Supporting Information

Synthesis and biological evaluation of natural product-inspired, aminoalkyl substituted 1-benzopyrans as novel antiplasmodial agents

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1. Purity data of the test compounds

Most of the test compounds represent aminophenols. The purification of the amphoteric compounds appeared quite difficult due to strong tailing during chromatographic purification. Also the determination of the exact purity values was problematic due to the amphoteric character of the compounds. Nevertheless, the values are given here, but have to be interpreted critically. Thus, some of the given data show purity values below 95 % at a detection wavelength of 210 nm.

Table S1: Purity of the prepared compounds

compd.	purity by HPLC
8a	94 %
8b	96 %
8c	89 %
8d	95 %
9a	92 %
9b	86 %
9c	95 %
9d	98 %
10a	90 %
10b	91 %
10c	95 %
10d	98 %
12a	96 %
12b	95 %
12c	96 %
12d	94.40 %
19a	94.44 %
19c	94 %
25	96 %

2. Experimental, Chemistry

2.1. Chemistry, general

Oxygen and moisture sensitive reactions were carried out under nitrogen, dried with molecular sieves (3 Å and 4 Å) and in dry glassware (Schlenk flask or Schlenk tube). Reaction mixtures were stirred with magnetic stirrer MR 3001 K (Heidolph) or RCT CL (IKA). Temperatures were controlled with dry ice/acetone (-78 °C), ice/water (0 °C), Cryostat (Julabo FT 901 or Huber TC100E-F), magnetic stirrer MR 3001 K (Heidolph) or RCT CL (IKA®), together with temperature controller EKT HeiCon (Heidolph) or VT-5 (VWR) and PEG or silicone bath or IKA heating block. All solvents were of analytical grade quality. Demineralized water was used. Water free solvents were freshly distilled under N_2 atmosphere prior to use or dried with molecular sieves. Thin layer chromatography (tlc): tlc silica gel 60 F_{254} on aluminum sheets (VWR). Flash chromatography (fc): Silica gel 60 (40–63 µm, Machery-Nagel); parentheses include: diameter of the column (ø), length of the stationary phase (*h*), eluent, and fraction size (V). Automated flash chromatography: IsoleraTM Spektra One (Biotage®). Silica gel 60 (40 – 63 µm, Macherey-Nagel) in standard SNAP cartridges. Biotage® SNAP KP-Sil, SNAP HP-Sil and SNAP Ultra cartridges were used as supplied by the manufacturer; parentheses include: cartridge type and size, flow rate, eluent, fraction volume. All component ratios of mixed eluents are referring to a total of 100 parts. Kugelrohr distillation: Glass Oven B-585 (Büchi). Melting point: Melting point system MP50 (Mettler Toledo, Gießen, Germany), open capillary, uncorrected. MS: MicroTOFQII mass spectrometer (Bruker Daltonics, Bremen, Germany); deviations of the found exact masses from the calculated exact masses were 5 mDa or less; the data were analyzed with DataAnalysis® (Bruker Daltonics). NMR: NMR spectra were recorded in deuterated solvents on Agilent DD2 400 MHz and 600 MHz spectrometers (Agilent, Santa Clara CA, USA); chemical shifts (δ) are reported in parts per million (ppm) against the reference substance tetramethylsilane and calculated using the solvent residual peak of the undeuterated solvent; coupling constants are given with 0.5 Hz resolution; assignment of ^{1}H and ^{13}C NMR signals was supported by 2-D NMR techniques where necessary. IR: FT/IR Affinity®-1 spectrometer (Shimadzu, Düsseldorf, Germany) using ATR technique. HPLC was used to determine the purity of the synthesized compounds and was carried out at room temperature.

2.2. HPLC method for the determination of the purity

Equipment 1: Pump: L-7100, degasser: L-7614, autosampler: L-7200, UV detector: L-7400, interface: D-7000, data transfer: D-line, data acquisition: HSM-Software (all from Merck Hitachi, Darmstadt, Germany); Equipment 2: Pump: LPG-3400SD, degasser: DG-1210, autosampler: ACC-3000T, UV-detector: VWD-3400RS, interface: DIONEX UltiMate 3000, data acquisition: Chromeleon 7 (equipment and software from Thermo Fisher Scientific, Lauenstadt, Germany); column: LiChrospher® 60 RP-select B (5 µm), LiChroCART® 250-4 mm cartridge; flow rate: 1.0 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: demineralized water with 0.05 % (V/V) trifluoroacetic acid, B: CH_3CN with 0.05 % (V/V) trifluoroacetic acid; gradient elution (% A): 0 - 4 min: 90 %; 4 - 29 min: gradient from 90 % to 0 %; 29 - 31 min: 0 %; 31 - 31.5min: gradient from 0 % to 90 %; 31.5 - 40 min: 90 %. Unless otherwise mentioned, the purity of all test compounds is greater than 95 %.

2.3. Preparative HPLC to purify some compounds

Equipment: Pump: L-7150; autosampler: L-7200; UV-detector: L-7400; interface: D-7000, data acquisition: HSM-Software (all from LaChrom, Merck Hitachi); column: Phenomenex® Gemini (5 µm C18 110 Å) LC Column 250 x 21.2 mm AXIA packed; guard column: Phenomenex® SecurityGuard PREP Cartridge (Gemini C18) 15 x 21.2 mm ID, Phenomenex® SecurityGuard PREP Cartridge Holder Kit 21.2 mm ID.

Method 1: Solvent: acetonitrile : H_2O 60 : 40 + 0.1 % (V/V) $NH_{3,\ aq}$, flow rate: 20.0 mL/min, injection volume: 400 µL, detection wavelength: 210 nm.

Method 2: Solvent: acetonitrile : H_2O 70 : 30 + 0.1 % (V/V) $NH_{3,\ aq}$, flow rate: 19.0 mL/min, injection volume: 400 µL, detection wavelength: 210 nm.

Method 3: Solvent: acetonitrile : H_2O 70 : 30 + 0.1 % (V/V) $NH_{3,\ aq}$, flow rate: 25.0 mL/min, injection volume: 400 µL, detection wavelength: 210 nm.

2.4. Synthetic procedures

5-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-carbaldehyde (5) and 7-Hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-carbaldehyde (6)[1,2]

2,4-Dihydroxybenzaldehyde (**4**, 5.00 g, 36.2 mmol) was suspended in $CHCl_3$ (160 mL) and the mixture was warmed to 70 °C. Isoprene (2.45 g, 36.0 mmol, 1.0 eq) and H_3PO_4 (85 wt-%, 7.55 g, 65.5 mmol, 1.8 eq) were added dropwise and the mixture was stirred at 70 °C for 65 h. After cooling to ambient temperature, H_2O was added and the

aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by repeated automated flash chromatography (1. SNAP 340 g, flow rate 100 mL/min, CyHex:CH_2Cl_2 50:50 → 20:80, V = 19 mL, 2. SNAP 50 g, 50 mL/min, CyHex:CH_2Cl_2 50:50 → 20:80, V = 19 mL). At first **5**, then **6** was eluted.

5: Colorless oil, R_f = 0.34 (CyHex:CH_2Cl_2 20:80), yield 2.28 g (11.0 mmol, 31 %), $C_{12}H_{14}O_3$ (206.2). Purity (HPLC): 99 %, t_R = 21.1 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.36 (s, 6H, 2 x CH_3), 1.82 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.69 (t, ^3J = 6.8 Hz, 2H, 4-CH_2), 6.42 (d, ^3J = 8.6 Hz, 1H, 8-CH), 7.26 (d, ^3J = 8.6 Hz, 1H, 7-CH), 9.66 (s, 1H, C*H*=O), 11.79 (s, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 16.1 (1C, C-4), 26.9 (2C, 2 x CH_3), 31.8 (1C, C-3), 76.3 (1C, C-2), 108.9 (1C, C-4a), 110.4 (1C, C-8), 114.1 (1C, C-6), 132.6 (1C, C-7), 161.7 (1C, C-8a), 162.0 (1C, C-5), 194.5 (1C, CH=O). FT-IR (neat): ṽ [cm^{-1}] = 2974 (w, CH), 2936 (w, CH), 2855 (w, H-C=O), 2832 (w, H-C=O), 1620 (s, C=O), 1582 (m, C=$C_{ar.}$), 1485 (s, C=$C_{ar.}$), 799 ($CH_{out\ of\ plane}$). HRMS (APCI): m/z = 207.1021 (calcd. 207.1016 for $C_{12}H_{15}O_3$ [M+H^+]).

6: Colorless solid, mp 104 °C (ref.[2]: 104 °C), R_f = 0.26 (CyHex:CH_2Cl_2 20 : 80), yield 2.71 g (13.1 mmol, 37 %), $C_{12}H_{14}O_3$ (206.2). Purity (HPLC): 96 %, t_R = 20.2 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.36 (s, 6H, 2 x CH_3), 1.83 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.75 (t, ^3J = 6.8 Hz, 2H, 4-CH_2), 6.32 (s, 1H, 8-CH), 7.21 (s, 1H, 5-CH), 9.66 (s, 1H, C*H*=O), 11.07 (s, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.6 (1C, C-4), 27.1 (2C, 2 x CH_3), 32.7 (1C, C-3), 76.4 (1C, C-2), 104.5 (1C, C-8), 113.9 (1C, C-4a), 115.4 (1C, C-6), 135.4 (1C, C-5), 162.2 (1C, C-7), 162.3 (1C, C-8a), 194.3 (1C, CH=O). FT-IR (neat): ṽ [cm^{-1}] = 2978 (w, CH), 2940 (w, H-C=O), 2886 (w, H-C=O), 1628 (s, C=O), 1582 (m, C=$C_{ar.}$), 1489 (s, C=$C_{ar.}$), 756 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 207.1029 (calcd. 207.1016 for $C_{12}H_{15}O_3$ [M+H^+]).

7-Hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbaldehyde (7)

Under N_2 atmosphere, aldehyde **6** (370 mg, 1.79 mmol) was dissolved in dry toluene (5 mL). 2,3-Dichloro-5,6-dicyano-1,4-bezoquinone (DDQ, 488 mg, 2.15 mmol, 1.2 eq) was added and the reaction mixture was heated to 120 °C for 16 h. After cooling to rt the mixture was filtered through a sintered glass filter funnel (Por. 4) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (ø = 3 cm, *h* = 26 cm, toluene:CyHex 90:10, V = 10 mL). Colorless crystals, mp 97 °C (ref.[3]: 94 – 96 °C), R_f = 0.30 (toluene:CyHex 90:10), yield 227 mg (1.11 mmol, 62 %), $C_{12}H_{12}O_3$

(204.2). Purity (HPLC): 87 %, t_R = 20.5 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.45 (s, 6H, 2 x CH_3), 5.59 (d, *J* = 10.0 Hz, 1H, 3-CH), 6.29 (d, *J* = 9.9 Hz, 1H, 4-CH), 6.33 (s, 1H, 8-CH), 7.11 (s, 1H, 5-CH), 9.66 (s, 1H, C*H*=O), 11.43 (s, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 28.8 (2C, 2 x CH_3), 78.4 (1C, C-2), 104.3 (1C, C-8), 114.6 (1C, C-4a), 115.4 (1C, C-6), 120.8 (1C, C-4), 129.1 (1C, C-3), 131.5 (1C, C-5), 161.4 (1C, C-8a), 164.4 (1C, C-7), 194.2 (1C, CH=O). FT-IR (neat): ṽ [cm^{-1}] = 3055 (w, OH), 2970 (w, CH), 2928 (w, H-C=O), 2897 (w, H-C=O), 1624 (s, C=O), 1585 (s, $C=C_{ar.}$), 1485 (m, $C=C_{ar.}$), 775 ($CH_{out\ of\ plane}$), 760 (w, $CH_{out\ of\ plane}$). HRMS (APCI): m/z: 205.0857, (calcd. 205.0859 for $C_{12}H_{13}O_3$ [$M+H^+$]).

6-[(Benzylamino)methyl]-2,2-dimethyl-3,4-dihydro-*2H*-1-benzopyran-5-ol (8a)

Under N_2 atmosphere, aldehyde **5** (244 mg, 1.18 mmol) was dissolved in dry THF (10 mL). Benzylamine (214 mg, 2.0 mmol, 1.7 eq) and $Ti(OEt)_4$ (440 mg, 1.93 mmol, 1.6 eq) were added and the solution was heated to 75 °C for 18 h. After cooling to 0 °C, dry CH_3OH (5 mL) and $NaBH_4$ (46 mg, 1.22 mmol, 4.1 eq) were added and the reaction mixture was stirred for 26 h while warming to rt. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL, 1 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 25 g, flow rate = 25 mL/min, CyHex:EtOAC 70:30, V = 19 mL). Colorless resin, R_f = 0.22 (CyHex:EtOAc 70:30), yield 60 mg (0.20 mmol, 17 %), $C_{19}H_{23}NO_2$ (297.4). Purity (HPLC): 94 %, t_R = 16.9 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.30 (s, 6H, 2 x CH_3), 1.76 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.69 (t, ^3J = 6.8 Hz, 2H, 4-CH_2), 3.87 (s, 2H, NHCH_2Ph), 3.91 (s, 2H, NHCH_2Ar), 6.30 (d, ^3J = 8.2 Hz, 1H, 8-CH_2), 6.76 (d, ^3J = 8.3 Hz, 1H, 7-CH_2), 7.28 – 7.33 (m, 1H, *p*-Ph), 7.33 – 7.38 (m, 4H, *o*-Ph, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.3 (1C, C-4), 26.8 (2C, 2 x CH_3), 32.4 (1C, C-3), 50.2 (1C, NHCH_2Ar), 51.8 (1C, NHCH_2Ph), 74.1 (1C C-2), 108.6 (1C C-8), 110.3 (1C, C-4a), 111.9 (1C, C-6), 127.6 (1C, C-7), 128.2 (1C, *p*-Ph), 129.0 (2C, *m*-Ph), 129.0 (2C, *o*-Ph), 136.3 (1C, $C_{q,\ Phenyl}$), 155.2 (1C, C-8a), 155.7 (1C, C-5). FT-IR (neat): ṽ [cm^{-1}] = 3306 (w, NH/OH), 2970 (w, CH), 2928 (w, CH), 2847 (w, CH), 1624 (m, $C=C_{ar.}$), 1589 (m, $C=C_{ar.}$), 1450 (s, $C=C_{ar.}$), 1161 (s, C-O), 1069 (s, C-O), 799 (m, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 298.1817 (calcd. 298.1802 for $C_{19}H_{24}NO_2$ [$M+H^+$]).

2,2-Dimethyl-6-{[(2-phenylethyl)amino]methyl}-3,4-dihydro-2*H*-1-benzopyran-5-ol (8b)

Under N_2 atmosphere, aldehyde **5** (208 mg, 1.01 mmol) was dissolved in dry THF (10 mL). 2-Phenylethan-1-amine (176 mg. 1.45 mmol, 1.4 eq) and $Ti(OEt)_4$ (355 mg, 1.56 mmol, 1.5 eq) were added dropwise and the reaction mixture was heated to 75 °C for 20 h. After cooling to 0 °C, dry CH_3OH (2.5 mL) and $NaBH_4$ (44 mg, 1.16 mmol, 4.6 eq) were added. The reaction mixture was stirred for 24 h while slowly warming to rt. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 25 g, flow rate 25 mL/min, CyHex:EtOAc 50:50, 19 mL). The resulting yellow oil was dissolved in CH_3OH (10 mL), cooled to 0 °C, and $NaBH_4$ (29 mg, 0.69 mmol, 2.73 eq) was added. The reaction mixture was stirred for 21 h while slowly warming to rt. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by repeated automated flash chromatography (1. SNAP 25 g, flow rate 25 mL/min, CyHex:EtOAc 70:30, V = 19 mL, 2. SNAP Ultra 10 g, flow rate 36 mL/min, CyHex:EtOAc 90:10, V = 19 mL). Colorless solid, mp 67 °C, R_f = 0.15 (CyHex:EtOAc 70:30), yield 29 mg (0.09 mmol, 9 %), $C_{20}H_{25}NO_2$ (311.4). Purity (HPLC): 96 %, t_R = 17.8 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.26 (s, 6H, 2 x CH_3), 1.71 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.67 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 2.99 (t, ^3J = 7.4 Hz, 2H, NHCH_2CH_2Ph), 3.05 (t, ^3J = 7.2 Hz, 2H, NHCH_2CH_2Ph), 3.95 (s, 2H, NHCH_2Ar), 6.34 (d, ^3J = 8.2 Hz, 1H, 8-CH), 6.85 (d, ^3J = 8.4 Hz, 1H, 7-CH), 7.16 – 7.26 (m, 3H, *o*-Ph, *p*-Ph), 7.27 – 7.32 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.4 (1C, C-4), 26.7 (2C, 2 x CH_3), 32.2 (1C, C-3), 33.8 (1C, NHCH_2CH_2Ph), 48.6 (1C, NHCH_2CH_2Ph), 49.7 (1C, NHCH_2Ar), 74.2 (1C, C-2), 109.6 (1C, C-8), 111.0 (1C, C-6), 111.2 (1C, C-4a), 127.1 (1C, *p*-Ph), 128.6 (1C, C-7), 128.9 (2C, *o*-Ph), 129.0 (2C, *m*-Ph), 137.5 (1C, $C_{q,\ Phenyl}$), 154.9 (1C, C-5), 155.8 (1C, C-8a). FT-IR (neat): ṽ [cm^{-1}] = 3279 (w, NH/OH), 2978 (w, CH), 2936 (w, CH), 2832 (w, CH), 1620 (m, C=$C_{ar.}$), 1589 (m, C=$C_{ar.}$), 1454 (s, C=$C_{ar.}$), 1161 (s, C-O), (1065 (s, C-O), 806 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 312.1956 (calcd. 312.1958 for $C_{20}H_{26}NO_2$ [M+H$^+$]).

2,2-Dimethyl-6-{[(3-phenylpropyl)amino]methyl}-3,4-dihydro-2*H*-1-benzopyran-5-ol (8c)

Under N_2 atmosphere, aldehyde **5** (112 mg, 0.54 mmol) was dissolved in dry THF (10 mL). 3-Phenylpropan-1-amine (113 mg, 0.84 mmol, 1.6 eq) and $Ti(OEt)_4$ (188 mg, 0.82 mmol, 1.5 eq) were added, and the solution was heated to 75 °C for 16 h. After cooling to 0 °C $NaBH_4$ (34 mg, 0.90 mmol, 1.7 eq) was added and the reaction mixture was stirred at rt for 5 h. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 25 g, flow rate 25 mL/min, CH_2Cl_2:CH_3OH 100:0 + 1 % DMEA → 95:5 + 1 % DMEA, V = 19 mL). The resulting yellow resin was dissolved in CH_3OH (10 mL), cooled to 0 °C and $NaBH_4$ (10 mg, 0.26 mmol, 1.9 eq) was added. The reaction mixture was slowly warmed to rt and stirred for 20 h, then it was cooled to 0 °C again and further $NaBH_4$ (12 mg, 0.32 mmol, 2.4 eq) was added. After stirring for 144 h, H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by repeated automated flash chromatography (1. SNAP 10g, flow rate = 12 mL/min, CyHex:EtOAc 60:40, V = 19 mL, 2. SNAP 10 g, flow rate = 12 mL/min, CyHex:EtOAc 70:30, V = 19 mL, 3. SNAP Ultra 10 g, flow rate = 36 mL/min, CyHex:EtOAc 90:10 → 80:20, V = 19 mL). Colorless oil, R_f = 0.12 (CyHex:EtOAc 70:30), yield 17 mg (0.05 mmol, 9 %), $C_{21}H_{27}NO_2$ (325.5). Purity (HPLC): 89 %, t_R = 18.5 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.30 (s, 6H, 2 x CH_3), 1.76 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 1.95 (quint., ^3J = 7.5 Hz, 2H, NHCH$_2$C*H*$_2$CH$_2$Ph), 2.67 (t, ^3J = 7.6 Hz, 2H, NHCH$_2$CH$_2$C*H*$_2$Ph), 2.69 (t, ^3J = 6.9 Hz, 2H, 4-CH_2), 2.73 – 2.78 (m, 2H NHC*H*$_2$CH$_2$CH$_2$Ph), 3.90 (s, 2H, NHC*H*$_2$Ar), 6.30 (d, ^3J = 8.4 Hz, 1H, 8-CH), 6.77 (d, ^3J = 8.4 Hz, 1H, 7-CH), 7.13 – 7.22 (m, 3H, *o*-Ph, *p*-Ph), 7.24 – 7.29 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.3 (1C, C-4), 26.8 (2C, 2 x CH_3), 30.1 (1C, NHCH$_2$*C*H$_2$CH$_2$Ph), 32.4 (1C, C-3), 33.3 (1C, NHCH$_2$CH$_2$*C*H$_2$Ph), 47.4 (1C, NH*C*H$_2$CH$_2$CH$_2$Ph), 50.9 (1C, NH*C*H$_2$Ar), 74.1 (1C, C-2), 108.6 (1C, C-8), 110.5 (1C, C-4a), 112.0 (1C, C-6), 126.2 (1C, *p*-Ph), 127.6 (1C, C-7), 128.5 (2C, *o*-Ph), 128.6 (2C, *m*-Ph), 141.1 (1C, $C_{q,\ Phenyl}$), 155.2 (1C, C-8a), 155.7 (1C, C-5). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3314 (w, NH/OH), 2970 (w, CH), 2932 (w, CH), 2851 (w, CH), 1620 (m, C=$C_{ar.}$), 1593

(m, C=$C_{ar.}$), 1450 (s, C=$C_{ar.}$), 1161 (s, C-O), 1065 (s, C-O), 799 (m, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 326.2108 (calcd. 326.2115 for $C_{21}H_{28}NO_2$ [M+H^+]).

2,2-Dimethyl-6-{[(4-phenylbutyl)amino]methyl}-3,4-dihydro-2*H*-1-benzopyran-5-ol (8d)

Under N_2 atmosphere, aldehyde **5** (212 mg, 1.03 mmol) was dissolved in dry THF (10 mL). 4-Phenylbutan-1-amine (245 mg, 1.64 mmol, 1.6 eq) and $Ti(OEt)_4$ (367 mg, 1.61 mmol, 1.6 eq) were added and the reaction mixture was heated to 75 °C for 19 h. After cooling to 0 °C, dry CH_3OH (2.5 mL) and $NaBH_4$ (47 mg, 1.24 mmol, 4.8 eq) were added. The reaction mixture was stirred for 24 h while warming slowly to rt. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 25 g, CyHex:EtOAc 50:50, V = 19 mL). The resulting yellow solid was dissolved in dry CH_3OH (10 mL), cooled to 0 °C, and $NaBH_4$ (24 mg, 0.63 mmol, 2.4 eq) was added. The reaction mixture was stirred for 3 h while warming to rt. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by repeated automated flash chromatography (1. SNAP 25 g, flow rate = 25 mL/min, CyHex:EtOAc 70:30, V = 19 mL, 2. SNAP Ultra 10 g, flow rate 36 mL/min, V = 19 mL). Yellow oil, R_f = 0.1 (CyHex:EtOAc 80:20), yield 35 mg (0.10 mmol, 10 %), $C_{22}H_{29}NO_2$ (339.5). Purity (HPLC): 95 %, t_R = 19.3 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.30 (s, 6H, 2 x CH_3), 1.62 – 1.72 (m, 4H, NHCH$_2$C*H*$_2$C*H*$_2$CH$_2$Ph), 1.76 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.62 (t, ^3J = 7.1 Hz, 2H, NHCH$_2$CH$_2$CH$_2$C*H*$_2$Ph), 2.68 (t, ^3J = 6.8 Hz, 2H, 4-CH_2), 2.73 (t, J = 6.9 Hz, 2H, NHC*H*$_2$CH$_2$CH$_2$CH$_2$Ph), 3.90 (s, 2H, NHC*H*$_2$Ar), 6.29 (d, ^3J = 8.4 Hz, 1H, 8-CH), 6.77 (d, ^3J = 8.2 Hz, 1H, 7-CH), 7.14 – 7.19 (m, 3H, *o*-Ph, *p*-Ph), 7.25 – 7.30 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.3 (1C, C-4), 26.8 (2C, 2 x CH_3), 28.3 (1C, NHCH$_2$*C*H$_2$CH$_2$CH$_2$Ph), 28.9 (1C, NHCH$_2$CH$_2$*C*H$_2$CH$_2$Ph), 32.4 (1C, C-3), 35.7 (1C NHCH$_2$CH$_2$CH$_2$*C*H$_2$Ph), 47.9 (1C, NH*C*H$_2$CH$_2$CH$_2$CH$_2$Ph), 51.1 (1C, NH*C*H$_2$Ar), 74.1 (1C, C-2), 108.4 (1C, C-8), 110.3 (1C, C-4a), 112.2 (1C, 1C, C-6), 126.0 (1C, *p*-Ph), 127.4 (1C, C-7), 128.5 (2C, *m*-Ph), 128.5 (2C, *o*-Ph), 142.0 (1C, $C_{q,\ Phenyl}$), 155.1 (1C, C-8a), 155.8 (1C, C-5). FT-IR (neat): ṽ [cm^{-1}] = 3302 (w, NH/OH), 2970 (w, CH), 2928 (w, CH), 2851 (w, CH), 1620 (m, C=$C_{ar.}$), 1593 (m, C=$C_{ar.}$), 1454 (s,

C=$C_{ar.}$), 1161 (s, C-O), 1069 (s, C-O), 799 (m, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 340.2246 (calcd. 340.2271 for $C_{22}H_{30}NO_2$ [M+H$^+$]).

6-[(Benzylamino)methyl]-2,2-dimethyl-3,4-dihydro-*2H*-1-benzopyran-7-ol (9a)

Under N_2, aldehyde **6** (100 mg, 0.48 mmol) was dissolved in dry THF (10 mL). Benzylamine (66 mg, 0.62 mmol, 1.3 equiv.) and $Ti(OEt)_4$ (155 mg, 0.68 mmol, 1.4 equiv.) were added and the solution was heated to reflux under N_2 for 14 h. The reaction mixture was cooled to 0 °C, $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) was added and the mixture was stirred at rt for 3 h. Water was added and the reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried with anhydrous Na_2SO_4, the solvent was removed in vacuo and the residue was purified by flash column chromatography (ø = 2.0 cm, *h* = 24 cm, CyHex:EtOAc 70:30 + 1% NEt_3, V = 10 mL). Colorless solid, mp 104 °C (R_f = 0.32, CyHex:EtOAc 85:15), yield 100 mg (71 %), $C_{19}H_{23}NO_2$ (297.4). Purity (HPLC): 92 %, t_R = 17.5 min. ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 1.28 (s, 6H, CH_3), 1.74 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.64 (dt, ^3J = 6.8 Hz, ^4J = 0.9 Hz, 2H, 4-CH_2), 3.79 (s, 2H, NHCH_2Ph), 3.90 (s, 2H, NCH_2-Ar), 6.16 (s, 1H, 8-CH), 6.67 (t, ^4J = 0.9 Hz, 1H, 5-CH), 7.24 – 7.45 (m, 5H, CH_{Phenyl}). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (CD_2Cl_2): δ (ppm) = 22.2 (1C, C-4), 27.1 (2C, CH_3), 33.6 (1C, C-3), 52.0 (1C, NCH_2-Ar), 53.0 (1C, NHCH_2Ph), 74.5 (1C, C-2), 104.6 (1C, C-8), 112.0 (1C, C-4a), 115.2 (1C, C-6), 127.9 (1C, *p*-Ph), 128.9 (2C, *o*-Ph), 129.1 (2C, *m*-Ph), 129.5 (1C, C-5), 139.5 (1C, $C_{q,\ Phenyl}$), 154.9 (1C, C-8a), 158.0 (1C, C-7). FT-IR (neat): ṽ [cm^{-1}] = 3313 (m, NH/OH), 2974 (m, CH), 1624 (m, C=$C_{ar.}$), 1593 (m, C=$C_{ar.}$), 1492 (s, C=$C_{ar.}$), 733 (s, $CH_{out\ of\ plane}$), 694 (m, $CH_{out\ of\ plane}$).

HRMS (APCI): m/z = 298.1815 (calcd. 298.1802 for $C_{19}H_{24}NO_2$ [M+H$^+$]).

2,2-Dimethyl-6-{[(2-phenylethyl)amino]methyl}-3,4-dihydro-2*H*-1-benzopyran-7-ol (9b)

Under N_2, aldehyde **6** (101 mg, 0.49 mmol) was dissolved in dry THF (10 mL). 2-Phenylethan-1-amine (81 mg, 0.67 mmol, 1.4 equiv.) and $Ti(OEt)_4$ (181 mg, 0.79 mmol, 1.6 equiv.) were added and the solution was heated to reflux under N_2 for 14 h. After cooling to 0 °C, $NaBH_4$ (29 mg, 0.77 mmol, 1.6 equiv.) was added and the reaction mixture was stirred at rt for 3 h. Water was added and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried with

anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (ø = 2 cm, *h* = 19 cm, CyHex:EtOAc 50:50, V = 10 mL). Yellow resin (R_f = 0.22, CyHex:EtOAc 50:50), yield 75 mg (49 %), $C_{20}H_{25}NO_2$ (311.4). Purity (HPLC): 86 %, t_R = 18.3 min. ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 1.27 (s, 6H, CH_3), 1.73 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.62 (t, ^3J = 6.8 Hz, 2H, 4-CH_2), 2.83 (t, ^3J = 6.8 Hz, 2H, NHCH$_2$C*H*$_2$Ph), 2.92 (t, ^3J = 6.7 Hz, 2H, NHC*H*$_2$CH$_2$Ph), 3.86 (s, 2H, NC*H*$_2$-Ar), 6.12 (s, 1H, 8-CH), 6.64 (s, 1H, 5-CH), 7.12 – 7.25 (m, 3H, *o*-Ph, *p*-Ph), 7.25 – 7.43 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 22.2 (1C, C-4), 27.1 (2C, CH_3), 33.6 (1C, C-3), 36.3 (1C, NHCH$_2$*C*H$_2$Ph), 50.2 (1C, NH*C*H$_2$CH$_2$Ph), 52.6 (1C, N*C*H$_2$-Ar), 74.5 (1C, C-2), 104.5 (1C, C-8), 111.8 (1C, C-4a), 115.4 (1C, C-6), 126.8 (1C, *p*-Ph), 129.1 (2C, *m*-Ph), 129.3 (3C, C-5, *o*-Ph), 140.1 (1C, $C_{q,\ Phenyl}$), 154.8 (1C, C-8a), 158.0 (1C, C-7). FT-IR (neat): ṽ [cm^{-1}] = 3290 (w, NH/OH), 2970 (m, CH), 1628 (m, C=$C_{ar.}$), 1593 (m, C=$C_{ar.}$), 1493 (s, C=$C_{ar.}$), 748 (m, $CH_{out\ of\ plane}$), 698 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 312.1955 (calcd. 312.1958 for $C_{20}H_{26}NO_2$ [M+H$^+$]).

2,2-Dimethyl-6-{[(3-phenylpropyl)amino]methyl}-3,4-dihydro-2*H*-1-benzopyran-7-ol (9c)

Under N_2, aldehyde **6** (101 mg, 0.49 mmol) was dissolved in dry THF (10 mL). 3-Phenylpropan-1-amine (89 mg, 0.66 mmol, 1.3 equiv.) and $Ti(OEt)_4$ (166 mg, 0.73 mmol, 1.5 equiv.) were added and the solution was heated to reflux under N_2 for 12 h. The reaction mixture was cooled to 0 °C, $NaBH_4$ (32 mg, 0.85 mmol, 1.7 equiv.) was added and the mixture was stirred at rt for 5 h. Then $NaBH_4$ (19 mg, 0.49 mmol, 1 equiv.) was added and the solution was stirred at rt over night. Water was added and the mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography (ø = 2 cm, *h* = 19 cm, CyHex:EtOAc 70:30, V = 10 mL). Yellow resin (R_f = 0.08, CyHex:EtOAc 70:30), yield 66 mg (41 %), $C_{21}H_{27}NO_2$ (325.4). Purity (HPLC): 95 %, t_R = 19.0 min. ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 1.28 (s, 6H, CH_3), 1.74 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 1.84 (quint., ^3J = 7.4 Hz, 2H, NHCH$_2$C*H*$_2$CH$_2$Ph), 2.61 – 2.70 (m, 6H, 4-CH_2, NHC*H*$_2$CH$_2$C*H*$_2$Ph), 3.86 (s, 2H, NC*H*$_2$-Ar), 6.14 (s, 1H, 8-CH), 6.65 (t, ^4J = 0.8 Hz, 1H, 5-CH), 7.13 – 7.22 (m, 3H, *p*-Ph, *o*-Ph), 7.22 – 7.31 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (101 MHz, CD_2Cl_2): δ

(ppm) = 22.2 (1C, C-4), 27.1 (2C, CH_3), 31.9 (1C, $NHCH_2\mathit{C}H_2CH_2Ph$), 33.6 (1C, C-3), 34.0 (1C, $NHCH_2CH_2\mathit{C}H_2Ph$), 48.7 (1C, $NH\mathit{C}H_2CH_2CH_2Ph$), 52.7 (1C, NCH_2-Ar), 74.5 (1C, C-2), 104.5 (1C, C-8), 111.8 (1C, C-4a), 115.5 (1C, C-6), 126.4 (1C, *p*-Ph), 128.9 (2C, *m*-Ph), 128.9 (2C, *o*-Ph), 129.2 (1C, C-5), 142.5 (1C, $C_{q,\ Phenyl}$), 154.8 (1C, C-8a), 158.1 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3313 (w, NH/OH), 2970 (m, CH), 1628 (m, $C{=}C_{ar.}$), 1593 (m, $C{=}C_{ar.}$), 1493 (s, $C{=}C_{ar.}$), 806 (w, $CH_{out\ of\ plane}$), 745 (m, $CH_{out\ of\ plane}$), 698 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 326.2111 (calcd. 326.2115 for $C_{21}H_{28}NO_2$ [$M+H^+$]).

2,2-Dimethyl-6-{[(4-phenylbutyl)amino]methyl}-3,4-dihydro-2*H*-1-benzopyran-7-ol (9d)

Under N_2 atmosphere, aldehyde **6** (100 mg, 0.48 mmol) was dissolved in dry THF (10 mL). 4-Phenylbutan-1-amine (89 mg, 0.60 mmol, 1.3 eq) and $Ti(OEt)_4$ (133 mg, 0.58 mmol, 1.2 eq) were added, and the reaction mixture was heated to reflux for 14 h. After cooling to 0 °C, $NaBH_4$ (28 mg, 0.74 mmol, 1.5 eq) was added and the reaction mixture was stirred at rt for 3 h. H_2O was added and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (ø = 2 cm, *h* = 21 cm, CyHex:EtOAc 30:70, V = 10 mL). Colorless resin, R_f = 0.22 (CyHex:EtOAc 30:70), yield 112 mg (0.33 mmol, 69 %), $C_{22}H_{29}NO_2$ (339.5). Purity (HPLC): 98 %, t_R = 19.9 min. ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 1.28 (s, 6H, 2 x CH_3), 1.51 – 1.60 (m, 2H, $NHCH_2C\mathit{H}_2CH_2CH_2Ph$), 1.60 – 1.69 (m, 2H, $NHCH_2CH_2C\mathit{H}_2CH_2Ph$), 1.74 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.59 – 2.68 (m, 6H, 4-CH_2, $NHC\mathit{H}_2CH_2CH_2C\mathit{H}_2Ph$), 3.86 (d, ^4J = 0.8 Hz, 2H, $ArC\mathit{H}_2NH$), 6.12 (s, 1H, 8-CH), 6.65 (t, ^4J = 0.9 Hz, 1H, 5-CH), 7.13 -7.21 (m, 3H, *o*-Ph, *p*-Ph), 7.22 – 7.30 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 22.2 (1C, C-4), 27.1 (2C, 2 x CH_3), 29.6 (1C, $NHCH_2CH_2\mathit{C}H_2CH_2Ph$), 29.8 (1C, $NHCH_2\mathit{C}H_2CH_2CH_2Ph$), 33.6 (1C, C-3), 36.2 (1C, $NHCH_2CH_2CH_2\mathit{C}H_2Ph$), 49.0 (1C, $NH\mathit{C}H_2CH_2CH_2CH_2Ph$), 52.7 (1C, $ArCH_2NH$), 74.4 (1C, C-2), 104.5 (1C, C-8), 111.8 (1C, C-4a), 115.5 (1C, C-6), 126.2 (1C, *p*-Ph), 128.8 (2C, *m*-Ph), 128.9 (2C, *o*-Ph), 129.2 (1C, C-5), 143.0 (1C, $C_{q,\ Phenyl}$), 154.7 (1C, C-8a), 158.2 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3298 (w, NH/OH), 3024 (w, $C\text{-}H_{ar.}$), 2974 (w, CH), 2928 (w, CH), 2851 (w, CH), 1628 (m, $C{=}C_{ar.}$), 1593 (m, $C{=}C_{ar.}$), 1493 (s, $C{=}C_{ar.}$), 1153 (s, C-O), 1115 (s, C-O), 895 (w, $CH_{out\ of\ plane}$), 841 (w, $CH_{out\ of\ plane}$), 745 (m, $CH_{out\ of}$

$_{plane}$), 698 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 340.2276 (calcd. 340.2271 for $C_{22}H_{30}NO_2$ [M+H$^+$]).

6-[(Benzylamino)methyl]-2,2-dimethyl-2*H*-1-benzopyran-7-ol (10a)

Under N_2 atmosphere, aldehyde **7** (100 mg, 0.49 mmol) was dissolved in dry THF (10 mL). Benzylamine (100 mg, 0.93 mmol, 1.9 eq) and $Ti(OEt)_4$ (164 mg, 0.72 mmol, 1.5 eq) were added dropwise, and the reaction mixture was heated to 80 °C for 15 h. After cooling to 0 °C, $NaBH_4$ (30 mg, 0.79 mmol, 1.6 eq) was added and the reaction mixture was stirred at rt for 5 h. H_2O was added and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (ø = 2 cm, *h* = 21 cm, CyHex:EtOAc 60:40, V = 10 mL), followed by preparative HPLC (method 1). Colorless resin, R_f = 0.30 (CyHex:EtOAc 60:40), yield 17 mg (0.06 mmol, 12 %), $C_{19}H_{21}NO_2$ (295.4). Purity (HPLC): 90 %, t_R = 17.4 min. ^{1}H NMR (600 MHz, CD_2Cl_2): δ (ppm) = 1.38 (s, 6H, 2 x CH_3), 3.80 (s, 2H, NHC*H*$_2$Ph), 3.90 (s, 2H, C*H*$_2$NHCH$_2$Ph), 5.45 (d, ^3J = 9.7 Hz, 1H, 3-CH), 6.21 (s, 1H, 8-CH), 6.22 (d, ^3J = 9.7 Hz, 1H, 4-CH), 6.61 (s, 1H, 5-CH), 7.27 – 7.33 (m, 3H, *o*-Ph, *p*-Ph), 7.33 – 7.45 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (151 MHz, CD_2Cl_2): δ (ppm) = 28.3 (2C, 2 x CH_3), 51.8 (1C, *C*H$_2$NHCH$_2$Ph), 52.9 (1C, NH*C*H$_2$Ph), 76.6 (1C, C-2), 104.7 (1C, C-8), 113.8 (1C, C-4a), 115.3 (1C, C-6), 122.3 (1C, C-4), 126.6 (1C, C-5), 128.0 (1C, *p*-Ph), 128.0 (1C, C-3), 128.9 (2C, *o*-Ph), 129.2 (2C, *m*-Ph), 139.3 (1C, $C_{q,\ Phenyl}$), 154.3 (1C, C-8a), 160.0 (1C, C-7). FT-IR (neat): ṽ [cm^{-1}] = 3302 (w, NH/OH), 3028 (w, NH/OH), 2970 (w, CH), 2924 (w, CH), 2847 (w, CH), 1620 (m, C=C$_{ar.}$), 1585 (m, C=C$_{ar.}$), 1489 (s, C=C$_{ar.}$), 1157 (m, C-O), 1123 (s, C-O), 891 (m $CH_{out\ of\ plane}$), 845 (m, $CH_{out\ of\ plane}$), 756 (s, $CH_{out\ of\ plane}$), 698 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 296.1644 (calcd. 296.1645 for $C_{19}H_{22}NO_2$ [M+H$^+$]).

2,2-Dimethyl-6-{[(2-phenylethyl)amino]methyl}-2*H*-1-benzopyran-7-ol (10b)

Under N_2 atmosphere, aldehyde **7** (100 mg, 0.49 mmol) was dissolved in dry THF (10 mL). 2-Phenylethan-1-amine (74 mg, 0.61 mmol, 1.2 eq) and $Ti(OEt)_4$ (133 mg, 0.58 mmol, 1.2 eq) were added, and the reaction mixed was heated to reflux for 15 h. After cooling to 0 °C, $NaBH_4$ (30 mg, 0.79 mmol, 1.6 eq) was added and the reaction mixture was stirred at rt for 4 h. H_2O was added and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered,

and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (ø = 2 cm, *h* = 22 cm, CyHex:EtOAc 30:70, V = 10 mL), followed by preparative HPLC (method 2). Colorless resin, R_f = 0.32 (CyHex:EtOAc 30:70), yield 13 mg (0.04 mmol, 8 %), $C_{20}H_{23}NO_2$ (309.4). Purity (HPLC): 91 %, t_R = 18.6 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.37 (s, 6H, 2 x CH_3), 2.93 (t, ^3J = 7.1 Hz, 2H, NHCH$_2$C*H*$_2$Ph), 2.99 (t, ^3J = 7.0 Hz, 2H, NHC*H*$_2$CH$_2$Ph), 3.91 (s, 2H, NHC*H*$_2$Ar), 5.42 (d, ^3J = 9.8 Hz, 1H, 3-CH), 6.18 (d, ^3J = 9.8 Hz, 1H, 4-CH), 6.42 (s, 1H, 8-CH), 6.62 (s, 1H, 5-CH), 7.12 – 7.25 (m, 3H, *o*-Ph, *p*-Ph), 7.25 – 7.32 (m, 2H, *m*-Ph). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 28.2 (2C, 2 x CH_3), 34.6 (1C, NHCH$_2$*C*H$_2$Ph), 48.8 (1C, NH*C*H$_2$CH$_2$Ph), 50.5 (1C, NH*C*H$_2$Ar), 76.4 (1C, C-2), 105.0 (1C, C-8), 112.7 (1C, C-6), 113.8 (1C, C-4a), 121.7 (1C, C-4), 126.9 (1C, *p*-Ph), 127.1 (1C, C-5), 128.0 (1C, C-3), 128.9 (2C, *o*-Ph), 128.9 (2C, *m*-Ph), 138.2 (1C, $C_{q,\ Phenyl}$), 154.6 (1C, C-8a), 158.4 (1C, C-7). FT-IR (neat): ṽ [cm^{-1}] = 3314 (w, NH/OH), 3028 (w, NH/OH), 2970 (w, CH), 2924 (w, CH), 2851 (w, CH), 1620 (m, C=C$_{ar.}$), 1585 (m, C=C$_{ar.}$), 1489 (s, C=C$_{ar.}$), 1153 (m C-O), 1123 (s, C-O), 891 (w, CH$_{out\ of\ plane}$), 845 (w, CH$_{out\ of\ plane}$), 752 (m, CH$_{out\ of\ plane}$), 698 (m, CH$_{out\ of\ plane}$). HRMS (APCI): m/z = 310.1780 (calcd. 310.1802 for $C_{20}H_{24}NO_2$ [M+H$^+$]).

2,2-Dimethyl-6-{[(3-phenylpropyl)amino]methyl}-2*H*-1-benzopyran-7-ol (10c)

Under N_2, aldehyde **7** (101 mg, 0.49 mmol) was dissolved in dry THF (10 mL). 3-Phenylpropylamine (87 mg, 0.64 mmol, 1.3 equiv.) and Ti(OEt)$_4$ (140 mg, 0.61 mmol, 1.2 equiv.) were added and the solution was heated to reflux under N_2 for 14 h. The reaction mixture was cooled to 0 °C, $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) was added and the mixture was stirred for 3 h at rt. Water was added, and the reaction mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by flash chromatography (ø = 2 cm, *h* = 21 cm, CyHex:EtOAc 40:60, V = 10 mL). Yellow oil (R_f = 0.28, CyHex/EtOAc 40/60), yield 97 mg (61 %), $C_{21}H_{25}NO_2$ (323.4). Purity (HPLC): 87 %, t_R = 19.3 min. ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 1.38 (s, 6H, CH_3), 1.84 (quint., ^3J = 7.4 Hz, 2H, NHCH$_2$C*H*$_2$CH$_2$Ph), 2.63 – 2.71 (m, 4H, NHC*H*$_2$CH$_2$C*H*$_2$Ph), 3.87 (s, 2H, NC*H*$_2$-Ar), 5.44 (d, ^3J = 9.7 Hz, 1H, 3-CH), 6.18 (s, 1H, 8-CH), 6.22 (d, ^3J = 9.7 Hz, 1H, 4-CH), 6.59 (s, 1H, 5-CH), 7.13 – 7.23 (m, 3H, *p*-Ph, *o*-Ph), 7.23 – 7.32 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 28.2 (2C, CH_3), 31.9 (1C,

$NHCH_2CH_2CH_2Ph$), 33.9 (1C, $NHCH_2CH_2CH_2Ph$), 48.6 (1C, $NHCH_2CH_2CH_2Ph$), 52.6 (1C, NCH_2-Ar), 76.6 (1C, C-2), 104.6 (1C, C-8), 113.6 (1C, C-4a), 115.7 (1C, C-6), 122.3 (1C, C-4), 126.4 (2C, C-5, *p*-Ph), 127.9 (1C, C-3), 128.9 (4C, *o*-Ph, *m*-Ph), 142.2 (1C, $C_{q,\ Phenyl}$), 154.2 (1C, C-8a), 160.1 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3302 (w, NH/OH), 2970 (m, CH), 1620 (m, $C{=}C_{ar.}$), 1585 (m, $C{=}C_{ar.}$), 1489 (s, $C{=}C_{ar.}$), 802 (w, $CH_{out\ of\ plane}$), 752 (m, $CH_{out\ of\ plane}$), 698 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 324.1970 (calcd. 324.1958 for $C_{21}H_{26}NO_2$ [$M+H^+$]).

2,2-Dimethyl-6-{[(4-phenylbutyl)amino]methyl}-2*H*-1-benzopyran-7-ol (10d)

Under N_2 atmosphere, aldehyde **7** (100 mg, 0.49 mmol) was dissolved in dry THF (10 mL). 4-Phenylbutan-1-amine (95 mg, 0.64 mmol, 1.3 eq) and $Ti(OEt)_4$ (133 mg, 0.58 mmol, 1.2 eq) were added and the solution was heated to 75 °C for 15 h. After cooling to 0 °C, $NaBH_4$ (22 mg, 0.58 mmol, 1.2 eq) was added and the reaction mixture was stirred at rt for 4 h. H_2O was added and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (ø = 3 cm, *h* = 20.5cm, toluene:EtOAc 40:60 + 1 % NEt_3, V = 10 mL). Colorless resin, R_f = 0.26 (toluene:EtOAc 40:60 + 1 % NEt_3), yield 70 mg (0.21 mmol, 43 %), $C_{22}H_{27}NO_2$ (337.5). Purity (HPLC): 98 %, t_R = 20.1 min. ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 1.37 (6H, 2 x CH_3), 1.50 – 1.60 (m, 2H, $NHCH_2CH_2CH_2CH_2Ph$), 1.60 – 1.68 (m, 2H, $NHCH_2CH_2CH_2CH_2Ph$), 2.62 (t, ^3J = 7.5 Hz, 2H, $NHCH_2CH_2CH_2CH_2Ph$), 2.66 (t, ^3J = 7.0 Hz, 2H, $NHCH_2CH_2CH_2CH_2Ph$), 3.87 (s, 2H, NCH_2Ar), 5.44 (d, ^3J = 9.7 Hz, 1H, 3-CH), 6.17 (s, 1H, 8-CH), 6.22 (d, ^3J = 9.8 Hz, 1H, 4-CH), 6.59 (s, 1H, 5-CH), 7.12 – 7.22 (m, 3H, *o*-Ph, *p*-Ph), 7.22 – 7.31 (m, 2H, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 28.2 (2C, 2 x CH_3), 29.6 ($NHCH_2CH_2CH_2CH_2Ph$), 29.7 (1C, $NHCH_2CH_2CH_2CH_2Ph$), 36.2 (1C, $NHCH_2CH_2CH_2CH_2Ph$), 48.9 (1C, $NHCH_2CH_2CH_2CH_2Ph$), 52.6 (1C, NCH_2Ar), 76.5 (1C, C-2), 104.6 1C, C-8), 113.6 (1C, C-4a), 115.7 (1C, C-6), 122.3 (1C, C-4), 126.2 (1C, *p*-Ph), 126.4 (1C, C-5), 127.9 (1C, C-3), 128.8 (2C, *m*-Ph), 128.9 (2C, *o*-Ph), 143.0 (1C, $C_{q,\ Phenyl}$), 154.2 (1C, C-8a), 160.2 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3024 (w, NH/OH), 2970 (w, CH), 2928 (w, CH), 2855 (w, CH), 1620 (m $C{=}C_{ar.}$), 1585 (m, $C{=}C_{ar.}$), 1489 (s, $C{=}C_{ar.}$), 1153 (m, C-O), 1126 (s, C-O), 891 (m, $CH_{out\ of\ plane}$), 845 (m, $CH_{out\ of\ plane}$), 748 (s, $CH_{out\ of\ plane}$), 698 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 338.2091 (calcd. 338.2115 for $C_{22}H_{28}NO_2$ [$M+H^+$]).

2,2,8,8-Tetramethyl-3,4,9,10-tetrahydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-6-carbaldehyde (11)

2,4-Dihydroxybenzaldehyde (**4**, 2.50 g, 18.1 mmol) was suspended in CH_2Cl_2 (80 mL). Isoprene (2.47 g, 36.2 mmol, 2.0 eq) and H_3PO_4 (85 wt-%, 3.78 g, 32.8 mmol, 1.8 eq) were added dropwise, and the reaction mixture was stirred at rt for 120 h. Subsequently, the temperature was increased to 50 °C and the reaction mixture was stirred for 23 h. After cooling to rt H_2O was added, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 340, flow rate 100 mL/min, CyHex:EtOAc 100:0 → 82:18, V = 19 mL). Colorless solid, mp 99 °C (crystallized from CyHex:EtOAc 90:10) (ref.[4]: 76 - 77 °C), R_f = 0.35 (CyHex:EtOAc 85:15), yield 2.12 g (7.7 mmol, 43 %), $C_{17}H_{22}O_3$ (274.4). Purity (HPLC): 96 %, t_R = 24.2 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.34 (s, 6H, 2 x 2-CH_3), 1.36 (s, 6H, 2 x 8-CH_3), 1.79 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 1.79 (t, ^3J = 6.8 Hz, 2H, 9-CH_2), 2.60 (t, ^3J = 6.8 Hz, 2H, 10-CH_2), 2.72 (t, ^3J = 6.8 Hz, 2H, 4-CH_2), 7.47 (s, 1H, 5-CH), 10.29 (s, 1H, CH=O). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.1 (1C, C-10), 21.8 (1C, C-4), 26.8 (2C, 2 x 8-CH_3), 27.4 (2C, 2 x 2-CH_3), 32.0 (1C, C-9), 32.8 (1C, C-3), 74.9 (1C, C-8), 75.9 (1C, C-2), 109.5 (1C, C-10a), 112.5 (1C, C-4a), 117.8 (1C, C-6), 126.9 (1C, C-5), 156.7 (1C, C-6a), 158.2 (1C, C-10b), 189.2 (1C, C=O). FT-IR (neat): ṽ [cm^{-1}] = 2978 (w, CH), 2932 (w, H-C=O), 2916 (w, H-C=O), 2847 (w, CH), 1670 (m, C=O), 1601 (m, C=$C_{ar.}$), 1582 (m, C=$C_{ar.}$), 1153 (m, C-O), 1111 (s, C-O), 891 (w, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 275.1666 (calcd. 275.1642 for $C_{17}H_{23}O_3$ [M+H$^+$]).

***N*-Benzyl-1-(2,2,8,8-tetramethyl-3,4,9,10-tetrahydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-6-yl)methanamine (12a)**

Under N_2 atmosphere, benzodipyran **11** (202 mg, 0.74 mmol) was dissolved in dry CH_2Cl_2 (15 mL). Benzylamine (166 mg, 1.55 mmol, 2.1 eq) and conc. CH_3COOH (89 mg, 1.48 mmol, 2.0 eq) were added dropwise and the reaction mixture was stirred at rt. After 22 h, $NaBH(OAc)_3$ (315 mg, 1.49 mmol, 2.0 eq) was added and the reaction mixture was further stirred at rt for 144 h. Saturated $NaHCO_3$ solution was added, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 25 g, flow rate 25 mL/min, CyHex:CH_2Cl_2 50:50 + 1 % NEt_3 → 10:90 + 1 % NEt_3, V = 19 mL). Colorless oil, R_f =

0.22 (CyHex:CH_2Cl_2 50:50 + 1 % NEt_3), yield 224 mg (0.61 mmol, 82 %), $C_{24}H_{31}NO_2$ (365.5). Purity (HPLC): 96 %, t_R = 22.7 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.27 (s, 6H, 2 x 8-CH_3), 1.31 (s, 6H, 2 x 2-CH_3), 1.74 (t, ^3J = 6.7 Hz, 2H, 9-CH_2), 1.76 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.60 (t, ^3J = 6.8 Hz, 2H, 10-CH_2), 2.68 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 3.76 (s, 2H, ArC*H*$_2$NH), 3.81 (s, 2H, NHC*H*$_2$Ph), 6.76 (s, 1H, 5-CH), 7.30 – 7.34 (m, 3H, *m*-Ph, *p*-Ph), 7.34 - 7.38 (m, 2H, *o*-Ph). A signal for the NH-proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.3 (1C, C-10), 22.1 (1C, C-4), 27.0 (2C, 2 x 8-CH_3), 27.2 (2C, 2 x 2-CH_3), 32.3 (1C, C-9), 33.1 (1C, C-3), 49.1 (1C, Ar*C*H$_2$NH), 52.5 (1C, NH*C*H$_2$Ph), 74.1 (1C, C-8), 74.2 (1C, C-2), 109.7 (1C, C-10a), 111.0 (1C, C-4a), 117.2 (1C, C-6), 127.3 (1C, *p*-Ph), 128.3 (1C, C-5), 128.6 (2C, *m*-Ph), 128.7 (2C, *o*-Ph), 139.4 (1C, $C_{q,\ Phenyl}$), 151.0 (1C, C-6a), 151.5 (1C, C-10b). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3337 (w, NH), 2970 (w, CH), 2928 (w, CH), 2847 (w, CH), 1597 (w, C=$C_{ar.}$), 1450 (m, C=$C_{ar.}$), 1153 (s, C-O), 1111 (s, C-O), 887 (w, $CH_{out\ of\ plane}$). HRMS (APCI$^+$): m/z = 366.2460 (calcd. 366.22428 for $C_{24}H_{32}NO_2$ [M+H$^+$]).

2-Phenyl-*N*-[(2,2,8,8-tetramethyl-3,4,9,10-tetrahydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-6-yl)methyl]ethan-1-amine (12b)

Under N_2 atmosphere, benzodipyran **11**(202 mg, 0.74 mmol) was dissolved in dry CH_2Cl_2 (15 mL). 2-Phenylethan-1-amine (180 mg, 1.49 mmol, 2.0 eq) and conc. CH_3COOH (98 mg, 1.63 mmol, 2.2 eq) were added dropwise. The reaction mixture was stirred at rt for 21 h. $NaBH(OAc)_3$ (319 mg, 1.51 mmol, 2.0 eq) was added, and the mixture was further stirred at rt. After 145 h saturated $NaHCO_3$ solution was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by repeated automated flash chromatography (1. SNAP 25 g, flow rate 25 mL/min, CyHex:CH_2Cl_2 50:50 + 1% NEt_3 → 10:90 + 1 % NEt_3, V = 19 mL, 2. SNAP Ultra 10 g, flow rate 36 mL/min, EtOAc:CH_3OH 100:0 → 95:5, V = 19 mL). Colorless oil, R_f = 0.20 (CyHex:CH_2Cl_2 50:50 + 1% NEt_3), yield 114 mg (0.30 mmol, 41 %), $C_{25}H_{33}NO_2$ (379.5). Purity (HPLC): 95 %, t_R = 23.1 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.13 (s, 6H, 2 x 8-CH_3), 1.29 (s, 6H, 2 x 2-CH_3), 1.66 (t, ^3J = 6.8 Hz, 2H, 9-CH_2), 1.74 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.56 (t, ^3J = 6.7 Hz, 2H, 10-CH_2), 2.65 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 2.85 – 2.90 (m, 4H, NHC*H*$_2$C*H*$_2$Ph), 3.71 (s, 2H, ArC*H*$_2$NH), 6.72 (s, 1H, 5-CH), 7.17 – 7.22 (m, 3H, *o*-Ph, *p*-Ph), 7.25 – 7.29 (m, 2H, *m*-Ph). A signal for the NH-proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.3 (1C, C-10), 22.0

(1C, C-4), 26.7 (2C, 2 x 8-CH_3), 27.2 (2C, 2 x 2-CH_3), 32.3 (1C, C-9), 33.1 (1C, C-3), 36.2 (1C, NHCH$_2$*C*H$_2$Ph), 49.7 (1C, Ar*C*H$_2$NH), 50.1 (1C, NH*C*H$_2$CH$_2$Ph), 73.8 (1C, C-8), 74.1 (1C, C-2), 109.5 (1C, C-10a), 110.8 (1C, C-4a), 117.8 (1C, C-6), 126.3 (1C, *p*-Ph), 128.0 (1C, C-5), 128.6 (2C, *m*-Ph), 128.9 (2C, *o*-Ph), 140.0 (1C, $C_{q,\ Phenyl}$), 150.9 (1C, C-6a), 151.30 (1C, C-10b). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3321 (w, NH), 2970 (w, CH), 2928 (w, CH), 2847 (w, CH), 1597 (w, C=$C_{ar.}$), 1450 (m, C=$C_{ar.}$), 1153 (s, C-O), 1115 (s, C-O), 887 (w, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 380.2596 (calcd. 380.2584 for $C_{25}H_{34}NO_2$ [M+H$^+$]).

3-Phenyl-*N*-[(2,2,8,8-tetramethyl-3,4,9,10-tetrahydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-6-yl)methyl]propan-1-amine (12c)

Under N_2 atmosphere, benzodipyran **11** (100 mg, 0 36 mmol) was dissolved in dry THF (15 mL). 3-Phenylpropan-1-amine (102 mg, 0.75 mmol, 2.1 eq) and conc. CH_3COOH (42 mg, 0.70 mmol, 1.9 eq) were added dropwise. The reaction mixture was stirred at rt for 26 h. $NaBH(OAc)_3$ (153 mg, 0.72 mmol, 2.0 eq) was added and the mixture was further stirred at rt. After 96 h saturated $NaHCO_3$-solution was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (ø = 2 cm, *h* = 16.5 cm, CH_2Cl_2:CH_3OH 98:2 + 1% NEt_3, V = 10 mL), followed by automated flash column chromatography (SNAP Ultra 10 g, flow rate 36 mL/min, EtOAc:CH_3OH 100:0 → 95:5, V = 19 mL). Colorless oil, R_f = 0.36 (CH_2Cl_2:CH_3OH 98:2 + 1% NEt_3), yield 28 mg (0.07 mmol, 19 %), $C_{26}H_{35}NO_2$ (393.6). Purity (HPLC): 96 %, t_R = 23.6 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.29 (s, 6H, 2 x 8-CH_3), 1.30 (s, 6H, 2 x 2-CH_3), 1.74 (t, ^3J = 6.7 Hz, 2H, 9-CH_2), 1.75 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 1.98 (quint, ^3J = 7.8 Hz, 2H, NHCH$_2$C*H*$_2$CH$_2$Ph), 2.59 (t, ^3J = 6.9 Hz, 2H, 10-CH_2), 2.61 – 2.69 (m, 4H, NHCH$_2$CH$_2$C*H*$_2$Ph, 4-CH_2), 2.74 (t, ^3J = 7.4 Hz, 2H, NHC*H*$_2$CH$_2$CH$_2$Ph), 3.85 (s, 2H, NHC*H*$_2$Ar), 6.81 (s, 1H, 5-CH), 7.12 – 7.20 (m, 3H, *o*-Ph, *p*-Ph), 7.21 – 7.31 (m, 2H, *m*-Ph). A signal for the NH-proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.2 (1C, C-10), 22.0 (1C, C-4), 27.0 (2C, 2 x 8-CH_3), 27.2 (2C, 2 x 2-CH_3), 29.9 (1C, NHCH$_2$*C*H$_2$CH$_2$Ph), 32.3 (1C, C-9), 33.0 (1C, C-3), 33.3 (1C, NHCH$_2$CH$_2$*C*H$_2$Ph), 46.9 (1C, NH*C*H$_2$CH$_2$CH$_2$Ph), 48.3 (1C, NH*C*H$_2$Ar), 74.4 (1C, C-2), 74.6 (1C, C-8), 109.8 (1C, C-10a), 111.5 (1C, C-4a), 113.9 (1C, C-6), 126.1 (1C, *p*-Ph), 128.5 (2C, *o*-Ph), 128.6 (2C, *m*-Ph), 128.9 (1C, C-5), 141.2 (1C, $C_{q,\ Phenyl}$), 151.0 (1C, C-6a), 152.2 (1C, C-10b). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3310 (w,

NH), 2970 (w, CH), 2928 (w, CH), 2851 (w, CH), 1597 (w, C=$C_{ar.}$), 1454 (m, C=$C_{ar.}$), 1153 (s, CO_{Phenol}), 1115 (s, CO_{Phenol}), 887 (w, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 394.2760 (calcd. 394.2741 for $C_{26}H_{36}NO_2$ [M+H$^+$]).

4-Phenyl-*N*-[(2,2,8,8-tetramethyl-3,4,9,10-tetrahydro-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-6-yl)methyl]butan-1-amine (12d)

Under N_2 atmosphere, benzodipyran **11** (201 mg, 0.73 mmol) was dissolved in dry CH_2Cl_2 (15 mL). 4-Phenylbutan-1-amine (221 mg, 1.48 mmol, 2.0 eq) and conc. CH_3COOH (94 mg, 1.57 mmol, 2.2 eq) were added and the reaction mixture was stirred at rt for 20 h. $NaBH(OAc)_3$ (309 mg, 1.46 mmol, 2.0 eq) was added and the reaction mixture was further stirred at rt. After 147 h, saturated $NaHCO_3$ solution was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 25 g, flow rate 25 mL/min, CyHex:CH_2Cl_2 50:50 + 1 % NEt_3 → 10:90 + 1 % NEt_3, V = 19 mL). Colorless oil, R_f = 0.20 (CyHex:CH_2Cl_2 50:50 + 1 % NEt_3), yield 198 mg (0.49 mmol, 67 %), $C_{27}H_{37}NO_2$ (407.6). Purity (HPLC): 94.40 %, t_R = 24.5 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.27 (s, 6H, 2 x 8-CH_3), 1.30 (s, 6H, 2 x 2-CH_3), 1.57 (quint., ^3J = 7.2 Hz, 2H, NHCH$_2$C*H*$_2$CH$_2$CH$_2$Ph), 1.65 (quint., ^3J = 7.3 Hz, 2H, NHCH$_2$CH$_2$C*H*$_2$CH$_2$Ph), 1.73 (t, ^3J = 6.8 Hz, 2H, 9-CH_2), 1.75 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 2.56 – 2.64 (m, 6H, 10-CH_2, NHC*H*$_2$CH$_2$CH$_2$C*H*$_2$Ph), 2.67 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 3.67 (s, 2H, NHC*H*$_2$Ar), 6.74 (s, 1H, 5-CH), 7.14 - 7.19 (m, 3H, *o*-Ph, *p*-Ph), 7.23 – 7.28 (m, 2H, *m*-Ph). A signal for the NH-proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 17.3 (1C, C-10), 22.1 (1C, C-4), 27.0 (2C, 2 x 8-CH_3), 27.2 (2C, 2 x 2-CH_3), 29.3 (1C, NHCH$_2$CH$_2$*C*H$_2$CH$_2$Ph), 29.6 (1C, NHCH$_2$*C*H$_2$CH$_2$CH$_2$Ph), 32.3 (1C, C-9), 33.1 (1C, C-3), 35.9 (1C, NHCH$_2$CH$_2$CH$_2$*C*H$_2$Ph), 48.6 (1C, NH*C*H$_2$CH$_2$CH$_2$CH$_2$Ph), 49.4 (1C, NH*C*H$_2$Ar), 73.8 (1C, C-8), 74.1 (1C, C-2), 109.5 (1C, C-10a), 110.8 (1C, C-4a), 118.3 (1C, C-6), 125.8 (1C, *p*-Ph), 128.0 (1C, C-5), 128.4 (2C, *m*-Ph), 128.5 (2C, *o*-Ph), 142.6 (1C, $C_{q,\ Phenyl}$), 150.9 (1C, C-6a), 151.2 (1C, C-10b). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2970 (w, CH), 2927 (m, CH), 2851 (w, CH), 1597 (w, C=$C_{ar.}$), 1454 (m, C=$C_{ar.}$), 1153 (s, C-O), 1115 (s, C-O), 887 (w, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 408.2933 (calcd. 408.2897 for $C_{27}H_{38}NO_2$ [M+H$^+$]).

2,2-Dimethyl-3,4-dihydro-2*H*-1-benzopyran-7-ol (14)

Resorcinol (**13**, 2.55 g, 23.2 mmol,) was suspended in $CHCl_3$ (80 mL) and the mixture was heated to 70 °C. Isoprene (1.58 g, 23.2 mmol, 1.0 eq) and H_3PO_4 (85 wt-%, 4.91 g, 42.6 mmol, 1.8 eq) were added dropwise and the reaction mixture was stirred at 70 °C for 45 h. After cooling to ambient temperature H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 100 g, flow rate 50 mL/min, CyHex:EtOAc 100:0 → 70:30, V = 19 mL). Colorless solid, mp 64 °C (Ref[5]: 60 - 62 °C), R_f = 0.33 (CyHex:EtOAc 85:15), yield 3.16 g (17.7 mmol, 77 %), $C_{11}H_{14}O_2$ (178.2). Purity (HPLC): 99 %, t_R = 17.4 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.32 (s, 6H, 2 x CH_3), 1.77 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.69 (t, ^3J = 6.8 Hz, 2H, 4-CH_2), 6.27 (d, ^4J = 2.5 Hz, 1H, 8-CH), 6.34 (dd, ^3J = 8.2 Hz, ^4J = 2.6 Hz, 1H, 6-CH), 6.90 (d, ^3J = 8.1 Hz, 1H, 5-CH). A signal for the OH-proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.9 (1C, C-4), 27.0 (2C, 2 x CH_3), 33.1 (1C, C-3), 74.5 (1C, C-2), 103.9 (1C, C-8), 107.4 (1C, C-6), 113.5 (1C, C-4a), 130.2 (1C, C-5), 154.9 (1C, C-7), 155.0 (1C, C-8a). FT-IR (neat): ṽ [cm^{-1}] = 3213 (m, OH), 2967 (w, CH), 2851 (w, CH), 1539 (m, C=$C_{ar.}$), 1504 (m, C=$C_{ar.}$), 1150 (s, C-O), 1115 (s, C-O), 849 (m, $CH_{out\ of\ plane}$), 799 (m, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 179.1075 (calcd. 179.1067 for $C_{11}H_{15}O_2$ [M+H$^+$]).

2-Chloro-1-(7-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)ethan-1-one (15)

Under N_2 atmosphere, benzopyran **14** (3.00 g, 16.8 mmol) was dissolved in dry CH_2Cl_2 (150 mL) and the solution was cooled to 0 °C. Chloroacetyl chloride (2.08 g, 18.5 mmol, 1.1 eq) was added dropwise. Anhydrous $AlCl_3$ (2.48 g, 18.6 mmol, 1.1 eq) was then added stepwise within 30 min. The solution turned to an orange color after the first addition. The reaction mixture was stirred for 39 h while slowly warming to rt. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The reside was purified by automated flash chromatography (SNAP 100 g, flow rate 50 mL/min, CyHex:CH_2Cl_2 50:50 → 0:100, V = 19 mL). Colorless solid, mp 154 °C, R_f = 0.26 (CyHex:CH_2Cl_2 50:50), yield 2.95 g (11.6 mmol, 69 %), $C_{13}H_{15}ClO_3$ (254.7). Purity (HPLC): 98 %, t_R = 21.3 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.36

(s, 6H, 2 x CH_3), 1.83 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.74 (td, ^3J = 6.8 Hz, ^4J = 1.1 Hz, 2H, 4-CH_2), 4.60 (s, 2H, CH_2Cl), 6.35 (s, 1H, 8-CH), 7.40 (t, ^4J = 1.0 Hz, 1H, 5-CH), 11.75 (s, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.9 (1C, C-4), 27.1 (2C, 2 x CH_3), 32.8 (1C, C-3), 44.9 (1C, CH_2Cl), 76.5 (1C, C-2), 105.2 (1C, C-8), 111.5 (1C, C-6), 113.6 (1C, C-4a), 131.3 (1C, C-5), 162.5 (1C, C-8a), 163.7 (1C, C-7), 194.4 (1C, C=O). FT-IR (neat): ṽ [cm^{-1}] = 2982 (w, CH), 2940 (w, CH), 1639 (s, C=O), 1581 (m, C=C$_{ar.}$), 1489 (s, C=C$_{ar.}$), 760 (s, CH$_{out\ of\ plane}$). HRMS (APCI): m/z = 255.0802 (calcd. 255.0782 for $C_{13}H_{16}ClO_3$ [M+H$^+$]).

2-Azido-1-(7-hydroxy-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)ethan-1-one (16)

Chloroacetophenone **15** (2.50 g, 9.8 mmol) was dissolved in DMF (40 mL) and the solution was cooled to 0 °C. NaN_3 (775 mg, 11.9 mmol, 1.2 eq) was added and the reaction mixture was stirred at 0 °C for 2 h. H_2O was added, and the precipitate was filtered off using a glass filter funnel (Por 4.), washed with a small amount of H_2O, and dried *in vacuo*. Colorless crystals, mp 116 °C, R_f = 0.48 (CyHex:EtOAc 85:15), yield 2.21 g (8.5 mmol, 87 %), $C_{13}H_{15}N_3O_3$ (261.3). Purity (HPLC): 96 %, t_R = 21.4 min. ^{1}H NMR (400 MHz, CD_2Cl_2): δ (ppm) = 1.34 (s, 6H, 2 x CH_3), 1.83 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.73 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 4.49 (s, 2H, COCH_2N$_3$), 6.30 (s, 1H, 8-CH), 7.30 (s, 1H, 5-CH), 11.67 (s, 1H, OH). ^{13}C NMR (101 MHz, CD_2Cl_2): δ (ppm) = 22.2 (1C, C-4), 27.3 (2C, 2 x CH_3), 33.1 (1C, C-3), 54.4 (1C, CO*C*H$_2$N$_3$), 77.0 (1C, C-2), 105.2 (1C, C-8), 112.0 (1C, C-6), 114.3 (1C, C-4a), 131.0 (1C, C-5), 162.8 (1C, C-8a), 163.5 (1C, C-7), 197.1 (1C, C=O). FT-IR (neat): ṽ [cm^{-1}] = 2978 (w, CH), 2936 (w, CH), 2889 (w, CH), 2099 (s, N_3), 1639 (s, C=O), 1612 (s, C=C$_{ar.}$), 1582 (s, C=C$_{ar.}$), 1489 (s, C=C$_{ar.}$), 760 (s, CH$_{out\ of\ plane}$). HRMS (APCI): m/z = 262.1170 (calcd. 262.1186 for $C_{13}H_{16}N_3O_3$ [M+H$^+$]).

6-(2-Azido-1-hydroxyethyl)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-7-ol (17)

Under N_2 atmosphere, azidoacetophenone **16** (604 mg, 2.3 mmol) was dissolved in dry CH_3OH (50 mL) and the solution was cooled to 0 °C. $NaBH_4$ (83 mg, 2.2 mmol, 3.8 eq) was added and the reaction mixture was stirred while warming to rt. After 20 h, H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The product was used without further purification. Colorless solid, mp

127 °C, R_f = 0.54 (CyHex:EtOAc 85:15), yield 560 mg (2.1 mmol, 91 %), $C_{13}H_{17}N_3O_3$ (263.3). Purity (HPLC): 98 %, t_R = 17.5 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 6H, 2 x CH_3), 1.76 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.66 (t, ^3J = 6.8 Hz, 2H, 4-CH_2), 2.95 (d, ^3J = 3.5 Hz, 1H, CHO*H*), 3.47 (dd, ^2J = 12.6 Hz, ^3J = 3.8 Hz, 1H, CH_2N_3), 3.65 (dd, ^2J = 12.6 Hz, ^3J = 9.2 Hz, 1H, CH_2N_3), 4.88 (dt, ^3J = 9.2 Hz, 3.6 Hz, 1H, C*H*OH), 6.30 (s, 1H, 8-CH), 6.71 (s, 1H, 5-CH), 7.12 (s, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.8 (1C, C-4), 27.0 (2C, 2 x CH_3), 33.0 (1C, C-3), 56.7 (1C, CH_2N_3), 74.1 (1C, CHOH), 74.6 (1C, C-2), 105.5 (1C, C-8), 113.1 (1C, C-4a), 115.8 (1C, C-6), 128.1 (1C, C-5), 154.6 (1C, C-7), 155.2 (1C, C-8a). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3348 (w, OH), 2974 (w, CH), 2928 (w, CH), 2099 (s, N_3), 1593 (w, C=$C_{ar.}$), 1493 (m, C=$C_{ar.}$), 883 (w, $CH_{out\ of\ plane}$), 845 (w, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 246.1246 (calcd. 246.1237 for $C_{13}H_{16}N_3O_2$ [M-H_2O+H^+]).

6-(2-Amino-1-hydroxyethyl)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-7-ol (18)

Under N_2 atmosphere, a Schlenk flask was charged with Pd/C (15 mg, 10 wt-%) and dry CH_3OH (5 mL) was added. Azide **17** (150 mg, 0.57 mmol) was dissolved in dry CH_3OH (15 mL) and the solution was added to the flask. The reaction mixture was stirred under H_2-atmosphere (0.8 bar) at rt for 90 min. After filtration over Celite® the solvent was removed *in vacuo*. The product was used without further purification. Pale brown solid, mp could not be determined, decomposition above 150 °C, R_f = 0.14 (CH_2Cl_2 100 %), yield 129 mg (0.54 mmol, 95 %), $C_{13}H_{19}NO_3$ (237.3). Purity (HPLC): 98 %, t_R = 17.5 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.30 (s, 6H, 2 x CH_3), 1.75 (t, ^3J = 6.8 Hz, 2H, 3-CH_2), 2.64 (td, ^3J = 6.8 Hz, ^4J = 2.9 Hz, 2H, 4-CH_2), 2.93 (dd, ^2J = 12.7 Hz, ^3J = 4.5 Hz, 1H, C*H*$_2$$NH_2$), 3.24 (dd, ^2J = 12.7 Hz, ^3J = 4.7 Hz, 1H, C*H*$_2$$NH_2$), 4.67 (t, ^3J = 4.7 Hz, 1H, C*H*OH), 6.33 (s, 1H, 8-CH), 6.72 (s, 1H, 5-CH). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.8 (1C, C-4), 27.0 (2C, 2 x CH_3), 33.2 (1C, C-3), 46.2 (1C, CH_2NH_2), 74.3 (1C, C-2), 75.0 (1C, CHOH), 106.1 (1C, C-8), 111.8 (1C, C-4a), 119.6 (1C, C-6), 129.8 (1C, C-5), 155.1 (1C, C-8a), 155.3 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3449 (w, NH_2/OH), 3348 (w, NH_2/OH), 2970 (w, CH), 2936 (w, CH), 2847 (w, CH), 1620 (m, C=$C_{ar.}$), 1516 (m, C=$C_{ar.}$), 1439 (m, C=$C_{ar.}$), 1150 (m, C-O), 1115 (s, C-O), 880 (s, $CH_{out\ of\ plane}$), 833 (m, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 238.1419 (calcd. 238.1438 for $C_{13}H_{20}NO_3$ [M+H^+]).

6-[2-(Benzylamino)-1-hydroxyethyl]-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-7-ol (19a)

Under N_2 atmosphere, amine **18** (100 mg, 0.42 mmol) was dissolved in dry CH_2Cl_2 (20 mL). Benzaldehyde (47 mg, 0.44 mmol, 1.0 eq) was added and the solution was stirred at rt for 1 h. $NaBH(OAc)_3$ (97 mg, 0.46 mmol, 1.1 eq) was added and the reaction mixture was stirred at rt for further 13 d. The reaction mixture was poured into ice cold H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (ø = 3 cm, *h* = 26 cm, CH_2Cl_2:CH_3OH 99:1 + 1 % NEt_3, V = 10 mL), followed by automated flash chromatography (SNAP Ultra 10 g, flow rate 36 mL/min, EtOAc:CH_3OH 100:0 → 95:5, V = 19 mL). Colorless resin, R_f = 0.12 (EtOAc 100 %), yield 12 mg (0.04 mmol, 10 %), $C_{20}H_{25}NO_3$ (327.4). Purity (HPLC): 94.44 %, t_R = 16.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.30 (s, 6H, 2 x CH_3), 1.74 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.63 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 2.87 (dd, ^2J = 12.4 Hz, ^3J = 4.9 Hz, 1H, NHC*H*$_2$CHOHAr), 3.16 (dd, ^2J = 12.4 Hz, ^3J = 4.6 Hz, 1H, NHC*H*$_2$CHOHAr), 3.87 (d, ^2J = 13.1 Hz, 1H, NHC*H*$_2$Ph), 3.92 (d, ^2J = 13.1 Hz, 1H, NHC*H*$_2$Ph), 4.78 (t, ^3J = 4.7 Hz, 1H, NHCH$_2$C*H*OHAr), 6.33 (s, 1H, 8-CH), 6.70 (s, 1H, 5-CH), 7.26 – 7.33 (m, 1H, *p*-Ph), 7.32 – 7.38 (m, 4H, *o*-Ph, *m*-Ph). Signals for the NH- and OH-protons are not observed in the spectrum. ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 21.8 (1C, 4-CH_2), 27.0 (1C, CH_3), 27.0 (1C, CH_3), 33.2 (1C, 3-CH_2), 53.0 (1C, NH*C*H$_2$CHOHAr), 53.3 (1C, NH*C*H$_2$Ph), 73.3 (1C, NHCH$_2$*C*HOHAr), 74.3 (1C, C-2), 106.1 (1C, C-8), 111.7 (1C, C-4a), 119.0 (1C, C-6), 128.0 (1C, *p*-Ph), 128.7 (2C, *o*-Ph), 128.9 (2C, *m*-Ph), 130.0 (1C, C-5), 137.5 (1C, $C_{q,\ Phenyl}$), 155.2 (1C, C-8a), 155.5 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3298 (w, NH/OH), 2974 (w, CH), 2932 (w, CH), 2851 (w, CH), 1624 (w, C=C$_{ar.}$), 1493 (m, C=C$_{ar.}$), 1450 (m, C=C$_{ar.}$), 1153 (s, C-O), 1115 (s, C-O), 887 (w, CH$_{out\ of\ plane}$), 845 (m, CH$_{out\ of\ plane}$), 729 (m, CH$_{out\ of\ plane}$), 698 (m, CH$_{out\ of\ plane}$). HRMS (APCI): m/z = 328.1912 (calcd. 328.1907 for $C_{20}H_{26}NO_3$ [M+H$^+$]).

6-{1-Hydroxy-2-[(3-phenylpropyl)amino]ethyl}-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-7-ol (19c)

Under N_2 atmosphere, amine **18** (50 mg, 0.21 mmol) was dissolved in dry CH_2Cl_2 (10 mL). 3-Phenylpropionaldehyde (28 mg, 0.21 mmol, 1.0 eq) and $NaBH(OAc)_3$ (48 mg, 0.23 mmol, 1.1 eq) were added and the reaction mixture was stirred at rt. After 120 h, it was poured into ice cold H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 10

mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (ø = 1 cm, *h* = 22 cm, CH_2Cl_2:CH_3OH 99:1 + 1 % NEt_3, V = 10 mL), followed by preparative HPLC (method 3). Colorless resin, R_f = 0.42 (CH_2Cl_2:CH_3OH 99:1 + 1 % NEt_3), yield 8 mg (0.02 mmol, 10 %), $C_{22}H_{29}NO_3$ (355.5). Purity (HPLC): 94 %, t_R = 17.9 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.29 (s, 6H, 2 x CH_3), 1.73 (t, ^3J = 7.0 Hz, 2H, 3-CH_2), 1.85 – 2.02* (m, 2H, NHCH$_2$C*H*$_2$CH$_2$Ph), 2.58 – 2.69* (m, 4H, 4-CH_2, NHCH$_2$CH$_2$C*H*$_2$Ph), 2.70 – 2.81* (m, 2H, NHC*H*$_2$CH$_2$CH$_2$Ph), 2.86* (broad s, 1H, NHC*H*$_2$CHOHAr), 3.17* (broad s, 1H, NHC*H*$_2$CHOHAr), 4.73 – 4.93* (m, 1H, NHCH$_2$C*H*OHAr), 6.29 – 6.36* (m, 1H, 8-CH), 6.72 (s, 1H, 5-CH), 7.12 – 7.21 (m, 3H, *o*-Ph, *p*-Ph)), 7.21 – 7.32 (m, 2H, *m*-Ph). Signals for the NH- and OH-protons are not observed in the spectrum. *Signal resolution is impaired due to residual salts from preparative HPLC. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 24.3 (1C, C-4), 29.5 (1C, CH_3), 29.5 (1C, CH_3), 32.7 (1C, NHCH$_2$*C*H$_2$CH$_2$Ph), 35.7 (1C, C-3), 35.8 (1C, NHCH$_2$CH$_2$*C*H$_2$Ph), 56.0 (1C, NH*C*H$_2$CHOHAr), 58.9 (1C, NH*C*H$_2$CH$_2$CH$_2$Ph), 75.1 (1C, NHCH$_2$*C*HOHAr), 76.9 (1C, C-2), 108.6 (1C, C-8), 114.3 (1C, C-4a), 121.5 (1C, C-6), 128.7 (1C, *p*-Ph), 131.0 (2C, *o*-Ph), 131.1 (2C, *m*-Ph), 132.5 (1C, C-5), 143.7 (1C, $C_{q,\ Phenyl}$), 157.7 (1C, C-8a), 157.9 (1C, C-7). FT-IR (neat): ṽ [cm^{-1}] = 3024 (w, $CH_{ar.}$), 2974 (w, CH), 2924 (w, CH), 2851 (w, CH), 1624 (m, C=$C_{ar.}$), 1493 (m, C=$C_{ar.}$), 1450 (m, C=$C_{ar.}$), 1150 (s, C-O), 1115 (s, C-O), 907 (m, $CH_{out\ of\ plane}$), 849 (w, $CH_{out\ of\ plane}$), 729 (s, $CH_{out\ of\ plane}$), 698 (m, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 356.2233 (calcd. 356.2220 for $C_{22}H_{30}NO_3$ [M+H$^+$]).

7-(Methoxymethoxy)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-carbaldehyde (20)

Under N_2, aldehyde **6** (700 mg, 3.4 mmol) was dissolved in dry DMF (20 mL). Anhydrous Na_2CO_3 (1091 mg, 10.3 mmol, 3.0 eq) was added and the mixture was stirred at rt for 15 min. $ClCH_2OCH_3$ (MOM-Cl, 810 mg, 10.1 mmol, 3.0 eq) was added dropwise and the mixture was stirred at rt for another 65 h. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified using automated flash chromatography (SNAP 100 g, flow rate 50 mL/min, CH_2Cl_2 100 %, V = 19 mL). Colorless solid, mp 58 °C, R_f = 0.28 (CH_2Cl_2), yield 770 mg (3.1 mmol, 91 %), $C_{14}H_{18}O_4$ (250.3). Purity (HPLC): 98 %, t_R =

20.5 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.35 (s, 6H, 2 x CH_3), 1.81 (t, ^{3}J = 6.7 Hz, 2H, 3-CH_2), 2.74 (td, ^{3}J = 6.8 Hz, ^{4}J = 1.1 Hz, 2H, 4-CH_2), 3.50 (s, 3H, OCH_3), 5.23 (s, 2H, O-CH_2-O), 6.57 (s, 1H, 8-CH), 7.61 (t, ^{3}J = 1.1 Hz, 1H, 5-CH), 10.30 (s, 1H, CH=O). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.6 (1C, C-4), 27.1 (2C, CH_3), 32.7 (1C, C-3), 56.6 (1C, O*C*H_3), 76.2 (1C, C-2), 94.8 (1C, O-*C*H_2-O), 103.2 (1C, C-8), 115.2 (1C, C-4a), 119.0 (1C, C-6), 130.0 (1C, C-5), 159.8 (1C, C-7), 161.1 (1C, C-8a), 188.6 (1C, CH=O). FT-IR (neat): ṽ [cm^{-1}] = 2974 (w, CH), 2936 (w, CH), 2874 (w, CH), 1667 (s, C=O), 1609 (s, C=$C_{ar.}$), 1570 (s, C=$C_{ar.}$), 1485 (s, C=$C_{ar.}$), 1107 (s, C-O), 918 (m, $CH_{out\ of\ plane}$), 891 (m, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 251.1275 (calcd. 251.1278 for $C_{14}H_{19}O_4$ [M+H^+]).

(*E*)- and (*Z*)-3-[7-(methoxymethoxy)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl]propenenitrile ((*E*)-21 and (*Z*)-21)

Under N_2 atmosphere, aldehyde **20** (401 mg, 1.6 mmol) was dissolved in dry toluene (20 mL). (Triphenylphosporanylidene)acetonitrile (966 mg, 3.2 mmol, 2.0 eq) was added, and the reaction mixture was heated to 120 °C for 112 h. After cooling to rt, the solvent was removed *in vacuo*, and the residue was purified by automated flash chromatography (SNAP 50 g, flow rate 25 mL/min, CH_2Cl_2:CyHex 90:10, V = 19 mL). At first (*Z*)-**21** was eluted, followed by a mixture of (*Z*)-**21** and (*E*)-**21**. Then (*E*)-**21** was eluted.

(*Z*)-**21**: Colorless solid, mp 79 °C, R_f = 0.28 (CH_2Cl_2:CyHex 90:10), yield 136 mg (0.50 mmol, 31 %), $C_{16}H_{19}NO_3$ (273.3). Purity (HPLC): 99 %, t_R = 21.0 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.34 (s, 6H, 2 x CH_3), 1.81 (t, ^{3}J = 6.7 Hz, 2H, 3-CH_2), 2.77 (t, ^{3}J = 6.7, Hz, 2H, 4-CH_2), 3.46 (s, 3H, OCH_3), 5.16 (s, 2H, OC*H*$_2$$OCH_3$), 5.23 (d, ^{3}J = 12.3 Hz, 1H, ArCH=C*H*CN), 6.56 (s, 1H, 8-CH), 7.48 (d, ^{3}J = 12.2 Hz, 1H, ArC*H*=CHCN), 7.95 (s, 1H, 5-CH). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.9 (1C, C-4), 27.1 (2C, 2 x CH_3), 32.8 (1C, C-3), 56.5 (1C OCH_3), 75.6 (1C, C-2), 90.9 (1C, ArCH=*C*HCN), 94.9 (1C, O*C*$H_2$$OCH_3$), 103.2 (1C, C-8), 114.8 (1C, C-4a), 116.0 (1C, C-6), 118.7 (1C, CN), 129.1 (1C, C-5), 142.9 (1C, Ar*C*H=CHCN), 155.4 (1C, C-7), 157.8 (1C, C-8a). FT-IR (neat): ṽ [cm^{-1}] = 2974 (w, CH), 2951 (w, CH), 2928 (w, CH), 2199 (m, CN), 1620 (m, C=$C_{ar.}$), 1597 (s, C=C), 1566 (m, C=$C_{ar.}$), 1489 (s, C=$C_{ar.}$), 1111 (s, C-O), 1069 (s, C-O), 918 (s, $CH_{out\ of\ plane}$), 887 (m, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 274.1450 (calcd. 274.1438 for $C_{16}H_{20}NO_3$ [M+H^+]).

(*E*)-**21**: Colorless resin, R_f = 0.20 (CH_2Cl_2:CyHex 90:10), yield 55 mg (0.20 mmol, 13 %), $C_{16}H_{19}NO_3$ (273.3). Purity (HPLC): 91 %, t_R = 22.4 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.33 (s, 6H, 2 x CH_3), 1.79 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.71 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 3.47 (s, 3H, OCH_3), 5.18 (s, 2H, OC*H*$_2$$OCH_3$), 5.85 (d, *J* = 16.7 Hz, 1H, ArCH=C*H*CN), 6.56 (s, 1H, 8-CH), 7.10 (s, 1H, 5-CH), 7.55 (d, ^3J = 16.7 Hz, 1H, ArC*H*=CHCN). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.7 (1C, C-4), 27.0 (2C, 2 x CH_3), 32.7 (1C, C-3), 56.5 (1C, OCH_3), 75.6 (1C, C-2), 93.2 (1C, ArCH=*C*HCN), 94.6 (1C, O*C*H$_2$$OCH_3$), 103.5 (1C, C-8), 114.9 (1C, C-4a), 115.8 (1C, C-6), 119.9 (1C, CN), 129.7 (1C, C-5), 146.3 (1C, Ar*C*H=CHCN), 155.7 (1C, C-7), 157.9 (1C, C-8a). FT-IR (neat): ṽ [cm^{-1}] = 2974 (w, CH), 2932 (w, CH), 2210 (m, CN), 1601 (s, C=C), 1566 (s, C=C$_{ar.}$), 1489 (s, C=C$_{ar.}$), 1115 (s, C-O), 1069 (s, C-O), 926 (m, CH$_{out\ of\ plane}$), 907 (m, CH$_{out\ of\ plane}$). HRMS (APCI): m/z = 274.1469 (calcd. 274.1438 for $C_{16}H_{20}NO_3$ [M+H$^+$]).
Mixture of (*Z*)-**21** and (*E*)-**21**: Colorless resin, yield 222 mg (0.81 mmol, 51 %), ratio (*Z*)-**21** : (*E*)-**21** = 1 : 1 (HPLC).

3-[7-(Methoxymethoxy)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl]propanenitrile (22)

Under N_2, a Schlenk flask was charged with Pd/C (57 mg, 10 wt-%) and dry CH_3OH (5 mL) was added. Acrylonitrile (*E*/*Z*)-**21** (553 mg, 2.02 mmol, 1.0 eq) was dissolved in dry CH_3OH (20 mL) and the solution added slowly. The reaction mixture was stirred under H_2 atmosphere (1 bar) for 6 h, followed by filtration. The solvent was removed *in vacuo*. ^{1}H NMR spectroscopy showed significant amounts of remaining starting material. Therefore, the mixture was hydrogenated once more as described above for further 4 h. Colorless oil, R_f = 0.30 (CH_2Cl_2:CyHex 90:10), yield 479 mg (1.74 mmol, 86 %), $C_{16}H_{21}NO_3$ (275.4). Purity (HPLC): 67 %, t_R =21.0 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 6H, 2 x CH_3), 1.76 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 2.59 (t, ^3J = 7.5 Hz, 2H, ArCH_2C*H*$_2$CN), 2.68 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 2.87 (t, ^3J = 7.4 Hz, 2H, ArC*H*$_2$$CH_2$CN), 3.46 (s, 3H, OCH_3), 5.14 (s, 2H, OC*H*$_2$$OCH_3$), 6.54 (s, 1H, 8-CH), 6.84 (s, 1H, 5-CH). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 18.2 (1C, ArCH_2*C*H$_2$CN), 21.8 (1C, C-4), 26.7 (1C, Ar*C*H$_2$$CH_2$CN), 27.0 (2C, 2 x CH_3), 33.0 (1C, C-3), 56.3 (1C, OCH_3), 74.5 (1C, C-2), 94.6 (1C, O*C*H$_2$$OCH_3$), 103.2 (1C, C-8), 114.0 (1C, C-4a), 118.5 (1C, C-6), 120.0 (1C, CN), 130.7 (1C, C-5), 154.1 (1C, C-8a), 154.3 (1C, C-7). FT-IR (neat): ṽ [cm^{-1}] = 2970 (m, CH), 1932 (m, CH), 2245 (w, CN), 1620 (m, C=C$_{ar.}$), 1585 (m, C=C$_{ar.}$), 1497 (s,

C=$C_{ar.}$), 1115 (s, C-O), 1065 (s, C-O), 922 (m, $CH_{out\ of\ plane}$), 883 (w, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 276.1569 (calcd. 276.1594 for $C_{16}H_{22}NO_3$ [M+H$^+$]).

3-[7-(Methoxymethoxy)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl]propan-1-amine (23)

Under N_2, propanenitrile **22** (200 mg, 0.73 mmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (20 mL). After cooling to 0 °C, $LiAlH_4$ (114 mg, 3.00 mmol, 4.1 eq) was added and the reaction mixture was stirred for 23 h while warming to rt. Saturated Na-K-tartrate solution was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by high-vacuum Kugelrohr distillation. Colorless oil, bp 160 °C at 5.5 x 10^{-2} mbar, R_f = 0.12 (CH_2Cl_2:CyHex 90:10 + 1 % NEt_3), yield 155 mg (0.55 mmol, 75 %), $C_{16}H_{25}NO_3$ (279.4). Purity (HPLC): 93 %, t_R = 16.1 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 6H, 2 x CH_3), 1.71 – 1.78 (m, 4H, 3-CH_2, $CH_2CH_2CH_2NH_2$), 2.08 (broad s, 2H, NH_2), 2.56 – 2.60 (m, 2H, $CH_2CH_2CH_2NH_2$), 2.67 (t, ^3J = 6.7 Hz, 2H, 4-CH_2), 2.74 (t, ^3J = 7.0 Hz, 2H, $CH_2CH_2CH_2NH_2$), 3.46 (s, 3H, OCH_3), 5.13 (s, 2H, OCH_2OCH_3), 6.52 (s 1H, 8-CH), 6.80 (s, 1H, 5-CH). ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.9 (1C, C-4), 26.8 (1C, $CH_2CH_2CH_2NH_2$), 27.0 (2C, 2 x CH_3), 33.1 (1C, C-3), 34.0 (1C, $CH_2CH_2CH_2NH_2$), 41.7 (1C, $CH_2CH_2CH_2NH_2$), 56.2 (1C, OCH_3), 74.2 (1C, C-2), 94.7 (1C, OCH_2OCH_3), 103.2 (1C, C-8), 113.8 (1C, C-4a), 122.3 (1C, C-6), 130.3 (1C, C-5), 152.9 (1C, C-8a), 154.3 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3372 (w, NH_2), 2970 (w, CH), 2924 (m, CH), 2851 (w, CH), 1620 (m, C=$C_{ar.}$), 1585 (m, C=$C_{ar.}$), 1493 (s, C=$C_{ar.}$), 1111 (s, C-O), 1067 (s, C-O), 922 (m, $CH_{out\ of\ plane}$), 887 (w, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 280.1912 (calcd. 280.1907 for $C_{16}H_{26}NO_3$ [M+H$^+$]).

***N*-Benzyl-3-[7-(methoxymethoxy)-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl]propan-1-amine (24)**

Amine **23** (204 mg, 0.73 mmol) was dissolved in CH_2Cl_2 (5 mL) and benzaldehyde (75 mg, 0.71 mmol, 1.0 eq) was added. The reaction mixture was stirred at rt for 20 h. The mixture was cooled to 0 °C, $NaBH_4$ (97 mg, 2.56 mmol, 14.0 eq) was added, and the reaction mixture was stirred at rt for 119 h. After cooling to 0 °C, CH_3OH (5 mL) was added and the mixture was stirred for 19 h while warming slowly to rt. H_2O was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic

layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP 50 g, flow rate 50 mL/min, CyHex:EtOAc 70:30 + 1 % DMEA, V = 19 mL). Colorless oil, R_f = 0.14 (CyHex:EtOAc + 1 % DMEA 70:30), yield 194 mg (0.53 mmol, 73 %), $C_{23}H_{31}NO_3$ (369.5). Purity (HPLC): 89 %, t_R = 19.7 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 6H, 2 x CH_3), 1.76 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 1.83 (quint, ^3J = 7.5 Hz, 2H, $CH_2CH_2CH_2NH$), 2.54 – 2.60 (m, 2H, $CH_2CH_2CH_2NH$), 2.66 (t, J = 6.7 Hz, 2H, 4-CH_2), 2.66 – 2.71 (m, 2H, $CH_2CH_2CH_2NH$), 3.43 (s, 3H, OCH_3), 3.81 (s, 2H, $NHCH_2Ph$), 5.10 (s, 2H, OCH_2OCH_3), 6.52 (s, 1H, 8-CH), 6.78 (s, 1H, 5-CH), 7.29 – 7.39 (m, 5H, Phenyl-CH). A signal for the NH-proton is not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.9 (1C, C-4), 27.0 (2C, 2 x CH_3), 27.3 (1C, $CH_2CH_2CH_2NH$), 30.2 (1C, $CH_2CH_2CH_2NH$), 33.1 (1C, C-3), 48.8 (1C, $CH_2CH_2CH_2NH$), 53.7 (1C, $NHCH_2Ph$), 56.1 (1C, OCH_3), 74.2 (1C, C-2), 94.7 (1C, OCH_2O), 103.2 (1C, C-8), 113.7 (1C, C-4a), 122.4 (1C, C-6), 127.3 (1C, *p*-Ph), 128.5 (2C, *m*-Ph), 128.6 (2C, *o*-Ph), 130.3 (1C, C-5), 139.5 (1C, $C_{q,\ Phenyl}$), 152.9 (1C, C-8a), 154.3 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2970 (w, CH), 2928 (m, CH), 2851 (w, CH), 1620 (m, C=C$_{ar.}$), 1585 (m, C=C$_{ar.}$), 1493 (s, C=C$_{ar.}$), 1115 (s, CO$_{Phenol}$), 1065 (s, CO$_{Phenol}$), 922 (m, CH$_{out\ of\ plane}$), 887 (w, CH$_{out\ of\ plane}$), 733 (s, CH$_{out\ of\ plane}$), 698 (s, CH$_{out\ of\ plane}$). HRMS (APCI): m/z = 370.2376 (calcd. 370.2377 for $C_{23}H_{32}NO_3$ [M+H$^+$]).

6-[3-(Benzylamino)propyl]-2,2-dimethyl-3,4-dihydro-2*H*-benzopyran-7-ol (25)

The MOM-protected benzopyran **24** (100 mg, 0.27 mmol) was dissolved in CH_3OH (40 mL) and the solution was cooled to 0 °C. Conc. $HCl_{aq.}$ (2 mL) was slowly added. The reaction mixture was stirred at rt for 23 h. H_2O was added and the solution was brought to pH = 7 – 8 using aqueous NaOH solution (1 M). The aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automated flash chromatography (SNAP HP-Sil 10 g, flow rate = 12 mL/min, CH_2Cl_2:EtOAc 100:0 → 0:100, V = 19 mL). Colorless solid, mp 123 °C, R_f = 0.20 (CH_2Cl_2:EtOAc 0:100), yield 37 mg (0.11 mmol, 41 %), $C_{21}H_{27}NO_2$ (325.5). Purity (HPLC): 96 %, t_R = 20.2 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 6H, 2 x CH_3), 1.75 (t, ^3J = 6.7 Hz, 2H, 3-CH_2), 1.83 (quint, ^3J = 6.2 Hz, 2H, $NHCH_2CH_2CH_2Ar$), 2.63 (t, ^3J = 6.0 Hz, 2H, $NHCH_2CH_2CH_2Ar$), 2.64 – 2.70 (m, 4H, 4-CH_2, $NHCH_2CH_2CH_2Ar$), 3.80 (s, 2H, $NHCH_2Ph$), 6.36 (s, 1H, 8-CH), 6.70 (s, 1H, 5-CH), 7.27

– 7.31 (m, 1H, *p*-Ph), 7.33 - 7.39 (m, 4H, *o*-Ph, *m*-Ph). Signals for the OH- and NH-protons are not observed in the spectrum. ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) = 21.9 (1C, C-4), 25.8 (1C, $NHCH_2CH_2\mathit{C}H_2Ar$), 27.0 (2C, 2 x CH_3), 29.5 (1C, $NHCH_2\mathit{C}H_2CH_2Ar$), 33.3 (1C, C-3), 45.1 (1C, $NH\mathit{C}H_2CH_2CH_2Ar$), 53.0 (1C, $NH\mathit{C}H_2Ph$), 73.9 (1C, C-2), 105.3 (1C, C-8), 112.5 (1C, C-4a), 119.0 (1C, C-6), 127.9 (1C, *p*-Ph), 128.9 (2C, *o*-Ph), 128.9 (2C, *m*-Ph), 130.7 (1C, C-5), 137.6 (1C, $C_{q,\ Phenyl}$), 153.5 (1C, C-8a), 156.0 (1C, C-7). FT-IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3302 (w, NH/OH), 2970 (m, CH), 2943 (w, CH), 2928 (w, CH), 1624 (m, $C{=}C_{ar.}$), 1585 (m, $C{=}C_{ar.}$), 1489 (s, $C{=}C_{ar.}$), 1157 (C-O), 1115 (C-O), 899 (m, $CH_{out\ of\ plane}$), 849 (m, $CH_{out\ of\ plane}$), 748 (s, $CH_{out\ of\ plane}$), 698 (s, $CH_{out\ of\ plane}$). HRMS (APCI): m/z = 326.2119 (calcd. 326.2115 for $C_{21}H_{28}NO_2$ [$M+H^+$]).

3. Experimental procedures to determine antiprotozoal activity *in vitro*

3.1. Investigation of the antiprotozoal activity *in vitro*

In vitro assays for activity against *Trypanosoma brucei rhodesiense* (bloodstream trypomastigote stage, STIB 900 strain), *T. cruzi* (intracellular amastigote stage, Tulahuen C4 strain), *Leishmania donovani* (axenic amastigote stage, MHOM/ET/67/L82) and *Plasmodium falciparum* (erythrocytic stage, NF54 strain) as well as cytotoxicity determinations against L6 rat skeletal myoblasts were carried out at the Swiss Tropical and Public Health Institute according to established standard protocols described earlier.[6] Compounds used as positive controls were of commercial origin, with the exception of melarsoprol, which was a gift from WHO. Their purity (generally >95%) was specified by the manufacturers.

3.2. Activity against *Trypanosoma brucei rhodesiense* STIB900

This stock was isolated in 1982 from a human patient in Tanzania and after several mouse passages cloned and adapted to axenic culture conditions.[7] Minimum Essential Medium (MMEM, 50 µL) supplemented with 25 mM HEPES, 1g/L additional glucose, 1% MEM non-essential amino acids (100x), 0.2 mM 2-mercaptoethanol, 1mM Na-pyruvate and 15% heat inactivated horse serum was added to each well of a 96-well microtiter plate. Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/mL were prepared. Then $4x10^3$ bloodstream forms of *T. b. rhodesiense* STIB 900 in 50 µL was added to each well and the plate incubated at 37 °C under a 5 % CO_2 atmosphere for 70 h. 10 µL resazurin solution (resazurin, 12.5 mg in 100 mL double-distilled water) was then added to each well and incubation continued for a further 2-4 h. [8] Then the plates were read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wave length of 536 nm and an emission wave length of 588 nm. Data were analyzed with the graphic programme Softmax Pro (Molecular Devices Cooperation, Sunnyvale, CA, USA), which calculated IC_{50} values by linear regression[9] and 4-parameter logistic regression from the sigmoidal dose inhibition curves. Melarsoprol (Arsobal Sanofi-Aventis, received from WHO) is used as control.

3.3. Activity against *Trypanosoma cruzi*

Rat skeletal myoblasts (L-6 cells) were seeded in 96-well microtitre plates at 2000 cells/well in 100 µL RPMI 1640 medium with 10% FBS and 2 mM l-glutamine. After

24 h the medium was removed and replaced by 100 µL per well containing 5000 trypomastigote forms of *T. cruzi* Tulahuen strain C2C4 containing the β-galactosidase (Lac Z) gene.[10] After 48 h the medium was removed from the wells and replaced by 100 µL fresh medium with or without a serial drug dilution of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/mL. After 96 h of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterility. Then the substrate CPRG/Nonidet (50 µL) was added to all wells. A color reaction developed within 2–6 h and could be read photometrically at 540 nm. Data were analyzed with the graphic programme Softmax Pro (Molecular Devices), which calculated IC_{50} values by linear regression[9] and 4-parameter logistic regression from the sigmoidal dose inhibition curves. Benznidazole is used as control (IC50 0.5±0.2 µg/mL).

3.4. Activity against *Leishmania donovani axenic amastigotes*

Amastigotes of *L. donovani* strain MHOM/ET/67/L82 are grown in axenic culture at 37 °C in SM medium[11] at pH 5.4 supplemented with 10% heat-inactivated fetal bovine serum under an atmosphere of 5% CO_2 in air. One hundred microlitres of culture medium with 10^5 amastigotes from axenic culture with or without a serial drug dilution are seeded in 96-well microtitre plates. Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/mL are prepared. After 70 h of incubation the plates are inspected under an inverted microscope to assure growth of the controls and sterile conditions. 10 µL of resazurin (12.5 mg resazurin dissolved in 100 mL distilled water) are then added to each well and the plates incubated for another 2 h. Then the plates are read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wave length of 536 nm and an emission wave length of 588 nm. From the sigmoidal inhibition curves the IC_{50} values are calculated by linear regression[9] and 4-parameter logistic regression using SoftmaxPro software (Molecular Devices Cooperation, Sunnyvale, CA, USA).

3.5. Cytotoxicity assay

Assays were performed in 96-well microtiter plates, each well containing 100 µL of RPMI 1640 medium supplemented with 1 % L-glutamine (200 mM) and 10 % fetal bovine serum, and 4000 L-6 cells (a primary cell line derived from rat skeletal myoblasts).[12,13] Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/mL were prepared. After 70 h of incubation the plates were inspected under an

inverted microscope to assure growth of the controls and sterile conditions. 10 µL of Alamar Blue was then added to each well and the plates incubated for another 2 h. Then the plates were read with a Spectramax Gemini XS microplate fluorimeter (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wave length of 536 nm and an emission wave length of 588 nm. The IC_{50} values were calculated by non linear regression[9] from the sigmoidal dose inhibition curves using SoftmaxPro® software (Molecular Devices Cooperation, Sunnyvale, CA, USA). Podophyllotoxin (Sigma P4405) is used as control.

4. Mechanistic studies

4.1. Inhibition of *Plasmodium falciparum* dihydroorotate dehyrogenase (PfDHODH)

*Pf*DHODH activity was assessed using a colorimetric continuous assay that monitors 2,6-dichloroindophenol (DCIP) reduction. Change in absorbance at 600 nm was monitored in a range of 0 to 60 s at 25 °C using a microplate reader (Molecular Devices, SpectraMax 384 Plus, California, USA). The enzymatic reaction was analyzed in a total volume of 195 µL containing 50 mM Tris, pH 8.15, 150 mM, KCl, 0.1% (v/v) Triton X-100, 500 µM L-dihydroorotate, 18 µM decylubiquinone (CoQ_D), and 60 µM DCIP. The assay was started with 5 µL of 2.0 µM stock of enzyme prepared in a buffer containing 50 mM HEPES, pH 7.7, 400 mM NaCl, 10% (v/v) glycerol, 0.05% (v/v) Thesit®, and 1 mM EDTA, which resulting in a final concentration of *Pf*DHODH enzyme at 50 nM. A reference measurement was obtained by preparing the same solution without enzyme and atovaquone was used as control. Compounds were prepared as a 10 mM stock solution in DMSO. From this solution, dilutions were prepared in the assay mixture to achieve the compound final concentration of 10 µM and 50 µM and were analyzed in triplicate. Control enzyme activity in the absence of inhibitor was taken as 100 %.[14]

4.2. Inhibition of *Plasmodium falciparum* formate-nitrate-transporter (PfFNT)

The lactate transport inhibition assays were conducted by the group of Professor Beitz at the Christian-Albrechts-Universität of Kiel (Kiel, Germany). His contribution is gratefully acknowledged.

