Exploring Symmetry-Based Logic for a Synthesis of Palau'amine

*Qingyi Li, Paul Hurley, Hui Ding, Andrew G. Roberts, Radha Akella and Patrick G. Harran**

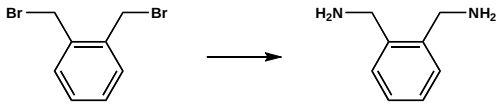
Department of Chemistry and Biochemistry
University of California Los Angeles
607 Charles E. Young Drive East
Los Angeles, CA 90095-1569
And
Department of Biochemistry
University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Blvd
Dallas, Texas 75390-9038

SUPPORTING INFORMATION

Experimental

Unless stated otherwise, reactions were performed under an argon atmosphere in flame-dried glassware. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), toluene (C_7H_8), benzene (C_6H_6) and acetonitrile (CH_3CN) were passed through Glass Contour solvent drying systems prior to use. Chemical reagents were obtained from commercial sources and used without further purification. Column chromatography was performed on silica gel 60 (240-400 mesh). Thin layer chromatography and preparative layer chromatography utilized pre-coated plates (silica gel 60 PF254, 0.25mm or 0.5mm).

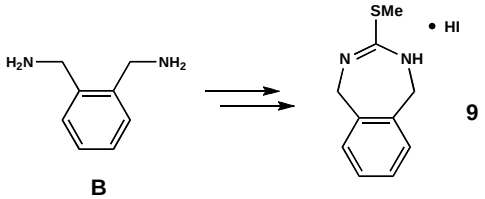
o-Xylylene diamine (B)



B

To a solution of *o*-xylylene dibromide (100 g, 378 mmol) in THF (1.3 L), EtOH (1 L) and H_2O (0.33 L) was added NaN_3 (53.7 g, 826 mmol) in H_2O (0.33 L). The solution was heated at reflux for 1 h. After cooling to rt, PPh_3 (248 g, 947 mmol) was added in small portions. When the evolution of N_2 (g) ceased, the solution was heated at reflux for 2h. Upon cooling to rt and standing overnight, needle shaped crystals had formed, which partially dissolved with the addition of 100 mL H_2O. Solid NaOH was added to the aqueous solution until a pink oily layer appeared. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The slightly pink oil obtained was used without further purification.

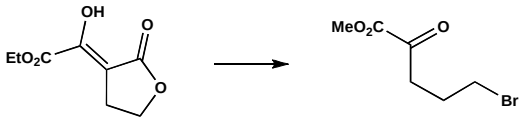
2, 5-Dihydro-3-(methylthio)-1*H*-2,4-benzodiazepine hydroiodide (9)



B 9

These procedures were carried out as described in Elslager, E.; Worth, D. F.; Haley, N. F.; Perricone, S. C. *J. Heterocycl. Chem.* **1968**, 5, 609-613.

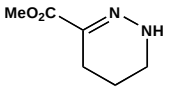
Methyl 5-bromo-2-oxopentanoate (7)



C **7**

A solution of lactone **C** (46.6 g, 249 mmol – prepared according to Cushman, M.; Gerhardt, S.; Huber, R.; Fischer, M.; Kis, K.; and Bacher, A. *J. Org. Chem.* **2002**, *67*, 5807–5816. Note: the EtOH used was freshly distilled from Mg turnings) in 30% HBr/AcOH (150 mL) was heated at 110°C for 2h. An additional 100 mL of 30% HBr/HOAc was added and the reaction maintained at 110°C for 14h. The mixture was concentrated *in vacuo* to afford a brown oil that was dissolved in 250 mL MeOH. Concentrated aqueous H_2SO_4 (0.5 mL) was added and the solution stirred at rt for 14h. The reaction was concentrated and the incipient residue dissolved in Et_2O. Saturated aqueous $NaHCO_3$ was carefully added until gas evolution ceased. The organic layer was separated and washed with H_2O and dried over Na_2SO_4. Concentration *in vacuo* provided a brown oil that was used without further purification.

Methyl-1,4,5,6-tetrahydro-3-pyridazinecarboxylate (D)

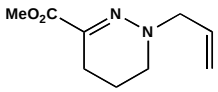


16

Hydrazine hydrate (20.4 g, 398 mmol) was dissolved in a mixture of MeOH (300 mL) and water (37.5 mL). Glacial AcOH (7 mL) was added and the solution cooled in an ice-bath. A solution of crude **7** in MeOH (50 mL) was added over 30 min wherein a white precipitate formed. The ice-bath was removed wherein the solids dissolved. The pH of the mixture was maintained between 4 and 7 with 3M aq K_2CO_3. After the pH had stabilized at rt, the reaction was immersed into an oil-bath pre-heated to 60 °C and 3M aq K_2CO_3 was used to adjust the pH to ~5. The reaction was heated at 60 °C for 1 h at which time the pH was 6. After removing MeOH *in vacuo*, the residue was dissolved in a minimum amount of water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated to afford a solid that was recrystallized from EtOAc to afford **16** (42.5 g, 81%).

16: colorless crystals [m.p. 72 °C]; R_f = 0.5 (2:3 EtOAc/CH_2Cl_2); IR (film): 3200, 2957, 1694, 1588, 1442, 1303, 1237, 1190, 115, 972, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.1-5.9 (bs, 1H), 3.78 (s, 3H), 3.23 (t, 2H, *J* = 5.2 Hz), 2.45 (t, 2H, *J* = 6.8 Hz,), 2.02-1.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 132.0, 52.1, 41.9, 21.2, 17.6. MS (positive electrospray) calcd for $(C_6H_{10}N_2O_2+H)^+$: 143.07; found: 143.06.

Methyl-1-allyl-1,4,5,6-tetrahydro-3-pyridazinecarboxylate (E)

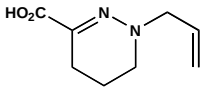


E

A solution of **16** (5.2 g, 35.9 mmol) in THF (180 mL) was cooled to −30 °C. KHMDS (0.5 M in toluene, 73.3 mL) was added over 5 min. The reaction was stirred for 10 min before adding allyl bromide (3.8 mL, 43.2 mmol). The reaction was stirred at −25 °C for 1h, quenched with MeOH, warmed to rt, and filtered through a pad of Celite. Concentration *in vacuo* followed by flash chromatography on silica gel (3:7 EtOAc/hexanes) afforded **E** (5.88 g, 90%) as colorless solid.

E: R_f= 0.5 (1:1 EtOAc/Hexanes); IR (film): 3079, 2925, 2844, 1700, 1562, 1439, 1261, 1108, 983, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.88-5.80 (m, 1H), 5.21 (tdd, 2H, *J* = 6.2, 10.1, 16.5 Hz), 4.01-3.95 (m, 2H), 3.78 (s, 3H), 3.08-3.02 (m, 2H), 2.39 (t, 2H, *J* = 6.7 Hz), 1.98-1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 133.5, 129.5, 118.1, 61.3, 51.7, 44.6, 20.3, 17.6. MS (positive electrospray) calcd for $(C_9H_{14}N_2O_2+ H)^+$: 183.11; found: 183.11.

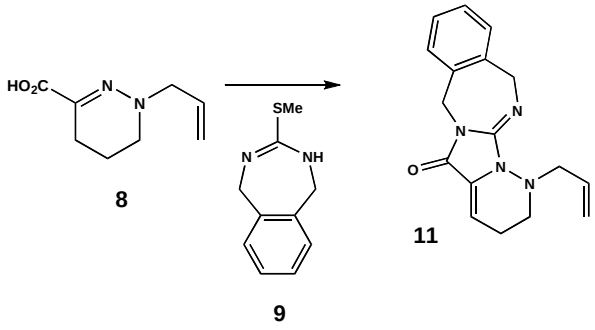
1-Allyl-1,4,5,6-tetrahydro-3-pyridazinecarboxylic acid (8)



8

Solid LiOH (0.78 g, 32.7 mmol) was added to a solution of ester **E** (5.4 g, 29.7 mmol) in THF/MeOH/H_2O (40 mL/15 mL/20 mL). The resultant solution was stirred at rt for 3h and then neutralized with 10% aq citric acid. The solvents were removed *in vacuo* and the residue dissolved in EtOAc. The solution was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated. The crude acid was pure by ^1H NMR and was used in the next step without purification.

Heterocycle 11

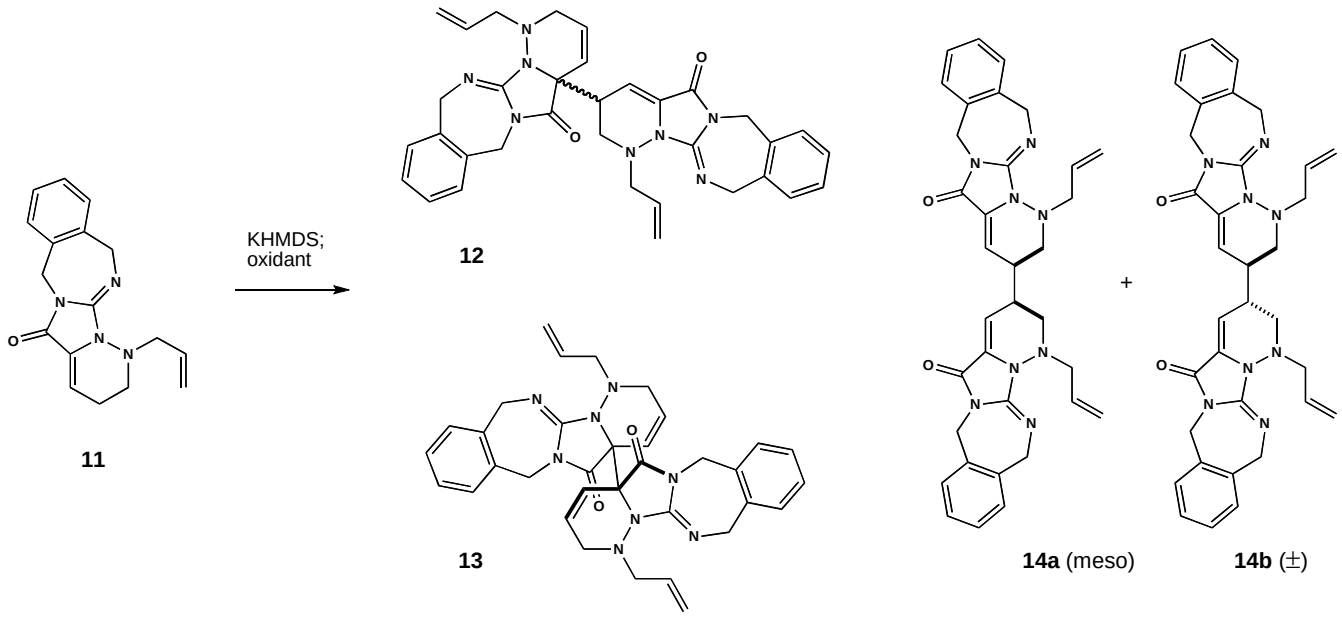


8 **9** **11**

TBTU (0.27 g, 0.84 mmol) was added to a portion of crude **8** (0.14 g, 0.94 mmol) and **9** (0.3 g, 0.94 mmol) in DMF (4.5 mL). i-Pr_2NEt (0.44 mL, 2.51 mmol) was added and the resultant yellow solution stirred at rt for 2 h. The mixture was placed under house vacuum and heated at 70°C overnight. The residue was dissolved in 20 mL EtOAc and washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (4:1 EtOAc/hexanes) provided **11** (0.173 g, 71%) as a light brown solid.

11: R_f = 0.45 (2:3 EtOAc/CH_2Cl_2); IR (film): 3411, 2947, 1734, 1620, 1451, 1409, 1180, 1013, 761, 667 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.40-7.25 (m, 4H), 5.87 (tdd, 1H, *J* = 6.7, 10.2, 17 Hz), 5.7 (t, 1H, *J* = 4.6 Hz), 5.20 (d, 1H, *J* = 17.2 Hz), 5.11 (d, 1H, *J* = 10.1 Hz), 4.94, (s, 2H), 4.65 (s, 2H), 3.33 (d, 2H, *J* = 6.6 Hz), 2.92 (t, 2H, *J* = 5.5 Hz), 2.21 (dd, 2H, *J* = 5.3, 10.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 158.8, 141.0, 140.1, 134.2, 133.6, 128.3, 128.0, 127.9, 127.5, 127.1, 118.7, 101.7, 56.0, 48.2, 44.8, 42.2, 16.2. HRMS (ESI-TOF) calcd for $(C_{17}H_{18}N_4O+H)^+$: 295.1553; found: 295. 1565.

Regioisomeric dimerization products 12, 13 and 14



Procedure A: I_2 as oxidant

The THF used in this reaction was degassed via the freeze-pump-thaw method prior to use. Monomer **11** (1.03 g, 3.51 mmol) was dissolved in THF (10 mL) and cooled to -78°C. This solution was added via cannulating needle to a flask containing KHMDS (7.38 mL, 0.5M in toluene) at –78°C and the resulting dark red mixture was stirred at –78°C for 30 minutes. A solution of I_2 (0.445 g, 1.76 mmol) in THF (0.5 mL) was then added and the reaction was stirred at -78°C for 3 h. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography (4:1 EtOAc/hexanes) to afford 485 mg (47%) of α,α dimer **13** and 250 mg (24%) of α,γ dimers **12**.

13: light pink solid; R_f = 0.75 (EtOAc); IR (film): 3412, 1743, 1671, 1394, 1371, 1287, 1154, 1064, 968, 741, 667 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.42-7.18 (m, 8H), 5.97 (dd, 2H, *J* = 4.0, 9.9 Hz), 5.79 (d, 2H, *J* = 9.9 Hz), 5.62 (tdd, 2H, *J* = 6.2, 10.3, 12.3 Hz), 5.07 (d, 2H, *J* = 17.2 Hz), 4.92 (d, 2H, *J* = 10.3 Hz), 4.90-4.49 (m, 8H), 3.80 (d, 4H, *J* = 5.8 Hz), 3.50 (d, 2H, *J* = 16.8 Hz), 2.87 (ddd, 2H, *J* = 1.3, 5.0, 16.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.2, 168.3, 147.4, 140.9, 135.5, 135.3, 129.4, 128.7, 128.6, 128.3, 128.0, 127.8, 123.4, 122.3, 117.6, 68.3, 62.6, 62.4, 58.4, 57.7, 49.4, 49.0, 44.6, 43.6. MS (Positive electrospray) calcd for $(C_{34}H_{34}N_8O_2+H)^+$: 587.28; found: 587.25. Crystals of **13** suitable for X-ray diffraction were grown from benzene (slow evaporation). Details of the crystallographic analysis are provided in a separate CIF file.

α,γ dimers **12**: yellow solid; R_f = 0.3 (EtOAc). Two diastereomers of this material were separated by preparative thin layer chromatography (1:19 MeOH/PhH).

Diastereomer 1: yellow crystals, R_f = 0.65 (1:19 MeOH/PhH), IR (film): 3640, 2980, 1739, 1675, 1413, 1150, 820, 740, 558 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 7.40-7.22 (m, 8H), 6.05 (ddd, 1H, *J* = 1.4, 5.2, 9.9 Hz), 5.92-5.78 (m, 2H), 5.68 (dddd, 1H, *J* = 5.5, 7.2, 10.2, 17.4 Hz), 5.42 (t, 1H, *J* = 1.7 Hz), 5.24-5.03 (m, 3H), 4.91 (s, 2H), 4.90-4.88 (m, 1H), 4.81 (s, 2H), 4.78-4.61 (m, 4H), 3.99 (tdd, 1H, *J* = 1.5, 5.3, 13.8 Hz), 3.78 (dd, 1H, *J* = 7.2, 13.8 Hz), 3.69-3.50 (m, 1H), 3.48 (dd, 1H, *J* = 5.0, 13.2 Hz), 3.38-3.23 (m, 2H), 3.11 (ddd, 1H, *J* = 2.4, 5.0, 10.5 Hz), 3.01-2.92 (m, 1H), 2.28-2.25 (m, 1H); HRMS (ESI-TOF) calcd for $(C_{34}H_{34}N_8O_2+H)^+$: calcd: 587.2877; found: 587.2878. Crystals of this material suitable for X-ray diffraction were grown from a mixture of CH_2Cl_2 and CH_3CN (slow evaporation). Details of the crystallographic analysis are provided in a separate CIF file.

Diastereomer 2. Yellow solid, R_f = 0.60 (1:19 MeOH/PhH), IR (film): 3640, 2980, 1739, 1675, 1413, 1150, 820, 740, 558 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 7.40-7.21 (m, 8H), 6.08 (ddd, 1H, *J* = 1.5, 5.2, 9.9 Hz), 5.87-5.78 (m, 2H), 5.76-5.60 (m, 2H), 5.13-5.02 (m, 4H), 4.91 (s, 2H), 4.86-4.80 (m, 2H), 4.78-4.57 (m, 4H), 4.05-3.99 (m, 1H), 3.67 (ddd, 1H, *J* = 1.7, 4.9, 13.5 Hz), 3.58-3.42 (m, 1H), 3.37-2.85 (m, 5H), 2.28-2.12 (m, 1H). MS (positive electrospray) calcd for $(C_{34}H_{34}N_8O_2+H)^+$: 587.28; found: 587.25.

Procedure B. $FeCl_2(DMF)_3FeCl_4$ as oxidant

The THF used in this reaction was degassed via the freeze-pump-thaw method prior to use. Monomer **11** (0.150 g, 0.51 mmol) in THF (2.6 mL) was cooled to −78°C and added via cannulating needle to a flask containing KHMDS (1.12 mL, 0.5M in toluene) at −78°C. After stirring the resulting dark red mixture at −78 °C for 30 minutes, a solution of $[FeCl_2(DMF)_3][FeCl_4]$ (0.141 g, 0.26 mmol) in THF (0.4 mL) was added via syringe. The reaction was stirred at −78 °C for 3 hours. The reaction was quenched with pH 8.0 EDTA (3 mL). The majority of the solvent was removed *in vacuo* and the residue diluted in CH_2Cl_2. The solution was washed with pH 8.0 EDTA (0.35M, 3 x10 mL), water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (progression from 4:1 EtOAc/hexanes → EtOAc → 99:1 EtOAc/MeOH) to afford α, α dimer **13** (16 mg, 11%), α,γ dimers **12** (87 mg, 55%) and γ,γ dimers **14a**/**b** (16 mg, 11%) as orange solids.

γ, γ **dimers 14a**/**b**; R_f = 0.2 (3:7 CH_3CN: $CHCl_3$); IR (film): 3400, 1669, 1456, 1404, 1181, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.25 (m, 8H), 6.03-5.84 (m, 2H), 5.59-5.53 (m, 2H), 5.12-5.06 (m, 4H), 5.02-4.86 (m, 4H), 4.80-4.62 (m, 4H), 3.62-3.57 (m, 2H), 3.28-3.08 (m, 4H), 2.80-2.42 (m, 4H). ^{13}C NMR

(75MHz, $CDCl_3$): δ 159.7, 141.2, 140.9, 134.0, 133.2, 129.1, 128.9, 128.8, 128.7, 120.0, 119.9, 102.4, 101.8, 58.2, 58.1, 49.7, 49.3, 48.4, 29.2, 28.5. HRMS (ESI-TOF) calcd for $(C_{34}H_{34}N_8O_2+H)^+$: 587.2877; found: 587.2885.

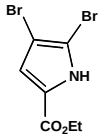
Procedure C. $Cu(OTf)_2$ as oxidant.

The THF used in this reaction was degassed via the freeze-pump-thaw method prior to use. Monomer **11** (0.20 g, 0.68 mmol) was dissolved in THF (3.4 mL) and cooled to -78°C. This solution was added via cannulating needle to a flask containing KHMDS (1.23 mL, 0.5M in toluene) at -78°C. After stirring the resulting dark red mixture at -78°C for 30 min, a solution of $Cu(OTf)_2$ (0.177 g, 0.7 mmol) in THF (0.7 mL) was added via syringe. The reaction was stirred at −78°C for 3 h and quenched with aq pH 8.0 EDTA (0.35M) solution (3 mL). The mixture was concentrated *in vacuo* and diluted in CH_2Cl_2. The solution was washed with aqueous pH 8.0 EDTA solution (3 x 10 mL), water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (progression from 4:1 EtOAc/Hexanes → EtOAc → 99:1 EtOAc/MeOH) to afford α,α dimer **13** (47 mg, 24%), α,γ dimers **12** (73 mg, 37%) and γ,γ dimers **14a/b** (50 mg, 25%) as orange solids.

Procedure D. Using [*i*-PrCp]$_2$TiCl$_2$ additive and $Cu(OTf)_2$ as oxidant.

The THF used in this reaction was degassed via the freeze-pump-thaw method prior to use. KHMDS (7.3 mL, 0.5 M in toluene) was added dropwise to a solution of **11** (0.98 g, 3.33 mmol) in THF (18 mL) at −78°C. After stirring at −78°C for 30 min, the reaction mixture was added to a solution of [*i*-PrCp]$_2$TiCl$_2$ (1.2 g, 3.53 mmol) in THF (24 mL). The reaction mixture was stirred at −78°C for 3 h before being added to a solution of $Cu(OTf)_2$ (1.97 g, 5.39 mmol) in THF (26.7 mL) at −78°C. The resulting mixture was stirred at −78°C for an additional 3.75 hours and quenched with aq pH 8.0 EDTA (0.35M) solution (20 mL). The reaction mixture was concentrated *in vacuo* and diluted in CH_2Cl_2. The solution was washed with aqueous pH 8.0 EDTA solution (3 x 50 mL), water, brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by silica gel chromatography (gradient from EtOAc to 99:1 EtOAc/MeOH) to afford **14a/b** as an orange solid (0.78 g, 80%).

4,5-Dibromo-1H-pyrrole-2-carboxylate ethyl ester (G)

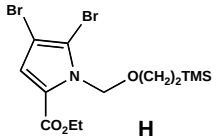


G

Sodium (0.66 g, 28.7 mmol) was dissolved in dry 180 mL EtOH. 2-(trichloroacetyl) pyrrole (50 g, 235 mmol) was added to the NaOEt solution over 10 minutes. The resultant dark red solution was stirred at rt for 40 min. The solvent was removed *in vacuo* and the residue diluted in Et_2O. The ether solution was washed with 3N HCl. The black cotton-like solid was removed by filtration. The acidic aqueous washings were extracted with ether. The combined organic layers were washed the saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a light brown solid (32.1 g, 98%) that was used without further purification.

The crude ester from the previous step was dissolved in glacial AcOH (1275 mL). A solution of bromine (23.7 mL, 462 mmol) in AcOH (272 mL) was added via addition funnel over 2 h. The resultant solution was stirred at rt for 3 h. Removal of acetic acid *in vacuo* provided a pink solid (67.6 g, 99%) that was used without further purification.

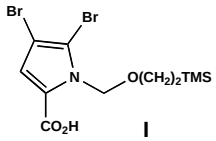
4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2-carboxylate ethyl ester (H)



H

Et_3N (38.4 mL, 274 mmol) was slowly added to a solution of **G** (67.6 g, 228 mmol) in THF (900 mL). The reaction was stirred at rt for 10 minutes and treated with SEM-Cl (38.34 g, 230 mmol). The reaction was stirred at rt for 2 h. The mixture was concentrated and the residue was taken up in CH_2Cl_2. The resulting solution was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **H** as a brown oil (94.4 g, 97%). This material was used without further purification.

4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2-carboxylic acid (I)



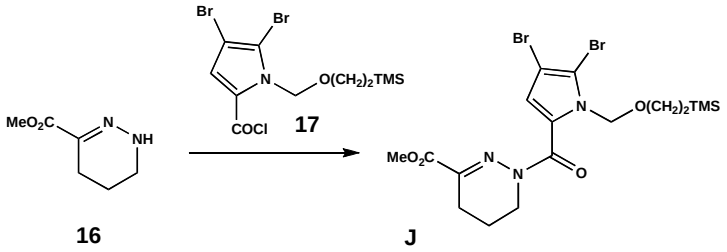
I

A solution of NaOH (17.6 g, 439 mmol) in H_2O (218 mL) was added to a solution of **H** (94.4 g, 221 mmol) in THF/MeOH (1000 mL / 70 mL). The resulting solution was stirred at 65°C for 5 hours. The reaction was quenched with 10% aq citric acid. The solvents were removed *in vacuo* and the residue taken up in CH_2Cl_2. The solution was washed with saturated NH_4Cl, water and brine. The organic layer was

dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **I** as an off white solid (86.5g, 98%). This material was used without further purification.

I: IR (film): 3400, 1652, 1635, 1338, 1250, 1148, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 1H), 5.81 (s, 2H), 3.60 (t, 2H, *J* = 8.4 Hz), 0.91 (t, 2H, *J* = 8.4 Hz), 0.02 (s, 9H). ^{13}C NMR (75MHz, $CDCl_3$): δ 164.3, 123.2, 122.7, 115.3, 101.1, 75.5, 66.3, 17.8, -1.5. MS (positive electrospray) for $(C_{11}H_{17}Br_2NO_3Si+H)^+$ calcd: 399.93; found: 400.10.

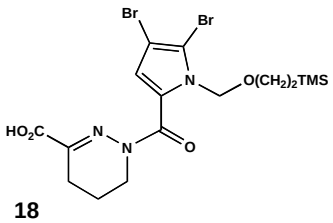
Methyl 1-(4,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2-carbonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylate (J)



Oxalyl chloride (20.3 mL, 236 mmol) was added to a solution of acid **I** (47.1 g, 118 mmol) in CH_2Cl_2 (400 mL). DMF (0.5 mL) was added and the resulting mixture was stirred at rt for 1 hour. The solvent was removed *in vacuo* to give a brown oily residue (**17**) that was dissolved in CH_3CN (370 mL). To this solution was added **16** (16.8 g, 118 mmol), pyridine (19 mL, 236 mmol) and DMAP (50 mg) and the resulting mixture was stirred at rt overnight. The solvent was removed *in vacuo* and the residue taken up in CH_2Cl_2. The solution was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (10→20% EtOAc/hexanes) provided **J** (58 g, 94%) as a white solid.

J: R_f = 0.3 (1:4 EtOAc/CH_2Cl_2); IR (film): 1711, 1648, 1413, 1337, 1267, 1239, 1090, 973, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 5.84 (s, 2H), 3.90-3.82 (m, 5H), 3.56 (t, 2H, *J* = 8.0 Hz), 2.56 (t, 2H, *J* = 6.4 Hz), 1.96 (td, 2H, *J* = 6.3, 12.4 Hz), 0.89 (t, 2H, *J* = 8.0 Hz), 0.04 (s, 9H); ^{13}C NMR (75MHz, $CDCl_3$): δ 164.5, 160.0, 139.3, 125.2, 124.1, 113.2, 100.3, 76.0, 66.0, 52.5, 39.6, 21.8, 17.8, 16.6, -1.5. HRMS (ESI-TOF) calcd for $(C_{17}H_{25}Br_2N_3O_4Si+H)^+$ 522.0054; found: 522.0057.

1-(4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2-carbonyl)-1,4,5,6-tetrahydropyridazine-3-carboxylic acid (18)

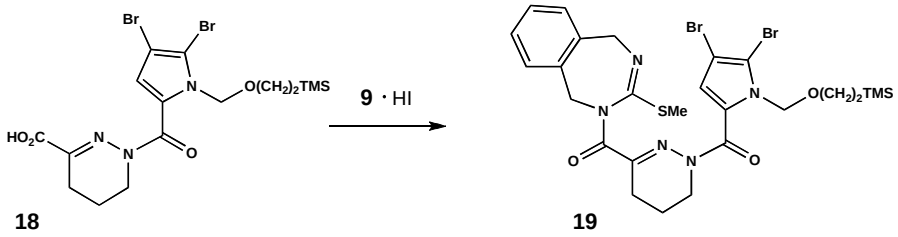


18

A solution of ester **J** (66 g, 126 mmol) in THF/H_2O (520 mL / 250 mL) was stirred for 30 min in an ice-water bath. A solution of LiOH (30 mL. aq 0.5M) was added and the resulting mixture stirred at 4 °C for 1 h. The reaction was quenched with 10% aq citric acid and concentrated *in vacuo*. The residue was taken up in EtOAc and washed with saturated NH_4Cl, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting white solid (62.2 g, 97%) was used without further purification.

18: IR (film): 3203, 2951, 1715, 1652, 1422, 1240, 1179, 1096, 1096, 969, 860. 742, 684, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 6.95 (bs, 1H) 5.74 (s, 2H), 3.86 (t, 2H, *J* = 5.6 Hz), 3.55 (t, 2H, *J* = 8 Hz), 2.61 (t, 2H, *J* = 6.4 Hz), 2.01 (td, 2H, *J* = 6.3, 12.3 Hz), 0.88 (t, 2H, *J* = 8 Hz), 0.06 (s, 9H). ^{13}C NMR (75MHz, $CDCl_3$): δ 163.8, 160.5, 139.8, 128.3, 125.2, 121.5, 113.0, 100.4, 75.8, 66.4, 40.0, 21.0, 17.7, 16.4, -1.5. HRMS (ESI-TOF) calcd for $(C_{16}H_{23}Br_2N_3O_4Si+H)^+$ 507.9897; found: 507.9898.

(4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrol-2-yl)(3-(3-(methylthio)-2,5-dihydro-1H-benzo[e][1,3]diazepine-2-carbonyl)-5,6-dihydropyridazin-1(4H)-yl)methanone (19)



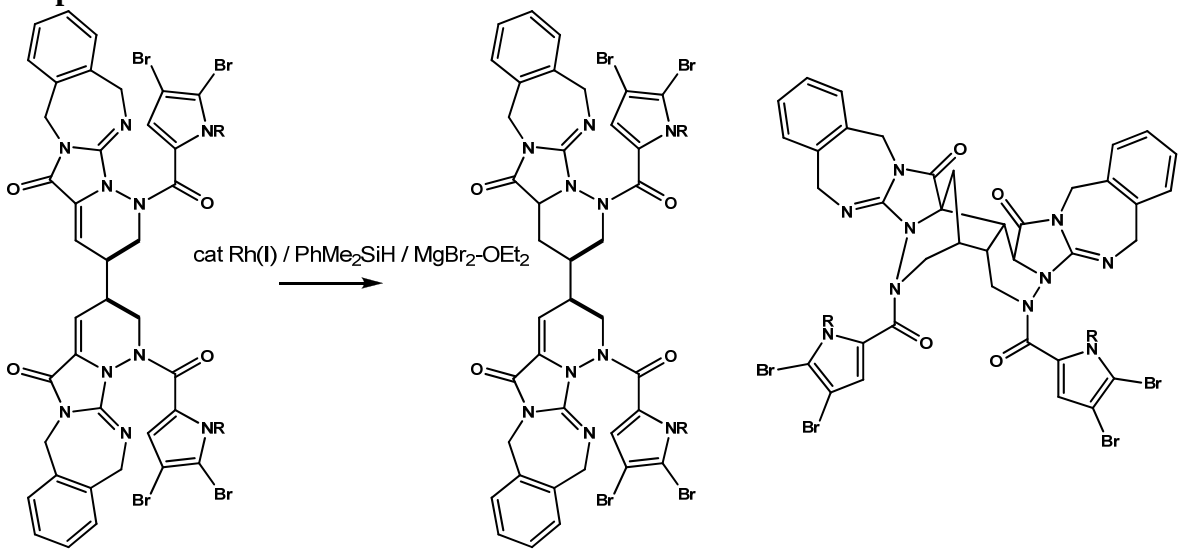
18 **19**

HI salt **9** (9.2 g, 28.9 mmol) was added to a solution of **18** (14 g, 27.5 mmol) in DMF (183 mL) at 0°C. TBTU (9.7 g, 30.3 mmol) was added, followed by the slow addition of $(i\text{-}Pr)_2NEt$ (14.4 mL, 82.5 mmol). The resulting mixture was stirred at rt for 3 h. The reaction mixture was diluted with 1L EtOAc and washed with sat. NH_4Cl (2 x 200 mL), water (8 x 200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **19** as a slightly pink foam (18.5 g, 99%). This material was used without further purification.

