

Synthesis of spiro[4.4]thiadiazole derivatives via double 1,3-dipolar cycloaddition of hydrazonyl chlorides with carbon disulfide

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Supporting Information

Table of contents

1. General methods	2
2. General procedure for the synthesis of spiro[4.4]thiadiazole derivatives	2
3. Crystal data and structural refinement for 3h	5
4. Copies of NMR spectra	7

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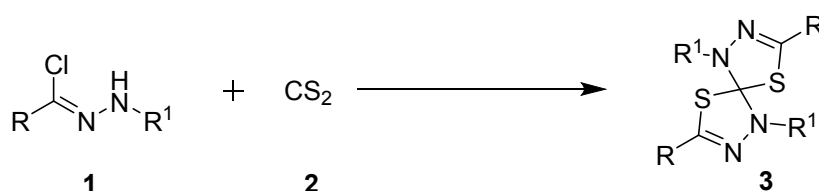
E-mail address: sunailify@126.com

1. General methods

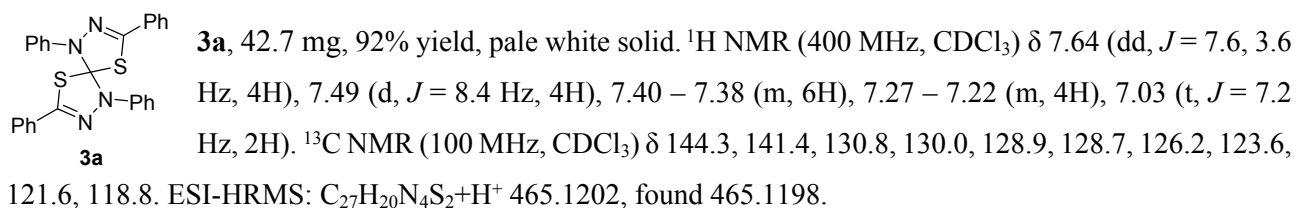
NMR data were obtained for ^1H at 400 MHz, and for ^{13}C at 100 MHz. Chemical shifts were given in parts per million (δ) from tetramethylsilane with the solvent resonance as the internal standard in CDCl_3 solution. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. ESI HRMS was recorded on a Waters SYNAPT G2. Column chromatography was performed on silica gel (200-300 mesh) eluting with ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates. UV light, I_2 , and solution of potassium permanganate were used to visualize products. All chemicals were used without purification as commercially available unless otherwise noted. Petroleum ether (PE) and ethyl acetate (EtOAc) were distilled. THF was freshly distilled from sodium/benzophenone. Unless otherwise noted, experiments involving moisture and/or air sensitive components were performed under a positive pressure of argon in oven-dried glassware equipped with a rubber septum inlet. Dried solvents and liquid reagents were transferred by oven-dried syringes. The hydrazone chlorides **1** were prepared according to the literature procedures [1].

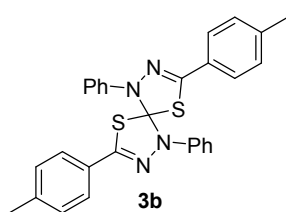
- [1] (a) Wang, G.; Liu, X.; Huang, T.; Kuang, Y.; Lin, L.; Feng, X., *Org. Lett.* **2013**, *15*, 76-79; (b) Sibi, M. P.; Stanley, L. M.; Soeta, T., *Adv. Synth. Catal.* **2006**, *348*, 2371-2375; (c) Su, Y.; Zhao, Y.; Chang, B.; Zhao, X.; Zhang, R.; Liu, X.; Huang, D.; Wang, K.-H.; Huo, C.; Hu, Y., *J. Org. Chem.* **2019**, *84*, 6719-6728; (d) Voronin, V. V.; Ledovskaya, M. S.; Gordeev, E. G.; Rodygin, K. S.; Ananikov, V. P., *J. Org. Chem.* **2018**, *83*, 3819-3828; (e) Liu, H.; Jia, H.; Wang, B.; Xiao, Y.; Guo, H., *Org. Lett.* **2017**, *19*, 4714-4717.

2. General procedure for the synthesis of spiro[4.4]thiadiazole derivatives

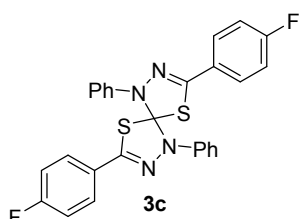


The nitrile imine precursor of the hydrazone chlorides **1** (0.2 mmol), carbon disulfide **2** (0.3 mmol), and the cesium carbonate (0.2 mmol) were dissolved in CH_2Cl_2 (1.0 mL). Then the solution was stirred at rt for 12 h. After completion, the mixture was directly purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (50:1 to 25:1) to afford the product **3**.

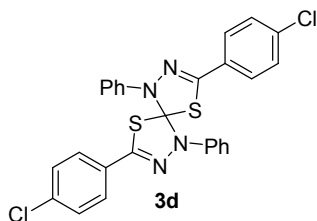




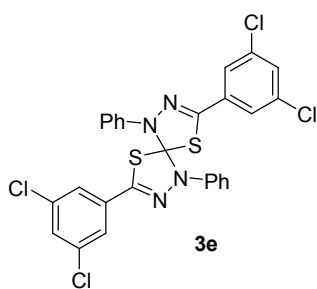
3b, 44.3 mg, 90% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, J = 8.0 Hz, 4H), 7.47 (d, J = 8.4 Hz, 4H), 7.25 – 7.18 (m, 8H), 7.00 (t, J = 7.6 Hz, 2H), 2.36 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.4, 141.5, 140.3, 129.4, 128.8, 128.0, 126.1, 123.3, 121.3, 118.6, 21.4. ESI-HRMS: $\text{C}_{29}\text{H}_{24}\text{N}_4\text{S}_2+\text{H}^+$ 493.1515, found 493.1510.



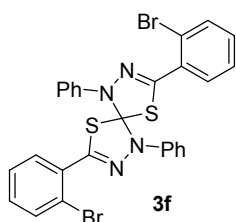
3c, 47.5 mg, 95% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.62 (dd, J = 8.8, 5.2 Hz, 4H), 7.47 (d, J = 7.6 Hz, 4H), 7.28 – 7.24 (m, 4H), 7.11 – 7.03 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.7 (d, J = 249.6 Hz), 143.4, 141.3, 128.9, 128.0 (d, J = 8.3 Hz), 127.0 (d, J = 3.3 Hz), 123.8, 122.4, 118.9, 115.9 (d, J = 22.2 Hz). ESI-HRMS: $\text{C}_{27}\text{H}_{18}\text{F}_2\text{N}_4\text{S}_2+\text{H}^+$ 501.1014, found 501.1009.



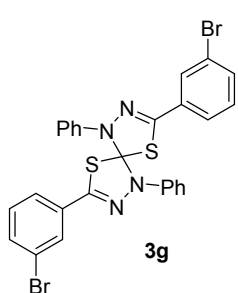
3d, 50.0 mg, 94% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, J = 8.4 Hz, 4H), 7.45 (d, J = 8.0 Hz, 4H), 7.36 (d, J = 8.4 Hz, 4H), 7.28 – 7.24 (m, 4H), 7.06 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.2, 141.2, 135.9, 129.2, 128.98, 128.96, 127.3, 123.9, 122.2, 119.0. ESI-HRMS: $\text{C}_{27}\text{H}_{18}\text{Cl}_2\text{N}_4\text{S}_2+\text{H}^+$ 533.0423, found 533.0416.



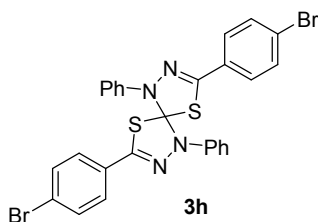
3e, 56.0 mg, 93% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.49 (s, 4H), 7.43 (d, J = 8.8 Hz, 4H), 7.37 (s, 2H), 7.30 (t, J = 7.6 Hz, 4H), 7.11 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 141.6, 140.8, 135.5, 133.4, 129.7, 129.1, 124.6, 124.3, 122.9, 119.4. ESI-HRMS: $\text{C}_{27}\text{H}_{18}\text{Cl}_2\text{N}_4\text{S}_2+\text{H}^+$ 600.9643, found 600.9639.



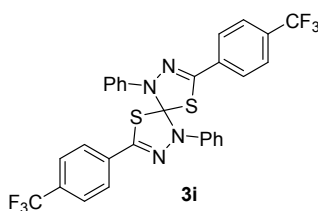
3f, 58.8 mg, 95% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.68 – 7.64 (m, 4H), 7.49 (d, J = 8.4 Hz, 4H), 7.35 (t, J = 7.6 Hz, 2H), 7.30 – 7.22 (m, 6H), 7.06 (t, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.3, 141.1, 134.2, 131.4, 130.85, 130.83, 128.9, 127.5, 123.7, 121.5, 121.3, 119.0. ESI-HRMS: $\text{C}_{27}\text{H}_{18}\text{Br}_2\text{N}_4\text{S}_2+\text{H}^+$ 622.9392, found 622.9383.



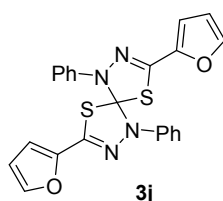
3g 59.4 mg, 96% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.83 (s, 2H), 7.50 – 7.44 (m, 8H), 7.29 – 7.25 (m, 4H), 7.23 – 7.21 (m, 2H), 7.06 (t, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.8, 141.1, 132.9, 132.7, 130.3, 129.1, 128.8, 124.9, 124.2, 123.0, 122.3, 119.2. ESI-HRMS: $\text{C}_{27}\text{H}_{18}\text{Br}_2\text{N}_4\text{S}_2 + \text{H}^+$ 622.9392, found 620.9384.



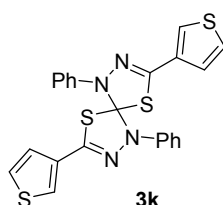
3h, 58.8 mg, 95% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.44 (m, 12H), 7.28 – 7.24 (m, 4H), 7.06 (t, $J = 7.6$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.3, 141.1, 131.9, 129.6, 129.0, 127.5, 124.1, 124.0, 122.2, 119.0. ESI-HRMS: $\text{C}_{27}\text{H}_{18}\text{Br}_2\text{N}_4\text{S}_2 + \text{H}^+$ 622.9392, found 622.9384.



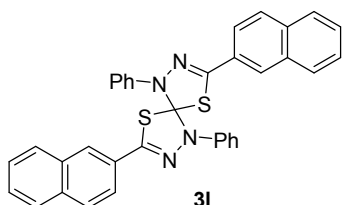
3i, 56.4 mg, 94% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 8.0$ Hz, 4H), 7.65 (d, $J = 8.4$ Hz, 4H), 7.47 (d, $J = 8.0$ Hz, 4H), 7.28 (t, $J = 7.2$ Hz, 4H), 7.09 (t, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 142.8, 141.0, 134.0, 131.6 (q, $J = 32.5$ Hz), 129.1, 126.3, 125.8 (q, $J = 3.7$ Hz), 125.1, 124.4, 122.5, 121.3 (q, $J = 220.3$ Hz), 119.3. ESI-HRMS: $\text{C}_{29}\text{H}_{18}\text{F}_6\text{N}_4\text{S}_2 + \text{H}^+$ 601.0950, found 601.0942.



3j, 40.4 mg, 91% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.45 (m, 6H), 7.28 – 7.24 (m, 4H), 7.05 (t, $J = 7.2$ Hz, 2H), 6.70 (d, $J = 3.2$ Hz, 2H), 6.49 – 6.48 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 145.2, 143.9, 141.3, 135.8, 129.0, 124.0, 119.5, 111.9, 110.3. ESI-HRMS: $\text{C}_{23}\text{H}_{16}\text{N}_4\text{O}_2\text{S}_2 + \text{H}^+$ 445.0787, found 445.0783.

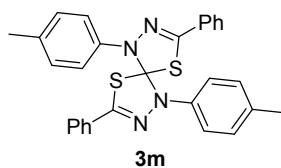


3k, 44.3 mg, 93% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.45 (m, 6H), 7.38 – 7.34 (m, 4H), 7.28 – 7.24 (m, 4H), 7.04 (t, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 141.4, 140.2, 132.6, 128.9, 126.7, 125.2, 124.5, 123.6, 121.8, 118.9. ESI-HRMS: $\text{C}_{23}\text{H}_{16}\text{N}_4\text{S}_4 + \text{H}^+$ 477.0331, found 477.0326.

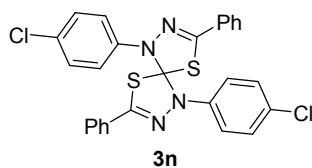


3l, 53.6 mg, 95% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.12 – 7.99 (m, 2H), 7.88 (s, 1H), 7.85 – 7.80 (m, 7H), 7.56 (d, $J = 8.0$ Hz, 4H), 7.49 (dd, $J = 7.6, 3.6$ Hz, 4H), 7.28 (d, $J = 7.6$ Hz, 3H), 7.23 (s, 1H), 7.04 (t, $J = 7.2$

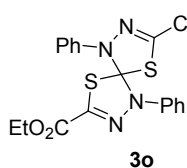
Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.4, 141.4, 134.0, 133.0, 129.0, 128.5, 128.31, 128.27, 127.9, 127.1, 126.8, 126.5, 123.7, 122.8, 121.4, 118.9. ESI-HRMS: $\text{C}_{35}\text{H}_{24}\text{N}_4\text{S}_2+\text{H}^+$ 565.1515, found 565.1510.



