HFIP Promoted Thio(hetero)arylation of Imidazoheterocycles under Metal- and Base-Free Conditions

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General Information:

Proton and carbon magnetic resonance spectra were recorded on a Varian (1H NMR at 400 or 300 MHz, ^{13}C NMR at 100 or 75 MHz) FTNMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual deuterium in the solvent (1H NMR: CDCl3 at 7.26 ppm). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent peak (^{13}C NMR: $CDCl_3$ at 77.0 ppm). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet and m = multiplet), coupling constant (*J*, Hz), and integration. Analytical thin layer chromatography (TLC) was performed on Merck Kieselgel 60 GF254 plates (thickness 0.25 mm). Visualization was performed with a 254 nm UV lamp and by staining in I_2 chamber. Organic solutions were concentrated under reduced pressure using a Heidolph rotary evaporator. Purification of the crude products was carried out by column chromatography using silica gel 100 – 200 mesh. All the reactions of the present protocol were carried out in a sealed vial. Yield refers to the isolated analytically pure material.

Materials:

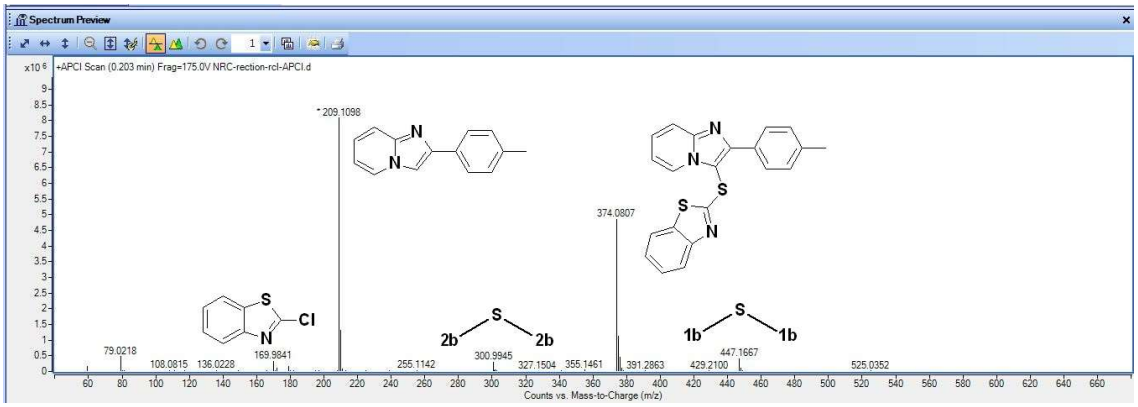
All the 2-arylimidazo[1,2-a]pyridines **1a-1h** were prepared from corresponding acetophenones and respective 2-aminopyridine following the reported procedure.[1] Similarly, different 6-aryllimidazo-[2,1-b]-thiazole **1i-1k** were synthesized from 2-aminothiazoles and corresponding acetophenones using reported protocol.[2] All the 2-chloroheteroarene derivatives **2a-2k** were purchased from TCI Chemicals Ltd.

Typical Experimental Procedure for Thioheteroarylation of Imidazoheterocycles:

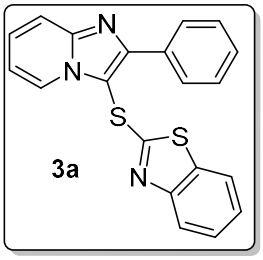
Sulphur powder (48 mg) was added to a solution of 2-phenylimidazo[1,2-a]pyridines **1** (0.5 mmol) in a mixture of DMSO and HFIP (1 mL:1 mL). Now 2-chloroheteroarene 2 (1 mmol) was added and the resulting mixture was heated at 120 °C in a sealed tube for 6-12 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with dichloromethane. The organic layer was dried over sodium sulphate and evaporated. The crude residue was purified by column chromatography in ethylacetate (20 to 40%) and hexane to obtain the pure sulfenylated product **3**.

HRMS Analysis of Reaction Mixture:

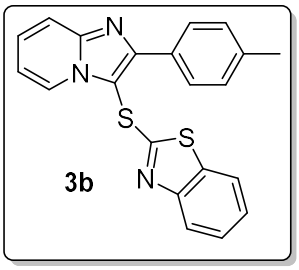
HRMS analysis of reaction mixture at an interval of 60 minutes when a reaction was carried out using **1b** and **2a** under optimized conditions.



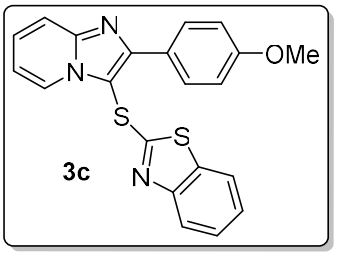
Physical and Spectral Data:



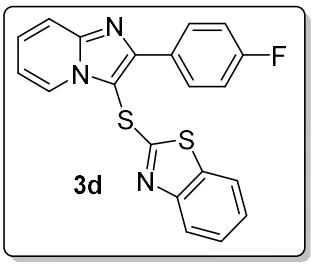
Yield 154 mg (86%); Yellow solid (mp 176-180 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.35 (d, *J* = 6.8 Hz, 1H), 8.14 (d, *J* = 7.1 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.36 (m, 5H), 7.19 (dd, *J* = 8.5, 5.9 Hz, 1H), 6.92 (t, *J* = 6.5 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.50, 154.46, 151.86, 147.39, 135.46, 132.10, 129.23, 128.59, 128.48, 127.93, 126.33, 124.63, 124.45, 122.10, 121.04, 117.74, 113.97, 104.23. **HRMS:** Calculated for $C_{20}H_{13}N_3S_2$ (M + Na) 382.0449; Observed 382.0437.



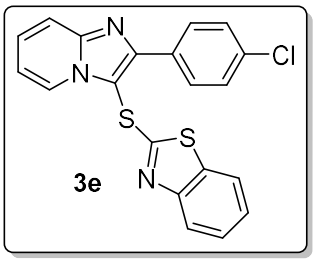
Yield 154 mg (83%); Yellow solid (mp 158-162 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.29 (d, *J* = 6.8 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.20 – 7.13 (m, 3H), 6.84 (t, *J* = 6.8 Hz, 1H), 2.28 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.28, 154.50, 152.40, 147.66, 139.05, 135.40, 129.76, 129.13, 128.15, 127.41, 126.21, 124.47, 124.26, 121.97, 120.97, 117.75, 113.54, 103.71, 21.29. **HRMS:** Calculated for $C_{21}H_{15}N_3S_2$ (M + H) 374.0786; Observed 374.0771.



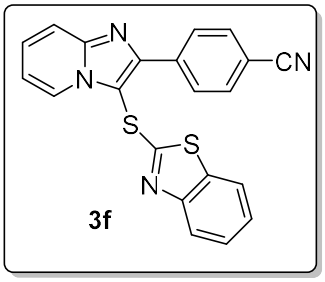
Yield 157 mg (81%); Pale yellow coloured viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.40 (d, *J* = 6.8 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.42-7.37 (m, 2H), 7.24 (m, 1H), 7.03 – 6.92 (m, 3H), 3.85 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.51, 160.40, 154.64, 152.31, 147.76, 135.50, 129.78, 127.45, 126.29, 125.27, 124.55, 124.33, 122.07, 121.06, 117.72, 114.03, 113.53, 55.28. **HRMS:** Calculated for $C_{21}H_{15}N_3OS_2$ (M + Na) 412.0554; Observed 412.0547.



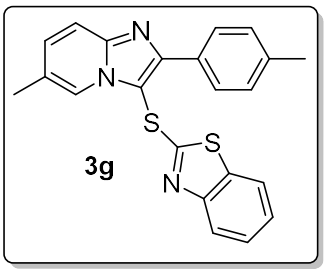
Yield 145 mg (77%); Pale yellow viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.38 (d, *J* = 6.4 Hz, 1H), 8.20 (dd, *J* = 8.2, 5.7 Hz, 2H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.40 (s, 2H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 8.5 Hz, 2H), 6.95 (t, *J* = 6.5 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.6, 163.3 (d, *J* = 247 Hz), 154.4, 151.4, 147.6, 135.3, 130.3 (d, *J* = 8 Hz), 127.6, 126.3, 124.6, 124.3, 122.1, 121.0, 117.8, 115.6, 115.4, 113.7, 103.9. **HRMS:** Calculated for $C_{20}H_{12}FN_3S_2$ (M + H) 378.0535; Observed 378.0513.



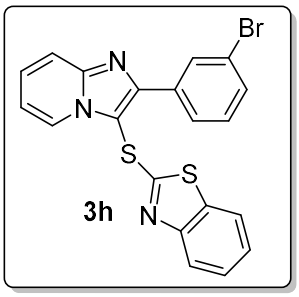
Yield 153 mg (78%); white solid (mp 186-190 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.38 (d, *J* = 6.8 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.40 (m, 4H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 6.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.45, 154.47, 151.11, 147.73, 135.40, 135.16, 131.17, 129.64, 128.78, 127.74, 126.37, 124.69, 124.41, 122.14, 121.04, 117.94, 113.87, 104.27 (s); **HRMS:** Calculated for $C_{20}H_{12}ClN_3S_2$ (M + H) 394.0239; Observed 394.0230.



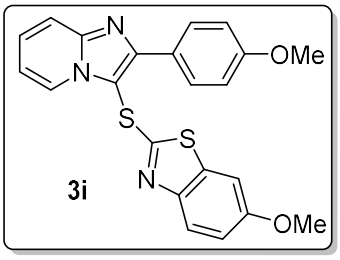
Yield 142 mg (74%); white thick gum; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.45 (d, *J* = 6.8 Hz, 1H), 8.37 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.46 (m, 2H), 7.31 – 7.26 (m, 1H), 7.03 (t, *J* = 6.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.42, 154.44, 149.93, 147.85, 137.12, 135.31, 132.35, 128.87, 128.15, 126.54, 124.91, 124.55, 122.30, 121.10, 118.73, 118.25, 114.32, 112.46, 105.22; **HRMS:** Calculated for $C_{21}H_{12}N_4S_2$ (M + H) 385.0582; Observed 385.0550.



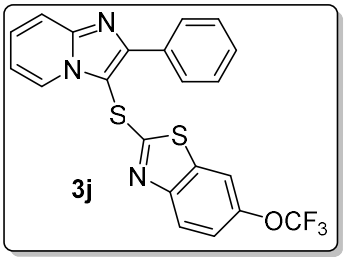
Yield 158 mg (82%); white solid (mp 191 °C); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.09 (s, 1H), 8.01 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 9.1 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.16 (m, 4H), 2.28 (s, 3H), 2.25 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.93, 154.64, 152.26, 146.71, 138.92, 135.48, 130.55, 129.92, 129.22, 128.18, 126.21, 124.44, 123.60, 122.03, 121.9, 121.00, 117.11, 103.26, 21.30, 18.30. **HRMS:** Calculated for $C_{22}H_{17}N_3S_2$ (M + Na) 410.0762; Observed 410.0768.



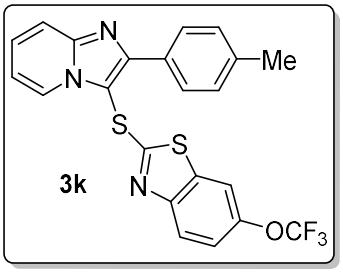
Yield 164 mg (75%); yellow coloured thick gum; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.44 (d, *J* = 6.8 Hz, 1H), 8.41 (t, *J* = 1.7 Hz, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.50 – 7.42 (m, 2H), 7.36 – 7.29 (m, 2H), 7.02 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 167.27, 154.39, 150.62, 147.67, 135.37, 134.65, 132.00, 131.32, 130.01, 127.85, 126.84, 126.36, 124.69, 124.43, 122.74, 122.13, 121.05, 117.99, 114.00, 104.61. **HRMS:** Calculated for $C_{20}H_{12}BrN_3S_2$ (M + H) 437.9734; Observed 437.9714.



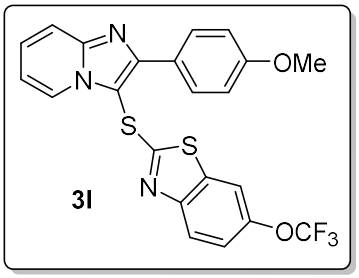
Yield 180 mg (86%); pale yellow coloured viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.32 (d, *J* = 6.8 Hz, 1H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.68 (dd, *J* = 8.8, 6.7 Hz, 2H), 7.32 (m, 1H), 6.99 – 6.81 (m, 5H), 3.76 (s, 3H), 3.69 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.79, 160.33, 157.23, 152.10, 149.01, 147.62, 136.81, 129.75, 127.34, 125.29, 124.33, 122.50, 117.60, 115.16, 113.97, 113.42, 104.07, 103.47, 55.71, 55.24. **HRMS:** Calculated for $C_{22}H_{17}N_3O_2S_2$ (M + Na) 442.0660; Observed 442.0654.



Yield 177 mg (80%); yellow coloured viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.29 (d, *J* = 6.5 Hz, 1H), 8.09 (d, *J* = 7.1 Hz, 2H), 7.76 (d, *J* = 8.9 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.41 – 7.20 (m, 5H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.87 (t, *J* = 6.7 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.53, 153.01, 152.56, 147.82, 145.88, 136.22, 132.50, 129.15, 128.54, 128.39, 127.67, 124.23, 122.75, 120.36 (q, *J* = 258 Hz), 120.12, 117.97, 113.83, 113.76, 103.64. **HRMS:** Calculated for $C_{21}H_{12}F_3N_3OS_2$ (M + H) 444.0452; Observed 444.0428.

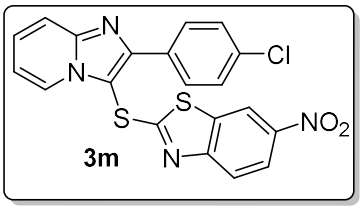


Yield 189 mg (83%); yellow coloured viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.35 (d, *J* = 6.8 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.24 (d, *J* = 7.8 Hz, 3H), 6.93 (t, *J* = 6.8 Hz, 1H), 2.35 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8, 153.0. 152.6, 147.8, 145.9, 139.2, 136.2, 129.6, 129.3, 128.2, 127.5, 124.0, 122.6, 120.3 (q, *J* = 250 Hz), 120.0, 117.8, 113.8, 113.7, 103.3, 21.3. **HRMS:** Calculated for $C_{22}H_{14}F_3N_3OS_2$ (M + H) 458.0609; Observed 458.0584.



