Electronic supplementary materials *Mendeleev Commun.*, 2019, **29**, 288–291

Synthesis of new pharmacologically oriented heterocyclic ensembles, [2-(1*H*-pyrazol-1-yl)thiazol-4-yl]furoxans

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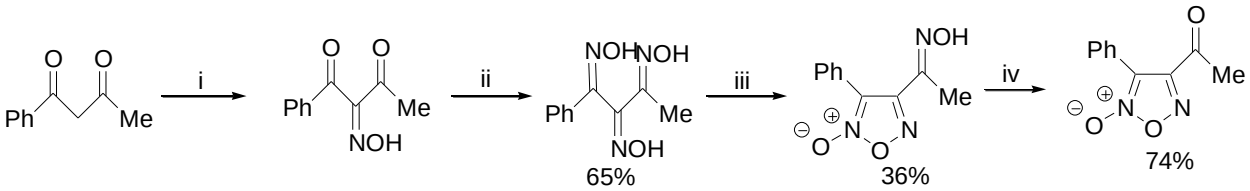
General remarks

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AM-300 (300.13, 75.47 and 282.40 MHz respectively) spectrometer and referenced to residual solvent peak. The chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz. The IR spectra were recorded on a Bruker "Alpha" spectrometer in the range 400-4000 cm^{-1} (resolution 2 cm^{-1}) as pellets with KBr or as a thin layer. The melting points were determined on Stuart SMP20 apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was carried out on Merck 25 TLC silica gel 60 F_{254} aluminum sheets. The visualization of the TLC plates was accomplished with a UV light. High resolution mass spectra were recorded on a Bruker microTOF spectrometer with electrospray ionization (ESI). Elemental analysis was performed by the CHN Analyzer Perkin–Elmer 2400. 4-(2-Hydrazinylthiazol-4-yl)-3-methylfuroxan, 4-amino-3-(2-hydrazinylthiazol-4-yl)furoxan and 3-(2-hydrazinylthiazol-4-yl)-4-(1-pyrrolyl)furoxan hydrobromides **1a-c** were prepared according to the published procedure.[S1]

Synthetic procedures and characteristics of compounds

Synthesis of 4-acetyl-3-phenylfuroxan



Scheme S1 Reagents and conditions: i. $NaNO_2$, AcOH, H_2O, 10 °C; ii. $AcONa{\cdot}3H_2O$, $NH_2OH{\cdot}HCl$, H_2O, 80 °C, 20 h; iii. N_2O_4, ether, 0 °C; iv. HCl/H_2O(1:1 v/v), 100 C, 40 min.

Step 1. *1-Phenylbutane-1,3-dione 2-oxime.* A solution of $NaNO_2$ (18.0 g ,0.26 mol) in water (50 ml) was added dropwise to the solution of benzoylacetone (32.4 g, 0.2 mol) in AcOH (200 mL) at ≤ 10 °C. The reaction mixture was stirred for 1 h at 5 °C and then 1 h at 20 °C. Then water was added to volume 1000 ml, the solid formed was filtered off, washed with water and dried in air. Yield: 35.9 g (94%), white solid, mp. 128 °C, R_f 0.26 ($CHCl_3$). The spectral characteristics of compound **11** were similar to those published previously.[S2]

Step 2. *1-Phenylbutane-1,2,3-trione trioxime.* Solid AcONa $3H_2O$ (95.2 g, 0.7 mol) and $NH_2OH{\cdot}HCl$ (48.7 g, 0.7 mol) were added to a suspension of 1-phenylbutane-1,3-dione 2-oxime (38.2 g, 0.2 mol) in water (500 ml). The reaction mixture was stirred for 20 h at 80 °C (TLC control), cooled to 20 °C, the precipitate was filtered off, washed with water and dried in air. White solid, yield 28.7 g (65%), mp 204-205 °C (dec.), R_f 0.65 ($CHCl_3$-EtOAc, 1:1). IR (KBr): 3243, 1437, 1118, 983, 939, 906, 689 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.07 (s, 3H), 7.31-7.40 (m, 3H), 7.41-7.48 (m, 2H), 11.24 (s, 1H), 11.50 (s, 1H), 11.59 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 9.6, 125.5, 128.5, 128.8, 133.5, 150.2, 150.8, 151.2. Calc. for $C_{10}H_{11}N_3O_3$: C, 54.29, H 5.01, N, 19.00%. Found: C, 54.70, H 5.16, N, 18.89%.

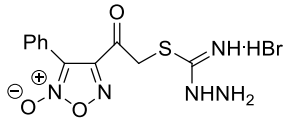
Step 3. *4-Acetyl-3-phenylfuroxan oxime.* Nitrogen tetroxide N_2O_4 (11.0 g, 120 mmol) was added dropwise to a suspension of 1-phenylbutane-1,2,3-trione trioxime (11.0 g, 50 mmol) in Et_2O (150 ml) at 0-2 °C. The red-brown solution formed was stirred for 1 h at 20 °C, washed with 10% aqueous Na_2CO_3, then with water, and Et_2O was evaporated. The oily residue was stirred with 5% NaOH (70 ml), filtered and acidified with conc. HCl to pH 6. The precipitate formed was filtered off, washed with water, dried in air and crystallized from benzene-hexane (1:1) mixture. Yellowish solid, yield 4.02 g (36%), mp 135 °C (dec.), R_f 0.77 ($CHCl_3$). IR (KBr): 3292, 1593, 1508, 1445, 1371, 1118, 976, 923, 829, 773, 665 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.21 (s, 3H), 7.49-7.55 (m, 3H), 7.59-7.65 (m, 2H), 12.11 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 11.9, 114.3, 124.1, 128.9, 130.1, 145.9, 154.9. Calc. for $C_{10}H_9N_3O_3$: C, 54.79, H 4.14, N, 19.17%. Found: C, 54.44, H 4.01, N, 19.48%.

Step 4. *4-Acetyl-3-phenylfuroxan***.** A suspension of 4-acetyl-3-phenylfuroxan oxime **13** (4.4 g, 20 mmol) in a 1:1 mixture of HCl:H_2O (40 ml) was refluxed for 1 h. After cooling to 20 °C the precipitate formed was filtered off, washed with water, dried in air and crystallized from EtOH:H_2O (1:1). Yellowish solid, yield 3.10 g (74%), mp 85 °C (dec.), R_f 0.55 ($CHCl_3$-CCl_4, 1:2). IR (KBr): 3411, 1717, 1590, 1472, 1360, 1185, 1118, 947, 832, 775, 693, 605 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.67 (s, 3H), 7.51-7.59 (m, 3H), 7.67-7.74 (m, 2H). ^{13}C NMR

(75.5 MHz, DMSO-d_6) δ: 27.4, 113.1, 123.3, 128.3, 129.5, 130.6, 154.2, 189.6. Calc. for $C_{10}H_8N_2O_3$: C, 58.82, H 3.95, N, 13.72%. Found: C, 58.64, H 3.88, N, 13.85%.

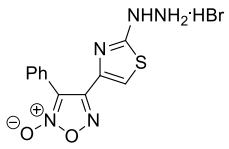
Step 5. *4-Bromoacetyl-3-phenylfuroxan***.** Bromine (3.20 g, 20 mmol) was added to a suspension of 4-acetyl-3-phenylfuroxan (4.08 g, 20 mmol) in a mixture of AcOH (6 ml) and 47% HBr (12 ml). The reaction mixture was stirred at 50-55 °C for ~ 1.5 h (TLC control), diluted with water (50 ml), the precipitate formed was filtered off, washed with water and with a little amount of EtOH and dried in air. Cream solid, yield 4.41 g (74%), mp 97-98 °C (dec.), R_f 0.46 (CCl_4). IR (KBr): 3441, 2946, 1730, 1590, 1467, 1008, 950, 778, 693, 641 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.63 (s, 2H), 7.47-7.58 (m, 3H), 7.64-7.75 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 30.9, 112.6, 121.0, 128.8, 129.0, 131.3, 151.6, 183.3. Calc. for $C_{10}H_7BrN_2O_3$: C, 42.43, H 2.49, N, 9.90%. Found: C, 42.59, H 2.35, N, 10.02%.

Step 6. *4-{2-[(Hydrazinyl)(imino)methyl]thio}acetyl-3-phenylfuroxan hydrobromide* **2b**.



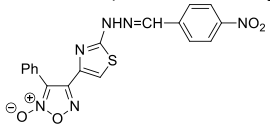
A suspension of 4-bromoacetyl-3-phenylfuroxan (1.7 g, 6 mmol) and thiosemicarbazide (0.54 g, 6 mmol) in MeCN (30 ml) was stirred at room temperature for 12 h, washed with water and dried in air. Yellow solid, yield 2.00 g (89%), mp 162-163 °C (dec.), IR (KBr): 3125, 2963, 2806, 1707, 1685, 1609, 1539, 1509, 1212, 1146, 801, 667 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.69 (d, 1H, ^2J 12.7 Hz,), 3.99 (d, 1H, ^2J 12.7 Hz), 5.35 (br s, 2H), 7.47-7.60 (m, 3H), 7.61-7.70 (m, 2H), 8.52 (s, 1H), 9.52 (s, 1H), 10.13 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 36.8, 92.2, 115.0, 122.1, 128.7, 128.9, 130.8, 156.1, 169.5. Calc. for $C_{11}H_{12}BrN_5O_3S$: C, 35.31, H 3.23, N, 18.71%. Found: C, 35.45, H 3.17, N, 18.84%.

Step 7. *4-(2-Hydrazinylthiazol-4-yl)-3-phenylfuroxan hydrobromide* **1b**.



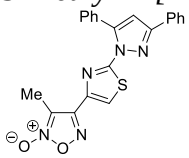
A suspension of compound **2b** in AcOH (20 ml) was stirred at 80 °C for 7 h. The reaction mixture was cooled to room temperature, the precipitate was filtered off, washed with AcOH and dried in air. White solid, yield 1.60 g (90%), mp 208-209 °C, IR (KBr): 3350, 3119, 1667, 1586, 1483, 1264, 1200, 1113, 984, 926, 843, 783, 709 cm^{-1}; Calc. for $C_{11}H_{10}BrN_5O_2S$: C 37.07, H 2.83, N, 19.66 %. Found: C 37.20, H 2.94, N, 19.49 %. The product was characterized as hydrazone of 4-nitrobenzaldehyde.

4-{2-[2-(4-Nitrobenzylidene)hydrazinyl]thiazol-4-yl}-3-phenylfuroxan



4-Nitrobenzaldehyde (0.151 g, 1 mmol) was added to a solution of compound **1b** (0.356 g, 1 mmol) in DMSO (2 ml), and the mixture was stirred for 12 h at room temperature. The precipitate formed was filtered off, washed with EtOH and dried in air. Yellow-orange solid, yield 0.36 g (88%), mp 218-219 °C, R_f 0.32 ($CHCl_3$). IR (KBr) cm^{-1}: 2962, 2876, 1734, 1585, 1565, 1508, 1459, 1334, 1140, 1029, 840, 805; ^{1}H NMR (300 MHz, DMSO-d_6) 7.33 (s, 1H), 7.49-7.61 (m. 3H), 7.62-7.72 (m, 2H), 7.84 (d, 2H, ^3J 7.8 Hz), 8.09 (s, 1H), 8.26 (d, 2H, ^3J 7.8 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 113.1, 114.0, 122.9, 123.7, 124.1, 127.1, 128.5, 129.0, 130.8, 137.7, 140.1, 148.0, 151.4, 169.2. HRMS (ESI) m/z for $C_{18}H_{13}N_6O_4S$ $(M+H)^+$: calc.409.0722, found: 409.0728.

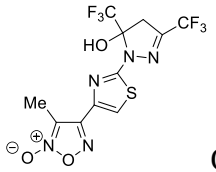
3-Methyl-4-[2-(3,5-diphenyl-1H-pyrazol-1-yl)thiazol-4-yl]furoxan **4b**.



Cream solid, yield 0.33 g (82%), mp 212-213 °C, R_f 0.49 ($CHCl_3$). IR (KBr): 3085, 1602, 1557, 1528, 1470, 1363, 1179, 1037, 951, 823, 763, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.67 (s, 3H), 6.80 (s, 1H), 7.84 (s, 1H), 7.93 (s, 1H), 7.95 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 9.3, 110.0, 113.6, 118.2, 127.3, 129.4, 130.0, 130.2, 130.3, 130.6, 131.5, 132.5, 132.6, 140.8, 146.6, 152.6, 155.1. HRMS (ESI) m/z for $C_{21}H_{16}N_5O_2S$ $(M+H)^+$: calc.402.1019, found: 402.1010.

4-[2-(5-Hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl]-3-methylfuroxan **4'c**.

The mixture of compounds **1a** (0.1 mmol) and **3a** (2 mmol) in EtOH (6 ml) in the presence of conc. H_2SO_4 (0.35 equiv) was refluxed for 5 h. The reaction mixture was cooled to room temperature, poured into water (10 ml), the formed precipitate was filtered, washed with water and EtOH (1 ml) and dried in air.

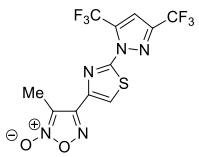


Cream solid, yield 0.17 g (65%), mp 179-180 °C, R_f 0.11 ($CHCl_3$-CCl_4, 1:1). IR (KBr): 3377, 1600, 1572, 1478, 1410, 1268, 1199, 1143, 1085, 1012, 807 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.36 (s, 3H), 3.56 (d, 1H, ^2J 19.5 Hz), 4.04 (d, 1H, ^2J 19.5 Hz), 8.04 (s, 1H, CH), 8.97 (s, 1H, OH). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 8.5, 42.4, 94.6 (q, ^1J 34.2 Hz), 112.6, 116.4, 120.8 (d, ^2J 42.5 Hz), 124,3, 138.5, 142.5 (q, ^1J 39.4 Hz), 152.3, 163.0. ^{19}F NMR (282.4 MHz, DMSO-d_6) δ: -78.0 (s, CF_3), -66.3 (s, CF_3). HRMS (ESI) m/z for $C_{11}H_8F_6N_5O_3S$ $(M+H)^+$: calc. 404.0243, found: 404.0247.

4-[2-(3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl)thiazol-4-yl]-3-methylfuroxan **4c**.

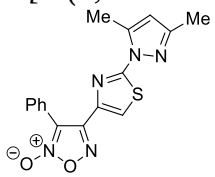
The compound **4c** was prepared by two methods.

1) In addition to the general method (see paper, page 2): the reaction mixture of compounds **1a** and **3a** was refluxed for 11 h (yield 86%).
2) Conc. H_2SO_4 (1 mmol) was added to a suspension of compound **4'c** (0.4 g, 1 mmol) in AcOH (4 ml), the reaction mixture was heated at 80 °C for 5 h, cooled to room temperature, poured into water (10 ml), the precipitate formed was filtered off, washed with water and *i*PrOH and dried in air (yield 81%).



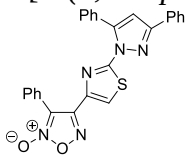
White solid, yield 0.33 g (86%), mp 159-160 °C, R_f 0.42 ($CHCl_3$-CCl_4, 1:1). IR (KBr): 3375, 1601, 1572, 1529, 1478, 1410, 1268, 1199, 1143, 1085, 1012, 876, 807 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.35 (s, 3H), 8.03 (s, 1H), 8.52 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 8.4, 111.5, 112.3, 117.3 (d, ^2J 102 Hz), 120.9 (d, ^2J 102 Hz), 122.8, 132.7 (q, ^1J 43 Hz), 138.9, 143.3 (q, ^1J 40 Hz), 151.7, 159.1. ^{19}F NMR (282.4 MHz, DMSO-d_6) δ_F: -62.6 (s, CF_3), -59.7 (s, CF_3). HRMS (ESI) m/z for $C_{11}H_6F_6N_5O_2S$ $(M+H)^+$: calc.386.0154 found: 386.0147.

4-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)thiazol-4-yl]-3-phenylfuroxan **4d**



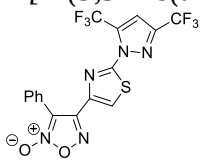
Cream solid, yield 0.22 g (65%), mp 181-182 °C, R_f 0.58 ($CHCl_3$). IR (KBr): 3128, 1594, 1576,1553, 1473, 1377, 1140, 1024, 969, 801, 775, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.18 (s, 3H), 2.27 (s, 3H), 5.94 (s, 1H), 7.40-7.54 (m, 3H), 7.56-7.74 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.0, 13.6, 110.1, 114.5, 117.8, 123.1, 128.8 129.3, 130.5, 139.2, 142.1, 151.6, 152.4, 163.1. HRMS (ESI) Calcd for $C_{16}H_{14}N_5O_2S$ $(M+H)^+$: 340.0869; Found: 340.0877.

4-[2-(3,5-Diphenyl-1H-pyrazol-1-yl)thiazol-4-yl]-3-phenylfuroxan **3e**



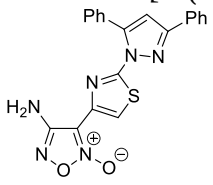
Cream solid, yield 0.39 g (84%), mp 182-183 °C, R_f 0.30 ($CHCl_3$-CCl_4 = 1:1). IR (KBr): 3113, 3060, 1585, 1557, 1524, 1469, 1356, 1031, 952, 803, 755, 685 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 7.19-7.24 (m, 3H, Ar), 7.32-7.36 (m, 1H, Ar), 7.43-7.50 (m, 12H, Ar), 7.95 (d, 2H, ^3J 7.3 Hz), 8.03 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 108.9, 114.2, 122.1, 122.4, 125.9, 127.8, 128.8, 128.9, 129.0, 129.1, 129.2, 129.4, 130.7, 131.0, 137.7, 145.7, 151.7, 153.2, 161.9; HRMS (ESI) Calcd for $C_{26}H_{18}N_5O_2S$ $(M+H)^+$: 464.1203; Found: 464.1212.

4-[2-(3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl)thiazol-4-yl]-3-phenylfuroxan **3f**



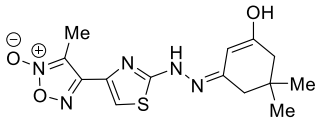
Cream solid, yield 0.42 g (94%), mp 110-111 °C (acetone), R_f 0.49 ($CHCl_3$-CCl_4, 1:1). IR (KBr): 3119, 1598, 1471, 1390, 1297, 1252, 1230, 1169, 1120, 1031, 965, 801; ^1H NMR (300 MHz, DMSO-d_6) δ_H: 7.42-7.56 (m, 3H), 7.59-7.69 (m, 2H), 7.93 (s, 1H), 8.20 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 111.0, 114.3, 116.2, 119.8, 122.1, 124.8, 128.8, 128.9, 130.6, 132.9 (q, ^1J 42.7 Hz), 138.3, 143.2 (q, ^1J 39.7 Hz), 151.3, 158.9. ^{19}F NMR (282.4 MHz, DMSO-d_6) δ: -62.6 (s, CF_3), -59.7 (s, CF_3). HRMS (ESI) Calcd for $C_{16}H_8F_6N_5O_2S$ $(M+H)^+$: 448.0326; Found: 448.0333.

4-Amino-3-[2-(3,5-diphenyl-1H-pyrazol-1-yl)thiazol-4-yl]furoxan **5**.