3m, 44.3 mg, 90% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.64 – 7.62 (m, 4H), 7.40 – 7.38 (m, 10H), 7.06 (d, $J = 8.4$ Hz, 4H), 2.26 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.9, 139.1, 133.3, 131.0, 129.8, 129.5, 128.7, 126.1, 122.4, 119.1, 20.7. ESI-HRMS: $\text{C}_{29}\text{H}_{24}\text{N}_4\text{S}_2+\text{H}^+$ 493.1515, found 493.1512.

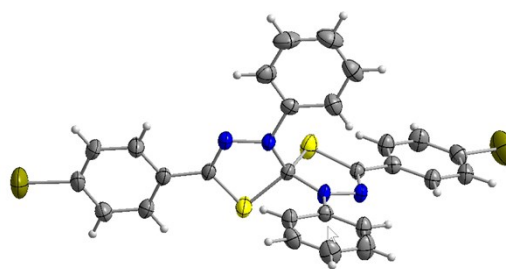
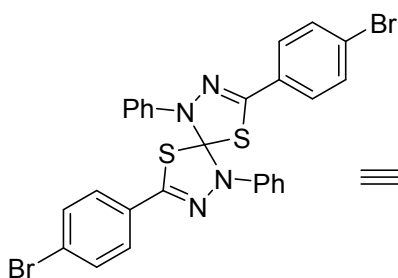


3n, 49.5 mg, 93% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.64 – 7.62 (m, 4H), 7.42 – 7.41 (m, 6H), 7.38 – 7.36 (m, 4H), 7.24 – 7.20 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 145.0, 139.7, 130.4, 130.3, 129.0, 128.8, 126.2, 120.9, 119.7. ESI-HRMS: $\text{C}_{27}\text{H}_{18}\text{Cl}_2\text{N}_4\text{S}_2+\text{H}^+$ 533.0423, found 533.0421.



3o, 41.5 mg, 91% yield, pale white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.37 (d, $J = 8.0$ Hz, 4H), 7.31 (t, $J = 7.8$ Hz, 4H), 7.18 (t, $J = 7.2$ Hz, 2H), 4.35 (q, $J = 6.4$ Hz, 4H), 1.36 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.6, 140.1, 135.9, 129.3, 125.9, 123.2, 120.9, 62.7, 14.2. ESI-HRMS: $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_4\text{S}_2+\text{H}^+$ 457.0999, found 457.0990.

3. Crystal data and structural refinement for **3h**

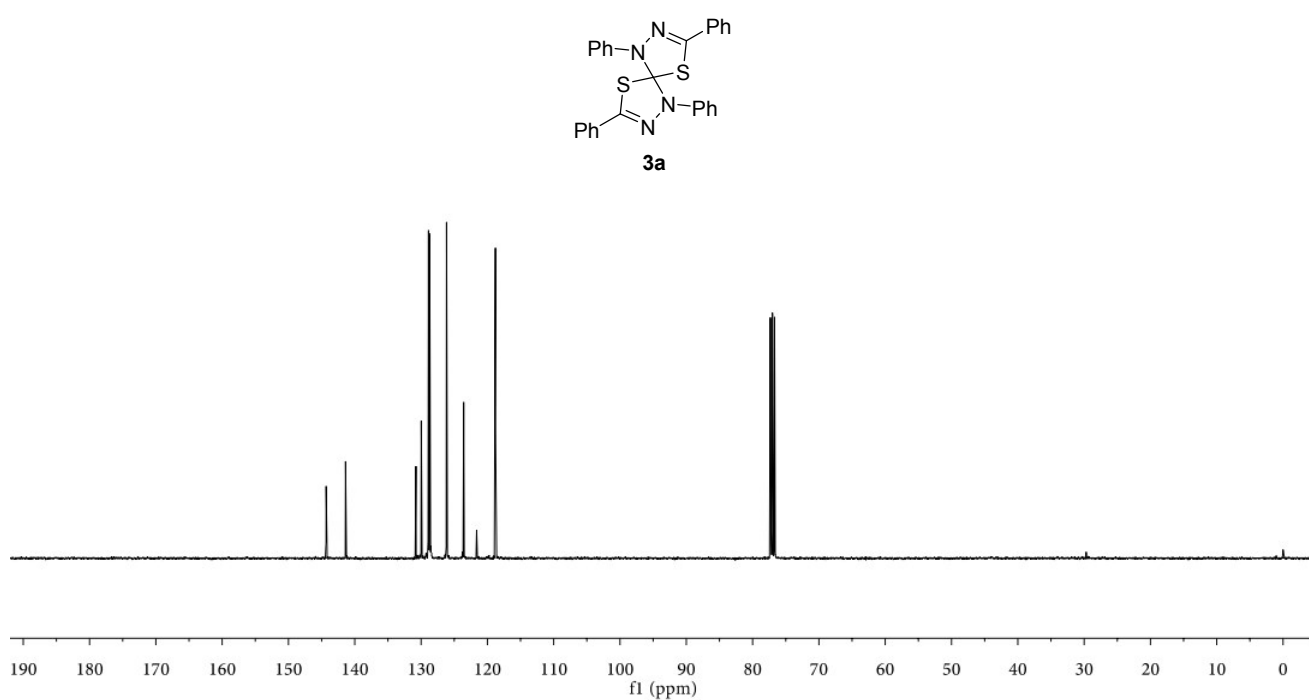
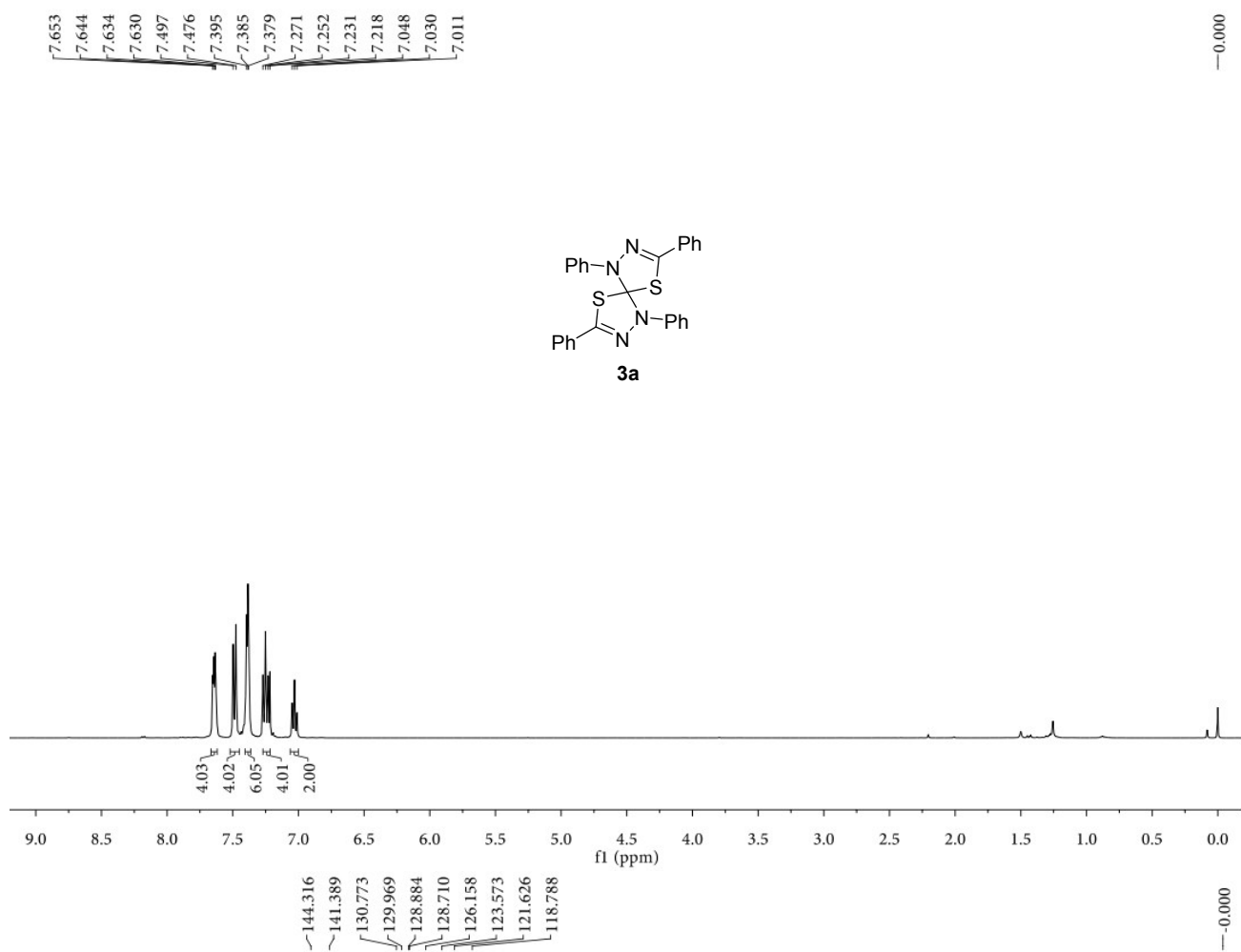


