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Synthesis of bicyclic 1,4-thiazepines as novel anti-*Trypanosoma brucei brucei* agents.

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SUPPORTING INFORMATION

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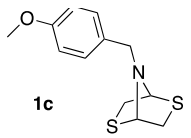
General Methods

All reactions and chromatographic separations were monitored by analytical thin layer chromatography (TLC) 0.25 mm Silica gel plastic sheets (Macherey–Nagel, Polygram® SIL G/UV 254). TLC plates were analyzed under 254 nm UV light, using iodine vapor or ninhydrin spray. Flash chromatography on Silica gel 60 (J. T. Baker, 40 mm average particle diameter) was used to purify the crude reaction mixtures. NMR spectra were recorded at 400 MHz and 100 MHz (^{1}H NMR, ^{13}C NMR) using a Bruker AVANCE DPX-400 spectrometer at 21°C. Chemical shifts (δ) are reported as follows: chemical shift (multiplicity, coupling constant, integration). Mass spectrometry experiments were measured on a Shimadzu GC 2010 Plus Mass Spectrometer using EI ionization. Melting points were determined using a Laboratory Devices Gallenkamp apparatus. All solvents were purified according to literature procedures. All yields refer to isolated compounds after the final purification process, unless otherwise stated. Microwave assisted synthesis was performed in a CEM Discover reactor.

Synthetic procedures

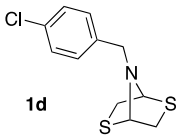
Synthesis of 1b is representative for the preparation of other 2,5-dithio-7azabicyclo[2.2.1]heptane derivatives. To a stirred solution of 2,5-dihydroxy-1,4-dithiane (1.7 g, 11.2 mmol) in EtOH, benzylamine (1.0 g, 9.2 mmol) and *p*-TsOH (10 mg) were added. The reaction mixture was kept under reflux for 2 h and stirred overnight at r.t. The solvent was then removed at reduced pressure, the residue was poured into water (30 mL) and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (EtOAc/Hexanes 1:8) to give bicycle **1b** as a white solid (1.5 g; 76% yield).

Compounds, **1b**, **1e** and **1f** have been reported previously.[1]



1c

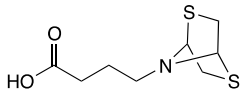
7-(4-methoxybenzyl)-2,5-dithia-7-azabicyclo[2.2.1]heptane (**1c**). The title compound was obtained starting from 4-methoxybenzylamine (0.23 g, 1.64 mmol), following the general procedure for dithiane **1b**. The crude product was purified by chromatography on SiO_2 (EtOAc/hexanes = 1:6) to afford **1b** (0.27 g, 64%) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (d, *J* = 9.4 Hz, 2H), 3.35 (dd, *J* = 9.4, 3.0 Hz, 2H), 3.51 (s, 2H), 3.80 (s, 3H), 4.76 (d, *J* = 3.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.30 ppm (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 52.2, 55.3, 69.5, 76.8, 77.2, 77.5, 113.9, 129.5, 130.0, 159.1 ppm. MS (EI): *m/z* 253 (M^+, 4%), 206 (23), 134 (6), 121 (100)



1d

7-(4-chlorobenzyl)-2,5-dithia-7-azabicyclo[2.2.1]heptane (**1d)**. The title compound was obtained starting from 4-chlorobenzylamine (0.5 g, 3.53 mmol) following the general procedure for dithiane **1b**. The crude was purified by chromatography on SiO_2 (EtOAc/hexanes = 1:6) to afford **1c** (0.75 g, 85%) as a pale yellow solid; mp = 68.0–69.5°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (d, *J* = 9.5 Hz, 2H), 3.36 (dd, *J* = 9.6, 3.0 Hz, 2H), 3.56 (s, 2H), 4.76 (d, *J* = 3.1 Hz, 2H), 7.32 ppm (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 52.2, 69.6, 128.8, 130.1, 133.5, 135.9 ppm. MS (EI): *m*/*z* 257 (M^+, 1%), 213 (3), 210 (50), 165 (6), 125 (100).

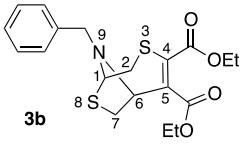
1g



4-(2,5-dithia-7-azabicyclo[2.2.1]heptan-7-yl)butanoic acid (**1g**). The title compound was obtained starting from 4-aminobutanoic acid (500 mg, 4.85 mmol), following the general procedure for dithiane **1b.** The crude was purified by chromatography on SiO_2 (EtOAc/hexanes = 1:6) to afford **1g** (100 mg, 13%) as an oil. . ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (p, *J* = 7.1 Hz, 2H), 2.46 (m, 3H), 2.57 (dt, *J* = 13.0, 6.7 Hz, 1H), 3.21 (d, *J* = 9.4 Hz, 2H), 3.32 (dd, *J* = 9.5, 3.2 Hz, 2H), 4.84 (d, *J* = 3.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ, 23.6, 32.0, 43.8, 47.8, 69.8, 178.8. MS (EI): *m*/*z* 219 (M^+, 1%), 172 (100), 101 (20), 86 (85).

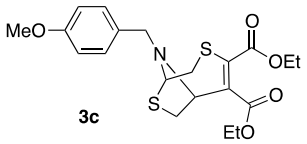
Compounds **2b**, **2c**, **2d,** and **2e** have been described previously.[2]

Synthesis of 3b is representative for the preparation of other thiazolidinyl-thiazepine derivatives. A solution of Michael acceptor diethylacetylenedicarboxylate **2b** (91.8 mg, 0.54 mmol) in MeCN (1 mL) was treated with azadithiane **1b** (100 mg, 0.45 mmol) and DABCO (0.05 eq). The reaction mixture was stirred at 78 °C for 30 min under microwave irradiation (50 W). The solvent was removed under reduced pressure. The residue was poured into water (15 mL) and extracted with AcOEt (3×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude was finally purified by flash chromatography on SiO_2 (eluting with 100% to 80% hexanes/EtOAc) to yield **3b** as oil (67%).



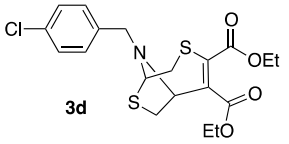
3b

Diethyl-9-benzyl-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4,5-dicarboxylate (**3b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 2.98 (dd, *J* = 14.1, 6.1 Hz, 1H), 3.31 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.37 (dd, *J* = 14.1, 3.3 Hz, 1H), 3.57 (dd, *J* = 11.1, 9.3 Hz, 1H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 4.10 (m, 2H), 4.26 (m, 2H), 4.76 (ddd, *J* = 9.3, 3.4, 0.9 Hz, 1H), 4.84 (ddd, *J* = 6.1, 3.3, 0.9 Hz, 1H), 7.32 (m, 3H), 7.40 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 38.7, 45.0, 60.9, 61.8, 62.2, 68.8, 75.0, 127.6, 128.6, 129.1, 138.2, 138.4, 142.9, 165.5, 166.6 ppm. MS (EI): *m*/*z* 393 (M^+, 3%), 360 (8), 256 (9), 138 (31), 91 (100).



3c

Diethyl-9-(4-methoxybenzyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4,5-dicarboxylate (**3c**). The title compound was obtained starting from dithiane **1c** (70 mg, 0.28 mmol) and diethylacetylenedicarboxylate **2b** (56.2 mg, 0.33 mmol), following the general procedure for thiazolinyl-thiazepine **3b**. Compound **3c** was isolated as a colorless oil (85 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 2H), 2.96 (dd, *J* = 14.1, 6.2 Hz, 1H), 3.30 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.33 (dd, *J* = 14.1, 3.3 Hz, 1H), 3.55 (dd, *J* = 11.0, 9.4 Hz, 1H), 3.67 (d, *J* = 12.9 Hz, 1H), 3.76 (d, *J* = 12.9 Hz, 1H), 3.79 (s, 3H), 4.11 (dd, *J* = 7.1, 6.3 Hz, 1H), 4.24 (qd, *J* = 7.1, 1.9 Hz, 1H), 4.74 (dd, *J* = 9.2, 3.3 Hz, 1H), 4.82 (m, 1H), 6.85 (m, 2H), 7.30 ppm (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 38.7, 45.1, 55.4, 60.3, 61.8, 62.3, 68.7, 74.7, 77.2, 114.0, 130.4, 138.5, 142.9, 159.2, 165.6, 166.6 ppm. MS (EI): *m*/*z* 423 (M^+, 1%), 303 (26), 293 (36), 160 (27), 121 (100), 110 (26).



3d

Diethyl-9-(4-chlorobenzyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4,5-dicarboxylate (**3d**). The title compound was obtained starting from dithiane **1d** (55 mg, 0.21 mmol) and diethylacetylenedicarboxylate **2b** (43.6 mg, 0.26 mmol), following the general procedure for thiazolinyl-thiazepine **3b**. Compound **3d** was isolated as a colorless oil (129 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 3.00 (dd, *J* = 14.2, 6.2 Hz, 1H), 3.31 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.36 (dd, *J* = 14.2, 3.5 Hz, 1H), 3.56 (dd, *J* = 11.2, 9.5 Hz, 1H), 3.71 (d, *J* = 13.4 Hz, 1H), 3.83 (d, *J* = 13.4 Hz, 1H), 4.12 (m, 2H), 4.26 (m, 2H), 4.72 (ddd, *J* = 9.5, 3.5, 0.9 Hz, 1H), 4.79 (ddd, *J* = 6.2, 3.5, 0.9 Hz, 1H), 7.35 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 13.9, 38.5, 45.0, 60.2, 61.8, 62.2, 68.6, 74.8,

77.0, 128.6, 130.3, 133.3, 136.7, 137.9, 143.1, 165.3, 166.5 ppm. MS (EI): m/z 427 (M^+, 1%), 346 (6), 228 (14), 137 (26), 91 (100), 65 (7).

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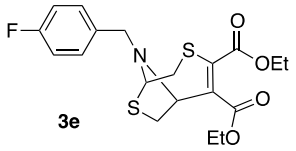
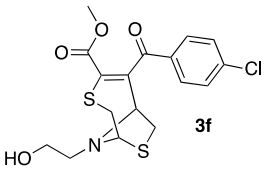


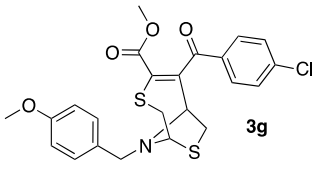
3e

Diethyl-9-(4-fluorobenzyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4,5-dicarboxylate (**3e**). The title compound was obtained starting from dithiane **1e** (80 mg, 0.33 mmol) and diethylacetylenedicarboxylate **2b** (68 mg, 0.40 mmol), following the general procedure for thiazolinyl-thiazepine **3b**. Compound **3e** was isolated as a colorless oil (83 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 2.99 (dd, *J* = 14.2, 6.2 Hz, 1H), 3.31 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.36 (dd, *J* = 14.2, 3.4 Hz, 1H), 3.56 (dd, *J* = 11.1, 9.3 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.82 (d, *J* = 13.2 Hz, 1H), 4.12 (m, 2H), 4.26 (m, 2H), 4.72 (ddd, *J* = 9.3, 3.5, 0.8 Hz, 1H), 4.84 (ddd, *J* = 6.2, 3.4, 0.8 Hz, 1H), 7.01 (m, 2H), 7.37 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 38.5, 45.0, 60.0, 61.8, 62.2, 68.5, 74.7, 115.2, 115.4, 130.5, 130.6, 133.8, 133.9, 138.0, 142.9, 161.0, 163.4, 165.3, 166.4 ppm. MS (EI): m/z 411 (M^+, 4%), 256 (17), 227 (16), 155 (22), 109 (100).



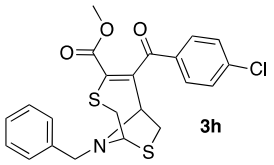
3f

Methyl-5-(4-chlorobenzoyl)-9-(2-hydroxyethyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4-carboxylate (**3f**). The title compound was obtained starting from dithiane **1f** (1.26 g, 9.2 mmol) and Michael acceptor **2c** (2.16 g, 11.4 mmol), following the general procedure for thiazolinyl-thiazepine **3b**. Compound **3f** was isolated as a colorless oil (41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (ddd, *J* = 13.3, 5.8, 3.6 Hz, 2H), 2.85 (ddd, *J* = 13.3, 7.1, 3.9 Hz, 1H), 3.07 (dd, *J* = 14.4, 6.3 Hz, 1H), 3.48 (m, 7H), 3.62 (bs, 1H), 4.24 (ddd, *J* = 9.1, 3.6, 0.7 Hz, 1H), 4.95 (ddd, *J* = 6.3, 3.5, 0.7 Hz, 1H), 7.46 (m, 2H), 7.83 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9, 44.7, 53.1, 59.8, 60.7, 70.1, 76.8, 77.2, 77.5, 129.5, 130.2, 132.8, 134.0, 140.3, 153.4, 165.0, 195.2 ppm. MS (EI): *m/z* 399 (M^+, 8%), 366 (34), 352 (67), 260 (100), 139 (82), 111 (61)..



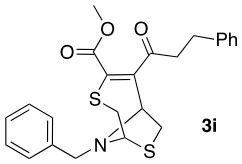
3g

Methyl-5-(4-chlorobenzoyl)-9-(4-methoxybenzyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4-carboxylate (**3g**). The title compound was obtained starting from dithiane **1c** (1.26 g, 74.1 mmol) and **2c** (1.7 g, 88.9 mmol), following the general procedure for thiazolinyl-thiazepine **3b**. Compound **3g** was isolated as a pale yellow solid (83%); mp = 134–135 °C. ^{1}H NMR ($CDCl_3$) δ 3.00 (dd, *J* = 14.3, 6.1 Hz, 1H), 3.41 (dd, *J* = 14.3, 3.0 Hz, 1H), 3.46 (d, *J* = 12.7 Hz, 1H), 3.53 (m, 5H), 3.74 (d, *J* = 12.7 Hz, 1H), 3.77 (s, 3H), 4.16 (ddd, *J* = 8.2, 4.2, 0.7 Hz, 1H), 4.95 (ddd, *J* = 6.1, 3.0, 0.7 Hz, 1H), 6.73 (m, 2H), 7.16 (m, 2H), 7.38 (m, 2H), 7.75 ppm (m, 2H). ^{13}C NMR ($CDCl_3$) δ 38.0, 44.5, 53.1, 55.3, 60.4, 69.4, 75.7, 77.2, 113.9, 129.0, 129.6, 130.4, 130.5, 132.3, 134.0, 139.8, 154.5, 159.2, 165.1, 195.3 ppm. MS (EI): *m*/*z* 475 (1%), 354 (7), 323 (3), 139 (9), 121 (100).



3h

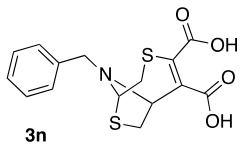
Methyl-9-benzyl-5-(4-chlorobenzoyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4-carboxylate (**3h**). The title compound was obtained starting from dithiane **1b** (100 mg, 0.45 mmol) and **2c** (105 mg, 0.54 mmol), following the general procedure for thiazolinyl-thiazepine **3b**. Compound **3h** was isolated as a pale yellow solid (34%); mp = 148.0–149.5 °C. ^{1}H NMR ($CDCl_3$) δ 3.00 (dd, *J* = 14.2, 6.1 Hz, 1H), 3.42 (dd, *J* = 14.2, 2.9 Hz, 1H), 3.54 (m, 6H), 3.83 (d, *J* = 13.0 Hz, 1H), 4.19 (ddd, *J* = 7.9, 4.5, 0.7 Hz, 1H), 4.94 (ddd, *J* = 6.1, 2.9, 0.7 Hz, 1H), 7.25 (m, 5H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.78 ppm (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 38.0, 44.3, 52.9, 61.0, 69.8, 75.6, 127.7, 128.5, 129.0, 130.2, 134.0, 137.5, 139.7, 154.2, 165.0, 195.1 ppm. MS (EI):*m*/*z* 445 (M^+, 4%), 398 (18), 322 (13), 306 (19), 139 (36), 91 (100).



