Room Temperature Dithiocarbamation of 2-Tetralones with Elemental Sulfur and Isothiocyanates S_8/R-N=C=S: Atom-Efficient Access to 4-Hydroxythiazolidine-2-thiones

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General information

Reagents were obtained from commercial supplier and used without further purification. Analytical thin layer chromatography (TLC) was purchased from Merck KGaA (silica gel 60 F254). Visualization of the chromatogram was performed by UV light (254 nm) or phosphomolybdic acid or vanilline stains. Flash column chromatography was carried out using kieselgel 35-70 μm particle sized silica gel (230-400 mesh). NMR Chemical shifts are reported in (δ) ppm relative to tetramethylsilane (TMS) with the residual solvent as internal reference ($CDCl_3$, δ 7.26 ppm for ^1H, 77.0 ppm for ^{13}C. DMSO-d6, δ 2.50 ppm for 1 H and δ 39.5 ppm for 13C). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration.

General procedure for the synthesis of 4-hydroxythiazolidine-2-thiones 3 via dithiocarbamation of 2-tetralones 1 with elemental sulfur and isothiocyanates 2

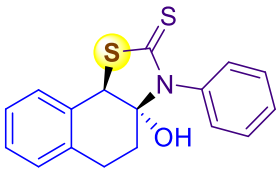
A mixture of 2-tetralone **1** (1 mmol), isothiocyanate **2** (1.2 mmol), S (1.5 mmol, 48 mg) and *N*-methylpiperidine (0.2 mmol, 20 mg) in a 7-mL test tube equipped with a magnetic stirring bar was vigorously stirred at rt for 30 min. The reaction mixture became instantaneously hot with dissolution of sulfur, 2-tetralone and isothiocyanate (if the two organic substrates are solid at rt) and solidification. The reaction tube could be shaken manually from time to time if needed. The crude mixture was triturated with methanol (2 mL) to form a slurry of off-white or pale-yellow product, which was next filtered and washed with cold methanol (2 mL) and dried in vacuo to afford **3**. In case of products **3** derived from alkyl isothiocyanates, due to their high solubility in methanol, the purification by column chromatography on silica gel (eluent CH_2Cl_2) was needed.

General procedure for dehydration of 4-hydroxythiazolidine-2-thiones 3 to thiazole-2-thiones 4

Solid 4-hydroxythiazolidine-2-thione **3** (0.25 mmol) in a 7-mL test tube equipped with a magnetic stirring bar was soaked with TFA (1 mmol) and vigorously stirred at rt for 5 min. The reaction mixture was diluted in CH_2Cl_2 (2 mL) and neutralized with a saturated aqueous solution of $NaHCO_3$ (2 mL). The dichloromethane layer was separated, dried with solid $NaHCO_3$ and filtered through a short pad of silica gel (2-cm height filled in a cotton-plugged pipette) to a round-bottomed flask. Additional CH_2Cl_2 (2 x 2 mL) was used to extract **4** from aqueous layer and elute product **4**. Evaporation of CH_2Cl_2 afforded thiazole-2-thione **4** as white or pale-yellow solid.

Characterization of products

(3a*R*,9b*R*)-3a-Hydroxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3a)



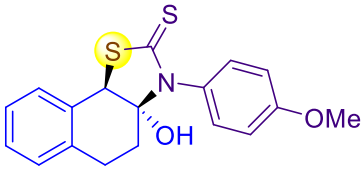
Pale yellow solid (282 mg, 90%). The 5-mmol scale reaction was performed in the same manner in a 7-mL test tube to provide product as a pale yellow solid (1.33 mg, 85%).

^{1}H NMR (300 MHz, DMSO) δ 7.55-7.46 (m 4H), 7.39-7.35 (m 2H), 7.31-7.18 (m 4H), 5.21 (s, 1H), 2.85-2.64 (m 2H), 2.15-2.06 (m 1H), 1.98-1.89 (m 1H).

^{13}C NMR (75 MHz, DMSO) δ 195.6, 137.8, 134.8, 133.2, 129.8 (2C), 129.6, 128.9 (2C), 128.6, 128.5, 127.5, 126.8, 98.9, 54.2, 30.2, 25.3.

HRMS (ESI+) calcd for $C_{17}H_{16}NOS_2$ $[M + H]^+$ 314.0673. Found 314.0670.

(3a*R*,9b*R*)-3a-Hydroxy-3-(4-methoxyphenyl)-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3b)



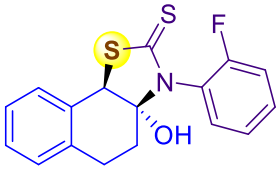
Pale yellow solid (285 mg, 83%).

^{1}H NMR (300 MHz, DMSO) δ 7.38 (s, 1H), 7.31-7.14 (m, 6H), 7.04 (d, J = 9.0 Hz, 2H), 5.16 (s, 1H), 3.81 (s, 3H), 2.87-2.61 (m, 2H), 2.16-2.01 (m, 1H), 1.98-1.81 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 195.6, 159.0, 134.8, 133.2, 130.7, 130.2, 129.5, 128.5, 127.3, 126.7, 114.0, 98.6, 55.2, 53.9, 30.1, 25.3.

HRMS (ESI+) calcd for $C_{18}H_{18}NO_2S_2$ $[M + H]^+$ 344.0779. Found 344.0783.

(3a*R*,9b*R*)-3-(2-Fluorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3c)



Pale yellow solid (278 mg, 84%).

Mixture 2:1 of two isomers

1H Signals of the major isomer

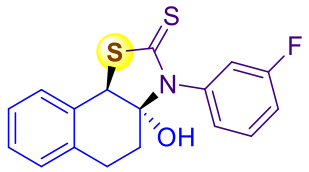
^{1}H NMR (300 MHz, DMSO) δ 7.58-7.50 (m, 3H), 7.44-7.34 (m, 2H), 7.32-7.17 (m, 4H), 5.25 (s, 1H), 2.75-2.70 (m, 2H), 2.14-2.03 (m, 1H), 1.94-1.85 (m, 1H).
Some characteristic of the minor isomer

^{1}H NMR (300 MHz, DMSO) δ 5.39 (s, 1H), 2.96-2.85 (m, 2H), 2.40-2.30 (m, 1H).

^{13}C NMR (75 MHz, DMSO) major isomer: δ 195.7, 158.0 (d, J = 250.1 Hz), 135.0, 132.9, 131.5, 131.0 (d, J = 7.8 Hz), 129.6, 128.6, 127.6, 126.8, 124.9 (d, J = 3.6 Hz), 116.7, 116.3 (d, J = 19.8 Hz), 99.2, 54.6, 30.1, 25.0. Some characteristic of the minor isomer δ 194.3, 157.1, 134.9, 132.9, 131.1 (d, J = 6.2 Hz), 128.9, 127.8, 127.6, 126.7, 124.6 (d, J = 3.7 Hz), 116.7, 99.1, 52.9, 28.9, 25.4.

^{19}F NMR (282 MHz, DMSO) δ -115.59 (major isomer), -117.58 (minor isomer),
HRMS (ESI+) calcd for $C_{17}H_{15}FNOS_2$ $[M + H]^+$ 332.0579. Found 332.0585.

(3a*R*,9b*R*)-3-(3-Fluorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3d)

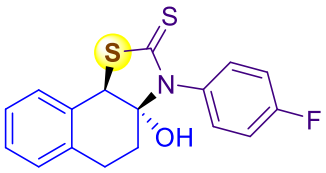


Pale yellow solid (275 mg, 83%).

^{1}H NMR (300 MHz, DMSO) δ 7.61-7.49 (m, 2H), 7.38-7.15 (m, 7H), 5.21 (s, 1H), 2.89-2.60 (m, 2H), 2.17-2.06 (m, 1H), 2.00-1.88 (m, 1H).
^{13}C NMR (75 MHz, DMSO) δ 233.7, 201.0, 197.8, 176.8 (d, J = 10.3 Hz), 172.4, 170.7, 167.9 (d, J = 9.2 Hz), 167.1, 166.2, 165.1, 164.3, 163.8 (d, J = 2.9 Hz), 153.9 (dd, J = 112.9, 21.8 Hz), 136.6, 92.0, 67.8, 62.9.

^{19}F NMR (282 MHz, DMSO) δ -112.33.
HRMS (ESI+) calcd for $C_{17}H_{15}FNOS_2$ $[M + H]^+$ 332.0579. Found 332.0588.

(3a*R*,9b*R*)-3-(4-Fluorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3e)



Pale yellow solid (288 mg, 87%).

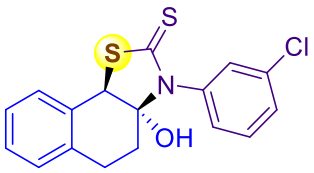
^{1}H NMR (300 MHz, DMSO) δ 7.50 (s, 1H), 7.44-7.31 (m, 4H), 7.29-7.16 (m, 4H), 5.19 (s, 1H), 2.83-2.64 (m, 2H), 2.12-2.03 (m, 1H), 1.95-1.86 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 196.0, 161.7 (d, J = 245.6 Hz), 134.8, 133.9 (d, J = 3.2 Hz), 133.1, 132.0 (d, J = 8.9 Hz), 129.6, 128.6, 127.5, 126.8, 115.7 (d, J = 22.7 Hz), 98.8, 54.1, 30.2, 25.3.

^{19}F NMR (282 MHz, DMSO) δ -113.04.

HRMS (ESI+) calcd for $C_{17}H_{15}FNOS_2$ $[M + H]^+$ 332.0579. Found 332.0572.

(3a*R*,9b*R*)-3-(3-Chlorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3f)



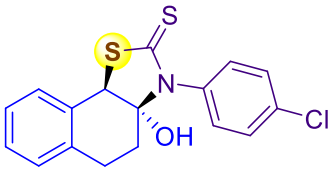
Pale yellow solid (312 mg, 90%).

^{1}H NMR (300 MHz, DMSO) δ 7.57-7.55 (m, 3H), 7.47-7.45 (m, 1H), 7.40-7.33 (m, 1H), 7.30-7.18 (m, 4H), 5.22 (s, 1H), 2.85-2.65 (m, 2H), 2.16-2.07 (m, 1H), 1.98-1.89 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 196.1, 139.0, 134.8, 133.0, 132.9, 130.4, 129.7, 129.6, 128.8, 128.7, 127.5, 126.8, 99.0, 54.3, 30.1, 25.3 (1 signal missing due to overlap).

HRMS (ESI+) calcd for $C_{17}H_{15}ClNOS_2$ $[M + H]^+$ 348.0284. Found 348.0289.

(3a*R*,9b*R*)-3-(4-Chlorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3g)



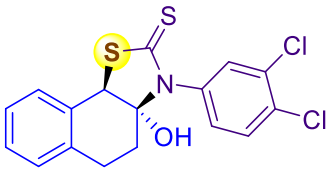
Pale yellow solid (302 mg, 87%).

^{1}H NMR (300 MHz, DMSO) δ 7.75-7.65 (m, 2H), 7.55-7.45 (m, 1H), 7.32 (dd, J = 7.0, 1.7 Hz, 2H), 7.28-7.14 (m, 4H), 5.20 (s, 1H), 2.87-2.61 (m, 2H), 2.15-2.01 (m, 1H), 2.00-1.79 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 196.0, 137.1, 134.8, 133.1, 132.0, 129.6, 128.6, 127.5, 126.8, 125.6, 121.8, 98.9, 54.3, 30.2, 25.3.

HRMS (ESI+) calcd for $C_{17}H_{15}ClNOS_2$ $[M + H]^+$ 348.0284. Found 348.0279.

(3a*R*,9b*R*)-3-(3,4-Dichlorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3h)



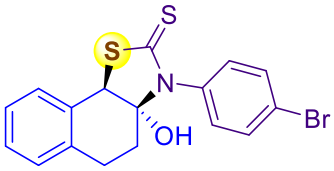
Pale yellow solid (339 mg, 89%).

^{1}H NMR (300 MHz, DMSO) δ 7.82-7.79 (m, 1H), 7.69-7.68 (m, 1H), 7.59 (brs, 1H), 7.46-7.39 (m, 1H), 7.30-7.18 (m, 4H), 5.23 (s, 1H), 2.85-2.65 (m, 2H), 2.18-2.09 (m, 1H), 1.98-1.90 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 196.4, 137.6, 134.8, 132.9, 131.8, 131.6, 131.2, 130.8, 130.5, 129.6, 128.7, 127.6, 126.8, 99.0, 54.4, 30.2, 25.3.

HRMS (ESI+) calcd for $C_{17}H_{14}Cl_2NOS_2$ $[M + H]^+$ 381.9894. Found 381.9890.

(3a*R*,9b*R*)-3-(4-Bromophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3i)



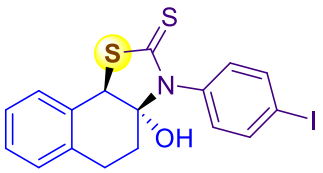
Pale yellow solid (360 mg, 92%).

^{1}H NMR (300 MHz, DMSO) δ 7.58 (d, J = 8.7 Hz, 2H), 7.50 (s, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.31-7.15 (m, 4H), 5.20 (s, 1H), 2.86-2.61 (m, 2H), 2.16-2.03 (m, 1H), 2.00-1.82 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 196.0, 136.5, 134.7, 133.2, 133.0, 131.6, 129.5, 128.9, 128.5, 127.4, 126.7, 98.8, 54.2, 30.2, 25.2.

HRMS (ESI+) calcd for $C_{17}H_{15}BrNOS_2$ $[M + H]^+$ 391.9778. Found 391.9782.

(3a*R*,9b*R*)-3a-Hydroxy-3-(4-iodophenyl)-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3j)



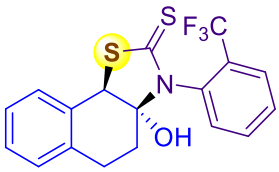
Pale yellow solid (386 mg, 88%).

^{1}H NMR (500 MHz, DMSO) δ 7.89, 7.88 (m, 2H), 7.53 (s, 1H), 7.29-7.16 (m, 6H), 5.20 (m, 1H), 2.79-2.71 (m, 2H), 2.11-2.06 (m, 1H), 1.95-1.90 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 195.9, 137.8, 137.5, 134.8, 133.1, 132.0, 129.6, 128.6, 127.5, 126.8, 98.9, 95.0, 54.3, 30.2, 25.3.

HRMS (ESI+) calcd for $C_{17}H_{15}INOS_2$ $[M + H]^+$ 439.9640. Found 439.9645.

(3a*R*,9b*R*)-3a-Hydroxy-3-(2-(trifluoromethyl)phenyl)-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3k)



Pale yellow solid (297 mg, 78%).

Mixture 5:1 of two isomers

1H Signals of the major isomer

^{1}H NMR (300 MHz, DMSO) δ 7.92-7.89 (m, 1H), 7.86-7.79 (m, 1H), 7.76-7.69 (m, 1H), 7.48-7.46 (m, 1H), 7.33 (brs, 1H), 7.31-7.23 (m, 4H), 5.29 (s, 1H), 2.97-2.87 (m, 2H), 2.57-2.52 (m, 1H), 2.22-2.15 (m, 1H).

Some characteristic of the minor isomer

^{1}H NMR (300 MHz, DMSO) δ 7.65-7.56 (m, 2H), 5.24 (s, 1H), 2.83-2.74 (m, 2H), 2.46-2.44 (m, 1H).

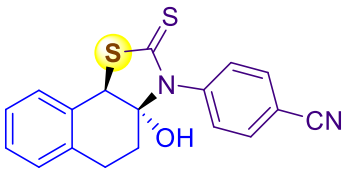
^{13}C NMR (75 MHz, DMSO) major isomer: δ 193.2, 134.6, 133.0, 132.8, 132.4 (d, J = 26.3 Hz), 130.0, 129.8, 129.7, 129.1, 128.1 (q, J = 4.2 Hz), 127.9, 126.7, 123.3 (d, J = 274.2 Hz), 99.2, 52.5, 27.8, 25.3.

Some characteristic of the minor isomer: δ 135.4, 134.8, 133.3, 129.5, 128.3, 127.6, 121.4, 99.6, 55.1, 30.3.

^{19}F NMR (282 MHz, DMSO) δ -57.21 (major isomer), -56.80 (minor isomer).

HRMS (ESI+) calcd for $C_{18}H_{15}F_3NOS_2$ $[M + H]^+$ 382.0547. Found 382.0556.

4-((3a*R*,9b*R*)-3a-Hydroxy-2-thioxo-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazol-3(2*H*)-yl)benzonitrile (3l)



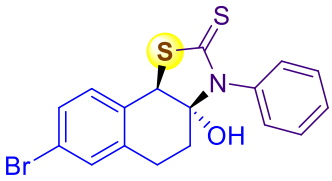
Pale yellow solid (284 mg, 84%).

^{1}H NMR (300 MHz, DMSO) δ 8.04-7.99 (m, 2H), 7.68 (s, 1H), 7.64-7.59 (m, 2H), 7.32-7.17 (m, 4H), 5.24 (s, 1H), 2.81-2.63 (m, 2H), 2.14-2.05 (m, 1H), 1.99-1.90 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 196.4, 142.1, 134.7, 133.1, 133.0, 131.0, 129.6, 128.6, 127.5, 126.8, 118.2, 111.4, 99.3, 54.7, 30.3, 25.3.

HRMS (ESI+) calcd for $C_{18}H_{15}N_2OS_2$ $[M + H]^+$ 339.0626. Found 339.0630.

(3a*R*,9b*R*)-7-Bromo-3a-hydroxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3m)



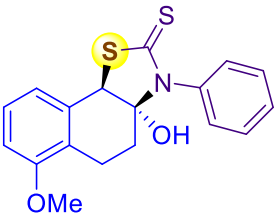
Pale yellow solid (348 mg, 89%).

^{1}H NMR (300 MHz, DMSO) δ 7.54-7.51 (m, 2H), 7.50-7.45 (m, 2H), 7.43 (brs, 2H), 7.38-7.34 (m, 2H), 7.30-7.26 (m, 1H), 5.15 (s, 1H), 2.84-2.63 (m, 2H), 2.09-2.00 (m, 1H), 1.96-1.87 (m, 1H).

^{13}C NMR (126 MHz, DMSO) δ 195.7, 137.7, 137.6, 133.0, 131.8, 131.1, 129.6 (3C), 128.9 (2C), 128.6, 120.5, 98.6, 53.8, 29.9, 25.1.

HRMS (ESI+) calcd for $C_{17}H_{15}BrNOS_2$ $[M + H]^+$ 391.9778. Found 391.9768.

(3a*R*,9b*R*)-3a-Hydroxy-6-methoxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3n)



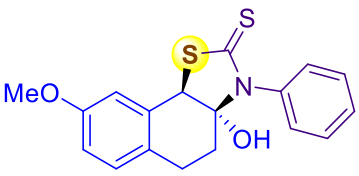
Pale yellow solid (299 mg, 87%).

^{1}H NMR (300 MHz, DMSO) δ 7.55-7.43 (m, 4H), 7.43-7.31 (m, 2H), 7.26-7.21 (m, 1H), 6.90-6.85 (m, 2H), 5.17 (s, 1H), 3.79 (s, 3H), 2.70-2.55 (m, 2H), 2.13-2.04 (m, 1H), 1.97-1.88 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 195.4, 156.4, 137.7, 134.0, 129.7, 128.8, 128.5, 127.5, 123.3, 121.4, 109.1, 98.5, 55.4, 53.9, 29.1, 19.3 (1 signal missing due to overlap).

HRMS (ESI+) calcd for $C_{18}H_{18}NO_2S_2$ $[M + H]^+$ 344.0779. Found 344.0785.

(3a*R*,9b*R*)-3a-Hydroxy-8-methoxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3o)



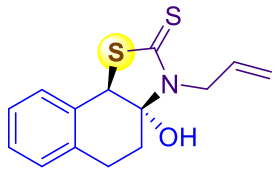
Pale yellow solid (302 mg, 88%).

^{1}H NMR (300 MHz, DMSO) δ 7.54-7.42 (m, 4H), 7.37-7.33 (m, 2H), 7.11-7.08 (m, 1H), 6.87-6.81 (m, 2H), 5.14 (s, 1H), 3.75 (s, 3H), 2.75-2.57 (m, 2H), 2.10-2.01 (m, 1H), 1.93-1.85 (m, 1H).

^{13}C NMR (75 MHz, DMSO) δ 195.7, 158.0, 137.8, 134.4, 129.7 (2C), 129.6, 128.8 (2C), 128.4, 126.7, 114.1, 114.0, 98.9, 55.2, 54.5, 30.6, 24.5.

HRMS (ESI+) calcd for $C_{18}H_{18}NO_2S_2$ $[M + H]^+$ 344.0779. Found 344.0773.

(3a*R*,9b*R*)-3-Allyl-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3p)



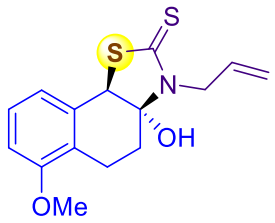
Purification of the crude mixture by column chromatography (DCM: 100%) afforded the product (211 mg, 76%).

^{1}H NMR (300 MHz, DMSO) δ 7.32 (s, 1H), 7.26-7.14 (m, 4H), 6.04-5.80 (m, 1H), 5.32 (dd, J = 17.3, 1.5 Hz, 1H), 5.19 (dd, J = 10.2, 1.4 Hz, 1H), 5.04 (s, 1H), 4.45-4.28 (m, 2H), 2.96-2.65 (m, 2H), 2.25-1.94 (m, 2H).

^{13}C NMR (75 MHz, DMSO) δ 192.1, 134.9, 133.0, 131.8, 129.4, 128.6, 127.5, 126.6, 117.8, 98.1, 52.1, 46.8, 29.1, 25.4.

HRMS (ESI+) calcd for $C_{14}H_{16}NOS_2$ $[M + H]^+$ 278.0673. Found 278.0678.

(3a*R*,9b*R*)-3-Allyl-3a-Hydroxy-6-methoxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3q)



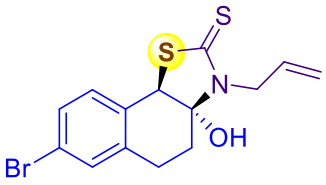
Purification of the crude mixture by column chromatography (DCM: 100%) afforded the product (224 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, J = 8.0 Hz, 1H), 6.73 (dd, J = 16.3, 7.9 Hz, 2H), 6.10-6.00 (m, 1H), 5.99-5.22 (m, 2H), 4.94 (s, 1H), 4.61-4.53 (m, 1H), 4.43-4.35 (m, 1H), 3.89 (s, 1H), 3.84 (s, 3H), 2.82-2.77 (m, 2H), 2.32-2.22 (m, 1H), 2.19-2.10 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 156.8, 132.9, 132.7, 127.6, 123.9, 121.4, 118.5, 109.1, 98.4, 55.5, 54.0, 47.8, 28.8, 19.6.

HRMS (ESI+) calcd for $C_{15}H_{18}NO_2S_2$ $[M + H]^+$ 308.0779. Found 308.0783.

(3a*R*,9b*R*)-3-Allyl-7-bromo-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3r)



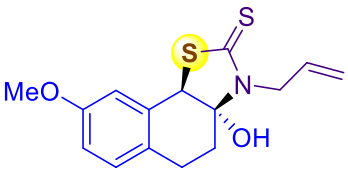
Purification of the crude mixture by column chromatography (DCM: 100%) afforded the product (291 mg, 82%).

^{1}H NMR (300 MHz, DMSO) δ 7.45-7.37 (m, 3H), 7.20-7.17 (m, 1H), 5.99-5.86 (m, 1H), 5.36-5.29 (m, 1H), 5.22-5.17 (m, 1H), 5.01 (s, 1H), 4.42-4.29 (m, 2H), 2.88-2.71 (m, 2H), 2.19-2.00 (m, 2H).

^{13}C NMR (75 MHz, DMSO) δ 192.1, 137.8, 133.0, 131.6, 131.6, 131.2, 129.6, 120.6, 118.0, 98.0, 51.7, 46.9, 28.9, 25.3.

HRMS (ESI+) calcd for $C_{14}H_{15}BrNOS_2$ $[M + H]^+$ 355.9778. Found 355.9781.

(3a*R*,9b*R*)-3-Allyl-3a-hydroxy-8-methoxy-3a,4,5,9b-tetrahydronaphtho[2,1-d]thiazole-2(3*H*)-thione (3s)



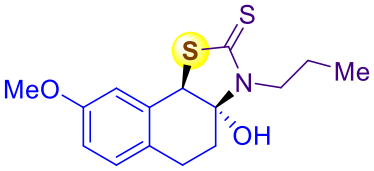
Purification of the crude mixture by column chromatography (DCM: 100%) afforded the product (236 mg, 77%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05-7.03 (m, 1H), 6.83-6.76 (m, 1H), 6.59-6.58 (m, 1H), 6.05-5.99 (m, 1H), 5.36-5.32 (m, 1H), 5.24-5.21 (m, 1H), 4.89 (s, 1H), 4.57-4.52 (m, 1H), 4.40-4.36 (m, 1H), 3.95 (broad s, 1H), 3.76 (s, 3H), 2.84-2.79 (m, 1H), 2.75-2.71 (m, 1H), 2.30-2.26 (m, 1H), 2.15-2.11 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 194.6, 158.5, 132.9, 132.7, 129.8, 126.8, 118.5, 114.5, 113.9, 98.7, 55.5, 54.4, 47.8, 30.0, 25.1.

HRMS (ESI+) calcd for $C_{15}H_{18}NO_2S_2$ $[M + H]^+$ 308.0779. Found 308.0785.

(3a*R*,9b*R*)-3a-Hydroxy-8-methoxy-3-propyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3t)



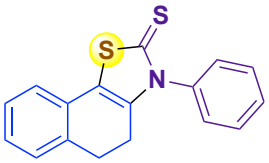
Purification of the crude mixture by column chromatography (DCM: 100%) afforded the product (226 mg, 73%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 (d, J = 8.5 Hz, 1H), 6.77 (dd, J = 8.5, 2.7 Hz, 1H), 6.58 (d, J = 2.6 Hz, 1H), 4.90 (s, 1H), 4.07 (brs, 1H), 3.91-3.87 (m, 1H), 3.76-3.75 (m, 3H), 3.49-3.44 (m, 1H), 2.88-2.83 (m, 1H), 2.75-2.71 (m, 1H), 2.27-2.23 (m, 1H), 2.09-2.13 (s, 1H), 1.87-1.78 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 193.7, 158.4, 132.4, 129.8, 126.7, 114.6, 113.9, 98.5, 55.5, 54.2, 47.4, 29.4, 25.1, 21.8, 11.6.

HRMS (ESI+) calcd for $C_{15}H_{20}NO_2S_2$ $[M + H]^+$ 310.0935. Found 310.0940.

3-Phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4a)



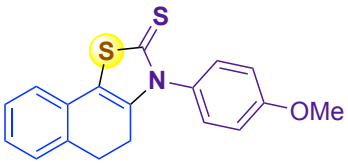
Pale yellow solid (72 mg, 98%).

^{1}H NMR (500 MHz, DMSO) δ 7.63-7.59 (m, 2H), 7.57-7.54 (m, 1H), 7.47-7.44 (m, 2H), 7.28-7.20 (m, 3H), 7.16-7.14 (m, 1H), 2.98-2.95 (m, 2H), 2.46-2.43 (m, 2H).

^{13}C NMR (126 MHz, DMSO) δ 186.4, 140.4, 136.8, 133.1, 129.6 (2C), 129.5, 128.2 (2C), 128.1, 127.8, 127.6, 127.3, 122.6, 118.6, 27.0, 23.4.

HRMS (ESI+) calcd for $C_{17}H_{14}NS_2$ $[M + H]^+$ 296.0568. Found 296.0572.

3-(4-Methoxyphenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4b)



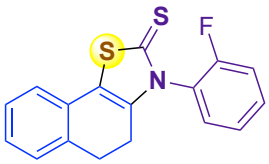
Pale yellow solid (79 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.16 (m, 6H), 7.07 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H), 3.00 (t, J = 8.0 Hz, 2H), 2.50 (t, J = 8.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.29 (s), 160.2, 139.6, 132.9, 129.7, 129.0, 128.4, 128.0, 127.6, 127.4, 122.8, 120.2, 115.1, 55.6, 27.9, 24.0.

HRMS (ESI+) calcd for $C_{18}H_{16}NOS_2$ $[M + H]^+$ 326.0673. Found 326.0665.

3-(2-Fluorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4c)



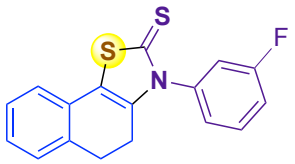
Pale yellow solid (77 mg, 98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.50 (m, 1H), 7.47-7.32 (m, 3H), 7.31-7.17 (m, 3H), 7.08 (d, J = 7.6 Hz, 1H), 3.02 (t, J = 8.1 Hz, 2H), 2.63-2.39 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 159.2, 155.8, 138.9, 132.9, 131.93 (d, J = 7.8 Hz), 130.4, 128.3, 128.1, 127.8, 127.5, 125.26 (d, J = 3.8 Hz), 122.9, 120.6, 117.25 (d, J = 19.2 Hz), 27.9, 23.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -119.68 (s).

HRMS (ESI+) calcd for $C_{17}H_{13}FNS_2$ $[M + H]^+$ 314.0473. Found 314.0469.

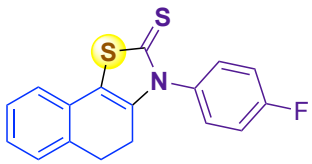
3-(3-Fluorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4d)



Pale yellow solid (74 mg, 95%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 14.2, 8.0 Hz, 1H), 7.30-7.19 (m, 4H), 7.17-7.05 (m, 3H), 3.02 (t, J = 8.0 Hz, 2H), 2.51 (t, J = 8.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 188.0, 164.6, 161.3, 138.7, 138.3 (d, J = 9.9 Hz), 132.8, 131.1 (d, J = 9.0 Hz), 128.1 (d, J = 3.7 Hz), 127.8, 127.4, 124.0 (d, J = 3.3 Hz), 122.9, 120.7, 117.0 (d, J = 20.9 Hz), 115.9 (d, J = 23.5 Hz), 27.9, 23.9.

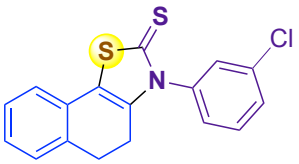
^{19}F NMR (282 MHz, $CDCl_3$) δ -109.57.
HRMS (ESI+) calcd for $C_{17}H_{13}FNS_2$ $[M + H]^+$ 314.0473. Found 314.0477.

3-(4-Fluorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4e)



Pale yellow solid (75 mg, 96%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 2H), 7.32-7.26 (m, 3H), 7.25-7.19 (m, 2H), 7.10 (d, J = 7.3 Hz, 1H), 3.02 (t, J = 8.0 Hz, 2H), 2.51 (t, J = 8.0 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 188.3, 162.9 (d, J = 250.6 Hz), 139.0, 133.0, 132.8, 130.0 (d, J = 8.9 Hz), 128.2, 128.1, 127.8, 127.5, 122.9, 120.8, 117.1 (d, J = 23.2 Hz), 27.9, 23.9.
^{19}F NMR (282 MHz, DMSO) δ -113.04.
HRMS (ESI+) calcd for $C_{17}H_{13}FNS_2$ $[M + H]^+$ 314.0473. Found 314.0468.

3-(3-Chlorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4f)



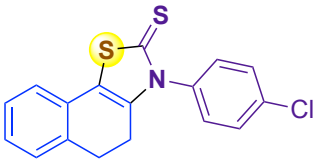
Pale yellow solid (77 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.48 (m, 2H), 7.37 (d, J = 1.3 Hz, 1H), 7.32-7.17 (m, 4H), 7.08 (d, J = 7.6 Hz, 1H), 3.02 (t, J = 8.0 Hz, 2H), 2.62-2.40 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.2, 138.7, 138.2, 135.5, 132.9, 130.9, 130.1, 128.5, 128.2, 128.1, 127.9, 127.5, 126.5, 123.0, 120.9, 27.9, 24.0.

HRMS (ESI+) calcd for $C_{17}H_{13}ClNS_2$ $[M + H]^+$ 330.0178. Found 330.0183.

3-(4-Chlorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4g)



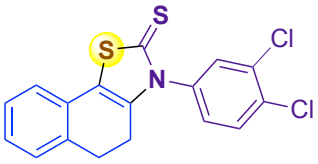
Pale yellow solid (76 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2H), 7.33-7.19 (m, 5H), 7.08 (d, J = 7.2 Hz, 1H), 3.02 (t, J = 8.0 Hz, 2H), 2.51 (t, J = 8.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.1, 138.8, 135.8, 135.5, 132.8, 130.2, 129.5, 128.1, 127.9, 127.5, 123.0, 120.9, 27.9, 23.9 (1 signals missing due to overlap).

HRMS (ESI+) calcd for $C_{17}H_{13}ClNS_2$ $[M + H]^+$ 330.0178. Found 330.0171.

3-(3,4-Dichlorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4h)



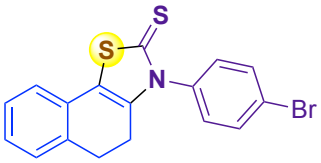
Pale yellow solid (86 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.32-7.19 (m, 4H), 7.07 (d, J = 7.1 Hz, 1H), 3.04 (t, J = 8.0 Hz, 2H), 2.61-2.41 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.1, 138.4, 136.1, 134.4, 133.9, 132.8, 131.6, 130.2, 128.1, 128.0, 127.7, 127.5, 123.0, 121.1, 27.9, 23.9 (1 signal missing due to overlap).

HRMS (ESI+) calcd for $C_{17}H_{12}Cl_2NS_2$ $[M + H]^+$ 363.9788. Found 363.9792.