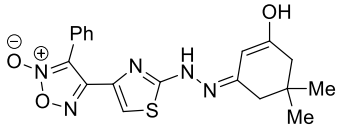
Brown solid, yield 0.28 g (70%), mp 259-260 °C, R_f 0.53 ($CHCl_3$). IR (KBr): 3414, 3315, 1625, 1561, 1540, 1459, 1375, 1179, 950, 761, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.53 (br s, 2H), 7.28 (s, 1H), 7.40-7.55 (m, 6H, Ar), 7.58-7.57 (m, 2H, Ar), 7.98 (d, 2H, ^3J 7.24 Hz), 8.27 (s, 1H). ^{13}C NMR spectrum was not registered due to very low solubility of this compound in common solvents. HRMS (ESI) Calcd for $C_{20}H_{15}N_6O_2S$ $(M+H)^+$: 403.0972; Found: 403.0978.

4-{2-[2-(3-Hydroxy-5,5-dimethylcyclohex-2-enylidene)hydrazinyl]thiazol-4-yl}-3-methylfuroxan **6a**



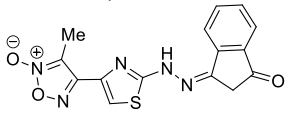
Cream solid, yield 0.25 g (75%), mp 136-137 °C, R_f 0.42 (EtOAc); IR (KBr): 3170, 1590, 1511, 1325, 1262, 1120, 1103, 822 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.02 (s, 6H), 2.05 (s, 2H), 2.17 (s, 2H), 2.36 (s, 3H), 5.01 (s, 1H), 7.35 (s, 1H), 9.28 (br s, 1H, OH), 10.12 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 9.0, 28.0, 33.0, 50.5, 95.4, 112.7, 113.6, 136.9, 152.1, 164.2, 173.2; HRMS (ESI) Calcd for $C_{14}H_{18}N_5O_3S$ $(M+H)^+$: calc. 336.1125, Found: 336.1118.

4-{2-[2-(3-Hydroxy-5,5-dimethylcyclohex-2-enylidene)hydrazinyl]thiazol-4-yl}-3-phenylfuroxan **6b**



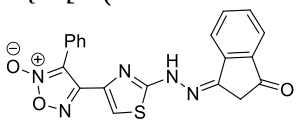
Cream solid, yield 0.25 g (74%), mp 155-156 °C, R_f 0.34 (EtOAc); IR (KBr): 3188, 1585, 1507, 1371, 1248, 1142, 1112, 807, 691 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.00 (s, 6H), 2.04 (s, 2H), 2.19 (s, 2H), 5.04 (s, 1H)), 7.16 (s, 1H), 7.52-7.58 (m, 3H), 7.60-7.67 (m, 2H), 9.23 (br s, 1H, OH), 9.93 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 28.2, 33.2, 50.9, 96.0, 113.4, 114.7, 123.1, 129.3, 129.4, 131.2, 138.0, 152.5, 163.0, 173.5; HRMS (ESI) m/z for $C_{19}H_{20}N_5O_3S$ $(M+H)^+$: calc. 398.1290; Found: 398.1296.

4-{2-[2-(3-Oxoindan-1-ylidene)hydrazinyl]thiazol-4-yl}-3-methylfuroxan **6c**.



Brown solid, yield 0.24 g (75%), mp 260-261 ºC, R_f 0.12 ($CHCl_3$); IR (KBr): 2960, 1679, 1585, 1507, 1443, 1249, 1142, 807, 691 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.34 (s, 3H), 3.52 (s, 2H), 7.56-7.97 (m, 4H), 7.68 (s, 1H), 11.85 (br s 1H, NH). ^{13}C NMR spectrum was not registered due to very low solubility of this compound in common solvents. HRMS (ESI) m/z for $C_{15}H_{11}N_5O_3S$ $(M+H)^+$: 342.0655; Found: 342.0662.

4-{2-[2-(3-Oxoindan-1-ylidene)hydrazinyl]thiazol-4-yl}-3-phenylfuroxan **6d**



Yellow-brown solid, yield 0.28 g (70%), mp 231-232 °C; IR (KBr): 3569, 3483, 1717, 1569, 1545, 1471, 1266, 1264, 1136, 1027, 801, 764 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.45 (s, 2H), 7.24 (m, 1H), 7.51-7.98 (m, 9H), 11.85 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 39.4, 114.4, 114.7, 121.6, 123.1, 123.5, 129.5, 131.2, 136.0, 138.0, 138.3, 146.6, 146.7, 152.7, 170.4, 198.8. HRMS (ESI) m/z for $C_{20}H_{14}N_5O_3S$ $(M+H)^+$: calc. 404.0821, found: 404.0826.

Compound 4f: crystal structure determination, DFT calculations and QTAIM analysis

The X-ray diffraction study of the crystal of **4f** was performed using the Bruker Apex II Duo CCD diffractometer (MoKα-radiation, graphite monochromator, w-scans). All refinement details are given in the Table S1. All calculations were performed using the SHELX software.[S3]

Table S1. The main crystal data and refinement details of the **4f** structure.

Formula	$C_{16}H_7F_6N_5O_2S$
Mass	447.33
T, K	120
Crystal system	Monoclinic
Space group	C2/c
Z	8
a, Å	20.6989(15)
b, Å--	14.7854(11)
c, Å	13.9162(10)
α, °	90
β, °	123.6480(10)
γ, °	90
V, $Å^3$	3545.4(4)
d_{calc}, $g·cm^{-3}$	1.676
μ, cm^{-1}	2.69
F(000)	1792
$2\theta_{max}$, °	50
Reflns measured	32152
Independent reflns	4278
Reflns with I>2σ(I)	3403
Number of parameters	281
R_1	0.0434
wR_2	0.1248
GOF	1.041
Residual electron density, $e·Å^{-3}$ (d_{min}/d_{max})	0.747/-0.493

In crystal, the molecular structure of **4f** (Figure S1) corresponds to a compact conformation with the C(7)C(6)C(1)C(2), C(1)C(2)C(3)N(3) and S(1)C(5)N(4)N(5) torsion angles equal to 46.0(3)°, 28.2(3)° and 10.3(2)°, respectively. It implies that the π-conjugation between phenyl, furoxanyl and thiazolyl rings is violated, whereas a strong π-conjugation

persists between the thiazolyl and pyrazolyl cycles. The PBE0-D3/6-311++G(d,p) geometry optimization[4] were performed for **3f** both in the isolated state and with the accounting on non-specific solvation effects (ε=78.3553). While no significant influence of crystal media on the conformation was observed (the weighted r.m.s. deviation is less than 0.23 Å, Figure S2), the QTAIM analysis of the isolated state has revealed that the conformation can be additionally stabilized by a number of intramolecular non-covalent interactions such as F(1)…N(3), F(2)…N(3), F(1)…C(7), N(3)…C(7), O(1)…H-C(11) (Figure S3). The binding nature of the F…N interactions between electronegative atoms is also confirmed 1) by the negative sign of corresponding IQA interaction energies (B3LYP/6-311++G(d,p)[S4] and 2) by smaller mean-square displacement amplitudes of the F(1) and F(2) atoms in crystal with respect to fluorine atoms of the another, disordered CF_3 group (Figure S4). Note, that the energy of the intramolecular non-covalent interactions, estimated by the electron density-based correlation,[S5] is larger on 1.5 kcal mol^{-1} than that in an another less stable conformer of **3f** with the S(1)C(5)N(4)N(5) torsion angle equals to 105° (Figure S5). As the conformer's total energies differs on 3.0 kcal/mol (and on 3.6 kcal mol^{-1} accounting on the zero-point vibrational energies) in favor of the conformer observed in crystal, this non-covalent binding, hence, contributes significantly into the stabilization of the **3f** conformation. The other stabilization effects could be stereoelectronic interactions and the π-conjugation itself; corresponding details are given in the Supporting Information. The NBO analysis[S7] of the isolated **4f** demonstrated no significant anomeric effects involving lone electronic pairs of the sulfur atom and pyridine-type nitrogen atoms (all less 0.7 kcal mol^{-1}). While the conjugation between phenyl and furoxanyl rings has been known to be significantly dependent on the furoxanyl substituent nature,[S8] the conjugation within the thiazolyl-furoxanyl fragments has not been studied so far neither structurally nor theoretically. According to the CSD search, the S(1)C(5)N(4)N(5) torsion angle in pyrazolyl-thiazolyl fragments, in its turn, varies from 0.6° to 36° in organic structures and from 174° to 180° in metal complexes where the pyrazolyl-thiazoles are chelating ligands owing to coordination bonds formed by pyridine-type nitrogen atoms of both cycles. Two model compounds (both in two stable planar conformations, Figures S6,S7) were calculated (B3LYP/6-311++G(d,p)) to study π-conjugation and possible non-bonded interactions stabilizing the structure of thiazolyl-furoxanyl and pyrazolyl-thiazolyl fragments.[S9] The conformers with the cis-arrangement of pyridine-type nitrogen atoms (hereafter, cis-conformers, Figures S6a and S7a) were found to be less stable in both cases. Both in thiazolyl-furoxan and pyrazolyl-thiazole, the largest difference in the IQA atomic energy between conformers corresponds to the atoms neighboring to the bond between two heterocycles (up to 8 kcal mol^{-1}), though the atoms involved directly in this bond are also significantly more stable (up to 2.6 kcal mol^{-1}) in the trans-conformers (Figures S6b and S7b) that indicates on more pronounced π-conjugation between cycles. In cis-conformers, the IQA partitioning has revealed the positive interatomic interaction energies between the pyridine-type nitrogen atoms. Besides the absence of this steric repulsion between lone pairs of nitrogen atoms, the trans-conformers are also more stable due to the sound stabilizing 1-4 interactions. Namely, in the pyrazolyl-thiazole there is a binding interaction between the sulfur atom of thiazole and the pyridine-type nitrogen atom of pyrazolyl ring, whereas in the thiazolyl-furoxan there is binding 1-4 interaction between the pyridine-type nitrogen atoms and the hydrogen atoms. Noteworthy, these interactions are not observed within the conventional QTAIM method, however, the NCI-RDG[S10] approach allows to visualize them as weakly bounding ones (for instance, see Figure S8).

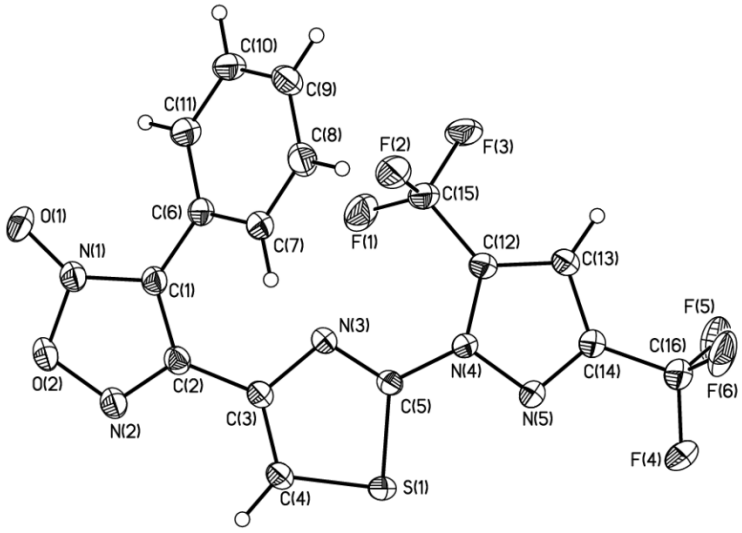


Figure S1. The general view of the **4f** molecule. Atoms are represented by probability ellipsoids of atomic vibrations (ρ=50%).

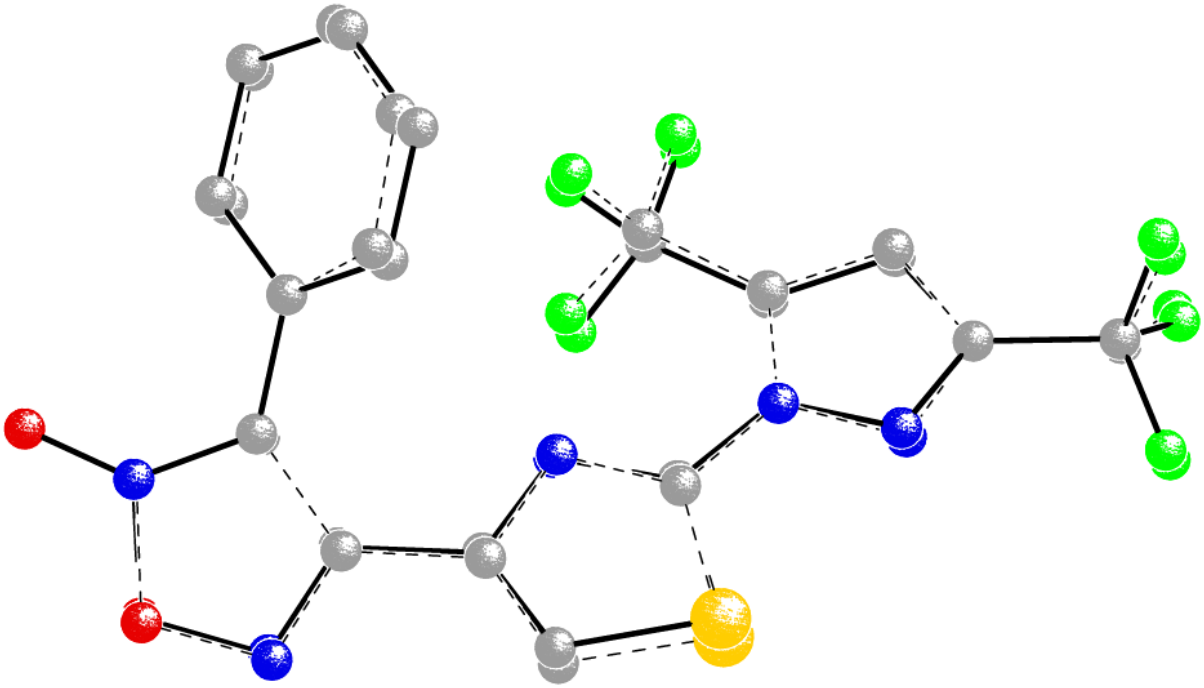


Figure S2. The structural deviation of the calculated isolated molecule of **4f** with its crystal structure.

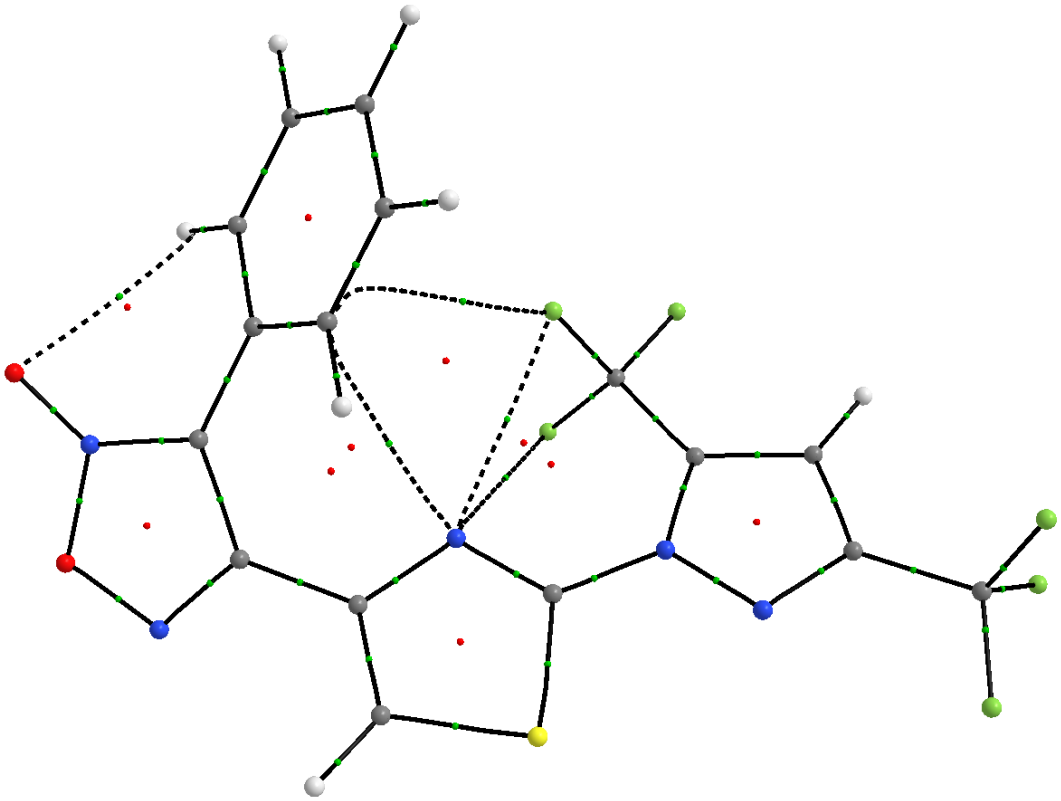


Figure S3. Atomic connectivity graph of the isolated molecule **4f** basing on the electron density topological analysis. The small green circle denote (3,-1) critical points; red ones – (3,+1) critical points. Weak non-covalent interactions are shown by dashed lines (bond paths).

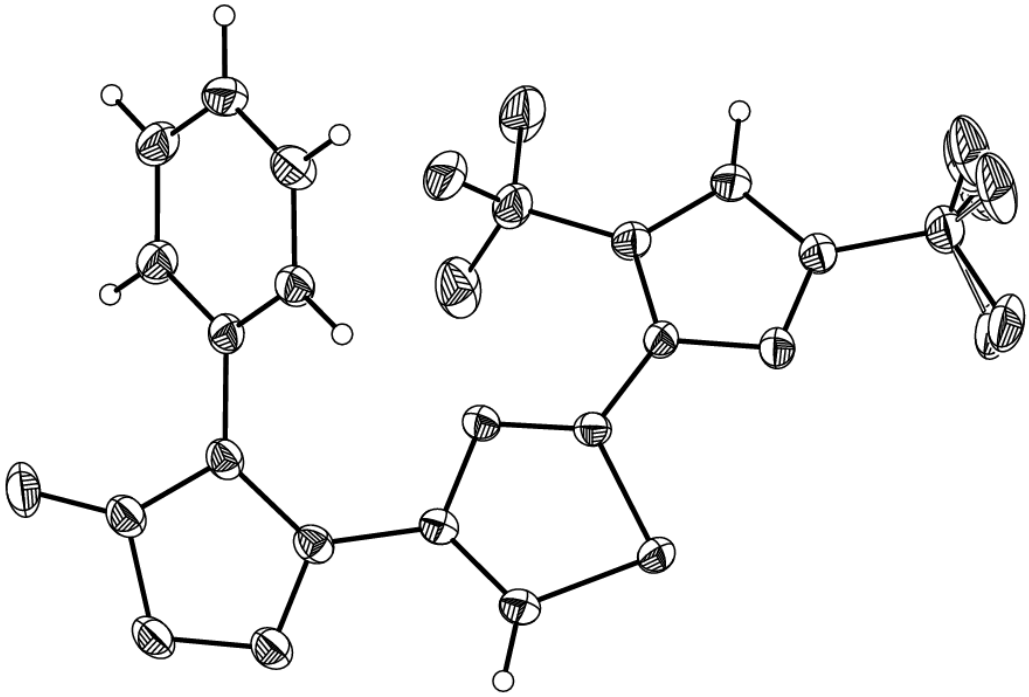


Figure S4. The molecular structure of **4f** in crystal with the view of the disordered CF_3 group (probability ellipsoids at the 0.5 level).