3i

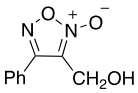
Methyl-9-benzyl-5-(3-phenylpropanoyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4-carboxylate (**3i**). The title compound was obtained starting from dithiane **1b** (100 mg, 0.45 mmol) and **2d** (116 mg, 0.54 mmol), following the general procedure for thiazolinyl-thiazepine **3b**. Compound **3i** was isolated as a yellow solid (65%); mp = 130 °C (decomp). ^{1}H NMR ($CDCl_3$) δ 2.43 (ddd, *J* = 17.4, 8.6, 6.8 Hz, 1H), 2.71 (ddd, *J* = 17.4, 9.3, 5.8 Hz, 1H), 2.82 (m, 2H), 2.87 (dd, J = 14.1, 6.0 Hz, 1H), 3.29 (dd, *J* = 14.1, 2.5 Hz, 1H), 3.35 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.44 (dd, *J* = 11.1, 9.1 Hz, 1H), 3.52 (d, *J* = 13.1 Hz, 1H), 3.72 (s, 3H), 3.79 (d, *J* = 13.1 Hz, 1H), 4.05 (ddd, *J* = 9.1, 3.4, 0.7 Hz, 1H), 4.89 (ddd, *J* = 6.0, 2.5, 0.7 Hz, 1H), 7.09 (m, 2H), 7.25 ppm (m, 8H). ^{13}C NMR ($CDCl_3$) δ 29.9, 38.1, 44.1, 44.2, 53.3, 61.2, 68.7, 76.2, 126.2, 128.0, 128.5, 128.6, 128.8, 129.4, 131.7, 137.9, 141.0, 156.7, 165.8, 204.3 ppm. MS (EI): *m*/*z* 439 (M^+, 3%), 404 (4), 131 (5), 91 (100).

4-(4,5-bis(ethoxycarbonyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-en-9-yl)butanoic acid (**3k**). The title compound was obtained starting from dithiane **1g** (100 mg, 0.45 mmol) and **2b** (116 mg, 0.54 mmol), following the general procedure for thiazolinyl-thiazepine **3b**. The crude of this reaction was used to prepare **3l** without further purification.



3n

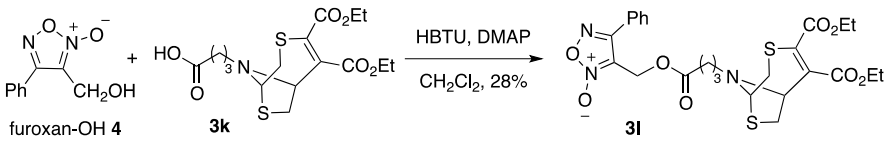
9-benzyl-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4,5-dicarboxylic acid (**3n**). The title compound was obtained by hydrolysis of thiazolidinyl-tiazepine **3b**. Compound **3b** (250 mg, 0.74 mmol) was dissolved in THF (10 mL) and treated with a solution of LiOH 10% (10 mL). Once reagent consumption was evidenced by TLC, the mixture was acidified to pH 2 using aqueous HCl (5%) and the resulting precipitate was filtered to provide the product as a white solid (230 mg, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (m, 2H), 3.45 (dd, *J* = 13.7, 2.1 Hz, 1H), 3.56 (dd, *J* = 10.9, 6.1 Hz, 1H), 3.73 (d, *J* = 13.1 Hz, 1H), 3.85 (d, *J* = 13.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 4.79 (d, *J* = 6.0 Hz, 1H), 5.13 (dd, *J* = 5.0, 2.1 Hz, 1H), 7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.7, 21.1, 31.0, 40.3, 40.8, 65.2, 73.1, 128.2, 127.7, 127.8, 146.8, 163.4, 176.6. MS (EI): *m/z* 337 (M^+, 48%), 326 (80), 292 (76), 181 (100), 104 (15), 89 (15).



furoxan-OH **4**

The preparation of furoxan-OH (**4**) has been reported previously by David J. Maloney group.[3]

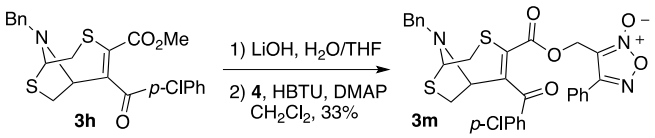
Preparation of thiazolidinyl-thiazepine esters 3l, 3m and 3o.



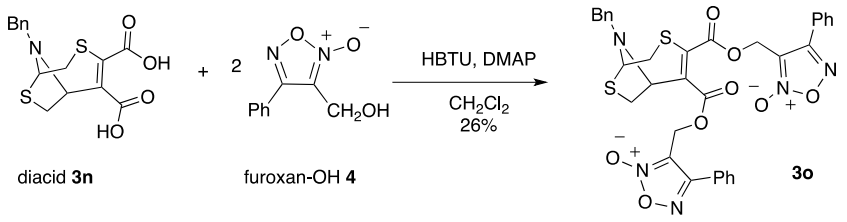
furoxan-OH **4** **3k** **3l**

3-((4-(4,5-bis(ethoxycarbonyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-en-9-yl)butanoyloxy)methyl)-4-phenyl-1,2,5-oxadiazole-2-oxide (**3l**). The title compound was obtained starting from the corresponding thiazolidinyl-thiazepine (**3k**) and furoxan-OH (**4**), following the general procedure for thiazolinyl-thiazepine ester **3m**. Compound **3l** was isolated as colorless oil (28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (m, 6H), 1.84 (m, 2H), 2.50 (m, 3H), 2.66 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.95 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.26

(dd, *J* = 11.0, 3.2 Hz, 1H), 3.35 (dd, *J* = 14.0, 3.1 Hz, 1H), 3.47 (dd, *J* = 11.0, 9.4 Hz, 1H), 4.21 (m, 4H), 4.71 (dd, *J* = 9.4, 3.2 Hz, 1H), 4.82 (dd, *J* = 5.2, 3.1 Hz, 1H), 5.16 (s, 2H), 7.55 (m, 3H), 7.72 ppm (dd, *J* = 7.7, 1.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 24.1, 31.4, 38.4, 45.0, 54.1, 56.7, 62.0, 62.3, 68.5, 76.3, 111.5, 126.2, 127.8, 129.6, 131.5, 137.9, 143.2, 156.8, 165.4, 172.7 ppm. MS (EI): *m/z* 563 (M^+, 16 %), 476 (20), 357 (15), 249 (16), 139 (100), 142 (23).



3-(((9-benzyl-5-(4-chlorobenzoyl)-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene-4-carbonyl)oxy)methyl)-4-phenyl-1,2,5-oxadiazole-2-oxide (**3m**). The title compound was obtained starting from the corresponding thiazolidinyl-thiazepine (**3h**) and furoxan-OH (**4**). Compound **3h** (130 mg, 0.33 mmol) was dissolved in THF (10 mL) and treated with an aqueous solution of LiOH 10% (10 mL). Once reagent consumption was evidenced by TLC, the mixture was acidified to pH 2 with HCl 5%, extracted with EtOAc (3x10 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The acid thiazepine was coupled with furoxan-OH **4,** following the general procedure for thiazolinyl-thiazepine ester **3o** and compound **3m** was obtained as a light yellow solid (33%); mp = 129–132°C. ^{1}H NMR ($CDCl_3$) δ 2.99 (dd, *J* = 14.3, 6.1 Hz, 1H), 3.41 (dd, *J* = 14.3, 2.9 Hz, 1H), 3.54 (m, 3H), 3.82 (d, *J* = 13.0 Hz, 1H), 4.14 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.95 (dd, *J* = 6.1, 2.9 Hz, 1H), 4.97 (s, 2H), 7.24 (m, 5H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.55 (m, 5H), 7.67 ppm (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.0, 44.5, 55.4, 61.1, 69.8, 75.8, 110.3, 125.8, 127.7, 128.0, 128.7, 129.2, 129.3, 129.6, 130.4, 131.3, 131.6, 133.3, 137.5, 140.4, 155.7, 156.7, 163.9, 194.7 ppm. MS (EI): *m/z* 605 (M^+, 1%), 572 (3), 558 (5), 430 (6), 322 (10), 139 (23), 91 (100).



4,5-bis(((2-oxido-4-phenyl-1,2,5-oxadiazol-3-yl)methoxy)carbonyl)-9-benzyl-3,8-dithia-9-azabicyclo[4.2.1]non-4-ene (**3o**). Compound **3o** was prepared starting from diacid **3n**. A solution of diacid-**3n** (135 mg, 0.4 mmol) in CH_2Cl_2 (12 mL) was cooled at 0 °C and HBTU (2.4 eq), DIPEA (4 eq) and catalytic amount of DMAP were added with stirring. After 15 minutes, a solution of **4** (163 mg, 0.8 mmol) in of CH_2Cl_2 (2 mL) was added. The mixture was stirred at room temperature overnight. Then, the crude was poured into water and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were

dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/Hexanes 1:3) to give compound **3o** as pale yellow oil (70 mg; 26% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (dd, *J* = 14.1, 6.2 Hz, 1H), 3.11 (dd, *J* = 11.2, 3.4 Hz, 1H), 3.33 (m, 2H), 3.58 (d, *J* = 13.2 Hz, 1H), 3.77 (d, *J* = 13.2 Hz, 1H), 4.50 (dd, *J* = 9.2, 3.0 Hz, 1H), 4.82 (dd, *J* = 5.7, 3.5 Hz, 1H), 5.06 (d, *J* = 13.5 Hz, 1H), 5.15 (d, *J* = 13.5 Hz, 1H), 5.21 (m, 2H), 7.28 (m, 4H), 7.53 (m, 7H), 7.74 (m, 2H), 7.62 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.4, 45.2, 55.3, 55.6, 60.8, 68.0, 110.7, 110.8, 125.8, 125.9, 127.6, 127.7, 127.8, 128.5, 129.0, 129.4, 129.5, 131.4, 131.5, 144.4, 156.4, 156.9, 165.3, 164.0 ppm. MS (EI): *m/z* 685 (2%), 510 (5), 227 (6), 162 (7), 175 (8), 129 (12), 131 (25), 115 (30), 91 (100).

MATERIALS AND METHODS

TGR Inhibition Studies. The screening was performed using the DTNB assay for TR activity.[4]

Reduction of 5,5´-dithiobis(2-dinitrobenzoic acid) (DTNB) with concomitant NADPH oxidation was determined by the increase in absorbance at 412 nm (T70+ UV/VIS Spectrometer, PG instruments Ltd, UK) due to the formation of 5-thionitrobenzoic acid (TNB) (ε = 13600 $M^{-1}{\cdot}cm^{-1}$). The reaction mixture contained 100 µM of NADPH and 5 mM of DTNB in phosphate buffer 50 mM, EDTA 1 mM, pH 7. For inhibition studies, a 100 mM stock solution of each inhibitor was prepared in DMSO. Fractions containing wild-type *E. granulosus* recombinant TGR (1nM) were preincubated with NADPH and the corresponding inhibitor for three minutes. Reaction started with the addition of DTNB and was followed for three minutes. All assays were performed in duplicate. In every case, controls for reaction without enzyme and without inhibitor were carried out in parallel. TGR activity inhibition is expressed as that measured at [inh] = 50 µM.

***Caenorhabditis elegans* motility assay**

Compounds toxicity in *C. elegans* was evaluated through an automatized motility assay using a WMicrotracker-One TM (PhylumTech) device. Each compound was evaluated at 100 µM with 1% DMSO and eight replicates were made. Motility of about 80 synchronized L4 worms/well seeded in 80 µL K buffer and containing 0.015% BSA was measured during 30 minutes to normalize 100% motility. Then, compounds were added in a final volume of 100 µL and motiliy tracked during 17.5 hours. Mean motility at final time was compared to that corresponding to control wells (1% DMSO).

Cytotoxicity against Trypanosoma b. brucei and murine macrophages

The biological activity of the compounds was evaluated in the bloodstream form of *T. brucei brucei* strain 427, cell line 449 (encoding one copy of the tet-represor protein: Pleo transfected with a construct encoding a redox biosensor (Franco et al. 2017). The assay was performed as described in the article Franco et al 2017.[5]

The cytotoxic effect of the compounds against mammalian cells was evaluated against mouse macrophages from the cell line J774. The assay was performed as described in the article Franco et al 2017.[6]

Viability assays for T. brucei and murine macrophages

The bloodstream form of *T. b. brucei* strain 427 was grown in HMI-9 medium complemented with 10% (v/v) Fetal Bovine Serum (FBS; GIBCO®), 10 U/mL penicillin and 10 mg/mL streptomycin. Cells were incubated aerobically in a humidified incubator containing 5% CO_2 at 37 °C. The cytotoxic effect of the distamycin analogues was evaluated as described by Maiwald et al. [41]. Briefly, 200 mL of a cell

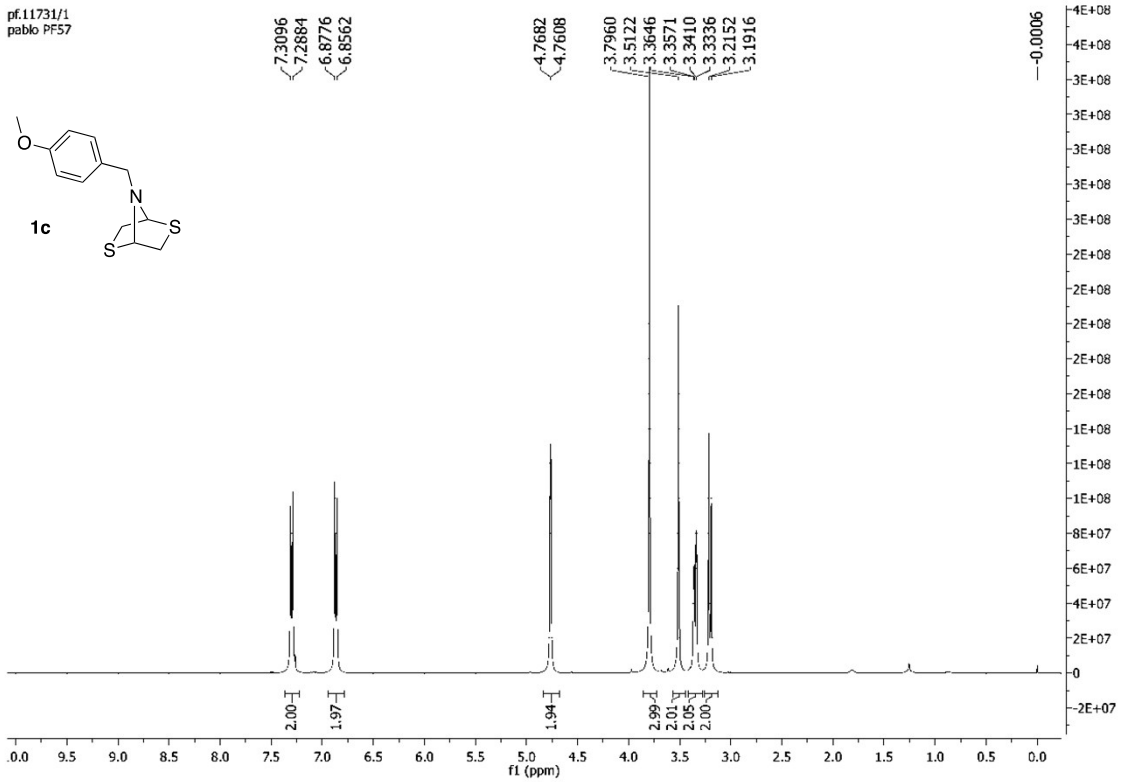
suspension containing 5 x 10^5 parasites/mL in exponential growth phase were seeded per well in a 96-well culture plate and 2 mL each compound prepared at different concentrations in 100% v/v DMSO were added. For the screening and EC_{50} assays the final concentrations of compounds tested were 5 and 30 mM, and between 0.005 and 150 mM, respectively. Control wells included cells treated with 1% v/v DMSO or 15 mM nifurtimox. After addition of the test and control compounds, the culture plates were incubated at 37 °C, 5% CO_2 for 24 h. Then, 100 mL from each well was transferred to a 2mL tube or to a 96 U bottom well plate containing 200 mL of sterile phosphate-buffered saline (PBS) 1% glucose (m/v) (pH 7.4), 2 mg/mL propidum iodide (PI) and analyzed by flow cytometry using a CyAn™ADP (Beckman Coulter) or an Accuri™C6 (BD) devices with laser λ_{ex} = 488 nm and filter λ_{em} = 613/20 nm for the CyAn™ and λ_{em} = 540/85 for the Accuri™ C6. The data were analyzed with the Summit (Dako) software or Accuri C6 software (BD).

