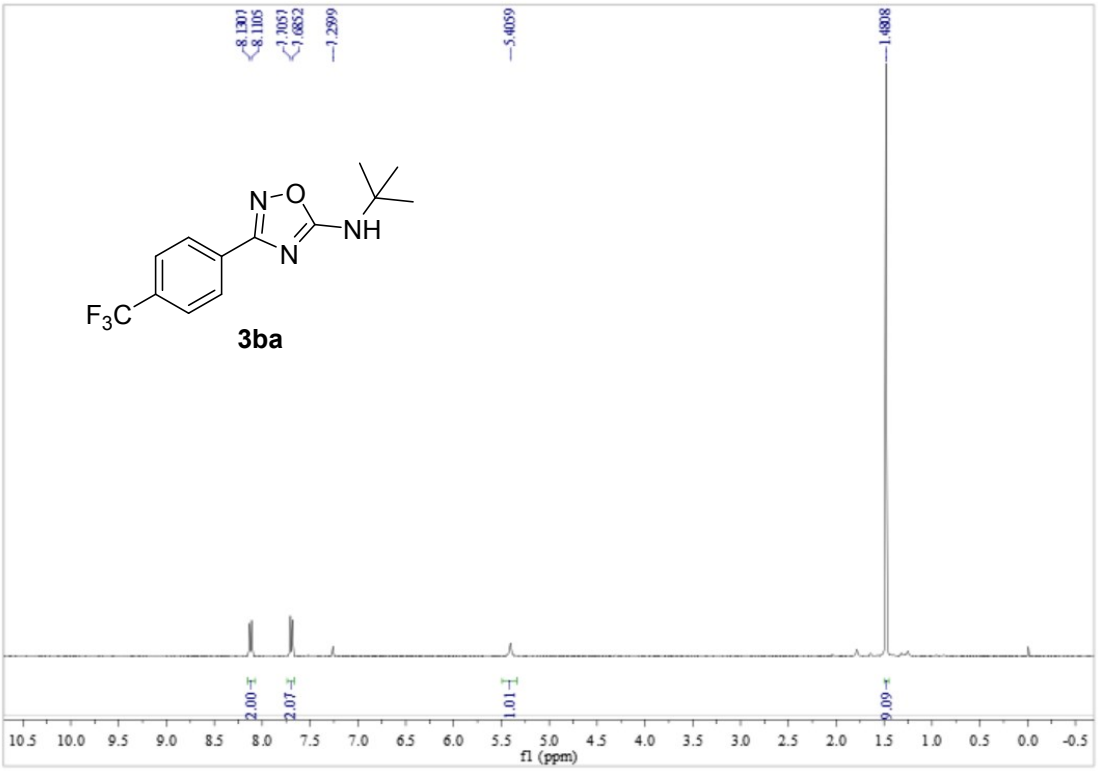


3-phenyl-1,2,4-oxadiazol-5-amine (**4aa**): Purified *via* flash column chromatography with 40% ethyl acetate/petroleum ether, yielding 82% (26.4 mg) as a yellow solid: 146-147 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$, δ ppm) 7.93 (d, J = 6.9 Hz, 2H), 7.48-7.45 (m, 3H), 6.06 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$, δ ppm) 171.2, 168.4, 131.0, 128.8, 127.2, 127.1. **HRMS** (ESI) m/z: calcd for $C_8H_8N_3O$ $[M + H]^+$ 162.0662; found 162.0660.

4. Copies of ^{1}H NMR and ^{13}C NMR Spectra of Products



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7.7053
7.6852
7.2999
5.4059
1.4808
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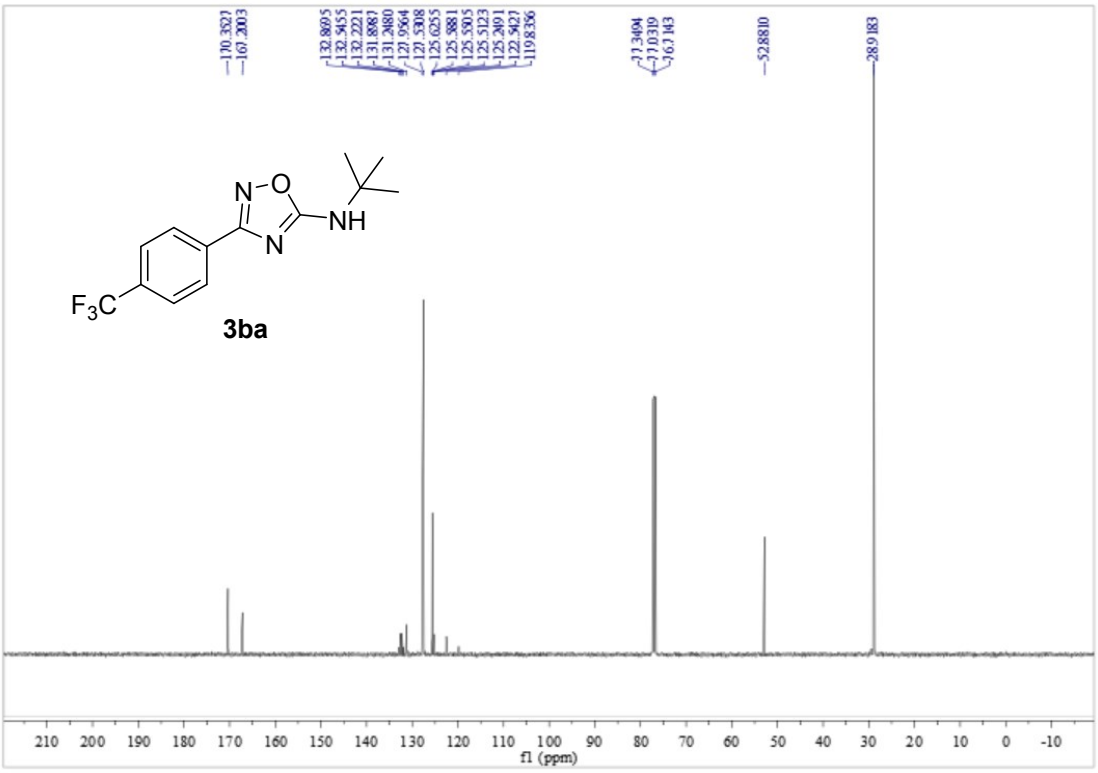
O
N
NH
F3C
3ba
2.00
2.07
1.01
9.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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132.8695
132.5455
132.2221
131.8867
131.2480
127.9564
121.5308
125.6255
125.5881
125.5505
125.5123
125.2491
122.5427
119.8356
77.3494
77.0319
76.7143
52.8810
28.9183
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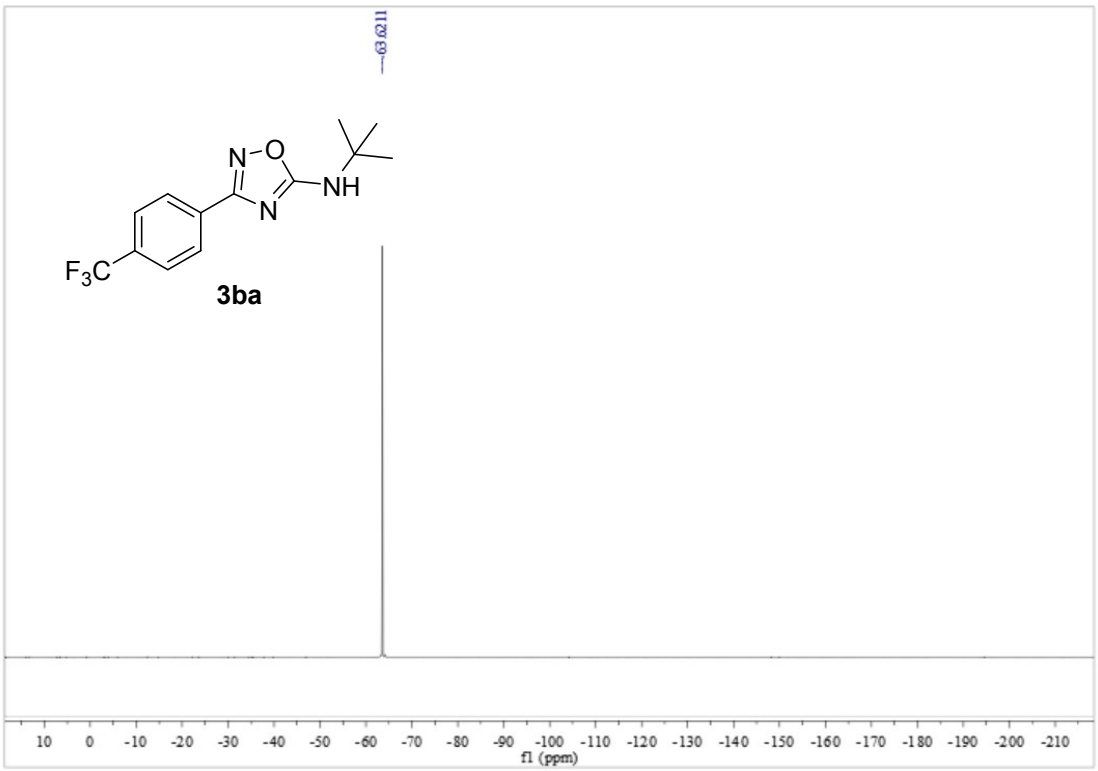
O
N
NH
F3C
3ba
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-63.0211
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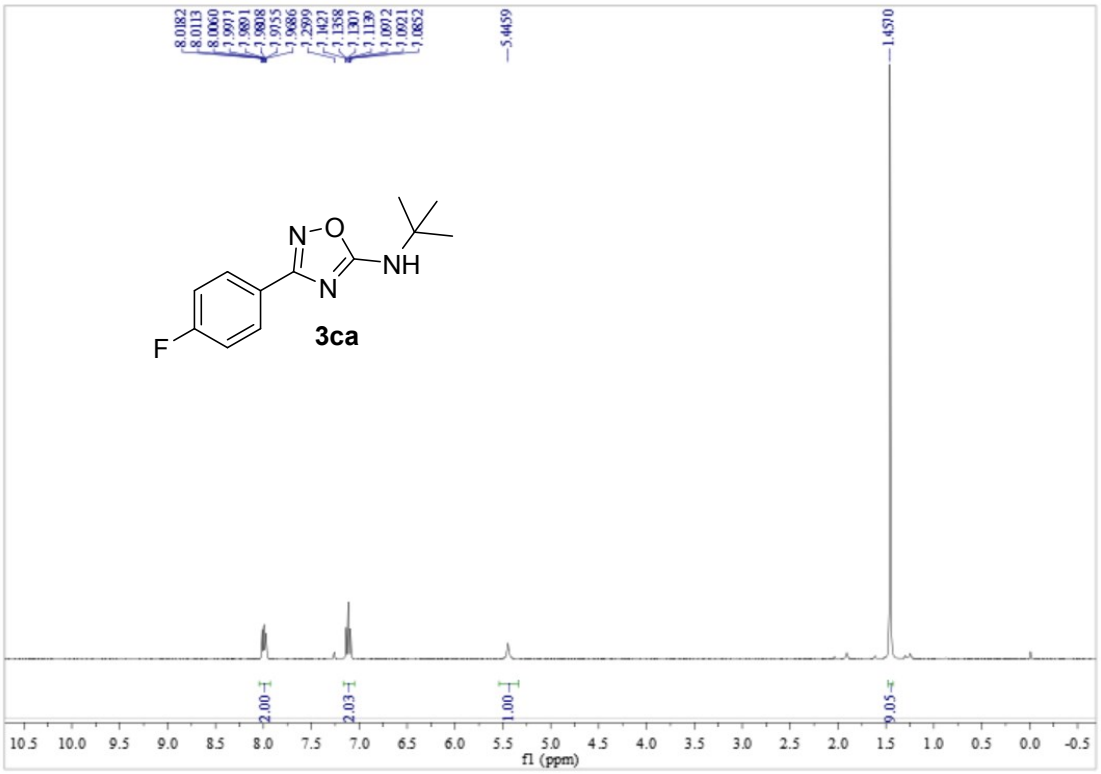
O
NH
N
F3C
3ba
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)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7.9891
7.9838
7.9755
7.9686
7.2999
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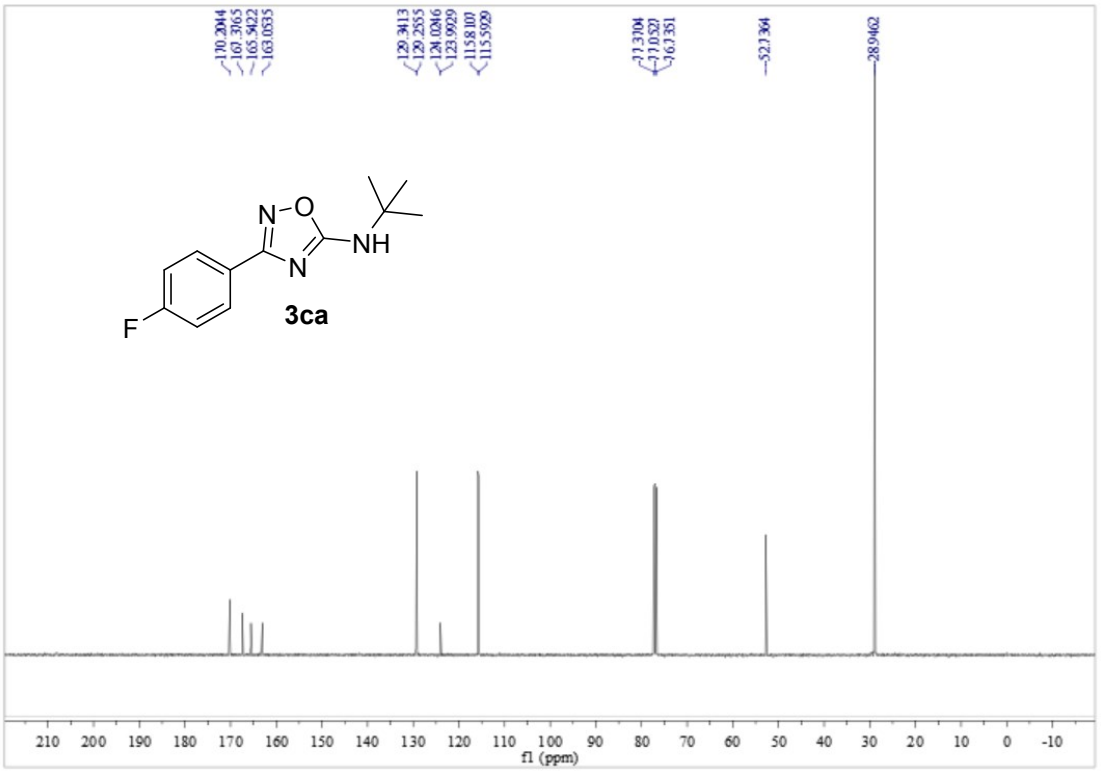
7.1358
7.1303
7.1139
7.0972
7.0921
7.0852
5.4459
1.4530
N
O
NH
N
F
3ca
2.00
2.03
1.00
9.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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163.0535
129.3413
129.2555
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77.0327
76.7351
52.7364
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O
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N
F
3ca
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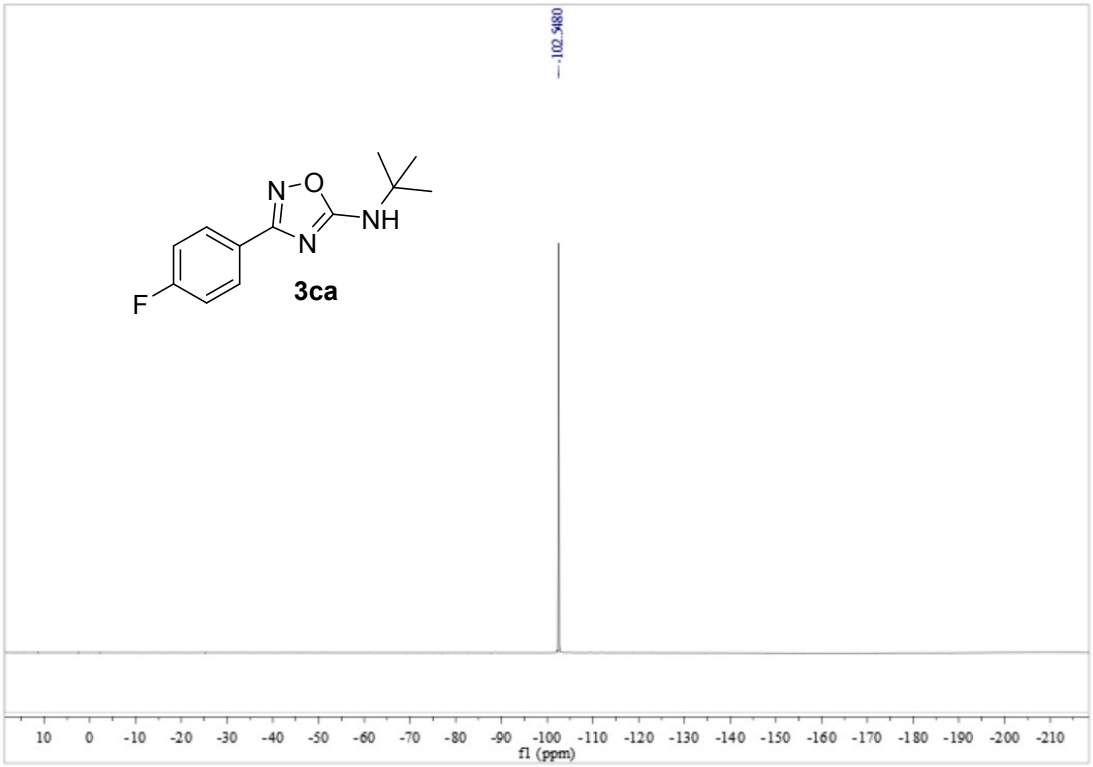
f1 (ppm)


