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Supporting Information

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S1. General Experimental Procedures.

Optical rotations were measured at 25 °C on an Anton Paar MCP 300 polarimeter. UV spectra were recorded on a Varian Cary 100 UV-vis spectrophotometer. CD spectra were measured at 25 °C on a JASCO J-810 spectropolarimeter. NMR spectra were recorded on a Bruker 500 MHz instrument (Avance 500) for compounds **3**, **16**, **17**, **19** to **21** and **23**, **24**, **26** and **27** and on a Bruker 600 MHz instrument (Avance 600) for compounds **1**, **2**, **4**, **5**, **22** and **28**. Chemical shifts (relative to $CDCl_3$) are in ppm, and coupling constants are in Hz. Kinetex analytical and semi-preparative C_{18} columns (250 × 4.6 mm and 250 × 10 mm; 5 μm Phenomenex) and a Nucleodur PFP semi-preparative column (250 × 10 mm; 5 μm Macherey-Nagel) were used for HPLC separations using a Dionex system equipped with a sample manager (Gilson 215 Liquid Handler), a column fluidics organizer, a binary pump (Dionex HPG-3200BX), a UV−vis diode array detector (190−600 nm, Dionex UVD340U), and a PL-ELS 1000 ELS Polymer Laboratory detector. HPLC separation were also undertaken using a Waters alliance system equipped with a binary pump (Waters 2525), a UV−vis diode array detector (190−600 nm, Waters 2996) and an ELS detector (Waters 2424). Disconnected from ELSD, this system was also used in preparative mode to purify small amounts of products. HRMS data were acquired either using the LC-MS^2 method and instrumentation described below or using an Acquity Waters UPLC coupled to a Waters LCT Premier XE mass spectrometer. The UPLC system was equipped with a Waters Acquity PDA dectector. Separation was achieved on a $BEHC_{18}$ column (1.7 μm, 2.1 mm × 50 mm) at a flow rate of 0.6 $mL.min^{-1}$. Elution was conducted with a H_2O-CH_3CN + 0.1% formic acid gradient as follows: 95:5 to 0:100 in 5.5 min. The ionization was carried out using an electrospray ionization source in the positive mode (range 80−1500 *m/z*). All solvents were purchased from Carlo Erba (France) or SDS (Peypin, France) and analytical plates (Si gel 60 F254) were from Merck (France). Chloroperoxidase (CPO, EC 1.11.1.10) from *Caldariomyces fumago* was purchased from Sigma-Aldrich as a brown aqueous suspension (3,000 and >10,000 U/mL) and used as received. Prepacked GraceResolv silica cartridges were used for flash chromatography using a Teledyne Isco Combiflash Rf 200i.

S2. NMR Chemical shifts and spectroscopic data of compounds **1** to **5**.

	1		**2**		**3**		**4**		**5**	
Position	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	-	-	-	-	-	9.25 brs	-	-	-	-
2	156.5	-	162.9	-	163.4	-	162.7	-		-
3	99.8	-	106.3	-	106.0	-	105.7	-	105.1	-
4	176.7	-	157.5	-	159.4	-	158.7	-	159.2	-
4a	124.6	-	116.9	-	116.4	-	117.1	-	116.9	-
5	126.9	8.43 dd (7.8, 1.4)	123.4	7.98 dd (8.0, 1.4)	123.2	7.87 d (8.1)	123.7	7.90 d (8.0)	123.5	7.95 dd (8.1, 1.3)
6	123.0	7.32 dd (7.8, 7.2)	121.8	7.23 dd (8.0, 7.1)	122.4	7.17 dd (8.1, 7.2)	122.7	7.18 dd (8.0, 7.2)	122.5	7.23 dd (8.1,7.2)
7	131.6	7.58 ddd (8.5, 7.2, 1.4)	130.6	7.55 ddd (8.5, 7.1, 1.4)	130.7	7.45 dd (8.3, 7.2)	131.1	7.46 dd (8.5, 7.2)	130.9	7.51 ddd (8.5, 7.2, 1.3)
8	114.6	7.38 d (8.5)	114.1	7.34 d (8.5)	115.1	7.13 d (8.3)	113.9	7.26 d (8.5)	113.5	7.30 d (8.5)
8a	139.2	-	139.0	-	136.9	-	137.9	-	137.5	-
1′	72.1	-	72.4	-	72.6	-	72.5	-	71.7	-
2′	65.3	6.07 brs	65.5	5.81 brs	65.0	5.76 brs	65.1	5.58 brs	72.4	5.09 brs
3′	35.7	3.82 dd (11.7, 2.2)	36.0	3.60 dd (11.4, 2.6)	35.6	3.54 brd (11.1)	35.8	3.46 dd (11.4, 2.3)	35.6	3.16 dd (11.8, 2.2)
4′	40.1	2.14 ddd (12.2, 11.7, 3.0)	40.1	2.17 ddd (12.0, 11.4, 3.6)	39.8	2.13 ddd (12.2, 11.1, 3.0)	40.0	2.08 ddd (12.5, 11.4, 2.9)	39.2	2.02 ddd (12.4, 11.8, 2.9)
5′*α*	22.9	1.62 m	22.9	1.63 m	22.8	1.58 m	22.8	1.53 m	22.7	1.51 m[a]
5′*β*		1.66 dddd (13.0, 12.5, 12.2, 3.9)		1.66 m		1.64 m		1.58 m		1.59 m
6′*α*	33.0	1.90 ddd (13.7, 13.0, 4.8)	32.9	1.93 ddd (13.7, 12.9, 5.1)	32.9	1.92 ddd (13.7, 13.2, 4.7)	32.8	1.85 ddd (13.5, 13.5, 4.6)	33.1	1.78 ddd (13.9, 13.1, 4.5)
6′*β*		1.76 brd (13.7)		1.74 brd (13.7)		1.71 brd (13.7)		1.64 brd (13.5)		1.66 brd (13.9)
7′	29.1	1.43 s	29.4	1.47 s	29.5	1.45 s	29.4	1.37 s	28.3	1.33 s
8′	83.3	-	79.8	-	80.3	-	80.4	-	80.2	-
9′	27.6	1.53 s	27.6	1.56 s	27.6	1.54 s	27.6	1.49 s	27.4	1.53 s
10′	20.2	1.25 s	19.8	1.21 s	19.9	1.19 s	19.9	1.14 s	19.6	1.19 s
1″-a	30.8	3.65 s	29.6	3.70 s	-	-	66.1	6.25 brs	65.6	6.24 brs
1″-b	-	-	-	-	-	-	-	-	-	6.36 brs
2″	-	-	-	-	-	-	170.8	-	170.4	-
3″	-	-	-	-	-	-	21.1	2.03 s	20.8	2.08 s

[a]Overlapped

(1) Isochloroaustralasine A (1-methyl-2,8′-oxy-3-(1′*β*-hydroxy-2′*α*-chloro-3′*β*,4′*α*-para-menthyl-3′-yl)quinolin-4-one): White amorphous powder; $[\alpha]^{24}_{D}$ +170 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 214 (4.22), 239 (4.32), 316 (3.82), 329 (3.76) nm; ^{1}H and ^{13}C NMR, see Table above; HRESIMS *m/z* 362.1509 $[M + H]^+$ (calcd for $C_{20}H_{25}ClNO_3$, 362.1517).

(2) Chloroaustralasine A (1-methyl-4,8′-oxy-3-(1′*β*-hydroxy-2′*α*-chloro-3′*β*,4′*α*-para-menthyl-3′-yl)quinolin-2-one): White amorphous powder; $[\alpha]^{24}_{D}$ +186 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 233 (4.49), 276 (3.85), 286 (3.84), 317 (3.80), 330 (3.69) nm; ^{1}H and ^{13}C NMR, see Table above; HRESIMS *m/z* 362.1515 $[M + H]^{+}$ (calcd for $C_{20}H_{25}ClNO_{3}$, 362.1517).

(3) Chloroaustralasine B (4,8′-oxy-3-(1′*β*-hydroxy-2′*α*-chloro-3′*β*,4′*α*-para-menthyl-3′-yl)quinolin-2-one): White amorphous powder; $[\alpha]^{24}_{D}$ +162 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 232 (4.44), 274 (3.80), 284 (3.78), 316 (3.77), 329 (3.67) nm; ^{1}H and ^{13}C NMR, see Table above; HRESIMS *m/z* 348.1349 $[M + H]^{+}$ (calcd for $C_{19}H_{23}ClNO_{3}$, 348.1361).

(4) Chloroaustralasine C (1-acetoxymethyl-4,8′-oxy-3-(1′*β*-hydroxy-2′*α*-chloro-3′*β*,4′*α*-para-menthyl-3′-yl)quinolin-2-one): White amorphous powder; $[\alpha]^{24}_{D}$ +156 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 233 (4.54), 276 (3.89), 287 (3.87), 315 (3.86), 327 (3.75) nm; ^{1}H and ^{13}C NMR, see Table above; HRESIMS *m/z* 420.1561 $[M + H]^{+}$ (calcd for $C_{22}H_{27}ClNO_{5}$, 420.1572).

(5) *trans*-erioaustralasine hydrate (1-acetoxymethyl-4,8′-oxy-3-(1′*β*,2′*α*-dihydroxy-3′*β*,4′*α*-para-menthyl-3′-yl)quinolin-2-one): White amorphous powder; $[\alpha]^{24}_{D}$ +152 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 232 (4.42), 277 (3.78), 288 (3.75), 319 (3.74), 329 (3.66) nm; ^{1}H and ^{13}C NMR, see Table above; HRESIMS *m/z* 402.1904 $[M + H]^{+}$ (calcd for $C_{22}H_{28}NO_{6}$, 402.1911).

S3. Structural elucidation of compounds **1** to **5**.

Compound **1** showed a protonated molecular ion at *m/z* 362.1509 $[M + H]^+$ (calcd 362.1517) in the HRESIMS spectrum, corresponding to the molecular formula $C_{20}H_{24}ClNO_3$. The ^1H, ^{13}C and HSQC NMR spectra revealed the presence of four aromatic protons, two methylene groups, three methines, one of which is deshielded, four methyl groups, six quaternary carbons and one carbonyl. The COSY spectrum displayed two spin systems. The first one showed an ABCD pattern for the four aromatic protons δ_H 8.43 (dd, H-5), 7.32 (dd, H-6), 7.58 (ddd, H-7) and 7.38 (d, H-8) supporting the presence of a 1,2-disubstituted benzene ring system. HMBC correlations from H-7 and H_3-1'' to C-8a (δ_C 139.2), from H-6 to C-4a (δ_C 124.6), and from H-5 to the carbonyl C-4 (δ_C 176.7) suggesting a linkage between the benzene ring and a *N*-methyl-bearing 2,4-dioxygenated quinoline moiety. The COSY spectrum revealed the second spin system from CH-2' to CH_2-6'. HMBC correlations from H-3′ to C-2 (δ_C 156.5) and C-3 (δ_C 99.8) indicated that this fragment is linked to the quinolone moiety by a C-3-C-3' bond. Other HMBC correlations from H_3-9′ and H_3-10′ to C-2, C-4' and C-8', and H_3-1'' to C-2 revealed that a 2,2-dimethyldihydropyran moiety is attached to the quinolone moiety at C-2 and C-3. Finally, HMBC correlations from H_3-7′ (δ_H 1.43) to C-1′ (δ_C 72.4), C-2′ (δ_C 65.5), and C-6′ (δ_C 32.9) allowed a substituted cyclohexane moiety to be attached to the pyran ring at C-3' and C-4', forming a para-menthyl core. The chlorine atom and the hydroxyl function remaining to be accounted for were respectively linked at C-2′ and C-1′ given the shielded C-2' at δ_C 65.3).
The C-(3')H/C-(4')H *trans*-configuration was supported by a large ^3J coupling constant value of 11.7 Hz and absence of interaction in the ROESY experiment. In addition to the absence of correlation between H_3-7′ and H-3′, the strong ROESY correlation and a small vicinal coupling constant ($^3J_{H\text{-}2'/H\text{-}3'}$ = 2.2 Hz) between H-2′ and H-3′ suggested that the CH_3-7' group and the chlorine atom were α-oriented.
Compound **1** was crystallized by slow evaporation in methanol. The 2D structure and absolute configuration of **1** were confirmed by a single-crystal X-ray crystallography analysis.[1] Thus, compound **1,** which was named isochloroaustralasine A, was assigned a (1'*R*, 2'*R*, 3'*S*, and 4'*S*) absolute configuration.[2, 3]
Compound **2** was assigned the molecular formula $C_{20}H_{24}ClNO_3$, same as compound **1**, on the basis of the protonated ion peak $[M + H]^+$ at *m/z* 362.1515 (calcd 362.1517). From this formula and spectroscopic data, it was apparent that compound **2** shared a similar structure with **1**. However, careful comparison of the NMR spectroscopic data of **2** revealed substantial changes for the quinolone moiety while chemical shifts for the monoterpenyl part remained almost unchanged. These observations underpinned a different tetracyclic pattern. HMBC correlations from the deshielded *N*-methyl at δ_H 3.70 to C-8a (δ_C 139.0) and the carbonyl C-2 at δ_C 162.9, and from H_3-10′ (δ_H 1.56) and H-5 to C-4 (δ_C 157.5) pointed out the cyclisation of the para-menthyl subunit on the oxygen atom at position 4. The carbonyl was therefore located at C-2 (δ_C 162.9) to afford the quinoline-2-one core.
Coupling constants and ROESY correlations observed for compound **2** were similar to those of **1**, indicating that they shared the same relative configuration.
Finally, **2** was crystallised in a mixture of $MeOH/H_2O$ (9:1). The structure and (1'*R*, 2'*R*, 3'*S*, and 4'*S*) absolute configuration of compound **2** were confirmed by X-ray diffraction analysis. Compound **2** was named chloroaustralasine A.
The molecular formula $C_{19}H_{22}ClNO_3$ of compound **3** was established by HRESIMS from the protonated molecular ion at *m/z* 348.1349 (calcd for 348.1361). This molecular formula differs by

14 mass units from that of **2**. The NMR spectroscopic data of **3** were very similar to those of **2**, except for the *N*-methyl resonance, which was absent in the ^{1}H NMR spectrum. Instead, a broad deshielded proton at δ_H 9.25 showing no HSQC correlation supported the presence of a NH group.

From the comparison of ROESY/NOESY correlations observed for compounds **2** and **3**, respectively, it can be deduced that both compounds shared same relative configuration. The absolute configuration of compound **3** was determined by comparison of experimental ECDs with compounds **2**. Both of them showed identical positive Cotton effects at 230 and 315 nm and a negative Cotton effect at 280 nm (see S8). Thus, compound **3** was assigned a (1'*R*, 2'*R*, 3'*S*, and 4'*S*) absolute configuration and was named chloroaustralasine B.

The molecular formula $C_{22}H_{26}ClNO_5$ was assigned to compound **4** on the basis of HRESIMS data from the protonated molecular ion at *m/z* 420.1561 (calcd for $C_{22}H_{27}ClNO_5$, 420.1572). The ^{1}H and ^{13}C NMR spectroscopic data presented many similarities with those of compounds **2** and **3**. However, the isolated deshielded methylene resonance at δ_H 6.27 bearing an acetate function suggested the presence of a *N*-acetoxymethyl substituent.

The CD spectra of **4** showed positive Cotton effects at 230 and 315 nm and a negative Cotton effect at 280 nm as observed for compounds **2** and **3**, which together with the same biogenetic origin allowed the assignment of the absolute configuration of **4** as 1'*R*, 2'*R*, 3'*S*, and 4'*S* which was named chloroaustralasine C.

The HRESIMS of **5** showed a protonated molecular ion at *m/z* 402.1904 corresponding to the molecular formula $C_{22}H_{27}NO_6$ (calcd 402.1911). When comparing this formula and NMR spectroscopic data of **5** with those of compound **4**, it can be deduced that the chlorine atom was replaced by a hydroxyl group. This deduction was confirmed by the deshielded resonance of the methine C-2′ at δ_C 72.4 observed in the ^{13}C NMR. The relative configuration of compound **5**, identical to compounds **1-4**, was established by ROESY experiment and analysis of the coupling constant values of protons H-3'/H-4' (J = 11.8 Hz) and H-2'/H-3' ($J \approx$ 1-2 Hz).

The biogenetic origin of compound **5** together with closely similar Cotton effects (see S8) to those of compounds **2-4**, suggested that **5** shared same (1'*R*, 2'*R*, 3'*S*, and 4'*S*) absolute configuration as compounds **1-4**. Compound **5** was named *trans*-erioaustralasine hydrate.

S4. Data dependent LC-ESI-HRMS^2 analysis and molecular network parameters.

Data dependent LC-HRMS^2 analyses. LC analyses were performed with a Dionex Ultimate 3000 RSLC system equipped with an Accucore C_{18} column (2.1 × 100 mm; 2.6 μm, ThermoScientific). The mobile phase consisted of water-acetonitrile (MeCN) + 0.1 % formic acid with a flow rate fixed at 350 µL.min^{-1}. A linear gradient starting at 0 min from 95:5 to 0:100 in 14 min was applied, then this gradient was maintained at 100:0 for 6 min. The temperature of the column oven was set at 30 °C, the samples were concentrated at 1 mg.mL^{-1} and the injection volume was set at 5 μL.

LC-ESI-HRMS^2 analyses were achieved by coupling the LC system to a hybrid quadrupole time-of-flight mass spectrometer Agilent 6540 (Agilent Technologies, Massy, France) equipped with an ESI dual source, operating in positive-ion mode. Source parameters were set as followed: capillary temperature at 325 °C, source voltage at 3500 V, sheath gas flow rate at 7 L.min^{-1}, nebulizer pressure at 30 psi, drying-gas flow rate at 10 L.min^{-1}, drying-gas temperature at 350°C, stealth-gas temperature at 350° C, skimmer voltage at 45 V, fragmentor voltage at 150 V and nozzle voltage at 500 V.

MS scans were operated in full-scan mode from *m/z* 100 to 1700 (0.1s scan time) with a mass resolution of 20 000 at *m/z* 922. MS^1 scan was followed by MS^2 scans of the five most intense ions above an absolute threshold of 1000 counts. Selected parent ions were fragmented with collision energy fixed at 35 eV and an isolation window of 1.3 amu.[4]

Calibration solution, containing two internal reference masses (purine, $C_5H_4N_4$, *m/z* 121.0509, and HP-921 [hexakis-(1H,1H,3H-tetrafluoropentoxy)phosphazene], $C_{18}H_{18}O_6N_3P_3F_{24}$, *m/z* 922.0098), routinely led to mass accuracy below 2 ppm. LC-UV data were analyzed with Chromeleon software (Dionex) and MS data acquisition and processing were performed using MassHunter Workstation software (Agilent Technologies, Massy, France).

MZmine 2 Data-Preprocessing Parameters. Reliable networks were generated using the methodology previously described.[5] The 292 MS^2 data files were converted from the .d (Agilent) standard data-format to .mzXML format using the MSConvert software, part of the ProteoWizard package.[6] All .mzXML were then processed using MZmine 2 v31.[7] The mass detection was realized keeping the noise level at 20. The ADAP chromatogram builder was used using a minimum group size of scans of 4, a group intensity threshold of 3000, a minimum highest intensity of 4000 and *m/z* tolerance of 0.005 Da (or 20 ppm).[8] The ADAP wavelets deconvolution algorithm was used with the following standard settings: S/N threshold = 8, minimum feature height = 4000, coefficient/area threshold = 20, Peak duration range 0.05 - 1 min, RT wavelet range 0.01 - 0.07. These parameters were optimized for some samples. MS^2 scans were paired using a *m/z* tolerance range of 0.02 Da and RT tolerance range of 0.5 min. Isotopologues were grouped using the isotopic peaks grouper algorithm with a *m/z* tolerance of 0.005 Da (or 20 ppm) and a RT tolerance of 0.2 min. Peak alignment was performed using the join aligner module (*m/z* tolerance = 0.004 Da (or 10 ppm), weight for *m/z* = 2, weight for RT = 1, absolute RT tolerance 0.5 min). The peak list was gap-filled with the same RT and *m/z* range gap filler module (*m/z* tolerance of 0.004 Da (or 10 ppm)).

Eventually, the .mgf preclustered spectral data file and its corresponding .csv metadata file (for RT, areas and formulas integration) were exported using the dedicated "Export for GNPS" and "Export to CSV file" built-in options. See further documentation at https://bix-lab.ucsd.edu/display/Public/GNPS+data+analysis+workflow+2.0.

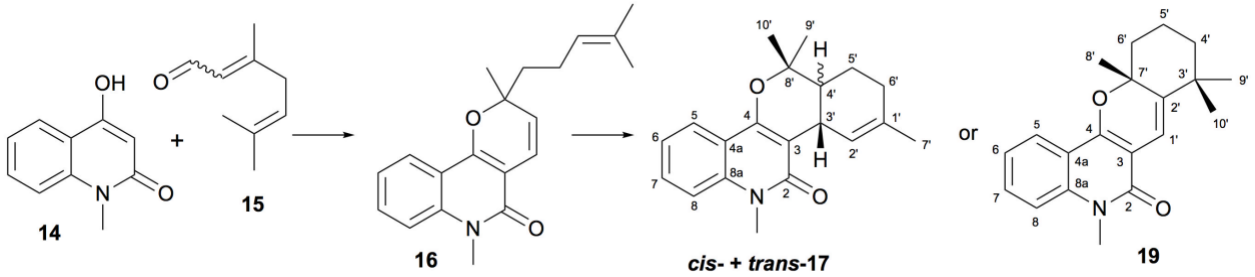
Molecular Network Analysis. The molecular networks were created using the online workflow at Global Natural Products Social molecular networking (http://gnps.ucsd.edu). MS^2 spectra were window filtered by choosing only the top 6 peaks in the +/- 50 Da window throughout the spectrum. The data were not clustered with MS-Cluster. A network was then created where edges were filtered to have a cosine score above 0.7 and more than 3 matched peaks. Further edges between two nodes were kept in the network if and only if each of the nodes appeared in each other's respective top 10 most similar nodes. The library spectra were filtered in the same manner as the input data. All matches kept between network spectra and library spectra were required to have a score above 0.7 and at least 4 matched peaks.

S5. Plant Material: Extraction and Isolation.

Plant Material. Stem and bark of *Codiaeum peltatum* were collected on the Mount Aoupinié (New Caledonia) in November 2001 and further authenticated by V. Dumontet. A voucher specimen (DUM-0109) has been deposited at the IRD Center of Nouméa.

Extraction and Isolation. The plant material (200 g, dry wt.) was extracted three times with EtOAc (0.5 L each). The EtOAc extract was concentrated *in vacuo* at 40 °C to yield 1.5 g of residue. This extract was further dissolved in 0.25 L of MeCN and subjected to a liquid/liquid partition with n-heptane (2 × 0.25 L) to afford 0.6 g of a MeCN-soluble fraction. This fraction was then directly subjected to a semi-preparative HPLC (Kinetex C_{18}, H_2O-MeCN 35:65 + 0.1% formic acid to 0:100 in 45 min at 4.5 mL.min^{-1}) to afford 20 fractions of decreasing polarity F1−F20. Purification of the fraction F8 (31.48 mg) by semi-preparative HPLC (Kinetex C_{18}, H_2O-MeCN 65:35 + 0.1% formic acid to 50:50 in 30 min at 4.5 mL.min^{-1}) furnished compound **1** (0.64 mg) (t_R: 23.0 min). F14 (35.19 mg) was purified by semi-preparative HPLC (Kinetex C_{18}, H_2O-MeCN 45:55 + 0.1% formic acid to 35:65 in 25 min at 4.5 mL.min^{-1}) to afford compound **2** (1.1 mg) (t_R: 13.2 min). F6 (7.87 mg) was subjected to a semi-preparative HPLC (Kinetex C_{18}, H_2O-MeCN 55:45 + 0.1% formic acid at 4.5 mL.min^{-1}) to afford compound **3** (1.17 mg) (t_R: 16.7 min). F9 (16.22 mg) was further purified by semi-preparative HPLC (Nucleodur PFP, H_2O-MeCN 45:55 + 0.1% formic acid at 4.5 mL.min^{-1}) to yield compound **4** (0.62 mg) (t_R: 9.0 min). Purification of the fraction F4 (2.68 mg) by analytical HPLC (Kinetex C_{18}, H_2O-(MeOH/MeCN) 50:50 + 0.1% formic acid at 1 mL.min^{-1}) furnished compound **5** (0.23 mg) (t_R: 15.0 min).

S6. Synthesis experiments.



Zanthosimuline 16. A solution of 4-hydroxy-1-methyl-2-(1H)-quinolone **14** (1.50 g, 8.56 mmol, 1 eq), citral **15** (1.47 mL, 8.56 mmol, 1 eq) and EDDA (0.30 g, 1.71 mmol, 0.2 eq) in anhydrous EtOH (15 mL) was heated under MW irradiation at 150 °C during 20 min. The mixture was concentrated under reduced pressure and the desired compound purified by flash chromatography on silica gel (80 g) using heptane/EtOAc from 10:0 to 5:5 to give zanthosimuline **16** as light yellow oil (2.45 g, 7.91 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.93 (H-5 d, J = 7.9 Hz, 1H), 7.52 (H-7 t, J = 8.0 Hz, 1H), 7.29 (H-8 d, J = 8.0 Hz, 1H), 7.20 (H-6 t, J = 8.0 Hz, 1H), 6.77 (H-1′ d, J = 10.0 Hz, 1H), 5.46 (H-2′ d, J = 10.0 Hz, 1H), 5.07 (H-6′ t, J = 7.0 Hz, 1H), 3.67 (H-1′′ s, 3H), 2.12 (H-5′ q, J = 7.0 Hz, 2H), 1.82–1.62 (H-4′ m, 2H), 1.60 (H-8′ s, 3H), 1.52 (H-9′ s, 3H), 1.45 (H-10′ s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 161.2 (C-2), 155.6 (C-4), 139.5 (C-8a), 132.2 (C-7′), C-7 (131.0), 125.4 (C-2′), 123.9 (C-6′), 123.3 (C-5), 121.9 (C-6), 118,6 (C-1′), 116.2 (C-4a), 114.2 (C-8), 105.7 (C-3), 81.5 (C-3′), 41.7 (C-4′), 29.5 (C-1′′), 27.2 (C-10′), 25.8 (C-8′), 22.8 (C-5′), 17.8 (C-9′). HRESIMS *m/z* 310.1804 [M + H]$^+$ (calcd for $C_{20}H_{24}NO_2$, 310.1802). Analytical data were consistent with those described by Wu and Chen.[9]

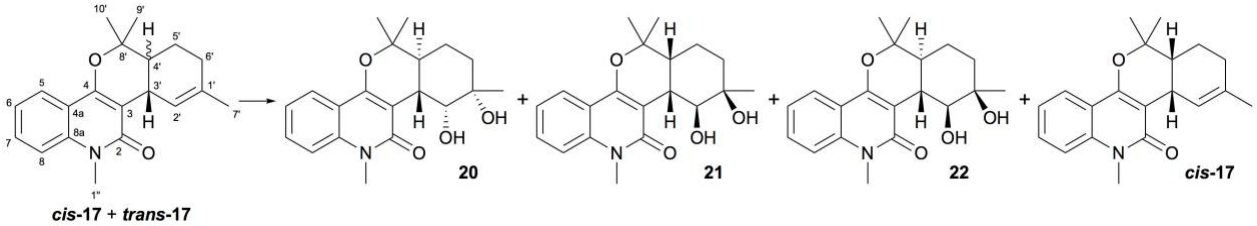
***cis*/*trans*-17 mixture.** To a solution of compound **16** (198 mg, 0.64 mmol, 1 eq) in anhydrous dichloromethane (6 mL) under Ar atm. was added a 1 M solution of Me_2AlCl in hexanes (1.28 mL, 1.28 mmol, 2 eq) was added. The reaction mixture was stirred at r.t. for 18 h before adding 0.5 mL of water. The mixture was dried over $MgSO_4$, filtrated over a Celite® pad and concentrated under reduced pressure to give a mixture of *cis*-**17** and *trans*-**17** 3:2 as pale yellow oil (196 mg, 0.64 mmol, >98%) without any purification. Analytical data were consistent with those described by M. J. Riveira *et al.*[10]

***cis*-17.** ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.93 (H-5 dd, J = 8.0, 1.3 Hz, 1H), 7.48 (H-7 overlapping bt, J = 8.0 Hz, 1H), 7.27 (H-8 d, J = 8.4 Hz, 1H), 7.17 (H-6 overlapping bt, J = 7.7 Hz, 1H), 6.47−6.41 (H-2′ m, 1H), 3.66 (H-1′′ s, 3H), 3.55 (H-3′, bs, 1H), 2.03−1.87 (H-6′ and H-5′ m, 3H), 1.87−1.75 (H-4′ m, 1H), 1.69 (H-7′ bs, 3H), 1.51 (H-9′ s, 3H), 1.44−1.32 (H-5′ m, 1H), 1.31 (H-10′ s, 3H).

***trans*-17.** δ 7.93 (H-5 dd, J = 8.0, 1.3 Hz, 1H), 7.48 (H-7 overlapping bt, J = 8.0 Hz, 1H), 7.27 (H-8 d, J = 8.4 Hz, 1H), 7.17 (H-6 overlapping bt, J = 7.7 Hz, 1H), 6.47−6.41 (H-2′ m, 1H), 3.67 (H-1′′ s, 3H), 3.24-3.19 (H-3′ m, 1H), 2.23−2.12 (H-6′ m, 2H), 2.03−1.87 (H-5′ m, 1H), 1.75−1.62 (H-4′ m, 1H), 1.69 (H-7′ bs, 3H), 1.53 (H-9′ s, 3H), 1.54−1.43 (H-5′ m, 1H), 1.14 (H-10′ s, 3H). HRESIMS *m/z* 310.1812 [M + H]$^+$ (calcd for $C_{20}H_{24}NO_2$, 310.1802).

Cyclisation product 19. To a solution of zanthosimuline **16** (50 mg, 0,16 mmol, 1 eq) in anhydrous dichloromethane (5 mL) under Argon was added $SnCl_4$ (84 mg, 0,32 mmol, 2 eq).

After 1 h at r.t. the mixture was quenched with water (0.2 mL). $MgSO_4$ was added to the solution and the solids were eliminated by filtration over a Celite® pad. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel (24 g) with heptane/EtOAc from 10:0 to 5:5 to give compound **19** as white solid (45 mg, 15 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.91 (H-5 d, J = 7.9 Hz, 1H), 7.50 (H-7 t, J = 8.0 Hz, 1H), 7.30 (H-8 d, J = 8.0 Hz, 1H), 7.20 (H-9 t, J = 8.0 Hz, 1H), 6.68 (H-1′ d, J = 10.0 Hz, 1H), 3.69 (H-1′′ s, 3H), 2.19 (H-6′ m, 1H), 1.97 (H-6′ dt, J = 12.9, 5.0 Hz, 1H), 1.72-1.69 (H-5′ m, 2H), 1.50−1.43 (H-4′ m, 1H), 1.44 (H-8′ s, 3H), 1.28 (H-9′ s, 3H), 1.17 (H-10′ s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 161.4 (C-2), 153.9 (C-4), 144.4 (C-2′), 139.2 (C-8a), 130.6 (C-7), 123.1 (C-5), 121.9 (C-6), 116.4 (C-4a), 114.2 (C-8), 112.4 (C-1′), 108.1 (C-3), 80.8 (C-7′), 40.1 (C-6′), 39.6 (C-4′), 36.1 (C-3′), 31.0 (C-9′), 30.8 (C-10′), 29.5 (C-1′′), 25.8 (C-8′), 19.2 (C-5′). HRESIMS *m/z* 310.1799 [M + H]$^+$ (calcd for $C_{20}H_{24}NO_2$, 310.1802).



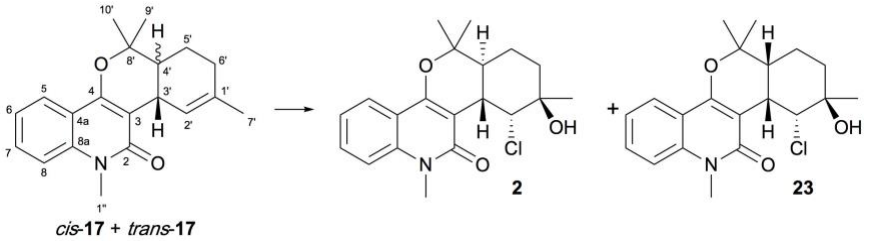
Upjohn dihydroxylation of *cis*/*trans*-17. *N*-methyl morpholine-*N*-oxide (100 mg, 0.85 mmol, 2.6 eq) was added to a solution of *cis*/*trans*-**17** (100 mg, 0.32 mmol, 1 eq) in a mixture of acetone/water 1:10 (2 mL). After 2 min, a 2.5% solution of OsO4 in *t*-BuOH (150 μL, 0.012 mmol, 0.04 eq) was added and the mixture was stirred at r.t. in the dark. After 36 h, an aqueous saturated solution of $Na_2S_2O_3$ (5 mL) was added and the mixture was extracted twice with dichloromethane (10 mL). After concentration under reduced pressure, the residue was submitted to a flash chromatography on silica gel using heptane/EtOAc 95:5 to 0:100 to obtain compounds **20** (17 mg, 0.049 mmol, 15%), **21** (17 mg, 0.049 mmol, 15%), **22** (2 mg, 0.004 mmol, 2%) and the recovered *cis*-**17** (17 mg, 0.011 mmol, 17%).

20. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.98 (H-5 dd, J = 8.0, 1.1 Hz, 1H), 7.54 (H-7 ddd, J = 8.6, 7.3, 1.1 Hz, 1H), 7.25 (H-8 d, J = 8.6 Hz, 1H), 7.23 (H-6 dd, J = 8.0, 7.3 Hz, 1H), 5.21 (H-2′ brs, 1H), 3.54 (H-1′′ s, 3H), 2.74 (H-3′ dd, J = 11.9, 1.6 Hz, 1H), 2.20 (H-4′ ddd, J = 12.6, 11.9, 1.7 Hz, 1H), 1.90 (H-6′α ddd, J = 13.4, 12.7, 4.1 Hz, 1H), 1.79 (H-5′α dddd, J = 12.6, 4.1, 3.1, 2.7 Hz, 1H), 1.73 (H-6′β ddd, J = 12.7, 3.7, 3.1 Hz, 1H), 1.57 (H-9′ s, 3H), 1.44 (H-7′ s, 3H), 1.20 (H-5′β dddd, J = 13.4, 12.6, 12.6, 3.7 Hz, 1H), 1.18 (H-10′ s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 163.0 (C-2), 157.0 (C-4), 139.0 (C-8a), 130.6 (C-7), 123.5 (C-5), 121.8 (C-6), 117.0 (C-4a), 114.0 (C-8), 106.0 (C-3), 79.8 (C-8′), 73.0 (C-1′), 72.3 (C-2′), 39.9 (C-4′), 37.5 (C-3′), 35.1 (C-6′), 29.2 (C-1′′), 27.8 (C-9′), 24.9 (C-5′), 24.5 (C-7′), 19.6 (C-10′). HRESIMS *m/z* 344.1844 [M + H]$^+$ (calcd for $C_{20}H_{26}NO_4$, 344.1862).

21. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.04 (H-5 dd, J = 8.1, 1.2 Hz, 1H), 7.60 (H-7 ddd, J = 8.5, 7.3, 1.2 Hz, 1H), 7.39 (H-8 d, J = 8.5 Hz, 1H), 7.29 (H-6 dd, J = 8.1, 7.3 Hz, 1H), 3.99 (H-2′ d, J = 9.3, 1H), 3.75 (H-1′′ s, 3H), 3.37 (H-3′ dd, J = 9.3, 6.4 Hz, 1H), 2.25 (H-4′ ddd, J = 6.4, 6.1, 3.8 Hz, 1H), 2.16 (H-5′β m, 1H), 1.85 (H-6′β m, 1H), 1.61 (H-5′α m, 1H), 1.59 (H-6′α m, 1H), 1.54 (H-10′ s, 3H), 1.52 (H-9′ s, 3H), 1.25 (H-7′ s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 166.1 (C-2), 156.8 (C-4), 138.6 (C-8a), 131.1 (C-7), 123.7 (C-5), 122.3 (C-6), 116.9 (C-

4a), 114.2 (C-8), 107.5 (C-3), 80.3 (C-8′), 75.9 (C-2′), 71.1 (C-1′), 40.6 (C-4′), 35.9 (C-3′), 32.9 (C-6′), 30.1 (C-1′′), 29.0 (C-10′), 27.7 (C-7′), 26.2 (C-9′), 20.4 (C-5′). HRESIMS *m/z* 344.1867 $[M + H]^+$ (calcd for $C_{20}H_{26}NO_4$, 344.1862).

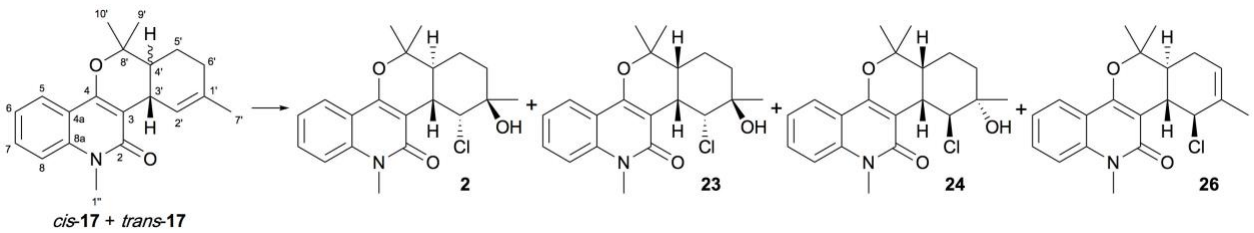
22. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ 8.96 (2′-OH s, 1H), 8.00 (H-5 d, J = 8.1 Hz, 1H), 7.59 (H-7 dd, J = 8.3, 7.2 Hz, 1H), 7.37 (H-8 d, J = 7.2 Hz, 1H), 7.27 (H-6 dd, J = 8.1, 7.2 Hz, 1H), 3.73 (H-1′′ s, 3H), 3.43 (H-2′ d, J = 9.3, 1H), 3.21 (1′-OH brs, 1H), 3.03 (H-3′ dd, J = 10.0, 9.3 Hz, 1H), 2.03 (H-6′b brd, J = 13.4 Hz, 1H), 1.58 (H-5′m, 2H), 1.57 (H-4′ m, 1H), 1.56 (H-9′ s, 3H), 1.46 (H-6′a m, 1H), 1.29 (H-7′ s, 3H), 1.17 (H-10′ s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ 166.1 (C-2), 158.4 (C-4), 138.3 (C-8a), 131.2 (C-7), 123.7 (C-5), 122.5 (C-6), 117.4 (C-4a), 114.2 (C-8), 108.7 (C-3), 80.1 (C-2′), 79.4 (C-8′), 72.2 (C-1′), 47.5 (C-4′), 38.1 (C-3′), 36.8 (C-6′), 30.3 (C-1′′), 28.4 (C-7′), 28.0 (C-9′), 23.3 (C-5′), 19.3 (C-10′). HRESIMS *m/z* 344.1845 $[M + H]^+$ (calcd for $C_{20}H_{26}NO_4$, 344.1862).



CPO-catalyzed hydroxychlorination of *cis*/*trans*-17 (Procedure A). To a solution of *cis*/*trans*-**7** (44 mg, 0.14 mmol, 1 eq) in a 1:3 mixture of *tert*-butanol/citric acid buffer (0.1 M, pH 3.5, 14 mL) were added an aqueous suspension of chloroperoxidase (3,000 U/mL) from *Caldariomyces fumago* (40 μL, 120 U) and NaCl (8 mg, 0.14 mmol, 1 eq). Then, a 30% H_2O_2 aqueous solution (20 μL, 0.16 mmol, 1 eq) was added portionwise after each 10 minute during 1 h. The mixture was then extracted twice with MTBE (14 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by semi-preparative HPLC (Kinetex C_{18}, H_2O-MeCN 45:55 at 4.7 mL.min^{-1}) to afford compound **2** (4 mg, 0.011 mmol, 8%, t_R: 13.3 min) and **23** (7 mg, 0.018 mmol, 13%, t_R: 12.4 min).

2. See table in S2.

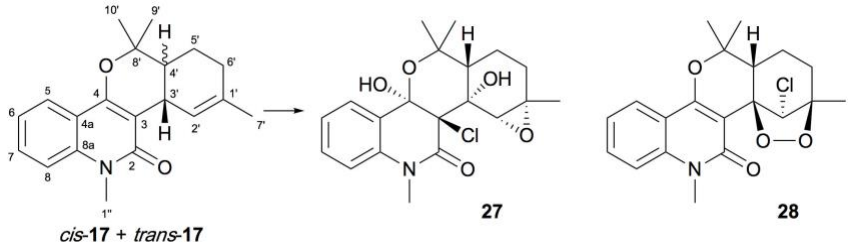
23. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.97 (H-5 dd, J = 8.0, 1.1 Hz, 1H), 7.53 (H-7 ddd, J = 8.5, 7.2, 1.1 Hz, 1H), 7.33 (H-8 d, J = 8.5 Hz, 1H), 7.21 (H-6 dd, J = 8.0, 7.2 Hz, 1H), 5.17 (H-2′ d, J = 5.6, 1H), 3.95 (H-3′ dd, J = 8.4, 5.6 Hz, 1H), 3.70 (H-1′′ s, 3H), 2.36 (H-4′ m, 1H), 2.02 (H-5′β m, 1H), 1.94 (H-6′β ddd, J = 13.8, 7.4, 6.2, 1H), 1.76 (H-5′α m, 1H), 1.60 (H-6′α m, 1H), 1.57 (H-9′ s, 3H), 1.47 (H-7′ s, 3H), 1.38 (H-10′ s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 163.3 (C-2), 156.6 (C-4), 139.0 (C-8a), 130.5 (C-7), 123.4 (C-5), 121.7 (C-6), 117.0 (C-4a), 114.0 (C-8), 108.4 (C-3), 79.5 (C-8′), 72.8 (C-1′), 64.6 (C-2′), 37.8 (C-4′), 33.4 (C-3′), 31.7 (C-6′), 30.3 (C-7′), 29.5 (C-1′′), 28.3 (C-10′), 26.2 (C-9′), 19.4 (C-5′). HRESIMS *m/z* 362.1537 $[M + H]^+$ (calcd for $C_{20}H_{25}ClNO_3$, 362.1523).



Hydroxychlorination of *cis*/*trans*-17 by *in situ* generated HOCl. To a solution of *cis*/*trans*-**17** (69 mg, 0.22 mmol, 1 eq) in a 1:5 mixture of water/acetone (0.06 M, 4 mL) was added trichloroisocyanuric acid (20.6 mg, 0.09 mmol, 0.4 eq). After 1.5 h, $CHCl_3$ (4 mL) was added and the resulting solids were eliminated by filtration. Then, the filtrate was washed twice with an aqueous solution of $Na_2S_2O_3$. The organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was submitted to semi-preparative HPLC (Kinetex C_{18}, H_2O-MeCN 40:60 at 4.7 mL.min^{-1}) to afford compound **2** (10 mg, 0.028 mmol, 13%, t_R: 9.5 min), **23** (10 mg, 0.028 mmol, 13%, t_R: 10.5 min), **24** (2 mg, 0.006 mmol, 3%, t_R: 11.5 min) and **26** (2 mg, 0.006 mmol, 3%, t_R: 18.2 min).

24. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.95 (H-5 dd, J = 8.0, 1.4 Hz, 1H), 7.51 (H-7 ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.28 (H-8 brd, J = 8.4 Hz, 1H), 7.18 (H-6 ddd, J = 8.0, 7.2, 0.7 Hz, 1H), 6.10 (H-2′ dd, J = 2.4, 1.4, 1H), 3.64 (H-1″ s, 3H), 3.48 (H-3′ brdd, J = 4.0, 2.4 Hz, 1H), 2.24 (H-4′ ddd, 12.7, 5.3, 4.0, 1H), 1.95 (H-6′α ddd, 14.0, 13.3, 4.2, 1H), 1.71 (H-5′α m, 1H), 1.53 (H-5′β m overlapping, 1H), 1.53 (H-9′ s, 3H), 1.49 (H-6′β m overlapping, 1H), 1.33 (H-7′ s, 3H), 1.27 (H-10′ s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 164.2 (C-2), 155.1 (C-4), 138.9 (C-8a), 130.7 (C-7), 123.7 (C-5), 121.8 (C-6), 116.8 (C-4a), 113.9 (C-8), 106.9 (C-3), 79.3 (C-8′), 72.2 (C-1′), 63.9 (C-2′), 38.8 (C-3′), 35.7 (C-4′), 31.6 (C-6′), 29.7 (C-7′), 29.5 (C-1′′), 26.4 (C-9′), 25.5 (C-10′), 18.7 (C-5′). HRESIMS *m/z* 362.1544 [M + H]$^+$ (calcd for $C_{20}H_{25}ClNO_3$, 362.1523).

26. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.97 (H-5 dd, J = 8.0, 1.5 Hz, 1H), 7.53 (H-7 ddd, J = 8.5, 7.2, 1.5 Hz, 1H), 7.32 (H-8 brd, J = 8.5 Hz, 1H), 7.20 (H-6 ddd, J = 8.0, 7.2, 0.7 Hz, 1H), 5.91 (H-2′ d, J = 3.3, 1H),5.60 (H-6′ m, 1H), 3.69 (H-1′′ s, 3H), 2.99 (H-3′ dd, J = 11.6, 3.3 Hz, 1H), 2.35 (H-4′ ddd, 12.2, 11.6, 4.8, 1H), 2.27 (H-5′β m, 1H), 1.93 (H-5′α m, 1H), 1.87 (H-7′ s, 3H), 1.54 (H-9′ s, 3H), 1.19 (H-10′ s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 163.0 (C-2), 157.0 (C-4), 139.3 (C-8a), 135.2 (C-1′), 130.7 (C-7), 124.1 (C-6′), 123.5 (C-5), 21.7 (C-6), 116.9 (C-4a), 114.1 (C-8), 106.6 (C-3), 79.2 (C-8′), 61.0 (C-2′), 38.0 (C-3′), 37.7 (C-4′), 29.3 (C-1′′), 27.9 (C-5′).27.3 (C-9′), 21.6 (C-7′), 19.3 (C-10′). HRESIMS *m/z* 344.1436 [M + H]$^+$ (calcd for $C_{20}H_{23}ClNO_2$, 344.1417).



CPO-catalyzed hydroxychlorination of *cis*/*trans*-17 (Procedure B). To a solution of *cis*/*trans*-**17** (50 mg, 0.16 mmol, 1 eq) in a 1:3 mixture of *tert*-butanol/citric acid buffer (0.1 M, pH 3.5, 16 mL) were added an aqueous suspension of chloroperoxidase (>10,000 U/mL) from

Caldariomyces fumago (50 µL, >500 U) and NaCl (10 mg, 0.16 mmol, 1 eq.) were added. Then, a 30% H_2O_2 aqueous solution (25 μL, 0.20 mmol, 1.25 eq) was added portionwise after 0, 15, 30, 45 and 60 minutes. After 5 hours, the solution was extracted twice with 15 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using heptane/EtOAc 95:5 to 0:100 to give a mixture of **27** and **27** (2:1, 11 mg). The resulting mixture was eluted on a silica preparative layer plate using heptane/EtOAc 70:30 to afford compounds **27** (5 mg, 0.012 mmol, 8%) and **28** (3 mg, containing 10% of impurity). **28** was further purified by semi-preparative HPLC (Kinetex C_{18}, H_2O-MeCN 60:40 + 0.1% formic acid at 4.5 mL.min^{-1}) to afford pure compound (2 mg, 0.003 mmol, 3%, t_R: 12.5 min).

27. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.69 (H-5 dd, J = 7.5, 1.2 Hz, 1H), 7.34 (H-7 ddd, J = 8.0, 7.7, 1.2 Hz, 1H), 7.14 (H-6 dd, J = 7.7, 7.5 Hz, 1H), 7.05 (H-8 d, J = 8.0 Hz, 1H), 3.98 (3′-OH s, 1H), 3.93 (H-2′ s, 1H), 3.43 (H-1′′ s, 3H), 2.21 (H-6′α dd, J = 15.0, 4.8, 1H), 2.05 (H-4′ dd, J = 12.1, 1.1, 1H), 1.79 (H-6′β ddd, J = 15.0, 12.4, 6.2, 1H), 1.61 (H-5′α m, 1H), 1.45 (H-9′ s, 3H), 1.35 (H-7′ s, 3H), 1.35 (H-10′ s, 3H), 1.29 (H-5′β m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 165.9 (C-2), 137.3 (C-8a), 130.0 (C-4a), 129.4 (C-7), 124.0 (C-5), 124.0 (C-6), 115.2 (C-8), 95.8 (C-4), 76.9 (C-8′), 72.8 (C-3′), 64.2 (C-2′), 64.2 (C-3), 61.4 (C-1′), 44.1 (C-4′), 31.8 (C-10′), 30.9 (C-6′), 30.4 (C-1′′), 25.3 (C-9′), 23.3 (C-7′), 16.8 (C-5′); HRESIMS *m/z* 376.1315 [M – H_2O + H]$^+$ (calcd for $C_{20}H_{23}ClNO_4$, 376.1316).

28. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ 8.00 (H-5 d, J = 7.9 Hz, 1H), 7.61 (H-7 dd, J = 8.5, 7.2 Hz, 1H), 7.32 (H-8 d, J = 8.5 Hz, 1H), 7.23 (H-6 dd, J = 7.9, 7.2 Hz, 1H), 6.44 (H-2′ s, 1H), 3.67 (H-1′ s, 3H), 2.91 (H-4′ dd, J = 12.7, 7.9 Hz, 1H), 2.08 (H-6′ m, 2H), 1.94 (H-5′α ddt, J = 13.2, 12.7, 10.1 Hz, 1H), 1.74 (H-5′β m, 1H), 1.59 (H-10′ s, 3H), 1.53 (H-7′ s, 3H), 1.46 (H-9′ s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ 162.9 (C-4), 161.7 (C-2), 140.3 (C-8a), 132.5 (C-7), 124.3 (C-5), 122.0 (C-6), 116.3 (C-4a), 114.1 (C-8), 99.2 (C-3), 83.4 (C-1′), 82.6 (C-8′), 82.1 (C-3′), 61.4 (C-2′), 52.0 (C-4′), 32.8 (C-6′), 29.4 (C-1′′), 29.3 (C-10′), 22.1 (C-7′), 21.0 (C-9′), 16.7 (C-5′); HRESIMS *m/z* 376.1319 [M + H]$^+$ (calcd for $C_{20}H_{23}ClNO_4$, 376.1316).

S7. X-ray Crystallographic analyses.

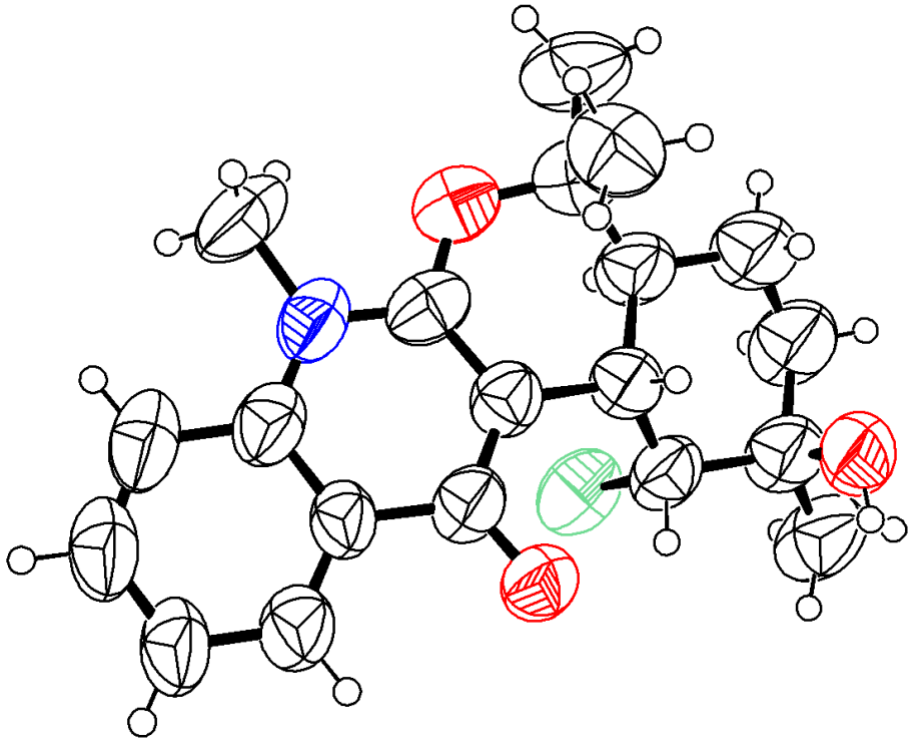
Colourless samples suitable for single crystal X-Ray Diffraction analyses were obtained by slow evaporation from a mixture of methanol/water solution for **1,** directly from methanol for compound **2** and **24**, from a mixture of $CH_2Cl_2/CDCl_3$ for **19**, and from a mixture of ether/methanol for the four other samples. XRD experiments were performed on a Rigaku MM007 HF rotating-anode diffractometer, using Cu-Kα radiation (λ =1.54187 Å) delivered through Osmic CMF optics and detected by a Rapid II curved Image Plate for compounds **1**, **2**, **20** and **27**. For compounds **19**, **23**, **24** and **28**, a RIGAKU XtaLabPro diffractometer equipped with a Mo microfocus sealed tube generator coupled to a double-bounce confocal Max-Flux® multilayer optic and a HPAD PILATUS3 R 200K detector was employed. All data were recorded at ambient temperature except for compound **19** that was preliminary coated by mineral oil and then dipped in liquid nitrogen for data record at 100K. Data reduction and scaling were carried out with an empirical absorption correction, as well as a treatment for Lorentz and polarization effects using either the program *Fs_Process*[11] as implemented into CrystalClear 2.0 software[11] that runs the XRD experiments on the rotating anode or the SCALE3 ABSPACK scaling algorithm as part of the CrysAlisPro 1.171.39.7b[12] dedicated to the microsource diffractometer. All the structures were solved by Intrinsic Phasing methods.[13] then refined by full matrix least squares on F^2 using the SHELXL-2017/1.[14] Anisotropic thermal parameters were used for all non-hydrogen atoms and if most of the H atoms were located in residual maps they all were refined as riding, with U_{eq} values set at $1.2U_{eq}$ (parent atom) (1.5 for the methyl groups or hydroxyl oxygen atoms). With respect to **1**, circular accessible voids (593 Å /unit cell) propagate in the ***ab*** plane between the molecular layers, in which diffuse solvent molecules like methanol that cannot be reliably modelled in terms of atomic sites. Therefore the SQUEEZE routine in PLATON[15] was used to treat these regions, removing the diffuse solvent contribution to the diffraction pattern and modified F_o^2 were written to a new HKL file. The number of electrons thus located, 82 per unit cell, was included in the formula, formula weight, calculated density, μ and $F(000)$. This residual electron density was assigned to 0.54 molecule of methanol solvent per compound **1**. With respect to **23**, a non-merohedral twin defined by the orientation matrix (-1 0 0 / 0 -1 0 / 0.698 0.205 1) was identified using the macro TwinRotMat using PLATON. As a result, a file with 1925 reflections that are considered to be overlaps from both domains was generated. Thus, the domain ratio could be refined in SHELXL to 0.215(2):0.785(2) *via* the HKLF5 command and an additional variable (BASF). Moreover, absolute configuration of enantiopure compounds **1** and **2** could be established by anomalous dispersion analyses on the faith of refined Flack parameter[16] and estimated Hooft parameter.[17]

The eight compounds share in common four fused heteromember rings, which consist of octahydro-isochromene (hexahydro-chromene for **19**) and methyl quinoline-4-one, which are peri-fused except **1** and **19**. The former one has quinolinone group ortho-fused with the pyrane moiety whereas the latter one has the chromene group ortho-fused with the pyridinone moiety. Compounds **2**, **23**, and **24** are diastereoisomers and **2** and **23** are epimers at C4'. They have a chlorine atom at C2' like **1** and **28** and hydroxyl group at C1' like **1** and **20**. Structures **1**, **20**, and **23** are made of two molecules in the asymmetric unit, which are assembled as pseudo-inversion (or inversion for **23**) related pairs through inter-molecular hydrogen bonds between the hydroxyl group at C7' and the carbonyl group of the quinolinone, making graph set[18] motif $R^2_2(16)$. In the case of **2,** only one molecule occupies the asu of the orthorhombic unit cell developing helically $C^1_1(8)$ chains along the crystallographic ***b*** axis through the aforementioned hydrogen bonds. For

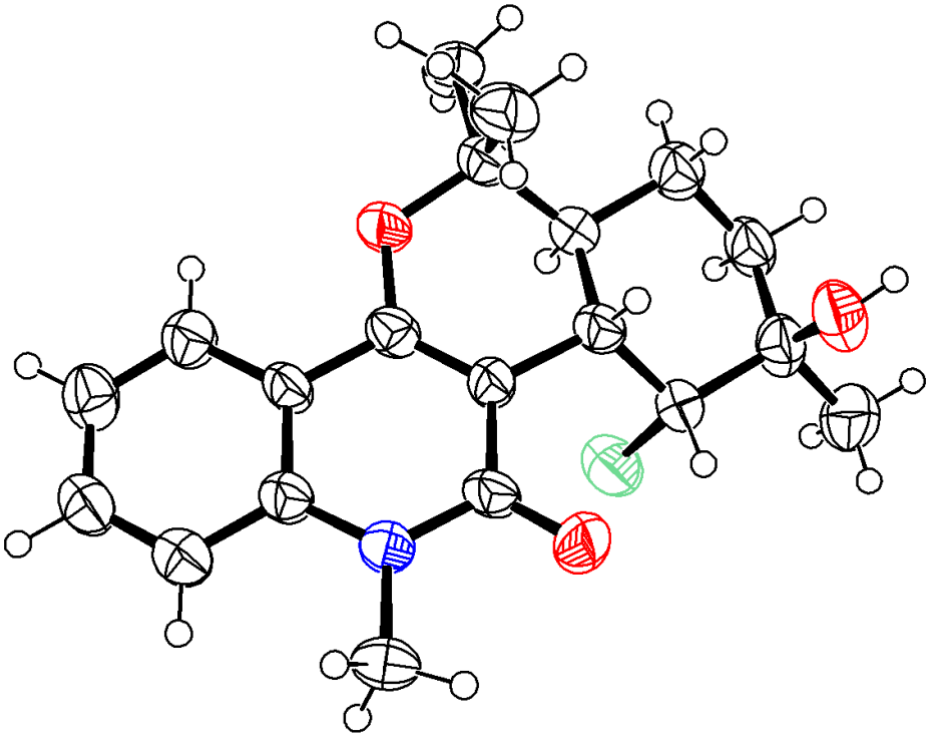
24, solvent water molecules mediate the crystal packing making $C^2_2(10)$ chains around a two-fold screw axis parallel to the ***b*** axis. Regarding **27** with an epoxy substitution at 1' and 2', shifting the chlorine atom at C3 and the hydroxyl at C3' (and that hydroxyl is further stabilized by an intramolecular Hbond developed by another hydroxyl group at C4), an inversion related dimer across two asu_s making graph set motif $R^2_2(12)$ also occurs involving the carbonyl and the C3' hydroxyl. Finally, with respect to **19** and **28**, missing hydrogen donors, and which belong to the same space group but in different unit cell dimensions accommodating one and two molecules respectively, the crystal packings are mainly controlled by π-π stacking interactions between inversion related quinolinone in **19** or non-conventional hydrogen bonds and van der Waals interactions *(C-H… π, C-H…O, C-H …Cl).*

Crystallographic data have been deposited in the Cambridge Crystallographic Data Center as entries 1554993-1554994 (compounds **1** and **2** respectively), 1589036-1589040 (compounds **19**, **20**, **23**, **27** and **28** respectively) and 1824664 (compound **24**) can be obtained, free of charge, on application to the Director, CCDC, 12 Union Rd., Cambridge CB21EZ, U.K. [fax, +44(0)-1233-336033; email, deposit@ccdc.cam.ac.uk].