The murine macrophages (cell line J774) were cultivated in DMEM medium supplemented with 10% (v/v) FCS (GIBCO®), 10 U/mL penicillin and 10 mg/mL streptomycin, at 37 °C, 5% CO_2 in a humidified incubator. The EC_{50} against macrophages was assayed only for compounds for which the corresponding EC_{50} towards parasites was previously determined. Cell viability was determined at 6-point concentrations of compound tested in triplicate, using the WST-1 reagent and the protocol described by Demoro *et al.* [7]

For all assays, cell viability was calculated as follows: viability (%) = 100 x (number of cells for compound Y at concentration X/ number of cells in the DMSO-treated control). All EC_{50} values were obtained from dose/response curves fitted to a sigmoidal Boltzmann equation (errors calculated using errors propagation) or extrapolated from non-linear fitting plots. The error is expressed as 2S.D and estimated as 2s (n-1).

***Nippostrongylus brasiliensis* L4**.

The assay was performed as described previously.[8]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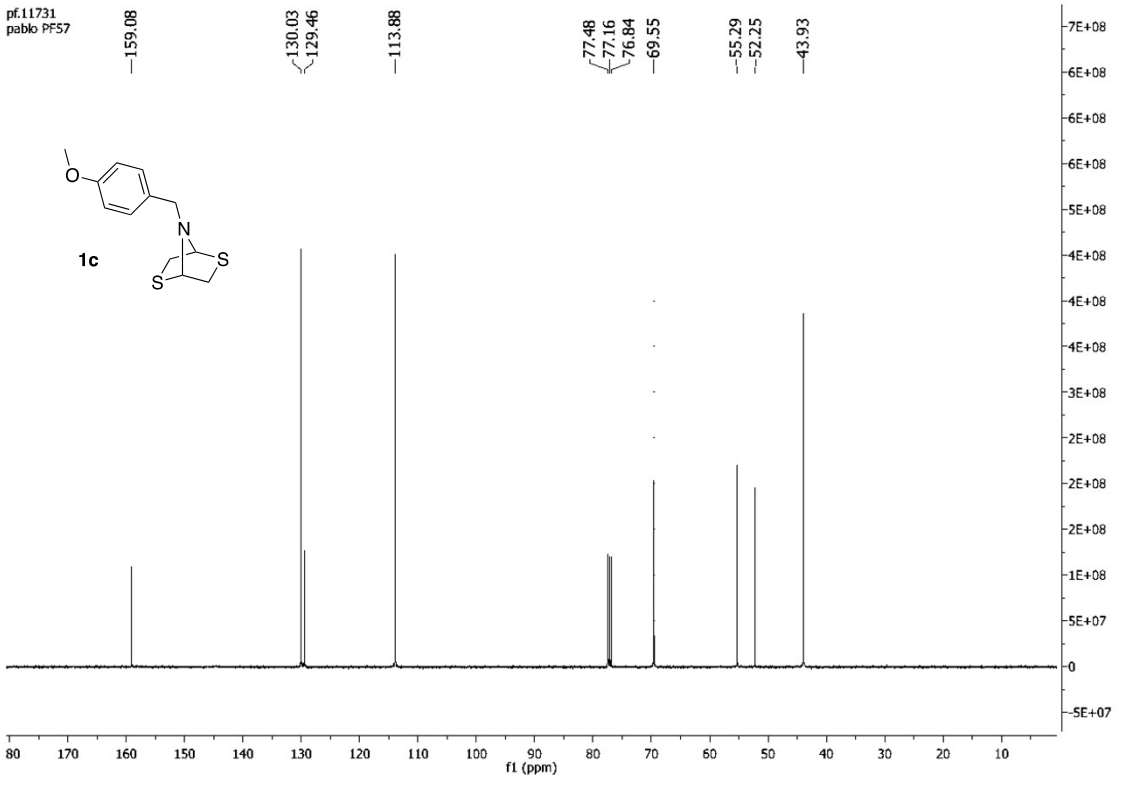
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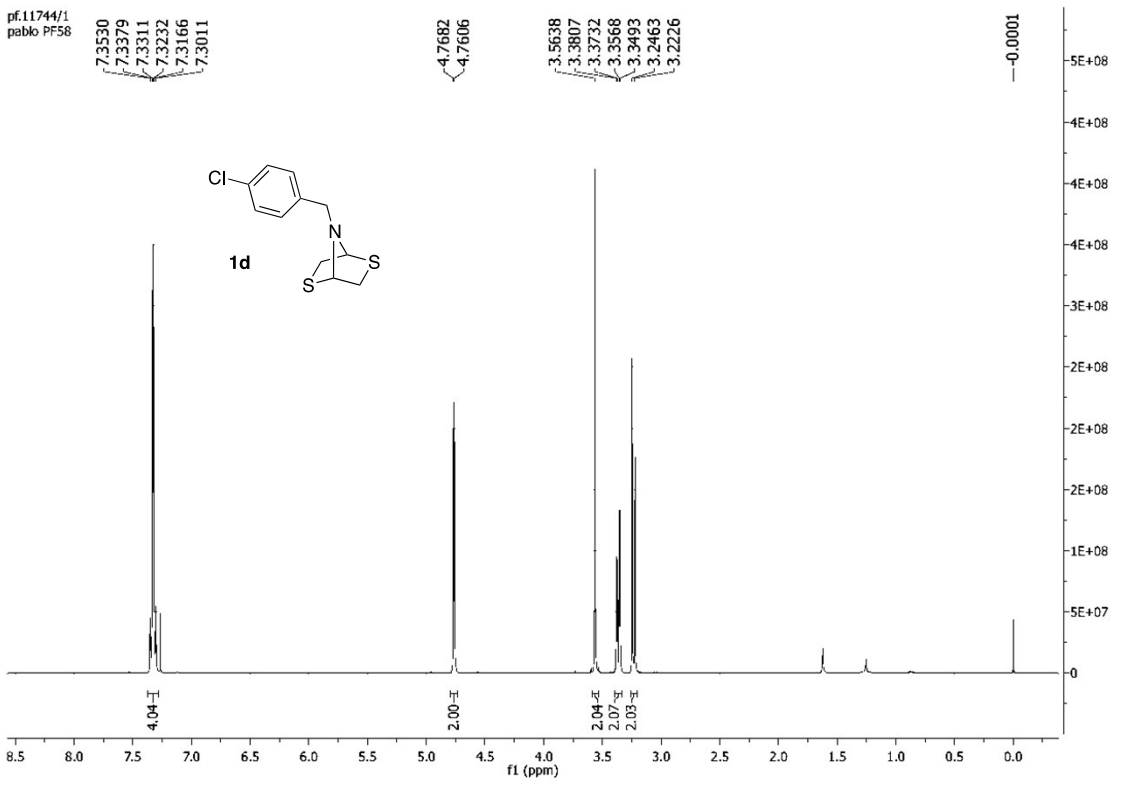
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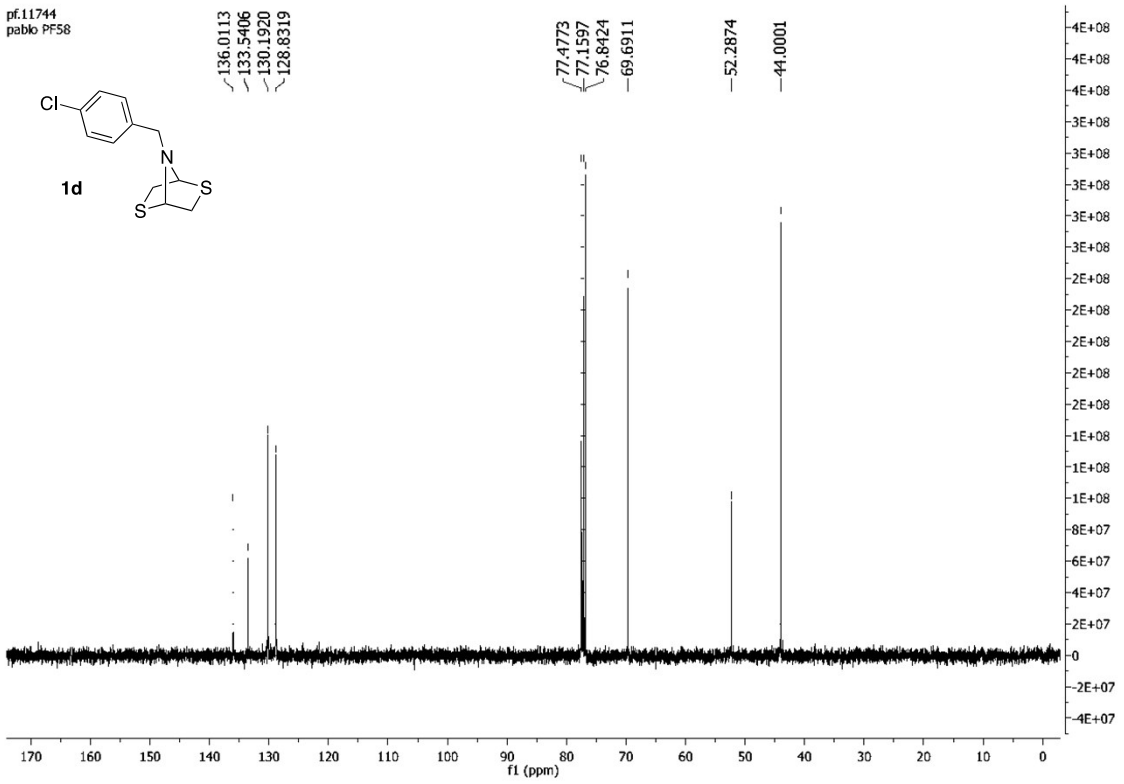
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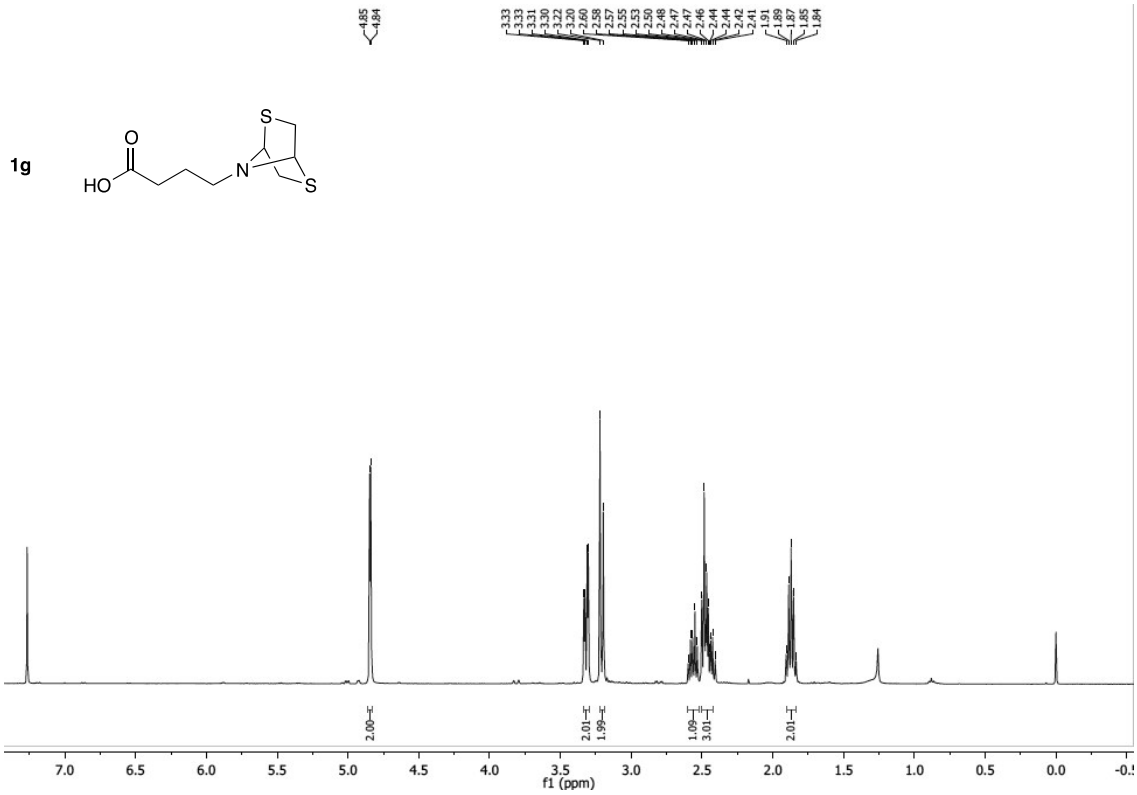
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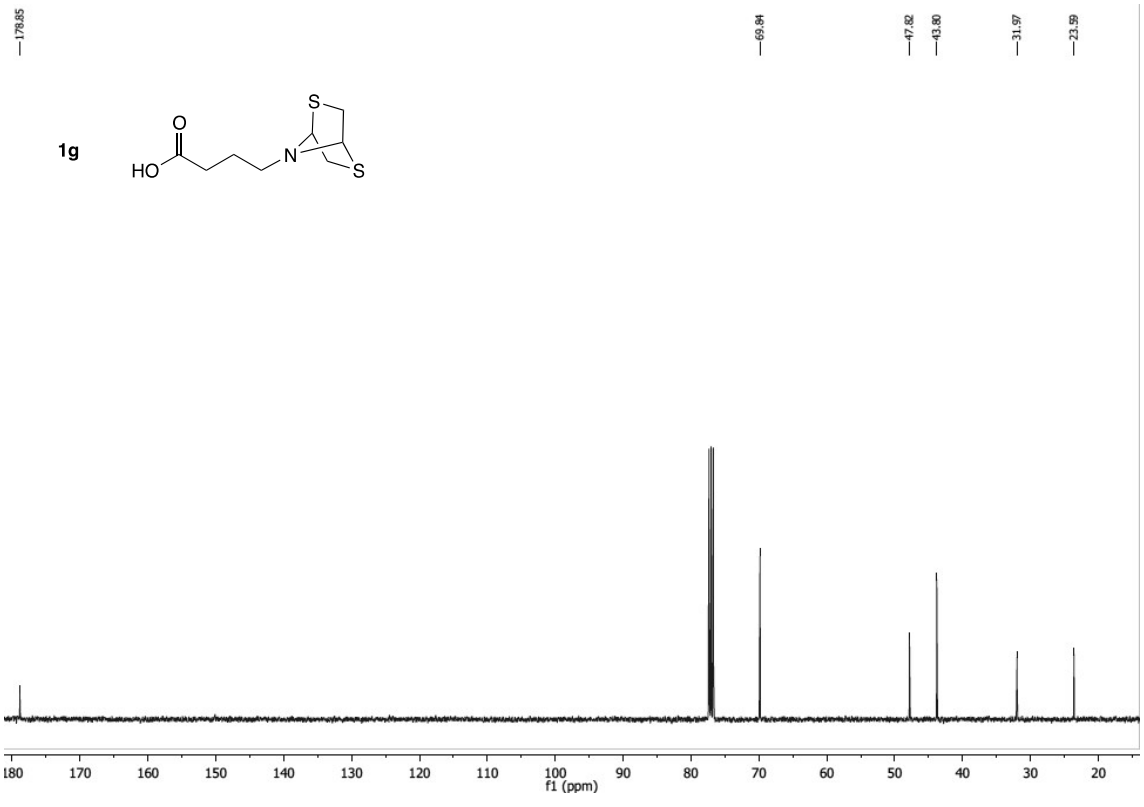
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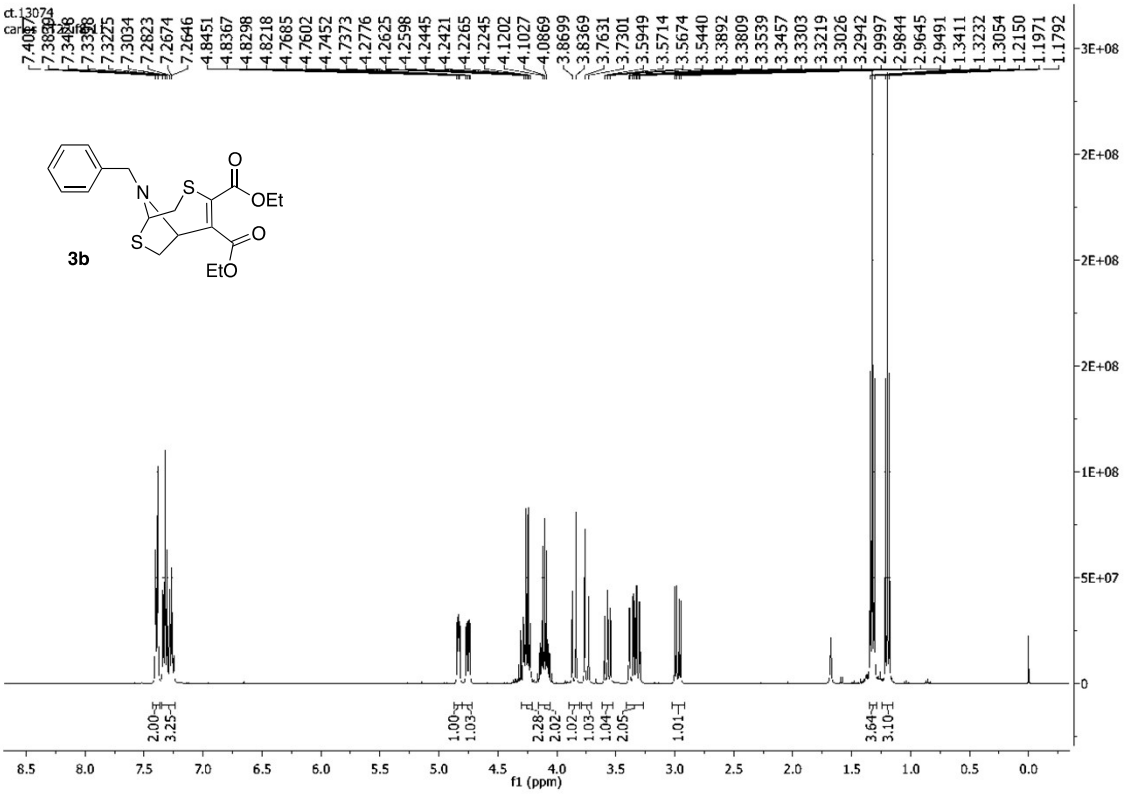
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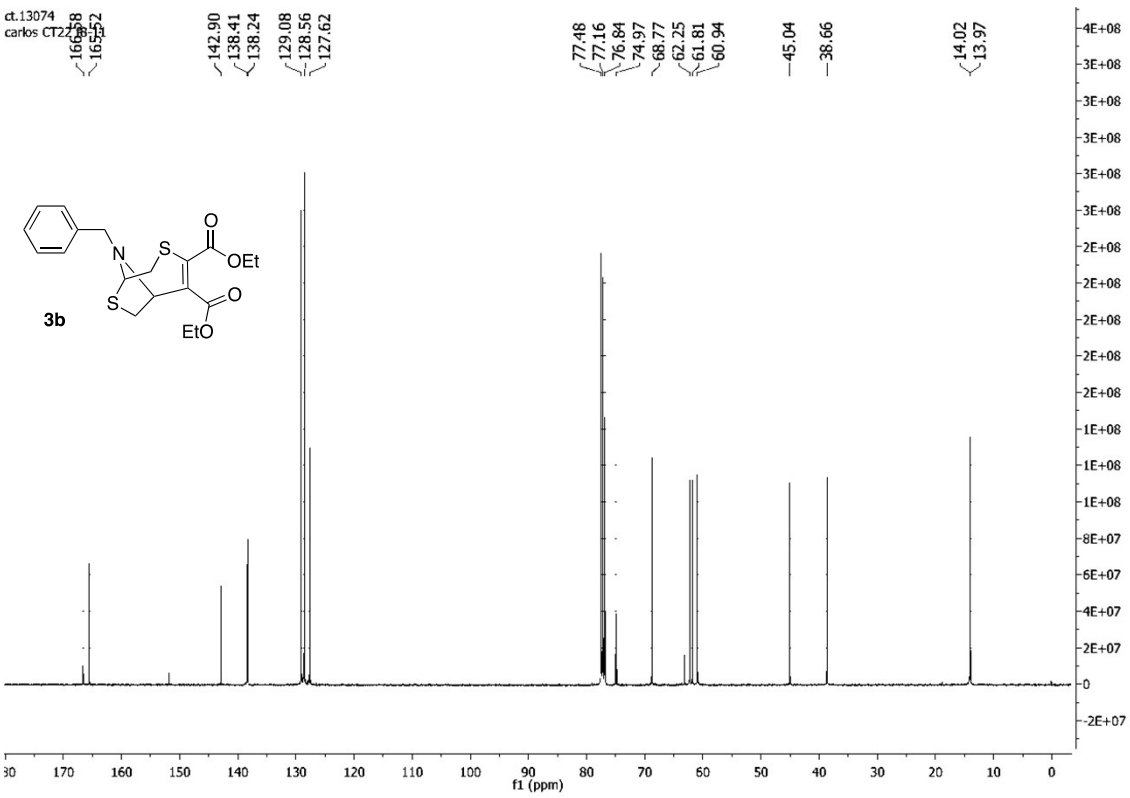
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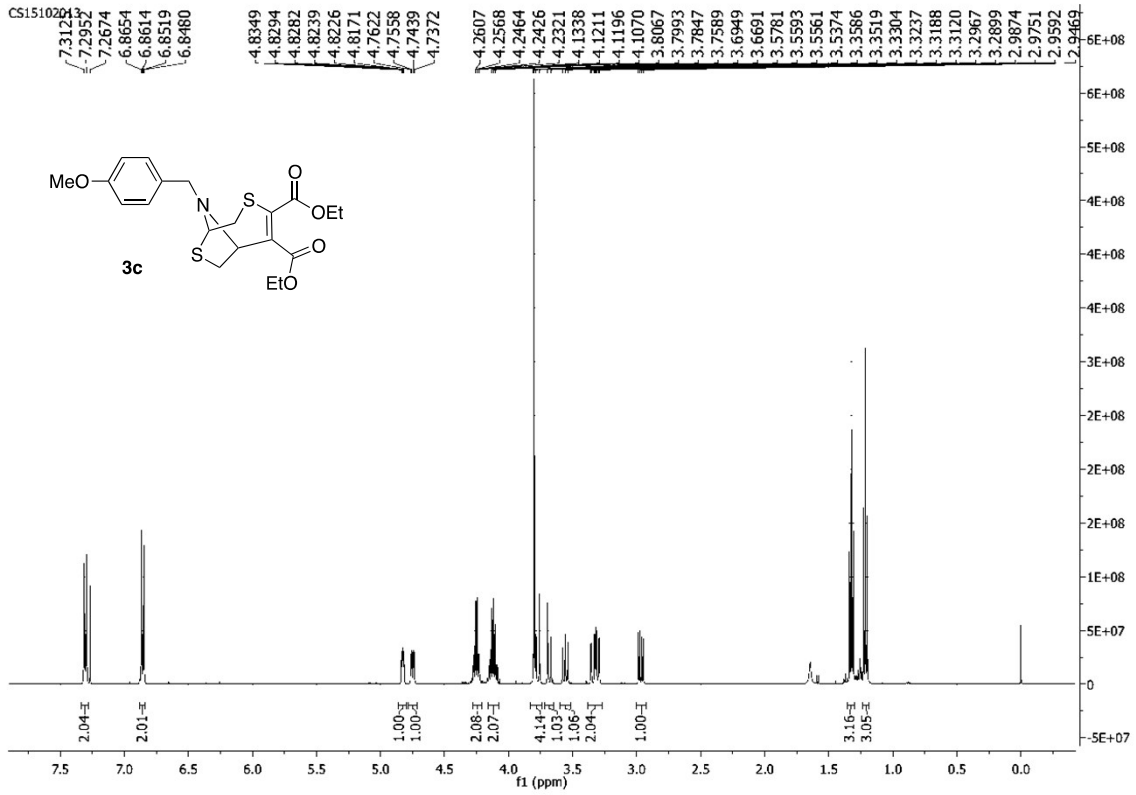