-102.5680
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O
NH
N
F
3ca
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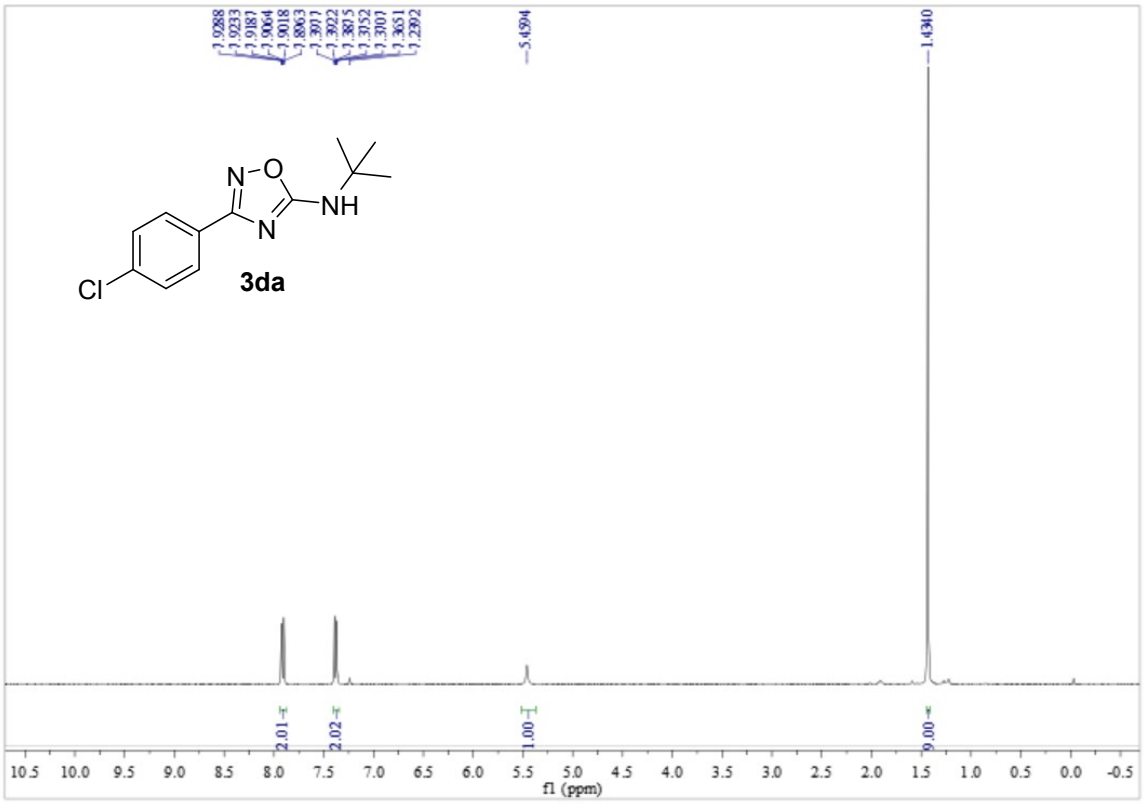
f1 (ppm)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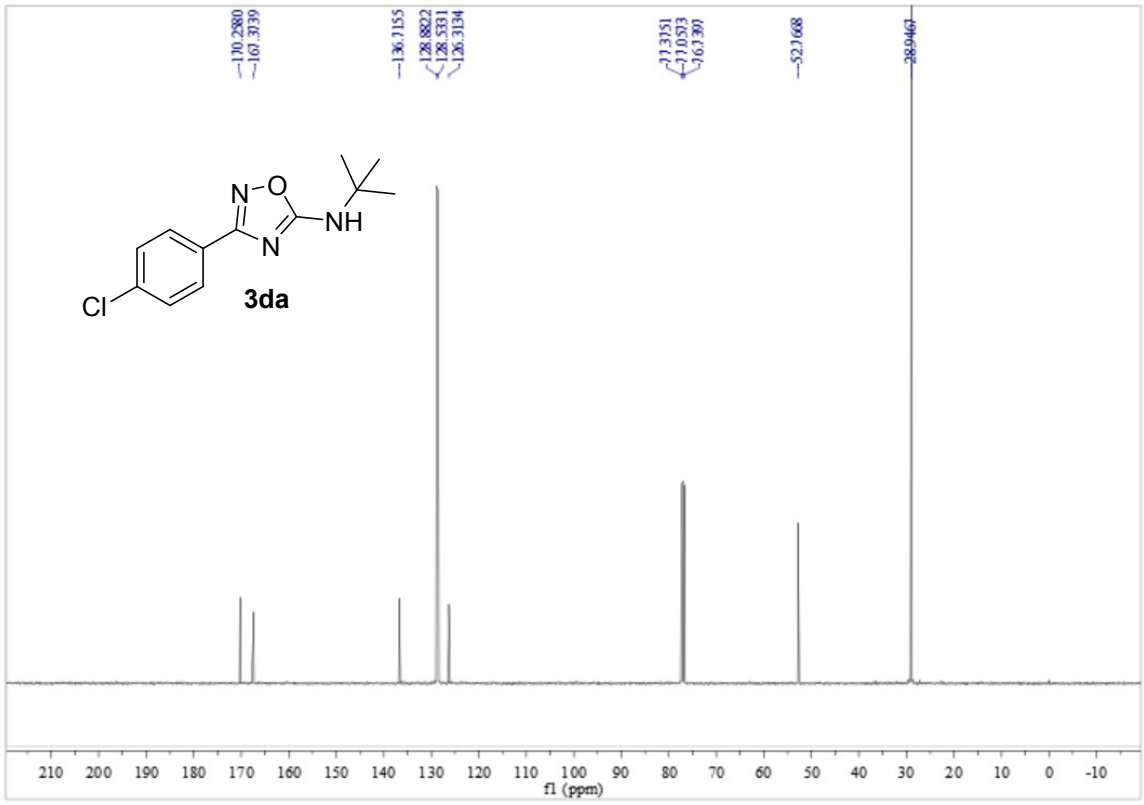
7.3707
7.3651
7.2892
5.4894
1.4340
N
O
N
NH
Cl
3da
2.01
2.02
1.00
9.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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Cl
3da
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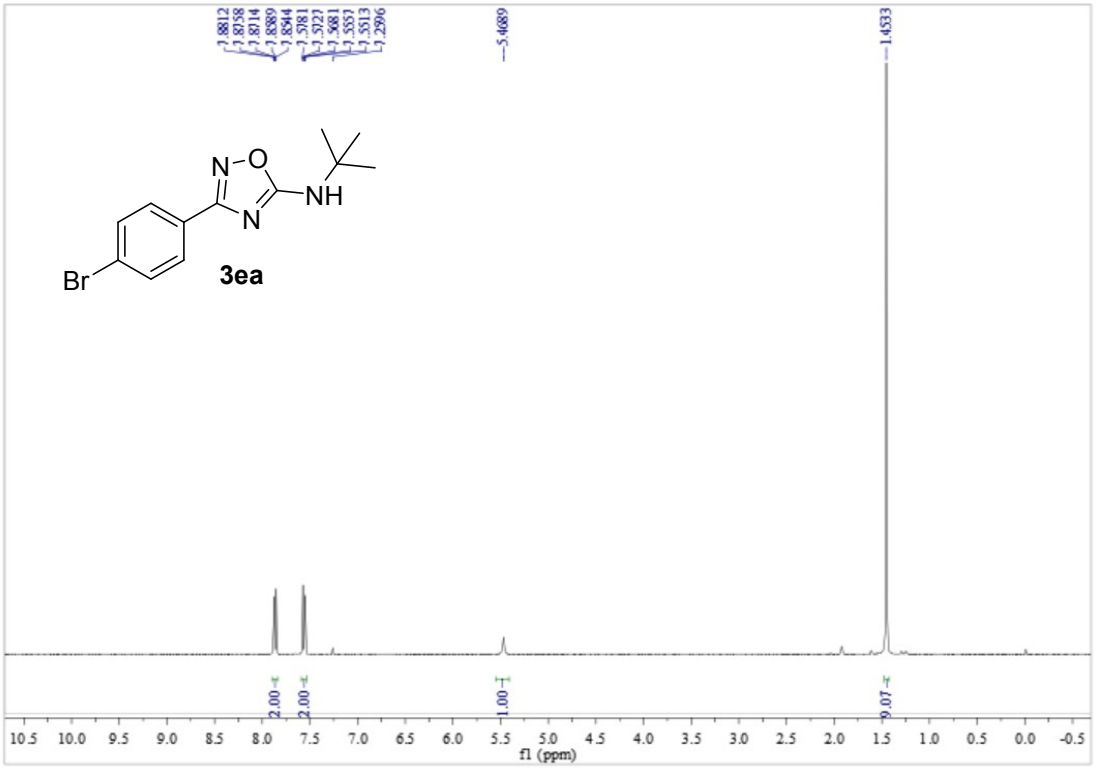
f1 (ppm)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7.8889
7.8944
7.5781
7.5727
7.5681
7.5557
7.5513
7.2996
5.4689
1.4533
N
O
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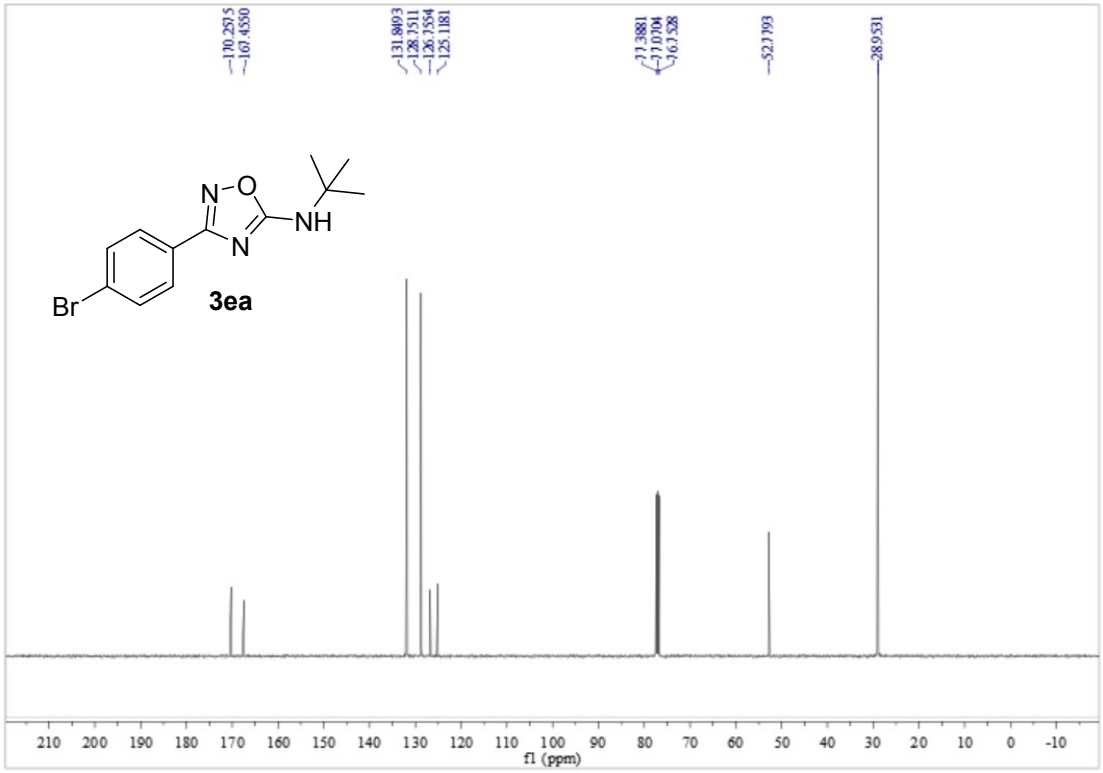
N
Br
3ea
2.00
2.00
1.00
9.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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131.8893
128.3511
126.1554
125.1181
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77.0704
76.7528
52.1793
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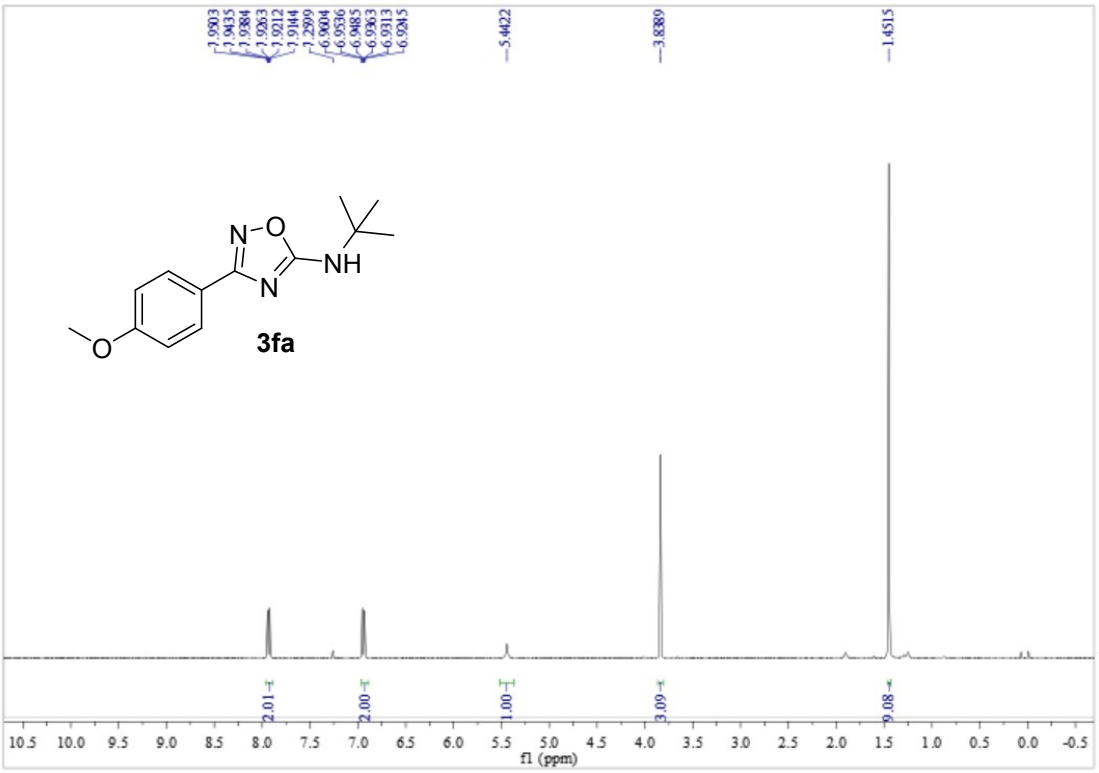
O
NH
N
Br
3ea
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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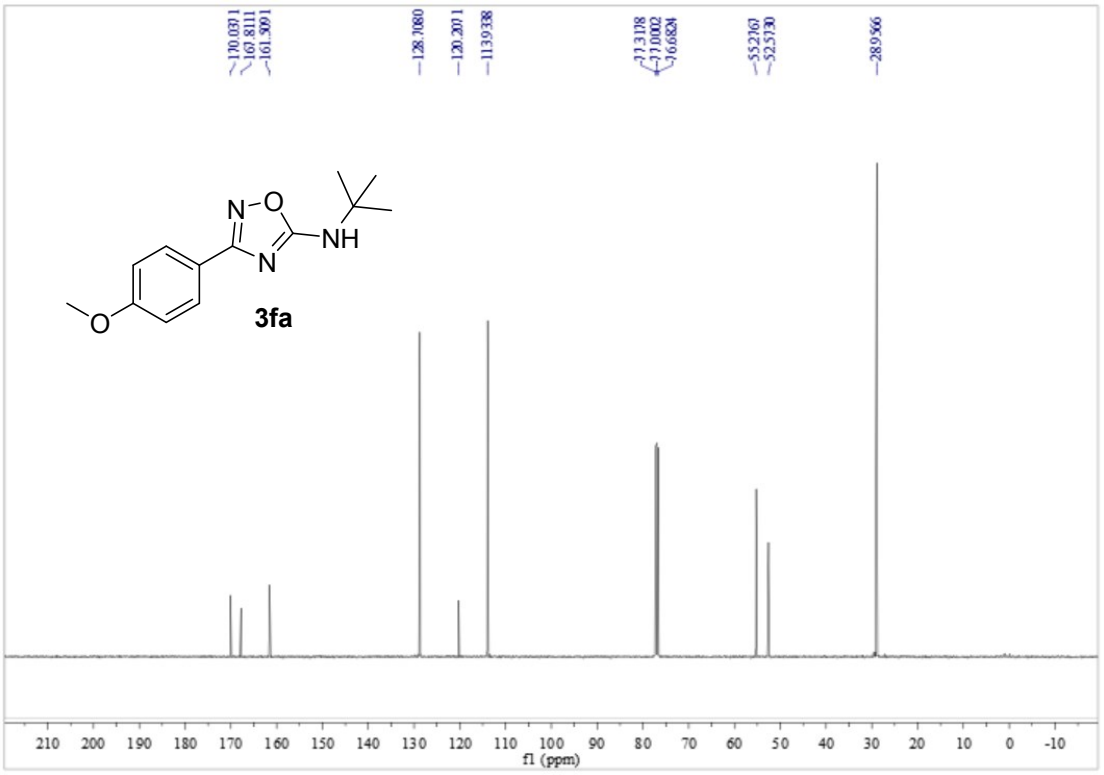
6.9485
6.9363
6.9313
6.9245
5.4422
3.8389
1.4515
N
O
N
NH
O
3fa
2.01
2.00
1.00
3.09
