Supporting Information

An electrochemical access to 2-amino-2,3-dihydro-1,4-benzodioxanes derived from hydroxytyrosol

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I- Material and methods

1- General methods

Solvents, reagents and starting materials, at the exception of compounds **1**, **2a-k**, **8** and **10**, were purchased from commercial suppliers, and used without further purification. Flash chromatography was performed on Macherey-Nagel Si 60 M silica gel (40-63 μm), or on Merck Kieselgel 60 H silica gel (5-40 μm). Preparative HPLC separations were performed with a Shimadzu system (LC-40 delivery system, SCL-40 control unit, FRC-40 fraction collector and SPD-M40 detector), using a Nucleodur C18 Htec column (250 × 32 mm, 5 μm), and a 10 mL Rheodyne manual injection valve. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance spectrometers operating at 300 and 75 MHz (or 400 and 100 MHz) respectively. 2D NMR experiments (COSY, HSQC, HMBC, NOESY) were performed using the standard pulse-sequences. Chemical shifts (δ) referred to the internal solvent signal are reported in parts per million (ppm), and coupling constants *J* are given in Hertz (Hz). The carbon type (methyl, methylene, methine, or quaternary) was determined by DEPT experiments. High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer operating in the positive ion mode. UV/vis spectra were recorded on a Varian Cary 100 spectrophotometer.

2- Electrochemistry

All electrochemical experiments were conducted under argon with a Metrohm Autolab model PGSTAT302N potentiostat/galvanostat. The working electrode used in the voltammetry measurements was a platinum anode carefully polished before each voltammogram with an aqueous alumina suspension. The potential was referred to a Ag/AgCl electrode 3M, the counter electrode being a platinum electrode. Controlled potential electrolysis were carried out in a divided cell (9.5 cm diameter). The working electrode was a cylindrical platinum grid (60 cm^2 area) or a cylindrical carbon graphite electrode (64.5 cm^2 area), and the counter-electrode, a platinum plate (or a carbon felt). The working electrode was immersed in the anodic compartment, and the counter-electrode being placed on the glass frit separating the anodic and cathodic compartments.

3- Crystallographic study

Crystallographic data were collected with a Bruker SMART APEX CCD diffractometer (Mo-Kα radiation graphite-monochromated radiation, λ = 0.71073 Å) controlled by APEX2 software package.[1] Data integration and global cell refinement were performed with the program SAINT.[2] Data were corrected for absorption by the multiscan semiempirical method implemented in SADABS.[3] The structure was solved by direct methods using SHELXS 97.[4] Refinement, based on F2, was carried out by full matrix least squares with SHELXL-97 software.[5] Non hydrogen atoms were refined anisotropic thermal parameters. The hydrogen atoms were placed in their geometrically generated positions and allowed to ride on their parent atoms with an isotropic thermal parameter 20 % higher to that of the atom of attachment.

4- Synthesis of starting materials 1, 8, 10 and 2a-k

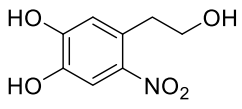
Synthesis of hydroxytyrosol 1

Hydroxytyrosol **1** was synthesized in two steps from 3,4-dihydroxyphenylacetic acid, through a procedure previously reported.[6]

Synthesis of compound 8

Compound **8** was synthesized by nitration with sodium nitrite in acetate buffer pH 3.8, through a procedure previously reported. [7]

2-(3,4-Dihydroxy-6-nitro-phenyl)ethanol **8**



8

^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (1H, s, H_{Ar}), 6.78 (1H, s, H_{Ar}), 3.77 (2H, t, *J* = 7 Hz, CH_2O), 3.06 (2H, t, *J* = 7 Hz, CH_2).

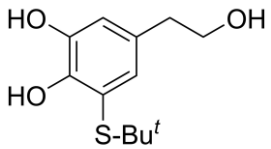
^{13}C NMR (100 MHz, CD_3OD) δ 152.0 (C), 145.0 (C), 141.7 (C), 129.0 (C), 119.4 (CH), 113.2 (CH), 63.0 (CH_2), 37.5 (CH_2).

Synthesis of compound 10

Compound **10** was obtained by a method derived from the results of C. Chai *et al*, [8] about the synthesis of thioether conjugates of *N*-acetyl-3,4-dihydroxy-phenylalanine methyl ester. The chemical oxidation using Ag_2O in acetone was replaced by an anodic oxidation in 95/5 MeCN/DMSO.

A solution of hydroxytyrosol **1** (77 mg, 0.5 mmol) and lithium perchlorate (1.06 g, 10 mmol) in 200 mL of 95/5 MeCN/DMSO mixture was oxidized under argon at a platinum electrode (E_{ox} = +1.0 V *vs* Ag/AgCl). After the complete oxidation (2.0 $F.mol^{-1}$), i.e. when the decay of the current exceeded 95%, a solution of *tert*-butyl mercaptan (110 µL, 1 mmol, 2 equiv.) and tetramethylammonium hydroxide (420 µL of 25% m/m methanolic solution, 1 mmol) in acetonitrile (2 mL) was added dropwise to the yellow solution of *o*-quinone. The resulting reaction mixture was stirred under argon until the solution became pale yellow, and sodium thiosulfate (1.1 equiv., 136 mg) was then added. After addition to a mixture of 100 mL of water and 20 mL of a phosphate buffer solution 1 M pH 7.0, acetonitrile was removed under reduced pressure at room temperature. The aqueous phase was extracted by successive small fractions of ethyl acetate (150 mL total volume). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure at room temperature. The crude residue was then purified by flash chromatography with ether petroleum/ethyl acetate 65/35 as the eluent, to give compound **10** (25 mg, 0.10 mmol, 20%), along with compound **10'** (10 mg, 0.03 mmol, 6%), and recovered reactant (56 mg, 0.21 mmol, 72.5%).

2-(5-*tert*-Butylthio-3,4-dihydroxyphenyl)ethanol **10**



10

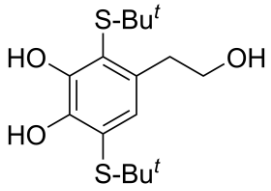
^{1}H NMR (300 MHz, CD_3OD) δ 6.80 (1H, s, H_{Ar}), 6.76 (1H, s, H_{Ar}), 3.71 (2H, t, *J* = 7 Hz, CH_2O), 2.69 (2H, t, *J* = 7 Hz, CH_2), 1.30 (9H, s, Bu^t).

^{13}C NMR (75 MHz, CD_3OD) δ 146.9 (C), 145.9 (C), 131.2 (C), 130.6 (CH), 118.9 (CH), 118.2 (C), 64.4 (CH_2), 48.1 (C), 39.4 (CH_2), 31.2 (3×CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 143.8 (C), 130.4 (C), 129.4 (CH), 117.7 (CH), 116.8 (C), 63.8 (CH_2), 48.3 (C), 38.6 (CH_2), 31.0 (3×CH_3).

HRMS (ESI$^+$) m/z , $[M + Na]^+$ calculated for $C_{12}H_{18}NaO_3S$ 265.0869, found 265.0871; $[M + H]^+$ calculated for $C_{12}H_{19}O_3S$ 243.1049, found 243.1052.

2-[2,5-*bis*-(*tert*-Butylthio)-3,4-dihydroxyphenyl]ethanol **10'**



10'

^{1}H NMR (400 MHz, CD_3OD) δ 6.99 (1H, s, H_{Ar}), 3.63 (2H, t, *J* = 7 Hz, CH_2O), 3.11 (2H, t, *J* = 7 Hz, CH_2), 1.33 (9H, s, *t*-Bu), 1.32 (9H, s, Bu^t).

^{13}C NMR (75 MHz, CD_3OD) δ 148.8 (C), 146.8 (C), 135.8 (C), 131.1 (CH), 120.8 (C), 120.3 (C), 64.2 (CH_2), 50.5 (C), 48.5 (C), 38.6 (CH_2), 31.6 (3×CH_3), 31.3 (3×CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4 (C), 144.6 (C), 134.6 (C), 129.4 (CH), 120.2 (CH), 119.4 (C), 63.9 (CH_2), 50.8 (C), 48.7 (C), 37.5 (CH_2), 31.4 (3×CH_3), 31.2 (3×CH_3).

HRMS (ESI$^+$) m/z , $[M + Na]^+$ calculated for $C_{16}H_{26}NaO_3S_2$ 353.1216, found 353.1223; $[M + H]^+$ calculated for $C_{16}H_{27}O_3S_2$ 331.1396, found 331.1394.

Synthesis of enamines 2a-k

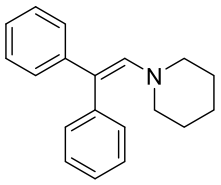
Enamines **2a**,[9] **2b,**[10] **2e**,[10] **2f**,[11] **2g**,[12] **2i**,[13] and **2k** [11,14] were prepared following reported methods, using as the solvent dichloromethane dried 48 h over activated 3Å molecular sieves. They were stored under argon at - 18°C before use. Their ^{1}H and ^{13}C spectra were in accordance with those previously described.

Enamine **2c**

A solution of diphenylacetaldehyde (890 μL, 10 mmol), piperidine (395 μL, 8 mmol) and *p*-toluenesulfonic acid in 10 mL of dry dichloromethane was stirred with 3Å molecular

sieves at room temperature for a night. After filtration and evaporation under reduced pressure, the crude product was obtained as a yellow oil, stored under argon at - 18°C before a rapid use.

1-(2,2-Diphenyl-vinyl)piperidine **2c**



2c

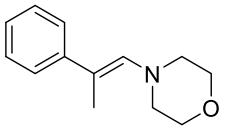
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07-7.31 (10H, m, 10×H_{Ph}), 6.30 (1H, s, =CHN), 2.84 (4H, m, 2×CH_2N_{piper}), 1.47 (6H, s, 3×$CH_{2\ piper}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7 (C), 141.3 (C), 138.9 (CH), 131.2 (2×CH), 128.0 (2×CH), 127.9 (2×CH), 126.7 (2×CH), 125.9 (CH), 124.6 (CH), 113.9 (C), 51.9 (2×CH_2), 25.9 (2×CH_2), 24.3 (CH_2).

Enamine **2d**

A solution of 2-phenylpropionaldehyde (1.33 mL, 10 mmol), piperidine (0.7 mL, 8 mmol) and *p*-toluenesulfonic acid in 10 mL of dry dichloromethane was stirred with 3Å molecular sieves at room temperature for 20h. After filtration and evaporation under reduced pressure, the resulting yellow oil was crystallised at low temperature (- 80°C) in petroleum ether / dry dichloromethane 99/1 to afford the enamine **2d**, as a pale yellow solid (m.p. 68 ± 2°C) stored under argon at - 18°C before use.

(*E*)-1-(2-Phenyl-propenyl)morpholine **2d**



2d

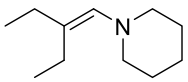
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.42 (5H, m, 5×H_{Ph}), 6.10 (1H, s, =CHN), 3.83 (2H, m, CH_2O_{morph}), 2.90 (2H, m, CH_2N_{morph}), 2.14 (3H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3 (C), 138.3 (C), 128.4 (2×CH), 126.4 (CH), 125.5 (2×CH), 123.8 (C), 67.0 (2×CH_2), 52.6 (2×CH_2), 15.7 (CH_3).

Enamines **2h** and **2j**

A solution of aldehyde (10 mmol), piperidine (8 mmol) and *p*-toluenesulfonic acid in 10 mL of dry dichloromethane was heated at reflux for a night, in the presence of 3Å molecular sieves. After filtration and evaporation under reduced pressure, the crude product was obtained as a pale yellow oil, and stored under argon at - 18°C before a rapid use.

1-(2-Ethyl-butenyl)piperidine **2h**

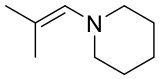


2h

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (1H, s, =CHN), 2.49 (4H, m, 2×CH_2N_{piper}), 2.15 (2H, q, *J* = 7.5 Hz, $CH_{2\ Et}$), 1.90 (2H, q, *J* = 7.5 Hz, $CH_{2\ Et}$), 1.54 (4H, m, 2×$CH_{2\ piper}$), 1.39 (2H, m, $CH_{2\ piper}$), 0.94 (2H, t, *J* = 7.5 Hz, $CH_{3\ Et}$), 0.93 (2H, t, *J* = 7.5 Hz, $CH_{3\ Et}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (CH), 133.0 (C), 54.8 (2×CH_2), 26.1 (CH_2), 26.0 (2×CH_2), 24.3 (CH_2), 21.7 (CH_2), 13.3 (CH_3), 12.6 (CH_3).

1-(2-Methyl-propenyl)piperidine **2j**



2j

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (1H, s, =CHN), 2.53 (4H, m, 2×CH_2N_{piper}), 1.65 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.54 (4H, m, 2×$CH_{2\ piper}$), 1.41 (2H, m, $CH_{2\ piper}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4 (CH), 121.1 (C), 54.3 (2×CH_2), 26.0 (2×CH_2), 24.3 (CH_2), 22.5 (CH_3), 17.6 (CH_3).

III- HMBC correlations of compounds 3 and 4

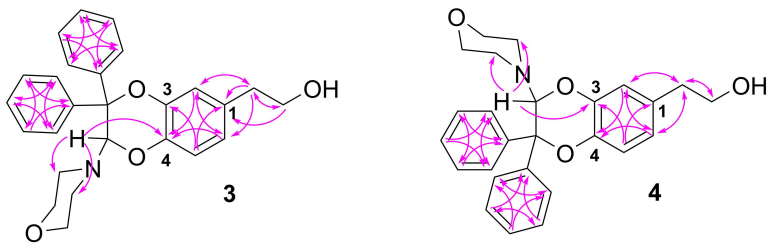


Figure S1 HMBC correlations of compounds **3** and **4**

IV. Cyclic voltammogram of hydroxytyrosol 1

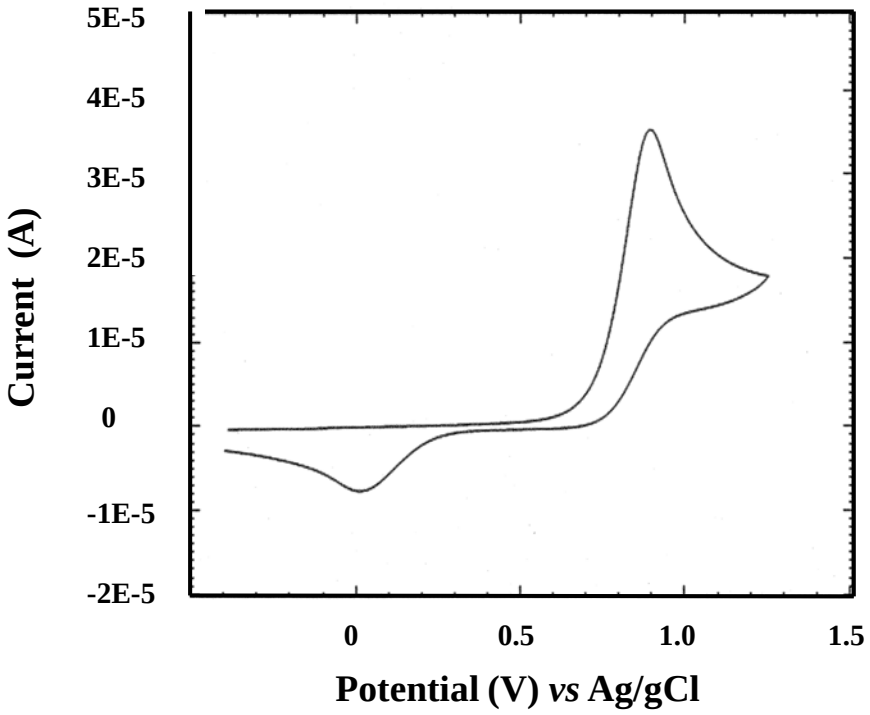


Figure S2 Cyclic voltammogram at a platinum anode of a deaerated solution of hydroxytyrosol **1** (1.25 mM) in 95/5 MeCN/DMSO with 0.05 M $LiClO_4$ as supporting electrolyte. Scan rate v = 0.1 $V.s^{-1}$.

V. Optimisation of the two-step one-pot reaction conditions

Solvent	Electrolyte	Anode	Cathode	Potential (V vs Ag/AgCl)	Enamine (equiv.)	Compounds 3/4 yield
50/50 phosphate buffer pH 8,0/MeCN	NaCl 0.05 M	Platinum grid	Platinum plate	1.8	5	65%
50/50 phosphate buffer pH 8,0/MeCN	$LiClO_4$ 0.05 M	Platinum grid	Platinum plate	1.8	5	61%
MeCN	$LiClO_4$ 0.05 M	Platinum grid	Platinum plate	1.4	5	/
MeCN	TEAHFP 0.02 M	Platinum grid	Platinum plate	1.4	5	/
MeOH	TEAHFP 0.02 M	Platinum grid	Platinum plate	1.0	5	/
MeOH + 5 equiv. morpholine + enamine	TEAHFP0.02 M	Platinum grid	Platinum plate	1.0	5	/
95/5 MeCN/DMSO	$LiClO_4$ 0.05 M	Platinum grid	Platinum plate	1.0	5	71%
95/5 MeCN/DMSO	$LiClO_4$ 0.05 M	Platinum grid	Platinum plate	1.0	2.5	90%
95/5 MeCN/DMSO	$LiClO_4$ 0.05 M	Platinum grid	Platinum plate	1.0	1.2	90%
95/5 MeCN/DMSO	$LiClO_4$ 0.05 M	Platinum grid	Carbon felt	1.0	2.5	90%
95/5 MeCN/DMSO	$LiClO_4$ 0.05 M	Platinum grid	Carbon felt	1.0	1.2	90%
95/5 MeCN/DMSO	$LiClO_4$ 0.05 M	Carbon graphite	Platinum plate	1.0	1.2	89%
95/5 MeCN/H_2O	$LiClO_4$ 0.05 M	Platinum grid	Platinum plate	1.0	5	63%
95/5 MeCN/H_2O	$LiClO_4$ 0.05 M	Platinum grid	Platinum plate	1.0	1.2	27%

Table S1 Optimisation of the conditions of the two-step one-pot synthesis

VI- Synthesis of compounds 3, 4, 6, 7, 9, 11, 13-34

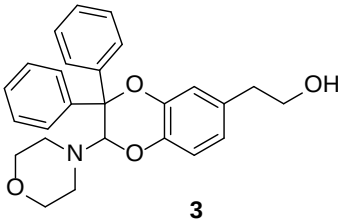
General procedure for the electrosynthesis of 2-amino-2,3-dihydro-1,4-benzodioxanes

A solution of catechol (0.25 mmol) and lithium perchlorate (1.06 g, 10 mmol) in 200 mL of 95/5 MeCN/DMSO mixture (or 95/5 MeCN/water mixture) was oxidized under argon at a platinum electrode (E_{ox} = +1.0 V *vs* Ag/AgCl or +1.4 V *vs* Ag/AgCl). After the complete oxidation (2.0 $F.mol^{-1}$), i.e. when the decay of the current exceeded 95%, a solution of enamine in acetonitrile (5 mL) was added to the yellow solution of *o*-quinone, in one part (enamines **2a-e**) or dropwise (enamines **2f-2k**). The resulting reaction mixture was stirred under argon until a colourless solution is obtained, and added to a mixture of 100 mL of water and 20 mL of a phosphate buffer solution 1M pH 7.0. After the acetonitrile was removed under reduced pressure at room temperature, the aqueous phase was extracted by successive small fractions of ethyl acetate (150 mL total volume). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure at room temperature. The crude residue was purified by flash chromatography on silica gel to give the desired products.

Compounds 3 and 4

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/DMSO mixture as the solvent, and enamine **2a** (79.5 mg, 1.2 equiv.), gave after oxidation at E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography with petroleum ether/ethyl acetate 45/55 as the eluent, compounds **3** and **4** (94 mg, 0.225 mmol) in 90% overall yield (24/76 ratio). The two products were obtained as 18 mg of compound **3** (white solid, m.p. 139 ± 2°C), 15 mg of mixture, and 61 mg of compound **4** (white solid, m.p. 150 ± 2°C).

[*R*,*S*]-2-[2-(Morpholin-1-yl)-3,3-diphenyl-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **3**



3

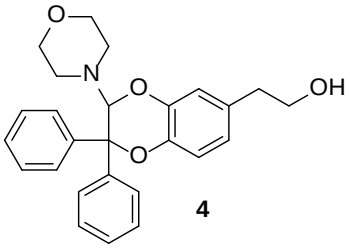
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.51 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.36 (2H, t, *J* = 7.5 Hz, H_{Ph}), 7.27 (3H, m, H_{Ph}), 7.18 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.90 (1H, d, *J* = 2 Hz, H_{Ar}), 6.78 (1H, d, *J* = 8 Hz, H_{Ar}), 6.70 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 5.70 (1H, s,

H_{dioxin}), 3.84 (2H, t, *J* = 6.5 Hz, CH_2O), 3.38 (4H, m, CH_2O_{morph}), 3.21 (2H, m, CH_2N_{morph}), 2.78 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.59 (2H, m, CH_2N_{morph}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6 (2×C), 142.4 (C), 141.6 (C), 131.2 (C), 128.4 (2×CH), 128.0 (2×CH), 127.6 (CH), 127.0 (CH), 126.7 (2×CH), 125.3 (2×CH), 123.0 (CH), 118.2 (CH), 116.0 (CH), 90.7 (CH), 81.7 (C), 66.9 (2×CH_2), 63.6 (CH_2), 48.9 (2×CH_2), 38.5 (CH_2).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{26}H_{28}NO_4$ 418.2013, found 418.2019.

[*R,S*]-2-[3-(Morpholin-1-yl)-2,2-diphenyl-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **4**



4

^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.50 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.35 (2H, t, *J* = 7.5 Hz, H_{Ph}), 7.27 (3H, m, H_{Ph}), 7.17 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.95 (1H, d, *J* = 8 Hz, H_{Ar}), 6.70 (1H, d, *J* = 2 Hz, H_{Ar}), 6.67 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 5.70 (1H, s, H_{dioxin}), 3.79 (2H, t, *J* = 6.5 Hz, CH_2O), 3.37 (4H, m, CH_2O_{morph}), 3.22 (2H, m, CH_2N_{morph}), 2.73 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.59 (2H, m, CH_2N_{morph}).

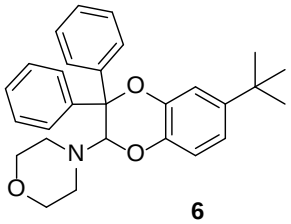
^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0 (C), 142.8 (C), 142.7 (C), 140.3 (C), 132.7 (C), 128.4 (2×CH), 127.9 (2×CH), 127.6 (CH), 126.9 (CH), 126.7 (2×CH), 125.3 (2×CH), 121.5 (CH), 117.8 (CH), 116.4 (CH), 90.9 (CH), 81.8 (C), 67.0 (2×CH_2), 63.5 (CH_2), 48.9 (2×CH_2), 38.6 (CH_2).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{26}H_{28}NO_4$ 418.2013, found 418.2018.

Compounds 6 and 7

The above general procedure, using 4-*tert*-butylcatechol **5** (41.5 mg, 0.25 mmol), 95/5 MeCN/DMSO mixture as the solvent, and enamine **2a** (79.5 mg, 1.2 equiv.), gave after oxidation at E_{ox} = +1.4 V *vs* Ag/AgCl and flash chromatography with cyclohexane/ethyl acetate 65/35 as the eluent, compounds **6** and **7** (101 mg, 0.24 mmol) in 95% overall yield and 31/69 ratio. These two products could be subsequently separated by column chromatography on silica gel 60 H with toluene/acetone 95/5, giving 41 mg of compound **7** (white solid), 21 mg of mixture, and 12 mg of compound **6**.

[*R*,*S*]-2,2-Dimethyl-2-[2-(morpholin-1-yl)-3,3-diphenyl-2,3-dihydro-1,4-benzodioxin-6-yl]-ethane **6**



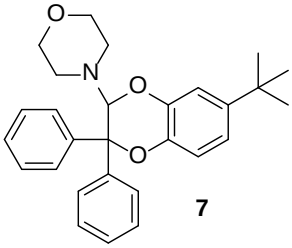
6

^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.64 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.63 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.34 (2H, t, *J* = 7.5 Hz, H_{Ph}), 7.23 (3H, m, H_{Ph}), 7.13 (1H, t, *J* = 7.5 Hz, H_{Ph}), 7.12 (1H, d, *J* = 2 Hz, H_{Ph}), 6.84 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 6.69 (1H, d, *J* = 8 Hz, H_{Ar}), 6.05 (1H, s, H_{dioxin}), 3.18-3.32 (4H, m, CH_2O), 3.14 (2H, m, CH_2N_{morph}), 2.64 (2H, m, CH_2N_{morph}), 1.26 (9H, s, Bu^t).

^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 144.76 (C), 144.28 (C), 144.21 (C), 142.84 (C), 142.09 (C), 129.05 (2×CH), 128.57 (2×CH), 128.18 (CH), 127.52 (CH), 127.47 (2×CH), 126.13 (2×CH), 120.08 (CH), 115.93 (CH), 115.48 (CH), 91.03 (CH), 82.63 (C), 67.45 (2×CH_2), 49.60 (2×CH_2), 34.67 (C), 31.84 (3×CH_3).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{28}H_{32}NO_3$ 430.2377, found 430.2376.

[*R*,*S*]-2,2-Dimethyl-2-[3-(morpholin-1-yl)-2,2-diphenyl-2,3-dihydro-1,4-benzodioxin-6-yl]-ethane **7**



7

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.65 (2H, 4, *J* = 7.5 Hz, H_{Ph}), 7.63 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.33 (2H, t, *J* = 7.5 Hz, H_{Ph}), 7.23 (3H, m, H_{Ph}), 7.13 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.99 (1H, d, *J* = 8 Hz, H_{Ar}), 6.85 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 6.81 (1H, d, *J* = 2 Hz, H_{Ar}), 6.10 (1H, s, H_{dioxin}), 3.30-3.17 (4H, m, CH_2O), 3.14 (2H, m, CH_2N_{morph}), 2.63 (2H, m, CH_2N_{morph}), 1.22 (9H, s, Bu^t).

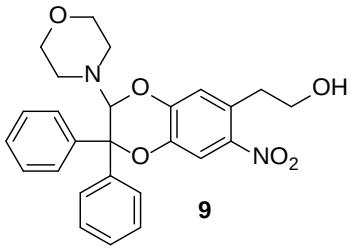
^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 146.3 (C), 144.5 (C), 144.3 (C), 144.2 (C), 140.3 (C), 129.1 (2×CH), 128.6 (2×CH), 128.2 (CH), 127.4 (3×CH), 126.0 (2×CH), 118.6 (CH), 117.9 (CH), 113.4 (CH), 91.0 (CH), 82.5 (C), 67.4 (2×CH_2), 49.5 (2×CH_2), 34.7 (C), 31.8 (3×CH_3).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{28}H_{32}NO_3$ 430.2377, found 430.2374.

Compound 9

The above general procedure, using 6-nitro-hydroxytyrosol **8** (50 mg, 0.25 mmol), 95/5 MeCN/DMSO mixture as the solvent, and enamine **2a** (79.5 mg, 1.2 equiv.), gave after oxidation at E_{ox} = +1.4 V *vs* Ag/AgCl and flash chromatography with ether petroleum/ethyl acetate 60/40 as the eluent, compound **9** (73 mg, 0.16 mmol) in 63% yield.

[*R*,*S*]-2-[3-(Morpholin-1-yl)-7-nitro-2,2-diphenyl-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **9**



9

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, s, H_{Ar}), 7.44 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.42 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.33 (2H, t, *J* = 7.5 Hz, H_{Ph}), 7.26 (3H, m, H_{Ph}), 7.18 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.79 (1H, s, H_{Ar}), 5.80 (1H, s, H_{dioxin}), 3.86 (2H, t, *J* = 6.5 Hz, CH_2O), 3.36 (2H, m, CH_2O_{morph}), 3.31 (2H, m, CH_2O_{morph}), 3.17 (2H, m, CH_2N_{morph}), 3.0-3.1 (2H, m, CH_2-Ar), 2.55 (2H, m, CH_2N_{morph}).

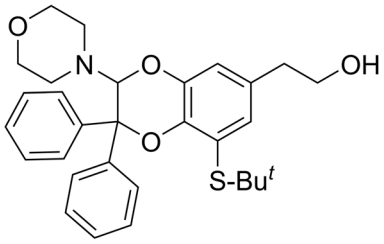
^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8 (C), 141.9 (C), 141.8 (C), 141.4 (C), 140.0 (C), 130.3 (C), 128.7 (2×CH), 128.2 (3×CH), 127.3 (CH), 126.7 (2×CH), 125.0 (2×CH), 119.3 (CH), 115.7 (CH), 92.1 (CH), 82.6 (C), 66.8 (2×CH_2), 62.6 (CH_2), 48.7 (2×CH_2), 36.6 (CH_2).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{26}H_{27}N_2O_6$ 463.1864, found 463.1869.

Compound 11

The above general procedure, using 5-S-*tert*-butyl-hydroxytyrosol **10** (24 mg, 0.1 mmol), 95/5 MeCN/DMSO mixture as the solvent, and enamine **2a** (32 mg, 1.2 equiv.), gave after oxidation at E_{ox} = +1.4 V *vs* Ag/AgCl and flash chromatography with ether petroleum/ethyl acetate 70/30 as the eluent, compound **11** (43 mg, 0.085 mmol) in 85% yield.

[*R*,*S*]-2-[3-(Morpholin-1-yl)-2,2-diphenyl-8-*tert*-butylthio-2,3-dihydro-1,4-benzodioxin-6-yl]-ethanol **11**



11

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.54 (2H, d, *J* = 7.5 Hz, H_{Ph}), 7.35 (2H, t, *J* = 7.5 Hz, H_{Ph}), 7.21 (3H, m, H_{Ph}), 7.11 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.92 (1H, d, *J* = 2 Hz, H_{Ar}), 6.72 (1H, d, *J* = 2 Hz, H_{Ar}), 5.79 (1H, s, H_{dioxin}), 3.77 (2H, t, *J* = 6.5 Hz, CH_2O), 3.37 (4H, m, CH_2O_{morph}), 3.18 (2H, m, CH_2N_{morph}), 2.71 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.62 (2H, m, CH_2N_{morph}), 1.42 (9H, s, Bu^t).

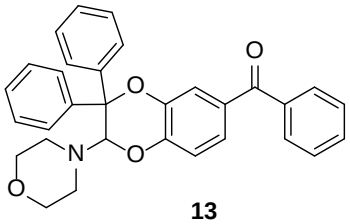
^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (C), 142.6 (C), 142.4 (C), 142.3 (C), 132.0 (CH), 131.7 (C), 128.6 (2×CH), 128.1 (2×CH), 127.7 (CH), 127.0 (CH), 126.5 (2×CH), 125.3 (2×CH), 121.5 (C), 117.6 (CH), 90.6 (CH), 82.3 (C), 66.9 (2×CH_2), 63.5 (CH_2), 48.7 (2×CH_2), 47.2 (C), 38.5 (CH_2), 31.6 (3×CH_3).

HRMS (ESI$^+$) m/z , $[M + H]^+$ calculated for $C_{30}H_{36}NO_4S$ 506.2360, found 506.2355.

Compounds 13 and 14

The above general procedure, using 3,4-dihydroxybenzophenone **12** (53.5 mg, 0.25 mmol), 95/5 MeCN/DMSO mixture as the solvent, and enamine **2a** (79.5 mg, 1.2 equiv.), gave after oxidation at E_{ox} = +1.4 V *vs* Ag/AgCl and flash chromatography with toluene/acetone 97.5/2.5 as the eluent, compounds **13** and **14** (85 mg, 0.18 mmol) in 71% overall yield and 81/19 ratio. The compound **13** could be separated from the mixture by column chromatography on silica gel 60 H with toluene/acetone 98/2 as the eluent, giving 20.5 mg of pure compound **13.**

[*R*,*S*]-[2-(Morpholin-1-yl)-3,3-diphenyl-2,3-dihydro-1,4-benzodioxin-6-yl](phenyl)methanone **13**



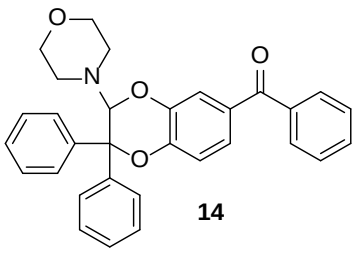
13

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 7.5 Hz, 2×H_{PhCO}), 7.58 (1H, d, *J* = 2 Hz, H_{Ar}), 7.56 (1H, t, *J* = 7.5 Hz, H_{PhCO}), 7.47 (6H, m, 2×H_{PhCO} and 4×H_{Ph}), 7.33 (3H, m, H_{Ar} and 2×H_{Ph}), 7.24 (3H, m, 3×H_{Ph}), 7.16 (1H, t, *J* = 7 Hz, H_{Ph}), 6.85 (1H, d, *J* = 8 Hz, H_{Ar}), 5.78 (1H, s, H_{dioxin}), 3.37 (4H, m, 2×CH_2O), 3.22 (2H, m, CH_2N_{morph}), 2.59 (2H, m, CH_2N_{morph}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (C), 148.5 (C), 142.3 (C), 142.0 (C), 141.5 (C), 138.2 (C), 131.9 (CH), 130.6 (C), 129.8 (2×CH), 128.5 (2×CH), 128.2 (2×CH), 128.0 (2×CH), 127.9 (CH), 127.1 (CH), 126.7 (2×CH), 126.1 (CH), 125.2 (2×CH), 120.1 (CH), 115.6 (CH), 91.8 (CH), 82.2 (C), 66.9 (2×CH_2), 48.8 (2×CH_2).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{31}H_{28}NO_4$ 478.2013, found 478.2014.

[*R*,*S*]-[3-(Morpholin-1-yl)-2,2-diphenyl-2,3-dihydro-1,4-benzodioxin-6-yl](phenyl)methanone **14**



14

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, m, 2×H_{PhCO}), 7.55 (1H, t, *J* = 7 Hz, H_{Ar}), 7.53 (1H, m, H_{PhCO}), 7.44 (6H, m, 2×H_{PhCO} and 4×H_{Ph}), 7.36 (1H, d, *J* = 2 Hz, H_{Ar}), 7.30 (2H, m, 2×H_{Ph}), 7.22 (3H, m, 3×H_{Ph}), 7.13 (1H, t, *J* = 7 Hz, H_{Ph}), 7.05 (1H, d, *J* = 8 Hz, H_{Ar}), 5.73 (1H, s, H_{dioxin}), 3.33 (4H, m, 2×CH_2O), 3.15 (2H, m, CH_2N_{morph}), 2.57 (2H, m, CH_2N_{morph}).

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (C), 146.0 (C), 143.7 (C), 142.1 (C), 138.1 (C), 137.9 (C), 132.1 (C), 132.0 (CH), 129.1 (2×CH), 128.3 (2×CH), 128.2 (2×CH), 128.0 (2×CH), 127.2 (CH), 126.6 (2×CH), 125.4 (CH), 125.3 (2×CH), 124.2 (CH), 118.4 (CH), 117.5 (CH), 91.2 (CH), 82.5 (C), 66.9 (2×CH_2), 48.8 (2×CH_2).

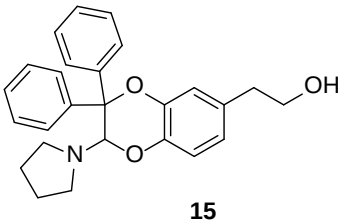
HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{31}H_{28}NO_4$ 478.2013, found 478.2008.

Compounds 15 and 16

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/DMSO mixture as the solvent, and enamine **2b** (75 mg, 1.2 equiv.), gave after oxidation at E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography with toluene/acetone 90/10 as the eluent, compounds **15** and **16** (74 mg, 0.185 mmol) in 74% overall yield and 27/73 ratio. As previously reported for compounds **6** and **7**, these two products could be separated

by column chromatography on silica gel 60 H with petroleum ether/ethyl acetate 75/25 as the eluent.

[*R*,*S*]-2-[3,3-Diphenyl-2-(pyrrolidin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **15**



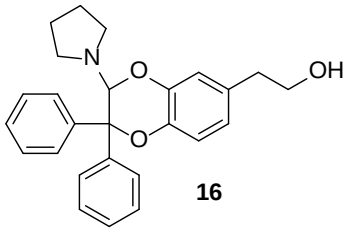
15

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (4H, d, *J* = 7 Hz, 4×H_{Ph}), 7.32 (2H, m, H_{Ph}), 7.24 (3H, m, 3×H_{Ph}), 7.14 (1H, t, *J* = 7 Hz, H_{Ph}), 6.92 (1H, br s, H_{Ar}), 6.71 (1H, br d, *J* = 8 Hz, H_{Ar}), 6.65 (1H, br d, *J* = 8 Hz, H_{Ar}), 6.03 (1H, s, H_{dioxin}), 3.82 (2H, t, *J* = 6.5 Hz, CH_2O), 3.10 (2H, m, CH_2N_{pyrrol}), 2.77 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.71 (2H, m, CH_2N_{pyrrol}), 1.53 (4H, m, 2×CH_2).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4 (C), 143.0 (2×C), 142.5 (C), 130.7 (C), 128.4 (2×CH), 128.0 (2×CH), 127.5 (CH), 126.8 (3×CH), 125.4 (2×CH), 122.6 (CH), 118.1 (CH), 115.9 (CH), 88.0 (CH), 81.9 (C), 63.7 (CH_2), 48.2 (2×CH_2), 38.6 (CH_2), 24.1 (2×CH_2).

HRMS (ESI$^+$) m/z , $[M + H]^+$ calculated for $C_{26}H_{28}NO_3$ 402.2064, found 402.2064.

[*R*,*S*]-2-[2,2-Diphenyl-3-(pyrrolidin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **16**



16

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (4H, d, *J* = 7 Hz, 4×H_{Ph}), 7.30 (2H, t, *J* = 7.5 Hz, 2×H_{Ph}), 7.21 (3H, m, 3×H_{Ph}), 7.12 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.95 (1H, d, *J* = 8.5 Hz, H_{Ar}), 6.62 (2H, m, 2×H_{Ar}), 6.04 (1H, s, H_{dioxin}), 3.74 (2H, t, *J* = 6.5 Hz, CH_2O), 3.09 (2H, m, CH_2-Ar), 2.68 (4H, t, *J* = 6.5 Hz, 2×CH_2N), 1.50 (4H, m, 2×$CH_{2\ pyrrol}$).

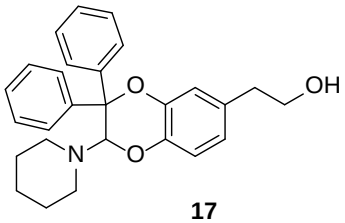
^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7 (C), 143.0 (2×C), 141.1 (C), 132.2 (C), 128.4 (2×CH), 127.9 (2×CH), 127.4 (CH), 126.8 (3×CH), 125.3 (2×CH), 121.1 (CH), 117.6 (CH), 116.2 (CH), 87.9 (CH), 81.8 (C), 63.5 (CH_2), 48.2 (2×CH_2), 38.6 (CH_2), 24.1 (2×CH_2).

HRMS (ESI$^+$) m/z , $[M + H]^+$ calculated for $C_{26}H_{28}NO_3$ 402.2064, found 402.2065.

Compounds 17 and 18

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/DMSO mixture as the solvent, and enamine **2c** (79 mg, 1.2 equiv.), gave after oxidation at E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography with ether petroleum/ethyl acetate 70/30 as the eluent, compounds **17** and **18** (68 mg, 0.16 mmol) in 65% overall yield. As previously reported for compounds **6** and **7**, these two products could be separated by column chromatography on silica gel 60 H with ether petroleum/ethyl acetate 72.5/27.5 as the eluent.

[*R*,*S*]-2-[3,3-Diphenyl-2-(piperidin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **17**



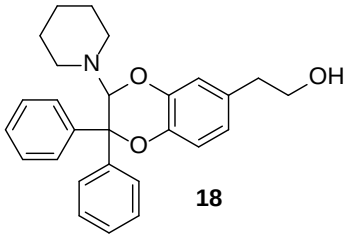
17

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (4H, d, *J* = 7.5 Hz, 4×H_{Ph}), 7.31 (2H, t, *J* = 7.5 Hz, 2×H_{Ph}), 7.22 (3H, m, 3×H_{Ph}), 7.13 (1H, t, *J* = 7 Hz, H_{Ph}), 6.86 (1H, d, *J* = 2 Hz, H_{Ar}), 6.73 (d, *J* = 8 Hz, H_{Ar}), 6.65 (d, *J* = 8 and 2 Hz, 1H, H_{Ar}), 5.72 (s, 1H, H_{dioxin}), 3.80 (1H, t, *J* = 6.5 Hz, 2H, CH_2O), 3.14 (2H, m, CH_2N_{morph}), 2.75 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.52 (2H, m, CH_2N_{morph}), 1.26 (6H, m, 3×$CH_{2\ piper}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (C), 143.0 (C), 142.9 (C), 141.9 (C), 130.9 (C), 128.4 (2×CH), 127.9 (2×CH), 127.6 (CH), 126.9 (3×CH), 125.7 (2×CH), 122.8 (CH), 118.2 (CH), 116.1 (CH), 91.7 (CH), 82.0 (C), 63.7 (CH_2), 49.9 (2×CH_2), 38.6 (CH_2), 29.9 (CH_2), 26.0 (CH_2), 24.2 (CH_2).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{27}H_{30}NO_3$ 416.2220, found 416.2215.

[*R*,*S*]-2-[2,2-Diphenyl-3(-piperidin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **18**



18

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (4H, d, *J* = 7.5 Hz, 4×H_{Ph}), 7.31 (2H, t, *J* = 7.5 Hz, H_{Ph}), 7.22 (3H, m, 3×H_{Ph}), 7.13 (1H, t, *J* = 7 Hz, H_{Ph}), 6.92 (1H, d, *J* = 8 Hz, H_{Ar}), 6.66 (d, *J* =

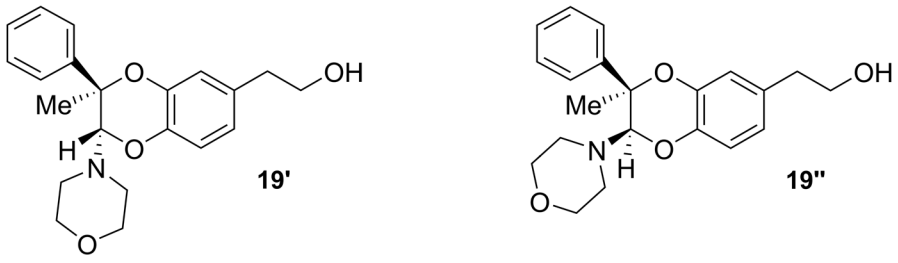
2 Hz, H_{Ar}), 6.63 (d, *J* = 8 and 2 Hz, 1H, H_{Ar}), 5.74 (s, 1H, H_{dioxin}), 3.78 (1H, t, *J* = 6.5 Hz, 2H, CH_2O), 3.14 (2H, m, CH_2N_{morph}), 2.71 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.52 (2H, m, CH_2N_{morph}), 1.26 (6H, m, 3×$CH_{2\ piper}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (C), 143.2 (2×C), 140.6 (C), 132.4 (C), 128.4 (2×CH), 127.8 (2×CH), 127.5 (CH), 126.8 (3×CH), 125.7 (2×CH), 121.3 (CH), 117.8 (CH), 116.4 (CH), 91.9 (CH), 81.9 (C), 63.6 (CH_2), 49.8 (2×CH_2), 38.7 (CH_2), 29.8 (CH_2), 26.1 (CH_2), 24.2 (CH_2).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{27}H_{30}NO_3$ 416.2220, found 416.2222.

Compounds 19', 19'', 20' and 20''

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/H_2O mixture as the solvent, and enamine **2d** (254 mg, 5 equiv.), gave after oxidation at E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography with ether petroleum/ethyl acetate 65/35 as the eluent, compounds **19'**, **19''**, **20'** and **20''** (70.5 mg, 0.20 mmol) in 79.5% overall yield and 18.5;12/44.5;25 ratio. These four products were obtained as 11 mg of diastereoisomers **19'** and **19"**, 28.5 mg of mixture, and 31 mg of diastereoisomers **20'** and **20"**.



Relative configurations

2-[(2*S**,3*R**)-3-Methyl-2-(morpholin-1-yl)-3-phenyl-2,3-dihydro-1,4-benzodioxin-6-yl]-ethanol **19'**

^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 7.5 Hz, 2×H_{Ph}), 7.18 (2H, t, *J* = 7.5 Hz, 2×H_{Ph}), 7.11 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.70 (1H, d, *J* = 2 Hz, H_{Ar}), 6.59 (1H, d, *J* = 8 Hz, H_{Ar}), 6.54 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.87 (1H, s, H_{dioxin}), 3.69 (2H, t, *J* = 6.5 Hz, CH_2O), 3.55 (4H, m, 2×CH_2O_{morph}), 3.11 (2H, m, CH_2N_{morph}), 2.65 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.48 (2H, m, CH_2N_{morph}), 1.59 (3H, s, CH_3).

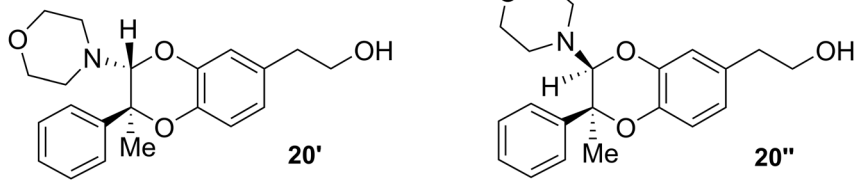
^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2 (C), 142.5 (C), 142.2 (C), 131.4 (C), 128.4 (2×CH), 127.5 (2×CH), 125.4 (CH), 122.3 (CH), 117.6 (CH), 116.1 (CH), 92.3 (CH), 79.1 (C), 67.2 (2×CH_2), 63.6 (CH_2), 49.3 (2×CH_2), 38.5 (CH_2), 26.1 (CH_3).

2-[(2*R**,3*R**)-3-methyl-2-(morpholin-1-yl)-3-phenyl-2,3-dihydro-1,4-benzodioxin-6-yl]-ethanol **19’’**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 7.5 Hz, 2×H_{Ph}), 7.26 (2H, t, *J* = 7.5 Hz, 2×H_{Ph}), 7.16 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.76 (1H, d, *J* = 8 Hz, H_{Ar}), 6.75 (1H, d, *J* = 2 Hz, H_{Ar}), 6.64 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.75 (1H, s, H_{dioxin}), 3.73 (2H, t, *J* = 6.5 Hz, CH_2O), 3.22 (4H, m, 2×CH_2O_{morph}), 2.83 (2H, m, CH_2N_{morph}), 2.69 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.35 (2H, m, CH_2N_{morph}), 1.52 (3H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6 (C), 141.8 (C), 141.5 (C), 131.6 (C), 128.0 (2×CH), 127.0 (CH), 124.7 (2×CH), 122.5 (CH), 117.9 (CH), 116.1 (CH), 93.3 (CH), 78.3 (C), 66.9 (2×CH_2), 63.6 (CH_2), 48.4 (2×CH_2), 38.6 (CH_2), 27.2 (CH_3).

HRMS **19’/19**” (ESI$^+$) m/z , [M + H]$^+$ calculated for $C_{21}H_{26}NO_4$ 356.1856, found 356.1863.



Relative configurations

2-[(2*S**,3*R**)-2-Methyl-3-(morpholin-1-yl)-2-phenyl-2,3-dihydro-1,4-benzodioxin-6-yl]-ethanol **20’**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (2H, t, *J* = 7.5 Hz, 2×H_{Ph}), 7.30 (2H, t, *J* = 7.5 Hz, 2×H_{Ph}), 7.22 (1H, t, *J* = 7.5 Hz, H_{Ph}), 6.89 (1H, d, *J* = 8 Hz, H_{Ar}), 6.69 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 6.65 (1H, d, *J* = 2 Hz, H_{Ar}), 5.02 (1H, s, H_{dioxin}), 3.76 (2H, t, *J* = 6.5 Hz, CH_2O), 3.67 (4H, m, 2×CH_2O_{morph}), 3.25 (2H, m, CH_2N_{morph}), 2.71 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.62 (2H, m, CH_2N_{morph}), 1.75 (3H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9 (C), 143.2 (C), 140.8 (C), 132.2 (C), 128.4 (2×CH), 127.4 (2×CH), 125.4 (CH), 121.7 (CH), 117.1 (CH), 116.4 (CH), 92.2 (CH), 79.0 (C), 67.2 (2×CH_2), 63.5 (CH_2), 49.3 (2×CH_2), 38.5 (CH_2), 26.4 (CH_3).

2-[(2*S**,3*S**)-2-Methyl-3-(morpholin-1-yl)-2-phenyl-2,3-dihydro-1,4-benzodioxin-6-yl]-ethanol **20''**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (2H, d, *J* = 7.5 Hz, 2×H_{Ph}), 7.38 (2H, t, *J* = 7.5 Hz, 2×H_{Ph}), 7.27 (1H, m, 1×H_{Ph}), 6.92 (1H, d, *J* = 8 Hz, H_{Ar}), 6.82 (1H, d, *J* = 2 Hz, H_{Ar}), 6.75 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.88 (1H, s, H_{dioxin}), 3.84 (2H, t, *J* = 6.5 Hz, CH_2O), 3.35 (4H, m, 2×CH_2O_{morph}), 2.95 (2H, m, CH_2N_{morph}), 2.80 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.48 (2H, m, CH_2N_{morph}), 1.68 (3H, s, CH_3).

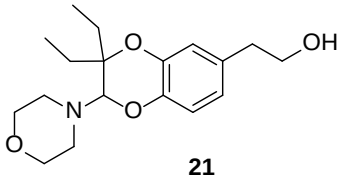
^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2 (C), 142.6 (C), 140.2 (C), 132.3 (C), 128.0 (2×CH), 127.0 (CH), 124.7 (2×CH), 121.8 (CH), 117.5 (CH), 116.5 (CH), 93.4 (CH), 78.2 (C), 66.9 (2×CH_2), 63.7 (CH_2), 48.4 (2×CH_2), 38.6 (CH_2), 27.1 (CH_3).

HRMS **20'/20"** (ESI^+) m/z , $[M + H]^+$ calculated for $C_{21}H_{26}NO_4$ 356.1856, found 356.1859.

Compounds 21 and 22

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/H_2O mixture as the solvent, and enamine **2f** (211 mg, 5 equiv.), gave after oxidation at E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography with ether petroleum/ethyl acetate 50/50 as the eluent, compounds **21** and **22** (52 mg, 0.16 mmol) in 65% overall yield and 28/72 ratio. These two products could be separated by HPLC with an H_2O/MeCN (60:40 - 35:65 v/v) gradient system (flow rate: 40 mL/min), giving 10 mg of compound **21** and 27 mg of compound **22**.

[*R*,*S*]-,2-[3,3-Diethyl-2-(morpholin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **21**



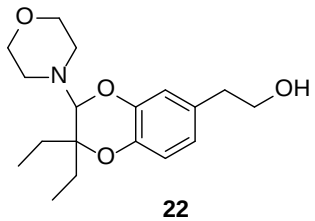
21

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (1H, d, *J* = 8 Hz, H_{Ar}), 6.70 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 6.66 (1H, d, *J* = 2 Hz, H_{Ar}), 4.46 (1H, s, H_{dioxin}), 3.82 2H, (t, *J* = 6.5 Hz, CH_2O), 3.67 (4H, m, 2×CH_2O_{morph}), 3.16 (2H, m, CH_2N_{morph}), 2.76 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.60 (2H, m, CH_2N_{morph}), 2.24 (1H, s, broad signal, OH), 1.86 (2H, m, $CH_{2\ Et}$), 1.72 (1H, m, $CH_{2\ Et}$), 1.57 (1H, m, $CH_{2\ Et}$), 0.95 (3H, t, *J* = 7.5 Hz, CH_3), 0.85 (3H, t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4 (C), 141.5 (C), 131.4 (C), 122.4 (CH), 118.0 (CH), 115.8 (CH), 91.3 (CH), 79.2 (C), 66.9 (2×CH_2), 63.7 (CH_2), 49.2 (2×CH_2), 38.6 (CH_2), 26.0 (CH_2), 25.0 (CH_2), 7.9 (CH_3), 7.2 (CH_3).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{18}H_{28}NO_4$ 322.2013, found 322.2020.

[*R*,*S*]-2-[2,2-Diethyl-3-(morpholin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **22**



22

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (1H, d, *J* = 8 Hz, H_{Ar}), 6.72 (1H, d, *J* = 2 Hz, H_{Ar}), 6.65 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.43 (1H, s, H_{dioxin}), 3.82 (2H, t, *J* = 6.5 Hz, CH_2O), 3.64 (4H, m, 2×CH_2O_{morph}), 3.14 2H, (m, CH_2N_{morph}), 2.77 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.56 (2H, m, CH_2N_{morph}), 1.86 (2H, m, $CH_{2\ Et}$), 1.72 (1H, m, $CH_{2\ Et}$), 1.56 1H, (s, broad signal, OH), 1.54 (1H, m, $CH_{2\ Et}$), 0.94 (3H, t, *J* = 7.5 Hz, CH_3), 0.84 (3H, t, *J* = 7.5 Hz, CH_3).

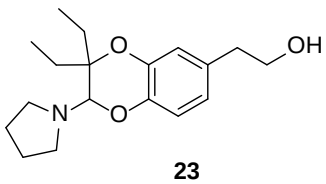
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1 (C), 140.2 (C), 132.0 (C), 121.5 (CH), 117.5 (CH), 116.1 (CH), 91.8 (CH), 79.2 (C), 67.2 (2×CH_2), 63.8 (CH_2), 49.1 (2×CH_2), 38.7 (CH_2), 26.1 (CH_2), 24.9 (CH_2), 8.0 (CH_3), 7.1 (CH_3).

HRMS (ESI^+) m/z , $[M + H]^+$ calculated for $C_{18}H_{28}NO_4$ 322.2013, found 322.2018.

Compounds 23 and 24

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/H_2O mixture as the solvent, and enamine **2g** (191 mg, 5 equiv.), gave after oxidation at E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography with ether petroleum/ethyl acetate 60/40 as the eluent, compounds **23** and **24** (66 mg, 0.22 mmol) in 87% overall yield and 26/74 ratio.

[*R*,*S*]-2-[3,3-Diethyl-2-(pyrrolidin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **23**

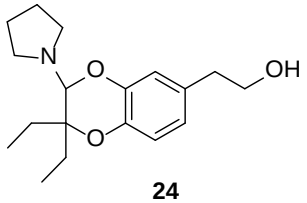


23

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, d, *J* = 8 Hz, H_{Ar}), 6.67 (1H, d, *J* = 2 Hz, H_{Ar}), 6.66 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.82 (1H, s, H_{dioxin}), 3.81 (2H, t, *J* = 6.5 Hz, CH_2O), 3.00-3.10 (2H, m, CH_2N_{pyrrol}), 2.80 (2H, m, CH_2N_{pyrrol}), 2.76 (2H, m, *J* = 6.5 Hz, CH_2-Ar), 1.60-1.90 (9H, m, 2×$CH_{2\ pyrrol}$, 2×$CH_{2\ Et}$, OH) , 0.90 (6H, m, 2×CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5 (C), 142.3 (C), 130.7 (C), 121.7 (CH), 117.7 (CH), 115.7 (CH), 89.00 (CH), 79.3 (C), 63.8 (CH_2), 48.2 (2×CH_2), 38.6 (CH_2), 25.4 (2×CH_2), 24.3 (2×CH_2), 7.8 (CH_3), 7.3 (CH_3).

[*R,S*]-2-[2,2-Diethyl-3-(pyrrolidin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **24**



24

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, d, *J* = 8 Hz, H_{Ar}), 6.69 (1H, d, *J* = 2 Hz, H_{Ar}), 6.63 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.83 (1H, s, H_{dioxin}), 3.83 (2H, t, *J* = 6.5 Hz, CH_2O), 3.00-3.10 (2H, m, CH_2N_{pyrrol}), 2.80 (2H, m, CH_2N_{pyrrol}), 2.76 (2H, m, *J* = 6.5 Hz, CH_2-Ar), 1.60-1.90 (9H, m, 2×$CH_{2\ pyrrol}$, 2×$CH_{2\ Et}$, OH) , 0.90 (6H, m, 2×CH_3).