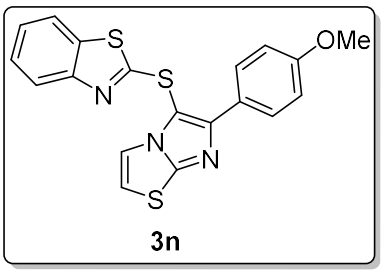
Yield 182 mg (77%); yellow coloured viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.38 (d, *J* = 6.8 Hz, 1H), 8.17 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.28 (d, *J* = 11.8 Hz, 1H), 7.01 – 6.93 (m, 3H), 3.83 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 170.09, 160.46, 153.16, 152.50, 147.84, 146.00, 136.26, 129.73, 127.64,

125.07, 124.19, 122.75, 120.38 (q, J = 255 Hz) 120.19, 117.80, 114.05, 113.85, 113.69, 102.73, 55.27. **HRMS:** Calculated for $C_{22}H_{14}F_3N_3O_2S_2$ (M + H) 474.0558; Observed 474.0540.



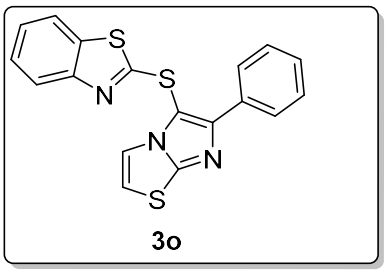
3m

Yield 171 mg (78%), Pale yellow coloured viscous oil; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.53 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 6.8 Hz, 1H), 8.32 (dd, J = 9.0, 2.1 Hz, 1H), 8.15 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.51 (dd, J = 8.4, 7.4 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.06 (t, J = 6.9 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 175.00, 158.27, 151.72, 148.08, 144.45, 135.74 , 135.55, 130.87, 129.63, 129.04, 128.15, 124.15, 122.18, 122.07, 118.21, 117.55, 114.36, 103.28. **HRMS:** Calculated for $C_{20}H_{11}ClN_4O_2S_2$ (M + H) 439.0090, Observed 439.0071.



3n

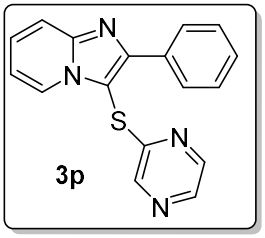
Yield 128 mg (65%); yellow coloured viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (d, J = 9.6 Hz, 2 H), 7.88 (d, J = 8 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 4.4 Hz, 1 H), 7.43-7.39 (m, 1 H), 7.26 (t, J = 8.0 Hz, 1 H), 6.96-6.90 (m, 3 H), 3.81 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.8, 160.0, 154.5, 153.7, 152.6, 135.5, 129.0, 126.3, 125.4, 124.6, 122.1, 121.1, 118.0, 114.0, 113.4, 104.2, 55.2. **HRMS** calculated for $C_{19}H_{13}N_3OS_3$ (M + H) 396.0299; Observed 396.0279.



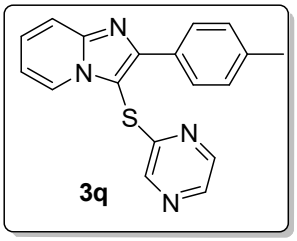
3o

Yield 124 mg (68%); yellow coloured viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.09 (dt, J = 6.4, 1.4 Hz, 2H), 7.92 – 7.85 (m, 1H), 7.62 (dd, J = 8.0, 1.2 Hz, 1H), 7.54 (d, J = 4.5 Hz, 1H), 7.42 – 7.31 (m, 4H), 7.31 – 7.23 (m, 1H), 6.93 (d, J = 4.5 Hz, 1H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ 168.47, 154.47, 153.79, 152.75, 135.53, 132.77, 128.74, 128.56, 127.68, 126.37,

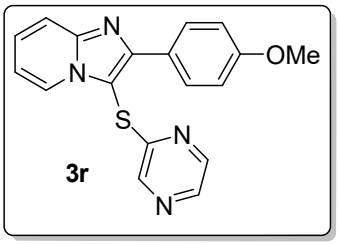
124.63, 122.11, 121.10, 118.02, 113.81, 105.20. **HRMS:** Calculated for $C_{18}H_{11}N_3S_3$ (M + H) 366.0193; observed 366.0186.



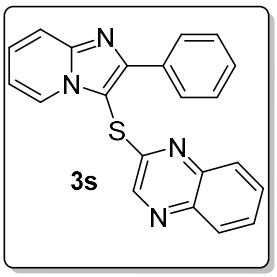
Yield 131 mg (86%); Thick yellow gum; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.34 – 8.16 (m, 3H), 8.11 – 7.94 (m, 3H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.33 (m, 4H), 6.86 (dd, *J* = 7.3, 6.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.80, 151.96, 147.56, 144.42, 141.70, 141.18, 133.07, 128.80, 128.46, 128.44, 126.98, 124.35, 117.94, 113.36. **HRMS:** Calculated for $C_{17}H_{12}N_4S$ (M + H) 305. 0861; Observed 305.0840.



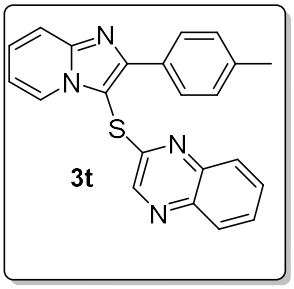
Yield 138 mg (87%); Thick yellow gum; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.22 (m, 3H), 7.98 (m, 3H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.34 – 7.24 (m, 1H), 7.20 – 7.14 (m, 2H), 6.89 – 6.78 (m, 1H), 2.31 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.89, 152.03, 147.51, 144.36, 141.65, 141.11, 138.77, 130.18, 129.18, 128.28, 126.88, 124.26, 117.81, 113.24, 21.31. **HRMS:** Calculated for $C_{18}H_{15}N_4S$ (M + H) 319.1017; Observed 319.1003.



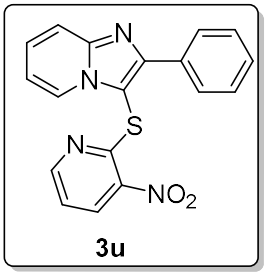
Yield 139 mg (83%); Thick yellow gum; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 (t, *J* = 9.5 Hz, 3H), 8.08 – 7.96 (m, 3H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.32 – 7.25 (m, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.83 (t, *J* = 6.7 Hz, 1H), 3.76 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.16, 155.91, 151.79, 147.49, 144.36, 141.64, 141.12, 129.70, 126.86, 125.62, 124.22, 117.65, 113.91, 113.16, 101.96, 55.25. **HRMS:** Calculated for $C_{18}H_{17}N_4OS$ (M + H) 335.0967; Observed 335.0947.



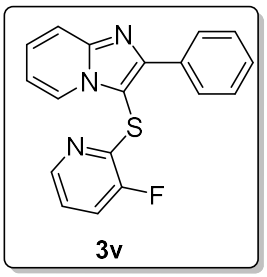
Yield 124 mg (70%); Yellow viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.24 (s, 1H), 8.17 (d, *J* = 6.8 Hz, 1H), 8.10 – 8.03 (m, 2H), 7.88 – 7.83 (m, 1H), 7.68 – 7.63 (m, 2H), 7.50 (m, 2H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 6.74 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.24, 151.89, 147.48, 142.33, 141.77, 140.26, 132.98, 130.55, 129.12, 129.01, 128.66, 128.38, 128.34, 128.14, 126.87, 124.37, 117.71, 113.19, 102.90. **HRMS:** Calculated for $C_{21}H_{14}N_4S$ (M + H) 355.1017; Observed 355.0996.



Yield 136 mg (74%); Yellow viscous oil; **^{1}H NMR (300 MHz, CDCl3)** δ 8.39 (s, 1H), 8.28 (d, *J* = 6.7 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 2H), 7.98 – 7.86 (m, 2H), 7.72 – 7.66 (m, 1H), 7.65 – 7.52 (m, 2H), 7.48 – 7.41 (m, 1H), 7.23 – 7.16 (m, 2H), 6.94 (t, *J* = 6.7 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 154.5, 152.0, 147.5, 142.4, 141.9, 140.3, 138.8, 130.6, 130.1, 129.3, 129.2, 129.1, 128.3, 128.2, 127.0, 124.4, 117.7, 113.2, 102.6, 21.3; **HRMS:** Calculated for $C_{22}H_{16}N_4S$ (M + H) 369.1174; Observed 369.1155.

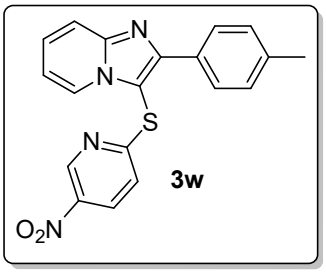


Yield 144 mg (83%); Thick yellowish gum; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.51 (d, *J* = 8.2 Hz, 1H), 8.31 (d, *J* = 3.7 Hz, 1H), 8.06 (d, *J* = 6.7 Hz, 1H), 8.03 – 7.94 (m, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.17 (dd, *J* = 8.1, 4.4 Hz, 1H), 6.82 (t, *J* = 6.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.87, 153.76, 151.97, 147.48, 142.23, 133.94 , 133.42, 128.55, 128.48, 128.31, 126.61, 124.54, 120.36, 117.66, 112.79, 105.00. **HRMS:** Calculated for $C_{18}H_{12}N_4O_2S$ (M + H) 349.0759; Observed 349.0742.



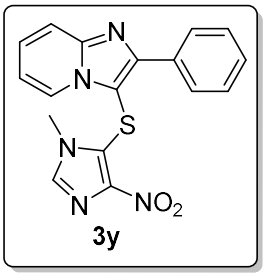
3v

Yield 112 mg (70%); Thick yellowish gum; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.24 (d, *J* = 6.9 Hz, 1 H), 8.10 (d, *J* = 6.9 Hz, 2 H), 8.00 (d, *J* = 4.5 Hz, 1 H), 7.72 (d, *J* = 9 Hz, 1 H), 7.45-7.28 (m, 5 H), 7.05-7.00 (m, 1 H), 6.86 (t, *J* = 6.6 Hz, 1 H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 158.3, 153.5 (d, *J* = 214.5 Hz), 147.6, 145.8 (d, *J* = 5.25 Hz), 145.2 (d, *J* = 17.2 Hz), 133.7, 128.7, 128.5, 128.4, 126.6, 125.0, 122.5, 122.3, 121.8, 117.7, 112.8, 103.0. **HRMS:** Calculated for $C_{18}H_{12}FN_3S$ (M + H) 322.0814; Observed 322.0804.



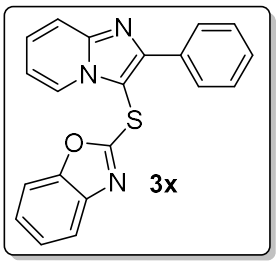
3w

Yield 145 mg (80%); Thick yellowish gum; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 9.13 (d, J = 2.1 Hz, 1 H), 8.15 (d, *J* = 6.9 Hz, 1 H), 8.10 (dd, *J* = 2.7, 9.0 Hz, 1 H), 7.70 (d, J = 9.0 Hz, 1 H), 7.33 (m, 1 H), 7.16 (d, *J* = 7.8 Hz), 6.88-6.84 (m, 1 H), 6.71 (d, *J* = 9.0 Hz); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 166.73, 152.22, 147.66, 145.65, 141.97, 139.04, 131.90, 129.87, 129.27, 128.13, 127.23, 124.09, 119.20, 117.87, 113.53, 102.70, 21.31. **HRMS:** Calculated for $C_{19}H_{14}N_4O_2S$ (M + H) 363.0916; Observed 363.0900.



3y

Yield 135 mg (77%); Yellow solid (mp 140-144 °C); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.57 (d, *J* = 10.0 Hz, 1 H), 8.07 (d, *J* = 7.5 Hz, 2 H), 7.69 (d, *J* = 10 Hz, 1 H), 7.55-7.46 (m, 4 H), 7.39-7.35 (m, 1 H), 7.28 (bs, 1 H), 6.99 (t, *J* = 7.5 Hz, 1 H), 3.05 (s, 1 H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 151.9, 147.2, 137.6, 133.1, 129.2, 129.1, 128.9, 128.8, 128.7, 127.4, 125.2, 117.8, 114.1, 103.6, 33.2. **HRMS** calculated for $C_{17}H_{13}N_5O_2S$ (M + H) 352.0868; Observed 352.0852.

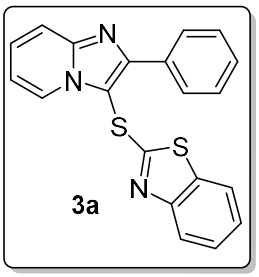


Yield 111 mg, Colourless viscous oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.39 (d, *J* = 6.8 Hz, 1H), 8.19 (d, *J* = 7.1 Hz, 2H), 7.85 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48 – 7.35 (m, 5H), 7.24 (dd, *J* = 8.5, 5.9 Hz, 1H), 6.97 (t, *J* = 6.5 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.46, 151.86, 147.39, 135.45, 132.20, 129.24, 128.59, 128.49, 127.93, 126.33, 124.64, 124.45, 122.10, 121.05, 117.75, 113.98, 104.36.