Codon-optimized PfFNT[15] was constitutively expressed from the pDR196 plasmid in W303-1A jen1Δady2Δ (MATa, can1-100, ade2-loc, his311-15, leu2-3,-112, trp1-1-1, ura3-1, jen1::kanMX4, ady2::hphMX4) yeast cells, kindly provided by M. Casal.[16] Cells were grown at 29 °C in uracil-free selective media with adenine, histidine, leucine, tryptophan and 2 % glucose. For the transport assays, yeast cultures were harvested at an OD_{600} of 0.9 to 1.0, and resuspended in 50 mM HEPES/Tris, pH 6.8 ± 0.1 to an OD_{600} of 50 ± 5. Aliquots of 80 µL yeast suspension in 1.5 ml reaction tubes were incubated for 15-20 min with 1 µL of DMSO alone or with DMSO-dissolved inhibitor to yield a final inhibitor concentration of 10 µM.[17] To initiate transport, 20 µL of substrate solution (end concentration 1 mM L-lactate and 0.04 µCi [1-^{14}C]L-lactate, specific activity 55 mCi mmol^{-1}; Hartmann Analytic) was added. Transport was stopped after 30 s by

adding 1 mL of ice-cold water and immediately transferring the samples onto a vacuum filtration unit with 0.45 µm GF/C filter membranes (Whatman). The filters were washed with 7 mL of ice-cold water and placed into scintillation vials containing 3 mL of scintillation cocktail (Quicksafe A; Zinsser Analytic) for analysis using a Packard TriCarb liquid scintillation counter (Perkin Elmer Inc). All measurements were done in triplicate and background radiolabel obtained from non-expressing yeast cells was subtracted.[18]

4.3. Inhibition of *Trypanosoma brucei brudei* trypanothione reductase

Recombinant *T. brucei* trypanothione reductase (TR) and trypanothione disulfide (TS_2) were prepared as described previously.[19,20] Shortly, TR activity was measured at 25 °C in a total volume of 1 mL in the presence of 100 µM NADPH and 5–20 mU enzyme in TR assay buffer (40 mM HEPES, 1 mM EDTA, pH 7.5) containing 5% DMSO. The reaction was started by adding TS_2, and NADPH consumption was followed spectrophotometrically at 340 nm. To determine the percentage of inhibition, the assays contained 100 µM or 40 µM TS_2, in the absence and presence of a fixed concentration of inhibitor. The type of inhibition was 1determined by a Lineweaver-Burk plot. The inhibitor constants were calculated by a non-linear regression fit with the program GraphPad Prism (Version 5.04, GraphPad Software, Inc., CA, USA).[21]

Table S2: Inhibition of *T. brucei* trypanothione recuctase (TR) by compounds **9c** and **10b**.

compd.	c (inhibitor) [µM]	TS_2 [µM]	TR activity [U/ml]	TR activity [%]	Inhibition [%]
DMSO 5 %	-	100	1.53	100	0
DMSO 5 %	-	40	1.25	100	0
9c	200	100	1.55	100	0
9c	200	40	1.23	99.6	0.4
10b	200	100	1.43	95	5
10b	200	40	1.19	97	3

4.4. Affinity towards σ_1 and σ_2 receptors[22-24]

General procedures for the receptor binding assays

The test compound solutions were prepared by dissolving approximately 10 µmol (usually 2-4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5 % aqueous polyethylenimine solution for 2 h at rt before use. All binding experiments were carried out in duplicates in the 96 well multiplates. The concentrations given are the final concentration in the assay. Generally, the assays were performed by addition of 50 µL of the respective assay buffer, 50 µL of test compound solution in various concentrations (10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} and 10^{-10} mol/L), 50 µL of the corresponding radioligand solution and 50 µL of the respective receptor preparation into each well of the multiplate (total volume 200 µL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500-600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration, each well was washed five times with 300 µL of water. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 min. After solidifying of the scintillator at rt, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat corresponding to one well of the multiplate was measured for 5 min with the [^{3}H]-counting protocol. The overall counting efficiency was 20 %. The IC_{50} values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC_{50} values were transformed into K_i values using the equation of Cheng and Prusoff.[25] The K_i values are given as mean value ± SEM from three independent experiments.

σ_1 receptor assay

The assay was performed with the radioligand [^{3}H]-(+)-pentazocine (22.0 Ci/mmol; Perkin Elmer). The thawed membrane preparation of guinea pig brain (about 100 µg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 µM unlabeled (+)-pentazocine. The K_d value of (+)-pentazocine is 2.9 nM.[26]

σ_2 receptor assay

The assays were performed with the radioligand [^{3}H]di-*o*-tolylguanidine (specific activity 50 Ci/mmol; ARC, St. Louis, MO, USA). The thawed rat liver membrane preparation (about 100 µg protein) was incubated with various concentrations of the test compound, 3 nM [^{3}H]di-*o*-tolylguanidine and buffer containing (+)-pentazocine (500 nM (+)-pentazocine in TRIS buffer (50 mM TRIS, pH 8.0)) at rt. The non-specific binding was determined with 10 µM non-labeled di-*o*-tolylguanidine. The K_d value of di-*o*-tolylguanidine is 17.9 nM.[27]

σ_1 and σ_2 receptor affinities of the synthesized 1-benzopyrans

Table S3: σ_1 and σ_2 receptor affinities of lead compounds and prepared amines.

	n	K_i ± SEM [nM]	
		σ_1	σ_2
rac-**2**	-	3290	3810
(*R*)-**2**	-	0 %	0 %
(*S*)-**2**	-	5100	4 %
rac-**3**	-	184	745
8a	1	300	14 %[a]
8b	2	1000	0 %[a]
8c	3	450	0 %[a]
8d	4	353	1200
9a	1	427	538
9b	2	168	1800
9c	3	74 ± 9	1000
9d	4	120	1050
10a	1	677	5 %[a]
10b	2	282	930
10c	3	146	296
10d	4	141	8000
12a	1	336	9 %[a]
12b	2	149	11 %[a]
12c	3	631	0 %[a]
12d	4	263	0 %[a]
19a	1	222	3600
19c	3	614	8 %[a]
23	-	414	0 %[a]
24	-	5.6 ± 0.8	337
25	-	2.4 ± 0.7	1300

[a]: values in % represent the inhibition of radioligand binding at a test compound concentration of 1 µM. Inhibition in % is given for compounds with very low affinity.
[b]: For low-affinity compounds (K_i > 100 nM) the K_i values were recorded only once.
SEM: standard error of the mean.

5. Pharmacokinetic studies

General incubation procedure for *in vitro* metabolism

Liver microsomes (7.8 mg protein/mL in case of mouse liver microsome batch 1, 3.7 mg protein/mL in case of mouse liver microsome batch 2) were added to an Eppendorf cap filled with sodium phosphate buffer pH 7.4 (PBS, 0.1 M), $MgCl_2$ solution (0.05 M), NADPH or UDPGA solution (2 mg/mL in PBS) and DMSO stock solution, giving a total volume of 200 µL. Final concentrations for the incubations were 75 mM PBS, 0.6 mM NADPH and/or 0.77 mM UDPGA, 1 mg/mL microsomal protein, 50 µM of the respective compound, 12.5 mM $MgCl_2$, and 0.5 % DMSO. The suspension was mixed vigorously and incubated (37 °C, 90 min, 900 rpm). Subsequently, the incubation was stopped by addition of CH_3CN/CH_3OH (1:1, 400 µL), the caps were cooled down (0 °C, 10 min) and the precipitated proteins were separated by centrifugation (4 °C, 15 min, 16000 rpm). Afterwards, the supernatant was analyzed by LC-MS (LC-qToF). With the same procedure, the empty value (without stock solution), blank value (without NADPH), buffer sample (parent incubated in PBS solution) and negative control (solvent (599 µL) and DMSO stock solution (1 µL)) were prepared.

Identification of metabolites *in vivo*

During the *in vivo* efficacy study, blood samples were taken 1 h before the last treatment and 1 h, 2 h, 4 h, 8 h, and 24 h after the last treatment. Sample acquisition was alternated between the respective subgroups for each route of administration (e.g. 1 h before treatment: A1; 1 h after treatment: A2, 2 h after treatment: A1 etc.). The samples were frozen at -80 °C to inactivate the *Plasmodium* parasites. Afterwards samples were thawed and cold acetonitrile (-20 °C, 500 µL) was added to each Eppendorf cap to induce protein precipitation. After vigorous stirring (5 s) of the suspension, the precipitated proteins were separated by centrifugation (4 °C, 8 min, 13.000 rpm). The supernatant (200 µL) was analyzed by LC-MS (LC-qToF).

LC-qToF setup

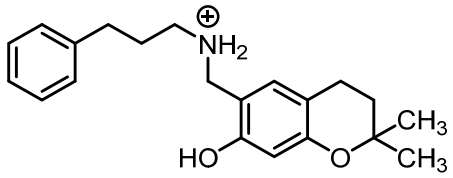
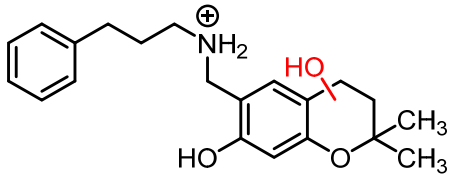
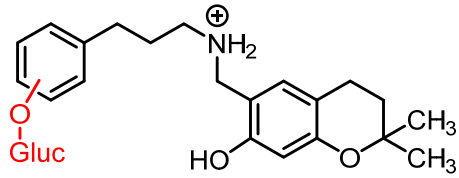
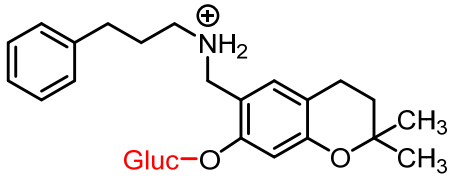
For the determination of exact masses and for conducting MS/MS experiments, an LC system was coupled with a quadrupole time-of-flight (qToF) mass spectrometer.

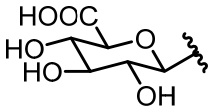
HPLC-DAD (Thermo Fisher Scientific, Dreieich, Germany): Solvent rack (SRD 3600); pump (DGP-3600RS); autosampler (WPS-3000RS); column oven (TCC-3000RS); precolumn: SecurityGuard™ Cartridge AQ C18 (4.0 x 2.0 mm, 4.0 µm particle size);

column: Synergi™ Hydro-RP (50 x 2.1 mm, 2.5 µm particle size, Phenomenex®, Aschaffenburg, Germany); temperature: 30 °C and DAD-detector (DAD-3000RS). The LC system was coupled with a micrOTOF-Q II (Bruker Daltonics, Bremen, Germany).
The ESI-qToF was operated in positive ion polarity in the full scan mode (*m/z* 70 –700, 200 – 1000 or 500 – 1600) with the following settings: capillary voltage 4500 V; end plate offset -500 V; collision cell RF 300.0 Vpp; nebulizer 2.0 bar; dry heater 200 °C; dry gas 9.0 L/min. To protect the MS from salts or other components of the matrices, a six-port valve was used to elute the first 2.0 min of each run into the waste (cut-off). In case of MS/MS experiments the isolation window of the first quadrupole was set to 10 *m/z* units (for *m/z* < 600) or 20 *m/z* units (for *m/z* > 600). The collision energy of the second quadrupole was set in the range of 10 – 35 eV and is given for each experiment. For data handling and control of the system the software Data Analysis and Hystar from Bruker Daltonics (Bremen, Germany) was used. The calibration of the ToF spectra was achieved by injection of $LiHCO_2$ (*m/z* < 700, *i*-propanol/H_2O 1:1, 10 mM) via a 20 µL sample loop within each LC run at 2.0 – 2.2 min.

LC parameters: mobile phase A: CH_3CN/H_2O 10:90 + 0.1% HCO_2H; mobile phase B: CH_3CN/H_2O 90:10 + 0.1% HCO_2H; mobile phase C: H_2O + 0.1% HCO_2H; pump 1: flow rate: 0 – 3 min: 0.1 mL/min, 3 – 3.1 min: from 0.1 mL/min to 0.4 mL/min, 3.1 – 17.9 min: 0.4 mL/min, 17.9 – 18 min: from 0.4 mL/min to 0.1 mL/min; gradient elution: (A% in B): 0 - 3.1 min: 100%, 3.1 – 12 min: gradient from 100% to 0%, 12 – 14.5 min: 0%, 14.5 – 15 min: gradient from 0% to 100%, 15 – 18 min: 100%; pump 2: flow rate: 0 – 3 min: 0.3 mL/min, 3 – 3.1 min: from 0.3 mL/min to 0.0 mL/min, 3.1 – 17.9 min: 0.0 mL/min, 17.9 – 18 min: from 0.0 mL/min to 0.3 mL/min; isocratic: (C%): 0 – 18 min: 100%.

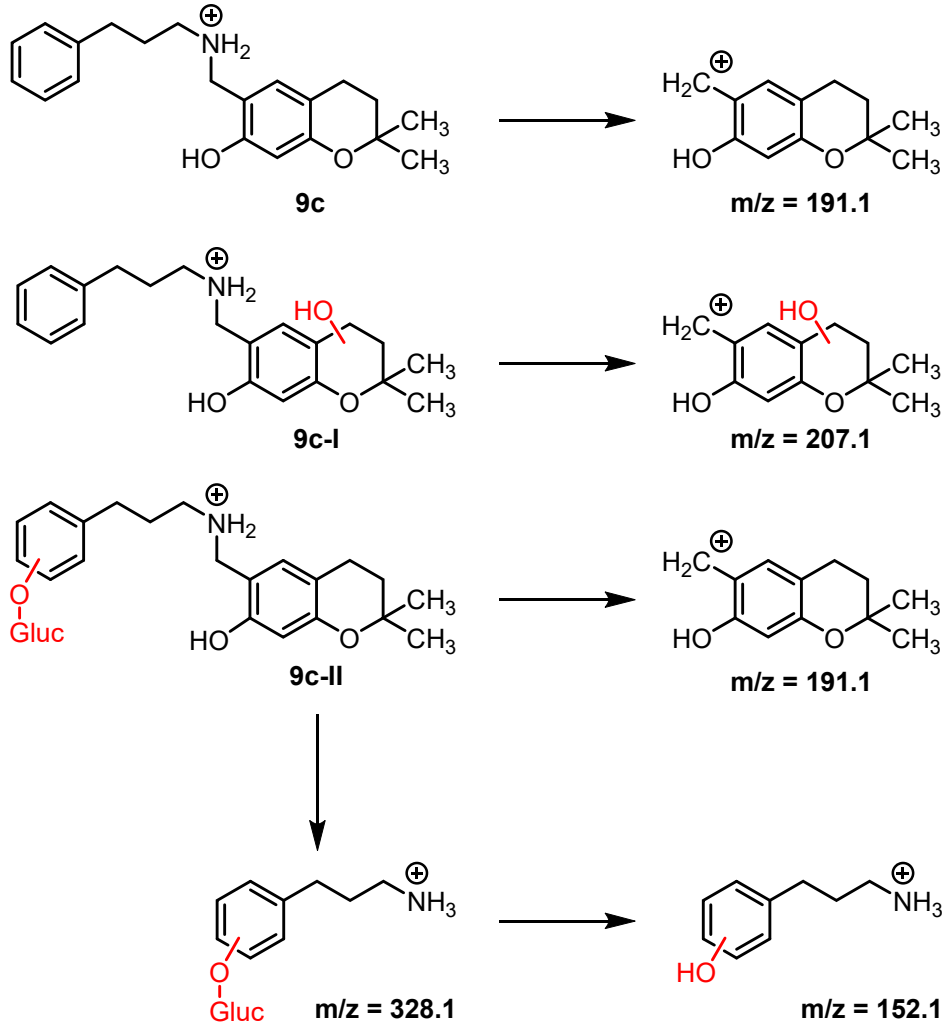
Table S4: Exact mass, retention time (t_R), and intensity (in mass counts/s) of 1-benzopyran-7-ol **9c** and possible metabolites formed *in vitro*, measured in positive ion mode ($M+H^+$)

compd.	formula	exact mass	t_R [min]	intensity [counts/s]
 **9c**	$C_{21}H_{28}NO_2^+$	326.2115	9.73	$1.1 * 10^5$
 **9c-I**	$C_{21}H_{28}NO_3^+$	342.2064	8.71	$7.1 * 10^4$
 **9c-II**	$C_{27}H_{36}NO_9^+$	518.5825	8.06	$0.88 * 10^4$
 **9c-III**	$C_{27}H_{36}NO_8^+$	502.2435	9.11	$1.9 * 10^4$

Gluc = 

t_R: retention time

Fragmentation pattern



Scheme S1: Fragmentation pattern and corresponding *m/z* values of the parent compound **9c** and the metabolites **9c-I** and **9c-II**.

6. References

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reductase from Trypanosoma cruzi. Catalytic properties of the enzyme and inhibition studies with trypanocidal compounds. *Eur. J. Biochem.* **1989**, *180*, 267–272.

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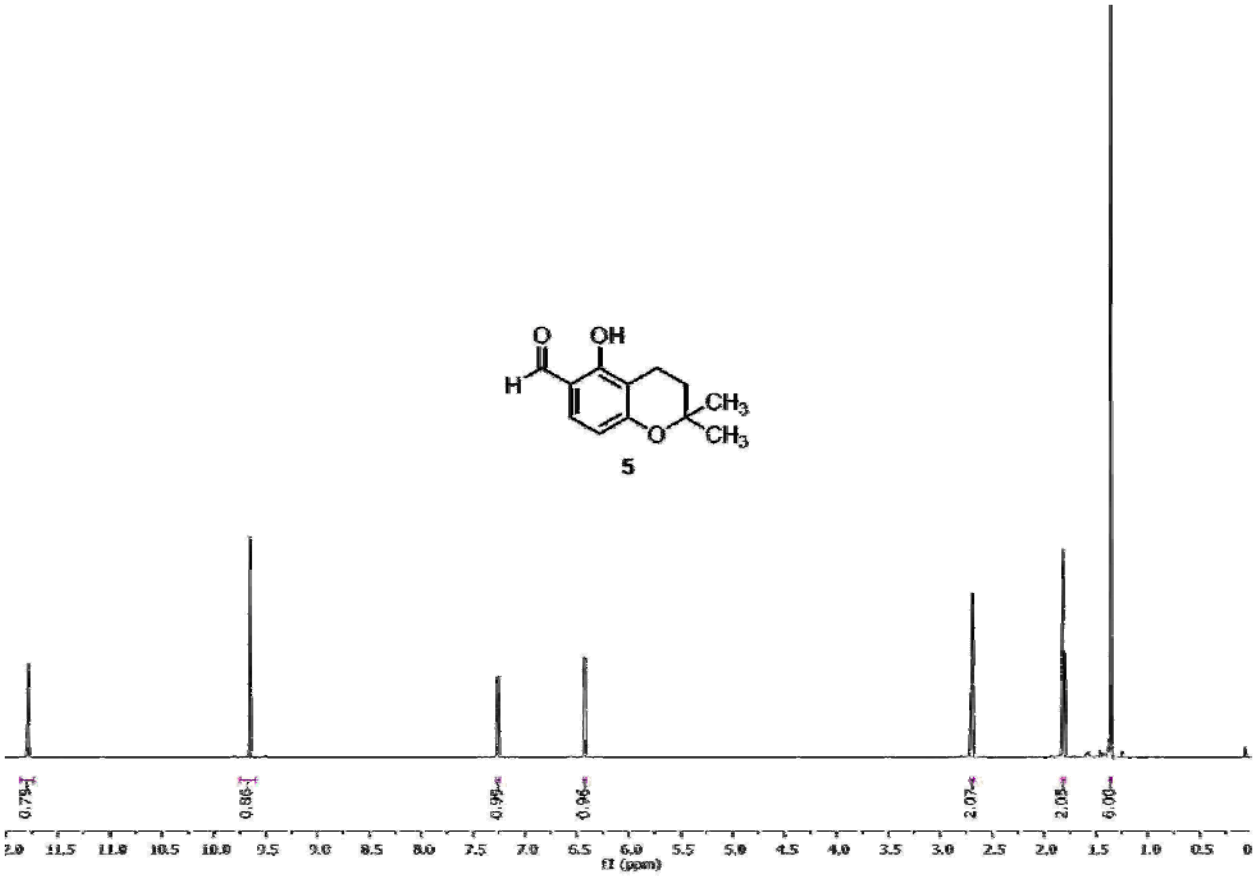
7. NMR spectra



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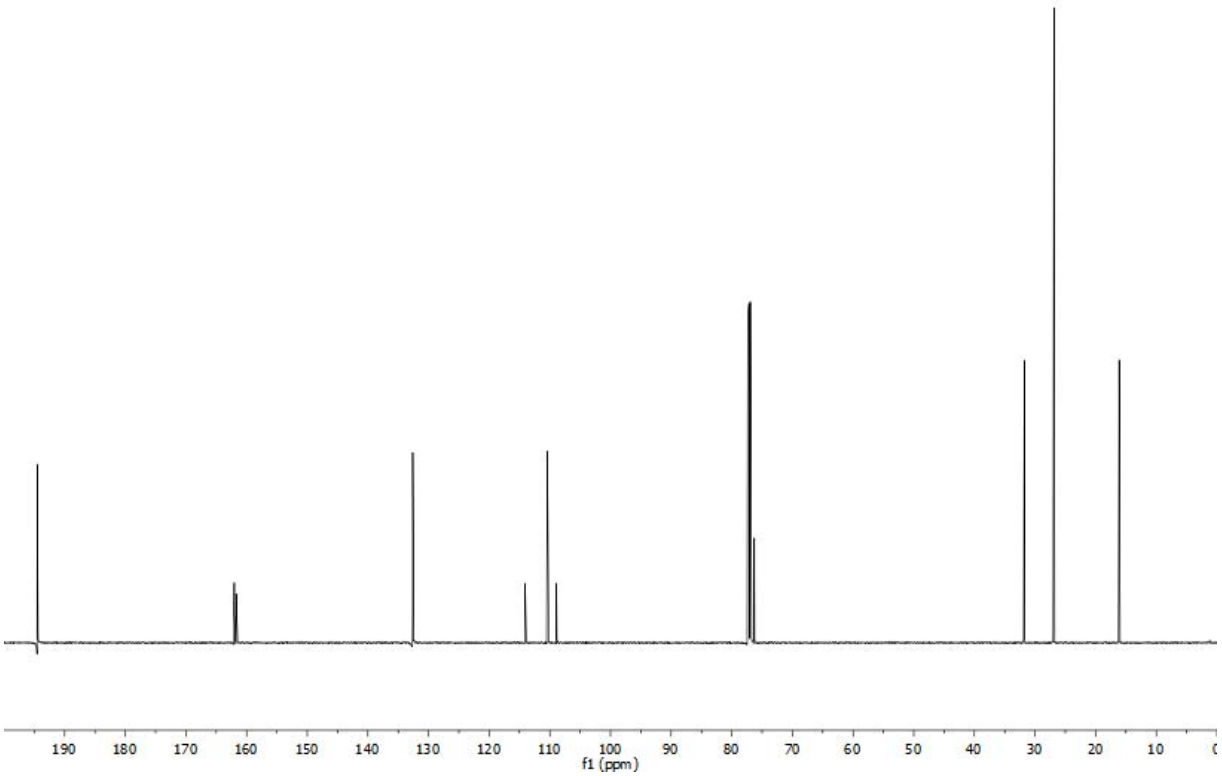

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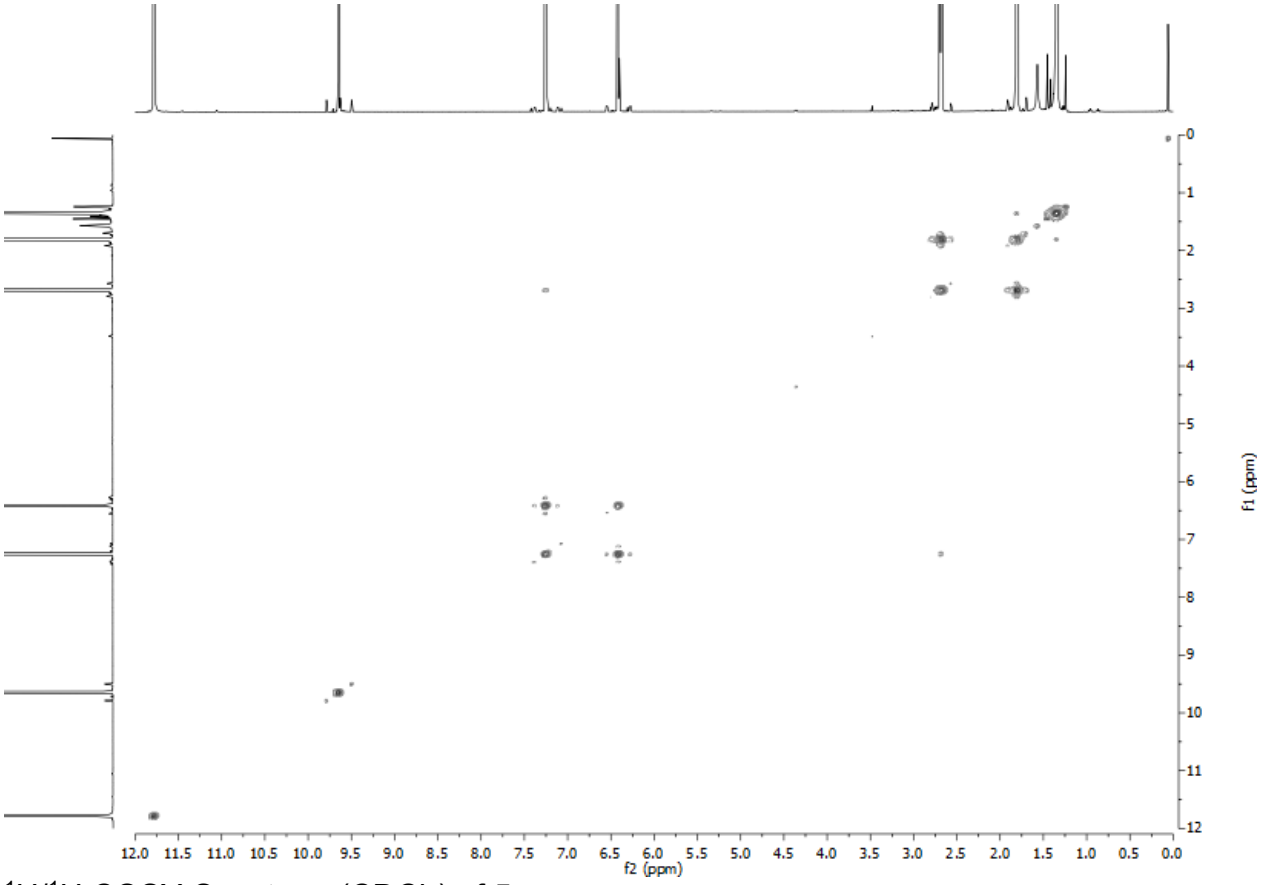
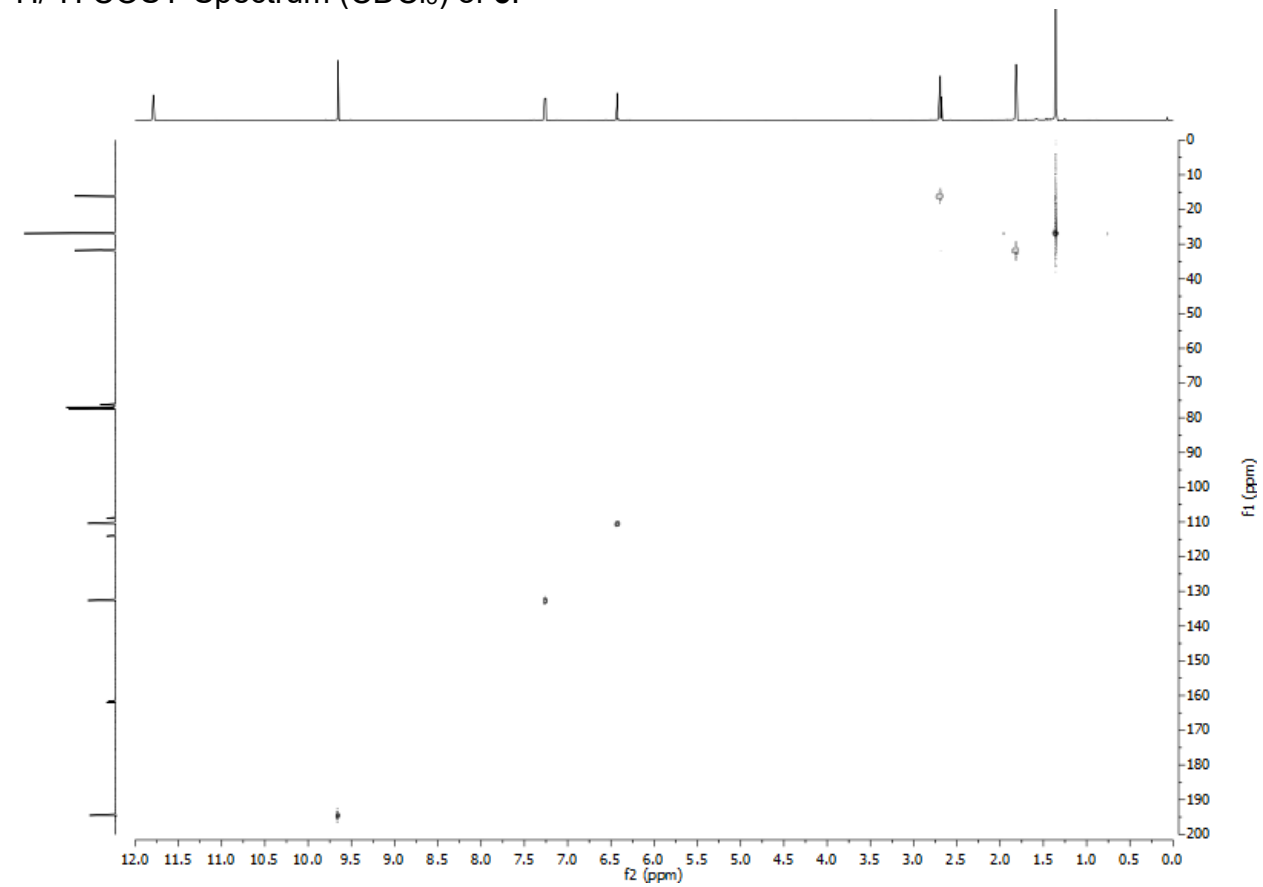
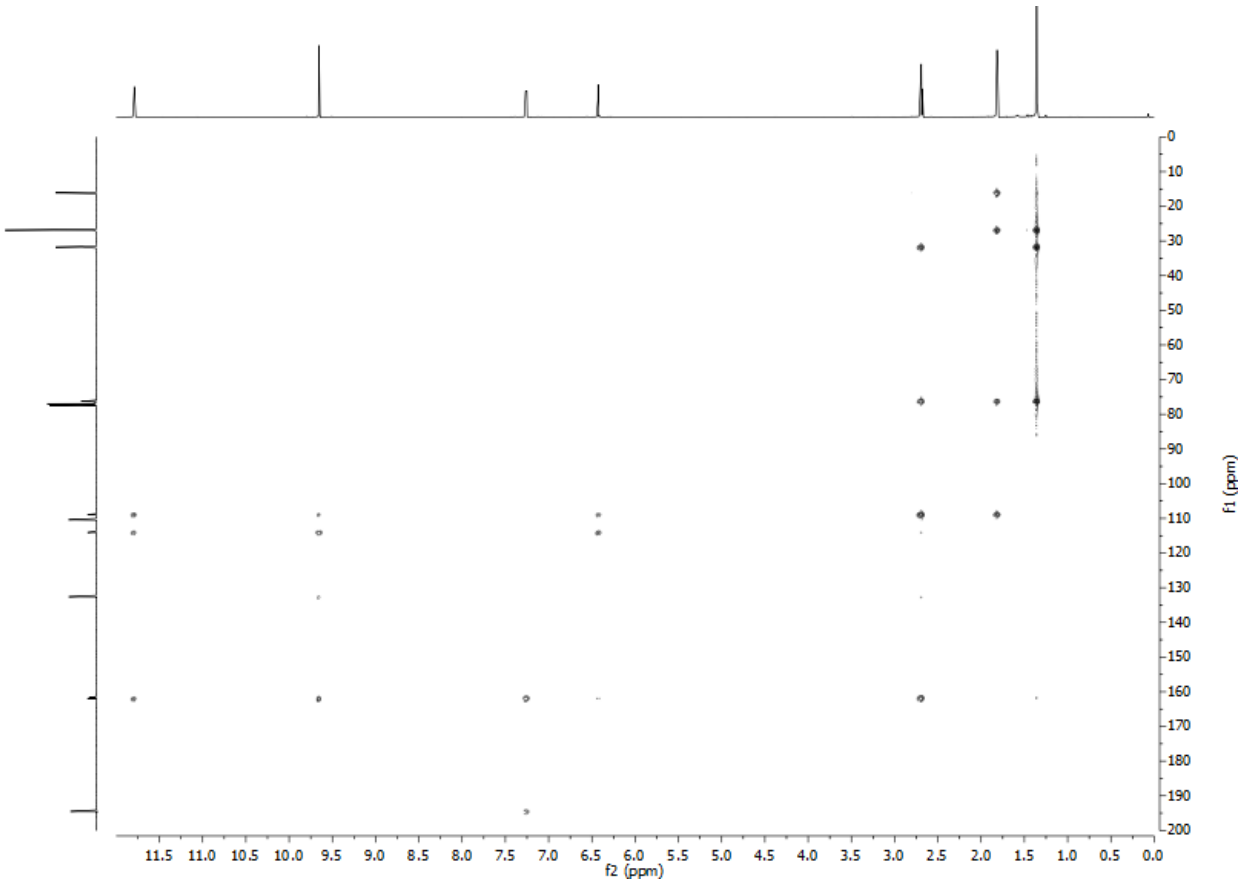


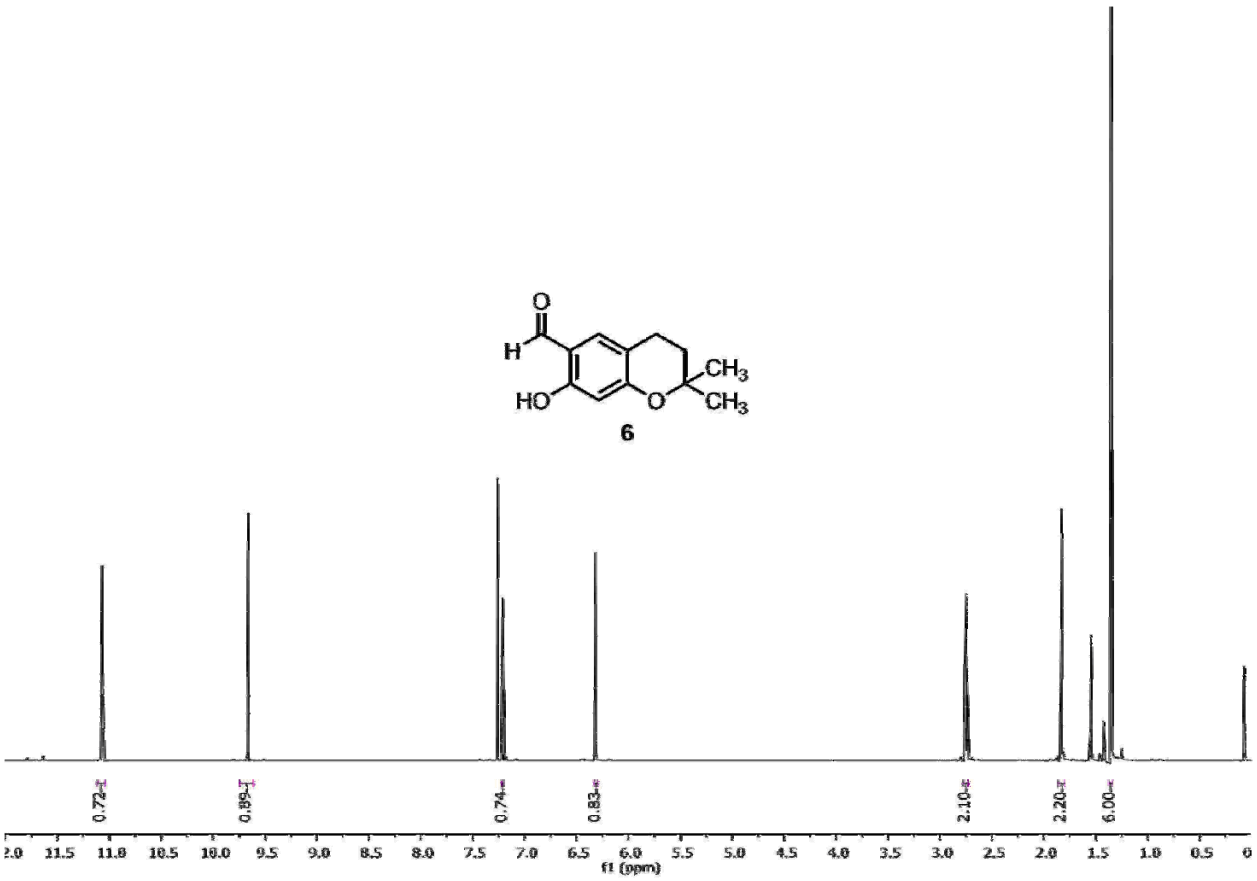
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **5**.



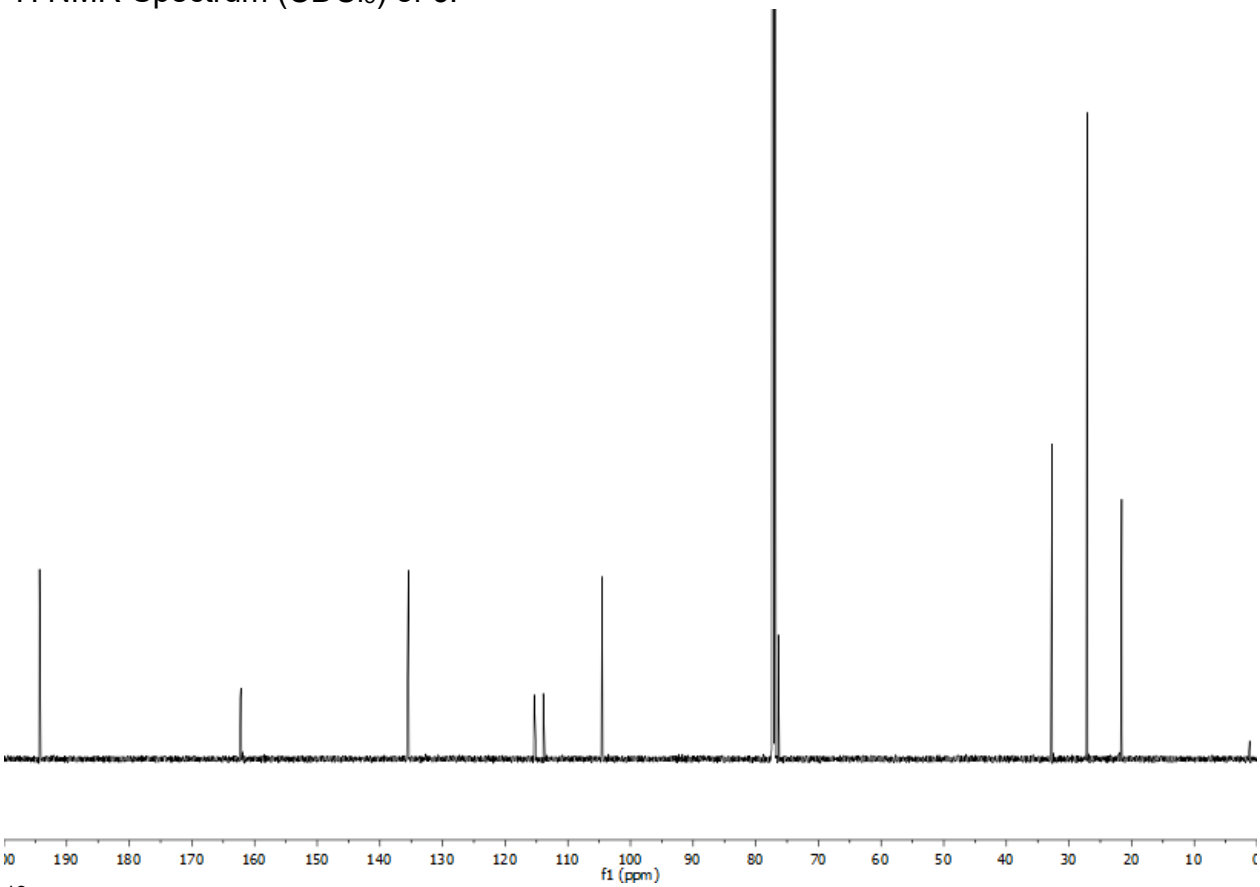
gHSQC-Spectrum ($CDCl_3$) of **5**.



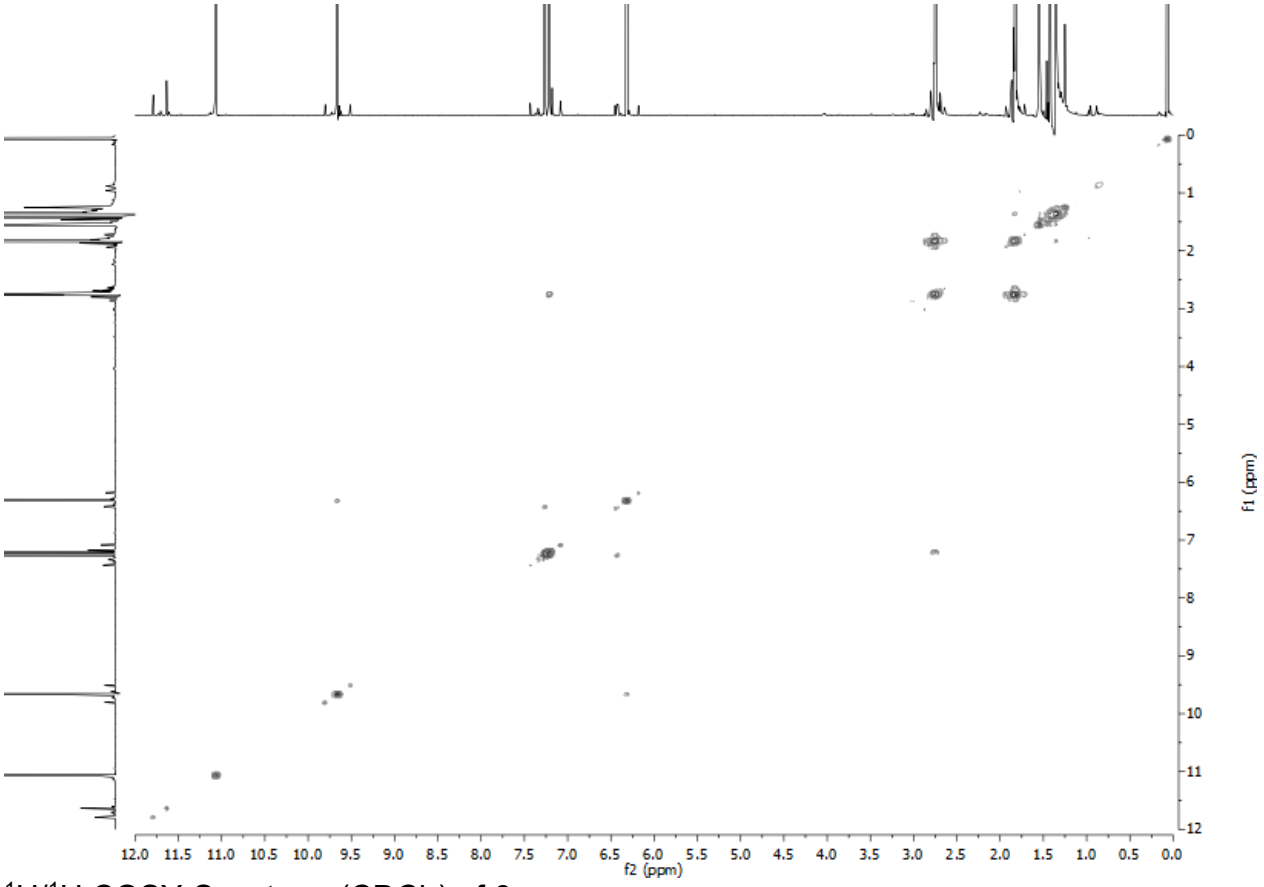
gHMBC-Spectrum ($CDCl_3$) of **5**.



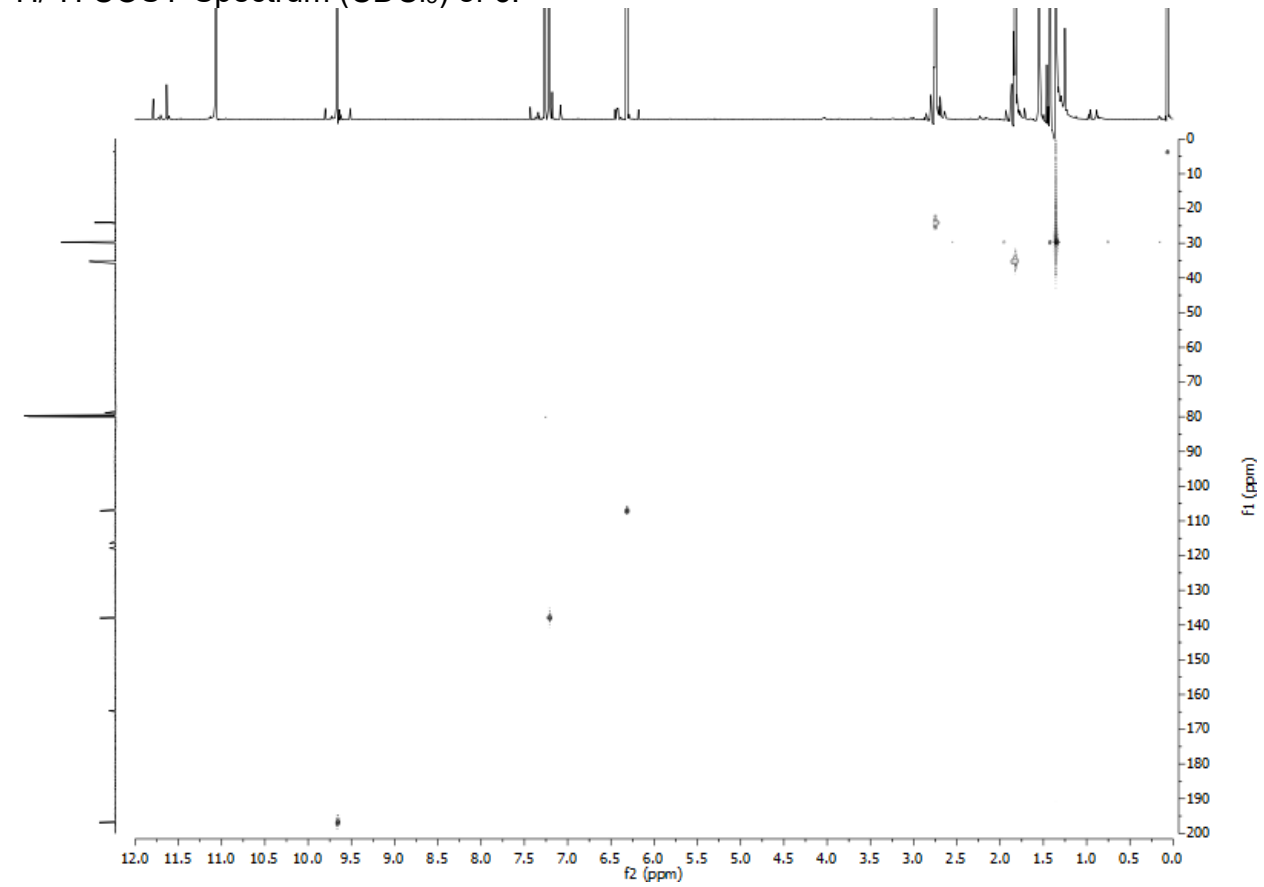
^{1}H NMR-Spectrum ($CDCl_3$) of **6**.



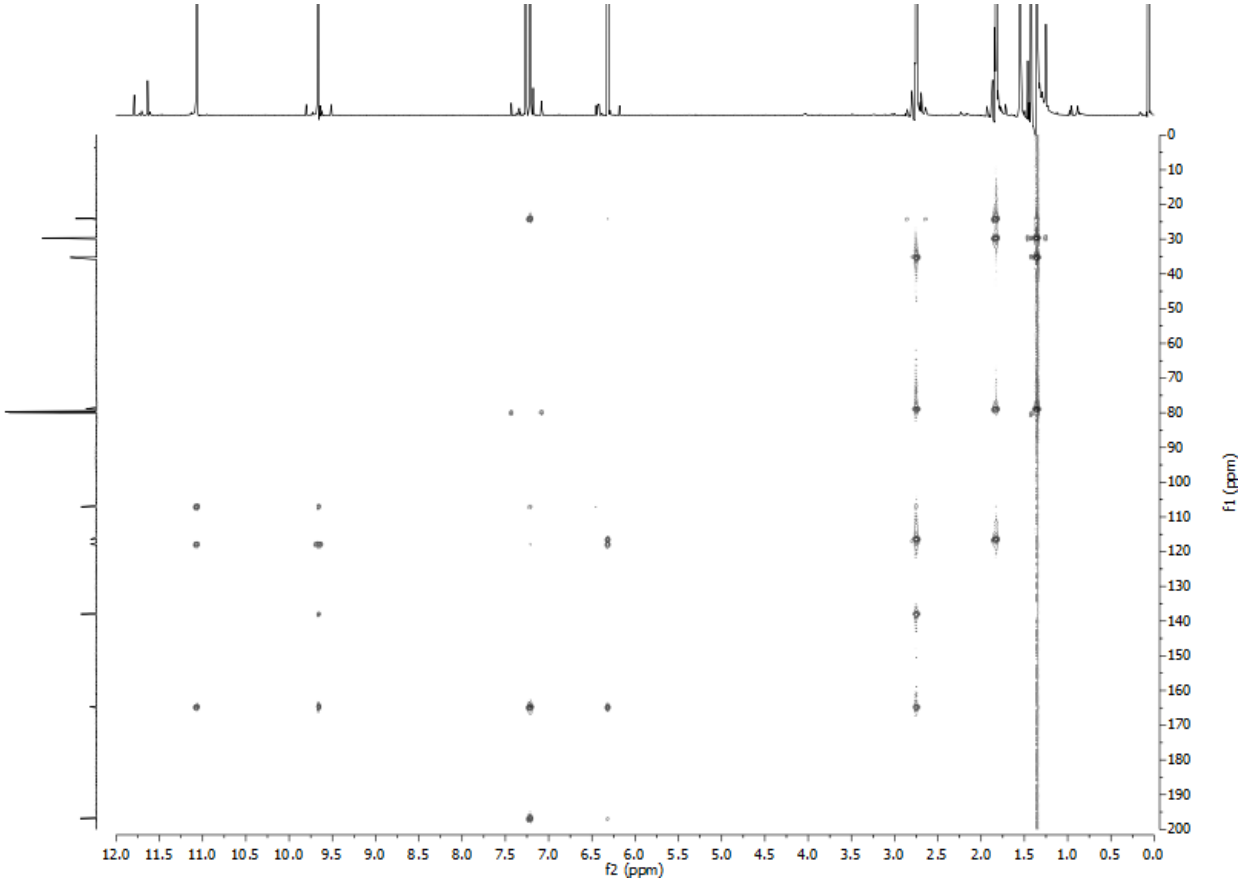
^{13}C NMR-Spectrum ($CDCl_3$) of **6**.



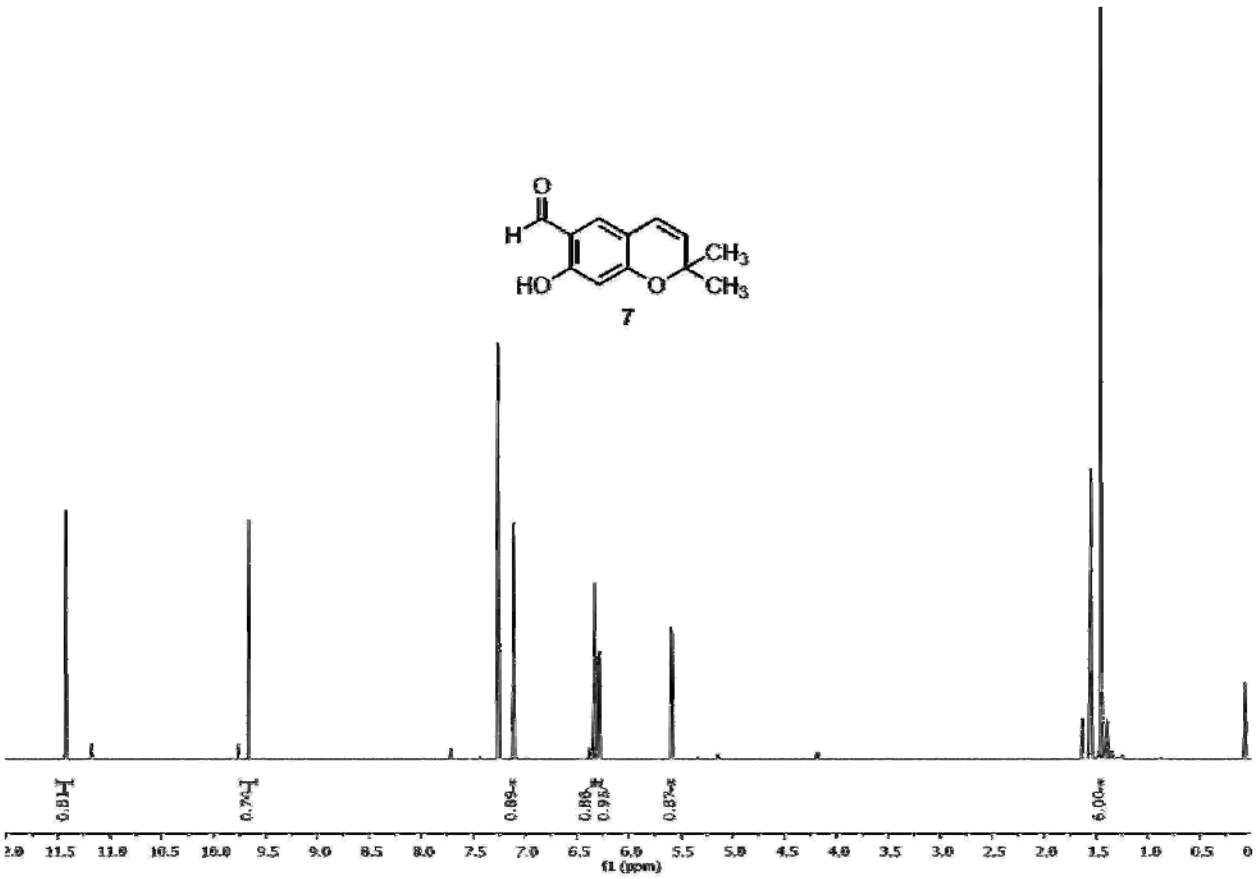
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **6**.



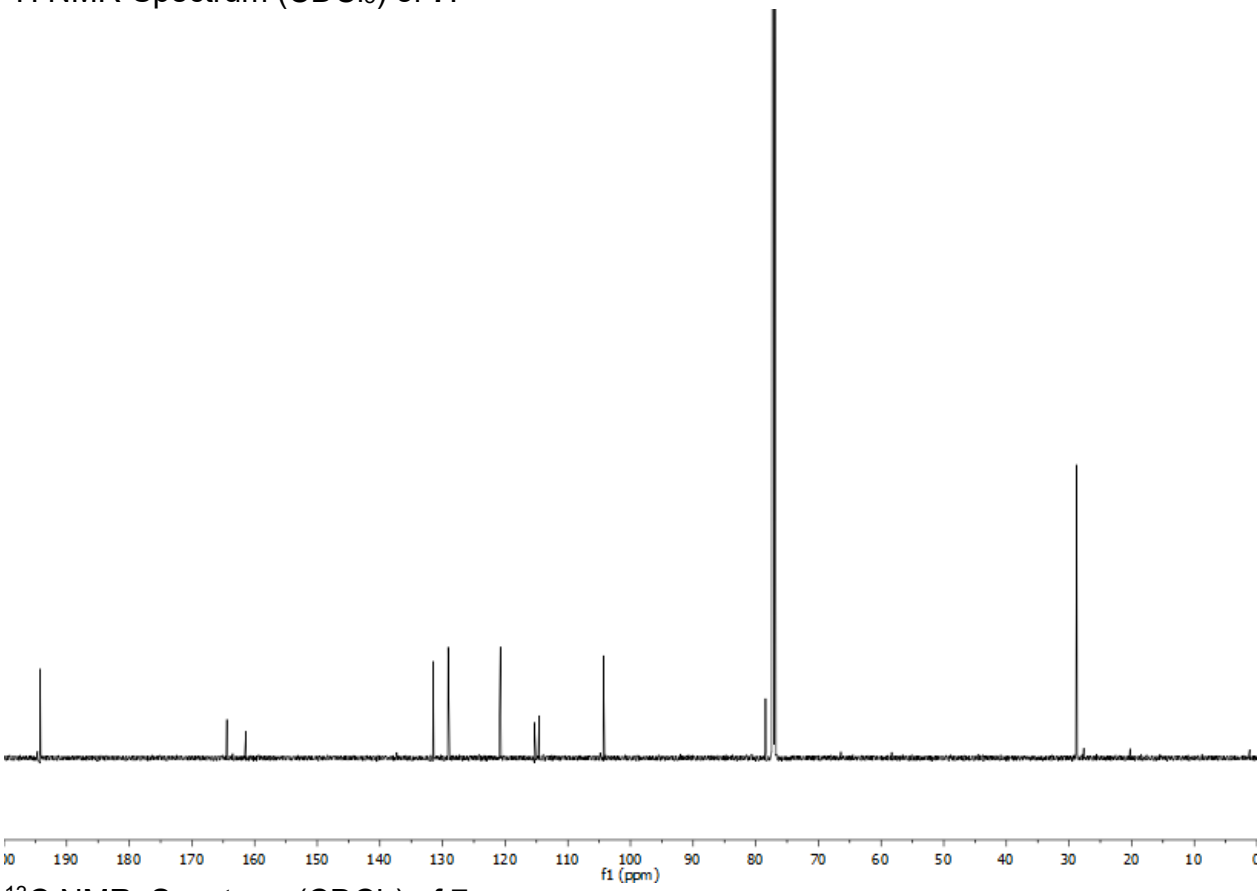
gHSQC-Spectrum ($CDCl_3$) of **6**.



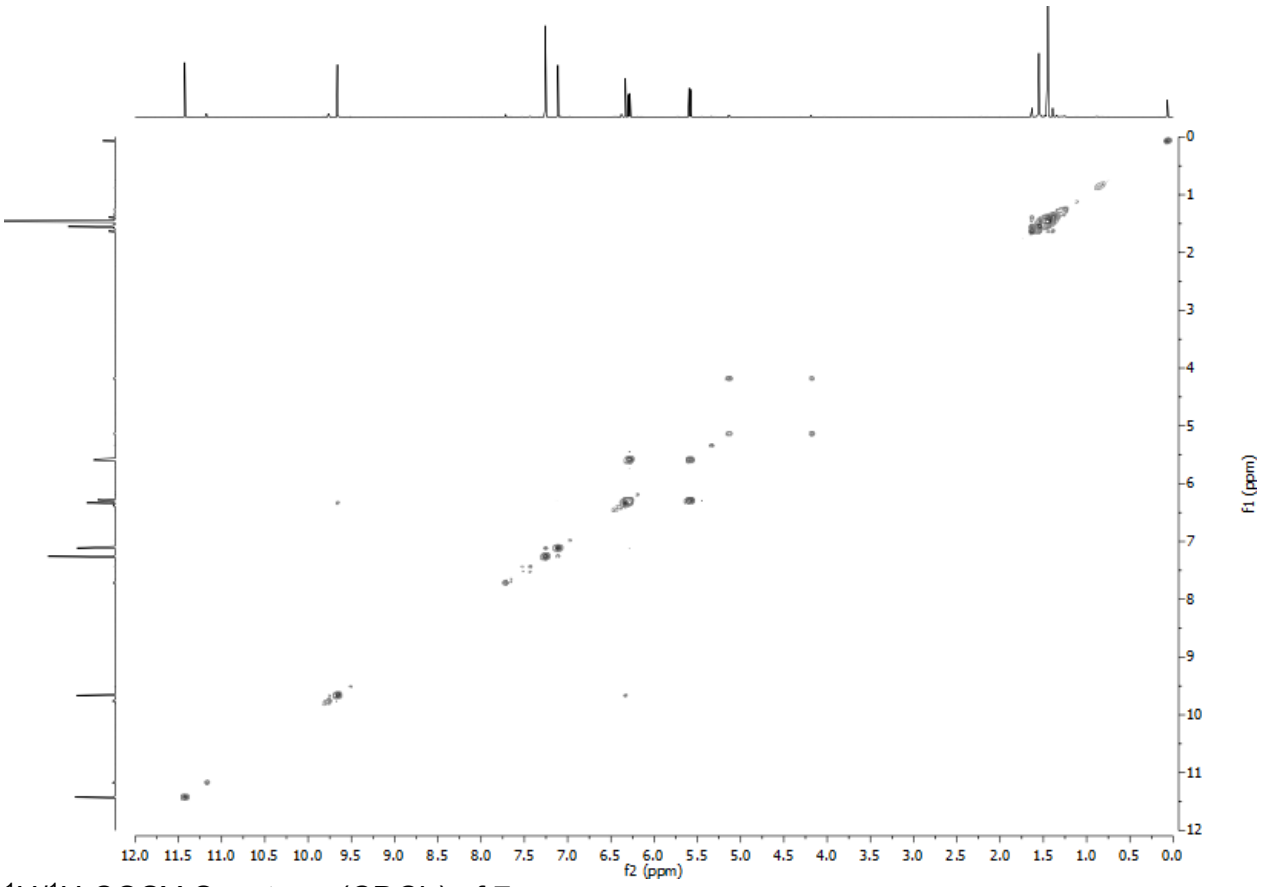
gHMBC-Spectrum ($CDCl_3$) of **6**.



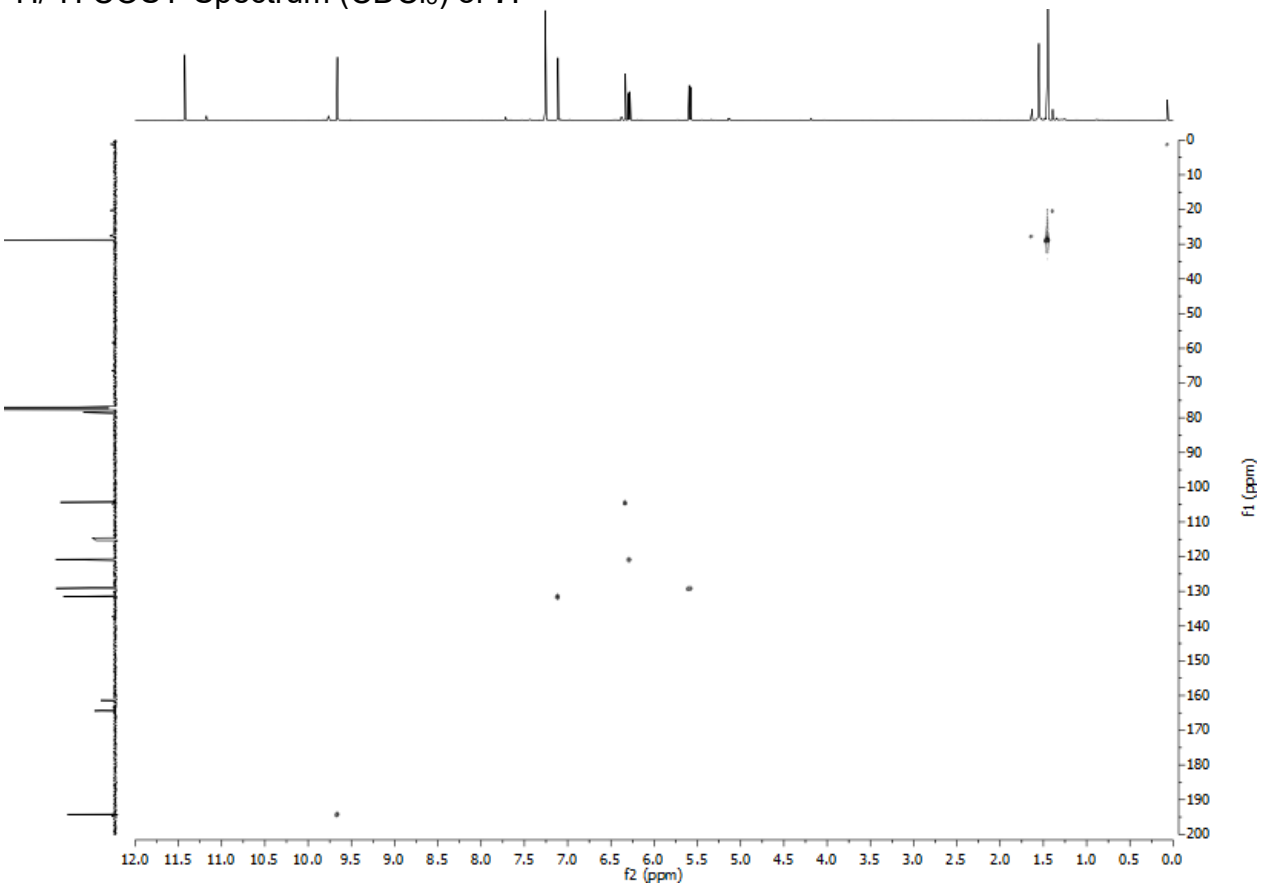
^{1}H NMR-Spectrum ($CDCl_3$) of **7**.



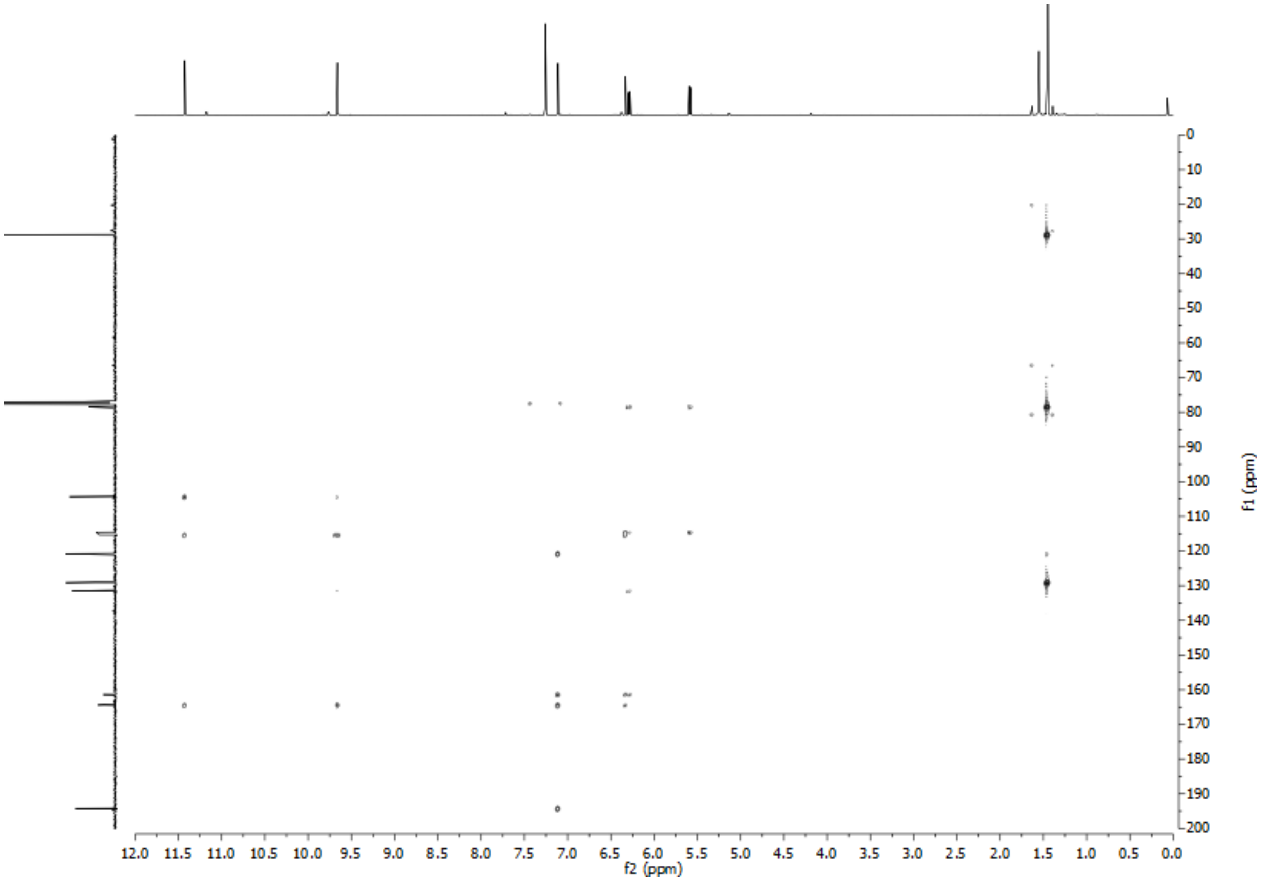
^{13}C NMR_Spectrum ($CDCl_3$) of **7**.



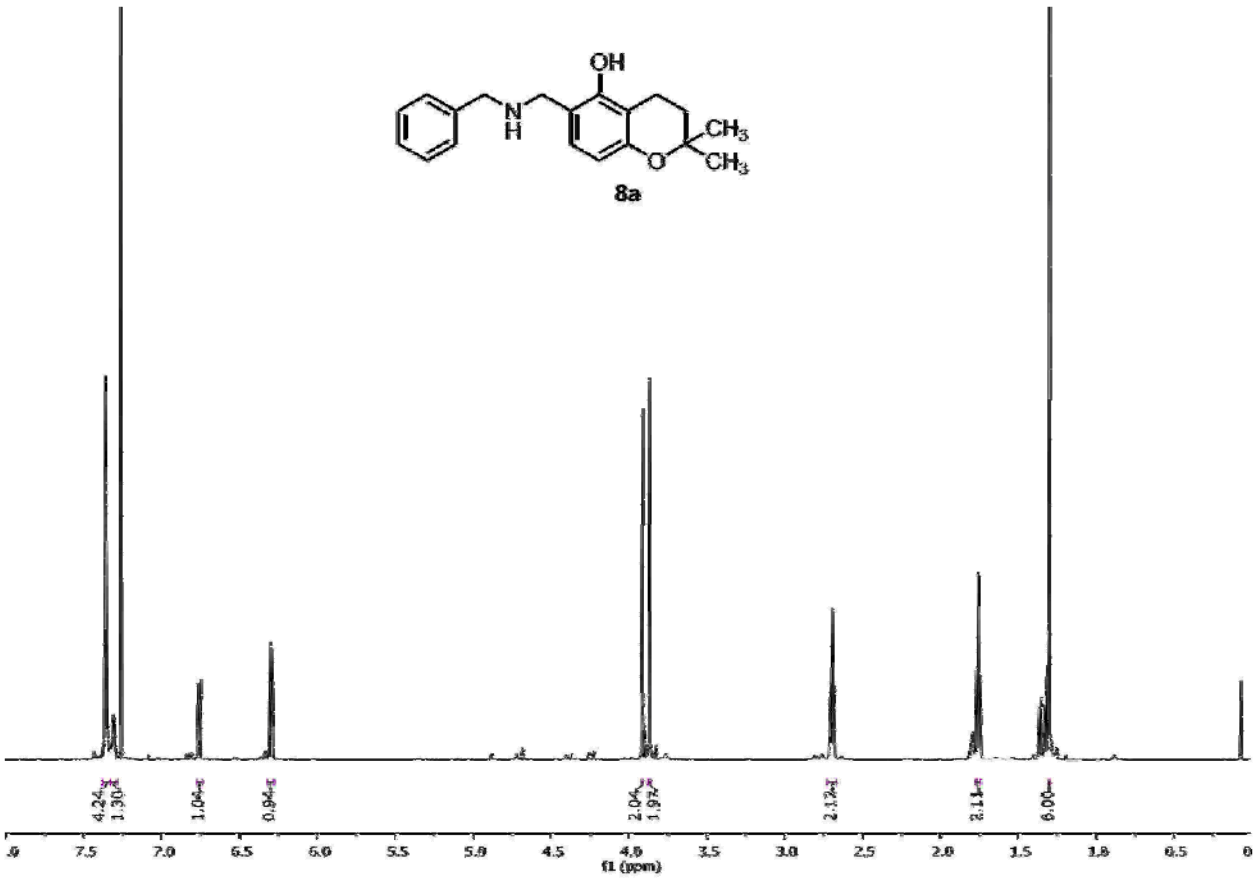
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **7**.



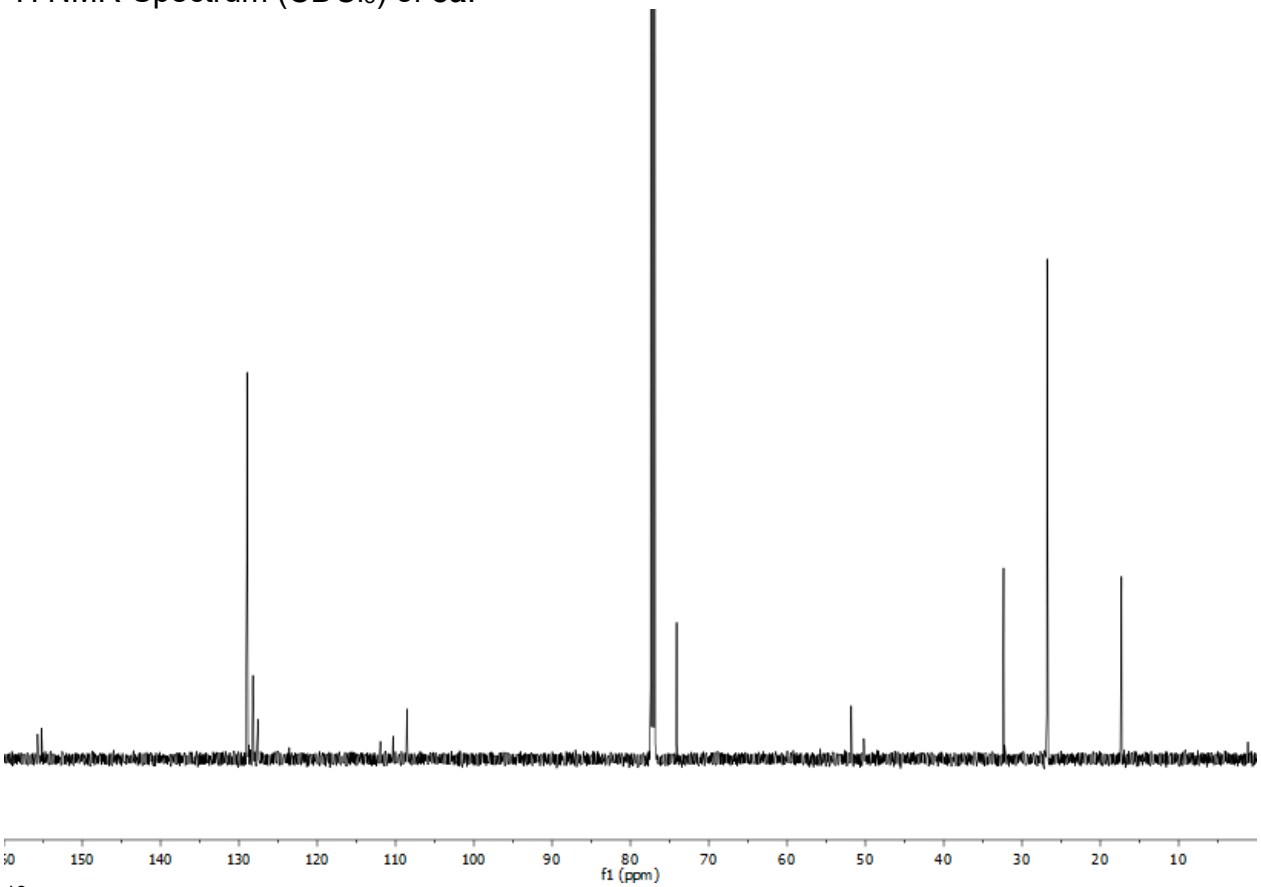
gHSQC-Spectrum ($CDCl_3$) of **7**.



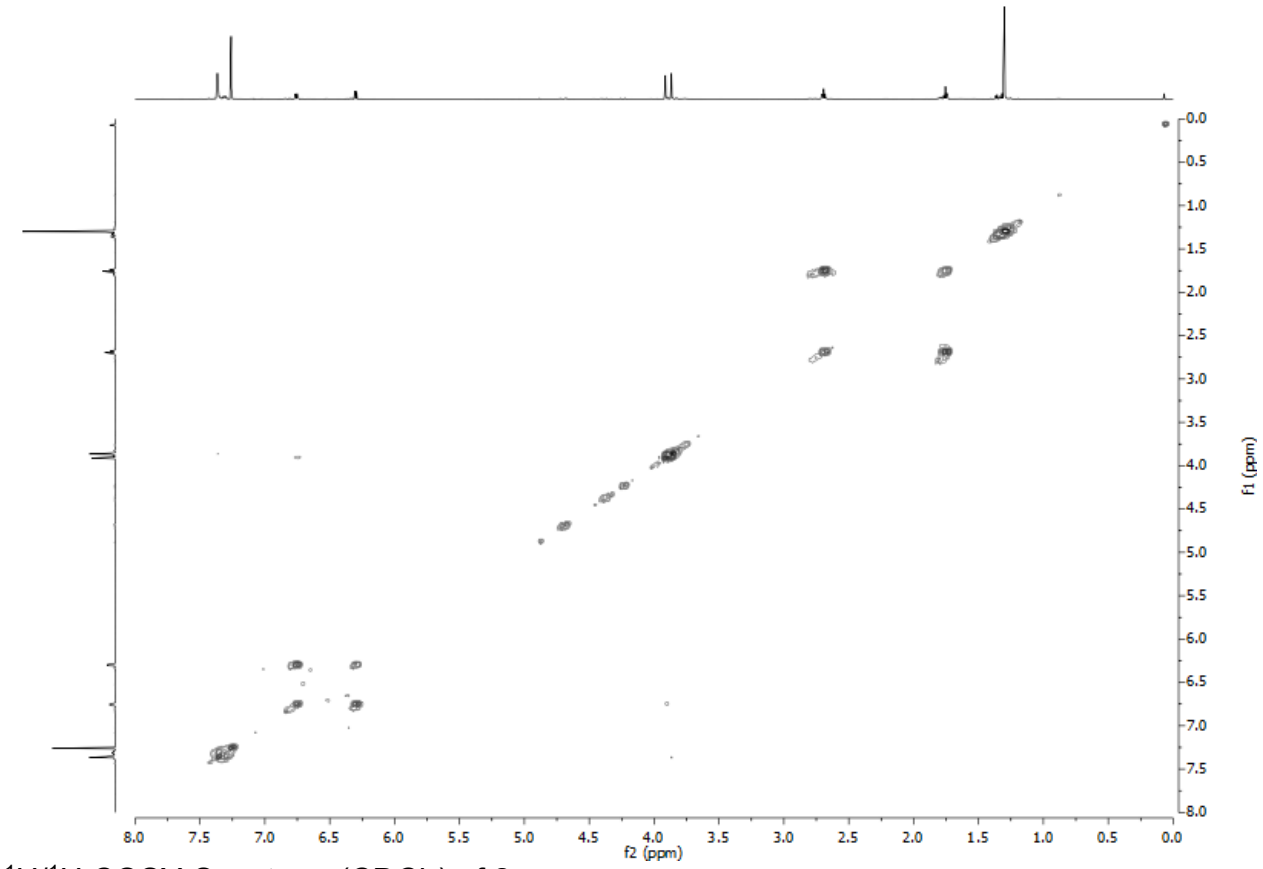
gHMBC-Spectrum ($CDCl_3$) of **7**.



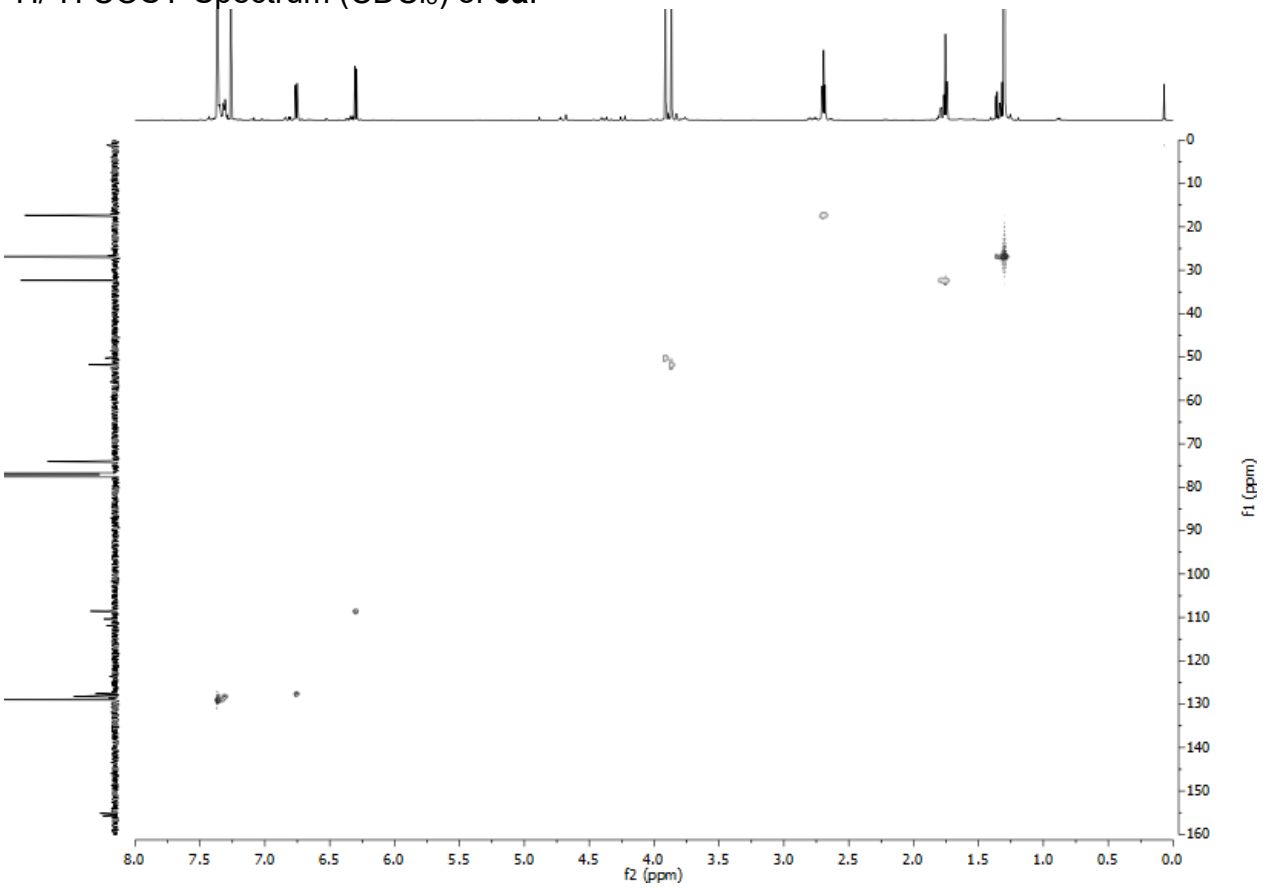
^{1}H NMR-Spectrum ($CDCl_3$) of **8a**.



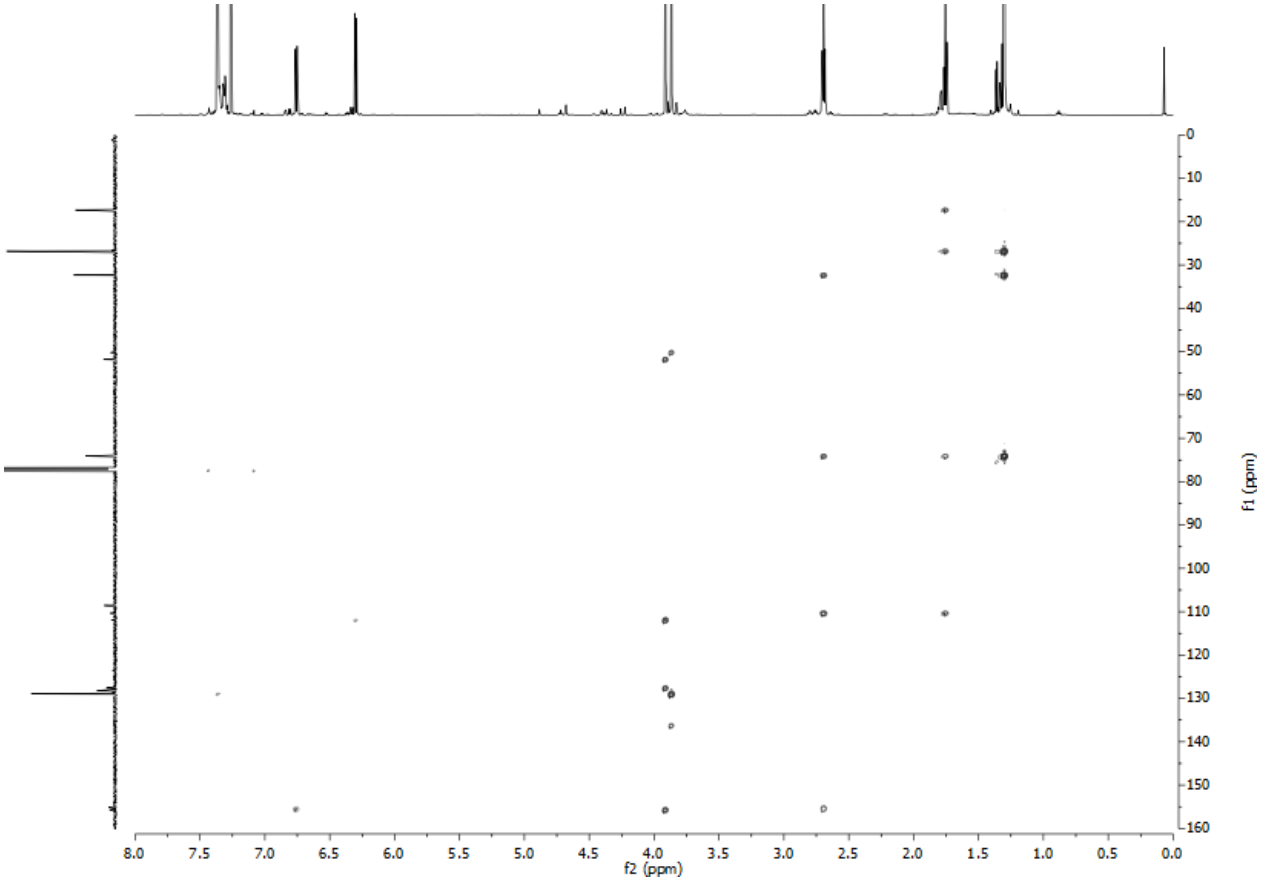
^{13}C NMR-Spectrum ($CDCl_3$) of **8a**.



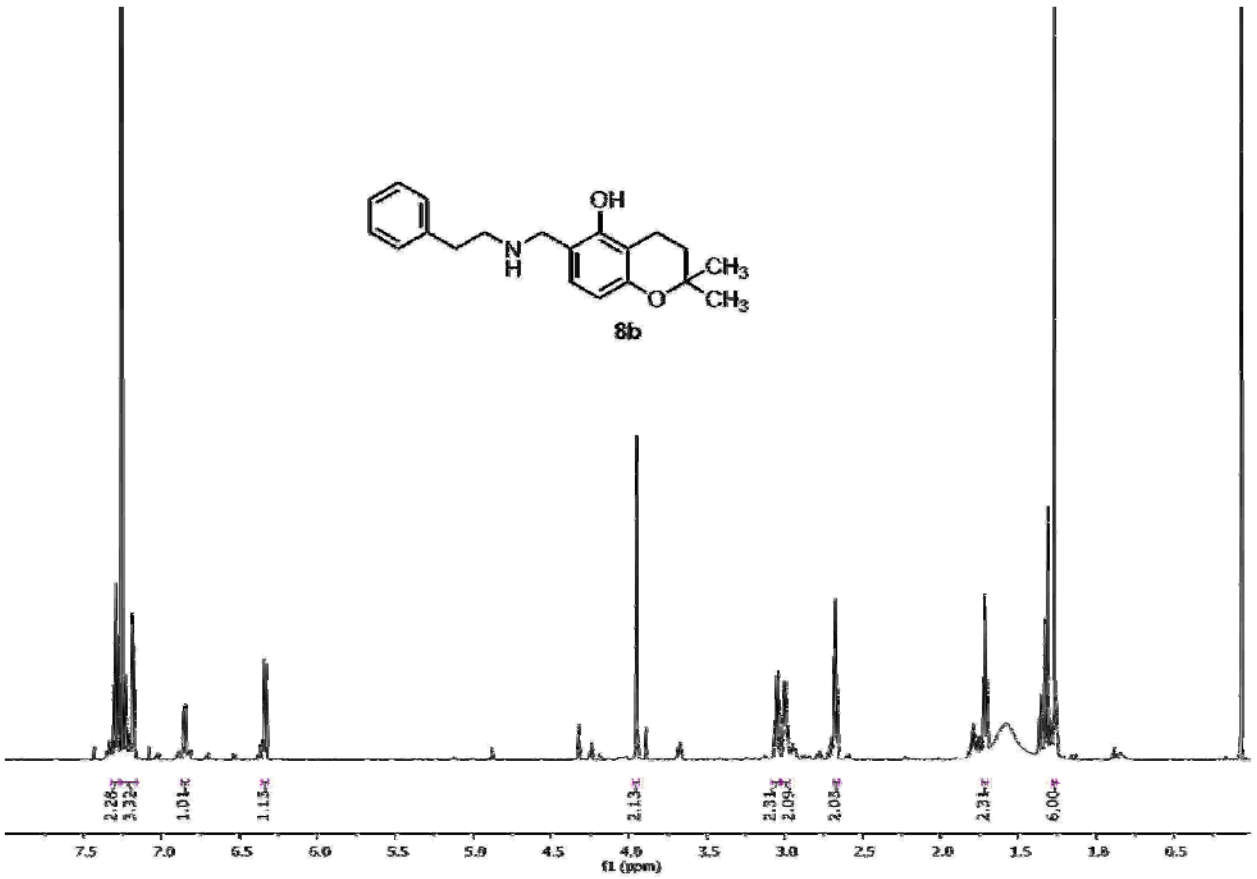
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **8a**.



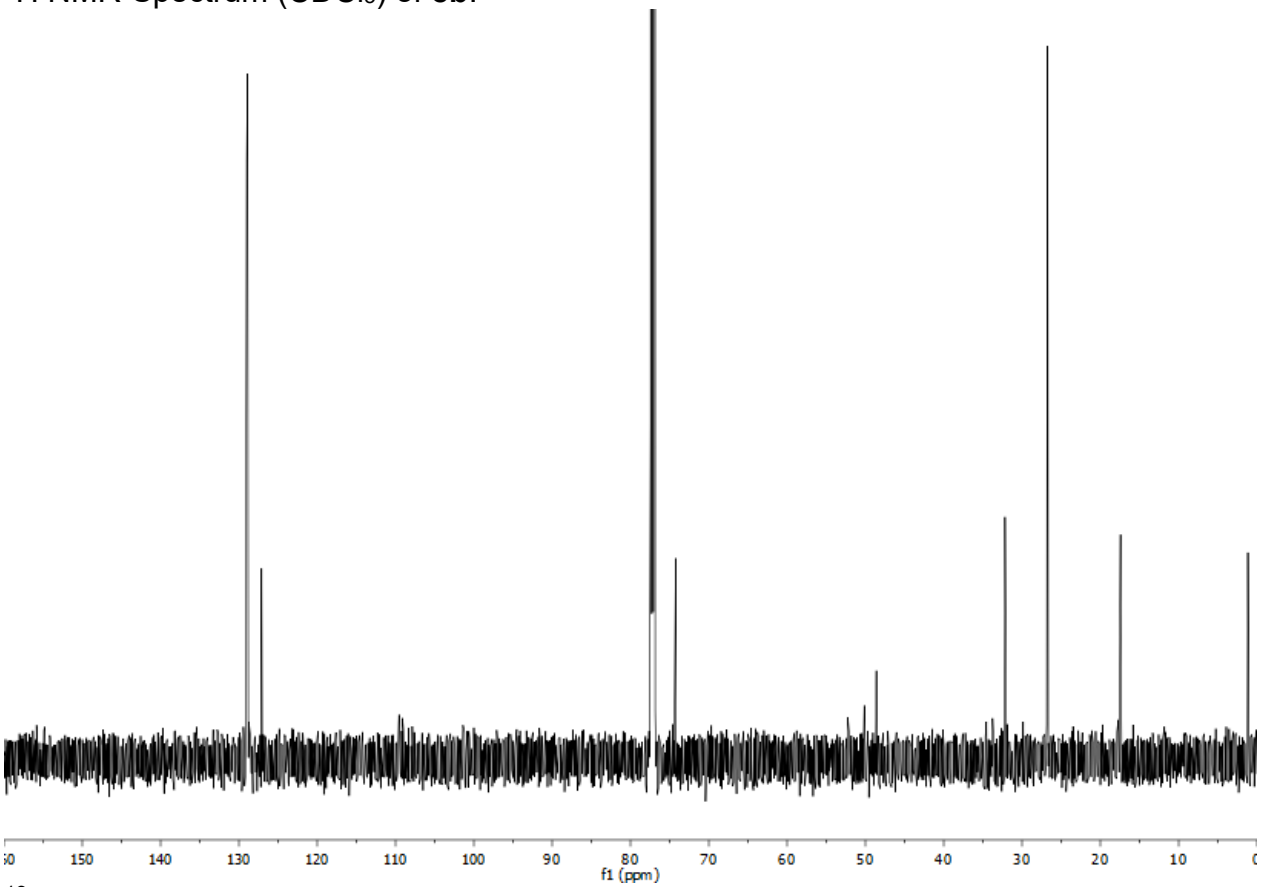
gHSQC-Spectrum ($CDCl_3$) of **8a**.



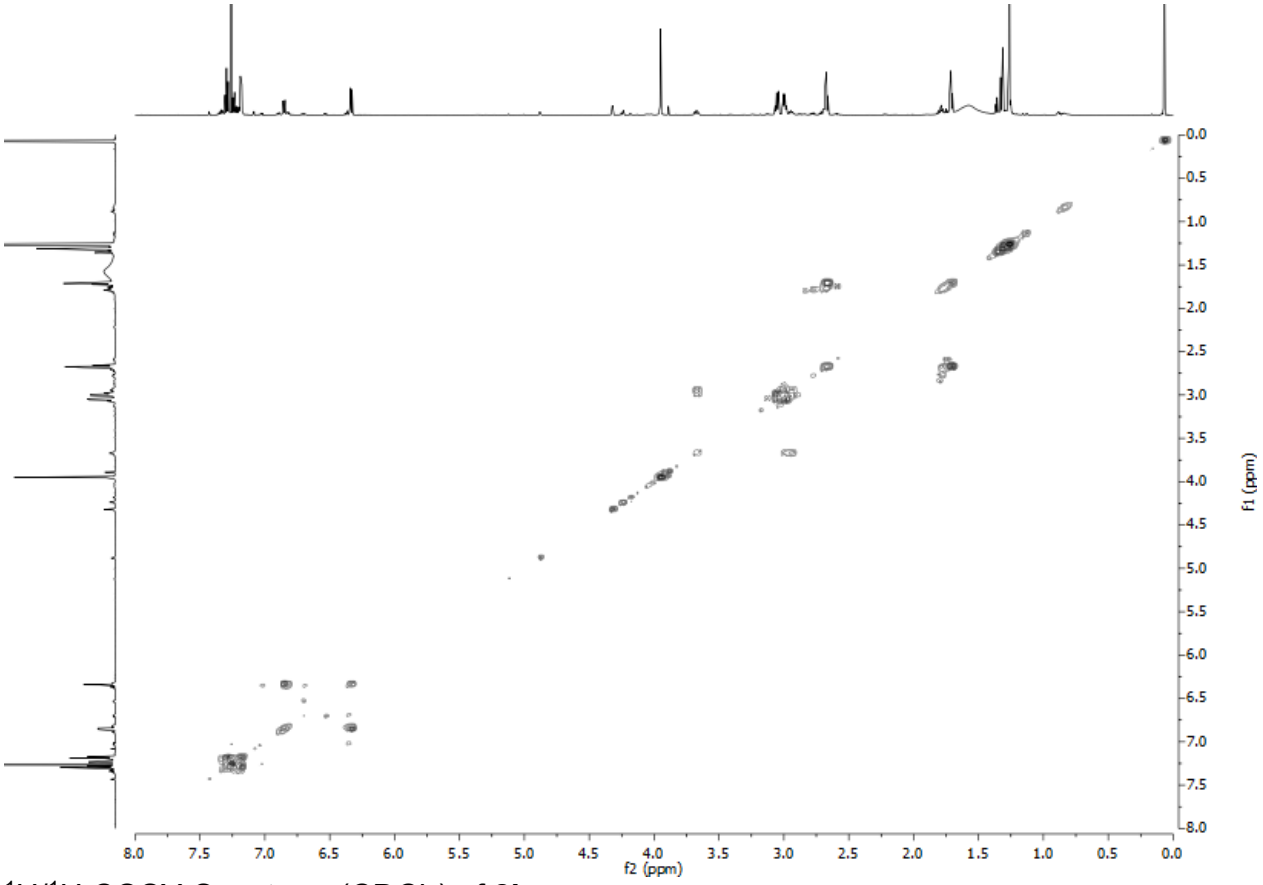
gHMBC-Spectrum ($CDCl_3$) of **8a**.



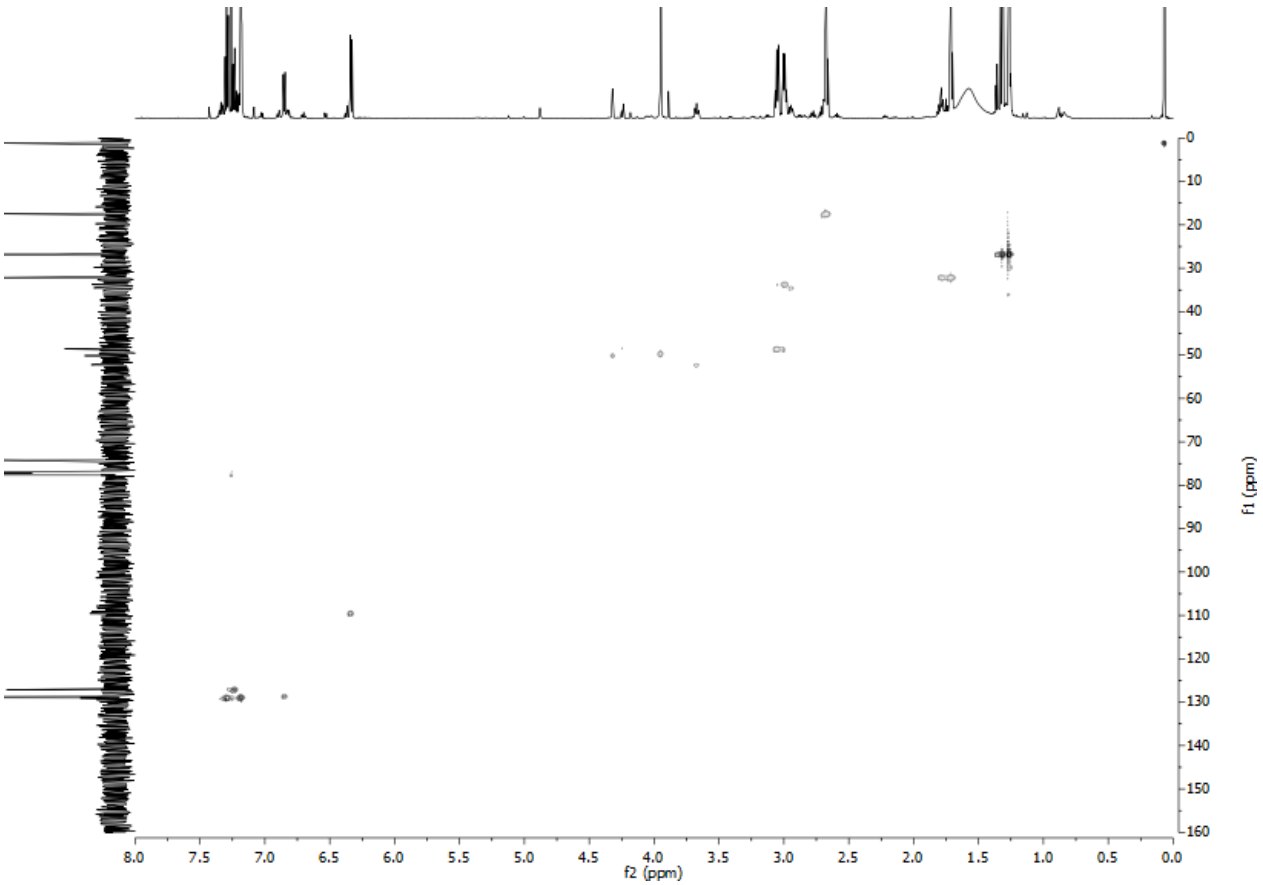
^{1}H NMR-Spectrum ($CDCl_3$) of **8b**.



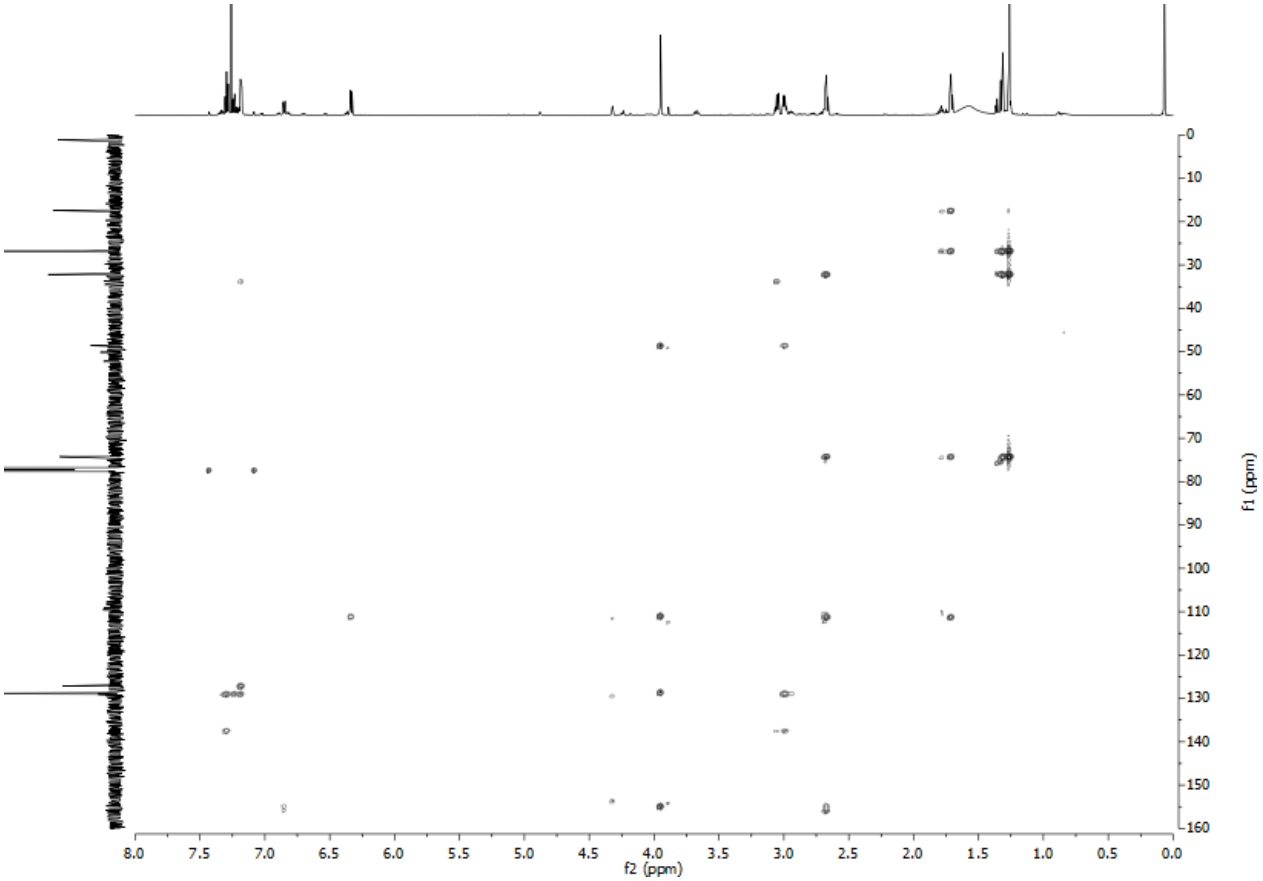
^{13}C NMR-Spectrum ($CDCl_3$) of **8b**.



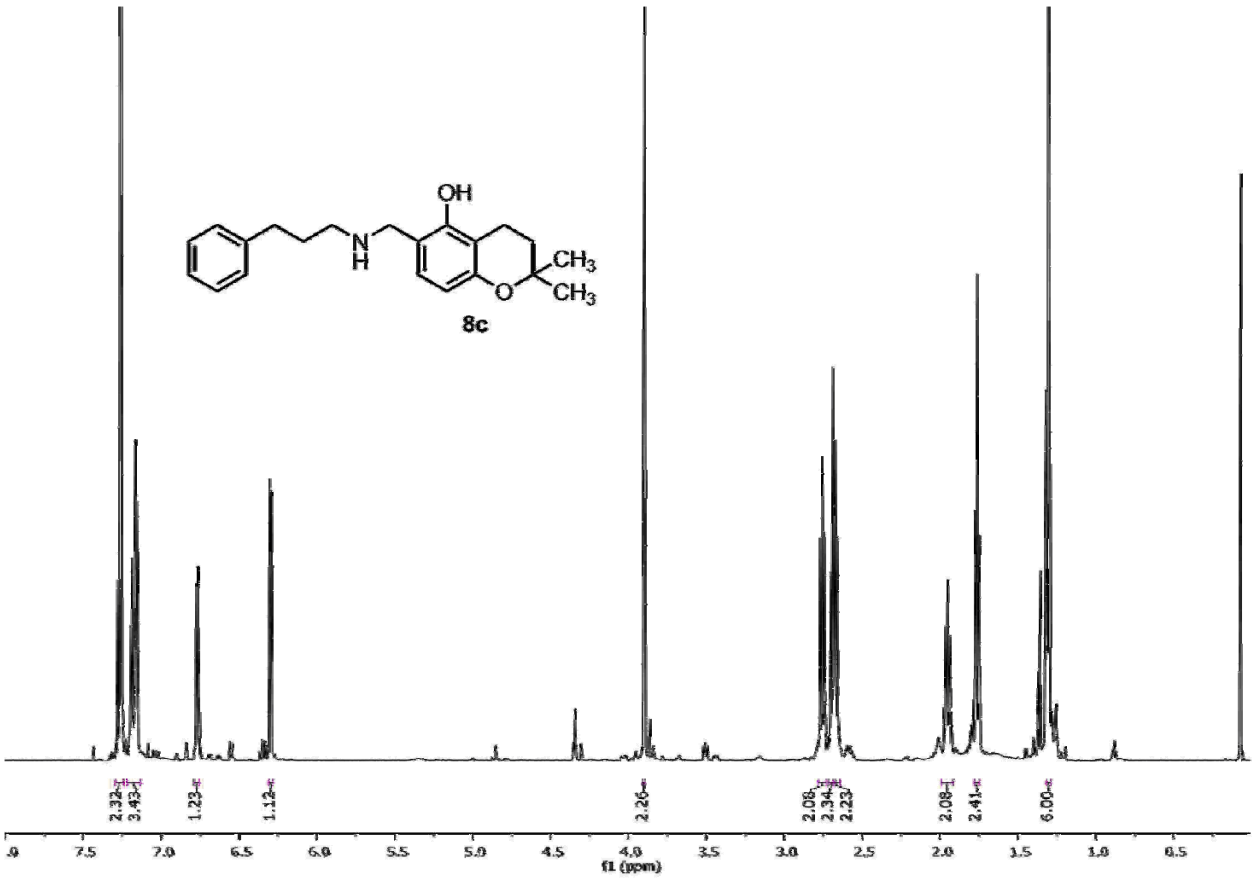
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **8b**.



