

Supporting Information

Thiols-promoted intermolecular cyclization to synthesize 1,2,4-oxadiazoles including *Tioxazafen* under transition metal-free conditions

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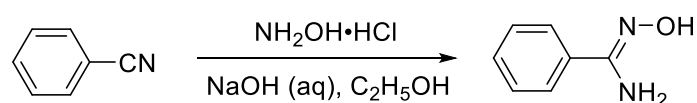
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1. General Information

^1H NMR, ^{13}C NMR, ^{19}F NMR were recorded in CDCl_3 at room temperature on the Bruker DPX-400 spectrometer (400 MHz, 101 MHz, 376 MHz). The chemical-shifts scale is based on internal TMS. Low-resolution mass spectra data were obtained by LC/MSD Trap XCT Melting points were measured using a WC-1 microscopic apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded on Thermo Scientific Q Exactive. All reactions were monitored and post-processing by TLC with Qingdao GF₂₅₄ silica gel-coated plates. Aryl nitriles and benzyl mercaptans were purchased from commercial suppliers such as Aladdin or J&K Scientific and used without further purification unless otherwise noted. The amidoximes were synthesized according to the synthetic methods reported in the literature (See 2.1).

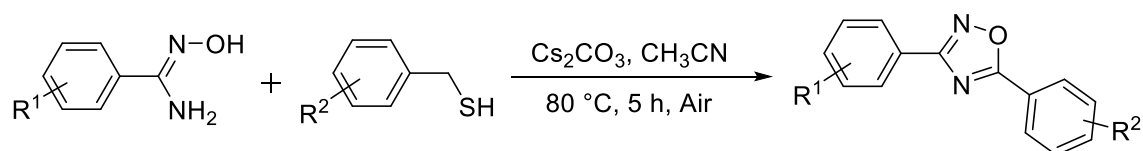
2. Experimental Procedure

2.1 Procedure for synthesis of amidoxime and its derivatives^[1]



In a round-bottom flask, under magnetic stirring, aryl nitrile (15 mmol) was dissolved in ethanol (25 mL), and to the solution hydroxylamine hydrochloride (2.085 g, 30 mmol) and aqueous NaOH (2 equiv., 10 mL) were added. The mixture was stirred at 80 °C for 2 to 3 h, and the reaction was monitored by TLC. Then, the solvent was removed by rotary evaporation and water was added to the crude mixture (20 mL). The mixture was extracted with ethyl acetate (3 x 10 mL) and the organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was removed by rotary evaporation and the crude product was purified through flash column chromatography on silica gel using petroleum ether/ethyl acetate = (1/1), and dried under reduced pressure.

2.2 Procedure for synthesis of 1,2,4-oxadiazole and its derivatives

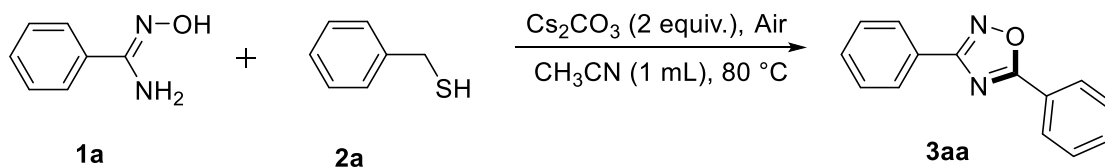


To a mixture of amidoxime (0.20 mmol), benzyl mercaptan (0.40 mmol), Cs_2CO_3 (130.3 mg, 2.0 equiv.), and CH_3CN (1 mL) were added in a 25 mL screw-cap Schlenk test tube. Then the mixture was stirred at 80 °C for 5 h under air atmosphere. The progress of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture was cooled to room temperature and then filtered with diatomite. The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by column chromatography to give the corresponding products (petroleum ether/dichloromethane = 3/1 - 5/1, 18%-95%).

3. Exploring the Mechanism

3.1 Exploring the Mechanism by high Resolution Mass Spectrometry Tracking

Experiments



A mixture of **1a** (0.2 mmol, 27.2 mg) and **2a** (0.4 mmol, 48 μ l), Cs_2CO_3 (130.3 mg), and CH_3CN (1.0 mL) was heated under an air atmosphere in a Schlenk tube at 80 °C. The reaction in sequence for 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, and 5 h. After the reaction was finished, the reaction mixture was cooled to room temperature. The mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The samples were detected by high resolution mass spectrometry. The test results are as follows.

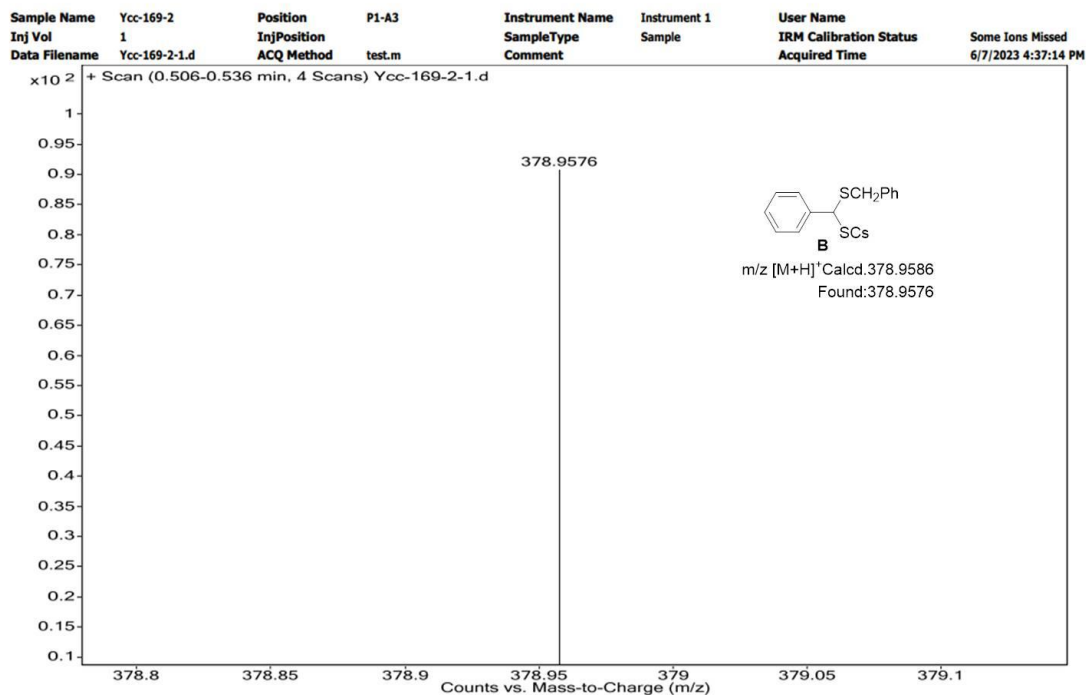


Figure 1 The mass spectrum for **2 h** of the reaction solution of **1a** and **2a**

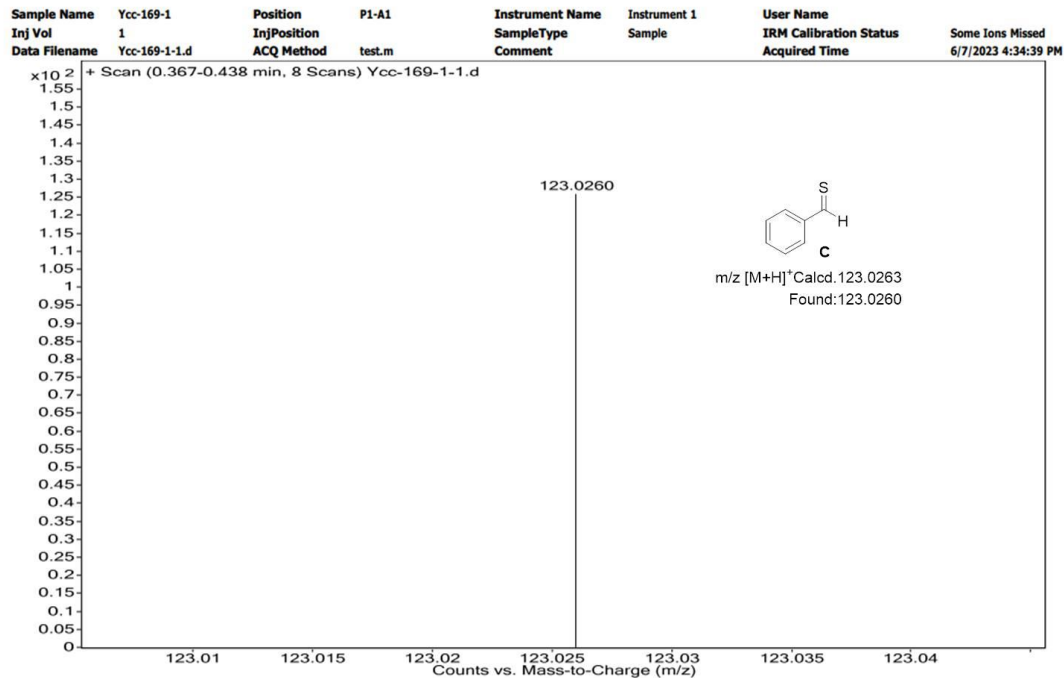


Figure 2 The mass spectrum for **1 h** of the reaction solution of **1a** and **2a**

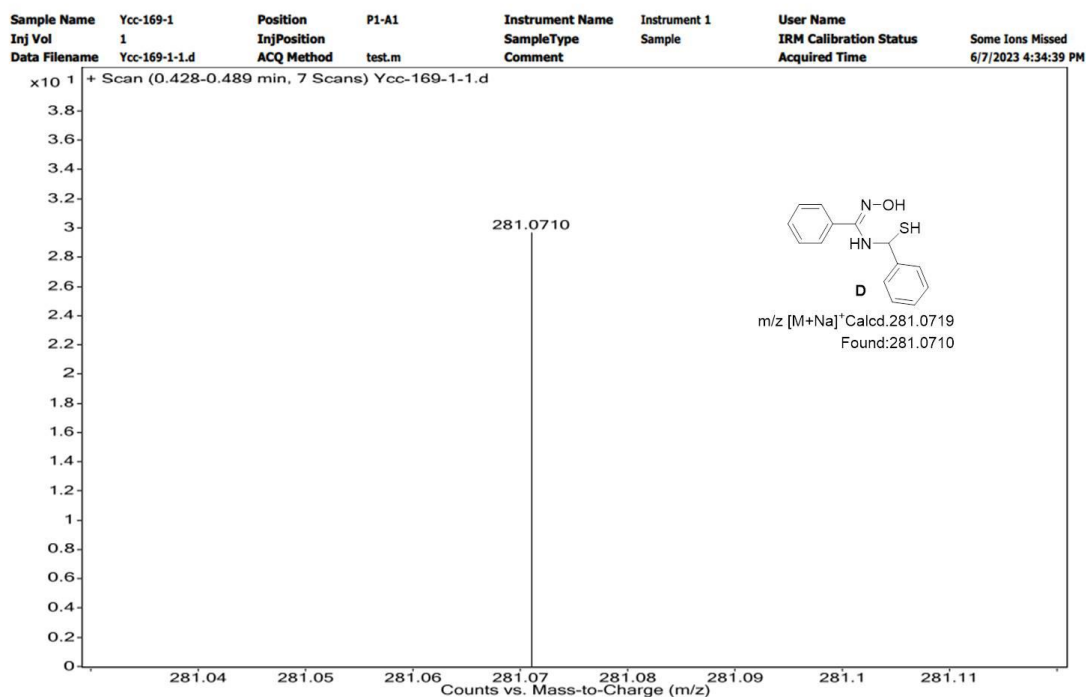


Figure 3 The mass spectrum for **1 h** of the reaction solution of **1a** and **2a**

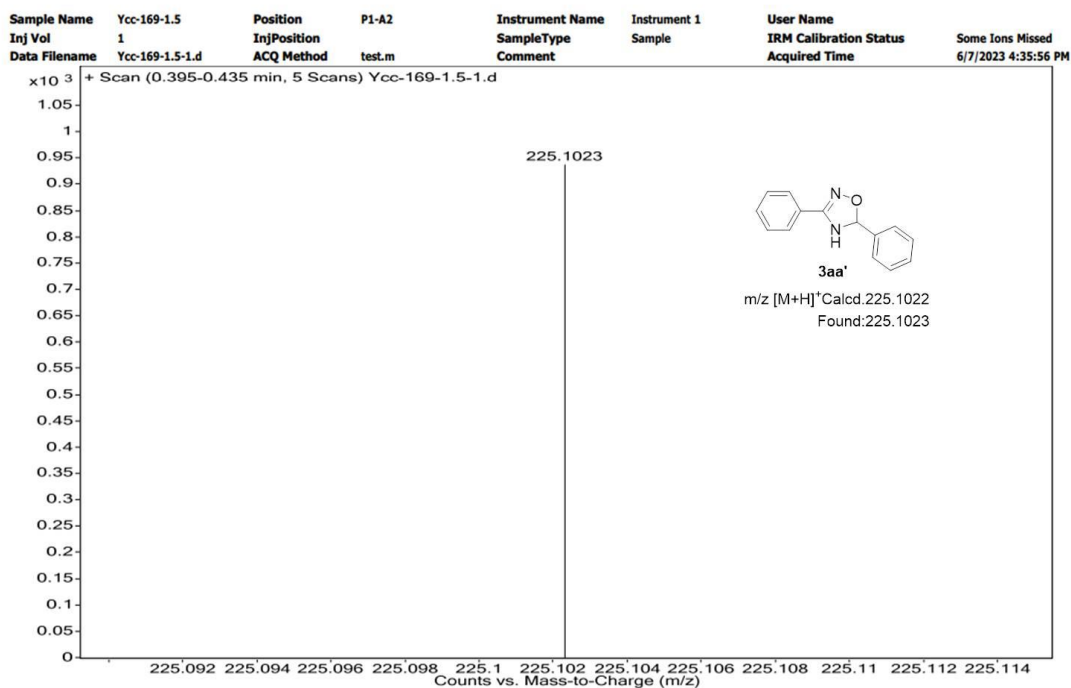


Figure 4 The mass spectrum for **1.5 h** of the reaction solution of **1a** and **2a**

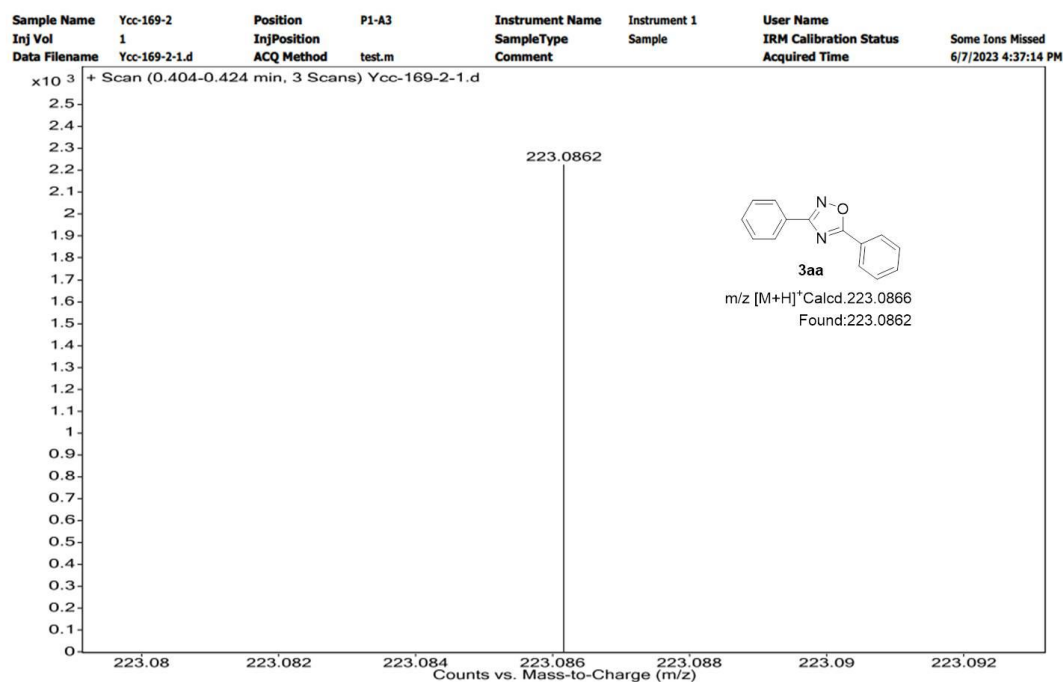
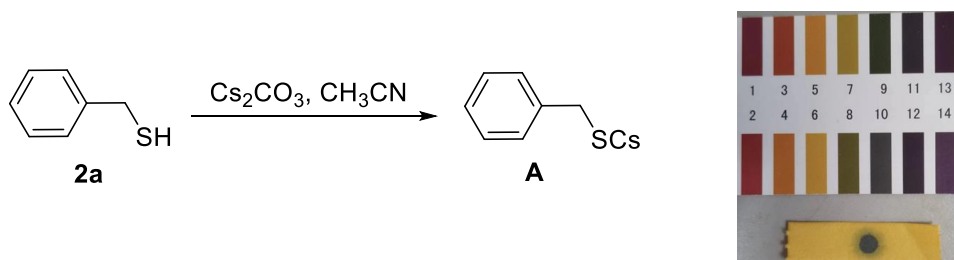


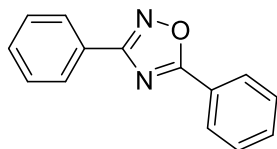
Figure 5 The mass spectrum for **2 h** of the reaction solution of **1a** and **2a**

3.2 Exploring the Mechanism by pH detection

Mix benzyl thiol (**2a**, 0.4 mmol, 48 μ l), Cs_2CO_3 (130.3 mg), and CH_3CN (1.0 mL) under an air atmosphere in a Schlenk tube. The pH of the mixed solution was detected to be 9, which further proved the possibility of producing intermediate **A**.

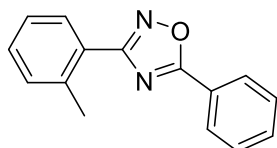


4. Characterization Data of Products



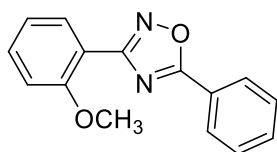
3,5-diphenyl-1,2,4-oxadiazole (3aa)^[2]

White solid; 95% yield (42.2 mg); mp: 107.5-109.1 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.23-8.17 (m, 4H), 7.62-7.48 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 175.73, 168.99, 132.75, 131.21, 129.12, 128.87, 128.19, 127.55, 127.00, 124.34.



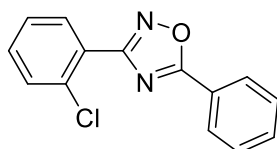
5-phenyl-3-(*o*-tolyl)-1,2,4-oxadiazole (3ba)^[3]

White solid; 70% yield (33.1 mg); mp: 110.3-111.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.21 (m, 2H), 8.10-8.08 (m, 1H), 7.62-7.52 (m, 3H), 7.42-7.38 (m, 1H), 7.35-7.33 (m, 2H), 2.69 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.73, 169.60, 138.28, 132.69, 131.40, 130.60, 129.12, 128.19, 126.26, 126.10, 124.37, 22.15.



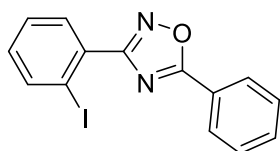
3-(2-methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (3ca)^[4]

White solid; 76% yield (38.4 mg); mp: 113.2-113.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.23-8.21 (m, 2H), 8.13-8.11 (m, 1H), 7.61-7.47 (m, 4H), 7.13-7.06 (m, 2H), 3.99 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.56, 167.46, 158.18, 132.61, 132.33, 131.44, 129.06, 128.20, 124.39, 120.71, 55.02.



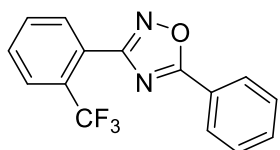
3-(2-chlorophenyl)-5-phenyl-1,2,4-oxadiazole (3da)^[5]

White solid; 86% yield (44.1 mg); mp: 86.7-87.7 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.23-8.21 (m, 2H), 8.03-8.01 (m, 1H), 7.63-7.59 (m, 1H), 7.57-7.53 (m, 3H), 7.47-7.39 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.28, 167.79, 133.55, 132.90, 131.79, 131.72, 130.95, 129.16, 128.24, 126.92, 126.29, 124.09.



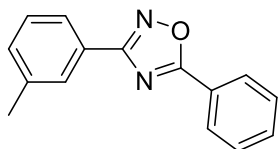
3-(2-iodophenyl)-5-phenyl-1,2,4-oxadiazole (3ea)

White solid; 66% yield (44.1 mg); mp: 68.3-68.9 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.24-8.21 (m, 2H), 8.06-8.04 (m, 1H), 7.83-7.80 (m, 1H), 7.64-7.51 (m, 3H), 7.49-7.47 (m, 1H), 7.21-7.17 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.47, 169.79, 140.90, 132.94, 132.23, 131.80, 131.45, 129.19, 128.26, 128.18, 124.12, 95.33; HRMS (m/z) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_9\text{IN}_2\text{O}$: 348.9832; found: 348.9832.



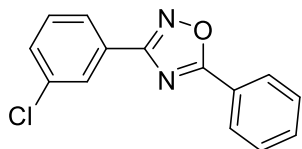
5-phenyl-3-(2-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3fa)

Colourless liquid; 76% yield (44.1mg); ^1H NMR (400 MHz, CDCl_3) δ 8.23-8.20 (m, 2H), 7.88-7.85 (m, 2H), 7.71-7.60 (m, 3H), 7.57-7.53 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.68, 168.15, 132.99, 131.87 (d, $J = 2.3$ Hz), 130.74, 129.52 (q, $J = 32.1$ Hz) 129.19, 128.25, 126.92 (q, $J = 5.3$ Hz), 125.86 (d, $J = 1.9$ Hz), 123.98, 123.48 (q, $J = 273.6$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -58.70; HRMS (m/z) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_9\text{F}_3\text{N}_2\text{O}$: 291.0740; found: 291.0740.



5-phenyl-3-(*m*-tolyl)-1,2,4-oxadiazole (3ga)^[2]

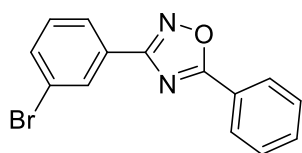
White solid; 88% yield (41.5 mg); mp: 85.1-85.5 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.23-8.21 (m, 2H), 8.00-7.97 (m, 2H), 7.62-7.52 (m, 3H), 7.39 (t, $J = 7.7$ Hz, 1H), 7.32 (d, $J = 7.7$ Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.65, 169.09, 138.66, 132.72, 131.99, 129.11, 128.79, 128.18, 128.09, 126.84, 124.68, 124.36, 21.40.



3-(3-chlorophenyl)-5-phenyl-1,2,4-oxadiazole (3ha)^[5]

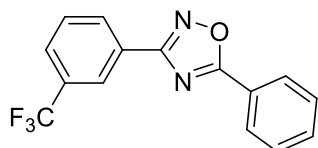
White solid; 90% yield (46.1 mg); mp: 102.1-103.2 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.21-8.17 (m, 3H), 8.07-8.04 (m, 1H), 7.63-7.60 (m, 1H), 7.56-7.52 (m, 2H),

7.50-7.47 (m, 1H), 7.43 (t, $J = 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.98, 167.97, 134.96, 132.92, 131.23, 130.18, 129.16, 128.72, 128.20, 127.65, 125.58, 124.10.



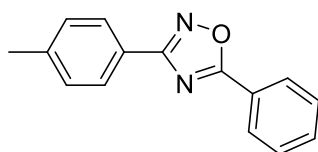
3-(3-bromophenyl)-5-phenyl-1,2,4-oxadiazole (3ia)^[6]

White solid; 84% yield (50.3 mg); mp: 91.5-92.4 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.33 (t, $J = 1.6$ Hz, 1H), 8.21-8.19 (m, 2H), 8.09 (d, $J = 7.7$ Hz, 1H), 7.65-7.59 (m, 2H), 7.56-7.52 (m, 2H), 7.37 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.98, 167.84, 134.16, 132.93, 130.53, 130.42, 129.16, 128.94, 128.20, 126.03, 124.09, 122.96.



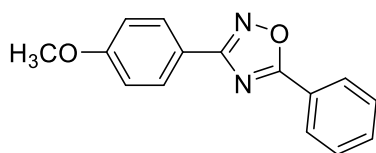
3-phenyl-3-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3ja)^[7]

White solid; 78% yield (45.2 mg); mp: 90.6-91.8 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.45 (s, 1H), 8.35 (d, $J = 8.0$ Hz, 1H), 8.23-8.21 (m, 2H), 7.77 (d, $J = 7.7$ Hz, 1H), 7.65-7.60 (m, 2H), 7.57-7.53 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.17, 167.94, 132.99, 131.46 (q, $J = 33.1$ Hz), 130.62, 129.44, 129.18, 128.22, 127.89, 127.75 (q, $J = 5.5$ Hz), 124.52 (q, $J = 3.9$ Hz), 124.01, 123.81 (q, $J = 273.2$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -62.79.



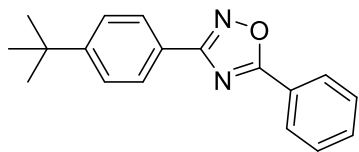
5-phenyl-3-(p-tolyl)-1,2,4-oxadiazole (3ka)^[2]

White solid; 81% yield (38.2 mg); mp: 101.0-102.1 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.22-8.19 (m, 2H), 8.06 (d, $J = 8.1$ Hz, 2H), 7.61-7.51 (m, 3H), 7.30 (d, $J = 8.1$ Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.56, 168.99, 141.51, 132.68, 129.58, 129.09, 128.17, 127.47, 124.41, 124.17, 21.62.



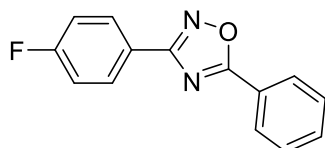
3-(4-methoxyphenyl)-5-phenyl-1,2,4-oxadiazole (3la)^[3]

White solid; 74% yield (37.3 mg); mp: 101.4-102.1 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.21-8.19 (m, 2H), 8.11 (d, *J* = 8.7 Hz, 2H), 7.61-7.51 (m, 3H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.44, 168.67, 161.94, 132.65, 129.14, 129.08, 128.15, 124.43, 119.45, 114.25, 55.40.



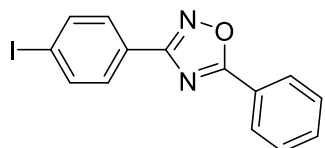
3-(4-(*tert*-butyl)phenyl)-5-phenyl-1,2,4-oxadiazole (3ma)^[8]

White solid; 90% yield (50 mg); mp: 135.5-136.7 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.23-8.21 (m, 2H), 8.11-8.09 (m, 2H), 7.61-7.52 (m, 5H), 1.37 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 175.56, 168.94, 154.61, 132.67, 129.09, 128.19, 127.34, 125.84, 124.44, 124.15, 35.10, 31.22.



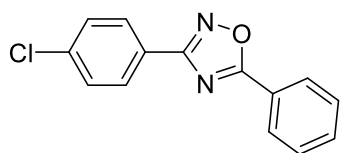
3-(4-fluorophenyl)-5-phenyl-1,2,4-oxadiazole (3na)^[8]

White solid; 81% yield (39.1 mg); mp: 111.3-112.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.21-8.15 (m, 4H), 7.62-7.52 (m, 3H), 7.22-7.16 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.80, 168.15, 164.60 (d, *J* = 254.5 Hz), 132.82, 129.69 (d, *J* = 8.8 Hz), 129.13, 128.17, 124.21, 123.22 (d, *J* = 3.1 Hz), 116.04 (d, *J* = 22.1 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -108.52.



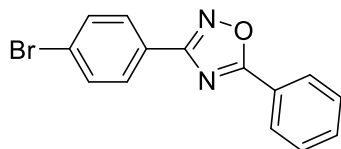
3-(4-iodophenyl)-5-phenyl-1,2,4-oxadiazole (3oa)

White solid; 91% yield (63.3 mg); mp: 126.4-126.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.21-8.19 (m, 2H), 7.91-7.84 (m, 4H), 7.63-7.59 (m, 1H), 7.57-7.53 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.93, 168.41, 138.12, 132.90, 129.16, 129.05, 128.20, 126.49, 124.14, 97.92; HRMS (*m/z*) [M+H]⁺ calculated for C₁₄H₉IN₂O: 348.9832; found: 348.9832.



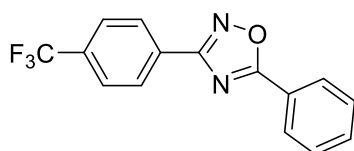
3-(4-chlorophenyl)-5-phenyl-1,2,4-oxadiazole (3pa)^[8]

White solid; 86% yield (47.4 mg); mp: 101.1-101.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.21-8.19 (m, 2H), 8.11 (d, *J* = 8.7 Hz, 2H), 7.63-7.53 (m, 3H), 7.49-7.47 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.90, 168.17, 137.34, 132.88, 129.19, 129.15, 128.85, 128.19, 125.49, 124.15.



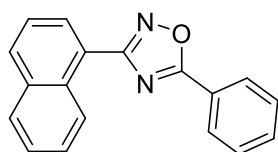
3-(4-bromophenyl)-5-phenyl-1,2,4-oxadiazole (3qa)^[8]

White solid; 79% yield (24 mg); mp: 110.8-112.1 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.22-8.20 (m, 2H), 8.06-8.04 (m, 2H), 7.66-7.64 (m, 2H), 7.62-7.60 (m, 1H), 7.58-7.54 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 175.94, 168.27, 132.90, 132.16, 129.16, 129.04, 128.20, 125.94, 125.76, 124.14.



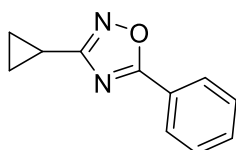
5-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3ra)^[9]

White solid; 90% yield (52.2 mg); mp: 125.2-126.7 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.29 (d, *J* = 8.1 Hz, 2H), 8.22-8.20 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.64-7.60 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 176.18, 167.96, 133.01, 132.89 (d, *J* = 32.7 Hz), 130.39, 129.19, 128.21, 127.88, 125.84 (q, *J* = 8.1 Hz), 124.02, 123.82 (d, *J* = 272.1 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.94



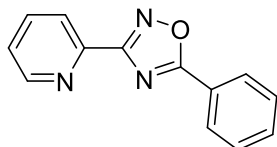
3-(naphthalen-1-yl)-5-phenyl-1,2,4-oxadiazole (3sa)^[8]

White solid; 73% yield (48.4 mg); mp: 121.7-122.1 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.98 (d, *J* = 8.5 Hz, 1H), 8.36 (d, *J* = 7.3 Hz, 1H), 8.29-8.26 (m, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.67-7.54 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 174.90, 169.43, 133.94, 132.82, 131.86, 130.74, 129.46, 129.18, 128.69, 128.29, 127.60, 126.35 (d, *J* = 8.2 Hz), 125.16, 124.31, 123.99.

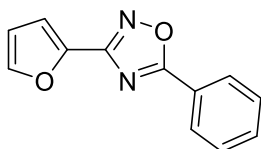


3-cyclopropyl-5-phenyl-1,2,4-oxadiazole (3ta)^[10]

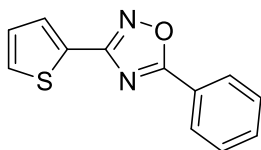
White solid; 51% yield (19.0 mg); mp: 35.8-36.3 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.09-8.07 (m, 2H), 7.59-7.54 (m, 1H), 7.52-7.48 (m, 2H), 2.18-2.12 (m, 1H), 1.15-1.06 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 175.14, 173.06, 132.51, 128.99, 128.03, 124.41, 7.76, 6.94.

**5-phenyl-3-(pyridin-2-yl)-1,2,4-oxadiazole (3ua)**^[5]

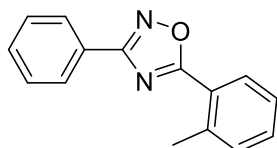
Yellow solid; 91% yield (40.7 mg); mp: 131.4-131.7 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.85-8.84 (m, 1H), 8.29-8.27 (m, 2H), 8.23-8.21 (m, 1H), 7.90-7.85 (m, 1H), 7.64-7.59 (m, 1H), 7.57-7.53 (m, 2H), 7.47-7.43 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 176.47, 168.78, 150.44, 146.46, 137.06, 132.95, 129.10, 128.33, 125.53, 123.99, 123.26.

**3-(furan-2-yl)-5-phenyl-1,2,4-oxadiazole (3va)**

White solid; 87% yield (36.9 mg); mp: 119.3-119.6 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.21-8.19 (m, 2H), 7.64 (d, *J* = 1.0 Hz, 1H), 7.63-7.59 (m, 1H), 7.54 (t, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 3.3 Hz, 1H), 6.59 (q, *J* = 1.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 175.74, 161.90, 145.20, 142.40, 132.98, 129.13, 128.26, 123.87, 113.78, 111.87; HRMS (*m/z*) [*M*+*H*]⁺ calculated for C₁₂H₈N₂O₂: 213.0659; found: 213.0660.

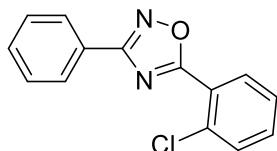
**5-phenyl-3-(thiophen-2-yl)-1,2,4-oxadiazole (3wa)**^[11]

White solid; 92% yield (42.0 mg); mp: 131.2-131.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.18 (m, 2H), 7.88-7.87 (m, 1H), 7.62-7.58 (m, 1H), 7.55-7.51 (m, 3H), 7.18-7.16 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 175.64, 165.05, 132.89, 129.64, 129.28, 129.12, 128.56, 128.24, 127.99, 124.03.

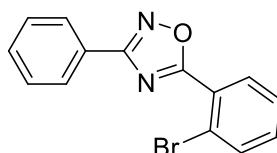


3-phenyl-5-(*o*-tolyl)-1,2,4-oxadiazole (3ab)^[2]

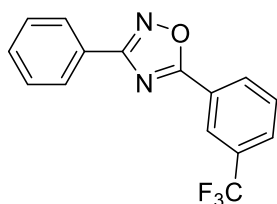
White solid; 44% yield (23.1 mg); mp: 55.2-55.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.15 (m, 3H), 7.52-7.45 (m, 4H), 7.38-7.35 (m, 2H), 2.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.36, 168.61, 139.17, 132.21, 131.92, 131.15, 130.22, 128.86, 127.54, 127.14, 126.29, 123.49, 21.99.

**5-(2-chlorophenyl)-3-phenyl-1,2,4-oxadiazole (3ac)**^[12]

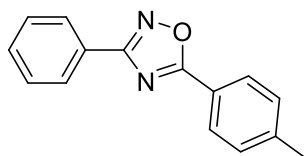
Colourless liquid; 32% yield (25.7 mg); mp: 55.1-56.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.18 (m, 2H), 8.17-8.14 (m, 1H), 7.61-7.58 (m, 1H), 7.54-7.50 (m, 4H), 7.47-7.43 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 176.34, 168.72, 133.91, 133.14, 131.95, 131.47, 131.31, 128.91, 127.60, 127.11, 126.78, 123.70.

**5-(2-bromophenyl)-3-phenyl-1,2,4-oxadiazole (3ad)**^[8]

Colourless liquid; 29% yield (17.5 mg); mp: 60.8-62.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.18 (m, 2H), 8.10-8.07 (m, 1H), 7.81-7.79 (m, 1H), 7.54-7.48 (m, 4H), 7.46-7.41 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 176.89, 168.72, 134.81, 133.14, 132.17, 131.33, 128.91, 128.19, 127.60, 126.76, 125.81, 122.17.

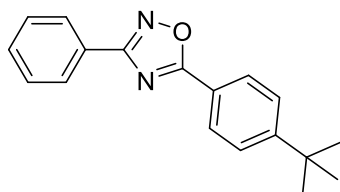
**3-phenyl-5-(3-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3ae)**^[13]

White solid; 78% yield (44.3 mg); mp: 94.4-95.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 8.39 (d, *J* = 7.7 Hz, 1H), 8.19-8.16 (m, 2H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.53-7.51 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.34, 169.18, 131.87 (q, *J* = 34.4 Hz), 131.44, 131.21, 129.84, 129.22 (q, *J* = 3.6 Hz), 128.94, 127.57, 126.58, 125.14 (q, *J* = 3.8 Hz), 123.49 (d, *J* = 272.54 Hz), 119.42; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.93



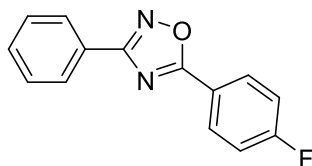
3-phenyl-5-(*p*-tolyl)-1,2,4-oxadiazole (3af)^[2]

White solid; 75% yield (35.4 mg); mp: 115.6-116.7 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.18-8.16 (m, 2H), 8.09 (d, *J* = 8.1 Hz, 2H), 7.51-7.49 (m, 3H), 7.33 (d, *J* = 7.7 Hz, 2H), 2.43 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.86, 168.89, 143.50, 131.14, 129.83, 128.85, 128.15, 127.54, 127.10, 121.59, 21.79.



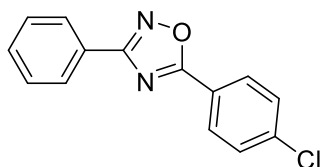
5-(4-(*tert*-butyl)phenyl)-3-phenyl-1,2,4-oxadiazole (3ag)

Colourless liquid; 67% yield (37.3 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.19-8.17 (m, 2H), 8.14 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.51-7.50 (m, 3H), 1.37 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 175.81, 168.92, 156.50, 131.14, 128.85, 128.04, 127.56, 127.12, 126.11, 121.55, 35.22, 31.12; HRMS (*m/z*) [M+H]⁺ calculated for C₁₈H₁₈N₂O: 279.1492; found: 279.1494.



5-(4-fluorophenyl)-3-phenyl-1,2,4-oxadiazole (3ai)^[8]

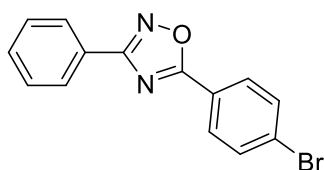
Yellow solid; 21% yield (10.0 mg); mp: 108.3-109.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.27-8.22 (m, 2H), 8.18-8.15 (m, 2H), 7.54-7.49 (m, 3H), 7.26-7.23 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 174.81, 169.02, 165.49 (d, *J* = 256.54 Hz), 131.28, 130.63 (d, *J* = 8.7 Hz), 128.89, 127.53, 126.84, 120.70 (d, *J* = 3.3 Hz), 116.51 (d, *J* = 22.3 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -105.13.