References:

1. H. Huang, P. Dang, L. Wu, Y. Liang, J. Liu, *Tetrahedron Lett.* 2016, 57, 574.

2. D. Liang, L. Li, C. Lynch, B. Mackowiak, W. D. Hedrich, Y. Ai, Y. Yin, S. Heyward, M. Xia, H. Wang, F. Xue *Eur. J. of Med. Chem.*, 2019,179, 84.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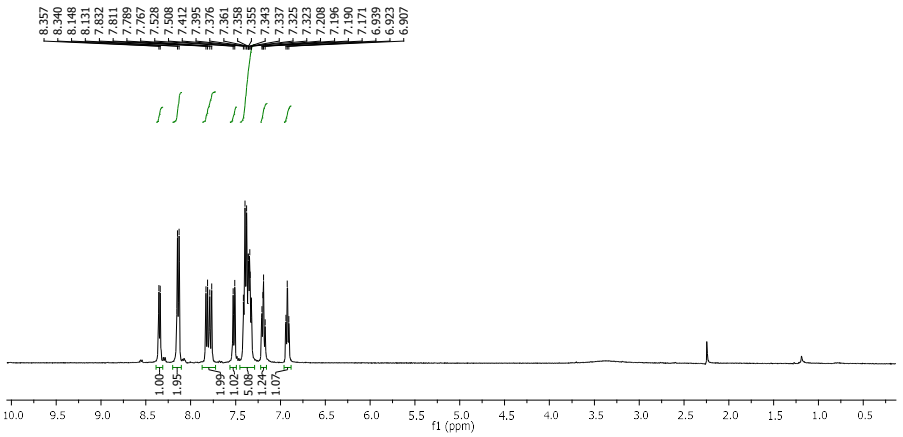
S
S
N
3a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7.412
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7.361
7.358
7.355
7.343
7.337
7.325
7.323
7.208
7.196
7.190
7.171
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6.923
6.907
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1.95
1.99
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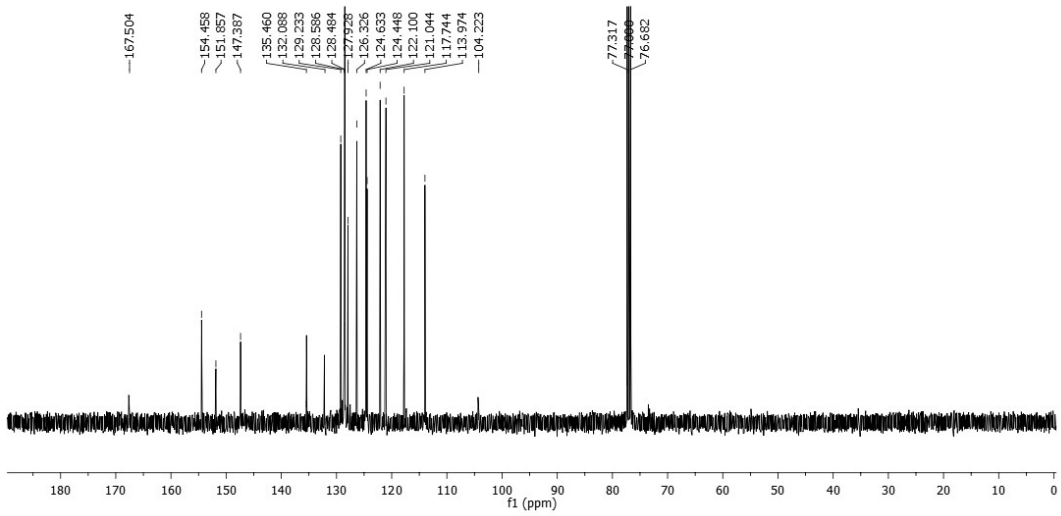
5.08
1.24
1.07
f1 (ppm)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129.233
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122.100
121.044
117.744
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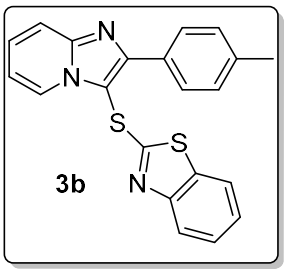
104.223
77.317
76.682
f1 (ppm)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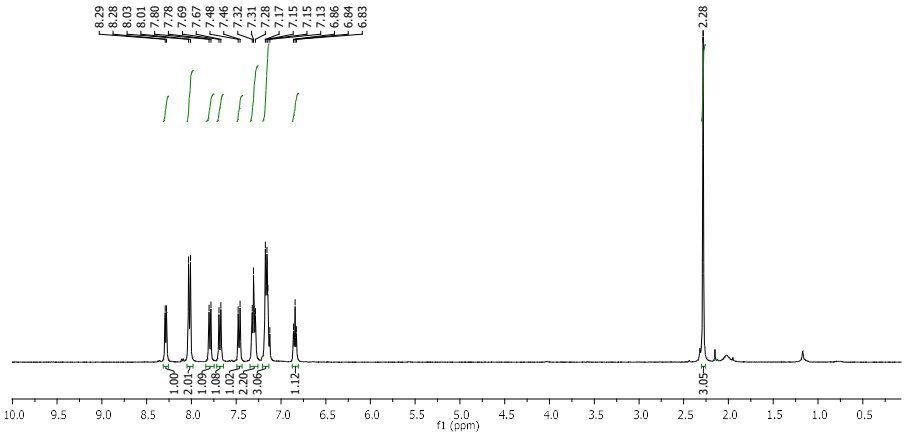
N
S
S
N
3b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7.67
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7.46
7.32
7.31
7.28
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7.15
7.15
7.13
6.86
6.84
6.83
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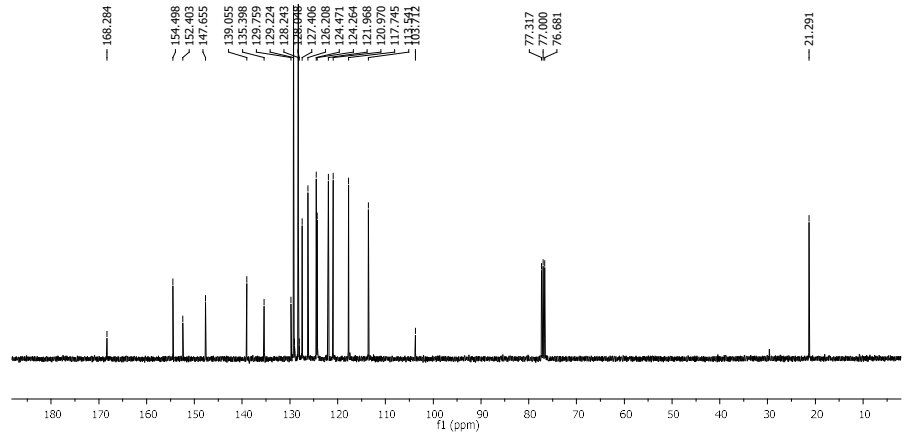
2.01
1.09
1.08
1.05
1.20
3.06
1.12
3.05
f1 (ppm)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135.398
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113.541
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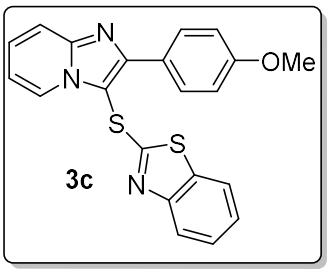
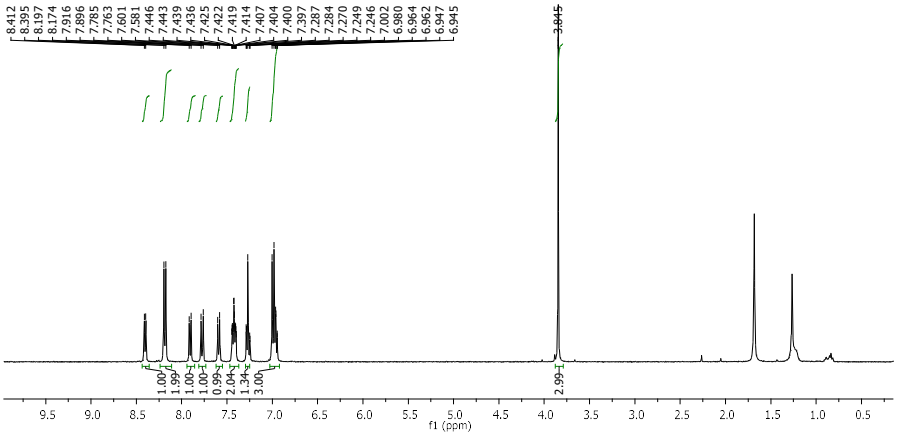
77.000
76.681
21.291
f1 (ppm)


N
N
OMe
S
S
N
3c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7.763
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7.581
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7.443
7.439
7.436
7.425
7.422
7.419
7.414
7.407
7.404
7.400
7.397
7.287
7.284
7.270
7.249
7.246
7.002
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6.964
6.962
6.947
6.945
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1.00
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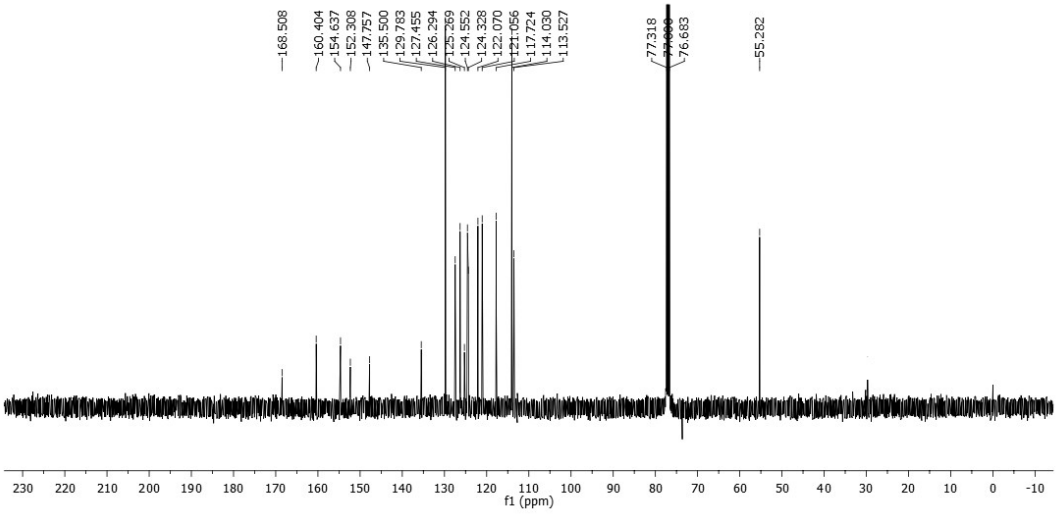
1.34
3.00
2.99
f1 (ppm)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135.500
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127.455
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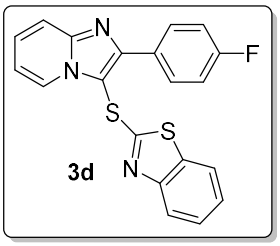
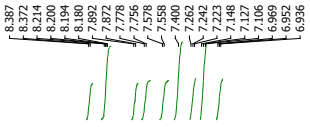
55.282
f1 (ppm)


N
N
F
S
S
N
3d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7.127
7.106
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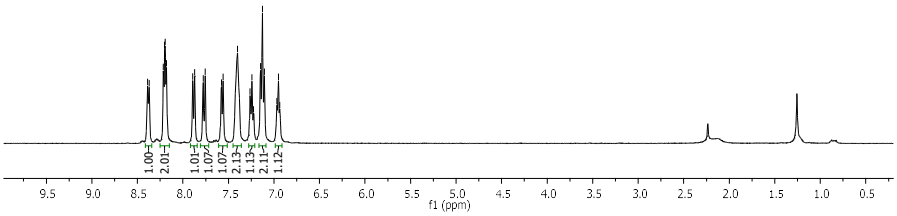
6.952
6.936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2.01
1.01
1.07
1.07
2.13
1.13
2.11
1.12
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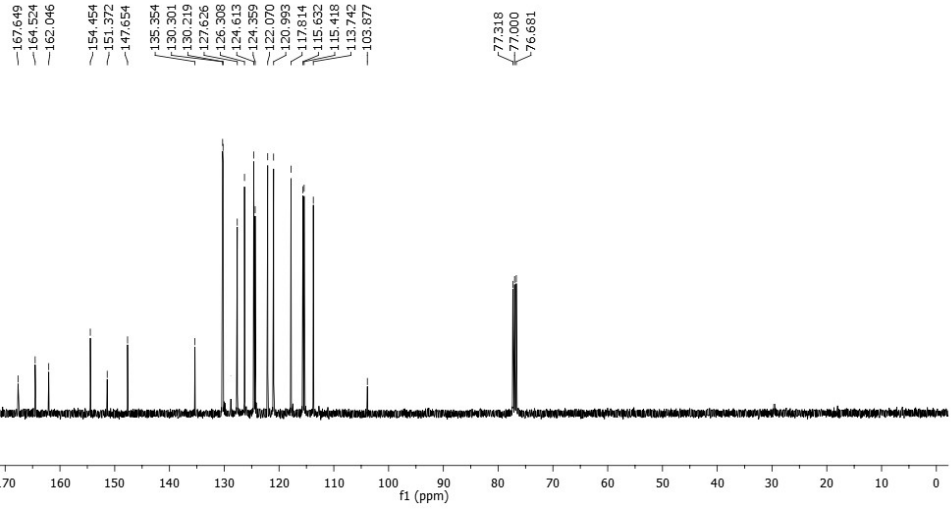
f1 (ppm)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124.359
122.070
120.993
117.814
115.632
115.418
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103.877
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77.000
76.681
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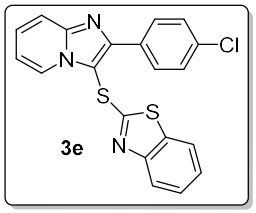
f1 (ppm)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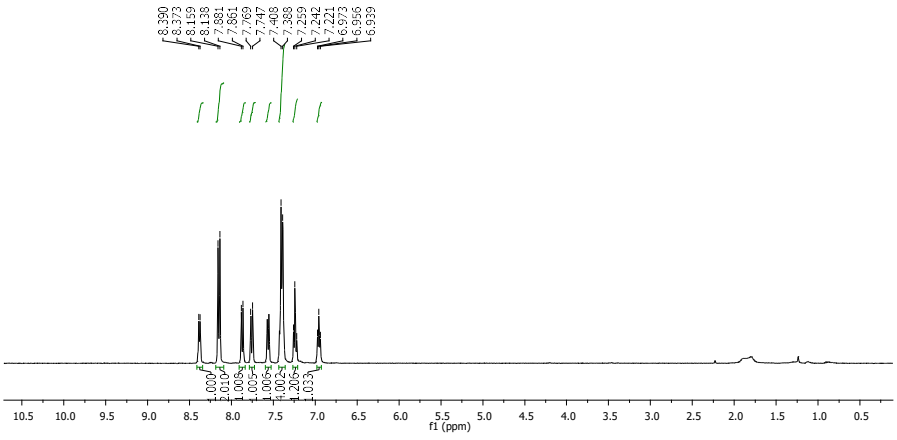
N
Cl
S
S
N
3e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7.221
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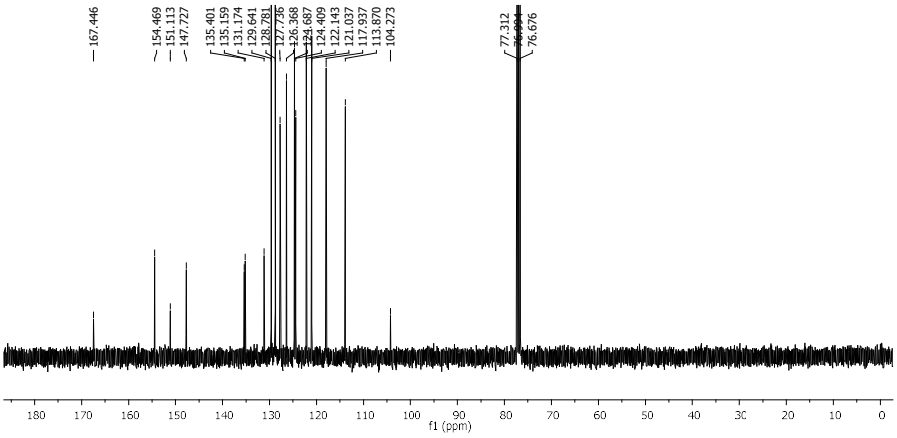
f1 (ppm)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122.143
121.037
117.937
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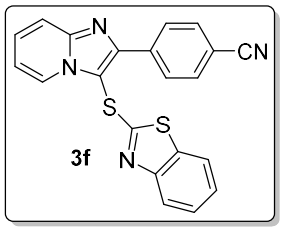
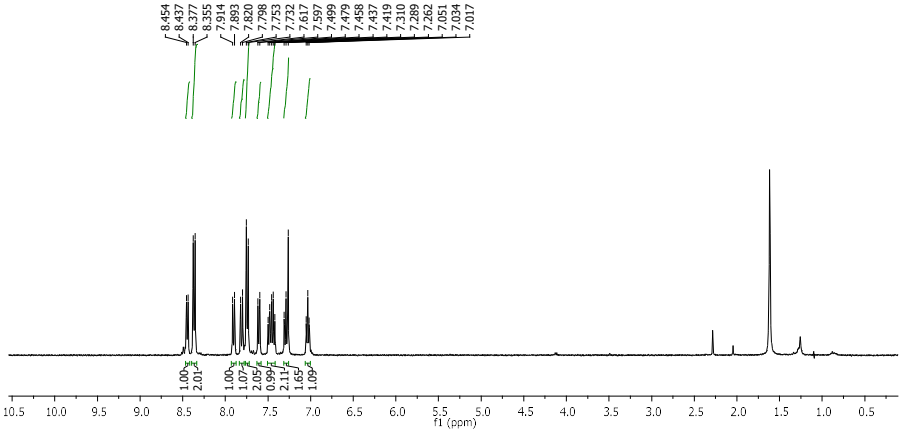
76.676
f1 (ppm)