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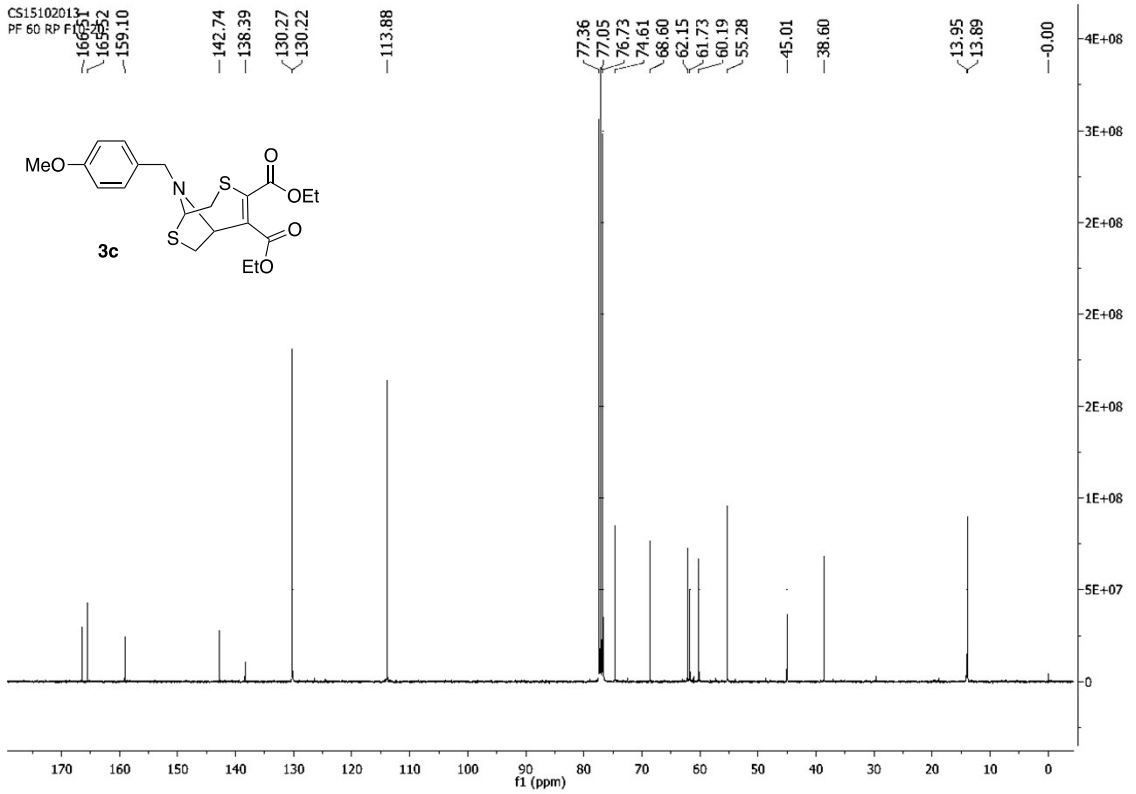
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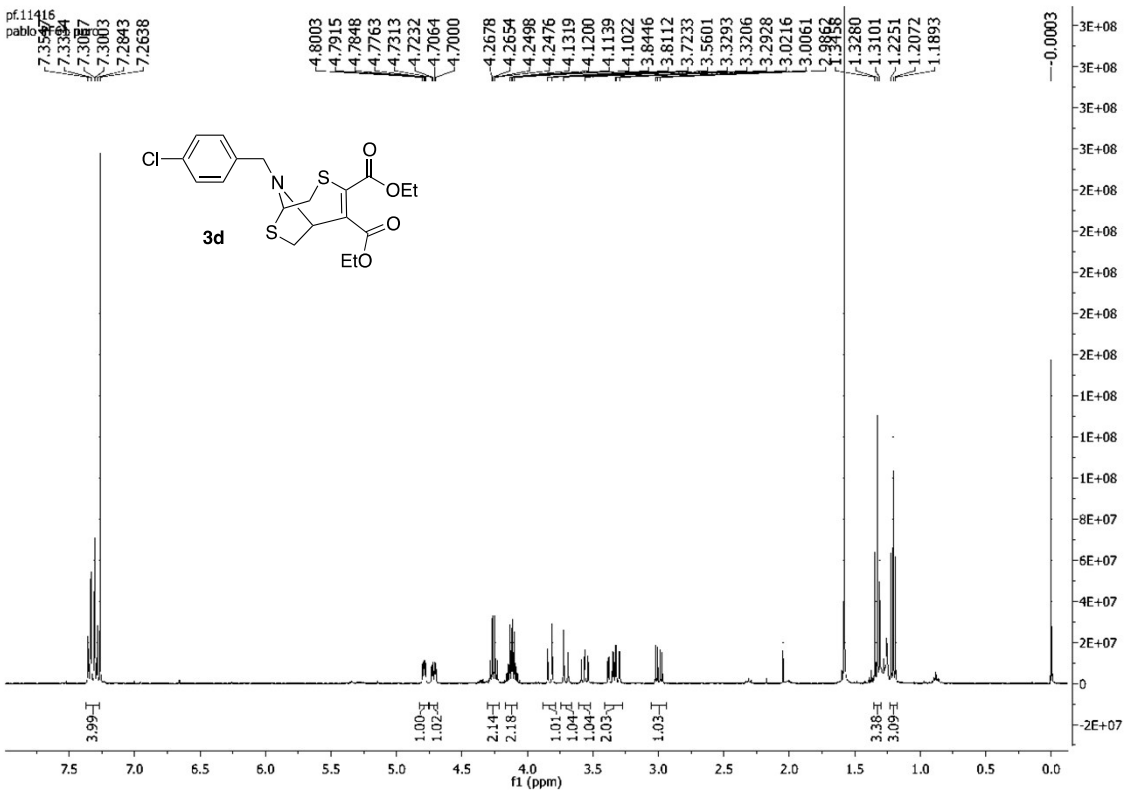
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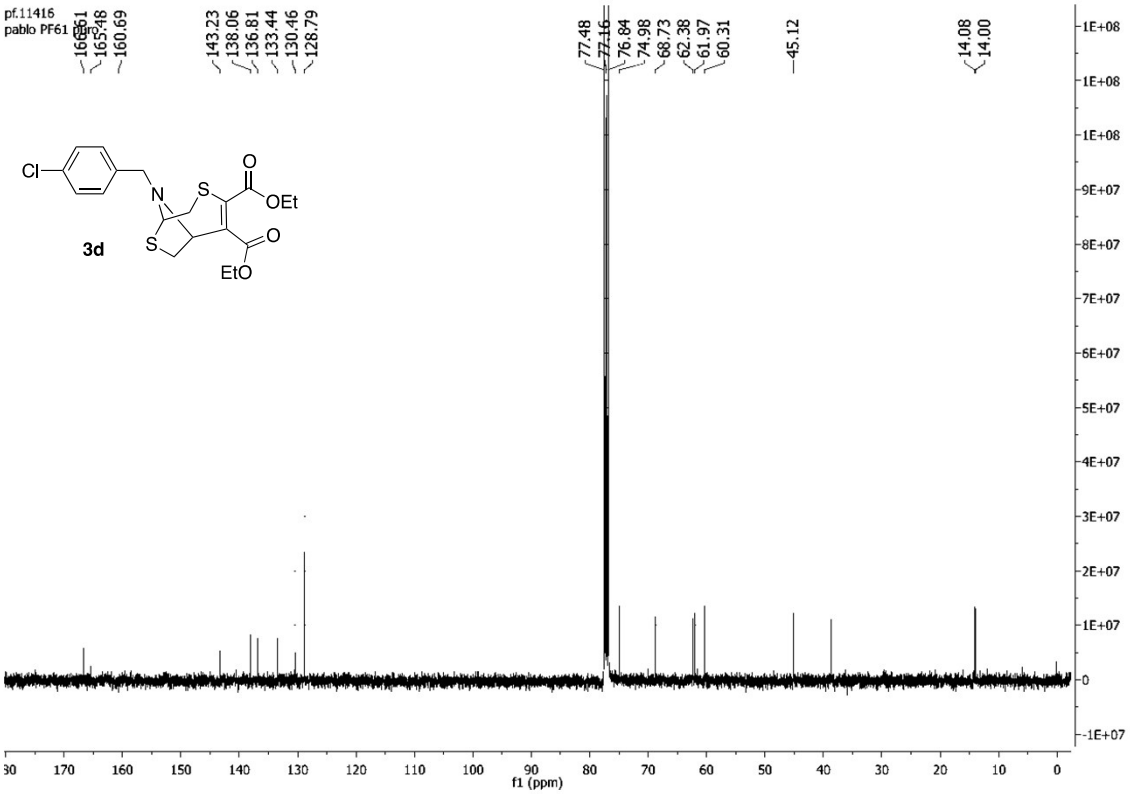
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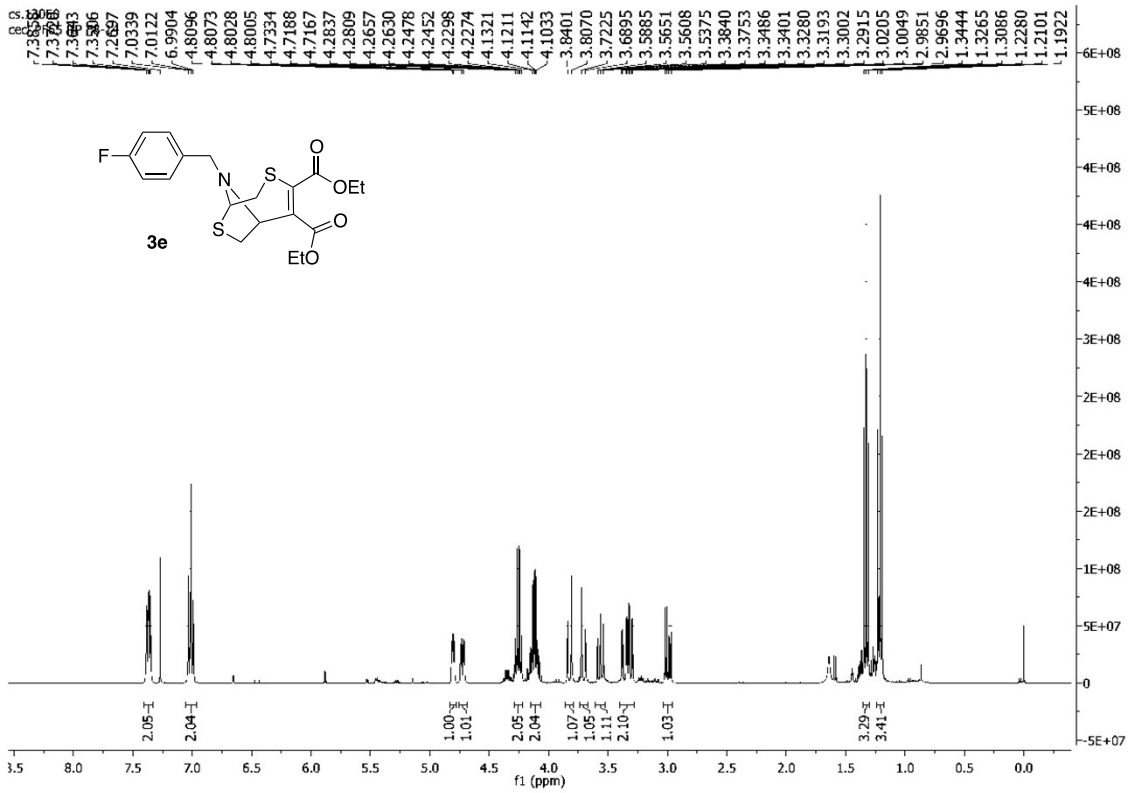
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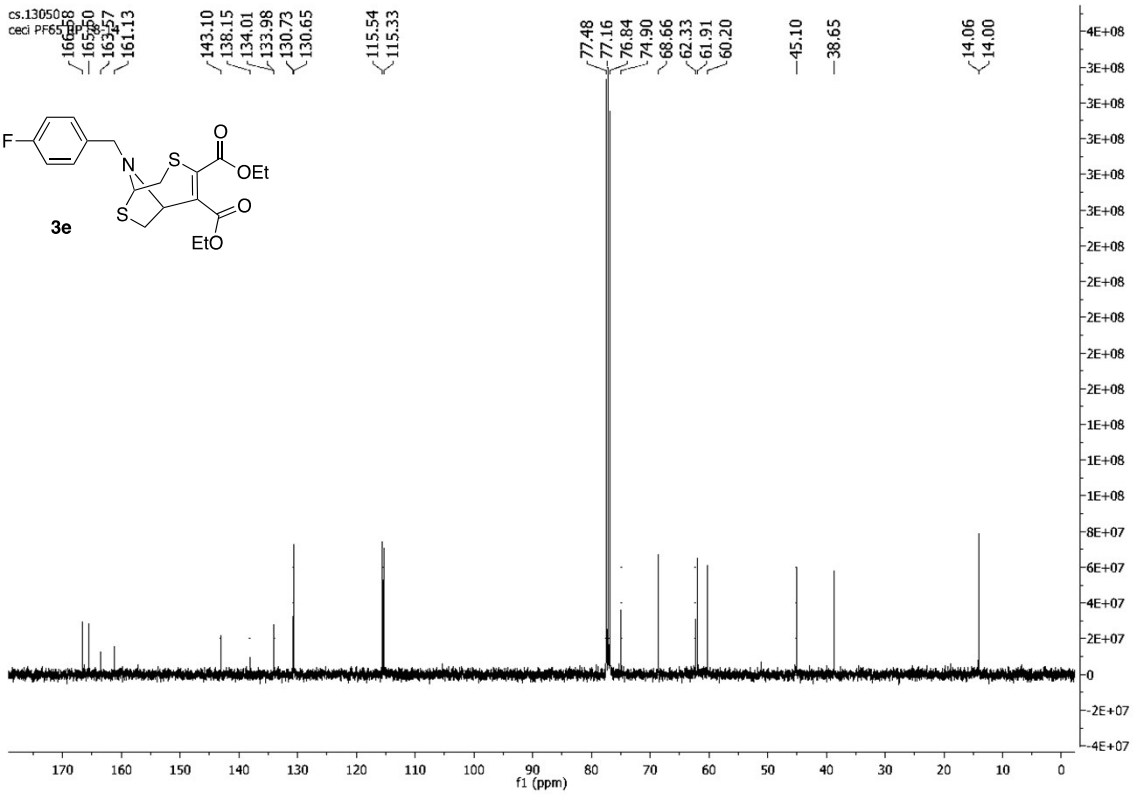
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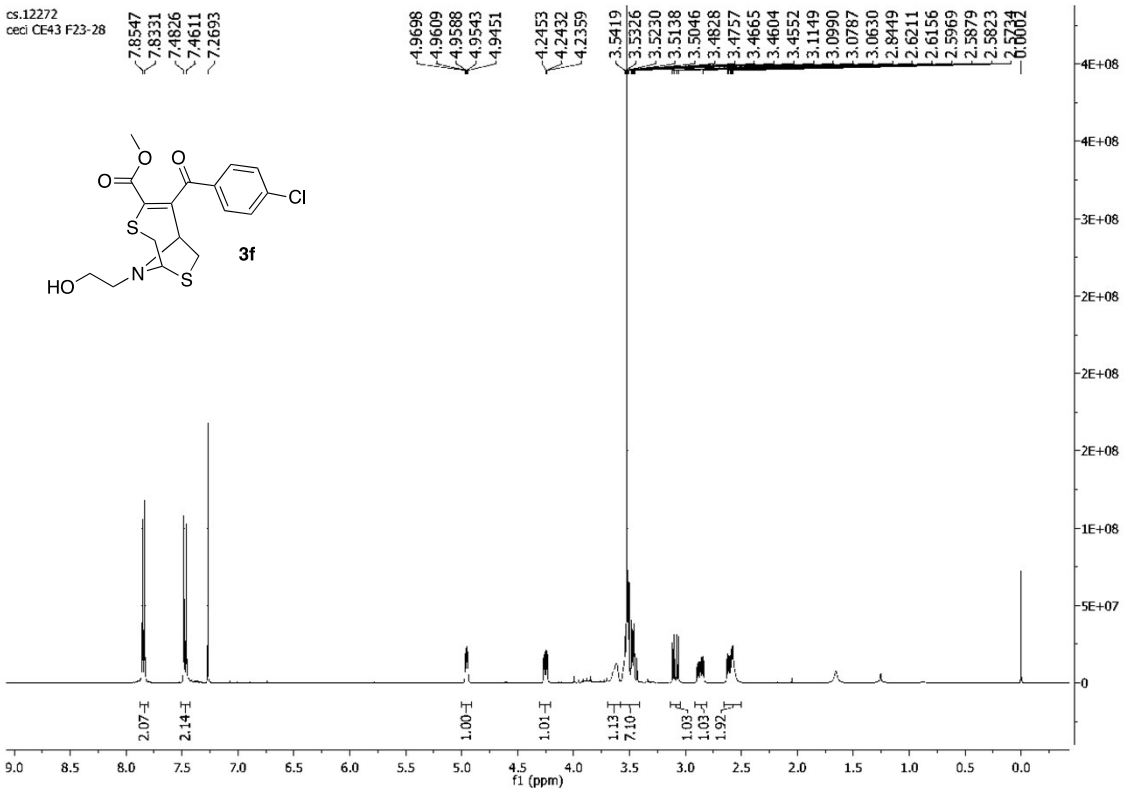
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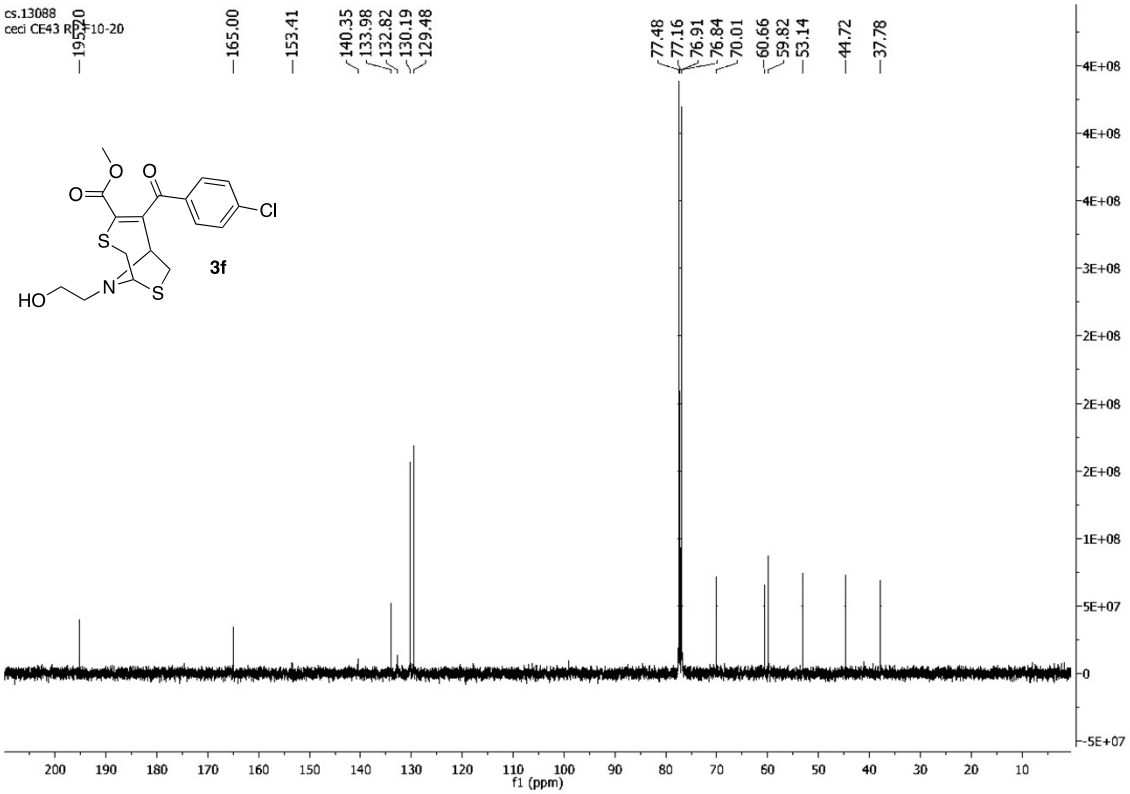
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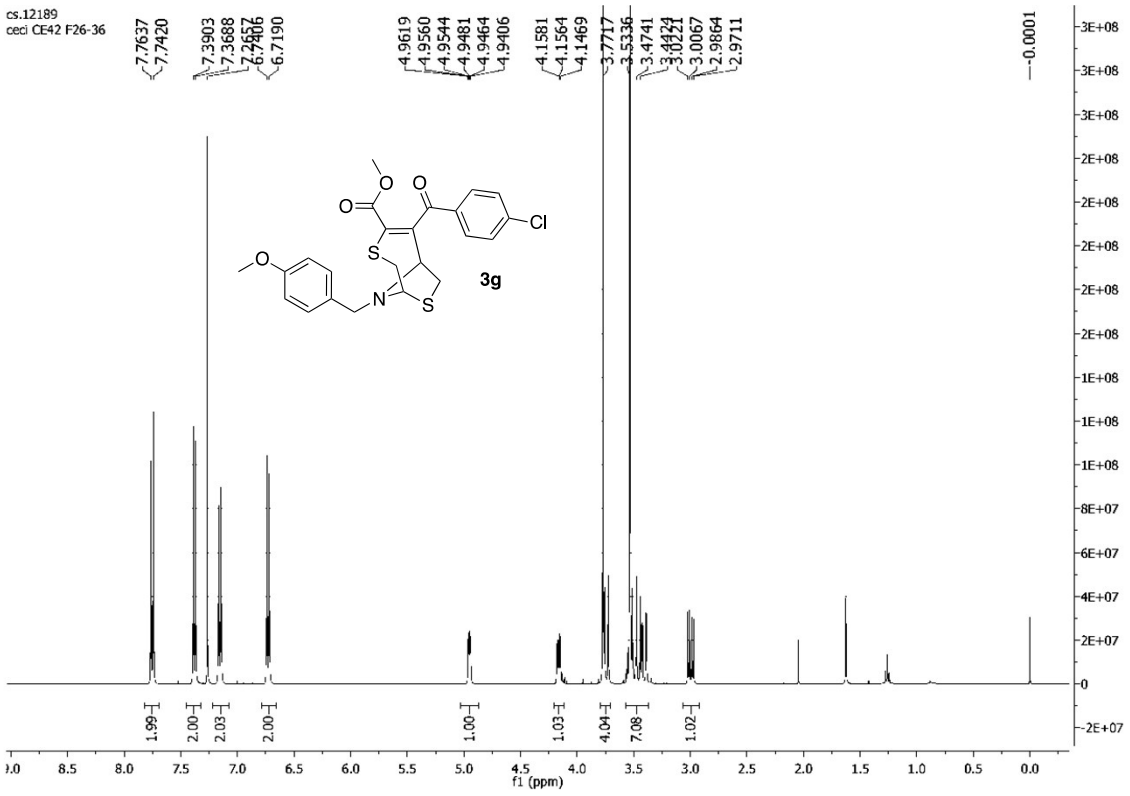
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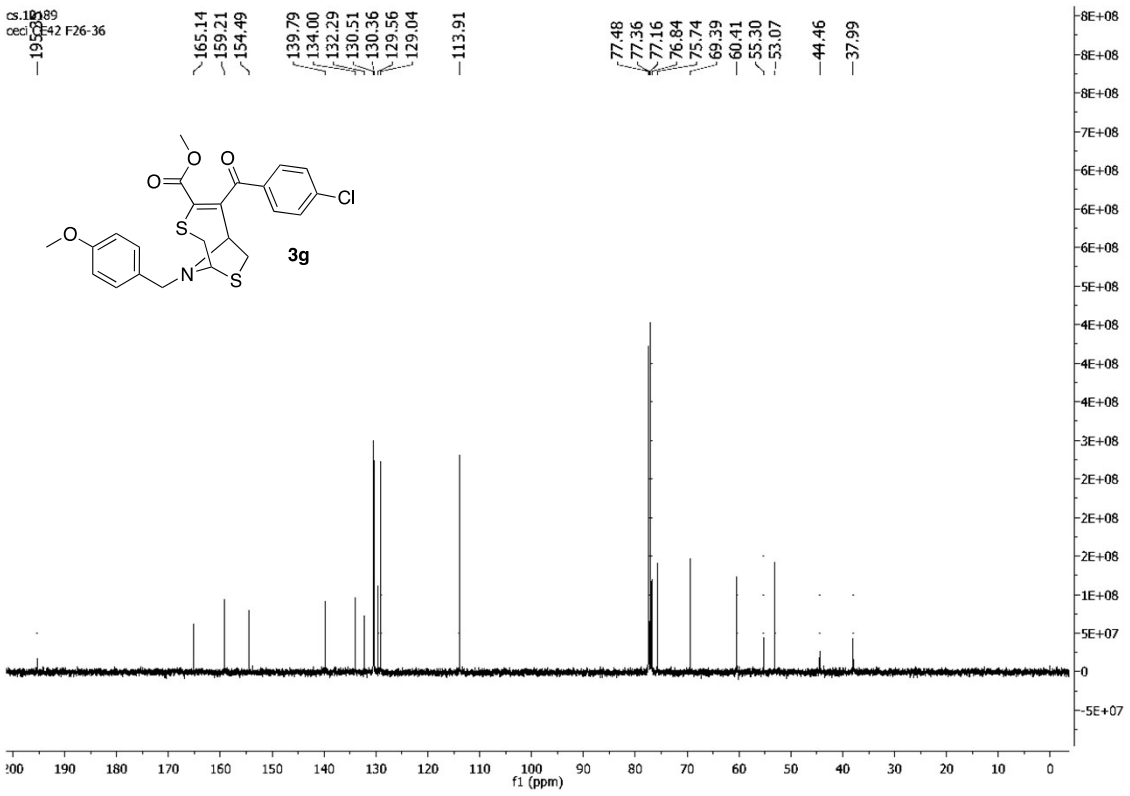