5-(4-chlorophenyl)-3-phenyl-1,2,4-oxadiazole (3aj)^[8]

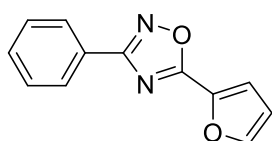
White solid; 60% yield (30.6 mg); mp: 125.6-126.4 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.18 (m, 2H), 8.17-8.14 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 174.80,

169.05, 139.19, 131.32, 129.53, 129.46, 128.90, 127.53, 126.77, 122.77.



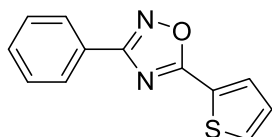
5-(4-bromophenyl)-3-phenyl-1,2,4-oxadiazole (3ak)^[14]

White solid; 43% yield (25.8 mg); mp: 116.8-118.1 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.17-8.14 (m, 2H), 8.09-8.06 (m, 2H), 7.71-7.68 (m, 2H), 7.53-7.48 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.91, 169.08, 132.51, 131.33, 129.57, 128.91, 127.75, 127.54, 126.75, 123.20.



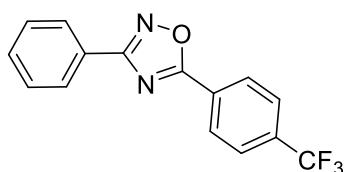
5-(furan-2-yl)-3-phenyl-1,2,4-oxadiazole (3al)^[2]

Yellow solid; 76% yield (32.2 mg); mp: 99.1-100.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.18-8.15 (m, 2H), 7.72 (s, 1H), 7.53-7.49 (m, 3H), 7.38 (d, *J* = 3.4 Hz, 1H), 6.66-6.65 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 168.70, 167.60, 146.74, 140.16, 131.38, 128.88, 127.63, 126.49, 116.64, 112.54.



3-phenyl-5-(thiophen-2-yl)-1,2,4-oxadiazole (3am)^[2]

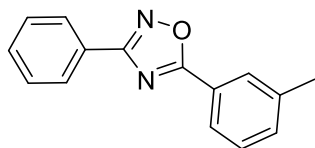
White solid; 56% yield (25.5 mg); mp: 106.7-107.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.16-8.14 (m, 2H), 7.96 (dd, *J* = 1.1, 3.8 Hz, 1H), 7.65 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.53-7.48 (m, 3H), 7.23-7.21 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 171.37, 168.87, 131.96, 131.89, 131.27, 128.85, 128.52, 127.59, 126.71, 125.92.



3-phenyl-5-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3ao)^[8]

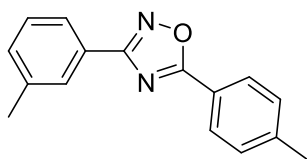
White solid; 64% yield (37.3mg); mp: 101.0-102.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.33 (d, *J* = 8.2 Hz, 2H), 8.18-8.16 (m, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.54-7.49 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) 174.37, 169.23, 134.25 (q, *J* = 32.8 Hz), 131.44,

128.94, 128.55 127.56, 127.44, 126.59, 126.16 (q, $J = 3.8$ Hz), 123.52 (q, $J = 271.7$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -63.19.



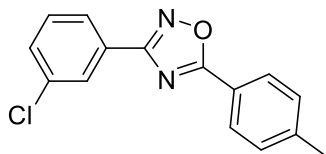
3-phenyl-5-(*m*-tolyl)-1,2,4-oxadiazole (3an)^[2]

White solid; 73% yield (34.5 mg); mp: 71.2-72.0 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.19-8.16 (m, 2H), 8.03-7.80 (m, 2H), 7.51-7.47 (m, 3H), 7.44-7.38 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.92, 168.93, 139.03, 133.56, 131.16, 129.02, 128.86 128.68, 127.54, 127.05, 125.33, 124.21, 21.34.



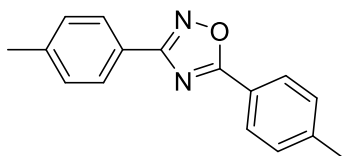
3-(*m*-tolyl)-5-(*p*-tolyl)-1,2,4-oxadiazole (3gf)^[3]

Yellow solid solid; 72% yield (43.1 mg); mp: 123.7-124.5 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.10 (d, $J = 8.2$ Hz, 2H), 7.99-7.96 (m, 2H), 7.39 (t, $J = 7.5$ Hz, 1H), 7.33 (t, $J = 8.2$ Hz, 3H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.79, 168.99, 143.46, 138.62, 131.92, 129.81, 128.76, 128.15, 128.07, 126.94, 124.66, 121.63, 21.78, 21.39.



3-(3-chlorophenyl)-5-(*p*-tolyl)-1,2,4-oxadiazole (3hf)^[15]

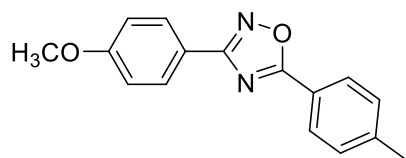
White solid; 62% yield (44.4 mg); mp: 103.8-104.2 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (t, $J = 1.6$ Hz, 1H), 8.08 (d, $J = 8.1$ Hz, 2H), 8.06-8.03 (m, 1H), 7.50-7.47 (m, 1H), 7.43 (t, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.13, 167.89, 143.73, 134.93, 131.16, 130.16, 129.87, 128.83, 128.17, 127.65, 125.57, 121.37, 21.80.



3,5-di-*p*-tolyl-1,2,4-oxadiazole (3kf)^[3]

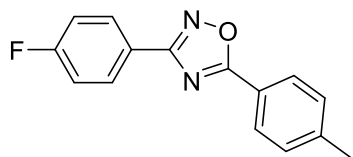
White solid; 68% yield (43.1 mg); mp: 135.1-135.7 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.07 (q, $J = 8.1$ Hz, 4H), 7.34-7.29 (m, 4H), 2.42 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.69, 168.89, 143.40, 141.42, 129.79, 129.55, 128.13, 127.45,

124.27, 121.67, 21.77, 21.61.



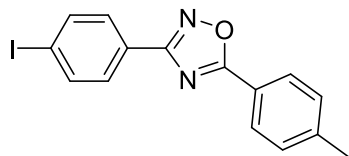
3-(4-methoxyphenyl)-5-(p-tolyl)-1,2,4-oxadiazole (3lf)^[16]

White solid; 68% yield (43.6 mg); mp: 113.4-113.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.09 (t, *J* = 8.7 Hz, 4H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.58, 168.58, 161.89, 143.37, 129.78, 129.12, 128.12, 121.70, 119.56, 114.22, 55.39, 21.77.



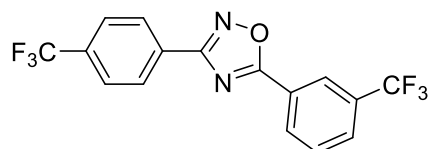
3-(4-fluorophenyl)-5-(p-tolyl)-1,2,4-oxadiazole (3nf)^[17]

White solid; 74% yield (37.5 mg); mp: 120.1-120.4 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.18-8.14 (m, 2H), 8.08 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.21-7.15 (m, 2H), 3.09 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.94, 168.05, 164.56 (d, *J* = 250.7 Hz), 143.60, 129.83, 129.66 (d, *J* = 8.5 Hz), 128.13, 123.33 (d, *J* = 3.1 Hz), 121.47, 116.00 (d, *J* = 22.0 Hz), 21.77; ¹⁹F NMR (376 MHz, CDCl₃) δ -108.68.



3-(4-iodophenyl)-5-(p-tolyl)-1,2,4-oxadiazole (3of)

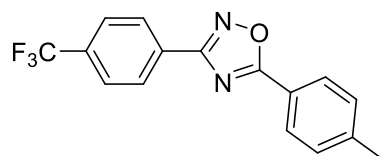
White solid; 76% yield (23.1 mg); mp: 144.8-145.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 8.1 Hz, 2H), 7.90-7.83 (m, 4H), 7.34 (d, *J* = 8.1 Hz, 2H), 2.45 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.06, 168.32, 143.69, 138.08, 129.86, 129.04, 128.16, 126.60, 121.40, 97.82, 21.80; HRMS (m/z) [M+H]⁺ calculated for C₁₅H₁₁IN₂O: 362.9989; found: 362.9988.



5-(3-(trifluoromethyl)phenyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3re)

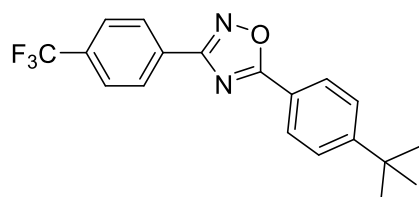
White solid; 98% yield (45.7 mg); mp: 104.2-104.7 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 8.39 (d, *J* = 7.9 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 2H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.73 (t, *J* = 7.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ

174.84, 168.20, 133.18 (q, $J = 32.5$ Hz), 132.02 (q, $J = 33.2$ Hz), 131.26, 129.96, 129.51 (q, $J = 3.6$ Hz), 128.71, 127.95, 125.95 (q, $J = 3.7$ Hz), 125.21 (q, $J = 4.0$ Hz), 124.83, 123.78 (q, $J = 271.3$ Hz), 123.45 (q, $J = 271.9$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -62.99, -63.03; HRMS (m/z) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{16}\text{H}_8\text{F}_6\text{N}_2\text{O}$: 359.0614; found: 359.0612.



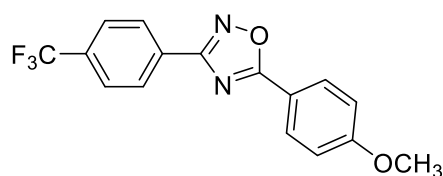
3-(*p*-tolyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3rf)^[19]

White solid; 72% yield (49.2 mg); mp: 107.2-107.7 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.29 (d, $J = 8.1$ Hz, 2H), 8.10 (d, $J = 8.4$ Hz, 2H), 7.76 (d, $J = 8.1$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.33, 167.88, 143.85, 132.83 (q, $J = 32.0$ Hz), 130.51, 129.90, 128.19, 127.87, 125.82 (q, $J = 3.7$ Hz), 123.83 (q, $J = 272.3$ Hz), 121.29, 21.80; ^{19}F NMR (376 MHz, CDCl_3) δ -62.94.



5-(4-(*tert*-butyl)phenyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3rg)

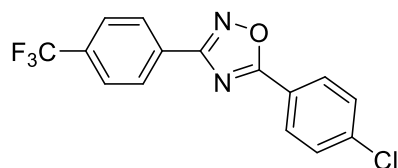
White solid; 69% yield (58.8 mg); mp: 103.2-103.7 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, $J = 7.9$ Hz, 2H), 8.14 (d, $J = 8.5$ Hz, 2H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.59-7.57 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.28, 167.91, 156.85, 132.83 (q, $J = 32.3$ Hz), 130.53, 128.08, 127.90, 126.19, 125.82 (q, $J = 3.6$ Hz), 123.84 (d, $J = 273.7$ Hz), 121.23, 35.26, 31.09; ^{19}F NMR (376 MHz, CDCl_3) δ -62.93; HRMS (m/z) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}$: 347.1366; found: 347.1365.



5-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3rh)^[7]

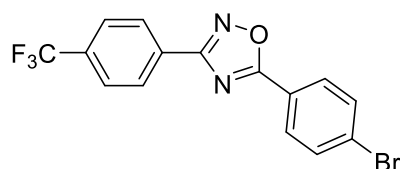
White solid; 78% yield (49.9 mg); mp: 142.9-143.4 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.27 (d, $J = 8.0$ Hz, 2H), 8.15 (d, $J = 9.0$ Hz, 2H), 7.75 (d, $J = 8.3$ Hz, 2H), 7.03 (d,

$J = 8.6$ Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.04, 167.79, 163.37, 132.76 (q, $J = 32.3$ Hz), 130.58, 130.13, 127.84, 125.78 (q, $J = 3.8$ Hz), 123.80 (q, $J = 272.3$ Hz), 116.53, 114.58, 55.53; ^{19}F NMR (376 MHz, CDCl_3) δ -62.93.



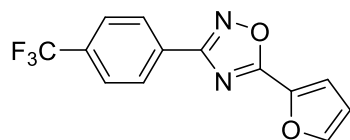
5-(4-chlorophenyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3rj)^[18]

White solid; 58% yield (37.6 mg); mp: 121.5-122.1 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.27 (d, $J = 8.2$ Hz, 2H), 8.16-8.13 (m, 2H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.55-7.52 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.26, 168.03, 139.52, 133.01 (q, $J = 32.4$ Hz), 130.15, 129.62, 129.48, 127.87, 125.88 (q, $J = 3.7$ Hz), 123.78 (q, $J = 273.8$ Hz), 122.43. ^{19}F NMR (376 MHz, CDCl_3) δ -62.98.



5-(4-bromophenyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3rk)

White solid; 44% yield (32 mg); mp: 128.6-128.9 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.28 (d, $J = 7.9$ Hz, 2H), 8.09-8.06 (m, 2H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.72-7.69 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.38, 168.06, 133.03 (q, $J = 32.4$ Hz), 132.60, 130.13, 129.58, 128.08, 127.88, 125.89 (q, $J = 3.7$ Hz), 123.77 (d, $J = 271.9$ Hz), 122.86. ^{19}F NMR (376 MHz, CDCl_3) δ -62.98; HRMS (m/z) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_8\text{BrF}_3\text{N}_2\text{O}$: 368.9845; found: 368.9845.

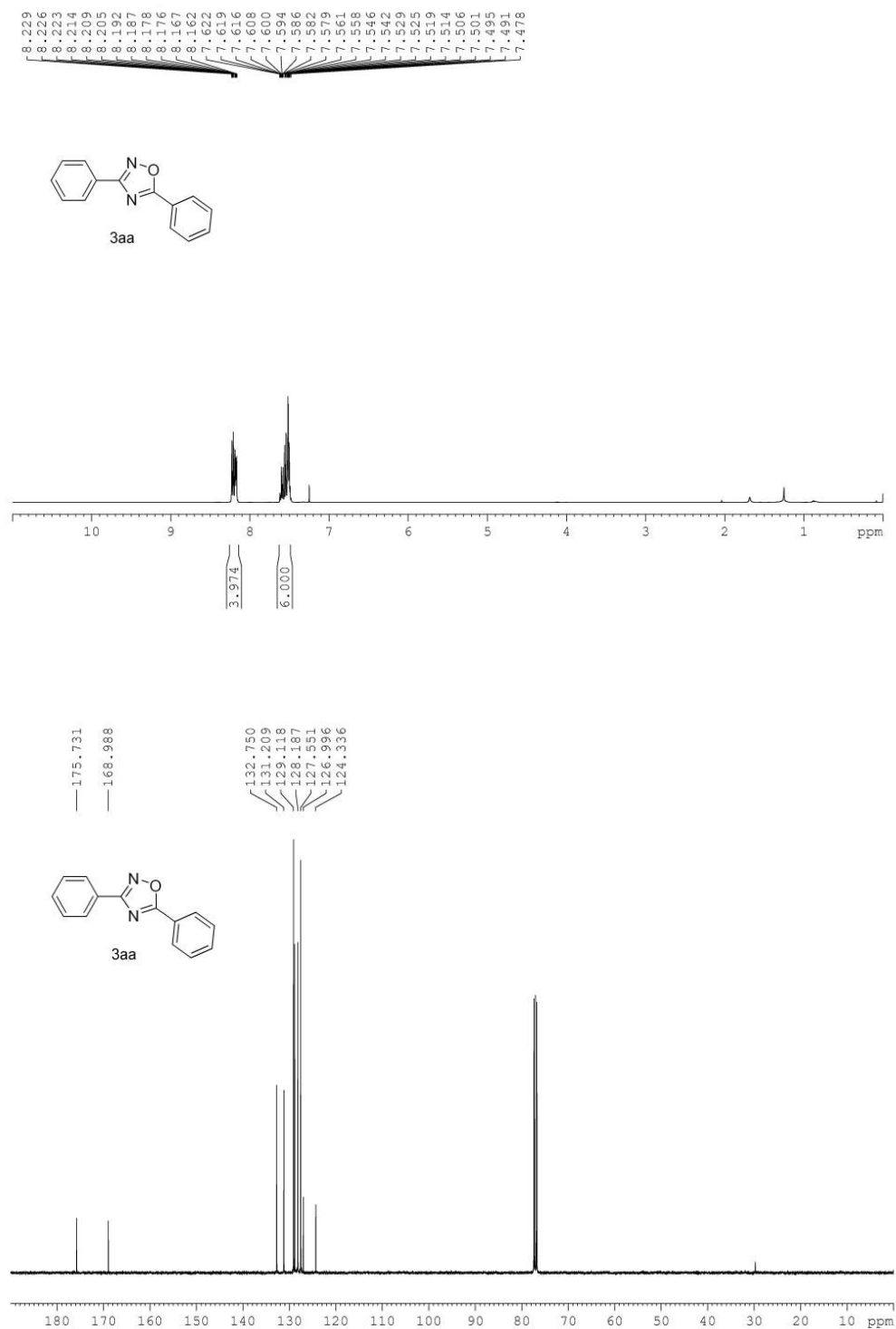


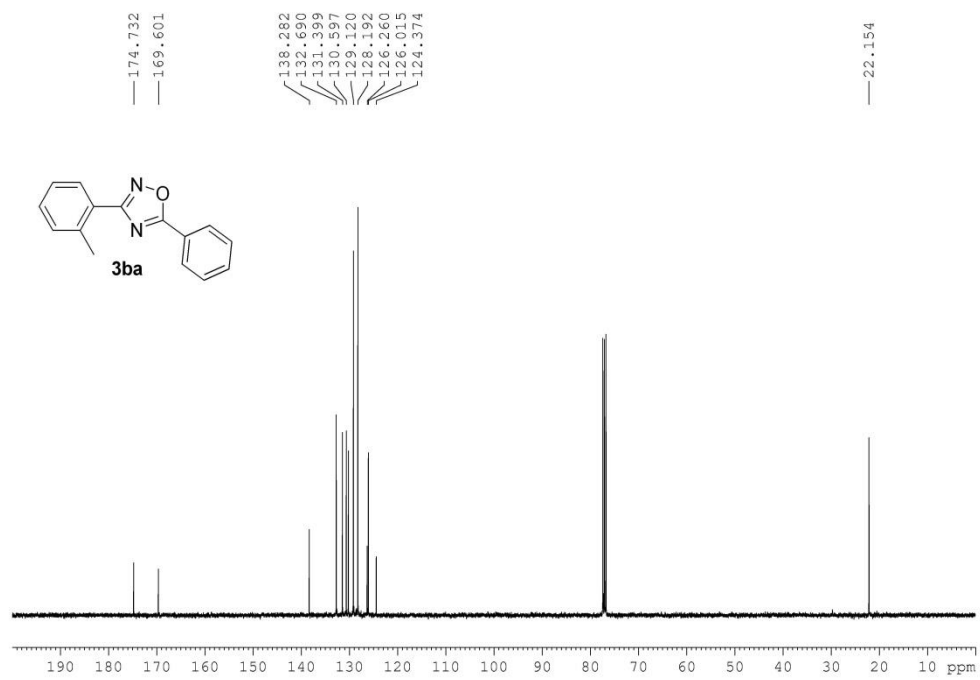
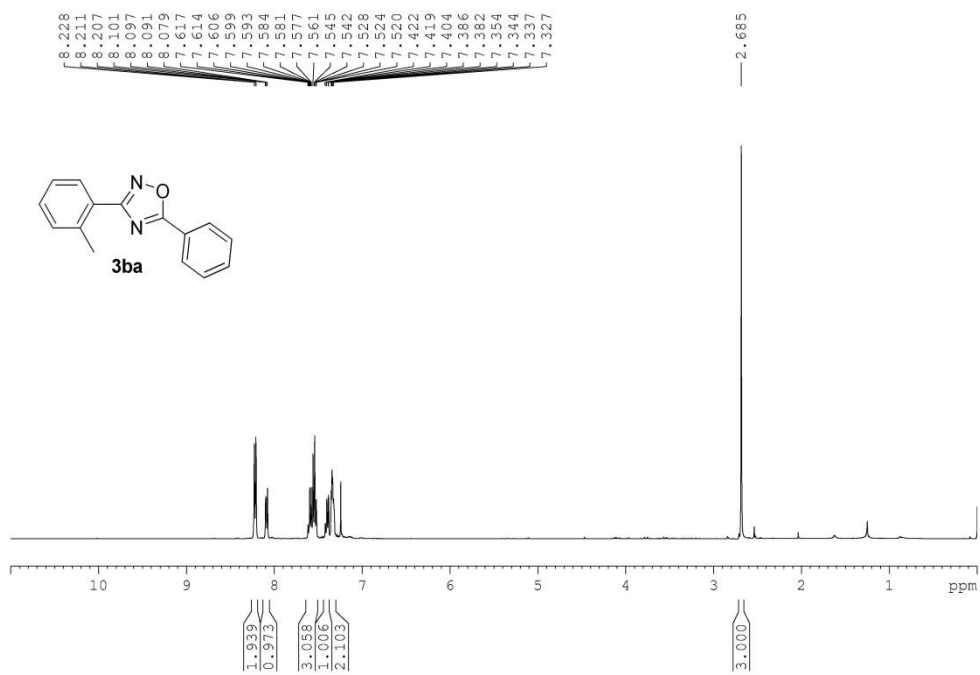
5-(furan-2-yl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (3rl)

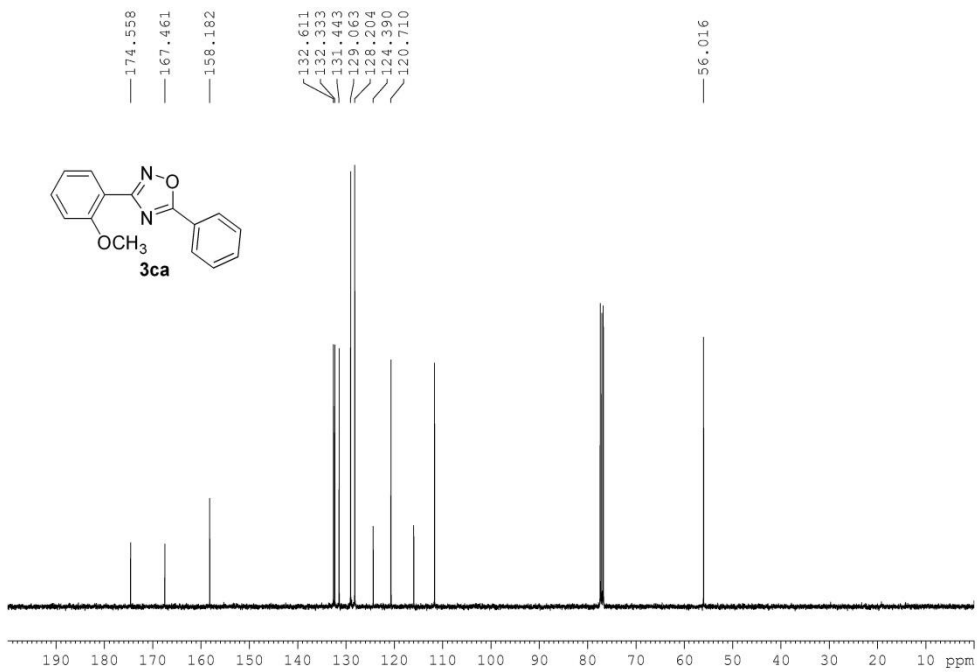
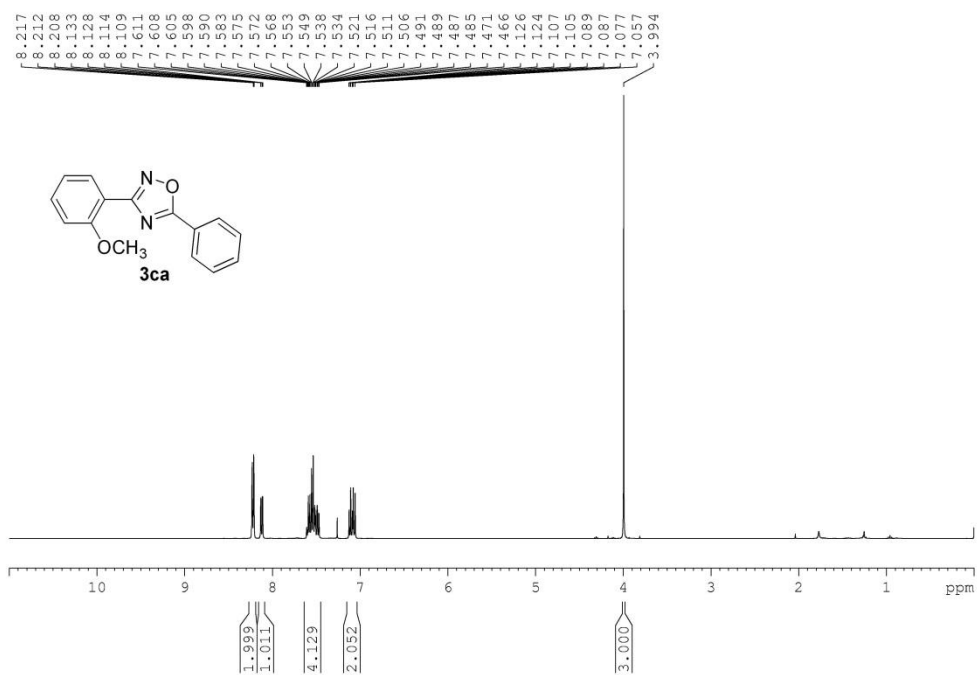
White solid; 77% yield (36.4 mg); mp: 104.9-105.3 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.29 (d, $J = 8.2$ Hz, 2H), 7.78-7.74 (m, 3H), 7.40 (d, $J = 3.5$ Hz, 1H), 6.67 (q, $J = 1.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.98, 167.70, 147.00, 139.89, 133.06 (q, $J = 32.4$ Hz), 129.91, 127.97, 125.87 (q, $J = 3.7$ Hz), 125.12 (q, $J = 272.4$ Hz), 117.05, 112.64; ^{19}F NMR (376 MHz, CDCl_3) δ -63.01; HRMS (m/z) $[\text{M}+\text{H}]^+$

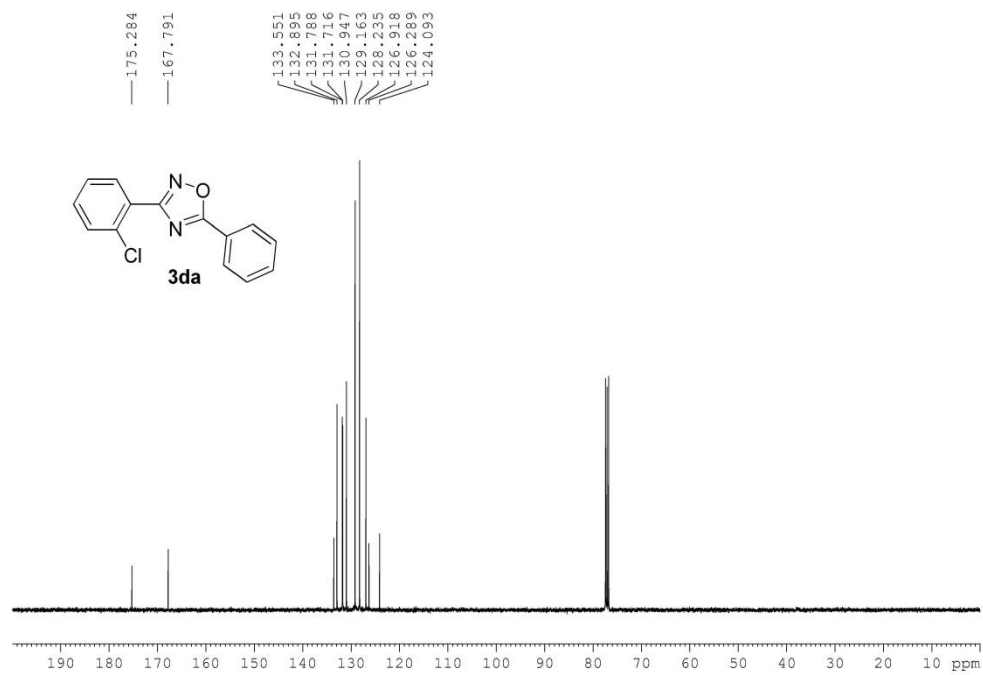
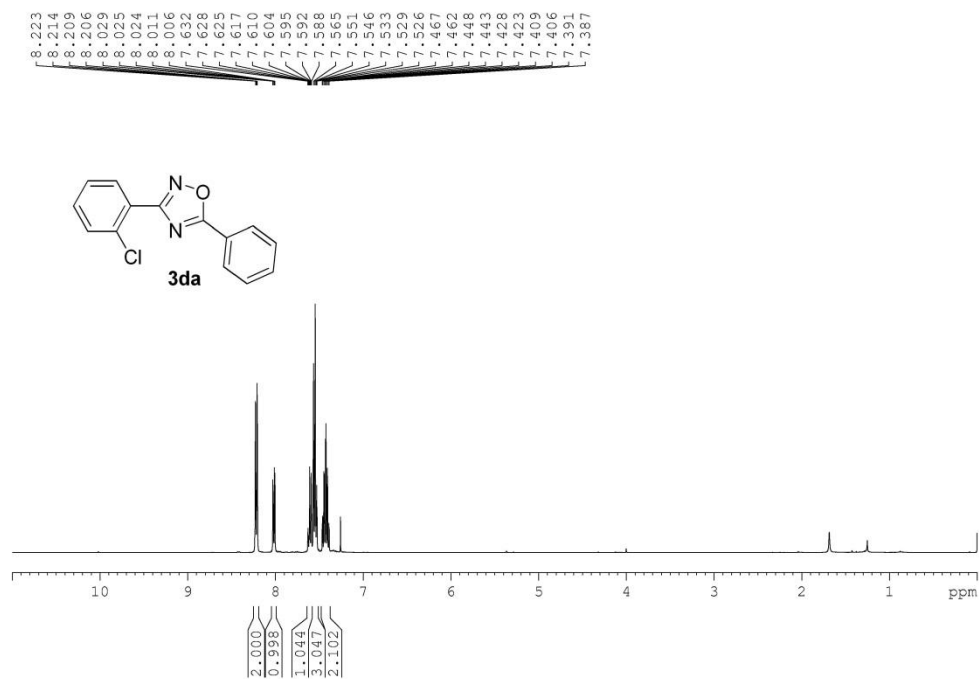
calculated for $C_{13}H_7F_3N_2O_2$: 281.0532; found: 281.0533.

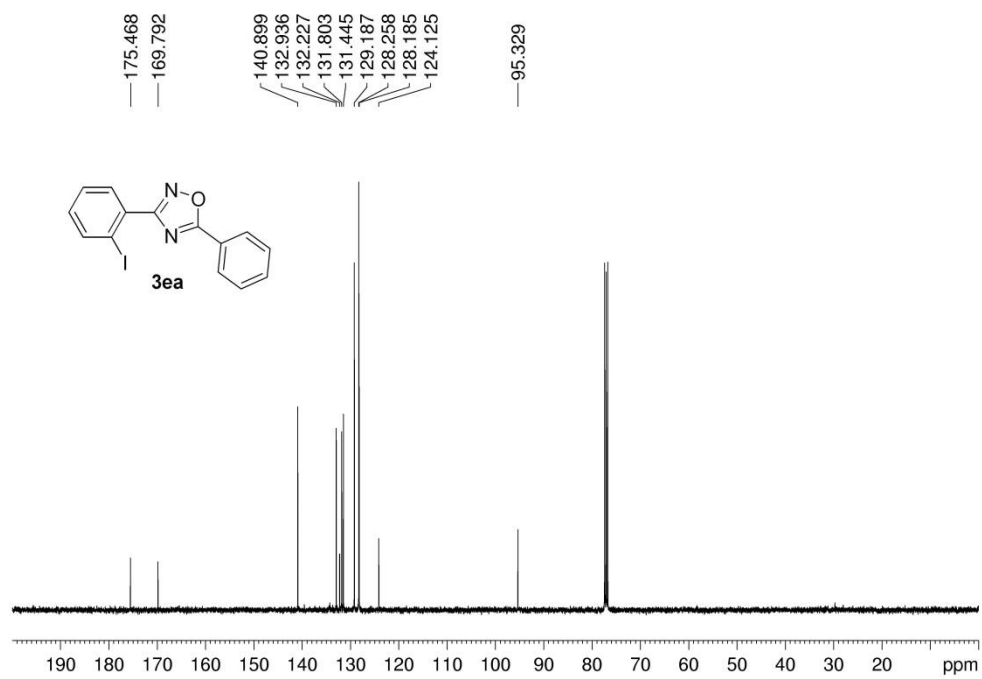
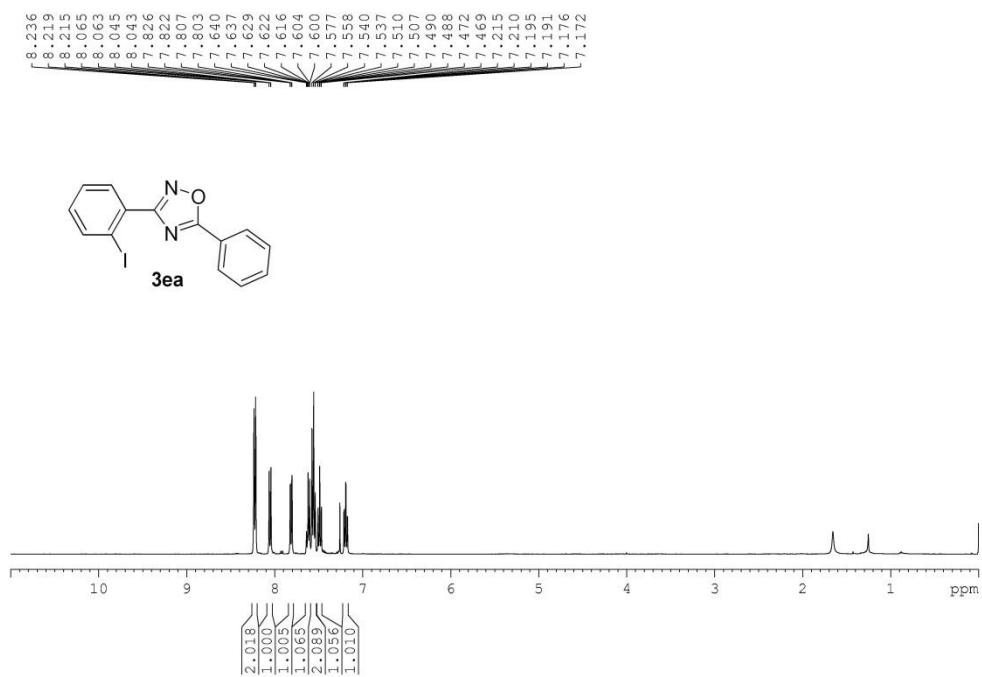
5. Copies of ^1H , ^{13}C , ^{19}F NMR Spectra for the Products



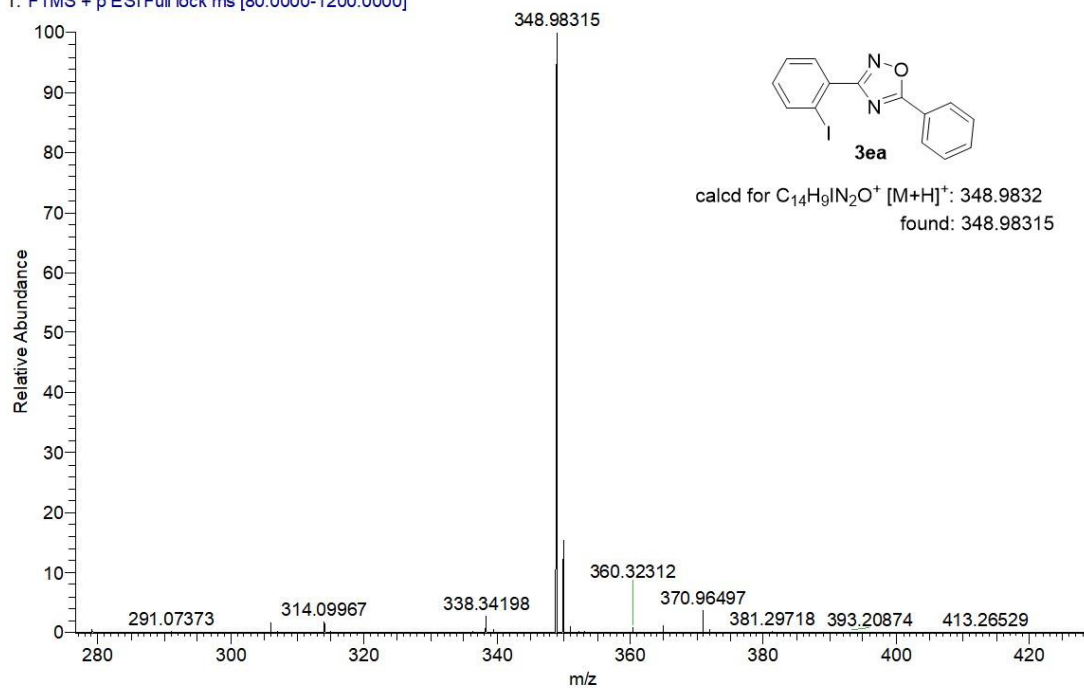




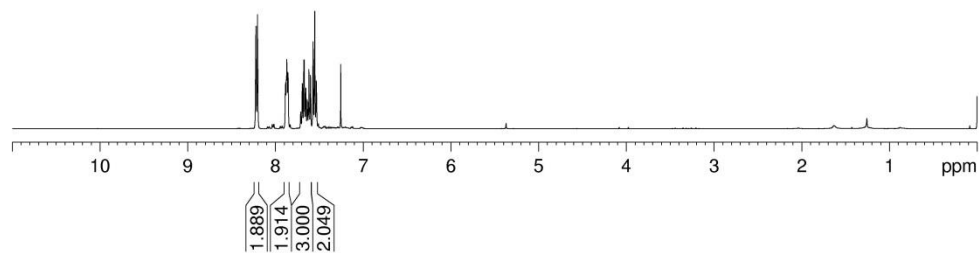
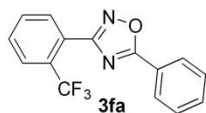