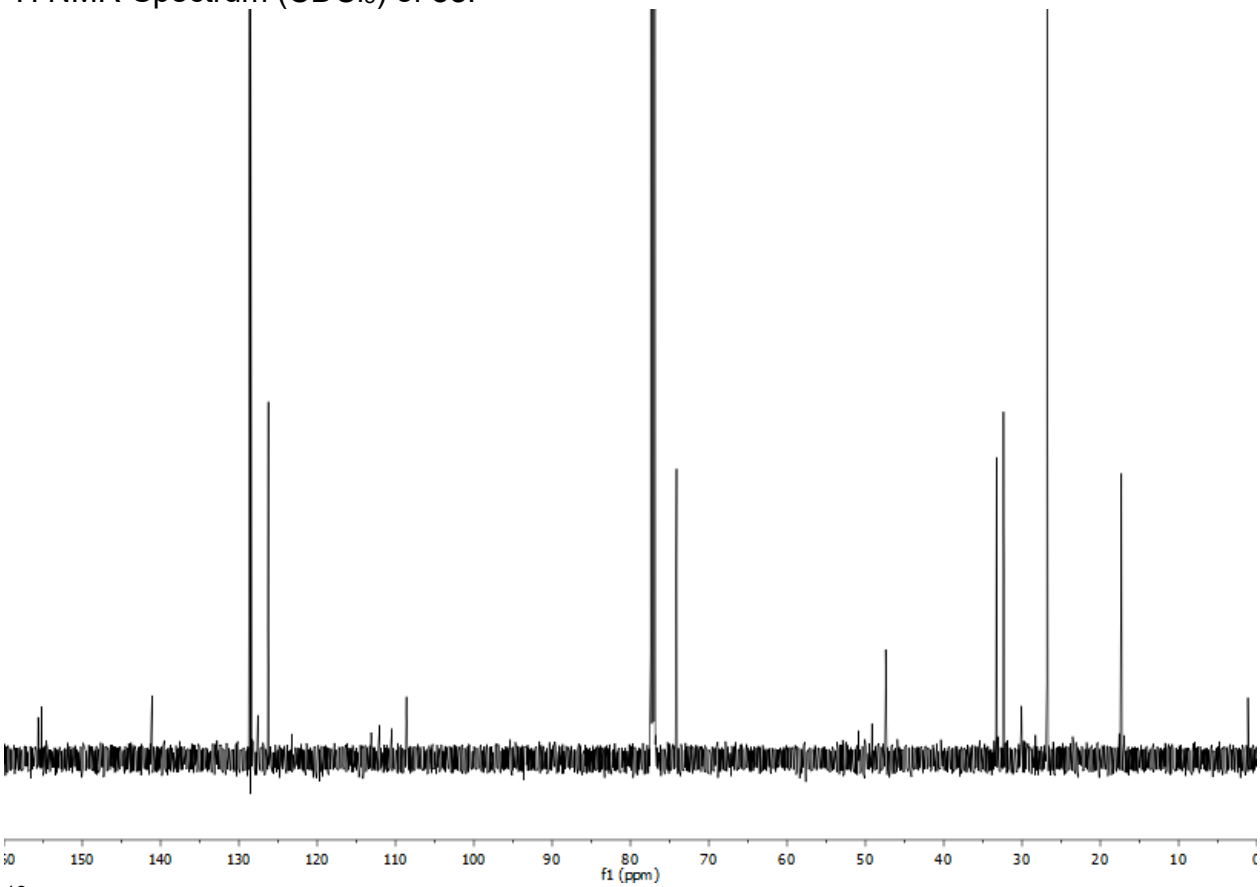
gHSQC-Spectrum ($CDCl_3$) of **8b**.



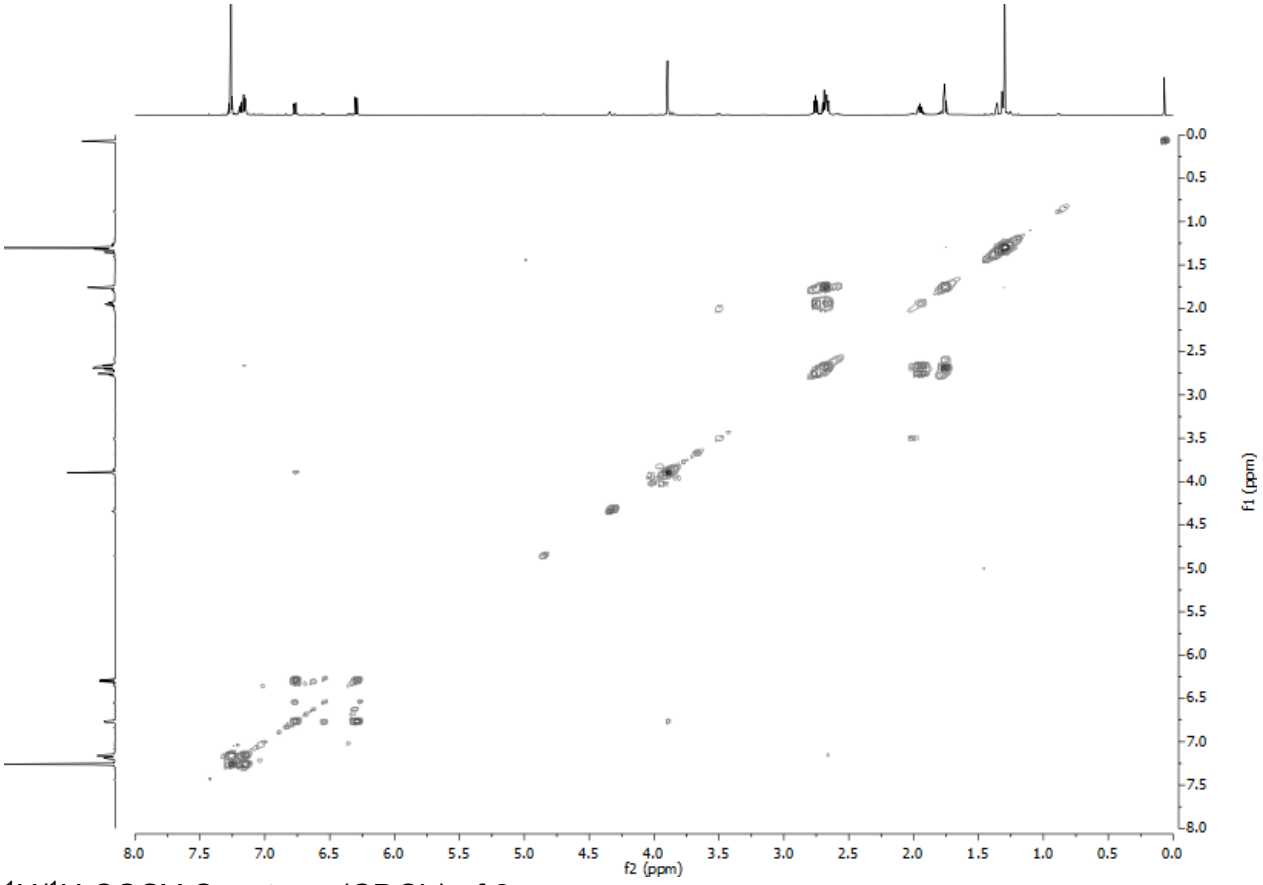
gHMBC-Spectrum ($CDCl_3$) of **8b**.



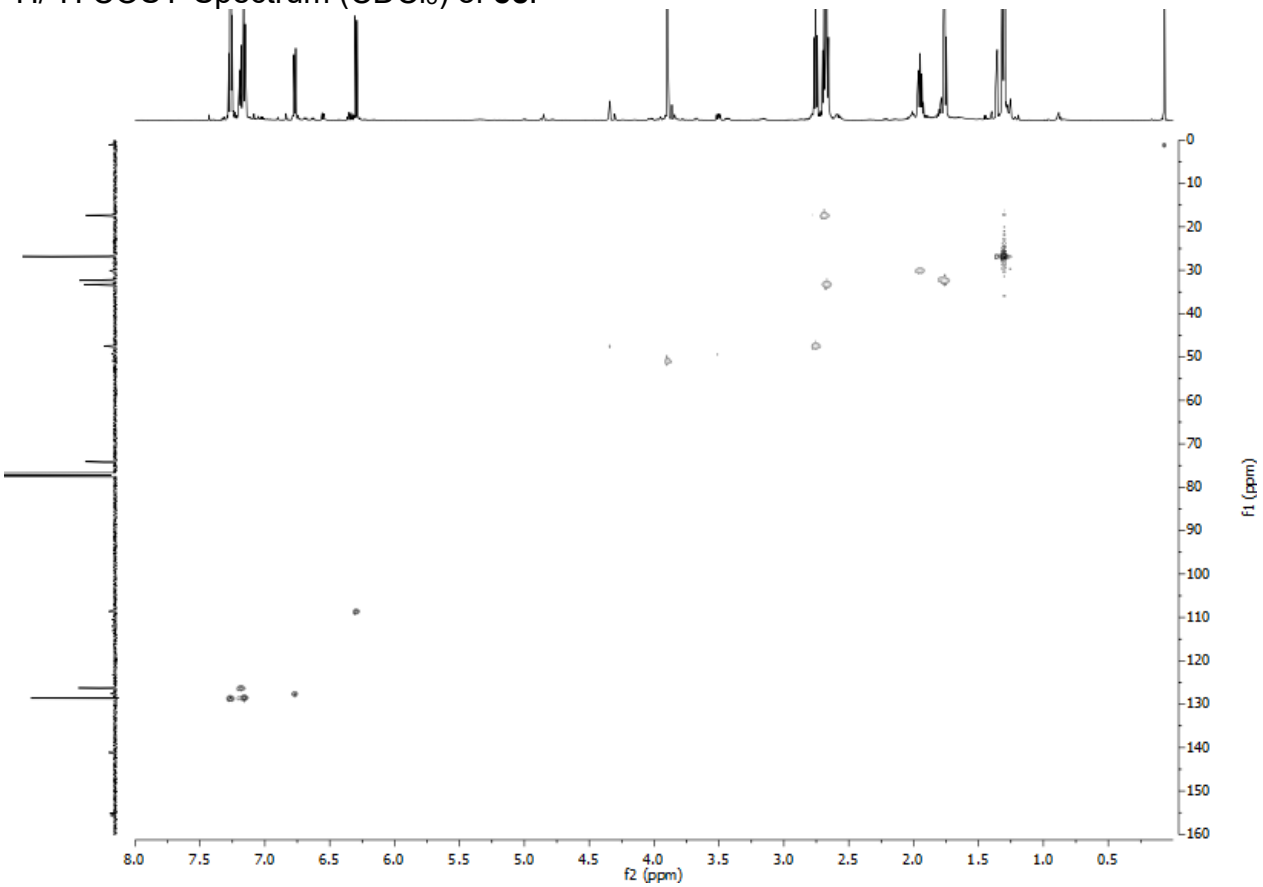
^{1}H NMR-Spectrum ($CDCl_3$) of **8c**.



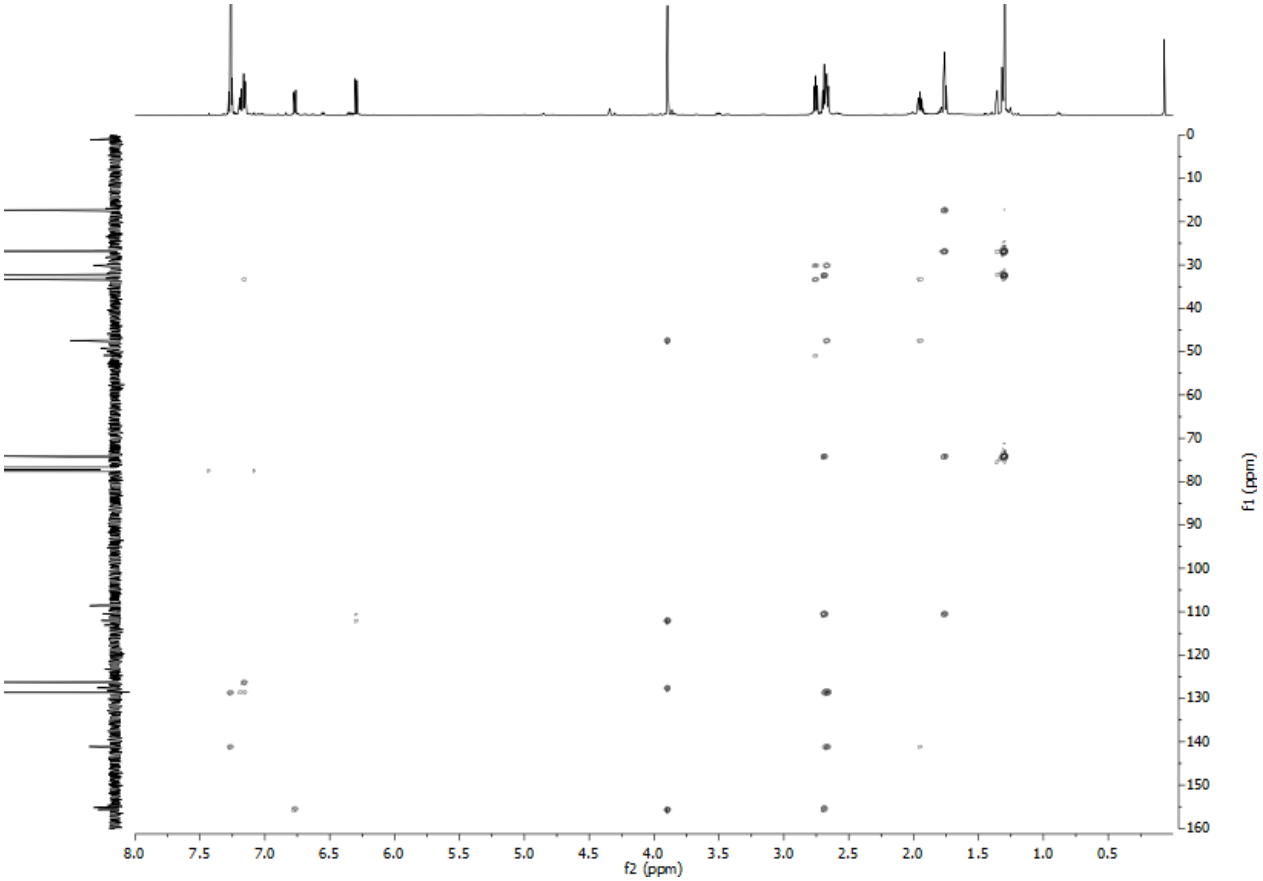
^{13}C NMR-Spectrum ($CDCl_3$) of **8c**.



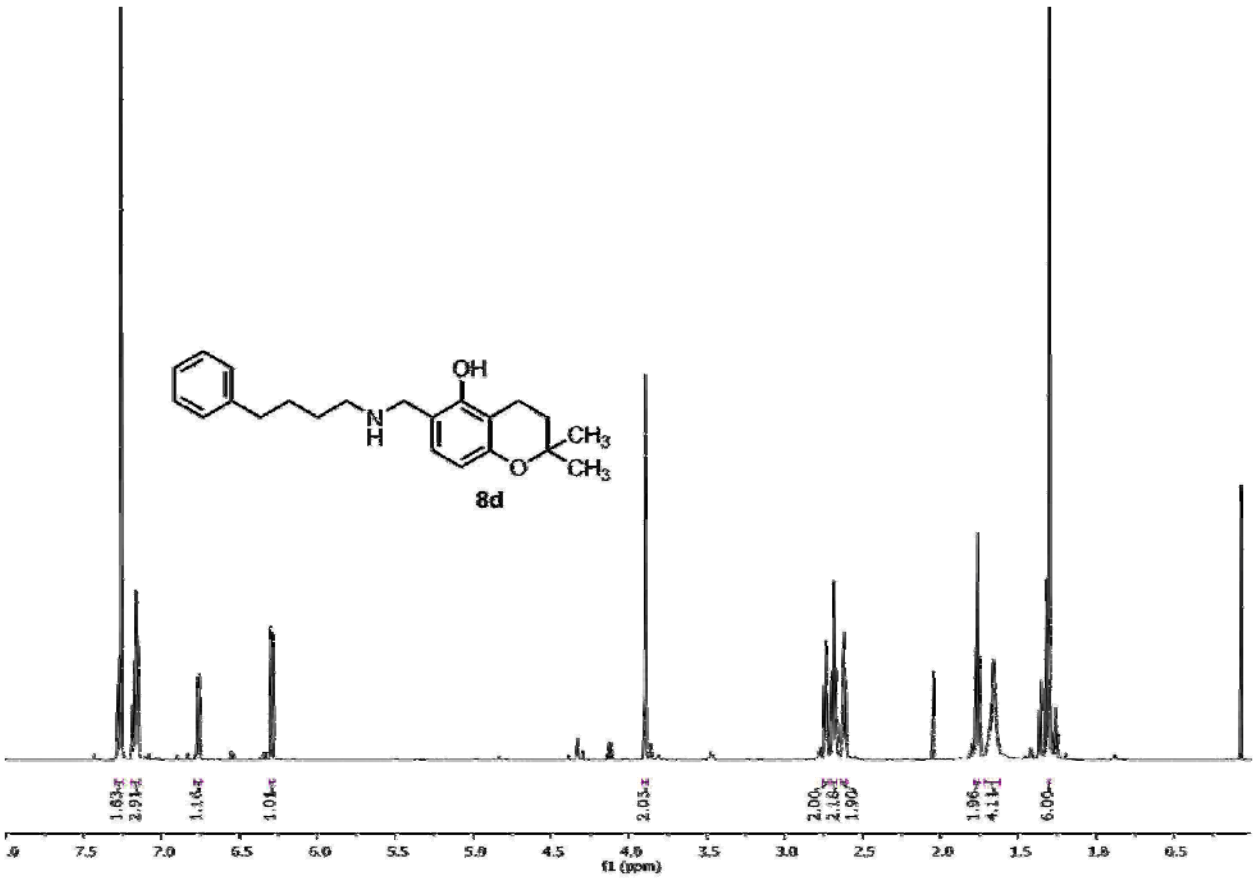
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **8c**.



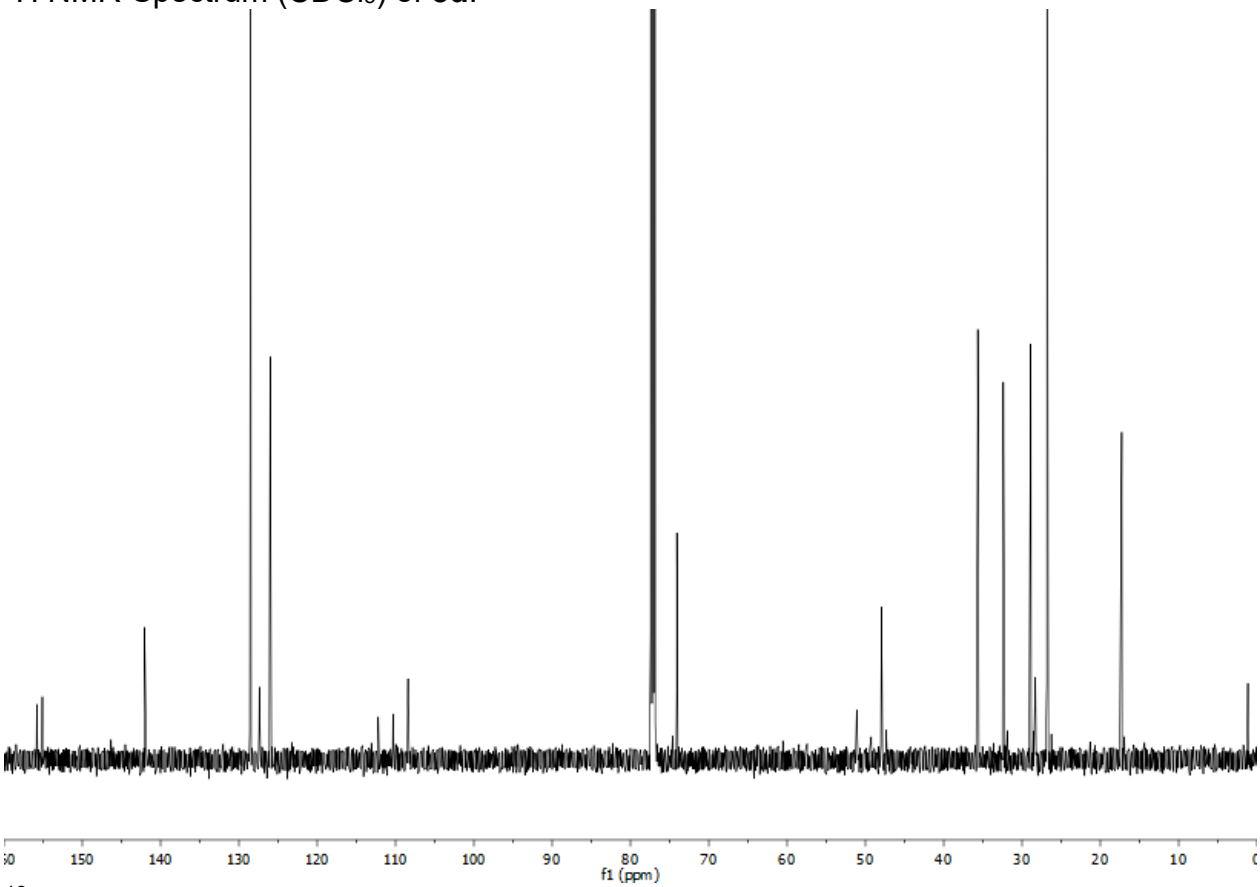
gHSQC-Spectrum ($CDCl_3$) of **8c**.



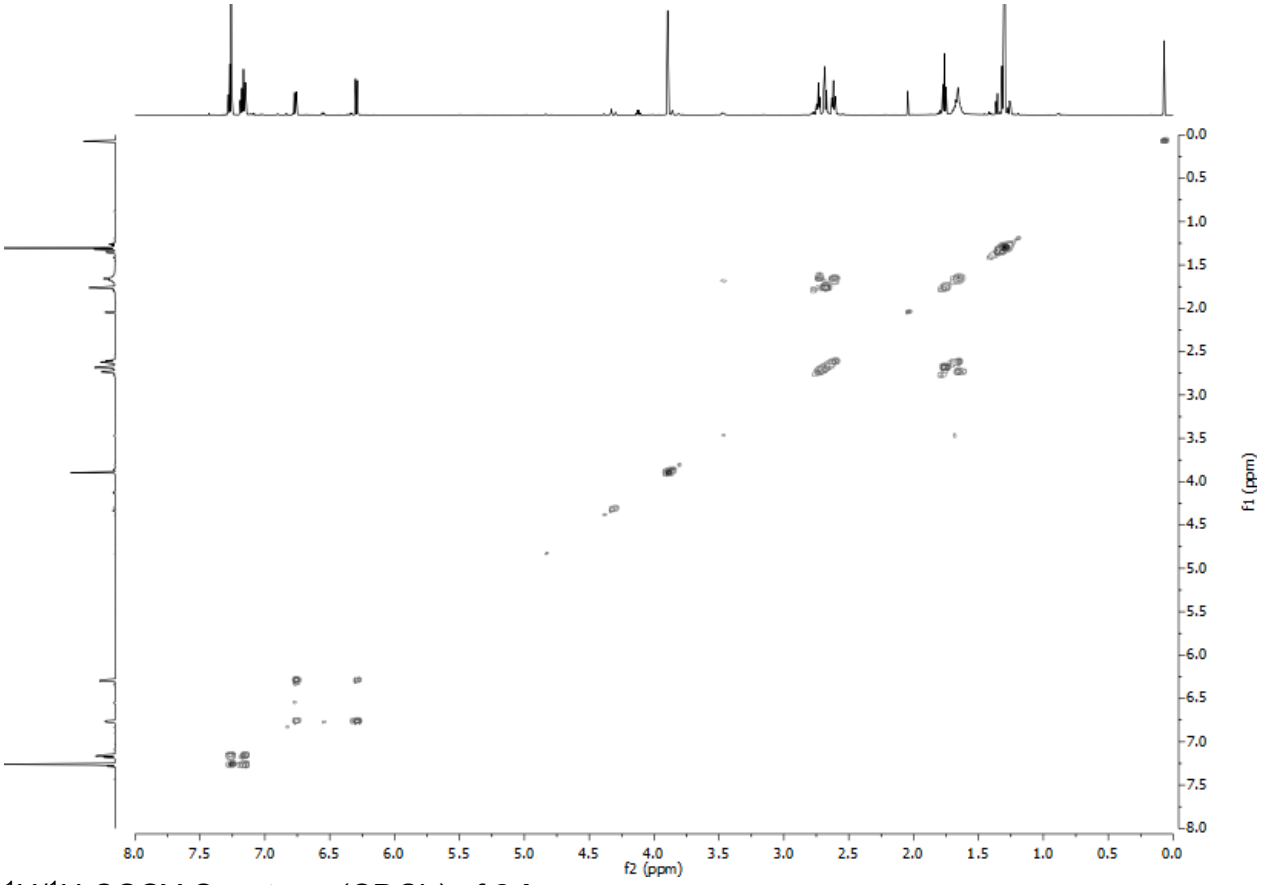
gHMBC-Spectrum ($CDCl_3$) of **8c**.



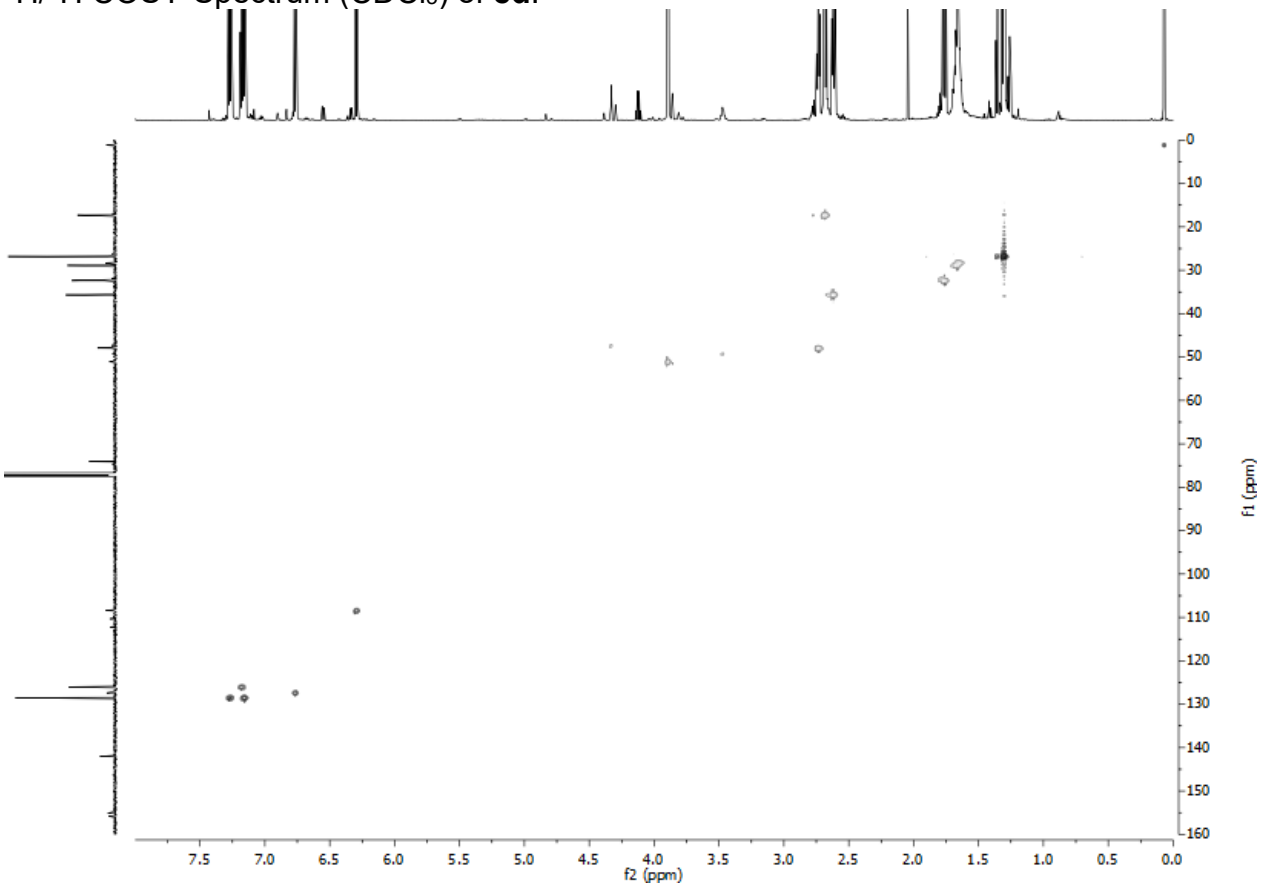
^{1}H NMR-Spectrum ($CDCl_3$) of **8d**.



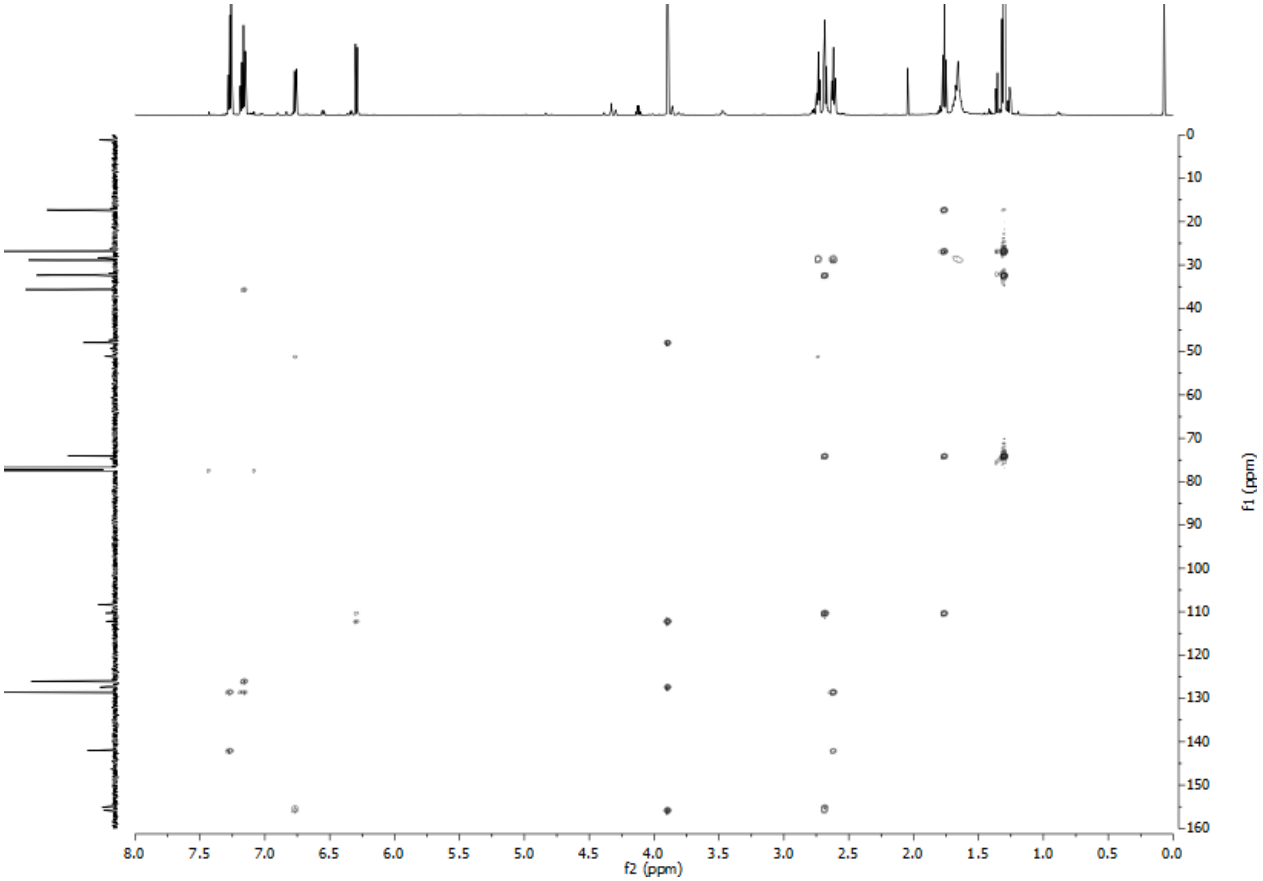
^{13}C NMR-Spectrum ($CDCl_3$) of **8d**.



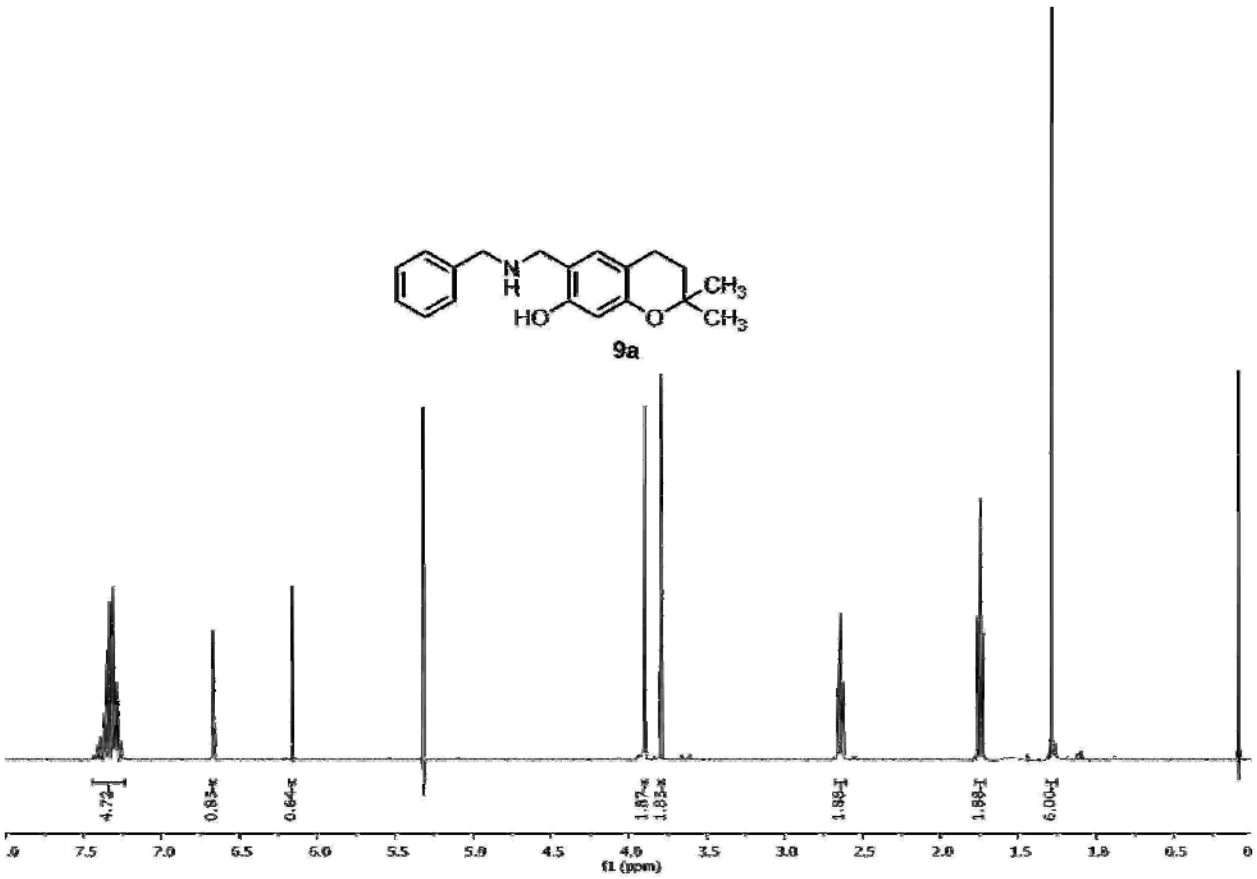
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **8d**.



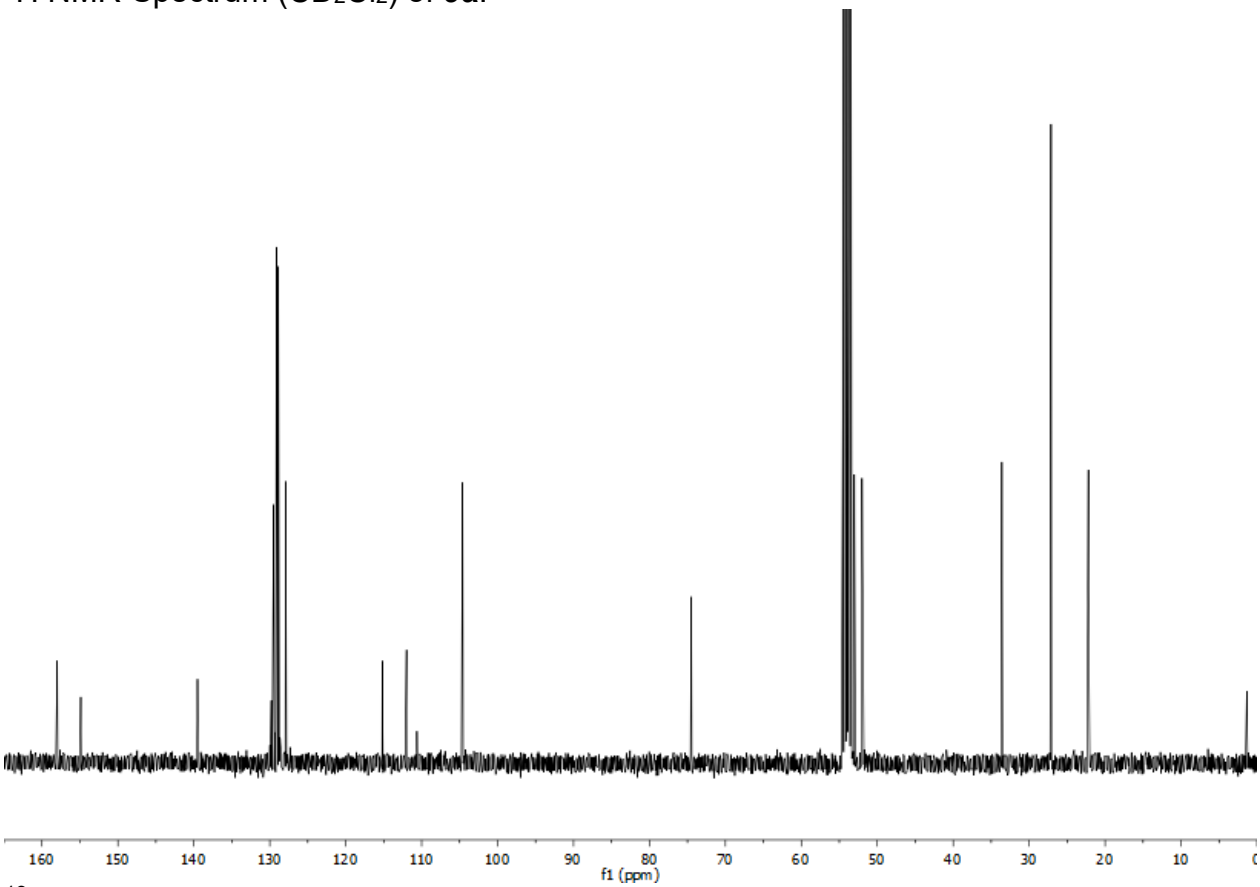
gHSQC-Spectrum ($CDCl_3$) of **8d**.



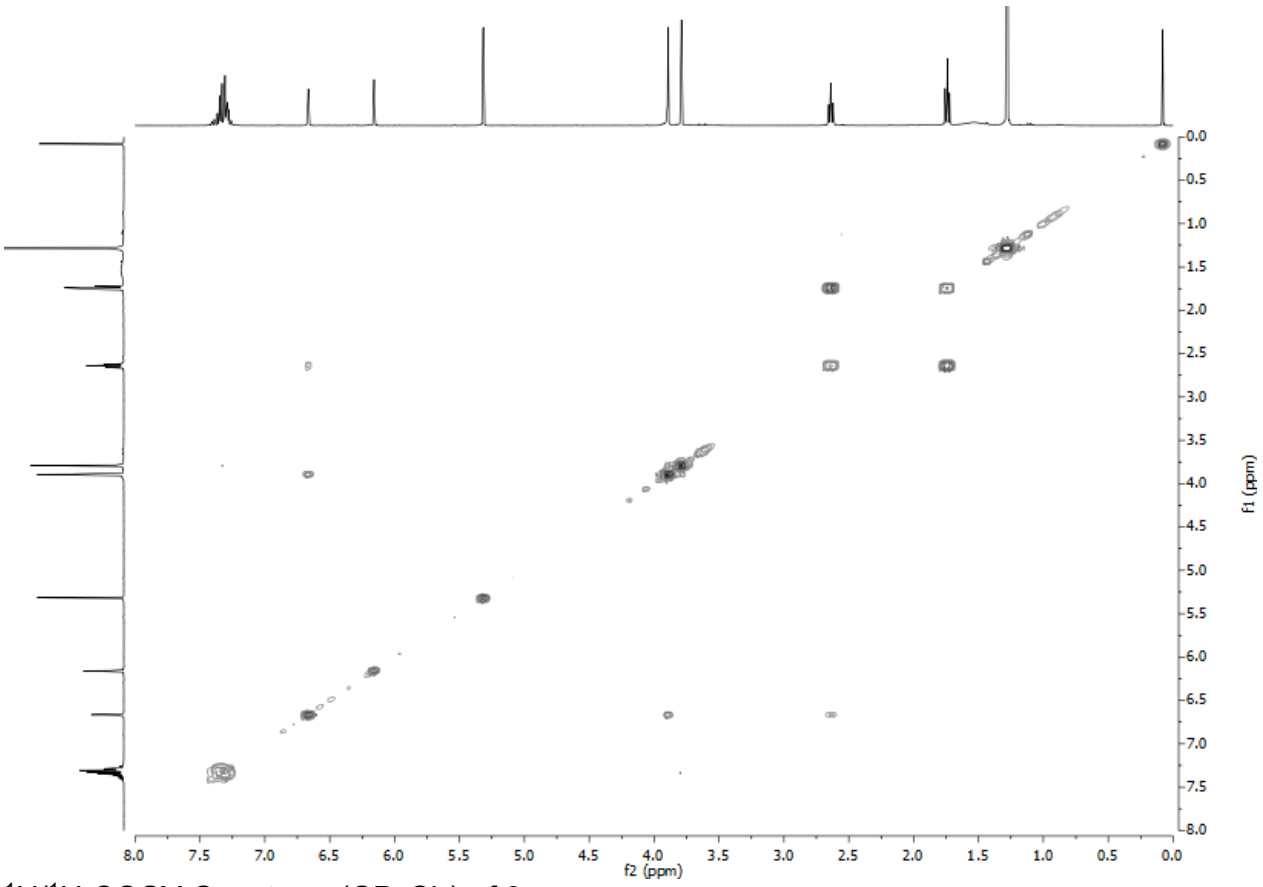
gHMBC-Spectrum ($CDCl_3$) of **8d**.



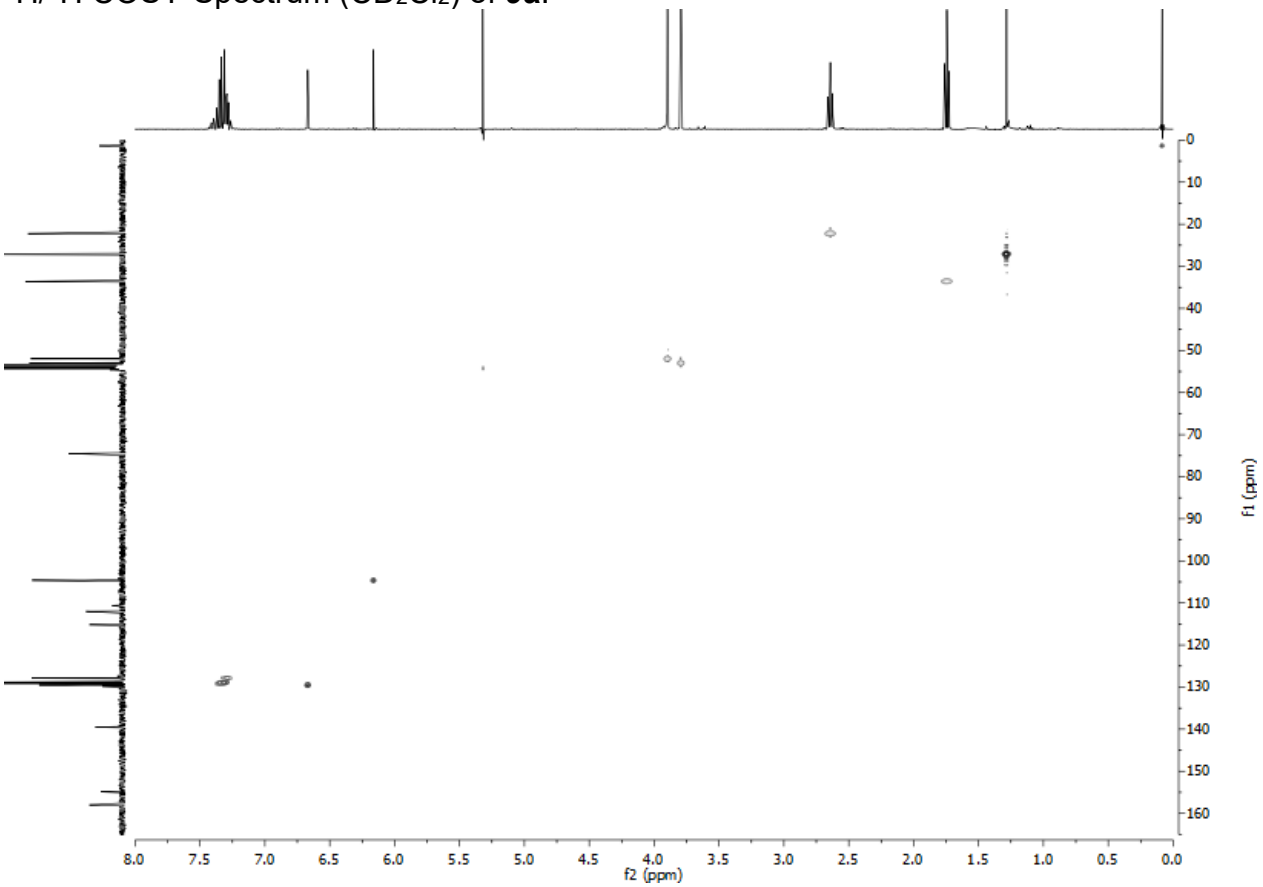
^{1}H NMR-Spectrum (CD_2Cl_2) of **9a**.



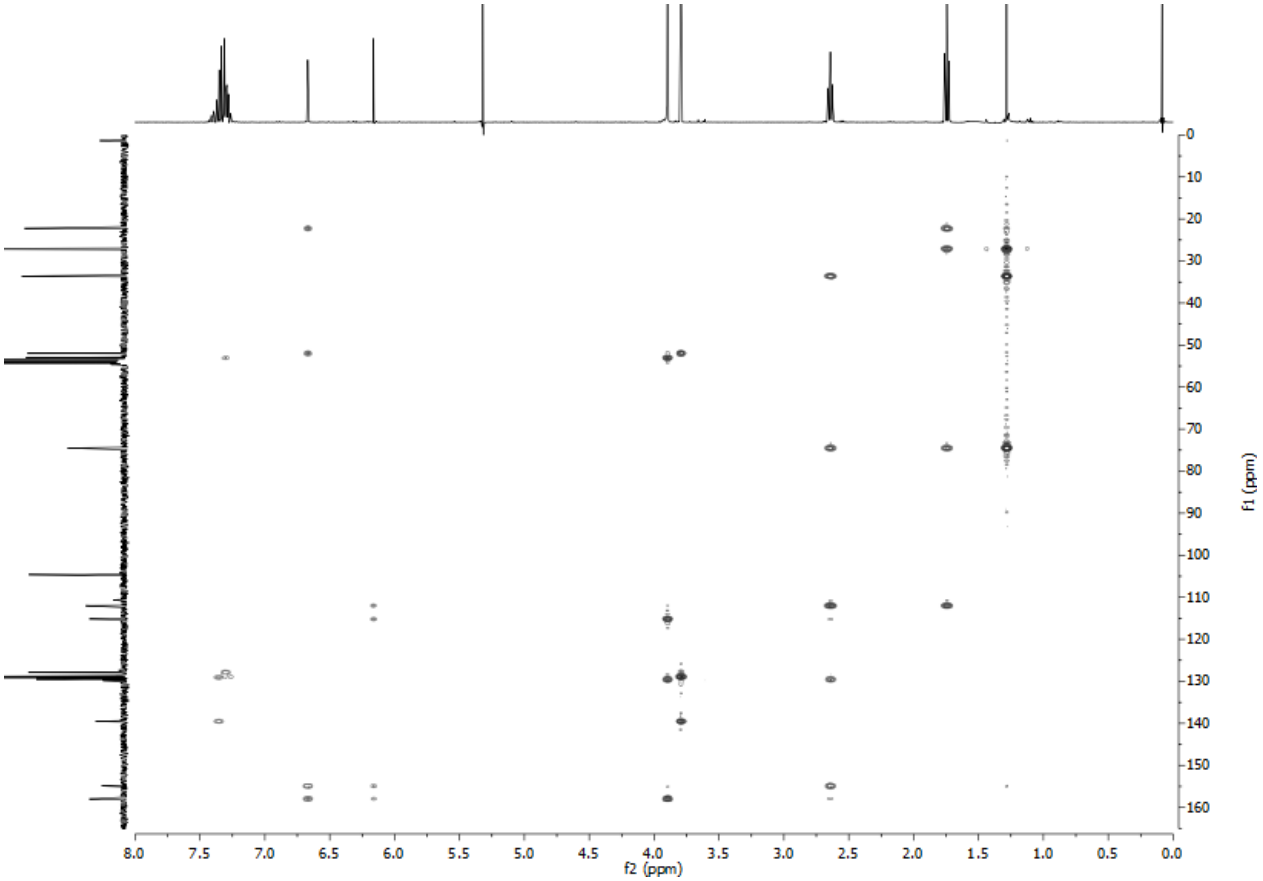
^{13}C NMR-Spectrum (CD_2Cl_2) of **9a**.



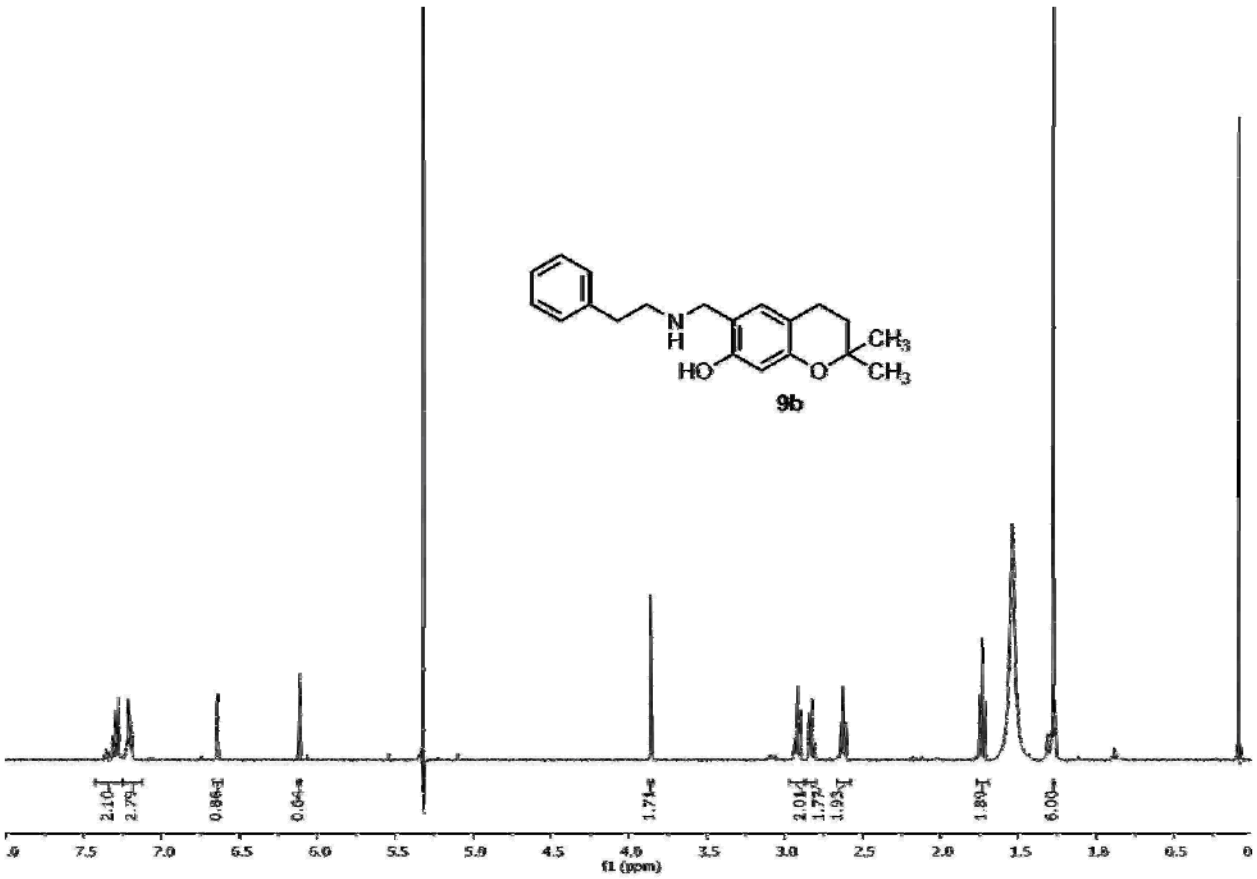
$^{1}H/^{1}H$ COSY-Spectrum (CD_2Cl_2) of **9a**.



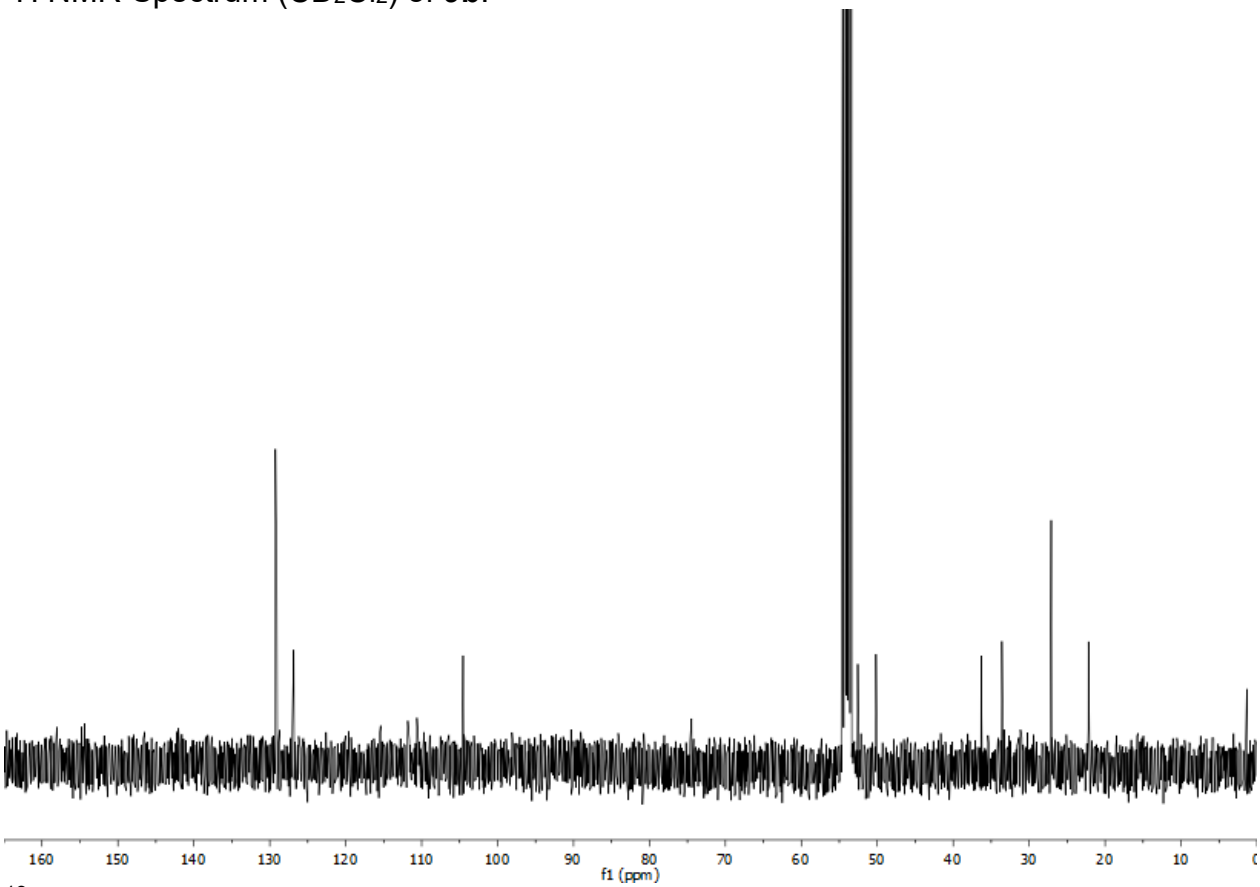
gHSQC-Spectrum (CD_2Cl_2) of **9a**.



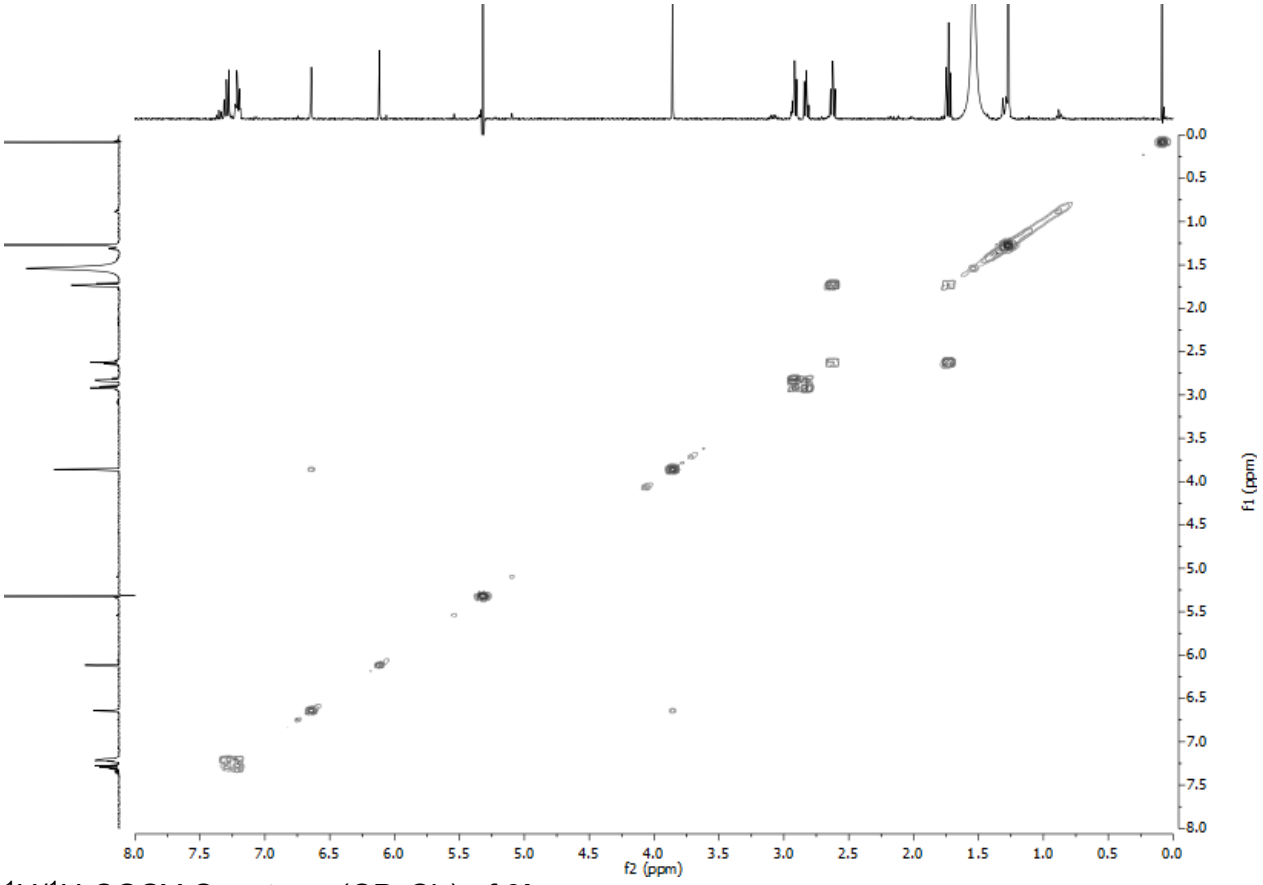
gHMBC-Spectrum (CD_2Cl_2) of **9a**.



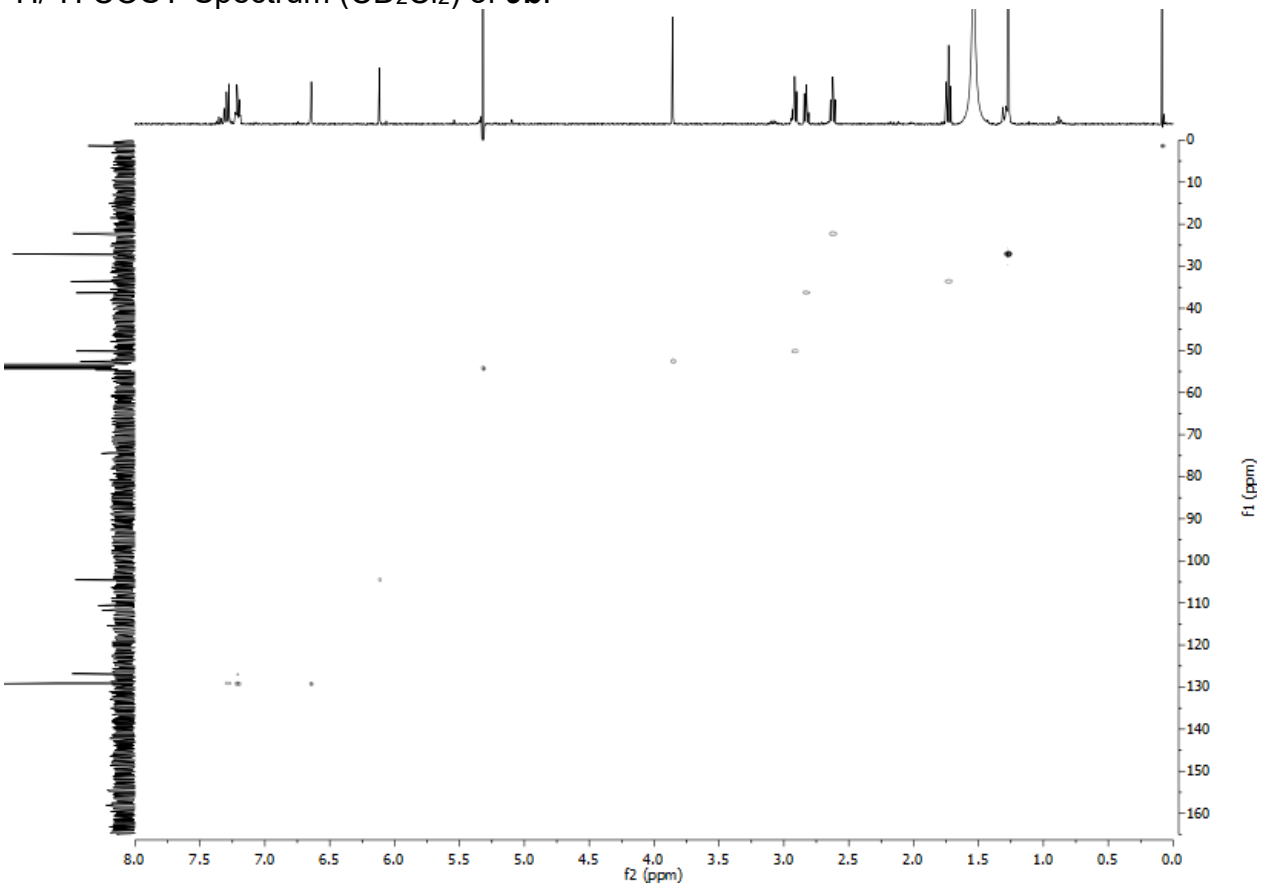
^{1}H NMR-Spectrum (CD_2Cl_2) of **9b**.



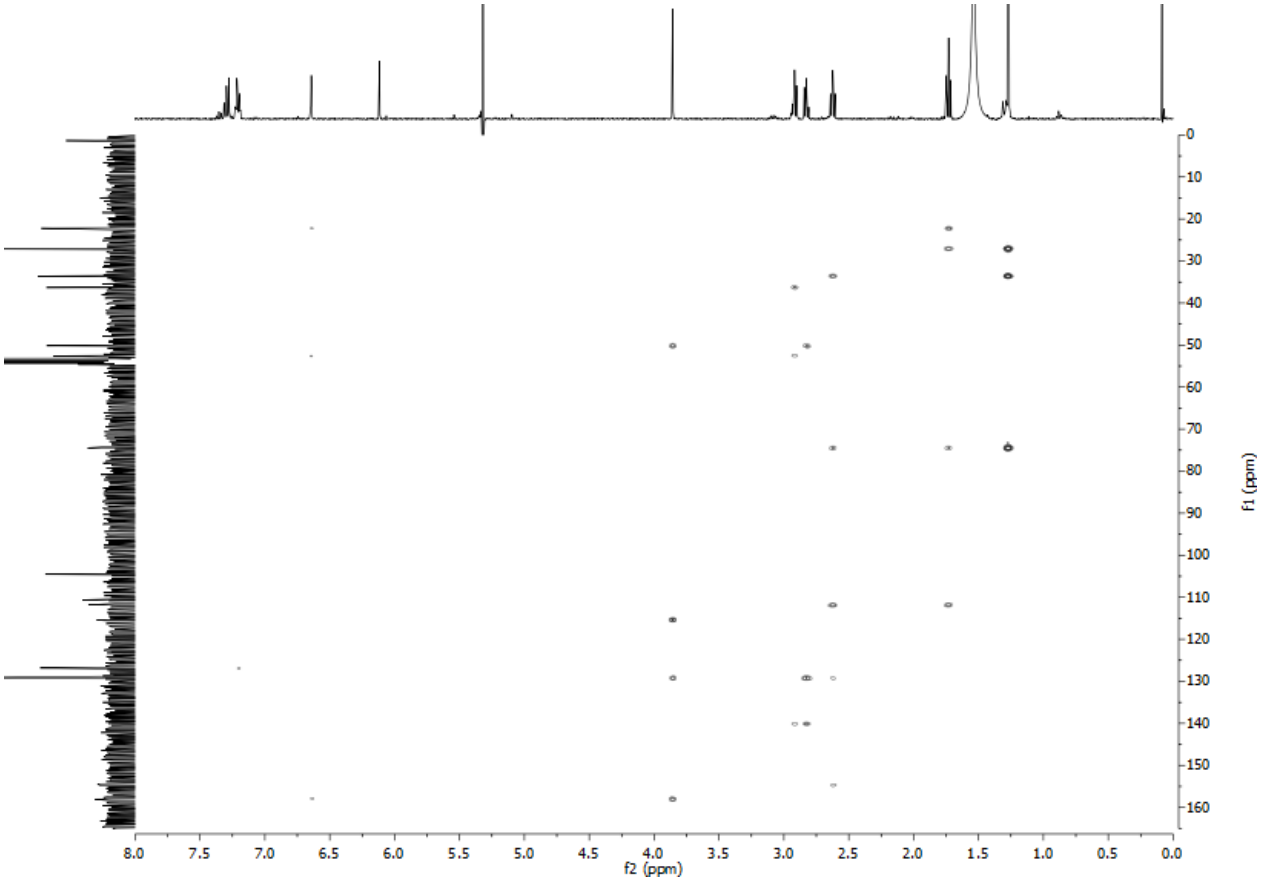
^{13}C NMR-Spectrum (CD_2Cl_2) of **9b**.



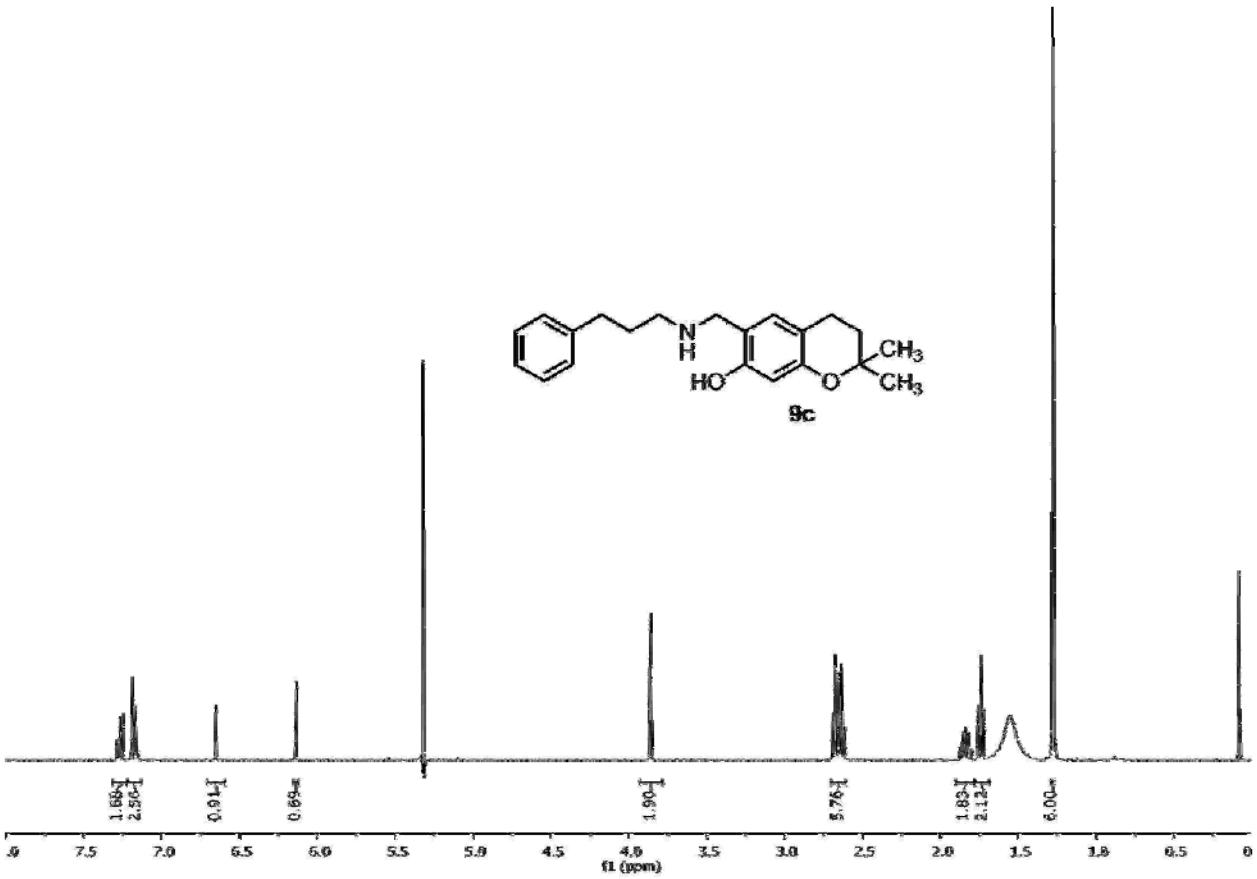
$^{1}H/^{1}H$ COSY-Spectrum (CD_2Cl_2) of **9b**.



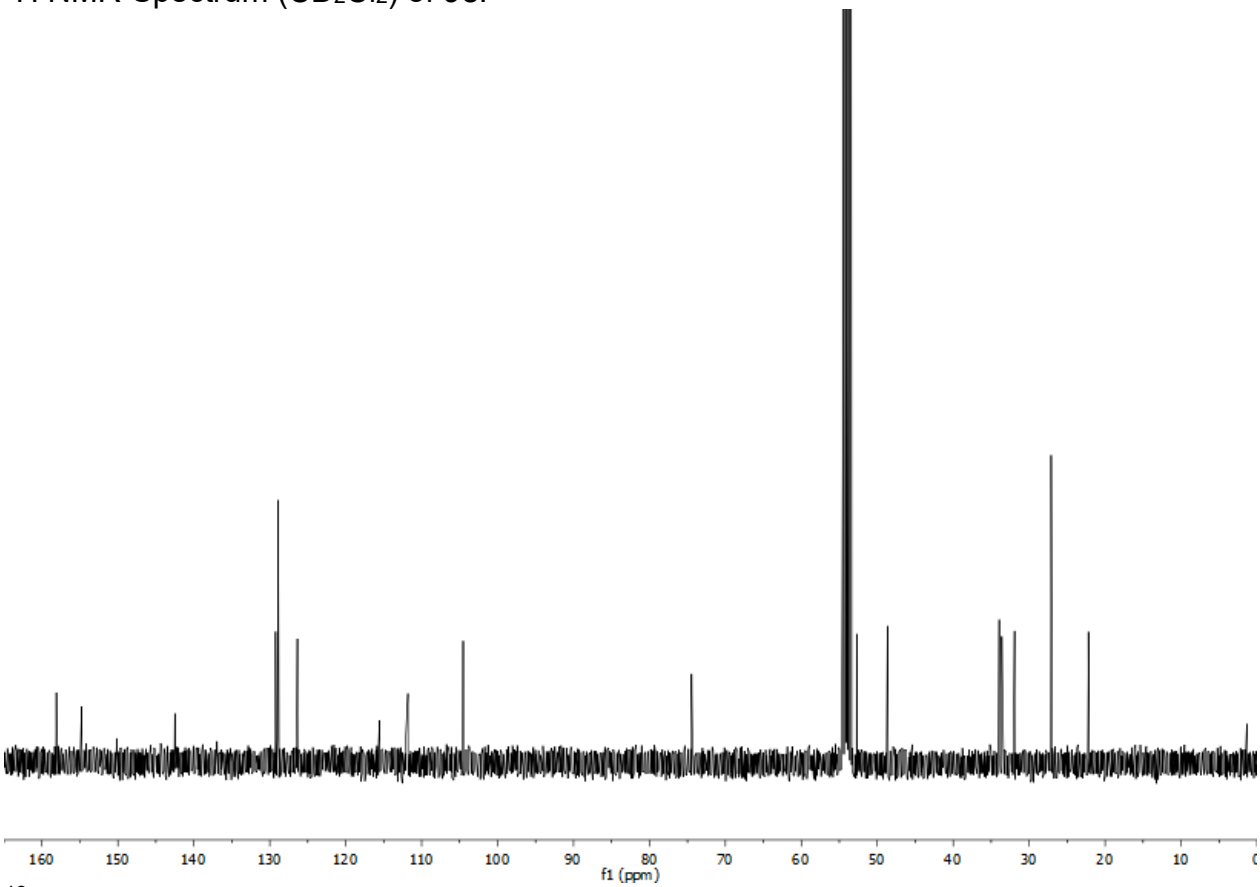
gHSQC-Spectrum (CD_2Cl_2) of **9b**.



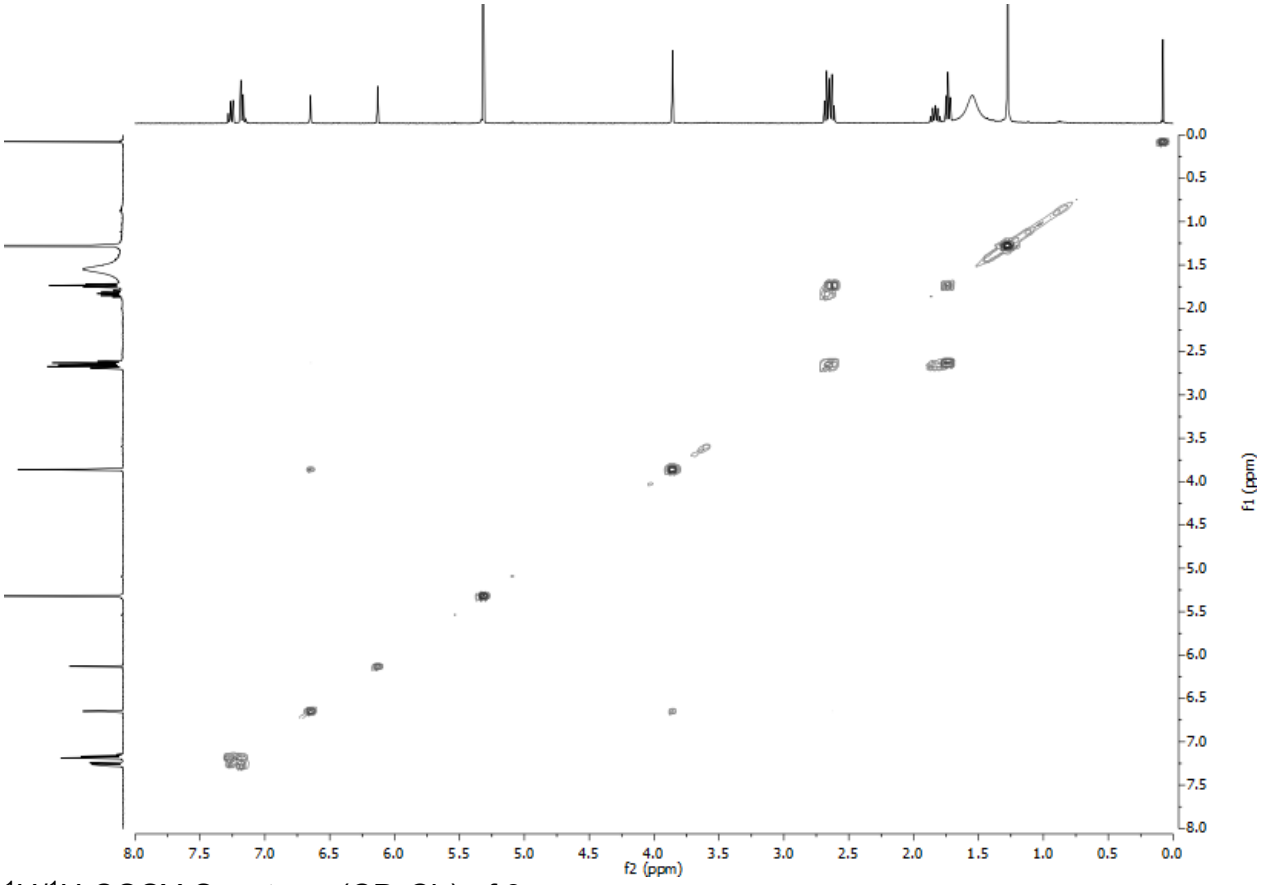
gHMBC-Spectrum (CD_2Cl_2) of **9b**.



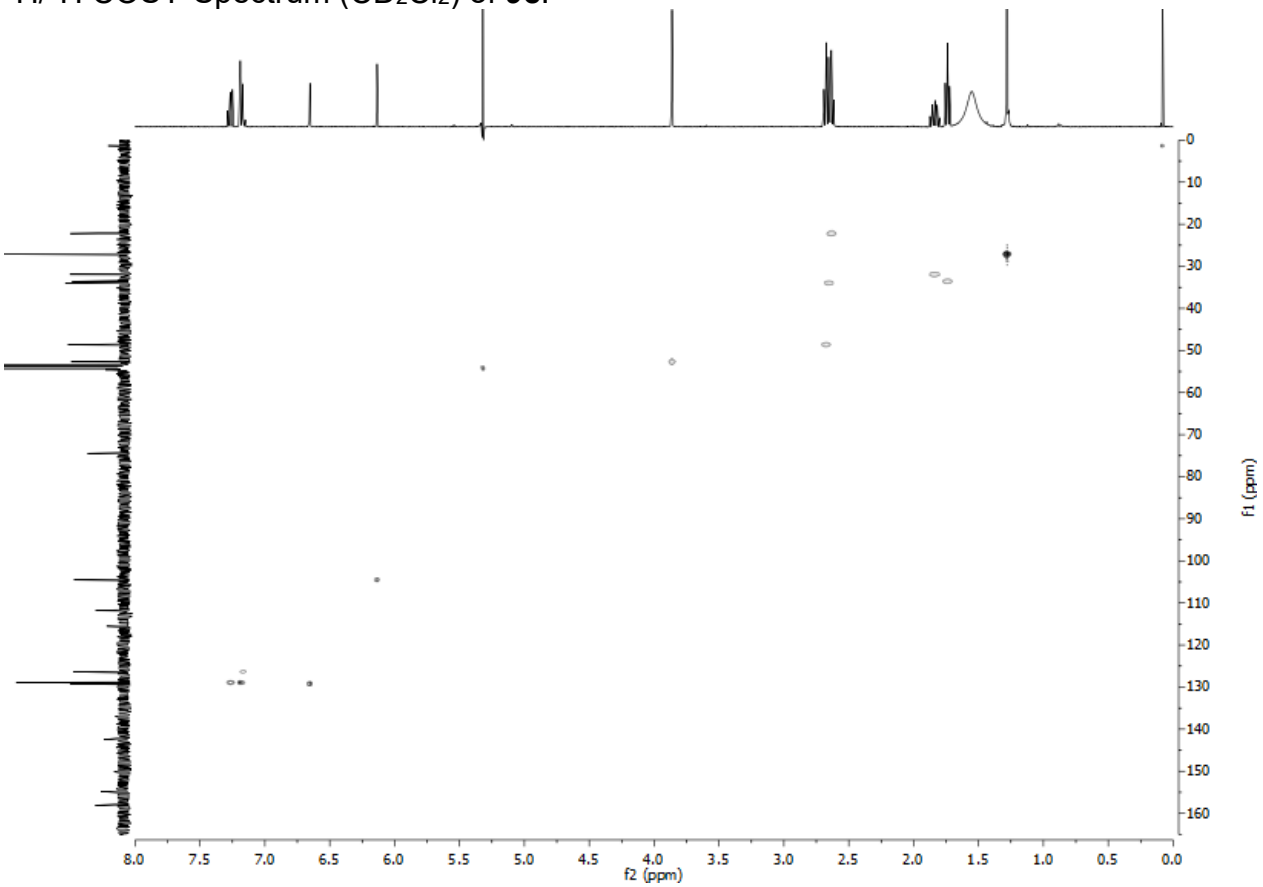
^{1}H NMR-Spectrum (CD_2Cl_2) of **9c**.



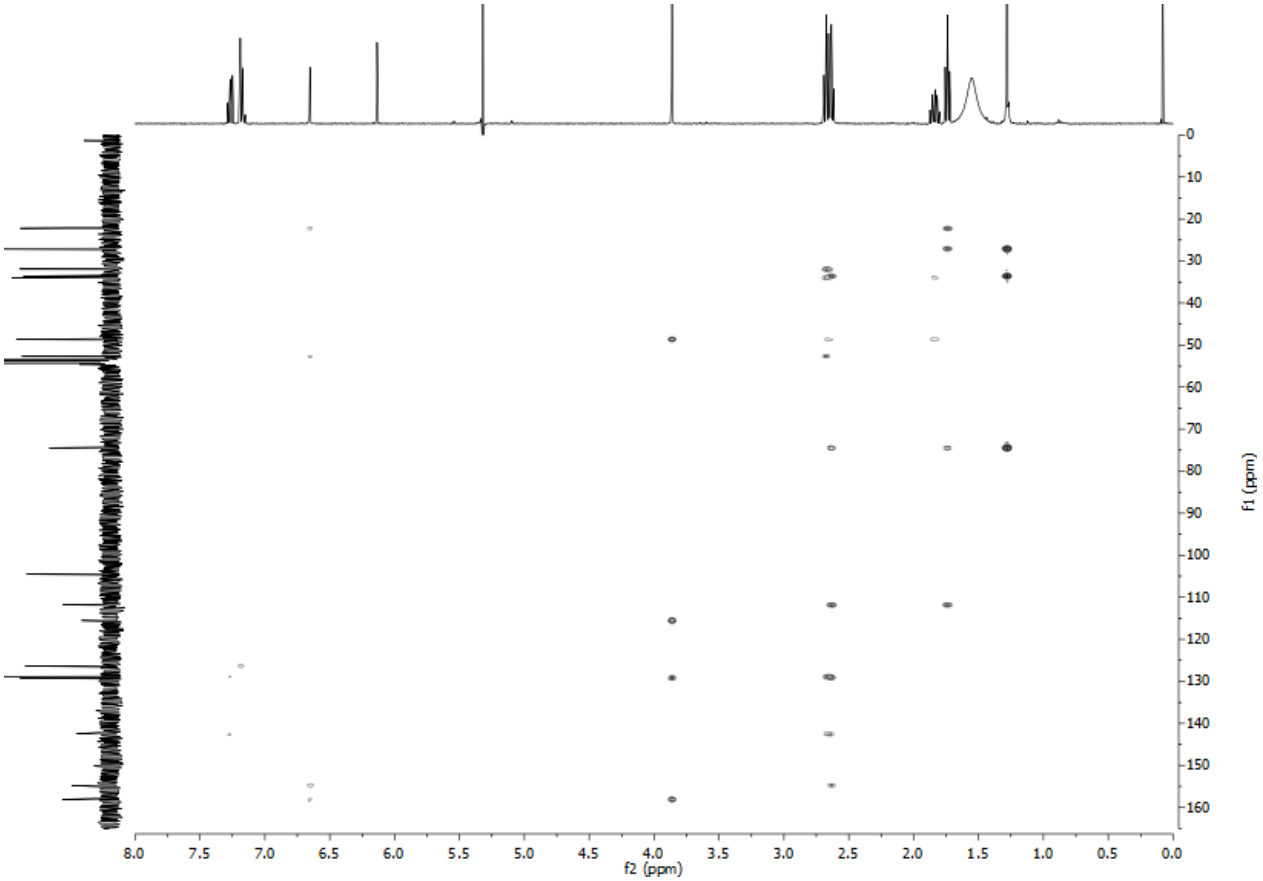
^{13}C NMR-Spectrum (CD_2Cl_2) of **9c**.



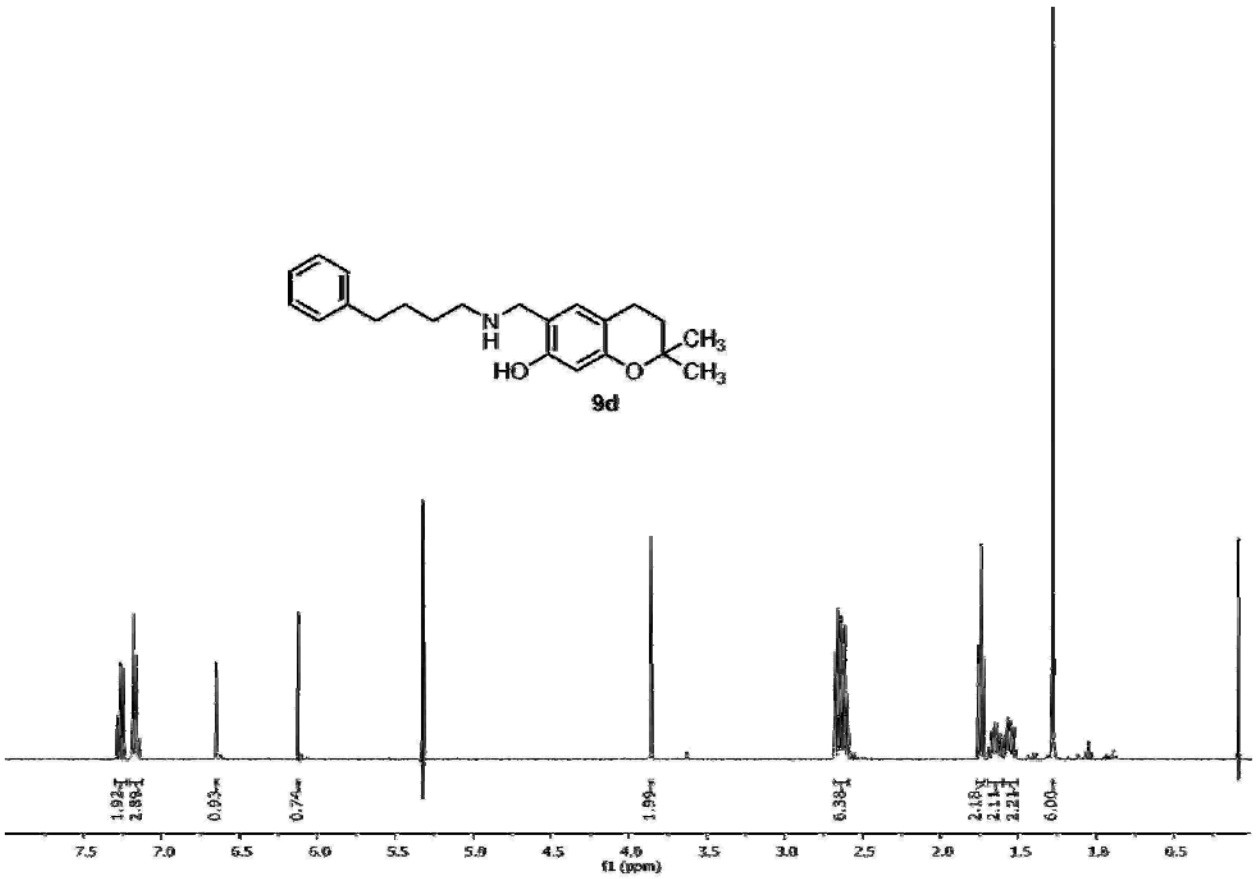
$^{1}H/^{1}H$ COSY-Spectrum (CD_2Cl_2) of **9c**.



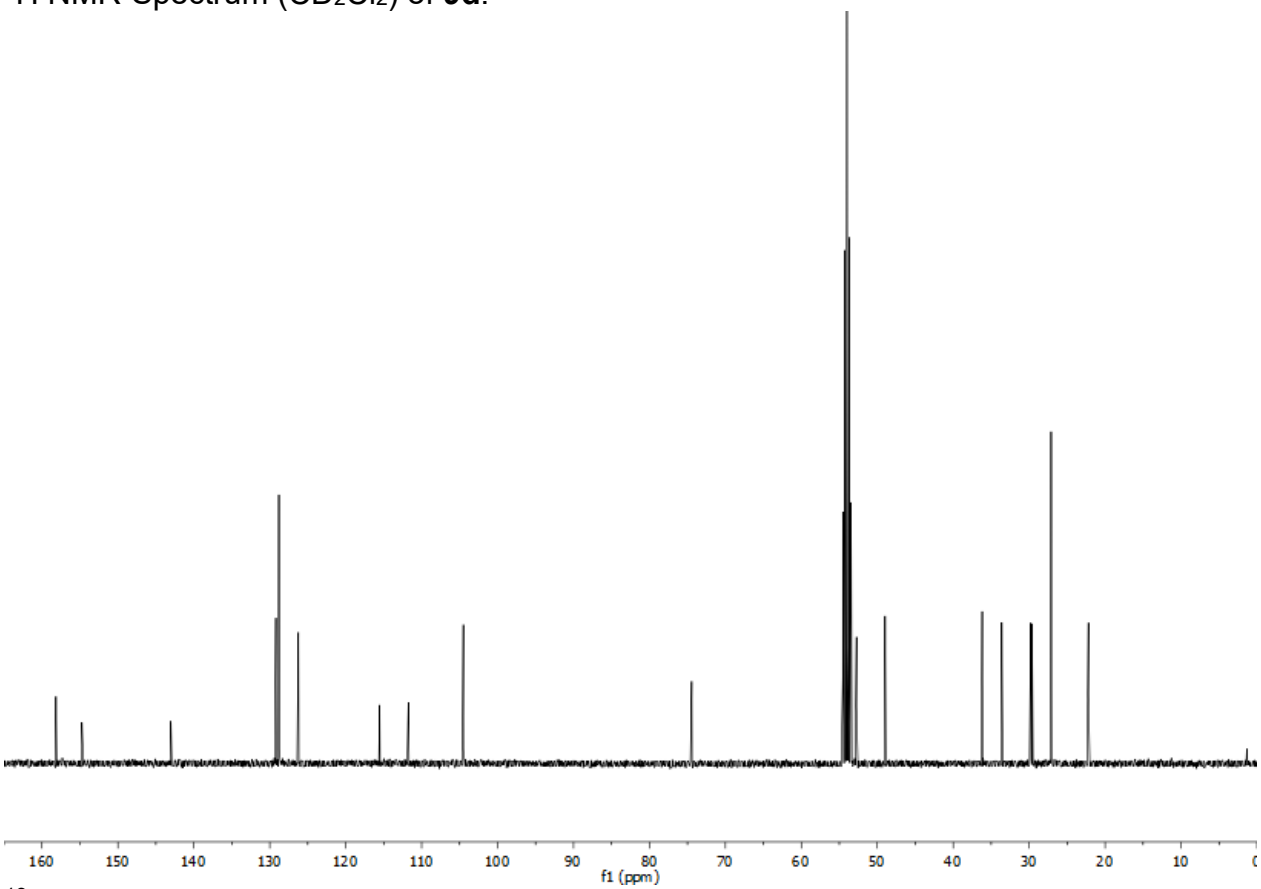
gHSQC-Spectrum (CD_2Cl_2) of **9c**.



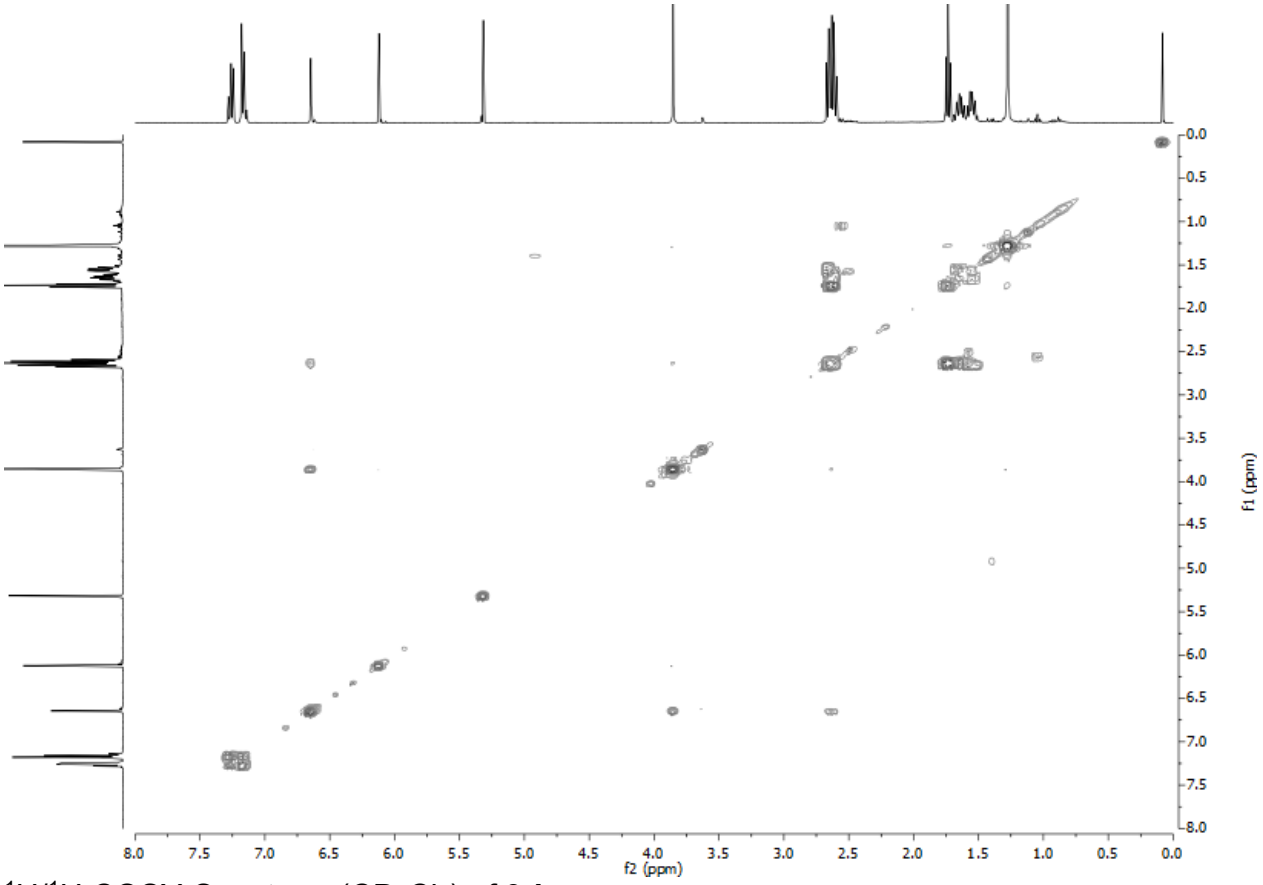
gHMBC-Spectrum (CD_2Cl_2) of **9c**.



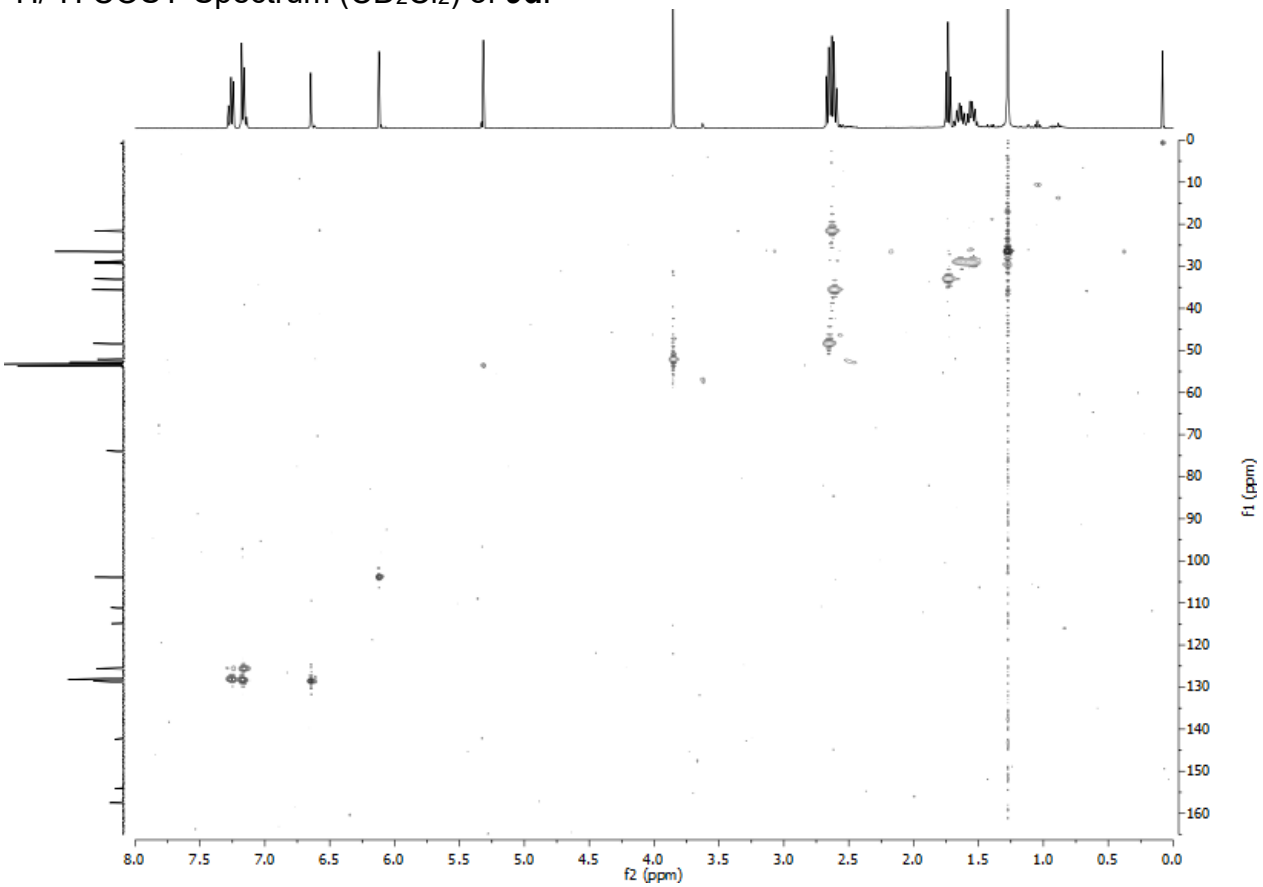
^{1}H NMR-Spectrum (CD_2Cl_2) of **9d**.



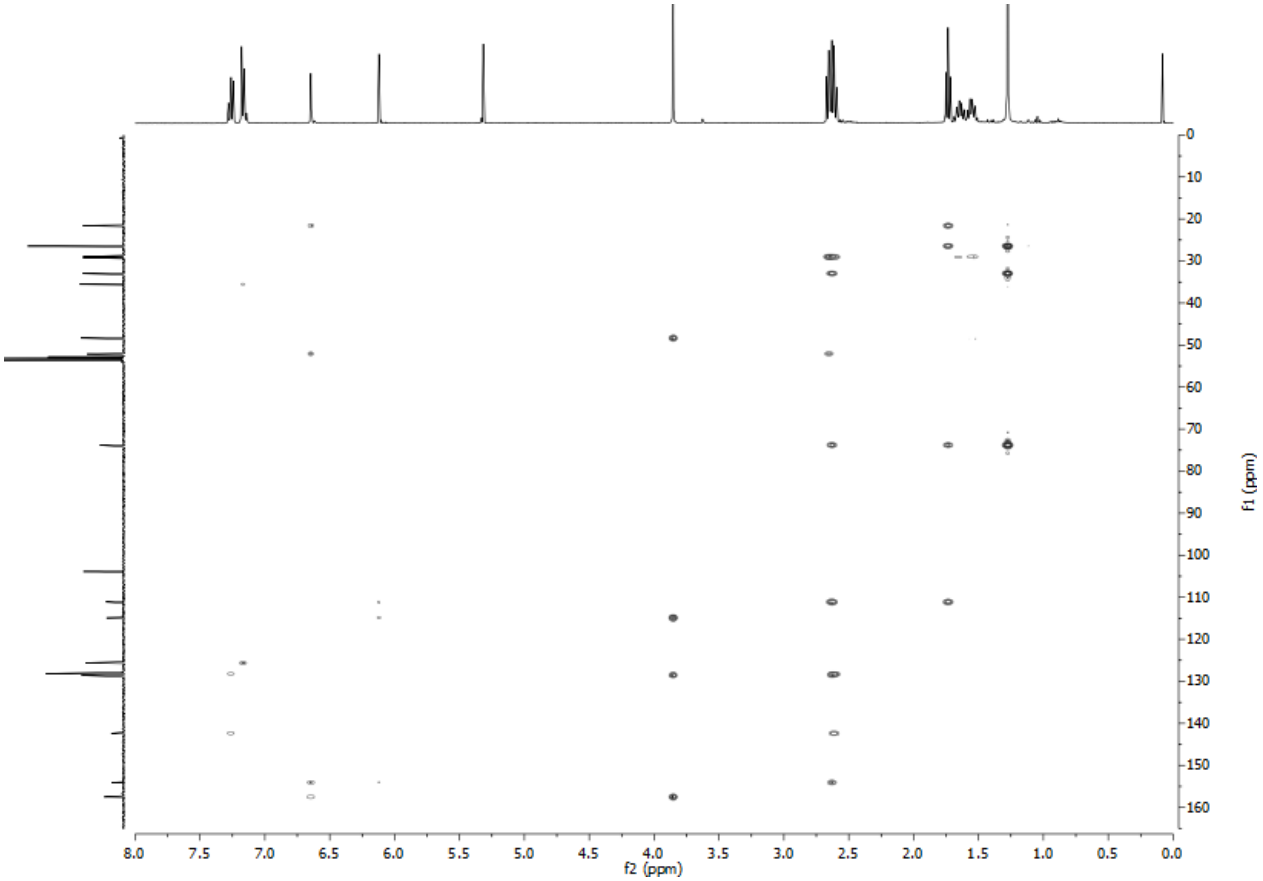
^{13}C NMR-Spectrum (CD_2Cl_2) of **9d**.



$^{1}H/^{1}H$ COSY-Spectrum (CD_2Cl_2) of **9d**.



gHSQC-Spectrum (CD_2Cl_2) of **9d**.