3-(4-Bromophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4i)



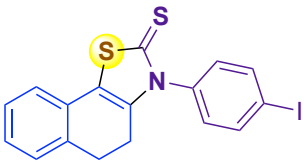
Pale yellow solid (88 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.67 (m, 2H), 7.35-7.17 (m, 5H), 7.08 (d, J = 7.4 Hz, 1H), 3.02 (t, J = 8.0 Hz, 2H), 2.50 (t, J = 8.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 138.6, 136.1, 133.2, 132.8, 129.7, 128.1, 127.8, 127.5, 126.6, 123.9, 122.9, 120.9, 27.9, 24.0.

HRMS (ESI+) calcd for $C_{17}H_{13}BrNS_2$ $[M + H]^+$ 373.9673. Found 373.9675.

3-(4-Iodophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4j)



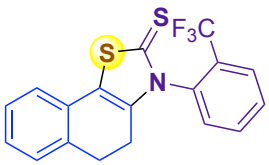
Pale yellow solid (102 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 2H), 7.30-7.25 (m, 1H), 7.25-7.19 (m, 2H), 7.10 (t, J = 7.9 Hz, 3H), 3.02 (t, J = 8.0 Hz, 2H), 2.51 (t, J = 8.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.0, 139.3, 138.7, 136.9, 132.9, 129.9), 128.2, 128.1, 127.9, 127.6, 126.9, 123.0, 121.1, 28.0, 24.0.

HRMS (ESI+) calcd for $C_{17}H_{13}INS_2$ $[M + H]^+$ 421.9534. Found 421.9536.

3-(2-(Trifluoromethyl)phenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4k)



Pale yellow solid (84 mg, 92%).

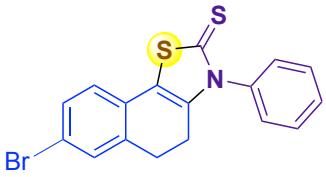
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 7.8 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.30-7.26 (m, 1H), 7.25-7.19 (m, J = 7.4 Hz, 2H), 7.10 (d, J = 7.3 Hz, 1H), 3.09-2.91 (m, 2H), 2.43 (t, J = 8.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.9, 139.3, 135.1, 133.9, 132.9, 131.2, 130.7, 128.2 (q, J = 3.8 Hz), 127.8, 127.5, 126.0, 124.4, 123.8, 120.5 (q, J = 274.1 Hz), 119.4, 27.8, 23.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -61.06 (s).

HRMS (ESI+) calcd for $C_{18}H_{13}F_3NS_2$ $[M + H]^+$ 364.0442. Found 364.0437.

7-Bromo-3-phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4m)



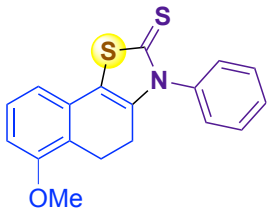
Pale yellow solid (86 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (t, J = 7.4 Hz, 2H), 7.54-7.48 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 7.2 Hz, 3H), 6.90 (d, J = 8.1 Hz, 1H), 2.95 (t, J = 8.0 Hz, 2H), 2.46 (t, J = 8.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.0, 139.5, 137.0, 134.9, 131.1, 130.4, 130.0 (2C), 129.9, 128.0 (2C), 127.4, 124.2, 121.0, 119.5, 27.7, 23.7.

HRMS (ESI+) calcd for $C_{17}H_{13}BrNS_2$ $[M + H]^+$ 373.9673. Found 373.9668.

6-Methoxy-3-phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4n)



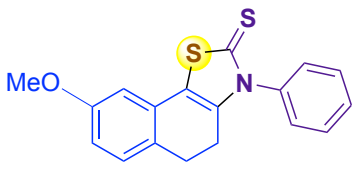
Pale yellow solid (77 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (t, J = 7.3 Hz, 2H), 7.54-7.50 (m, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.20 (t, J = 7.9 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 3.83 (s, 3H), 2.97 (t, J = 8.2 Hz, 2H), 2.44 (t, J = 8.2 Hz, 2H).

^{13}C NMR (126 MHz, DMSO) δ 195.3, 156.3, 137.7, 133.9, 129.7 (2C), 128.9 (2C), 128.5, 127.5, 123.2, 121.5, 109.0, 98.4, 55.4, 53.9, 28.9, 19.3.

HRMS (ESI+) calcd for $C_{18}H_{16}NOS_2$ $[M + H]^+$ 326.0673. Found 326.0676.

8-Methoxy-3-phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4o)



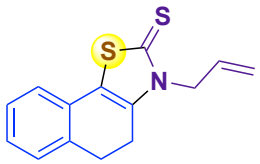
Pale yellow solid (72 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2H), 7.54-7.50 (m, 1H), 7.32 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.61 (s, 1H), 3.82 (s, 3H), 2.90 (t, J = 8.0 Hz, 2H), 2.45 (t, J = 8.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.1, 159.0, 139.8, 137.3, 130.0, 129.9, 129.4, 129.0, 128.0, 125.0, 120.6, 112.5, 109.1, 55.6, 27.2, 24.4.

HRMS (ESI+) calcd for $C_{18}H_{16}NOS_2$ $[M + H]^+$ 326.0673. Found 326.0679.

3-Allyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4p)



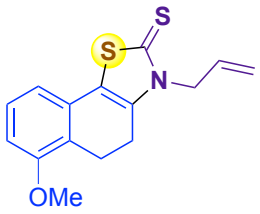
Pale yellow solid (58 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.15 (m, 3H), 7.03 (d, J = 7.1 Hz, 1H), 6.00-5.89 (m, 1H), 5.29 (d, J = 10.4 Hz, 1H), 5.16 (d, J = 17.2 Hz, 1H), 4.99-4.89 (m, 2H), 3.08 (t, J = 8.0 Hz, 2H), 2.84 (t, J = 8.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 186.4, 138.8, 132.7, 130.3, 128.2, 128.0, 127.7, 127.5, 122.9, 120.5, 118.1, 49.0, 28.0, 23.2.

HRMS (ESI+) calcd for $C_{14}H_{14}NS_2$ $[M + H]^+$ 260.0568. Found 260.0561.

3-Allyl-6-methoxy-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4q)



Pale yellow solid (66 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.11 (m, 1H), 6.74 (dd, J = 42.3, 8.0 Hz, 2H), 6.14-5.78 (m, 1H), 5.29 (d, J = 10.4 Hz, 1H), 5.16 (d, J = 17.2 Hz, 1H), 4.98-4.87 (m, 2H), 3.86 (s, 3H), 3.07 (t, J = 8.2 Hz, 2H), 2.80 (t, J = 8.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.7, 156.7, 138.8, 130.5, 129.3, 128.0, 120.6, 120.2, 118.1, 115.7, 110.3, 55.7, 49.0, 22.8, 20.4.

HRMS (ESI+) calcd for $C_{15}H_{16}NOS_2$ $[M + H]^+$ 290.0673. Found 290.0667.

Crystallographic data collection, structure determination and refinement

Colourless plate-like crystals of **3a** and **4o** were obtained *in the presence of DMSO*. X-ray diffraction data were recorded at room temperature from redundant ω scans, using a Rigaku XtaLabPro single-crystal diffractometer equipped with a microfocus Mo Kα radiation and a HPAD PILATUS3 R 200K detector. *CrysAlisPro*[1] was used for data processing applying an empirical absorption correction using spherical harmonics, combined with a numerical approach, as implemented in the *SCALE3 ABSPACK* scaling algorithm. The tested crystal of **3a** was a two-component non-merohedral twin by 2.44° degrees about the reciprocal [100] direction, with a twin ratio of 60:40. The structure was solved from the data of the larger twin component, by intrinsic phasing methods (*SHELXT* program).[2] A hklf-5 formatted datafile accounting for the twin law was produced in order to perform the twin refinement using full-matrix least-squares methods on F^2 with *SHELX-L*.[3] All equivalent reflections were merged and the BASF parameter refined to 0.404(1). The displacement parameters for all non-hydrogen atoms (21), present within the asymmetric unit (asu) of the monoclinic cell, space group *C*c, were refined anisotropically. The crystal structure is shown in Figure S1a and the crystal data, data collection and structure refinement details are summarized in Table S1. The positions of the hydrogen atoms were identified in the Fourier difference maps, however those attached to the carbon atoms were refined using the riding model, with U_{iso} set to $1.2U_{eq}$(C). The position of the hydroxyl hydrogen was freely refined, with U_{iso} set to $1.5U_{eq}$(O). The hydroxyl group forms a hydrogen bond with the sulfur atom S2 of the adjacent molecule at x-1, y, z, making infinite chains along the ***a*** direction, with a *C*(6) graph-set motif[4] (Figure S2a).

With respect to the second reduced complex **4o** shown in Figure S1b, the refinement of the model thanks to the high data quality, was pursued using the *Transferable aspherical atom model (TAAM)* approach within *Olex2*. [5] The aspherical atomic scattering factors computed by the DiSCaMB library [6] from the multipole model [7] and parametrized using the MATTS2021 data bank [8] were transferred into *NoSpherA2*[9] as a tsc file format. These form factors were utilized during the least-squares refinement against experimental intensities in an iterative cycle until convergence was achieved through *olex2.refine*.[10] The hydrogen atoms were therefore freely refined in an anisotropic manner. A search of the Cambridge Structural Database (version 5.45, last update: June 2024[11]) for the thiazolidine-2-thione motif yielded 805 crystal structures. With the exception of one complex with C60, only one structure was identified to be fused at the C1-C2 bond with a naphthalene-type ring, CCDC Refcode ZEPVAV. [12] **3a** exhibits a reduced C1=C2 bond, wherein the quasi-planarity of the three fused rings observed in the deposited structure is lost. The resulting relative stereogenic centres are identified as C1*R*, C2*R* (or C1*S*, C2*S*) (Figure S4). The five- and six-membered joint rings are puckered as envelope at C2 and at C7, respectively (see captions of figure S1). In the case of **4o** only the aforementioned six-membered ring is puckered to a reduced extent. The resulting dihedral angle between the hetero five-membered best plane and the naphthalene-like best plane in **3a** was about 47° compared to the quasi unfolded ZEPVAV platform, whereas it can be observed to be around 17° in the case of **4o**. The dihedral angles between the

phenyl group at N5 and the five-heteromembered ring ranged from -54.16 to -119.3° in the six independent copies of ZEPVAV (average value close to 90°), and took values of -93.78 and -76.05 in **3a** and **4o**, respectively.

CCDC 2371492 and 2375946 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References

1 Rigaku OD (2015). *CrysAlis PRO*. Rigaku Oxford Diffraction, Yarnton, Oxfordshire, England.

2 Sheldrick, G. M. (2015). *Acta Cryst.* **A**71, 3-8.

3 Sheldrick, G. M. (2015). *Acta Cryst.* **C**71, 3-8.

4 Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* B**46**, 256–262 ; Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.

5 Dolomanov, OV., Bourhis, LJ., Gildea, RJ., Howard, JAK. & Puschmann, H. (2009). *J. Appl. Cryst.* **42**. 339–341.

6 Chodkiewicz, ML., Migacz, S., Rudnicki, W., Makal, A., Kalinowski, JA., Moriarty, NW., Grosse-Kunstleve, RW., Afonine, PV., Adams, PD. & Dominiak, PM. (2018). *J. Appl. Cryst*. **51**, 193–199.

7 Hansen, NK. & Coppens, P. (1978). *Acta Cryst. A***34**, 909-921.

8 Jha, KK., Gruza, B., Sypko, A., Kumar, P., Chodkiewicz, ML. & Dominiak, PM. (2022). *J. Chem. Inf. Model.* **62**, 3752–3765.

9 Kleemiss, F., Dolomanov, OV., Bodensteiner, M., Peyerimhoff, N., Midgley, L., Bourhis, LJ., Genoni, A., Malaspina, LA., Jayatilaka, D., Spencer, JL., White, F., Grundkötter-Stock, B., Steinhauer, S., Lentz, D., Puschmann, H. & Grabowsky, S. (2021) Chem Sci. **12**, 1675–1692.

10 Bourhis, LJ., Dolomanov, OV., Gildea, RJ., Howard, JAK. & Puschmann, H. (2015). *Acta Cryst.* A**71**, 59–75.

11 Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). *Acta Cryst.* B**72**, 171–179. V5.44 (update June 2023).

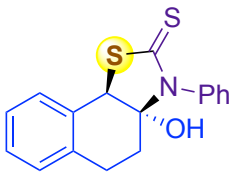
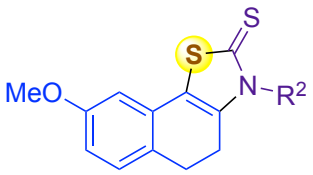
12 Sarker, J.C., Nash, R., Boorungsiman, S., Pugh, D., Hogarth, G. (2022) *Dalton Trans.***, 51**, 13061-13070.

13 Cremer, D., Pople, J.A. (1975) *J.Amer.Chem.Soc.*, **97**, 1354-1358.

14 Parsons, S., Flack; H. D. and Wagner, T. (2013) *Acta Cryst.* B**69**, 249-259.

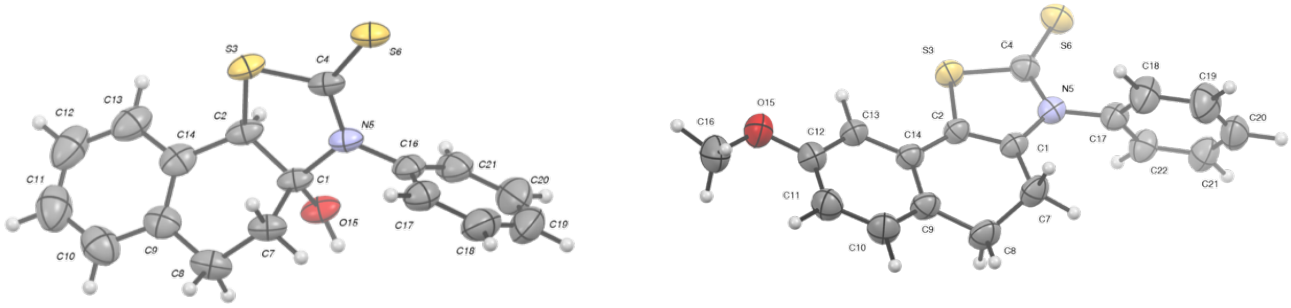
15 Spackman, M. A. & Jayatilaka, D. (2009). *CrystEngComm*, **11**, 19–32; Spackman, P. R., Turner, M. J., McKinnon, J. J., Wolff, S. K., Grimwood, D. J., Jayatilaka, D. & Spackman, M. A. (2021). *J. Appl. Cryst.* **54**, 1006–1011.

Table 1 Crystal data, data collection and structure refinement details for the **3a** and **4o**-compounds.

Compound	*rac*-(3a*R*,9b*R*)-3a-hydroxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho [2,1-d]thiazole-2(3*H*)-thione	8-methoxy-3-phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione
2D		
Empirical formula	$C_{17}H_{15}NOS_2$	$C_{18}H_{15}NOS_2$
Formula weight	313.42	325.46
Temperature (K)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system, space group	Monoclinic, *Cc*	Monoclinic, *P* 2_1/c
Unit cell dimensions | (Å) | (°)	7.2278(8) 22.429(6) 9.660(7) 98.99(3)	11.1398(10) 14.0582(10) 10.5753(9) 106.341(9)
Volume (Å^3)	1546.8(12)	1589.3(2)
Z, Calculated density (Mg/m^3)	4, 1.346	4, 1.360
Absorption coefficient (mm^{-1})	0.342	0.335
F(000)	656	680
Crystal size (mm)	0.65 x 0.27 x 0.03	0.36 x 0.10 x 0.05
θ range for data collection (°)	2.803 to 27.103	2.48 to 278.70
Limiting indices	-9 ≤ h ≤ 8, -28 ≤ k ≤ 28, -12 ≤ l ≤ 12	-14 ≤ h ≤ 14, -18 ≤ k ≤ 19, -13 ≤ l ≤ 14
Reflections collected / unique [R(int)	19727 / 6347 0.0392	21360 / 3884 0.0401
Completeness to θ $_{full}$ (%)	99.9	99.8
Absorption correction	Gaussian and equivalence	

Max. and min. transmission		0.990 and 0.900	1.000 and 0.799
Refinement method		IAM refinement + Full-matrix least-squares on F^2	TAAM refinement + Full-matrix least-squares on F^2
Data / restraints / parameters		6347 / 2 / 194	3881 / 0 / 334
Goodness-of-fit on F^2		0.985	1.0354
Final R indices [$I>2\sigma(I)$]	R1 wR2	0.0326 0.0829	0.0281 0.0492
R indices (all data)	R1 wR2	0.0414 0.0873	0.0491 0.0537
Flack parameter [14]		0.11(5)[$]	-
Largest Δ peak and hole (e.Å^{-3})		0.180 and -0.161	0.225 and -0.204
CCDC deposit number		2371492	2375946

[$] using 1110 quotients.



(a) (b)

Figure S1. Ortep view of (a) the structure of **3a** with the atom-labeling scheme and (b) the structure of **4o**. Displacement ellipsoids are shown at the 50% probability level. H atoms are presented as small spheres of arbitrary radius

CP Puckering parameters [13]	C1/C2/S3/C4/N5	C1/C7/C8/C9/C14/C2	C1/C7/C8/C9/C14/C2
Structure	**3a**	**3a**	**4o**
Q_2 (Å)	0.331(3)	0.364(4)	0.352(2)
Q_3 (Å)	-	0.298(4)	0.171(2)
Q ($Q^2=Q_2^2+Q_3^2$) (Å)	-	0.470(3)	0.391(2)
θ (°)	-	50.8(5)	64.1(2)
φ_2 (°)	313.3(5)	317.7(6)	257.3(2)

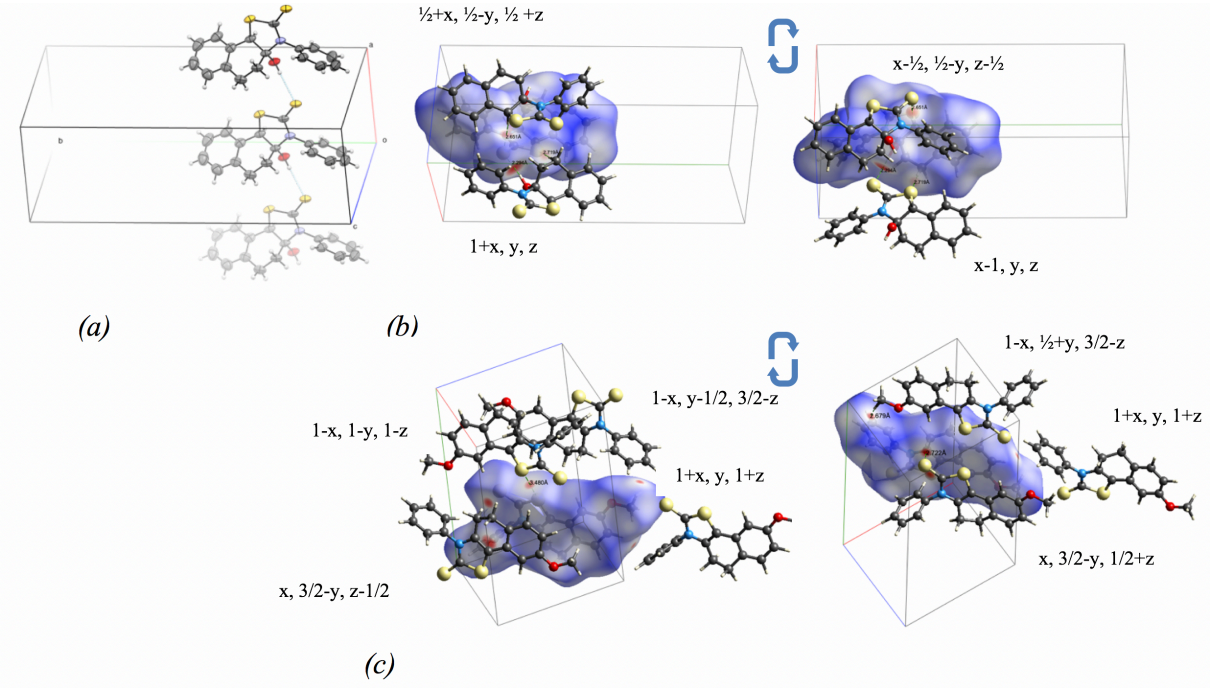
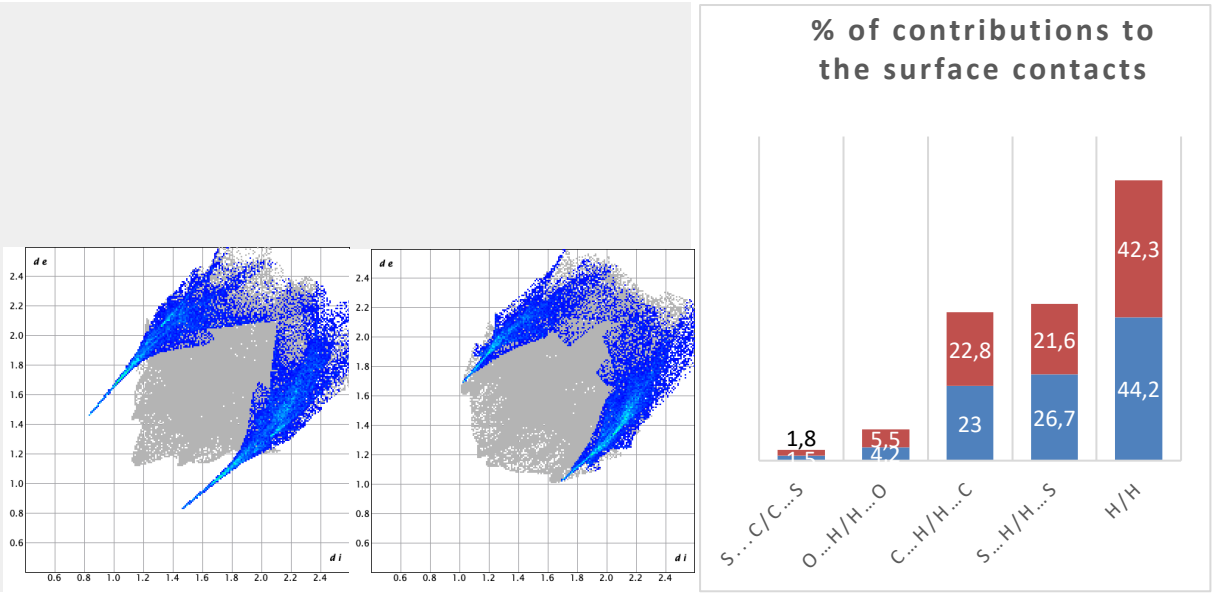


Figure S2 Partial view of the crystal **3a** highlighting the *C*(6) graph-set motif molecular chain along the ***a*** axis (the cyan dashed line indicates the intermolecular h-bond between O1 and S1$^{\#1}$, (*d* (O15–H15) = 0.87(5)Å, *d* (*O15*–H15···S6$^{\#1}$) = 2.40(6)Å, *d* (O15··· S6$^{\#1}$) = 3.238(3)Å, ∠(O15–H15··· S6$^{\#1}$) = 176(2)°; $^{\#1}$ *Symmetry transformation used to generate equivalent atoms*: x-1, y, z) *(a)* and Hirshfeld surface (HS) [14] graphical representations (d_{norm}). The regions with strongest inter-molecular interactions are shown in red for **3a** *(b)* and for **4o** *(c)*. The volume of the HS is 379,65 (389.68)Å^3, its area is 326,26 (*346.46*)Å^2, its globularity, 0.777 (*0.745*) and its asphericity, 0,204 (0.*285*) – the values in italic refer to **4o**.



(a) (b) (c)

Figure S3.

The two-dimensional fingerprint plots for **3a** (a) and **4o** (b) delineated in blue dots into S···H/H···S interactions to qualitatively highlight the crystal packing differences between the two structures due to the short interaction O-H…S present in the first complex compared to only C-H…S in the second structure. The di and de values are the closest internal and external distances (in Å) from given points on the Hirshfeld surface. (c) The relative contributions in % of the major contacts to the HS for **3a** and **4o.**

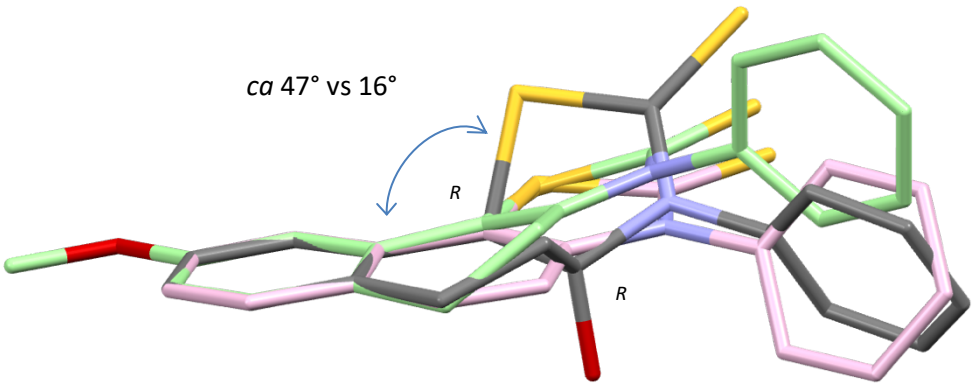
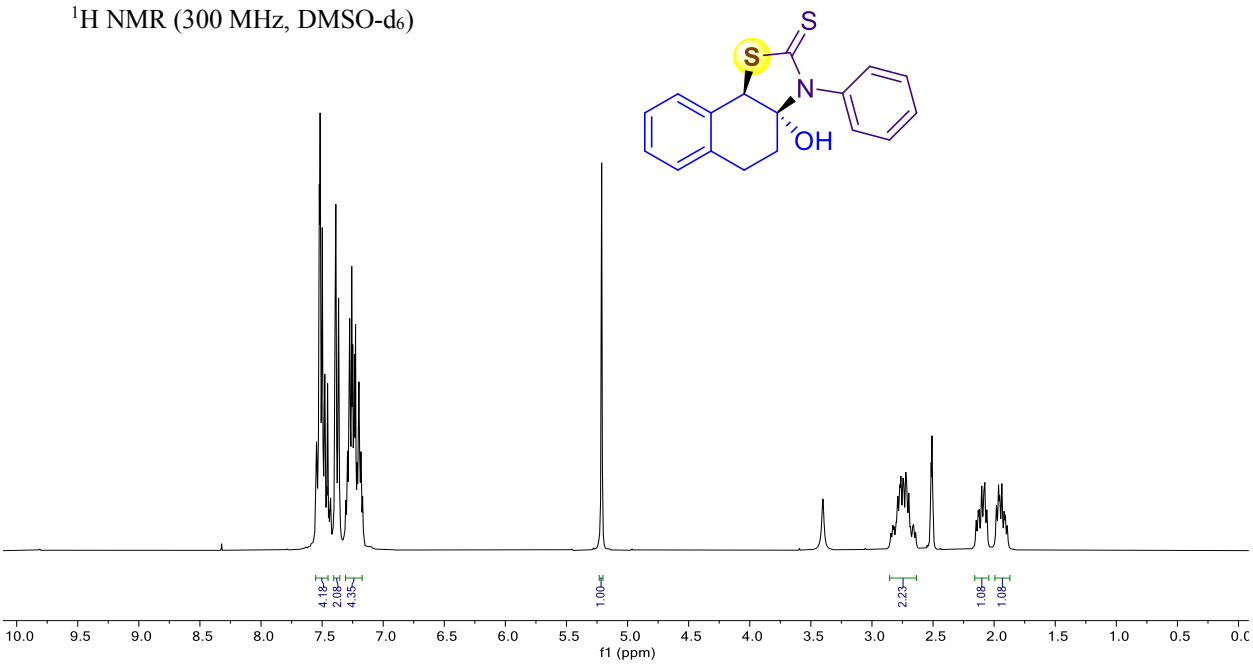


Figure S4. Overlay between **3a (*R*,*R*)**-(carbon atoms in grey), **4o** (carbon atoms in light green) and ZEPVAV (carbon atoms in pink) over the outer phenyl ring.

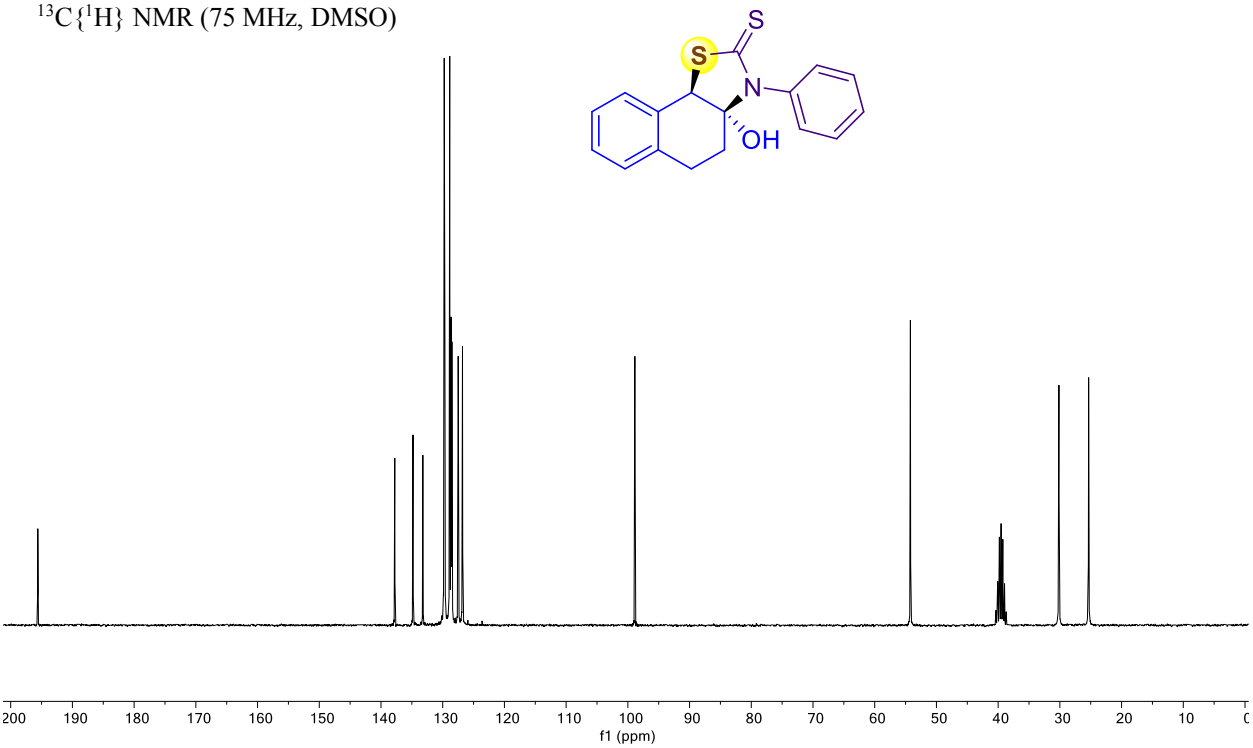
Copies of NMR spectra

(3a*R*,9b*R*)-3a-Hydroxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3a)

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

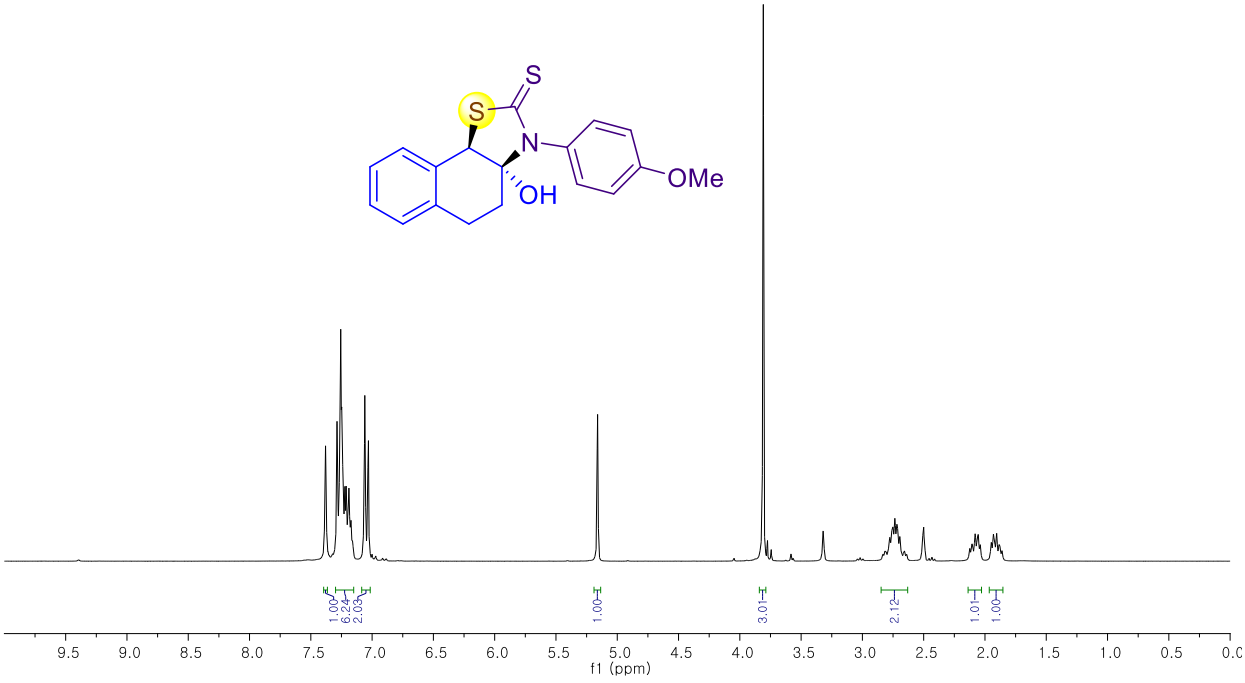


^{13}C{^{1}H} NMR (75 MHz, DMSO)

