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Diastereoselective cycloaddition of isatin azomethine ylides to 5-arylidene-2-thiohydantoins bearing 3-positioned chiral substituent

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Table S1. Isolation of the major diastereomers of compounds **4** from the mixtures

Compound	Method for isolation of the major diastereomer	Yield, %
4a	Recrystallization from 80% EtOH	18
4d	Recrystallization from 80% EtOH	25
4e	Recrystallization from 80% EtOH	22
4f	Column chromatography Petroleum ether: ethyl acetate = 2:1	58
4g	Column chromatography Petroleum ether: ethyl acetate = 2:1	49
4h	Recrystallization from 80% EtOH	21

Table S2. Synthesis of N-unsubstitued dispiroindolinone **2** from dispiroindolinones **4a-g**

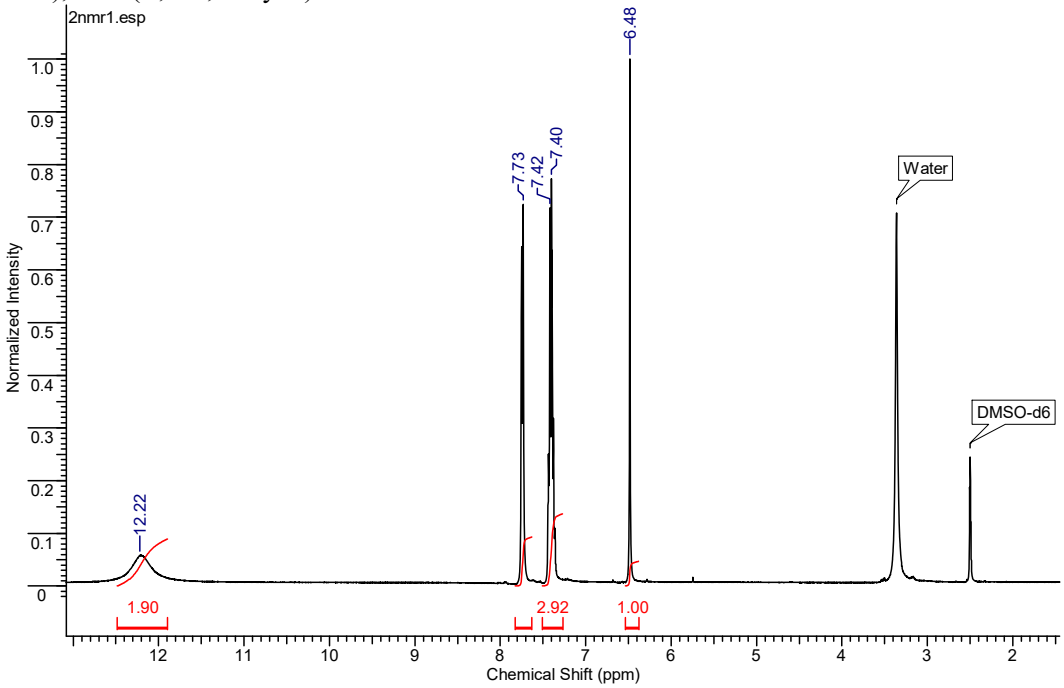
Starting compound	Conditions for removal of chiral auxiliary	Yield of **2**, %
4a	TFA	0
4b	TFA	0
4c	TFA + 10% CF_3SO_3H	Traces
4d	TFA	47
4e	TFA	51
4f	TFA	74
4g	TFA	63

Materials and methods. TLC analysis was carried out on silica gel plates Silufol UV254. ^{1}H and ^{13}C NMR spectra and 2D NMR experiments were recorded on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 and $CDCl_3$. Electrospray ionization high-resolution mass spectra were recorded in positive ion mode on a TripleTOF 5600+quadrupole time-of-flight mass spectrometer (ABSciex,Concord, Canada) equipped with DuoSpray ion source. The following MS parameters were applied: capillary voltage 5.5kV; nebulizing and curtain gas pressure – 15 and 25 psi, respectively; ion source temperature – ambient; declustering potential 20 V; m/z range 100–1200. Elemental compositions of the detected ions were determined based on accurate masses and isotopic distributions using Formula Finder software (ABSciex, Concord, Canada). The maximum allowed deviation of the experimental molecular mass from calculated one was 5 ppm. IR spectra were recorded on an IR200 Fourier transform IR spectrometer (TermoNicolet, USA) with a resolution of 4 cm^{-1} in KBr. Microwave-assisted synthesis was carried out using the Anton Paar Monowave 300 monomode microwave reactor in 30 ml glass vials.

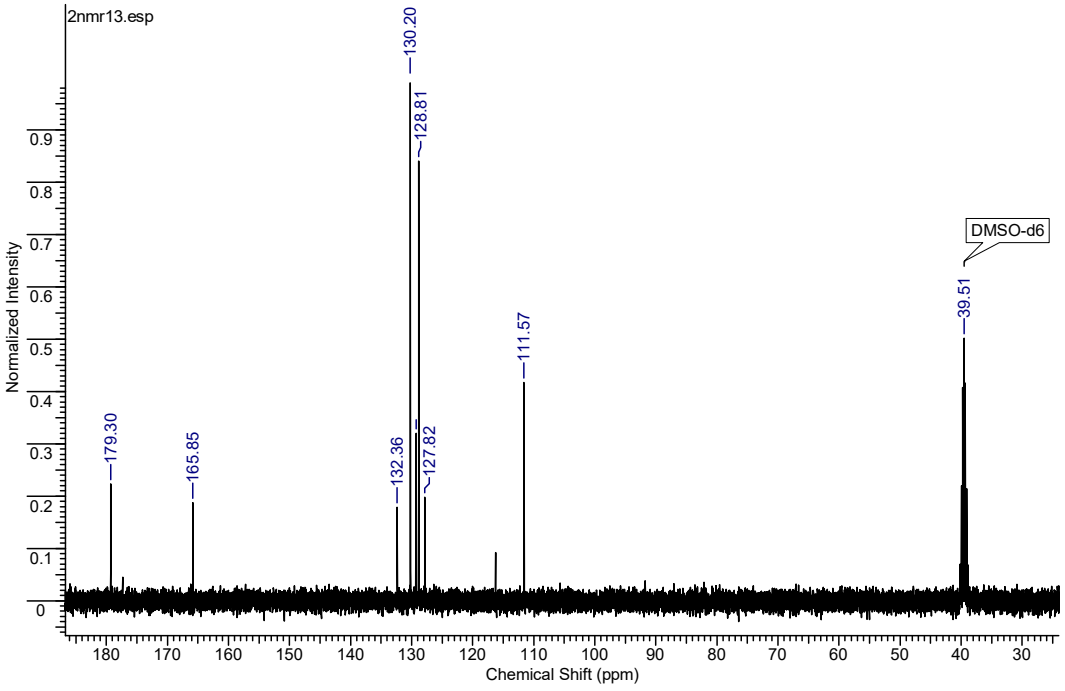
Synthesis of (Z)-5-Benzylidene-2-thioxoimidazolidin-4-one (1)

2-Thiohydantoin (1.16 g, 0.01 mol), benzaldehyde (1.167 g, 0.011 mol) and potassium acetate (1.08 g, 0.011 mol) of were mixed in acetic acid (15 ml). The reaction was carried out under the action of microwave radiation at 140 °C for 60 minutes (300 W, temperature controlled mode). The reaction mixture was cooled, the resulting yellow precipitate was recrystallized from acetic acid to afford. 1.61 g (80%) of a yellow crystalline substance.

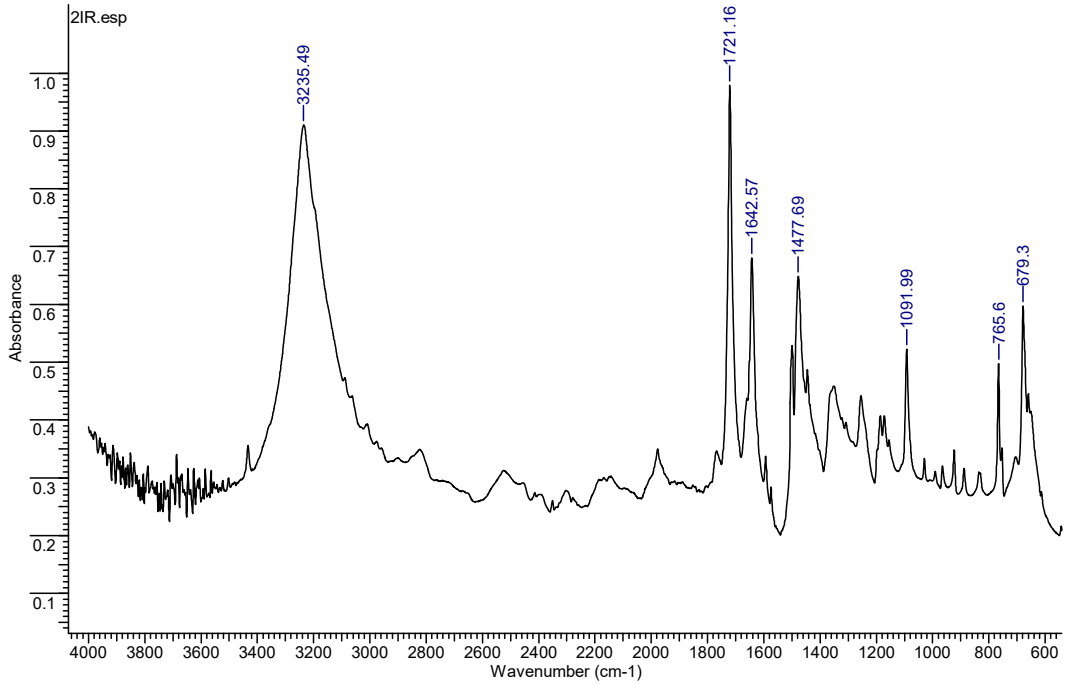
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 12.20 (br.s., 2H, NH), 7.75-7.73 (m., 2H, ArH), 7.44-7.36 (m., 3H, ArH), 6.48 (s., 1H, VinylH).



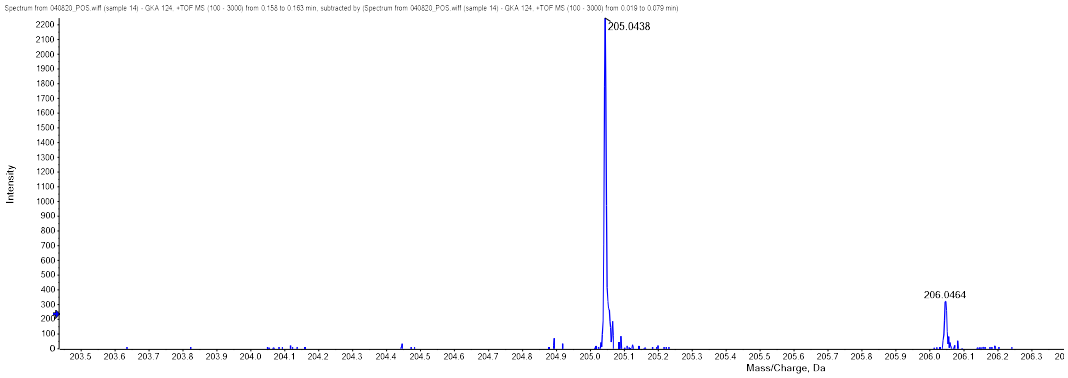
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 179.30, 165.85, 132.36, 130.20, 129.25, 128.81, 127.82, 111.57.



IR (KBr, ν(cm^{-1})): 3235 (NH), 1721(C=O), 1642, 1477(C=S), 1092



HRMS-ESI: m/z calculated for $[C_{10}H_8N_2OS+H]^+$: 205.0430; found 205.0438.

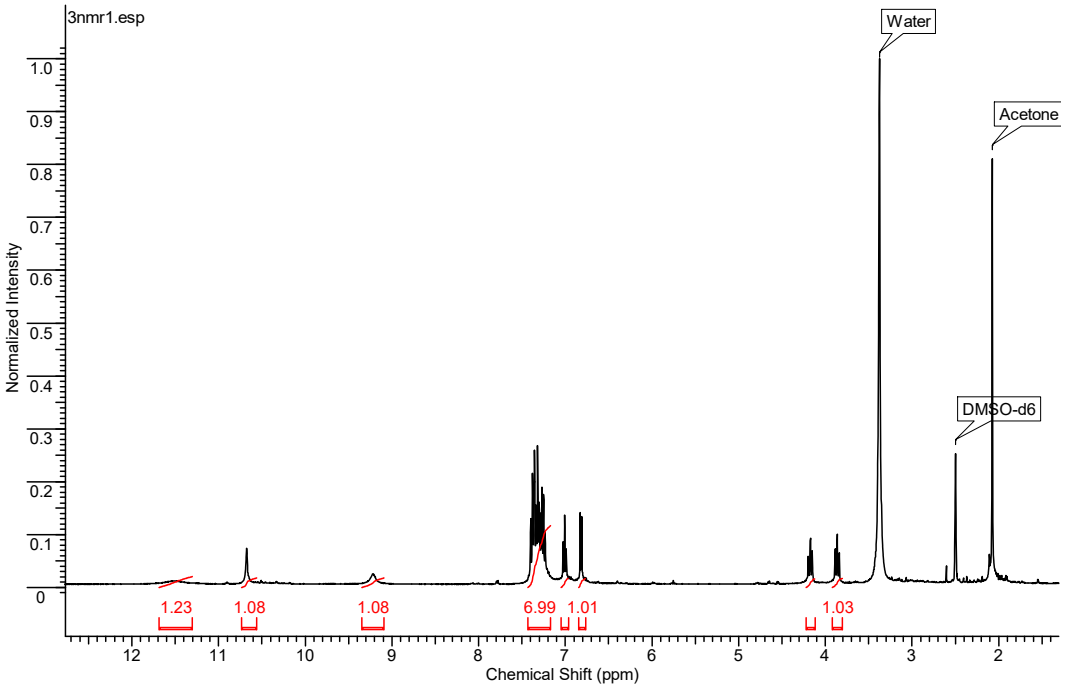


<u>Synthesis of (2'*S,4*R**,4'*R**)-1'-Methyl-4'-phenyl-2-thiooxodispiro[imidazolidine-4,3'-pyrrolidin-2',3''-indoline]-2'',5-dione (2)</u>**

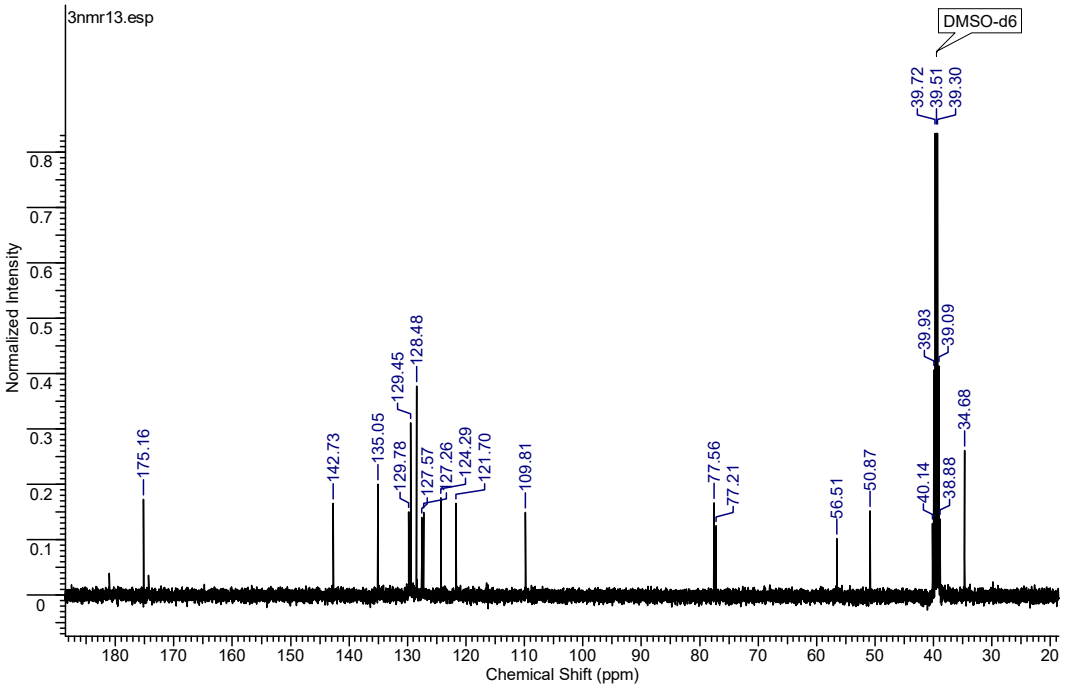
<u>Method A:</u> To a boiling solution of 5-benzylidene-2-thiohydantoin **1** (0.3 g, 1.5 mmol) and sarcosine (0.27 g, 3 mmol) in ethanol, isatin (0.44 g, 3 mmol) was added, and the mixture was refluxed for 6-8 h (TLC control). After the completion of the reaction and cooling of the solution, an excess of water was added and the formed precipitate was purified by column chromatography (petroleum ether:ethyl acetate 2:1) to afford 0.44 g (73%) of white solid, m.p. 169-170 ^{o}C.

<u>Method B:</u> Dispiroindolinone **4d-g** was dissolved in trifluoroacetic acid, and the solution was stirred at reflux for 30-90 seconds. After the completion of the reaction (monitoring by TLC), trifluoroacetic acid was evaporated under reduced pressure, and a saturated solution of $NaHCO_3$ was added to the resulting solid, followed by extraction with CH_2Cl_2. The organic phase was dried over sodium sulfate, the solvent was evaporated, and the resulting mixture was purified by column chromatography (petroleum ether 2:1 ethyl acetate). Yields: 47% from **4d** (50 mg, 0.9 mmol); 51% from Compound **4e** (50 mg, 1 mmol); 74% from **4f** (50 mg, 0.9 mmol); 63% from **4g** (50 mg, 0.8 mmol).

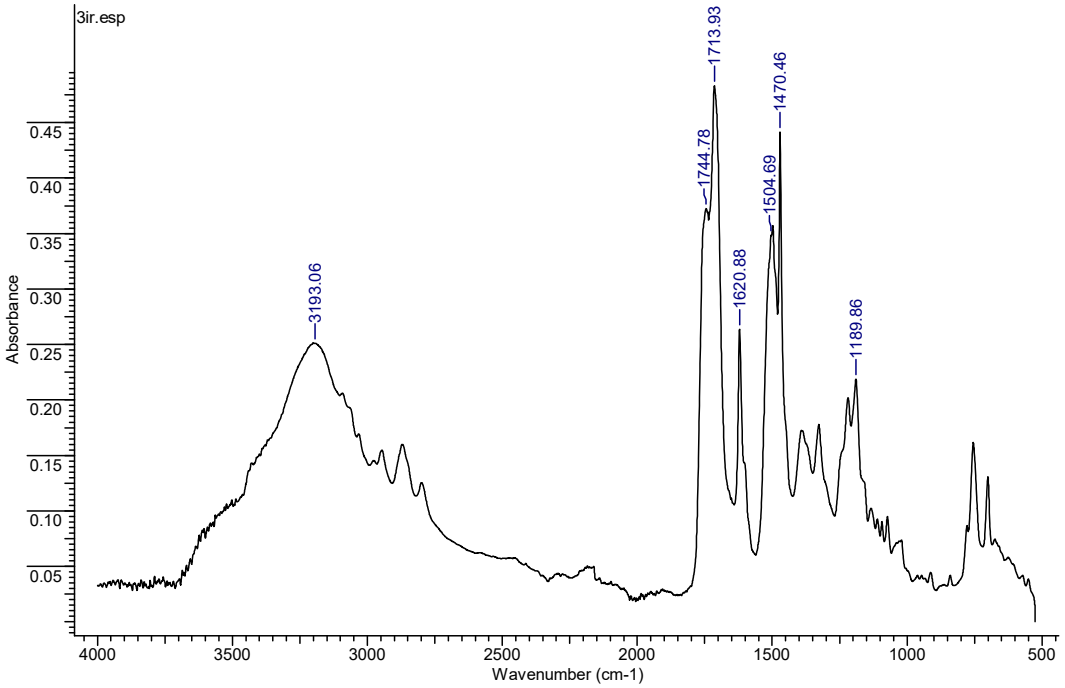
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 11.46 (s., 1H, NH), 10.54 (s.., 1H, NH), 9.28 (s., 1H, NH), 7.40-7.44 (m., 2H, ArH), 7.26-7.33 (m., 4H, ArH), 7.22-7.24 (m., 1H, ArH), 6.96-6.98 (m., 1H, ArH), 6.75 (d., J=7.6Гц, 1H, ArH), 4.12 (t., J=9.2 Hz, 1H), 3.76 (t., J=9.1Hz, 1H), 3.32 (t., J=8.4Hz, 1H), 2.07 (s., 3H, NCH_3).



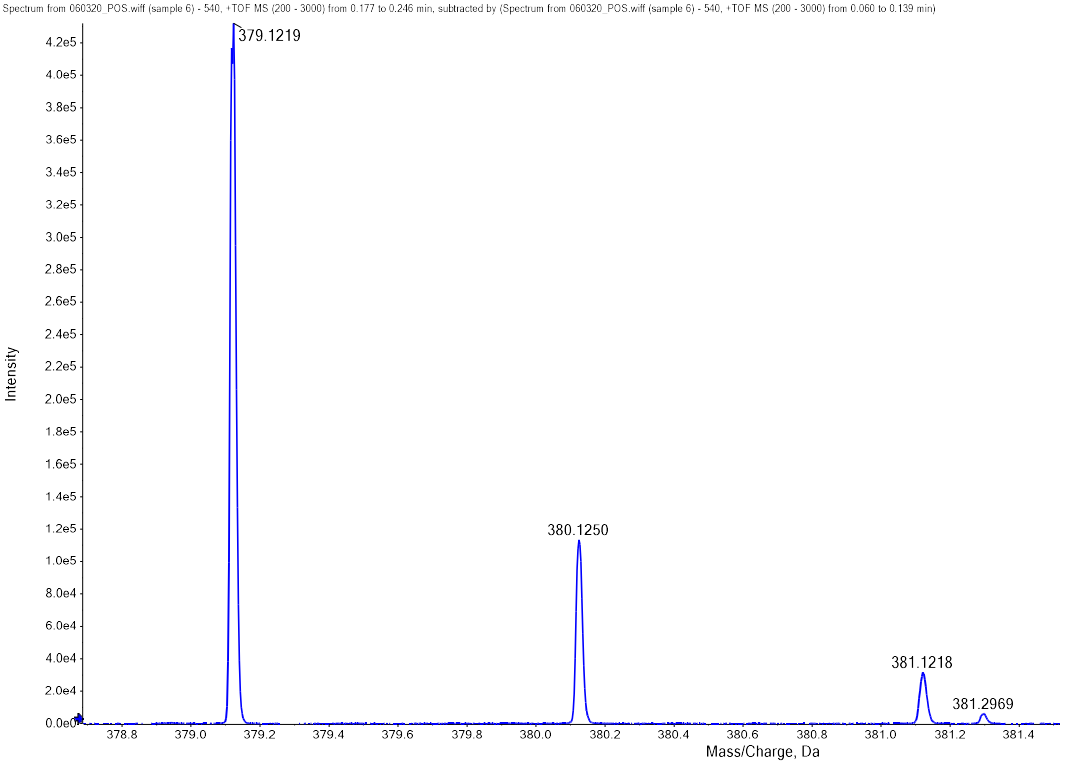
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 175.16, 142.73, 135.05, 129.78, 129.45, 128.48, 127.57, 127.26, 124.29, 121.70, 109.81, 77.56, 77.21, 56.51, 50.87, 34.68.



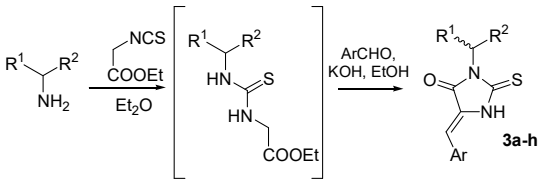
IR (KBr, ν(cm^{-1})): 3193, 1744 (C=O), 1714(C=O), 1620, 1505, 1470(C=S), 1190



HRMS-ESI: m/z calculated for $[C_{20}H_{18}N_4O_2S+H]^+$: 379.1223; found 379.1219.



Synthesis of 5-arylidene-2-thiohydantoins 3a-h

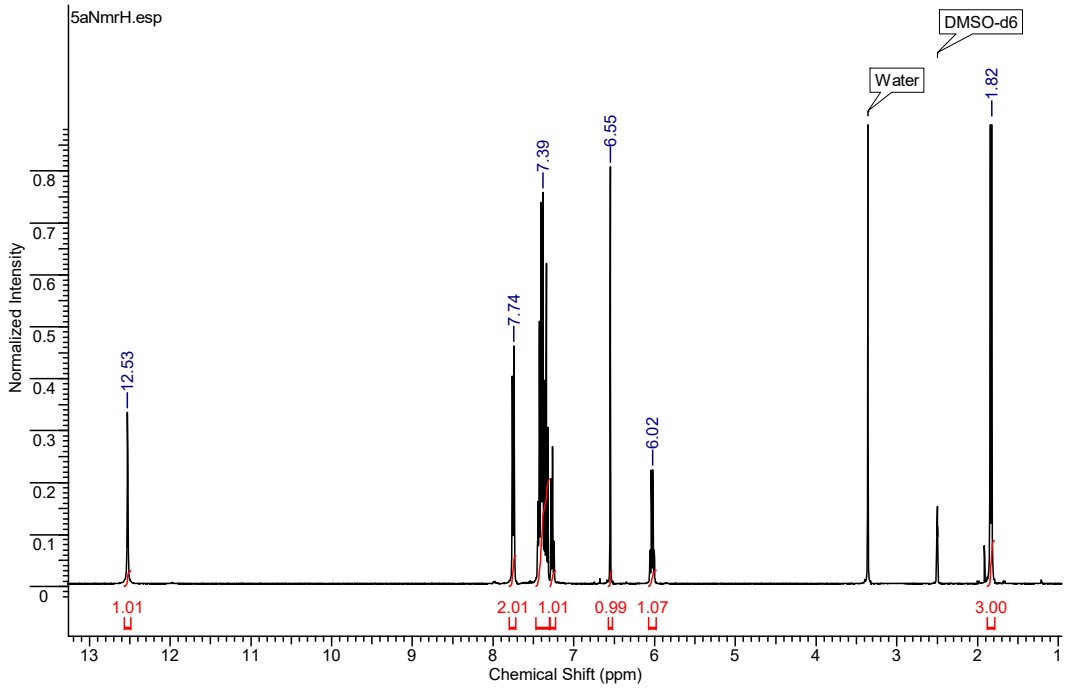


To a solution of the corresponding amine (1 mmol) in ether, ethyl isothiocyanatoacetate (1 mmol) was added. The mixture was stirred for 15 min at room temperature. The solvent was evaporated to leave a clear colorless oil. The resulting thiourea was dissolved in ethanol, and aromatic aldehyde (1.1 mmol) was added followed by KOH (3 mmol). The mixture was stirred for 2-3 h (TLC control). After the end of the reaction, an excess of a saturated ammonium chloride was added, a yellow precipitate was formed. It was filtered off and purified by column chromatography (petroleum ether/ethyl acetate, 5:1)

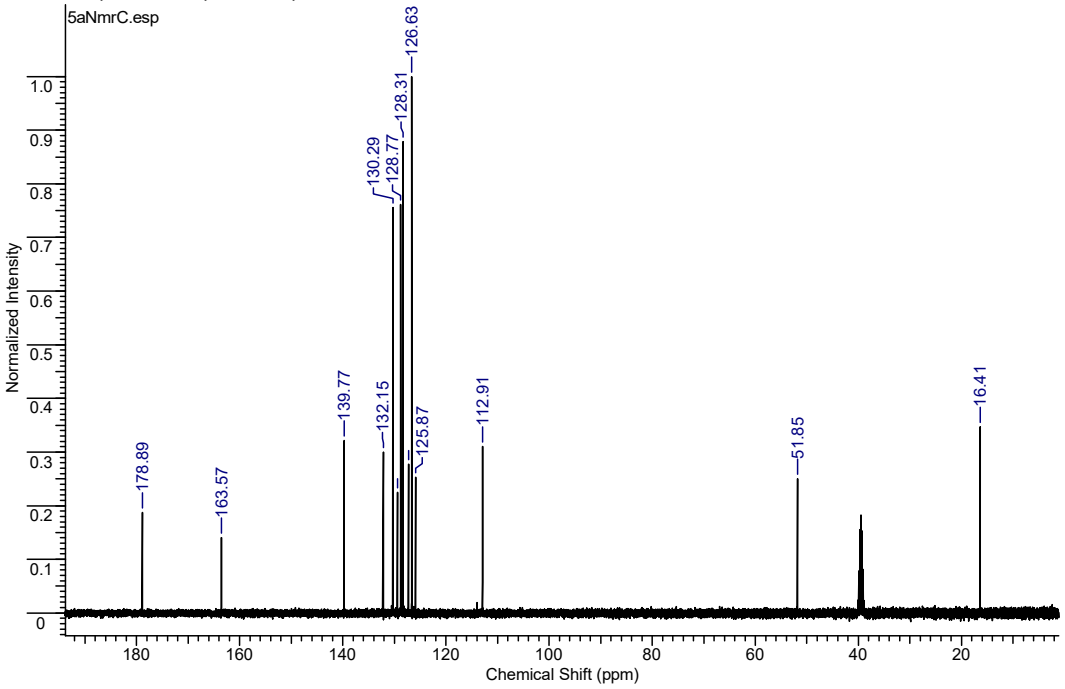
(*Z*)-5-Benzylidene-3-(1-phenylethyl)-2-thioxoimidazolidin-4-one (3a)

Using 1-phenylethylamine (121 mg), ethyl isothiocyanatoacetate (145 mg), benzaldehyde (117 mg) and KOH (168 mg), 237 mg (77%) of yellow crystalline substance (m.p. 105-106 °C) was obtained.

