Chrysophaentins A-H, Antibacterial Bisdiarylbutene Macrocycles that Inhibit the Bacterial Cell Division Protein FtsZ

Alberto Plaza,[†] *Jessica L. Keffer,*[†] *Giuseppe Bifulco,*[‡] *John R. Lloyd,*[†] *and Carole A. Bewley*[†]*

[†]Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, [‡]Dipartimento di Scienze Farmaceutiche, University of Salerno, Via Ponte Don Melillo, 84084 Fisciano, Salerno, Italy.

Email caroleb@mail.nih.gov

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Complete Ref. 9e: Haydon, D. J.; Stokes, N. R.; Ure, R.; Galbraith, G.; Bennet, J. M.; Brown, D. R. Baker, P. J.; Barniyin, V. V.; Rice, D. W.; Sedelnikova, S. E.; Heal, J. R.; Sheridan, J. M.; Aiwale, S. T.; Chauhan, P. K.; Srivastava, A.; Taneja, A.; Collins, I.; Errington, J.; Czaplewski, L. G. *Science* **2008**, *321*, 1673.

Complete Ref. 19: Czaplewski, L. G.; Collins, I.; Boyd, E. A.; Brown, D.; East, S. P.; Gardiner, M.; Fletcher, R.; Haydon, D. J.; Henstock, V.; Ingram, P.; Jones, C.; Noula, C.; Kennison, L.; Rockley, C.; Rose, V.; Thomaides-Brears, H. B.; Ure, R.; Whittaker, M.; Stokes, N. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 524.

General Experimental

Optical rotations were measured with a Jasco P-2000 polarimeter, IR spectra were recorded on a Perkin Elmer FT-IR Spectrum One spectrometer, and UV spectra were recorded on an Agilent 8453 spectrophotometer. The accurate mass electrospray ionization (ESI) mass spectra were measured on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. The instrument was operated in ω-mode at a nominal resolution of 10,000 and all data was recorded in the negative ion mode. The electrospray capillary voltage was set at 2 KV and the sample cone voltage at 30 V. The desolvation temperature was

set to 275 °C and nitrogen was used as the desolvation gas with a flow rate of 300 L/h. Accurate masses were obtained using the internal reference standard method. In-source fragmentation was induced by increasing the cone voltage to 125 V.

Table S1. ^{1}H and ^{13}C NMR Data for Compound **1a** (MeOH-d_4).

	1a	
position	δ_C[a]	δ_H[b] (*J* in Hz)
1	151.9	
2	120.6	
3	125.1	7.21 s
4	145.5	
OAc-4	20.7	2.32 s
5	132.5	
6	117.6	6.48 s
7	28.8	3.28[c]
8	127.4	5.92 t (8.2)
9	135.3	
10	33.4	3.71, 3.45 br s
11	133.8	
12	121.3	6.95[c]
13	148.6	
OAc-13	20.7	2.27
14	118.1	6.96[c]
15	143.7	
OAc-15	20.2	1.91
16	143.7	

1'	152.6	
2'	122.0	
3'	125.8	7.34 s
4'	145.1	
OAc-4'	20.6	2.37
5'	134.4	
6'	117.7	6.50 s
7'	29.1	3.28[c])
8'	127.5	6.04 t (8.4)
9'	136.4	
10'	39.9	3.63 br s
11'	136.7	
12', 16'	N.O.	N.O.
13', 15'	N.O.	
OAc-13',	20.1	2.04 br s
OAc-15'		
14'	N.O.	

[a]Recorded at 125 MHz; referenced to residual CD_3OD at δ 49.15 ppm.
[b]Recorded at 500 MHz; referenced to residual CD_3OD at δ 3.31 ppm.

Table S2. ^{1}H and ^{13}C NMR Data for Compounds **2**-**4** (MeOH-d_4).

	2		**3**		**4**	
Position	δ_C [a]	δ_H [b] (*J* in Hz)	δ_C [a]	δ_H [b] (*J* in Hz)	δ_C [a]	δ_H [b] (*J* in Hz)
1	148.0		149.2		149.0	
2	120.0		108.2		108.1	
3	117.1	6.81 s	119.7	6.99 s	119.9	6.97 s
4	150.3		150.6		150.5	
5	126.8		127.3		127.2	
6	115.9	6.17 s	115.9	6.16 s	115.9	6.16 s
7	30.6	3.22 d (8.7)	30.7	3.22 d (8.7)	30.6	3.22 d (8.7)
8	127.6	5.99 t (8.7)	127.5	5.99 t (8.7)	127.5	6.00 t (8.7)
9	134.4		134.4		134.4	
10	33.5	3.39 br s	33.6	3.39 br s	33.6	3.39 br s
11	133.0		133.0		132.8	
12	107.8	6.18 d (2.8)	107.7	6.18 d (2.8)	107.9	6.17 d (2.8)
13	155.6		155.6		155.4	
14	103.8	6.30 d (2.8)	103.8	6.30 d (2.8)	103.7	6.30 d (2.8)
15	151.3		151.2		151.1	
16	135.9		135.8		135.7	
1'	149.5		148.7		149.5	
2'	109.3		121.0		109.3	
3'	120.0	7.00 s	117.2	6.84 s	119.9	7.00 s
4'	150.8		150.6		150.8	
5'	127.6		127.1		127.7	

6'	116.3	6.25 s	116.4	6.27 s	116.2	6.25 s
7'	30.4	3.28 br d (8.1)	30.4	3.28 br d (8.1)	30.4	3.28 br d (8.1)
8'	127.6	6.06 t (8.1)	127.6	6.06 t (8.1)	127.7	6.05 t (8.1)
9'	134.2		134.2		134.1	
10'	40.5	3.57 br s	40.5	3.57 br s	40.4	3.57 br s
11'	136.7		136.3		136.3	
12', 16'	108.9	6.16 br s	108.8	6.16 br s	108.9	6.16 br s
13', 15'	151.8		151.8		151.6	
14'	129.7		129.7		129.7	

[a] Recorded at 125 MHz; referenced to residual MeOH-d_4 at δ 49.1. [b] Recorded at 500 MHz; referenced to residual MeOH-d_4 at δ 3.30.

Table S3. Spectroscopic NMR Data for Chrysophaentin F (**6**) in MeOH-d_4 and DMF-d_7

	6 (MeOH-d_4)				**6** (DMF-d_7)		
Position	δ_C[a]	δ_H[b] (*J* in Hz)	HMBC[c]	ROESY[d]	δ_C[e]	δ_H[f] (*J* in Hz)	HMBC[c]
1, 1'	148.2				147.0		
2, 2'	120.4				119.0		
3, 3'	117.3	6.90 s	1, 2, 4, 5, 6, 7		116.4	7.06 s	1, 2, 4, 5
4, 4'	150.7				150.1		
OH-4, OH-4'						9.98 s	3, 4, 5
5, 5'	126.5				125.9		
6, 6'	115.1	6.42 s	1, 2, 3, 4, 5, 7	7, 8, 12	114.3	6.55	1, 2, 4, 7
7, 7'	31.0	3.35 d (8.3)	4, 5, 6, 8, 9	10	30.3	3.43 d (8.5)	4, 5, 8, 9
8, 8'	127.2	5.89 t (8.3)	5, 7, 9, 10, 11	7	126.7	6.00 t (8.5)	9
9, 9'	134.3				133.2		
10, 10'	39.8	3.54 br s	8, 9, 11, 12, 16	7, 12	38.9	3.65 br s	8, 9, 11, 12
11, 11'	137.0				135.9		
12, 16, 12', 16'	110.0	6.23 s	9, 10, 11, 12, 13, 14, 15, 16	6, 10	108.6	6.34 s	10, 11, 12, 13, 14
13, 15, 13', 15'	151.3				151.1		
OH-13, OH-15 OH-13', OH-15'						9.79	NO
14, 14'	130.0				128.8		

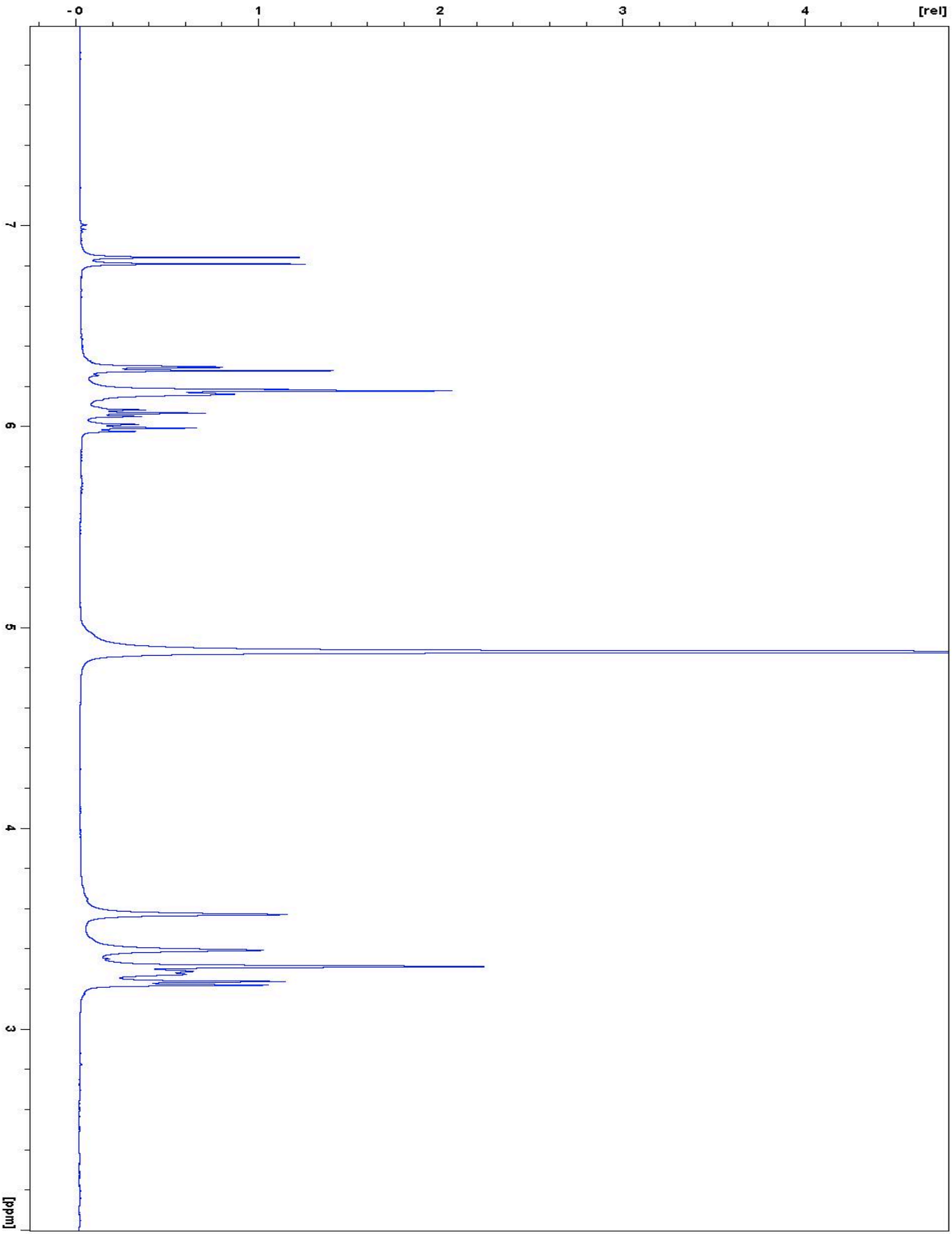
[a] Recorded at 125 MHz; referenced to residual MeOH-d_4 at δ 49.1. [b] Recorded at 500 MHz; referenced to residual MeOH-d_4 at δ 3.30. [c] Proton showing HMBC correlation to indicated carbon. [d] Proton showing ROESY correlation to indicated carbon. [e] Recorded at 125 MHz; referenced to residual DMF-d_7 at δ 34.89. [f] Recorded at 500 MHz; referenced to residual DMF-d_7 at δ 2.92.

Table S4. ^{1}H and ^{13}C NMR Data for Compounds **7** and **8** (MeOH-d_4)

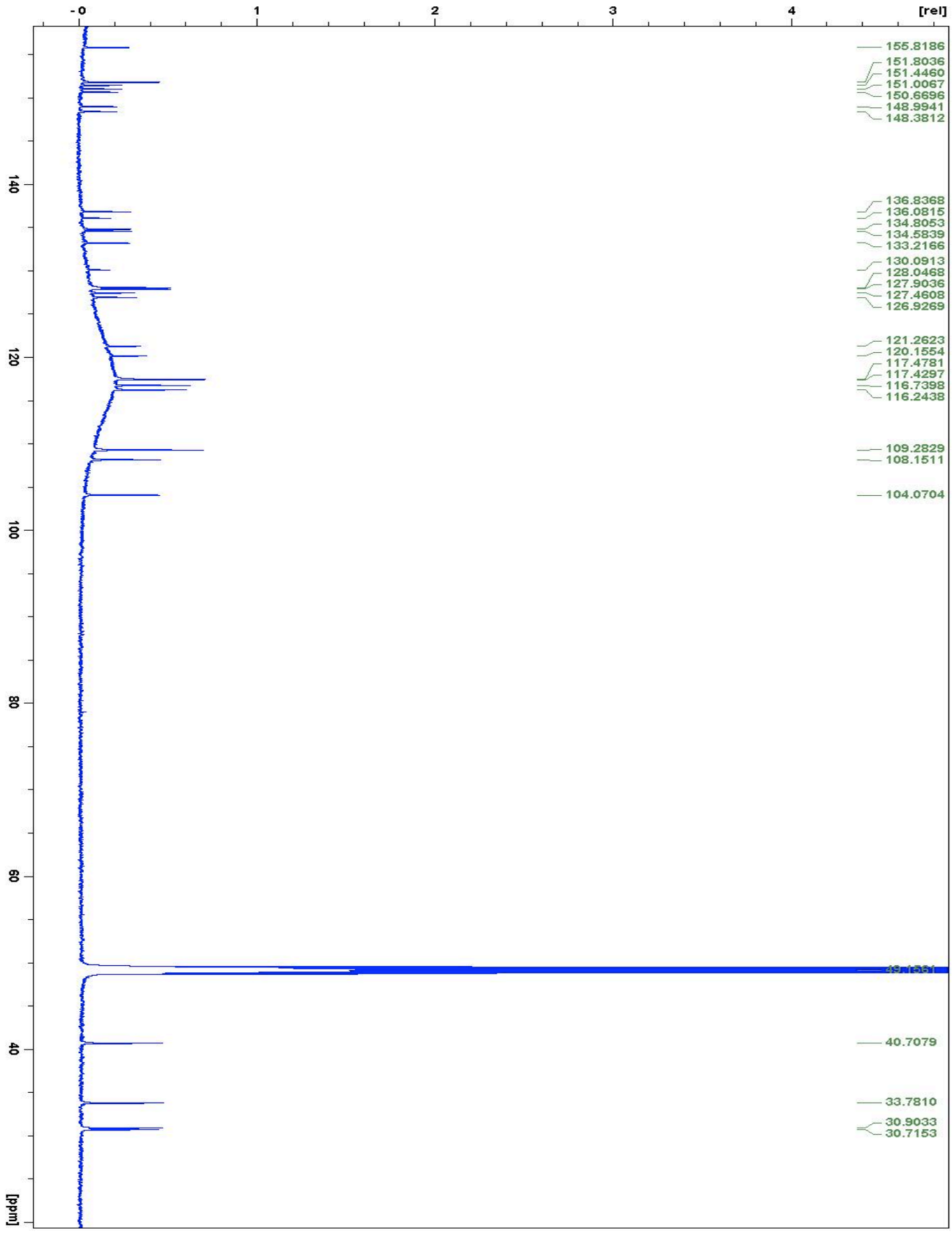
	7		**8**	
Position	δ_C [a]	δ_H [b] (*J* in Hz)	δ_C [a]	δ_H [b] (*J* in Hz)
1	148.1		147.7	
2	120.3		120.5	
3	117.3	6.90 s	117.3	6.91 s
4	150.7		151.0	
5	126.6		126.8	
6	115.1	6.42 s	115.1	6.41 s
7	31.1	3.35 d (8.0)	30.9	3.35 d (8.1)
8	127.2	5.89 t (8.0)	126.8	5.97 t (8.1)
9	134.3		134.4	
10	39.6	3.54 s	39.9	3.53 br s
11	137.0		137.1	
12, 16	110.1	6.22 s	130.1	6.21 s
13, 15	151.8		151.1	
14	130.2		130.0	
1'	149.3		148.1	
2'	108.9		120.3	
3'	120.3	7.06 s	117.3	6.90 s
4'	151.0		150.7	
5'	127.3		126.5	
6'	115.1	6.41 s	115.1	6.40 s
7'	31.1	3.34 d (8.0)	30.6	3.35 d (8.2)

8'	127.2	5.89 t (8.0)	127.8	5.89 t (8.2)
9'	134.3		133.5	
10'	39.6	3.54 s	38.6	3.89 br s
11'	137.0		135.8	
12'	110.05	6.23 s	106.3	
13'	151.2		146.1	
14'	130.0		130.7	
15'	151.2		150.0	
16'	110.0	6.23	109.1	6.22 s

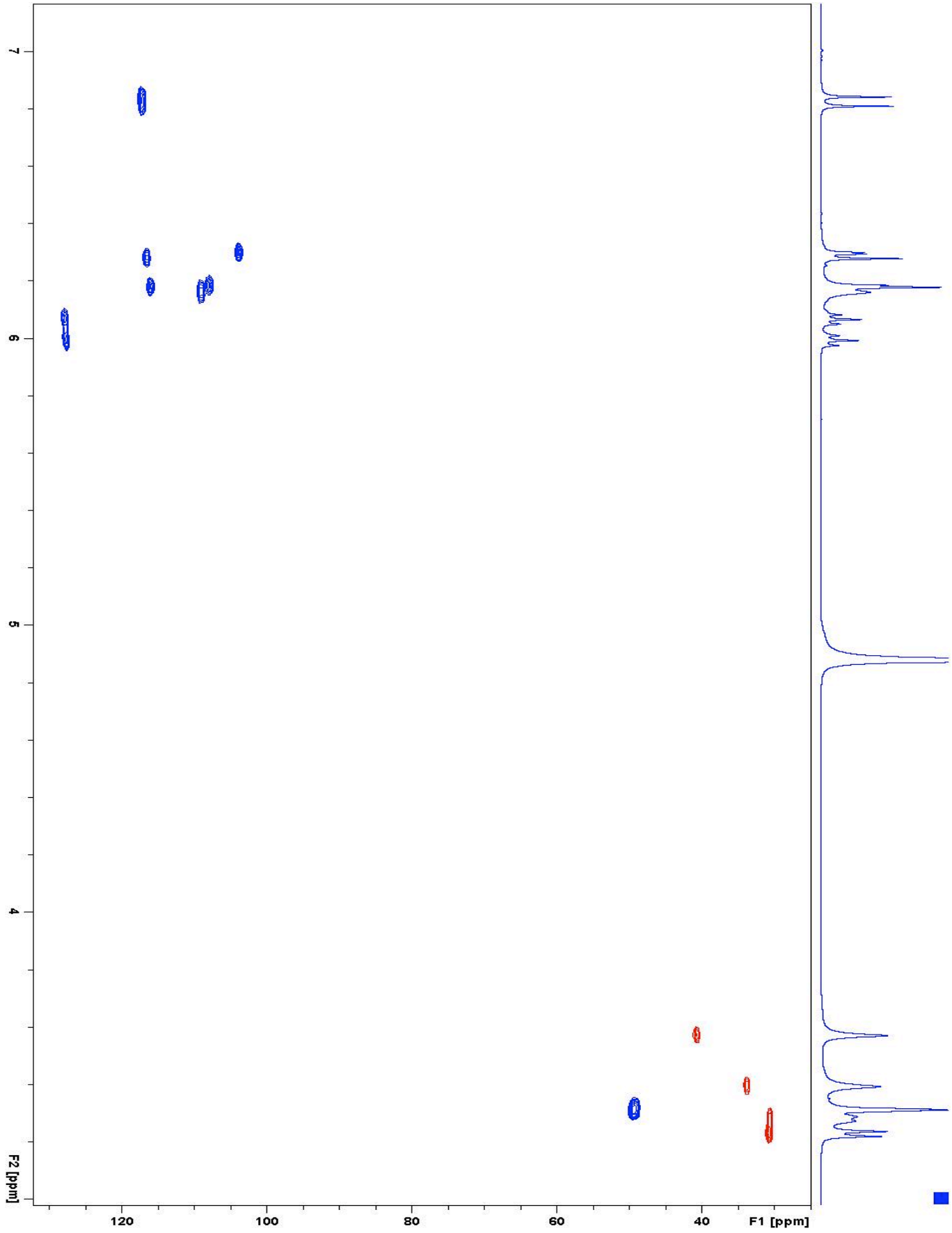
[a] Recorded at 125 MHz; referenced to residual MeOH-d_4 at δ 49.1. [b] Recorded at 500 MHz; referenced to residual MeOH-d_4 at δ 3.30.