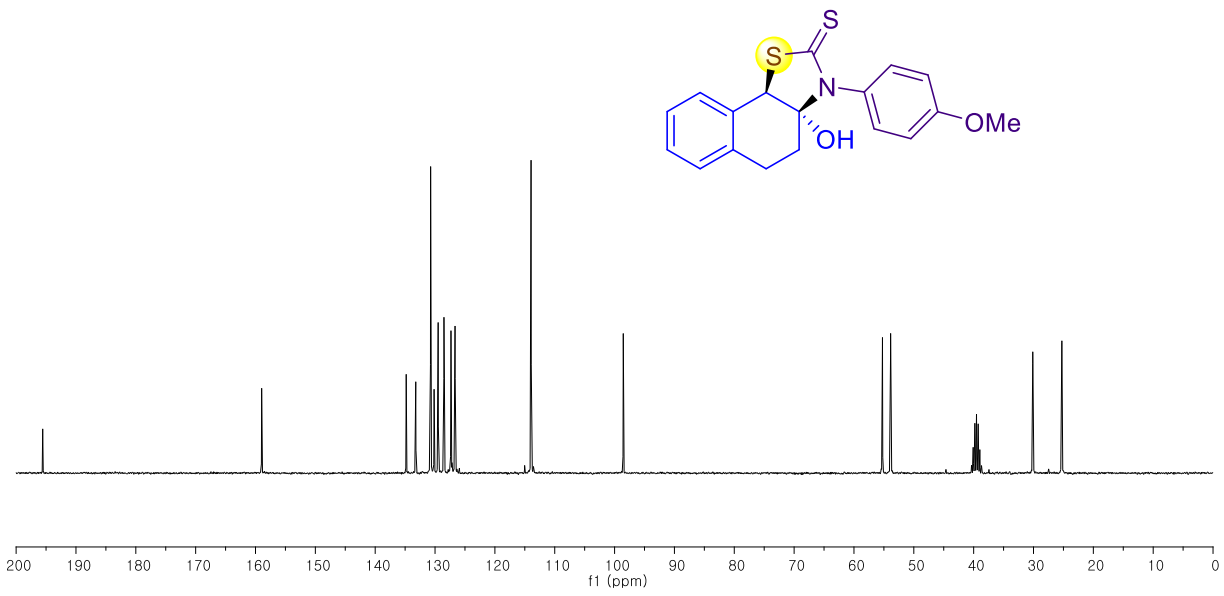


(3a*R*,9b*R*)-3a-Hydroxy-3-(4-methoxyphenyl)-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3b)

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

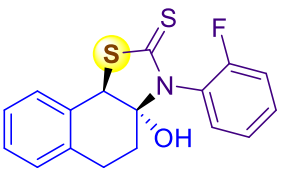


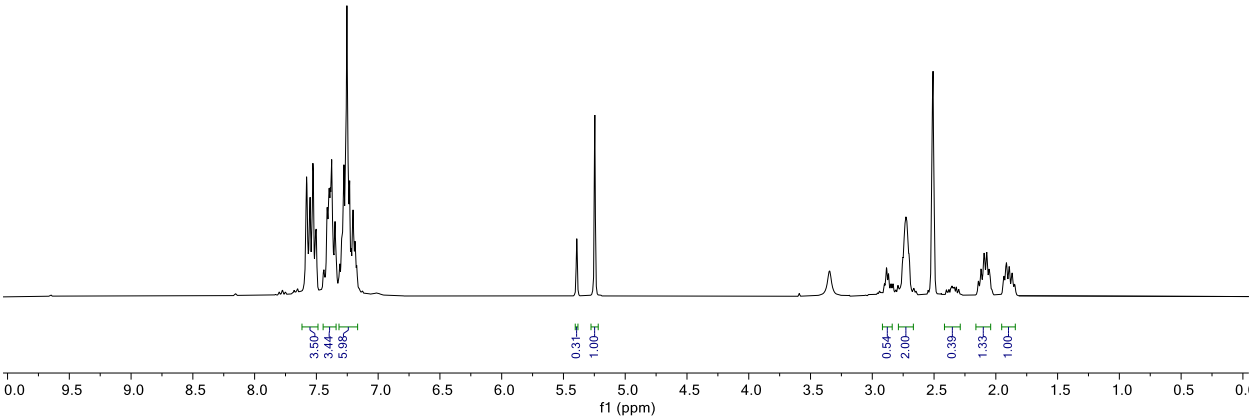
^{13}C{^{1}H} NMR (75 MHz, DMSO)



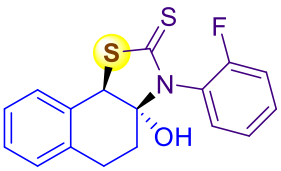
3a*R*,9b*R*)-3-(2-Fluorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3c)

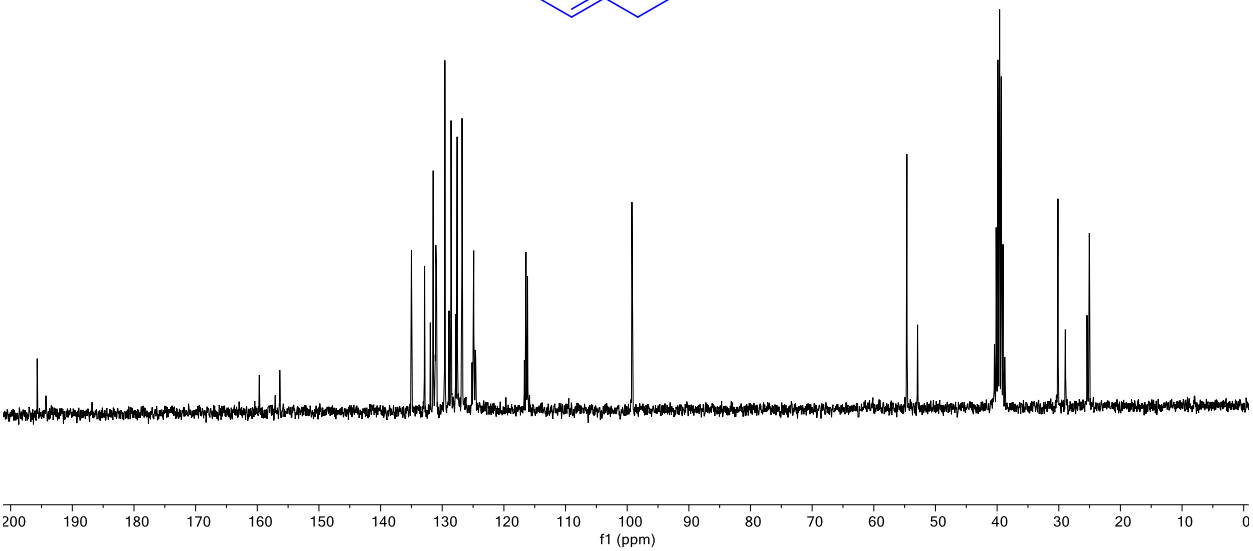
^{1}H NMR (300 MHz, DMSO)



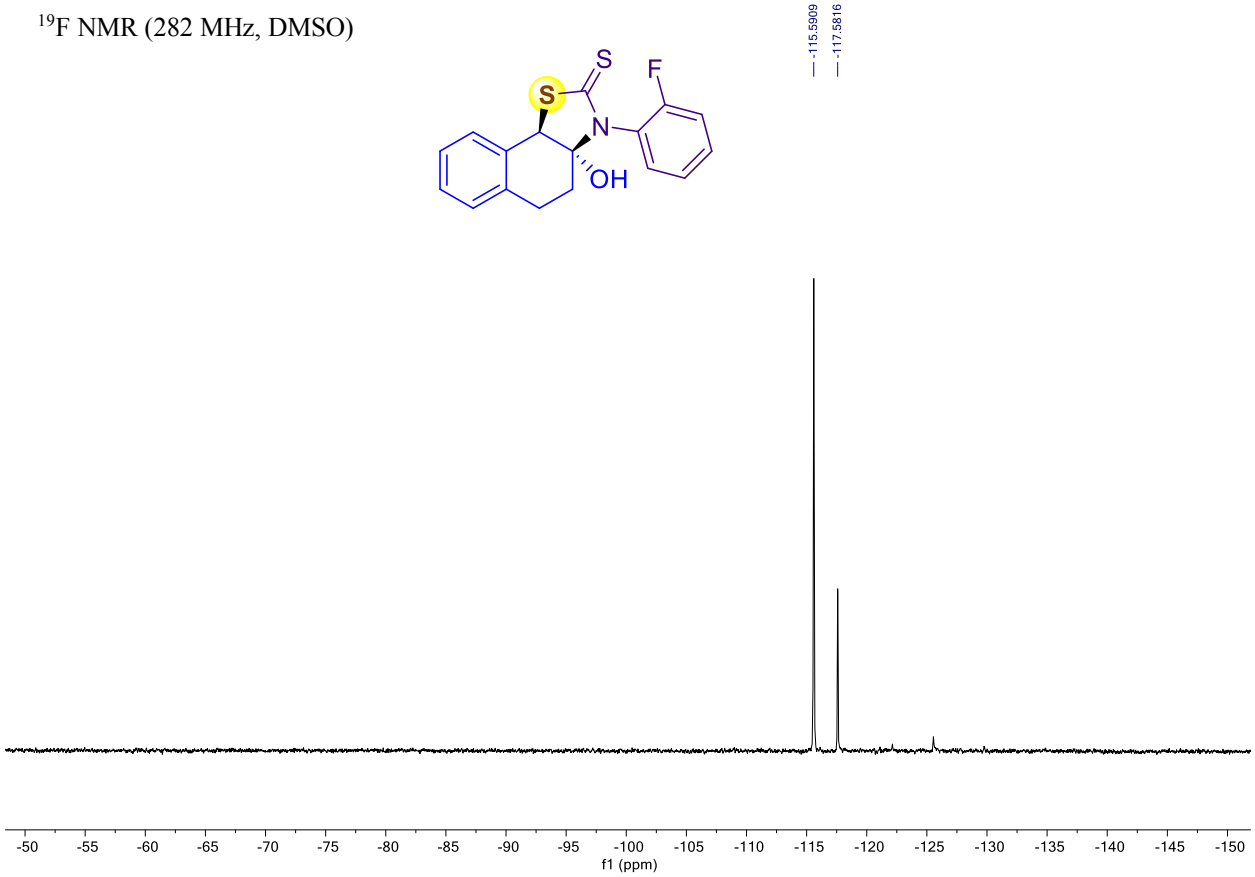


^{13}C{^{1}H} NMR (75 MHz, DMSO)



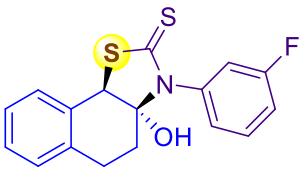


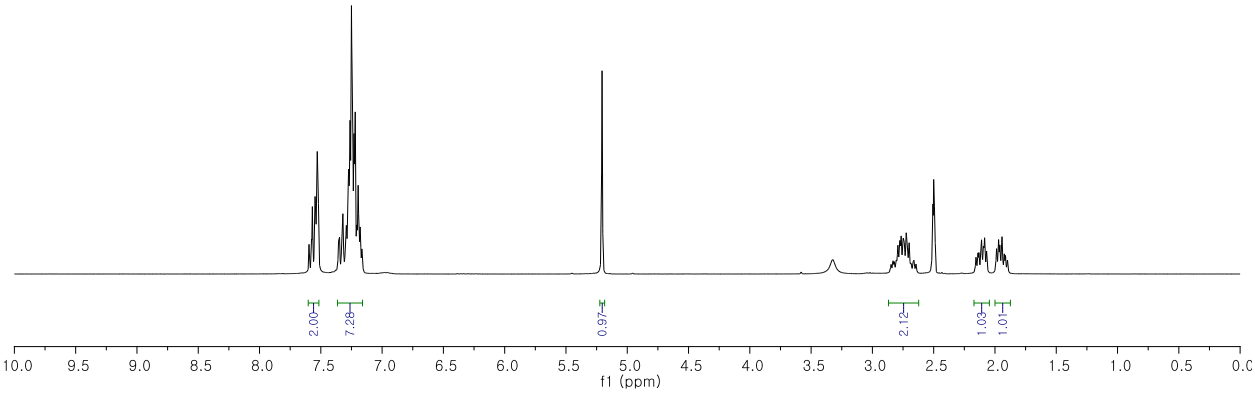
^{19}F NMR (282 MHz, DMSO)

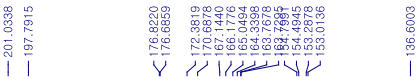


(3a*R*,9b*R*)-3-(3-Fluorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3d)

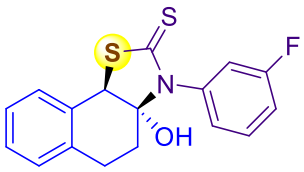
^{1}H NMR (300 MHz, DMSO)

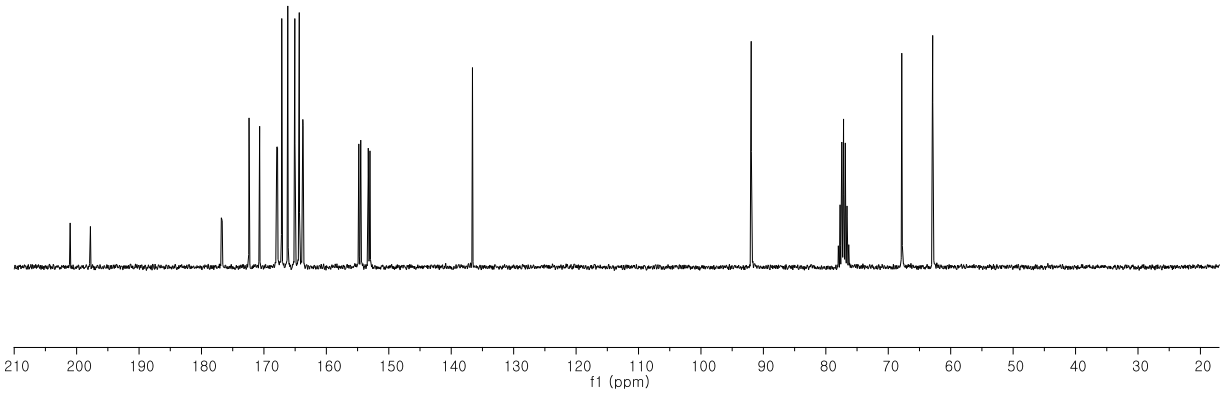




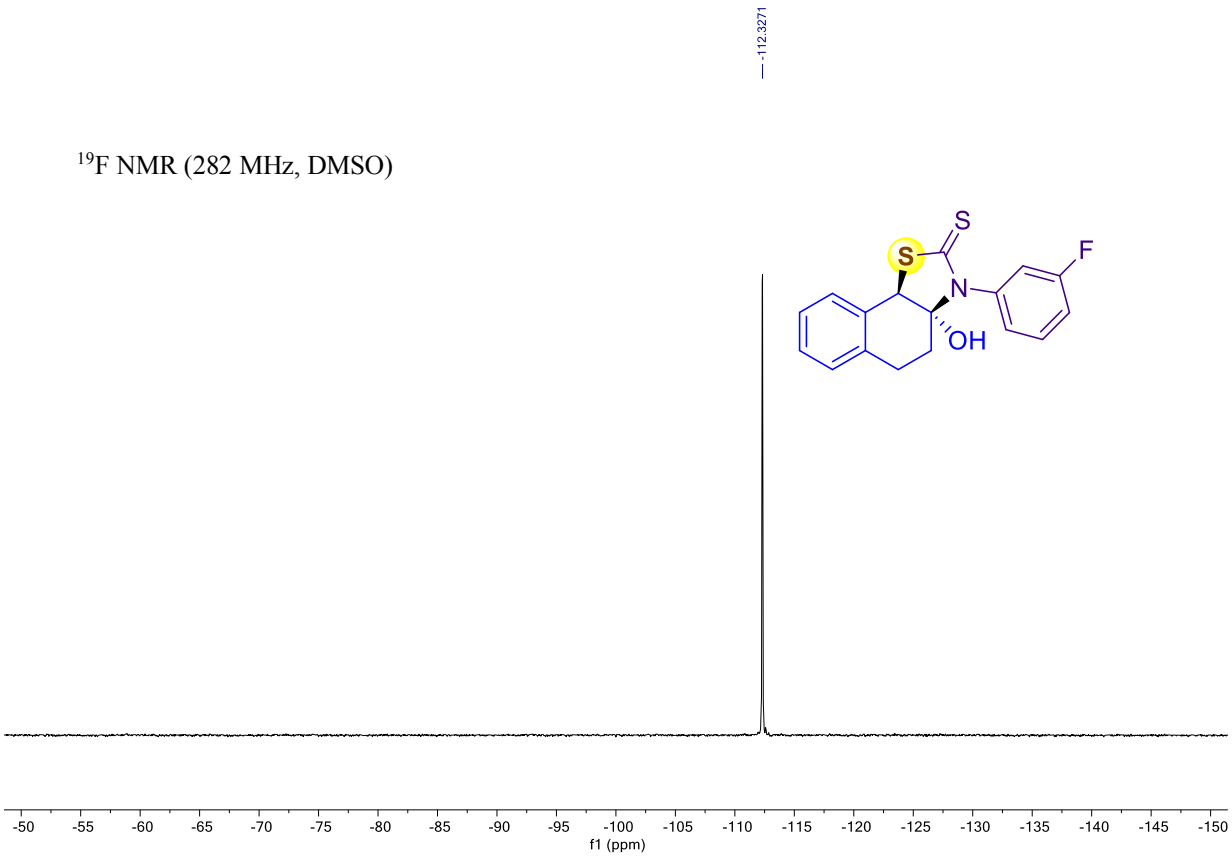


^{13}C{^{1}H} NMR (75 MHz, DMSO)



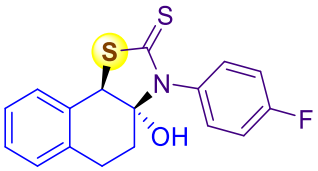


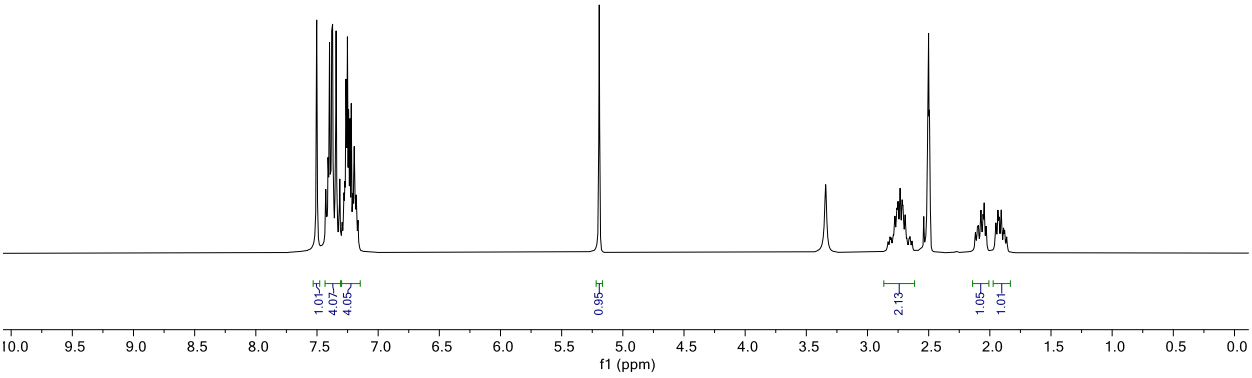
^{19}F NMR (282 MHz, DMSO)



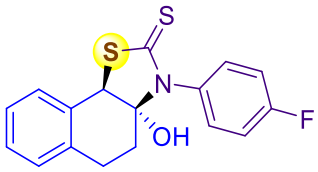
(3a*R*,9b*R*)-3-(4-Fluorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3e)

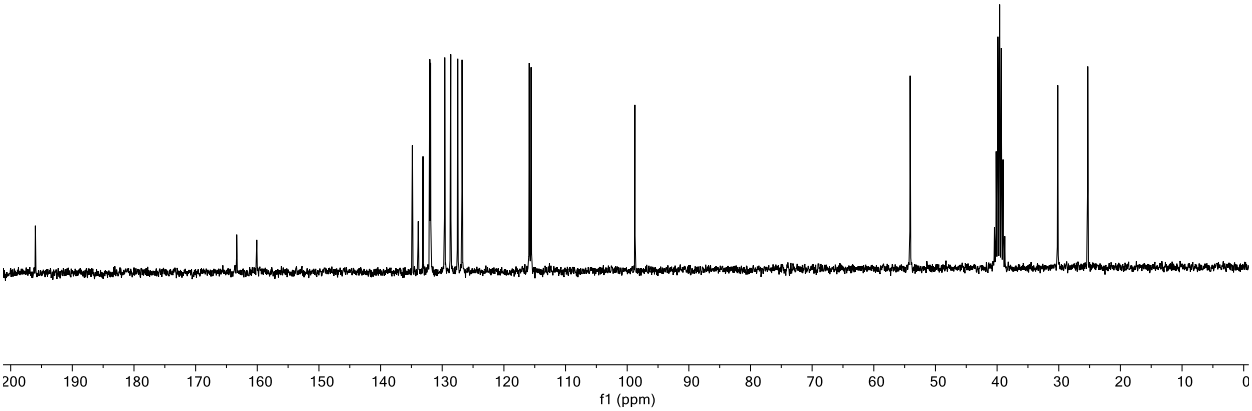
^{1}H NMR (300 MHz, DMSO)



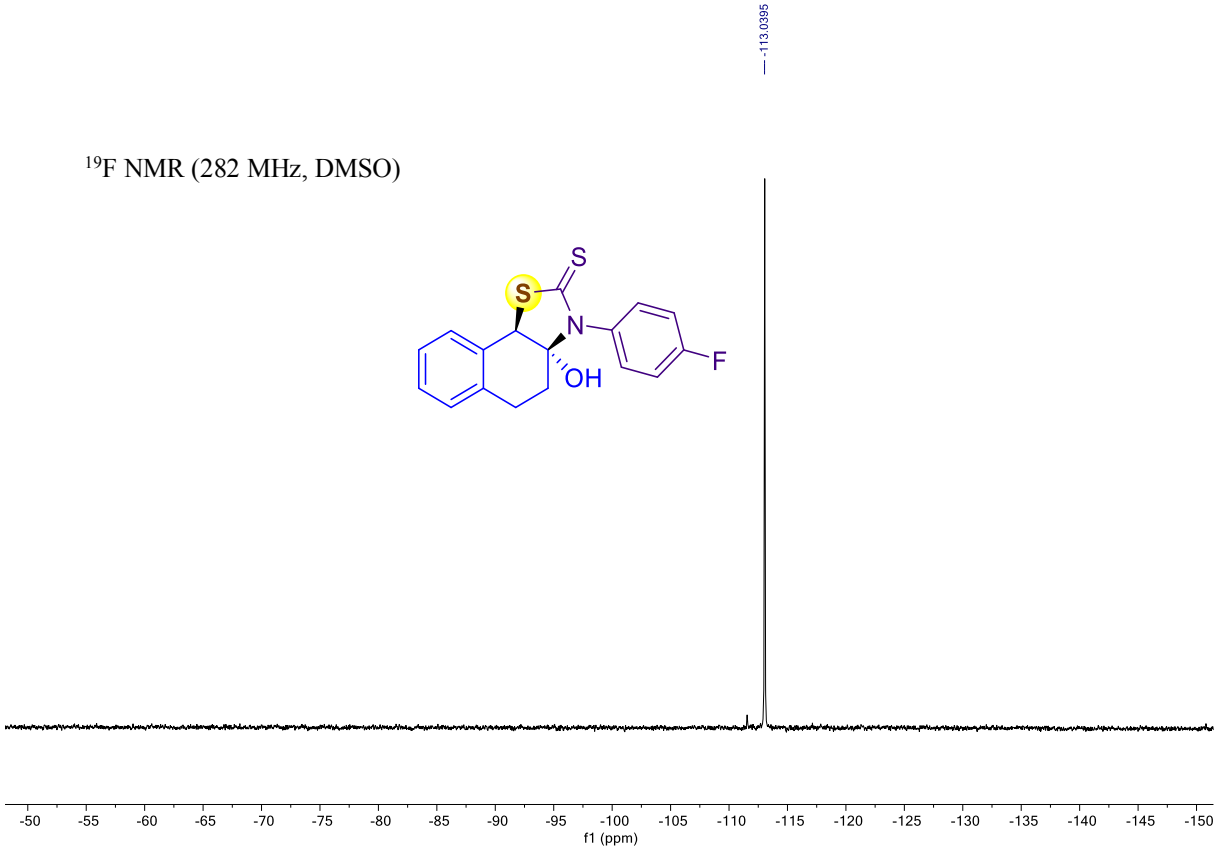


^{13}C{^{1}H} NMR (75 MHz, DMSO)



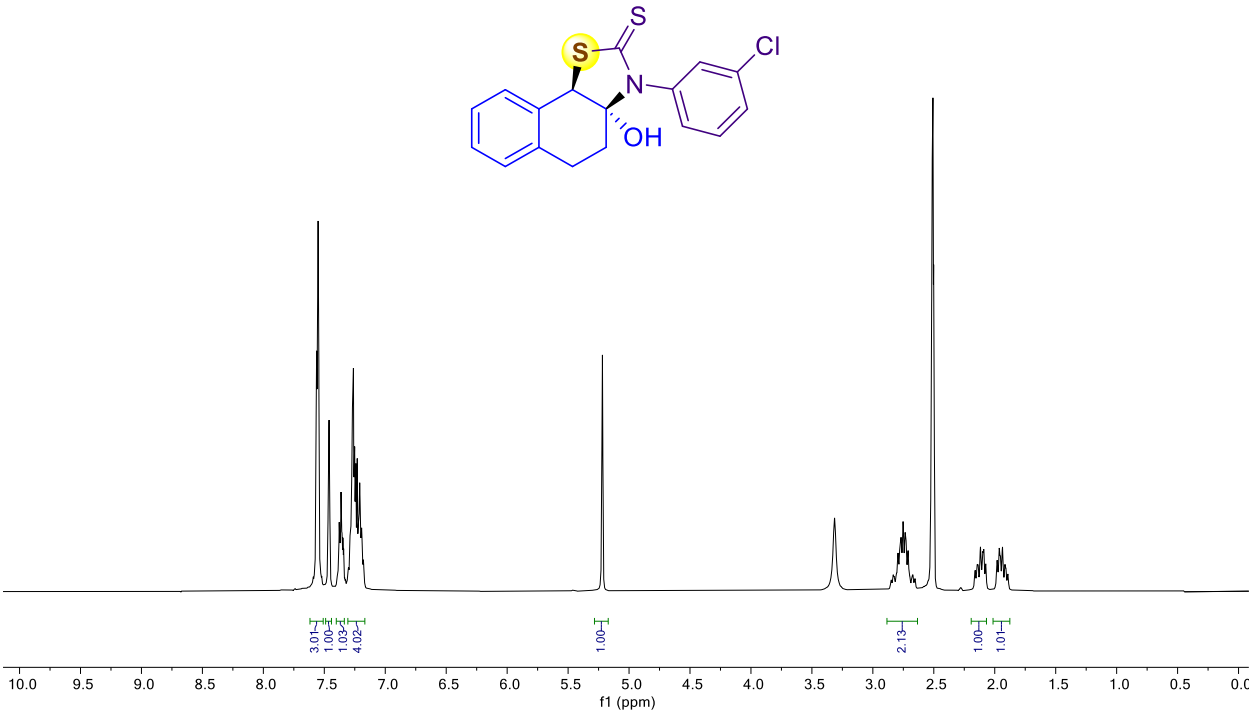


^{19}F NMR (282 MHz, DMSO)

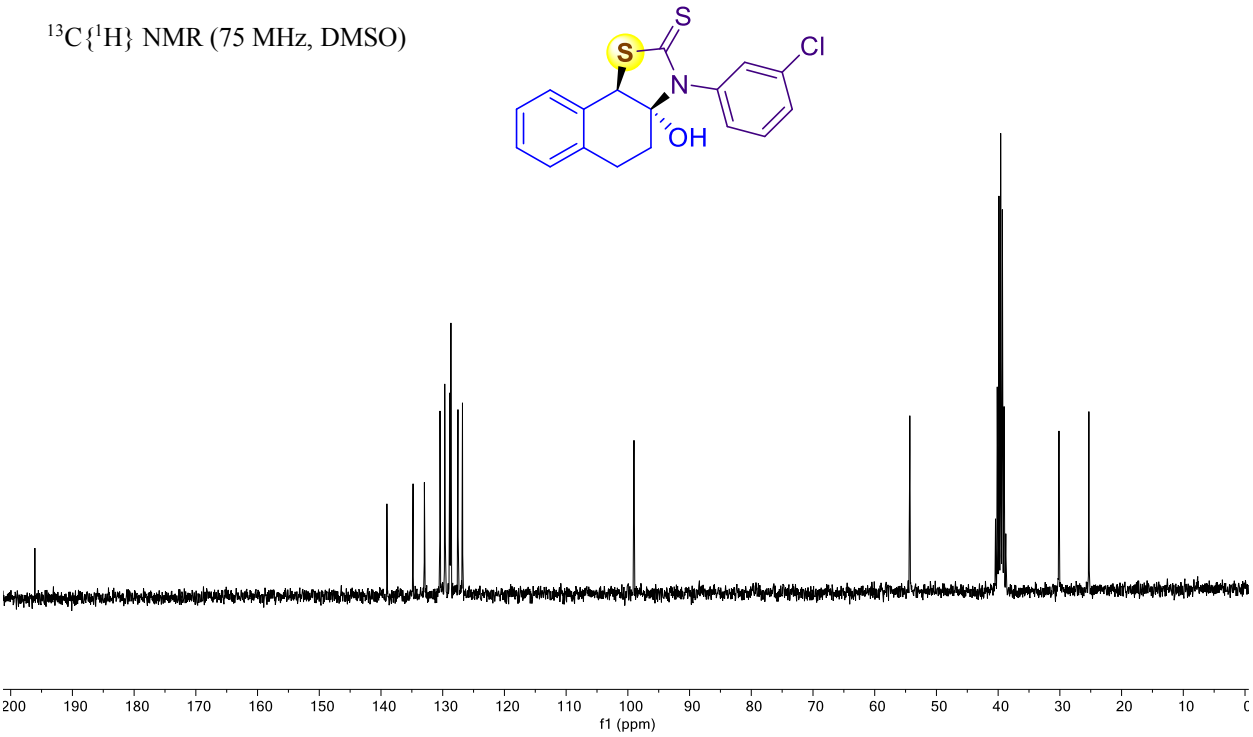


(3a*R*,9b*R*)-3-(3-Chlorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3f)

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

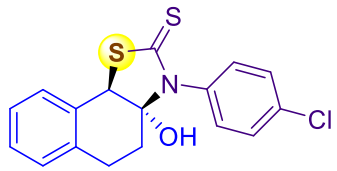


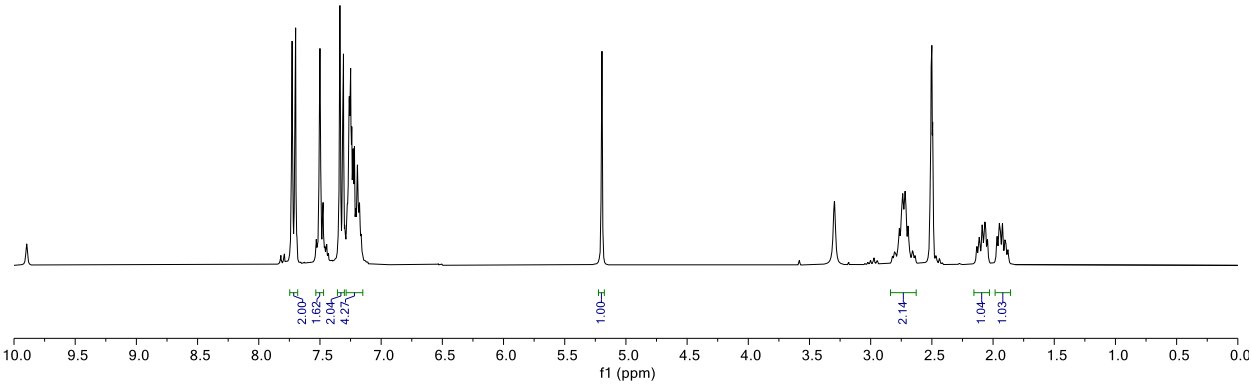
^{13}C{^{1}H} NMR (75 MHz, DMSO)



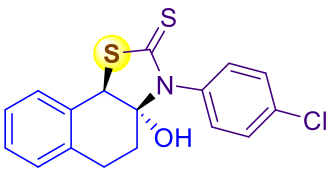
(3a*R*,9b*R*)-3-(4-Chlorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3g)