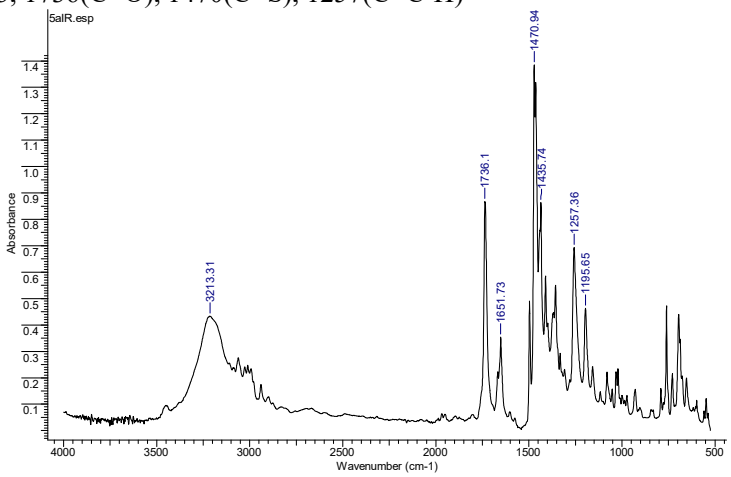
^{1}H NMR (DMSO-d$_6$, 400 MHz, δ, ppm): 12.53(s., 1H), 7.75(d., J=7.3 Hz, 2H), 7.21-7.48(m., 8H), 6.55(s., 2H), 6.02(q., J=7.2 Hz, 2H), 1.82(d., J=7.2 Hz, 3H)



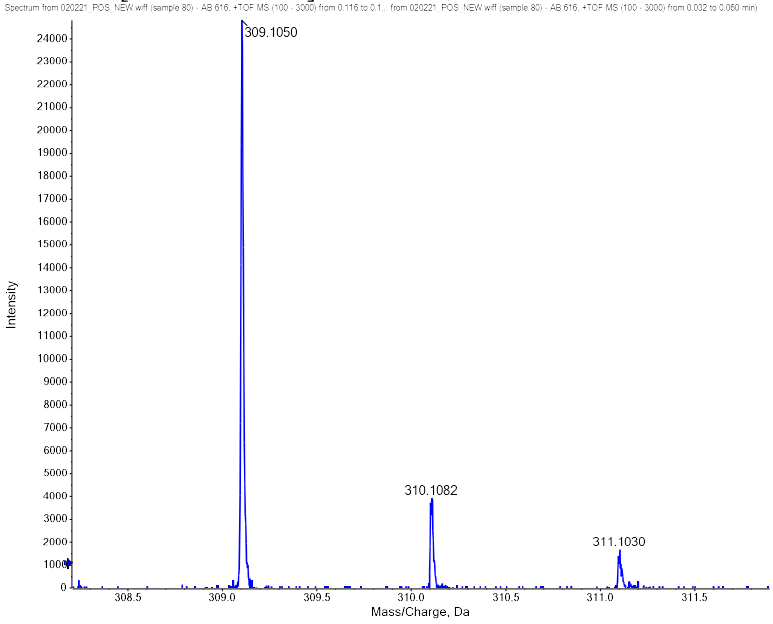
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 178.89, 163.57, 139.77, 132.15, 130.29, 128.77, 128.31, 126.63, 125.87, 112.91, 51.85, 16.41



IR (KBr, ν(cm^{-1})): 3213, 1736(C=O), 1470(C=S), 1257(C=C-H)



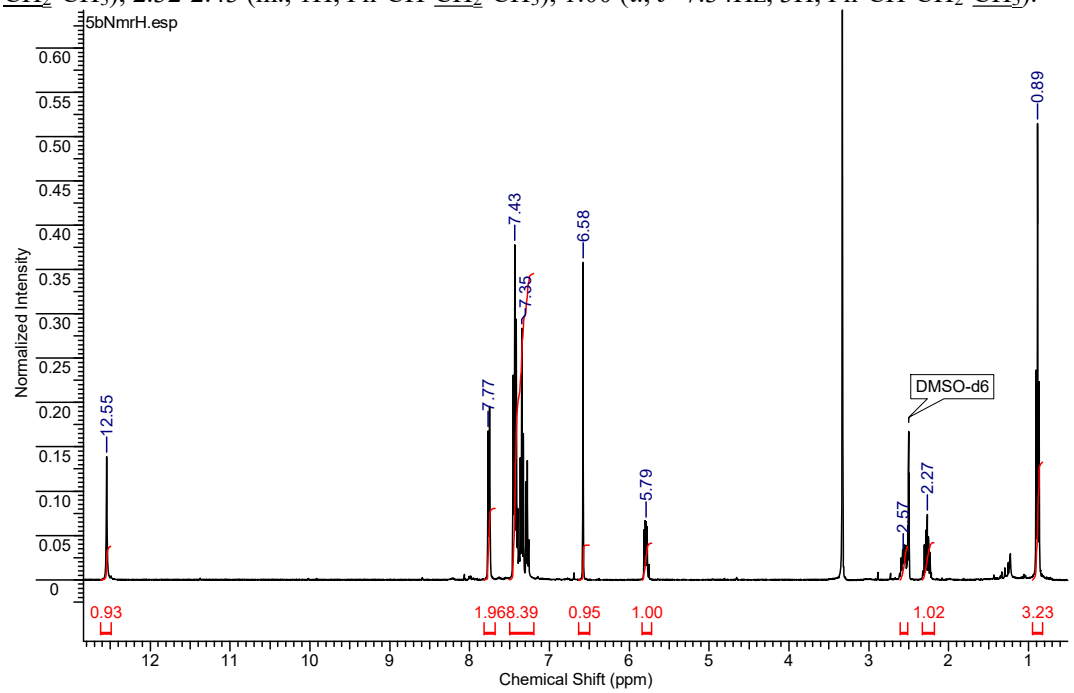
HRMS-ESI: m/z calculated for $[C_{18}H_{16}N_2OS+H]^+$: 309.1056; found 309.1050.



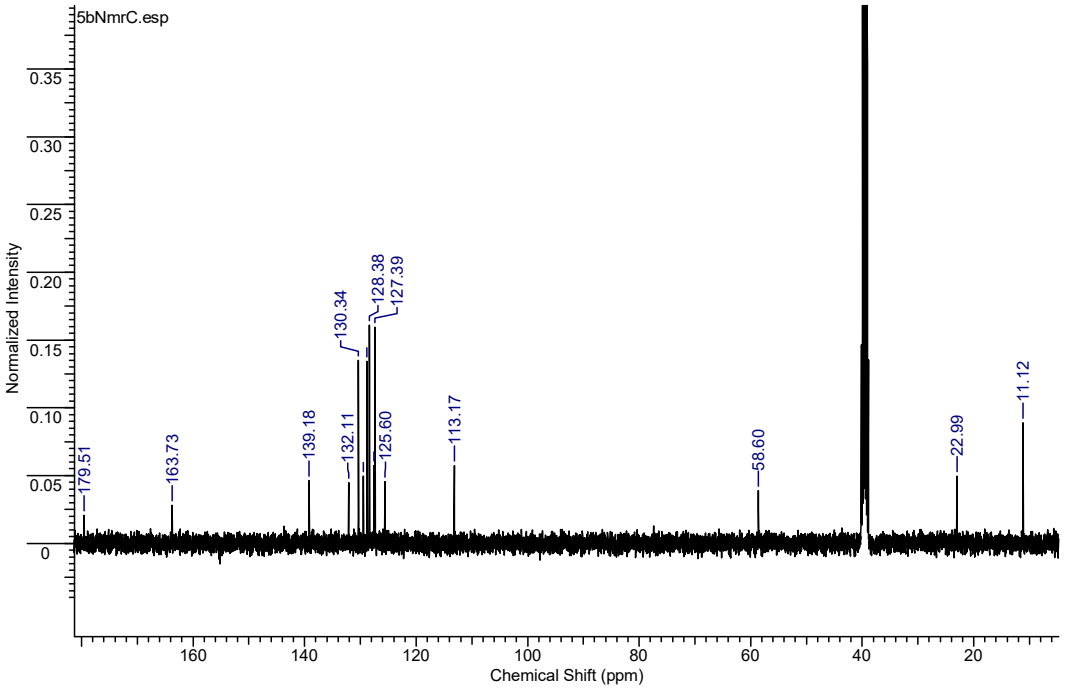
(*Z*)-5-Benzylidene-3-(1-phenylpropyl)-2-thioxoimidazolidin-4-one (3b).

Using 1-phenylpropylamine (135 mg), ethyl isothiocyanatoacetate (145 mg), benzaldehyde (117 mg) and KOH (168 mg), 142 mg (44%) of yellow crystalline substance (m.p. 107-108 ºC) was obtained.

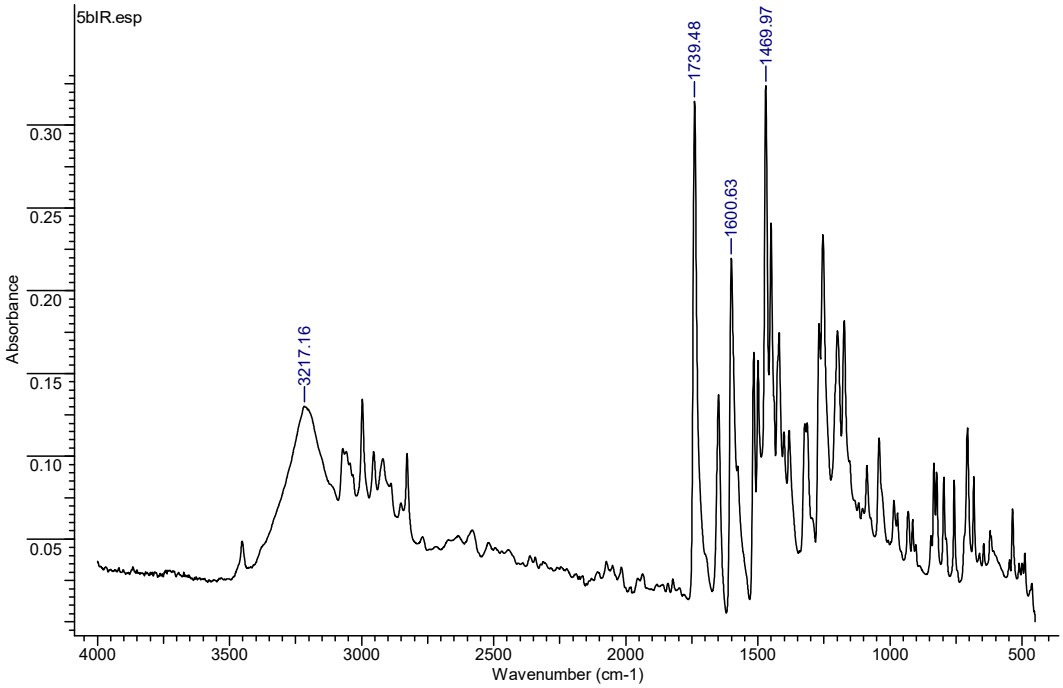
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 12.55(s., 1H), 7.77(d., J=6.4Hz, 2H), 7.38-7.47 (d., 5H, ArH), 7.27-7.38 (d., 3H, ArH), 6.64 (s., 1H, VinylH), 5.79 (d.d., J=9.6, 6.7Hz, 1H, Ph-CH-CH_2-CH_3), 2.61-2.74 (m., 1H, Ph-CH-CH_2-CH_3), 2.32-2.43 (m., 1H, Ph-CH-CH_2-CH_3), 1.00 (t., J=7.34Hz, 3H, Ph-CH-CH_2-CH_3).



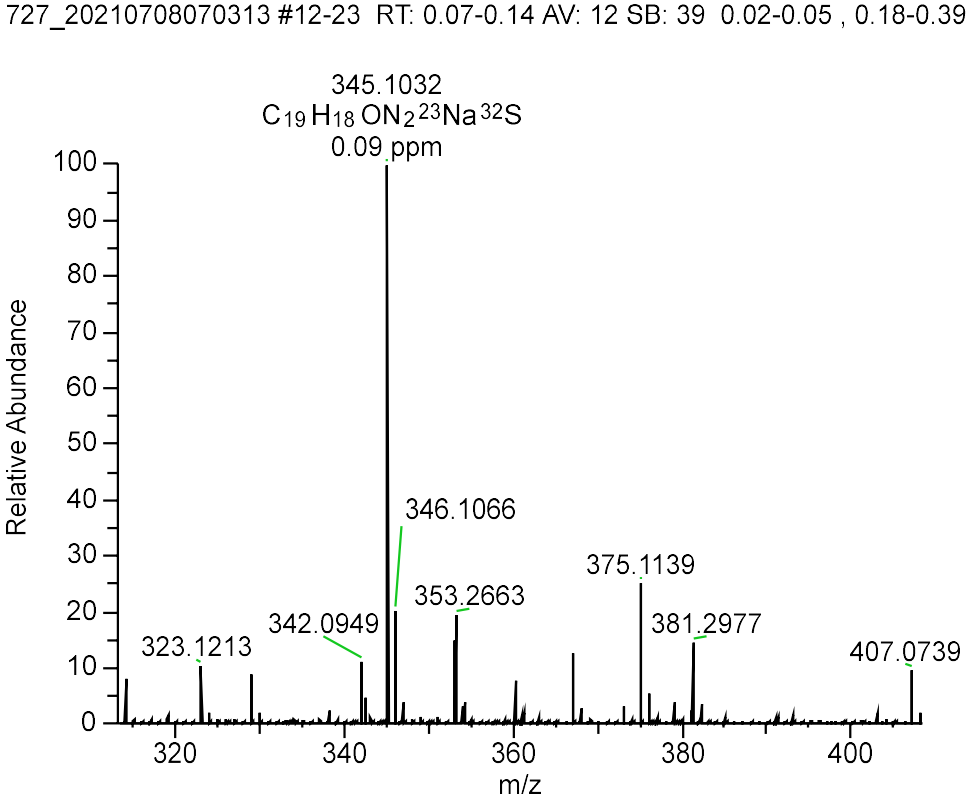
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 179.51, 163.73, 139.18, 132.11, 130.34, 129.51, 128.38, 127.55, 127.39, 113.17, 58.60, 22.99, 11.12.



IR (KBr, ν(cm^{-1})): 1739(C=O), 1601, 1470(C=S)



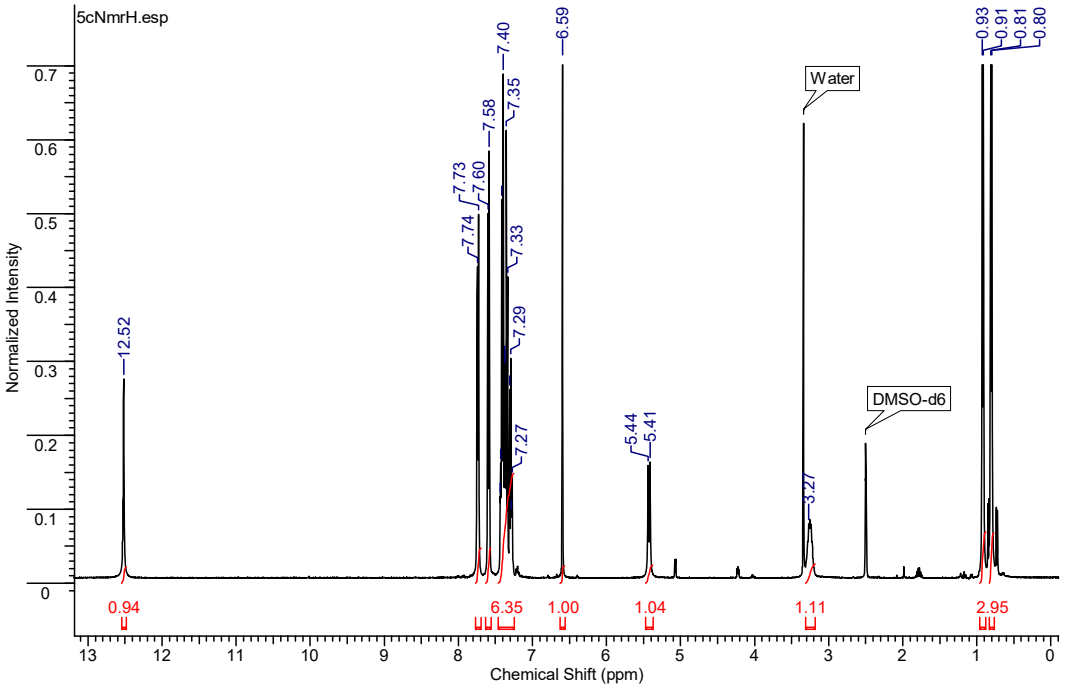
HRMS-ESI: m/z calculated for $[C_{19}H_{18}N_2OS+Na]^+$: 345.1032; found 345.1032.



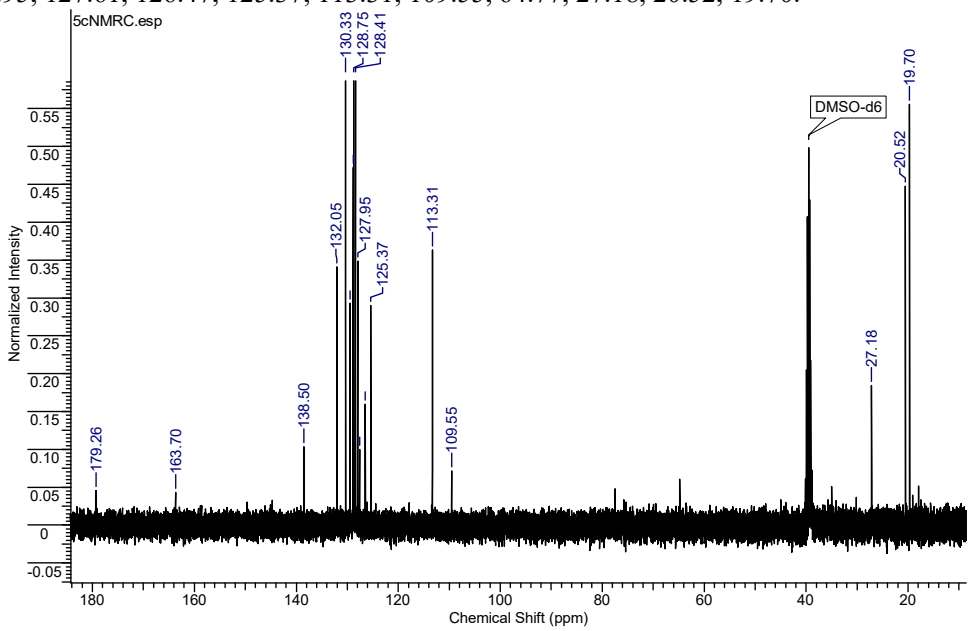
(*Z*)-5-Benzylidene-3-(2-methyl-1-phenylpropyl)-2-thioxoimidazolidin-4-one (3c).

Using 2-methyl-1-phenylpropylamine (149 mg), ethyl isothiocyanatoacetate (145 mg), PhCHO (117 mg) and KOH (168 mg), 108 mg (32%) of yellow crystalline substance (m.p. 111-112 ºC) was obtained.

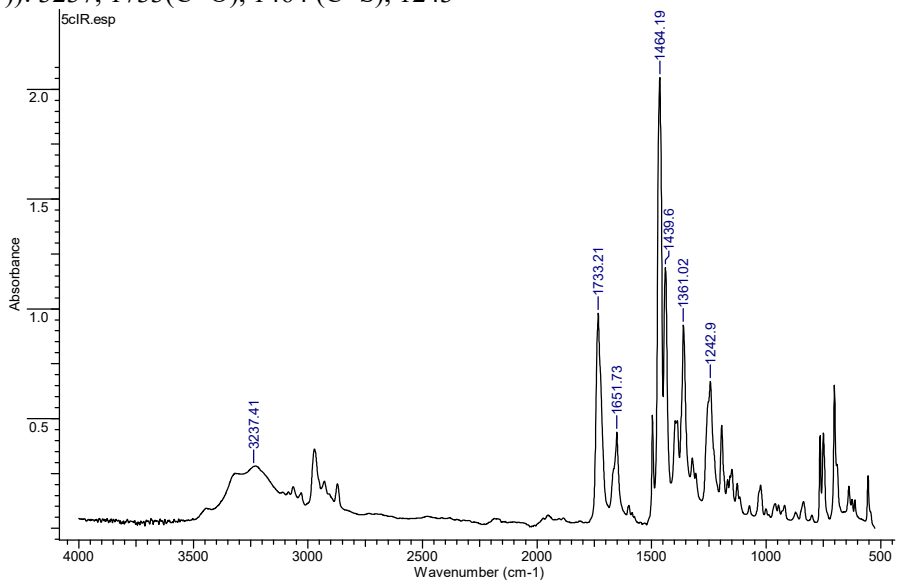
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 12.52(s., 1H, NH), 7.74(d., J=6.5Hz, 2H, ArH), 7.59(d., J=7.2Hz, 2H, ArH), 7.26-7.45(m, 6H, ArH), 6.59(s., 1H, VinylH), 5.43(d., J=11.5Hz, 1H, Ph-CH-CH$(CH_3)_2$), 3.27(m., 1H, Ph-CH-CH$(CH_3)_2$), 0.92(d., J=6.5Hz, 3H, Ph-CH-CH(CH_3)$_2$), 0.80(d., J=6.7Hz, 3H, Ph-CH-CH(CH_3)$_2$).



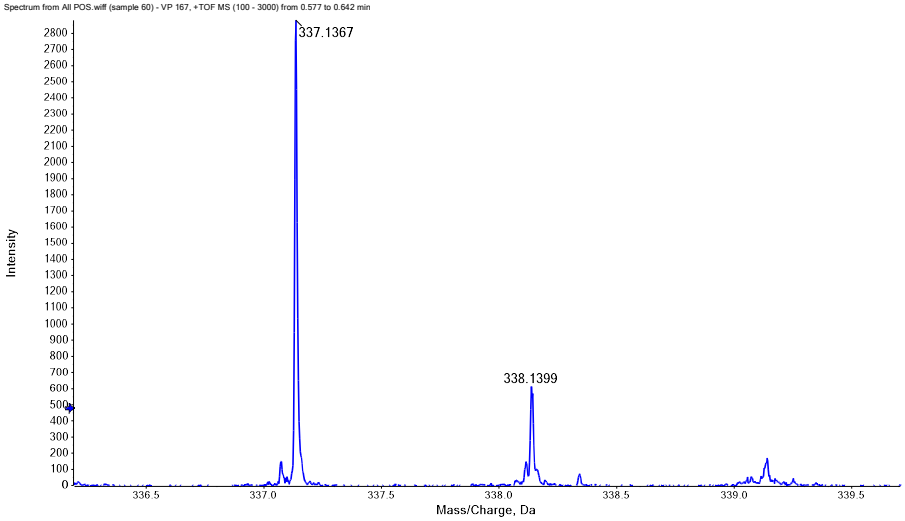
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 179.26, 163.70, 138.50, 132.05, 130.33, 129.49, 128.86, 128.75, 128.41, 127.95, 127.61, 126.47, 125.37, 113.31, 109.55, 64.77, 27.18, 20.52, 19.70.



IR (KBr, ν(cm^{-1})): 3237, 1733(C=O), 1464 (C=S), 1243



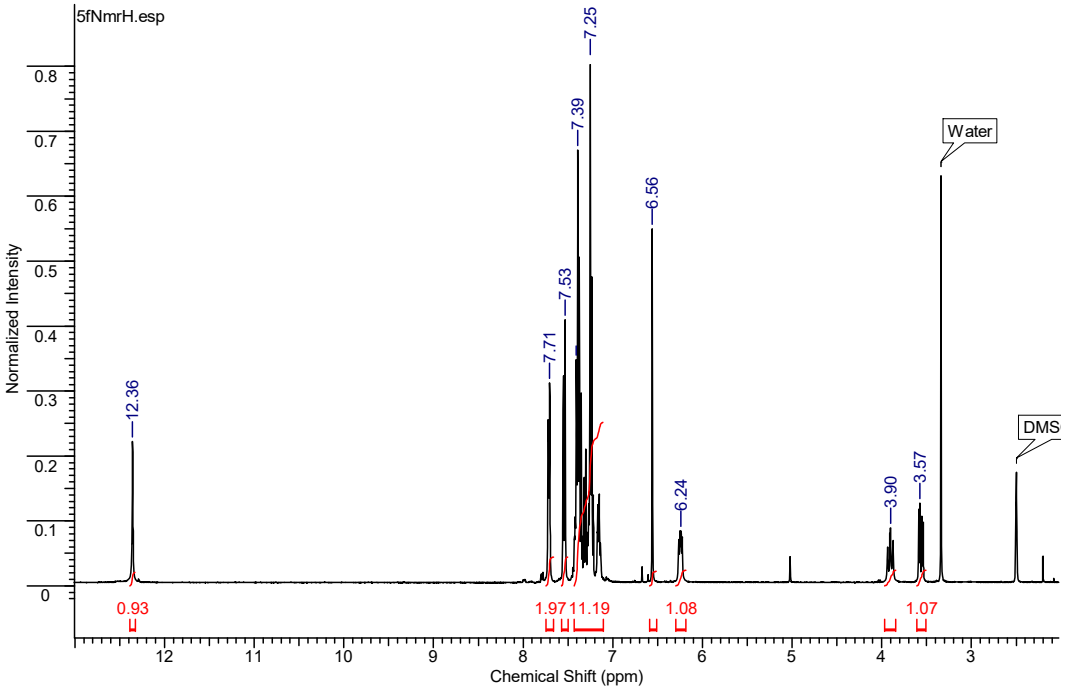
HRMS-ESI: m/z calculated for $[C_{20}H_{20}N_2OS+H]^+$: 337.1369; found 337.1367



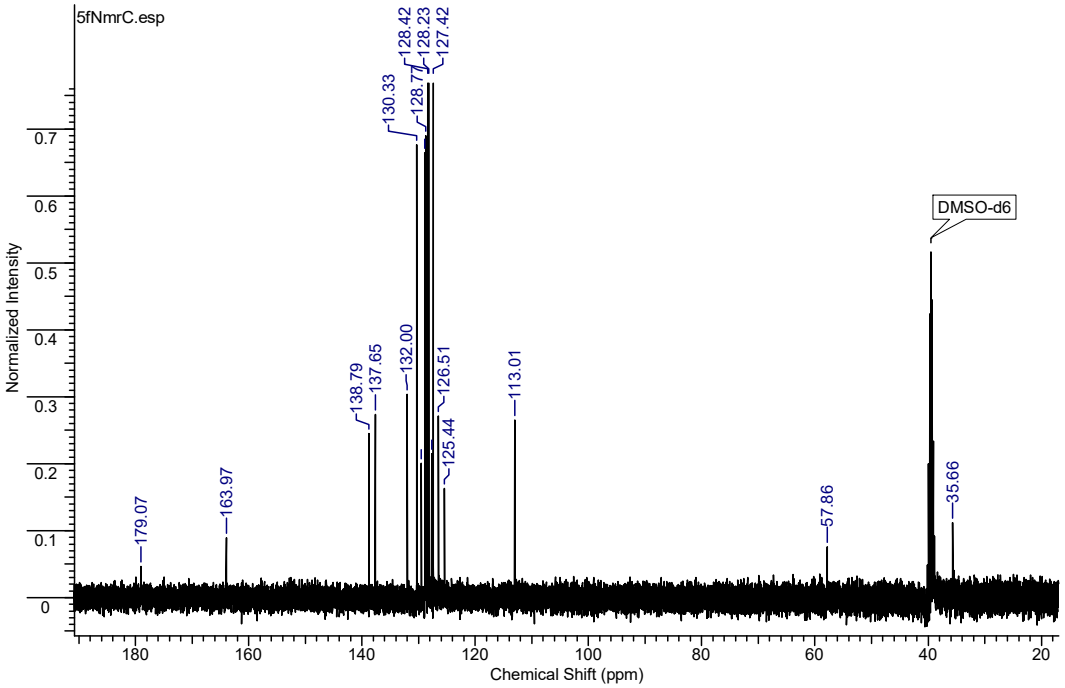
(*Z*)-5-Benzylidene-3-(1,2-diphenylethyl)-2-thioxoimidazolidin-4-one (3d).