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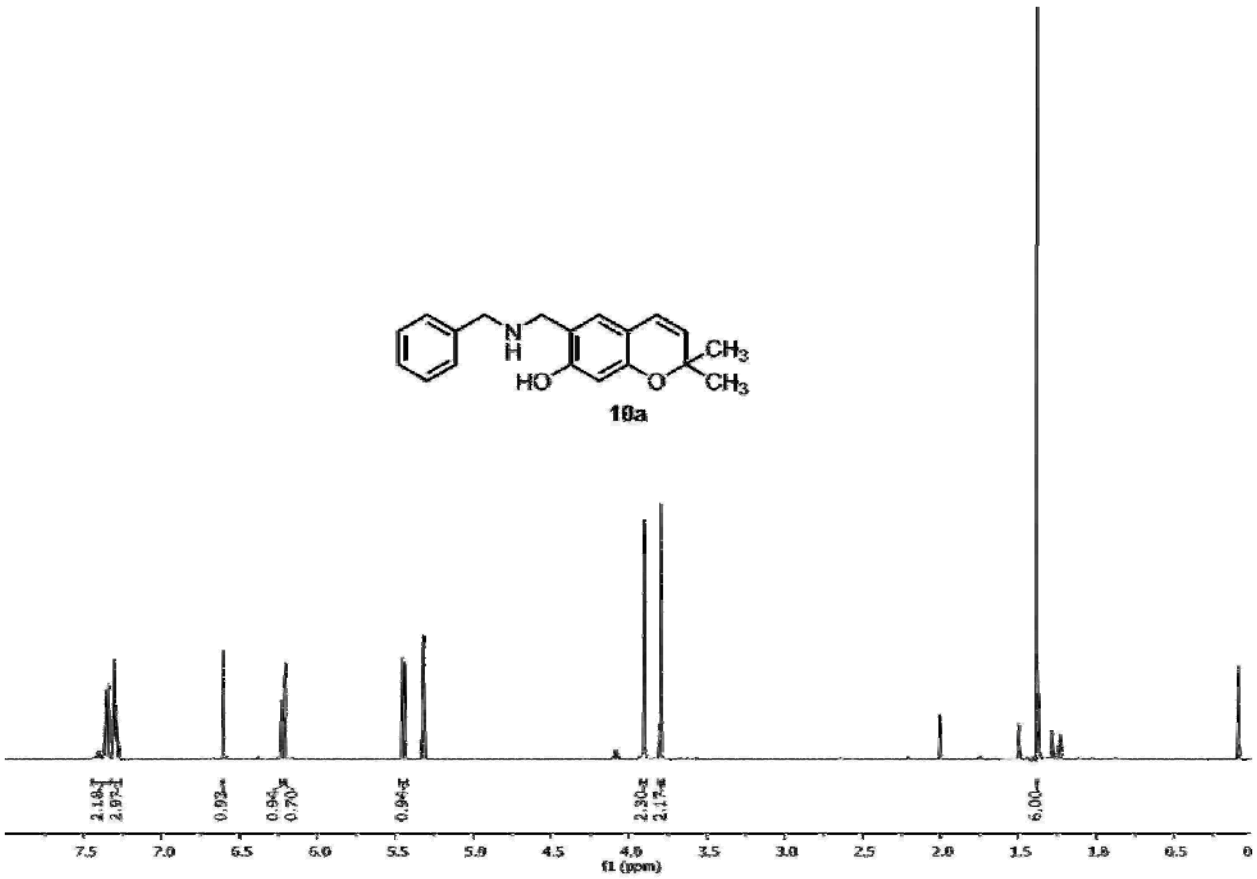
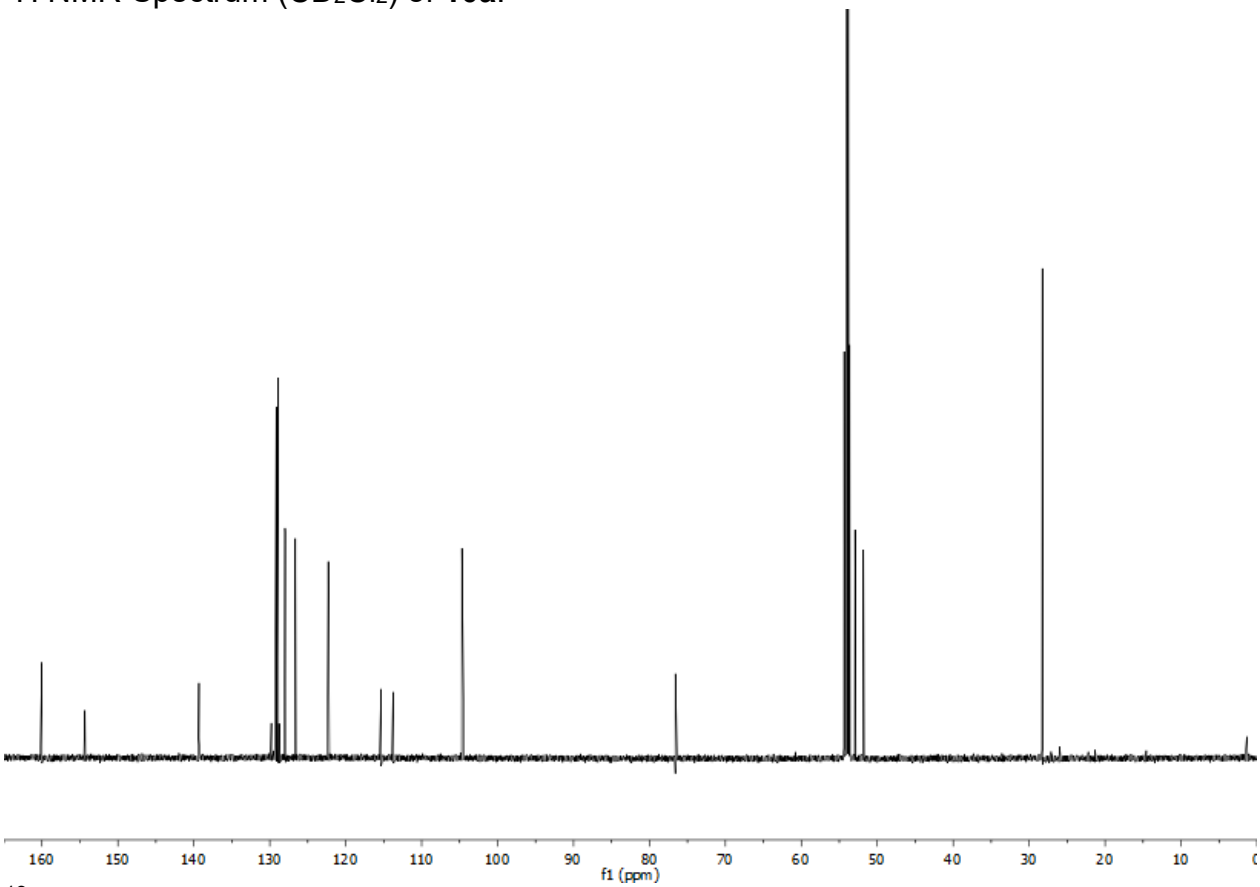
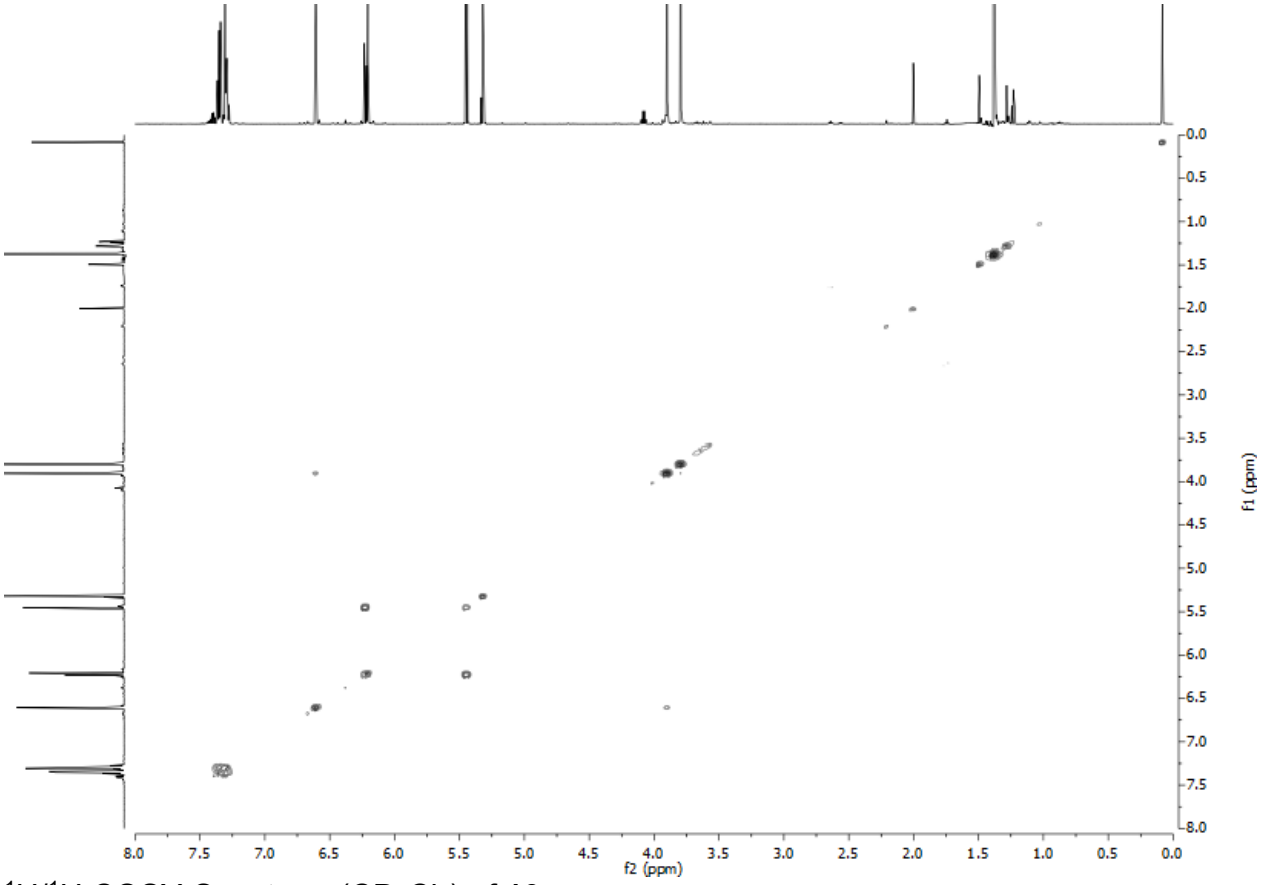


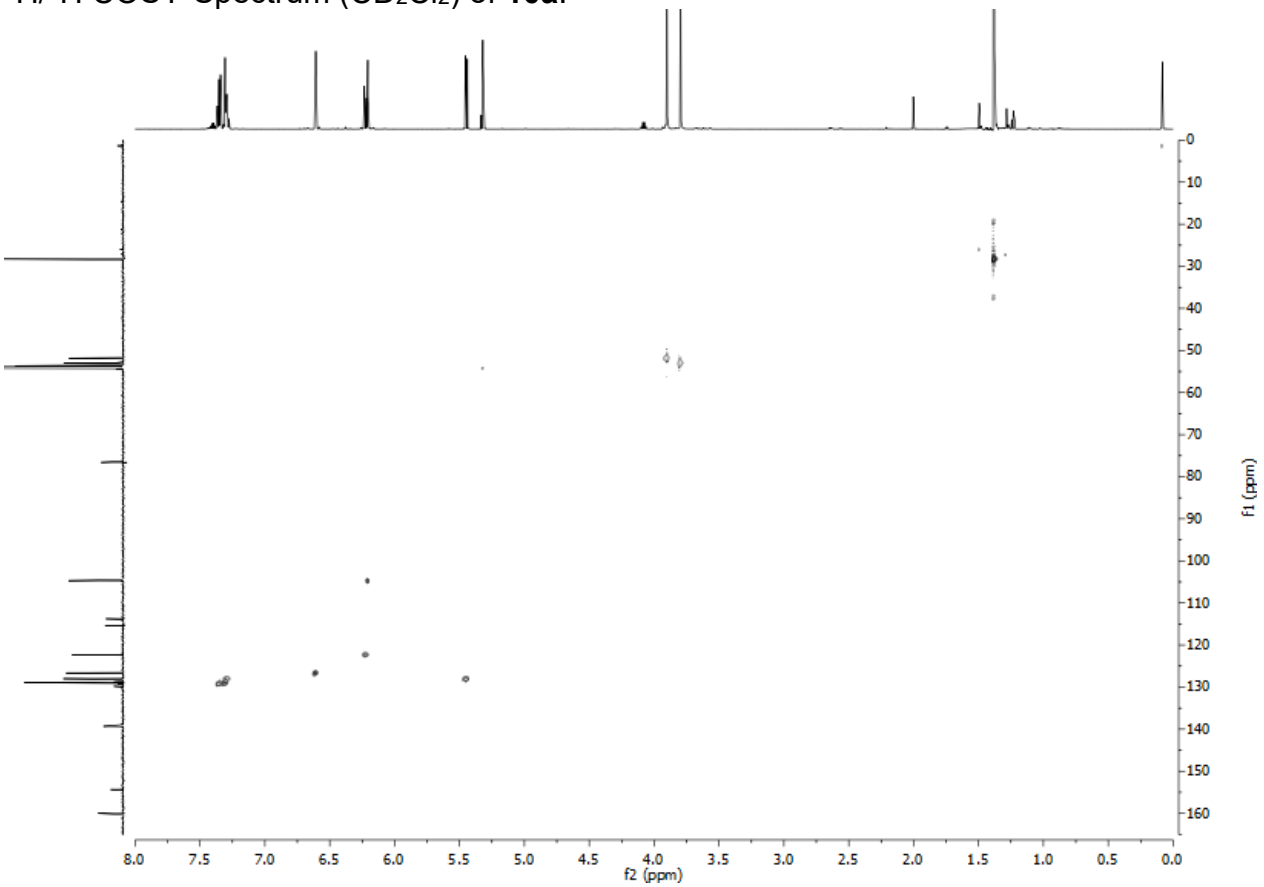
^{1}H NMR-Spectrum (CD_2Cl_2) of **10a**.



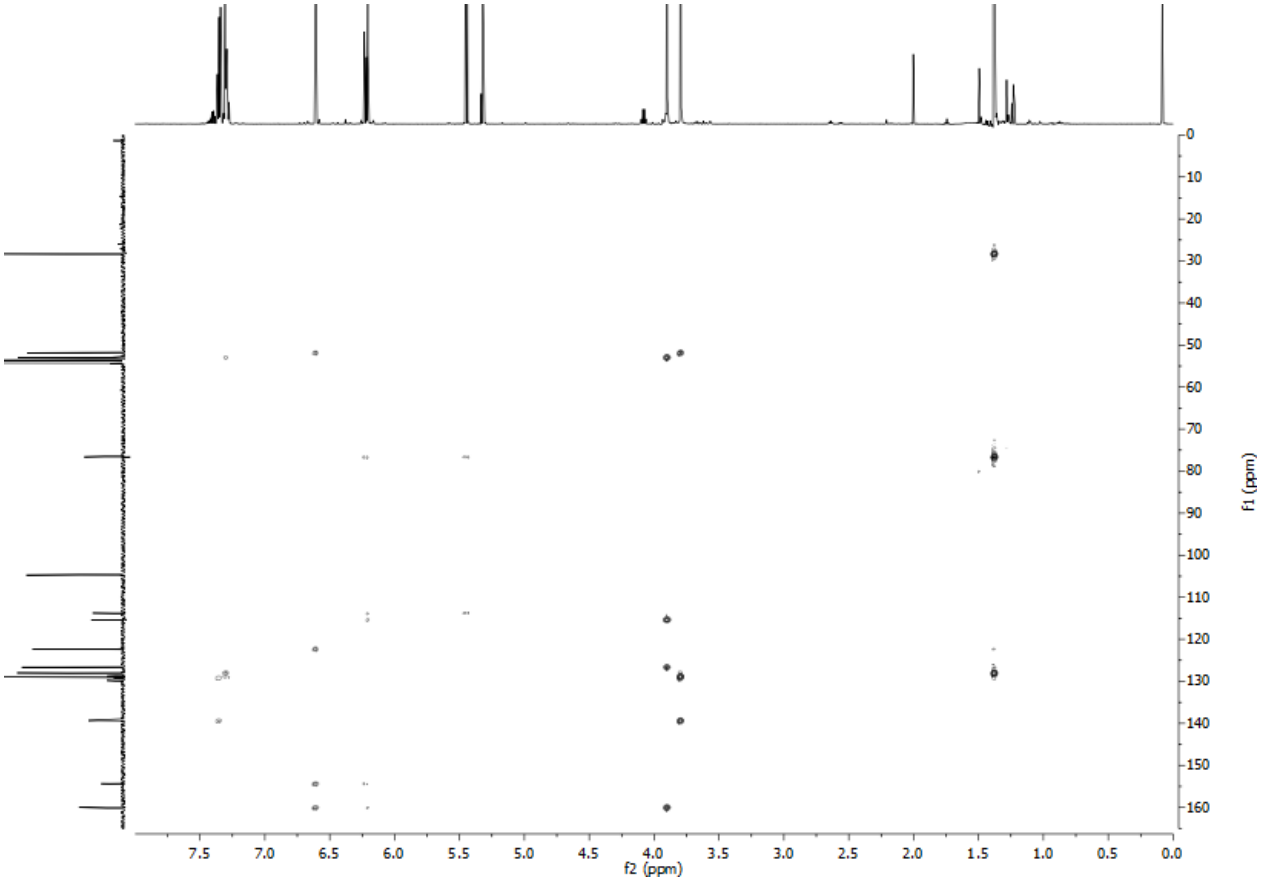
^{13}C NMR-Spektrum (CD_2Cl_2) of **10a**.



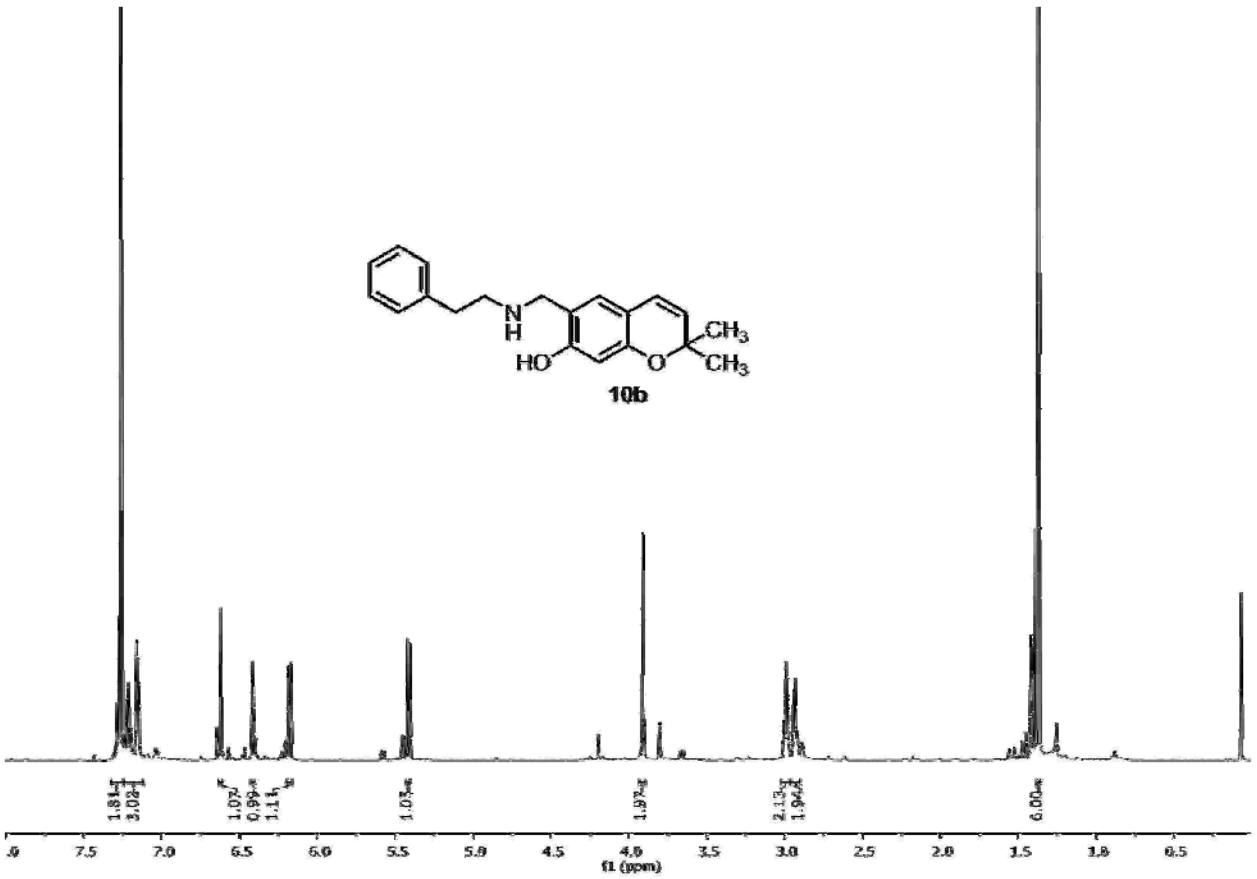
$^{1}H/^{1}H$ COSY-Spectrum (CD_2Cl_2) of **10a**.



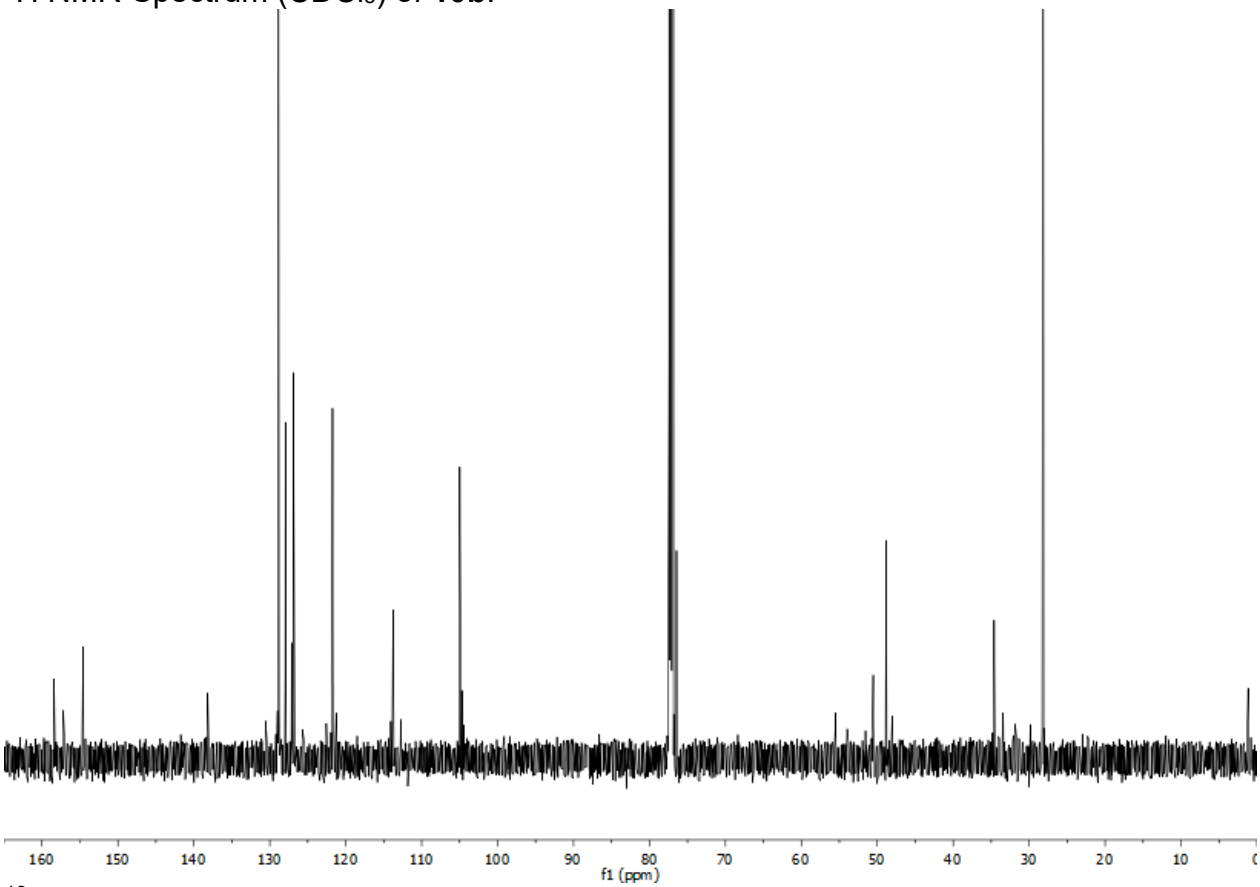
gHSQC-Spectrum (CD_2Cl_2) of **10a**.



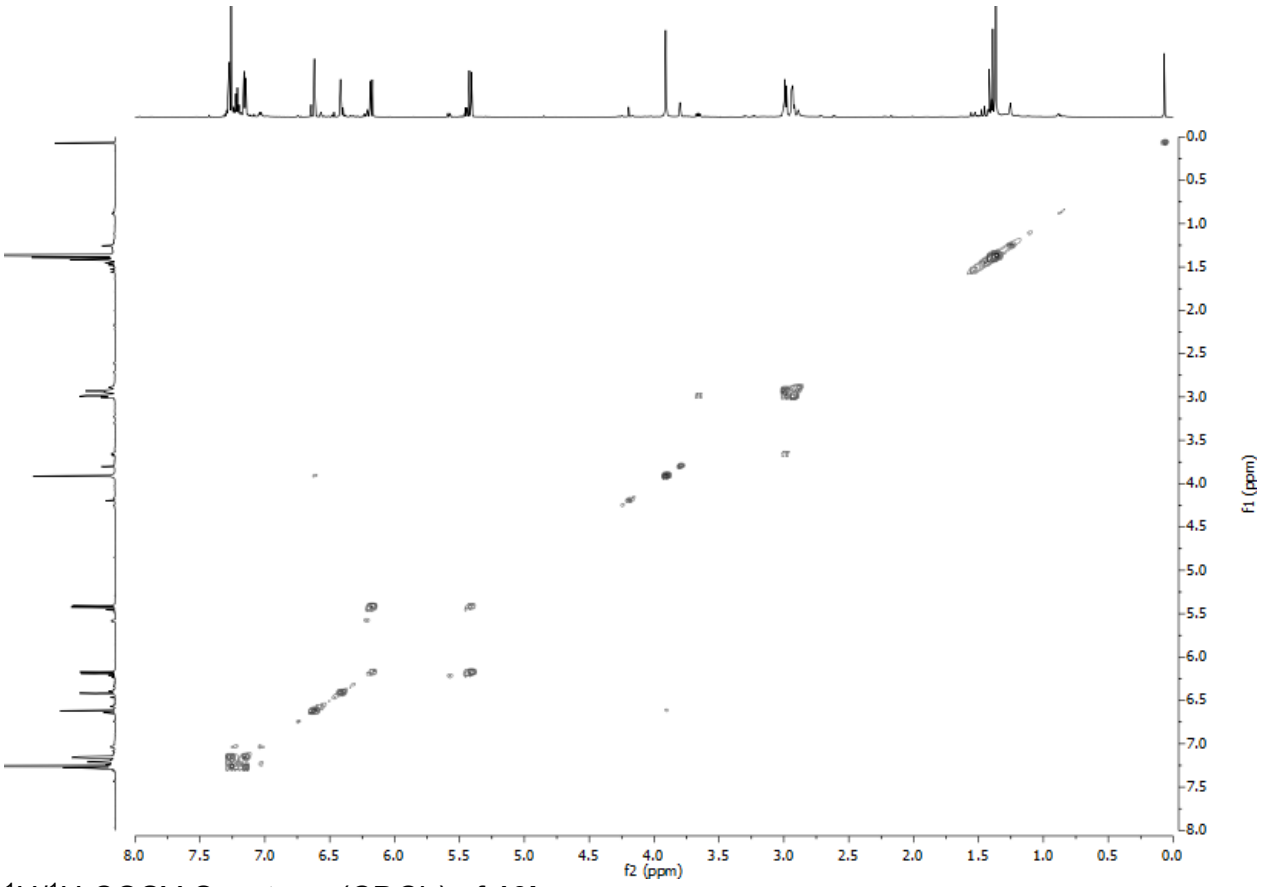
gHMBC-Spectrum (CD_2Cl_2) of **10a**.



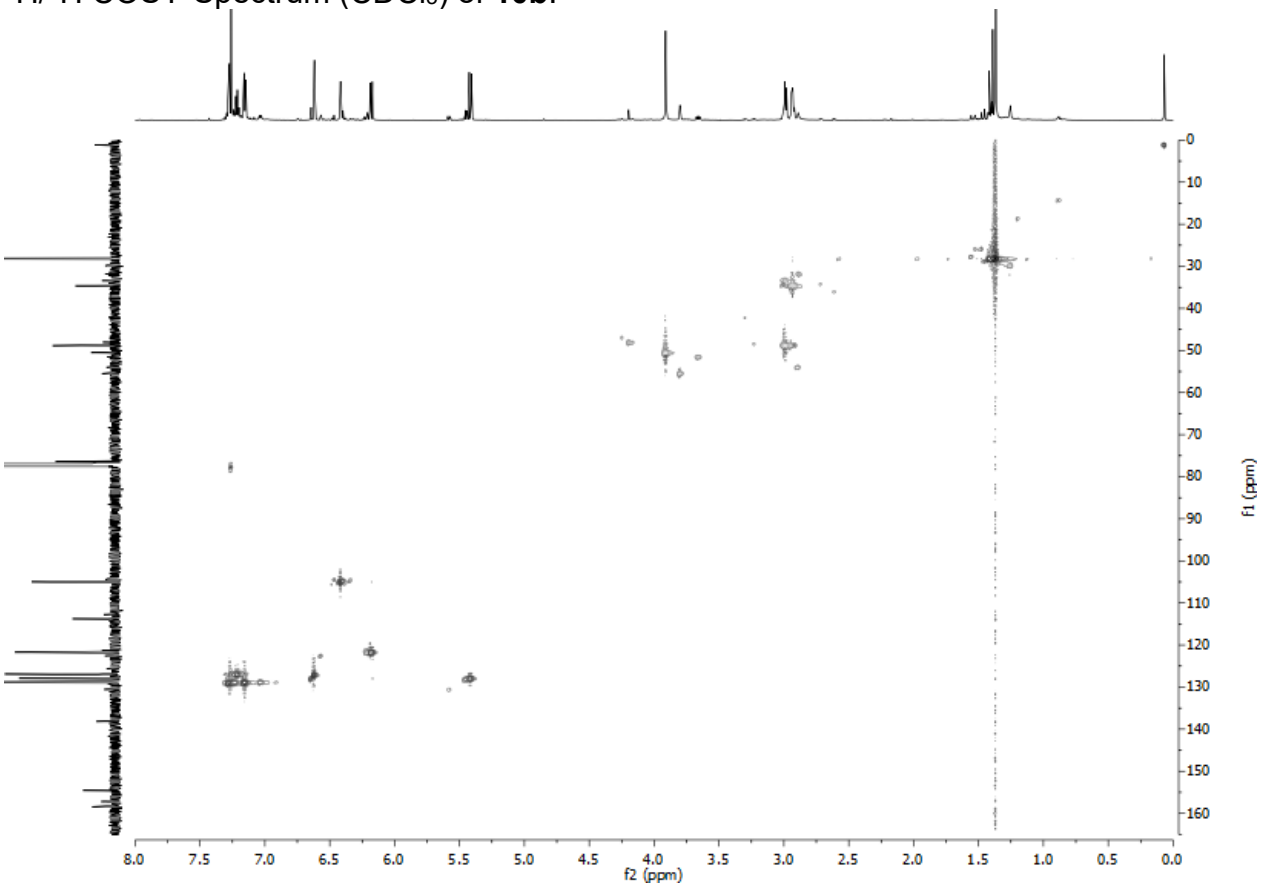
^{1}H NMR-Spectrum ($CDCl_3$) of **10b**.



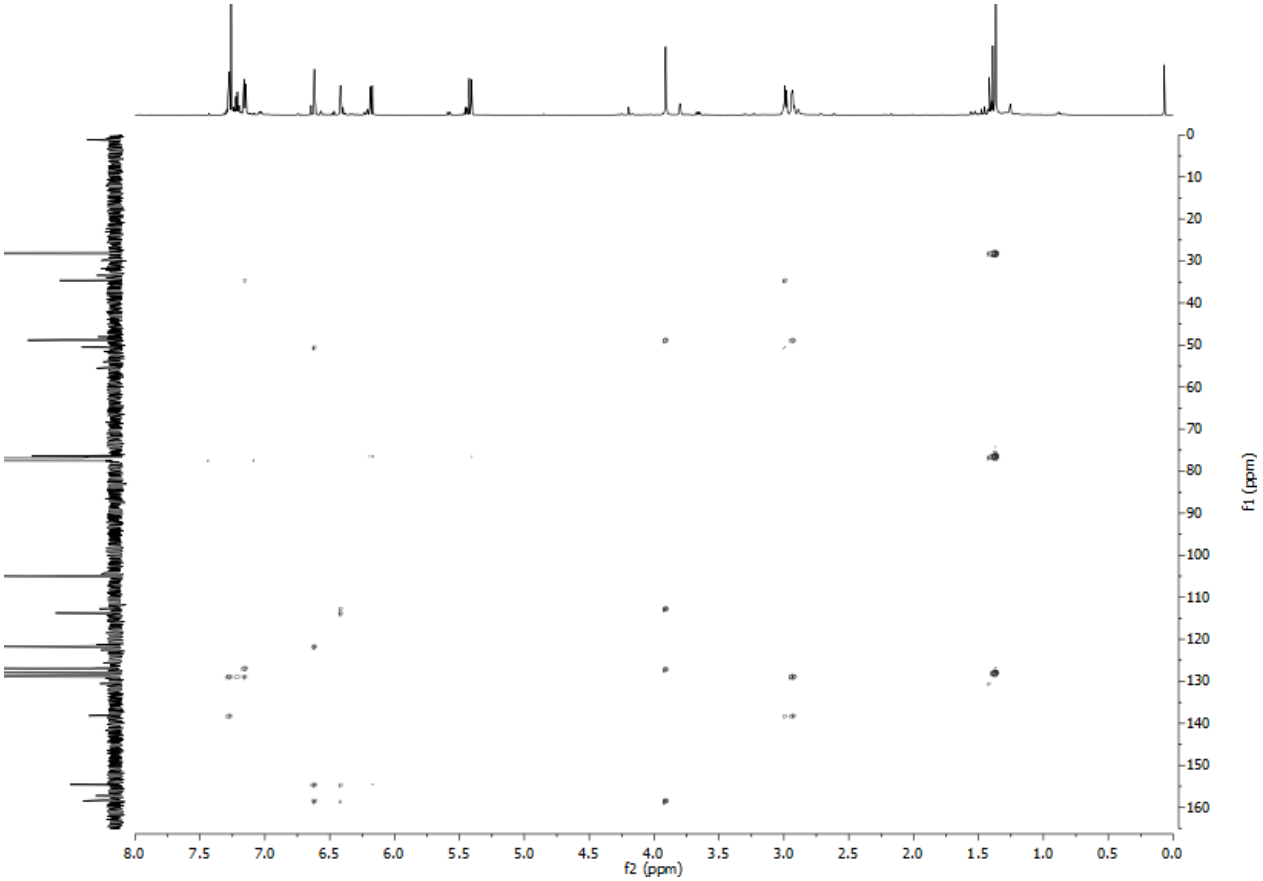
^{13}C NMR-Spectrum ($CDCl_3$) of **10b**.



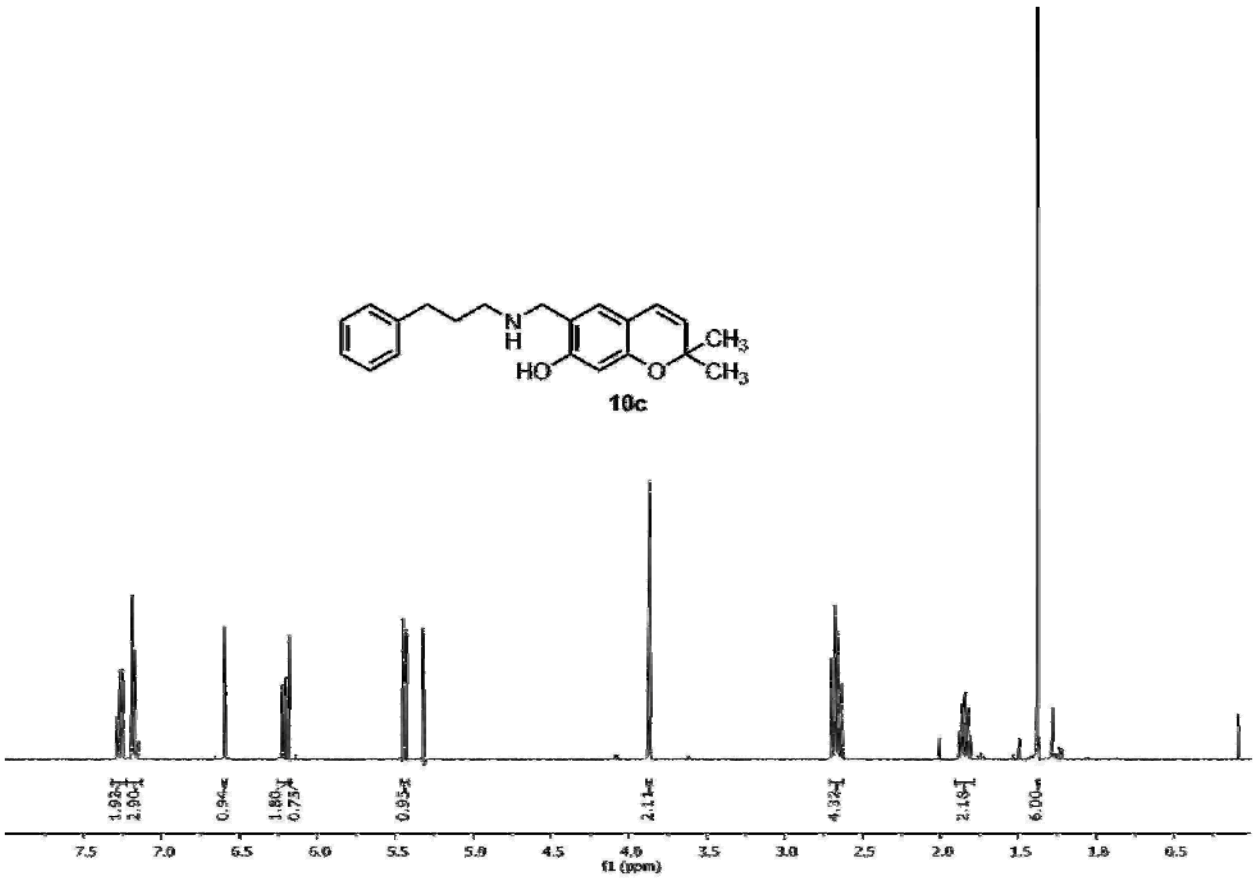
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **10b**.



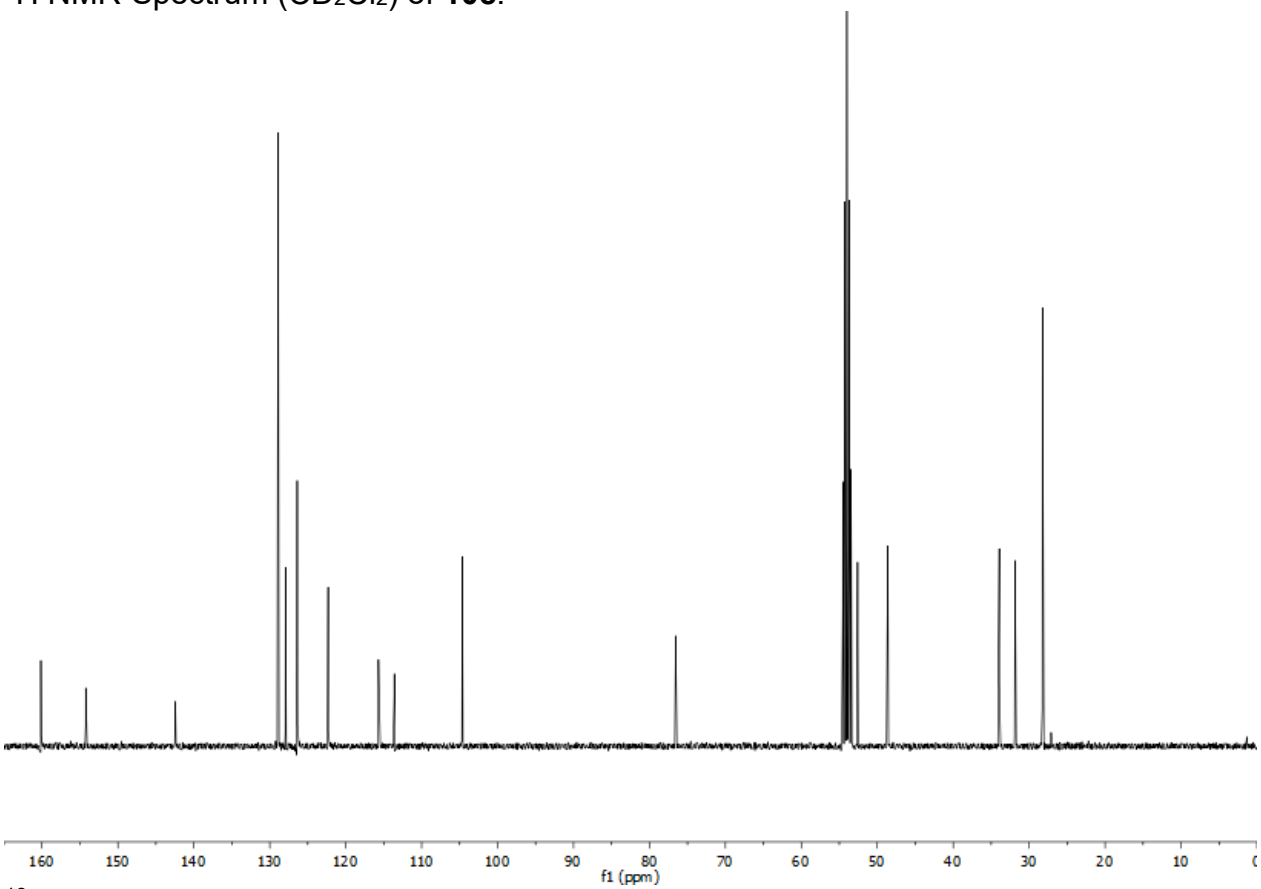
gHSQC-Spectrum ($CDCl_3$) of **10b**.



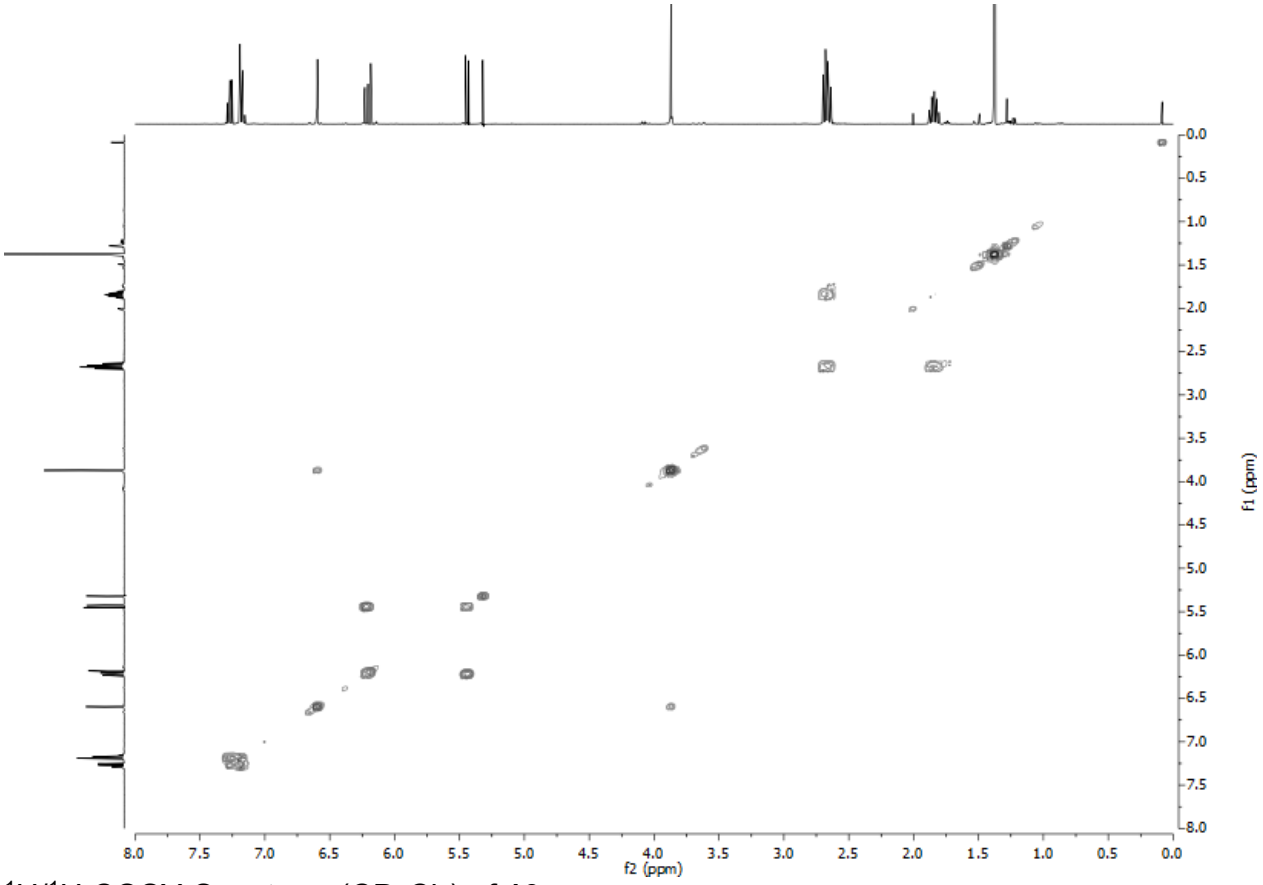
gHMBC-Spectrum ($CDCl_3$) of **10b**.



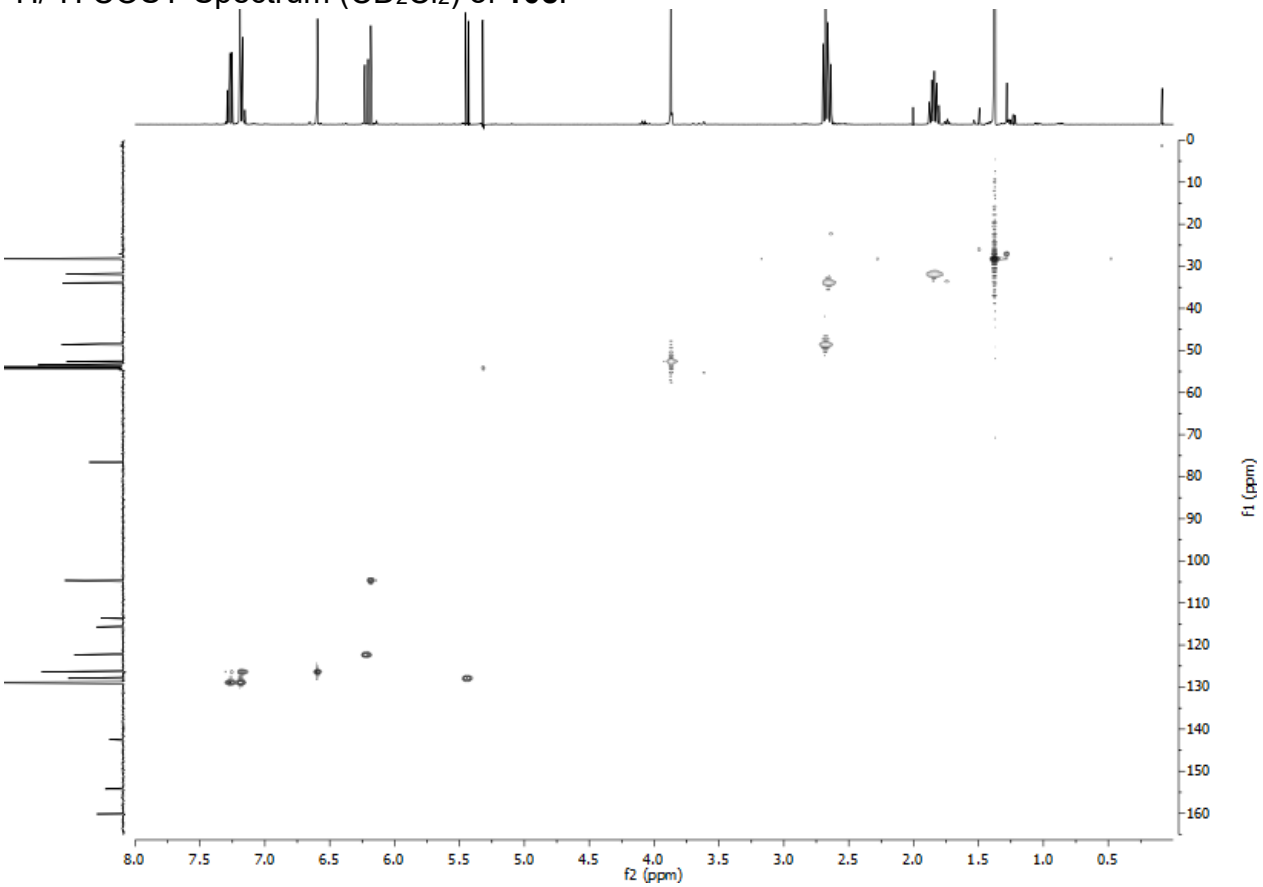
^{1}H NMR-Spectrum (CD_2Cl_2) of **10c**.



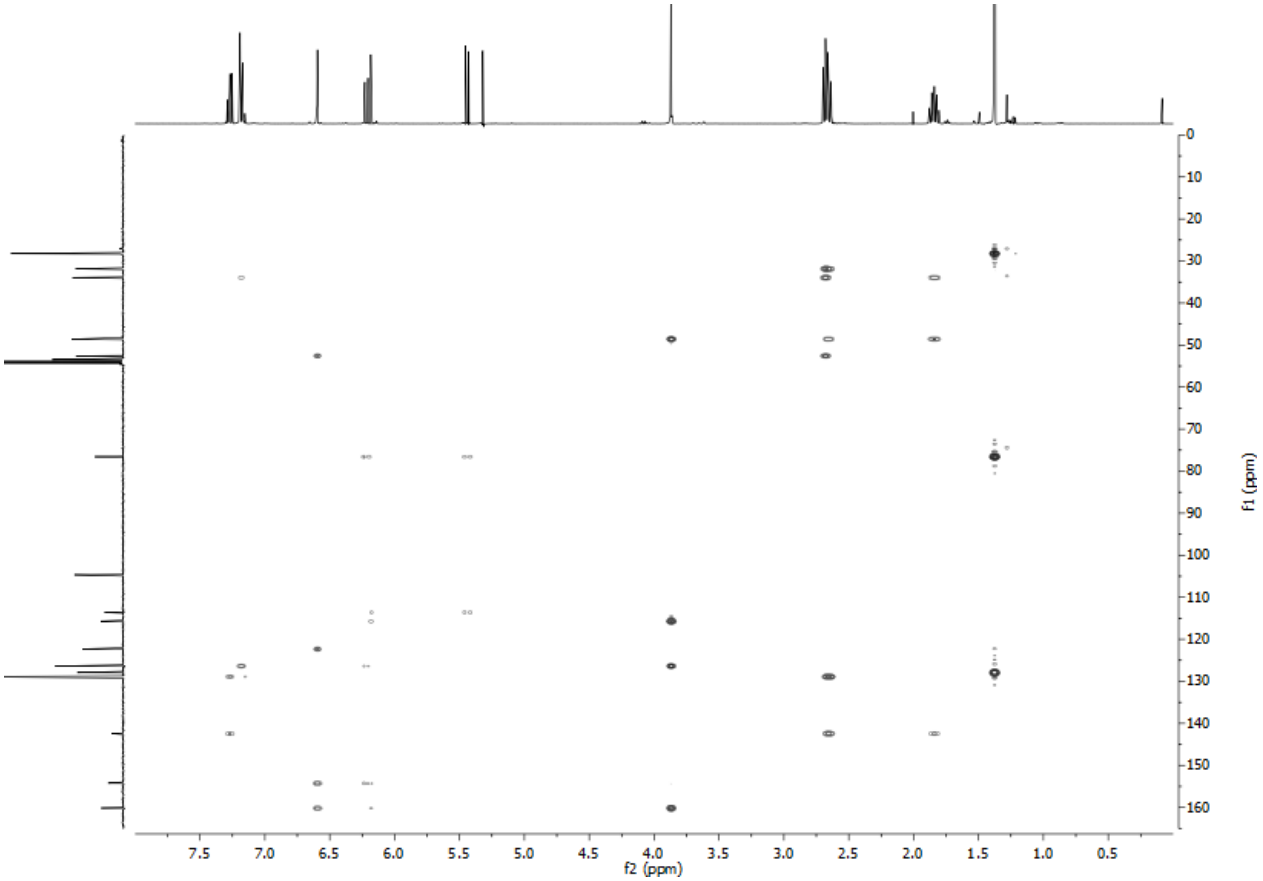
^{13}C NMR-Spectrum (CD_2Cl_2) of **10c**.



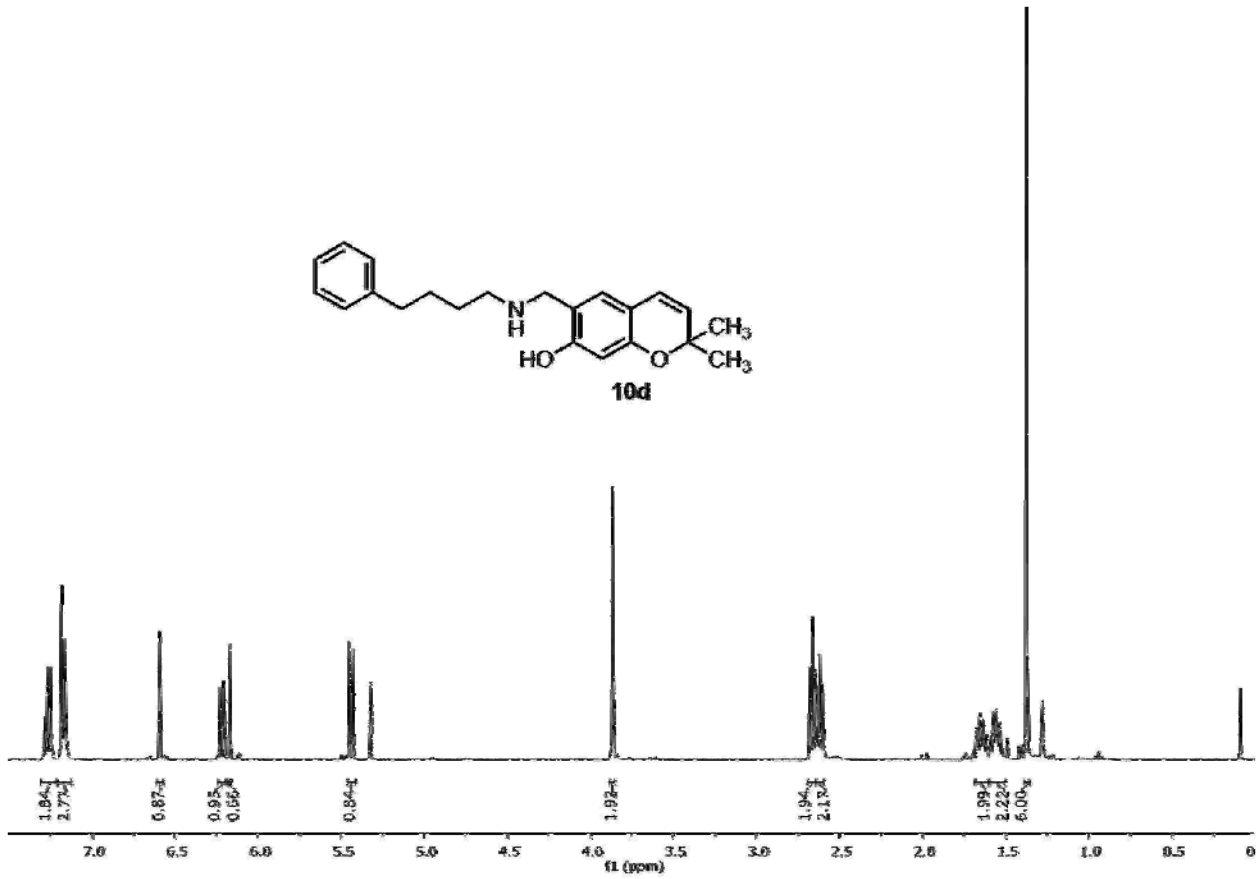
$^{1}H/^{1}H$ COSY-Spectrum (CD_2Cl_2) of **10c**.



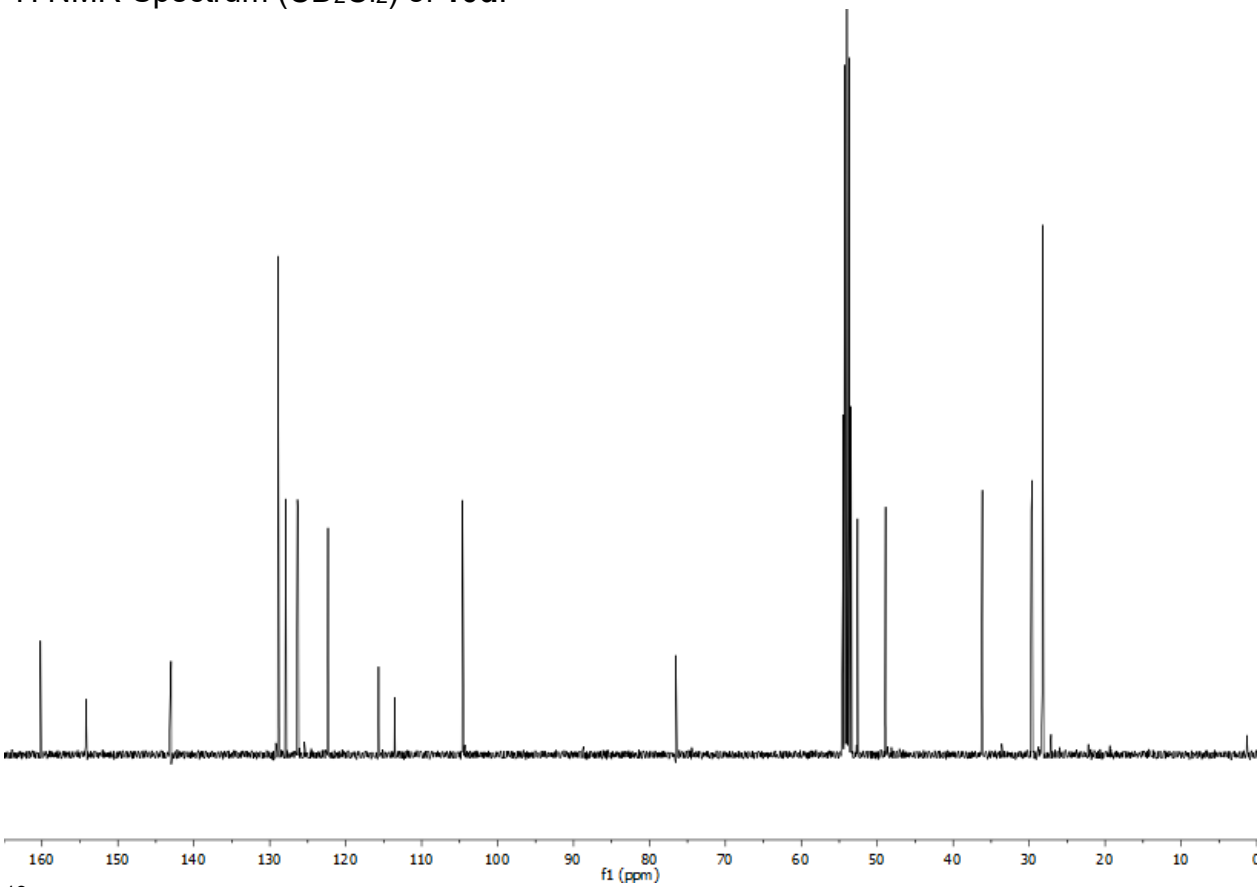
gHSQC-Spectrum (CD_2Cl_2) of **10c**.



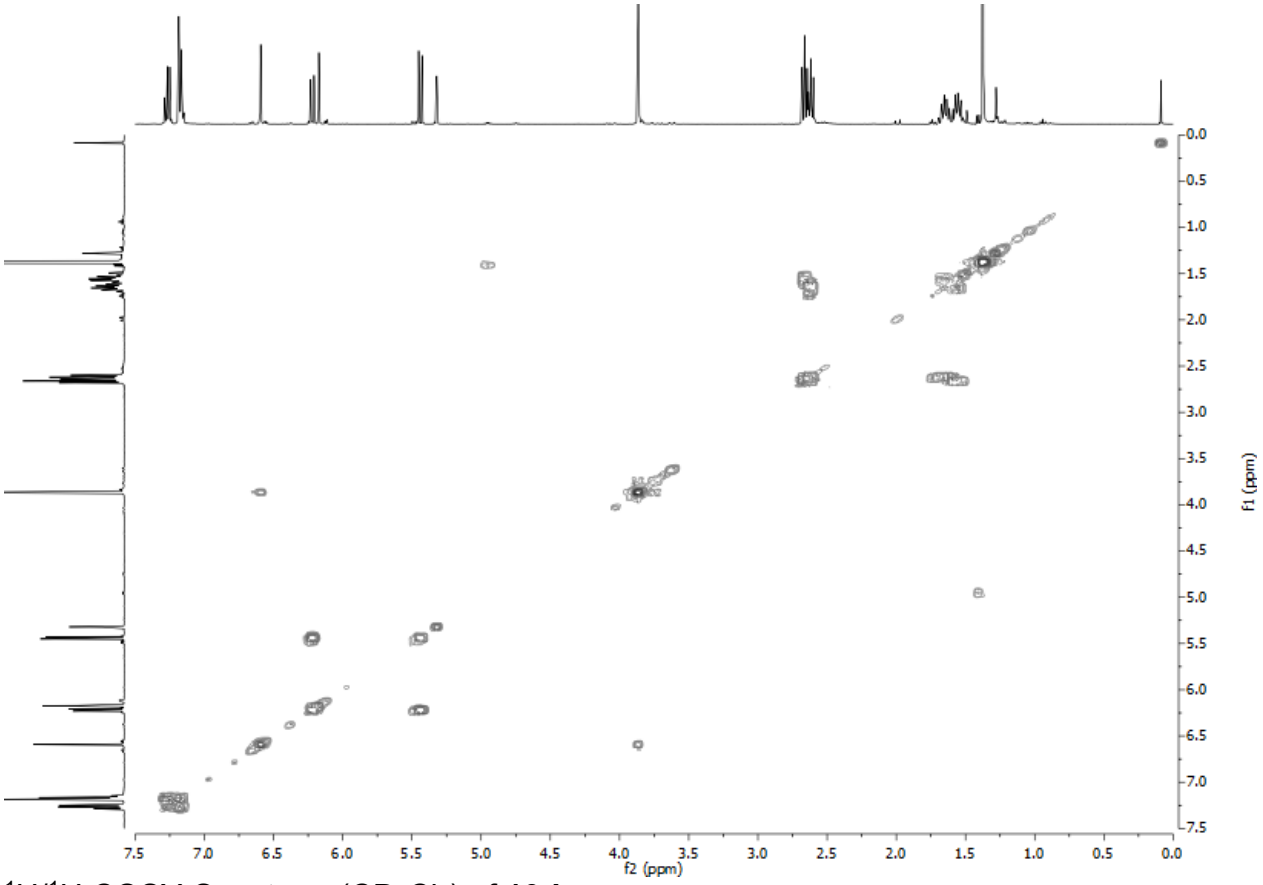
gHMBC-Spectrum (CD_2Cl_2) of **10c**.



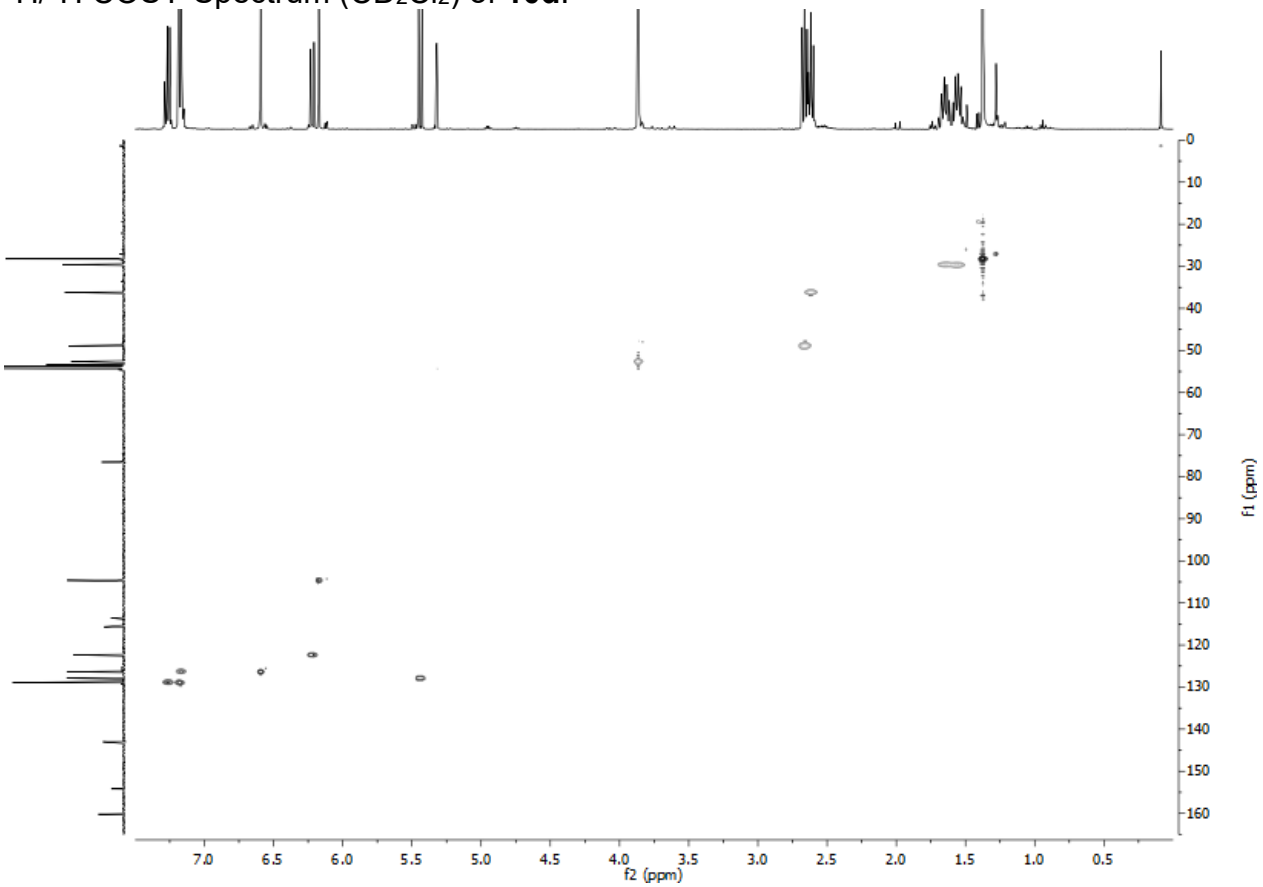
^{1}H NMR-Spectrum (CD_2Cl_2) of **10d**.



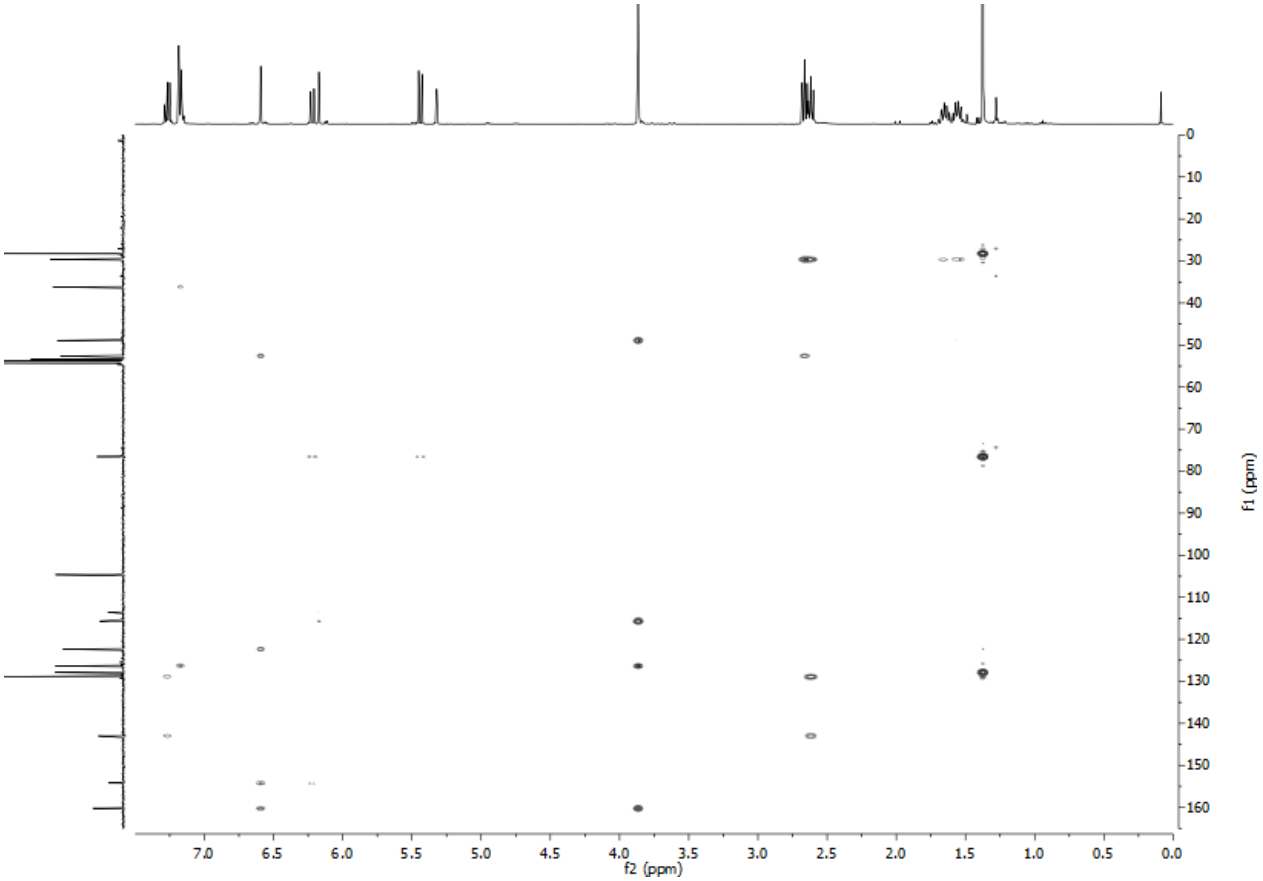
^{13}C NMR-Spectrum (CD_2Cl_2) of **10d**.



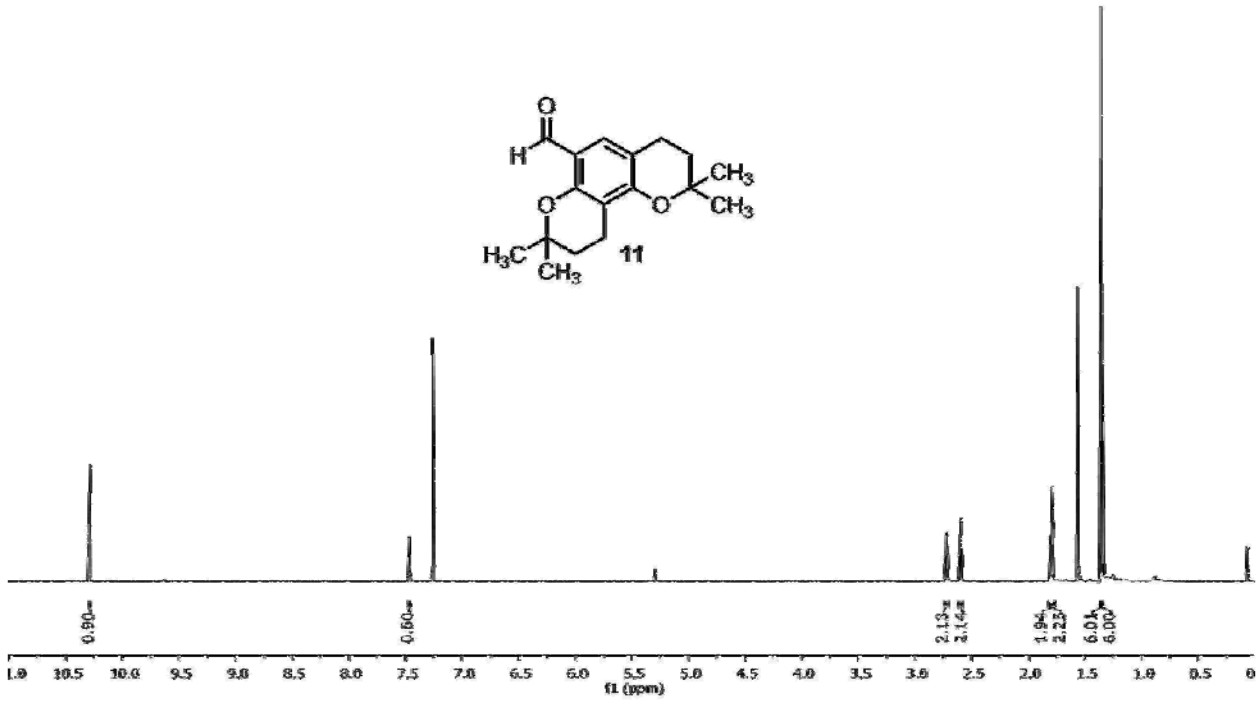
$^{1}H/^{1}H$ COSY-Spectrum (CD_2Cl_2) of **10d**.



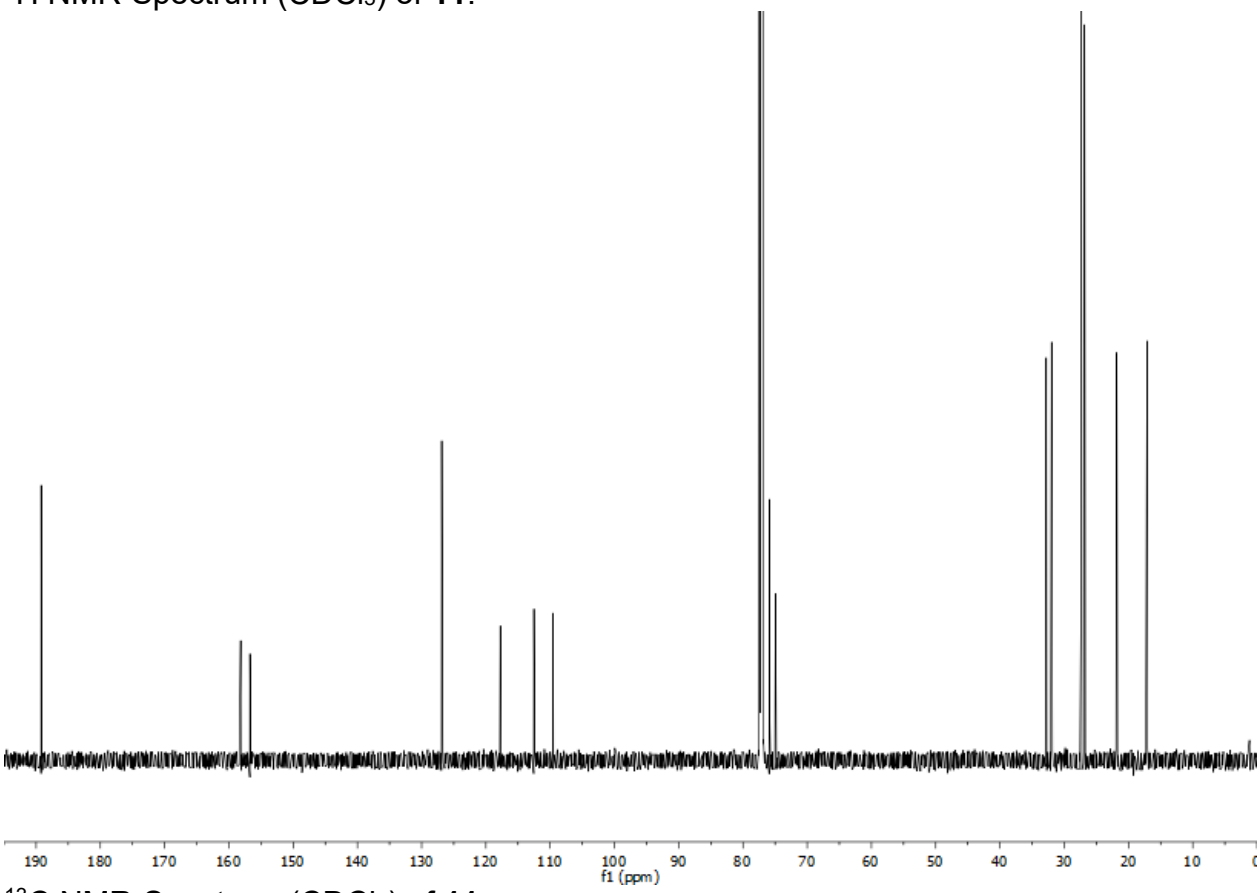
gHSQC-Spectrum (CD_2Cl_2) of **10d**.



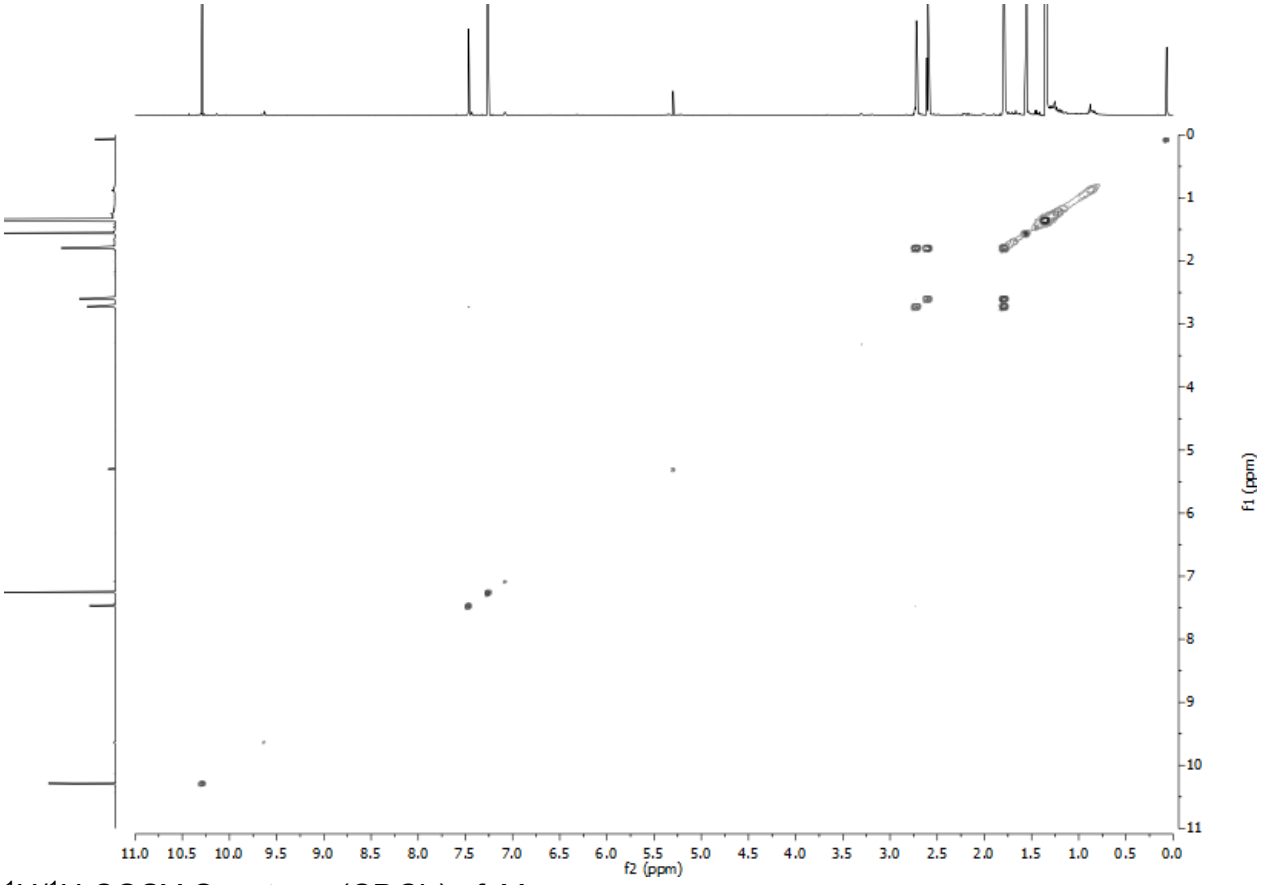
gHMBC-Spectrum (CD_2Cl_2) of **10d**.



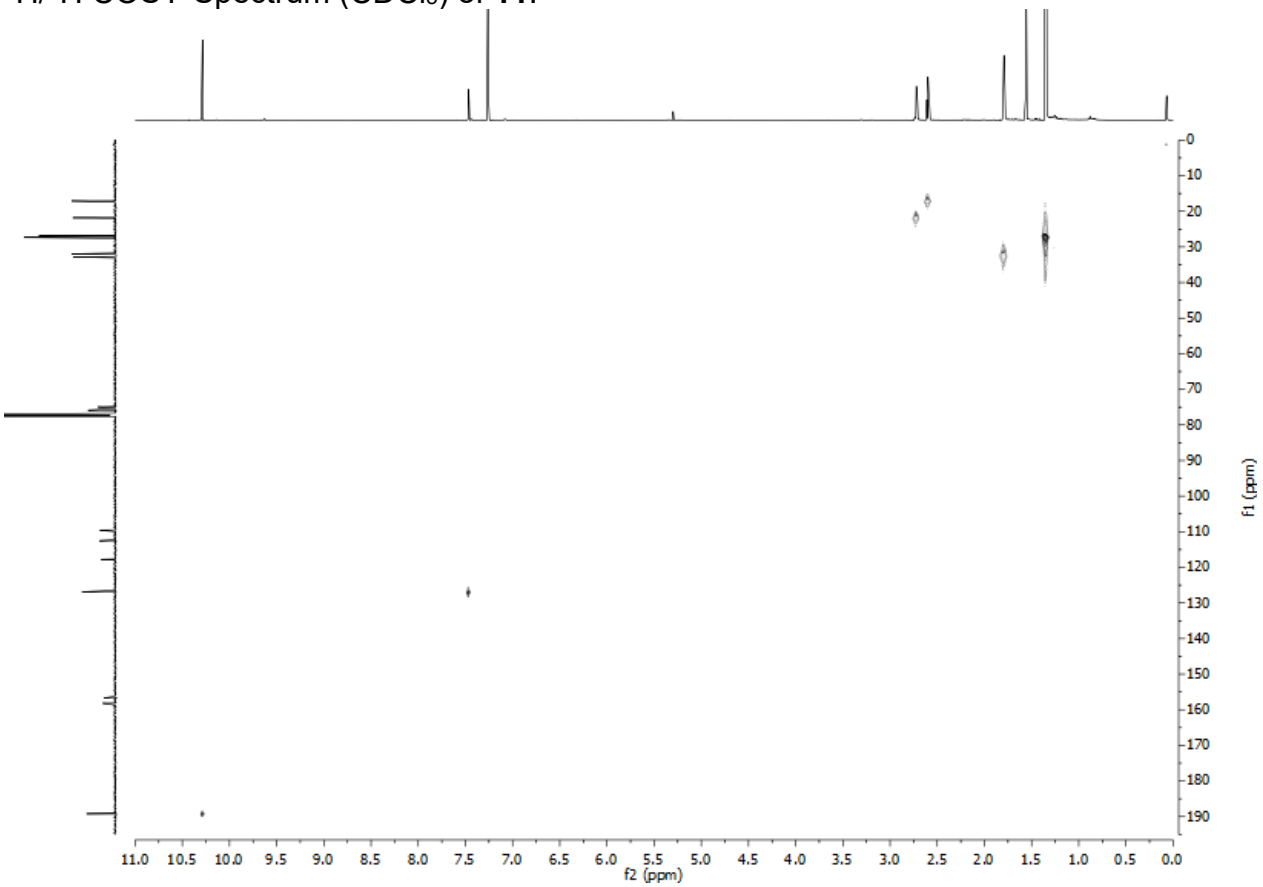
^{1}H NMR-Spectrum ($CDCl_3$) of **11**.



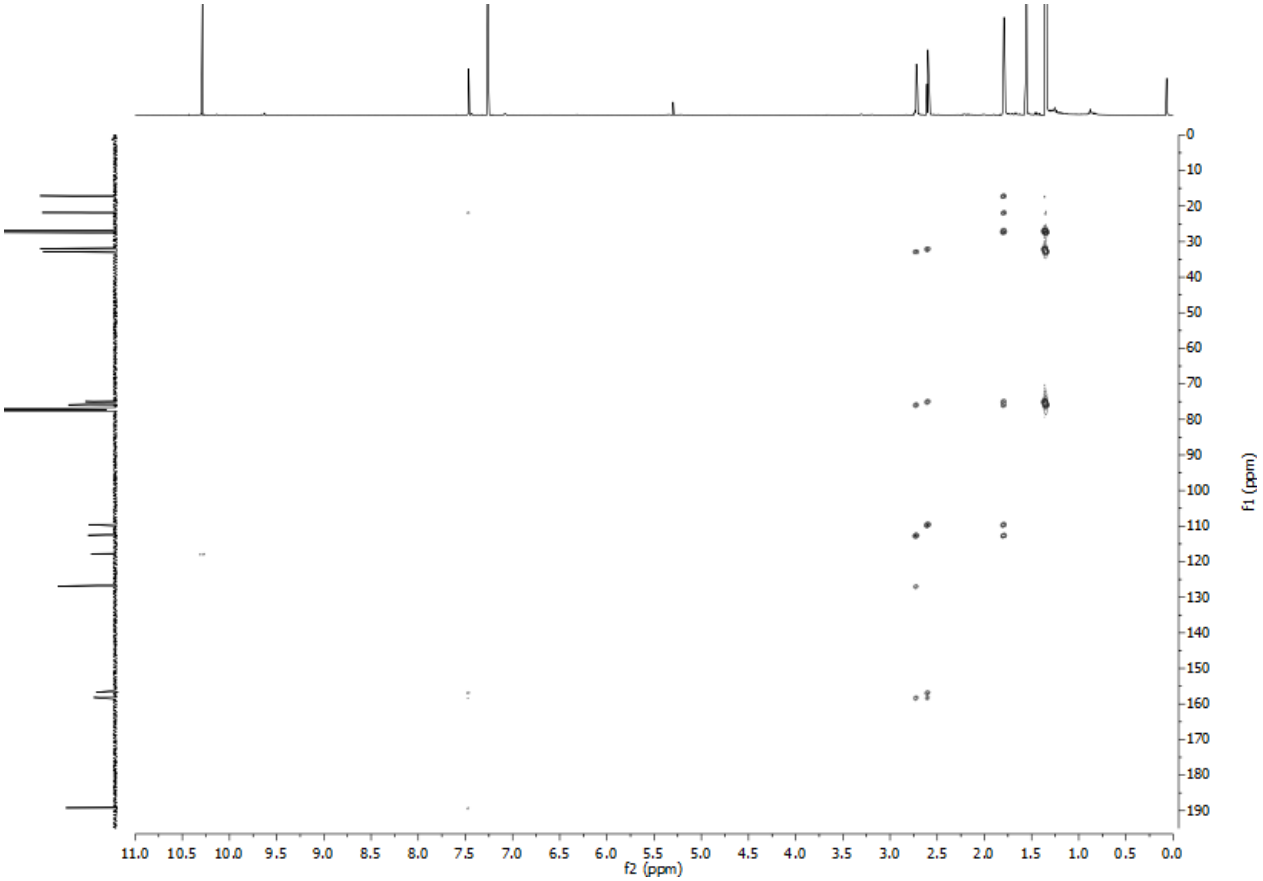
^{13}C NMR-Spectrum ($CDCl_3$) of **11**.



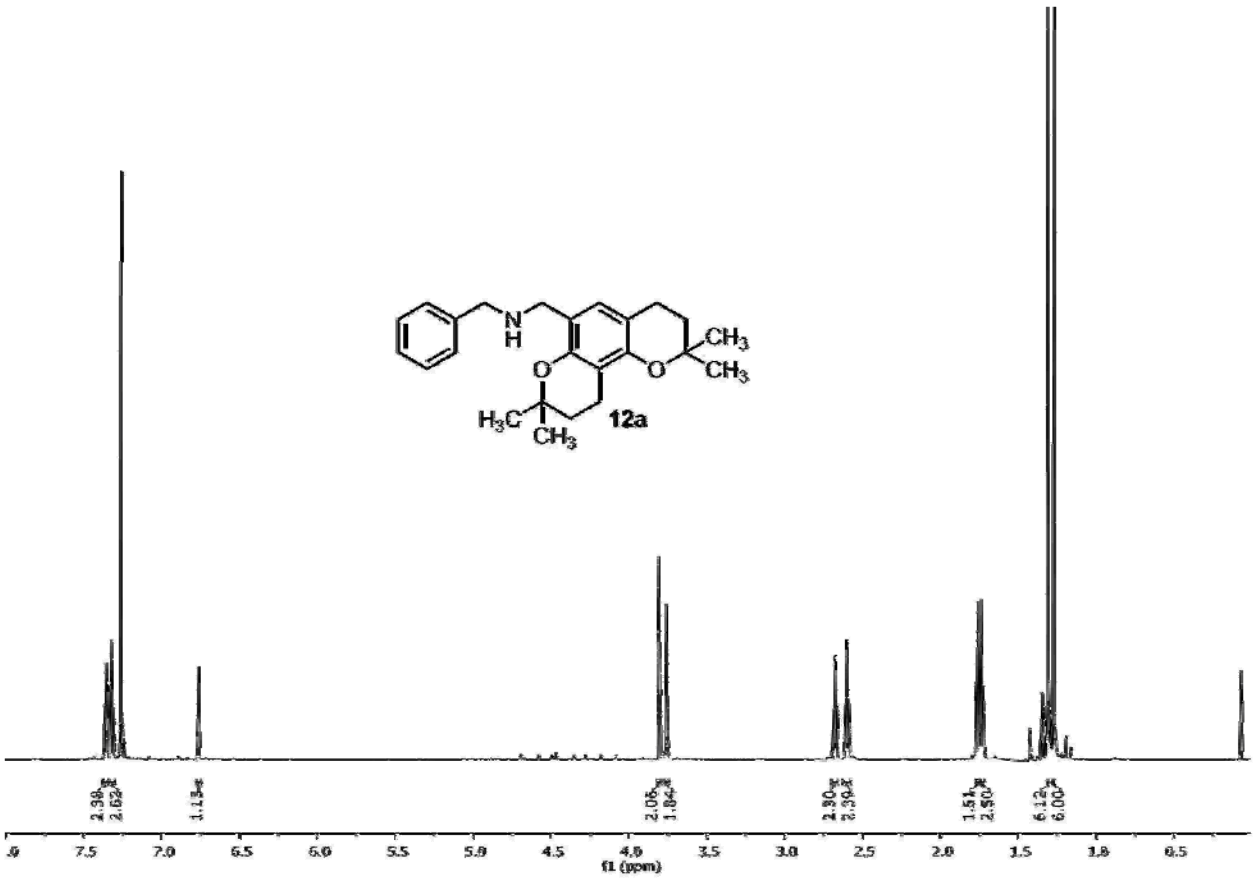
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **11**.



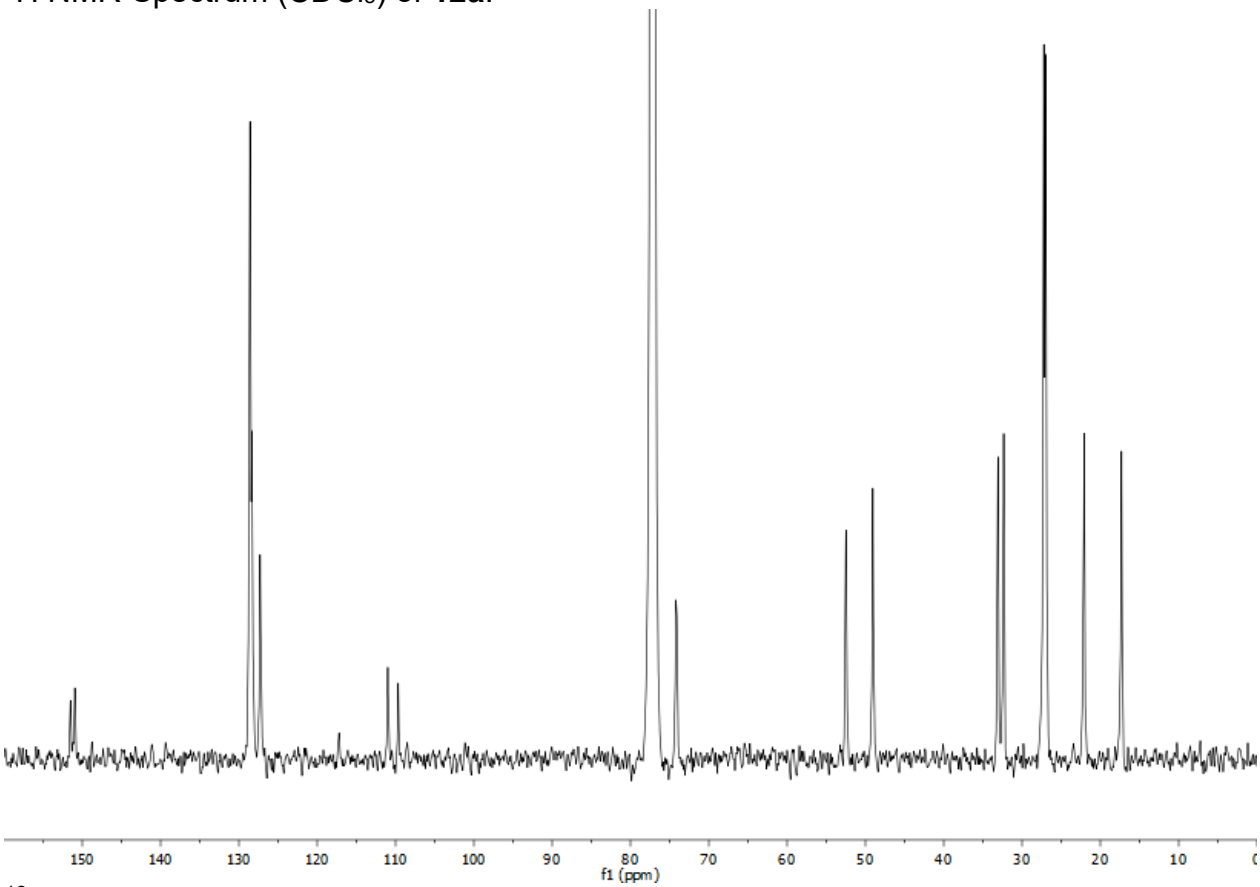
gHSQC-Spectrum ($CDCl_3$) of **11**.



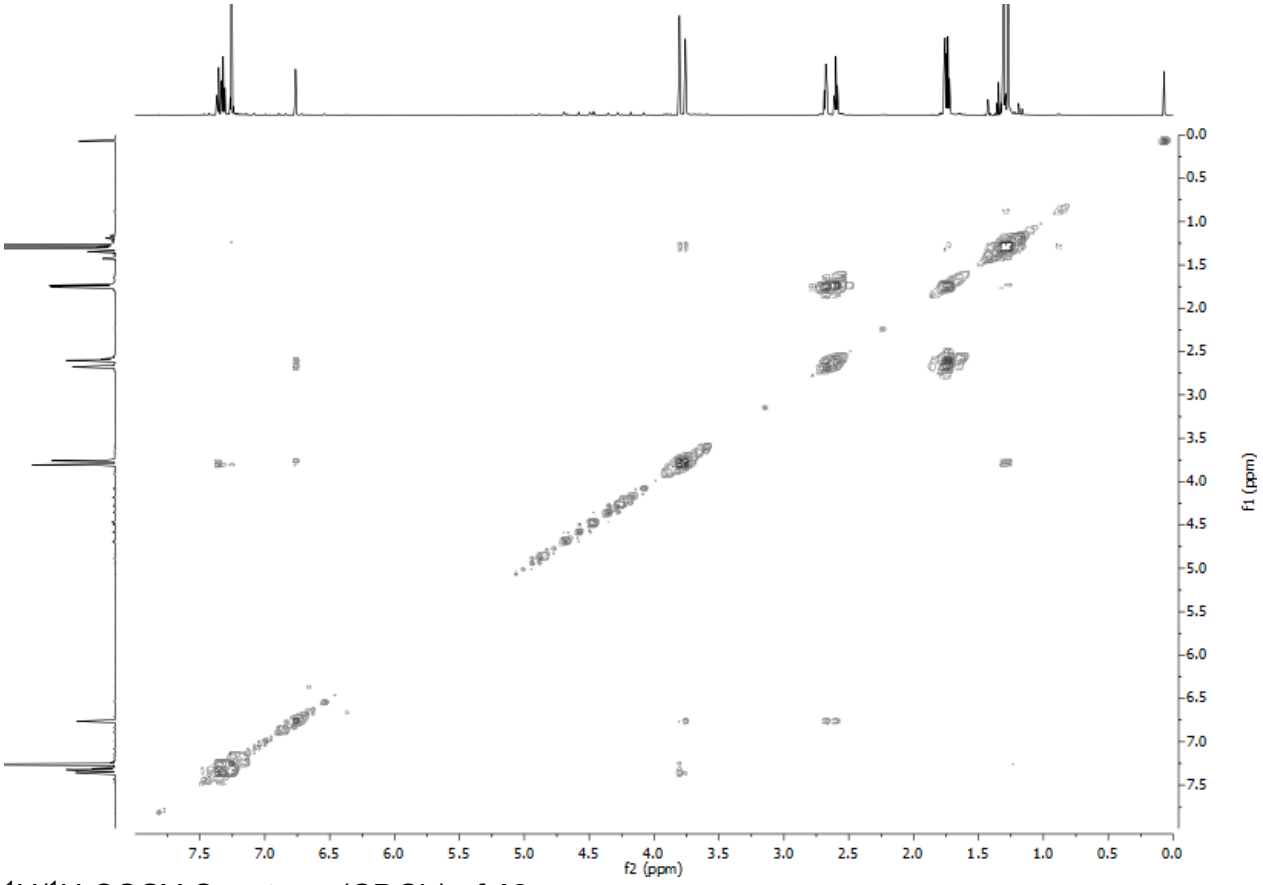
gHMBC-Spectrum ($CDCl_3$) of **11**.



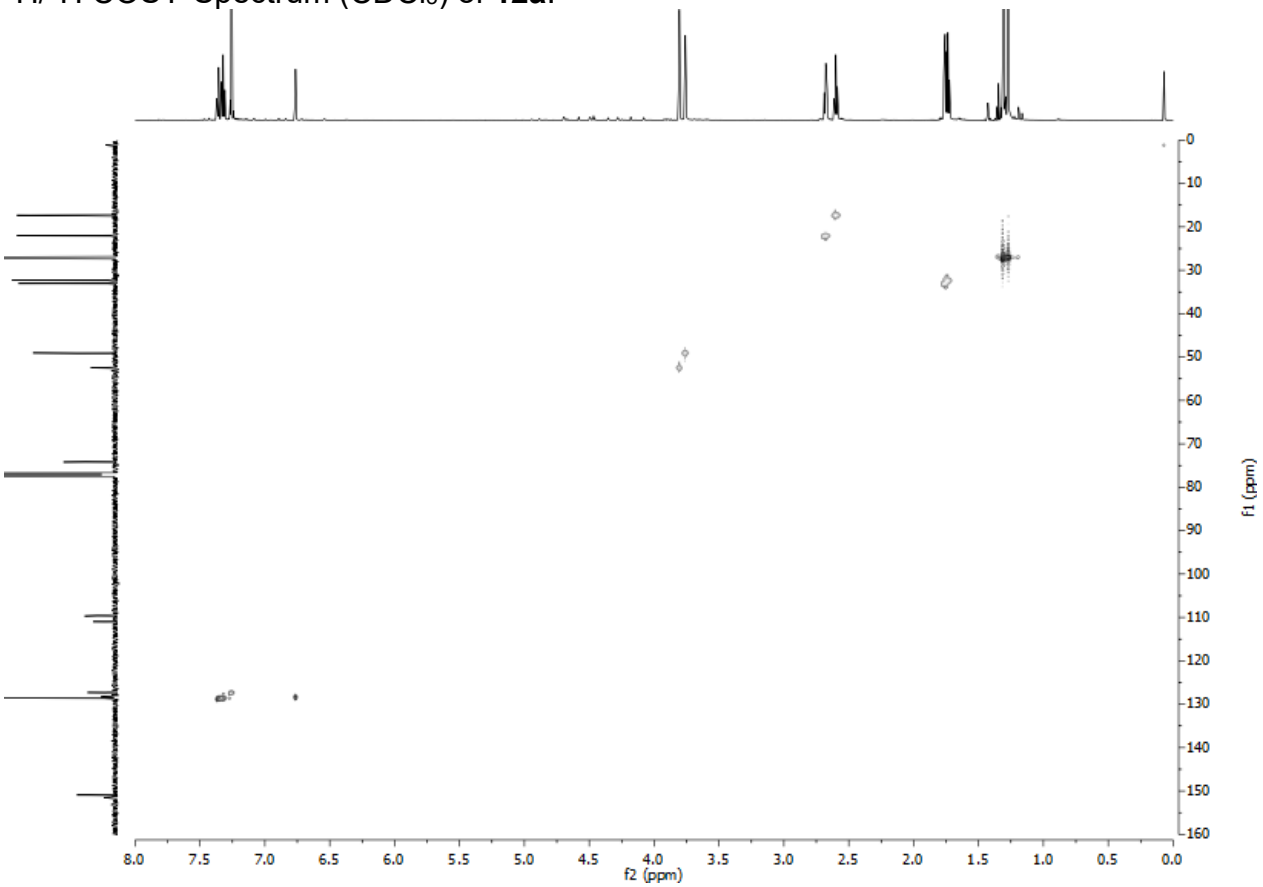
^{1}H NMR-Spectrum ($CDCl_3$) of **12a**.



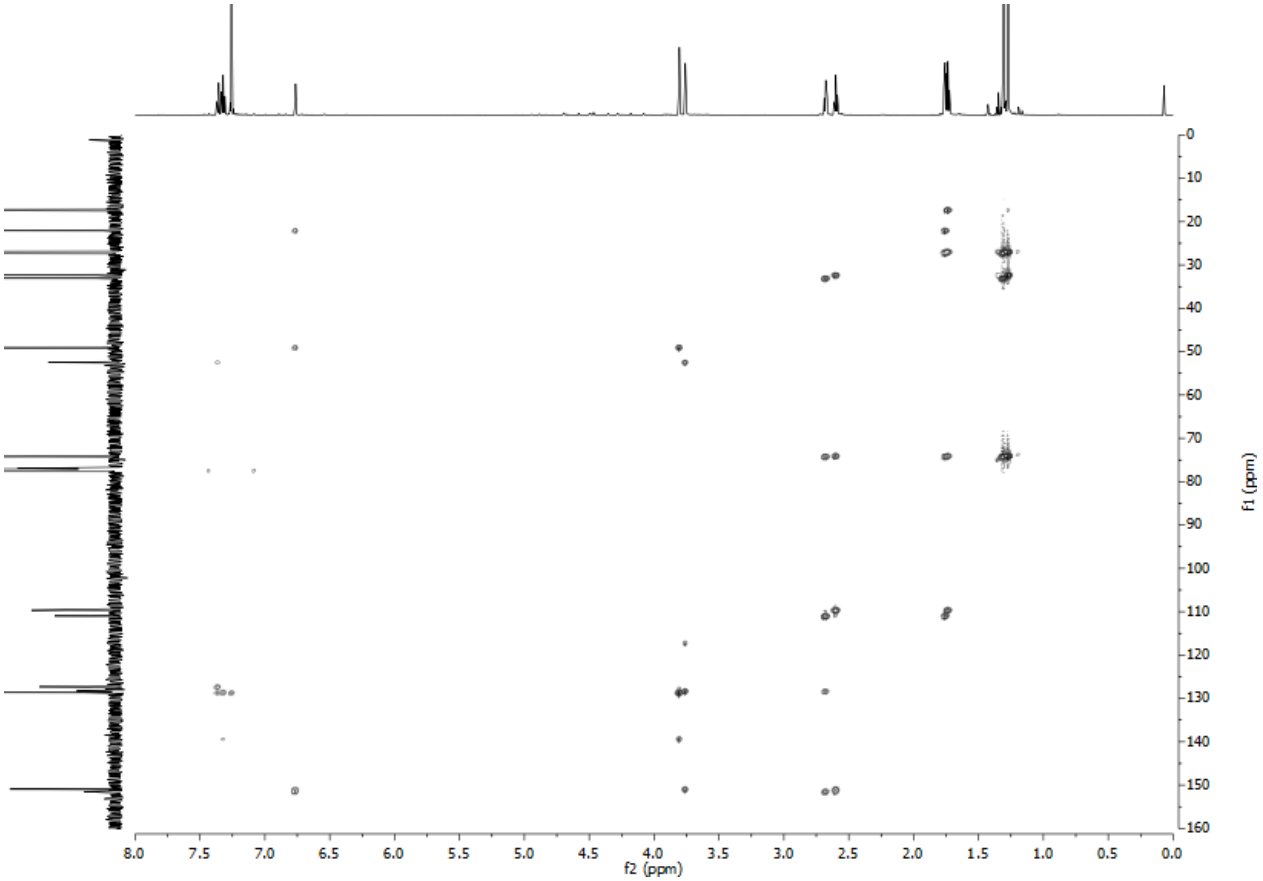
^{13}C NMR-Spectrum ($CDCl_3$) of **12a**.



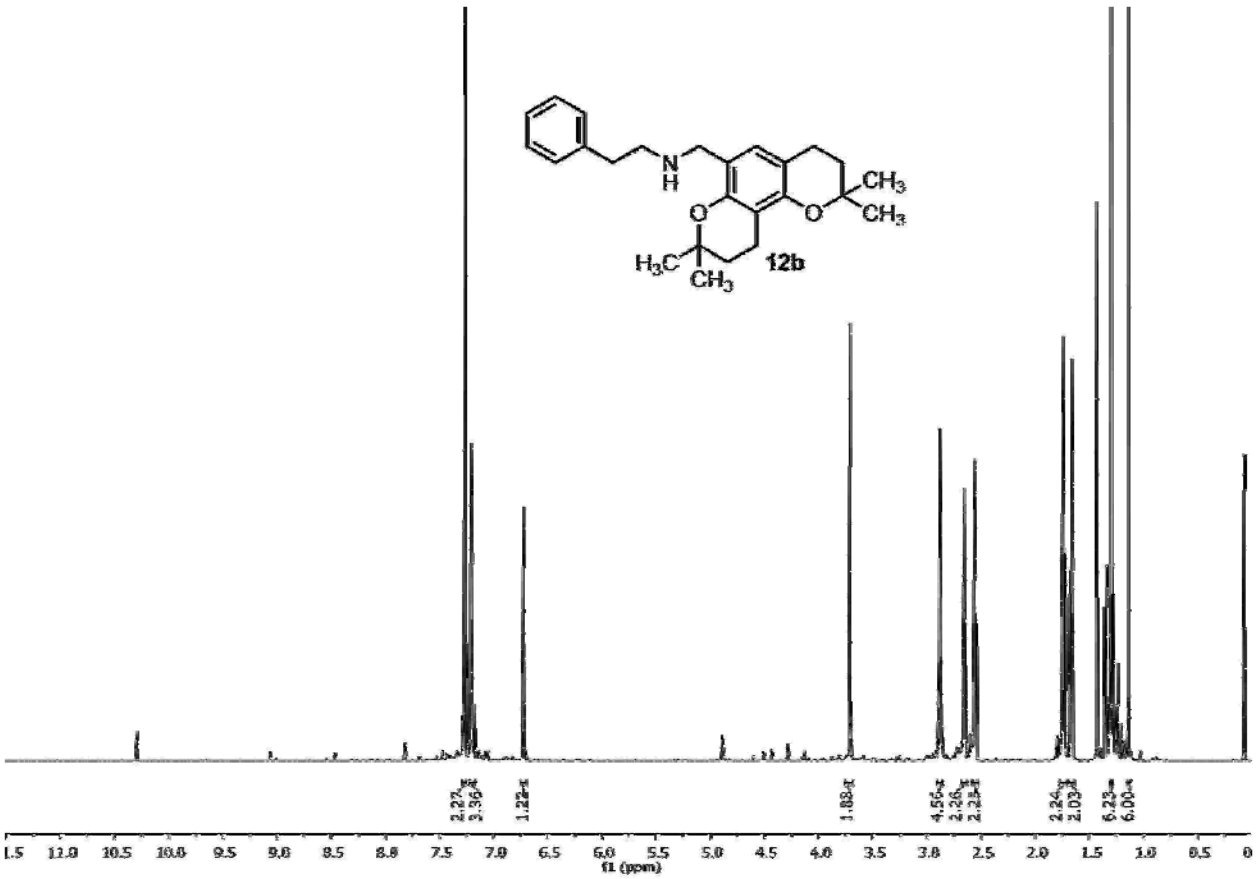
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **12a**.