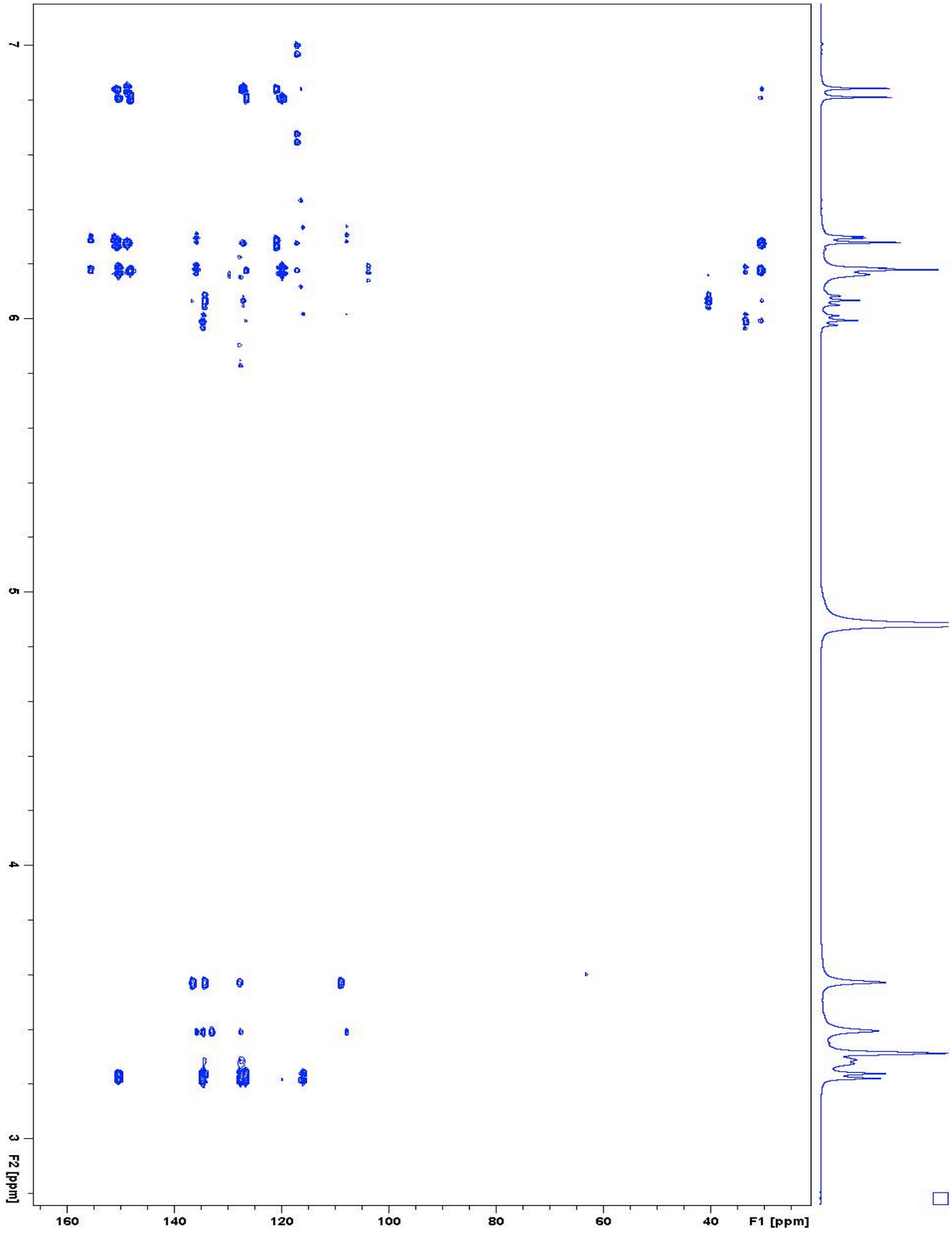
^{1}H NMR spectrum of chrysophentin A (**1**) in MeOD-d_4



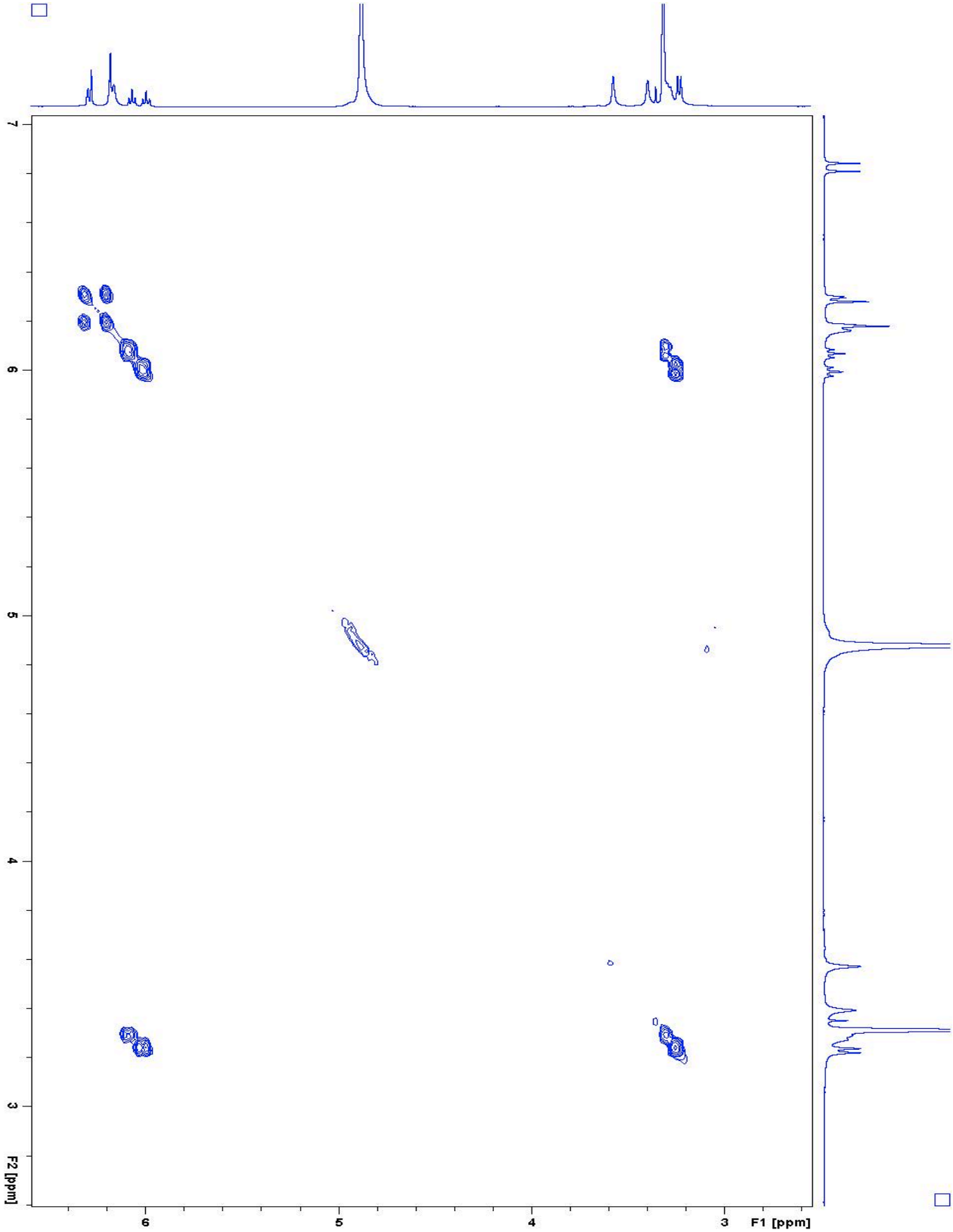
^{13}C NMR spectrum of chrysophentin A (**1**) in MeOD-d_4



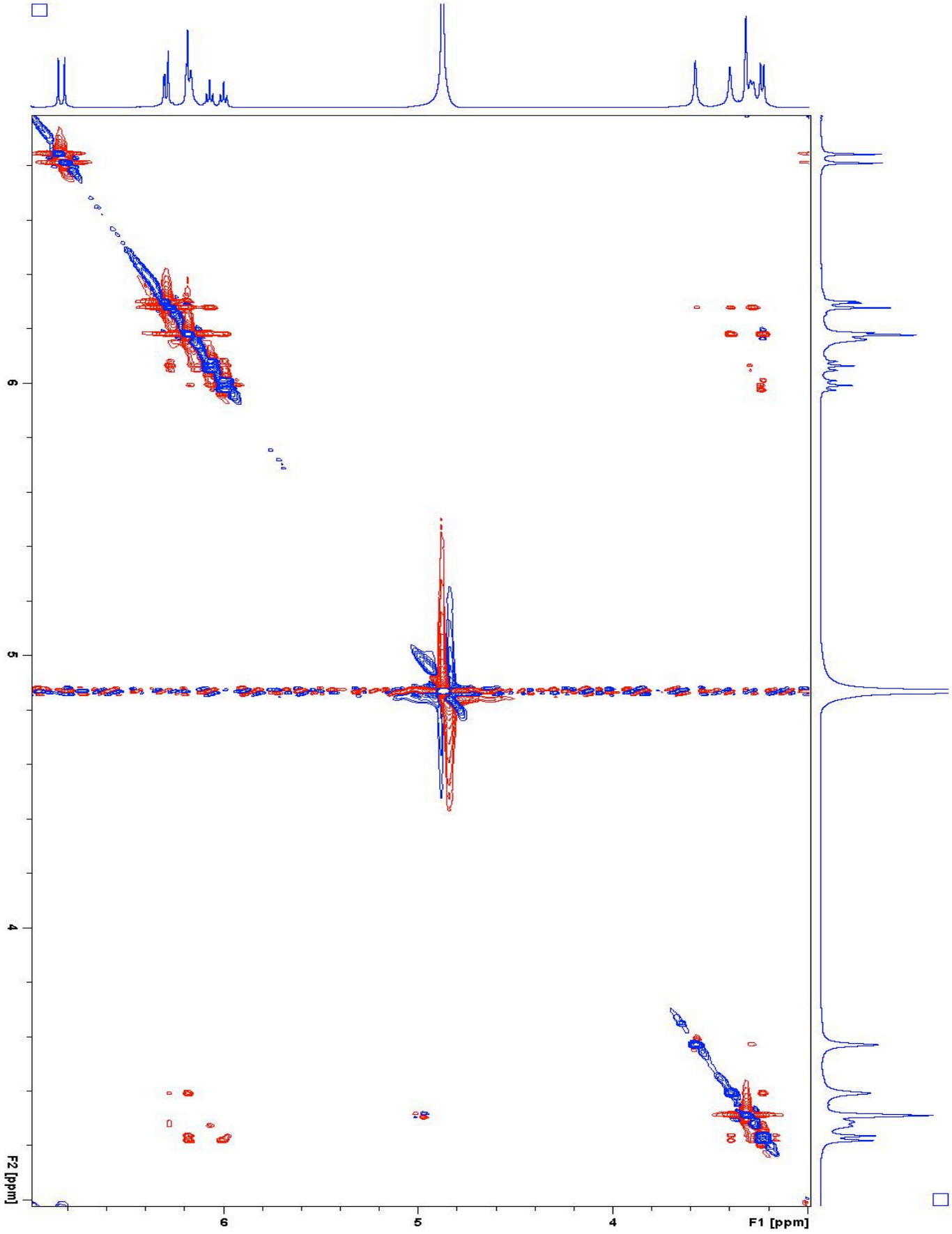
HSQC spectrum of chrysophentin A (**1**) in MeOD-d_4



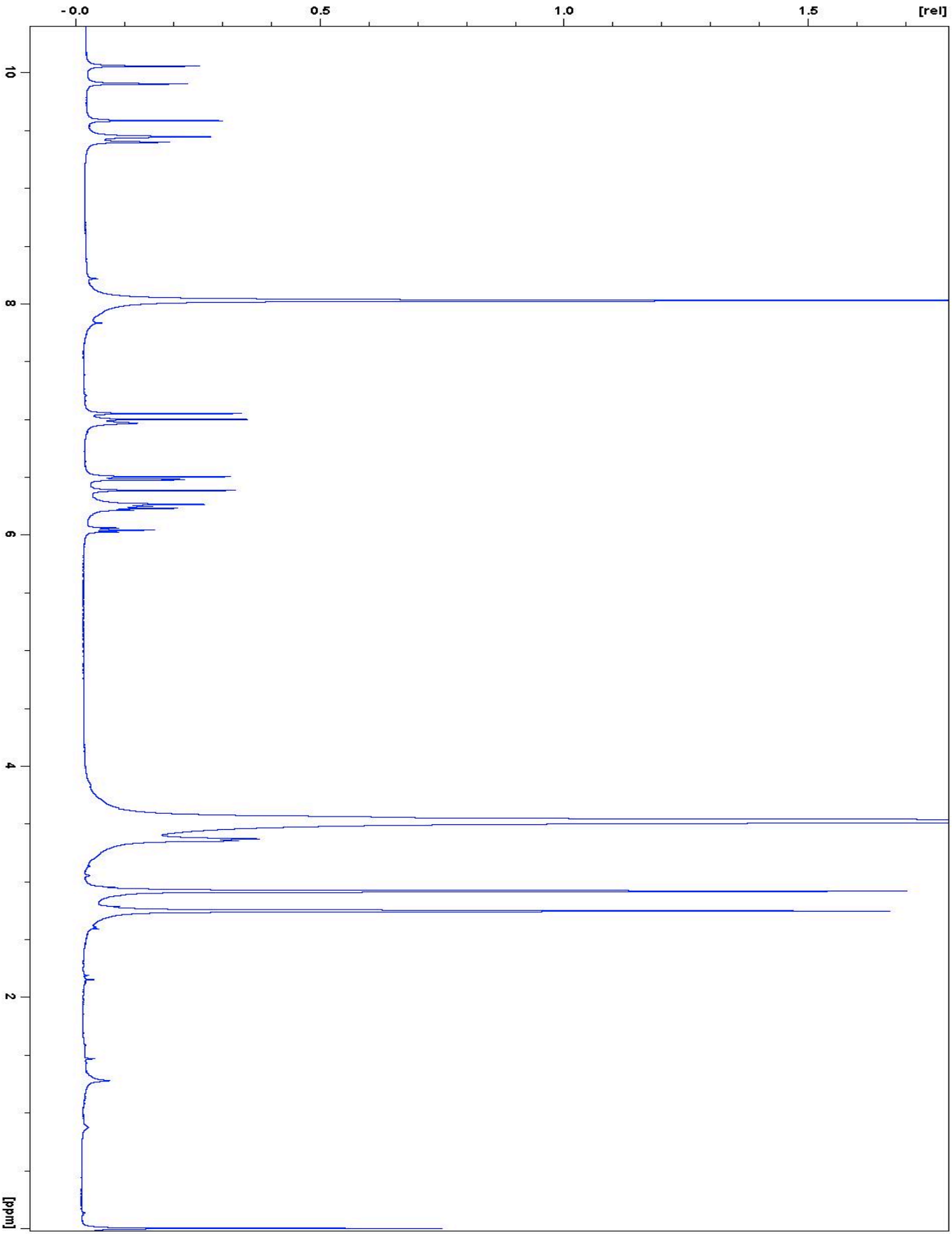
HMBC spectrum of chrysophentin A (**1**) in MeOD-d_4



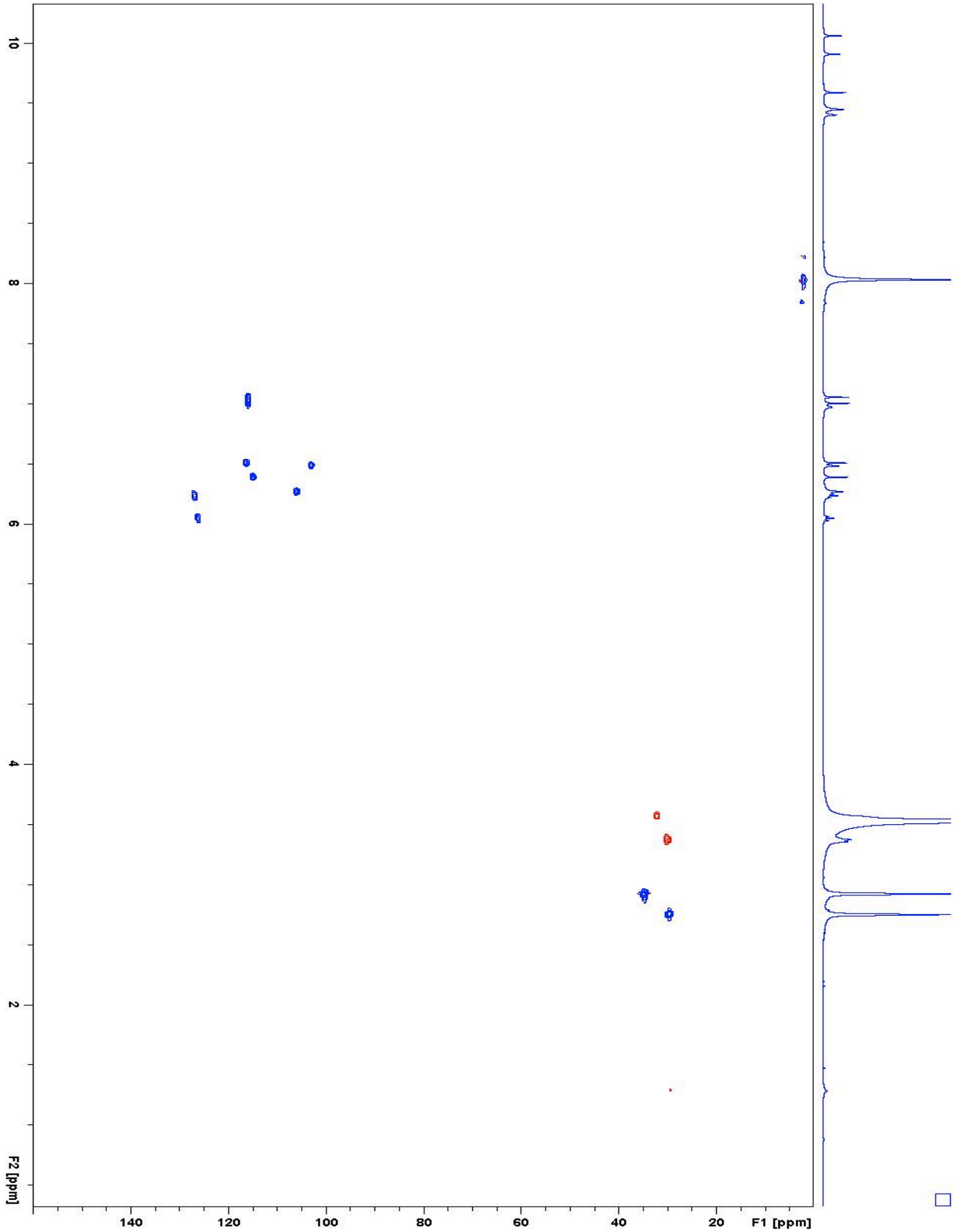
DQF-COSY spectrum of chrysophentin A (**1**) in MeOD-d_4



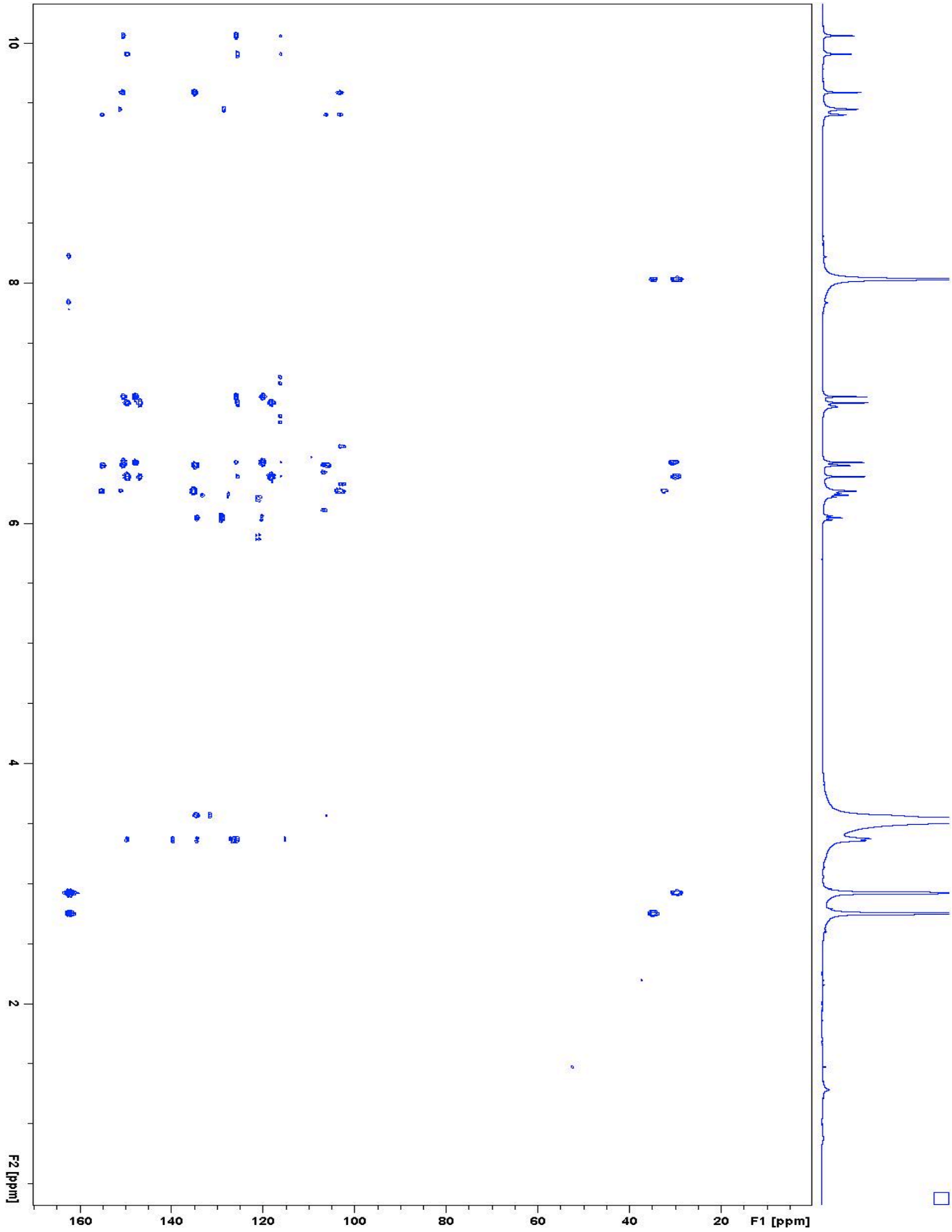
ROESY spectrum of chrysophentin A (**1**) in MeOD-d_4