Using 1,2-diphenylethylamine (394 mg, 2 mmol), ethyl isothiocyanatoacetate (290 mg, 2 mmol), benzaldehyde (234 mg, 2.2 mmol) and KOH (336 mg, 2 mmol), 276 mg (36%) of yellow crystalline substance (m.p. 122-123 ºC) was obtained.

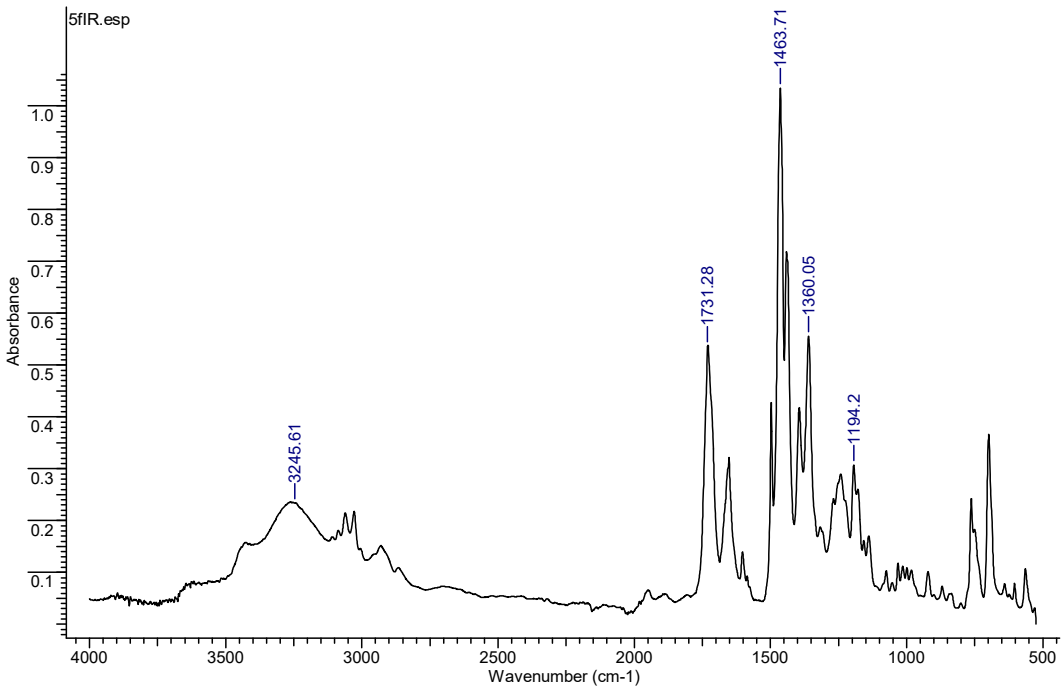
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 12.36 (s., 1H, NH), 7.72 (d., J=7.8Hz, 2H, ArH), 7.54 (d., J=7.6Hz, 2H, ArH), 7.33-7.45 (m., 5H, ArH), 7.31 (d., J=7.4Hz, 1H, ArH), 7.21-7.29 (m., 4H, ArH), 7.12-7.18 (m., 1H, ArH), 6.56 (s., 1H, VinylH), 6.25 (d.d., J=10.7, 5.8Hz, 1H, Ph-CH-CH_2-Ph), 3.86-3.95 (m., 1H, Ph-CH-CH_2-Ph), 3.56 (d.d., J=13.8, 6.0 Hz, 1H, Ph-CH-CH_2-Ph).



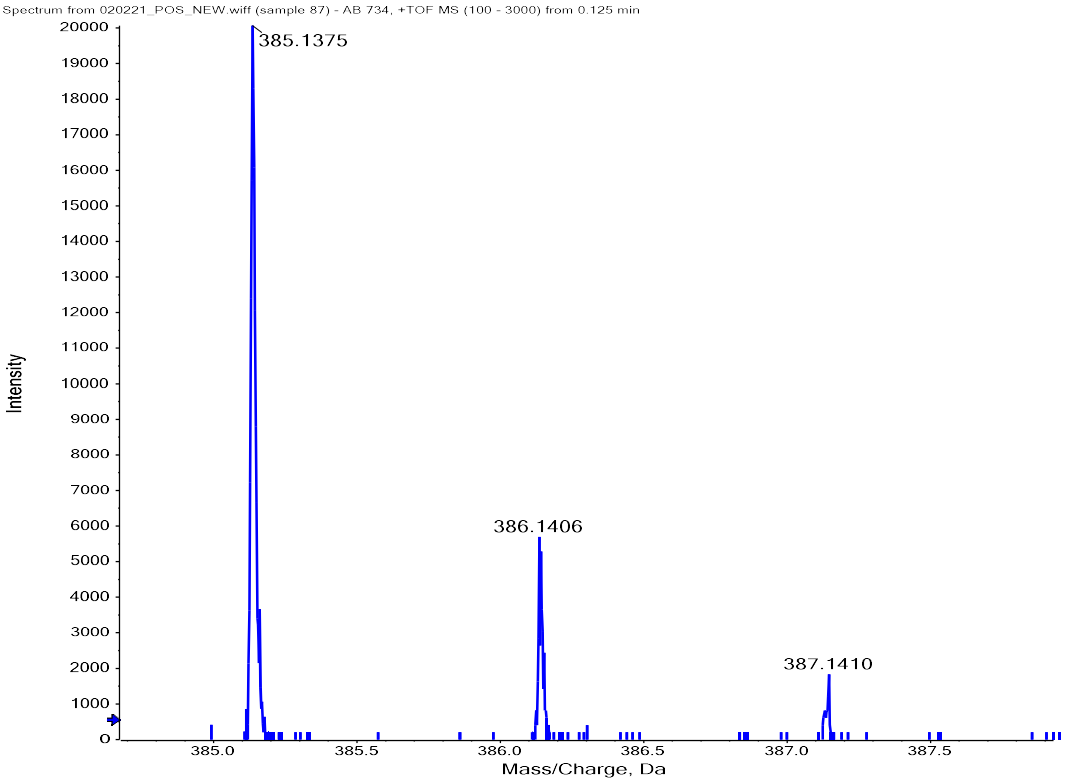
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 179.07, 163.97, 138.79, 137.65, 132.00, 130.33, 129.51, 128.88, 128.77, 128.42, 128.23, 127.68, 127.42, 126.51, 125.44, 113.01, 35.66.



IR (KBr, ν(cm^{-1})): 1731 (C=O), 1464 (C=S), 1360



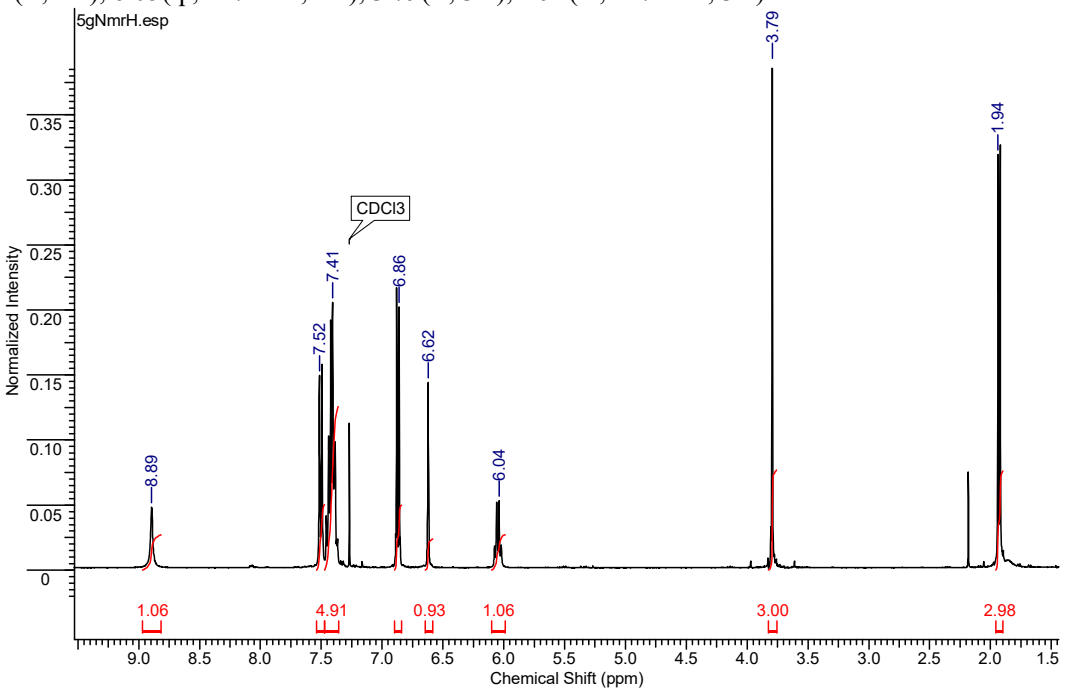
HRMS-ESI: m/z calculated for $[C_{24}H_{20}N_2OS+H]^+$: 385.1369; found 385.1375



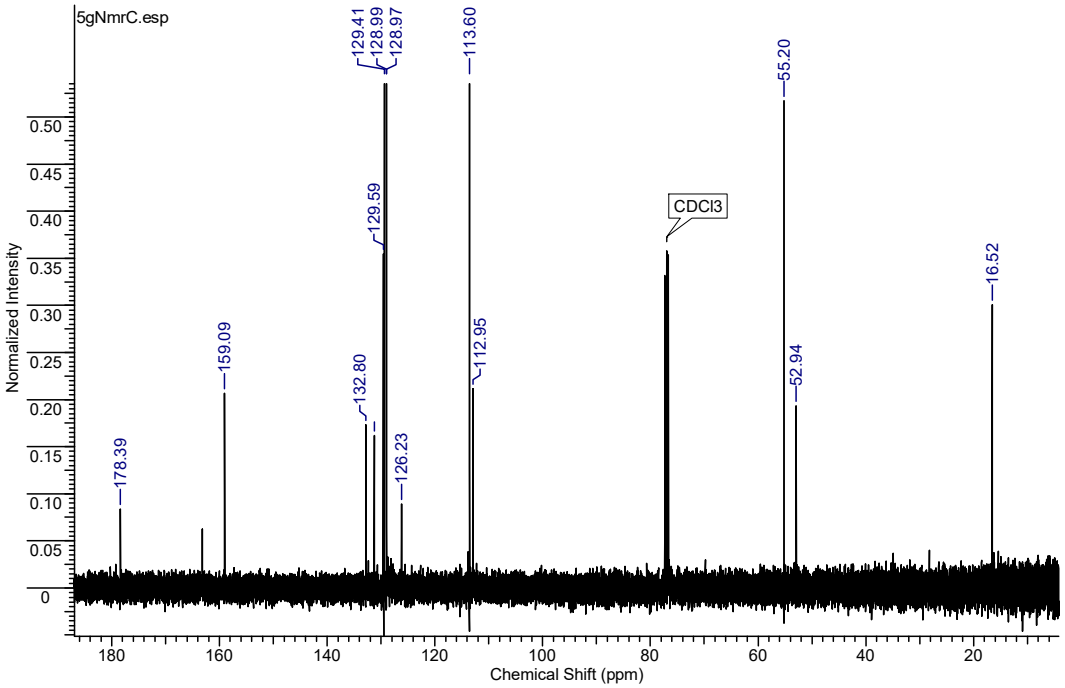
(*Z*)-5-Benzylidene-3-[1-(4-methoxyphenyl)ethyl]-2-thioxoimidazolidin-4-one (3e).

Using 1-(4-methoxyphenyl)ethylamine (151 mg), ethyl isothiocyanatoacetate (145 mg), benzaldehyde (117 mg) and KOH (168 mg), 254 mg (75%) of yellow crystalline substance (m.p. 127-128 ºC) was obtained.

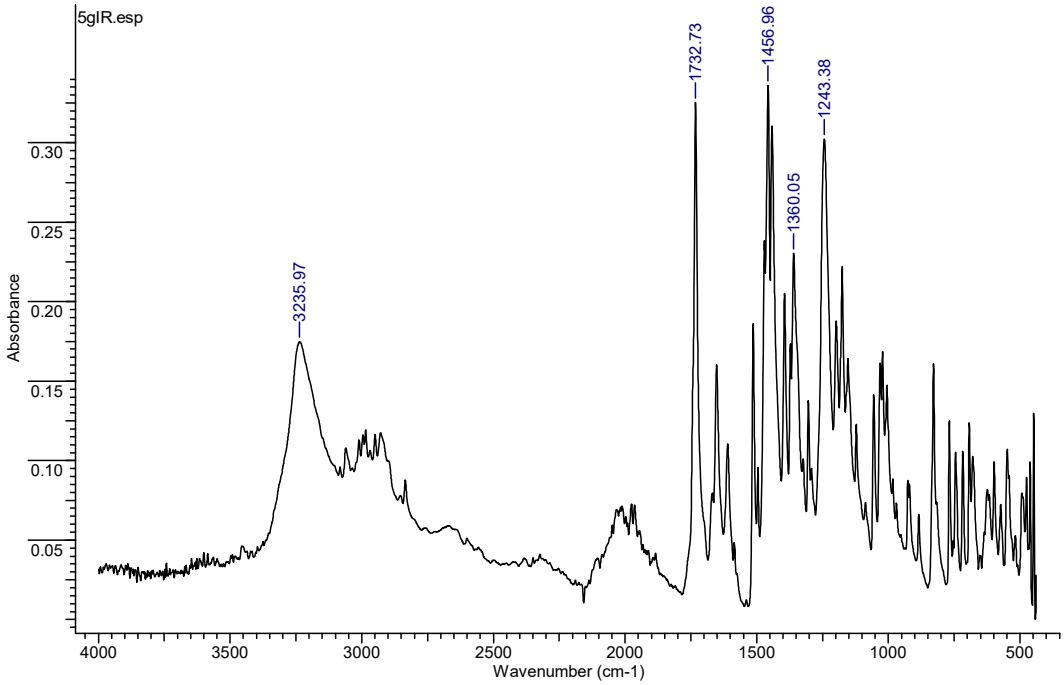
^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 8.89(s., 1H), 7.52(d., J=8.7Hz, 2H), 7.34-7.47(m., 4H), 6.87(d., J=8.7Hz, 2H), 6.62(s., 1H), 6.05(q., J=7.2Hz, 1H), 3.79(s., 3H), 1.94(d., J=7.4Hz, 3H)



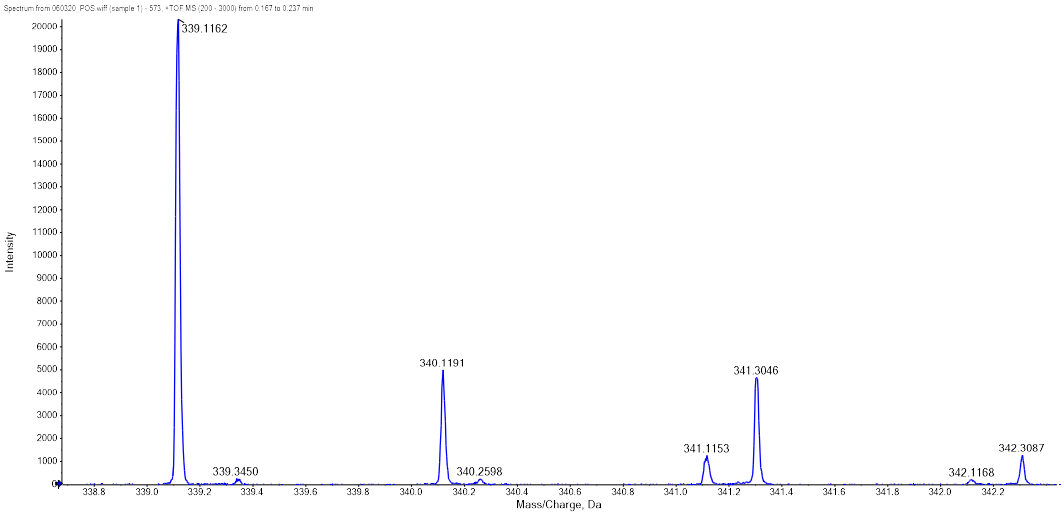
^{13}C NMR ($CDCl_3$, 101 MHz, δ, ppm): 178.39, 159.09, 132.80, 131.25, 129.59, 129.47, 128.97, 126.23, 113.60, 112.95, 55.20, 52.94, 16.52



IR (KBr, ν(cm^{-1})): 1733 (C=O), 1457 (C=S), 1243



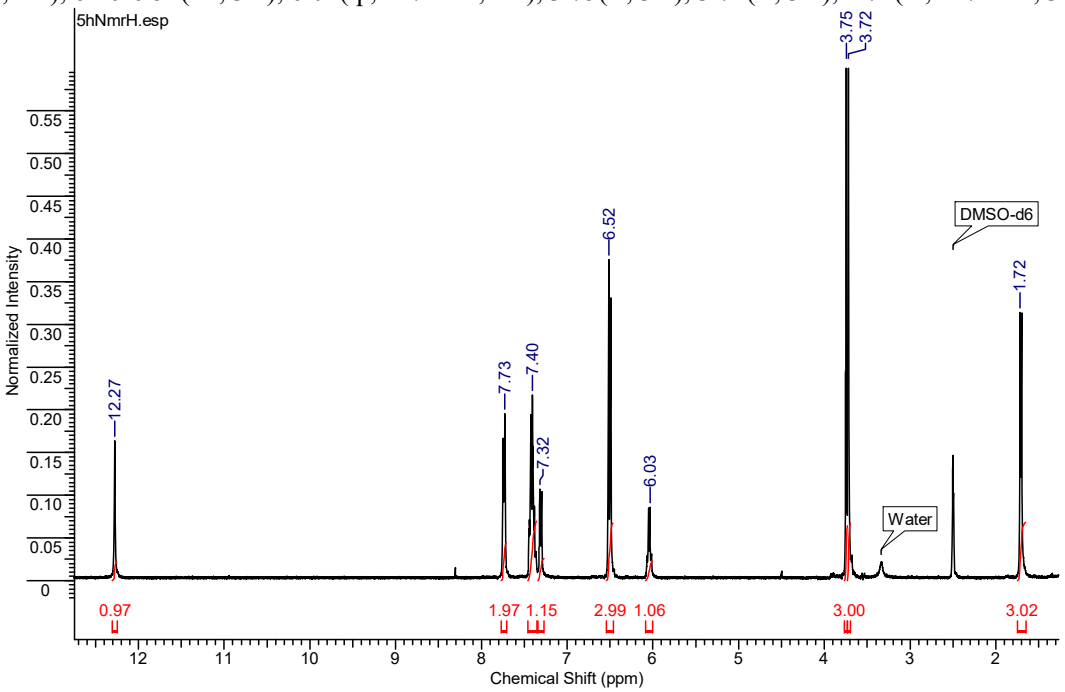
HRMS-ESI: m/z calculated for $[C_{19}H_{18}N_2O_2S+H]^+$: 339.1162; found 339.1162



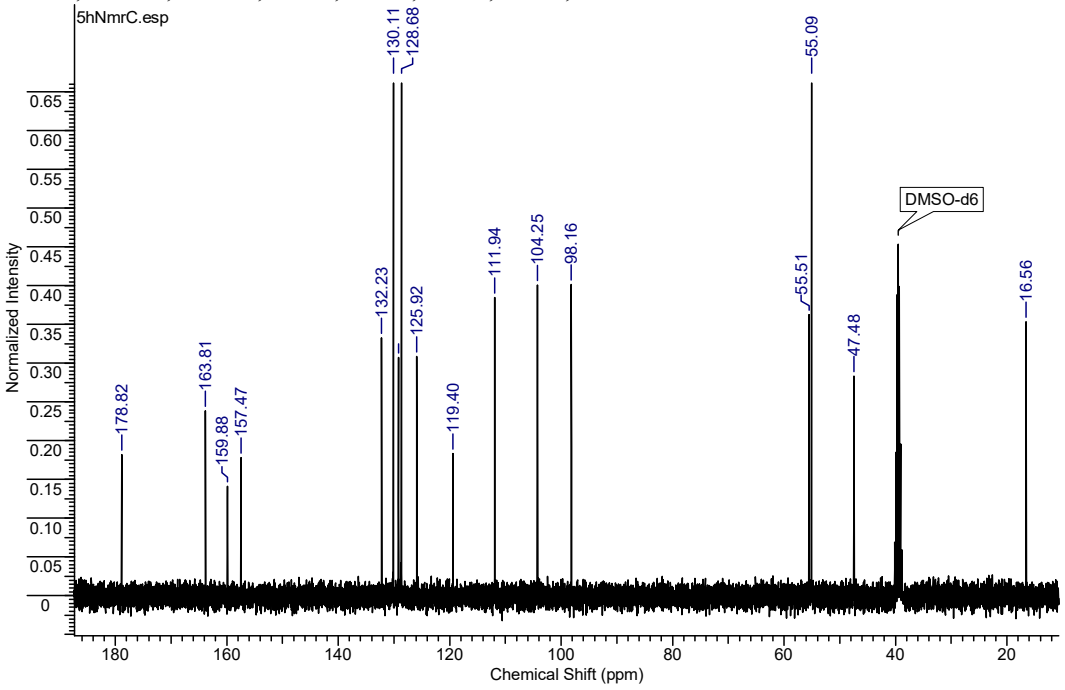
(*Z*)-5-Benzylidene-3-[1-(2,4-dimethoxyphenyl)ethyl]-2-thioxoimidazolidin-4-one (3f).

Using 1-(2,4-dimethoxyphenyl)ethylamine (181 mg), ethyl isothiocyanatoacetate (145 mg), benzaldehyde (117 mg) and KOH (168 mg), 201 mg (70%) of yellow crystalline substance (m.p. 139-140 ºC) was obtained.

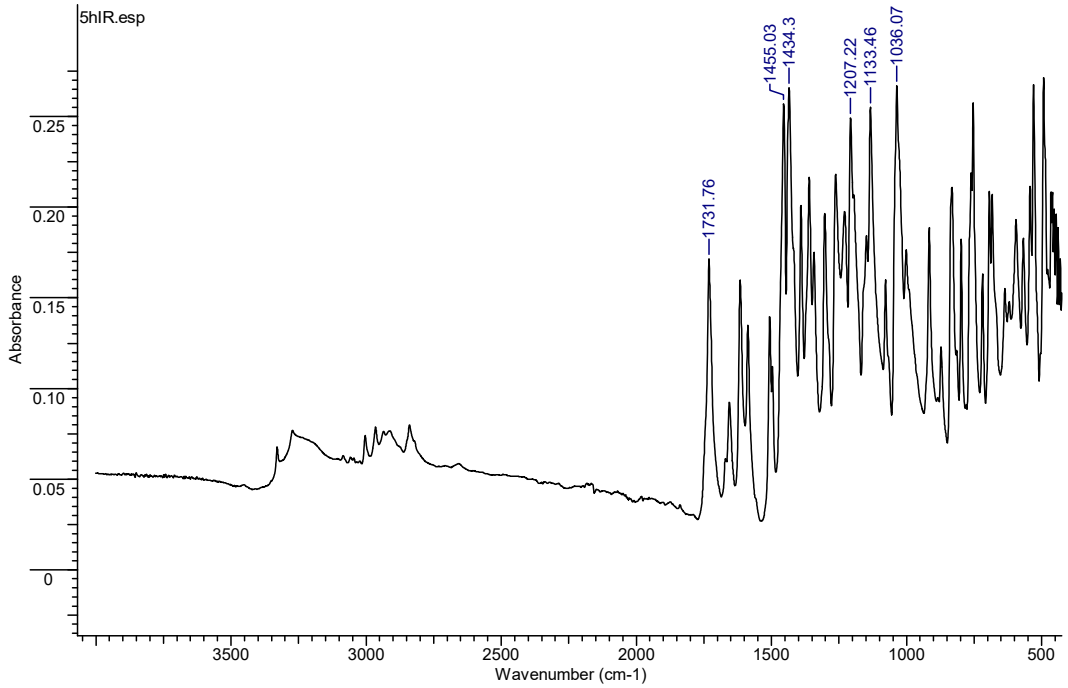
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 12.27(s., 1H), 7.74(d., J=8.2Hz, 2H), 7.36-7.45(m., 3H), 7.32(d., J=7.9Hz, 1H), 6.46-6.54(m., 3H), 6.04(q., J=7.1Hz, 1H), 3.75(s., 3H), 3.72(s., 3H), 1.71(d., J=7.2Hz, 3H)



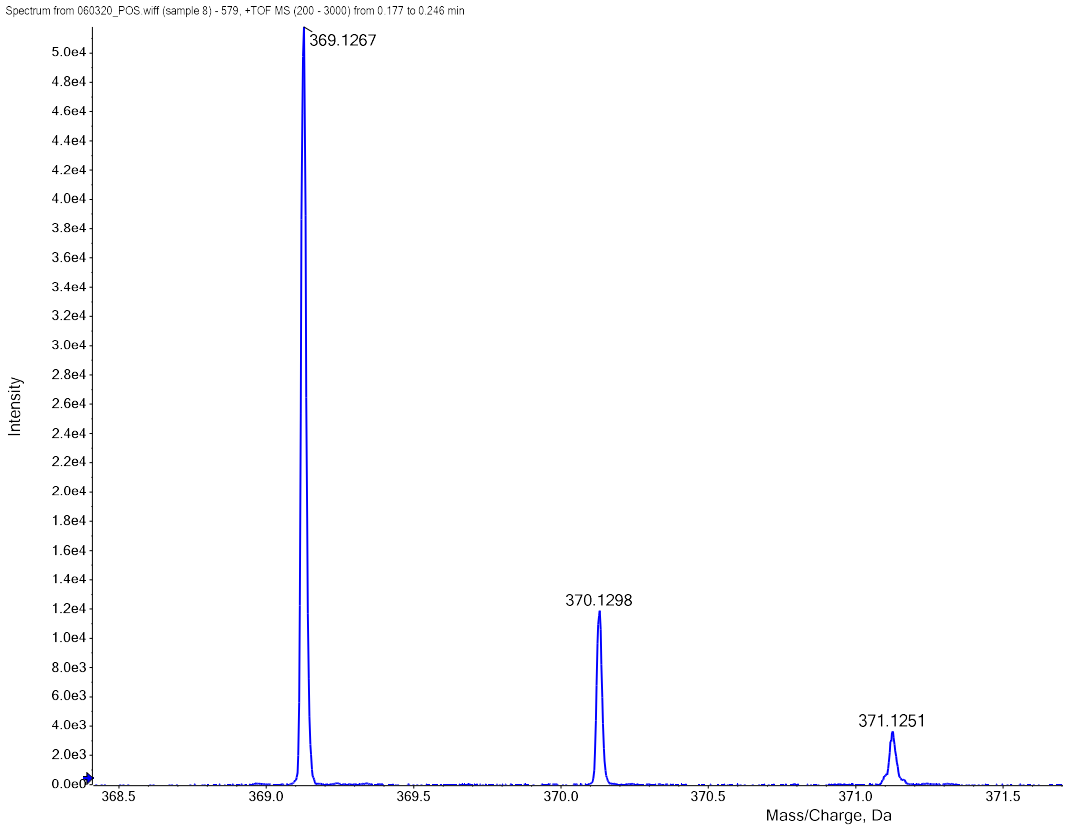
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 178.82, 163.81, 159.88, 157.47, 132.23, 130.11, 129.16, 128.68, 125.92, 119.40, 111.94, 104.25, 98.16, 55.51, 55.09, 47.48, 16.56