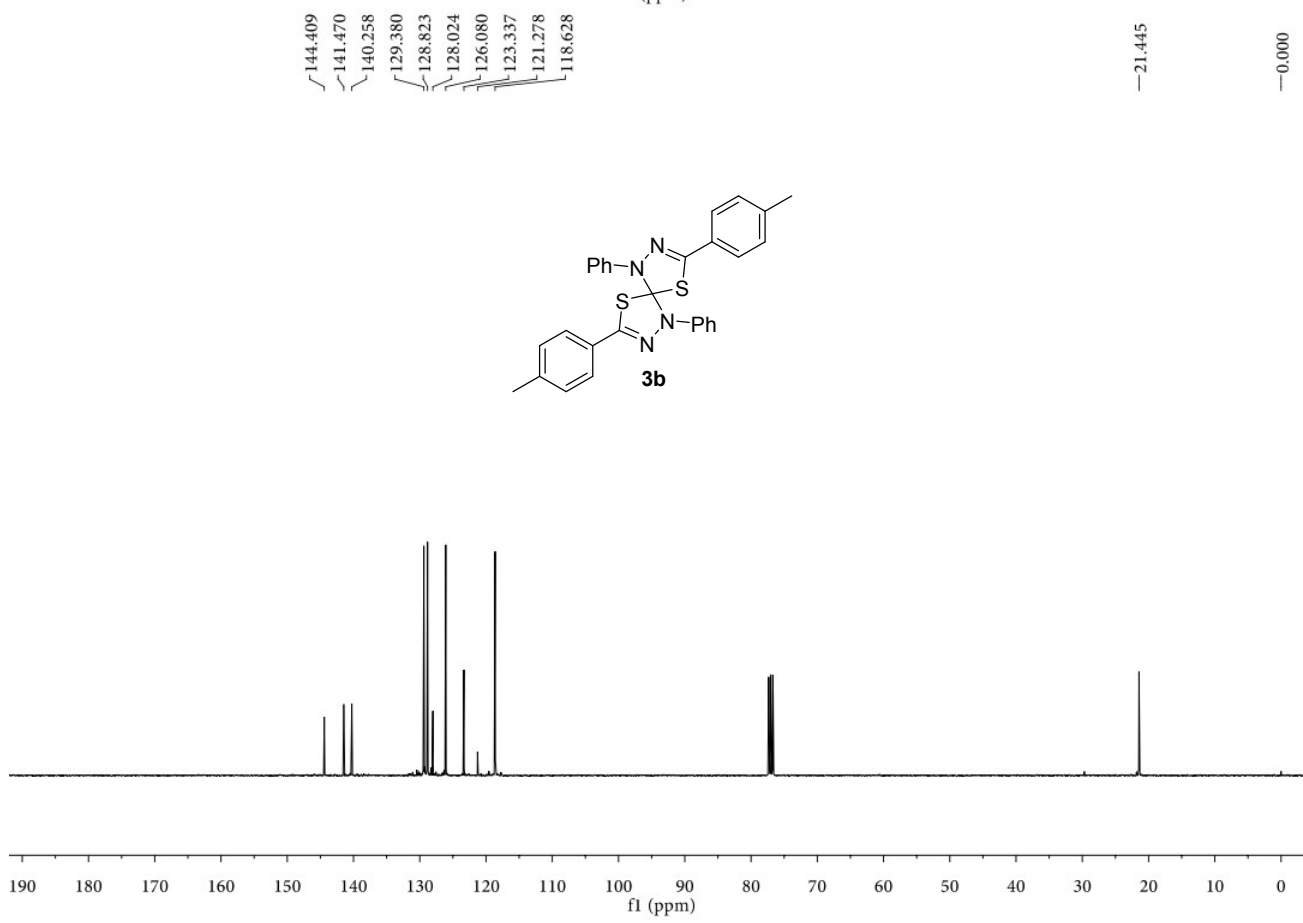
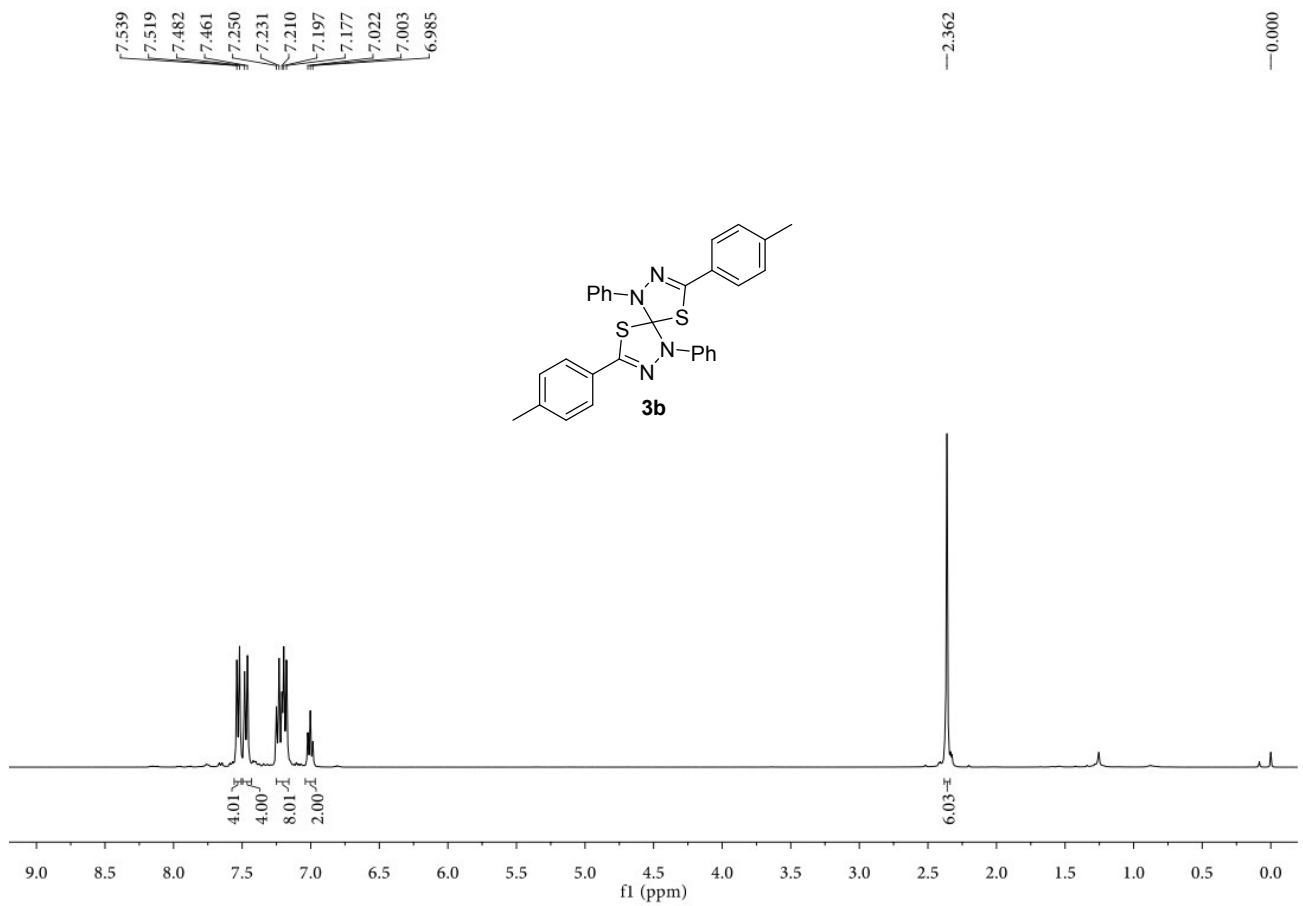
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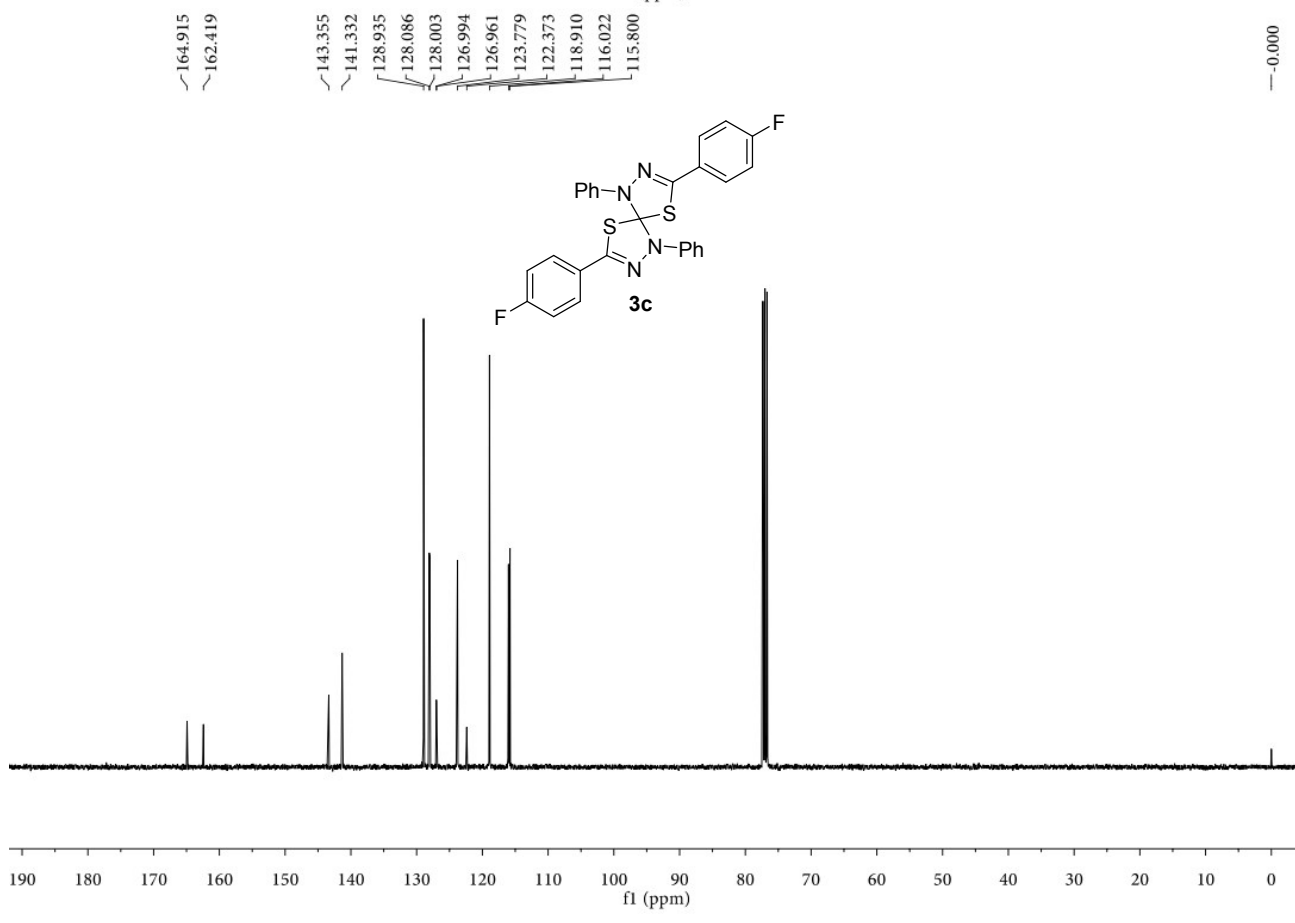
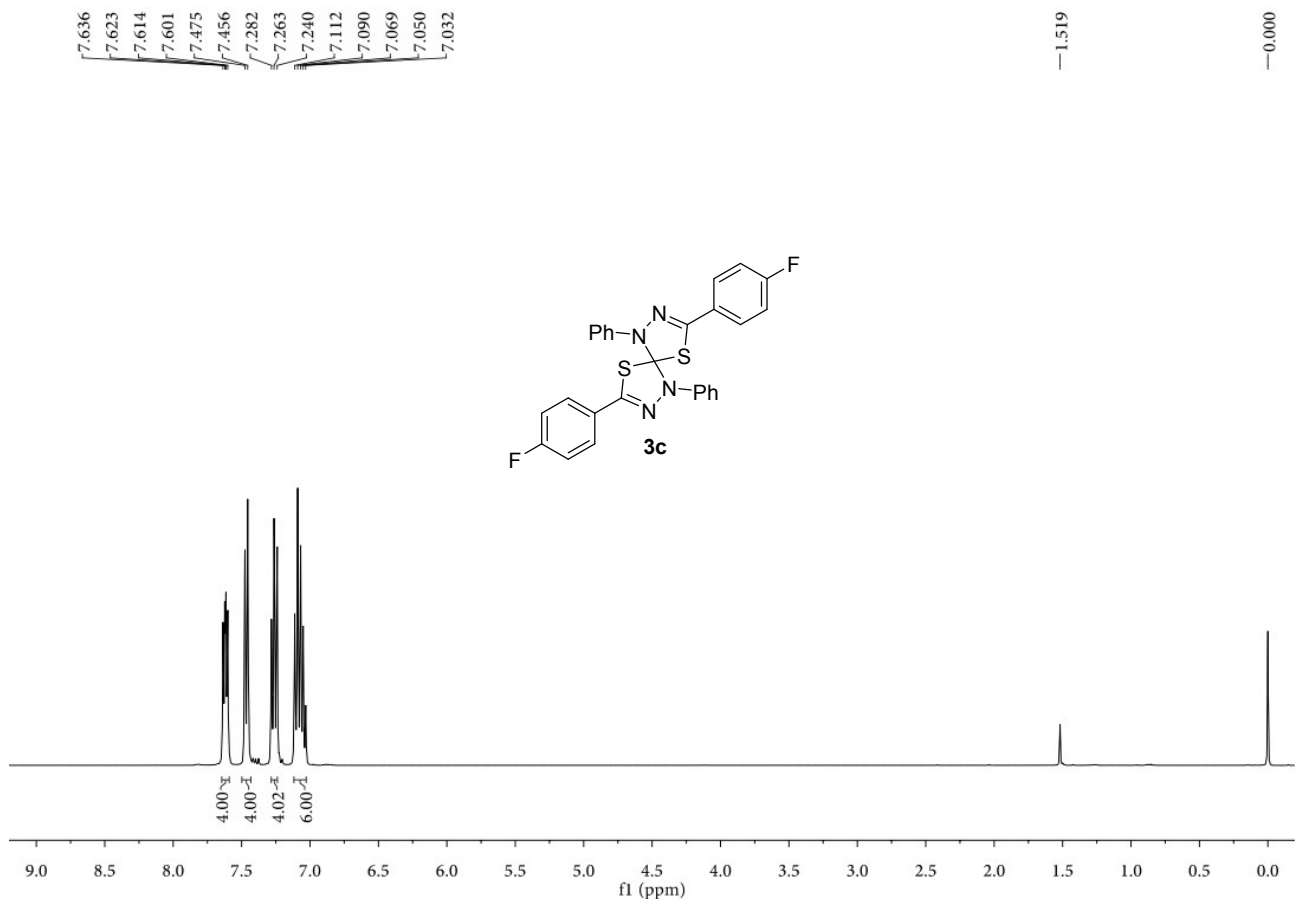
Identification code	3h
Empirical formula	$\text{C}_{27}\text{H}_{18}\text{Br}_2\text{N}_4\text{S}_2$
Formula weight	622.39
Temperature/K	273
Crystal system	triclinic
Space group	P -1 (2)

a/Å	7.8533(10)
b/Å	11.2055(14)
c/Å	14.9614(18)
α /°	109.965(2)
β /°	95.868(2)
γ /°	95.134(2)
Volume/Å ³	1220.1(3)
Z	2
ρ_{calc} /cm ³	1.694
μ /mm ⁻¹	3.519
F(000)	620.0
Crystal size/mm ³	0.26 × 0.25 × 0.24
Radiation	MoK α (λ = 0.71073)
2 Θ range for data collection/°	2.823 to 24.999
Index ranges	-9 ≤ h ≤ 9, -11 ≤ k ≤ 13, -16 ≤ l ≤ 17
Reflections collected	6270
Independent reflections	3282 [R_{int} = 0.0423, R_{sigma} = 0.0222]
Data/restraints/parameters	4262/0/316
Goodness-of-fit on F ²	0.947
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0333, wR_2 = 0.0863
Final R indexes [all data]	R_1 = 0.0518, wR_2 = 0.0924
Largest diff. peak/hole / e Å ⁻³	0.469/ -0.546 / 0.089