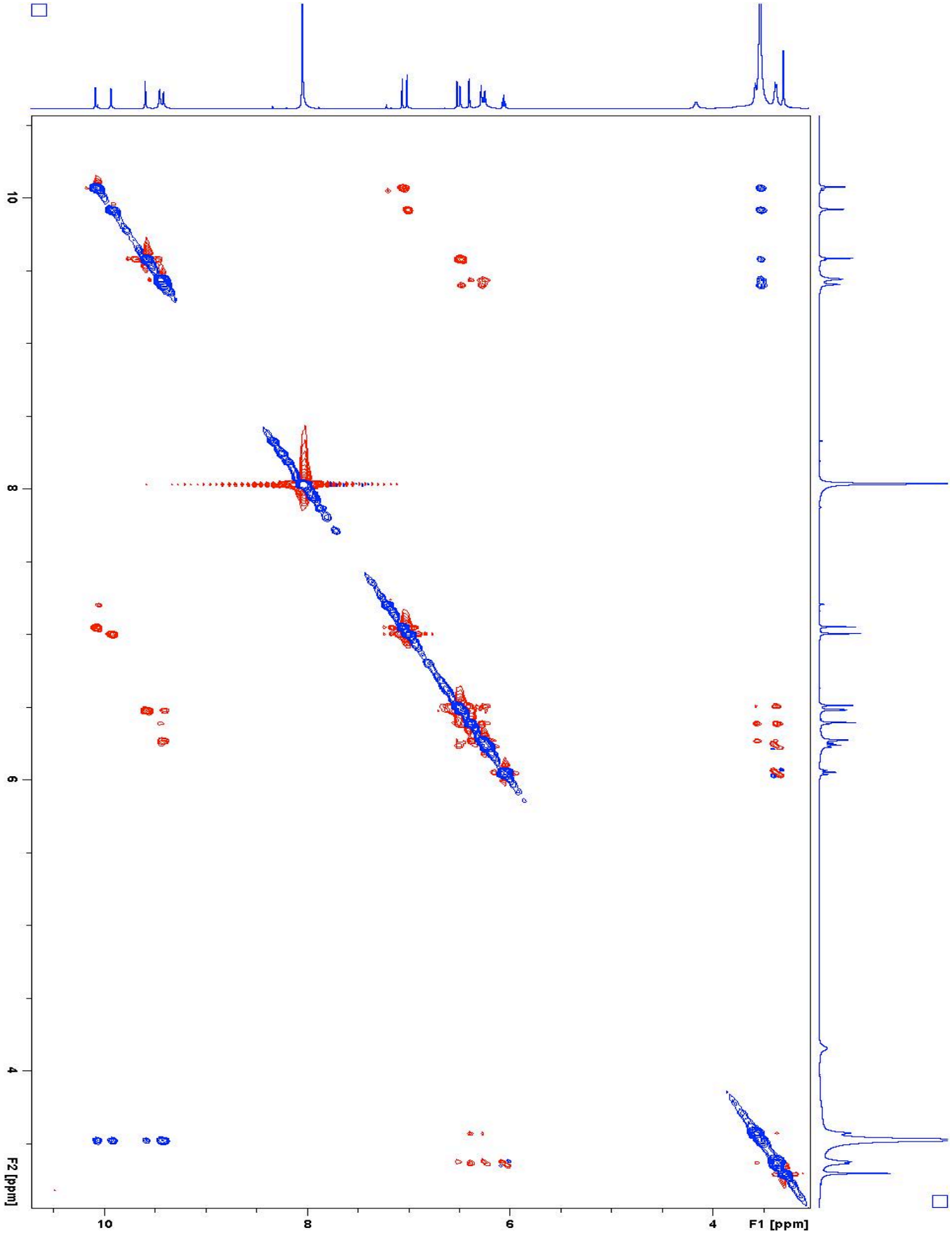
^{1}H NMR spectrum of chrysophentin A (**1**) in DMF-d_7



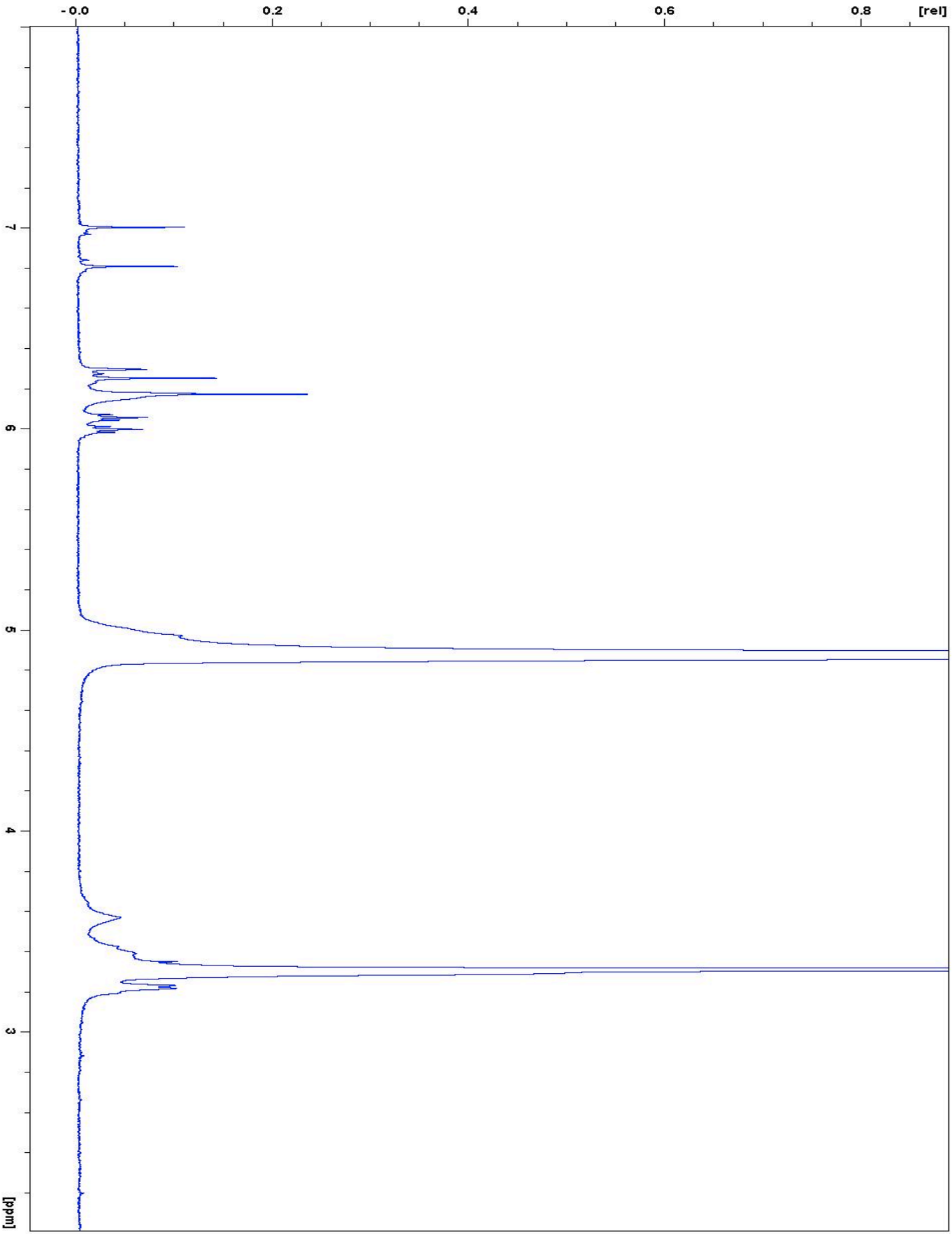
HSQC spectrum of chrysophentin A (**1**) in DMF-d_7



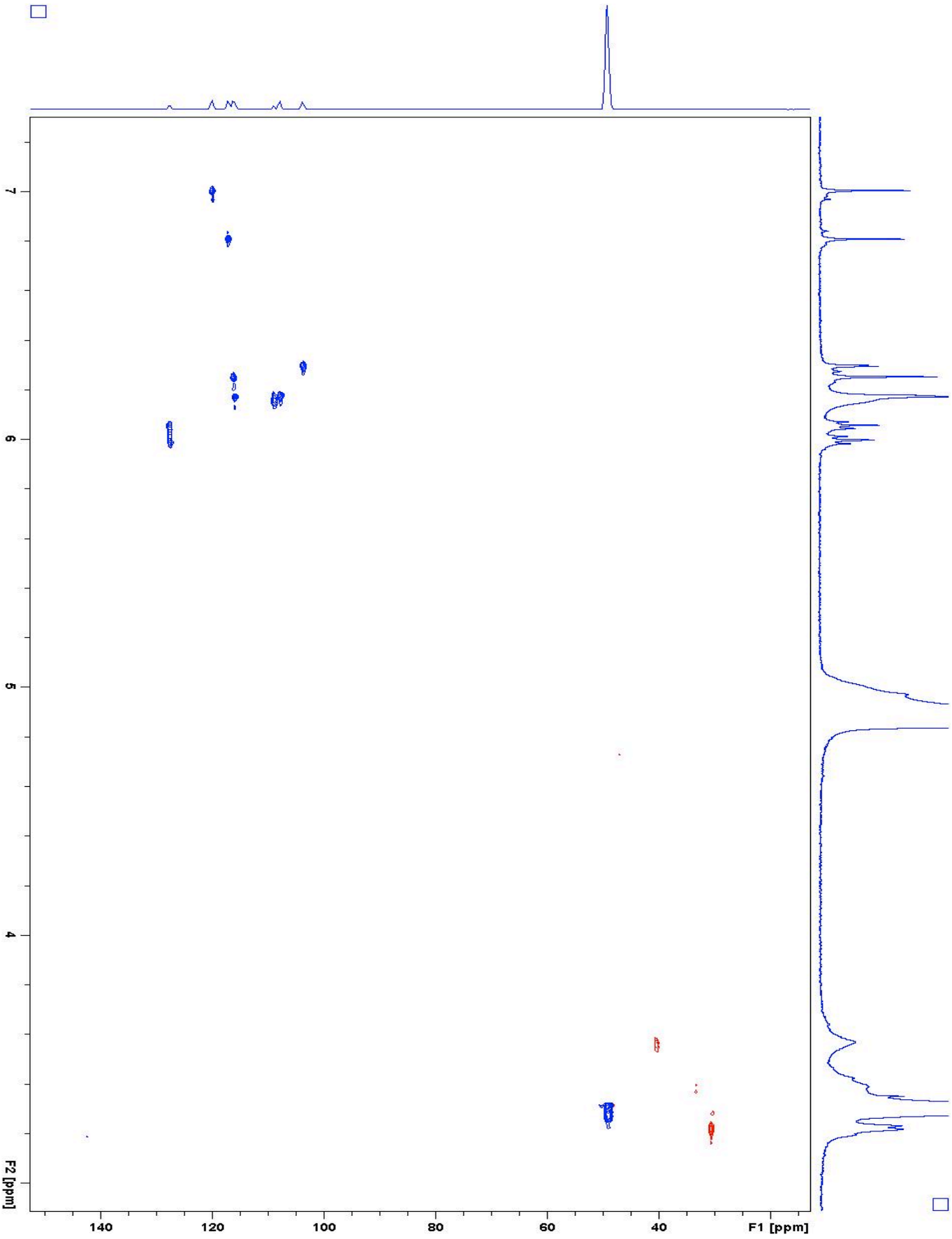
HMBC spectrum of chrysophentin A (**1**) in DMF-d_7



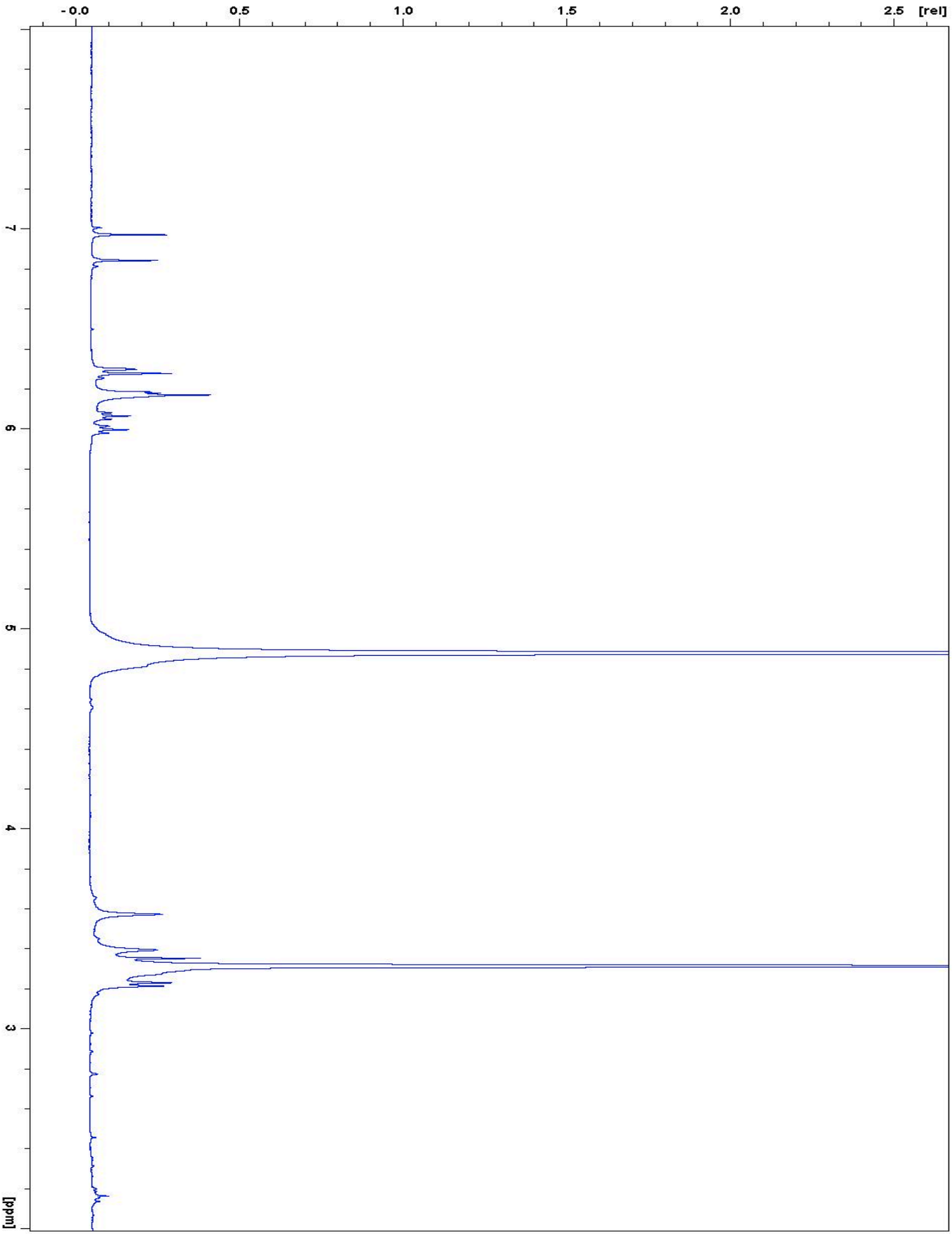
ROESY spectrum of chrysophentin A (**1**) in DMF-d_7



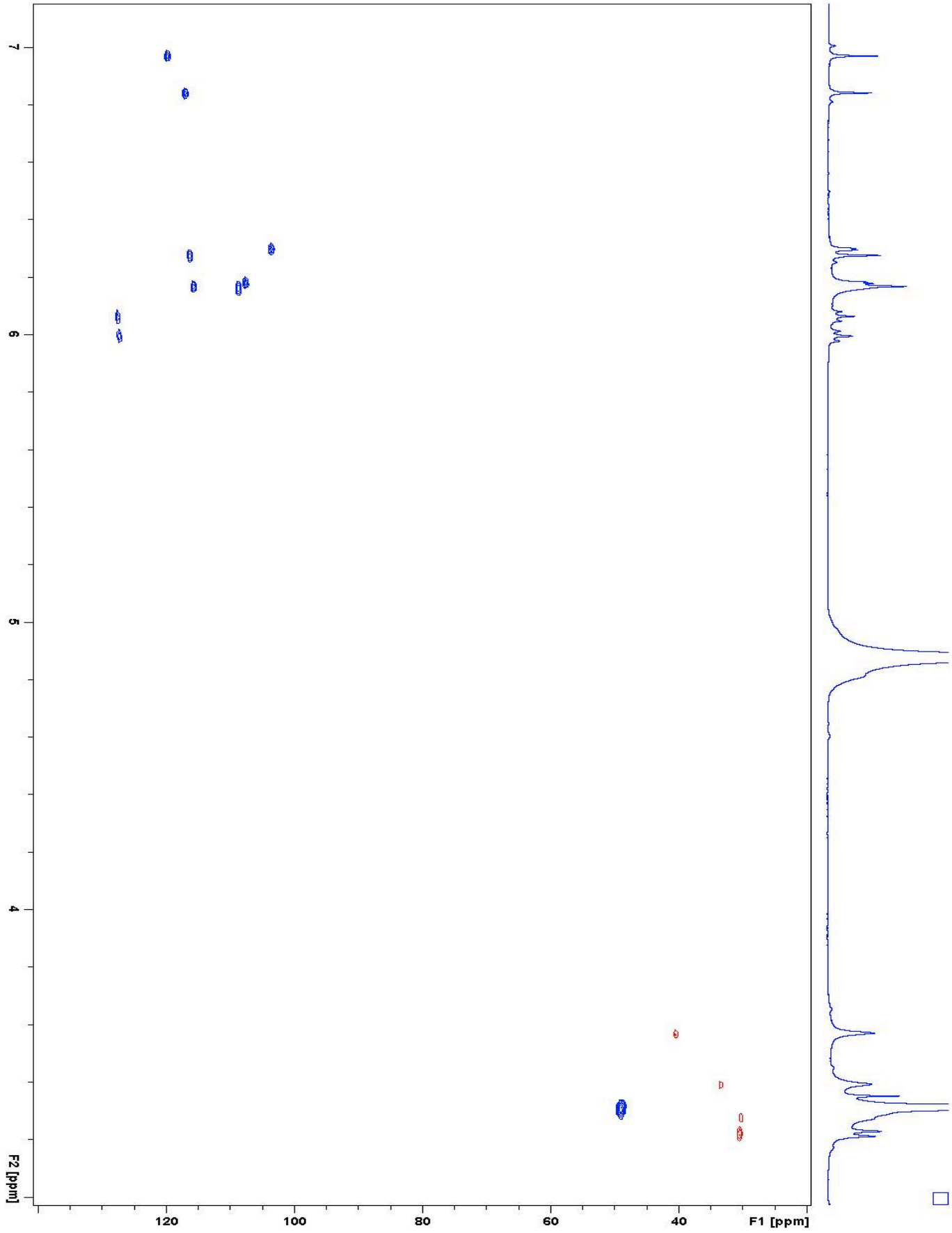
^{1}H NMR spectrum of chrysophentin B (**2**) in MeOD-d_4