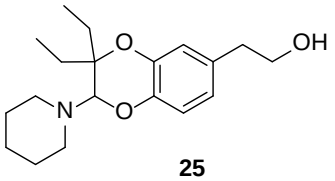
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9(C), 140.9 (C), 131.3 (C), 121.1 (CH), 117.3 (CH), 116.1 (CH), 89.2 (CH), 79.1 (C), 63.8 (CH_2), 48.2 (2×CH_2), 38.6 (CH_2), 25.4 (2×CH_2), 24.3 (2×CH_2), 7.8 (CH_3), 7.3 (CH_3).

HRMS **23/24** (ESI^+) m/z , $[M + H]^+$ calculated for $C_{18}H_{28}NO_3$ 306.2064, found 306.2068.

Compounds 25 and 26

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/H_2O mixture as the solvent, and enamine **2h** (209 mg, 5 equiv.), gave after oxidation at E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography with ether petroleum/ethyl acetate 65/35 as the eluent, compounds **25** and **26** (68 mg, 0.21 mmol) in 85% overall yield and 25/75 ratio. A small fraction of pure compound **26** (4 mg) was obtained through the separation by HPLC of 31 mg of the mixture, using H_2O/MeCN 37:63 v/v as the eluent in isocratic mode (flow rate: 45 mL/min).

[*R*,*S*]-2-[3,3-Diethyl-2-(piperidin -1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **25**

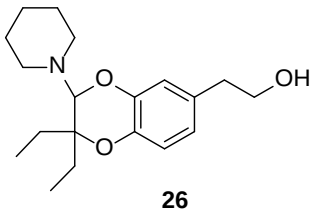


25

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, d, *J* = 8 Hz, H_{Ar}), 6.74 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 6.71 (1H, d, *J* = 2 Hz, H_{Ar}), 4.51 (1H, s, H_{dioxin}), 3.87 (2H, t, *J* = 6.5 Hz, CH_2O), 3.14 (2H, m, CH_2N_{piper}), 2.81 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.54 (2H, m, CH_2N_{piper}), 1.70-1.90 (4H, m, 2×$CH_{2\ Et}$), 1.55 (5H, m, 2×$CH_{2\ piper}$, OH), 1.45 (2H, m, $CH_{2\ piper}$), 0.99 (3H, t, *J* = 7.5 Hz, CH_3), 0.90 (3H, t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (C), 141.7 (C), 130.6 (C), 121.9 (CH), 117.8 (CH), 115.6 (CH), 92.8 (CH), 79.4 (C), 63.7 (CH_2), 49.9 (2×CH_2), 38.6 (CH_2), 26.4 (2×CH_2), 26.1 (CH_2), 25.3 (CH_2), 24.4 (CH_2), 7.9 (CH_3), 7.2 (CH_3).

[*R*,*S*]-2-[2,2-diethyl-3-(piperidin -1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **26**



26

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (1H, d, *J* = 8 Hz, H_{Ar}), 6.71 (1H, d, *J* = 2 Hz, H_{Ar}), 6.64 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.51 (1H, s, H_{dioxin}), 3.83 (2H, t, *J* = 6.5 Hz, CH_2O), 3.11 (2H, m, CH_2N_{piper}), 2.77 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.53 (2H, m, CH_2N_{piper}), 1.75-1.90 (2H, m, $CH_{2\ Et}$), 1.71 (2H, m, $CH_{2\ Et}$), 1.53 (5H, m, 2×$CH_{2\ piper}$, OH), 1.40 (2H, m, $CH_{2\ piper}$), 0.93 (3H, t, *J* = 7.5 Hz, CH_3), 0.84 (3H, t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (C), 140.3 (C), 131.7 (C), 121.2 (CH), 117.6 (CH), 116.1 (CH), 92.7 (CH), 79.3 (C), 63.8 (CH_2), 50.0 (2×CH_2), 38.7 (CH_2), 26.2 (2×CH_2), 26.0 (CH_2), 25.2 (CH_2), 24.3 (CH_2), 7.9 (CH_3), 7.2 (CH_3).

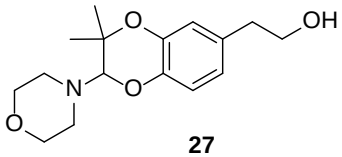
HRMS **25/26** (ESI^+) m/z , $[M + H]^+$ calculated for $C_{19}H_{30}NO_3$ 320.2220, found 320.2224.

Compounds 27, 28 and 33

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/H_2O mixture as the solvent, and enamine **2i** (176 mg, 5 equiv.), gave after oxidation at

E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography (ether petroleum/ethyl acetate 35/65), compounds **27** and **28** (68 mg, 0.065 mmol) in 26.5% overall yield (38/62 ratio), along with compound **33** (10 mg, 0.044 mmol) in 17.5% yield.

[*R*,S]-2-[3,3-Dimethyl-2-(morpholin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **27**

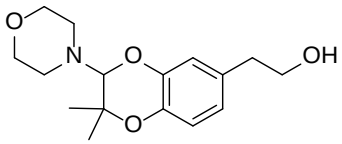


27

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (1H, d, *J* = 8 Hz, H_{Ar}), 6.71 (1H, m, H_{Ar}), 6.69 (1H, d, *J* = 2 Hz, H_{Ar}), 4.39 (1H, s, H_{dioxin}), 3.81 (2H, t, *J* = 6.5 Hz, CH_2O), 3.64 (4H, m, 2×CH_2O_{morph}), 3.11 (2H, m, CH_2N_{morph}), 2.75 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.57 (2H, m, CH_2N_{morph}), 1.32 (6H, s, 2×CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2 (C), 141.7 (C), 131.2 (C), 122.2 (CH), 117.8 (CH), 115.9 (CH), 93.6 (CH), 75.2 (C), 67.2 (2×CH_2), 63.8 (CH_2), 48.9 (2×CH_2), 38.6 (CH_2), 25.7 (CH_3), 24.5 (CH_3).

[*R*,*S*]-2-[2,2-Dimethyl-3-(morpholin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **28**



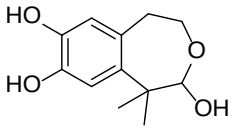
28

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (1H, m, H_{Ar}), 6.71 (1H, d, *J* = 8 Hz, H_{Ar}), 6.66 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.39 (1H, s, H_{dioxin}), 3.83 (2H, t, *J* = 6.5 Hz, CH_2O), 3.64 (4H, m, 2×CH_2O_{morph}), 3.11 (2H, m, CH_2N_{morph}), 2.77 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.57 (2H, m, CH_2N_{morph}), 1.45 (6H, s, 2×CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6 (C), 140.4 (C), 132.0 (C), 121.6 (CH), 117.5 (CH), 116.3 (CH), 93.7 (CH), 75.1 (C), 67.2 (2×CH_2), 63.8 (CH_2), 48.9 (2×CH_2), 38.6 (CH_2), 25.6 (CH_3), 24.6 (CH_3).

HRMS **27/28** (ESI^+) m/z , $[M + H]^+$ calculated for $C_{16}H_{24}NO_4$ 294.1700, found 294.1701.

[*R*,*S*]-1,1-Dimethyl-1,2,4,5-tetrahydrobenzo[d]oxepine-2,7,8-triol **33**



33

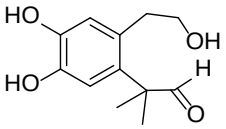
The 1,2,4,5-tetrahydrobenzo[d]oxepine [15,16] hemiacetal **33** exists in deuterated solvent in equilibrium with the corresponding aldehyde **33'**. Acetone-d_6 was selected as the solvent inducing the better separation of the aliphatic signals of **33** and **33'**.

Hemiacetal **33**

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 6.83 (1H, s, H_{Ar}), 6.53 (1H, s, H_{Ar}), 4.75 (1H, s, $H_{O\text{-}CH\text{-}OH}$), 4.08 (1H, ddd, *J* = 12.0, 11.5 and 1.5 Hz, $H_{oxepine\ CH2O}$), 3.53 (1H, ddd, *J* = 12.0, 5.0 and 2.5 Hz, $H_{oxepine\ CH2O}$), 3.24 (1H, ddd, *J* = 15.5, 11.5 and 2.5 Hz, $H_{oxepine\ CH2Ph}$), 2.96 (3H, broad s, 3×OH), 2.54 (1H, ddd, *J* = 15.5, 5.0 and 1.5 Hz, $H_{oxepine\ CH2Ph}$), 1.31 (3H, s, CH_3), 1.27 (3H, s, CH_3).

^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 143.3 (C), 143.0 (C), 136.3 (C), 132.7 (C), 119.0 (CH), 116.7 (CH), 101.2 (CH), 61.0 (CH_2), 45.9 (C), 39.8 (CH_2), 27.6 (CH_3), 25.7 (CH_3).

Aldehyde **33'**



33'

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.53 (1H, s, CHO), 6.86 (1H, s, H_{Ar}), 6.78 (1H, s, H_{Ar}), 3.61 (2H, t, *J* = 6.5 Hz, CH_2O), 2.52 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 1.34 (6H, s, 2×CH_3).

^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 204.3 (C), 144.8 (C), 144.1 (C), 132.6 (C), 129.8 (C), 118.6 (CH), 115.0 (CH), 64.0 (CH_2), 50.6 (C), 36.2 (CH_2), 24.1 (2×CH_3).

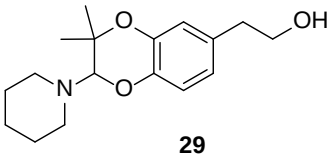
HRMS **33/33'** (ESI$^+$) m/z , $[M + H - H_2O]^+$ calculated for $C_{12}H_{15}O_3$ 207.1016, found 207.1022, $[M + Na]^+$ calculated for $C_{12}H_{16}NaO_4$ 247.0941, found 247.0947, $[M + H]^+$ calculated for $C_{12}H_{17}O_4$ 225.1121, found 225.1129.

Compounds 29, 30 and 33

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/H_2O mixture as the solvent, and enamine **2j** (174 mg, 5 equiv.), gave after oxidation at

E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography (ether petroleum/ethyl acetate 60/40), compounds **29** and **30** (30 mg, 0.10 mmol) in 41% overall yield (31/69 ratio), along with compound **33** (22.5 mg, 0.10 mmol) in 40.5% yield.

[*R,S*]-2-[3,3-Dimethyl-2-(piperidin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **29**

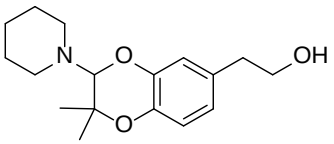


29

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, d, *J* = 8 Hz, H_{Ar}), 6.68 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 6.64 (1H, d, *J* = 2 Hz, H_{Ar}), 4.42 (1H, s, H_{dioxin}), 3.81 (2H, t, *J* = 6.5 Hz, CH_2O), 3.06 (2H, m, CH_2N_{piper}), 2.75 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.51 (2H, m, CH_2N_{piper}), 1.50 (5H, m, 2×$CH_{2\ piper}$, OH), 1.42 (3H, s, CH_3), 1.39 (2H, m, $CH_{2\ piper}$), 1.32 (3H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7 (C), 141.9 (C), 130.8 (C), 122.0 (CH), 117.8 (CH), 115.9 (CH), 94.6 (CH), 75.4 (C), 63.8 (CH_2), 49.7 (2×CH_2), 38.6 (CH_2), 26.4 (2×CH_2), 26.0 (2×CH_3), 24.5(CH_2).

[*R,S*]-2-[2,2-Dimethyl-3-(piperidin-1-yl)-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **30**



30

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (1H, d, *J* = 2 Hz, H_{Ar}), 6.71 (1H, d, *J* = 8 Hz, H_{Ar}), 6.63 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.42 (1H, s, H_{dioxin}), 3.82 (2H, t, *J* = 6.5 Hz, CH_2O), 3.06 (2H, m, CH_2N_{piper}), 2.77 (2H, t, *J* = 6.5 Hz, CH_2-Ar), 2.51 (2H, m, CH_2N_{piper}), 1.50 (5H, m, 2×$CH_{2\ pyrrol}$, OH), 1.42 (3H, s, CH_3), 1.39 (2H, m, $CH_{2\ piper}$), 1.31 (3H, s, CH_3).

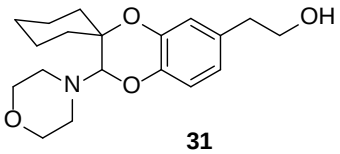
^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0 (C), 140.6 (C), 131.6 (C), 121.2 (CH), 117.4 (CH), 116.3 (CH), 94.8 (CH), 75.3 (C), 63.8 (CH_2), 49.7 (2×CH_2), 38.7 (CH_2), 26.4 (2×CH_2), 25.9 (2×CH_3), 24.5(CH_2).

HRMS **29/30** (ESI^+) m/z , $[M + H]^+$ calculated for $C_{17}H_{26}NO_3$ 292.1907, found 292.1908.

Compounds 31, 32 and 34

The above general procedure, using hydroxytyrosol **1** (38.5 mg, 0.25 mmol), 95/5 MeCN/H_2O mixture as the solvent, and enamine **2k** (228 mg, 5 equiv.), gave after oxidation at E_{ox} = +1.0 V *vs* Ag/AgCl and flash chromatography (toluene/acetone 75/25), compounds **31** and **32** (23 mg, 0.069 mmol) in 27% overall yield (28/72 ratio), along with compound **34** (32.5 mg, 0.12 mmol) in 49% yield.

[*R,S*]-2-[3-(Spirocyclohex-1-yl)-2-morpholino-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **31**

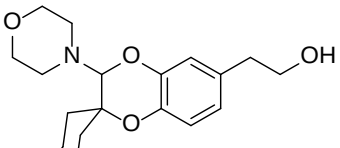


31

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, d, *J* = 8 Hz, H_{Ar}), 6.70 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 6.70 (1H, d, *J* = 2 Hz, H_{Ar}), 4.41 (1H, s, H_{dioxin}), 3.82 (2H, m, CH_2O), 3.63 (4H, m, 2×CH_2O_{morph}), 3.12 (2H, m, CH_2N_{morph}), 2.77 (2H, m, CH_2-Ar), 2.54 (2H, m, CH_2N_{morph}), 1.25-2.00 (10H, m, 5×$CH_{2\ Cyclohexyl}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7 (C), 141.4 (C), 131.0 (C), 122.2 (CH), 118.0 (CH), 115.7 (CH), 93.0 (CH), 75.5 (C), 67.2 (2×CH_2), 63.8 (CH_2), 48.9 (2×CH_2), 38.6 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 25.6 (CH_2), 21.2 (2×CH_2).

[*R,S*]-2-[2-(Spirocyclohex-1yl)-3-morpholino-2,3-dihydro-1,4-benzodioxin-6-yl]ethanol **32**



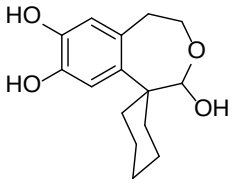
32

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, d, *J* = 8 Hz, H_{Ar}), 6.72 (1H, d, *J* = 2 Hz, H_{Ar}), 6.65 (1H, dd, *J* = 8 and 2 Hz, H_{Ar}), 4.41 (1H, s, H_{dioxin}), 3.82 (2H, m, CH_2O), 3.63 (4H, m, 2×CH_2O_{morph}), 3.12 (2H, m, CH_2N_{morph}), 2.77 (2H, m, CH_2-Ar), 2.54 (2H, m, CH_2N_{morph}), 1.25-2.00 (10H, m, 5×$CH_{2\ Cyclohexyl}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 140.0 (C), 132.0 (C), 121.3 (CH), 117.6 (CH), 116.1 (CH), 93.1 (CH), 75.4 (C), 67.2 (2×CH_2), 63.8 (CH_2), 48.9 (2×CH_2), 38.7 (CH_2), 33.1 (2×CH_2), 25.6 (CH_2), 21.4 (2×CH_2).

HRMS **31/32** (ESI^+) m/z , $[M + H]^+$ calculated for $C_{19}H_{28}NO_4$ 334.2013, found 334.2017.

[*R*,*S*]-1-(Spirocyclohex-1-yl)-2,7,8-triol-1,2,4,5-tetrahydro-benzo[d]oxepine **34**



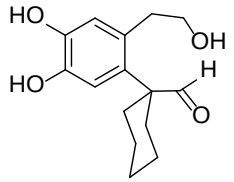
34

The 1,2,4,5-tetrahydrobenzo[d]oxepine [15,16] hemiacetal **34** exists in deuterated solvent in equilibrium with the corresponding aldehyde **34'**. Compared to methanol-d_3, acetone-d_6 induced a better separation of the aromatic signals of **34** and **34'**, even if the relative proportion of **34'** in solution was higher.

Hemiacetal **34**

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.70 (1H, broad s, $OH_{aromatic}$), 6.90 (1H, s, H_{Ar}), 6.53 (1H, s, H_{Ar}), 5.07 (1H, s, $H_{O\text{-}CH\text{-}OH}$), 4.03 (1H, t, *J* = 12.0 Hz, $H_{oxepine\ CH2O}$), 3.54 (1H, ddd, *J* = 12.0, 3.25 and 2.5 Hz, $H_{oxepine\ CH2O}$), 3.43 (1H, ddd, *J* = 15.5, 12.0 and 2.5 Hz, $H_{oxepine\ CH2Ph}$), 2.38 (1H, dd, *J* = 15.5 and 3.25 Hz, $H_{oxepine\ CH2Ph}$), 1.80-1.20 (10H, m, 5×$CH_{2\ cyclohexyl}$).

^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 143.1 (C), 142.9 (C), 135.1 (C), 133.2 (C), 119.4 (CH), 118.2 (CH), 98.1 (CH), 59.9 (CH_2), 54.5 (C), 39.9 (CH_2), 33.8 (CH_2), 32.8 (CH_2), 27.0 (CH_2), 23.6 (CH_2), 23.3 (CH_2).



34'

Aldehyde **34'**

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.34 (1H, s, CHO), 6.94 (1H, s, H_{Ar}), 6.74 (1H, s, H_{Ar}), 4.52 (1H, broad s, OH), 3.77 (1H, broad s, OH), 3.58 2H, (t, *J* = 7.5 Hz, CH_2O), 2.64 (2H, t, *J* = 7.5 Hz, CH_2-Ar), 2.17 (2H, m, $CH_{2\ cyclohexyl}$) 1.80-1.20 (8H, m, 2×$CH_{2\ cyclohexyl}$).

^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 203.1 (C), 144.8 (C), 144.2 (C), 131.1 (C), 130.7 (C), 119.4 (CH), 115.7 (CH), 64.4 (CH_2), 48.3 (C), 36.4 (CH_2), 35.1 (CH_2), 32.8 (CH_2), 26.3 (CH_2), 23.3 (CH_2), 22.9 (CH_2).

HRMS **34/34'** (ESI$^+$) m/z , $[M + H - H_2O]^+$ calculated for $C_{15}H_{19}O_3$ 247.1329, found 247.1327, $[M + H]^+$ calculated for $C_{15}H_{21}O_4$ 265.1434, found 265.1433 $[M + Na]^+$ calculated for $C_{15}H_{20}NaO_4$ 287.1254, found 287.1255.

VII- X-Ray analysis of compound 4

A colorless crystal of 0.27 × 0.03× 0.03 mm, crystallized from a 8/1 $Et_2O/CHCl_3$ mixture was used. Empirical formula $C_{26}H_{27}NO_4$, M = 417.48, T = 296(2) K. Monoclinic system, space group C 2/c, Z = 8, a = 39.383(3) Å, b = 6.2918(5) Å, c = 17.9687(14) Å, $\alpha = \gamma = 90°$, $\beta = 107.702(4)$ °, V = 4241.7(6) $Å^3$, d_{calc} = 1.308 g cm^{-3} , F(000) = 1776, $\mu = 0.088$ mm^{-1}, λ (Mo Kα) = 0.71073 Å. 48553 intensity data were collected with a Bruker diffractometer (Mo-Kα radiation) controlled by APEX2 software package, giving 6472 unique reflections. Refinement of 293 parameters on F^2 led to $R_1(F) = 0.1204$ calculated with 3101 observed reflections as $I \geq 2$ sigma (I) and $wR2(F^2) = 0.2906$ considering all the 6472 data. Goodness of fit = 1.040. CCDC deposition number: 2294269.

Table- Crystal data and structure refinements

Formula	$C_{26}H_{27}NO_4$
CCDC	2294269
Fw	417.48
T(K)	296(2)
wavelength (Å)	0.71073
crystal system	monoclinic
space group	C 2/c
unit cell dimension	
a (Å)	39.383(3)
b (Å)	6.2918(5)
c (Å)	17.9687(14)
α (°)	90
β (°)	107.702(4)
γ(°)	90
V ($Å^3$)	4241.7(6)
Z	8
d(calc) (Mg/m^3)	1.308
abs coeff (mm^{-1})	0.088
crystal size (mm^3)	0.27x0.03x0.03
F_{000}	1776
θ range [deg]	2.171 – 30.565
index ranges	-56<h<51
	-5<k<8
	-25<l<24
no. of reflns collected	48553
no. of indep reflns	6472
R(int)	0.1230
GOF on F^2	1.040
R1/wR2[a,b],[I>2σ(I)]	0.1204/0.2540
R1/wR2[a,b], all data	0.2139/0.2906
largest diff peak and hole [e.$Å^{-3}$]	0.491and 0.380

[a]R1 = Σ||*Fo*| – |*Fc*||/Σ|*Fo*|. [b] wR2 = {Σ[w($F_O^2 - F_c^2$)^2]/ Σ [w(F_O^2)2]} ; where w = $q/\sigma^2(F_O^2) + (qp)^2 + bp$. GOF = S = {Σ[w($F_O^2 - F_c^2$)^2]/ (n – p)$^{1/2}$}.

VIII- References

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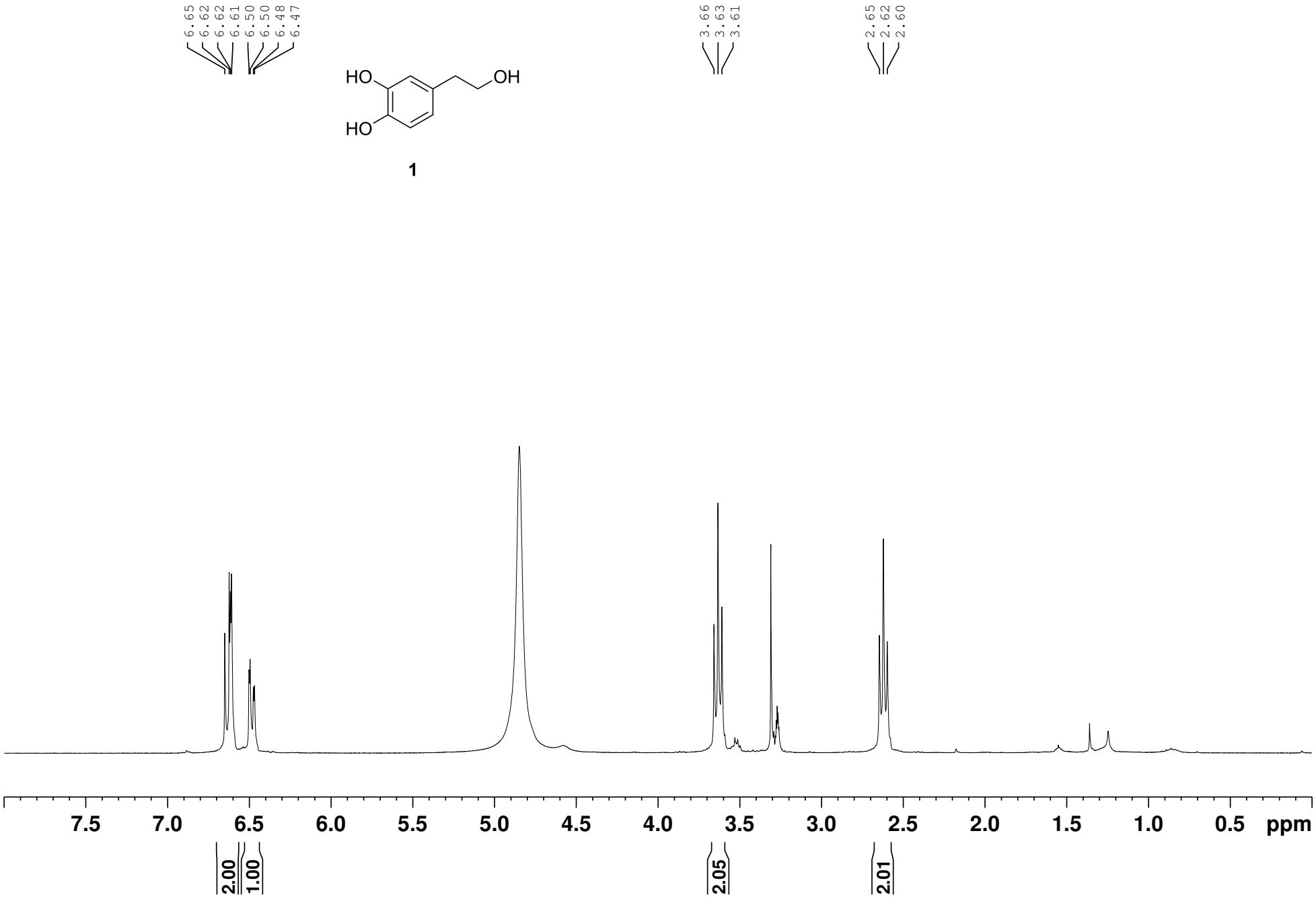
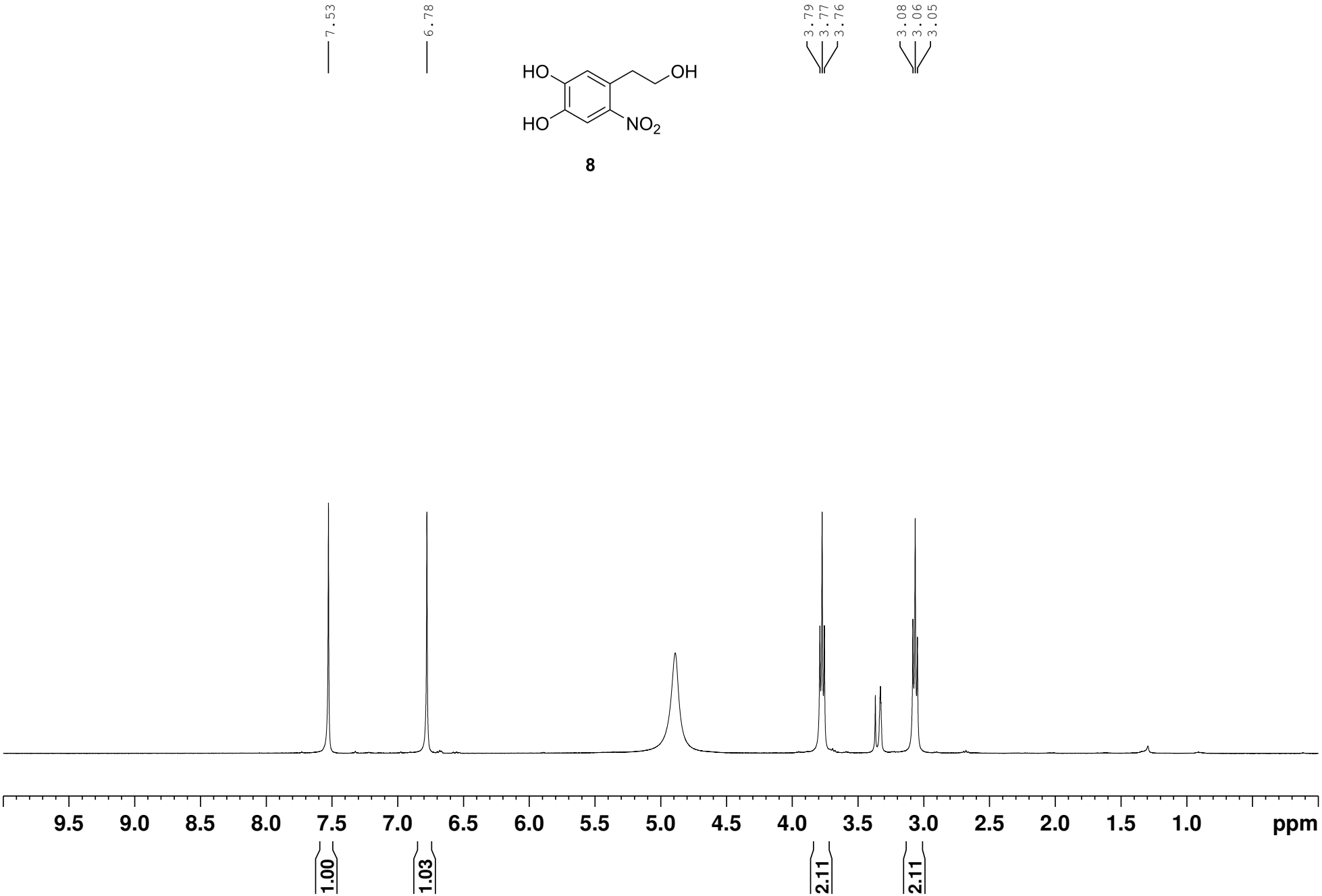
^{1}H NMR spectrum (300 MHz, $CDCl_3$) - Hydroxytyrosol **1**

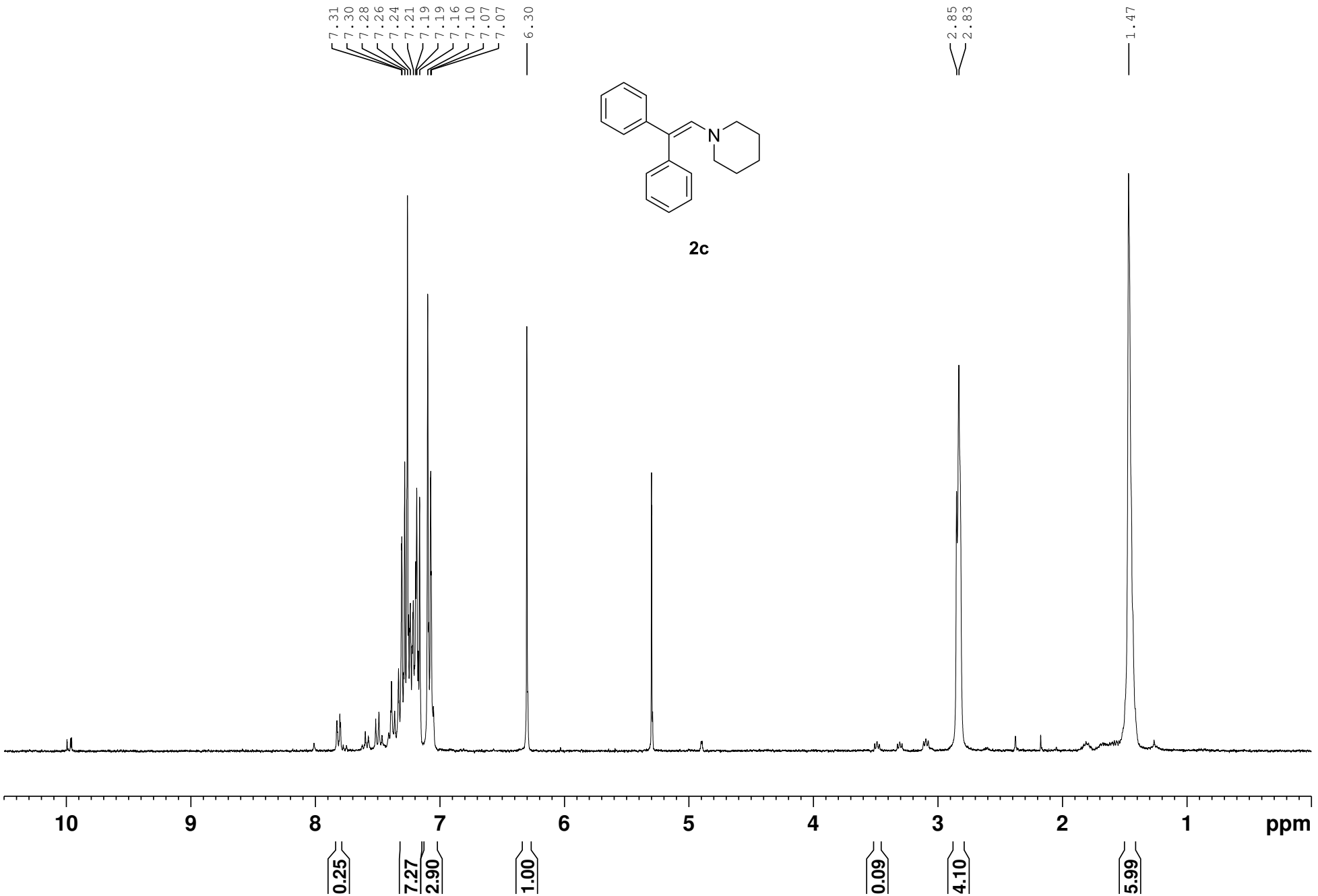


1

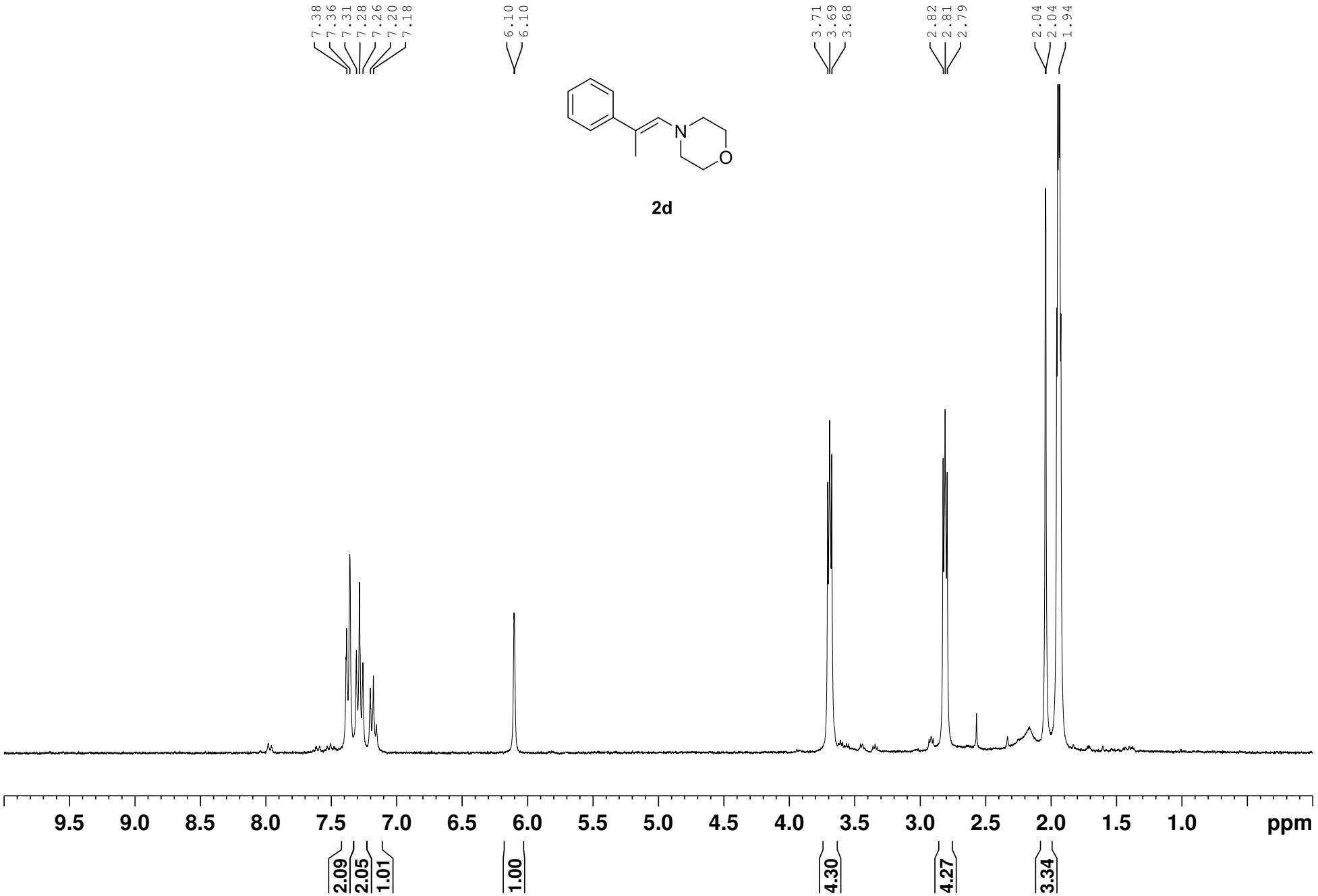
^{1}H NMR spectrum (300 MHz, $CDCl_3$) - Compound **8**



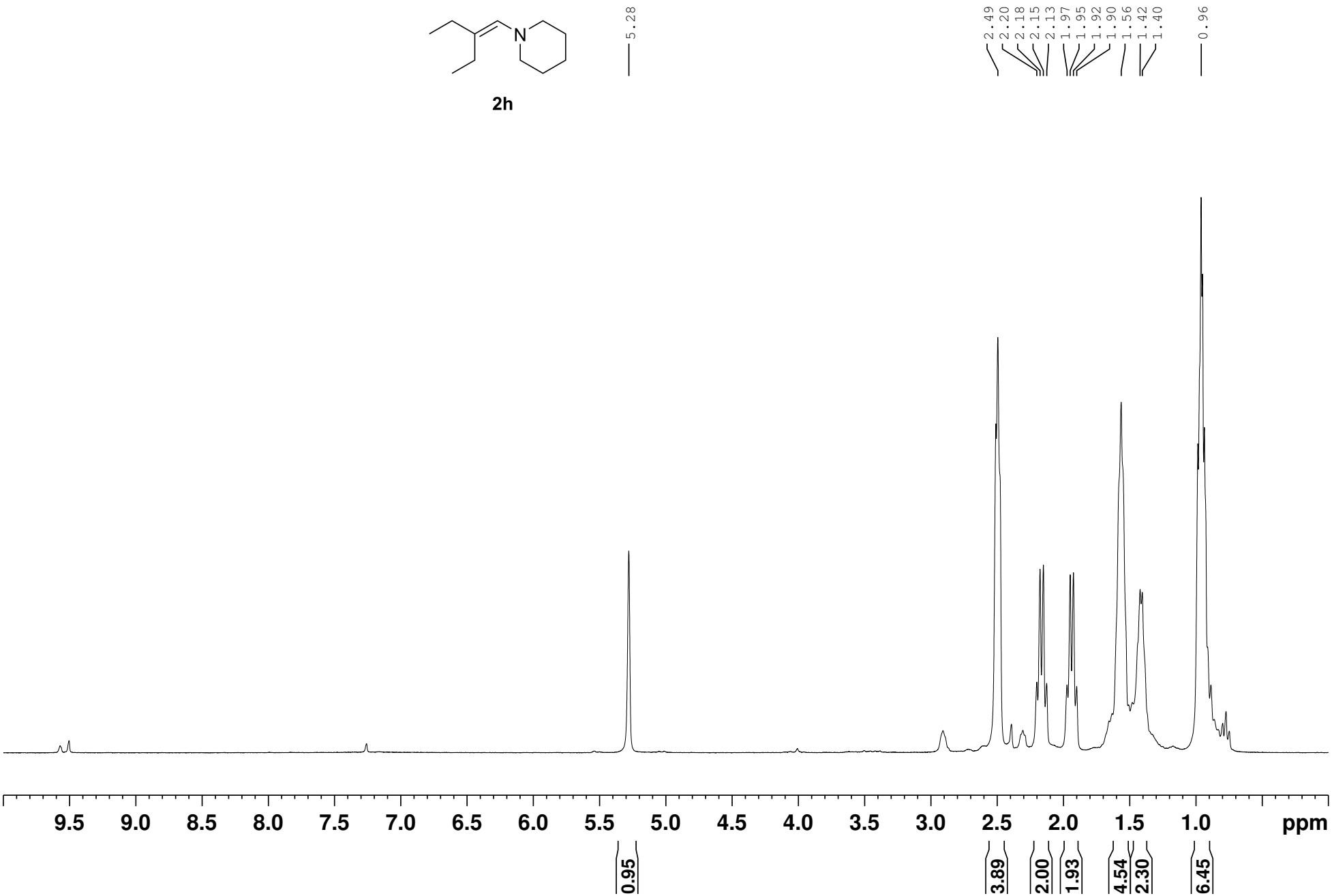
^{1}H NMR spectrum (300 MHz, $CDCl_3$) - Enamine **2c**



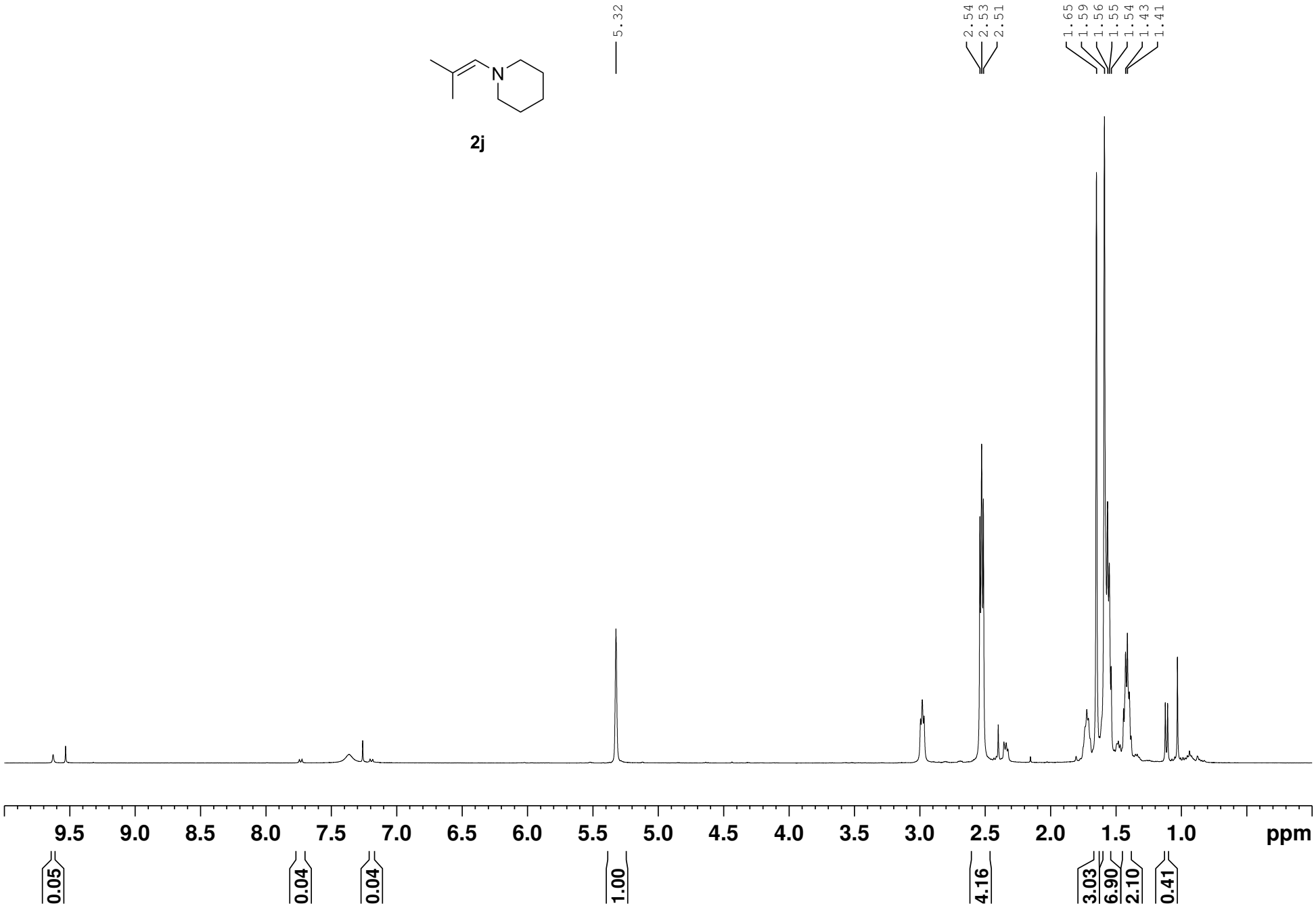
^{1}H NMR spectrum (300 MHz, CD_3CN) - Enamine **2d**



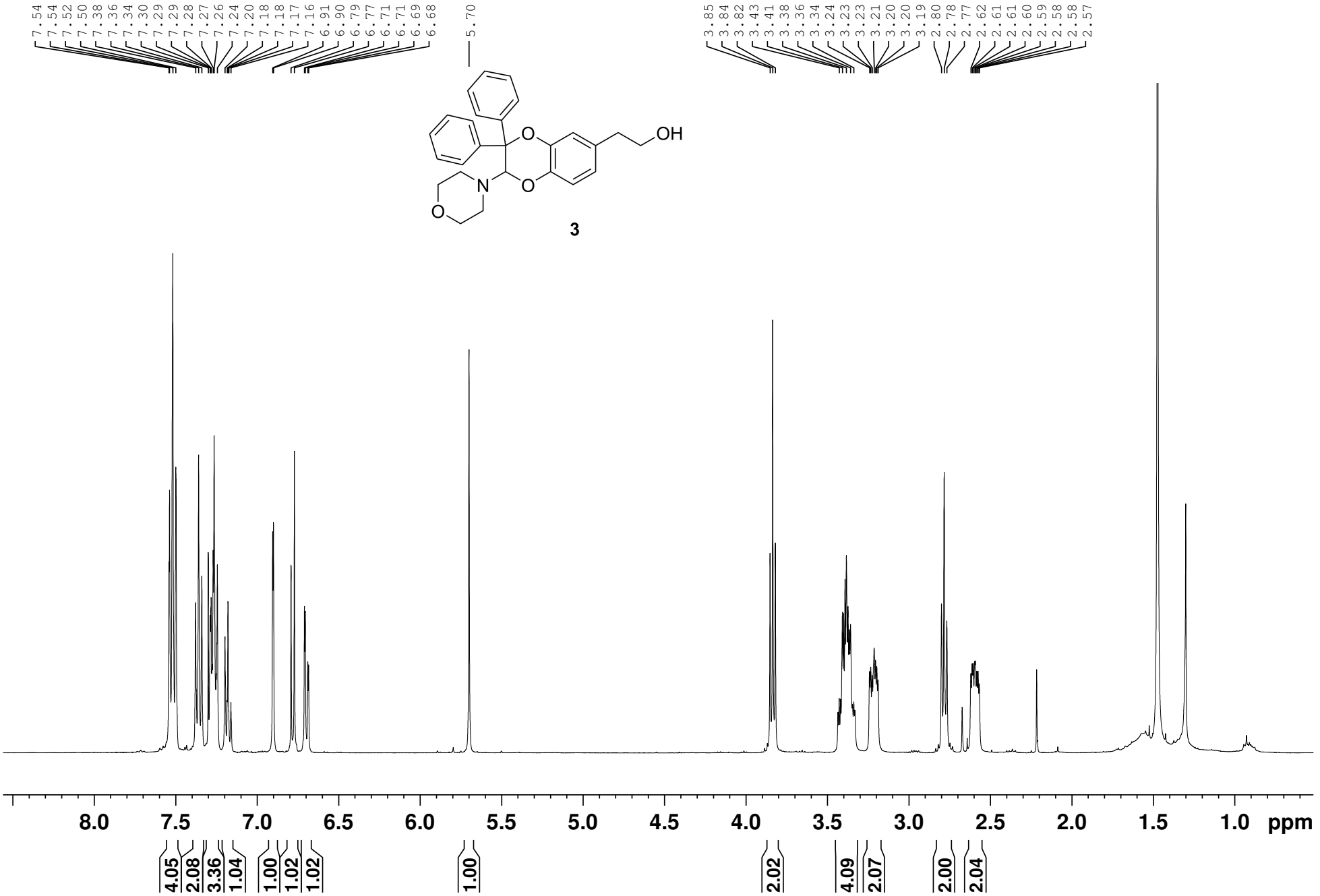
^{1}H NMR spectrum (300 MHz, $CDCl_3$) - Enamine **2h**



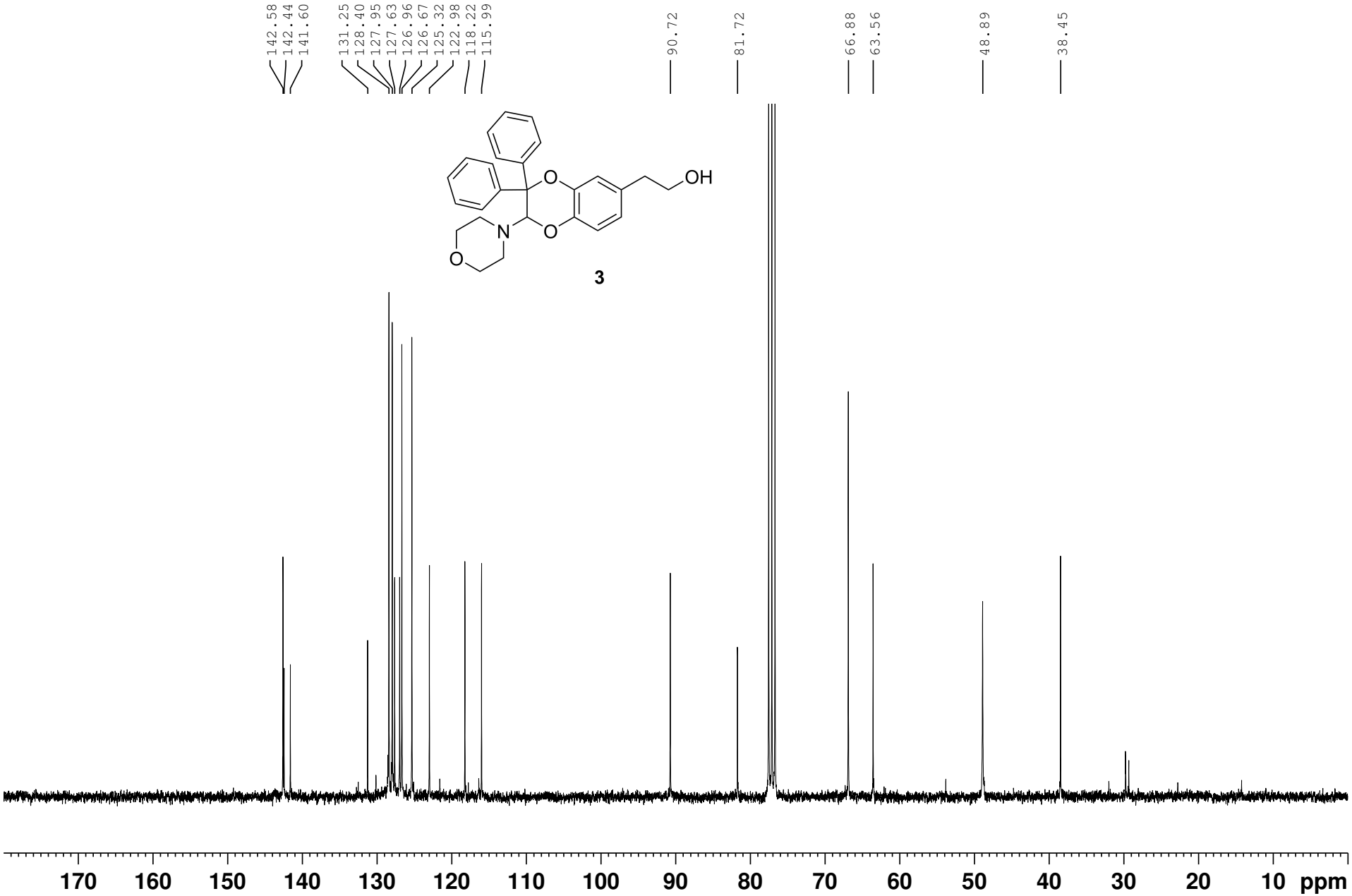
^{1}H NMR spectrum (300 MHz, $CDCl_3$) - Enamine **2j**



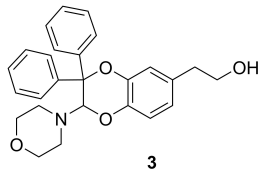
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **3**



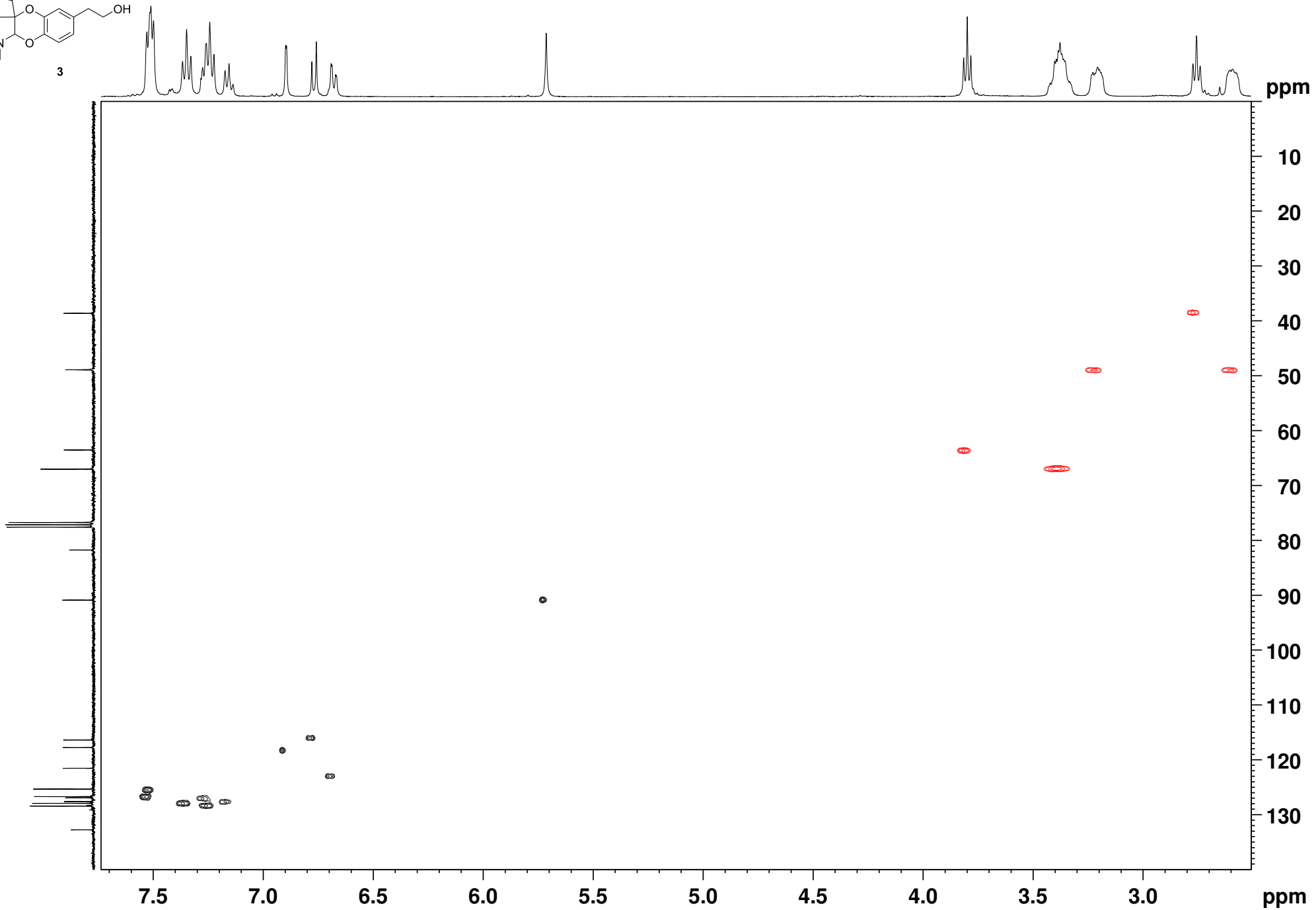
^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Compound **3**