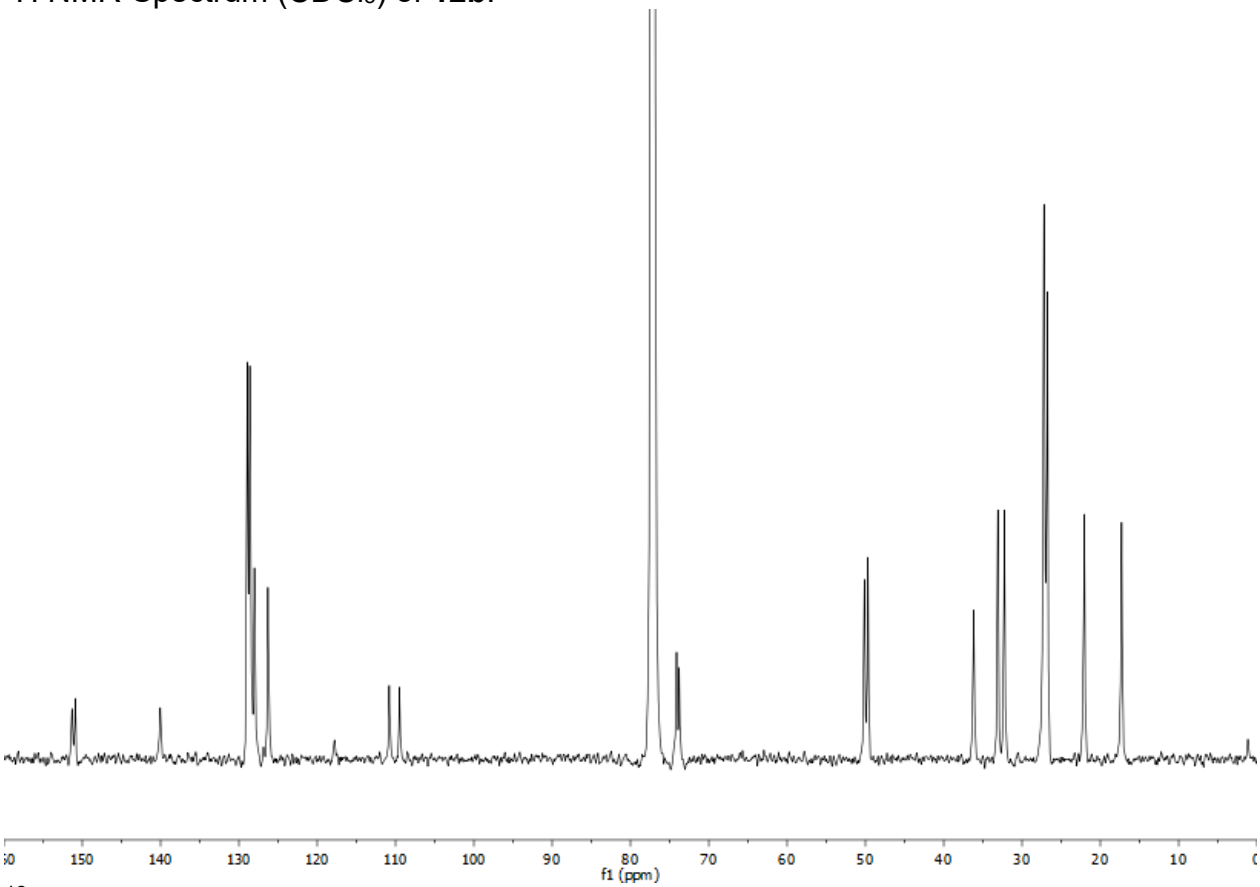
gHSQC-Spectrum ($CDCl_3$) of **12a**.



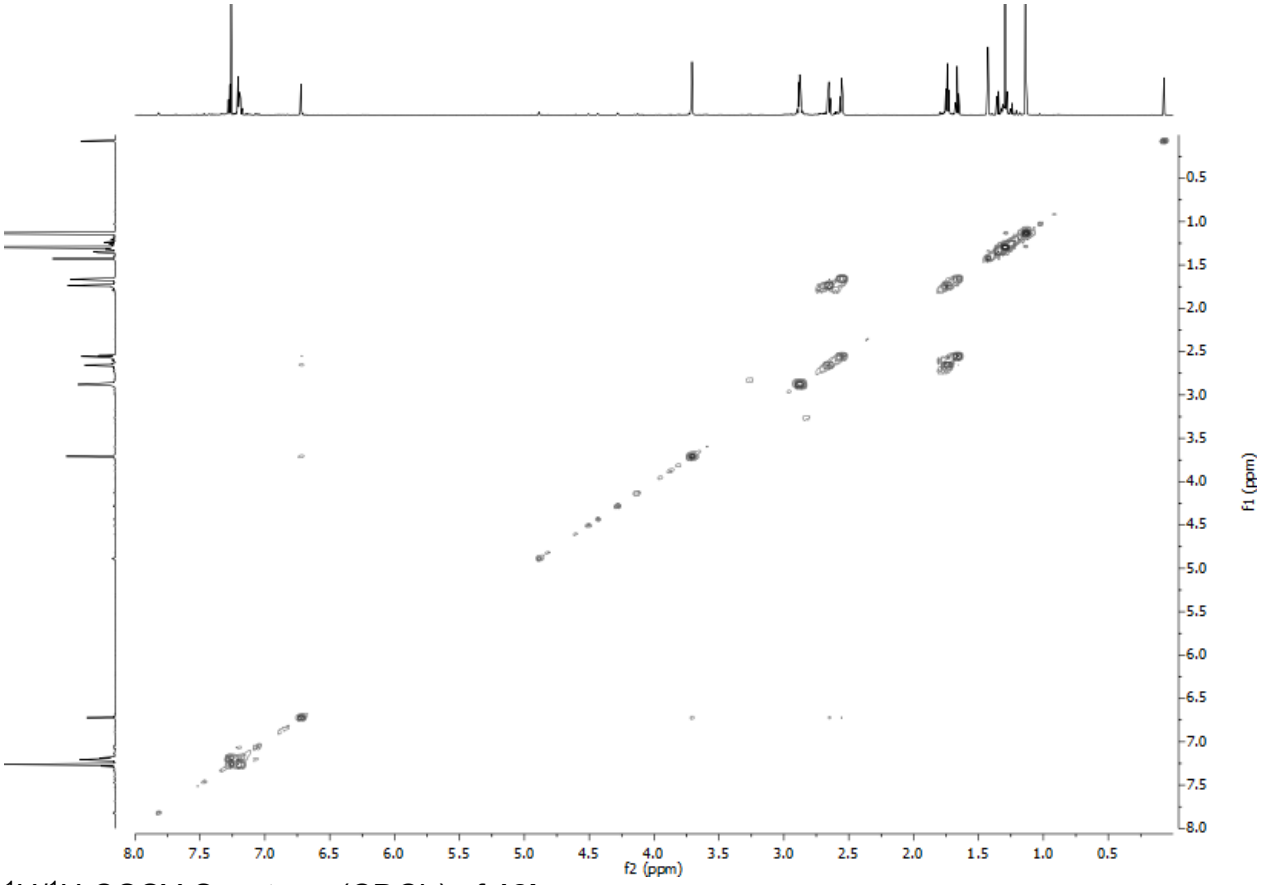
gHMBC-Spectrum ($CDCl_3$) of **12a**.



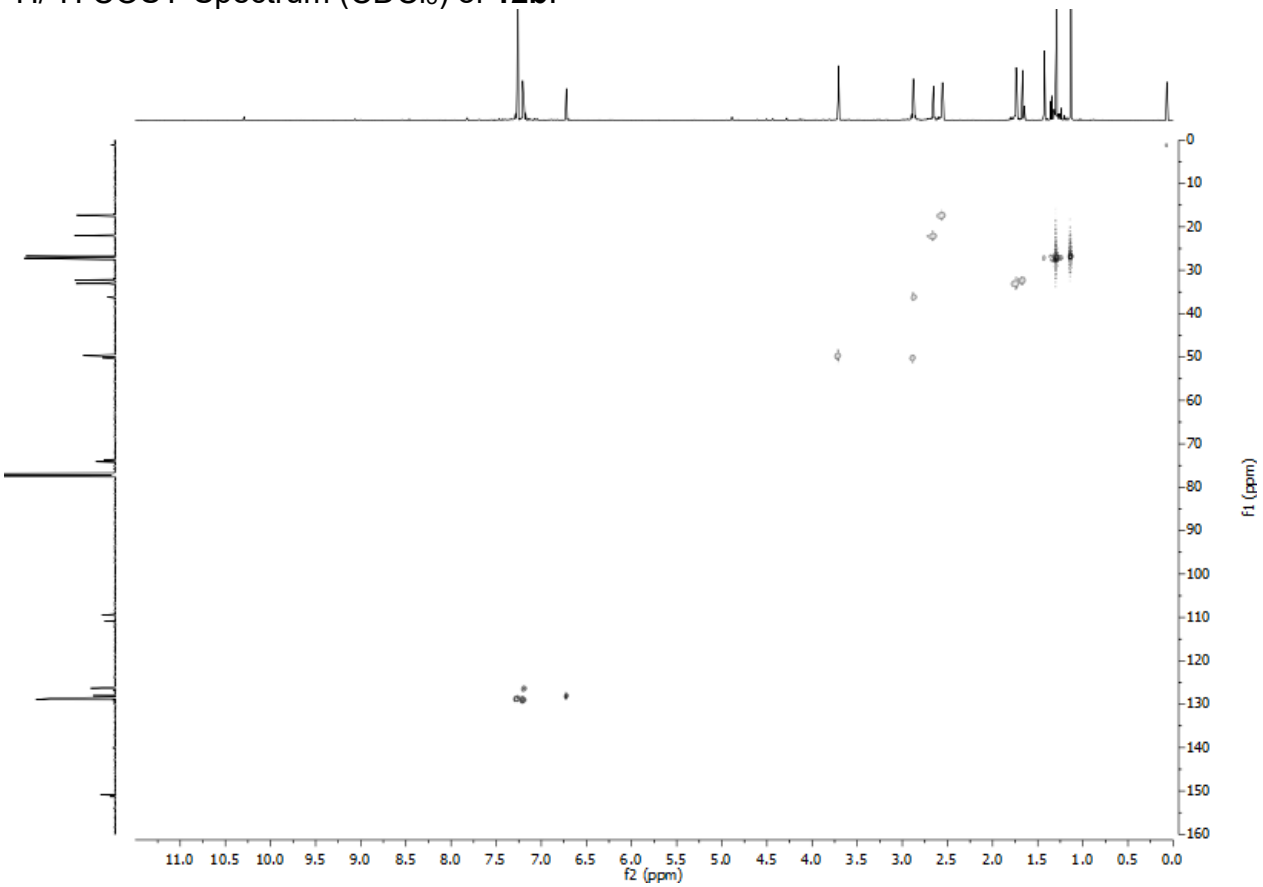
^{1}H NMR-Spectrum ($CDCl_3$) of **12b**.



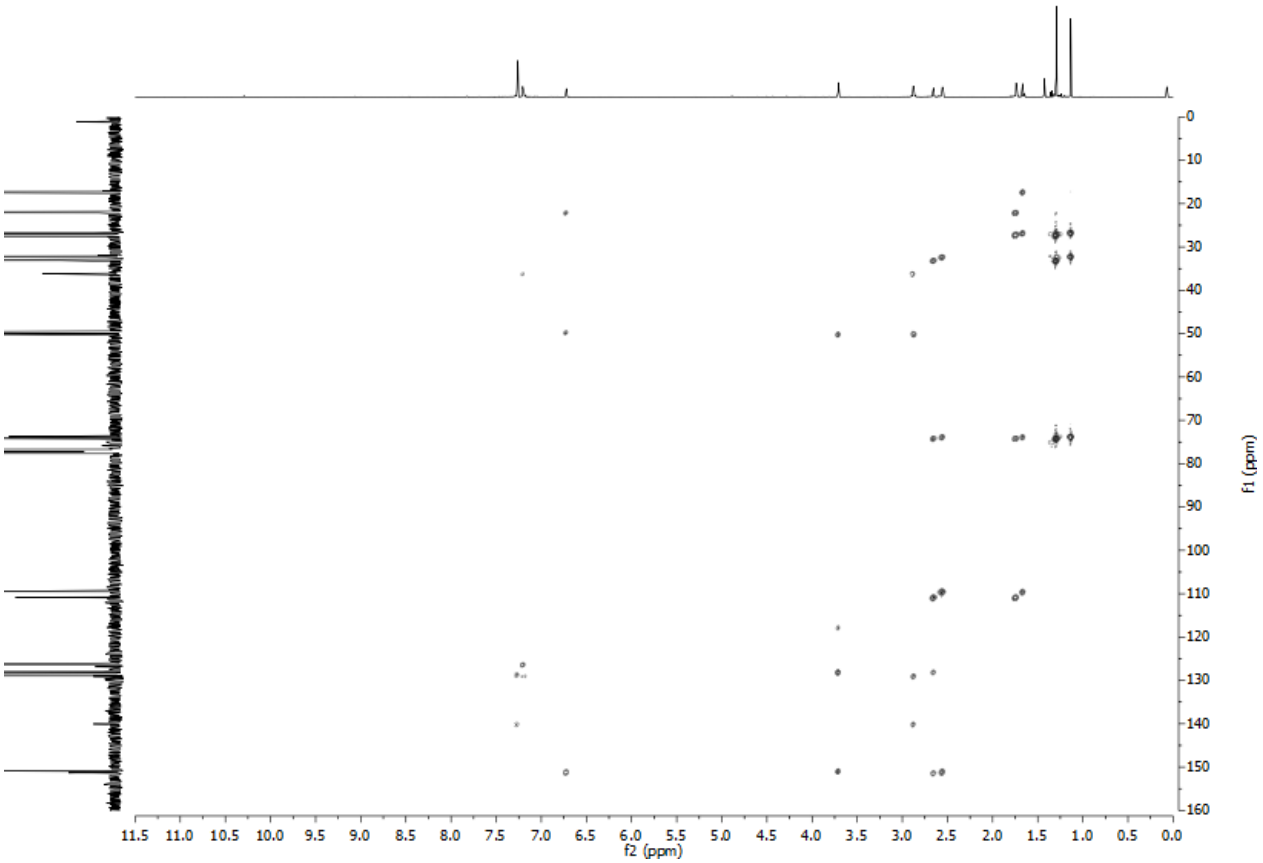
^{13}C NMR-Spectrum ($CDCl_3$) of **12b**.



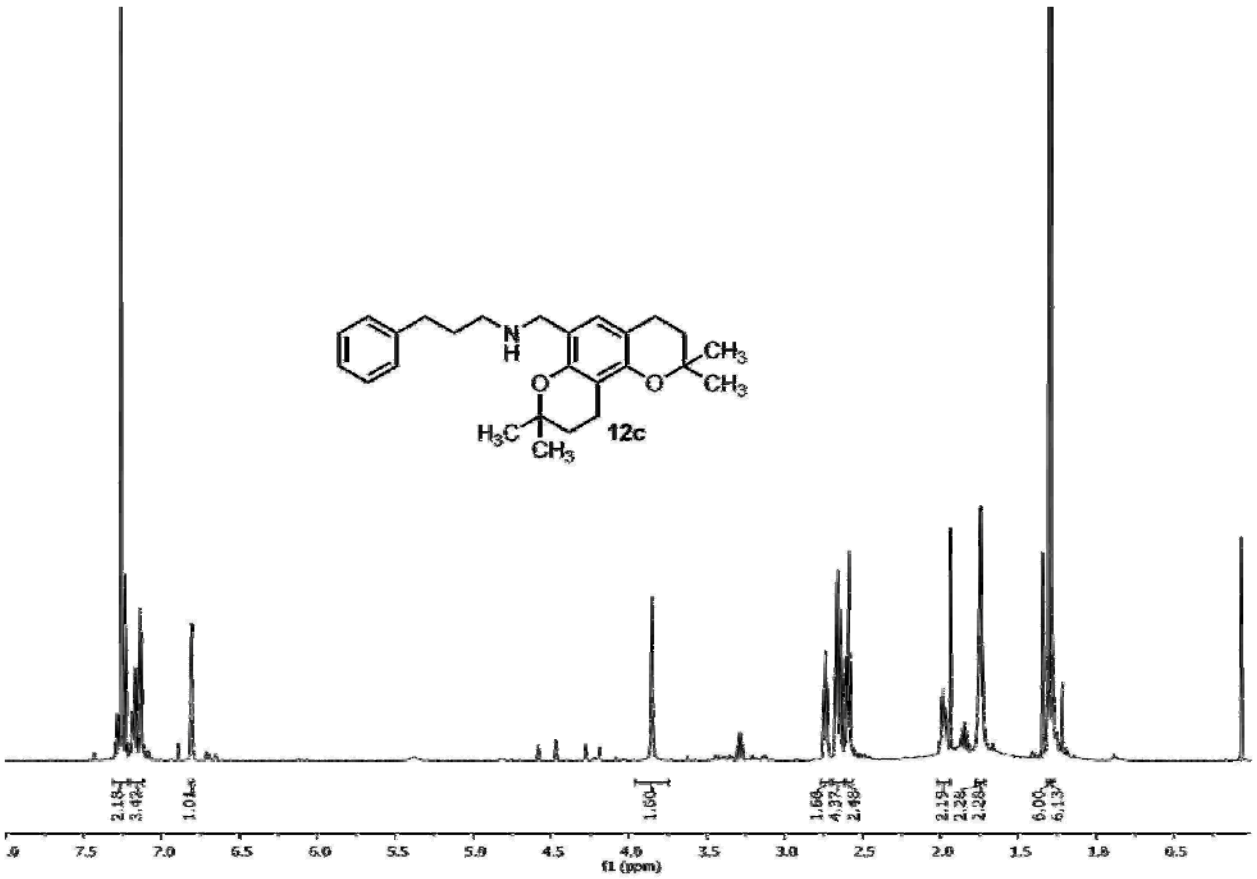
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **12b**.



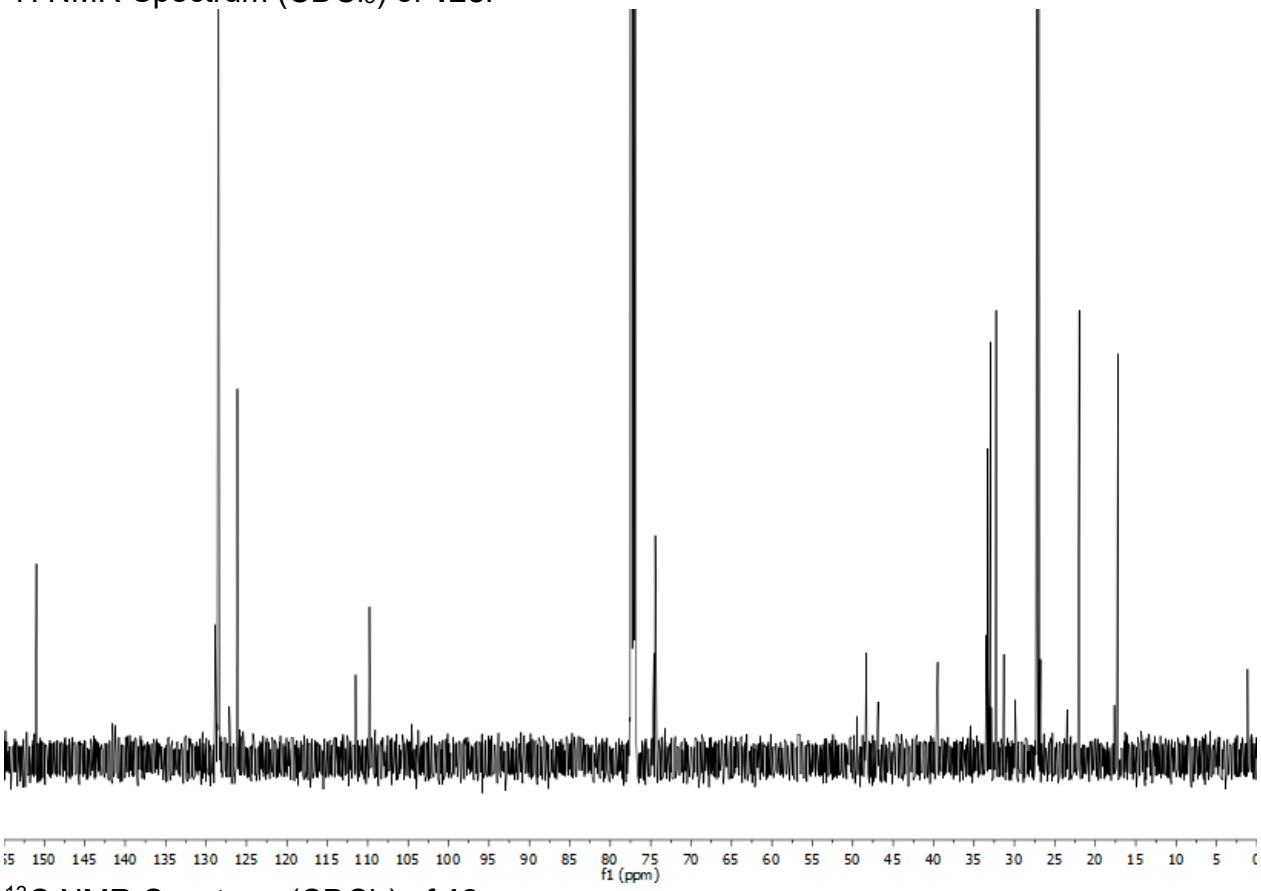
gHSQC-Spectrum ($CDCl_3$) of **12b**.



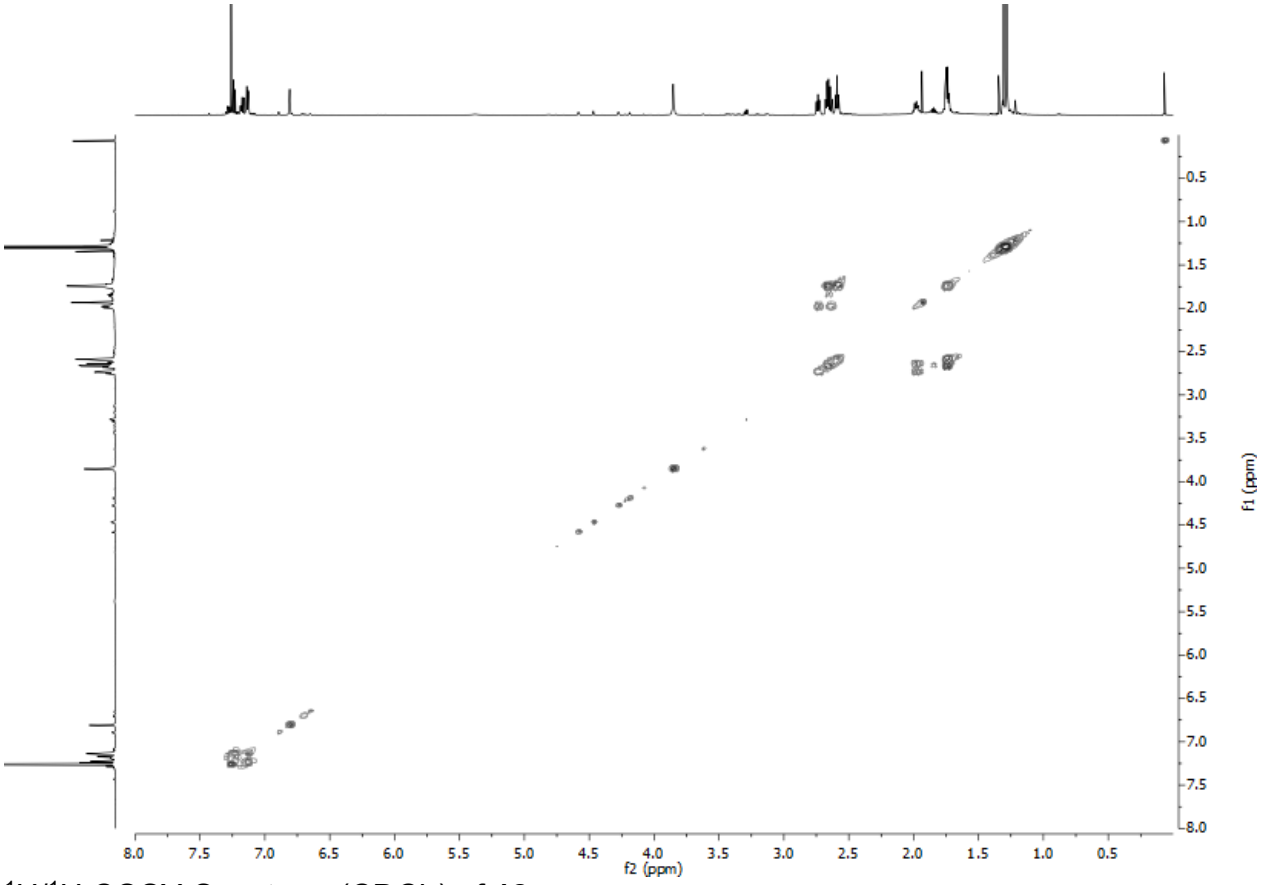
gHMBC-Spectrum ($CDCl_3$) of **12b**.



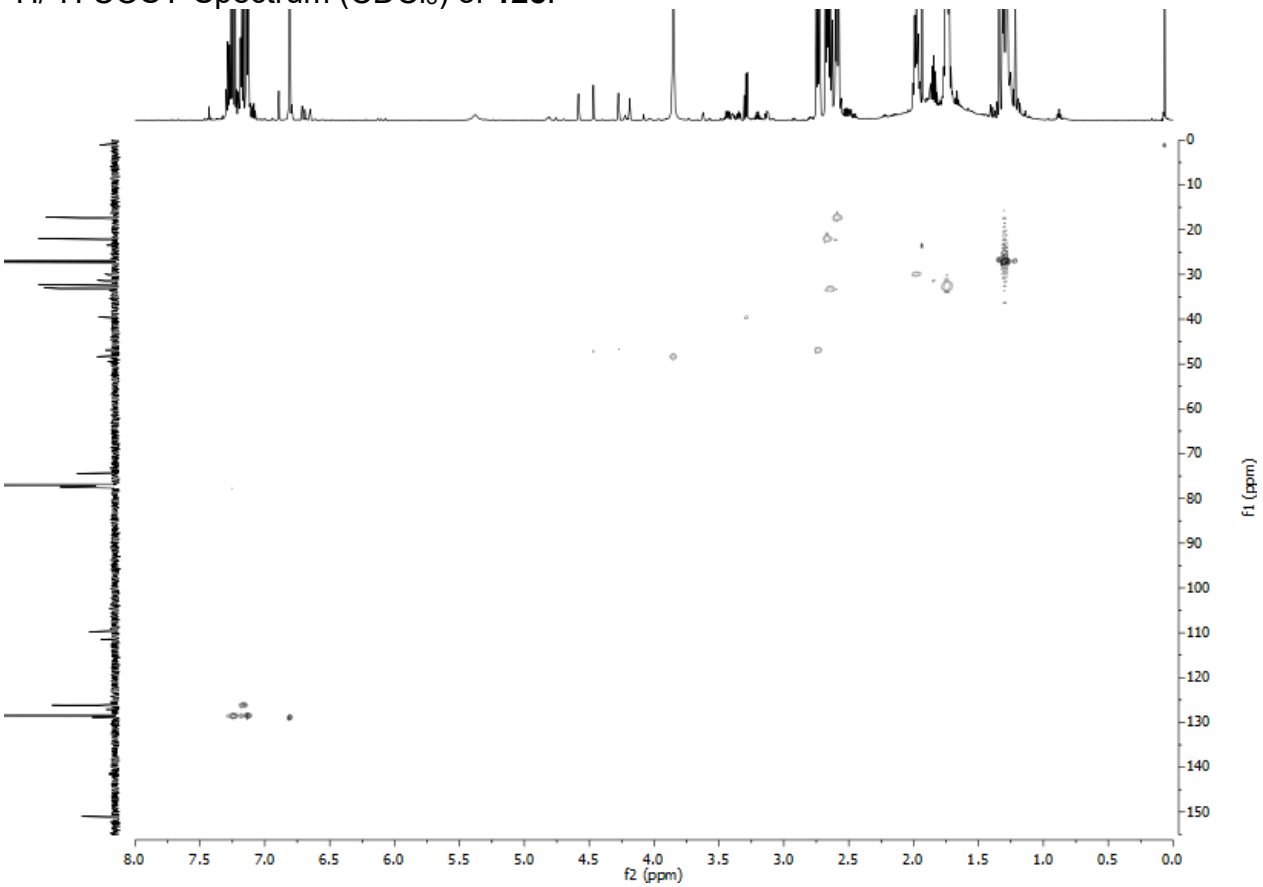
^{1}H NMR-Spectrum ($CDCl_3$) of **12c**.



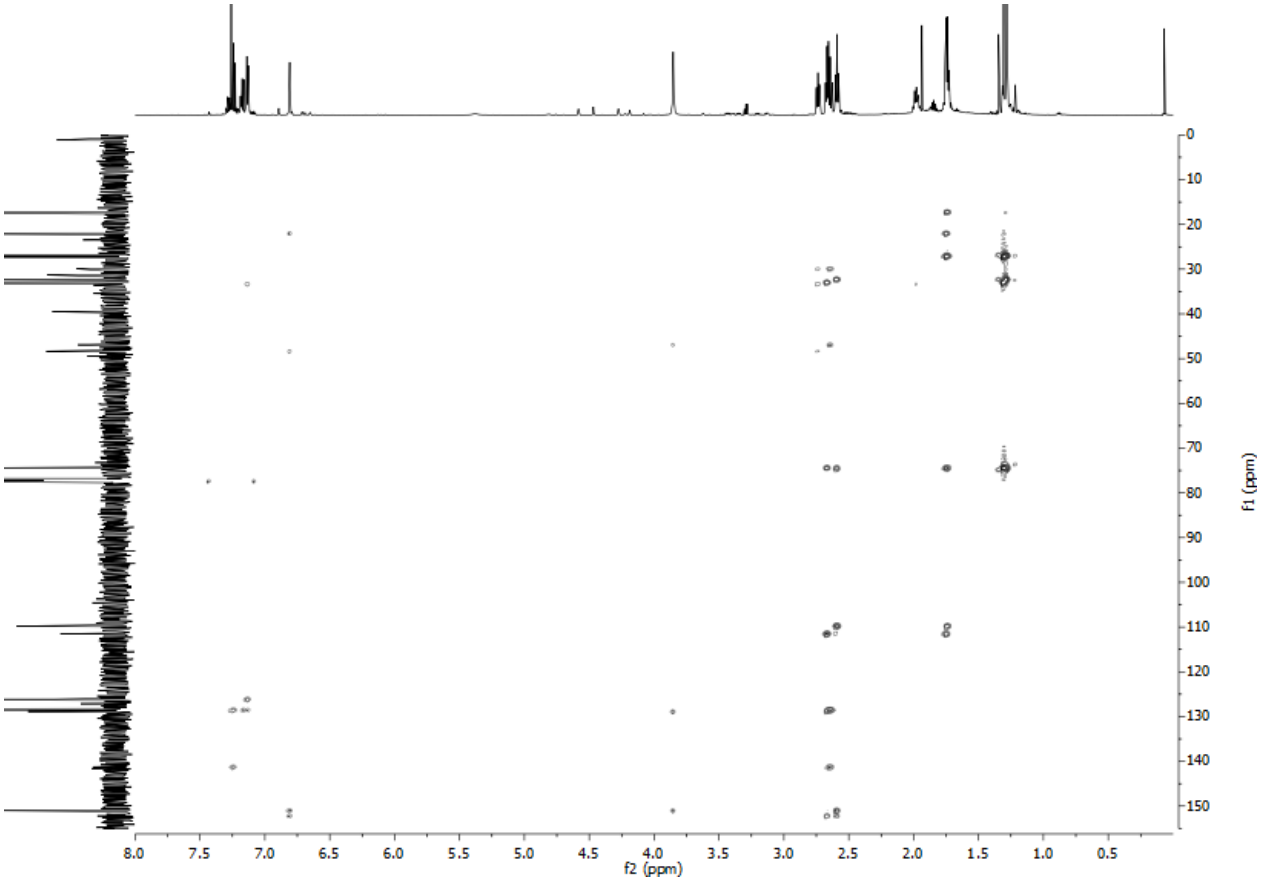
^{13}C NMR-Spectrum ($CDCl_3$) of **12c**.



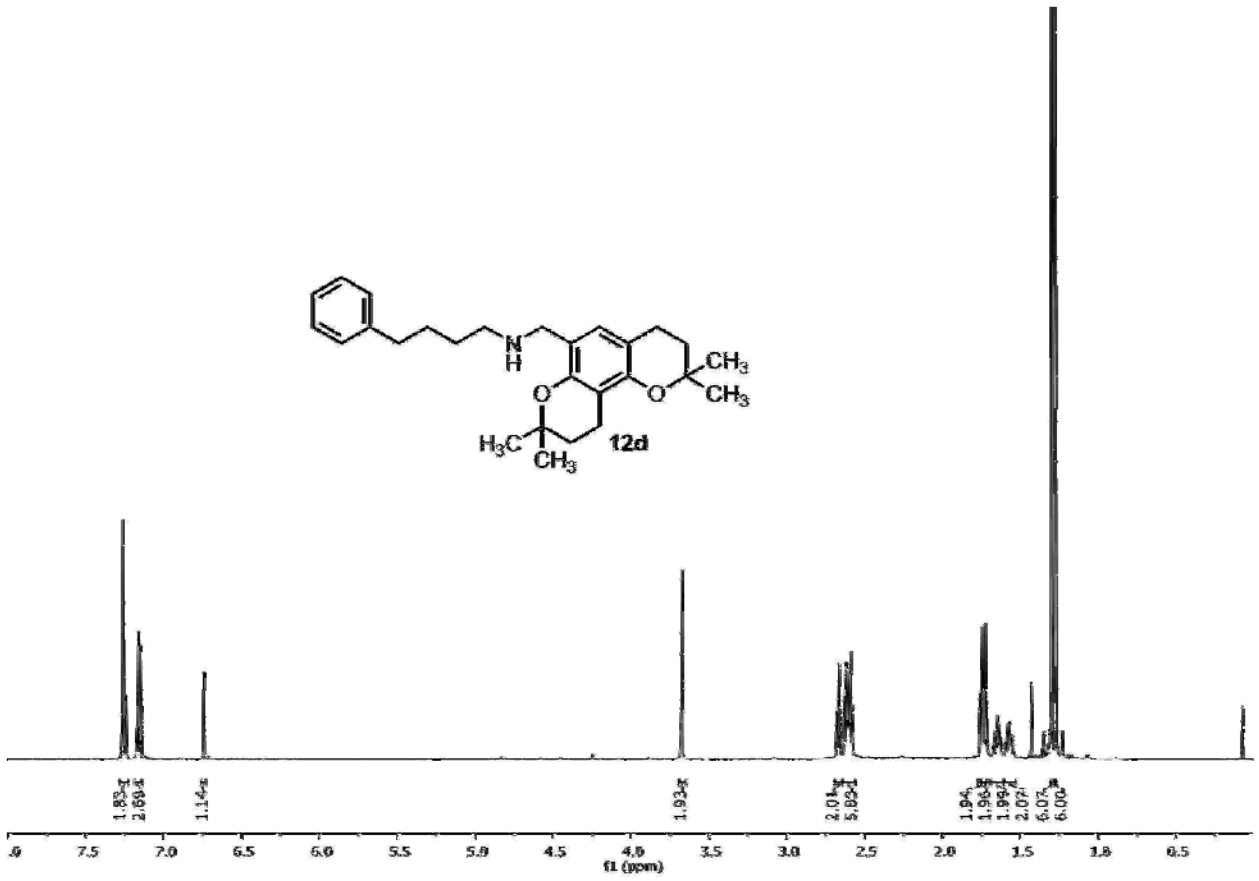
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **12c**.



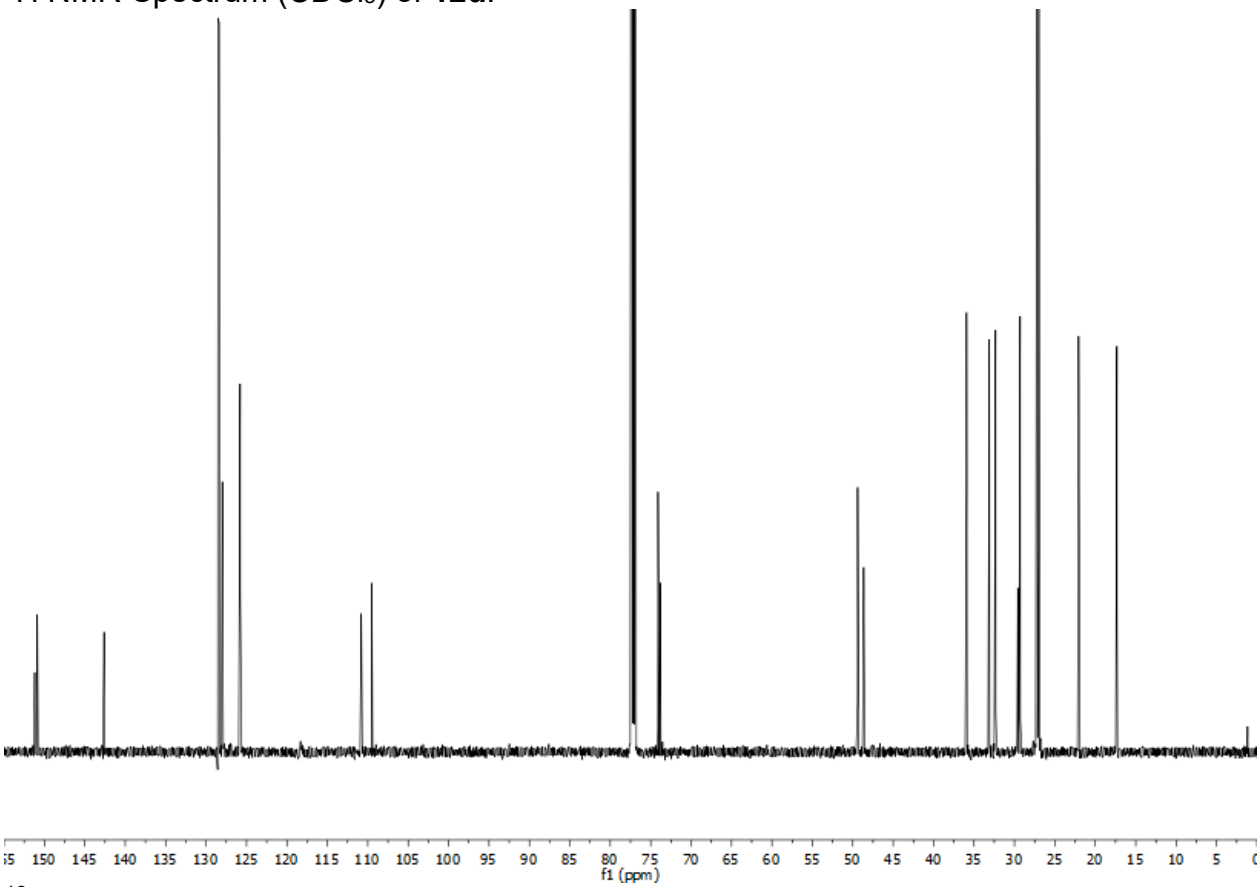
gHSQC-Spectrum ($CDCl_3$) of **12c**.



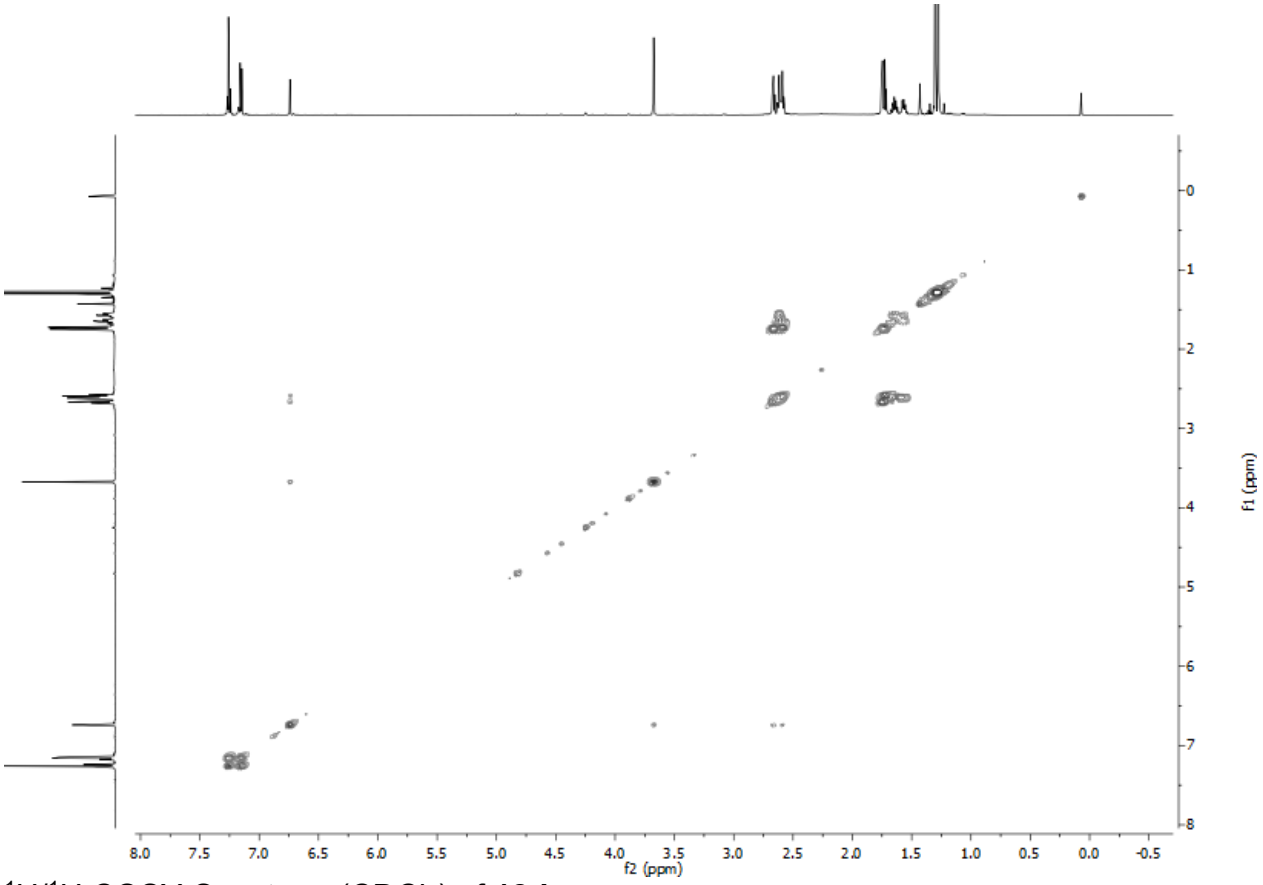
gHMBC-Spectrum ($CDCl_3$) of **12c**.



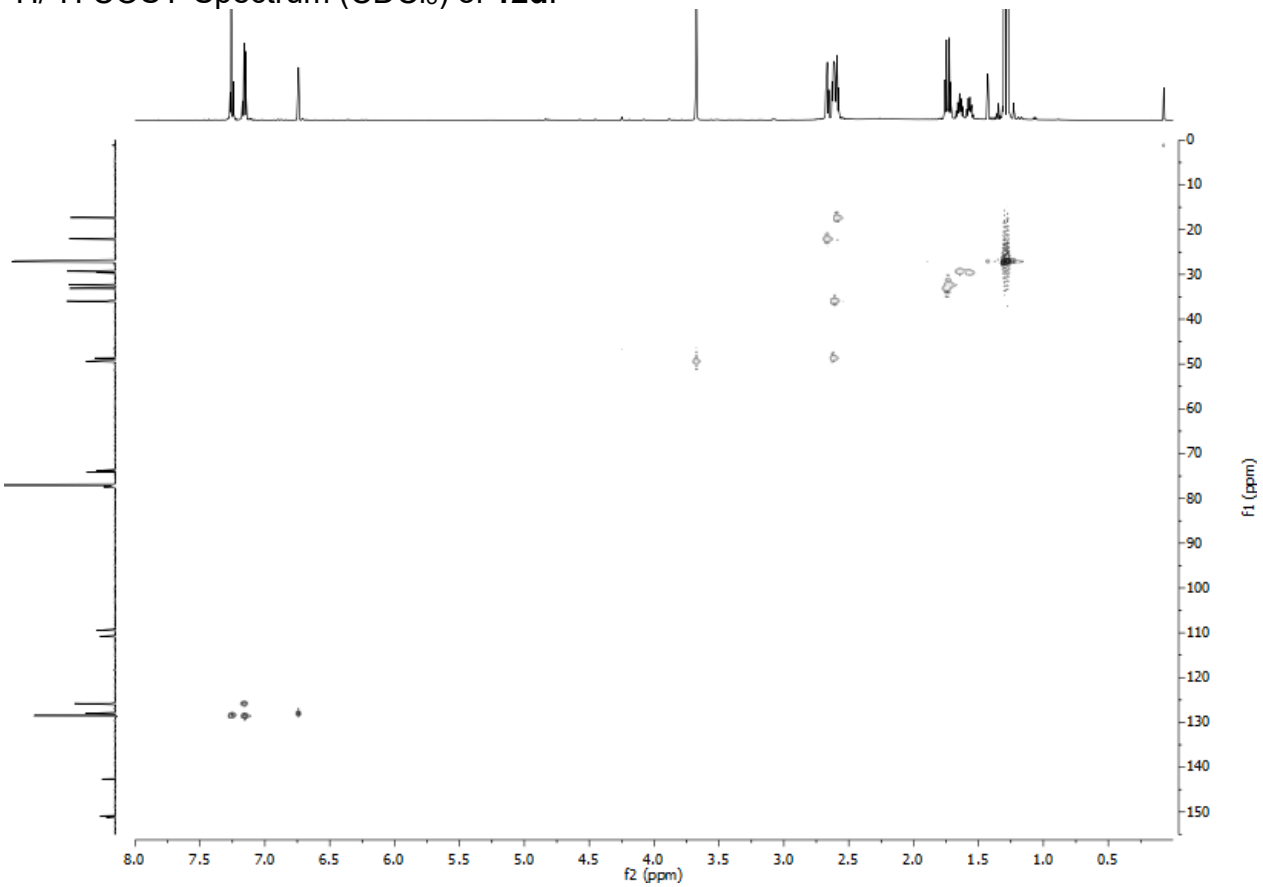
^{1}H NMR-Spectrum ($CDCl_3$) of **12d**.



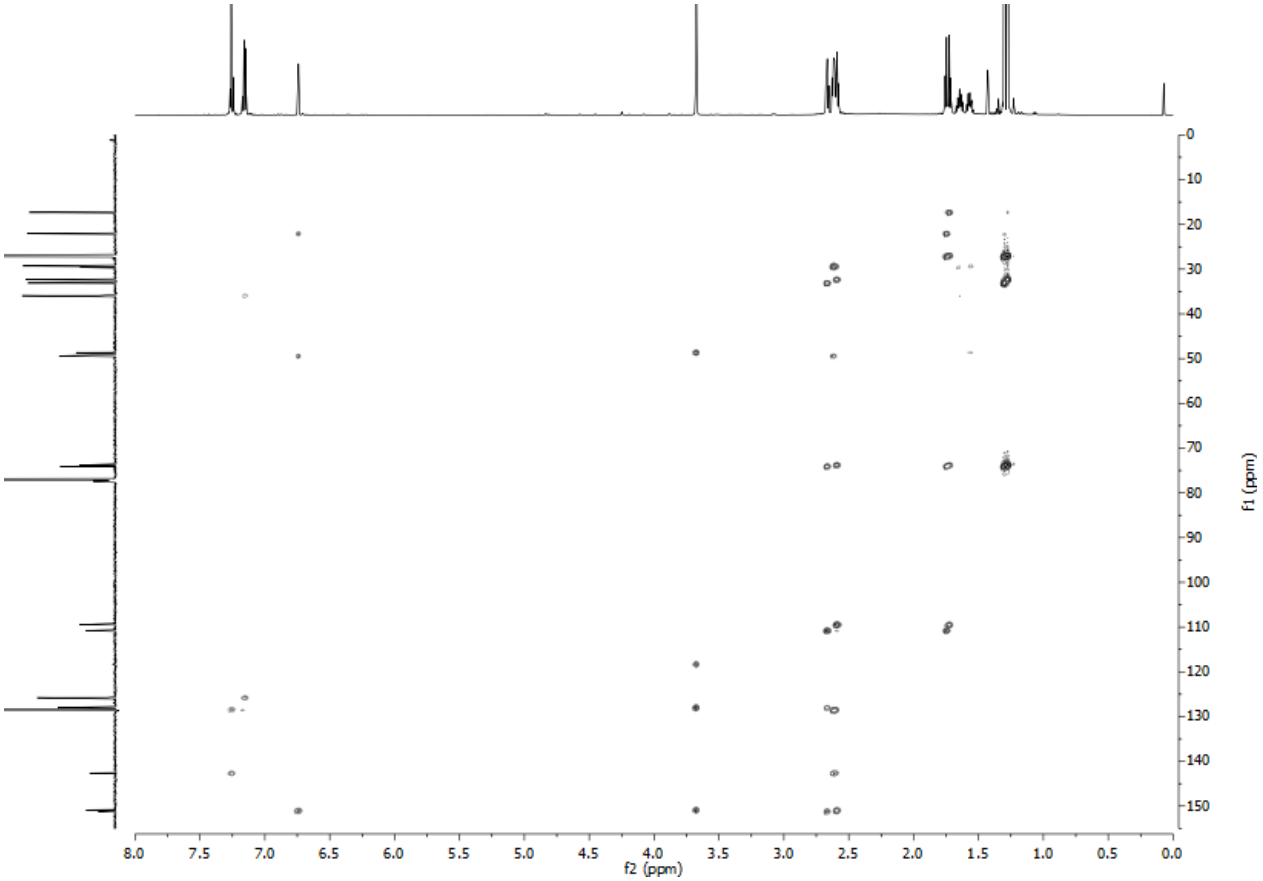
^{13}C NMR-Spectrum ($CDCl_3$) of **12d**.



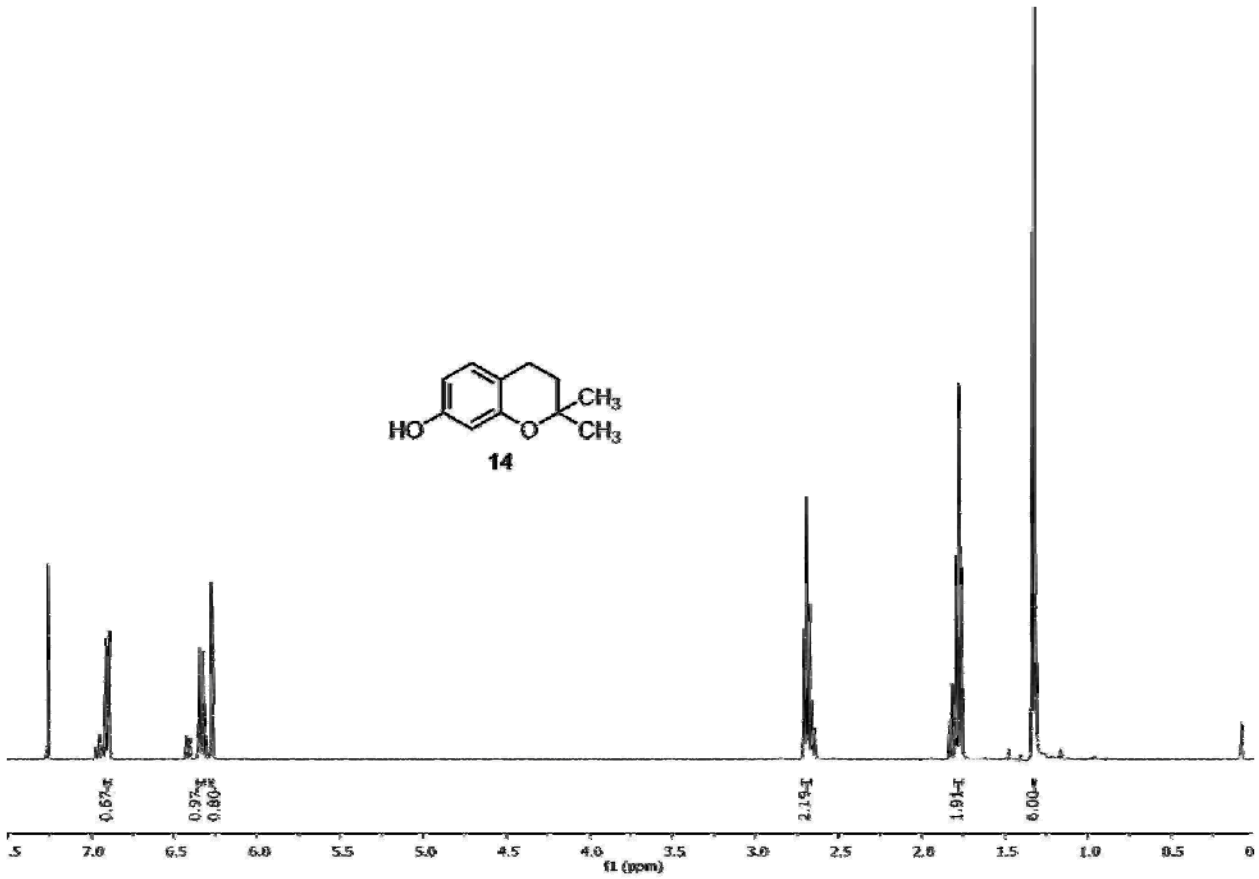
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **12d**.



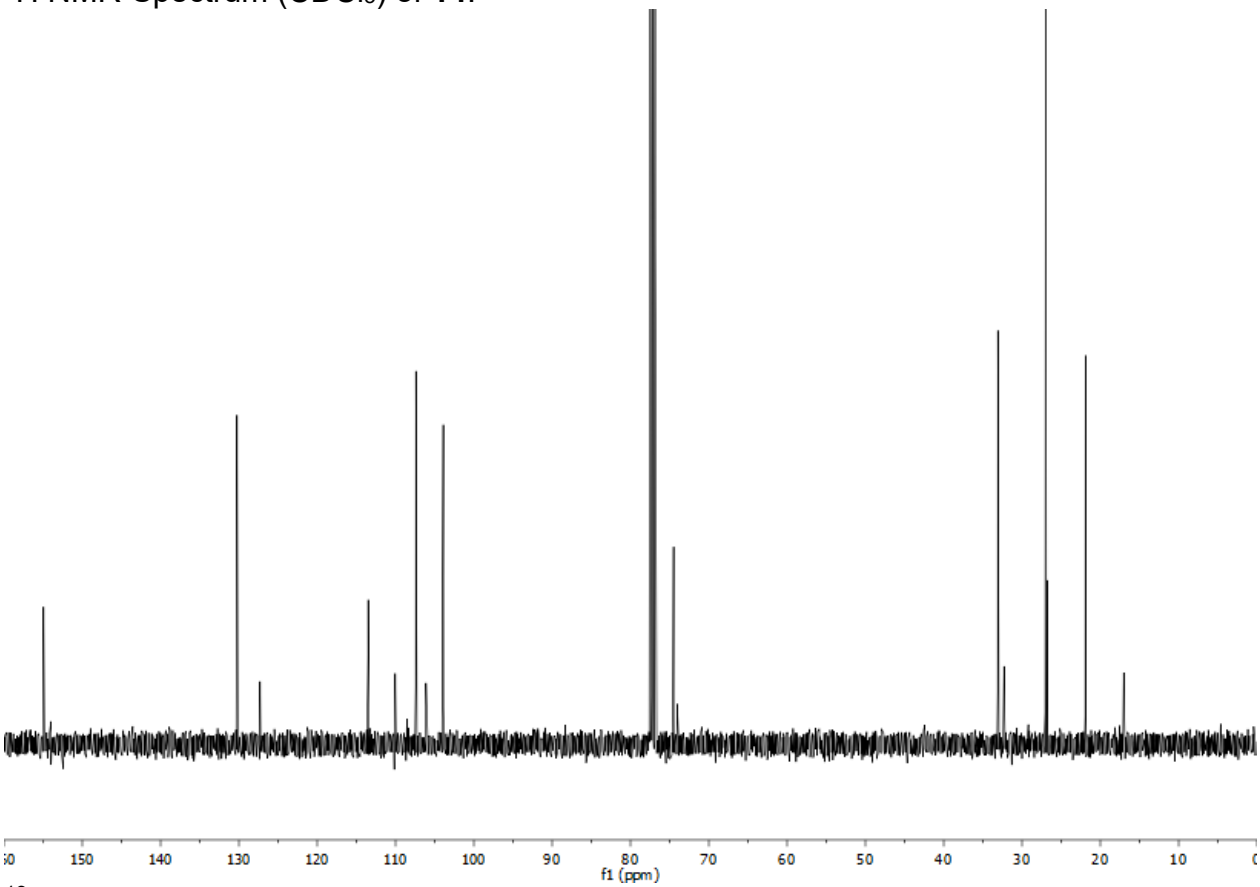
gHSQC-Spectrum ($CDCl_3$) of **12d**.



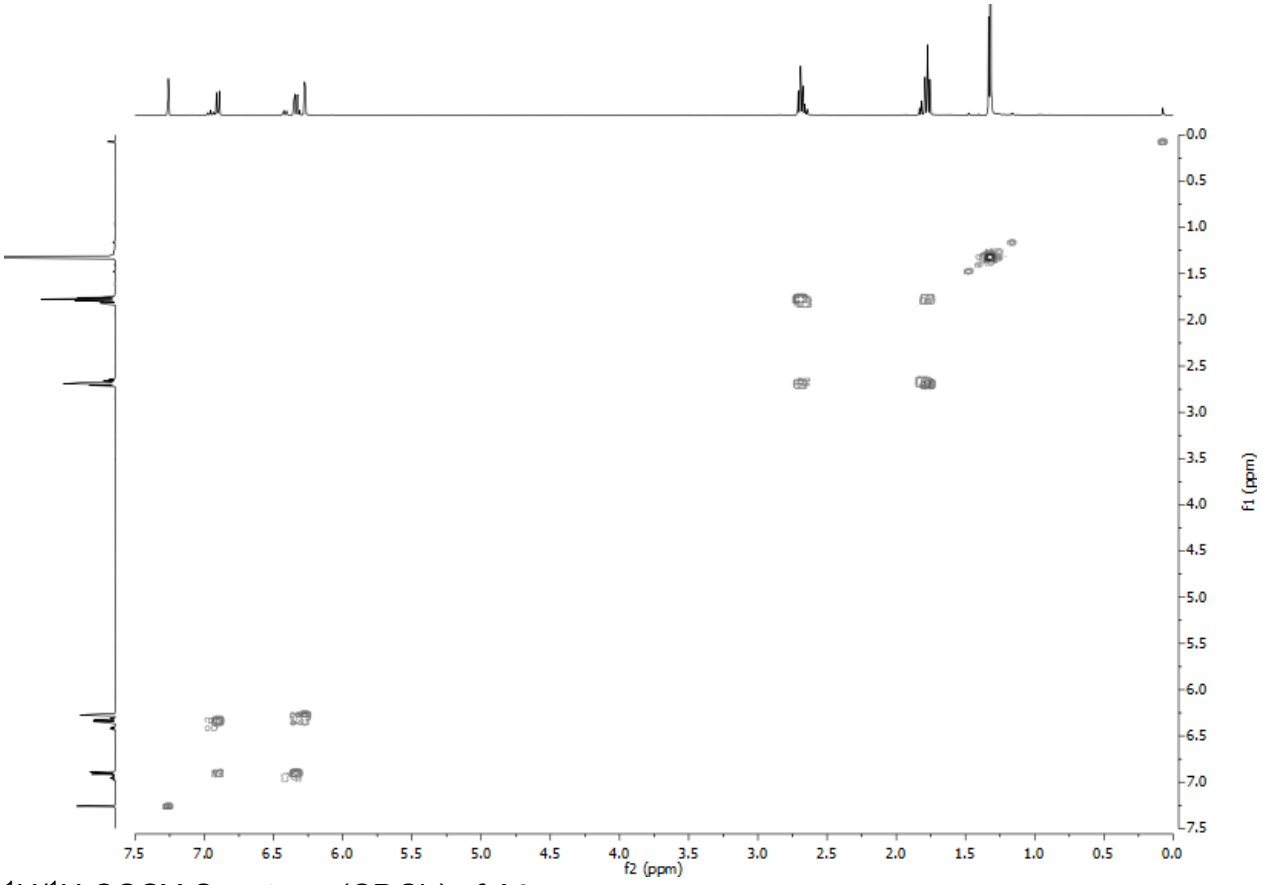
gHMBC-Spectrum ($CDCl_3$) of **12d**.



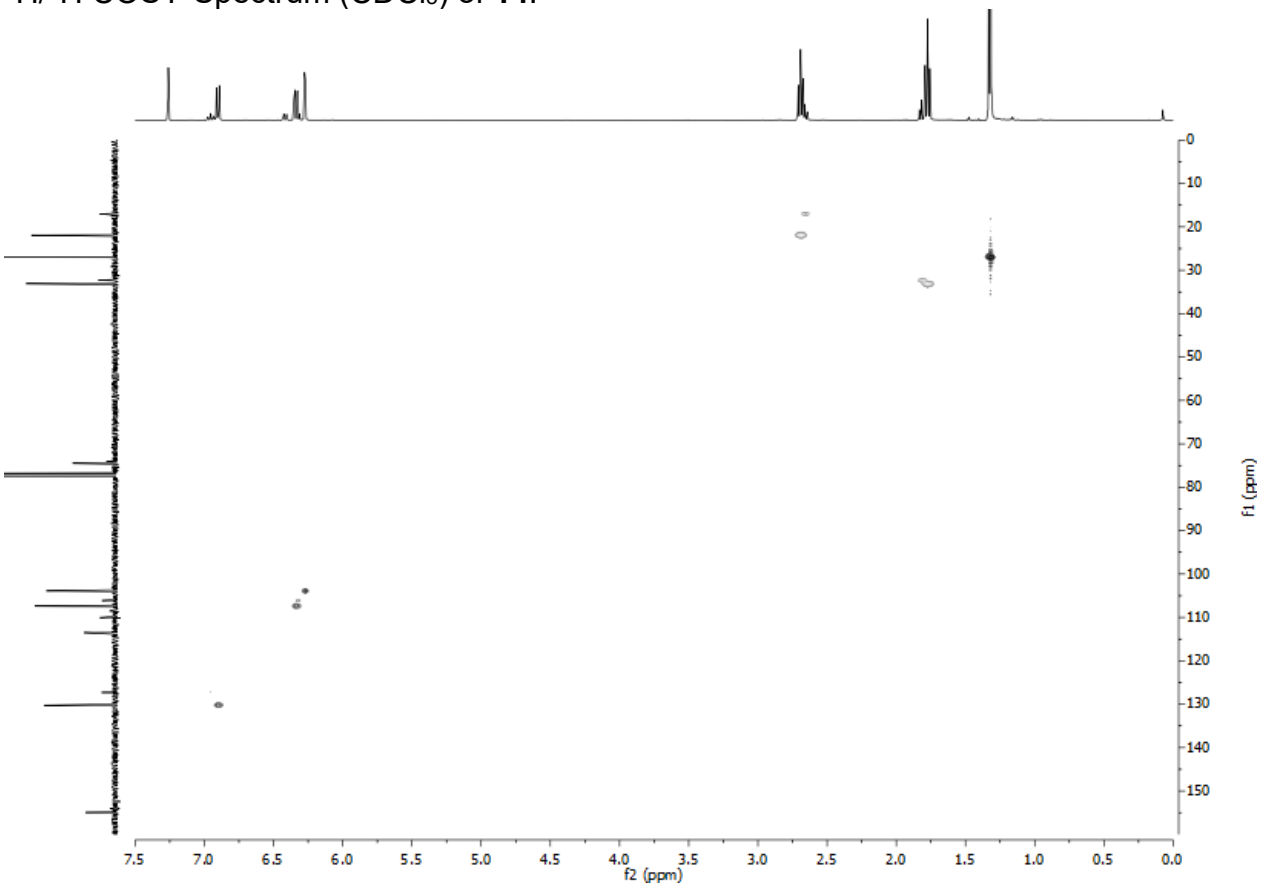
^{1}H NMR-Spectrum ($CDCl_3$) of **14**.



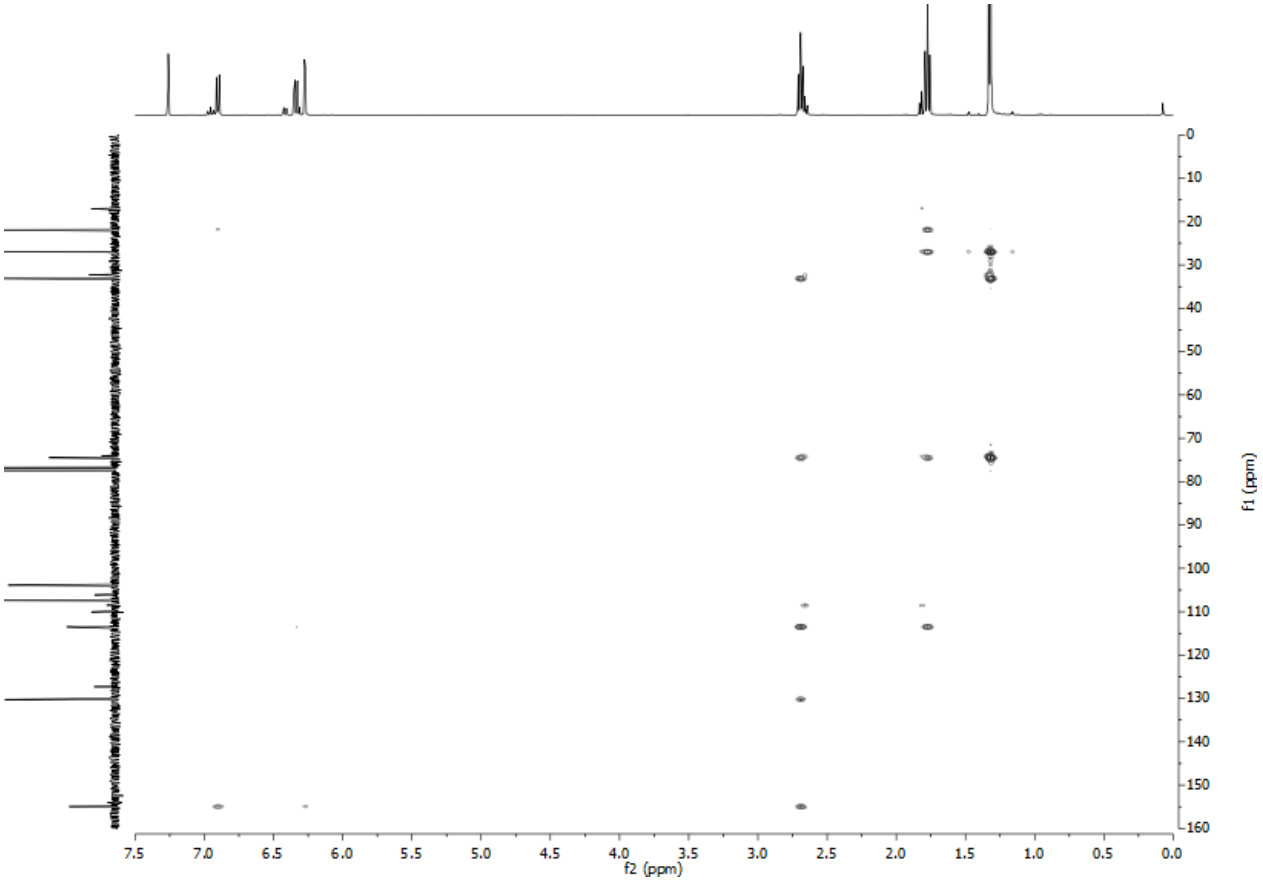
^{13}C NMR-Spectrum ($CDCl_3$) of **14**.



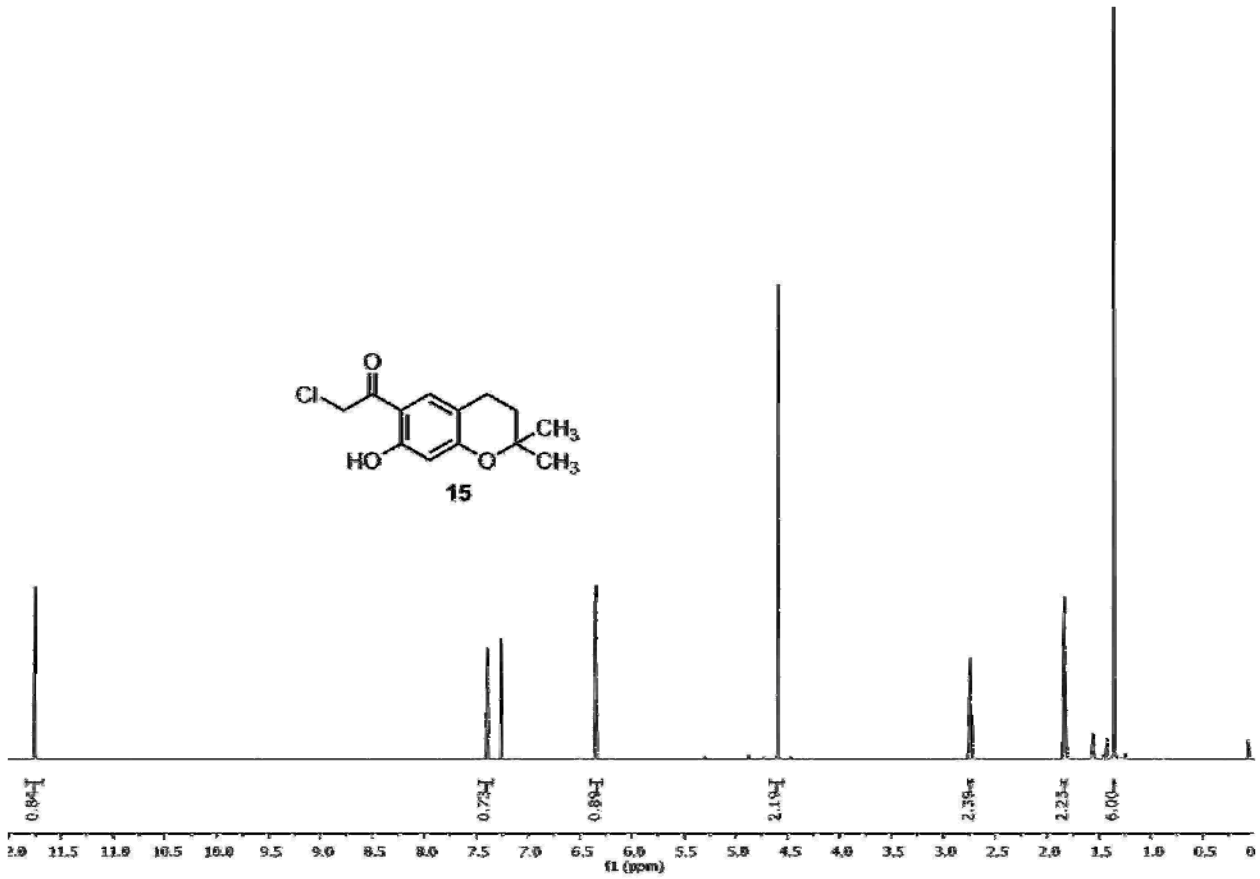
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **14**.



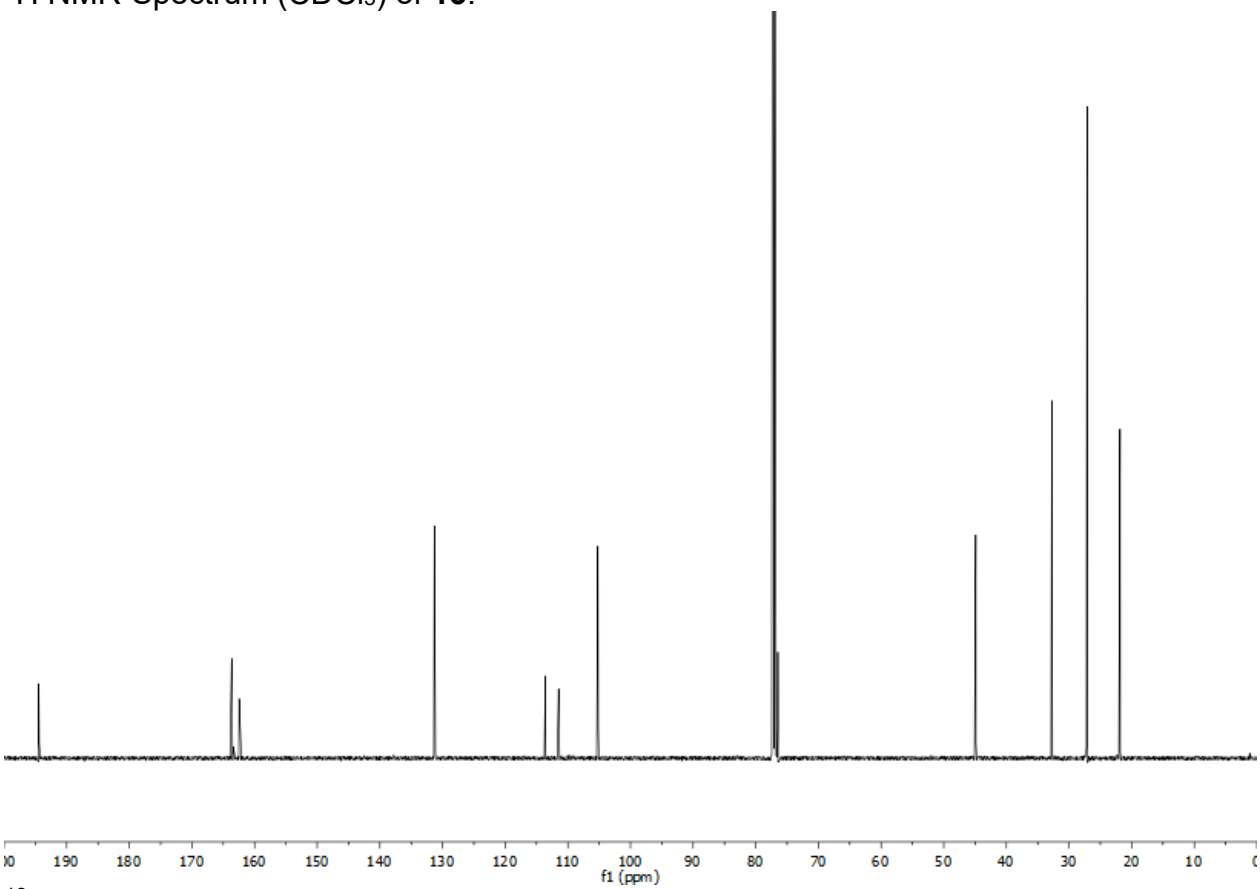
gHSQC-Spectrum ($CDCl_3$) of **14**.



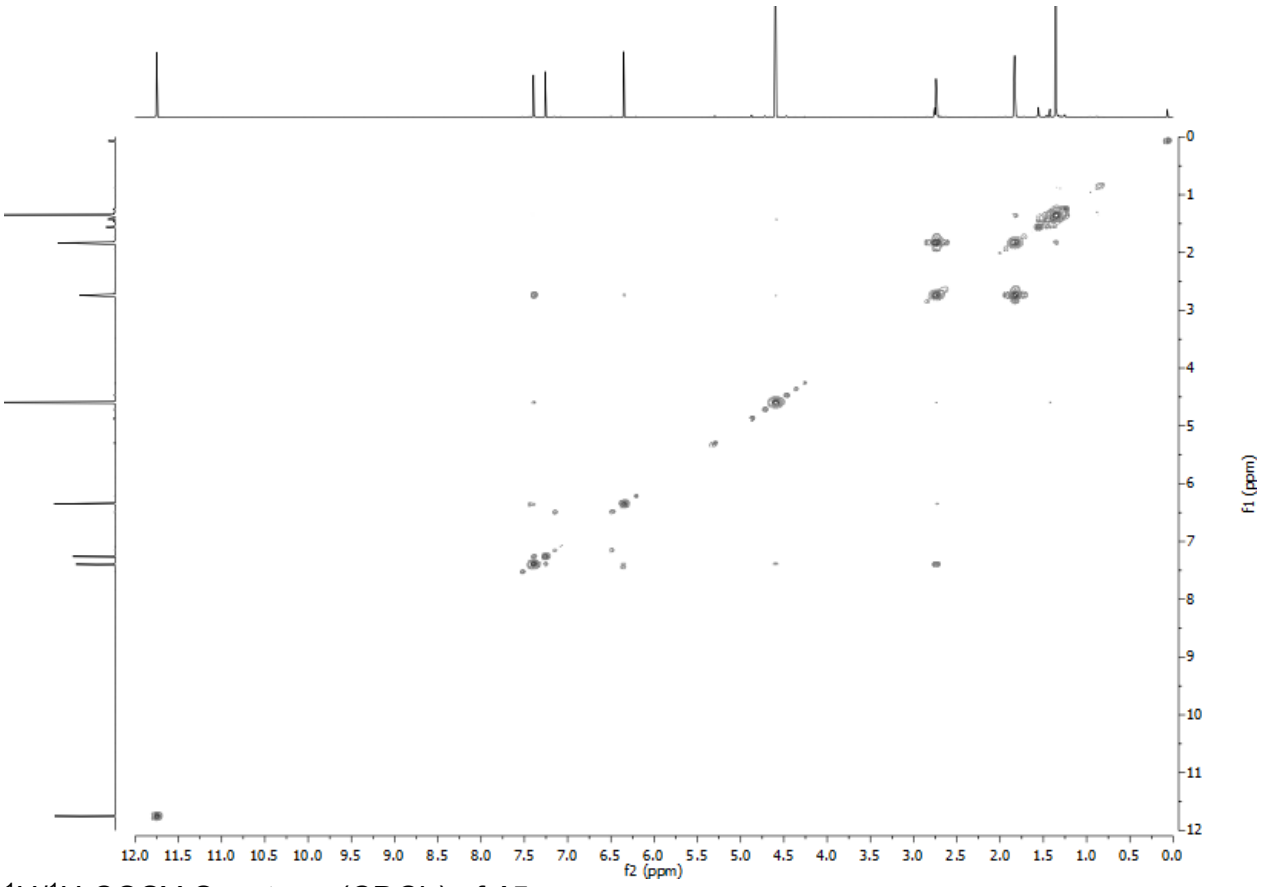
gHMBC-Spectrum ($CDCl_3$) of **14**.



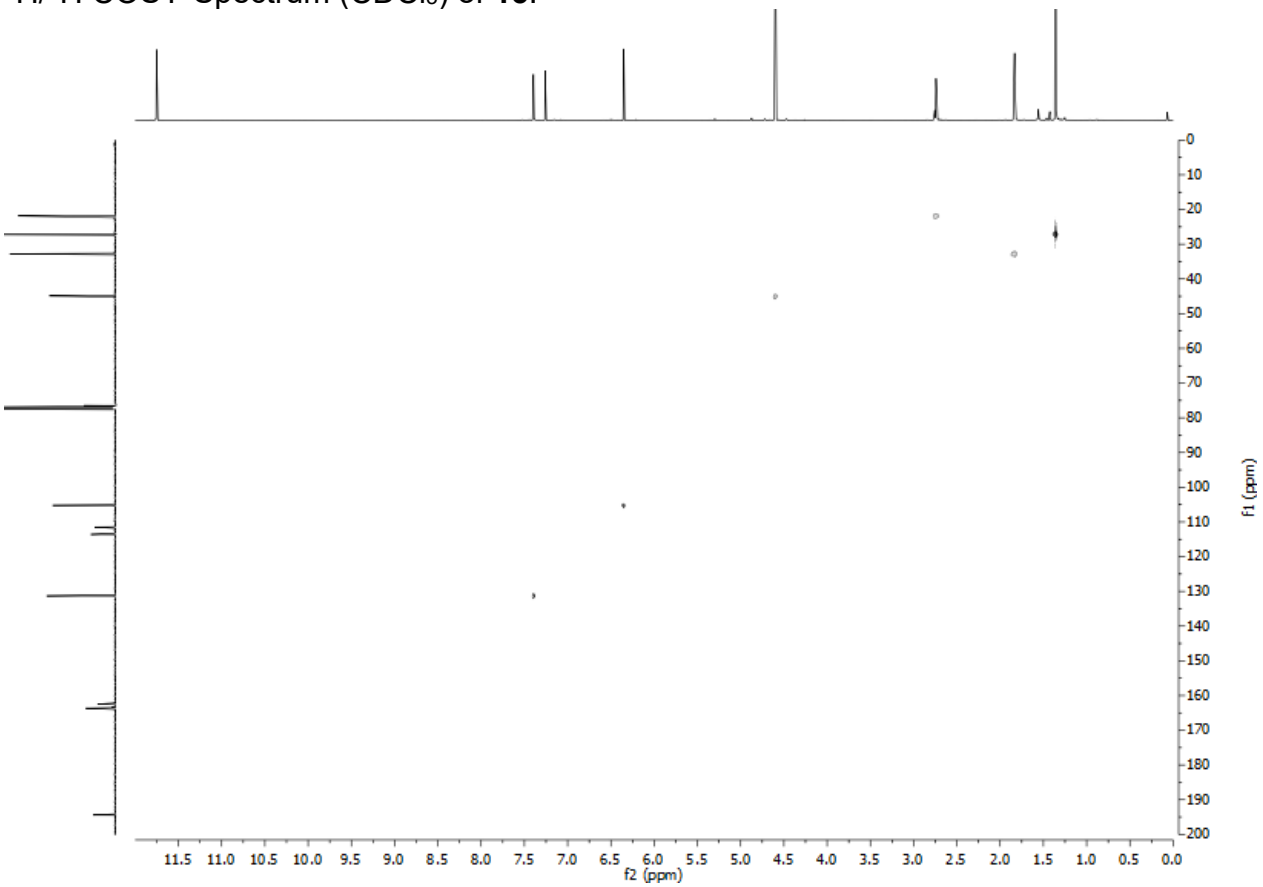
^{1}H NMR-Spectrum ($CDCl_3$) of **15**.



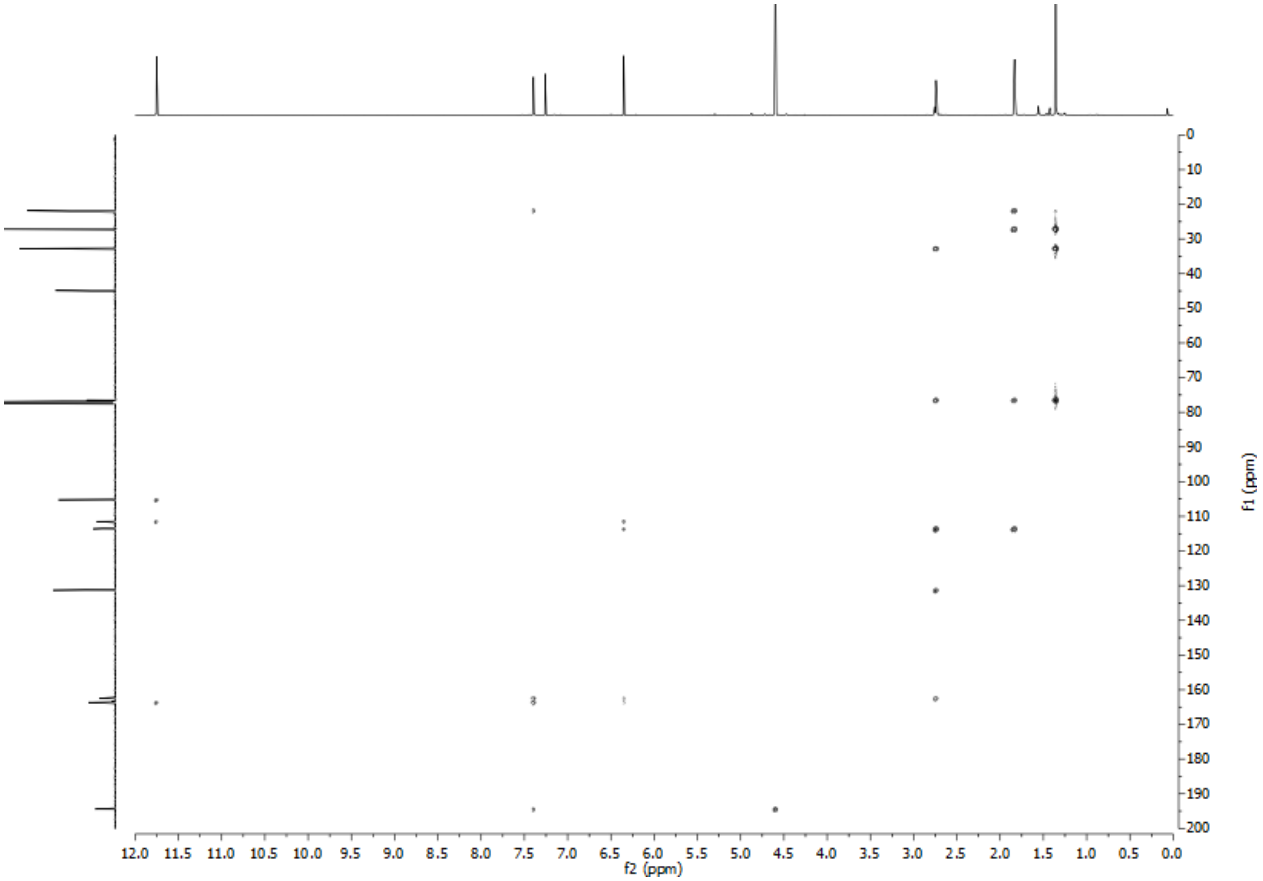
^{13}C NMR-Spectrum ($CDCl_3$) of **15**.



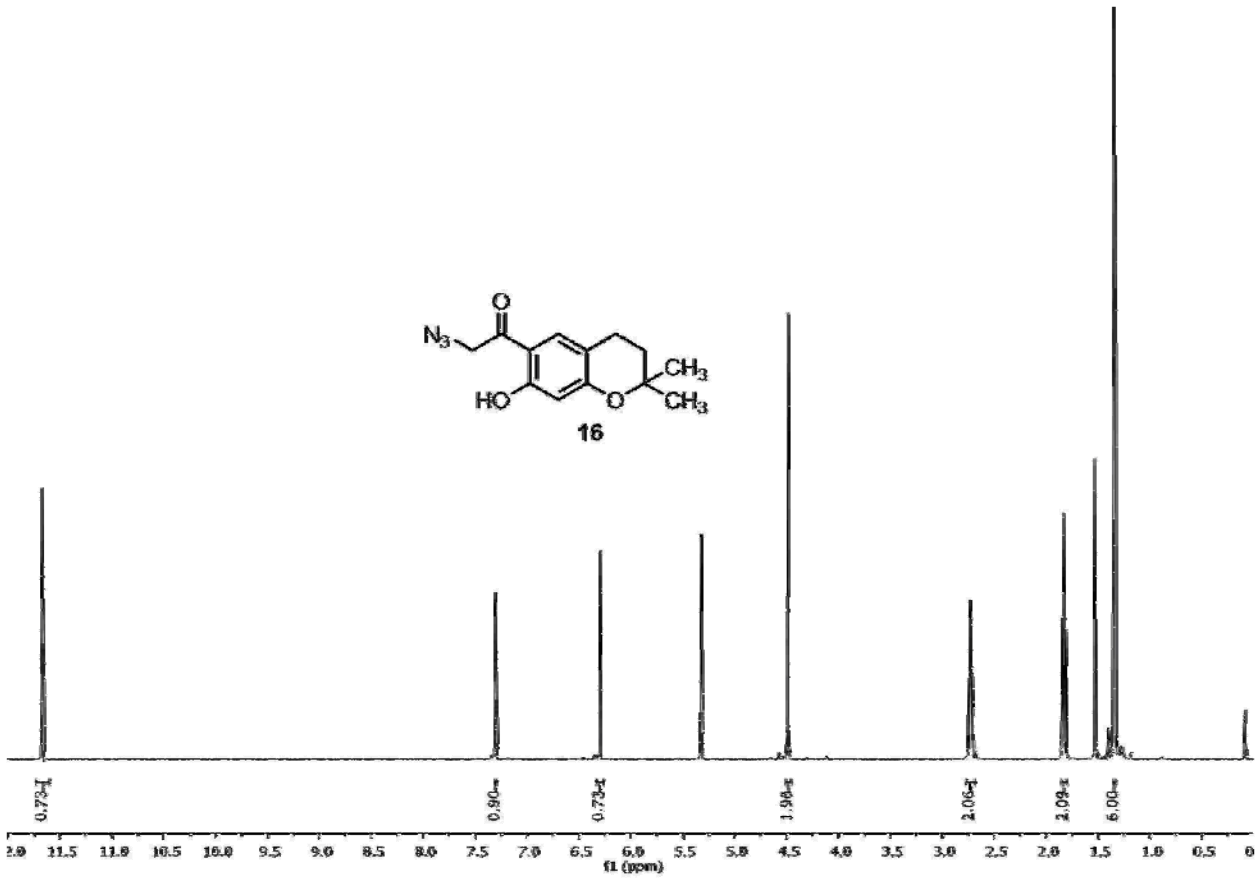
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **15**.



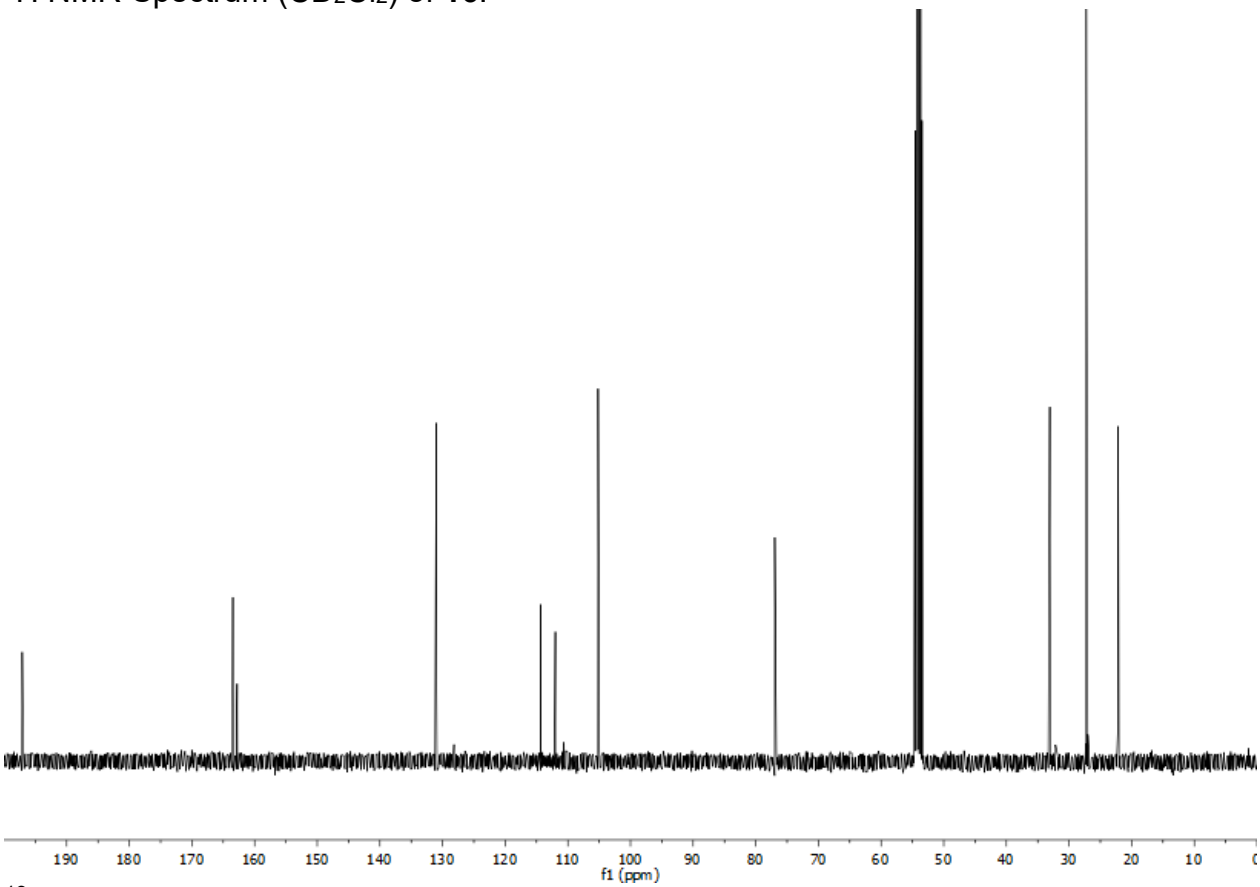
gHSQC-Spectrum ($CDCl_3$) of **15**.



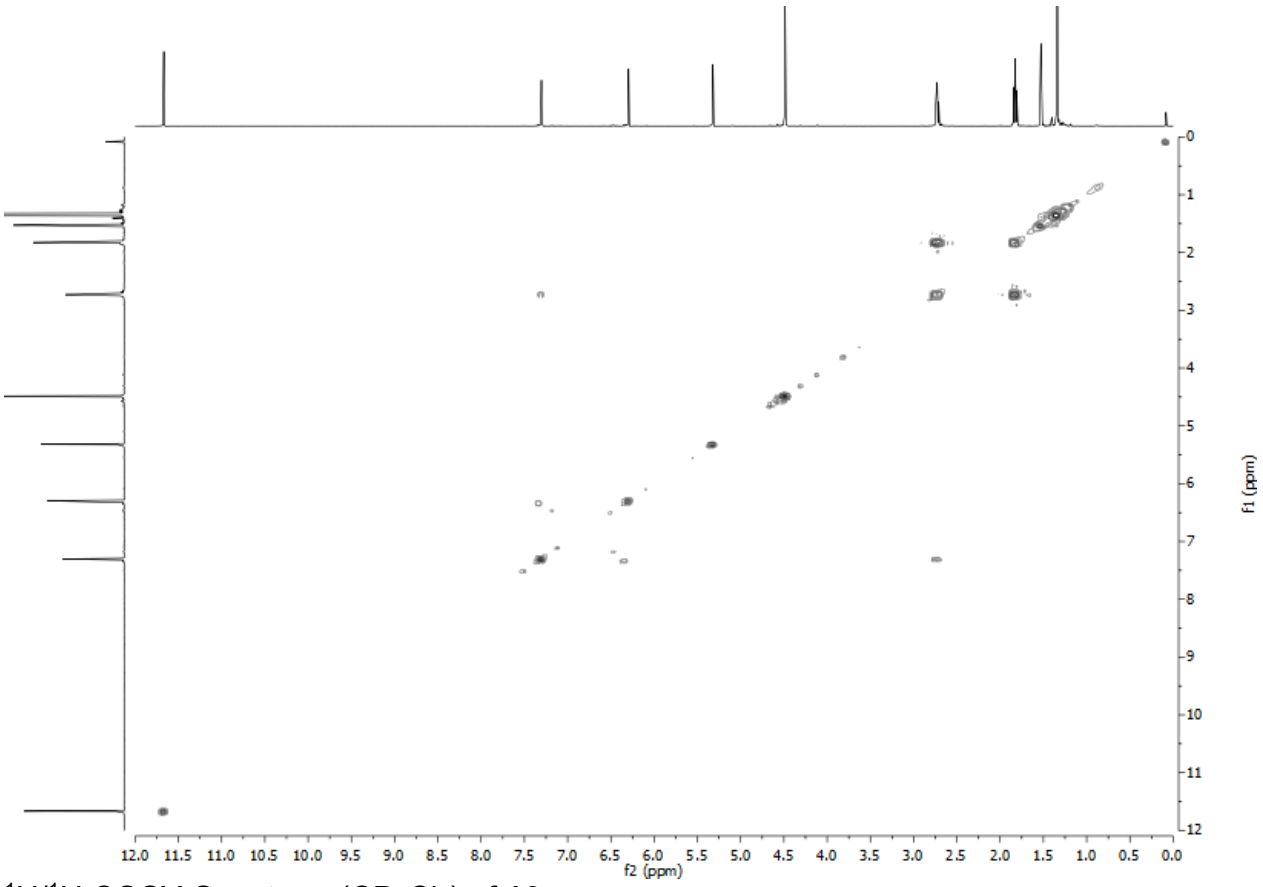
gHMBC-Spectrum ($CDCl_3$) of **15**.



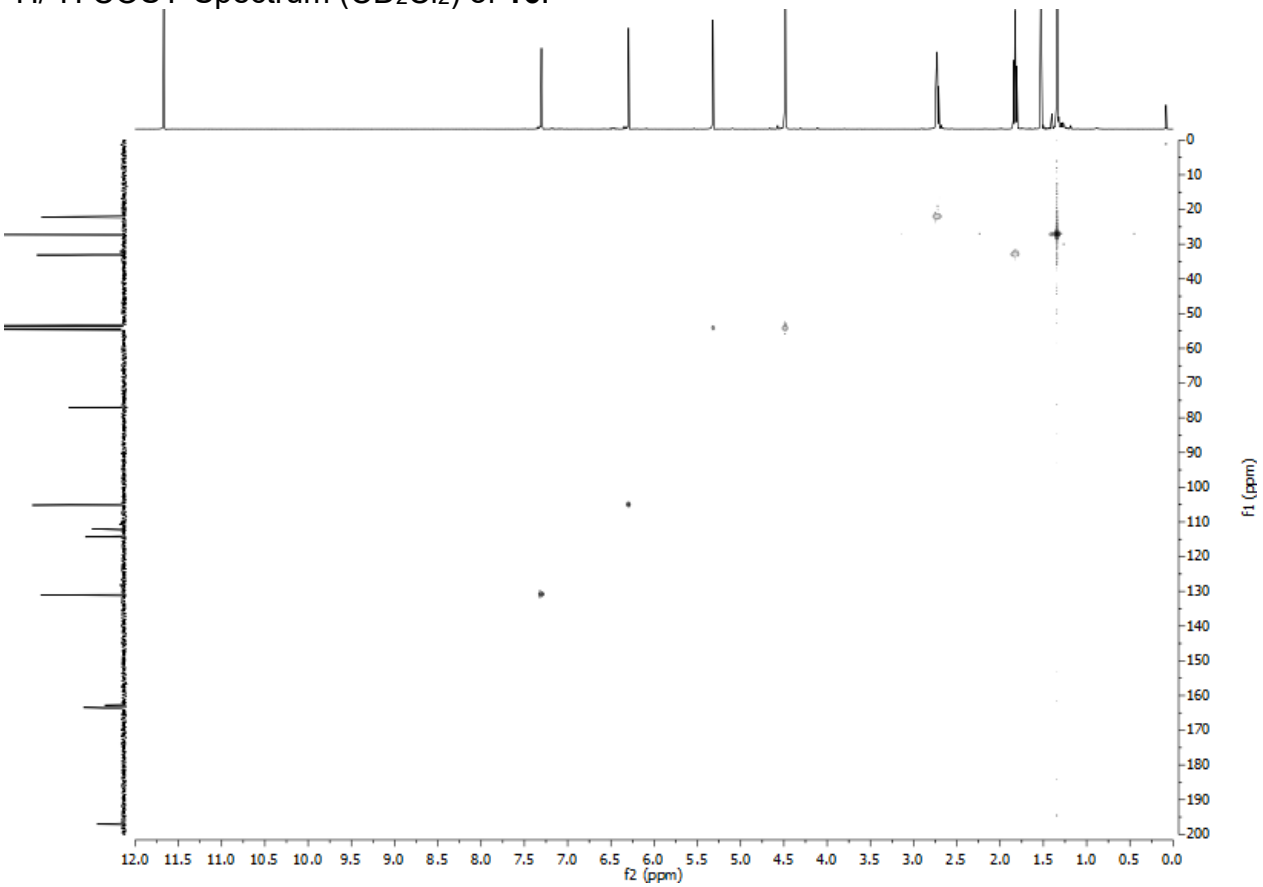
^{1}H NMR-Spectrum (CD_2Cl_2) of **16**.



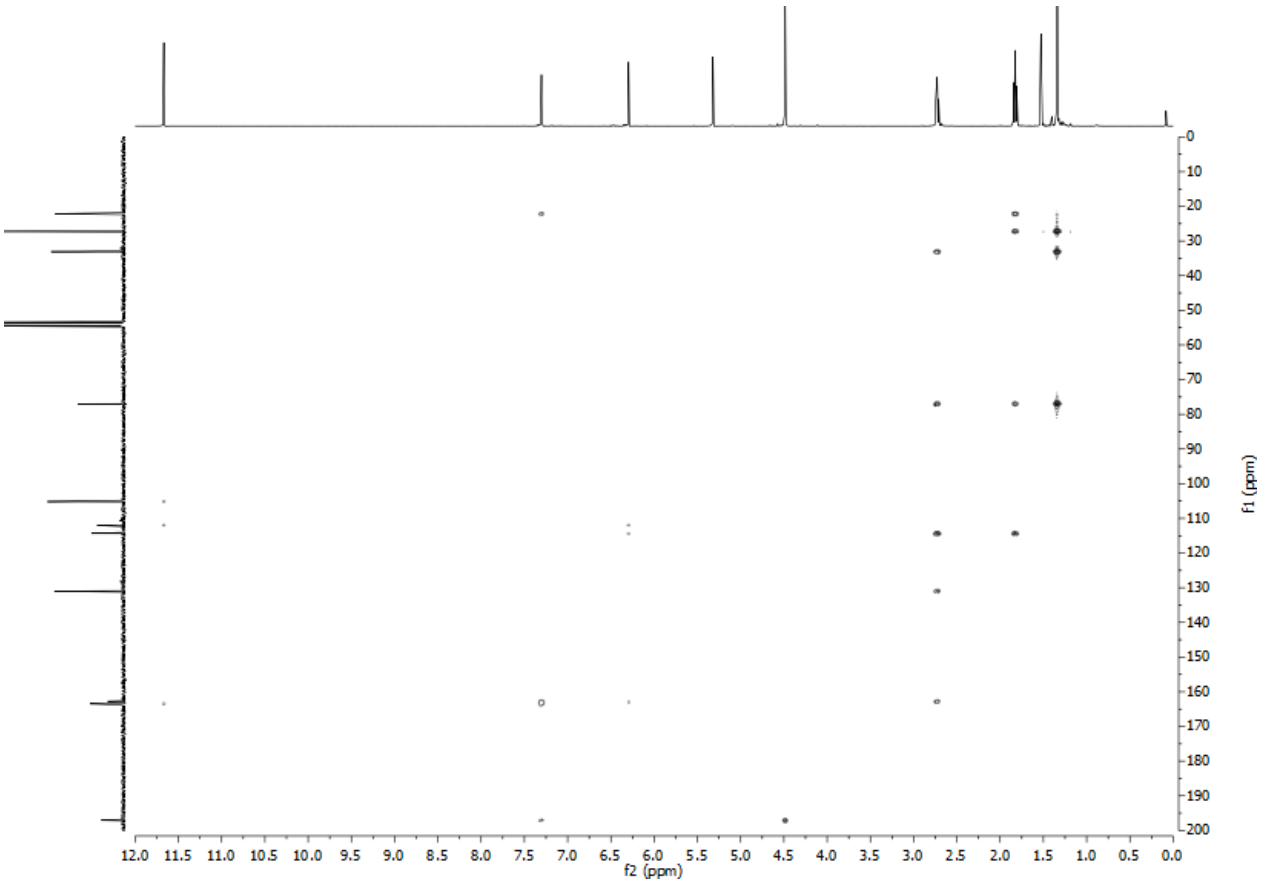
^{13}C NMR-Spectrum (CD_2Cl_2) of **16**.



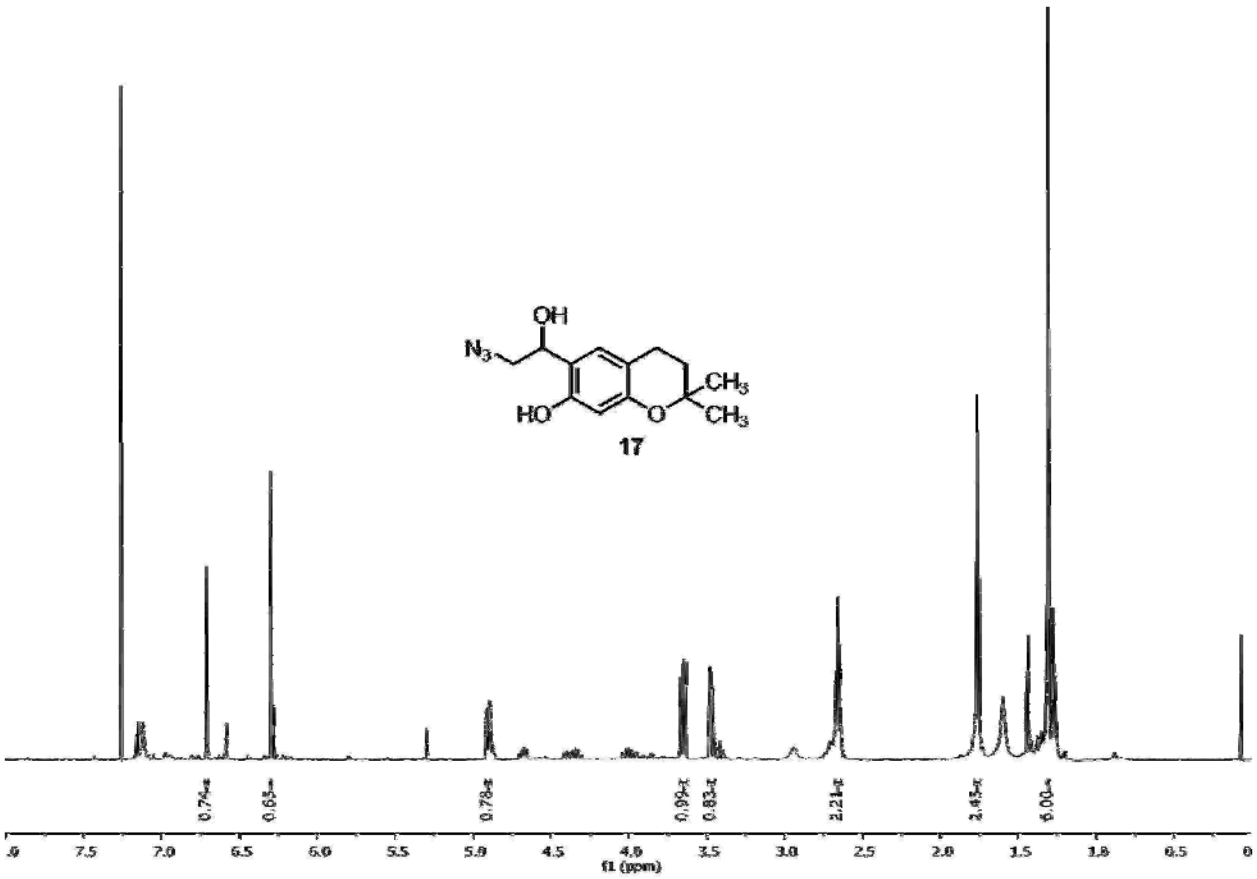
$^{1}H/^{1}H$ COSY-Spectrum (CD_2Cl_2) of **16**.