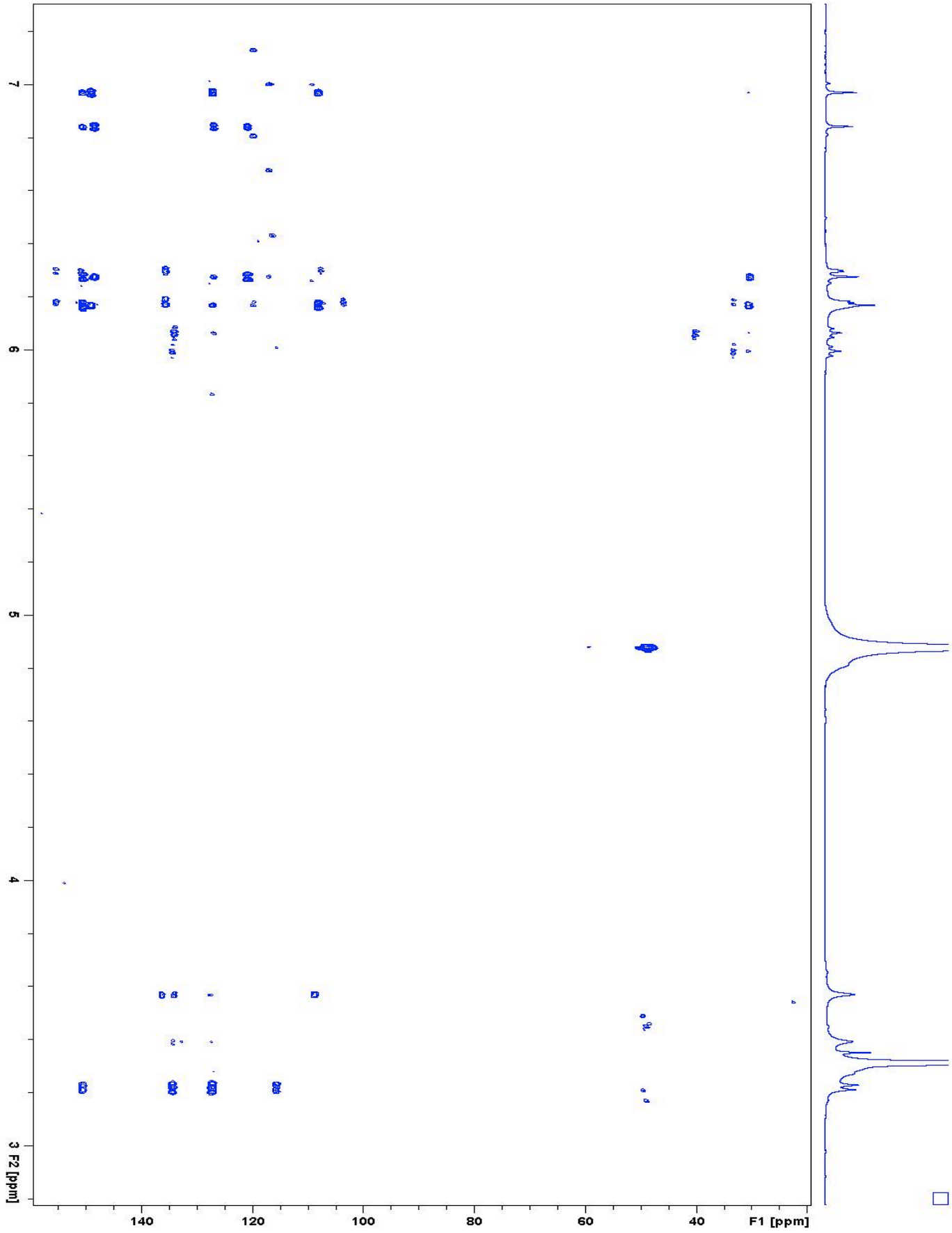
HSQC spectrum of chrysophentin B (**2**) in MeOD-d_4



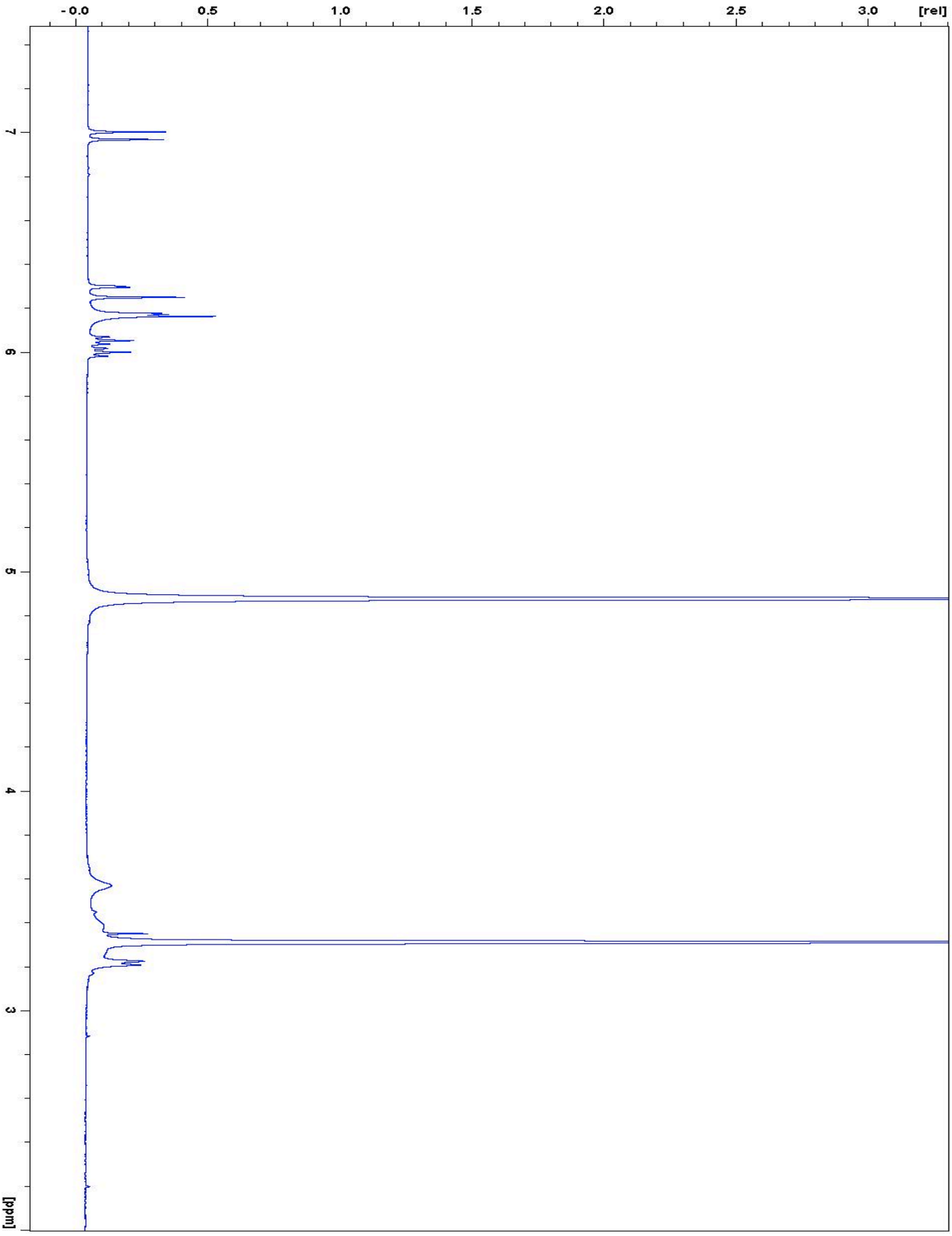
^{1}H NMR spectrum of chrysophentin C (**3**) in MeOD-d_4



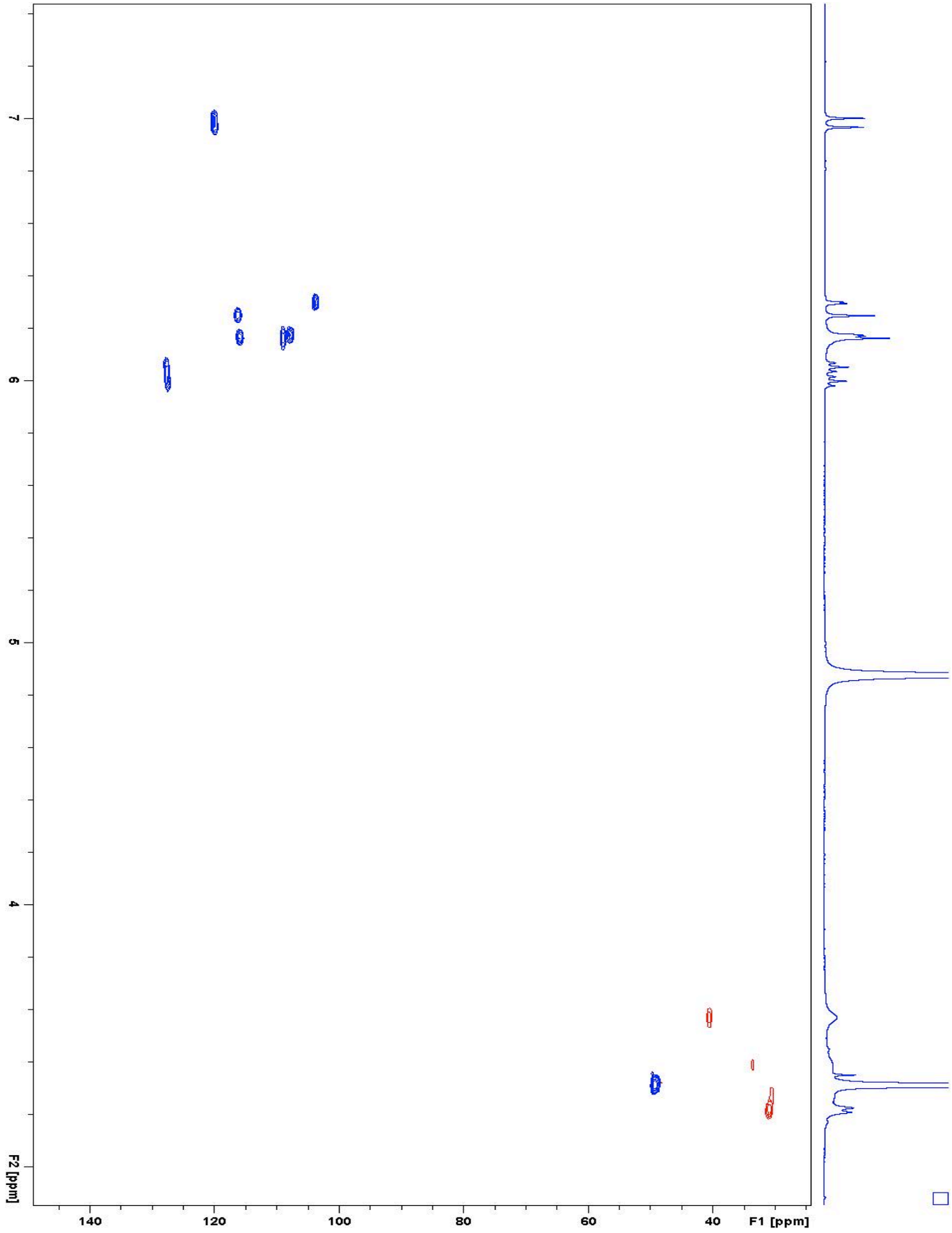
HSQC spectrum of chrysophentin C (**3**) in MeOD-d_4



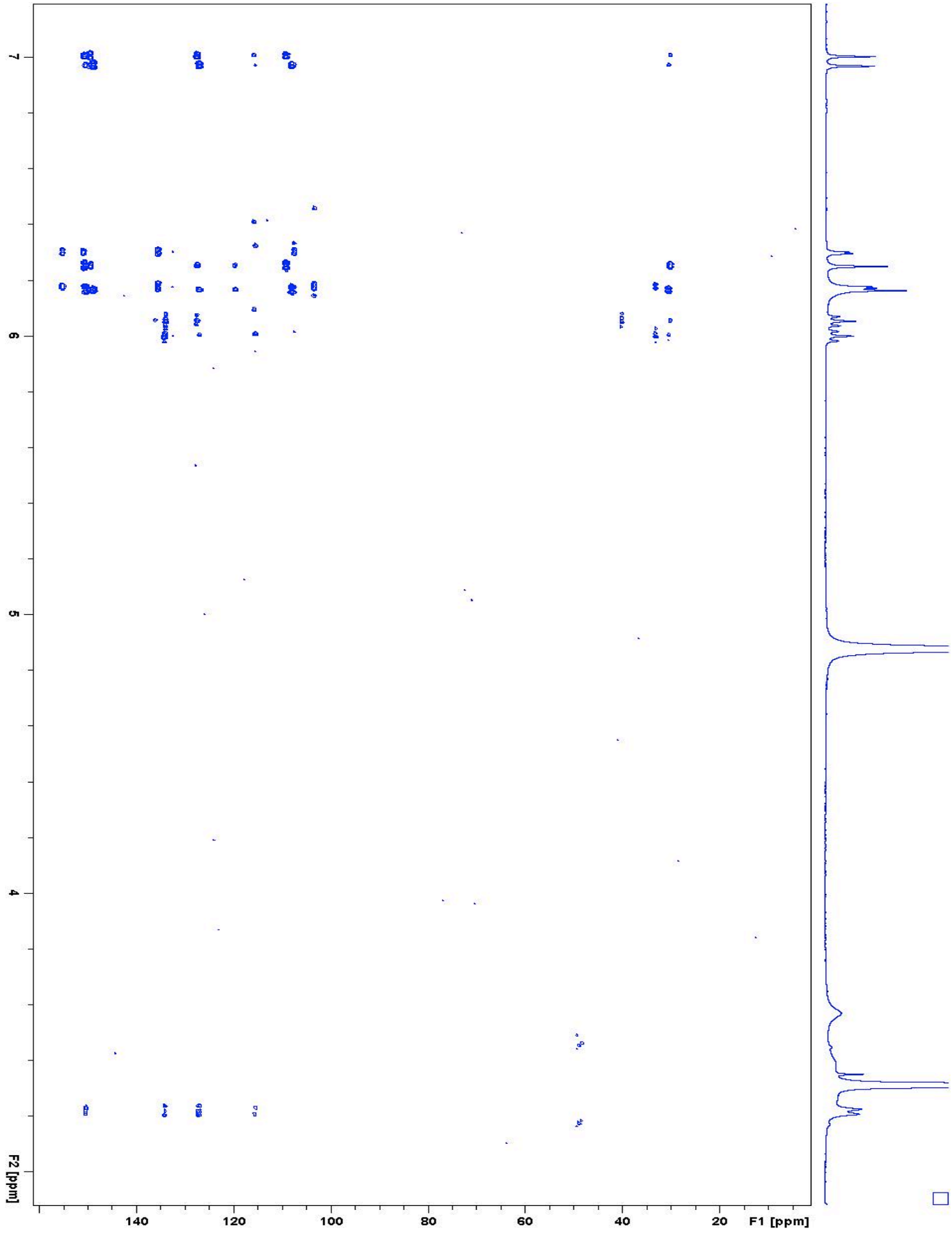
HMBC spectrum of chrysophentin C (**3**) in MeOD-d_4



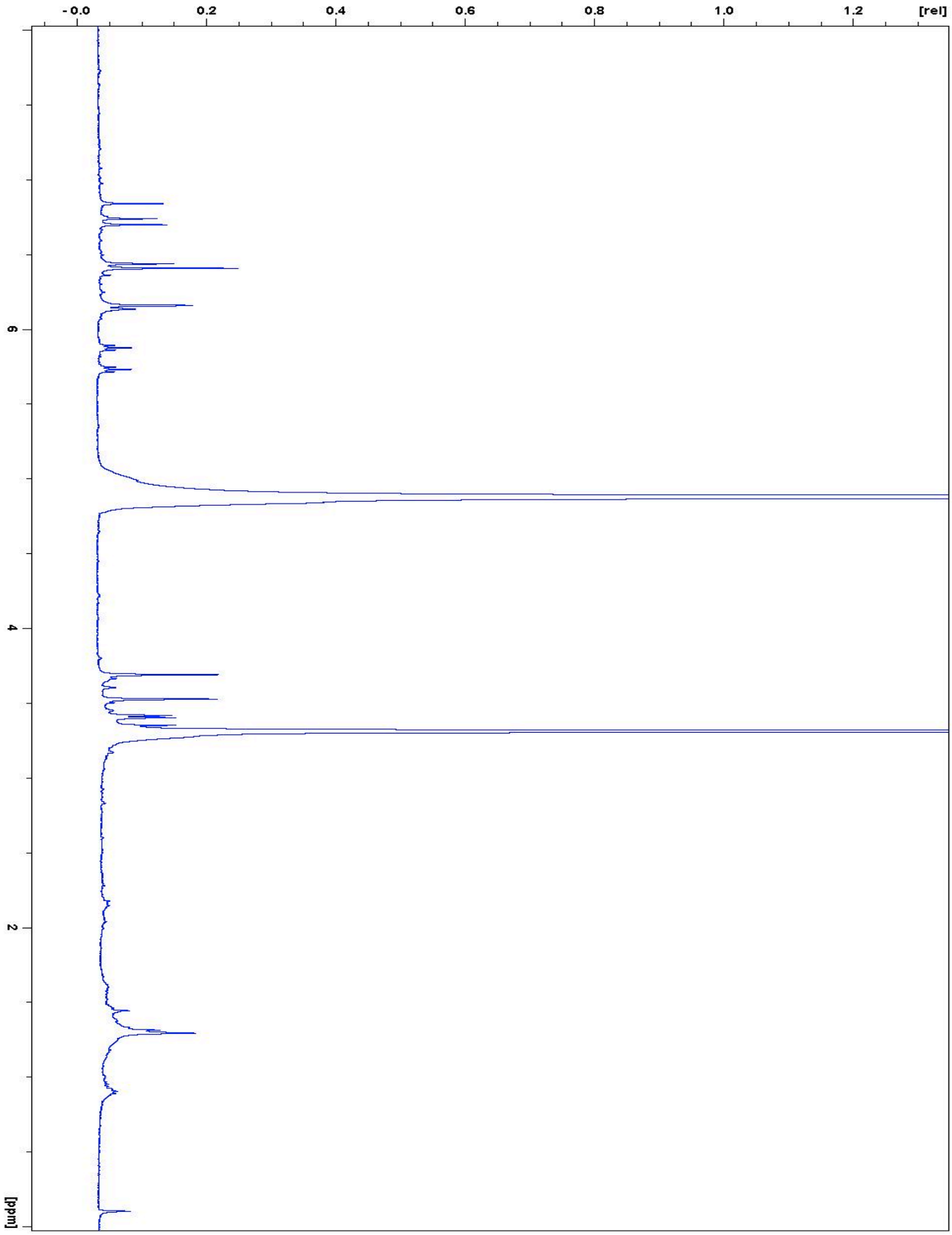
^{1}H NMR spectrum of chrysophentin D (**4**) in MeOD-d_4



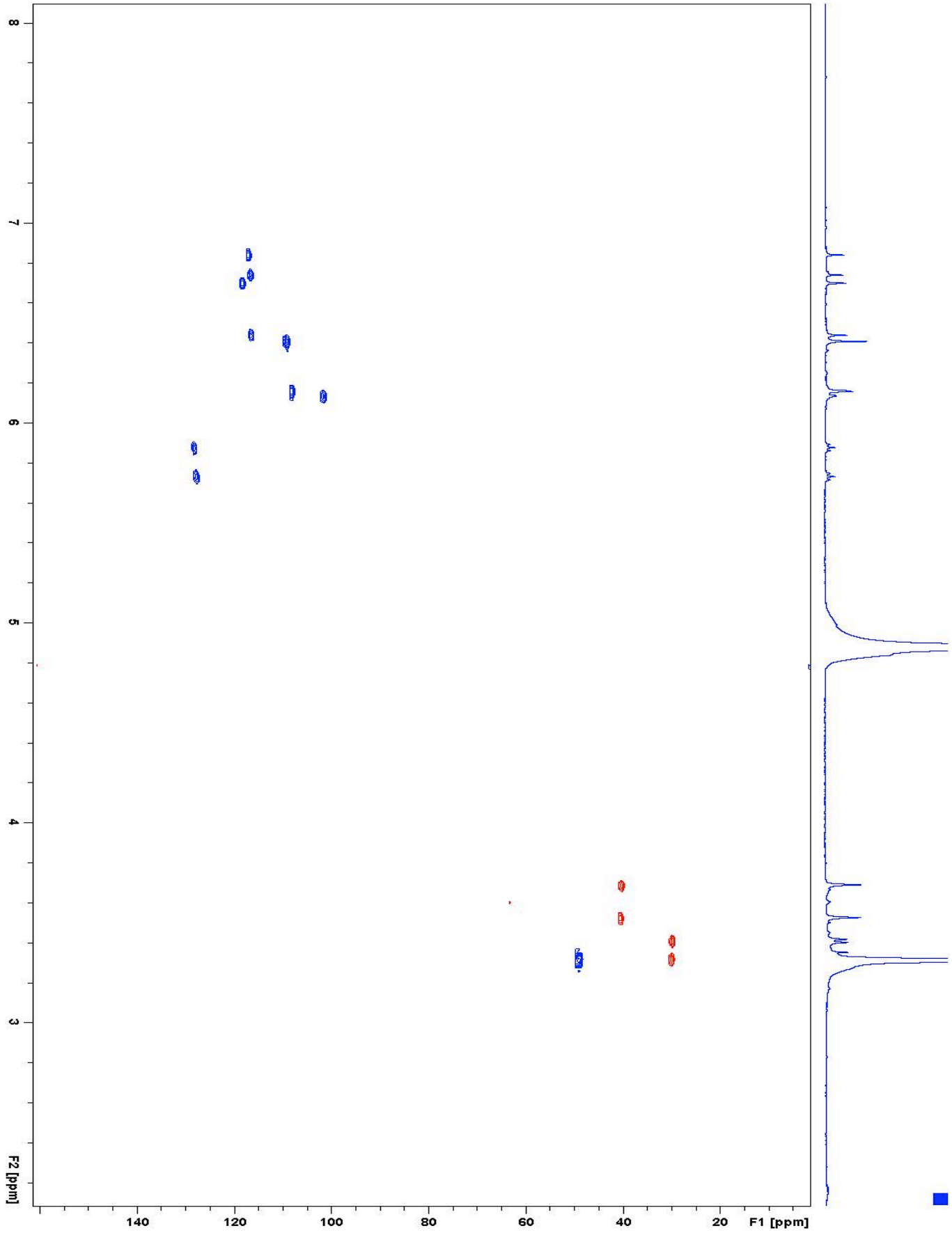
HSQC spectrum of chrysophentin D (**4**) in MeOD-d_4