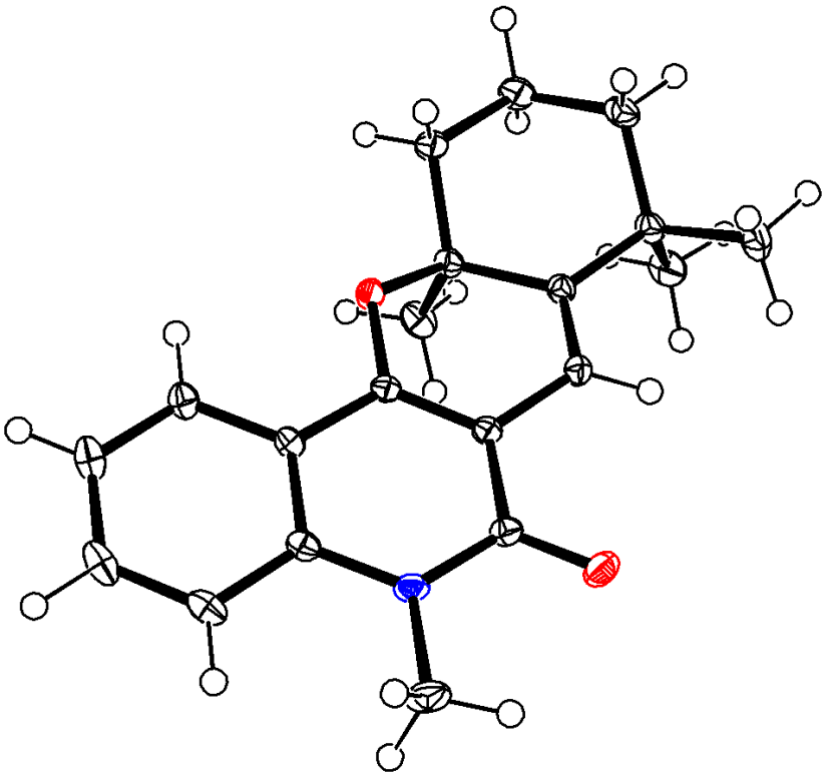
ORTEP representation of **1**.



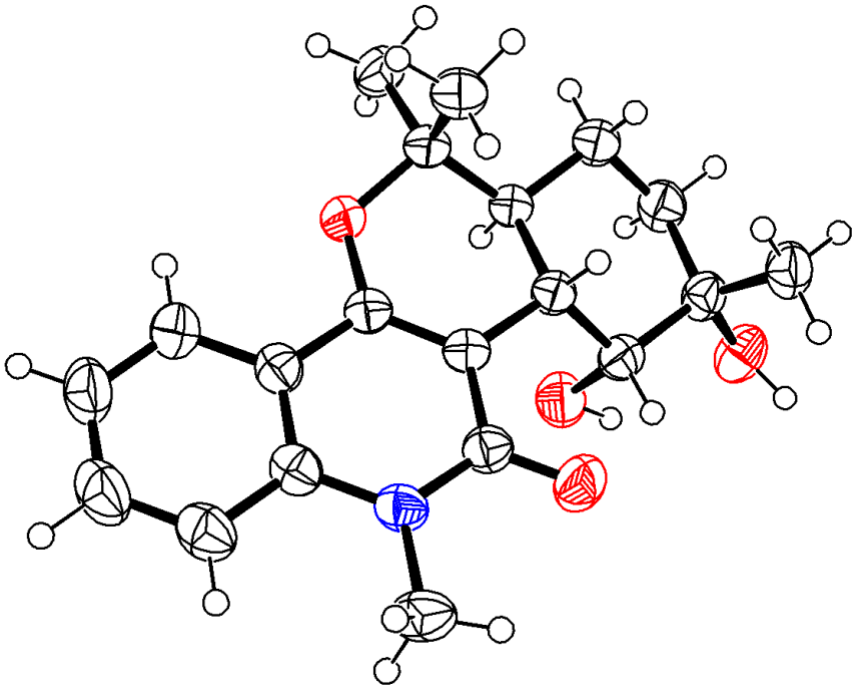
ORTEP representation of **2**.



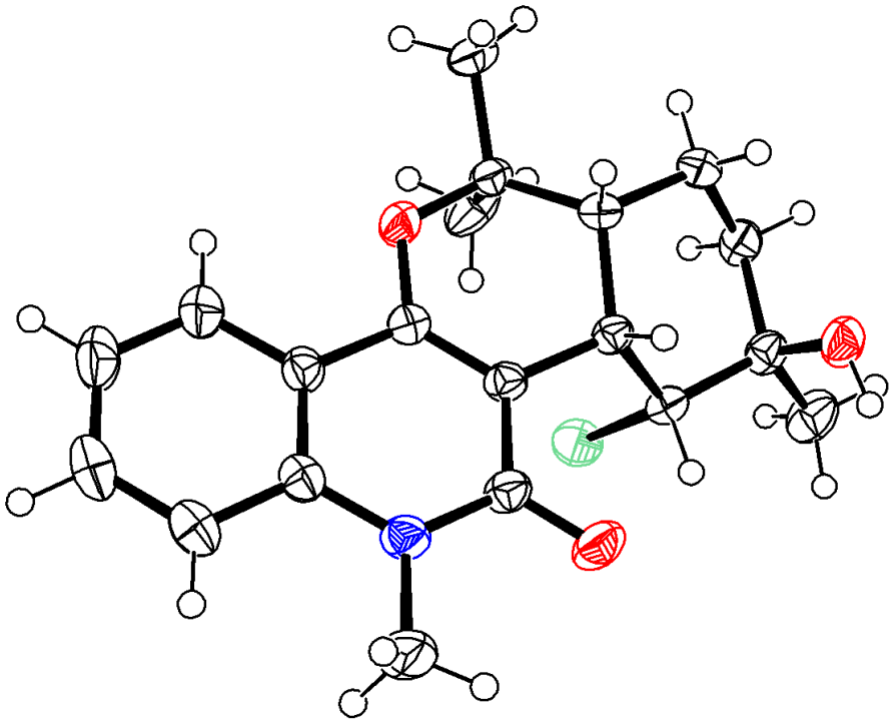
ORTEP representation of **19**.



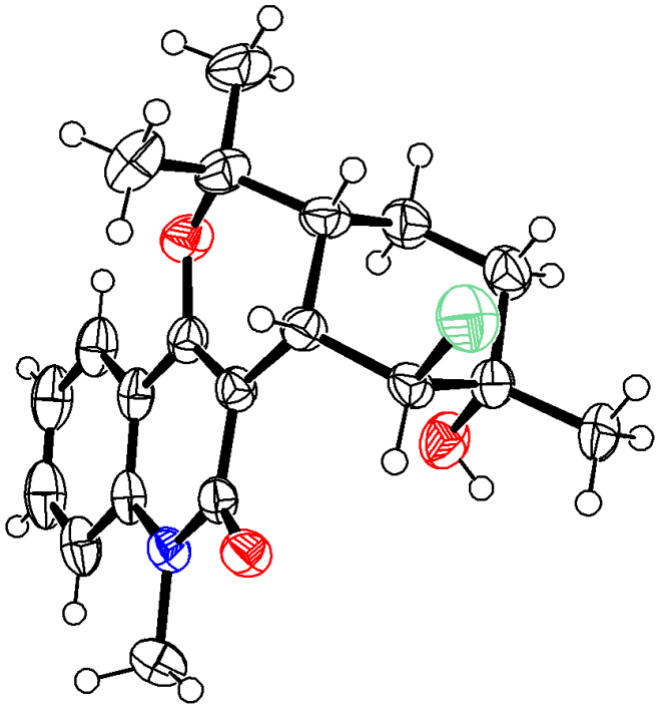
ORTEP representation of **20**.



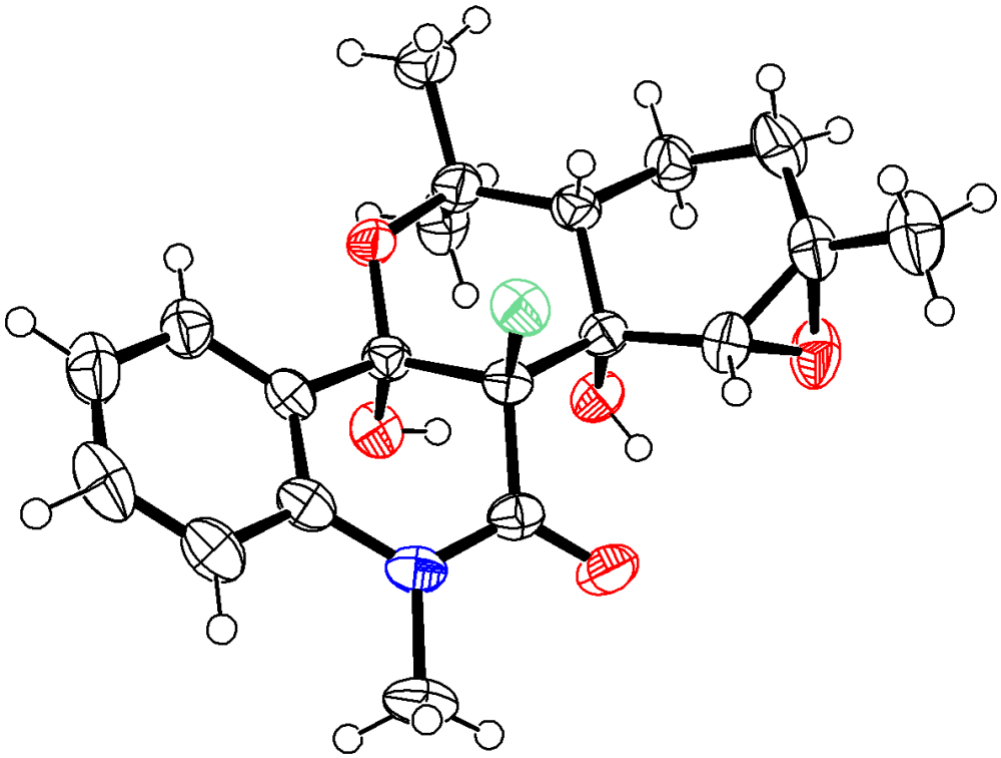
ORTEP representation of **23**.



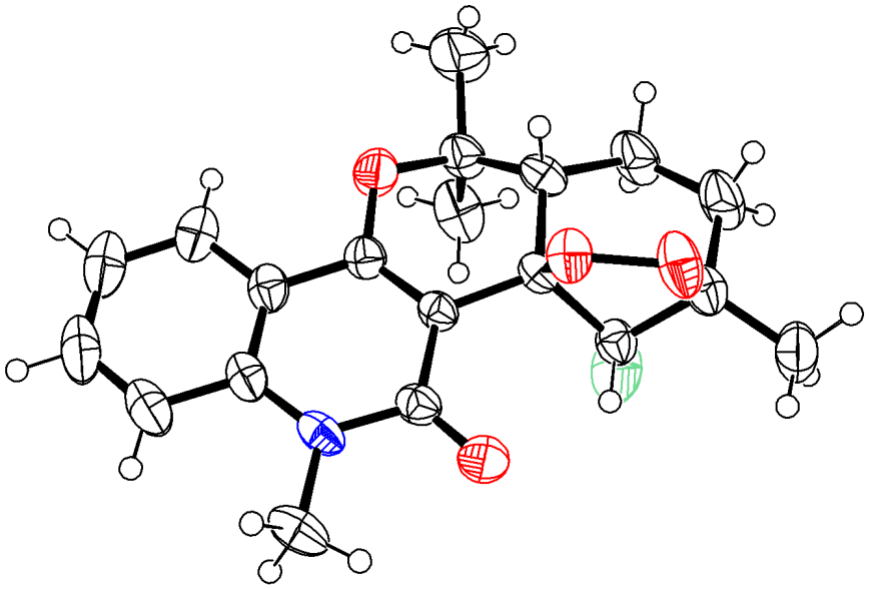
ORTEP representation of **24**.



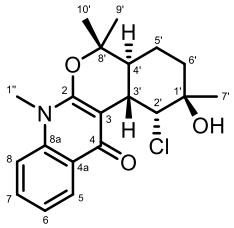
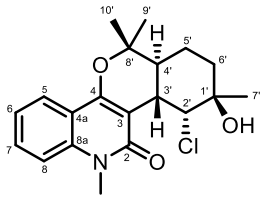
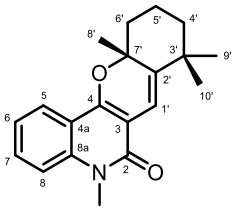
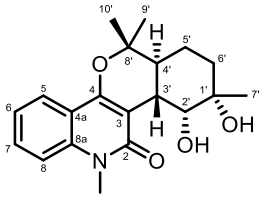
ORTEP representation of **27**.

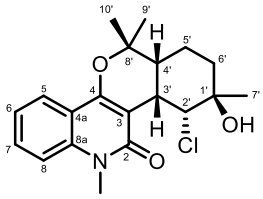
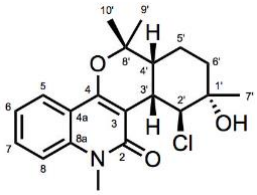
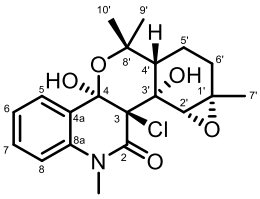
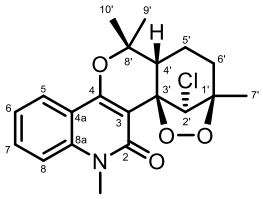


ORTEP representation of **28**.

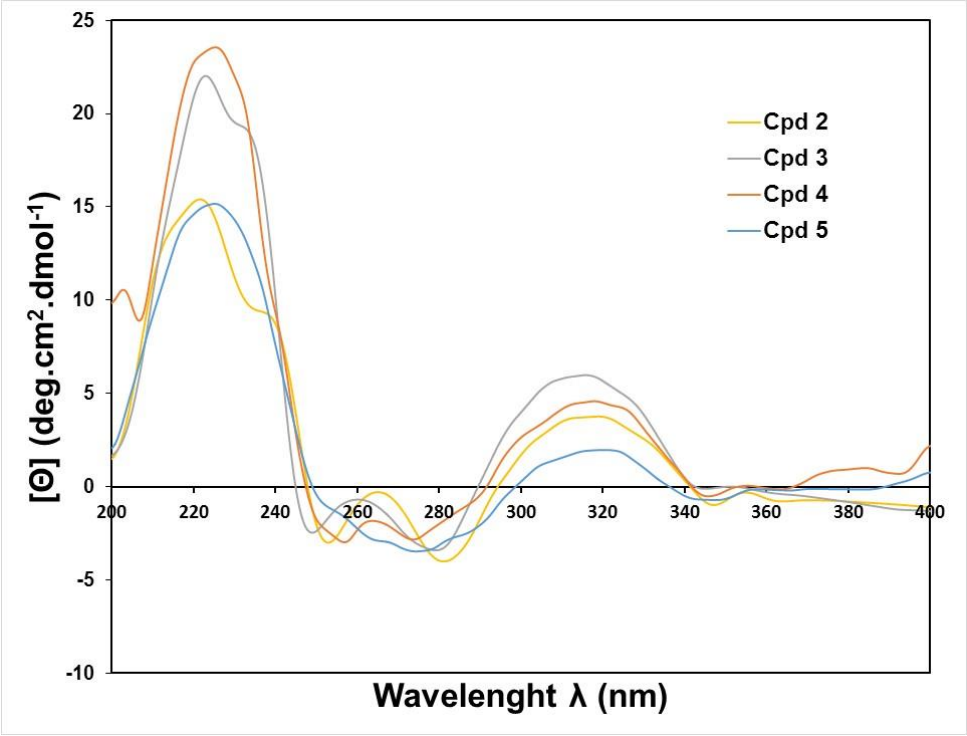


Crystal data and structure refinement for 1, 2, 19, 20, 23, 24, 27 and 28.

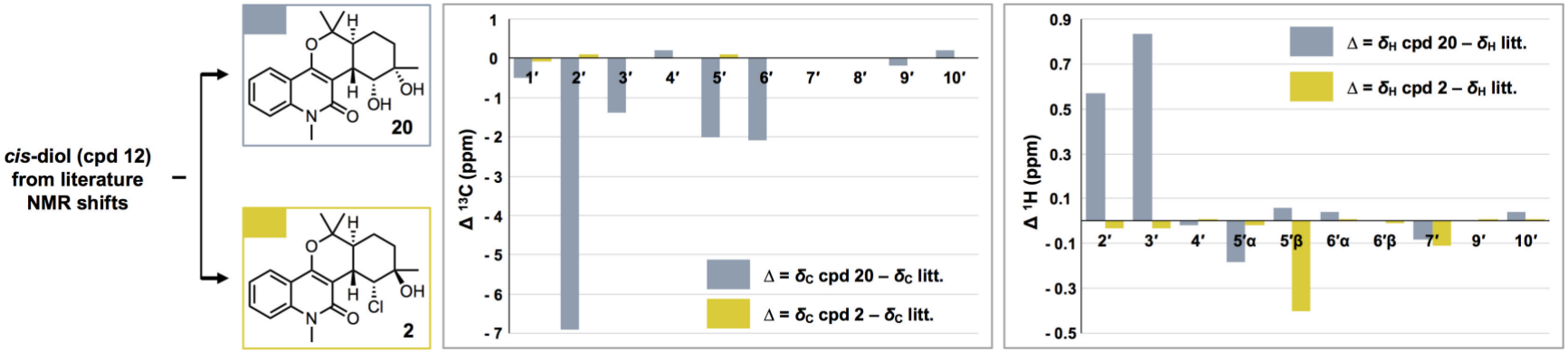
Reference	1	2	19	20
				
Empirical formula	$C_{20}H_{24}ClNO_3$, *0.57(C H₄ O)*	$C_{20}H_{24}ClNO_3$	$C_{20}H_{23}NO_2$	$C_{20}H_{25}NO_4$
Formula weight	380.07	361.85	309.39	343.41
Temperature (K)	293(2)	293(2)	100 (2)	293(2)
Wavelength (Å)	1.54187	1.54187	0.71073	1.54187
Crystal system,	Monoclinic,	Orthorhombic,	Monoclinic,	Monoclinic,
Space group	C 2	$P\ 2_12_12_1$	$P\ 2_1/n$	$P\ 2_1/c$
Unit cell dimensions:				
a | (Å)	18.4603(3)	7.5080(2)	10.2096(3)	17.0841(12)
b | (Å)	16.6736(3)	11.2397(3)	12.8487(4)	18.7193(11)
c | (Å)	13.8087(10)	21.9828(15)	12.9425(4)	11.1858(7)
α | (°)	90	90	90	90
β | (°)	103.239(7)	90	107.010(4)	100.620(4)
γ | (°)	90	90	90	90
Volume ($Å^3$)	4137.4(3)	1855.08(14)	1623.53(9)	3516.0(4)
Z	8,	4,	4,	8,
Calculated density (Mg/m^3)	1.220	1.296	1.266	1.297
Absorption coefficient (mm^{-1})	1.811	1.971	0.081	0.729
F(000)	1618	768	664	1472
Crystal size (mm)	0.25 x 0.23 x 0.09	0.28 x 0.20 x 0.08	0.50 x 0.35 x 0.18	0.59 x 0.27 x 0.06
θ range for data collection (°)	6.523 to 65.486	4.022 to 68.206	2.751 to 29.951	2.632 to 65.825
Limiting indices	$-21 \le h \le 21$, $-19 \le k \le 19$, $-16 \le l \le 15$	$-6 \le h \le 9$, $-13 \le k \le 12$, $-25 \le l \le 26$	$-14 \le h \le 14$, $-17 \le k \le 17$, $-18 \le l \le 18$	$-20 \le h \le 17$, $-18 \le k \le 22$, $-13 \le l \le 9$
Reflections collected / unique	22873 / 6991	10037 / 3348	38380 / 4453	18272 / 5900
R(int)	0.0370	0.0525	0.0405	0.0320
Completeness to θ_{full} (%)	99.6	99.7	99.9	96.1
Absorption correction		Semi-empirical from equivalents		
Max. and min. transmission	1.000 and 0.768	1.000 and 0.647	1.000 and 0.659	1.000 and 0.781
Refinement method		Full-matrix least-squares on F^2		
Data / restraints / parameters	6982 / 2 / 462	3348 / 0 / 231	4453 / 0 / 212	5866 / 1 / 471
Goodness-of-fit on F^2	1.043	1.140	1.069	1.135
Final R indices [$I>2\sigma(I)$] R1, wR2	0.0783, 0.2000	0.0543, 0.0940	0.0379, 0.1059	0.0402, 0.1050
R indices (all data): R1, wR2	0.1415, 0.2755	0.1108, 0.1408	0.0431, 0.1095	0.0540, 0.1242
Flack parameter	0.019(7)	0.034(10)	-	-
Hooft parameter	0.078(8)	0.040(12)	-	-
Extinction coefficient	0.0026(5)	-	-	-
Largest diff. peak and hole (e.$Å^3$)	0.386 and -0.430	0.364 and -0.655	0.393and -0.219	0.190 and -0.185

Reference	23	24	27	28
				
Empirical formula	$C_{20}H_{24}ClNO_3$	$C_{20}H_{24}ClNO_3, H_2O$	$C_{20}H_{24}ClNO_5$,	$C_{20}H_{22}ClNO_4$
Formula weight	361.85	379.87	380.07	375.83
Temperature (K)	293(2)	293(2)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073	1.54187	0.71073
Crystal system,	Triclinic,	Monoclinic,	Monoclinic,	Monoclinic,
Space group	P -1	$P\ 2_1/n$	$P\ 2_1/n$	$P\ 2_1/n$
Unit cell dimensions:				
a | (Å)	11.4568 (5)	16.1270(8)	11.3027(5)	17.278(2)
b | (Å)	11.4834(3)	7.2090(4)	7.2512(2)	12.6989(10)
c | (Å)	14.2866(7)	16.3705(9)	23.1020(16)	17.255(2)
α | (°)	94.508(3)	90	-	-
β | (°)	106.183(4)	91.080(5)	98.784(7)	102.191(13)
γ | (°)	90.764(2)	90	-	-
Volume ($Å^3$)	1798.31(13)	1902.90(18)	1871.19(17)	3700.4(7)
Z	4,	4	4,	8,
Calculated density (Mg/m^3)	1.337	1.326	1.398	1.349
Absorption coefficient (mm^{-1})	0.231	0.226	2.084	0.232
F(000)	768	808	832	1584
Crystal size (mm)	0.22 x 0.16 x 0.07	0.24 x 0.07 x 0.05	0.23 x 0.12 x 0.04	0.30 x 0.15 x 0.05
θ range for data collection (°)	3.601 to 30.482	3.514 to 29.698	3.872 to 68.191	3.549 to 30.661
Limiting indices	$-16 \le h \le 15$,	$-20 \le h \le 21$,	$-13 \le h \le 13$,	$-21 \le h \le 24$,
	$-16 \le k \le 16$,	$-9 \le k \le 10$,	$-8 \le k \le 8$,	$-12 \le k \le 18$,
	$-10 \le l \le 20$	$-21 \le l \le 20$	$-25 \le l \le 27$	$-20 \le l \le 24$
Reflections collected / unique	45746/9861	20009/4819	9812 / 3350	33386 / 10185
R(int)	0.051	0.0737	0.0451	0.0612
Completeness to θ_{full} (%)	98.8	99.4	97.4	99.6
Absorption correction		Semi-empirical from equivalents		
Max. and min. transmission	1.000 and 0.540	1.000 and 0.6213	1.000 and 0.691	1.000 and 0.716
Refinement method		Full-matrix least-squares on F^2		
Data / restraints / parameters	9814 / 0 / 467	4818/2/246	3338 / 0 / 254	10185 / 0 / 477
Goodness-of-fit on F^2	1.062	1.066	1.084	1.026
Final R indices [$I>2\sigma(I)$] R1,	0.0637,	0.0692,	0.0463,	0.0613,
wR2	0.1833	0.1793	0.1156	0.1331
R indices (all data): R1,	0.0761	0.0917	0.0596,	0.1125,
wR2	0.1899	0.1929	0.1277	0.1521
Largest diff. peak and hole (e.$Å^3$)	0.418 and -0.384	0.470 and -0.478	0.367 and -0.203	0.317 and -0.297

S8. Experimental ECD for compounds **2** to **5**.



S9. ^{1}H and ^{13}C NMR shifts difference between the *cis*-diol reported in literature (cpd **12**) and the synthesised compounds **20** or the crystallised natural product **2** in chart.



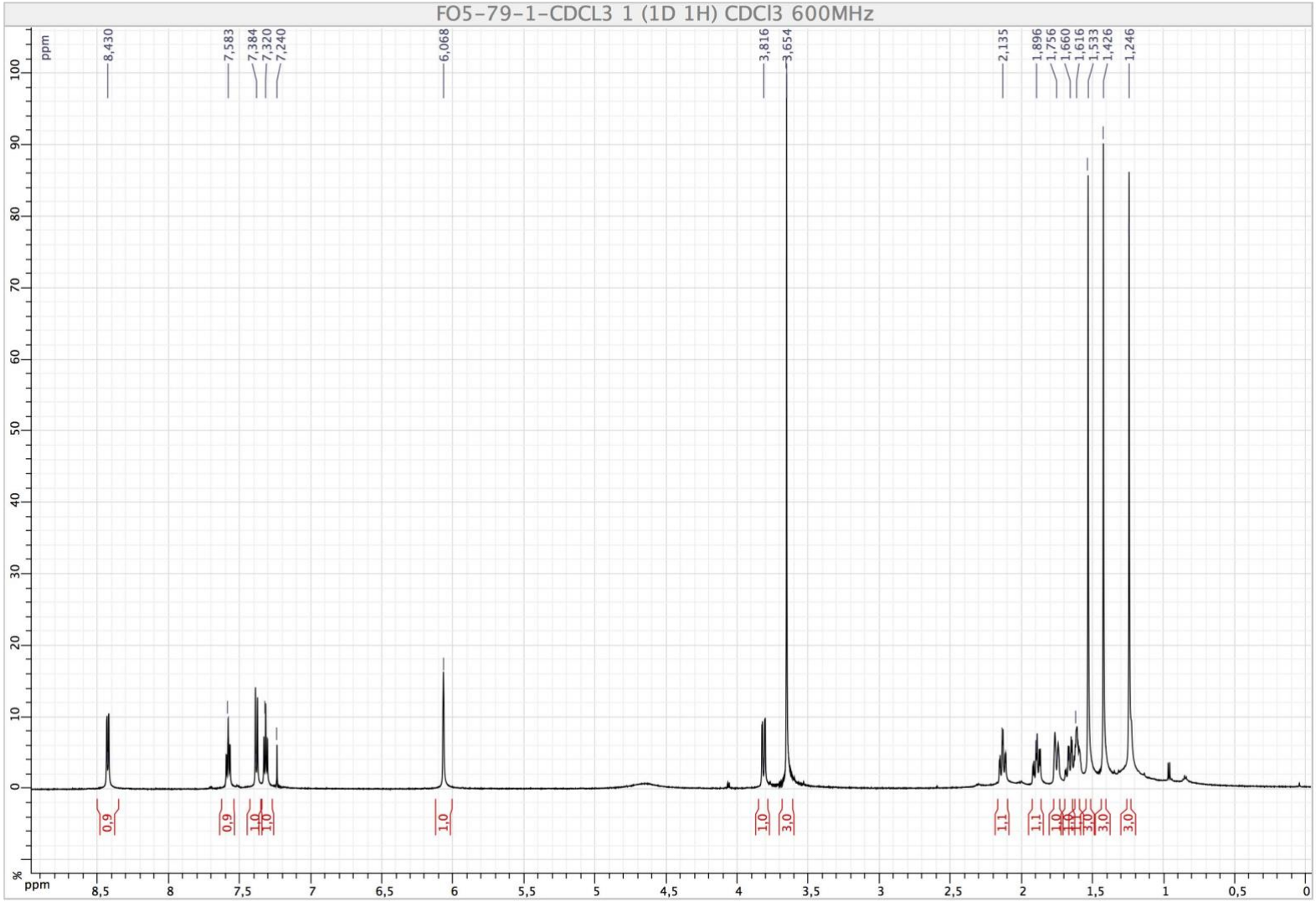
S10. ^{1}H and ^{13}C NMR shifts difference between the *cis*-diol reported in literature (cpd **12**) and the synthesised compounds **20** or the crystallised natural product **2** in table.

Position	**20 δ_C**	**12 δ_C**	**2 δ_C**	**Δ ^{1}H 12 - 20**	**Δ ^{1}H 12 - 2**
2	163	162.9	162.9	-0.1	0
3	106	106.3	106.3	0.3	0
4	157	157.4	157.5	0.4	-0.1
4a	117	116.9	116.9	-0.1	0
5	123.5	123.4	123.4	-0.1	0
6	121.8	121.7	121.8	-0.1	-0.1
7	130.6	130.6	130.6	0	0
8	114	114	114.1	0	-0.1
8a	139	139.1	139	0.1	0.1
N-Me	29.2	29.3	29.6	0.1	-0.3
1′	73	72.5	72.4	-0.5	0.1
2′	72.3	65.4	65.5	-6.9	-0.1
3′	37.5	36.1	36	-1.4	0.1
4′	39.9	40.1	40.1	0.2	0
5′	24.9	22.9	22.9	-2	0
6′	35.1	33	32.9	-2.1	0.1
7′	24.5	-	29.4	0	0
8′	79.8	79.8	79.8	0	0
9′	27.8	27.6	27.6	-0.2	0
10′	19.6	19.8	19.8	0.2	0

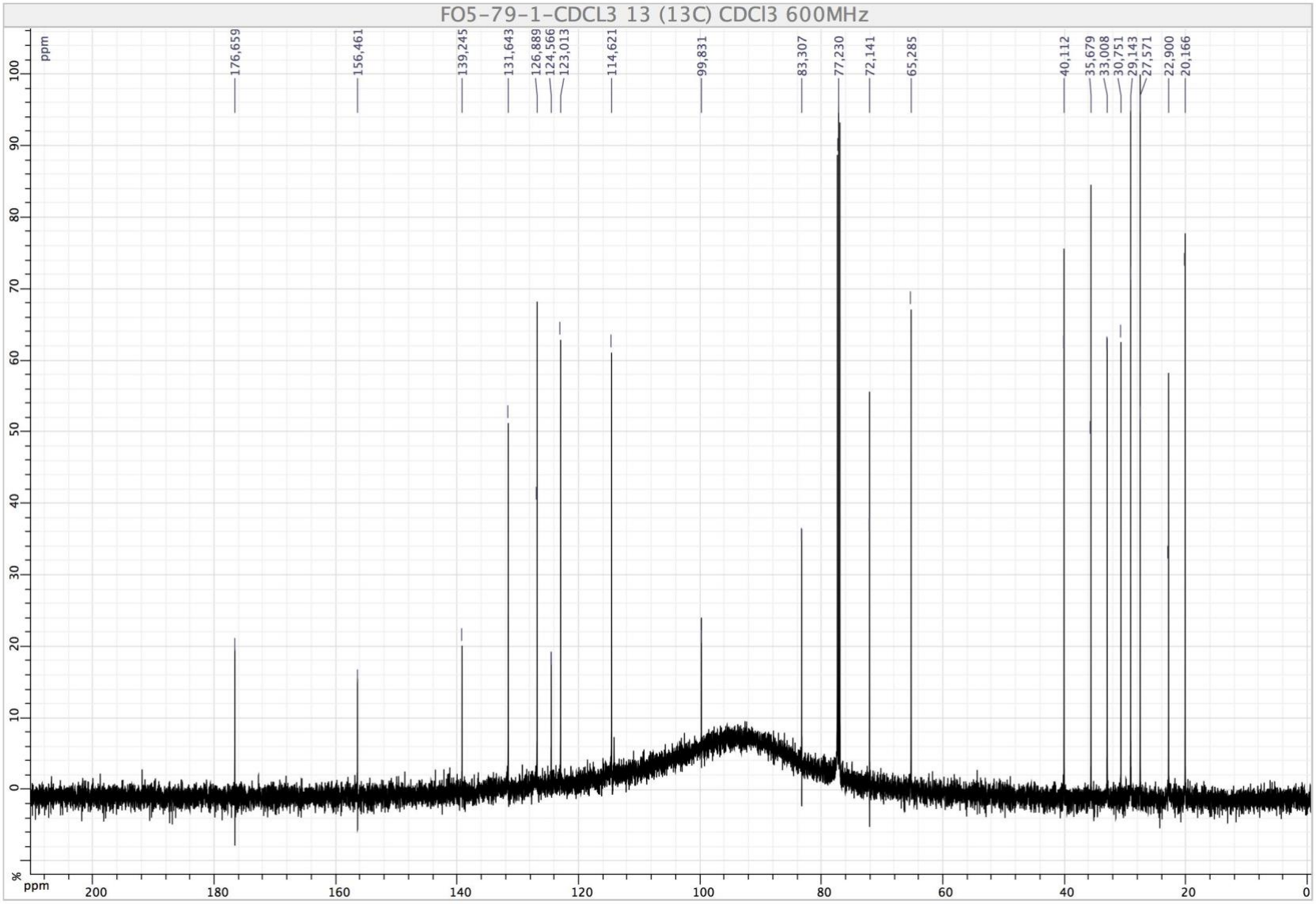
Position	**20 δ_H**	**12 δ_H**	**2 δ_H**	**Δ ^{13}C 12 - 20**	**Δ ^{13}C 12 - 2**
5	7.98	7.98	7.98	0	0
6	7.23	7.21	7.23	-0.02	-0.02
7	7.54	7.54	7.55	0	-0.01
8	7.25	7.24	7.34	-0.01	-0.1
N-Me	3.54	3.6	3.7	0.06	-0.1
2′	5.21	5.78	5.81	0.57	-0.03
3′	2.74	3.57	3.6	0.83	-0.03
4′	2.2	2.18	2.17	-0.02	0.01
5′α	1.79	1.61	1.63	-0.18	-0.02
5′β	1.2	1.26	1.66	0.06	-0.4
6′α	1.9	1.94	1.93	0.04	0.01
6′β	1.73	1.73	1.74	0	-0.01
7′	1.44	1.36	1.47	-0.08	-0.11
9′	1.57	1.57	1.56	0	0.01
10′	1.18	1.22	1.21	0.04	0.01

S11. NMR and HRESIMS spectra of compounds **1** to **5**, (±)-**2**, **16**, *cis*/*trans*-**17**, **19** to **24** and **26** to **28**.

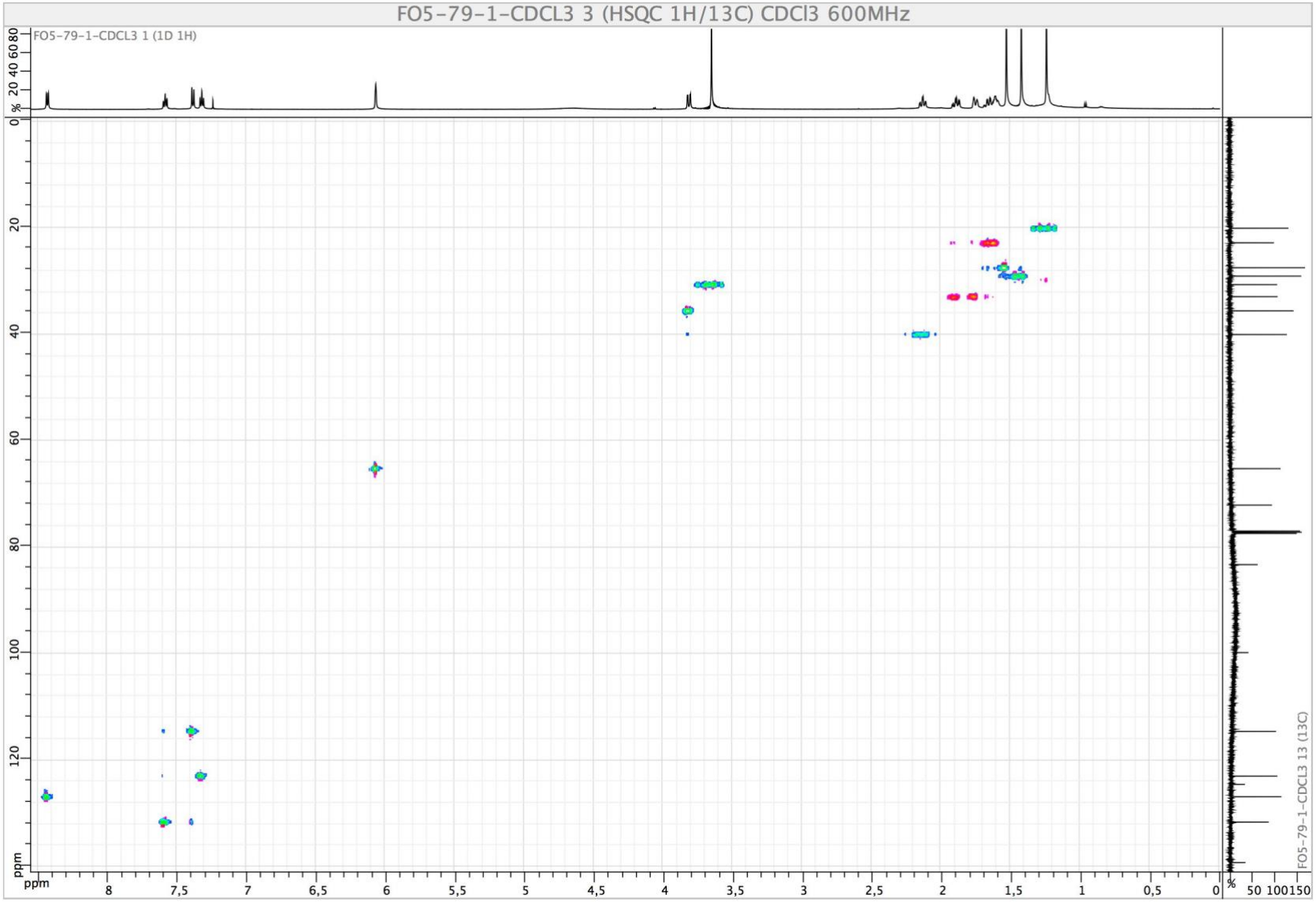
^{1}H NMR spectrum of **1** in $CDCl_3$ at 600 MHz.



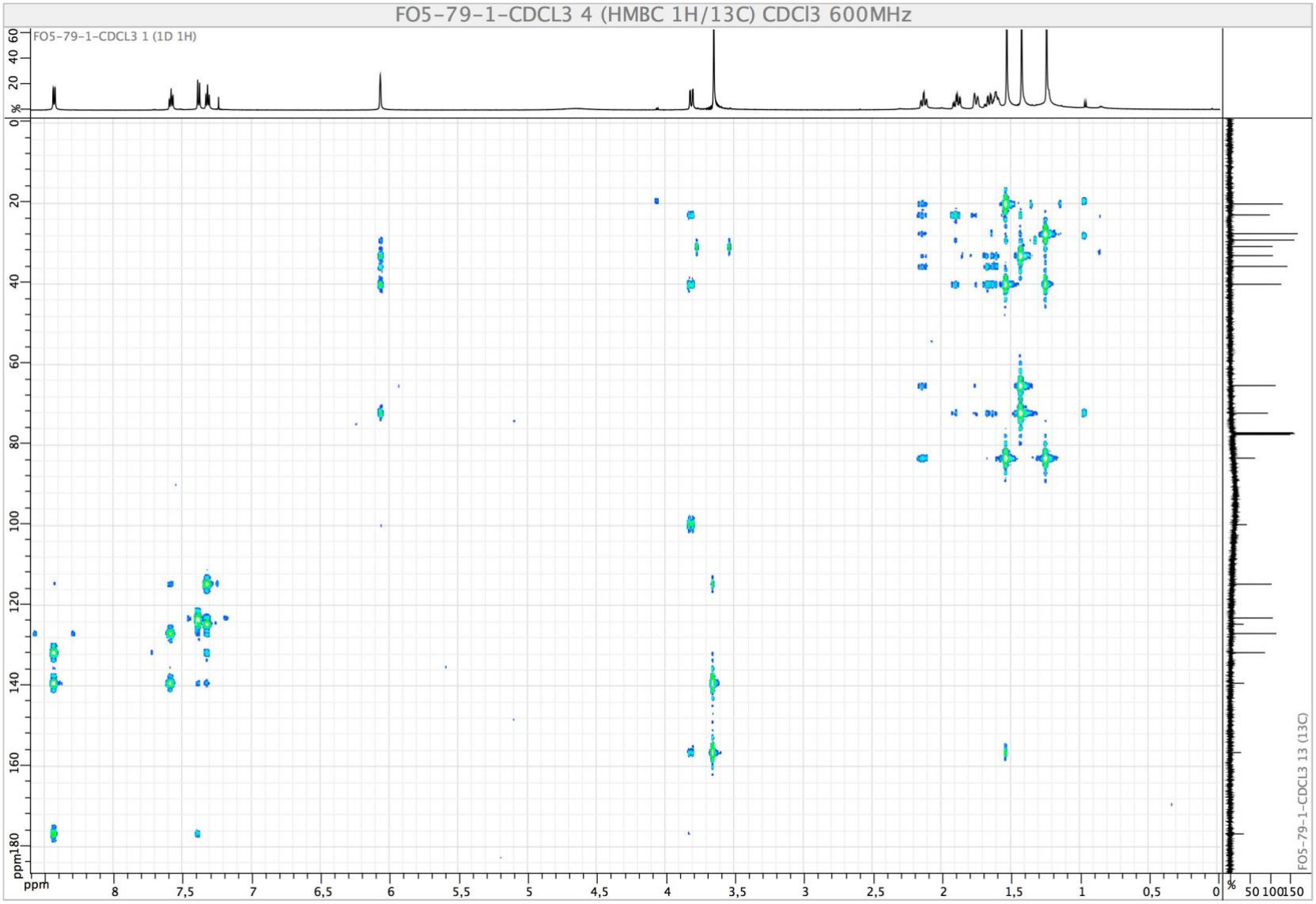
^{13}C NMR spectrum of **1** in $CDCl_3$ at 150 MHz.



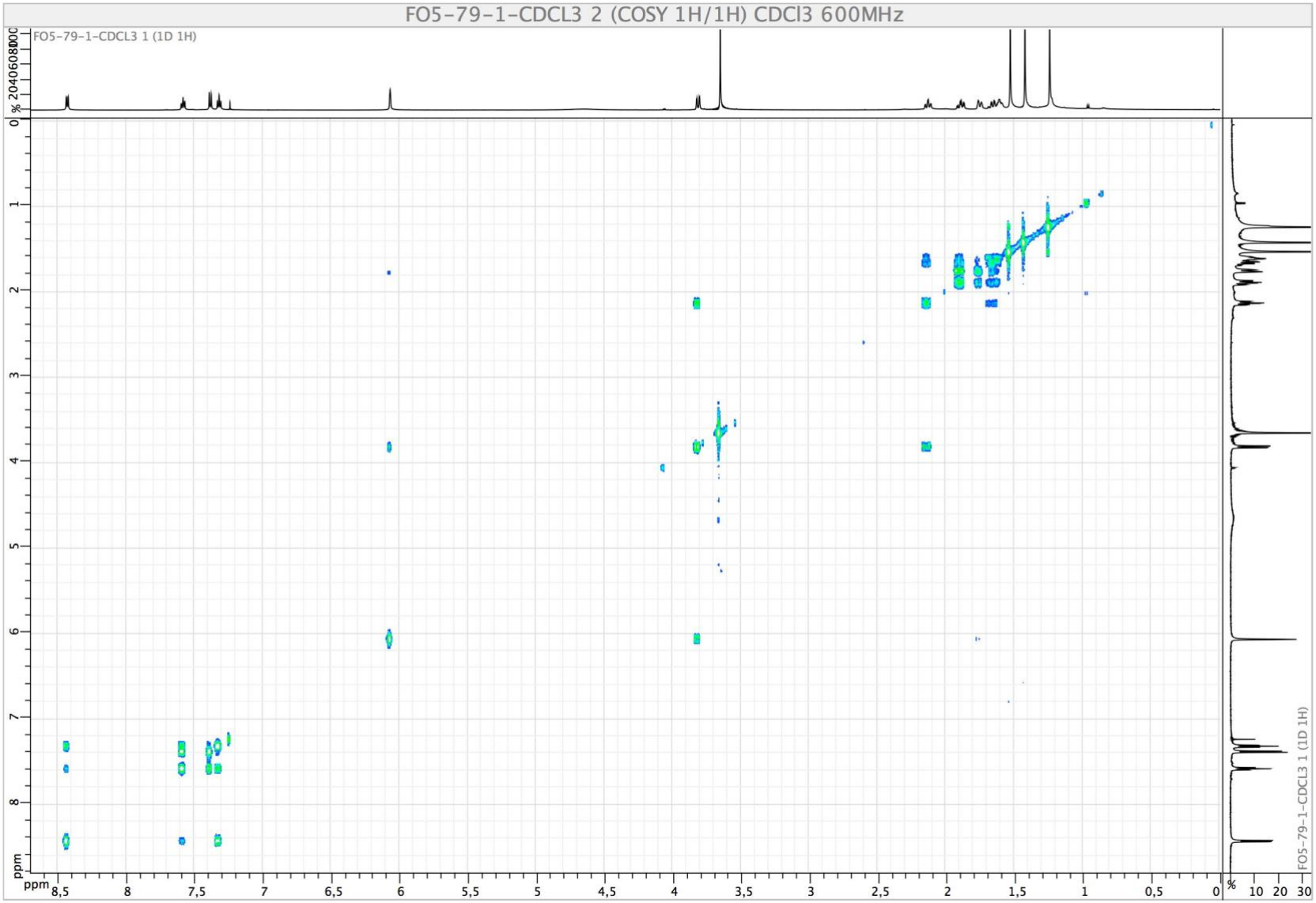
HSQC spectrum (600 MHz, 150 MHz) of **1** in $CDCl_3$.



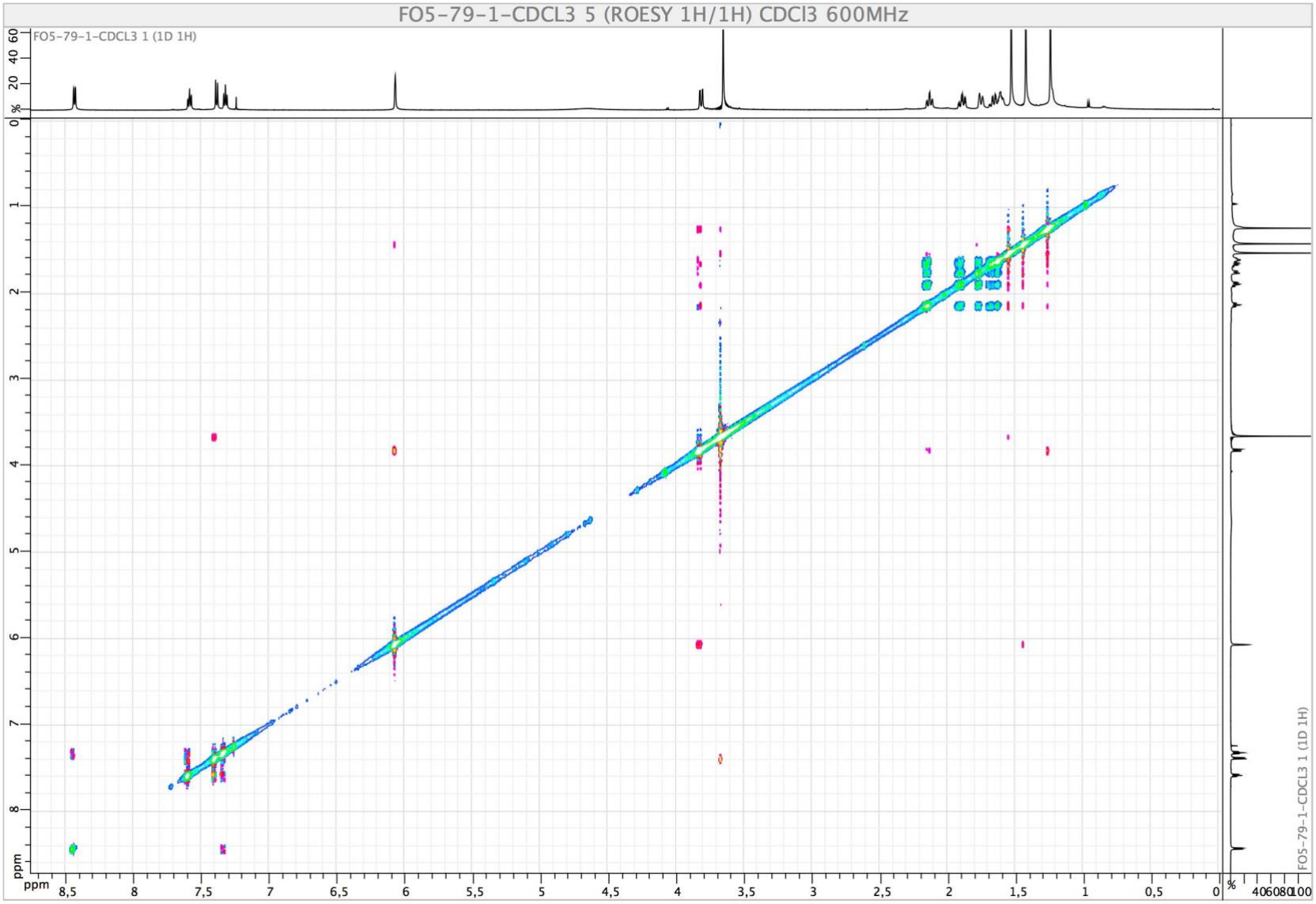
HMBC spectrum (600 MHz, 150 MHz) of **1** in $CDCl_3$.



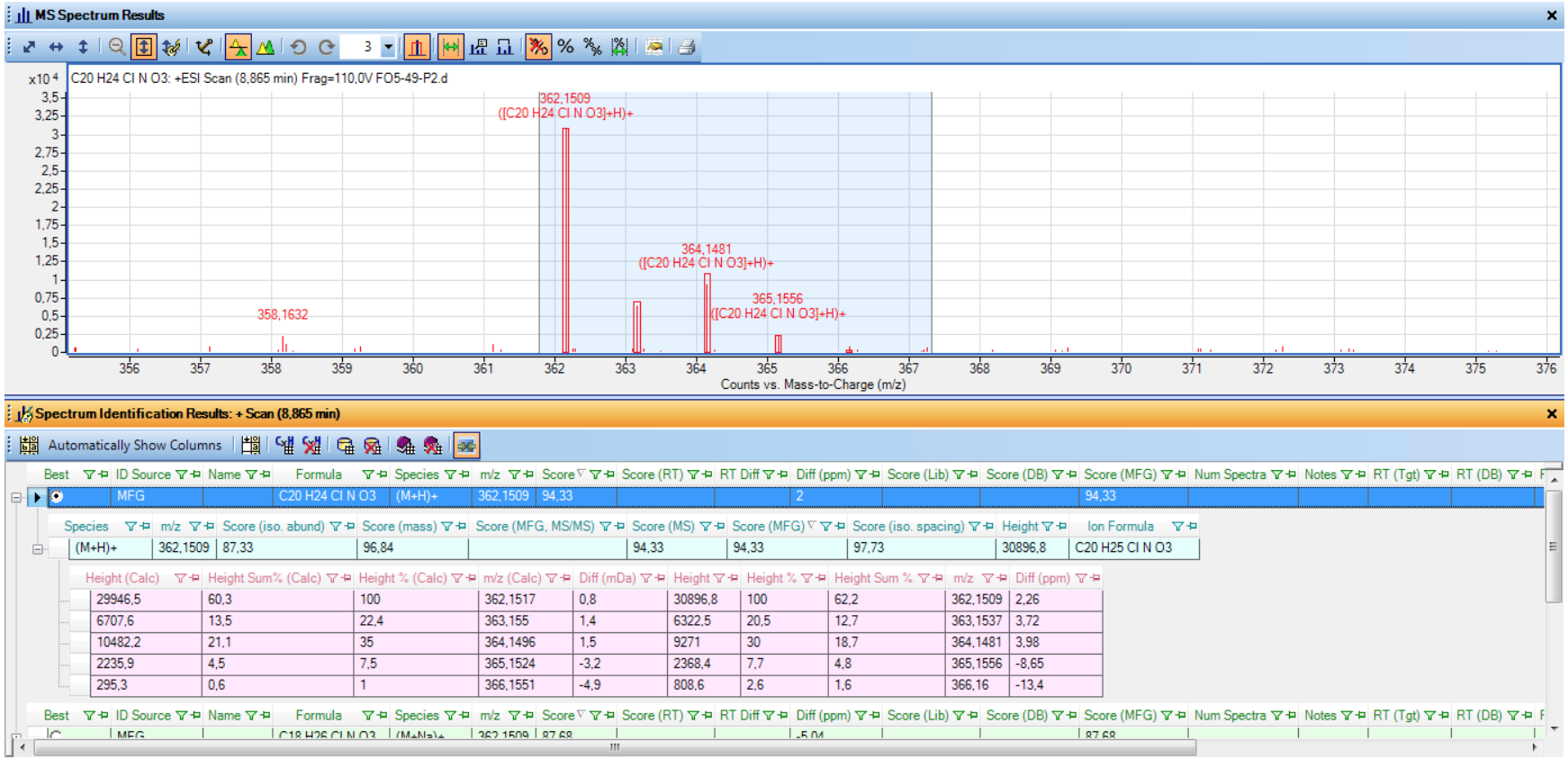
COSY spectrum (600 MHz) of **1** in $CDCl_3$.