9.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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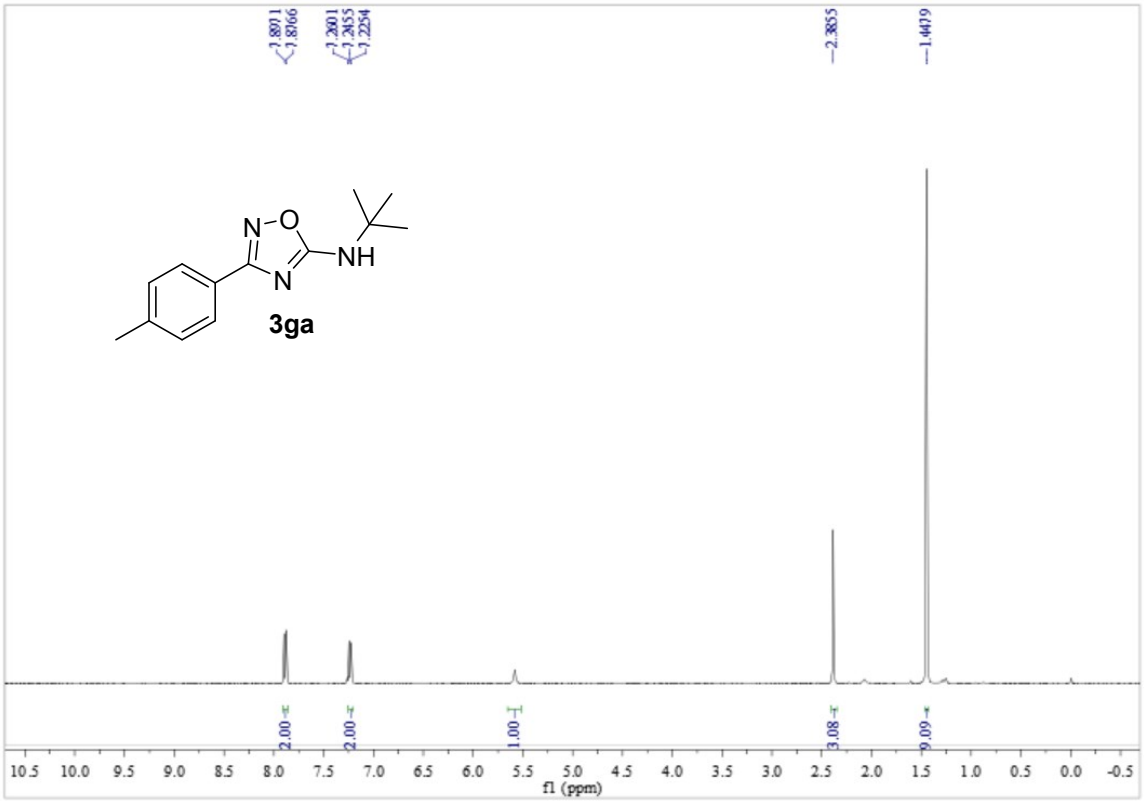
28.9566
N
O
N
NH
O
3fa
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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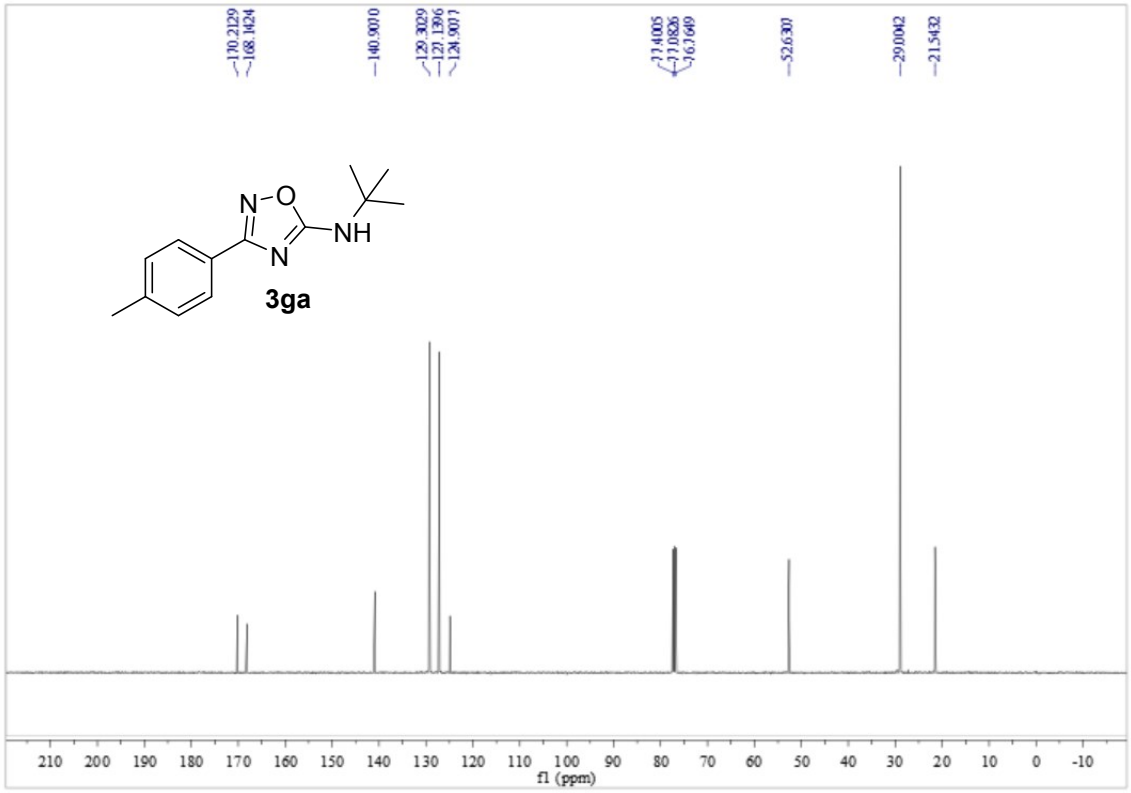
7.8766
7.2601
7.2455
7.2254
2.3855
1.4479
N
O
NH
N
3ga
2.00
2.00
1.00
3.08
9.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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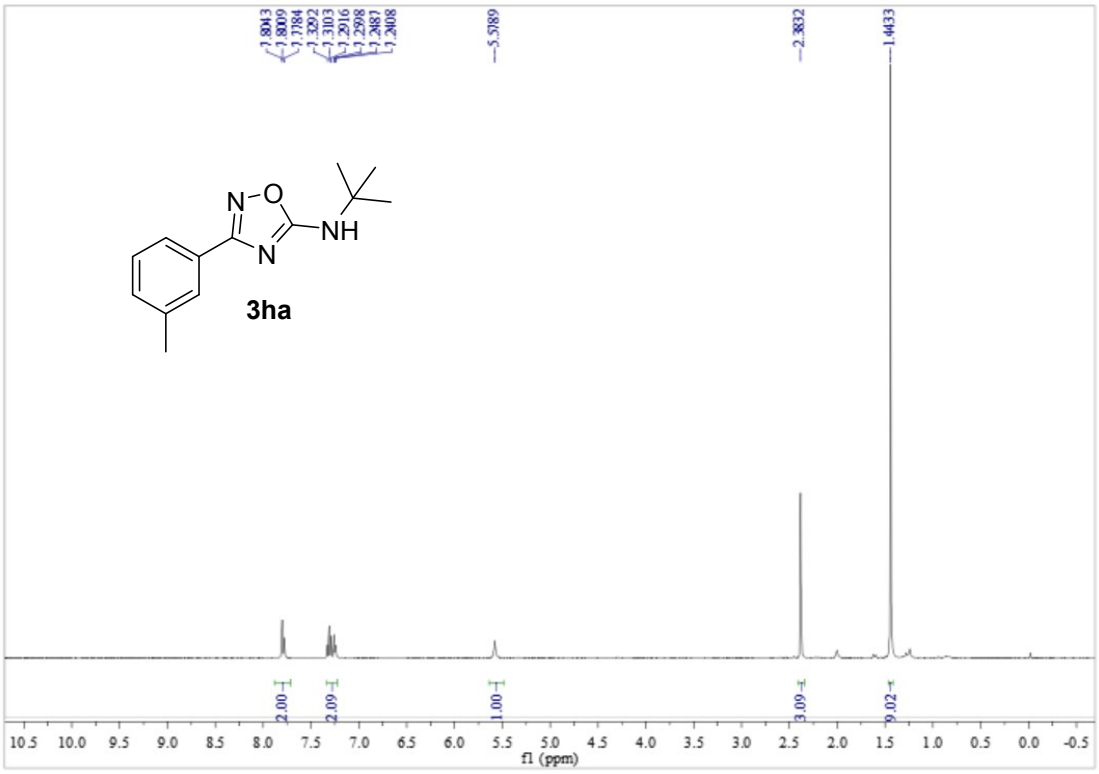
168.1424
140.9010
129.3029
127.1396
124.9077
77.4005
77.0826
76.7649
52.6307
29.0042
21.5432
N
O
NH
N
3ga
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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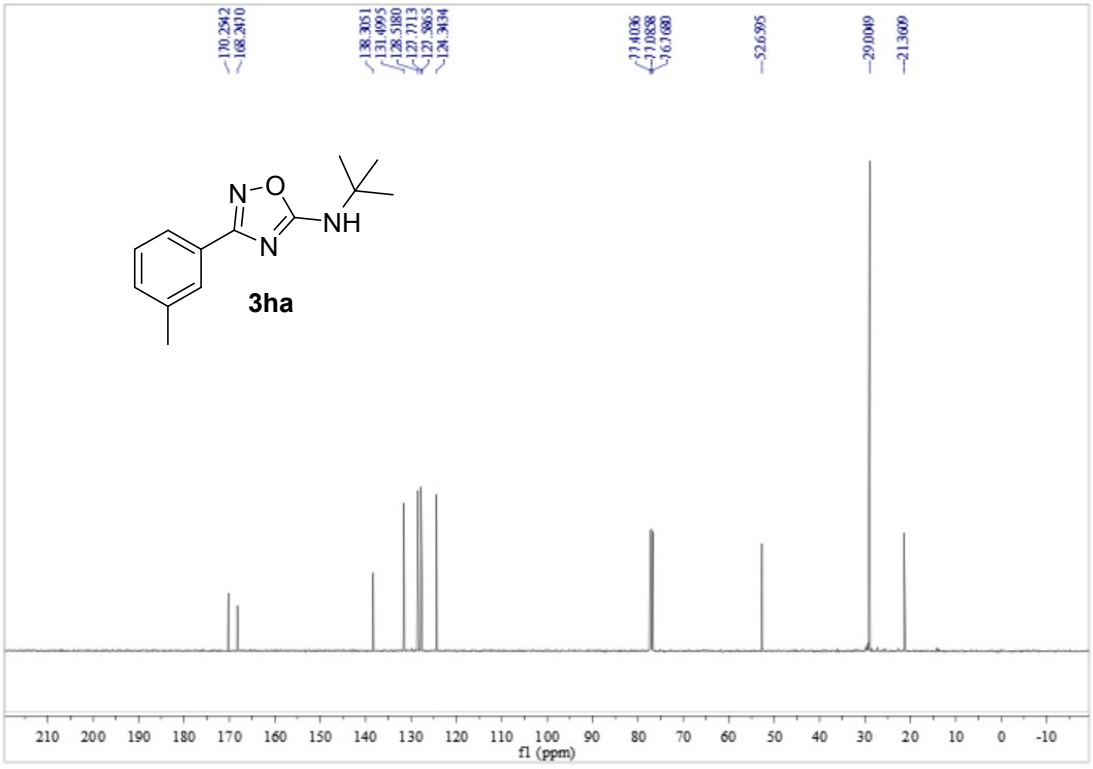
7.7784
7.3292
7.3103
7.2916
7.2698
7.2487
7.2408
5.5789
2.3832
1.4433
N
O
N
NH
3ha
2.00
2.09
1.00
3.09
9.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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138.3051
131.4995
128.5180
127.7713
127.3865
124.3434
77.4036
77.1038
76.7680
52.6395
29.0049
21.3609
N
O
N
NH
3ha
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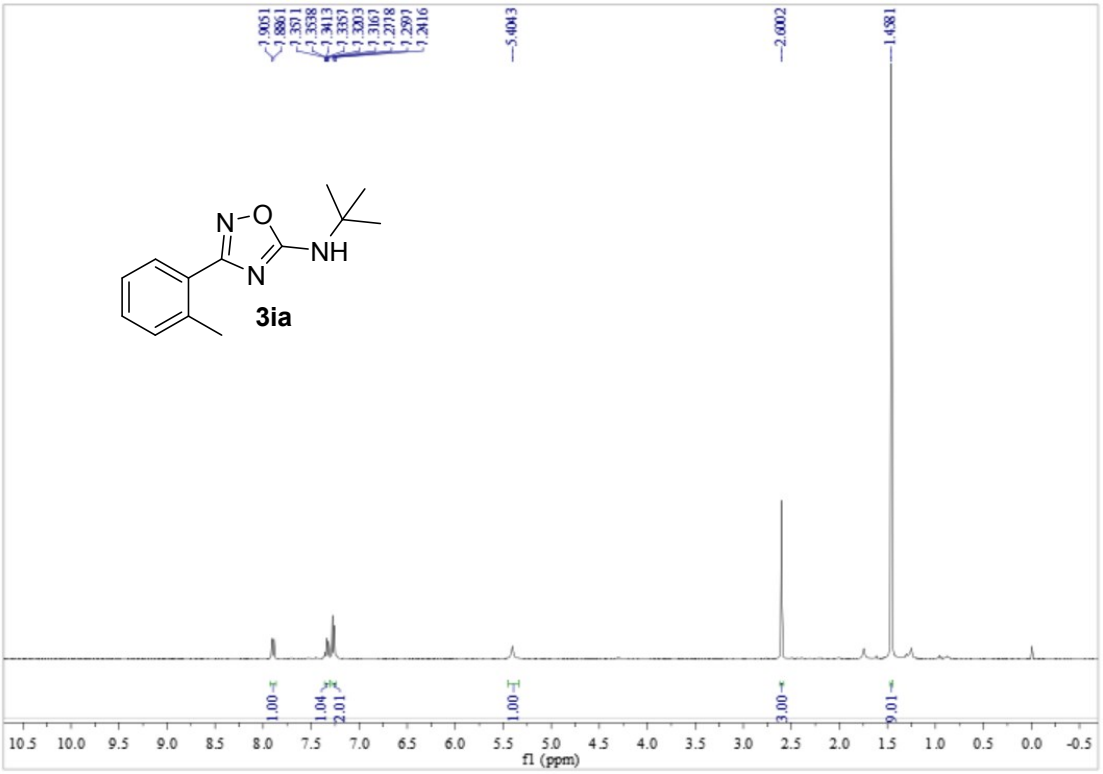
f1 (ppm)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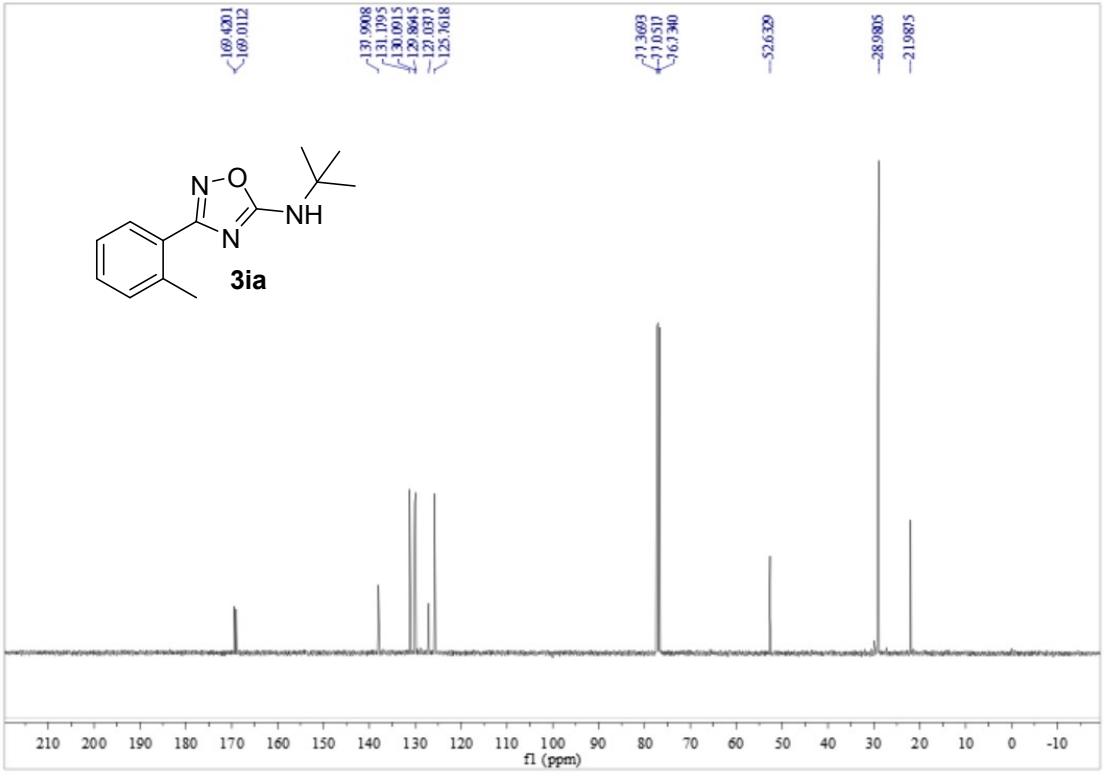
7.8861
7.3571
7.3538
7.3413
7.3353
7.3303
7.3167
7.2778
7.2697
7.2616
5.4043
2.6002
1.4881
N
O
N
NH
3ia
1.00
1.04
2.01
1.00
3.00