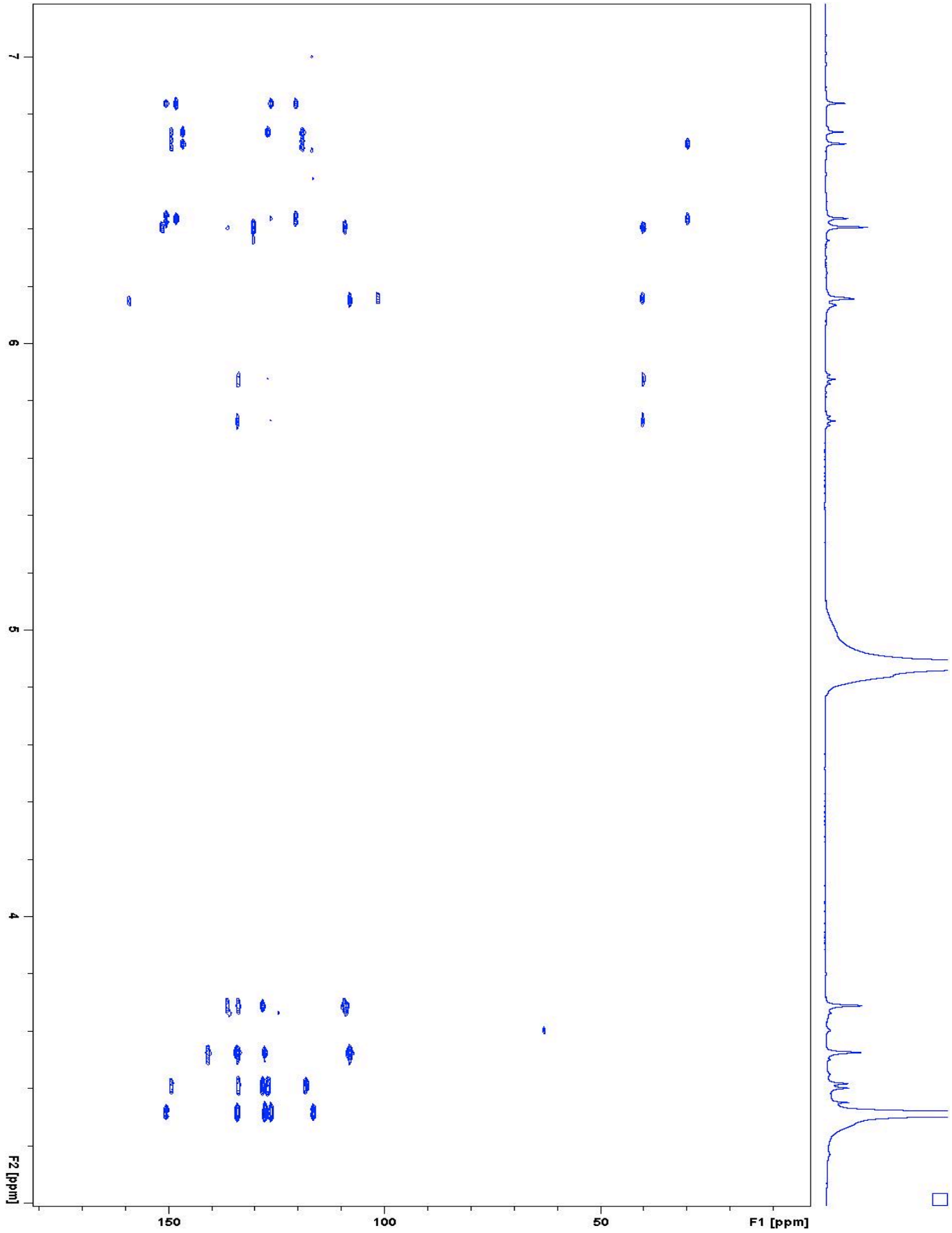
HMBC spectrum of chrysophentin D (**4**) in MeOD-d_4



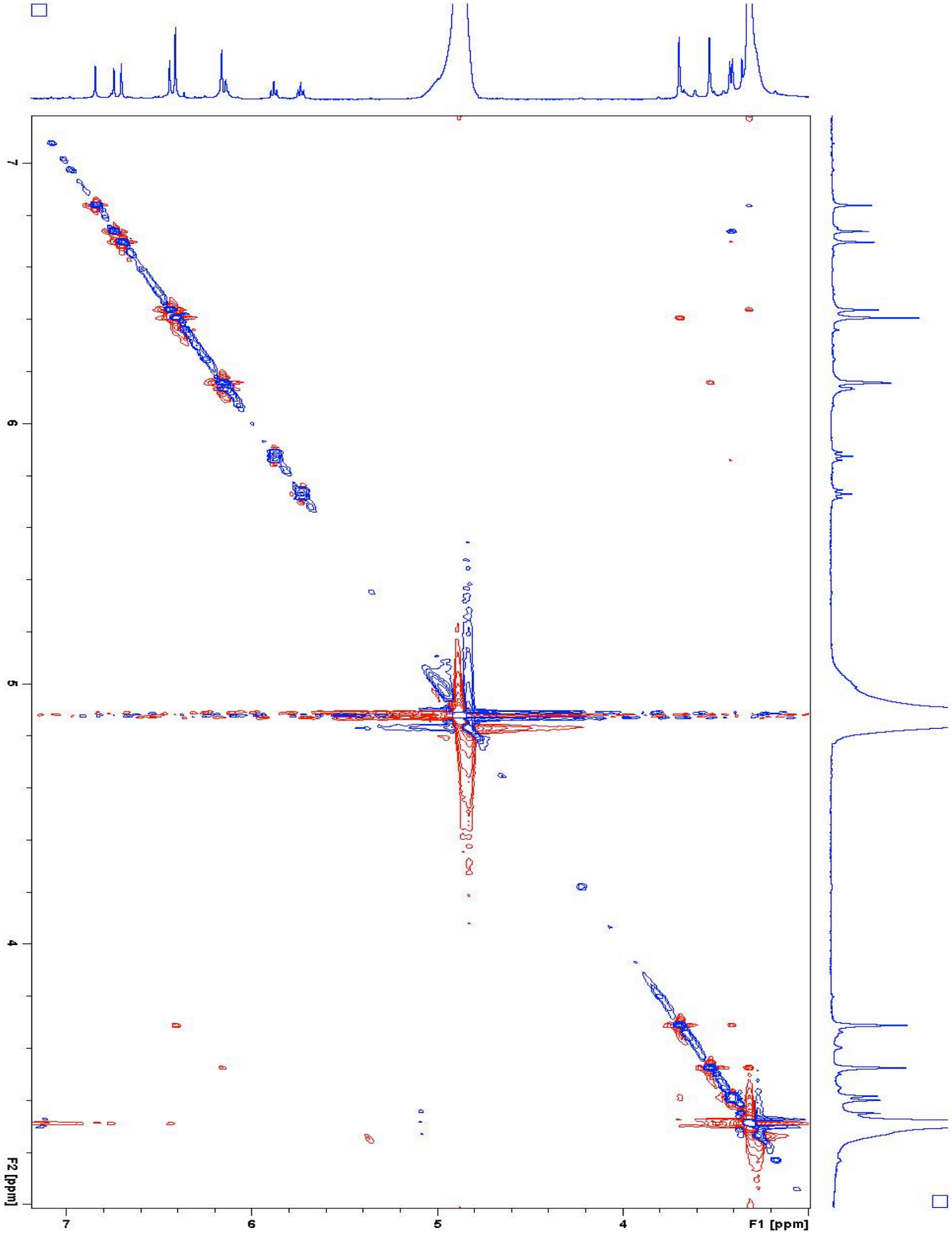
^{1}H NMR spectrum of chrysophentin E (**5**) in MeOD-d_4



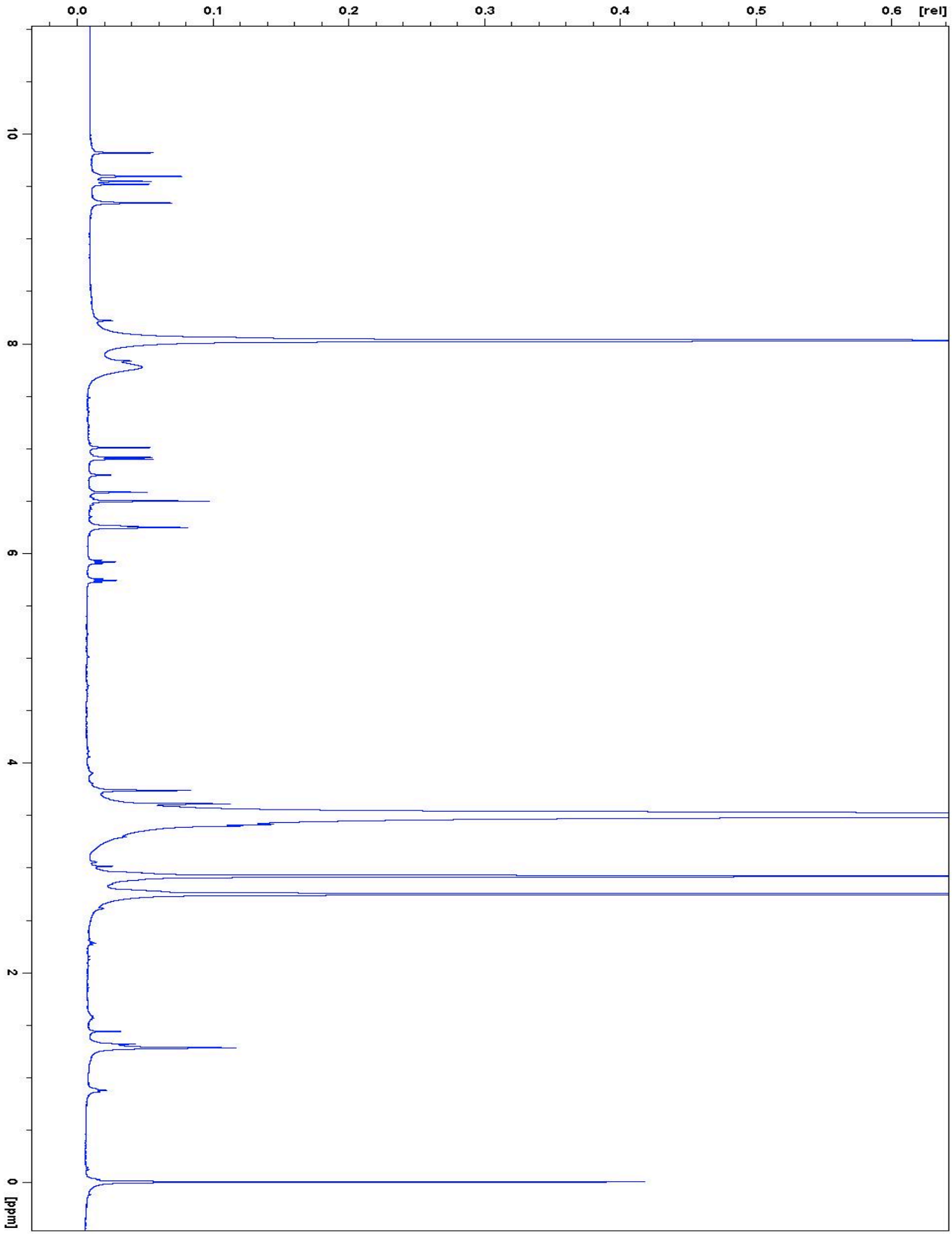
HSQC spectrum of chrysophentin E (**5**) in MeOD-d_4



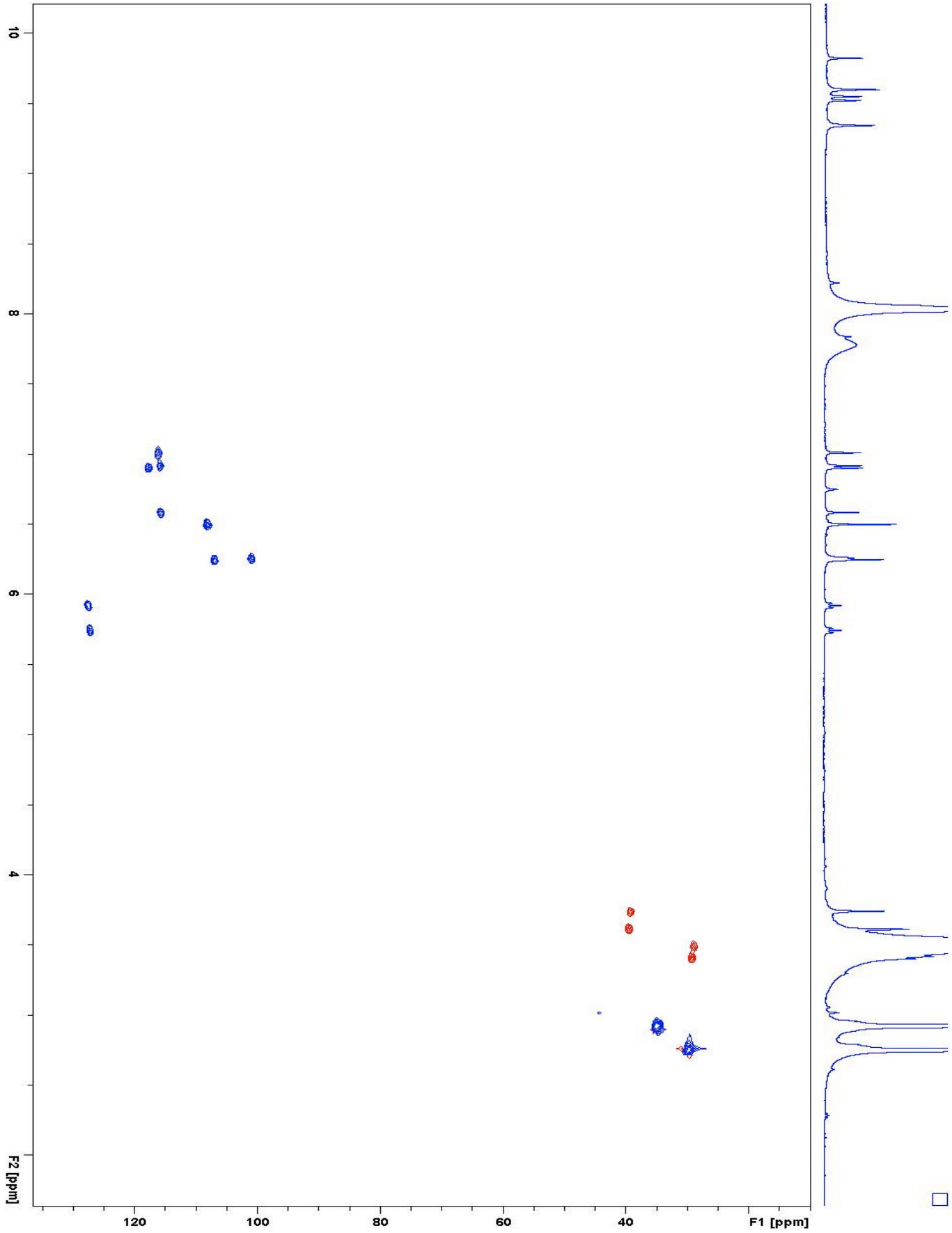
HMBC spectrum of chrysophentin E (**5**) in MeOD-d_4



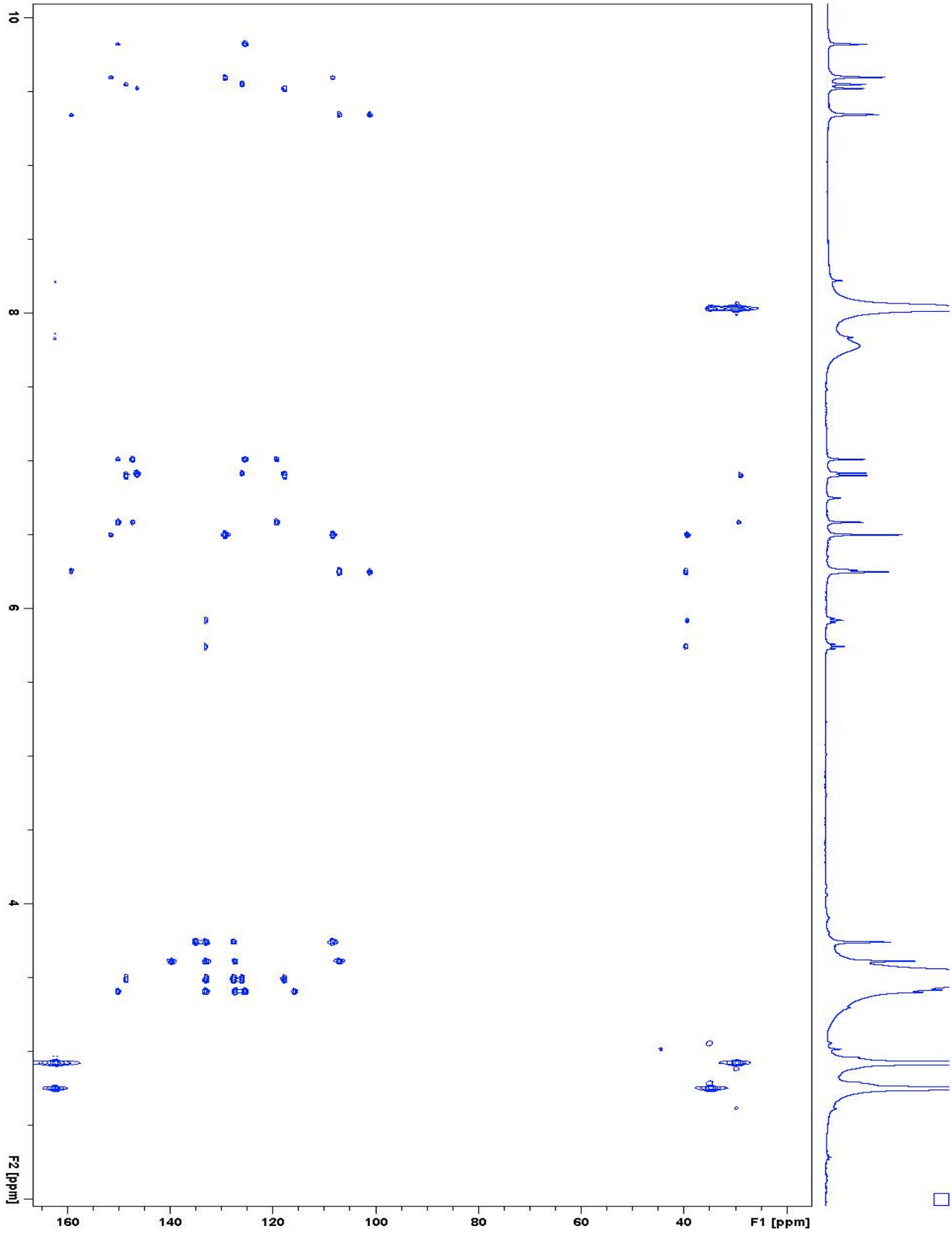
ROESY spectrum of chrysophentin E (**5**) in MeOD-d_4