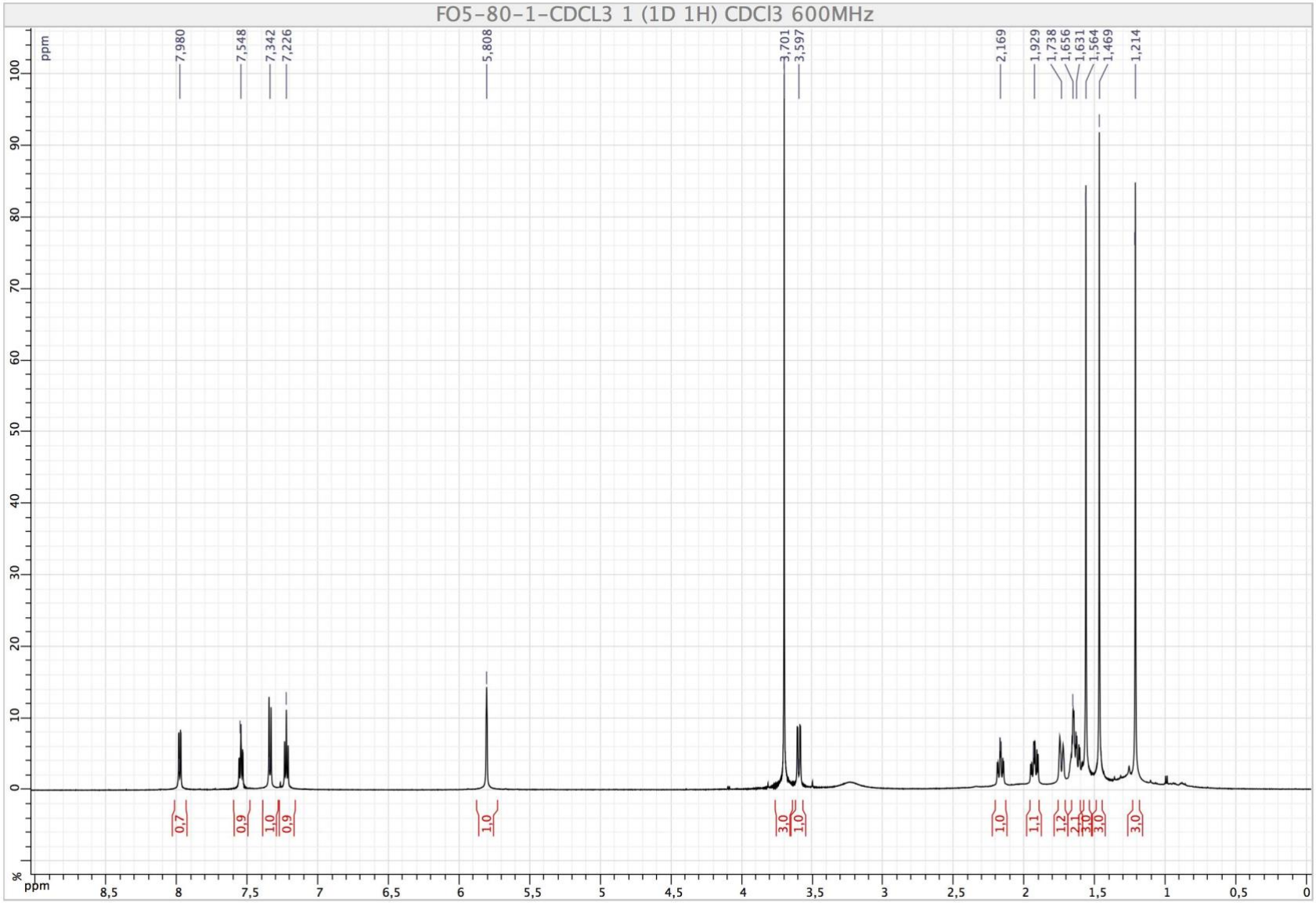
ROESY spectrum (600 MHz) of **1** in $CDCl_3$.



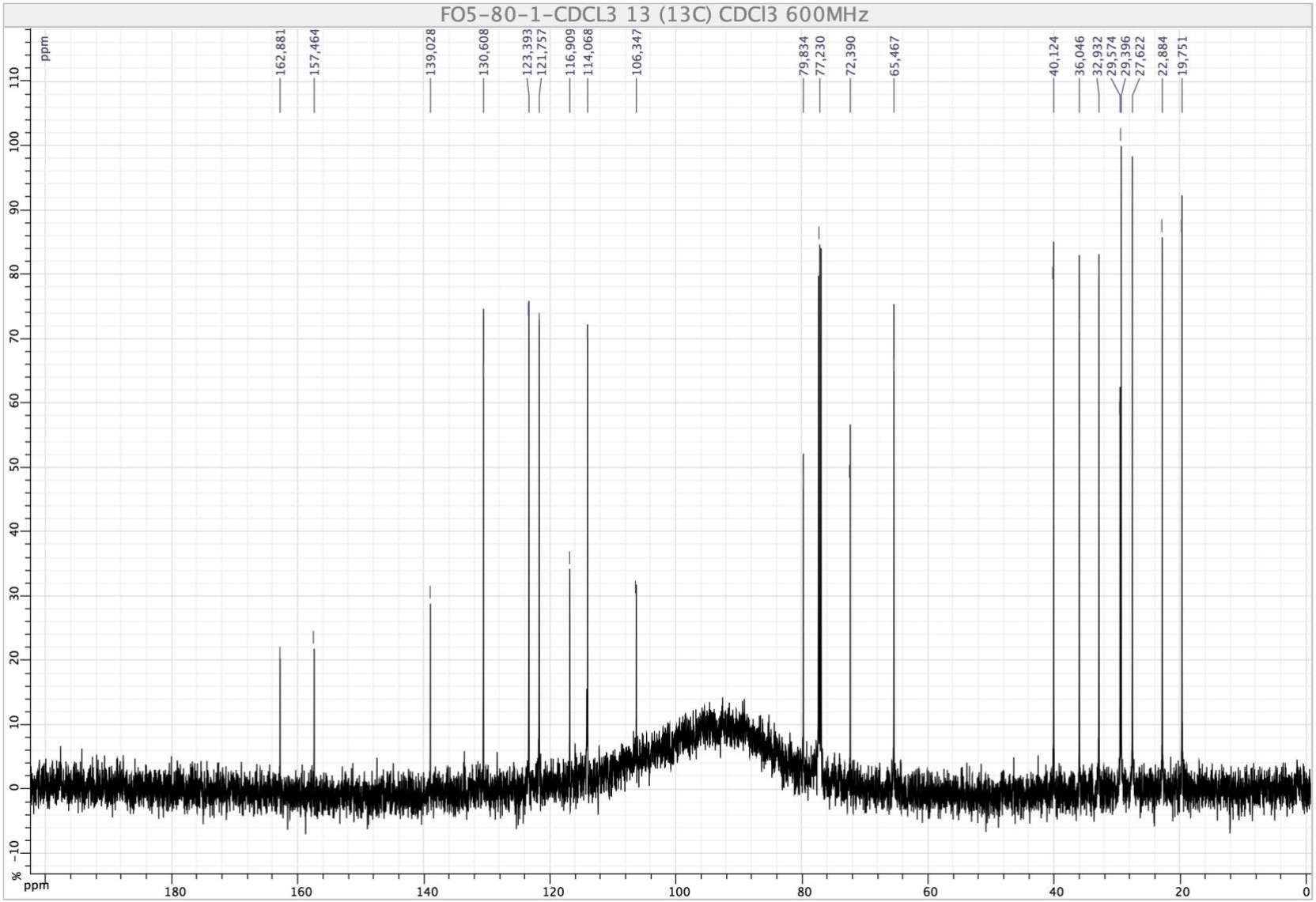
HRESIMS spectrum (TOF) of **1**.



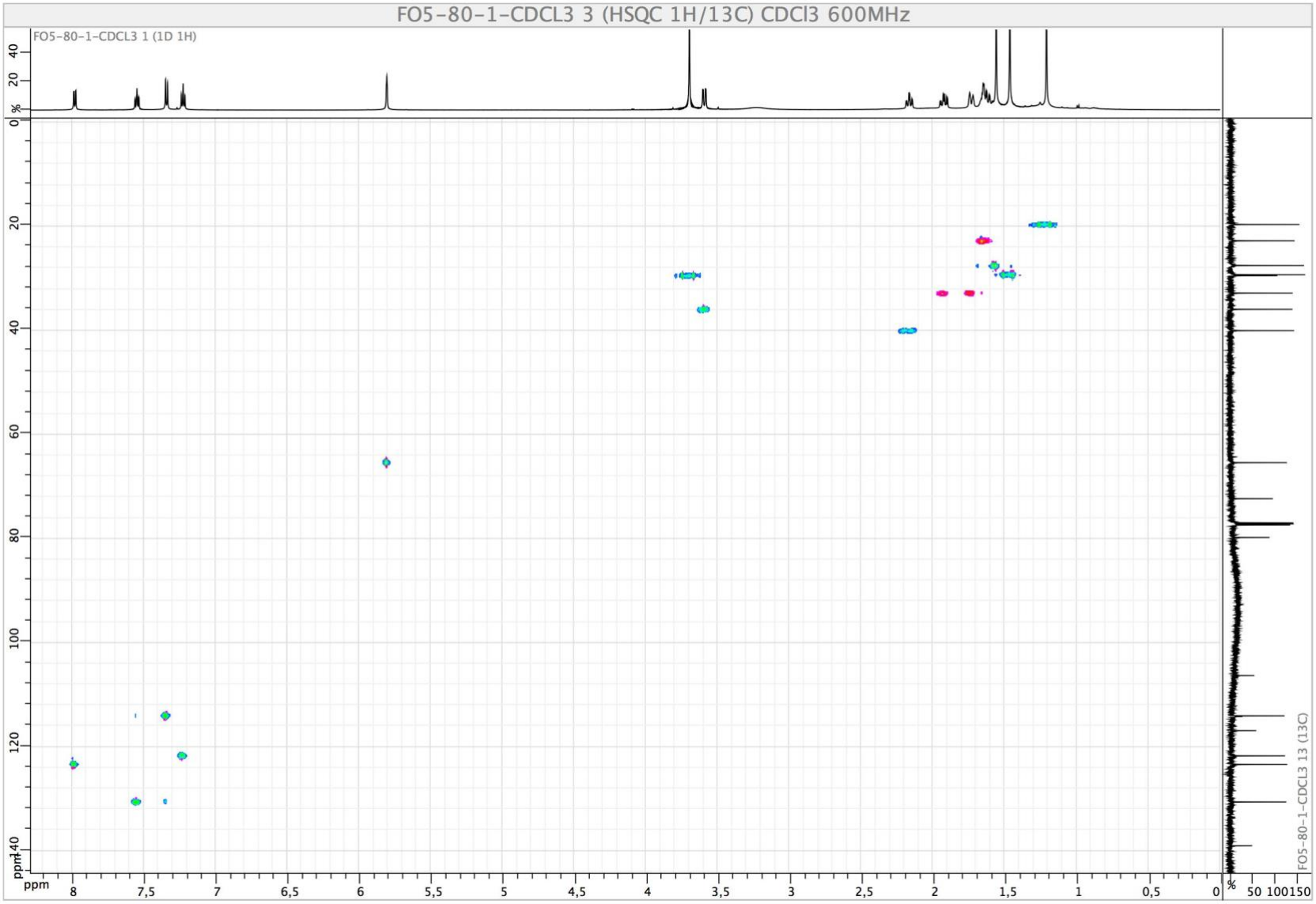
^{1}H NMR spectrum of **2** in $CDCl_3$ at 600 MHz.



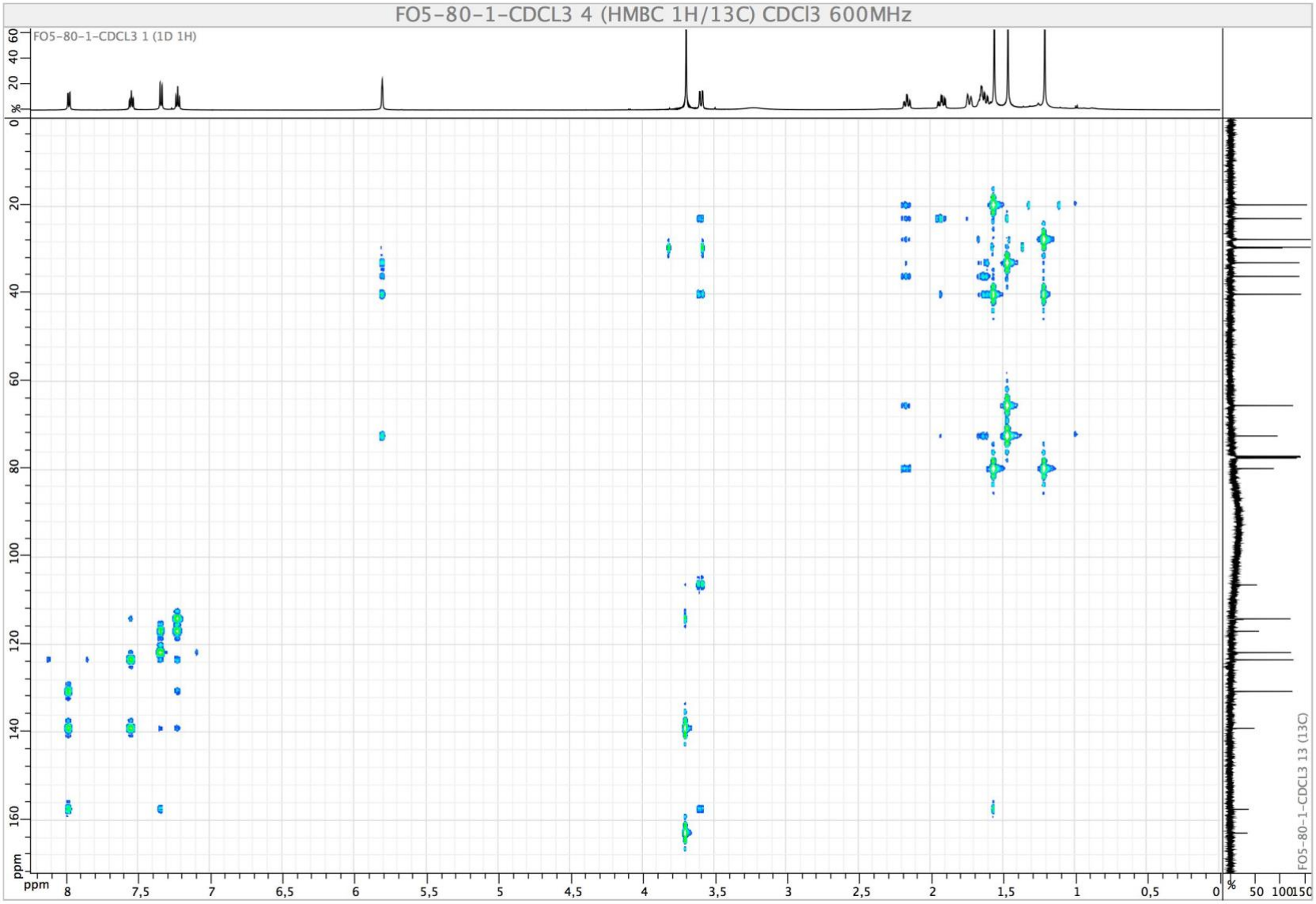
^{13}C NMR spectrum of **2** in $CDCl_3$ at 150 MHz.



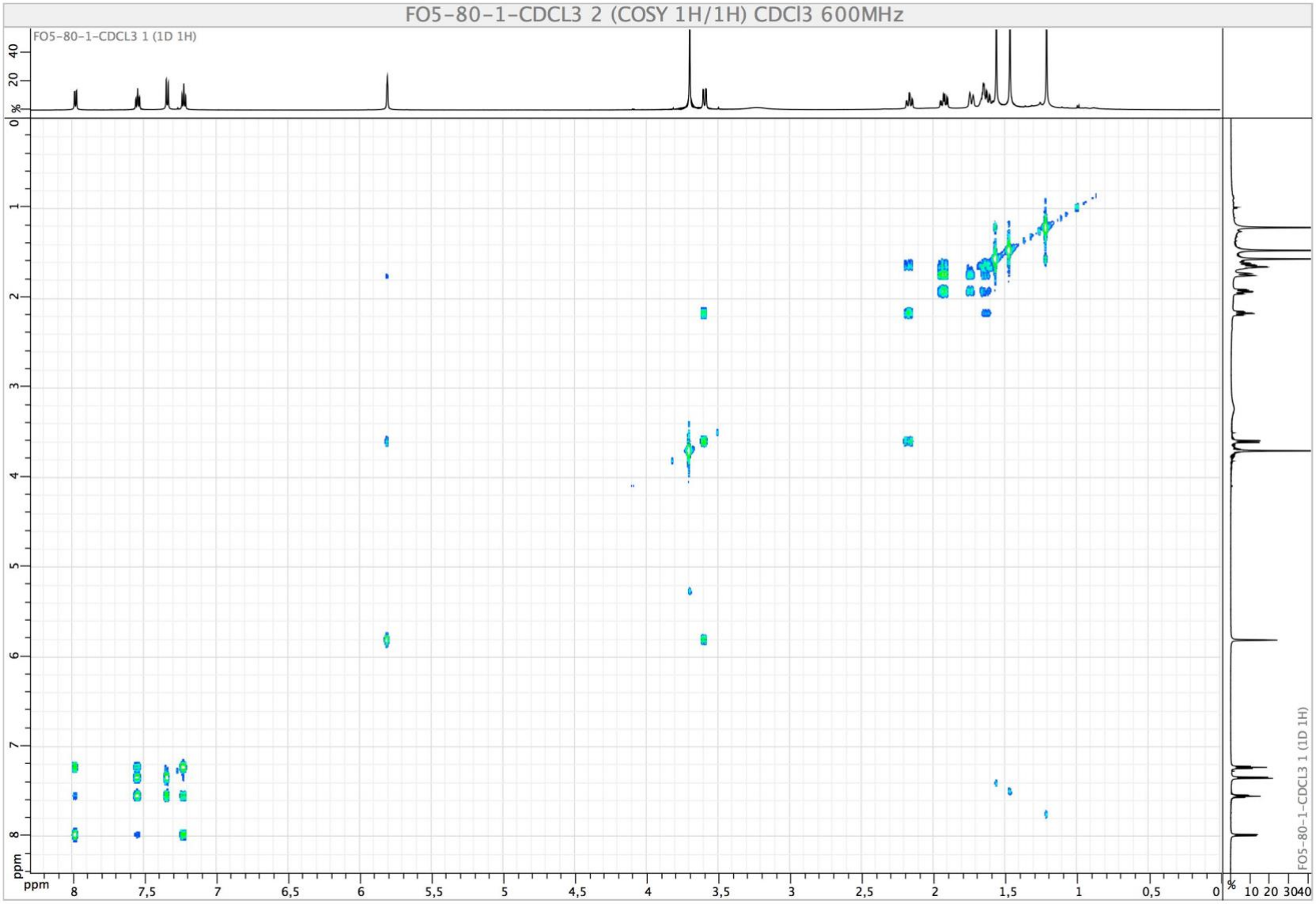
HSQC spectrum (600 MHz, 150 MHz) of **2** in $CDCl_3$.



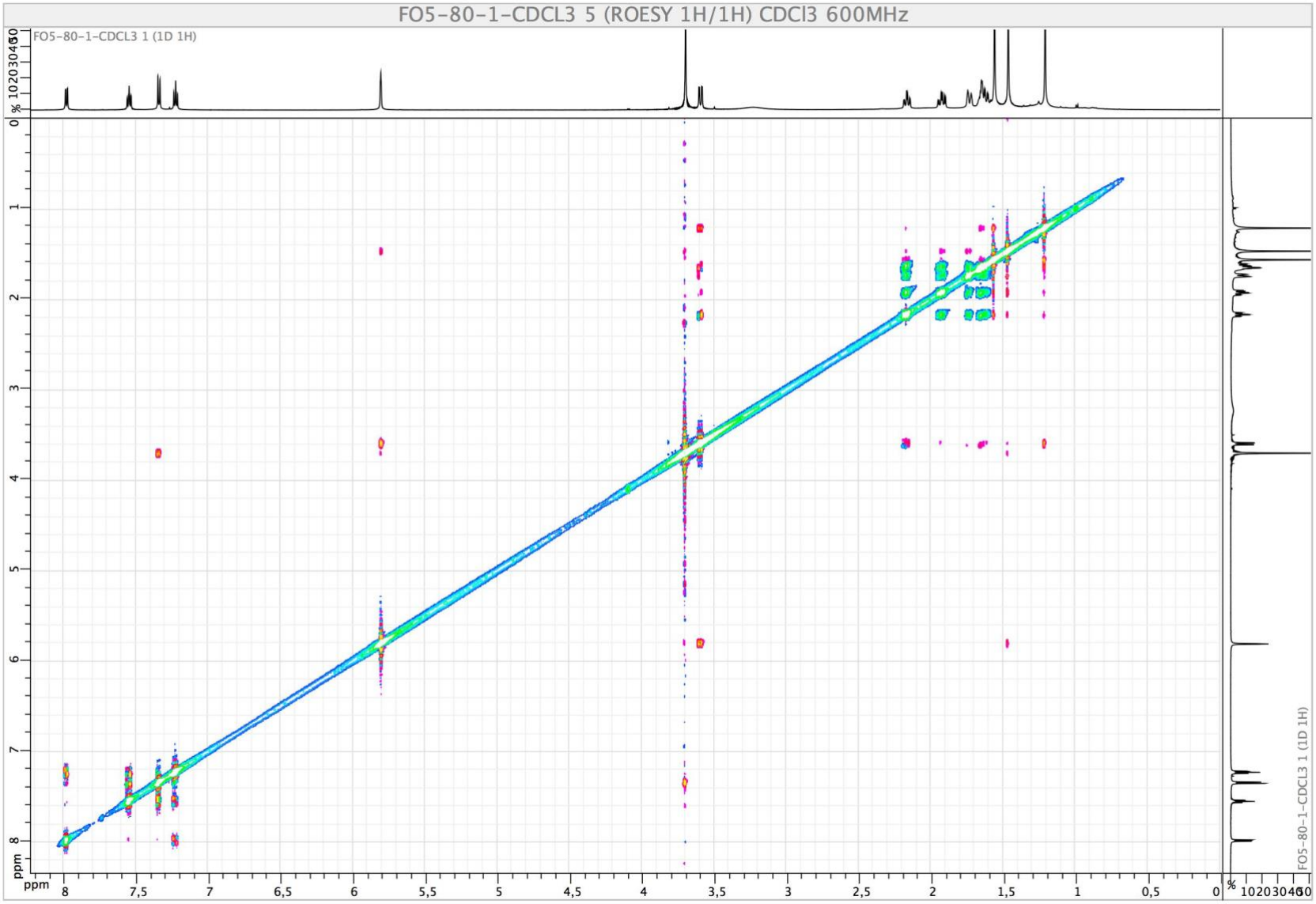
HMBC spectrum (600 MHz, 150 MHz) of **2** in $CDCl_3$.



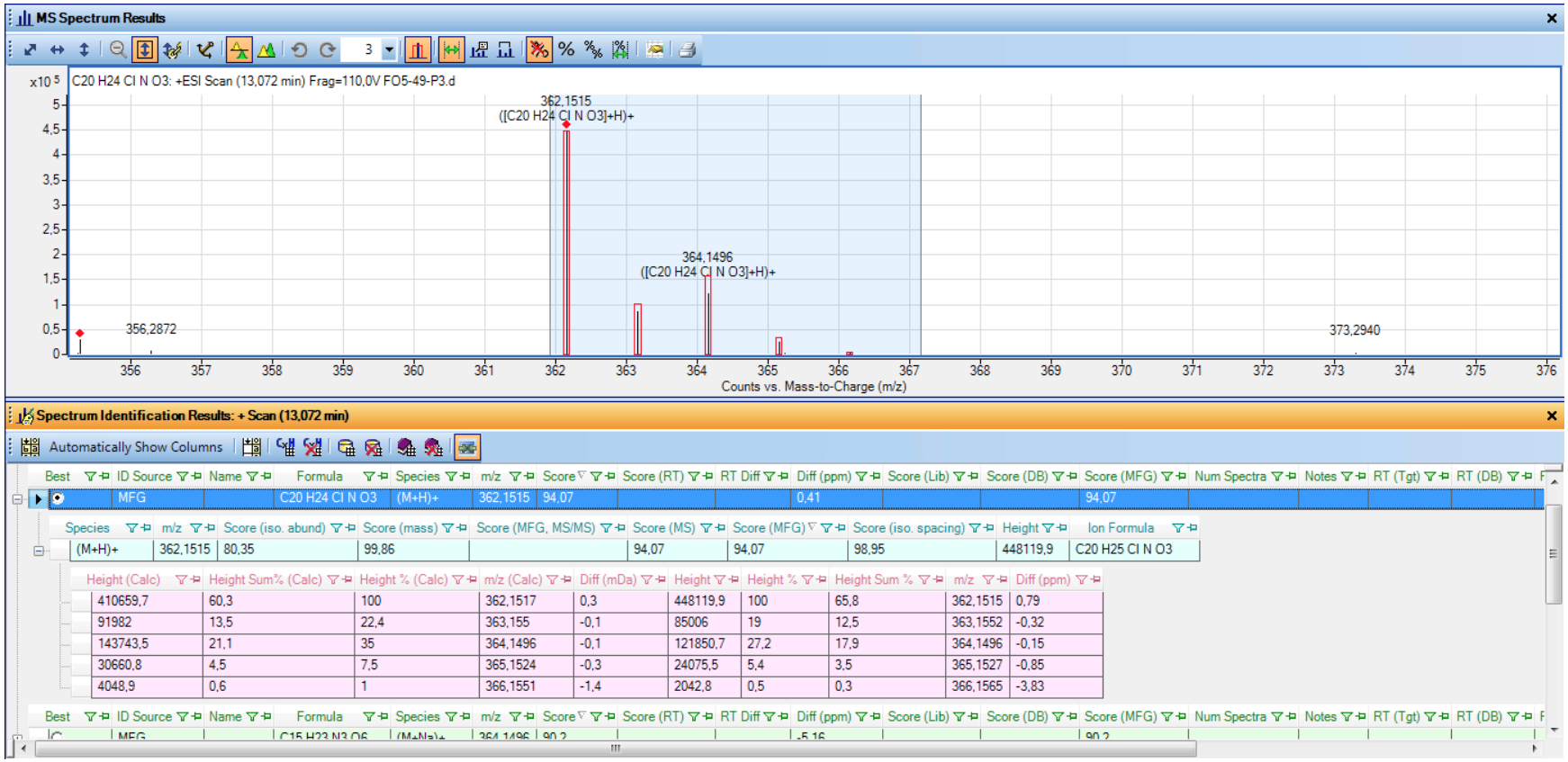
COSY spectrum (600 MHz) of **2** in $CDCl_3$.



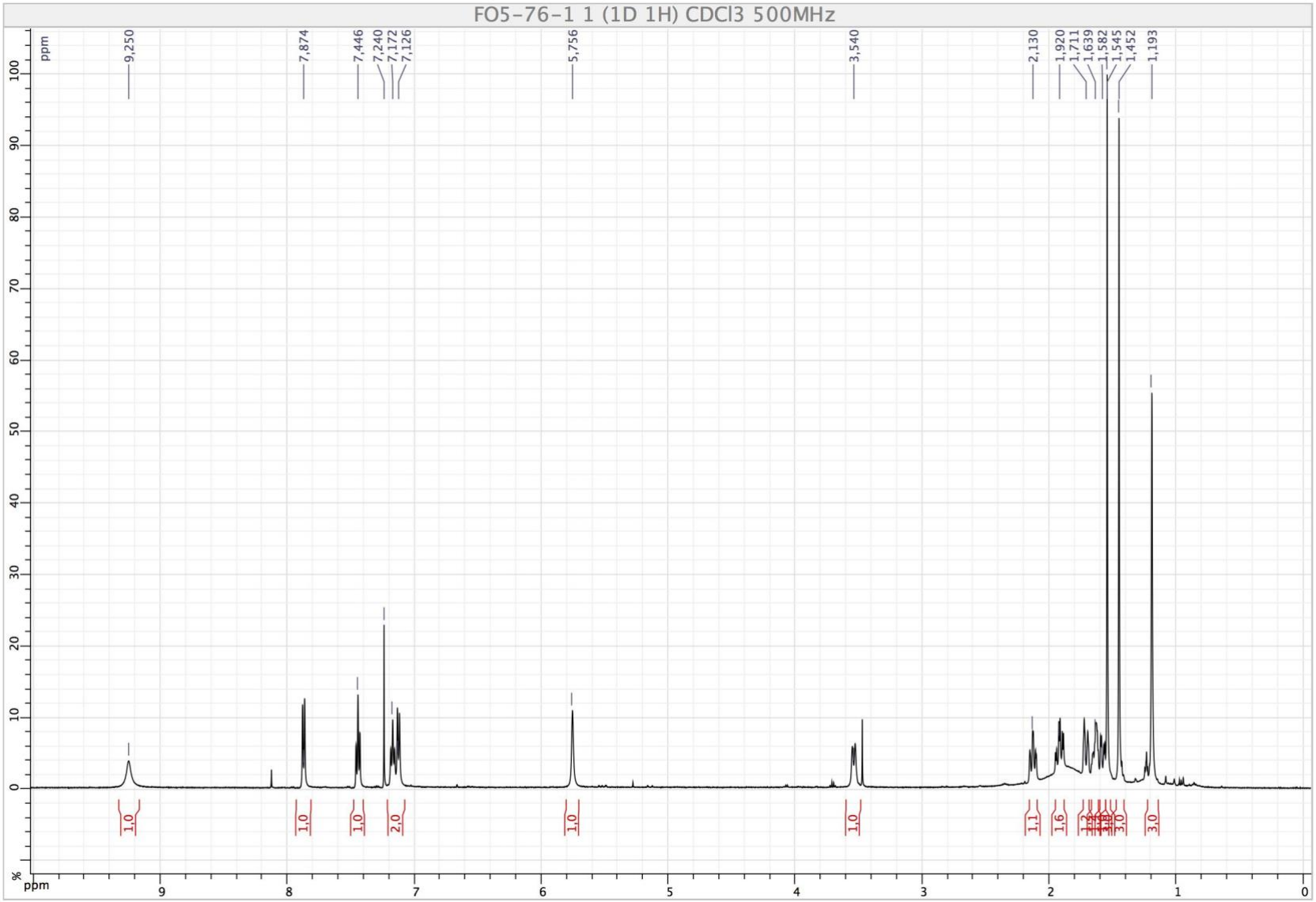
ROESY spectrum (600 MHz) of **2** in $CDCl_3$.



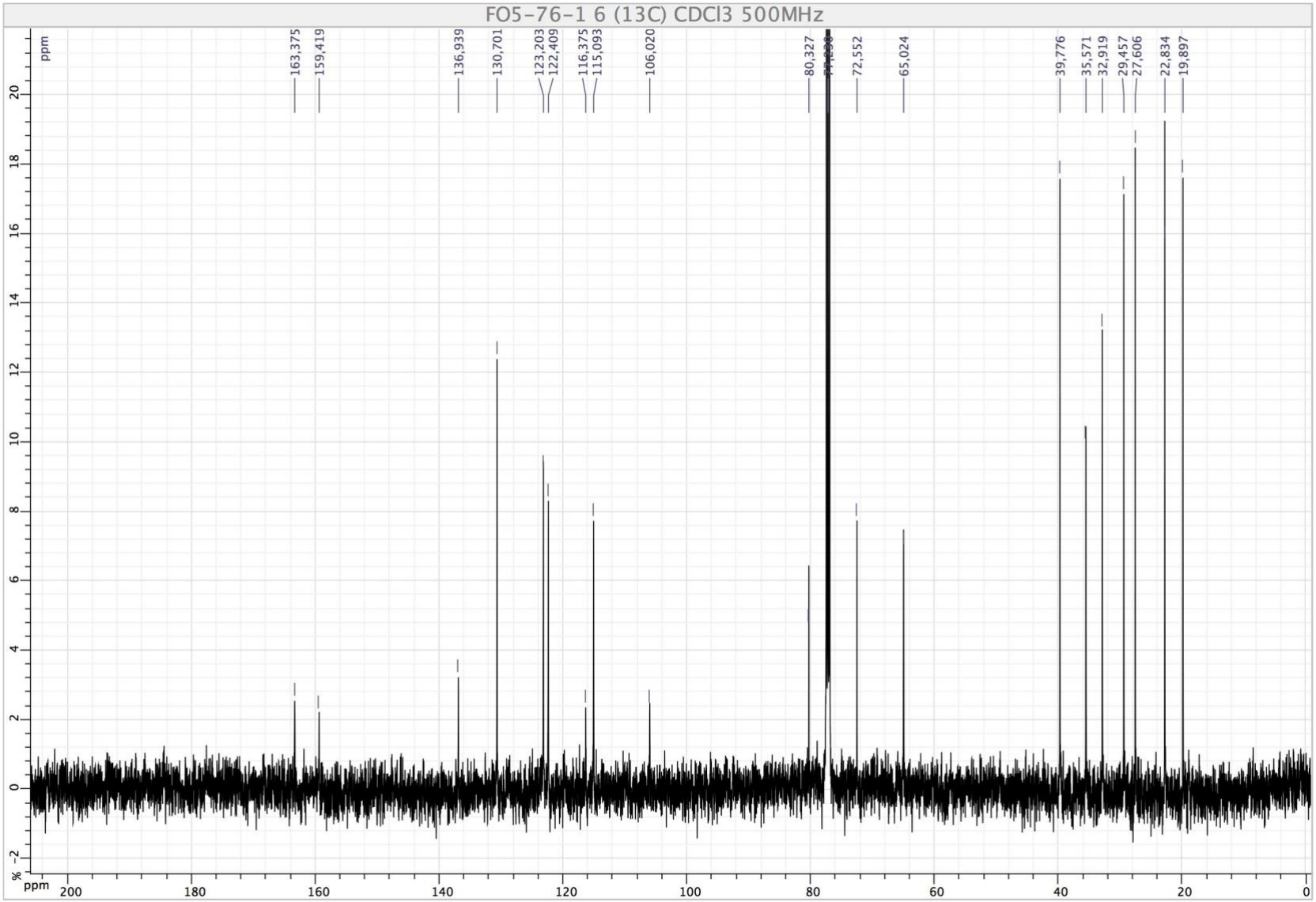
HRESIMS spectrum (TOF) of **2**.



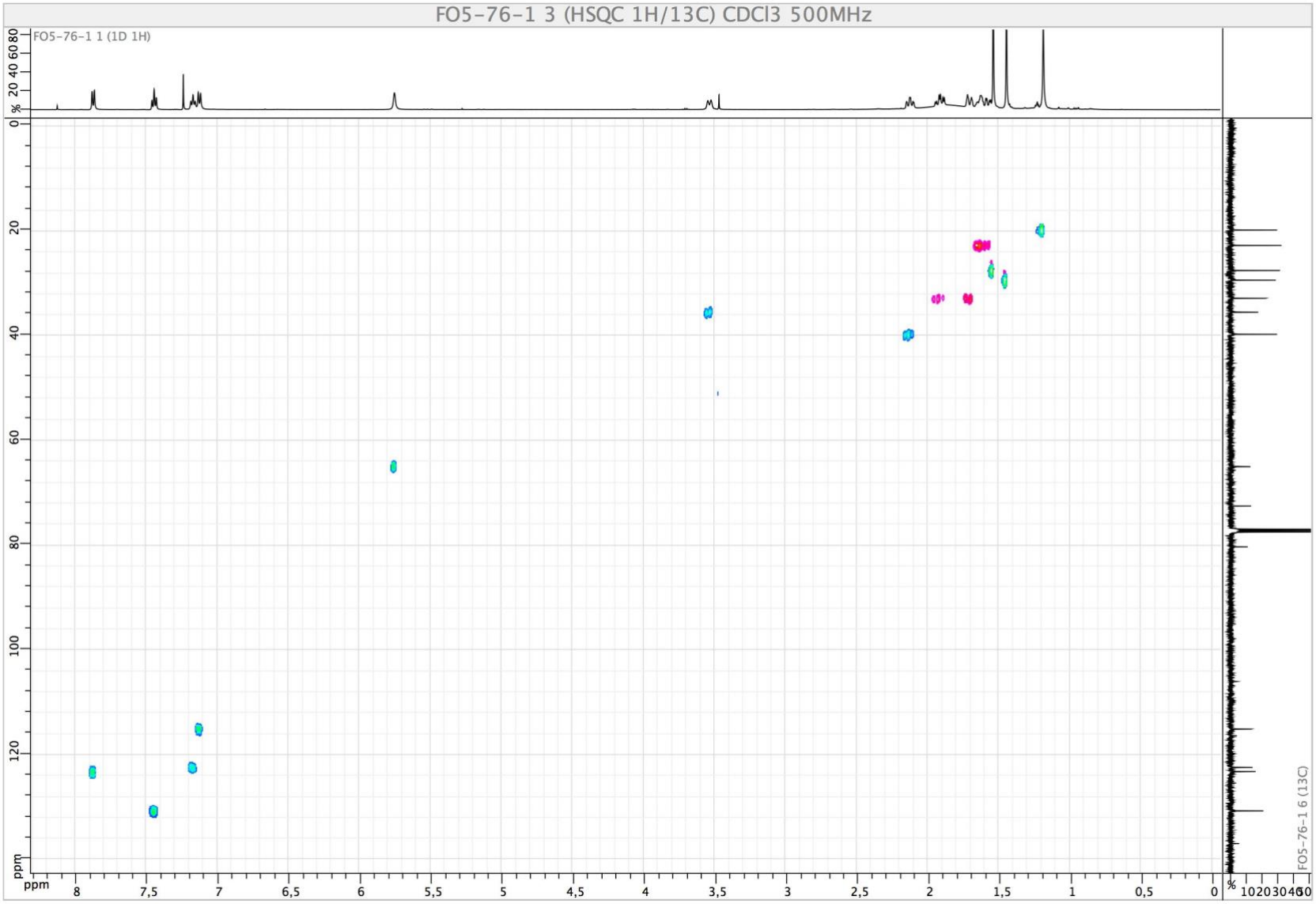
^{1}H NMR spectrum of **3** in $CDCl_3$ at 500 MHz.



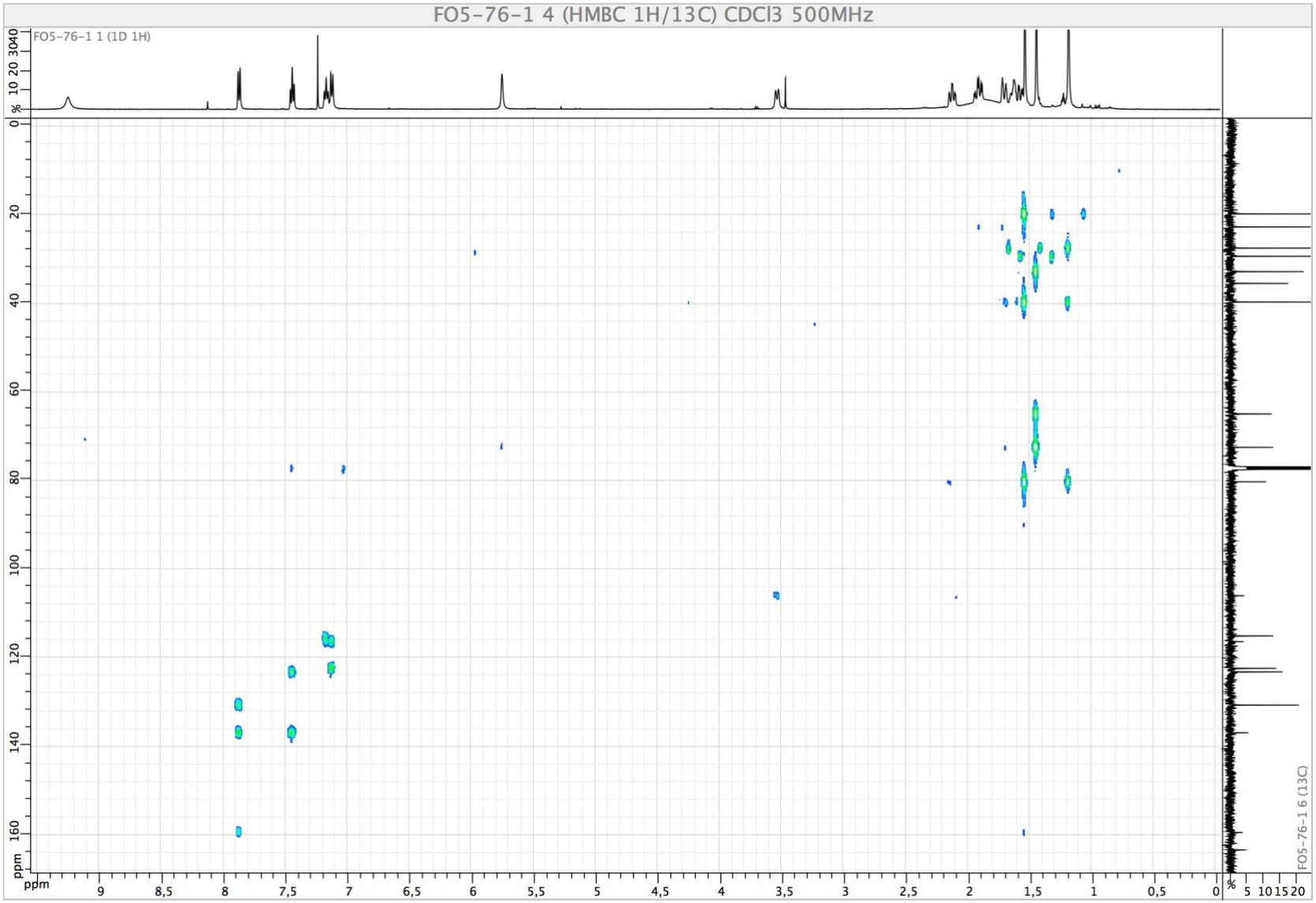
^{13}C NMR spectrum of **3** in $CDCl_3$ at 125 MHz.



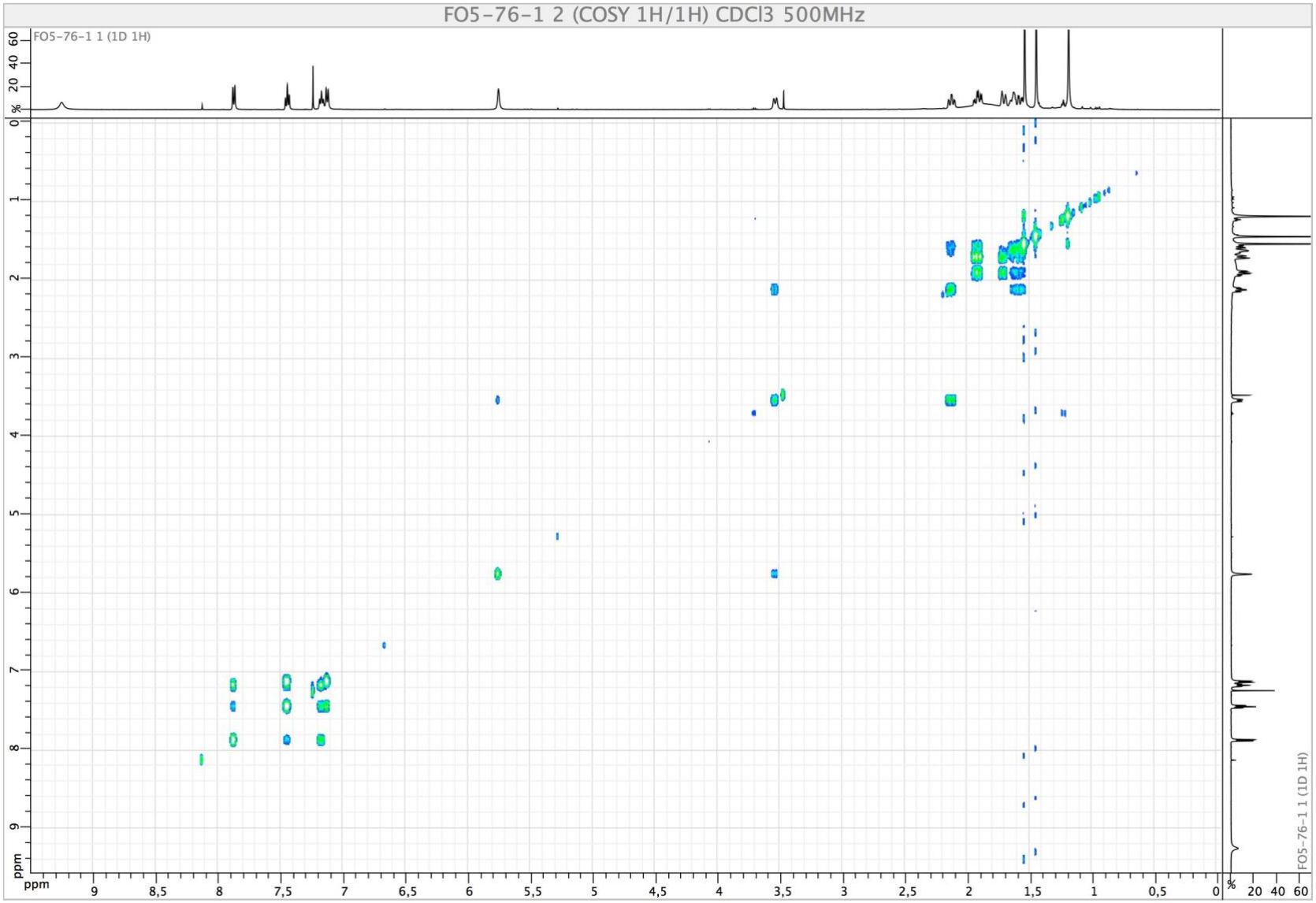
HSQC spectrum (500 MHz, 125 MHz) of **3** in $CDCl_3$.



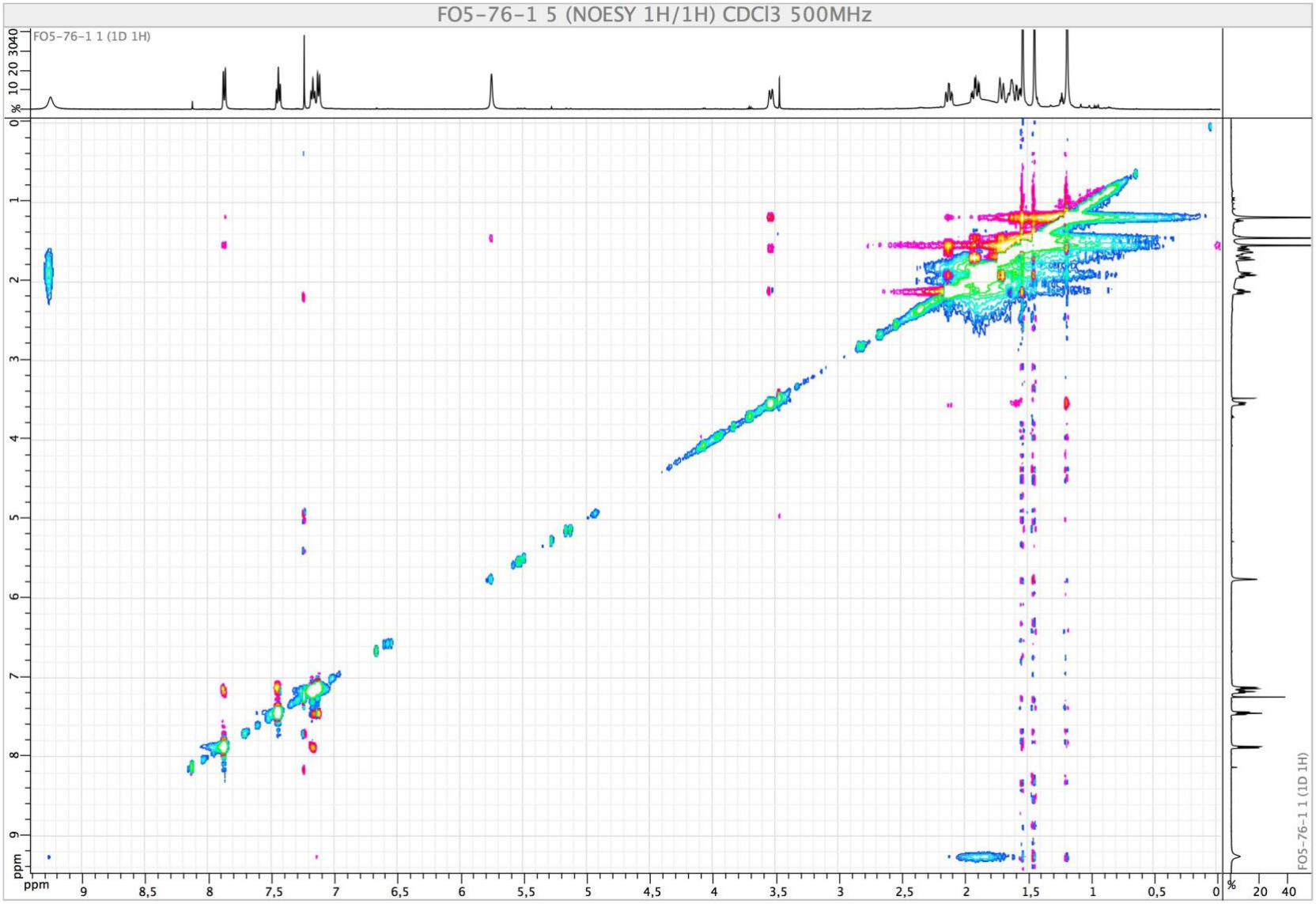
HMBC spectrum (500 MHz, 125 Hz) of **3** in $CDCl_3$.



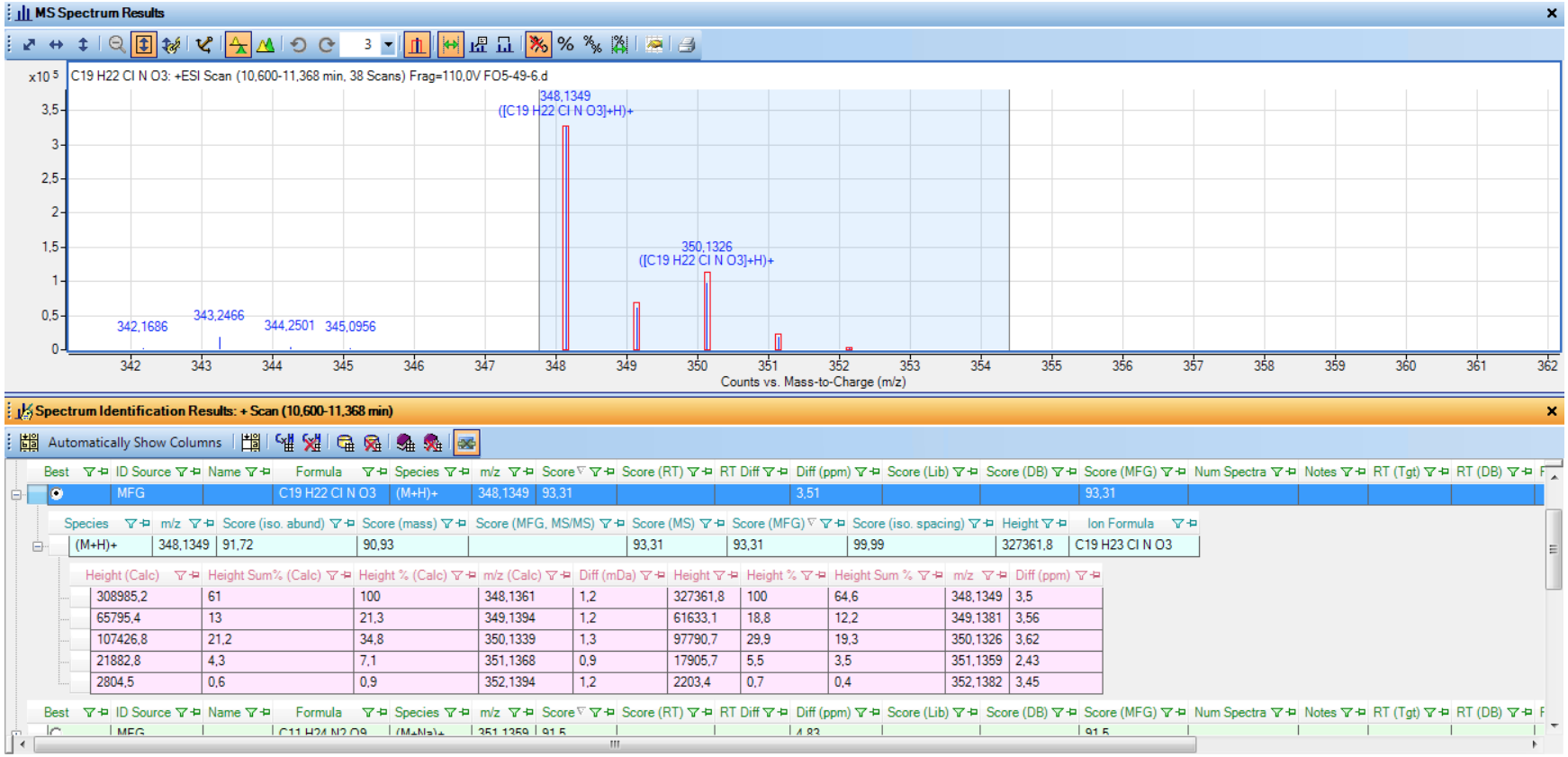
COSY spectrum (500 MHz) of **3** in $CDCl_3$.



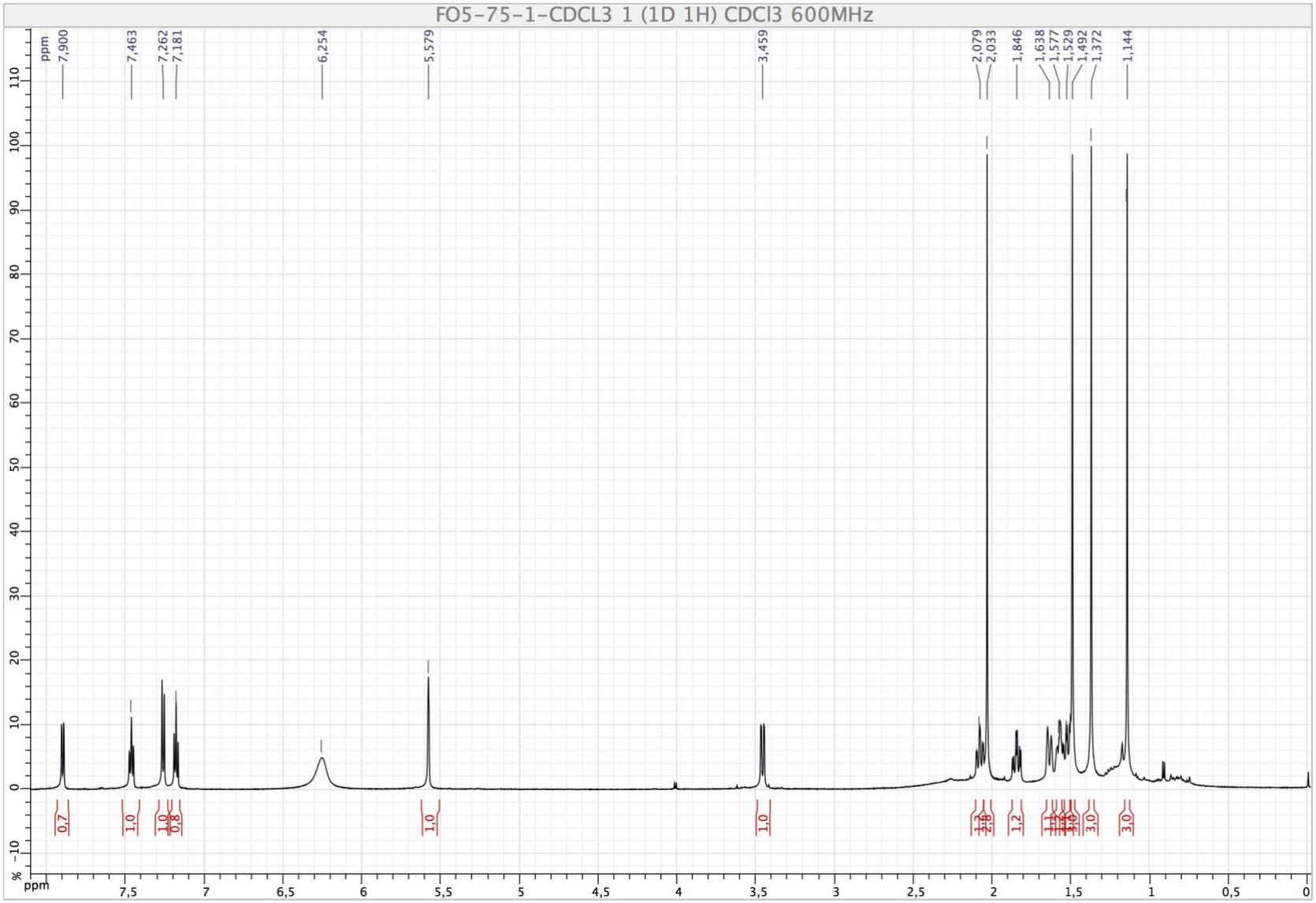
NOESY spectrum (500 MHz) of **3** in $CDCl_3$.