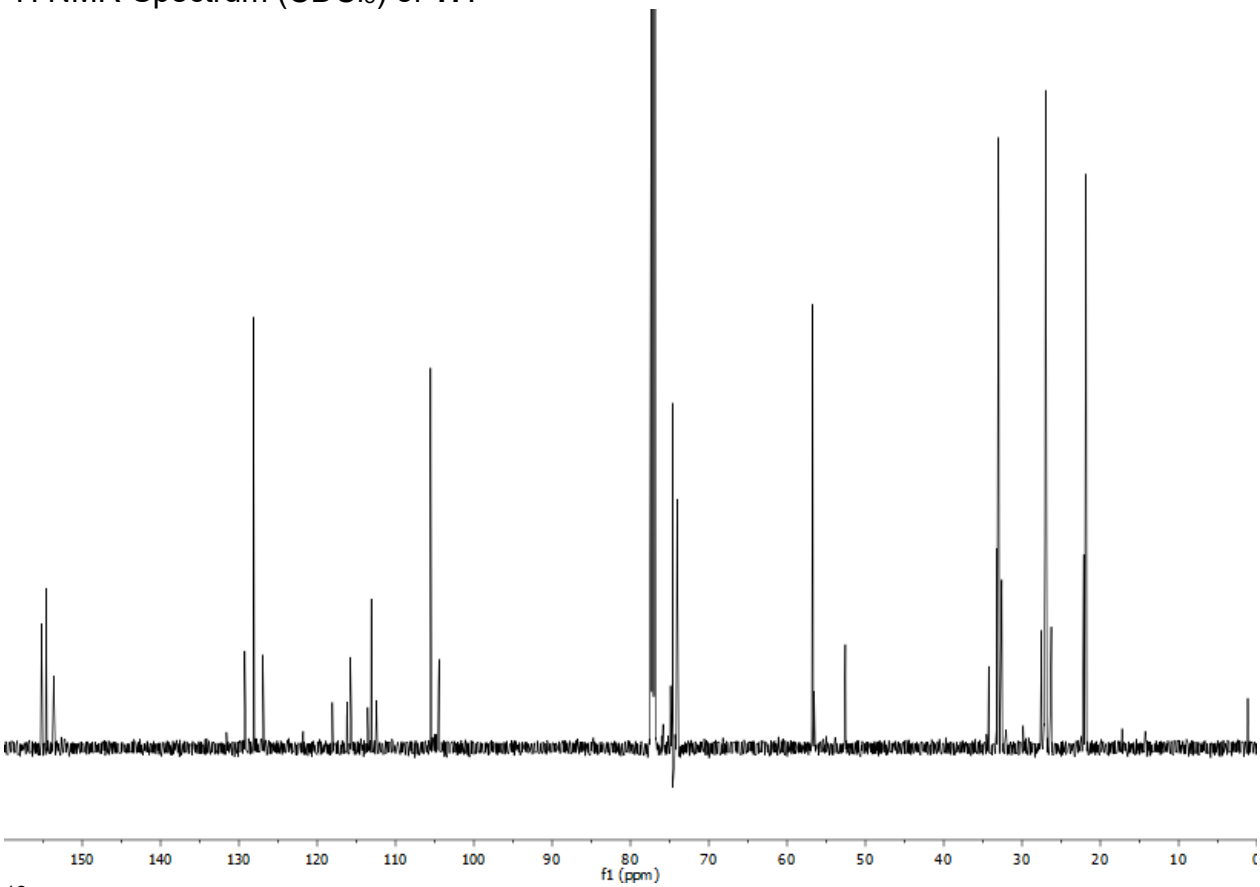
gHSQC-Spectrum (CD_2Cl_2) of **16**.



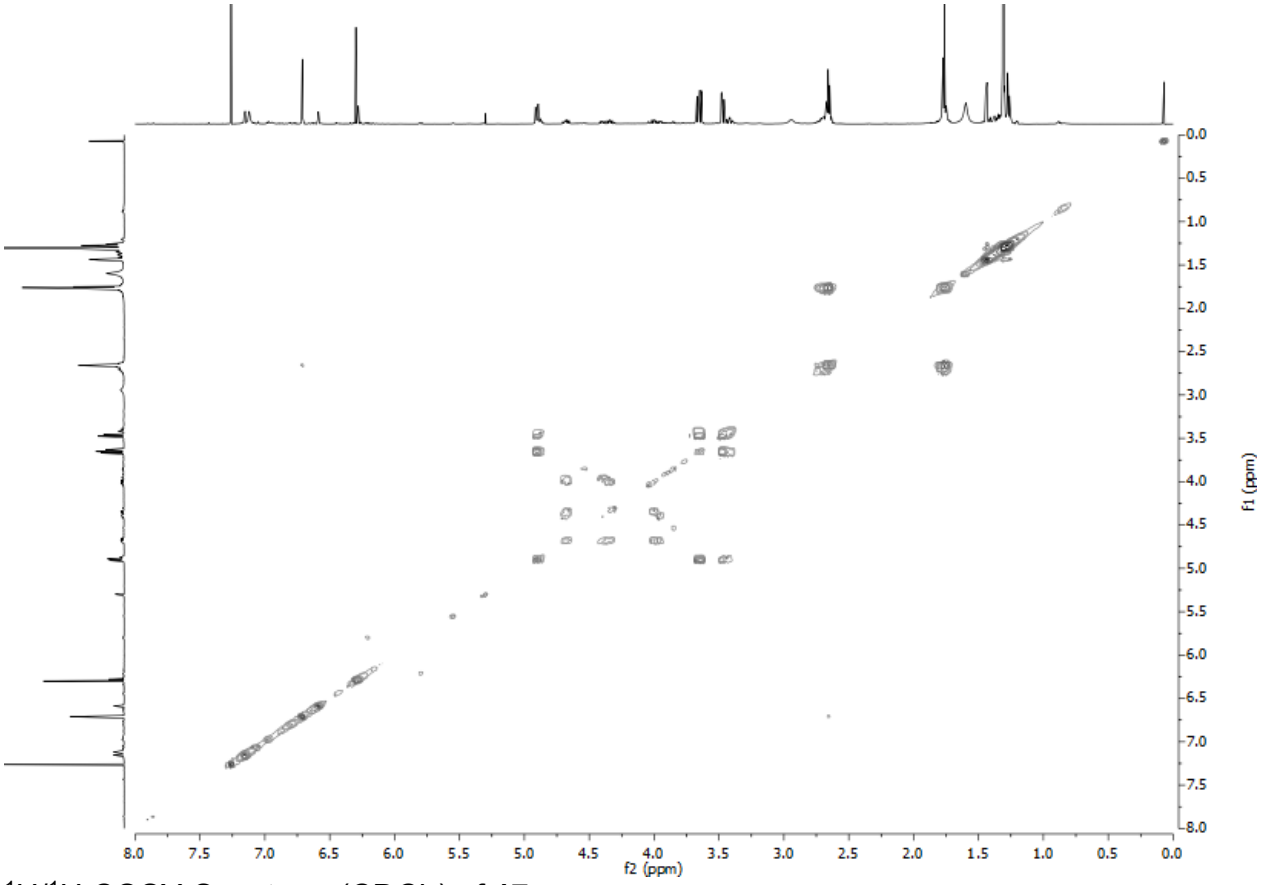
gHMBC-Spectrum (CD_2Cl_2) of **16**.



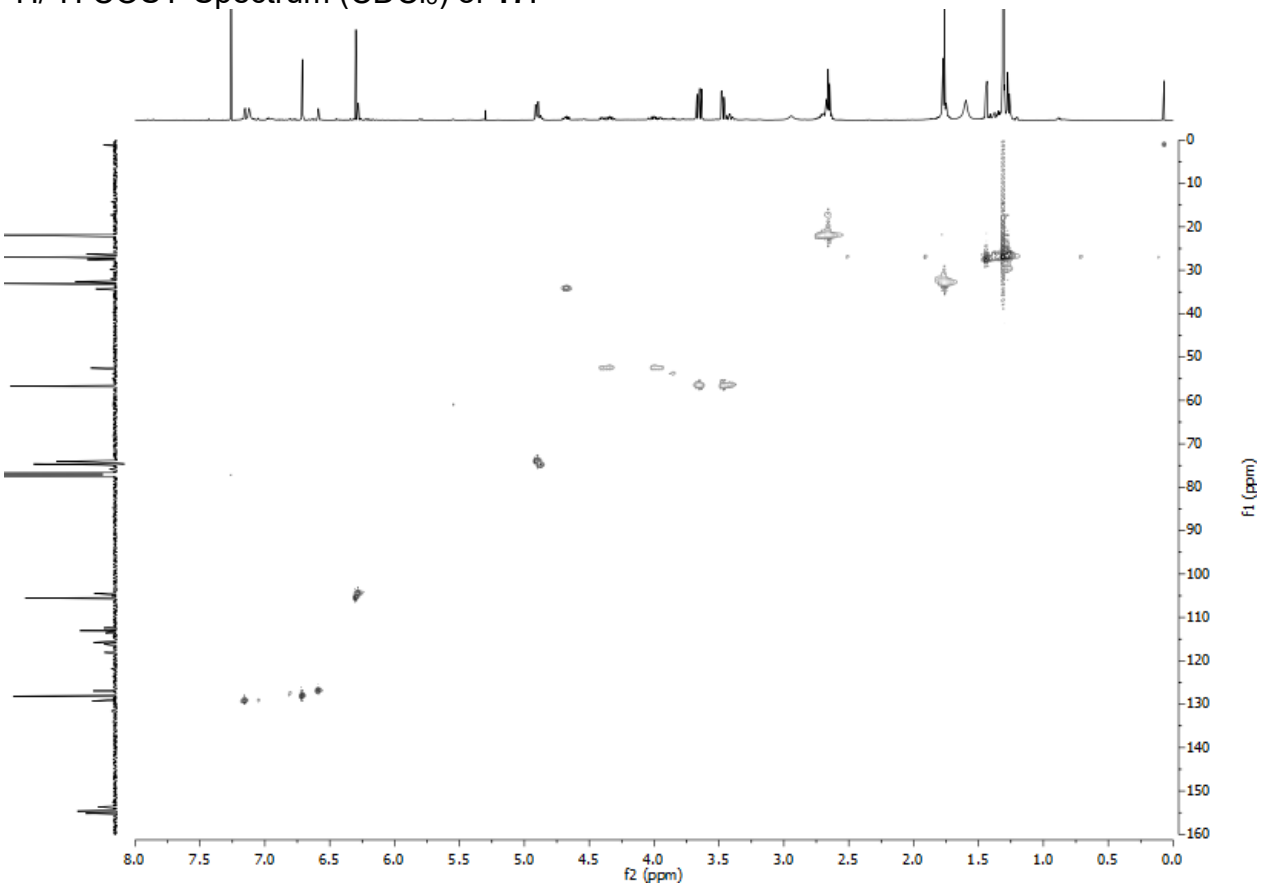
^{1}H NMR-Spectrum ($CDCl_3$) of **17**.



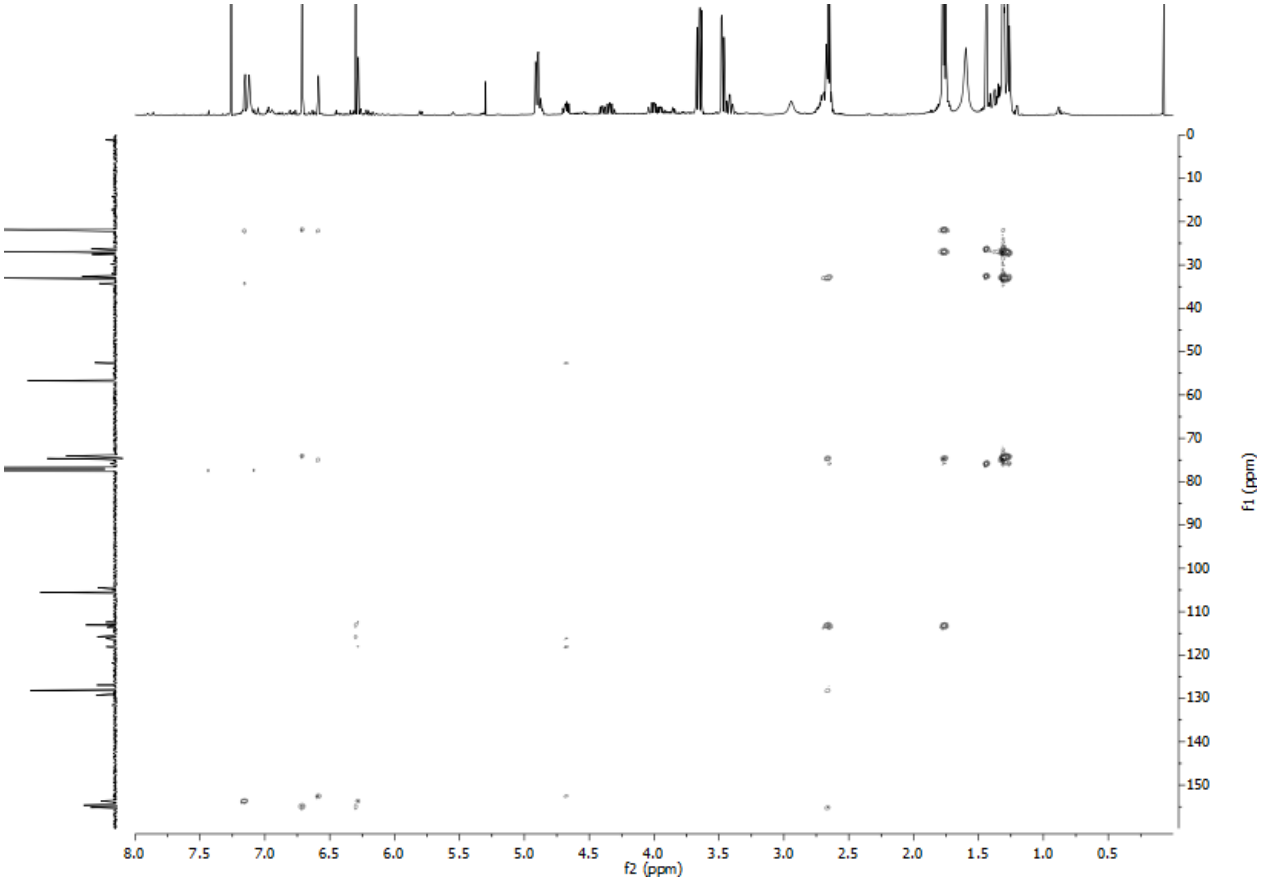
^{13}C NMR-Spectrum ($CDCl_3$) of **17**.



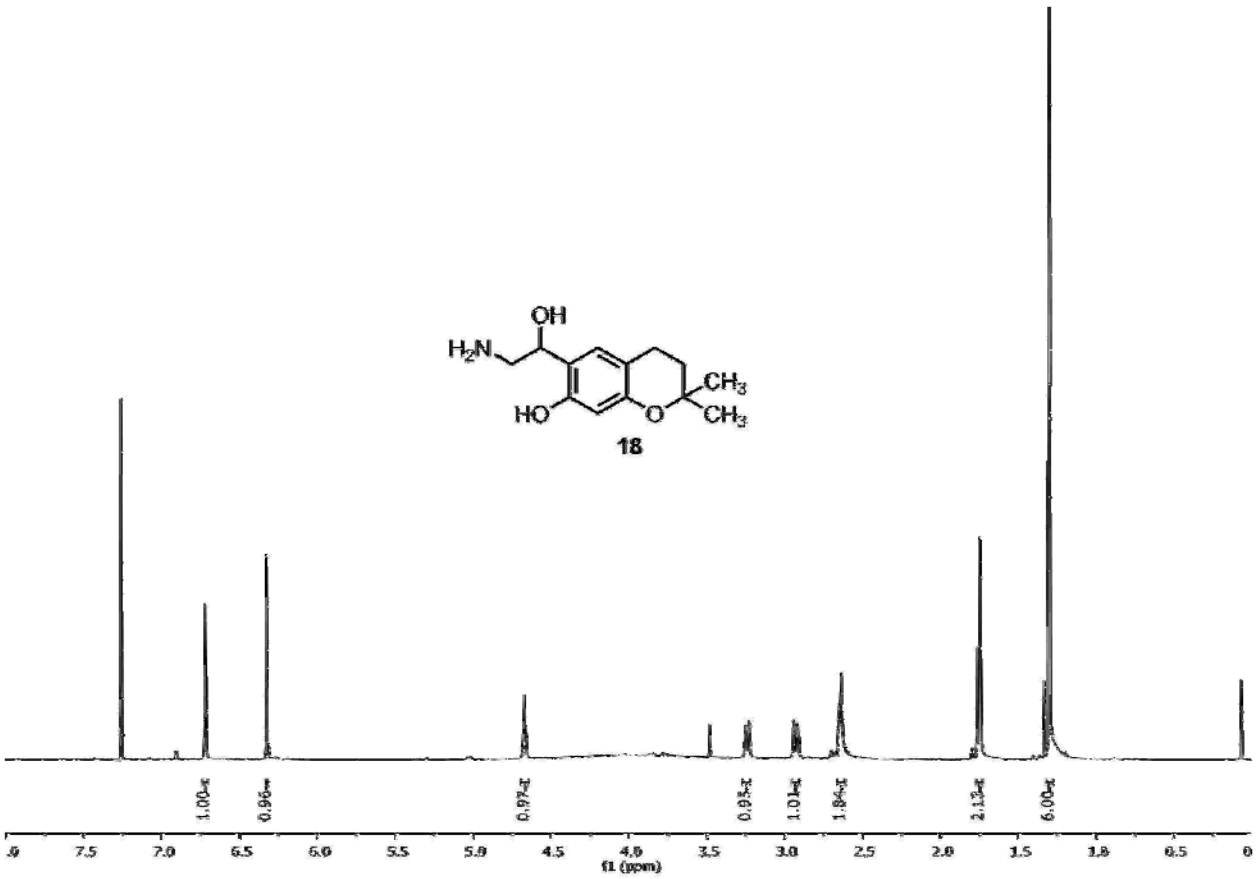
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **17**.



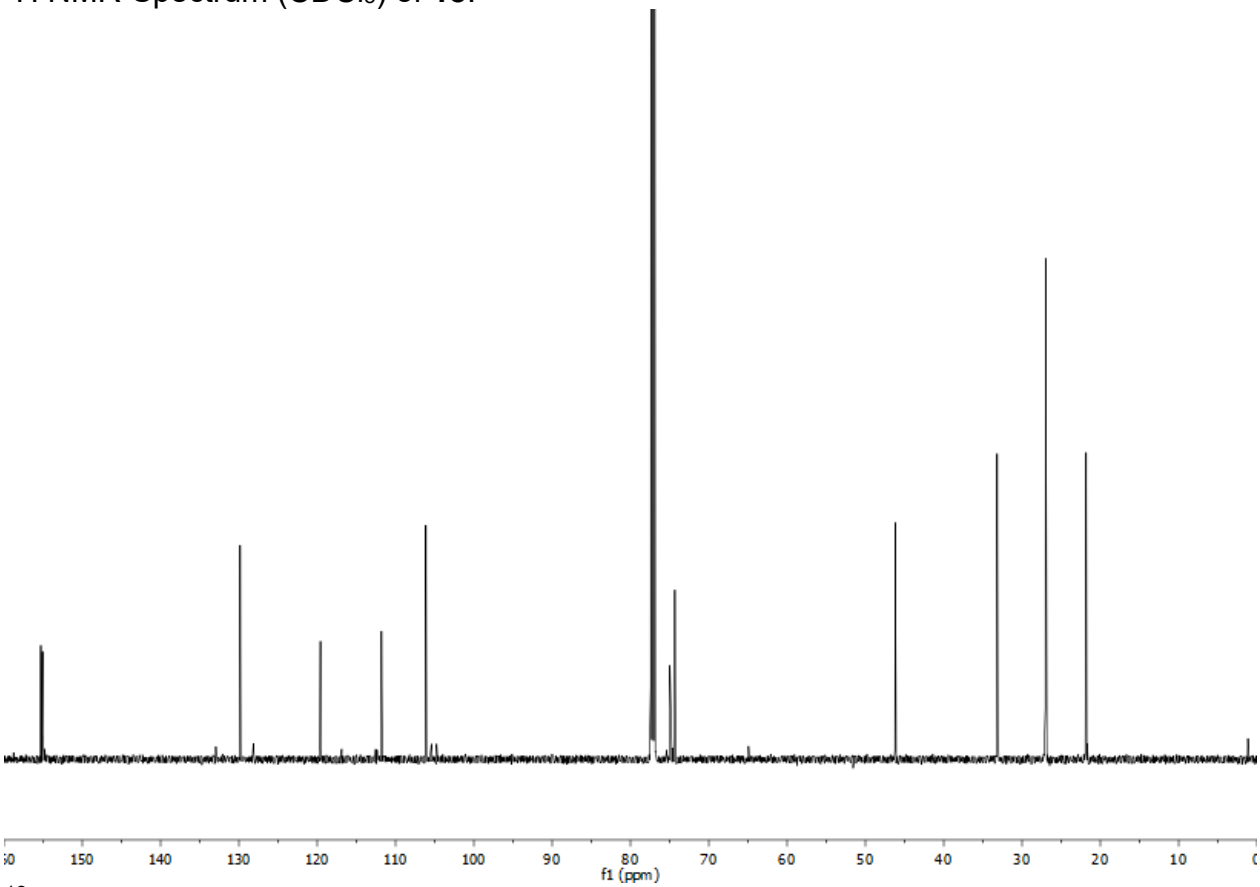
gHSQC-Spectrum ($CDCl_3$) of **17**.



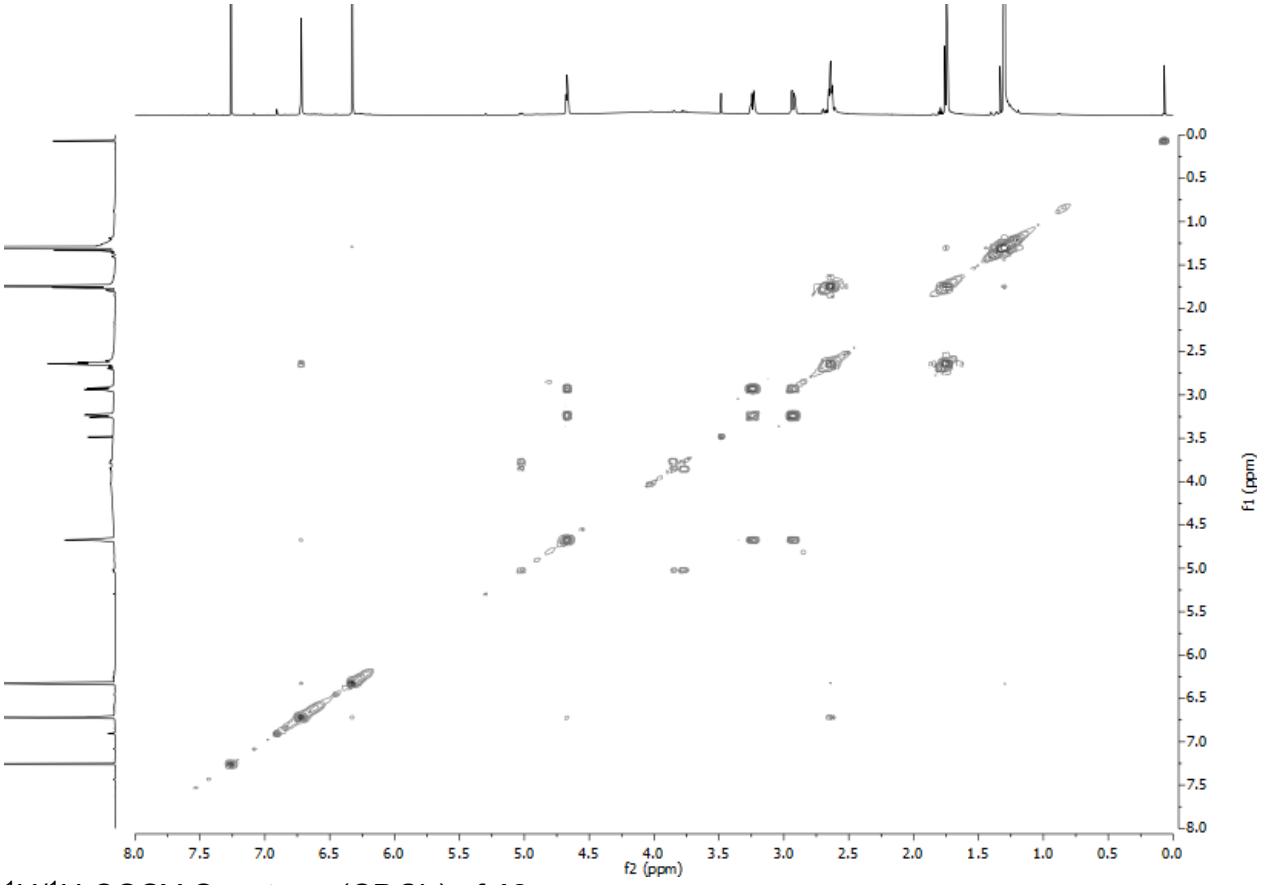
gHMBC-Spectrum ($CDCl_3$) of **17**.



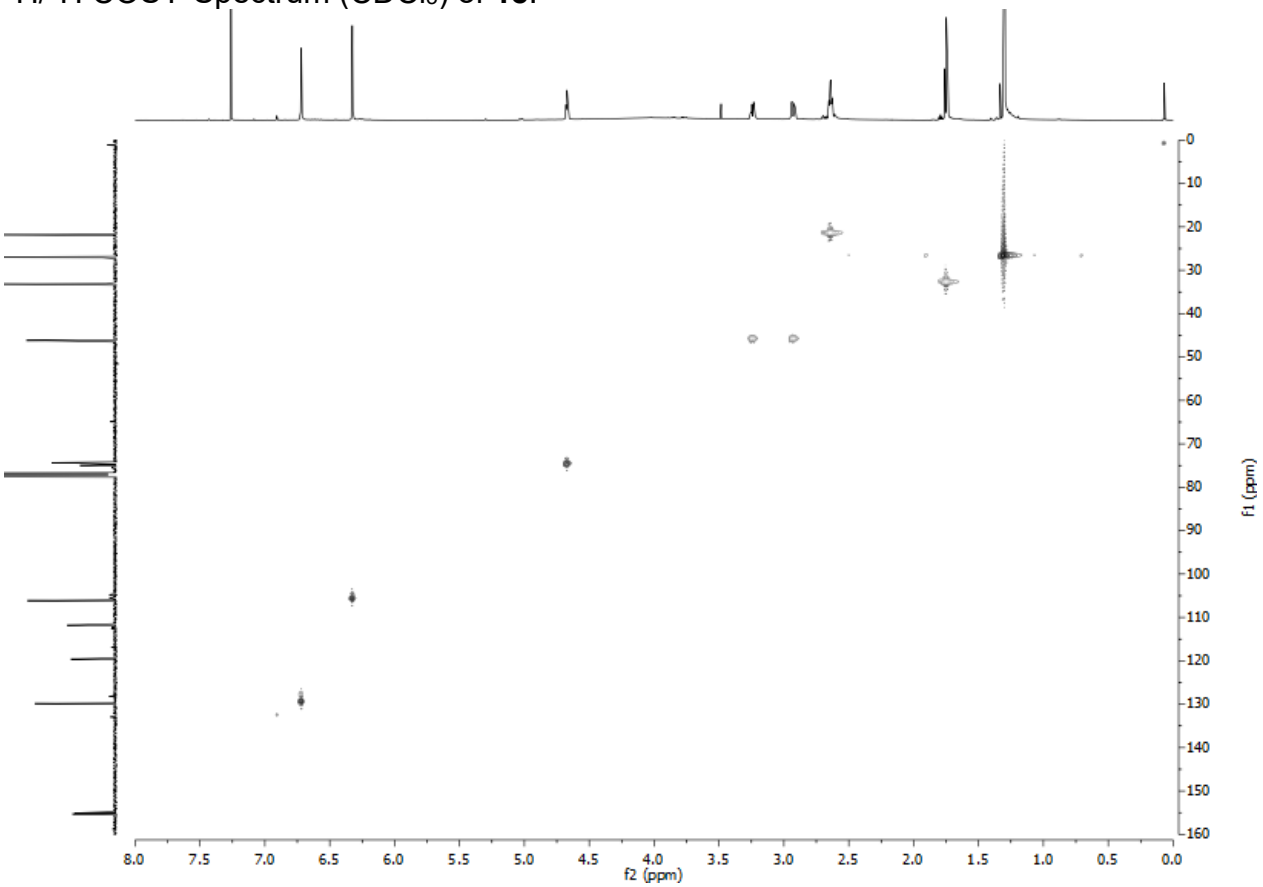
^{1}H NMR-Spectrum ($CDCl_3$) of **18**.



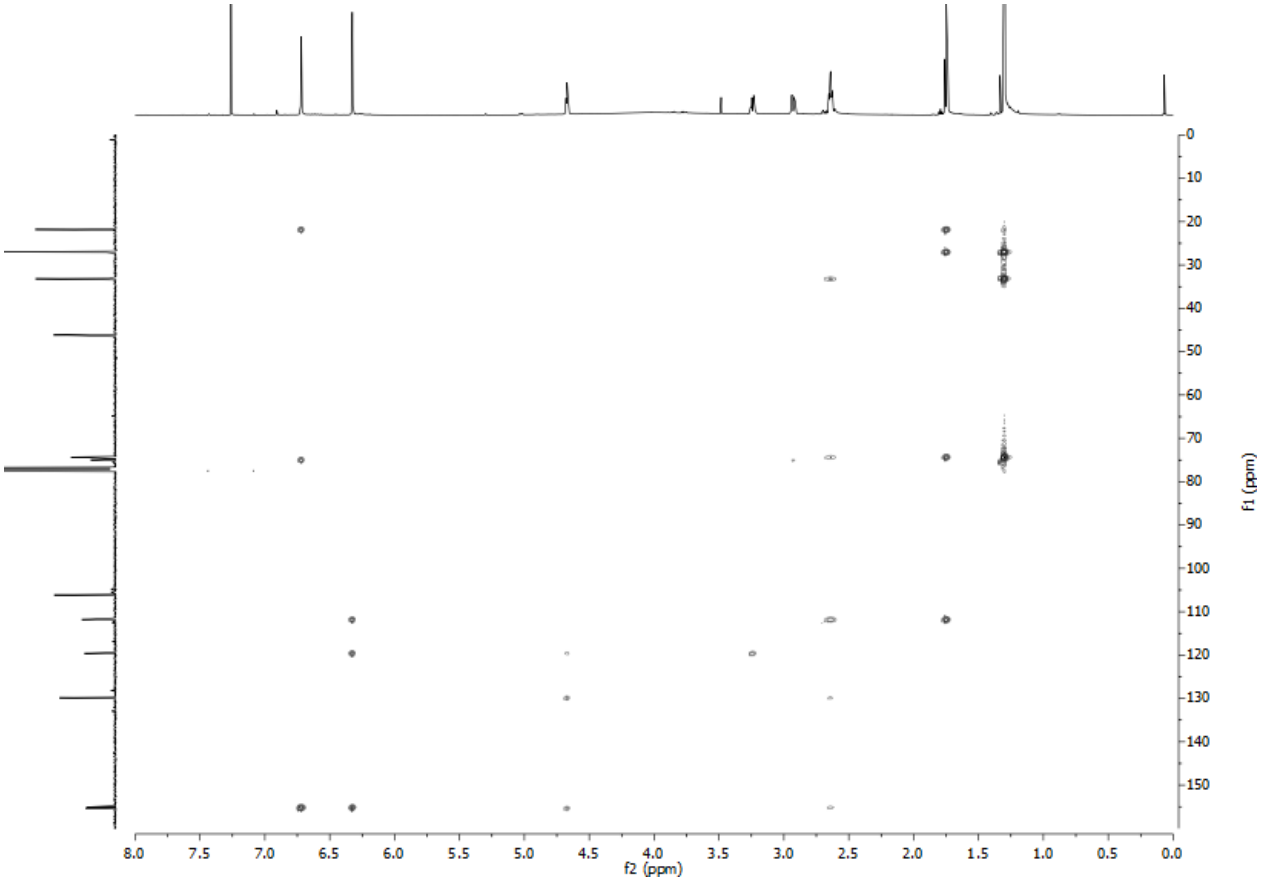
^{13}C NMR-Spectrum ($CDCl_3$) of **18**.



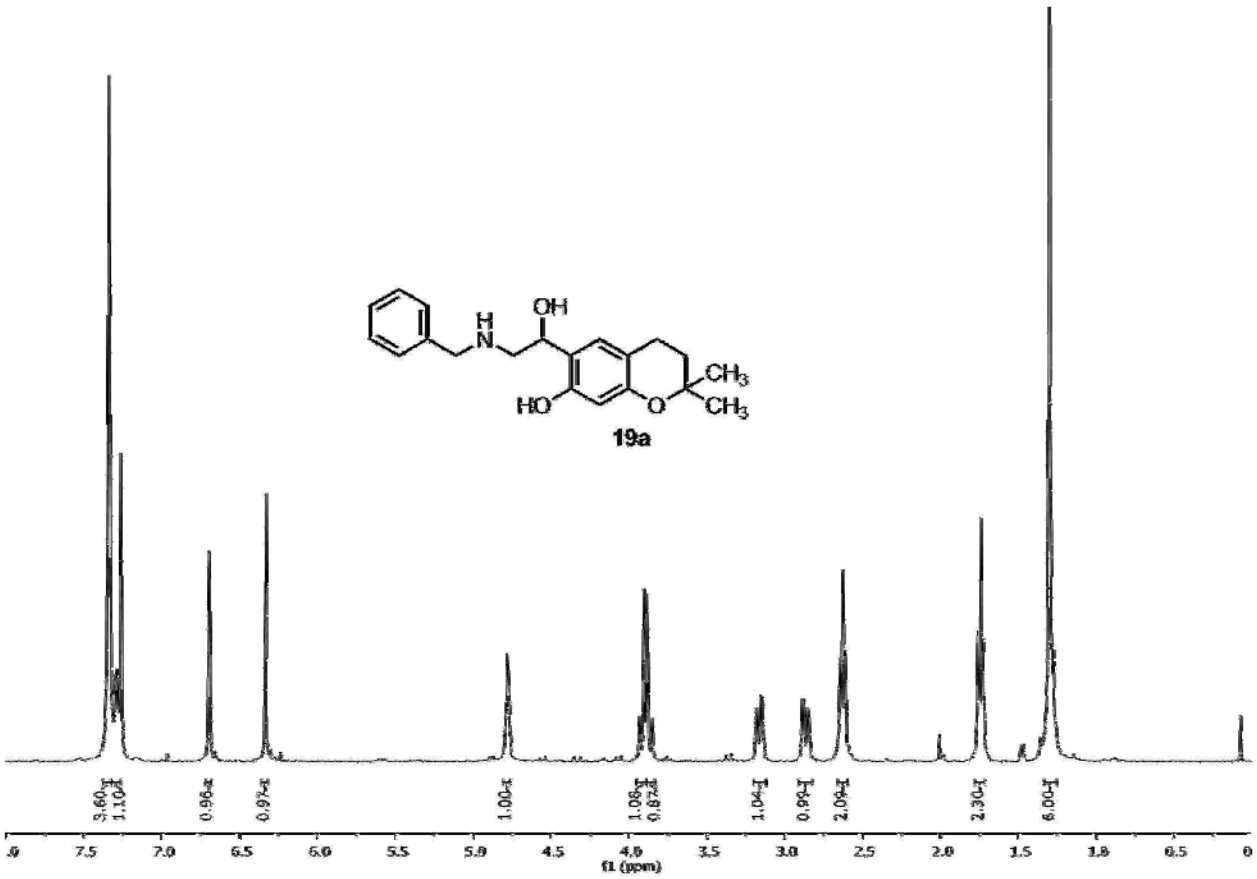
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **18**.



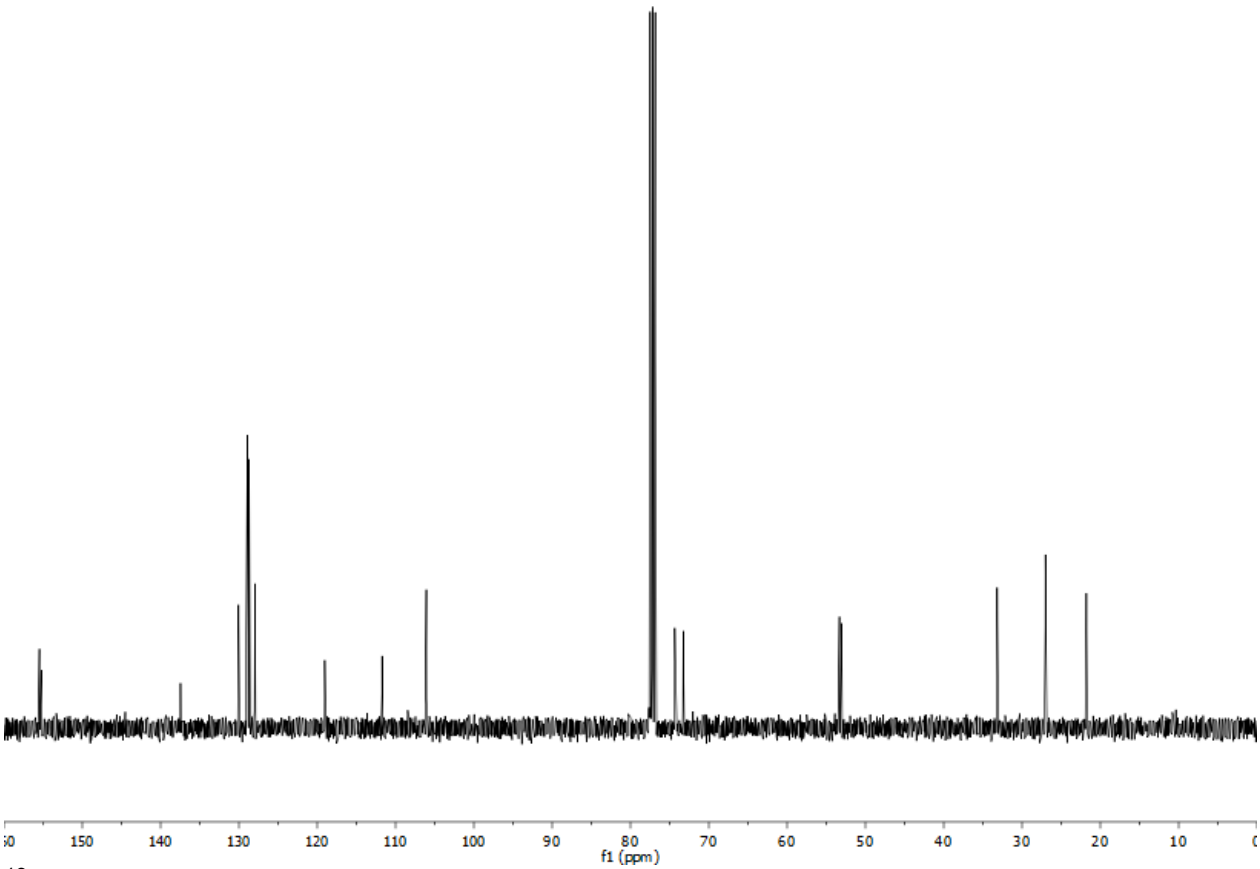
gHSQC-Spectrum ($CDCl_3$) of **18**.



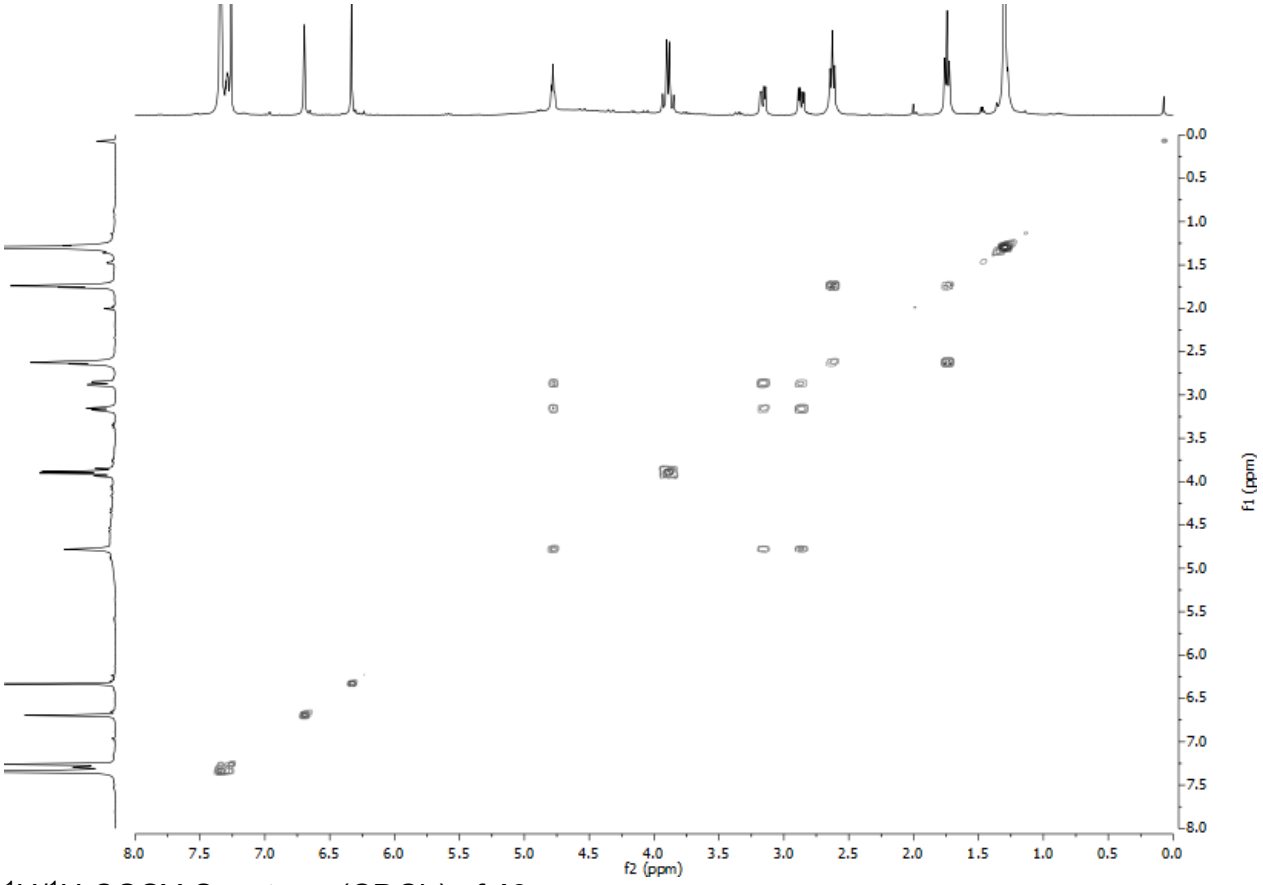
gHMBC-Spectrum ($CDCl_3$) of **18**.



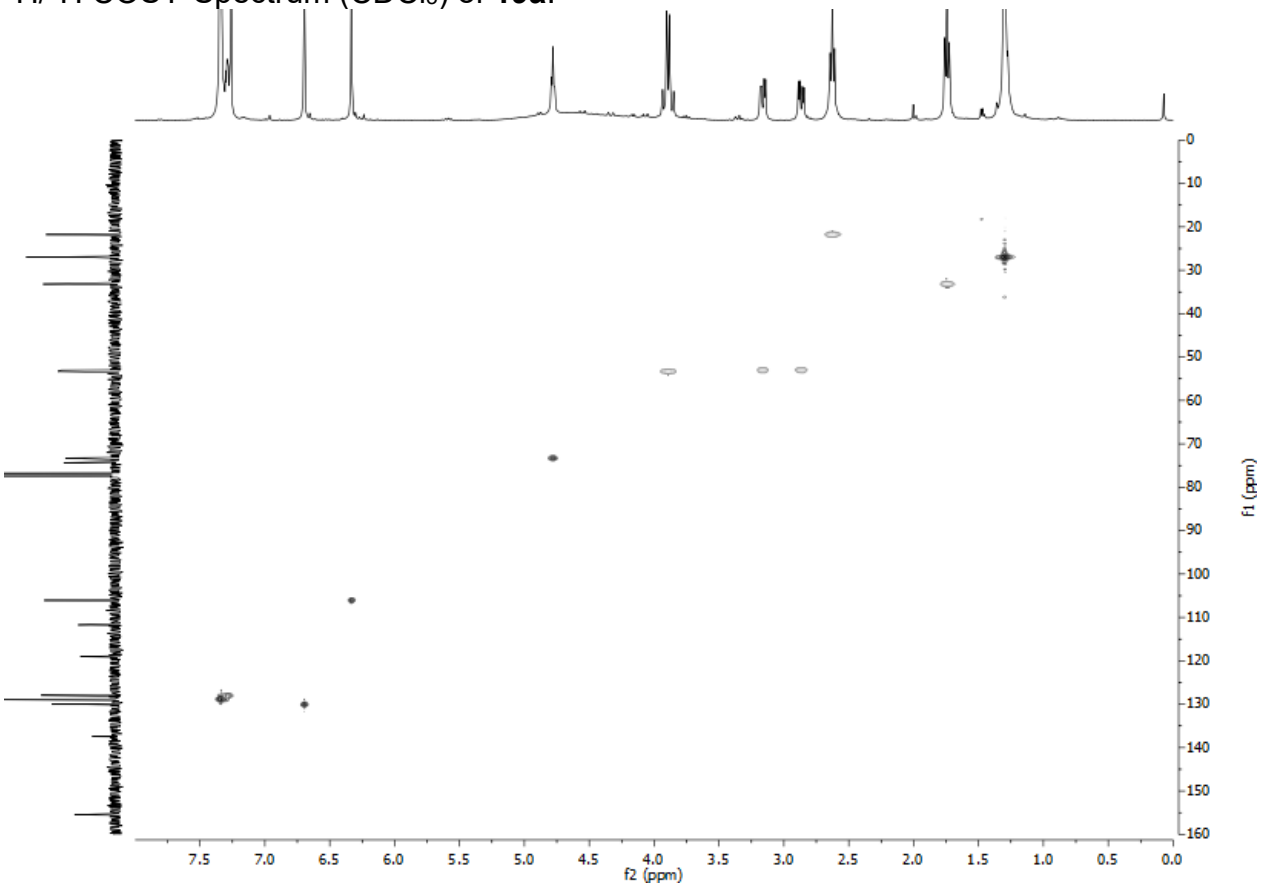
^{1}H NMR-Spectrum ($CDCl_3$) of **19a**.



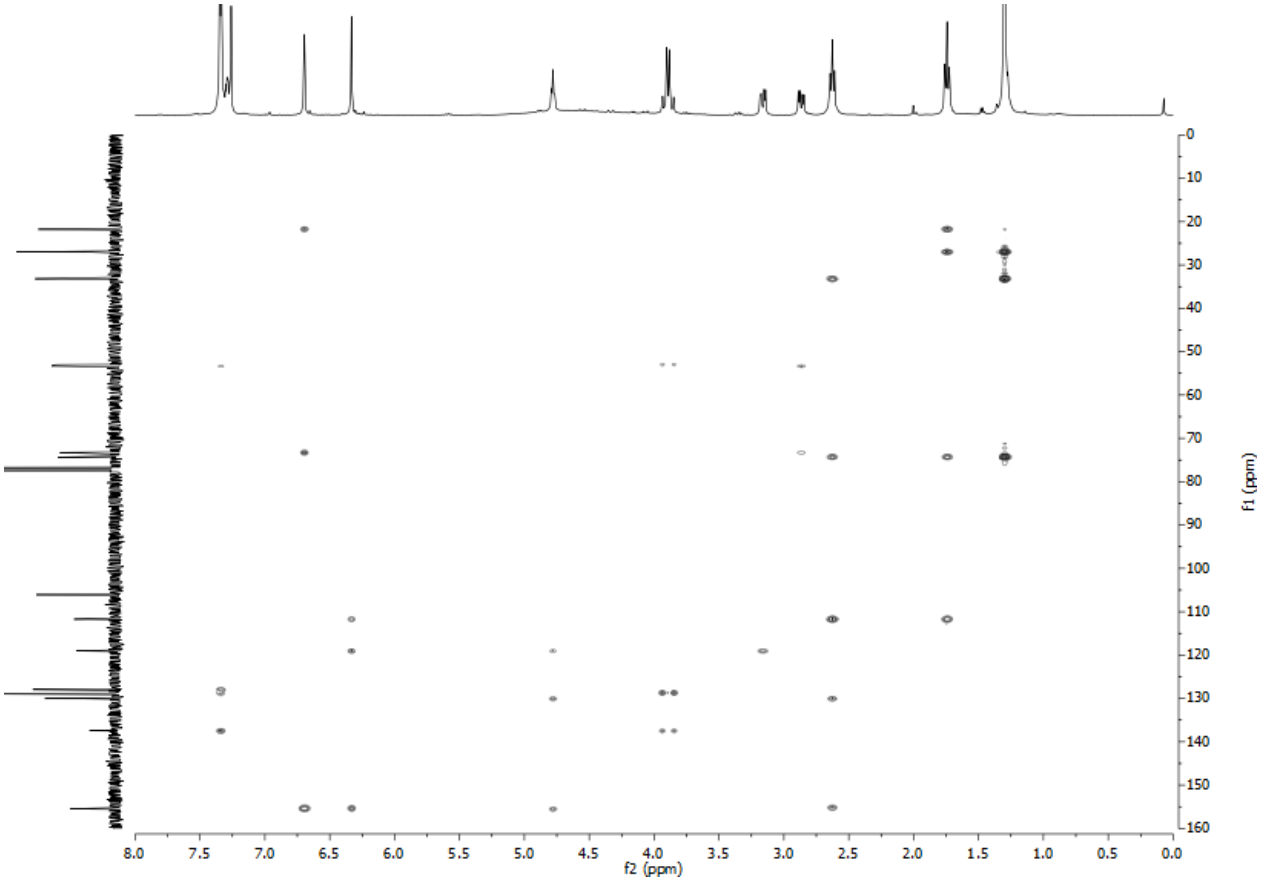
^{13}C NMR-Spectrum ($CDCl_3$) of **19a**.



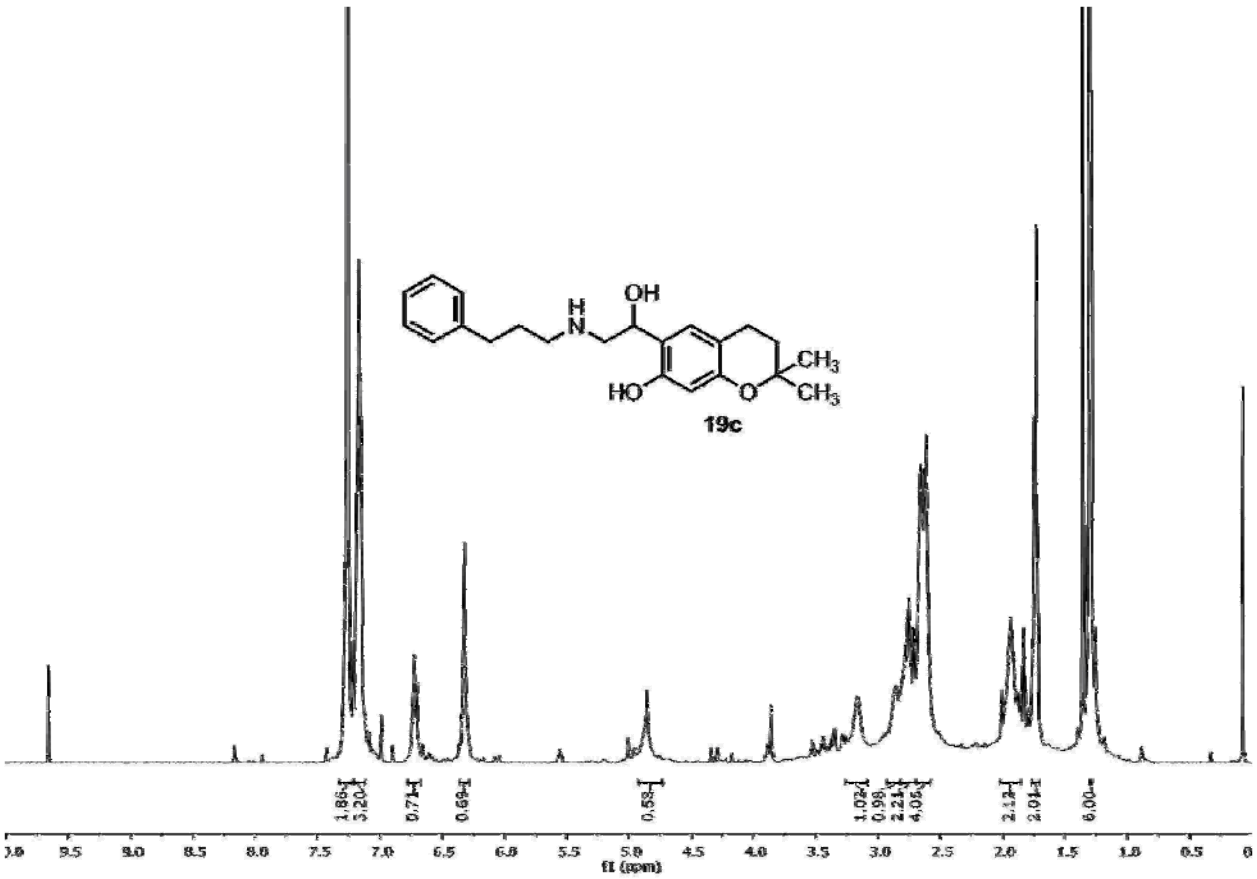
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **19a**.



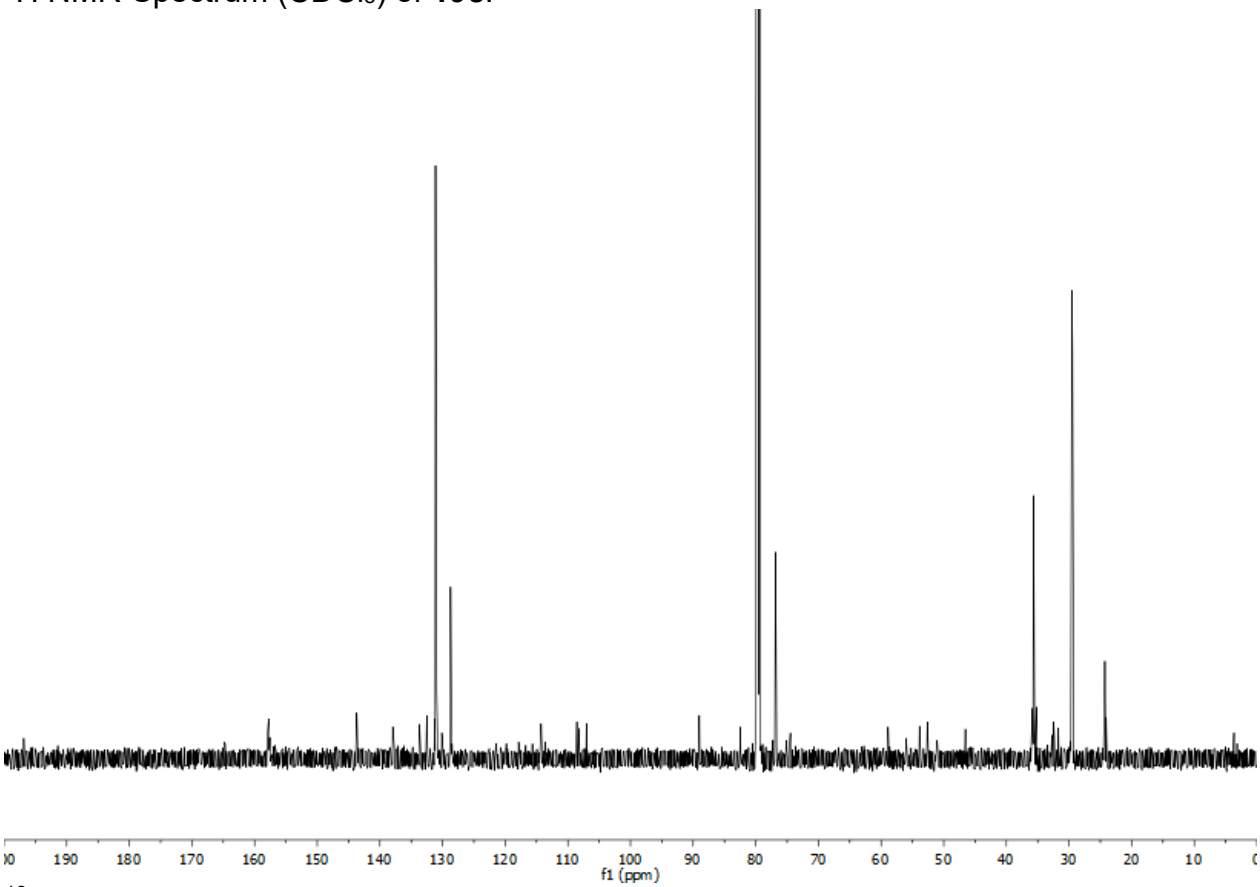
gHSQC-Spectrum ($CDCl_3$) of **19a**.



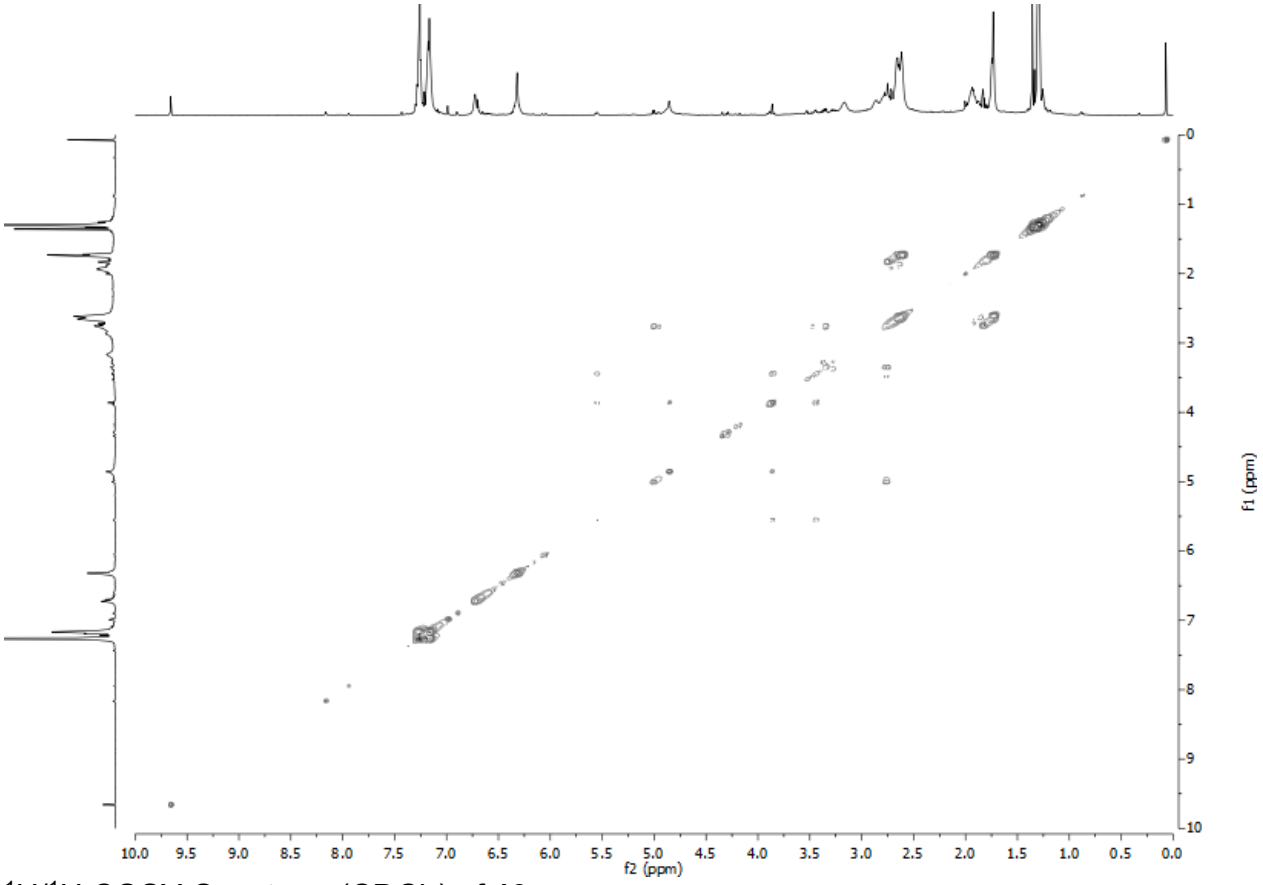
gHMBC-Spectrum ($CDCl_3$) of **19a**.



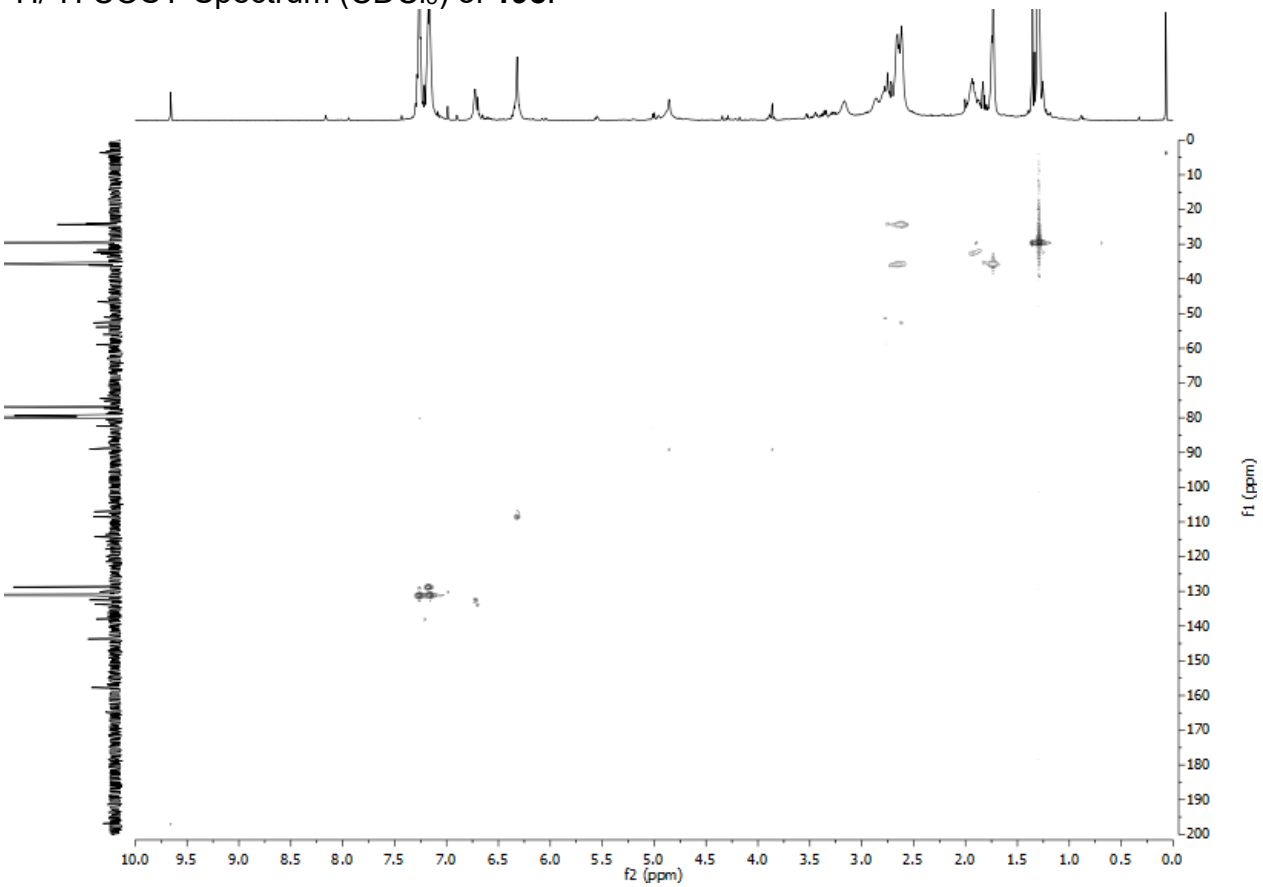
^{1}H NMR-Spectrum ($CDCl_3$) of **19c**.



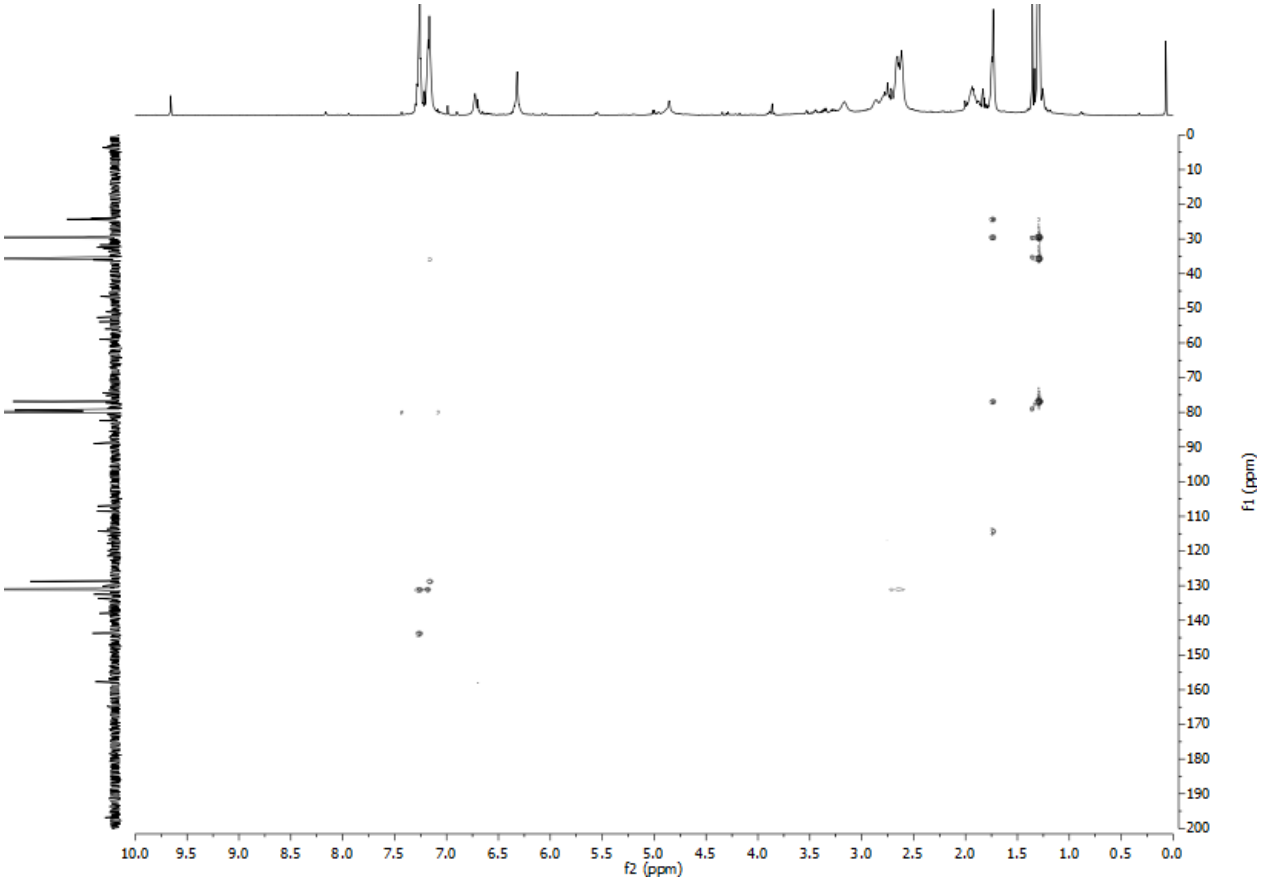
^{13}C NMR-Spectrum ($CDCl_3$) of **19c**.



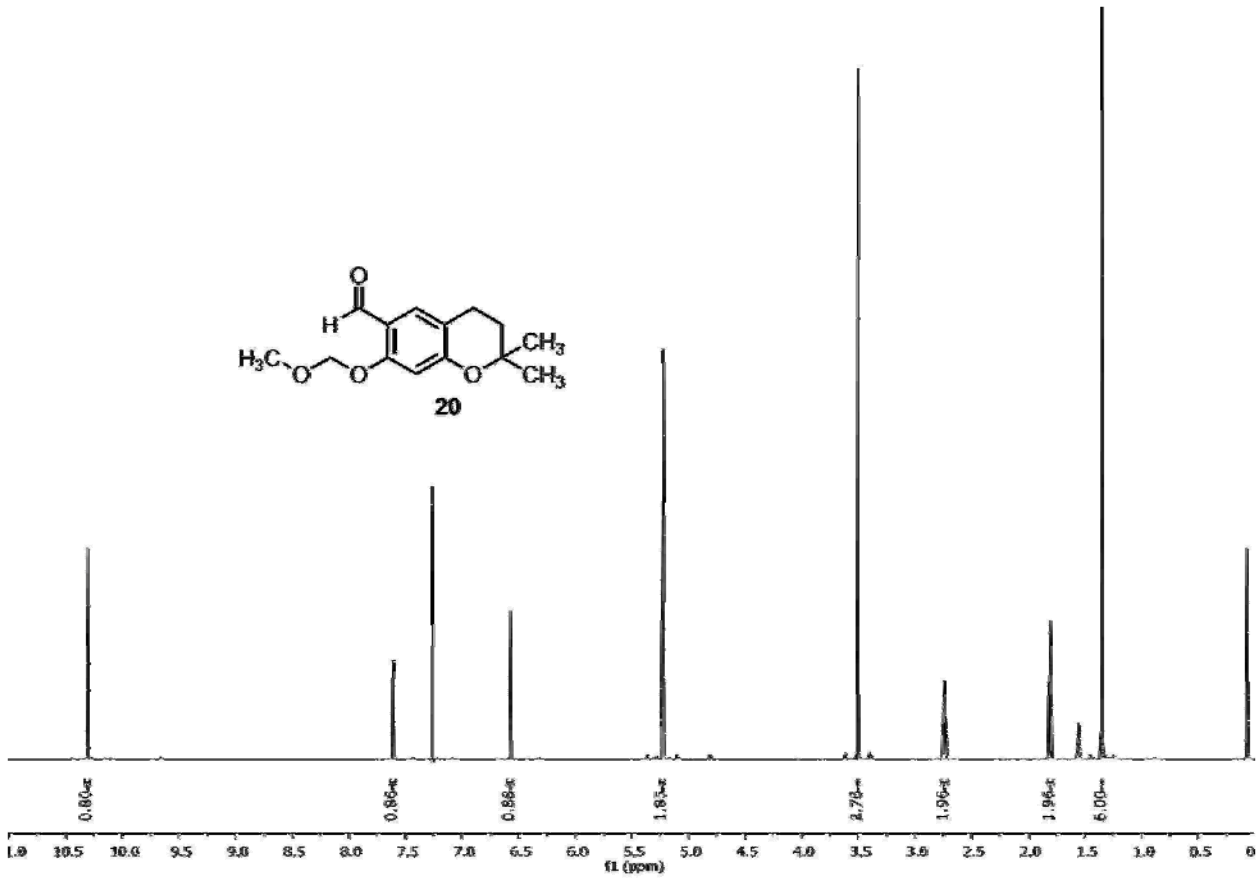
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **19c**.



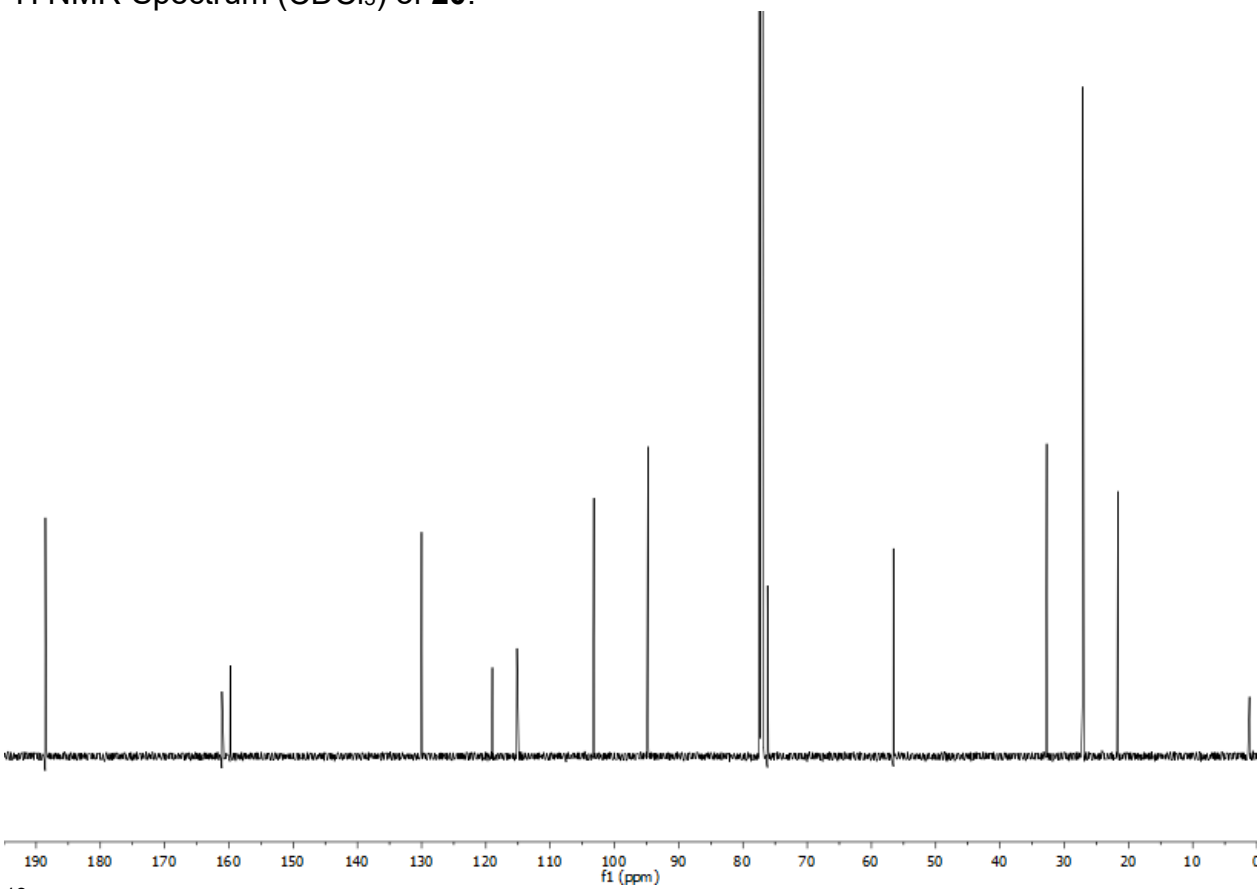
gHSQC-Spectrum ($CDCl_3$) of **19c**.



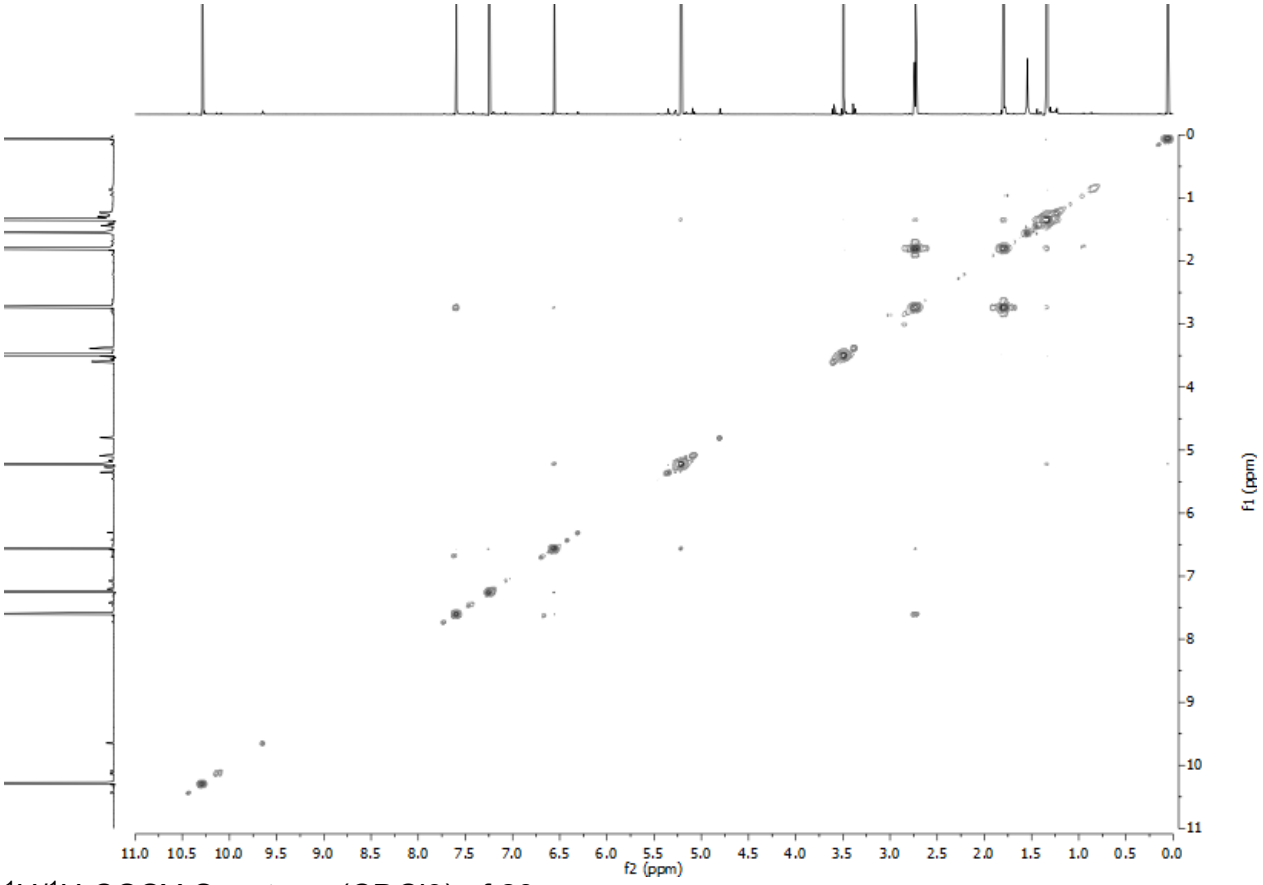
gHMBC-Spectrum ($CDCl_3$) of **19c**.



^{1}H NMR-Spectrum ($CDCl_3$) of **20**.



^{13}C NMR-Spectrum ($CDCl_3$) of **20**.



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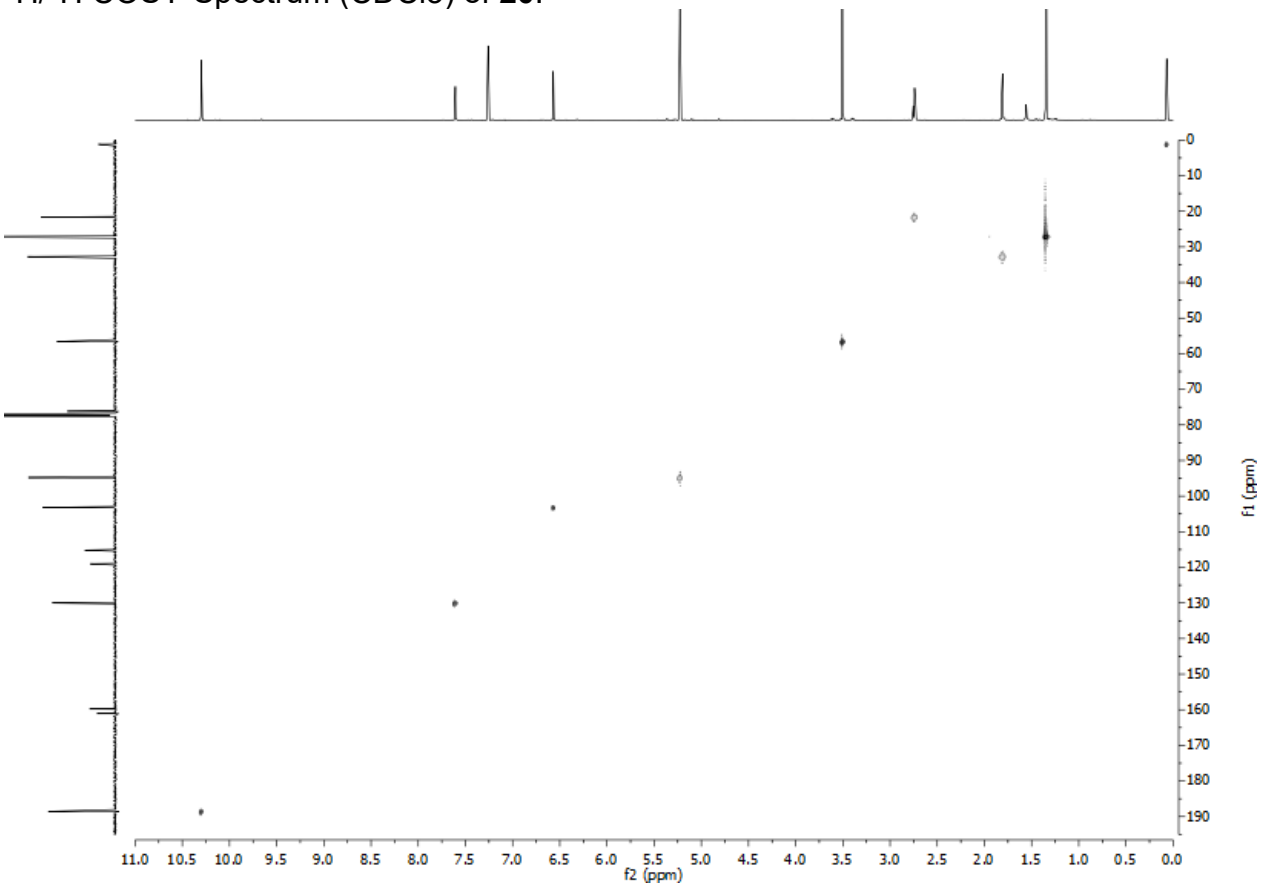
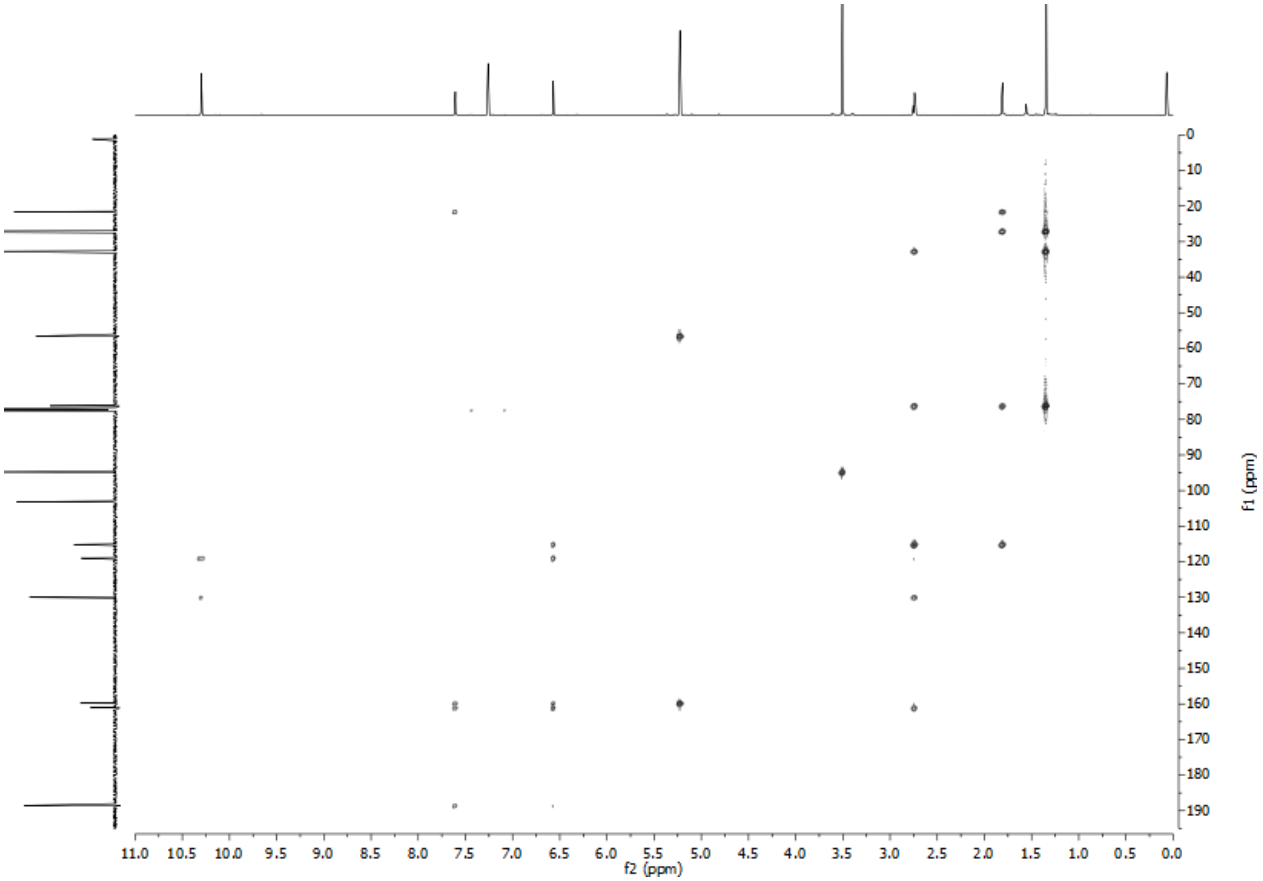
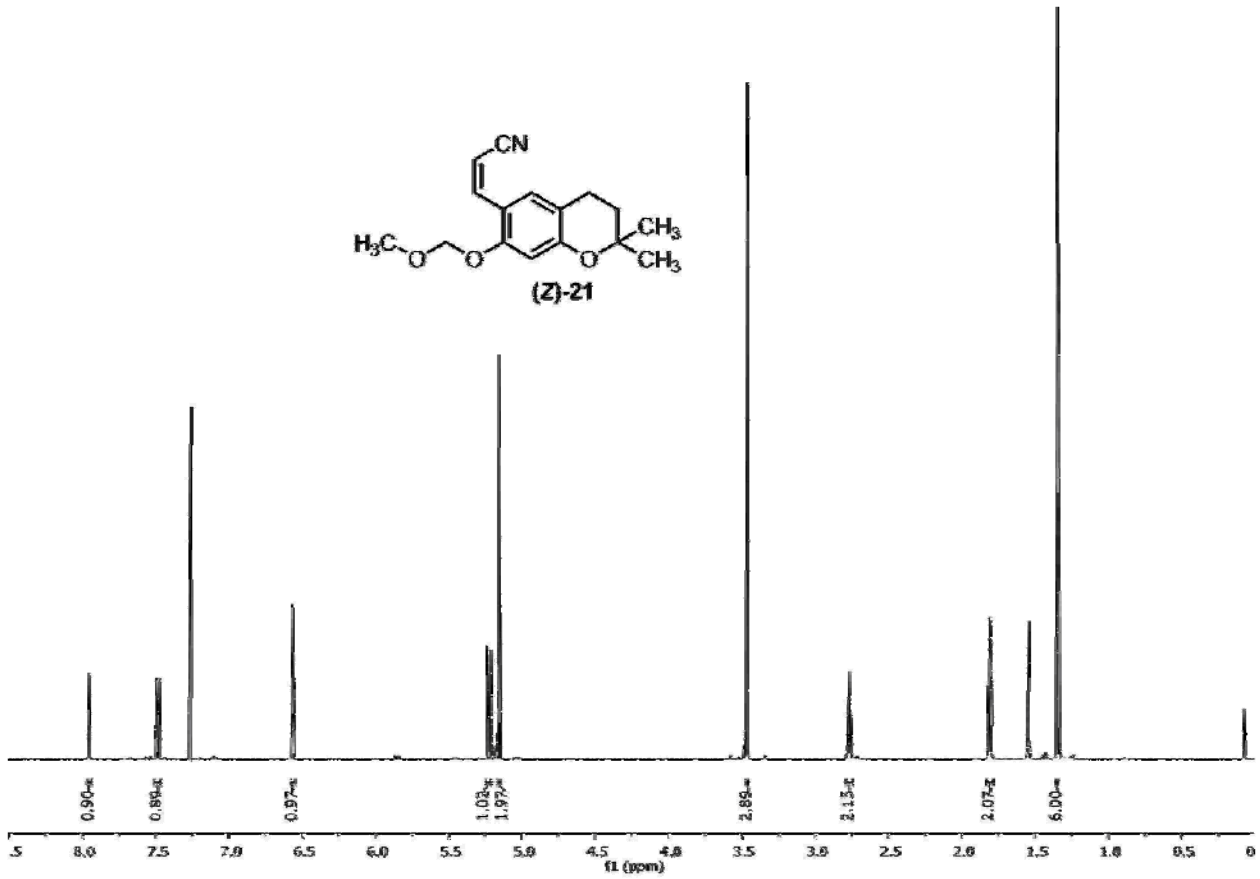


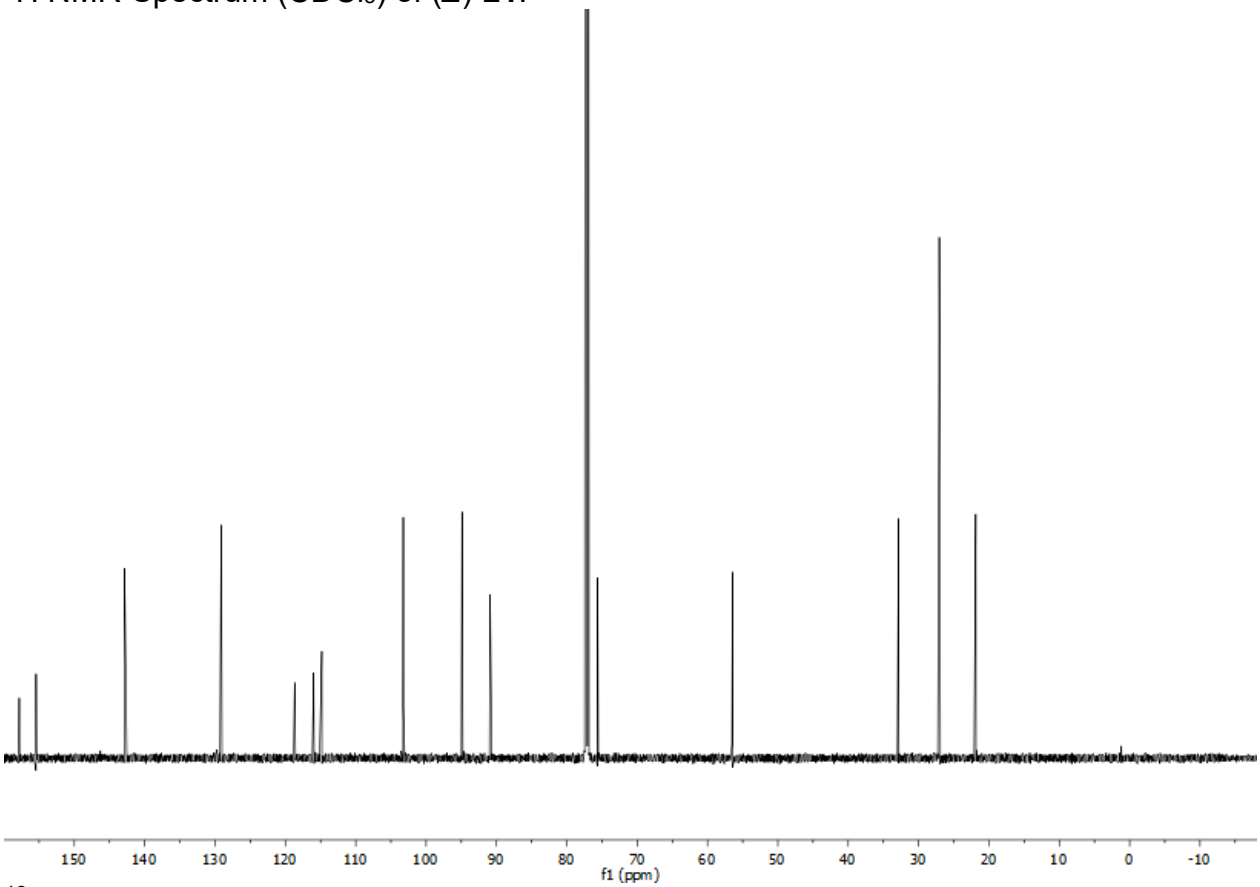
gHSQC-Spectrum ($CDCl_3$) of **20**.



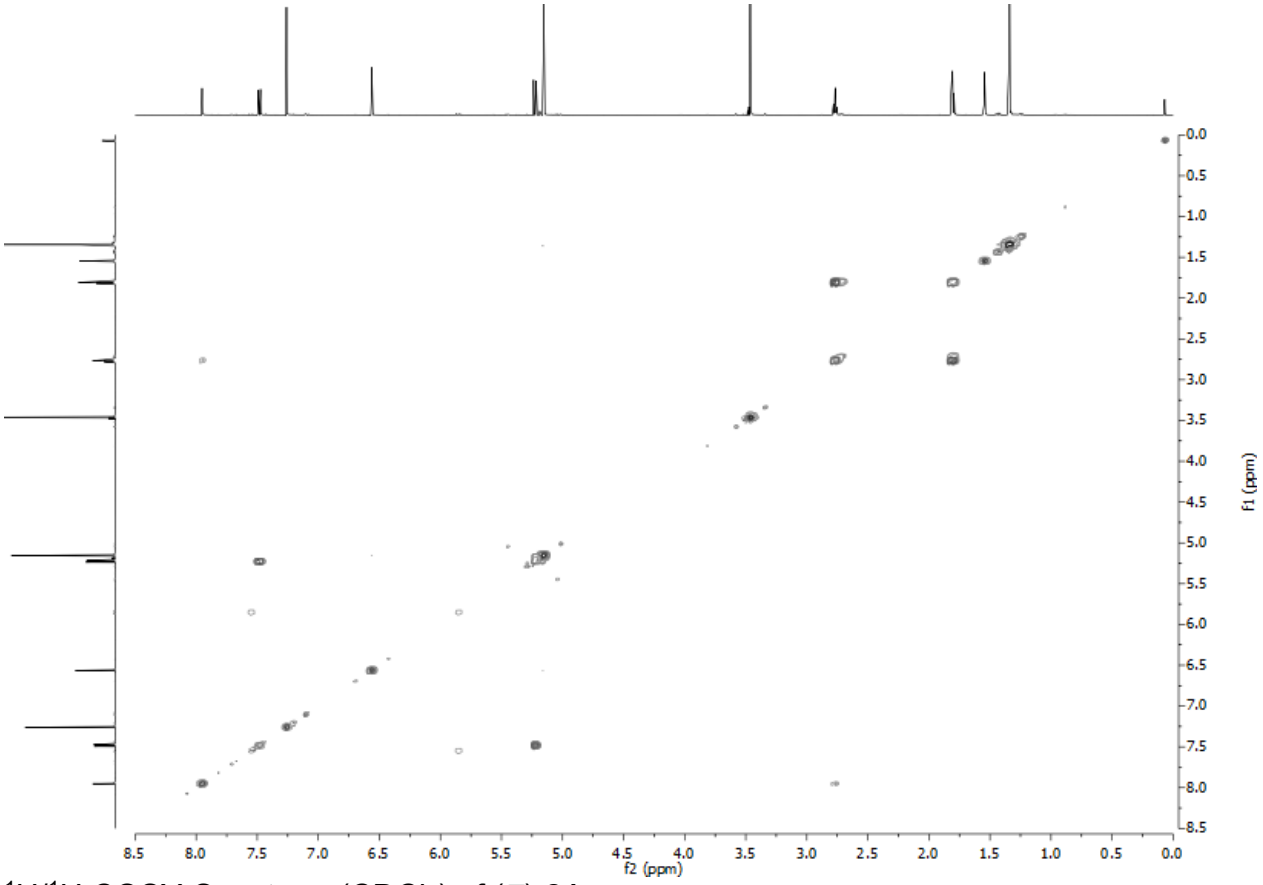
gHMBC-Spectrum ($CDCl_3$) of **20**.



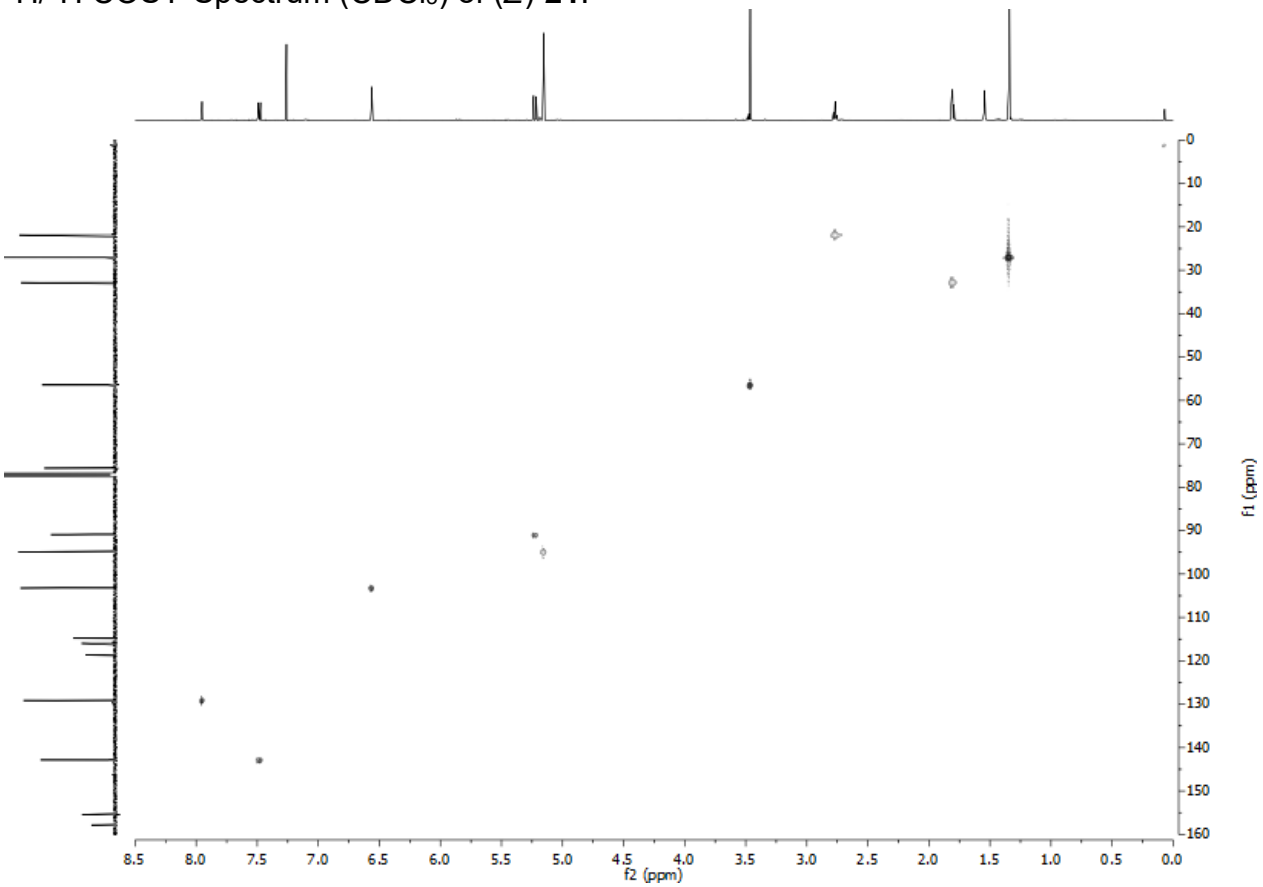
^{1}H NMR-Spectrum ($CDCl_3$) of (*Z*)-**21**.



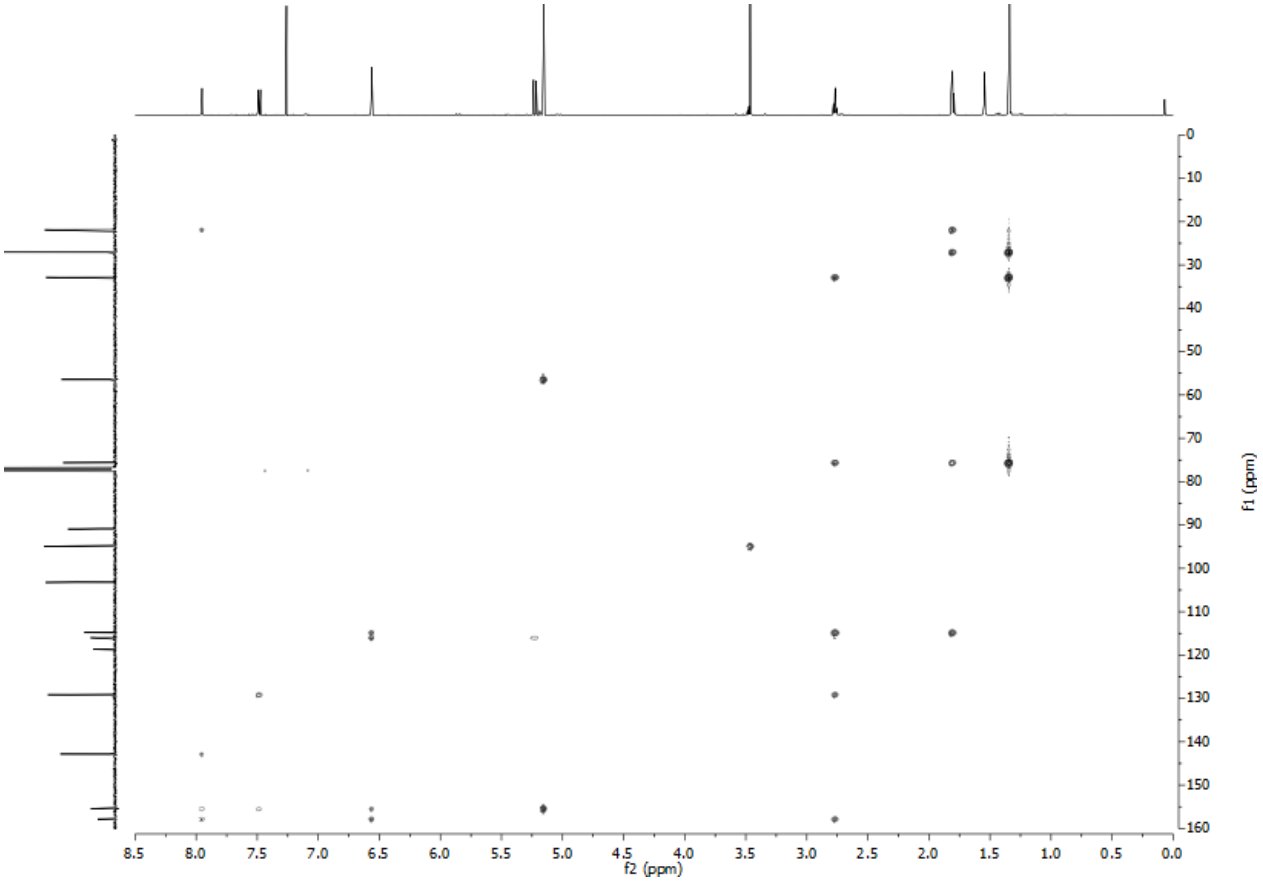
^{13}C NMR-Spectrum ($CDCl_3$) of (*Z*)-**21**.



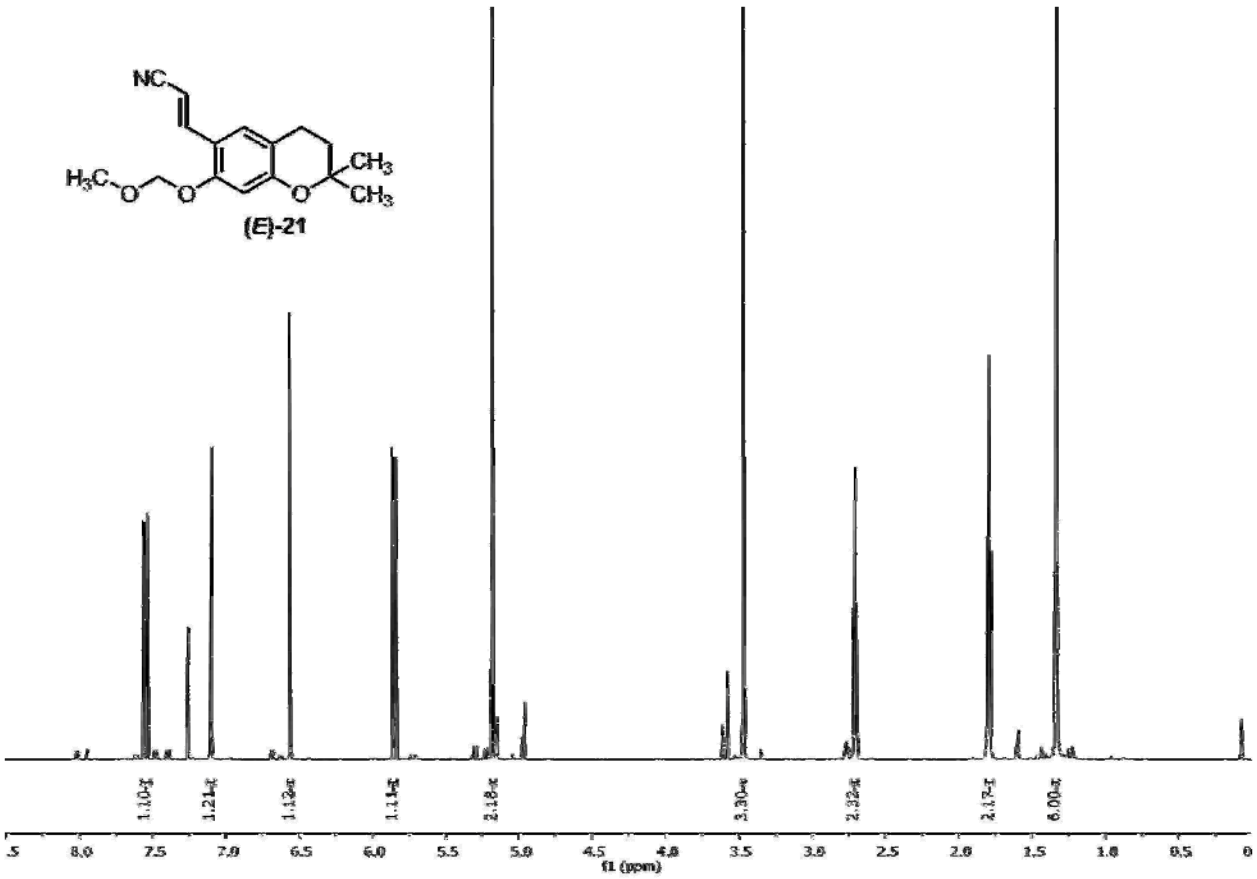
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of (*Z*)-**21**.