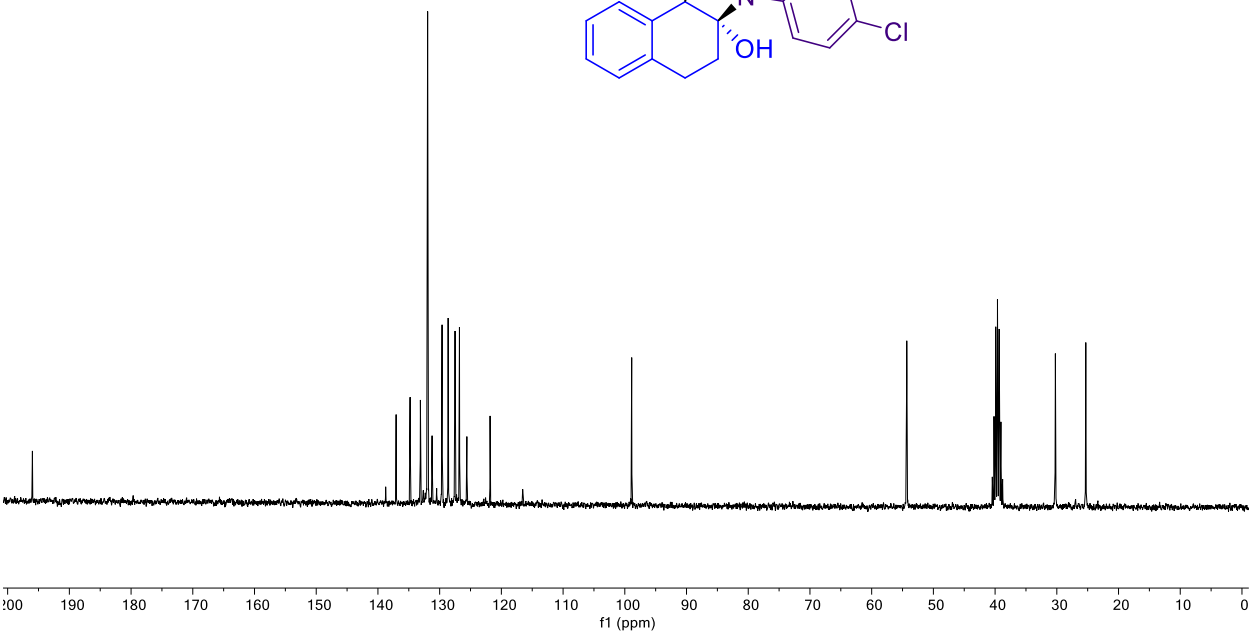
^{1}H NMR (300 MHz, DMSO)





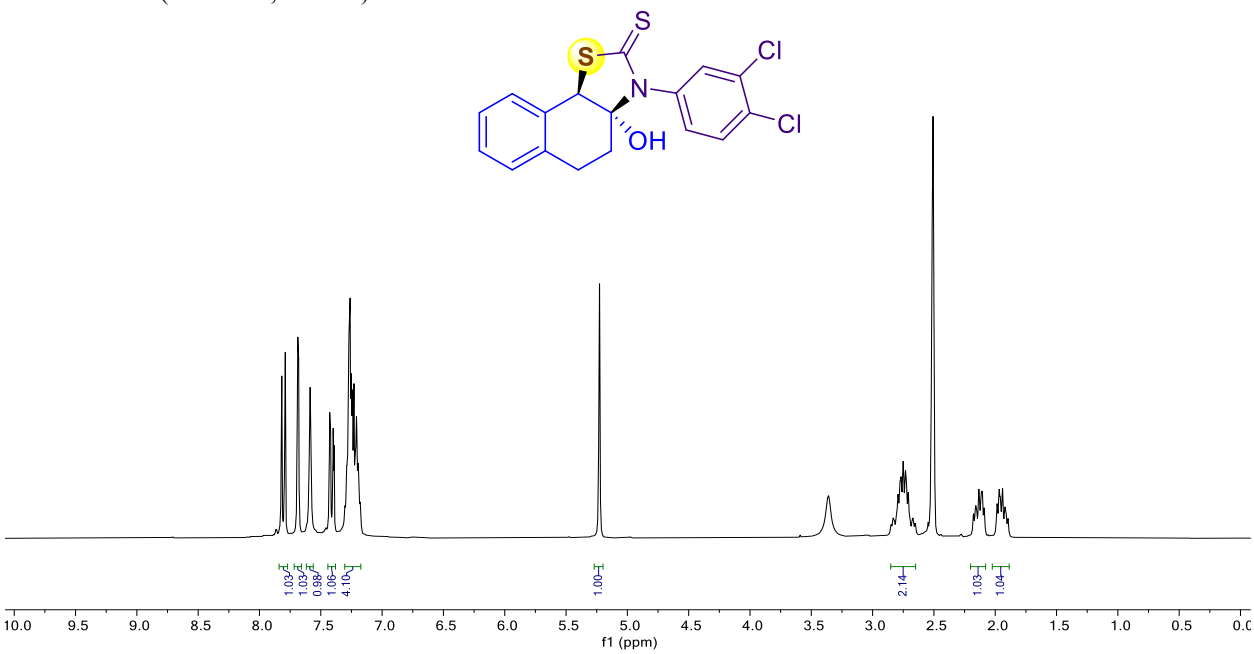
^{13}C{^{1}H} NMR (75 MHz, DMSO)



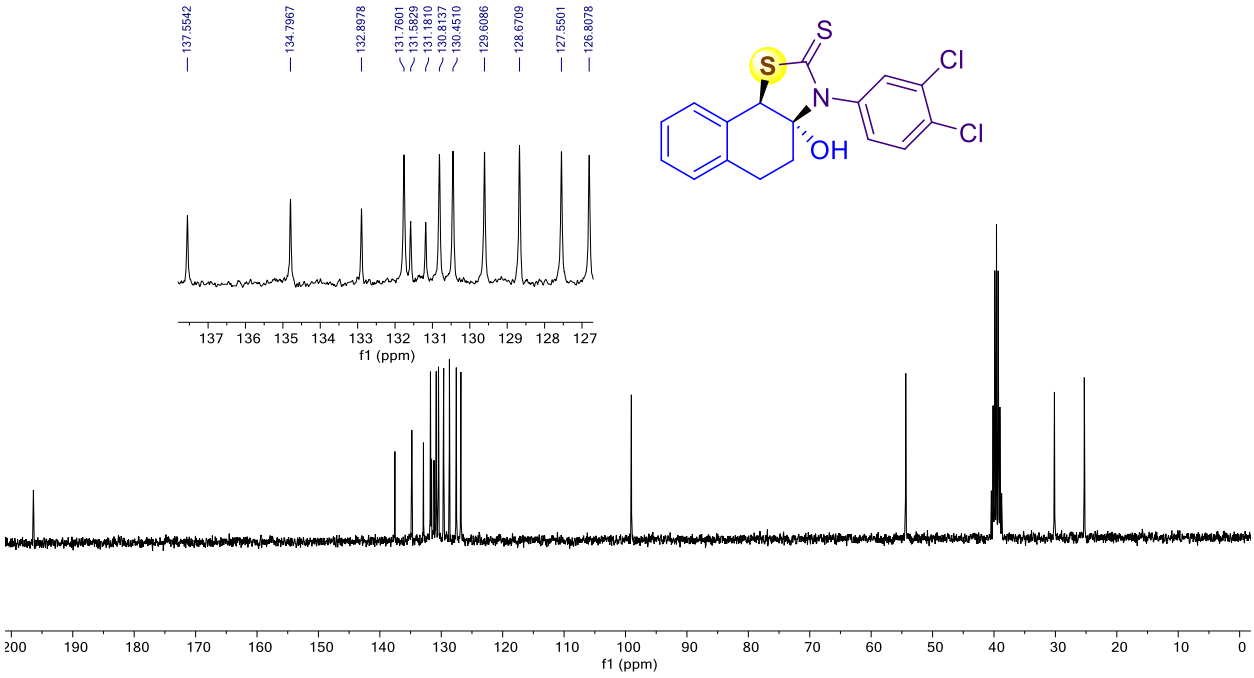


3a*R*,9b*R*)-3-(3,4-Dichlorophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3h)

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

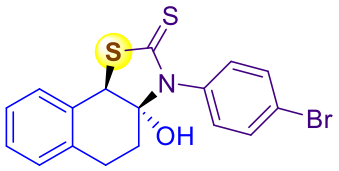


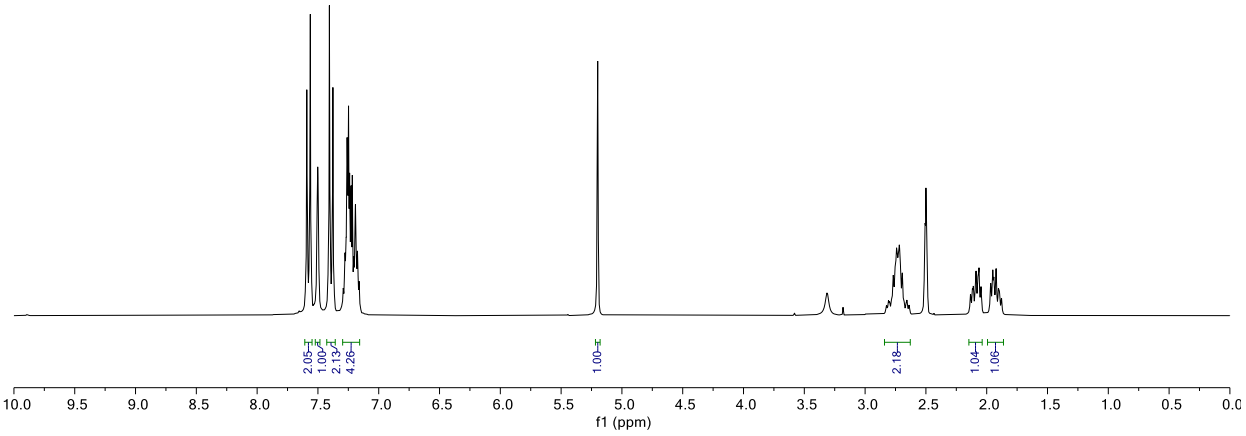
^{13}C{^{1}H} NMR (75 MHz, DMSO)



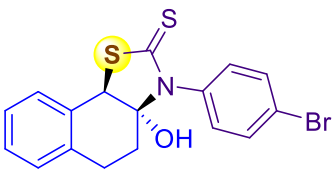
(3a*R*,9b*R*)-3-(4-Bromophenyl)-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3i)

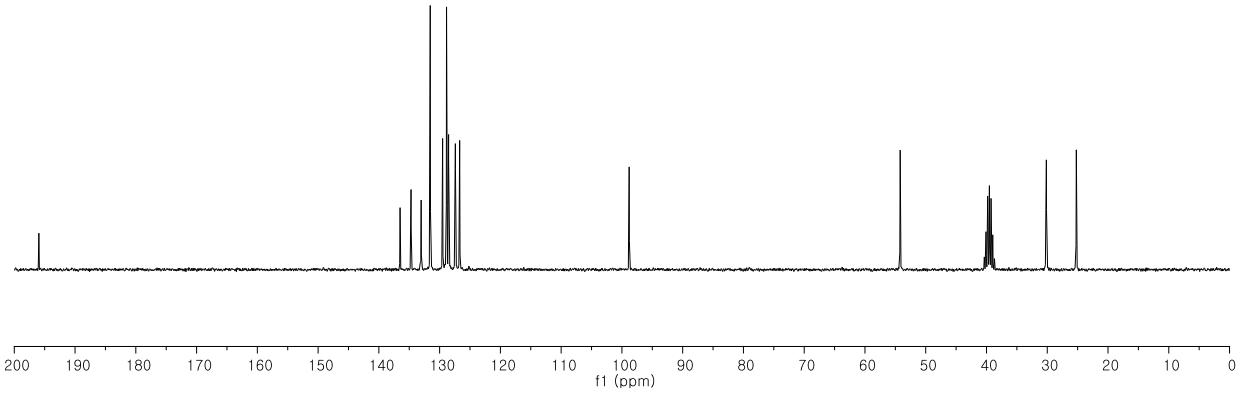
^{1}H NMR (300 MHz, DMSO)





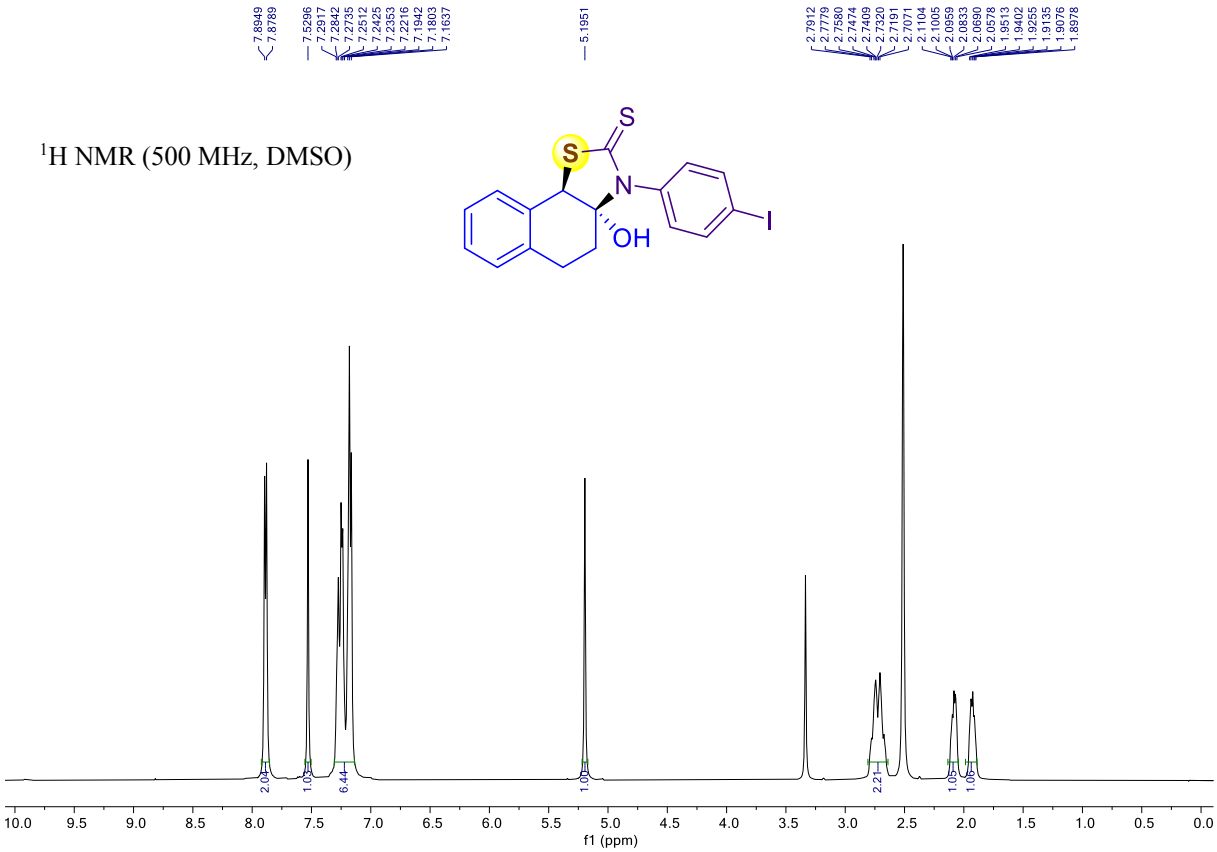
^{13}C{^{1}H} NMR (75 MHz, DMSO)



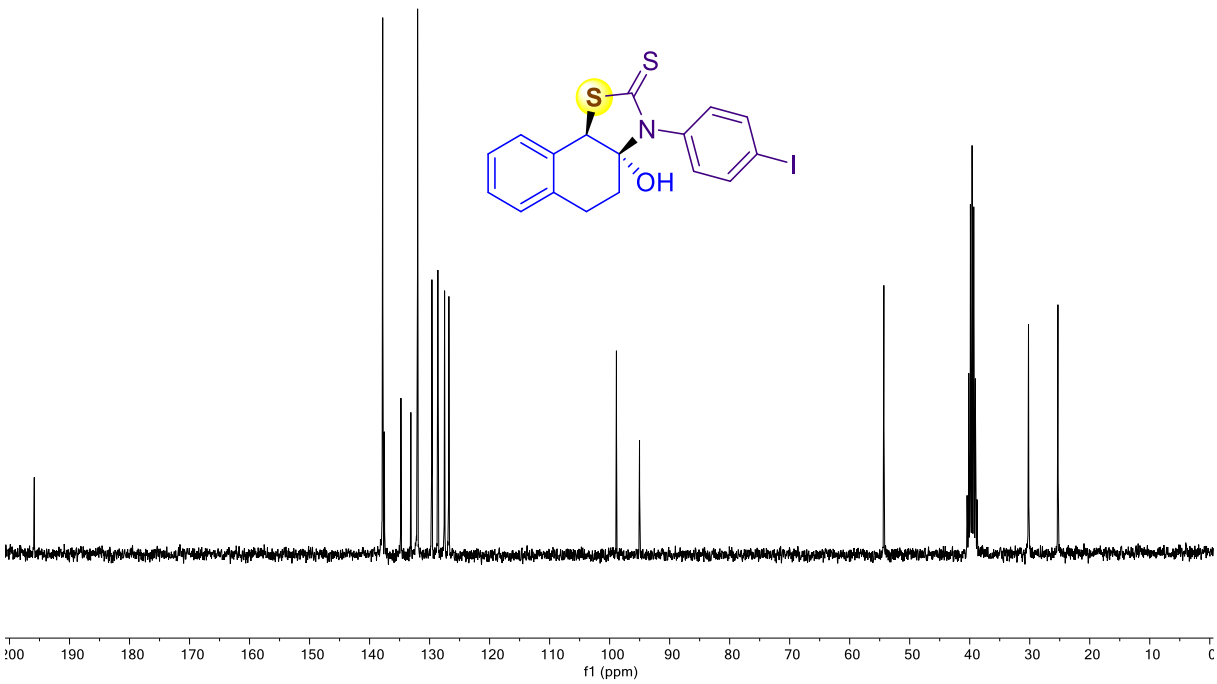


(3a*R*,9b*R*)-3a-Hydroxy-3-(4-iodophenyl)-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3j)

^{1}H NMR (500 MHz, DMSO)

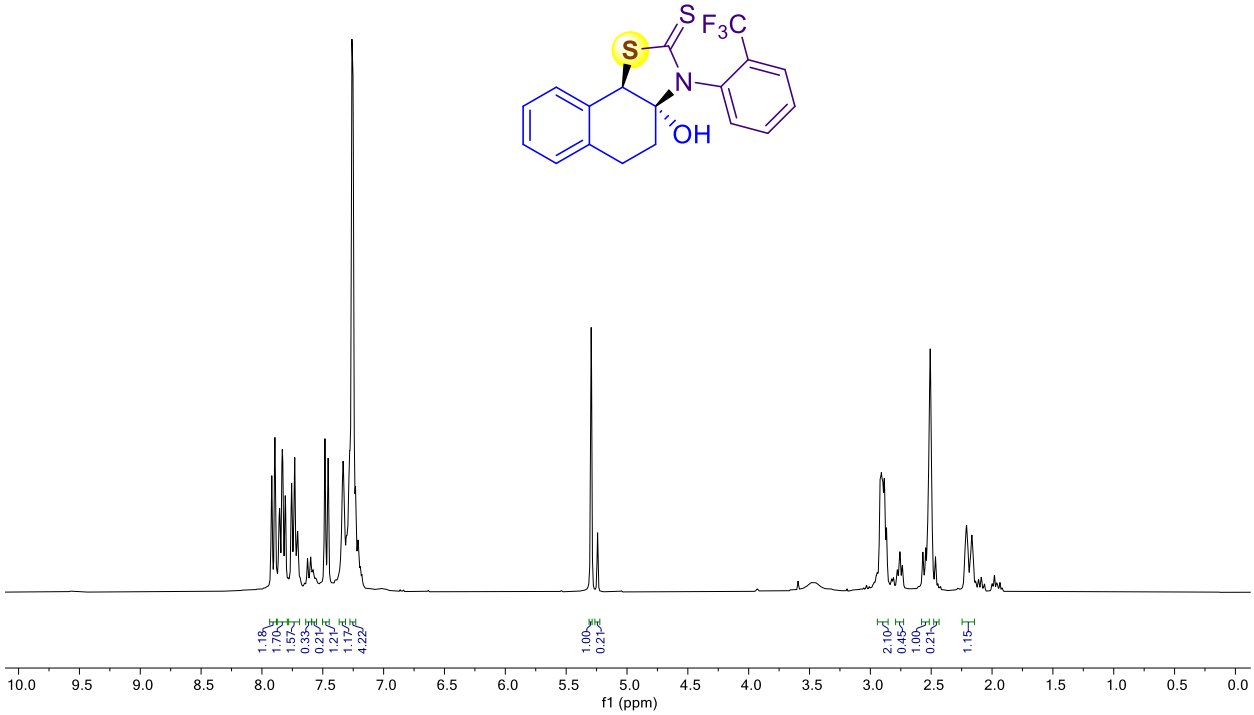


^{13}C{^{1}H} NMR (75 MHz, DMSO)

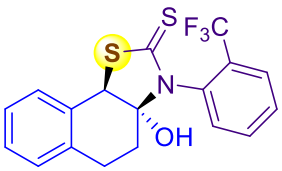


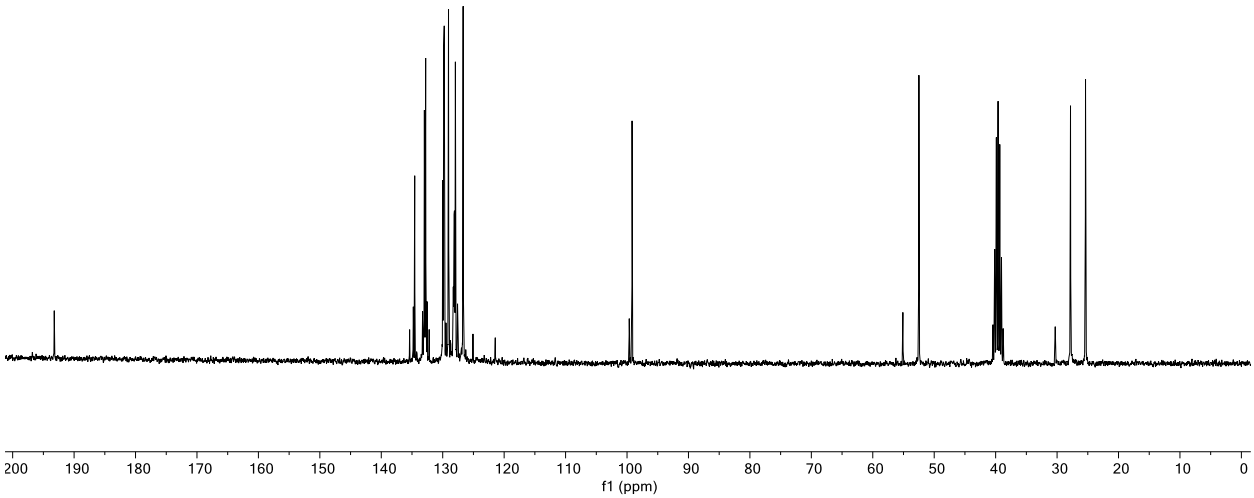
3a*R*,9b*R*)-3a-Hydroxy-3-(2-(trifluoromethyl)phenyl)-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3k)

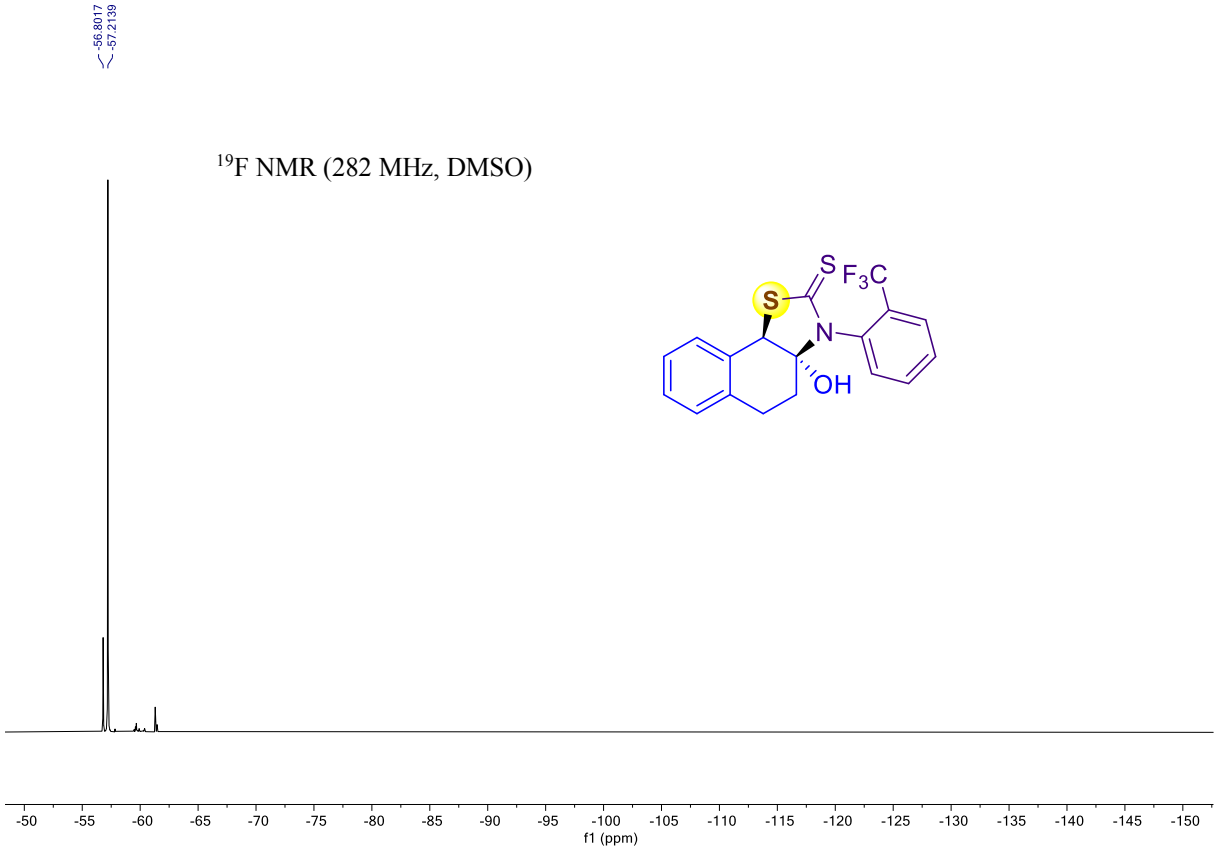
^{1}H NMR (300 MHz, DMSO)



^{13}C{^{1}H} NMR (75 MHz, DMSO)



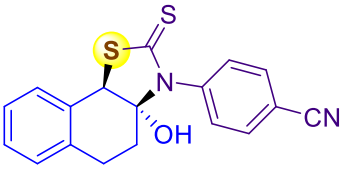


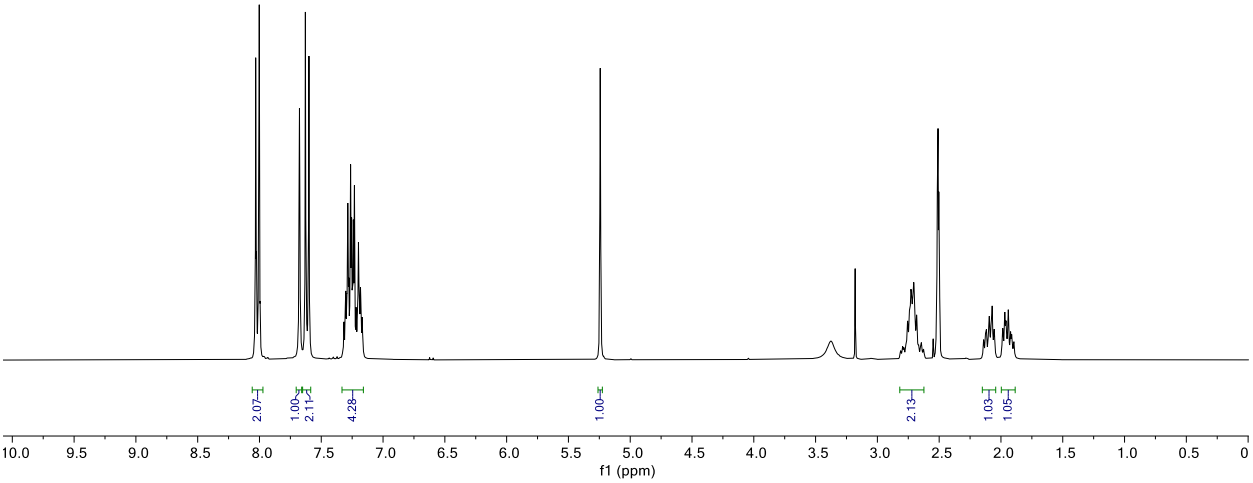


^{19}F NMR (282 MHz, DMSO)

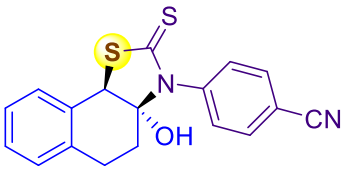
4-((3a*R*,9b*R*)-3a-Hydroxy-2-thioxo-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazol-3(2*H*)-yl)benzonitrile (3l)

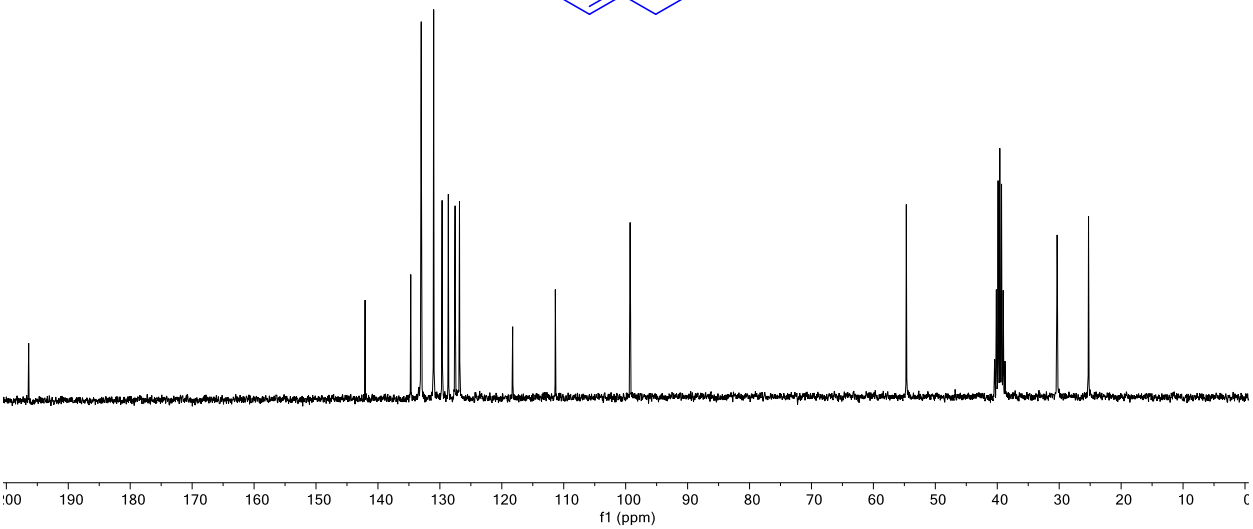
^{1}H NMR (300 MHz, DMSO)





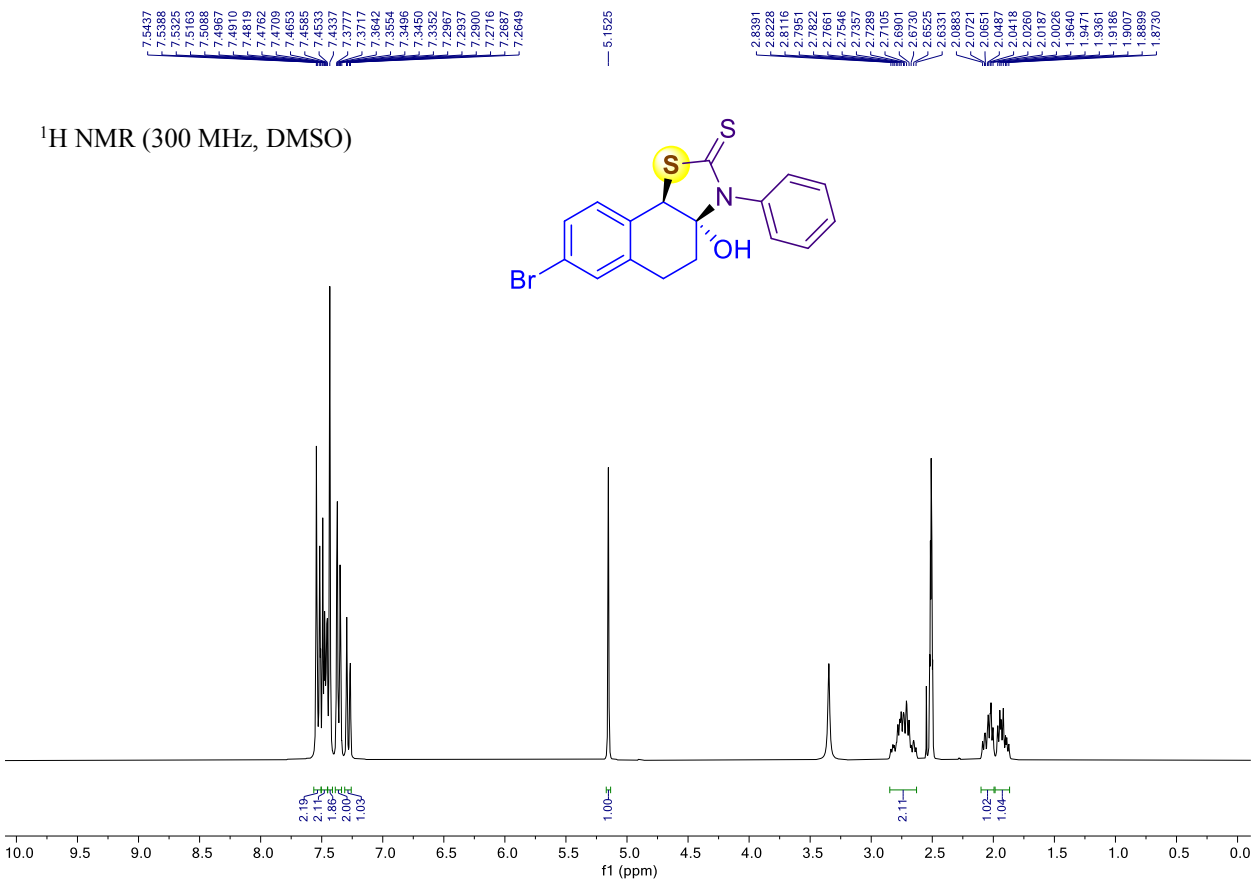
^{13}C{^{1}H} NMR (75 MHz, DMSO)