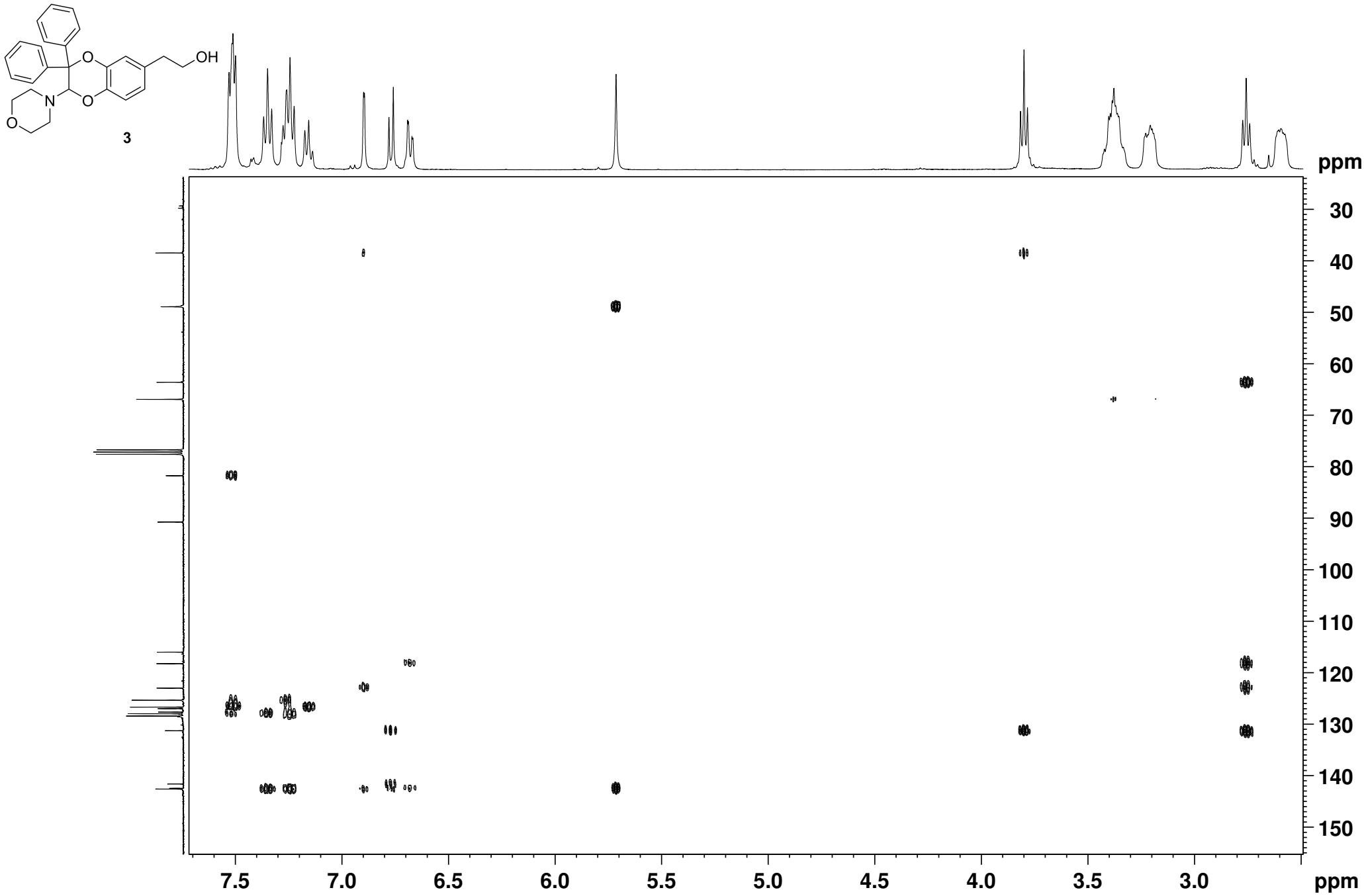
HSQC NMR spectrum (400 MHz, $CDCl_3$) - Compound **3**



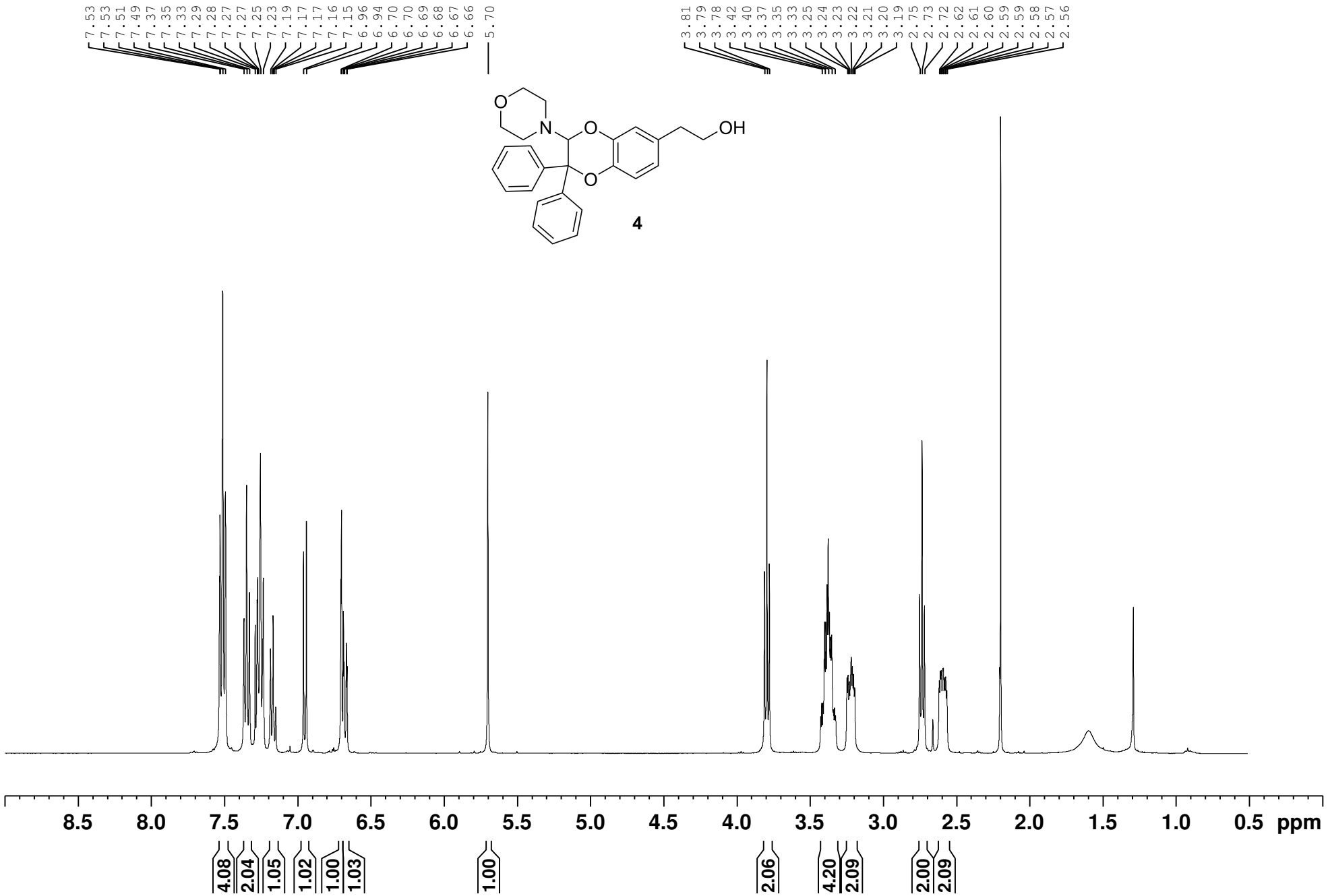
3



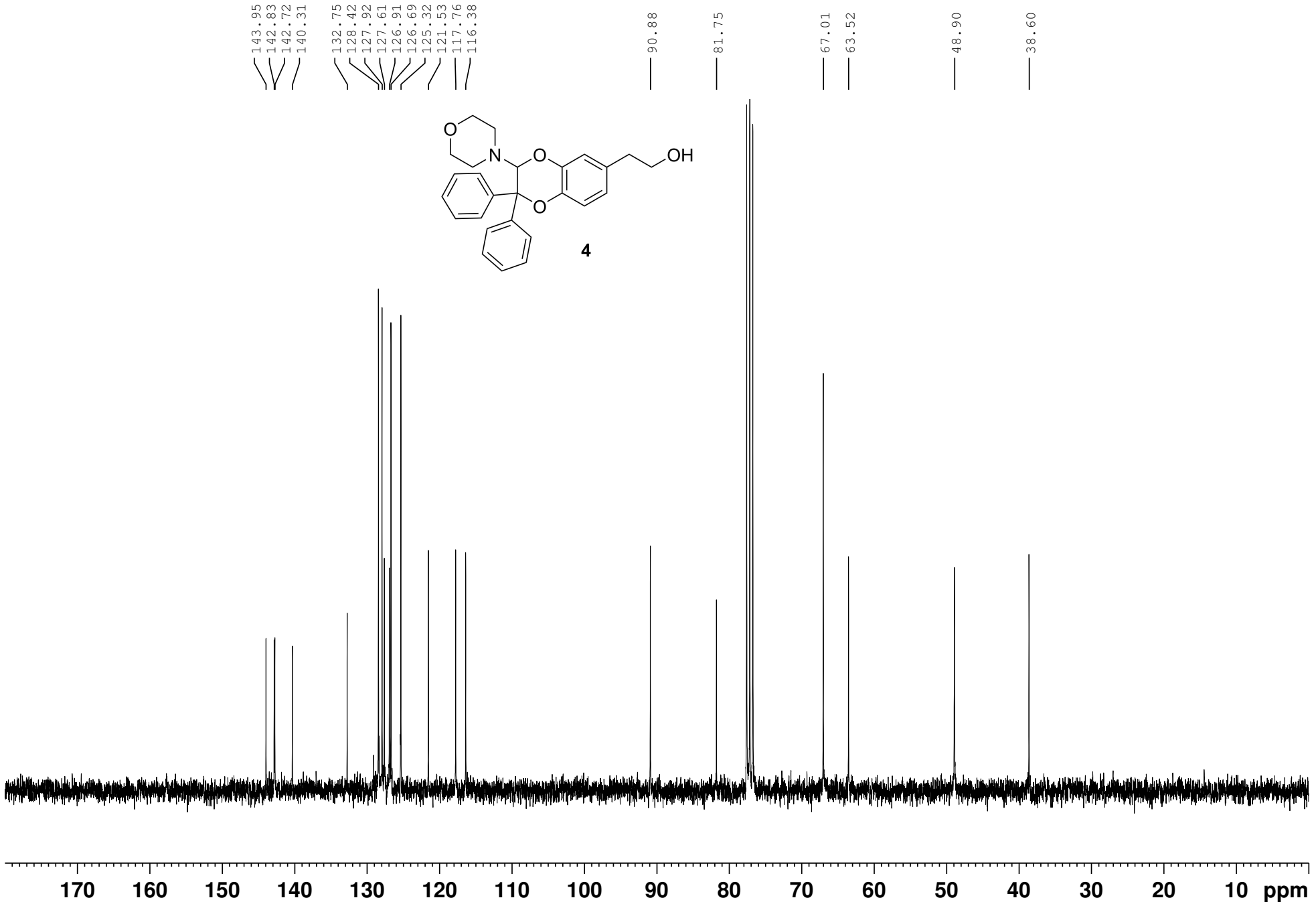
HMBC NMR spectrum (400 MHz, $CDCl_3$) - Compound **3**



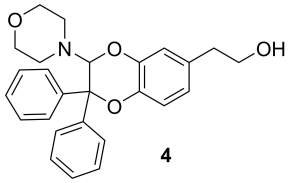
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **4**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Compound **4**

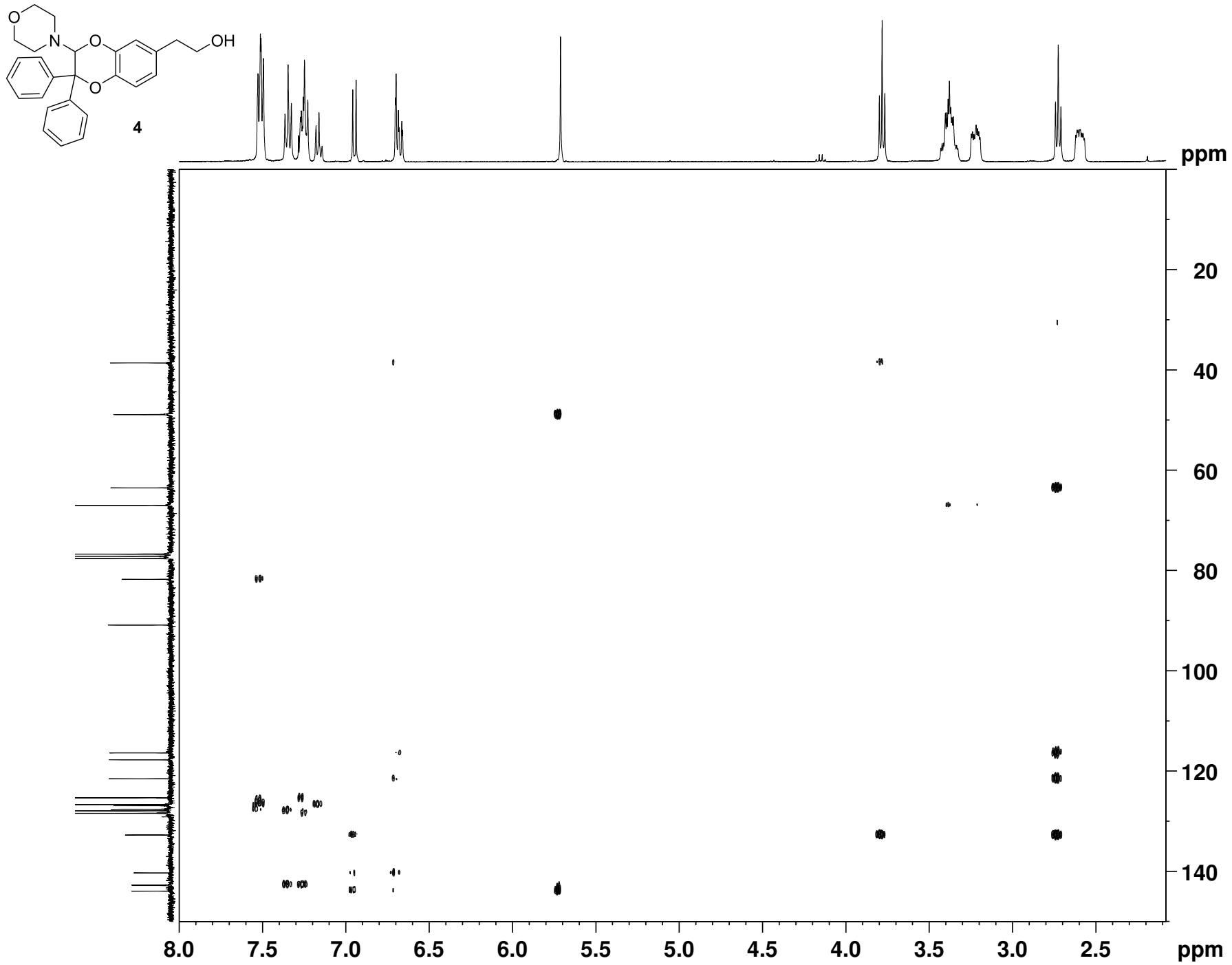


HSQC NMR spectrum (40MHz, $CDCl_3$) - Compound **4**

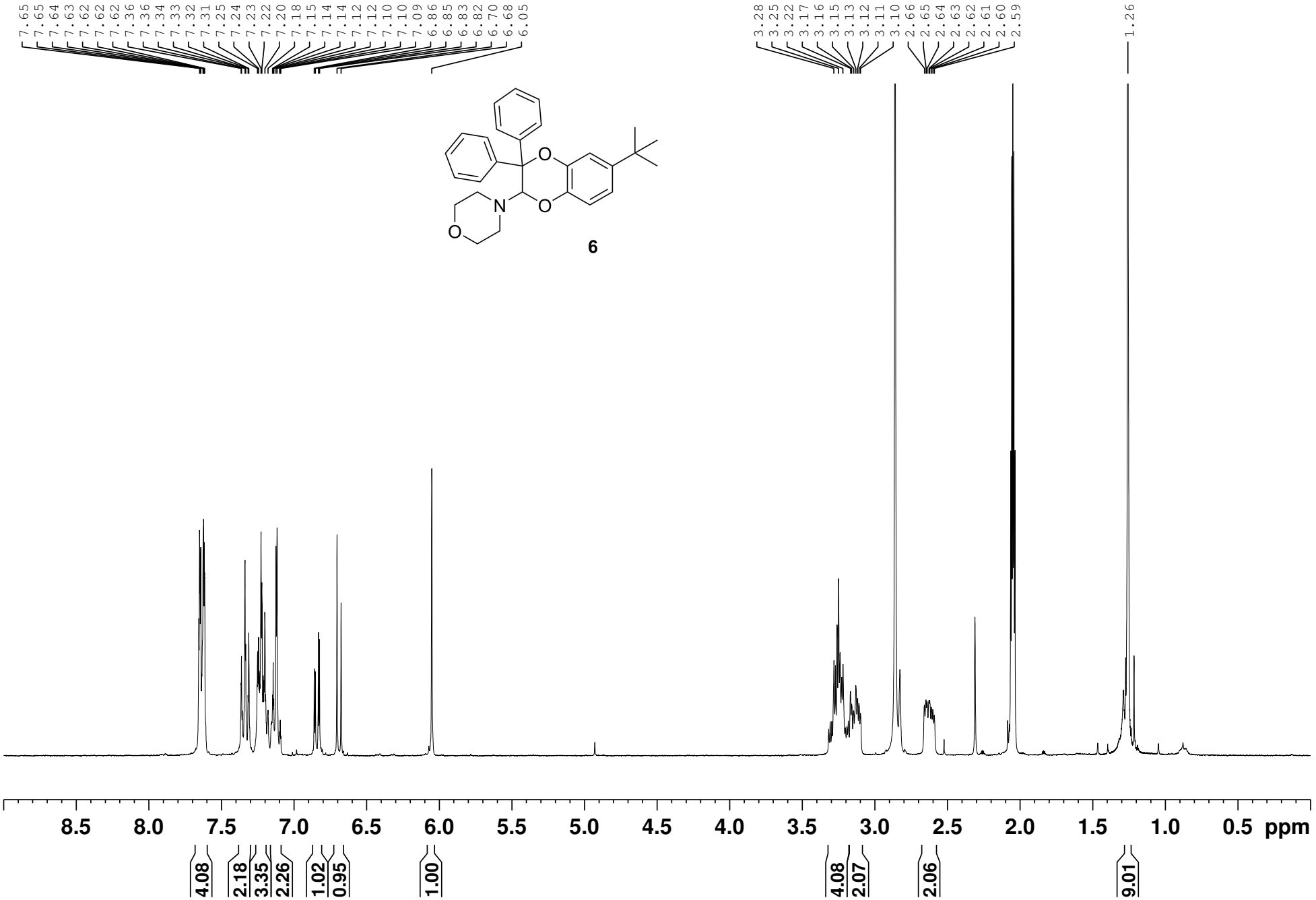


4

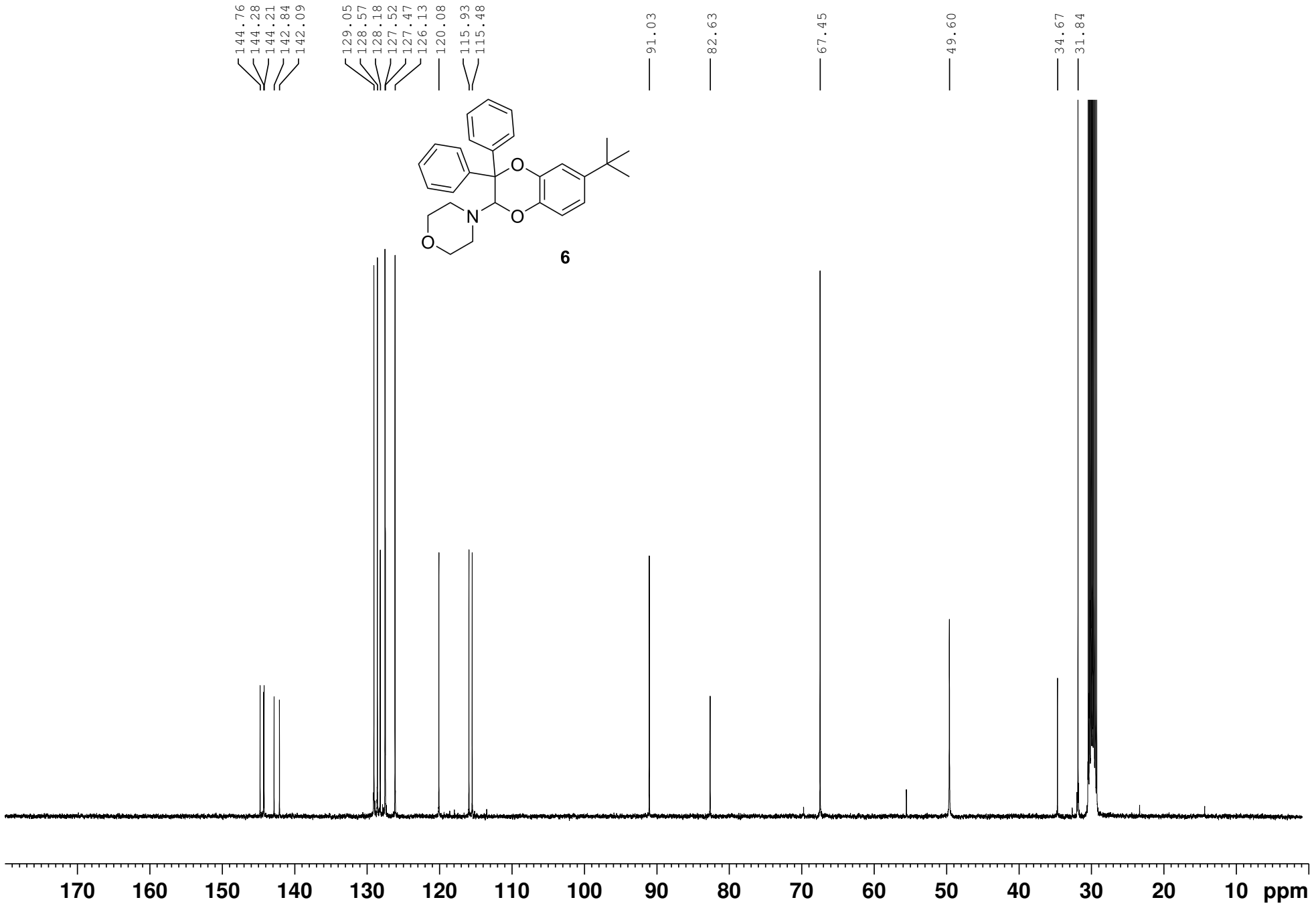
HMBC NMR spectrum (400 MHz, $CDCl_3$) - Compound **4**



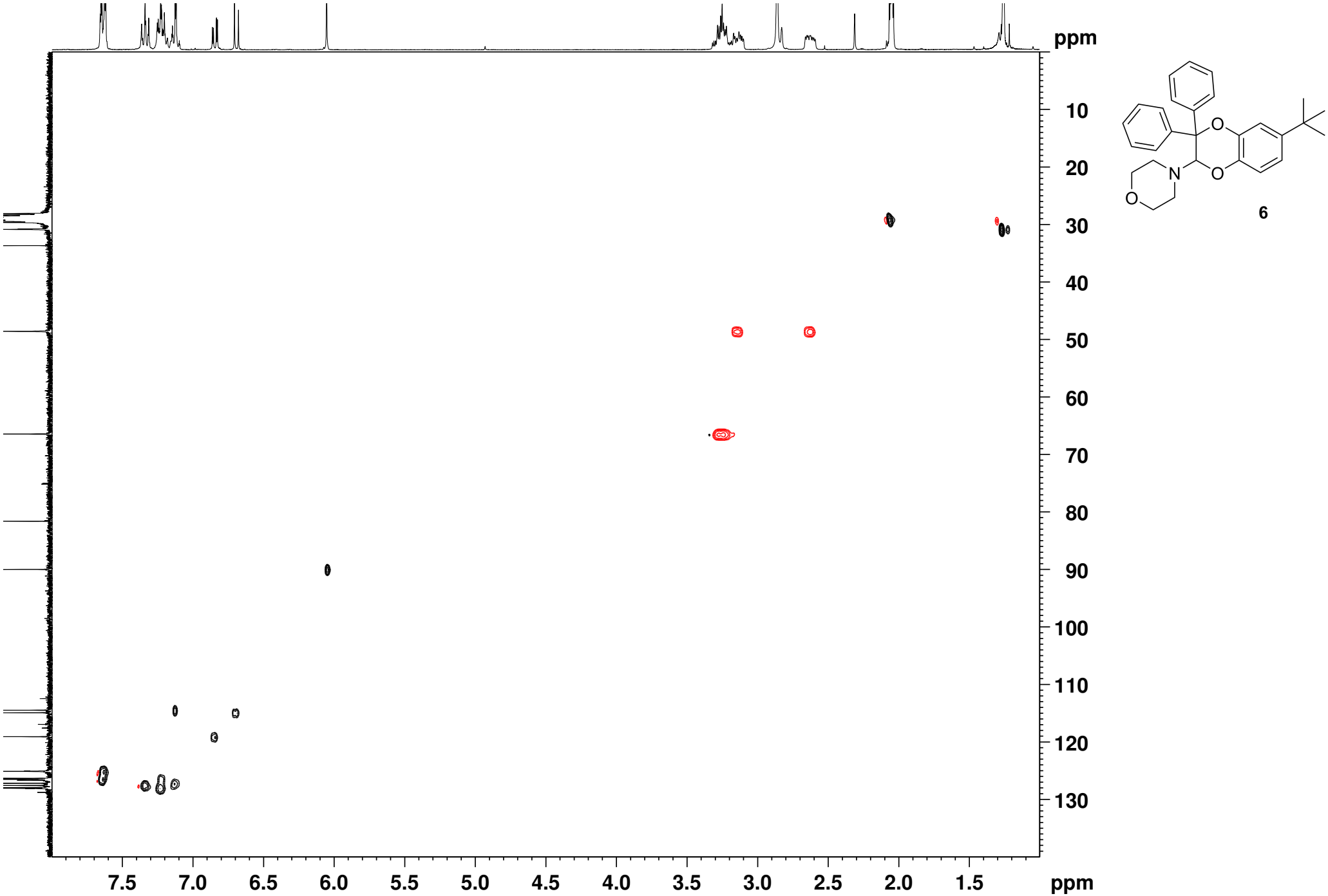
^{1}H NMR spectrum (300 MHz, $(CD_3)_2CO$) - Compound **6**



^{13}C NMR spectrum (100 MHz, $(CD_3)_2CO$) - Compound **6**

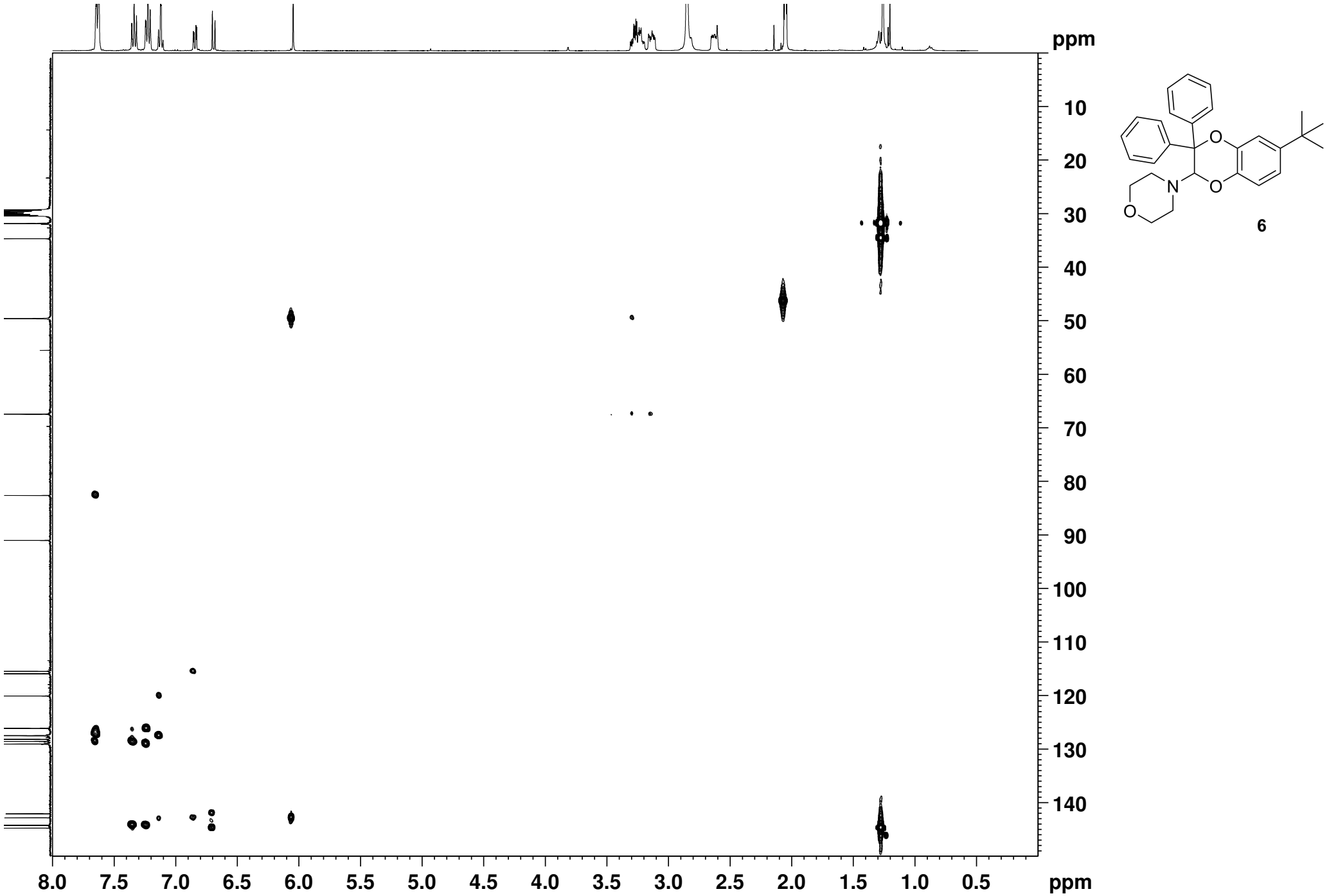


HSQC NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **6**



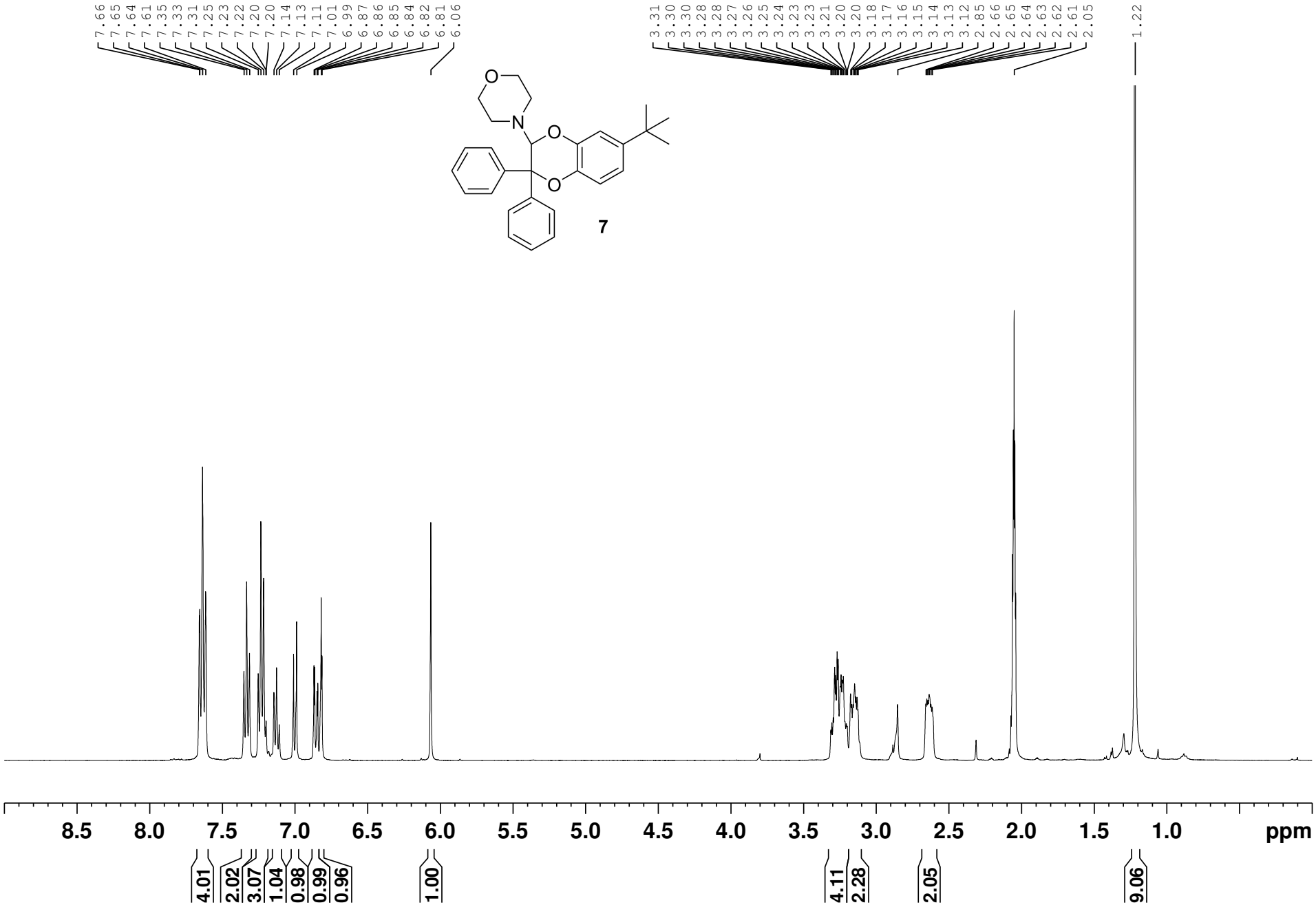
6

HMBC NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **6**

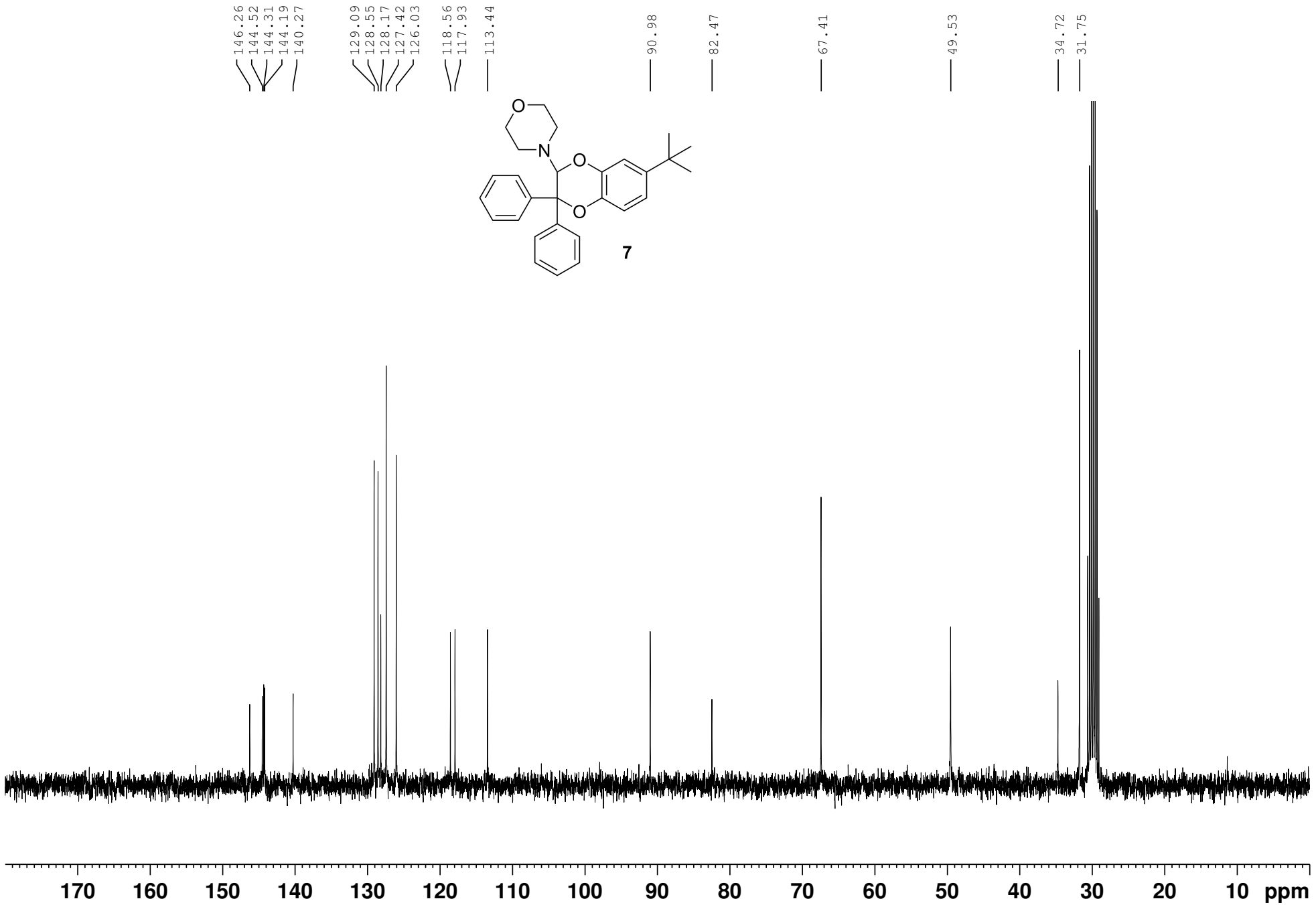


6

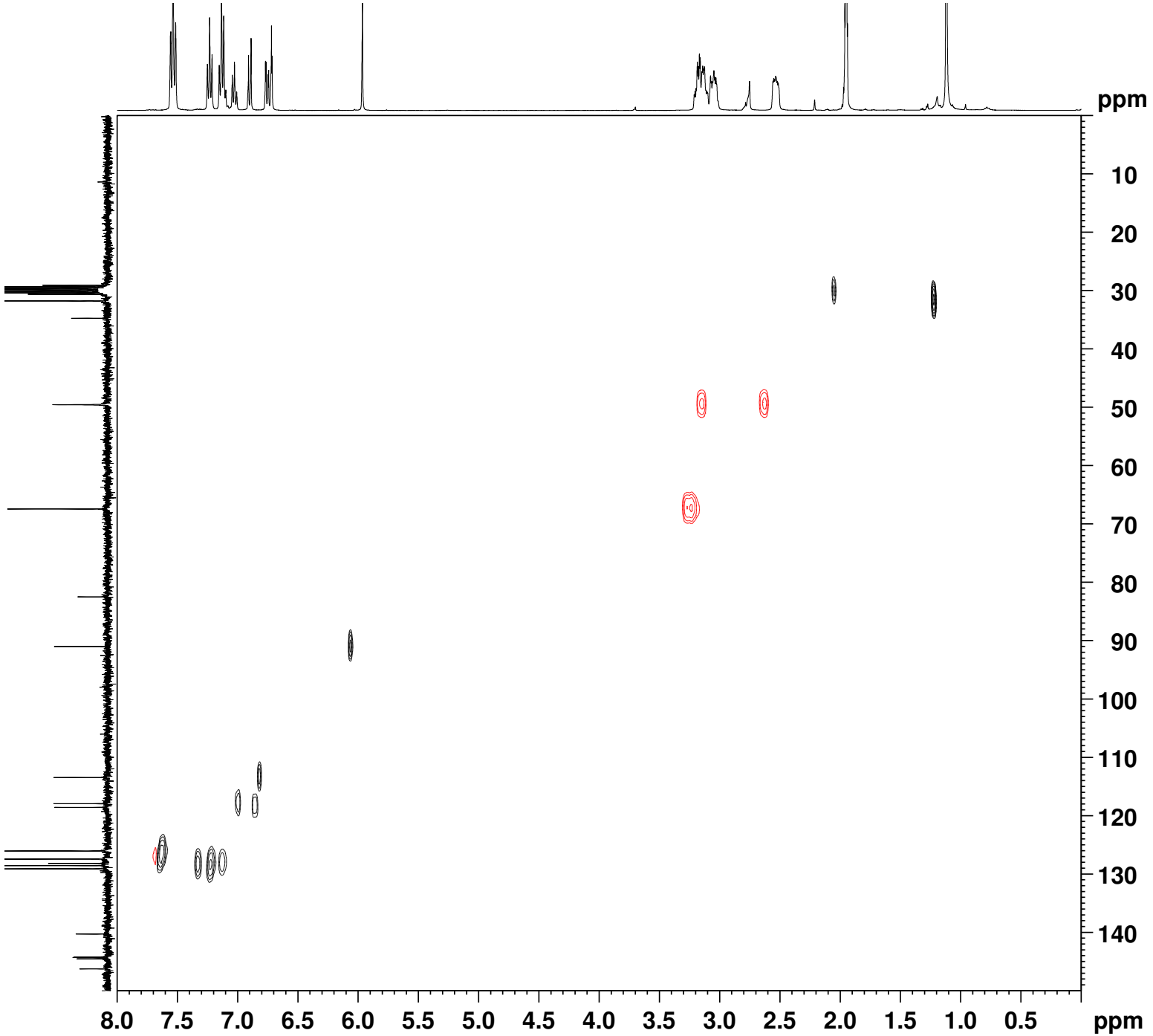
^{1}H NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **7**

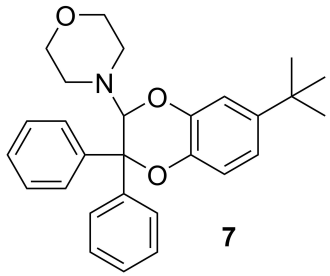


^{13}C NMR spectrum (100 MHz, $(CD_3)_2CO$) - Compound **7**

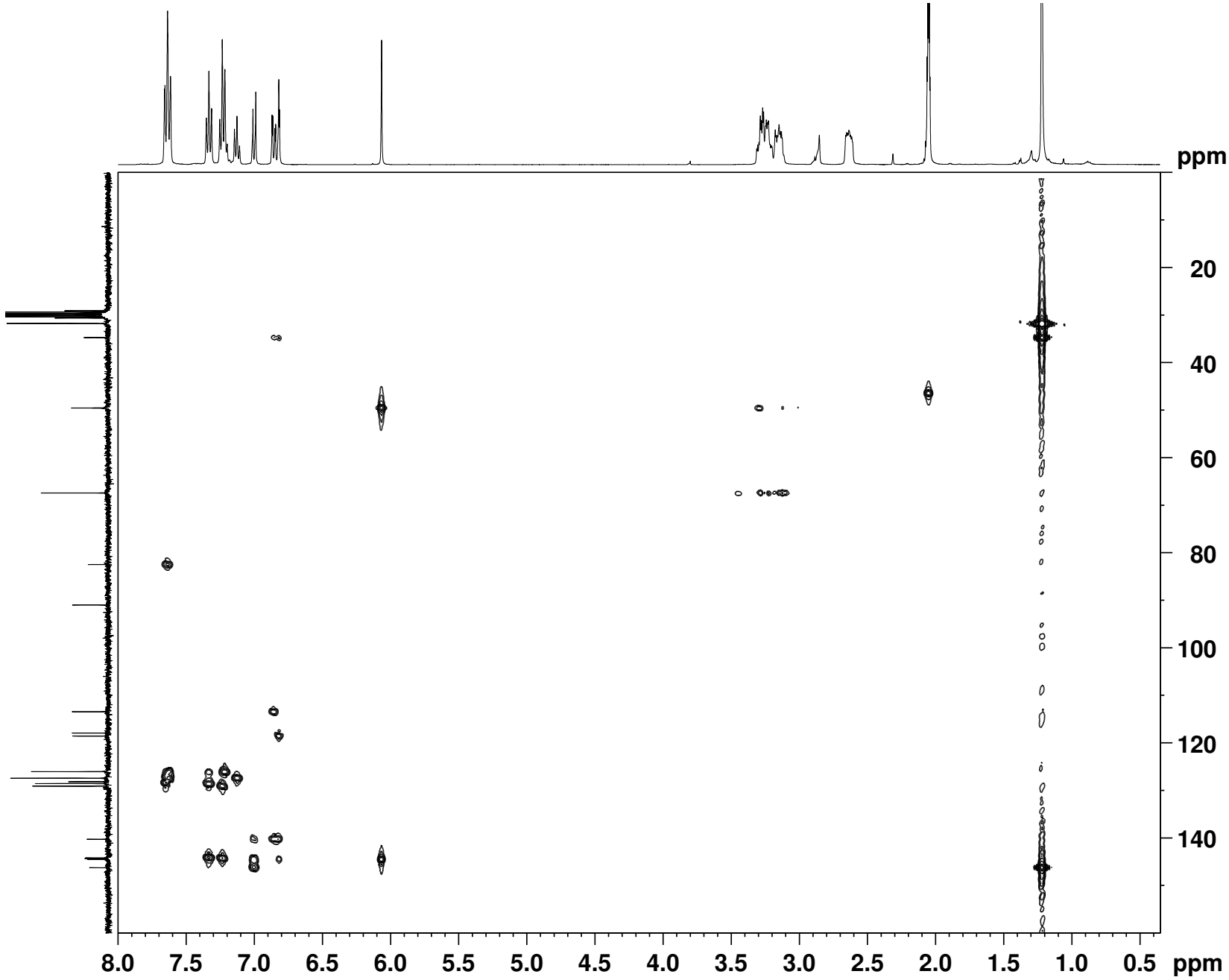


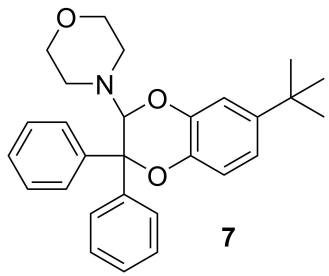
HSQC NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **7**



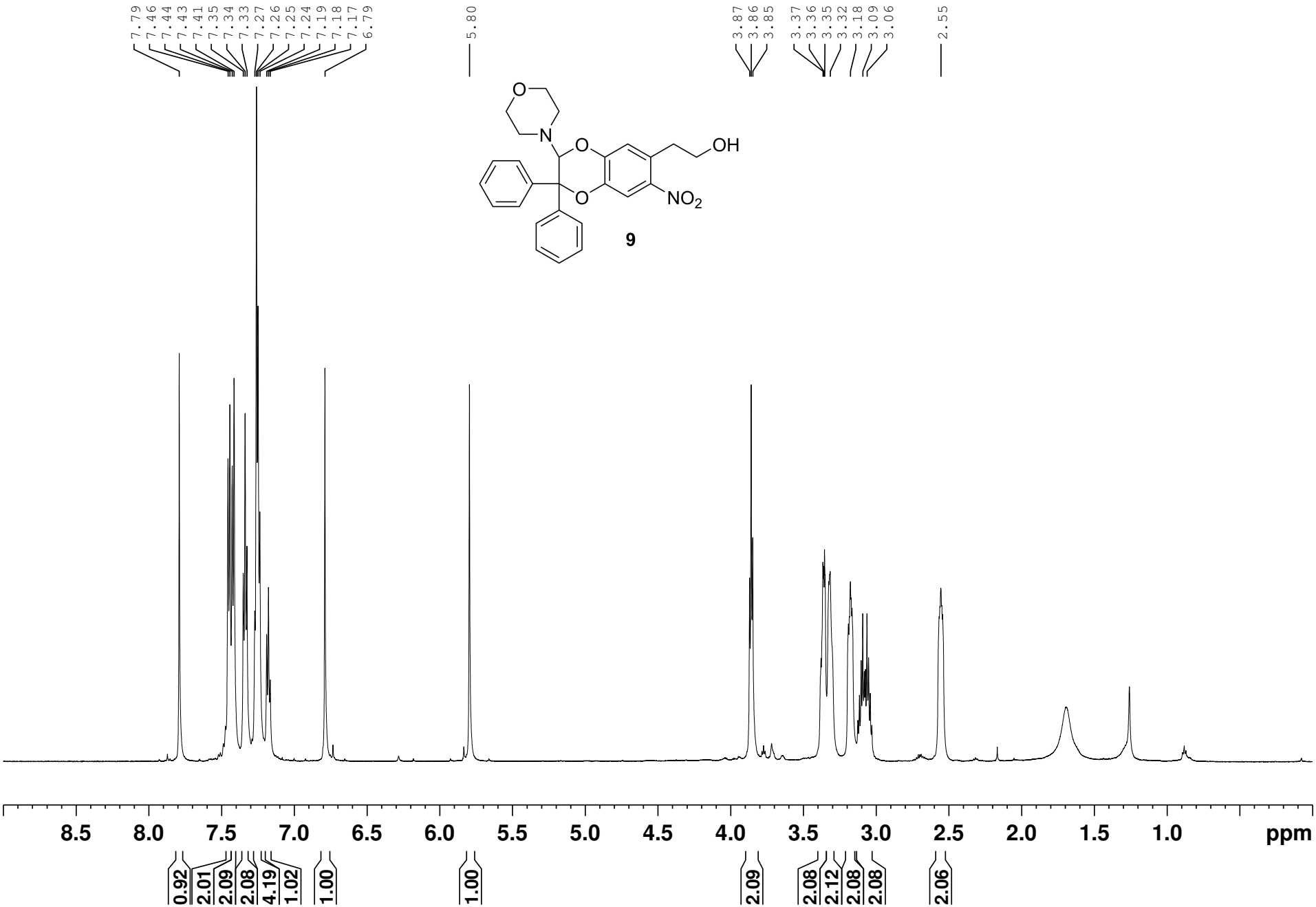


HMBC NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **7**

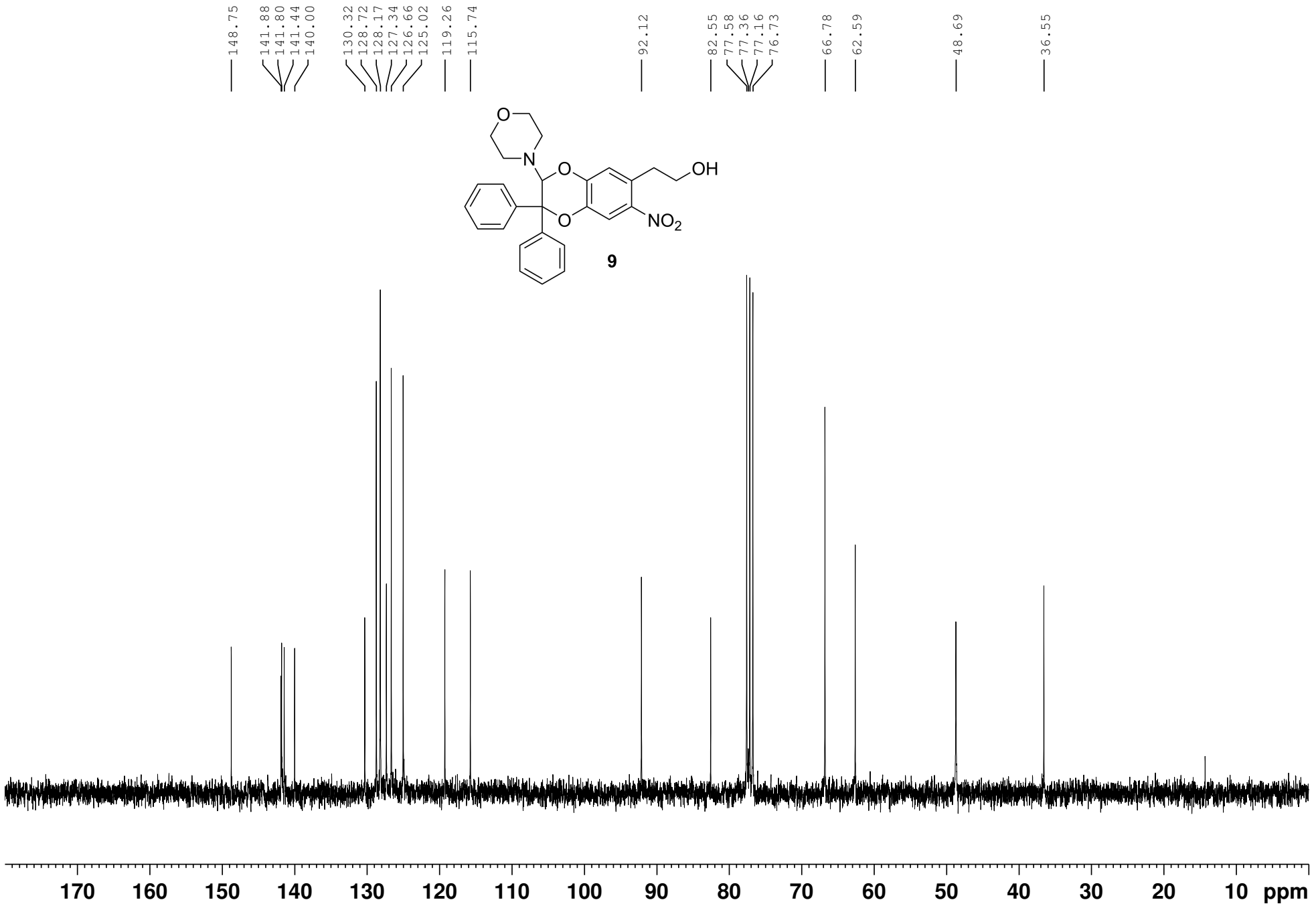




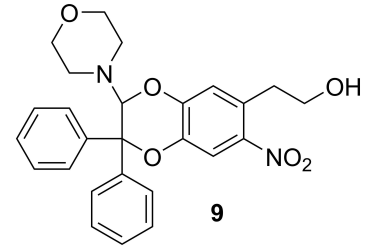
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **9**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Compound **9**



HSQC NMR spectrum (400 MHz, $CDCl_3$) - Compound **9**



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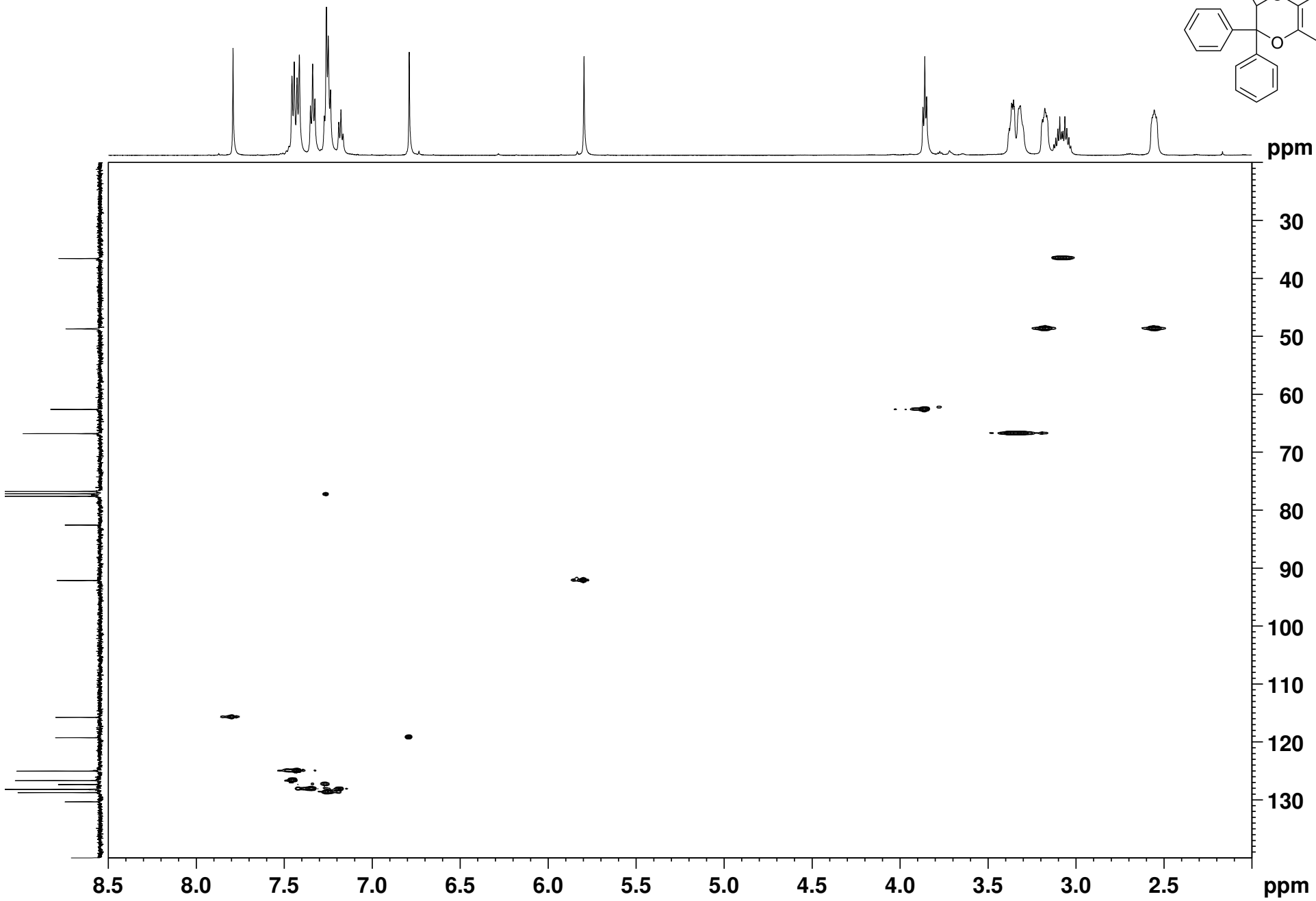
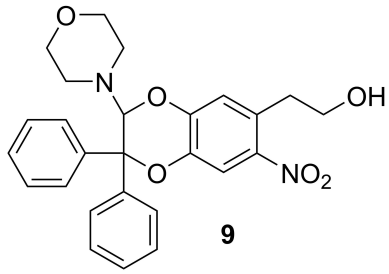