N
N
CN
S
S
N
3f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7.289
7.262
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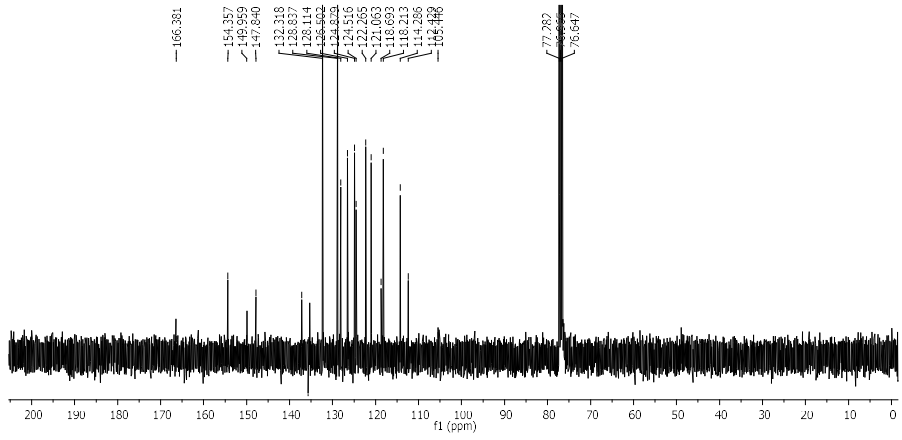
f1 (ppm)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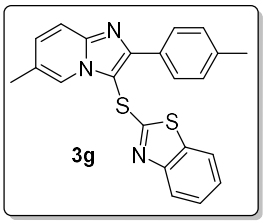
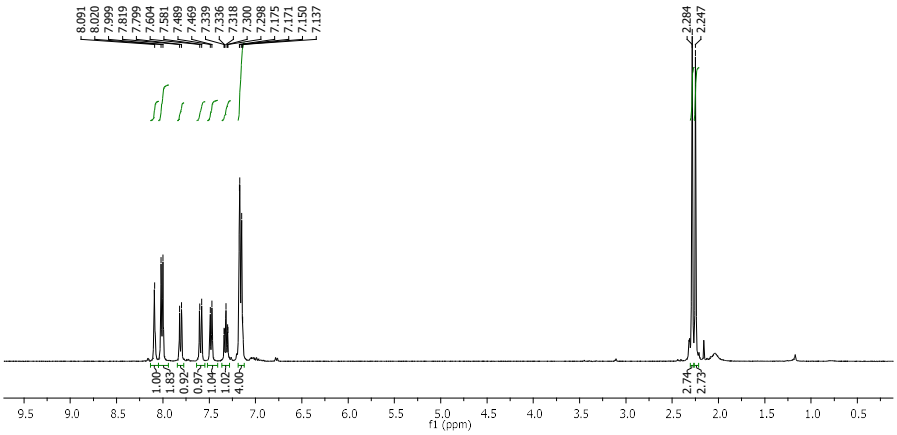
76.647
f1 (ppm)


N
N
S
S
N
3g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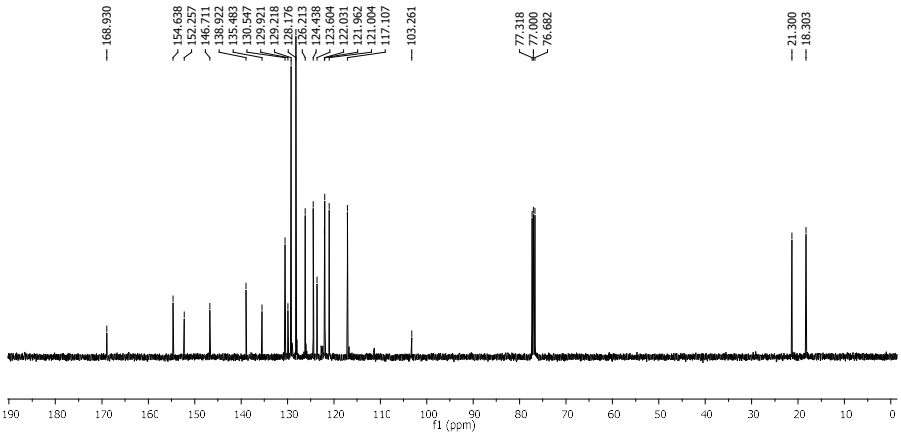
8.020
7.999
7.819
7.799
7.604
7.581
7.489
7.469
7.339
7.336
7.318
7.300
7.298
7.175
7.171
7.150
7.137
2.284
2.247
1.00
1.83
0.92
0.97
1.04
1.02
4.00
2.74
2.73
f1 (ppm)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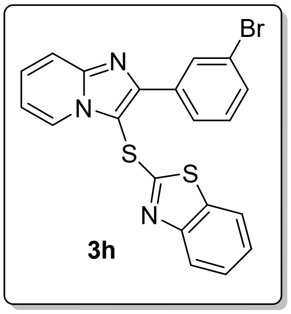
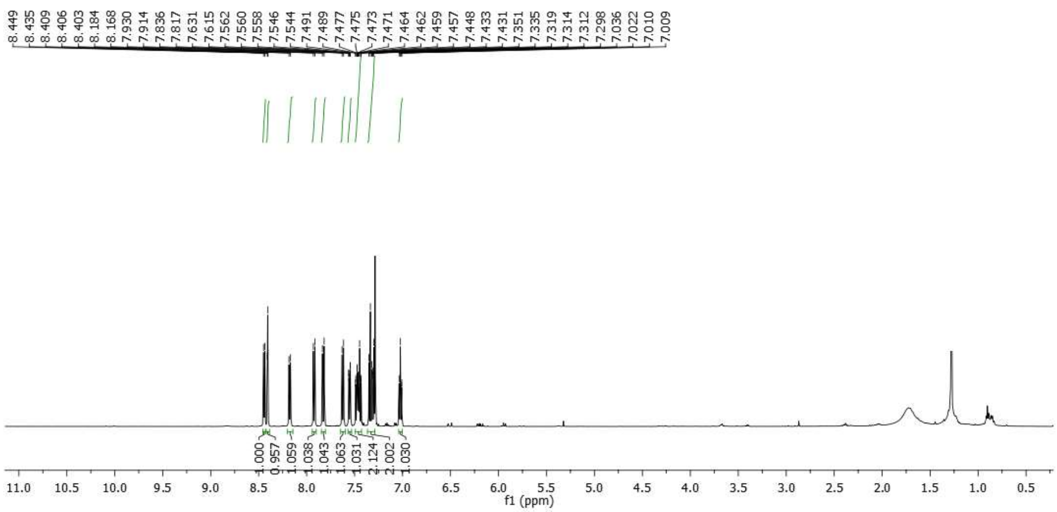
152.257
146.711
138.922
135.483
130.547
129.921
129.218
128.176
126.213
124.438
123.604
122.031
121.962
121.004
117.107
103.261
77.318
77.000
76.682
21.300
18.303
f1 (ppm)


Br
N
N
S
S
N

3h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8.435
8.409
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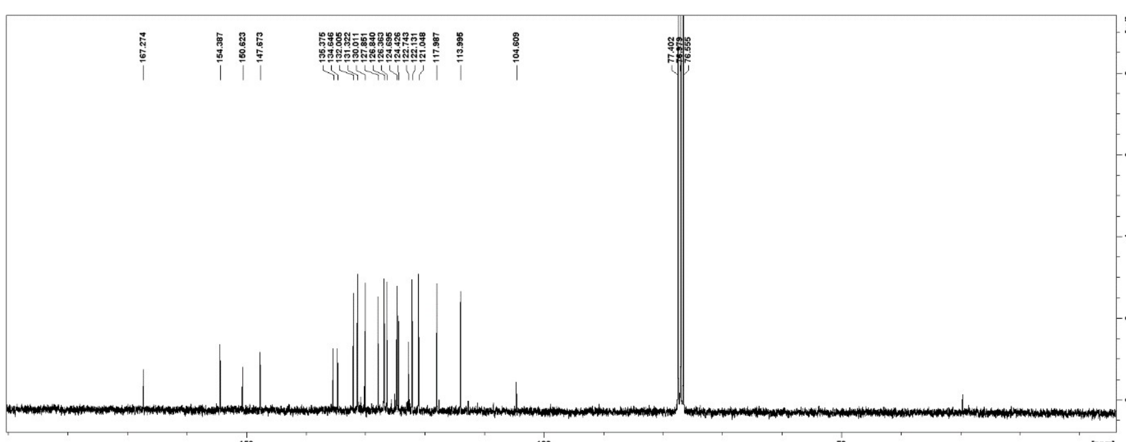
8.403
8.184
8.168
7.930
7.914
7.836
7.817
7.631
7.615
7.562
7.560
7.558
7.546
7.544
7.491
7.489
7.477
7.475
7.473
7.471
7.464
7.462
7.459
7.457
7.448
7.433
7.431
7.351
7.335
7.319
7.314
7.312
7.298
7.036
7.022
7.010
7.009
1.000
0.957
1.059
1.038
1.043
1.063
1.031
2.124
2.002
1.030
11.0
10.5
10.0
9.5
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
f1 (ppm)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150.623
147.673
135.375
134.646
122.131
121.048
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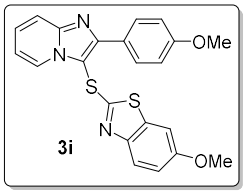
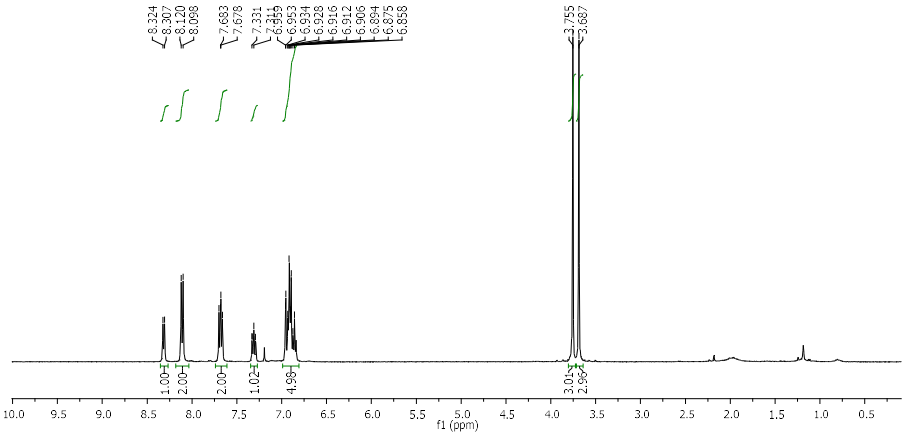
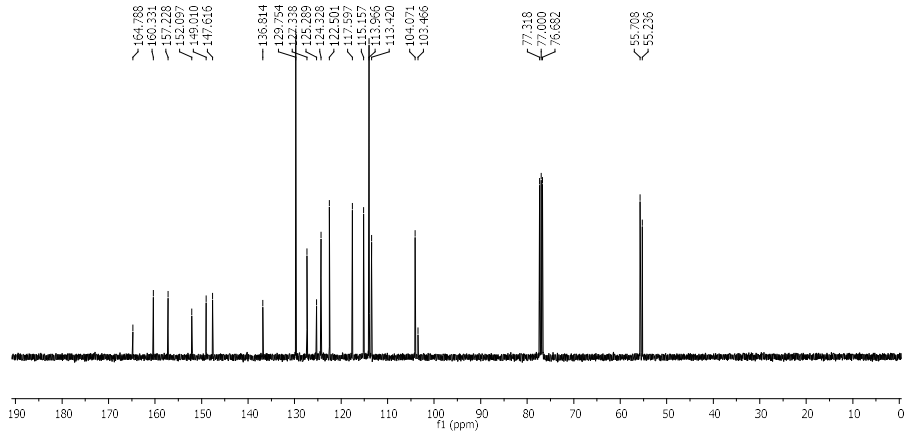
113.995
104.609
77.402
[rel]
8
6
4
2
0
150
100
50
[ppm]


N
N
OMe
S
S
N
OMe
3i


8.324
8.307
8.120
8.098
7.683
7.678
7.331
7.311
6.959
6.953
6.934
6.928
6.916
6.912
6.906
6.894
6.875
6.858
3.755
3.687
1.00
2.00
2.00
1.02
4.99
3.01
2.96
f1 (ppm)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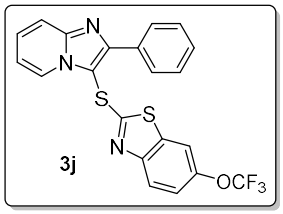
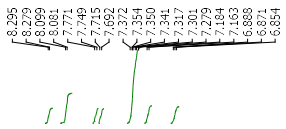
160.331
157.228
152.097
149.010
147.616
136.814
129.754
122.338
125.289
124.328
122.501
117.597
115.157
113.966
113.420
104.071
103.466
77.318
77.000
76.682
55.708
55.236
f1 (ppm)