9.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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137.9908
131.1995
130.0915
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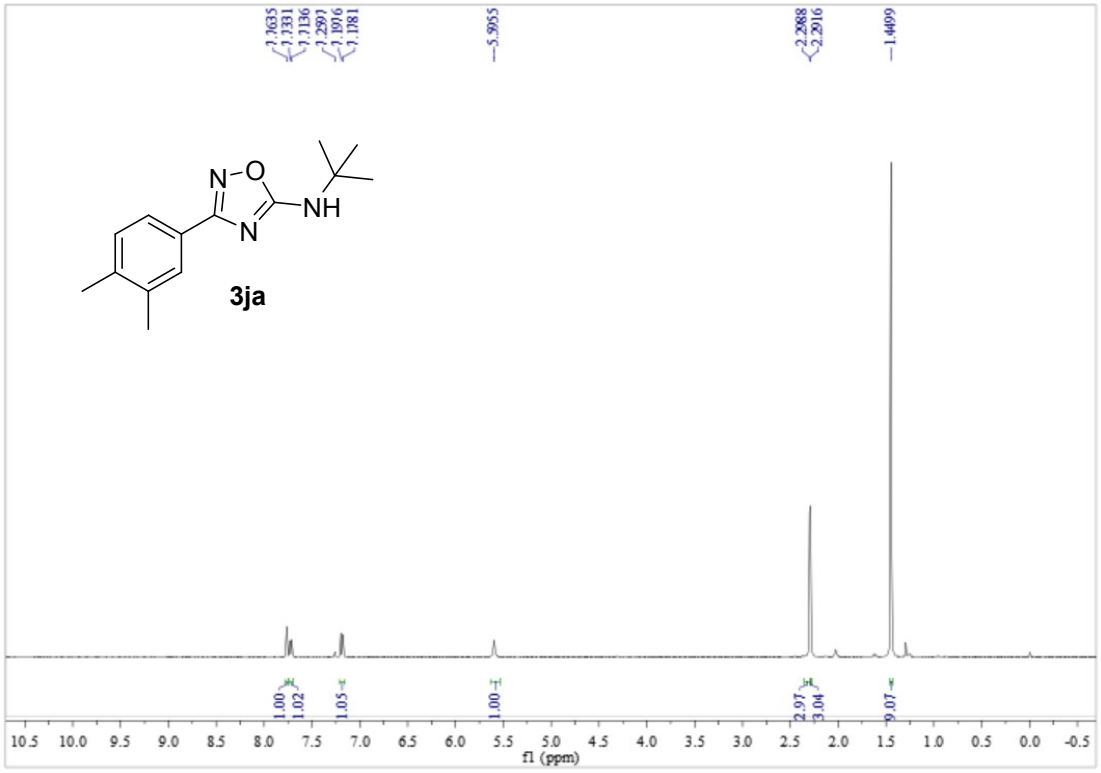
127.1037
125.7618
71.3693
71.0517
16.7340
52.6329
28.9805
21.9815
N
O
N
NH
3ia
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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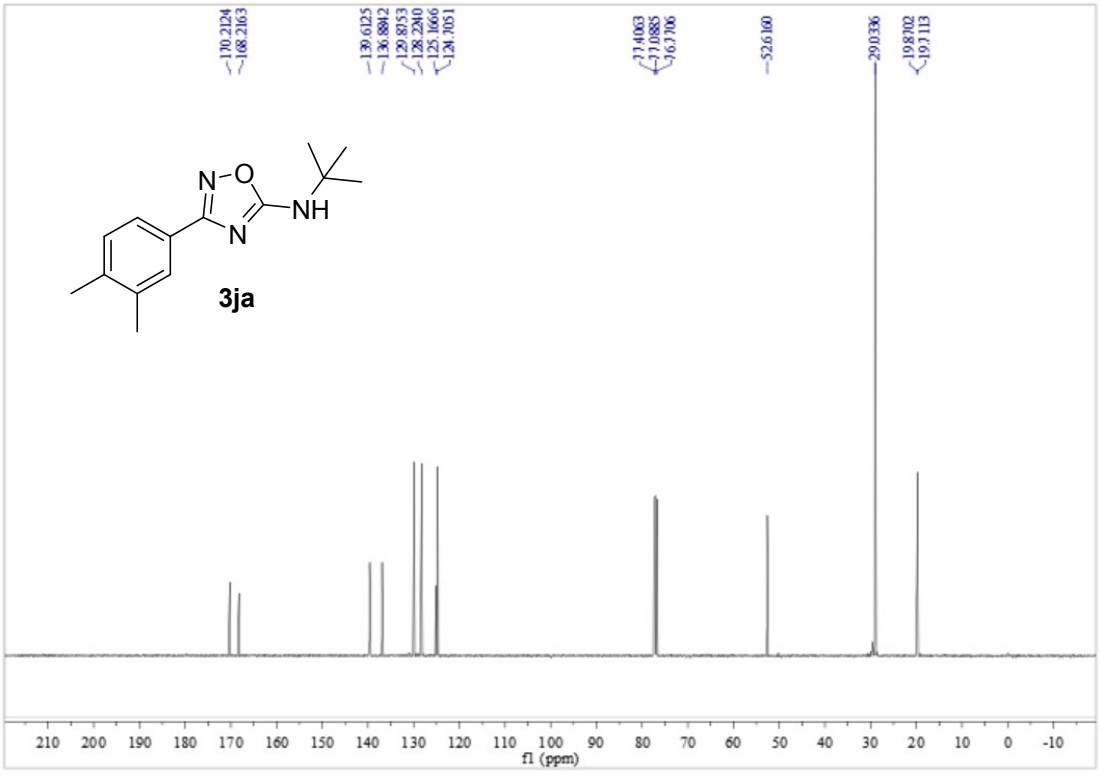
7.7136
7.2597
7.1976
7.1781
5.5955
2.2888
2.2916
1.4499
N
O
N
NH
3ja
1.00
1.02
1.05
1.00
2.97
3.04
9.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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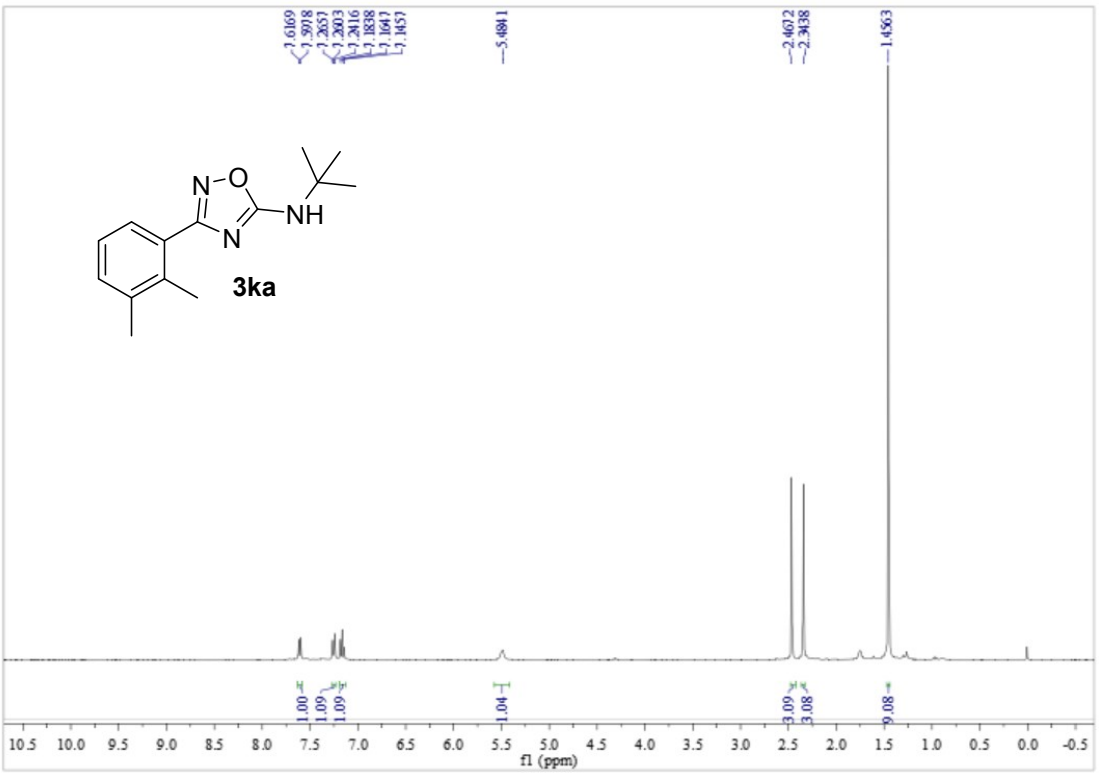
139.6125
136.8842
129.8153
128.2240
125.1666
124.7051
77.4063
77.0885
76.7706
52.6160
29.0336
19.8702
19.7113
N
O
N
NH
3ja
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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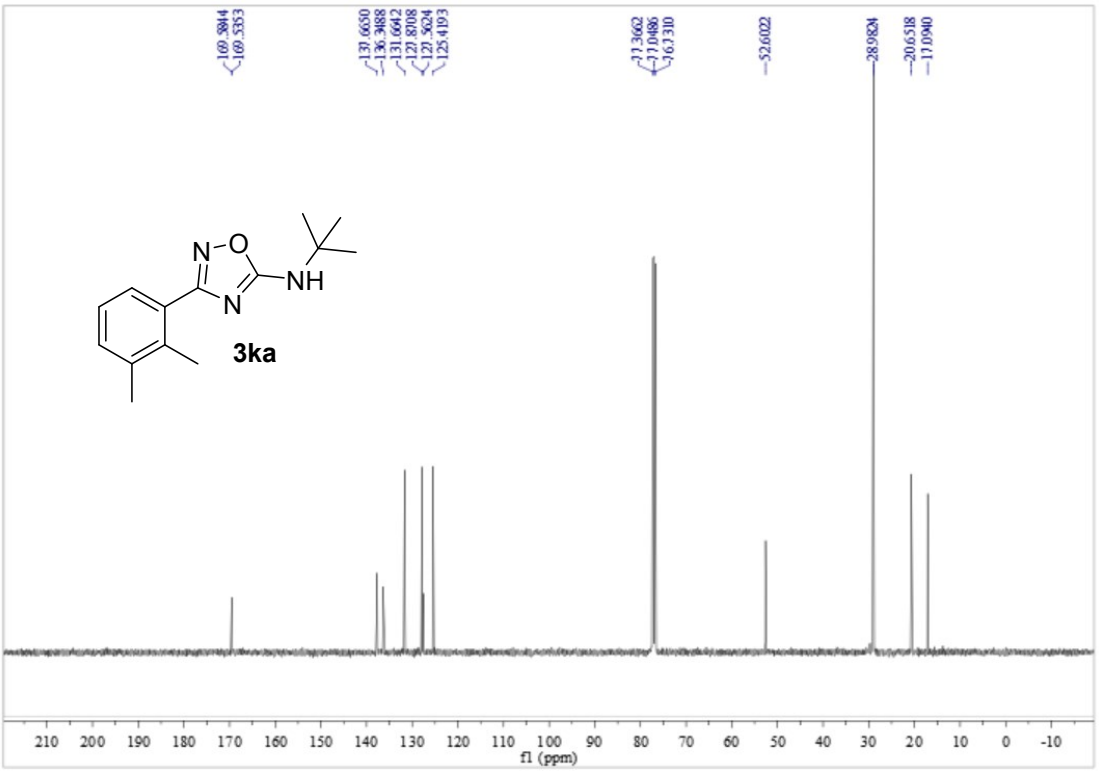
7.3978
7.2657
7.2603
7.2416
7.1838
7.1647
7.1457
5.4841
2.4612
2.3438
1.4563
N
O
N
NH
3ka
1.00
1.09
1.09
1.04
3.09
3.08
9.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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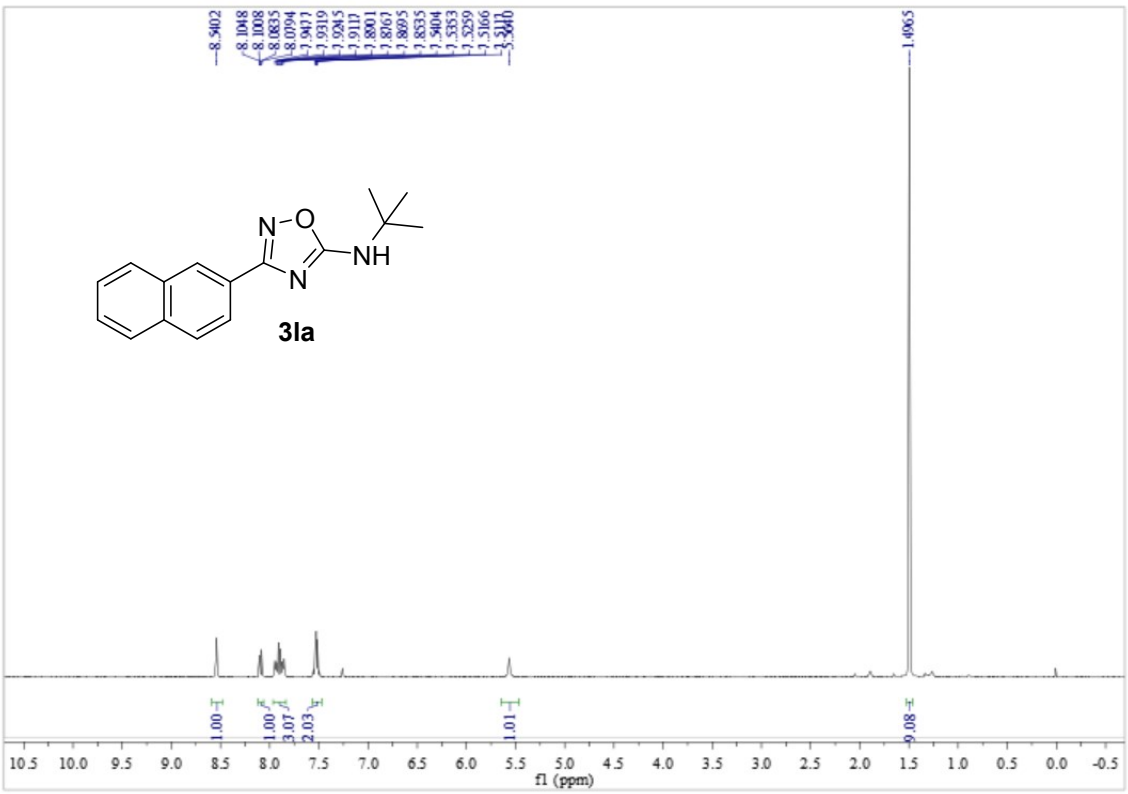
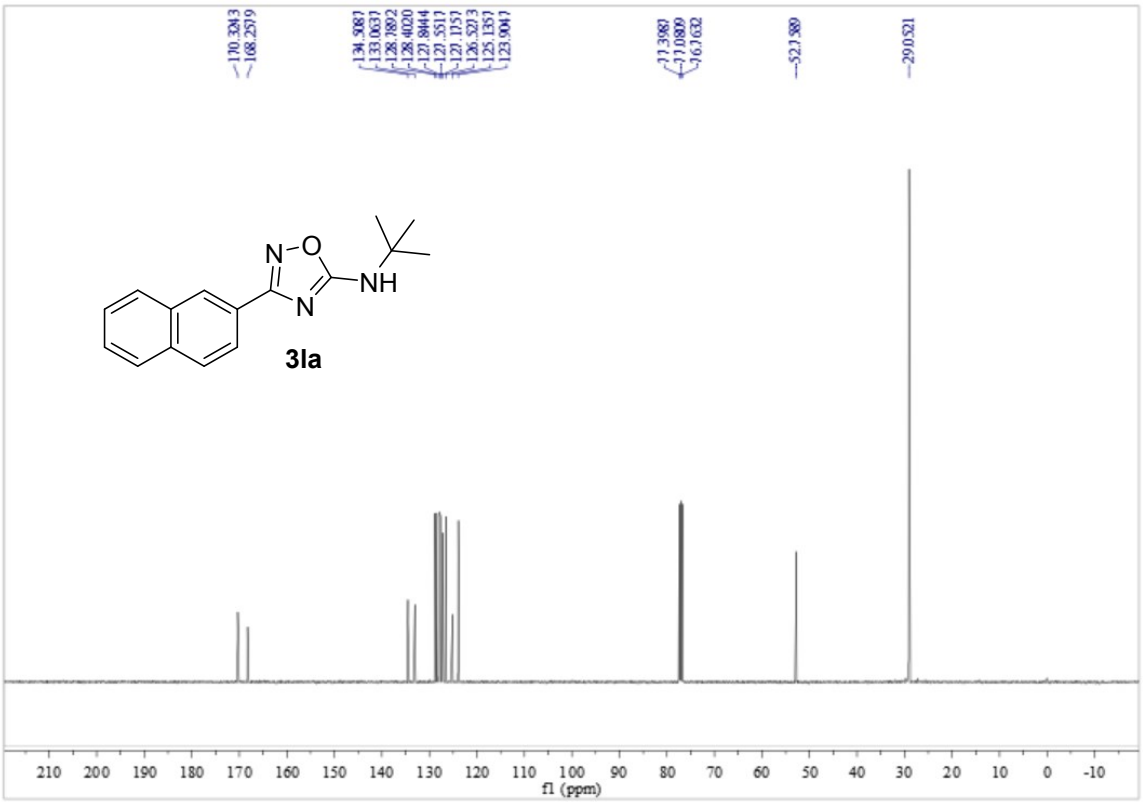
169.5353
131.6650
130.3488
131.6642
123.8108
121.5624
125.4193
77.3662
77.0486
76.7310
52.6022
28.9824
20.6518
17.0940
N
O
N
NH
3ka
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