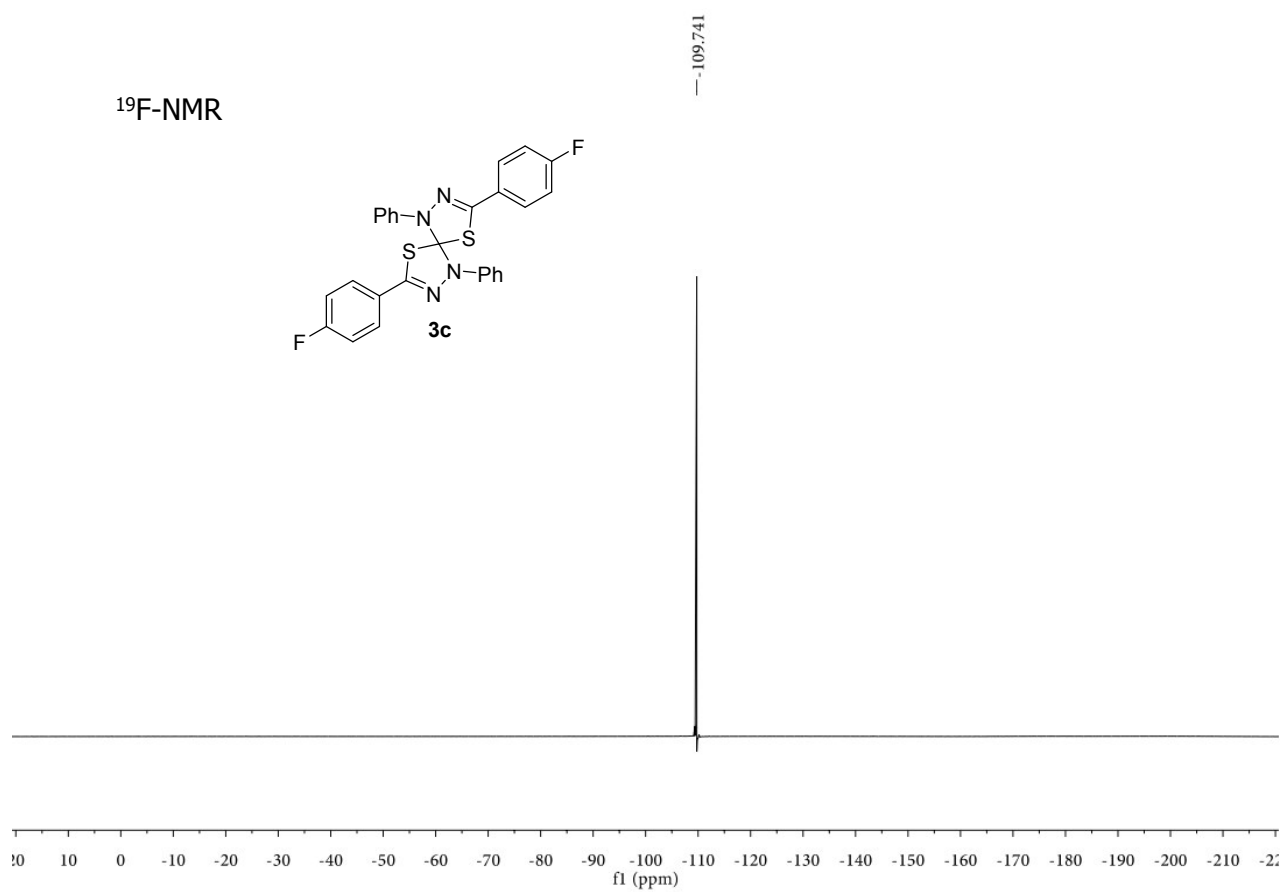
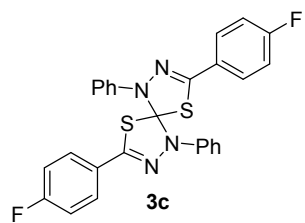
4. Copies of NMR spectra







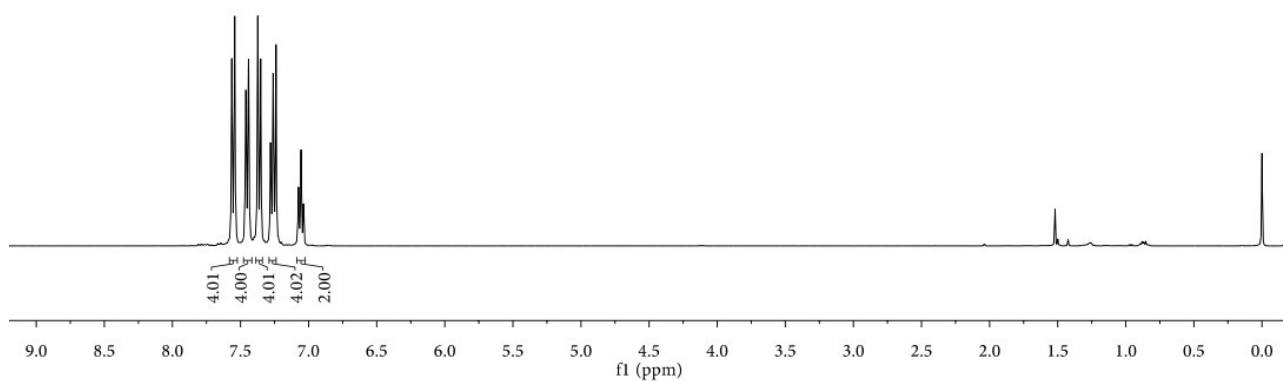
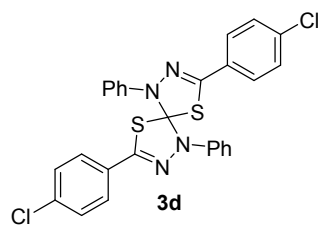
¹⁹F-NMR



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7.352
7.280
7.260
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7.056
7.037

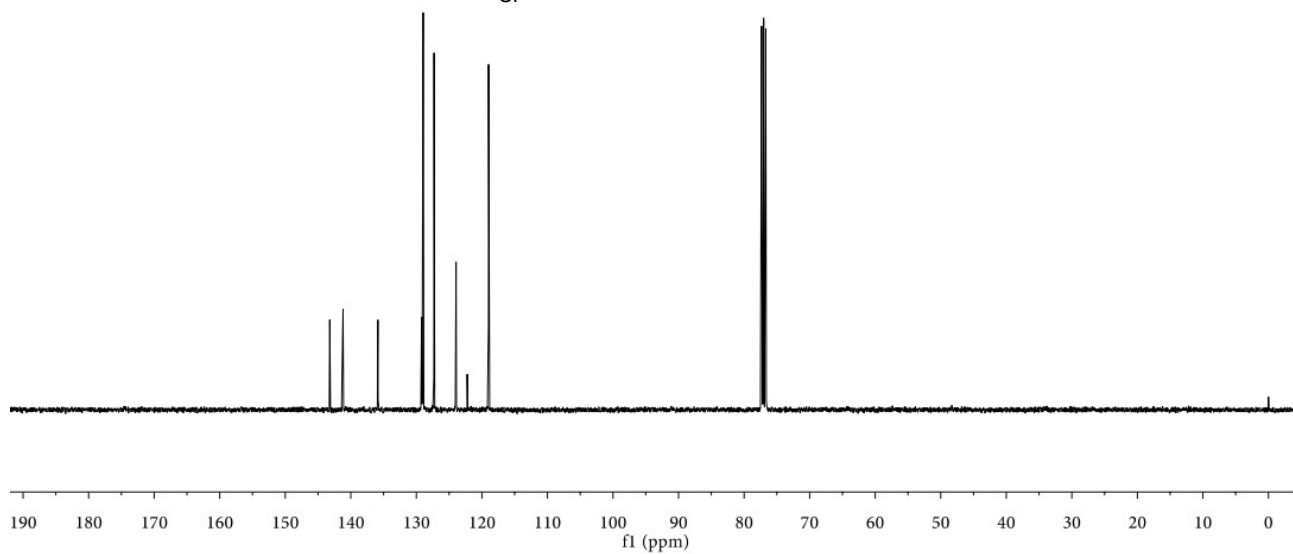
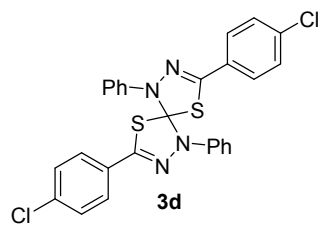
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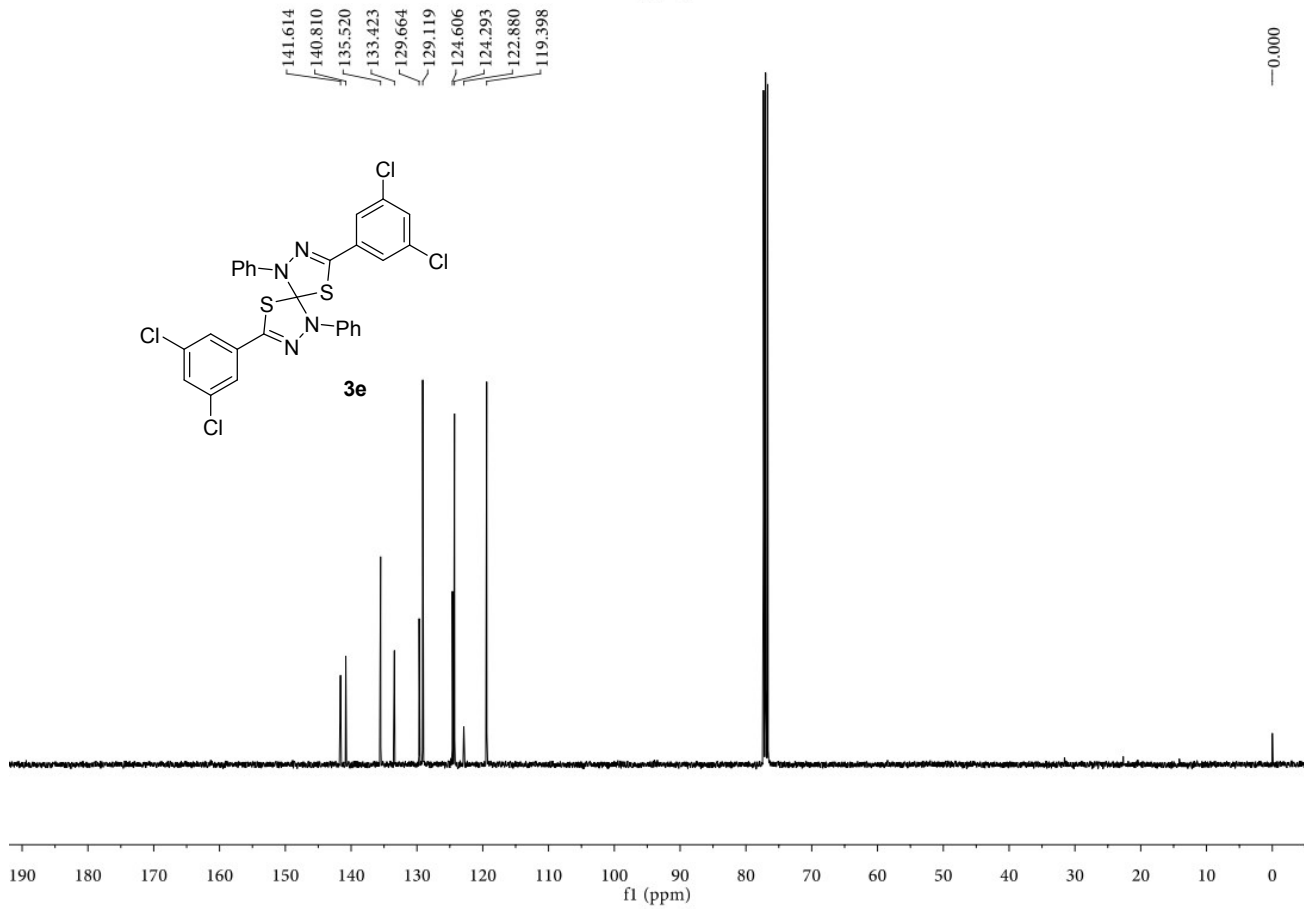
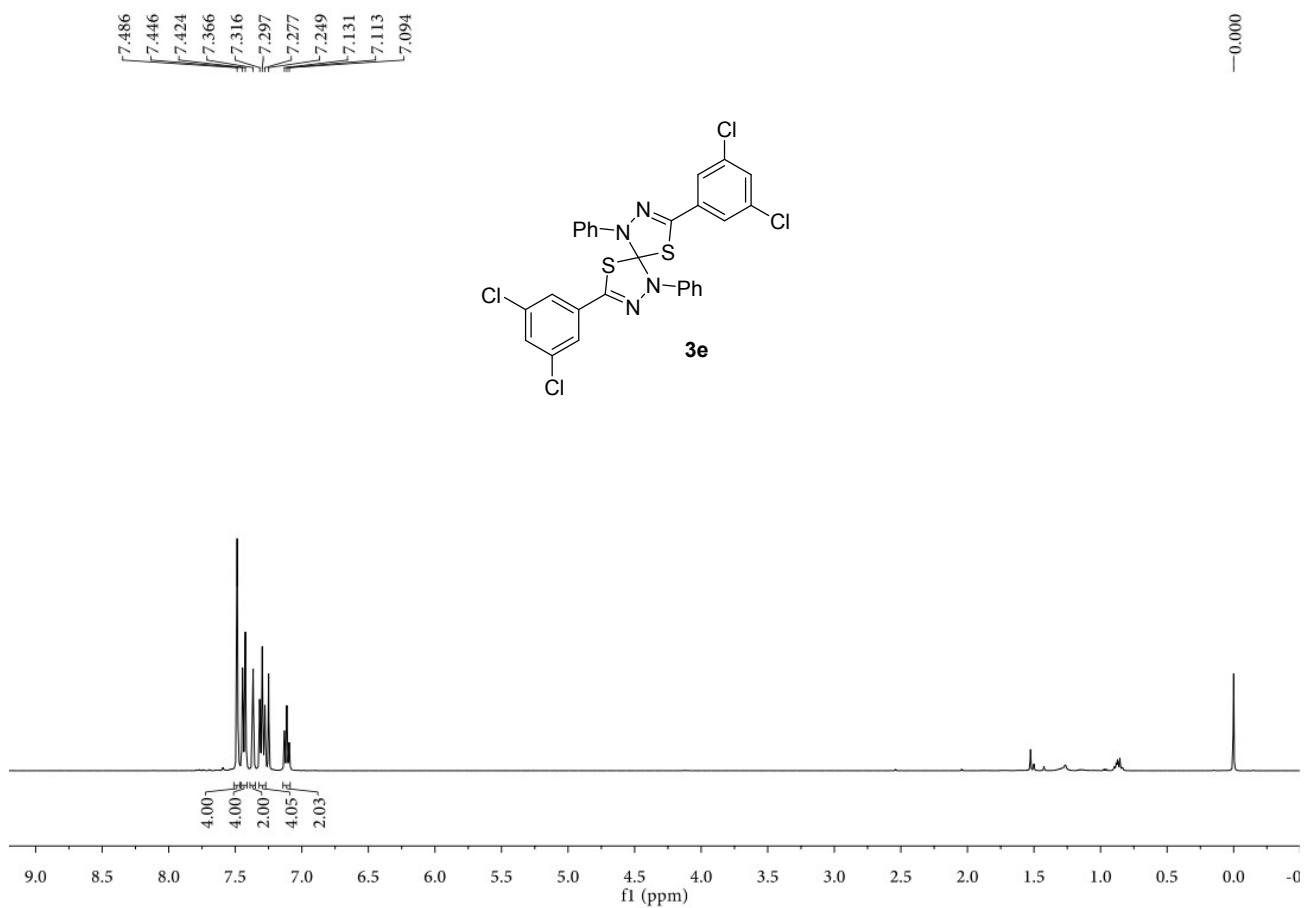
0.000