HMBC NMR spectrum (400 MHz, $CDCl_3$) - Compound **9**



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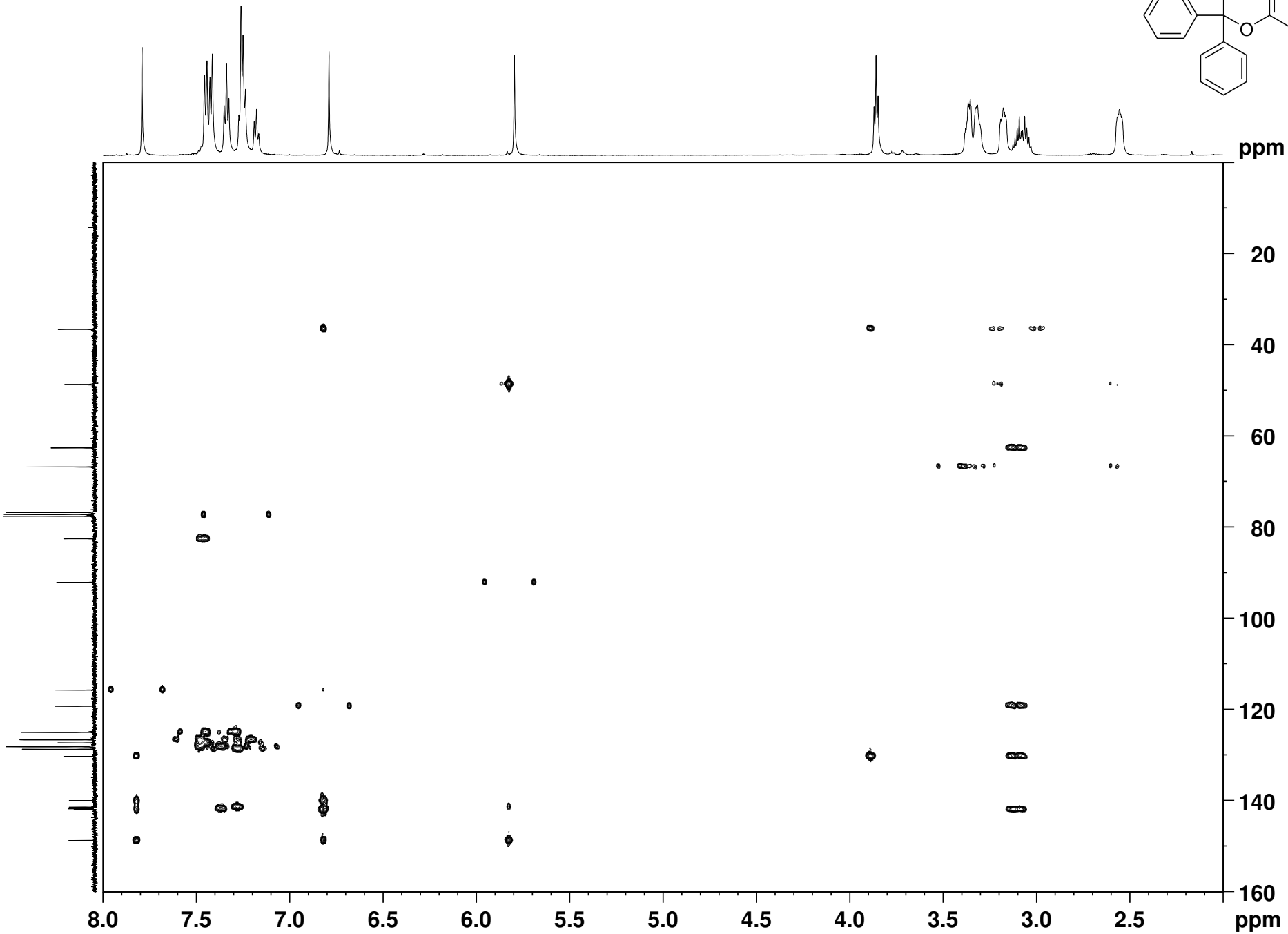
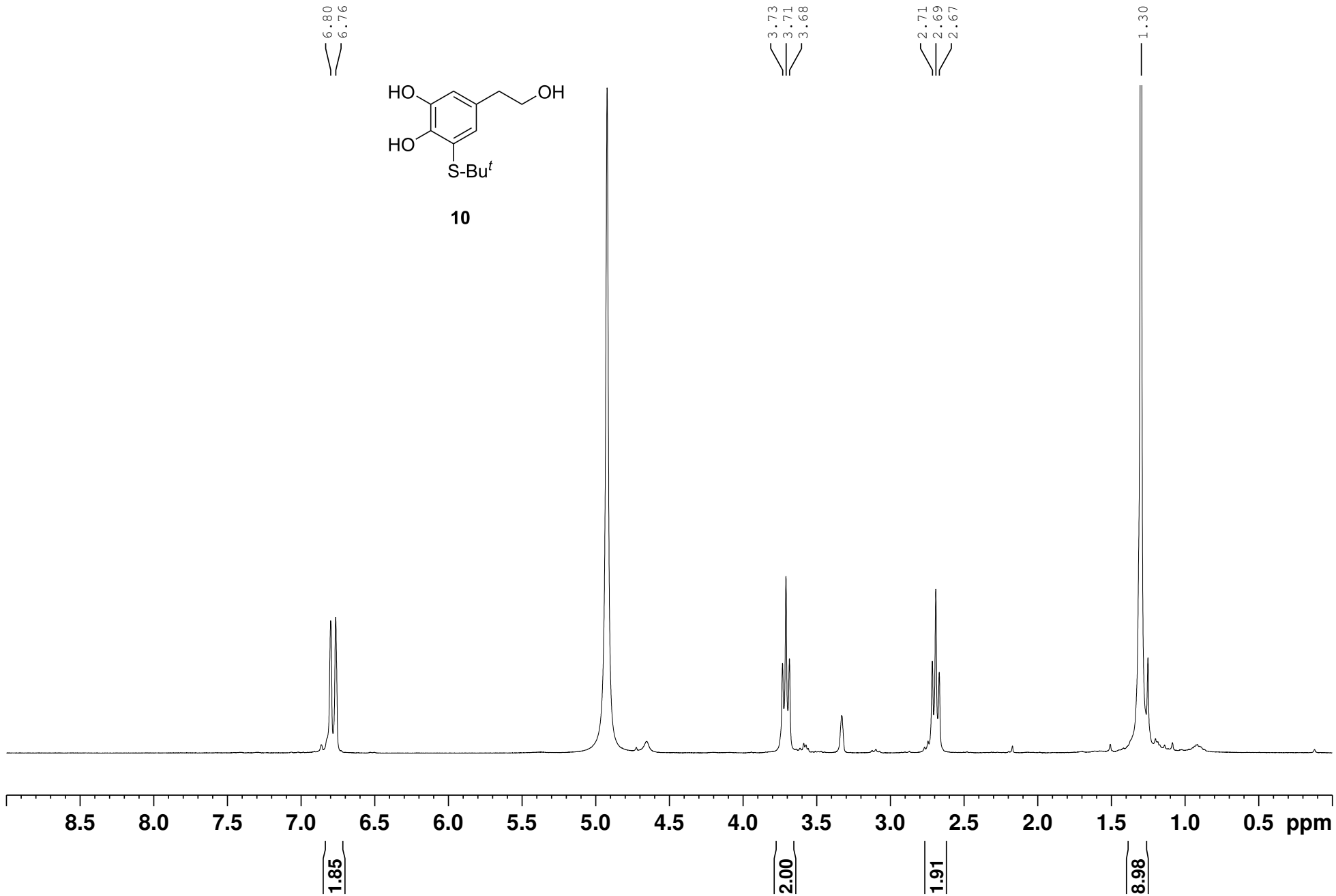
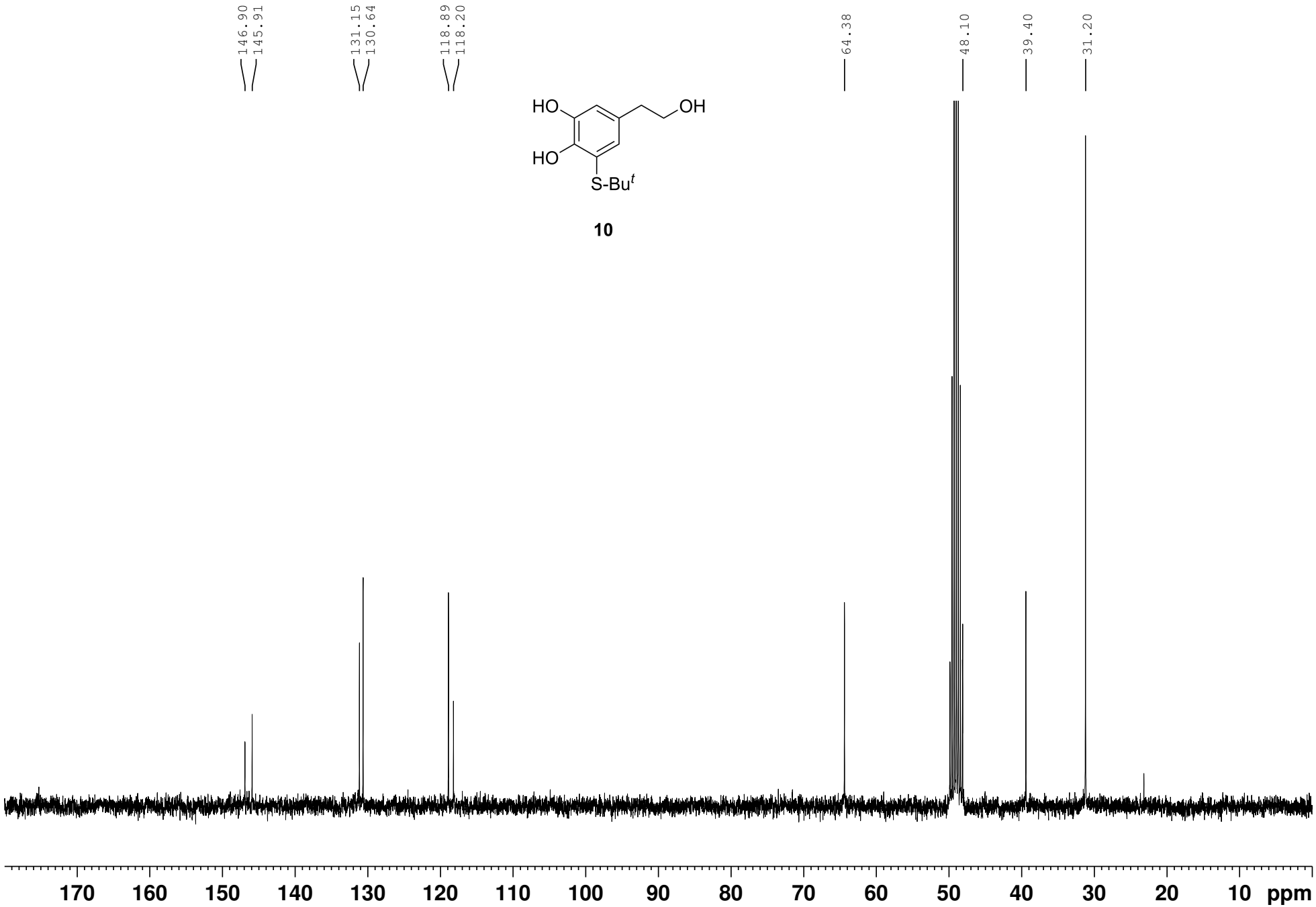


^{1}H NMR spectrum (300 MHz, CD_3OD) - Compound **10**

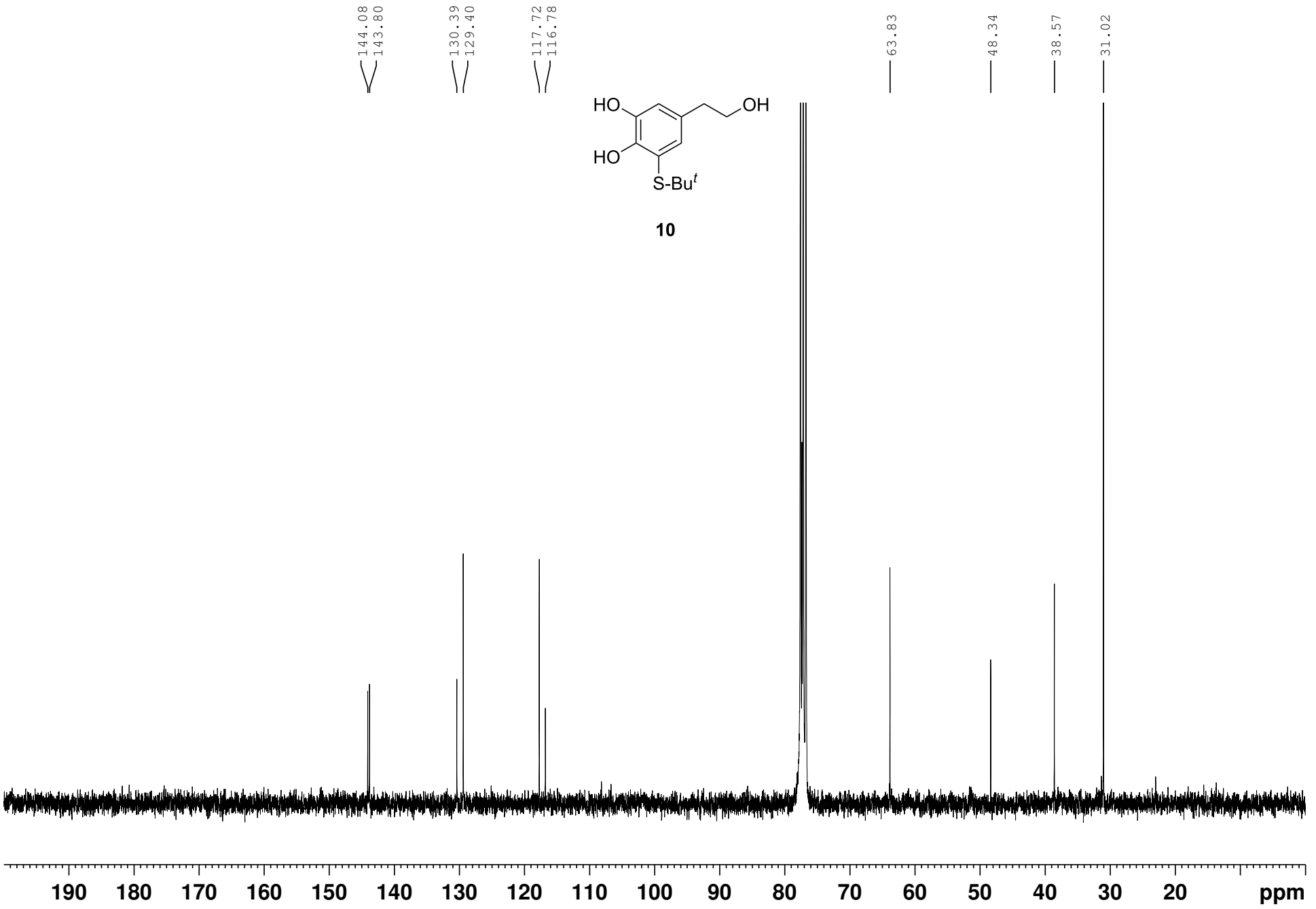


^{13}C NMR spectrum (75 MHz, CD_3OD) - Compound **10**



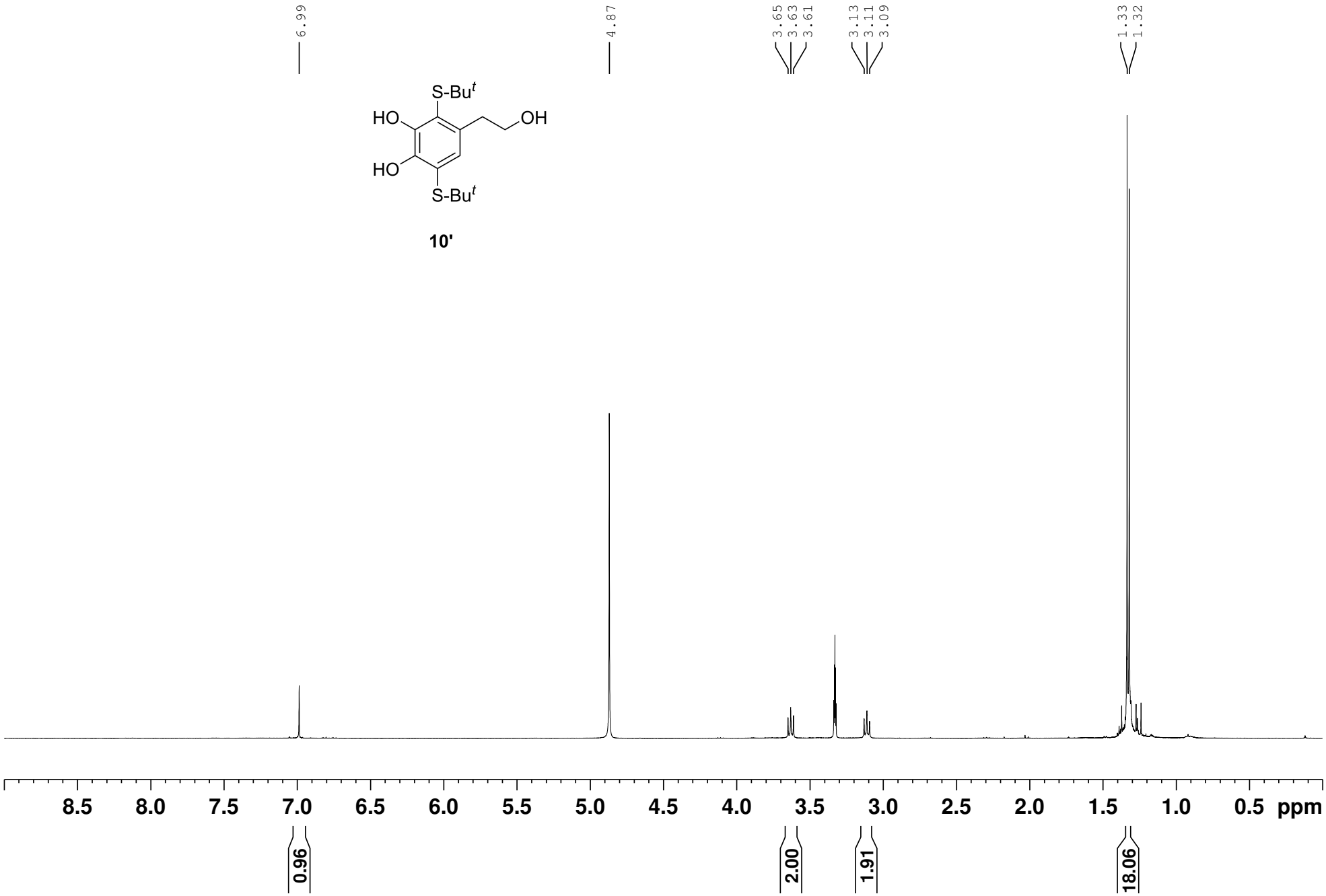
10

^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Compound **10**

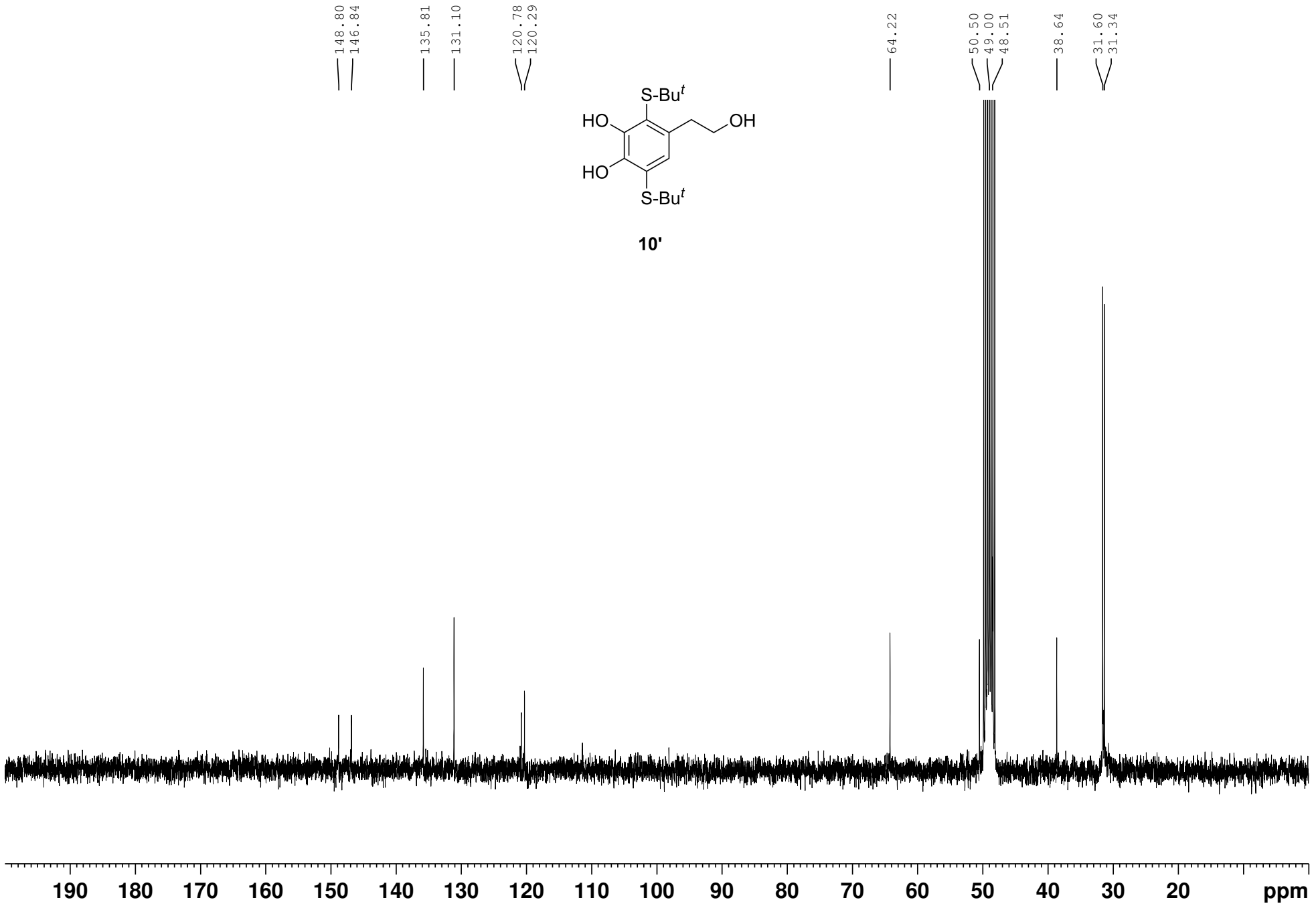


10

^{1}H NMR spectrum (400 MHz, CD_3OD) - 2,5-bis-tBu-hydroxytyrosol **10'**

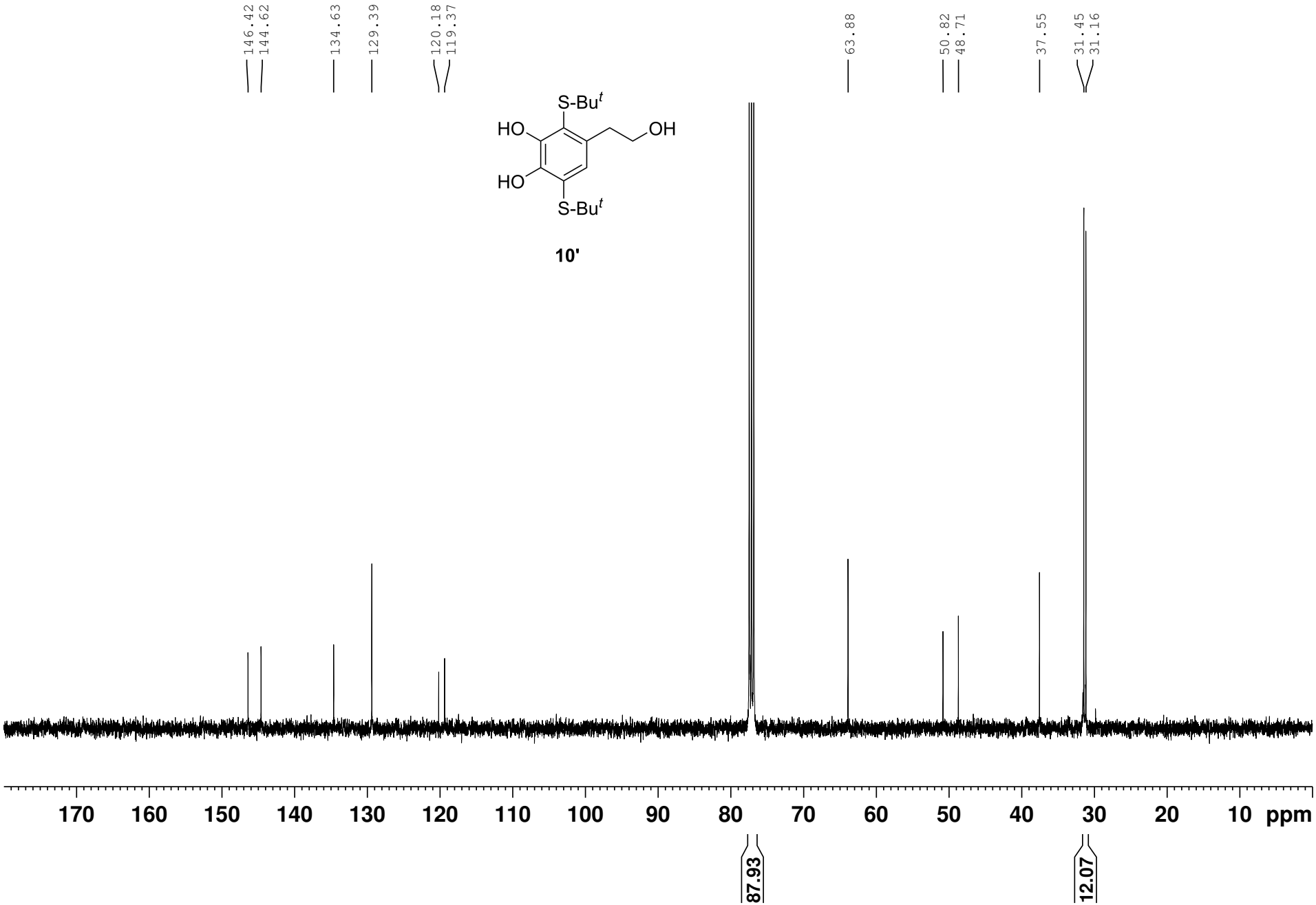


^{13}C NMR spectrum (75 MHz, CD_3OD) - 2,5-bis-tBu-hydroxytyrosol **10'**

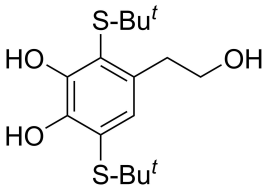


10'

^{13}C NMR spectrum (100 MHz, $CDCl_3$) - 2,5-*bis*-S-*t*Bu-hydroxytyrosol **10'**



HMBC NMR spectrum (400 MHz, $CDCl_3$) - 2,5-*bis*-S-*t*Bu-hydroxytyrosol **10'**



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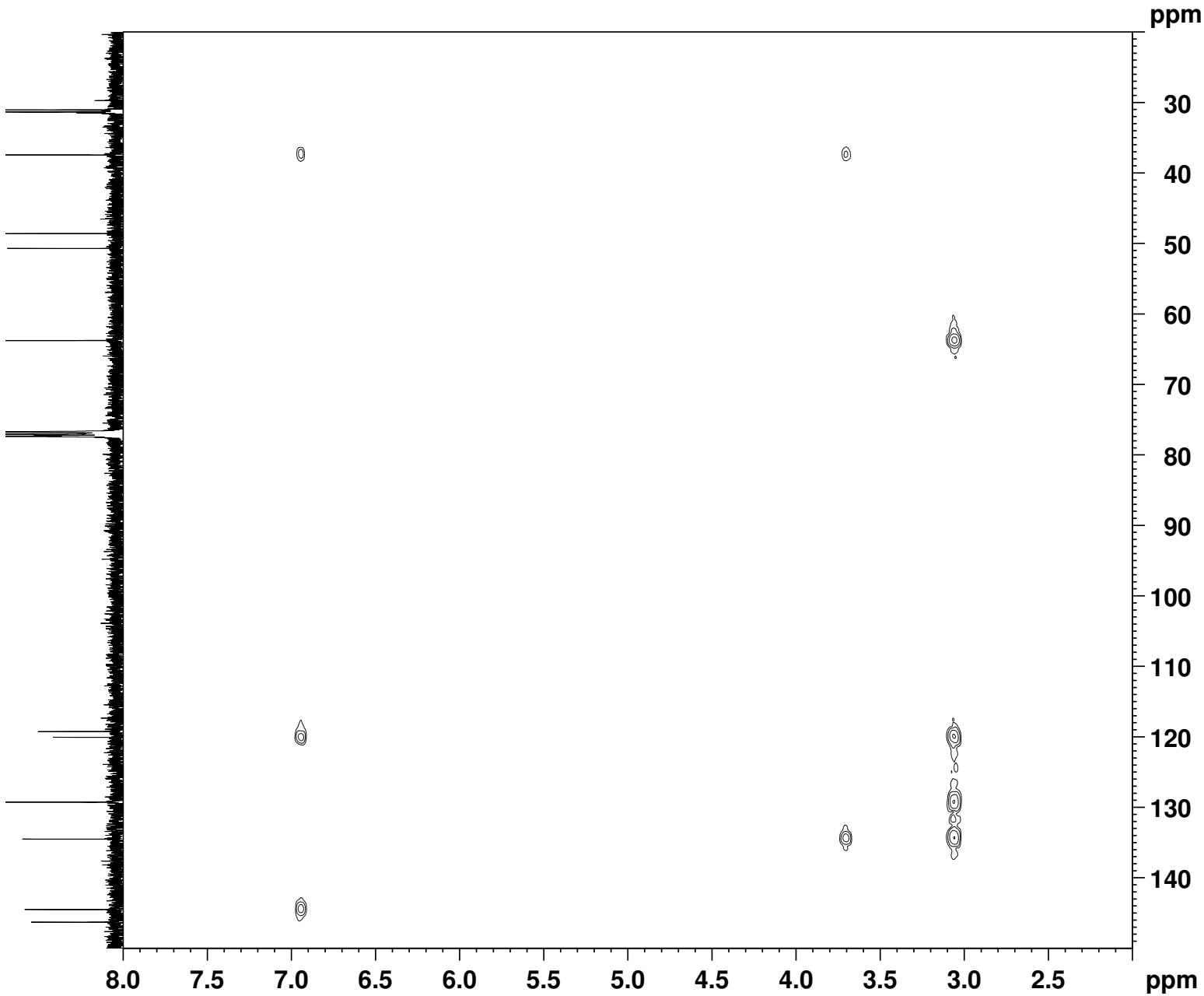
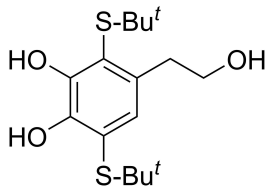


NOESY NMR spectrum (400 MHz, $CDCl_3$) - 2,5-*bis*-S-*t*Bu-hydroxytyrosol **10'**



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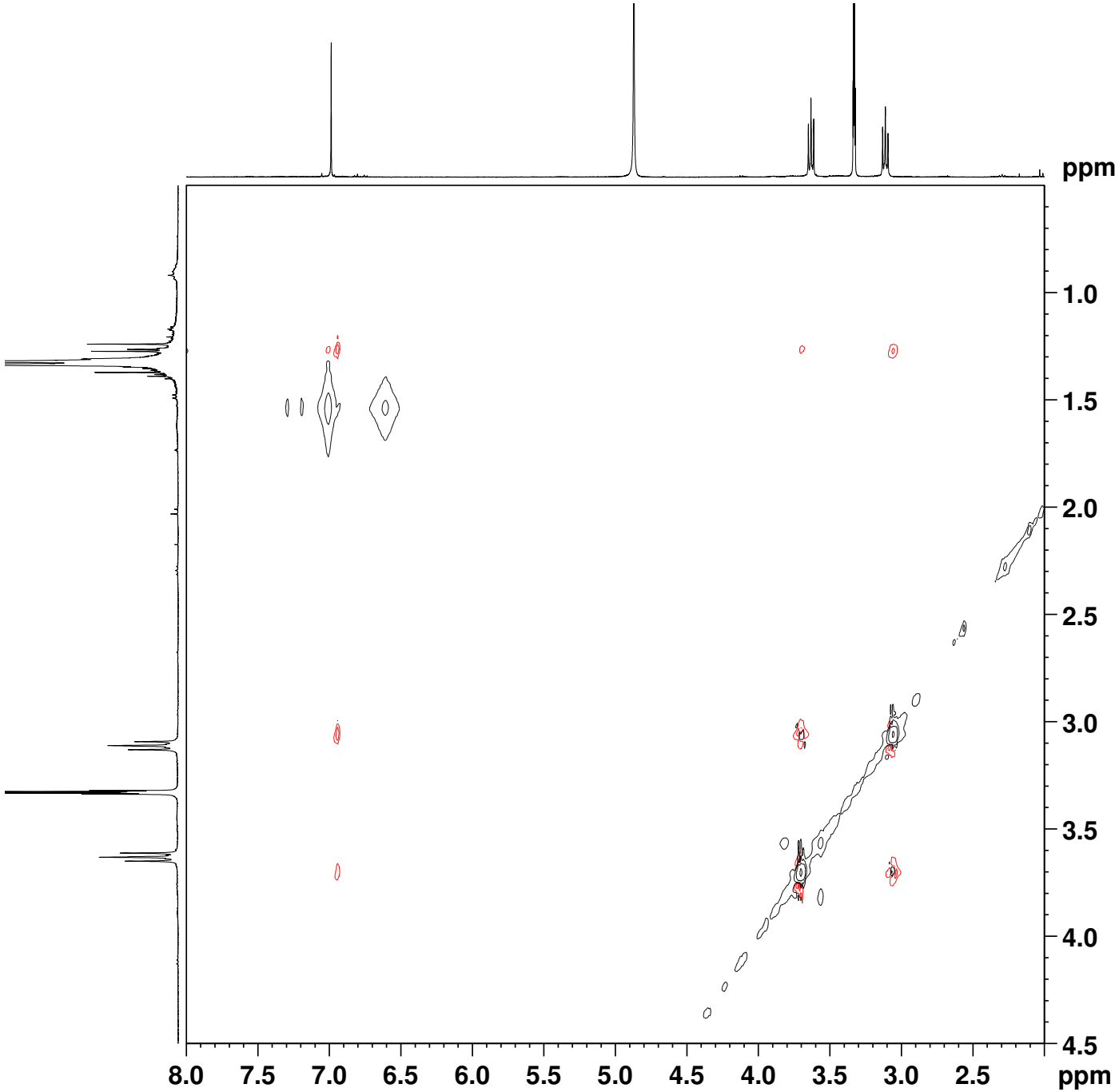
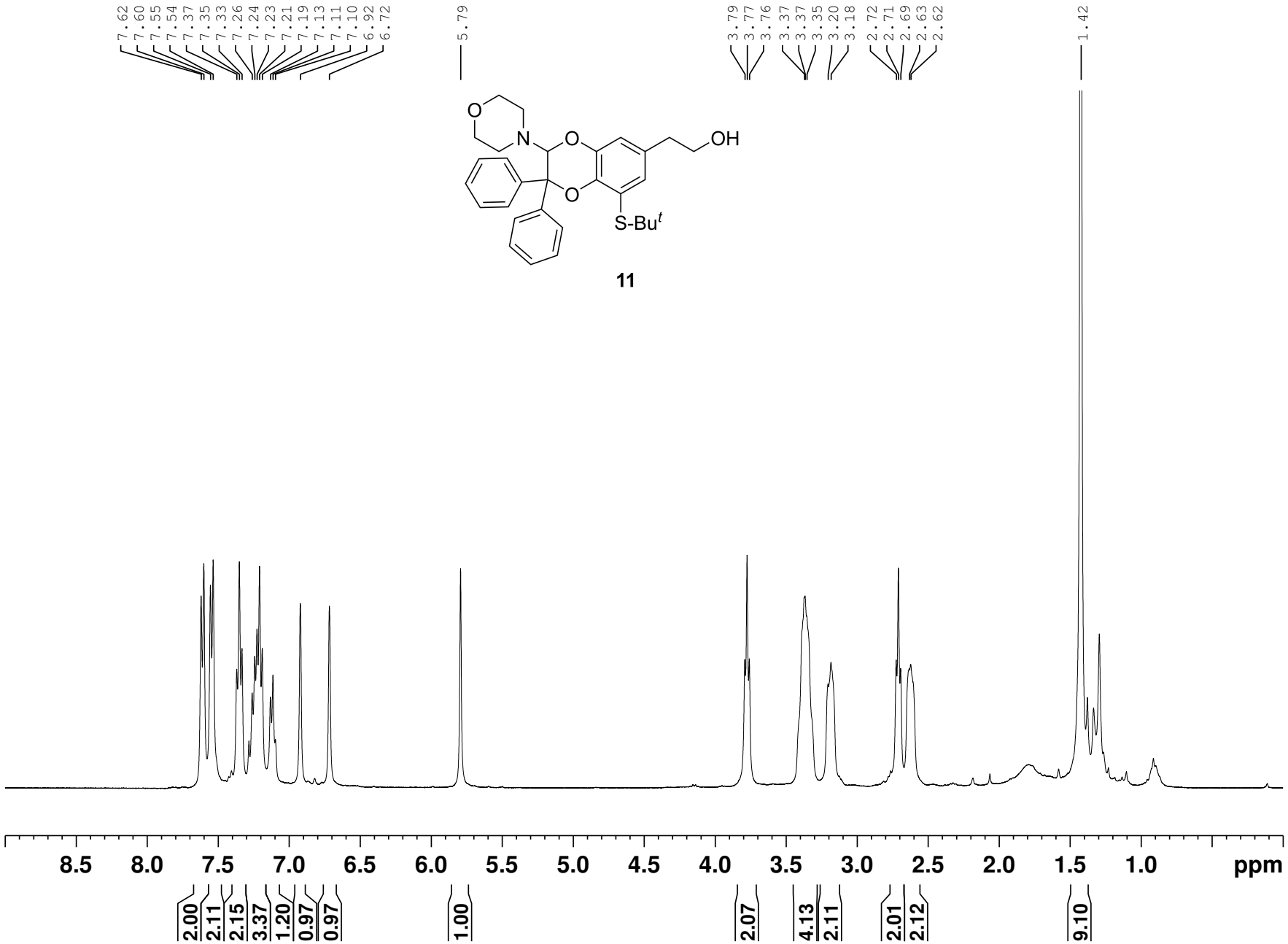
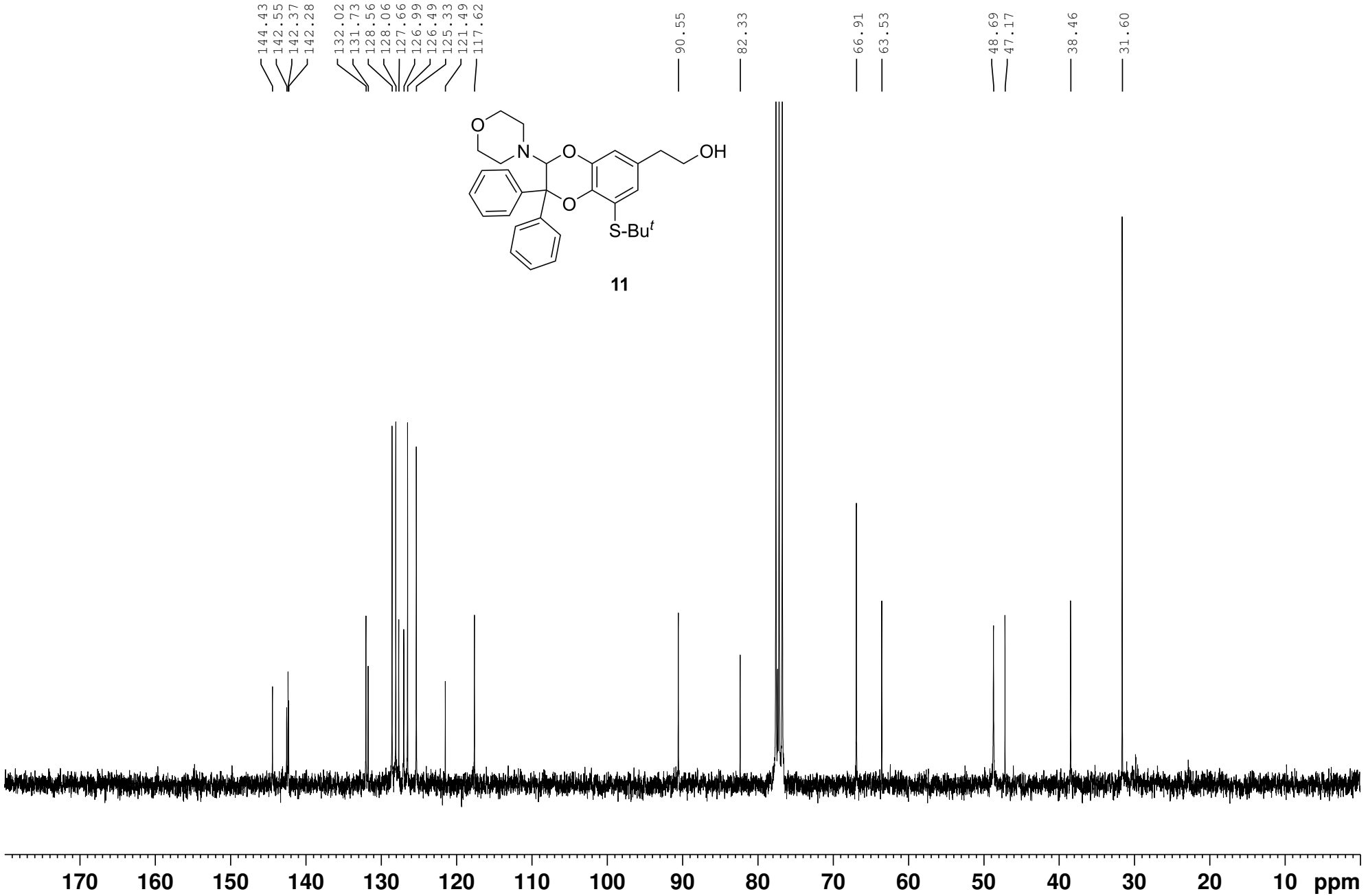


^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **11**

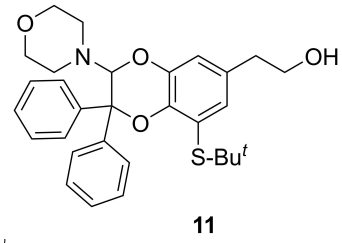


11

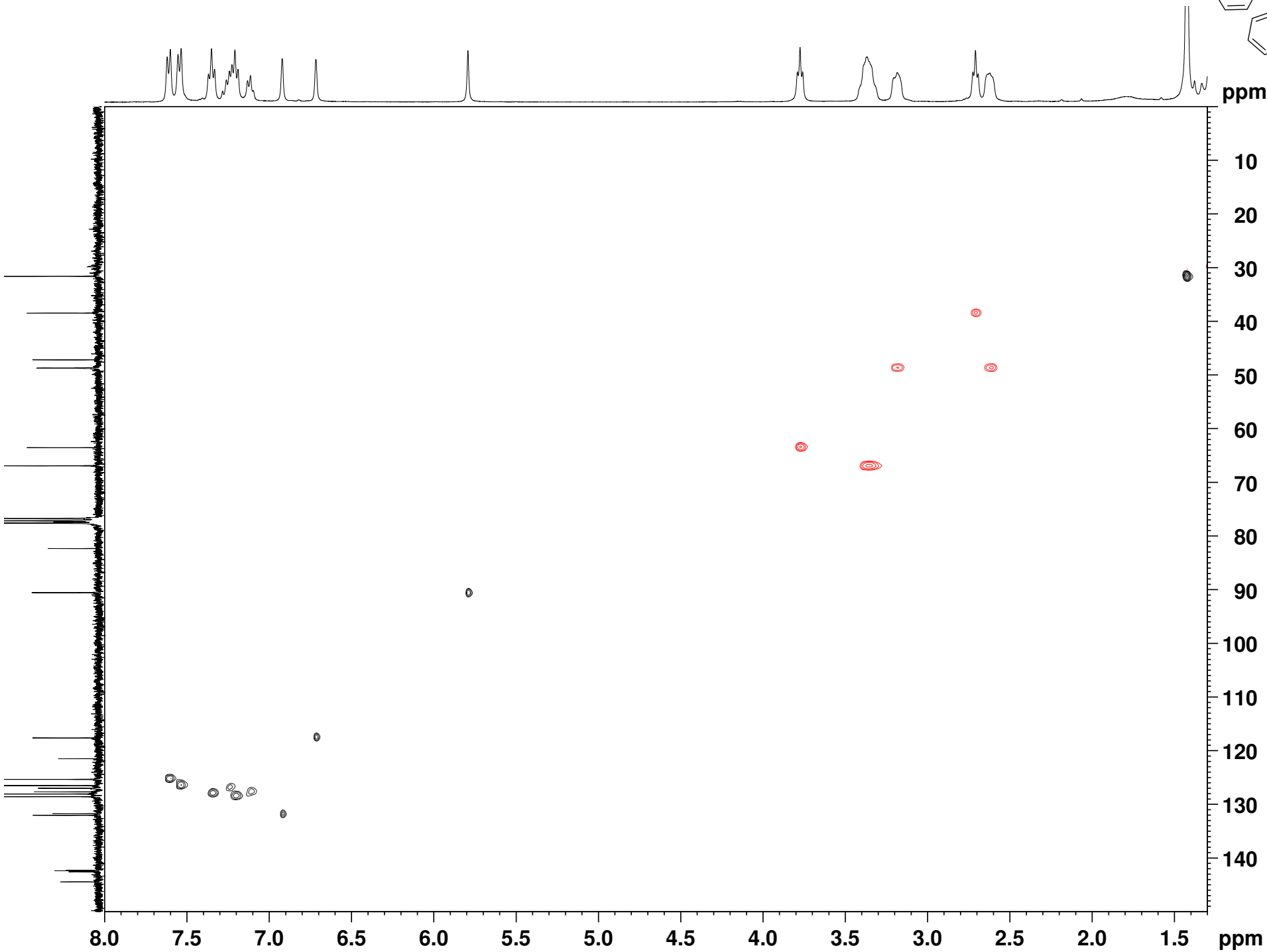
^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Compound **11**



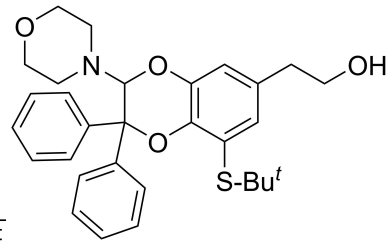
HSQC NMR spectrum (400 MHz, $CDCl_3$) - Compound **11**



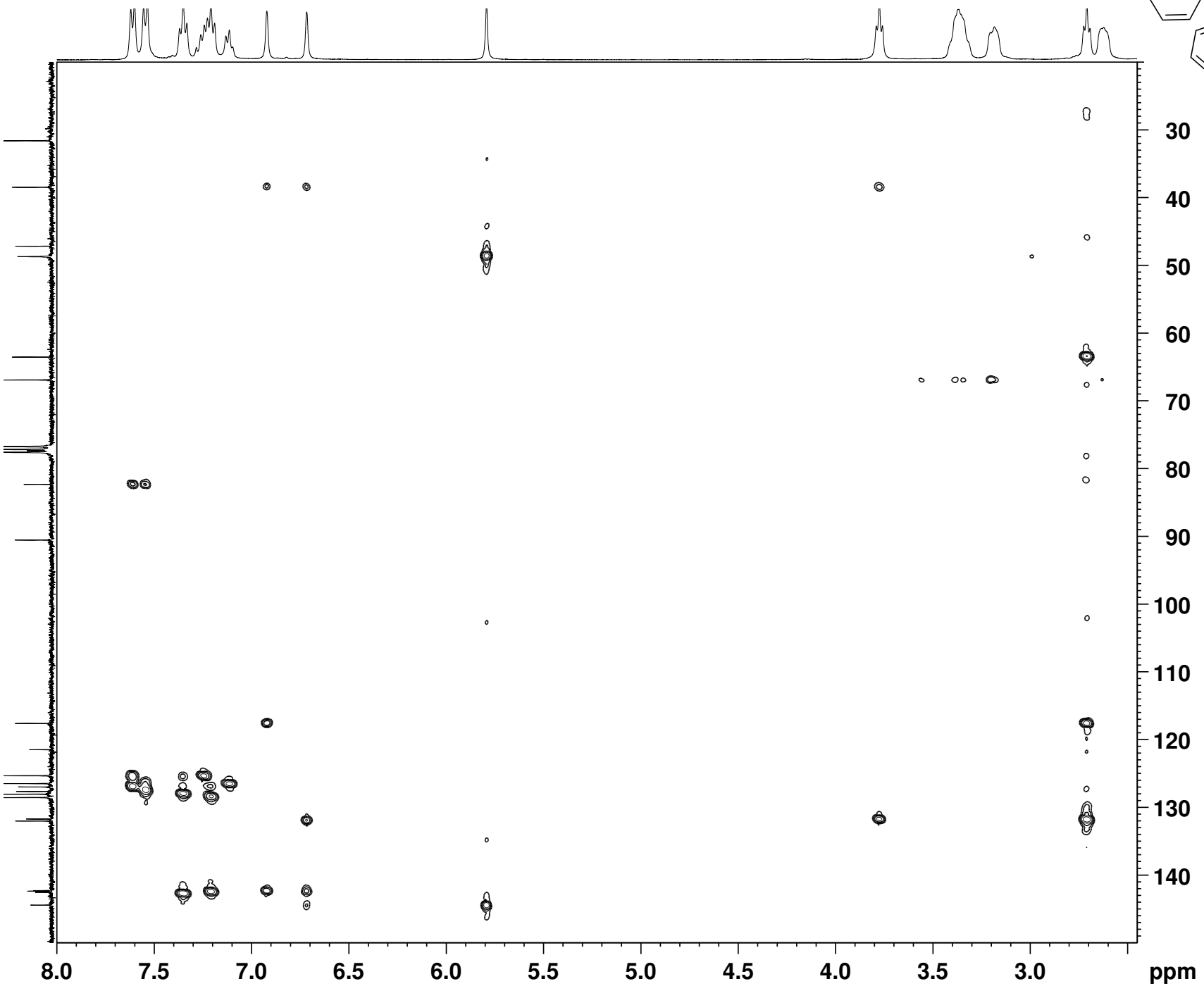
11



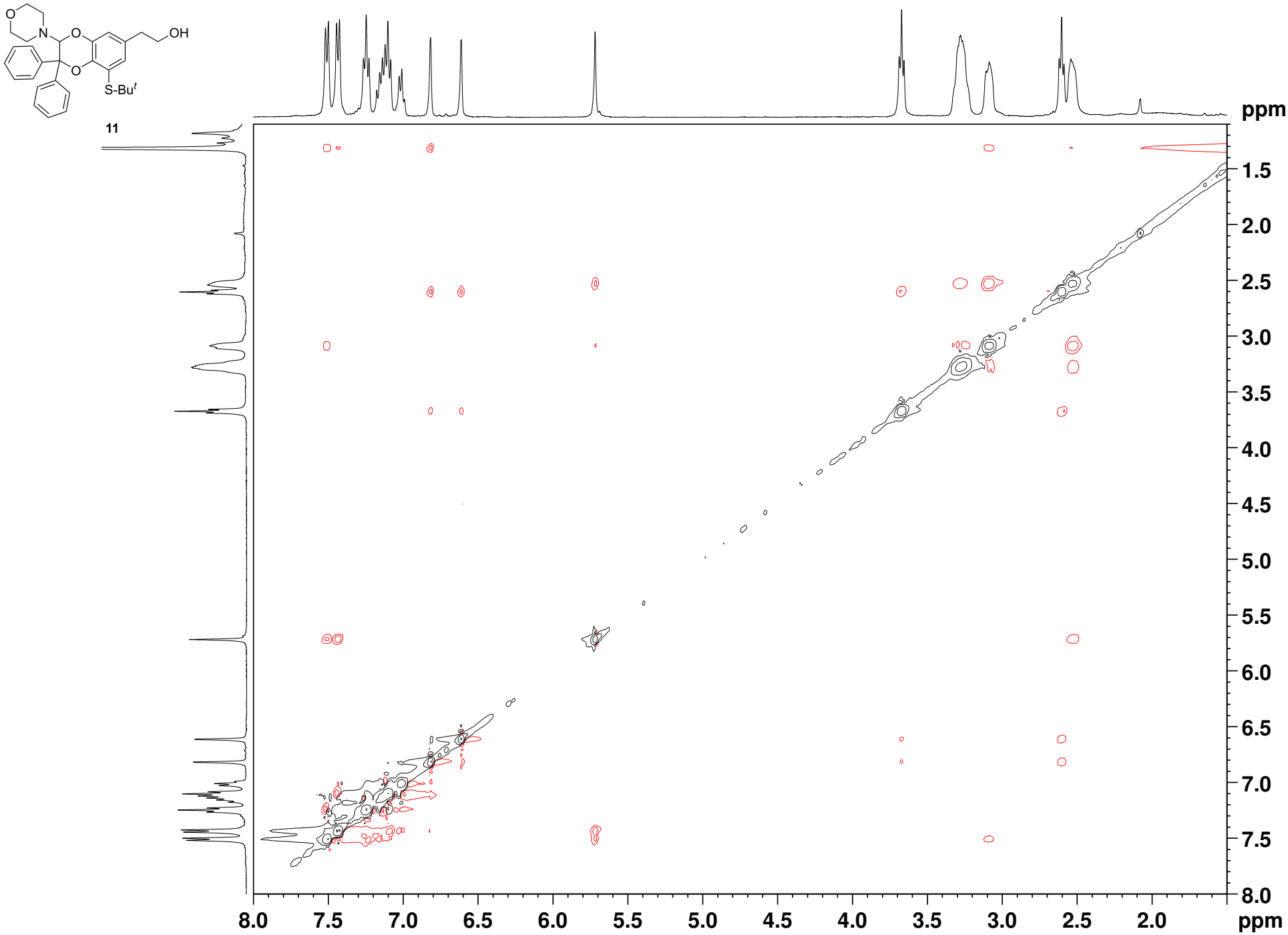
HMBC NMR spectrum (400 MHz, $CDCl_3$) - Compound **11**