3la
f1 (ppm)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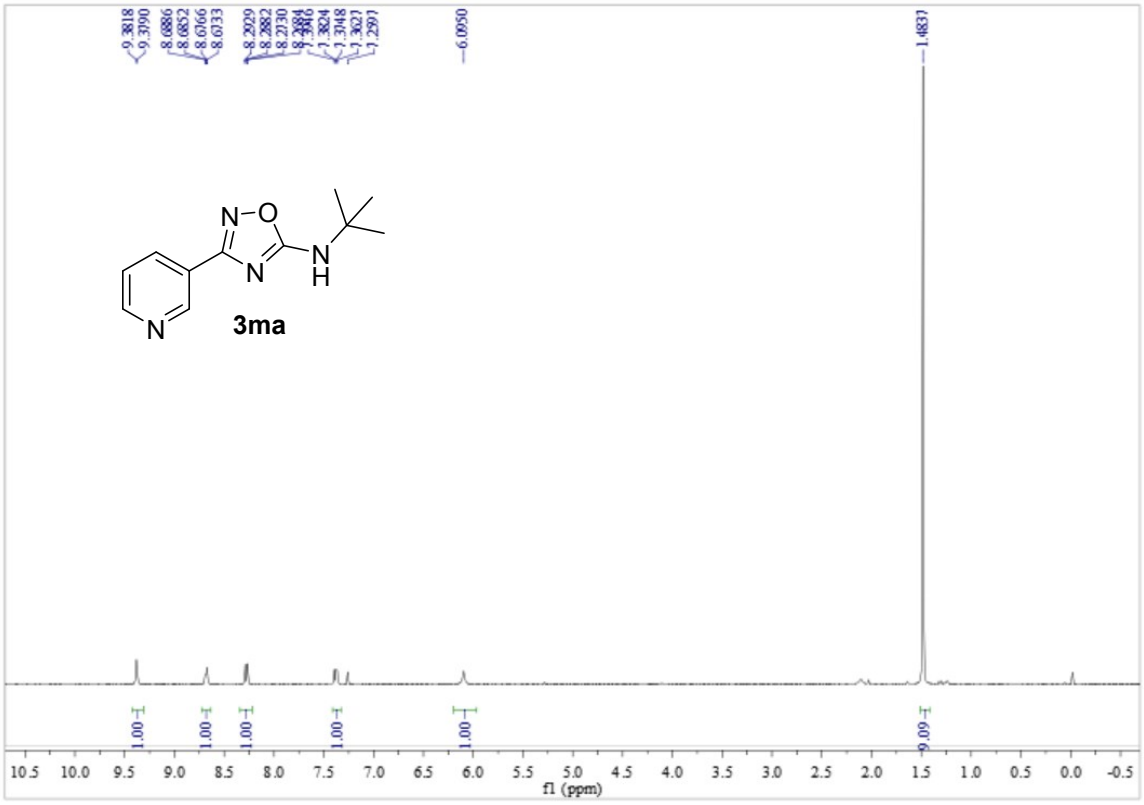
f1 (ppm)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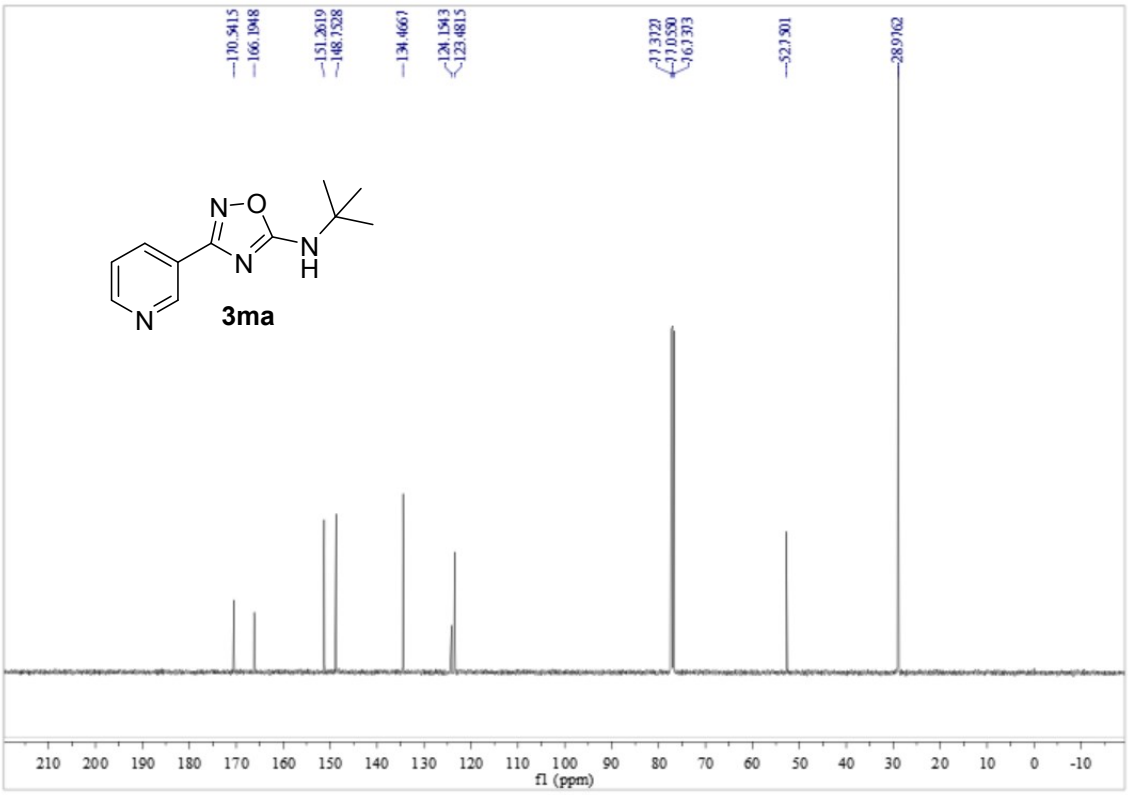
8.6886
8.6852
8.6366
8.6333
8.2929
8.2882
8.2730
8.2684
7.3824
7.3048
7.3021
7.2997
6.0950
1.4837
N
O
N
N
H
N
3ma
1.00
1.00
1.00
1.00
1.00
9.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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151.2619
148.7528
134.4667
124.1543
123.4815
77.3122
77.0550
76.7333
52.7301
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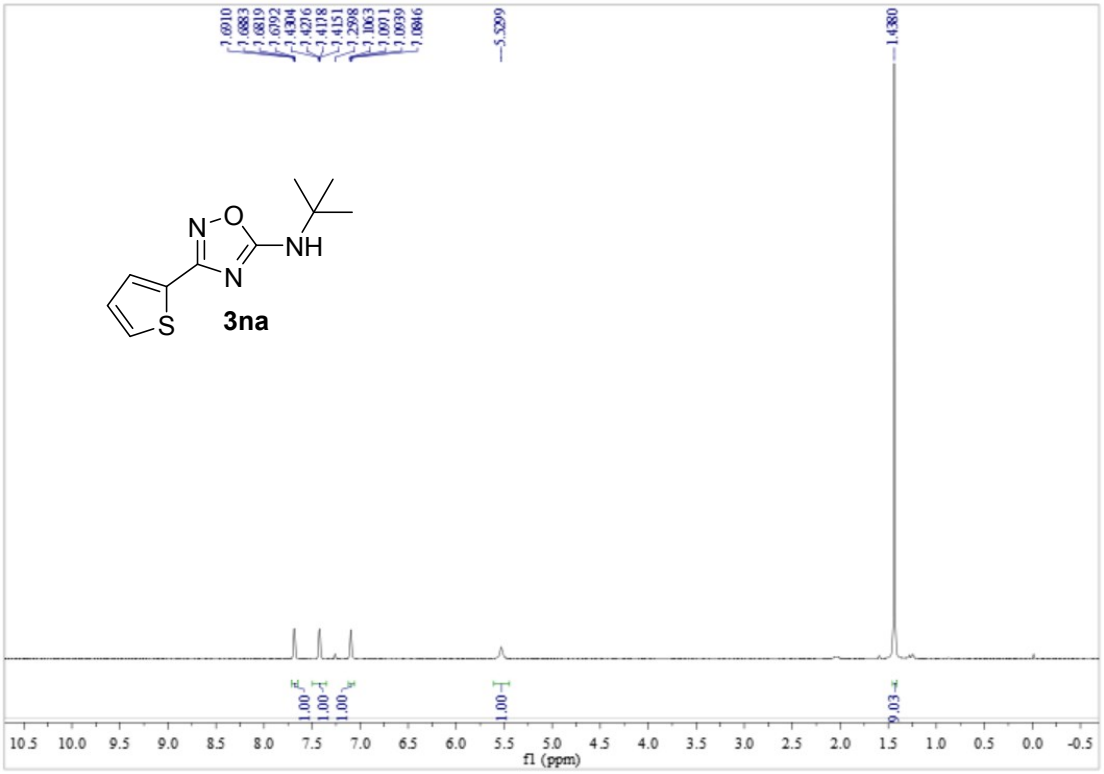
N
O
N
N
H
N
3ma
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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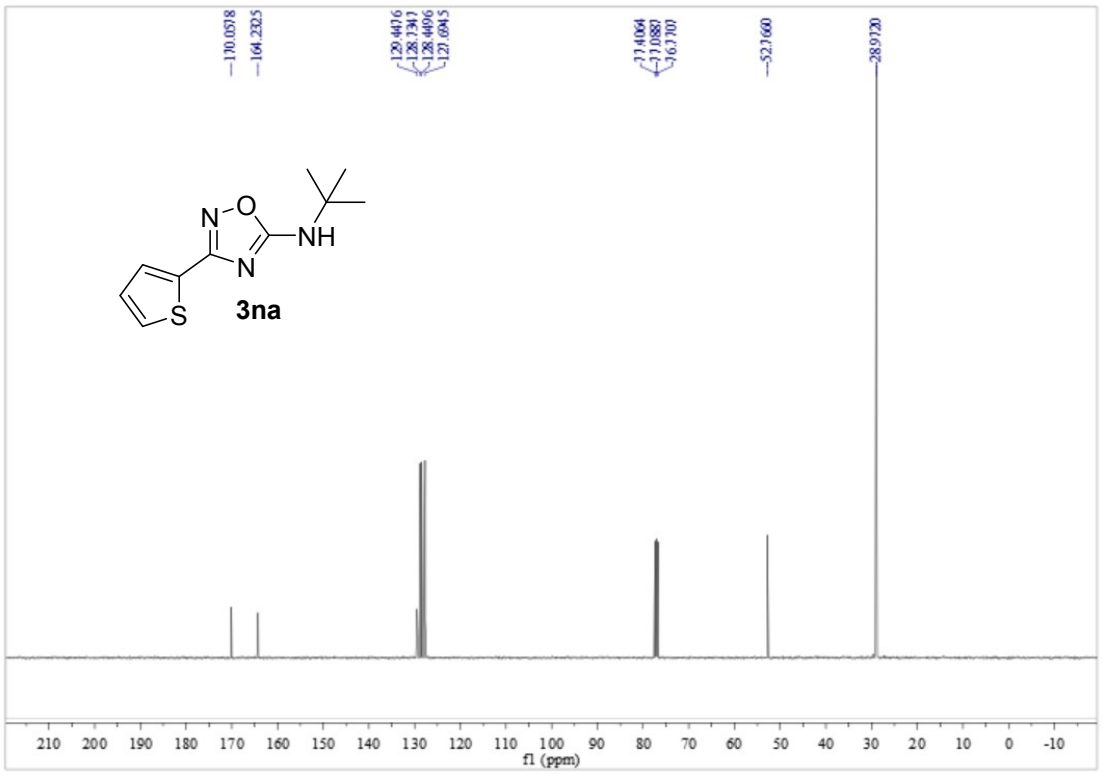
7.6883
7.6819
7.6792
7.4304
7.4276
7.4178
7.4151
7.2998
7.1063
7.0991
7.0939
7.0846
5.5299
1.4380
N
O
NH
N
S
3na
1.00
1.00
1.00
1.00
9.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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164.2325
129.4476
128.7347
128.4496
127.6945
77.4064
77.0887
76.7707
52.7660
28.9720
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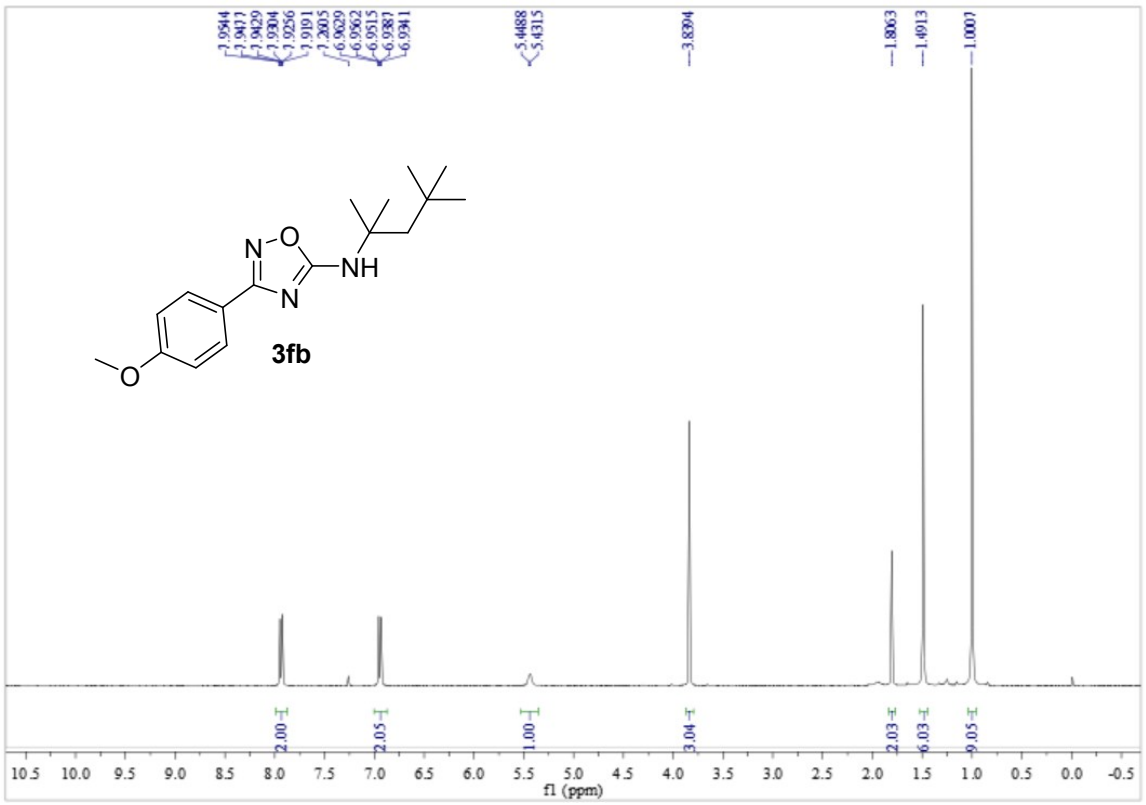
O
NH
N
S
3na
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.9429
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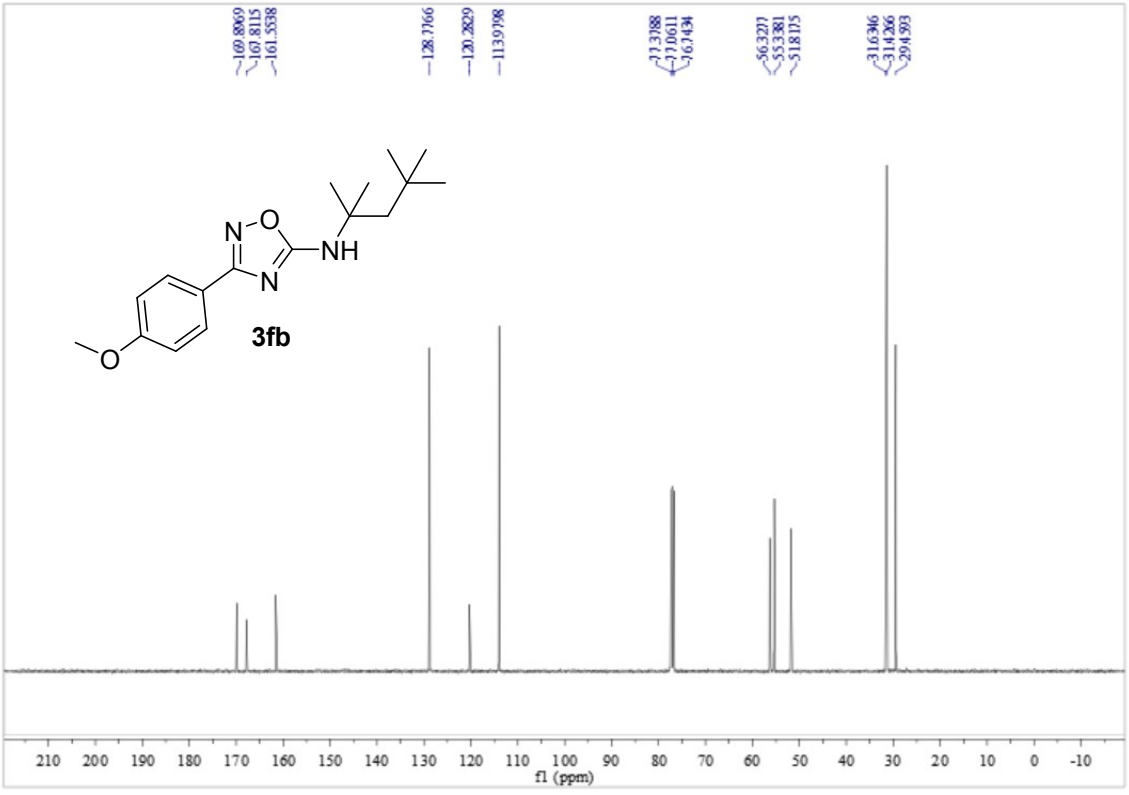
7.9256
7.9191
7.2005
6.9629
6.9562
6.9515
6.9387
6.9341
5.4488
5.4315
3.8394
1.8063
1.4913
1.0007
N
O
N
NH
O
3fb
2.00
2.05
1.00
3.04
2.03
6.03
9.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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120.2829
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77.3788
77.0611
76.7434
56.3227
55.3381
51.8175
31.6346
31.4266
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O
N
NH
O
3fb
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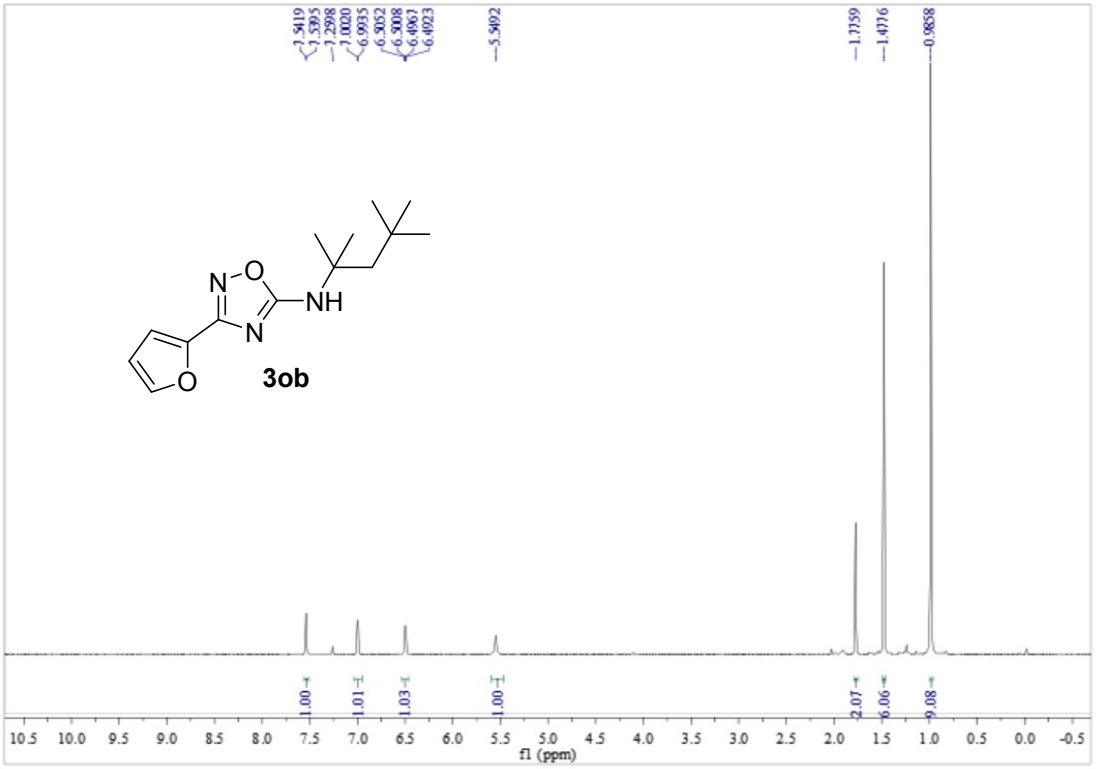
f1 (ppm)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7.2398
7.0020
6.9935
6.5052
6.5008
6.4961
6.4923
5.5092
1.7359
1.4716
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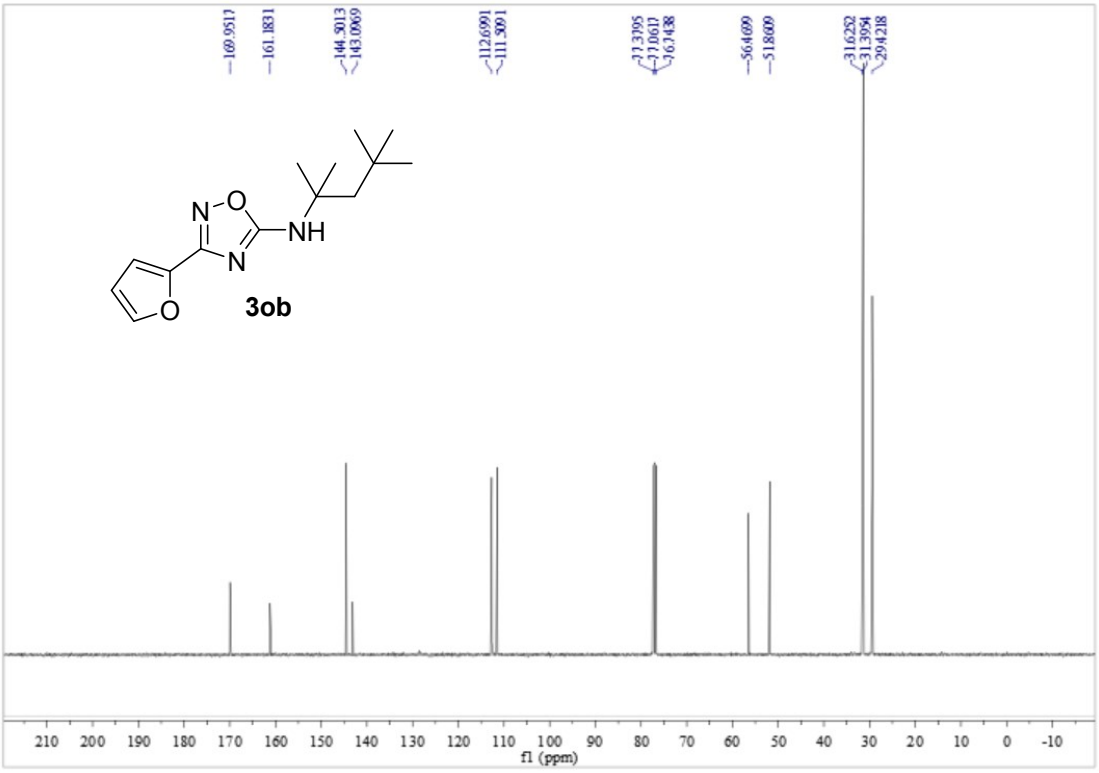
1.00
1.01
1.03
1.00
2.07
6.06
9.08
f1 (ppm)
3ob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161.1831
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111.5091
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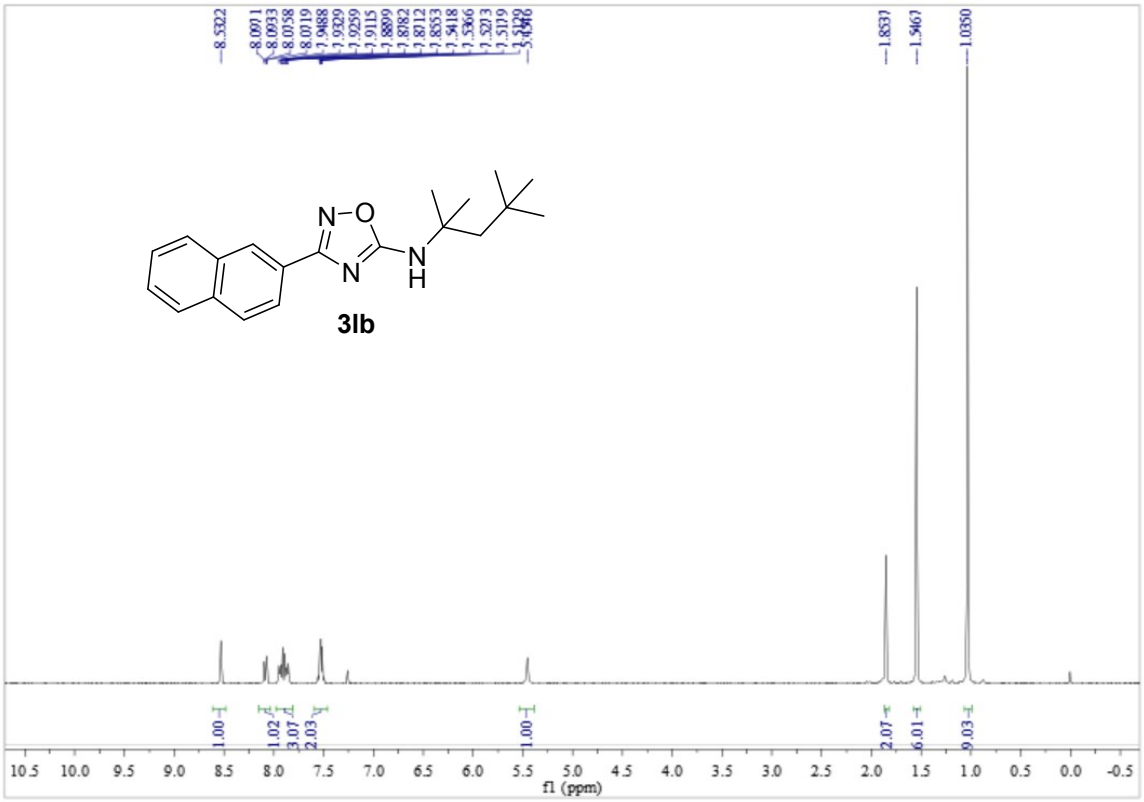
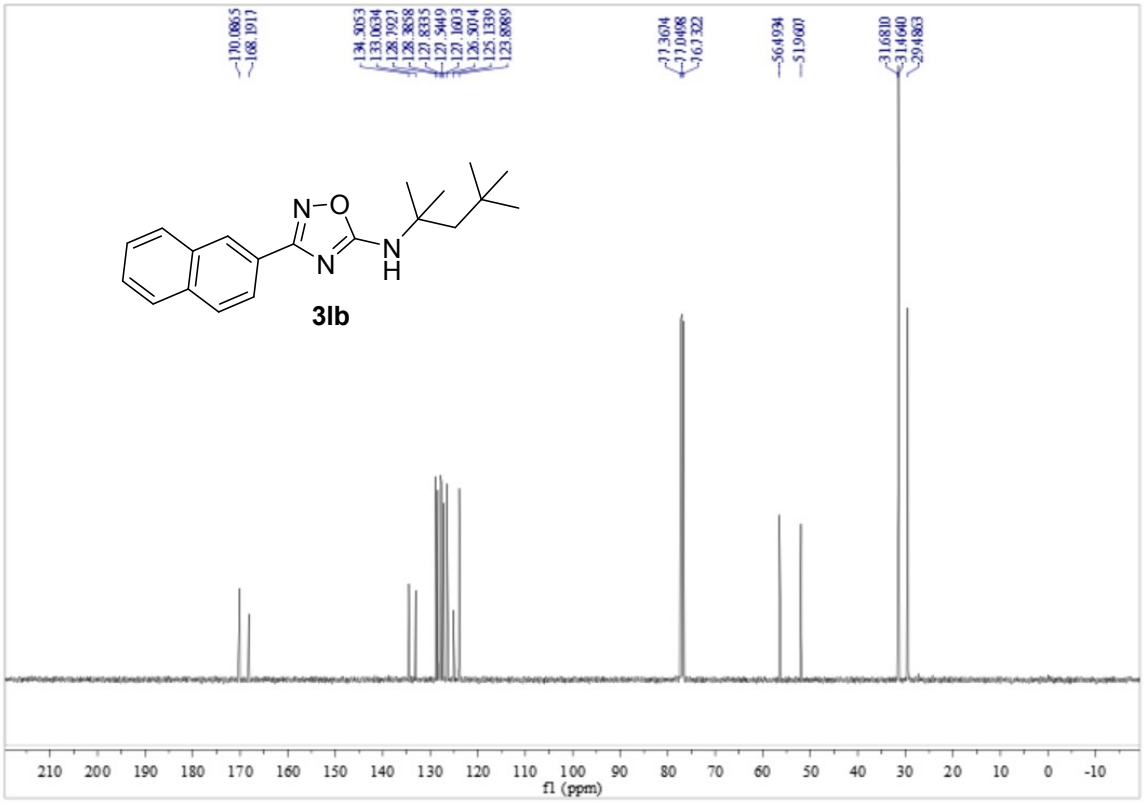
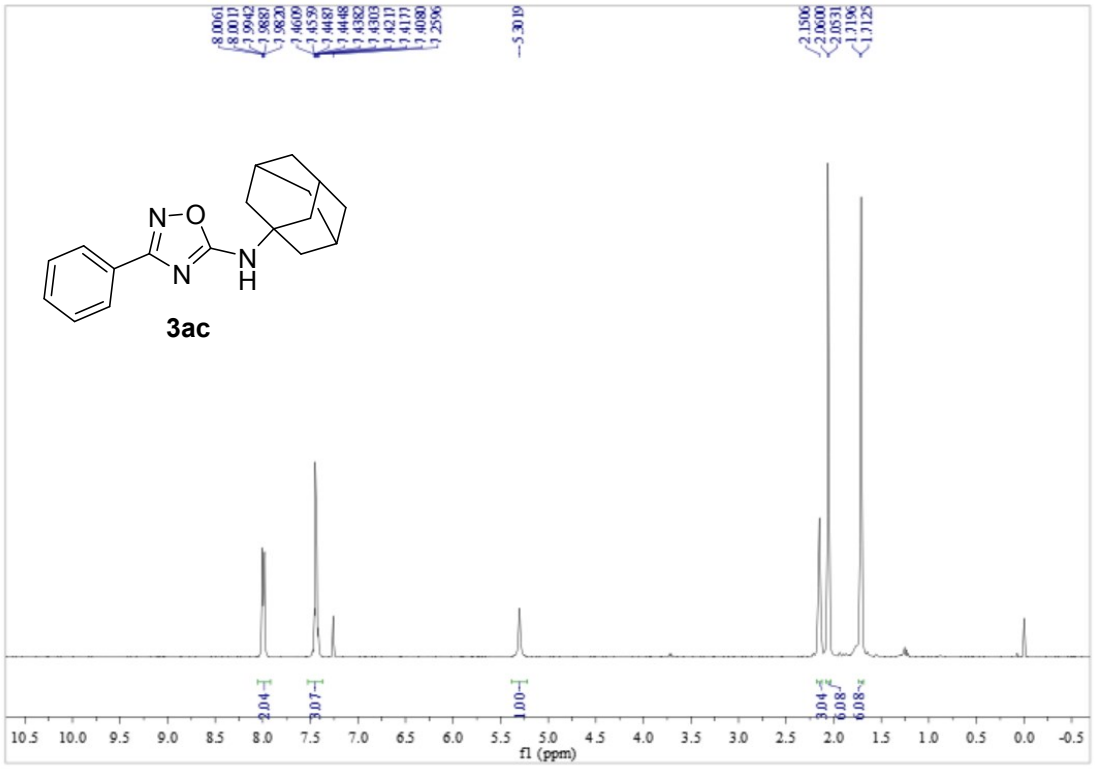
76.7838
56.4699
51.8609
31.6252
31.3994
29.4218
f1 (ppm)
3ob