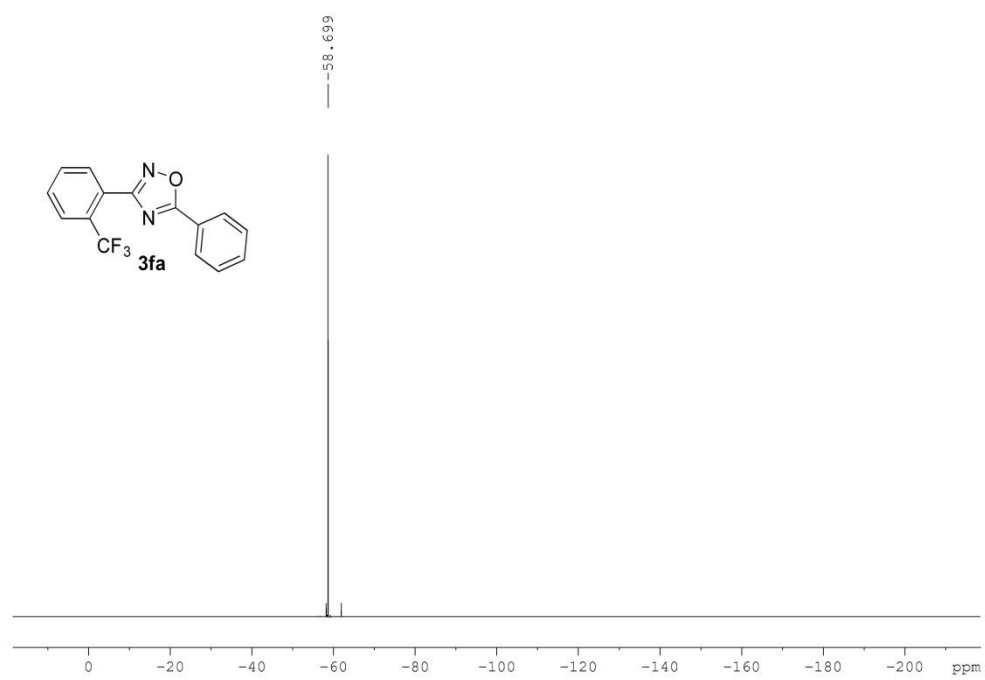
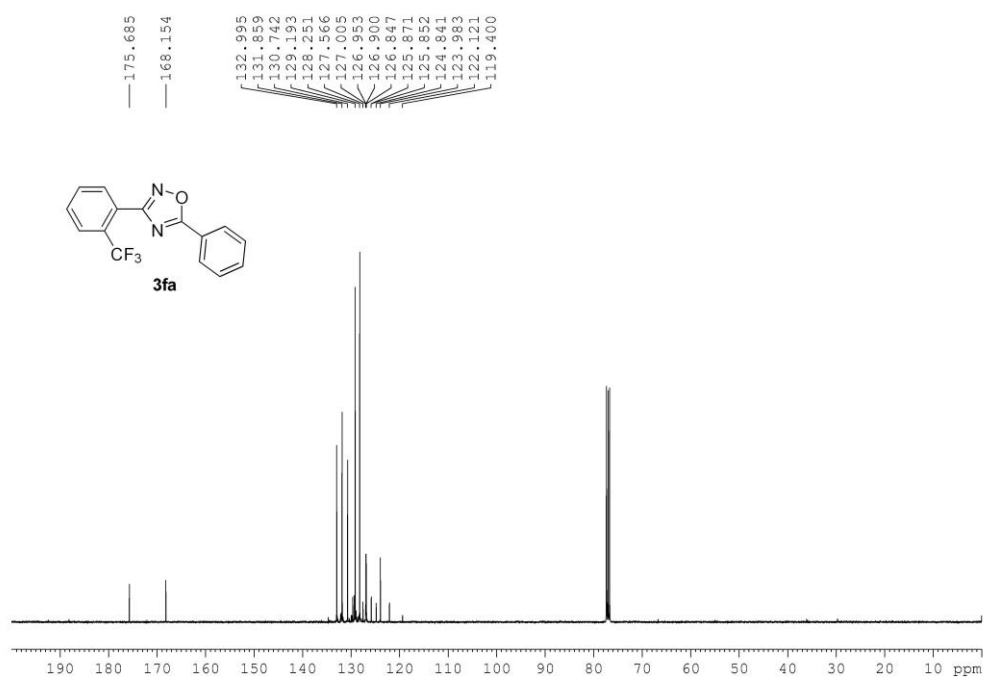


T: FTMS + p ESI Full lock ms [80.0000-1200.0000]

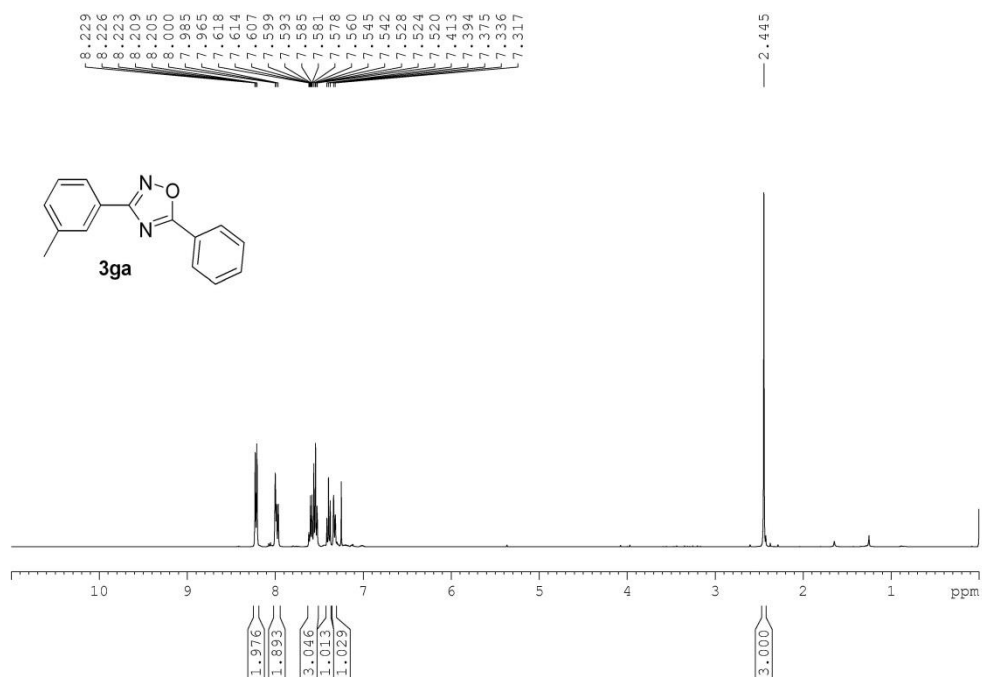
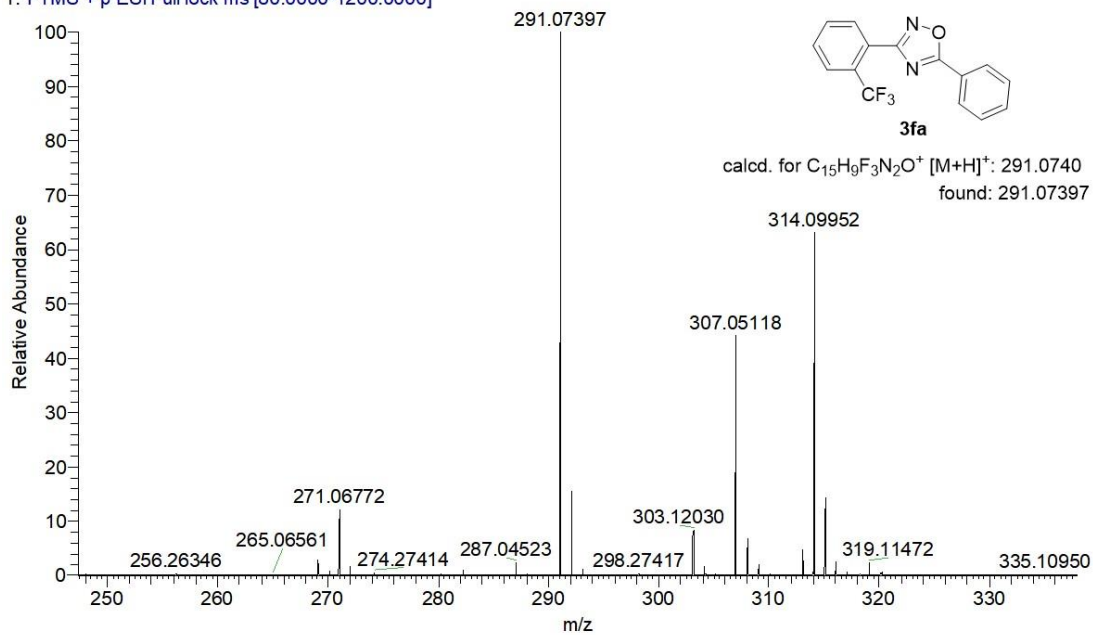


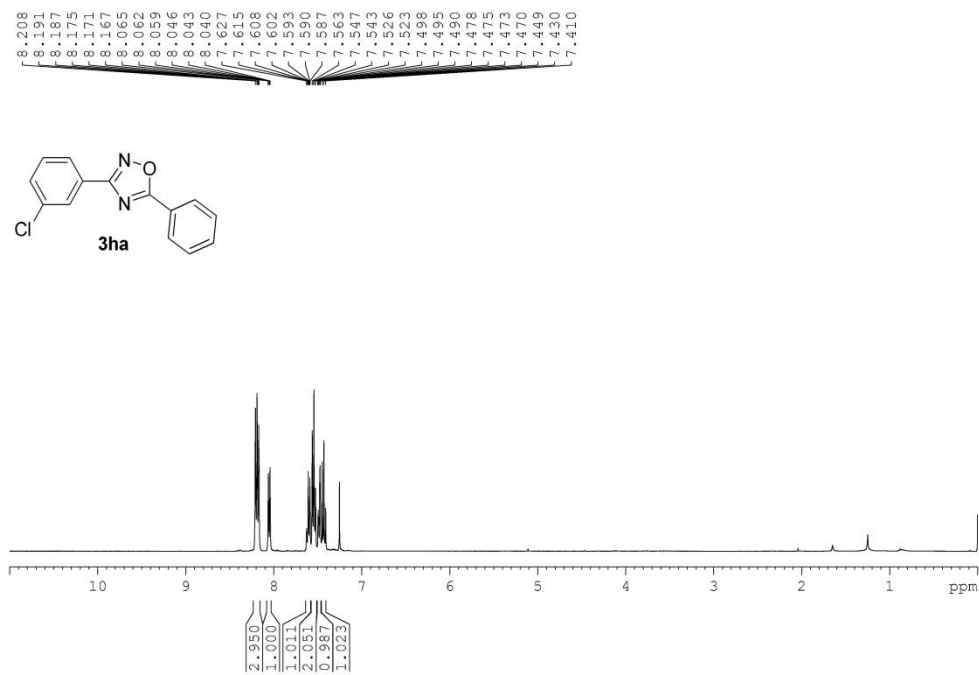
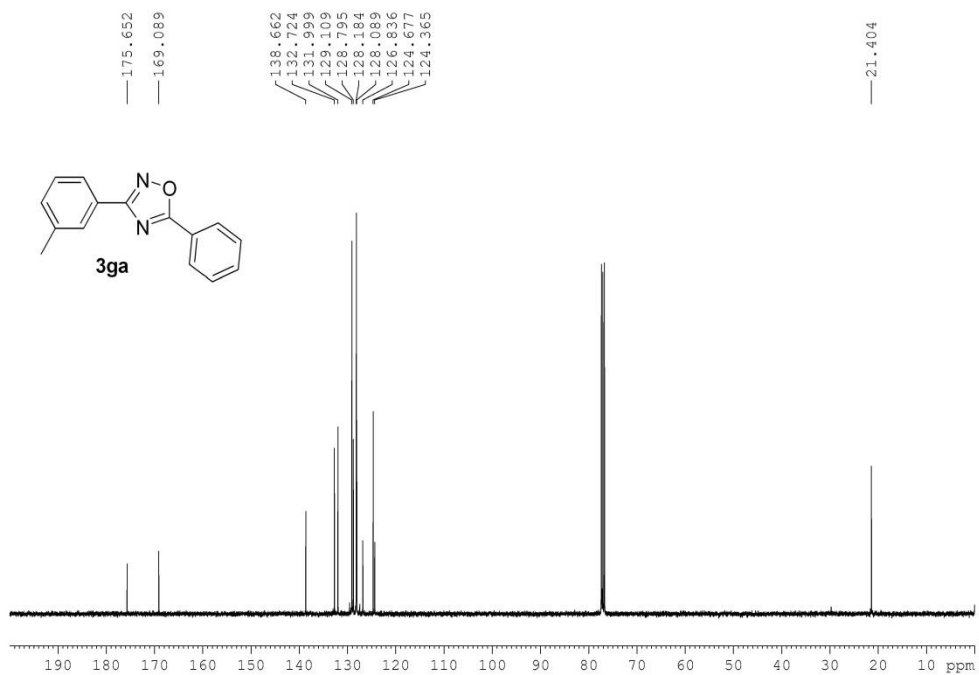
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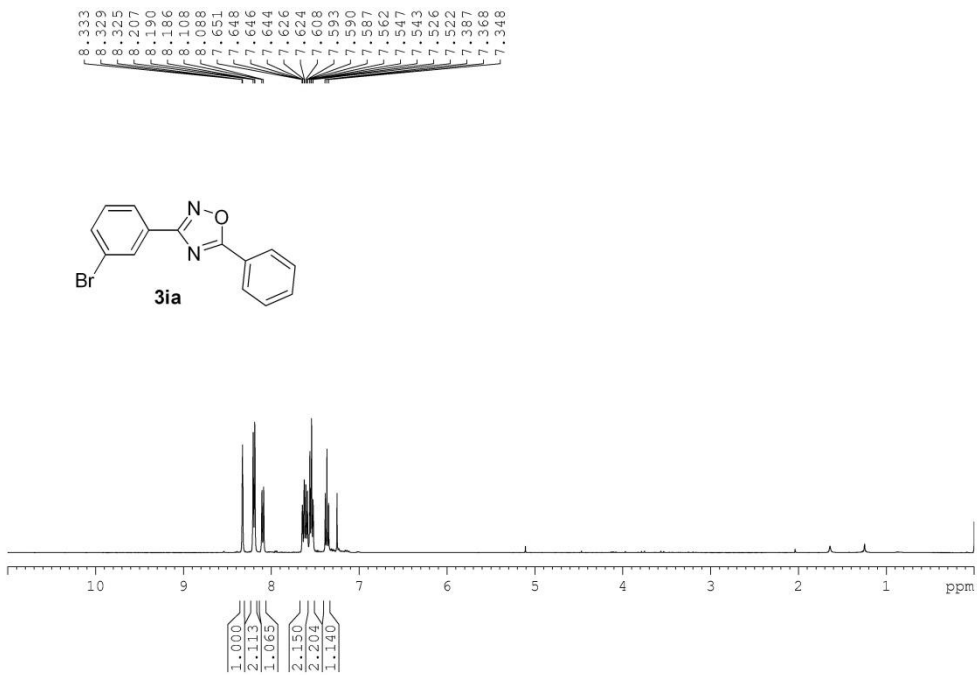
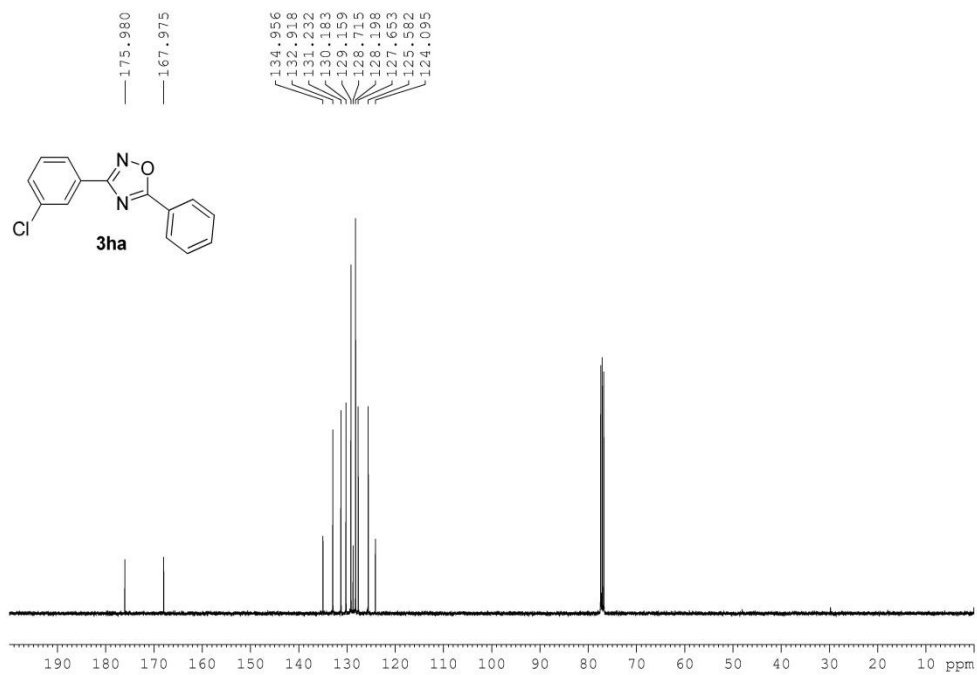


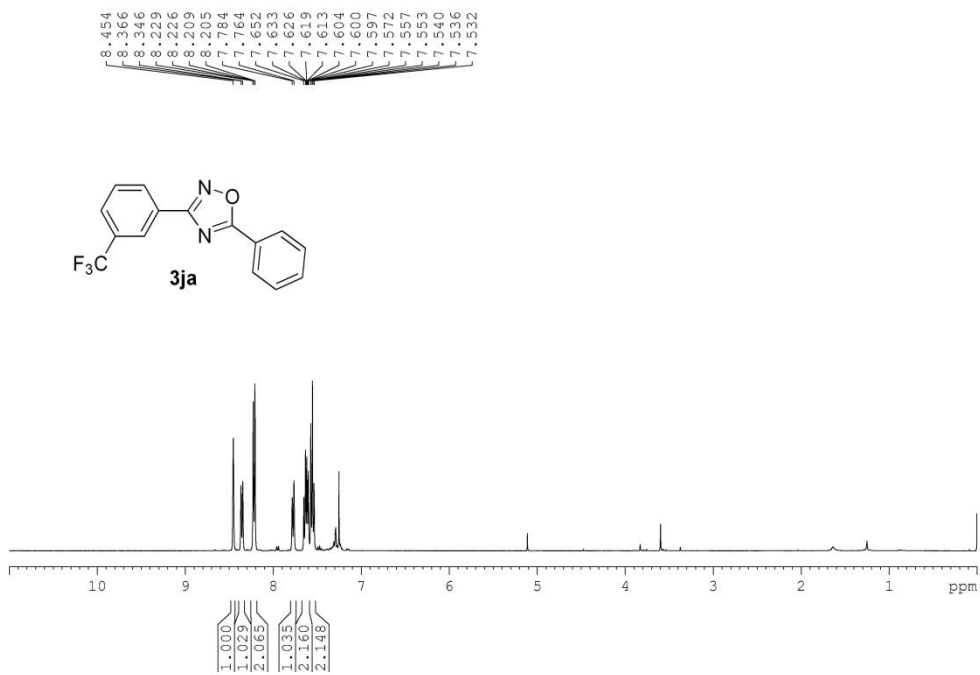
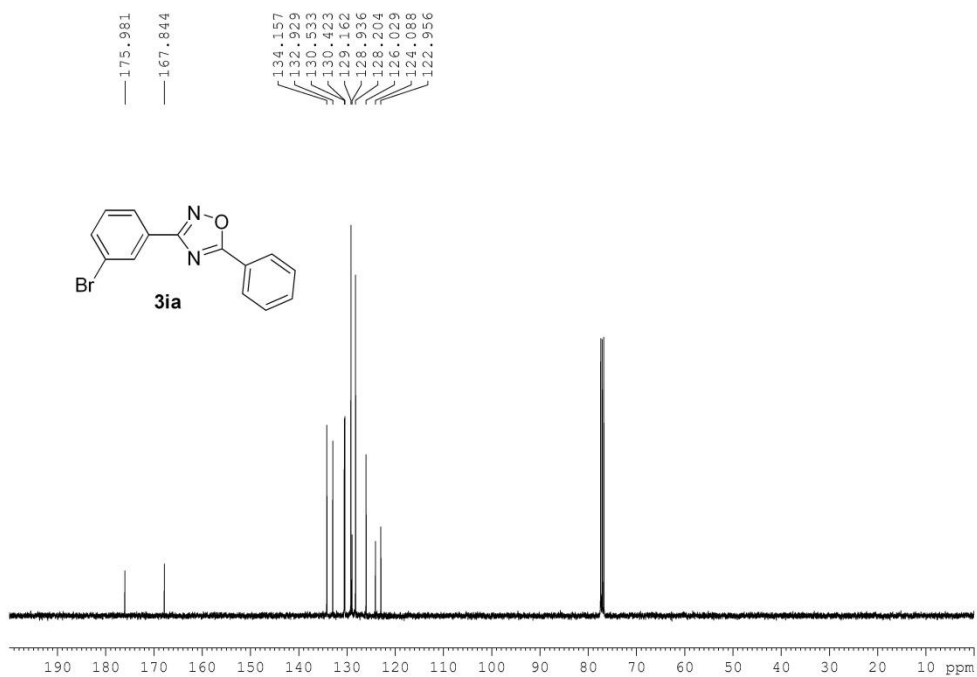


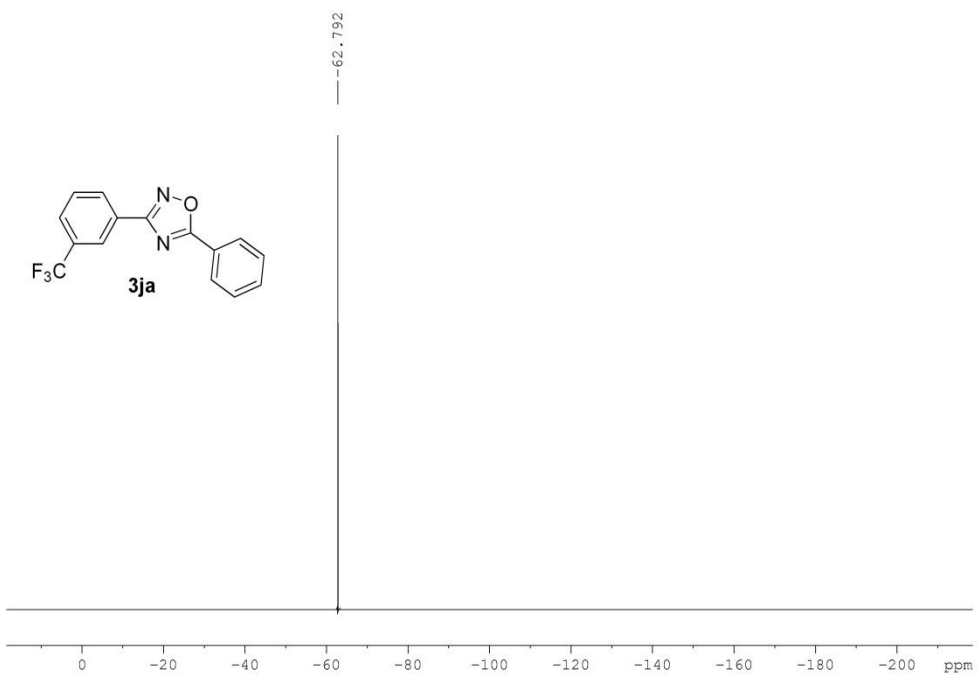
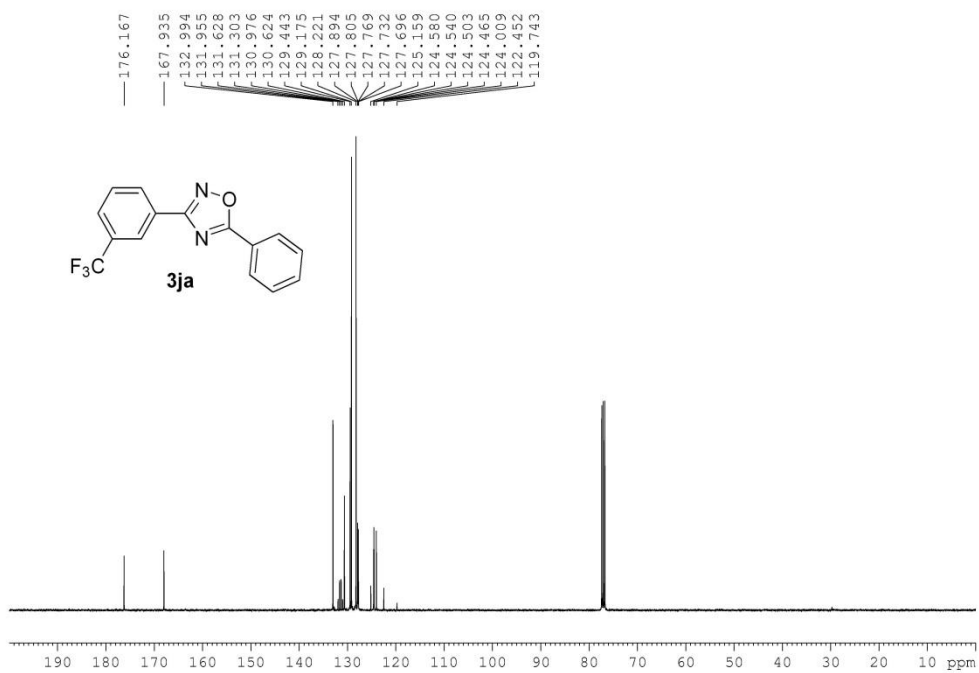
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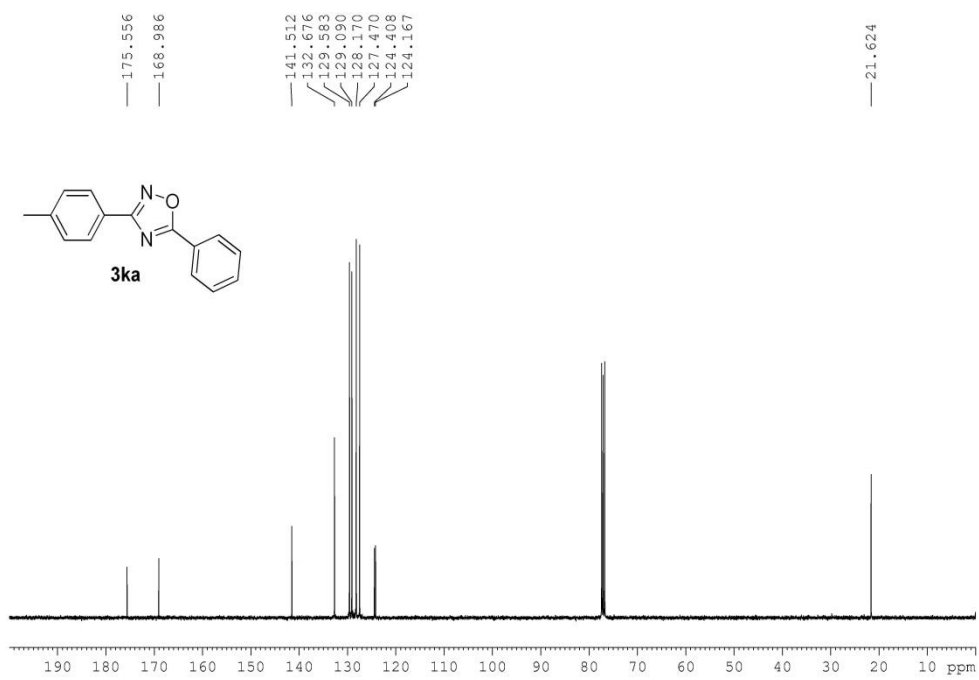
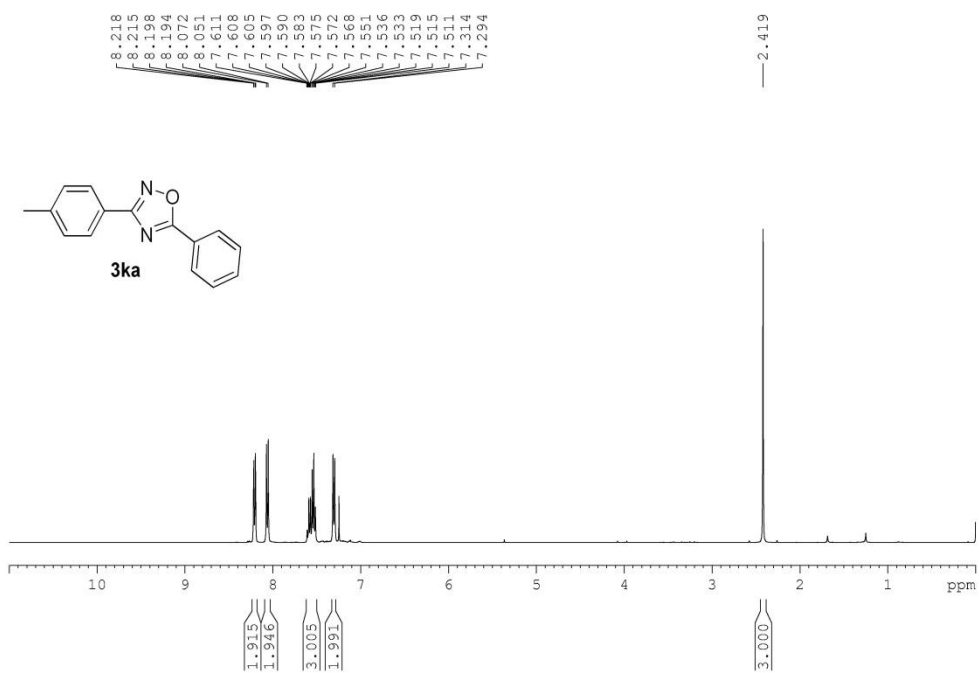


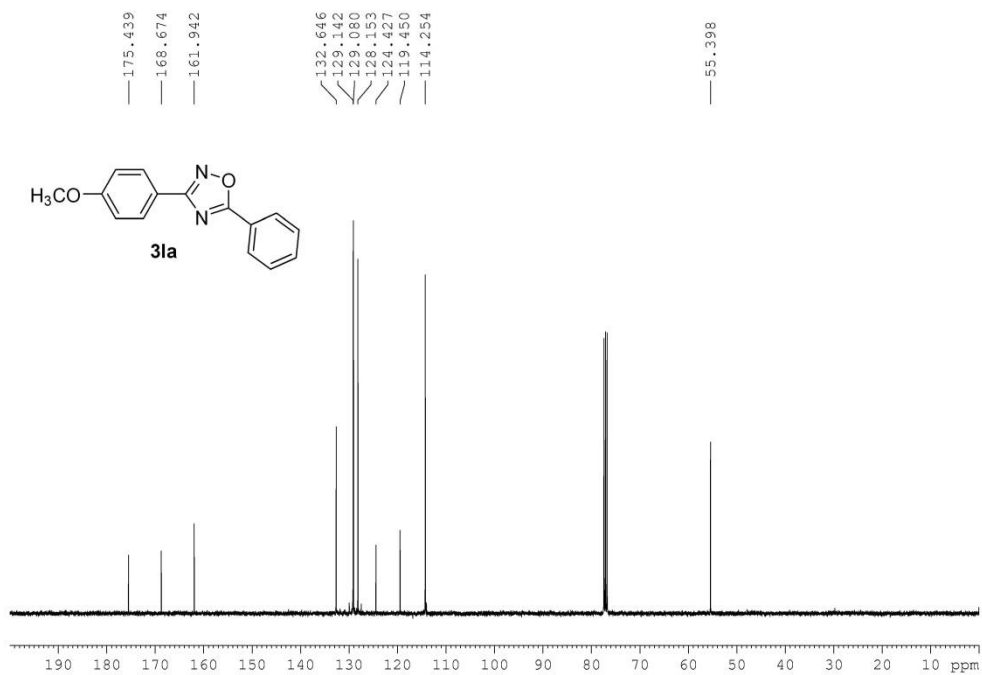


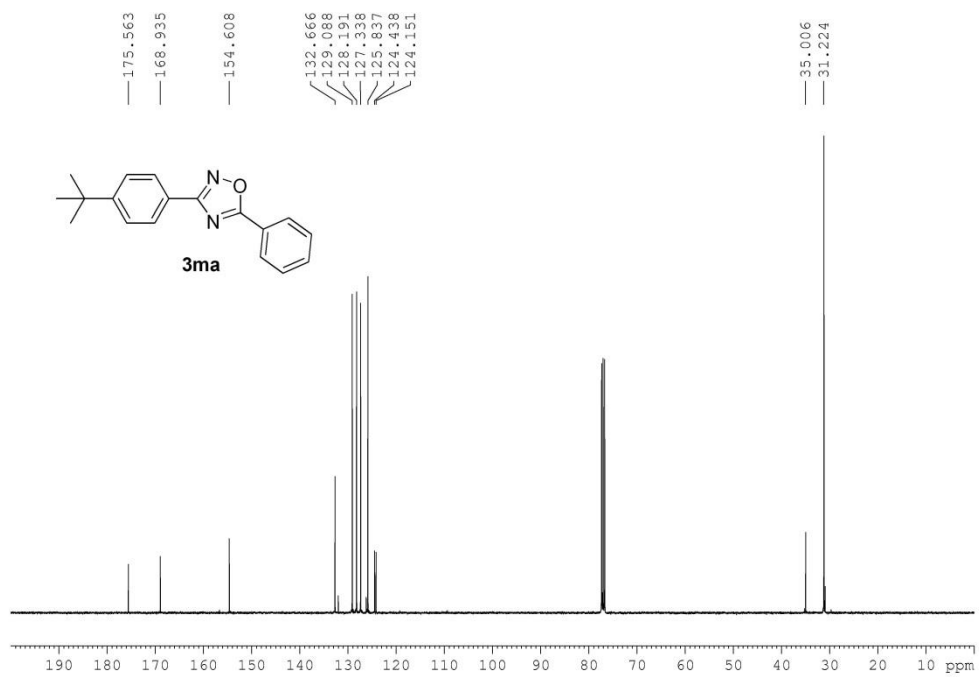
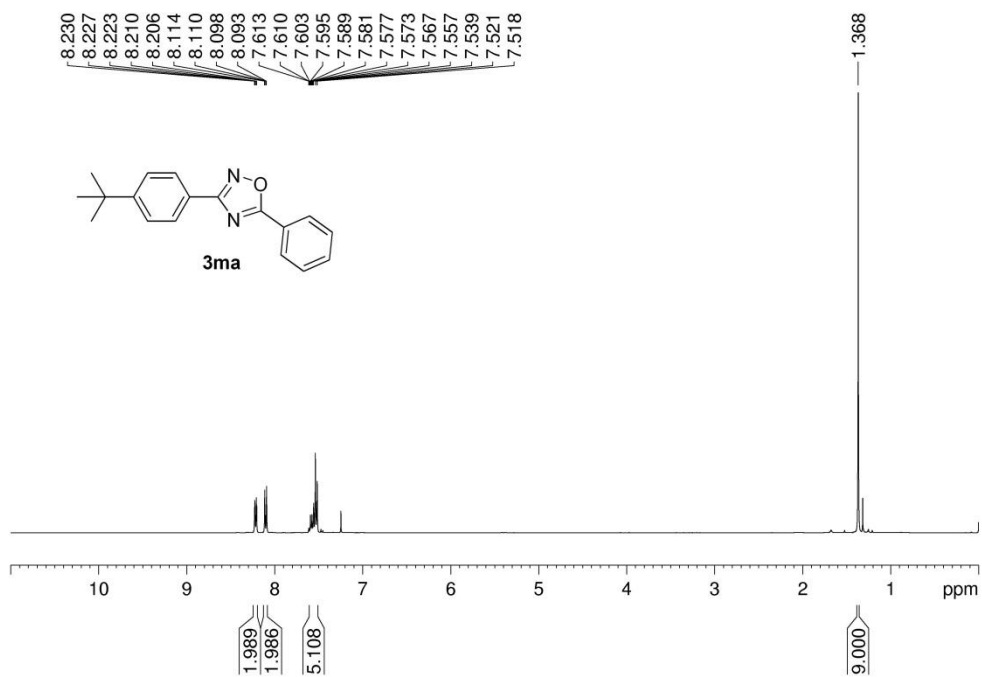