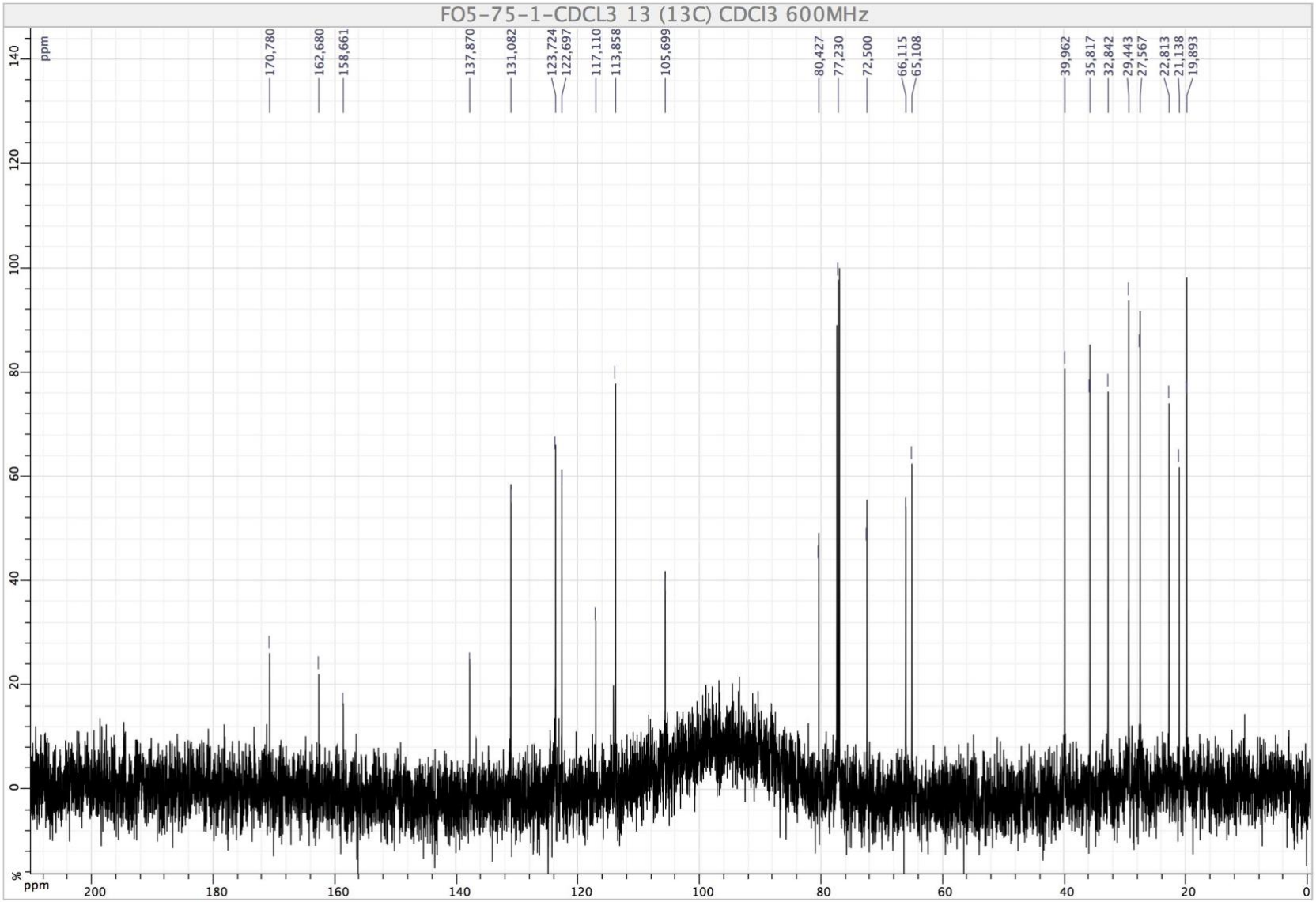
HRESIMS spectrum (TOF) of **3**.



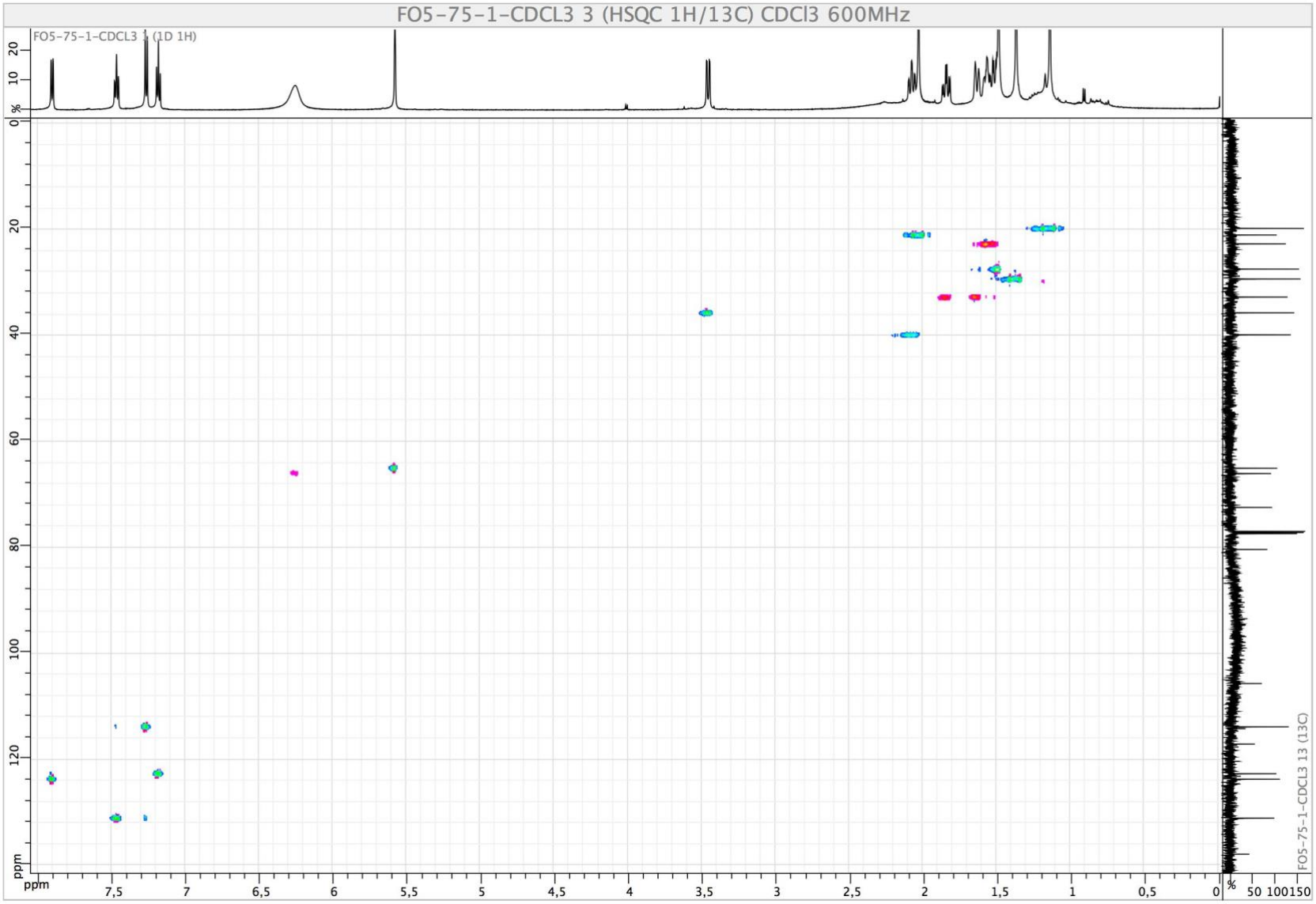
^{1}H NMR spectrum of **4** in $CDCl_3$ at 600 MHz.



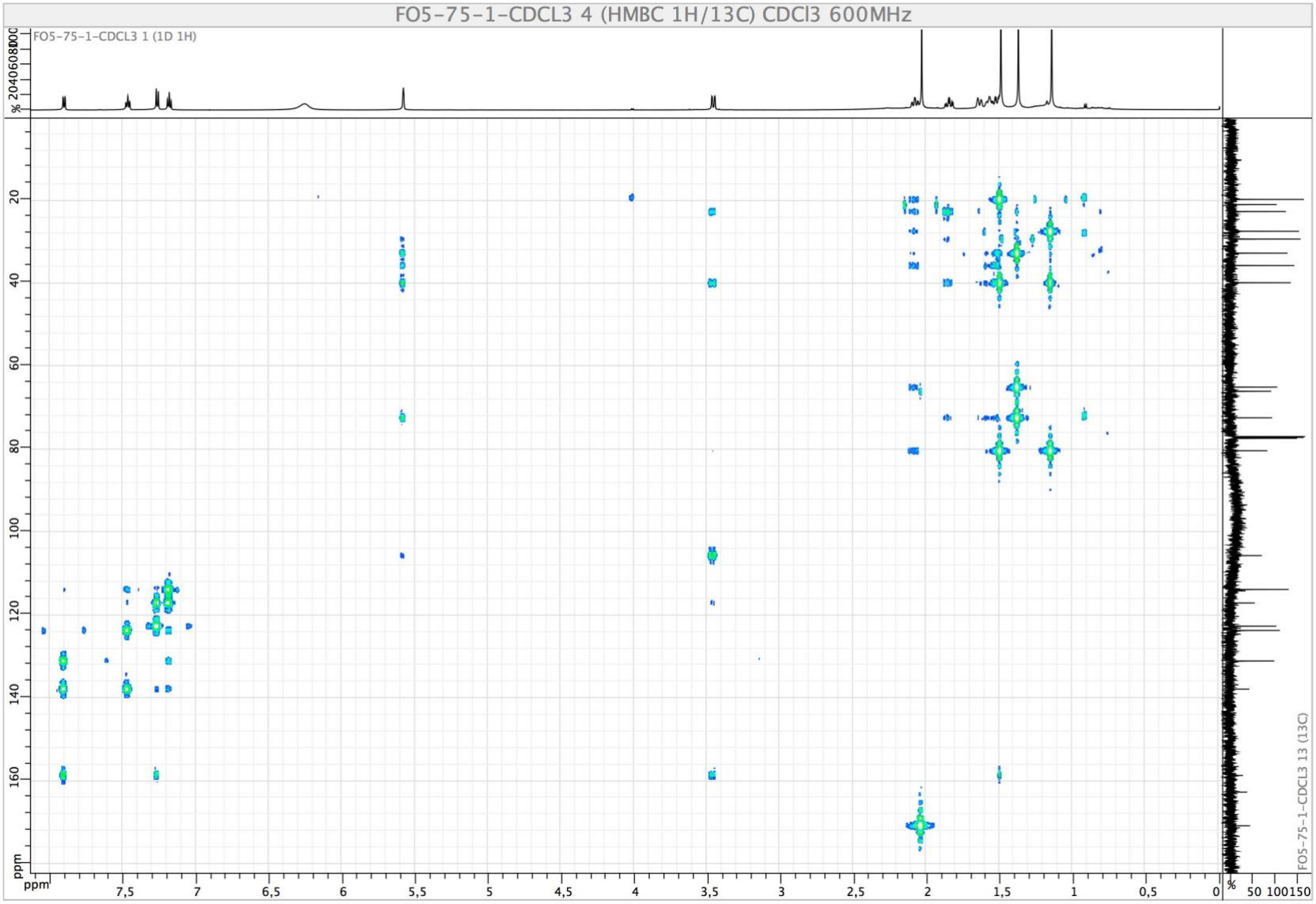
^{13}C NMR spectrum of **4** in $CDCl_3$ at 150 MHz.



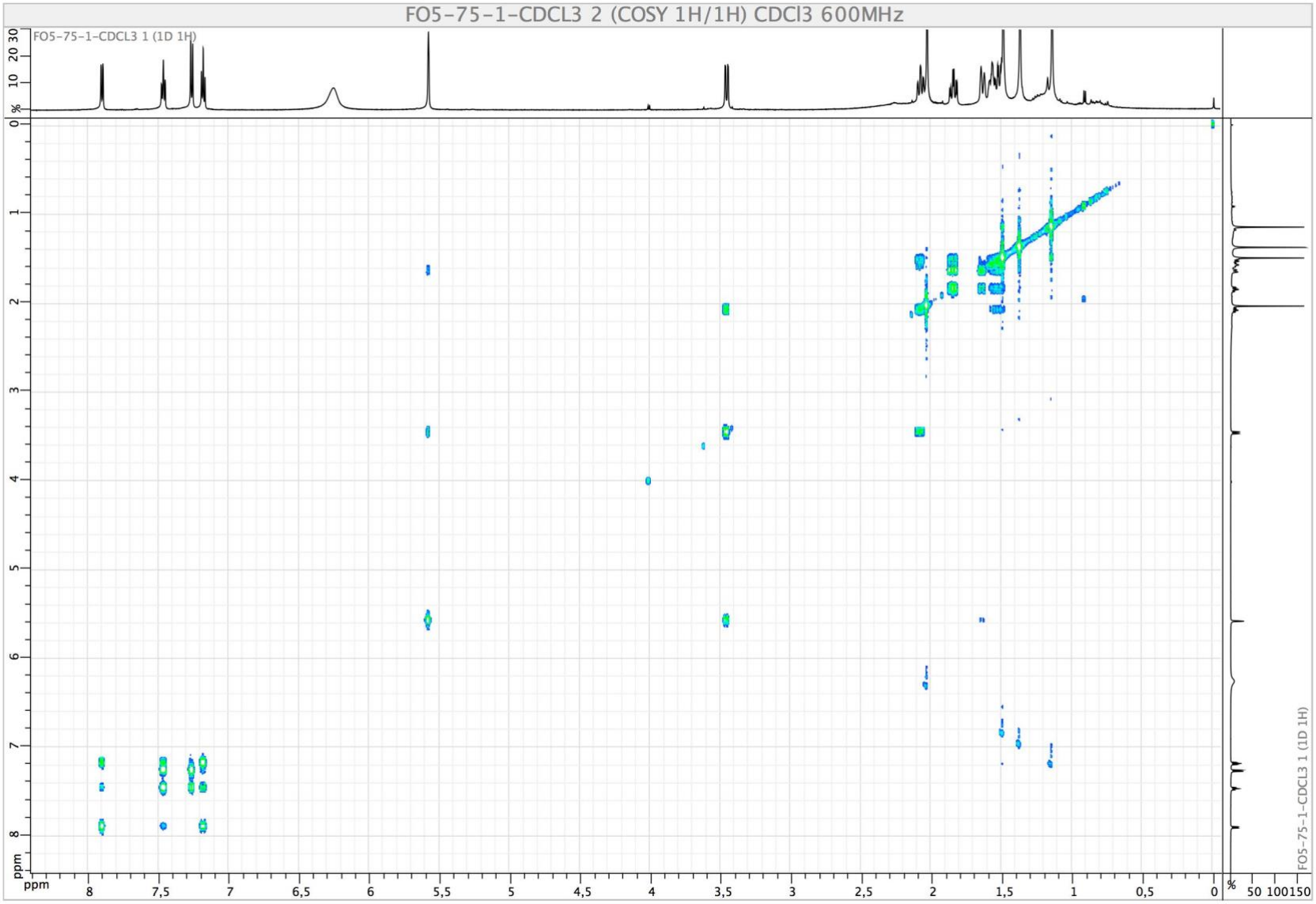
HSQC spectrum (600 MHz, 150 MHz) of **4** in $CDCl_3$.



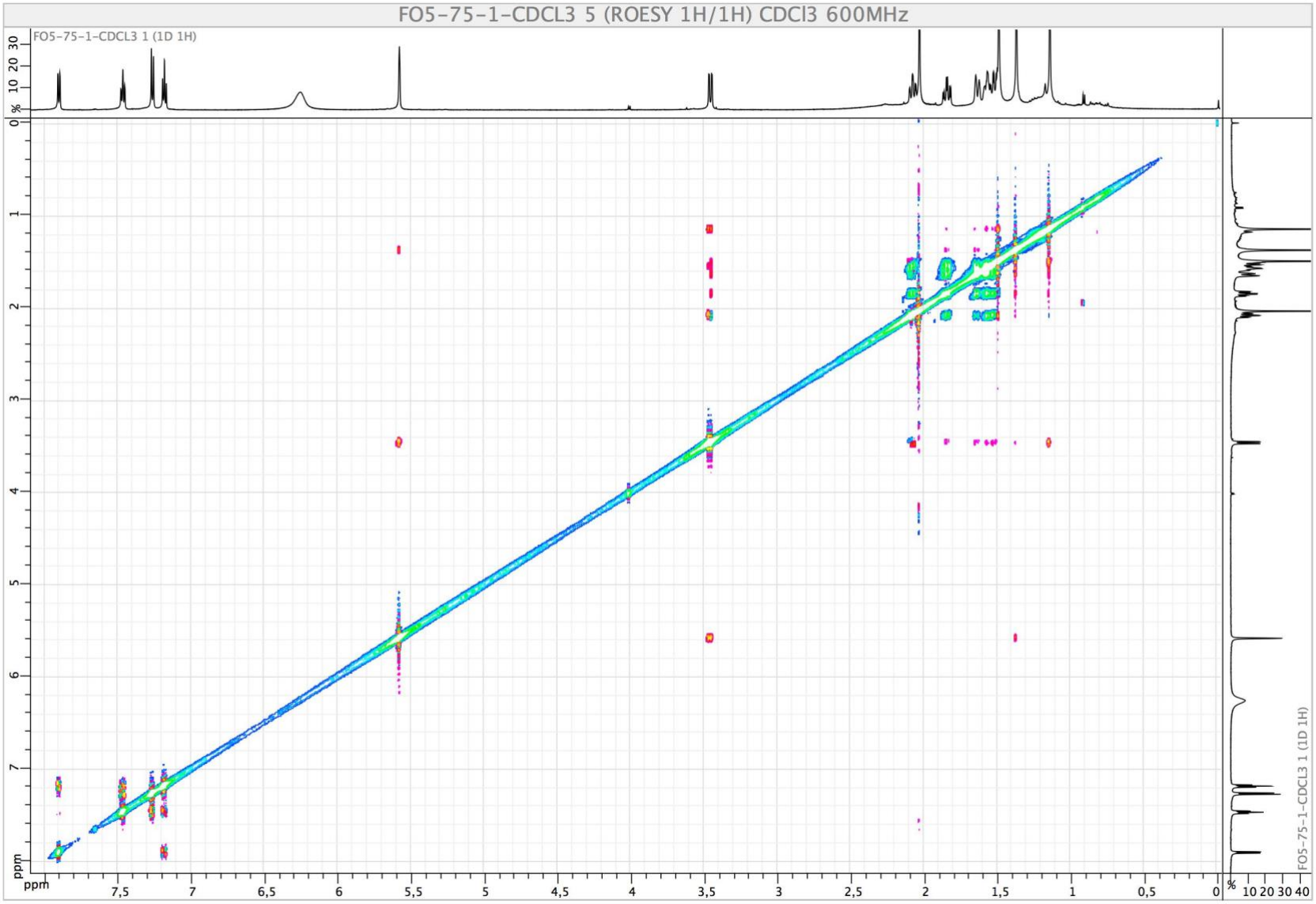
HMBC spectrum (600 MHz, 150 MHz) of **4** in $CDCl_3$.



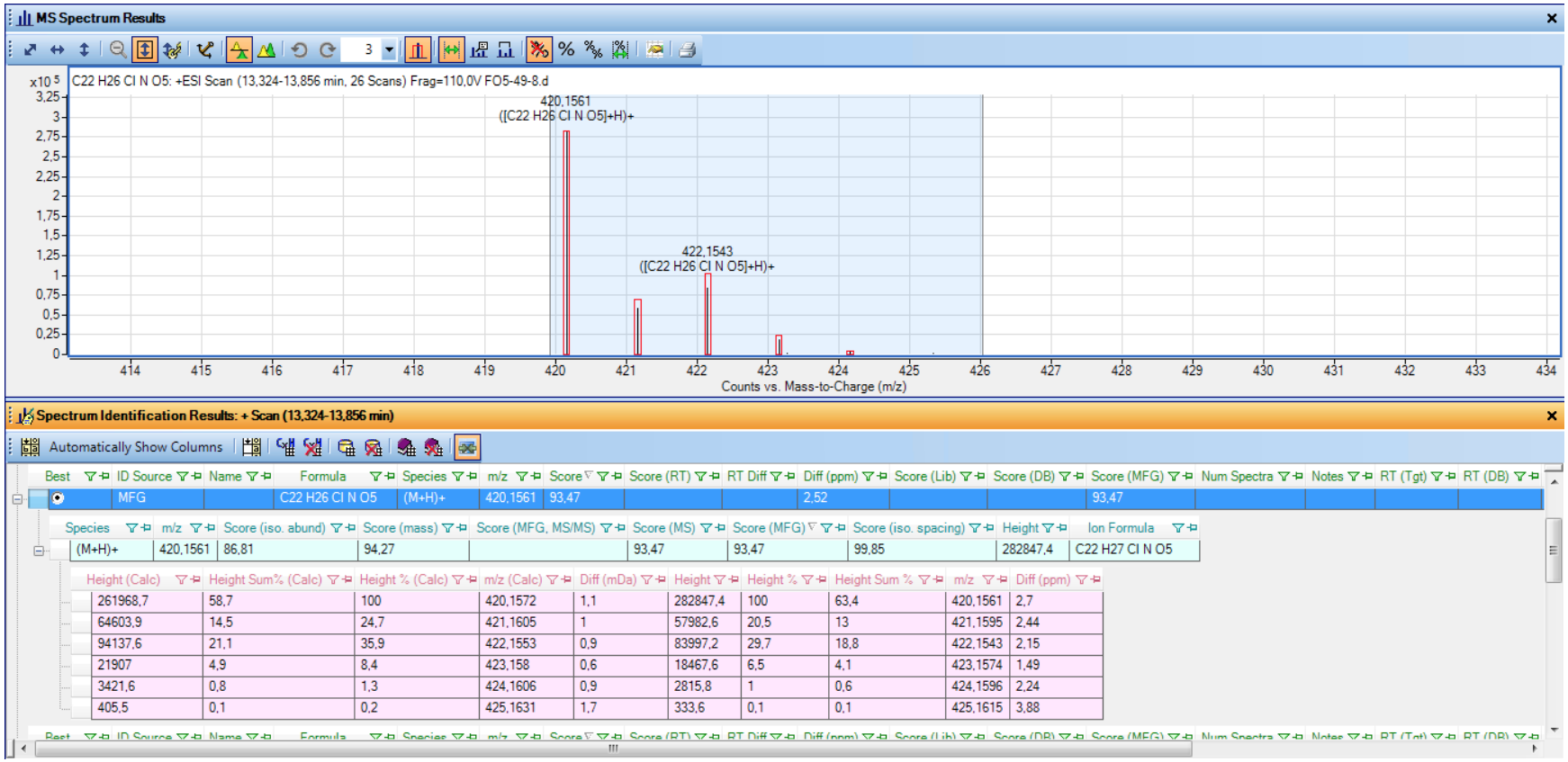
COSY spectrum (600 MHz) of **4** in $CDCl_3$.



ROESY spectrum (600 MHz) of **4** in $CDCl_3$.



HRESIMS spectrum (TOF) of **4**.

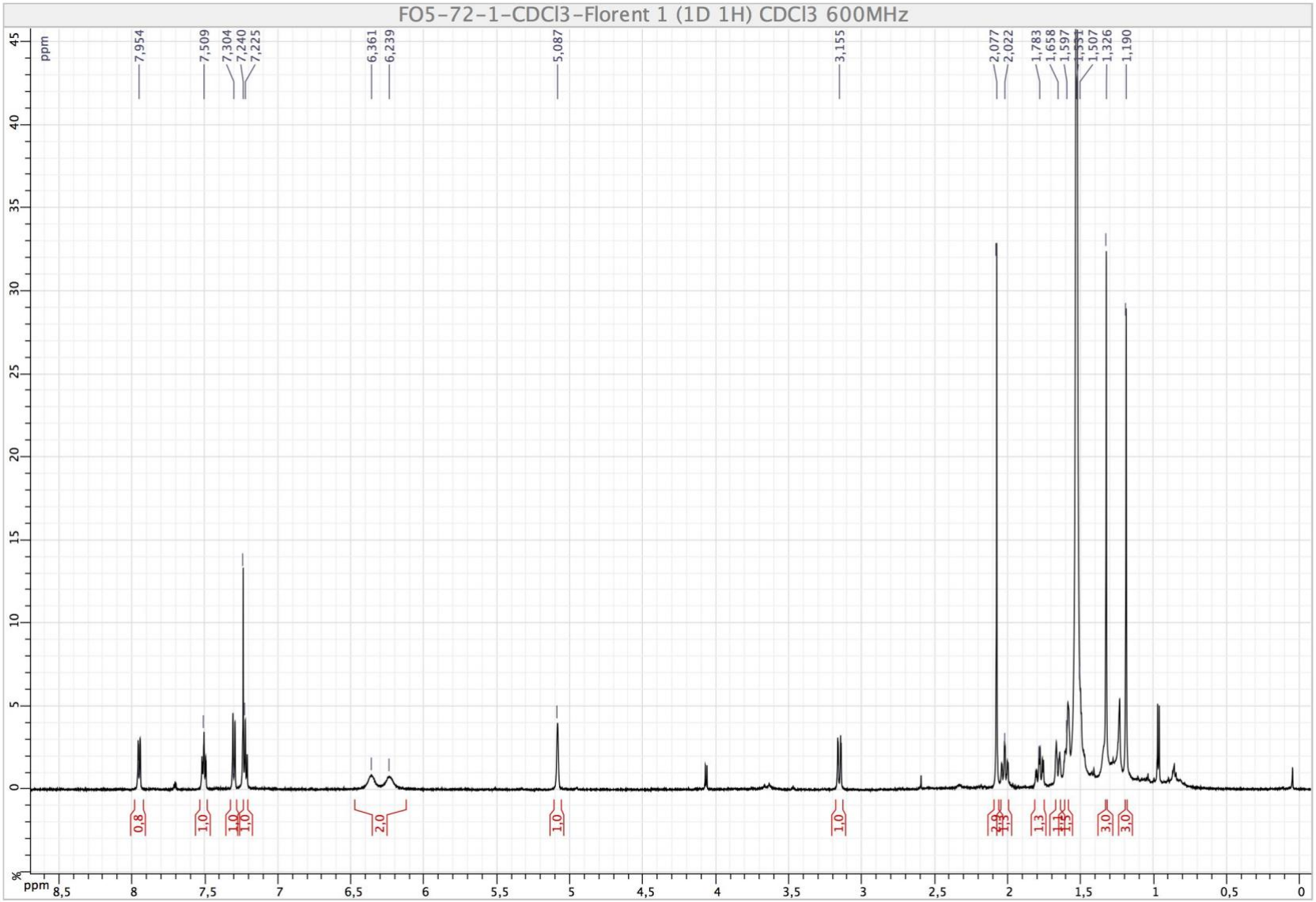


Best	ID Source	Name	Formula	Species	m/z	Score	Score (RT)	RT Diff	Diff (ppm)	Score (Lib)	Score (DB)	Score (MFG)	Num Spectra	Notes	RT (Tgt)	RT (DB)
	MFG		C22 H26 Cl N O5	(M+H)+	420,1561	93,47			2,52			93,47				

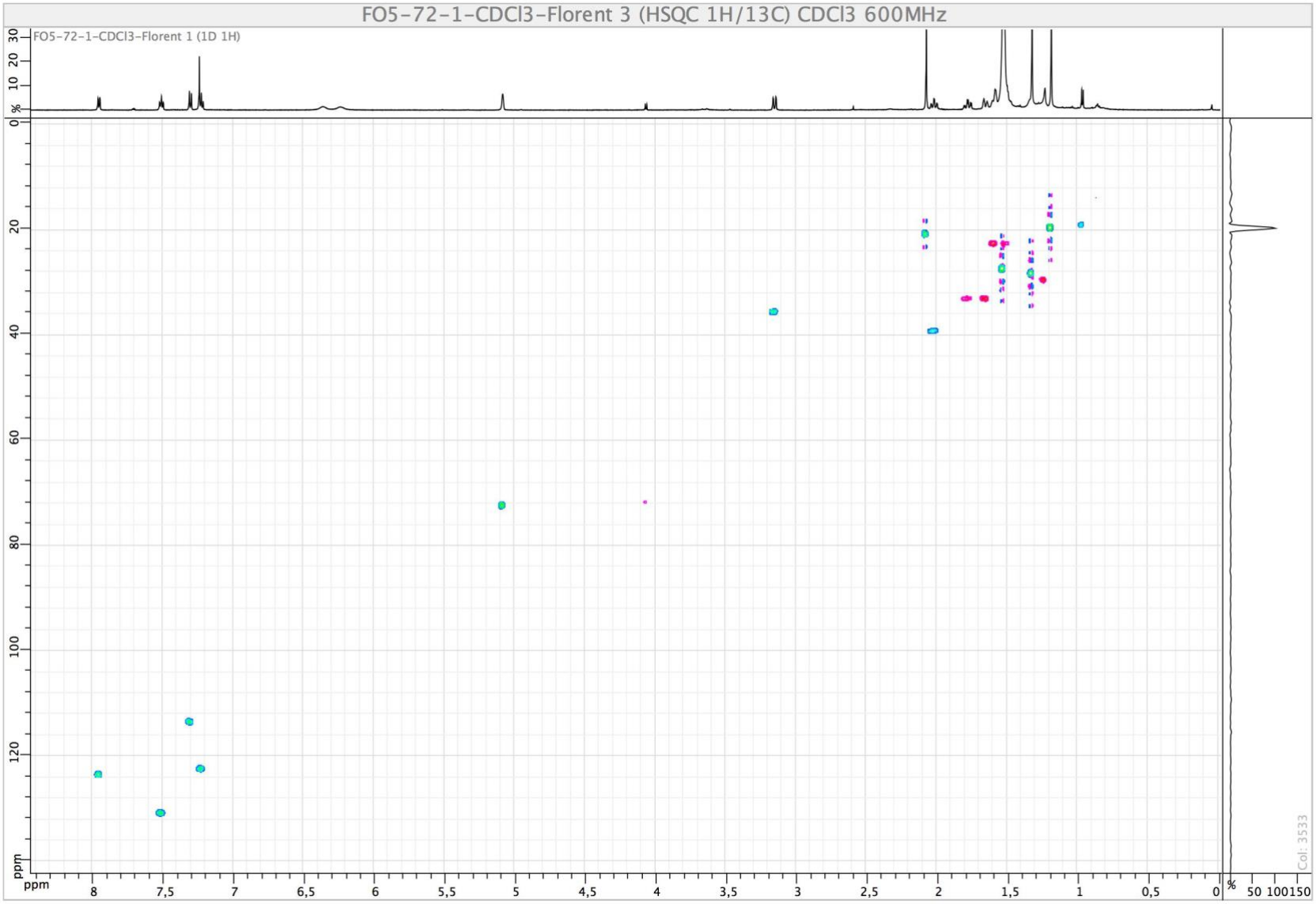
Species	m/z	Score (iso. abund)	Score (mass)	Score (MFG, MS/MS)	Score (MS)	Score (MFG)	Score (iso. spacing)	Height	Ion Formula
(M+H)+	420,1561	86,81	94,27		93,47	93,47	99,85	282847,4	C22 H27 Cl N O5

Height (Calc)	Height Sum% (Calc)	Height % (Calc)	m/z (Calc)	Diff (mDa)	Height	Height %	Height Sum %	m/z	Diff (ppm)
261968,7	58,7	100	420,1572	1,1	282847,4	100	63,4	420,1561	2,7
64603,9	14,5	24,7	421,1605	1	57982,6	20,5	13	421,1595	2,44
94137,6	21,1	35,9	422,1553	0,9	83997,2	29,7	18,8	422,1543	2,15
21907	4,9	8,4	423,158	0,6	18467,6	6,5	4,1	423,1574	1,49
3421,6	0,8	1,3	424,1606	0,9	2815,8	1	0,6	424,1596	2,24
405,5	0,1	0,2	425,1631	1,7	333,6	0,1	0,1	425,1615	3,88

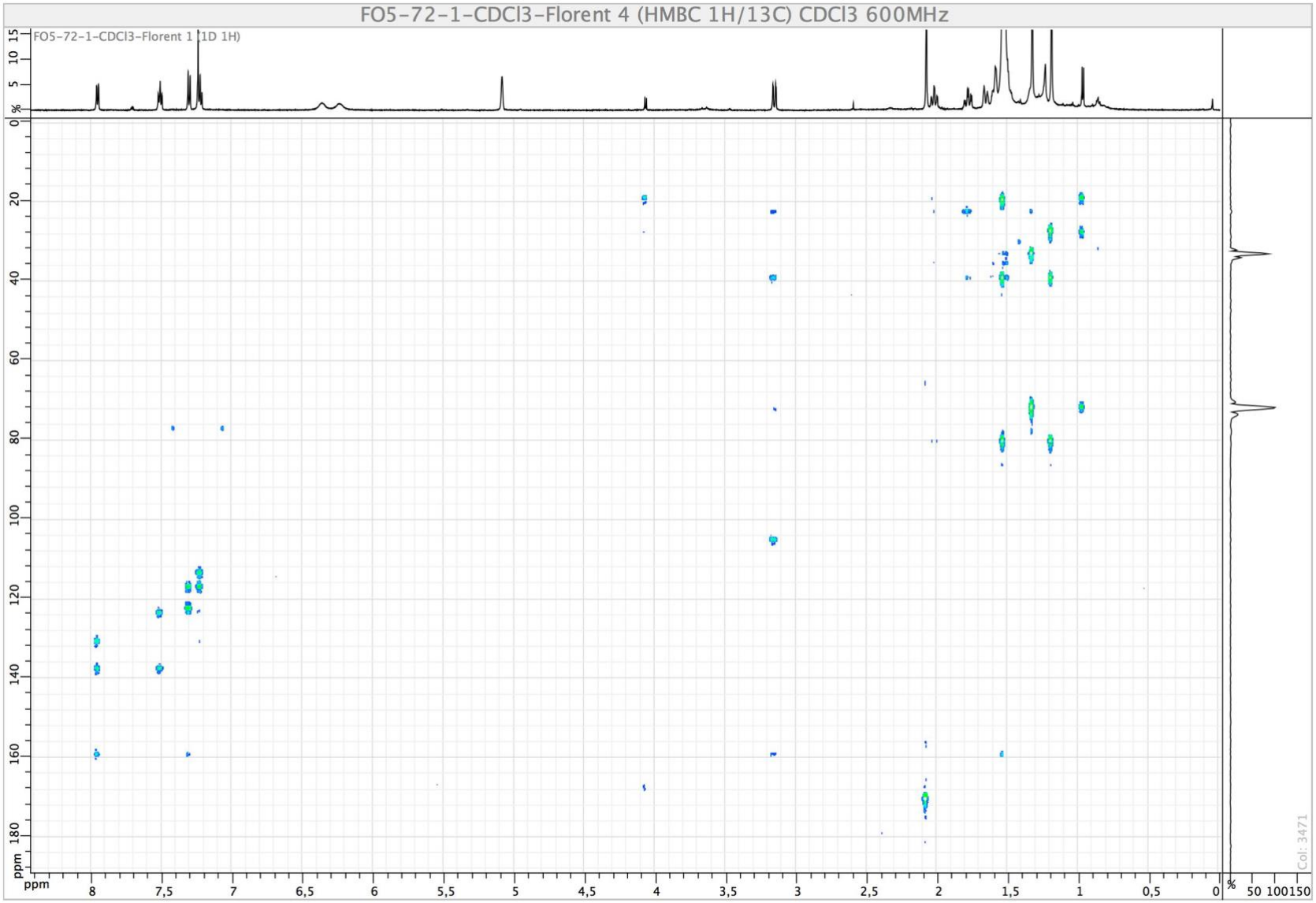
^{1}H NMR spectrum of **5** in $CDCl_3$ at 600 MHz.



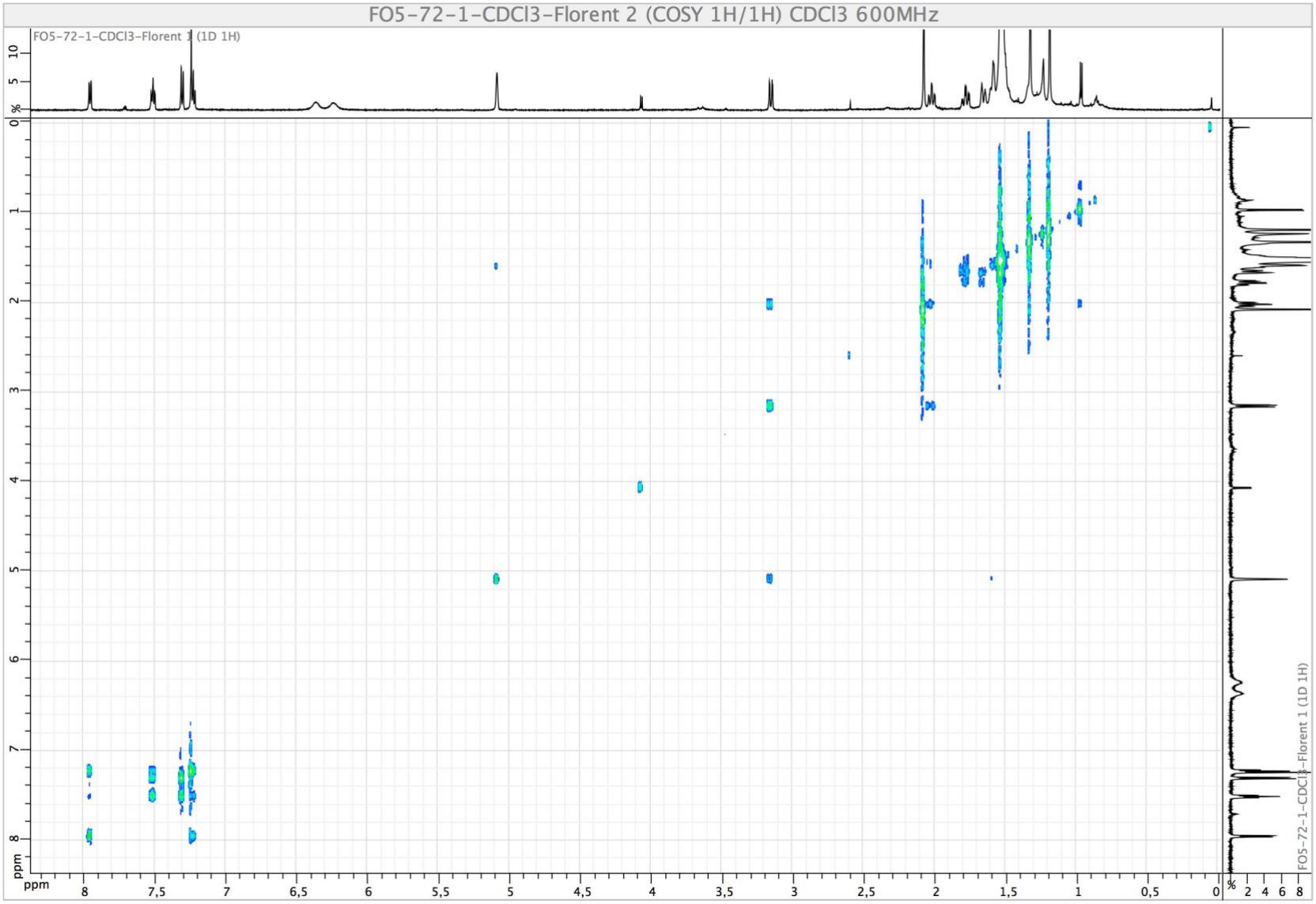
HSQC spectrum (600 MHz, 150 MHz) of **5** in $CDCl_3$.



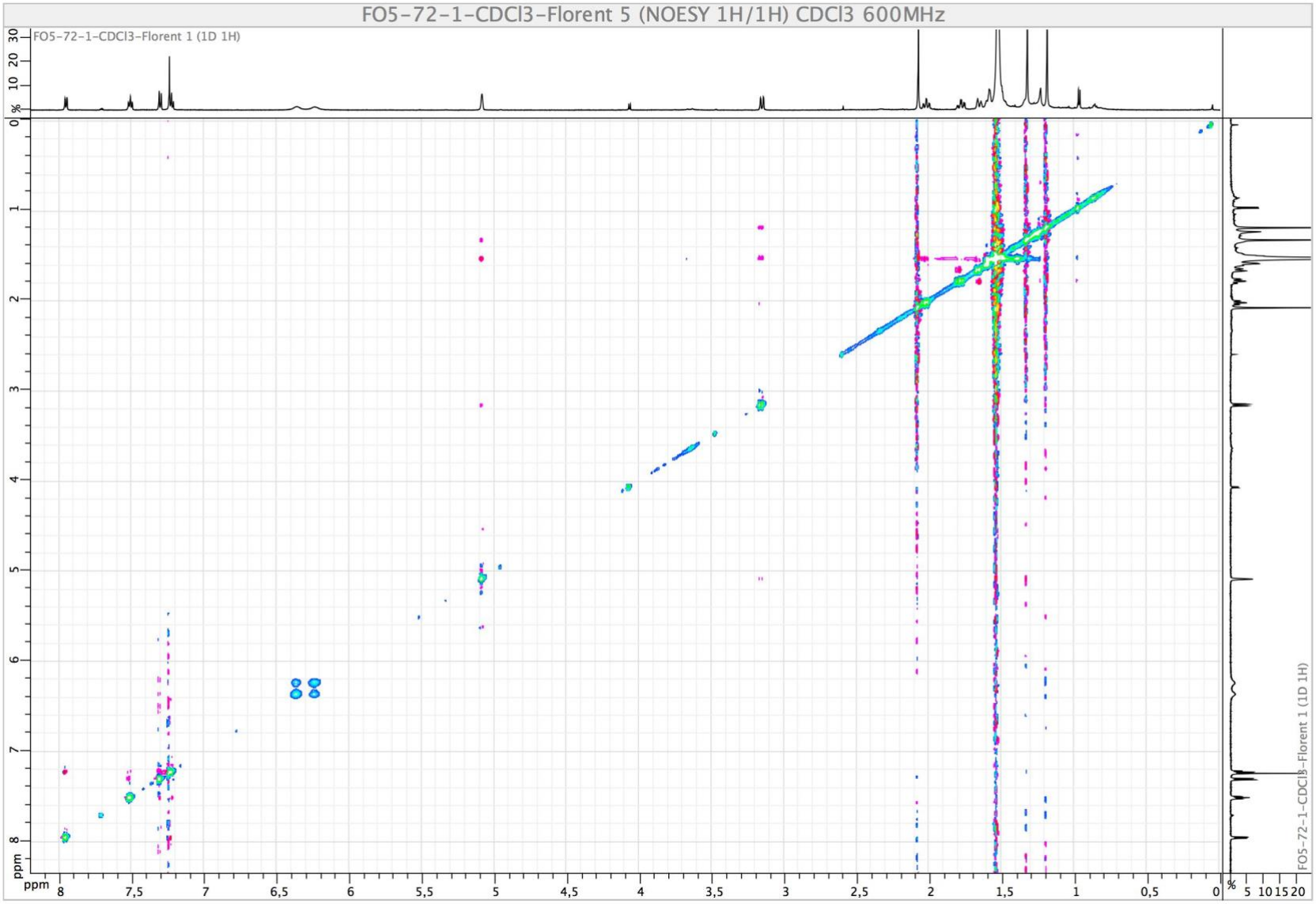
HMBC spectrum (600 MHz, 150 MHz) of **5** in $CDCl_3$.



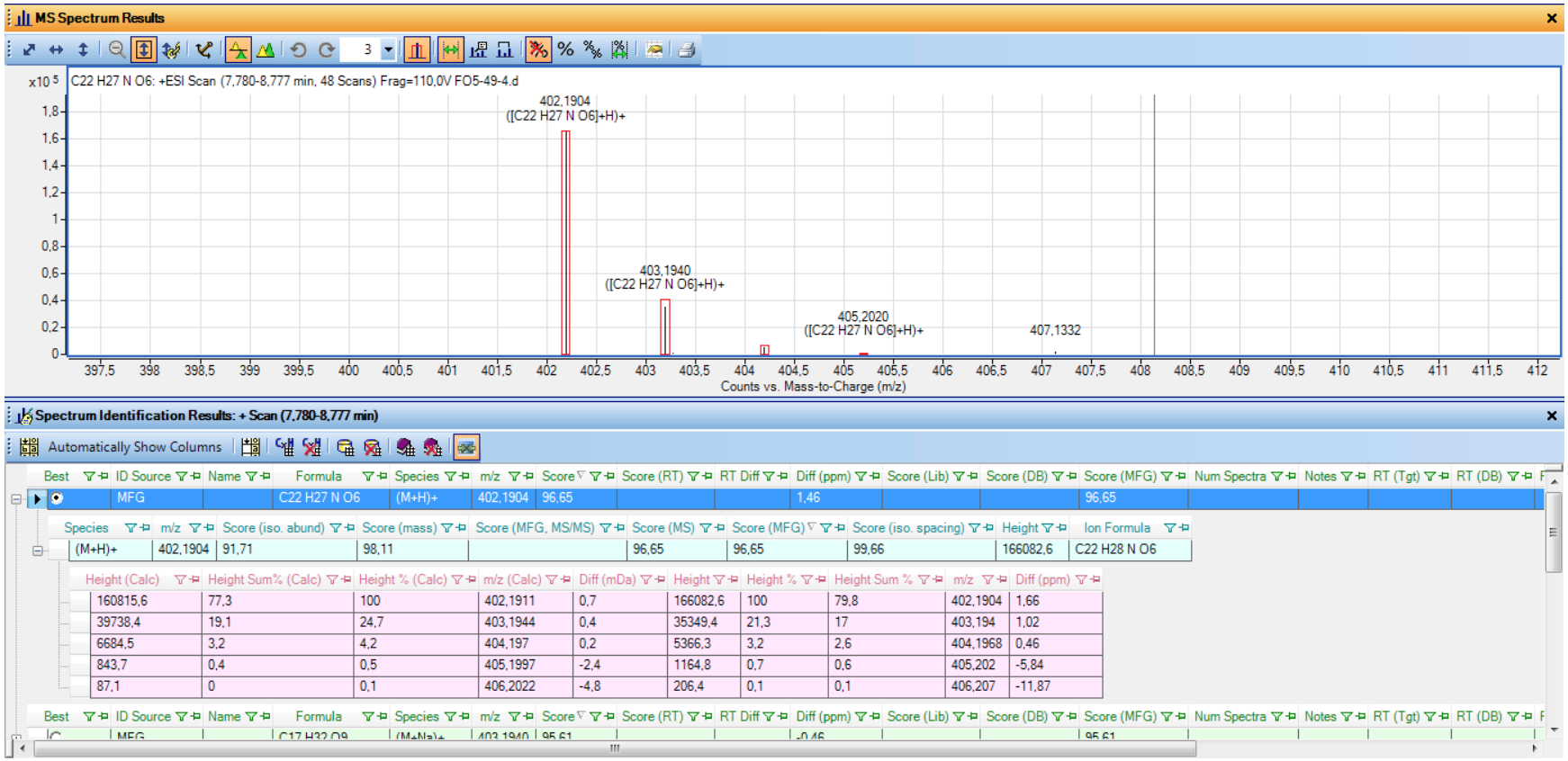
COSY spectrum (600 MHz) of **5** in $CDCl_3$.



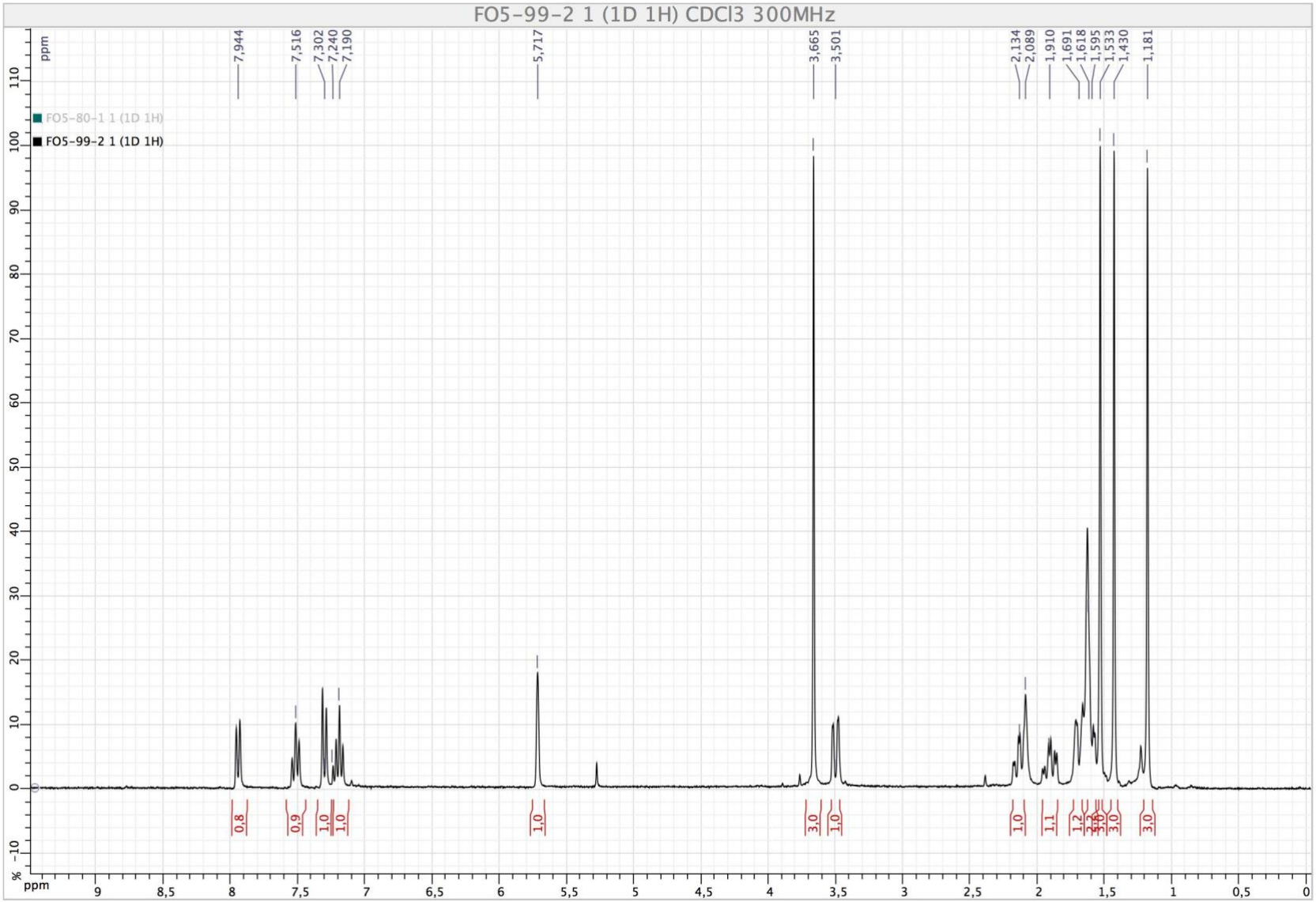
NOESY spectrum (600 MHz) of **5** in $CDCl_3$.



HRESIMS spectrum (TOF) of **5**.



^{1}H NMR spectrum of (±)-**2** in $CDCl_3$ at 500 MHz.



HRESIMS spectrum (TOF) of (±)-**2**.

Elemental Composition Report

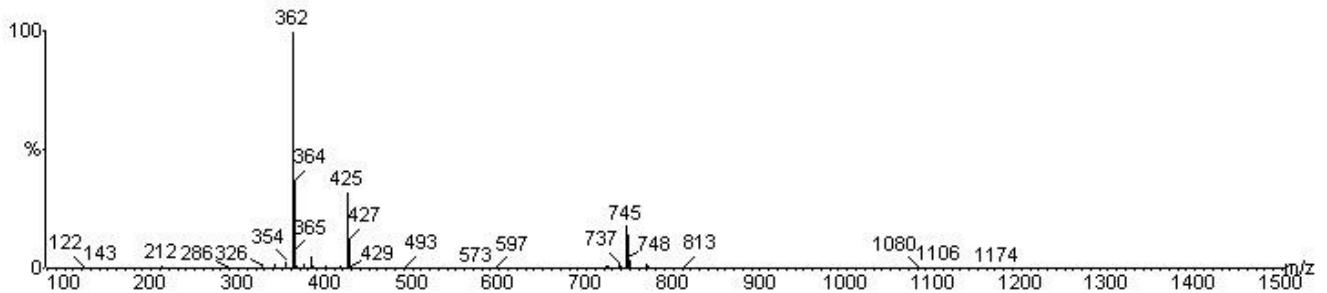
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1550 formula(e) evaluated with 9 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-5 O: 0-200 Cl: 0-8

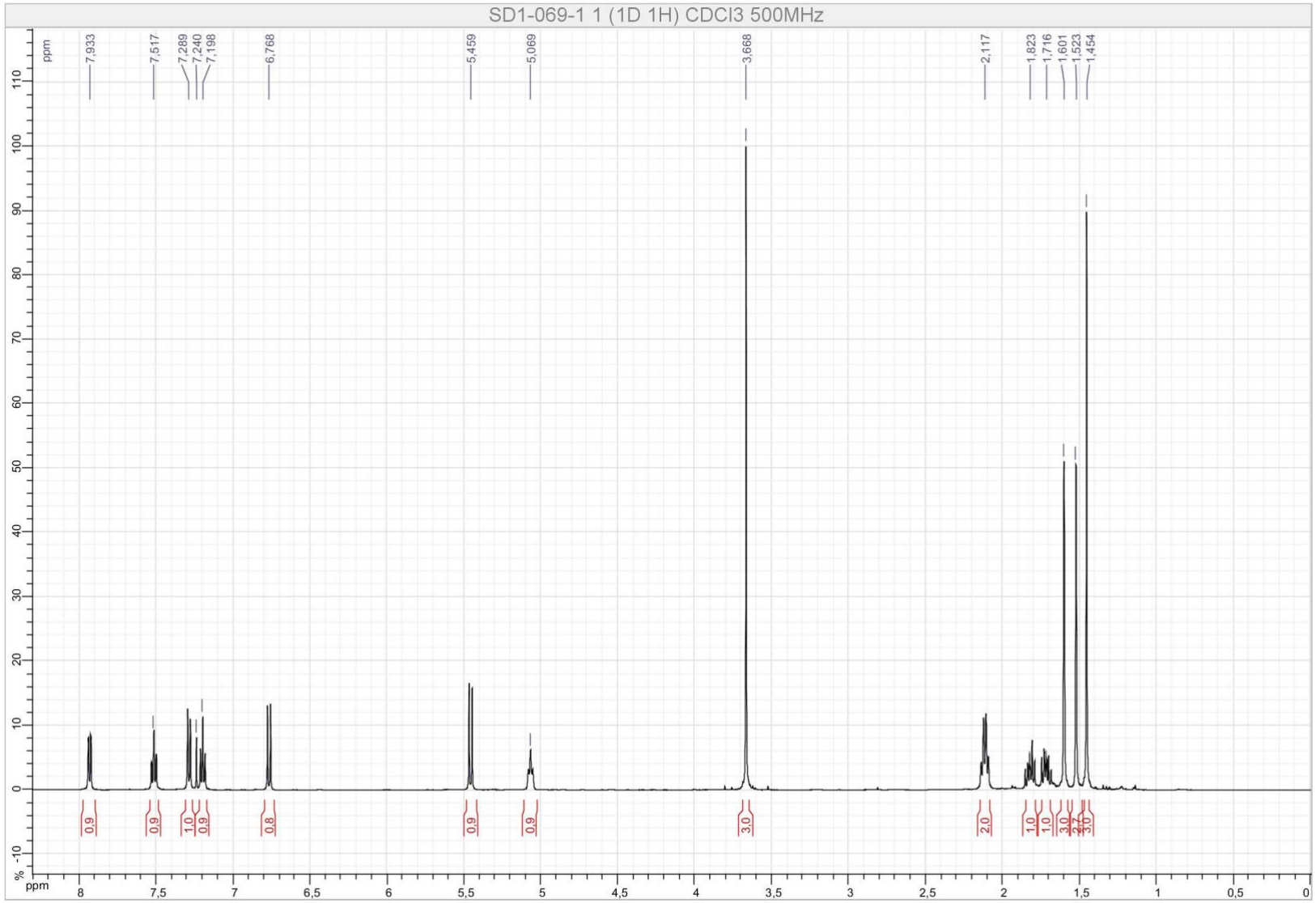
GUERITTE_olivon159-3 587 (2.732)

1: TOF MS ES+
1.98e+004

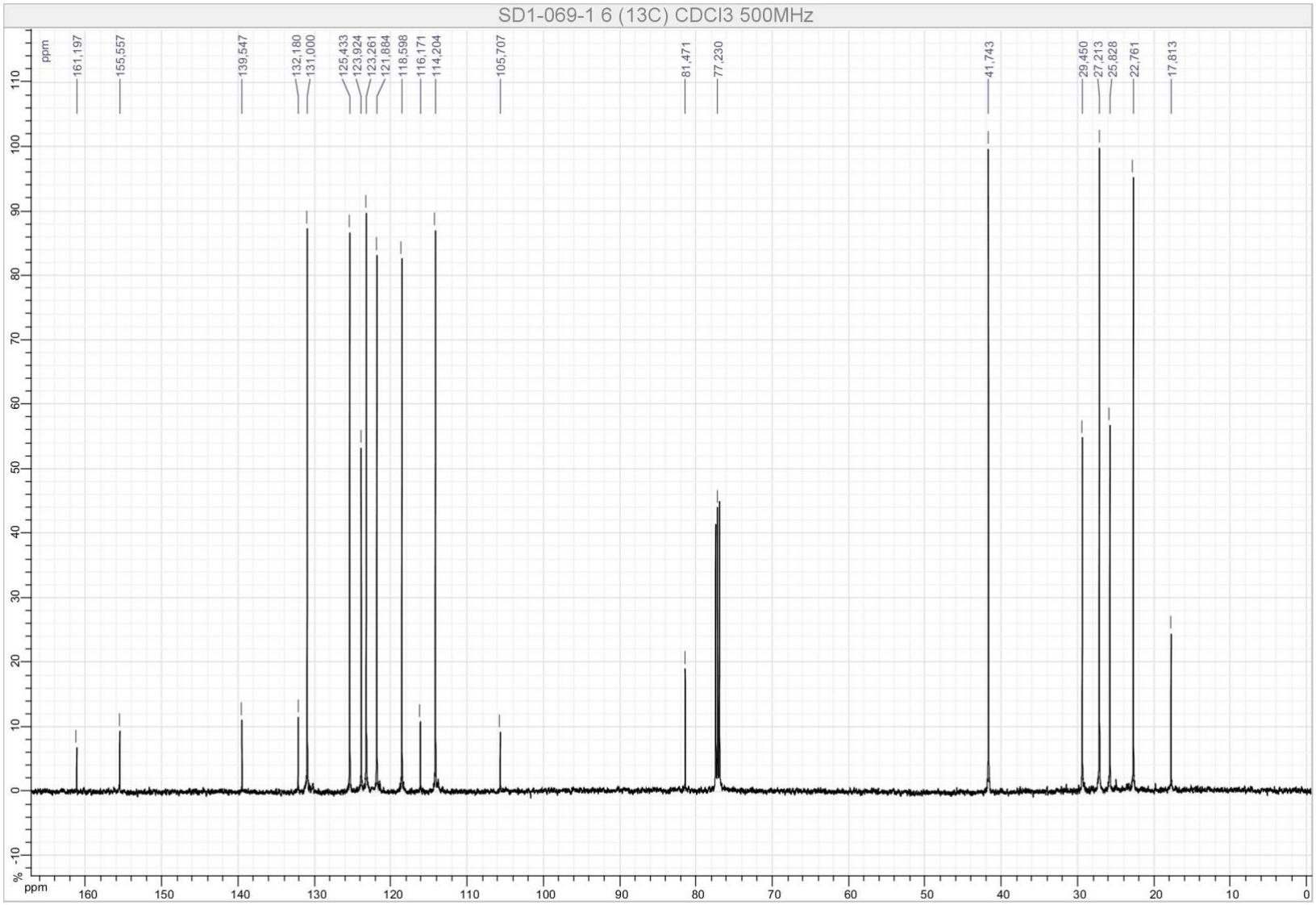


Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
362.1526	362.1523	0.3	0.8	8.5	288.4	0.0	C20 H25 N 03 Cl
	362.1483	4.3	11.9	4.5	292.4	4.0	C15 H25 N3 05 Cl
	362.1514	1.2	3.3	4.5	298.5	10.2	C15 H26 N5 0 Cl2
	362.1501	2.5	6.9	-0.5	299.0	10.7	C14 H30 N 05 Cl2
	362.1533	-0.7	-1.9	-0.5	300.8	12.4	C14 H31 N3 0 Cl3
	362.1523	0.3	0.8	0.5	302.8	14.4	C9 H24 N5 010
	362.1563	-3.7	-10.2	4.5	303.0	14.6	C14 H24 N3 08
	362.1505	2.1	5.8	13.5	303.3	15.0	C21 H20 N3 03
	362.1545	-1.9	-5.2	17.5	303.7	15.4	C26 H20 N 0

^{1}H NMR spectrum of **16** in $CDCl_3$ at 500 MHz.