IR (KBr, ν(cm^{-1})): 1732 (C=O), 1455 (C=S), 1207 (C-O-C), 1133 (C-O-C), 1036(C-O-C)



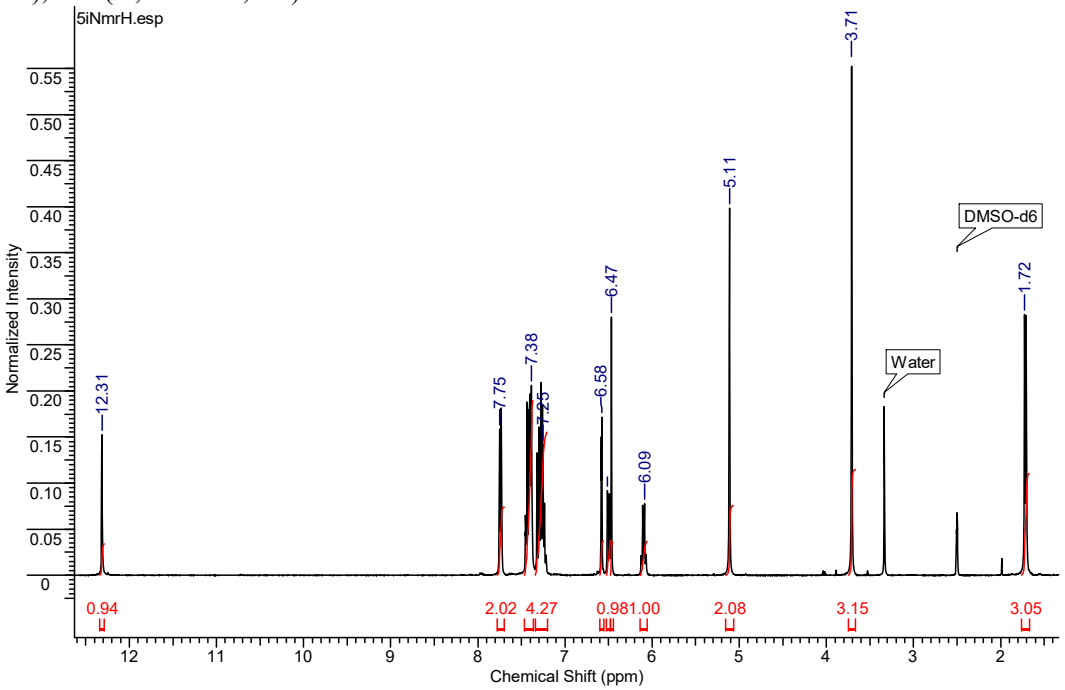
HRMS-ESI: m/z calculated for $[C_{20}H_{20}N_2O_3S+H]^+$: 369.1267; found 369.1267



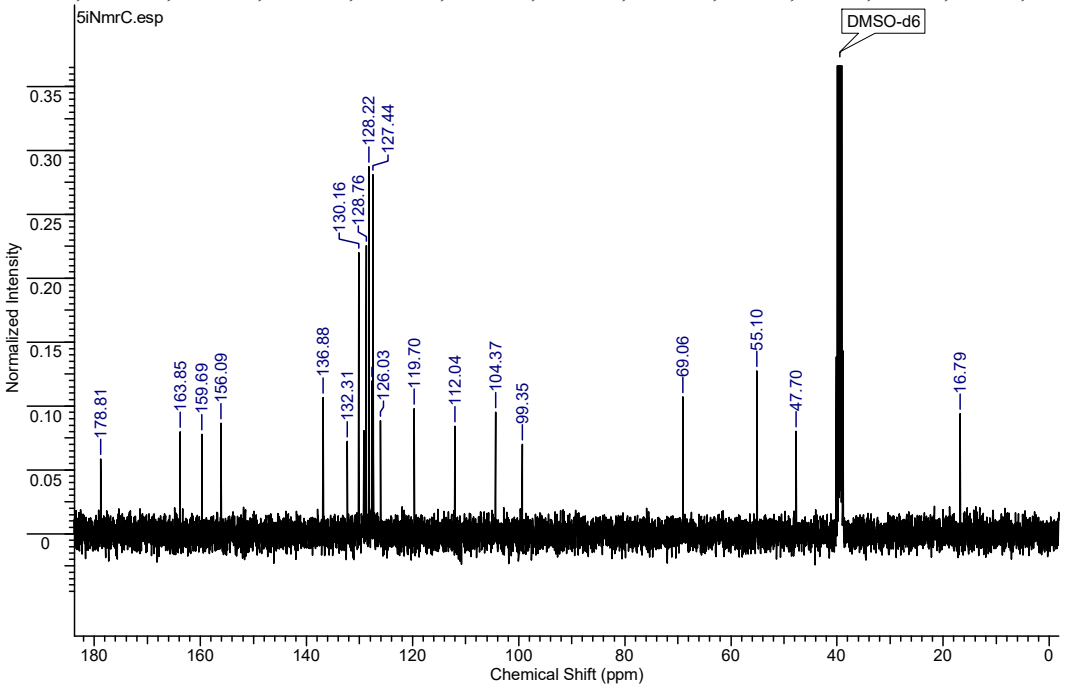
(*Z*)-5-Benzylidene-3-[1-(2-benzyloxy-4-methoxyphenyl)ethyl]-2-thioxoimidazolidin-4-one (3g).

Using 1-(2-benzyloxy-4-methoxyphenyl)ethylamine (257 mg), ethyl isothiocyanato-acetate (145 mg), benzaldehyde (117 mg) and KOH (168 mg), 320 mg (72%) of yellow crystalline substance (m.p. 138-139 ºC) was obtained.

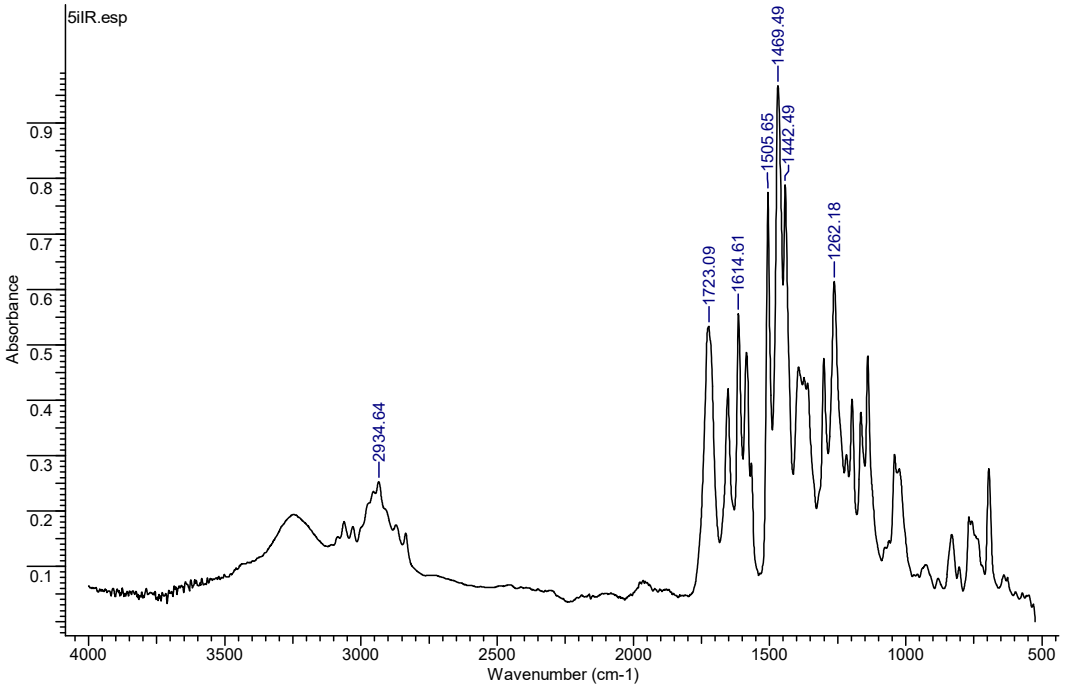
^{1}H NMR (DMSO-d$_6$, 400 MHz, δ, ppm): 12.31(s., 1H), 7.74(d., J=7.0 Hz, 2H), 7.36-7.49(m., 5H), 7.22-7.33(m., 4H), 6.58(d., J=2.4Hz, 1H), 6.48-6.52(m., 1H), 6.47(s., 1H), 6.10(q., J=7.2Hz, 1H), 5.11(s., 2H), 3.71(s., 3H), 1.72(d., J=7.2Hz, 3H)



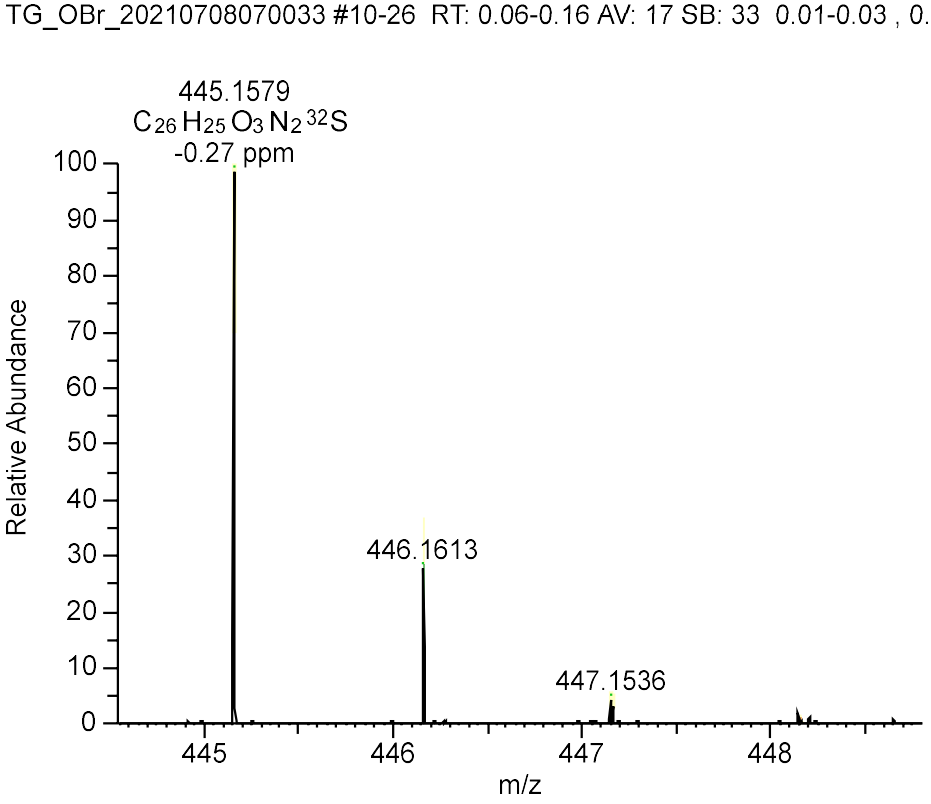
^{13}C NMR (DMSO-d$_6$, 101 MHz, δ, ppm): 178.81, 163.85, 159.69, 156.09, 136.88, 132.31, 130.16, 129.23, 128.82, 128.76, 128.22, 127.63, 127.44, 126.03, 119.70, 112.04, 104.37, 99.35, 69.06, 55.10, 47.70, 16.79



IR (KBr, ν(cm^{-1})): 1723 (C=O), 1469 (C=S), 1262 (C-O-C)



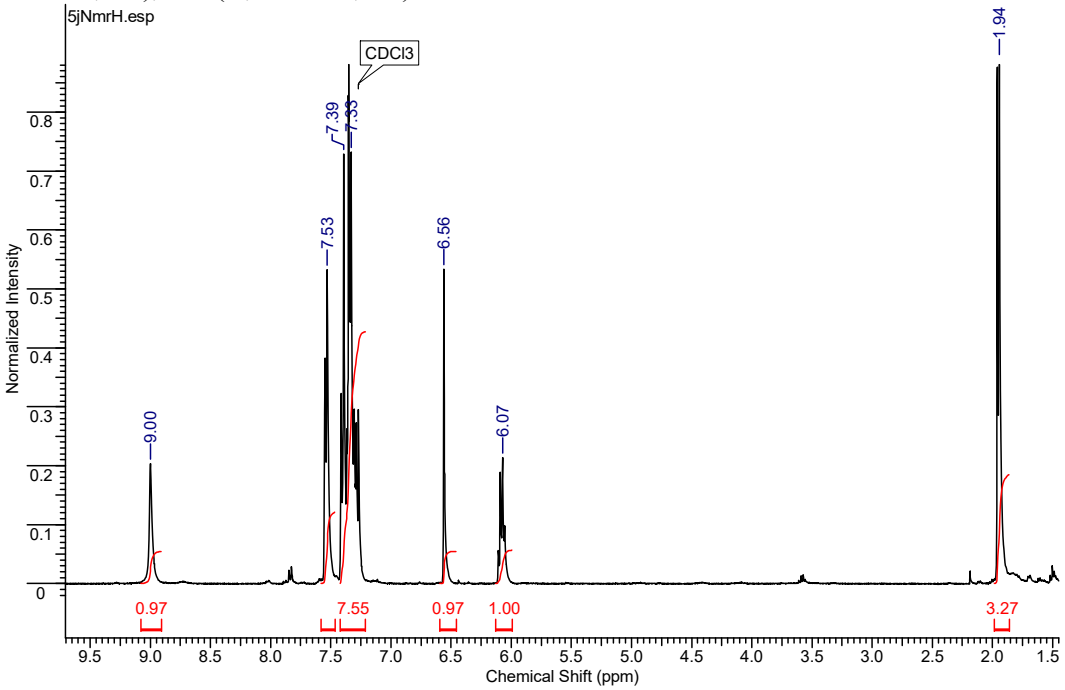
HRMS-ESI: m/z calculated for $[C_{26}H_{24}N_2O_3S+H]^+$: 445.1580; found 445.1579



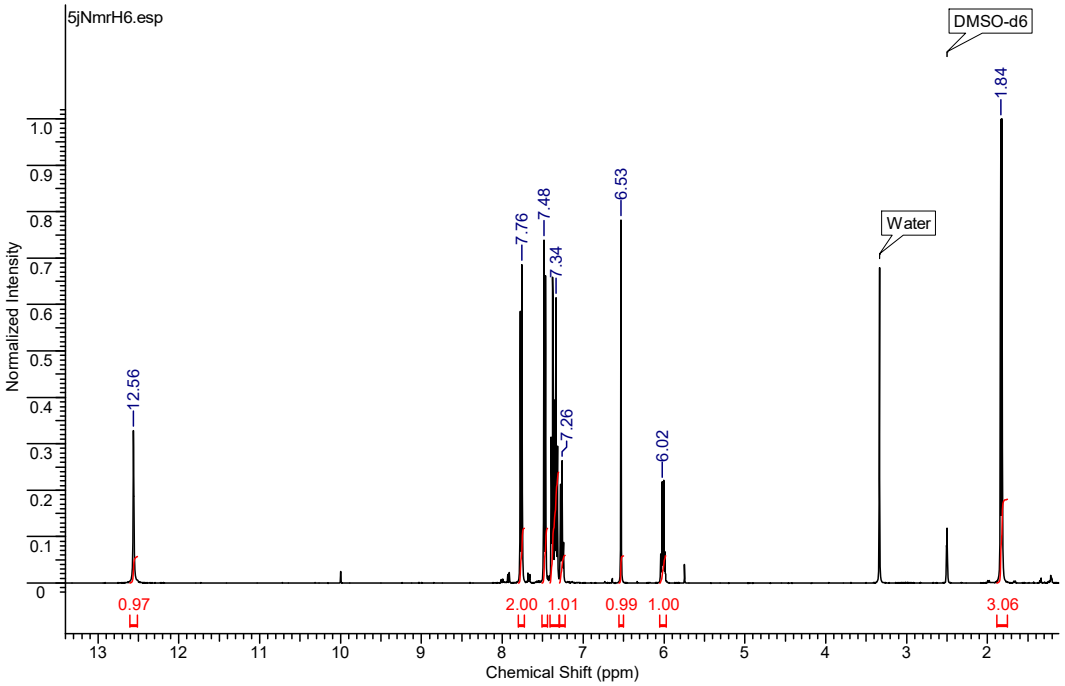
(*Z*)-5-(4-Chlorobenzylidene)-3-(1-phenylethyl)-2-thioxoimidazolidin-4-one (3h).

Using 1-phenylethylamine (121 mg), ethyl isothiocyanatoacetate (145 mg), 4-chloro-benzaldehyde (155 mg) and KOH (168 mg), 250 mg (73%) of yellow crystalline substance (m.p. 114-116 ºC) was obtained. Yield 73%

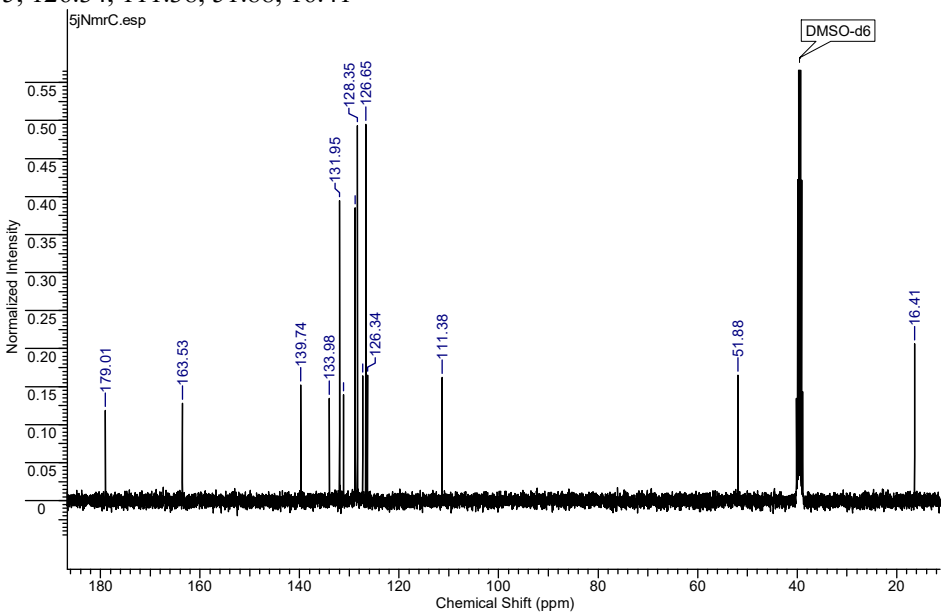
^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 9.00(s., 1H), 7.54(d., J=7.5Hz, 2H), 7.21-7.42(m., 8H), 6.56(s., 1H), 6.08(q., J=7.3Hz, 1H), 1.95(d., J=7.3Hz, 3H)



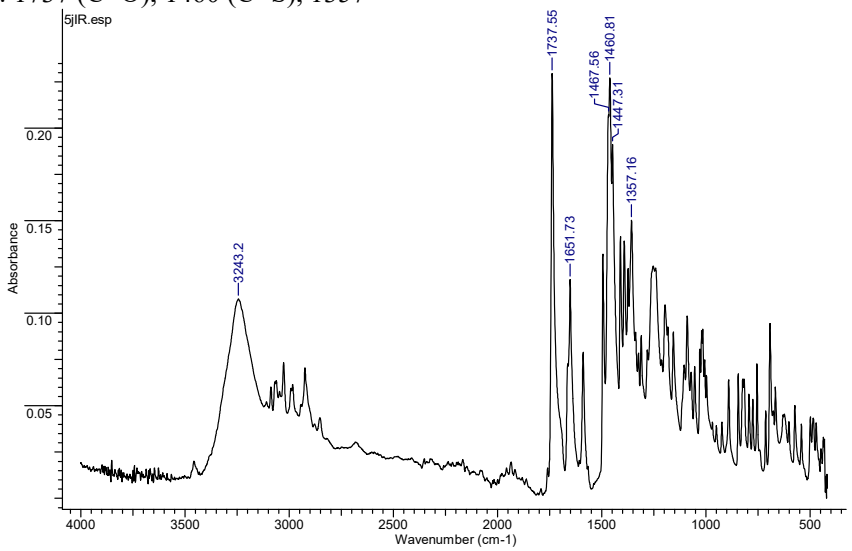
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 12.56(s., 1H), 7.77(d., J=8.5Hz, 2H), 7.47(d., J=8.5Hz, 2H), 7.23-7.41(m., 5H), 6.53(s., 1H), 6.02(q., J=7.3Hz, 1H), 1.84(d., J=7.2Hz, 3H)



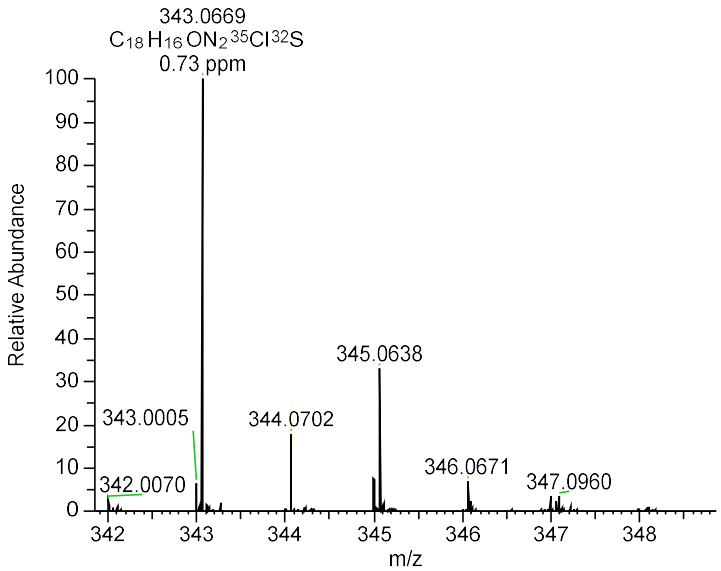
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 179.01, 163.53, 139.74, 133.98, 131.95, 131.14, 128.81, 128.35, 127.33, 126.65, 126.34, 111.38, 51.88, 16.41



IR (KBr, ν(cm^{-1})): 1737 (C=O), 1460 (C=S), 1357



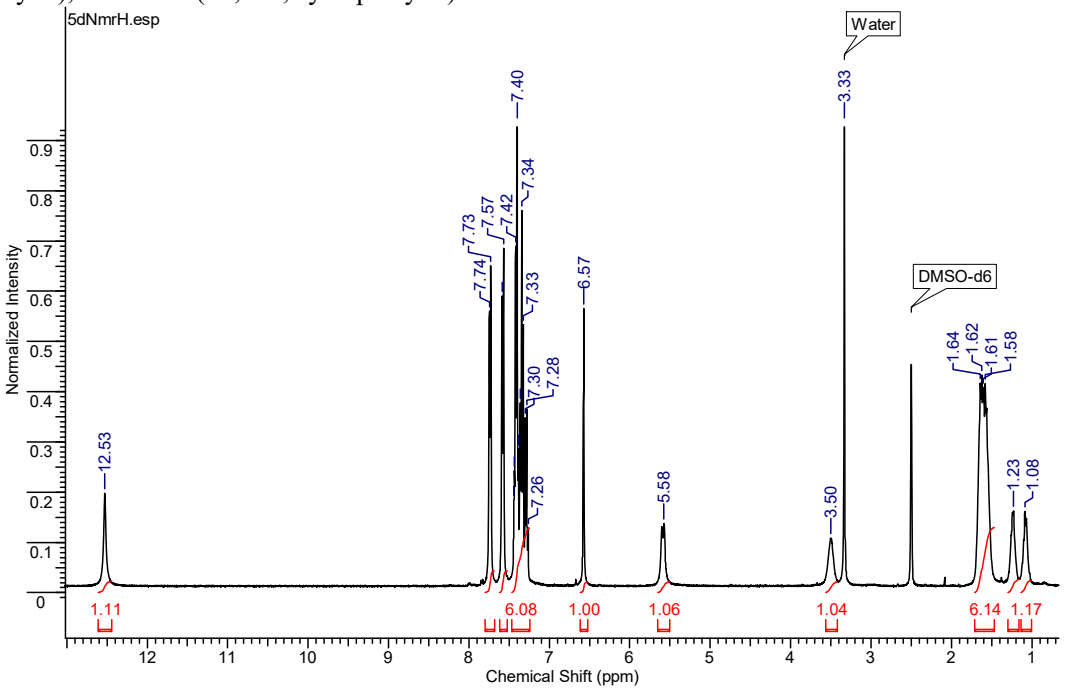
HRMS-ESI: m/z calculated for $[C_{18}H_{15}ClN_2OS+H]^+$: 343.0666; found 343.0669



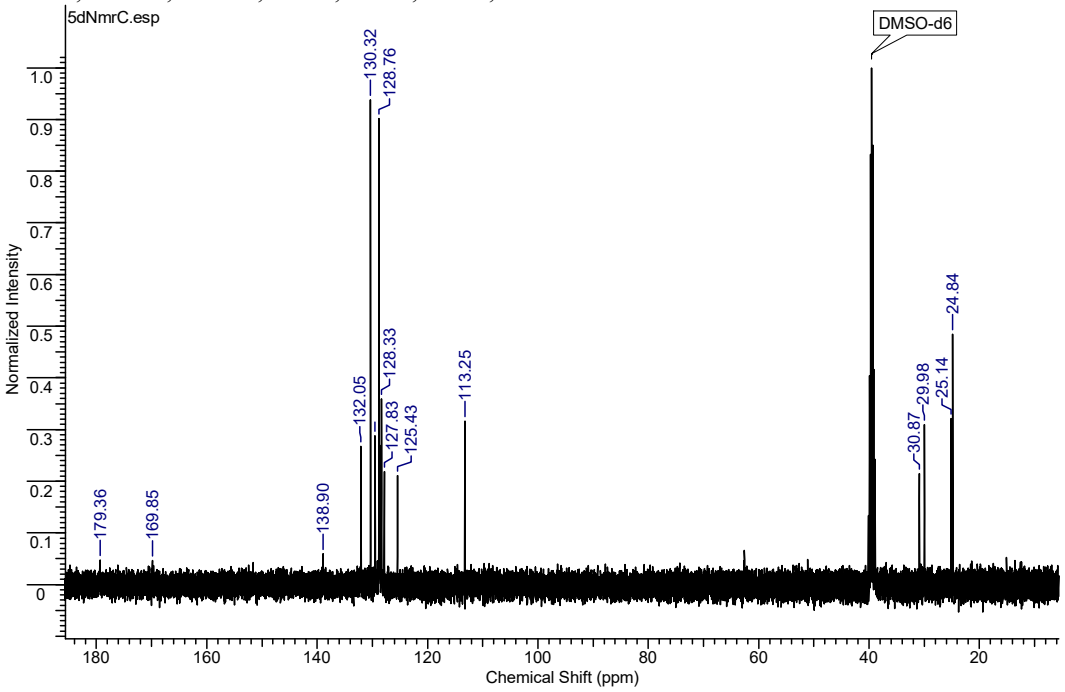
(Z)-5-Benzylidene-3-[cyclopentyl(phenyl)methyl]-2-thioxoimidazolidin-4-one.

Using cyclopentyl(phenyl)methylamine (175 mg), ethyl isothiocyanatoacetate (145 mg), benzaldehyde (117 mg) and KOH (168 mg), 123 mg (34%) of yellow crystalline substance was obtained.