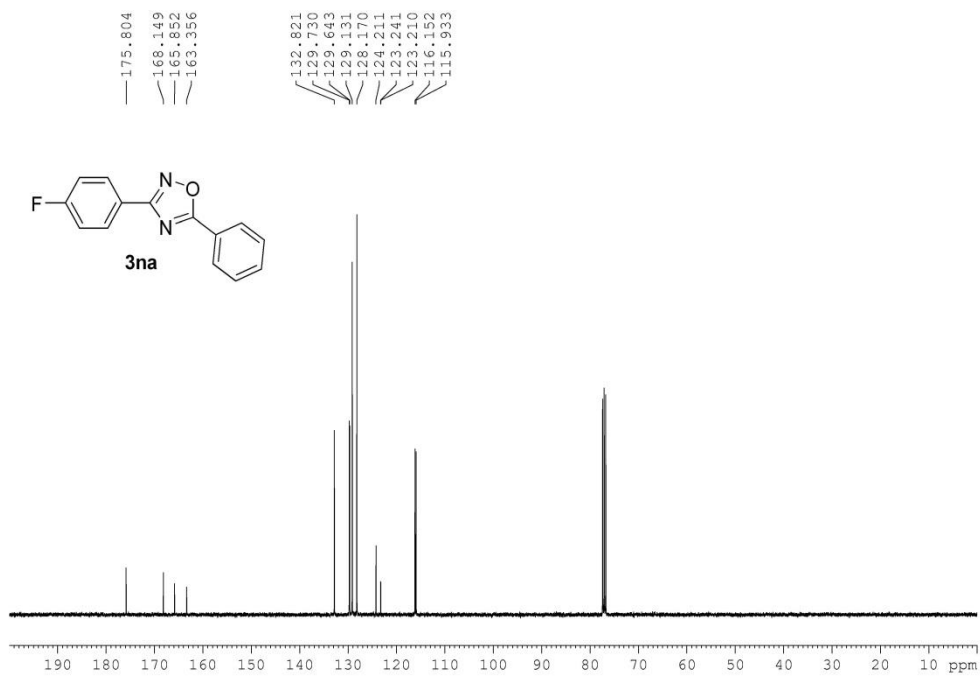
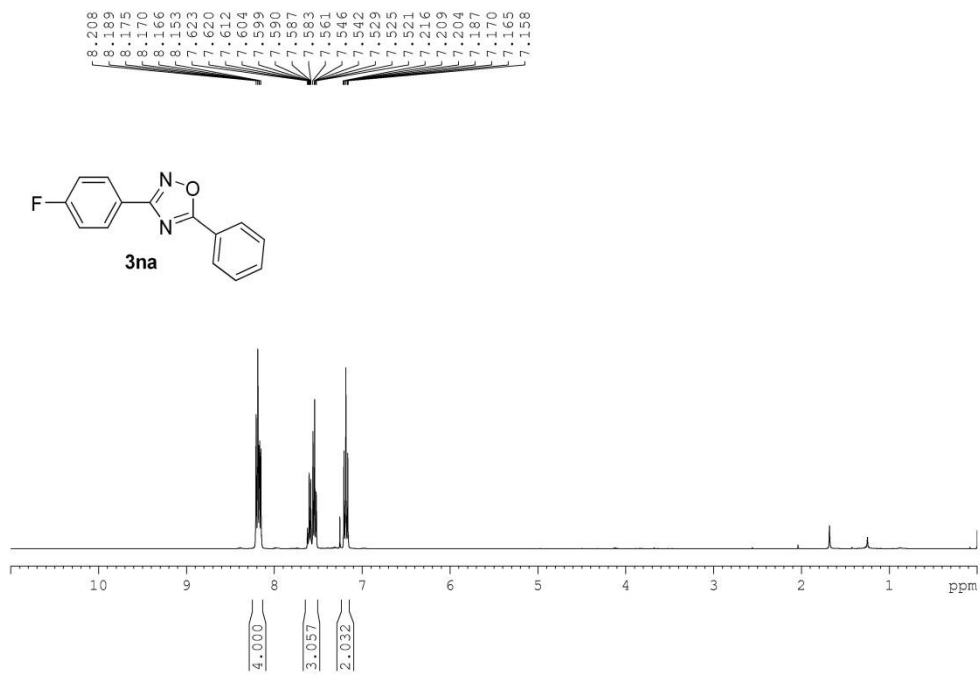


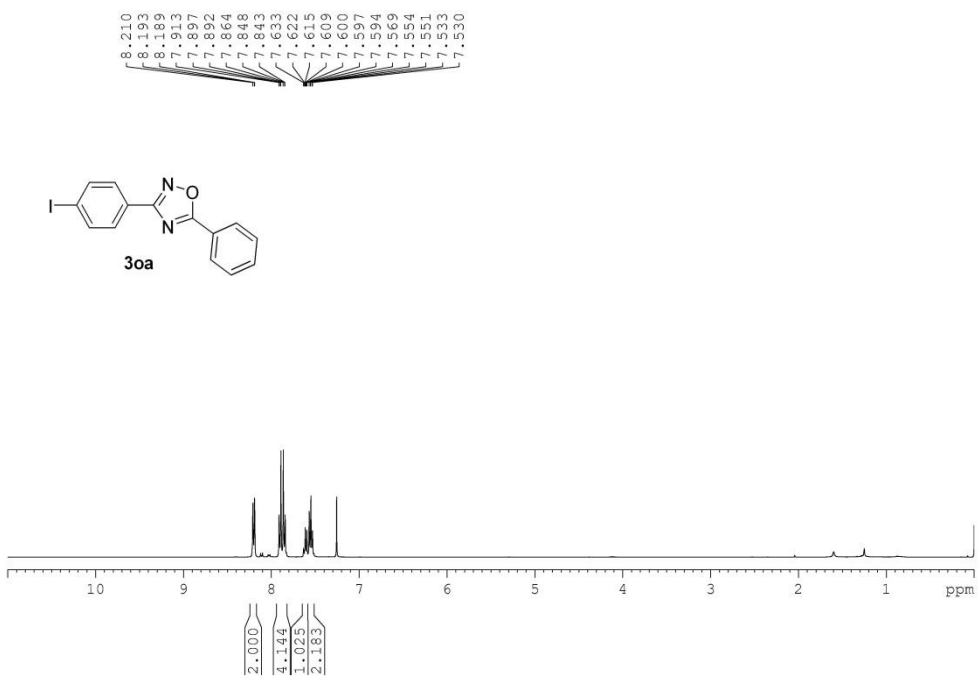
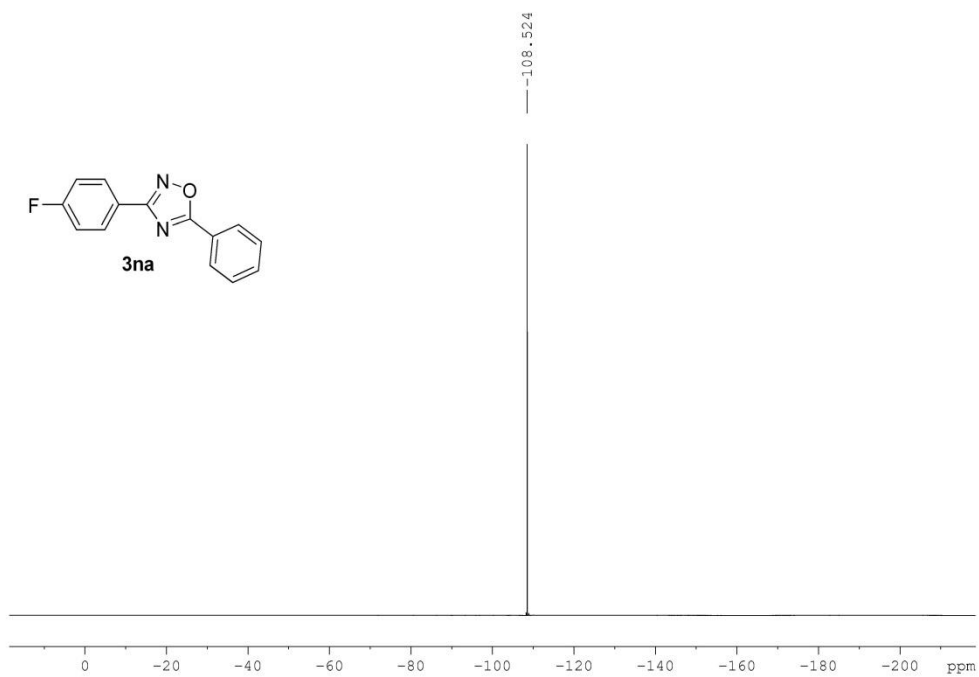


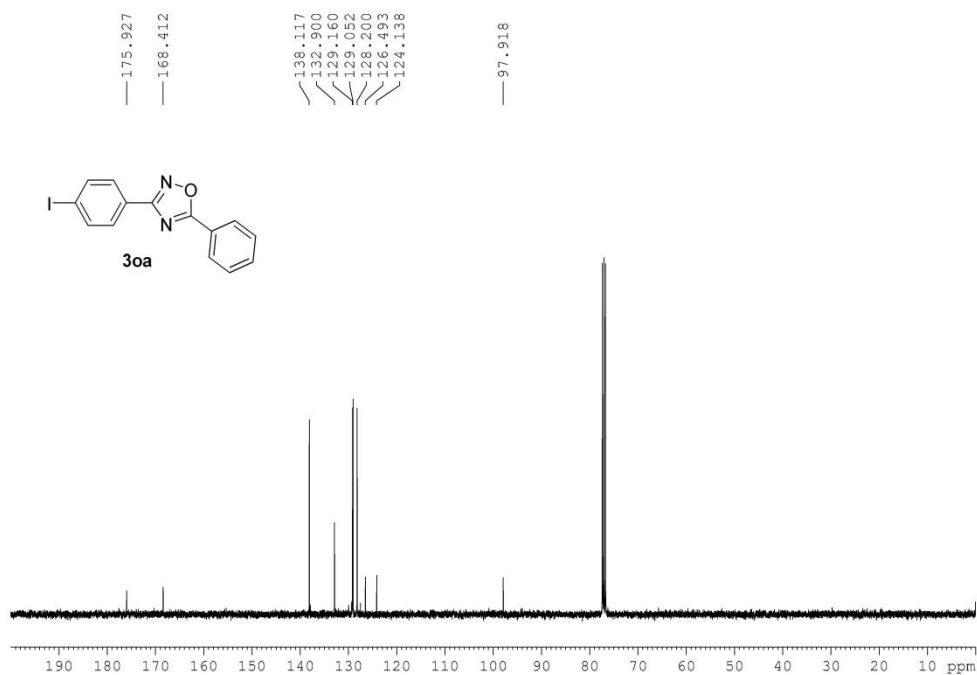




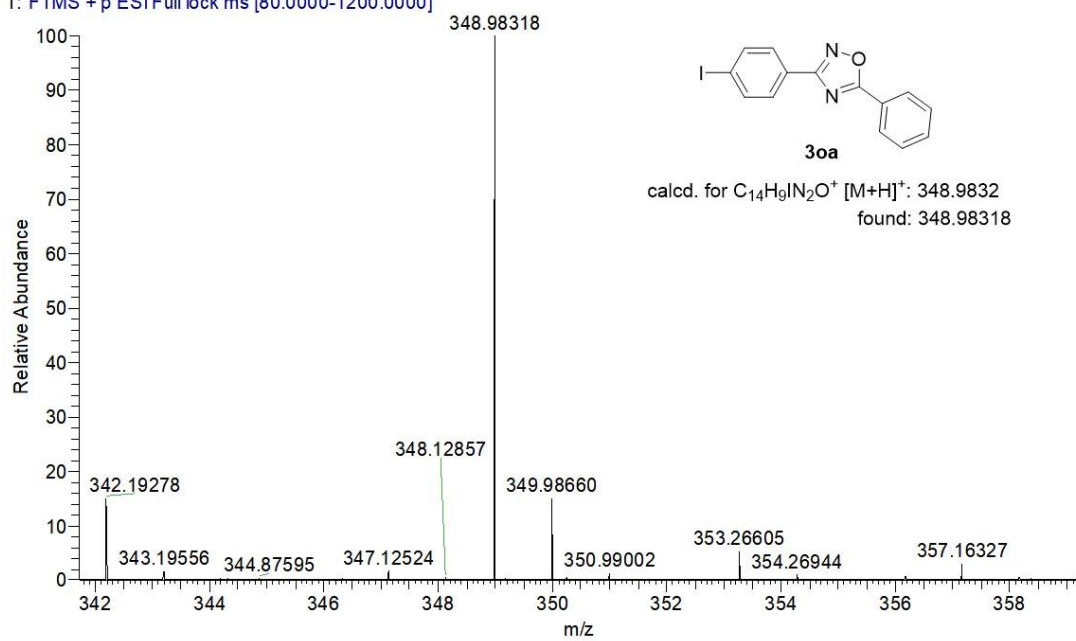


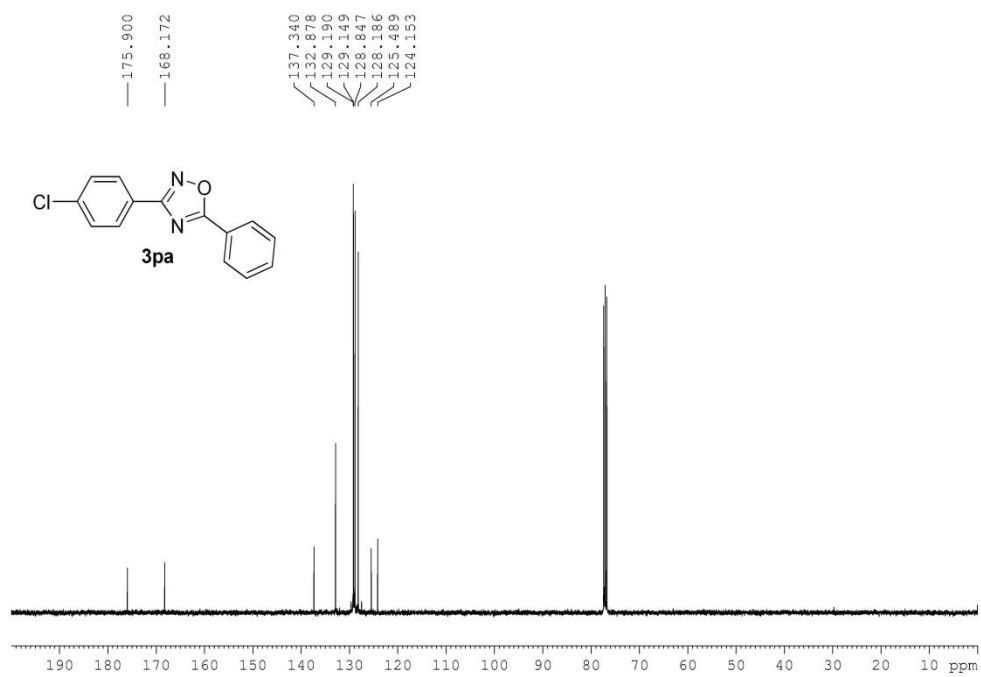
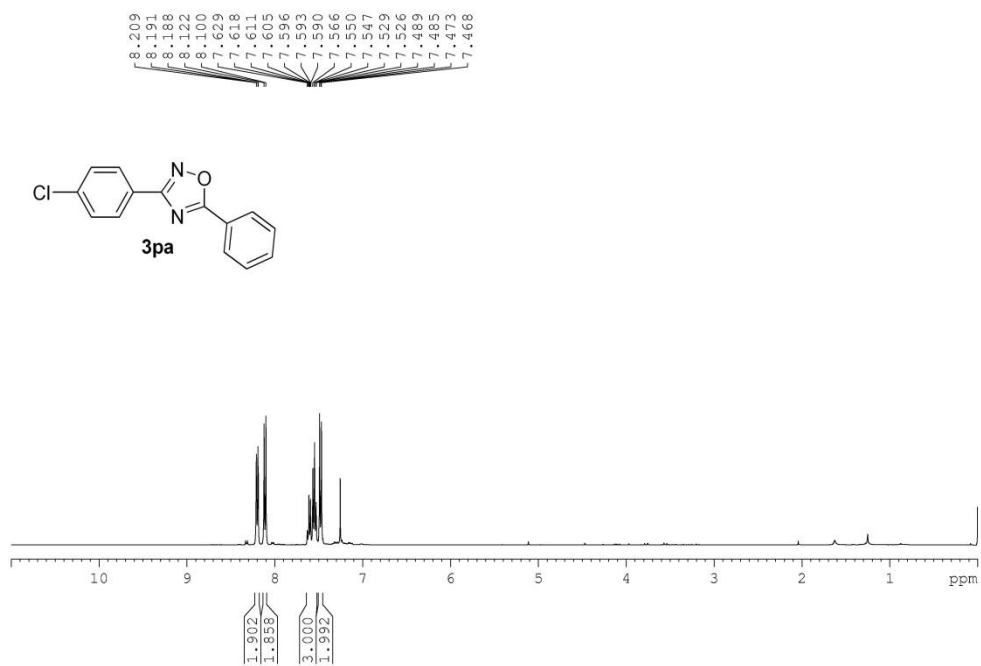


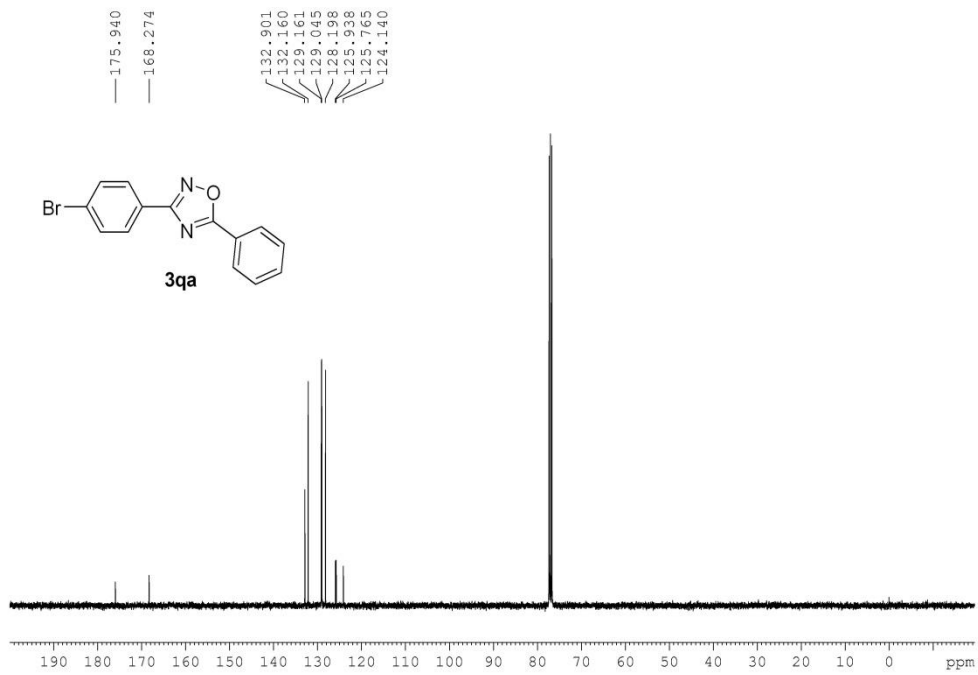
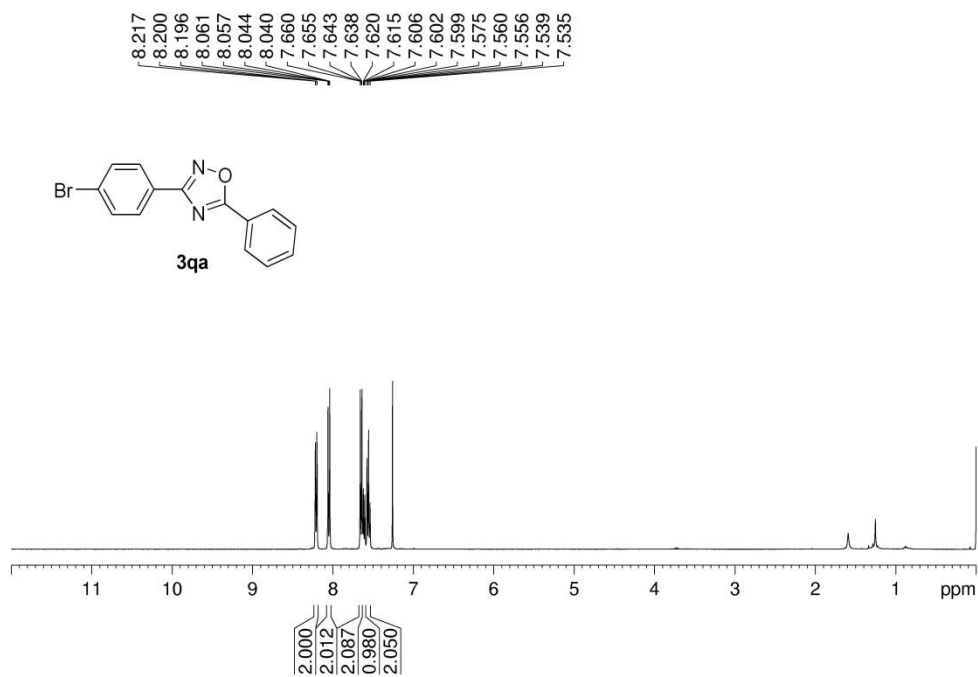


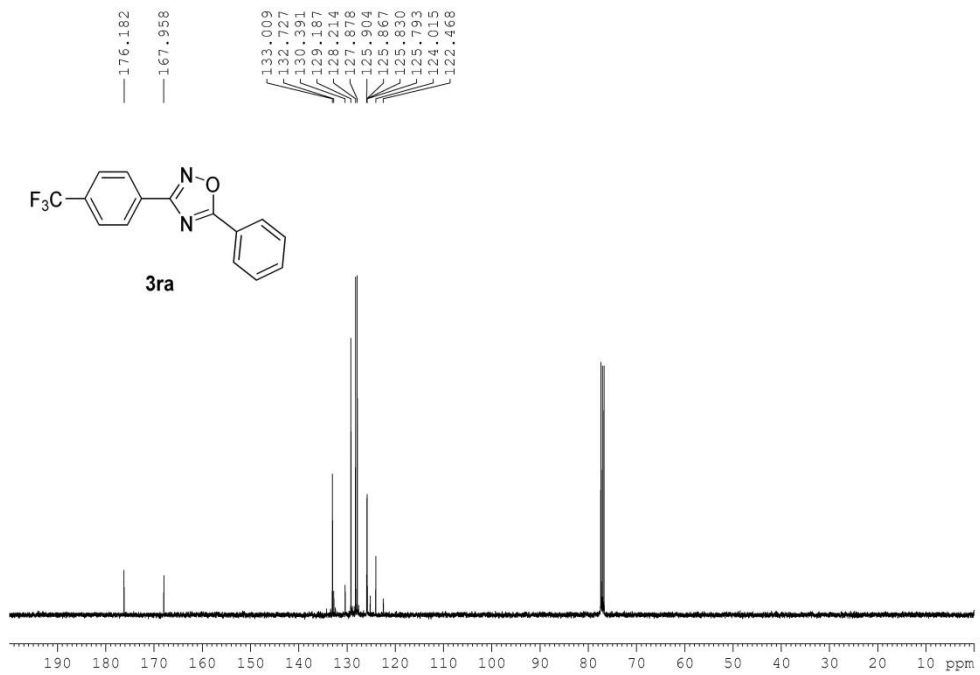
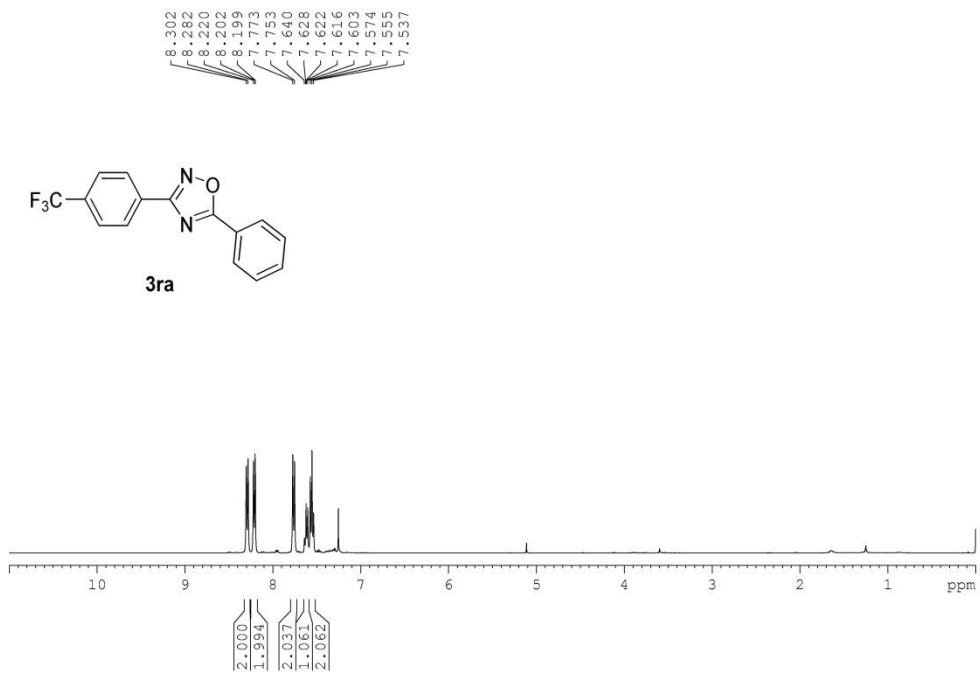


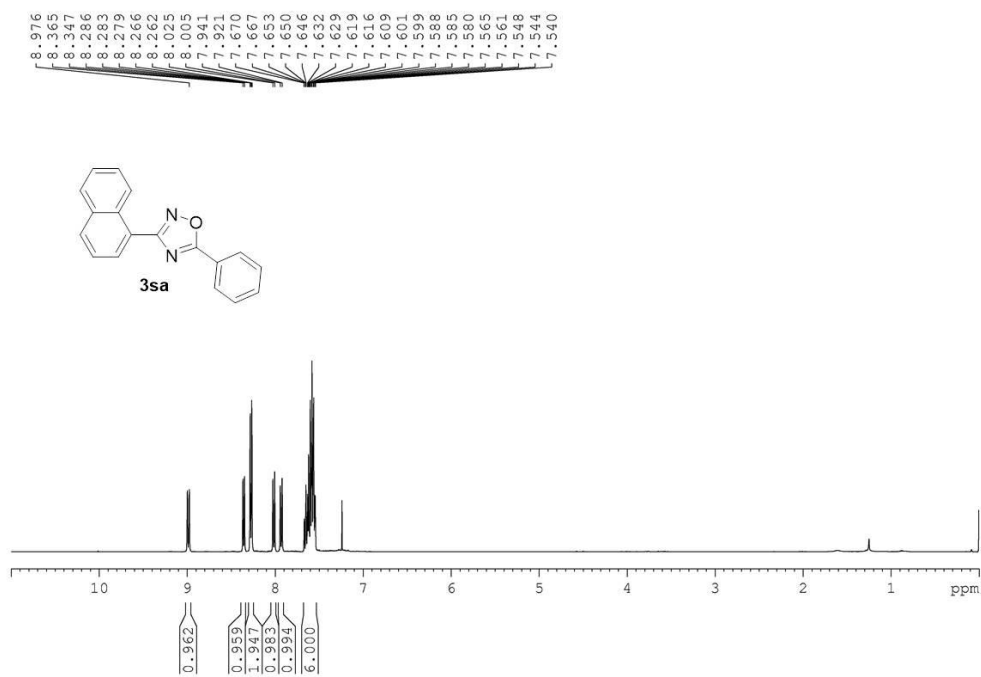
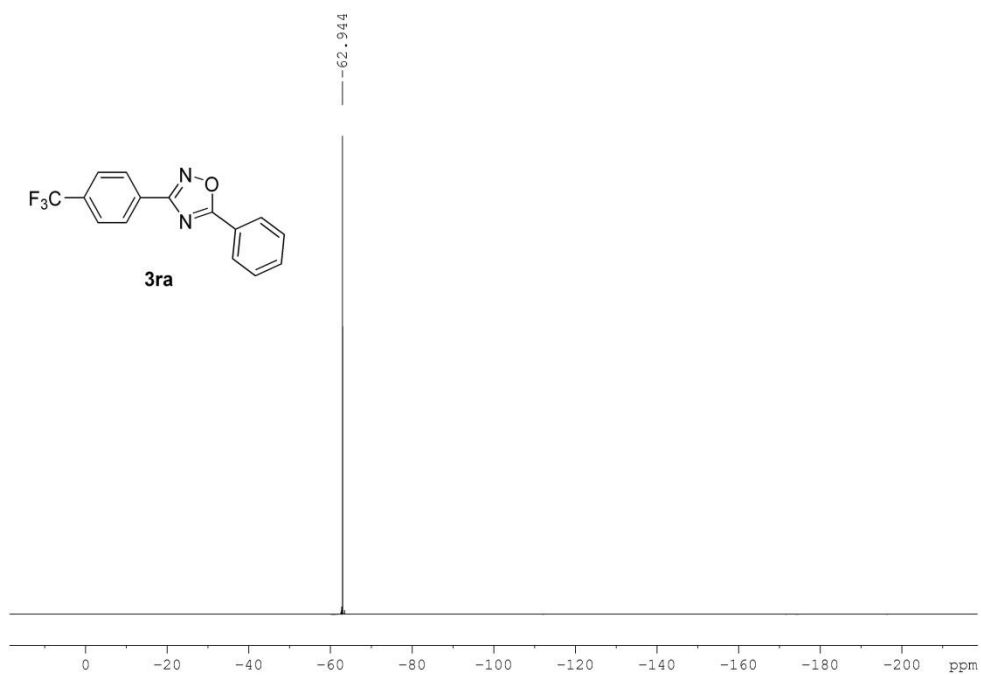
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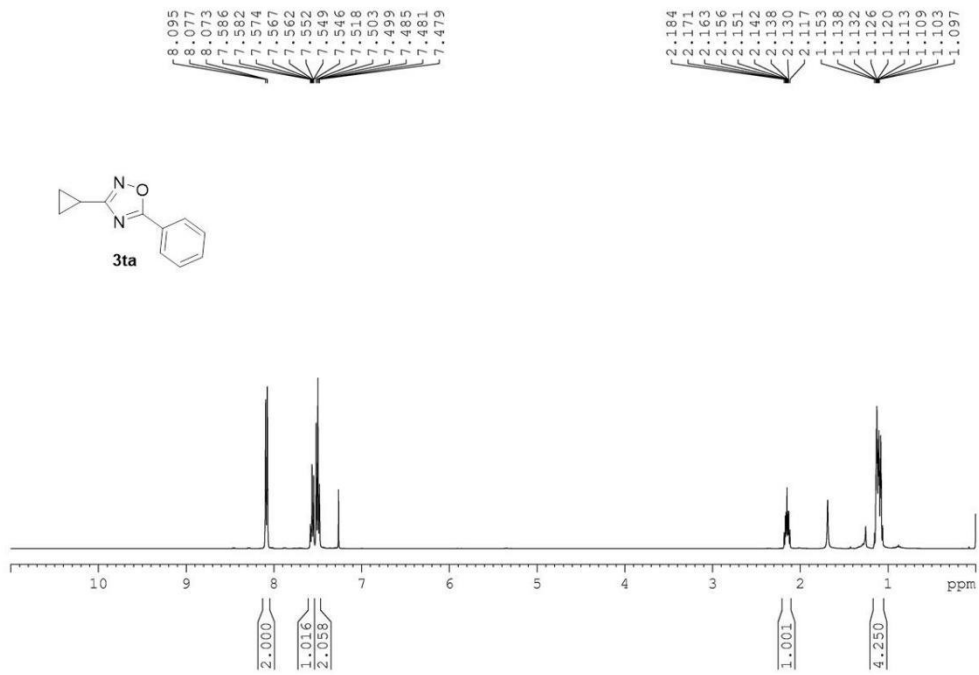
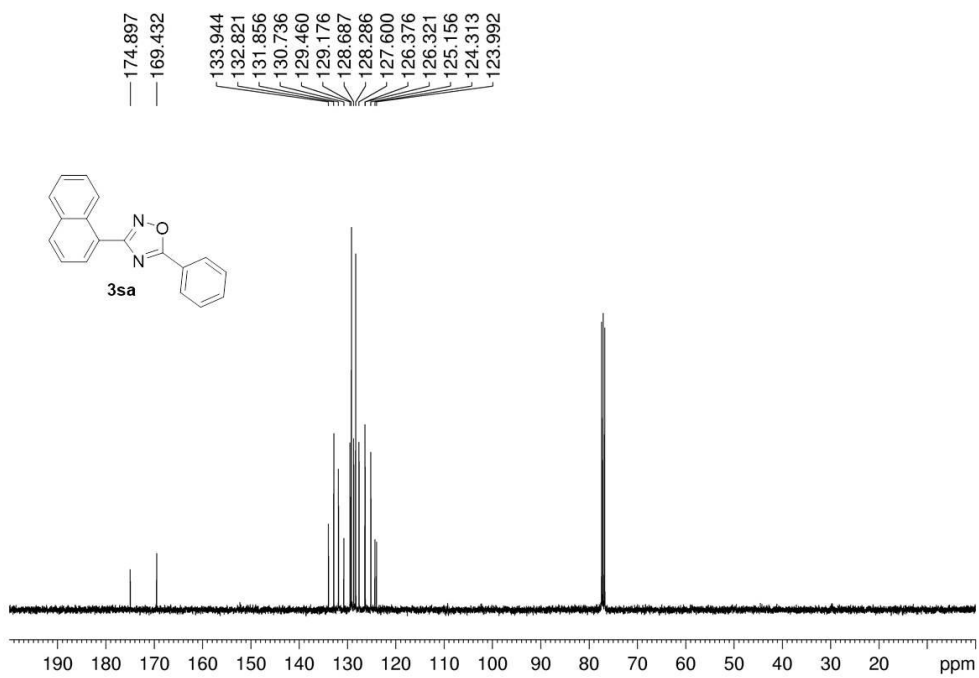


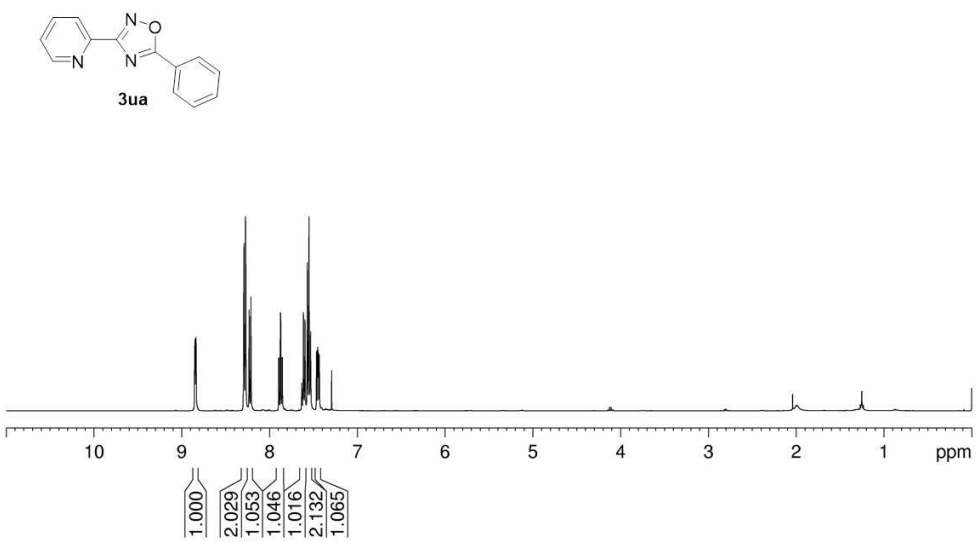
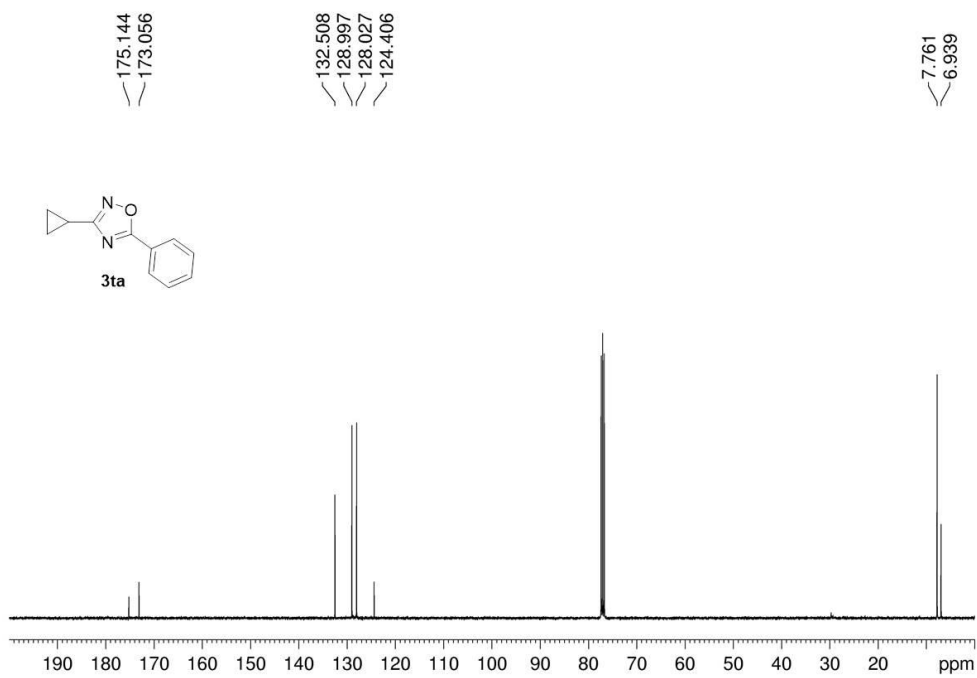




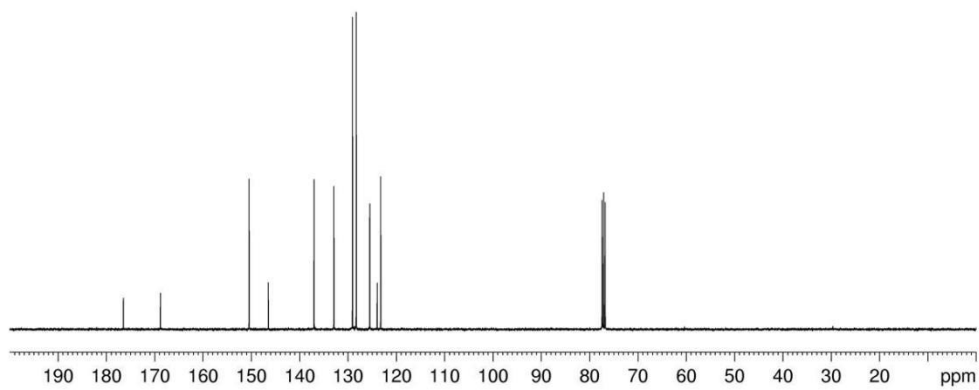
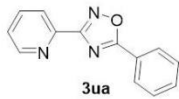




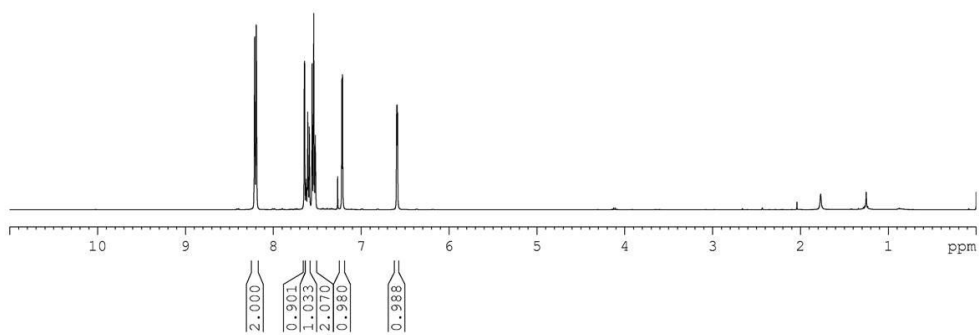
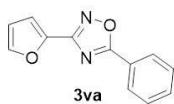