143.214
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118.983

0.000

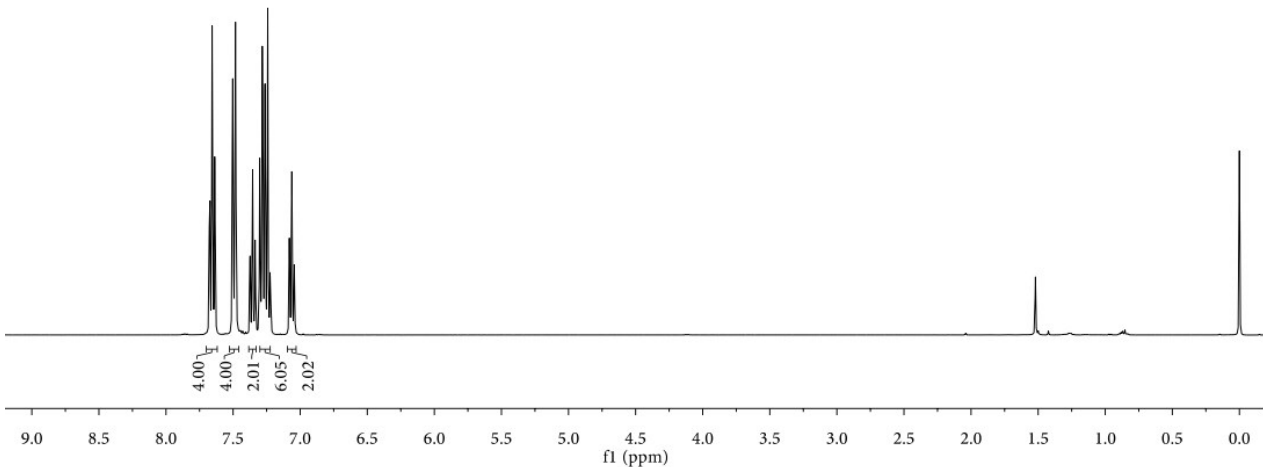
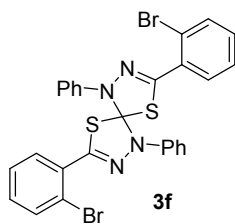




7.676
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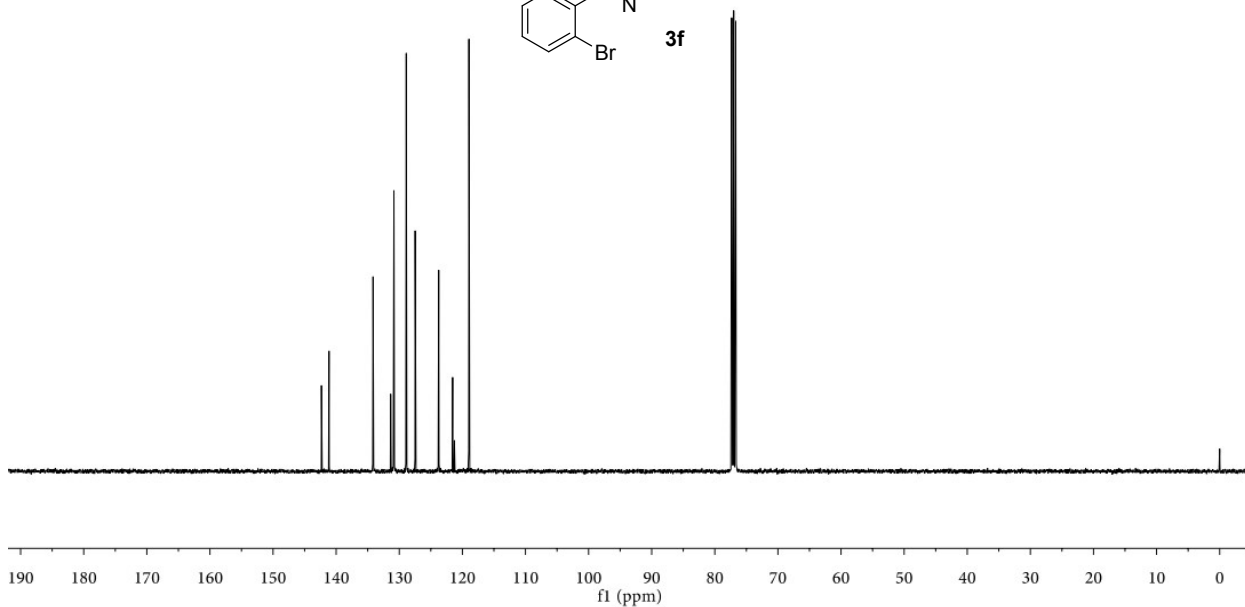
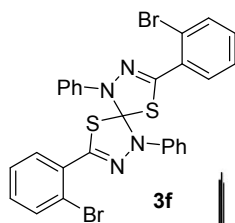
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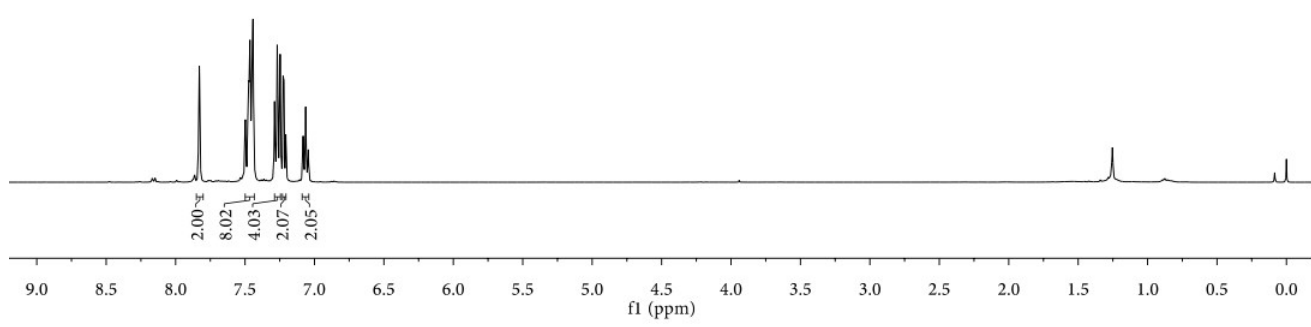
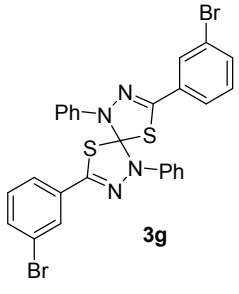


142.329
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131.356
130.845
130.833
128.897
127.481
123.747
121.541
121.265
118.959