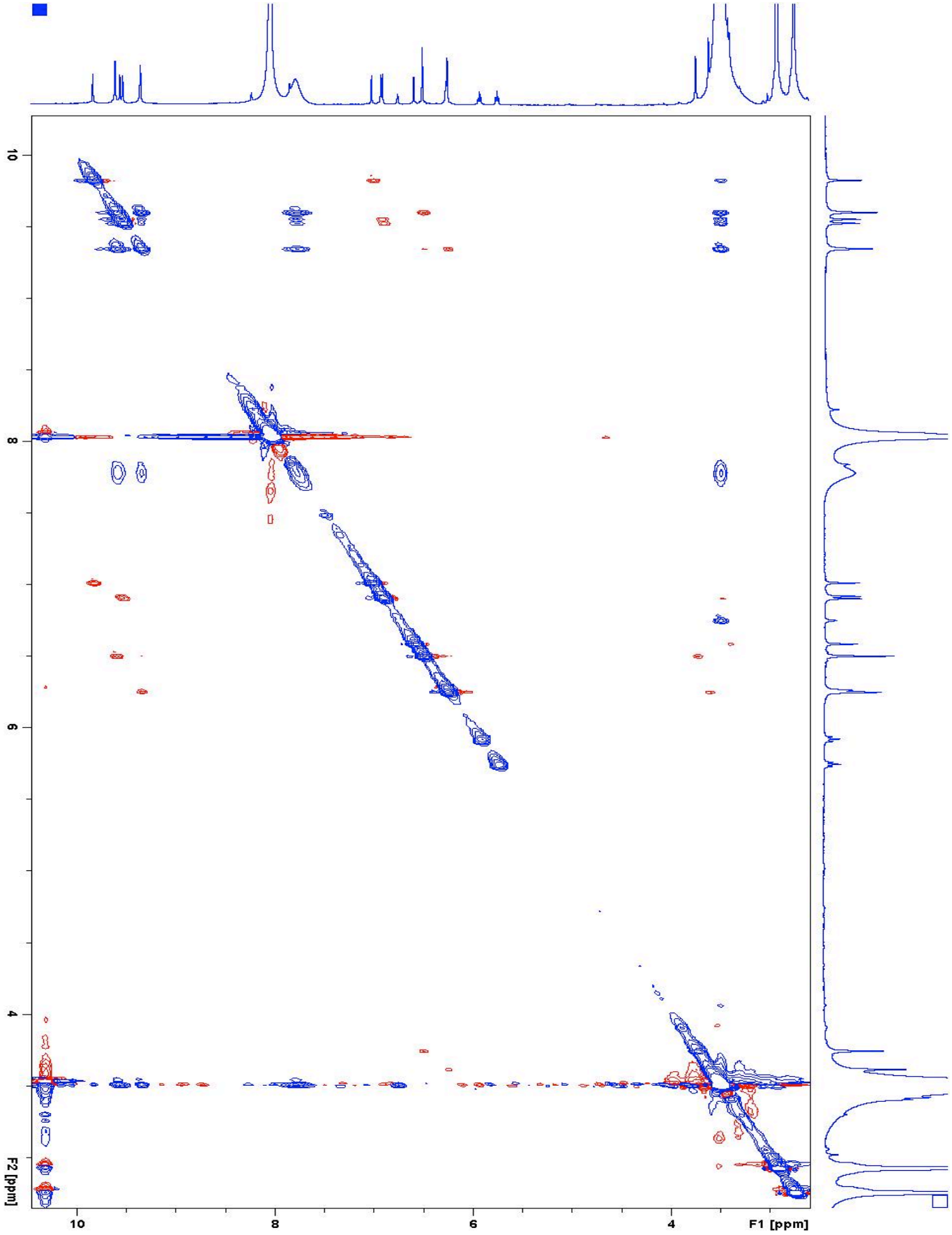
^{1}H NMR spectrum of chrysophentin E (**5**) in DMF-d_7



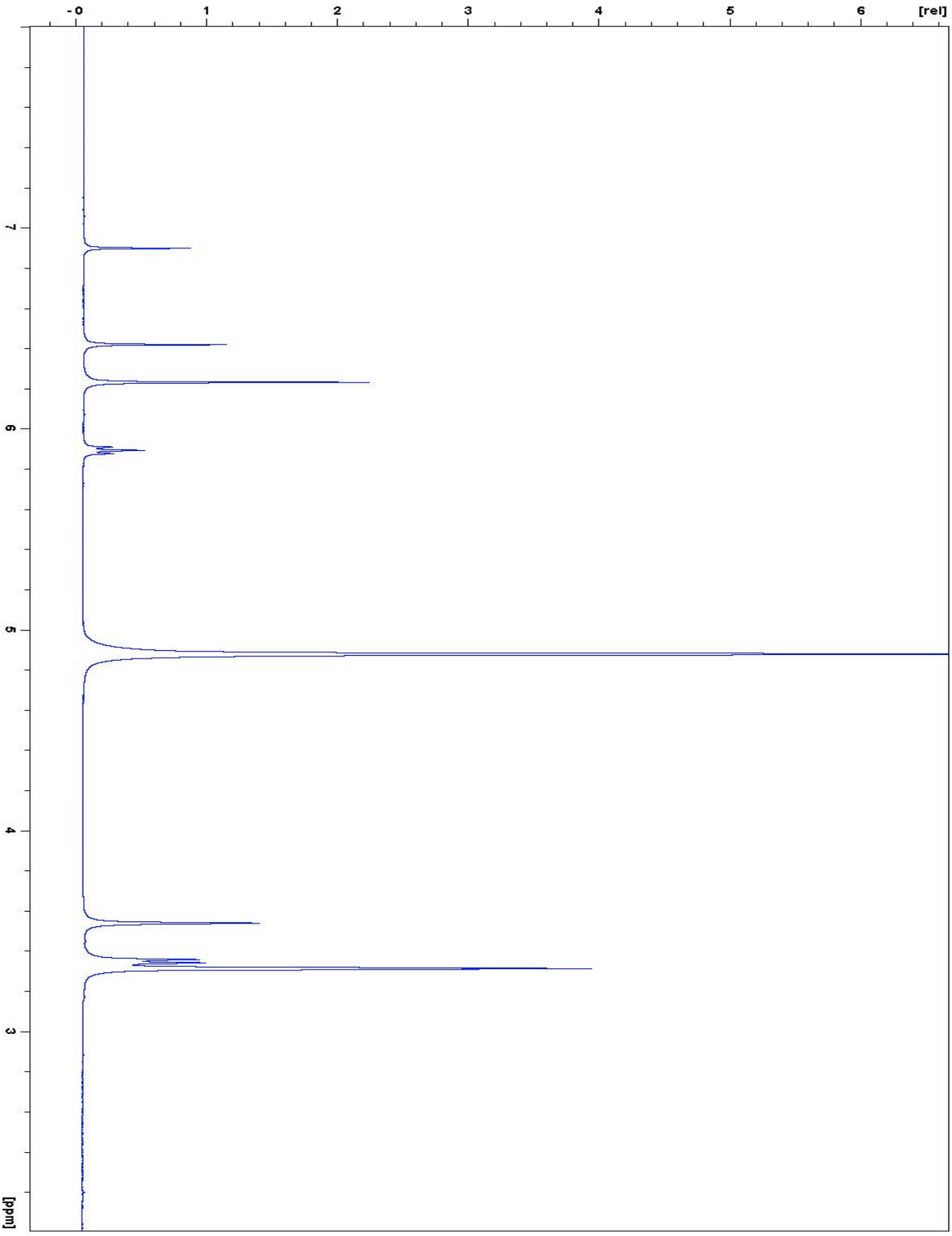
HSQC spectrum of chrysophentin E (**5**) in DMF-d_7



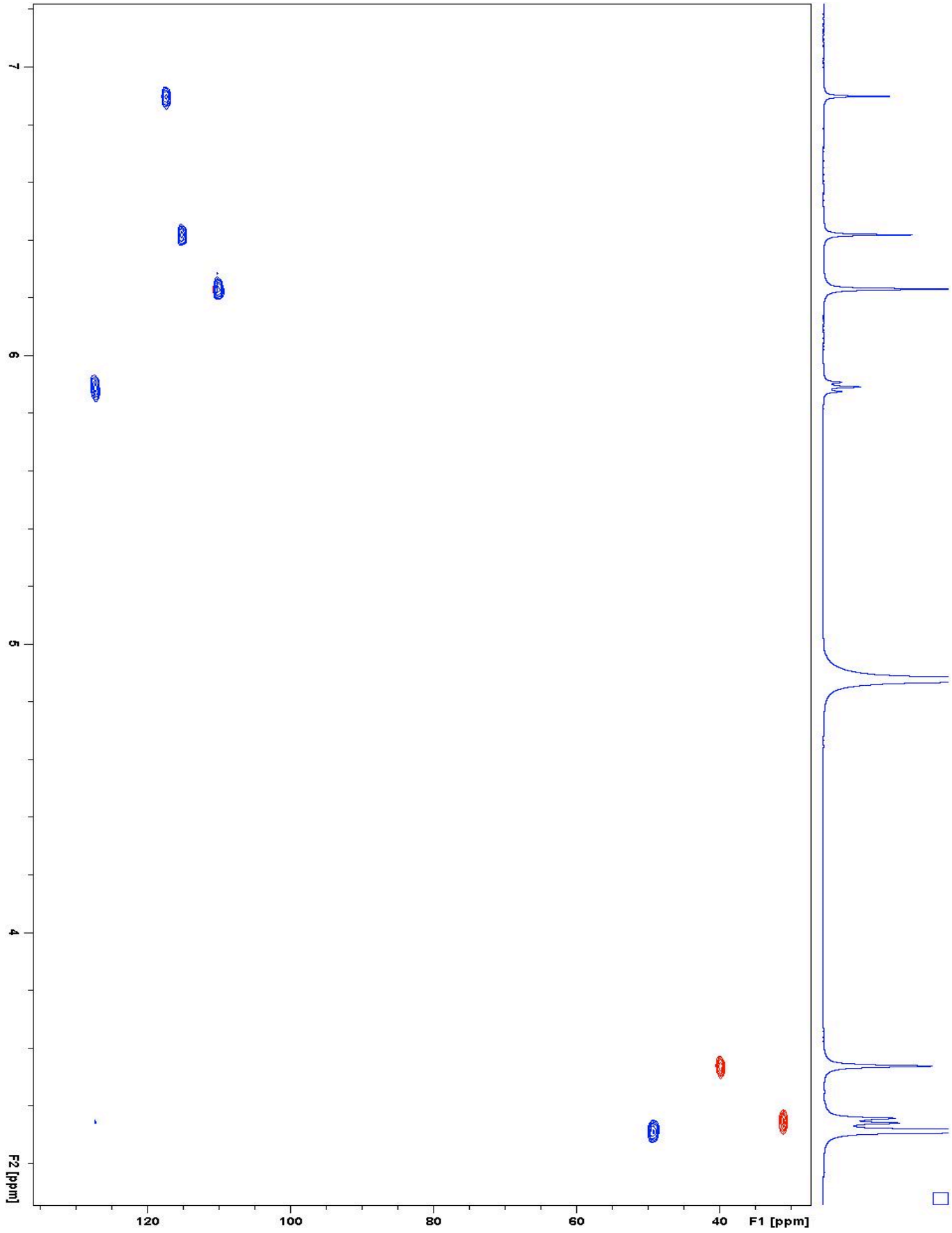
HMBC spectrum of chrysophentin E (**5**) in DMF-d_7



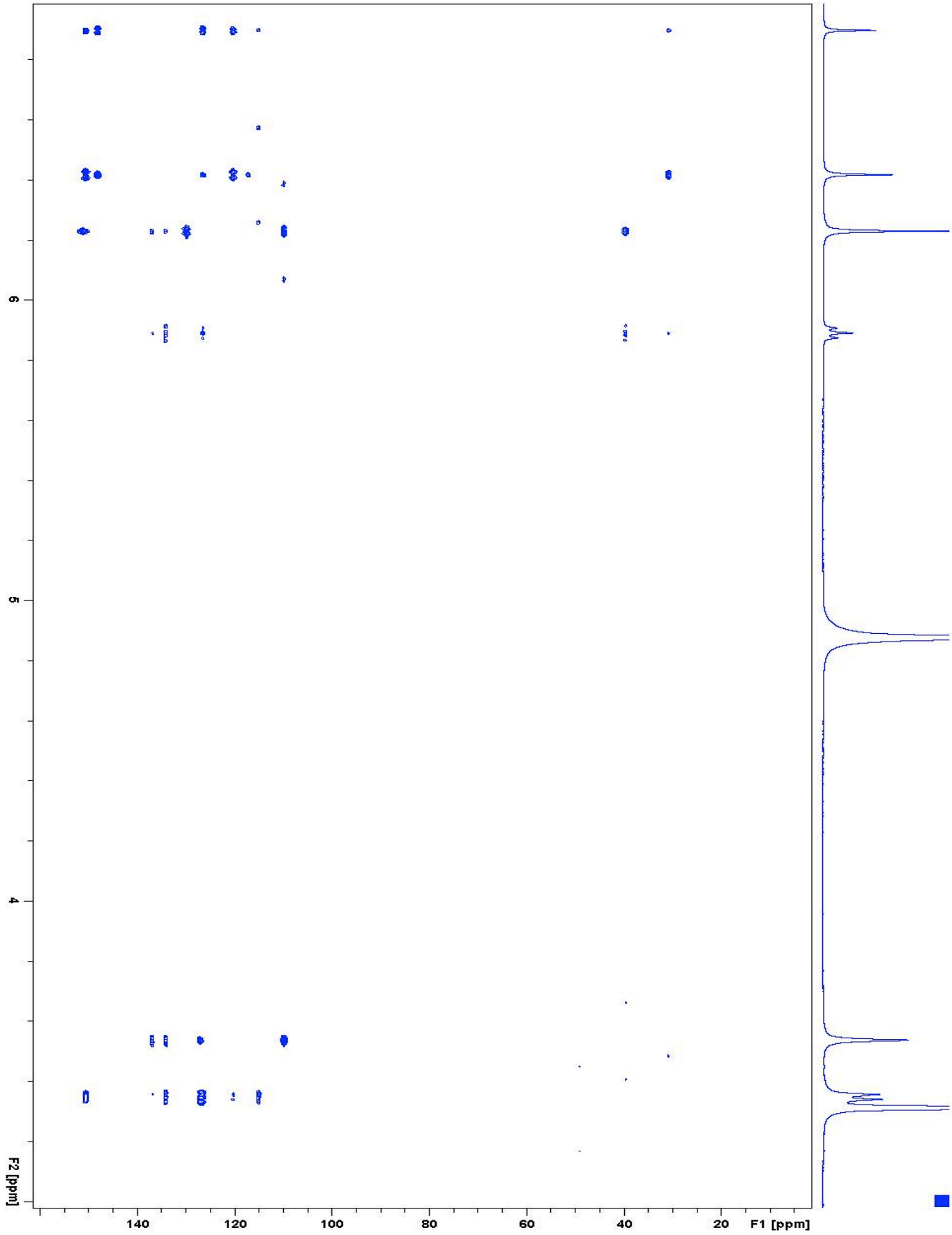
ROESY spectrum of chrysophentin E (**5**) in DMF-d_7



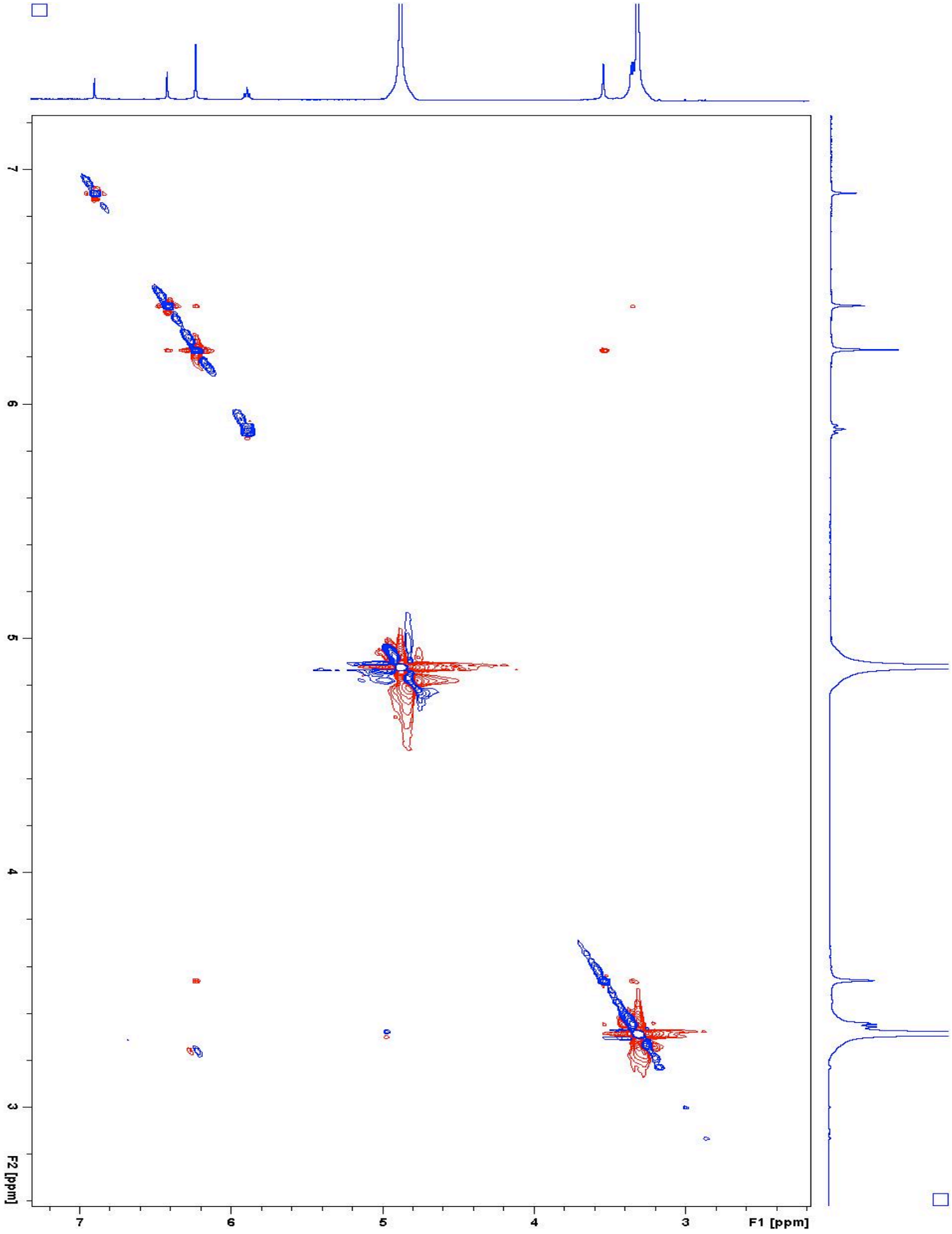
^{1}H NMR spectrum of chrysophentin F (**6**) in MeOD-d_4



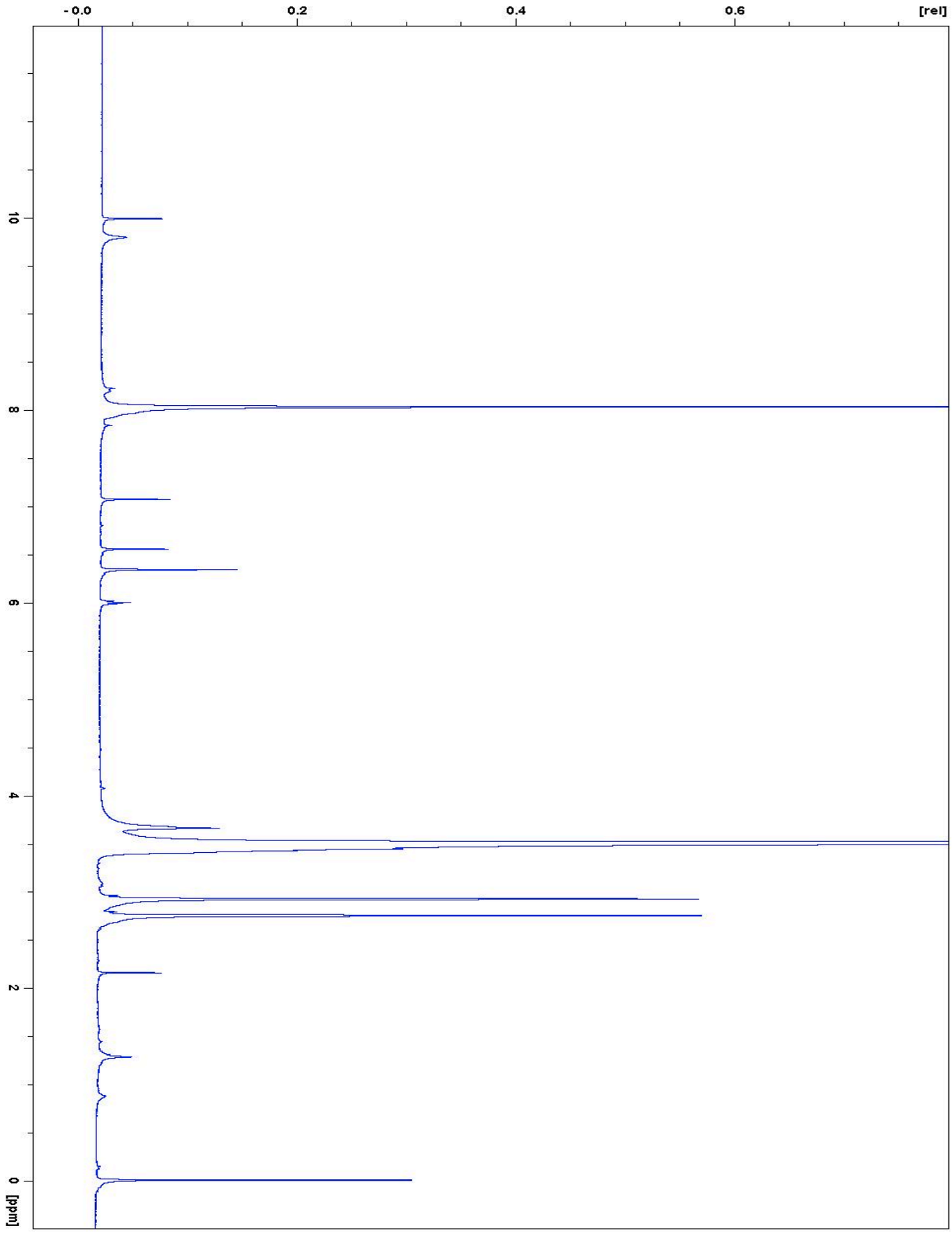
HSQC spectrum of chrysophentin F (**6**) in MeOD-d_4