N
N
S
S
N
OCF3
3j


8.295
8.279
8.099
8.081
7.771
7.749
7.715
7.692
7.372
7.354
7.350
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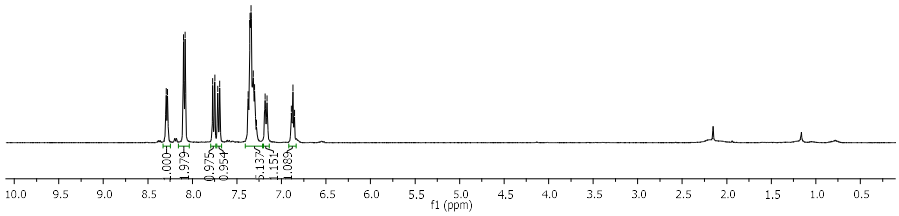
7.317
7.301
7.279
7.184
7.163
6.888
6.871
6.854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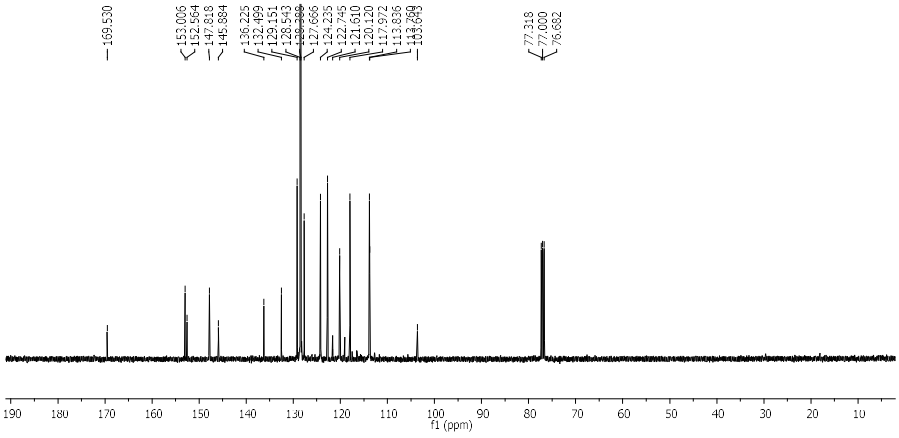
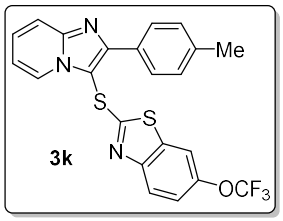
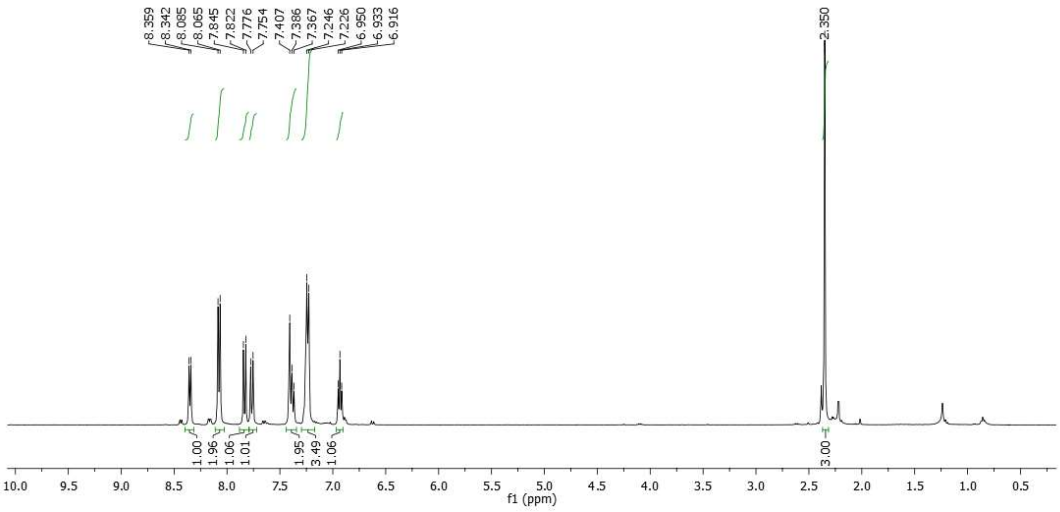
1.979
0.675
0.954
5.137
1.151
1.089
f1 (ppm)


169.530
153.006
152.564
147.818
145.884
136.225
132.499
129.151
128.543
127.666
124.235
122.745
121.610
120.120
117.972
113.836
77.318
77.000
76.682
f1 (ppm)


Me
S
S
N
N
3k
OCF3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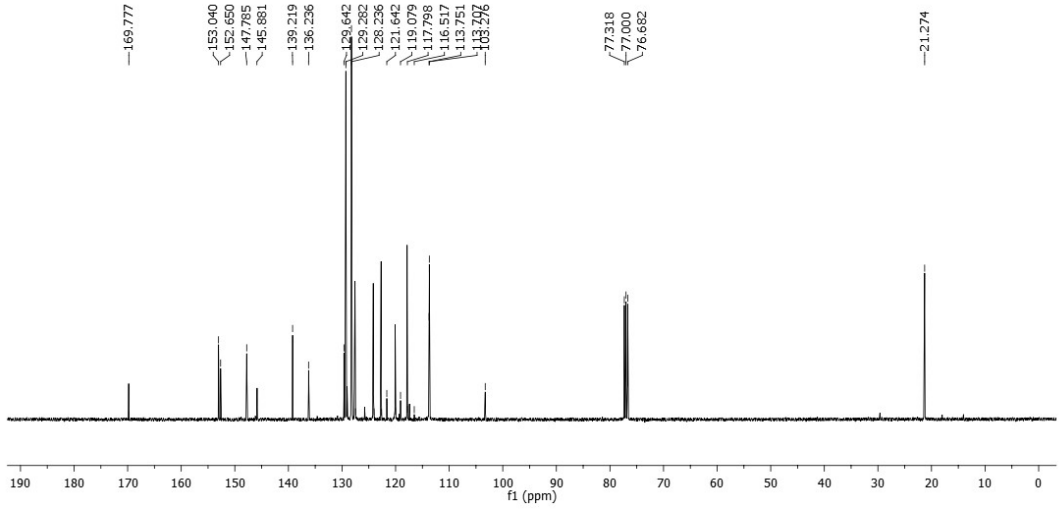
8.342
8.065
8.045
7.822
7.776
7.754
7.407
7.386
7.367
7.246
7.226
6.950
6.933
6.916
2.350
1.00
1.96
1.06
1.01
1.95
3.49
1.06
3.00
f1 (ppm)


169.777
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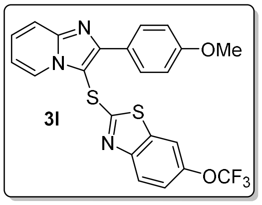
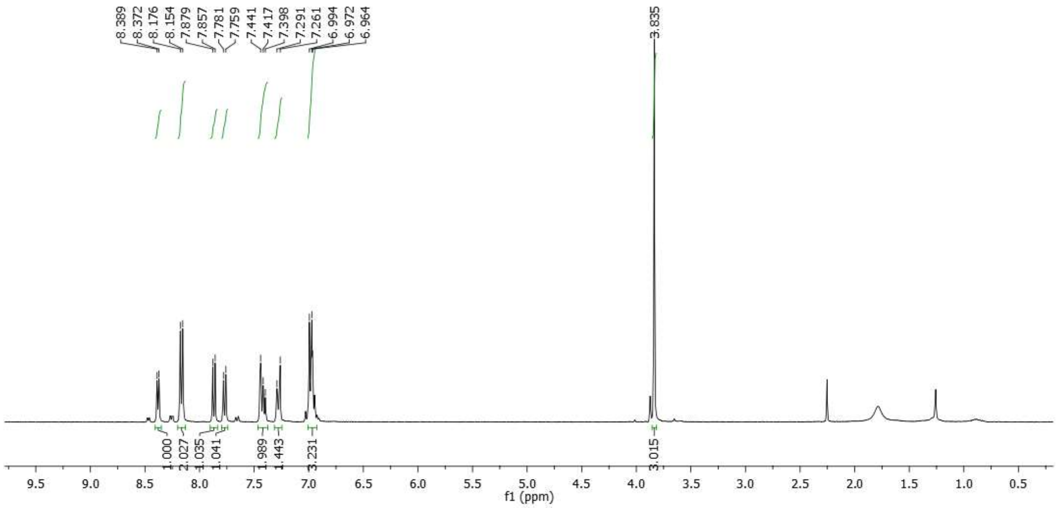
152.650
147.785
145.881
139.219
136.236
129.642
129.282
128.236
121.642
119.079
117.798
116.517
113.751
77.318
77.000
76.682
21.274
f1 (ppm)

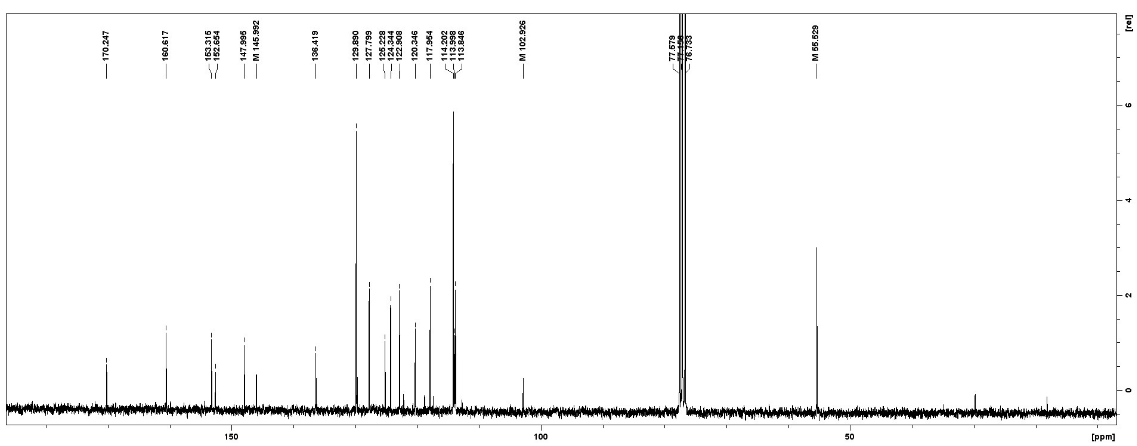


OMe
S
N
S
N
N
OCF3

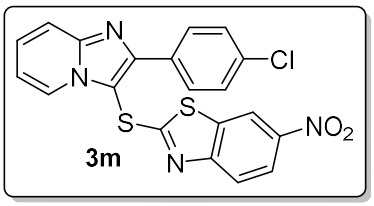
3l

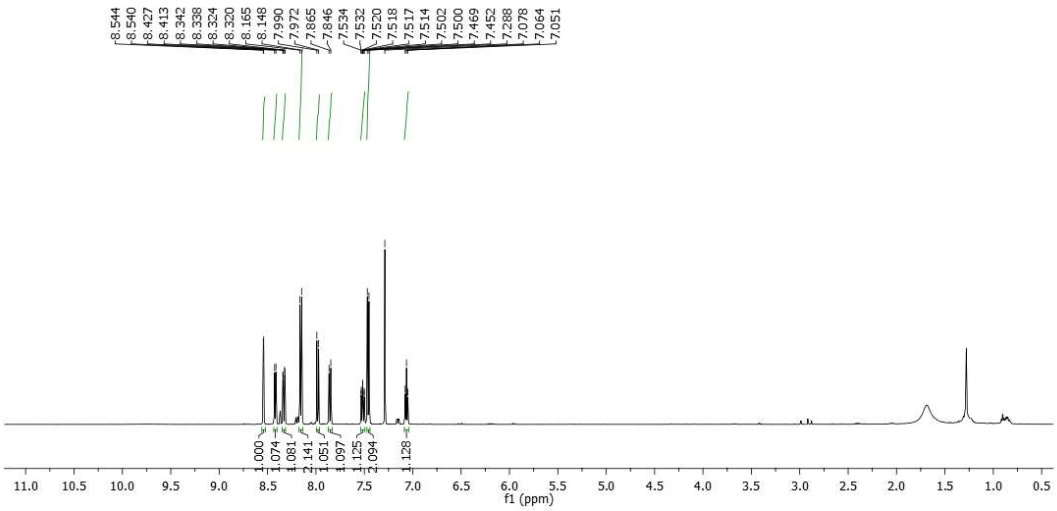


8.389
8.372
8.176
8.154
7.879
7.857
7.781
7.759
7.441
7.417
7.398
7.291
7.261
6.994
6.972
6.964
3.835
1.000
2.027
1.035
1.041
1.989
1.443
3.231
3.015
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)



170.247
160.617
153.315
152.654
147.995
M 145.992
136.419
129.890
127.799
125.228
124.344
122.908
120.346
117.954
114.202
113.998
113.846
M 102.926
77.579
76.733
M 55.529
[rel]
150
100
50
[ppm]