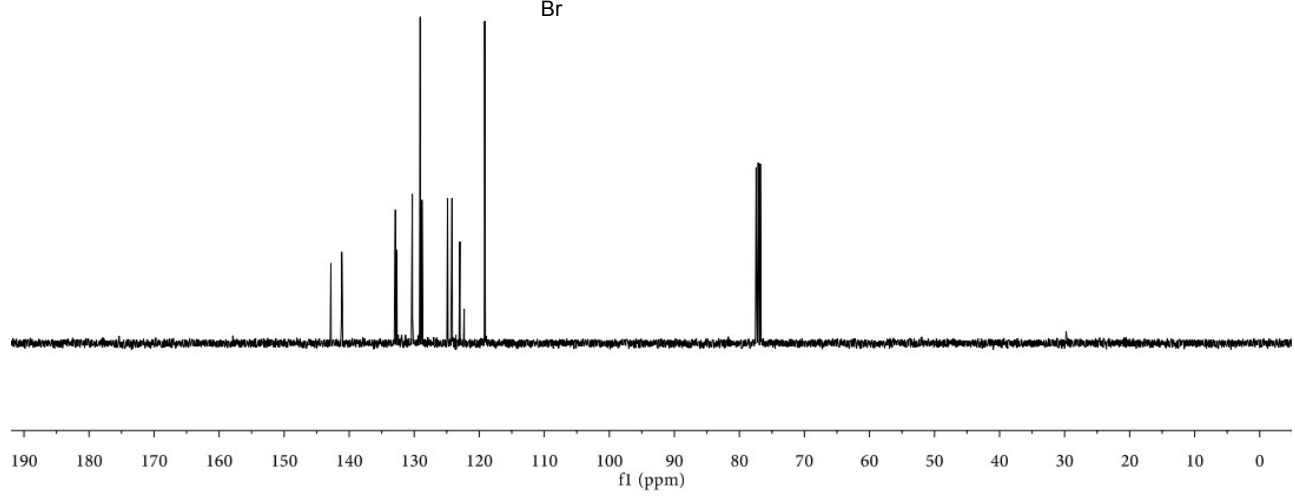
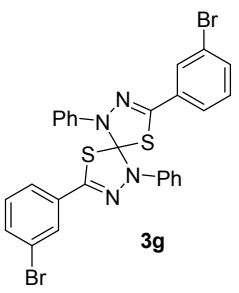
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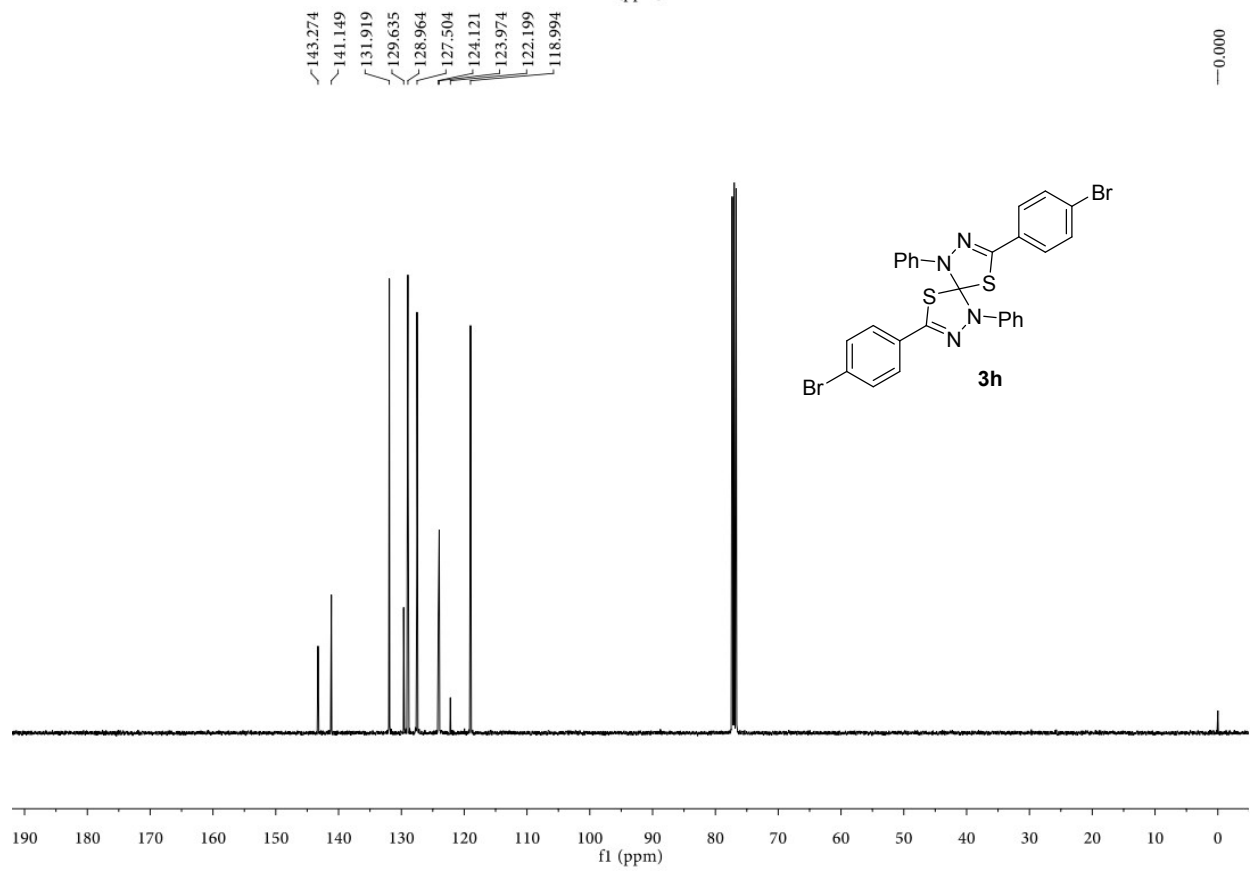
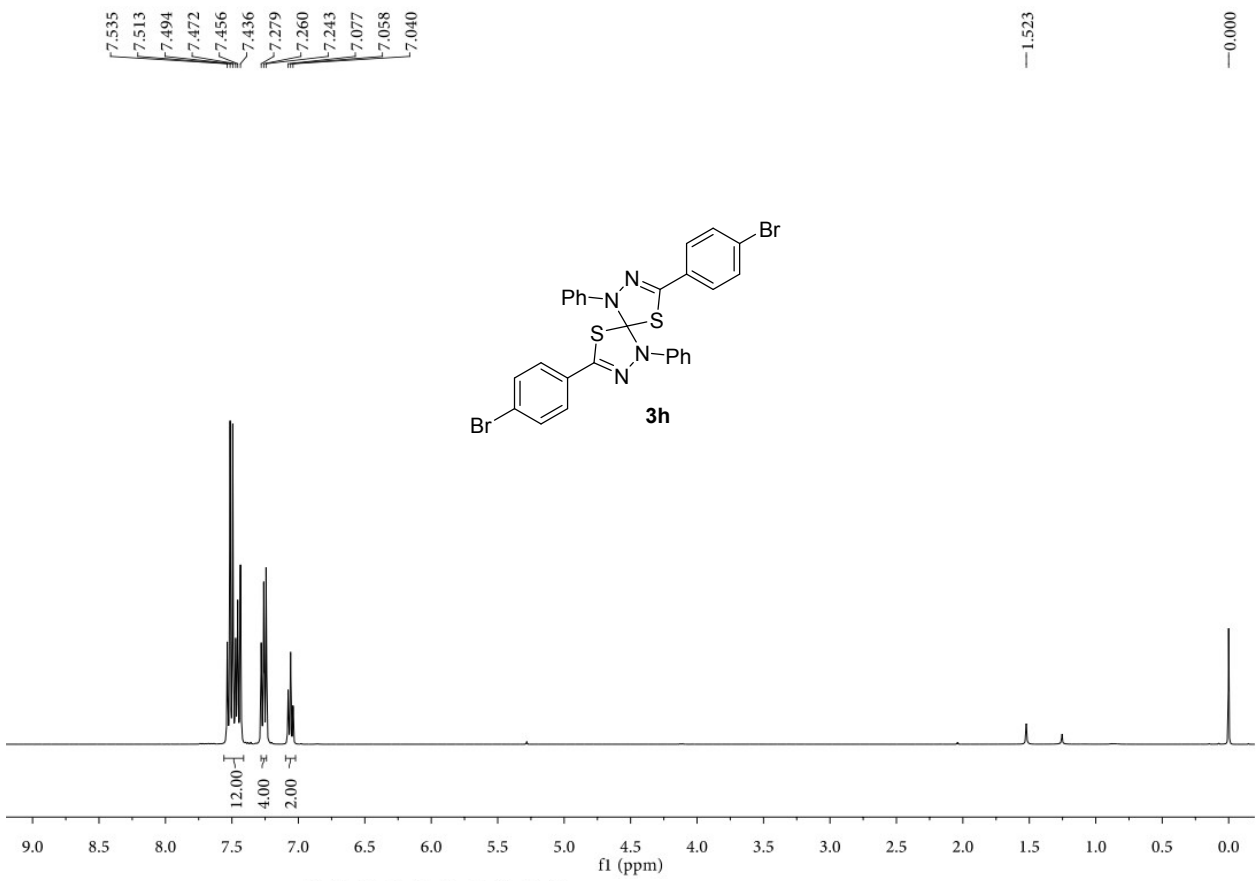


7.829
7.497
7.473
7.464
7.443
7.287
7.268
7.247
7.226
7.220
7.207
7.081
7.063
7.045



142.812
141.142
132.897
132.680
130.287
129.082
128.805
124.873
124.186
122.981
122.316
119.159

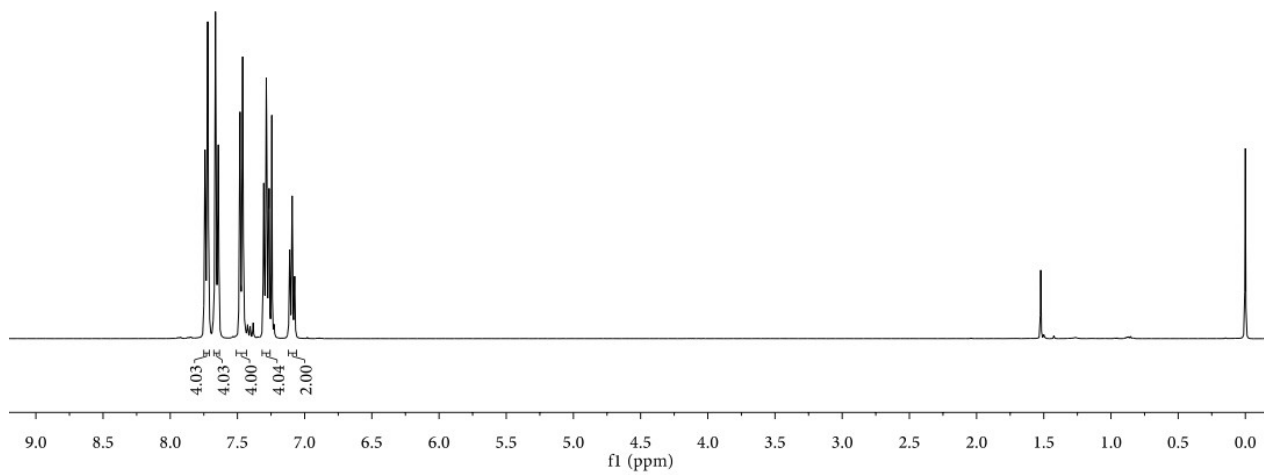
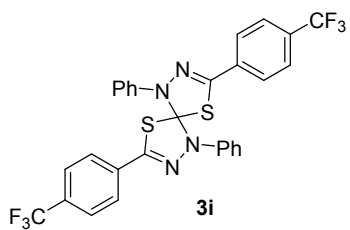




7.741
7.721
7.663
7.642
7.481
7.461
7.304
7.286
7.264
7.244
7.111
7.093
7.074

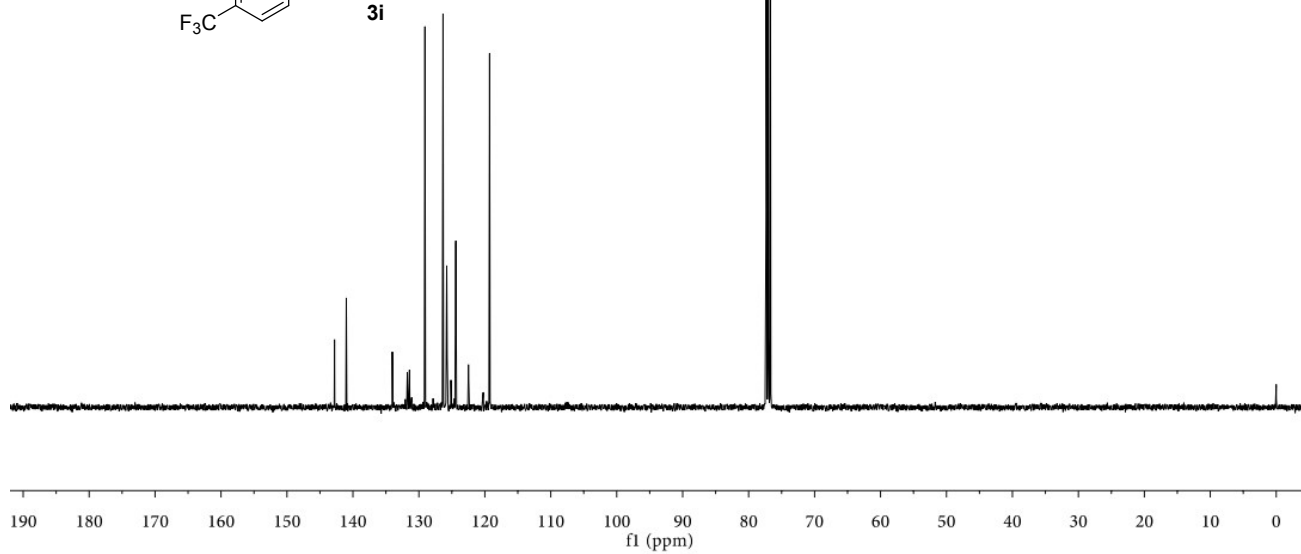
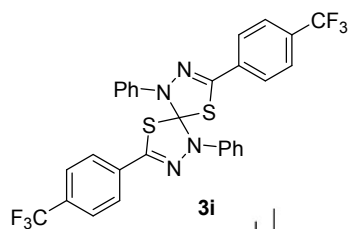
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—0.000



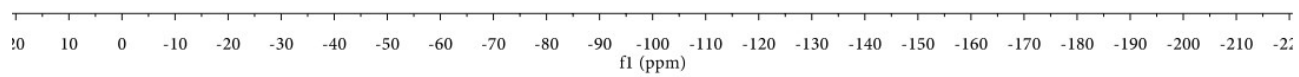
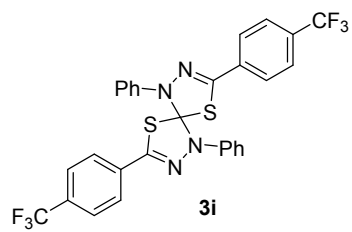
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141.000
134.023
132.076
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131.426
131.101
129.077
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125.742
125.144
124.396
122.479
122.440
120.237
119.282

—0.000



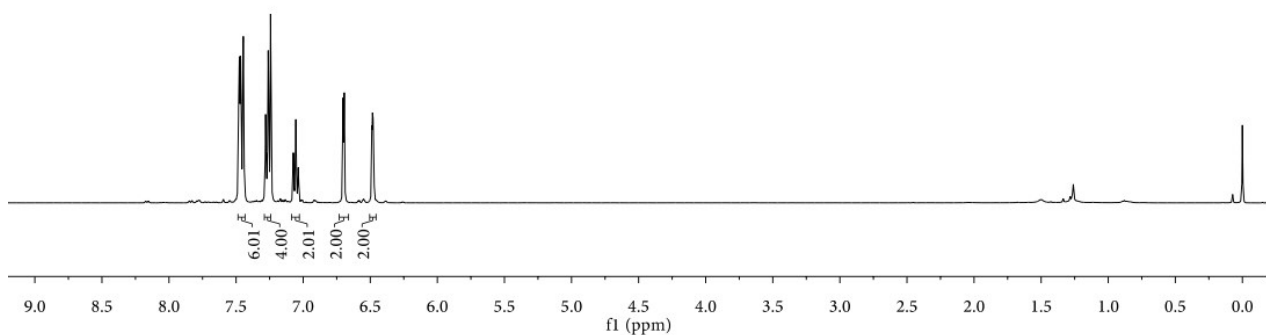
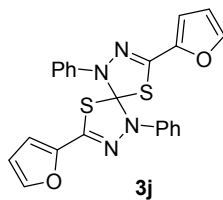
¹⁹F-NMR