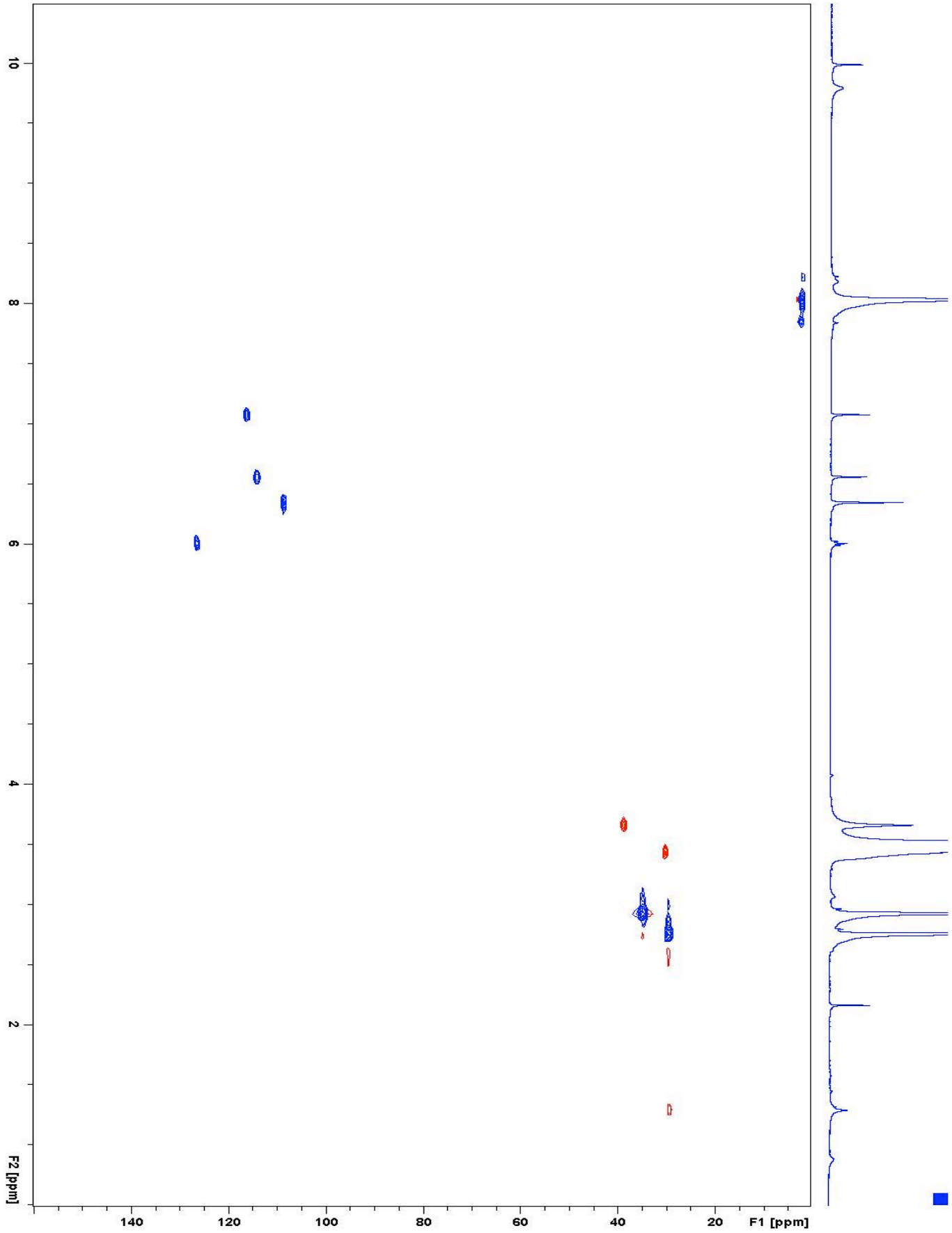
HMBC spectrum of chrysophentin F (**6**) in MeOD-d_4



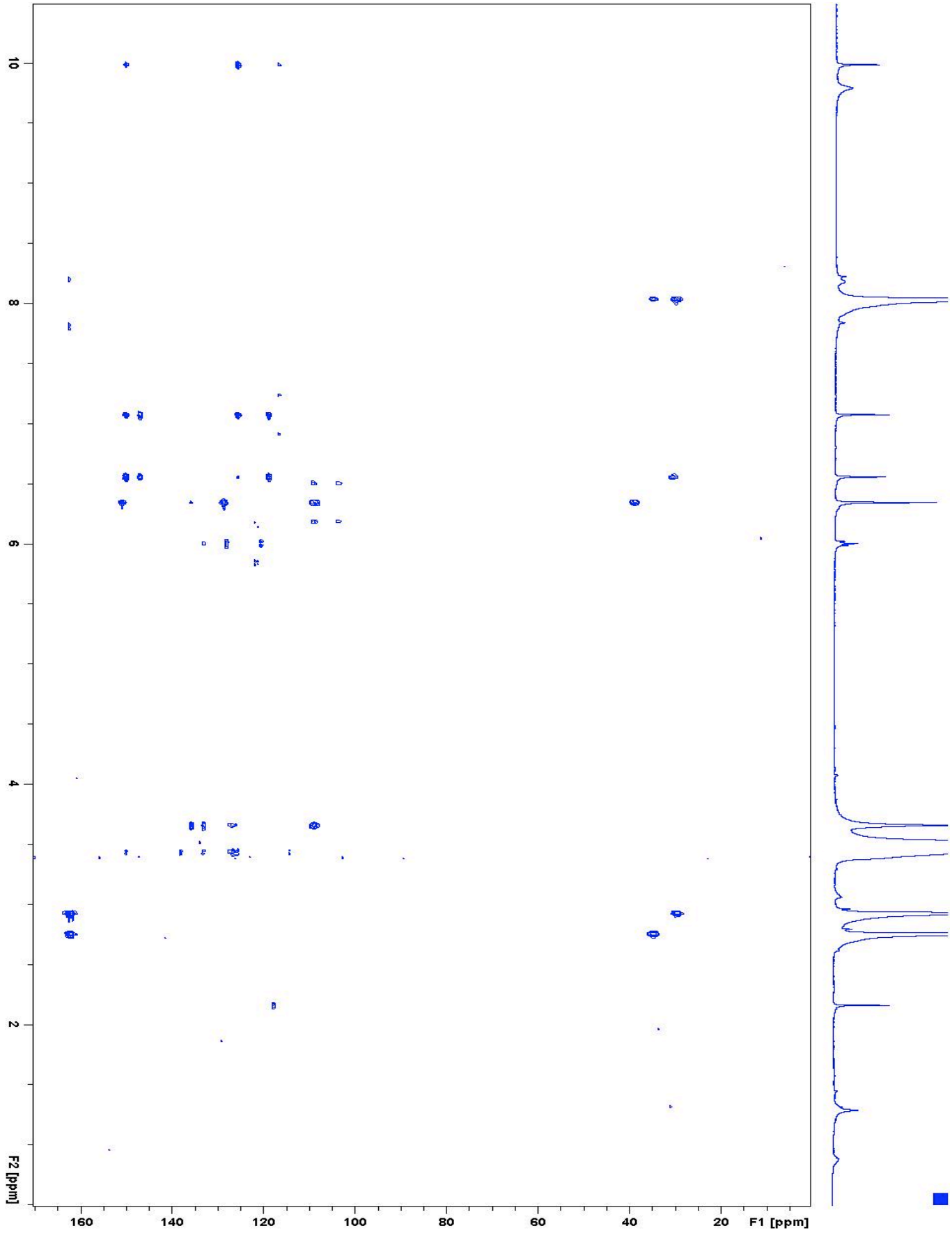
ROESY spectrum of chrysophentin F (**6**) in MeOD-d_4



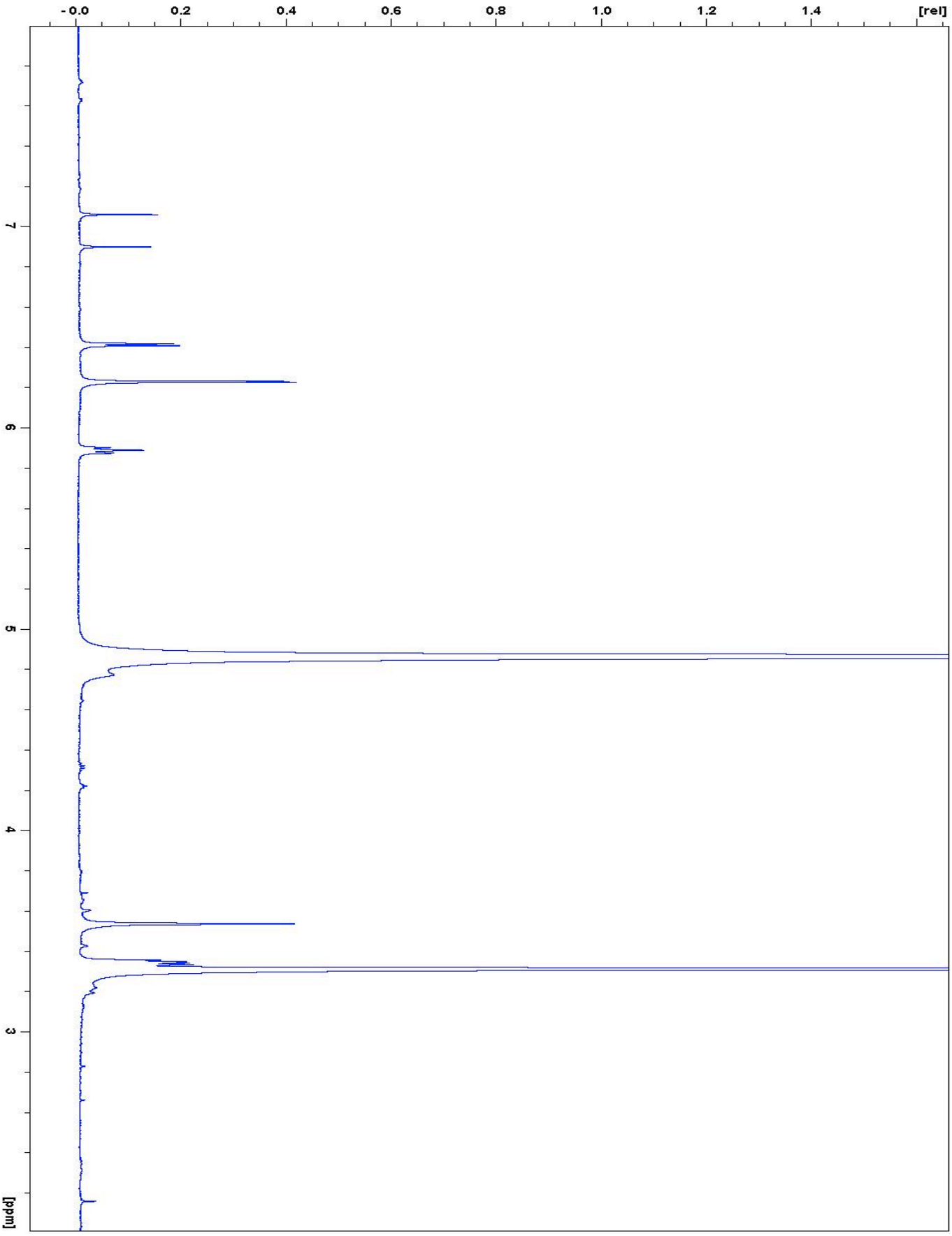
^{1}H NMR spectrum of chrysophentin F (**6**) in DMF-d_7



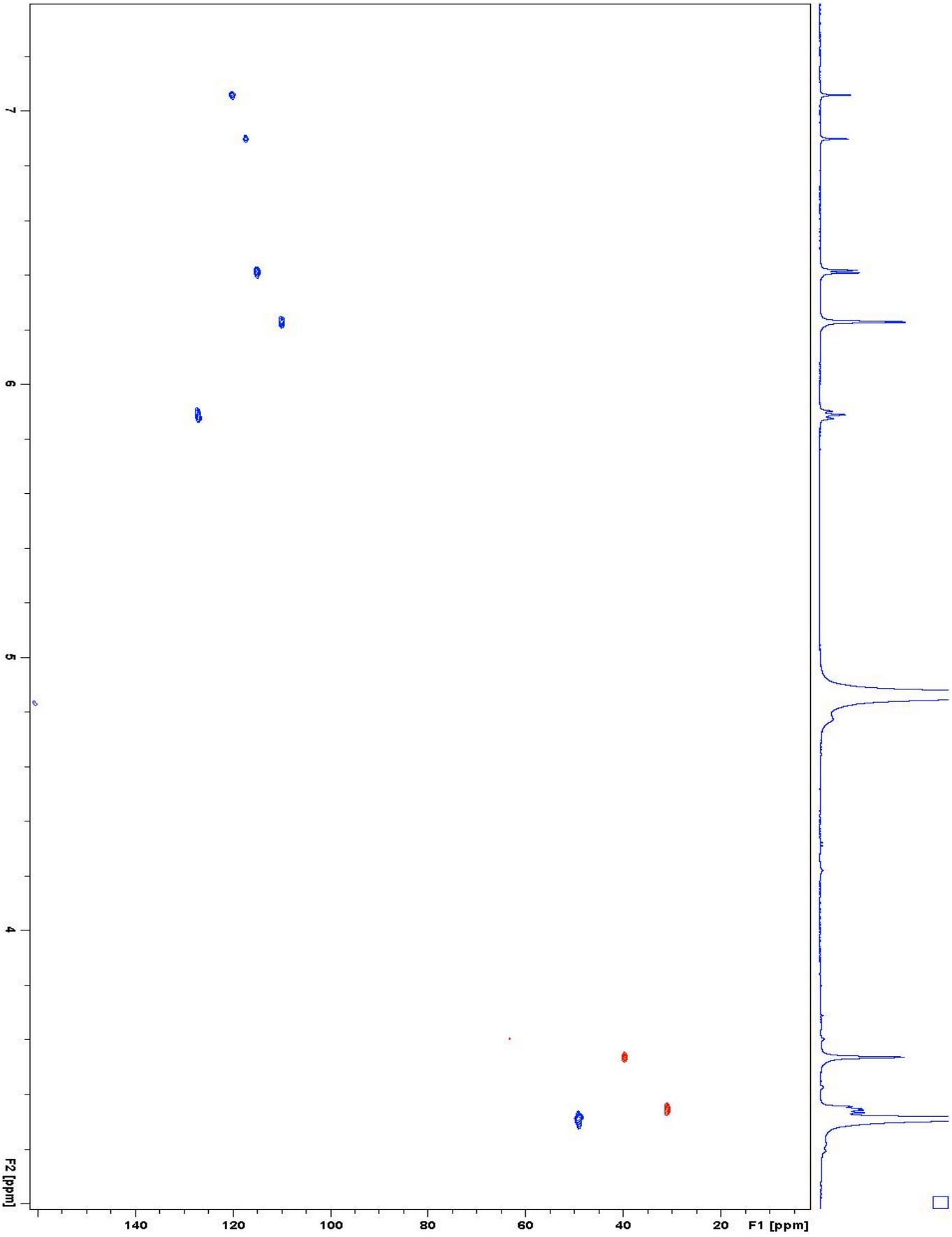
HSQC spectrum of chrysophentin F (**6**) in DMF-d_7



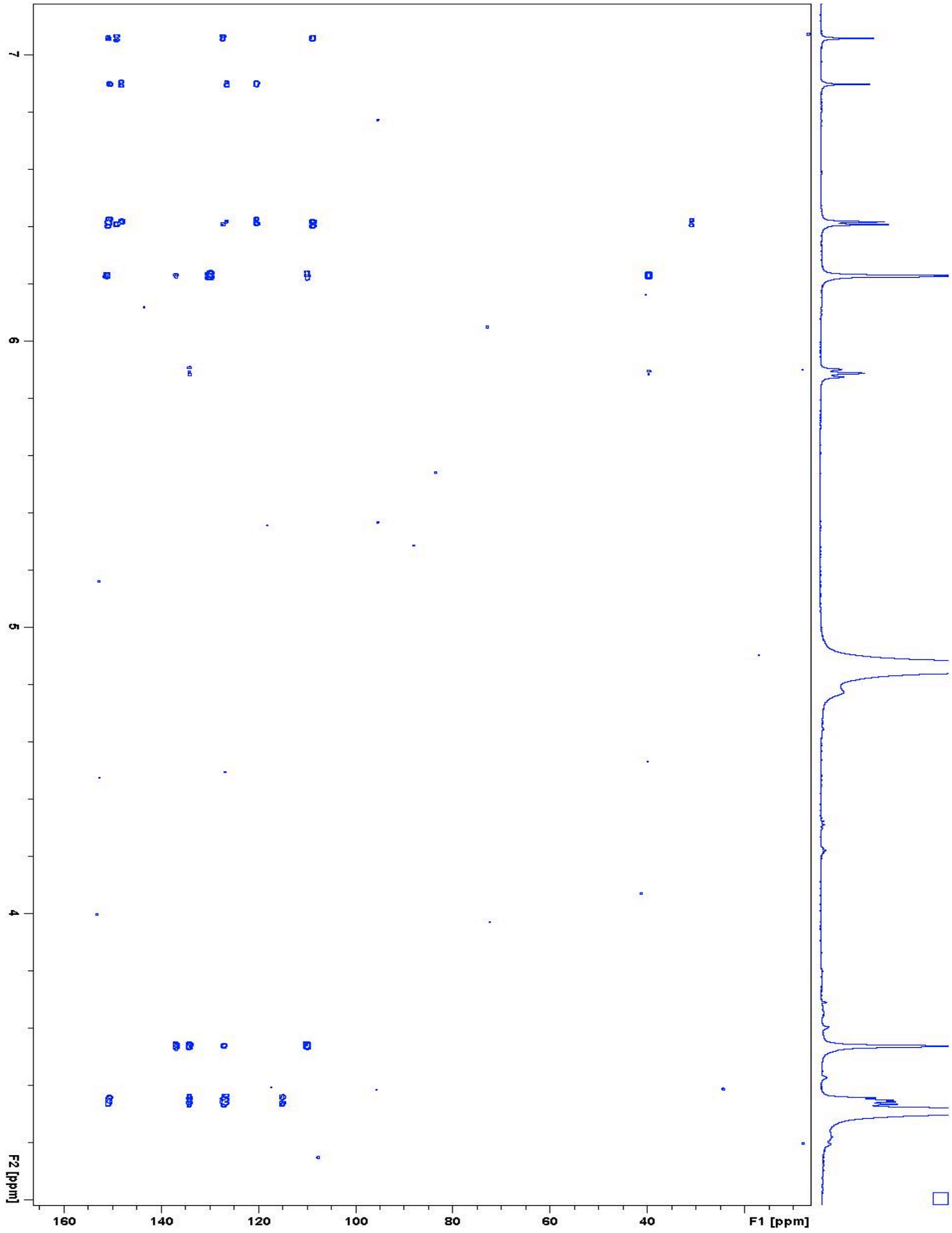
HMBC spectrum of chrysophentin F (**6**) in DMF-d_7