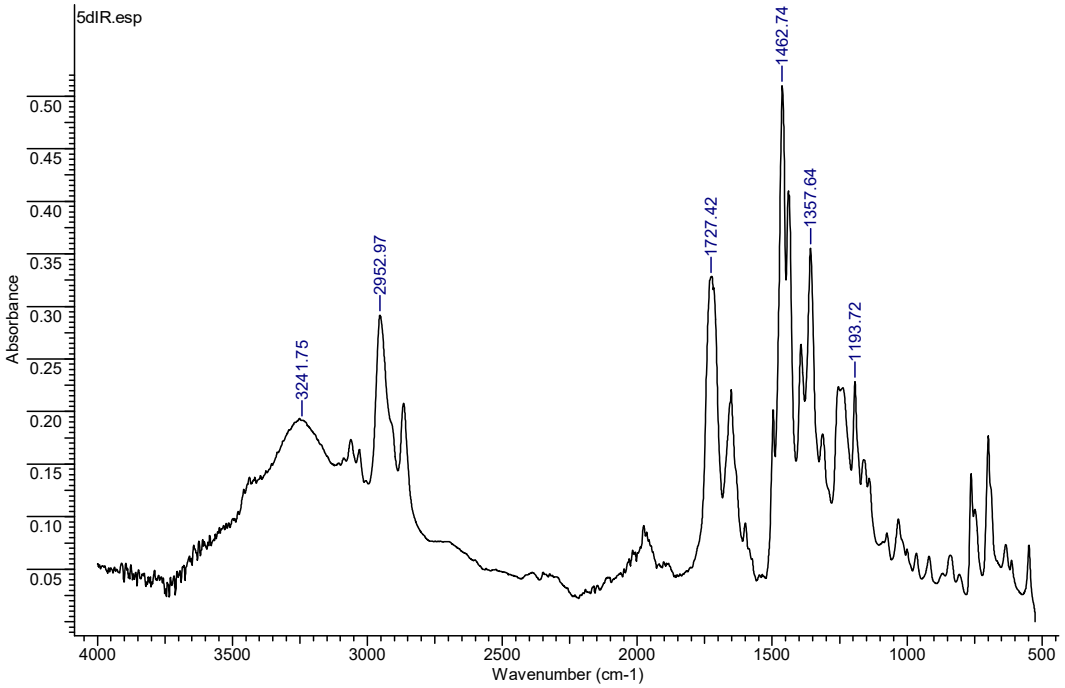
^{1}H NMR (DMSO-d$_6$, 400 MHz, δ, ppm): 12.53 (br.s., 1H, NH), 7.74 (d., J=6.5Hz, 2H, ArH), 7.58 (d., J=7.2Hz, 2H, ArH), 7.38-7.46 (m, 3H, ArH), 7.34 (t., J=7.24Hz, 2H, ArH), 7.24-7.31 (m., 1H, ArH), 6.57 (s., 1H, VinylH), 5.59 (d., J=11.0Hz, 1H, CH), 1.46-1.74 (m., 7H, cyclopentylH), 1.17-1.30 (m., 1H, cyclopentylH), 1.01-1.14 (m., 1H, cyclopentylH).



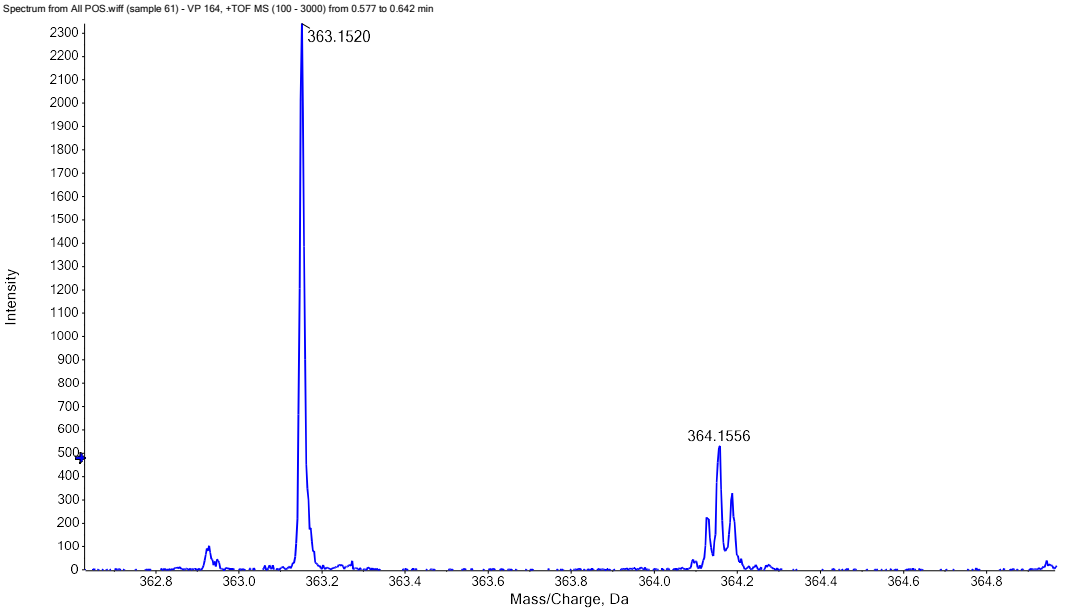
^{13}C NMR (DMSO-d$_6$, 101 MHz, δ, ppm): 179.36, 169.85, 138.90, 132.05, 130.32, 129.50, 128.76, 128.65, 128.33, 127.83, 125.43, 113.25, 30.87, 29.98, 25.14, 24.84.



IR (KBr, ν(cm^{-1})): 3242, 2952, 1727 (C=O), 1462 (C=S), 1357



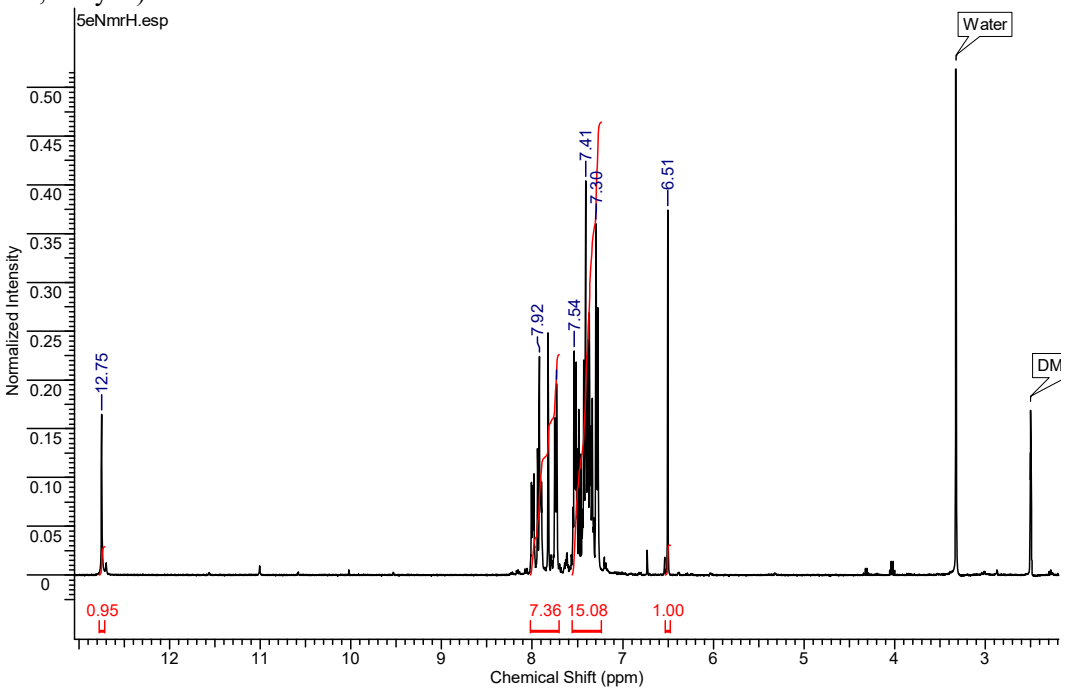
HRMS-ESI: m/z calculated for $[C_{22}H_{22}N_2OS+H]^+$: 363.1526; found 363.1520



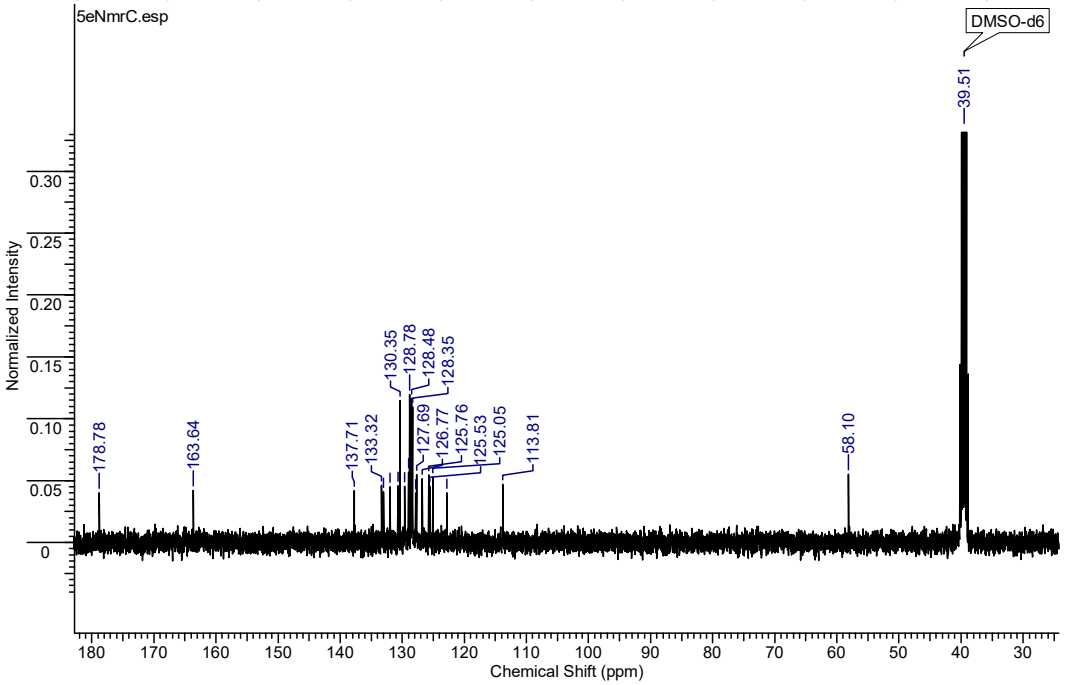
(Z)-5-Benzylidene-3-[naphthalen-2-yl(phenyl)methyl]-2-thioxoimidazolidin-4-one.

Using naphthalen-2-yl(phenyl)methyl amine (233 mg), ethyl isothiocyanatoacetate (145 mg), benzaldehyde (117 mg) and KOH (168 mg), 197 mg (47%) of yellow crystalline substance was obtained.

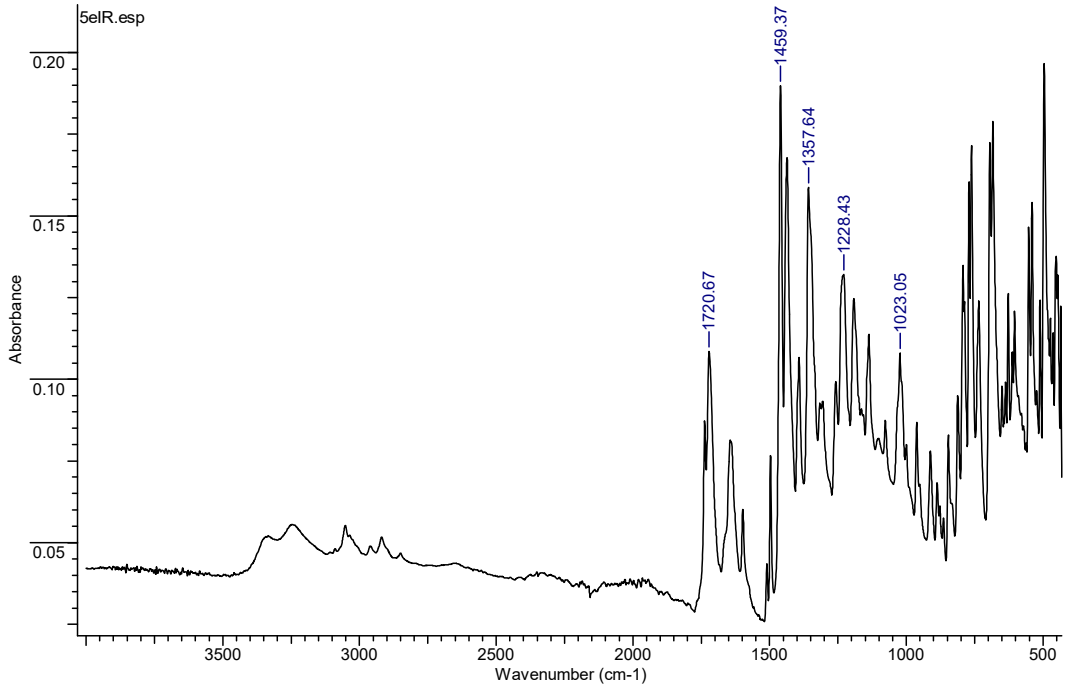
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 9.06 (br.s., 1H, NH), 7.98-8.05 (m., 1H, ArH), 7.89-7.94 (m., 2H, ArH), 7.83-7.89 (m., 2H, ArH), 7.47-7.54 (m., 4H, ArH), 7.42-7.46 (m., 3H, ArH), 7.35-7.42 (m., 5H, ArH), 6.59 (s., 1H, VinylH)



^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 178.78, 163.64, 137.71, 133.32, 132.99, 131.96, 130.71, 130.35, 129.60, 128.98, 128.78, 128.48, 128.35, 127.85, 127.69, 126.77, 125.76, 125.53, 125.05, 122.79, 113.81, 58.10

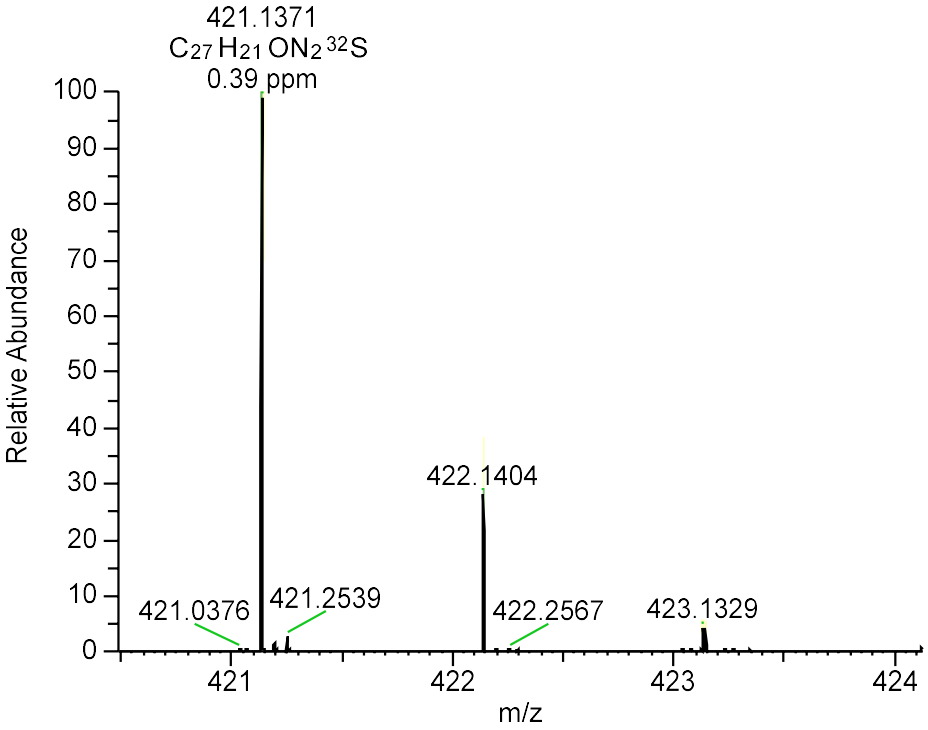


IR (KBr, ν(cm^{-1})): 1720 (C=O), 1459 (C=S), 1358



HRMS-ESI: m/z calculated for $[C_{27}H_{20}N_2OS+H]^+$: 421.1369; found 421.1371

TG_Naphtyl_20210708064953 #10-27 RT: 0.06-0.17 AV: 18 SB: 60 0.01-0.04 , 0 ...

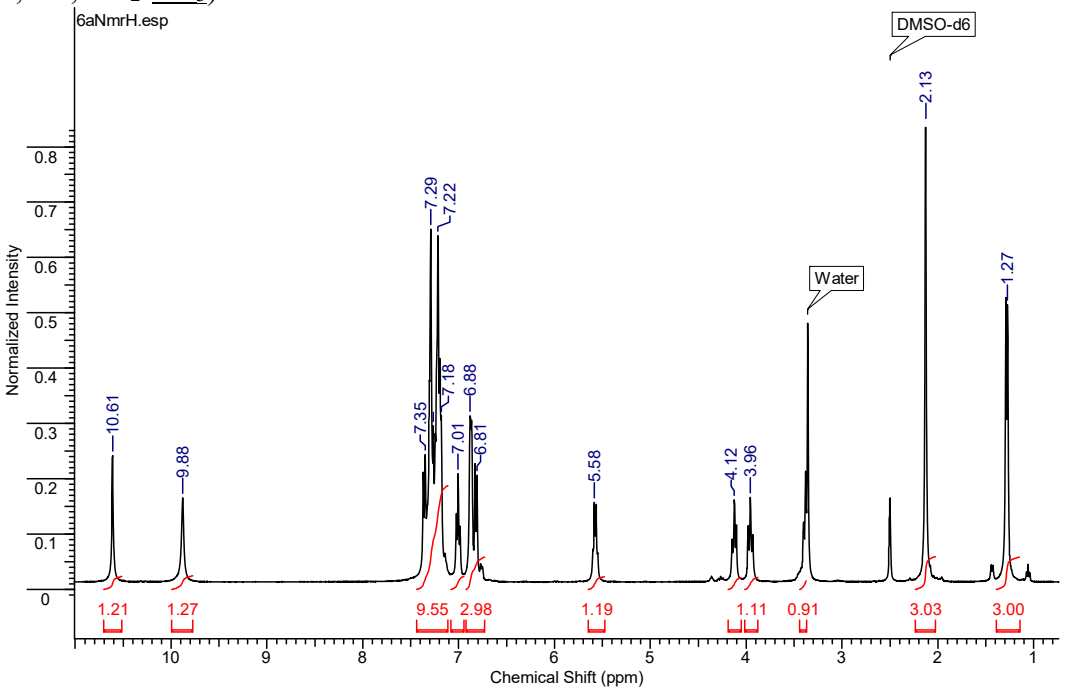


Synthesis of dispiroindolinones 4a-h

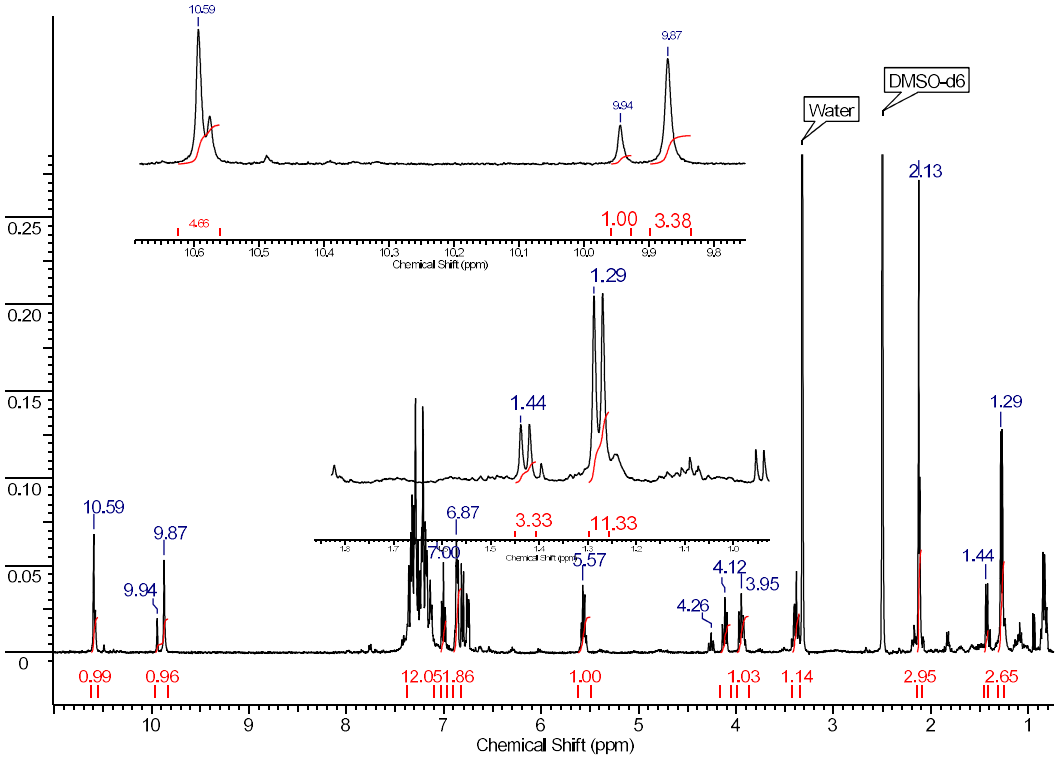
Isatin (4 equiv.) was added to a boiling solution of 2-thiohydantoin derivative **3a-h** (1 equiv.) and sarcosine (4 equiv.) in ethanol. The mixture was refluxed for 6-8 h (TLC control). After completion of the reaction and cooling of the solution, an excess of water was added, and the resulting precipitate was analyzed with ^{1}H NMR data to study the diastereomeric ratio. The mixture was then purified by recrystallization from 80% ethanol or by column chromatography (petroleum ether/ethyl acetate 2:1).

(2'*S**,3'*R**,4'*R**)-1-[(*S**)-1-Phenylethyl]-1'-methyl-4'-phenyl-2-thioxo-dispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (4a)

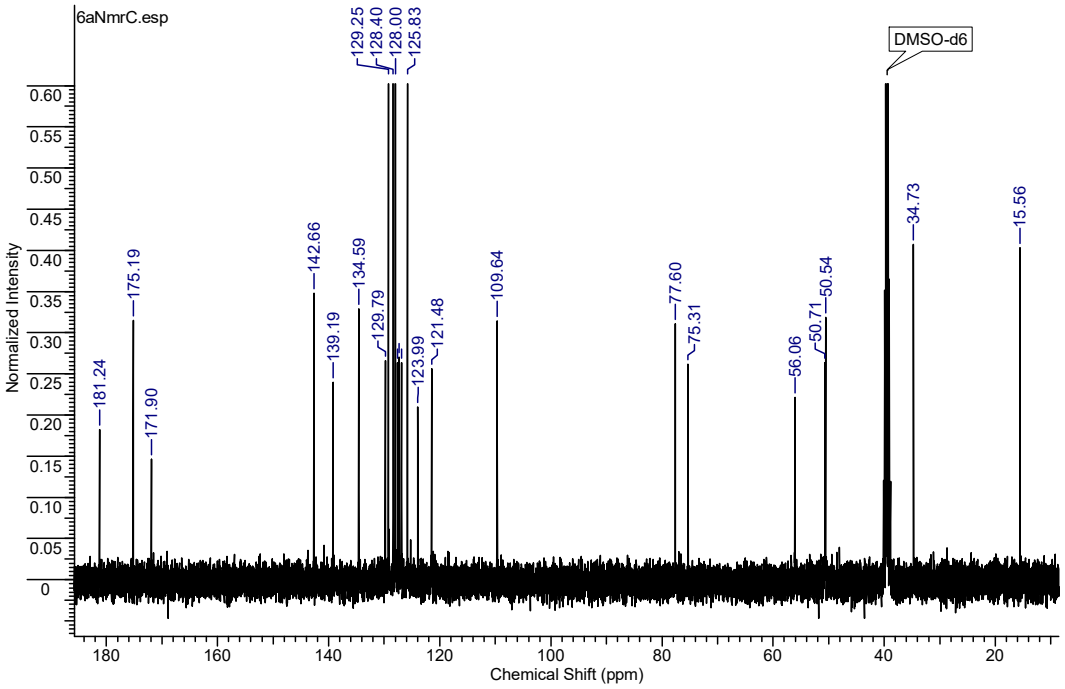
Using thiohydantoin **3a** (154 mg, 0.5 mmol), sarcosine (178 mg, 2 mmol) and isatin (294 mg, 2 mmol), 323 mg of a mixture of diastereomers was obtained (total yield 67%, *dr* = 3.4). The resulting mixture was recrystallized to give 87 mg (18%) of dispiroindolinone **4a**, m.p. 180-182 ºC.
^{1}H NMR (DMSO-d6, 400 MHz, δ, ppm): 10.61(s., 1H, NH), 9.88 (s., 1H, NH), 7.13-7.36(m., 11H, Ph), 7.01(t, =7.46Hz, 1H, Ph), 6.80-6.87 (m., 3H, Ph), 5.58(q., J=7.08Hz, 1H, CH-Ph), 4.12 (t., J=9.90 Hz, 1H), 3.96(t., J=9.1Hz, 1H), 3.36 (t., J=9.1Hz, 1H), 2.13(s., 3H, N-CH_3), 1.27(d., J=7.2Hz, 3H, CH_2-CH_3)



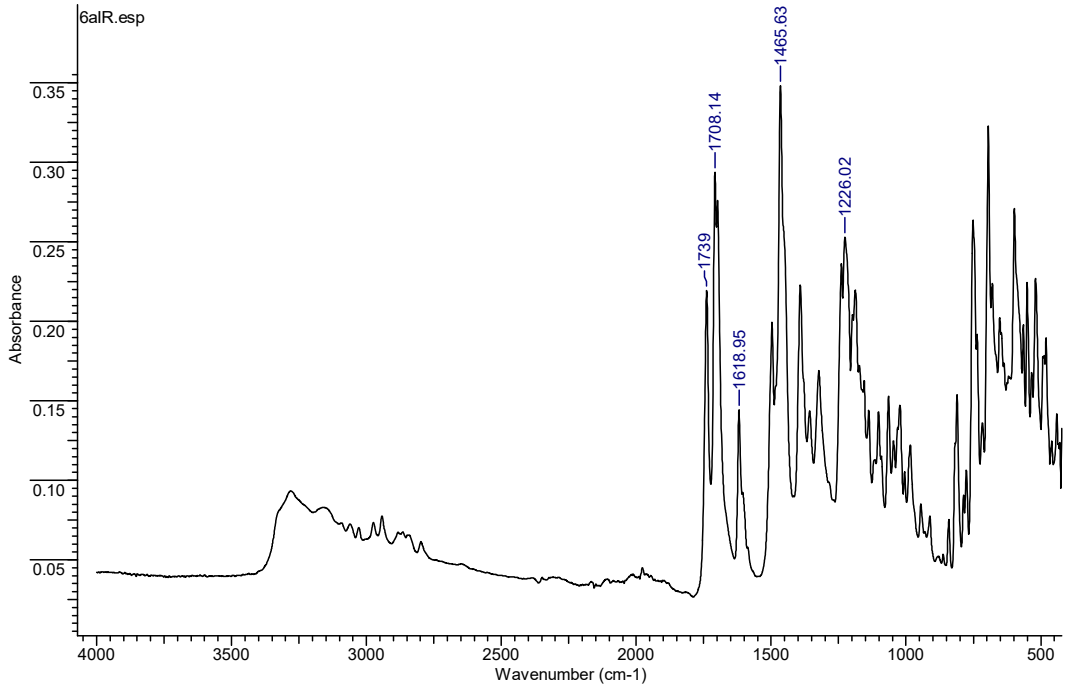
Reaction mixture of stereoisomers **4a**+**4'a** (*dr* = 3.4):



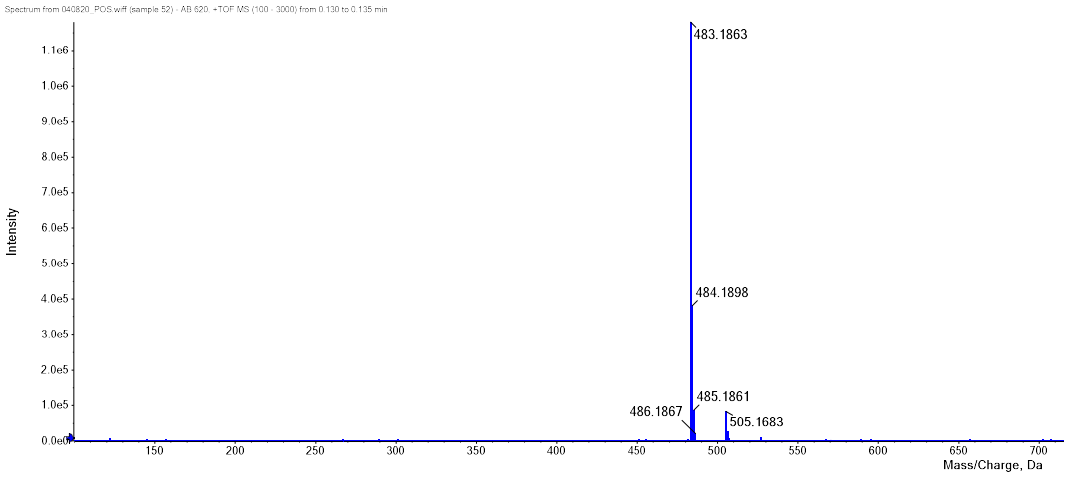
^{13}C NMR (DMSO-d$_6$, 101 MHz, δ, ppm): 181.24, 175.19, 171.90, 142.66, 139.19, 134.59, 129.79, 129.25, 128.40, 128.00, 127.56, 127.29, 126.88, 125.83, 123.99, 121.48, 109.64, 77.60, 75.31, 56.06, 50.71, 50.54, 34.73, 15.56