-62.762



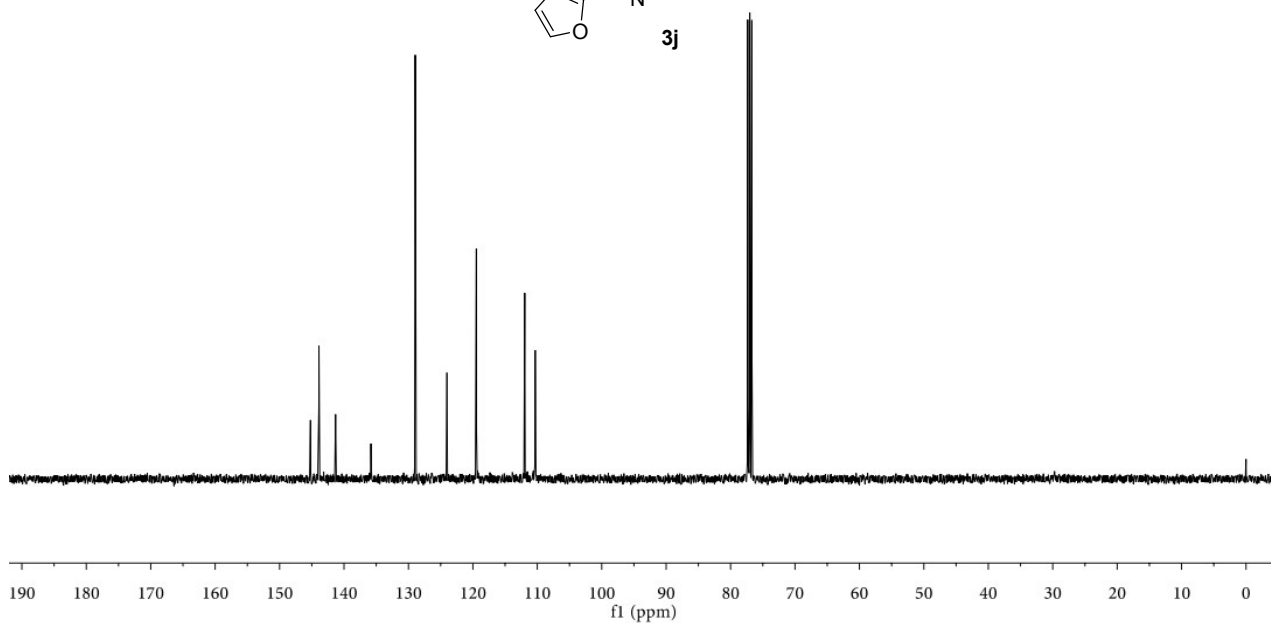
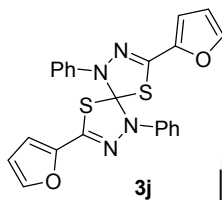
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7.280
7.261
7.243
7.073
7.055
7.036
6.702
6.694
6.487
6.484
6.480
6.475

-0.000



145.207
143.888
141.312
135.822
128.950
124.033
119.457
111.949
110.324

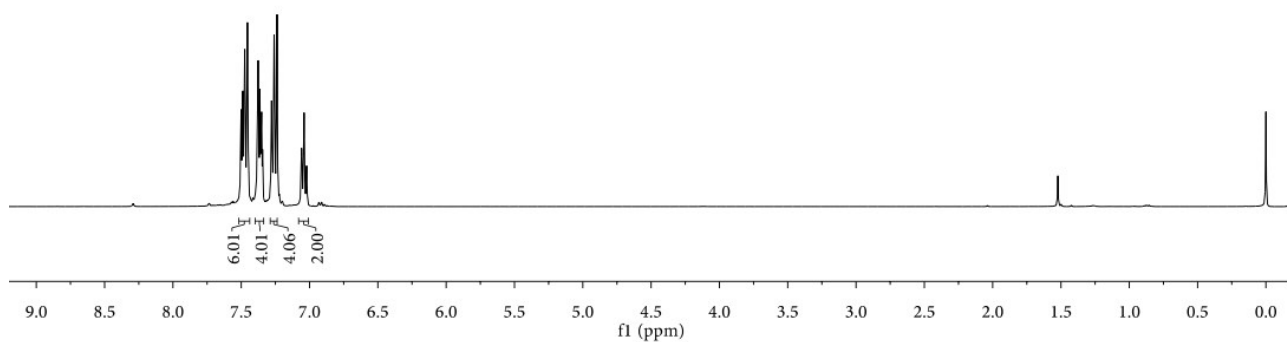
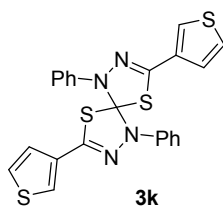
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7.503
7.501
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7.488
7.474
7.454
7.380
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7.373
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7.351
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7.040
7.022

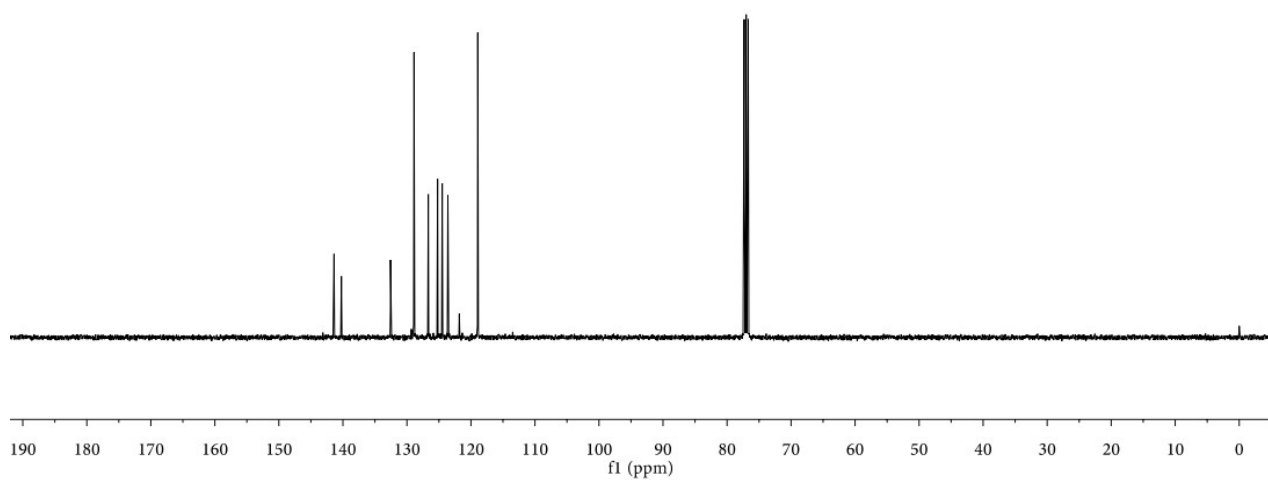
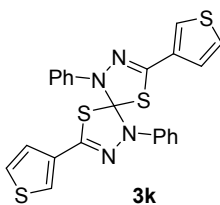
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0.000



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125.208
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121.819
118.932

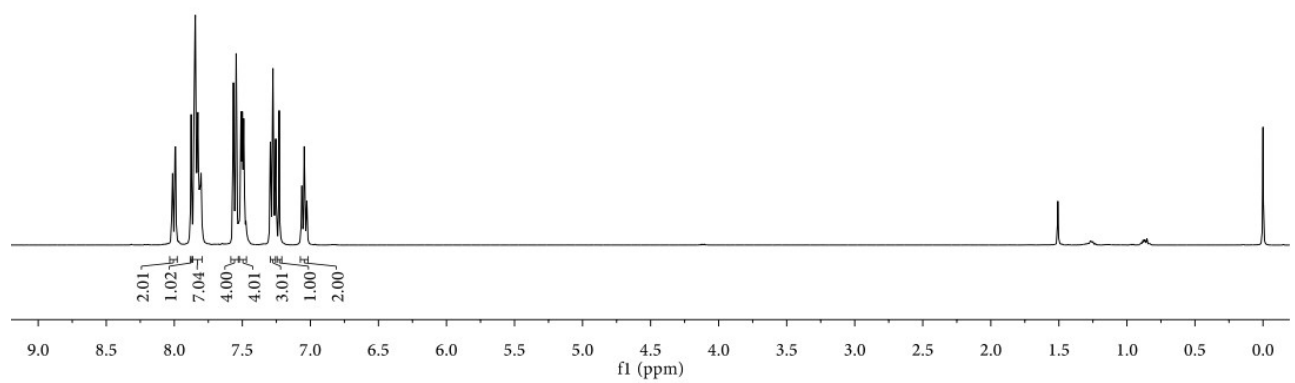
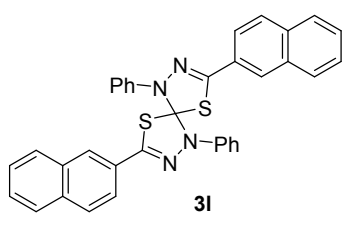
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8.016
8.012
7.994
7.991
7.876
7.845
7.827
7.812
7.803
7.565
7.545
7.525
7.509
7.500
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7.063
7.045
7.026