3Ib
fl (ppm)


3Ib
fl (ppm)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7.4303
7.4217
7.4177
7.4080
7.2596
5.3019
2.1506
2.0660
2.0531
1.7196
1.7125
2.04
3.07
1.00
3.04
6.08
6.08
10.5 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
f1 (ppm)
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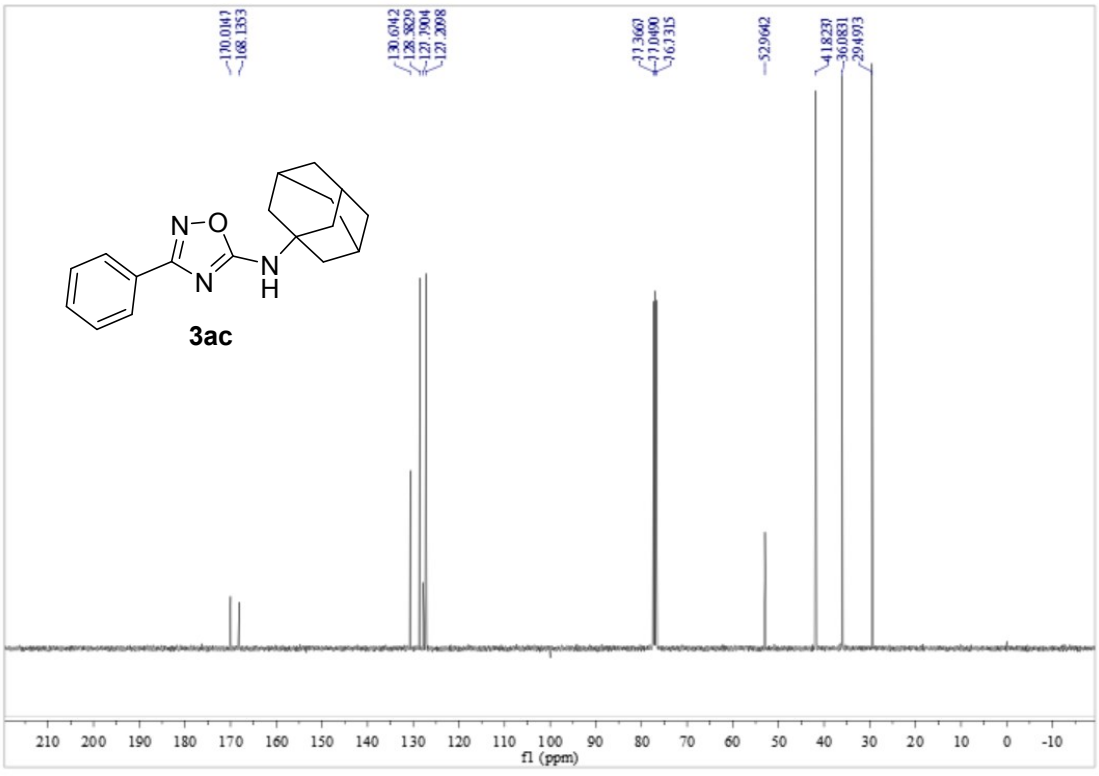
N
N
H
3ac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130.6742
128.3829
121.7904
121.2098
77.3667
77.0490
76.7315
52.9642
41.8237
36.0831
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f1 (ppm)
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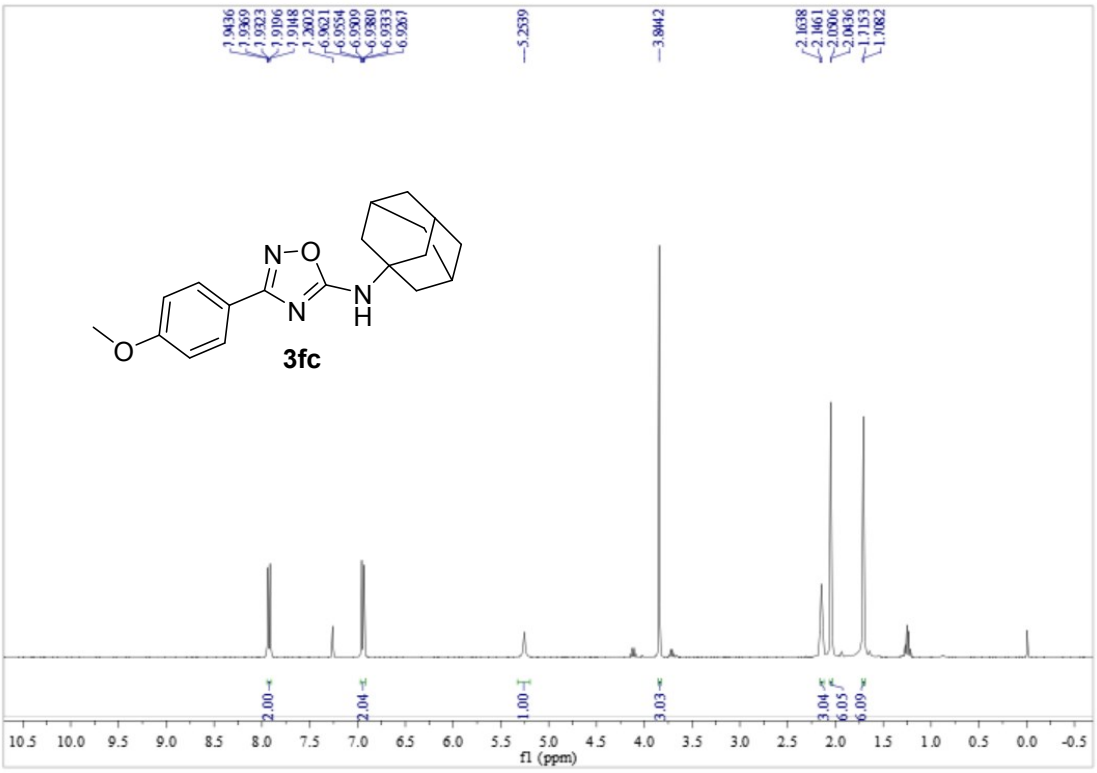
O
N
N
H
3ac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7.9323
7.9196
7.9148
7.2002
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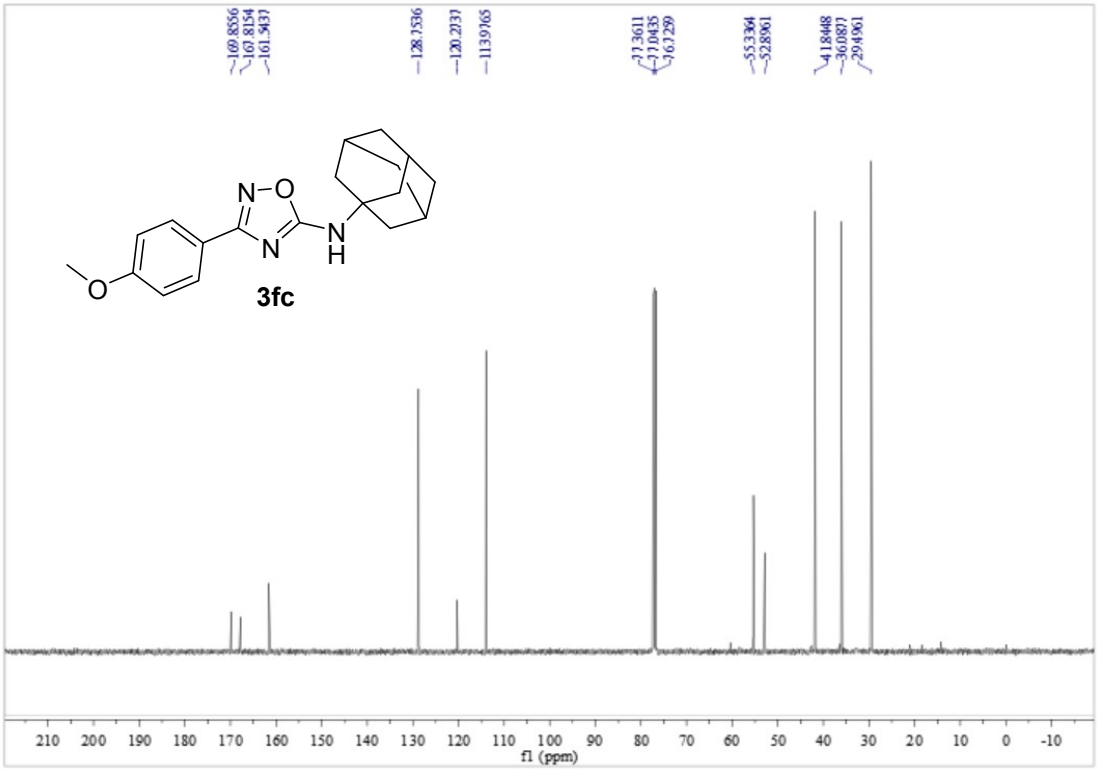
6.8909
6.8880
6.8333
6.8267
5.2539
3.8442
2.1638
2.1461
2.0006
2.0436
1.7153
1.7082
N
O
N
H
O
3fc
2.00
2.04
1.00
3.03
3.04
6.05
6.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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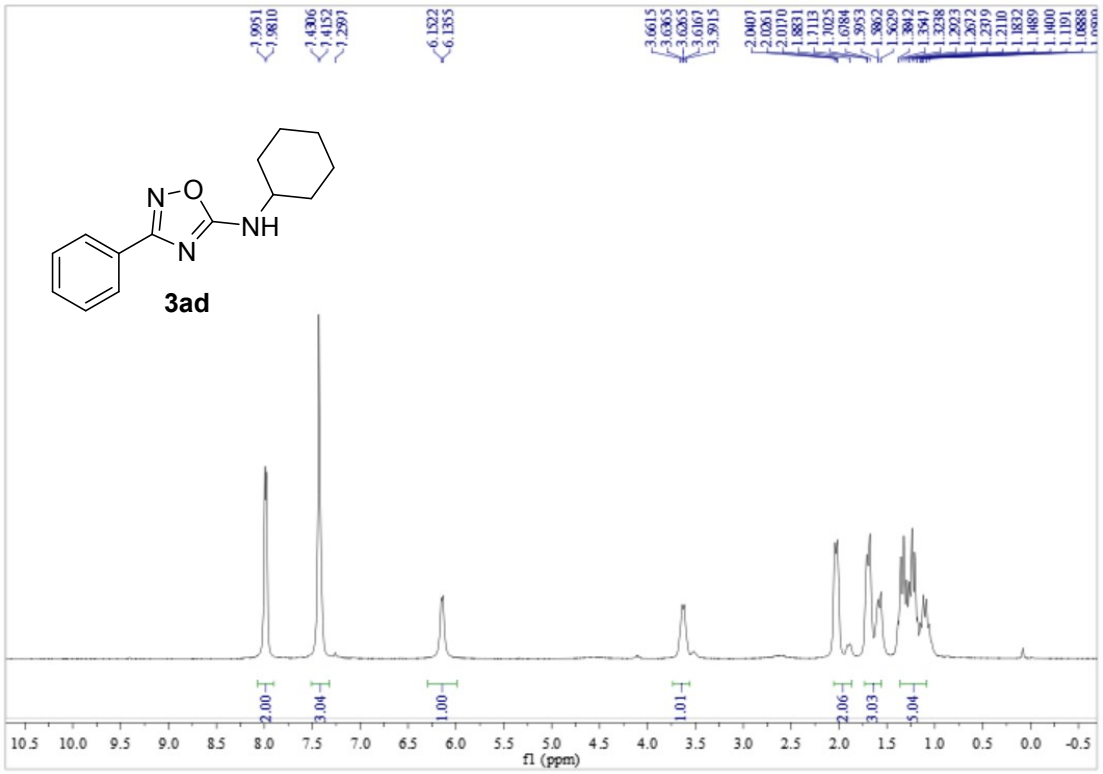
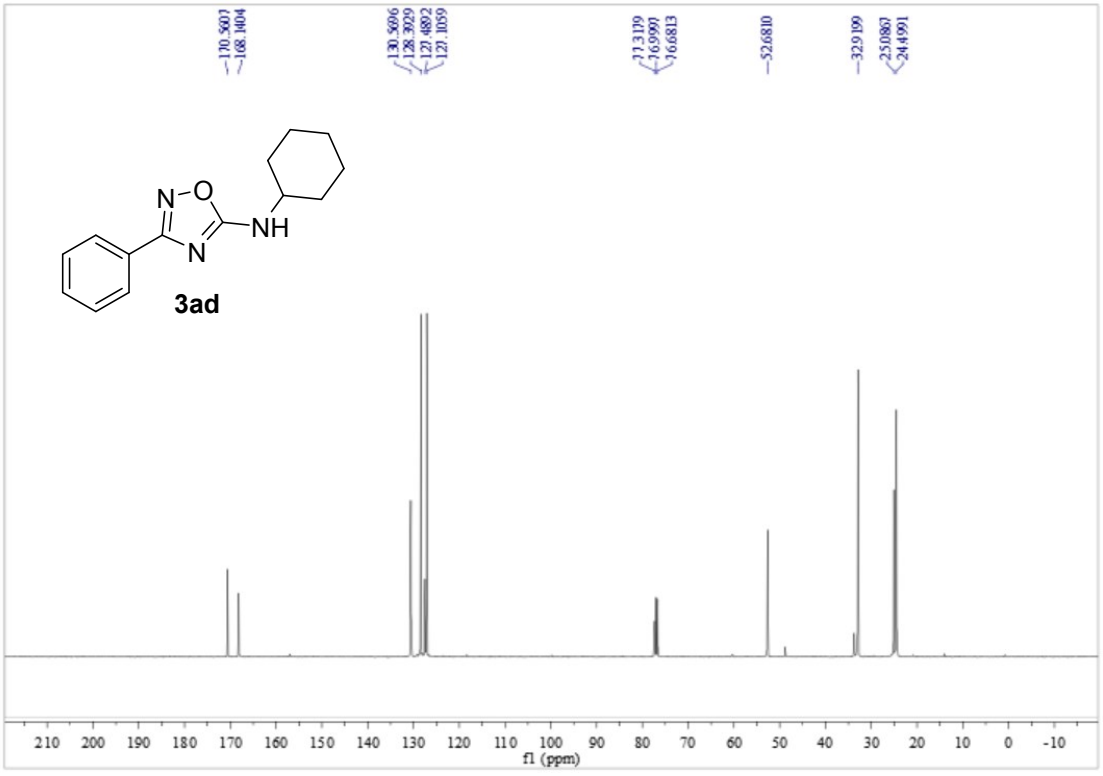
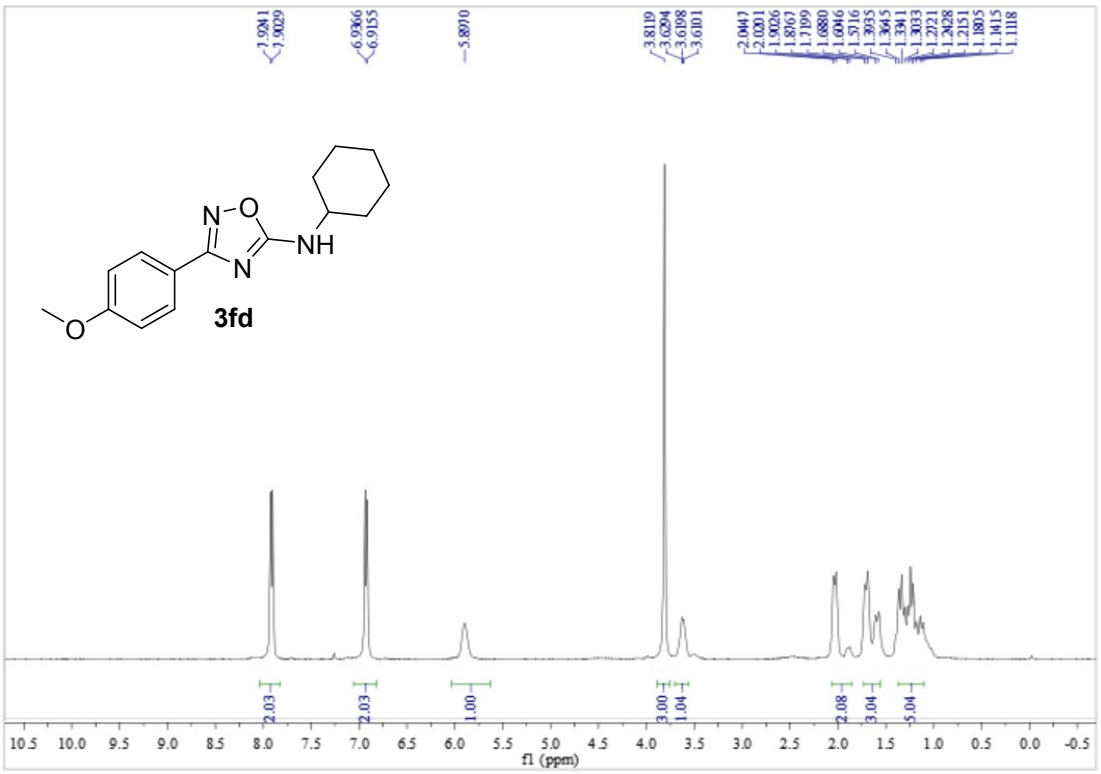
120.2337
113.9765
77.3611
77.0435
76.7259
55.5364
55.2896
41.8448
36.0897
29.4961
N
O
N
H
O
3fc
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