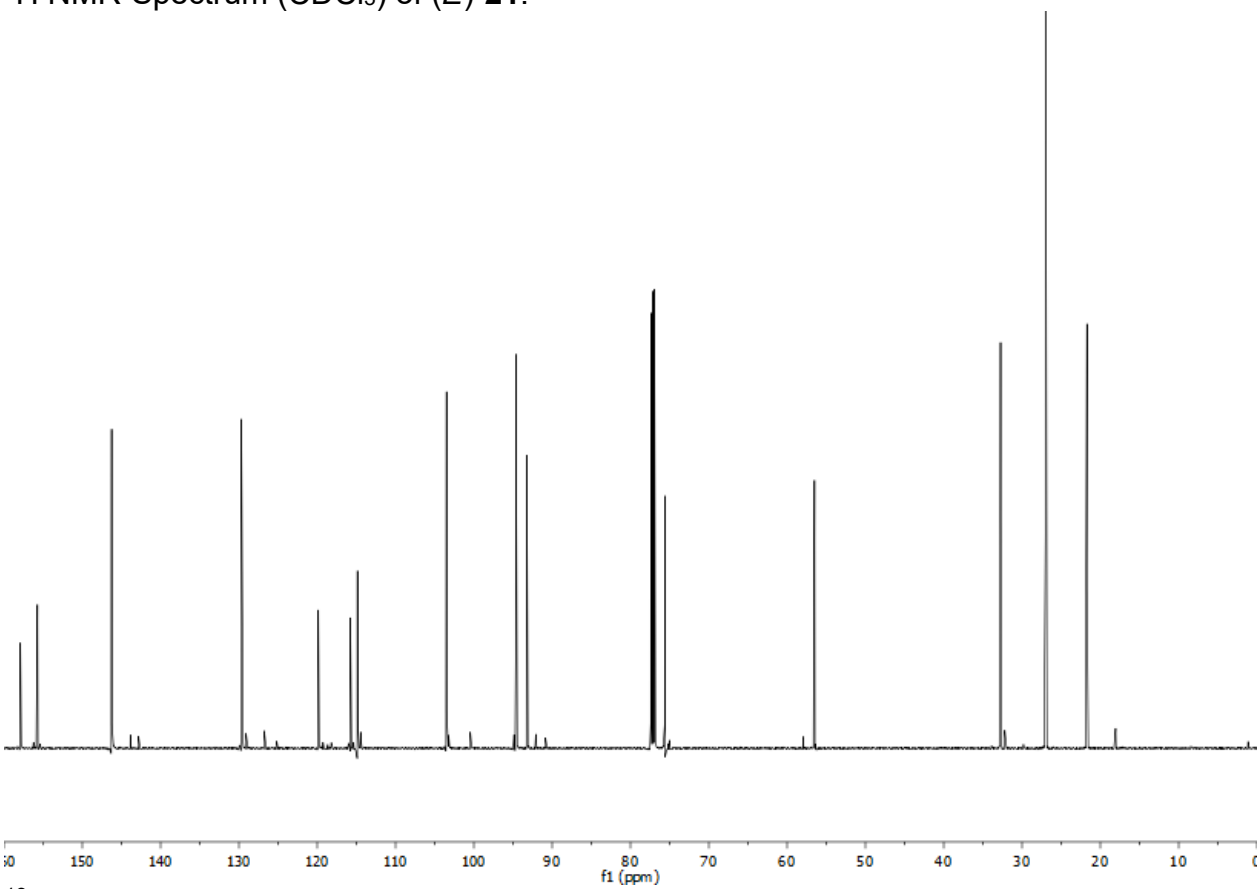
gHSQC-Spectrum ($CDCl_3$) of (*Z*)-**21**.



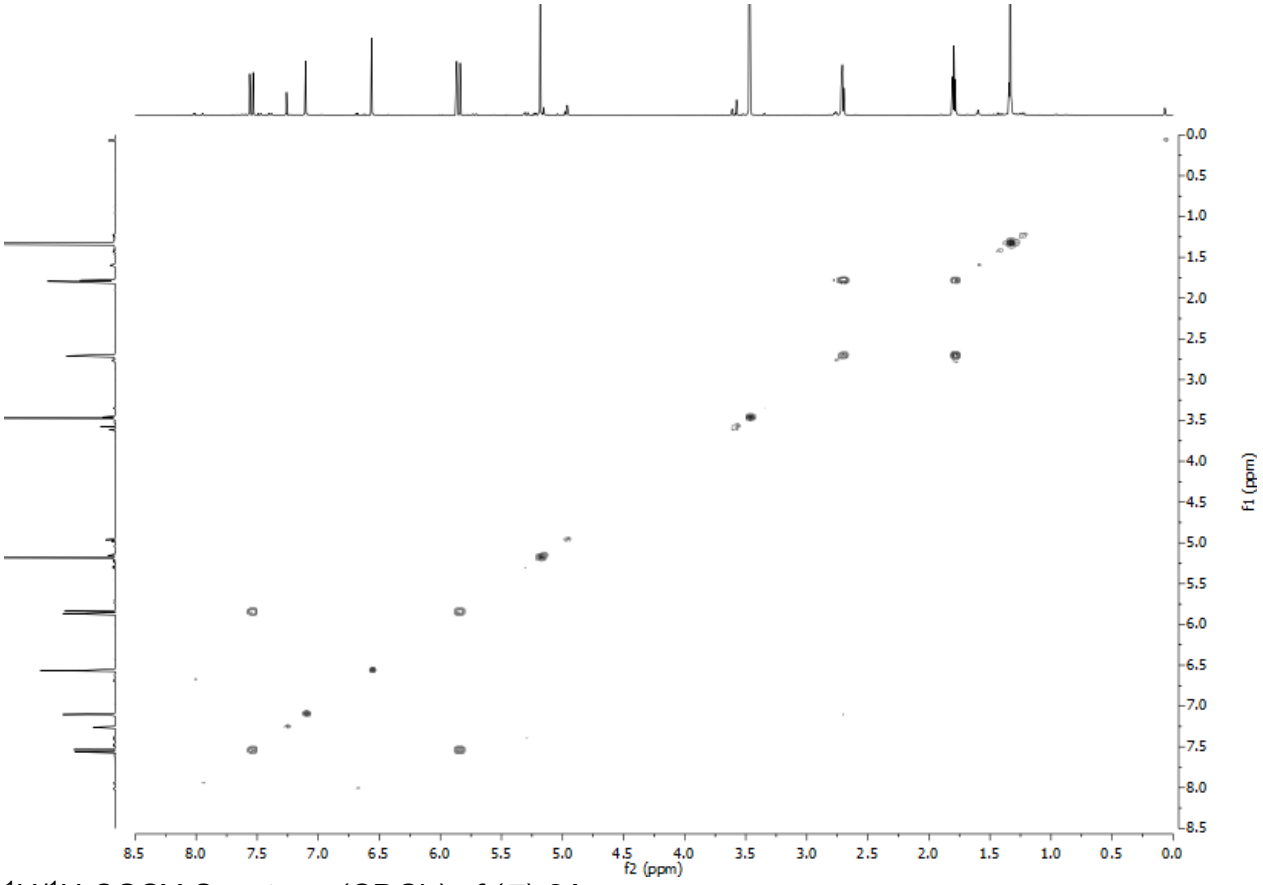
gHMBC-Spectrum ($CDCl_3$) of (*Z*)-**21**.



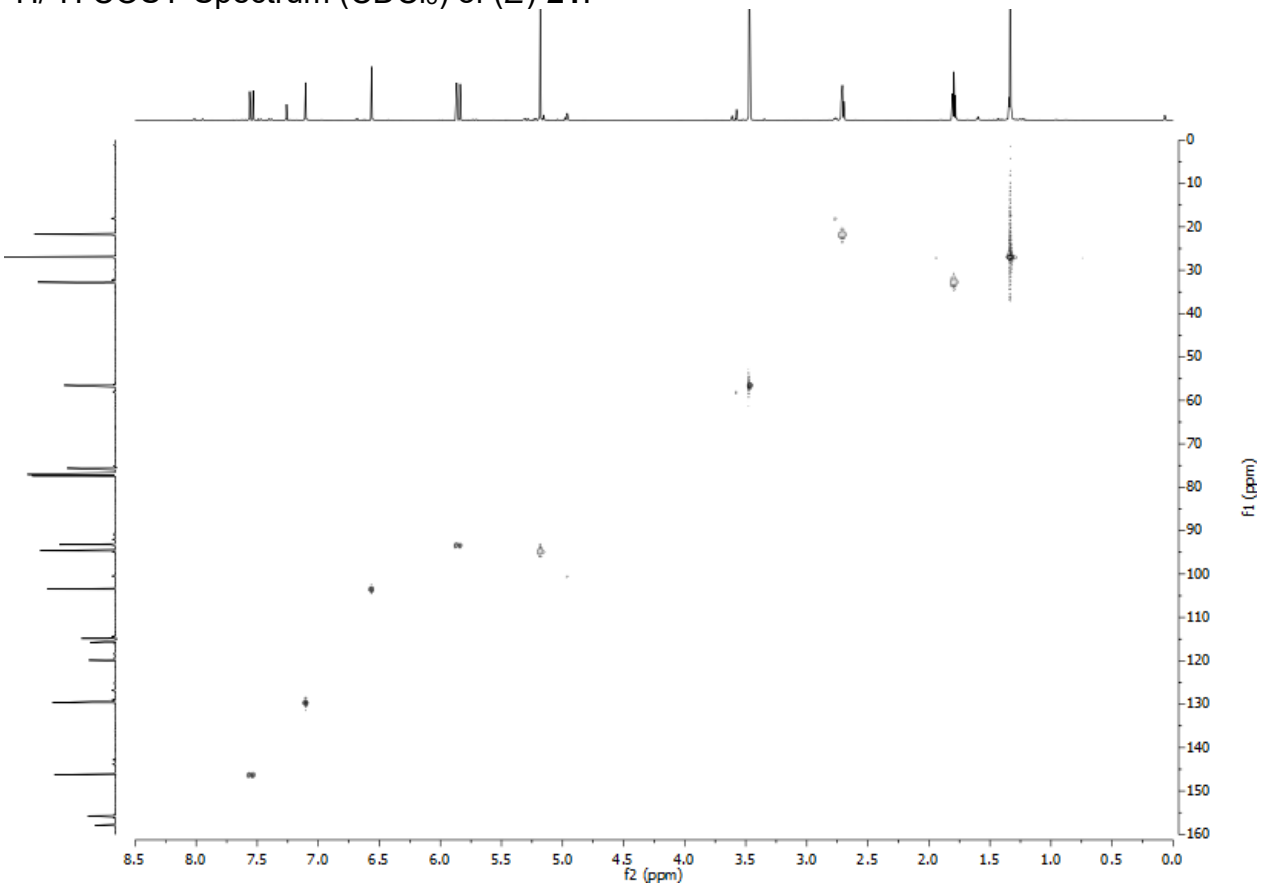
^{1}H NMR-Spectrum ($CDCl_3$) of (*E*)-**21**.



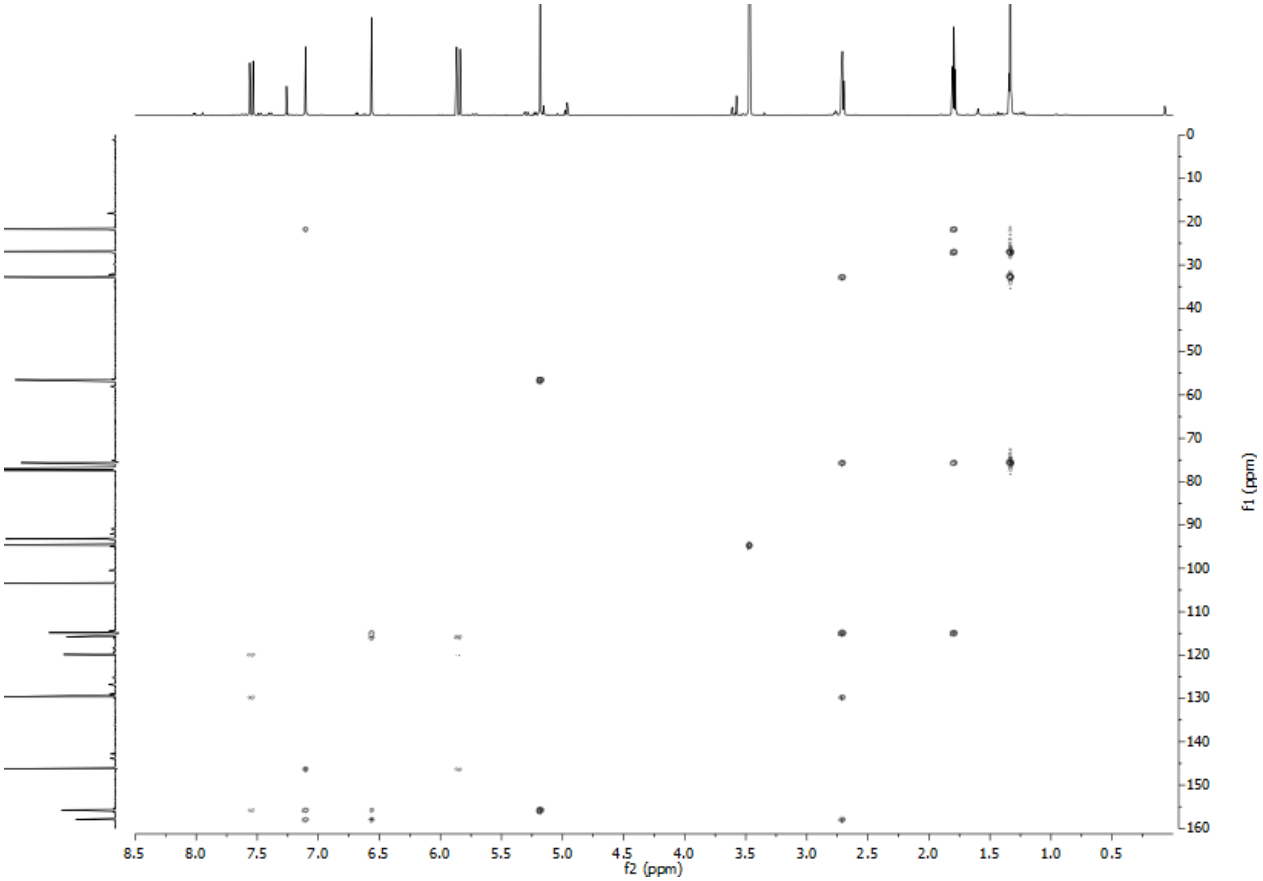
^{13}C NMR-Spectrum ($CDCl_3$) of (*E*)-**21**.



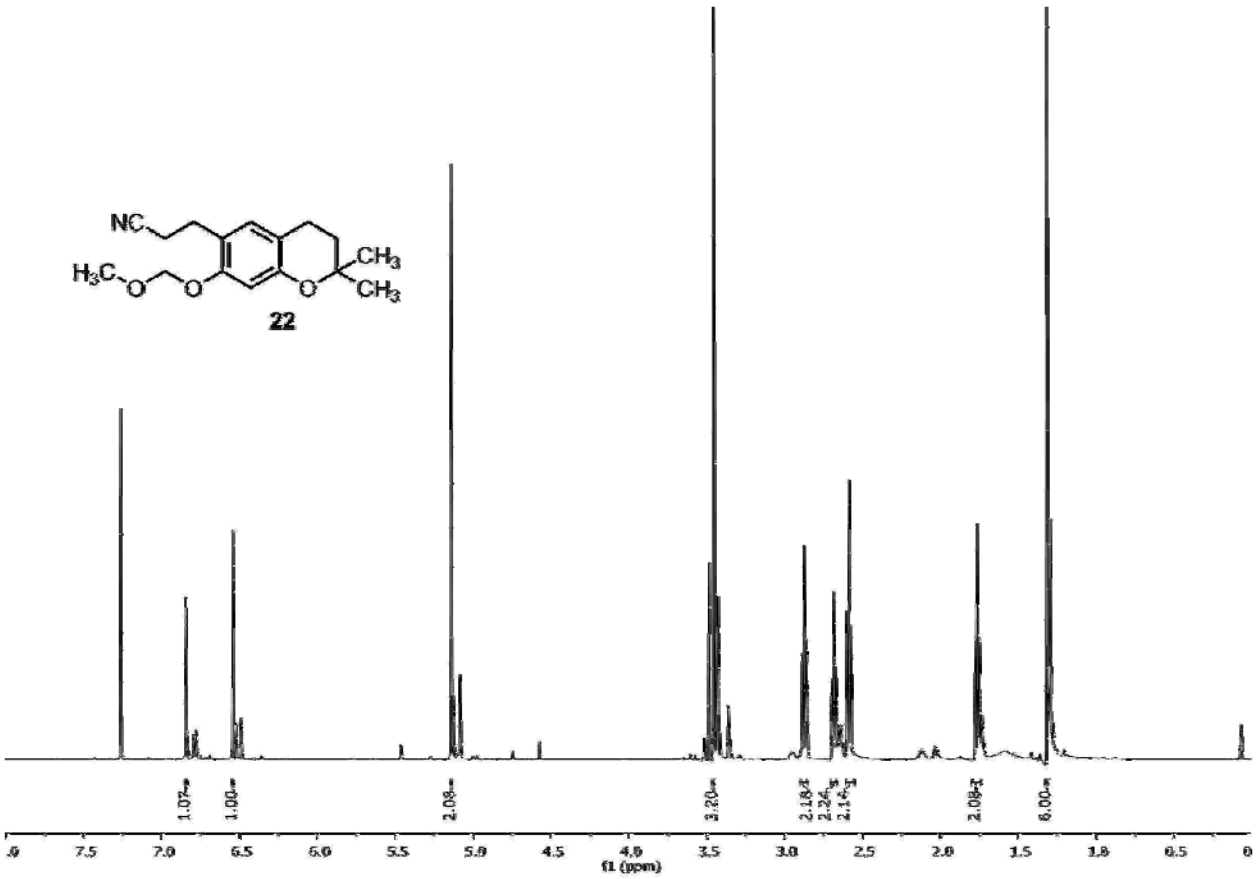
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of (*E*)-**21**.



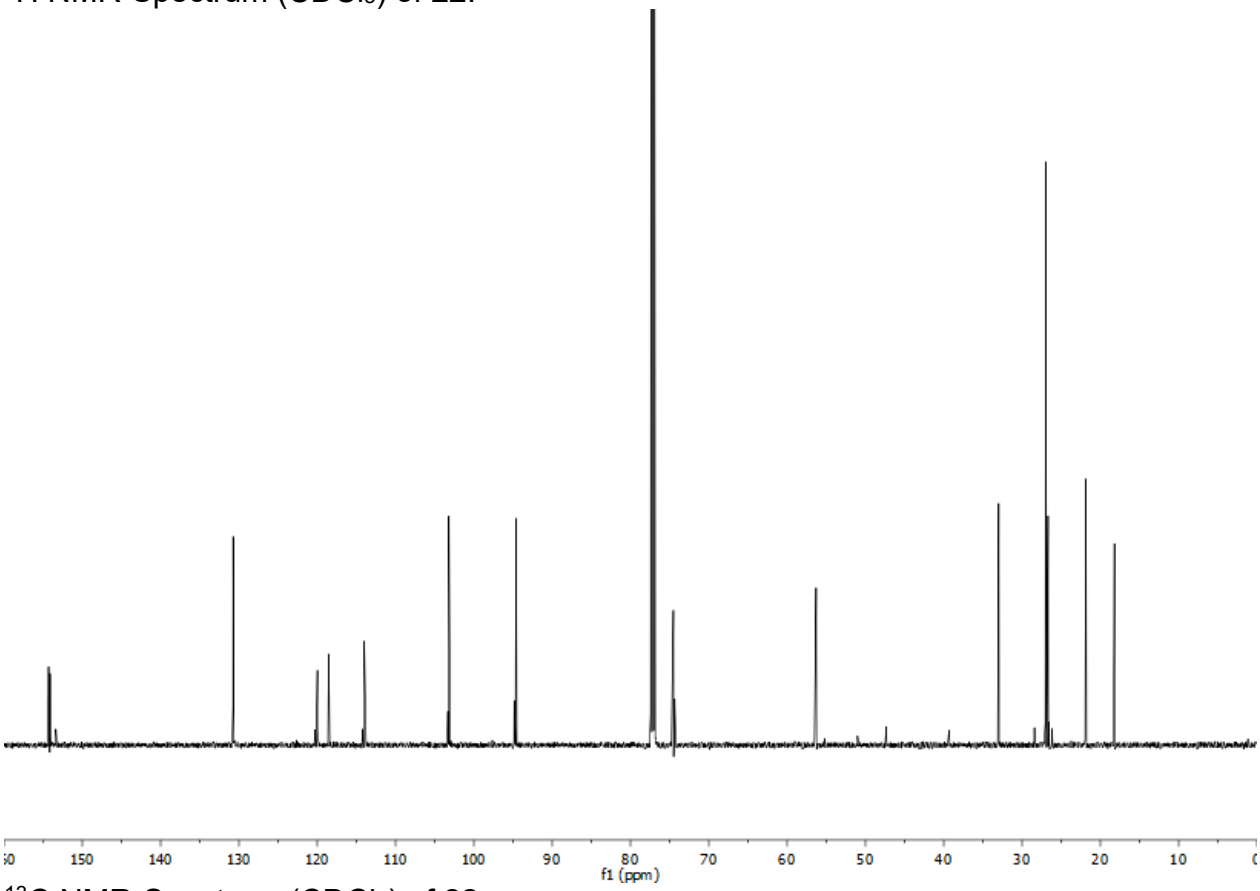
gHSQC-Spectrum ($CDCl_3$) of (*E*)-**21**.



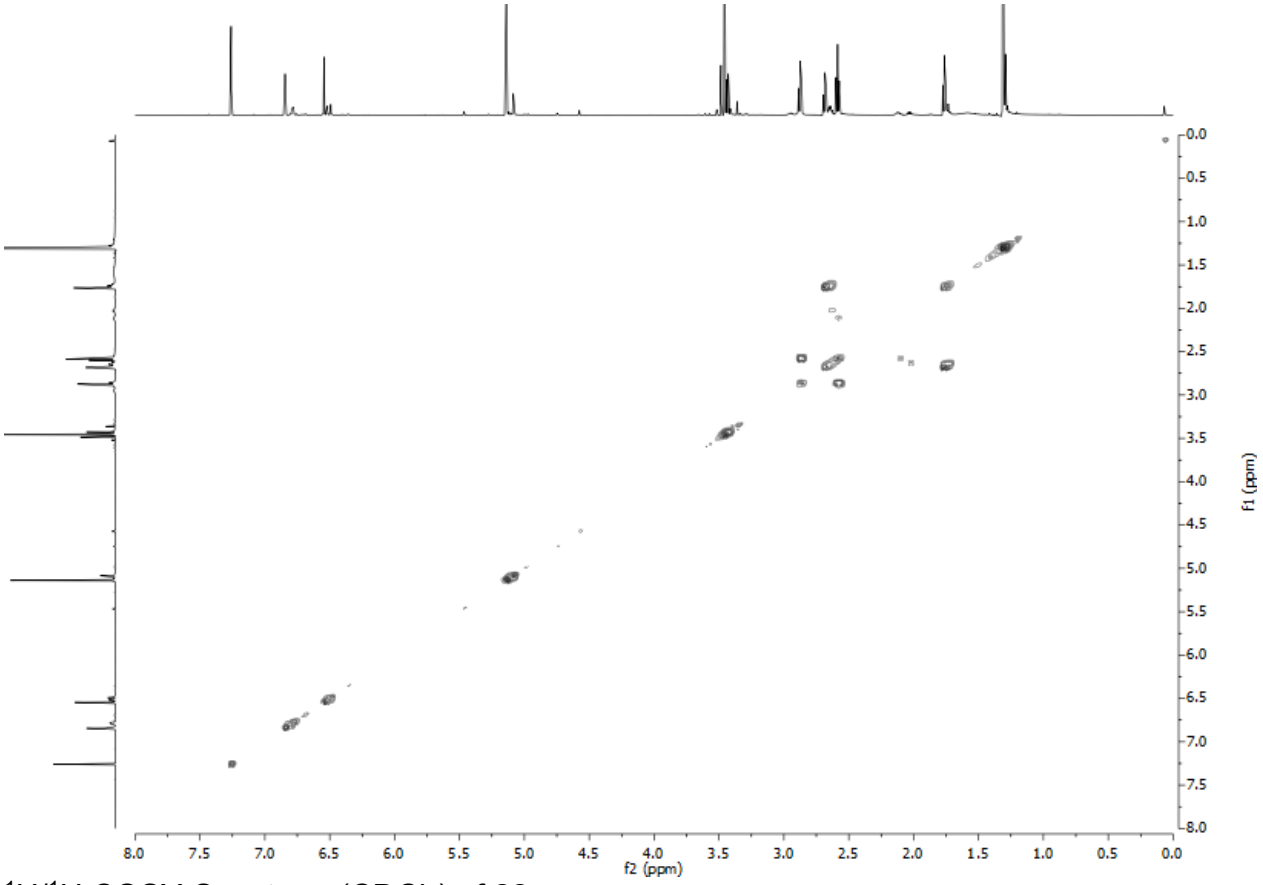
gHMBC-Spectrum ($CDCl_3$) of (*E*)-**21**.



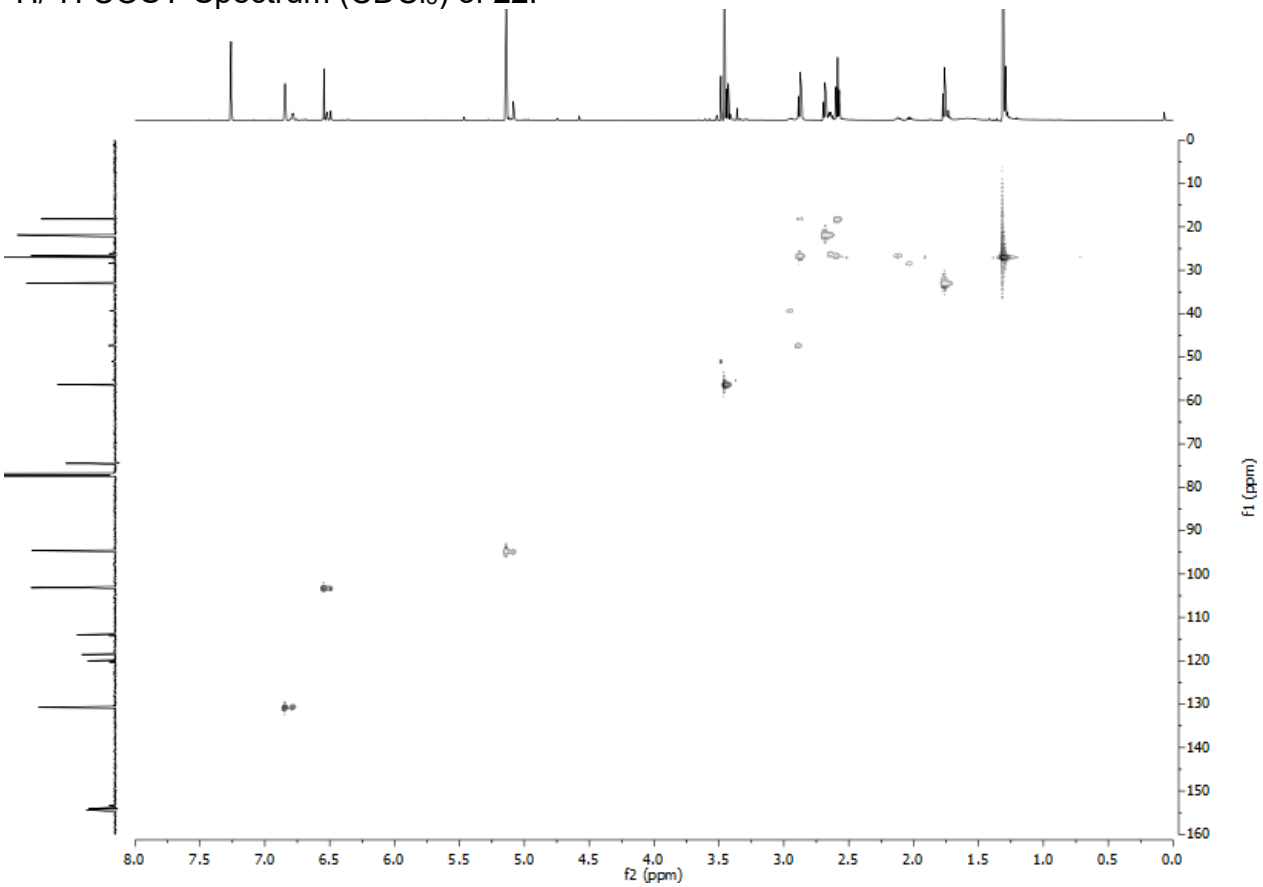
^{1}H NMR-Spectrum ($CDCl_3$) of **22**.



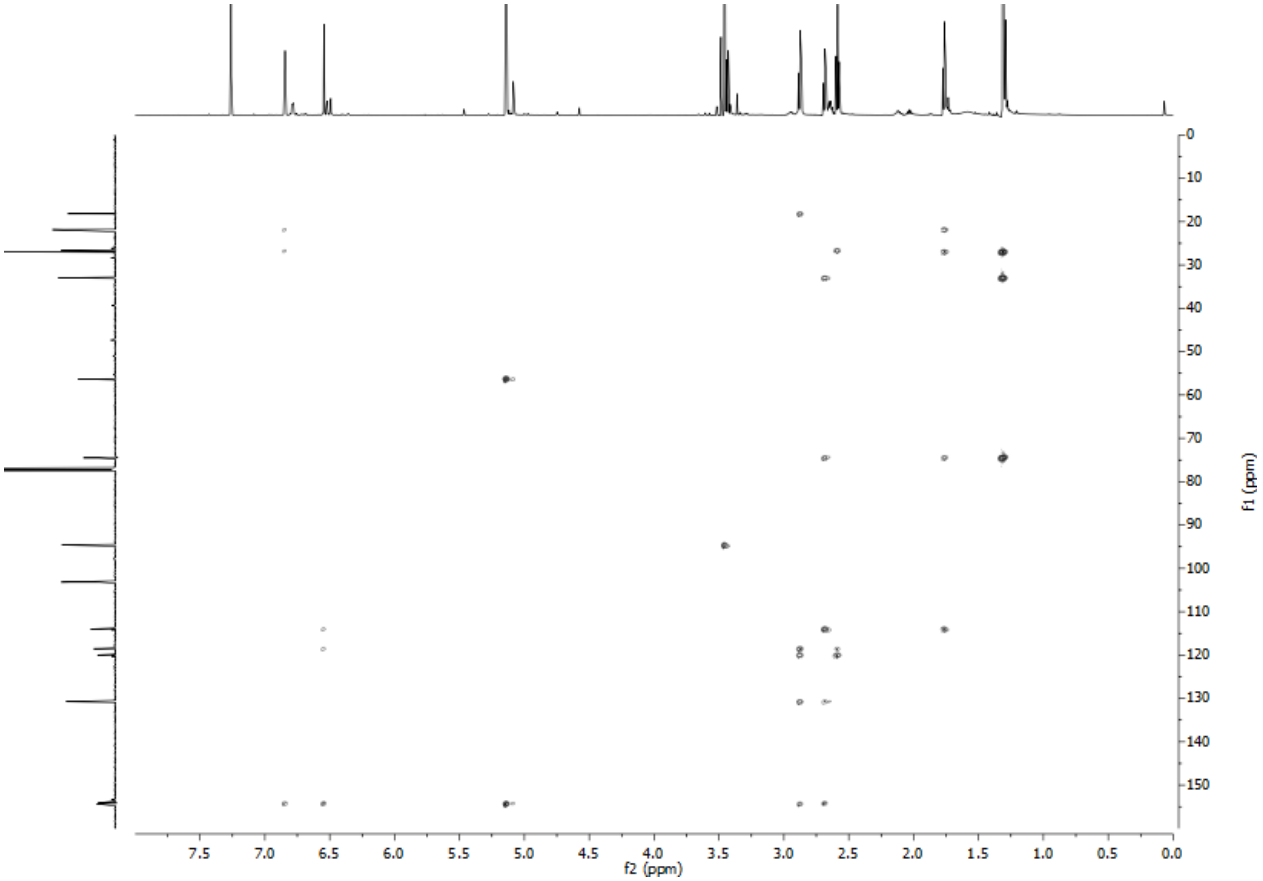
^{13}C NMR-Spectrum ($CDCl_3$) of **22**.



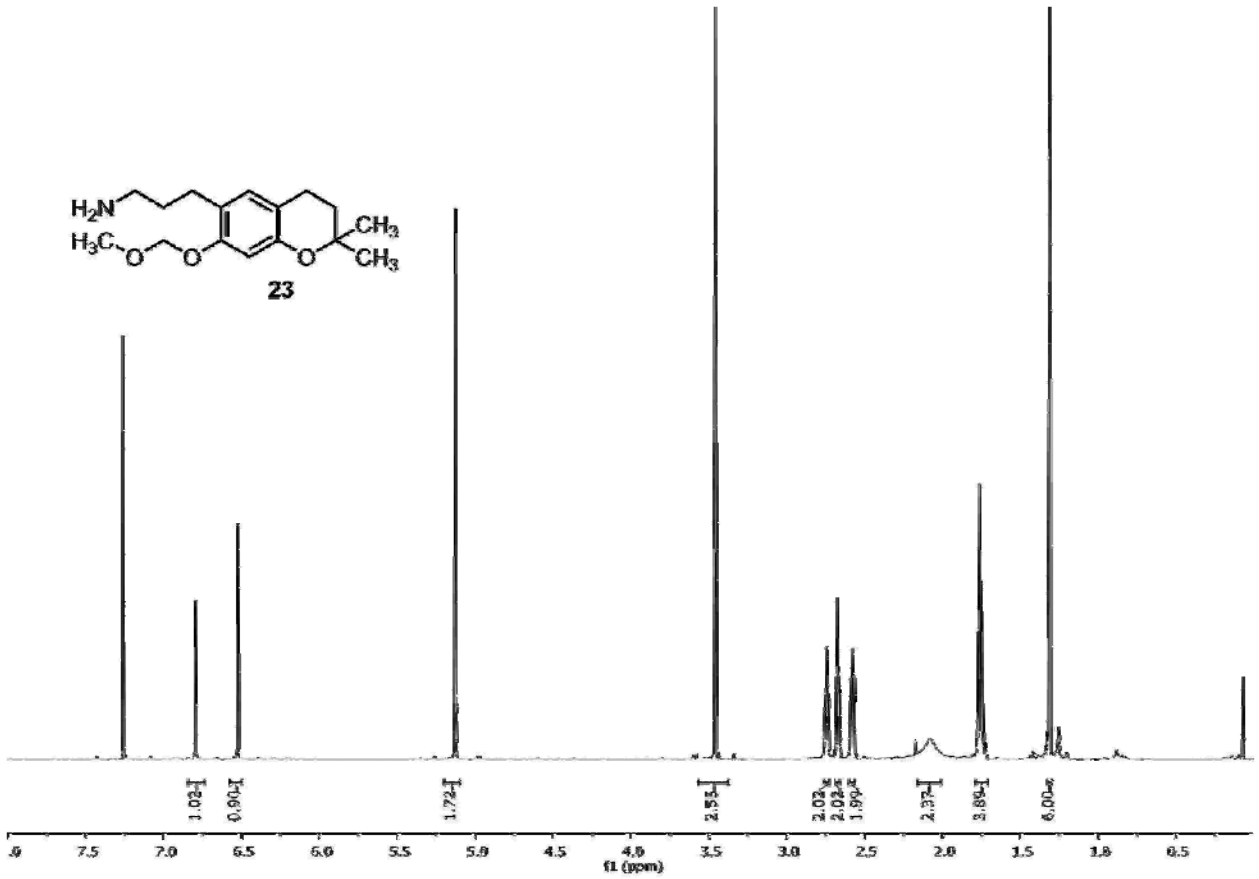
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **22**.



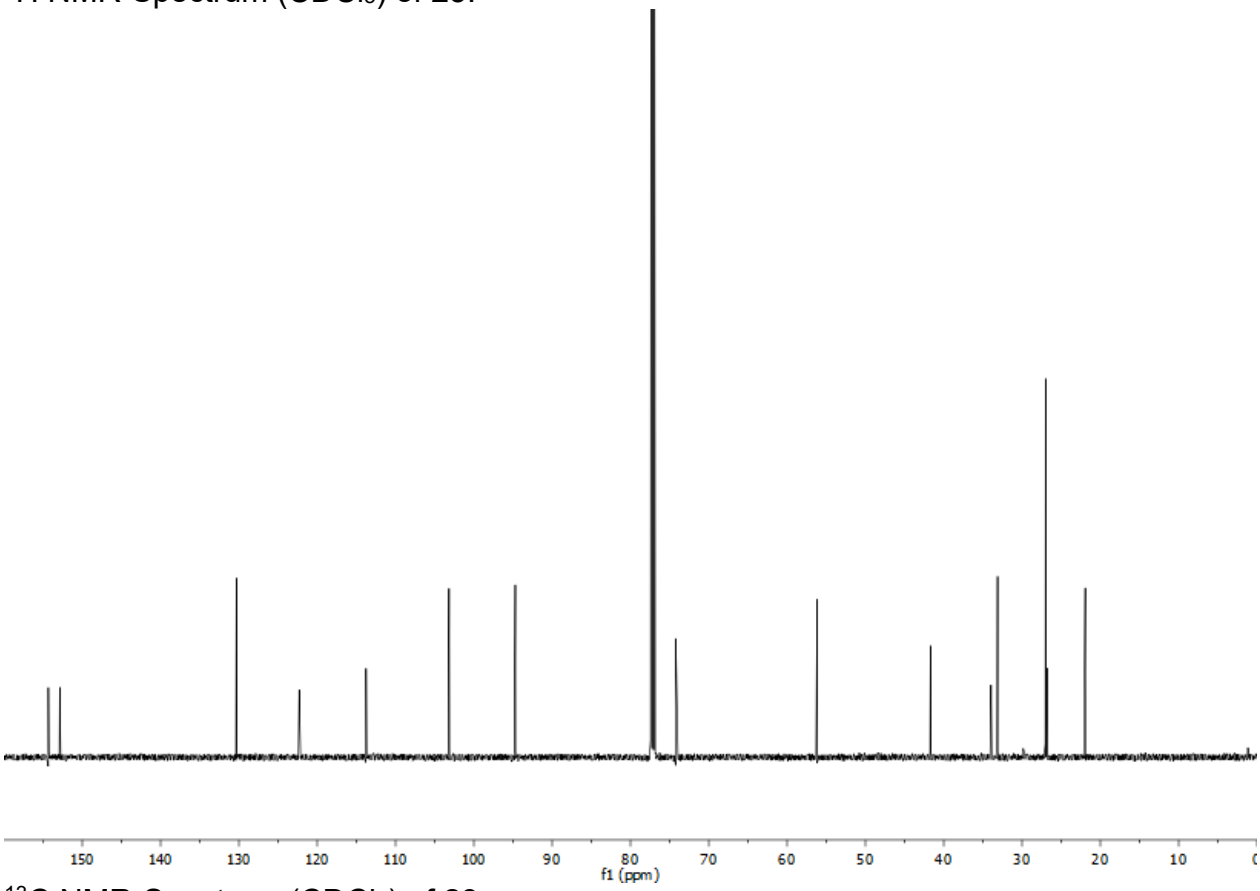
gHSQC-Spectrum ($CDCl_3$) of **22**.



gHMBC-Spectrum ($CDCl_3$) of **22**.



^{1}H NMR-Spectrum ($CDCl_3$) of **23**.



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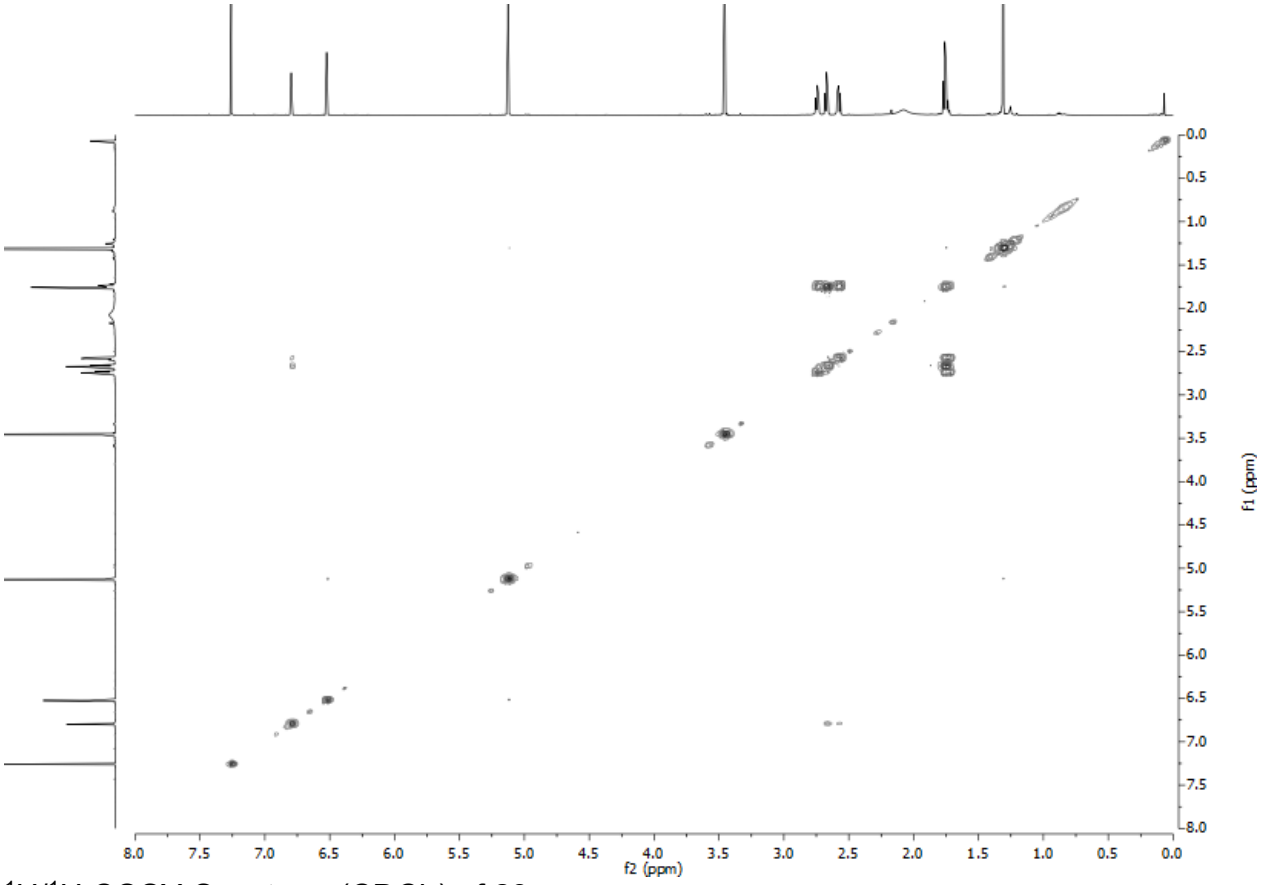
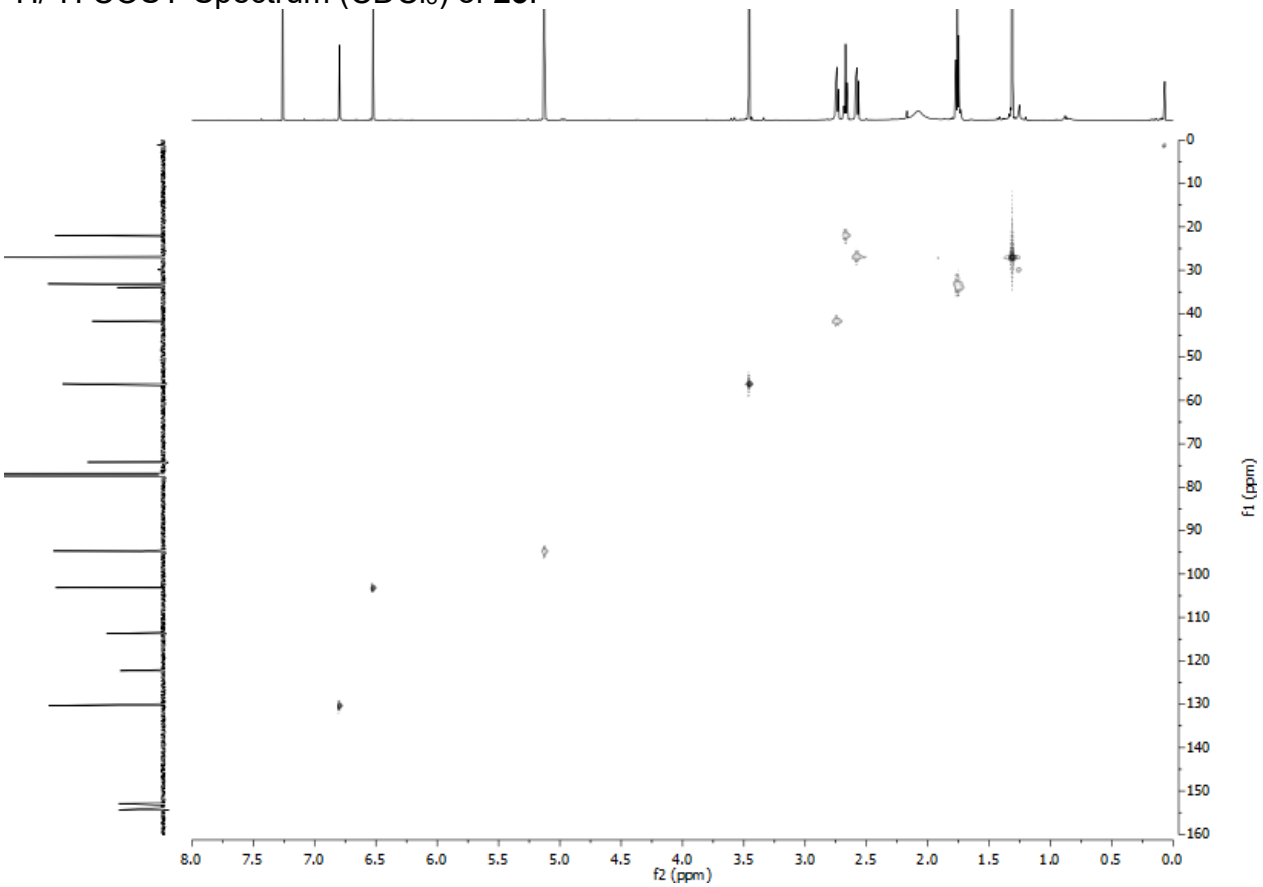
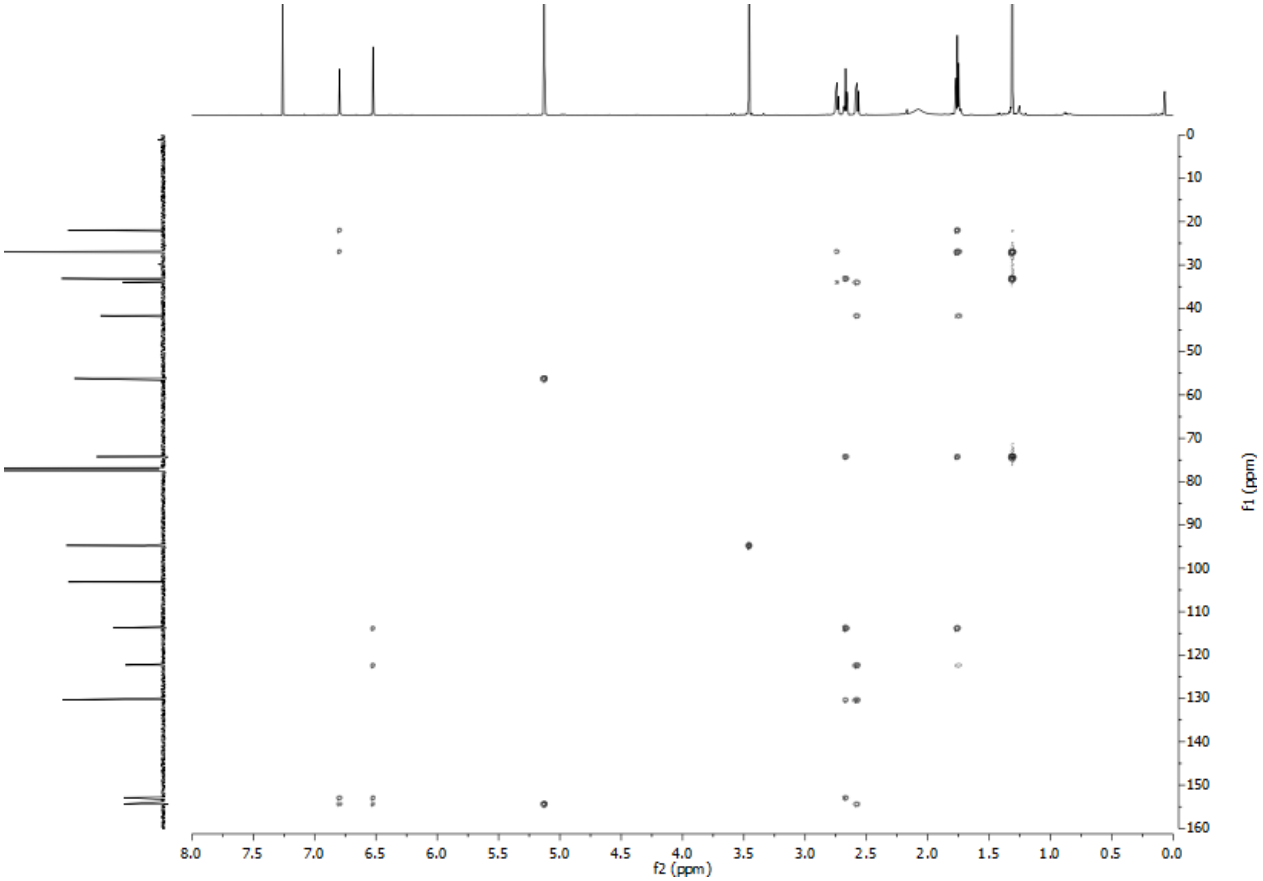


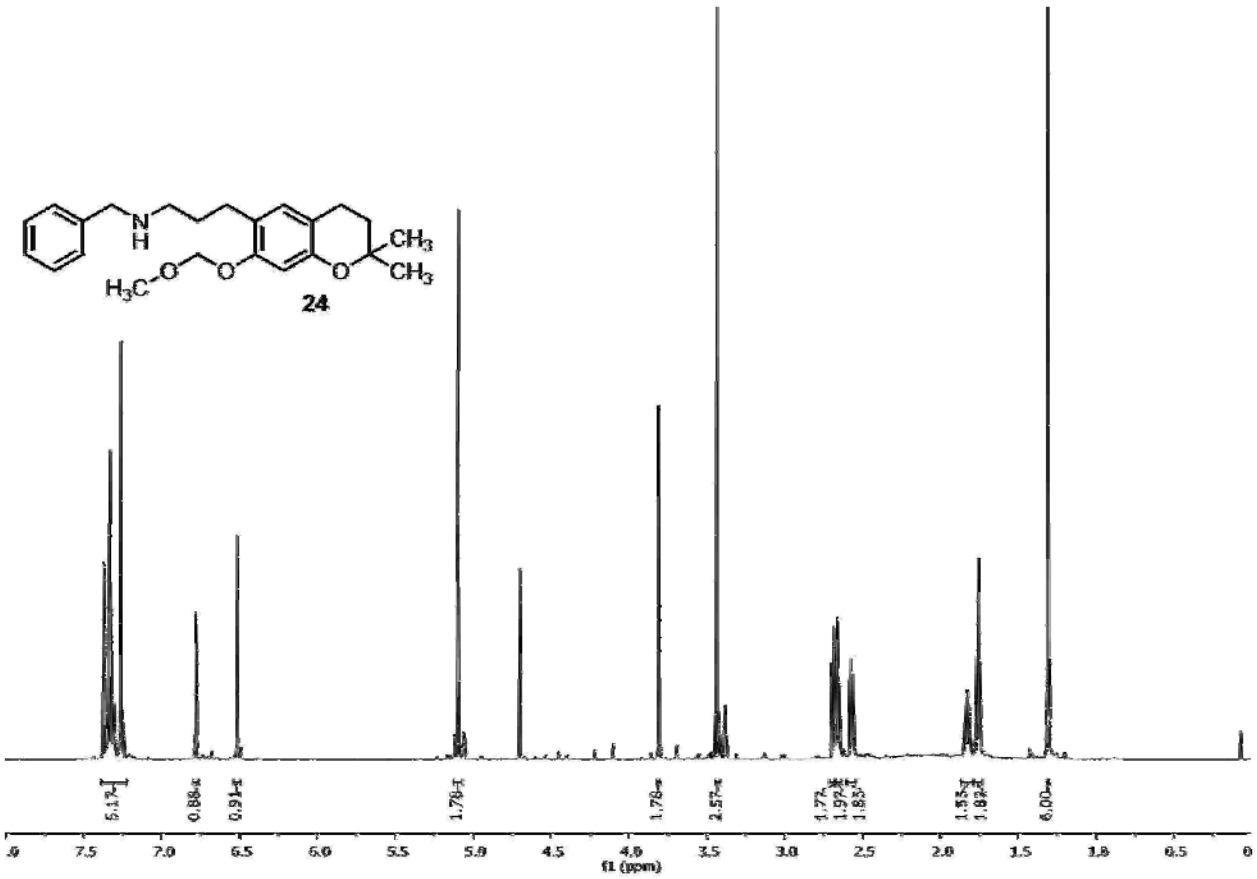
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **23**.



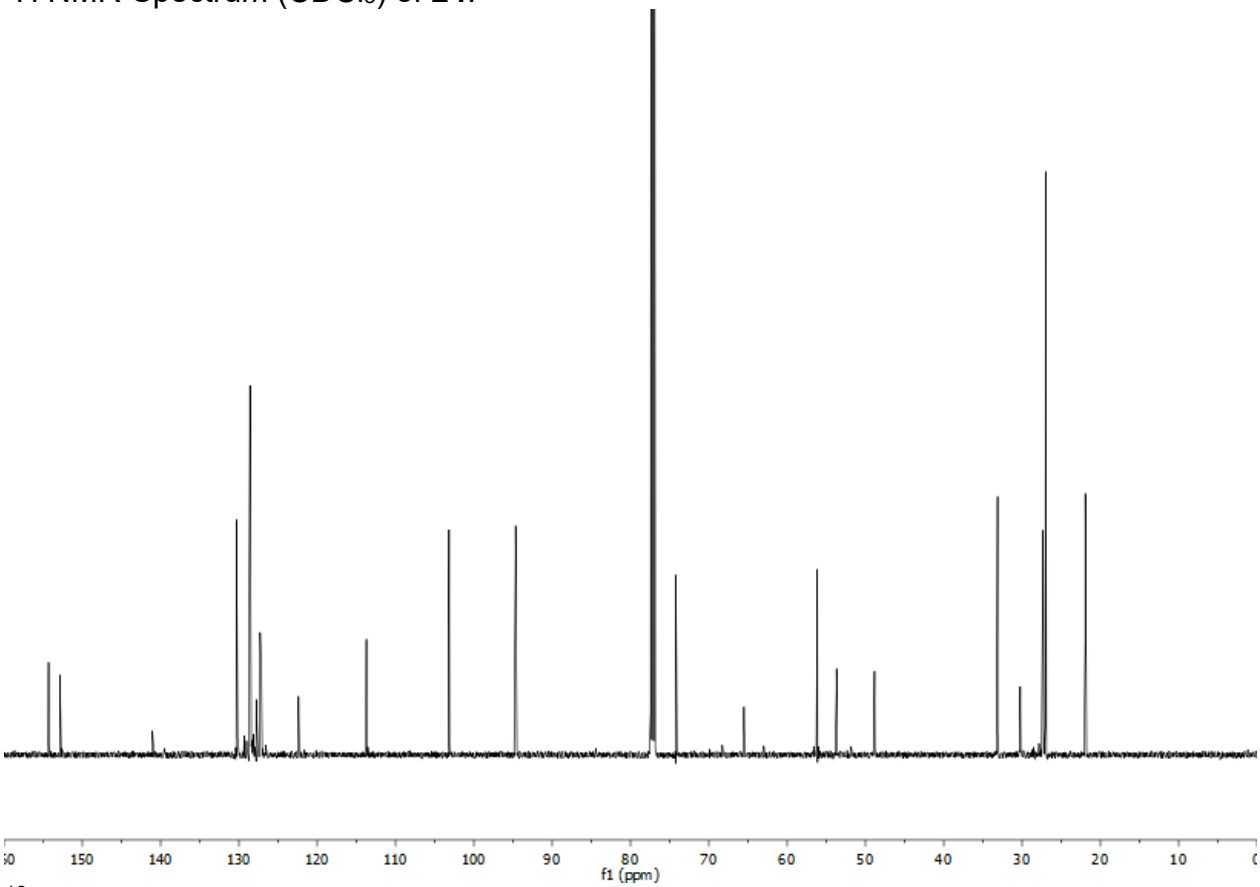
gHSQC-Spectrum ($CDCl_3$) of **23**.



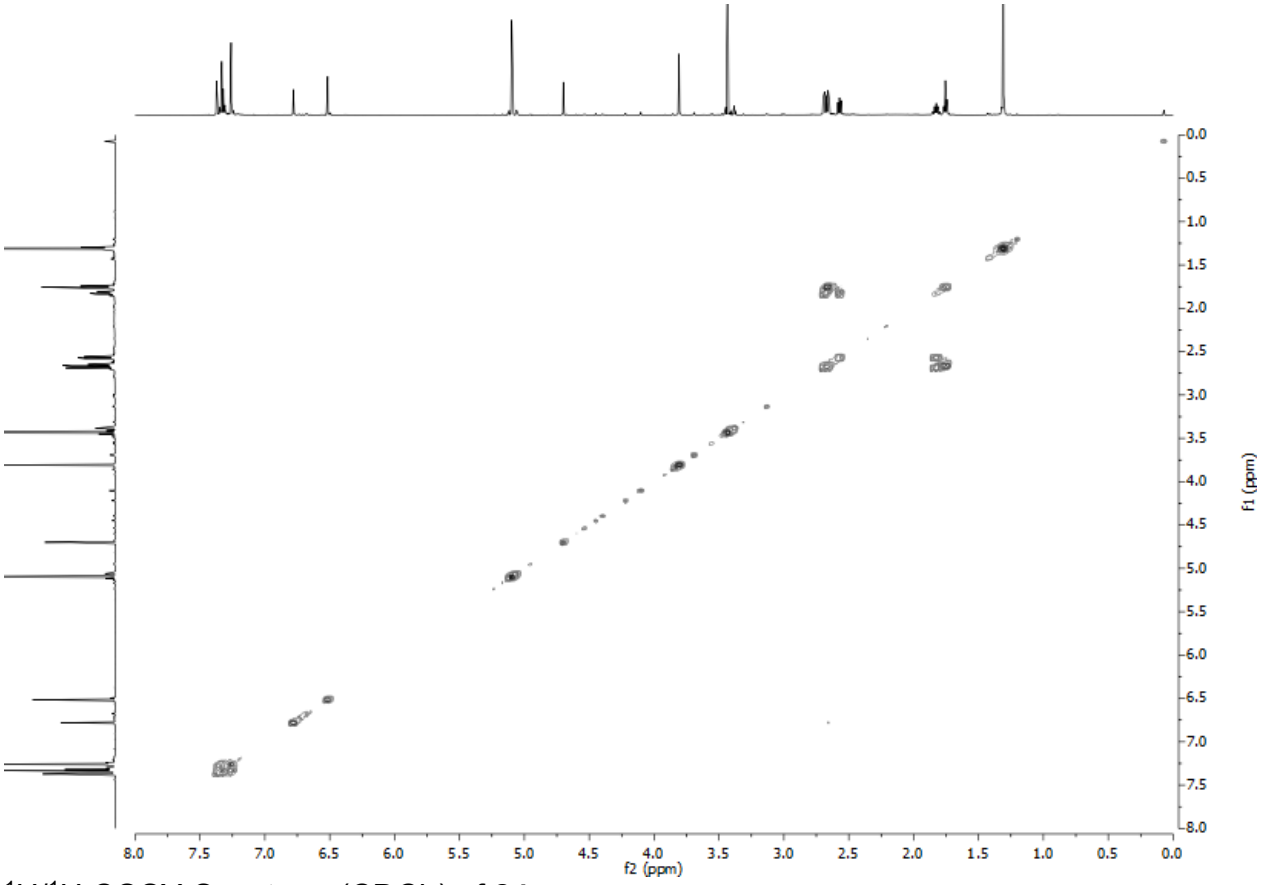
gHMBC-Spectrum ($CDCl_3$) of **23**.



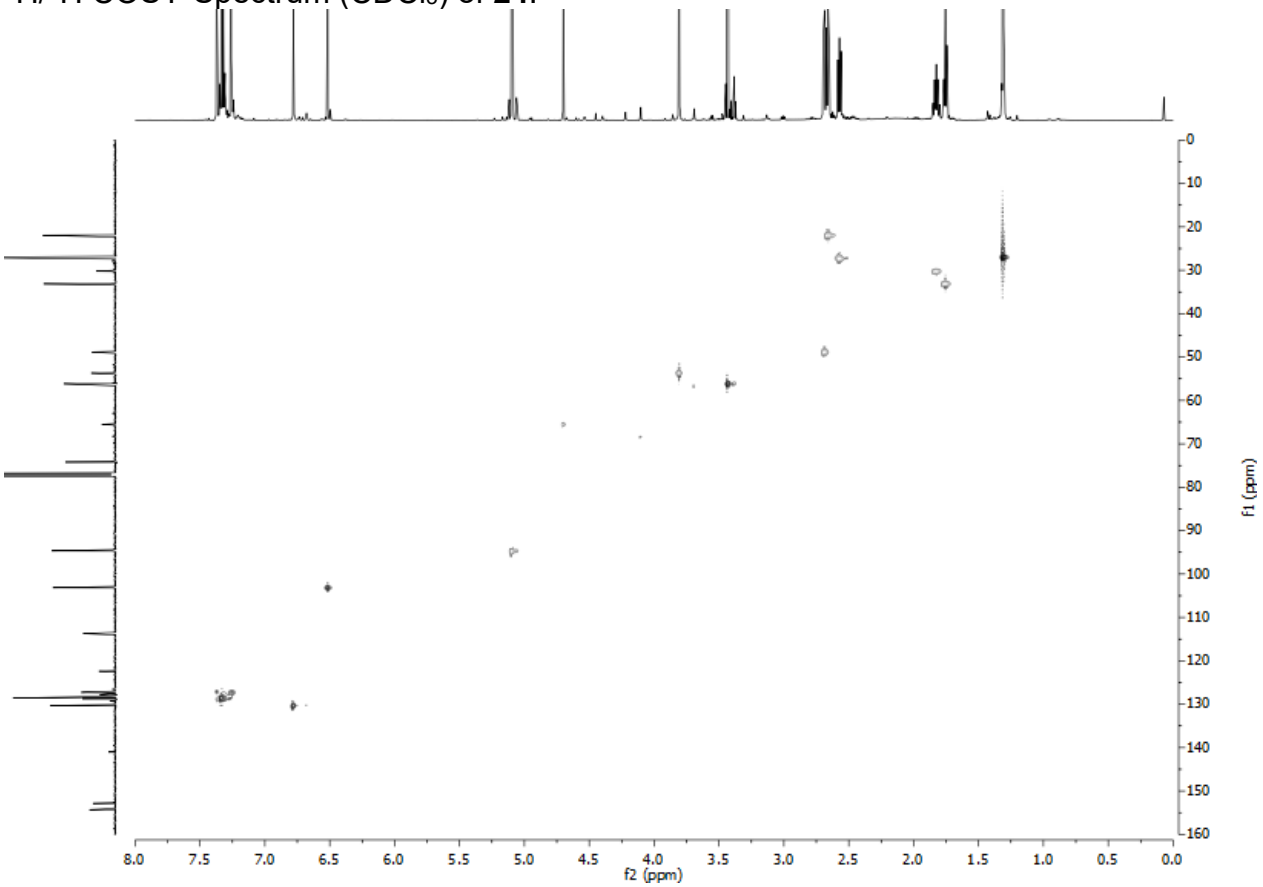
^{1}H NMR-Spectrum ($CDCl_3$) of **24**.



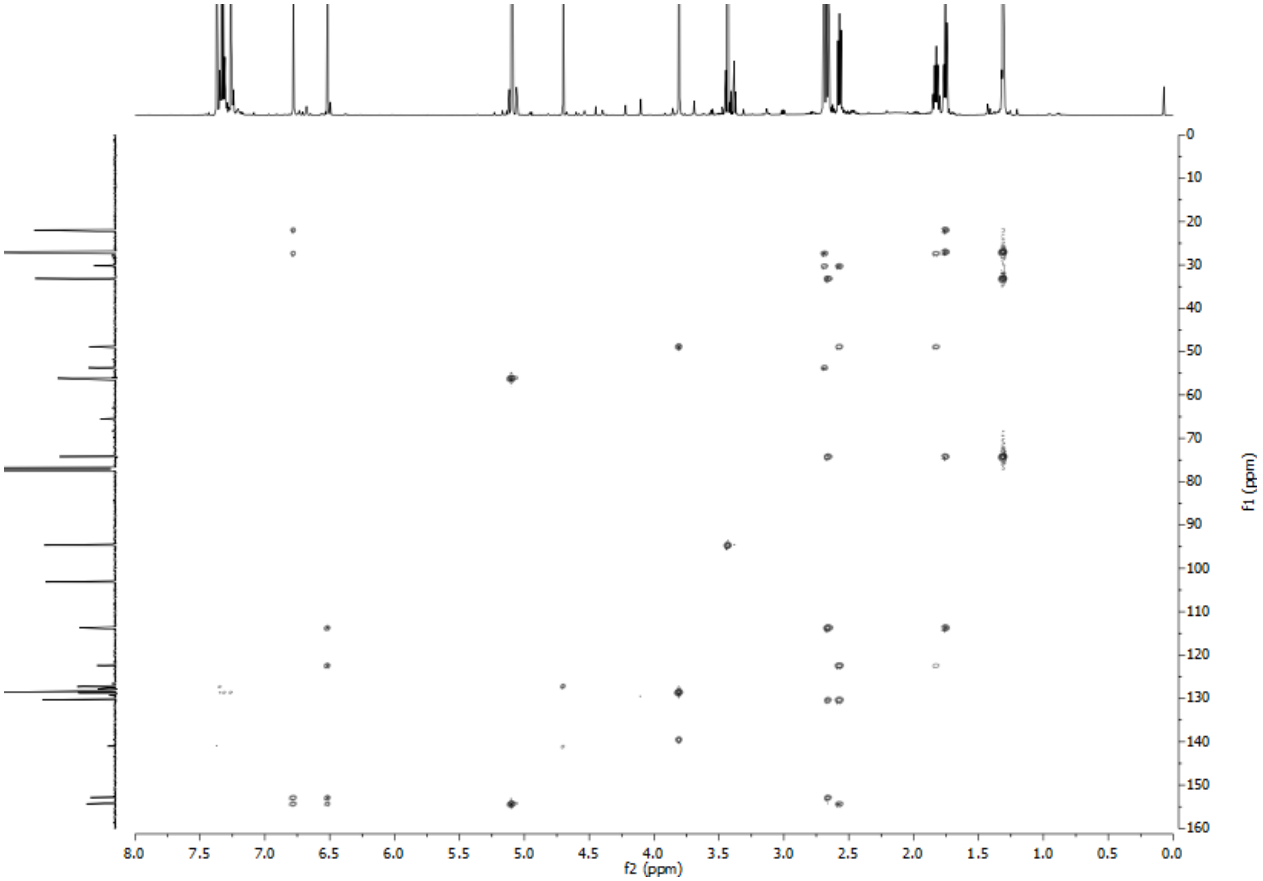
^{13}C NMR-Spectrum ($CDCl_3$) of **24**.



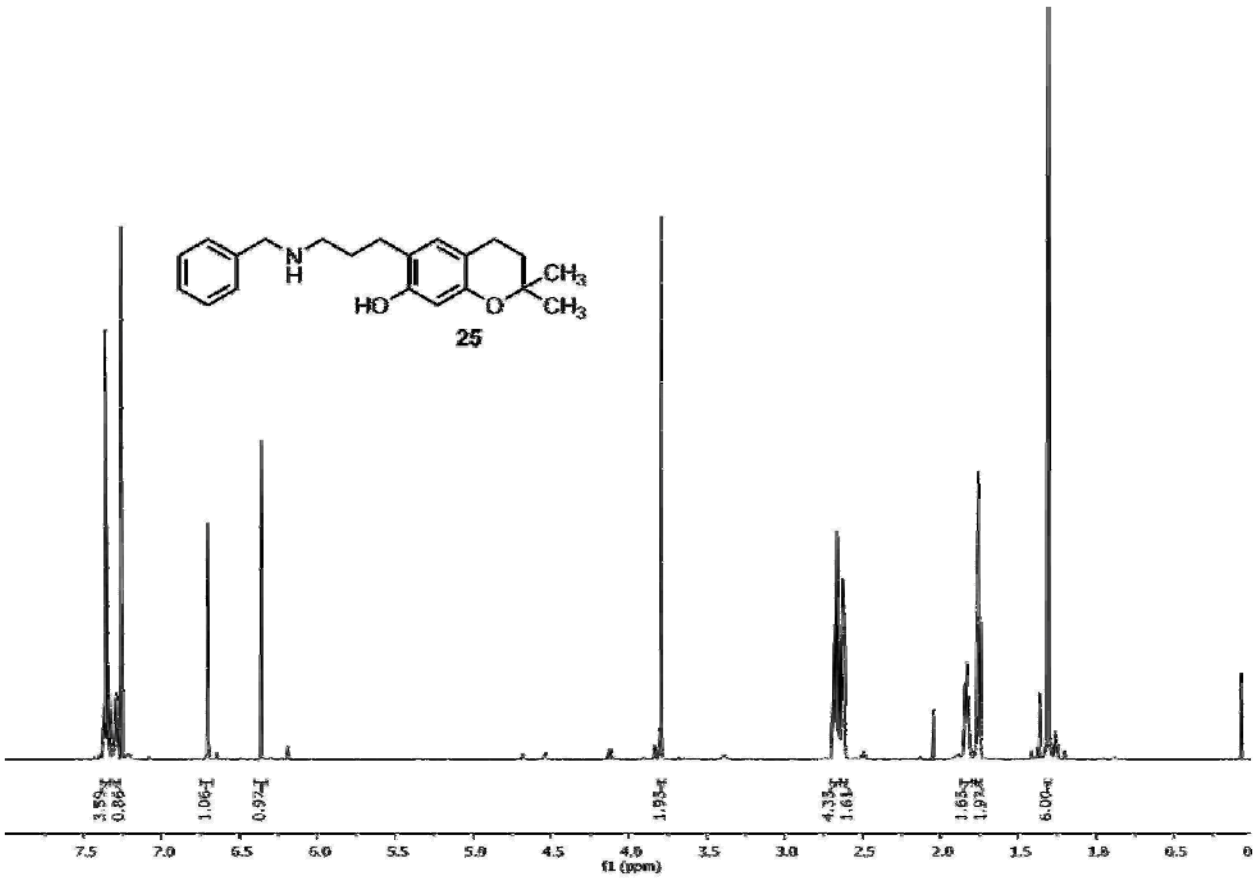
$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **24**.



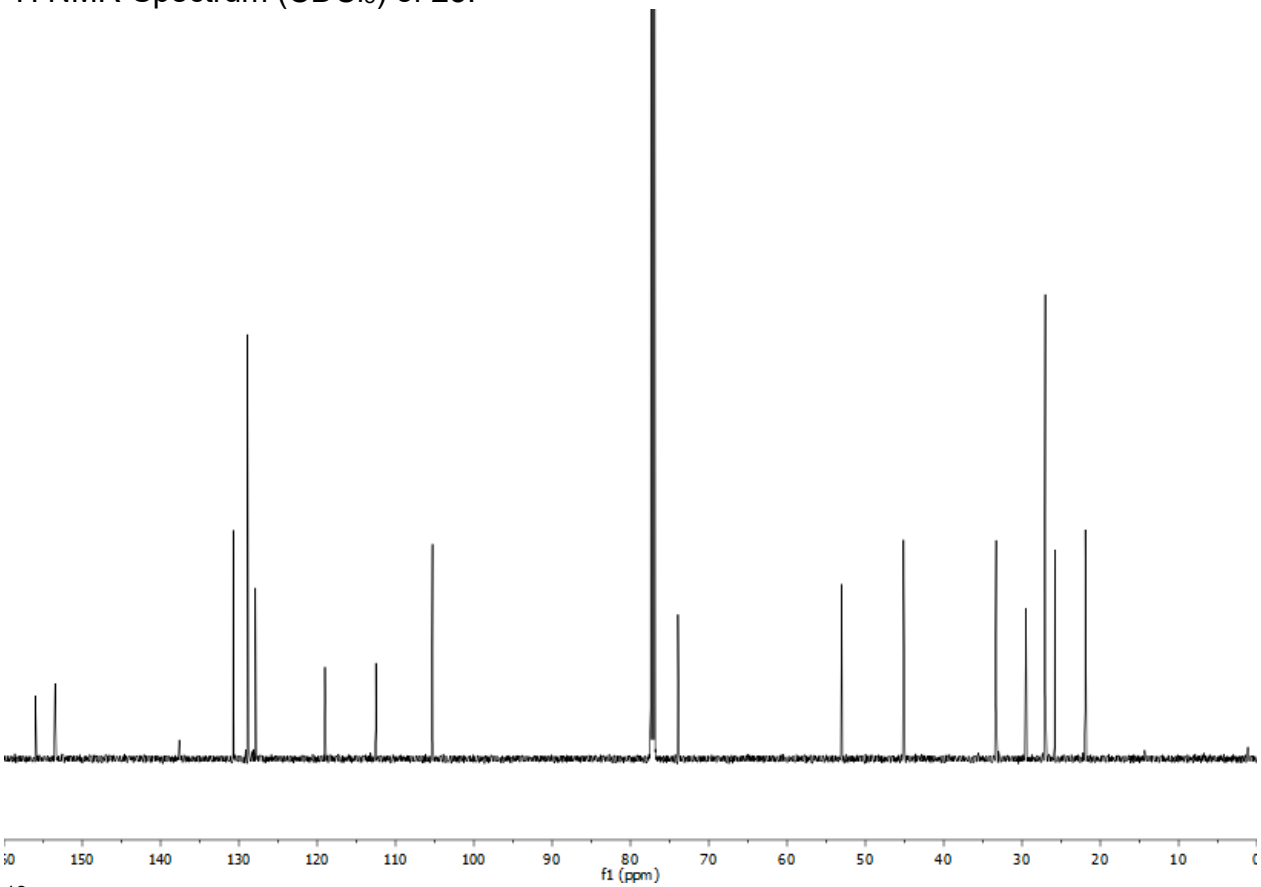
gHSQC-Spectrum ($CDCl_3$) of **24**.



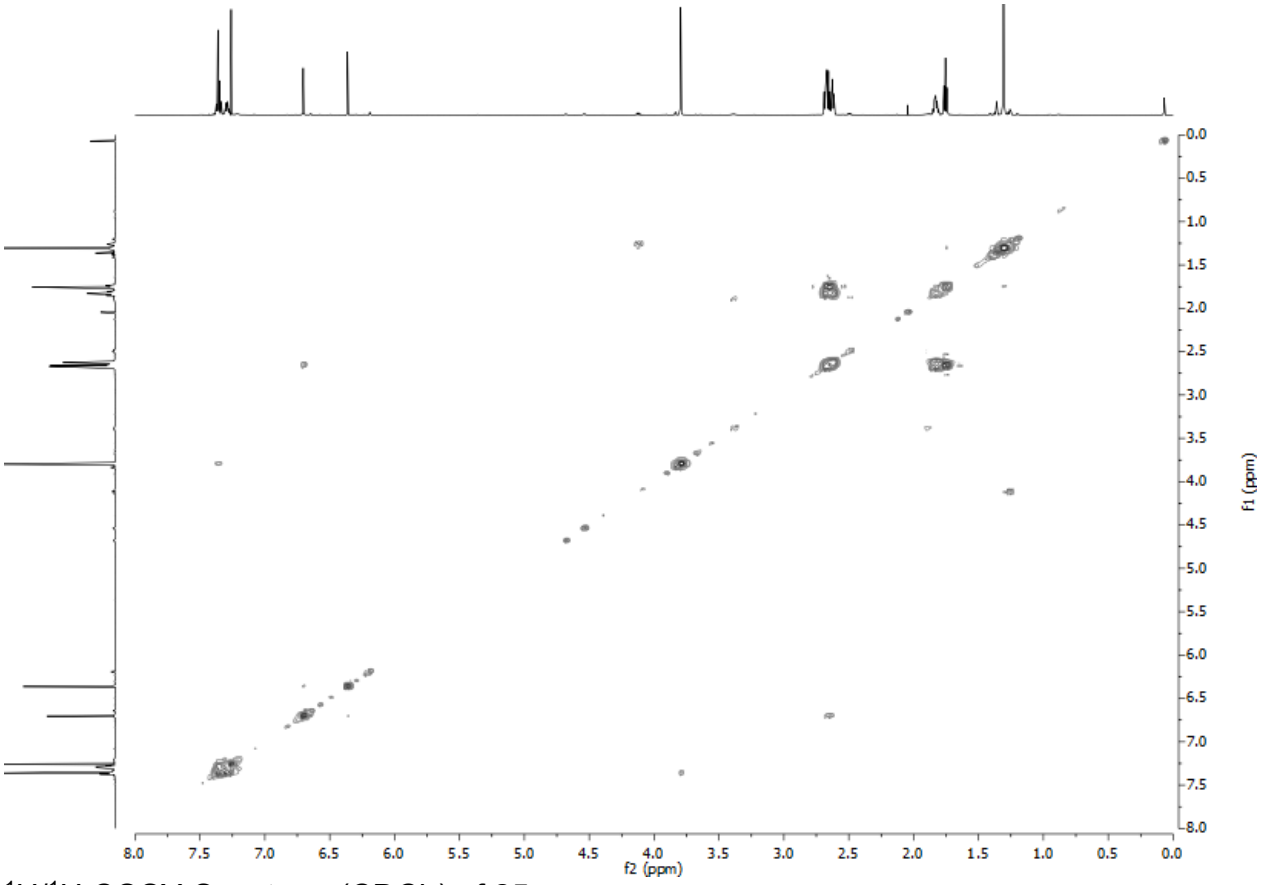
gHMBC-Spectrum ($CDCl_3$) of **24**.



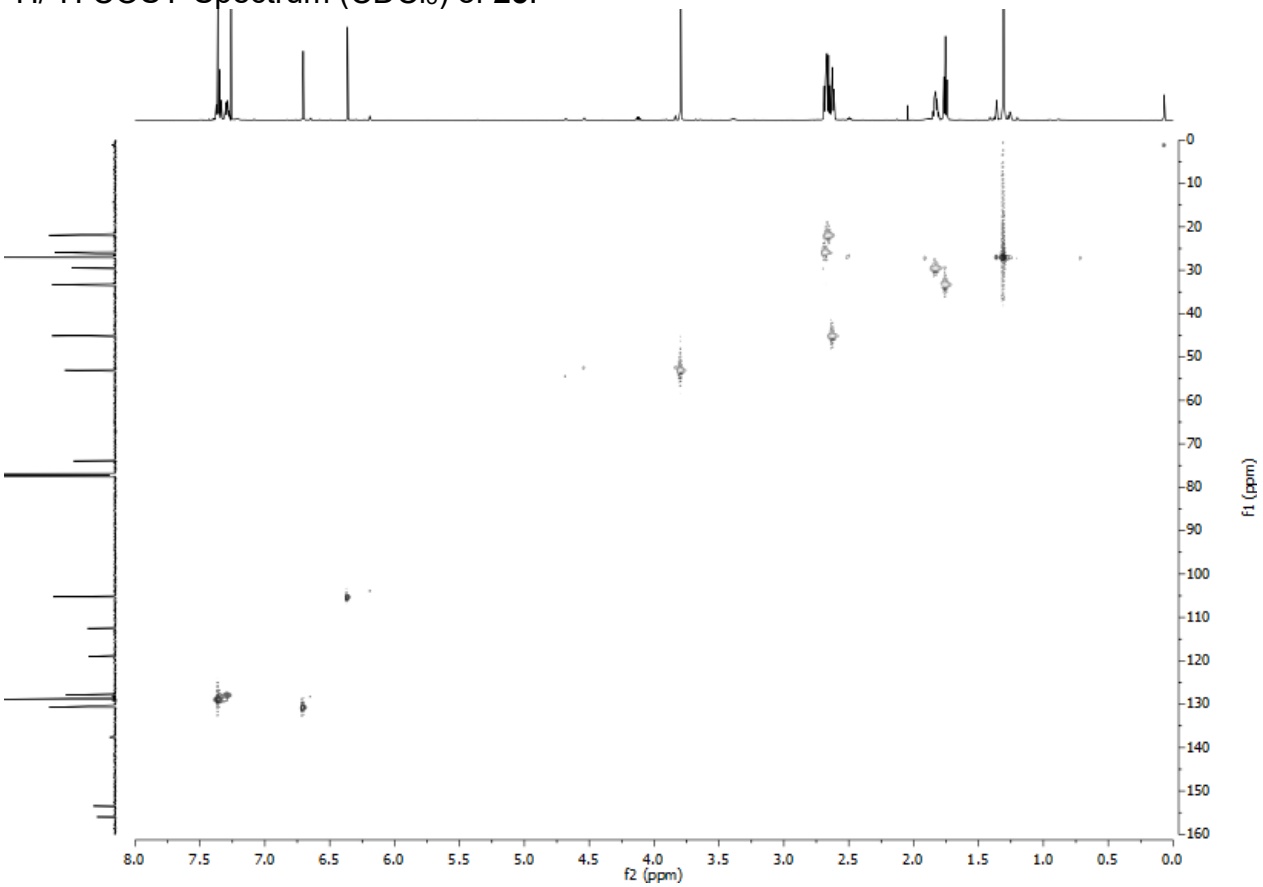
^{1}H NMR-Spectrum ($CDCl_3$) of **25**.



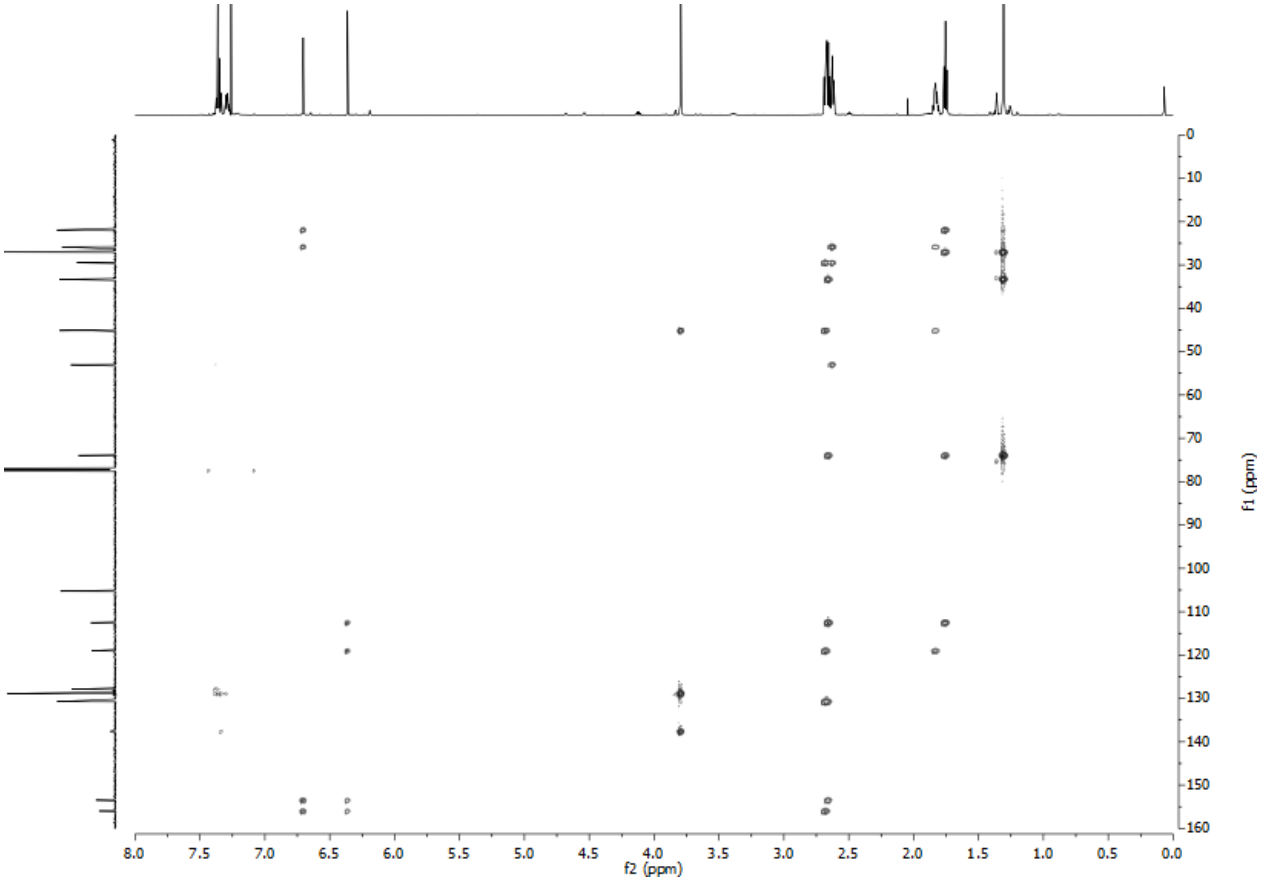
^{13}C NMR-Spectrum ($CDCl_3$) of **25**.



$^{1}H/^{1}H$ COSY-Spectrum ($CDCl_3$) of **25**.



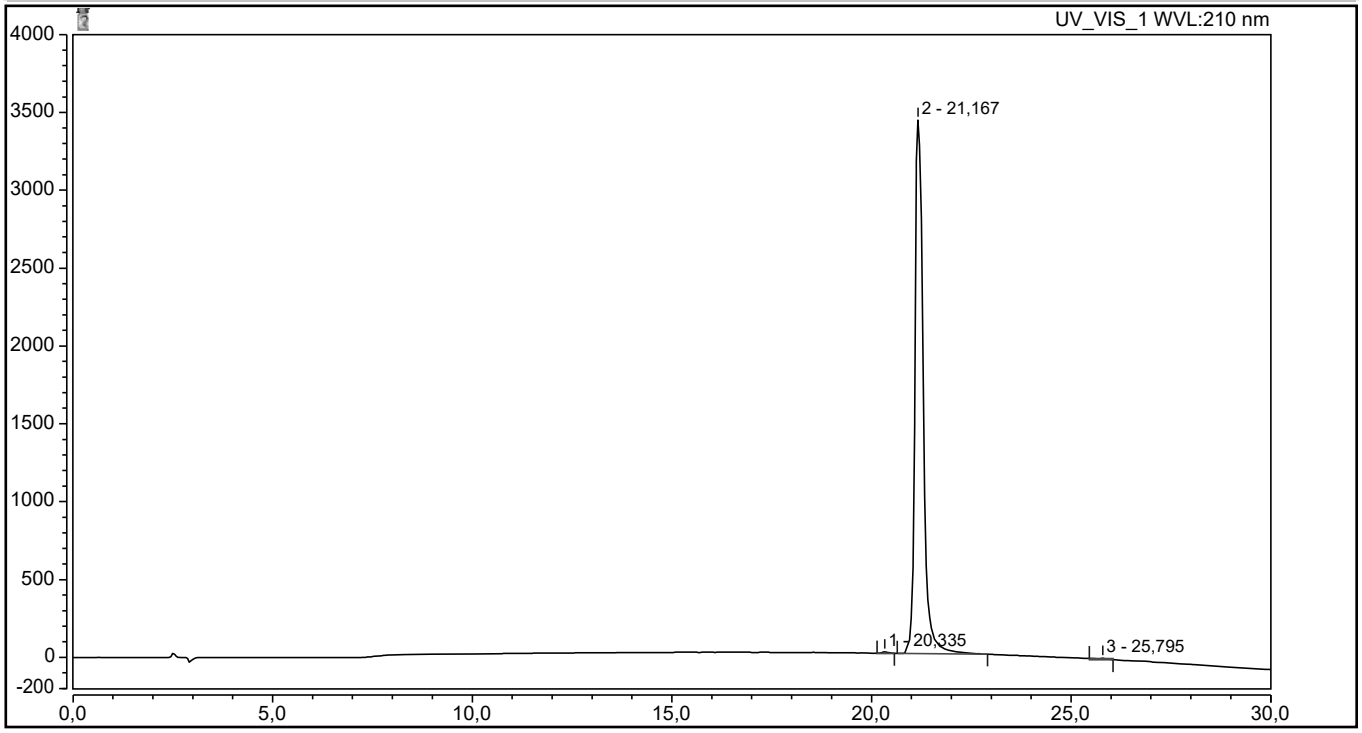
gHSQC-Spectrum ($CDCl_3$) of **25**.



gHMBC-Spectrum ($CDCl_3$) of **25**.

8. HPLC traces

Chromatogram

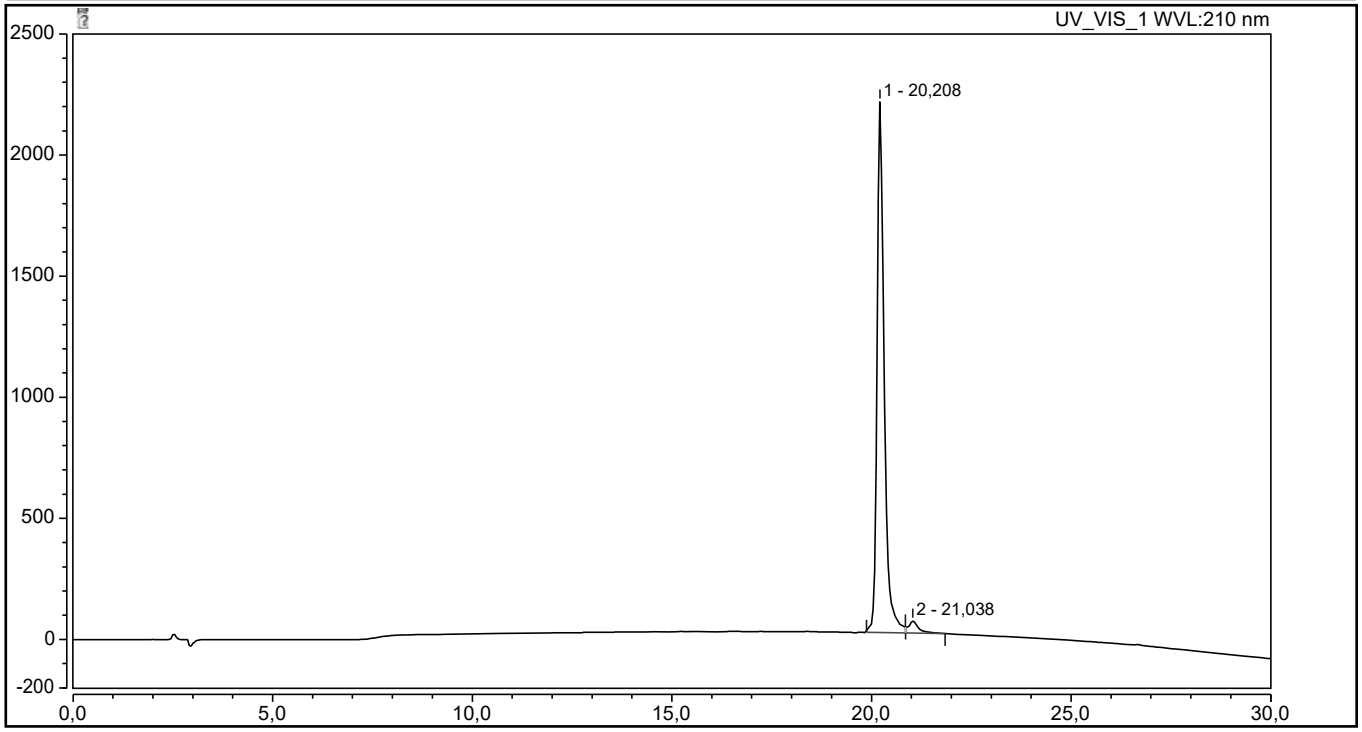


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		20,335	1,591	8,634	0,19	0,25	n.a.
2		21,167	832,844	3425,616	99,66	99,60	n.a.
3		25,795	1,255	5,077	0,15	0,15	n.a.
Total:			**835,690**	**3439,327**	**100,00**	**100,00**	

HPLC trace of **5**.

Chromatogram

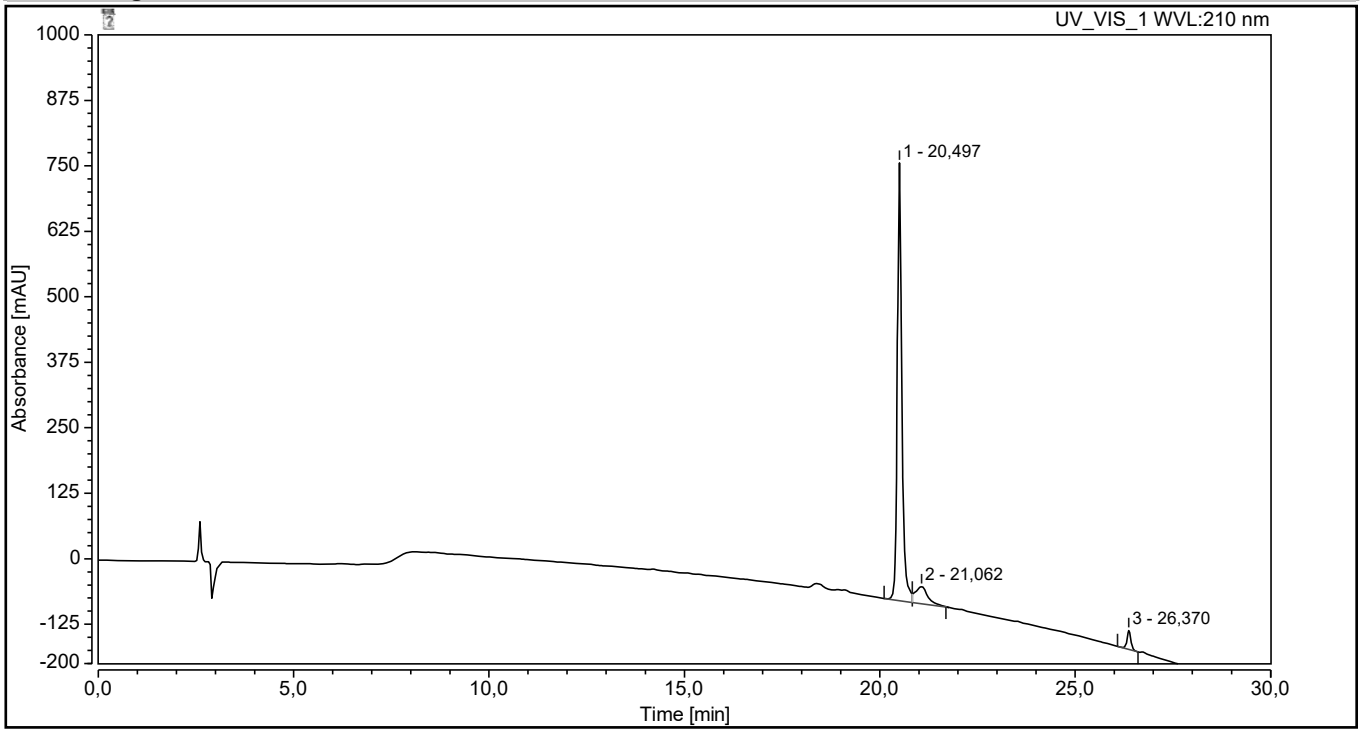


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		20,208	452,470	2190,732	96,77	97,77	n.a.
2		21,038	15,092	50,052	3,23	2,23	n.a.
Total:			**467,562**	**2240,784**	**100,00**	**100,00**	

HPLC trace of **6**.

Chromatogram

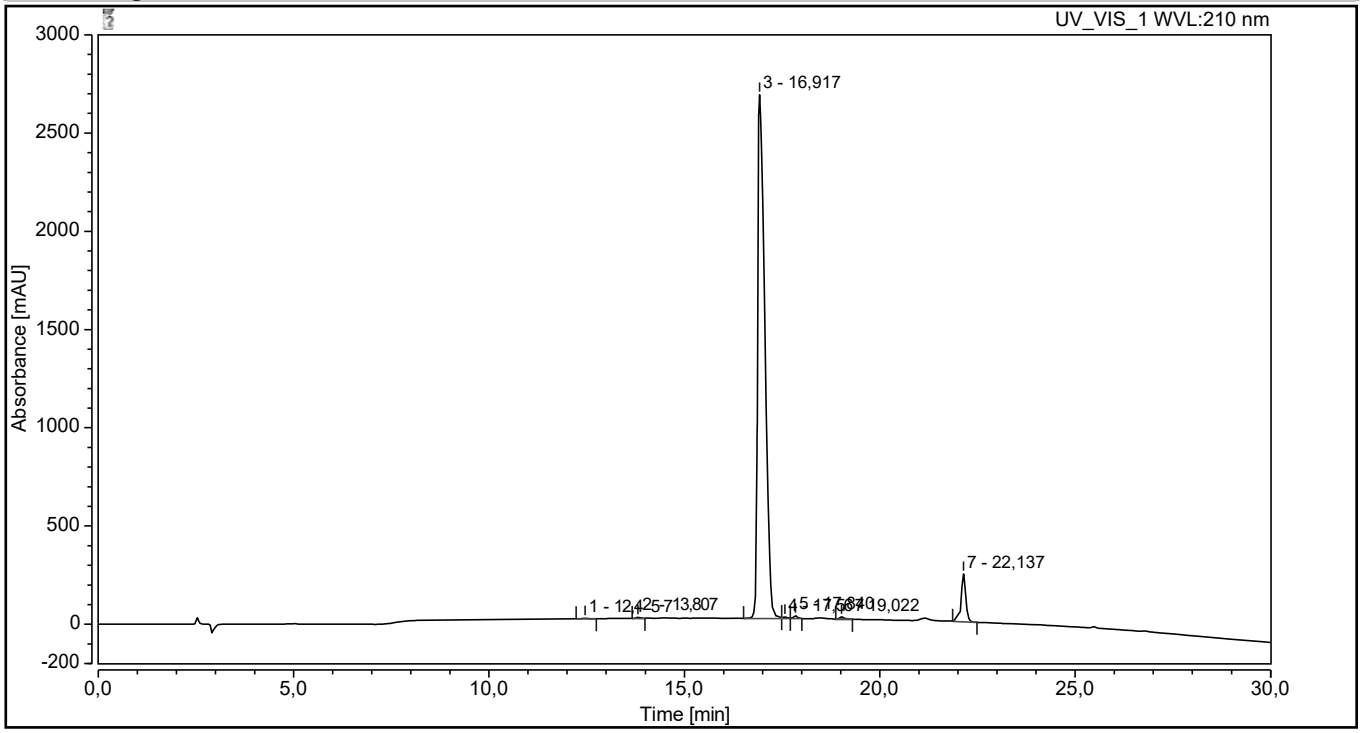


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		20,497	112,020	835,239	87,27	92,39	n.a.
2		21,062	12,135	32,534	9,45	3,60	n.a.
3		26,370	4,203	36,250	3,27	4,01	n.a.
Total:			**128,358**	**904,024**	**100,00**	**100,00**	

HPLC trace of **7**.

Chromatogram

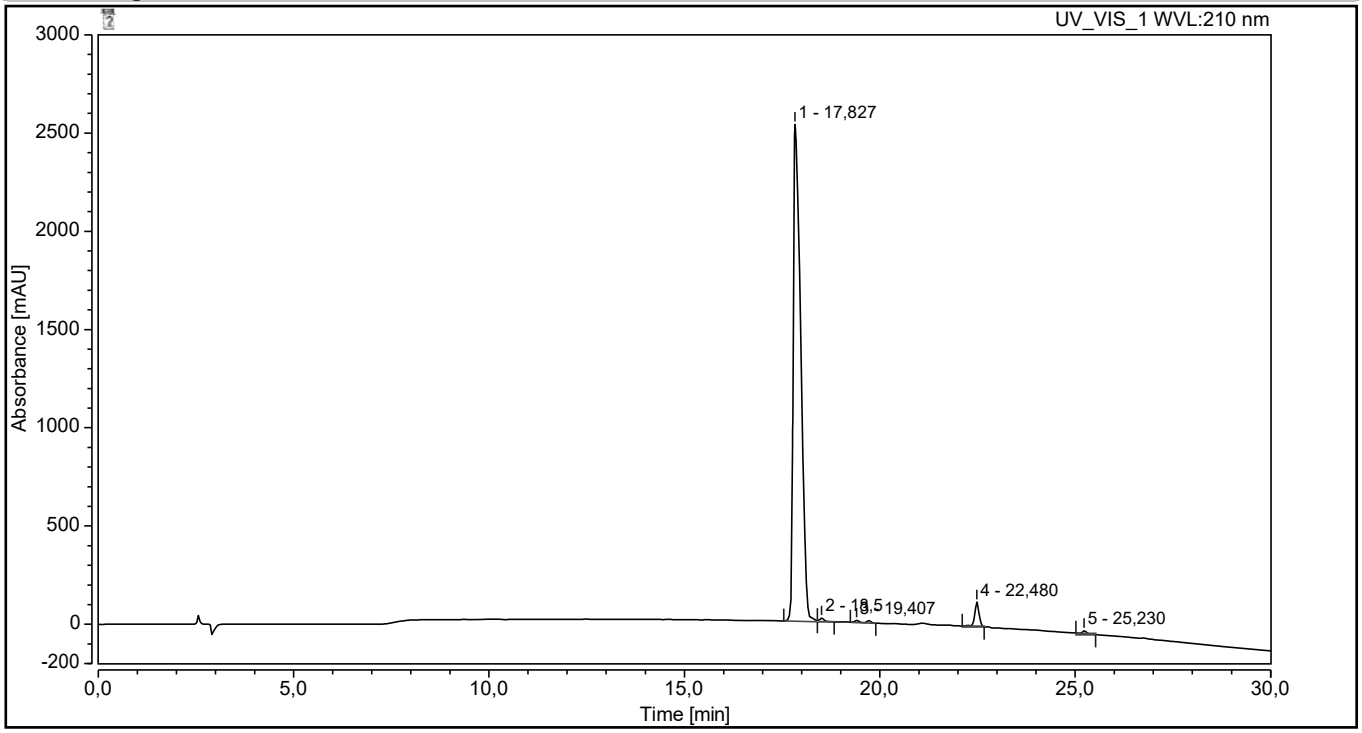


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12,457	0,371	2,628	0,06	0,09	n.a.
2		13,807	0,667	5,783	0,11	0,20	n.a.
3		16,917	560,181	2665,164	93,89	90,42	n.a.
4		17,567	0,780	6,789	0,13	0,23	n.a.
5		17,840	1,456	13,218	0,24	0,45	n.a.
6		19,022	1,588	10,685	0,27	0,36	n.a.
7		22,137	31,571	243,241	5,29	8,25	n.a.
Total:			**596,615**	**2947,509**	**100,00**	**100,00**	

HPLC trace of **8a**.

Chromatogram

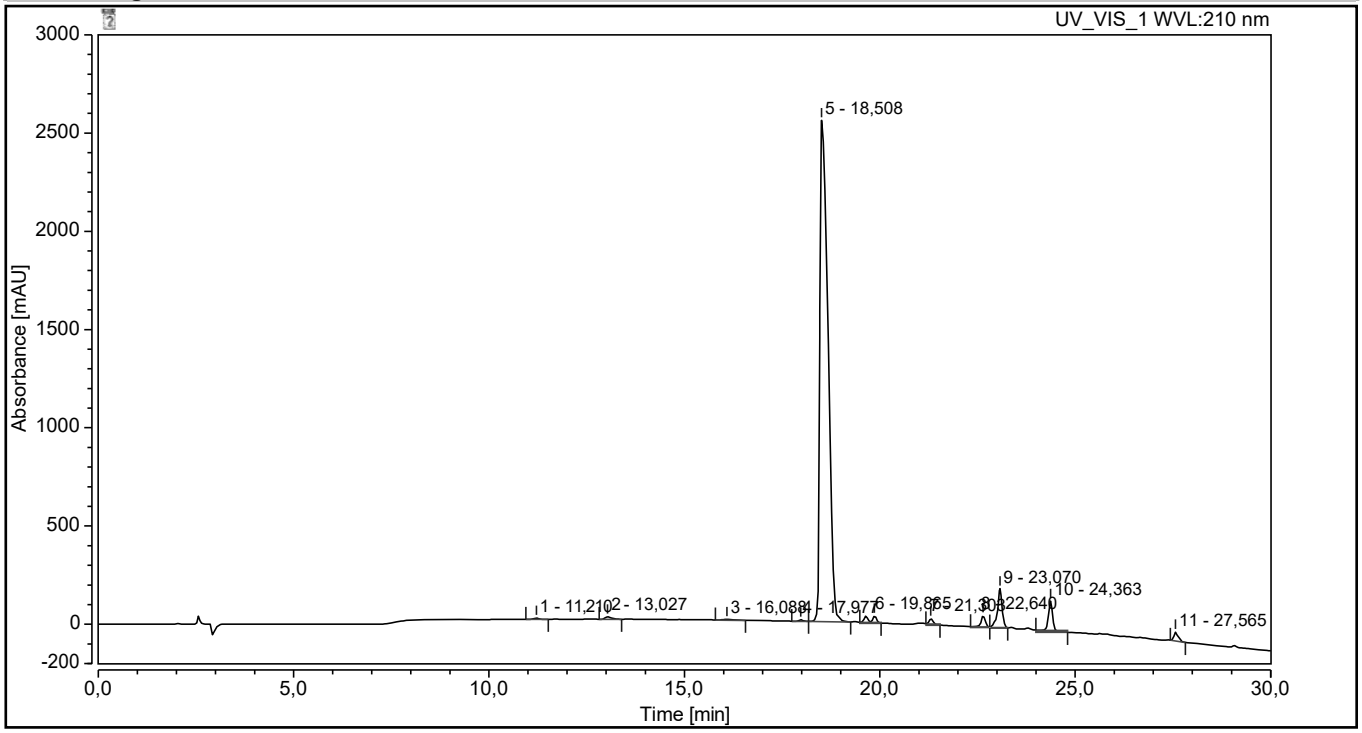


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17,827	559,175	2527,804	96,04	93,75	n.a.
2		18,510	2,401	17,671	0,41	0,66	n.a.
3		19,407	2,540	10,935	0,44	0,41	n.a.
4		22,480	16,162	124,613	2,78	4,62	n.a.
5		25,230	1,945	15,428	0,33	0,57	n.a.
Total:			**582,224**	**2696,451**	**100,00**	**100,00**	

HPLC trace of **8b**.

Chromatogram

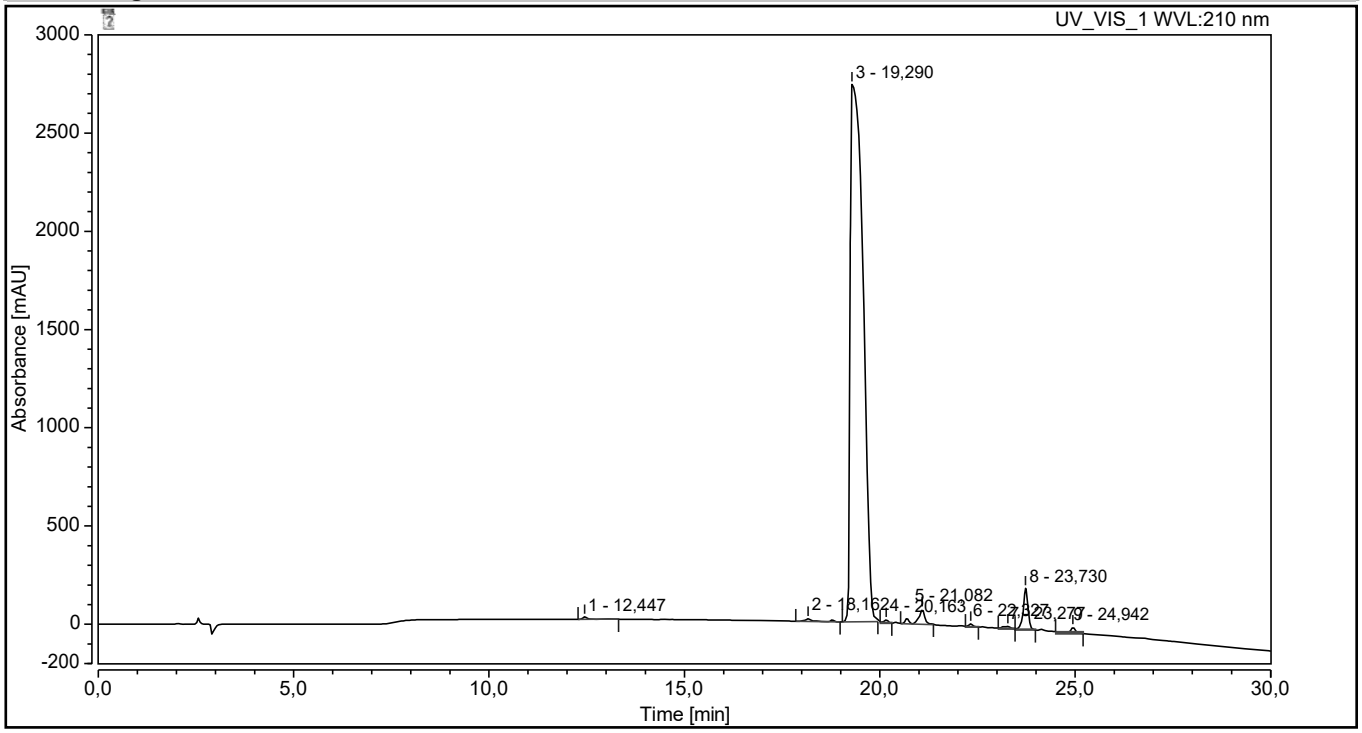


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		11,210	0,771	5,984	0,11	0,19	n.a.
2		13,027	2,400	12,306	0,35	0,40	n.a.
3		16,088	1,031	3,879	0,15	0,13	n.a.
4		17,977	0,909	7,824	0,13	0,25	n.a.
5		18,508	613,864	2551,324	89,22	82,31	n.a.
6		19,865	7,536	35,486	1,10	1,14	n.a.
7		21,303	3,205	28,287	0,47	0,91	n.a.
8		22,640	7,285	58,668	1,06	1,89	n.a.
9		23,070	27,211	198,248	3,95	6,40	n.a.
10		24,363	18,848	152,763	2,74	4,93	n.a.
11		27,565	4,955	44,871	0,72	1,45	n.a.
Total:			**688,015**	**3099,640**	**100,00**	**100,00**	

HPLC trace of **8c**.