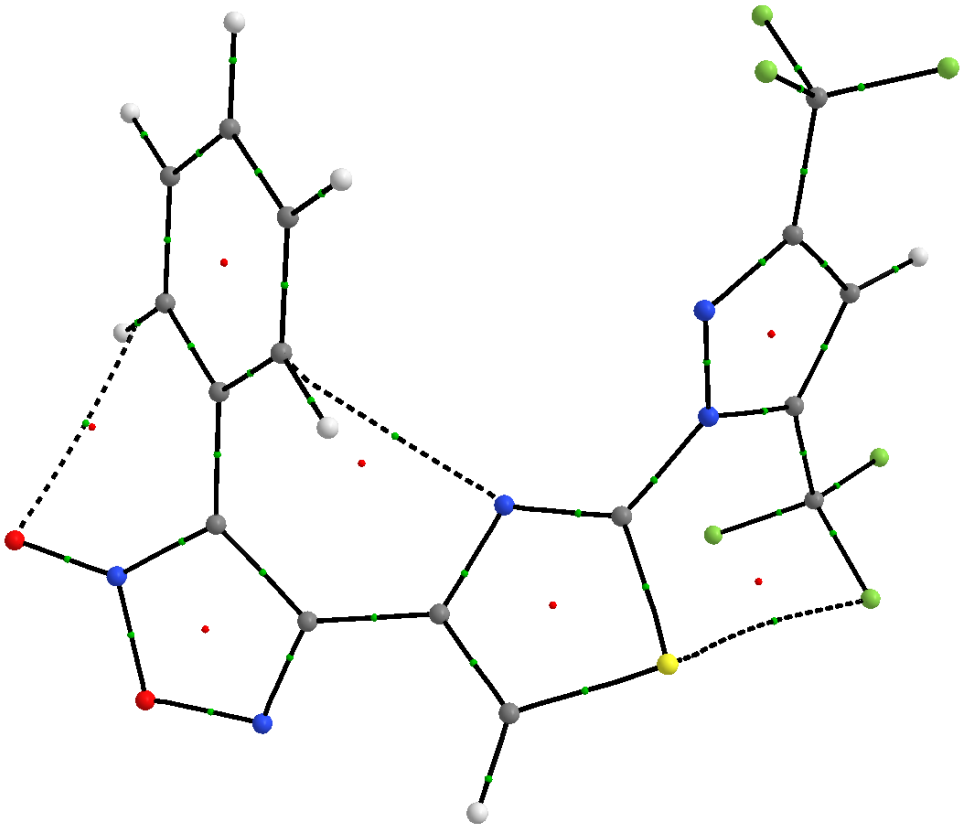
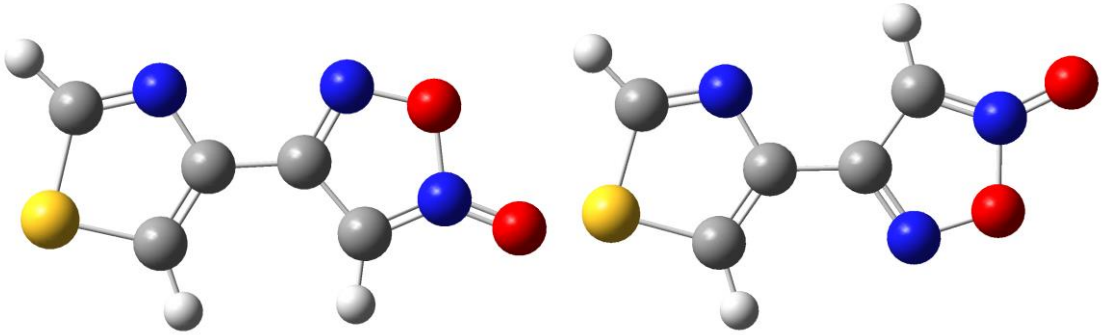


Figure S5. Atomic connectivity graph of the isolated molecule **4f** (less stable conformer with the S(1)C(5)N(4)N(5) torsion angle equals to 105°) basing on the electron density topological analysis. The small green circle denote (3,-1) critical points; red ones – (3,+1) critical points. Weak non-covalent interactions are shown by dashed lines (bond paths).



a b

Figure S6. The model thiazolyl-furoxan in cis (a) and trans (b) conformations. The NCCN torsion angle is equal to 3.53° and 179.97° for a and b, respectively.

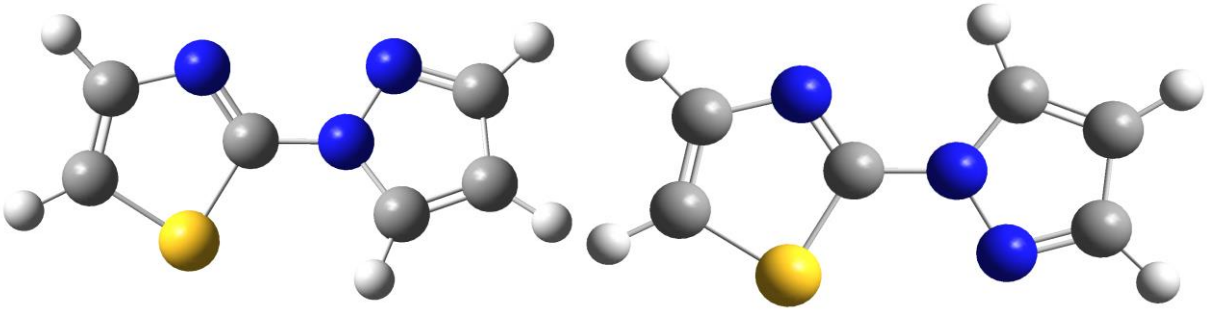


Figure S7. The model pyrazolyl-thiazol in cis (a) and trans (b) conformations. The NCCN torsion angle is equal to 25.64° and 179.99° for a and b, respectively.

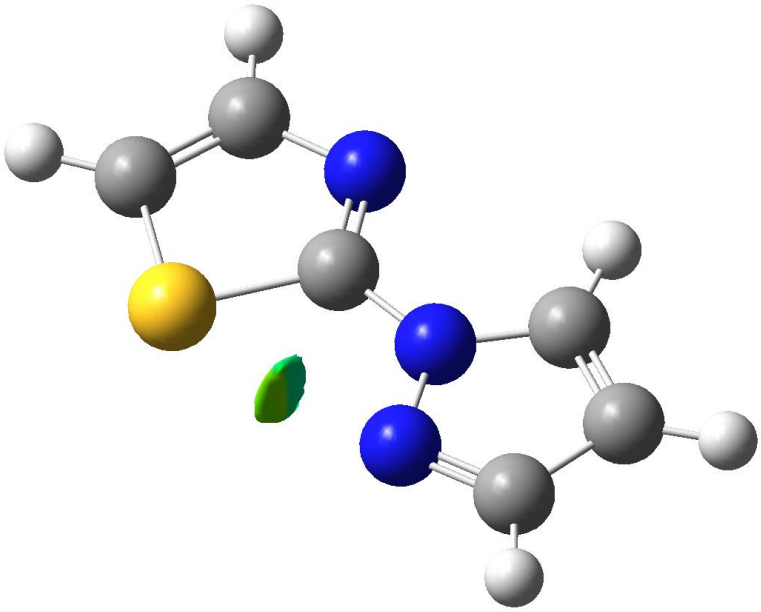


Figure S8. The isosurface of reduced density gradient (0.5) colored by the sign(λ_2)·ρ(r) function (ρ(r) – electron density, λ_2 – intermediate eigenvalue of the electron density Hessian matrix) in the region between sulphur and nitrogen atoms in the trans-conformer of model pyrazolyl-thiazole. The pronouncedly green color denotes the absence of strong repulsion between these atoms and indicates on weak Van der Waals interaction between them.

References

[S1] A. S. Kulikov, M. A. Epishina, A. I. Churakov, L. V. Anikina, L. L. Fershtat and N. N. Makhova, *Mendeleev Commun*., 2018, **28**, 623.

[S2] B. W. Ford and P. Watts, *J. Chem. Soc., Perkin Trans. II*, 1974, 1009.

[S3] (*a*) G. M. Sheldrick, *Acta Cryst., Sect. A*, 2008, **64**, 112; (*b*) G. M. Sheldrick, *Acta Cryst. Sect. C*, 2015, **71**, 3.

[S4] (*a*) C. Adamo and V. Barone, *J. Chem. Phys.* 1999, **110**, 6158; (*b*) K. Raghavachari, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.* 1980, **72**, 650; (*c*) S. Grimme, S. Ehrlich and L. Goerigk, *J. Comp. Chem.* 2011, **32**, 1456.

[S5] (*a*) A. D. Becke, *J. Chem. Phys.* 1993, **98**, 5648; (*b*) P. Maxwell, A. M. Pendas and P. L. A. Popelier, *Phys. Chem. Chem. Phys.* 2016, **18**, 20986.

[S6] A. A. Romanova, K. A. Lyssenko and I. V. Ananyev, *J. Comput. Chem.*, 2018, **39**, 1607.

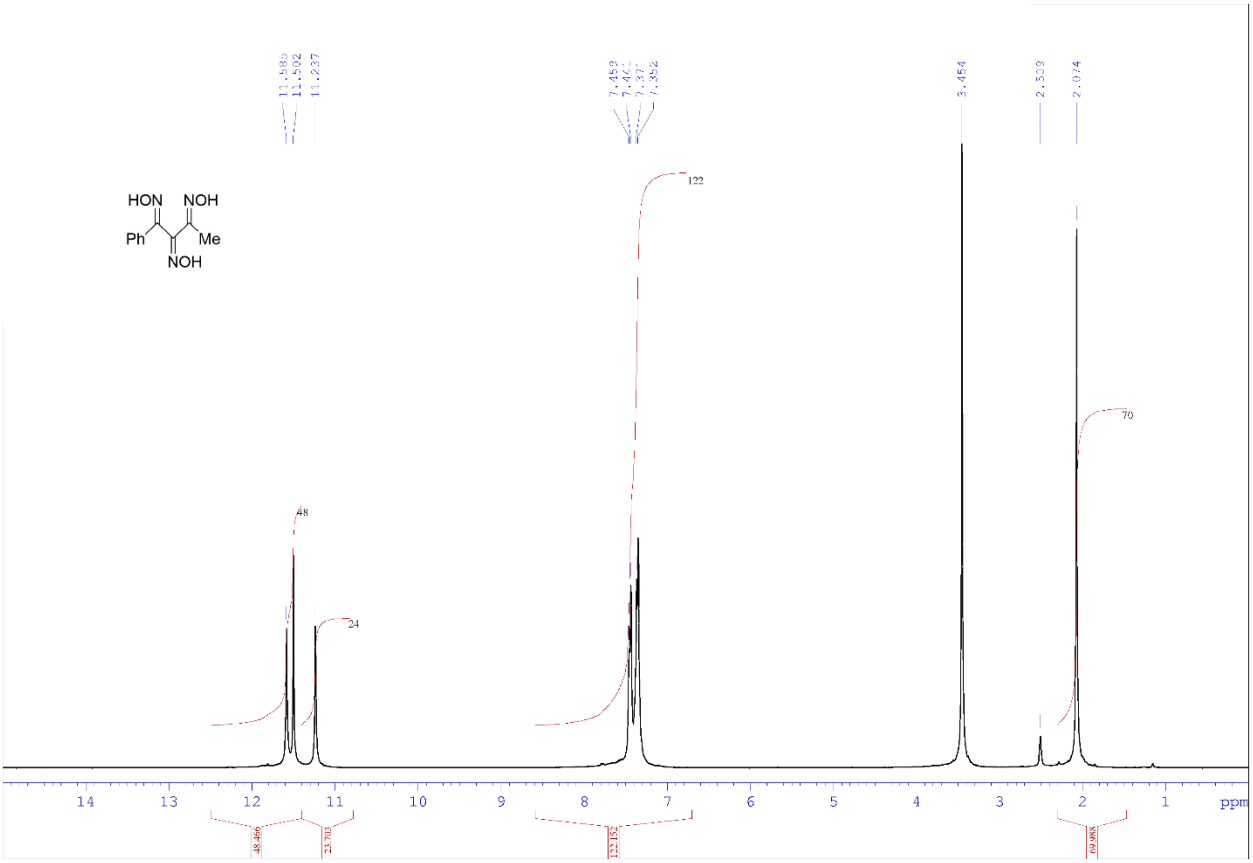
[S7] F. Weinhold and J. E. Carpenter, in *The Structure of Small Molecules and Ions*, Eds. R. Naaman and Z. Vager, Plenum, 1988, pp. 227-236.

[S8] (*a*) L. L. Fershtat, I. V. Ananyev and N. N. Makhova, *RSC Adv.*, 2015, **5**, 47248; (*b*) L. L. Fershtat, A. A. Larin, M. A. Epishina, A. S. Kulikov, I. V. Ovchinnikov, I. V. Ananyev and N. N. Makhova, *Tetrahedron Lett.*, 2016, **57**, 4268; (*c*) L. L. Fershtat, A. A. Larin, M. A. Epishina, I. V. Ovchinnikov, A. S. Kulikov, I. V. Ananyev and N. N. Makhova, *RSC Adv.*, 2016, **6**, 31526.

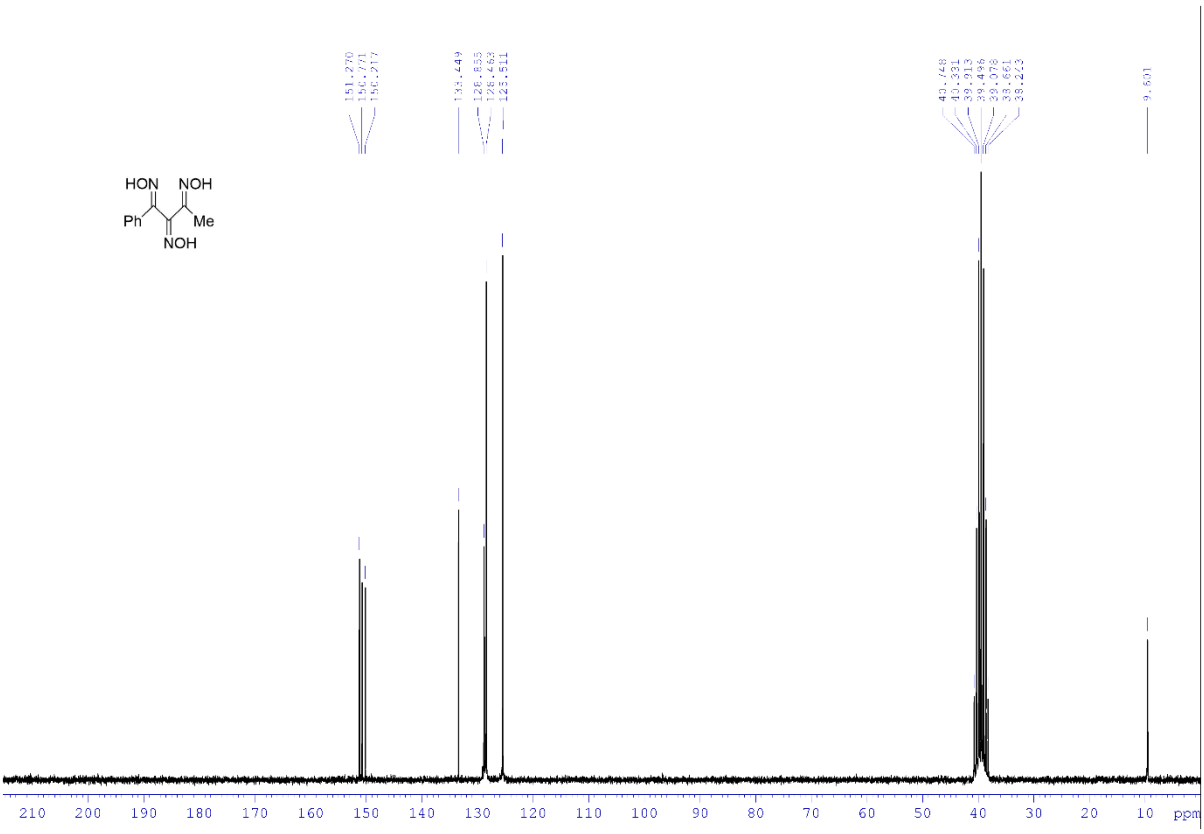
[S9] K. Eskandari and C. van Alsenoy, *J. Comput. Chem.* 2014, **35**, 1883.

[S10] E. R. Johnson, S. Keinan, P. Mori-Sanchez, J. Contreras-Garcia, A. J. Cohen and W. Yang, *J. Am. Chem. Soc.* 2010, **132**, 6498.

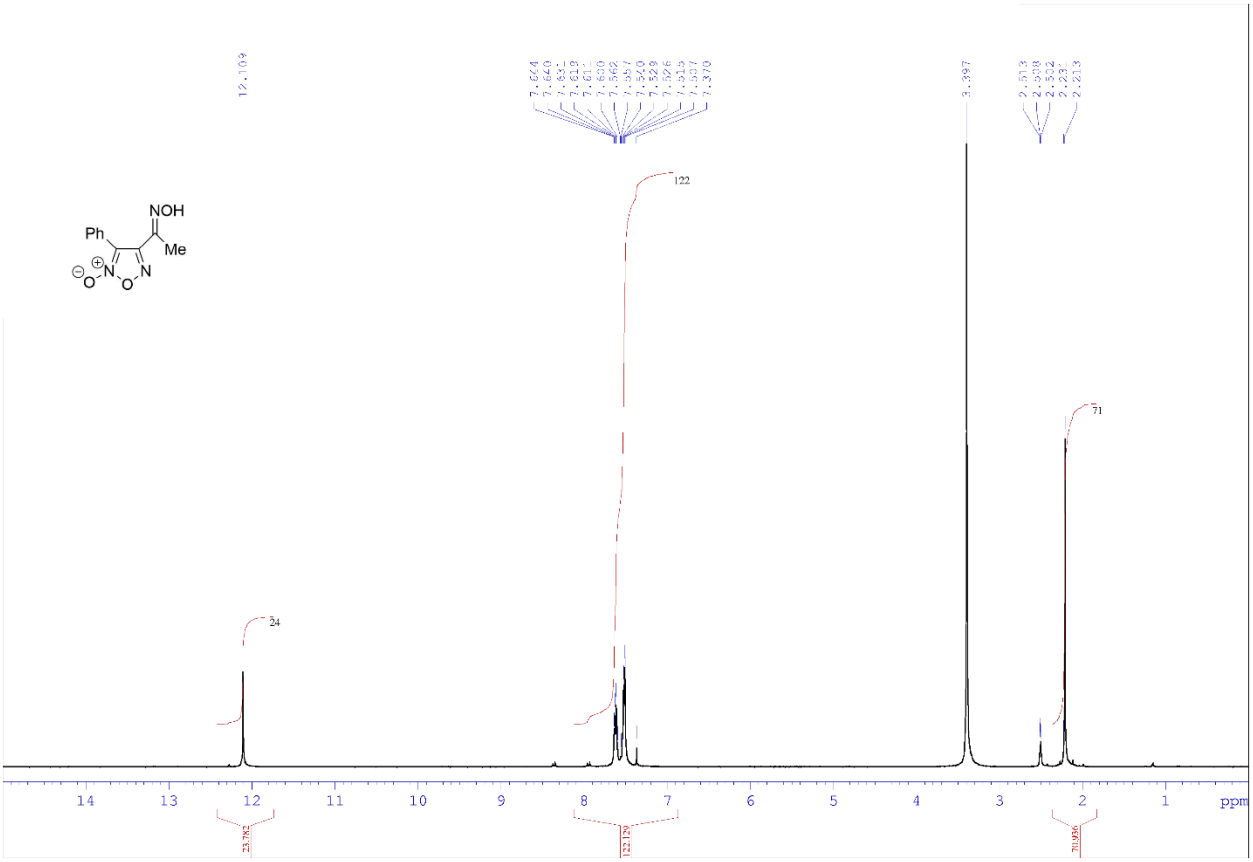
Copies of NMR spectra



^{1}H NMR (300 MHz, DMSO-d_6)