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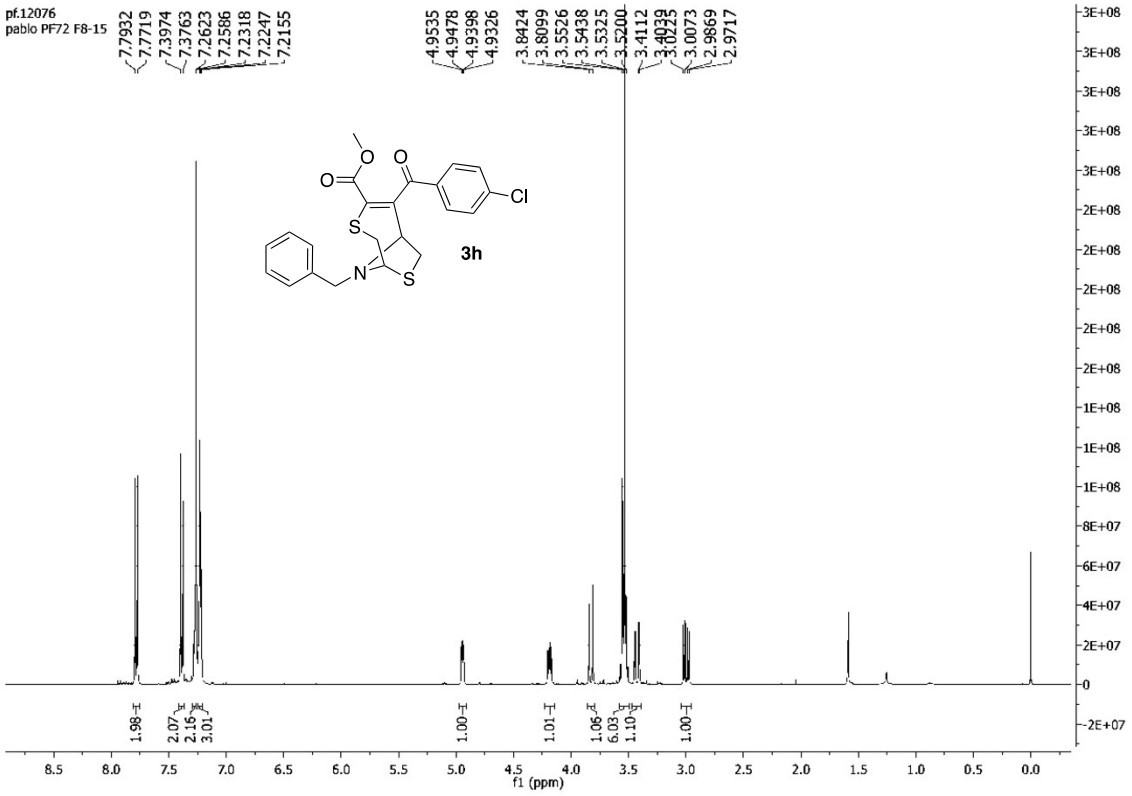
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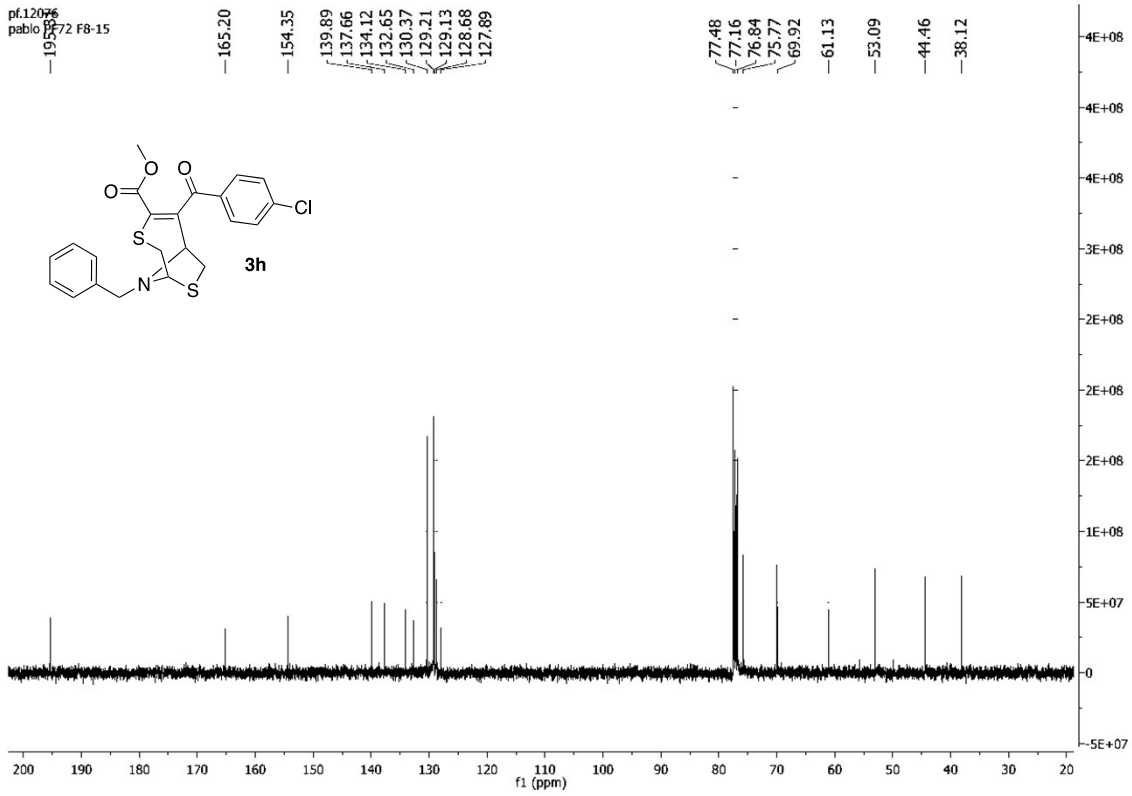
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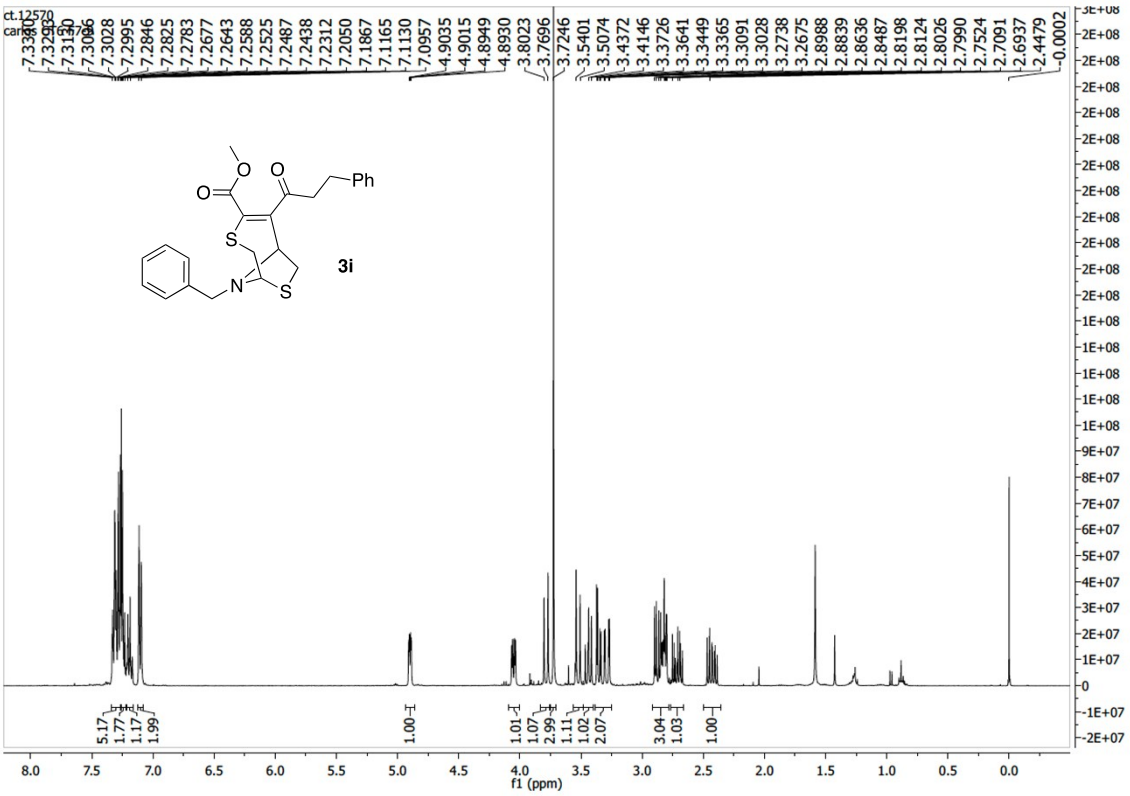
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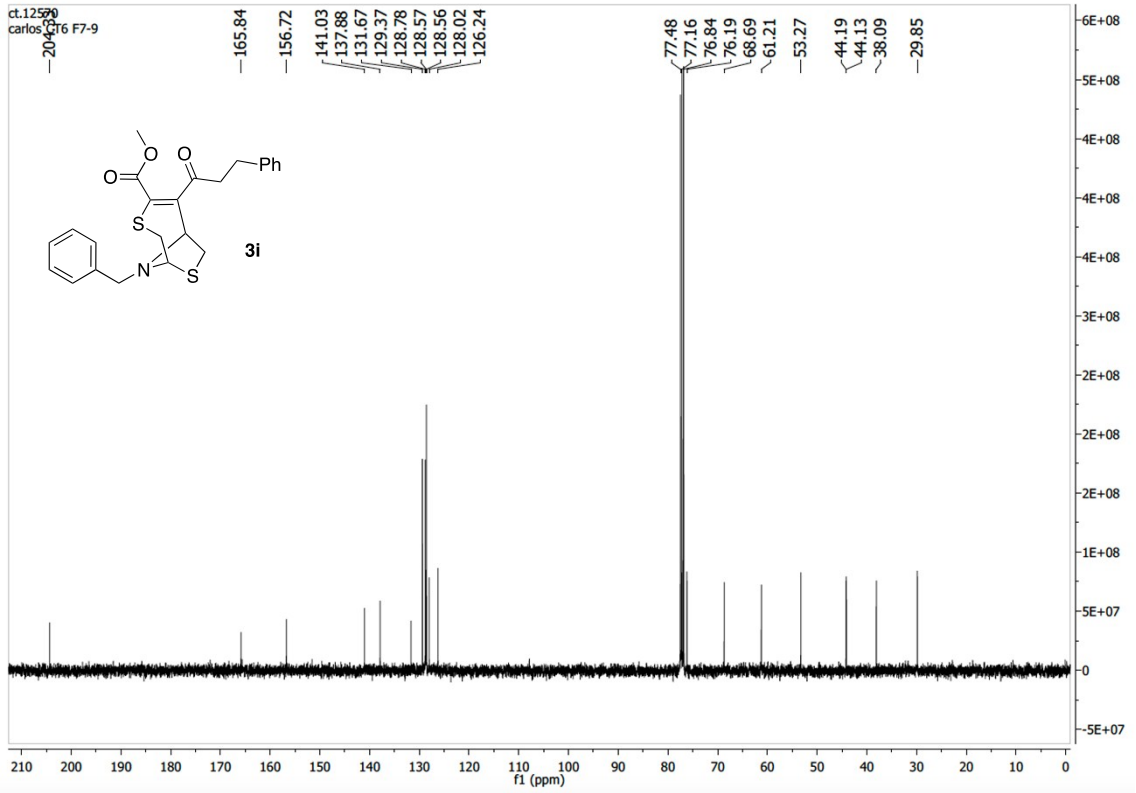
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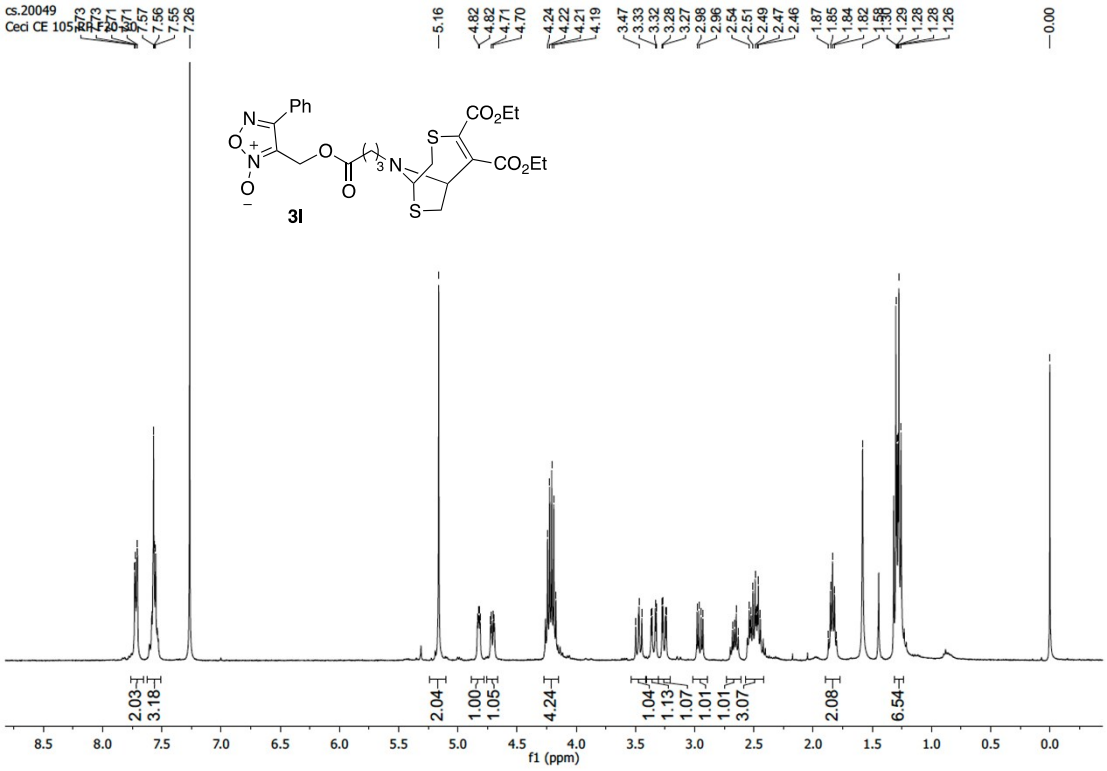
3i
f1 (ppm)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CO2Et
3l
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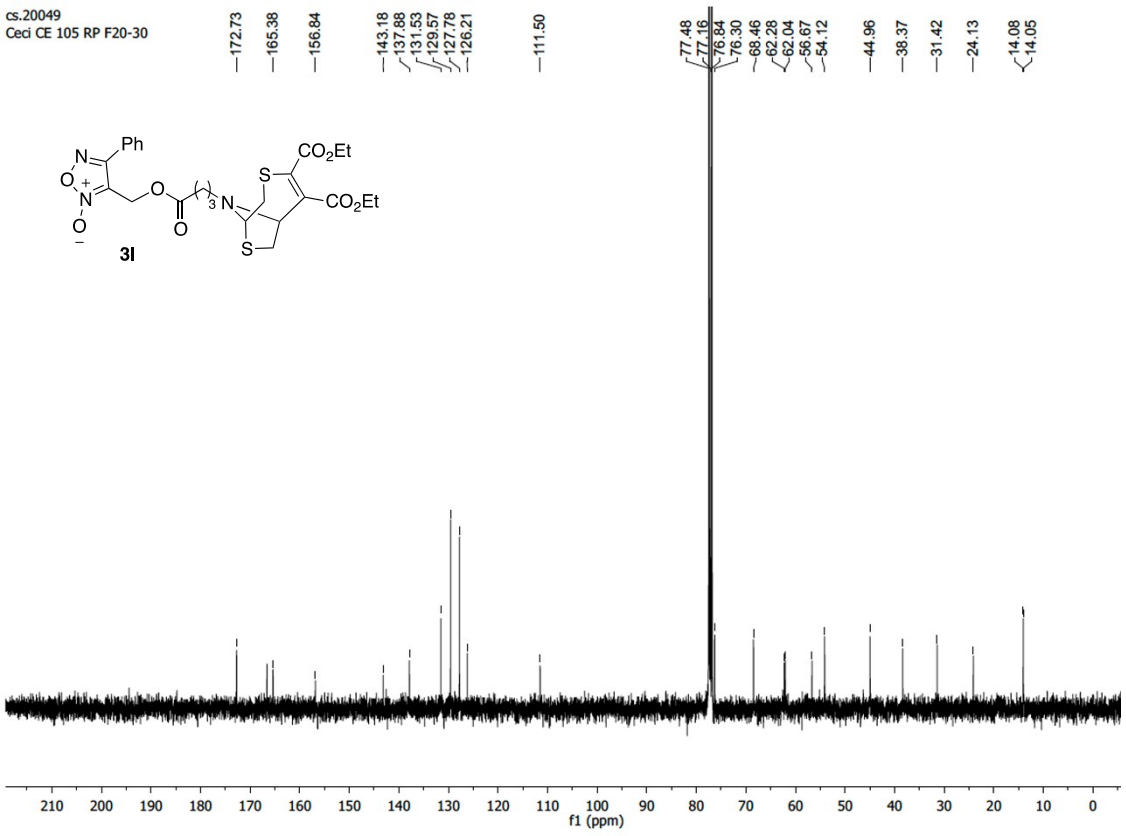
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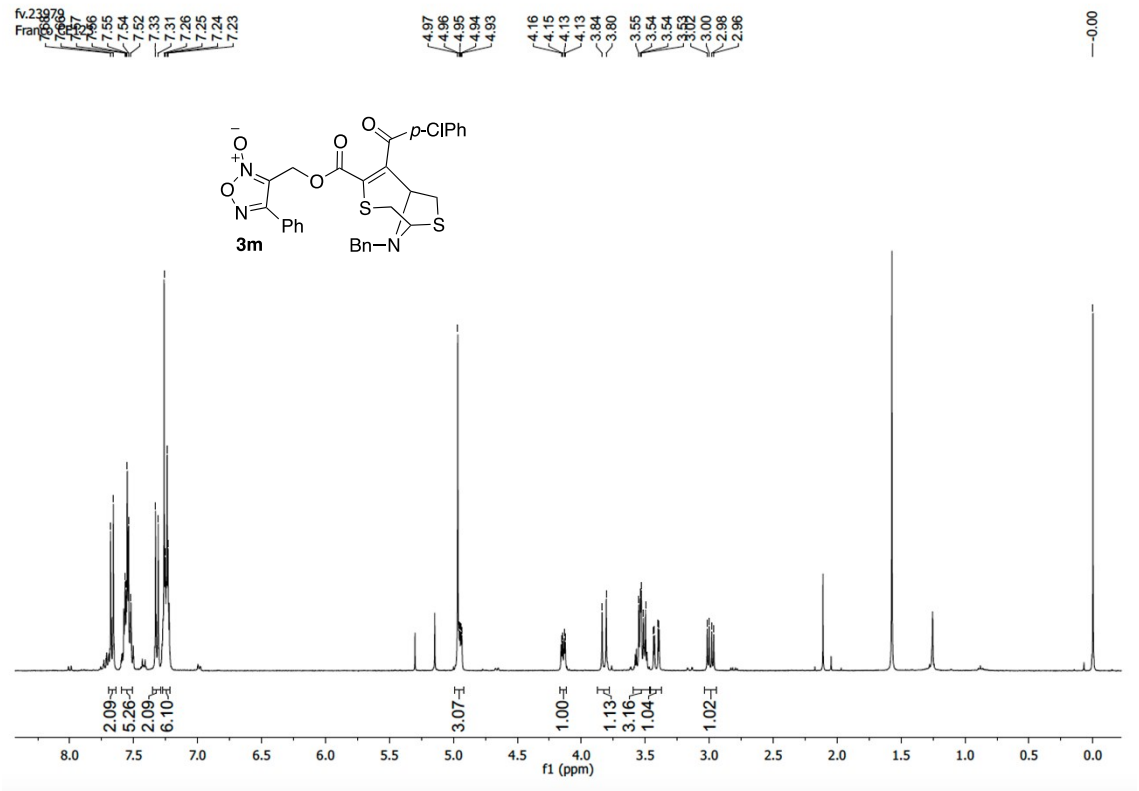
3l
f1 (ppm)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4.95
4.94
4.93
4.16
4.15
4.13
4.13
3.84
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3.54