N
N
Cl
S
S
NO2
N
3m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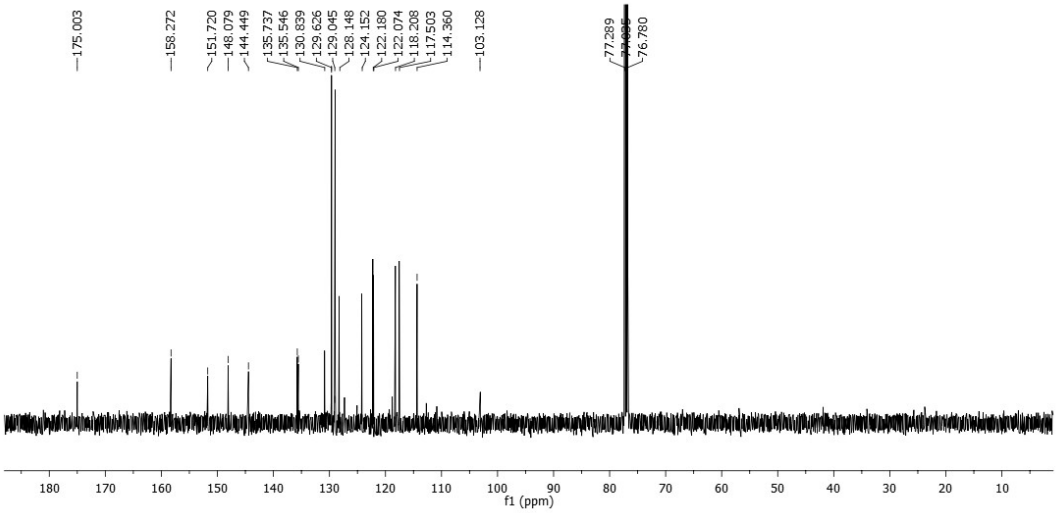
8.413
8.342
8.338
8.324
8.320
8.165
8.148
7.990
7.972
7.865
7.846
7.534
7.532
7.520
7.518
7.517
7.514
7.502
7.500
7.469
7.452
7.288
7.078
7.064
7.051
1.000
1.074
1.081
2.141
1.051
1.097
1.125
2.094
1.128
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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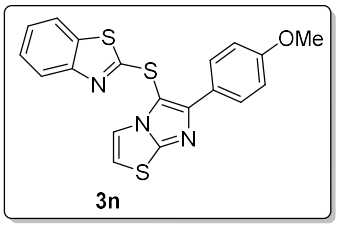
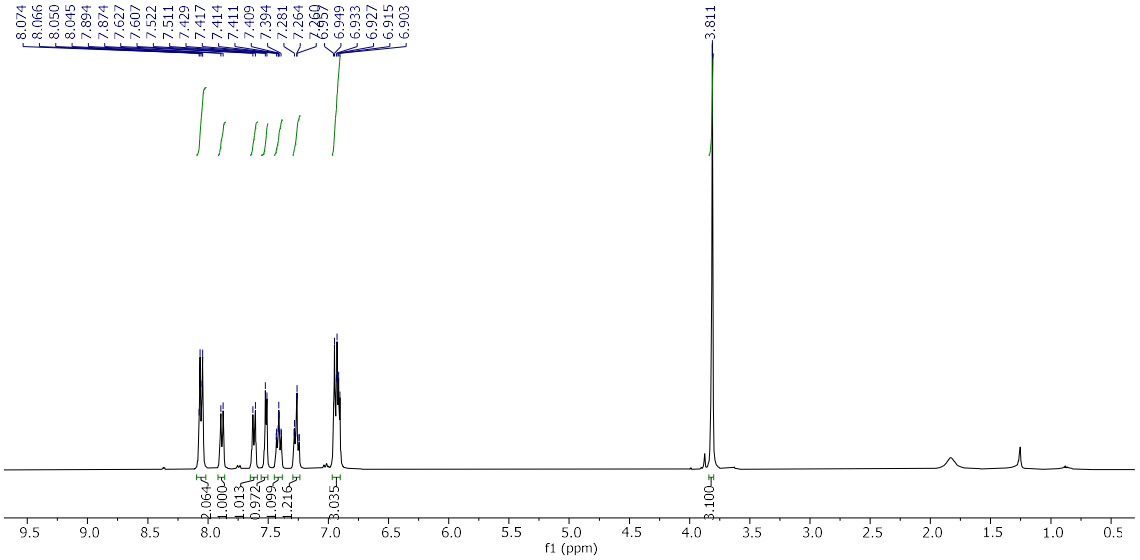
148.079
144.449
135.737
135.546
130.839
129.626
129.045
128.148
124.152
122.180
122.074
118.208
117.503
114.360
103.128
77.289
77.085
76.780
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


S
S
N
N
N
S
OMe

3n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8.045
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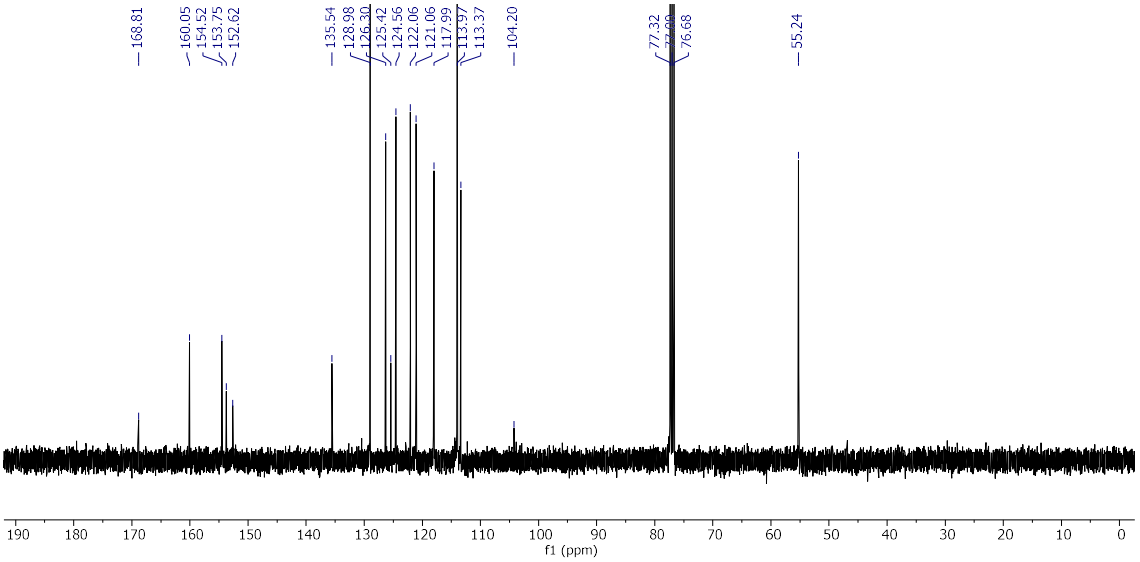
7.607
7.522
7.511
7.429
7.417
7.414
7.411
7.409
7.394
7.281
7.264
6.949
6.933
6.927
6.915
6.903
3.811
2.064
1.000
1.013
0.972
1.099
1.216
3.035
3.100
f1 (ppm)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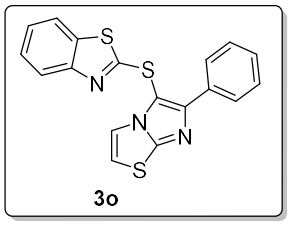
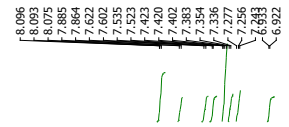
153.75
152.62
135.54
128.98
126.30
125.42
124.56
122.06
121.06
117.99
113.97
113.37
104.20
77.32
76.68
55.24
f1 (ppm)


3o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8.093
8.075
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7.864
7.622
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7.535
7.523
7.423
7.420
7.402
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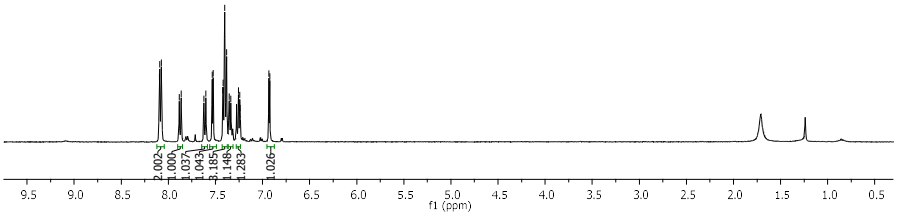
7.354
7.336
7.277
7.256
6.922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1.043
3.185
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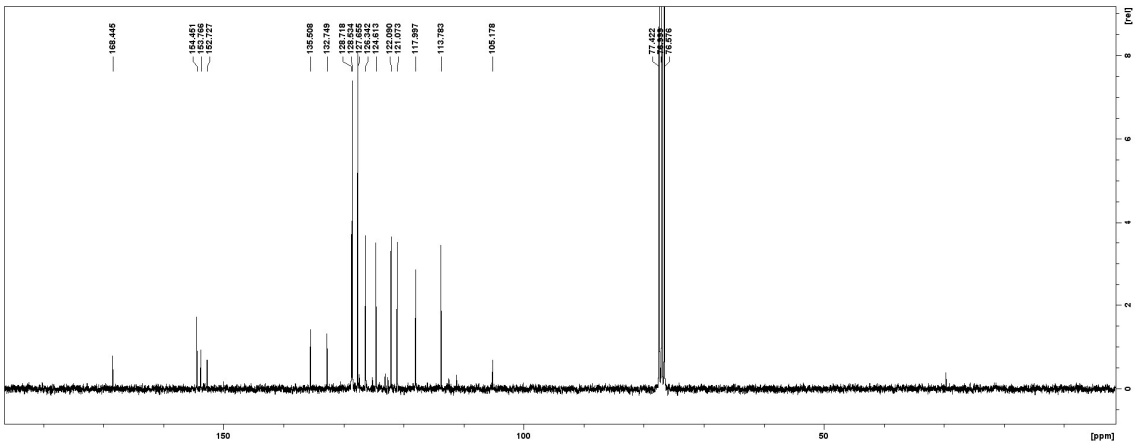
1.026
f1 (ppm)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132.749
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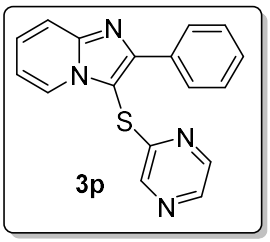
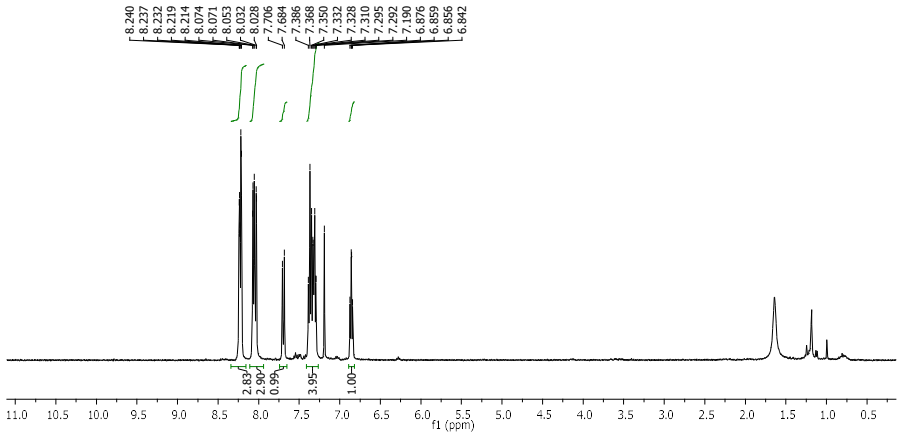
127.855
124.613
122.090
121.070
117.397
113.783
105.178
77.422
77.000
76.576
[ppm]


N
N
S
N
N
3p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8.219
8.214
8.074
8.071
8.053
8.032
8.028
7.706
7.684
7.386
7.368
7.350
7.332
7.328
7.310
7.295
7.292
7.190
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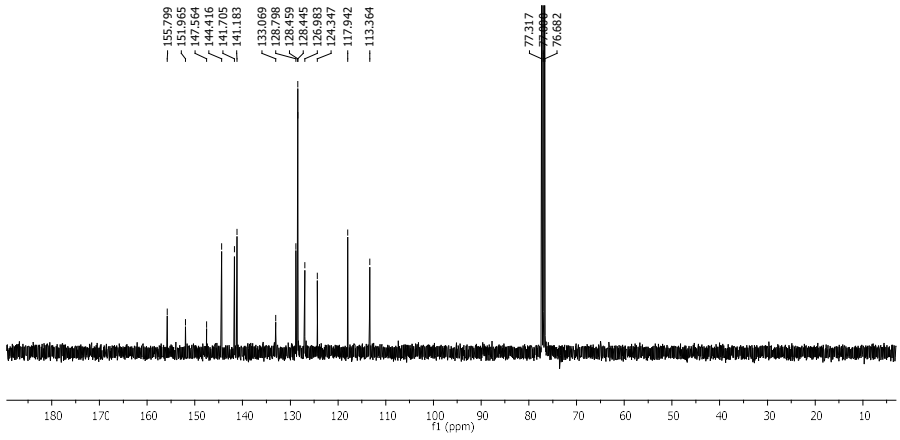
6.859
6.855
6.842
2.83
2.90
0.99
3.95
1.00
f1 (ppm)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144.416
141.705
141.183
133.069
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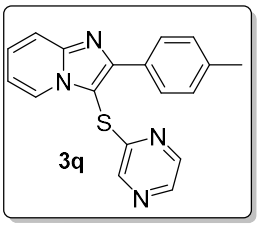
128.459
128.445
126.983
124.347
117.942
113.364
77.317
76.682
f1 (ppm)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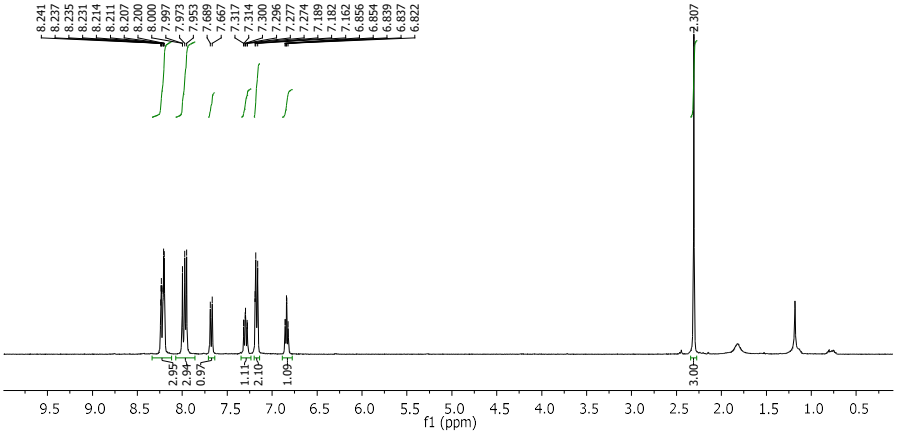
N
S
N
N
3q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8.231
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8.211
8.207
8.200
8.000
7.997
7.973
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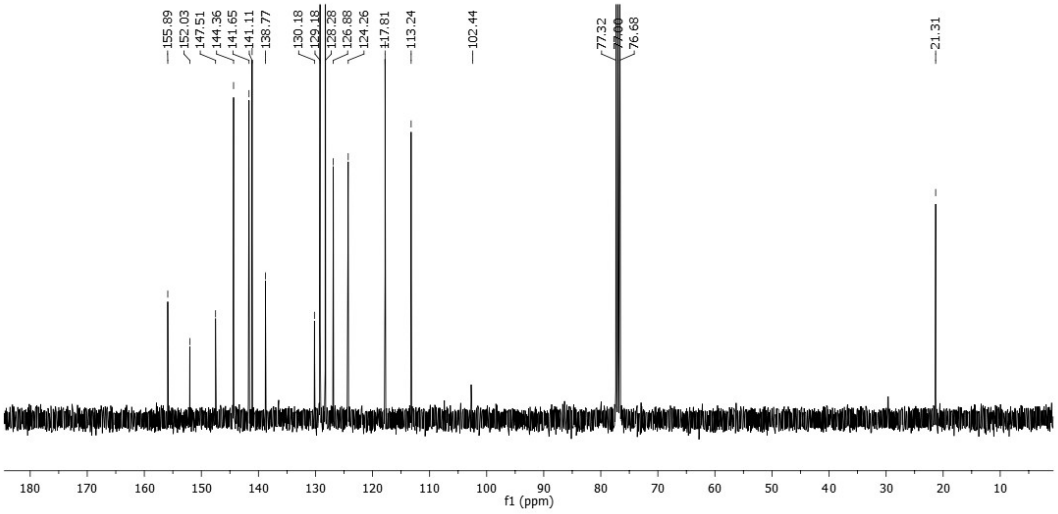
7.688
7.667
7.317
7.314
7.300
7.296
7.277
7.274
7.189
7.182
7.162
6.856
6.854
6.839
6.837
6.822
2.307
2.99
2.94
0.97
1.11
2.10
1.09
3.00
f1 (ppm)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144.36
141.65
141.11
138.77
130.18
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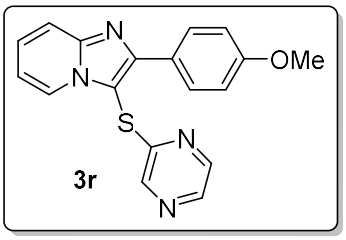
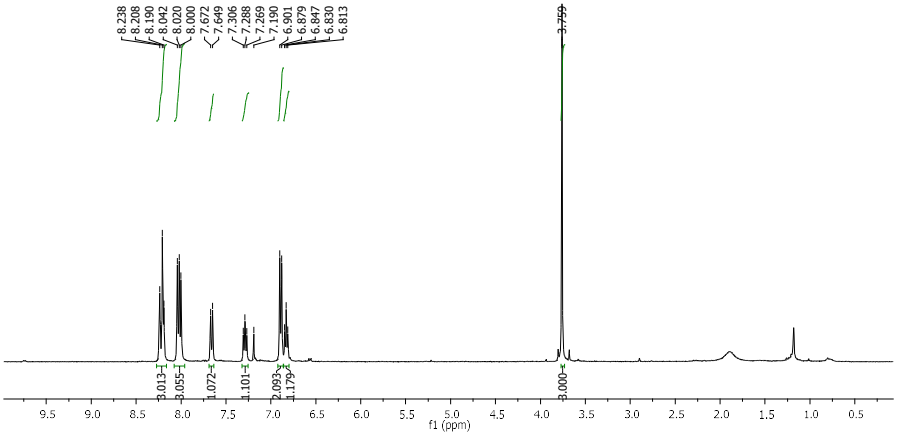
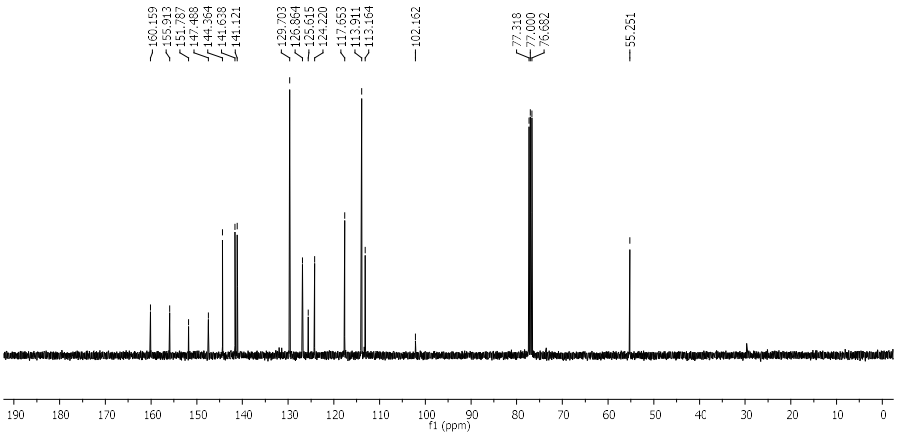
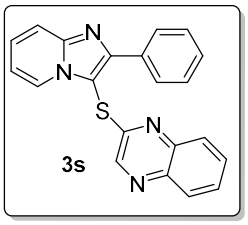
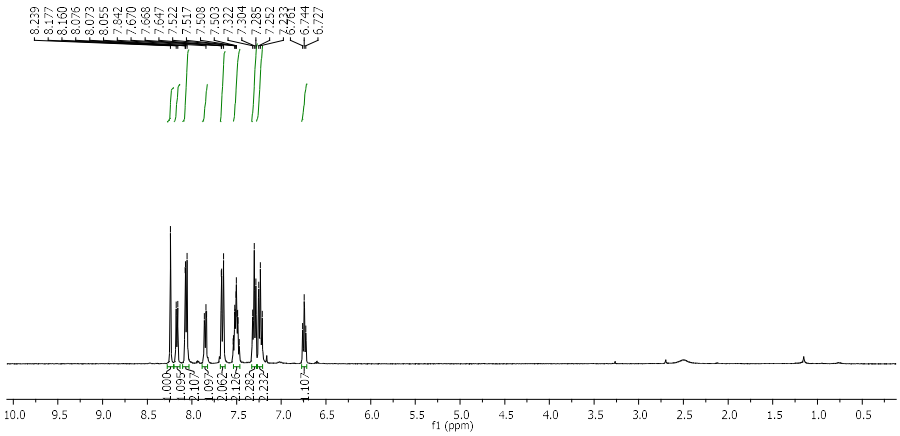
124.26
117.81
113.24
102.44
77.32
77.00
76.68
21.31
f1 (ppm)