IR (KBr, ν(cm^{-1})): 1739 (C=O),1708(C=O), 1466 (C=S), 1226



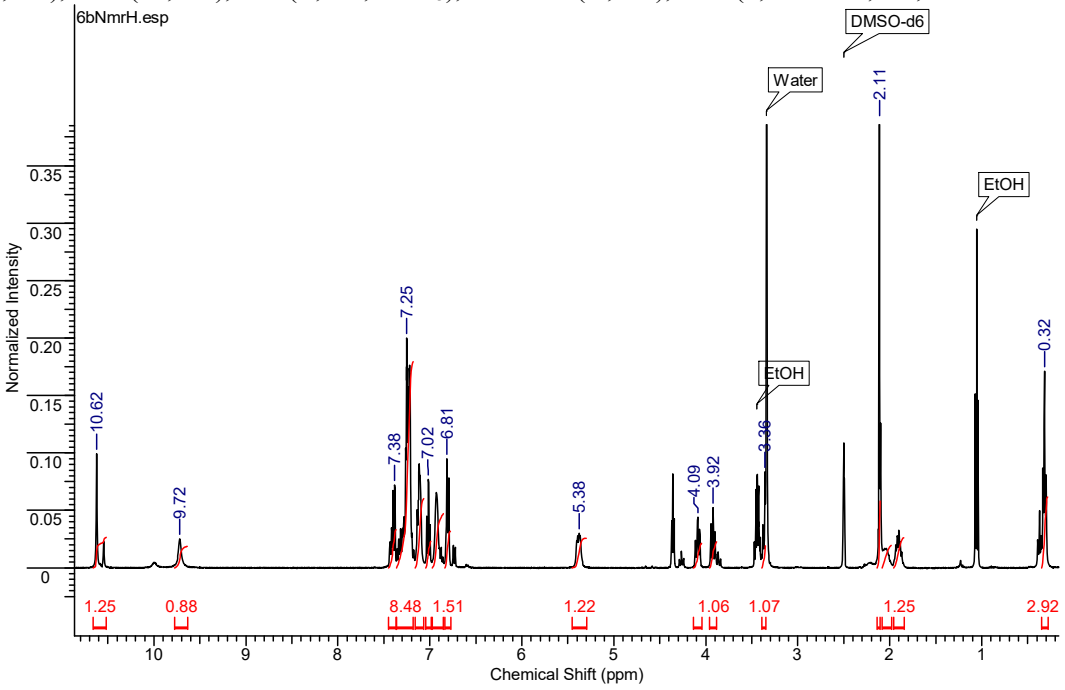
HRMS-ESI: m/z calculated for $[C_{28}H_{26}N_4O_2S+H]^+$: 483.1849; found 483.1863



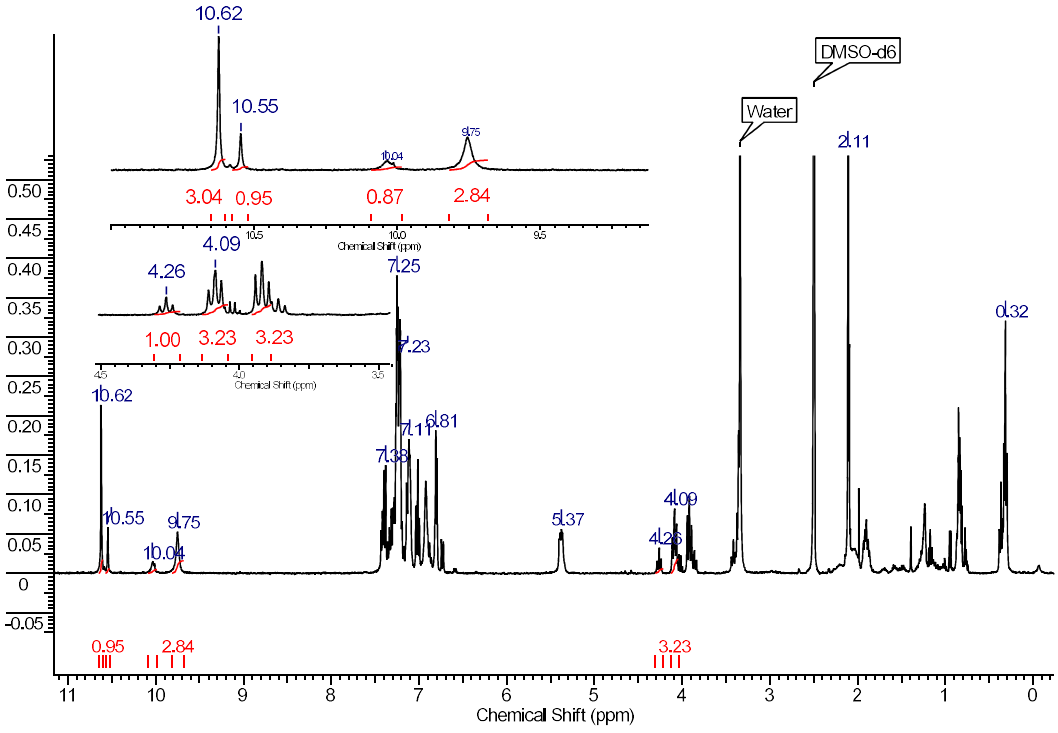
(2'*S,3'*R**,4'*R**)-1-[(*S**)-1-Phenylpropyl]-1'-methyl-4'-phenyl-2-thiooxo-dispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (4b).**

Using thiohydantoin **3b** (110 mg, 0.34 mmol), sarcosine (121 mg, 1.36 mmol) and isatin (200 mg, 1.36 mmol), 73 mg (43%) of a mixture of diastereomers (*dr* = 3.2) was obtained. Recrystallization did not lead to sufficient purification of dispiroindolinone **4b** (32 mg, yield 19%, *dr* = 5.0). M.p. 183-185 ºC.

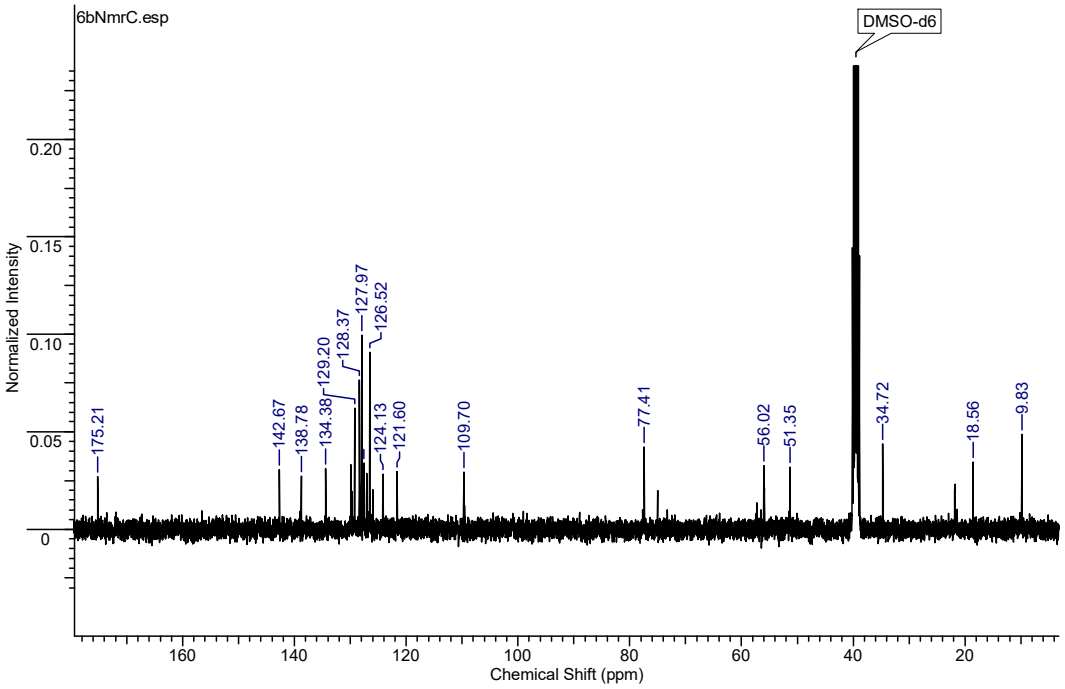
^{1}H NMR (DMSO-d$_6$, 400 MHz, δ, ppm): 10.62 (br.s., 1H, NH), 9.72 (s., 1H, NH), 7.38 (d., J=7.4Hz, 1H, ArH), 7.16-7.27 (m., 4H, ArH), 7.07-7.16 (m., 3H, ArH), 6.98-7.04 (m., 2H, ArH), 6.92 (d., J=7.3Hz, 2H, ArH), 6.81 (d., J=7.5Hz, 2H, ArH), 5.32-5.42 (m, 1H, Ph-CH-CH$_2$-CH$_3$), 4.09 (t., J=9.3Hz, 1H), 3.92 (t., J=9.5Hz, 1H), 3.36 (m., 1H), 2.11(s., 3H, NCH$_3$), 1.85-2.05(m, 2H), 0.32 (t., J=7.2Hz, 3H, Ph-CH-CH$_2$-CH$_3$).



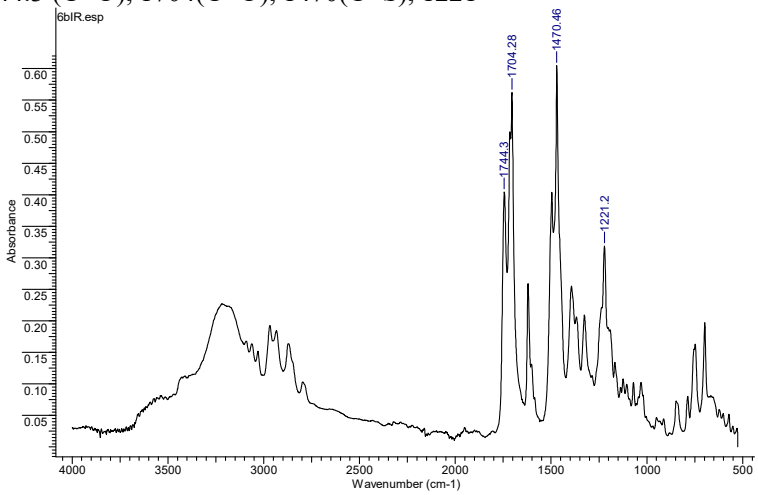
Reaction mixture of stereoisomers **4b**+**4'b** (*dr* = 3.2):



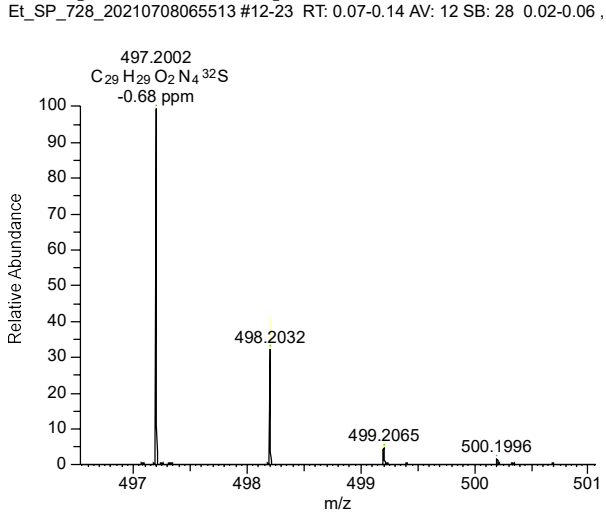
^{13}C NMR (DMSO-d$_6$, 101 MHz, δ, ppm): 175.21, 142.67, 138.78, 134.38, 129.88, 129.20, 128.37, 127.97, 127.55, 127.03, 126.52, 125.94, 124.13, 121.60, 106.70, 77.41, 56.02, 51.35, 34.72, 18.56, 9.83



IR (KBr, ν(cm^{-1})): 1744.3 (C=O), 1704(C=O), 1470(C=S), 1221



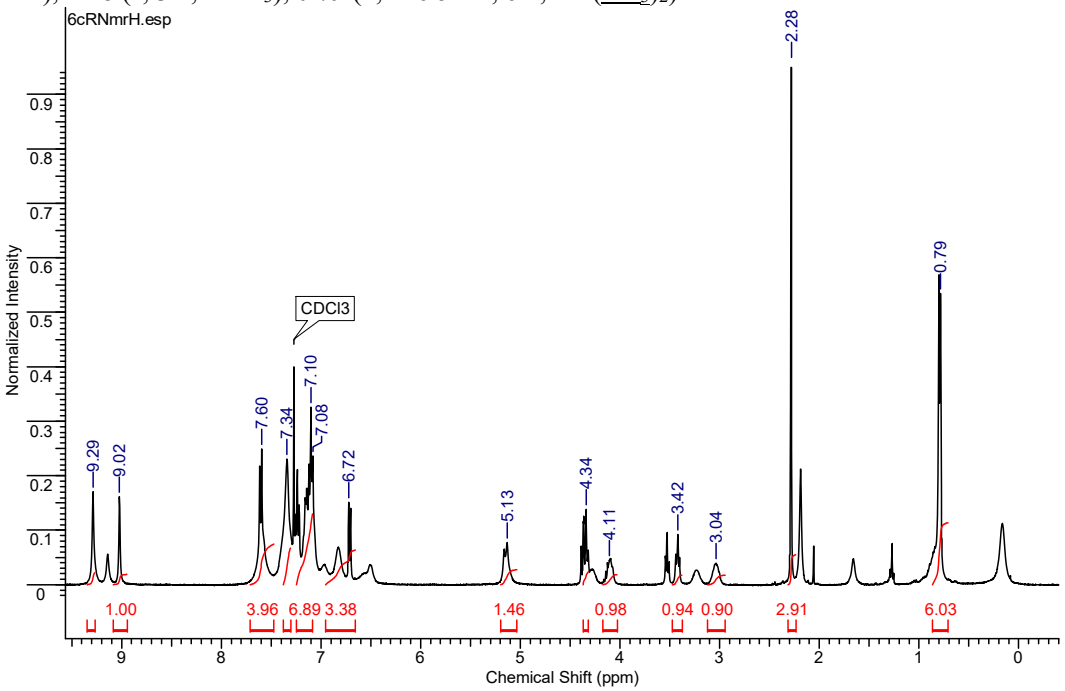
HRMS-ESI: m/z calculated for $[C_{29}H_{28}N_4O_2S+H]^+$: 497.2006; found 497.2002



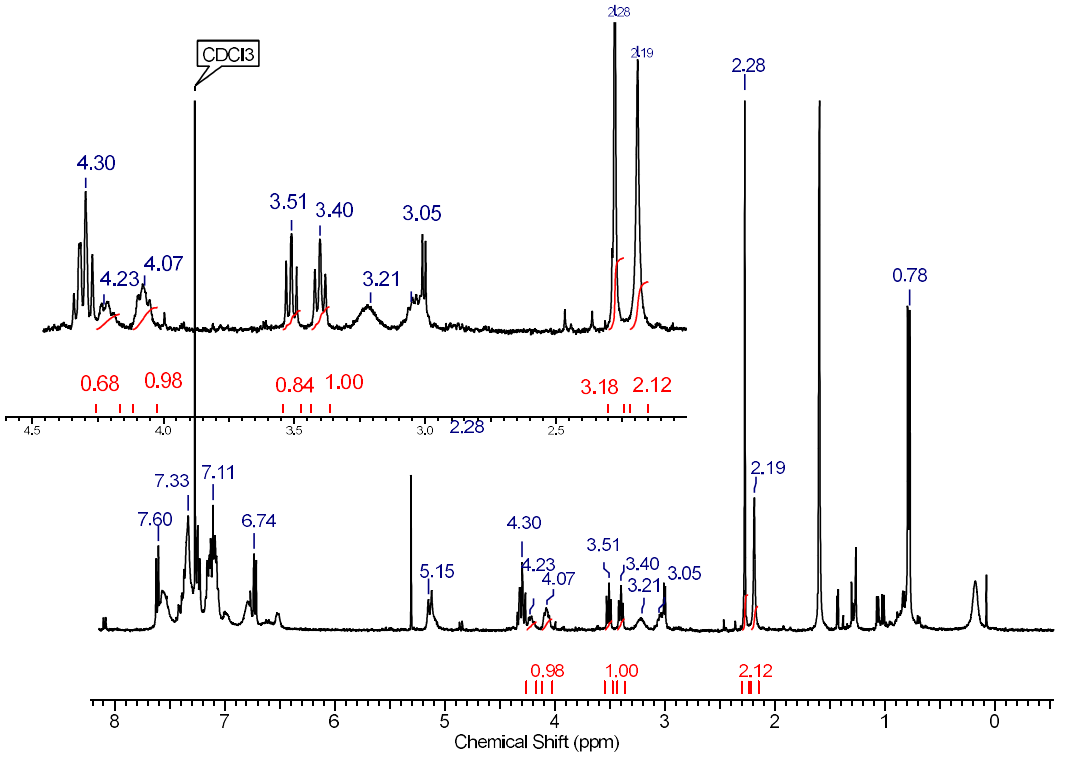
(2'*S,3'*R**,4'*R**)-1-[(*S**)-(2-Methyl-1-phenylpropyl]-1'-methyl-4'-phenyl-2-thiooxo-dispiro[imidazolidine-4,3'-pyrrolidine-2',3"-indoline]-2",5-dione (4c).**

Using thiohydantoin **3c** (90 mg, 0.27 mmol), sarcosine (95 mg, 1.07 mmol) and isatin (157 mg, 1.07 mmol), 78 mg (57%) of a mixture of diastereomers (*dr* = 1.5) was obtained. Recrystallization did not lead to sufficient purification of dispiroindolinone **4c** (37 mg, yield 27%, *dr* = 1.5), m.p. 187-189 °C.

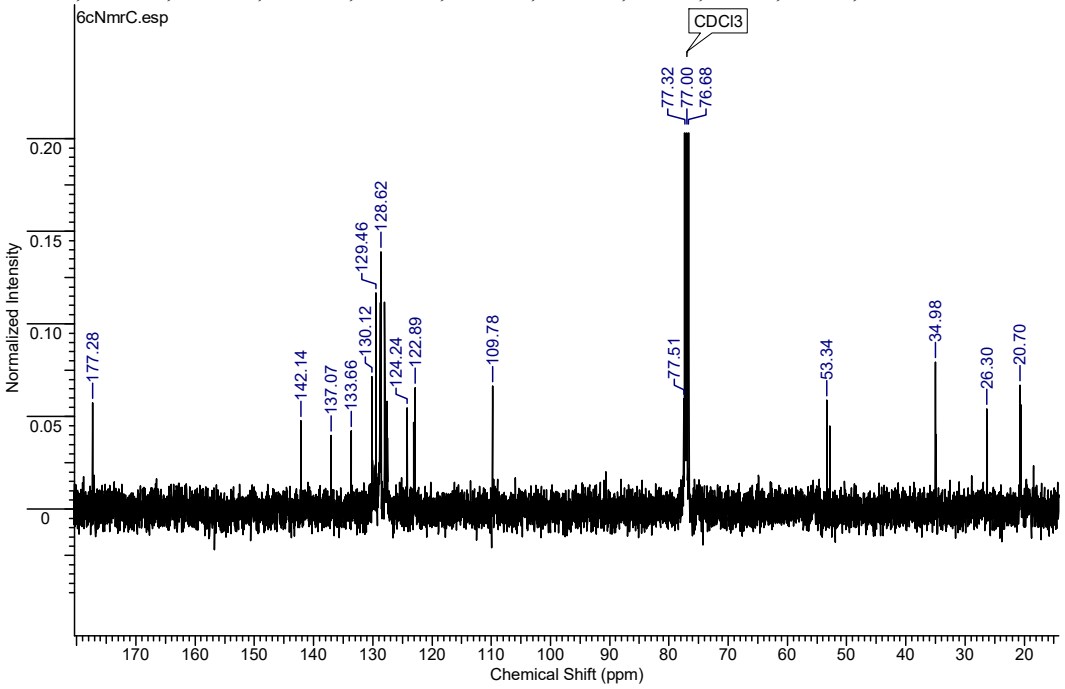
^{1}H NMR (CDCl3, 400 MHz, δ, ppm): 9.29 (s, 1H, NH), 9.02 (s, 1H, NH), 7.28-7.70 (m, 5H, ArH), 7.02-7.26 (m, 6H, ArH), 6.64-7.00 (m, 3H), 5.13 (m, 1H, Ph-CH-Pr^i), 4.34(m, 1H), 4.11(m, 1H), 3.42 (t, J=7.7 Hz, 1H), 3.04 (m, 1H), 2.28 (s, 3H, NCH_3), 0.79 (d, J=6.5 Hz, 6H, $CH(CH_3)_2$).



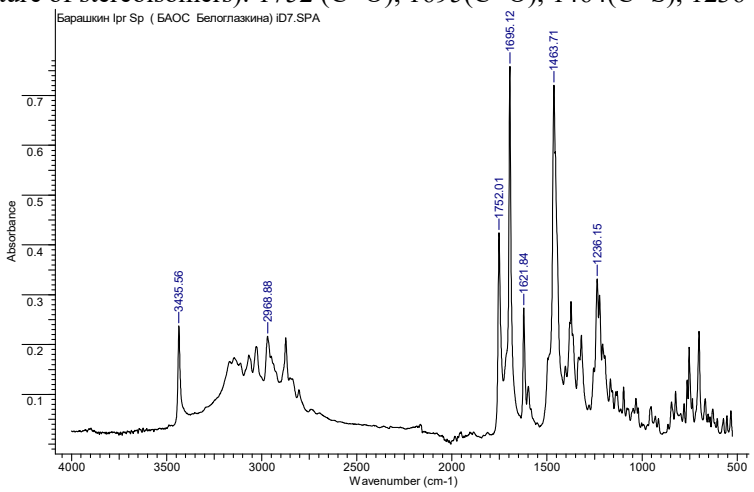
Reaction mixture of stereoisomers **4c**+**4'c** (*dr* = 1.5):



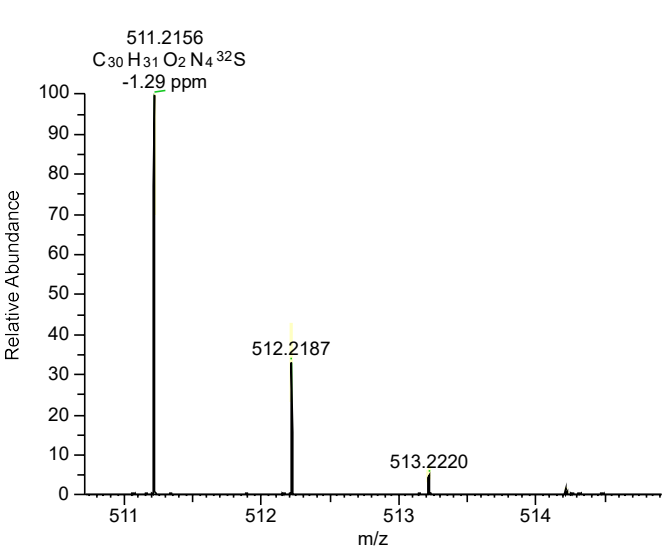
^{13}C NMR (DMSO-d_6, 101 MHz, isomer mixture): 177.28, 142.14, 137.07, 133.66, 130.12, 129.46, 128.74, 128.62, 128.02, 127.61, 127.50, 124.24, 123.07, 122.89, 109.78, 53.34, 34.89, 26.30, 20.70



IR (KBr, ν(cm^{-1}), mixture of stereoisomers): 1752 (C=O), 1695(C=O), 1464(C=S), 1236



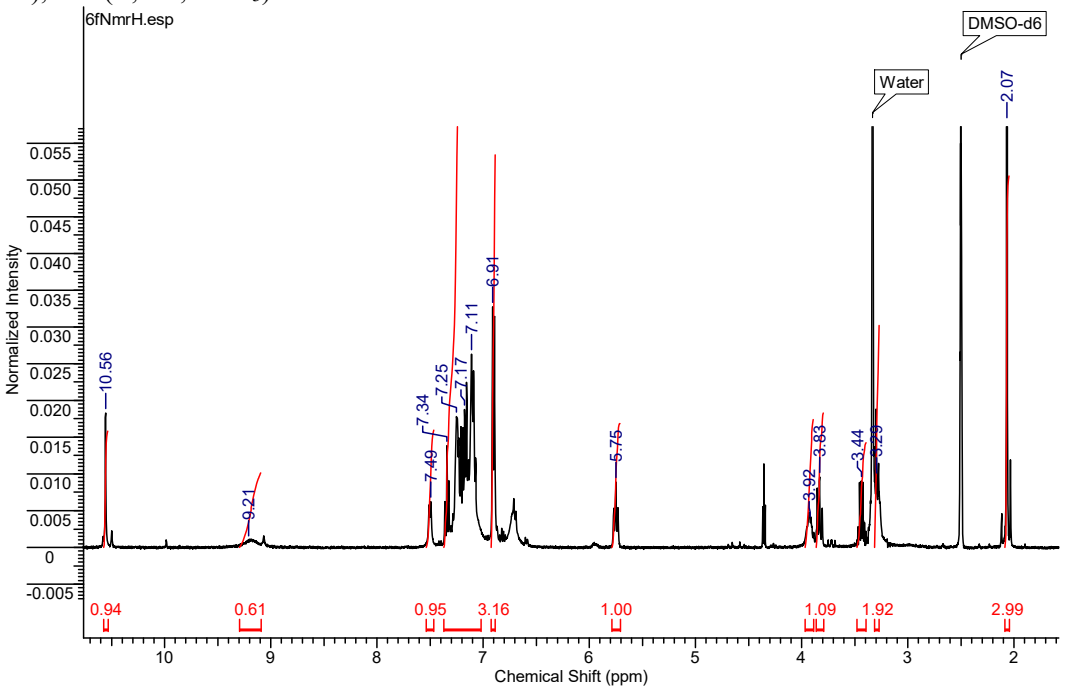
HRMS-ESI: m/z calculated for $[C_{30}H_{30}N_4O_2S+H]^+$: 511.2162; found 511.2156



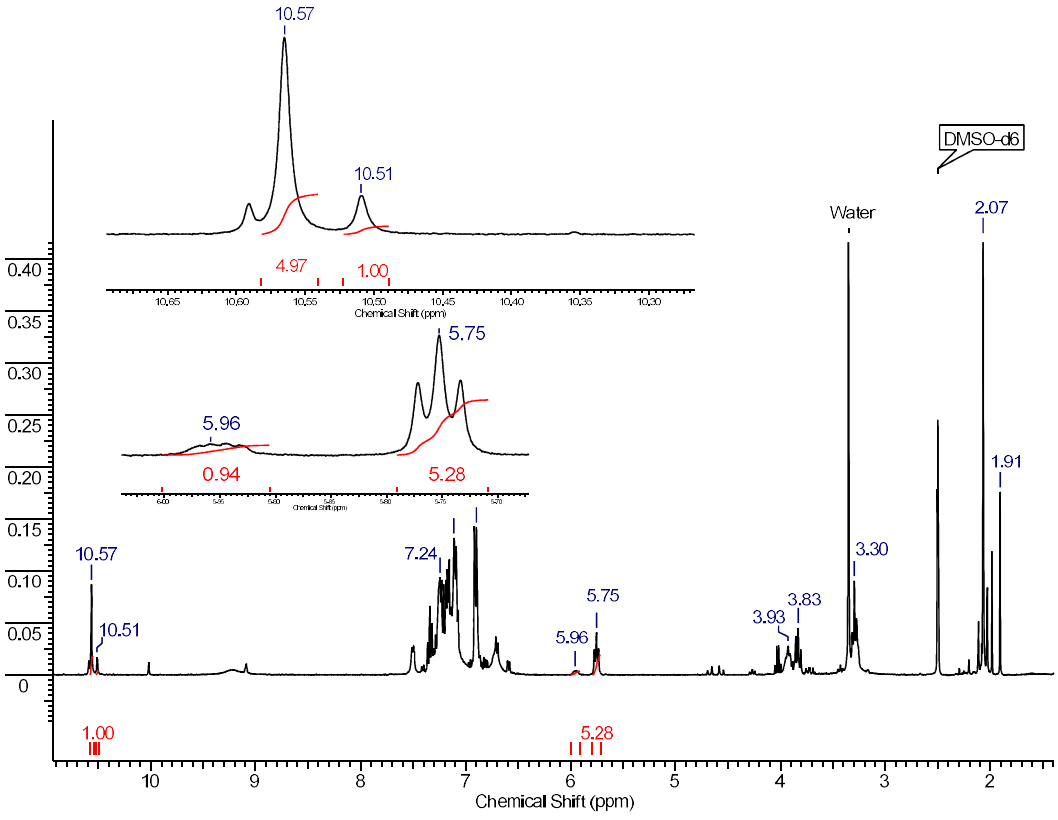
(2'*S,3'*R**,4'*R**)-1-[(*S**)-1,2-Diphenylethyl]-1'-methyl-4'-phenyl-2-thiooxodispiro-[imidazolidine-4,3'-pyrrolidine-2',3"-indoline]-2",5-dione (4d).**

Using thiohydantoin **3d** (192 mg, 0.5 mmol), sarcosine (178 mg, 2 mmol) and isatin (294 mg, 2 mmol), 125 mg of a mixture of diastereomers was obtained (total yield 45%, *dr* = 5.0). The resulting mixture was recrystallized to give 70 mg (25%) of dispiroindolinone **4d**, m.p. 192-193 ºC.