19: R_f = 0.9 (1:9 $CH_3CN/CHCl_3$); IR (film): 3420, 1645, 1430, 1340, 1241, 1130, 835, 750, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16-7.02 (m, 4H), 6.68 (s, 1H), 5.65 (s, 2H), 4.90 (s, 2H), 4.44 (s, 2H), 3.84 (t, 2H, *J* = 5.6 Hz), 3.46 (t, 2H, *J* = 8.0 Hz), 2.63 (t, 2H, *J* = 5.6 Hz), 2.31 (s, 3H), 2.04-1.98 (m, 2H), 0.86

(t, 2H, J = 8.0 Hz), -0.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 161.8, 157.4, 146.6, 134.0, 133.8, 129.7, 127.9, 127.7, 127.2, 126.1, 120.9, 111.3, 99.9, 75.8, 66.2, 54.8, 45.9, 40.4, 23.9, 17.9, 17.3, 15.3, -1.2. HRMS (ESI-TOF) calcd for $(C_{26}H_{33}Br_2N_5O_3SSi+H)^+$ calcd: 682.0513; found: 682.0513.

Reduction products 27 and 28



A solution of **21** ***meso*** (40 mg, 0.032 mmol) and $MgBr_2$•Et_2O (12 mg, 0.047 mmol) in THF (0.3 mL) was stirred at rt for 10 min before evaporation of the solvent. The residue was re-dissolved in a stock solution of Rh(I) catalyst **31** (1 mg), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (1.2 mg) and $HSiMe_2Ph$ (5.5 μL, 0.035 mmol) in CH_2Cl_2 (0.16 mL). The resulting mixture was heated at 40°C for 15 h. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (1:4 EtOAc/CH_2Cl_2) afforded polycycle **28** (18 mg, 45%) and mono reduction product **27** (12 mg, 30%).

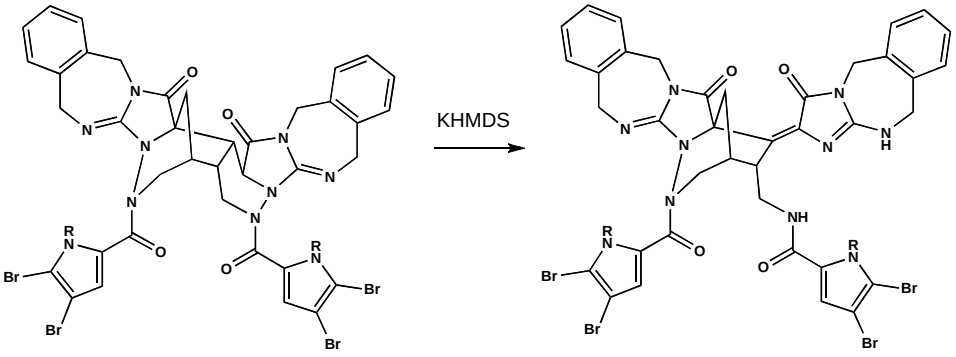
28: white film; R_f = 0.9 (1:9 $CH_3CN/CHCl_3$); IR (film): 3430, 2950, 1751, 1695, 1684, 1448, 1418, 1409, 1247, 1091, 858, 835, 756, 700 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN): δ 7.42-7.24 (m, 8H), 6.70 (s, 1H), 6.60 (s, 1H), 5.63 (dd, 2H, J = 2.8, 10.5 Hz), 5.58-5.42 (m, 2H), 5.18-4.90 (m, 4H), 4.68-4.55 (m 3H), 4.40 (dd, 1H, J = 7.1, 13.1 Hz), 4.26 (d, 1H, J = 11.2 Hz), 4.13 (d, 1H, J = 13.6 Hz), 3.74-3.46 (m, 4H), 3.41-3.24 (m, 2H), 3.05-2.93 (m, 1H), 2.88 (t, 1H, J = 11.6 Hz), 2.58 (t, 1H, J = 12.8 Hz), 2.66-2.45 (m, 1H), 1.92-1.88 (m, 1H), 1.42 (d, 1H, J = 11.8 Hz), 1.02-0.78 (m, 4H), -0.02 (s, 9H), -0.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 167.8, 163.8, 159.4, 146.3, 142.4, 140.2, 134.4, 133.1, 128.8, 128.7, 128.5, 128.4,

128.0, 127.9, 127.8, 124.6, 118.4, 113.7, 111.3, 108.4, 100.8, 99.6, 75.5, 75.1, 67.7, 66.1, 53.2, 49.9, 49.3, 48.8, 44.0, 43.4, 40.8, 40.4, 33.6, 33.5, 31.5, 17.9, 17.8, -1.4, -1.4. MS (positive electrospray) calcd for $(C_{50}H_{58}Br_4N_{10}O_6Si_2+H)^+$: 1271.08; found 1270.94.

Treatment of **28** with excess BF_3 etherate provided derivative **29**. Crystals of **29** (PTLC purified) suitable for X-ray diffraction were grown from CH_3CN (slow evaporation). Details of the crystallographic analysis are provided in a separate CIF file.

27: white foam; R_f = 0.65 (1:4 CH_3CN: $CHCl_3$); IR (film): 2951, 2873, 1749, 1630, 1403, 1248, 1092, 836, 667 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 7.40-7.18 (m, 8H), 6.76 (s, 1H), 6.69 (s, 1H), 5.82-5.79 (m, 1H), 5.62-5.38 (m, 4H), 5.00-4.56 (m, 8H), 4.44 (ddd, 1H, *J* = 1.8, 3.1, 12.9 Hz), 3.70 (dd, 1H, *J* = 11.6 Hz), 3.63 (t, 4H, *J* = 8.1 Hz), 3.48-3.38 (m, 1H), 2.54 (dd, 1H, *J* = 11.6, 12.8 Hz), 2.36 (dt, 1H, *J* = 5.2, 10.4 Hz), 2.08-2.03 (m, 1H), 2.01-1.98 (m, 1H), 1.78-1.62 (m, 1H), 1.35 (q, 1H, *J* = 12.3Hz), 0.93-0.76 (m, 4H), 0.02 (s, 9H), -0.03 (s, 9H). MS (positive electrospray) calcd for $(C_{50}H_{58}Br_4N_{10}O_6Si_2+H)^+$: 1271.08; found 1271.04.

Alkylidene 30



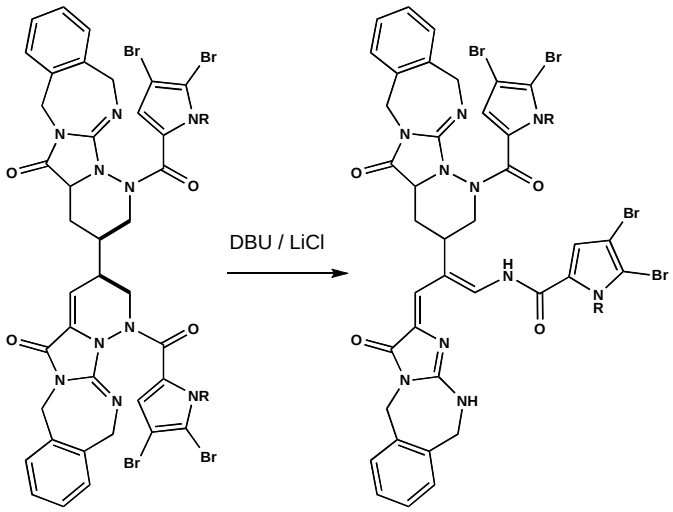
28 R = $CH_2O(CH_2)_2SiMe_3$ **30**

KHMDS (70 μL, 0.5 M in toluene) was added to a solution of **28** (22 mg, 0.017 mmol) in THF (100 μL) at −78°C. The dark pink solution was stirred at −78°C for 30 min and then warmed to rt. After stirring at rt for 30 min, 10 μL AcOH was added and the solution diluted with CH_2Cl_2. The organics were washed with saturated aq $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (3:7 $CH_3CN/CHCl_3$) afforded **30** as white film (18 mg, 80%).

30: R_f = 0.6 (3:7 $CH_3CN/CHCl_3$); ^1H NMR (400 MHz, CD_3CN): δ 9.27 (app d, 1H, *J* = 7.4 Hz), 7.45-7.18 (m, 8H), 6.74 (s, 1H), 6.61 (s, 1H), 5.87 (d, 1H, *J* = 10.8 Hz), 5.82 (d, 1H, *J* = 10.8 Hz), 5.66 (d, 1H, *J* = 10.8 Hz), 5.39 (d, 1H, *J* = 10.8 Hz), 5.04-4.83 (m, 4H), 4.76-4.60 (m, 2H), 4.46-4.37 (m, 2H), 3.80-3.75 (m, 1H), 3.62-3.38 (m, 4H), 3.36-3.20 (m, 1H), 3.03-2.85 (m, 2H), 2.62-2.58 (m, 1H), 2.12-2.07 (m, 1H),

2.02-1.98 (m, 1H), 1.64 (d, 1H, *J* = 11.8 Hz), 0.90-0.60 (m, 4H), -0.04 (s, 9H), -0.29 (s, 9H); MS (positive electrospray) calcd for $(C_{50}H_{58}Br_4N_{10}O_6Si_2+H)^+$: 1271.08; found 1270.94.

Ring-opened product 32



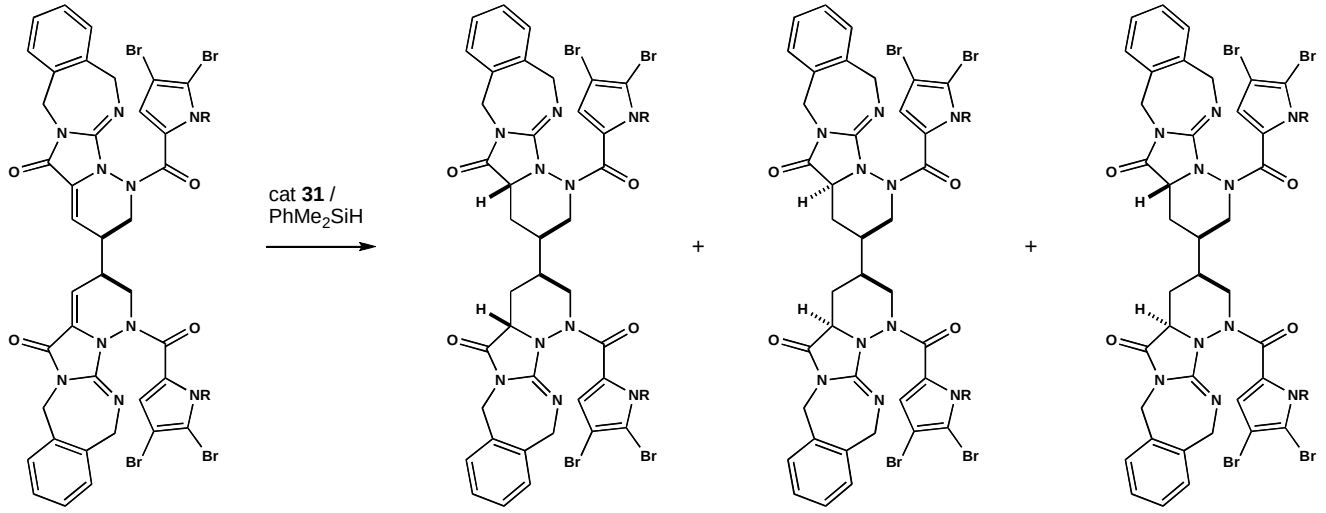
27 **32**

R = $CH_2O(CH_2)_2SiMe_3$

Reduction product **27** (20 mg, 0.016 mmol) was dissolved in a stock solution of LiCl (0.8 mg, 0.019 mmol) and DBU (3 μL, 0.021 mmol) in DMF (100 μL- argon sparged). After heating at 52°C for 3 h, the reaction mixture was quenched with acetic acid (5 μL) and diluted with CH_2Cl_2. The resulting solution was washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (1:4 $CH_3CN/CHCl_3$) to afford **32** as bright yellow solid (14 mg, 70%).

32: R_f = 0.8 (2:9 $CH_3CN/CHCl_3$); ^1H NMR (400 MHz, CD_3CN/D_2O): δ 7.20-7.45 (m, 8H), 6.87 (s, 1H), 6.82 (s, 1H), 6.75 (s, 1H), 5.92 (s, 1H), 5,79 (s, 2H), 5,64 (d, 1H, *J* = 10.8 Hz), 5.46 (d, 1H, *J* = 10.7 Hz), 4.88 (m, 5H), 4.50 (m, 3H), 4.31 (d, 1H, *J* = 12.4 Hz), 3.85 (dd, 1H, *J* = 4.6, 11.4 Hz), 3.50-3.57 (m, 4H), 2.75 (m, 1H), 2.53(tt, 1H, *J* = 3.0, 11.8Hz), 2.17 (m, 1H), 1.62 (m, 1H), 0.77-0.90 (m, 4H), -0.04 (s, 9H), -0.02 (s, 9H). MS (positive electrospray) calcd for $(C_{50}H_{58}Br_4N_{10}O_6Si_2+H)^+$: 1271.08; found 1271.45.

Saturated products 33



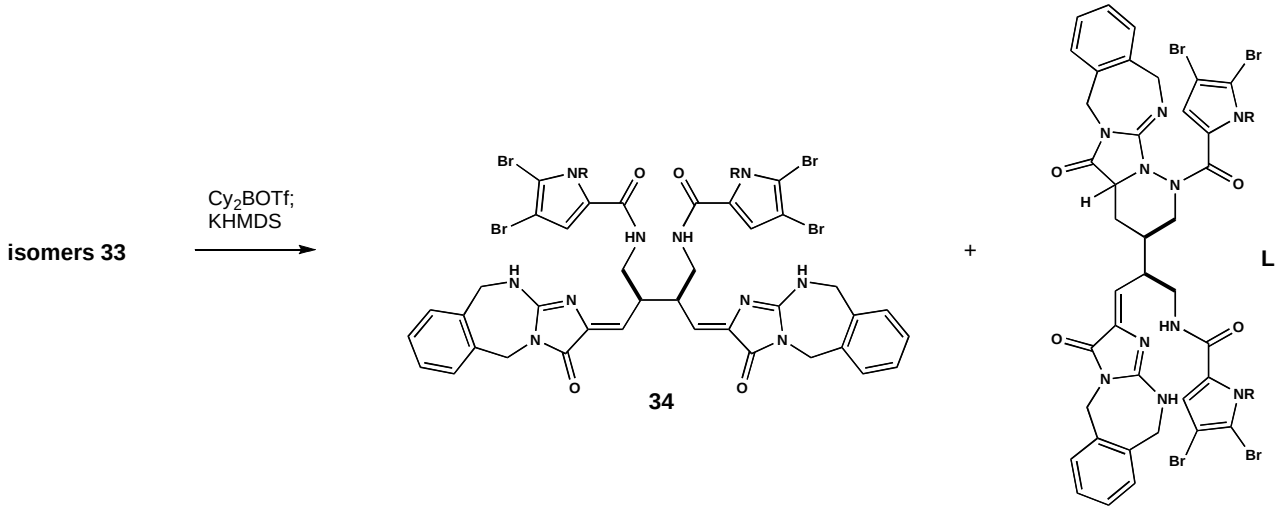
A solution of *meso* **21** (460 mg, 0.364 mmol), MgI_2 (50 mg, 0.18 mmol), and NH_4PF_6 (120 mg, 0.74 mmol) in THF (3 mL) was stirred at rt for 15 minutes and then the solvent was removed *in vacuo*. The residue was suspended in a stock solution of Rh(I) catalyst **31** (5.75 mg, 5 mol%), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (6.5 mg, 5.5 mol%) and $HSiMe_2Ph$ (170 μL, 1.10 mmol) in CH_2Cl_2 (2.45 mL). The reaction mixture was heated at 55°C for 36 h and then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (gradient from 1:9 → 1:4 EtOAc/CH_2Cl_2) to afford a mixture of **33a + 33b** (395 mg, 66%) followed by **33c** (85 mg, 16%).

33a + 33b: white solid; R_f = 0.45 (1:4 $CH_3CN/CHCl_3$); IR (film): 3422, 2950, 1753, 1704, 1651, 1403, 1248, 1067, 836, 740, 610 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 7.39-7.31 (m, 8H), 6.77 (s, 2H), 5.67 (d, 2H, *J* =10.6 Hz), 5.48 (d, 2H, *J* = 10.6 Hz), 4.92 (s, 4H), 4.78 (d, 2H, *J* = 14.4 Hz), 4.58 (d, 2H, *J* = 14.4 Hz), 4.42-4.38 (m, 2H), 3.78 (dd, 2H, *J* = 4.9, 11.6 Hz), 3.56 (t, 4H, *J* = 7.9 Hz), 2.49 (dd, 2H, *J* = 11.2, 12.8 Hz), 2.25-2.08 (m, 2H), 1.63-1.58 (m, 2H), 1.37-1.22 (m, 2H), 0.97-0.81 (m, 4H), 0.00 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 164.2, 145.6, 140.4, 133.4, 129.6, 128.9, 128.8, 117.7, 111.4, 99.8, 75.4, 66.5, 56.5, 49.6, 43.6, 43.4, 35.1, 30.5, 18.2, -1.1. MS (positive electrospray) calcd for $(C_{50}H_{60}Br_4N_{10}O_6Si_2+H)^+$: 1273.09; found 1273.1. Crystals of **33b** suitable for X-ray diffraction were grown from CH_3CN (slow evaporation). Details of the crystallographic analysis are provided in a separate CIF file.

33c: R_f = 0.2 (1:4 $CH_3CN/CHCl_3$); IR (film): 2952, 1754, 1693, 1403, 1299, 1248, 1155, 1092, 941 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 8H), 6.77 (s, 1H), 6.76 (s, 1H), 5.67-5.55 (m, 4H), 5.00-4.57

(m, 8H), 4.44-4.39 (m, 1H), 4.08-4.02 (m, 2H), 3.79 (dd, 1H, *J* = 4.9, 11.6 Hz) 3.52 (dd, 4H, *J* = 8.4, 16.9 Hz), 3.15 (dd, 1H, *J* = 4.9, 13.1 Hz), 2.32 (dd, 1H, *J* = 11.7, 12.6 Hz), 2.24-2.18 (m, 1H), 2.04-1.96 (m, 3H), 1.80-1.65 (m, 1H), 1.08-1.03 (m, 1H), 1.00-0.77 (m, 4H), -0.01 (s, 9H), -0.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 169.6, 163.7, 146.9, 145.3, 140.5, 140.1, 133.6, 129.5, 128.8, 128.7, 128.6, 128.5, 125.7, 117.4, 111.2, 110.9, 99.7, 99.6, 75.6, 75.3, 60.6, 56.5, 56.3, 49.6, 49.4, 43.9, 43.7, 43.5, 43.1, 33.0, 32.7, 30.8, 27.0, 21.3, 18.1, 18.0, 14.4, -1.1, -1.2. MS (positive electrospray) calcd for $(C_{50}H_{60}Br_4N_{10}O_6Si_2+H)^+$: 1273.09; found 1272.80.

Mono alkylidene L and symmetric bis-alkylidene 34



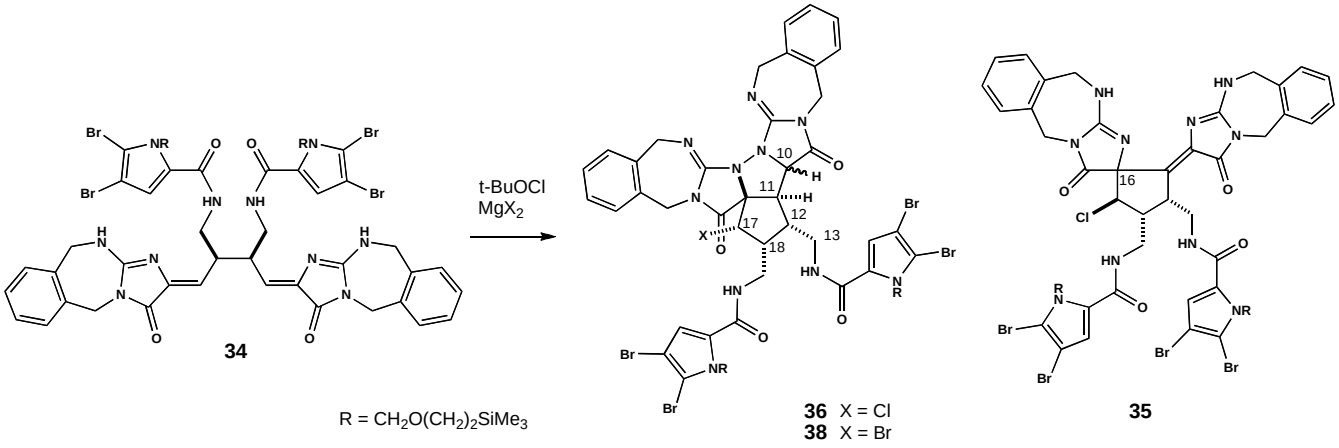
A solution of Cy_2BOTf (47 mg, 0.144 mmol) in THF (0.48 mL) was cooled to −78°C and added rapidly to a solution of **33a**/**b**/**c** (60 mg, 0.047 mmol) in THF (1.5 mL) at −78°C. KHMDS (0.5M in toluene, 470 μL) was then added and the cooling bath immediately removed. The red solution was warmed to rt and quenched with 20 μL AcOH. The reaction was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (1:49 MeOH/CH_2Cl_2) to afford **34** as light yellow solid (32 mg, 53%) along with mono alkylidene **L** (16 mg, 27%). Analytically pure **34** was obtained as a white powder following triturating with CH_3CN.

34: R_f = 0.5 (1:19 MeOH/CH_2Cl_2); IR (film): 1668, 1606, 1425, 1317, 1245, 1091, 836 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.30 (bs, 2H), 8.01 (bs, 2H), 7.38-7.31 (m, 8H), 6.76 (s, 2H), 5.71 (d, 4H, *J* = 10.5 Hz), 5.64 (d, 2H, *J* = 10.5 Hz), 5.56 (d, 2H, *J* = 7.2 Hz), 4.87 (s, 4H), 4.45 (s, 4H), 3.41 (t, 4H, *J* = 7.8 Hz), 3.15-2.95 (m, 4H), 0.71 (t, 4H, *J* = 7.8 Hz), -0.13 (s, 18H); ^{13}C NMR (125MHz, DMSO-d_6): δ 167.0, 159.4, 157.5, 142.1, 138.8, 135.1, 128.7, 128.6, 128.3, 128.2, 117.1, 114.8, 110.1, 98.8, 94.3, 74.3, 65.1,

43.3, 42.5, 41.8, 40.0, 17.0, -1.5; MS (positive electrospray) calcd for $(C_{50}H_{60}Br_4N_{10}O_6Si_2+H)^+$: 1273.09; found 1272.80.

L: off-white solid; R_f = 0.75 (1:19 MeOH/CH_2Cl_2); IR (film): 3400, 2952, 1644, 1418, 1247, 1068, 835 cm^{-1}; ^1H NMR (400 MHz, CD_3CN): δ 7.42-7.20 (m, 8H), 6.72 (s, 1H), 6.67 (s, 1H), 5.80-5.42 (m, 5H), 4.95-4.86 (m, 4H), 4.80-4.77 (m, 1H), 4.58-4.46 (m, 2H), 4.38-4.35 (m, 1H), 3.78 (dd, 1H, *J* = 11.6, 4.9 Hz), 3.62-3.43 (m, 5H), 3.37-3.26 (m, 1H), 2.76 (ddd, 1H, *J* = 4.1, 8.9, 13.4 Hz), 2.50-2.42 (m, 1H), 2.31-2.25 (m, 1H), 1.90-1.85 (m, 1H), 1.36-1.20 (m, 2H), 0.93-0.75 (m, 4H), -0.03 (s, 9H), -0.06 (s, 9H). ^{13}C NMR (125MHz, $CDCl_3$): δ 169.8, 166.8, 164.4, 160.3, 157.9, 145.8, 141.5, 140.6, 137.4, 134.5, 133.2, 129.6, 129.5, 129.1, 128.8, 128.7, 128.6, 128.6, 128.5, 125.5, 117.6, 116.5, 115.6, 111.2, 110.9, 99.7, 75.5, 75.1, 70.8, 70.5, 66.4, 66.3, 56.8, 49.4, 45.3, 44.2, 43.7, 43.4, 41.5, 40.2, 35.8, 34.6, 31.3, 30.4, 25.7, 24.4, 18.2, 18.0, -1.1, -1.2. MS (positive electrospray) calcd for $(C_{50}H_{60}Br_4N_{10}O_6Si_2+H)^+$: 1273.09; found 1272.80.

Spirocyclic products derived from 34



Procedure A. no additive

Bisalkylidene **34** (40 mg, 0.031 mmol) was dissolved in 1 mL THF and the resulting mixture was cooled to −78°C. A solution of freshly prepared *t*-BuOCl (see *Organic Syntheses*, Coll. Vol. 5, p.184 (1973) - 4.2 μL, 0.038 mmol) in CH_2Cl_2 (50 μL) was added and the reaction was stirred at -78°C for 2 h and rt for another 2 h. The solvent was removed *in vacuo* and the residue was purified by preparative thin layer chromatography (CH_3OH:CH_2Cl_2 = 1:19). This affords one impure diastereomer of **36** (**36b**) followed by a pure second diastereomer (**36a**) and impure alkylidene **35**.

36a: (4 mg, 10% yield): white film; R_f = 0.7 (MeOH:CH_2Cl_2= 5:95); IR (film, cm^{-1}): 2923, 1750, 1650, 1513, 1455, 1404, 1247, 1092, 948, 836; ^{1}H NMR (500 MHz,CD_3CN): 7.85 (dd, 1H, *J* = 4.5, 7.3 Hz), 7.57 (t, 1H, *J* = 5.6 Hz), 7.42-7.21 (m, 8H), 7.07 (s, 1H), 6.89 (s, 1H), 5.85-5.76 (m, 4H), 4.74 (d, 1H, *J* = 2.9 Hz), 4.70-4.55 (m, 3H), 4.53 (d, 1H, J = 3.9 Hz), 4.35-4.26 (m, 2H), 4.20-3.96 (m, 2H), 3.80-3.73 (m, 3H), 3.62 (ddd, 1H, *J* = 1.9, 5.7, 14.2 Hz), 3.52-3.45 (m, 4H), 3.41 (ddd, 1H, *J* = 4.5, 9.8, 14.0 Hz), 3.21-3.14 (m, 1H), 2.59 (td, 1H, *J* = 5.4, 9.4 Hz), 2.16 (1H, overlapped with H_2O peak), 0.96-0.87 (m, 4H), -0.09 (s, 9H), -0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): 170.0, 162.7, 161.2, 160.5, 148.4, 140.0, 133.5, 129.7, 129.6, 128.9, 128.8, 128.7, 128.4, 127.8, 127.5, 117.0, 116.4, 112.2, 111.6, 100.3, 100.0, 88.0, 77.5, 75.7, 75.3, 66.7, 66.2, 65.8, 58.0, 56.6, 49.0, 43.7, 43.4, 41.0, 38.6, 37.0, 35.9, 18.1, -1.2, -1.2. HRMS (ESI-TOF) calcd for $(C_{50}H_{59}Br_4ClN_{10}O_6Si_2+H)^+$: 1307.0539; found 1307.3955.

36b: impure material was subjected to a second preparative thin layer chromatography, eluting with 10% $CH_3CN/CHCl_3$, to afford **36b** (~1 mg) as a white film. **36b:** R_f = 0.8 (MeOH: CH_2Cl_2 = 5:95); IR (film): 2852, 1737, 1681, 1543, 1456, 1397, 1248, 1093, 949 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN): δ 7.57 (t, 1H, *J* = 5.0 Hz), 7.45 (t, 1H, *J* = 5.4 Hz), 7.38-7.20 (m, 8H), 7.06 (s, 1H), 6.90 (s, 1H), 5.84-5.63 (m, 4H), 5.25 (d, 1H, *J* = 4.0 Hz), 5.05-4.57 (m, 7H), 4.50 (m, 1H), 4.29 (d, 1H, *J* = 5.5 Hz), 4.17-4.12 (m, 1H), 3.63 (ddd, 1H, *J* = 3.5, 5.8, 14.9 Hz), 3.70-3.42 (m, 6H), 3.38-3.26 (m, 1H), 2.57 (tt, 1H, *J* = 5.7, 11.3 Hz), 2.30-2.25 (m, 1H), 0.97-0.78 (m, 2H), 0.76-0.62 (m, 2H), -0.05 (s, 9H), -0.12 (s, 9H). MS (MALDI) calcd for $(C_{50}H_{59}Br_4ClN_{10}O_6Si_2+H)^+$: 1307.05; found 1307.25.

35: impure material was subjected to a second preparative thin layer chromatography, eluting with 10% CH_3OH/CH_2Cl_2) to afford **35** as a white film (8 mg, 20% yield). **35**: R_f = 0.4 (MeOH:CH_2Cl_2= 1:9); IR (film): 2945, 1681, 1601, 1547, 1418, 1312, 1248, 1092, 857 cm^{-1}; ^{1}H NMR (400 MHz,CD_3CN): δ 8.52 (appr s, 1H), 7.42-7.27 (m, 8H), 7.05-7.02 (m, 1H), 6.85 (s, 1H), 6.72 (s, 1H), 5,87 (dd, 2H, *J* = 10.5, 12 Hz), 5.72 (t, 2H, *J* = 10.0 Hz), 4.90-4.45 (m, 7H), 4.30 (d, 1H, *J* = 14.8 Hz), 4.26 (d, 1H, *J* = 12.7 Hz), 3.76 (td, 2H, *J* = 3.9, 12.4 Hz), 3.74-3.40 (m, 7H), 3.24 (dt, 2H, *J* = 3.9, 12.5 Hz), 2.98-2.81 (m, 1H), 0.95-0.79 (m, 4H), -0.07 (s, 18H). MS (MALDI) calcd for $(C_{50}H_{59}Br_4ClN_{10}O_6Si_2+H)^+$: 1307.05; found 1307.50.

Procedure B. $MgCl_2$ additive

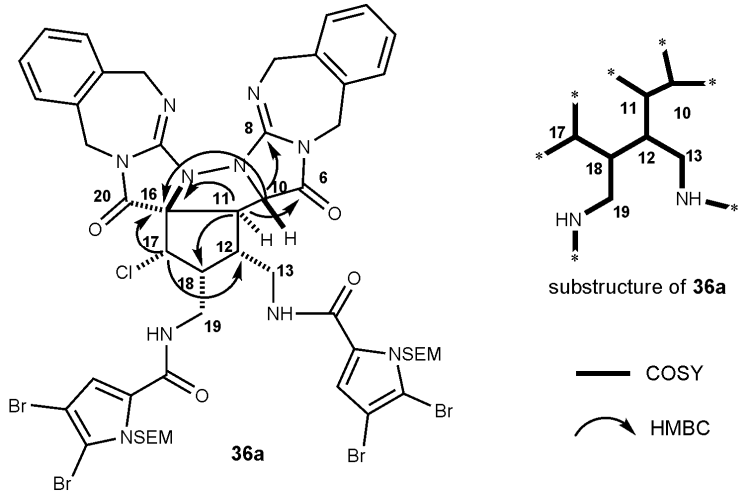
Bisalkylidene **34** (10 mg, 0.0075 mmol) and $MgCl_2$ (1.5 mg, 0.016mmol) were dissolved in THF (0.25 mL) and the mixture was cooled to −78°C. A solution of freshly prepared *t*-BuOCl (1 μL, 0.0075 mmol) in CH_2Cl_2 (50 μL) was added and the reaction mixture was stirred at -78^{o}C for 2 h and at rt for another 2 h.