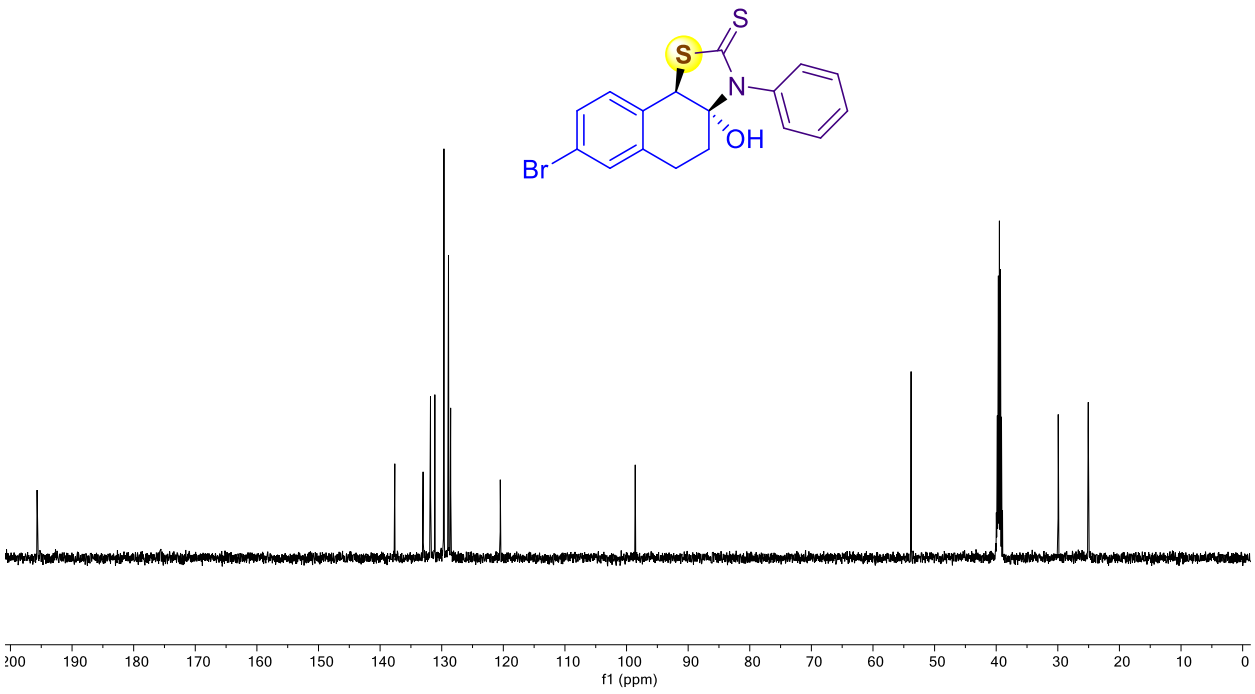


(3a*R*,9b*R*)-7-Bromo-3a-hydroxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3m)

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

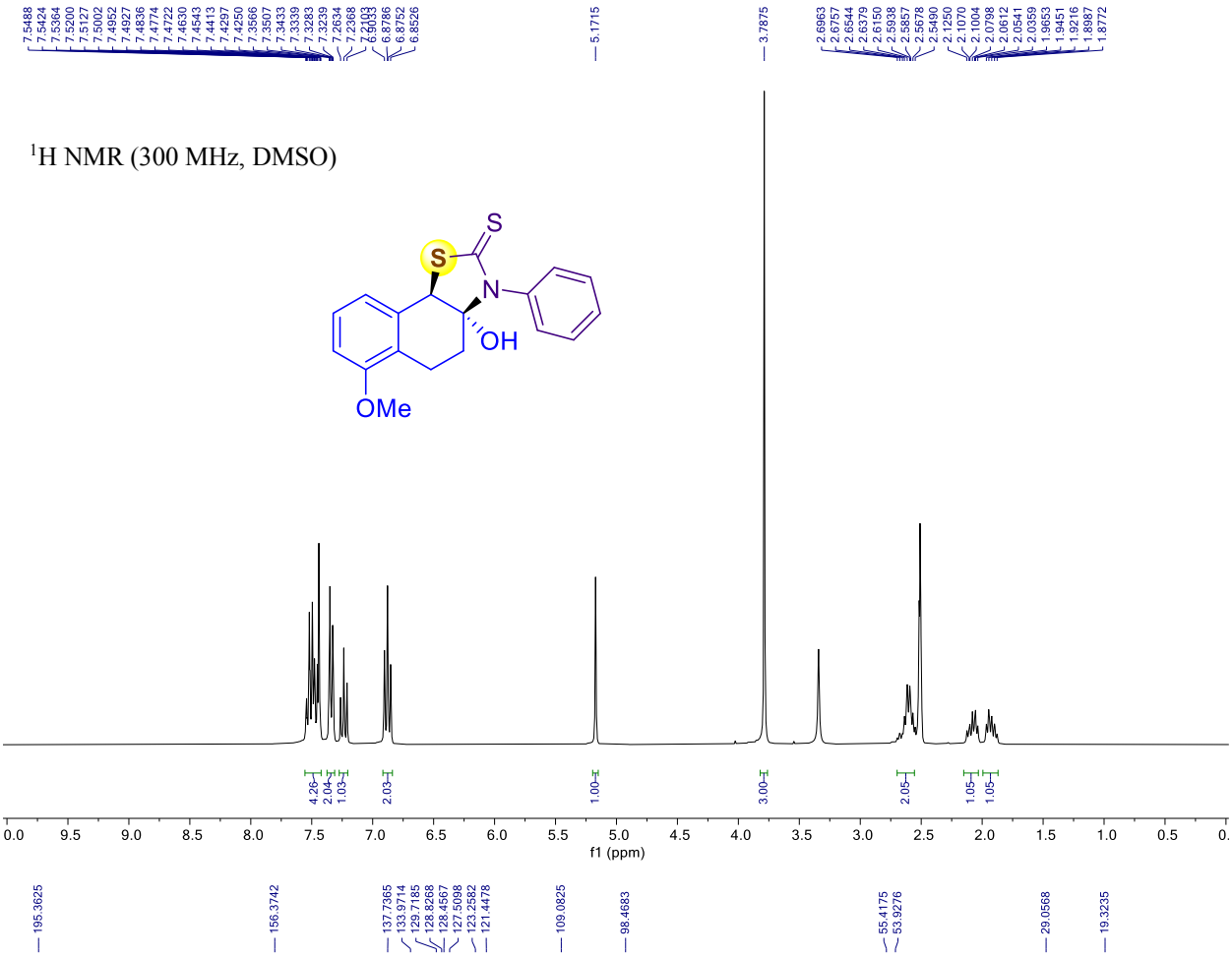


^{13}C{^{1}H} NMR (75 MHz, DMSO)

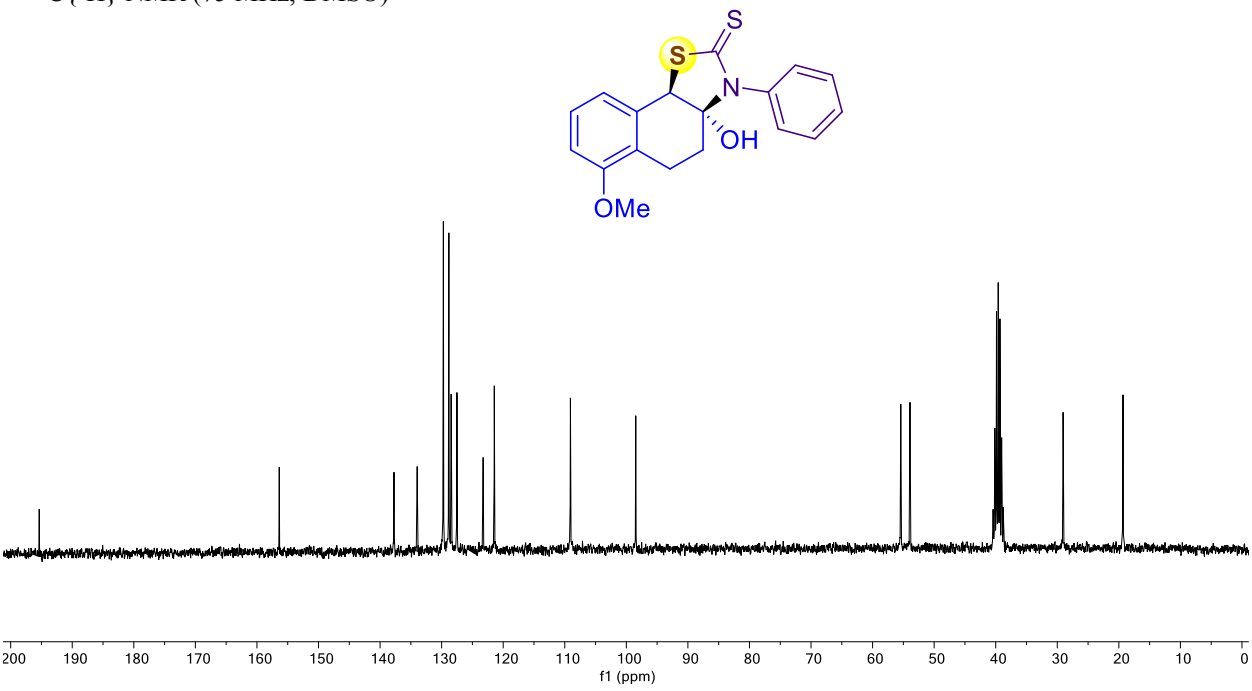


(3a*R*,9b*R*)-3a-Hydroxy-6-methoxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3n)

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

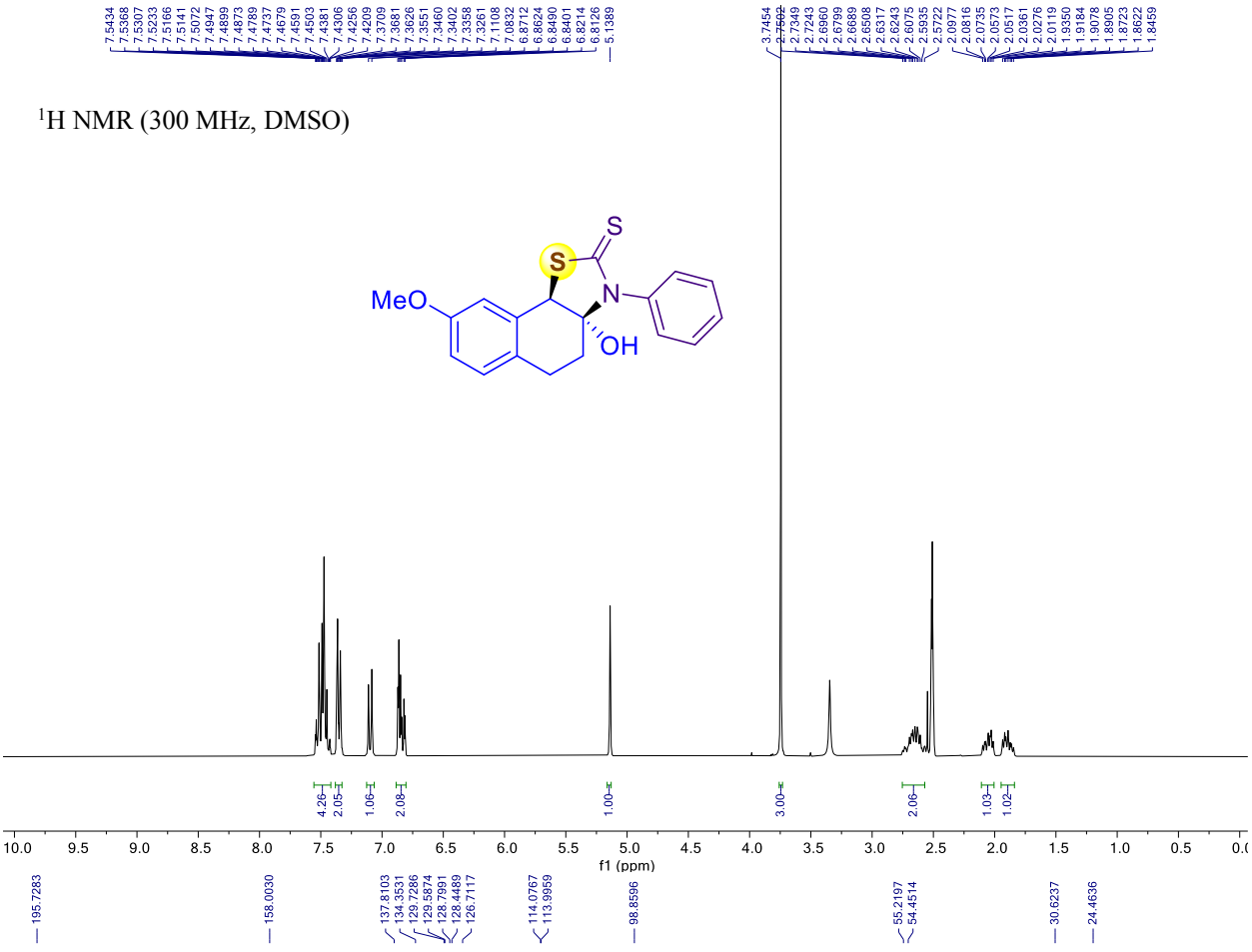


^{13}C{^{1}H} NMR (75 MHz, DMSO)

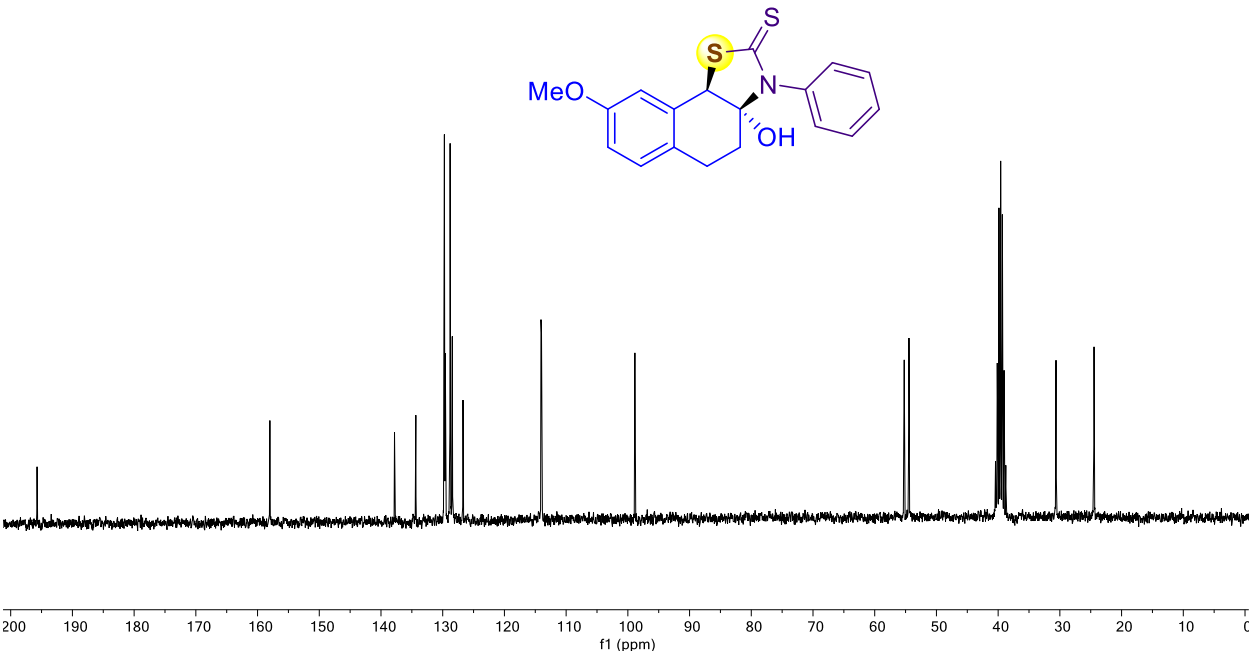


3a*R*,9b*R*)-3a-Hydroxy-8-methoxy-3-phenyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3o)

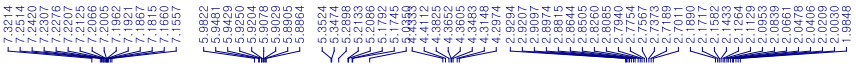
^{1}H NMR (300 MHz, DMSO)



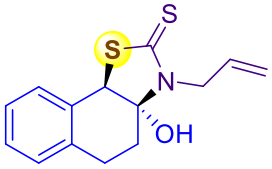
^{13}C{^{1}H} NMR (75 MHz, DMSO)

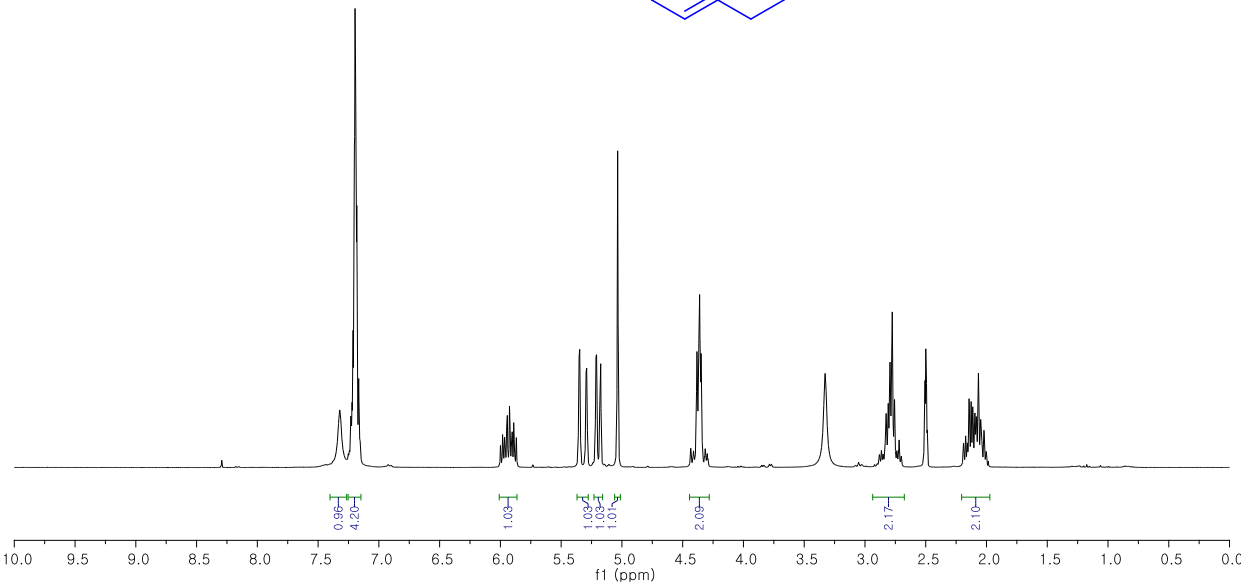


(3a*R*,9b*R*)-3-Allyl-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3p)

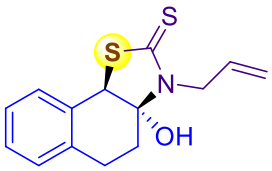


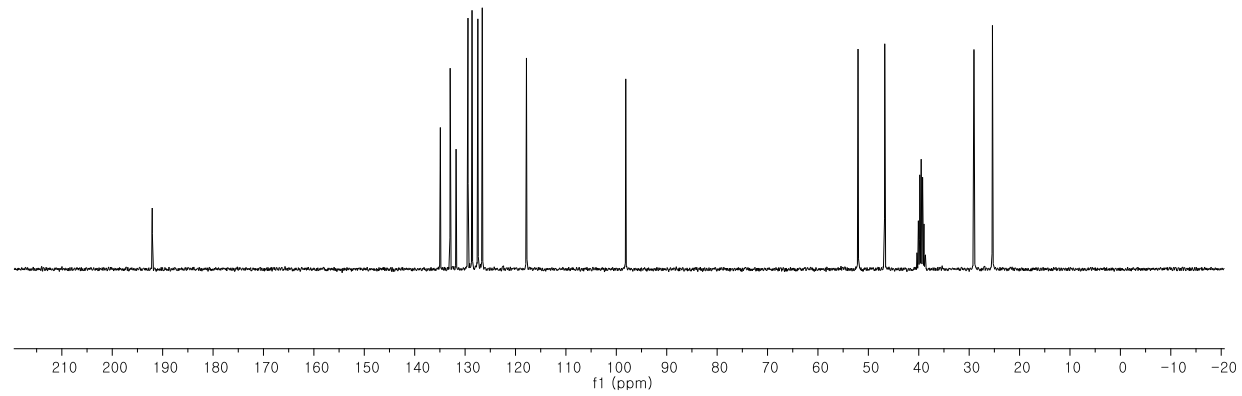
^{1}H NMR (300 MHz, DMSO)





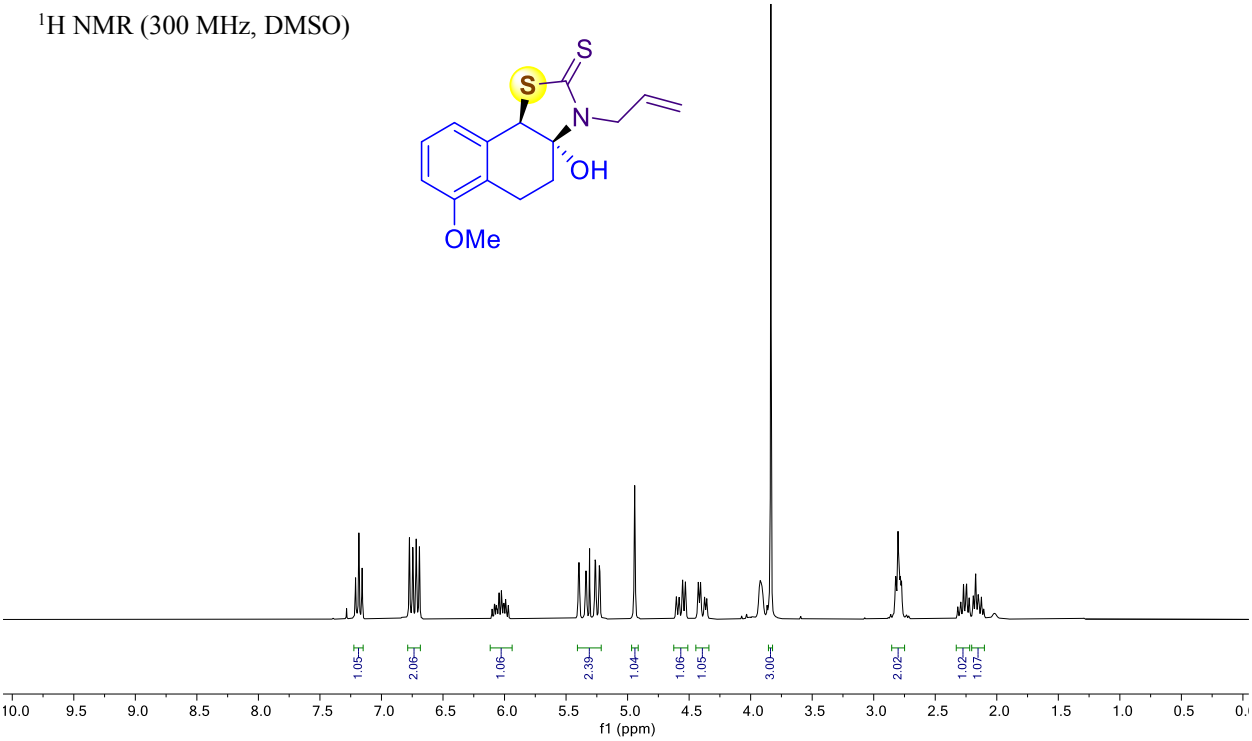
^{13}C{^{1}H} NMR (75 MHz, DMSO)



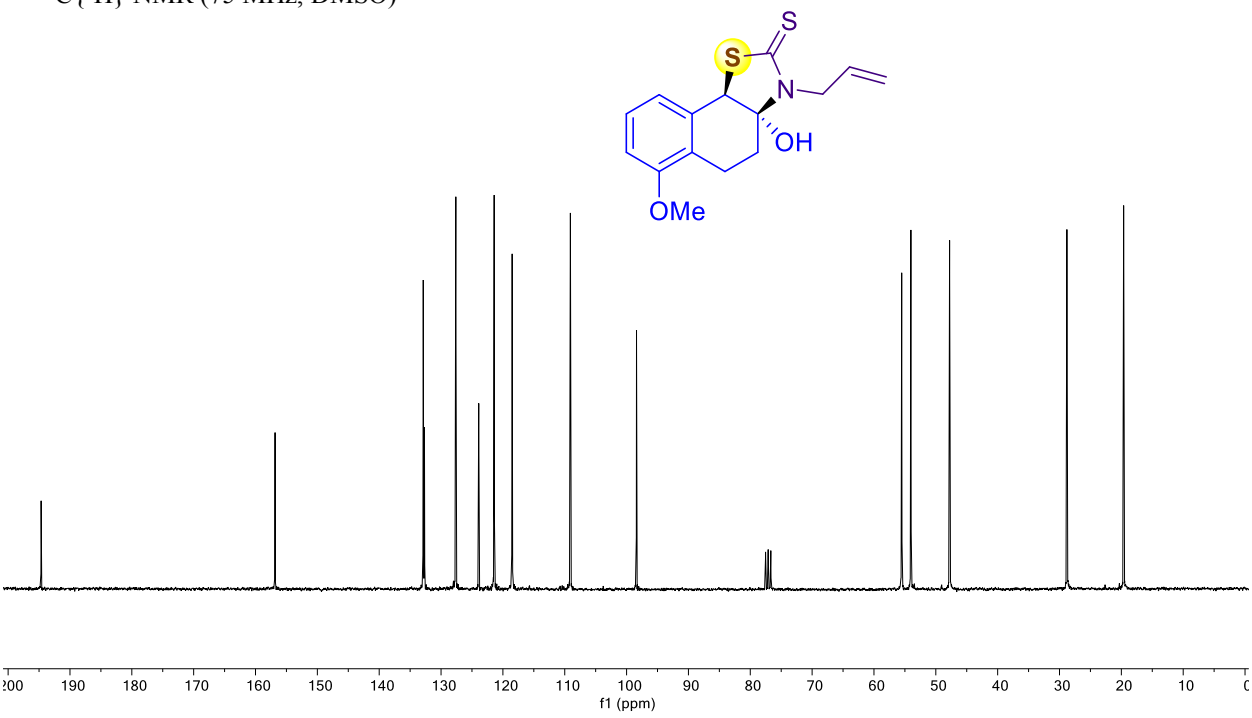


(3a*R*,9b*R*)-3-Allyl-3a-Hydroxy-6-methoxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3q)

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

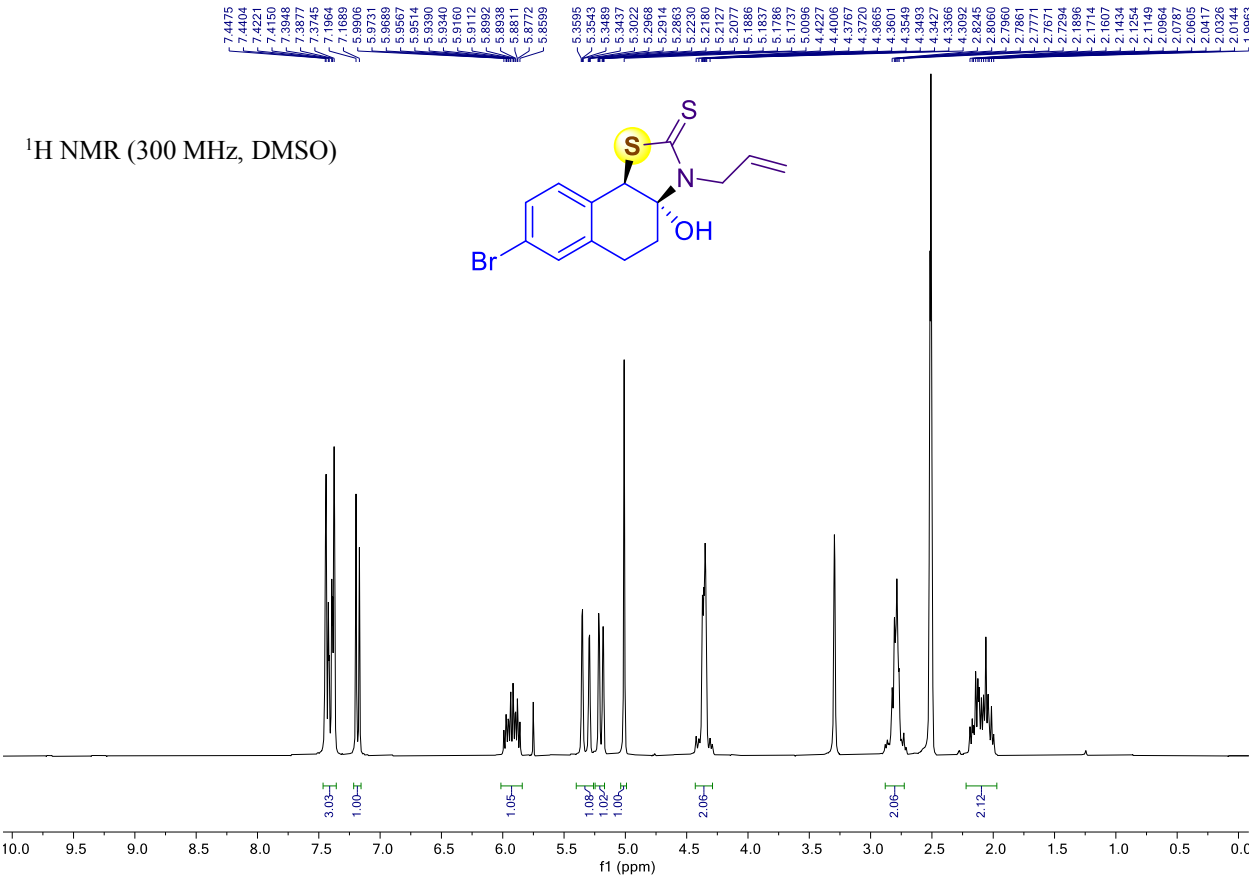


^{13}C{^{1}H} NMR (75 MHz, DMSO)

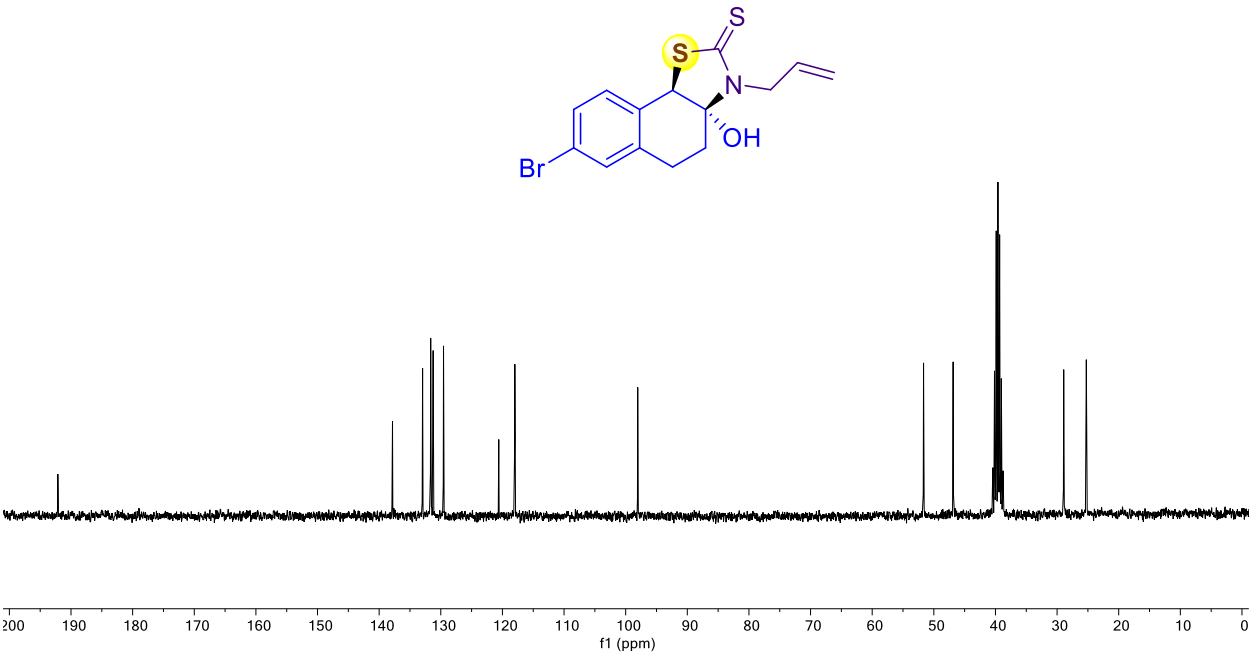


(3a*R*,9b*R*)-3-Allyl-7-bromo-3a-hydroxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3r)