^{13}C NMR (75.5 MHz, DMSO-d_6)



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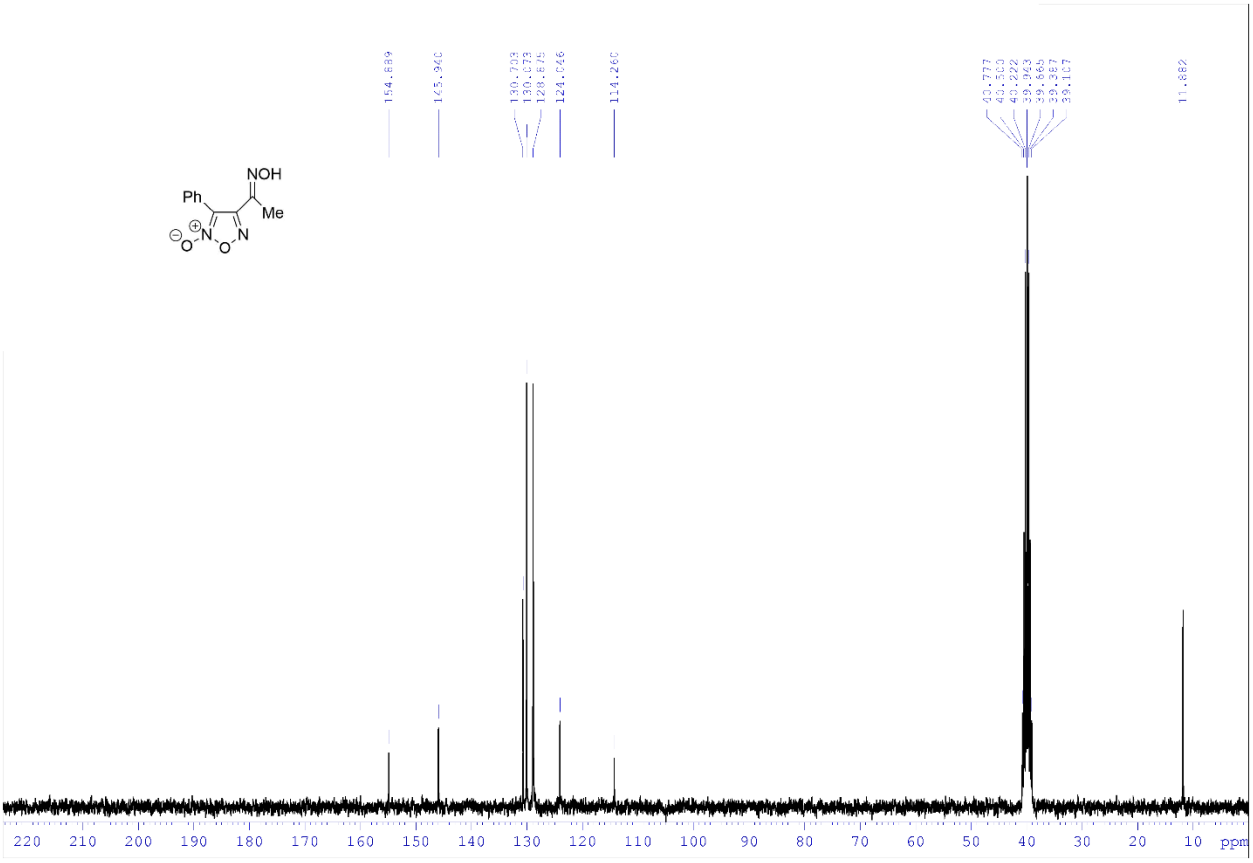
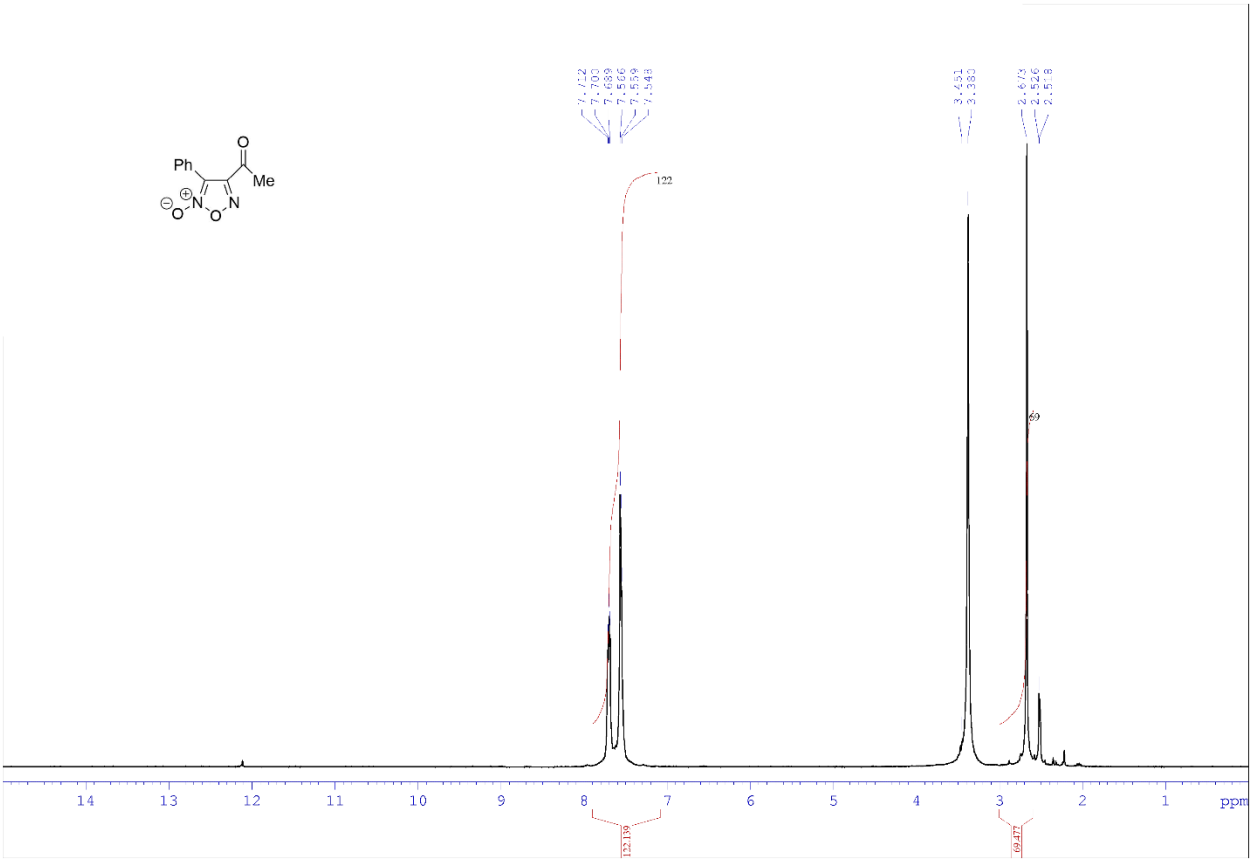


^{13}C NMR (75.5 MHz, DMSO-d$_6$)



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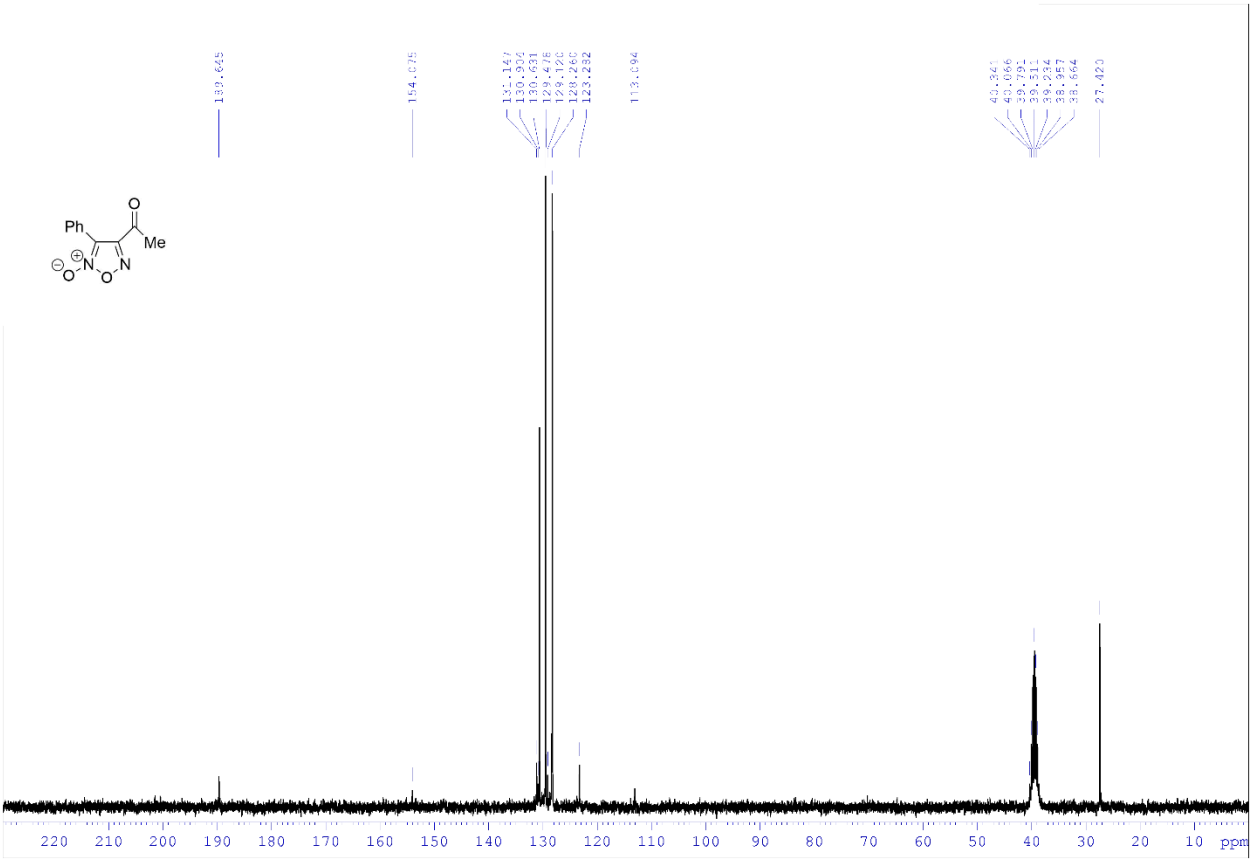

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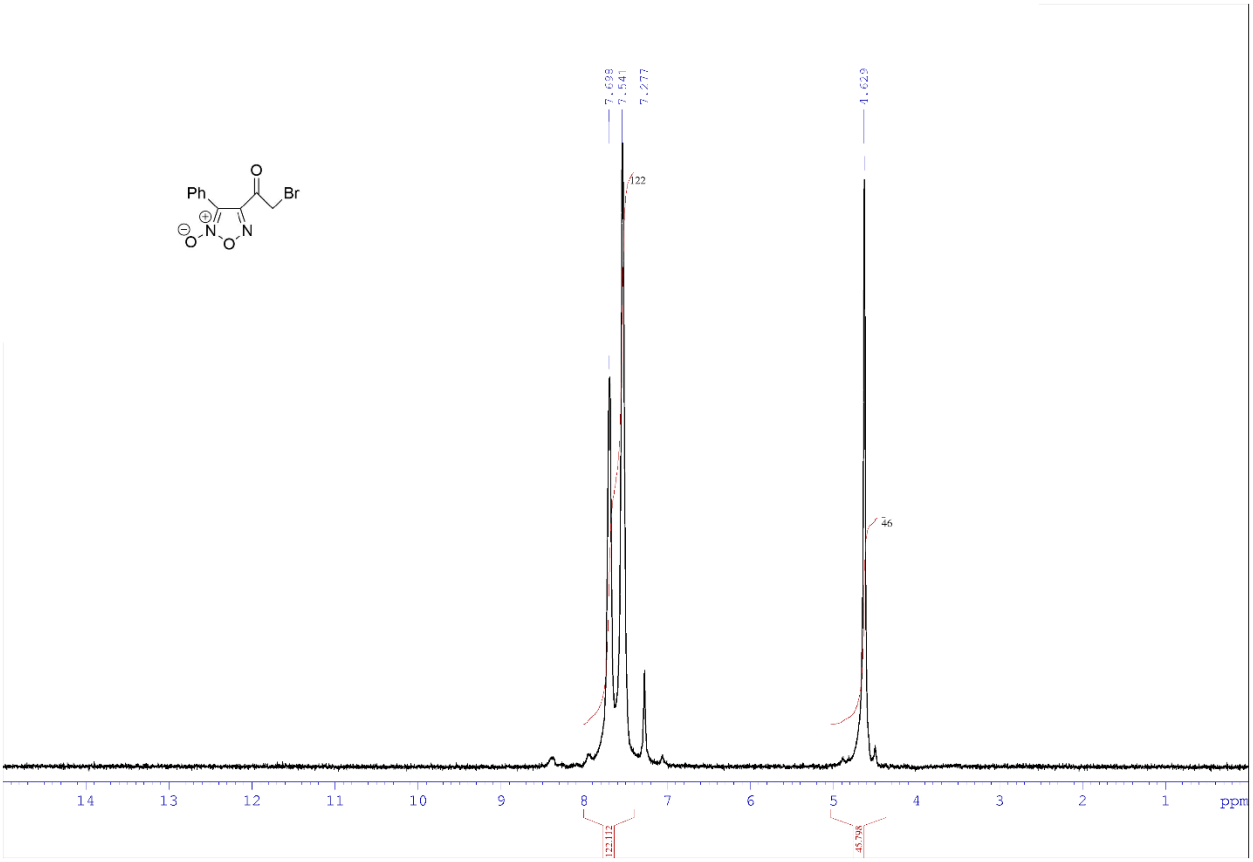
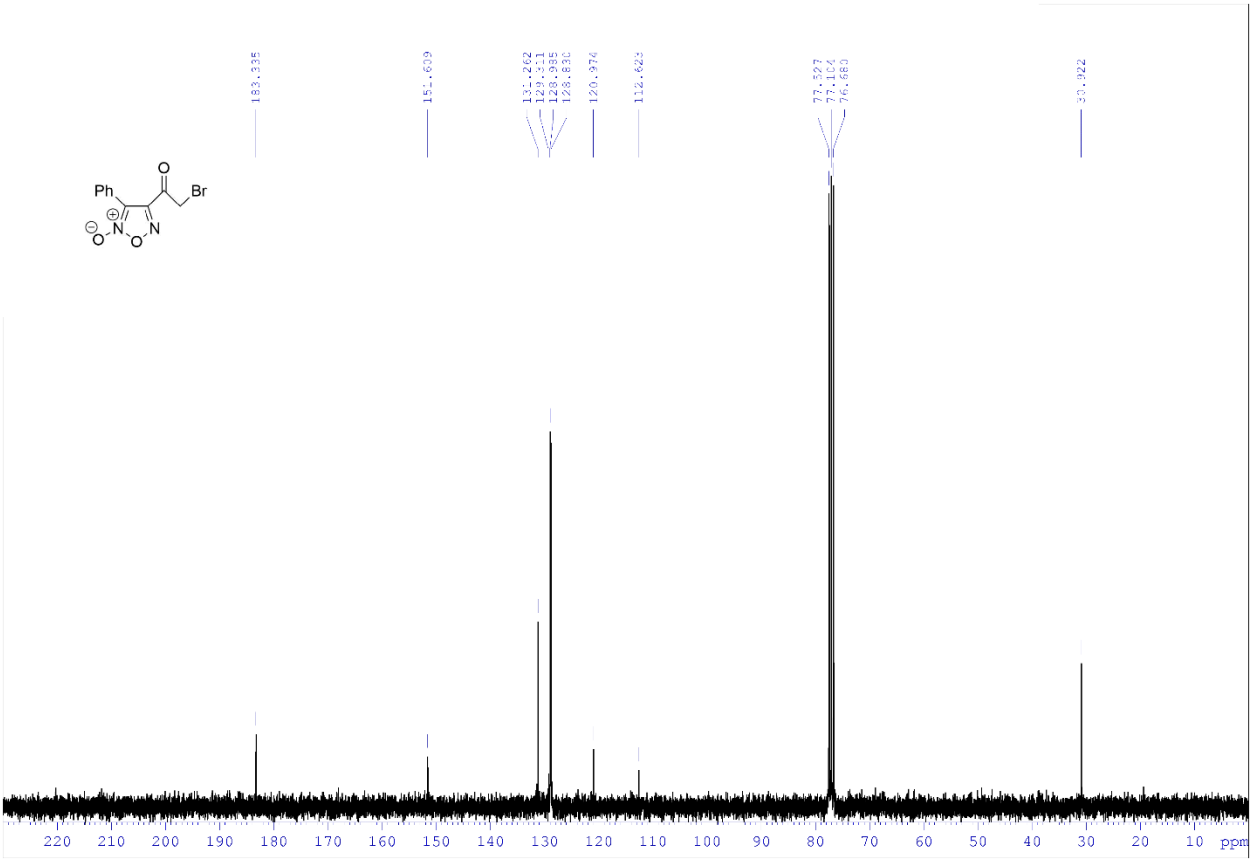
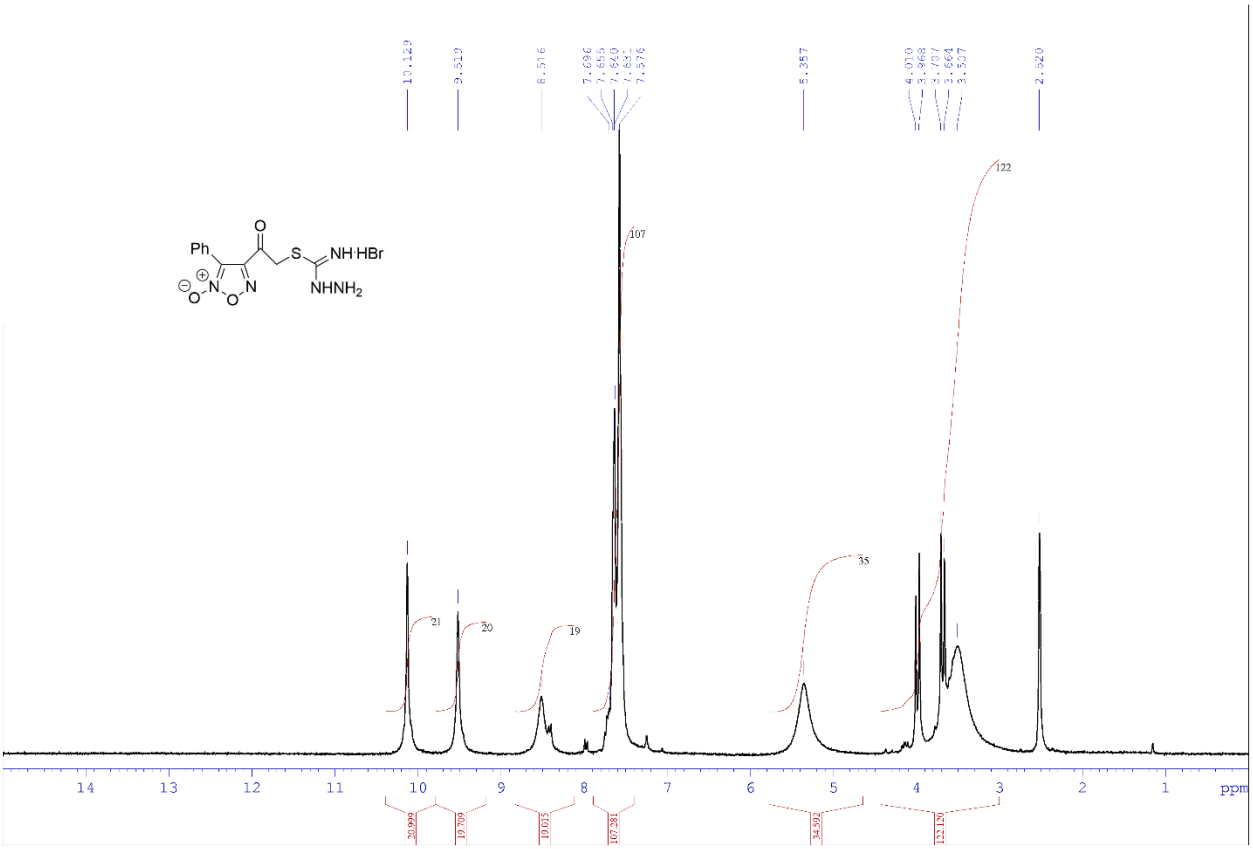