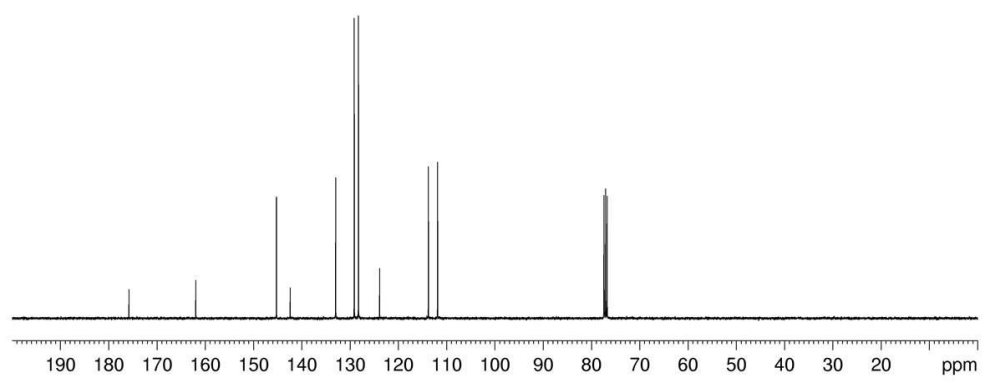
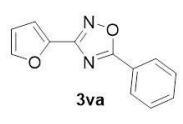
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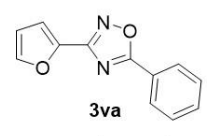
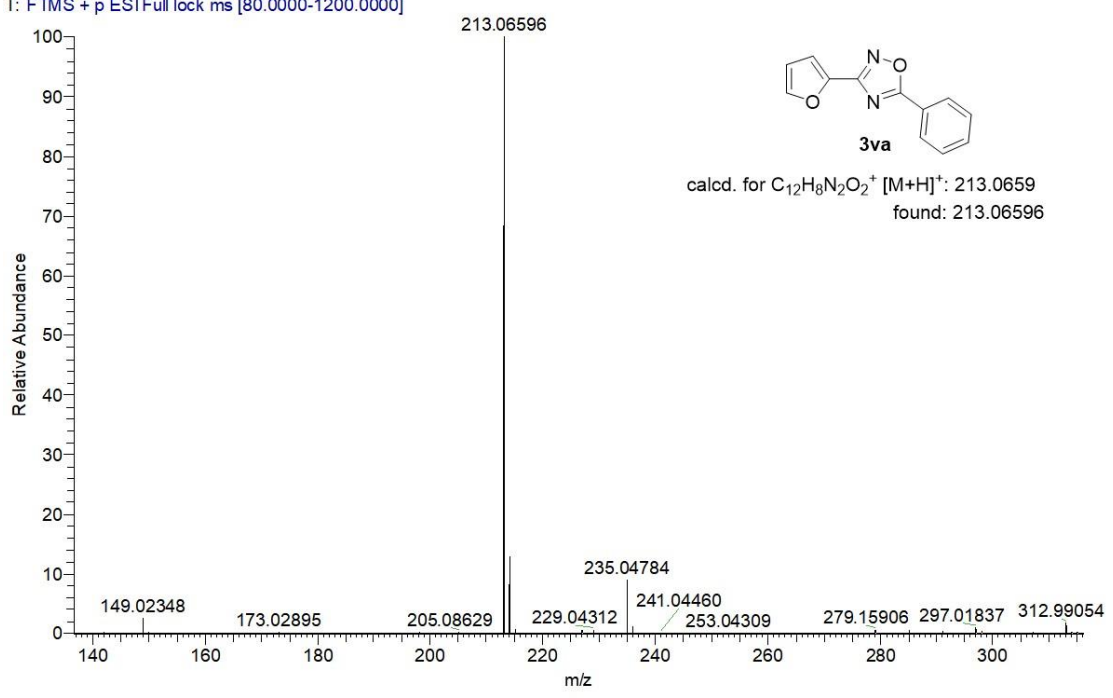
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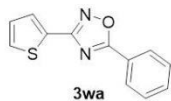
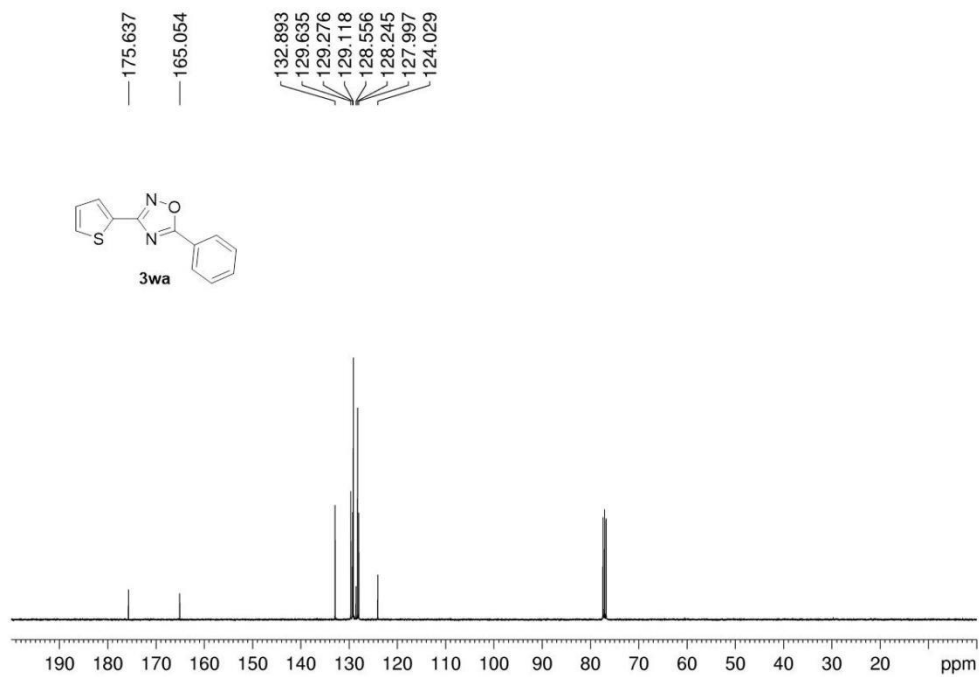
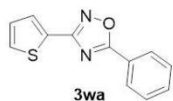
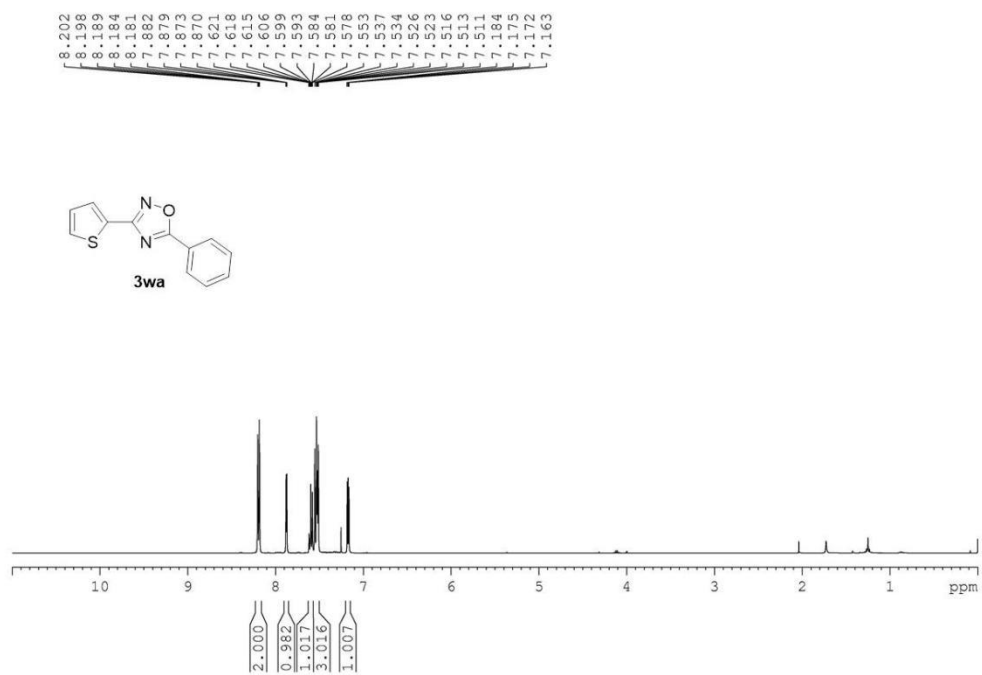


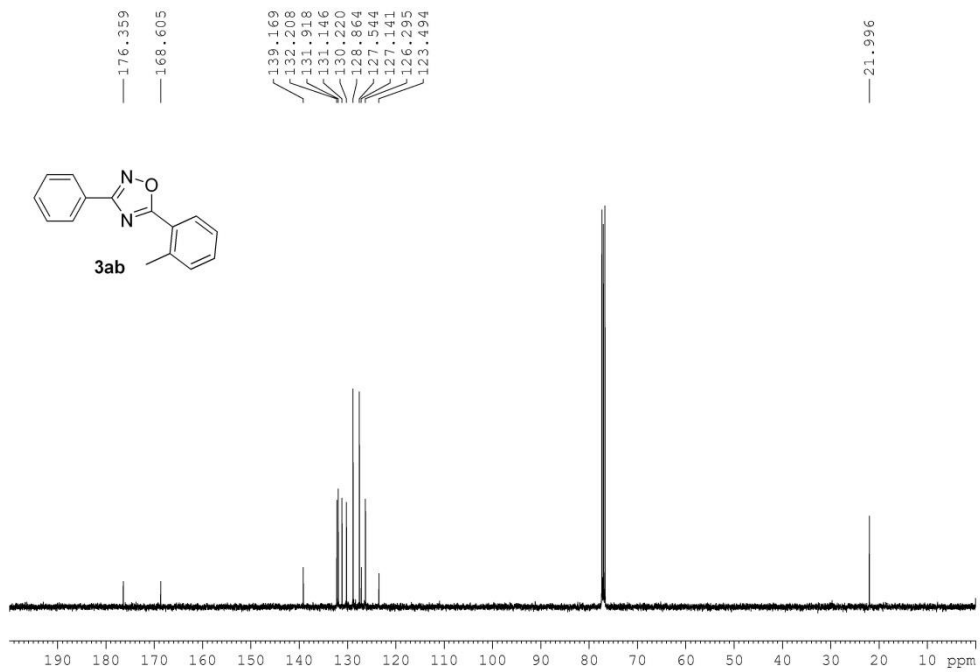
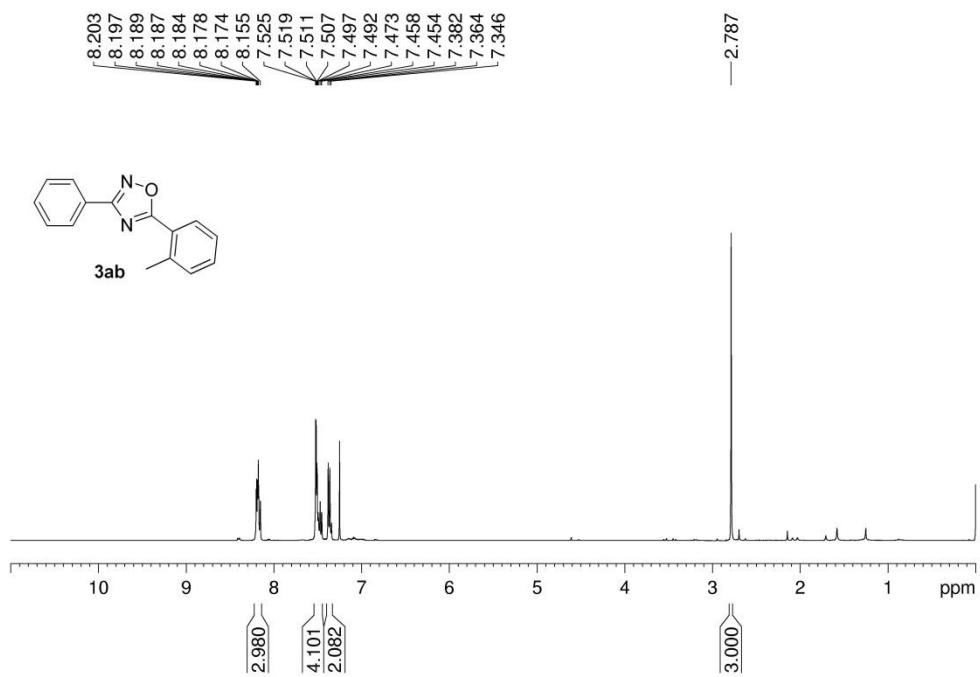
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 \ 132.982
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 \ 111.874

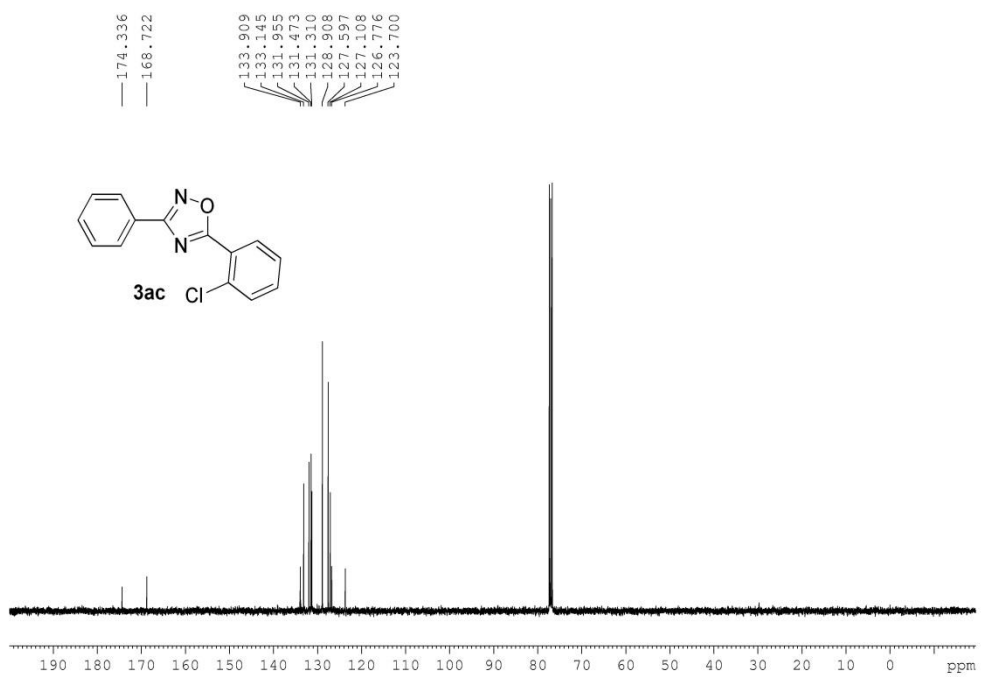
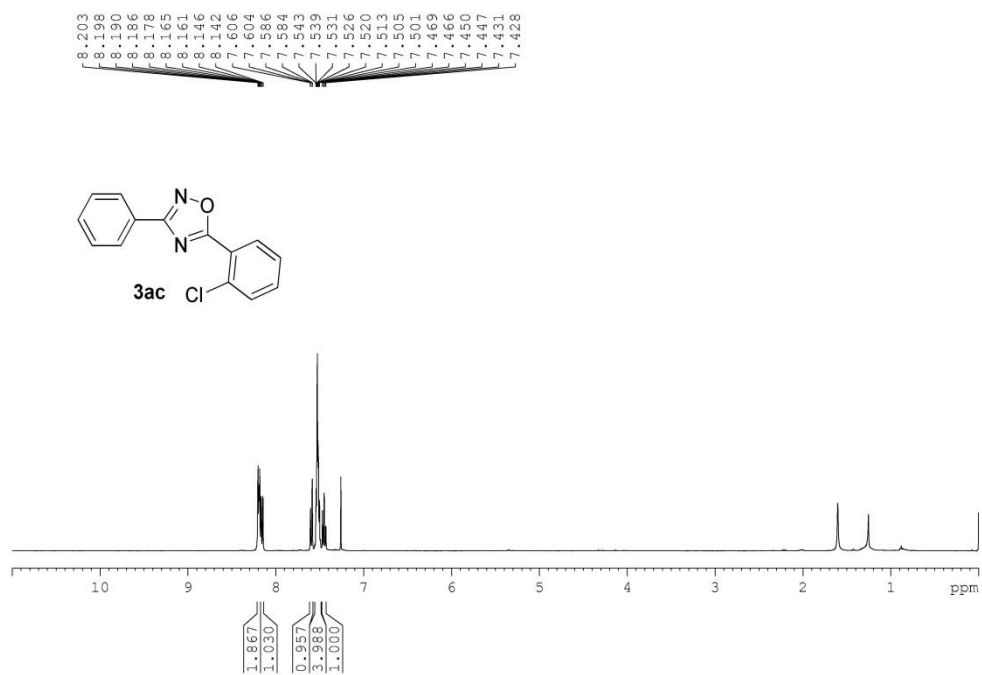


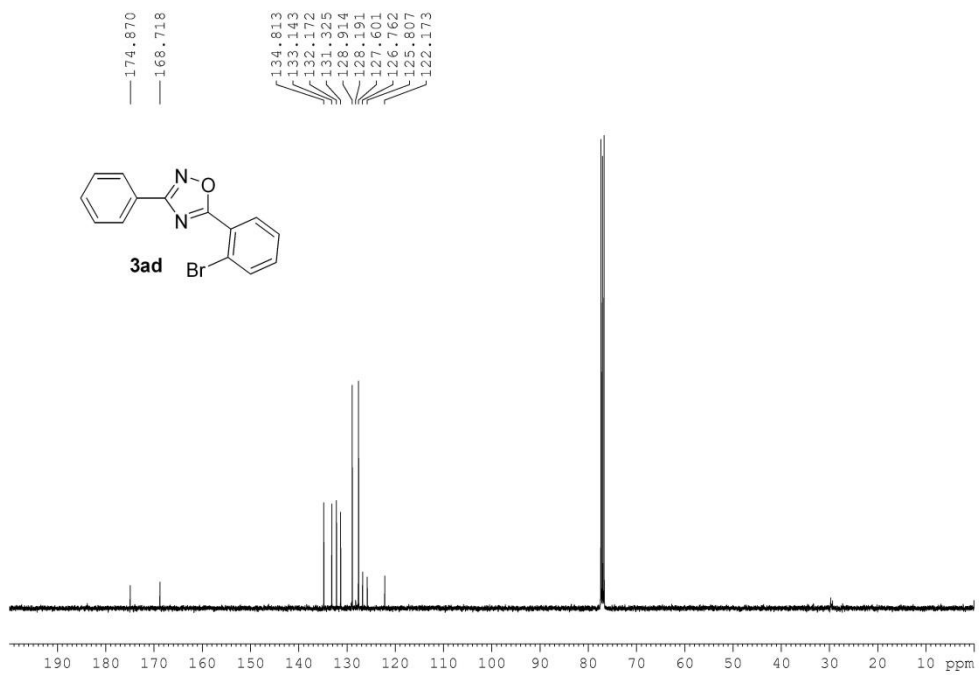
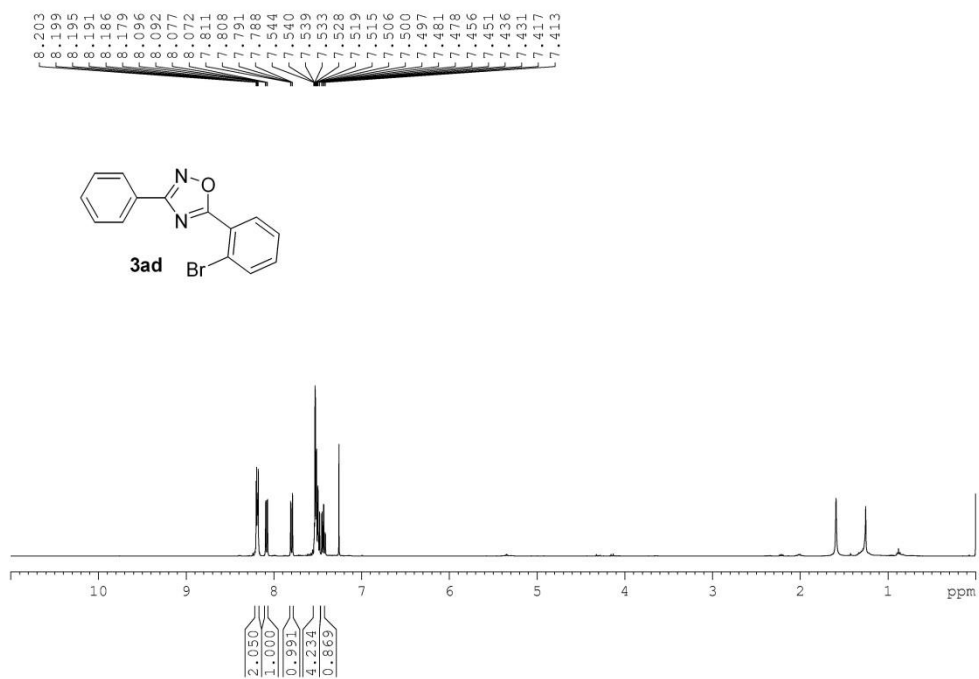
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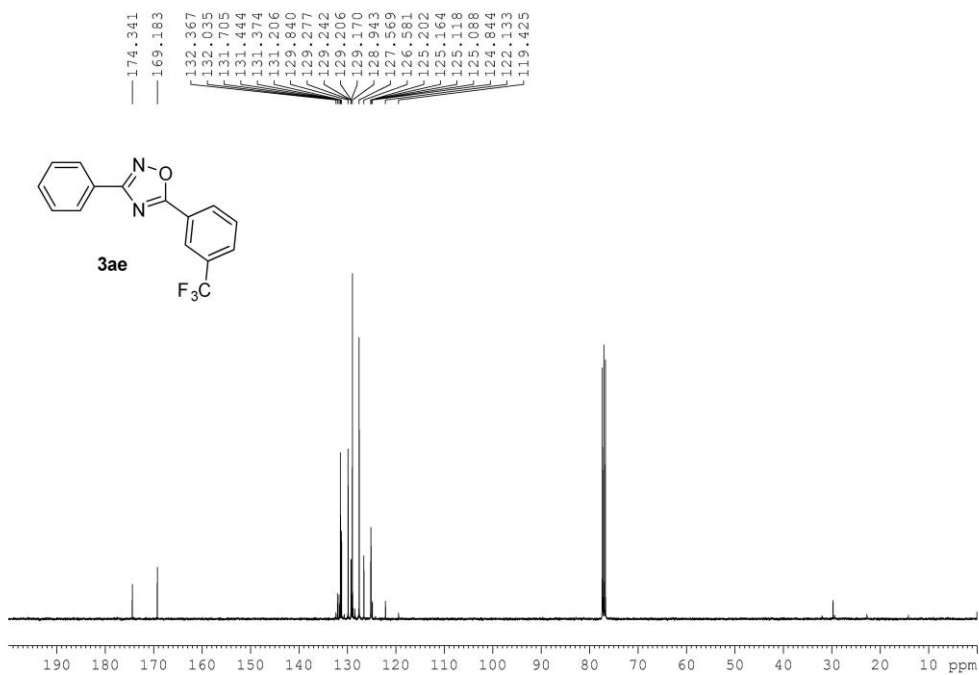
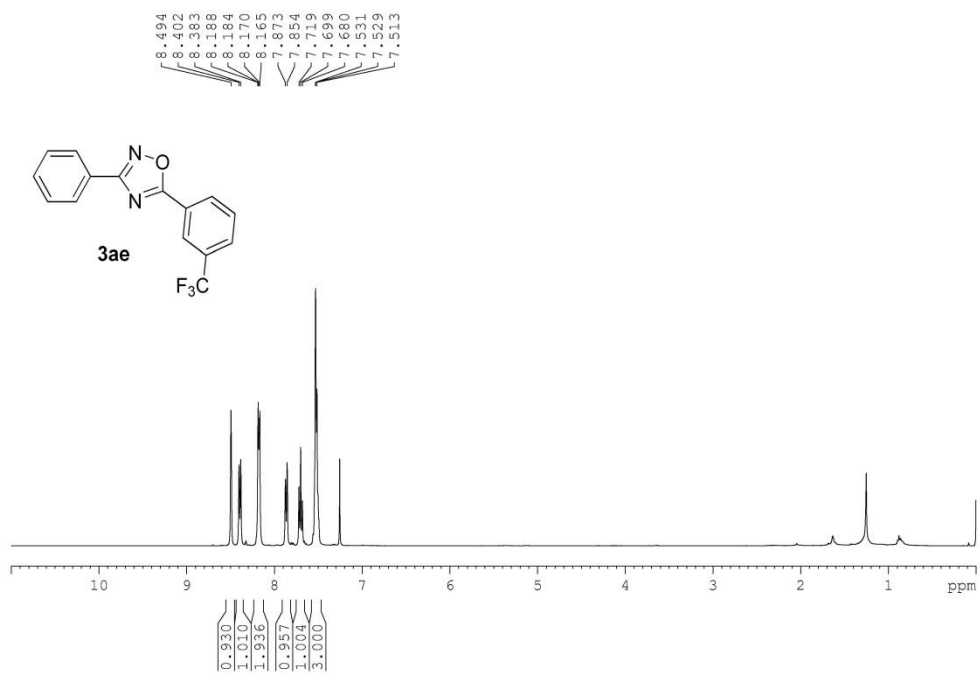


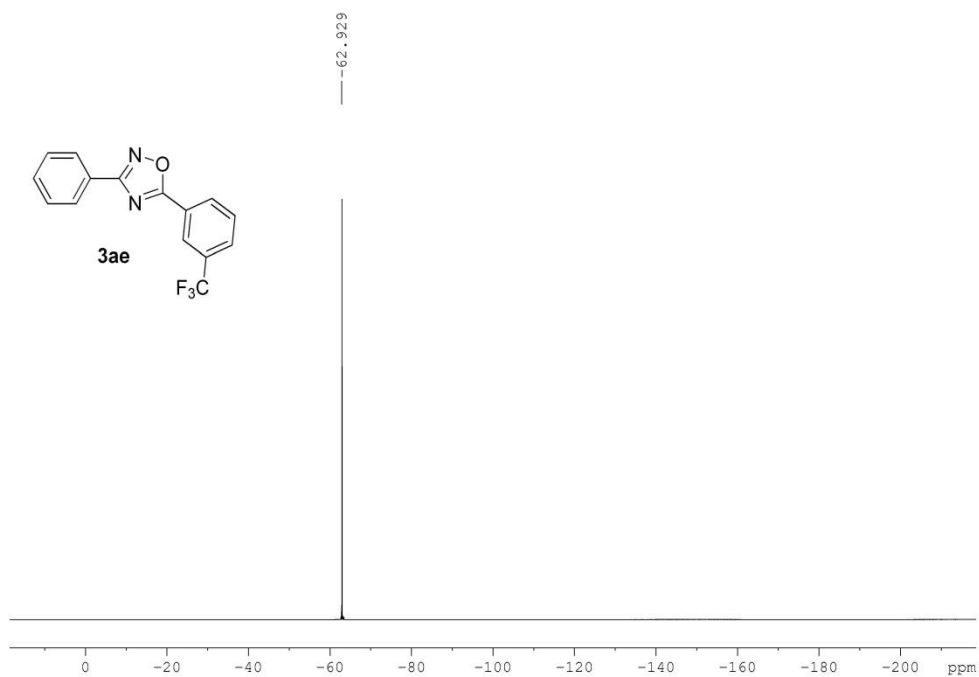


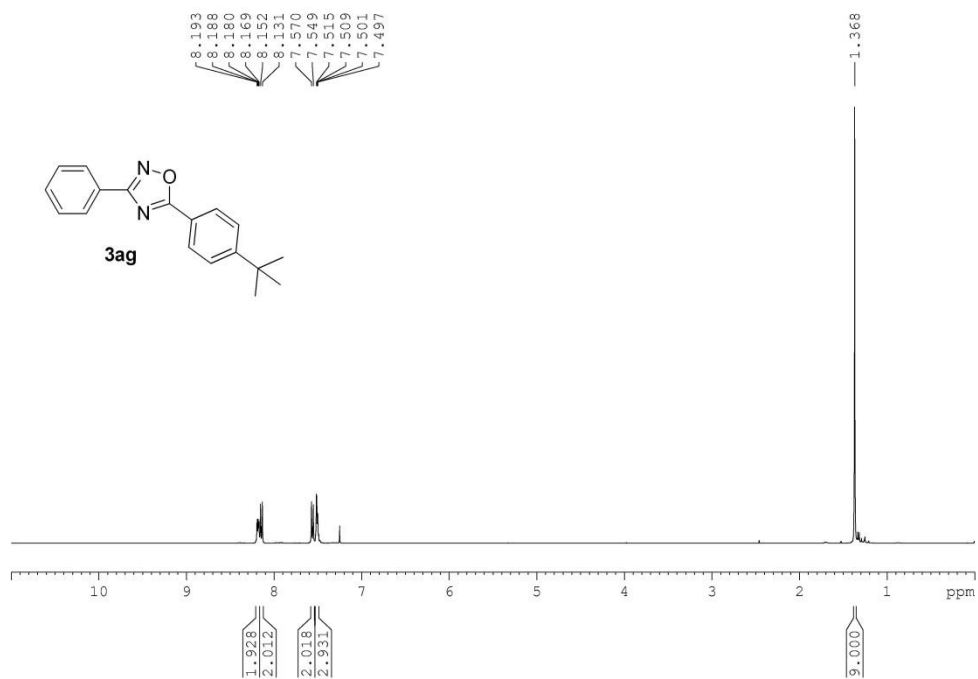
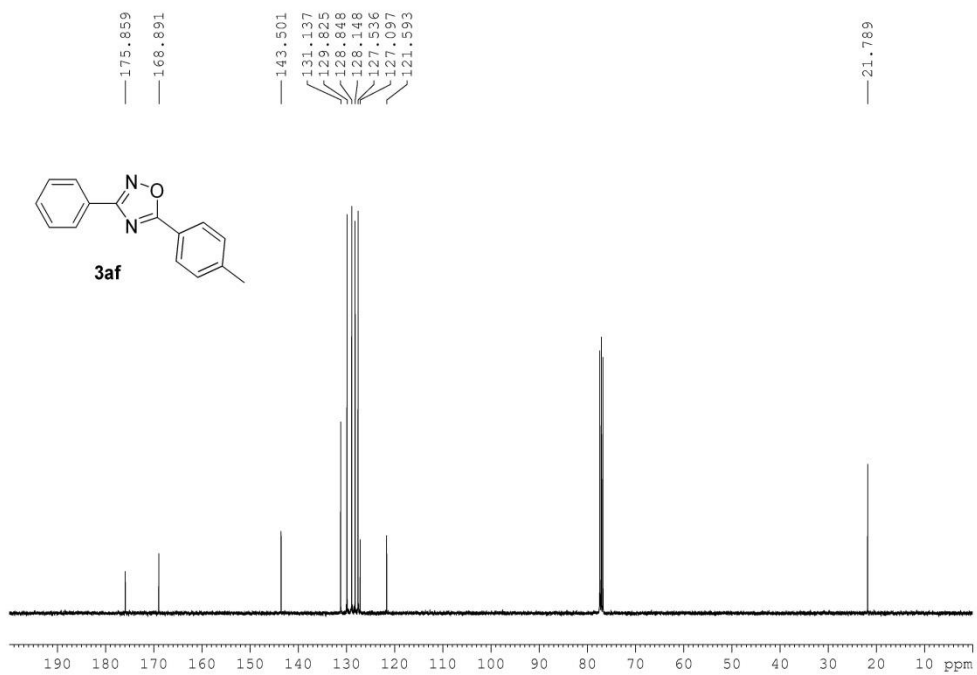


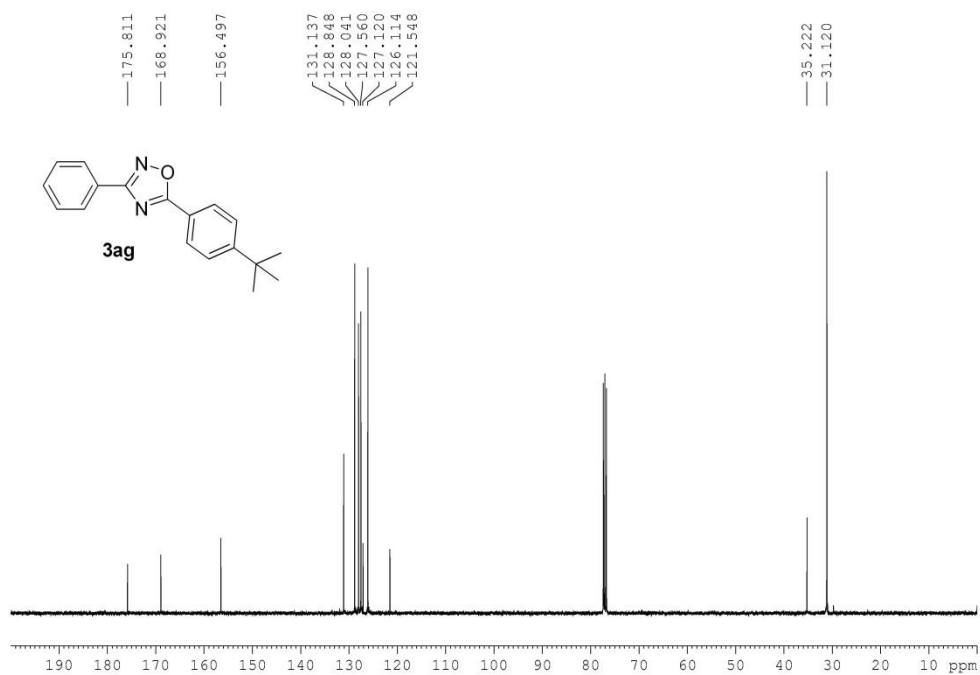




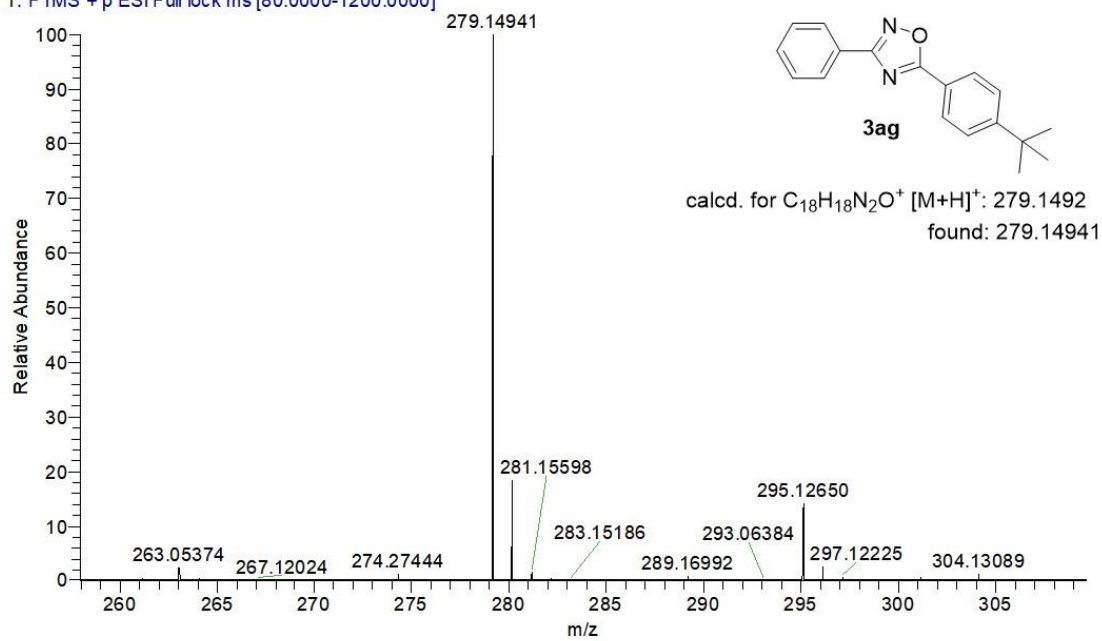


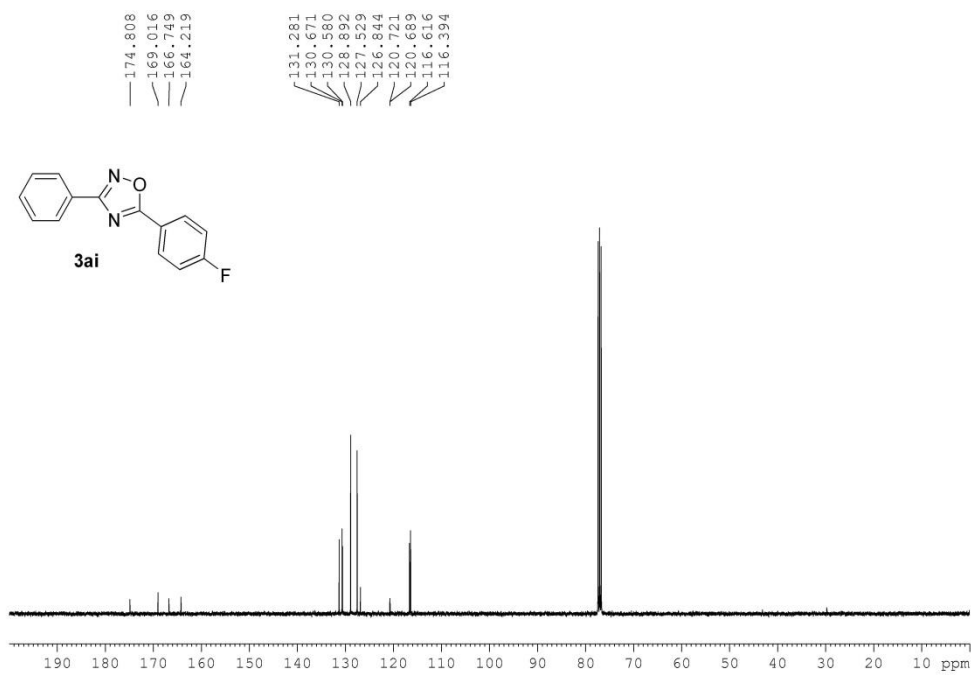
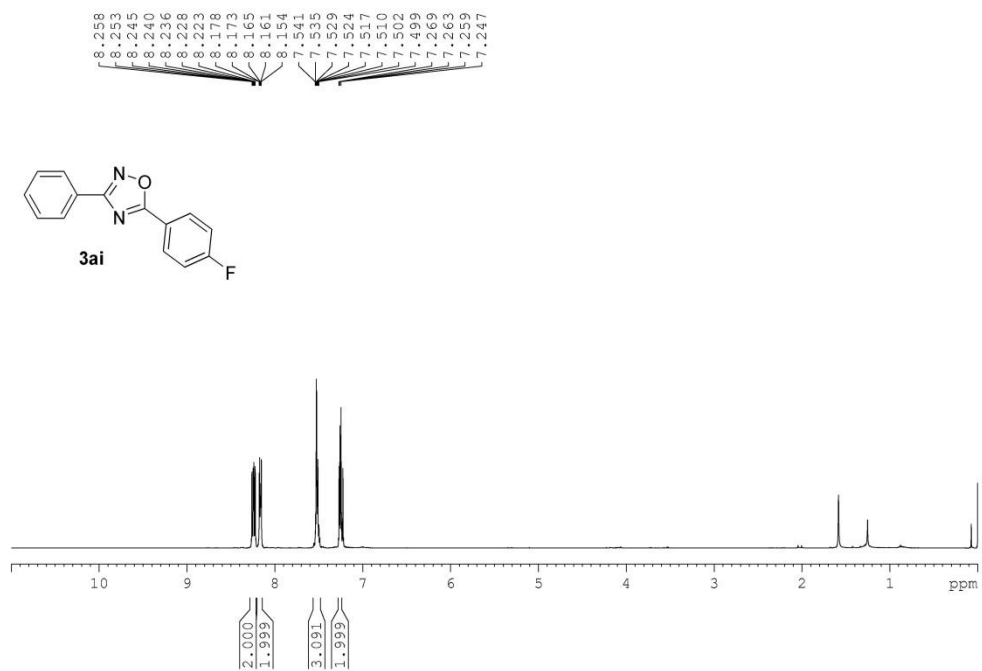