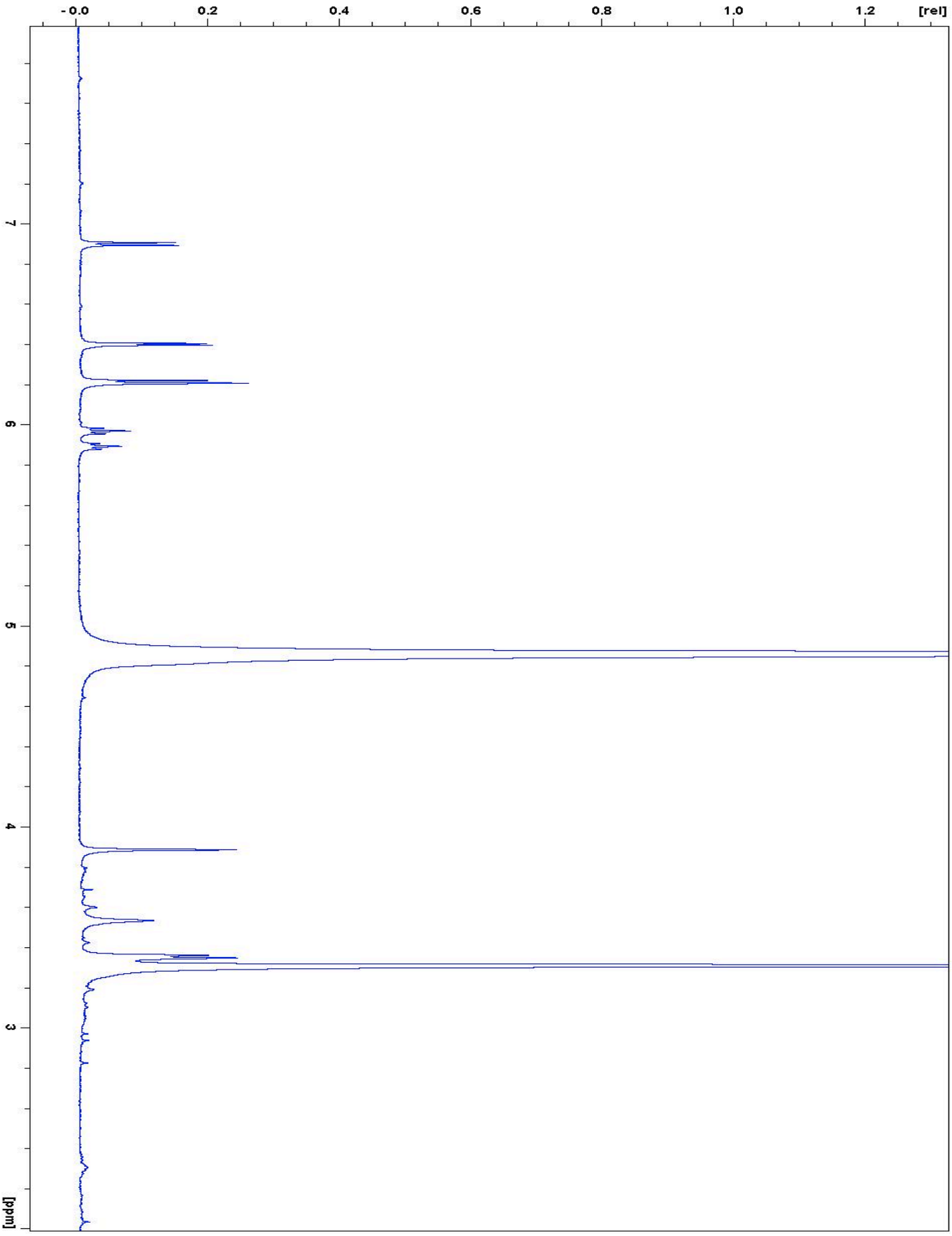
^{1}H NMR spectrum of chrysophentin G (**7**) in MeOD-d_4



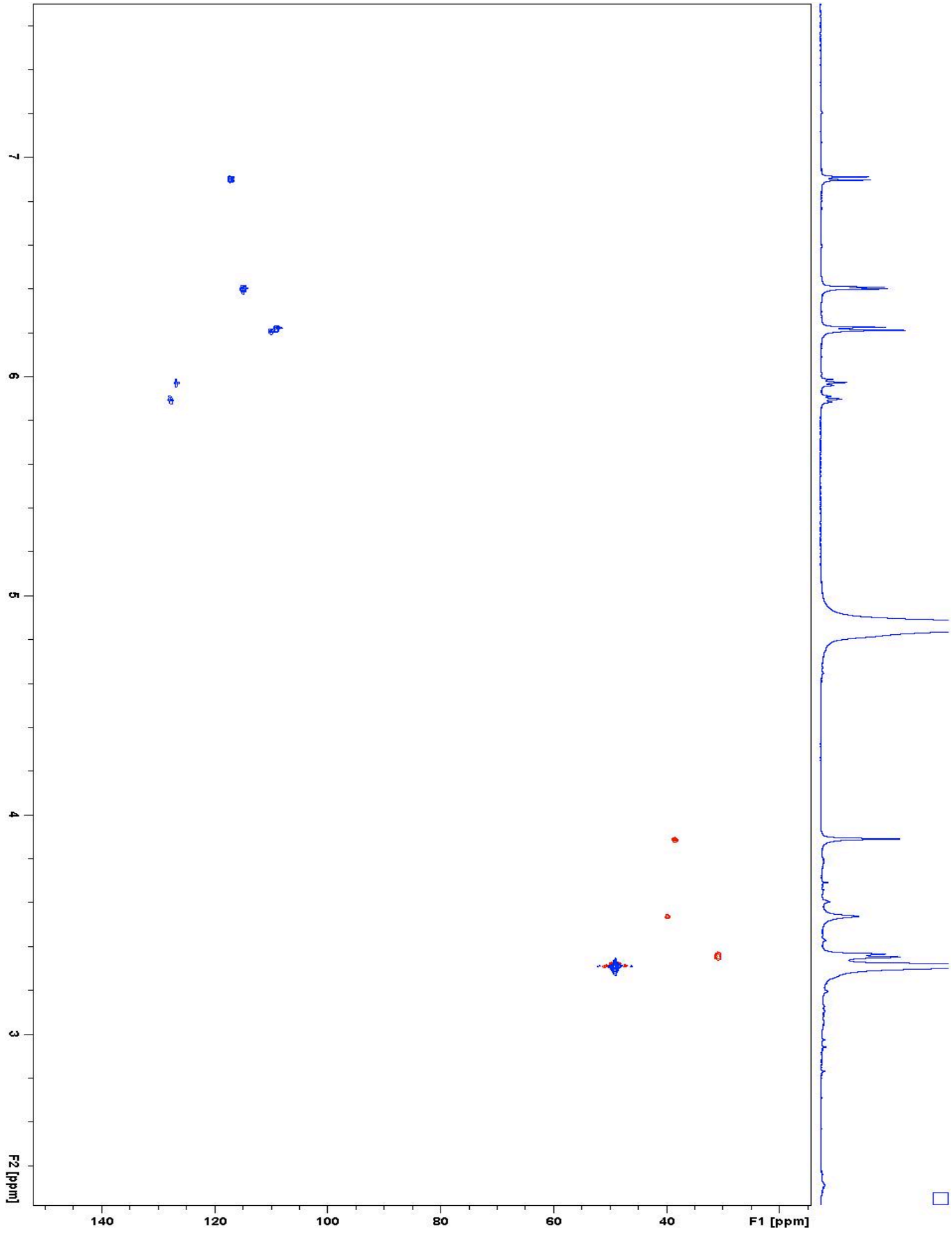
HSQC spectrum of chrysophentin G (**7**) in MeOD-d_4



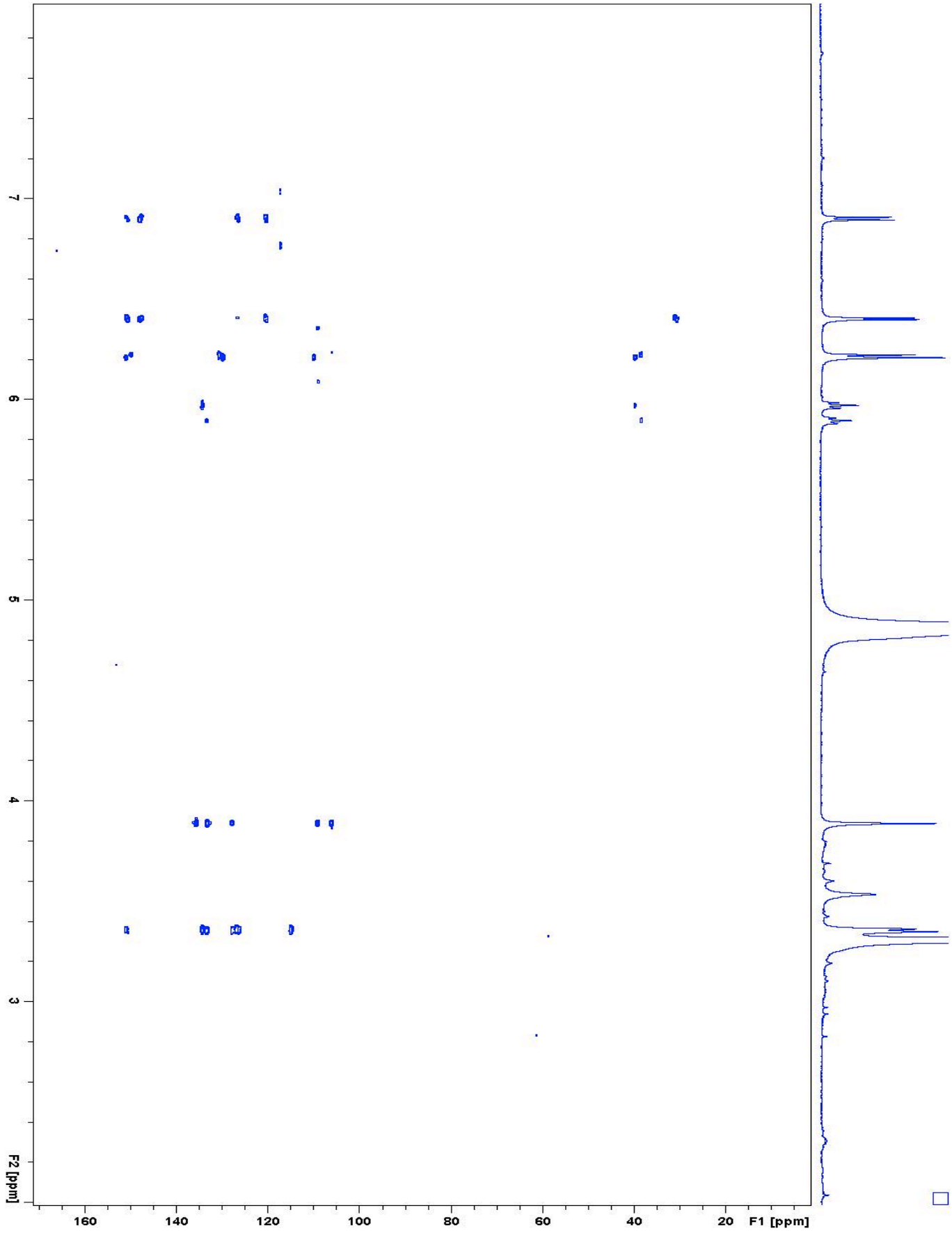
HMBC spectrum of chrysophentin G (**7**) in MeOD-d_4



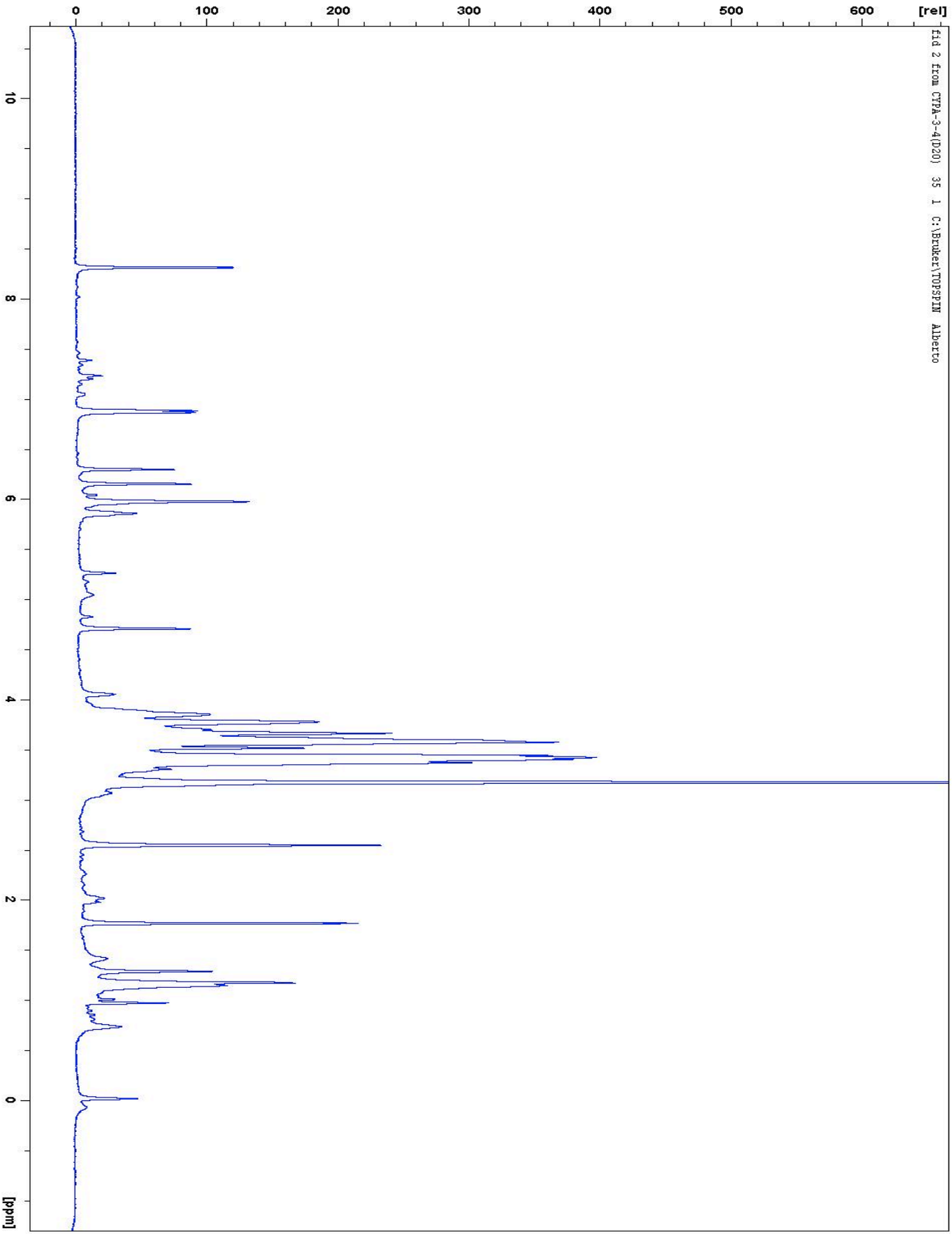
^{1}H NMR spectrum of chrysophentin H (**8**) in MeOD-d_4



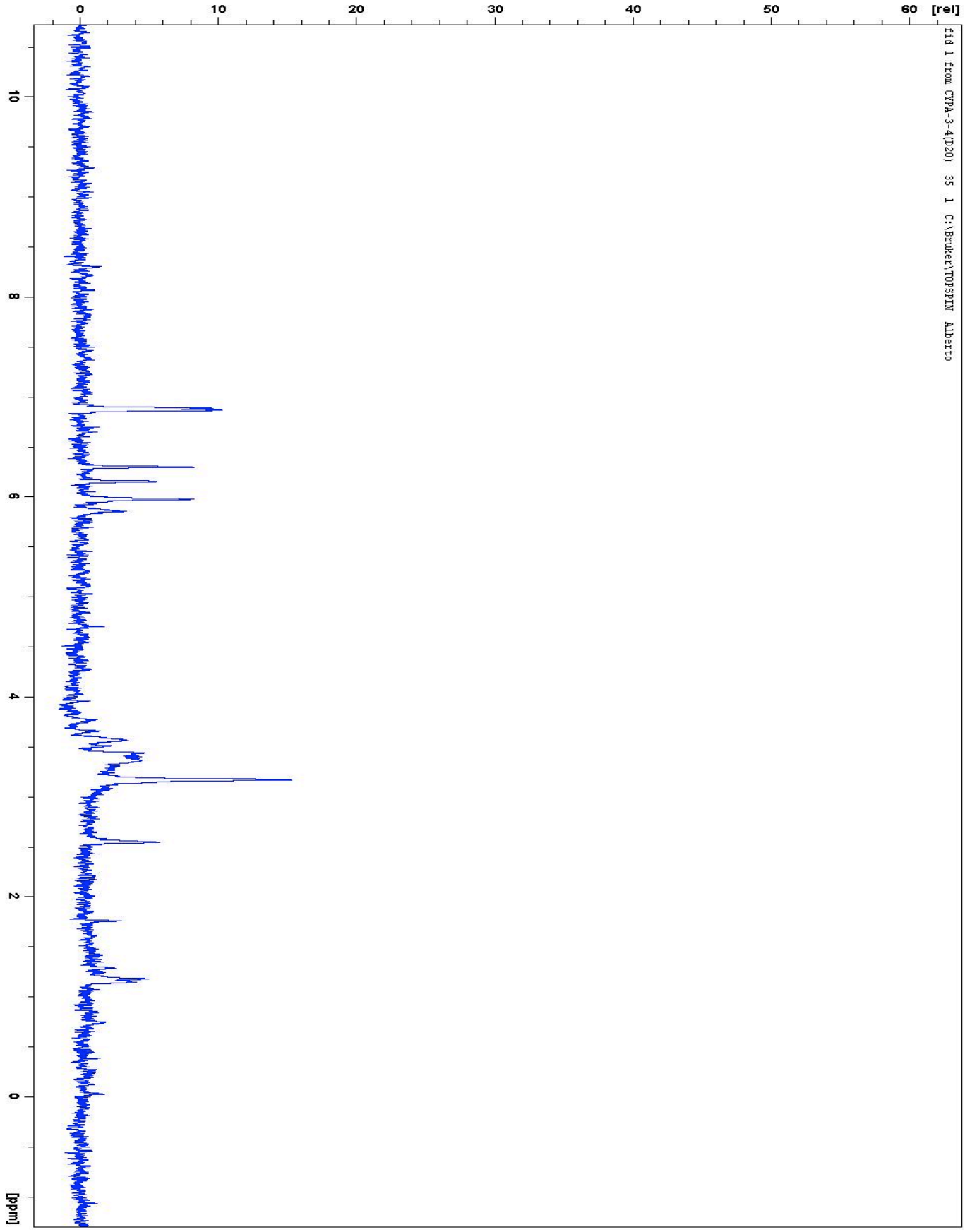
HSQC spectrum of chrysophentin H (**8**) in MeOD-d_4



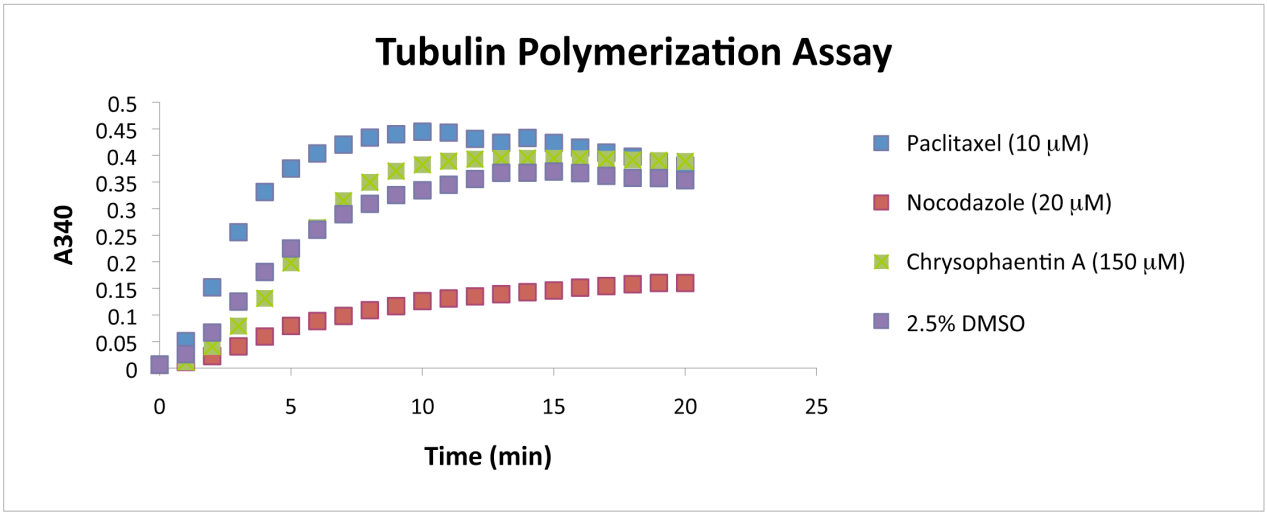
HMBC spectrum of chrysophentin H (**8**) in MeOD-d_4



^{1}H NMR Spectrum of complex chrysophentin A:FtsZ (100:1) in 20 mM $NaPO_4$, 50 mM NaCl, pH 6.8



STD NMR Difference Spectrum of a complex of chrysophentin A:FtsZ (100:1) in 20 mM $NaPO_4$, 50 mM NaCl, pH 6.8



Tubulin polymerization assay. Known microtubule stabilizing (paclitaxel) and disrupting (nocodazole) agents were tested at standardized concentrations, together with chrysophaentin A at 150 μM, a concentration 15 times greater than its IC_{50} value for inhibition of FtsZ. Chrysophaentin A was found to have no effect on tubulin polymerization.