The solvent was removed *in vacuo* and the residue purified by preparative thin layer chromatography (CH_3OH: CH_2Cl_2 = 1:19) to afford **36a** (2.8 mg, 26%), **35** (< 1 mg) and recovered **34** (3 mg, 30%).

Procedure C. $MgBr_2$•Et_2O additive

Bisalkylidene **34** (60 mg, 0.047 mmol) and $MgBr_2$•Et_2O (15 mg, 0.058mmol) were dissolved in 0.8 mL THF and the mixture cooled to -78°C. A solution of freshly prepared *t*-BuOCl (6 μL, 0.054 mmol) in CH_2Cl_2 (100 μL) was added and the reaction stirred at -78°C for 2 h and at rt for another 2 h. The solvent was evaporated and the residue was purified by preparative thin layer chromatography (CH_3OH:CH_2Cl_2 = 1:19) to afford two inseparable diastereomers of **38** as a light yellow solid (45 mg, 75%). These materials have ^{1}H NMR spectra that are identical to **36a**/**b**. They are distinguished only by mass: MS (MALDI) calcd for $C_{50}H_{59}Br_45N_{10}O_6Si_2(M+H)^+$: 1351.00; found 1350.80.

Table 1. Summary of ^{1}H and ^{13}C NMR data in CD_3CN for compound 36a.



position	$^a\delta_C$	$^b\delta_H$ (mult, *J* Hz)	COSY (H no.)	$^{2,3}J_{CH}$ HMBC (C no.)
6	171.2			
8	149			
10	58.8	3.77 (appr s)		6, 8, 12, 16
11	66.5	4.74 (d, J=2.9Hz)	12	6, 16, 18
12	41.3	2.15[a]	11, 13 (3.17), 18	
13	37.8	3.62 (ddd, J=1.9, 5.7, 14.2Hz)	13, N-H	17
		3.17 (m)	12, 13, N-H	17, 12
16	89			
17	57	4.53 (d, J=3.9Hz)	18	16, 12
18	36.4	2.59 (m)	17, 19(3.84, 3.42), 12	

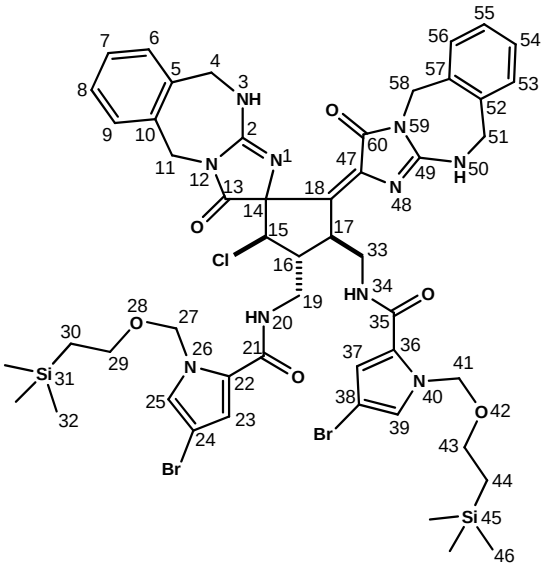
19	39.2	3.84 (m) 3.42 (ddd, J=4.5, 9.8, 14Hz)	18, NH 18, NH	12

Table 2. NOESY data for 36a.

position	$^{b}\delta_H$ (mult, *J* Hz)	NOESY
10	3.77 (appr s)	12, 18,
11	4.74 (d, J=2.9Hz)	12,13a
12	2.15	18, 10, 13a, 11
13b	3.62 (ddd, J=1.9, 5.7, 14.2Hz)	12,13a
13a	3.17 (m)	12, 13a,11
17	4.53 (d, J=3.9Hz)	18
18	2.59 (m)	10, 12
19b	3.84 (m)	19a
19a	3.42 (ddd, J=4.5, 9.8, 14Hz)	19,a

The relative stereochemistry in **36a** was assigned based on coupling constants and NOESY spectra. The 3.9 Hz coupling constant between H17 and H18 supports a *cis* stereochemistry. The correlations between H10, H12 and H10, H18 suggests these three protons are on the same face of the diazabicyclo[3.3.0]octane ring system. The small coupling constant between H11, H10 (J < 1 Hz) indicates a *trans* relationship. This only leaves the quaternary center C16 uncertain.

Table 2: NMR Data for Compound 44[a]

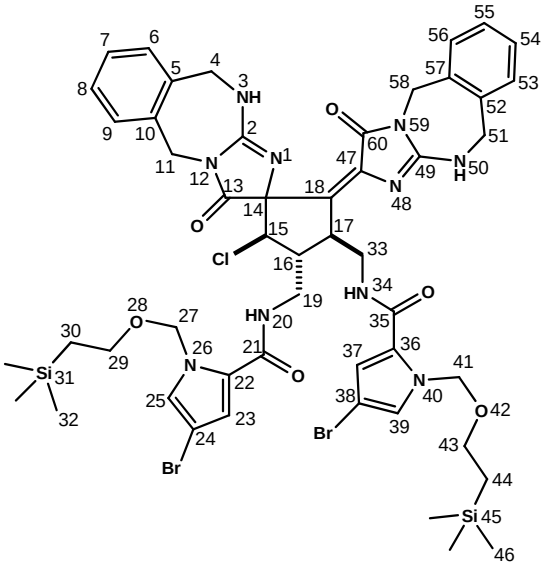


Carbon No.	^{13}C δ (ppm)[b]	Mult.	^{1}H δ (ppm) (mult J (Hz))[c,d,e]	HMBC Correlations[f]
2	158.7	Q		H4a, H-4b, H-11
4	45.7	CH_2	H-4a: 4.56 (d, 14.8) H-4b: 4.38 (d, 15.0)	
5	140.3	Q		
6		CH		
7		CH		
8		CH		
9		CH		
10	136.6	Q		
11	45.0	CH_2	H-11: 4.92 (s)	H-9
13	178.9	Q		H-15, H-11
14		Q		
15	69.7	CH	H-15: 4.01 (d, 11.6)	H-19a, H-19b
16	47.8	CH	H-16: 2.32-2.25 (m)	H-15, H-19a, H-19b, H-33a, H-33b
17	46.0	CH	H-17: 3.13 (ddd, 8.8, 4.1, 4.1)	H-19a, H-19b, H-33b
18	138.5	Q		
19	40.2	CH_2	H-19a: 3.65 (ddd, 14.3, 6.0, 4.3) H-19b: 3.49-3.38 (m)	H-15
21	162.4	Q		H-23, H-25
22	128.3	Q		H-23, H-25
23	116.5	CH	H-23: 6.75 (d, 1.9)	H-25
24	96.3	Q		H-25
25	127.8	CH	H-25: 7.02 (d, 1.9)	
27	78.0	CH_2	H-27a: 5.61 (d, 10.3) H-27b: 5.56 (d, 10.3)	H-25, H-29
29	67.2	CH_2	H-29: 3.49-3.38 (m)	H-27a, H-27b, H-30
30	18.6	CH_2	H-30: 0.79 (t, 2.0)	H-29
32	-1.0	CH_3	H-32: -0.14 (s)	H-30
33	42.9	CH_2	H-33a: 3.77 (ddd, 13.1, 4.1, 4.1) H-33b: 3.49-3.38 (m)	
35	162.5	Q		
36	129.0	Q		H-37, H-39
37	116.8	CH	H-37: 6.83 (d, 1.7)	H-39
38	96.4	Q		H-38
39	127.3	CH	H-39: 7.00 (d, 1.9)	

41	77.6	CH_2	H-41a: 5.59 (d, 10.3) H-41b: 5.58 (d, 10.3)	H-39, H-43
43	67.0	CH_2	H-43: 3.49-3.38 (m)	H-41, H-44
44	18.6	CH_2	H-44: 0.77-0.71 (m)	H-43
46	-1.0	CH_3	H-46: -0.10 (s)	H-44
47		Q		
49	158.7	Q		H-51a, H-51b, H-58
51	45.2	CH_2	H-51a: 4.49 (d, 15.0) H-51b: 4.38 (d, 15.0)	
52	139.8	Q		
53		CH		
54		CH		
55		CH		
56		CH		
57	136.4	Q		
58	44.1	CH_2	H-58: 4.73 (s, 2H)	H-56
60	166.5	Q		H-58

[a]The numbering scheme used here is unique to this analysis.
[b] Recorded at 150 MHz. [c] Recorded at 600 MHz. [d] Assignments based on HMQC data.
[e] Methylene protons are arbitrarily designated H-Xa and H-Xb.
[f] Only those correlations which could be unambiguously assigned are recorded.

Table 3: COSY Data for Compound 44

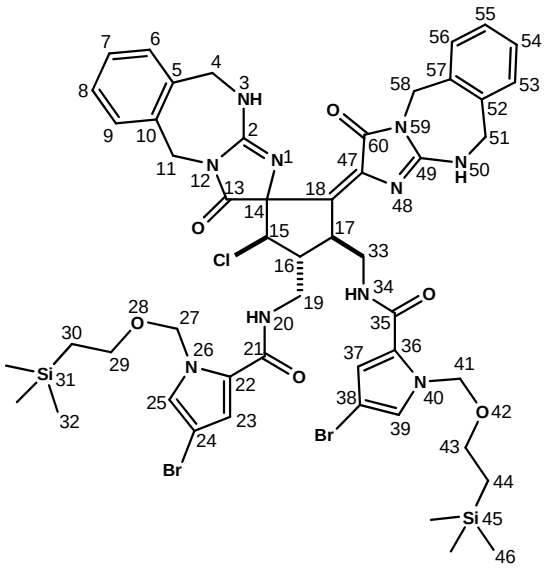


Proton No.	^{1}H δ (ppm) (mult J (Hz))[a,b]	COSY Correlation[c]
H-1		
H-4a	4.56 (d, 14.8)	H-4b
H-4b	4.38 (d, 15.0)	H-4a
H-6		
H-7		
H-8		
H-9		
H-11	4.92 (s)	
H-15	4.01 (d, 11.6)	H-16
H-16	2.32-2.25 (m)	H-15, H-17, H-19b

H-17	3.13 (ddd, 8.8, 4.1, 4.1)	H-16, H-33a, H-33b
H-19a	3.65 (ddd, 14.3, 6.0, 4.3)	H-19b
H-19b	3.49-3.38 (m)	H-19a
H-20	7.42-7.36 (m)	H-19a, H-19b
H-23	6.75 (d, 1.9)	H-25
H-25	7.02 (d, 1.9)	H-23
H-27a	5.61 (d, 10.3)	
H-27b	5.56 (d, 10.3)	
H-29	3.49-3.38 (m)	H-30
H-30	0.79 (t, 2.0)	H-29
H-32	-0.14 (s)	
H-33a	3.77 (ddd, 13.1, 4.1, 4.1)	H-33b
H-33b	3.49-3.38 (m)	H-33a
H-34	8.15 (s)	H-33a, H-33b
H-37	6.83 (d, 1.7)	H-39
H-39	7.00 (d, 1.9)	H-37
H-41a	5.59 (d, 10.3)	
H-41b	5.58 (d, 10.3)	
H-43	3.49-3.38 (m)	H-44
H-44	0.77-0.71 (m)	H-43
H-46		
H-48		
H-51a	4.49 (d, 15.0)	H-51b
H-51b	4.38 (d, 15.0)	H-51a
H-53		
H-54		
H-55		
H-56		
H-58a	4.73 (s, 2H)	

[a] Recorded at 500 MHz.
[b] Assignments are based on HMQC and HMBC data.
[c] Only those correlations that could be unambiguously assigned are recorded.

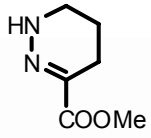
Table 4: ROESY Data for Compound 44



Proton No.	^{1}H δ (ppm) (mult J (Hz))[a,b]	ROESY Correlation[c]
H-1		
H-4a	4.56 (d, 14.8)	
H-4b	4.38 (d, 15.0)	
H-6		
H-7		
H-8		
H-9		H-11
H-11	4.92 (s)	H-9, H-4a, H-4b
H-15	4.01 (d, 11.6)	H-16, H-17, H-19a, H-19b
H-16	2.32-2.25 (m)	H-15, H-17, H-19a, H-19b, H-33a, H-33b, H-34
H-17	3.13 (ddd, 8.8, 4.1, 4.1)	H-15, H-16, H-19b, H-33a, H-33b
H-19a	3.65 (ddd, 14.3, 6.0, 4.3)	H-15, H-16, H-17, H-19b
H-19b	3.49-3.38 (m)	H-19a
H-20	7.42-7.36 (m)	
H-23	6.75 (d, 1.9)	H-25
H-25	7.02 (d, 1.9)	H-23
H-27a	5.61 (d, 10.3)	
H-27b	5.56 (d, 10.3)	
H-29	3.49-3.38 (m)	
H-30	0.79 (t, 2.0)	
H-32	-0.14 (s)	
H-33a	3.77 (ddd, 13.1, 4.1, 4.1)	H-16, H-17, H-33b, H-34
H-33b	3.49-3.38 (m)	H-33a
H-34	8.15 (s)	H-37
H-37	6.83 (d, 1.7)	H-39
H-39	7.00 (d, 1.9)	H-37
H-41a	5.59 (d, 10.3)	H-39
H-41b	5.58 (d, 10.3)	H-39
H-43	3.49-3.38 (m)	
H-44	0.77-0.71 (m)	H-43
H-46		
H-48		
H-51a	4.49 (d, 15.0)	
H-51b	4.38 (d, 15.0)	

H-53		
H-54		
H-55		
H-56		
H-58	4.73 (s, 2H)	H-51a, H-51b, H-56

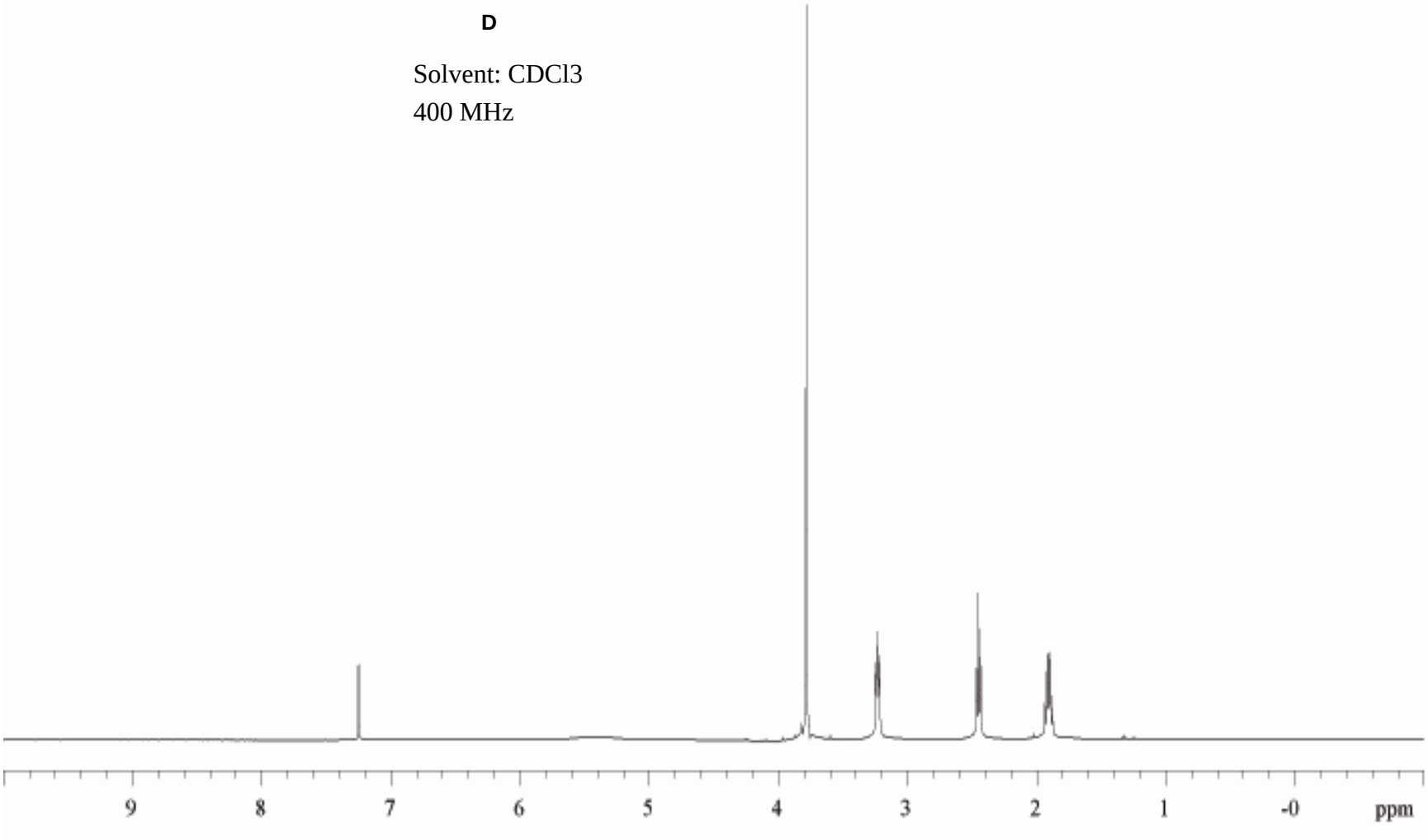
[a] Recorded at 400 MHz.
[b] Assignments based on COSY, HMQC and HMBC data.
[c] Only those correlations which could be unambiguously assigned are recorded.