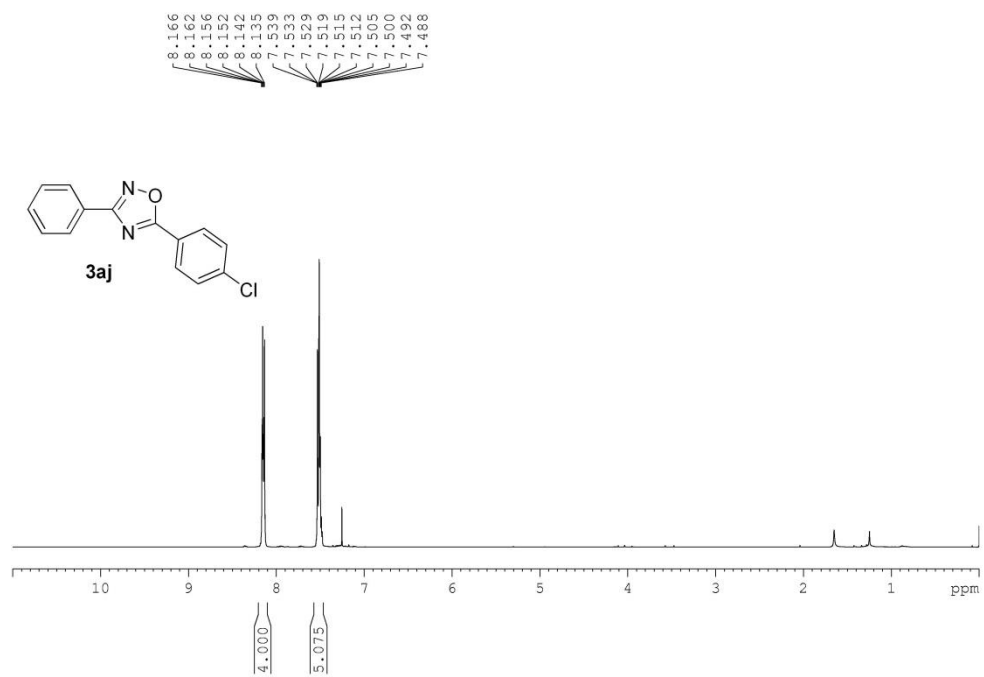
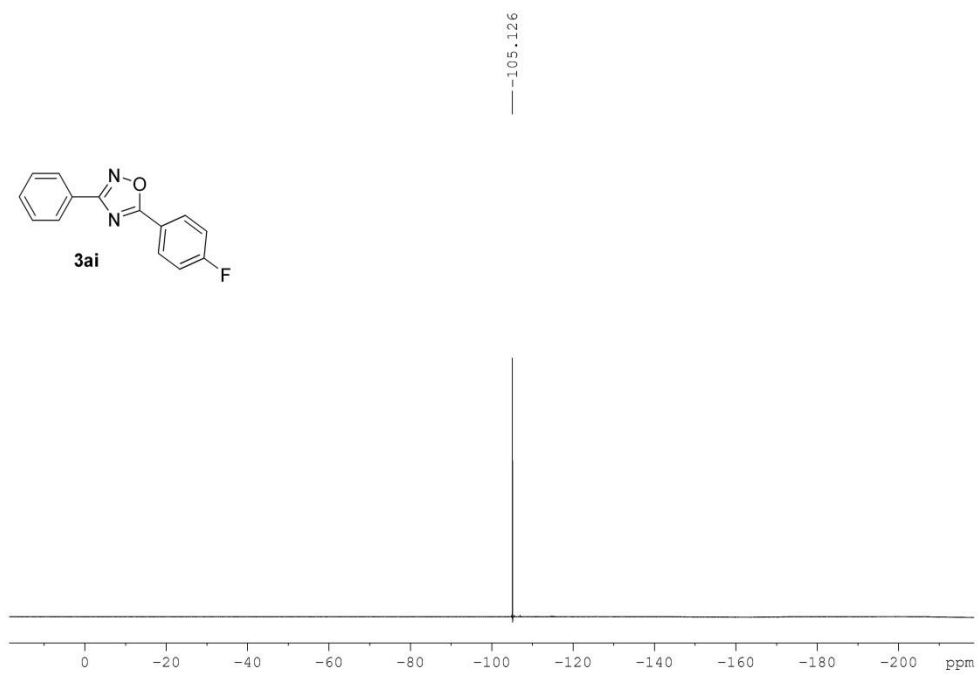


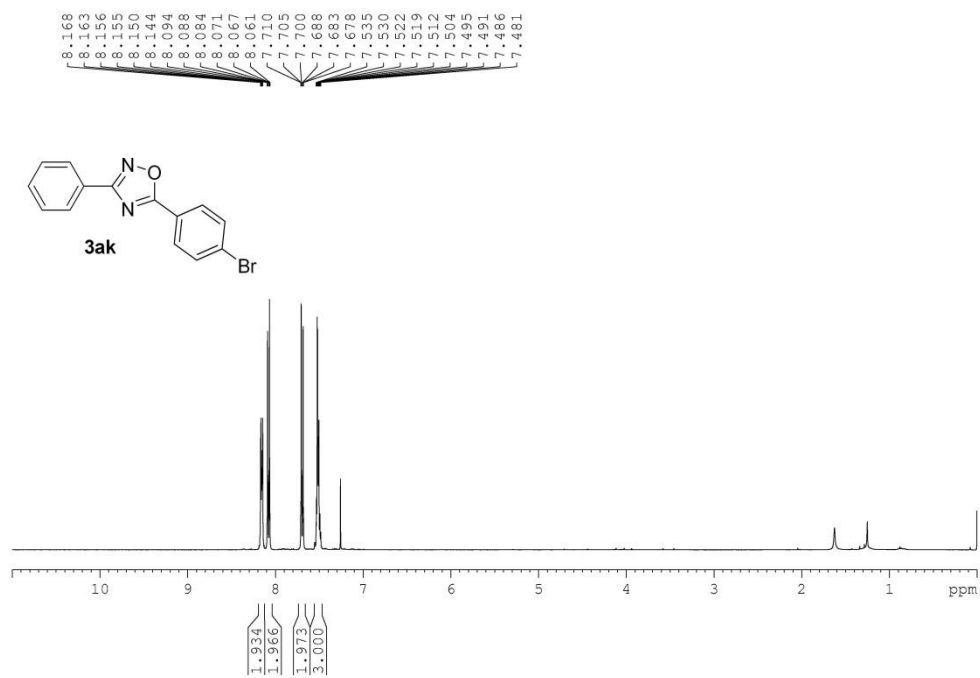
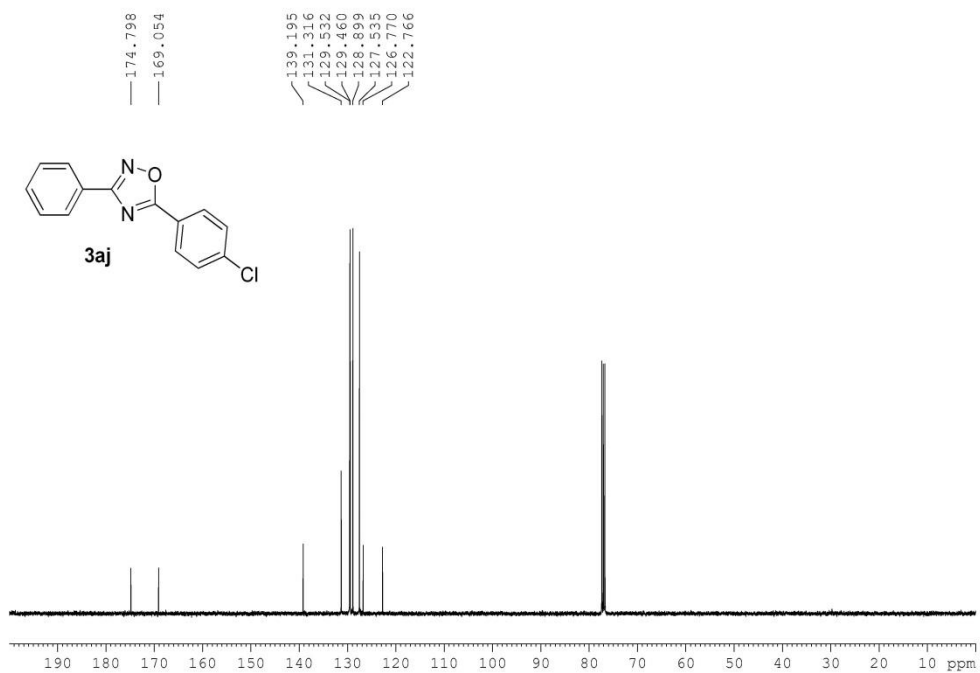


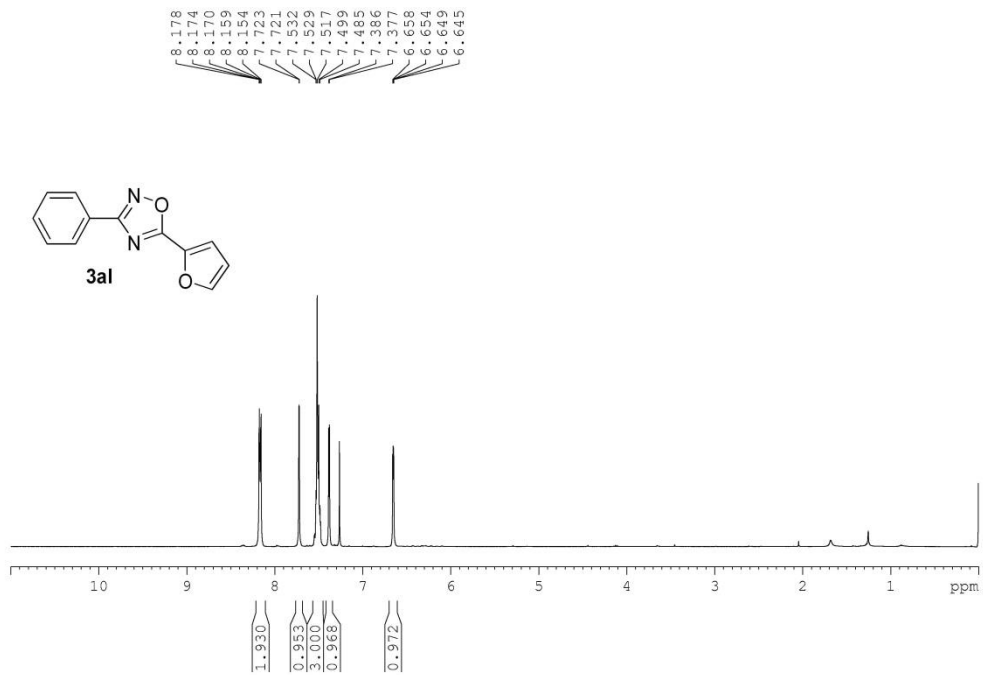
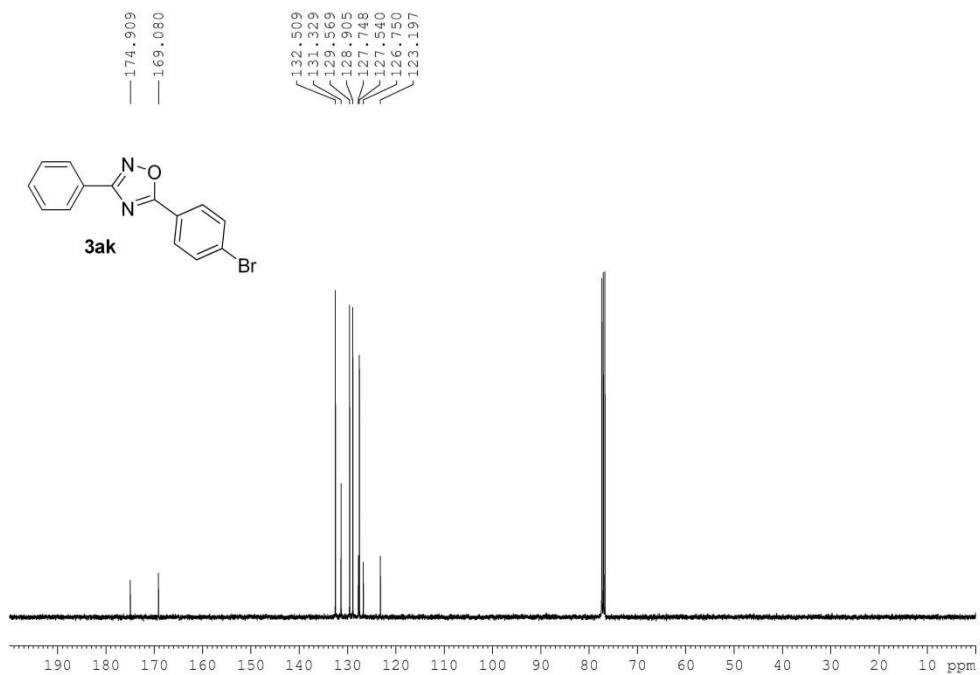
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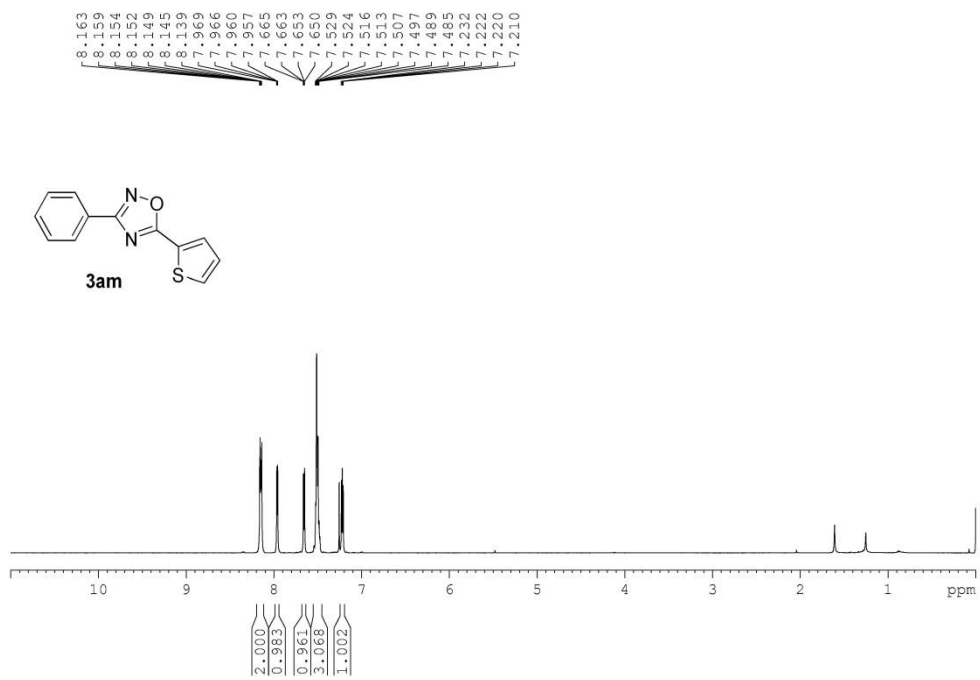
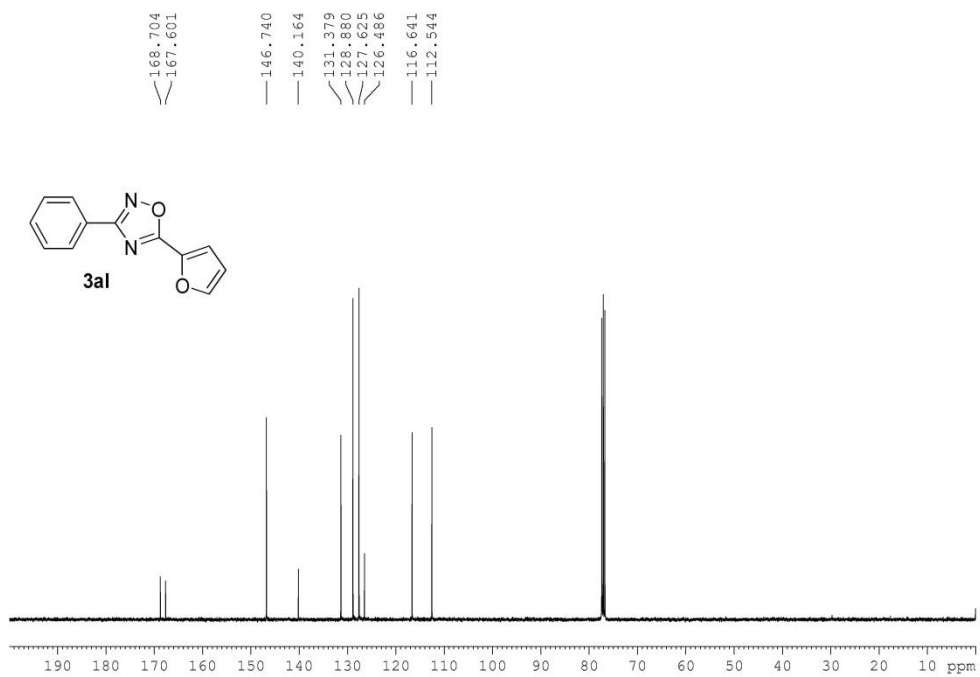


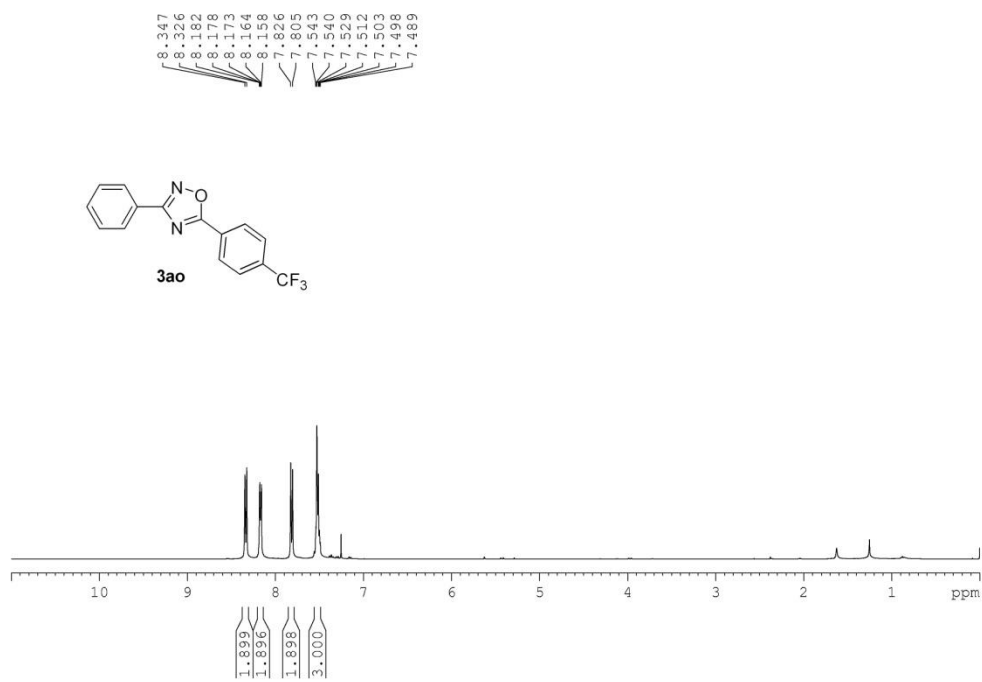
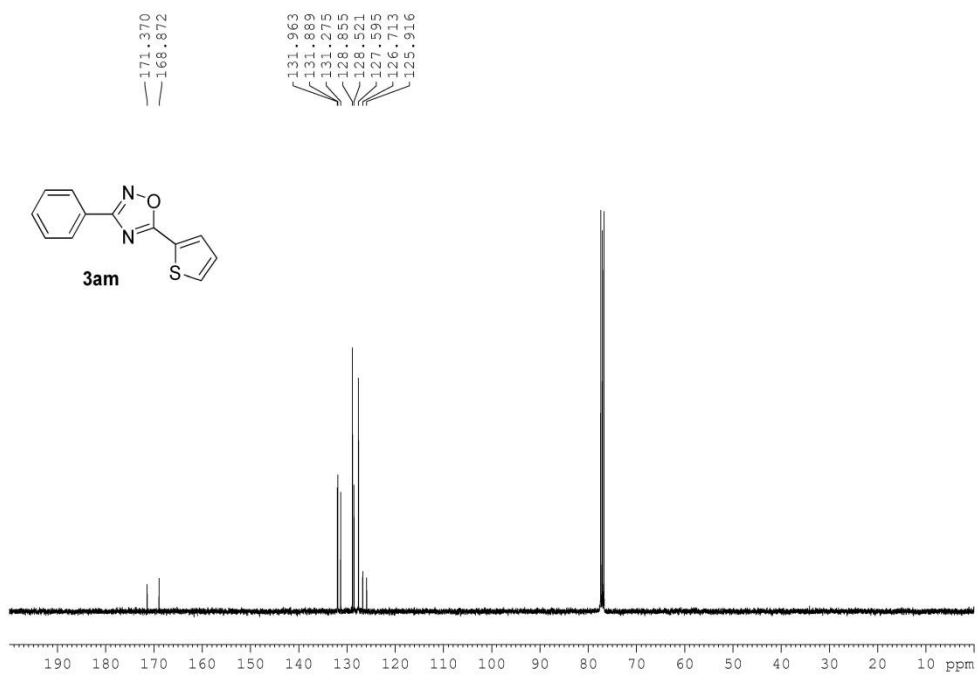


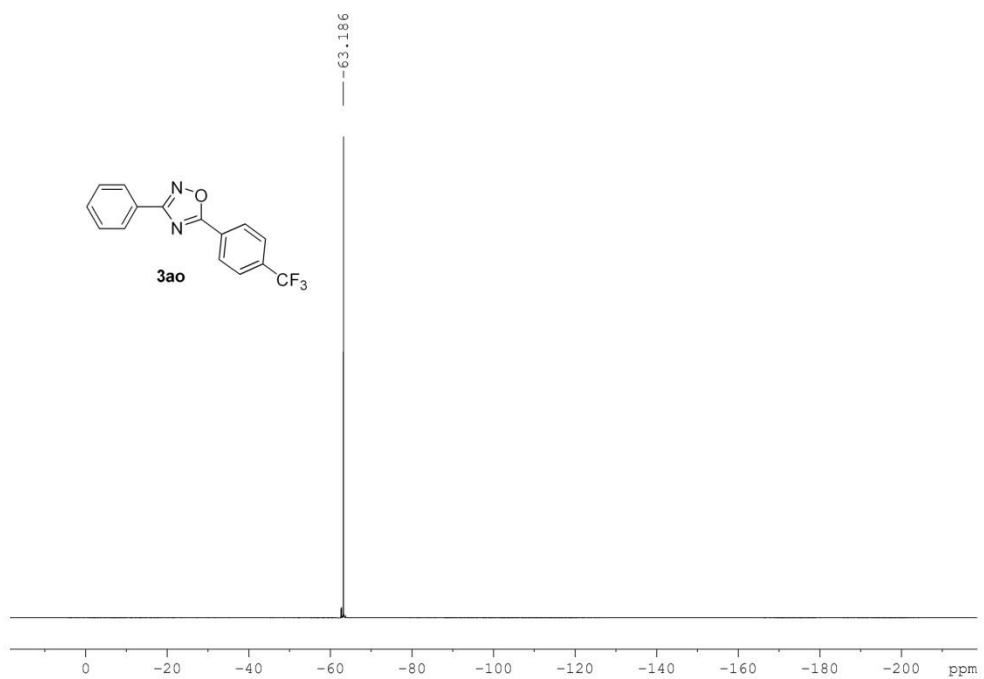
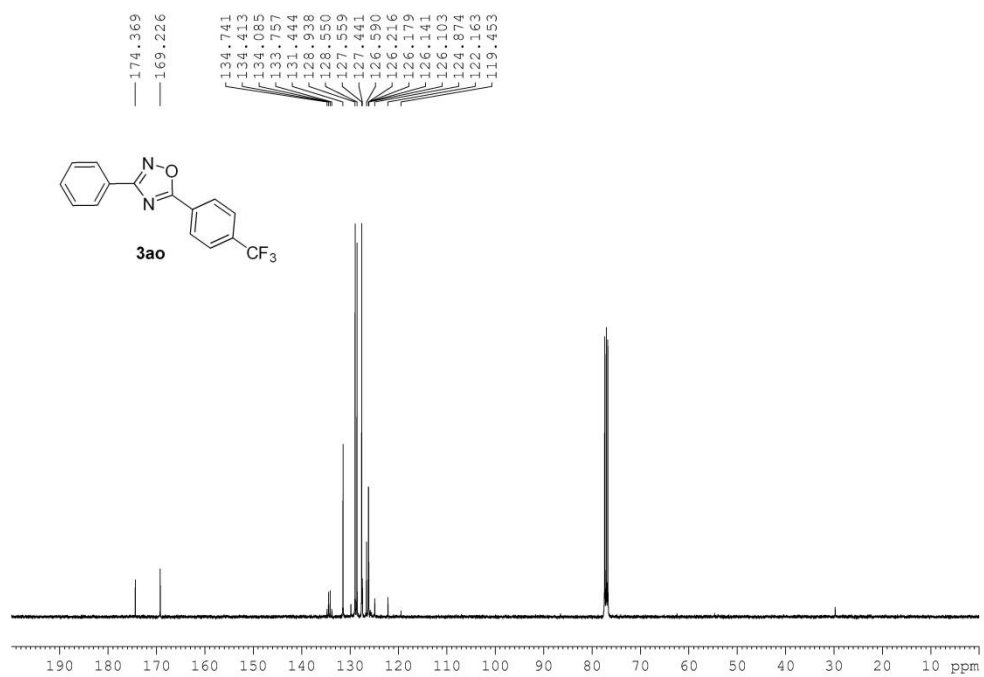


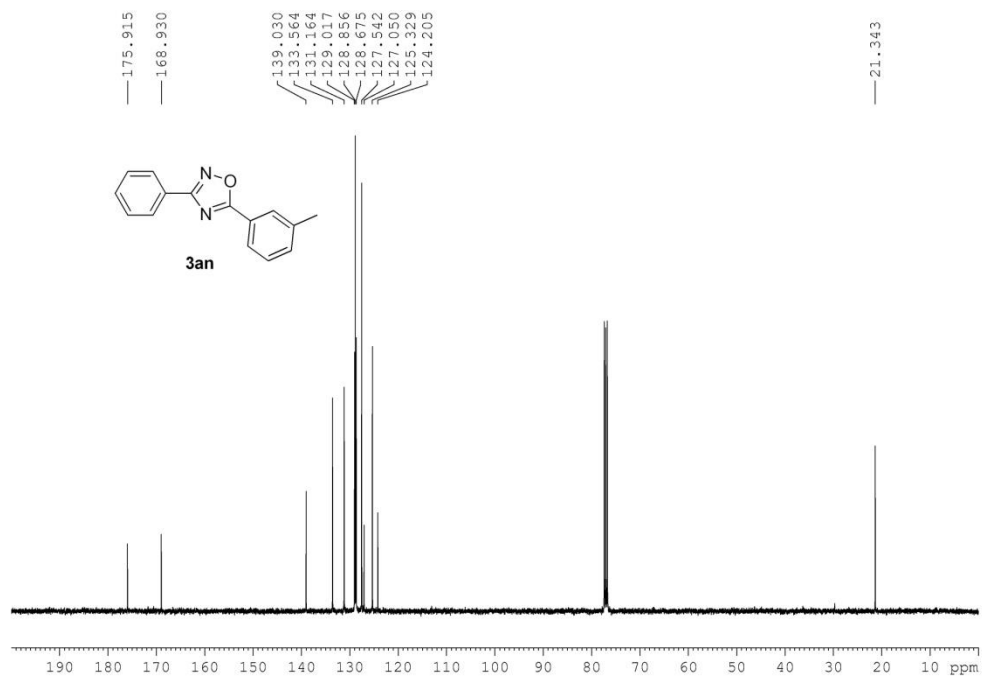
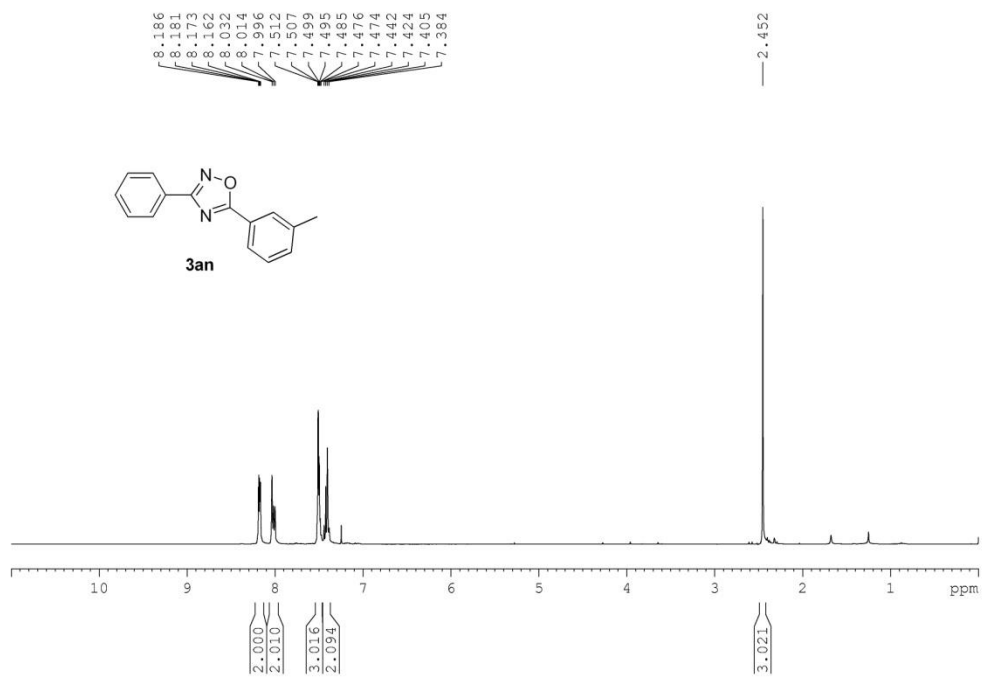


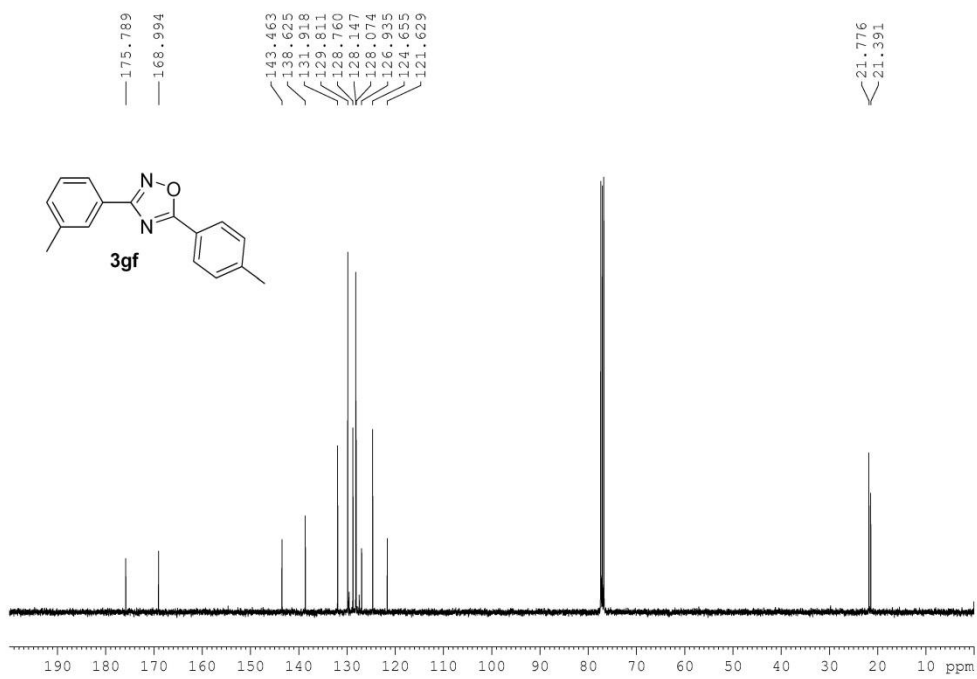
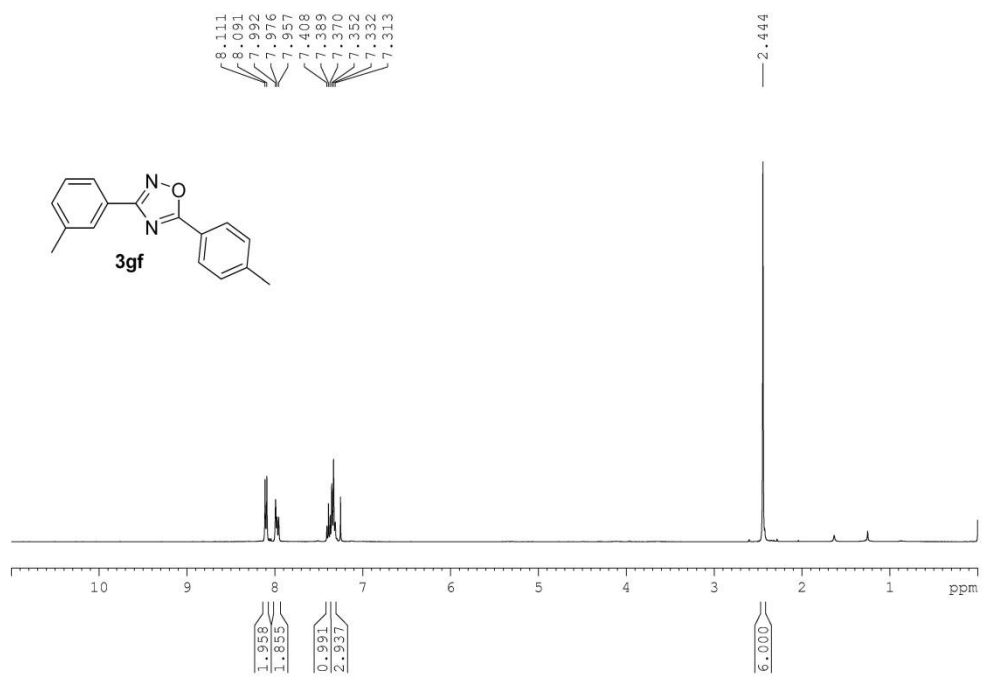