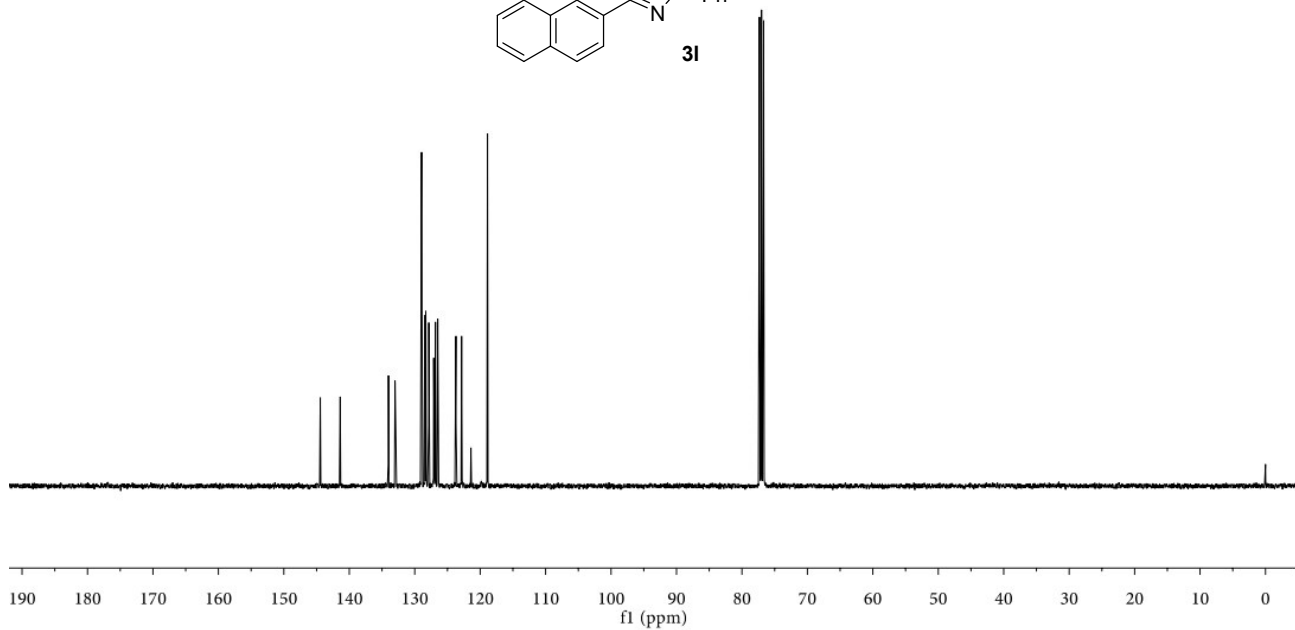
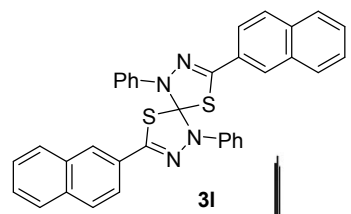
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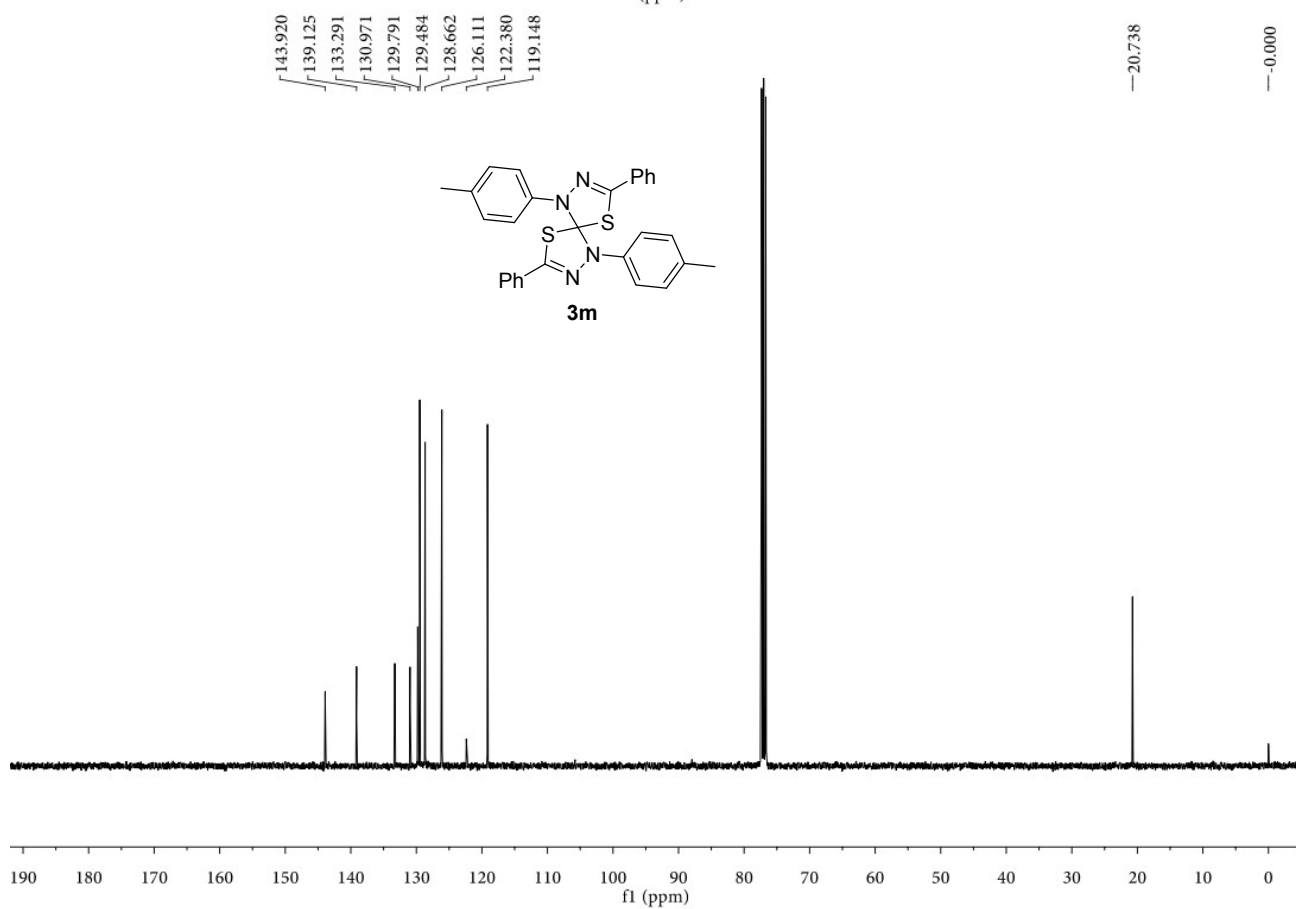
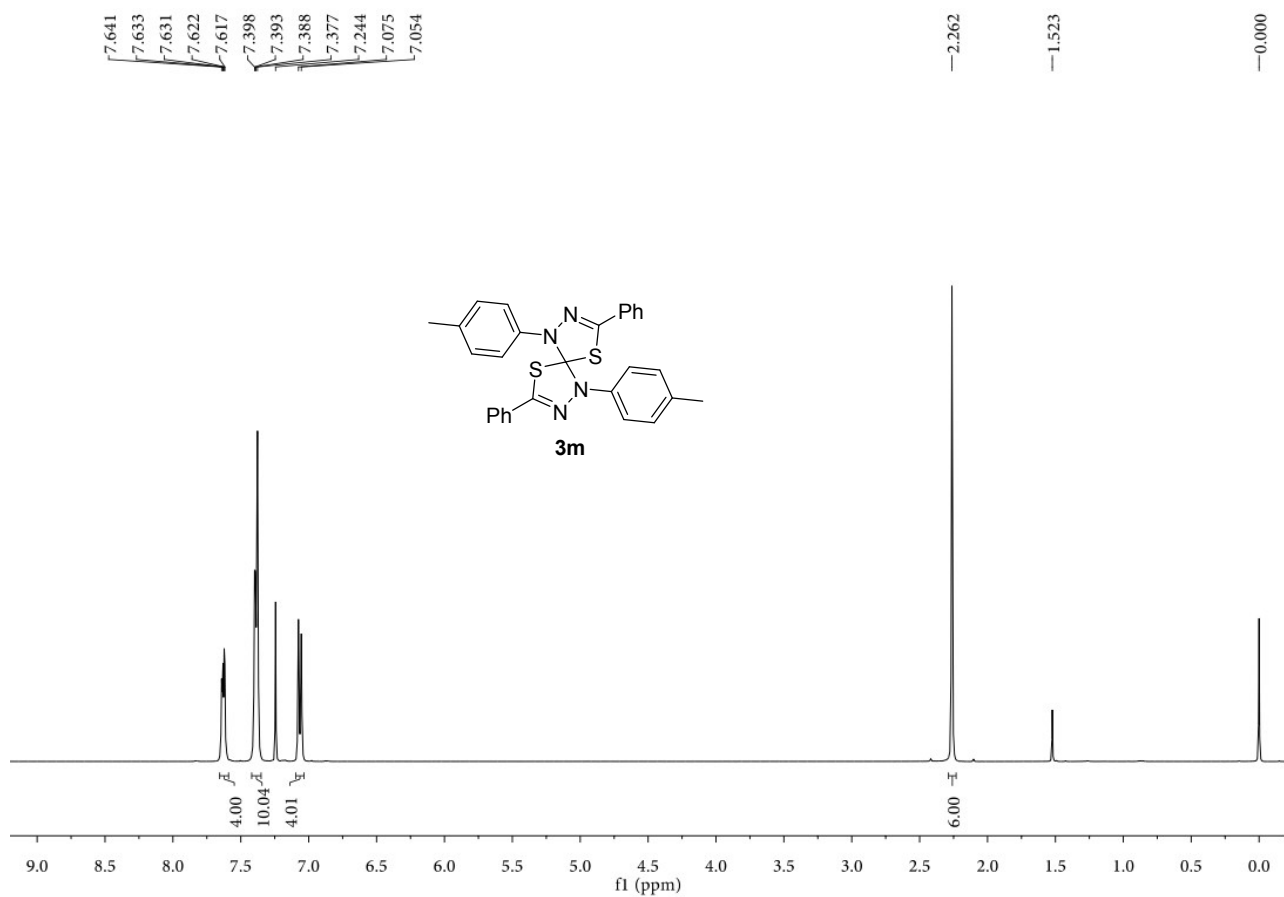
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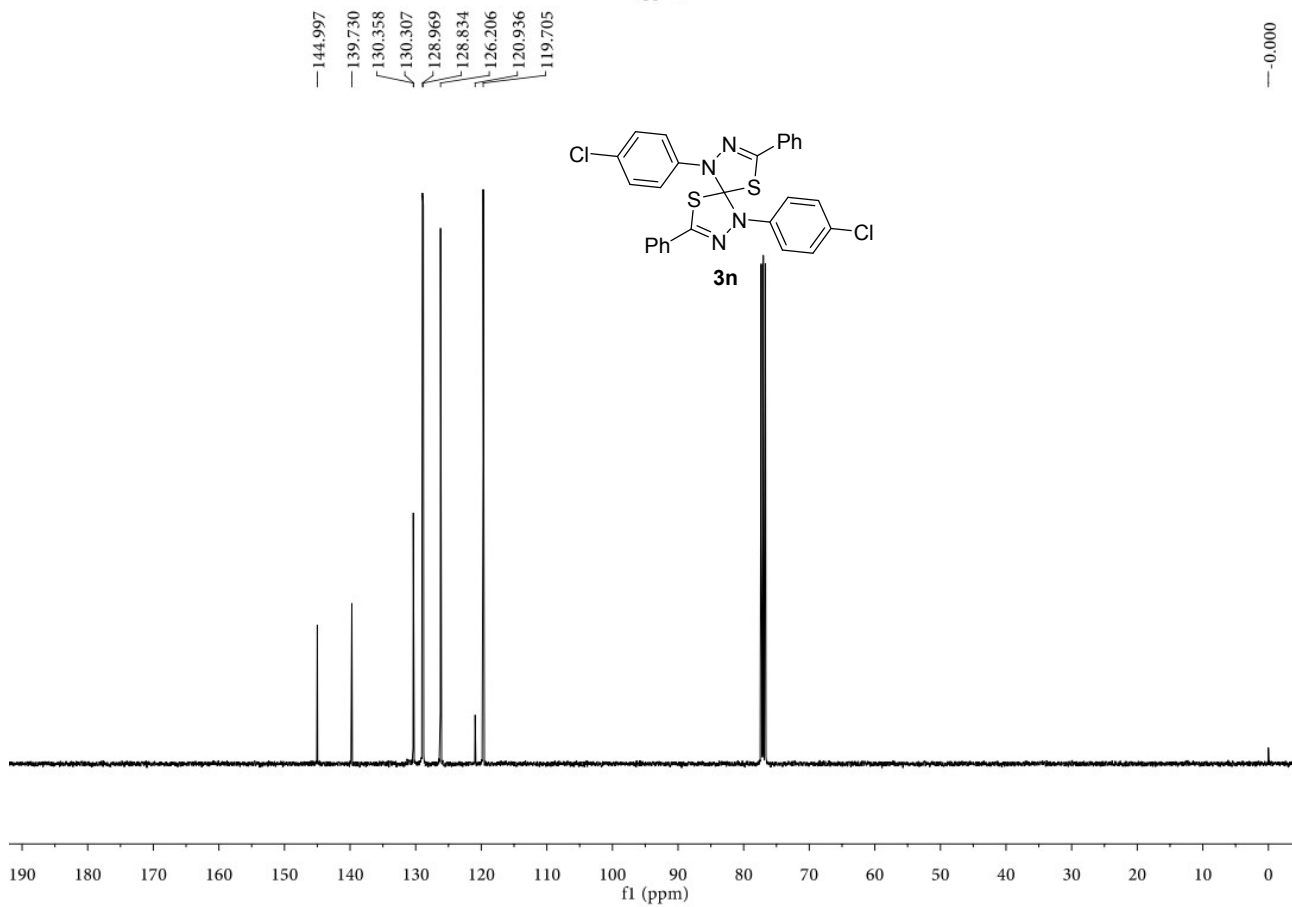
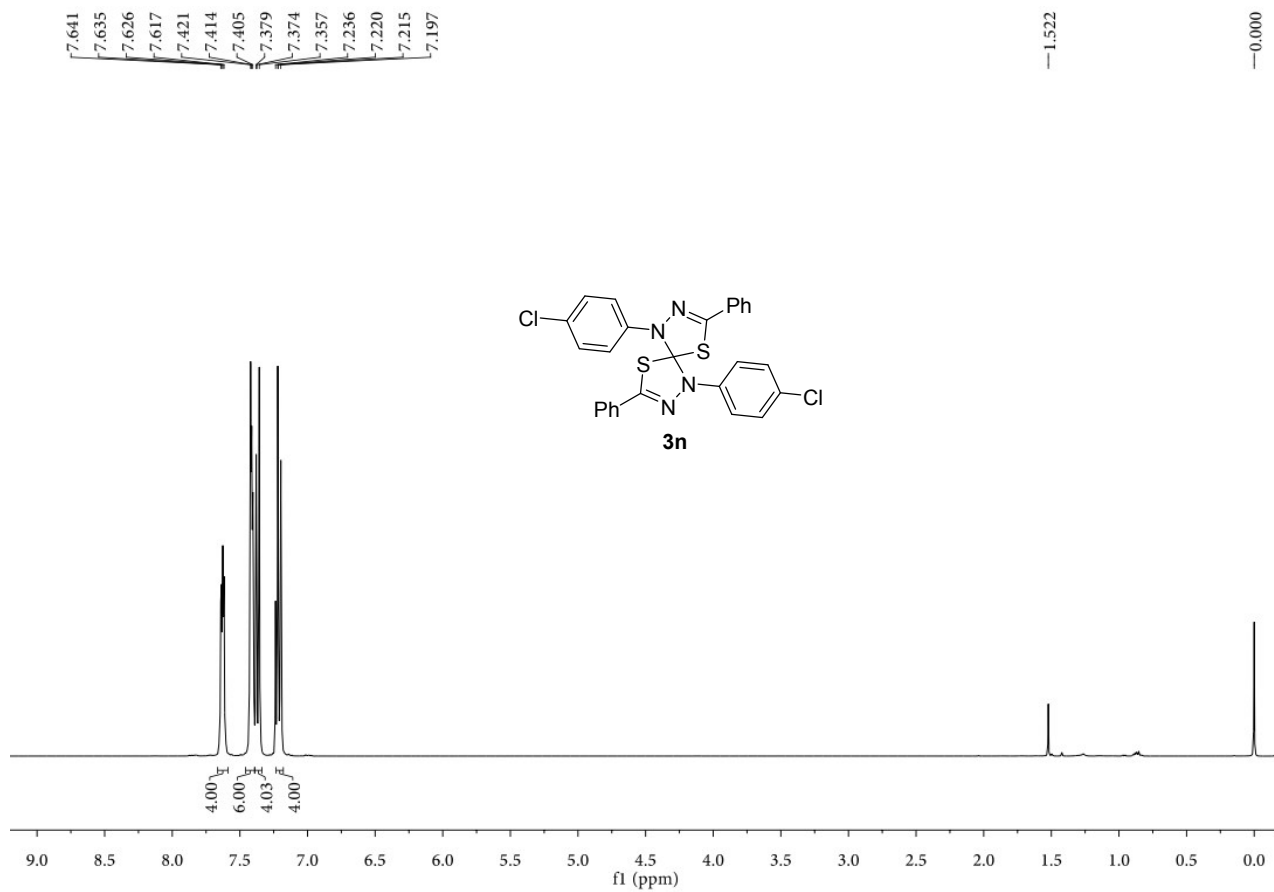


144.431
141.386
134.009
133.013
128.952
128.455
128.310
128.268
127.850
127.094
126.830
126.483
123.701
122.839
121.412
118.879

-0.000







7.384
7.364
7.326
7.308
7.287
7.252
7.195
7.177
7.159

4.379
4.361
4.343
4.326

1.373
1.355
1.338

-0.000