3ad
fl (ppm)


3ad
fl (ppm)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1.9026
1.8767
1.7199
1.6880
1.6046
1.5716
1.3935
1.3645
1.3341
1.3033
1.2721
1.2428
1.2151
1.1805
1.1415
1.1118
N
O
NH
O
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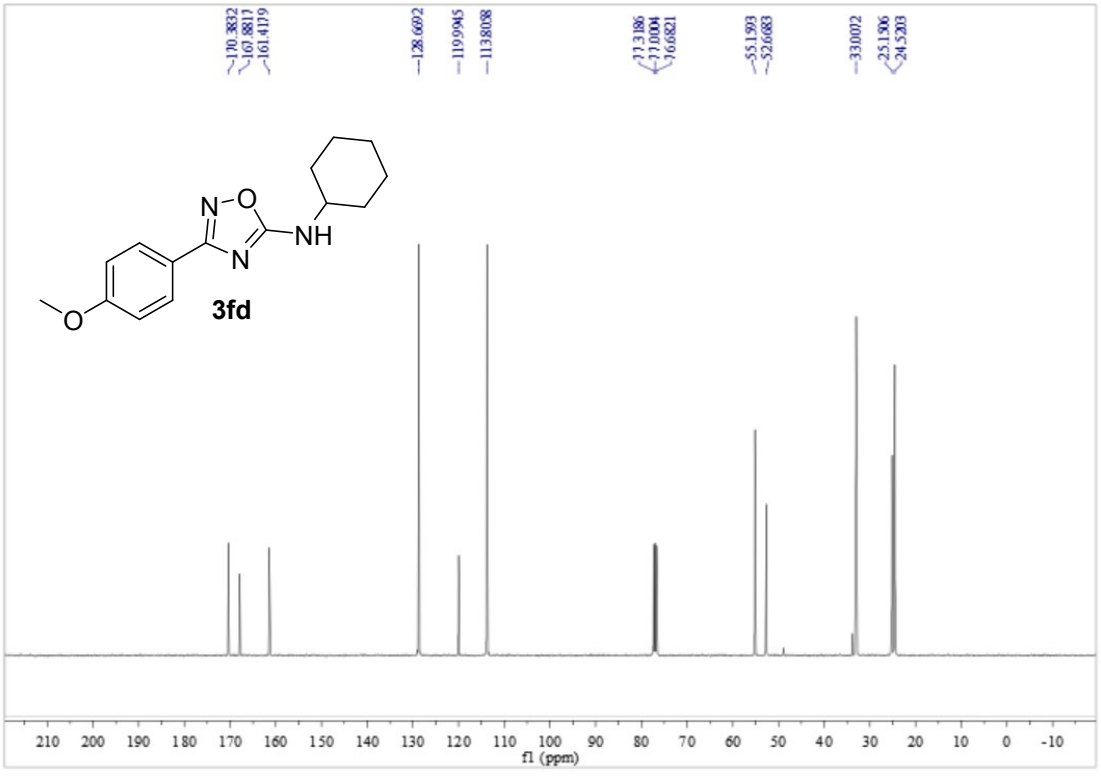
2.03
1.00
3.00
1.04
2.08
3.04
5.04
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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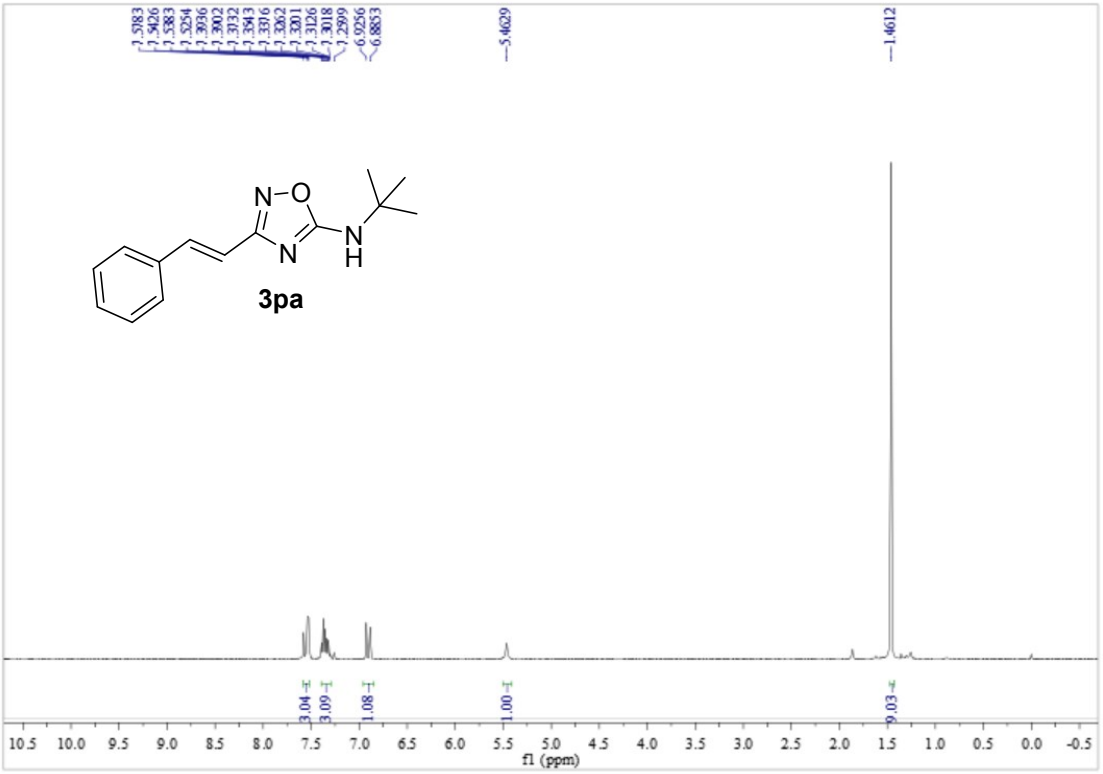
167.8817
161.4179
128.6692
119.9945
113.8038
77.3186
77.0004
76.6821
55.1993
52.6683
33.0072
25.1506
24.5203
N
O
NH
O
3fd
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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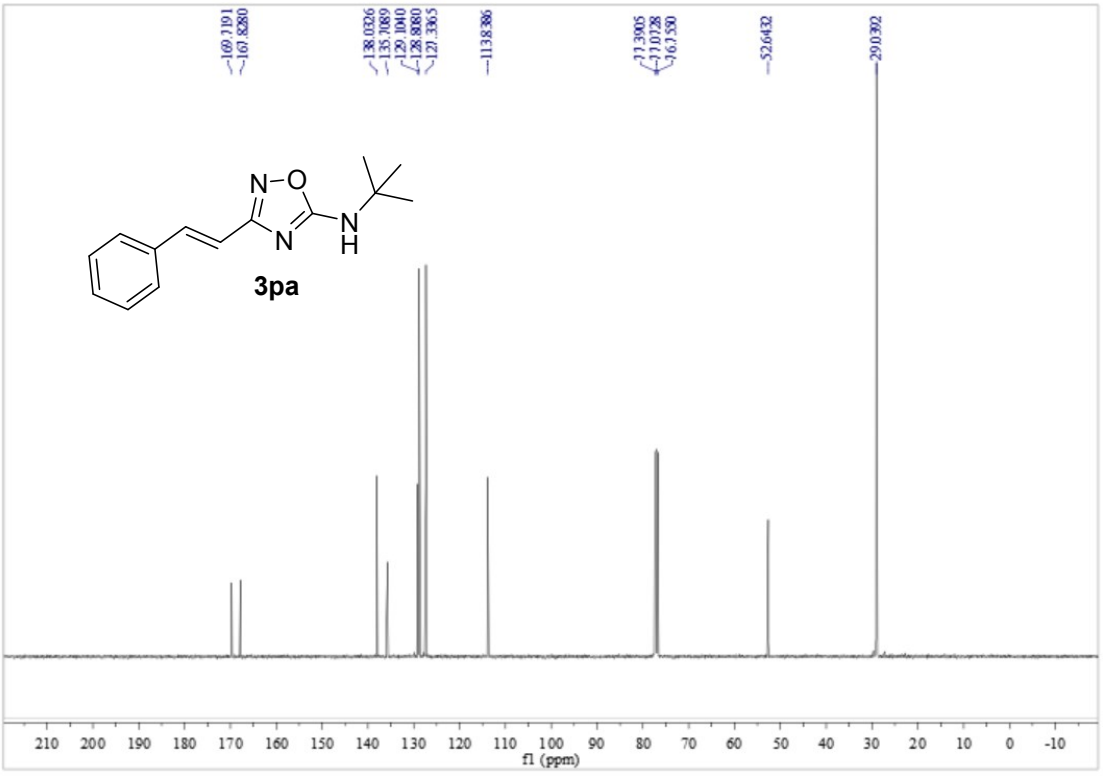
7.5426
7.5383
7.5254
7.3936
7.3902
7.3732
7.3543
7.3376
7.3262
7.3201
7.3126
7.3018
7.2999
6.9256
6.8853
5.4629
1.4612
3.04
3.09
1.08
1.00
9.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
N
O
N
N
H
3pa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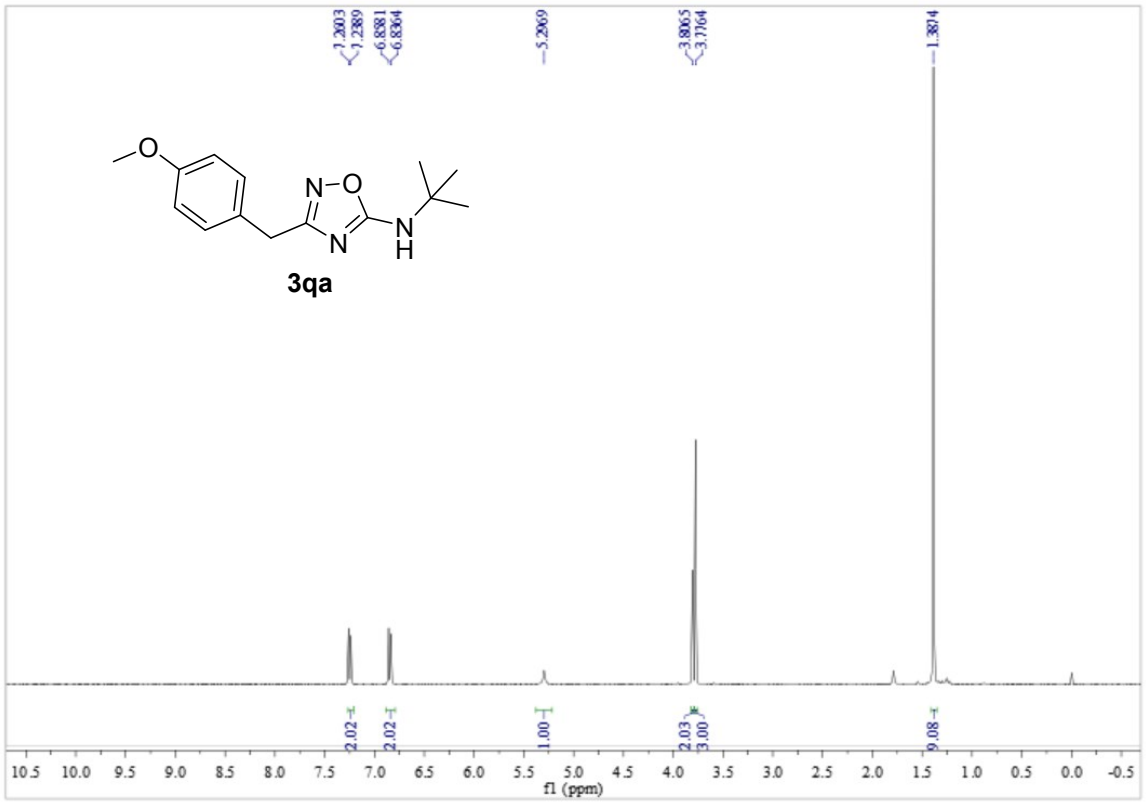
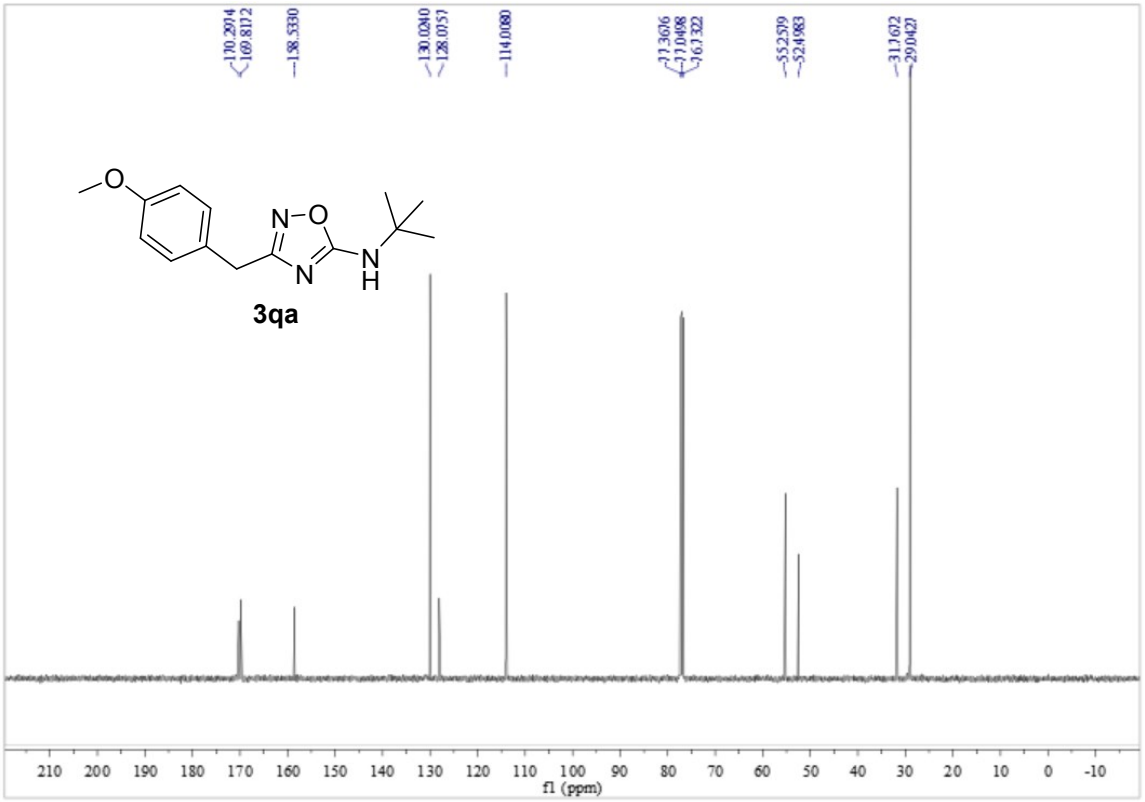
161.8280
138.0326
135.1089
129.1040
128.8980
127.3365
113.8386
77.3905
77.0728
76.7550
52.6432
29.0392
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
N
O
N
N
H
3pa