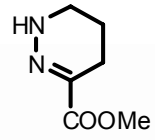


D

Solvent: CDCl3

400 MHz

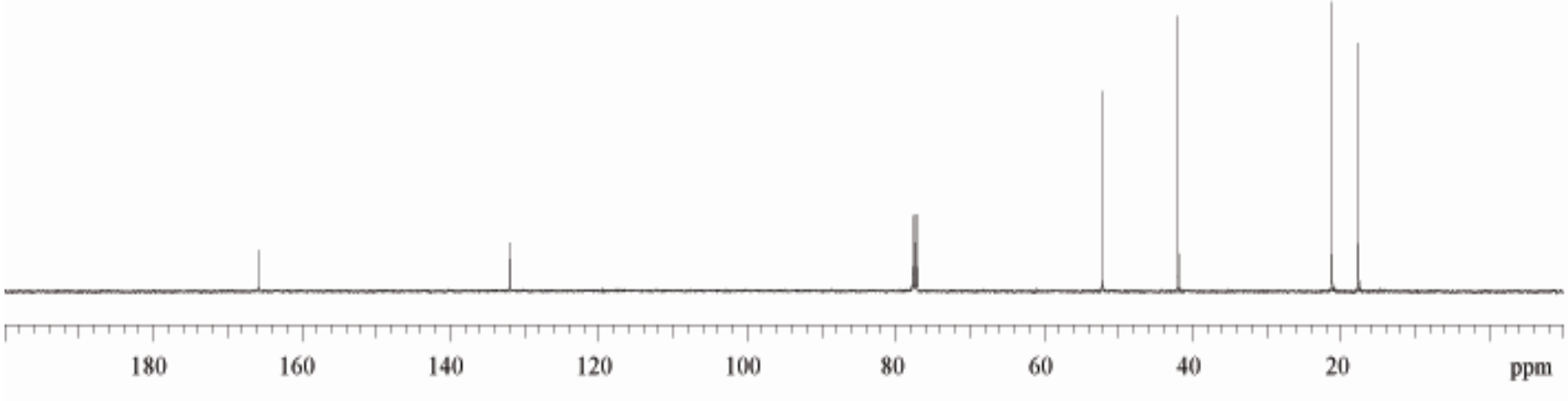


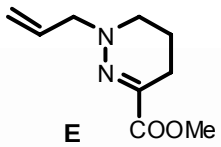


D

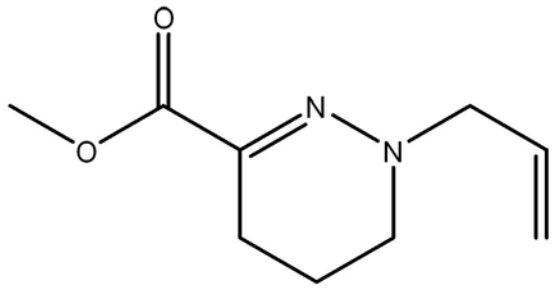
Solvent: CDCl3

100 MHz



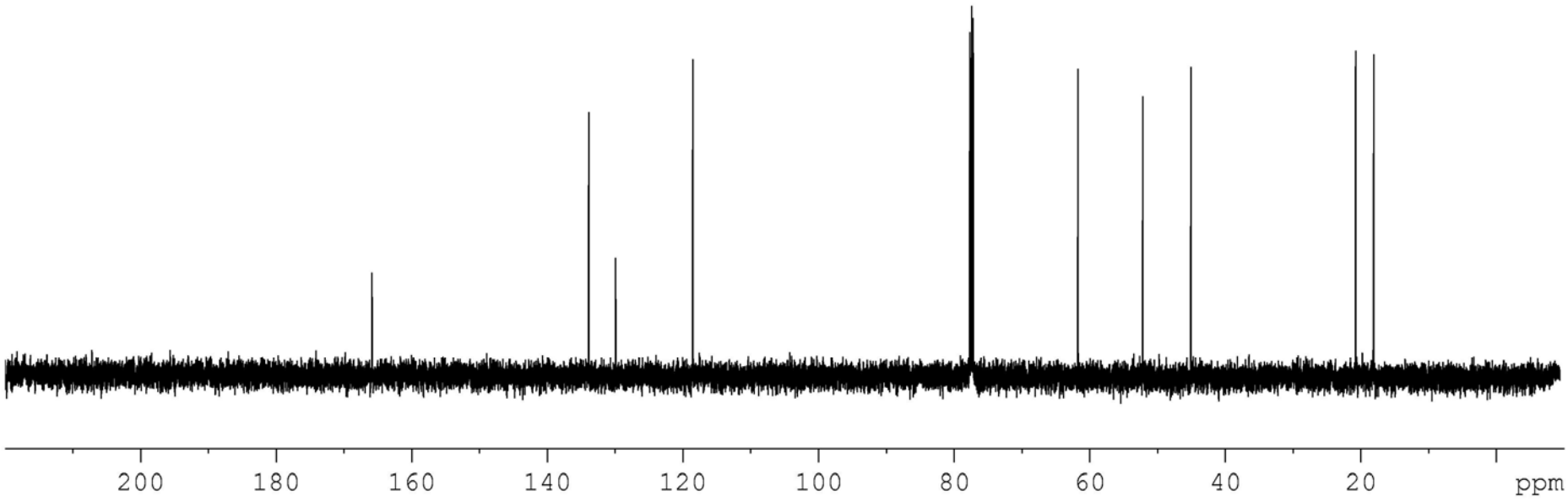


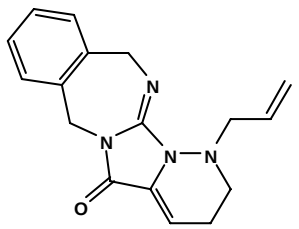
Solvent: CDCl3
400 MHz



E

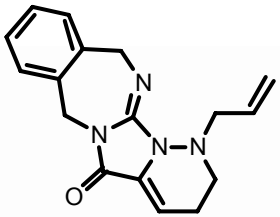
Solvent: CDCl3
100 MHz





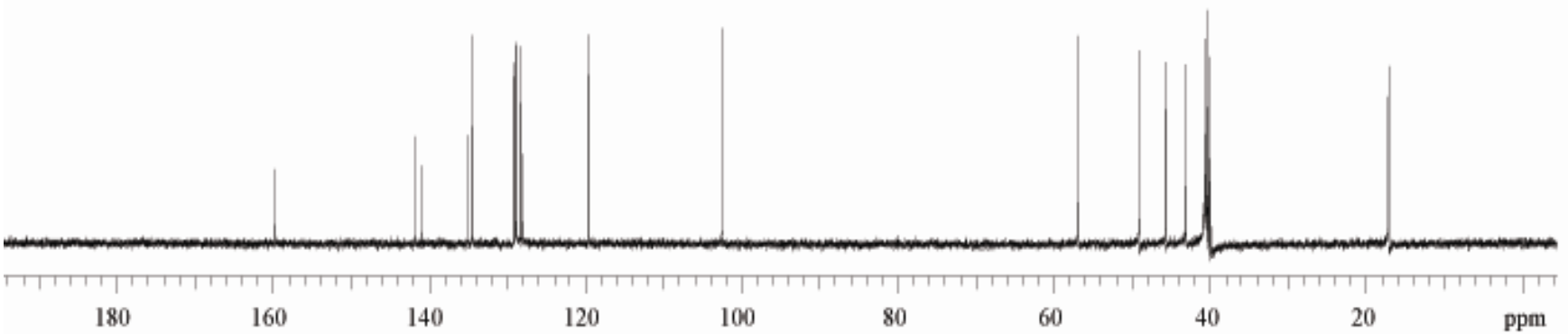
11

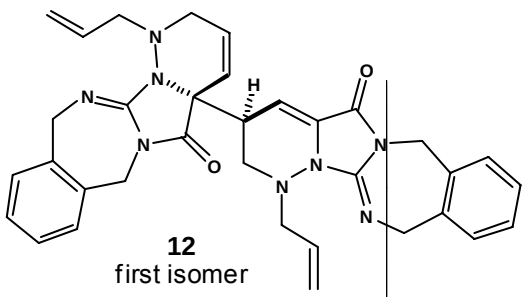
Solvent: DMSO-d_6
Temp: 25 °C; 500 MHz



11

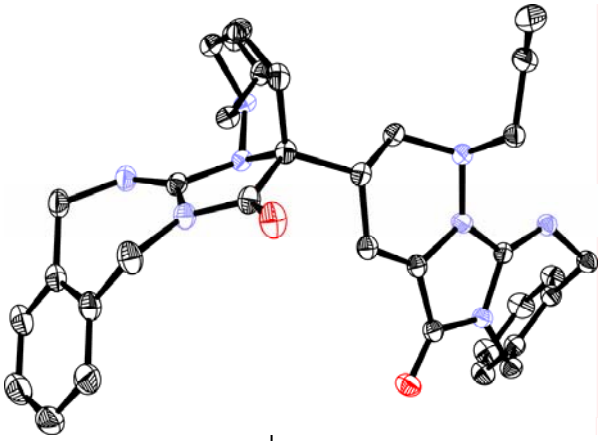
Solvent: DMSO-d6
400 MHz

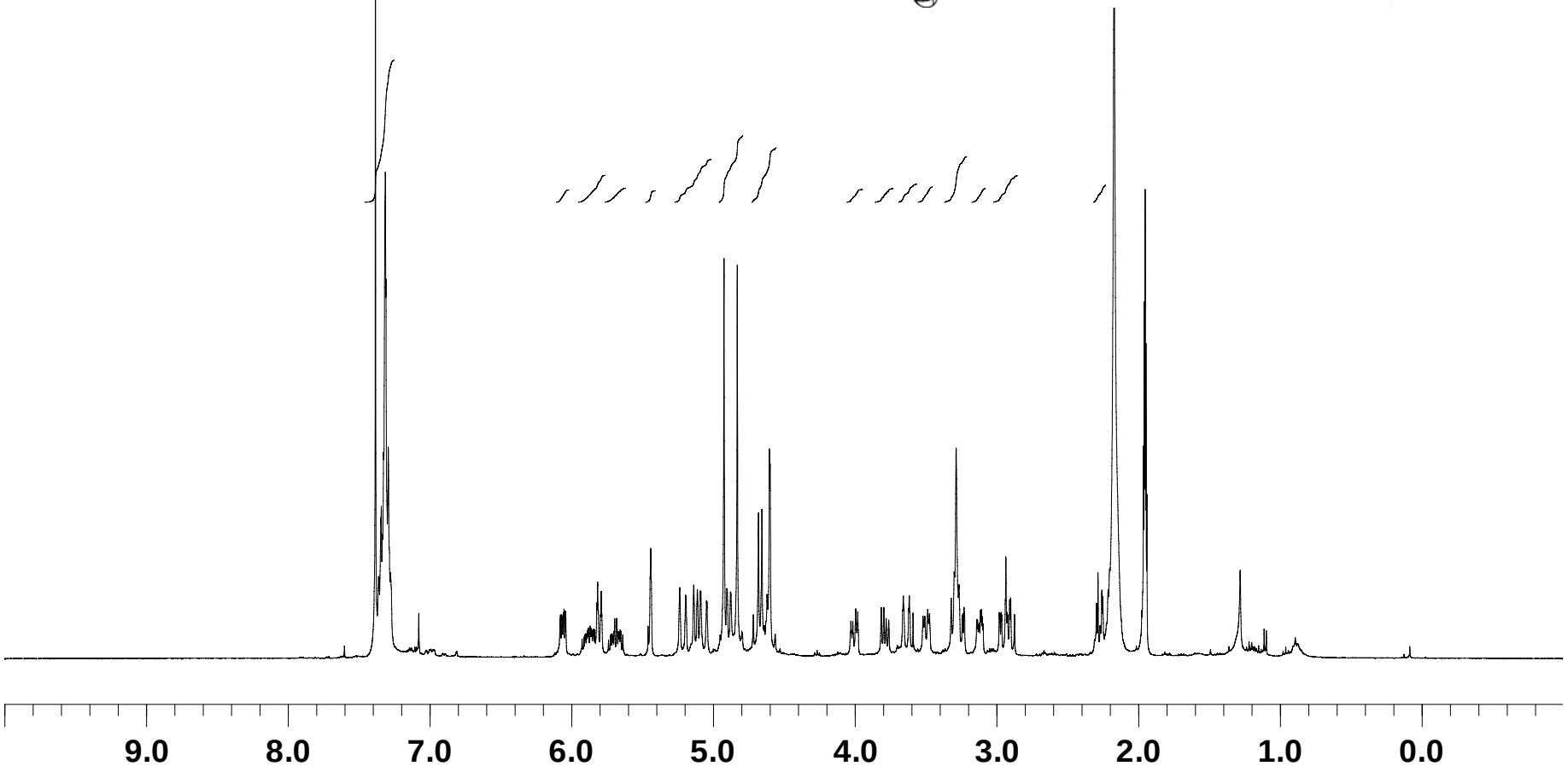


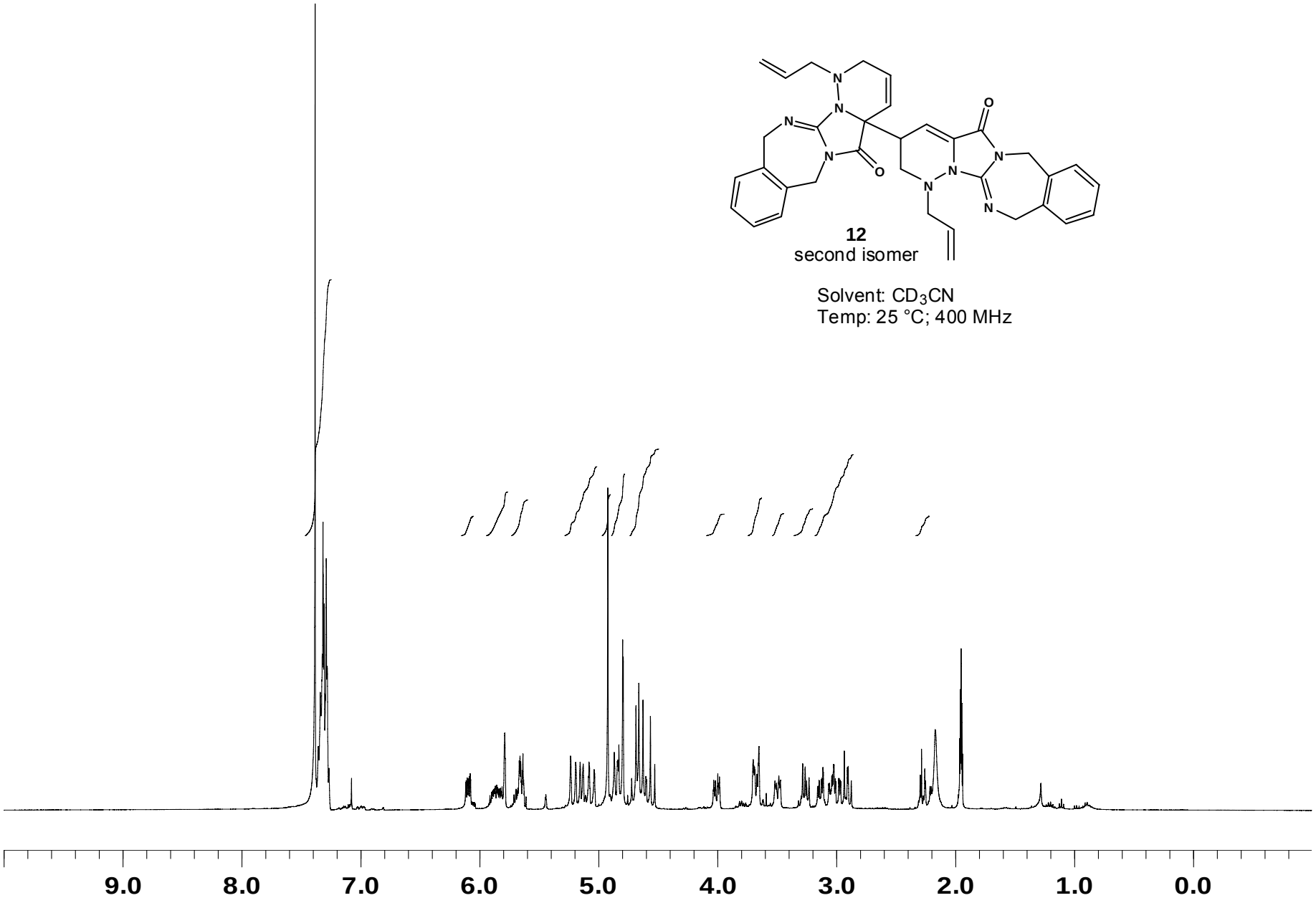


12
first isomer

Solvent: CD_3CN
Temp: 25 °C; 400 MHz

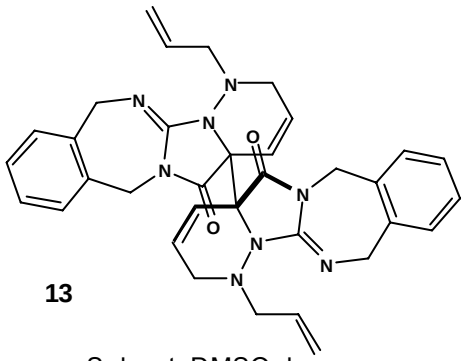






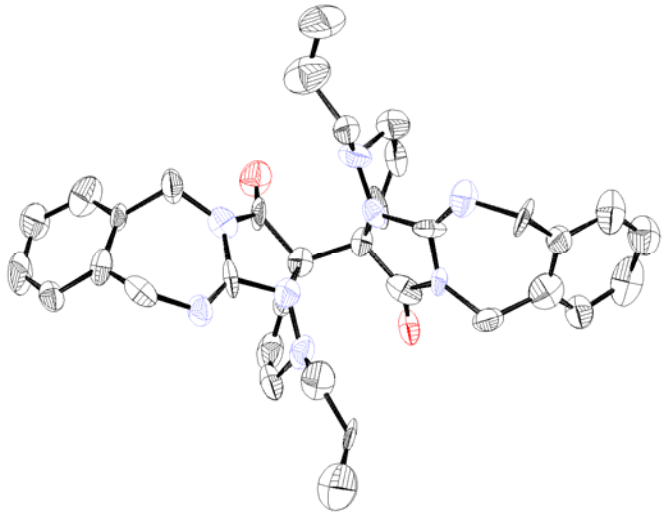
12
second isomer

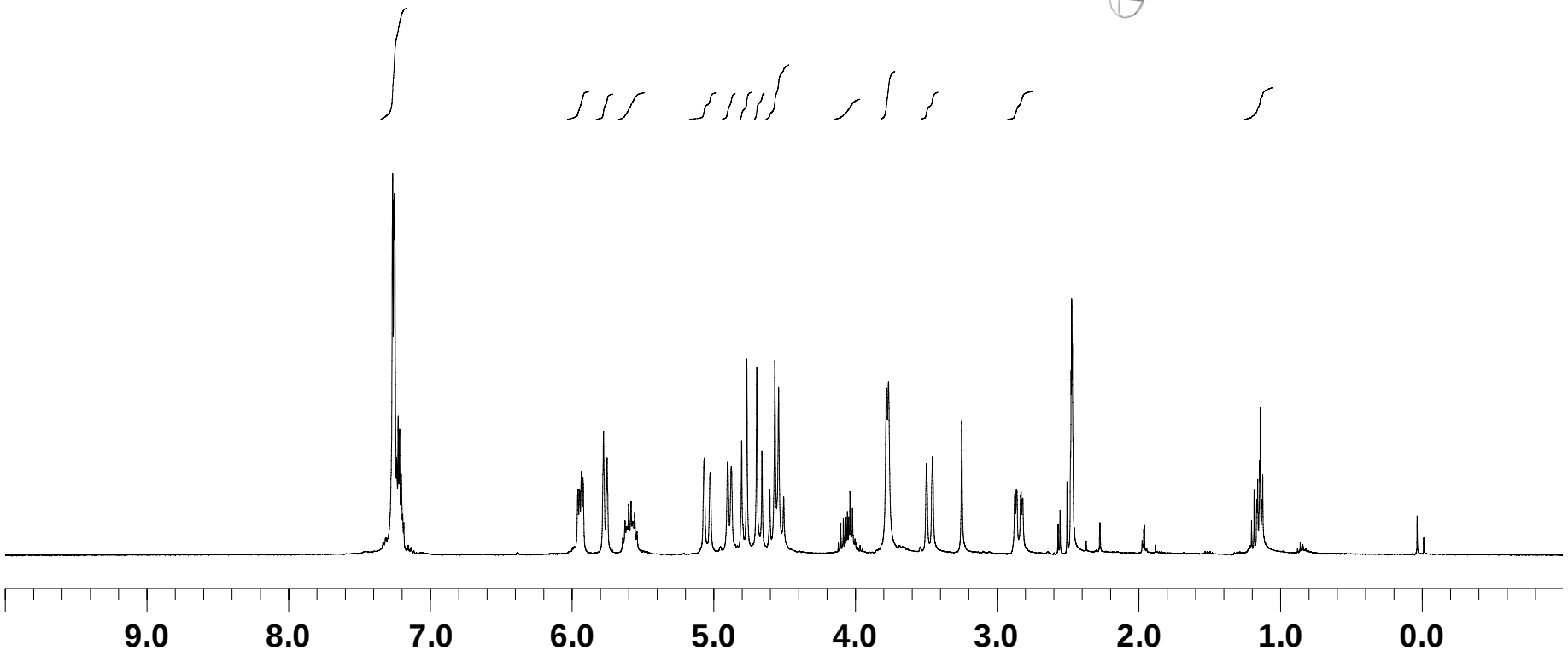
Solvent: CD_3CN
Temp: 25 °C; 400 MHz

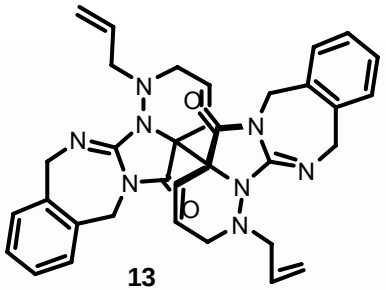


13

Solvent: DMSO-d_6
Temp: 25 °C; 500 MHz

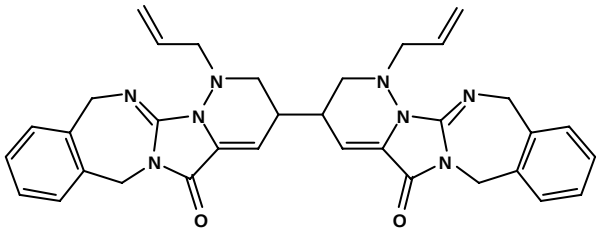






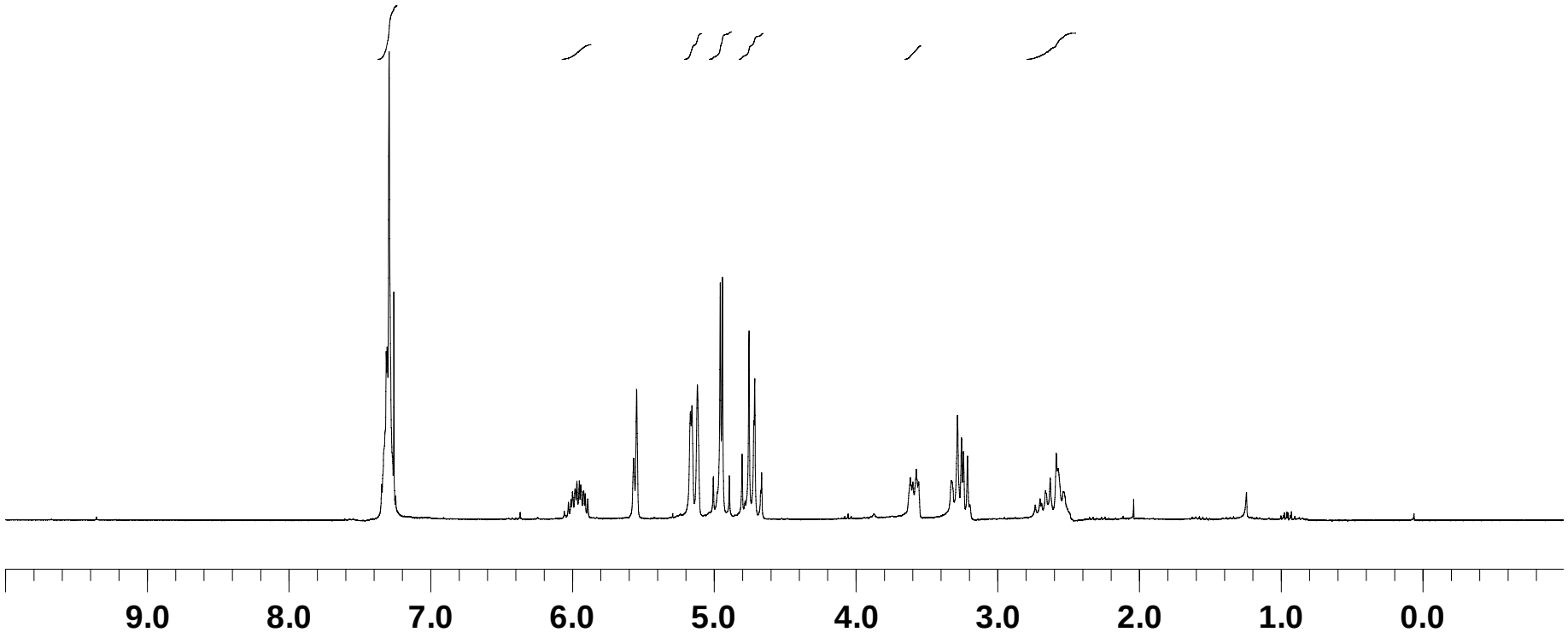
13

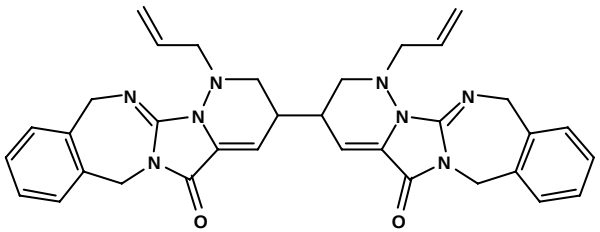
Solvent: DMSO-d6
400 MHz



14a/b

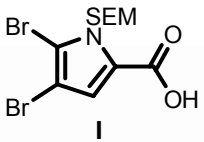
Solvent: $CDCl_3$
Temp: 25 °C; 300 MHz





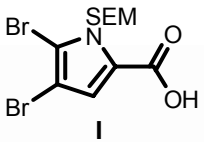
14a/b

Solvent: $CDCl_3$
Temp: 25 °C; 75 MHz
^{13}C APT



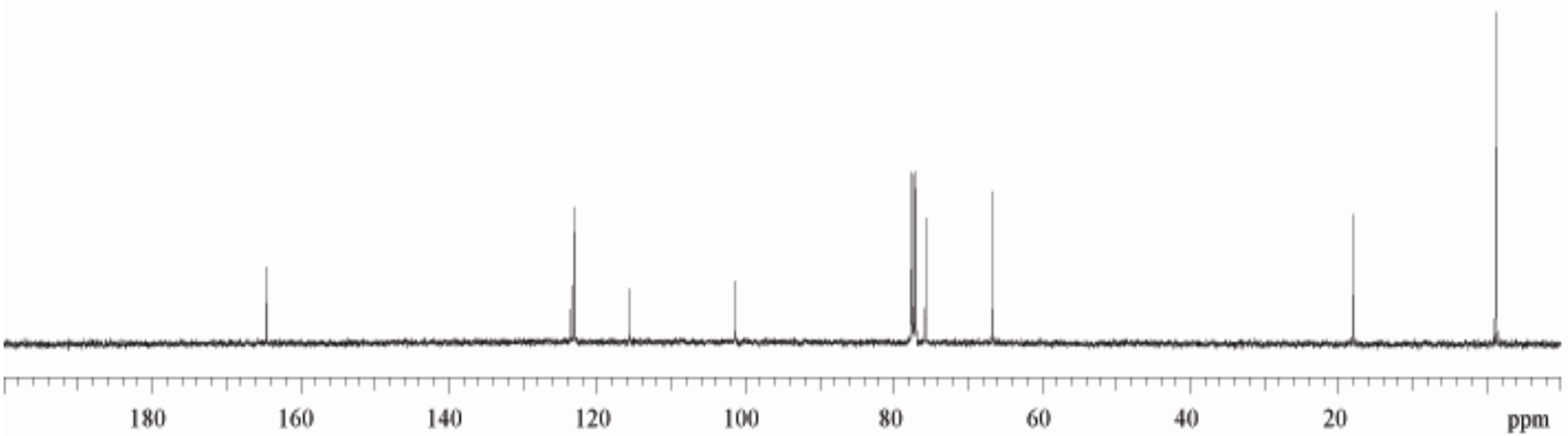
I

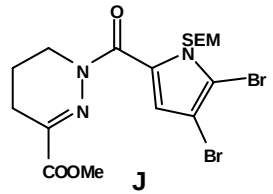
Solvent: CDCl3
400 MHz



I

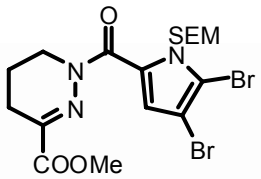
Solvent: CDCl3
75 MHz





J

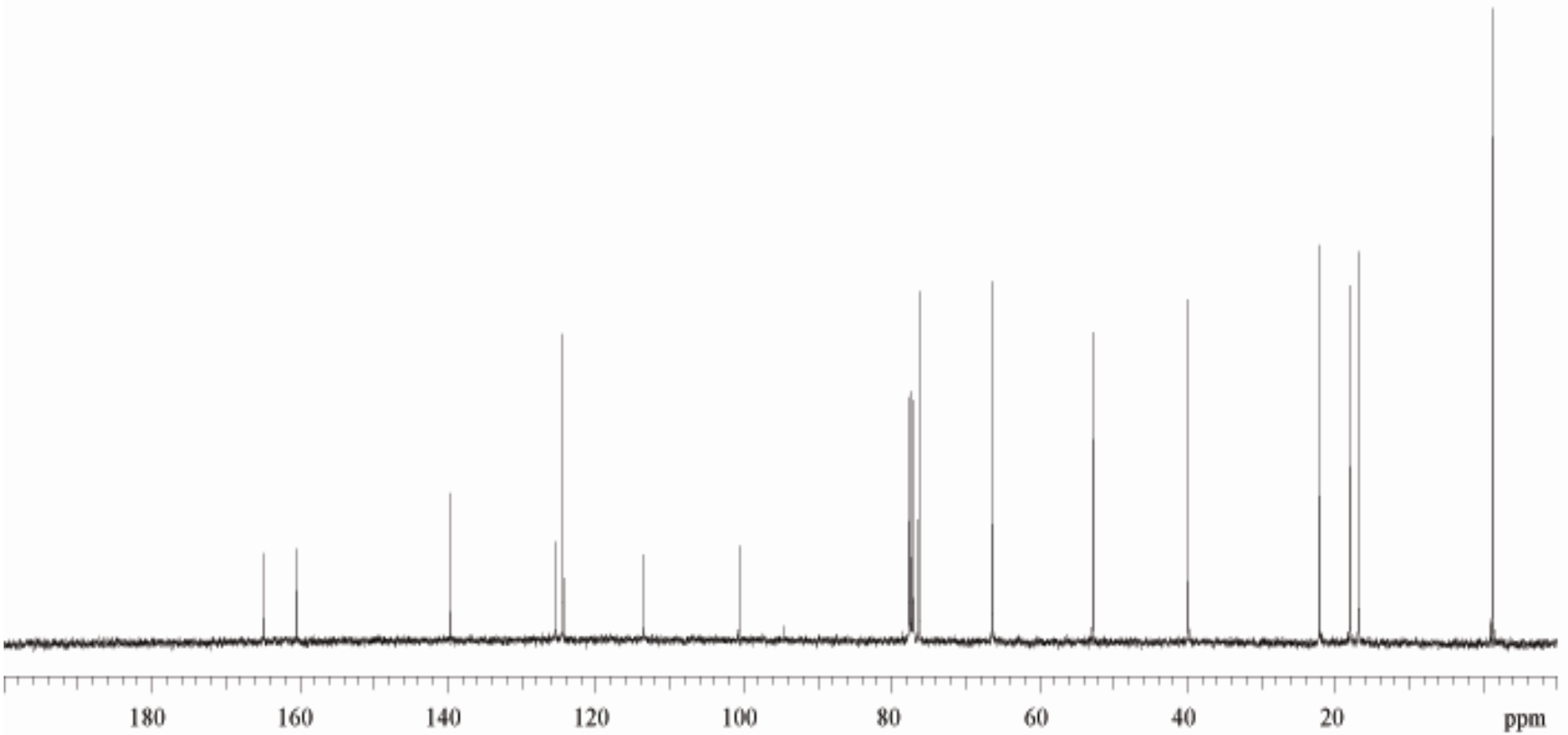
Solvent: $CDCl_3$
Temp: 25 °C; 400 MHz

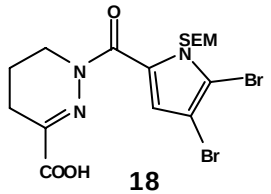


J

Solvent: CDCl3

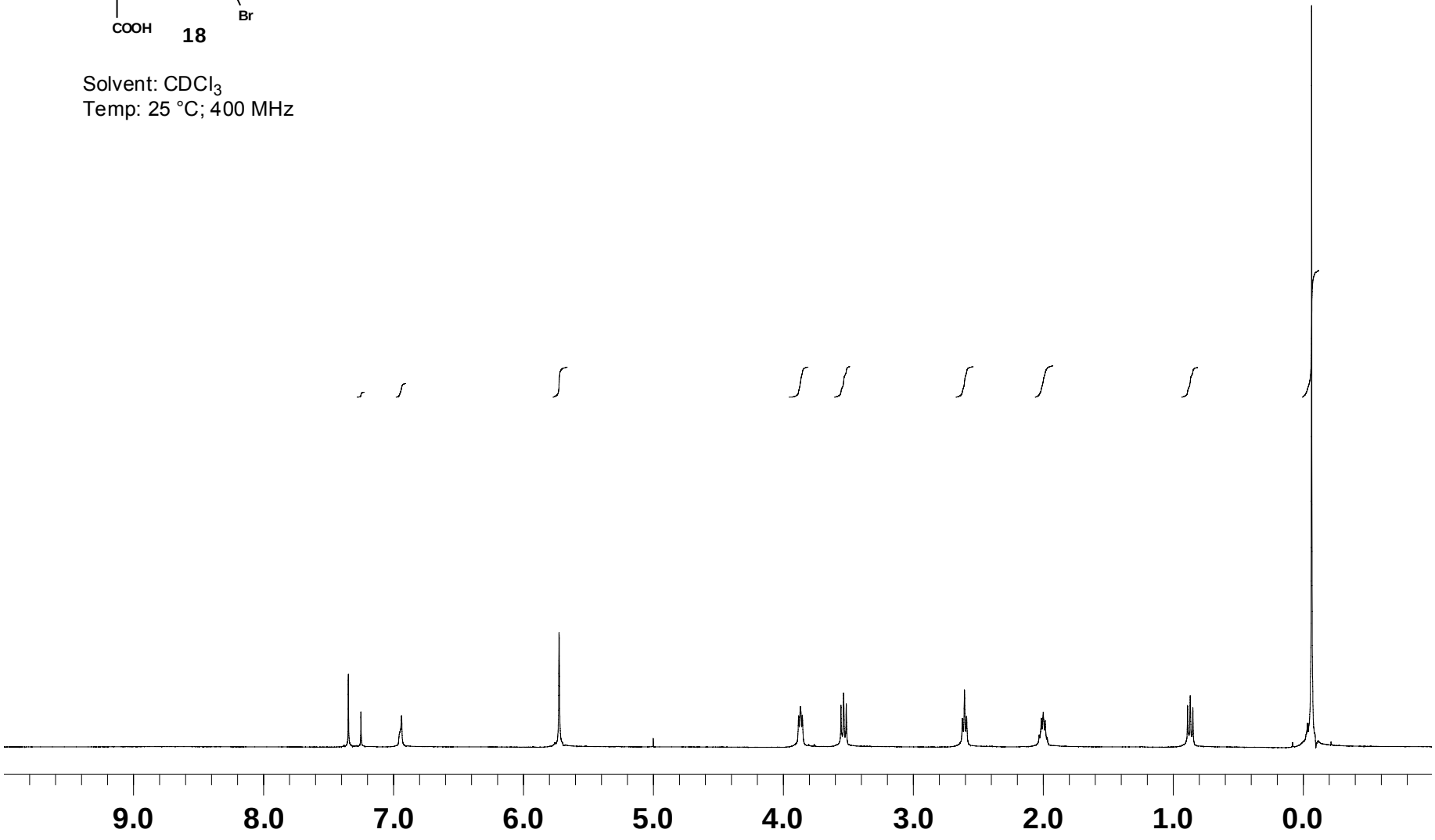
75 MHz

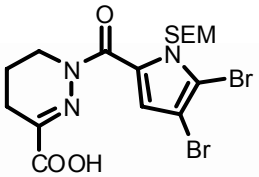




18

Solvent: $CDCl_3$
Temp: 25 °C; 400 MHz

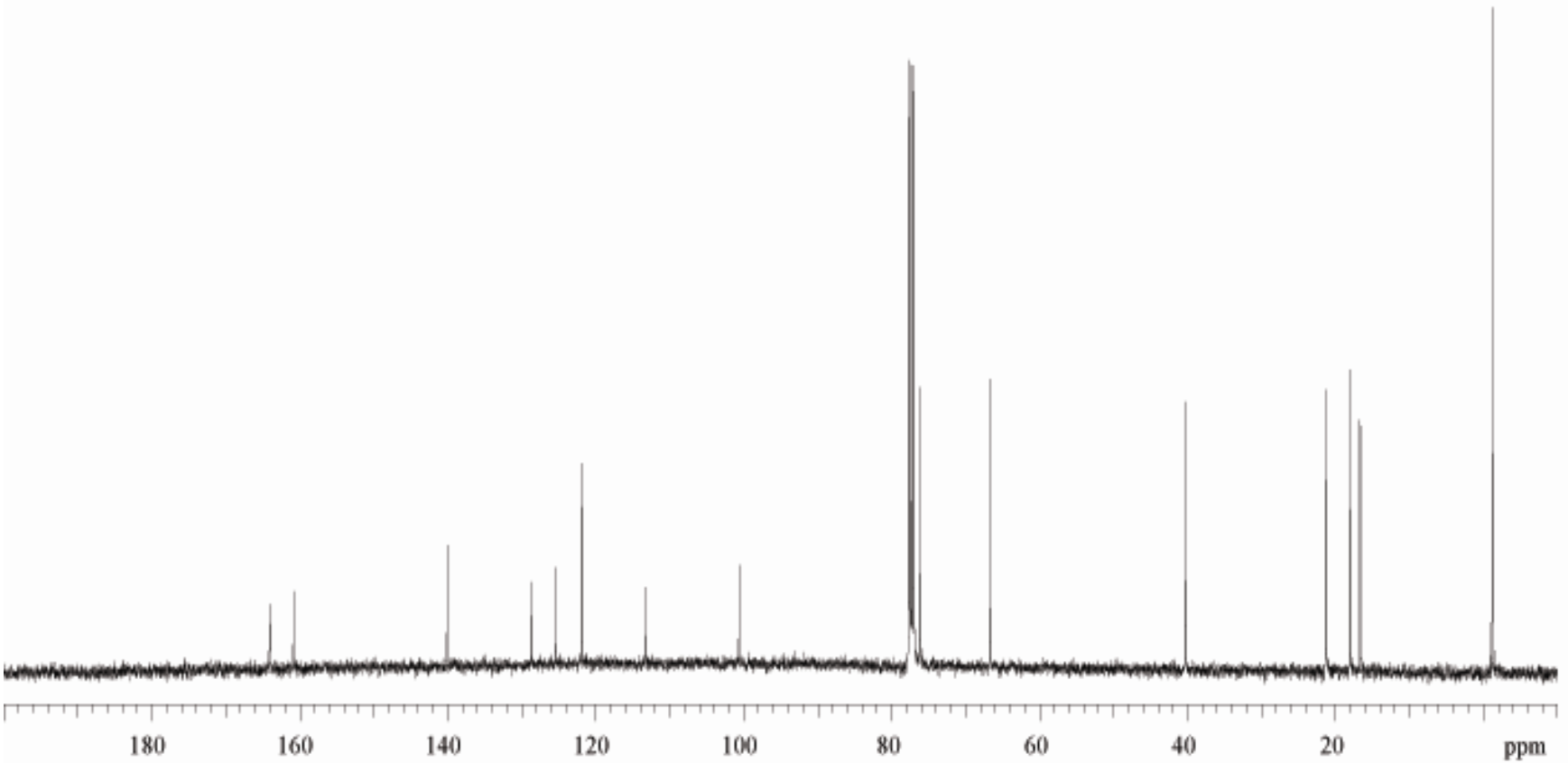


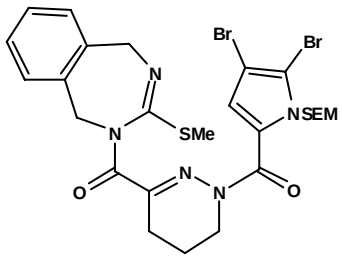


18

Solvent: CDCl3

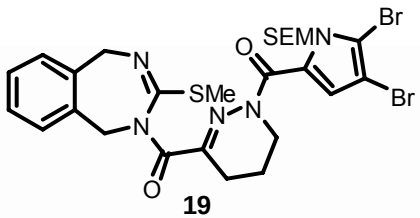
75 MHz





19

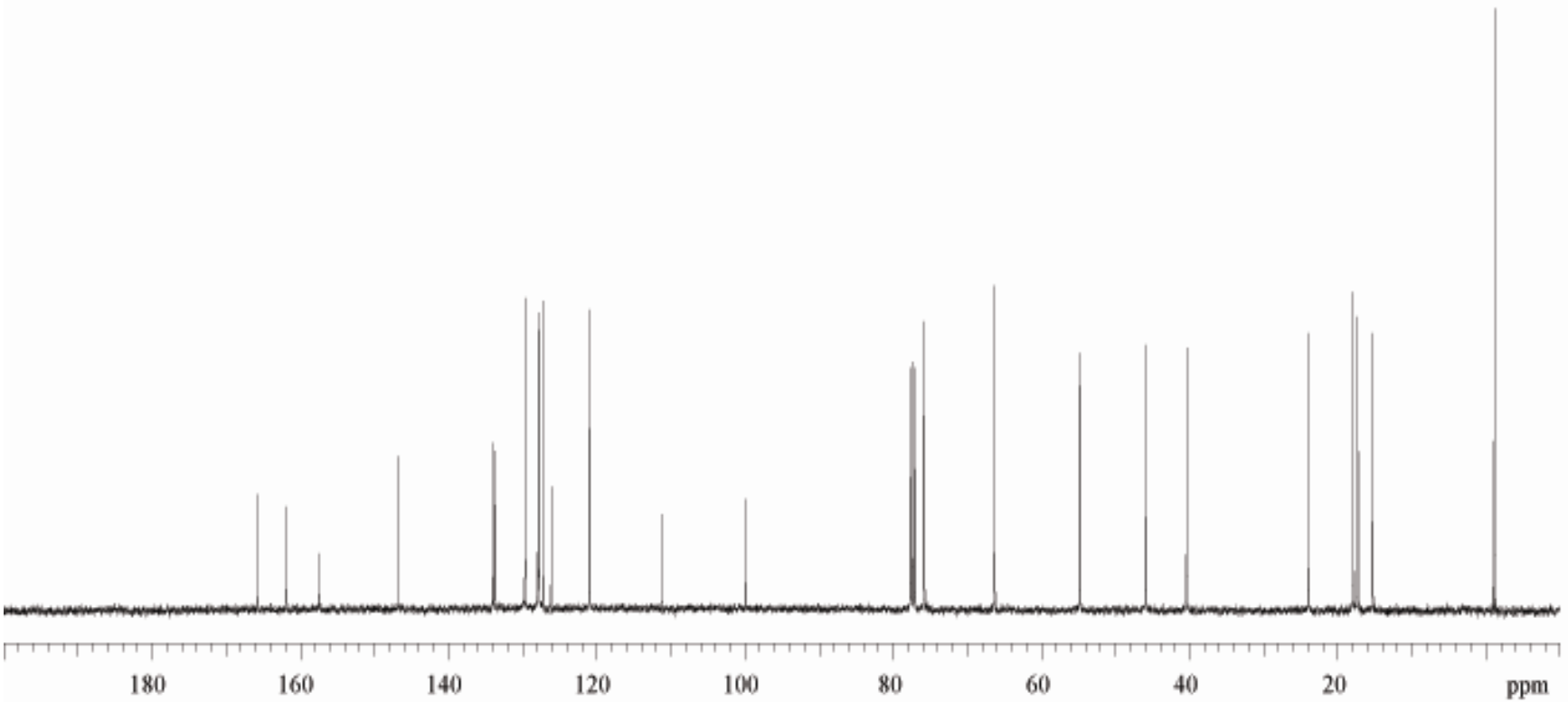
Solvent: $CDCl_3$
Temp: 25 °C; 400 MHz

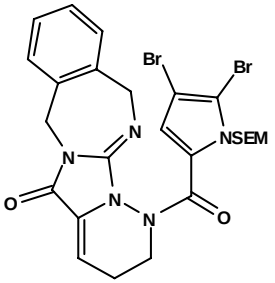


19

Solvent: CDCl3

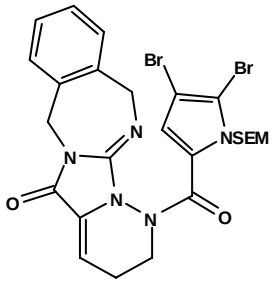
75 MHz





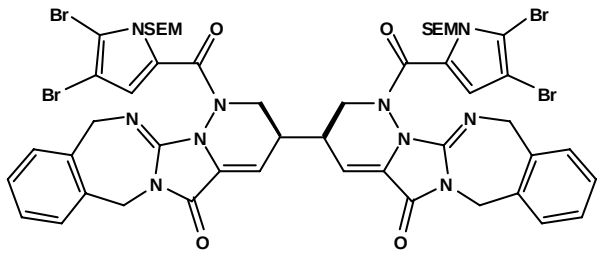
20

Solvent: CD_3CN
Temp: 70 °C; 400 MHz



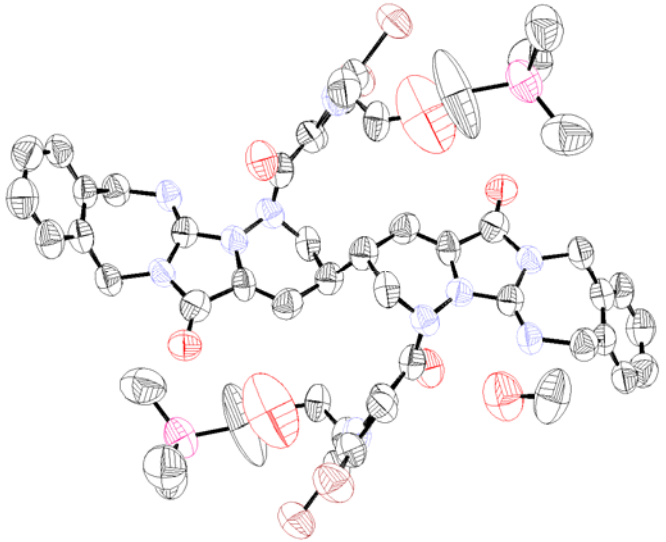
20

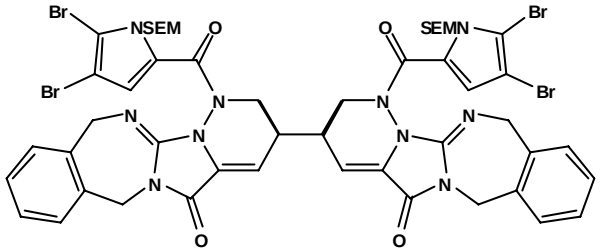
Solvent: CD_3CN
Temp: 70 °C; 100 MHz



21 (*meso*)