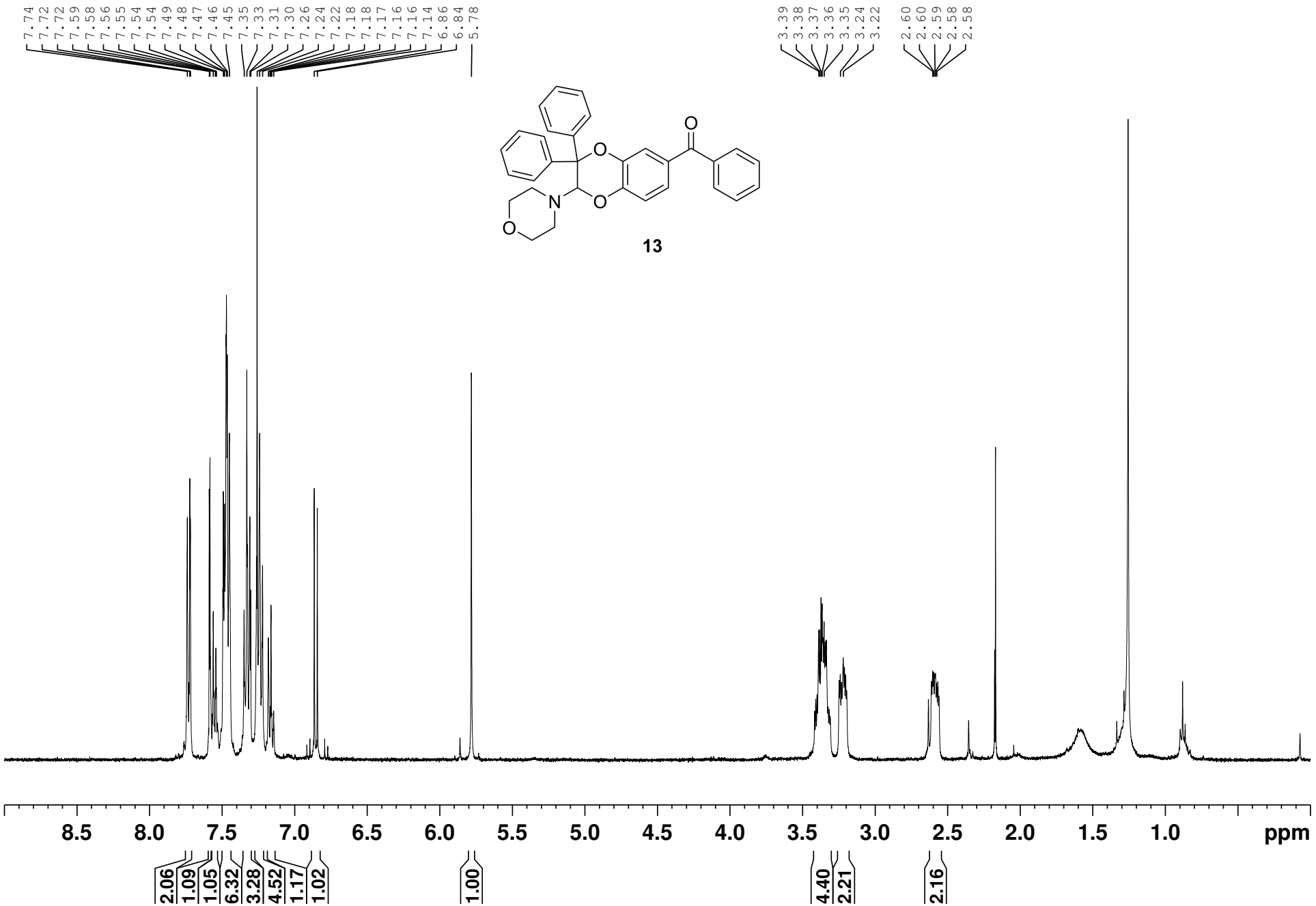
11



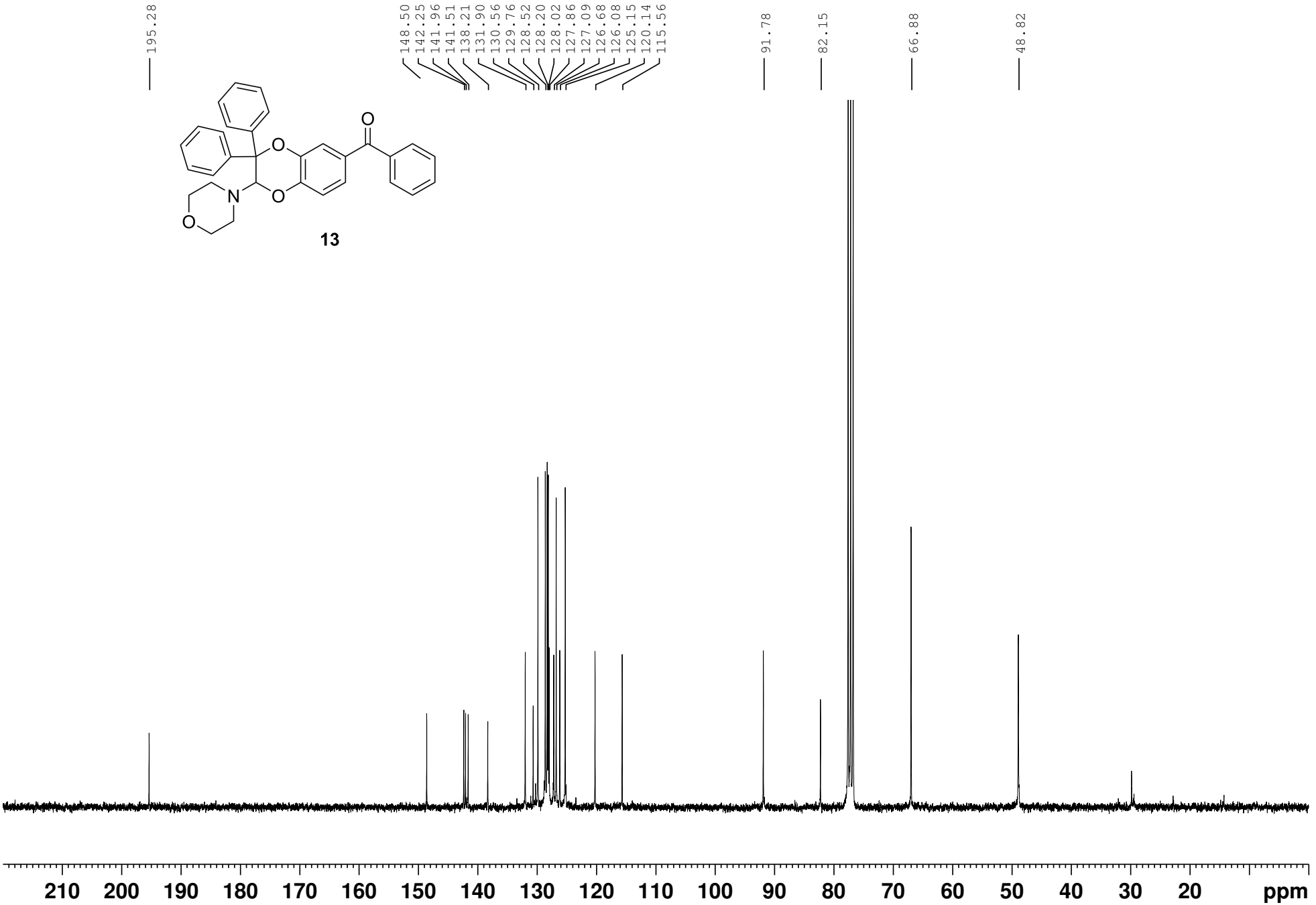
NOESY NMR spectrum (400 MHz, $CDCl_3$) - Compound **11**



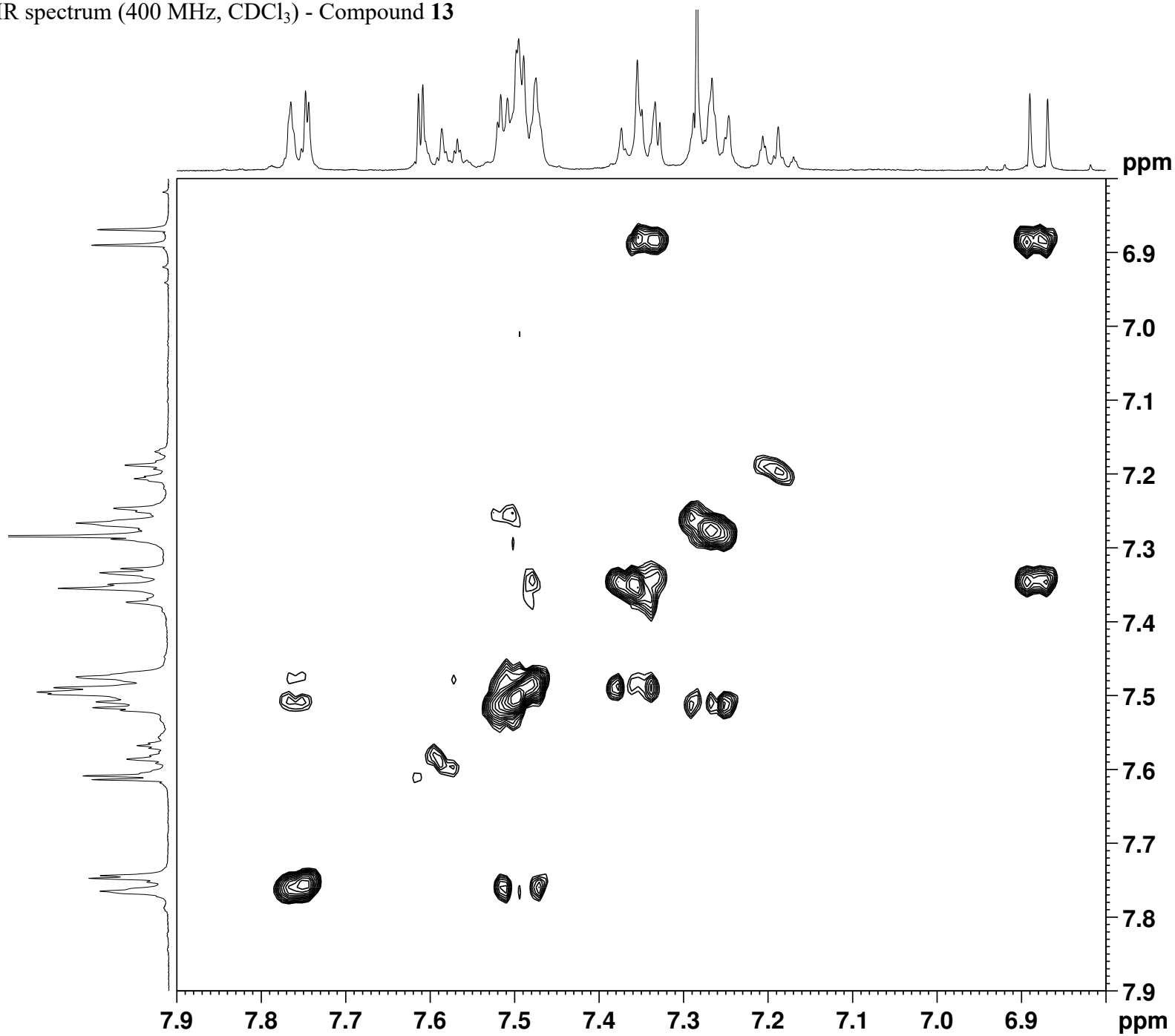
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **13**

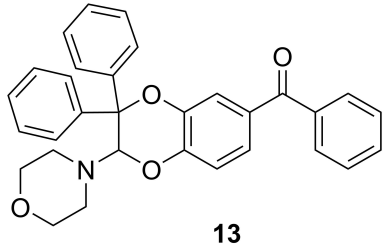


^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Compound **13**



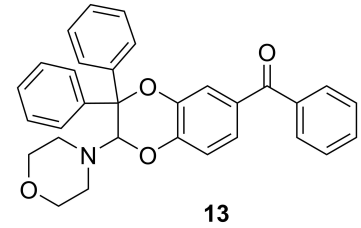
COSY NMR spectrum (400 MHz, $CDCl_3$) - Compound **13**



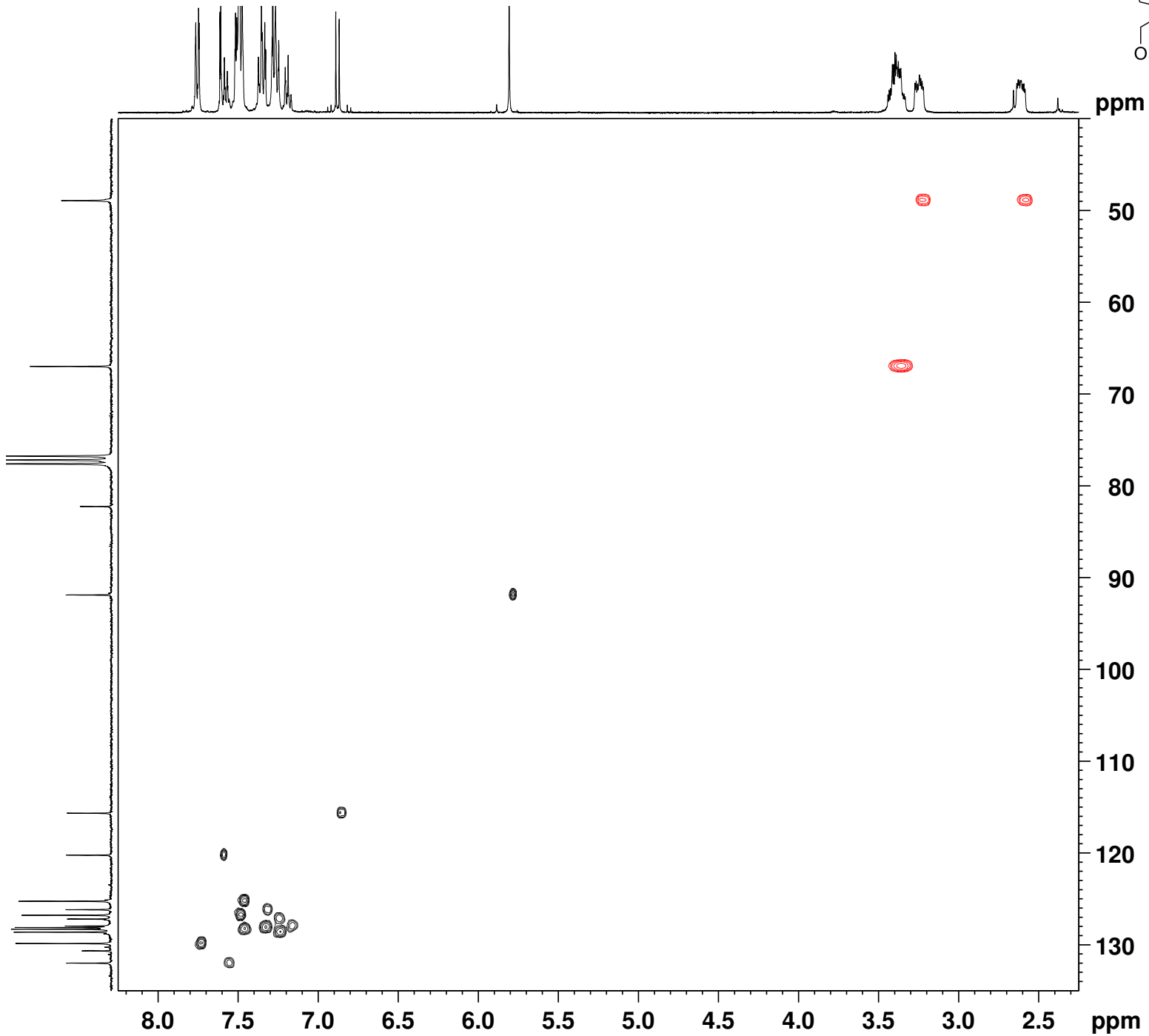


13

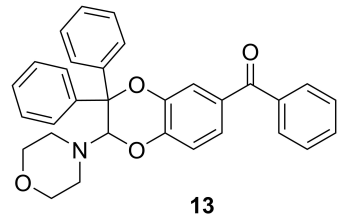
HSQC NMR spectrum (400 MHz, $CDCl_3$) - Compound **13**



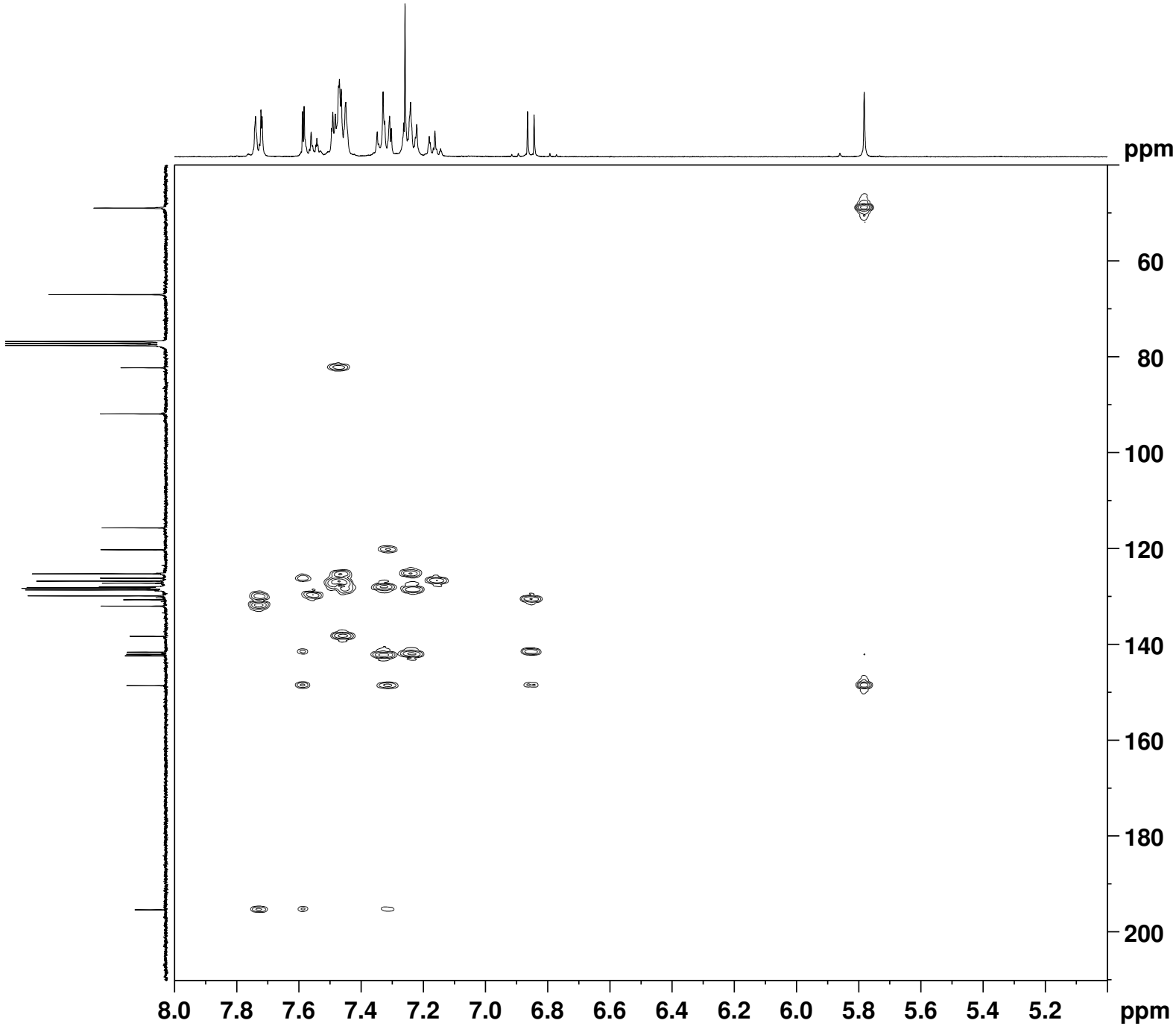
13



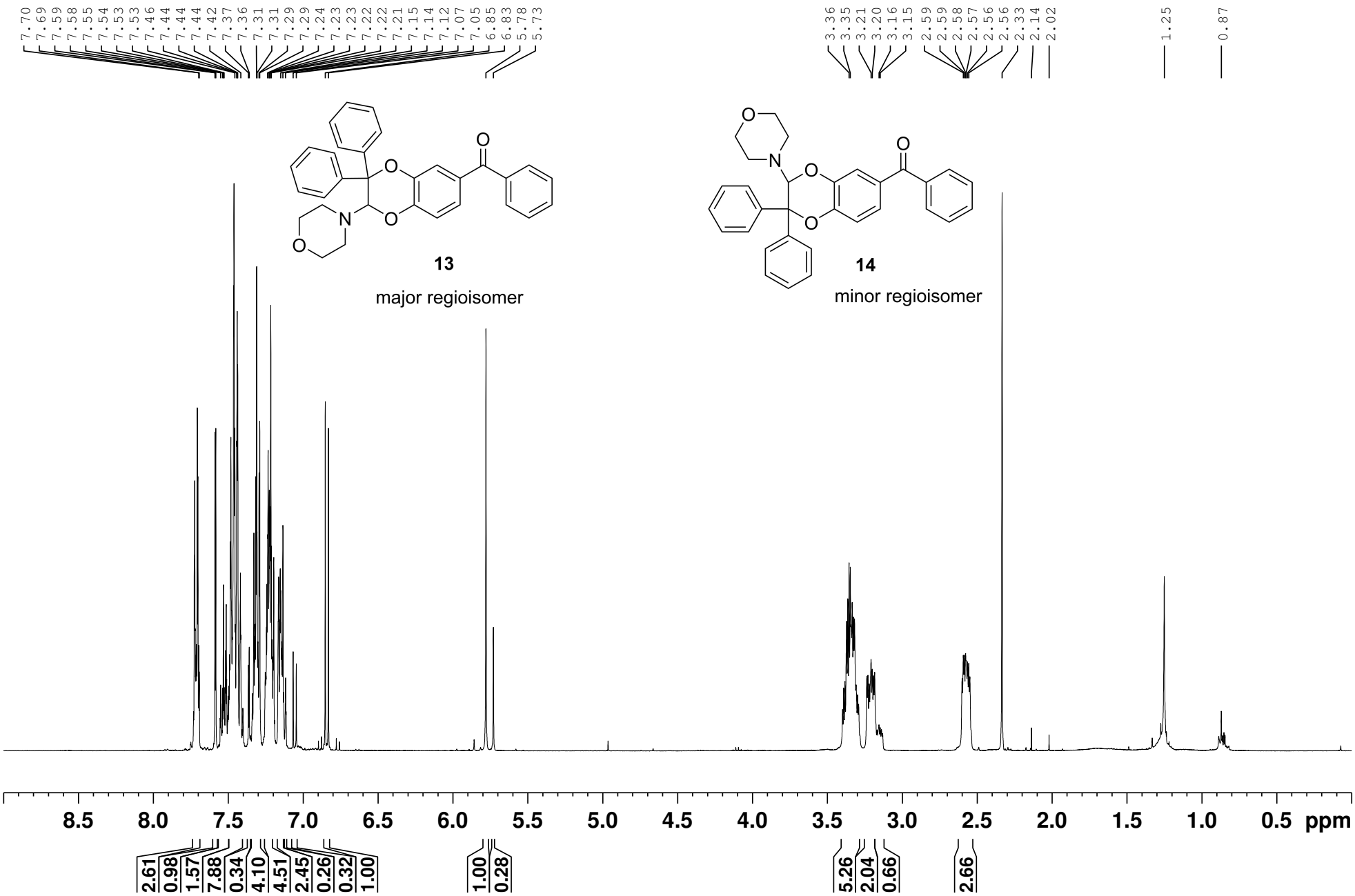
HMBC NMR spectrum (400 MHz, $CDCl_3$) - Compound **13**



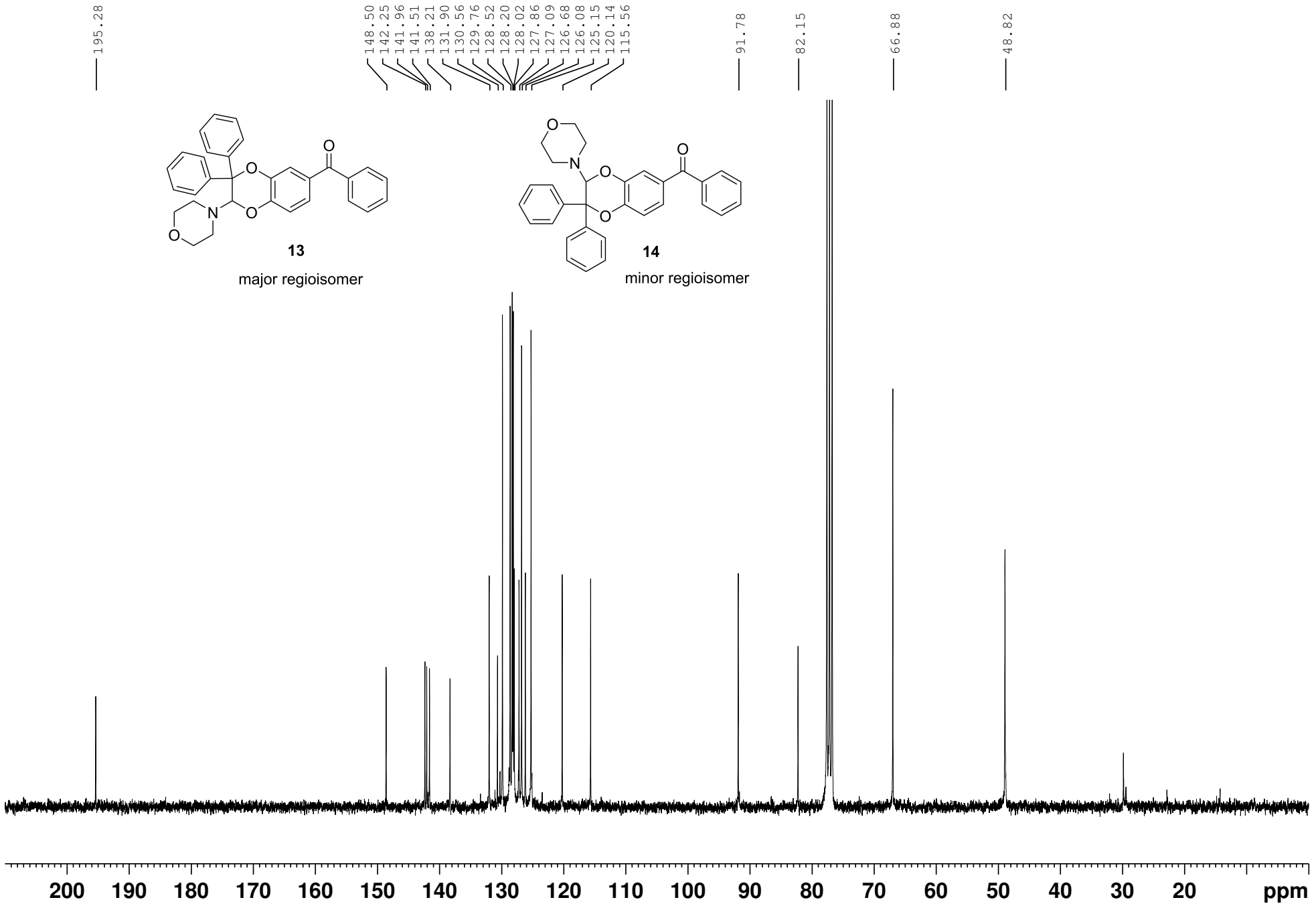
13



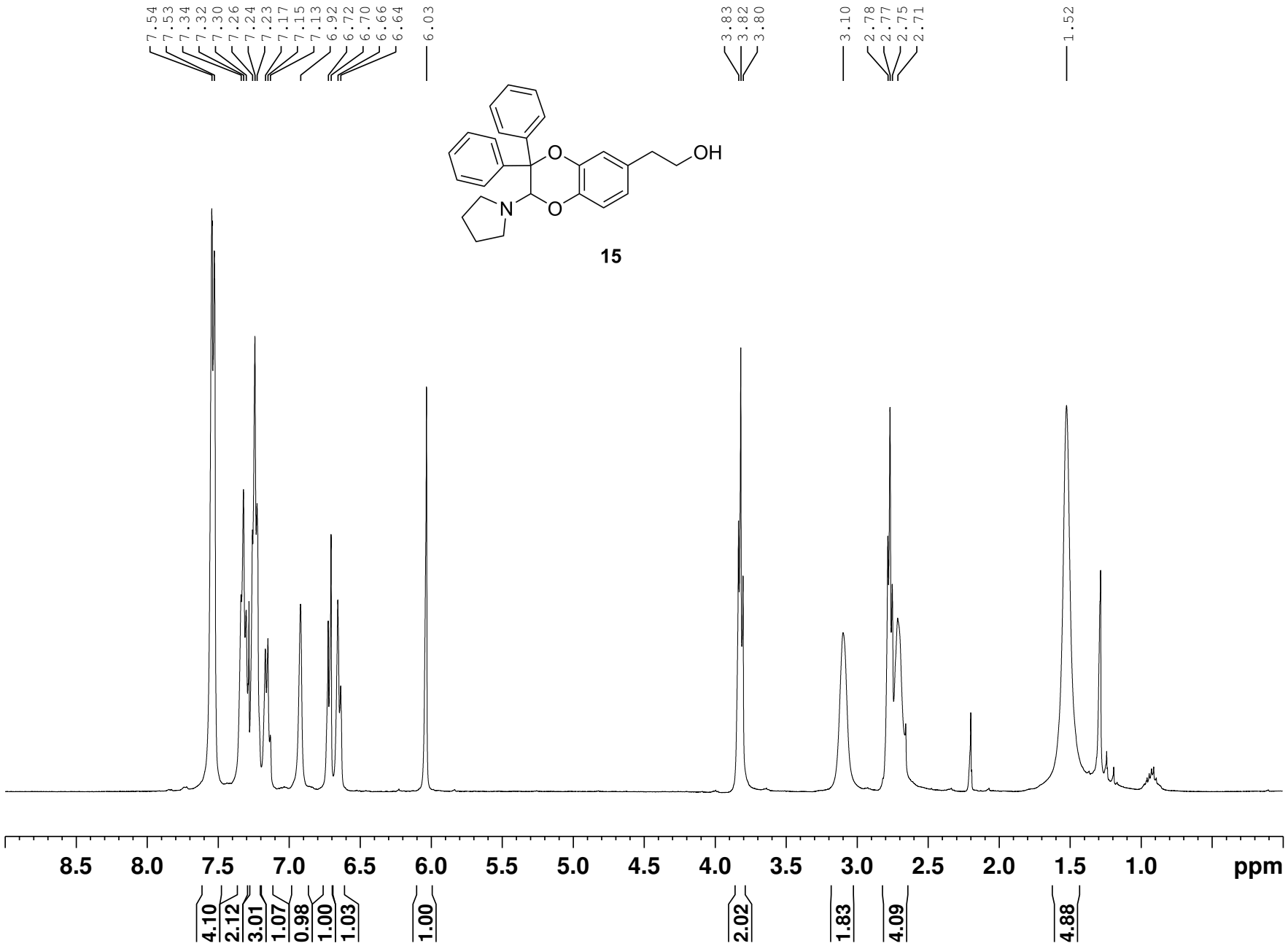
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Mixture of the major regioisomer **13** and minor regioisomer **14**



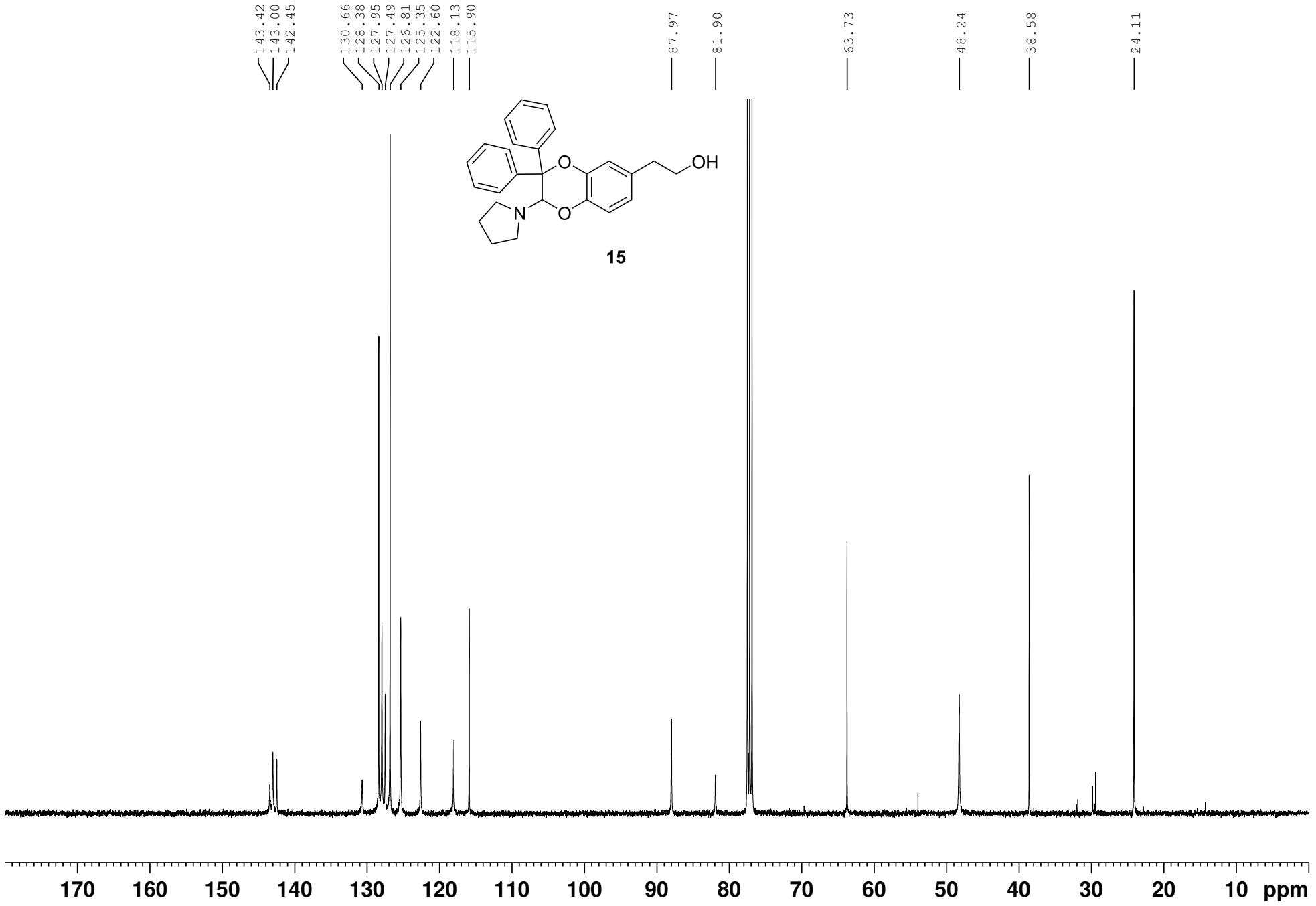
^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Mixture of the major regioisomer **13** and minor regioisomer **14**



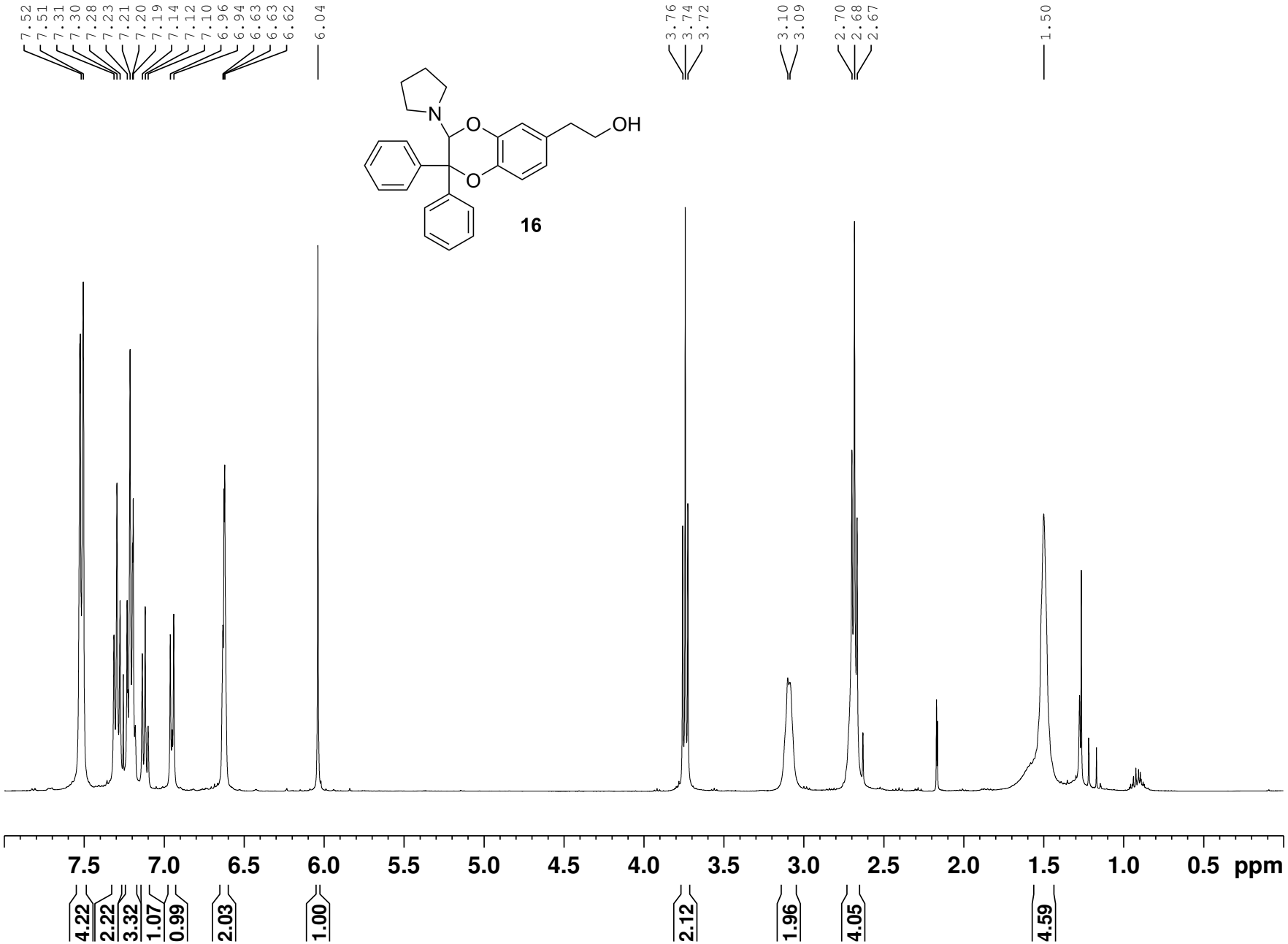
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **15**



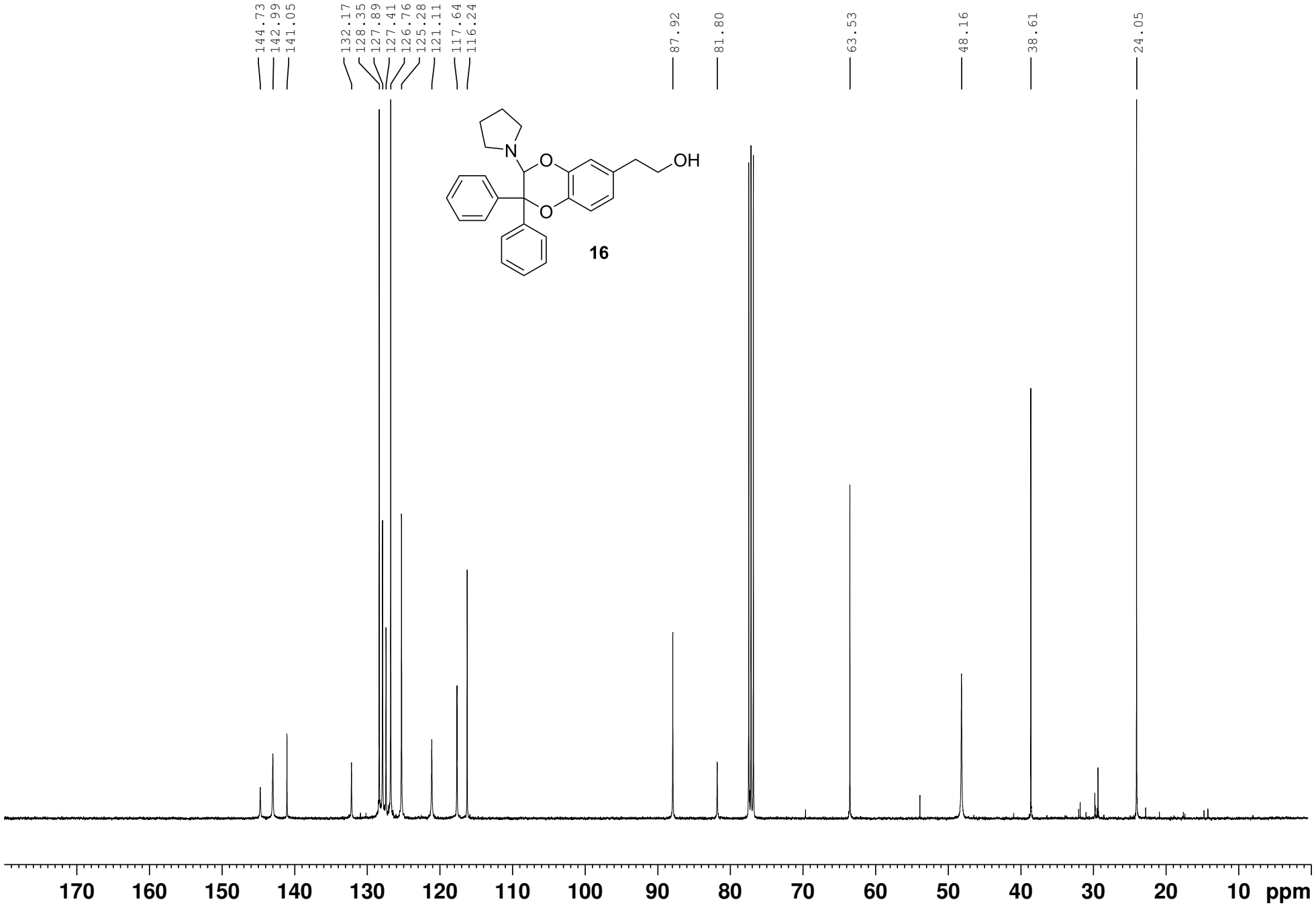
^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Compound **15**



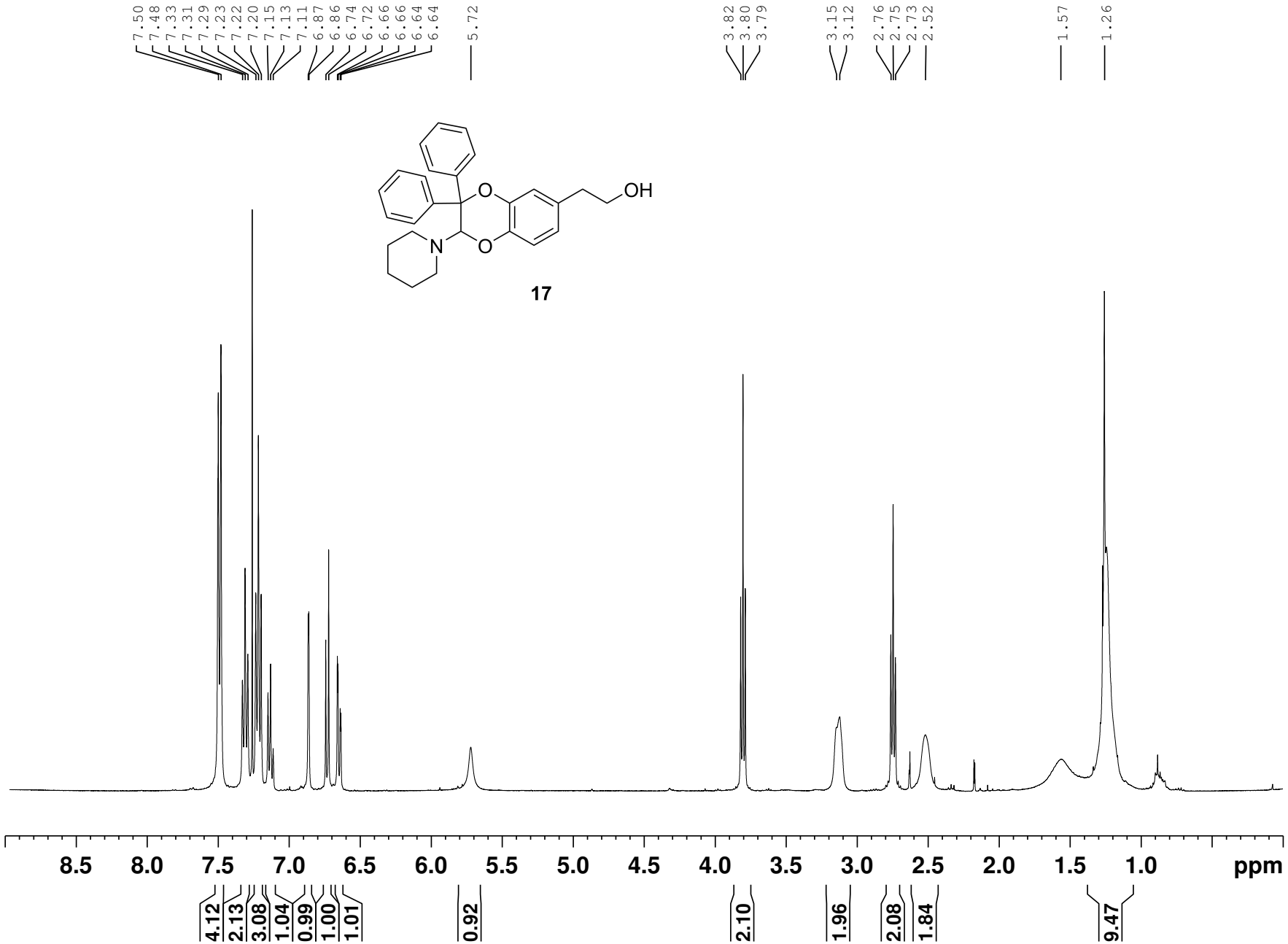
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **16**



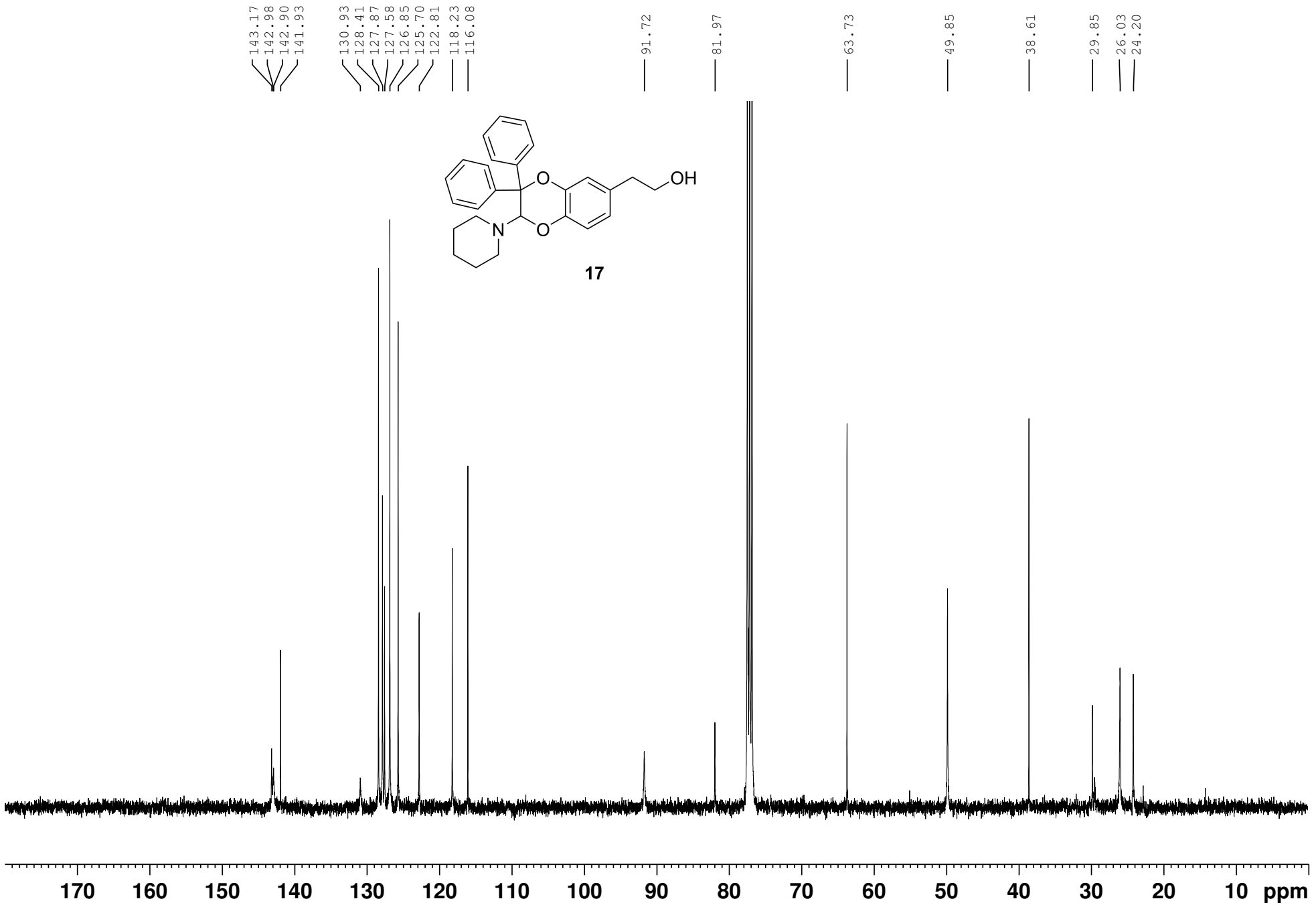
^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Compound **16**



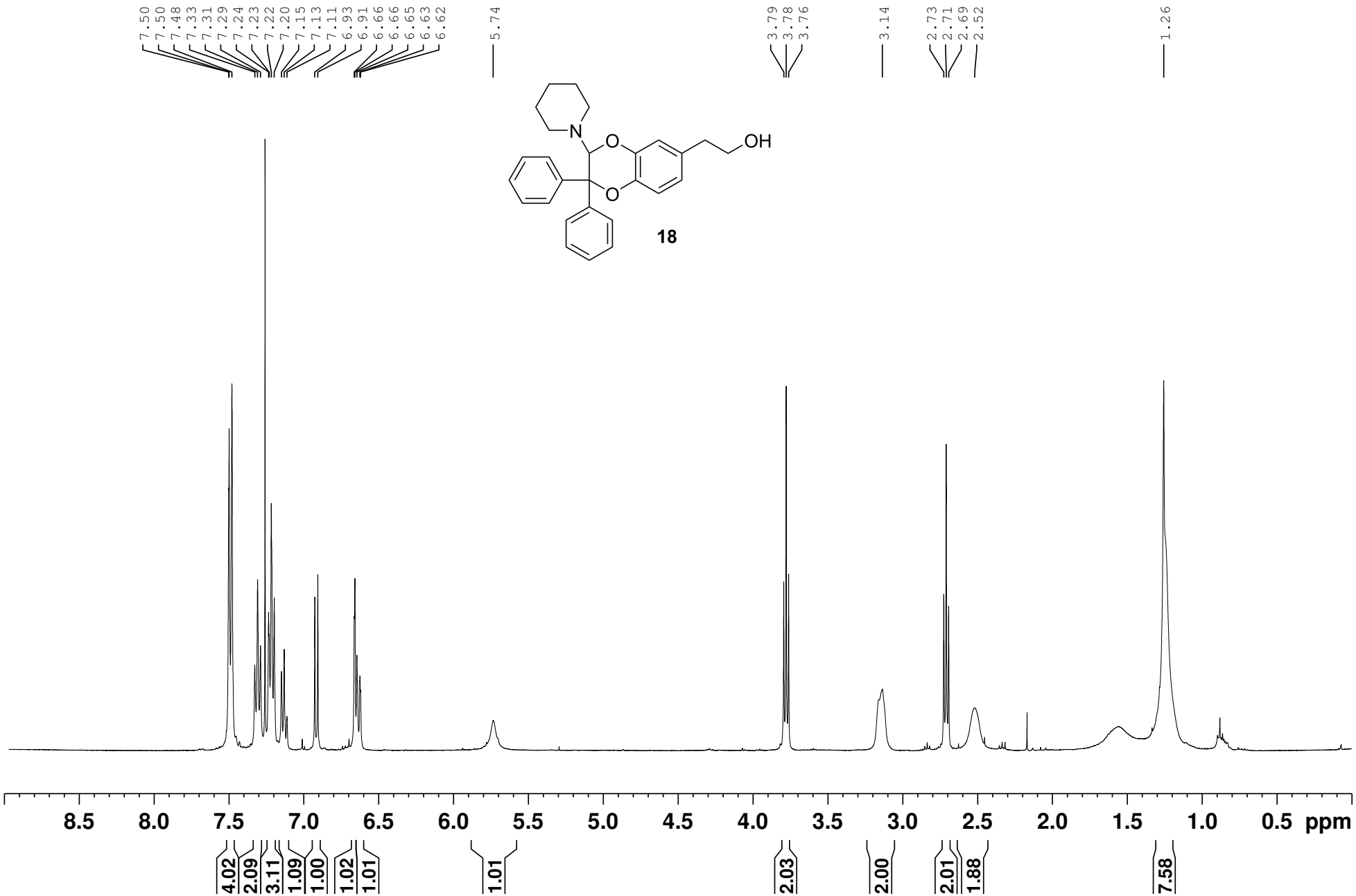
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **17**