7.2003
7.2389
6.8881
6.8364
5.2069
3.8065
3.7764
1.3874
O
N
O
N
N
H
3qa
2.02
2.02
1.00
2.03
3.00
9.08
10.5 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
f1 (ppm)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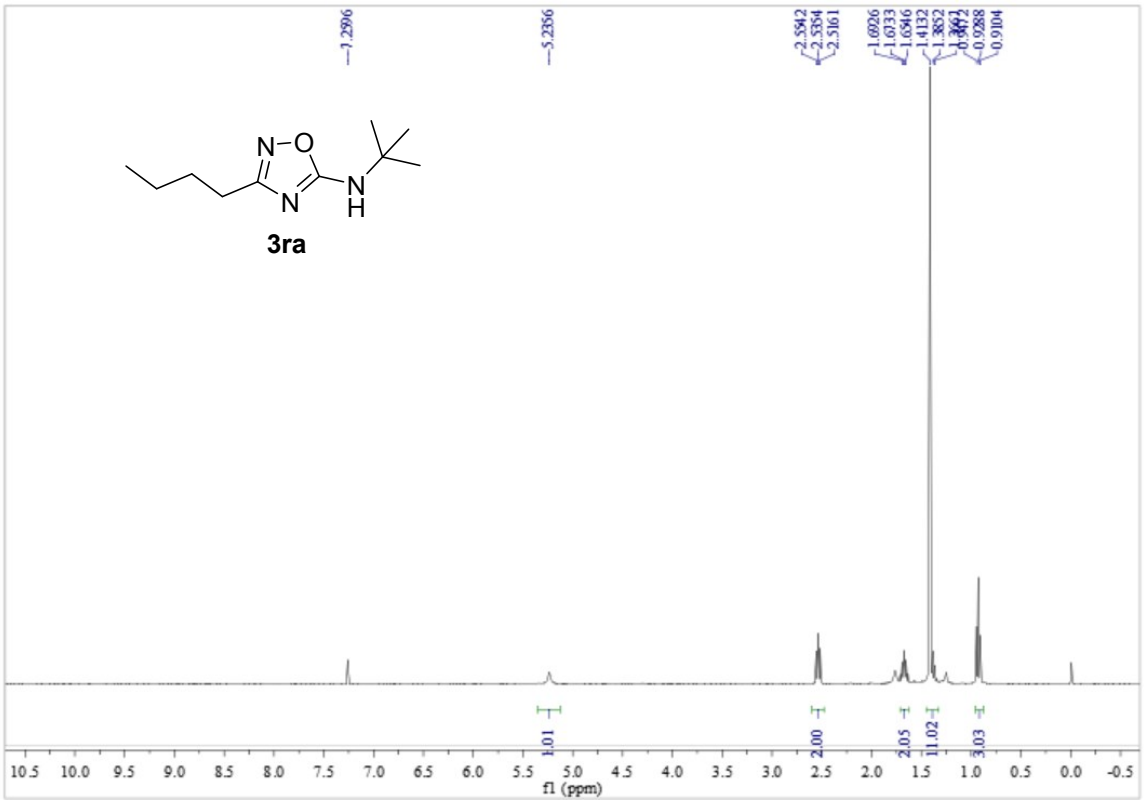
169.8172
158.5330
130.0240
128.0357
114.0080
77.3606
77.0498
76.7322
55.2539
52.4983
31.7612
29.0427
O
N
O
N
N
H
3qa
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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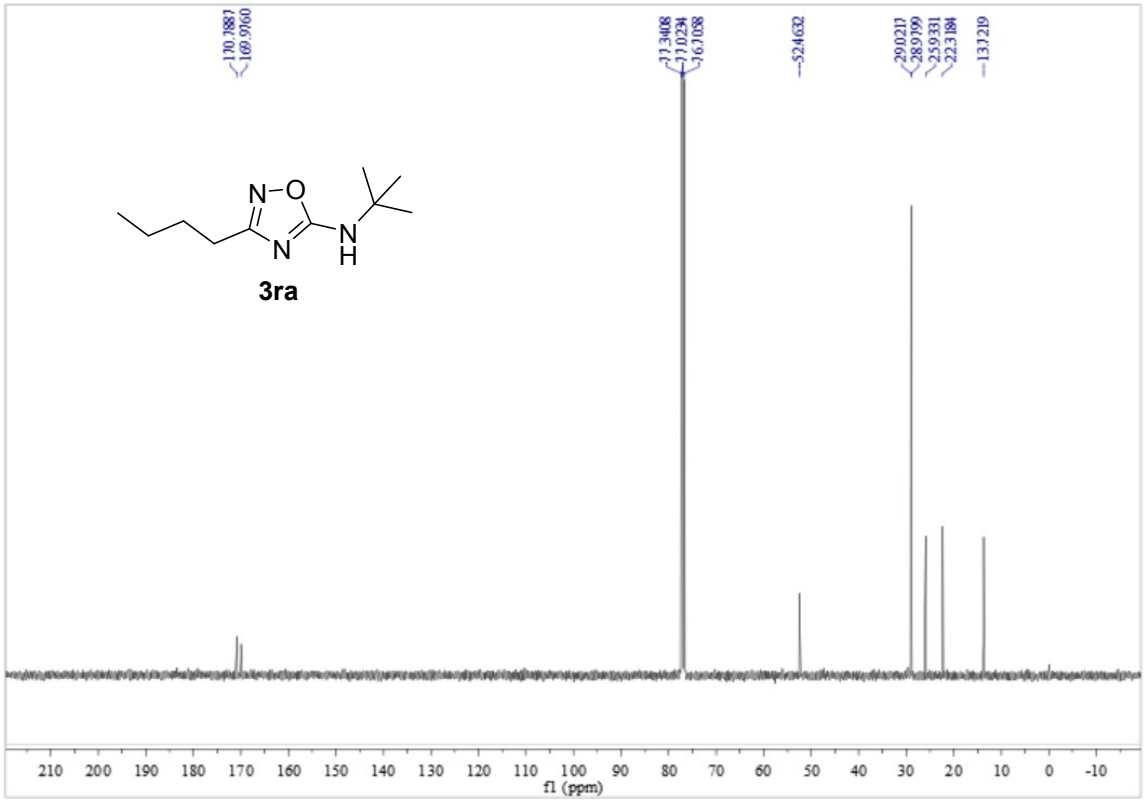
5.2356
2.5542
2.5354
2.5161
1.6926
1.6733
1.6546
1.4132
1.3852
0.9472
0.9288
0.9104
1.01
2.00
2.05
11.02
3.03
fl (ppm)

3ra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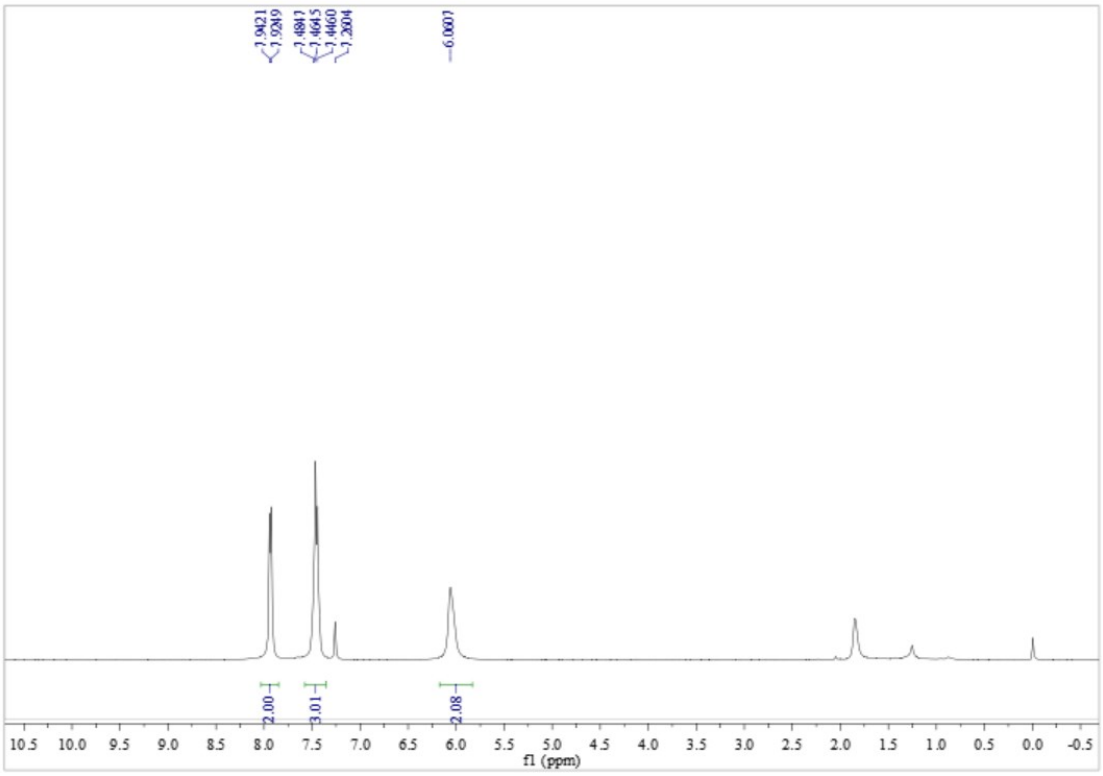
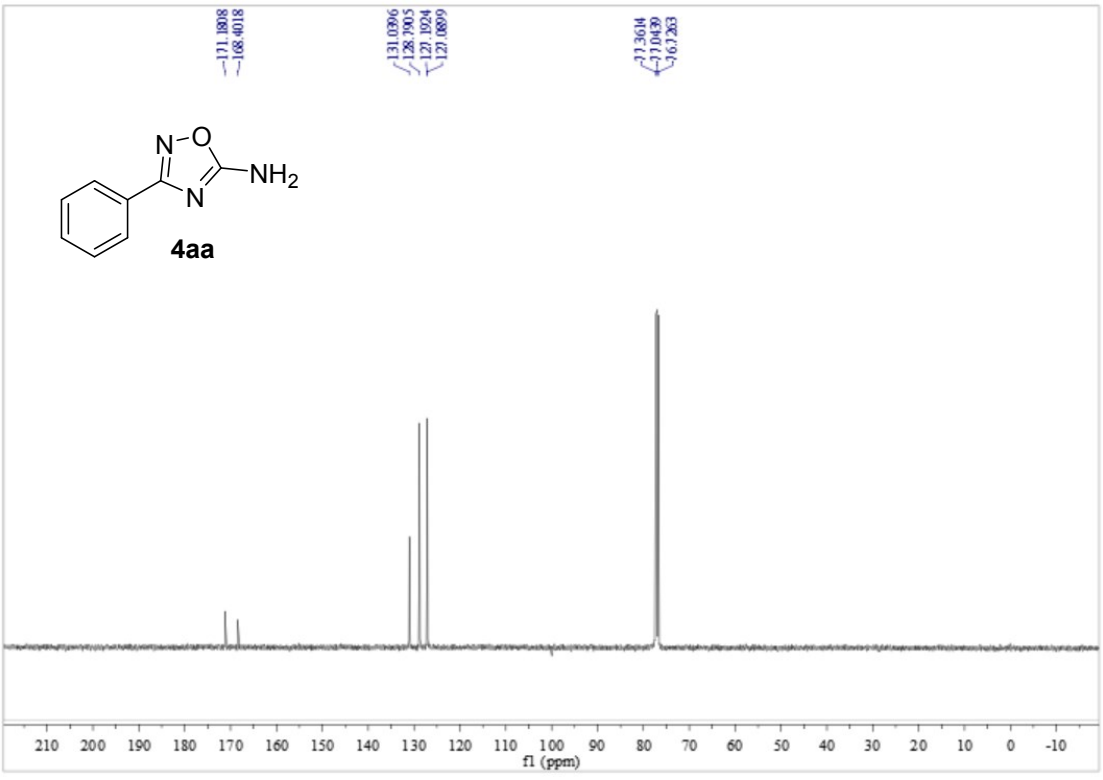
77.3408
77.0234
76.7058
52.4632
29.0217
28.9799
25.9331
22.3184
13.7219
fl (ppm)

3ra


7.9021
7.9249
7.4881
7.4645
7.4460
7.2604
6.0007
2.00
3.01
2.08
f1 (ppm)


171.1808
168.4018
131.0396
128.7905
127.1924
127.0899
31.3614
31.0439
16.7263
N
O
NH2
N
f1 (ppm)

4aa

5. References

1 V. Mercalli, A. Massarotti, M. Varese, M. Giustiniano, F. Meneghetti, E. Novellino and G. C. Tron, Multicomponent reaction of Z-chlorooximes, isocyanides, and hydroxylamines as hypernucleophilic traps. A one-pot route to aminodioximes and their transformation into 5-amino-1, 2, 4-oxadiazoles by mitsunobu–beckmann rearrangement, *J. Org. Chem.*, 2015, **80**, 9652-9661.