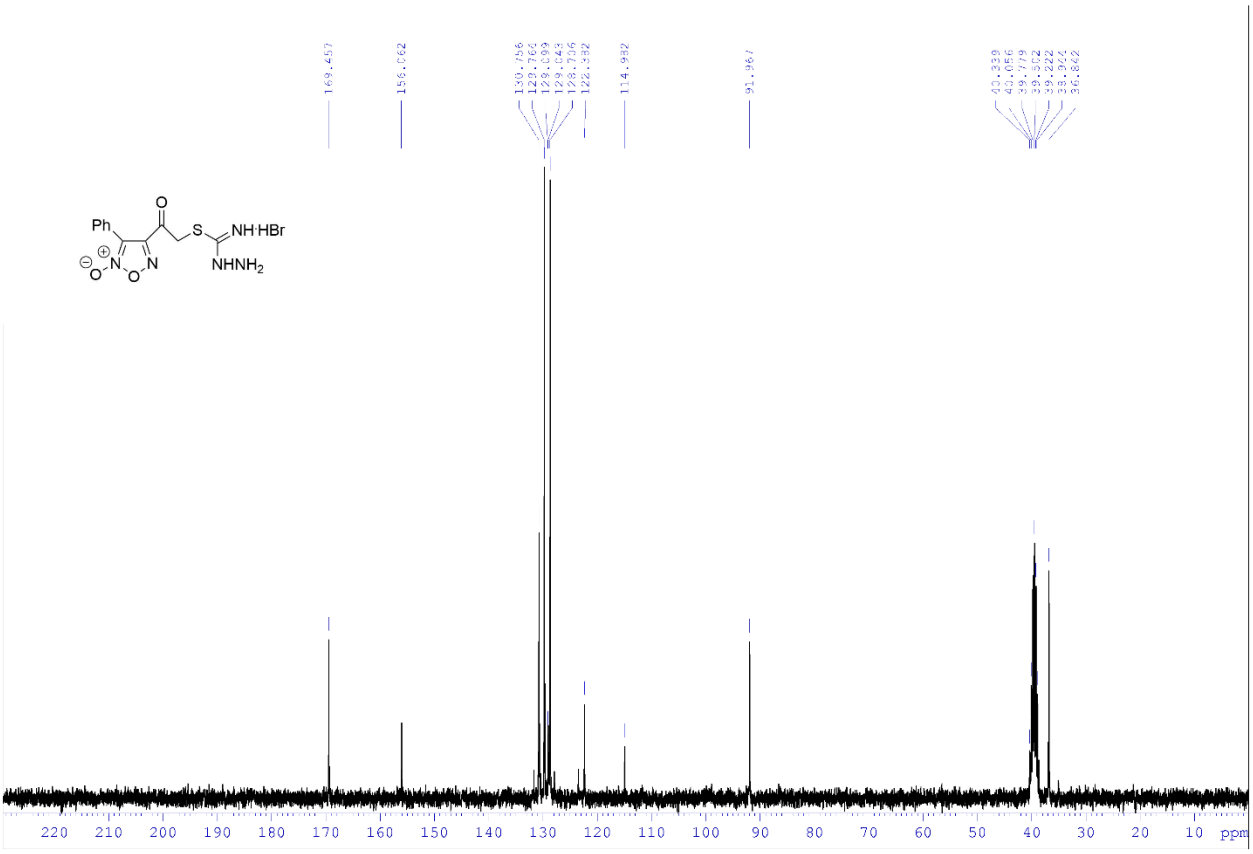
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75.5 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, DMSO-d_6) of **2b**



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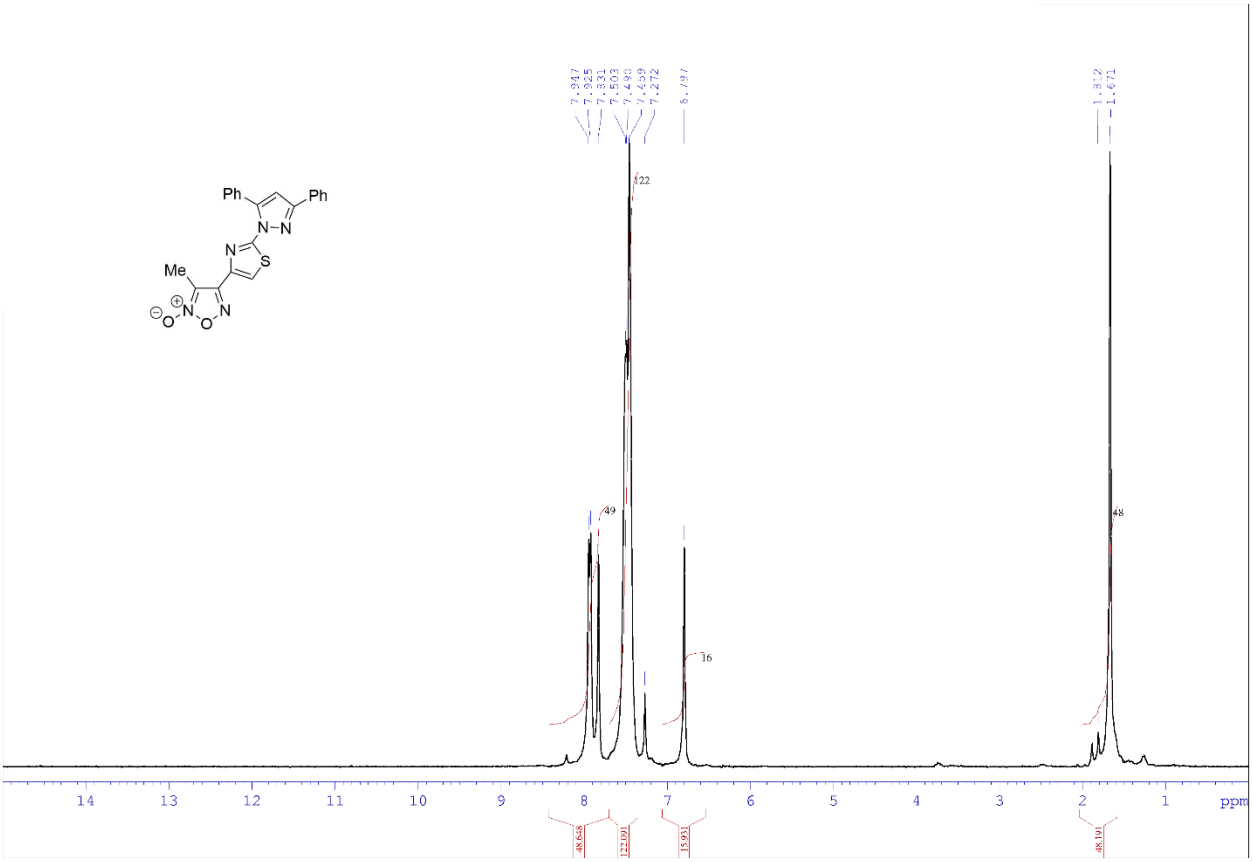
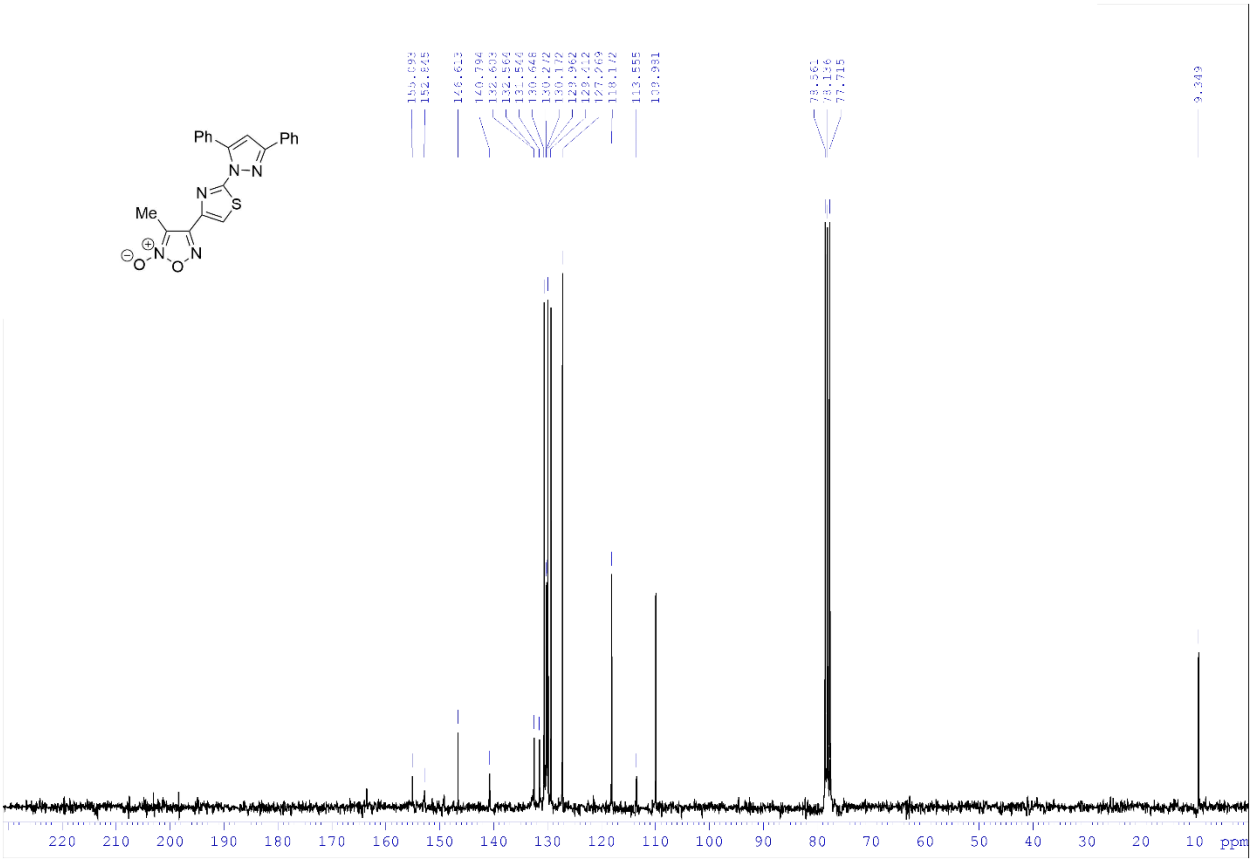
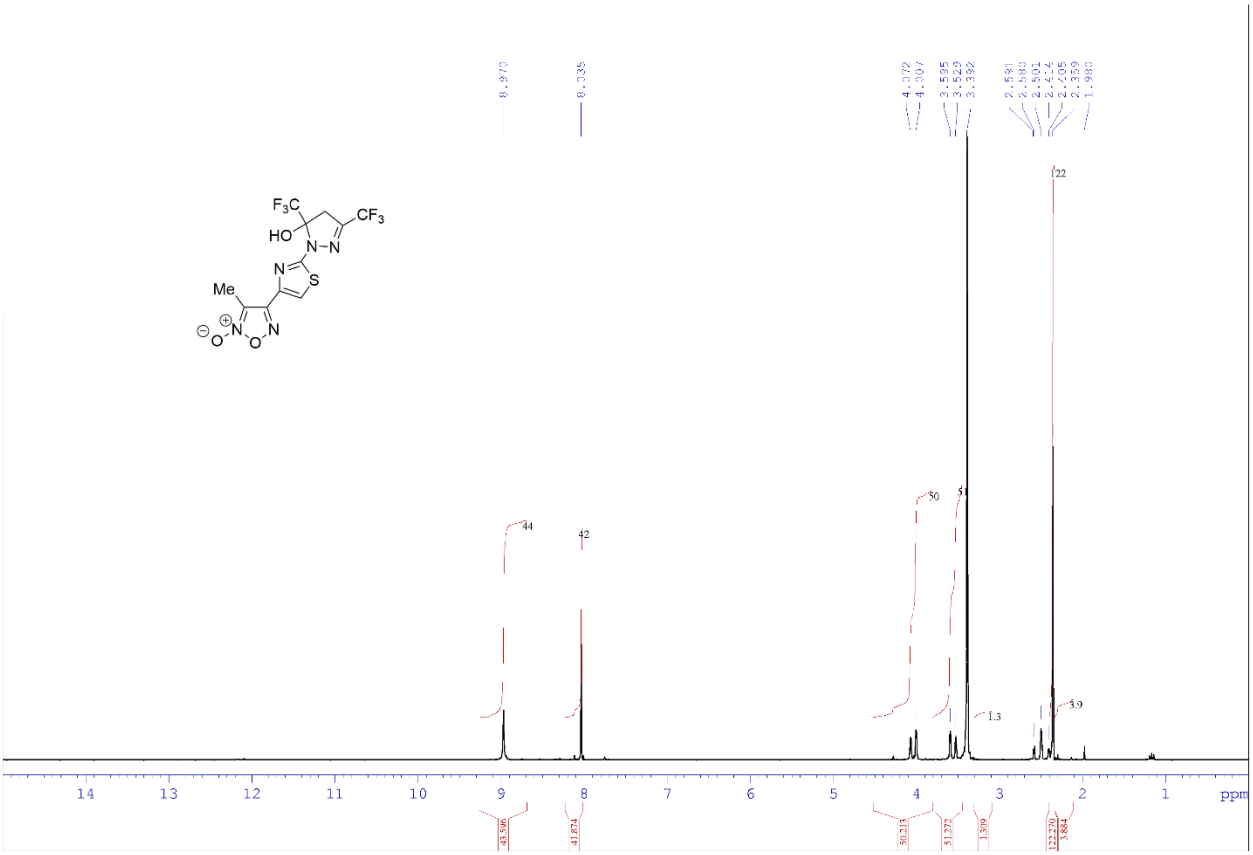


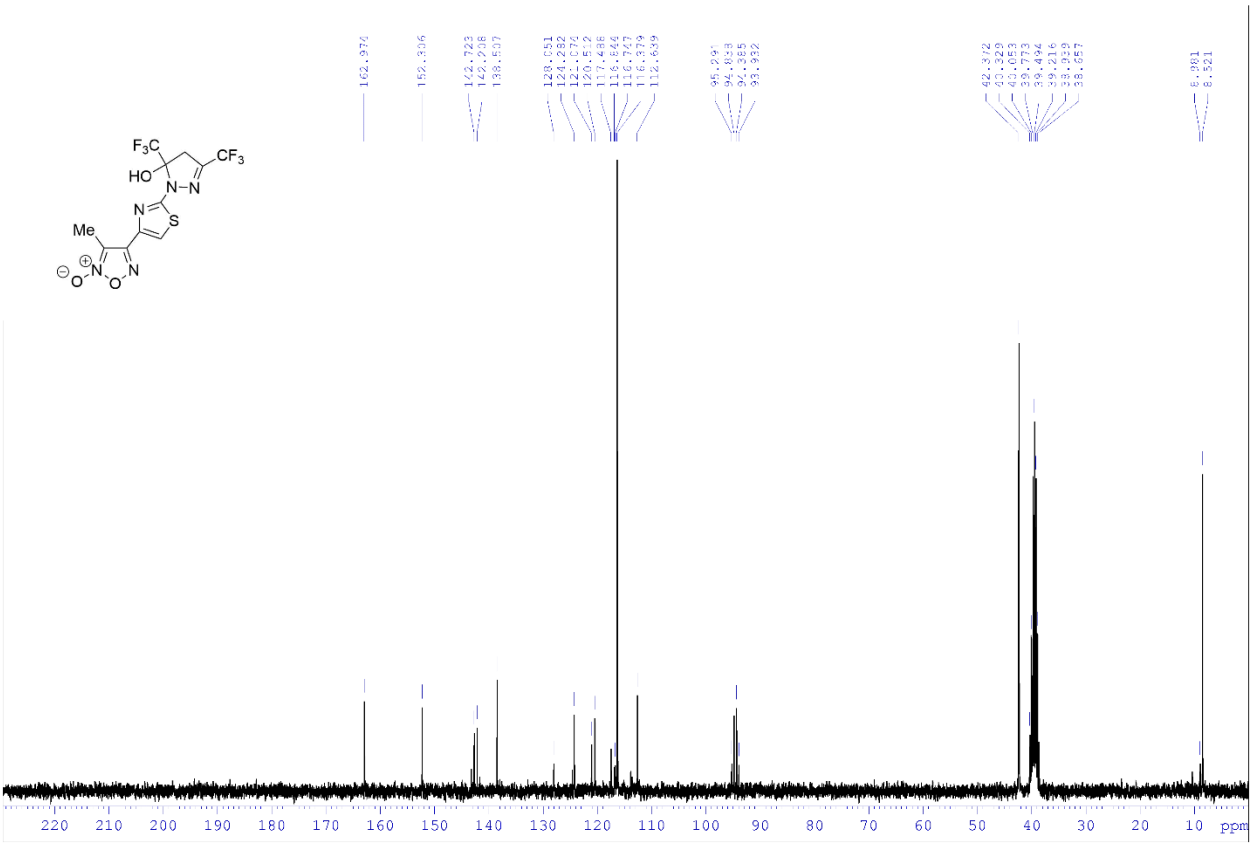
^{1}H NMR (300 MHz, $CDCl_3$) of **4b**



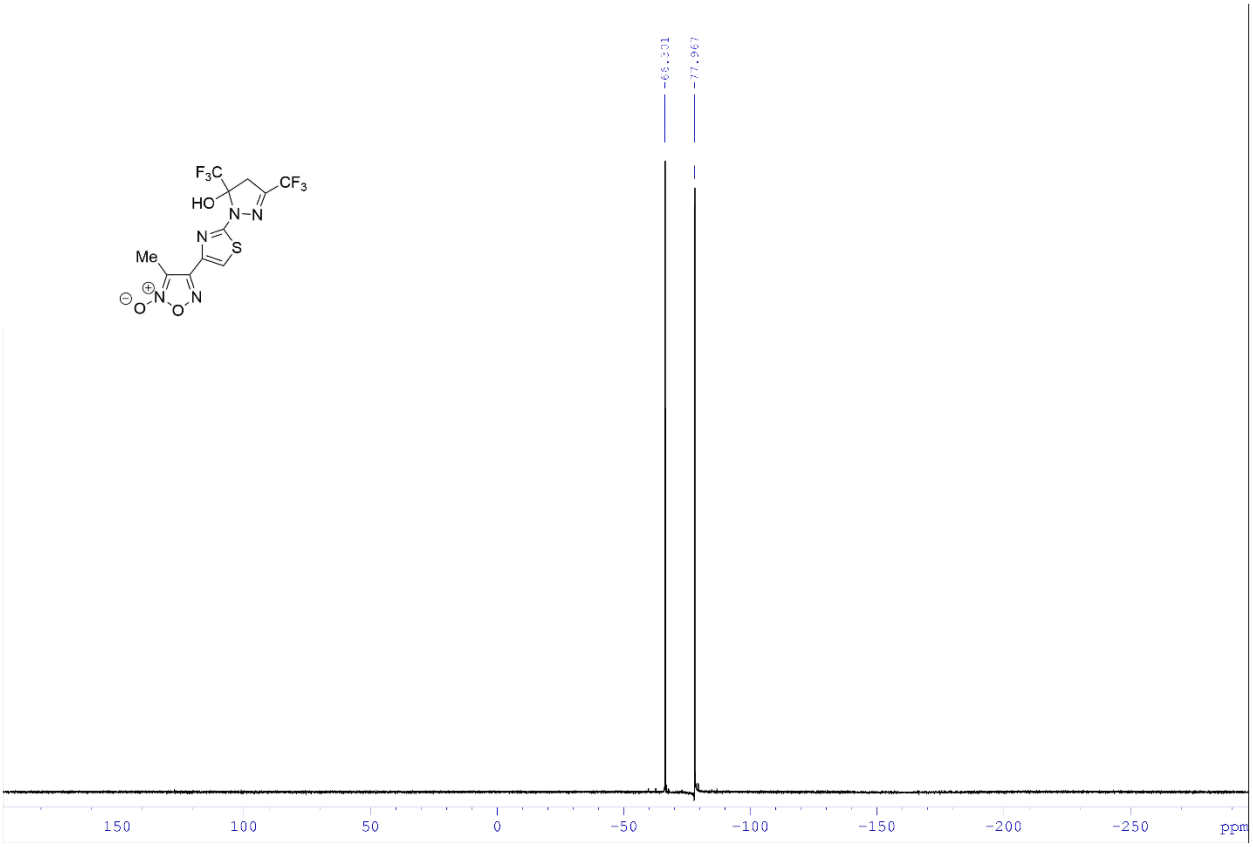
^{13}C NMR (75.5 MHz, $CDCl_3$) of **4b**