3.54
3.00
2.98
2.96
0.00
p-ClPh
Ph
Bn–N
3m
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3.07
1.00
1.13
3.16
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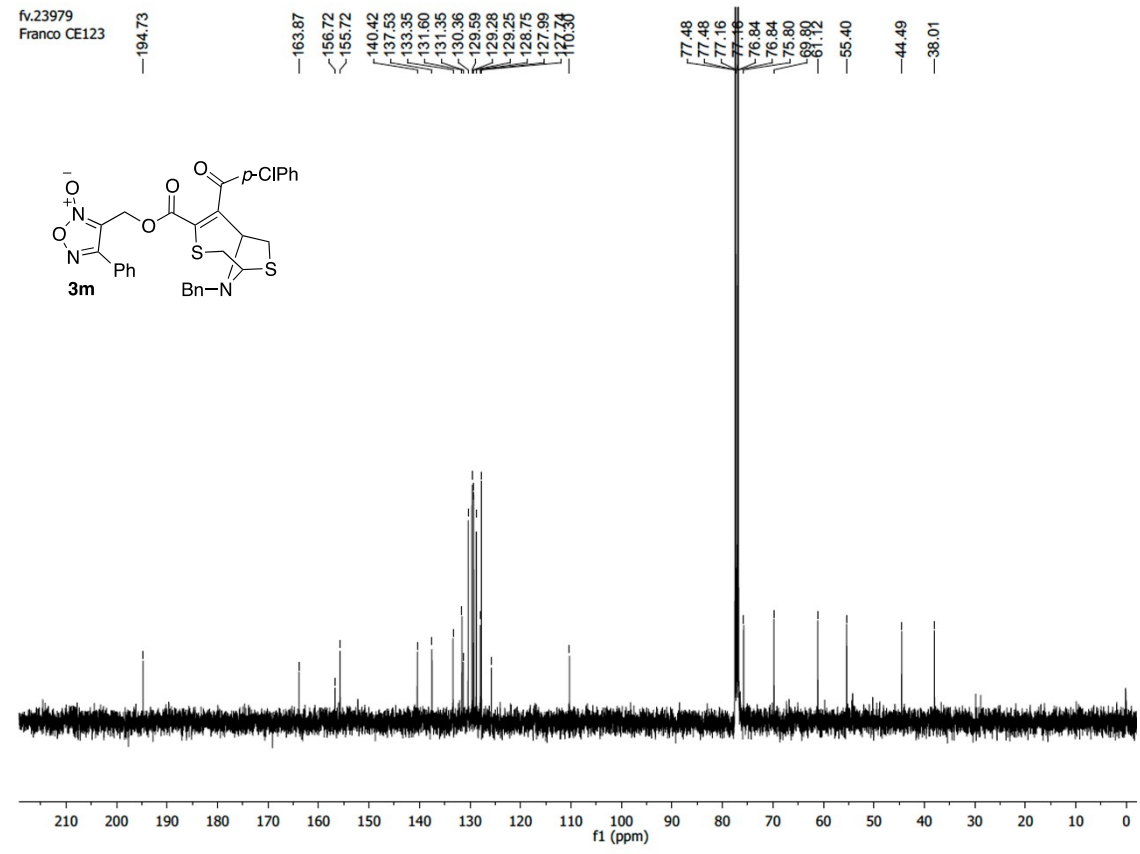
1.02
f1 (ppm)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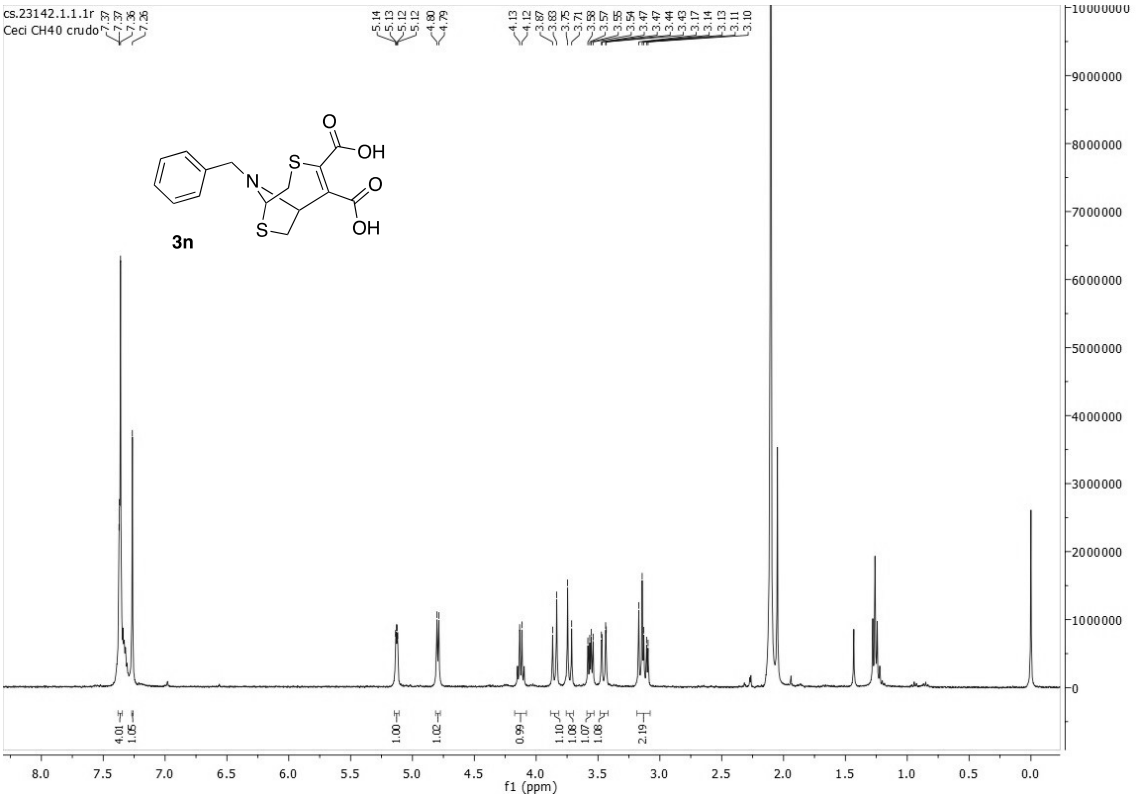
Bn–N
3m
f1 (ppm)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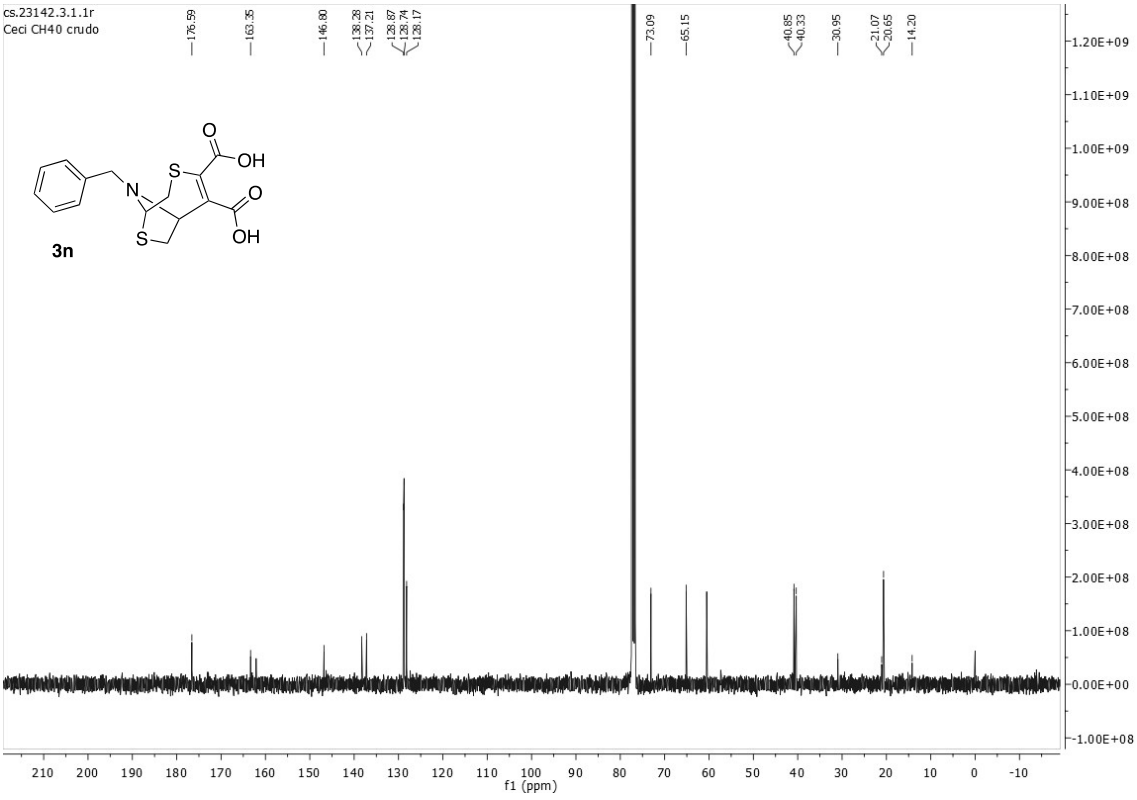
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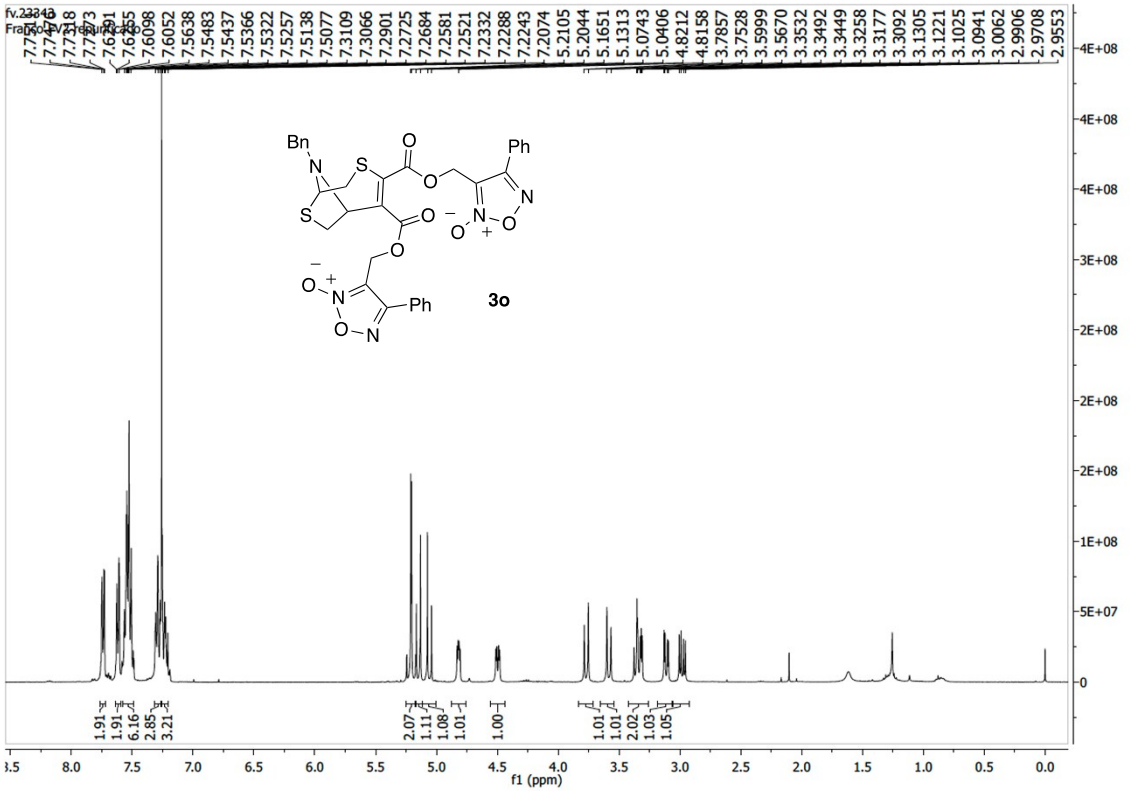
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N
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O
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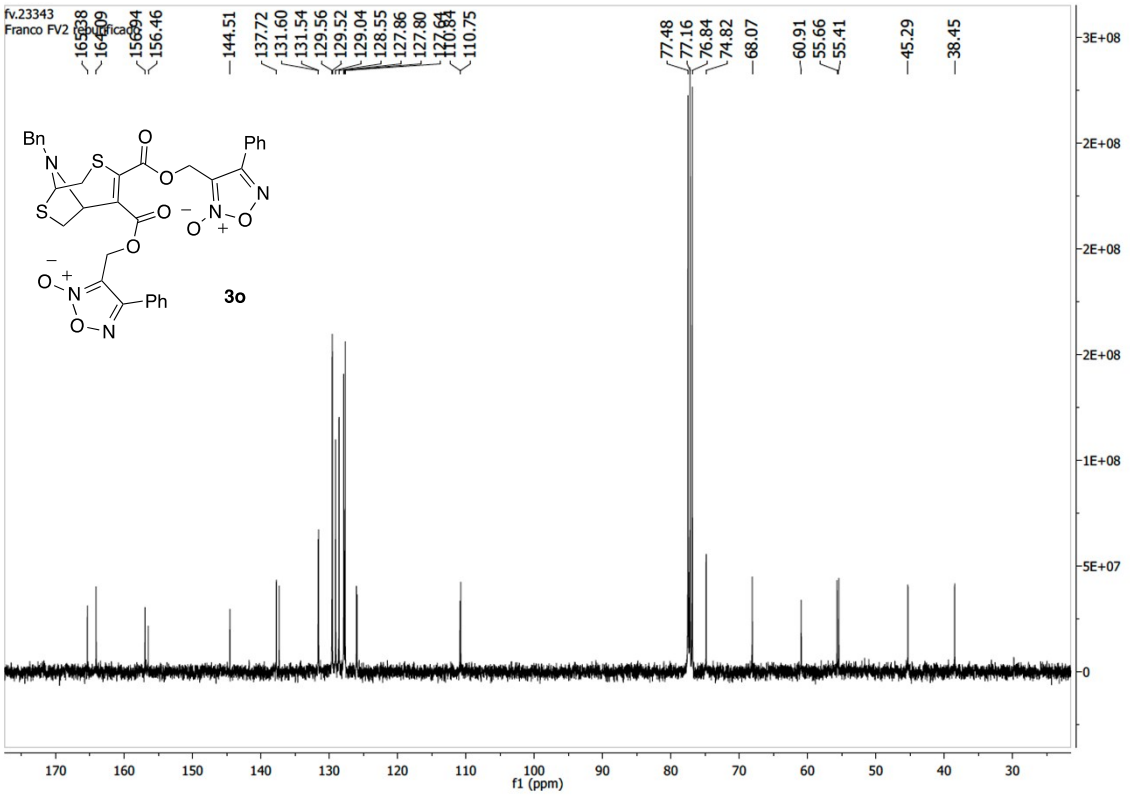
O
N
O
O
N
Ph
3o
f1 (ppm)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38.45
Bn
N
S
S
O
O
Ph
N
O
O
N
O
O
O
O
N
O
O
N
Ph
3o
f1 (ppm)