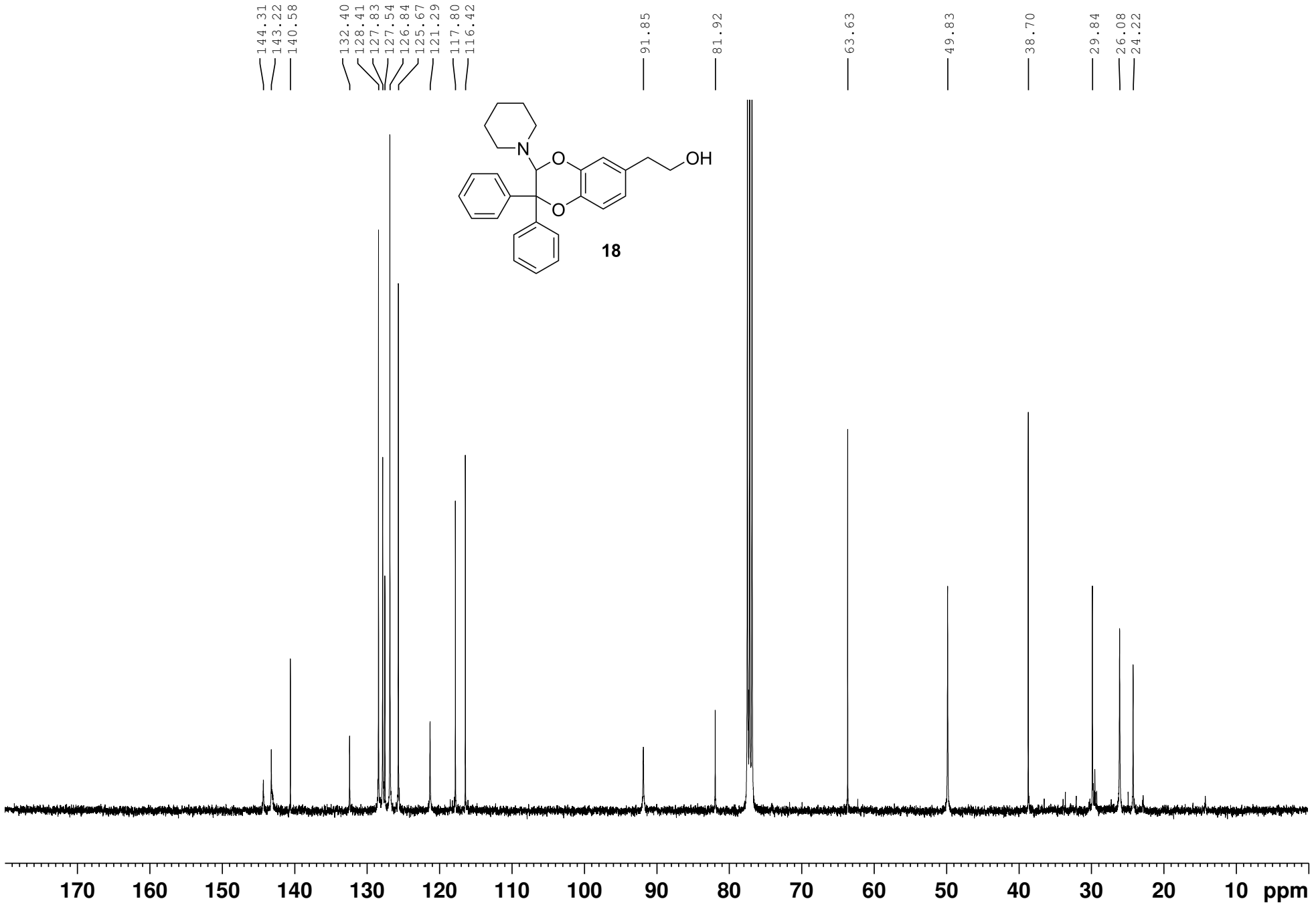
^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Compound **17**



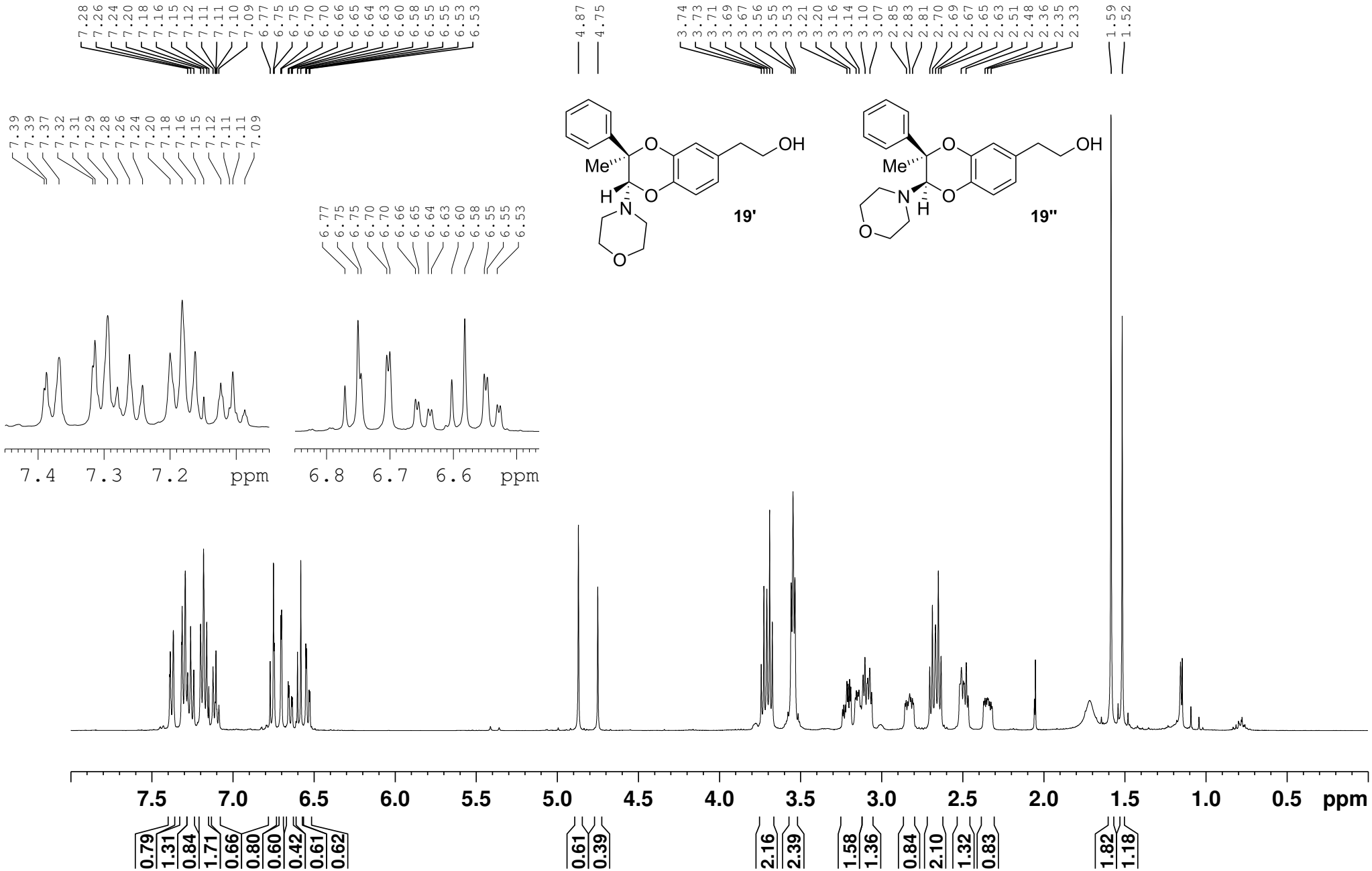
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **18**



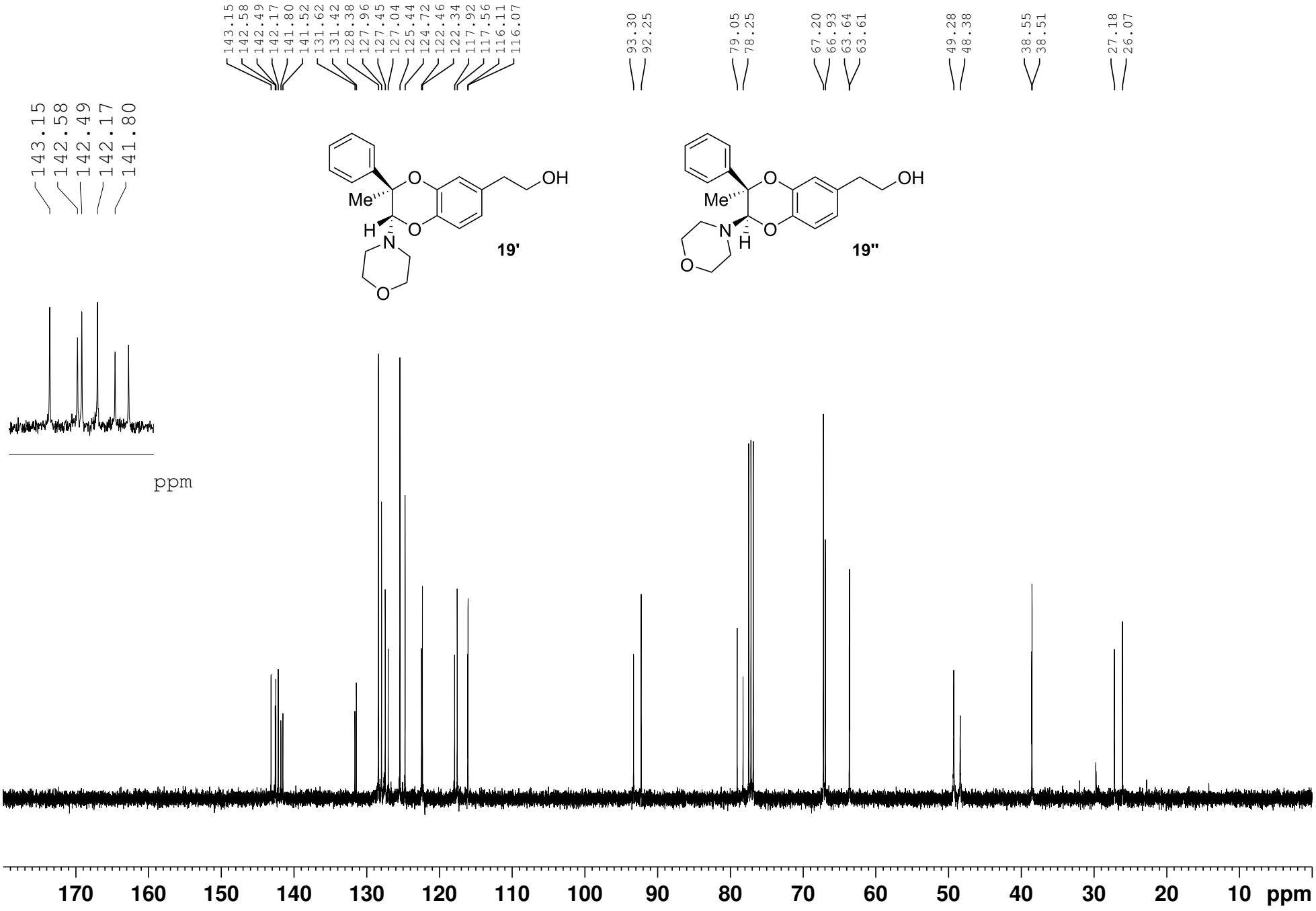
^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Compound **18**



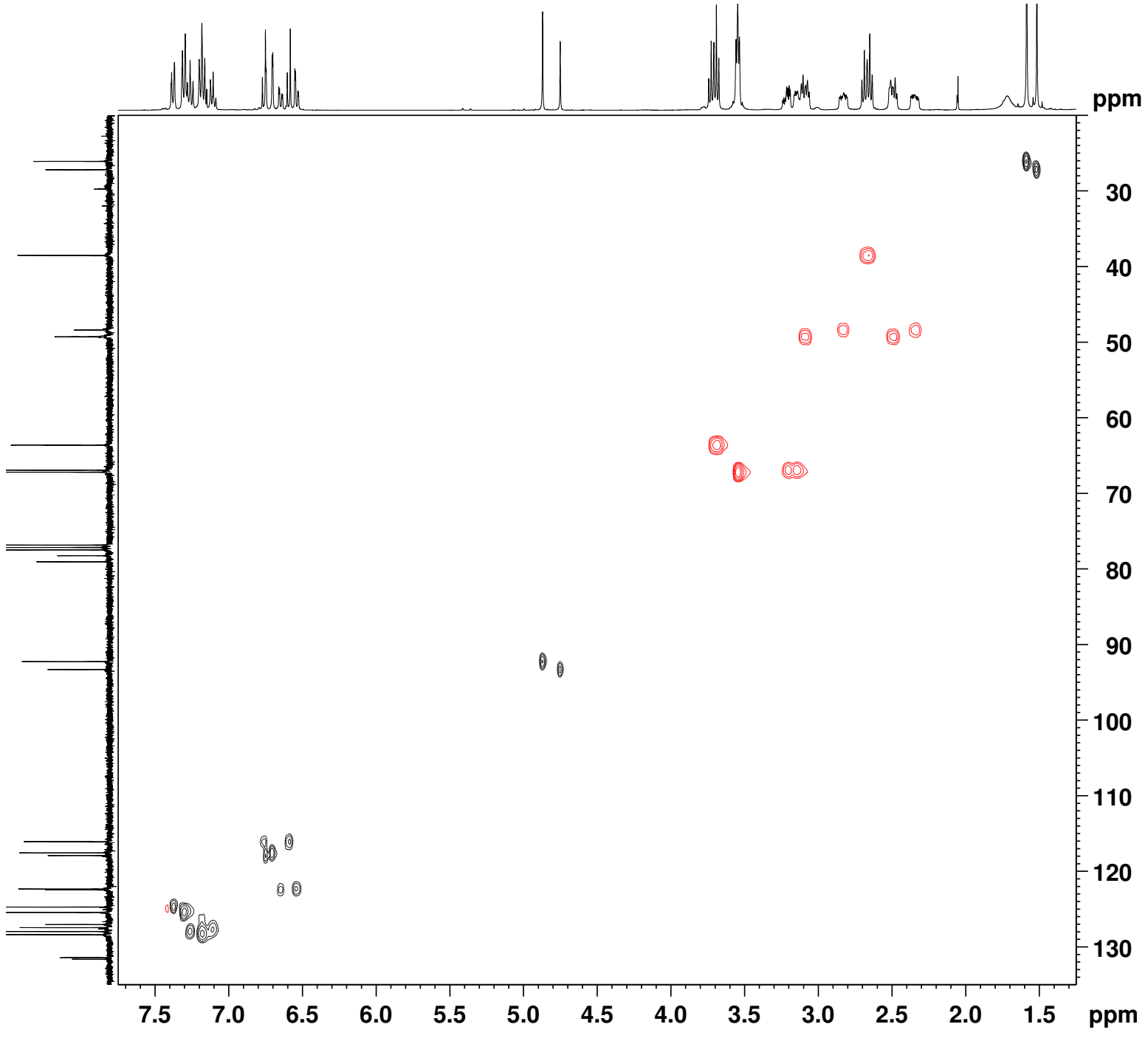
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **19'** and **19''**

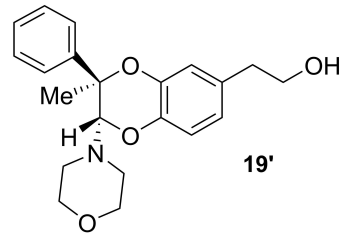


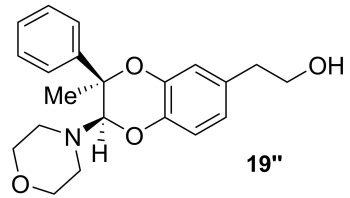
^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Diastereoisomers **19'** and **19"**



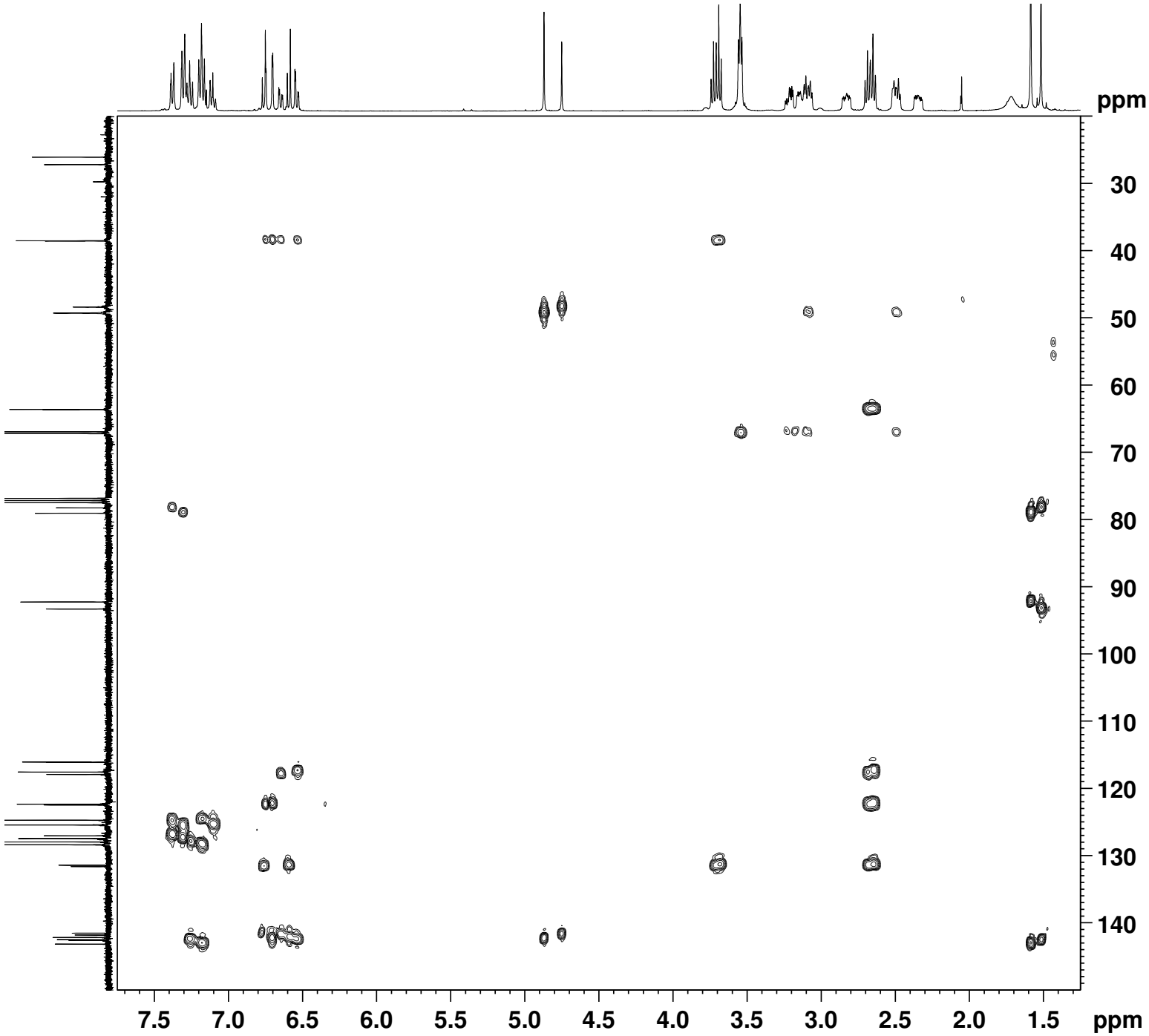
HSQC NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **19'** and **19''**

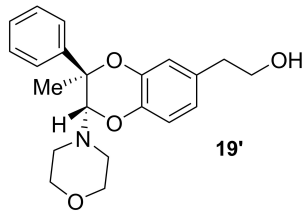


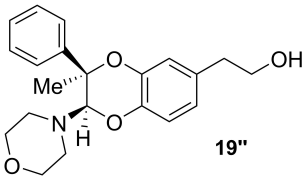




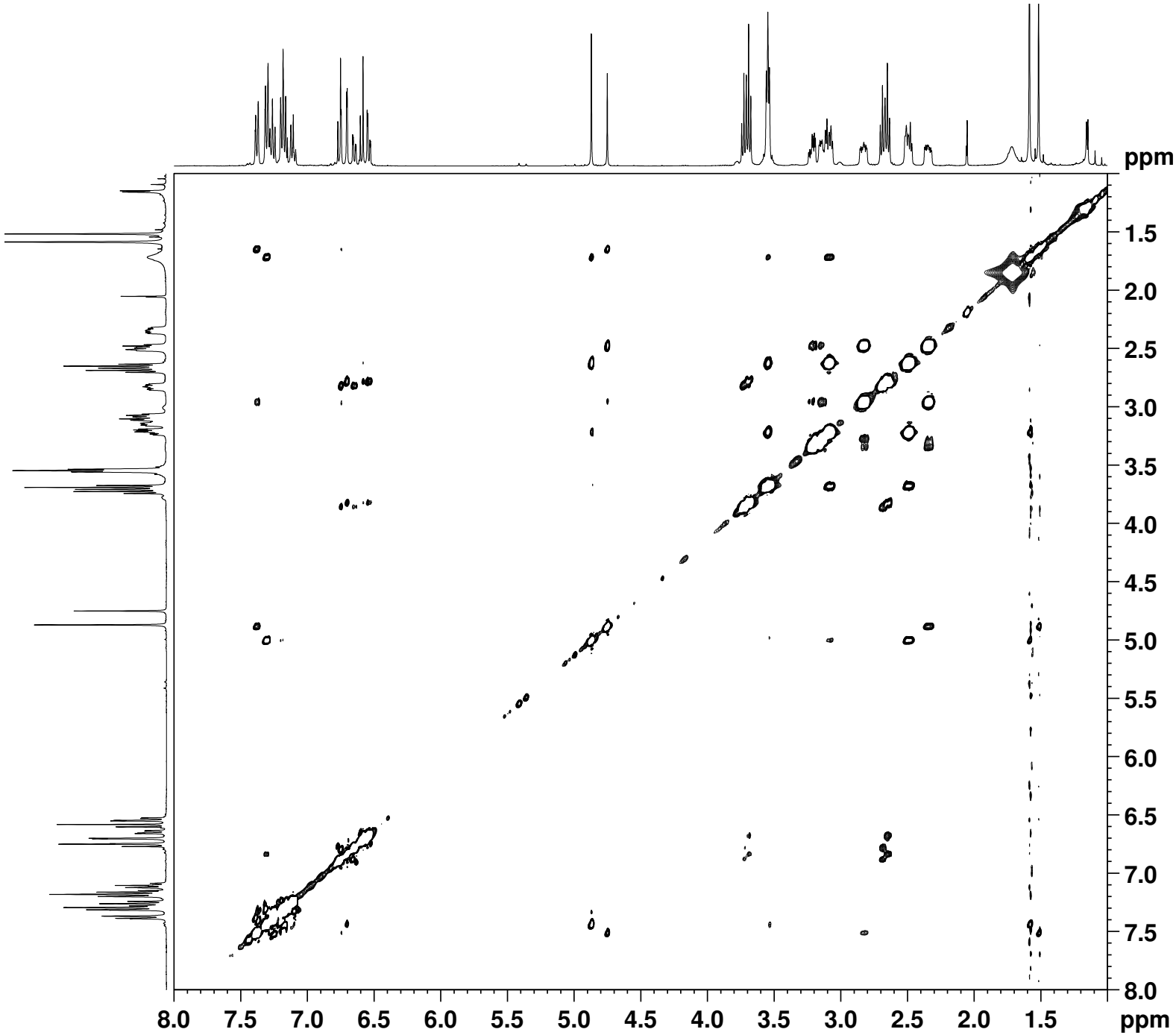
HMBC NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **19'** and **19''**

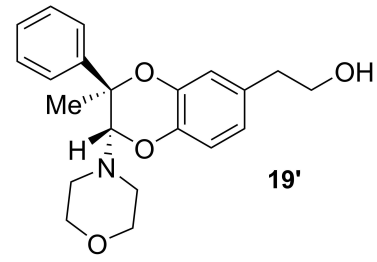




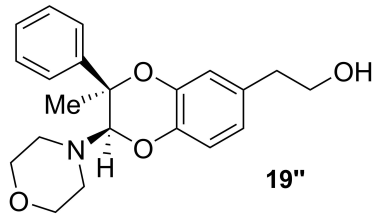


NOESY NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **19'** and **19''**



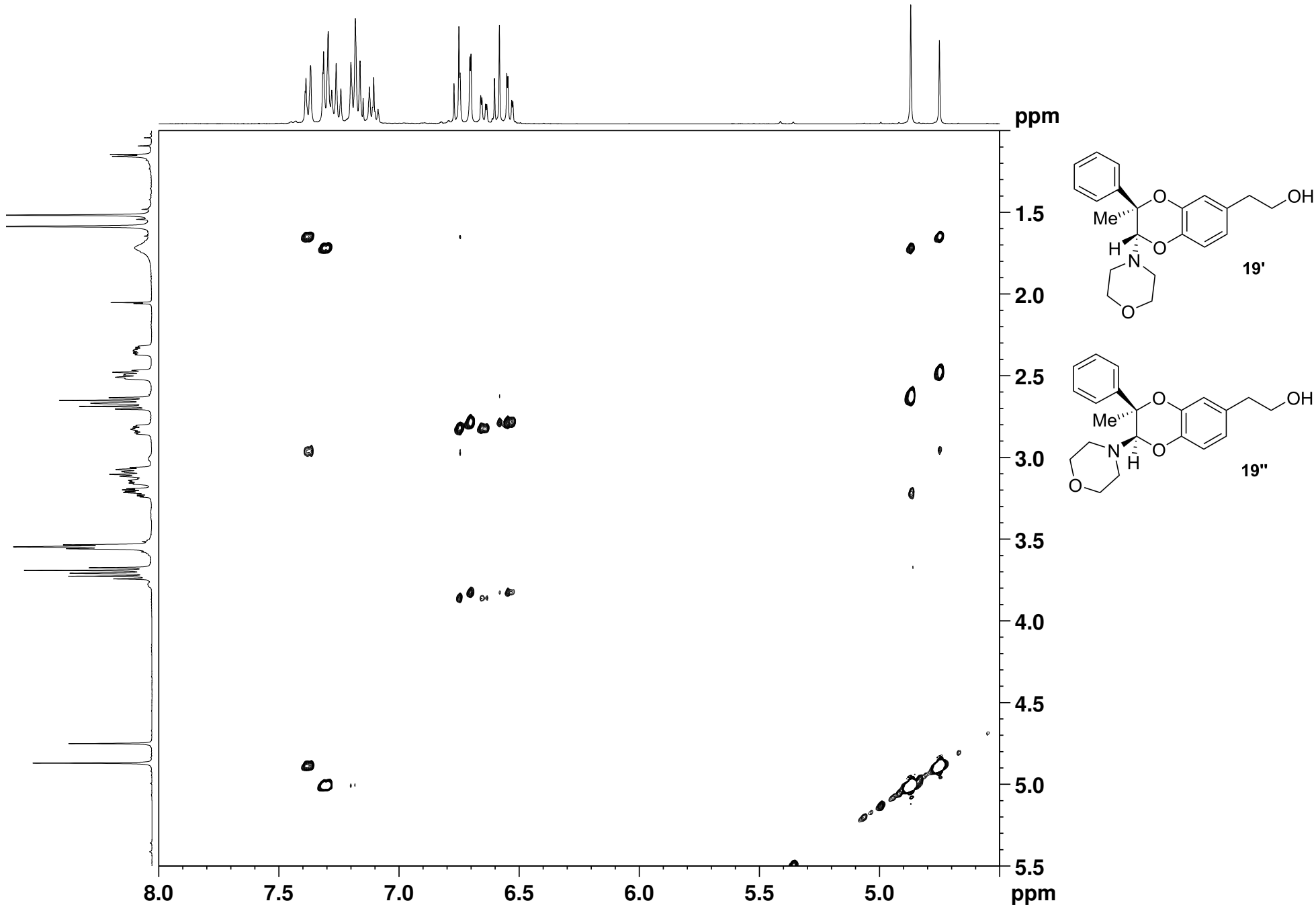


19'

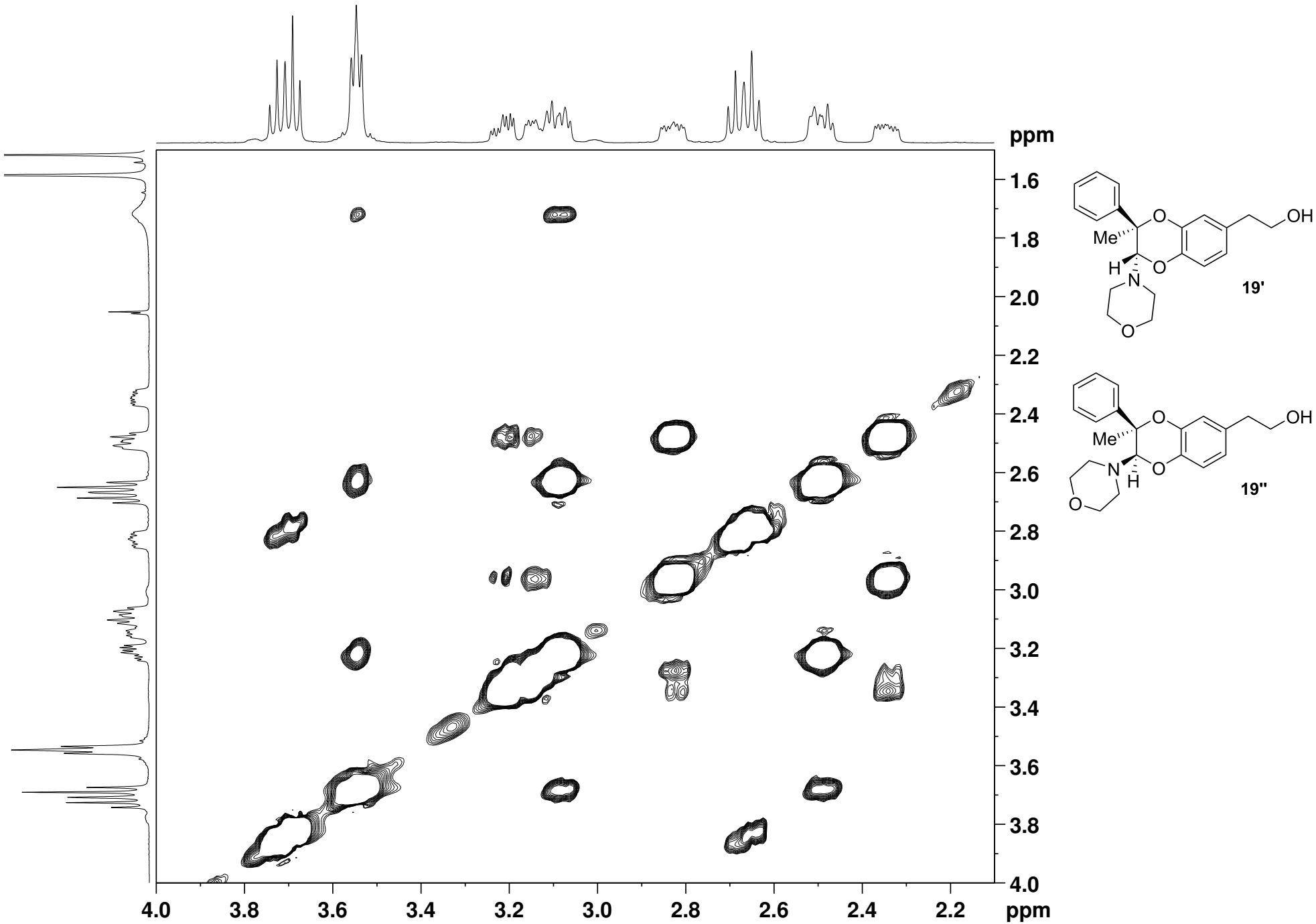


19''

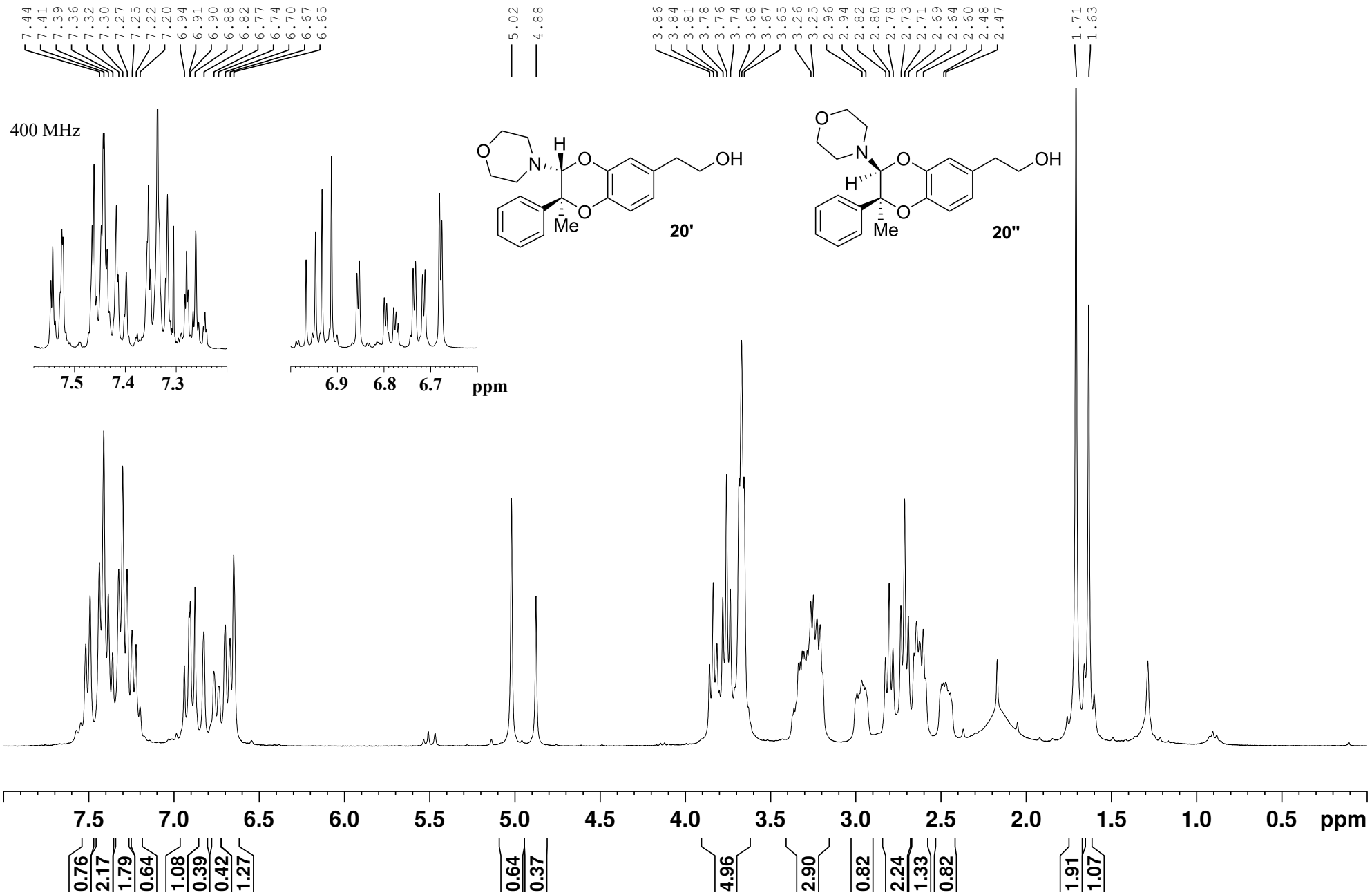
NOESY NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **19'** and **19''**



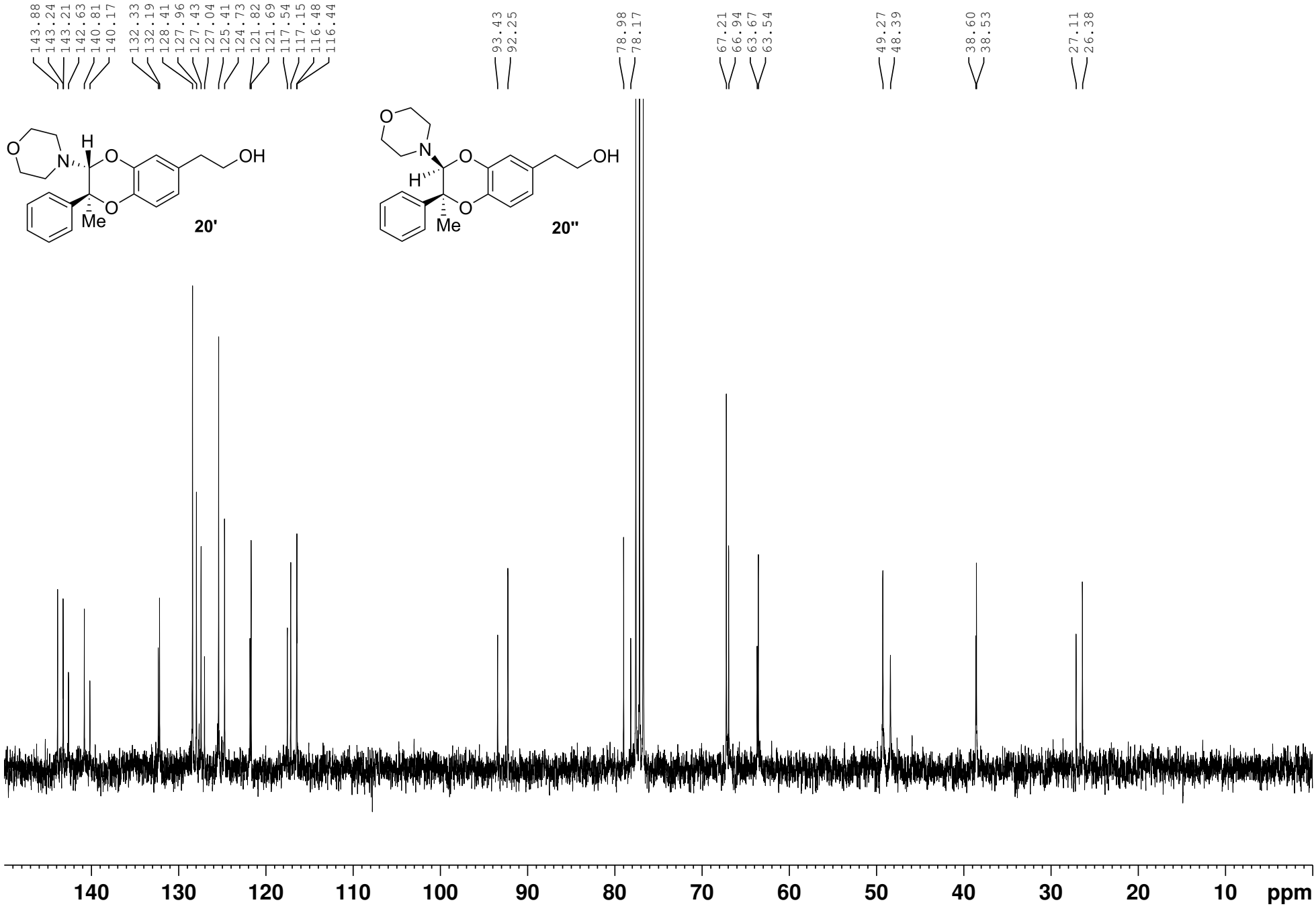
NOESY NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **19'** and **19''**



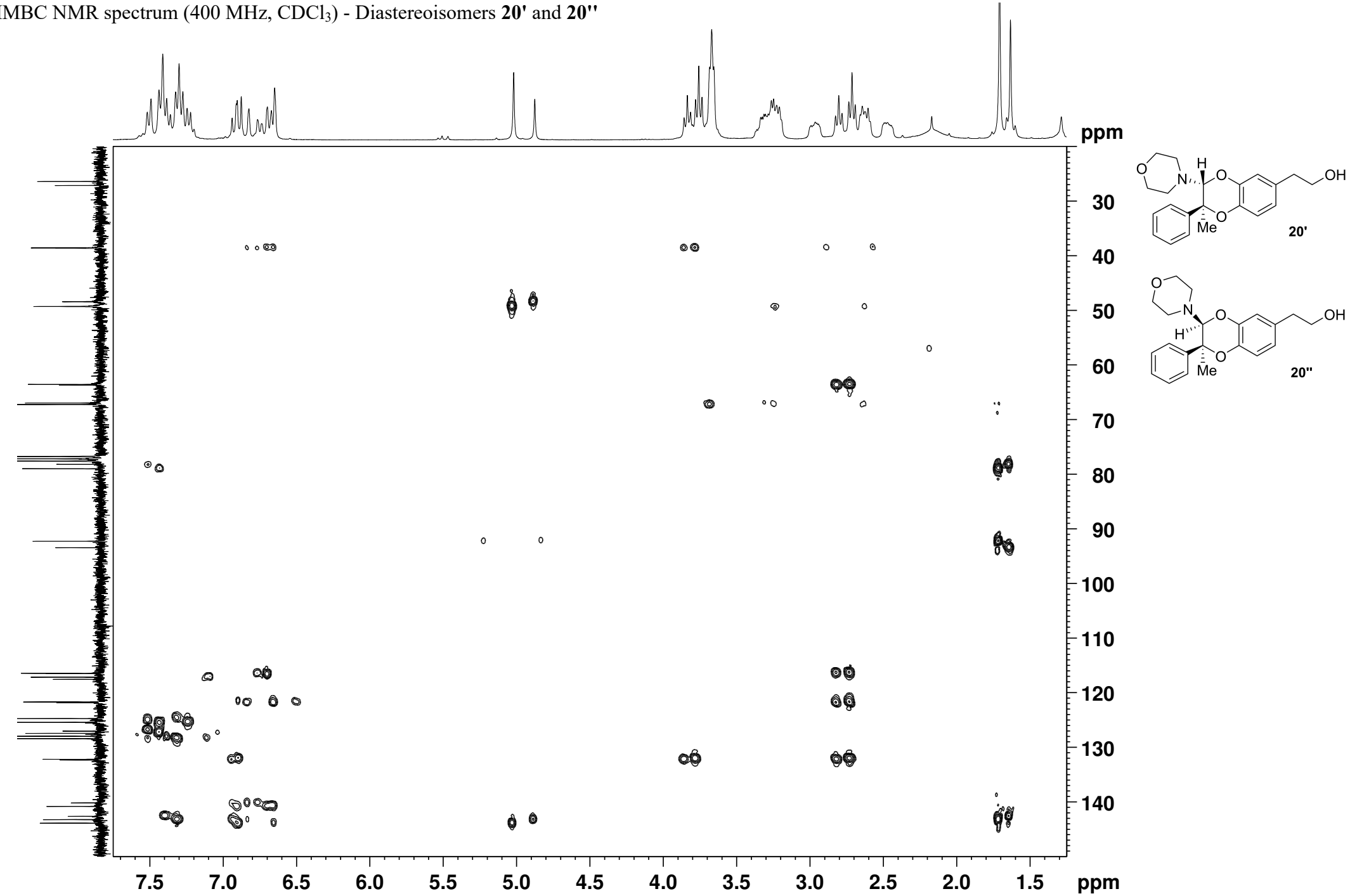
^{1}H NMR spectrum (300 MHz, $CDCl_3$) - Diastereoisomers **20'** and **20''**



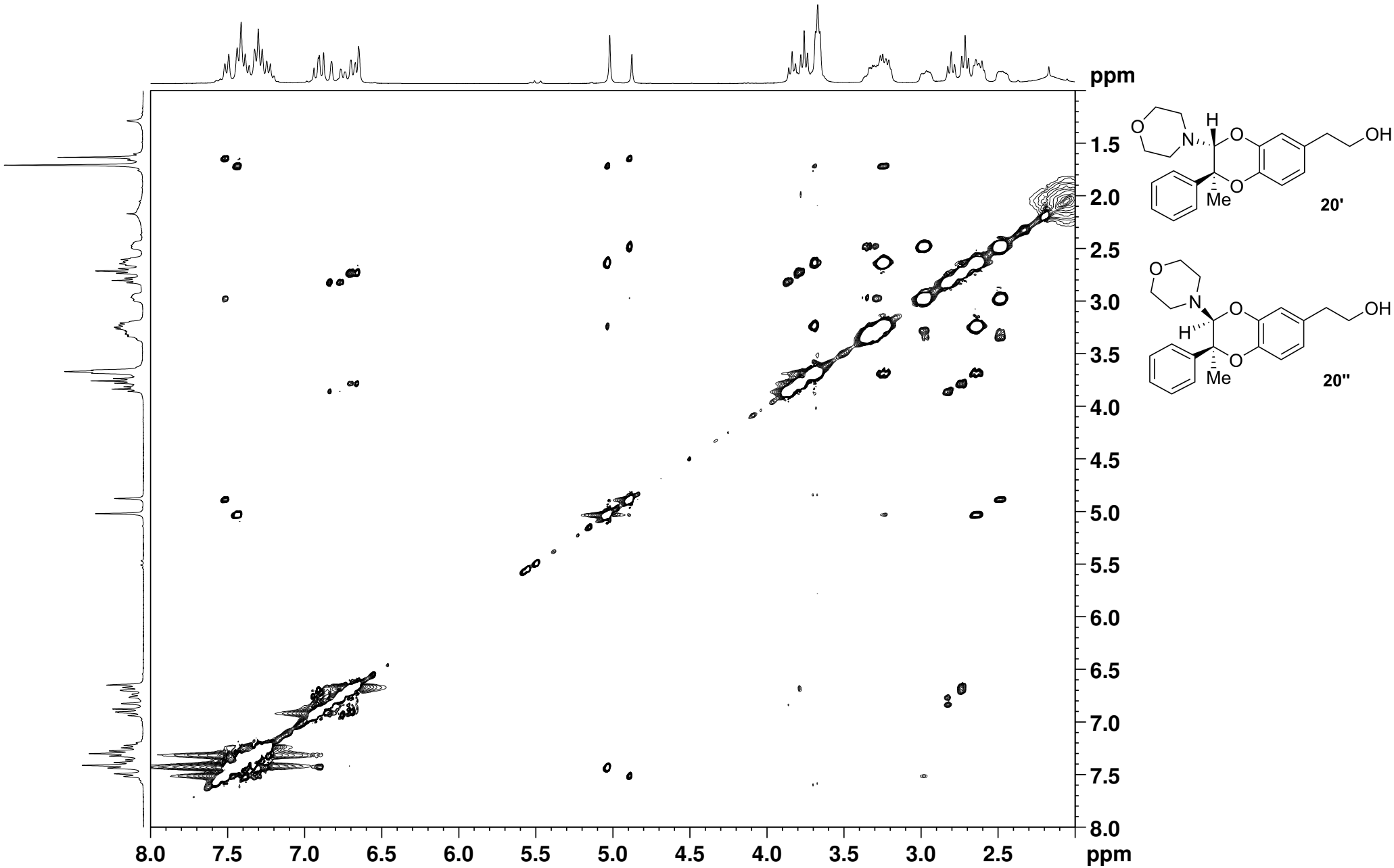
^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Diastereoisomers **20'** and **20''**



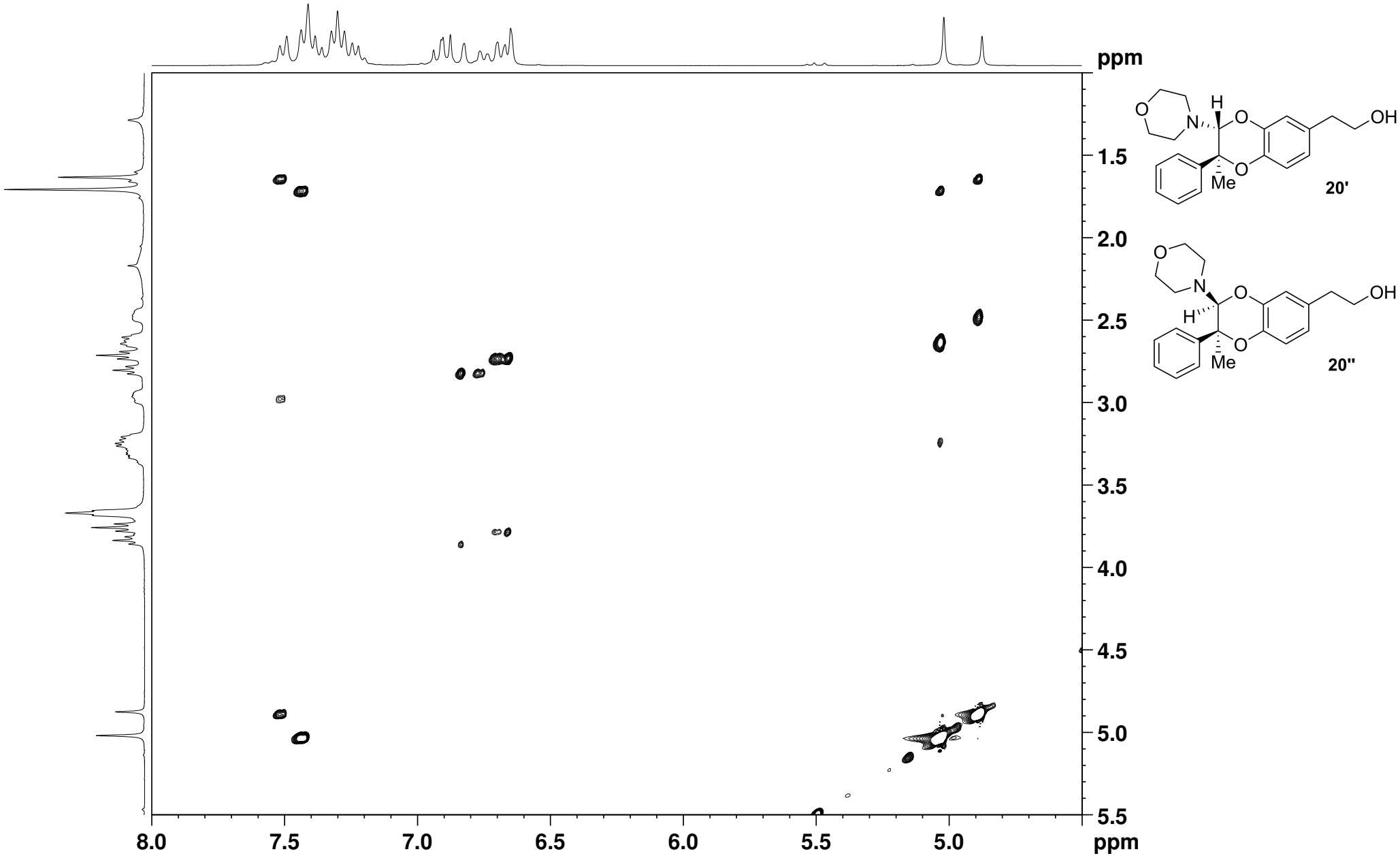
HMBC NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **20'** and **20''**



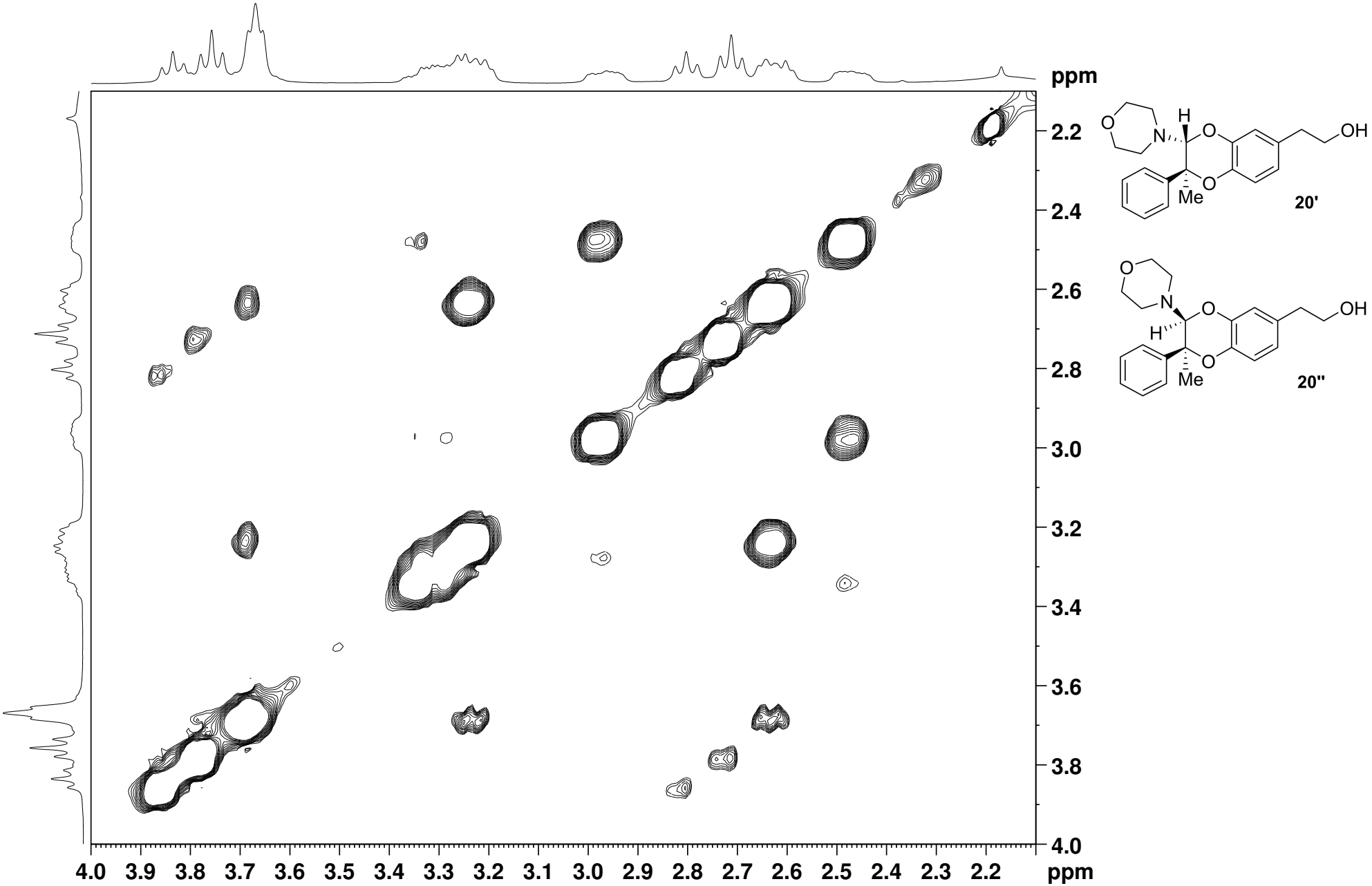
NOESY NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **20'** and **20''**



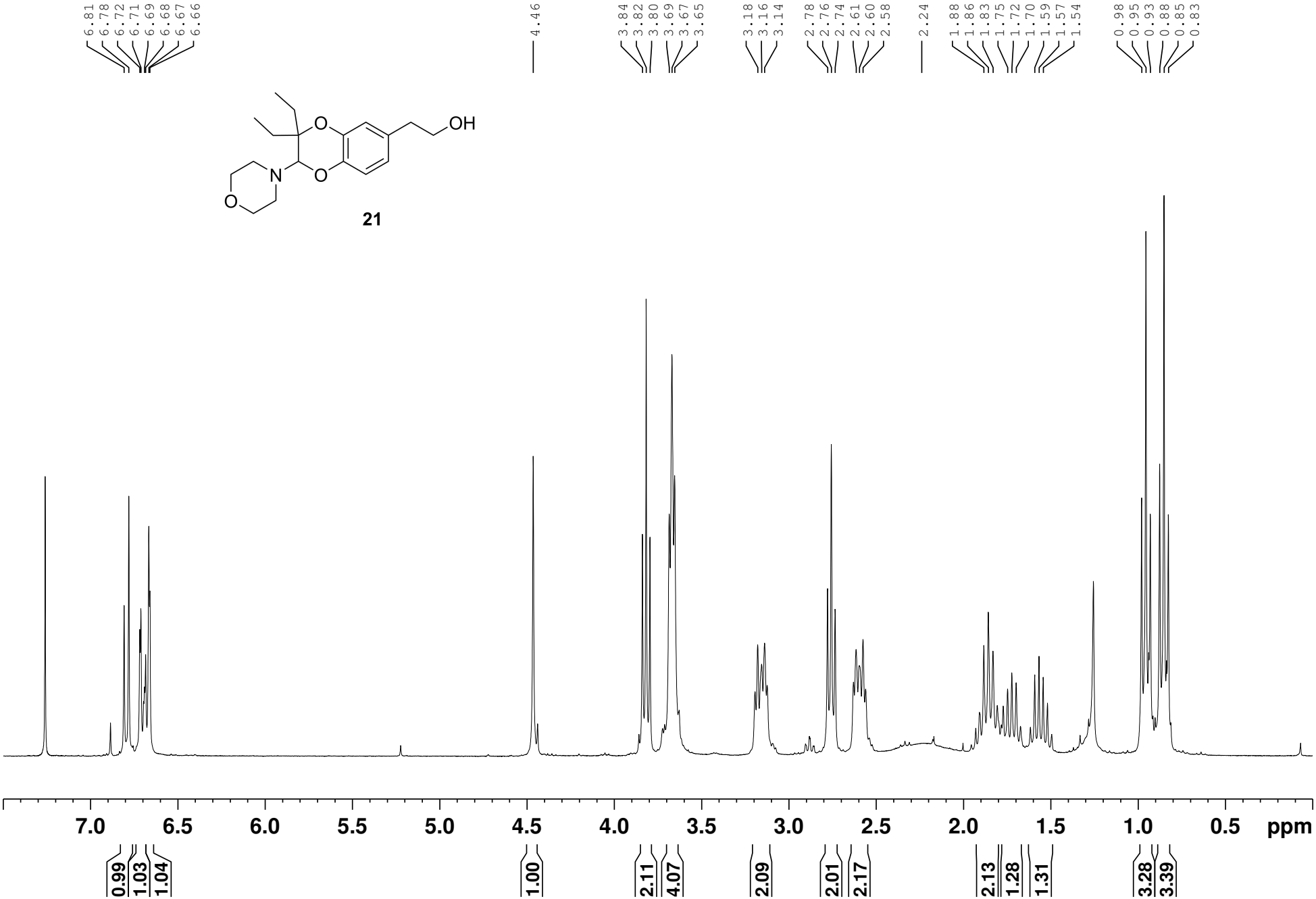
NOESY NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **20'** and **20''**