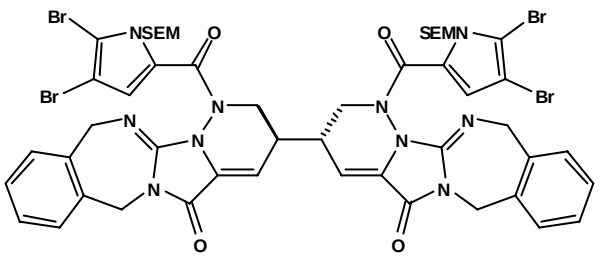
Solvent: CD_3CN
Temp: 70 °C; 400 MHz





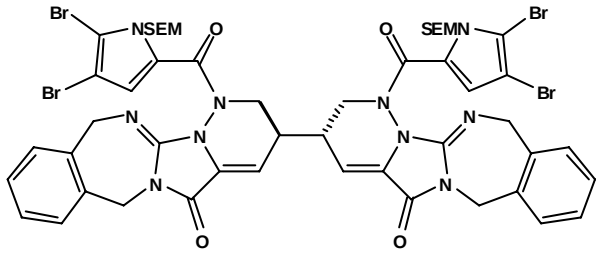
21 (*meso*)

Solvent: CD_3CN
Temp: 70 °C; 100 MHz



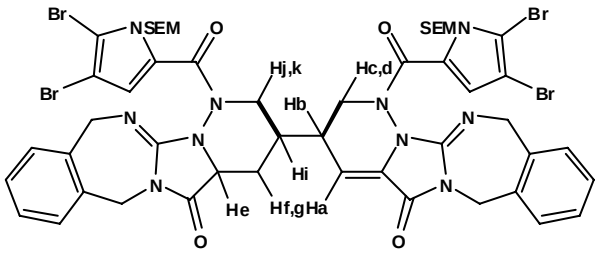
21 (C_2)

Solvent: CD_3CN
Temp: 70 °C; 400 MHz



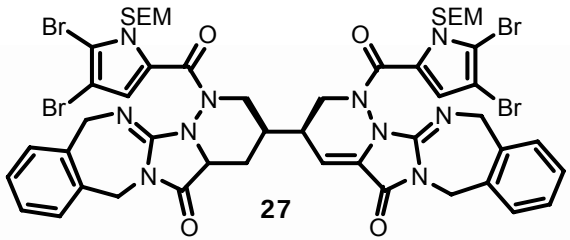
21 (C_2)

Solvent: CD_3CN
Temp: 70 °C; 100 MHz

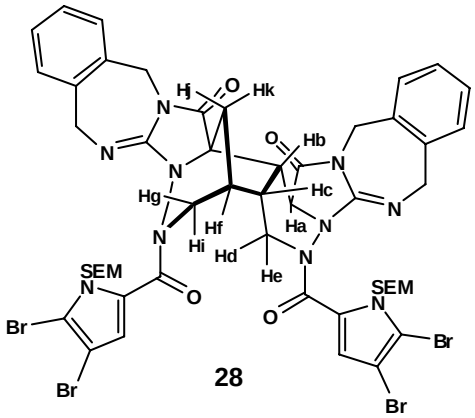


27
one isomer
unknown stereochemisty

Solvent: CD_3CN
Temp: 70 °C; 400 MHz

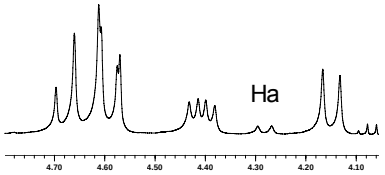


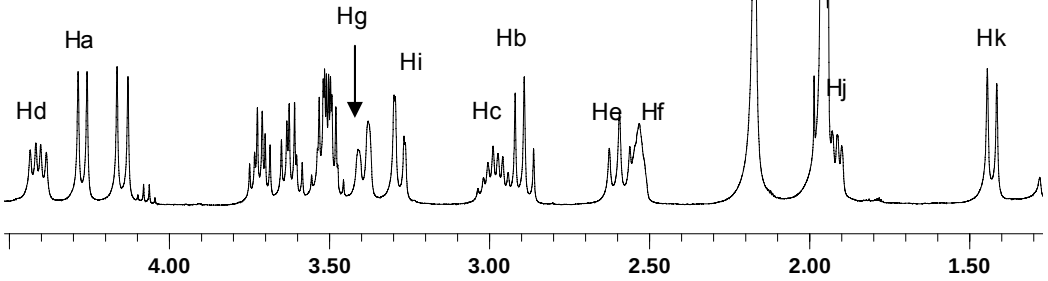
Solvent: CDCl3
75 MHz

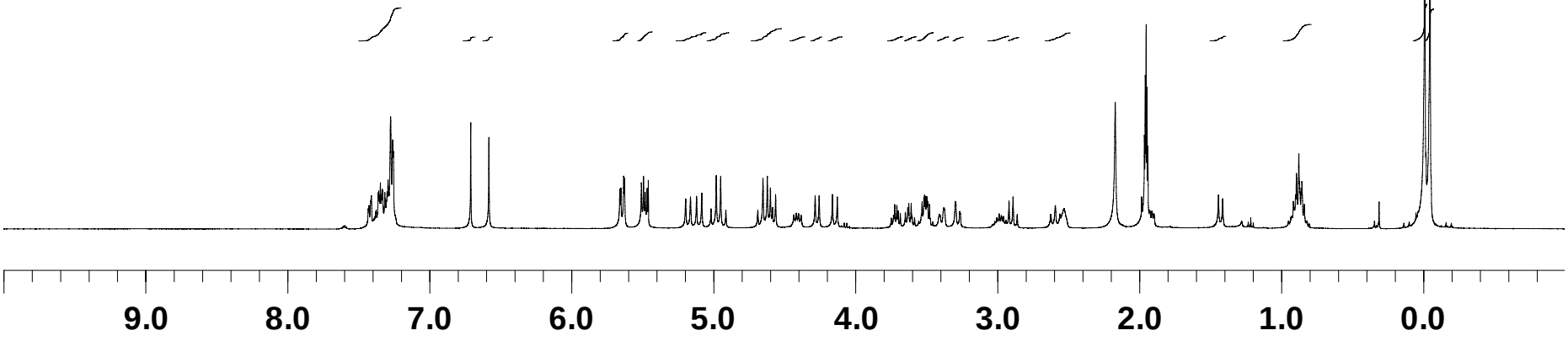


Solvent: CD_3CN
Temp: 25 °C; 400 MHz

Partial spectrum of the same sample being treated with D_2O overnight.



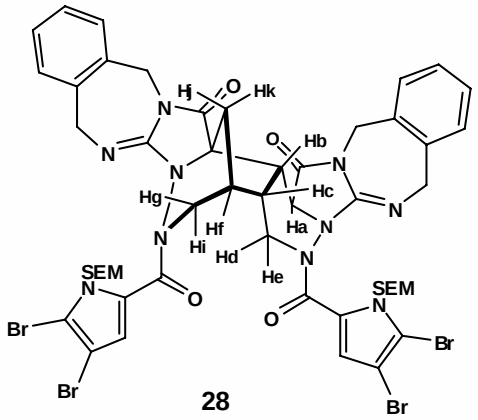




STANDARD 1H OBSERVE

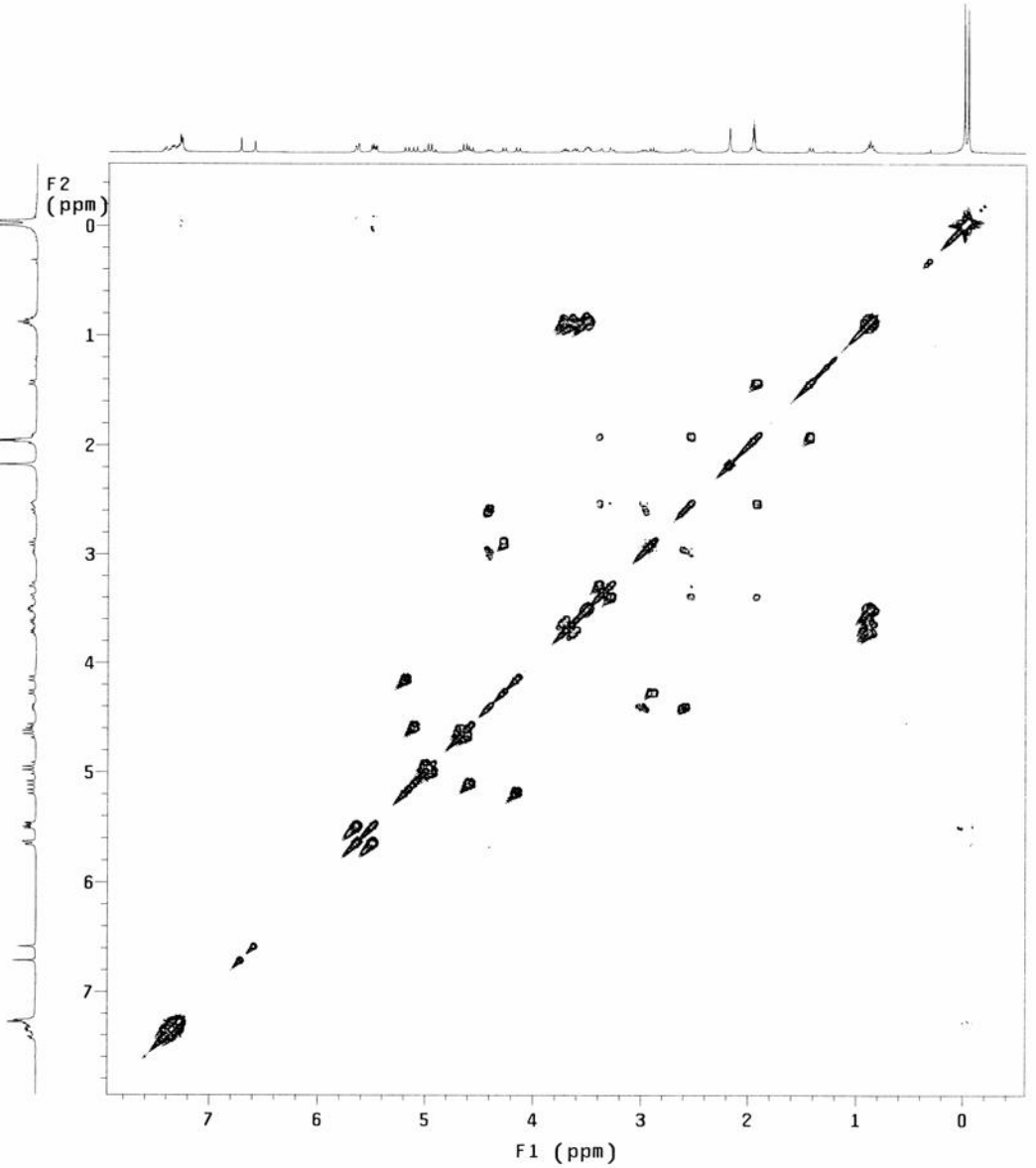
Pulse Sequence: relayh
Solvent: CD3CN
Ambient temperature
File: QL-IV-157-PTLC1-COSY
INOVA-400 "pele400"

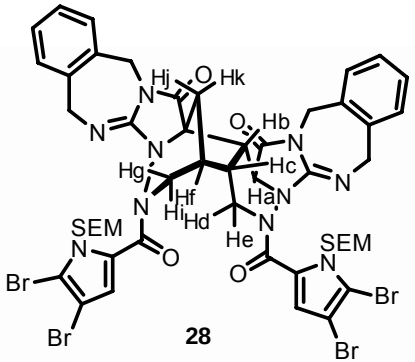
Relax. delay 1.000 sec
COSY 90-45
Acq. time 0.150 sec
Width 3414.1 Hz
2D Width 3414.1 Hz
2 repetitions
512 increments
OBSERVE H1, 399.7814203 MHz
DATA PROCESSING
Sine bell 0.075 sec
F1 DATA PROCESSING
Sine bell 0.074 sec
FT size 1024 x 1024
Total time 21 min, 7 sec



28

Solvent: CD3CN
400 MHz

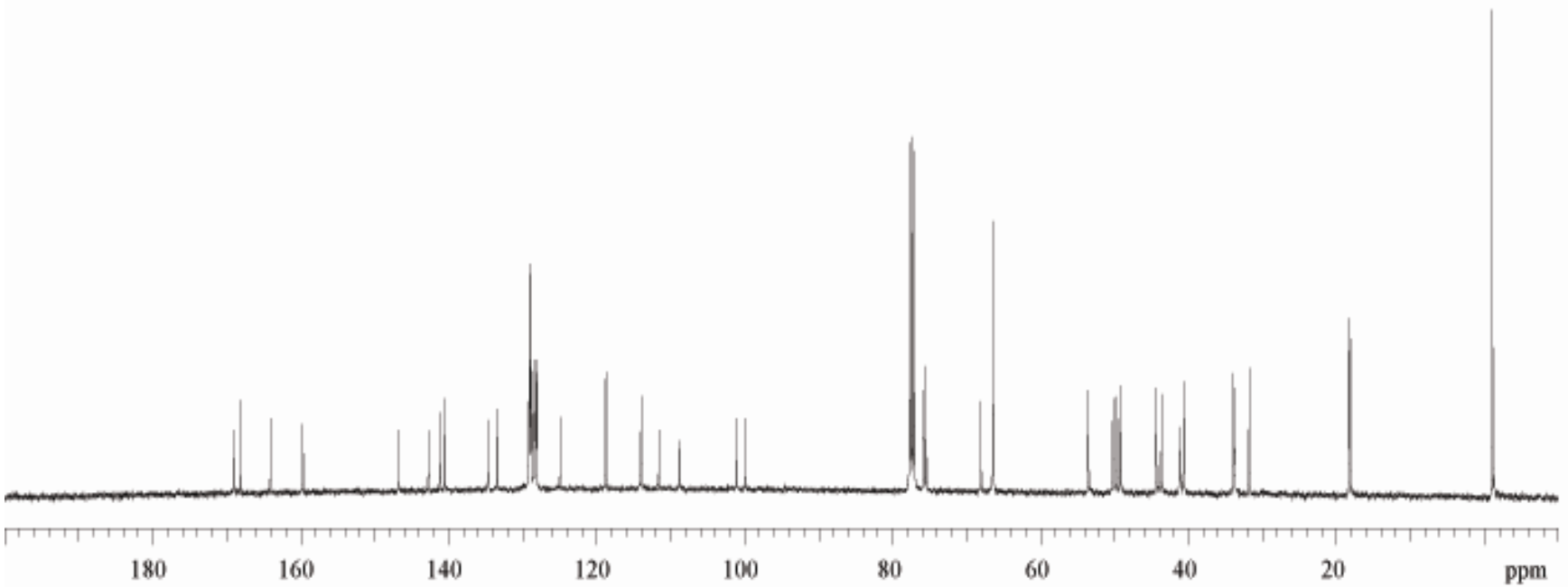


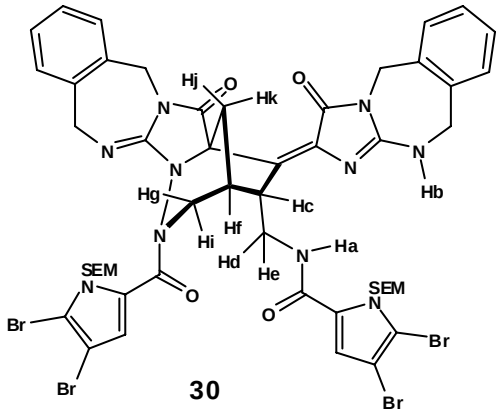


28

Solvent: CDCl3

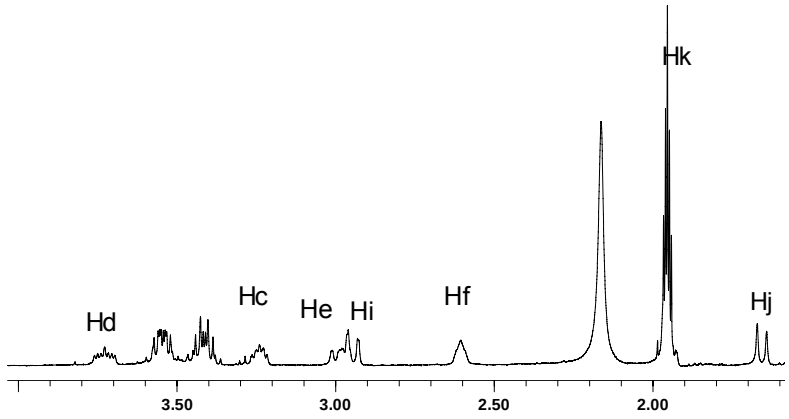
75 MHz

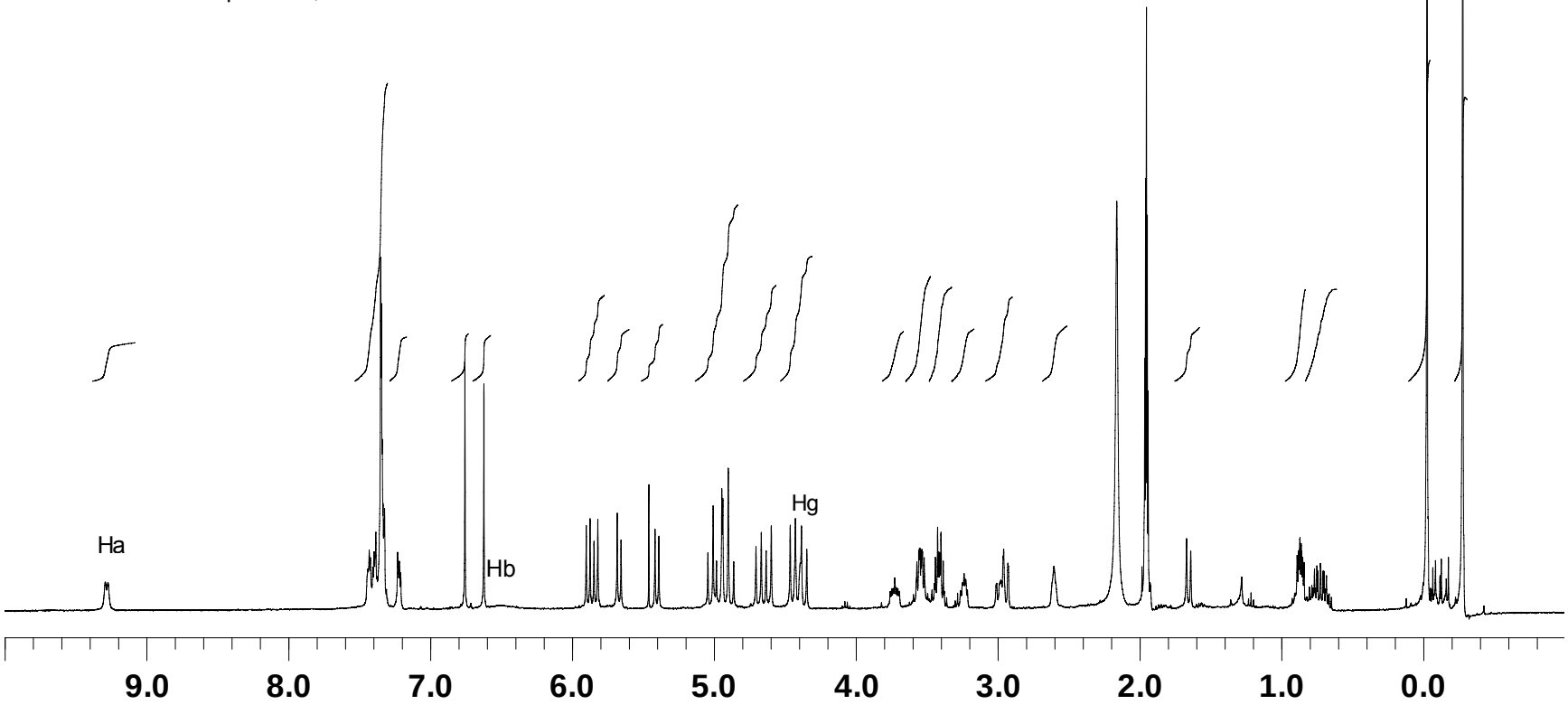




30

Solvent: CD_3CN
Temp: 50 °C; 400 MHz

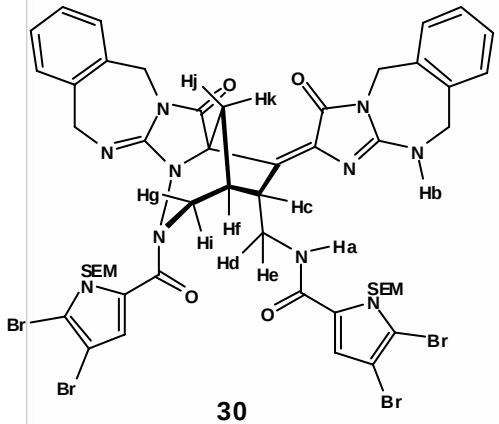




STANDARD 1H OBSERVE

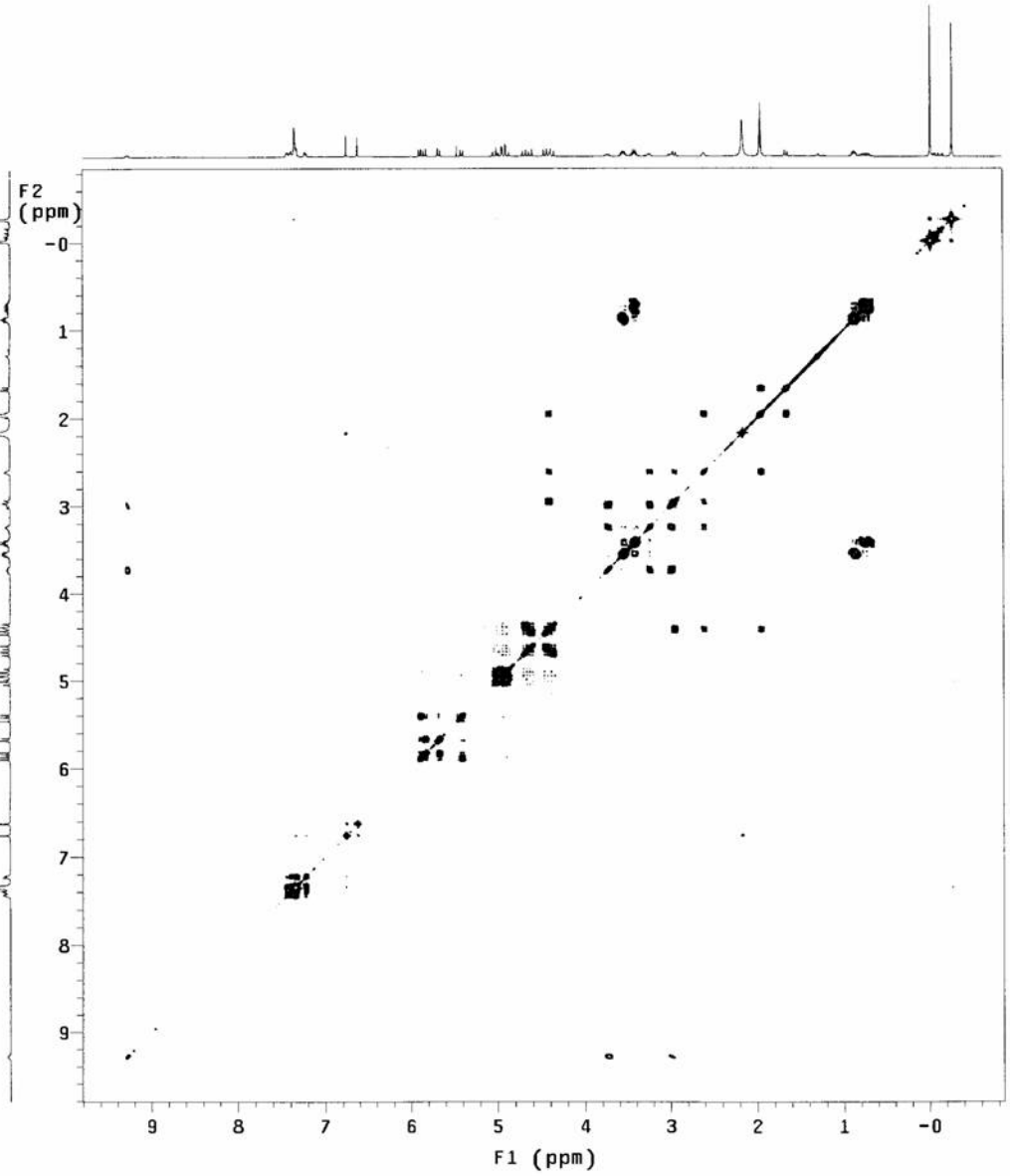
Pulse Sequence: relayh
Solvent: CD3Cn
Ambient temperature
INOVA-400 "pele400"

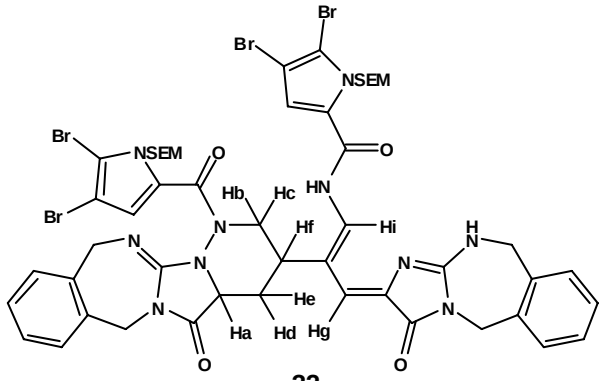
Relax. delay 1.000 sec
COSY 90-45
Acq. time 0.240 sec
Width 4265.8 Hz
2D Width 4265.8 Hz
4 repetitions
500 increments
OBSERVE H1, 399.7814203 MHz
DATA PROCESSING
Sine bell 0.120 sec
F1 DATA PROCESSING
Sine bell 0.121 sec
FT size 2048 x 2048
Total time 43 min, 40 sec