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

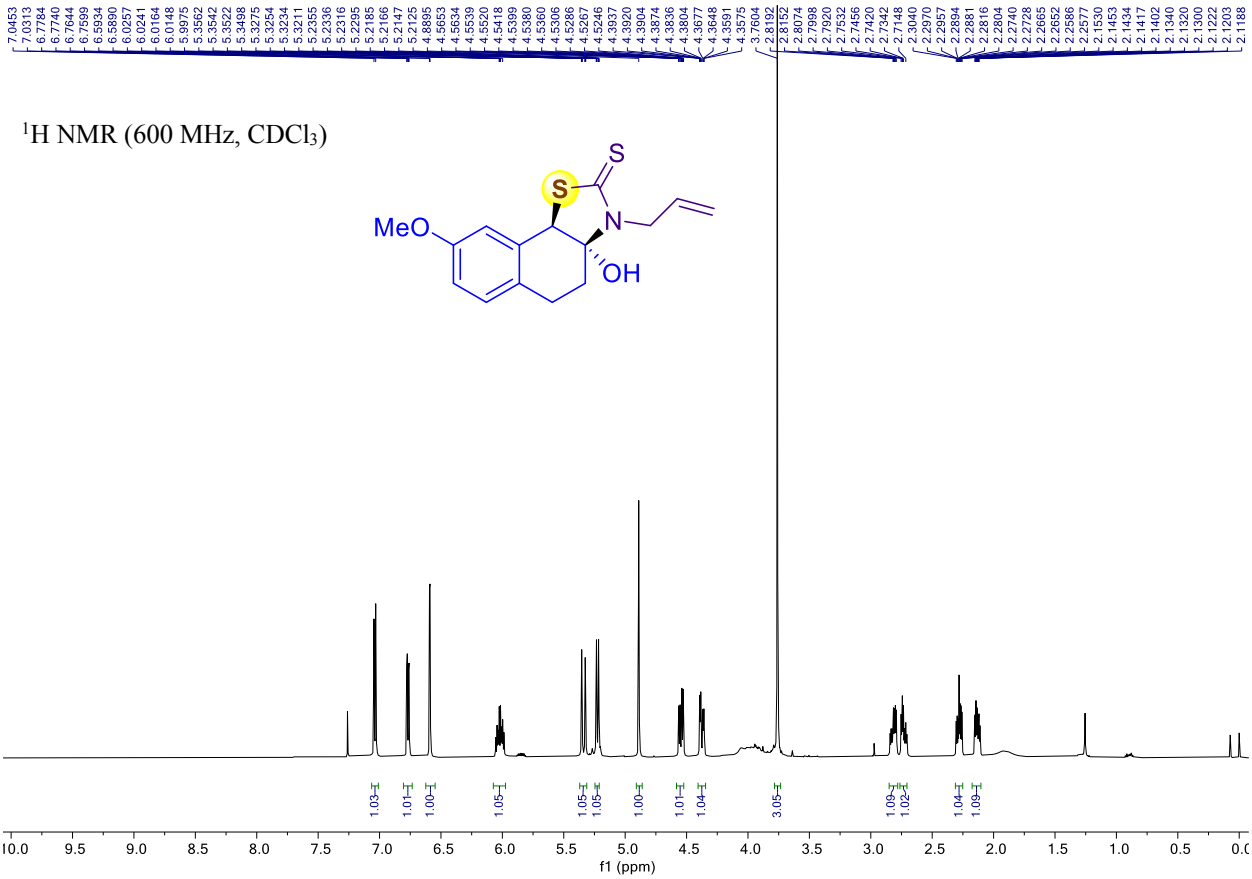


^{13}C{^{1}H} NMR (75 MHz, DMSO)

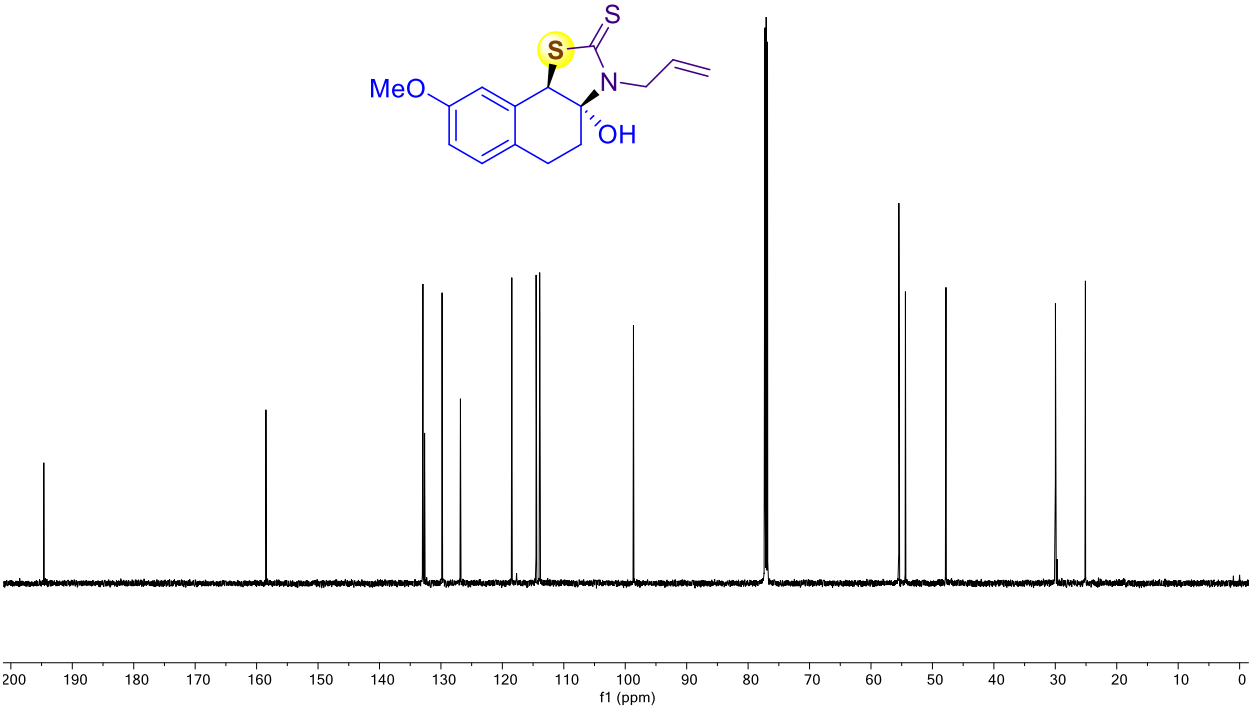


(3a*R*,9b*R*)-3-Allyl-3a-Hydroxy-8-methoxy-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3s)

^{1}H NMR (600 MHz, $CDCl_3$)

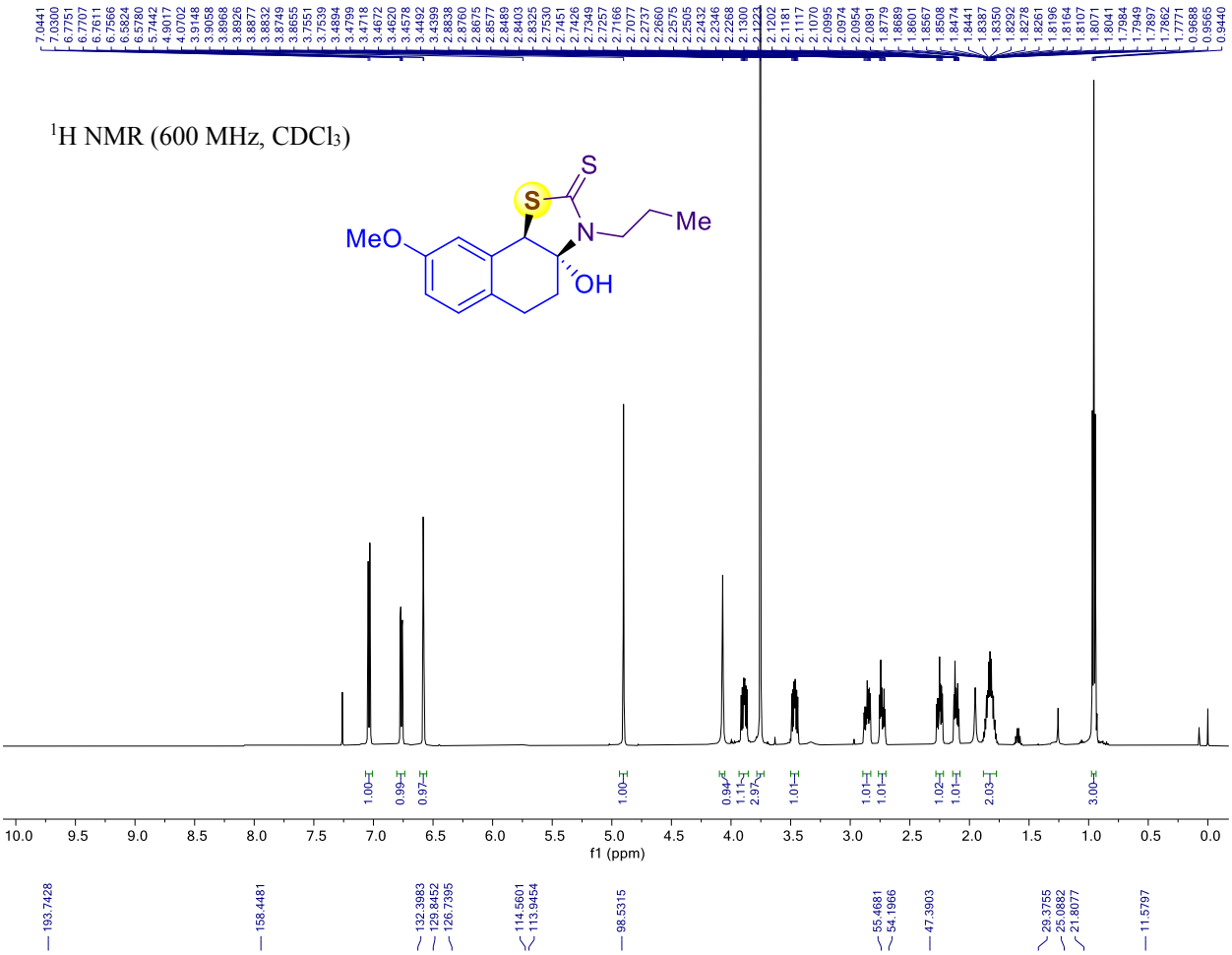


^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$)

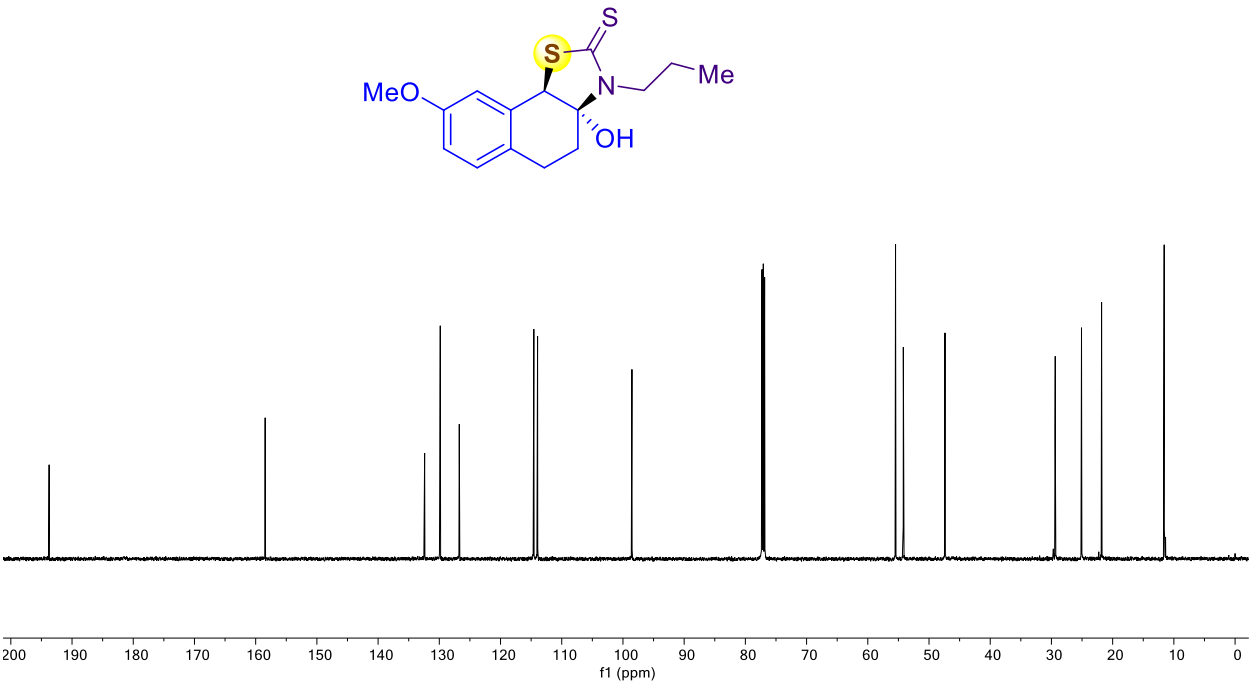


(3a*R*,9b*R*)-3a-Hydroxy-8-methoxy-3-propyl-3a,4,5,9b-tetrahydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (3t)

^{1}H NMR (600 MHz, $CDCl_3$)

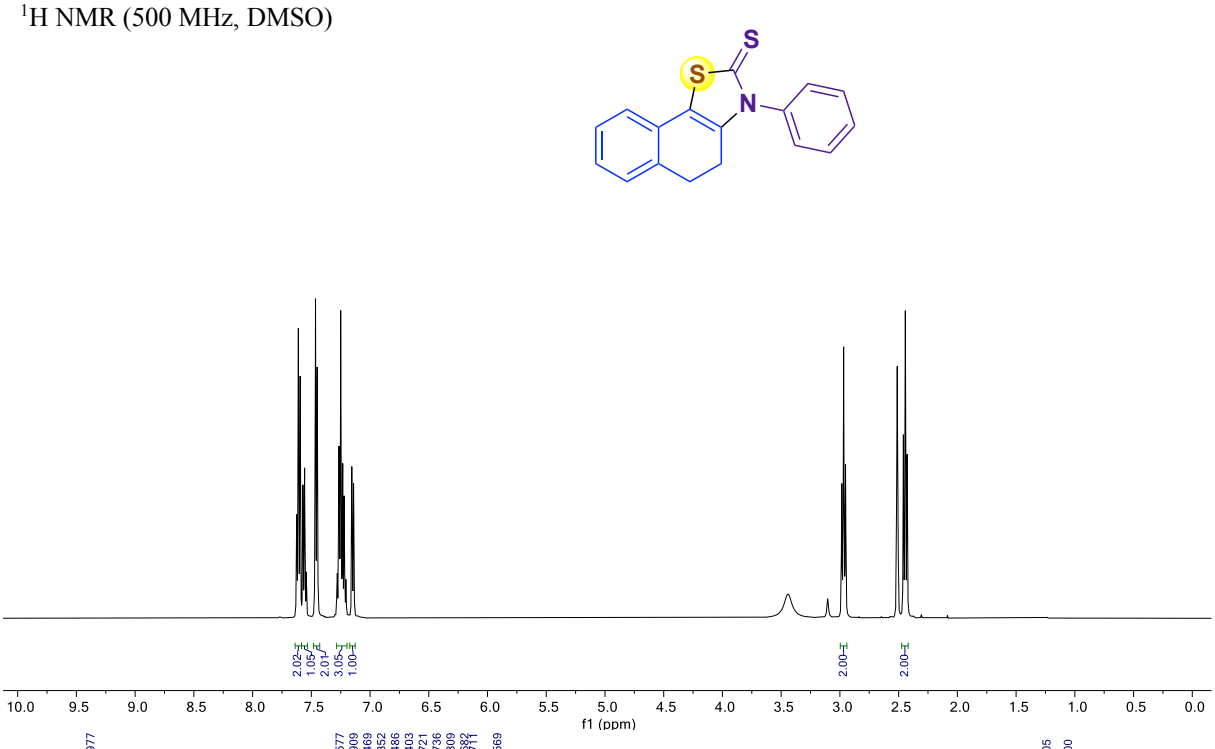


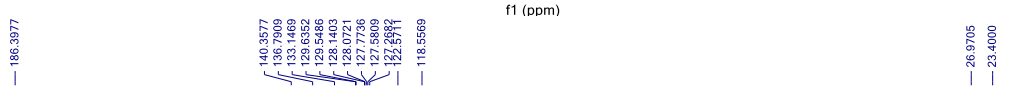
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$)



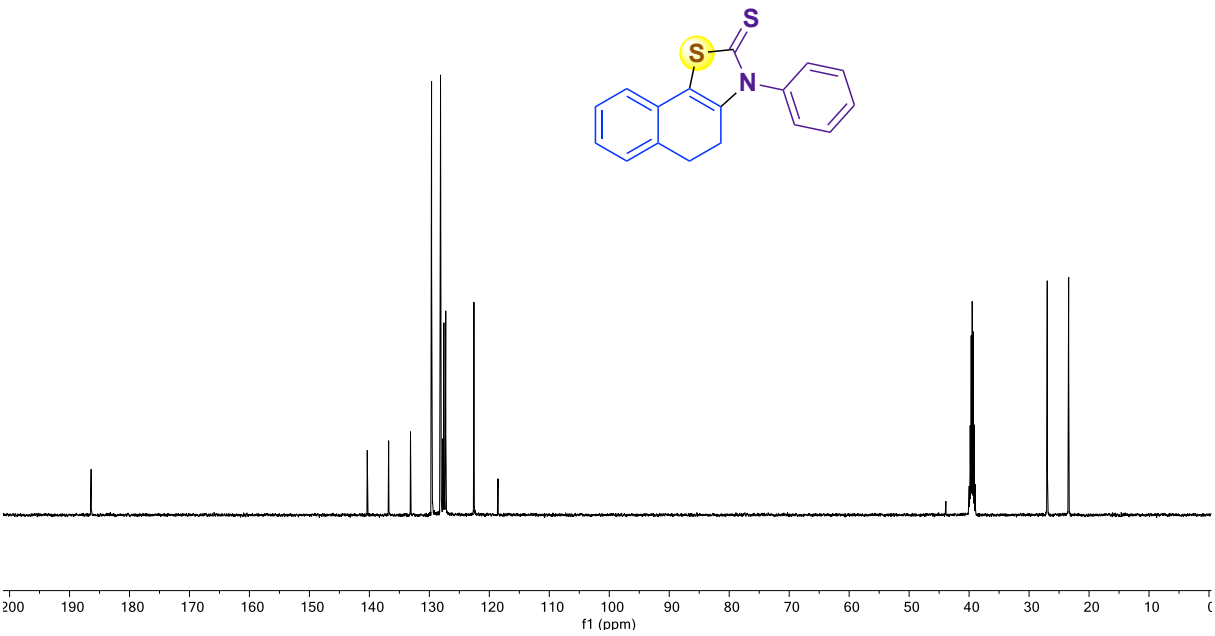
3-Phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4a)

^{1}H NMR (500 MHz, DMSO)



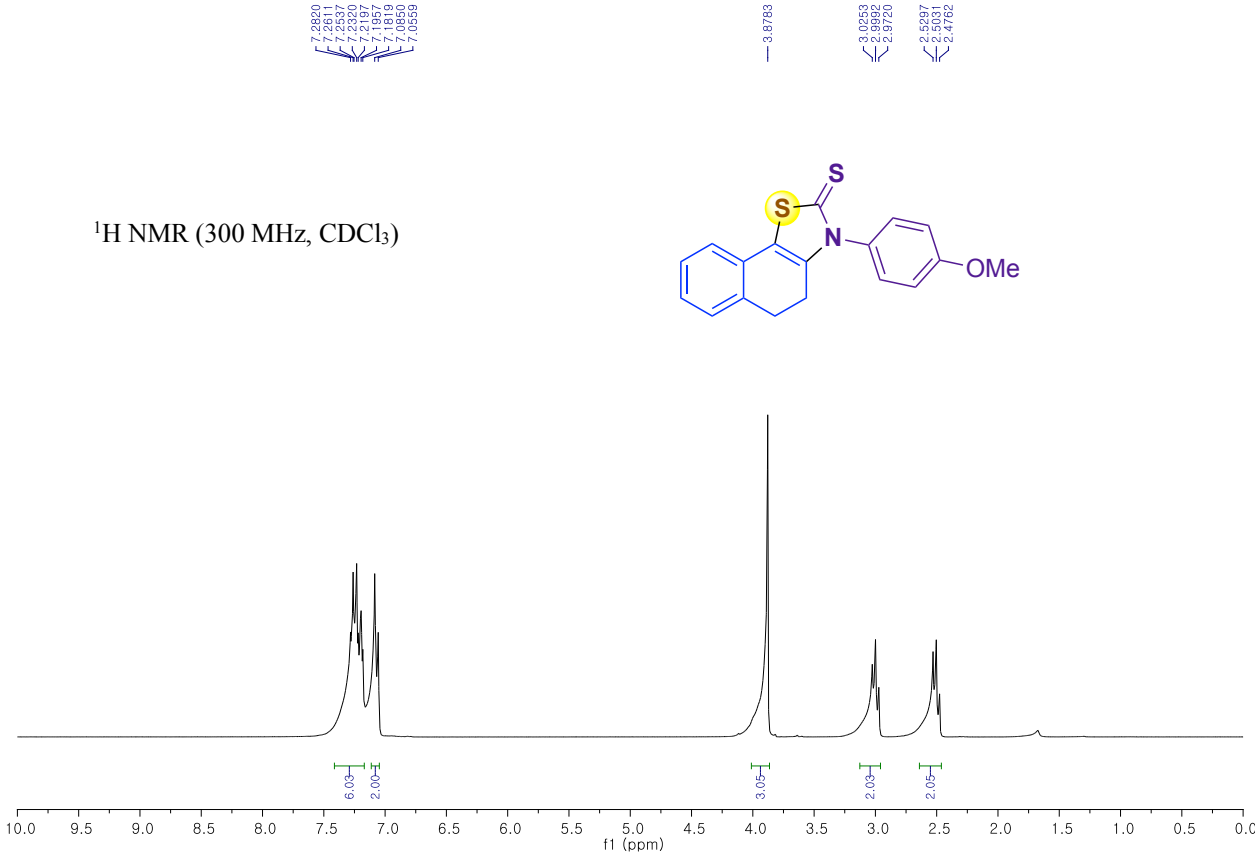


^{13}C{^{1}H} NMR (75 MHz, DMSO)

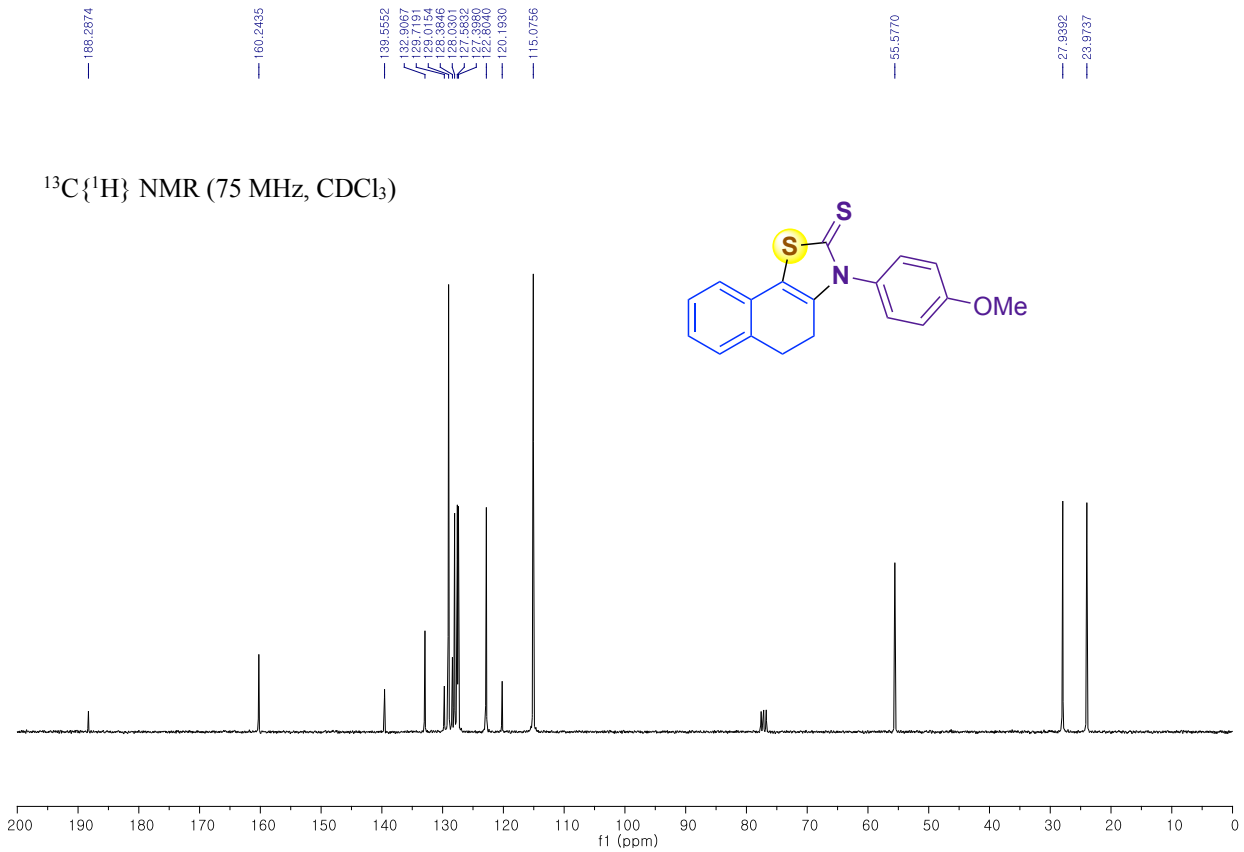


3-(4-Methoxyphenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4b)

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

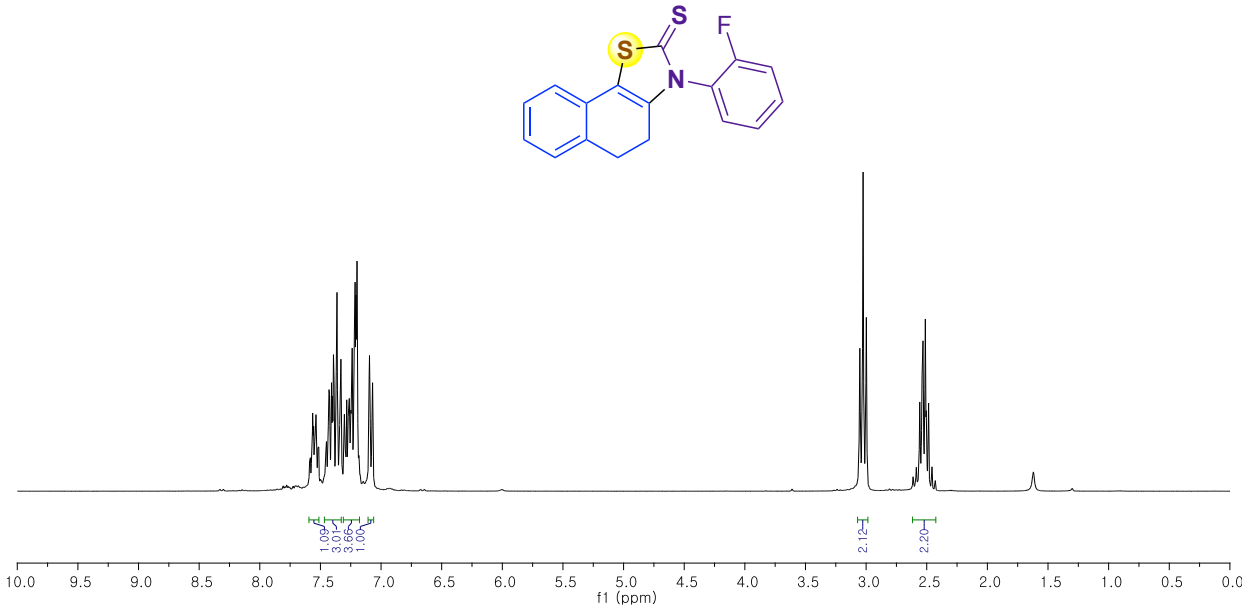


^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)

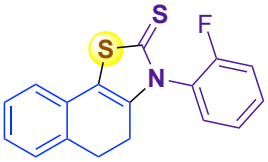


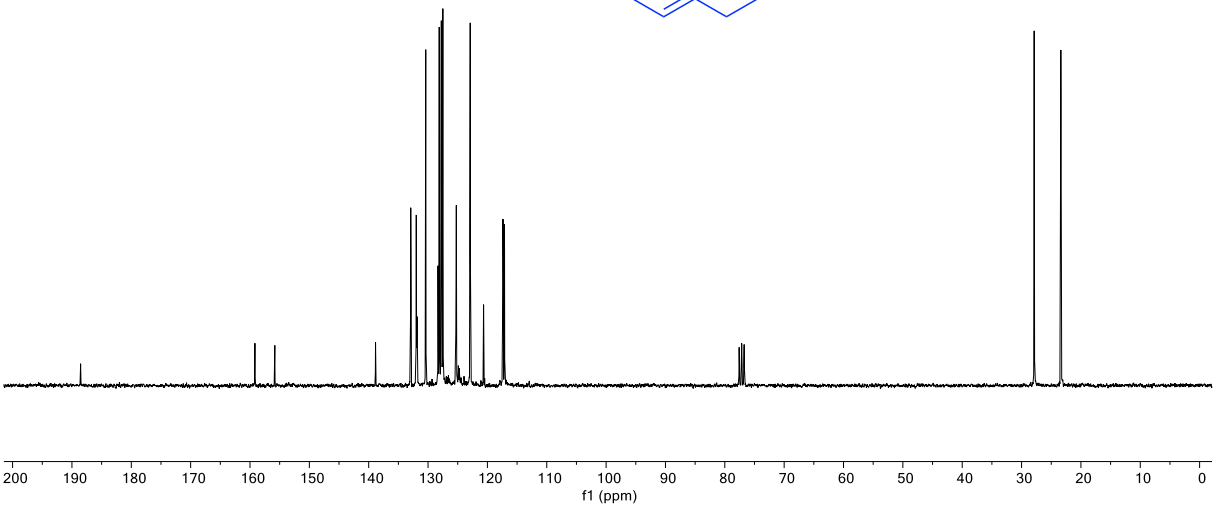
3-(2-Fluorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4c)

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

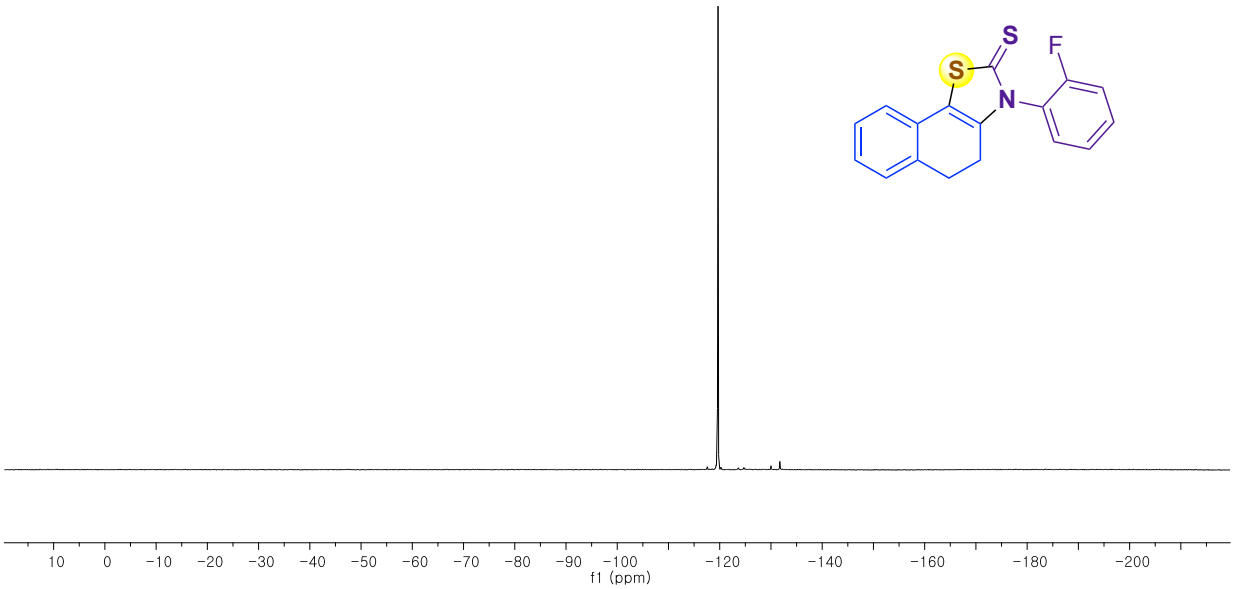


^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



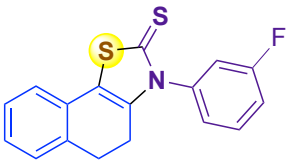


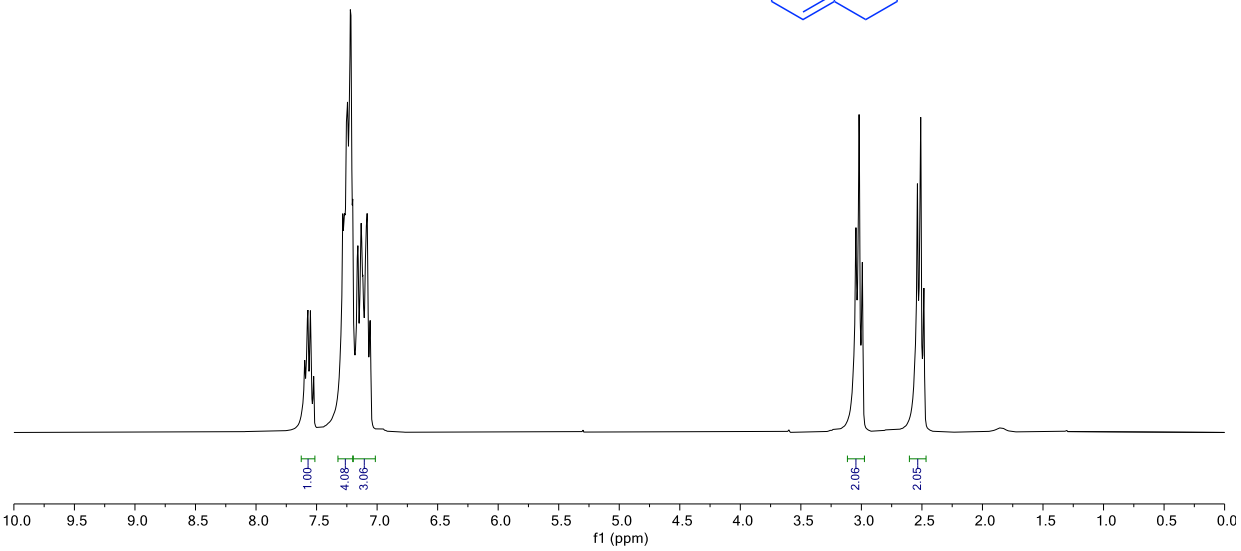
^{19}F NMR (282 MHz, $CDCl_3$)