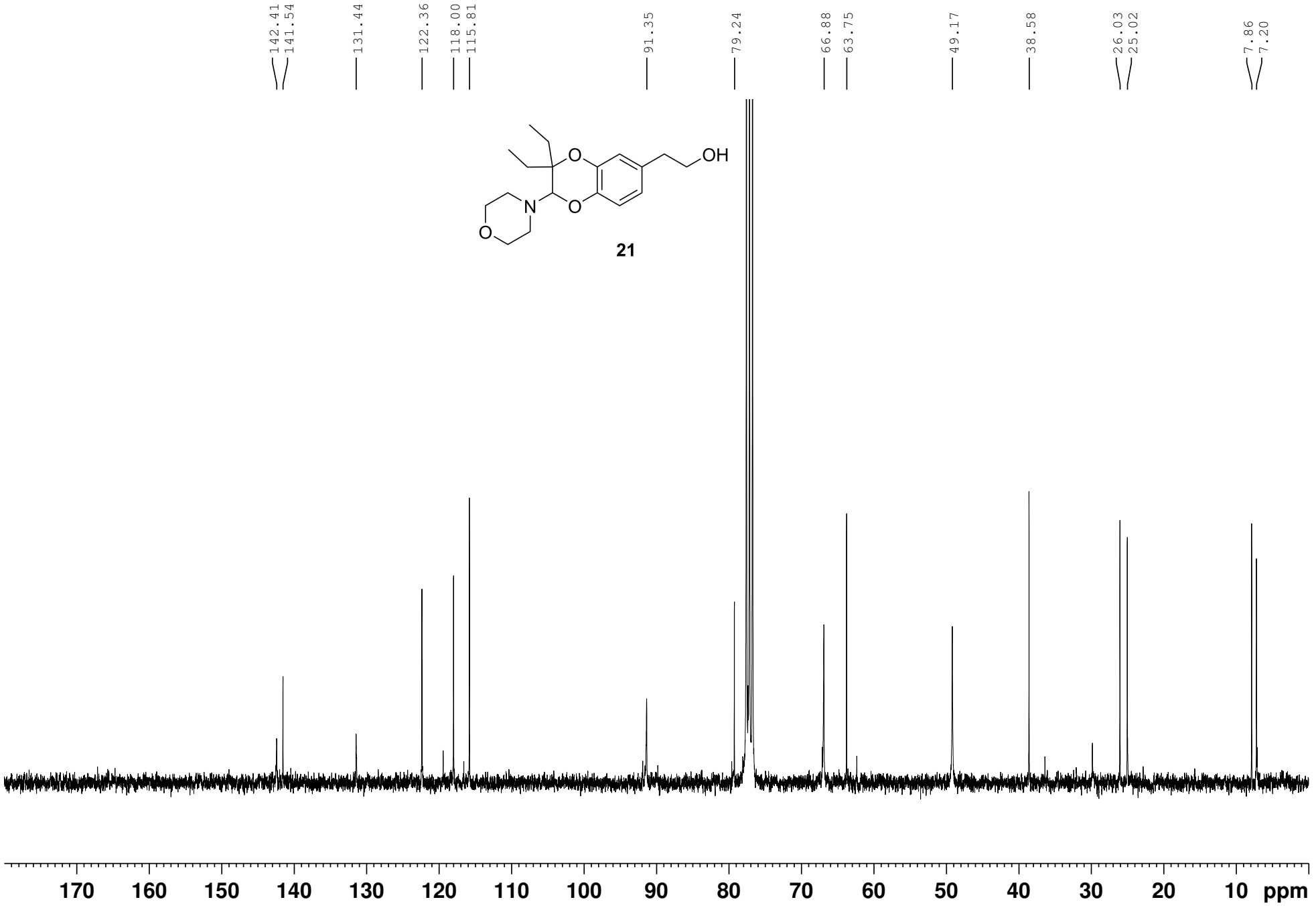
NOESY NMR spectrum (400 MHz, $CDCl_3$) - Diastereoisomers **20'** and **20''**



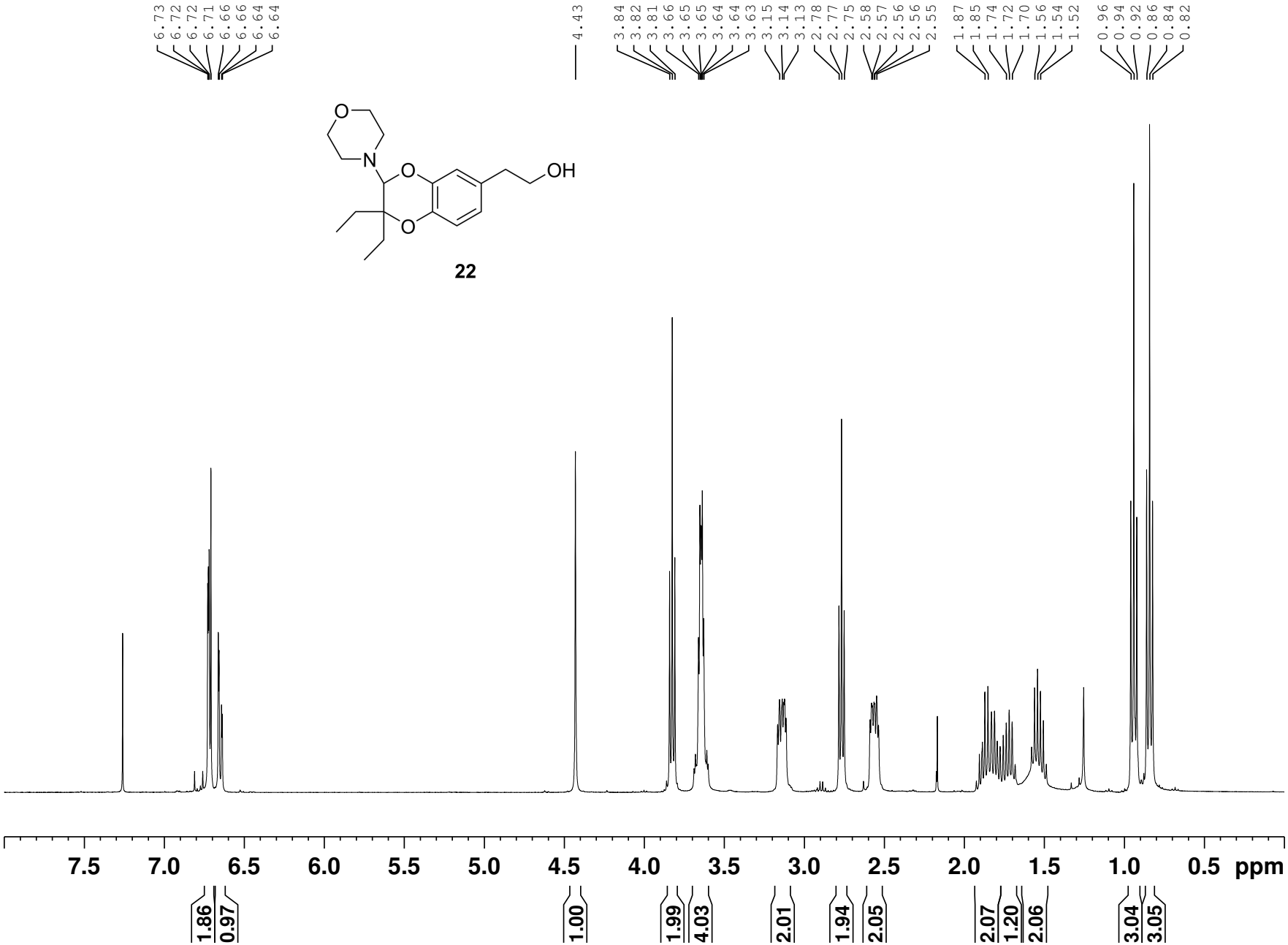
^{1}H NMR spectrum (300 MHz, $CDCl_3$) - Compound **21**



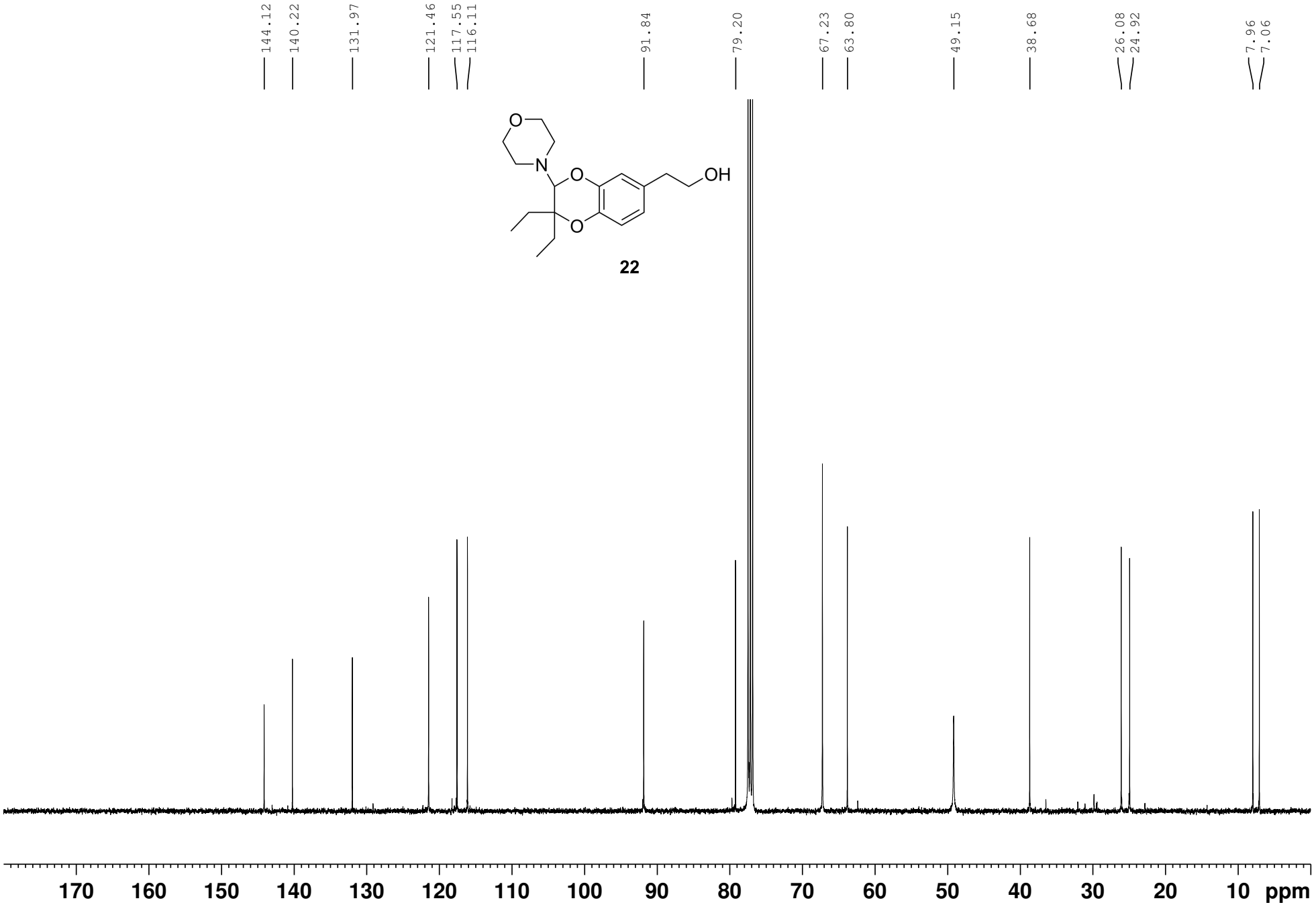
^{13}C NMR spectrum (75MHz, $CDCl_3$) - Compound **21**



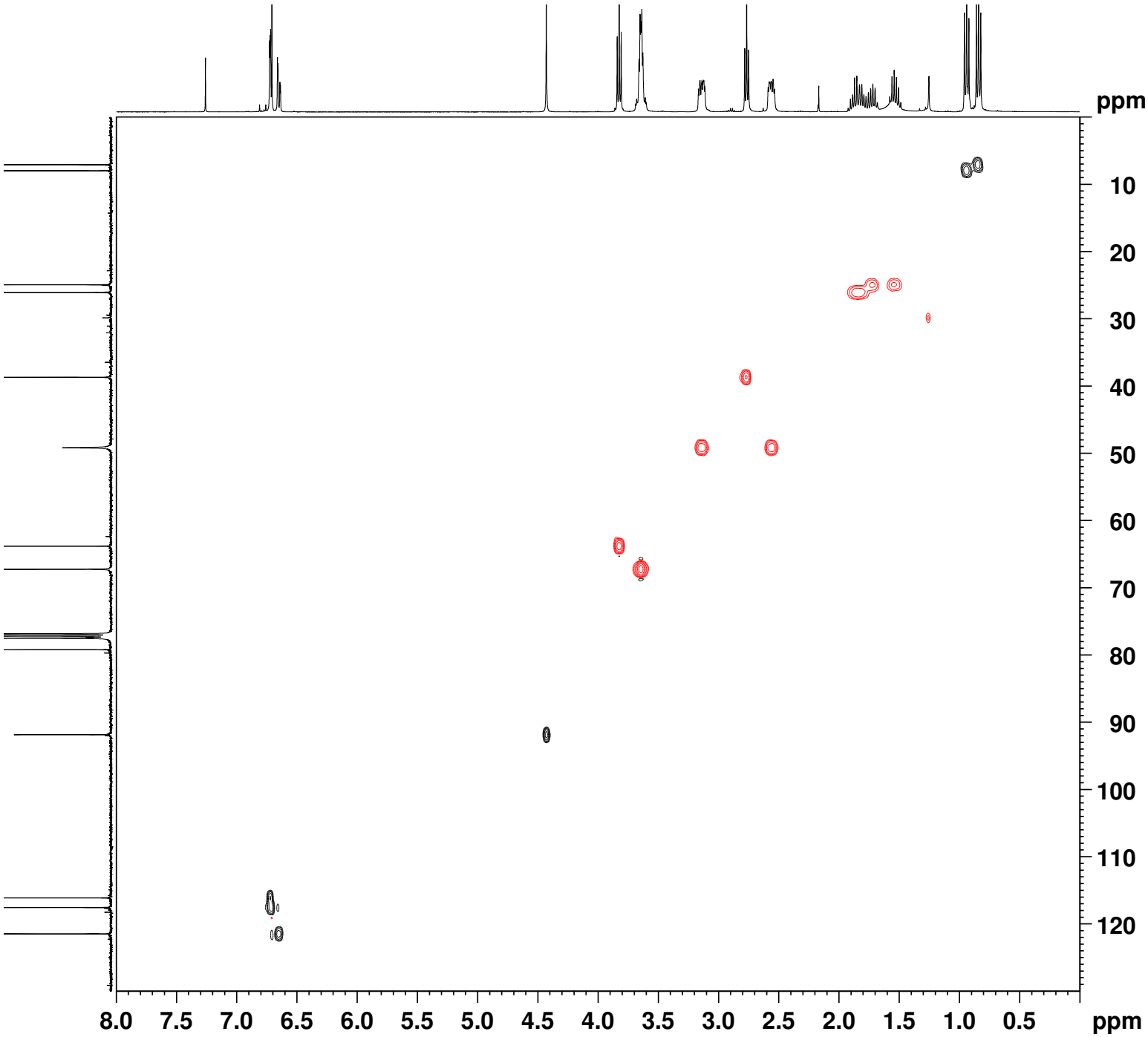
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **22**

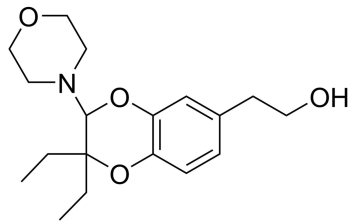


^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Compound **22**



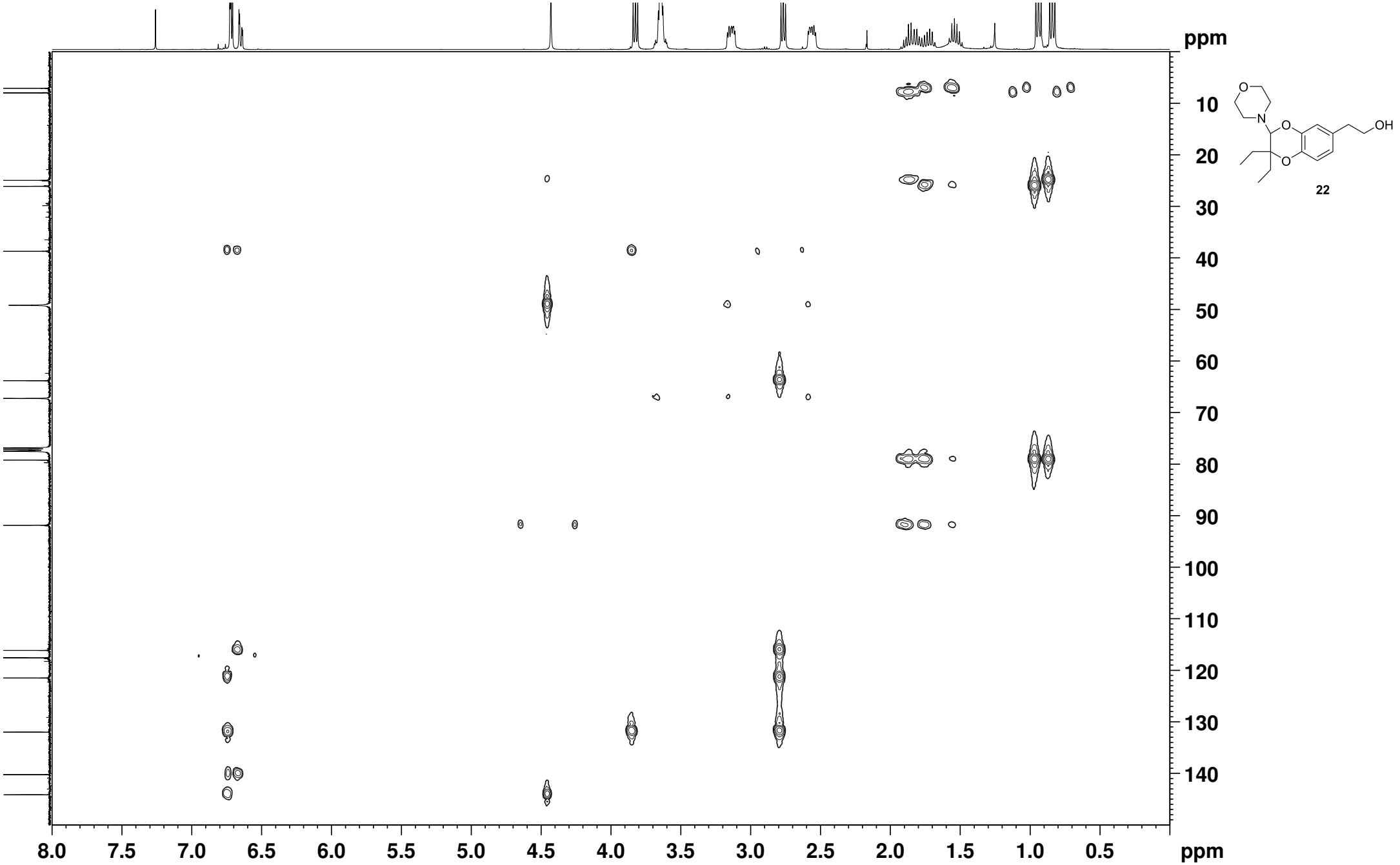
HSQC NMR spectrum (400 MHz, $CDCl_3$) - Compound **22**



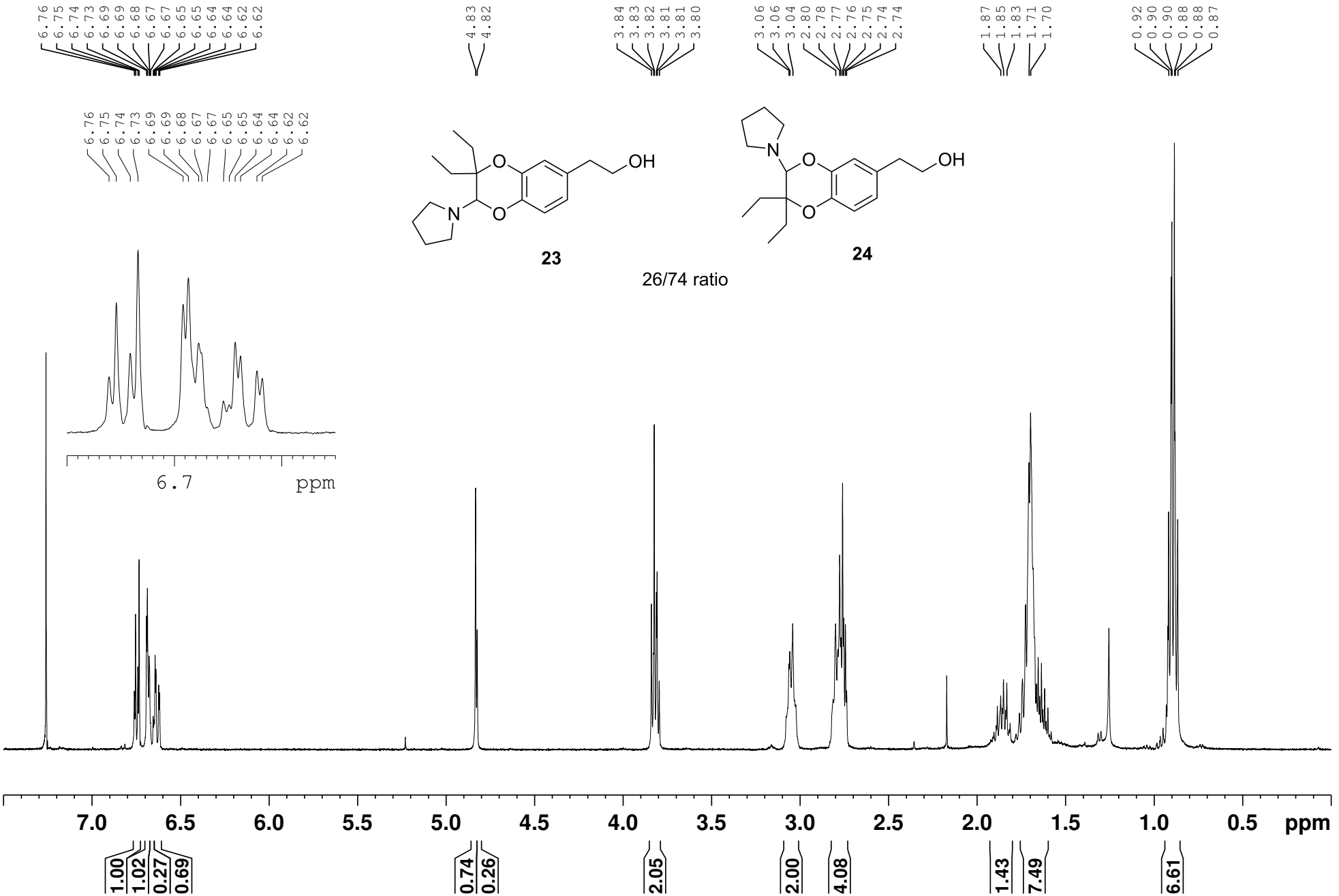


22

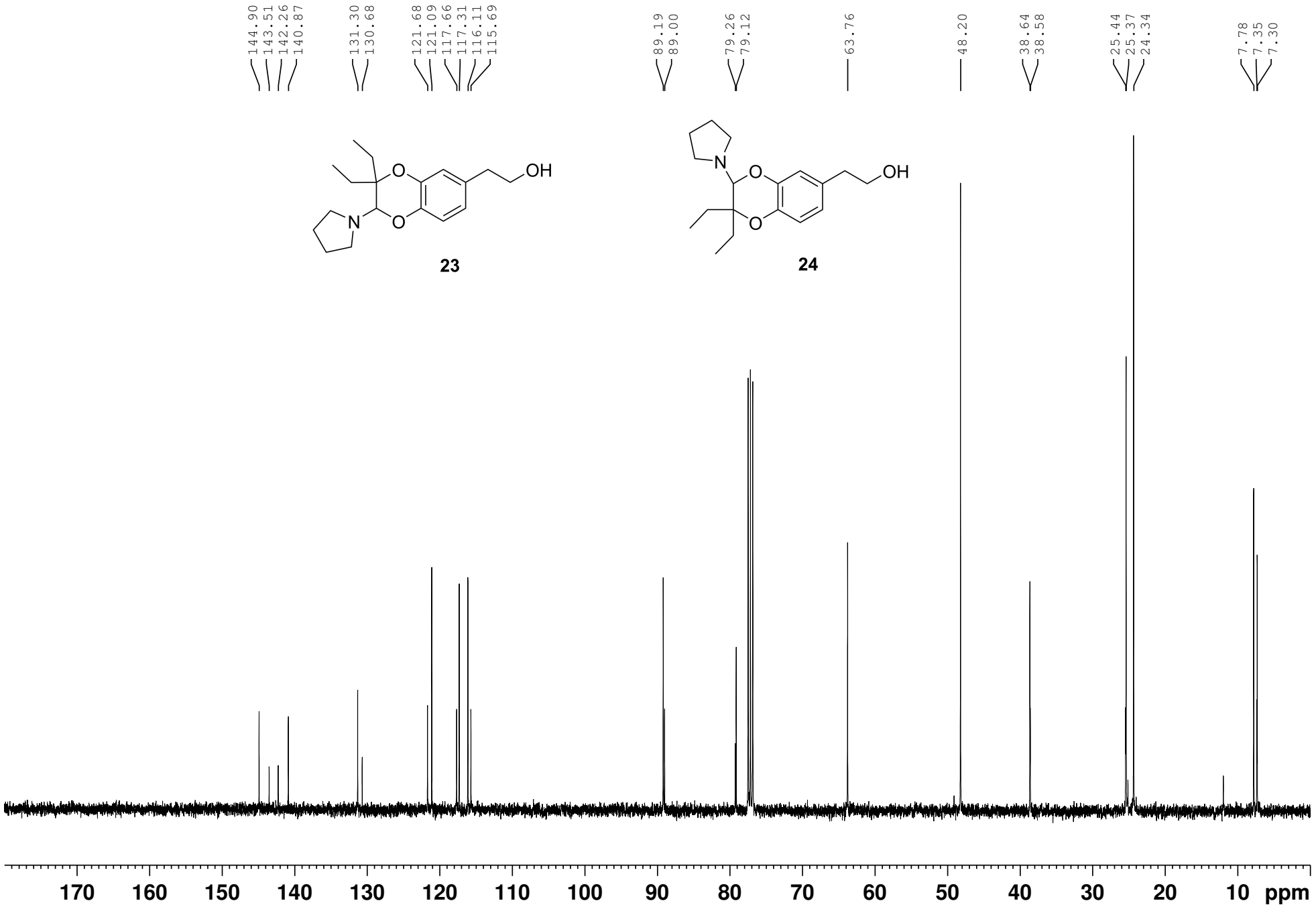
HMBC NMR spectrum (400 MHz, $CDCl_3$) - Compound **22**



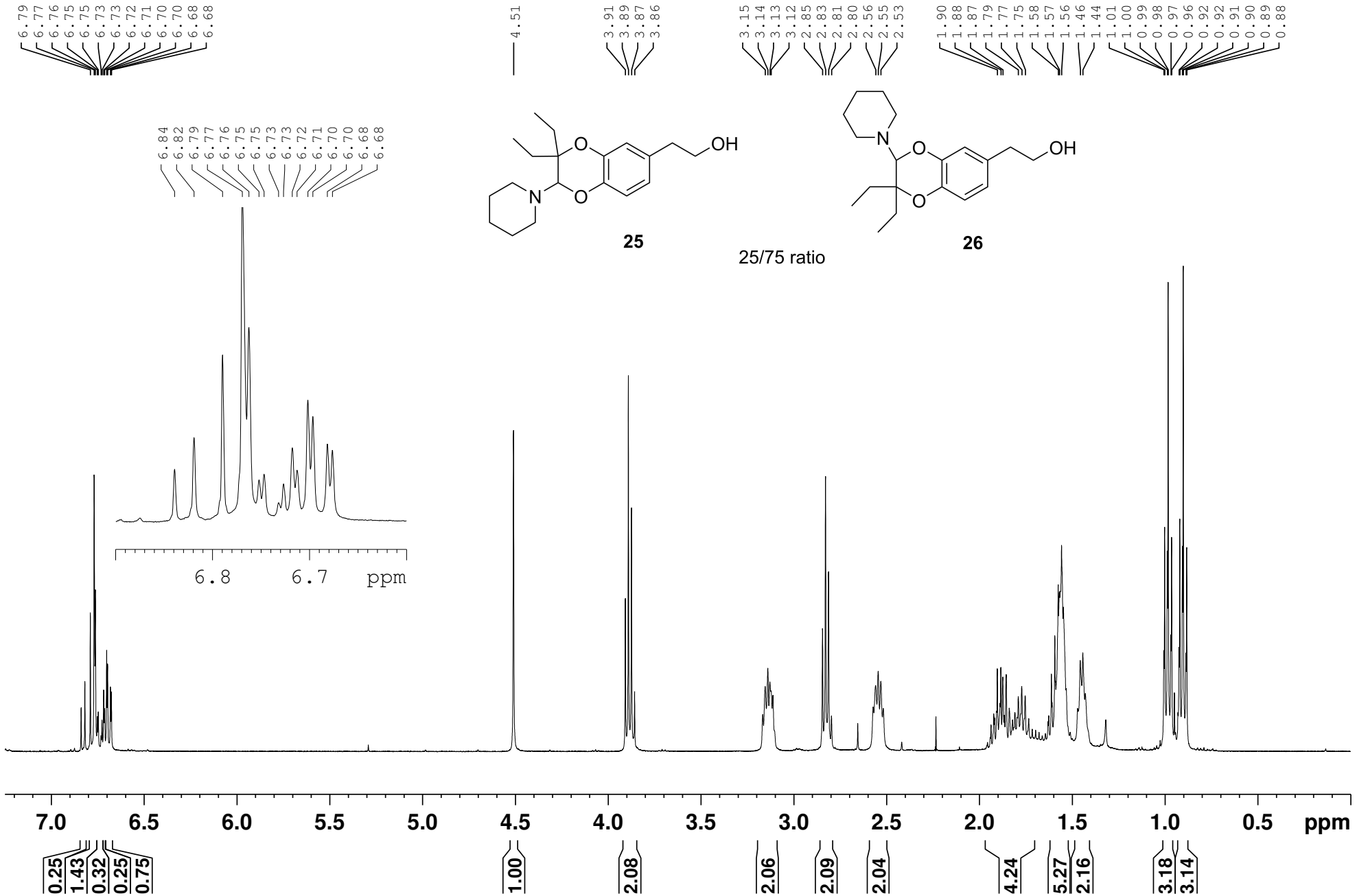
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compounds **23** and **24** after isolation in mixture



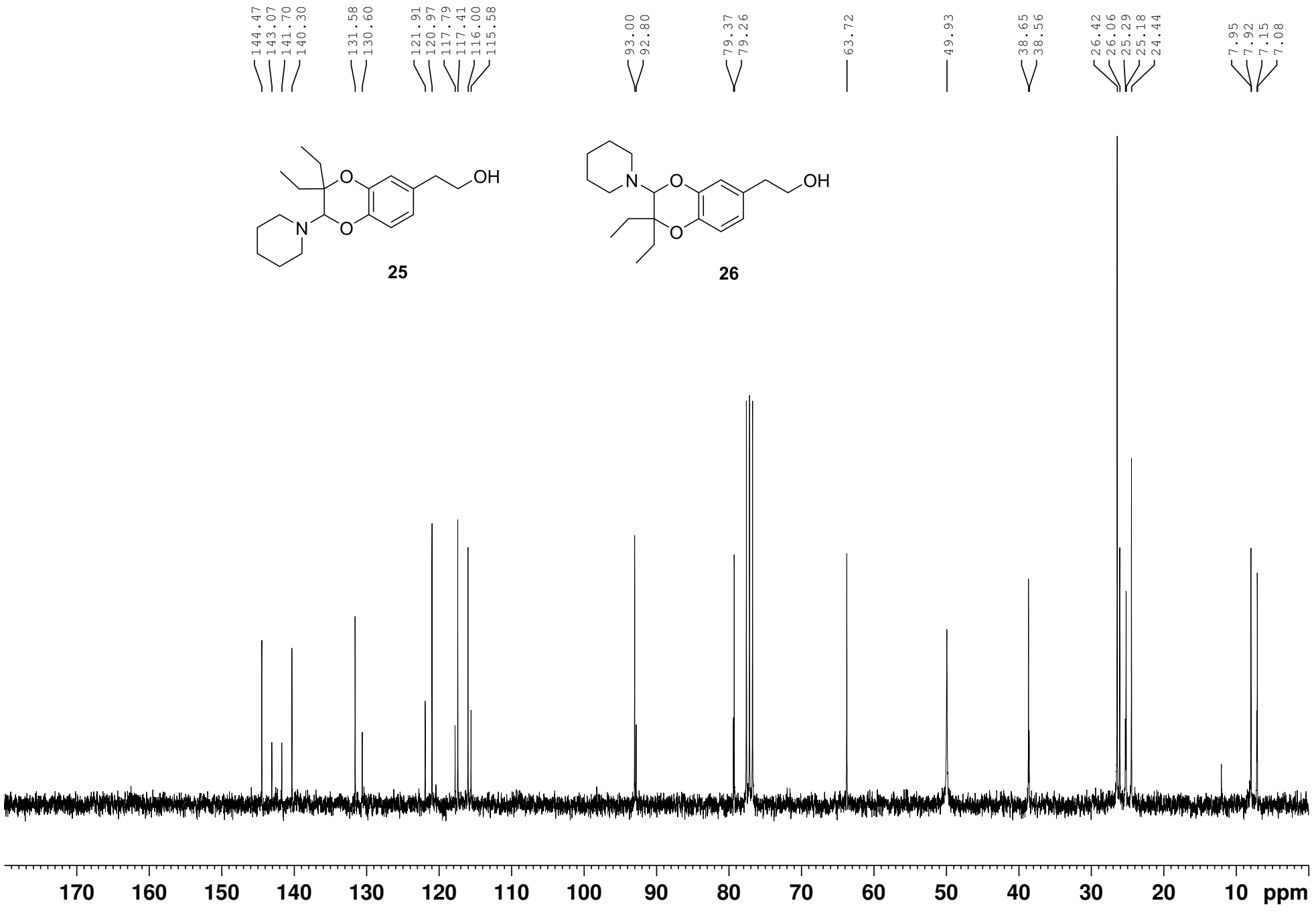
^{13}C NMR spectrum (400 MHz, $CDCl_3$) - Compounds **23** and **24** after isolation in mixture



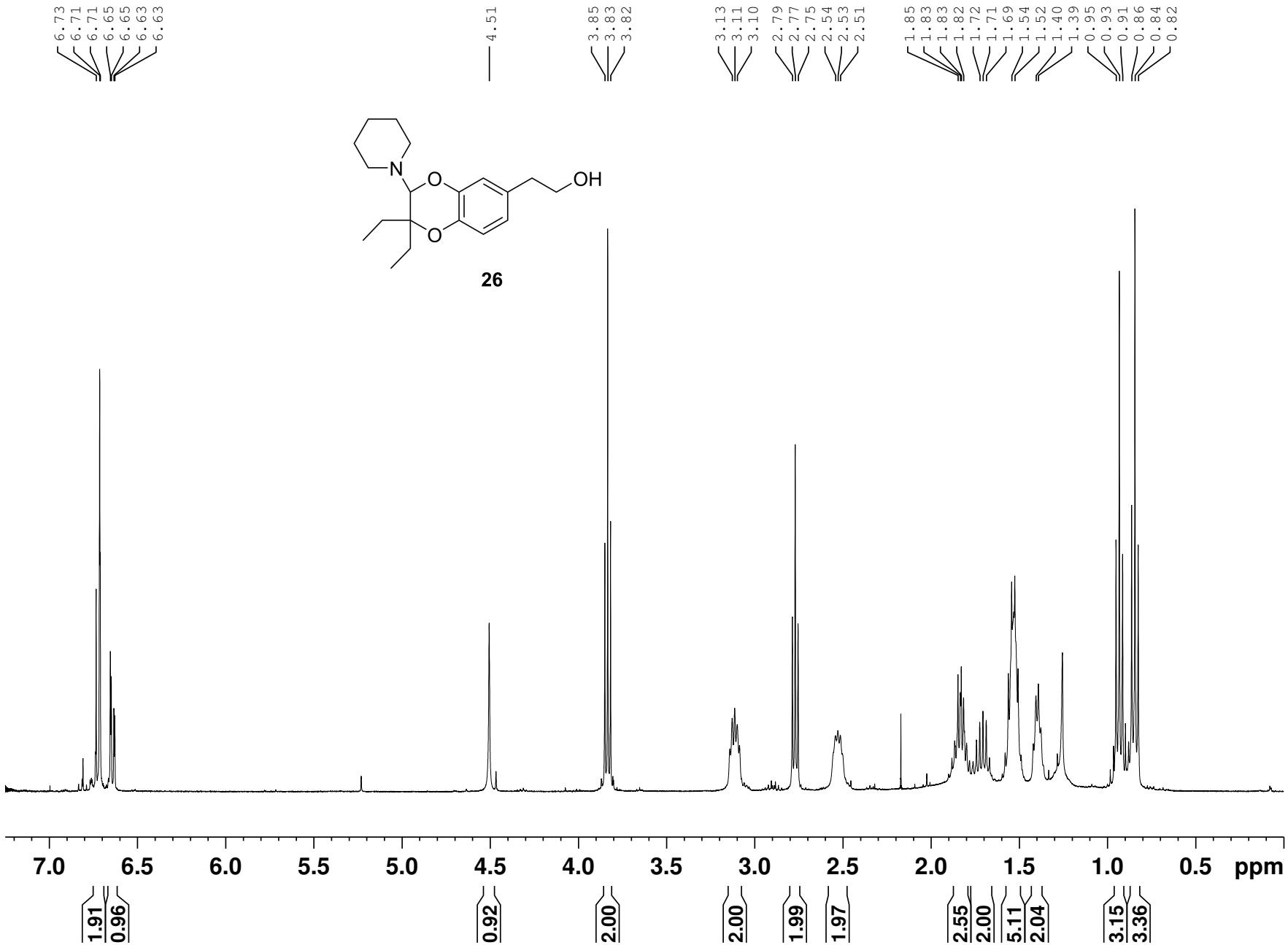
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compounds **25** and **26** after isolation in mixture



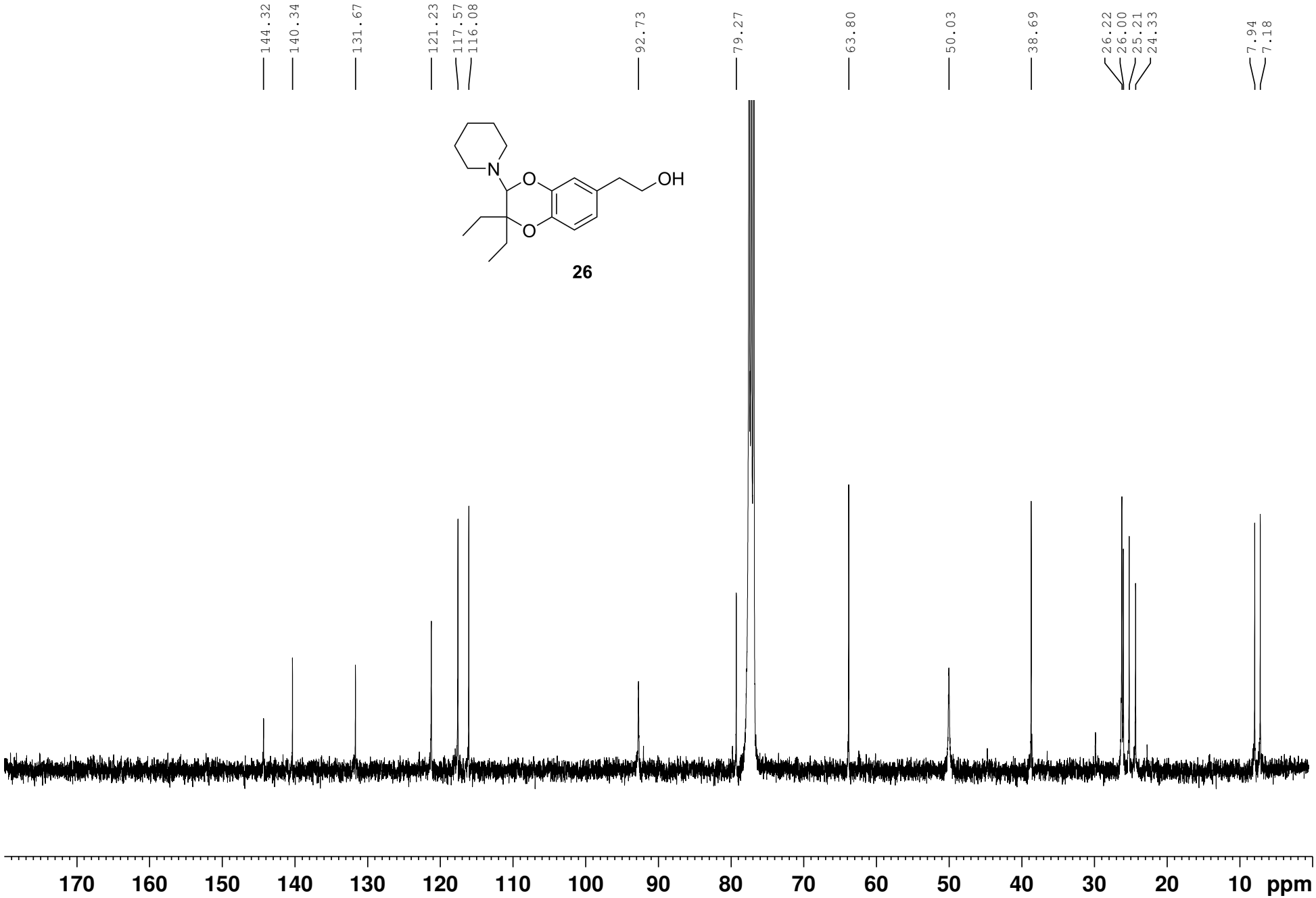
^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Compounds **25** and **26** after isolation in mixture



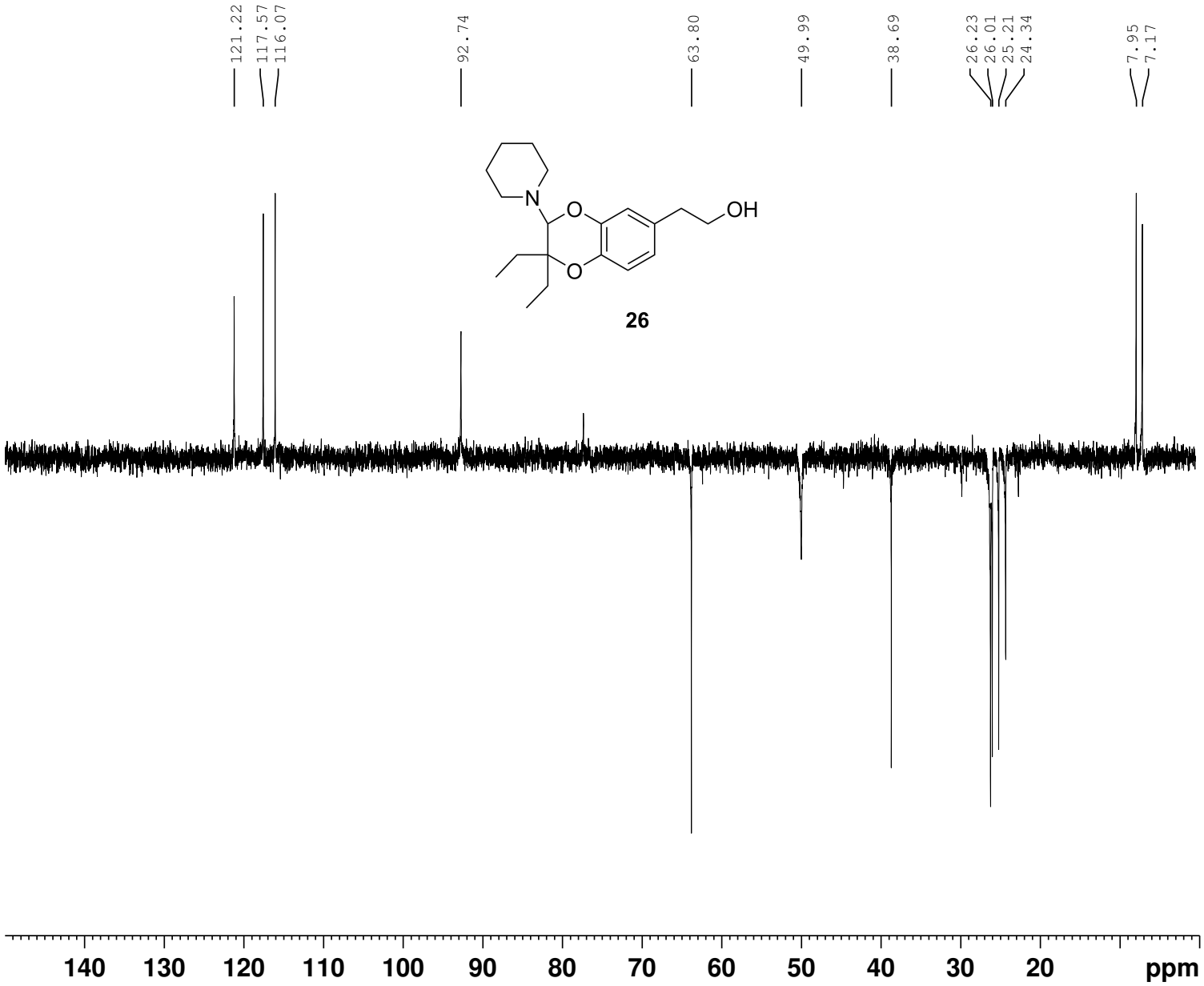
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compound **26**



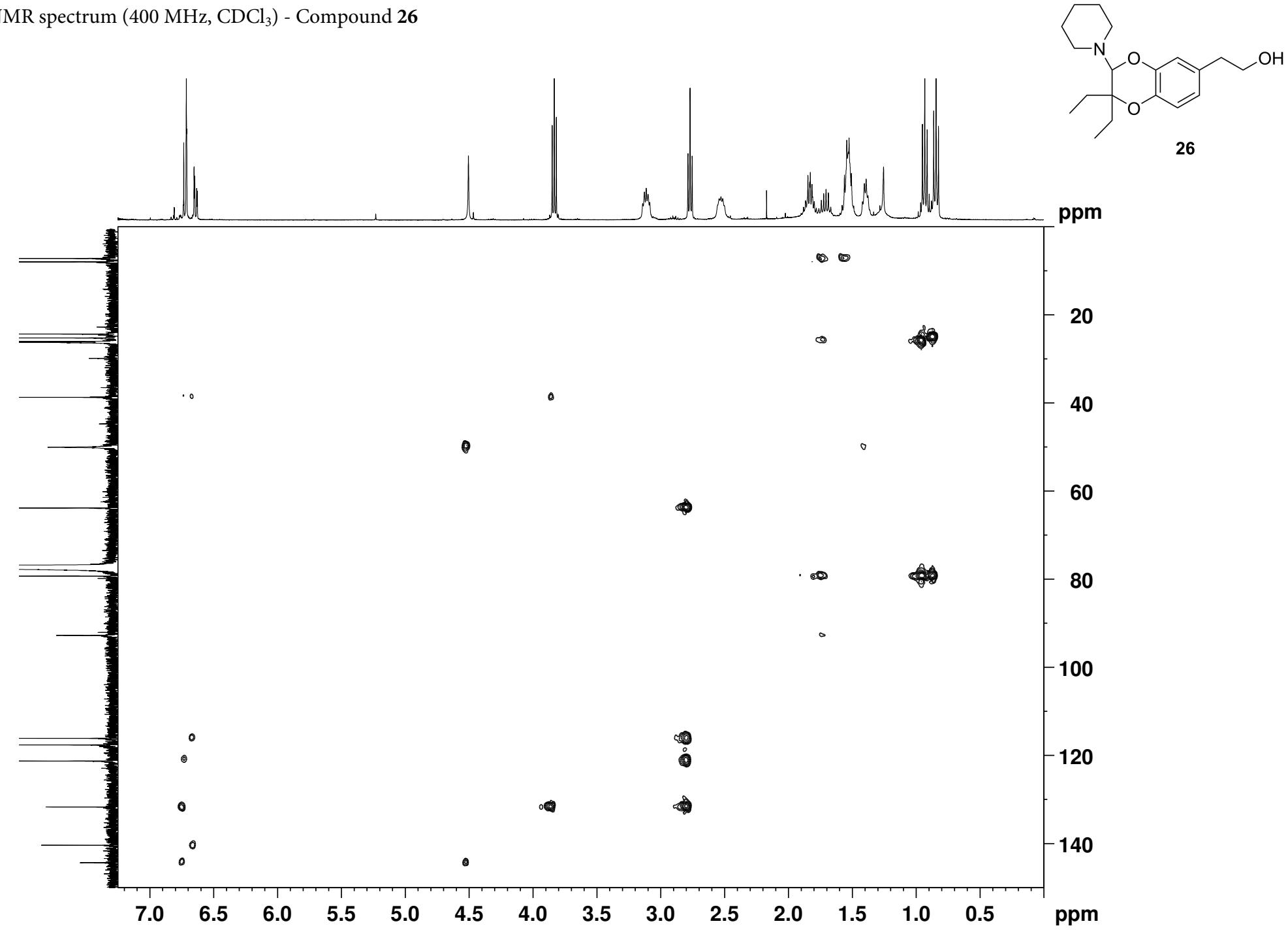
^{13}C NMR spectrum (100 MHz, $CDCl_3$) - Compound **26**



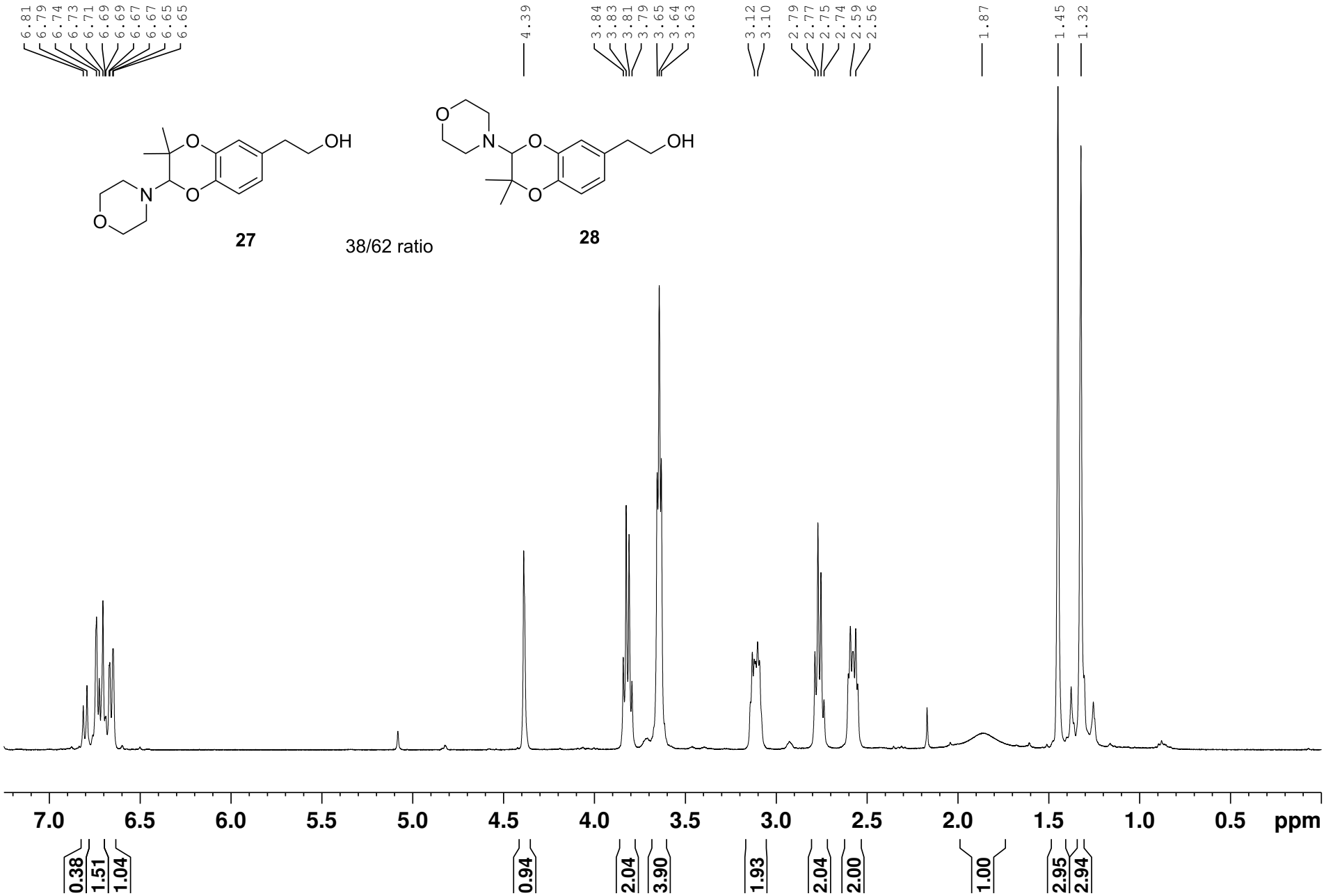
DEPT NMR experiment (100 MHz, $CDCl_{3)}$ - Compound **26**



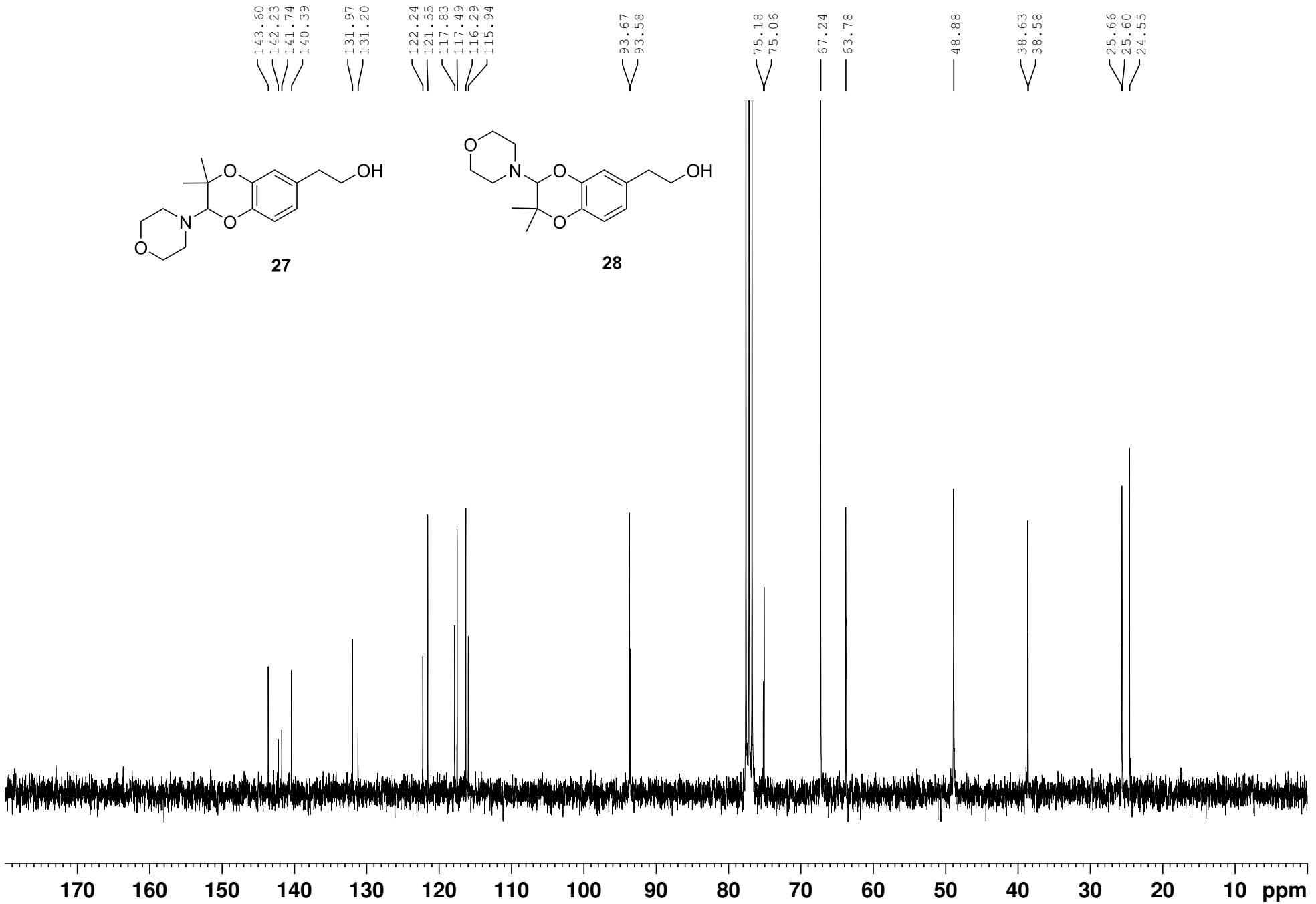
HMBC NMR spectrum (400 MHz, $CDCl_3$) - Compound **26**