Chromatogram

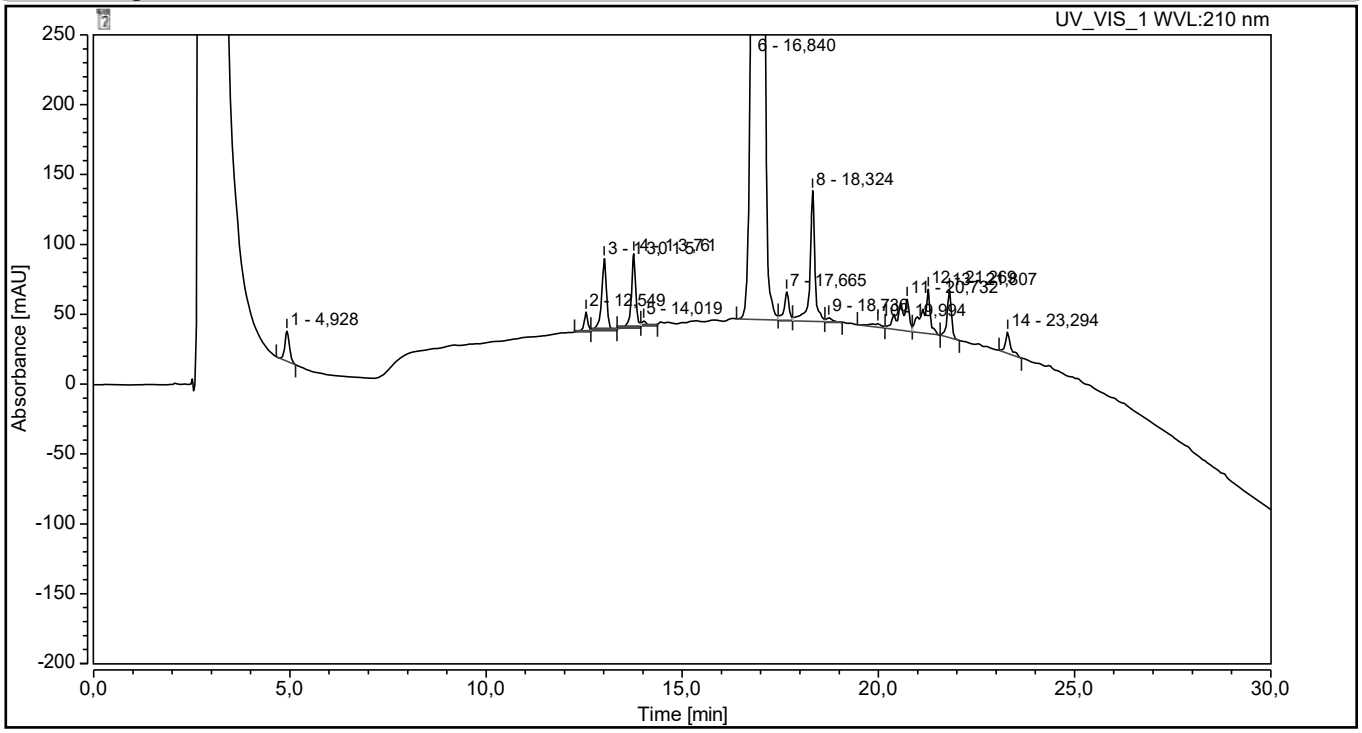


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12,447	2,021	13,073	0,18	0,42	n.a.
2		18,162	3,843	13,201	0,35	0,42	n.a.
3		19,290	1033,409	2735,502	94,53	87,85	n.a.
4		20,163	1,624	13,671	0,15	0,44	n.a.
5		21,082	15,298	75,178	1,40	2,41	n.a.
6		22,327	1,641	13,923	0,15	0,45	n.a.
7		23,277	2,248	10,775	0,21	0,35	n.a.
8		23,730	29,134	209,995	2,67	6,74	n.a.
9		24,942	3,961	28,476	0,36	0,91	n.a.
Total:			**1093,179**	**3113,792**	**100,00**	**100,00**	

HPLC trace of **8d**.

Chromatogram

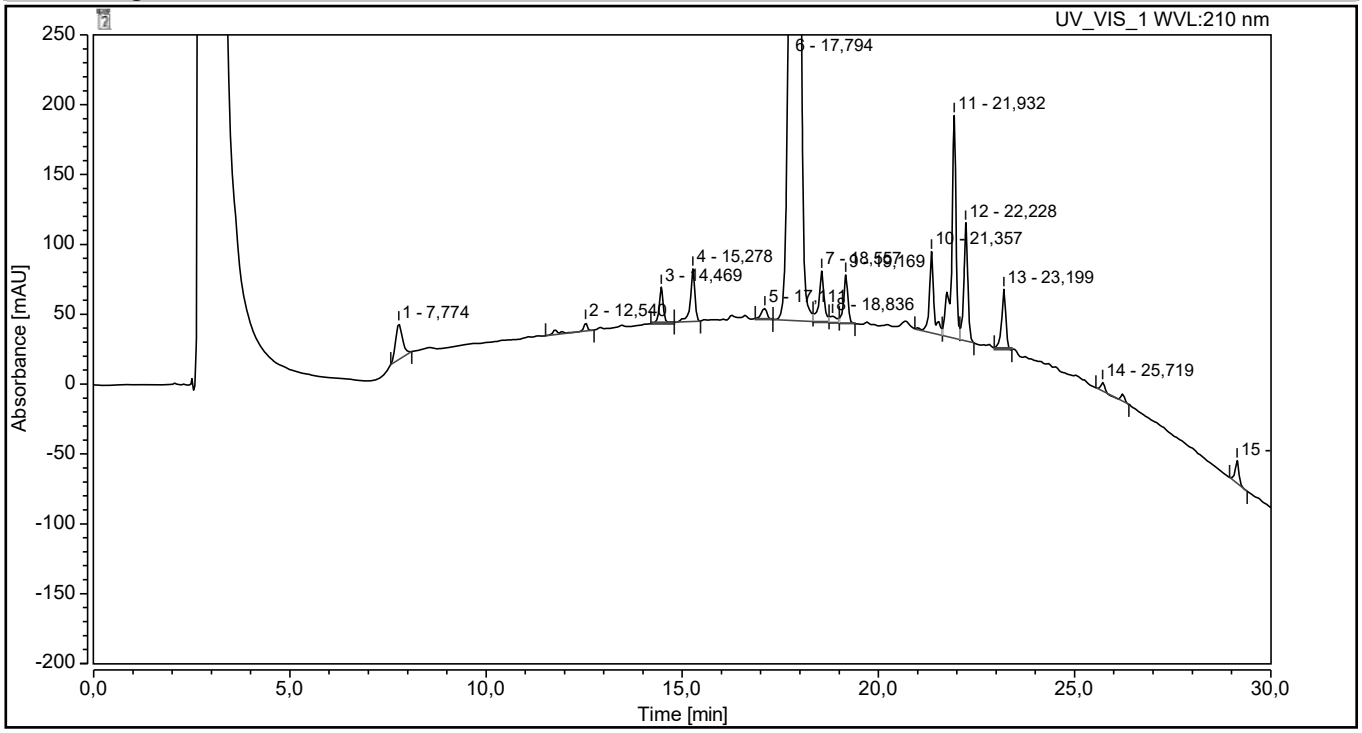


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4,928	2,876	21,534	0,40	0,58	n.a.
2		12,549	1,432	13,516	0,20	0,36	n.a.
3		13,015	7,129	50,649	0,99	1,35	n.a.
4		13,761	6,315	52,107	0,88	1,39	n.a.
5		14,019	0,375	3,246	0,05	0,09	n.a.
6		16,840	662,688	3374,913	92,17	90,27	n.a.
7		17,665	2,970	20,511	0,41	0,55	n.a.
8		18,324	13,655	93,511	1,90	2,50	n.a.
9		18,736	0,550	2,919	0,08	0,08	n.a.
10		19,994	0,821	2,696	0,11	0,07	n.a.
11		20,732	6,558	22,626	0,91	0,61	n.a.
12		21,269	7,163	31,618	1,00	0,85	n.a.
13		21,807	4,153	33,685	0,58	0,90	n.a.
14		23,294	2,316	15,338	0,32	0,41	n.a.
Total:			**719,002**	**3738,869**	**100,00**	**100,00**	

HPLC trace of **9a**.

Chromatogram

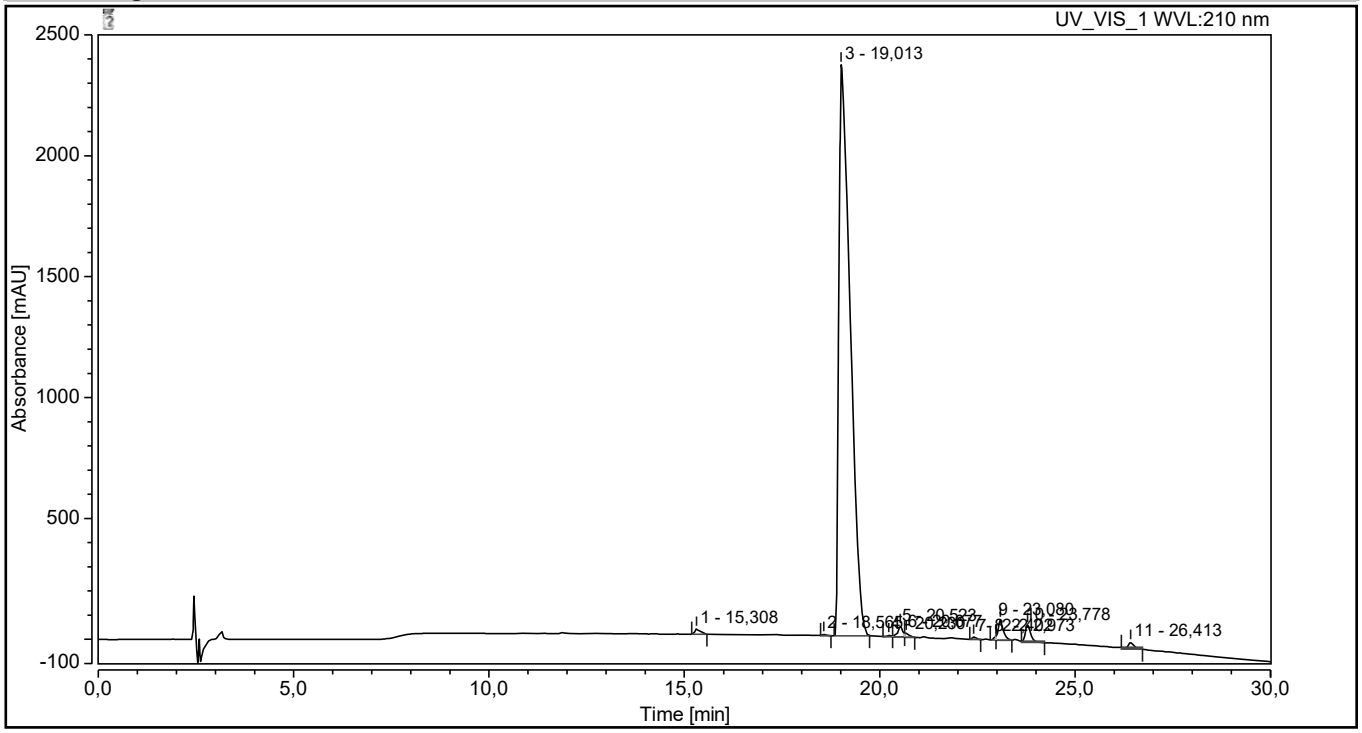


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7,774	5,262	25,842	0,99	0,90	n.a.
2		12,540	1,290	6,345	0,24	0,22	n.a.
3		14,469	3,020	25,787	0,57	0,90	n.a.
4		15,278	4,946	37,528	0,93	1,30	n.a.
5		17,111	1,255	7,536	0,24	0,26	n.a.
6		17,794	455,517	2331,045	86,03	81,03	n.a.
7		18,557	5,535	36,361	1,05	1,26	n.a.
8		18,836	0,982	4,526	0,19	0,16	n.a.
9		19,169	4,303	34,481	0,81	1,20	n.a.
10		21,357	7,923	58,058	1,50	2,02	n.a.
11		21,932	21,159	159,481	4,00	5,54	n.a.
12		22,228	10,091	84,648	1,91	2,94	n.a.
13		23,199	5,164	42,470	0,98	1,48	n.a.
14		25,719	1,153	6,348	0,22	0,22	n.a.
15		29,144	1,861	16,355	0,35	0,57	n.a.
Total:			**529,461**	**2876,811**	**100,00**	**100,00**	

HPLC trace of **9b**.

Chromatogram

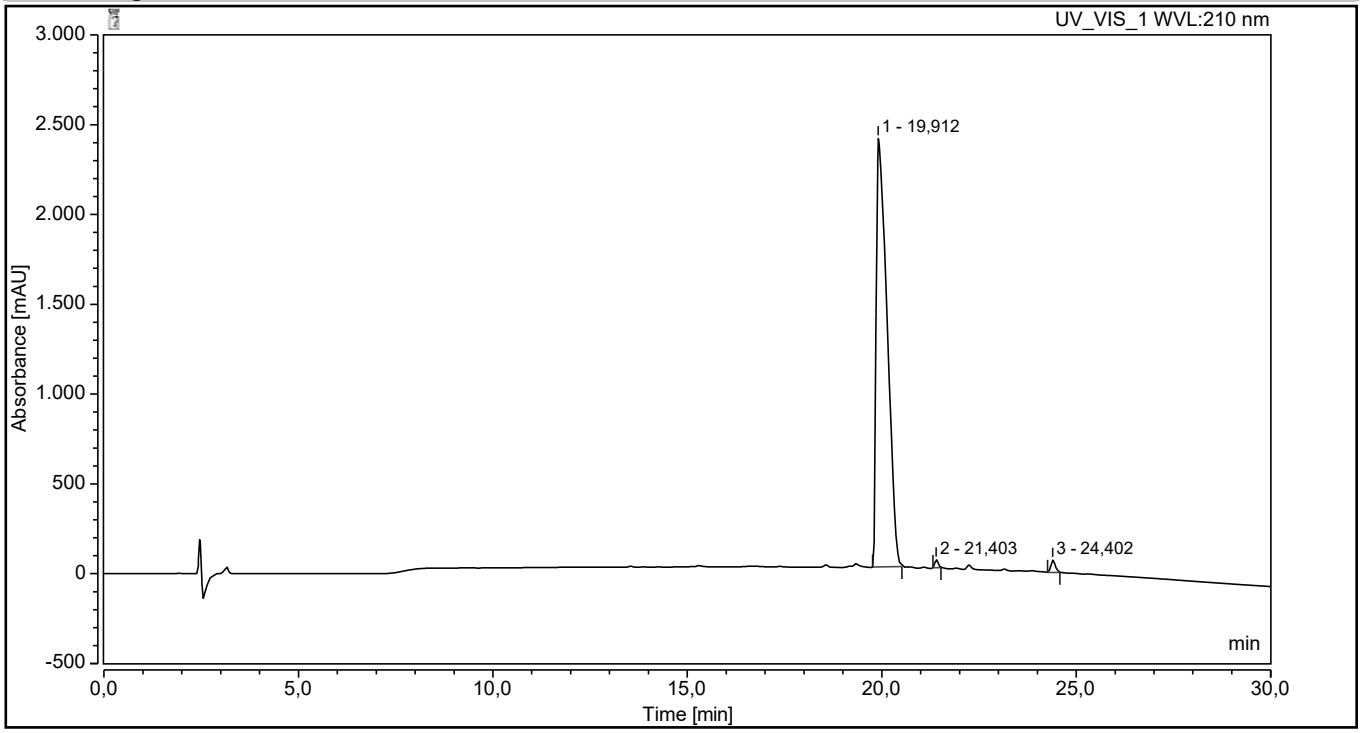


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15,308	2,745	21,522	0,33	0,81	n.a.
2		18,565	0,546	5,058	0,07	0,19	n.a.
3		19,013	792,917	2361,201	95,09	89,02	n.a.
4		20,230	0,766	5,453	0,09	0,21	n.a.
5		20,523	6,543	45,074	0,78	1,70	n.a.
6		20,677	1,934	15,845	0,23	0,60	n.a.
7		22,402	1,195	9,796	0,14	0,37	n.a.
8		22,973	0,946	13,682	0,11	0,52	n.a.
9		23,080	12,294	82,709	1,47	3,12	n.a.
10		23,778	10,338	67,736	1,24	2,55	n.a.
11		26,413	3,660	24,350	0,44	0,92	n.a.
Total:			**833,883**	**2652,424**	**100,00**	**100,00**	

HPLC trace of **9c**.

Chromatogram

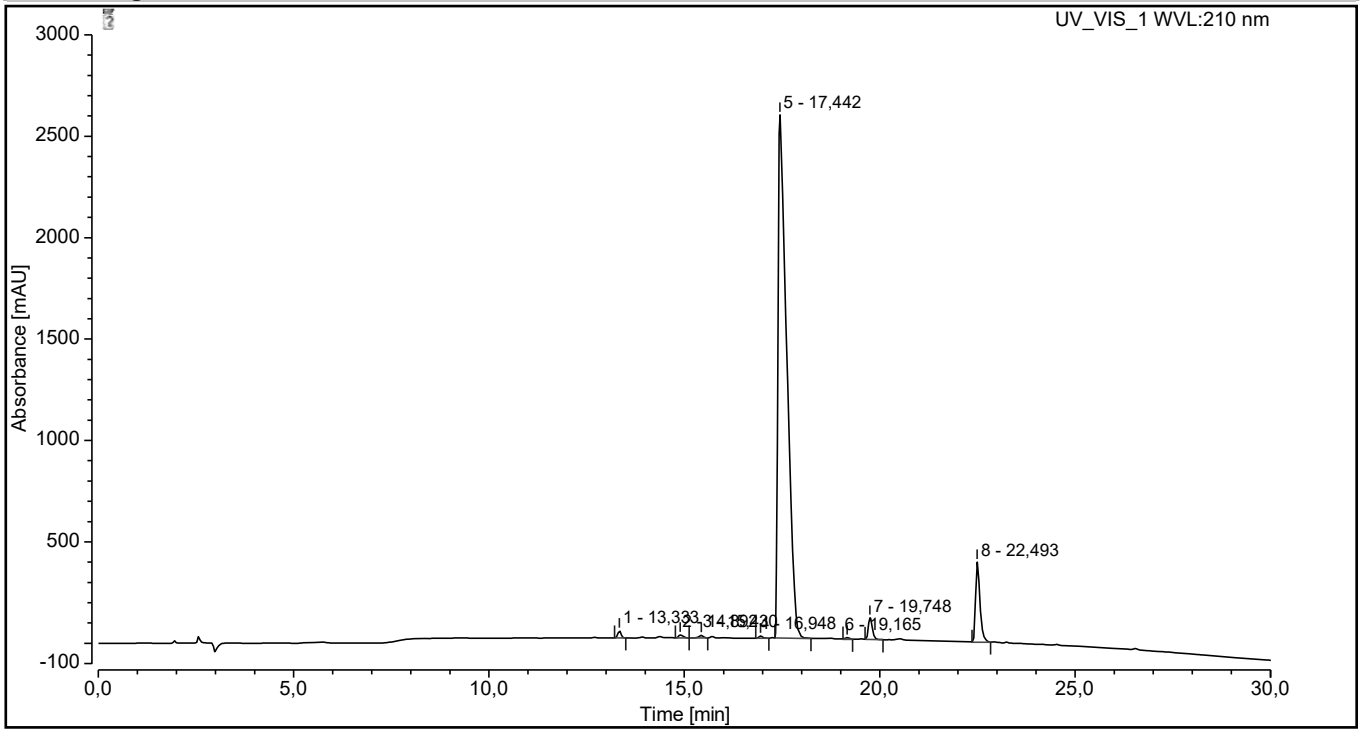


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		19,912	772,635	2383,640	98,29	95,52	n.a.
2		21,403	4,561	43,832	0,58	1,76	n.a.
3		24,402	8,842	67,854	1,12	2,72	n.a.
Total:			**786,038**	**2495,326**	**100,00**	**100,00**	

HPLC trace of **9d**.

Chromatogram

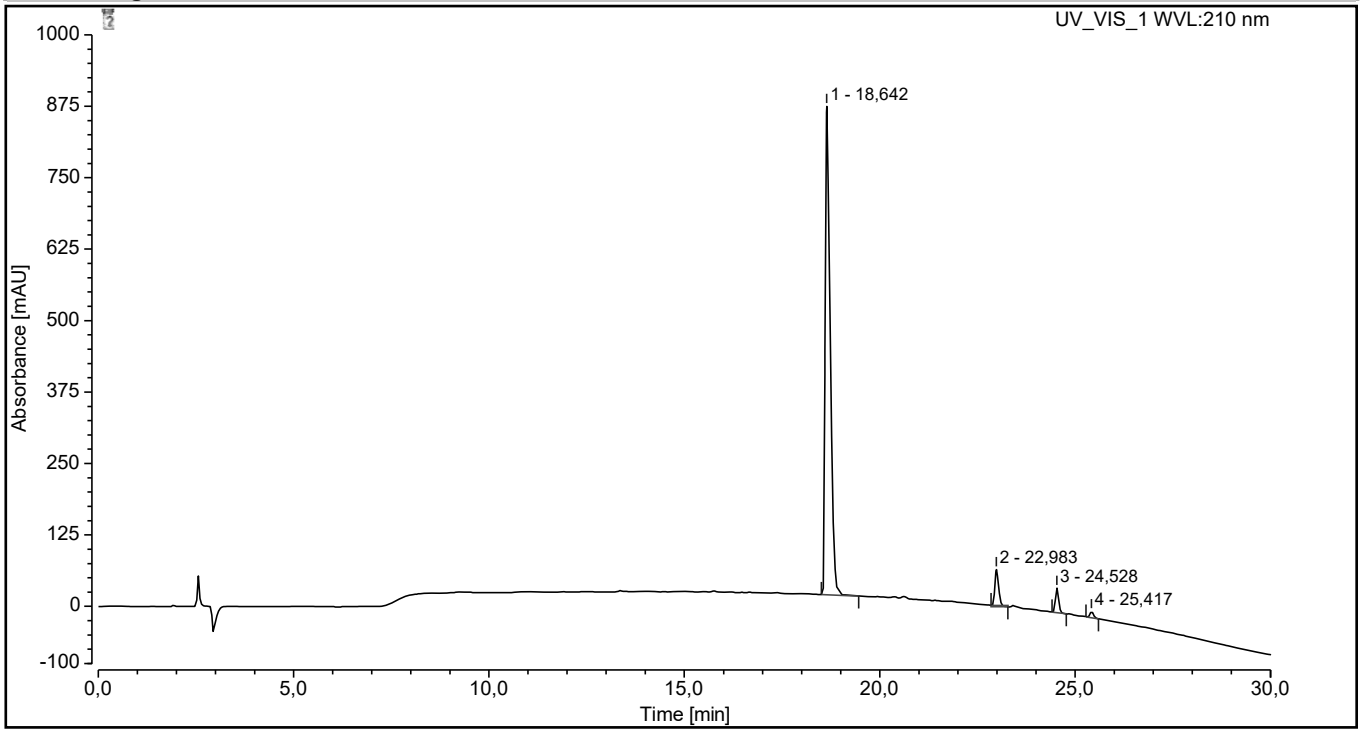


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13,333	3,527	35,818	0,47	1,13	n.a.
2		14,892	1,879	14,450	0,25	0,46	n.a.
3		15,430	1,609	12,533	0,22	0,40	n.a.
4		16,948	1,269	11,942	0,17	0,38	n.a.
5		17,442	670,423	2580,410	90,09	81,57	n.a.
6		19,165	0,714	6,558	0,10	0,21	n.a.
7		19,748	12,298	106,705	1,65	3,37	n.a.
8		22,493	52,450	395,199	7,05	12,49	n.a.
Total:			**744,171**	**3163,614**	**100,00**	**100,00**	

HPLC trace of **10a**.

Chromatogram

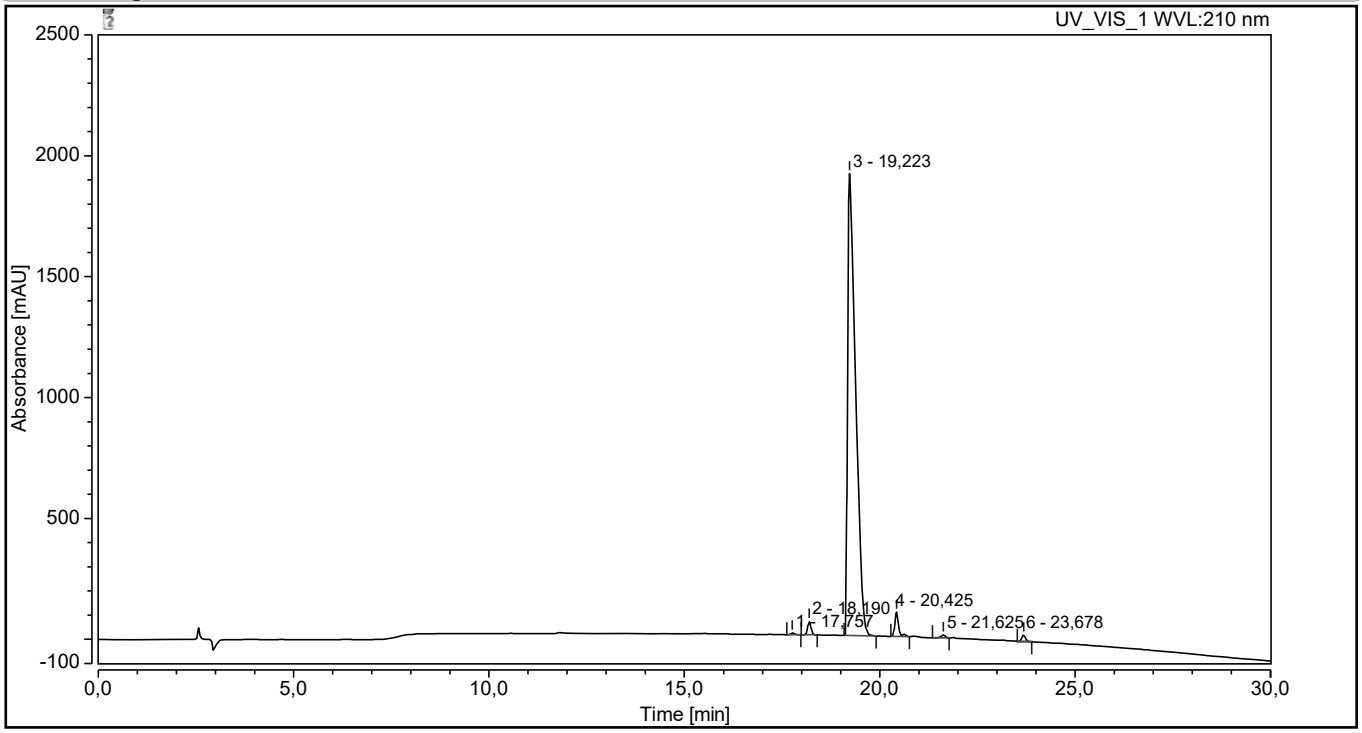


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		18,642	128,188	854,490	91,25	87,94	n.a.
2		22,983	7,060	63,439	5,03	6,53	n.a.
3		24,528	4,116	42,912	2,93	4,42	n.a.
4		25,417	1,121	10,833	0,80	1,11	n.a.
Total:			**140,485**	**971,674**	**100,00**	**100,00**	

HPLC trace of **10b**.

Chromatogram

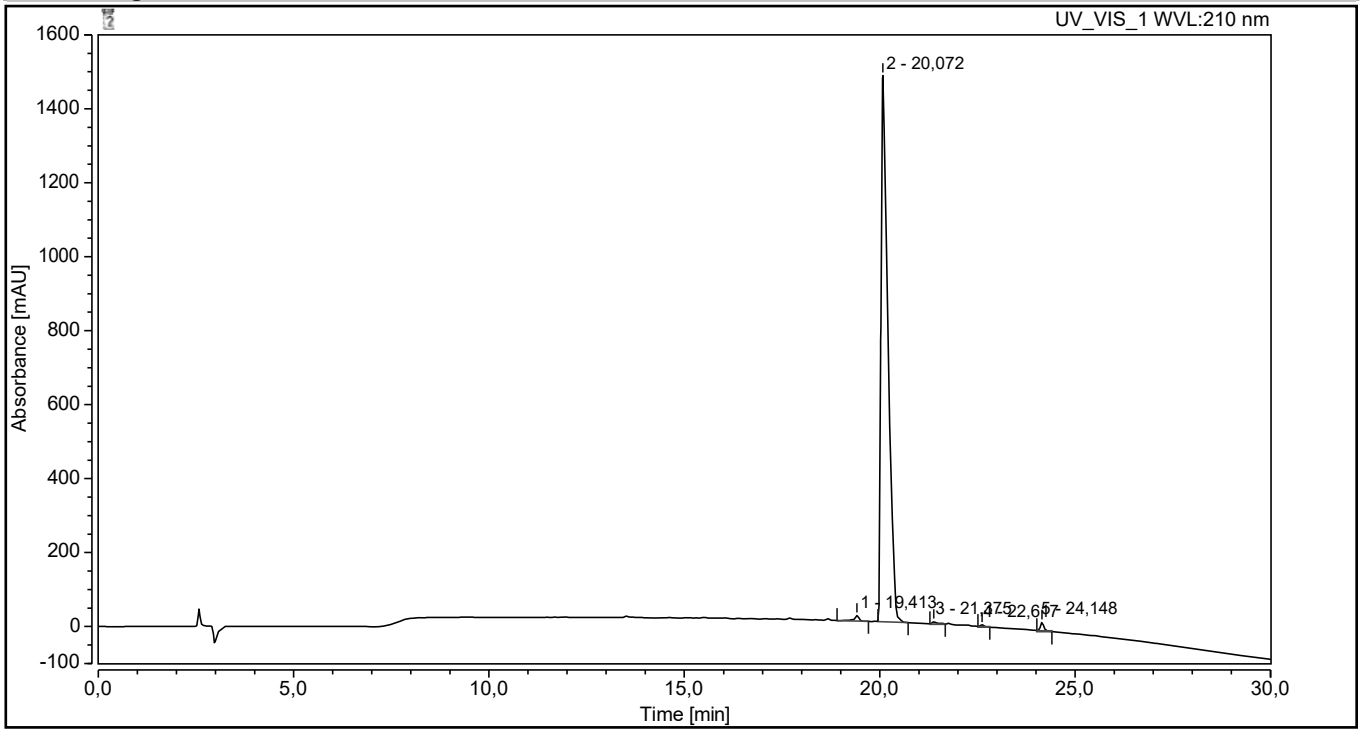


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17,757	0,883	7,659	0,19	0,36	n.a.
2		18,190	5,556	56,612	1,18	2,67	n.a.
3		19,223	448,010	1910,415	95,28	90,22	n.a.
4		20,425	11,061	101,137	2,35	4,78	n.a.
5		21,625	1,794	13,968	0,38	0,66	n.a.
6		23,678	2,882	27,820	0,61	1,31	n.a.
Total:			**470,186**	**2117,611**	**100,00**	**100,00**	

HPLC trace of **10c**.

Chromatogram

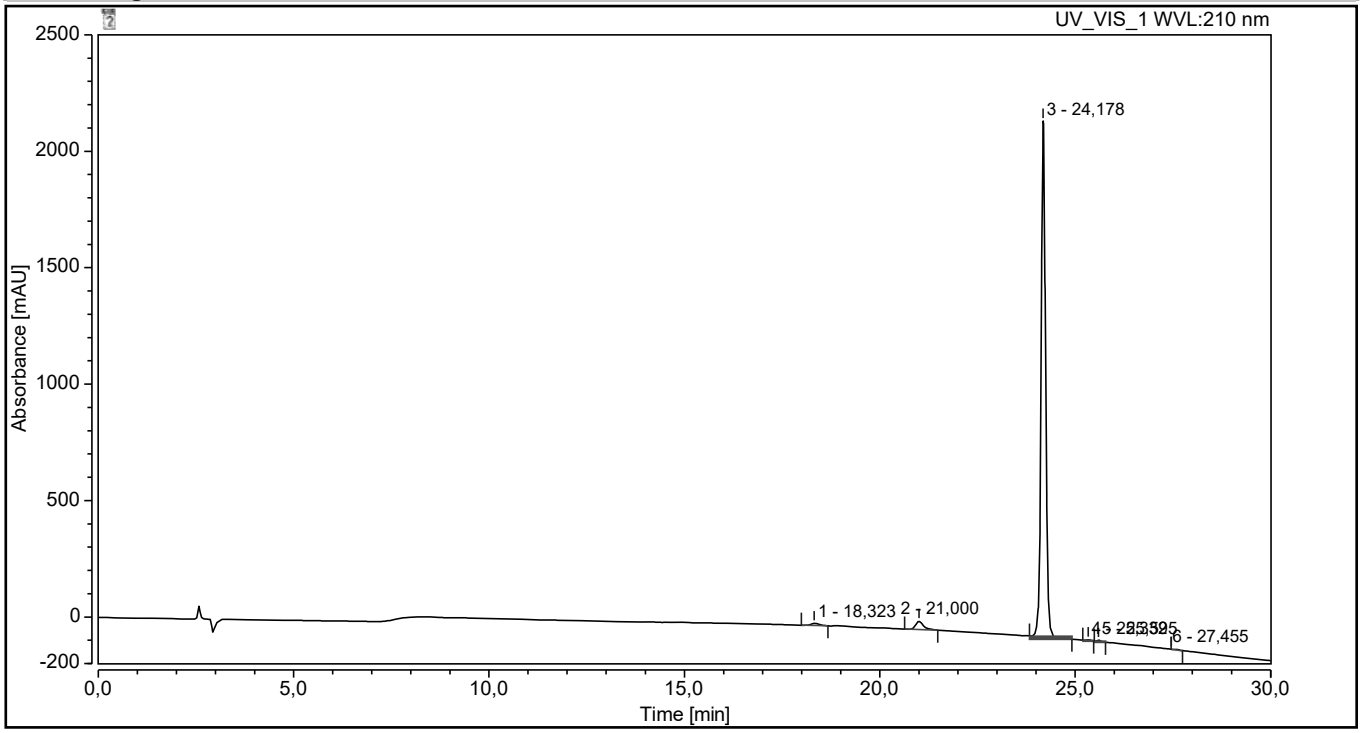


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		19,413	2,192	15,352	0,70	1,01	n.a.
2		20,072	305,488	1476,549	98,02	96,78	n.a.
3		21,375	0,981	5,919	0,31	0,39	n.a.
4		22,617	0,508	4,713	0,16	0,31	n.a.
5		24,148	2,488	23,216	0,80	1,52	n.a.
Total:			**311,658**	**1525,748**	**100,00**	**100,00**	

HPLC trace of **10d**.

Chromatogram

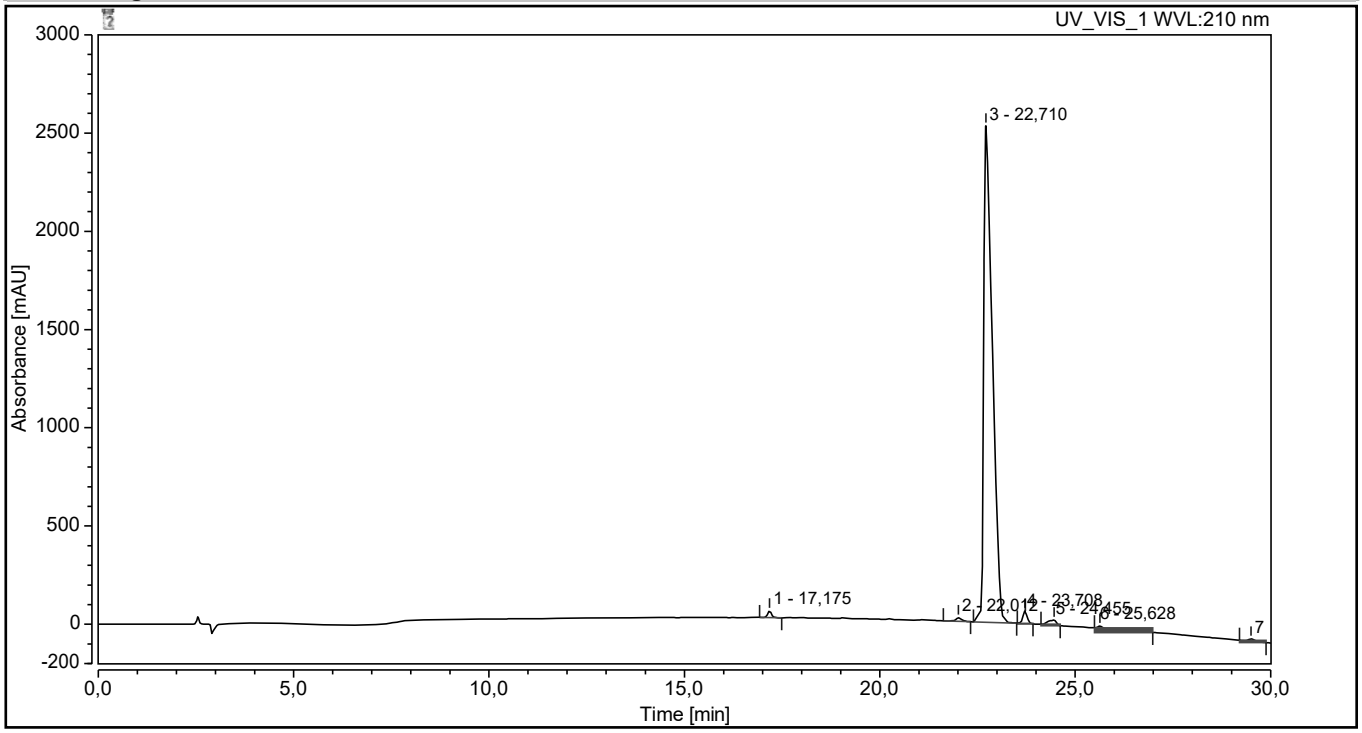


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		18,323	2,279	8,448	0,75	0,37	n.a.
2		21,000	8,043	35,513	2,65	1,56	n.a.
3		24,178	291,885	2215,765	96,15	97,63	n.a.
4		25,332	0,453	4,146	0,15	0,18	n.a.
5		25,595	0,676	5,637	0,22	0,25	n.a.
6		27,455	0,236	0,000	0,08	0,00	n.a.
Total:			**303,572**	**2269,509**	**100,00**	**100,00**	

HPLC trace of **11**.

Chromatogram

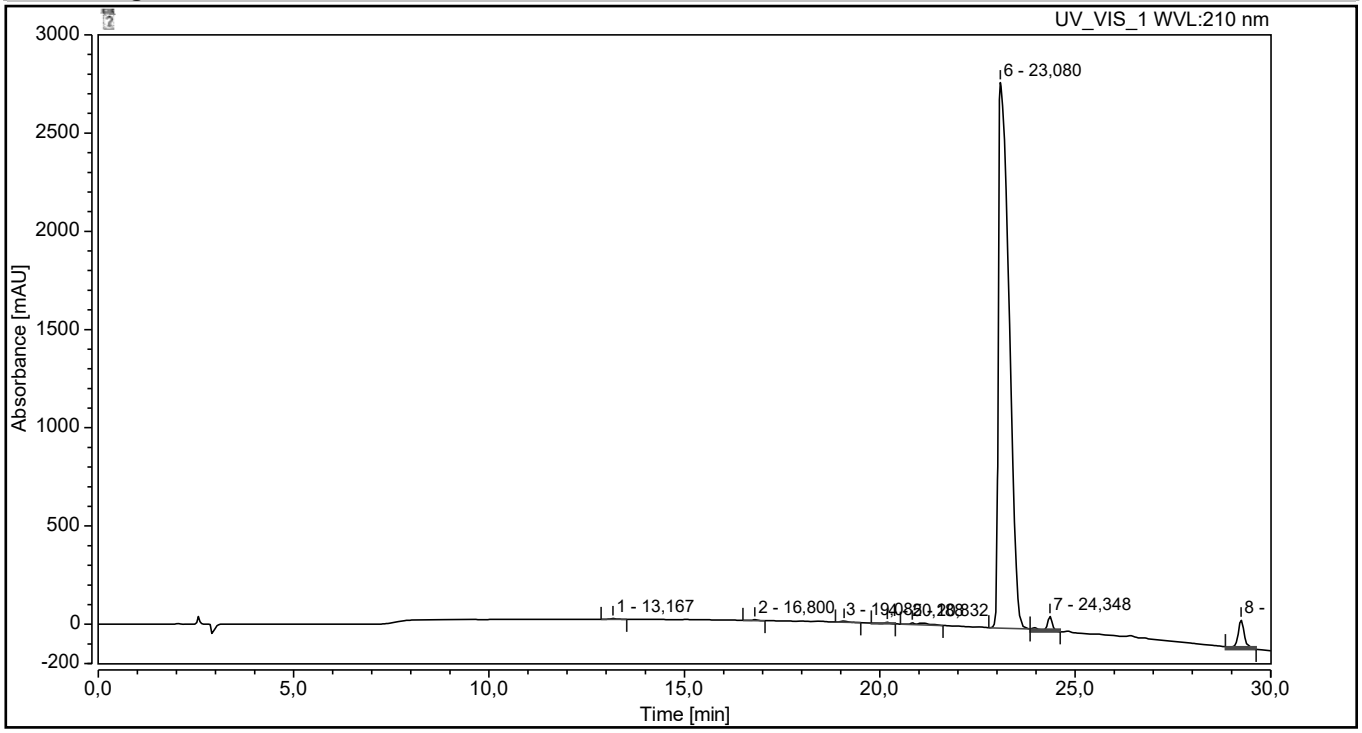


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17,175	3,899	34,283	0,58	1,27	n.a.
2		22,012	3,216	18,886	0,48	0,70	n.a.
3		22,710	638,767	2526,283	95,72	93,81	n.a.
4		23,708	8,309	63,353	1,25	2,35	n.a.
5		24,455	6,411	27,473	0,96	1,02	n.a.
6		25,628	4,459	10,765	0,67	0,40	n.a.
7		29,498	2,278	11,972	0,34	0,44	n.a.
Total:			**667,339**	**2693,015**	**100,00**	**100,00**	

HPLC trace of **12a**.

Chromatogram

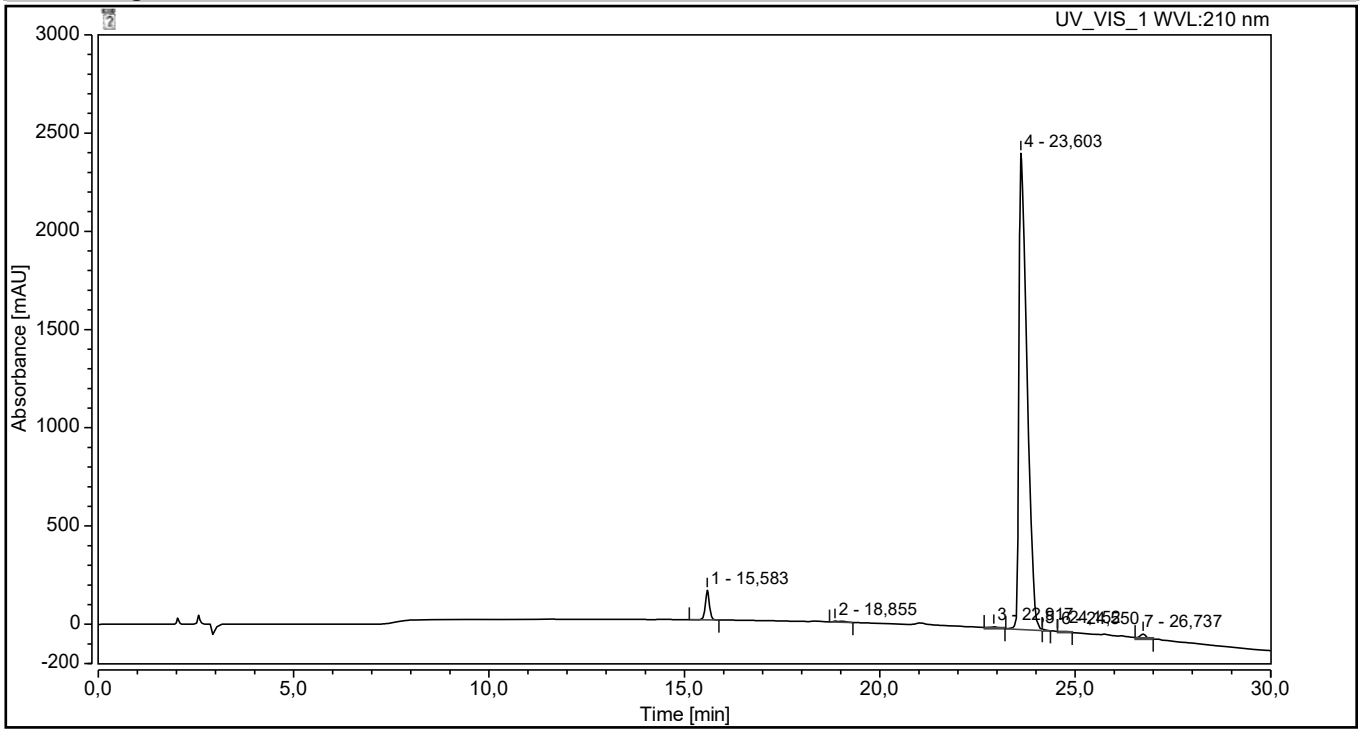


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13,167	0,627	3,874	0,07	0,13	n.a.
2		16,800	0,584	4,584	0,06	0,15	n.a.
3		19,082	1,359	6,120	0,15	0,20	n.a.
4		20,188	0,672	6,621	0,07	0,22	n.a.
5		20,832	3,727	7,598	0,40	0,25	n.a.
6		23,080	877,291	2776,958	95,31	91,86	n.a.
7		24,348	11,025	73,573	1,20	2,43	n.a.
8		29,238	25,179	143,697	2,74	4,75	n.a.
Total:			**920,464**	**3023,026**	**100,00**	**100,00**	

HPLC trace of **12b**.

Chromatogram

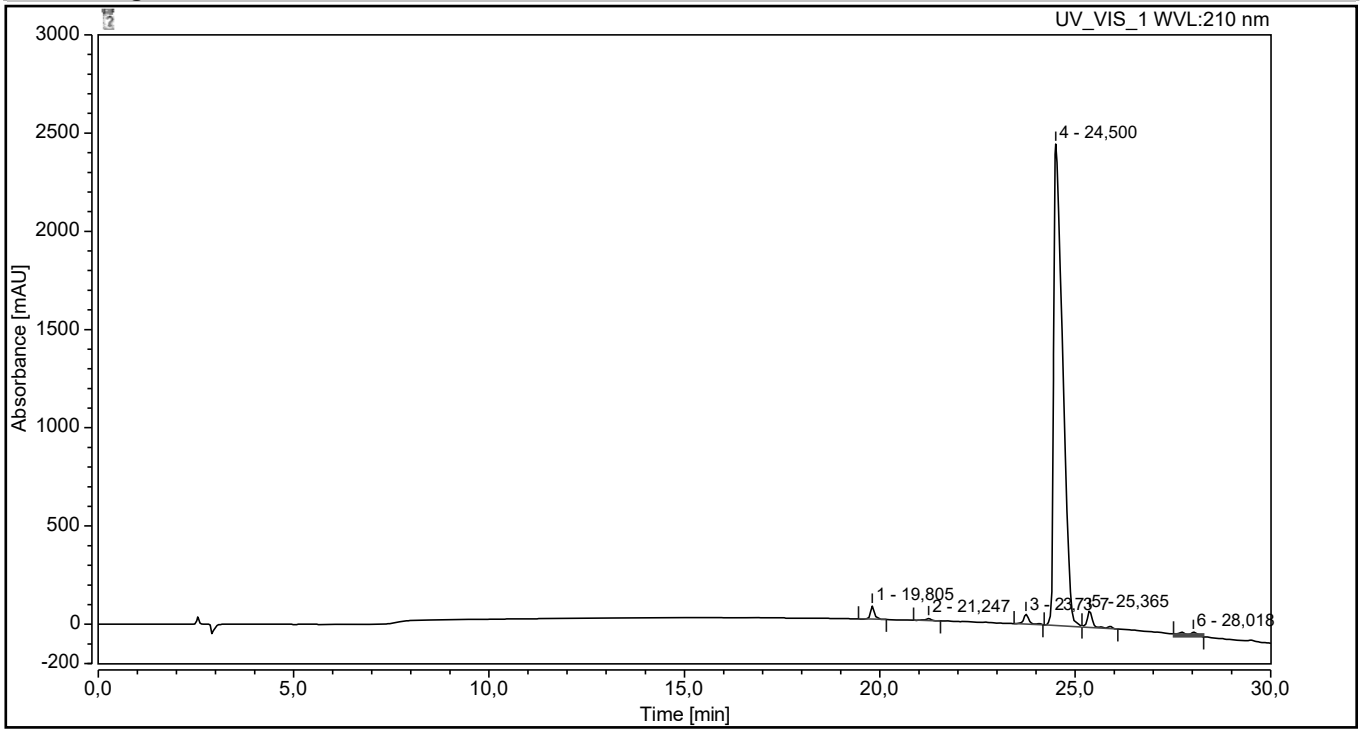


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15,583	17,950	150,534	2,99	5,76	n.a.
2		18,855	1,553	4,828	0,26	0,18	n.a.
3		22,917	1,117	6,566	0,19	0,25	n.a.
4		23,603	575,167	2423,235	95,82	92,78	n.a.
5		24,152	0,478	4,818	0,08	0,18	n.a.
6		24,550	0,454	0,000	0,08	0,00	n.a.
7		26,737	3,543	21,881	0,59	0,84	n.a.
Total:			**600,262**	**2611,862**	**100,00**	**100,00**	

HPLC trace of **12c**.

Chromatogram

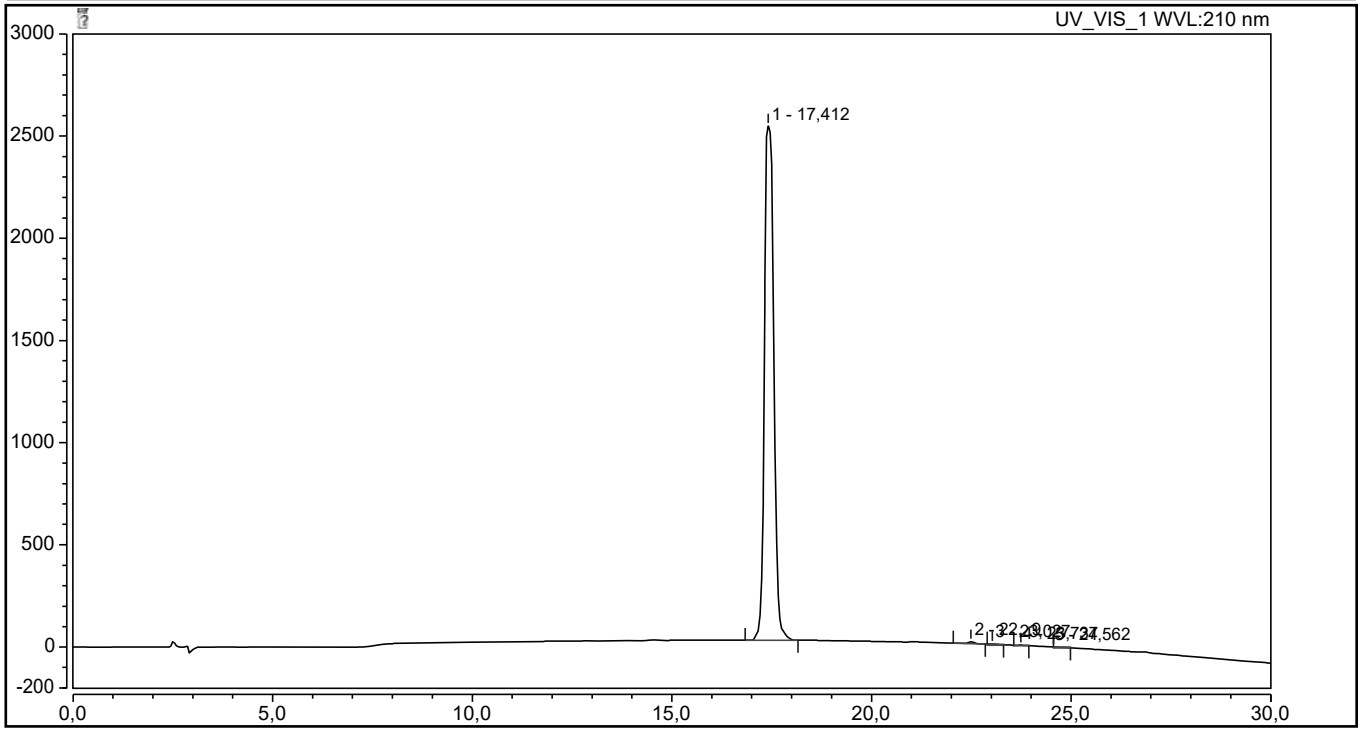


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		19,805	7,964	66,659	1,15	2,48	n.a.
2		21,247	2,073	11,186	0,30	0,42	n.a.
3		23,737	8,347	49,882	1,21	1,86	n.a.
4		24,500	651,234	2450,336	94,40	91,31	n.a.
5		25,365	15,238	86,521	2,21	3,22	n.a.
6		28,018	5,016	18,993	0,73	0,71	n.a.
Total:			**689,872**	**2683,576**	**100,00**	**100,00**	

HPLC trace of **12d**.

Chromatogram

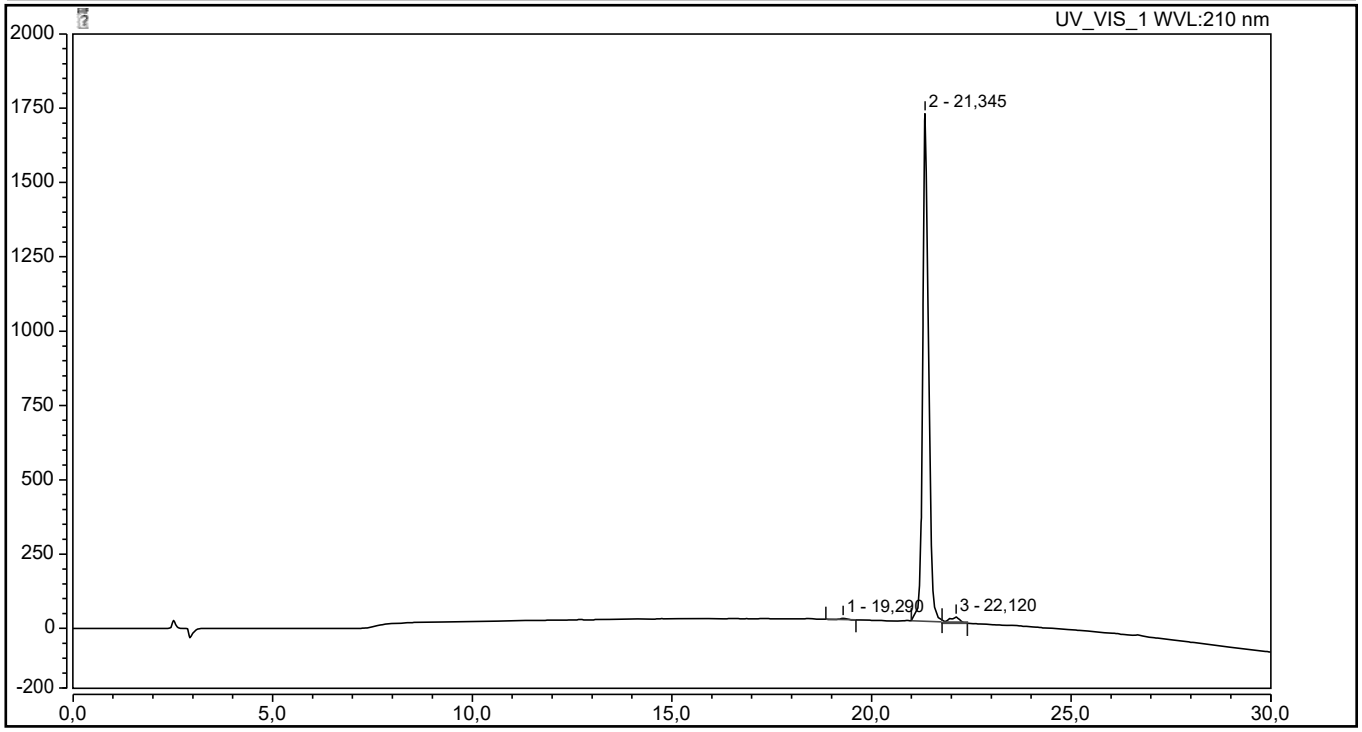


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17,412	674,290	2516,359	99,58	99,48	n.a.
2		22,490	1,939	9,207	0,29	0,36	n.a.
3		23,027	0,396	2,303	0,06	0,09	n.a.
4		23,737	0,287	1,640	0,04	0,06	n.a.
5		24,562	0,229	0,000	0,03	0,00	n.a.
Total:			**677,141**	**2529,508**	**100,00**	**100,00**	

HPLC trace of **14**.

Chromatogram

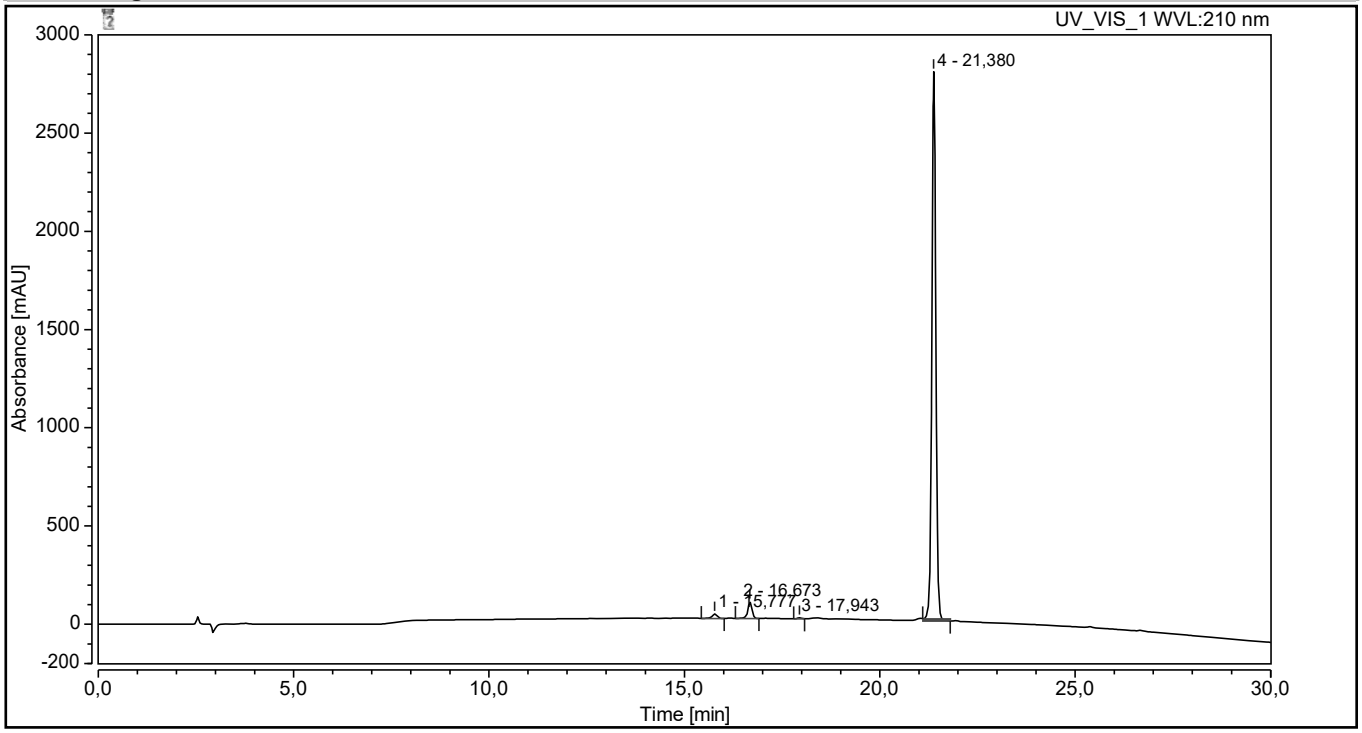


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		19,290	0,904	4,743	0,31	0,27	n.a.
2		21,345	289,982	1707,447	97,85	98,59	n.a.
3		22,120	5,470	19,729	1,85	1,14	n.a.
Total:			**296,355**	**1731,919**	**100,00**	**100,00**	

HPLC trace of **15**.

Chromatogram

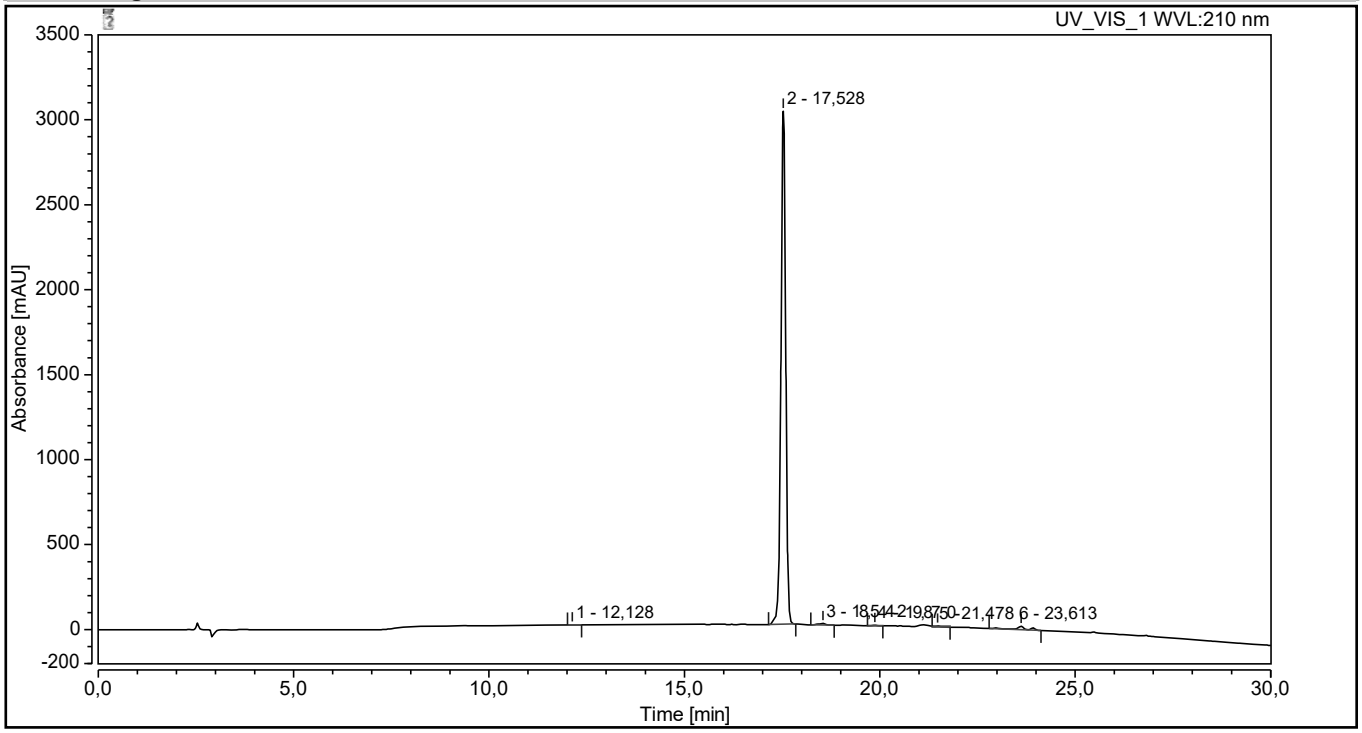


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15,777	3,353	22,171	0,98	0,76	n.a.
2		16,673	10,351	84,406	3,04	2,91	n.a.
3		17,943	0,559	5,291	0,16	0,18	n.a.
4		21,380	326,210	2788,329	95,81	96,14	n.a.
Total:			**340,474**	**2900,198**	**100,00**	**100,00**	

HPLC trace of **16**.

Chromatogram

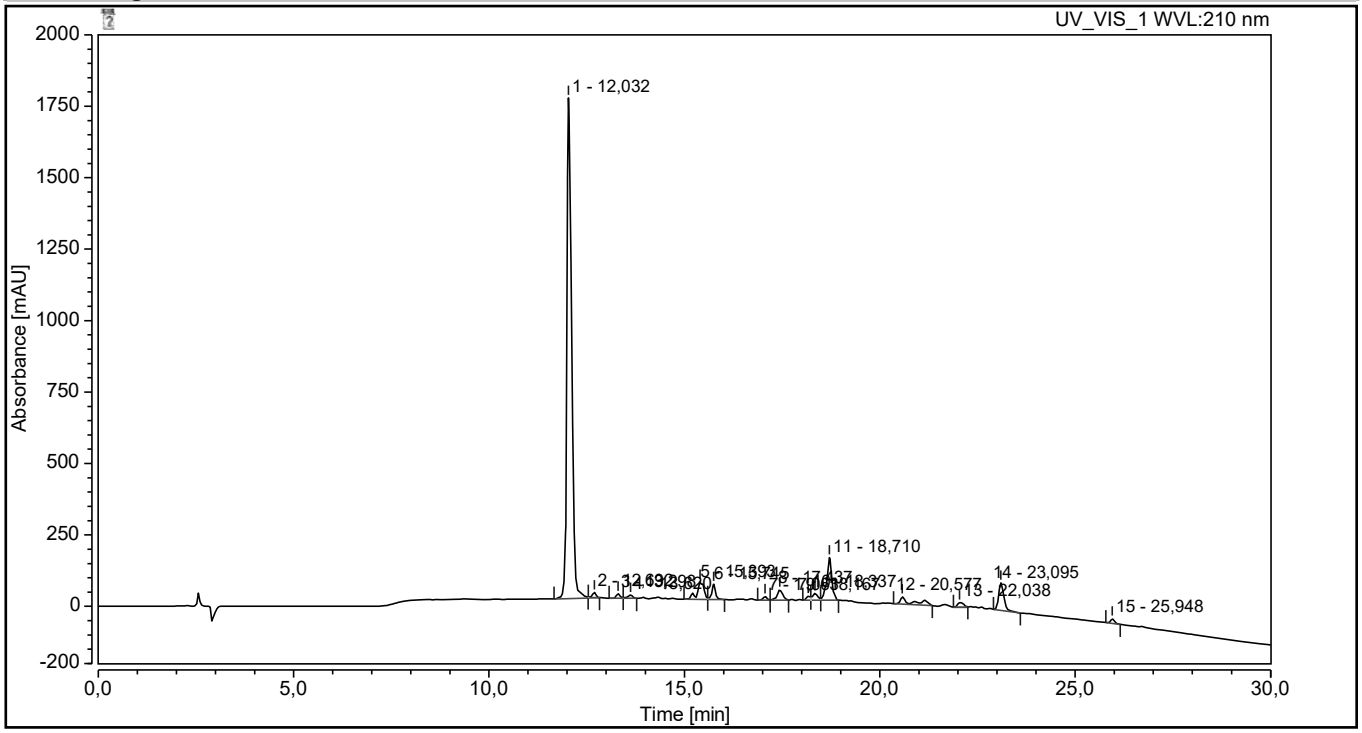


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12,128	0,208	1,698	0,05	0,06	n.a.
2		17,528	428,189	3020,761	98,10	98,74	n.a.
3		18,542	2,053	10,318	0,47	0,34	n.a.
4		19,870	0,426	3,573	0,10	0,12	n.a.
5		21,478	0,119	3,156	0,03	0,10	n.a.
6		23,613	5,472	19,916	1,25	0,65	n.a.
Total:			**436,466**	**3059,423**	**100,00**	**100,00**	

HPLC trace of **17**.

Chromatogram

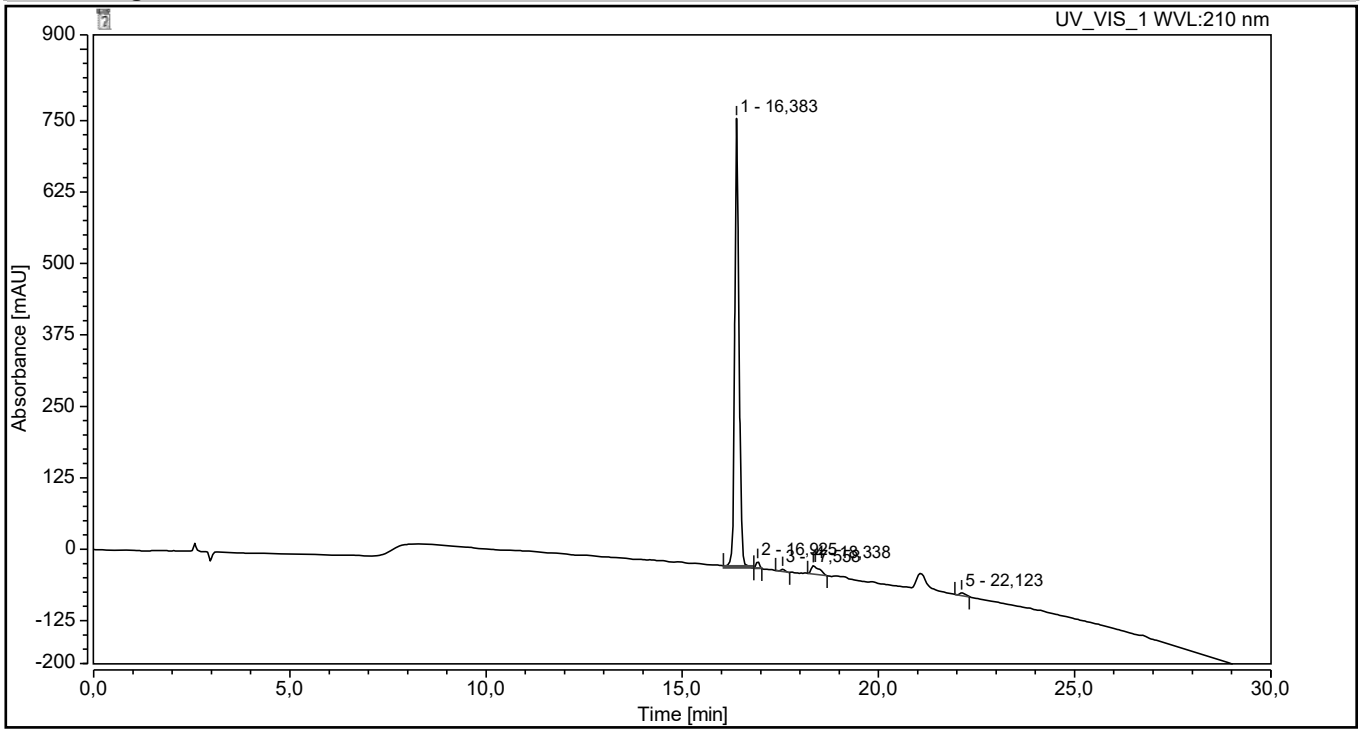


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12,032	243,071	1751,807	73,47	76,04	n.a.
2		12,692	2,154	18,864	0,65	0,82	n.a.
3		13,298	1,862	15,727	0,56	0,68	n.a.
4		13,620	1,738	11,619	0,53	0,50	n.a.
5		15,393	12,460	61,203	3,77	2,66	n.a.
6		15,745	5,986	53,365	1,81	2,32	n.a.
7		17,063	1,471	13,044	0,44	0,57	n.a.
8		17,437	6,145	36,322	1,86	1,58	n.a.
9		18,167	1,624	13,969	0,49	0,61	n.a.
10		18,337	3,745	23,967	1,13	1,04	n.a.
11		18,710	22,277	149,791	6,73	6,50	n.a.
12		20,577	8,706	26,180	2,63	1,14	n.a.
13		22,038	2,616	15,286	0,79	0,66	n.a.
14		23,095	15,210	96,566	4,60	4,19	n.a.
15		25,948	1,800	16,105	0,54	0,70	n.a.
Total:			**330,865**	**2303,814**	**100,00**	**100,00**	

HPLC trace of **18**.

Chromatogram

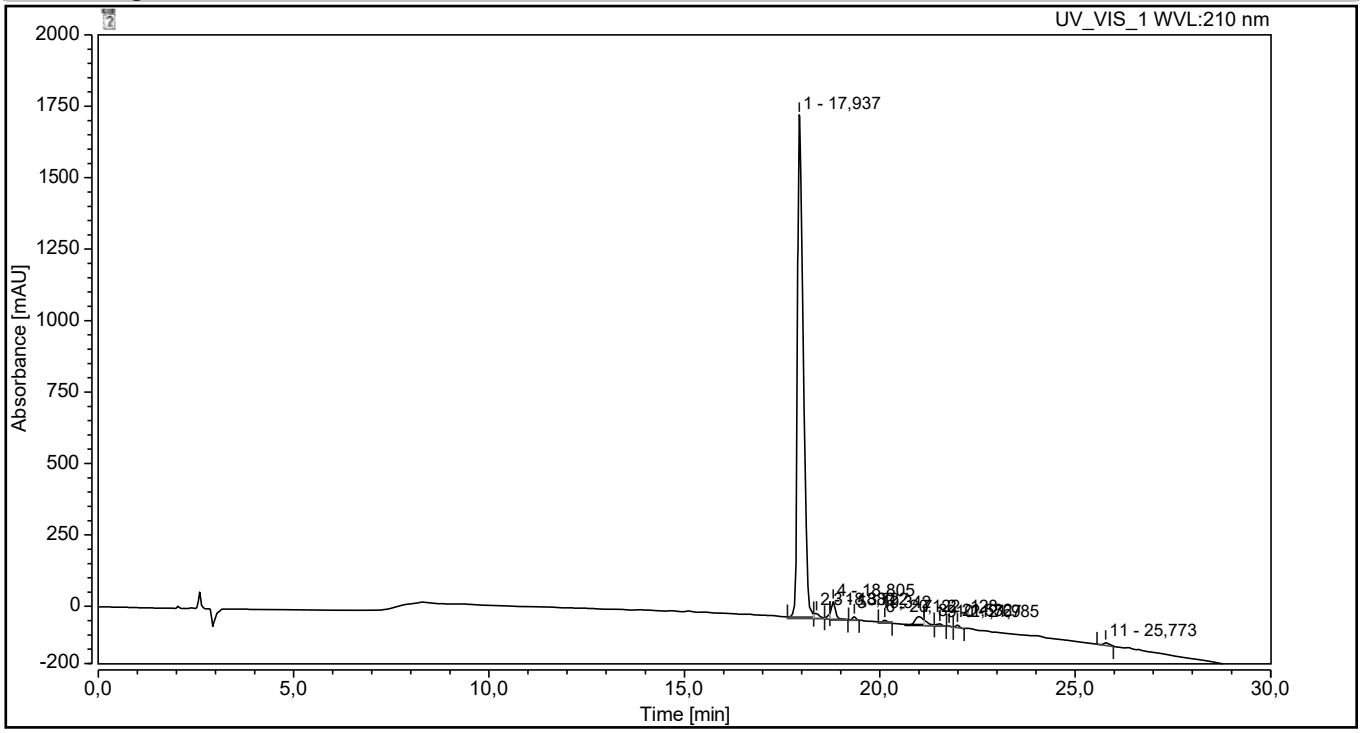


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		16,383	97,937	784,150	94,44	95,62	n.a.
2		16,925	1,175	12,101	1,13	1,48	n.a.
3		17,558	0,370	3,707	0,36	0,45	n.a.
4		18,338	3,609	14,931	3,48	1,82	n.a.
5		22,123	0,612	5,213	0,59	0,64	n.a.
Total:			**103,704**	**820,101**	**100,00**	**100,00**	

HPLC trace of **19a**.

Chromatogram

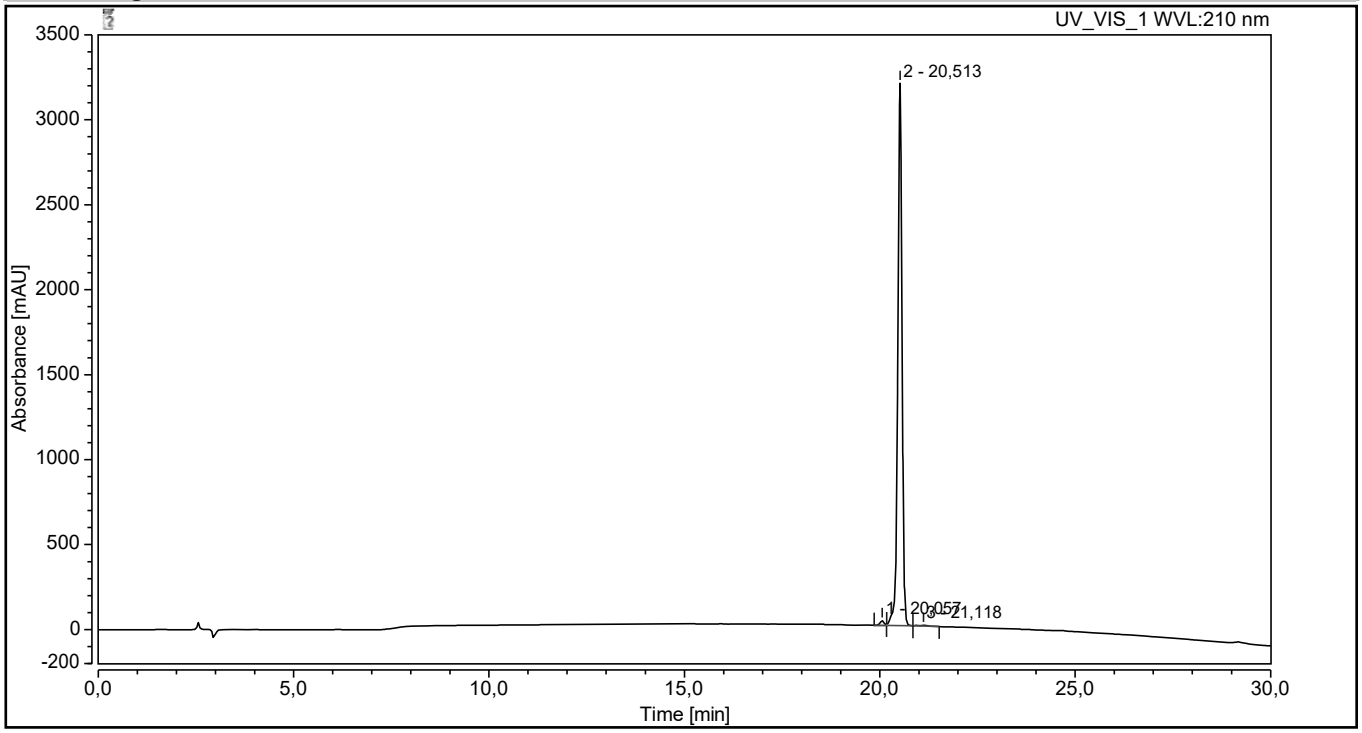


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17,937	299,237	1758,587	93,69	91,44	n.a.
2		18,380	2,980	16,891	0,93	0,88	n.a.
3		18,722	1,365	19,632	0,43	1,02	n.a.
4		18,805	7,897	61,578	2,47	3,20	n.a.
5		19,342	1,362	12,567	0,43	0,65	n.a.
6		20,122	1,066	7,769	0,33	0,40	n.a.
7		21,128	2,109	18,328	0,66	0,95	n.a.
8		21,532	1,139	6,955	0,36	0,36	n.a.
9		21,767	0,166	2,342	0,05	0,12	n.a.
10		21,985	0,969	9,519	0,30	0,49	n.a.
11		25,773	1,112	9,041	0,35	0,47	n.a.
Total:			**319,403**	**1923,208**	**100,00**	**100,00**	

HPLC trace of **19c**.

Chromatogram

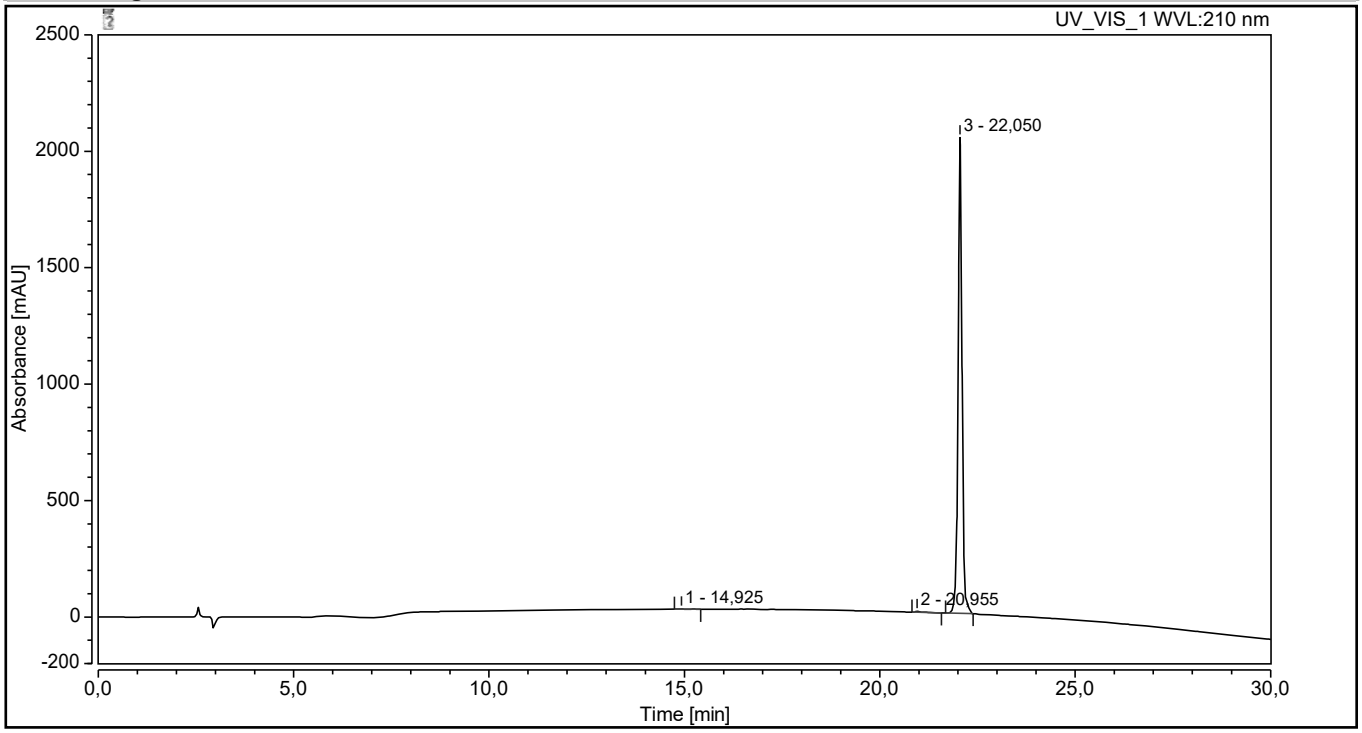


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		20,057	3,227	27,965	0,80	0,87	n.a.
2		20,513	396,388	3191,679	98,77	98,94	n.a.
3		21,118	1,727	6,296	0,43	0,20	n.a.
Total:			**401,342**	**3225,940**	**100,00**	**100,00**	

HPLC trace of **20**.

Chromatogram

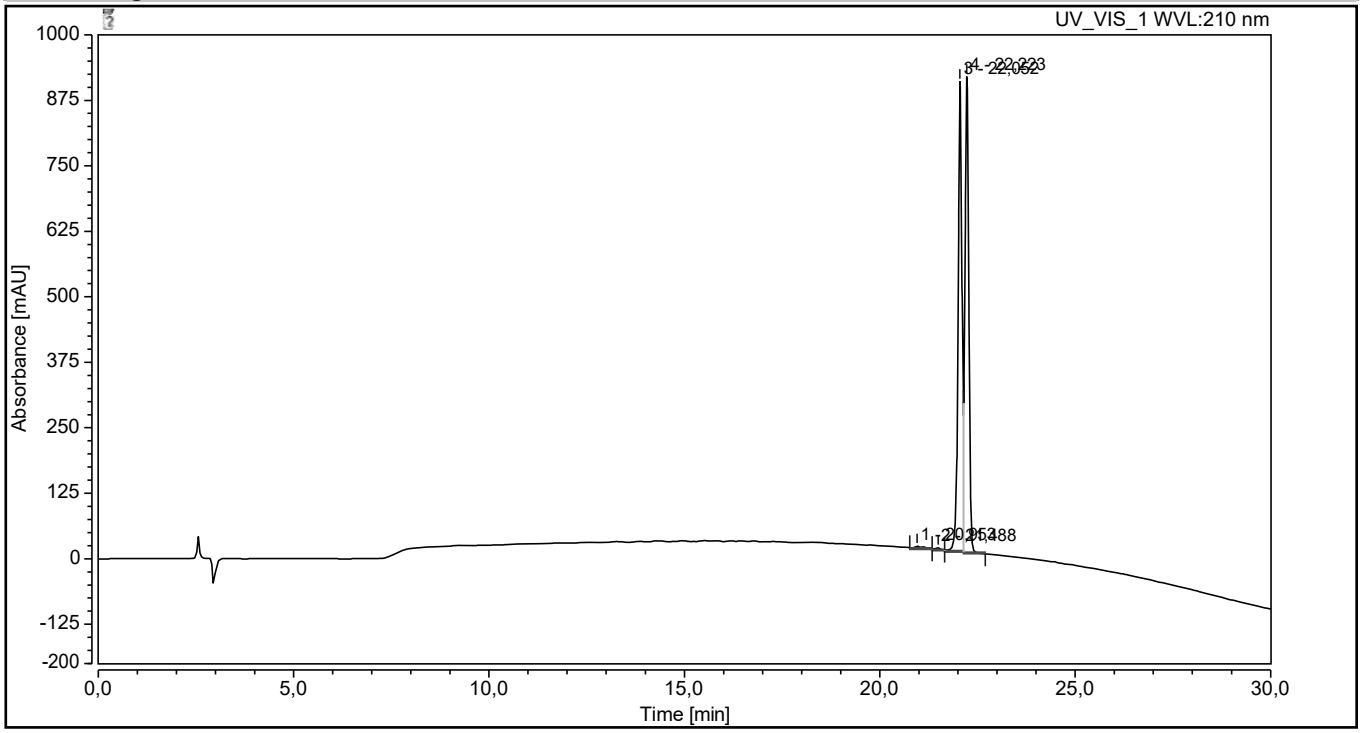


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		14,925	0,561	1,884	0,23	0,09	n.a.
2		20,955	0,953	3,674	0,40	0,18	n.a.
3		22,050	239,475	2043,221	99,37	99,73	n.a.
Total:			**240,990**	**2048,780**	**100,00**	**100,00**	

HPLC trace of (*Z*)-**21**.

Chromatogram

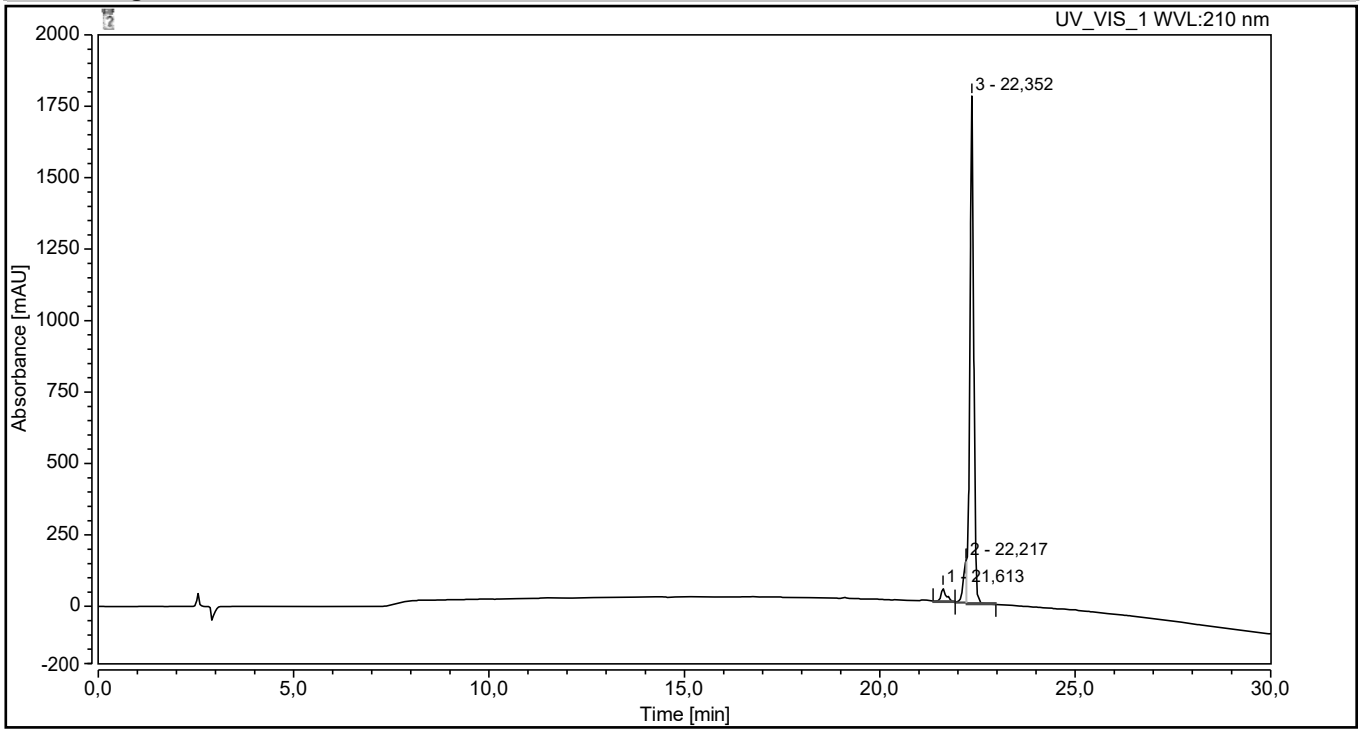


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		20,953	1,284	4,038	0,62	0,22	n.a.
2		21,488	0,732	4,234	0,35	0,23	n.a.
3		22,052	104,272	897,001	50,37	49,48	n.a.
4		22,223	100,712	907,602	48,65	50,06	n.a.
Total:			**207,000**	**1812,875**	**100,00**	**100,00**	

HPLC trace of (*Z*/*E*)-**21**.

Chromatogram

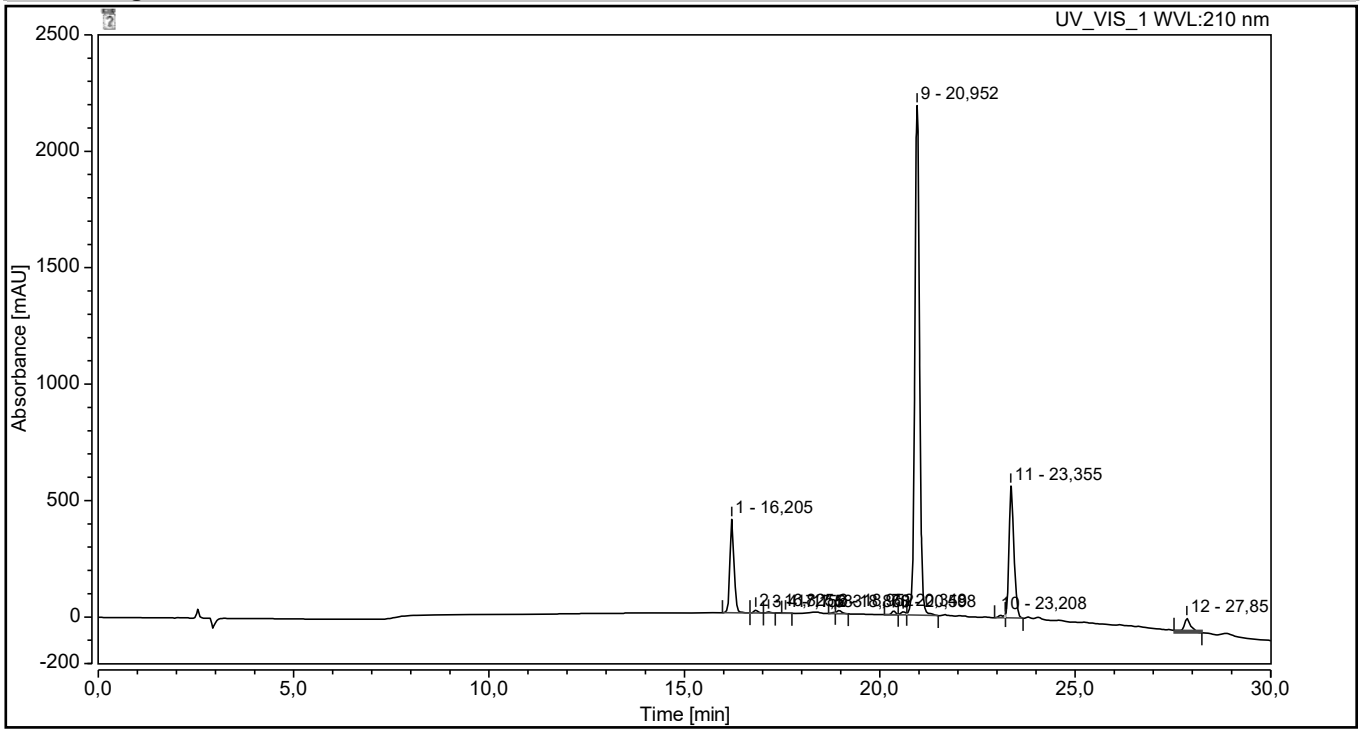


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		21,613	7,007	46,564	3,16	2,37	n.a.
2		22,217	13,568	144,861	6,11	7,37	n.a.
3		22,352	201,366	1773,405	90,73	90,26	n.a.
Total:			**221,940**	**1964,830**	**100,00**	**100,00**	

HPLC trace of (*E*)-**21**.

Chromatogram

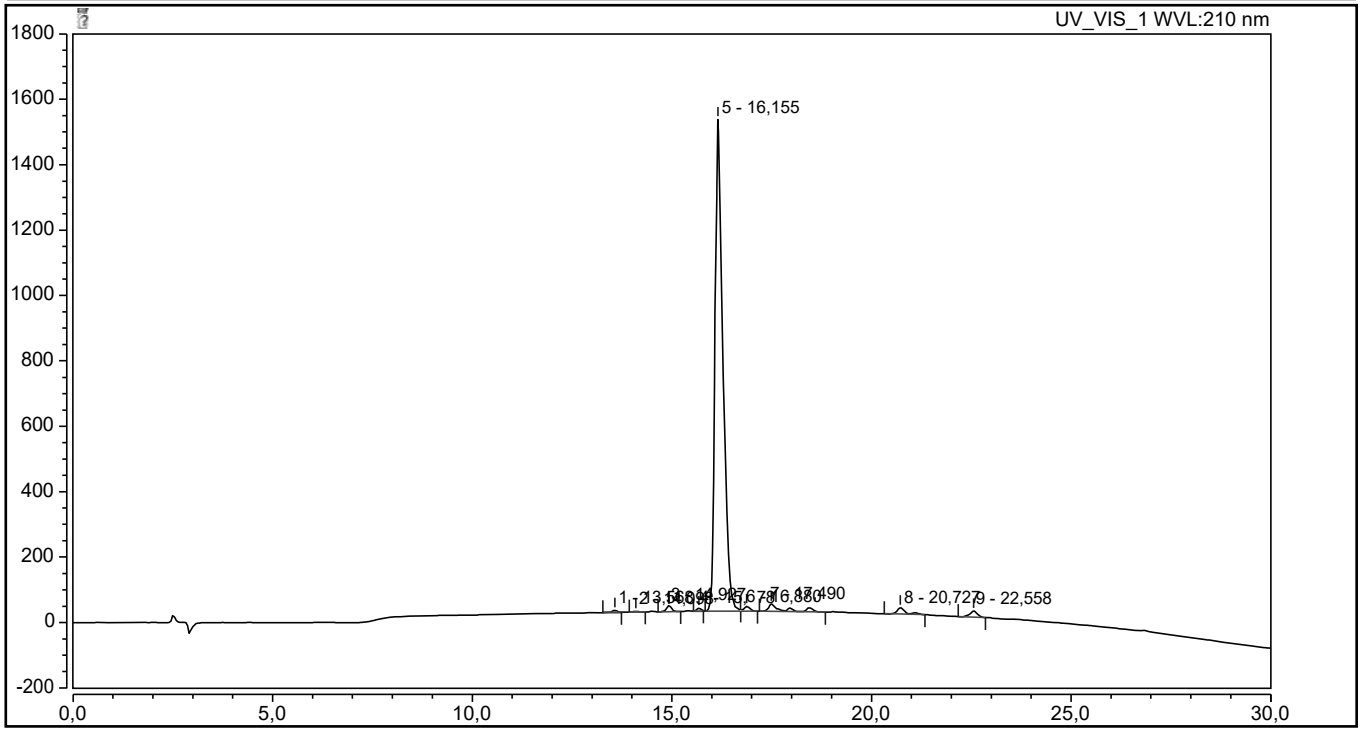


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		16,205	49,445	401,419	10,75	12,17	n.a.
2		16,825	1,529	12,714	0,33	0,39	n.a.
3		17,152	0,635	5,805	0,14	0,18	n.a.
4		17,583	0,219	2,163	0,05	0,07	n.a.
5		18,860	0,456	5,238	0,10	0,16	n.a.
6		18,952	2,038	14,042	0,44	0,43	n.a.
7		20,348	2,071	17,703	0,45	0,54	n.a.
8		20,598	2,021	13,715	0,44	0,42	n.a.
9		20,952	306,354	2187,853	66,61	66,33	n.a.
10		23,208	1,908	14,485	0,41	0,44	n.a.
11		23,355	83,828	567,101	18,23	17,19	n.a.
12		27,855	9,423	56,040	2,05	1,70	n.a.
Total:			**459,926**	**3298,277**	**100,00**	**100,00**	

HPLC trace of **22**.

Chromatogram

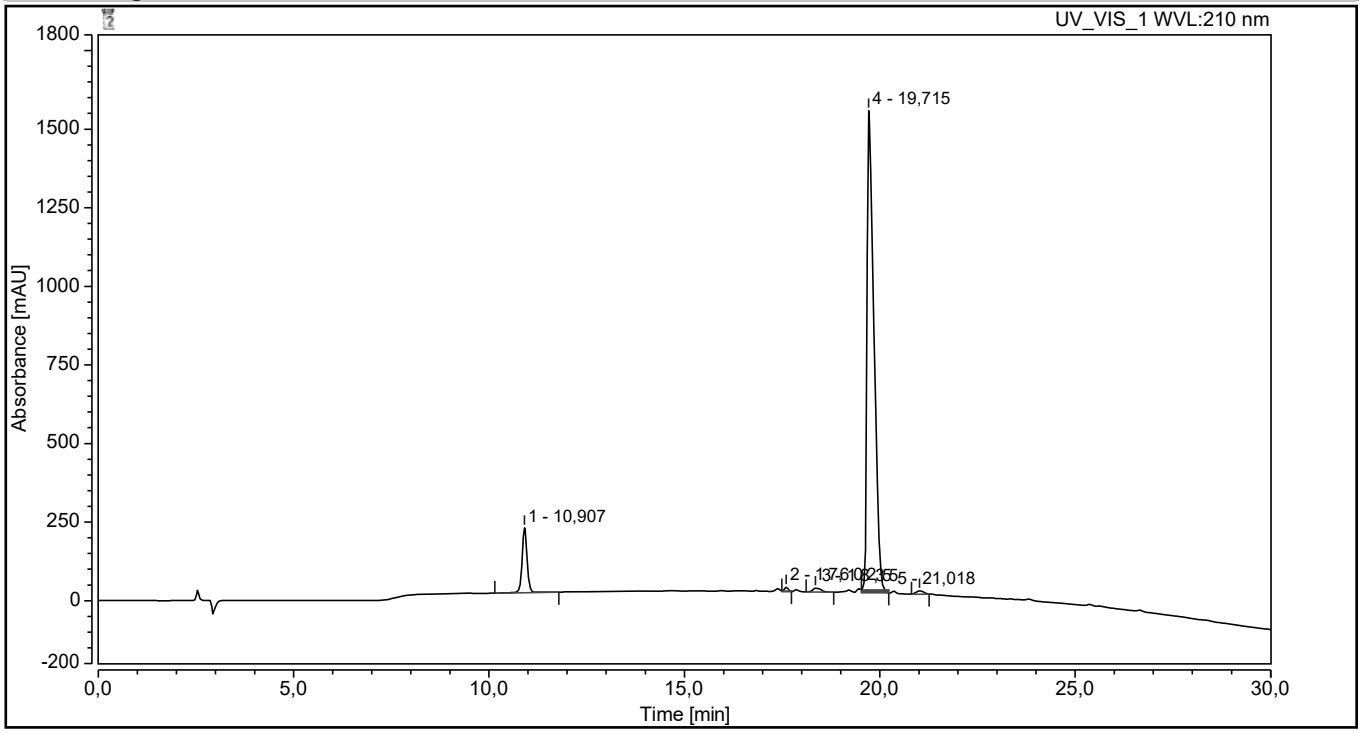


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13,568	0,895	6,029	0,24	0,37	n.a.
2		14,098	0,290	1,992	0,08	0,12	n.a.
3		14,927	2,781	18,051	0,75	1,12	n.a.
4		15,678	1,057	8,548	0,29	0,53	n.a.
5		16,155	342,196	1503,746	92,83	93,08	n.a.
6		16,880	2,661	15,191	0,72	0,94	n.a.
7		17,490	9,468	23,564	2,57	1,46	n.a.
8		20,727	5,165	19,589	1,40	1,21	n.a.
9		22,558	4,095	18,764	1,11	1,16	n.a.
Total:			**368,609**	**1615,474**	**100,00**	**100,00**	

HPLC trace of **23**.

Chromatogram

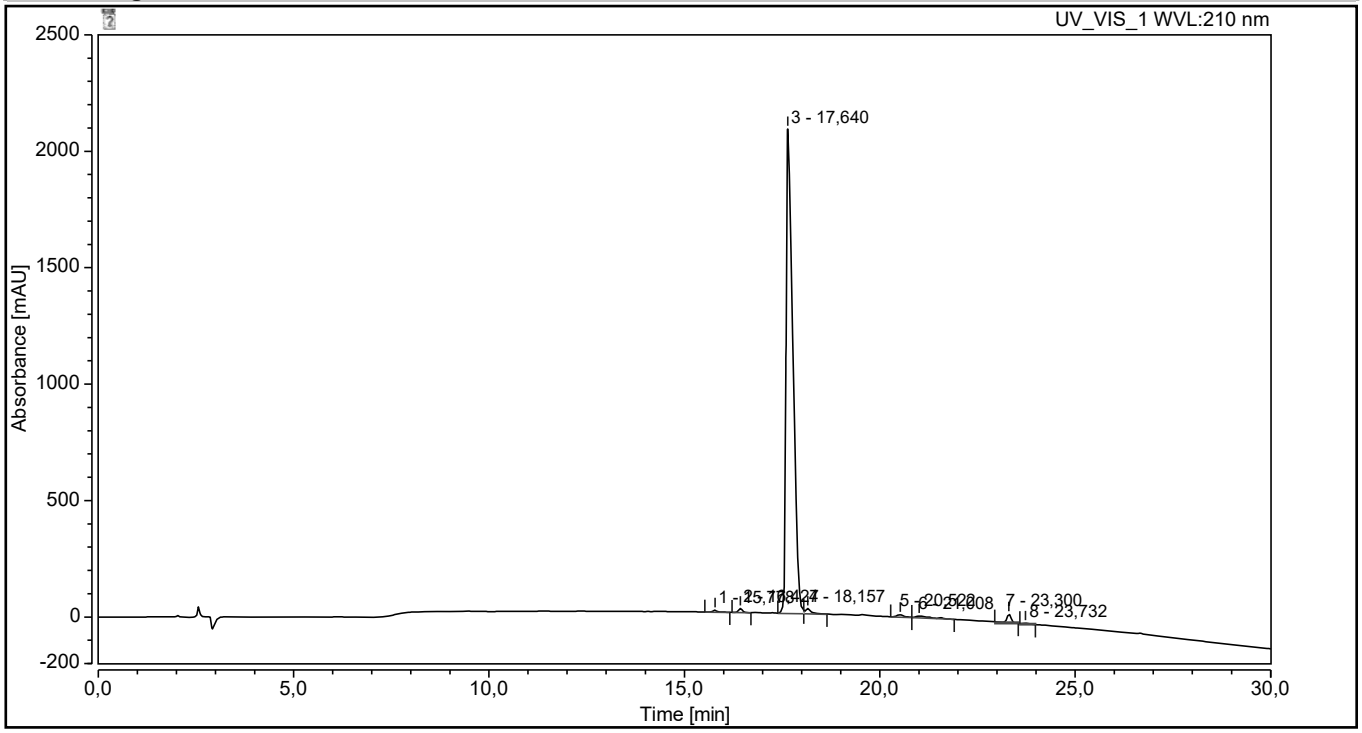


Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10,907	30,234	206,141	8,69	11,66	n.a.
2		17,602	1,288	12,530	0,37	0,71	n.a.
3		18,355	2,890	11,882	0,83	0,67	n.a.
4		19,715	311,265	1526,974	89,47	86,39	n.a.
5		21,018	2,226	10,023	0,64	0,57	n.a.
Total:			**347,904**	**1767,550**	**100,00**	**100,00**	

HPLC trace of **24**.

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15,778	1,124	8,209	0,26	0,38	n.a.
2		16,427	1,999	17,622	0,46	0,81	n.a.
3		17,640	420,209	2080,420	96,08	95,16	n.a.
4		18,157	3,971	23,043	0,91	1,05	n.a.
5		20,522	1,973	9,898	0,45	0,45	n.a.
6		21,008	2,948	6,362	0,67	0,29	n.a.
7		23,300	4,627	36,991	1,06	1,69	n.a.
8		23,732	0,512	3,580	0,12	0,16	n.a.
Total:			**437,364**	**2186,124**	**100,00**	**100,00**	

HPLC trace of **25**.