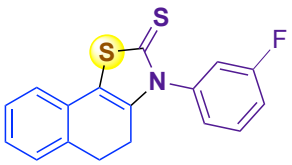
3-(3-Fluorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4d)

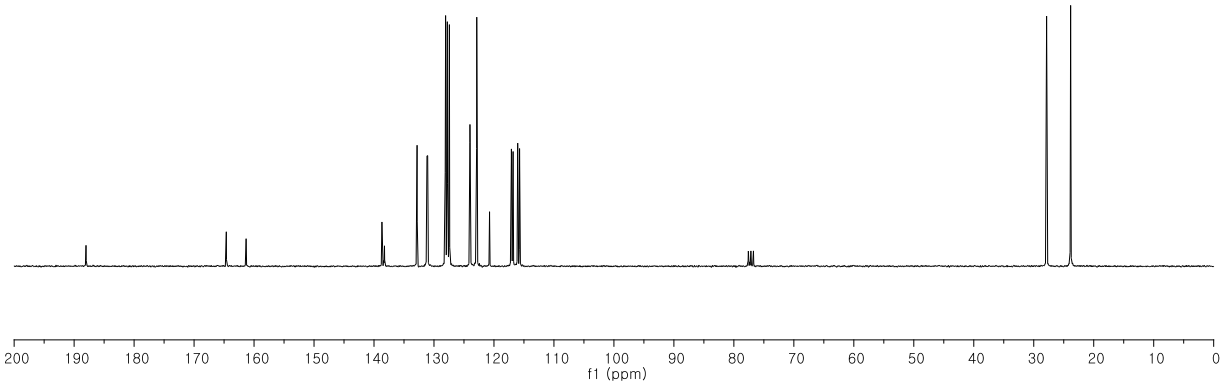
^{1}H NMR (300 MHz, $CDCl_3$)



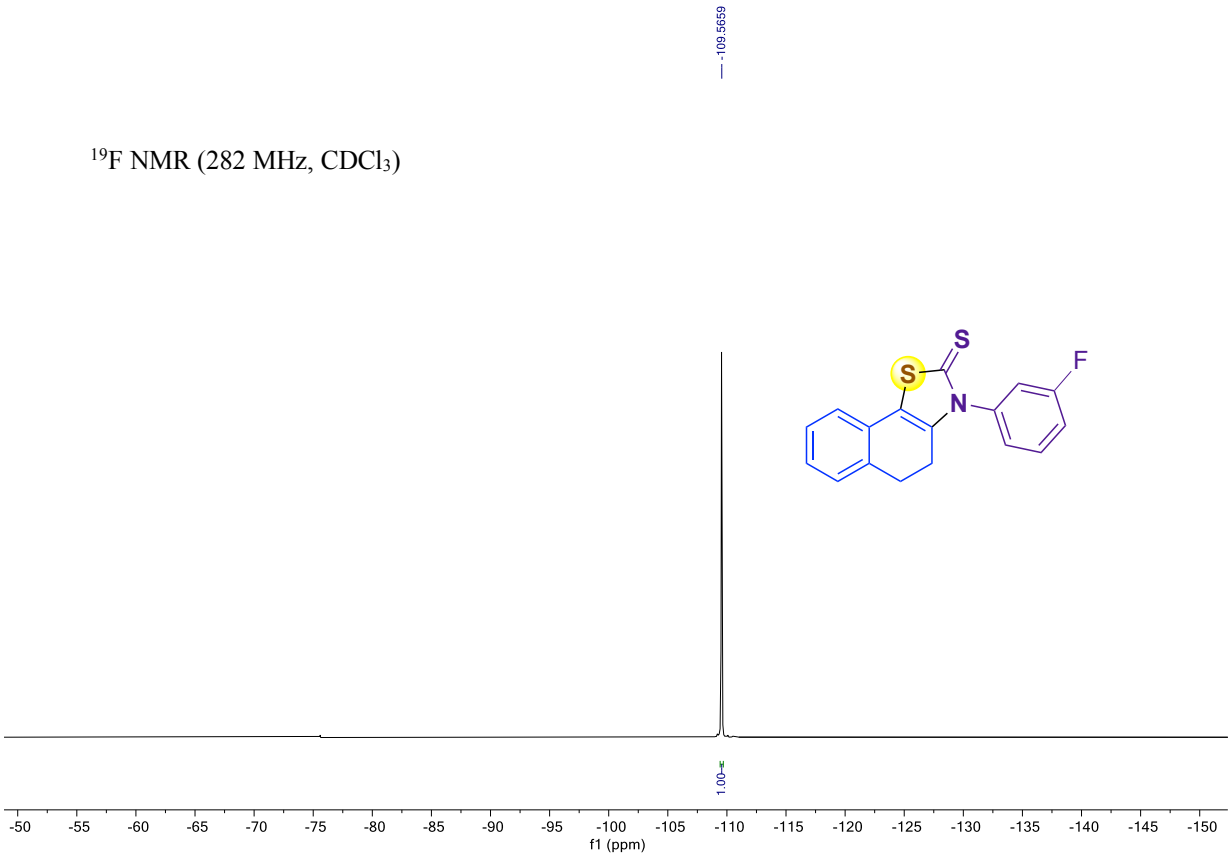


^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



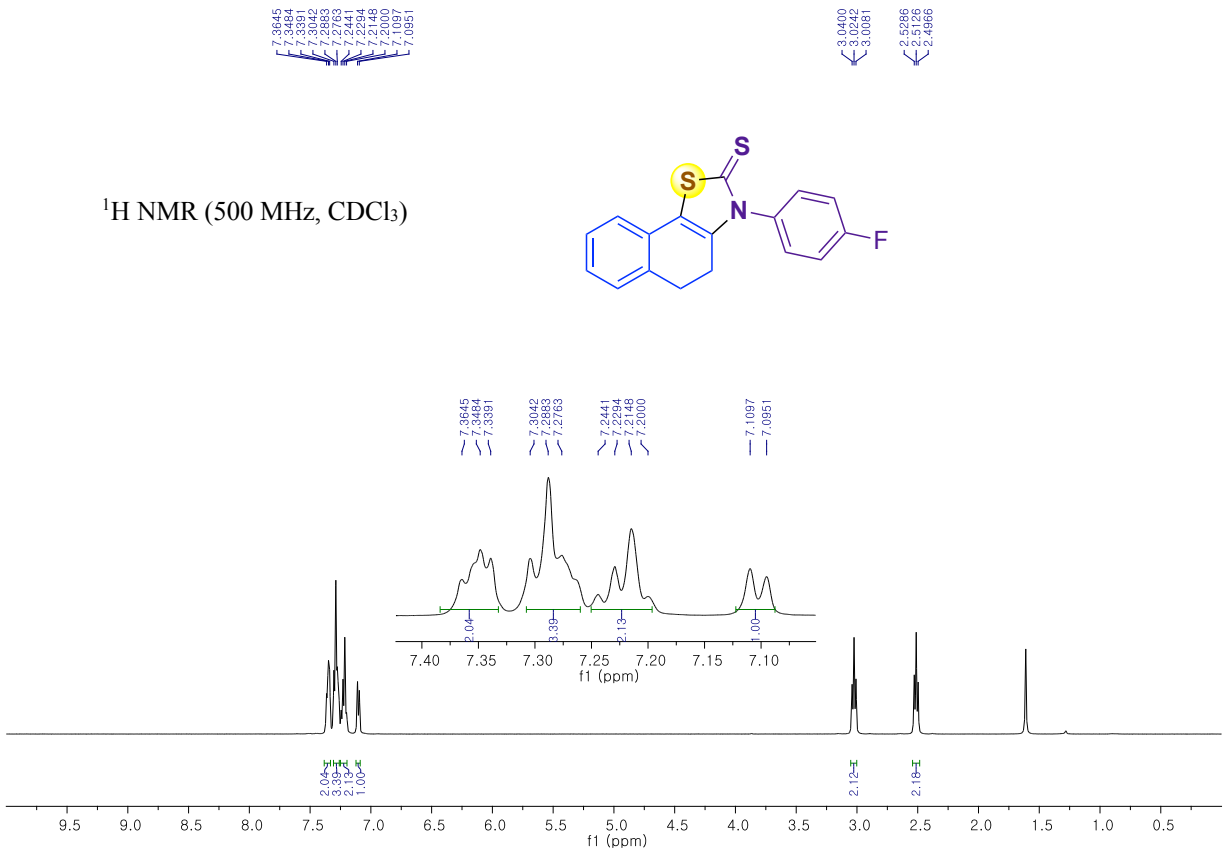


^{19}F NMR (282 MHz, $CDCl_3$)

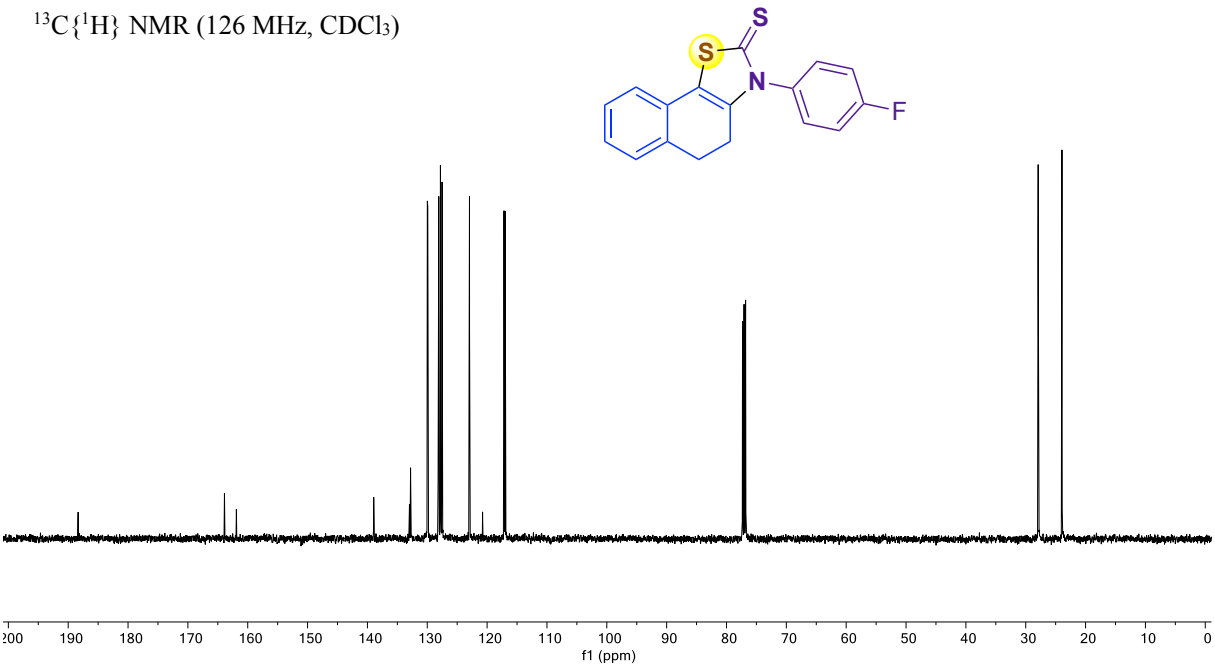


3-(4-Fluorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4e)

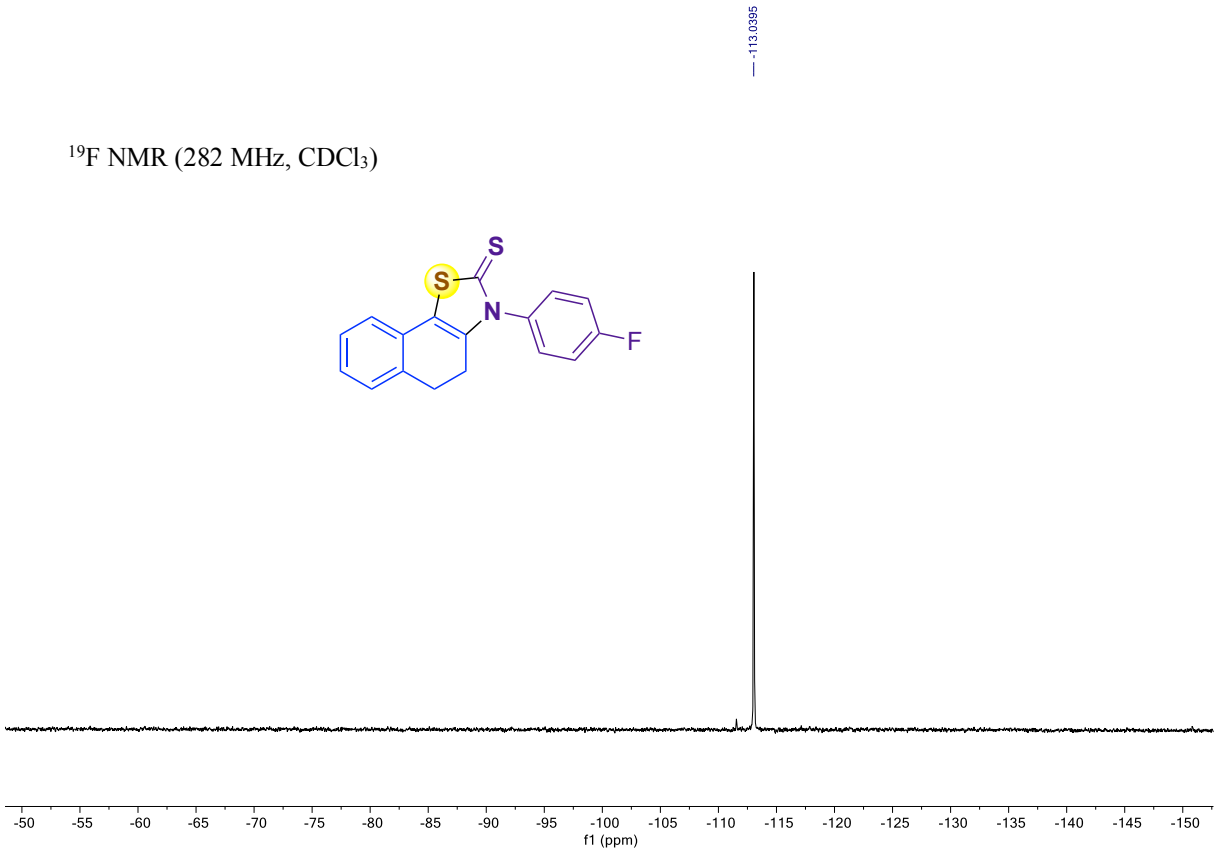
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)

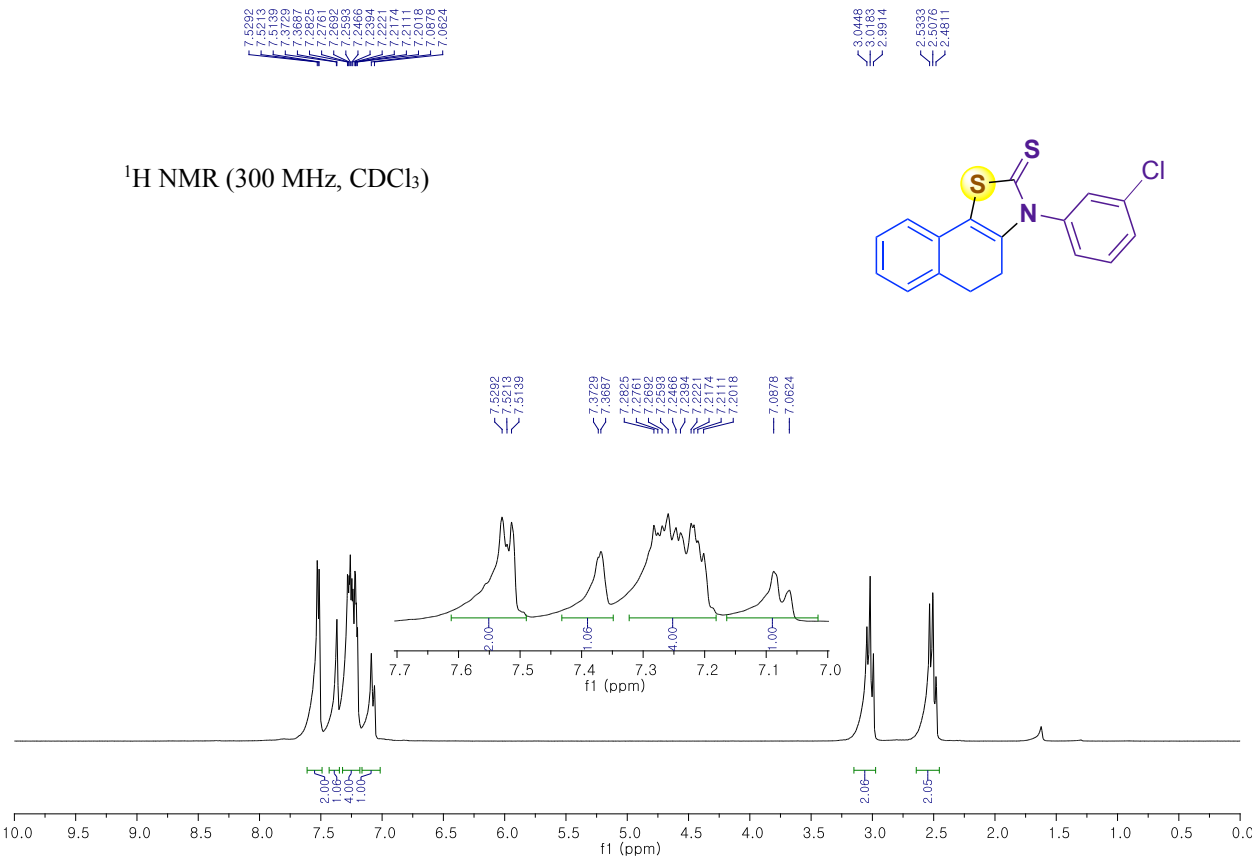


^{19}F NMR (282 MHz, $CDCl_3$)

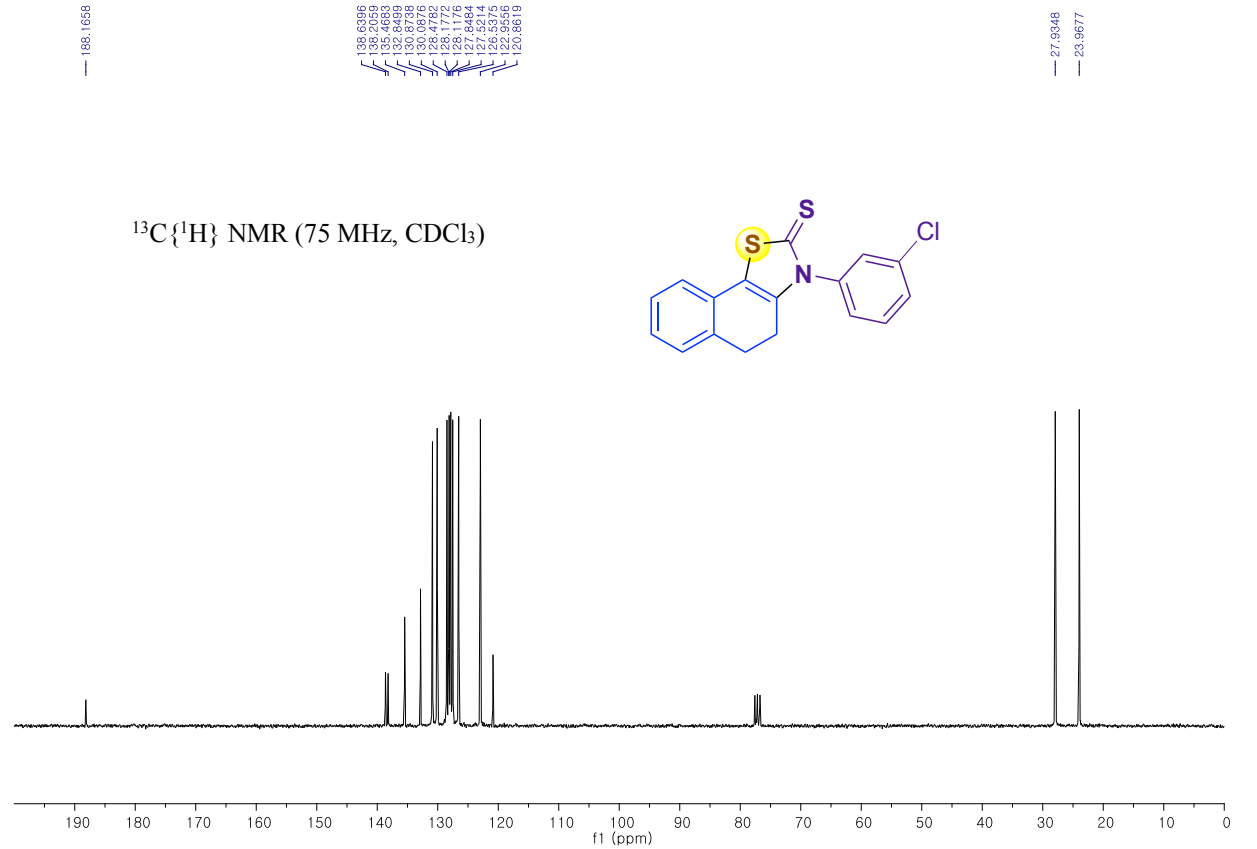


3-(3-Chlorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4f)

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

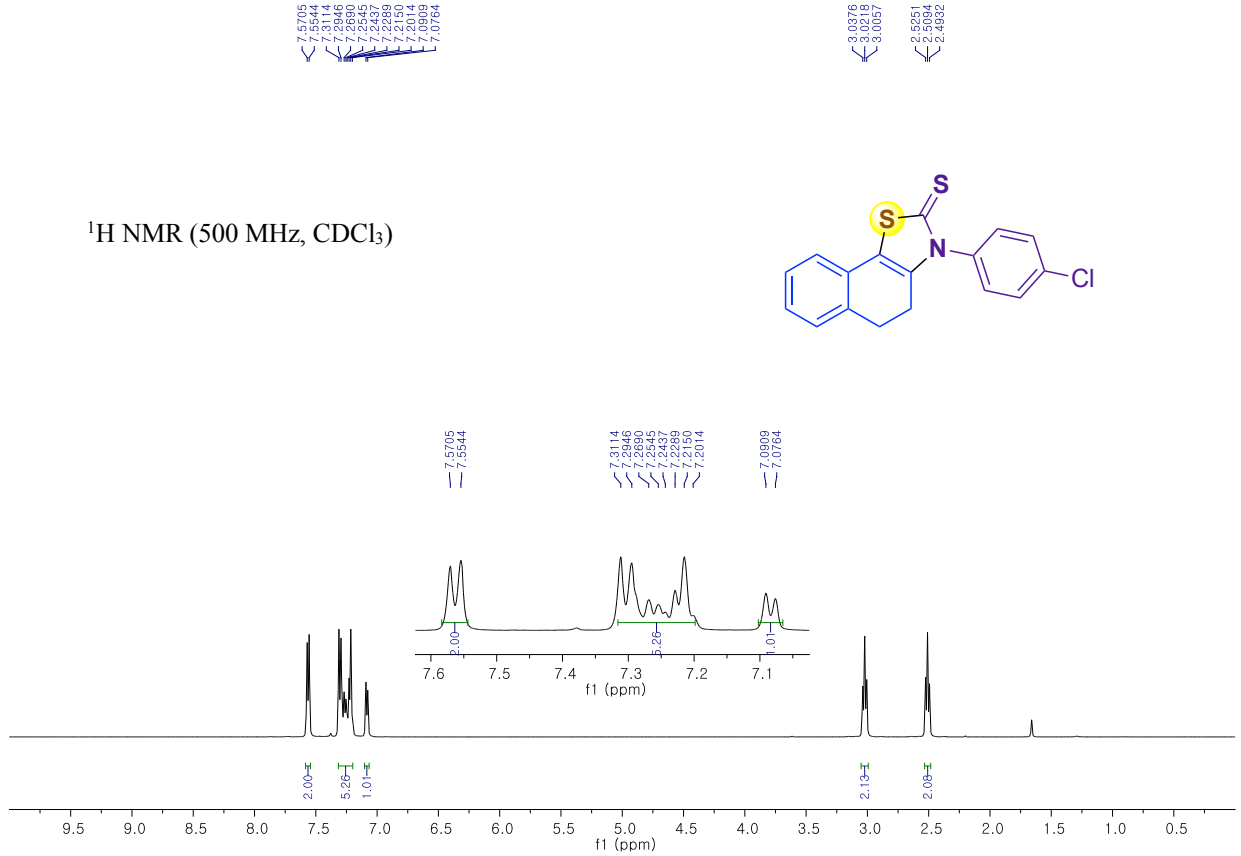


^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)

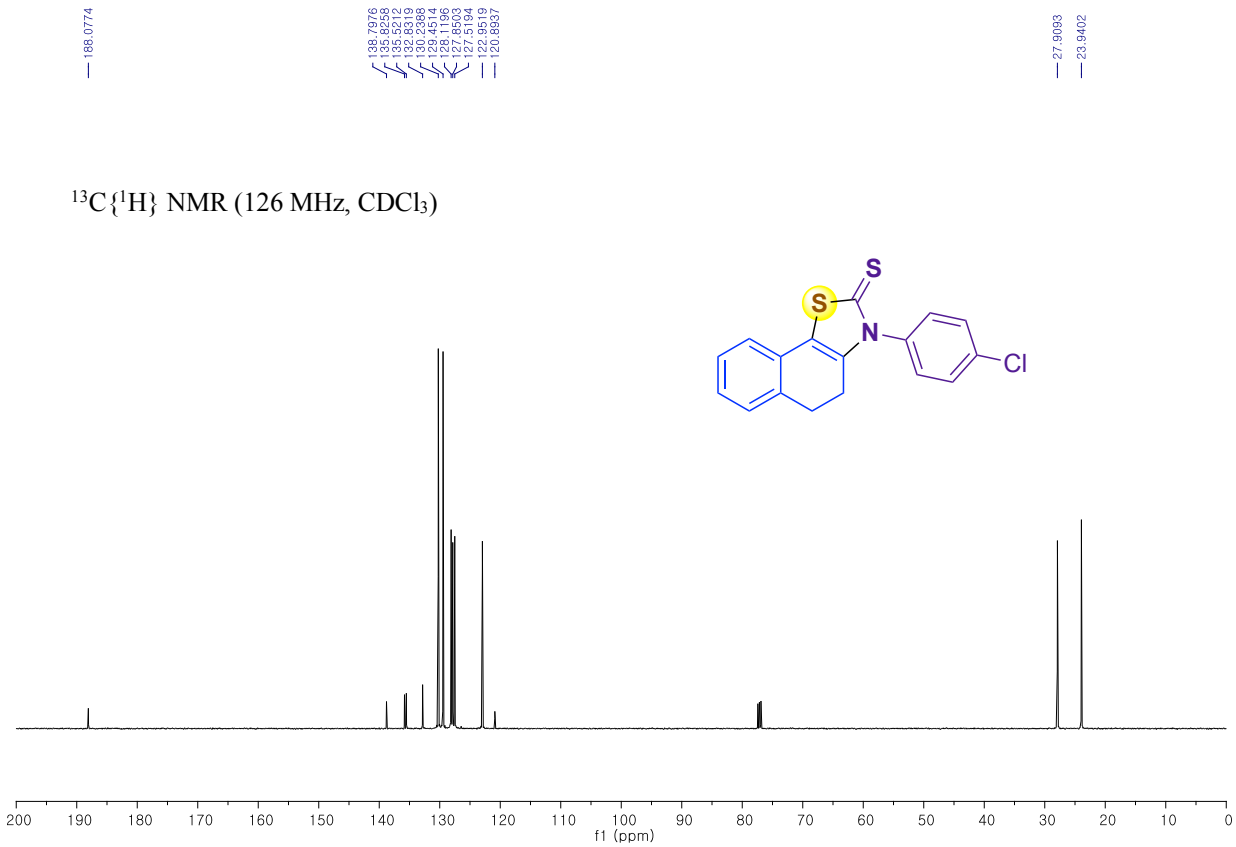


3-(4-Chlorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4g)

^{1}H NMR (500 MHz, $CDCl_3$)

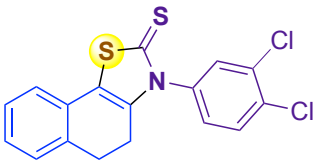


^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)

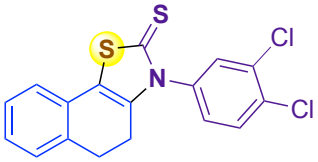


3-(3,4-Dichlorophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4h)

^{1}H NMR (500 MHz, $CDCl_3$)

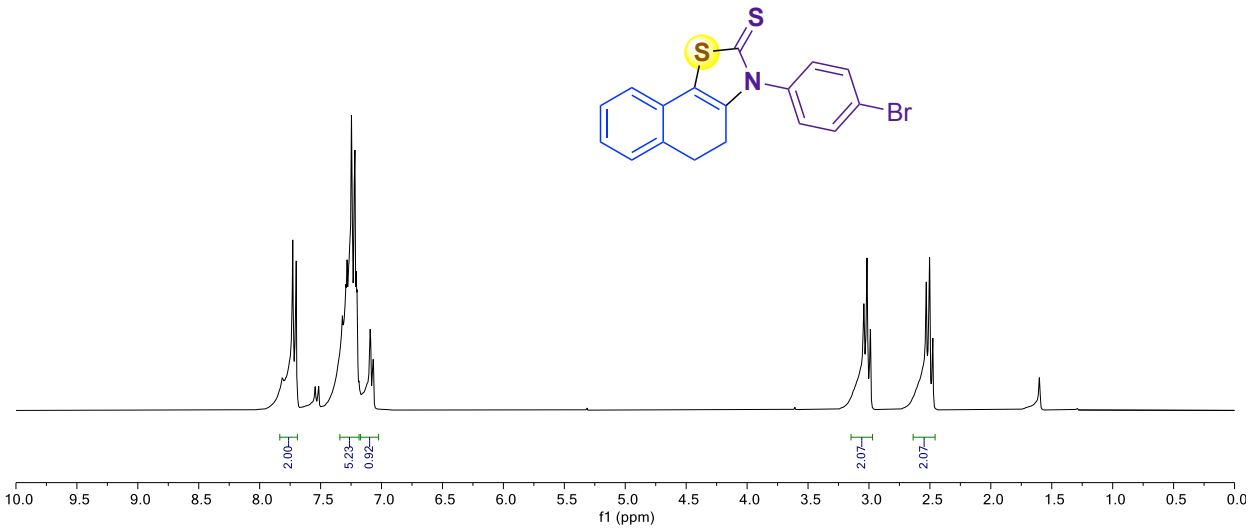


^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)

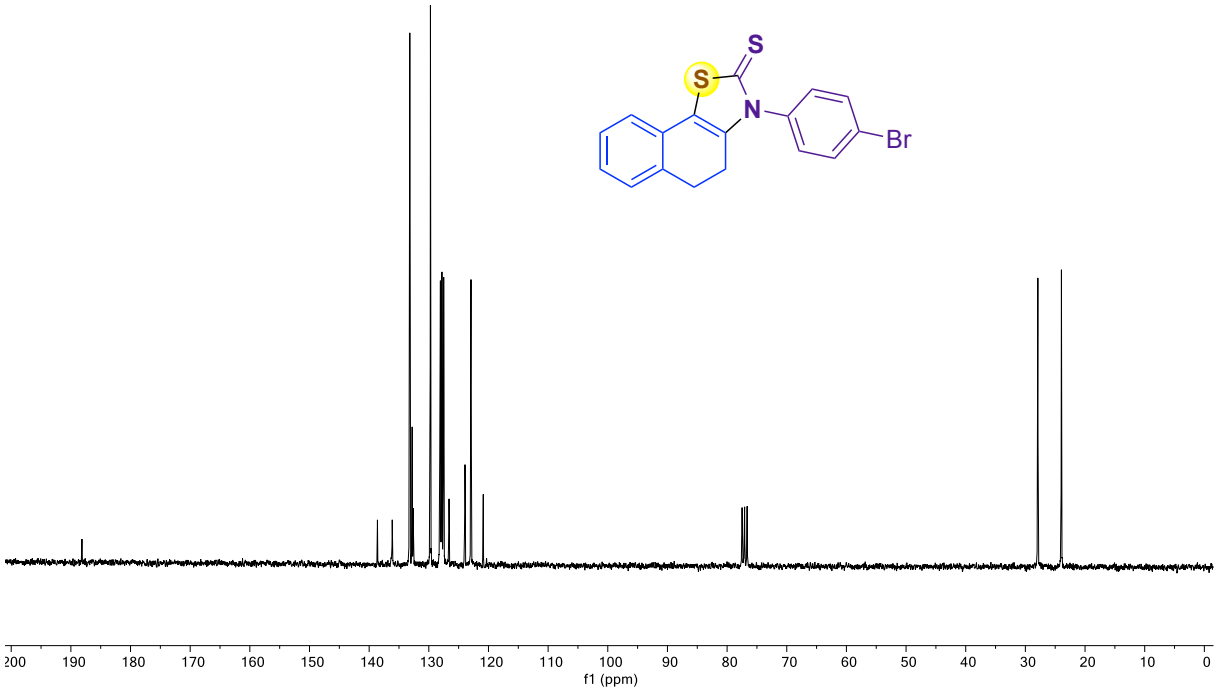


3-(4-Bromophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4i)