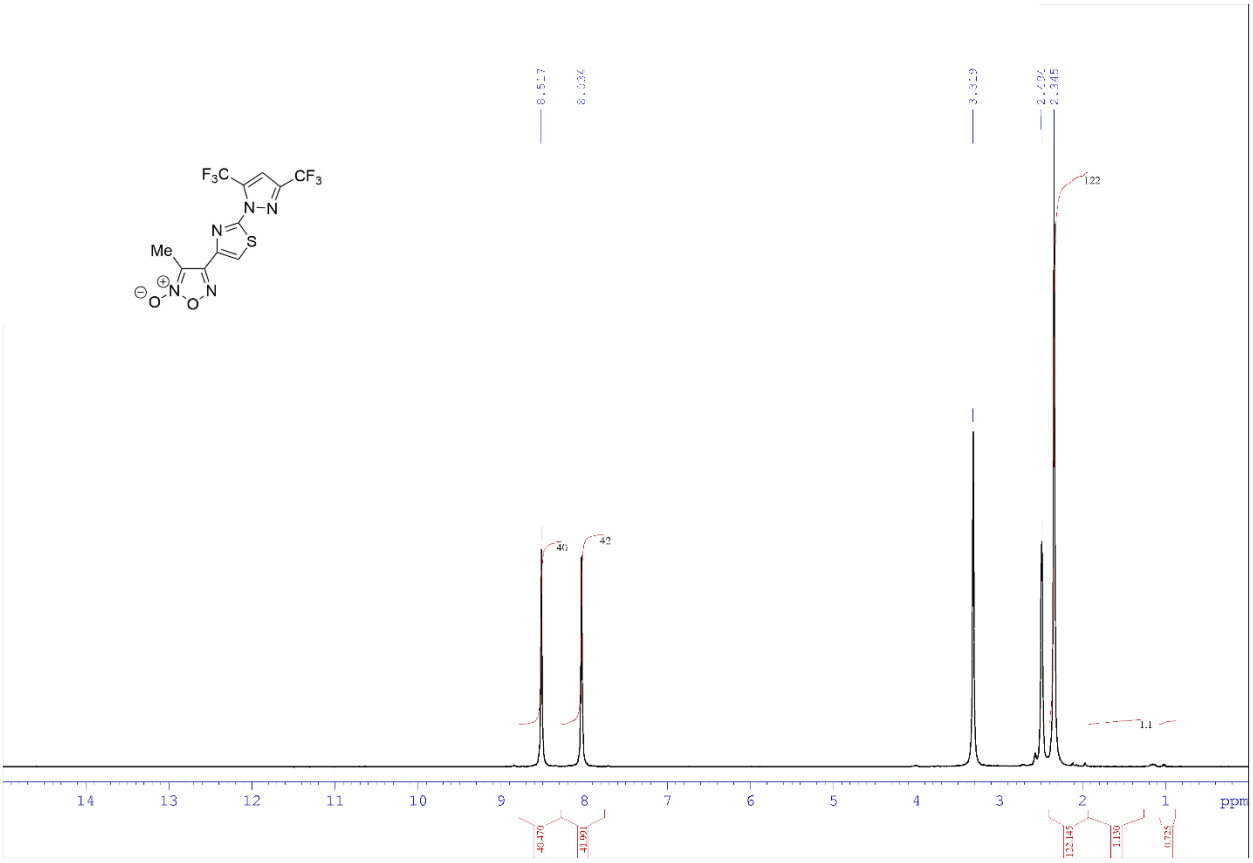
^{1}H NMR (300 MHz, DMSO-d_6) of **4'c**



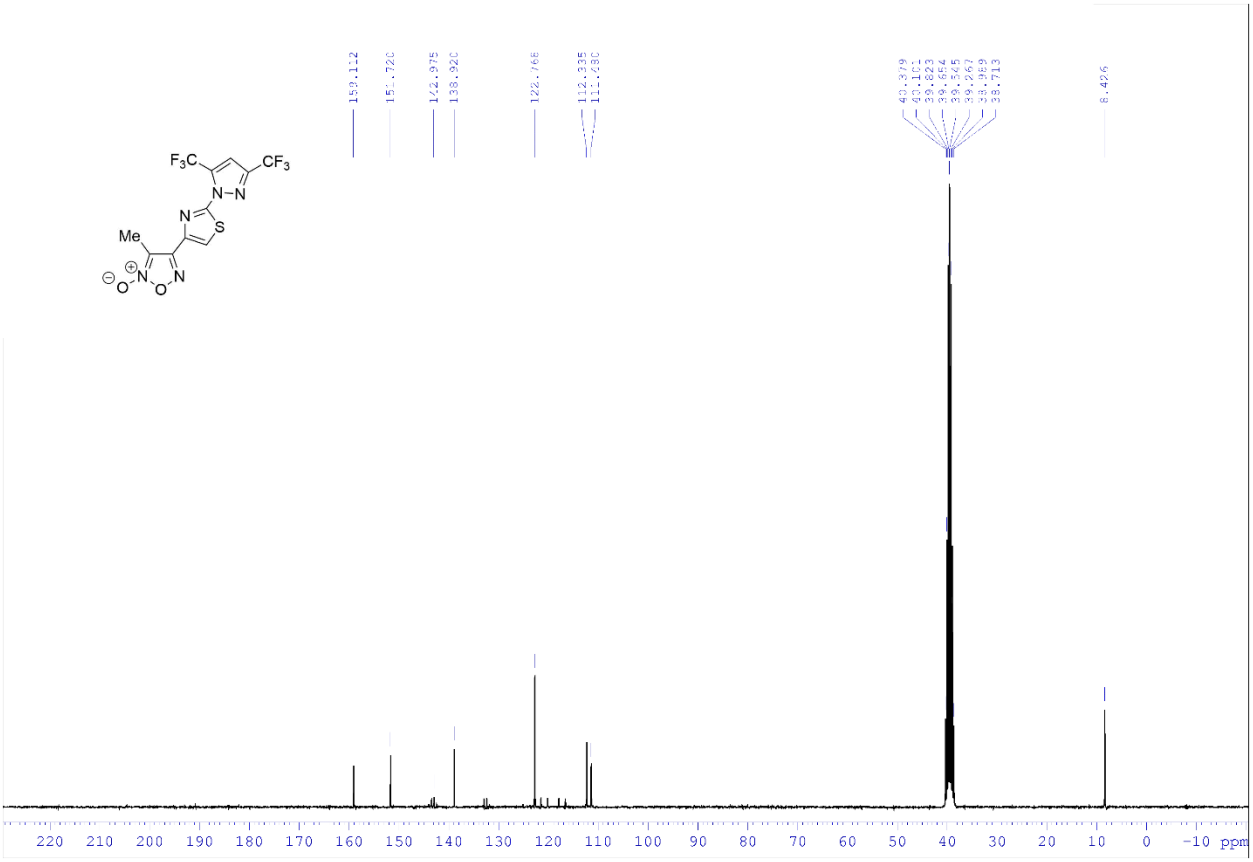
^{13}C NMR (75.5 MHz, DMSO-d_6) of **4'c**



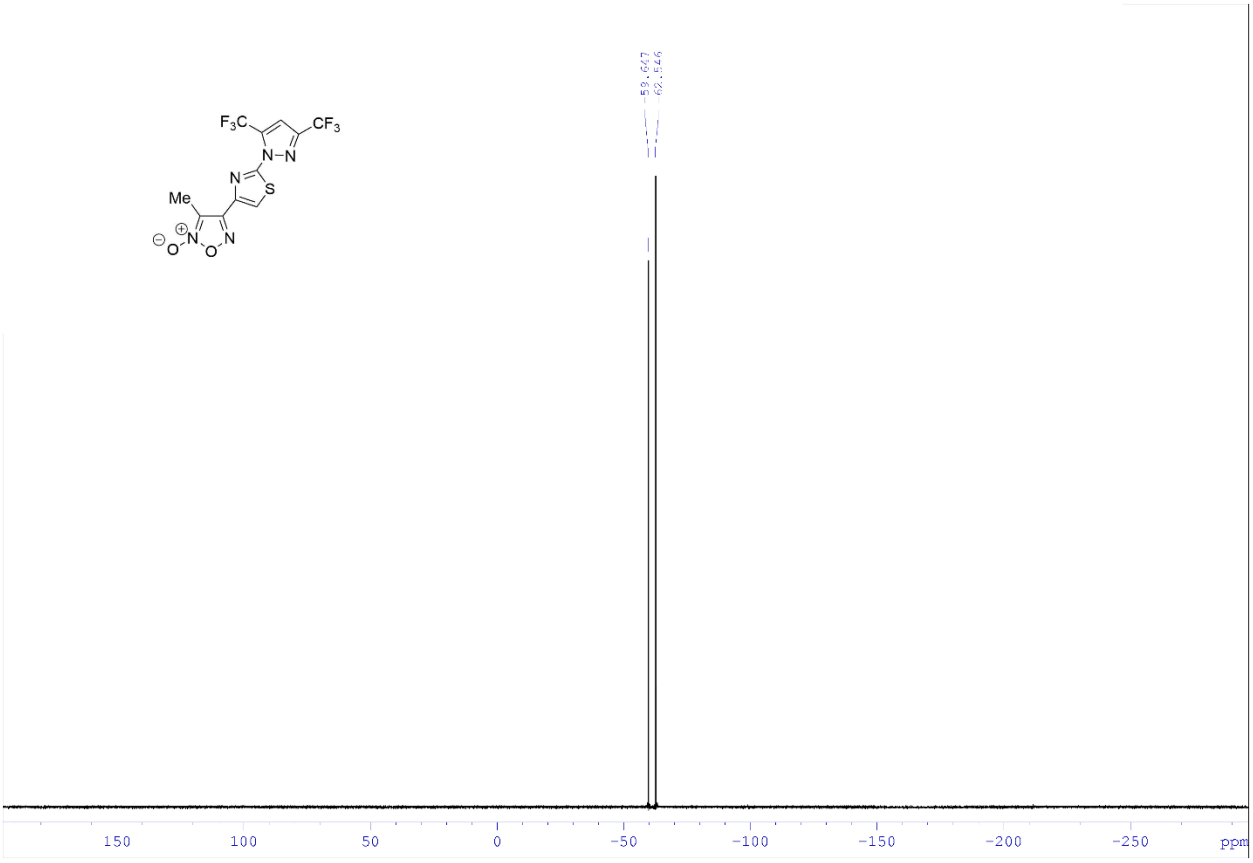
^{19}F NMR (282.4 MHz, DMSO-d_6) of **4'c**



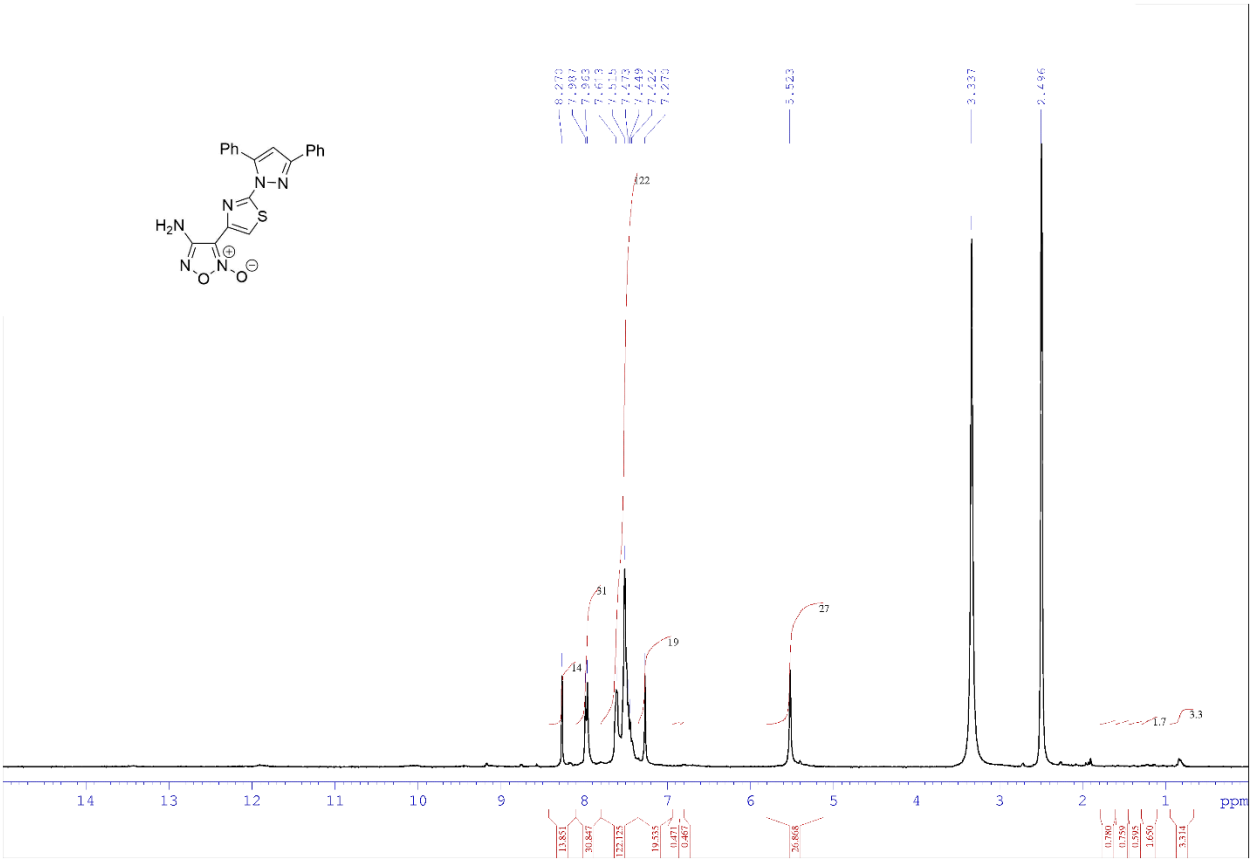
^{1}H NMR (300 MHz, DMSO-d_6) of **4c**



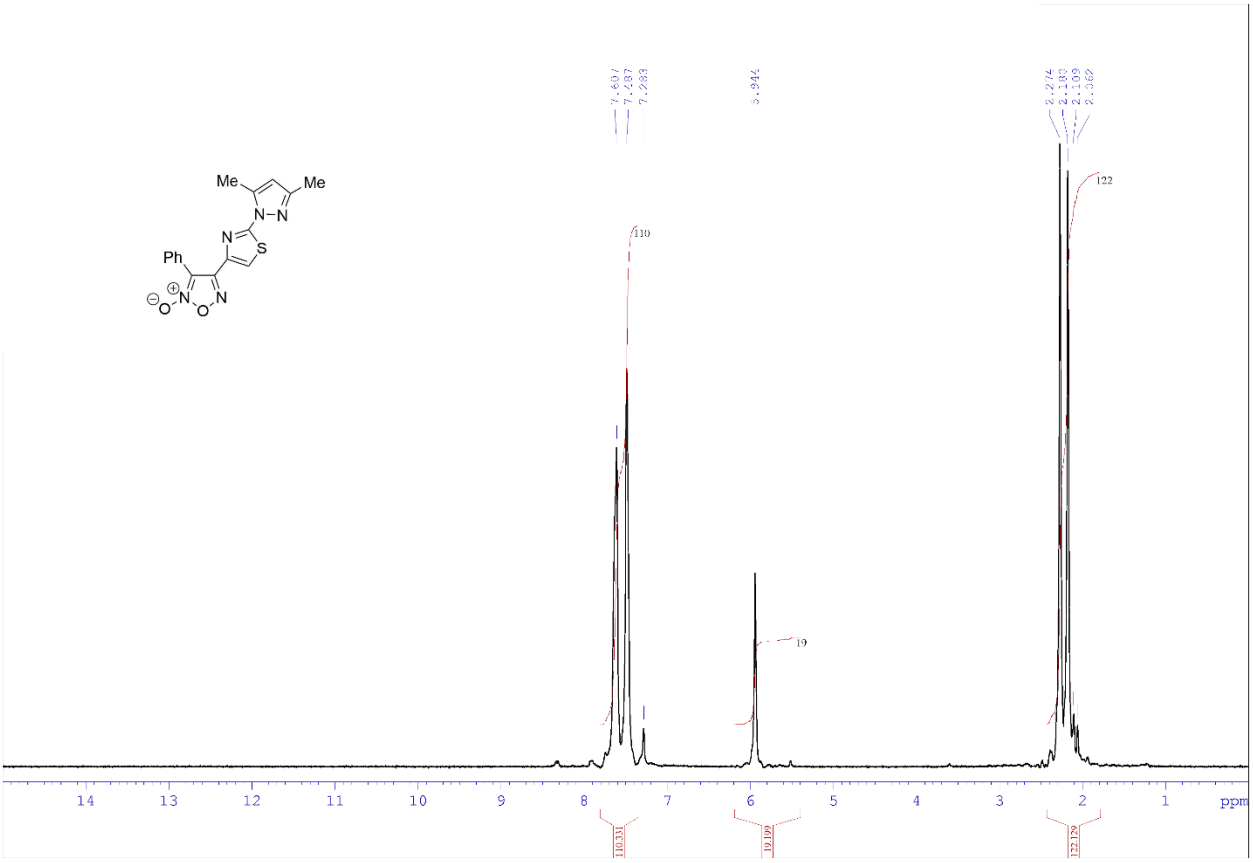
^{13}C NMR (75.5 MHz, DMSO-d_6) of **4c**