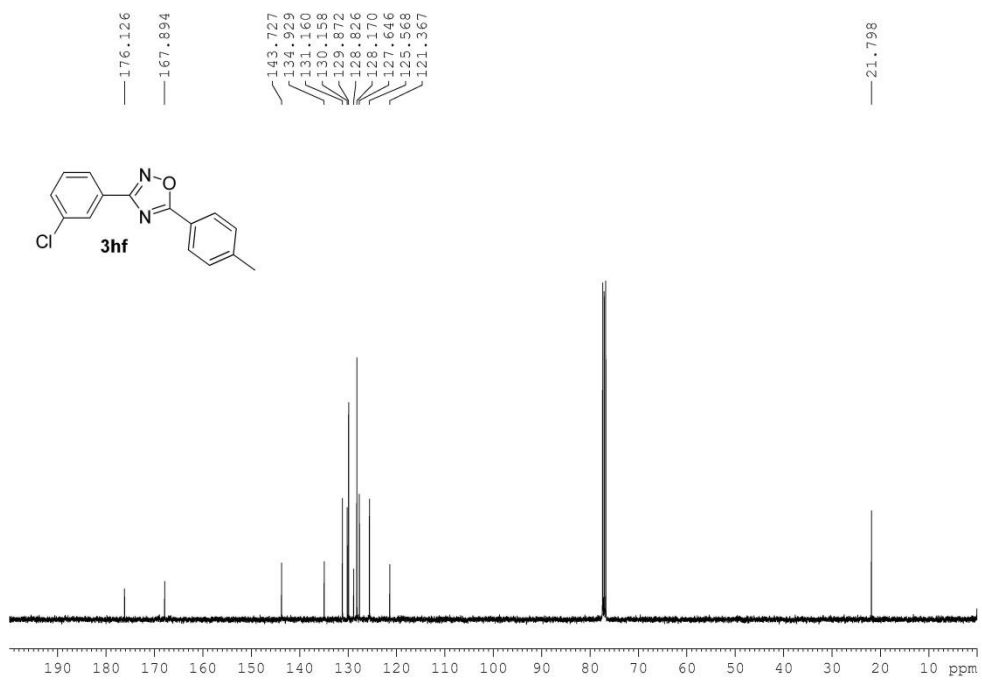
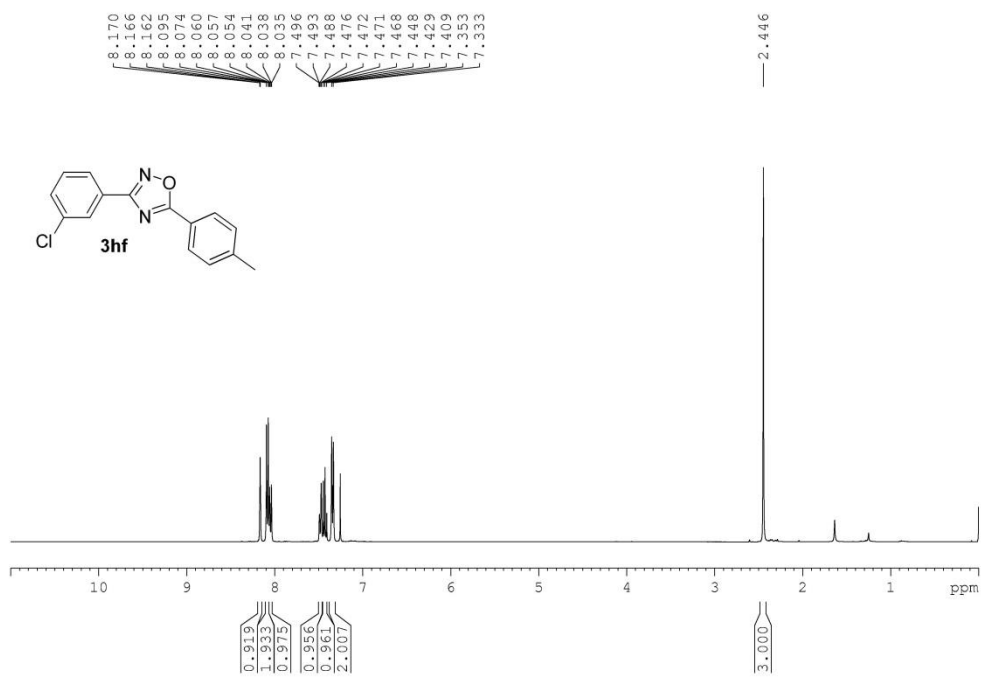


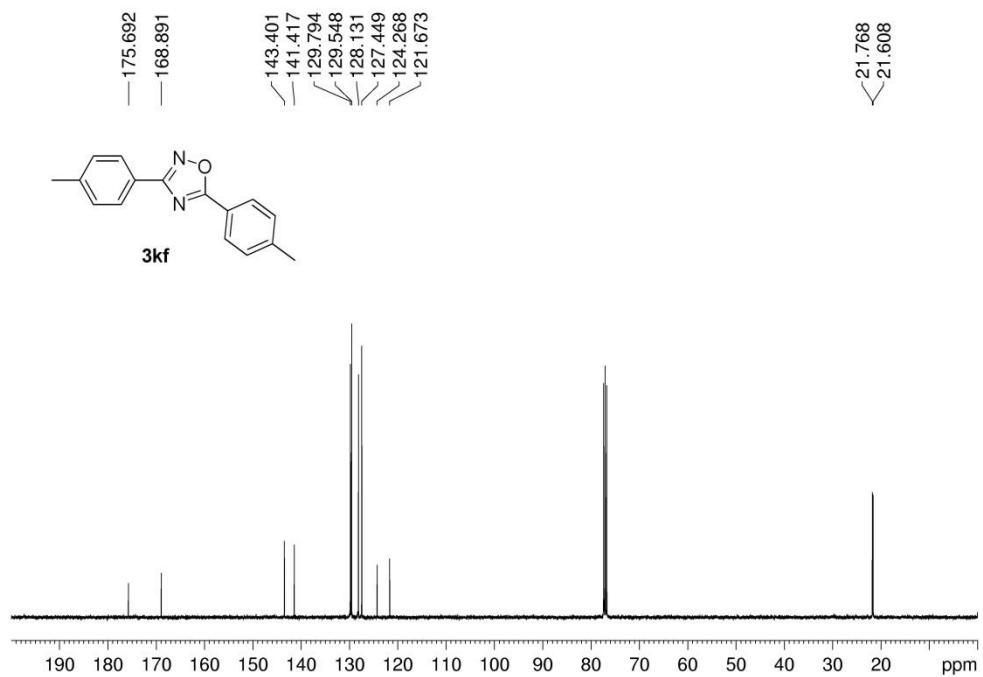
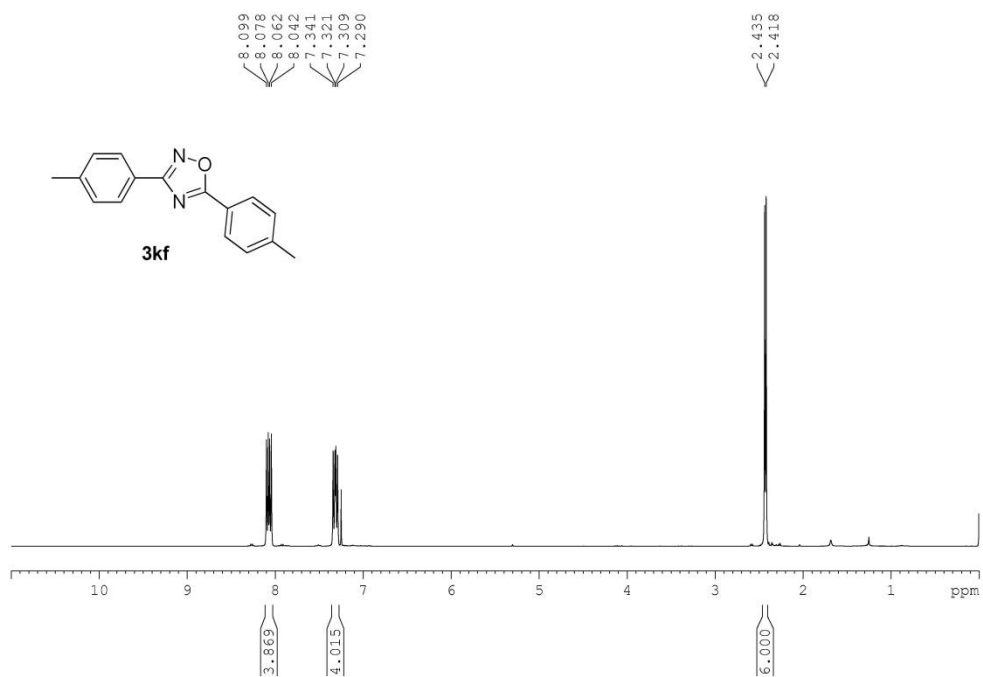


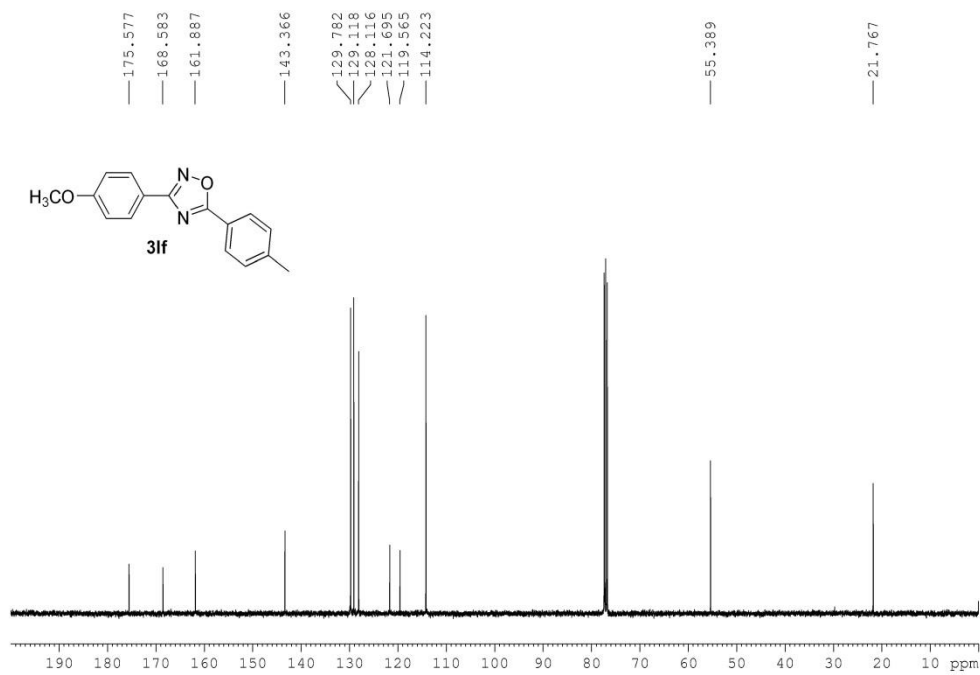
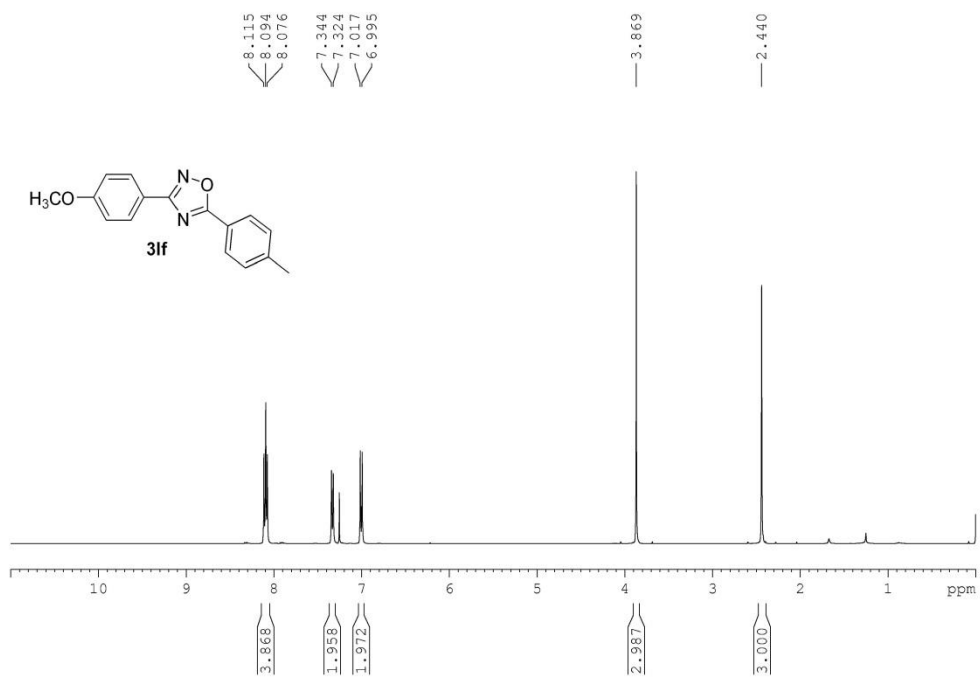


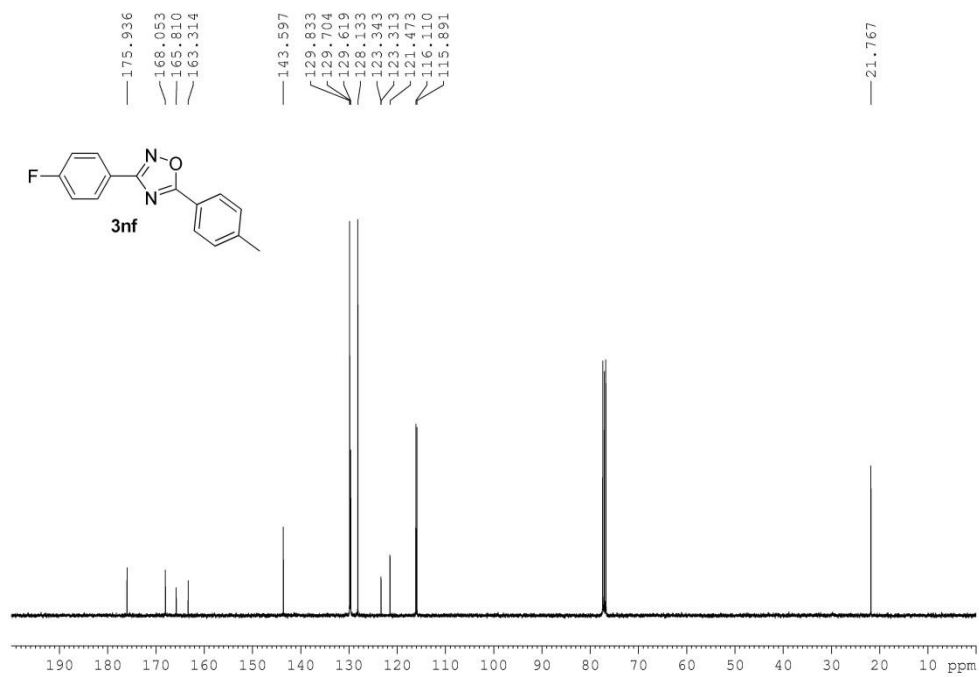
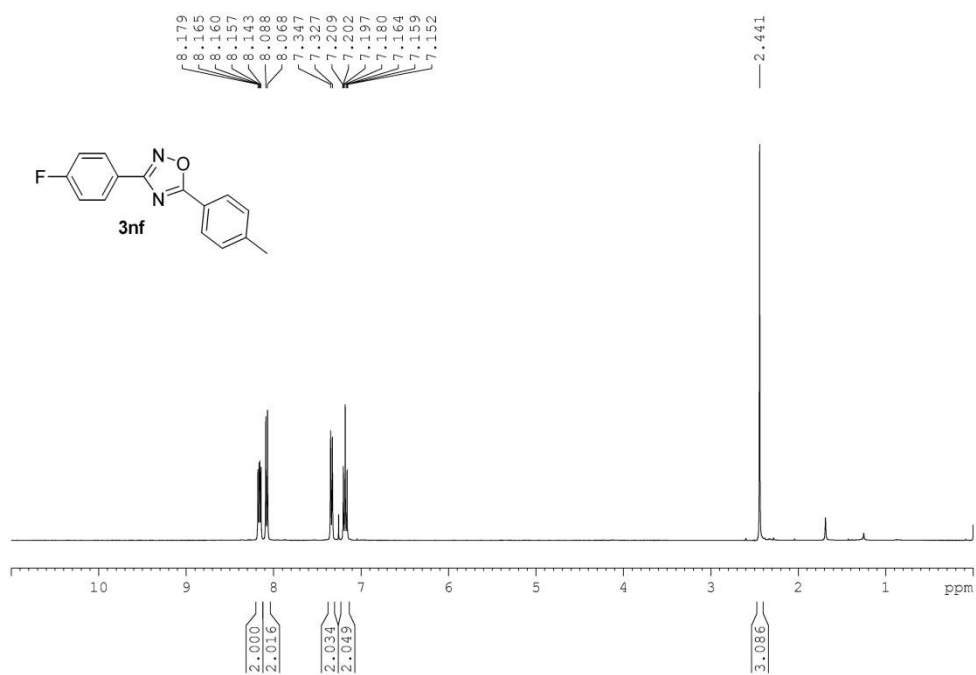


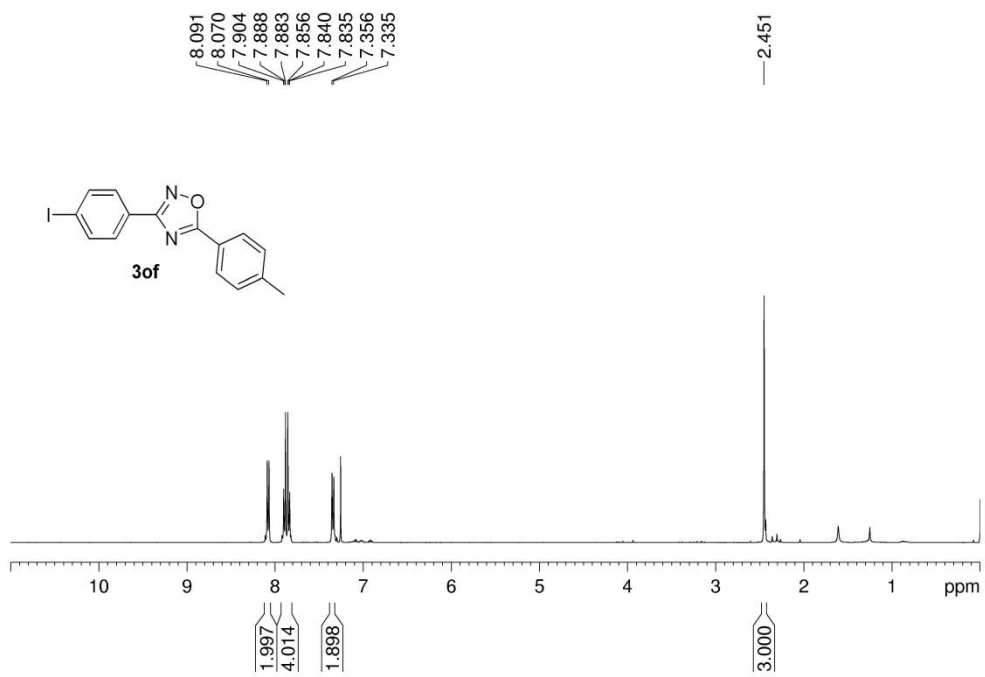
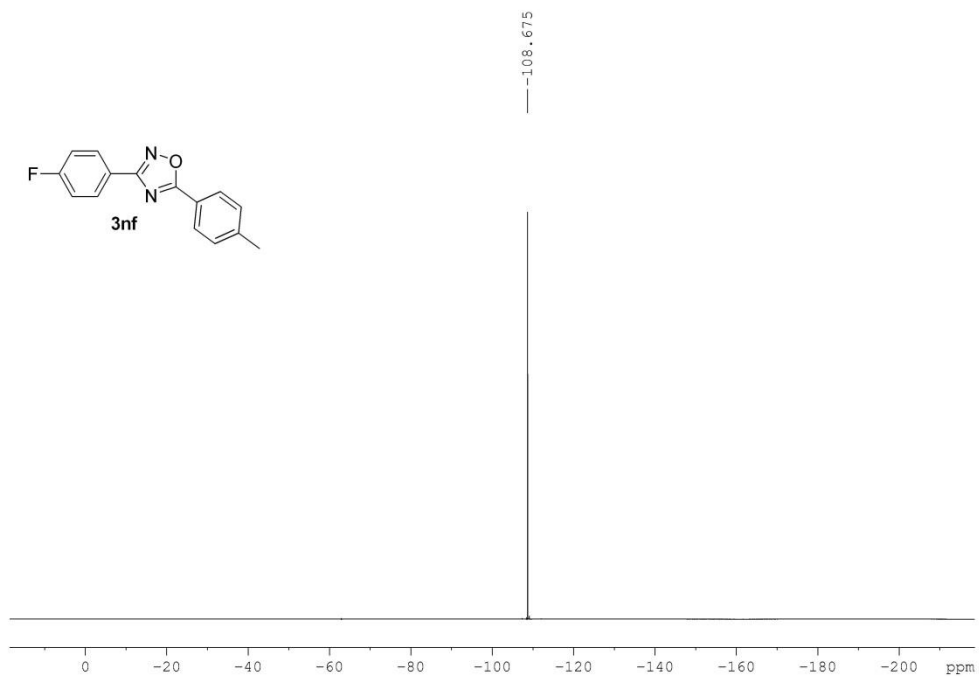


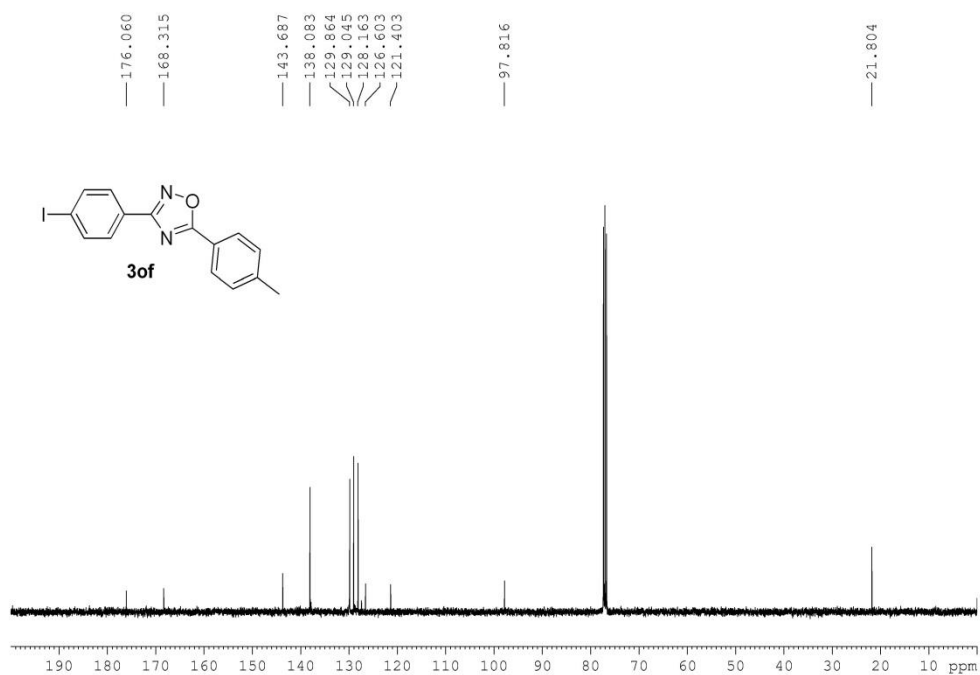




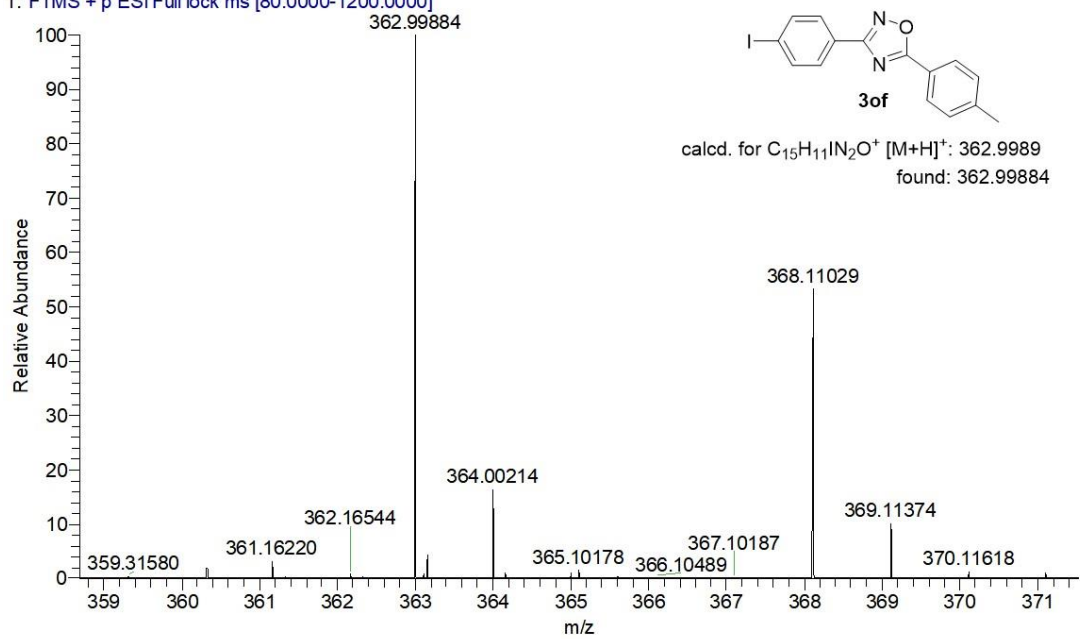




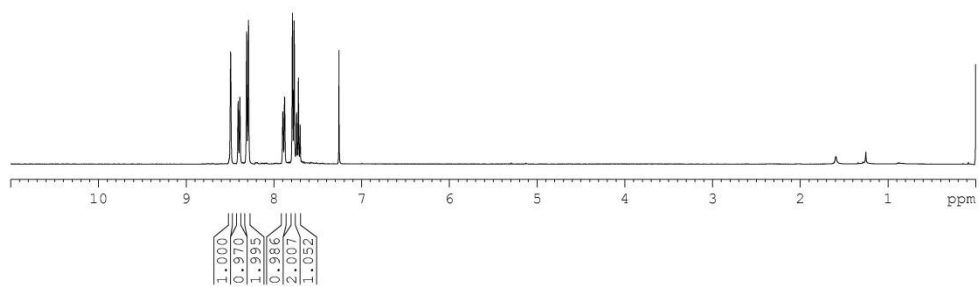
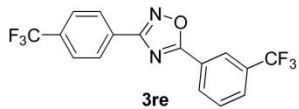




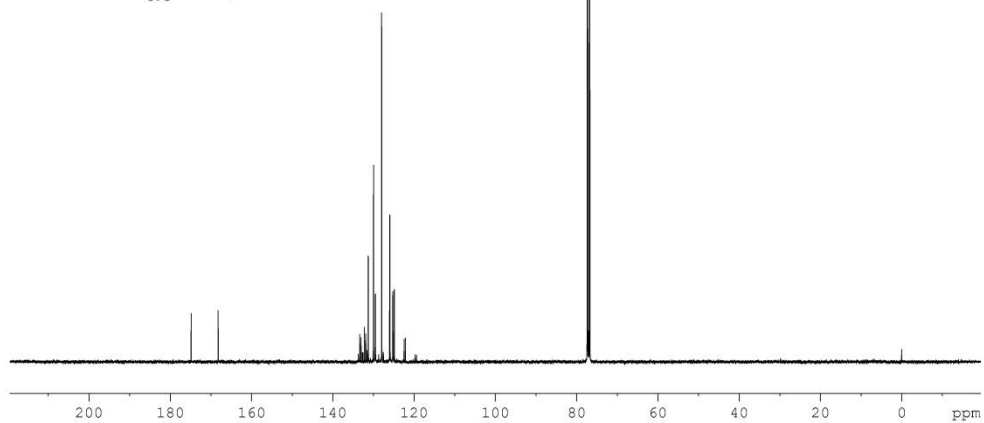
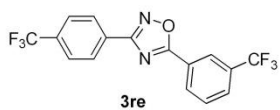
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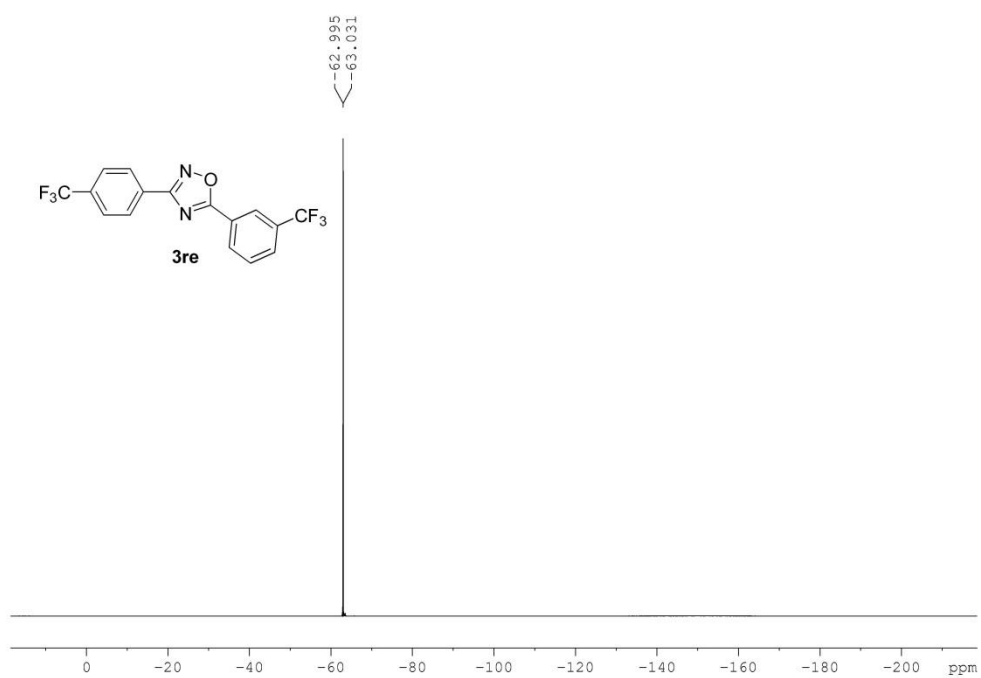


8.495
8.409
8.389
8.312
8.291
7.899
7.879
7.790
7.769
7.742
7.722
7.702

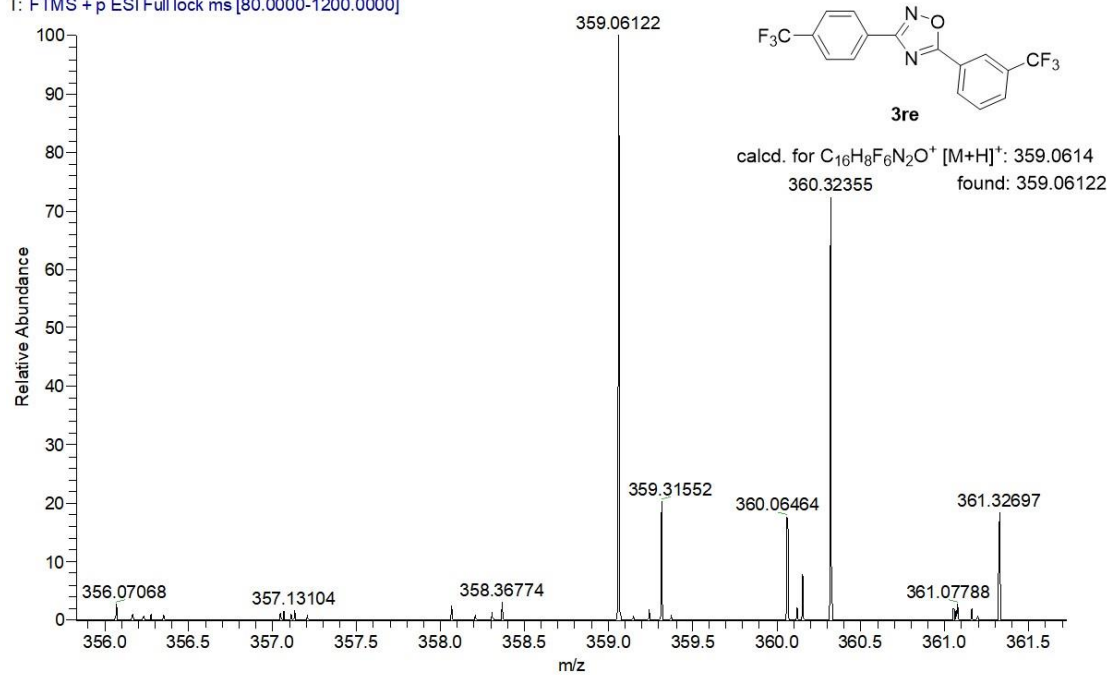


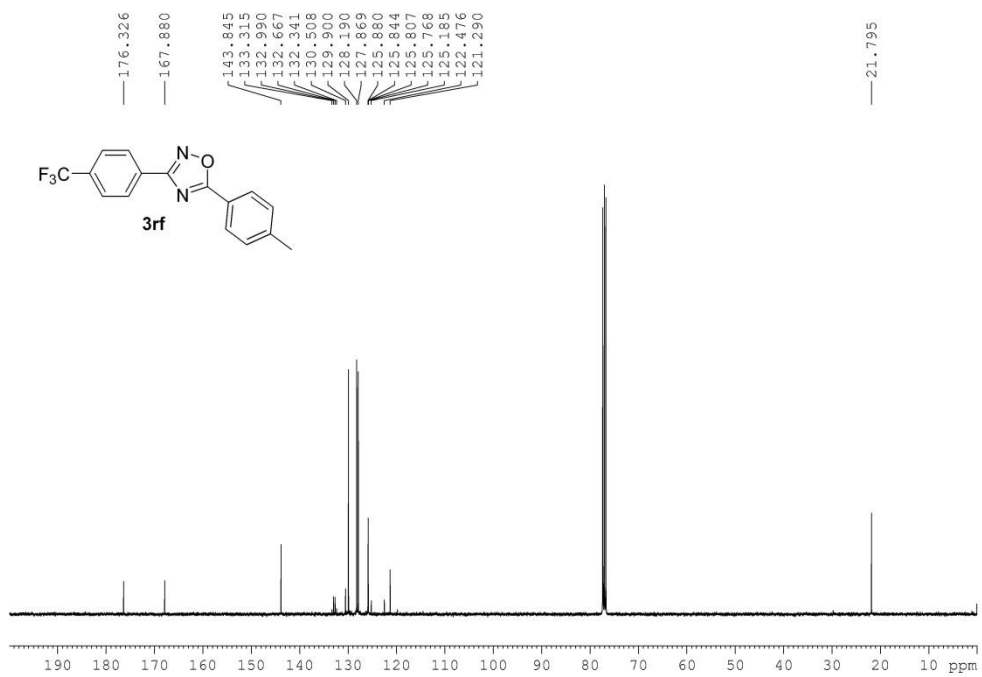
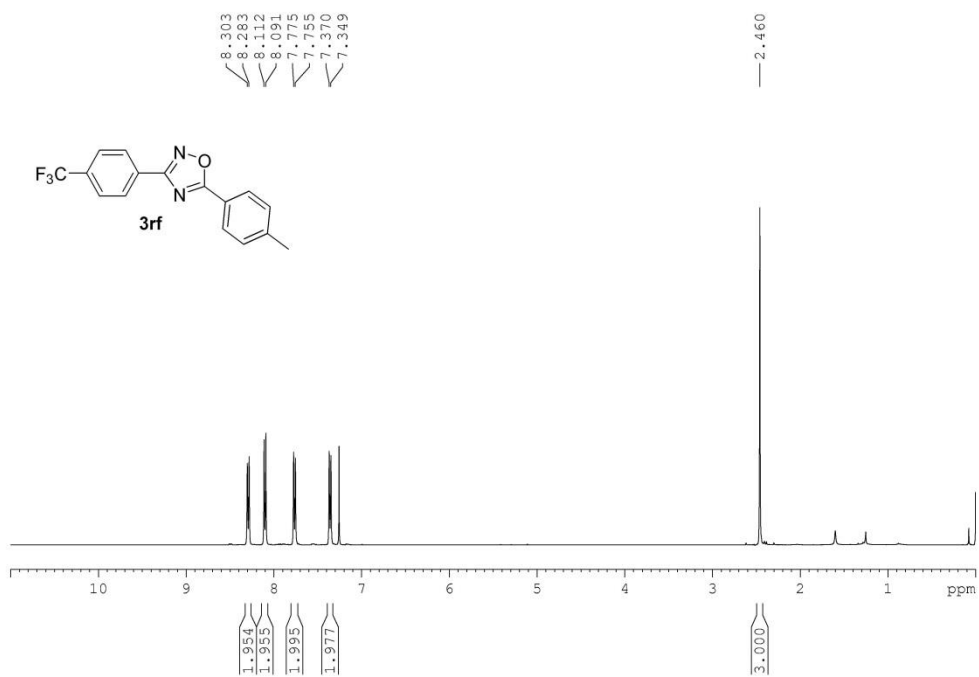
174.842
168.189
158.664
153.538
153.013
132.688
132.515
132.185
131.853
131.522
131.256
129.955
129.565
129.530
129.494
129.458
128.708
127.946
127.839
127.513
126.009
125.973
125.926
125.868
125.264
125.226
125.167
125.148
124.839
124.805
122.422
122.094
119.714
119.385

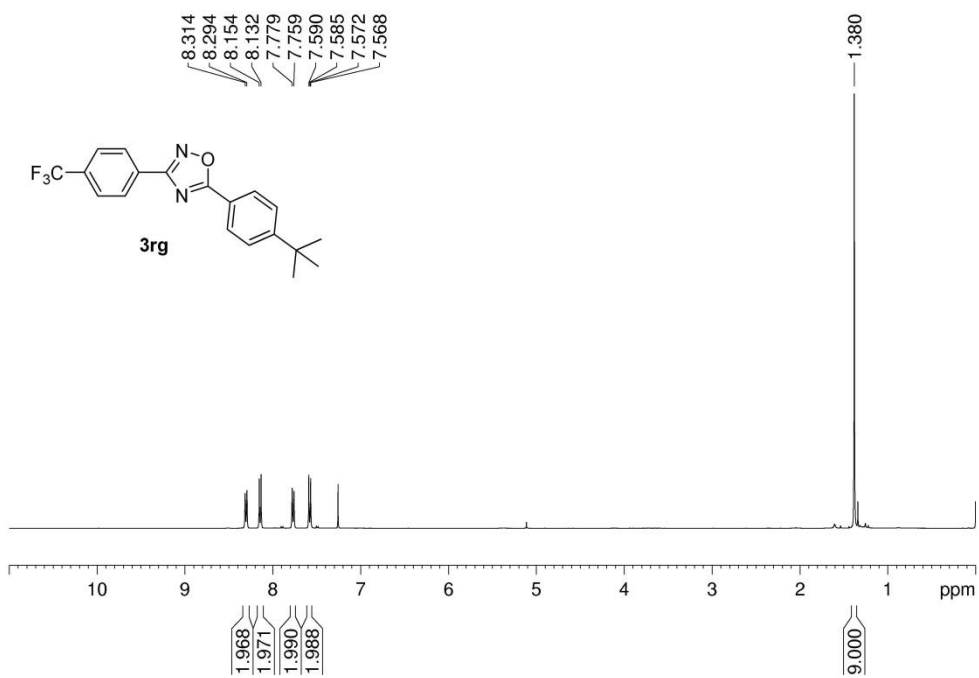
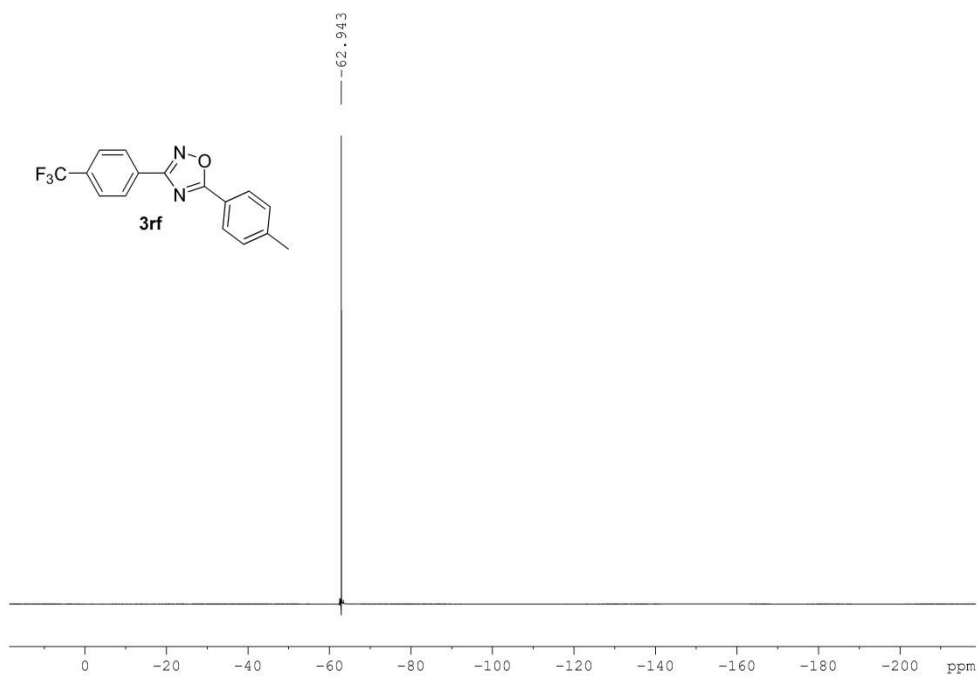