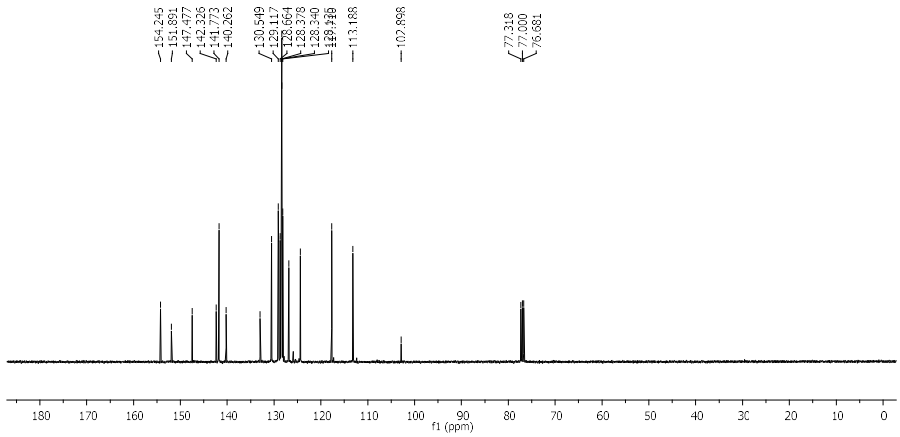

N
N
OMe
S
N
N
3r

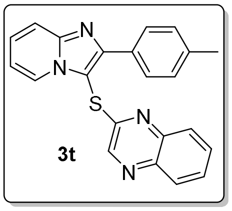

8.238
8.208
8.190
8.042
8.020
8.000
7.672
7.649
7.306
7.288
7.269
7.190
6.901
6.879
6.847
6.830
6.813
3.799
3.013
3.055
1.072
1.101
2.093
1.179
3.000
f1 (ppm)


160.159
155.913
151.787
147.368
144.364
141.638
141.121
129.703
126.864
125.615
124.220
117.653
113.911
113.164
102.162
77.318
77.000
76.682
55.251
f1 (ppm)

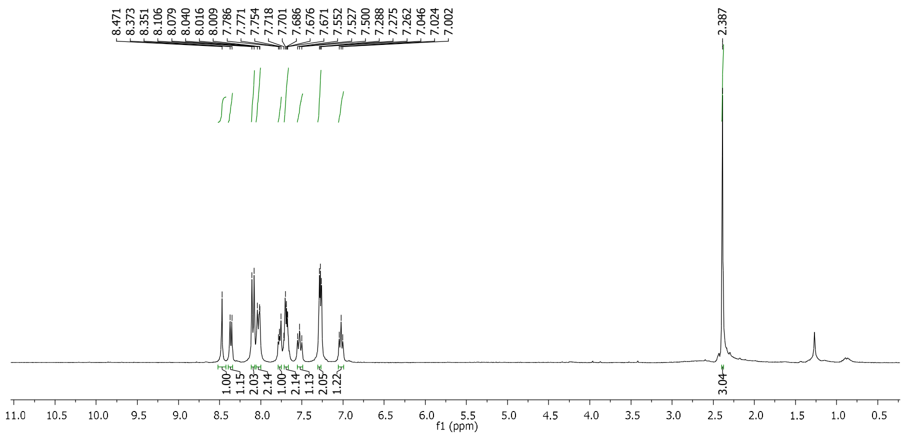

N
N
S
N
N
3s


8.239
8.177
8.160
8.076
8.073
8.055
7.842
7.670
7.668
7.647
7.522
7.517
7.508
7.503
7.322
7.304
7.285
7.252
6.763
6.744
6.727
1.000
1.095
2.107
1.097
2.062
2.126
2.283
2.232
1.107
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
f1 (ppm)


154.245
151.891
147.477
142.326
141.773
140.262
130.549
129.117
128.664
128.378
128.340
113.188
102.898
77.318
77.000
76.681
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


N
N
S
N
N

3t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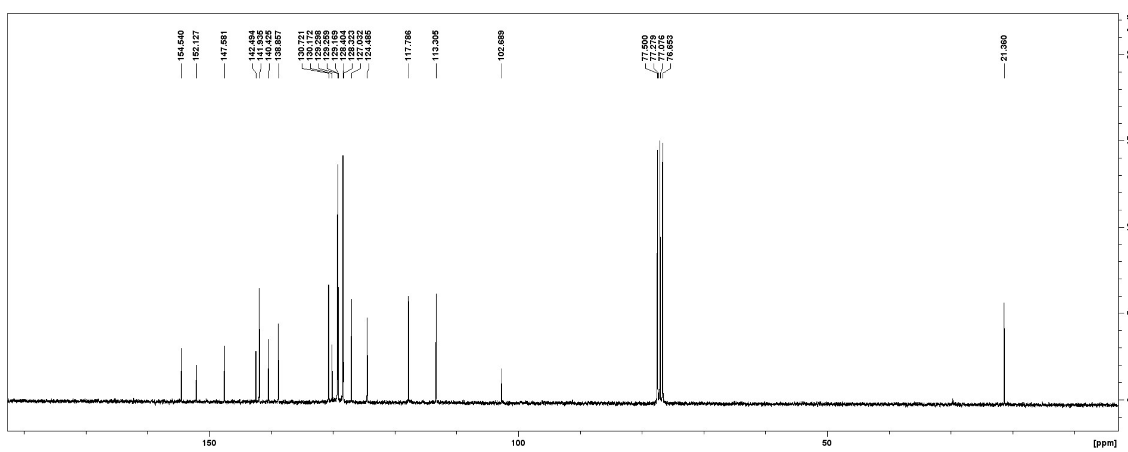
8.351
8.106
8.079
8.040
8.016
8.009
7.786
7.771
7.754
7.718
7.701
7.686
7.676
7.671
7.552
7.527
7.500
7.288
7.275
7.262
7.046
7.024
7.002
2.387
1.00
1.15
2.03
2.14
1.00
2.14
1.13
2.05
1.22
3.04
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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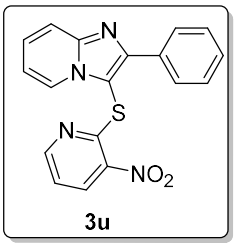
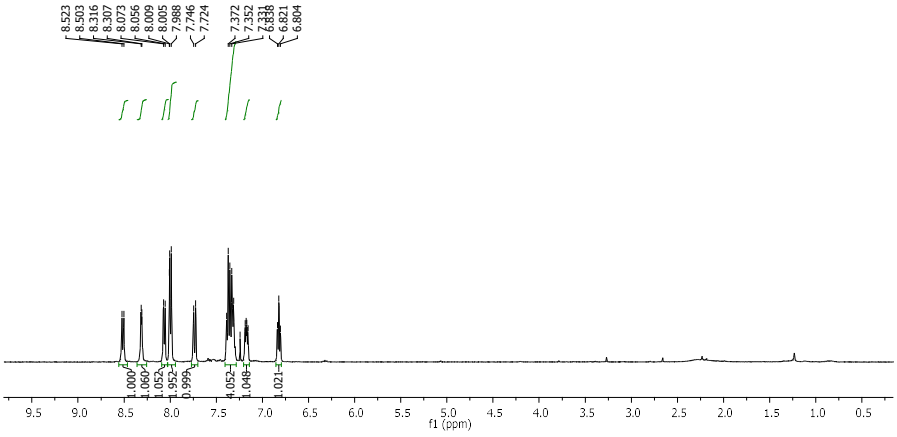
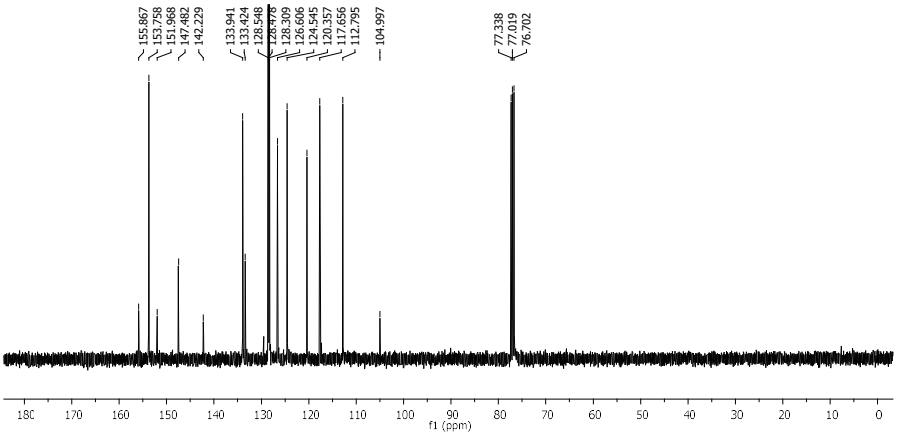
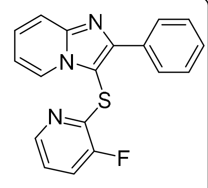
152.127
147.581
142.494
141.935
140.425
138.857
130.721
130.172
129.298
129.259
129.169
128.404
128.323
127.032
124.485
117.786
113.305
102.689
77.500
77.279
77.076
76.653
21.360
[rel]
20
15
10
5
0
150
100
50
[ppm]