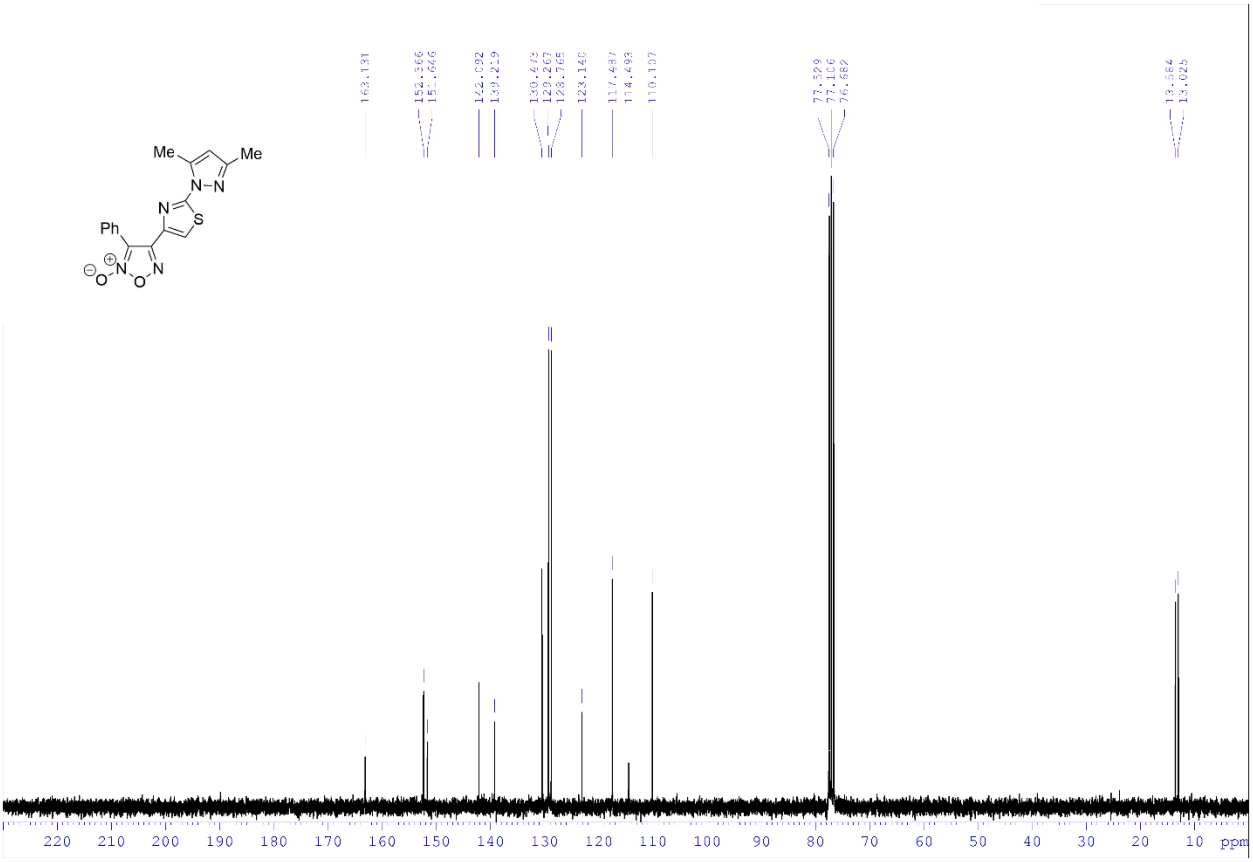
^{19}F NMR (282.4 MHz, DMSO-d_6) of **4c**



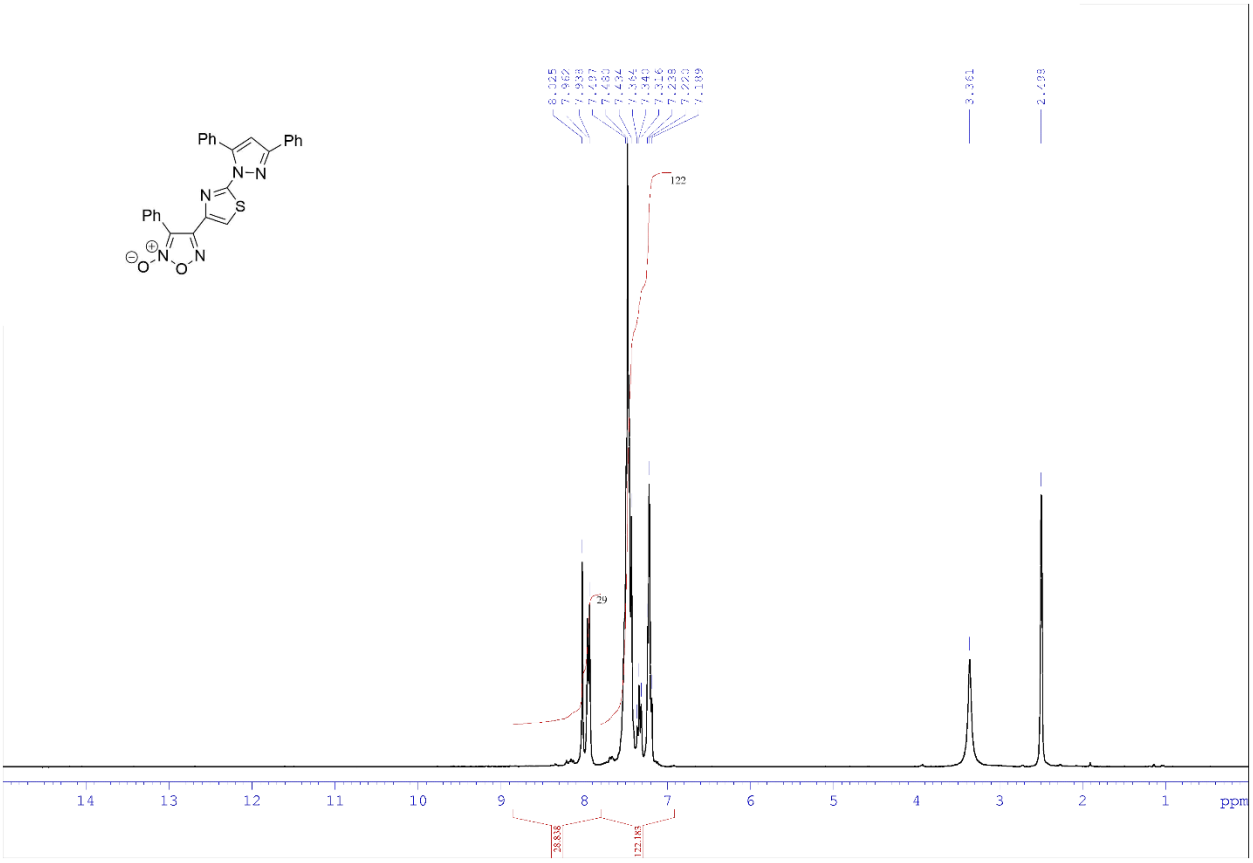
^{1}H NMR (300 MHz, DMSO-d_6) of **5**



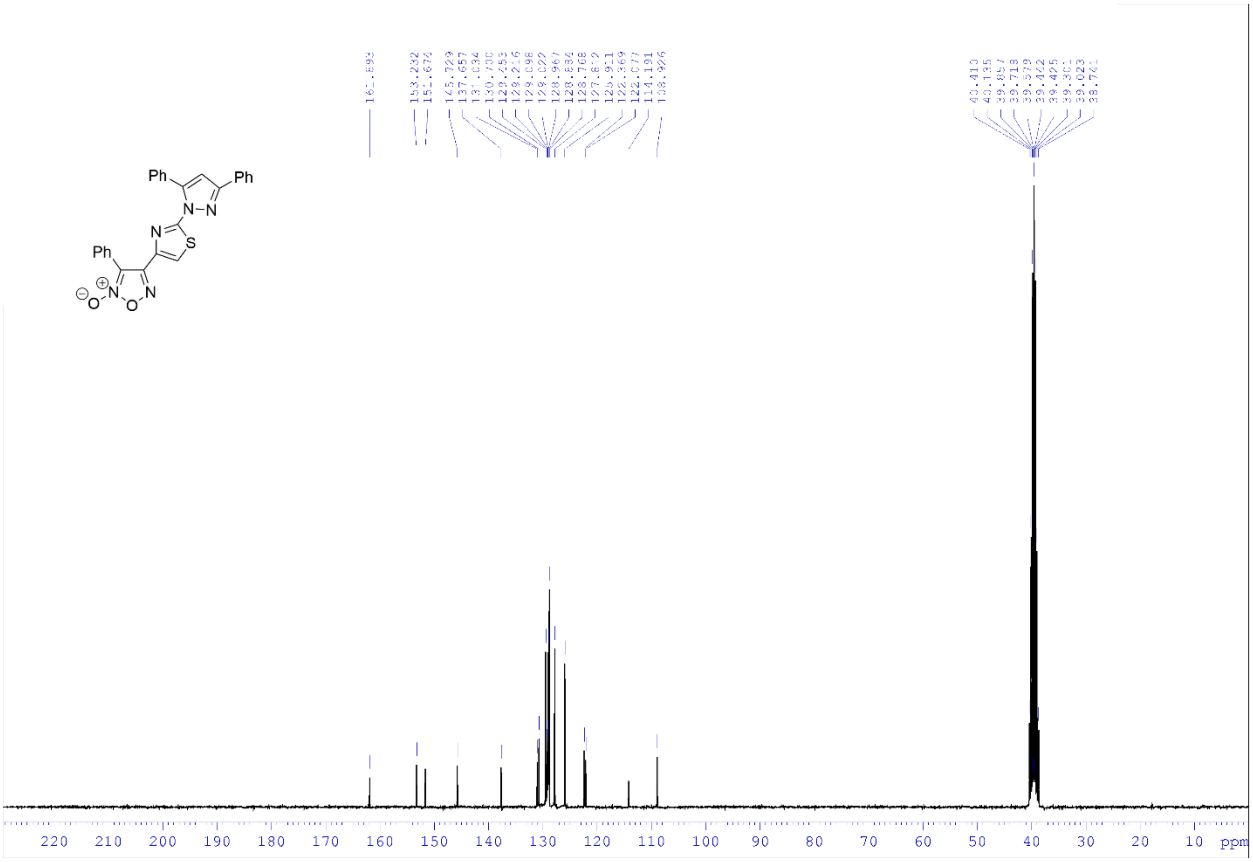
^{1}H NMR (300 MHz, $CDCl_3$) of **4d**



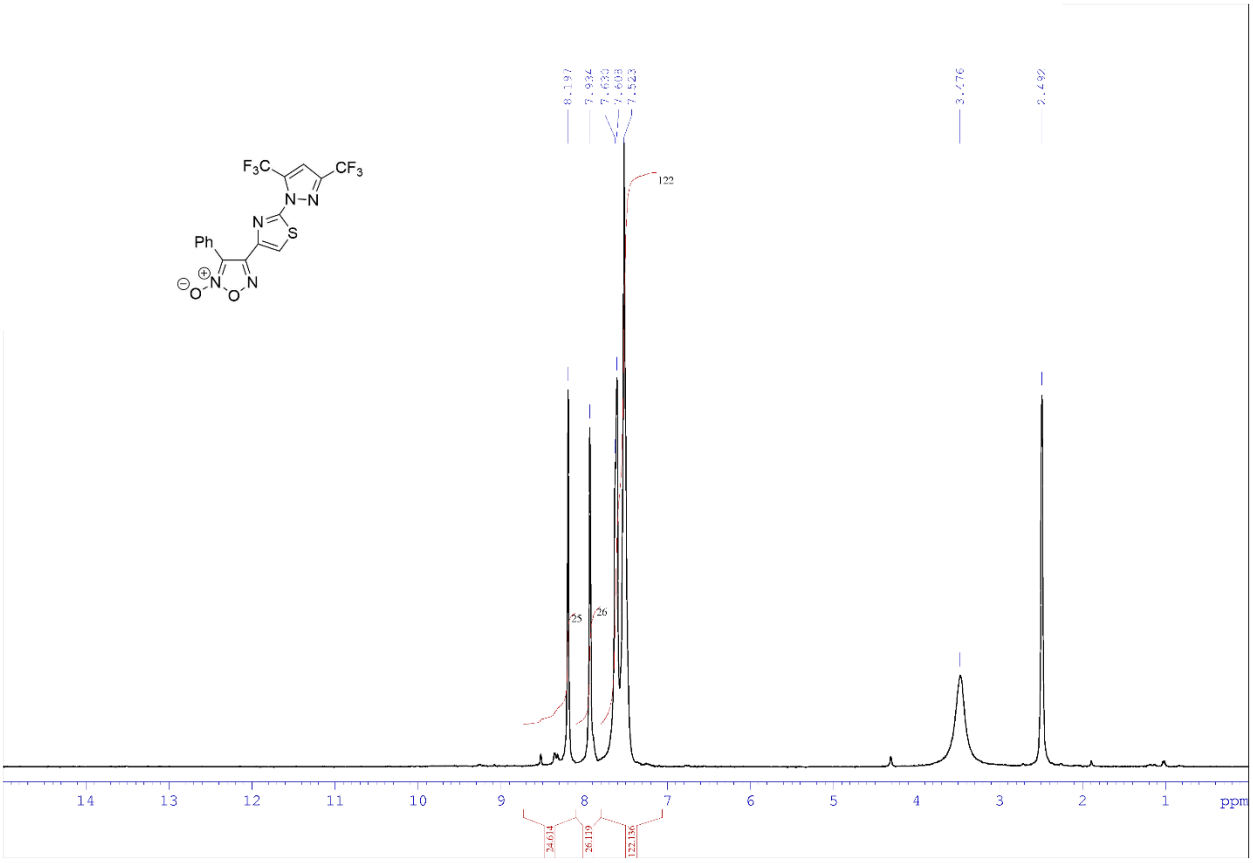
^{13}C NMR (75.5 MHz, $CDCl_3$) of **4d**



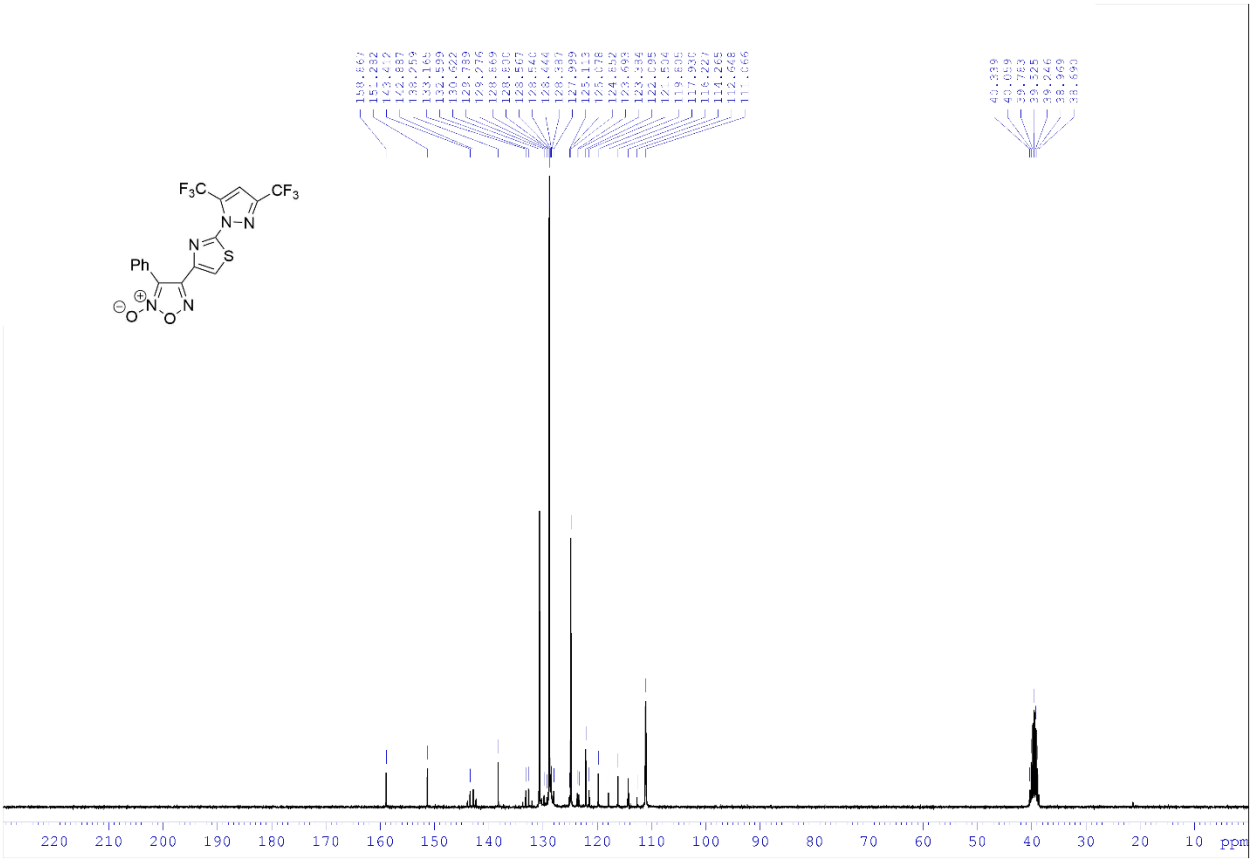
^{1}H NMR (300 MHz, DMSO-d_6) of **4e**



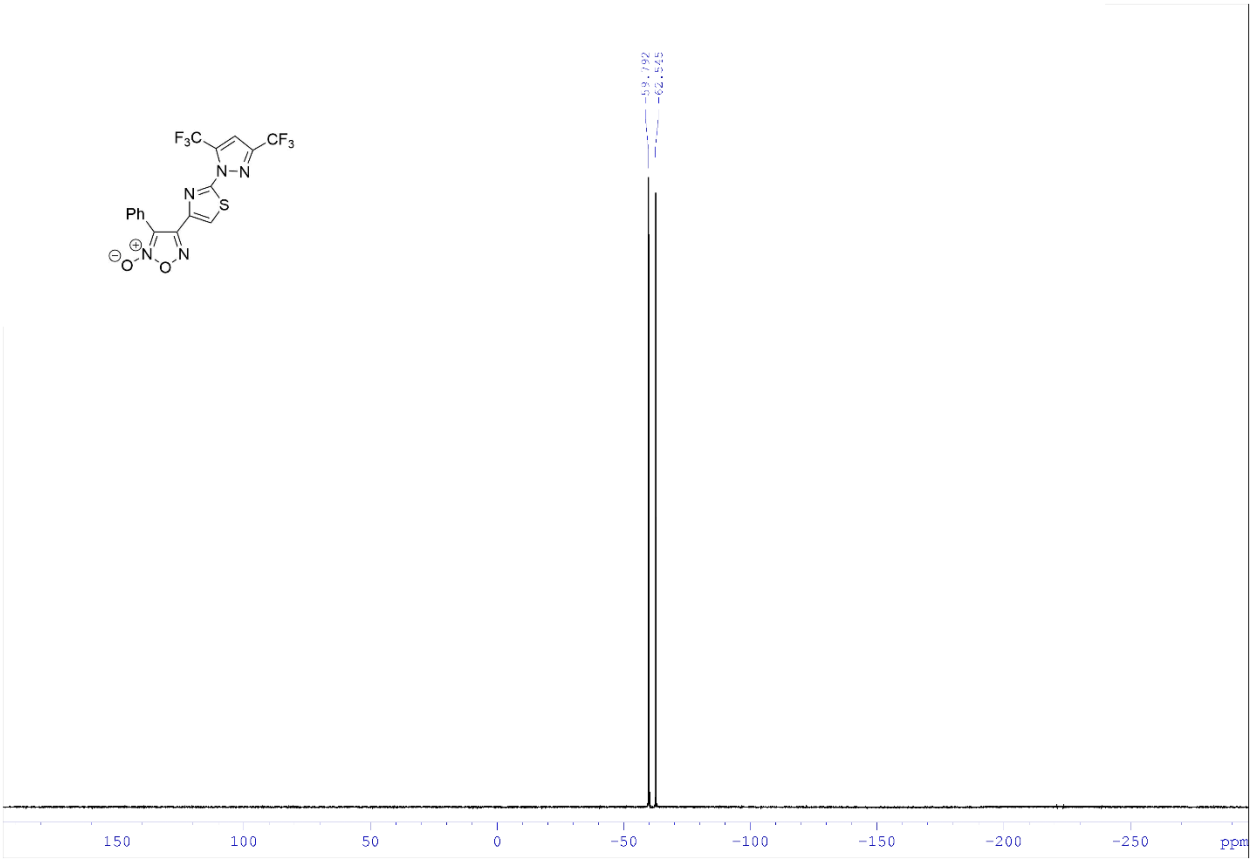
^{13}C NMR (75.5 MHz, DMSO-d_6) of **4e**