30

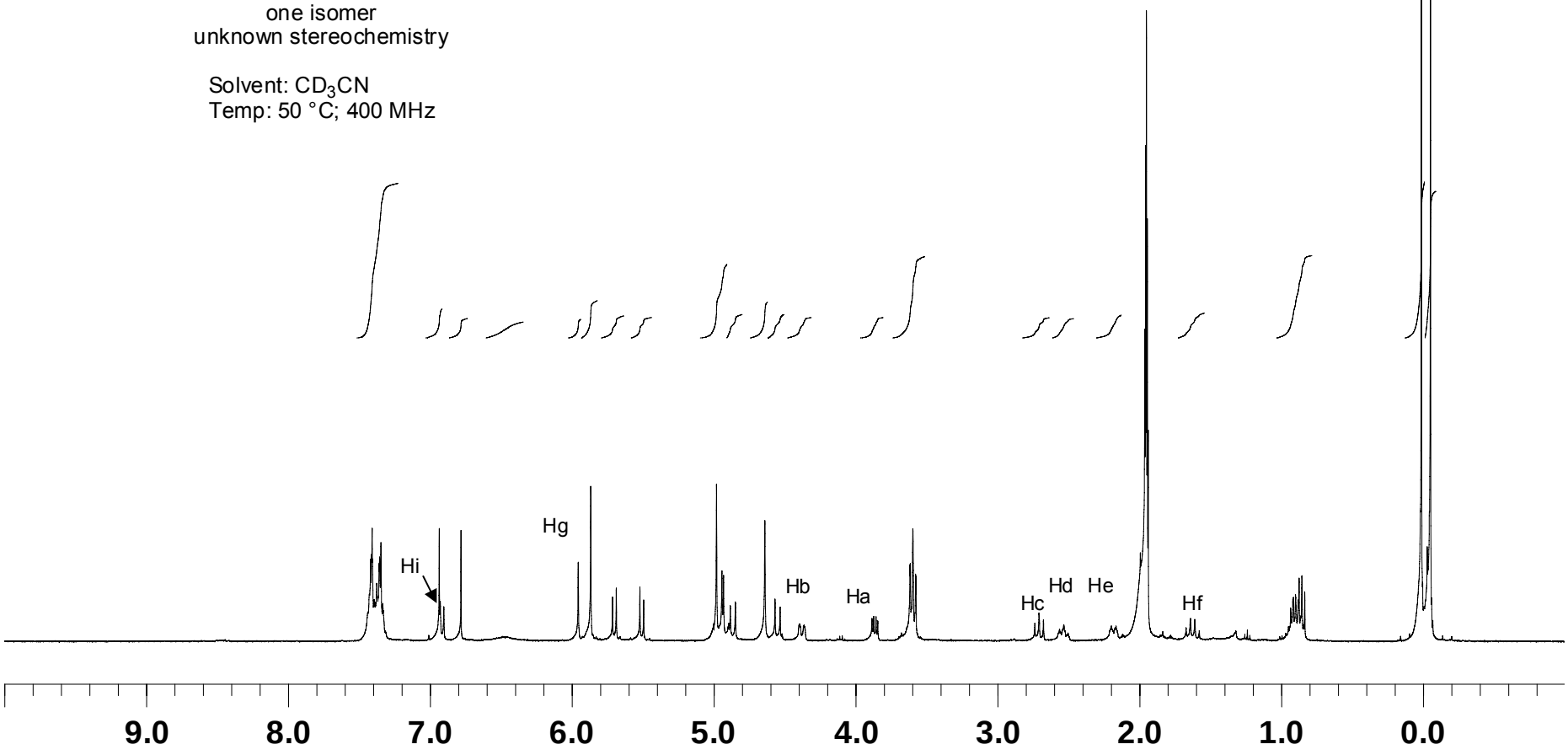
Solvent: CD3CN
400 MHz

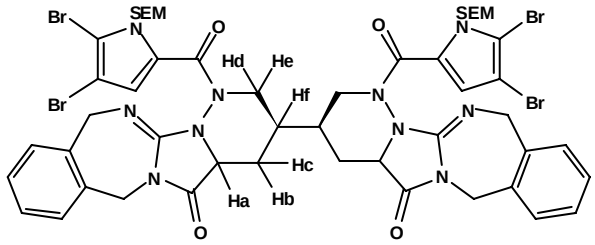




32
one isomer
unknown stereochemistry

Solvent: CD_3CN
Temp: 50 °C; 400 MHz

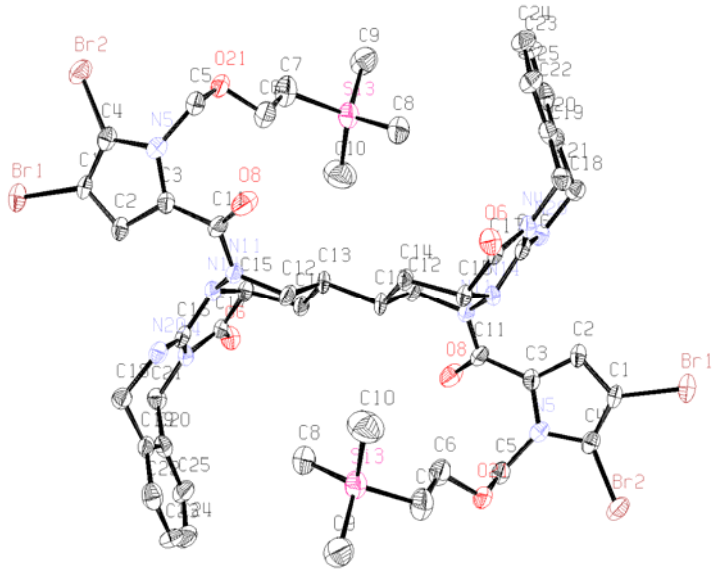


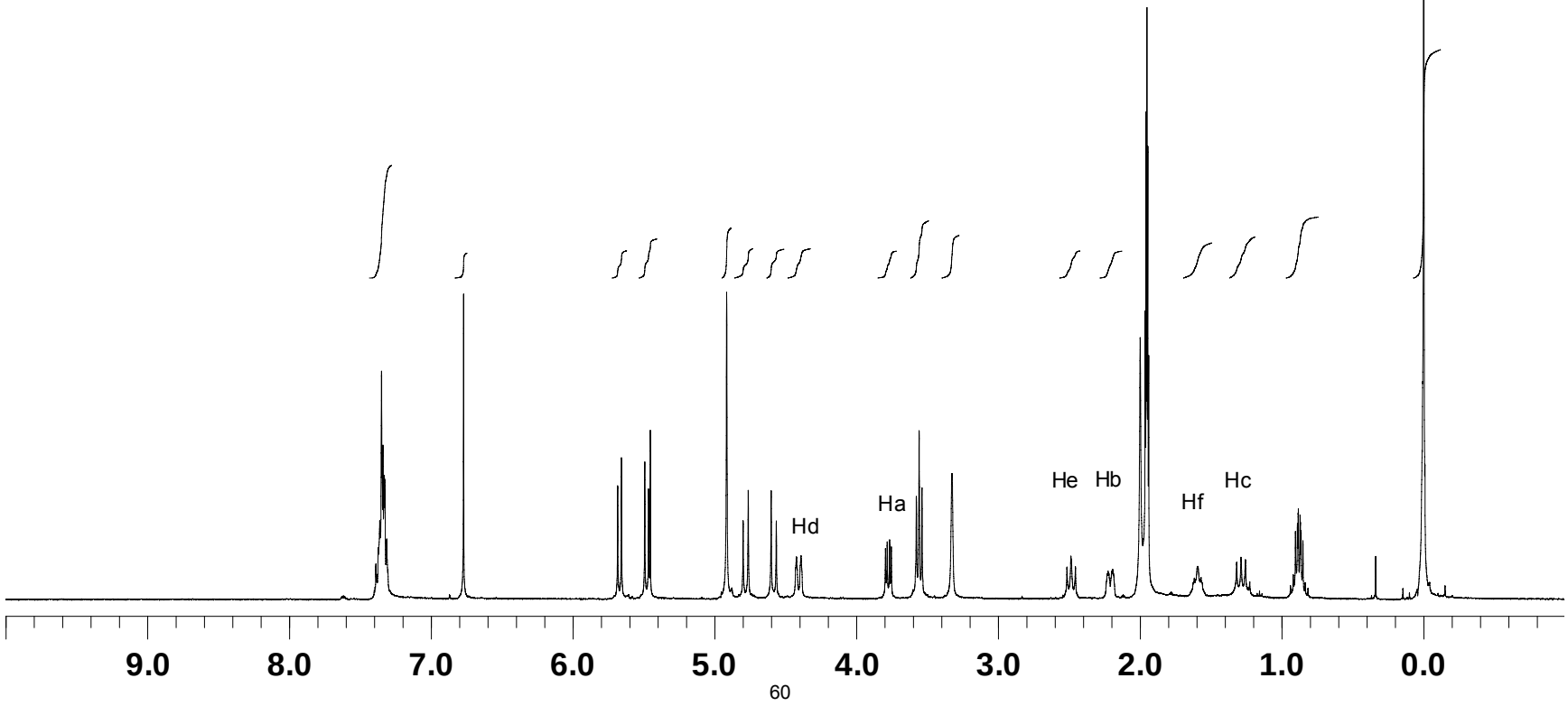


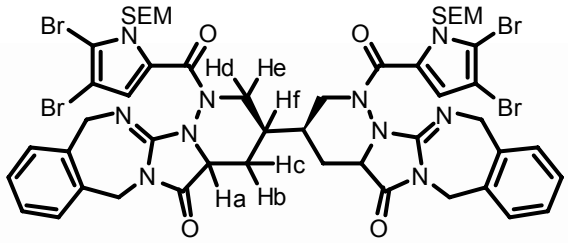
33

Solvent: CD_3CN
Temp: 50 °C; 400 MHz

Note: Spectral data appears to indicate one isomer. However, TLC and PTLC suggest a mixture of two closely related species.



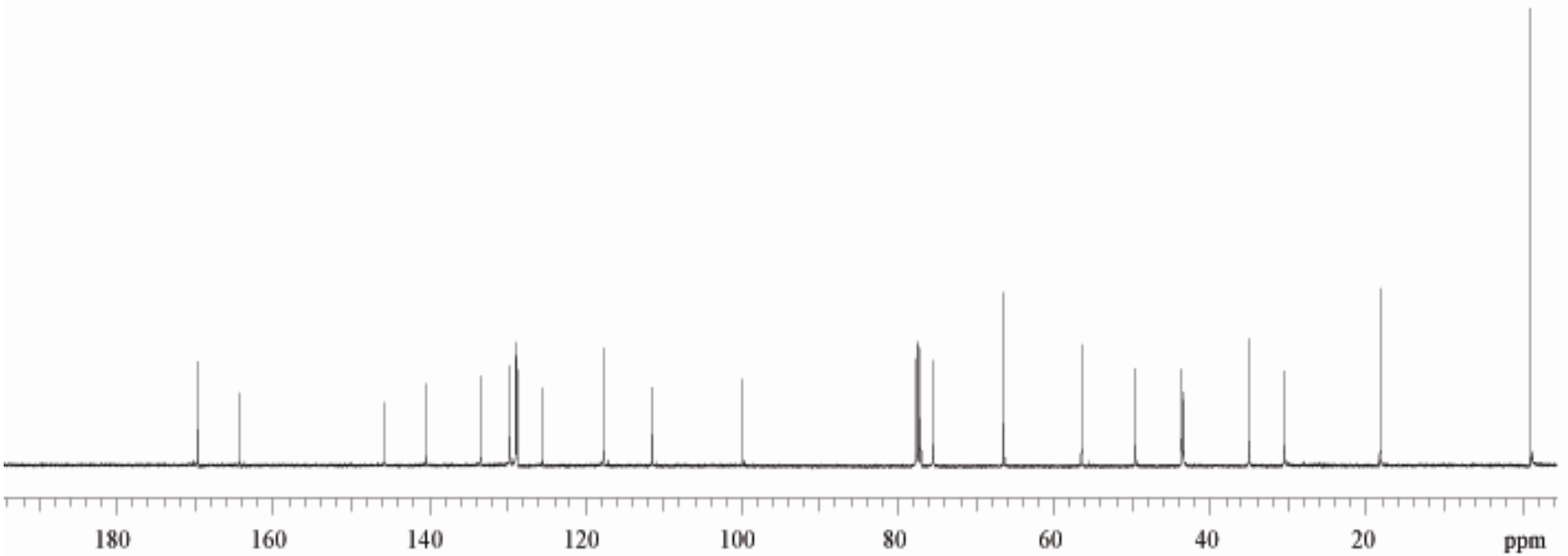


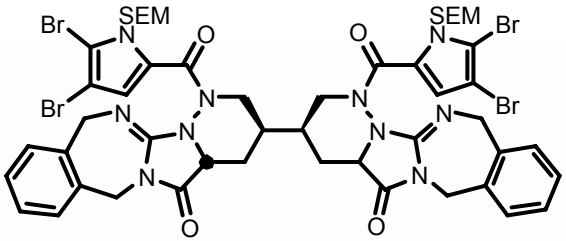


33a + 33b

Solvent: CDCl3

125 MHz

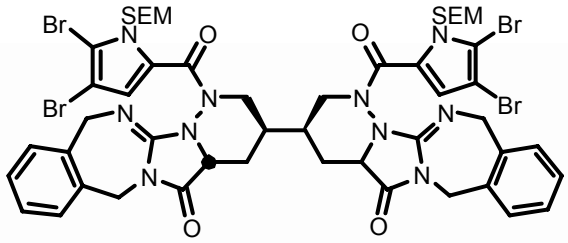




33c

Solvent: CDCl3

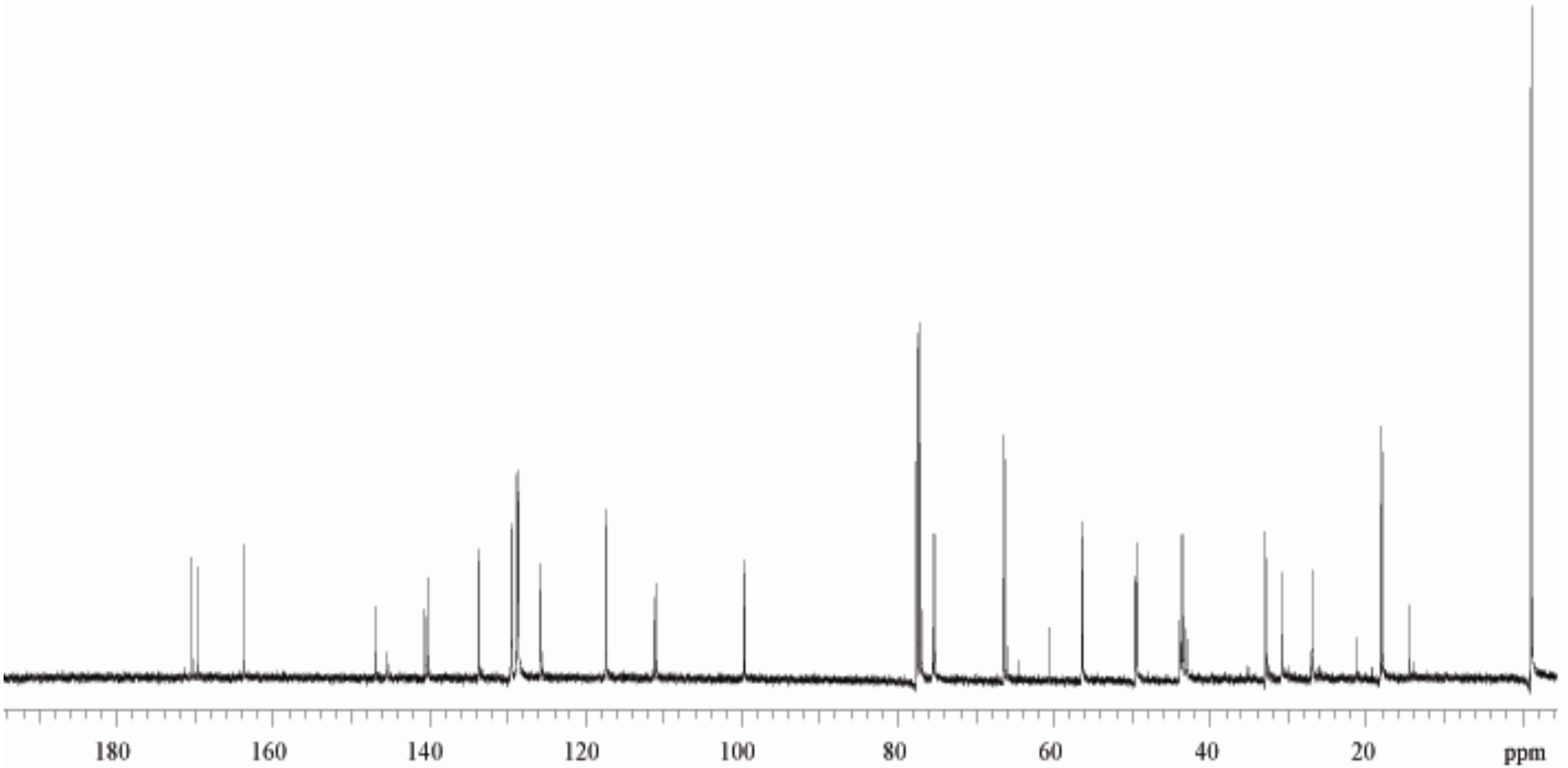
400 MHz

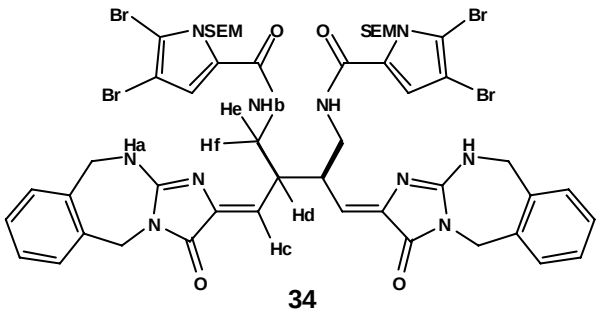


33c

Solvent: CDCl3

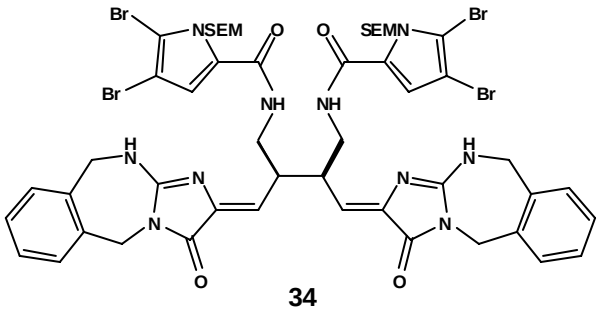
125 MHz





34

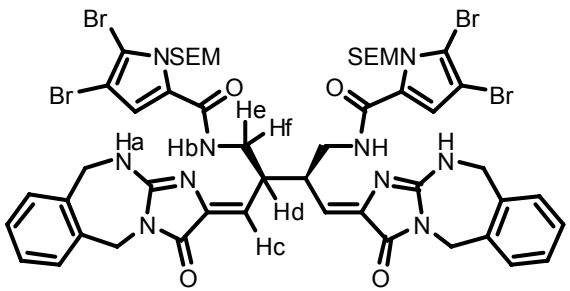
Solvent: DMSO-d_6
Temp: 50 °C; 500 MHz



34

Solvent: DMSO-d_6
Temp: 50 °C; 125 MHz

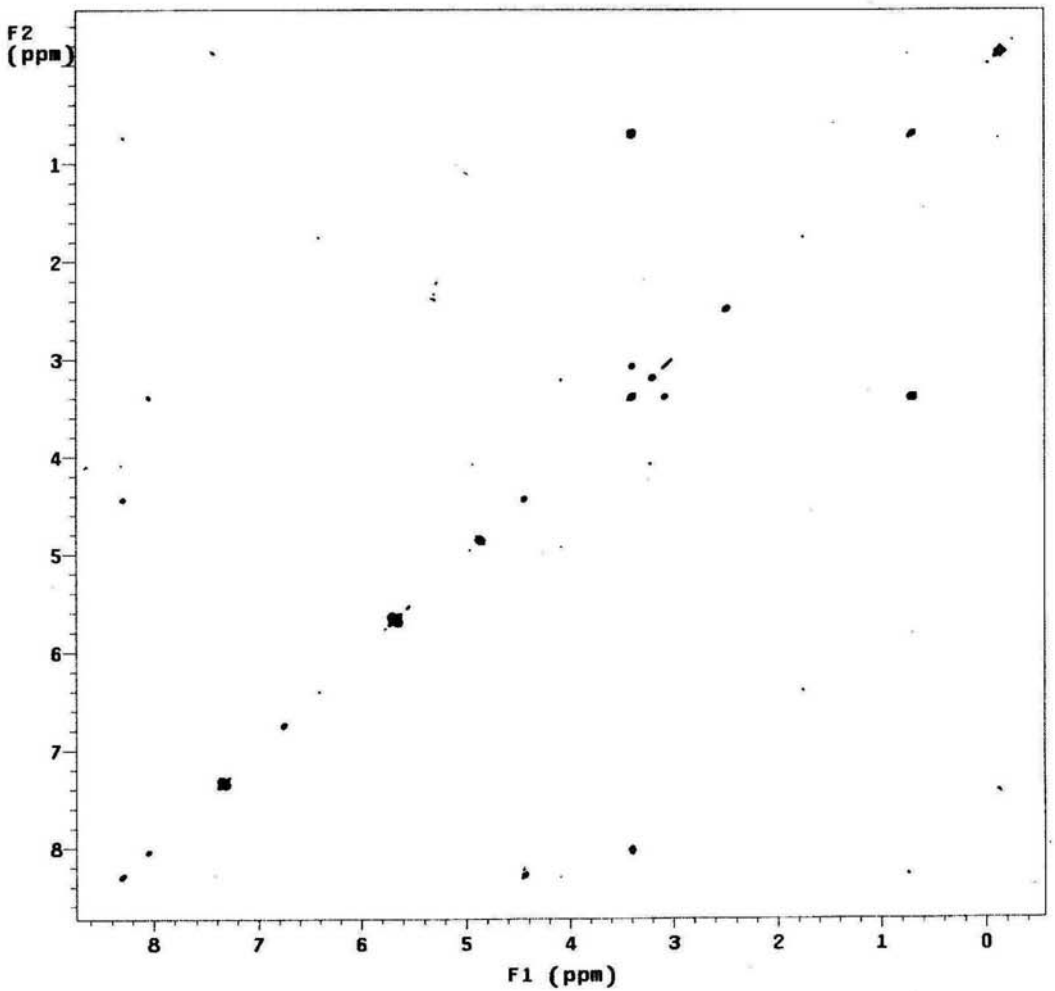
```
STANDARD PROTON PARAMETERS

Pulse Sequence: relayh
 Solvent: DMSO
 Temp. 45.0 C / 318.1 K
File: QL-V-bisalkylidene-HHCOSy
INOVA-500  "IRIS"

 Relax. delay 1.000 sec
 COSY 90-45
 Acq. time 0.220 sec
 Width    4646.0 Hz
 2D Width 4646.0 Hz
 4 repetitions
 512 increments
OBSERVE H1, 499.7802429 MHz
DATA PROCESSING
 Sine bell 0.110 sec
F1 DATA PROCESSING
 Sine bell 0.055 sec
FT size 2048 x 2048
Total time 43 min, 59 sec
```



34

Solvent: CDCl3

500 MHz

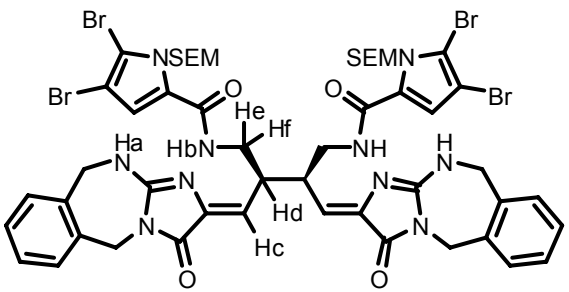


STANDARD PROTON PARAMETERS

Pulse Sequence: noesy

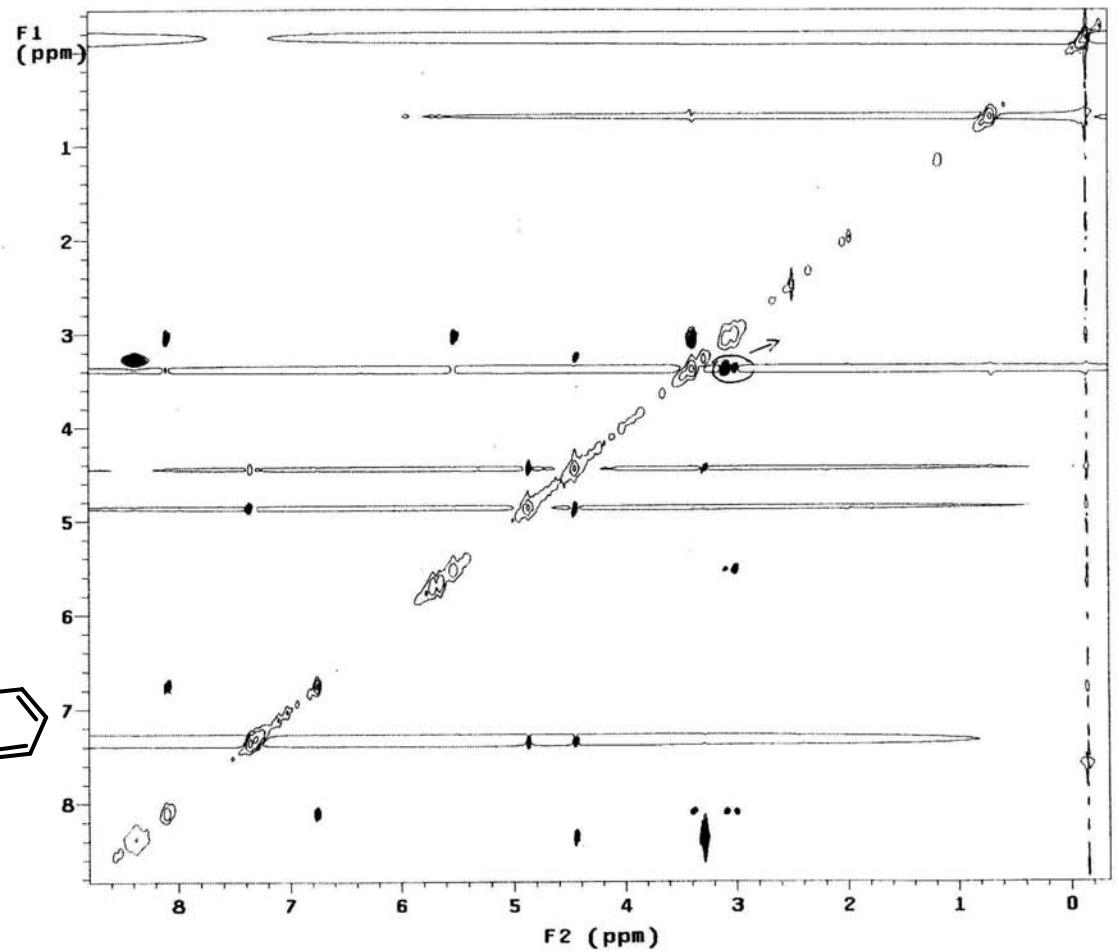
Solvent: DMSO
Temp. 34.0 C / 307.1 K
File: June13-noesy
INOVA-500 "IRIS"

Relax. delay 6.000 sec
Mixing 0.200 sec
Acq. time 0.204 sec
Width 5024.5 Hz
2D Width 5024.5 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 499.7802429 MHz
DATA PROCESSING
Gauss apodization 0.081 sec
F1 DATA PROCESSING
Gauss apodization 0.016 sec
FT size 2048 x 1024
Total time 11 hr, 30 min, 5 sec



34

Solvent: CDCl3
500 MHz

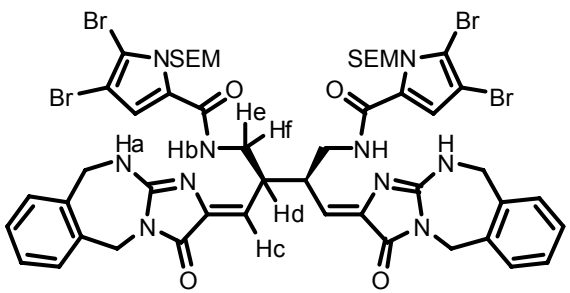


STANDARD PROTON PARAMETERS

Pulse Sequence: gHMQC

Solvent: DMSO
Temp. 34.0 C / 307.1 K
File: QL-V-bisalkylidene-HMQC
INOVA-500 "IRIS"

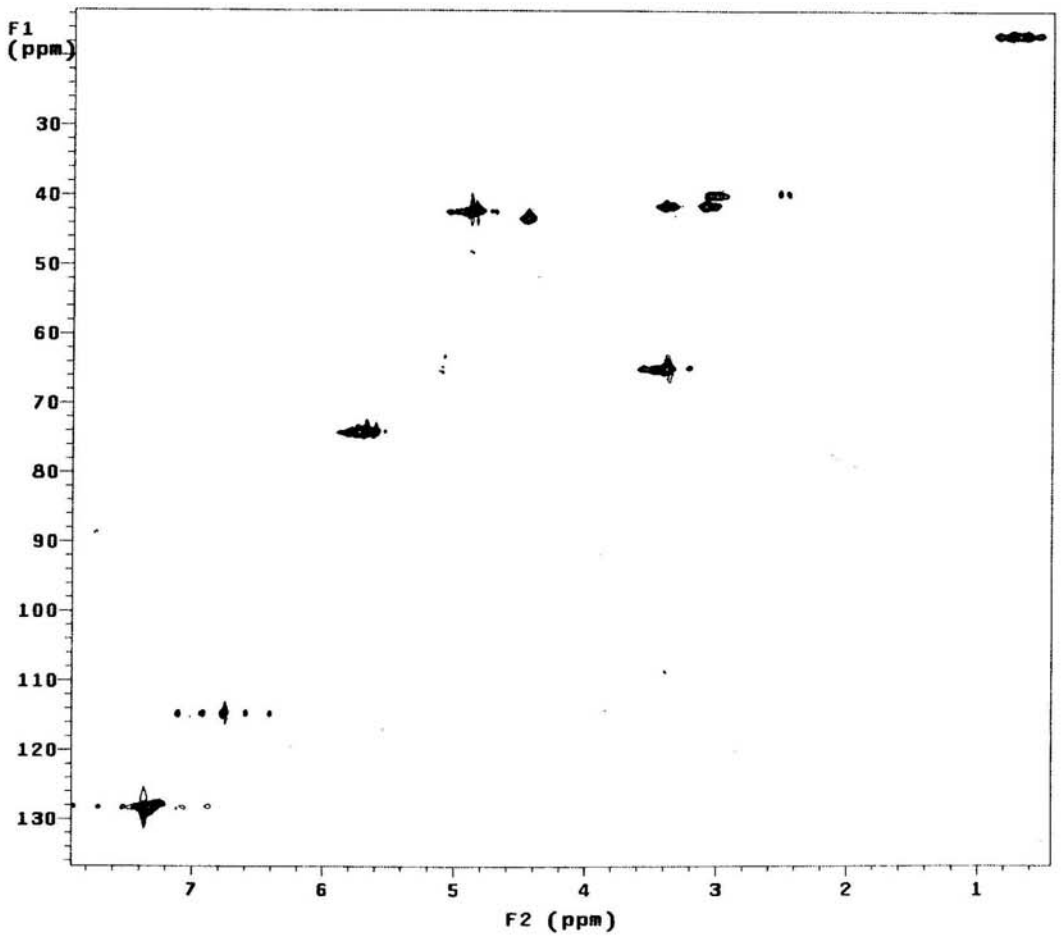
Relax. delay 1.000 sec
Acq. time 0.196 sec
Width 5213.8 Hz
2D Width 22008.3 Hz
48 repetitions
2 x 360 increments
OBSERVE H1, 499.7802429 MHz
DECOUPLE C13, 125.6809158 MHz
Power 34 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.070 sec
F1 DATA PROCESSING
Gauss apodization 0.007 sec
FT size 2048 x 2048
Total time 12 hr, 5 min, 7 sec

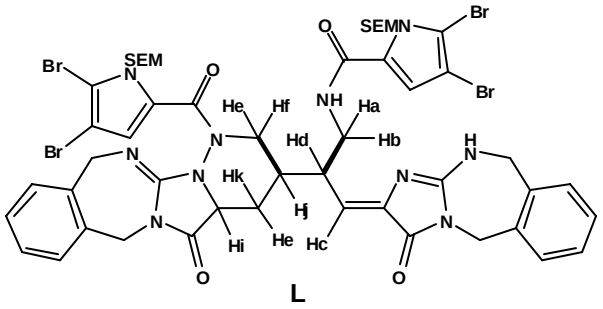


34

Solvent: CDCl3

500 MHz





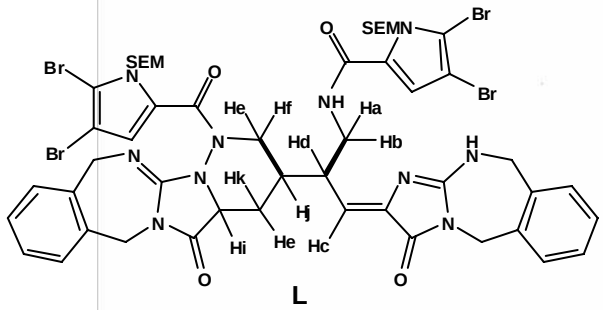
L

Solvent: CD_3CN
Temp: 50 °C; 400 MHz

STANDARD 1H OBSERVE

Pulse Sequence: relayh
Solvent: CD3Cn
Temp. 70.0 C / 343.1 K
INOVA-400 "pele400"