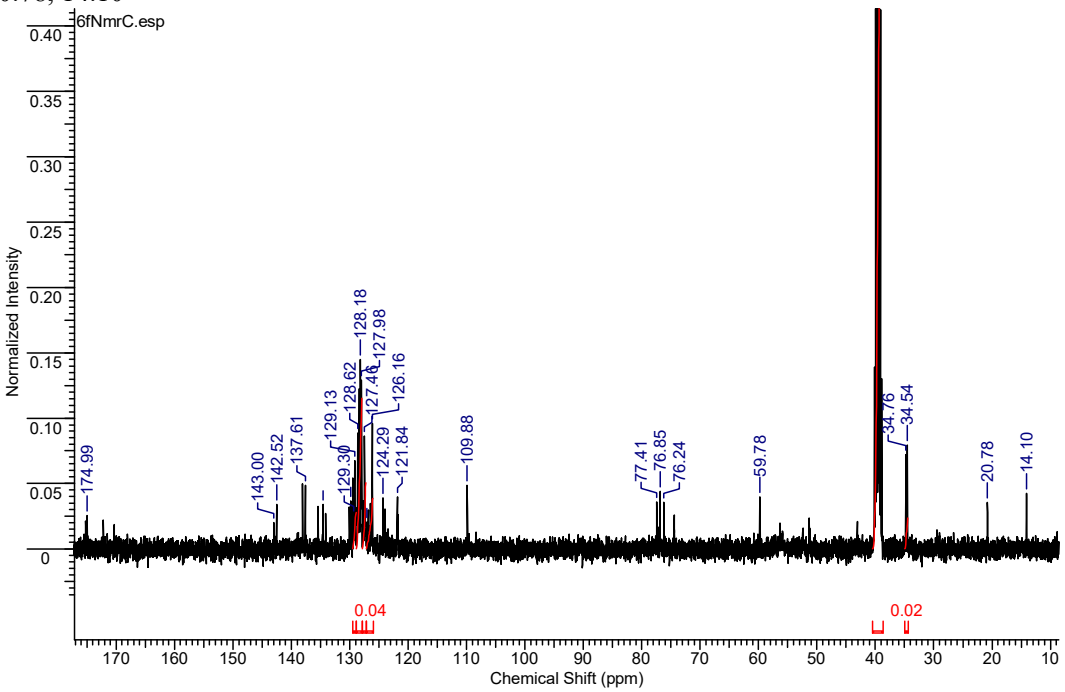
^{1}H NMR (DMSO-d$_6$, 400 MHz, δ, ppm): 10.56(s., 1H, NH), 9.17(br.s., 1H, NH), 7.50(d.,, J=7.0 Hz, 1H, ArH), 7.04-7.37(m., 13H, ArH), 6.90(d., J=7.6Hz, 3H, ArH), 6.70(d., J=7.8Hz, 2H, ArH), 5.75(t., J=7.6Hz, 1H, Ph-CH-CH$_2$-Ph), 3.92(m., 1H), 3.83(t., J=8.9Hz, 1H), 3.44(m., 1H, CH^1-Ar), 3.25-3.31(m., 2H, CH^2-Ar + 4-pyrrolidine), 2.07(s., 3H, NCH$_3$)



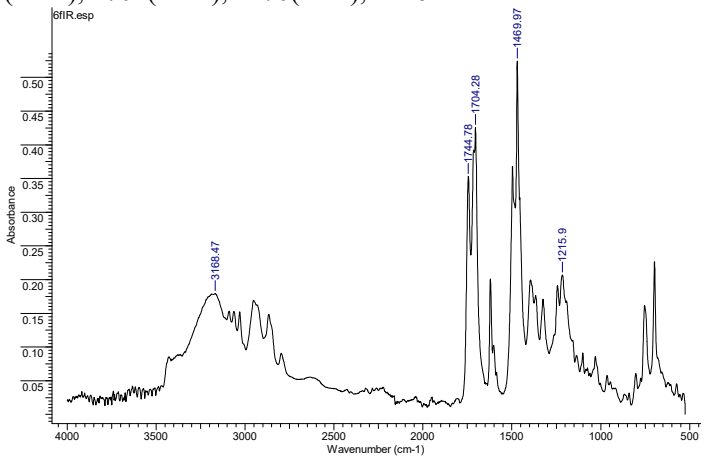
Reaction mixture of stereoisomers **4d**+**4'd** (*dr* = 5.0):



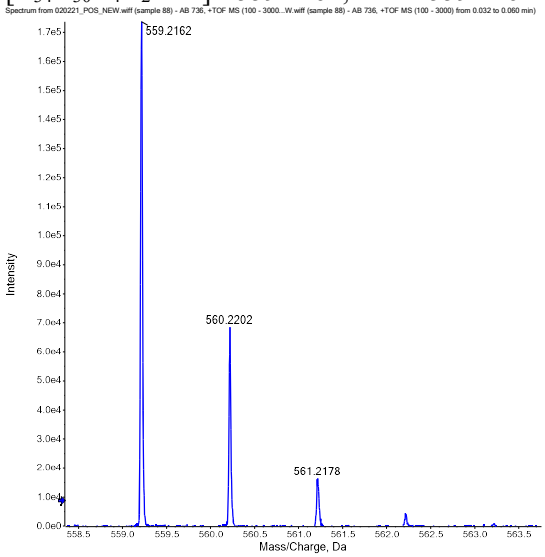
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 174.99, 143.00, 142.52, 137.61, 134.56, 129.84, 129.30, 129.13, 128.62, 128.18, 127.98, 127.46, 127.05, 126.16, 124.29, 121.84, 109.88, 77.41, 76.85, 76.24, 59.78, 34.76, 34.54, 20.78, 14.10



IR (KBr, ν(cm^{-1})): 1745 (C=O), 1704(C=O), 1470(C=S), 1216



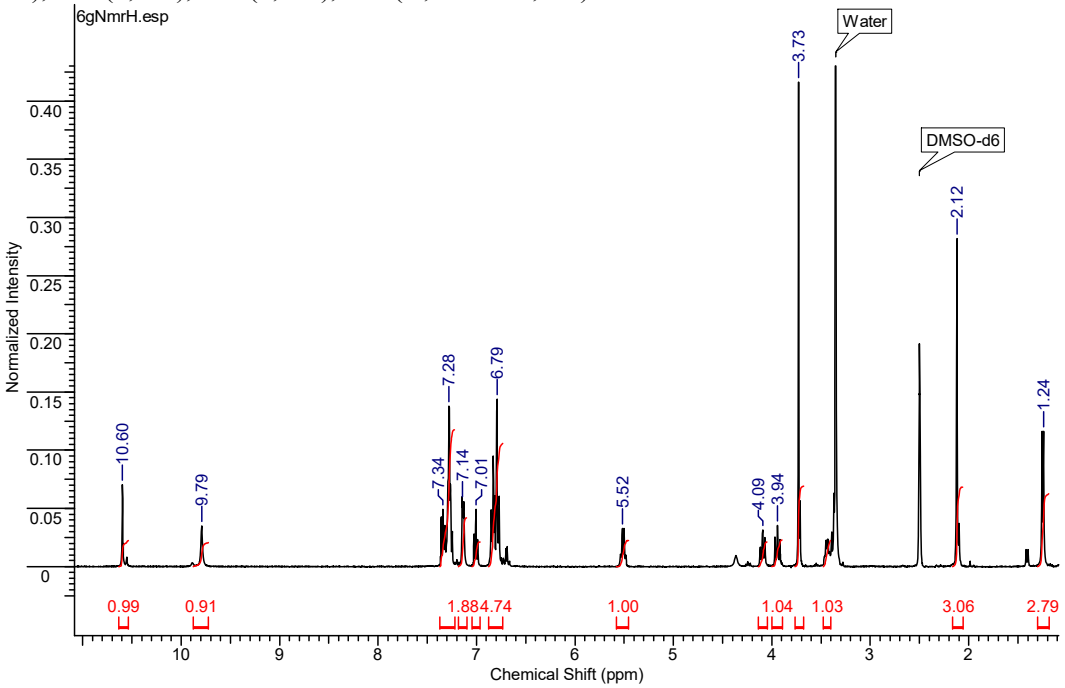
HRMS-ESI: m/z calculated for $[C_{34}H_{30}N_4O_2S+H]^+$: 559.2162; found 559.2162



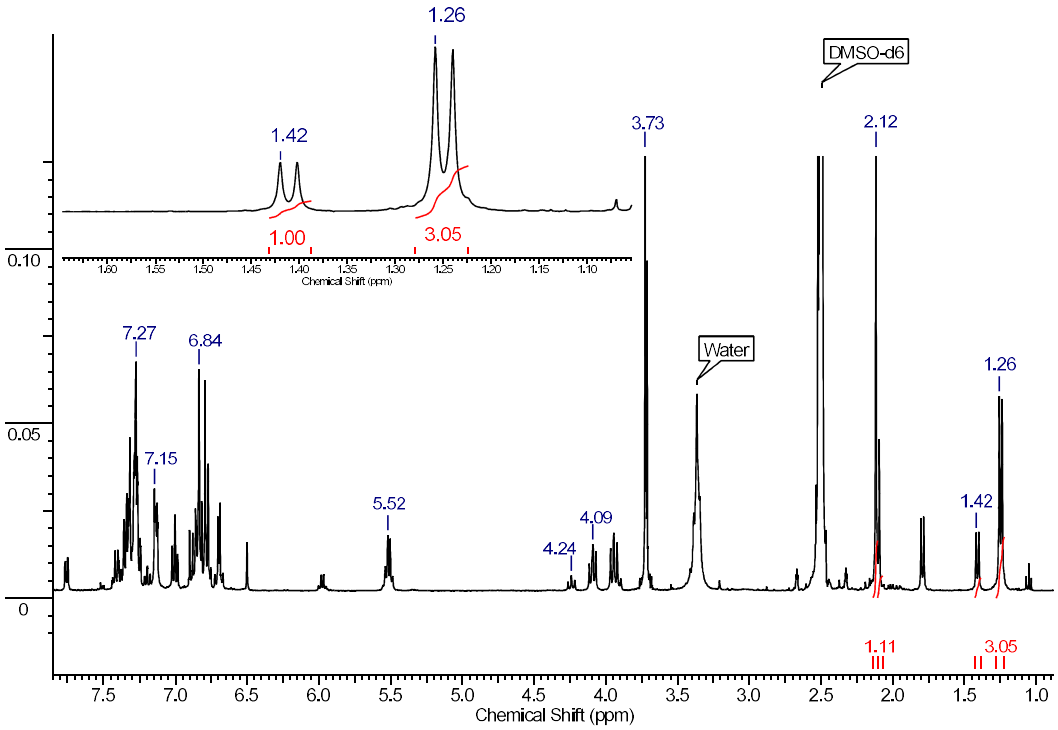
(2'*S,3'*R**,4'*R**)-1-[(*S**)-1-(4-Methoxyphenyl)ethyl]-1'-methyl-4'-phenyl-2-thiooxo-dispiro[imidazolidine-4,3'-pyrrolidine-2',3"-indoline]-2",5-dione (4e).**

Using thiohydantoin **3e** (169 mg, 0.5 mmol), sarcosine (178 mg, 2 mmol) and isatin (294 mg, 2 mmol), 154 mg of a mixture of diastereomers was obtained (total yield 60%, *dr* = 3.0). The resulting mixture was purified by recrystallization to give 56 mg (22%) of dispiroindolinone **4e**, m.p. 201-203 ºC.

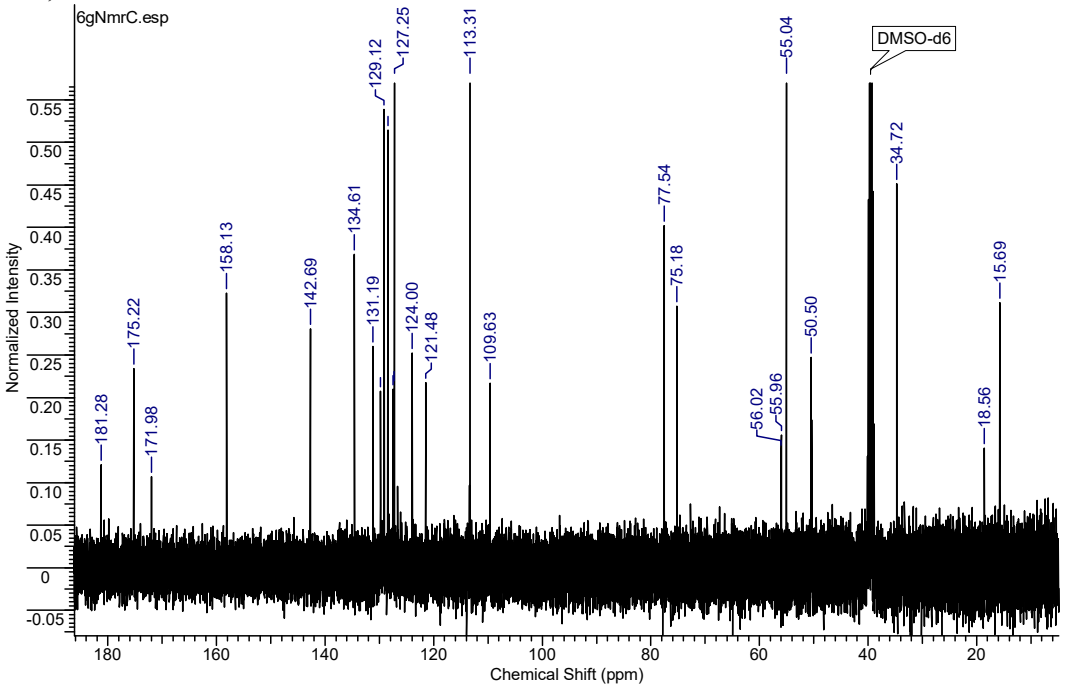
^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm): 10.60 (s., 1H), 9.79(s., 1H), 7.23-7.38(m., 5H), 7.10-7.18 (m., 2H), 7.01(t., J=7.5Hz, 1H), 6.70-6.88(m., 5H), 5.51(q., J = 7.1Hz, 1H), 4.09(t., J=10Hz, 1H), 3.94(t., J=9.8Hz, 1H), 3.73(s., 1H), 3.39(t., 1H), 2.12(t., 3H), 1.25(d., J=7.2Hz, 3H).



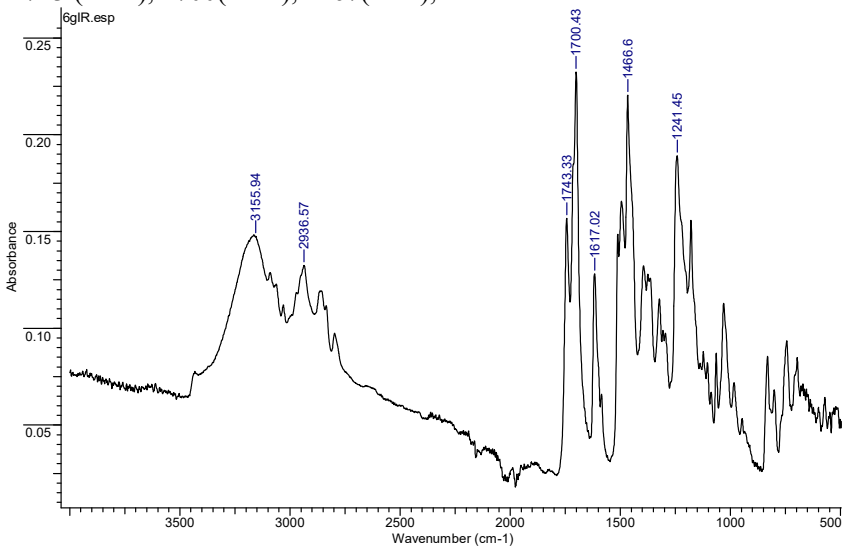
Reaction mixture of stereoisomers **4e**+**4'e** (*dr* = 3.0):



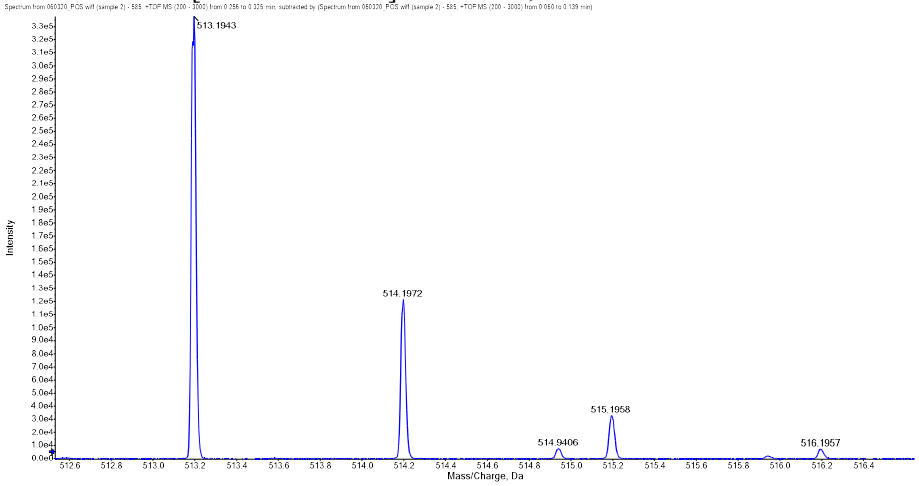
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 181.28, 175.22, 171.98, 158.13, 142.69, 134.61, 131.19, 129.80, 129.12, 128.41, 127.51, 127.31, 127.25, 124.00, 121.48, 113.31, 109.63, 77.54, 75.18, 56.02, 55.04, 50.50, 34.72, 18.56, 15.69



IR (KBr, ν(cm^{-1})): 1743 (C=O), 1700(C=O), 1467(C=S), 1241



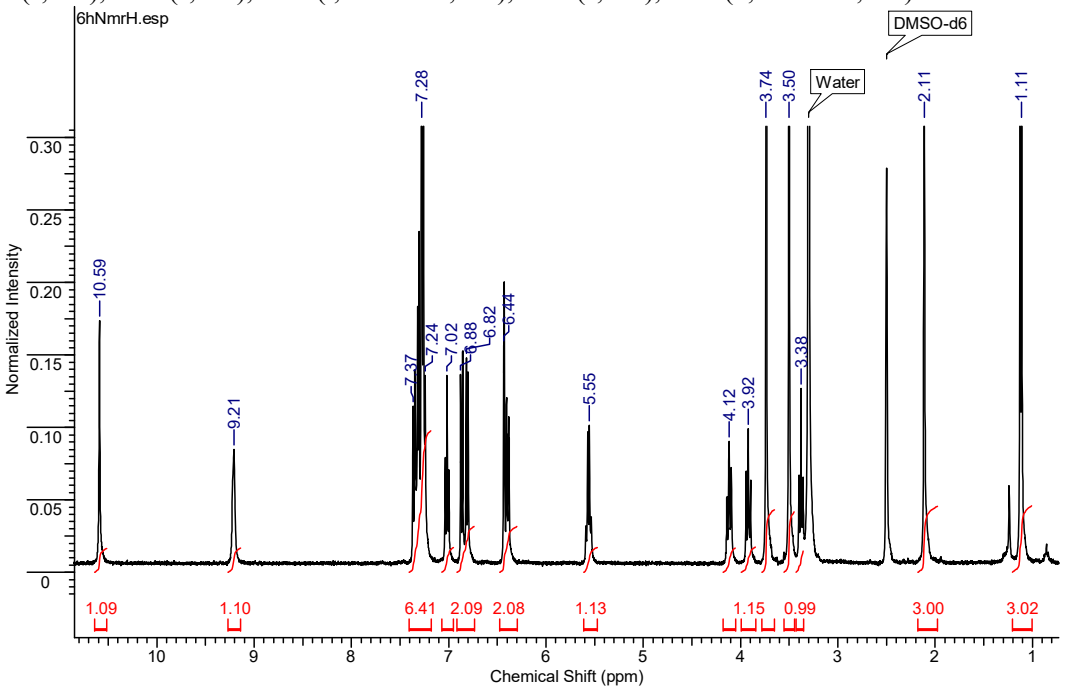
HRMS-ESI: m/z calculated for $[C_{29}H_{28}N_4O_3S+H]^+$: 513.1955; found 513.1943



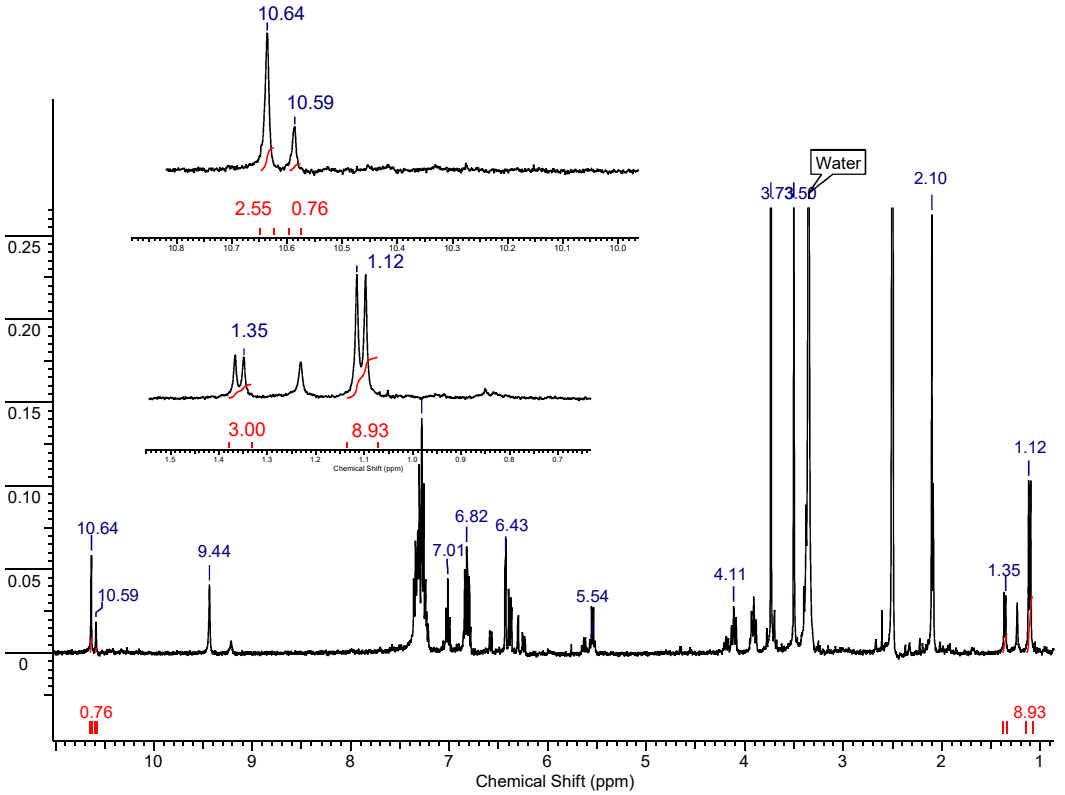
(2'*S,3'*R**,4'*R**)-1-[(*S**)-1-(2,4-Dimethoxyphenyl)ethyl]-1'-methyl-4'-phenyl-2-thiooxo-dispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (4f).**

Using thiohydantoin **3f** (184 mg, 0.5 mmol), sarcosine (178 mg, 2 mmol) and isatin (294 mg, 2 mmol), 212 mg of a mixture of diastereomers was obtained (total yield 78%, *dr* = 3.0). The resulting mixture was purified by column chromatography to give 157 mg (58%) of dispiroindolinone **4f**, m.p. 213-215 °C.