N
N
S
N
NO2

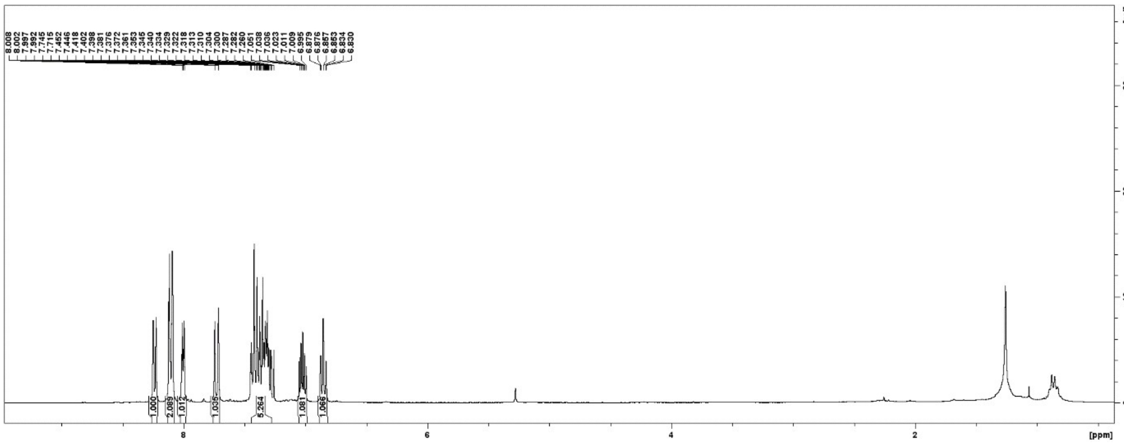
3u

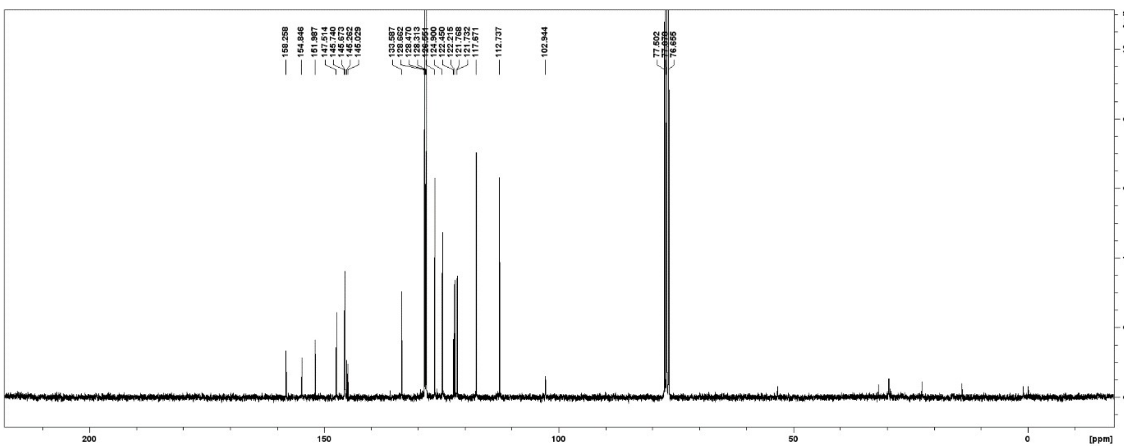

8.523
8.503
8.316
8.307
8.073
8.056
8.009
8.005
7.988
7.746
7.724
7.372
7.352
7.331
6.838
6.821
6.804
1.000
1.060
1.052
1.952
0.999
4.052
1.048
1.021
f1 (ppm)

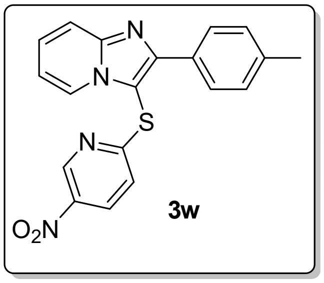

155.867
153.758
151.968
147.482
142.229
133.941
133.424
128.548
128.478
128.309
126.606
124.545
120.357
117.656
112.795
104.997
77.338
77.019
76.702
f1 (ppm)

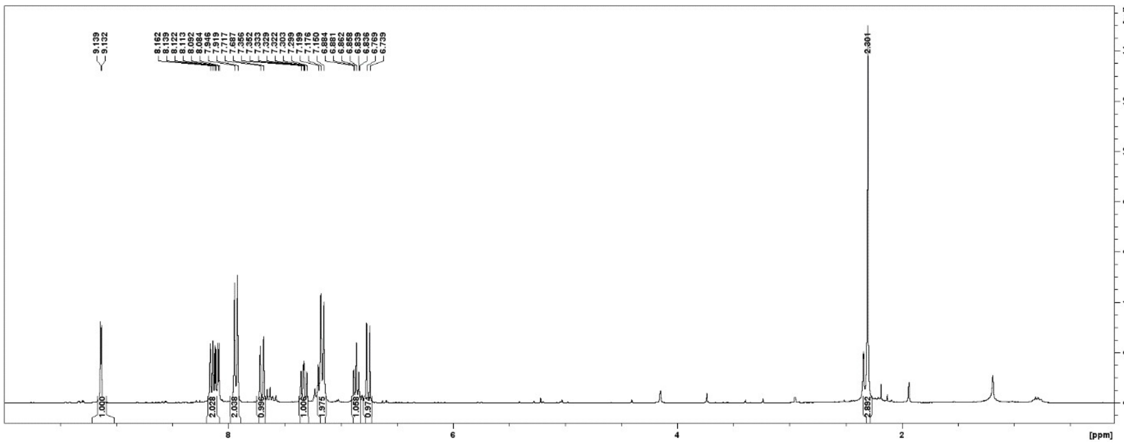


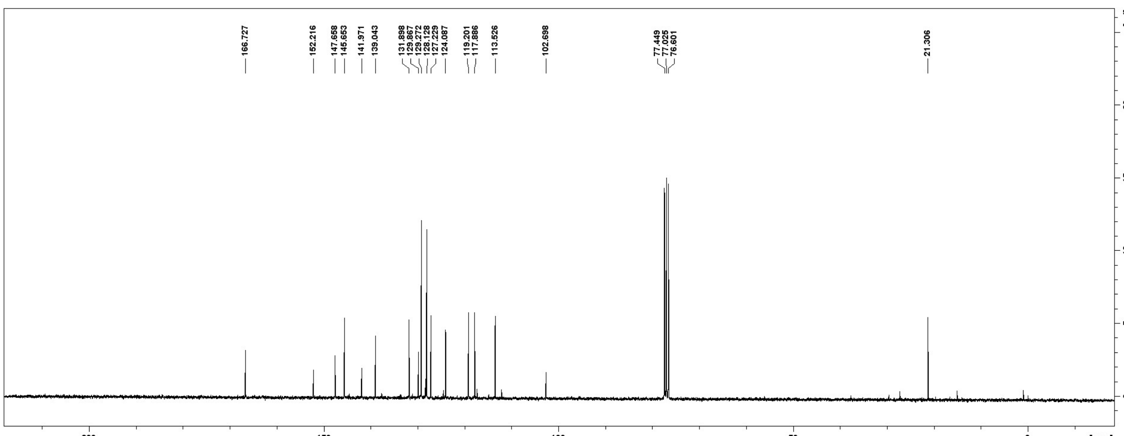
3v

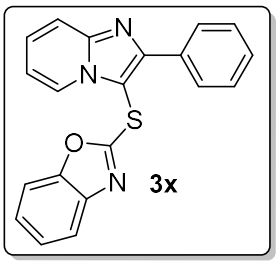


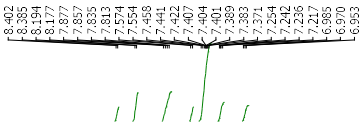


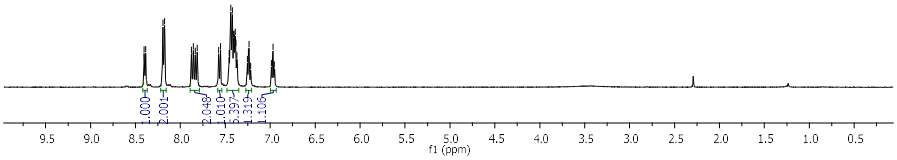

N
N
S
N
O_2N
3w

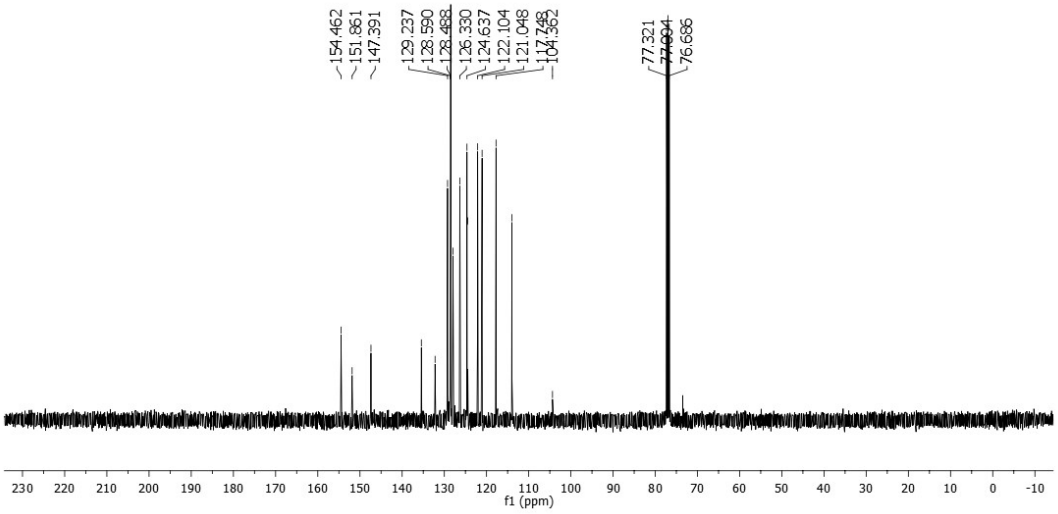


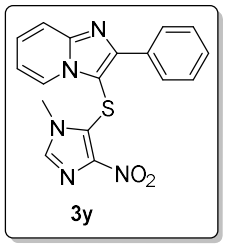

166.727
152.216
147.658
145.653
141.971
139.043
131.898
129.867
128.272
128.128
127.229
124.087
119.201
117.886
113.526
102.698
77.449
77.025
76.601
21.306
[ppm]


N
N
S
O
N
3x

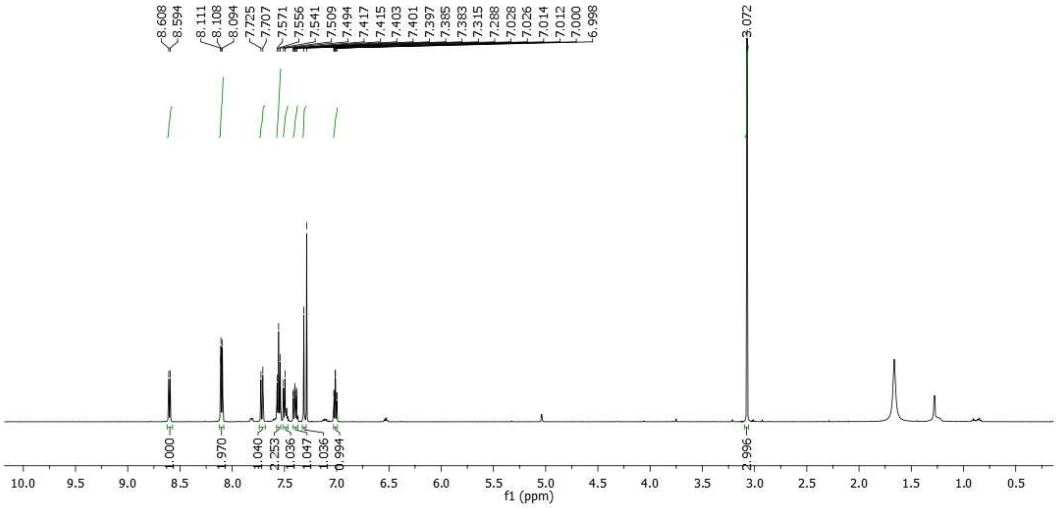

8.402
8.385
8.194
8.177
7.877
7.857
7.835
7.813
7.574
7.554
7.458
7.441
7.422
7.407
7.404
7.401
7.389
7.383
7.371
7.254
7.242
7.236
7.217
6.985
6.970
6.953

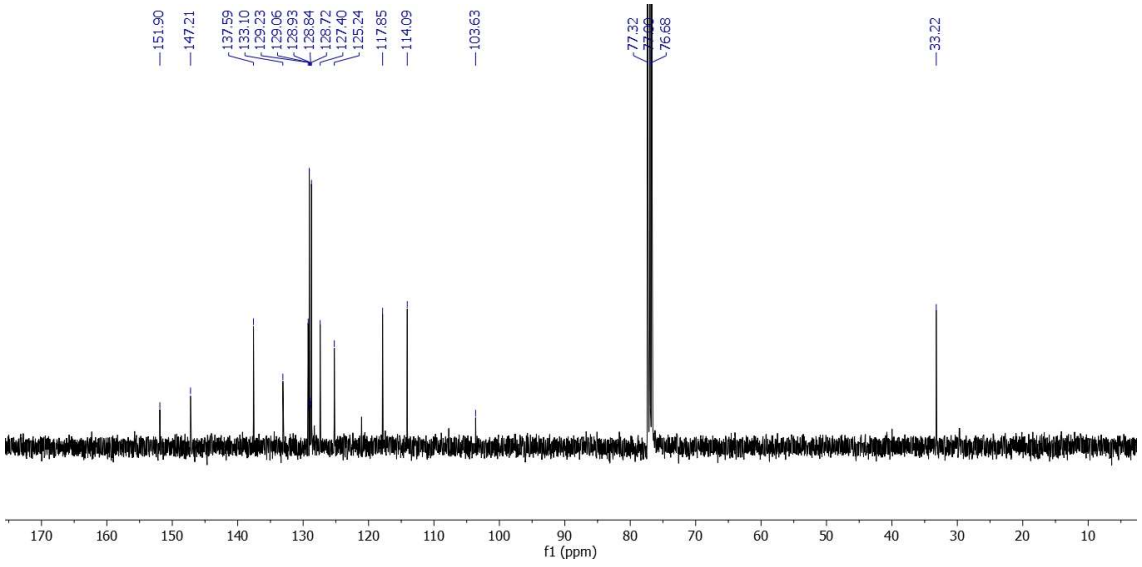

1.000
2.001
2.049
1.019
1.393
1.319
1.106
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


154.462
151.861
147.391
129.237
128.590
128.488
126.330
124.637
122.104
121.048
117.748
104.362
77.321
77.004
76.686
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


N
N
S
N
N
NO2

3y


8.608
8.594
8.111
8.108
8.094
7.725
7.707
7.571
7.556
7.541
7.509
7.494
7.417
7.415
7.403
7.401
7.397
7.385
7.383
7.315
7.288
7.028
7.026
7.014
7.012
7.000
6.998
3.072
1.000
1.970
1.040
2.253
1.036
1.047
1.036
0.994
2.996
f1 (ppm)


151.90
147.21
137.59
133.10
129.23
129.06
128.93
128.84
128.72
127.40
125.24
117.85
114.09
103.63
77.32
77.00
76.68
33.22
f1 (ppm)