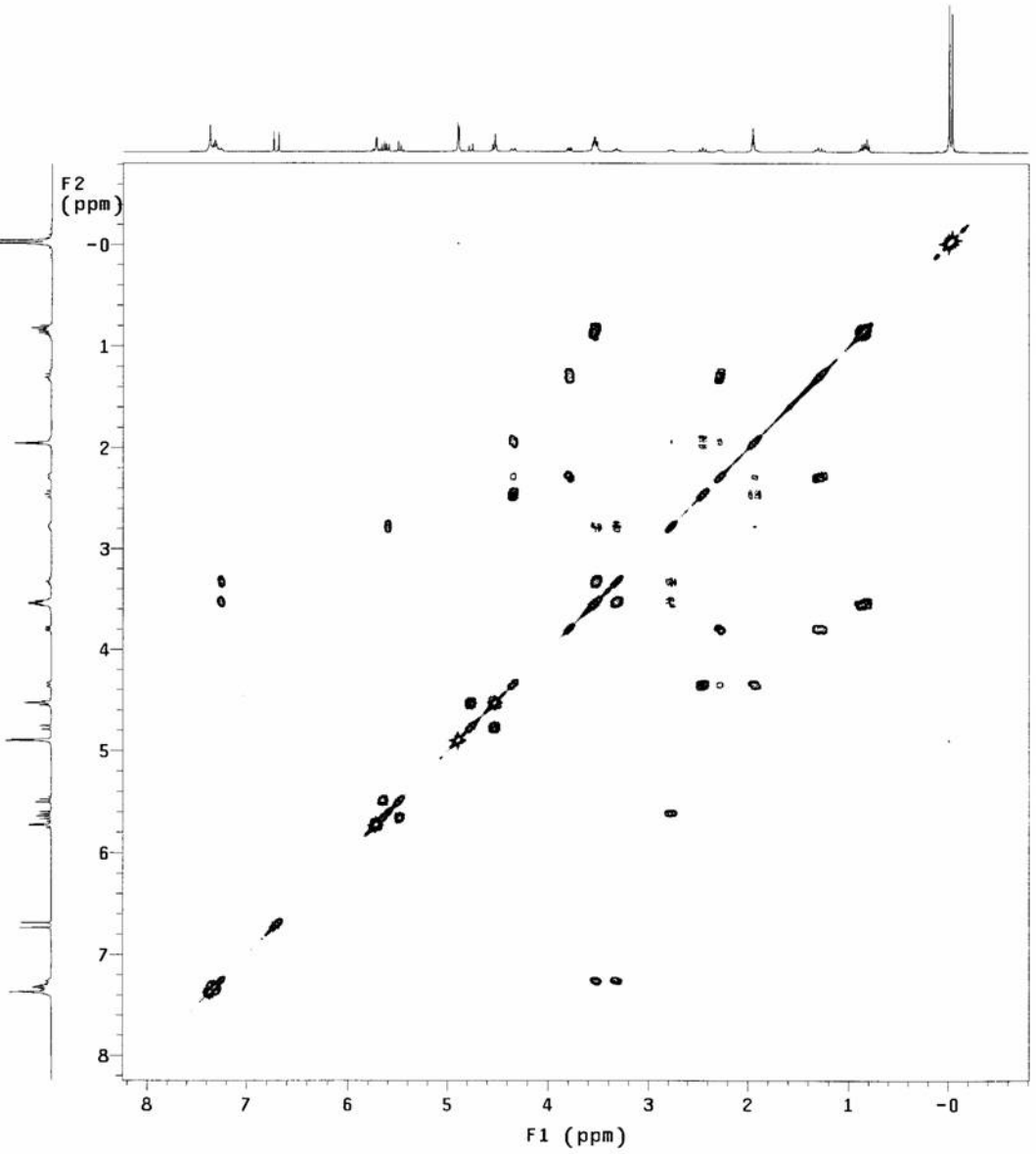
Relax. delay 1.000 sec
COSY 90-45
Acq. time 0.141 sec
Width 3627.0 Hz
2D Width 3627.0 Hz
4 repetitions
500 increments
OBSERVE H1, 399.7814203 MHz
DATA PROCESSING
Sine bell 0.071 sec
F1 DATA PROCESSING
Sine bell 0.071 sec
FT size 1024 x 1024
Total time 40 min, 42 sec

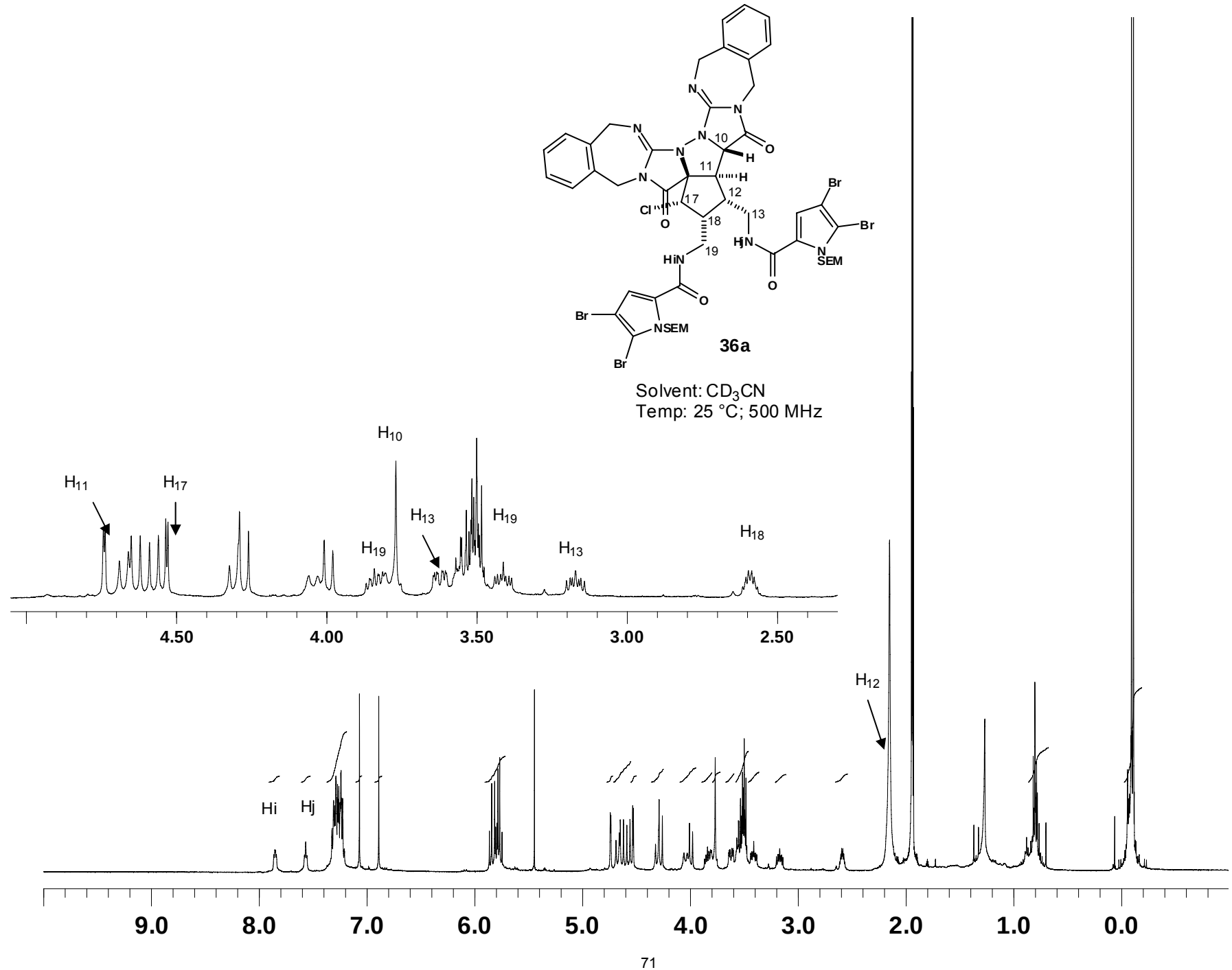


L

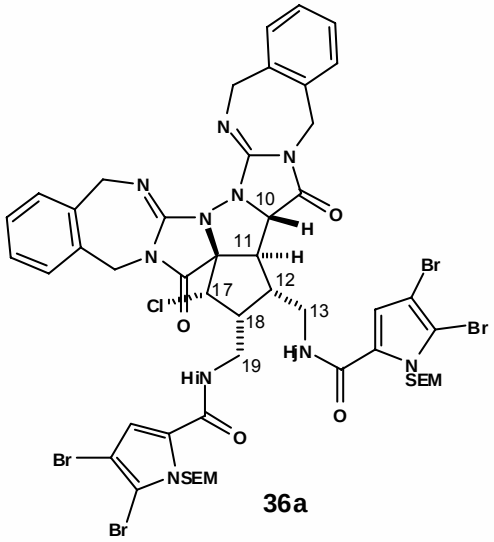
Solvent: CD3CN

400 MHz




36a
Solvent: CD_3CN
Temp: 25 °C; 500 MHz
H_{11}
H_{17}
H_{10}
H_{19}
H_{13}
H_{19}
H_{13}
H_{18}
H_{12}
Hi
Hj
4.50
4.00
3.50
3.00
2.50
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

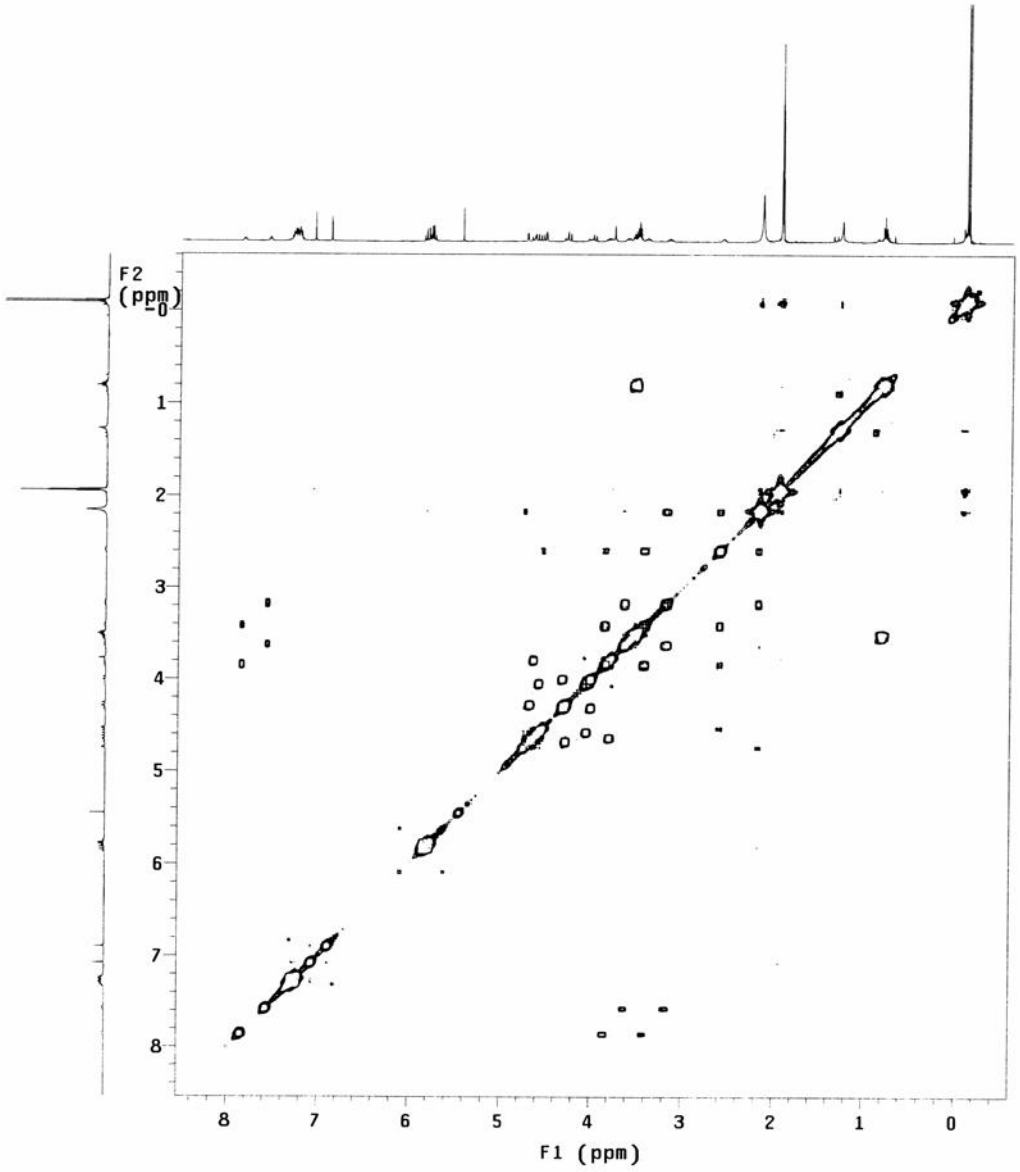
```
V-131-cosy

Pulse Sequence: relayh
 Solvent: CD3CN
 Temp. 24.2 C / 297.4 K
INOVA-500  "pele500"

 Relax. delay 2.000 sec
 COSY 90-90
 Acq. time 0.224 sec
 Width    4577.7 Hz
 2D Width 4571.4 Hz
 8 repetitions
 200 increments
OBSERVE   H1, 499.7271246 MHz
DATA PROCESSING
 Sine bell 0.112 sec
F1 DATA PROCESSING
 Sine bell 0.021 sec
FT size 2048 x 2048
Total time 1 hr, 27 sec
```

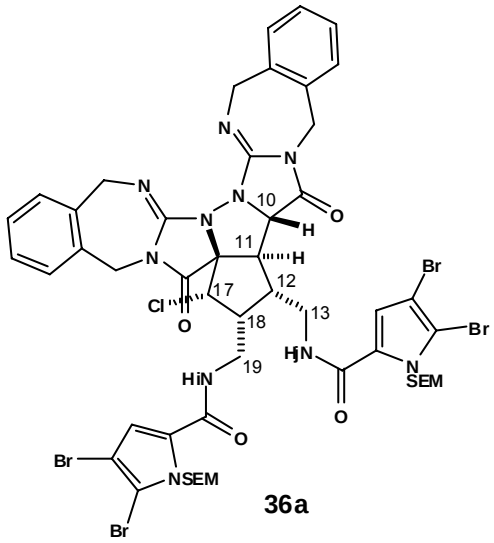


36a

Solvent: CD3CN

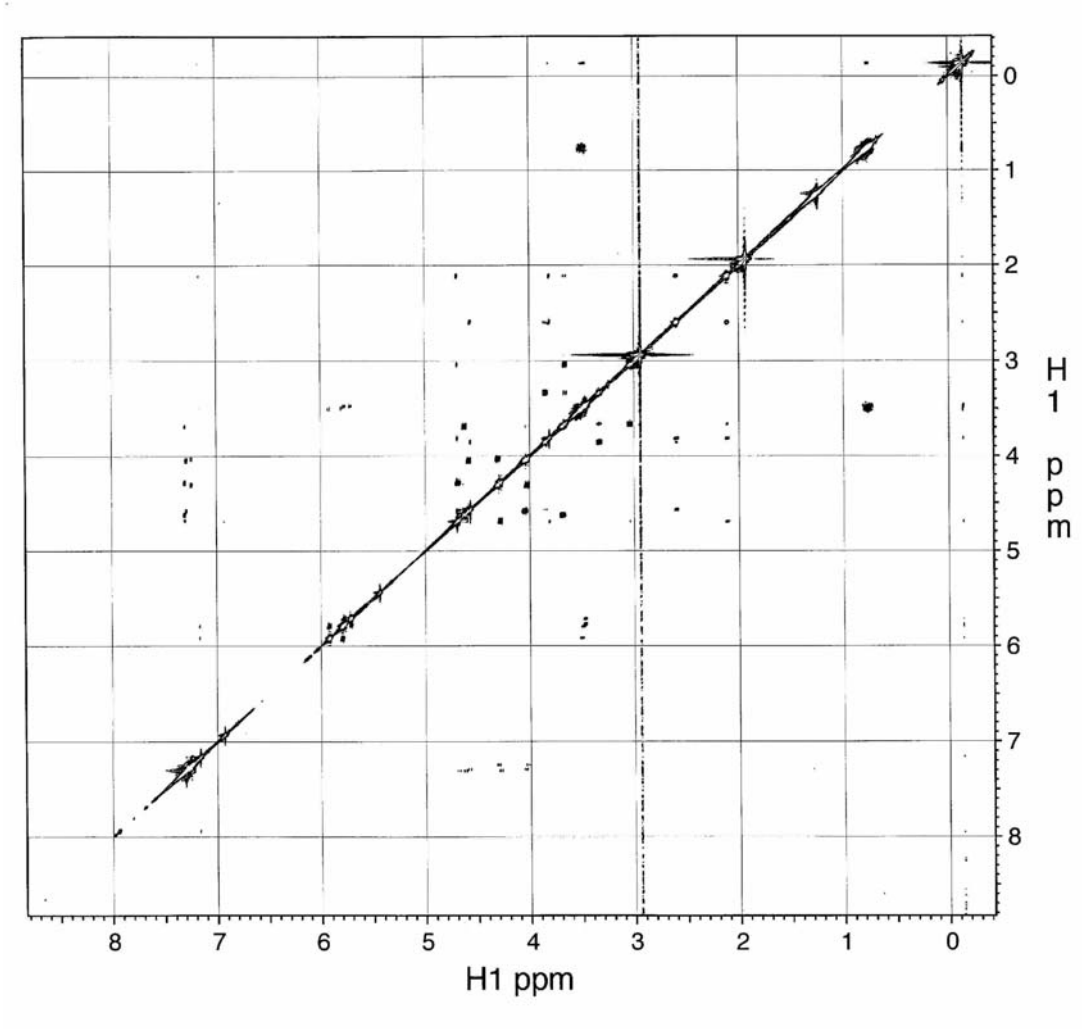
500 MHz

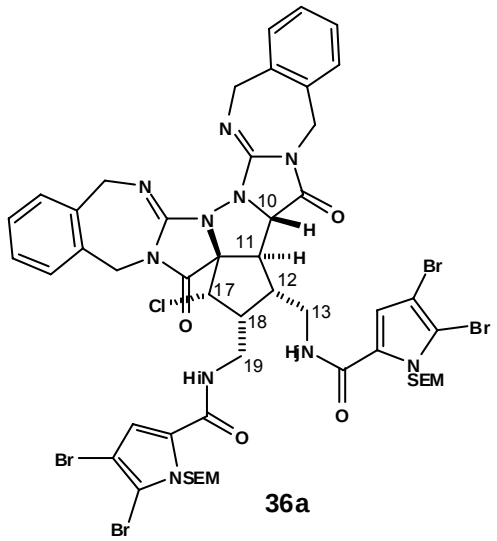




36a

Solvent: CD_3CN
Temp: 25 °C; 800 MHz
Pulse sequence: noesy

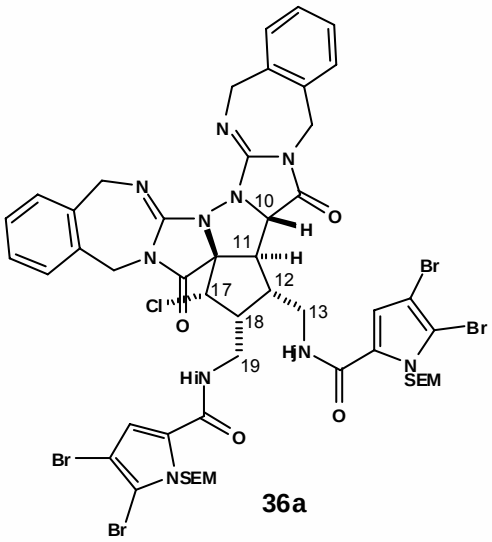




36a

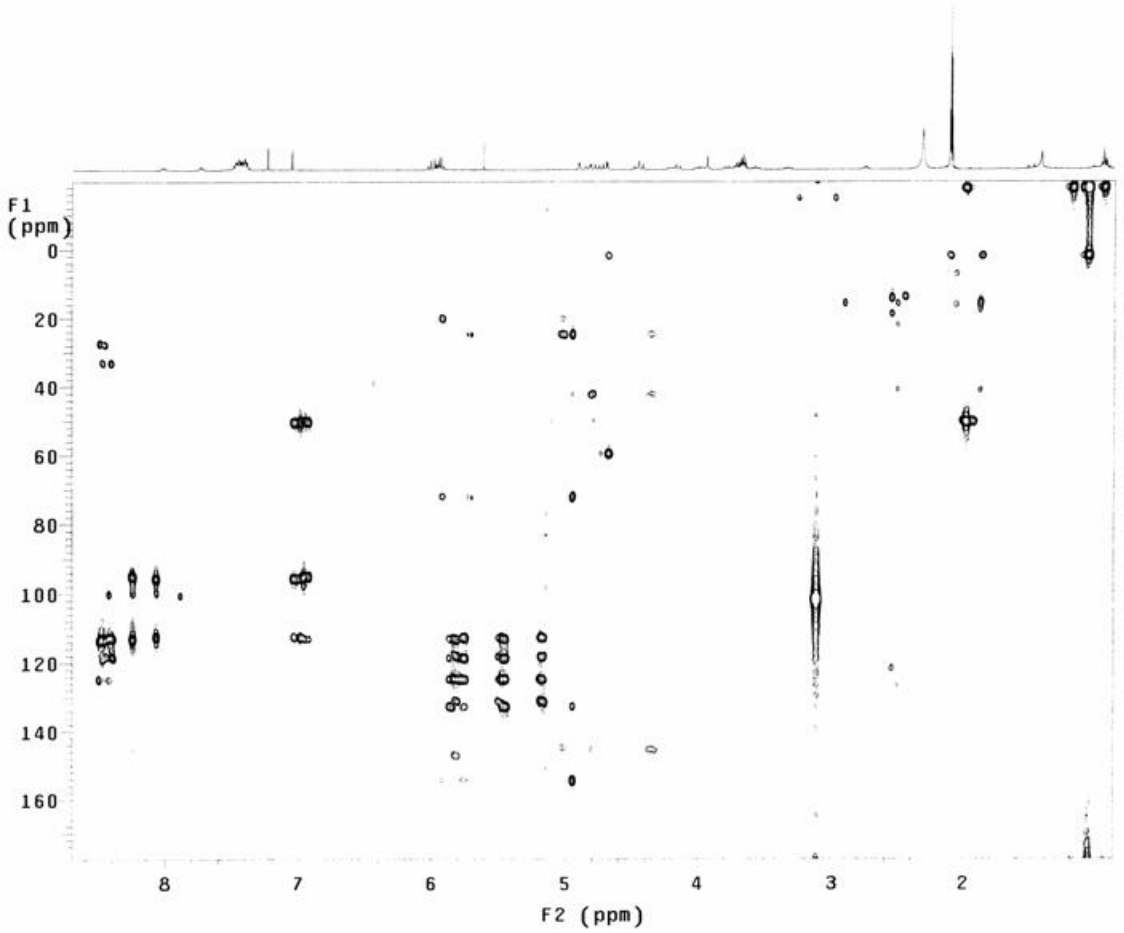
Solvent: CDCl3
Temp: 25 °C;125MHz

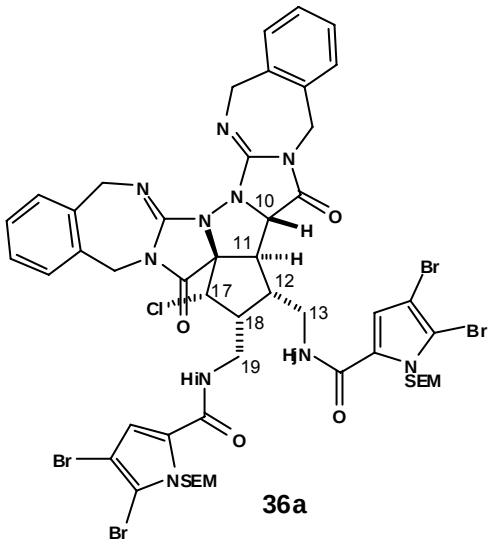
```
V-131-hmbc

Pulse Sequence: gHMBC
 Solvent: CD3CN
 Temp. 24.2 C / 297.4 K
INOVA-500  "pele500"

 Relax. delay 1.000 sec
 Acq. time 0.239 sec
 Width    4577.7 Hz
 2D Width 25000.0 Hz
 16 repetitions
 150 increments
OBSERVE   H1, 499.7265377 MHz
DATA PROCESSING
 Sine bell 0.065 sec
F1 DATA PROCESSING
 Sine bell 0.007 sec
FT size 2048 x 2048
Total time 53 min, 17 sec
```



36a

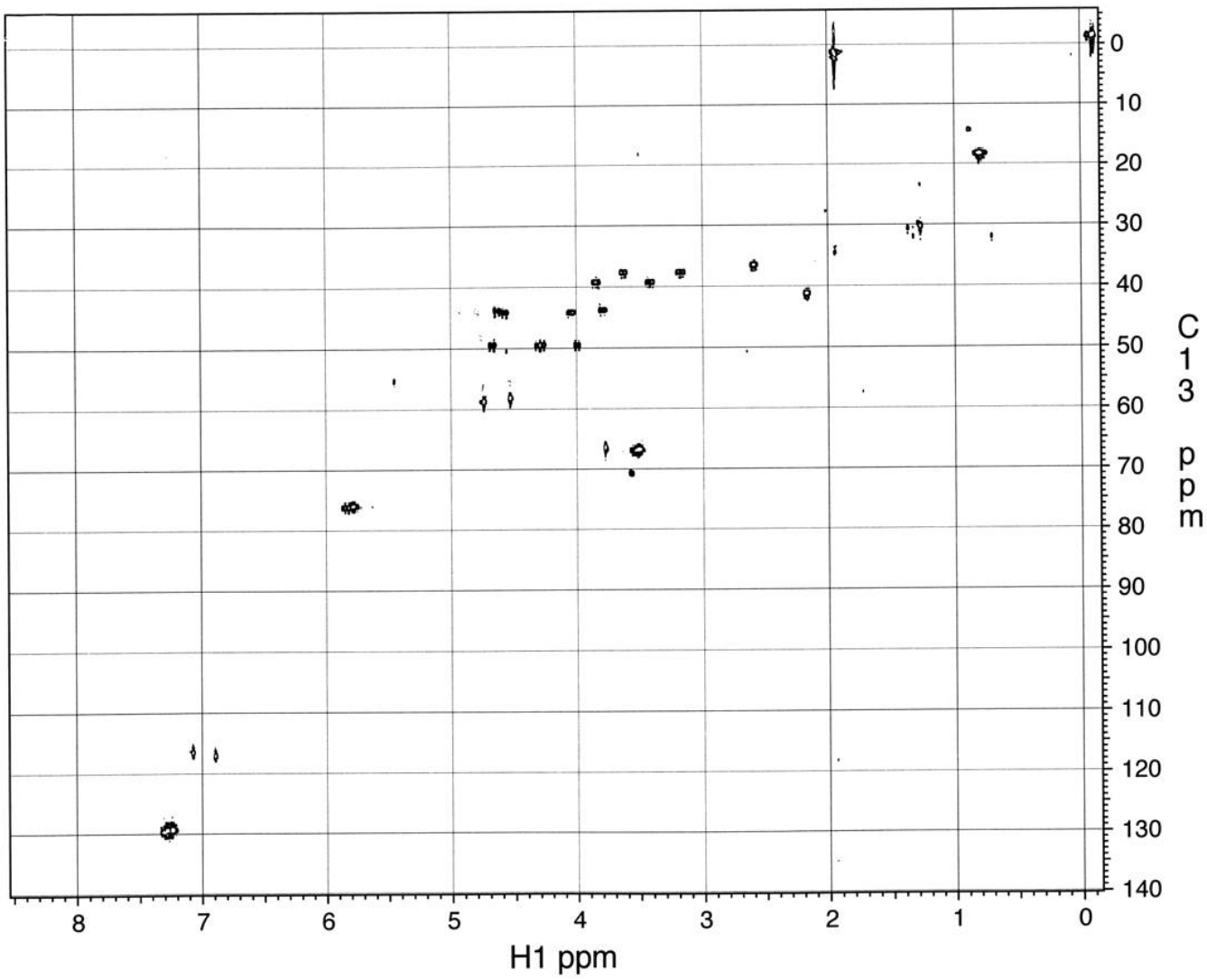
Solvent: CD_3CN
Temp: 25 °C; 800 MHz

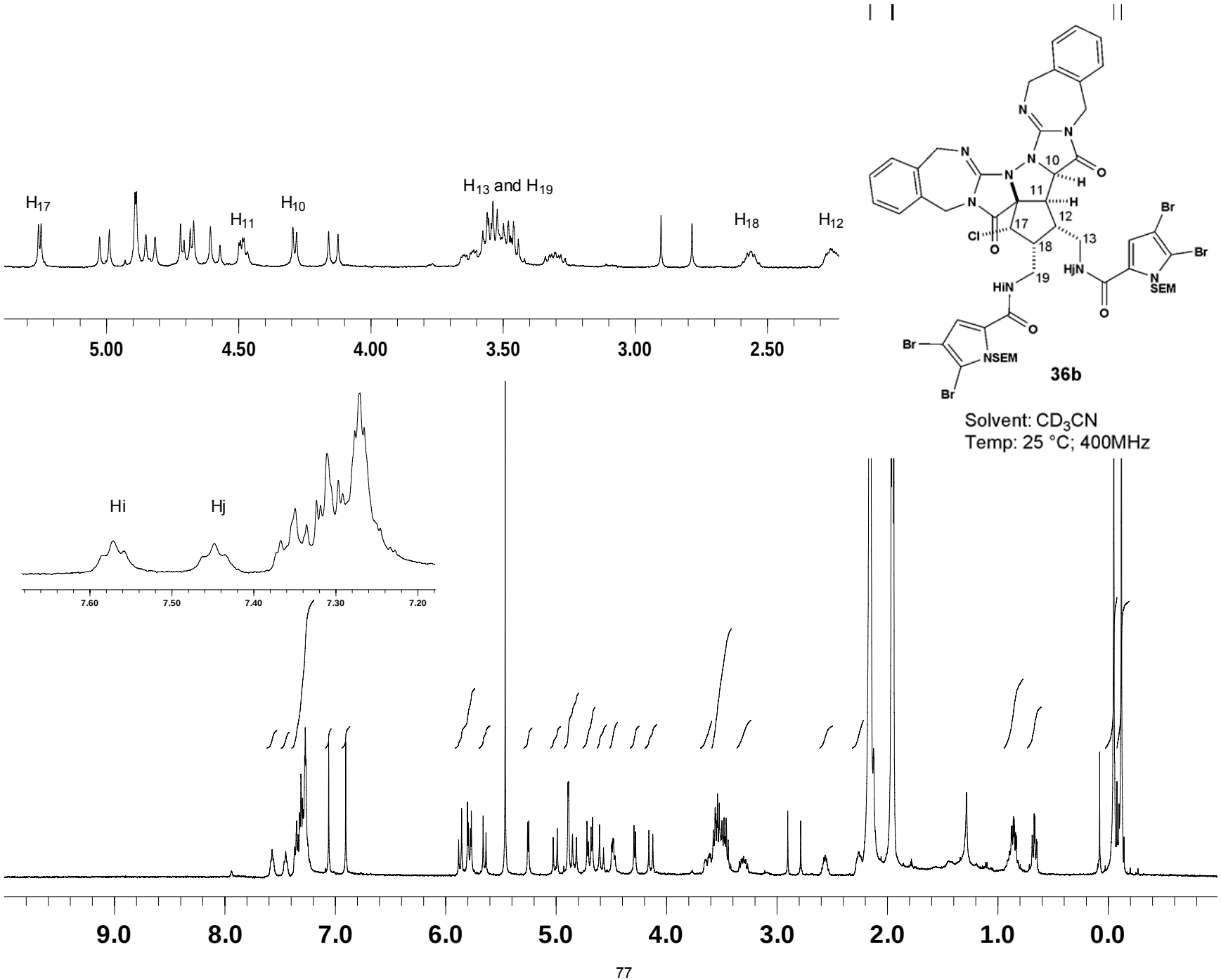




36a

Solvent: CD_3CN
Temp: 25 °C; 800 MHz
Pulse sequence: gChsqc

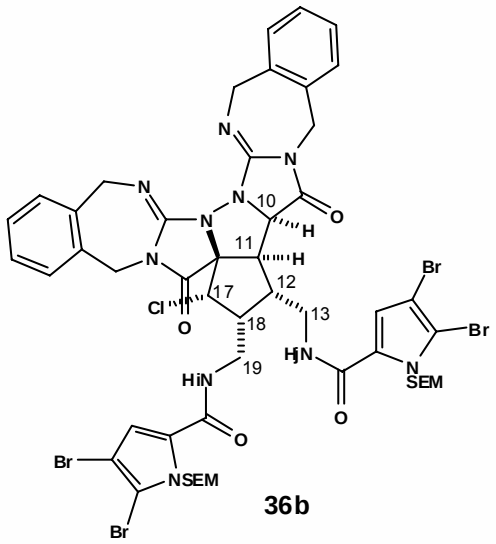



H17
H11
H10
H13 and H19
H18
H12
5.00
4.50
4.00
3.50
3.00
2.50
Hi
Hj
7.60
7.50
7.40
7.30
7.20
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Br
Br
Br
N
SEM
HjN
HiN
NSEM
Cl
O
H
10
11
12
13
17
18
19
36b
Solvent: CD3CN
Temp: 25 °C; 400MHz