Crystallographic data

Table S1: Selected bond lengths (Å) and angles (º) for compound **3d**.

Cl(27)−C(14)	1.748(6)	O(26)−C(18)	1.222(6)	C(10)−C(11)	1.509(7)
S(3)−C(4)	1.748(5)	N(9)−C(1)	1.453(6)	C(11)−C(12)	1.382(7)
S(3)−C(2)	1.810(5)	N(9)−C(10)	1.466(6)	C(11)−C(16)	1.390(8)
S(8)−C(7)	1.818(6)	N(9)−C(6)	1.475(6)	C(12)−C(13)	1.402(8)
S(8)−C(1)	1.851(5)	C(1)−C(2)	1.500(7)	C(13)−C(14)	1.385(8)
O(19)−C(17)	1.334(7)	C(4)−C(5)	1.342(7)	C(14)−C(15)	1.387(8)
O(19)−C(20)	1.464(6)	C(4)−C(17)	1.519(7)	C(15)−C(16)	1.394(8)
O(22)−C(17)	1.198(7)	C(5)−C(18)	1.487(7)	C(20)−C(21)	1.499(8)
O(23)−C(18)	1.334(6)	C(5)−C(6)	1.527(7)	C(24)−C(25)	1.482(9)
O(23)−C(24)	1.459(6)	C(6)−C(7)	1.566(7)		

C(4)-S(3)-C(2)	103.5(2)	C(1)-C(2)-S(3)	118.5(4)	C(6)-C(7)-S(8)	107.7(4)
C(7)-S(8)-C(1)	90.8(2)	C(5)-C(4)-C(17)	125.6(5)	N(9)-C(10)-C(11)	114.0(4)
C(17)-O(19)-C(20)	116.1(4)	C(5)-C(4)-S(3)	126.0(4)	O(22)-C(17)-O(19)	125.7(5)
C(18)-O(23)-C(24)	117.3(4)	C(17)-C(4)-S(3)	108.3(3)	O(22)-C(17)-C(4)	122.7(5)
C(1)-N(9)-C(10)	112.0(4)	C(4)-C(5)-C(18)	122.0(5)	O(19)-C(17)-C(4)	111.1(4)
C(1)-N(9)-C(6)	108.3(4)	C(4)-C(5)-C(6)	124.4(5)	O(26)-C(18)-O(23)	123.2(5)
C(10)-N(9)-C(6)	111.5(4)	C(18)-C(5)-C(6)	113.6(4)	O(26)-C(18)-C(5)	122.9(5)
N(9)-C(1)-C(2)	114.1(4)	N(9)-C(6)-C(5)	112.1(4)	O(23)-C(18)-C(5)	113.9(4)
N(9)-C(1)-S(8)	106.4(3)	N(9)-C(6)-C(7)	109.8(4)	O(19)-C(20)-C(21)	111.4(4)
C(2)-C(1)-S(8)	111.4(4)	C(5)-C(6)-C(7)	113.5(4)		

X-ray structure determination

Single crystal of compound **3d** was mounted on nylon loop and placed in the cold nitrogen stream (100 K) inside a Bruker APEX DUO diffractometer equipped with an Apex II CCD detector using CuK_α (λ = 1.54178 Å) Incoatec IμS microsource and multilayer optic monochromator. Frames were collected using omega scans and integrated with SAINT.[7] Multi-scan absorption correction (SADABS) was applied.[6] The structures were solved by direct methods (SHELXT)[7] and refined using full-matrix least-squares on F^2 with SHELXL[8] within the ShelXle GUI.[9] Weighted R factors, wR, and all goodness-of-fit indicators are based on F^2. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms of the C–H bonds were placed in idealized positions and refined with U_{iso} tied to the parent atom. Compound **3d** crystallized as a non-merohedral twin with a –1 0 0 0 –1 0 0.588 0 1 twin law (180º rotation around the 0 0 –1 reciprocal axis). The proportion of the two domains refined to 0.624:0.376. The molecular graphic was prepared using GRETEP, POV-RAY, and GIMP.[10,10,11]

Table S2: Data collection and refinement details for compound **3d**

	3d
Molecular formula	$C_{19}H_{22}ClNO_4S_2$
M_r, g·mol^{-1}	427.94
Crystal system	monoclinic
Space group	$P2_1/n$
T, K	100(2)
λ, Å	1.54178
a, Å	6.2050(2)
b, Å	8.3180(2)
c, Å	38.4608(11)
α, deg	90
β, deg	92.7485(15)
γ, deg	90
V, Å^3	1982.8(1)
Z	4
D_c, g·cm^{-3}	1.434
$\mu(Cu_{K\alpha})$, mm^{-1}	3.892
$F(000)$	896
Crystal size, mm^3	0.205 x 0.105 x 0.069
θ range, deg	2.300 to 71.554
Refl. collected	3910
Unique reflns (R_{int})	3910 (0.0761)
Data / restr. / par.	3910 / 0 / 247
GoF on F^2	1.043
R_1,[a] wR_2[b] ($I > 2\sigma(I)$)	0.0678, 0.1762
R_1,[a] wR_2[b] (all data)	0.0706, 0.1783
Residuals, e·Å^{-3}	0.508 / −0.731
CCDC	1885443

[a] $R_1 = \sum||F_o|-|F_c||/\sum|F_o|$.[b] $wR_2 = [\sum w(F_o^2-F_c^2)^2/\sum(F_o^2)^2]^{1/2}$.

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[11] GIMP 2.8: The GNU Image Manipulation Program. http://www.gimp.org.