^{13}C NMR spectrum of **16** in $CDCl_3$ at 125 MHz.



HRESIMS spectrum (TOF) of **16**.

Elemental Composition Report

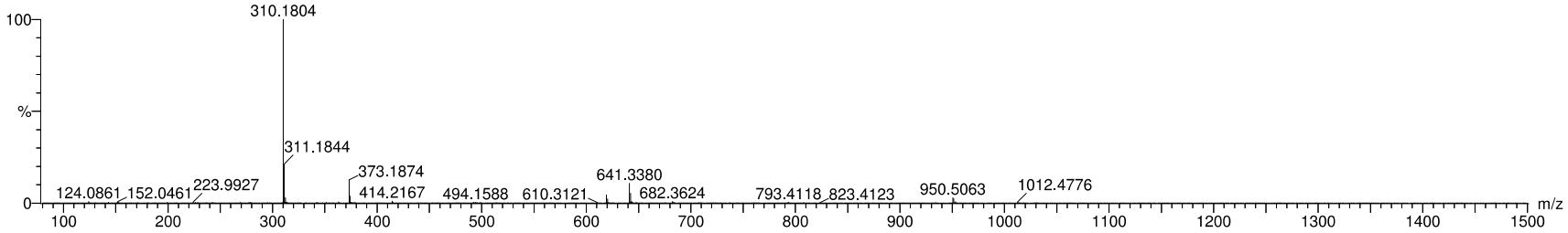
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 9

Monoisotopic Mass, Even Electron Ions
265 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-120 N: 0-6 O: 0-10

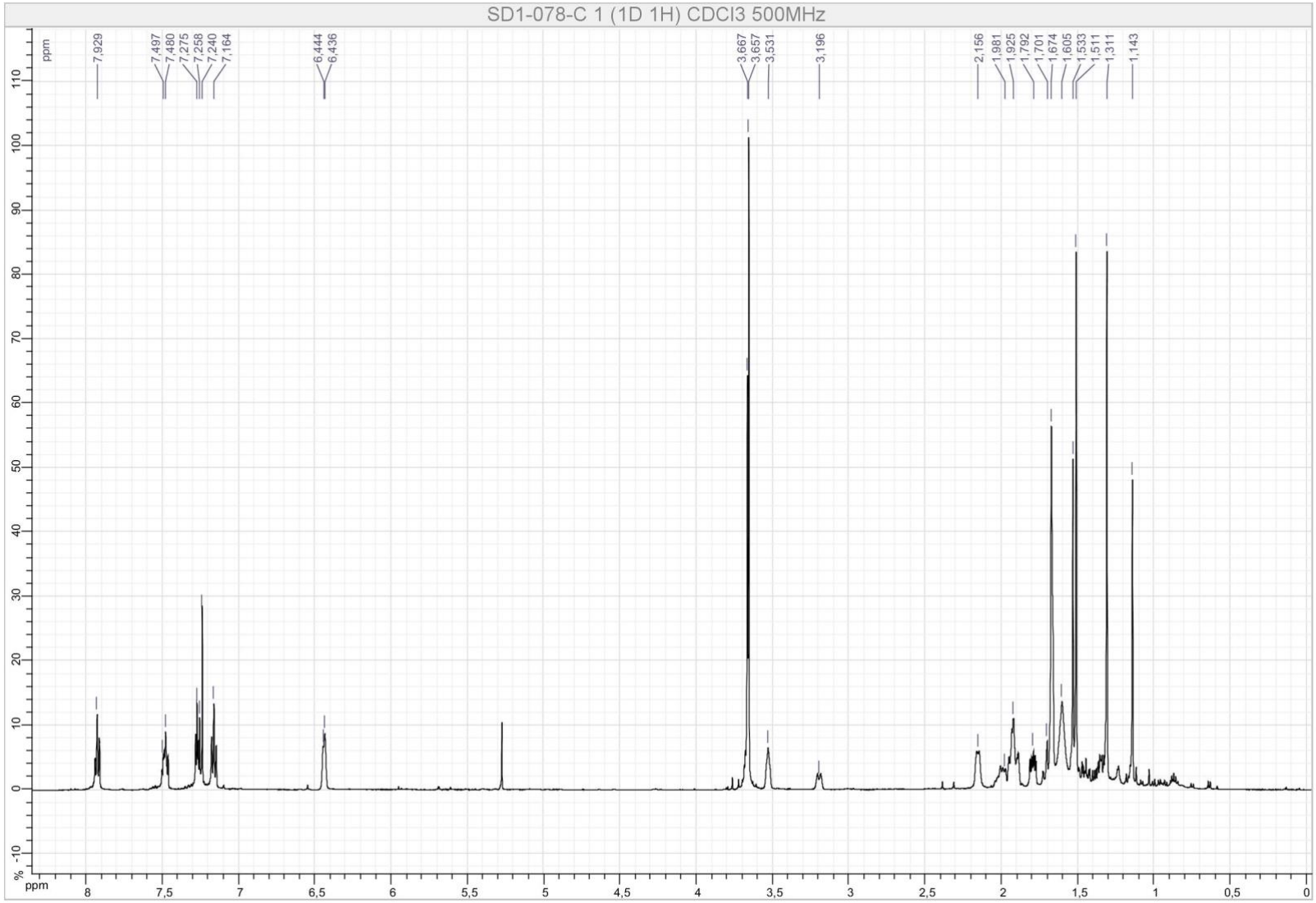
03-Jul-2017 15:52:36 LCT Premier XE KE483 GUERITTE_desrat45-1 655 (3.059)
1: TOF MS ES+

3.47e+004



Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
310.1804	310.1807	-0.3	-1.0	9.5	629.0	0.0	C20 H24 N O2

^{1}H NMR spectrum of *cis*/*trans*-**17** in $CDCl_3$ at 500 MHz.



HRESIMS spectrum (TOF) of **17**.

Elemental Composition Report

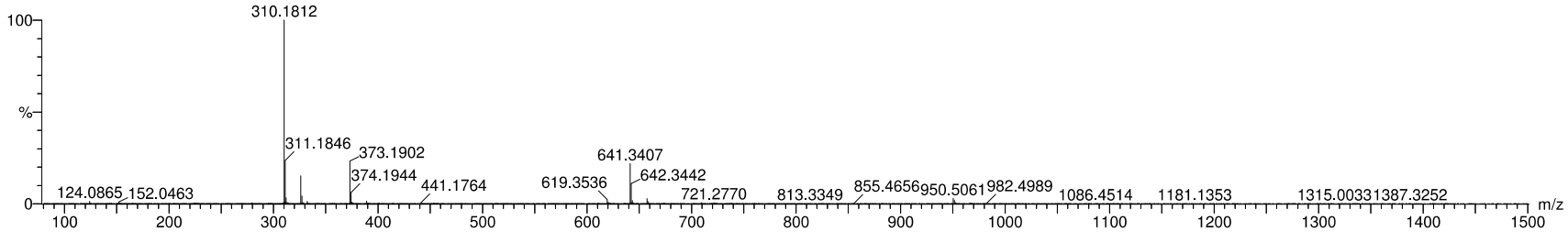
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 9

Monoisotopic Mass, Even Electron Ions
265 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-120 N: 0-6 O: 0-10

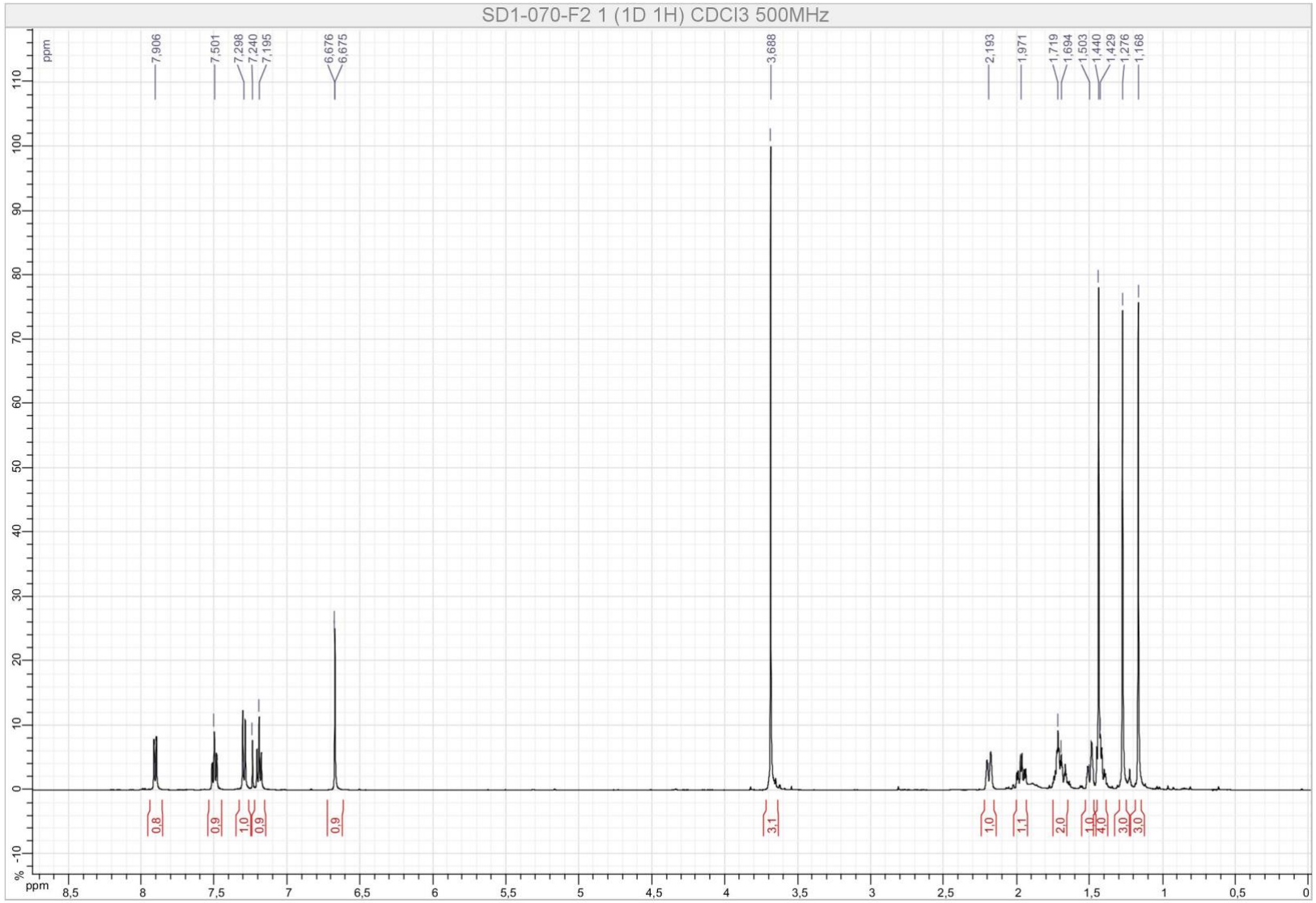
19-Jul-2017 15:19:42 LCT Premier XE KE483 GUERITTE_desrat57-1 665 (3.103)
1: TOF MS ES+

2.30e+004

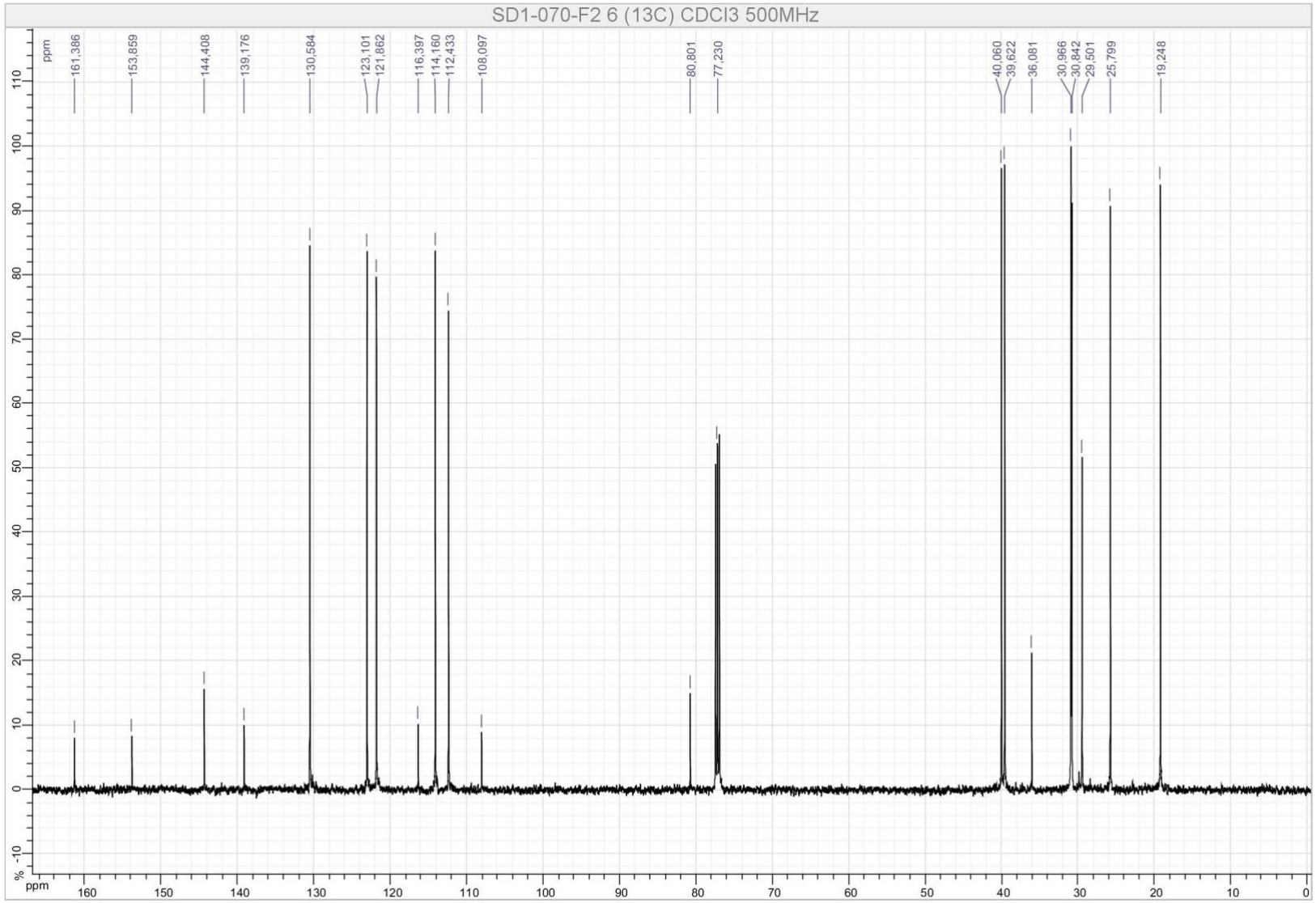


Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
310.1812	310.1807	0.5	1.6	9.5	568.9	0.0	C20 H24 N O2

^{1}H NMR spectrum of **19** in $CDCl_3$ at 500 MHz.



^{13}C NMR spectrum of **19** in $CDCl_3$ at 125 MHz.



HRESIMS spectrum (TOF) of **19**.

Elemental Composition Report

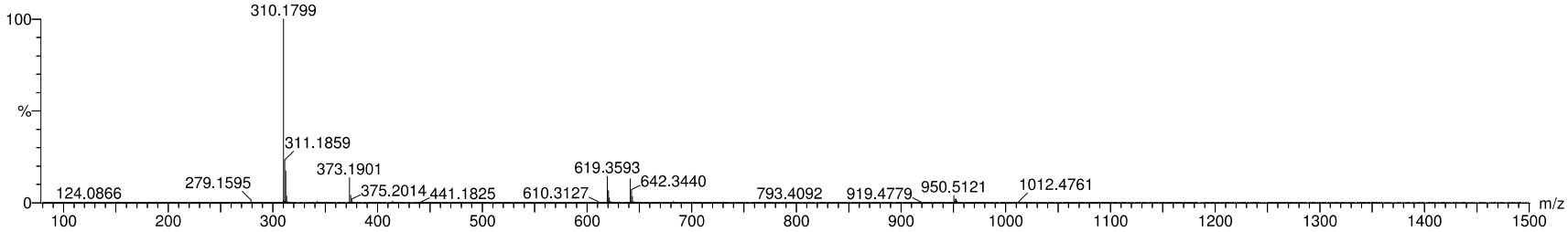
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 9

Monoisotopic Mass, Even Electron Ions
265 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-120 N: 0-6 O: 0-10

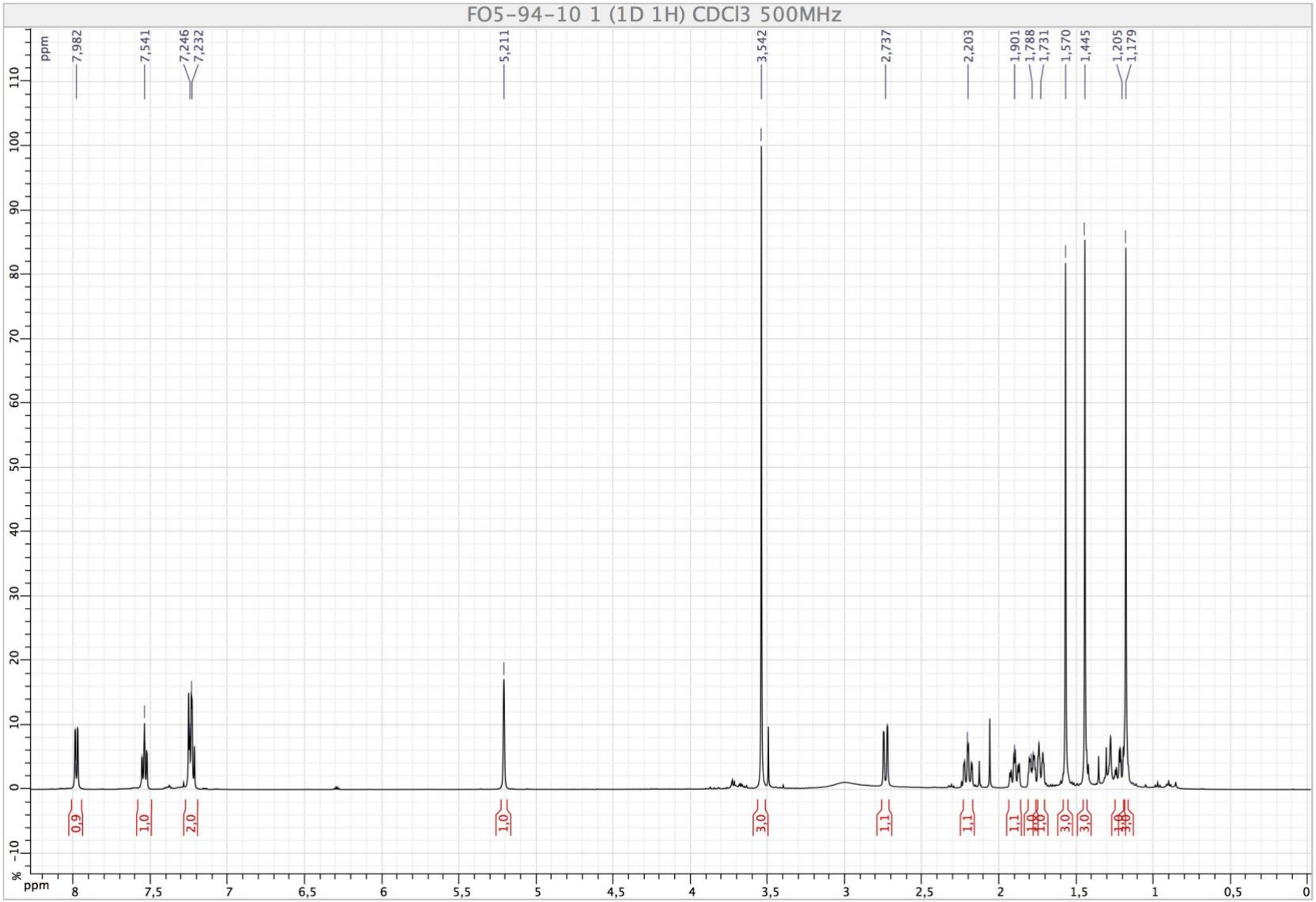
03-Jul-2017 16:03:54 LCT Premier XE KE483 GUERITTE_desrat45-2 642 (3.017)
1: TOF MS ES+

4.89e+004

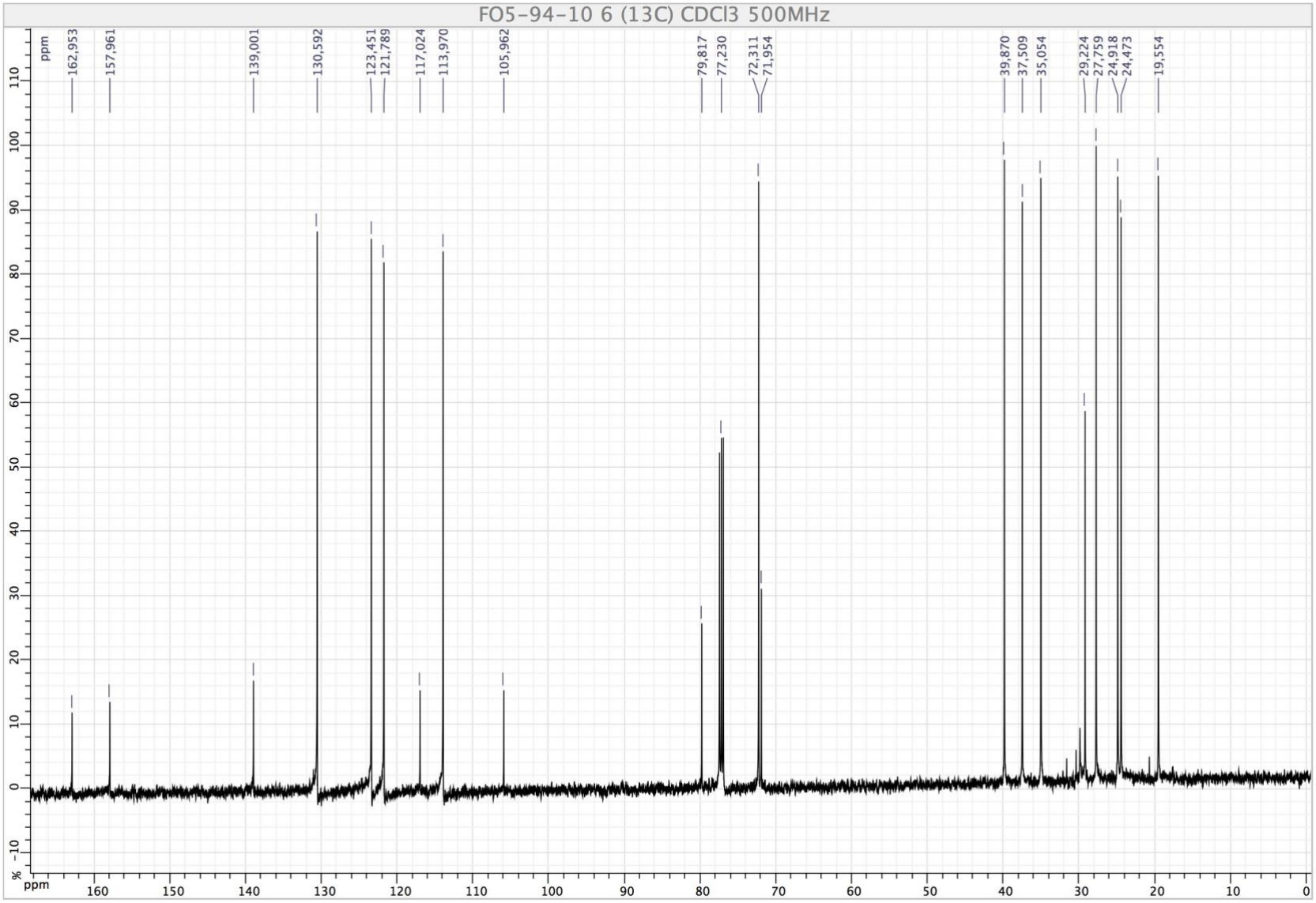


Minimum:				-1.5			
Maximum:		5.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
310.1799	310.1807	-0.8	-2.6	9.5	821.4	0.0	C20 H24 N O2

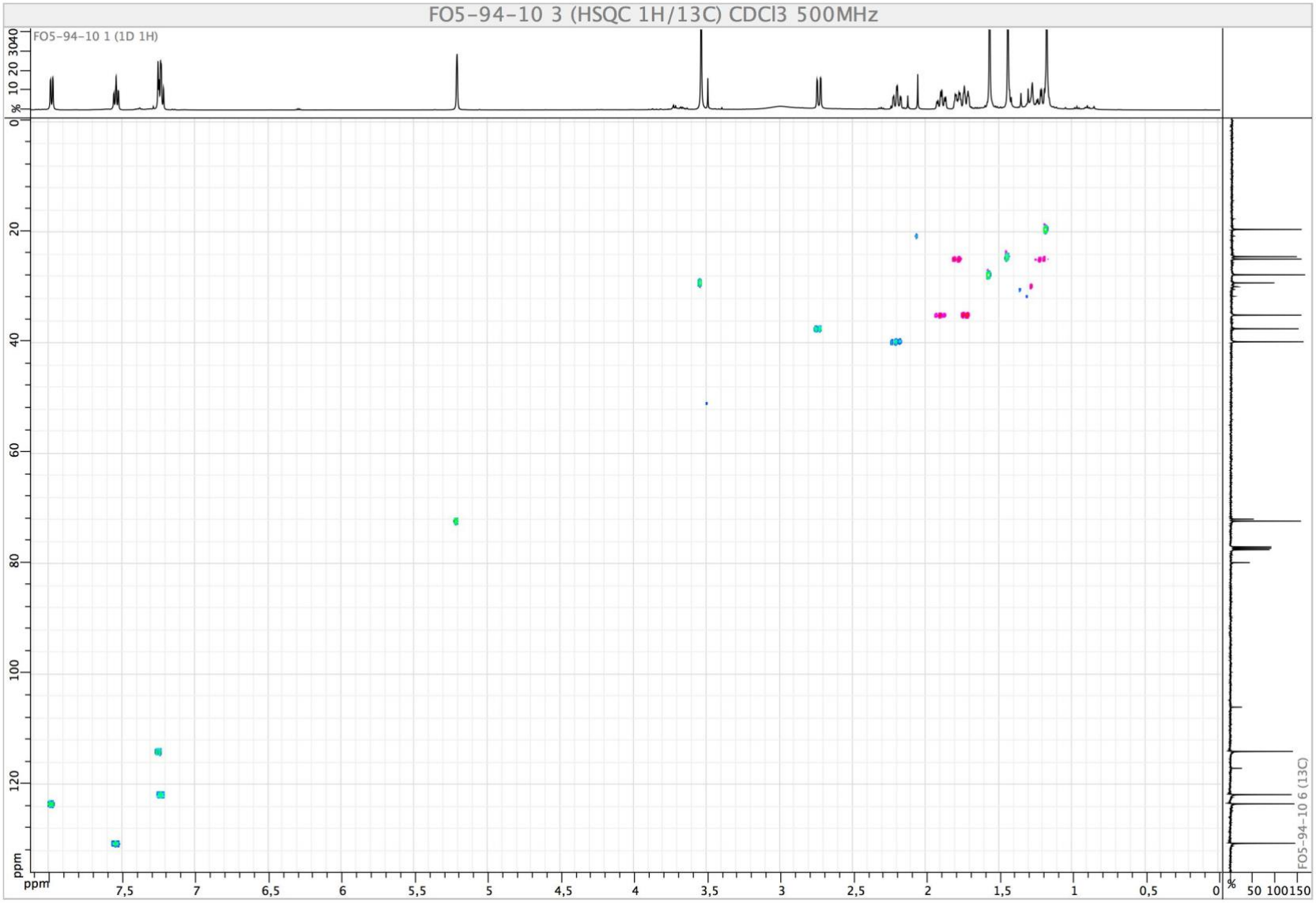
^{1}H NMR spectrum of **20** in $CDCl_3$ at 500 MHz.



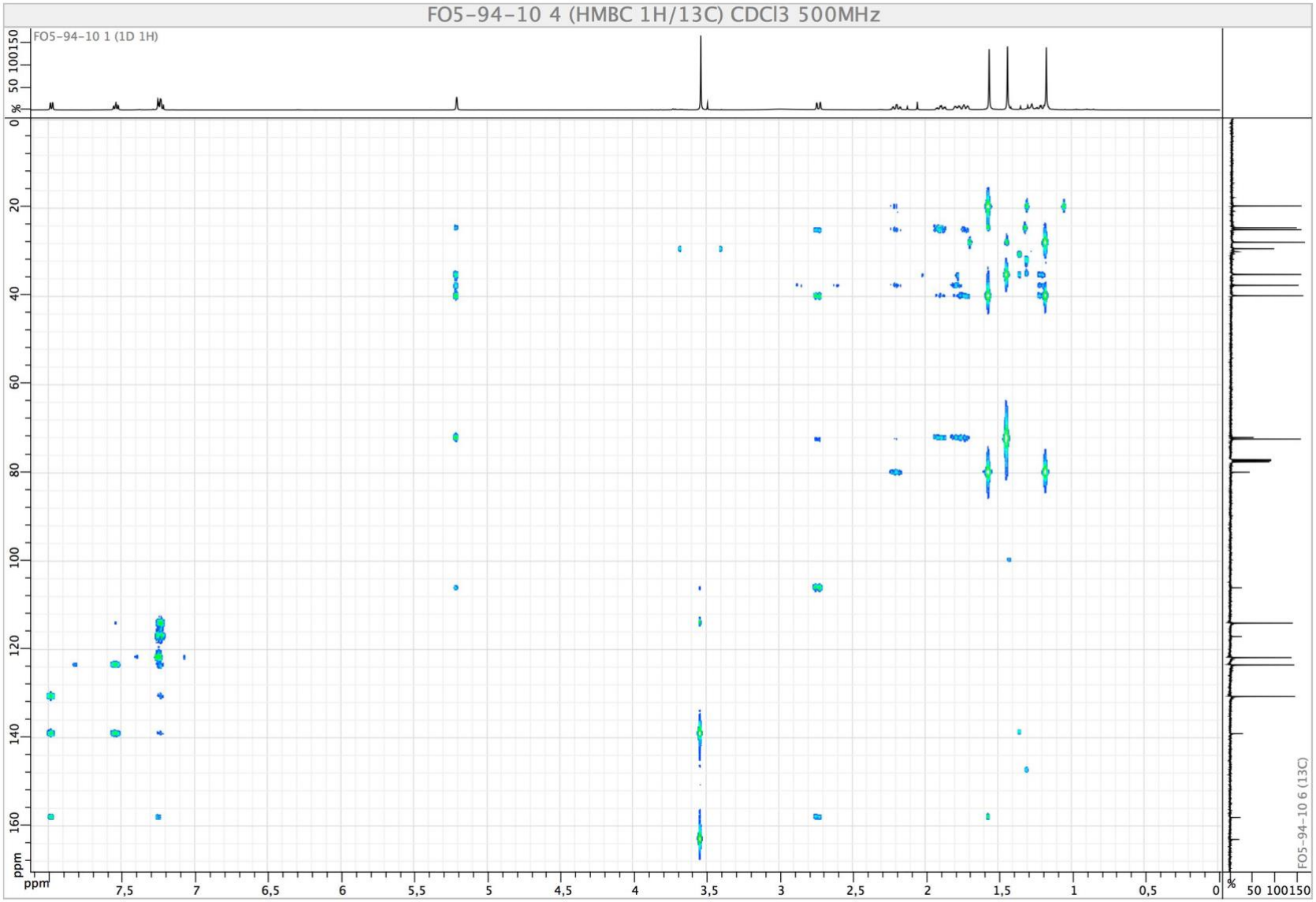
^{13}C NMR spectrum of **20** in $CDCl_3$ at 125 MHz.



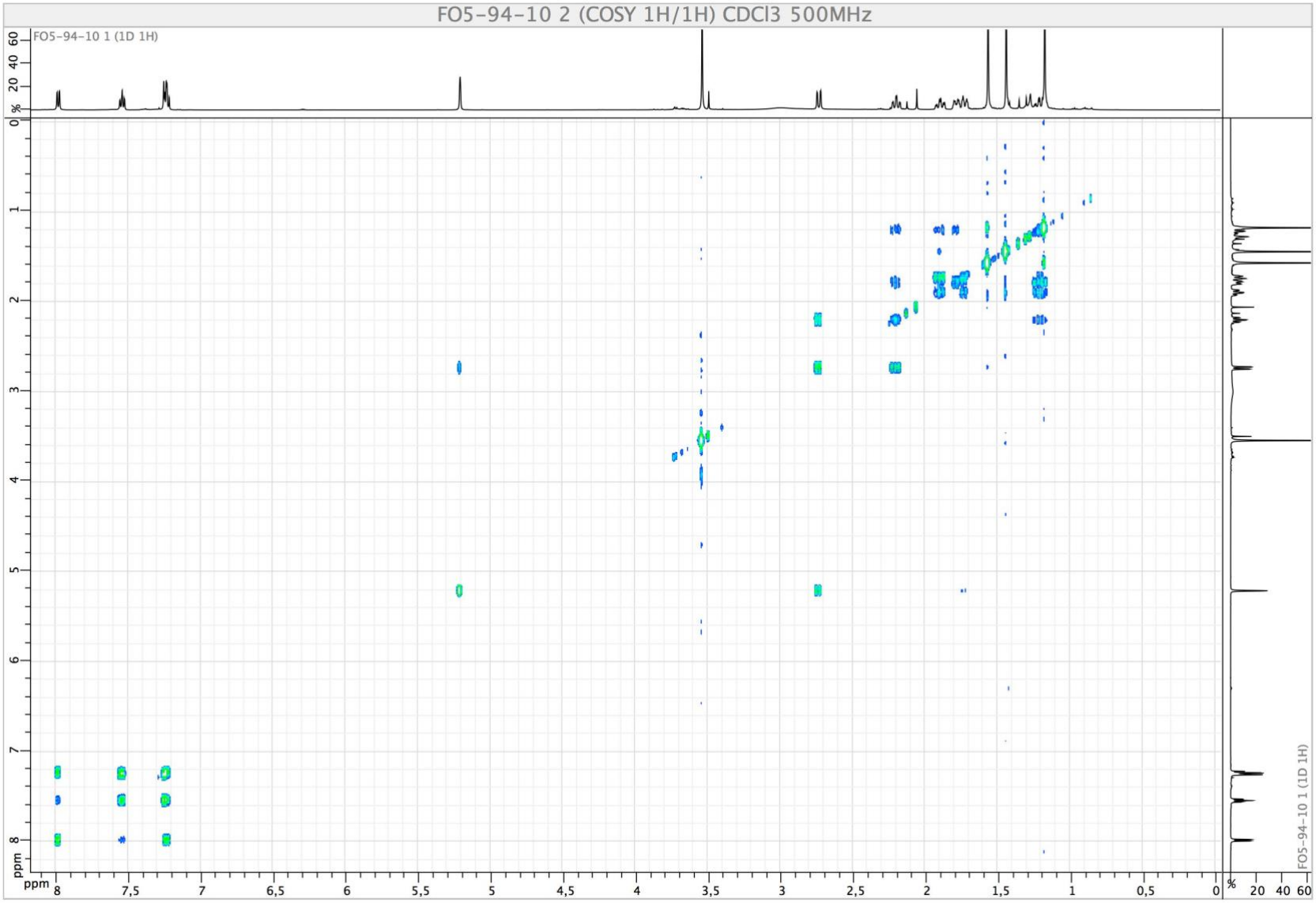
HSQC spectrum (500 MHz, 125 MHz) of **20** in $CDCl_3$.



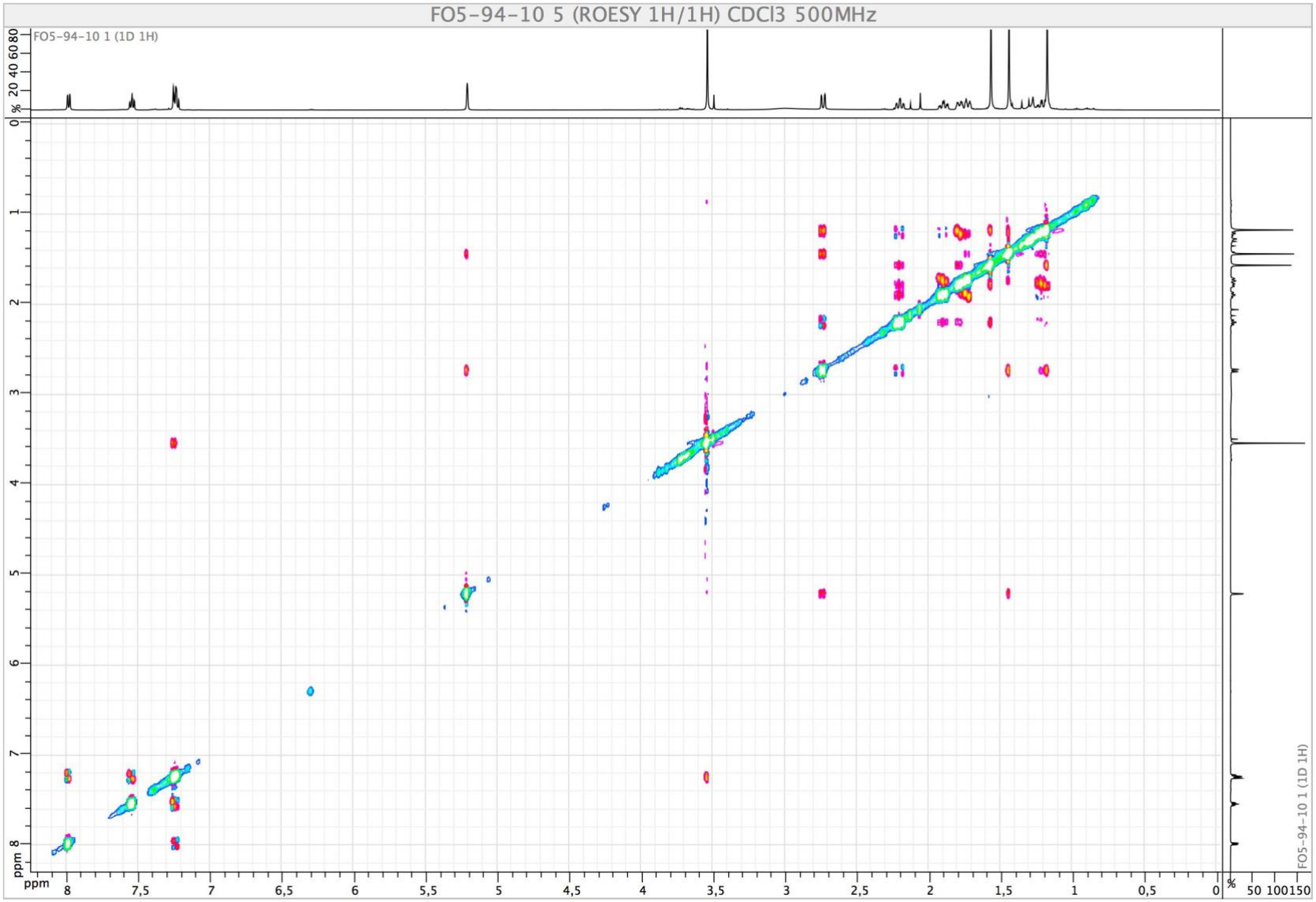
HMBC spectrum (500 MHz, 125 Hz) of **20** in $CDCl_3$.



COSY spectrum (500 MHz) of **20** in $CDCl_3$.



ROESY spectrum (500 MHz) of **20** in $CDCl_3$.



HRESIMS spectrum (TOF) of **20**.

Elemental Composition Report

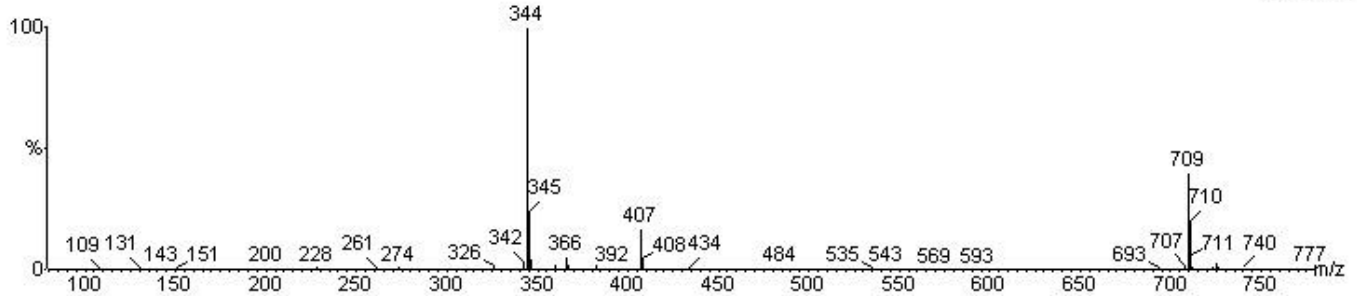
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1362 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-5 O: 0-200 Cl: 0-8

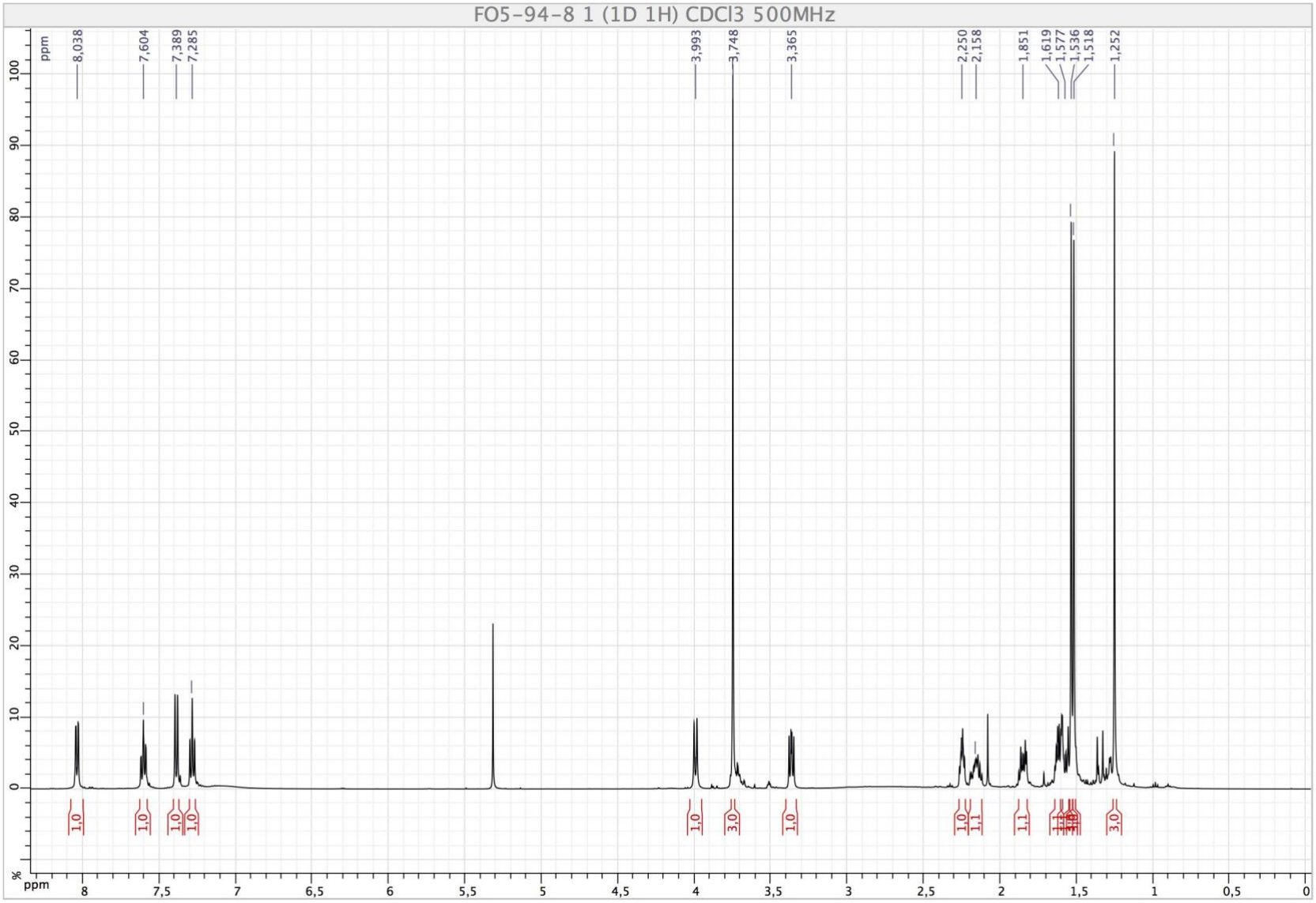
GUERITTE_olivon161-1 438 (2.075)

1: TOF MS ES+
2.91e+004

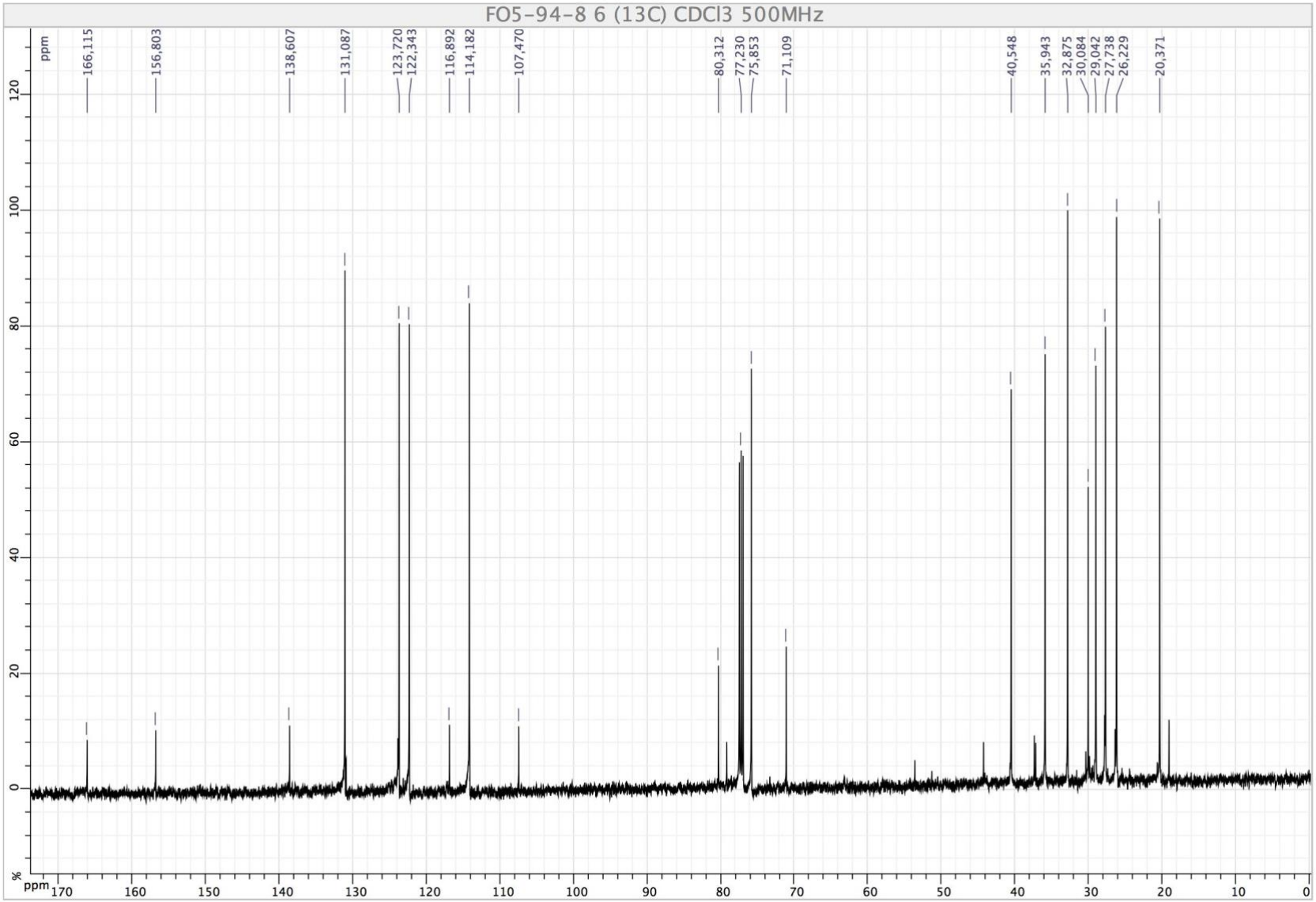


Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
344.1844	344.1862	-1.8	-5.2	8.5	347.9	0.2	C20 H26 N 04
	344.1875	-3.1	-9.0	13.5	349.6	1.9	C21 H22 N5
	344.1822	2.2	6.4	4.5	352.5	4.8	C15 H26 N3 06
	344.1894	-5.0	-14.5	8.5	362.9	15.2	C20 H27 N3 Cl
	344.1853	-0.9	-2.6	4.5	363.0	15.3	C15 H27 N5 02 Cl
	344.1840	0.4	1.2	-0.5	363.1	15.4	C14 H31 N 06 Cl
	344.1872	-2.8	-8.1	-0.5	364.2	16.5	C14 H32 N3 02 Cl2

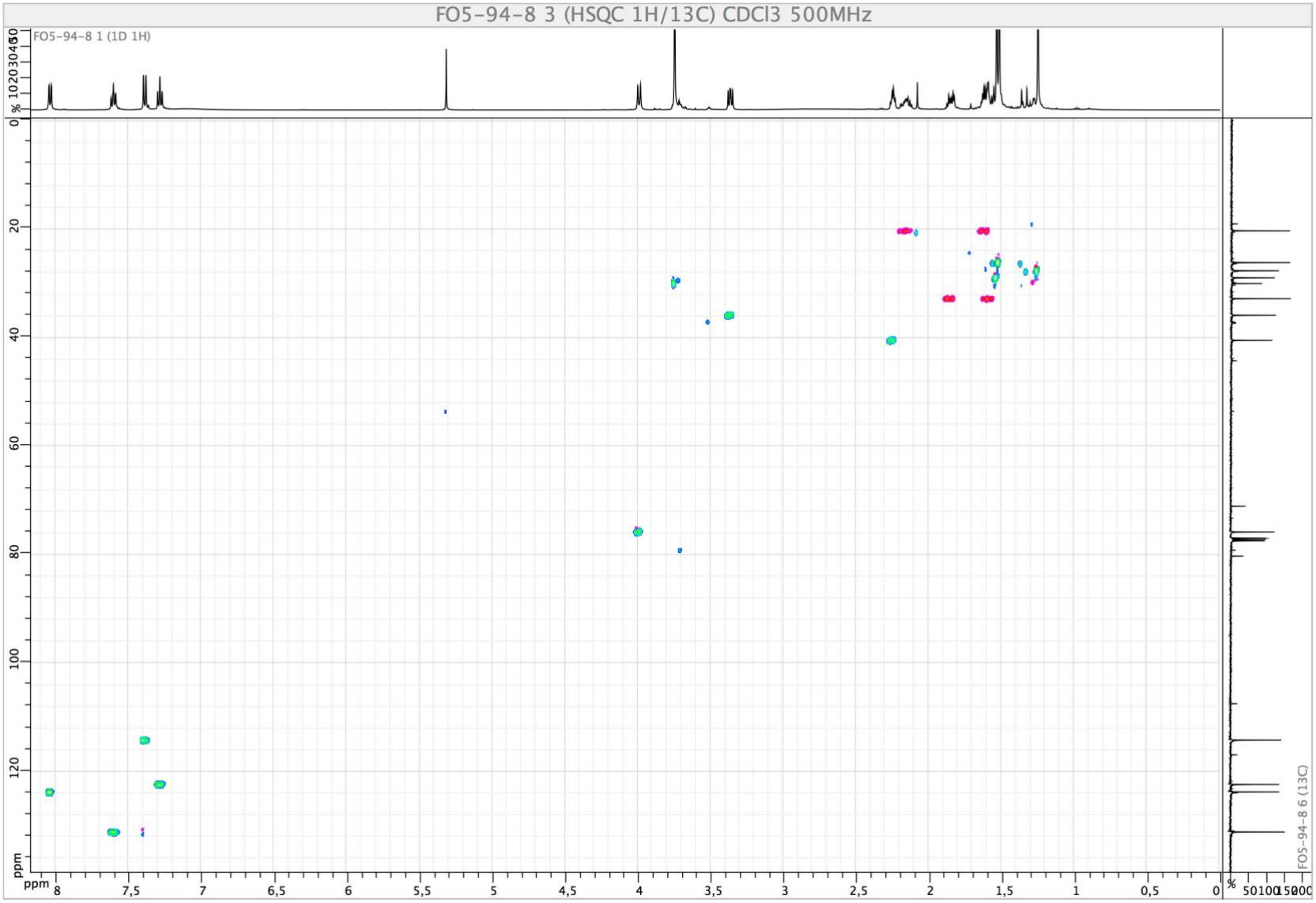
^{1}H NMR spectrum of **21** in $CDCl_3$ at 500 MHz.