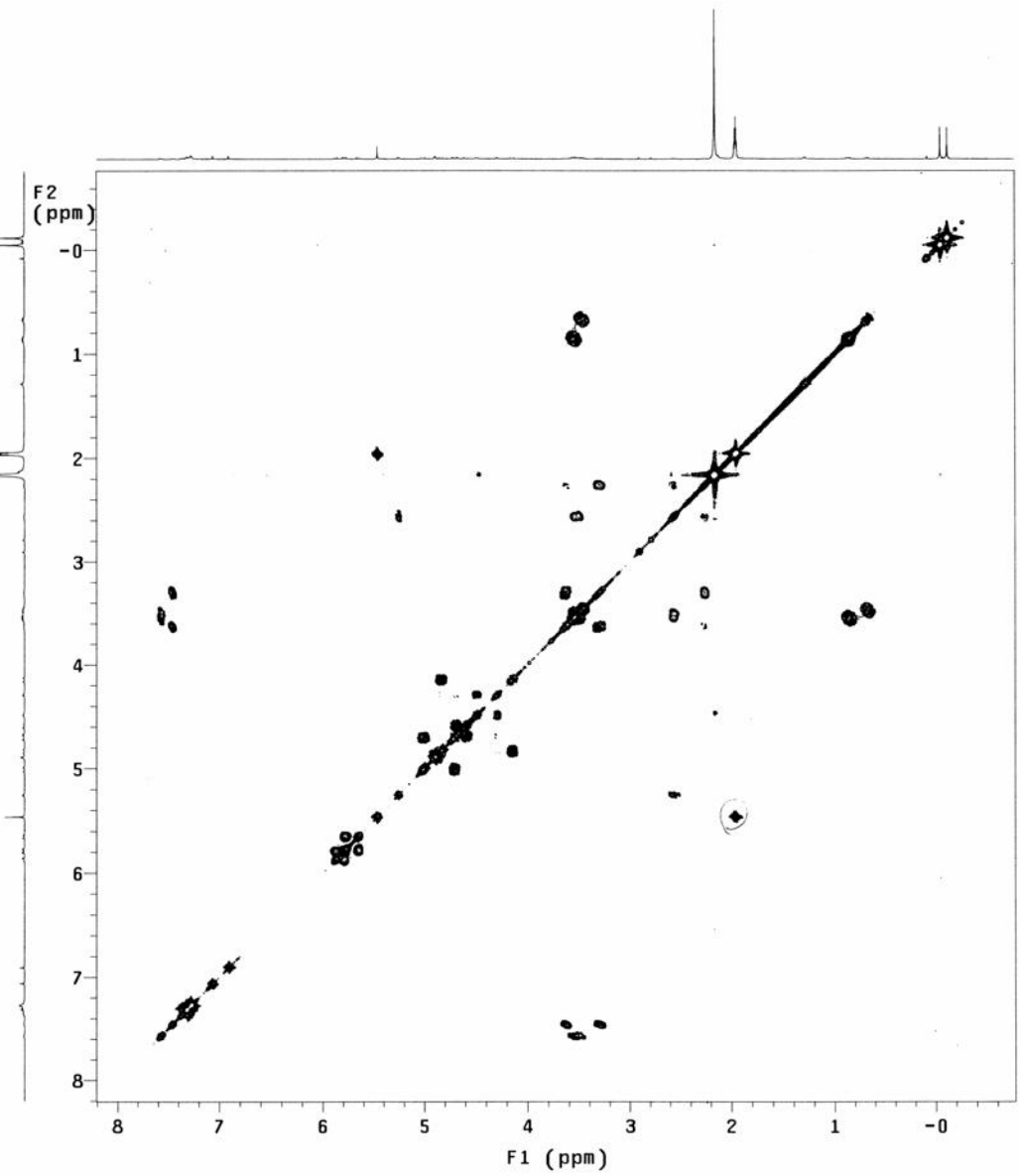
STANDARD 1H OBSERVE

Pulse Sequence: relayh
Solvent: CD3Cn
Ambient temperature
File: QL-V-221-A-1-1-cosy
INOVA-400 "pele400"

Relax. delay 1.000 sec
COSY 90-45
Acq. time 0.142 sec
Width 3595.5 Hz
2D Width 3595.5 Hz
56 repetitions
500 increments
OBSERVE H1, 399.7814203 MHz
DATA PROCESSING
Sine bell 0.071 sec
F1 DATA PROCESSING
Sine bell 0.071 sec
FT size 1024 x 1024
Total time 9 hr, 30 min, 22 sec



36b



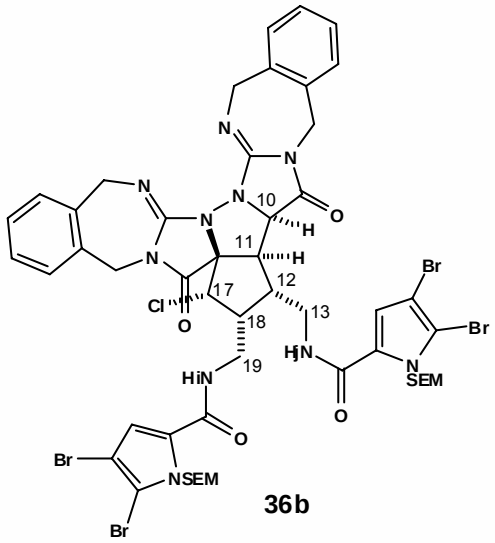
Solvent: CD3CN

400 MHz

13C HSQC

Pulse Sequence: gChsqc
Solvent: cd3cn
Temp. 26.3 C / 299.4 K
INOVA-500 "pele500"

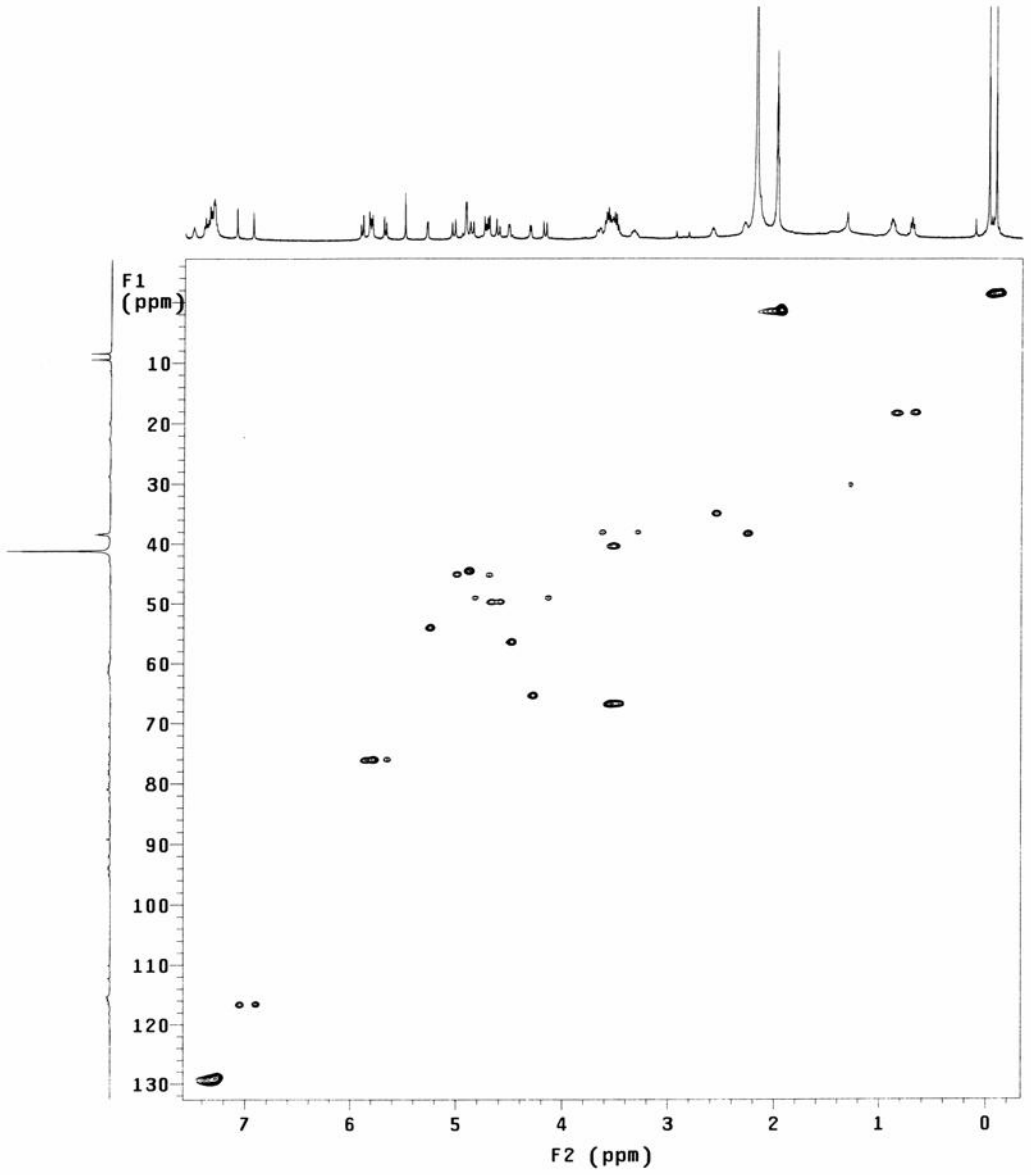
Relax. delay 1.000 sec
Acq. time 0.200 sec
Width 4821.6 Hz
2D Width 25132.0 Hz
32 repetitions
2 x 300 increments
OBSERVE H1, 499.7271231 MHz
DECOUPLE C13, 125.6605328 MHz
Power 47 dB
on during acquisition
off during delay
wurst140 modulated
DATA PROCESSING
Gauss apodization 0.022 sec
F1 DATA PROCESSING
Gauss apodization 0.005 sec
FT size 2048 x 2048
Total time 6 hr, 36 min, 44 sec



36b

Solvent: CD3CN

500 MHz

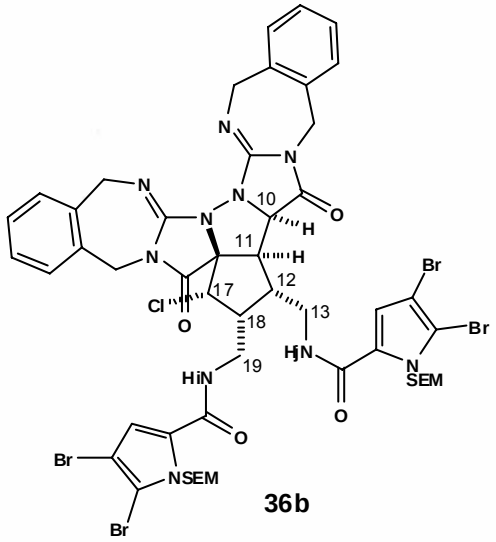


STANDARD PROTON PARAMETERS

Pulse Sequence: gHMBC

Solvent: cd3cn
Temp. 26.3 C / 299.4 K
INOVA-500 "pele500"

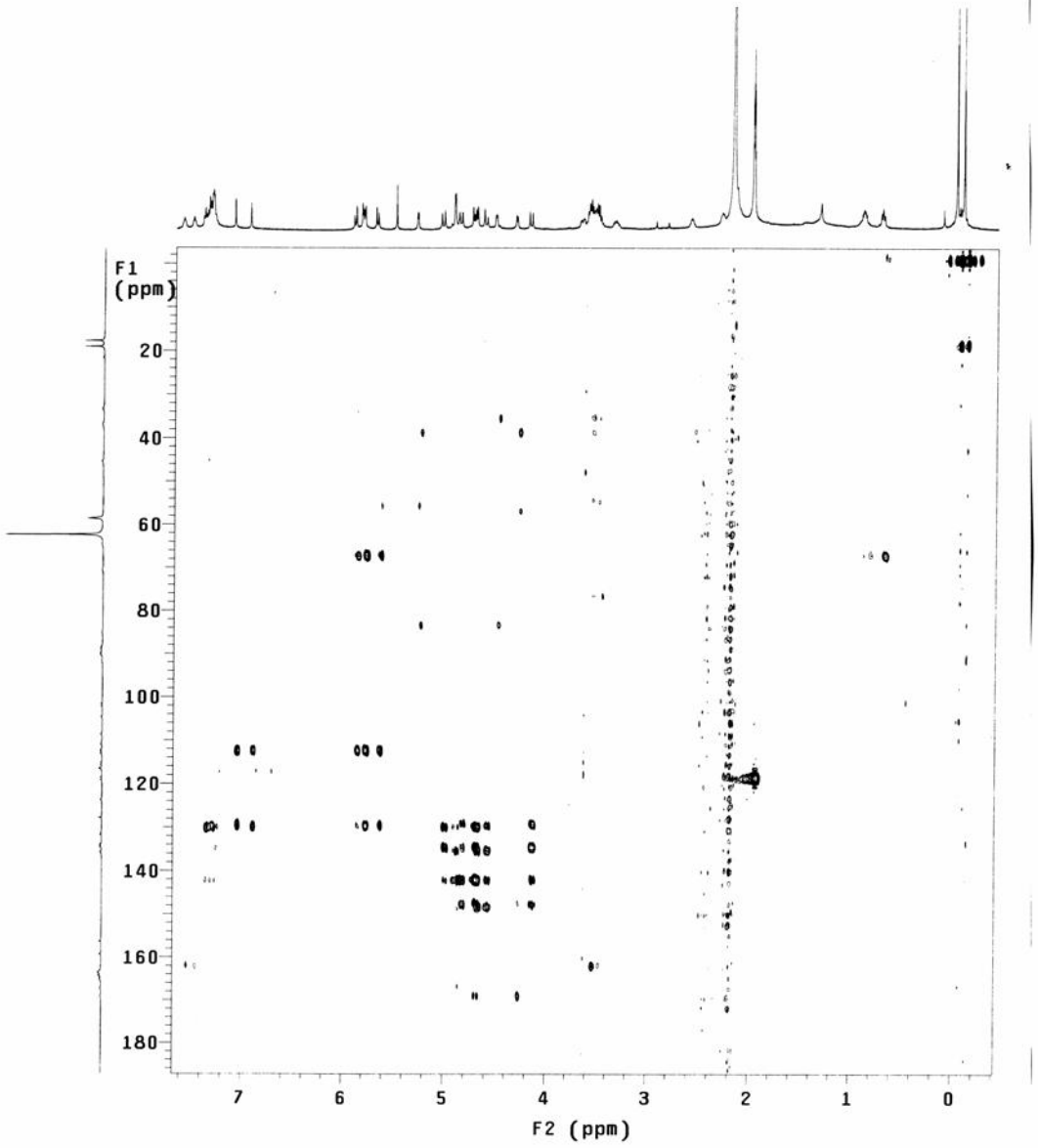
Relax. delay 1.000 sec
Acq. time 0.237 sec
Width 4821.6 Hz
2D Width 25133.5 Hz
128 repetitions
300 increments
OBSERVE H1, 499.7271262 MHz
DATA PROCESSING
Sine bell 0.106 sec
F1 DATA PROCESSING
Sine bell 0.004 sec
FT size 2048 x 2048
Total time 14 hr, 8 min, 41 sec

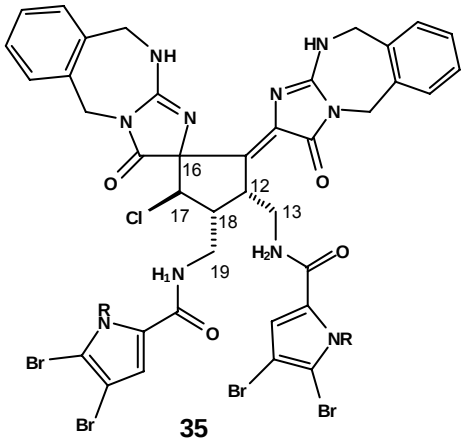


36b

Solvent: CD3CN

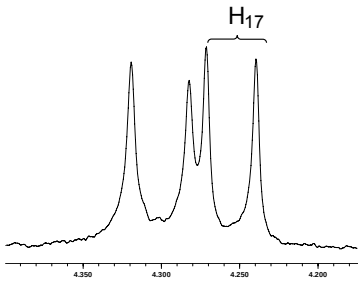
500 MHz

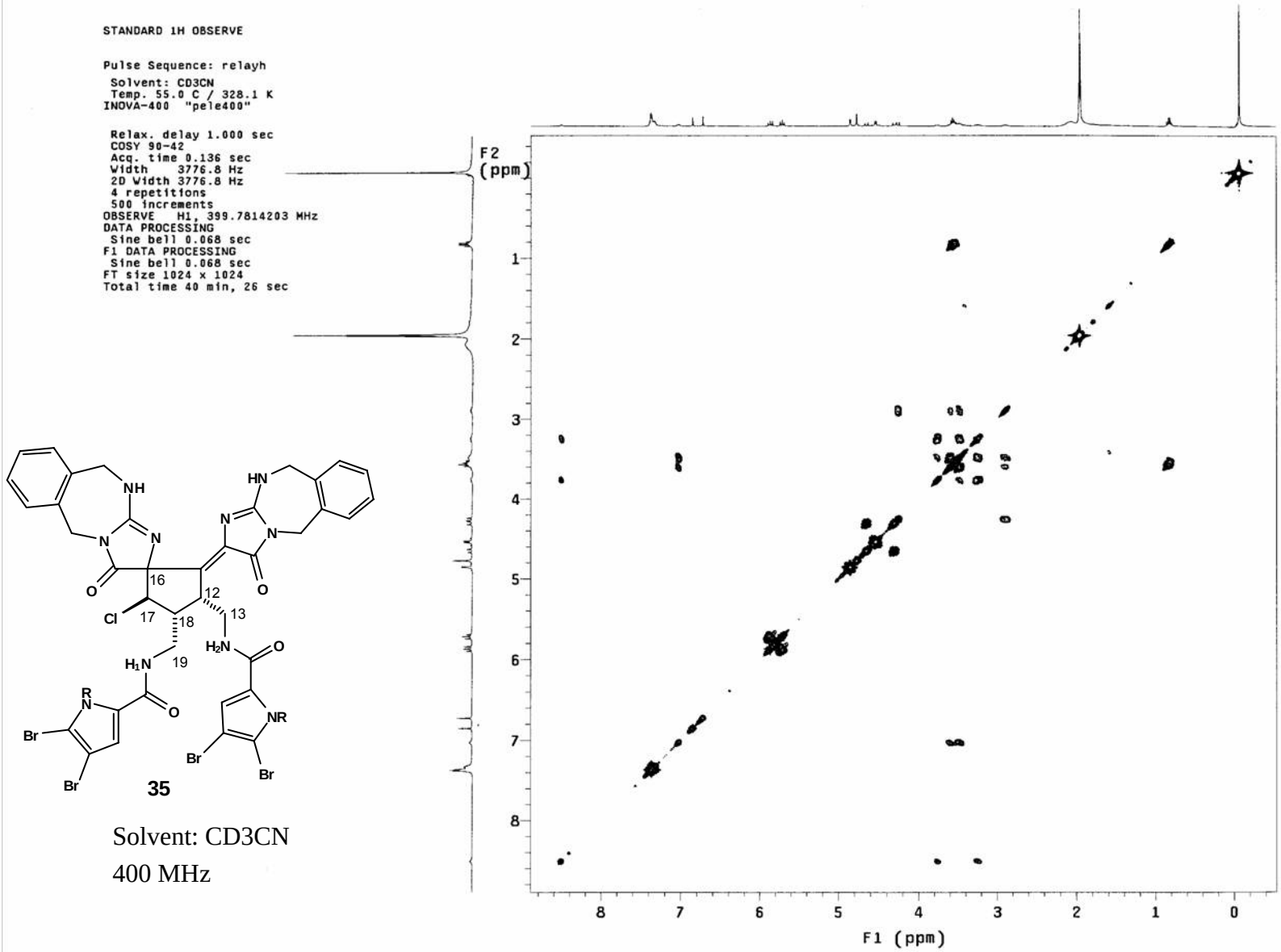




35

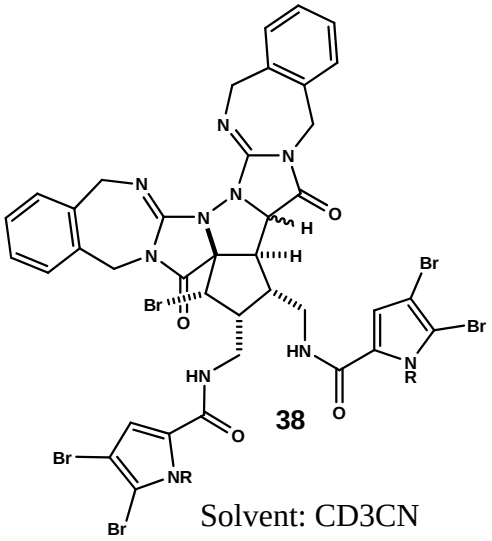
Solvent: CD_3CN
Temp: 55 °C; 400 MHz





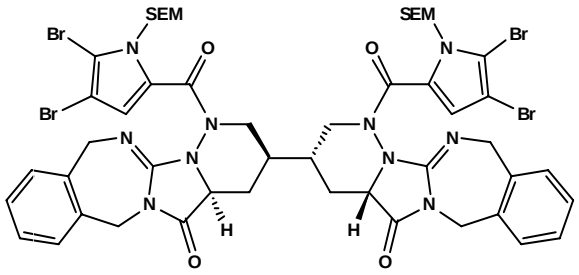
Solvent: CD3CN

400 MHz



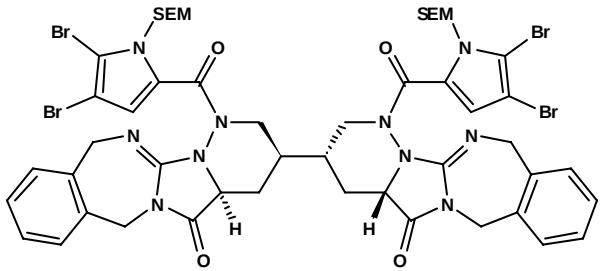
Solvent: CD3CN

500 MHz



40a

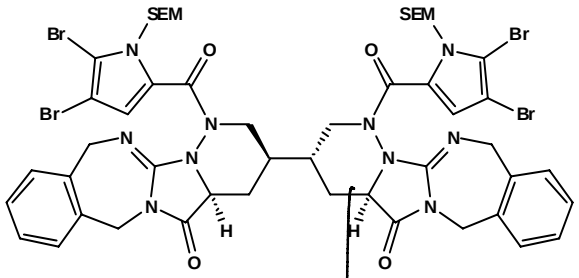
Solvent: $CDCl_3$
Temp: room temp; 500 MHz



40a

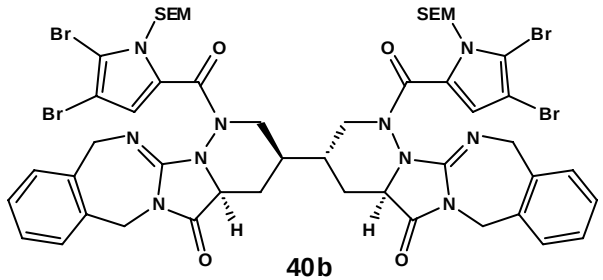
Solvent: CDCl3

100 MHz



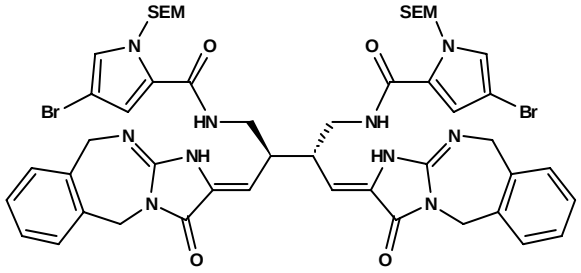
40b

Solvent: CD_3CN
Temp: 70 °C; 500 MHz



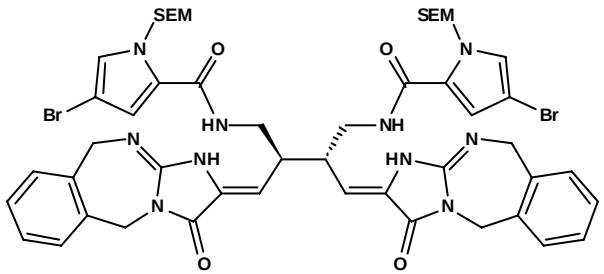
40b

Solvent: CD3CN
400 MHz



43

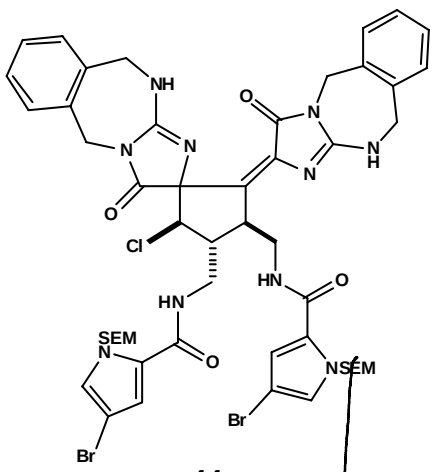
Solvent: CD_3CN
Temp: room temp; 500 MHz



43

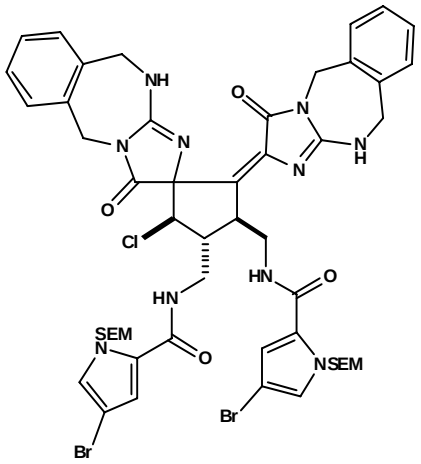
Solvent: CD3CN

100 MHz



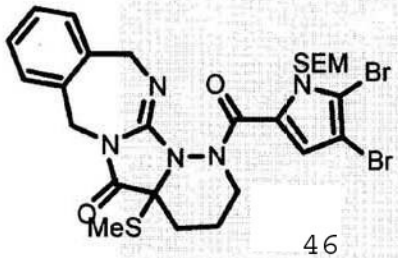
44

Solvent: CD_3CN
Temp: room temp; 500 MHz



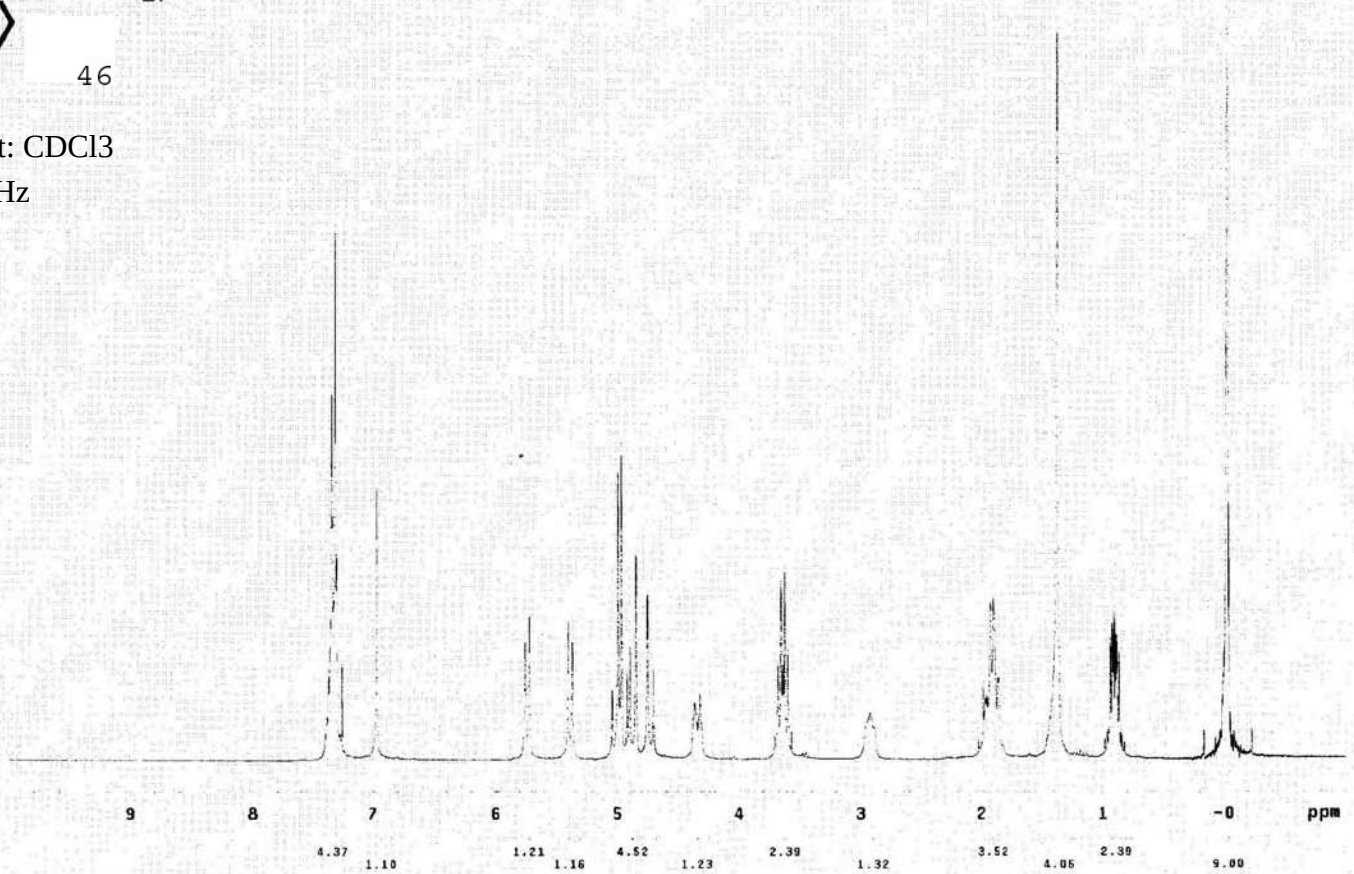
44

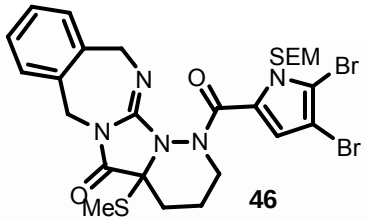
Solvent: CD_3CN
Temp: room temp; 125 MHz



46

Solvent: CDCl3
400 MHz





46

Solvent: CDCl3
100 MHz