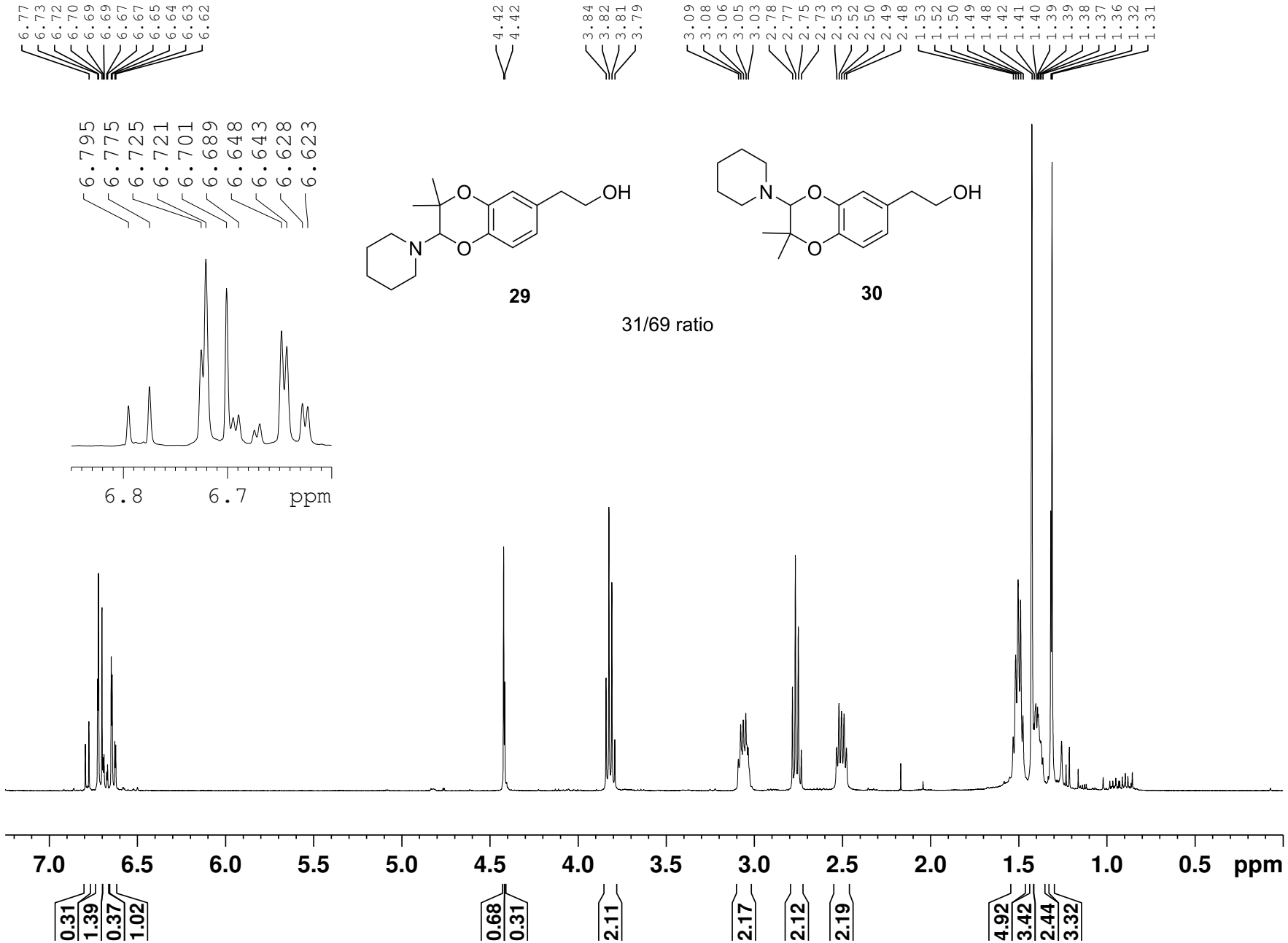
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compounds **27** and **28** after isolation in mixture



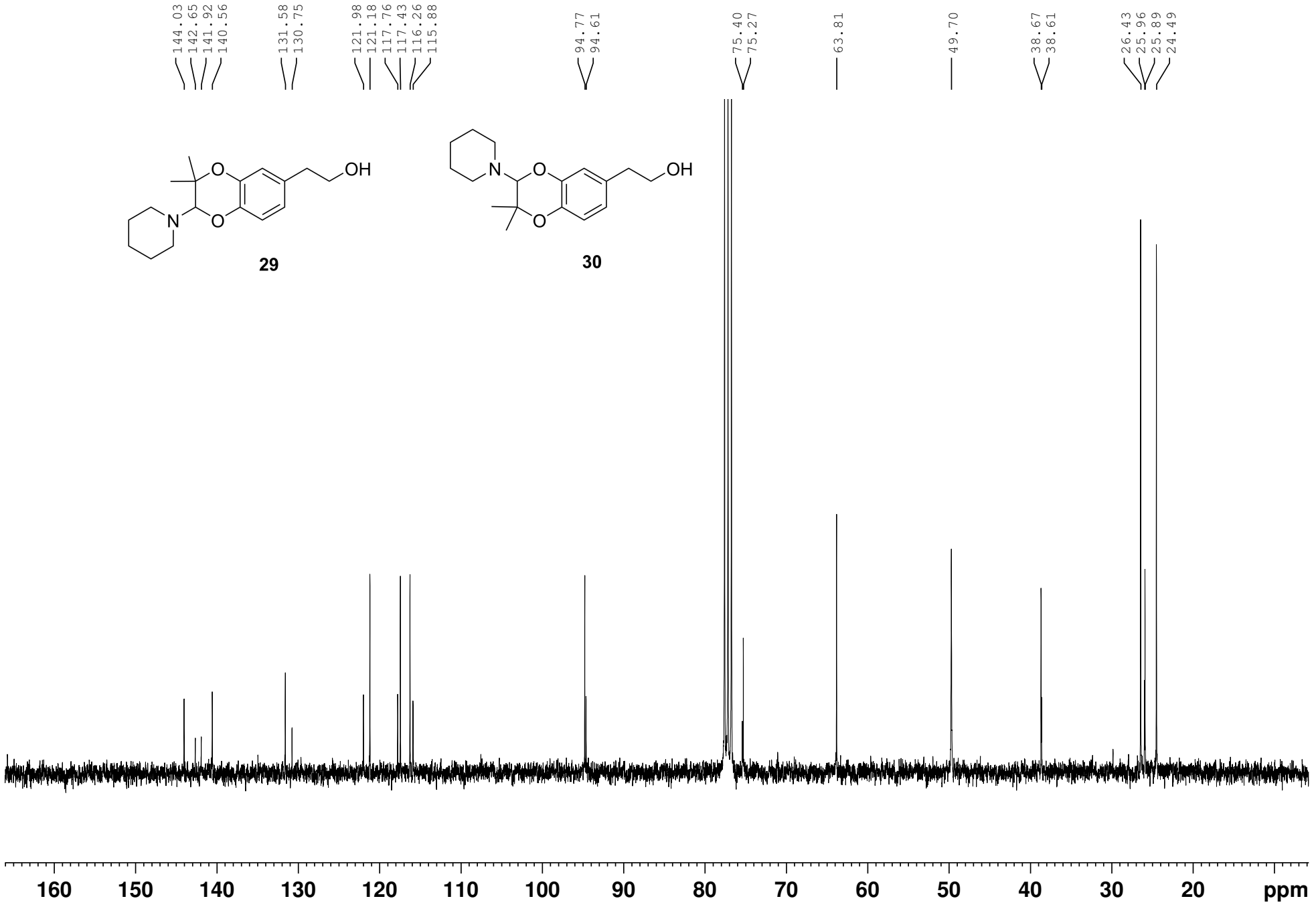
^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Compounds **27** and **28** after isolation in mixture



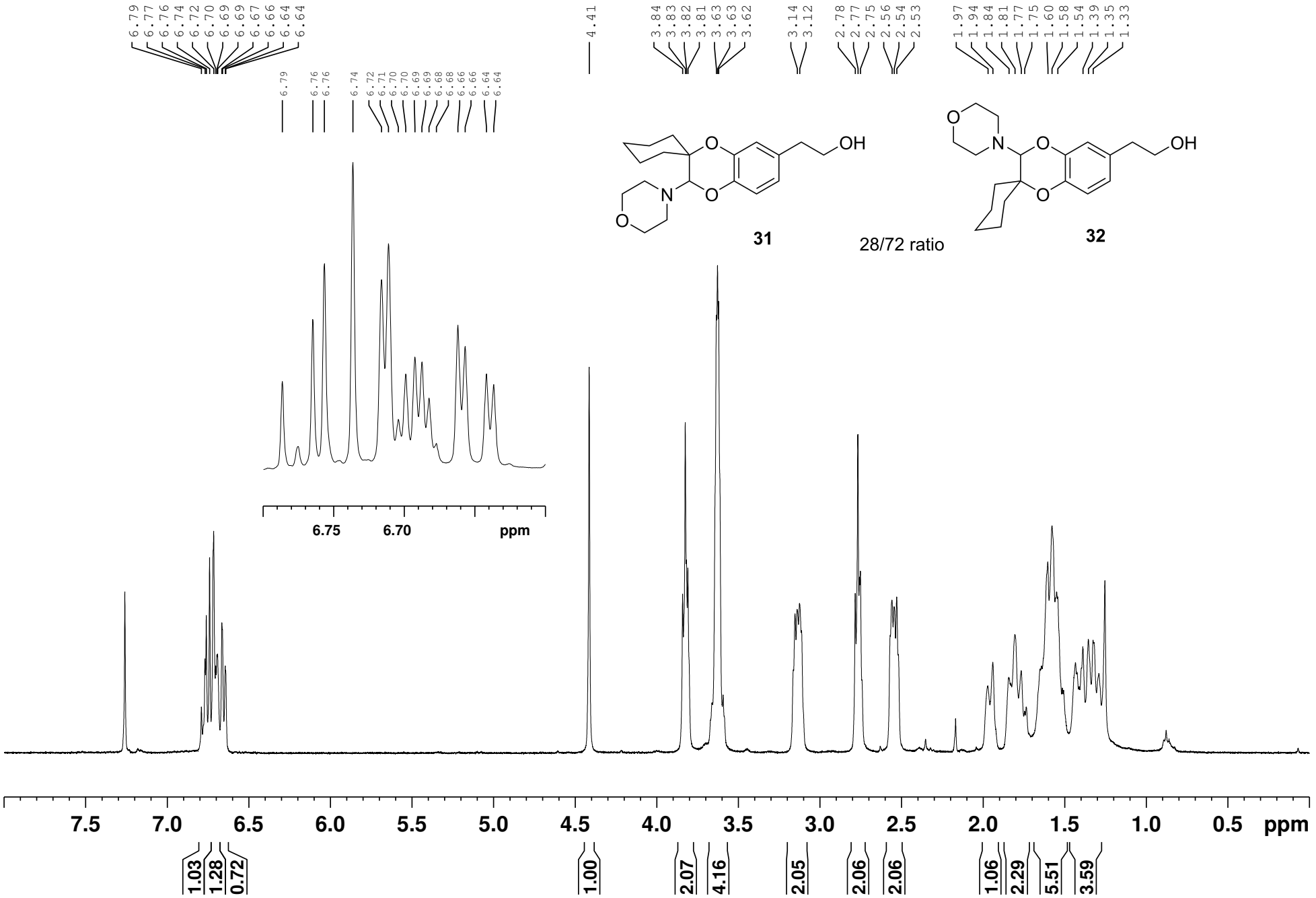
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compounds **29** and **30** after isolation in mixture



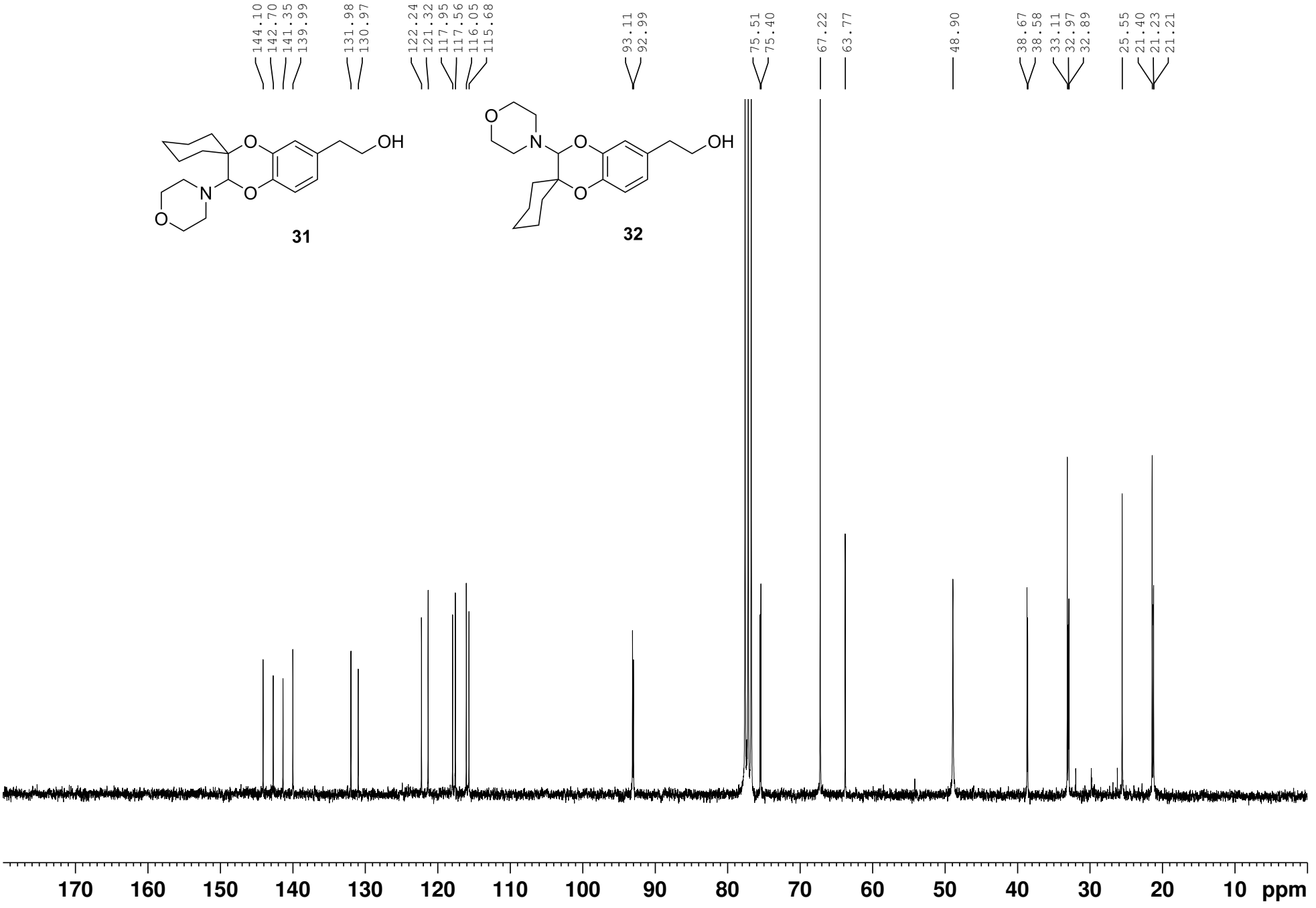
^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Compounds **29** and **30** after isolation in mixture



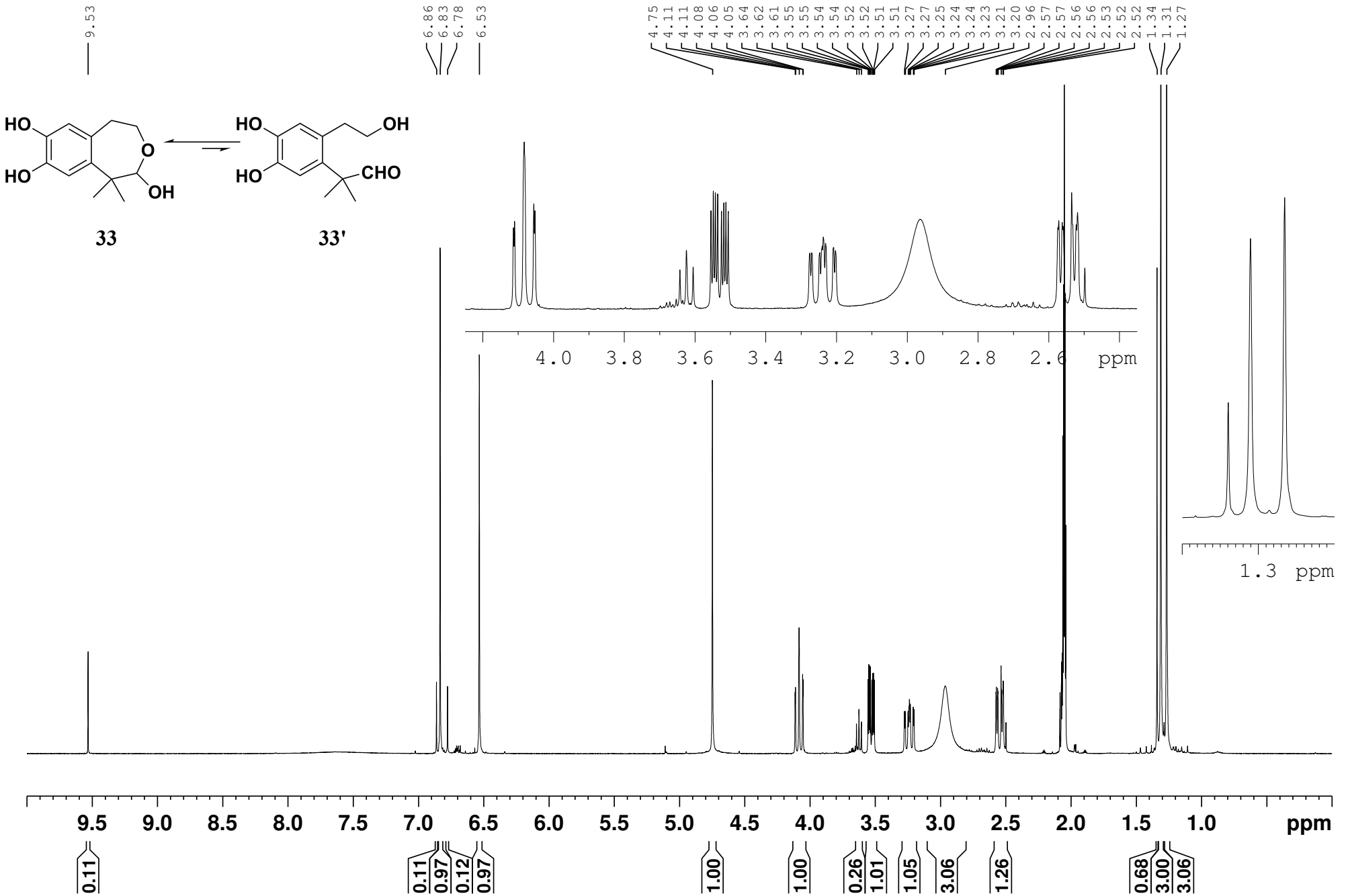
^{1}H NMR spectrum (400 MHz, $CDCl_3$) - Compounds **31** and **32** after isolation in mixture



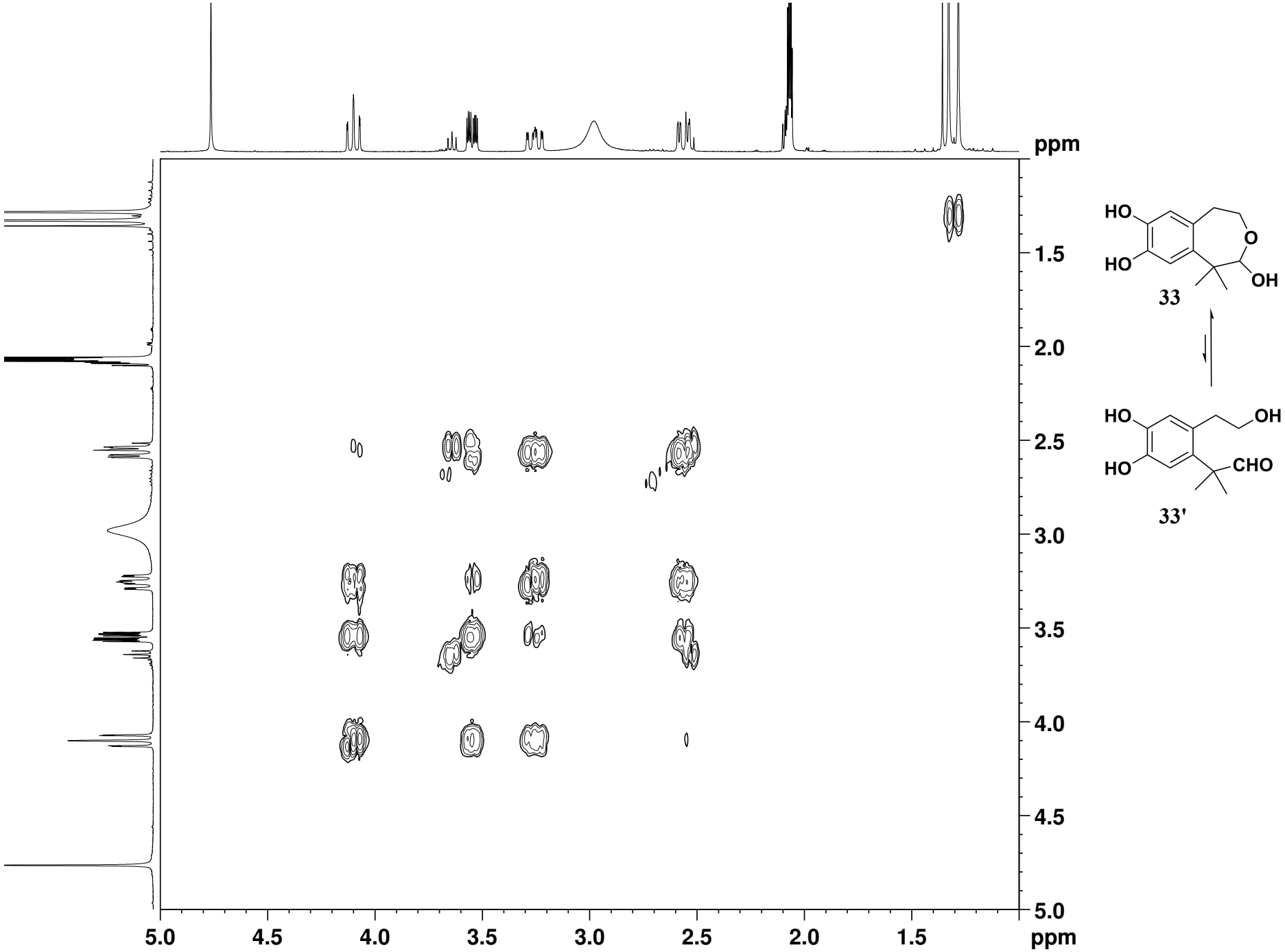
^{13}C NMR spectrum (75 MHz, $CDCl_3$) - Compounds **31** and **32** after isolation in mixture



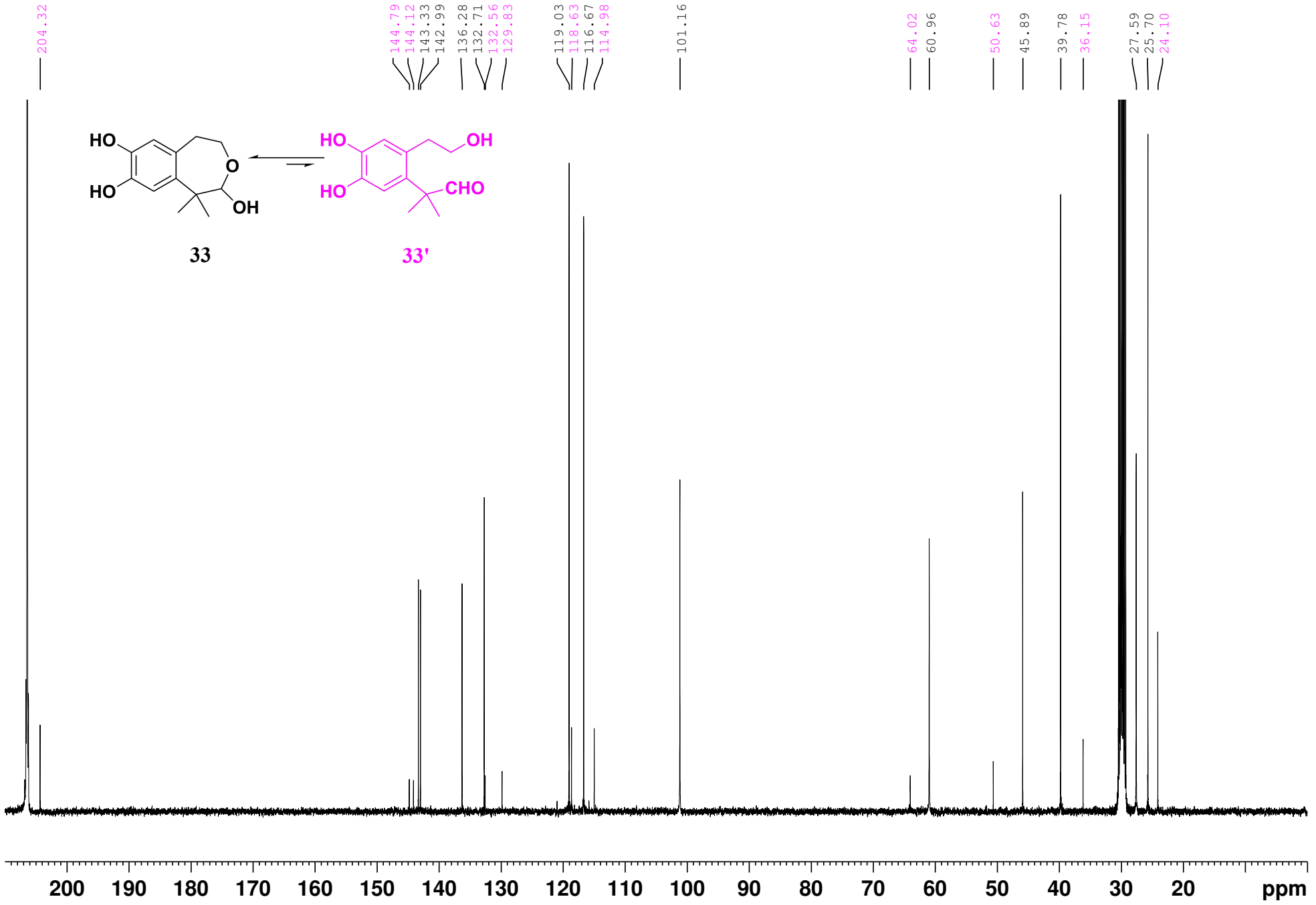
^{1}H NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **33**



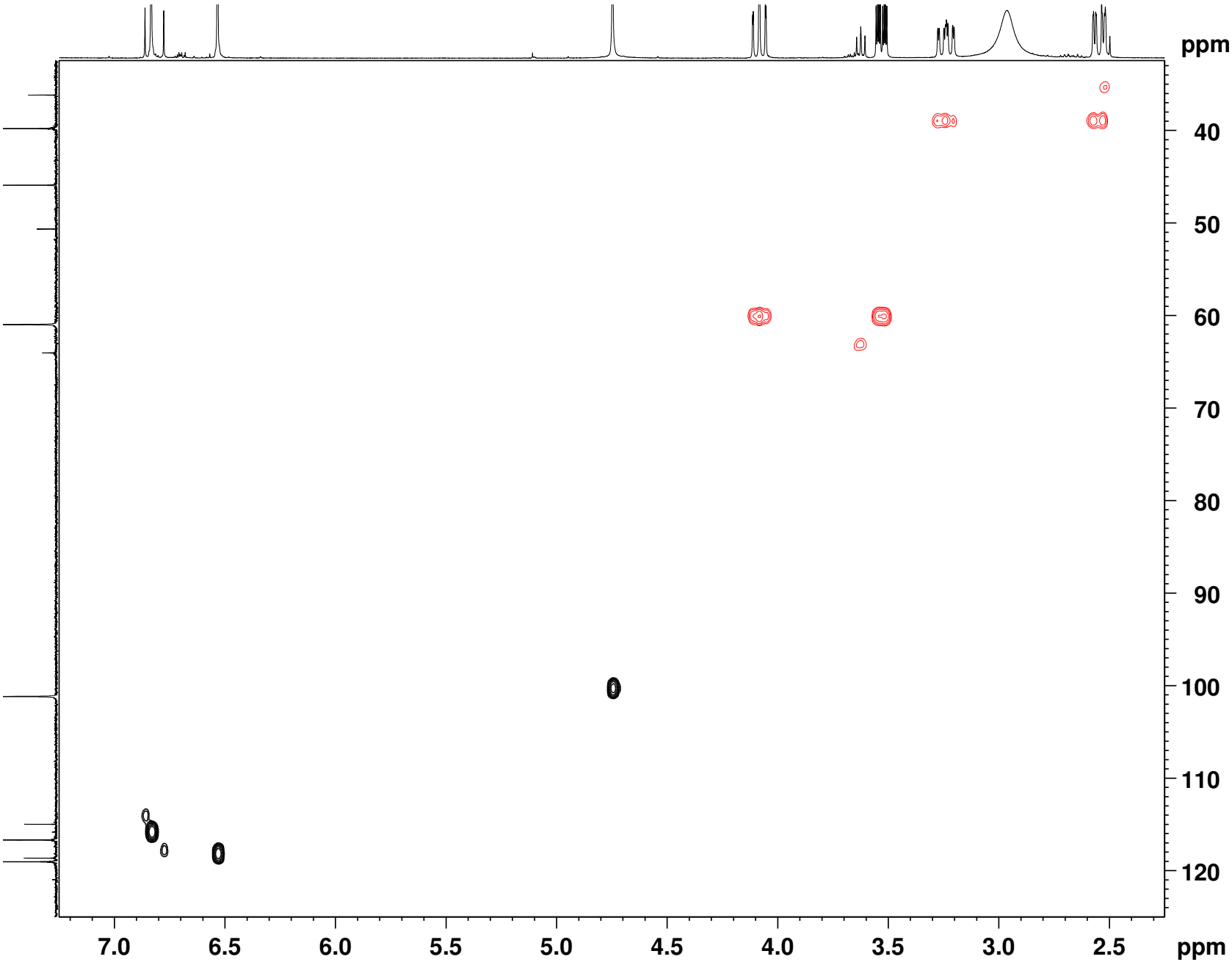
COSY NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **33**

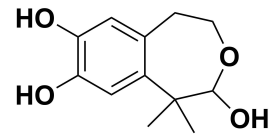


^{13}C NMR spectrum (100 MHz, $(CD_3)_2CO$) - Compound **33**

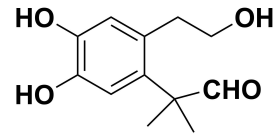


HSQC NMR experiment (100 MHz, $(CD_3)_2CO$) - Compound **33**



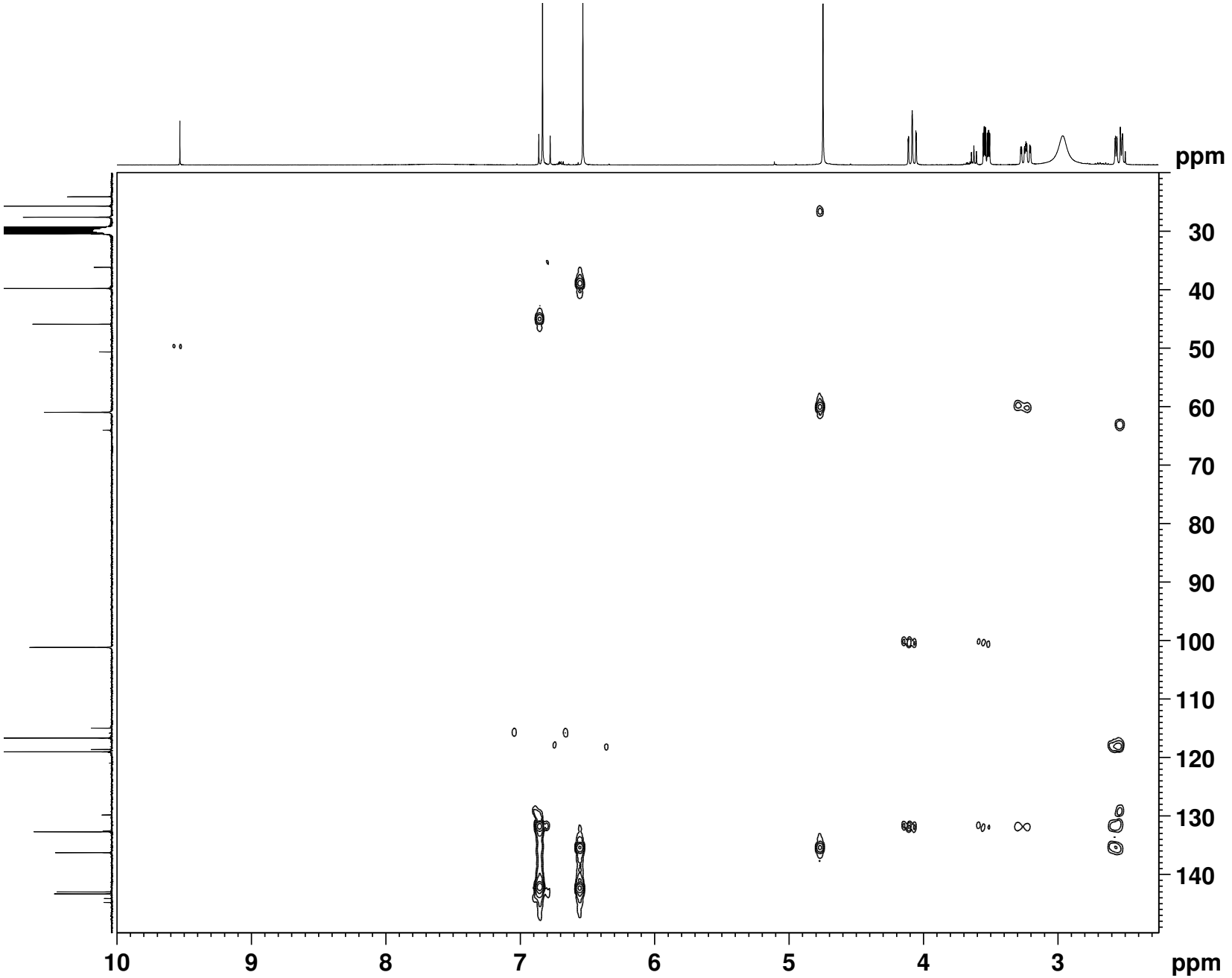


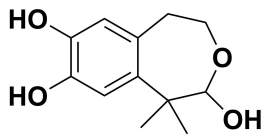
33



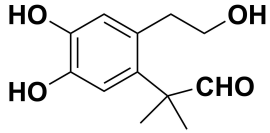
33'

HMBC NMR experiment (100 MHz, $(CD_3)_2CO$) - Compound **33**



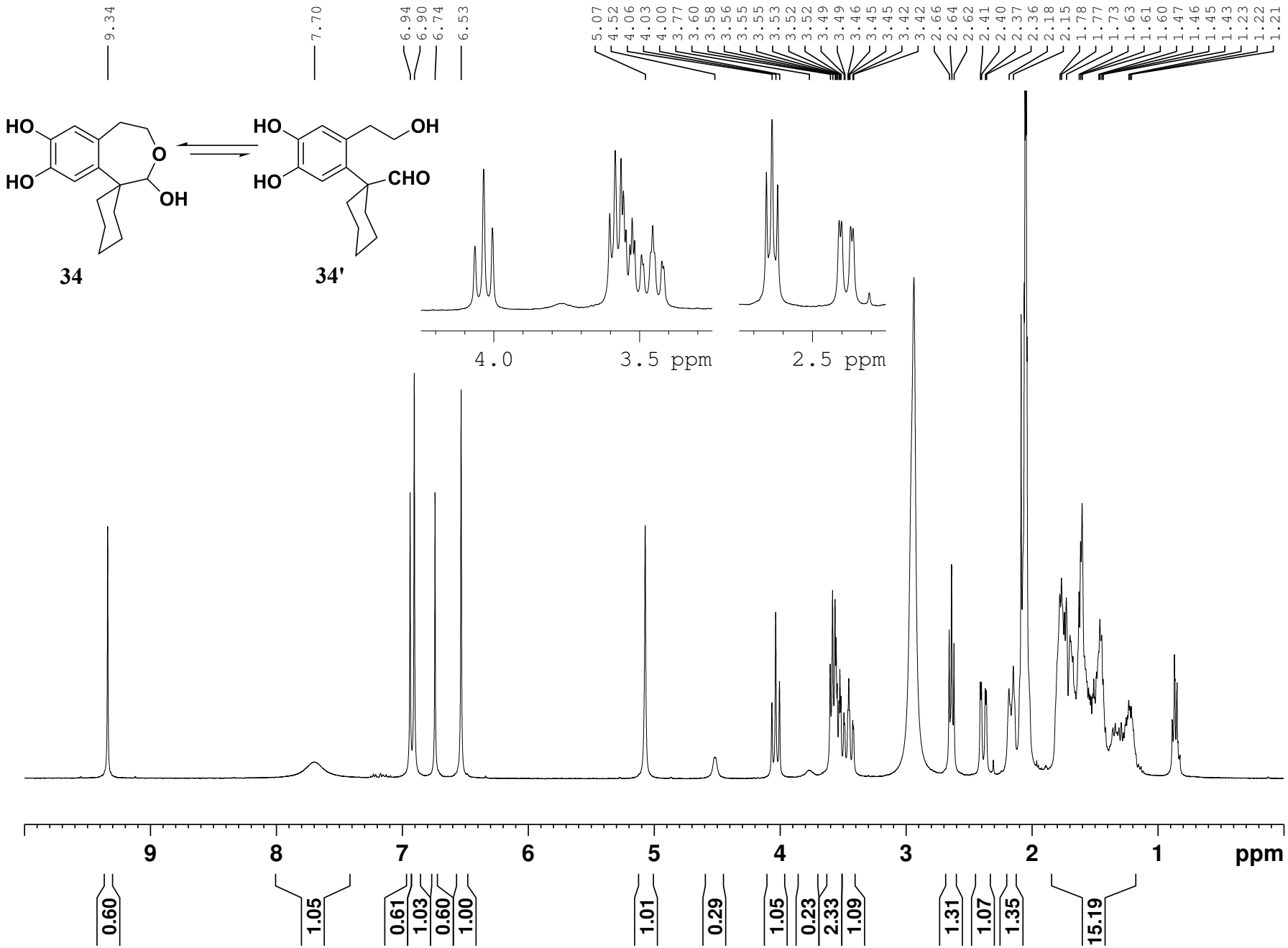


33

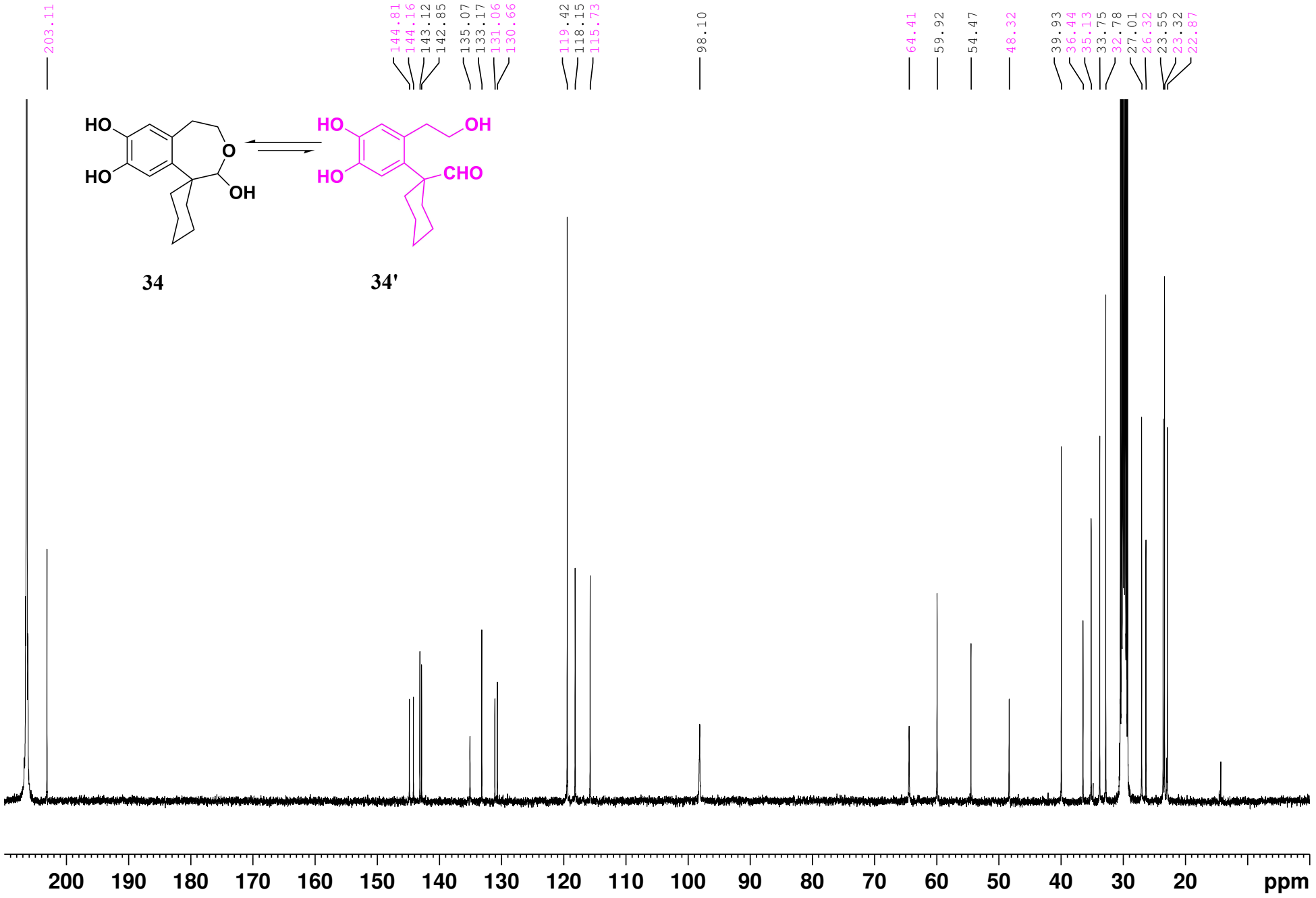


33'

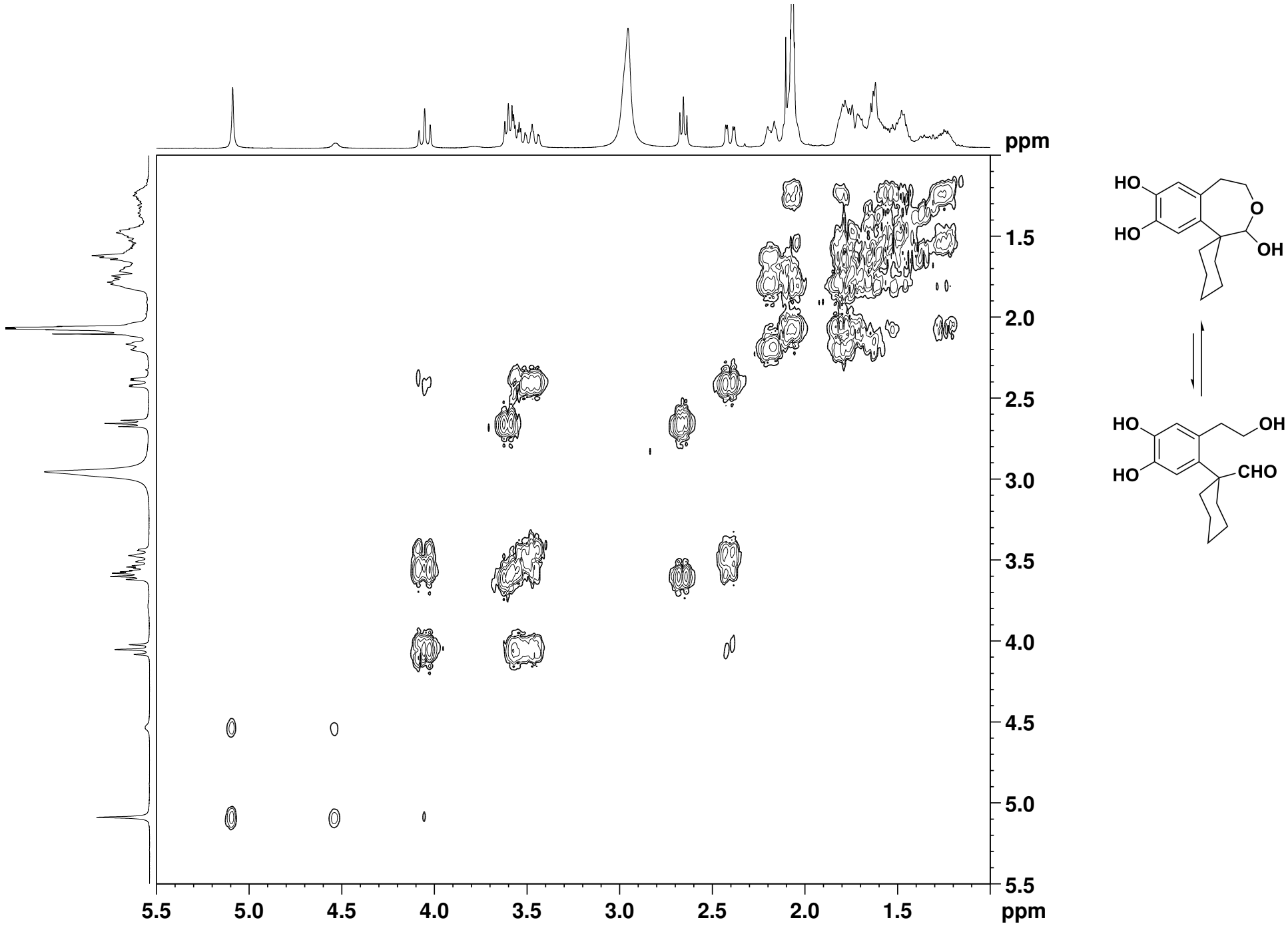
^{1}H NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **34**



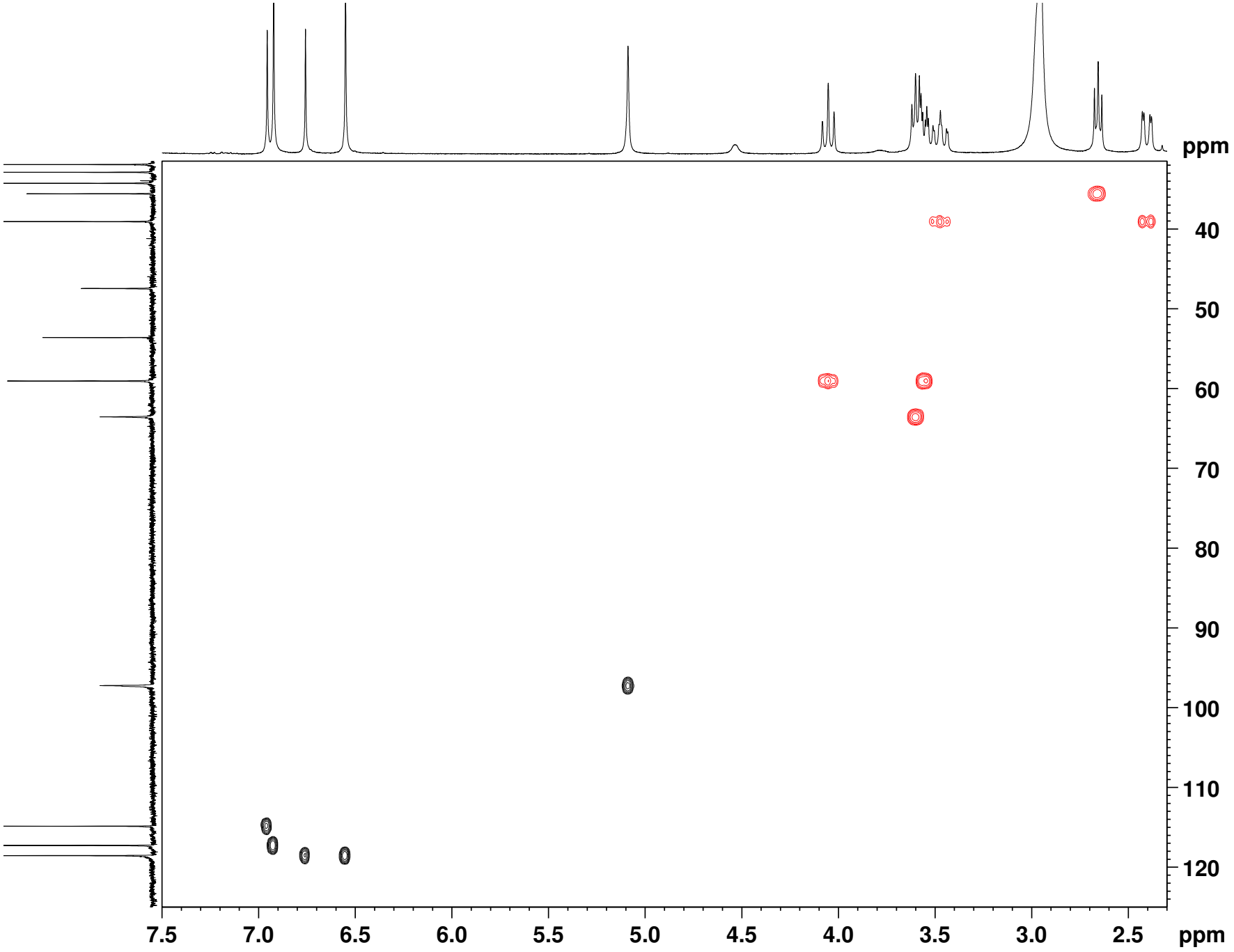
^{13}C NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **34**

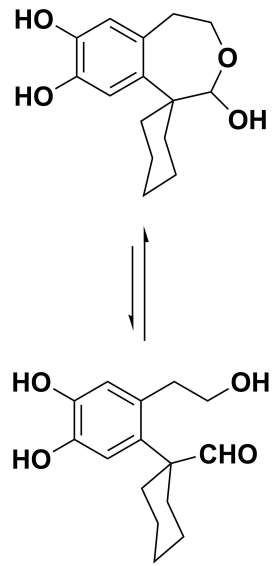


COSY NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **34**

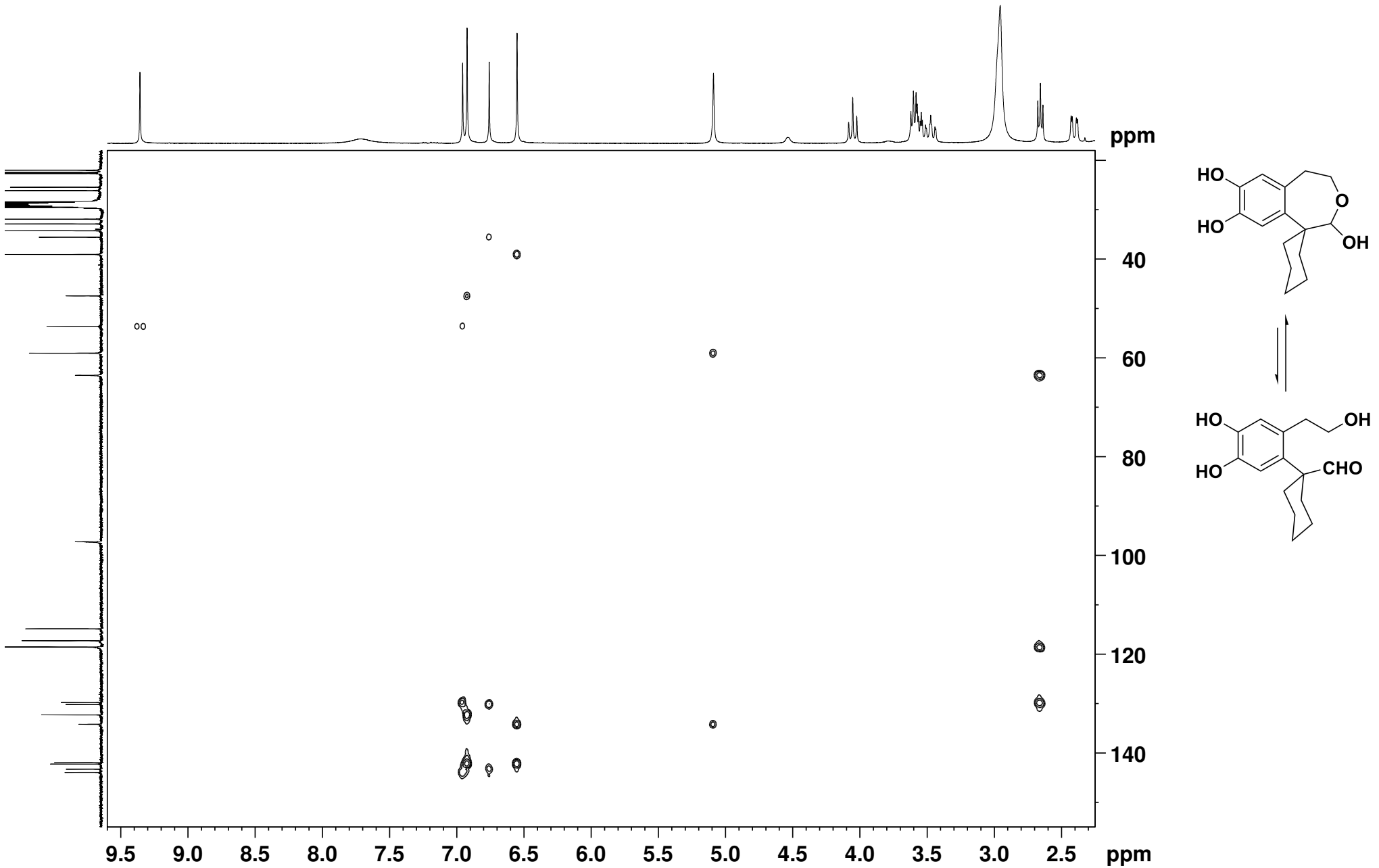


HSQC NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **34**





HMBC NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **34**



HMBC NMR spectrum (400 MHz, $(CD_3)_2CO$) - Compound **34**