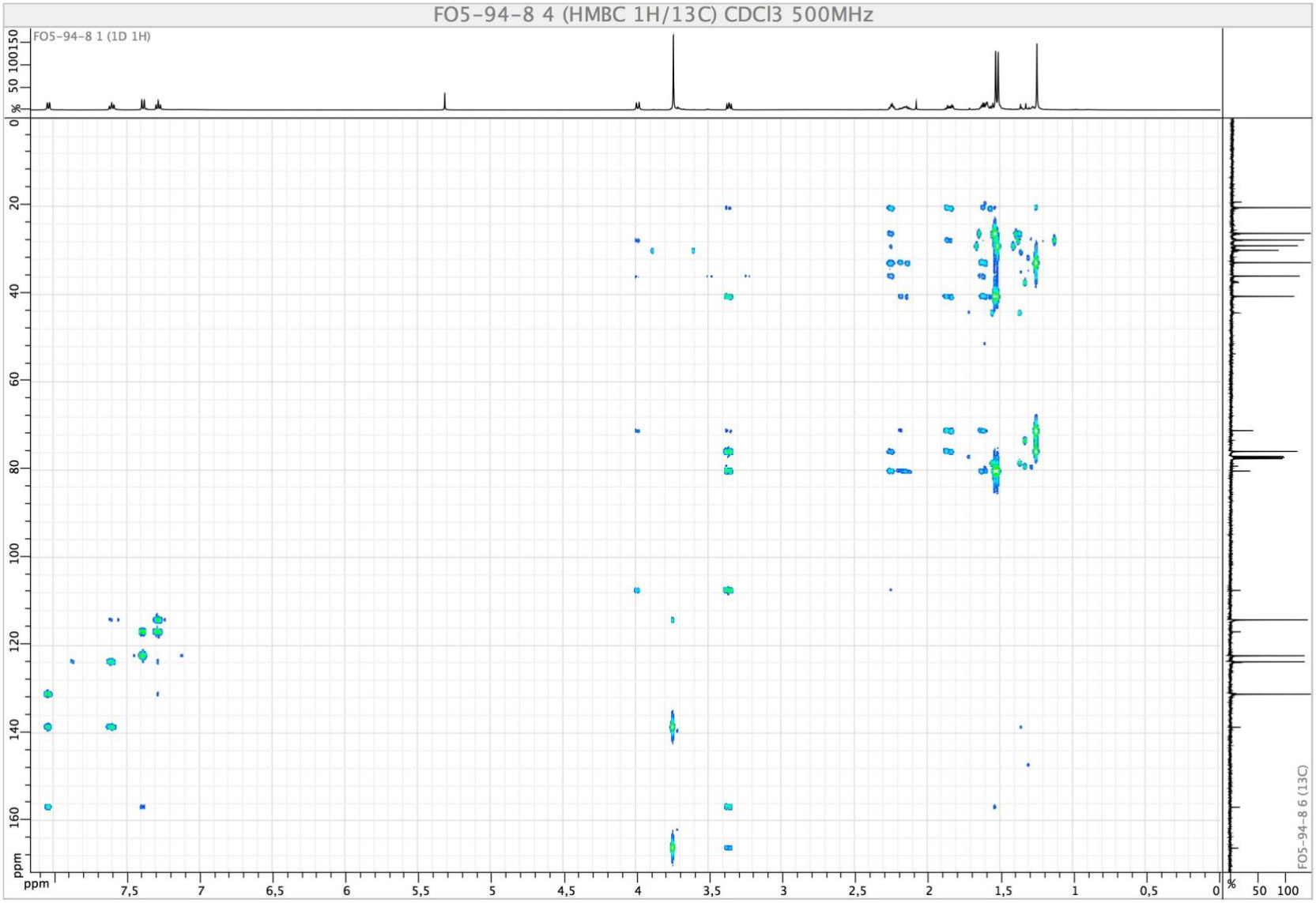
^{13}C NMR spectrum of **21** in $CDCl_3$ at 125 MHz.



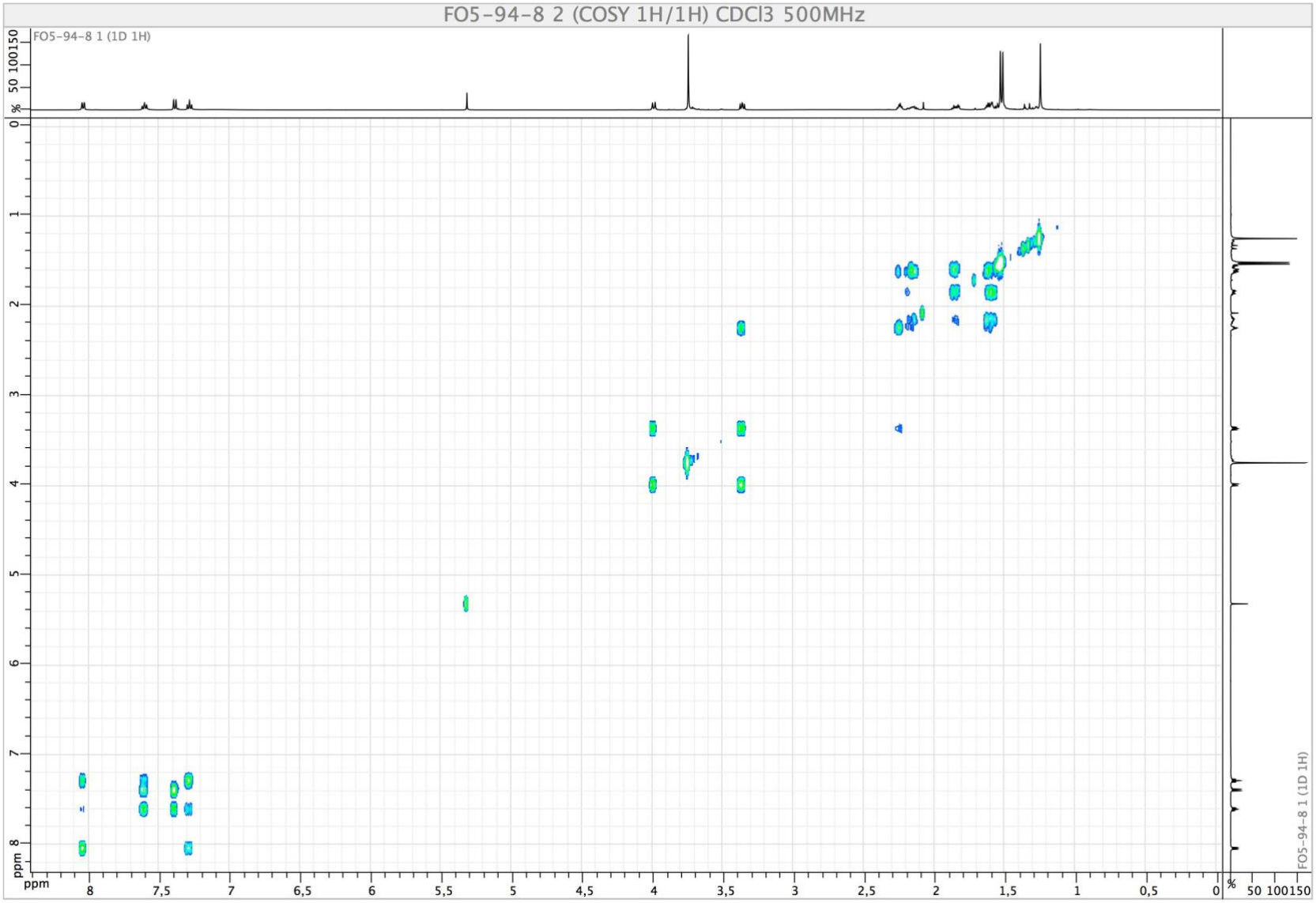
HSQC spectrum (500 MHz, 125 MHz) of **21** in $CDCl_3$.



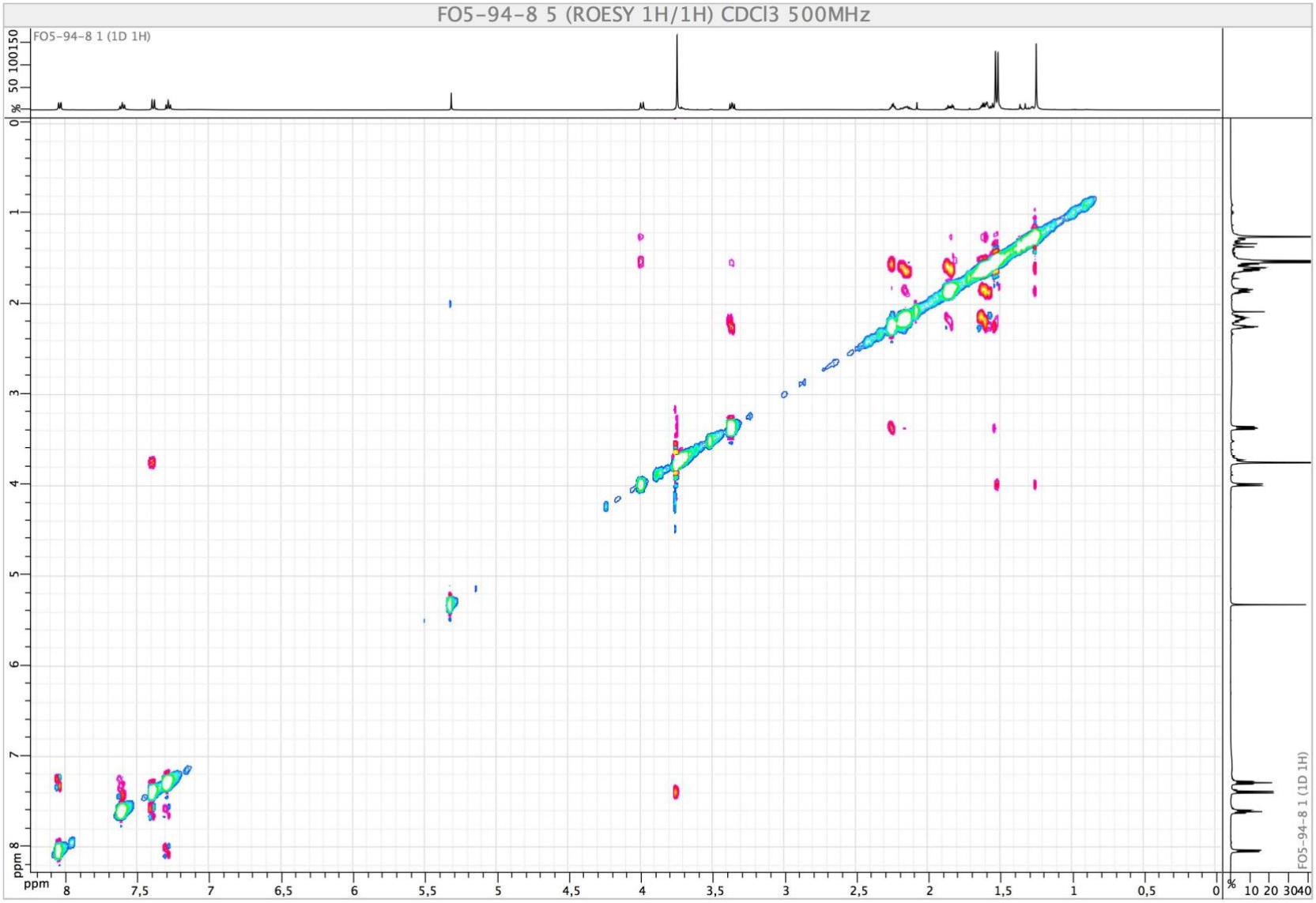
HMBC spectrum (500 MHz, 125 Hz) of **21** in $CDCl_3$.



COSY spectrum (500 MHz) of **21** in $CDCl_3$.



ROESY spectrum (500 MHz) of **21** in $CDCl_3$.



HRESIMS spectrum (TOF) of **21**.

Elemental Composition Report

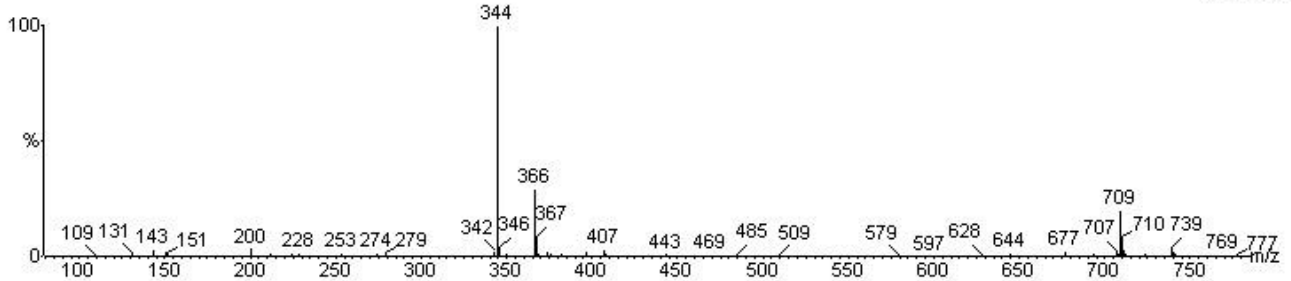
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1362 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-5 O: 0-200 Cl: 0-8

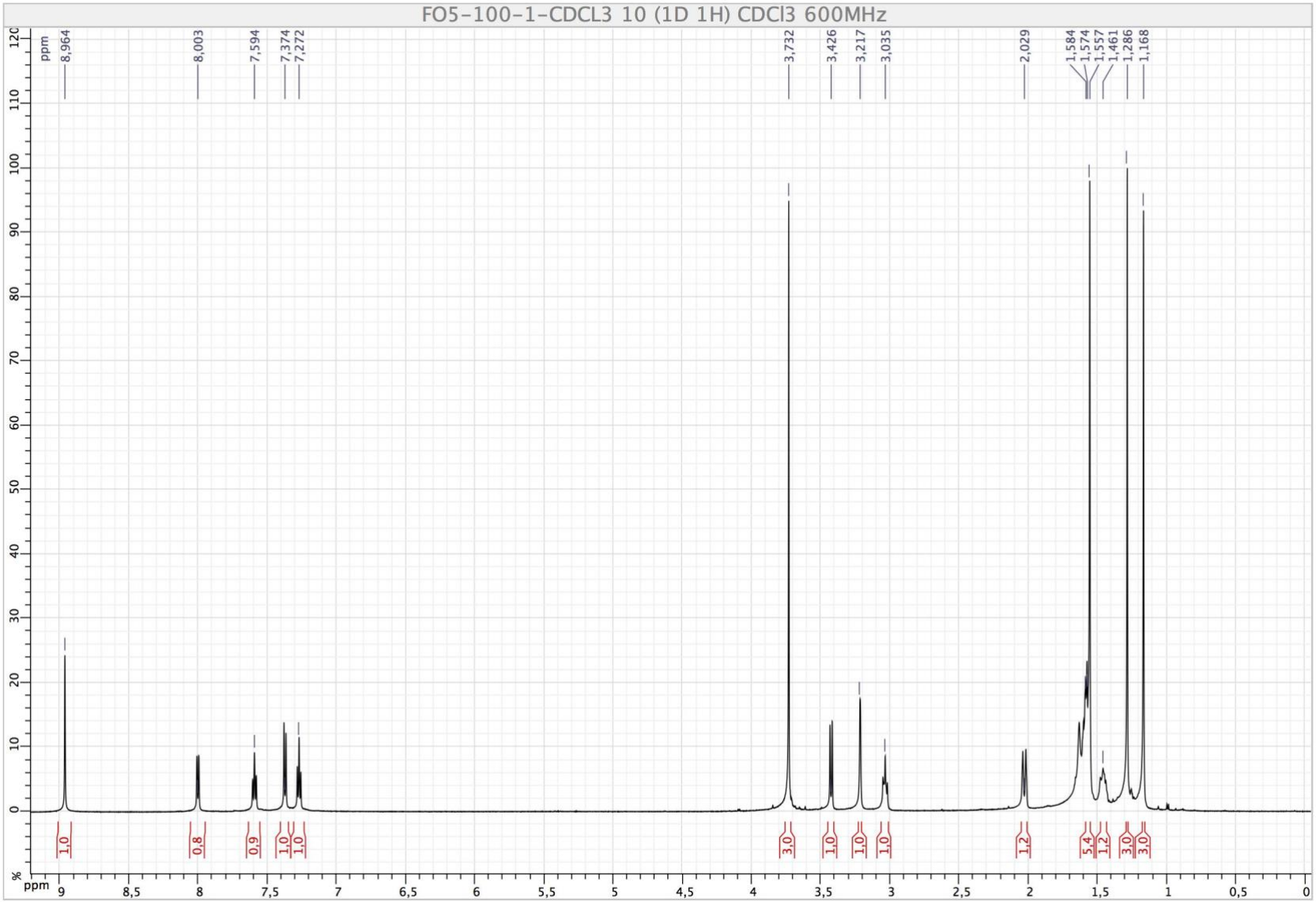
GUERITTE_olivon160-4 454 (2.137)

1: TOF MS ES+
1.14e+004

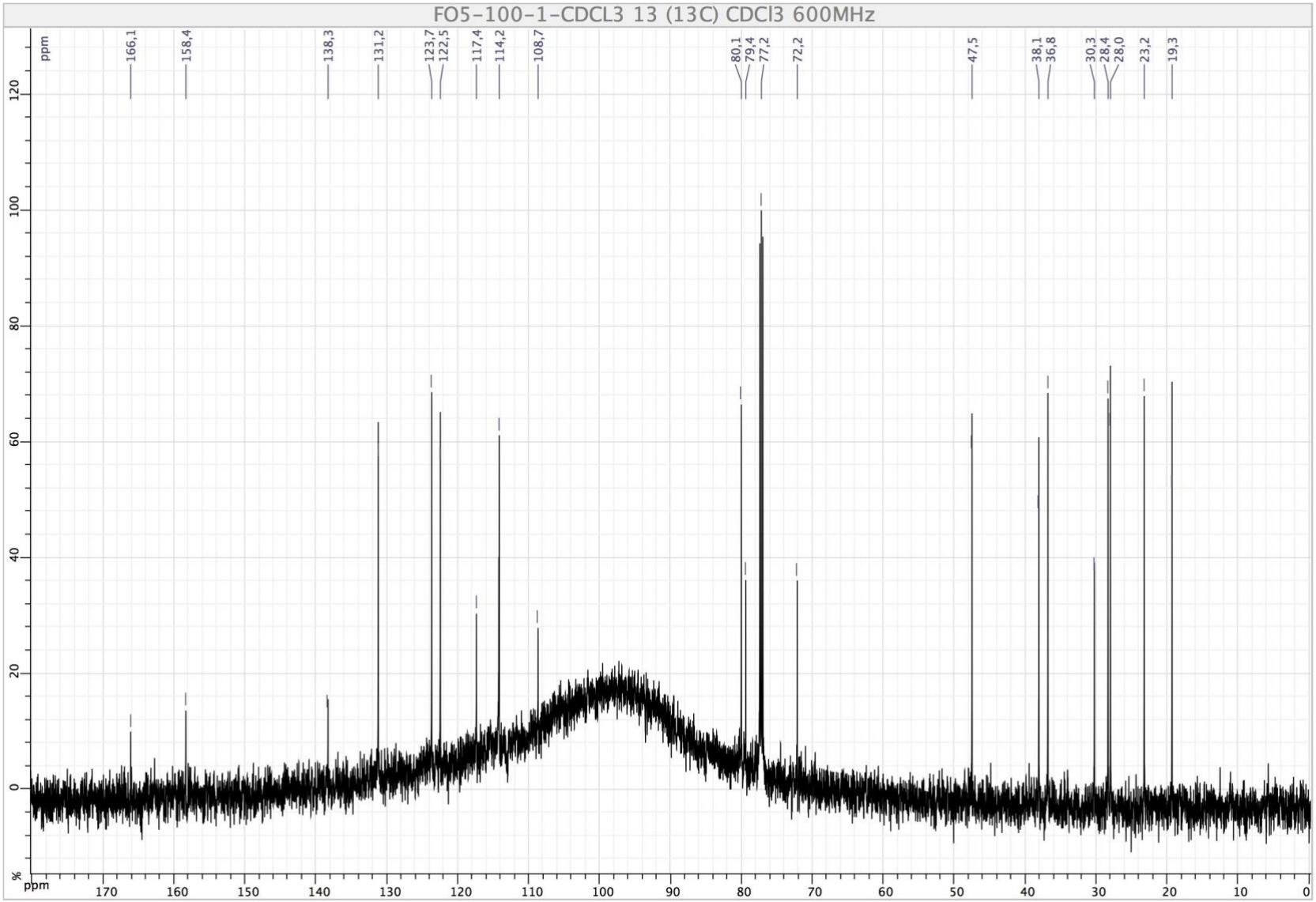


Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
344.1867	344.1862	0.5	1.5	8.5	281.0	0.2	C20 H26 N 04
	344.1875	-0.8	-2.3	13.5	282.8	1.9	C21 H22 N5
	344.1822	4.5	13.1	4.5	288.5	7.6	C15 H26 N3 06
	344.1894	-2.7	-7.8	8.5	298.7	17.8	C20 H27 N3 Cl
	344.1853	1.4	4.1	4.5	299.0	18.1	C15 H27 N5 02 Cl
	344.1840	2.7	7.8	-0.5	299.0	18.1	C14 H31 N 06 Cl
	344.1872	-0.5	-1.5	-0.5	300.0	19.1	C14 H32 N3 02 Cl2
	344.1912	-4.5	-13.1	3.5	300.0	19.1	C19 H32 N Cl2

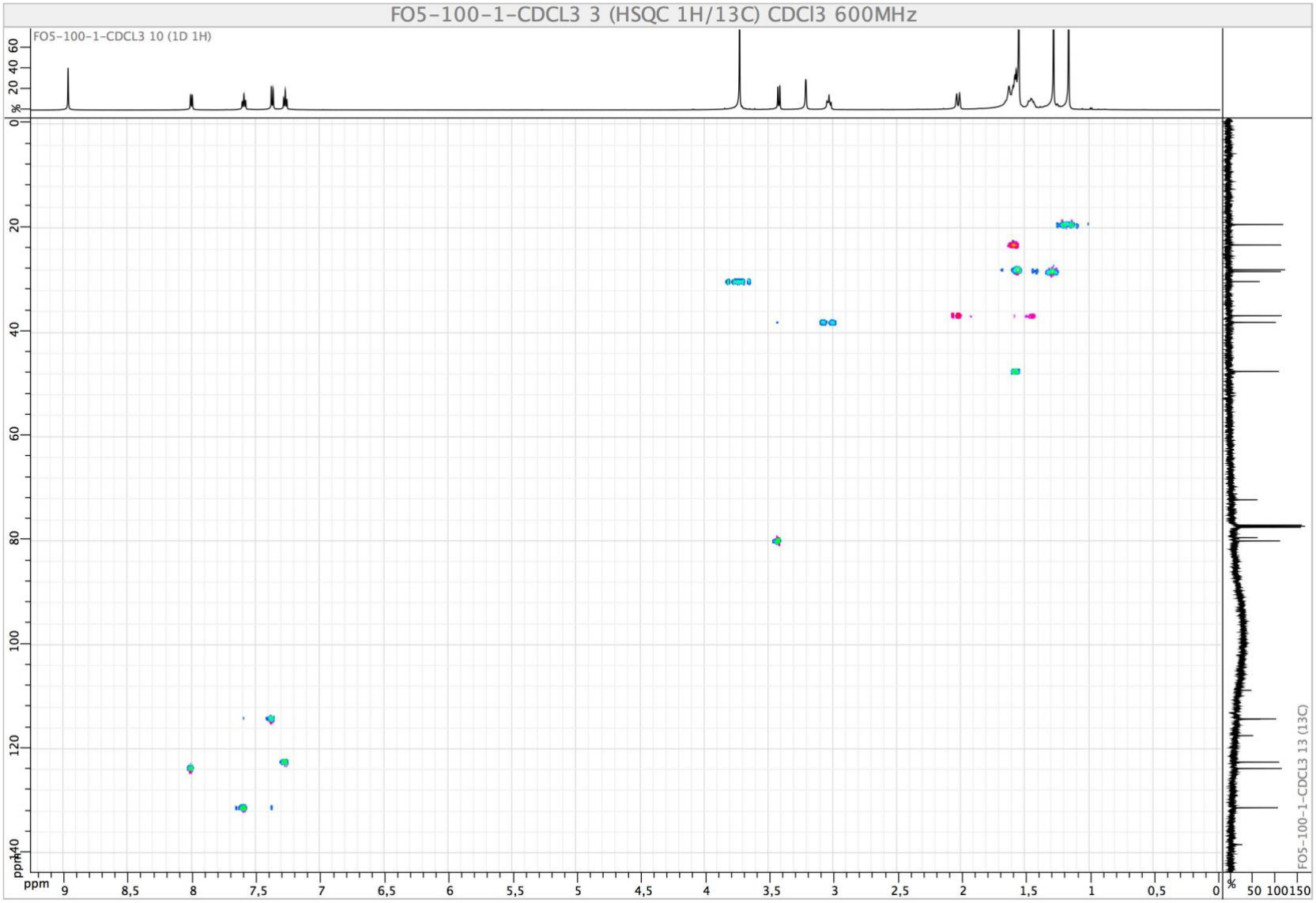
^{1}H NMR spectrum of **22** in $CDCl_3$ at 600 MHz.



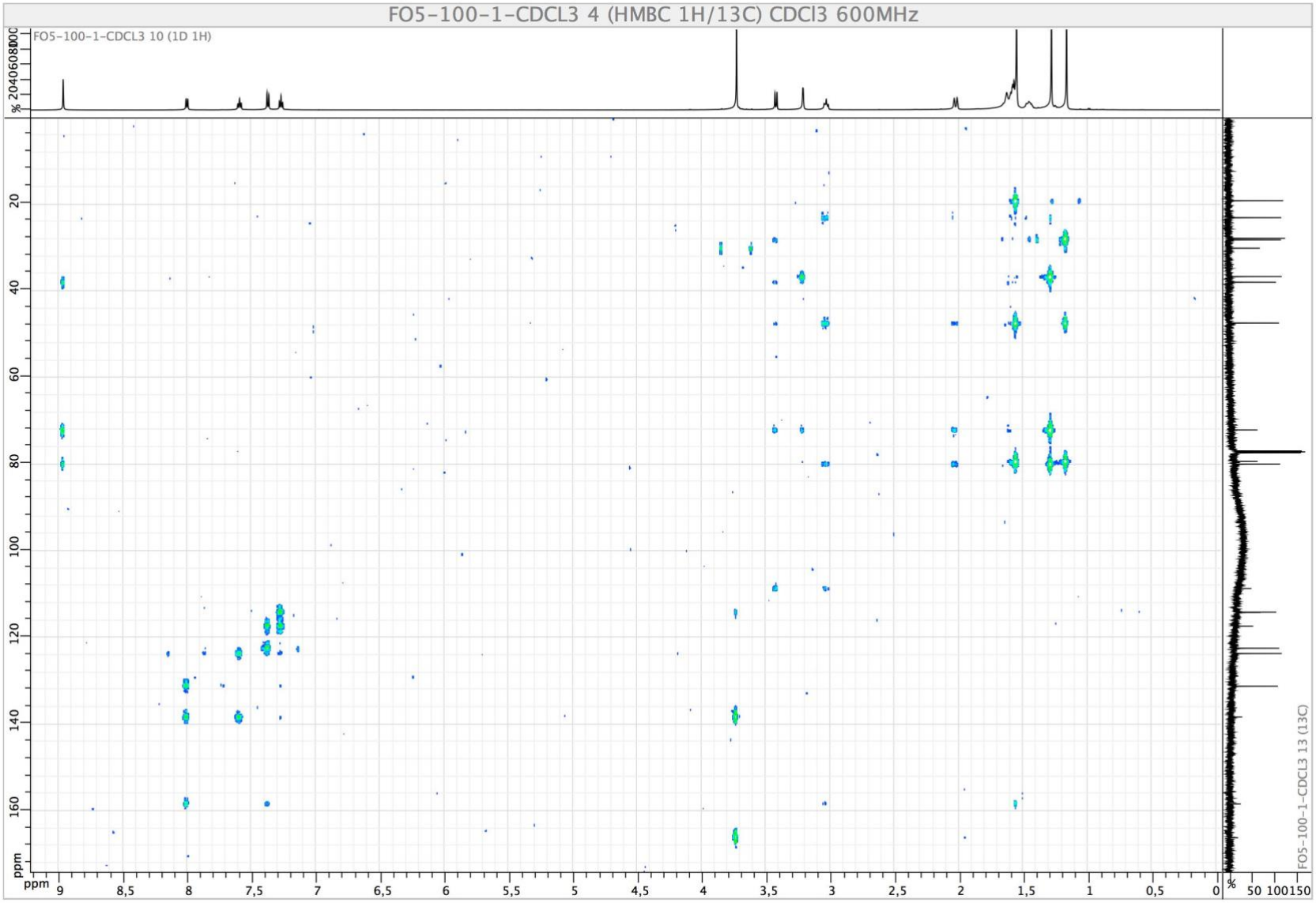
^{13}C NMR spectrum of **22** in $CDCl_3$ at 150 MHz.



HSQC spectrum (600 MHz, 150 MHz) of **22** in $CDCl_3$.

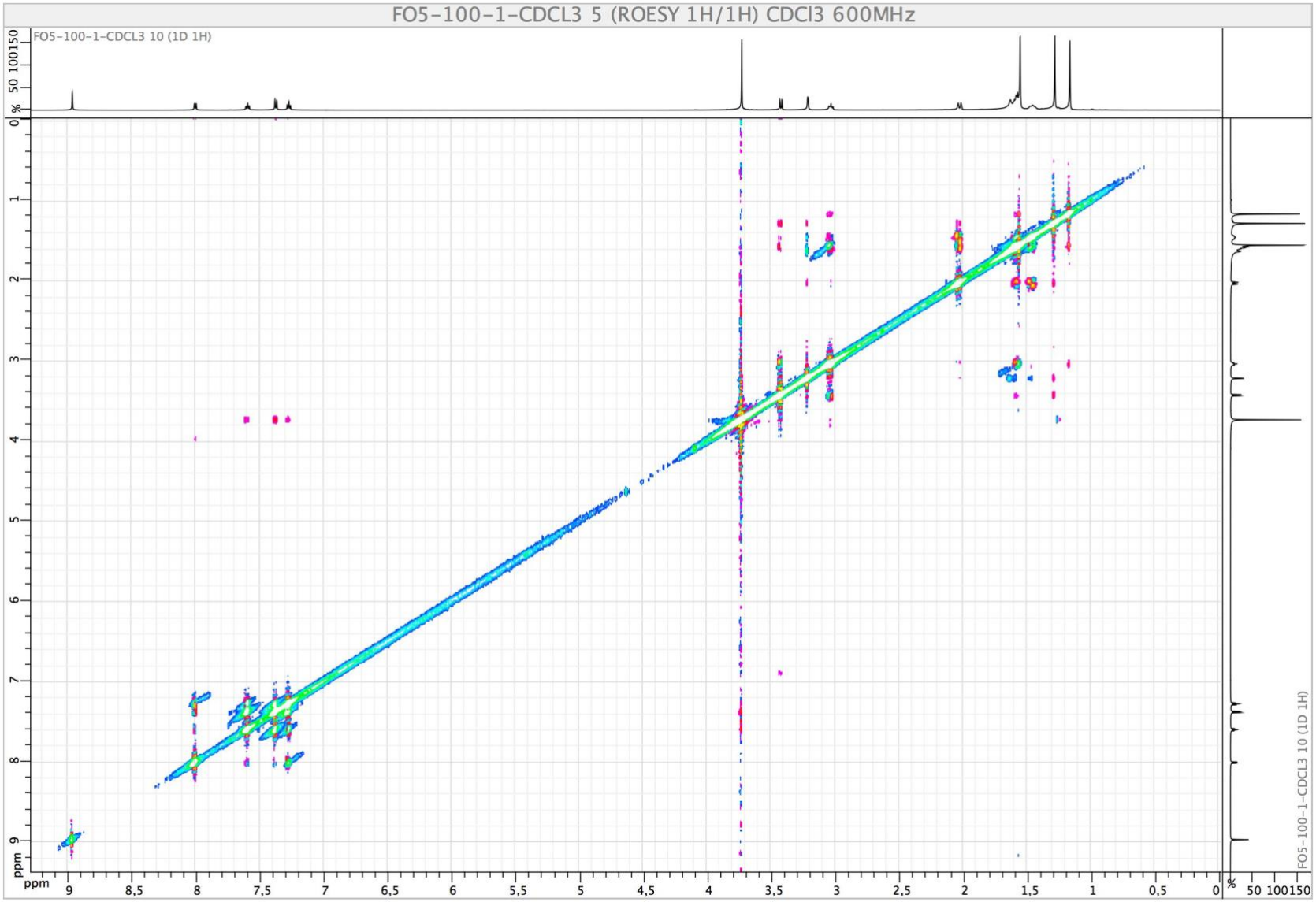


HMBC spectrum (600 MHz, 150 MHz) of **22** in $CDCl_3$.



COSY spectrum (600 MHz) of **22** in $CDCl_3$.

ROESY spectrum (600 MHz) of **22** in $CDCl_3$.



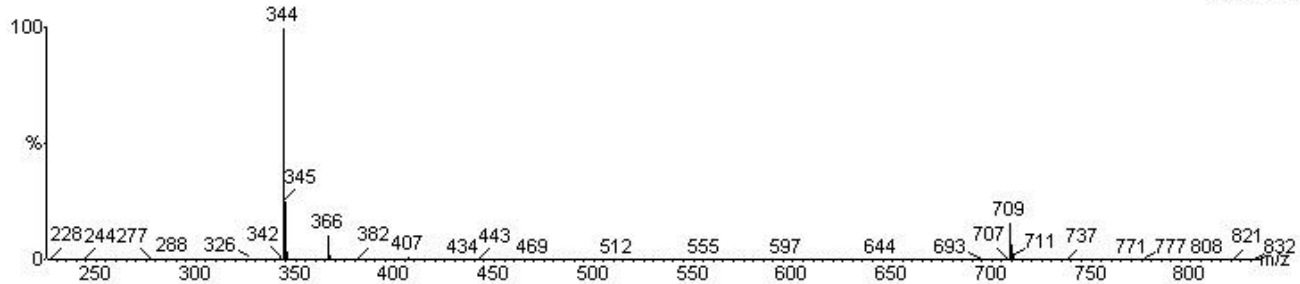
HRESIMS spectrum (TOF) of **22**.

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
974 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-3 O: 0-200 Cl: 0-8

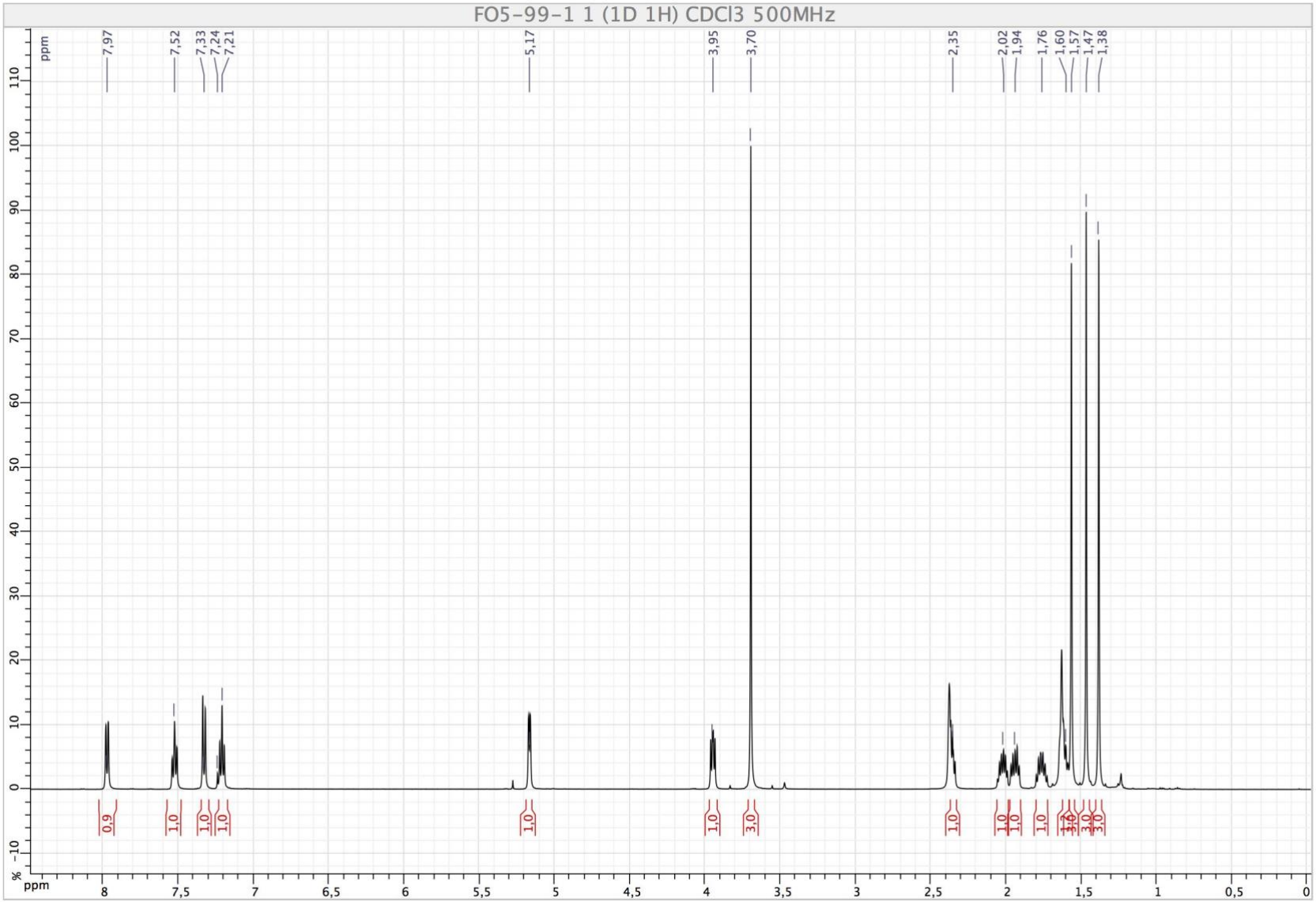
GUERITTE_olivon160-2 507 (2.377)

1: TOF MS ES+
4.27e+004

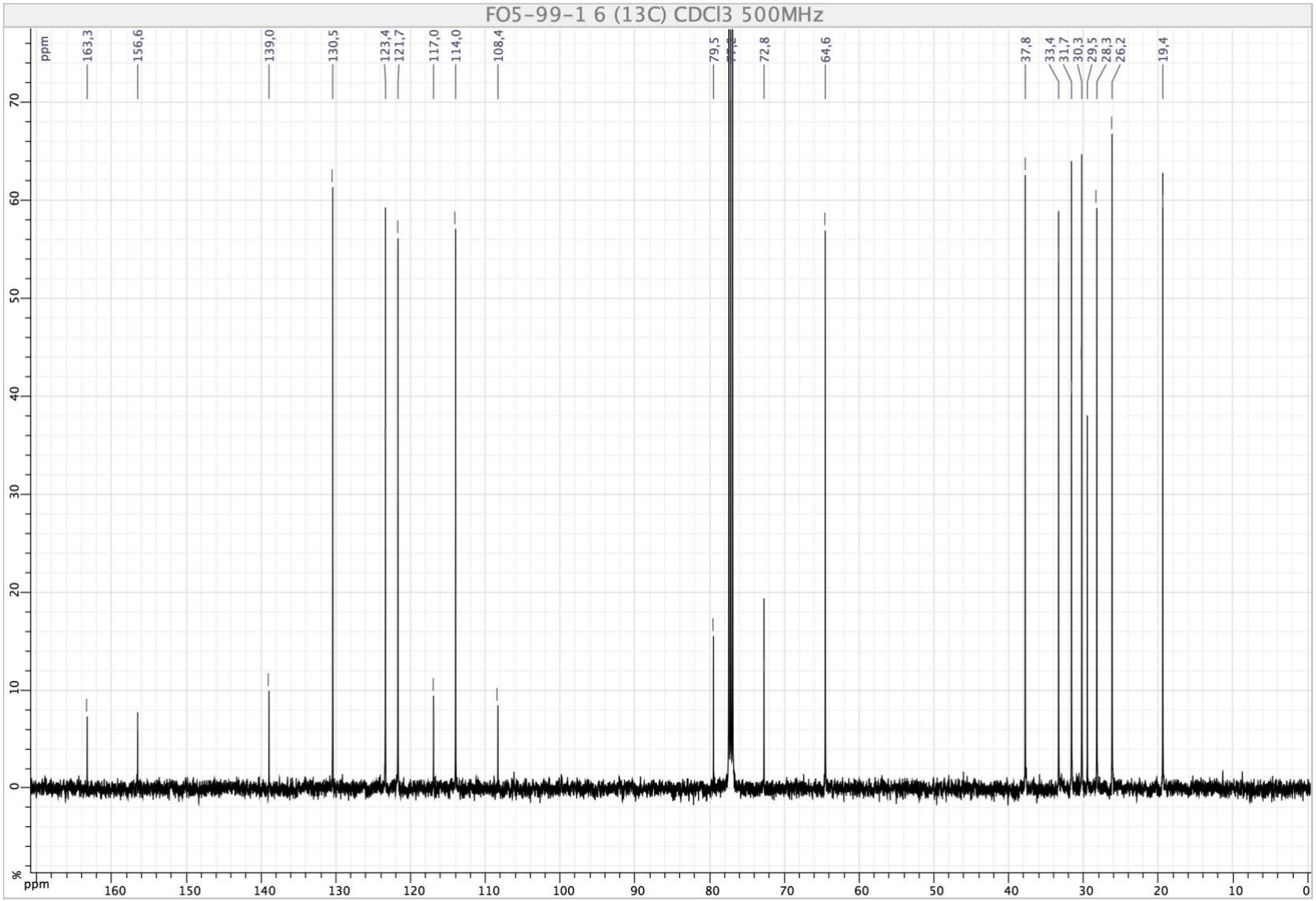


Minimum:				-1.5							
Maximum:		5.0	10.0	50.0							
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula				
344.1845	344.1862	-1.7	-4.9	8.5	342.6	0.0	C20	H26	N	04	
	344.1822	2.3	6.7	4.5	347.2	4.7	C15	H26	N3	06	
	344.1894	-4.9	-14.2	8.5	357.5	14.9	C20	H27	N3	Cl	
	344.1840	0.5	1.5	-0.5	357.6	15.1	C14	H31	N	06	Cl
	344.1872	-2.7	-7.8	-0.5	358.7	16.1	C14	H32	N3	02	Cl2

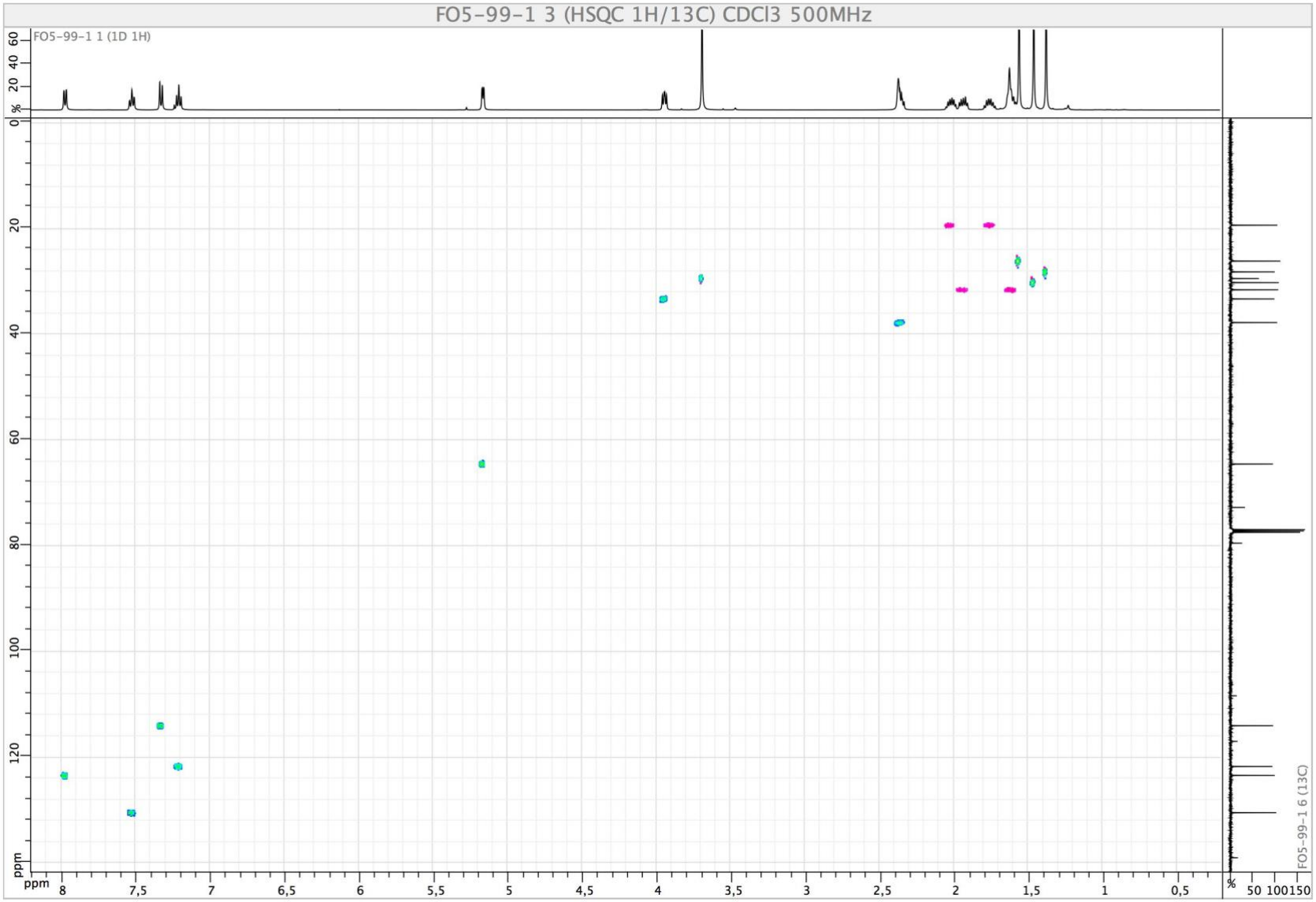
^{1}H NMR spectrum of **23** in $CDCl_3$ at 500 MHz.



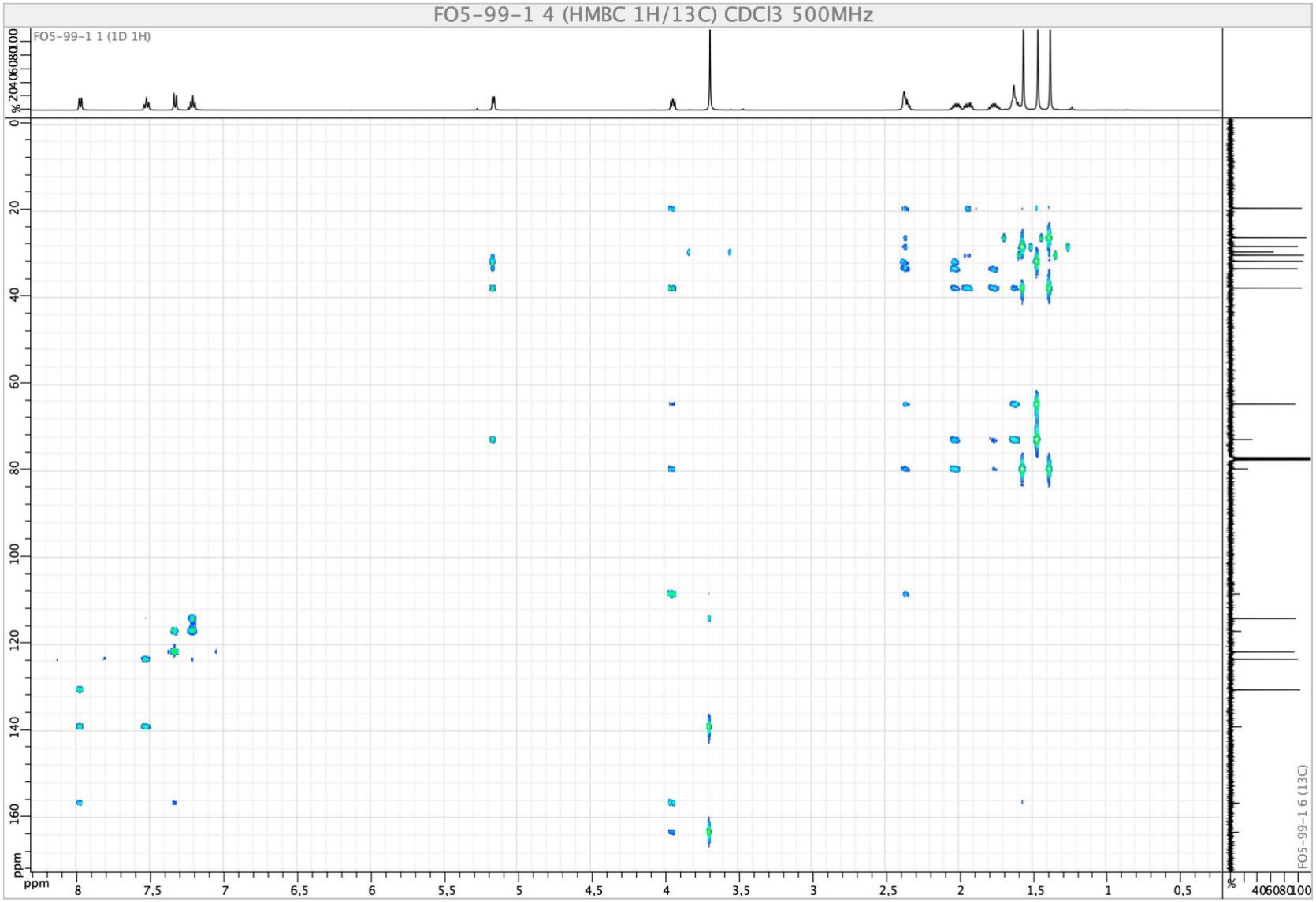
^{13}C NMR spectrum of **23** in $CDCl_3$ at 125 MHz.



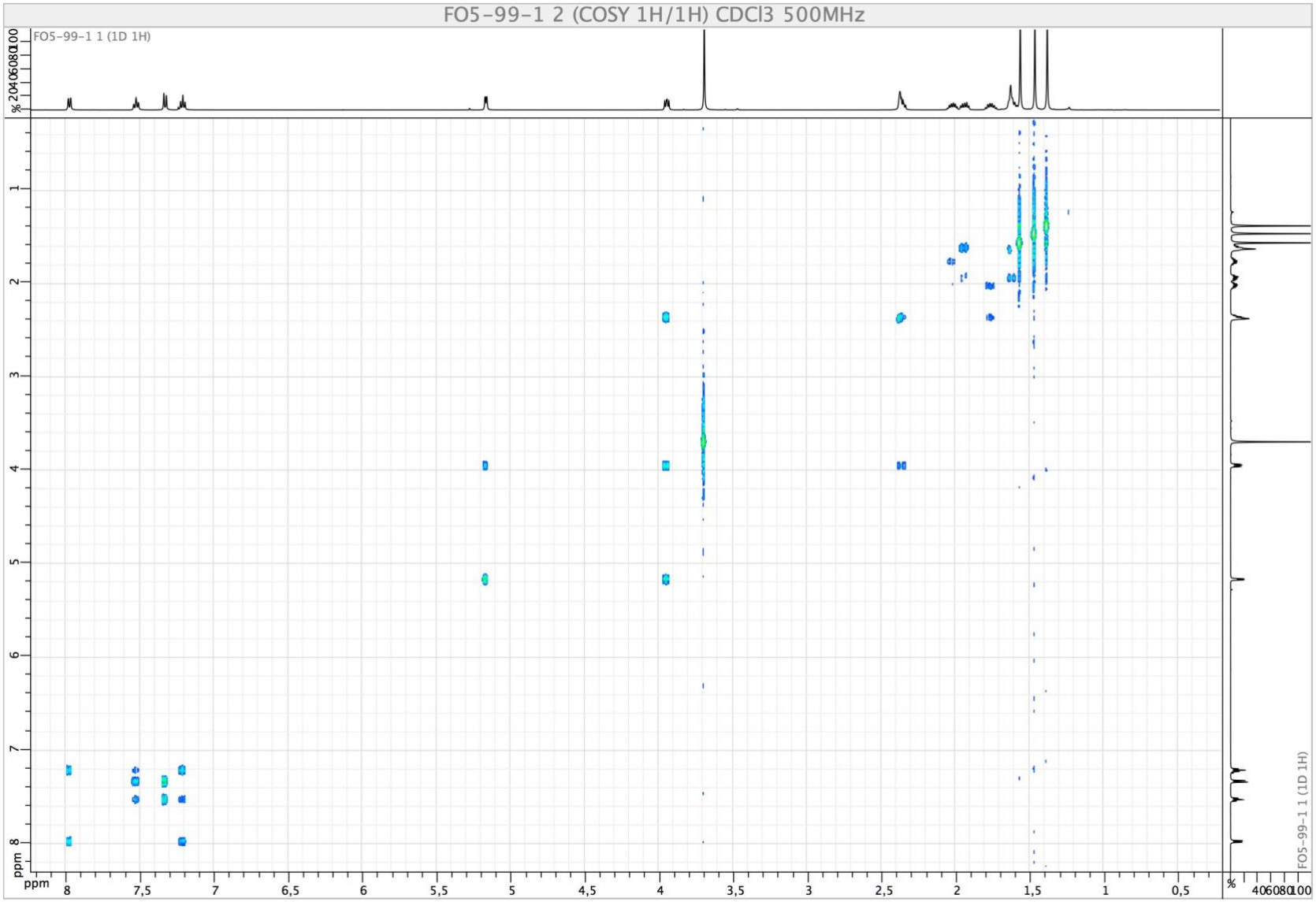
HSQC spectrum (500 MHz, 125 MHz) of **23** in $CDCl_3$.



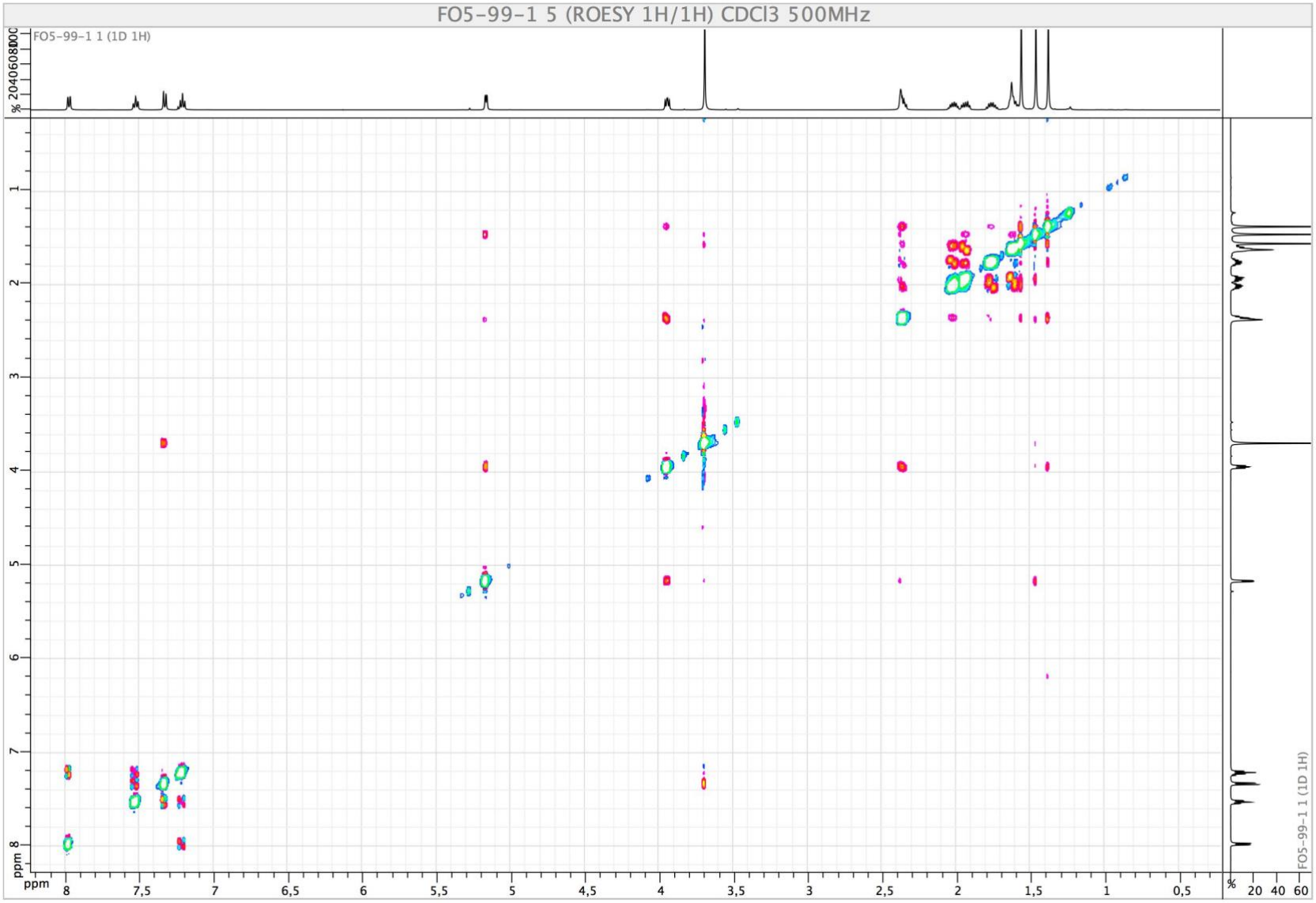
HMBC spectrum (500 MHz, 125 Hz) of **23** in $CDCl_3$.