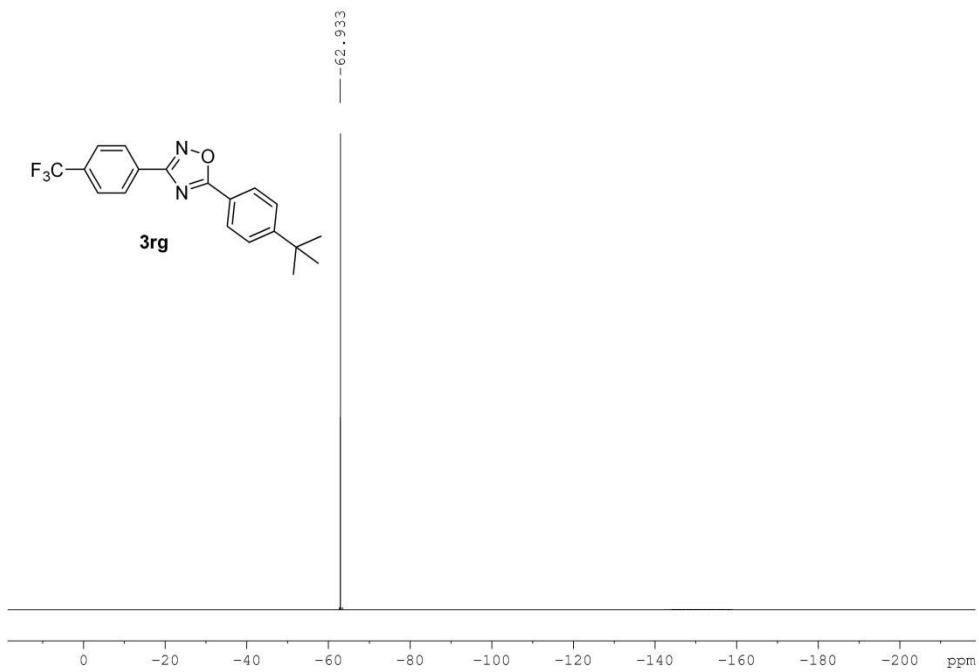
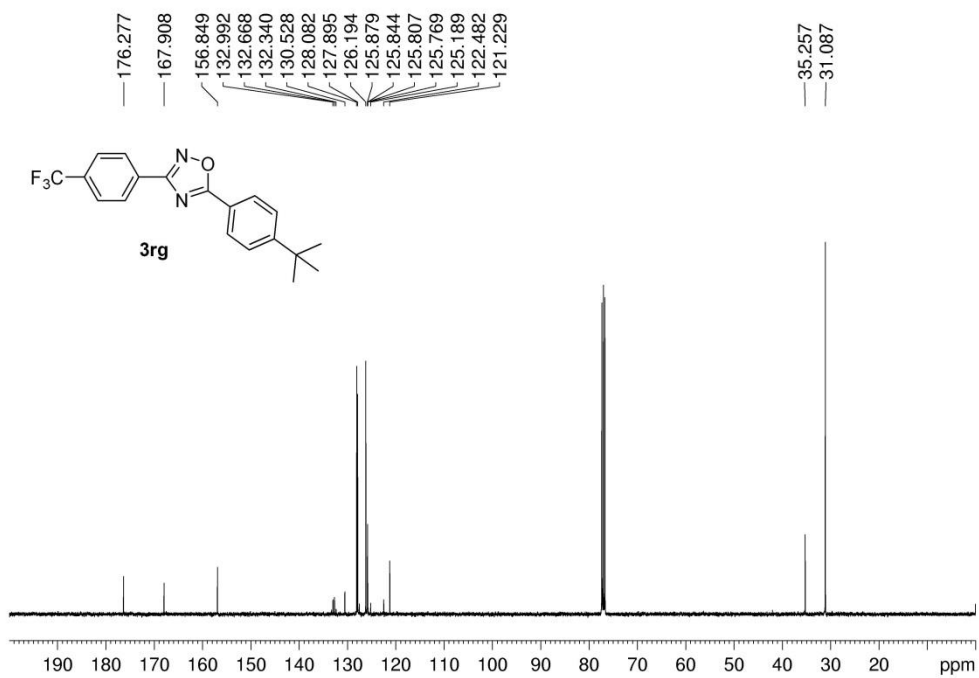


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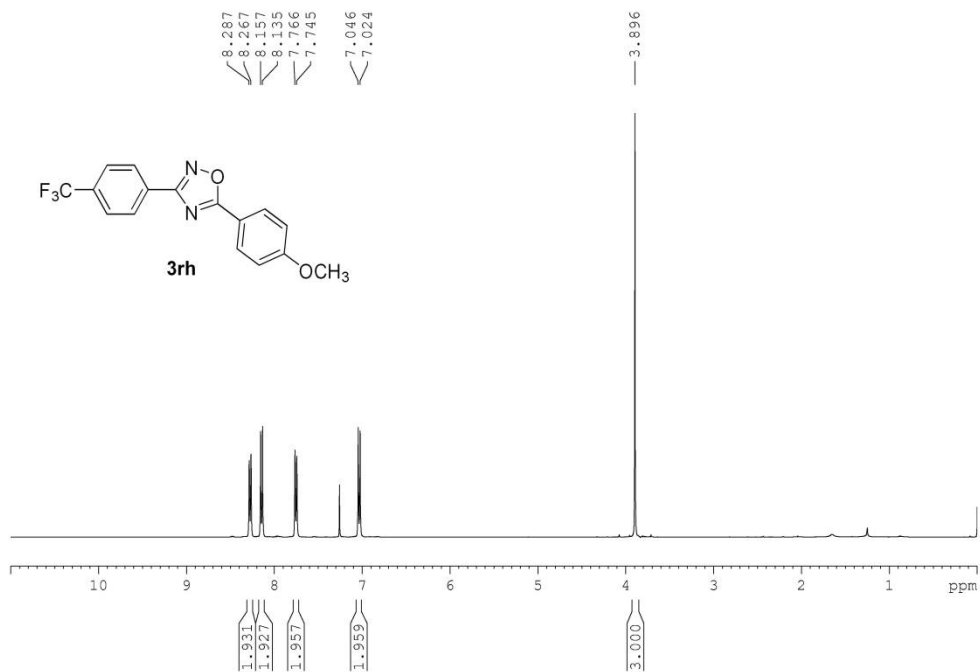
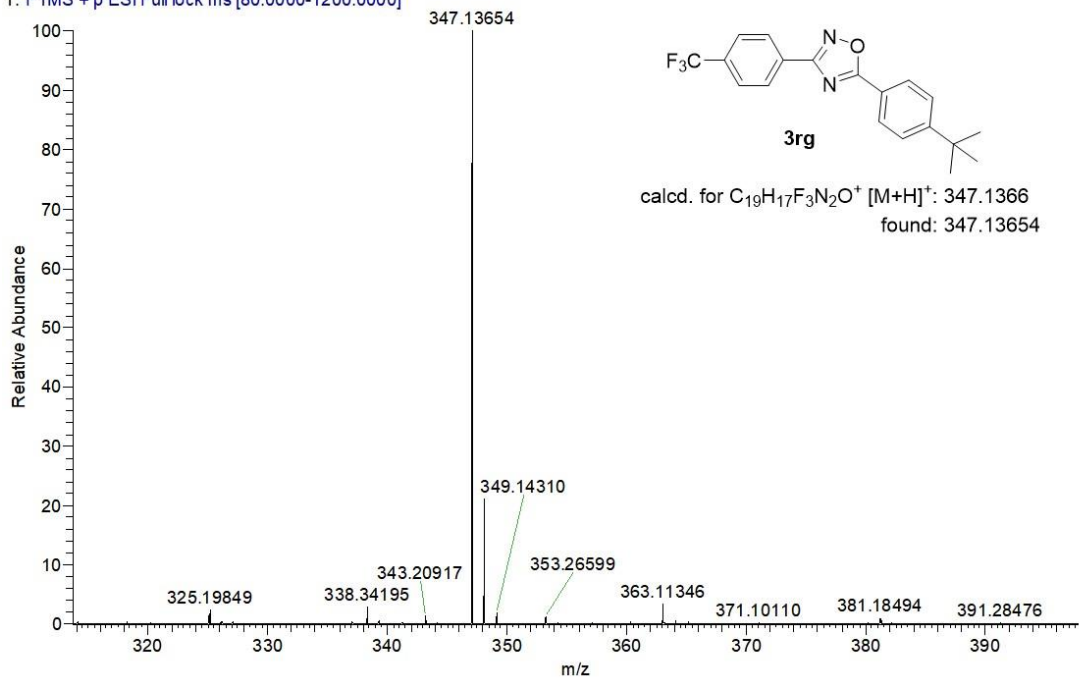


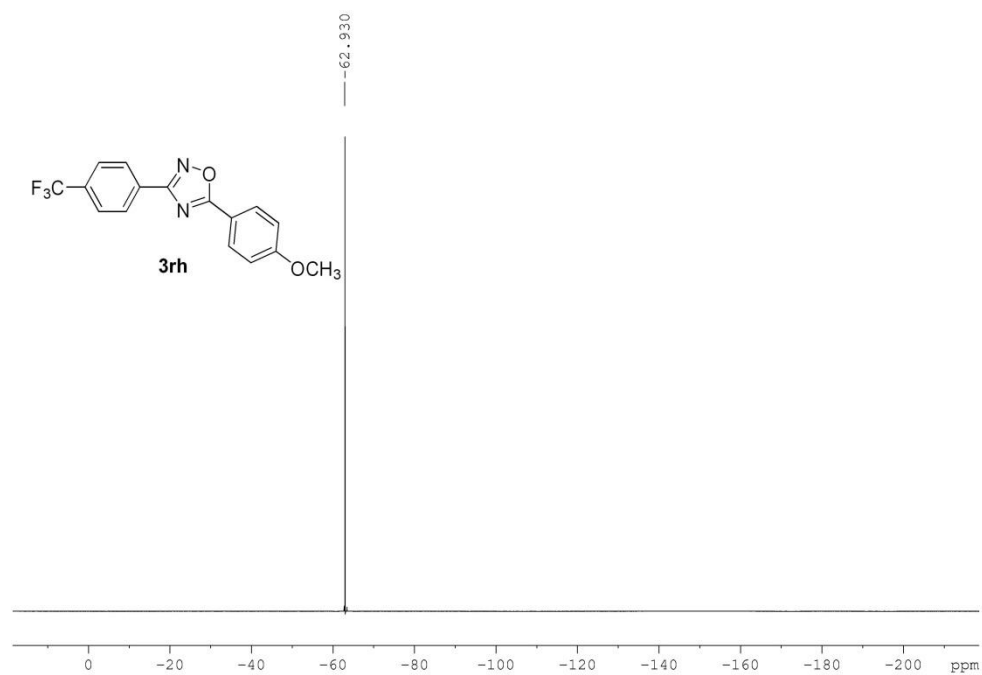
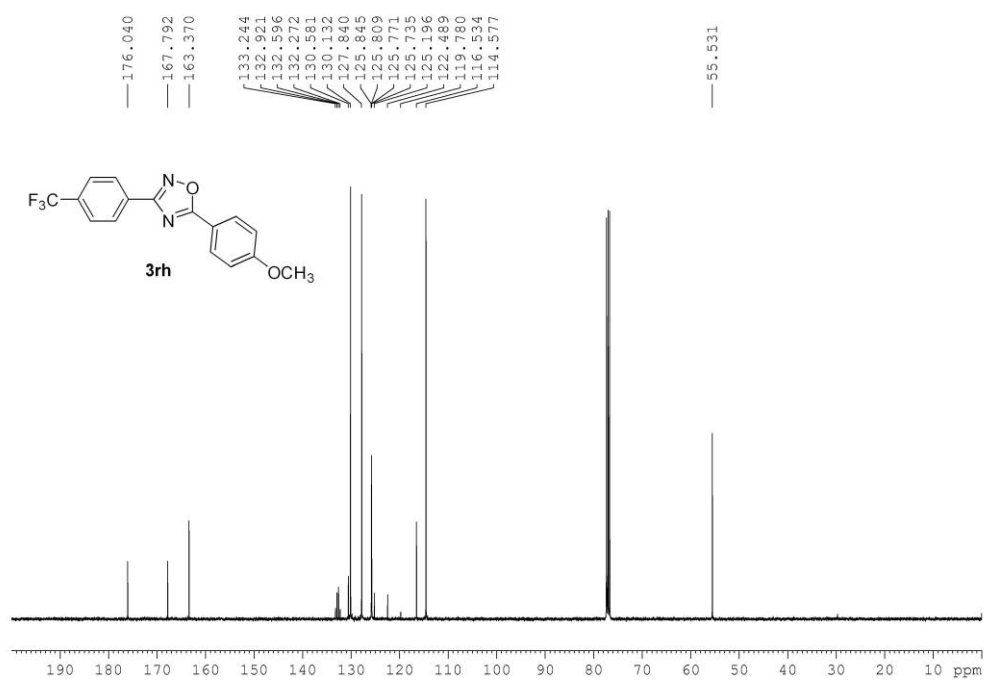


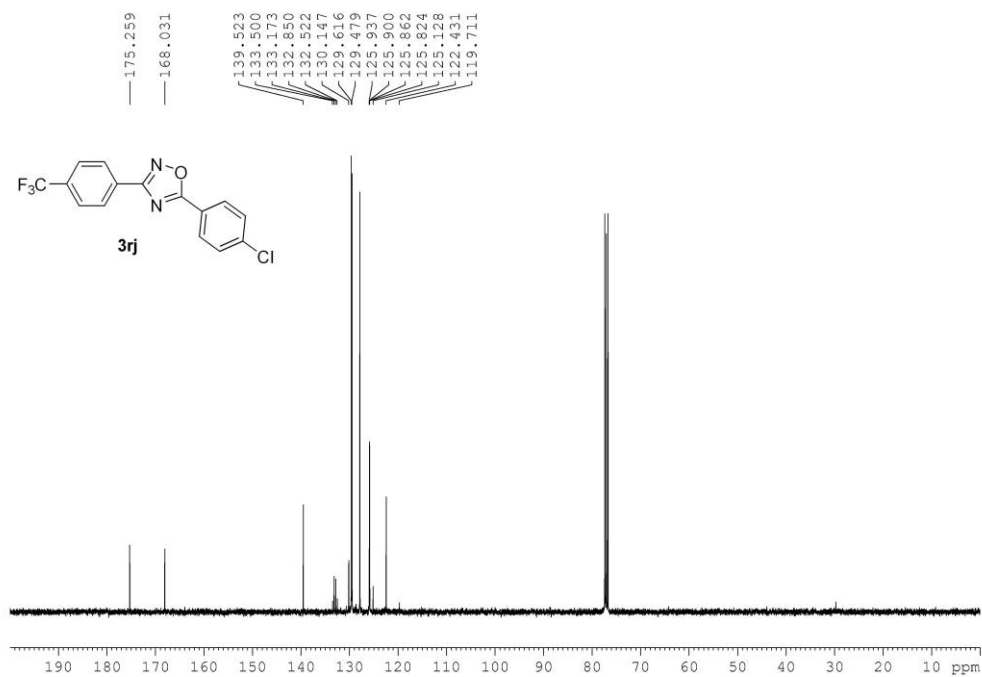
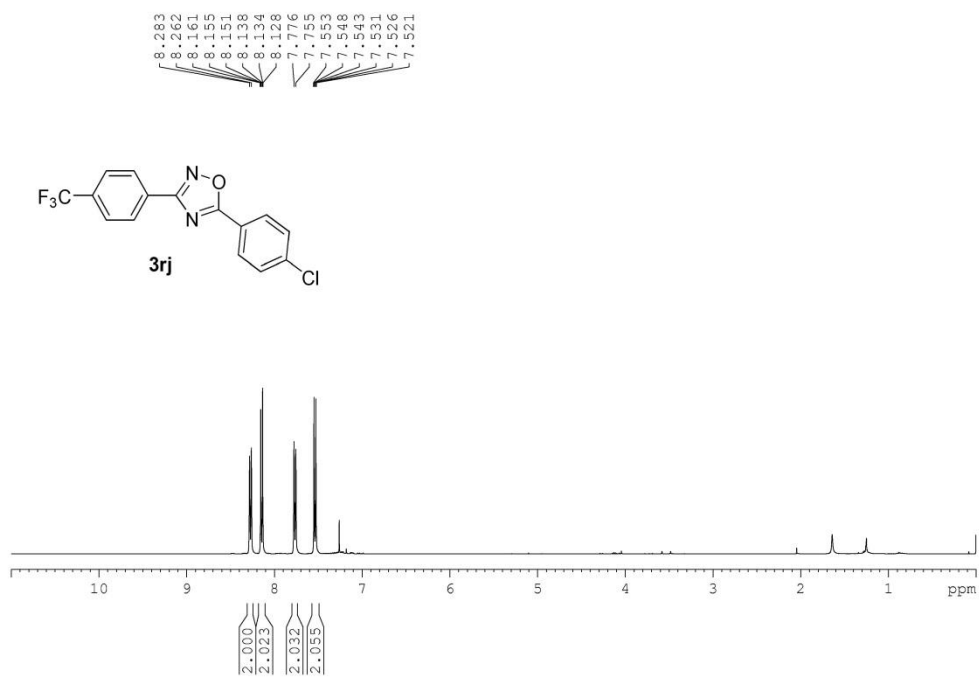


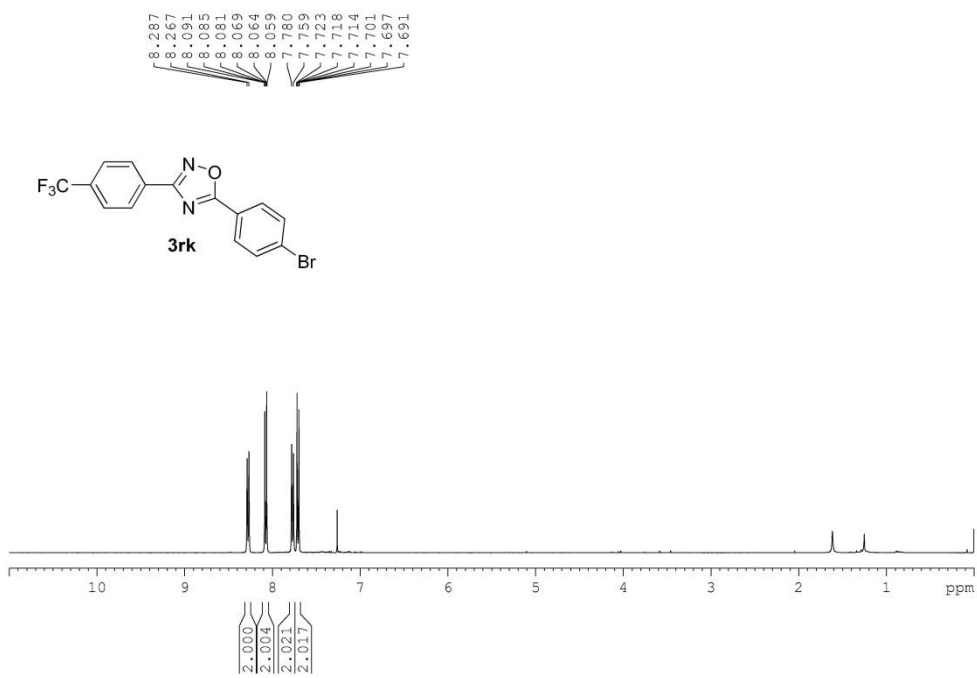
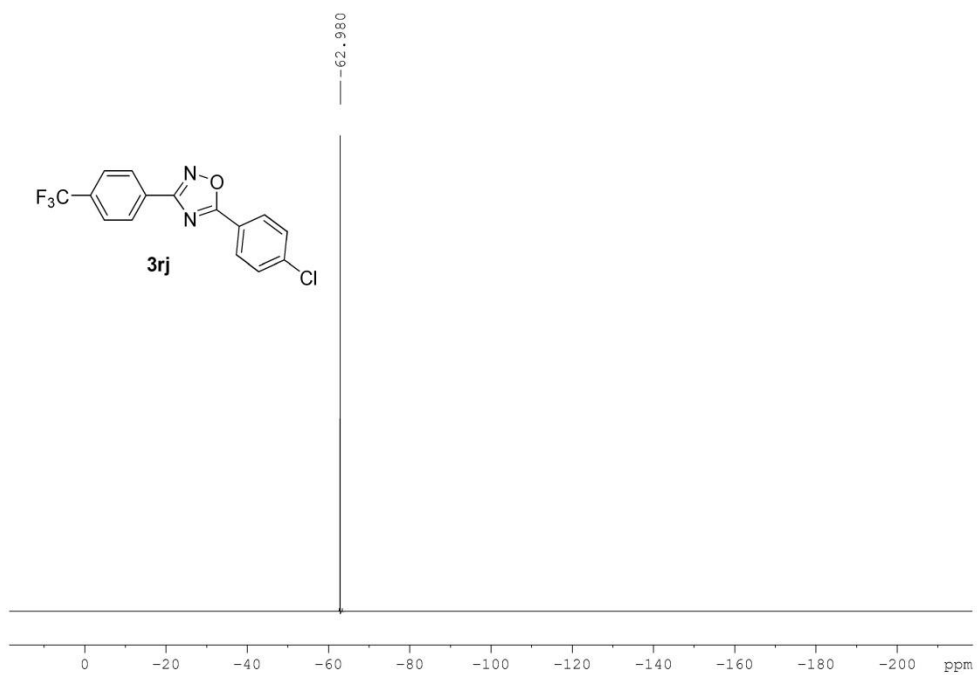


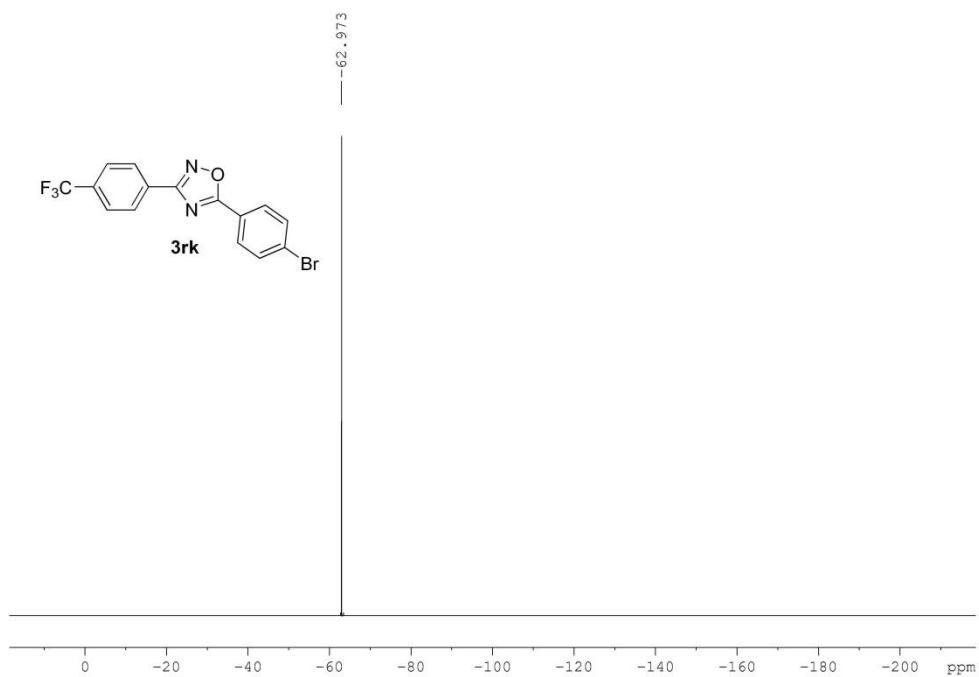
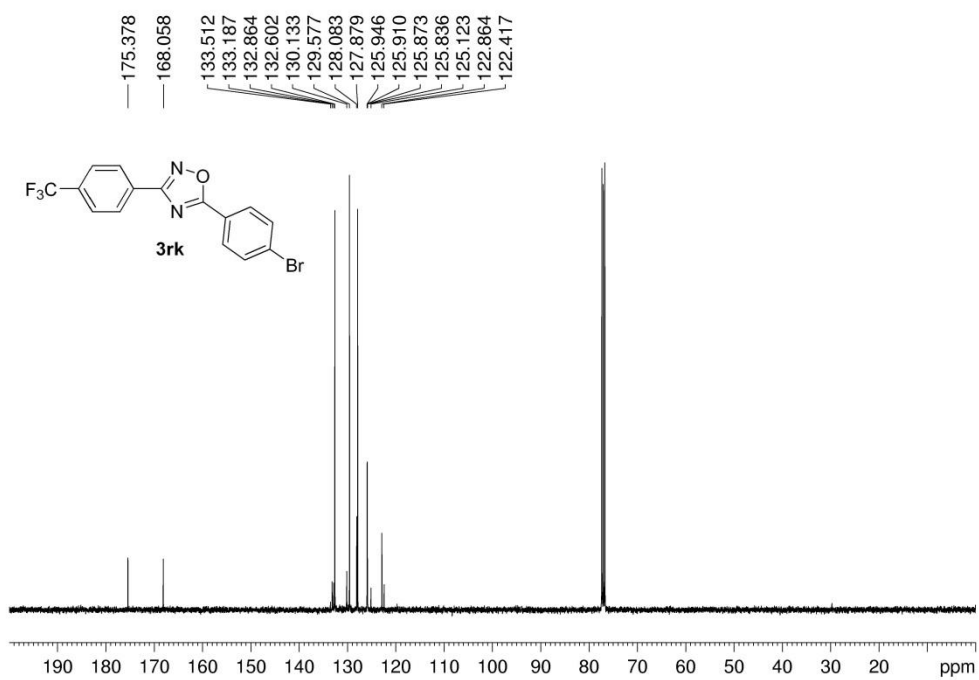
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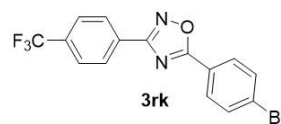
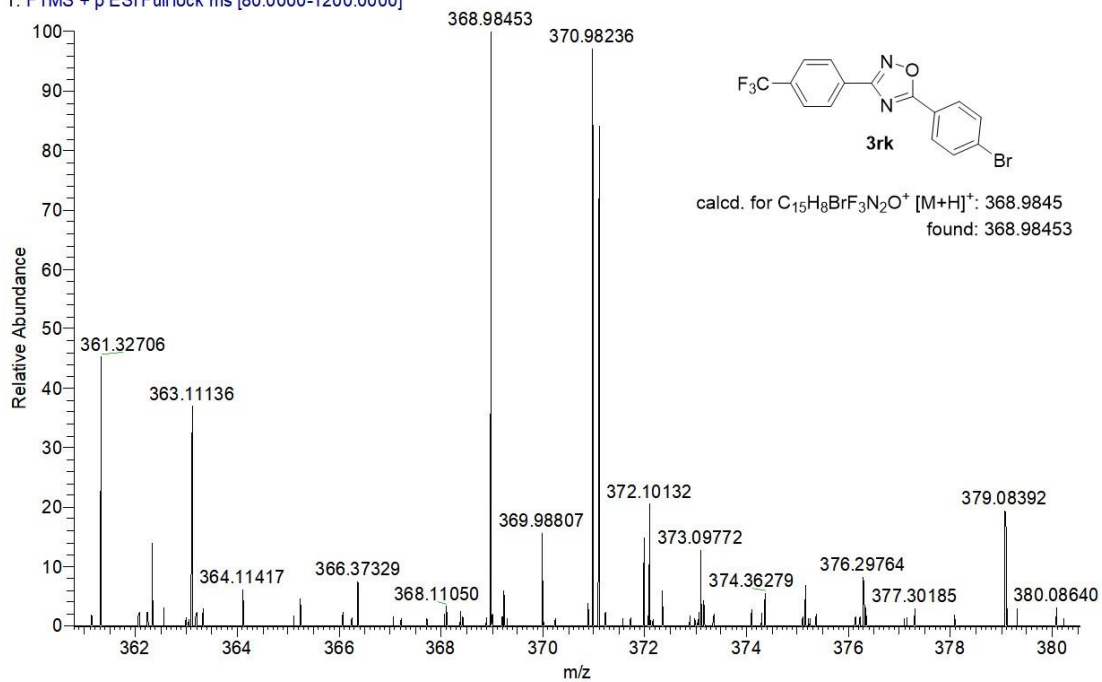






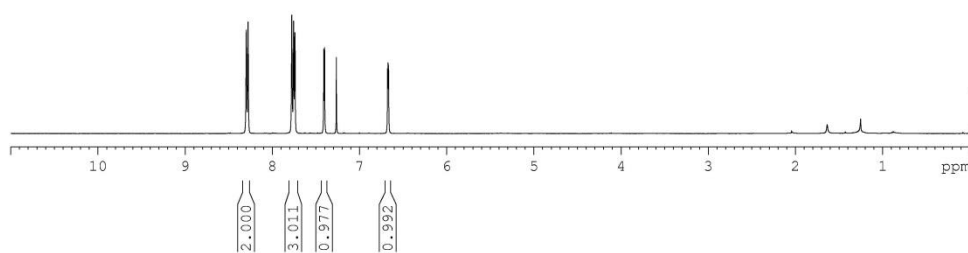
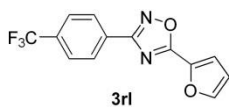


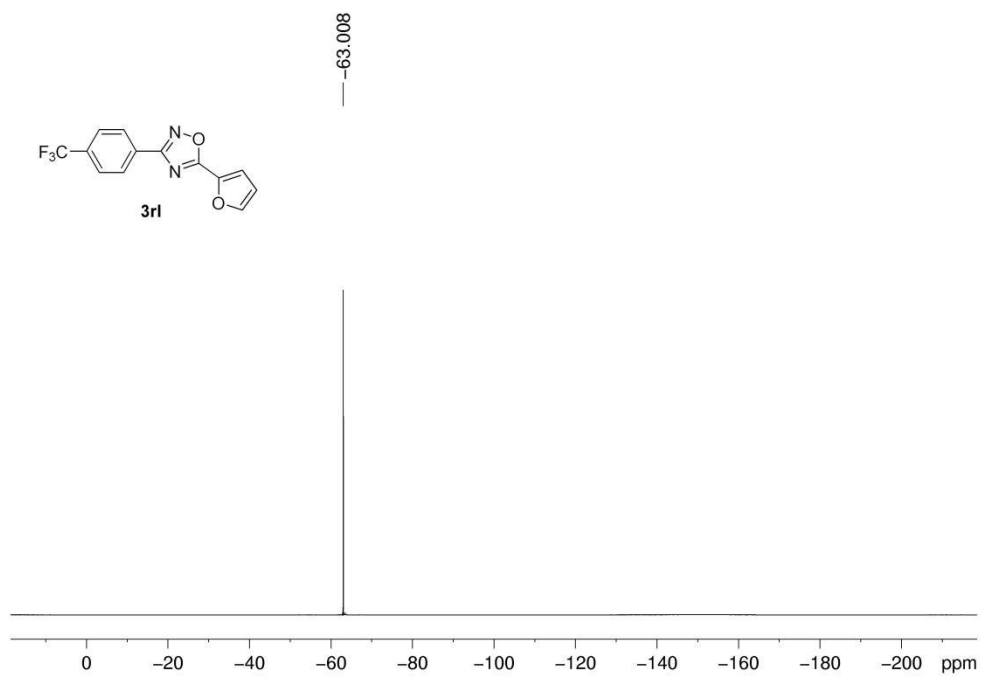
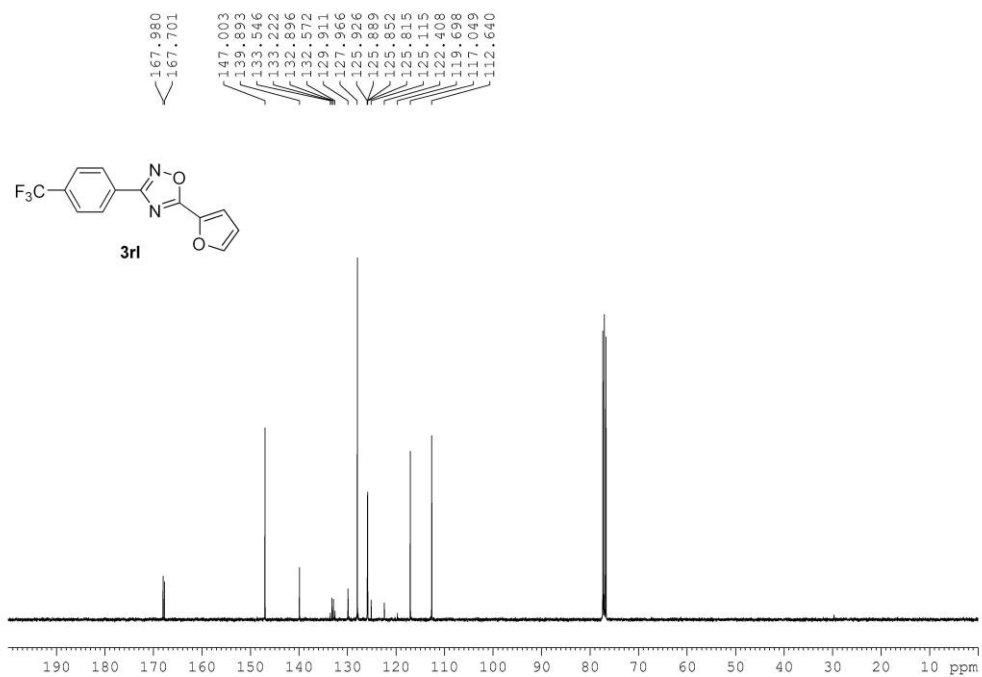
T: FTMS + p ESI Full lock ms [80.0000-1200.0000]



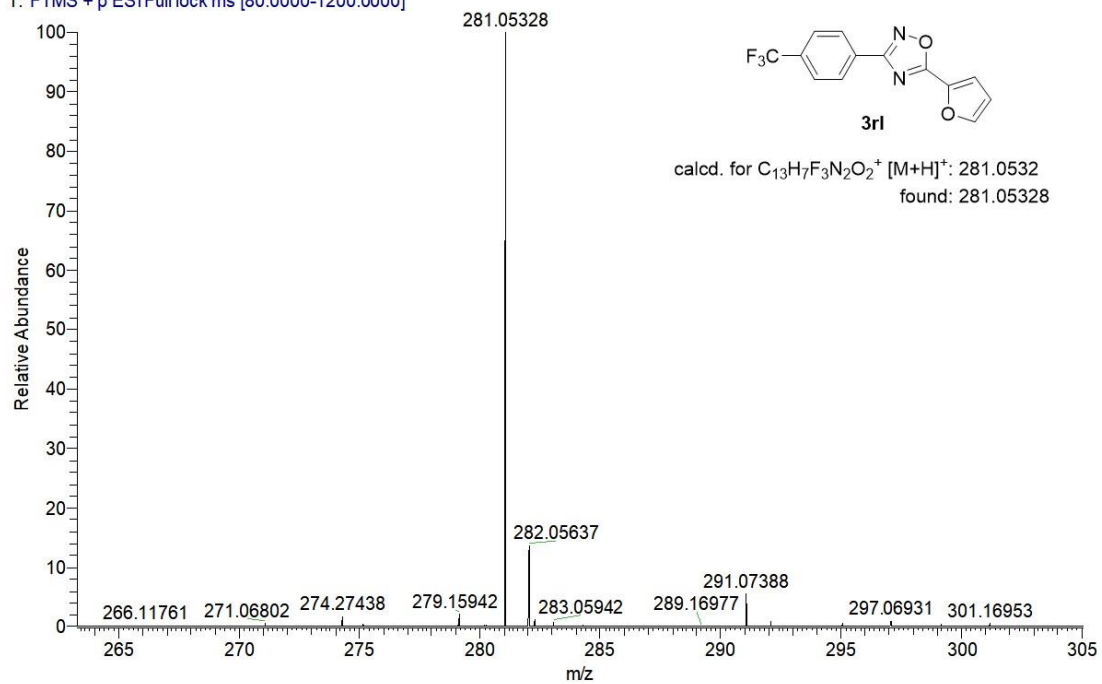
calcd. for $C_{15}H_8BrF_3N_2O^+$ $[M+H]^+$: 368.9845
found: 368.98453

8.300
8.279
7.778
7.757
7.744
7.741
7.410
7.402
6.679
6.671
6.666





I: FTMS + p ESI Full lock ms [80.0000-1200.0000]



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