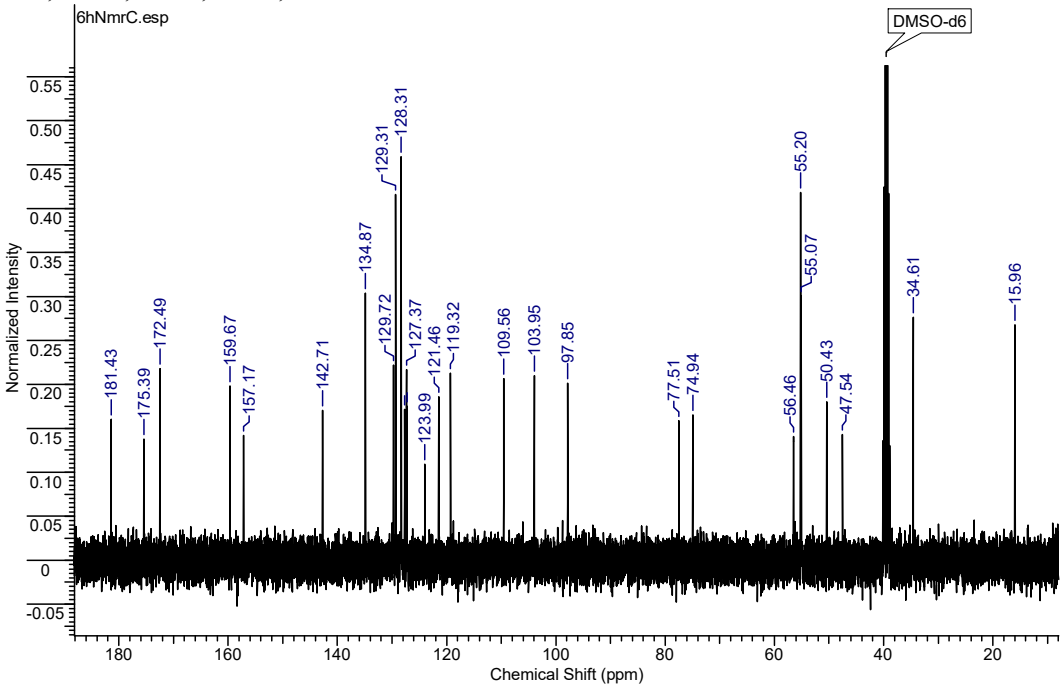
^{1}H NMR (DMSO-d$_6$, 400 MHz, δ, ppm): 10.59 (s, 1H), 9.21 (s, 1H), 7.20-7.38 (m, 5H), 7.02 (t, J=7.4 Hz, 1H), 6.78-6.90 (m, 2H), 6.35-6.45 (m, 2H), 5.56 (q, J=7.4 Hz, 1H), 4.12 (t, J = 9.8 Hz, 1H), 3.92 (t, J=9.0 Hz, 1H), 3.74 (s, 3H), 3.50 (s, 3H), 3.38 (t, J=8.6 Hz, 1H), 2.11 (s, 3H), 1.12 (d, J=7.4Hz, 3H)



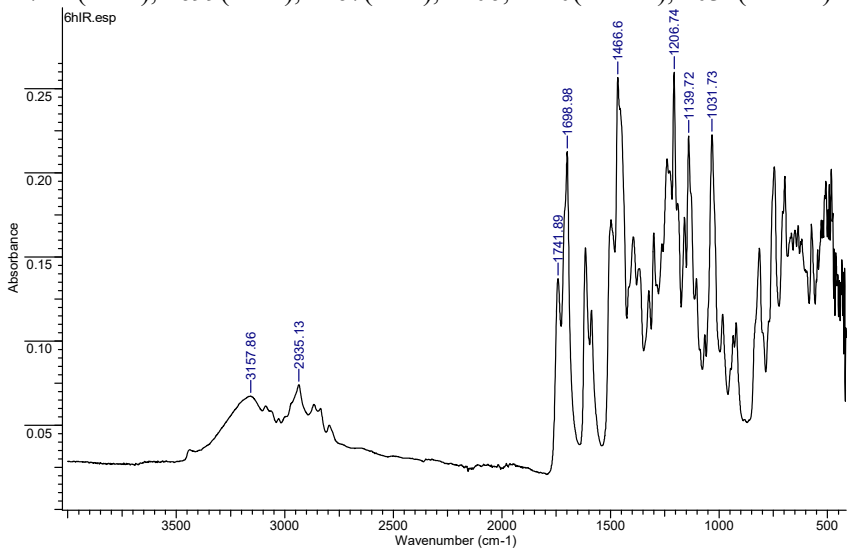
Reaction mixture of stereoisomers **4f**+**4'f** (*dr* = 3.0):



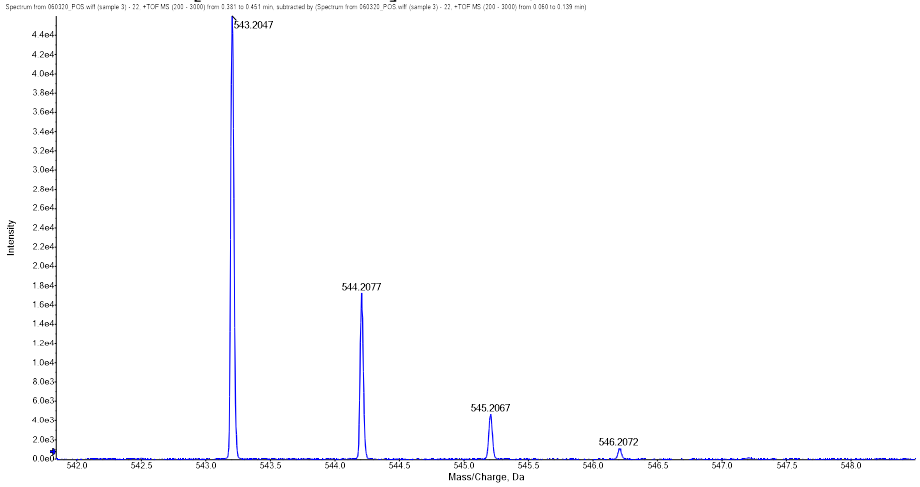
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 181.43, 175.39, 172.49, 159.67, 157.17, 142.71, 134.87, 129.72, 129.31, 128.31, 127.71, 127.37, 127.27, 123.99, 121.46, 119.32, 109.56, 103.95, 97.85, 77.51, 74.94, 56.46, 55.20, 55.07, 50.43, 47.54, 34.61, 15.96



IR (KBr, ν(cm^{-1})): 1742 (C=O), 1699(C=O), 1467(C=S), 1206, 1140(C-O-C), 1032(C-O-C)



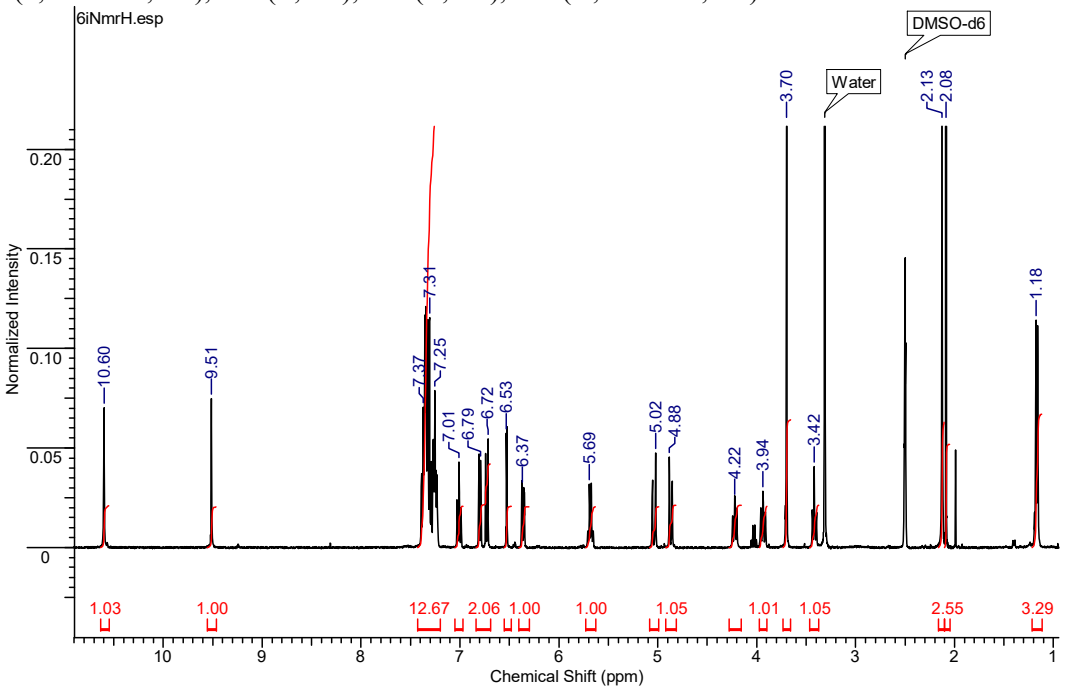
HRMS-ESI: m/z calculated for $[C_{30}H_{30}N_4O_4S+H]^+$: 543.2061; found 543.2047



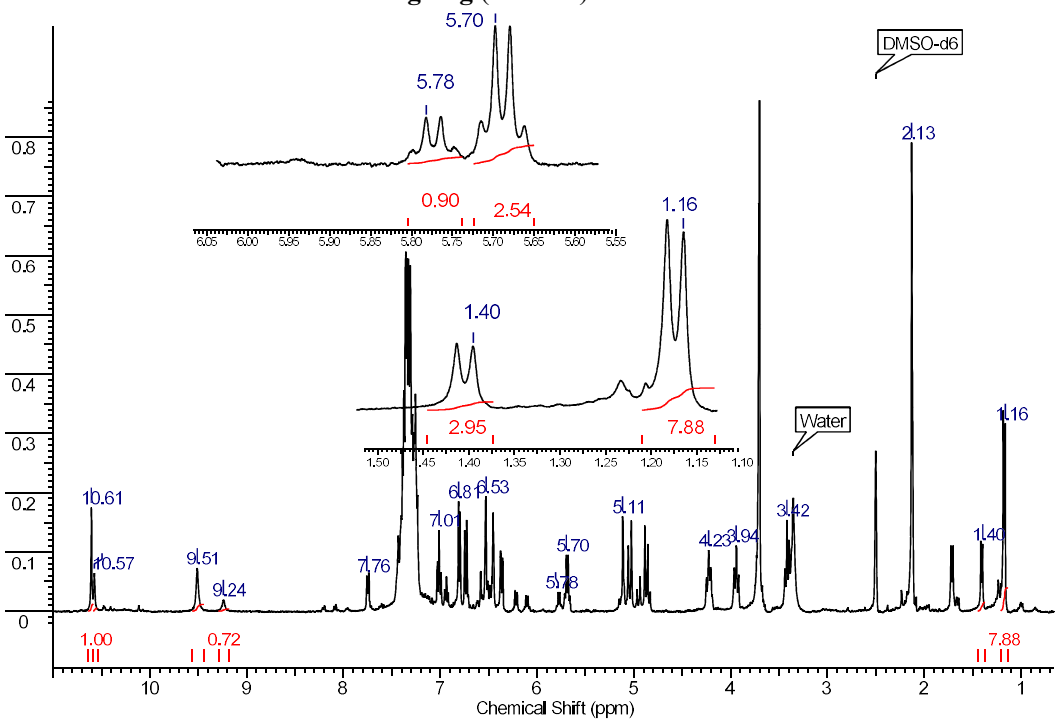
(2'*S,3'*R**,4'*R**)-1-[(*S**)-1-(2-Benzyloxy-4-methoxyphenyl)ethyl]-1'-methyl-4'-phenyl-2-thiooxodispiro[imidazolidine-4,3'-pyrrolidine-2',3"-indoline]-2",5-dione (4g).**

Using thiohydantoin **3g** (222 mg, 0.5 mmol), sarcosine (178 mg, 2 mmol) and isatin (294 mg, 2 mmol), 225 mg of a mixture of diastereomers was obtained (total yield 73%, *dr* = 2.8). The resulting mixture was purified by column chromatography to give 151 mg (49%) of dispiroindolinone **4g**, m.p. 211-213 ºC.

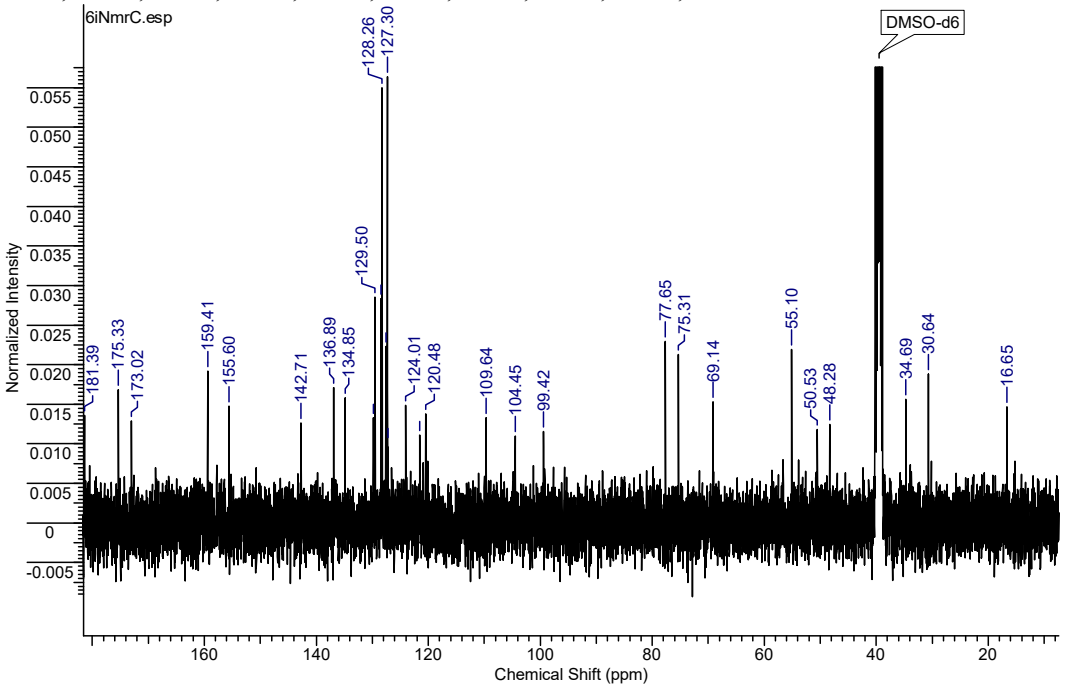
^{1}H NMR (DMSO-d$_6$, 400 MHz, δ, ppm): 10.60(s., 1H), 9.51(s., 1H), 7.22-7.40(m., 12H), 7.01(t., J=7.6Hz, 1H), 6.80(d., J=7.6Hz, 1H), 6.73 (d., J=8.5Hz, 1H), 6.49-6.52(m., 1H), 6.32-6.39(m., 1H), 5.68(q., J=7.2Hz, 1H), 5.03(d., J=12.5Hz, 1H), 4.87(d., J=12.4Hz, 1H), 4.22(t., J=8.6Hz, 1H), 3.94(t., J=9.1Hz, 1H), 3.70(s., 3H), 3.42(t., J=8.6Hz, 1H), 2.13(s., 3H), 2.08(s., 3H), 1.17(d., J=7.2Hz, 3H)



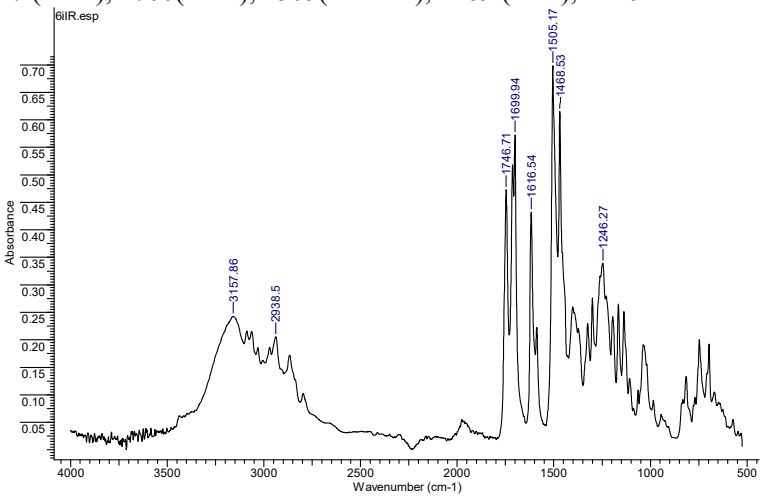
Reaction mixture of stereoisomers **4g**+**4'g** (*dr* = 2.8):



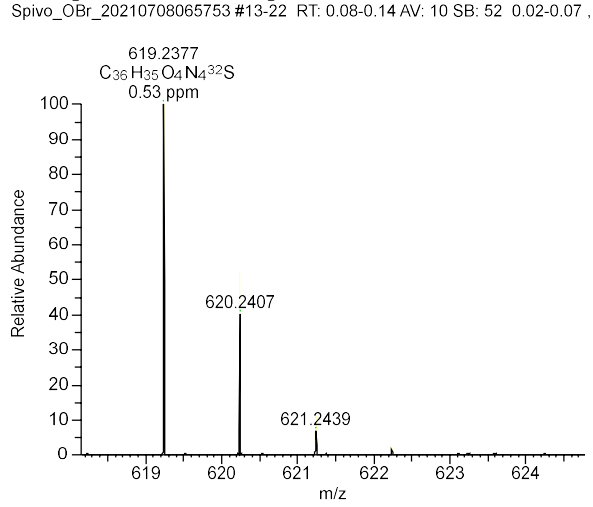
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 181.39, 175.33, 173.02, 159.41, 155.60, 142.71, 136.89, 134.85, 129.81, 129.50, 128.41, 128.26, 127.57, 127.51, 127.30, 127.25, 127.22, 124.01, 121.49, 120.48, 109.64, 104.45, 99.42, 77.65, 75.31, 69.14, 55.10, 50.53, 48.28, 34.69, 30.64, 16.65



IR (KBr, ν(cm^{-1})): 1747 (C=O), 1700(C=O), 1505(C-O-Ar), 1469 (C=S), 1246



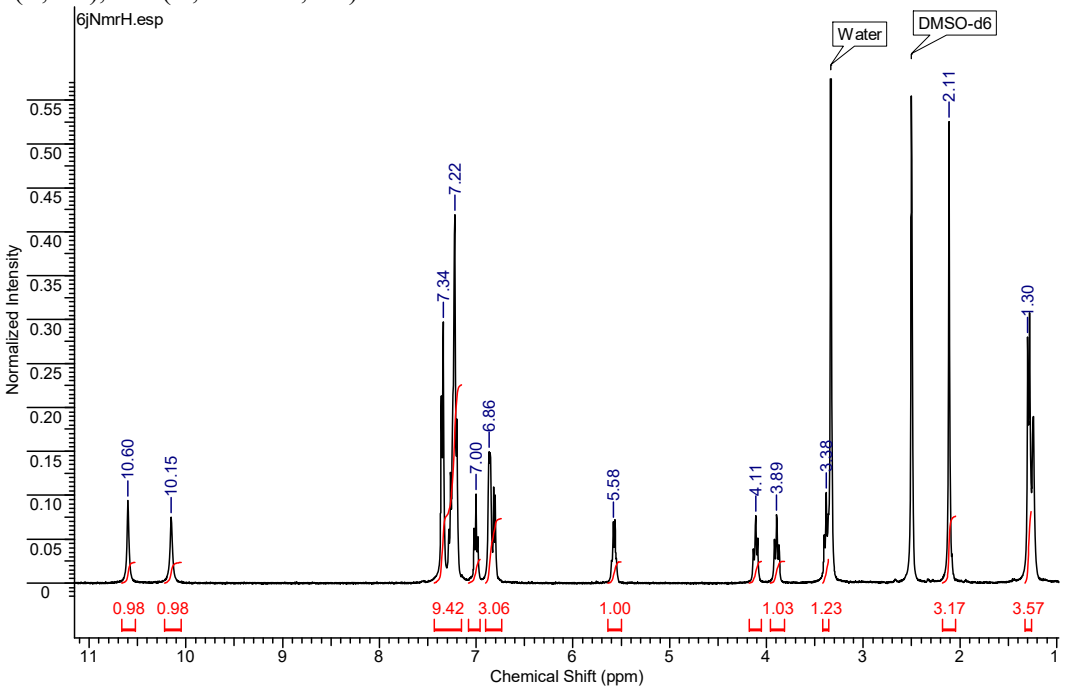
HRMS-ESI: m/z calculated for $[C_{36}H_{34}N_4O_4S+H]^+$: 619.2374; found 619.2377



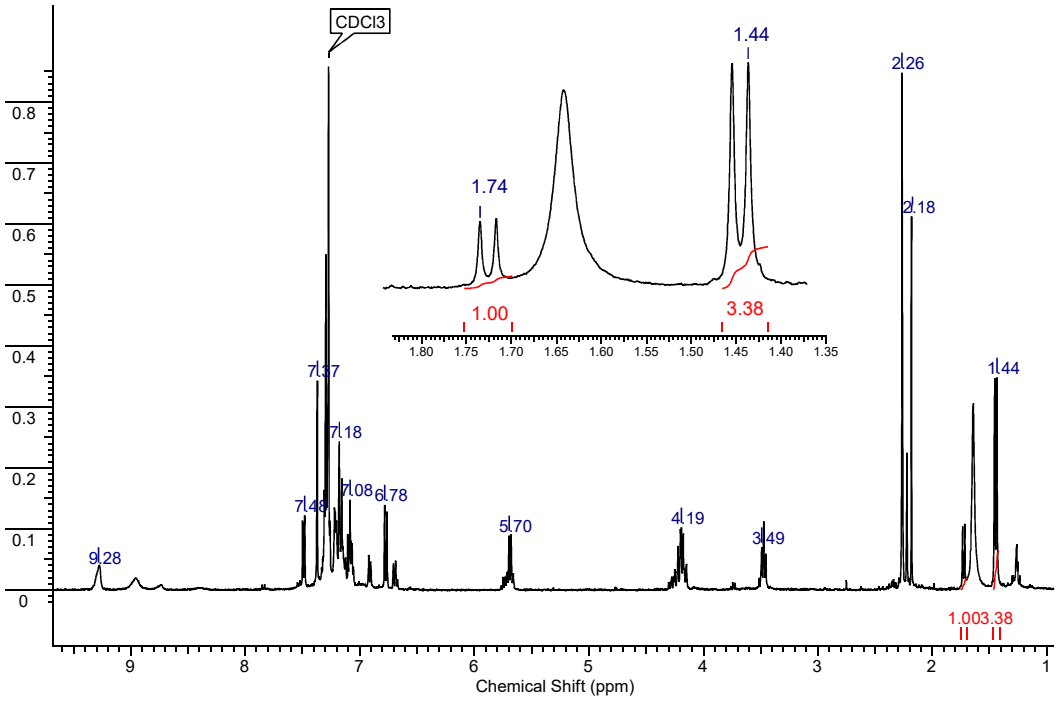
(2'*S,3'*R**,4'*R**)-1-[(*S**)-1-Phenylethyl]-1'-methyl-4'-(4-chlorophenyl)-2-thioxo-dispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (4h)**

Using thiohydantoin **3h** (171 mg, 0.5 mmol), sarcosine (178 mg, 2 mmol) and isatin (294 mg, 2 mmol), 178 mg of a mixture of diastereomers was obtained (total yield 69%, *dr* = 3.4). The resulting mixture was purified by recrystallization to give 54 mg (21%) of dispiroindolinone **4h**, m.p. 187-189 ºC.

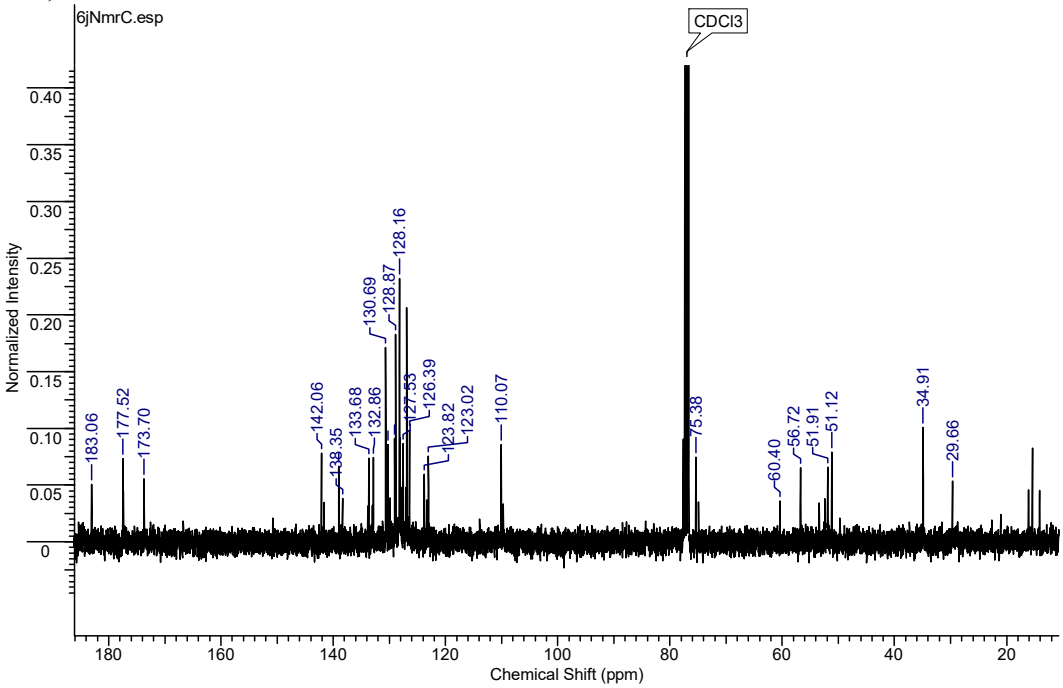
^{1}H NMR (DMSO-d$_6$, 400 MHz, δ, ppm): 10.60(s., 1H), 10.15(s., 1H), 7.14-7.40(m., 9H), 7.00(t., J=7.4Hz, 1H), 6.77-6.90(m., 3H), 5.58(q., J=7.2Hz, 1H), 4.11(t., J=9.4Hz, 1H), 3.89(t., J=9.4Hz, 1H), 3.38(t., J=8.5Hz, 1H), 2.11(s., 3H), 1.29(d., J=7.1Hz, 3H)



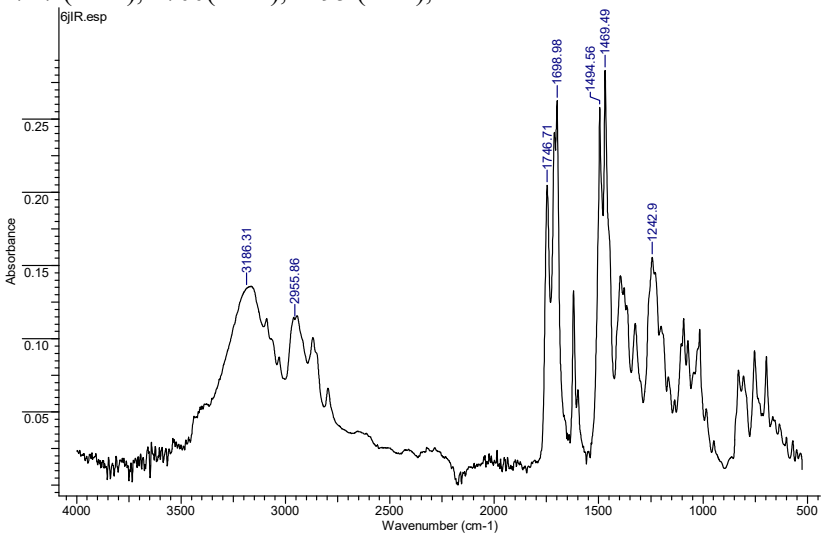
Reaction mixture of stereoisomers **4h**+**4'h** (*dr* = 3.4):



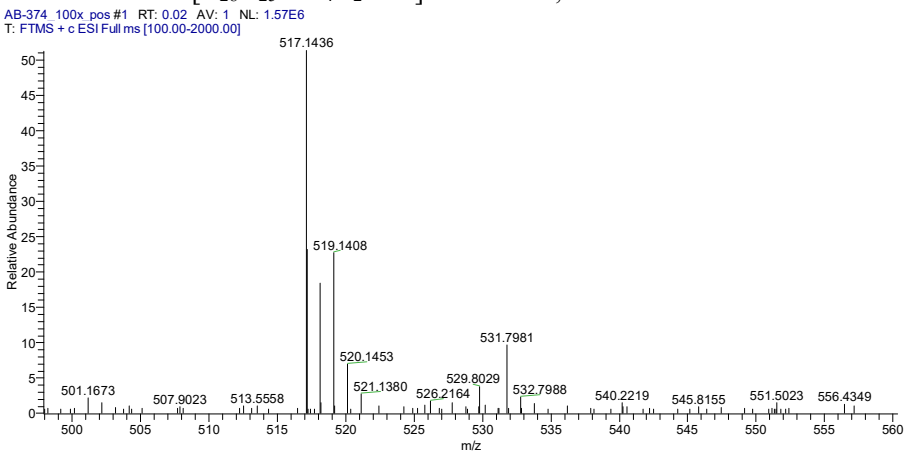
^{13}C NMR (DMSO-d_6, 101 MHz, δ, ppm): 183.06, 177.52, 173.70, 142.06, 139.00, 138.35, 133.68, 132.86, 130.69, 130.25, 129.07, 128.87, 128.16, 127.53, 126.39, 123.82, 123.02, 110.07, 75.38, 60.40, 56.72, 51.91, 51.12, 34.91, 29.66



IR (KBr, ν(cm^{-1})): 1747 (C=O), 1700(C=O), 1495 (C=S), 1242



HRMS-ESI: m/z calculated for $[C_{28}H_{25}ClN_4O_2S+H]^+$: 517.1460; found 517.1436



X-ray crystallography for 4h

Table S3. Crystal data and structure refinement for **4h**.

Empirical formula	C28H25 Cl N4 O2 S	
Formula weight	517.03	
Temperature	293(2) K	
Wavelength	1.54186 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.0648(3) Å	α= 90°.
	b = 22.4610(10) Å	β= 90°.
	c = 29.5280(10) Å	γ = 90°.
Volume	6012.0(4) $Å^3$	
Z	8	
Density (calculated)	1.142 Mg/m^3	
Absorption coefficient	2.002 mm^{-1}	
F(000)	2160	
Theta range for data collection	3.936 to 60.788°.	
Index ranges	-10<=h<=3, -25<=k<=25, -32<=l<=33	
Reflections collected	36023	
Independent reflections	8965 [R(int) = 0.2065]	
Completeness to theta = 60.788°	99.1 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8965 / 60 / 629	
Goodness-of-fit on F^2	0.565	
Final R indices [I>2sigma(I)]	R1 = 0.0536, wR2 = 0.0855	
R indices (all data)	R1 = 0.2099, wR2 = 0.1147	
Absolute structure parameter	0.01(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.181 and -0.178 $e.Å^{-3}$	