COSY spectrum (500 MHz) of **23** in $CDCl_3$.



ROESY spectrum (500 MHz) of **23** in $CDCl_3$.



HRESIMS spectrum (TOF) of **23**.

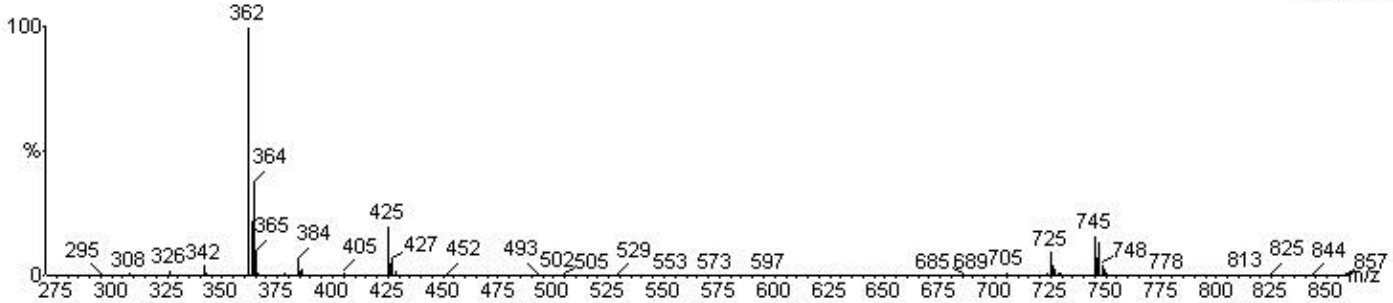
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1550 formula(e) evaluated with 9 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-5 O: 0-200 Cl: 0-8

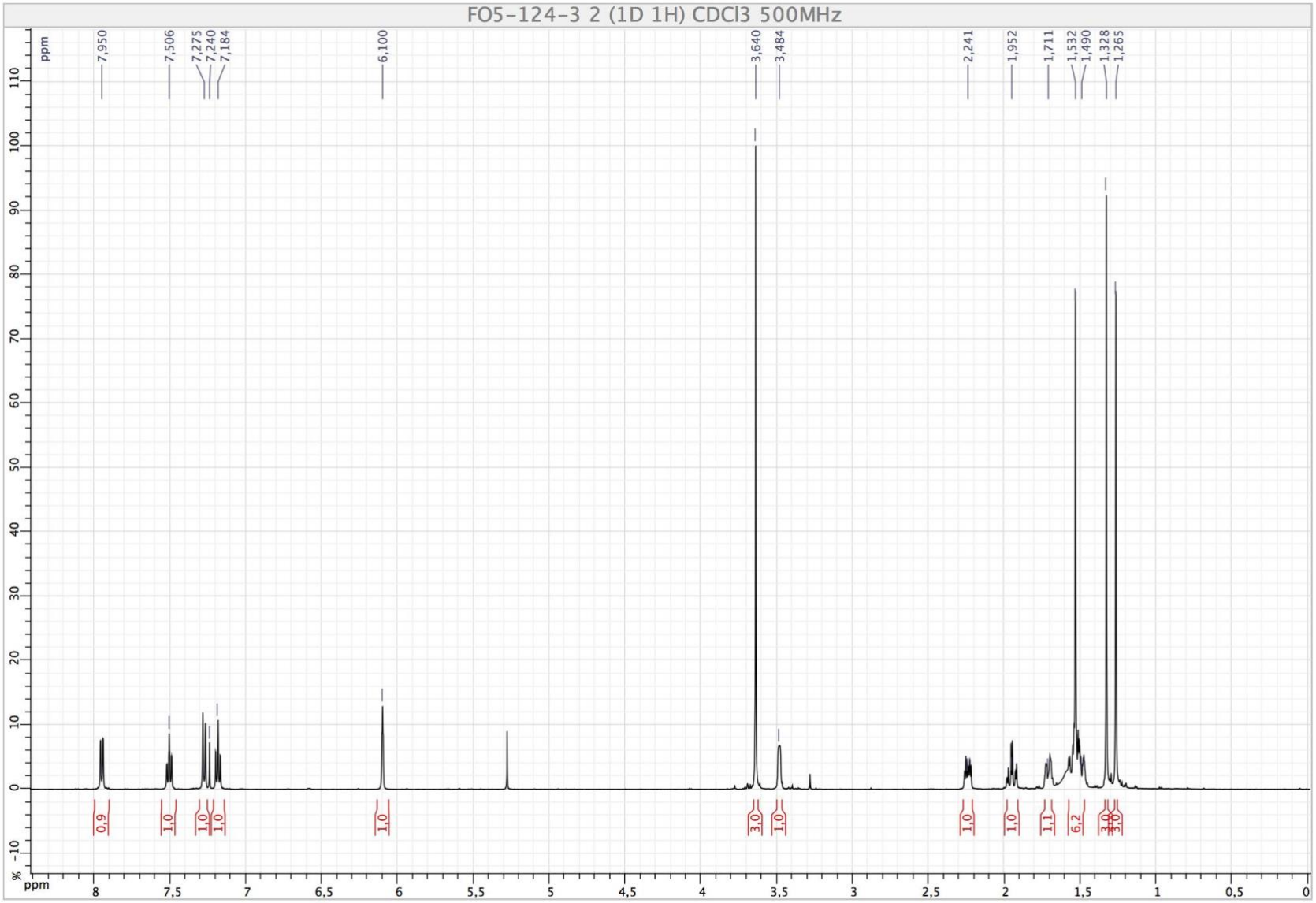
GUERITTE_olivon159-3 566 (2.642)

1: TOF MS ES+
2.55e+004

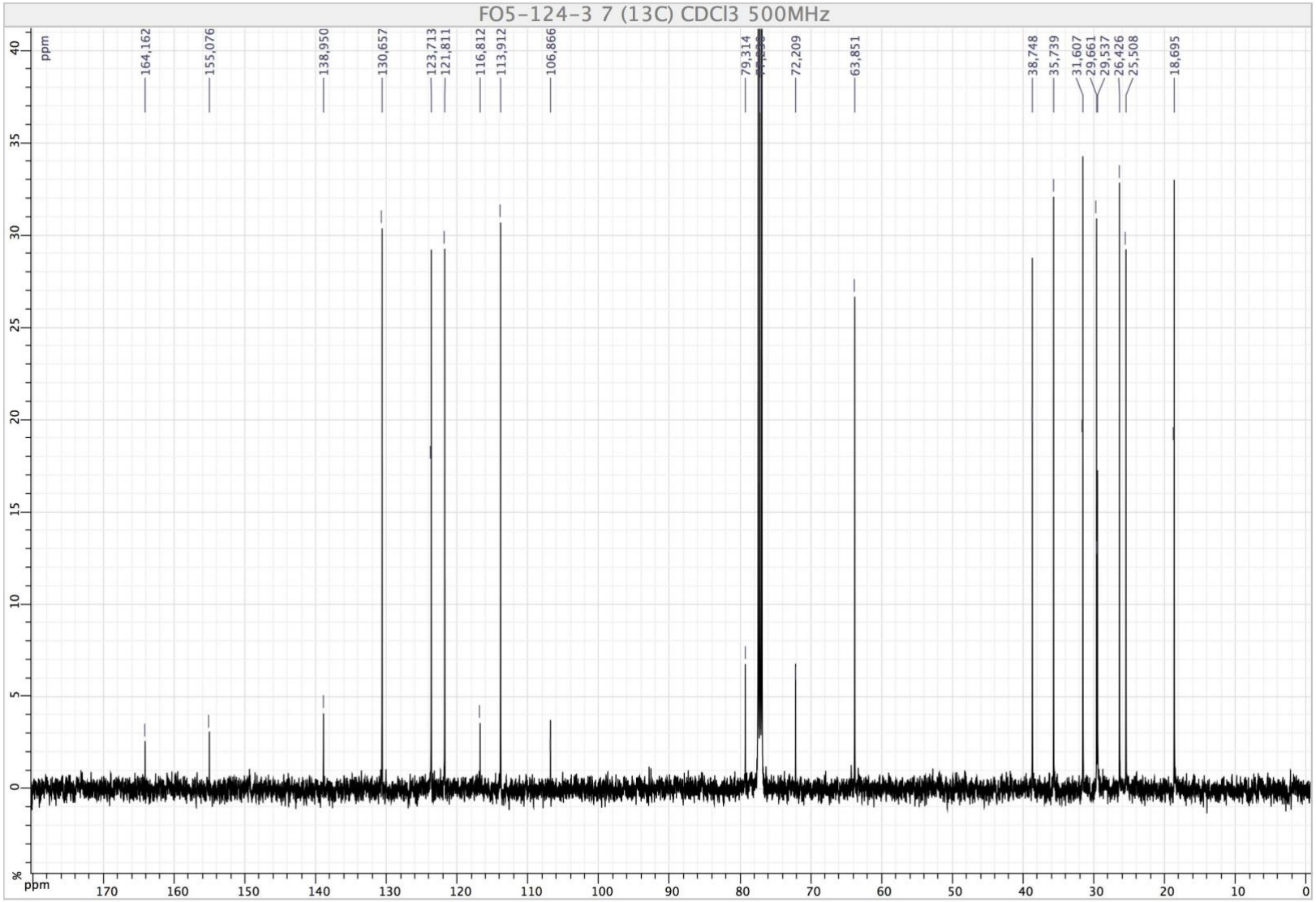


Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
362.1537	362.1523	1.4	3.9	8.5	336.2	0.0	C20 H25 N 03 Cl
	362.1582	-4.5	-12.4	-0.5	340.9	4.8	C13 H29 N 08 Cl
	362.1514	2.3	6.4	4.5	345.0	8.8	C15 H26 N5 0 Cl2
	362.1501	3.6	9.9	-0.5	345.6	9.4	C14 H30 N 05 Cl2
	362.1533	0.4	1.1	-0.5	347.2	11.1	C14 H31 N3 0 Cl3
	362.1523	1.4	3.9	0.5	349.6	13.4	C9 H24 N5 010
	362.1563	-2.6	-7.2	4.5	349.7	13.6	C14 H24 N3 08
	362.1505	3.2	8.8	13.5	350.1	14.0	C21 H20 N3 03
	362.1545	-0.8	-2.2	17.5	350.5	14.4	C26 H20 N 0

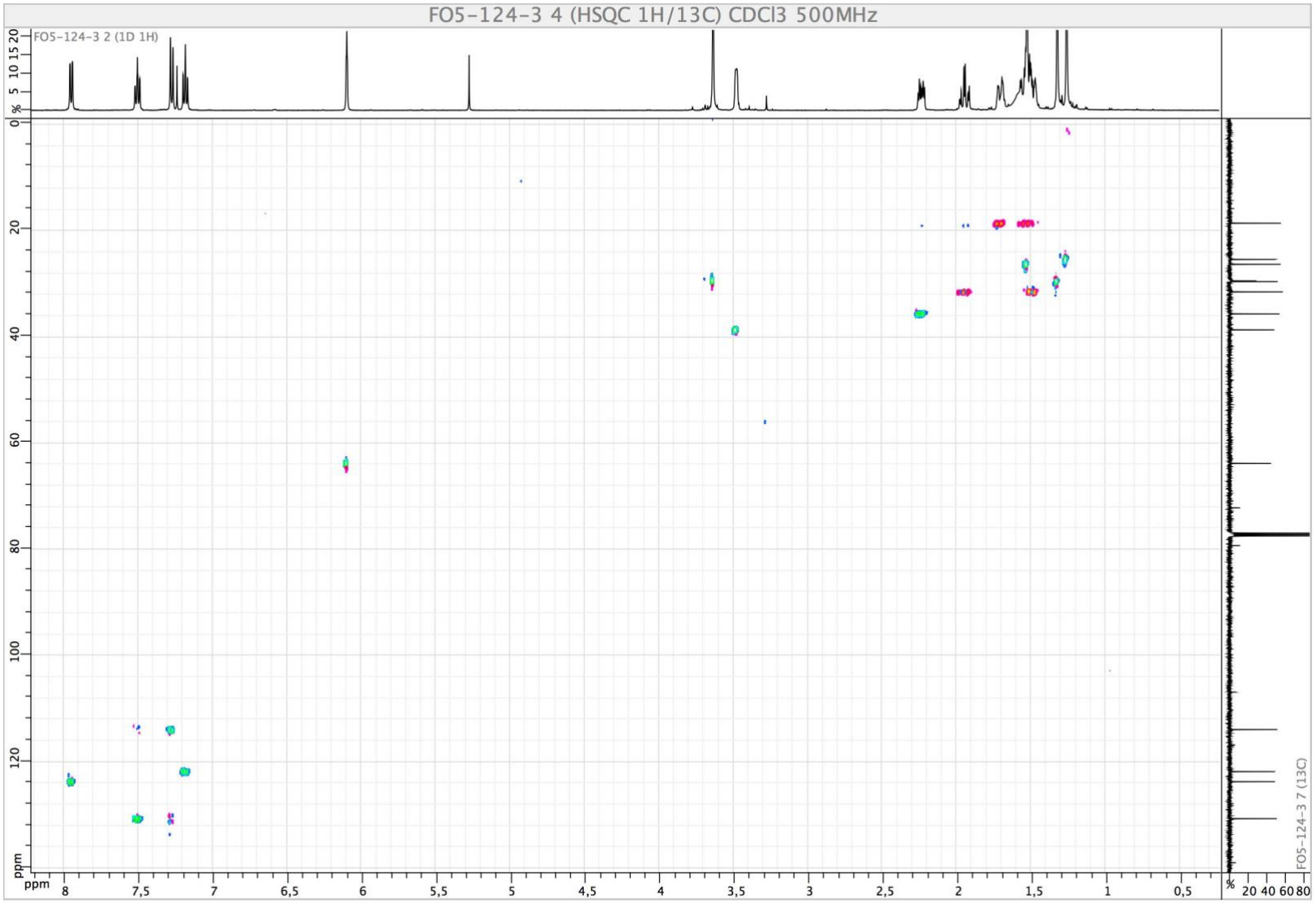
^{1}H NMR spectrum of **24** in $CDCl_3$ at 500 MHz.



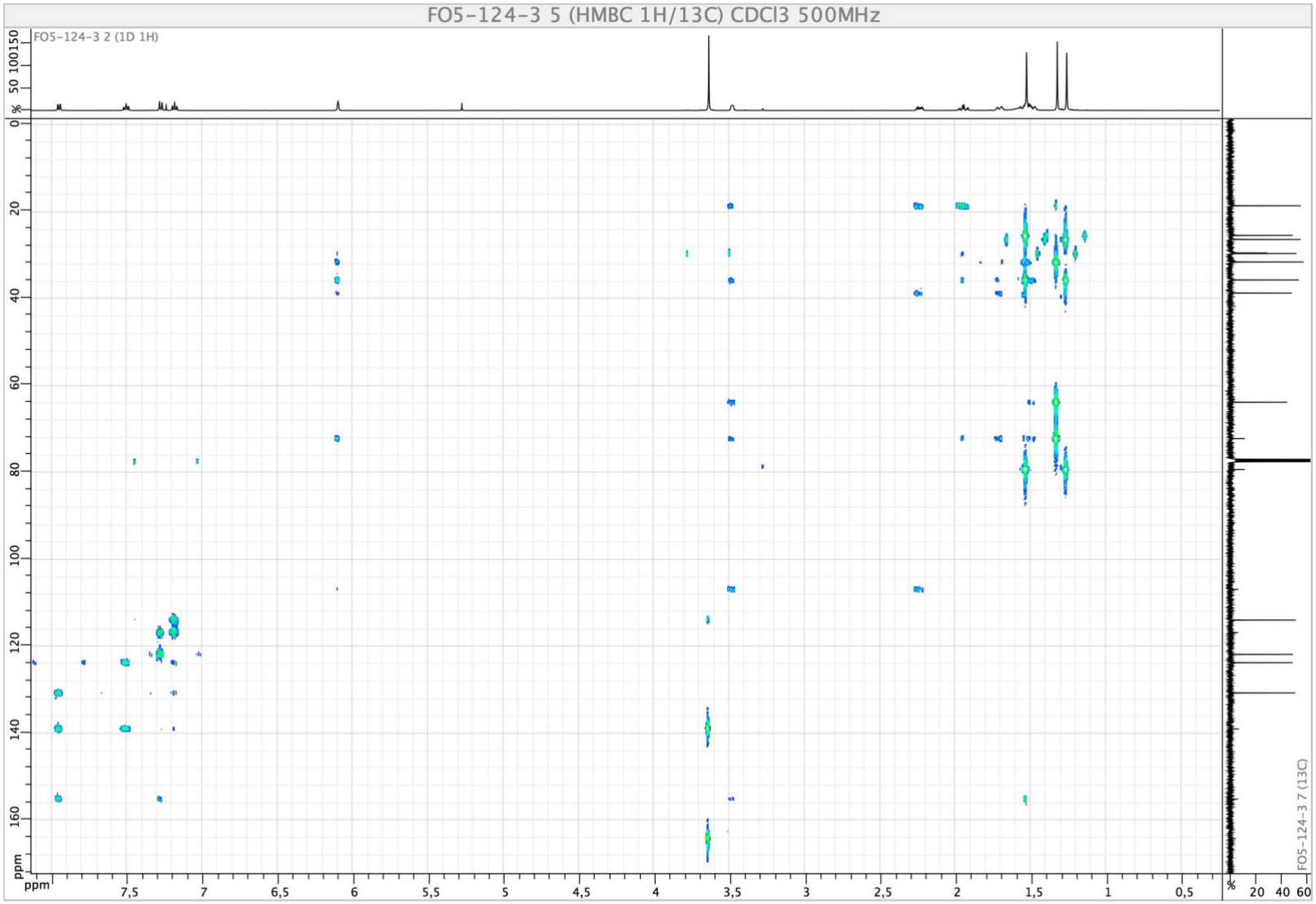
^{13}C NMR spectrum of **24** in $CDCl_3$ at 125 MHz.



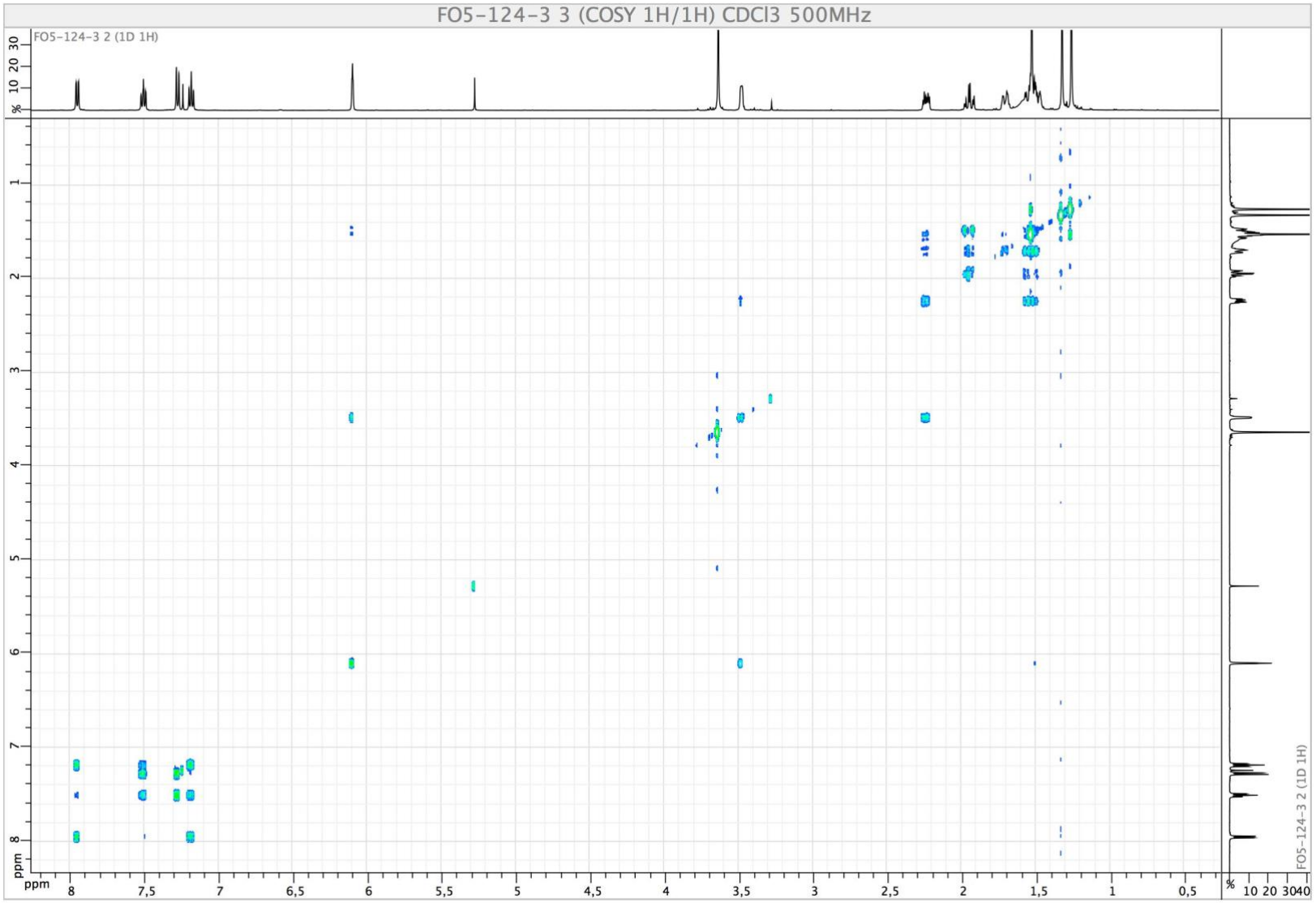
HSQC spectrum (500 MHz, 125 MHz) of **24** in $CDCl_3$.



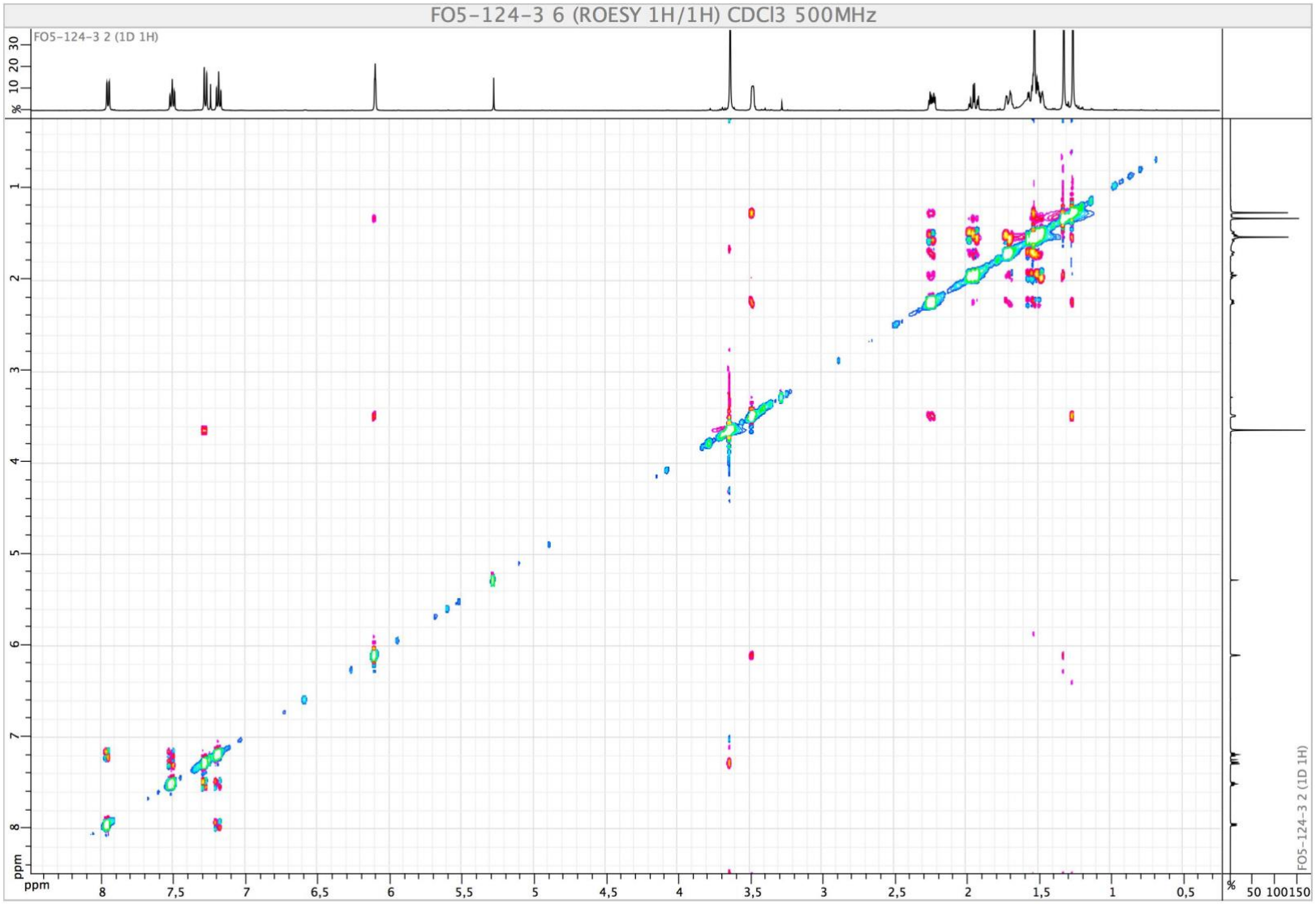
HMBC spectrum (500 MHz, 125 Hz) of **24** in $CDCl_3$.



COSY spectrum (500 MHz) of **24** in $CDCl_3$.



ROESY spectrum (500 MHz) of **24** in $CDCl_3$.



HRESIMS spectrum (TOF) of **24**.

Elemental Composition Report

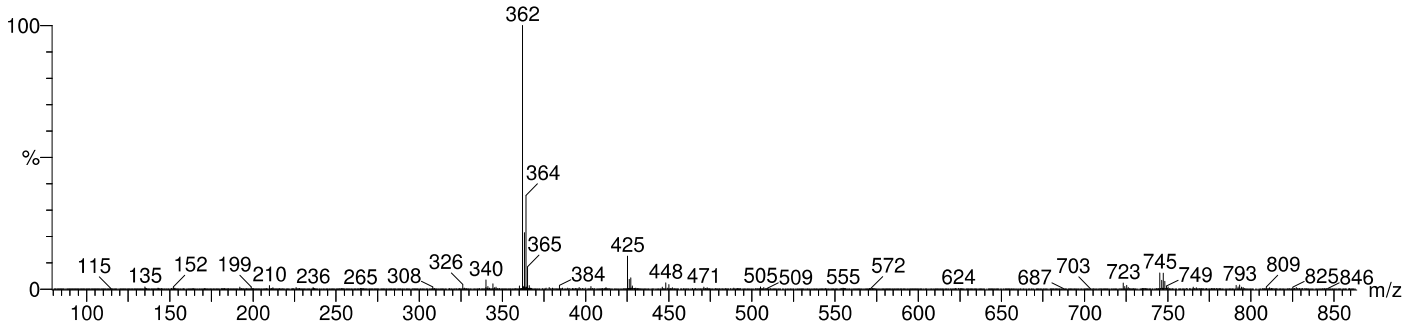
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
968 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-5 O: 0-200 Cl: 0-2

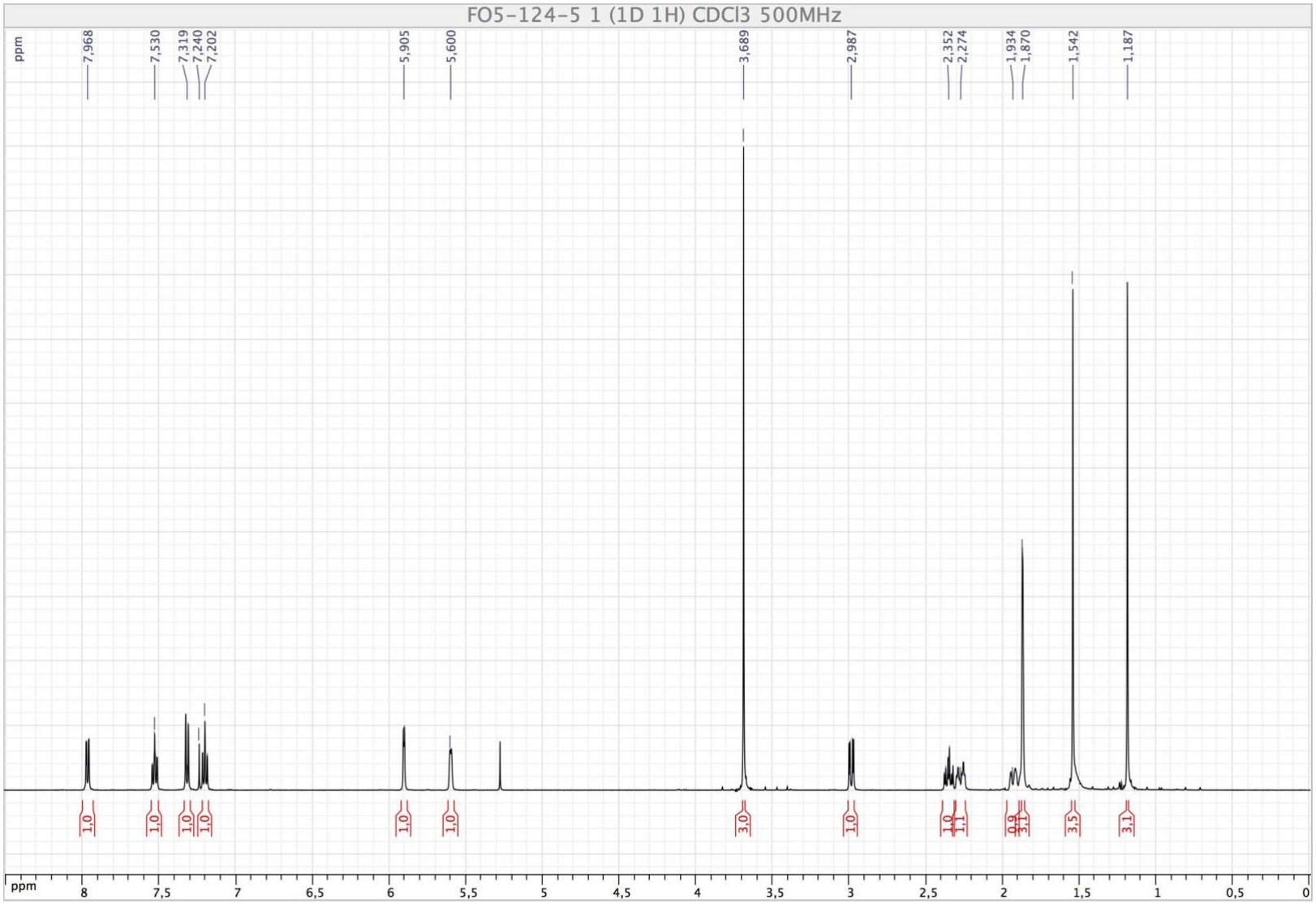
GUERITTE_olivon177-2 596 (2.776)

1: TOF MS ES+
2.51e+004

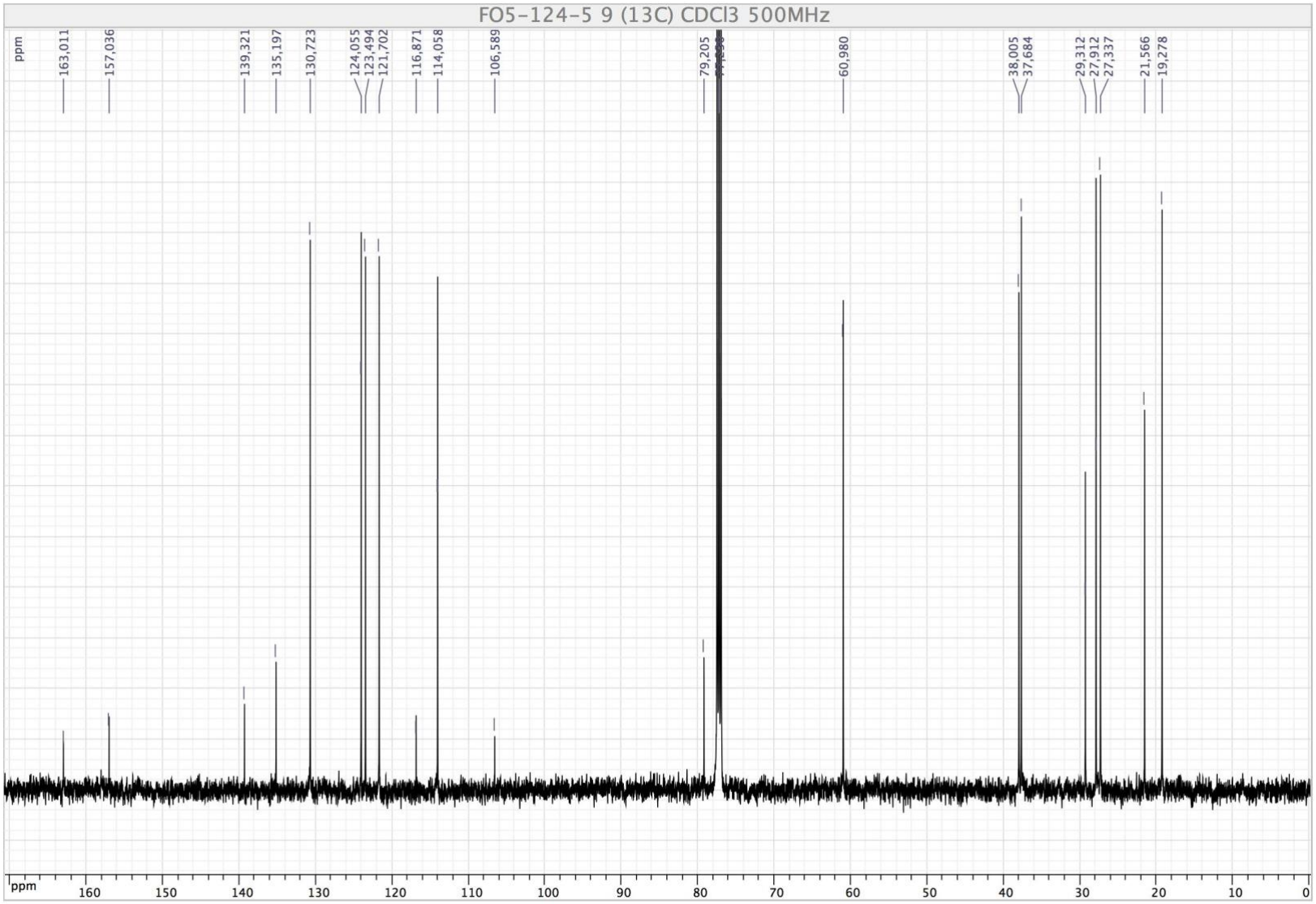


Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
362.1544	362.1523	2.1	5.8	8.5	337.8	0.0	C20 H25 N O3 Cl
	362.1582	-3.8	-10.5	-0.5	343.6	5.8	C13 H29 N O8 Cl
	362.1514	3.0	8.3	4.5	347.7	9.9	C15 H26 N5 O Cl2
	362.1501	4.3	11.9	-0.5	348.9	11.1	C14 H30 N O5 Cl2
	362.1523	2.1	5.8	0.5	354.5	16.7	C9 H24 N5 O10
	362.1563	-1.9	-5.2	4.5	354.7	16.8	C14 H24 N3 O8
	362.1505	3.9	10.8	13.5	355.0	17.1	C21 H20 N3 O3
	362.1545	-0.1	-0.3	17.5	355.3	17.5	C26 H20 N O

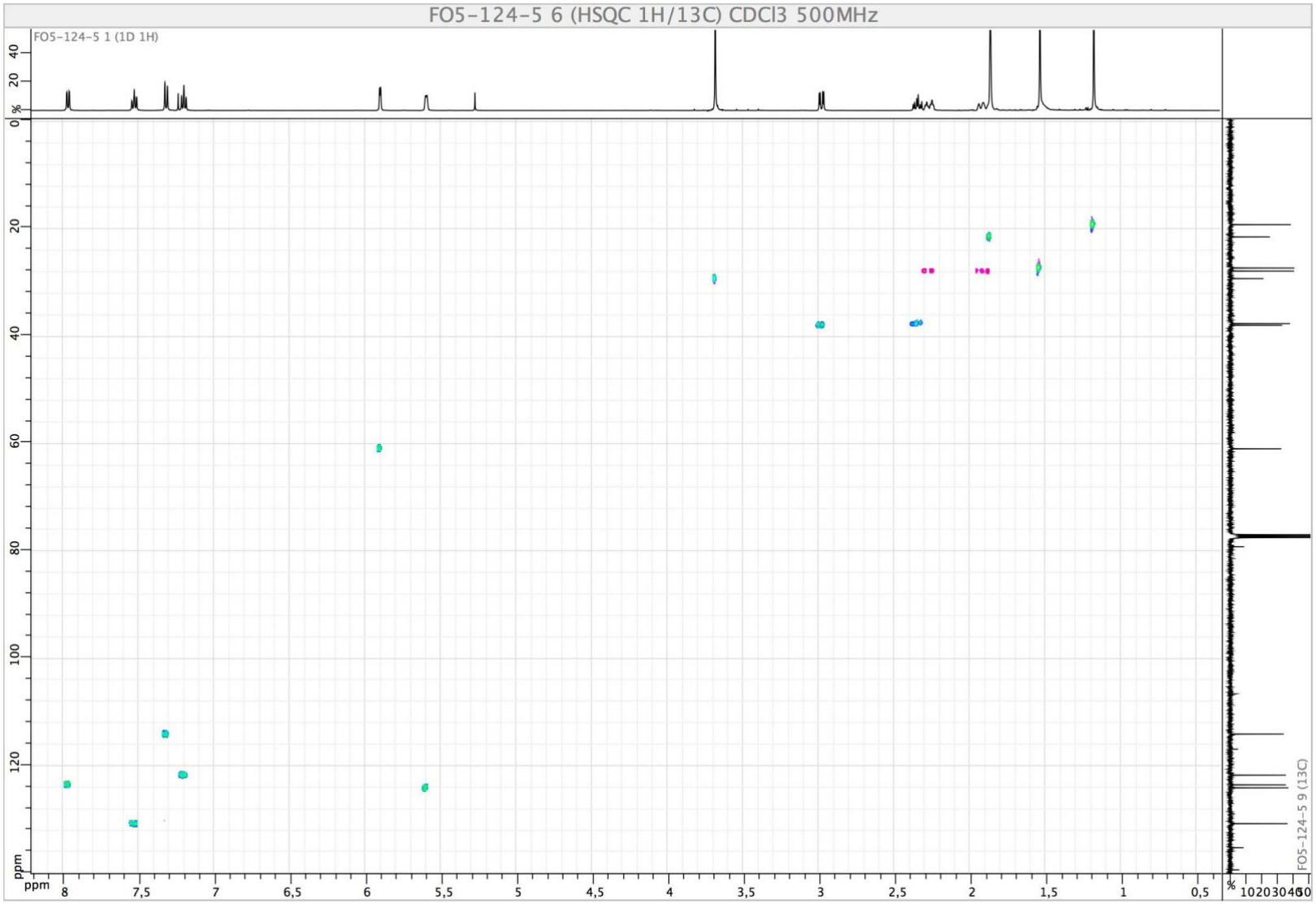
^{1}H NMR spectrum of **26** in $CDCl_3$ at 600 MHz.



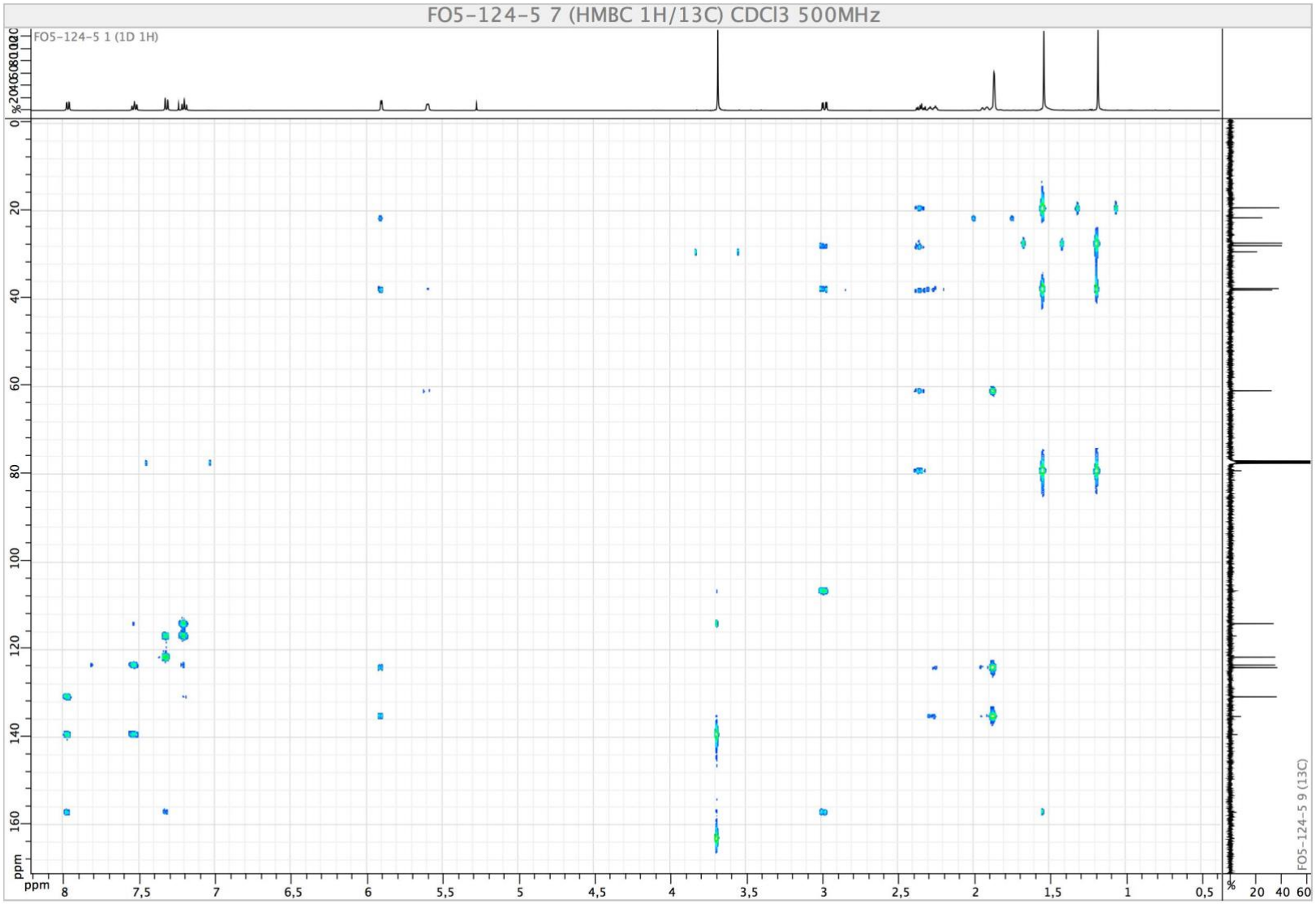
^{13}C NMR spectrum of **26** in $CDCl_3$ at 150 MHz.



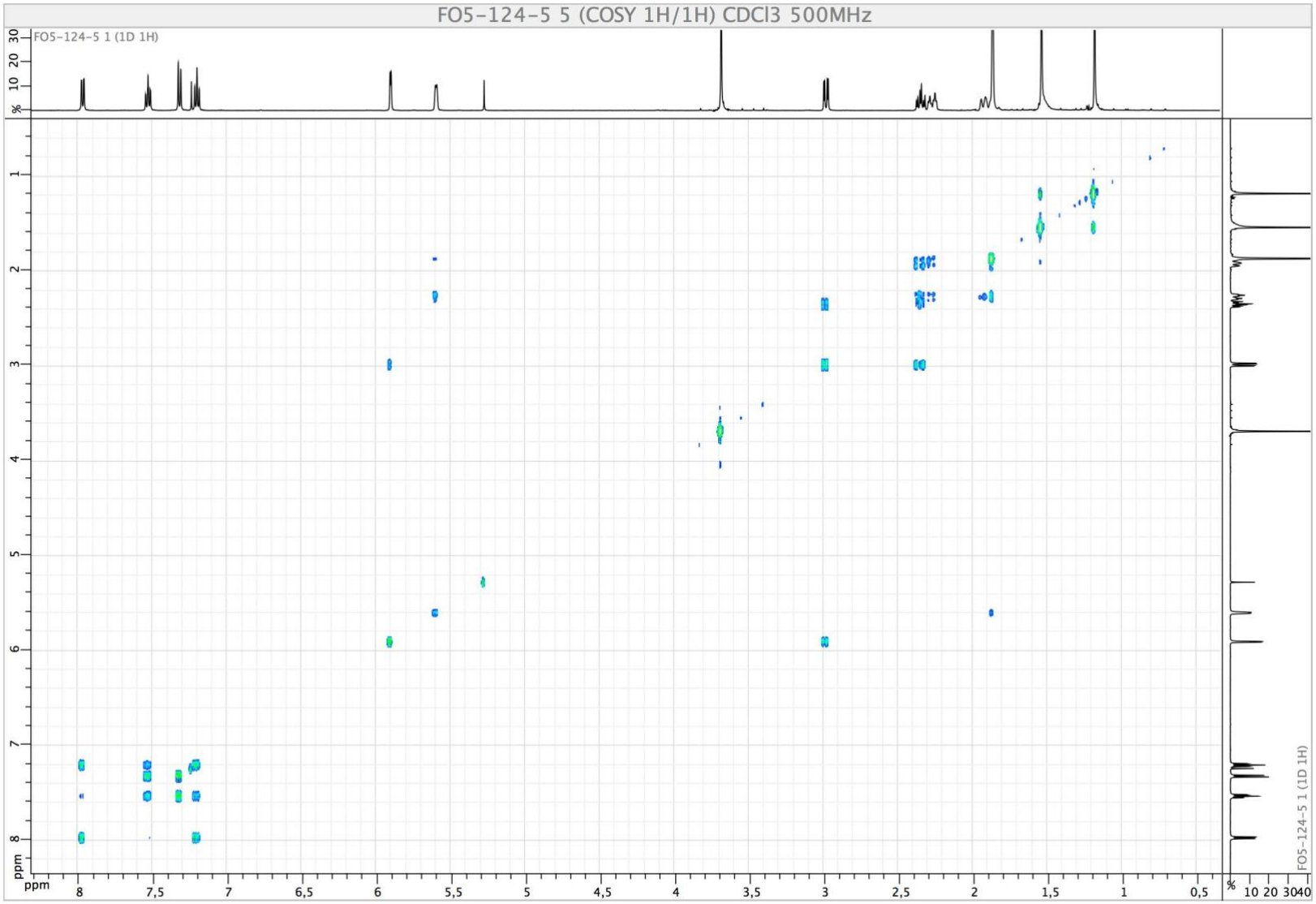
HSQC spectrum (600 MHz, 150 MHz) of **26** in $CDCl_3$.



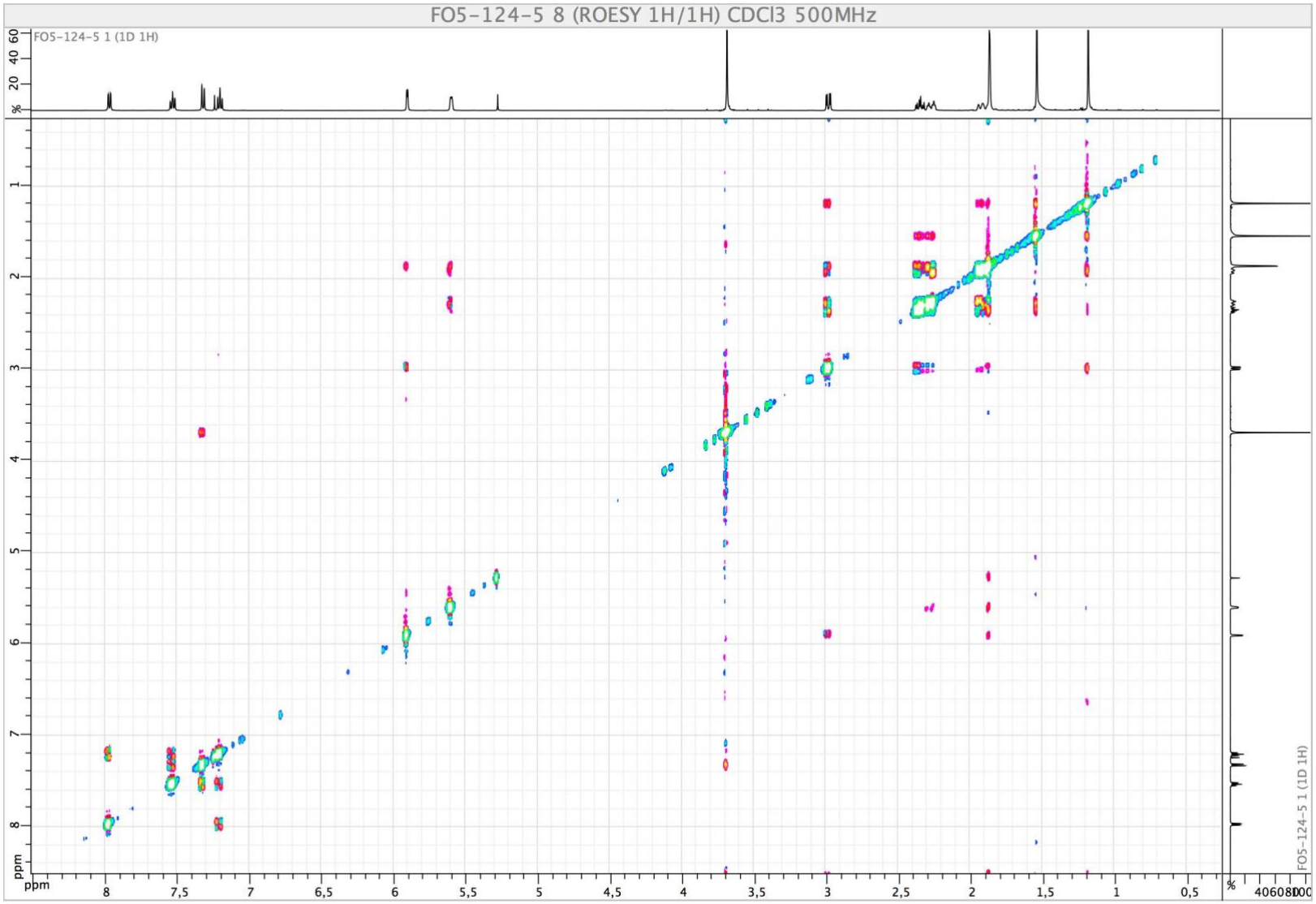
HMBC spectrum (600 MHz, 150 MHz) of **26** in $CDCl_3$.



COSY spectrum (600 MHz) of **26** in $CDCl_3$.



ROESY spectrum (600 MHz) of **26** in $CDCl_3$.



HRESIMS spectrum (TOF) of **26**.