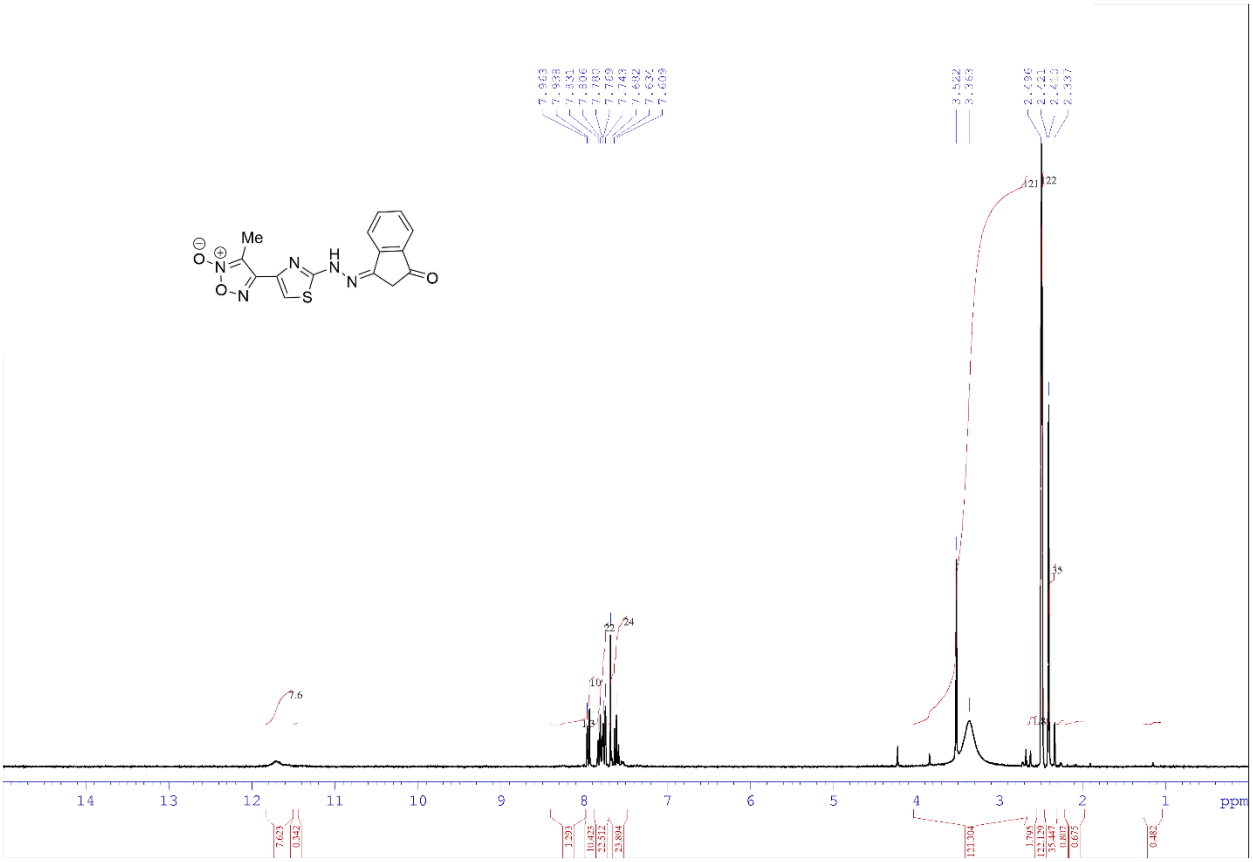
^{1}H NMR (300 MHz, DMSO-d_6) of **4f**



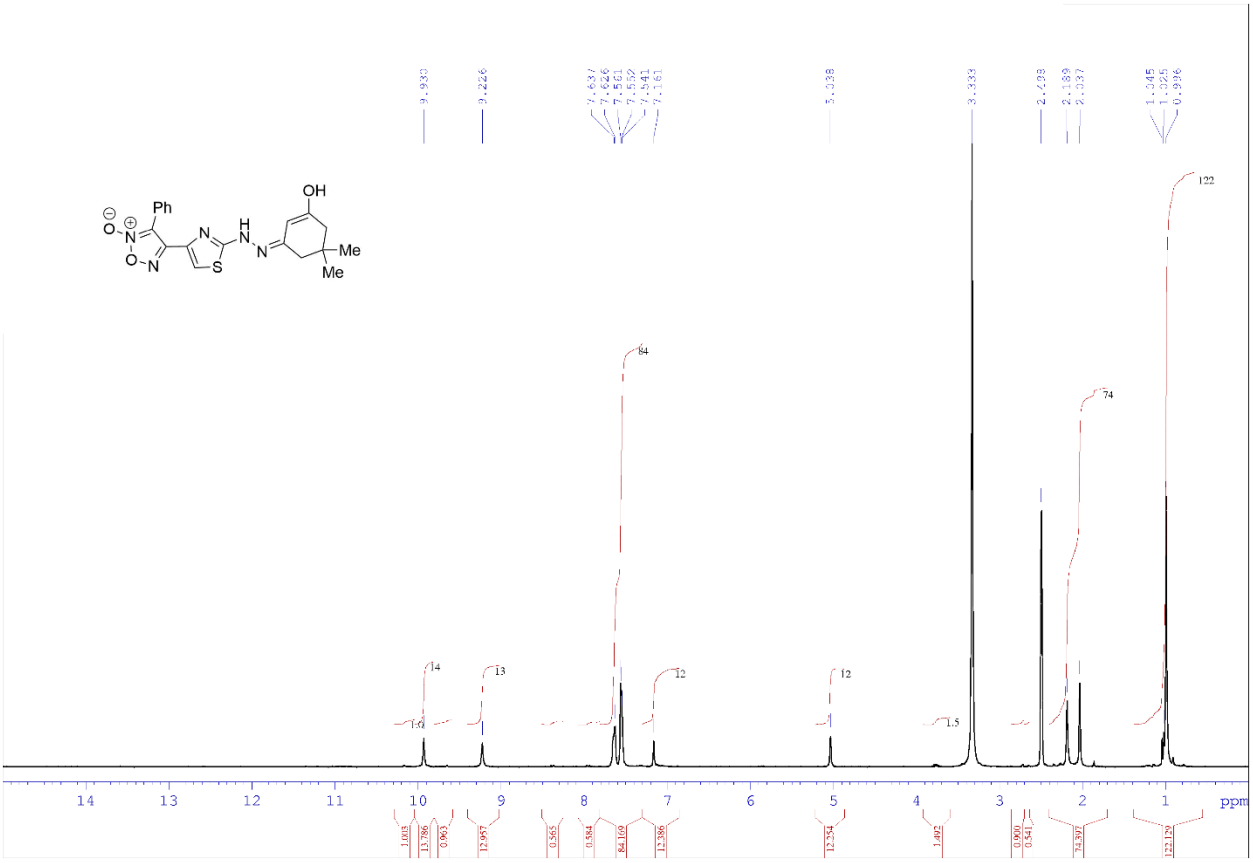
^{13}C NMR (75.5 MHz, DMSO-d_6) of **4f**



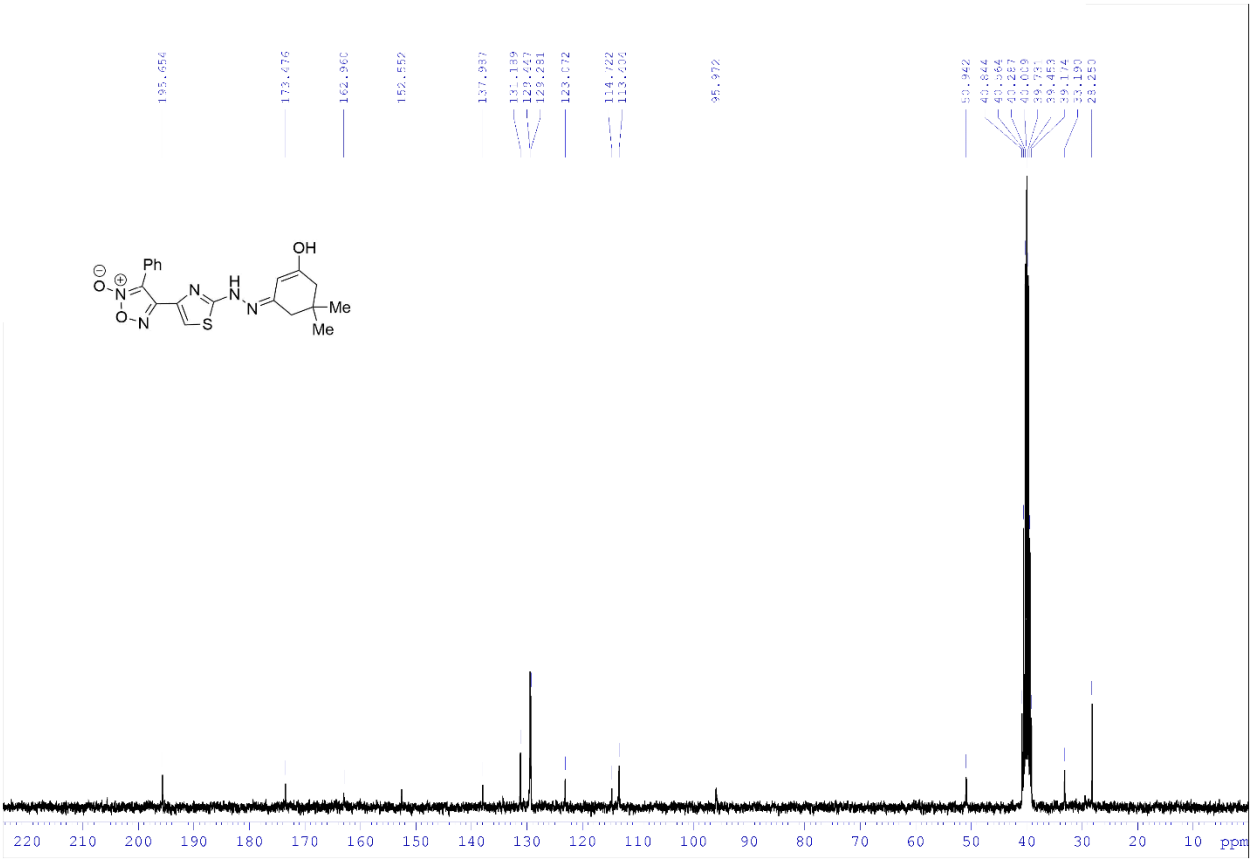
^{19}F NMR (282.4 MHz, DMSO-d$_6$) of **4f**



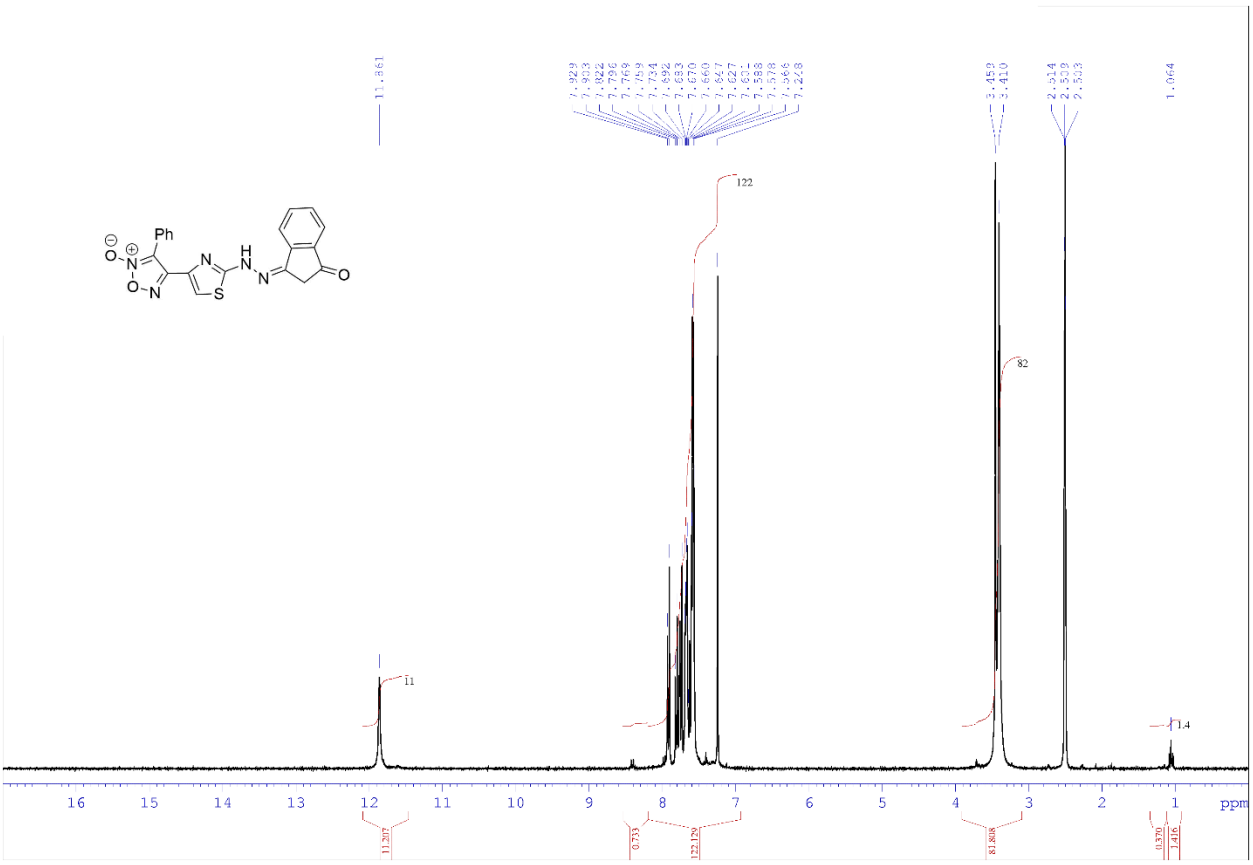
^{1}H NMR (300 MHz, DMSO-d$_6$) of **6c**



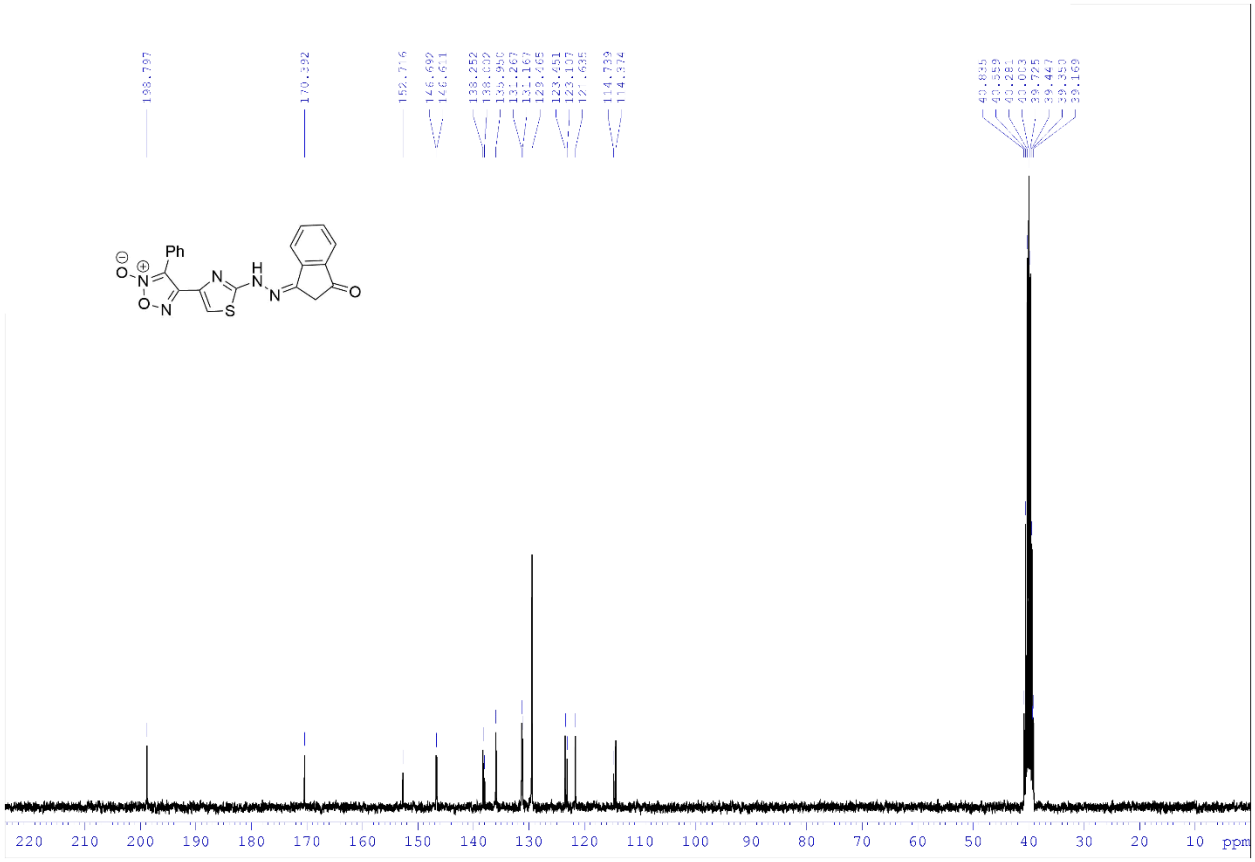
^{1}H NMR (300 MHz, DMSO-d_6) of **6b**



^{13}C NMR (75.5 MHz, DMSO-d_6) of **6b**



^{1}H NMR (300 MHz, DMSO-d_6) of **6d**



^{13}C NMR (75.5 MHz, DMSO-d_6) of **6d**