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

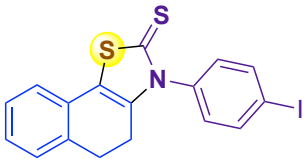


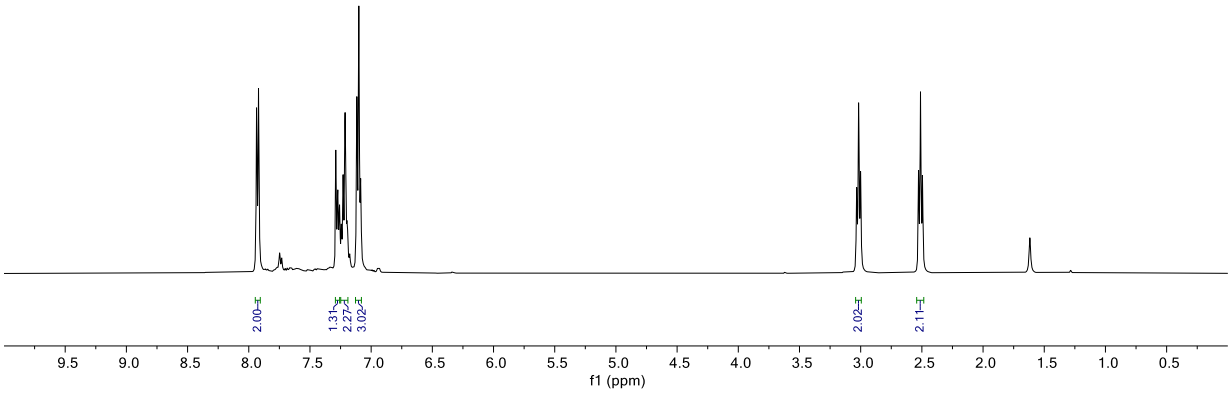
^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)



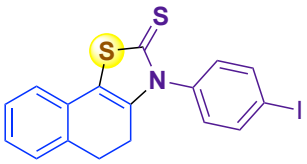
3-(4-Iodophenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4j)

^{1}H NMR (500 MHz, $CDCl_3$)

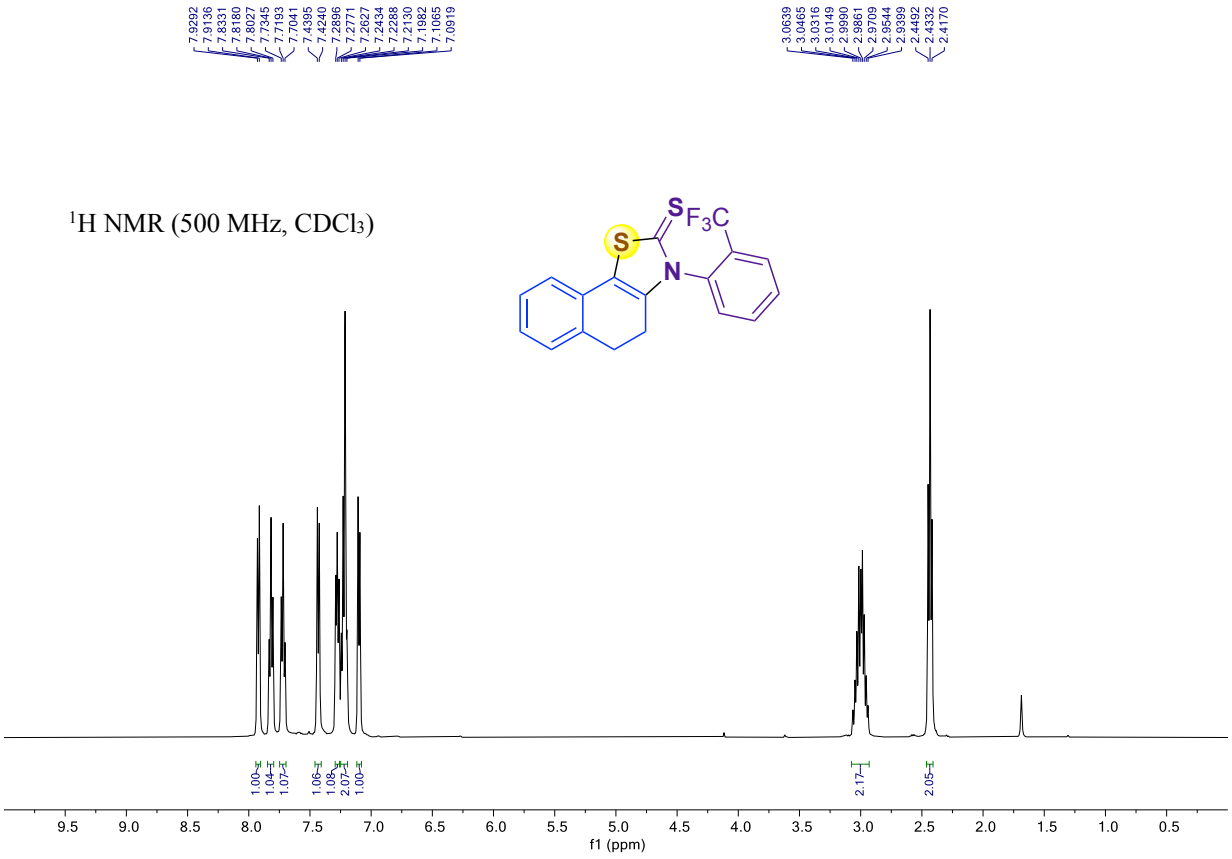


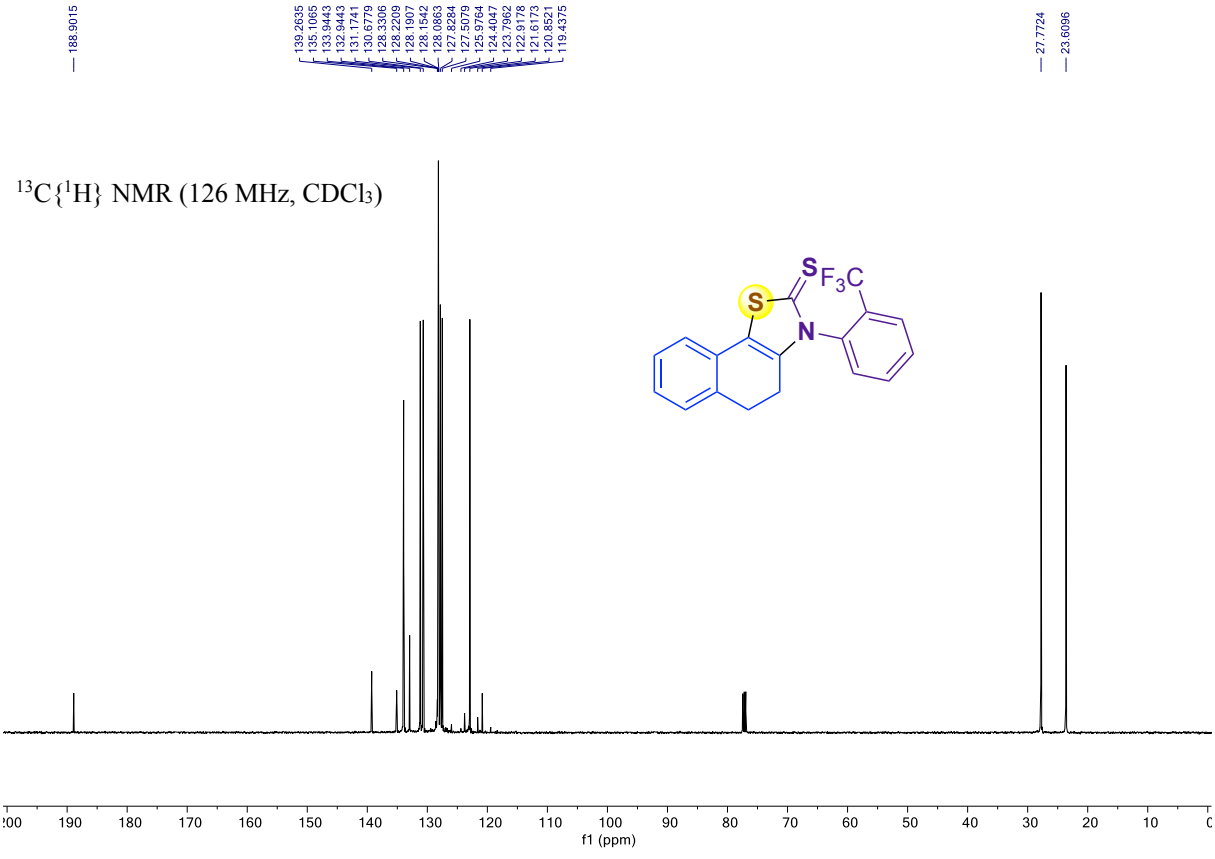


^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)

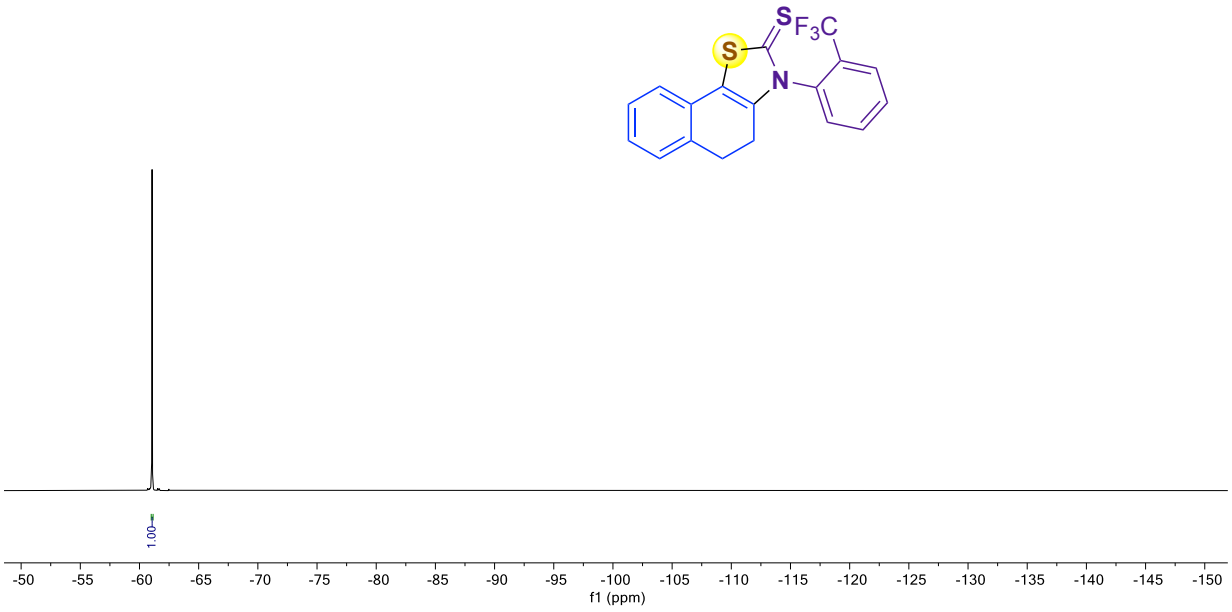


3-(2-(Trifluoromethyl)phenyl)-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4k)


7.9292
7.9136
7.8331
7.8180
7.8027
7.7345
7.7193
7.7041
7.4395
7.4240
7.2896
7.2771
7.2627
7.2434
7.2288
7.2130
7.1982
7.1065
7.0919
3.0639
3.0465
3.0316
3.0149
2.9990
2.9861
2.9709
2.9544
2.9399
2.4492
2.4332
2.4170
1H NMR (500 MHz, CDCl3)
S
F3C
S
N
1.00
1.04
1.07
1.06
1.08
2.07
1.00
2.17
2.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

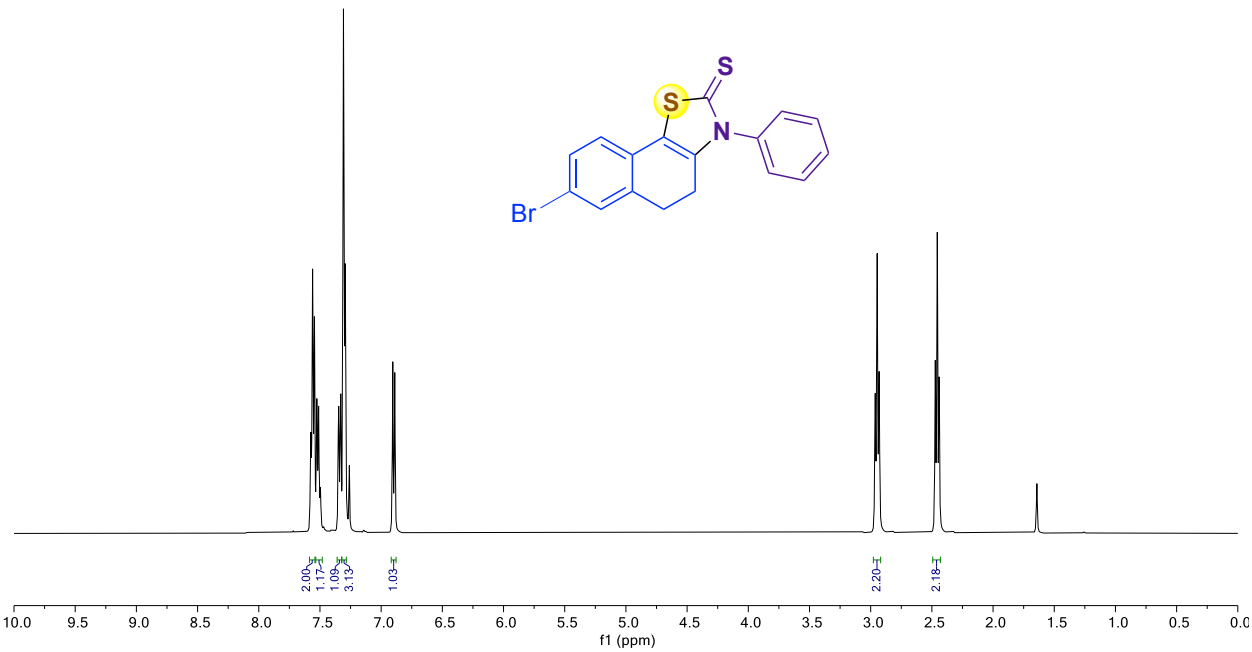

188.9015
139.2635
135.1065
133.9443
132.9443
131.1741
130.6779
128.3306
128.2209
128.1907
128.1542
128.0863
127.8284
127.5079
125.9764
124.4047
123.7962
122.9178
121.6173
120.8521
119.4375
27.7724
23.6096
13C{1H} NMR (126 MHz, CDCl3)
S
F3C
S
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{19}F NMR (282 MHz, $CDCl_3$)

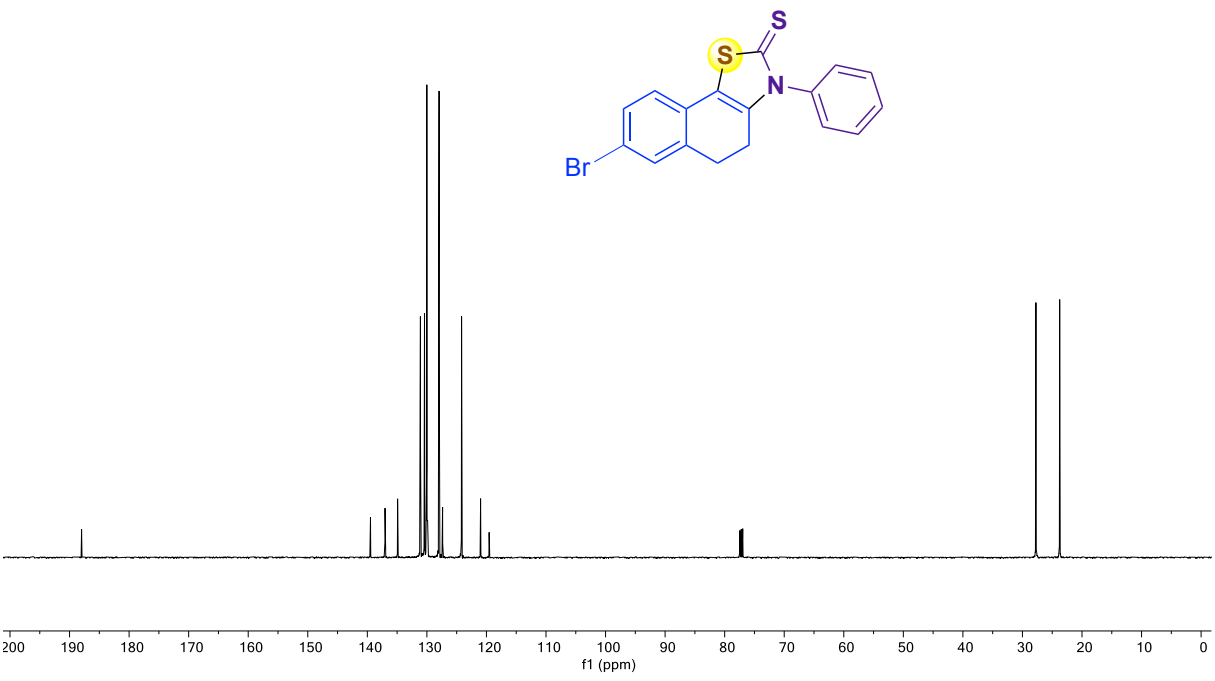


7-Bromo-3-phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4m)

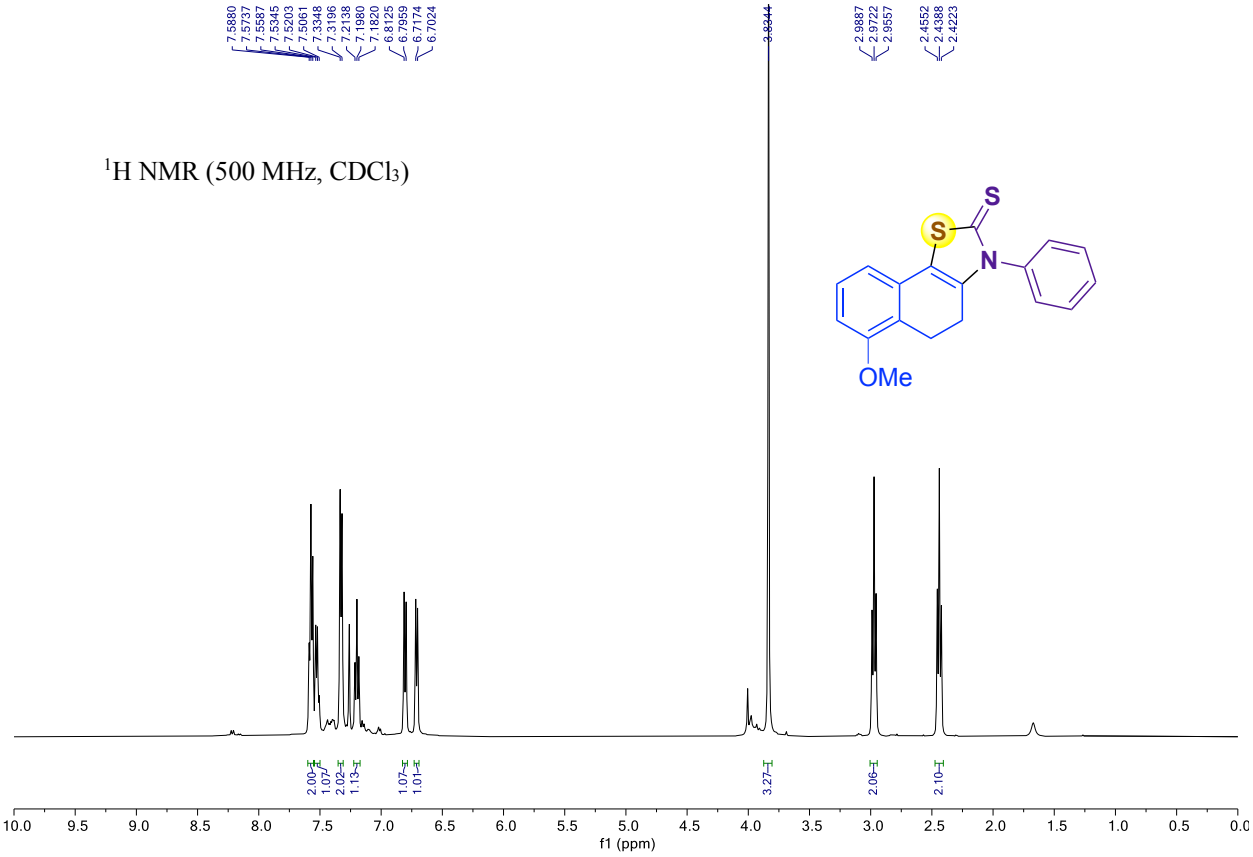
^{1}H NMR (500 MHz, $CDCl_3$)

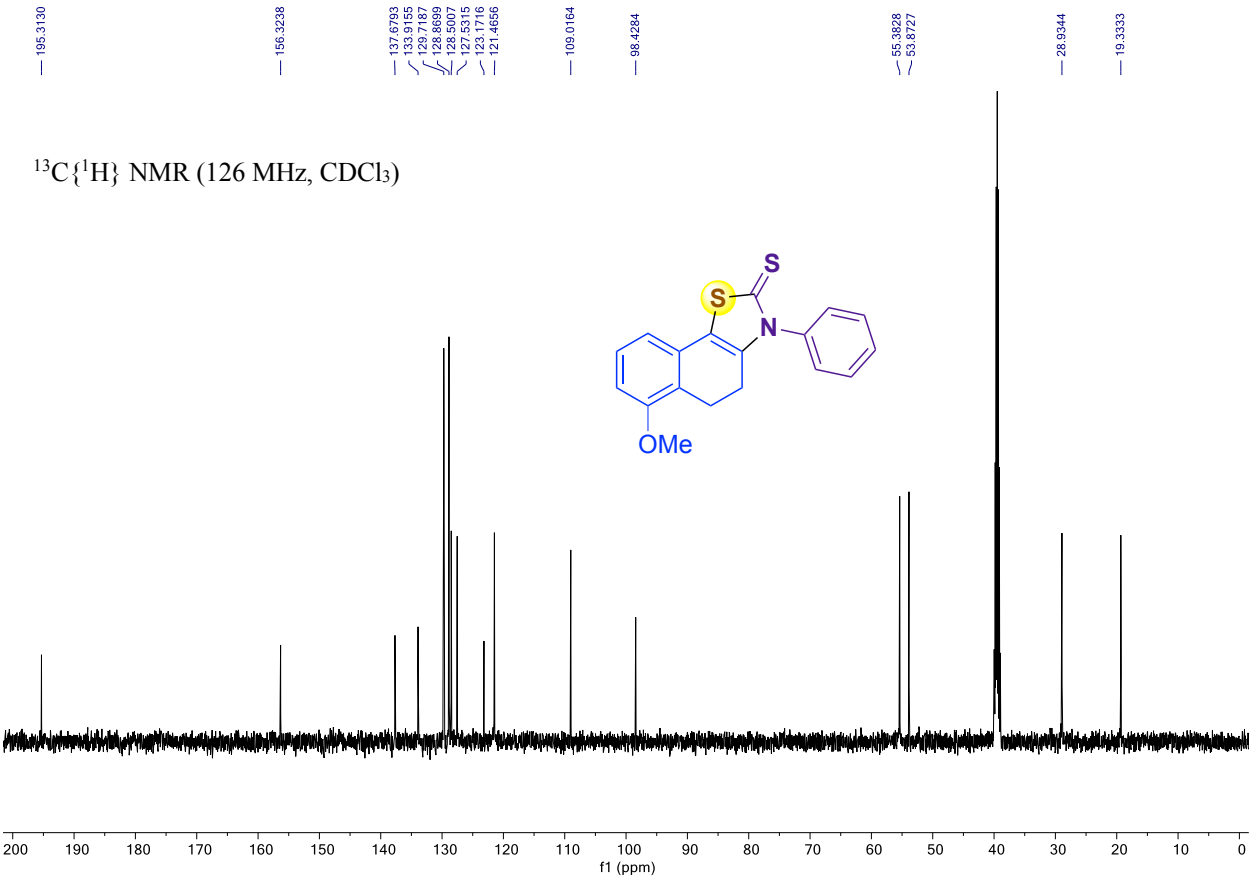


^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)



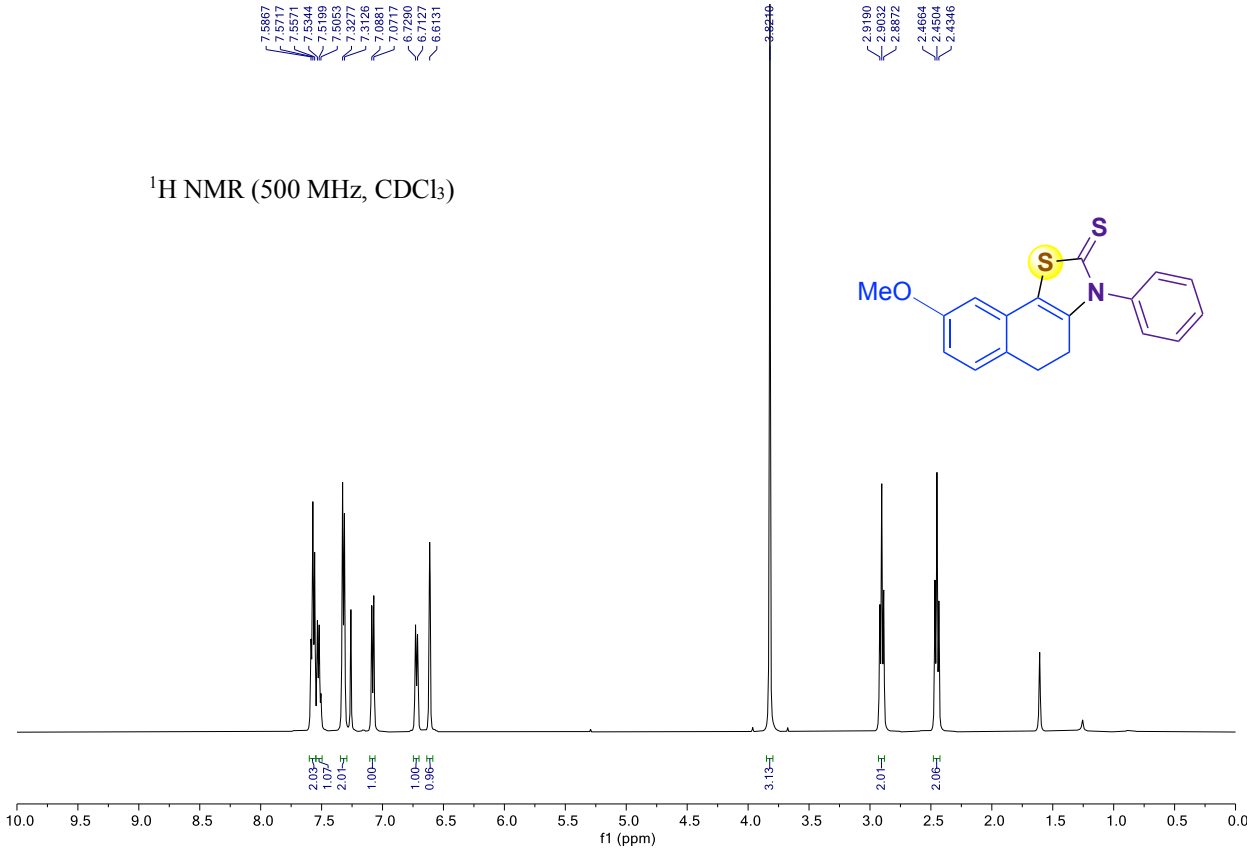
6-Methoxy-3-phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4n)



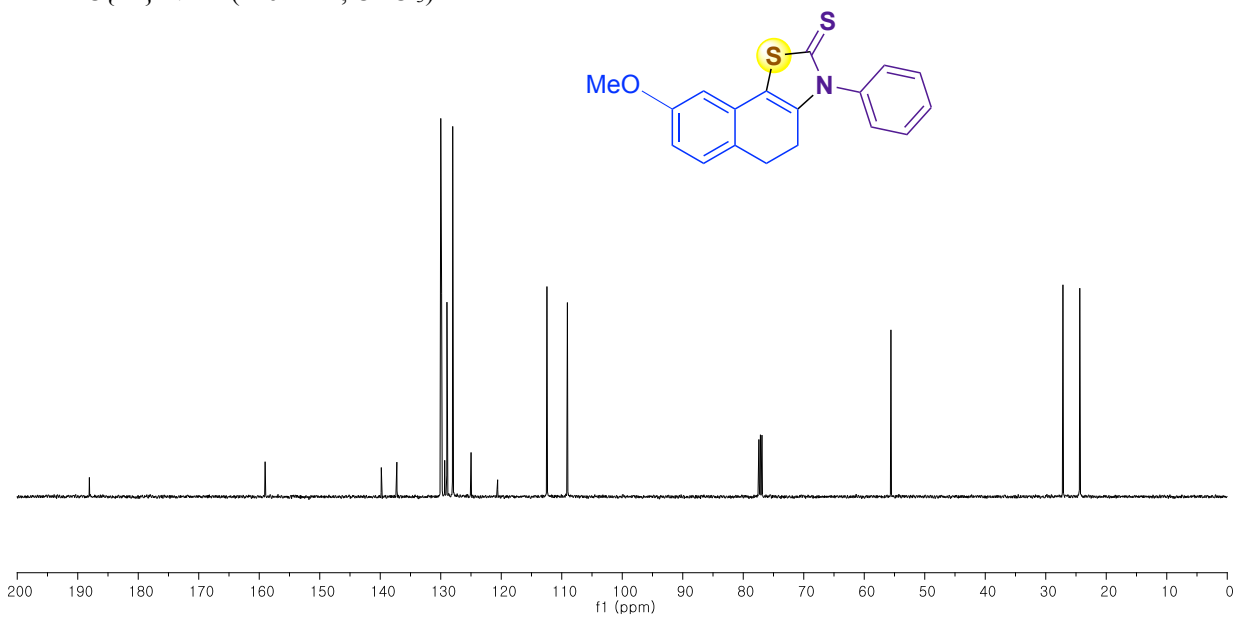


8-Methoxy-3-phenyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4o)

^{1}H NMR (500 MHz, $CDCl_3$)

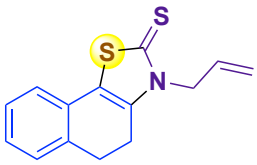


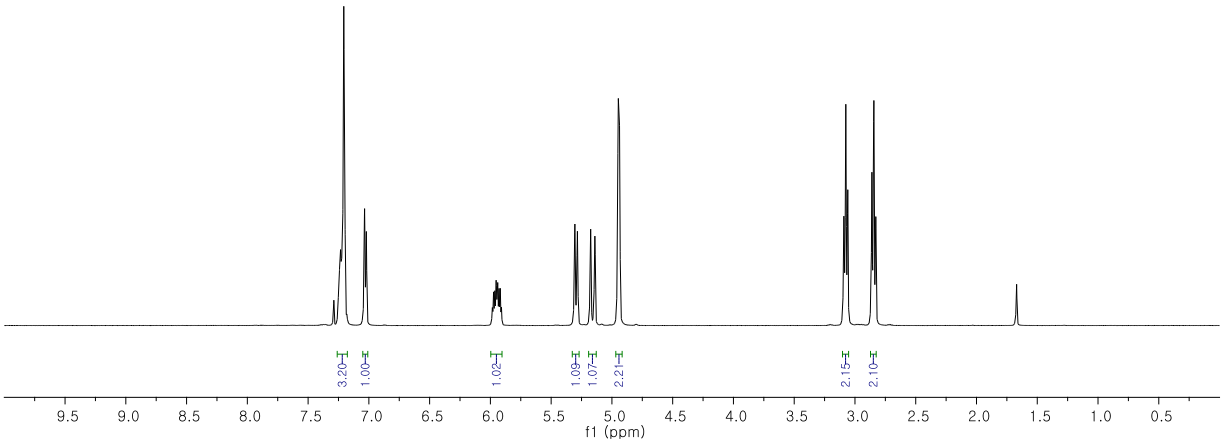
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)



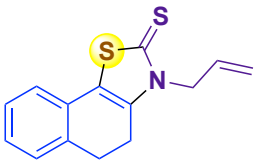
3-Allyl-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4p)

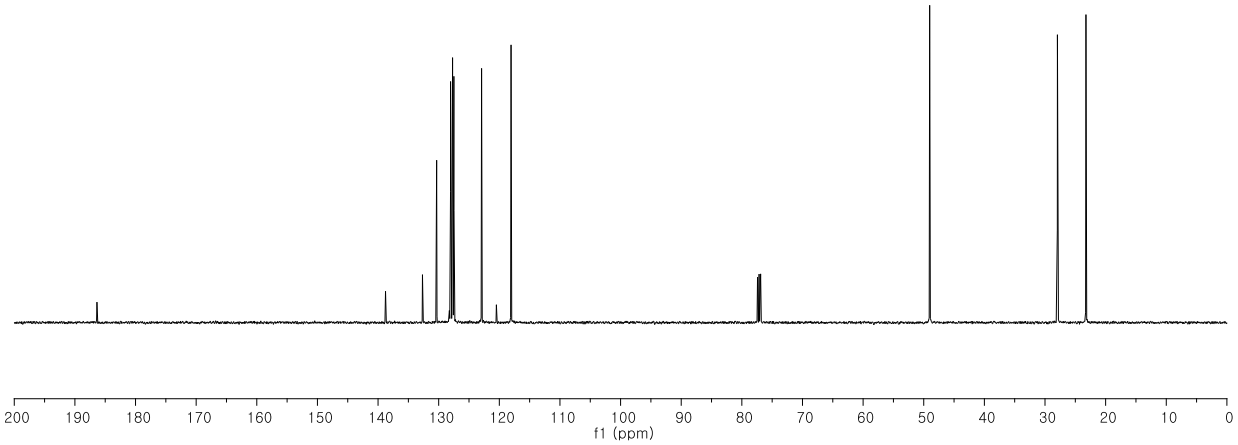
^{1}H NMR (500 MHz, $CDCl_3$)





^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)





3-Allyl-6-methoxy-4,5-dihydronaphtho[2,1-*d*]thiazole-2(3*H*)-thione (4q)