Elemental Composition Report

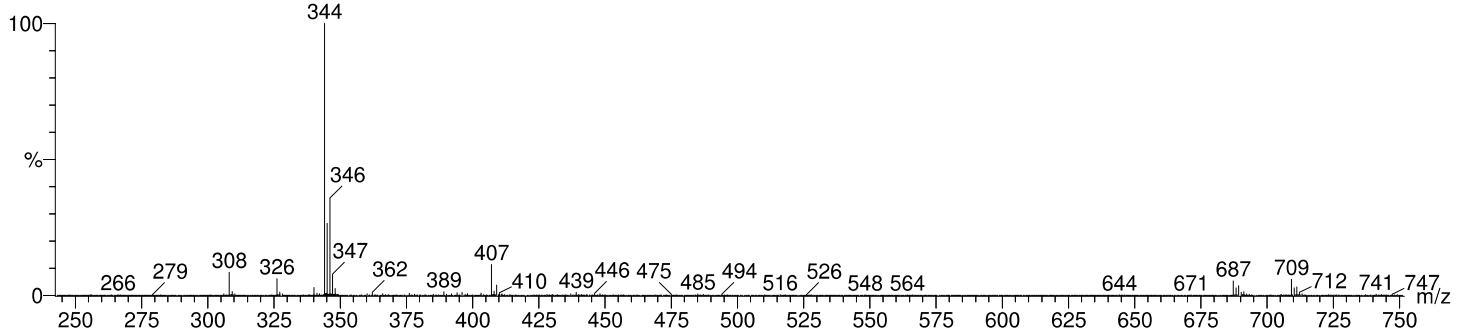
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
880 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-5 O: 0-200 Cl: 0-2

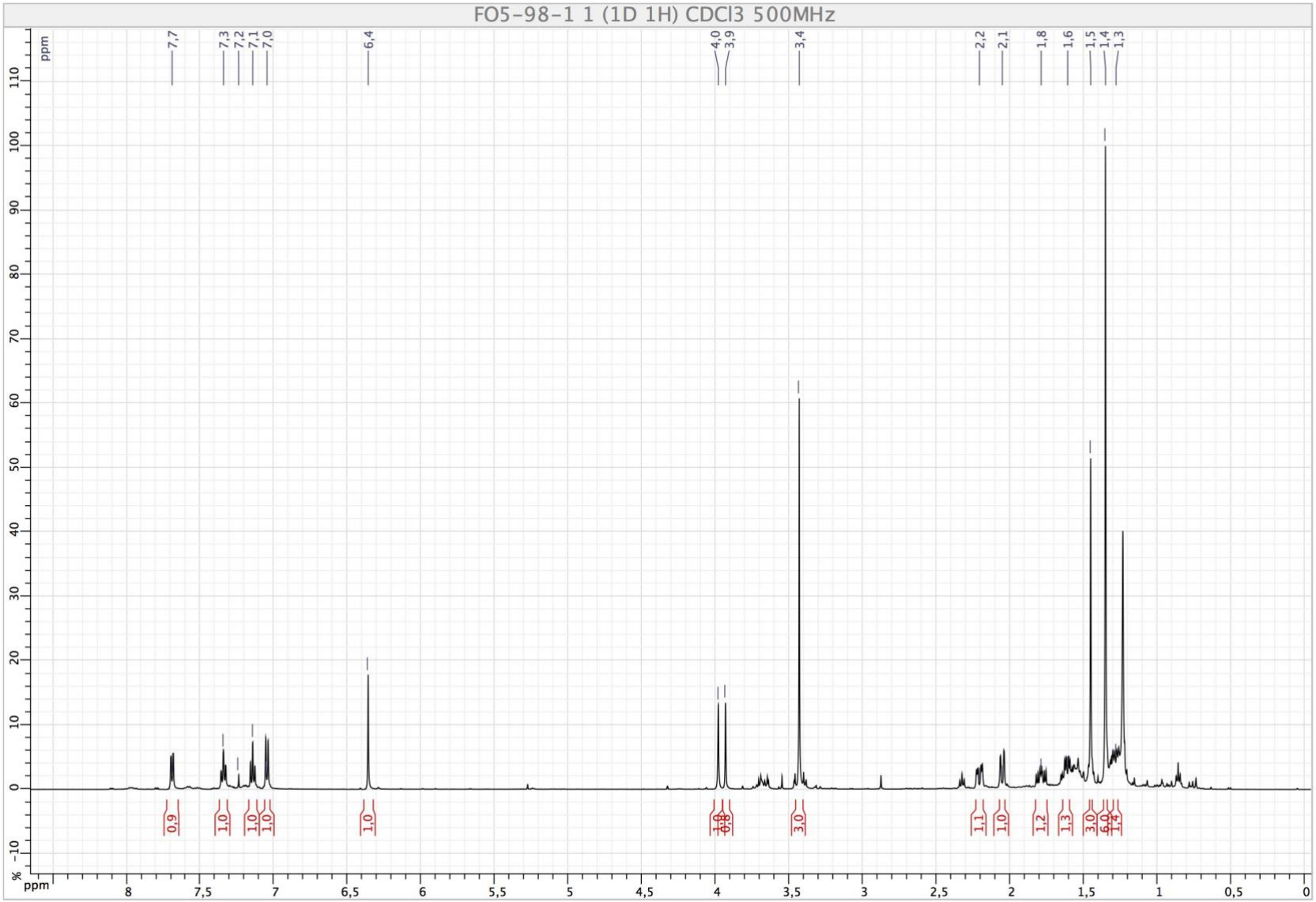
GUERITTE_olivon178-2 21 (0.572)

1: TOF MS ES+
2.80e+004

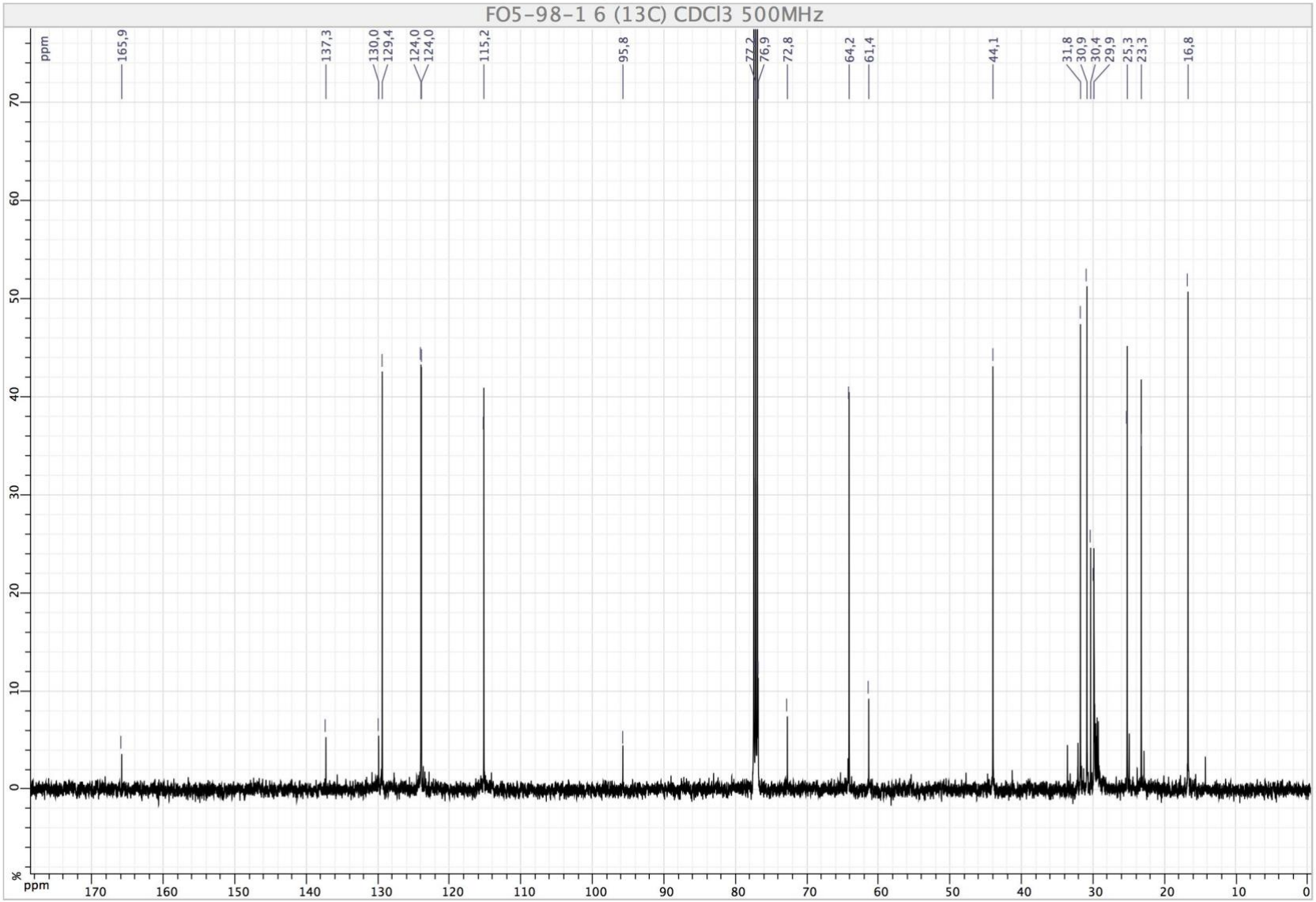


Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
344.1436	344.1417	1.9	5.5	9.5	271.9	0.0	C20 H23 N O2 Cl
	344.1476	-4.0	-11.6	0.5	277.5	5.7	C13 H27 N O7 Cl
	344.1409	2.7	7.8	5.5	280.3	8.5	C15 H24 N5 Cl2
	344.1395	4.1	11.9	0.5	281.2	9.3	C14 H28 N O4 Cl2
	344.1418	1.8	5.2	1.5	286.2	14.3	C9 H22 N5 O9
	344.1458	-2.2	-6.4	5.5	286.3	14.4	C14 H22 N3 O7
	344.1399	3.7	10.8	14.5	286.5	14.6	C21 H18 N3 O2
	344.1439	-0.3	-0.9	18.5	286.8	14.9	C26 H18 N

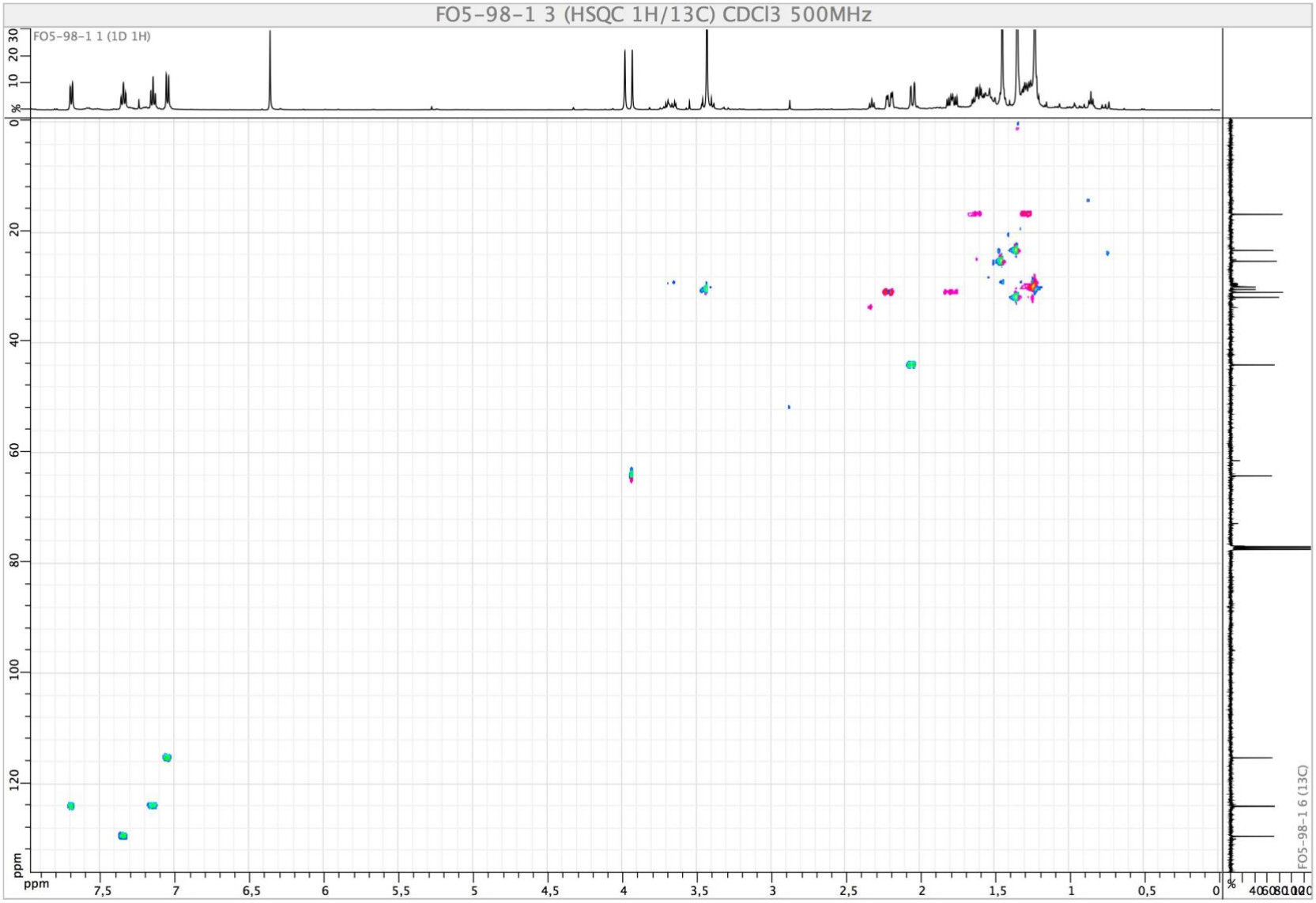
^{1}H NMR spectrum of **27** in $CDCl_3$ at 500 MHz.



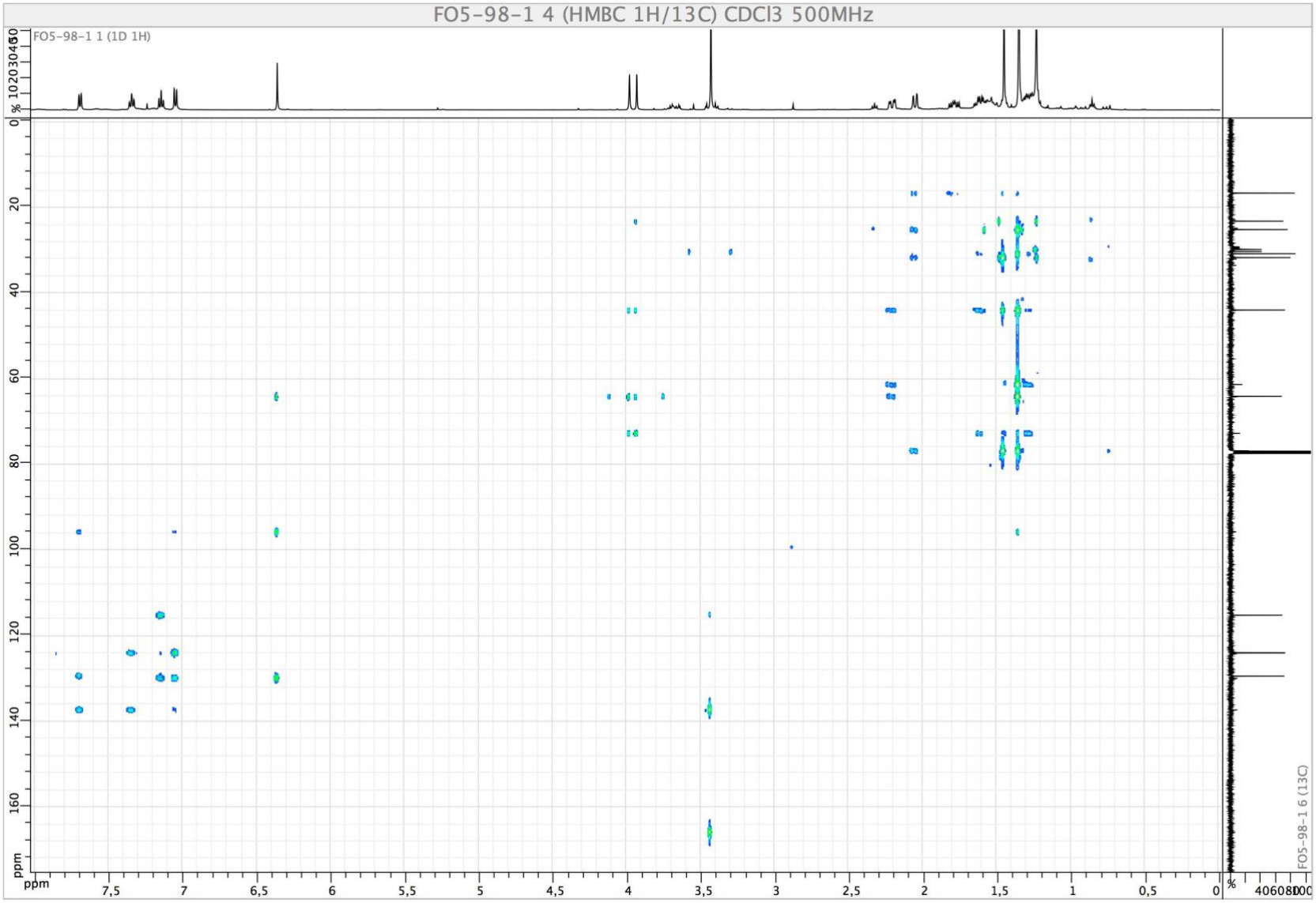
^{13}C NMR spectrum of **27** in $CDCl_3$ at 125 MHz.



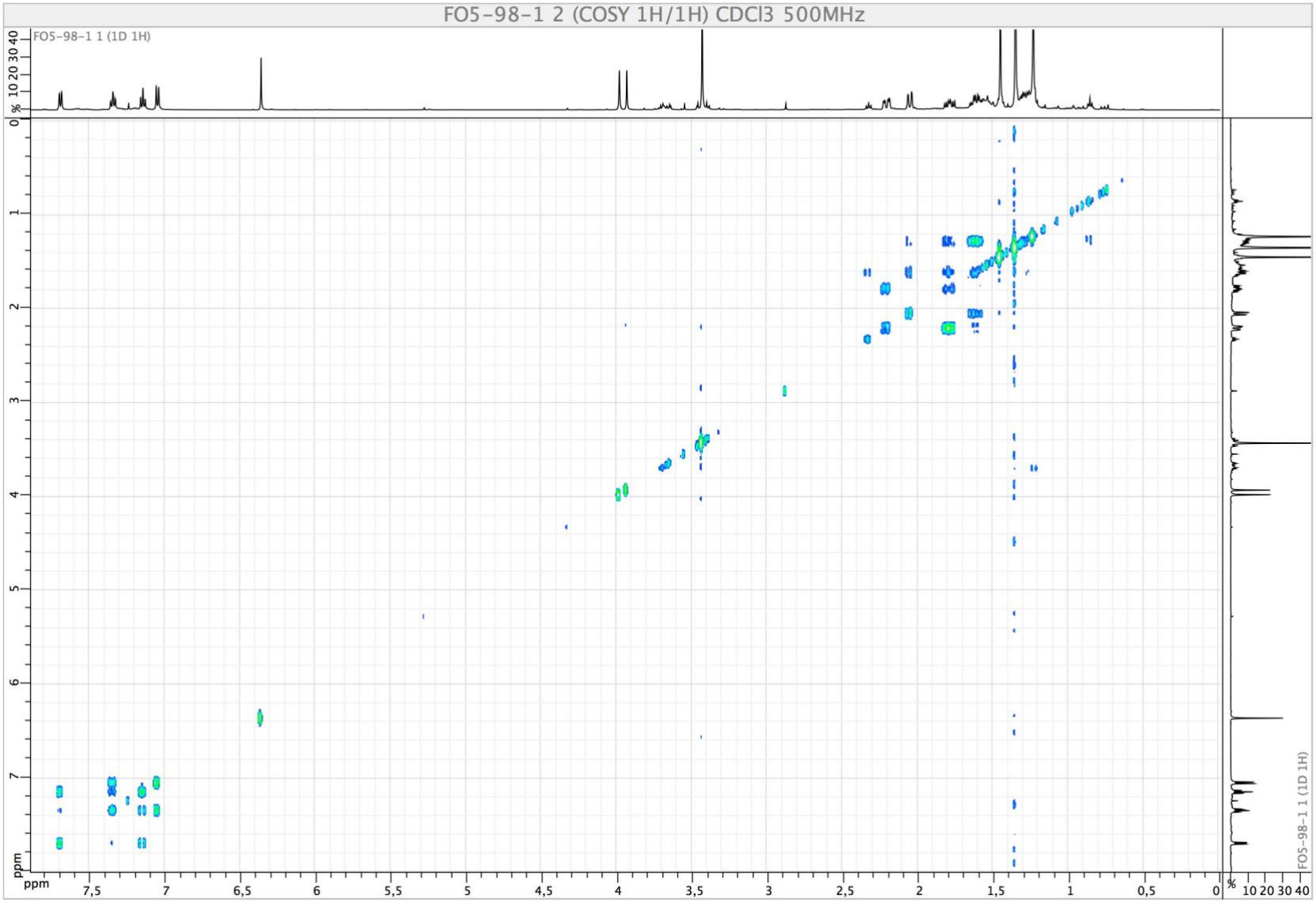
HSQC spectrum (500 MHz, 125 MHz) of **27** in $CDCl_3$.



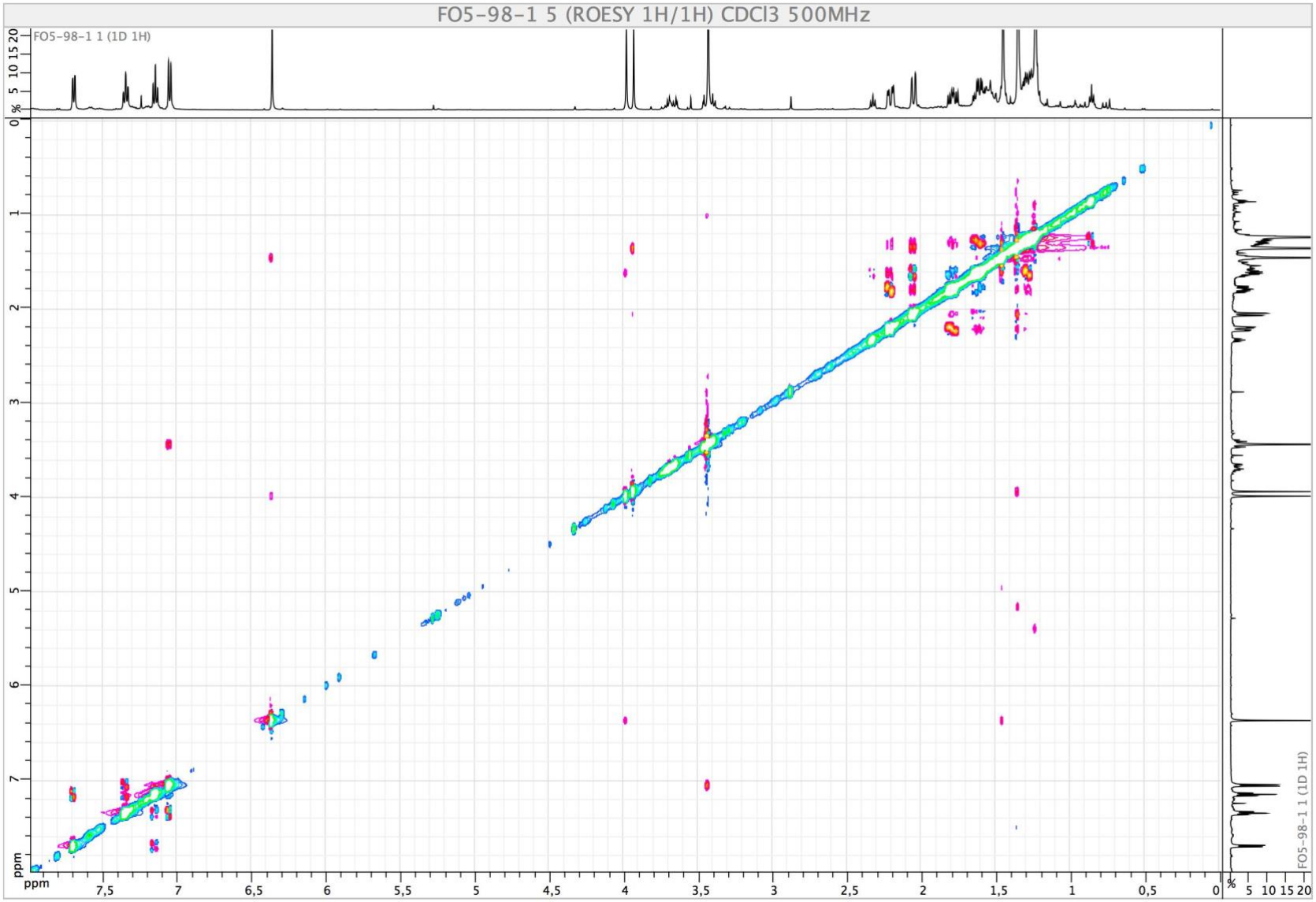
HMBC spectrum (500 MHz, 125 Hz) of **27** in $CDCl_3$.



COSY spectrum (500 MHz) of **27** in $CDCl_3$.



ROESY spectrum (500 MHz) of **27** in $CDCl_3$.



HRESIMS spectrum (TOF) of **27**.

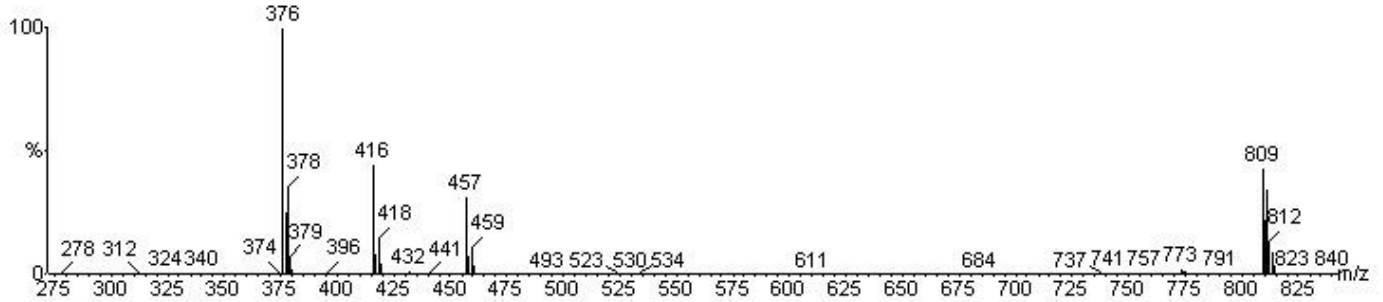
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1216 formula(e) evaluated with 8 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-3 O: 0-200 Cl: 0-8

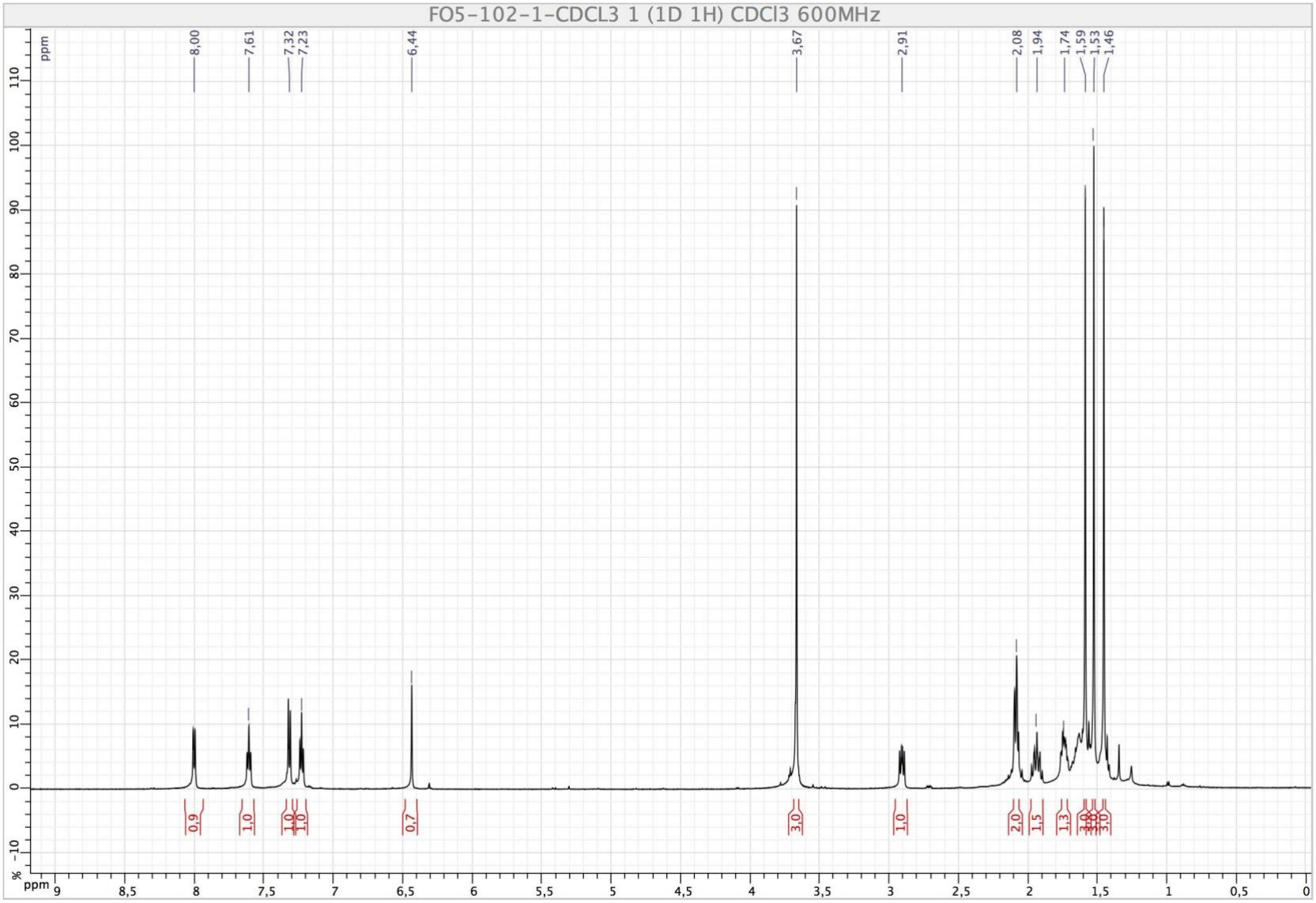
GUERITTE_olivon162-1 544 (2.571)

1: TOF MS ES+
2.36e+004

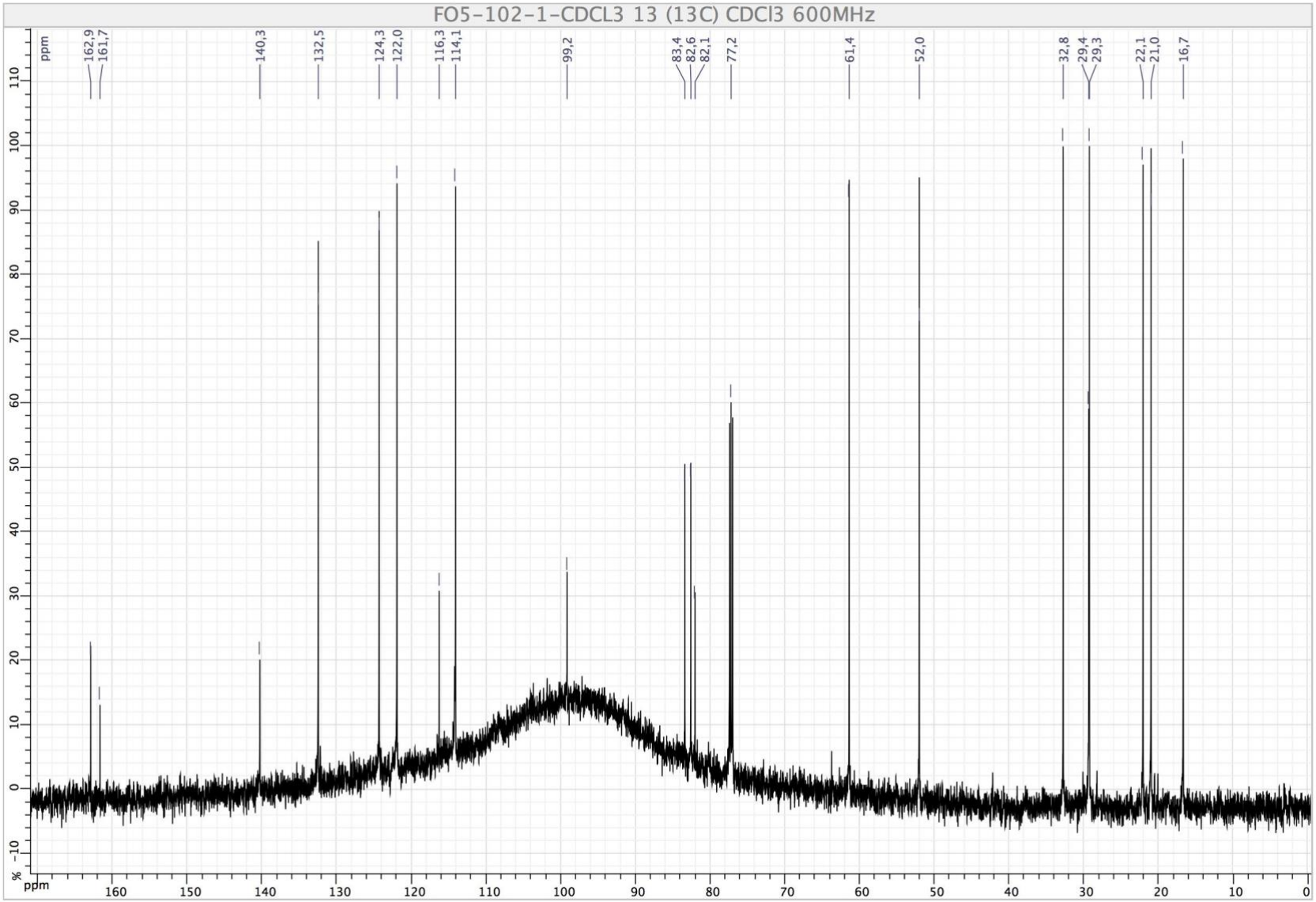


Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
376.1315	376.1316	-0.1	-0.3	9.5	332.8	0.0	C20 H23 N 04 Cl
	376.1325	-1.0	-2.7	0.5	344.7	11.9	C14 H29 N3 02 C13
	376.1297	1.8	4.8	14.5	348.1	15.3	C21 H18 N3 04
	376.1294	2.1	5.6	0.5	343.0	10.2	C14 H28 N 06 C12
	376.1338	-2.3	-6.1	18.5	348.3	15.5	C26 H18 N 02
	376.1347	-3.2	-8.5	9.5	342.5	9.7	C20 H24 N3 C12
	376.1275	4.0	10.6	5.5	338.5	5.7	C15 H23 N3 06 Cl
	376.1356	-4.1	-10.9	5.5	348.0	15.2	C14 H22 N3 09

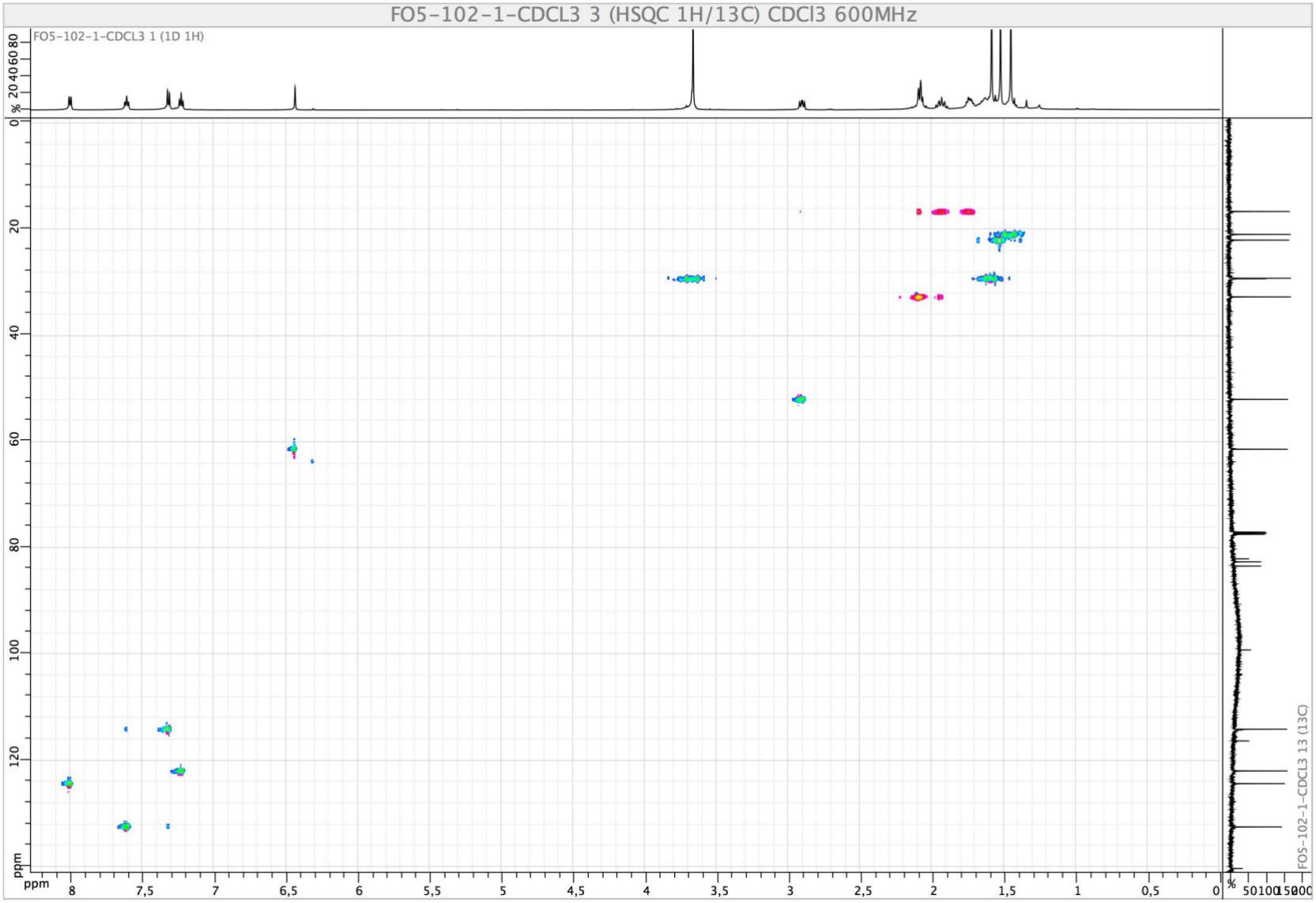
^{1}H NMR spectrum of **28** in $CDCl_3$ at 600 MHz.



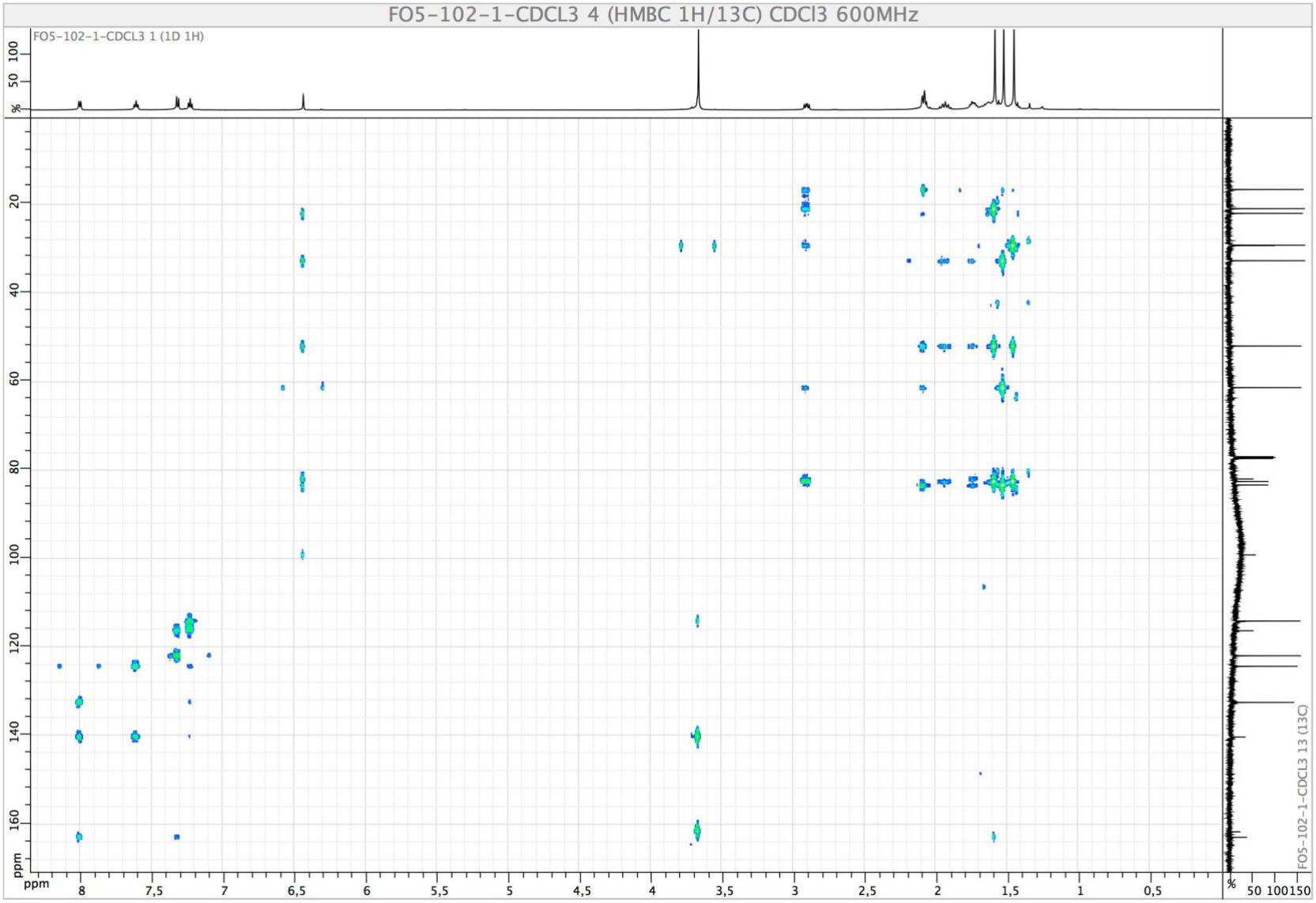
^{13}C NMR spectrum of **28** in $CDCl_3$ at 150 MHz.



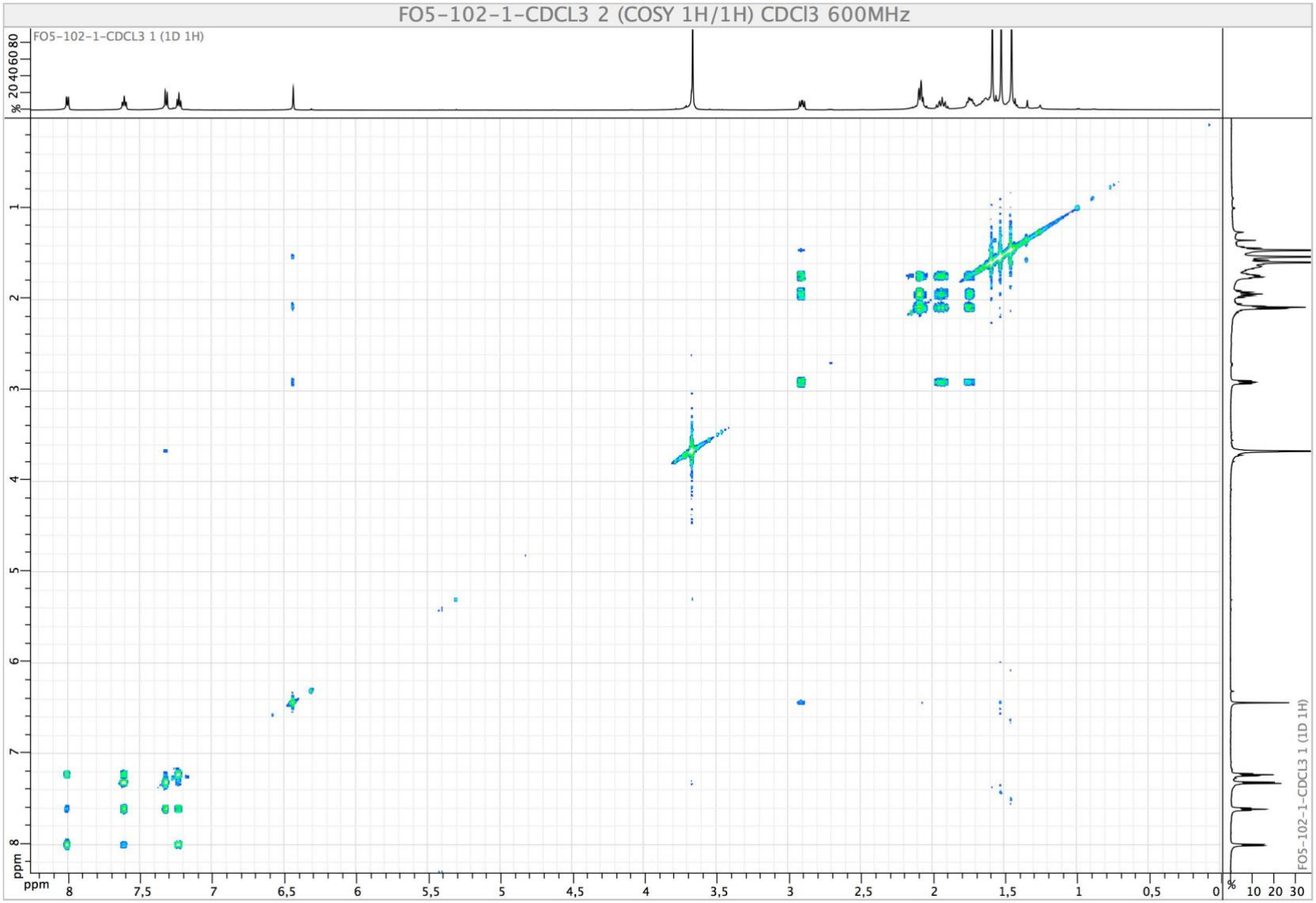
HSQC spectrum (600 MHz, 150 MHz) of **28** in $CDCl_3$.



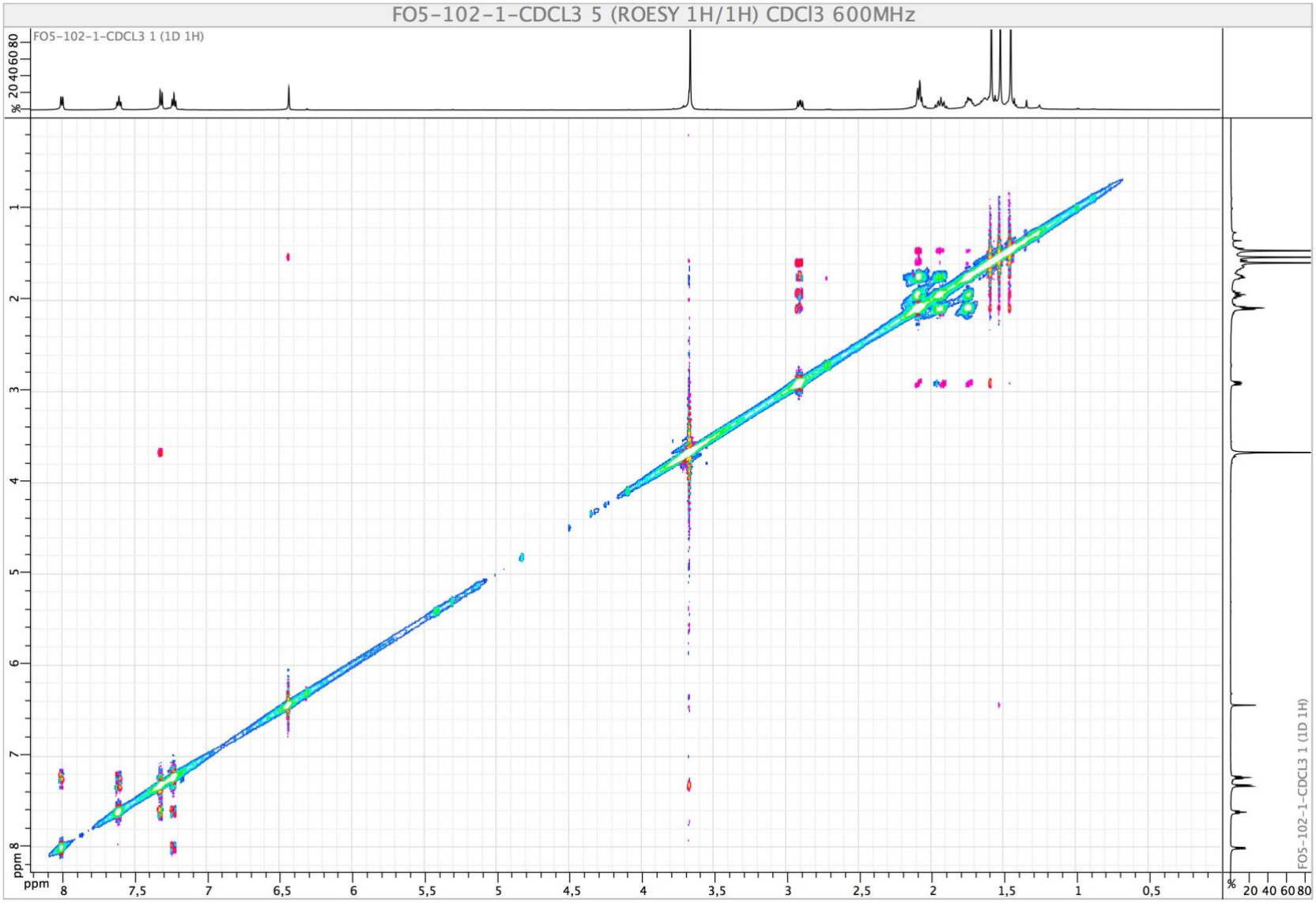
HMBC spectrum (600 MHz, 150 MHz) of **28** in $CDCl_3$.



COSY spectrum (600 MHz) of **28** in $CDCl_3$.



ROESY spectrum (600 MHz) of **28** in $CDCl_3$.



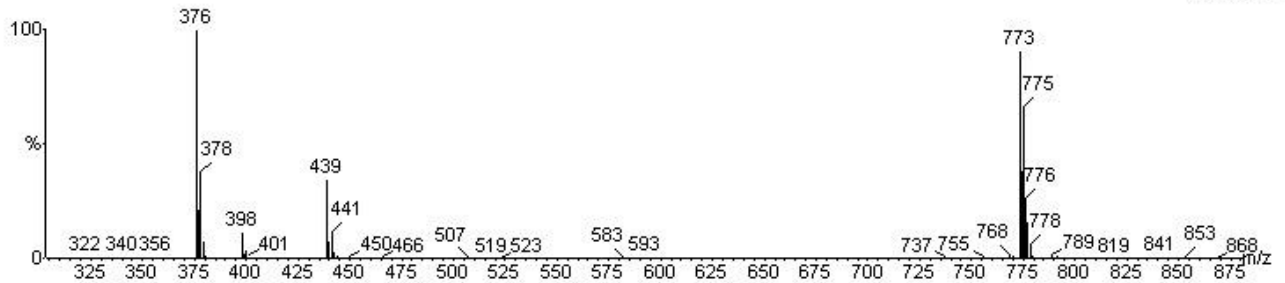
HRESIMS spectrum (TOF) of **28**.

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1711 formula(e) evaluated with 12 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-5 O: 0-200 Cl: 0-8

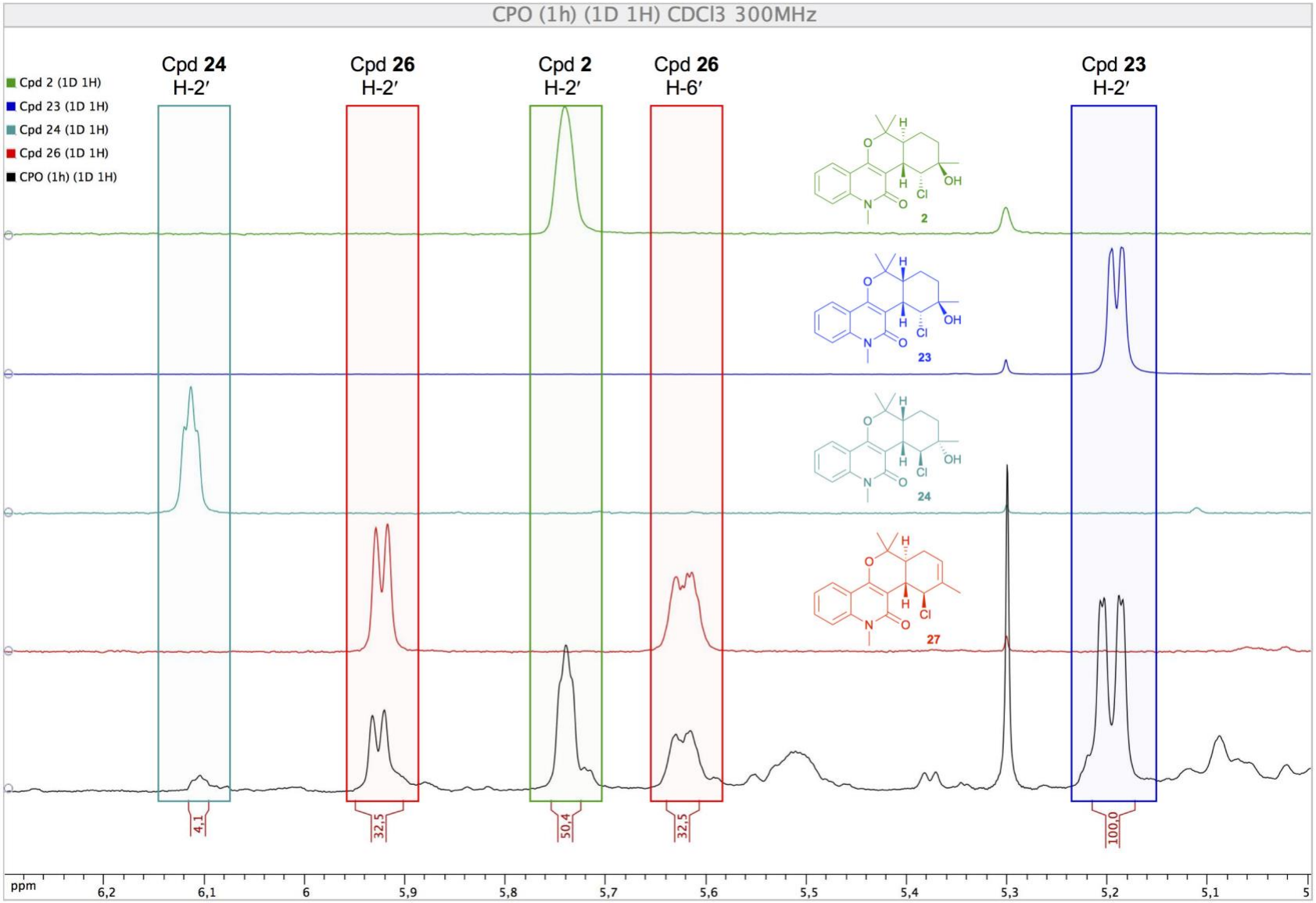
GUERITTE_olivon162-1 620 (2.906)

1: TOF MS ES+
2.27e+004

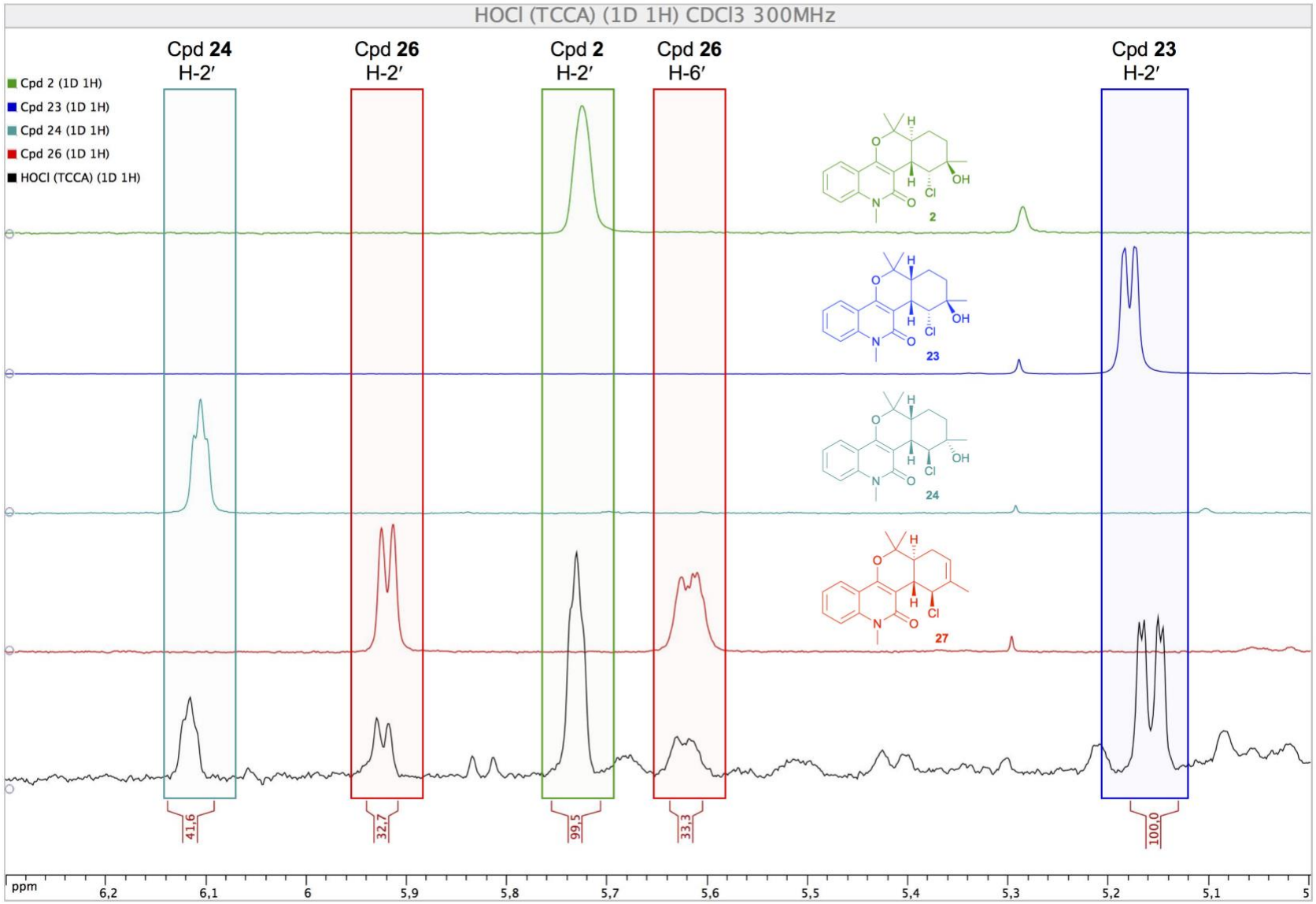


Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
376.1319	376.1316	0.3	0.8	9.5	315.6	0.1	C20 H23 N 04 Cl
	376.1275	4.4	11.7	5.5	318.2	2.7	C15 H23 N3 06 Cl
	376.1329	-1.0	-2.7	14.5	318.6	3.1	C21 H19 N5 Cl
	376.1347	-2.8	-7.4	9.5	324.1	8.6	C20 H24 N3 Cl2
	376.1307	1.2	3.2	5.5	324.7	9.3	C15 H24 N5 02 Cl2
	376.1294	2.5	6.6	0.5	324.8	9.3	C14 H28 N 06 Cl2
	376.1325	-0.6	-1.6	0.5	326.6	11.2	C14 H29 N3 02 Cl3
	376.1366	-4.7	-12.5	4.5	326.8	11.3	C19 H29 N Cl3
	376.1316	0.3	0.8	1.5	331.7	16.2	C9 H22 N5 011
	376.1356	-3.7	-9.8	5.5	331.7	16.2	C14 H22 N3 09
	376.1297	2.2	5.8	14.5	332.0	16.5	C21 H18 N3 04
	376.1338	-1.9	-5.1	18.5	332.3	16.9	C26 H18 N 02

S12. ^{1}H NMR spectra of the reactional mixture from CPO (1 h) used for diastereoisomer ratios calculation in Scheme 4.



S13. ^{1}H NMR spectra of the reactional mixture from HOCl (TCCA in water, 1.5 h) used for diastereoisomer ratios calculation in Scheme 4.



S14. References.

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5. Olivon, F.; Grelier, G.; Roussi, F.; Litaudon, M.; Touboul, D., MZmine 2 Data-Preprocessing To Enhance Molecular Networking Reliability. *Anal. Chem.* **2017,** *89*, 7836-7840.
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