Supplementary Information

Table S1. Conformer relative free energies with respect to the most stable form.

Compound	Conformer ID	Relative Free Energy ΔG (kj/mol)	Boltzmann Factor[a] $e^{(-\Delta G/RT)}$	Population %	Optical Rotation (degree)[b]
1	1a	0.00	1.00	37.44	-244.3
	1b	+2.8	0.32	11.89	-204.1
	1c	+3.1	0.29	10.74	-16.5
	1d	+3.2	0.27	10.26	67.0
	1e	+4.2	0.18	6.75	33.2
	1f	+4.3	0.17	6.50	-127.6
	1g	+5.3	0.12	4.48	192.7
	1h	+7.0	0.06	2.18	88.2
	1i	+7.4	0.05	1.87	-85.7
					-107.7[c]
2	2a	0.00	1.00	34.21	-88.5
	2b	+0.2	0.94	32.03	-89.5
	2c	+1.5	0.54	18.48	68.8
	2d	+4.4	0.17	5.82	223.6
	2e	+6.6	0.07	2.37	-37.8
	2f	+6.8	0.07	2.24	37.5
	2g	+7.4	0.05	1.70	38.4
					-32.6[c]
3	3a	0.00	1.00	37.62	-162.84
	3b	+0.9	0.69	25.82	65.13
	3c	+4.0	0.20	7.41	-10.52
	3d	+5.5	0.11	4.11	-119.51
	3e	+5.9	0.09	3.47	-10.25
	3f	+6.0	0.09	3.34	-13.39
	3g	+6.0	0.09	3.33	132.21
	3h	+6.7	0.07	2.52	-96.37
	3i	+6.9	0.06	2.35	-40.38
	3j	+8.6	0.03	1.16	8.17
					-49.8[c]

[a]Calculated at 298K.

[b]Calculated at B3LYP/6-31G* level of theory with the polarizable continuum model (PCM) for chloroform.

[c]Boltzmann-weighted mean optical rotation.

Table S2. Calculated auto-dock and MM/GBSA binding energies (Δ*G*) for the most and least active compounds complexed with the EGFR kinase domain.

Compound	IC_{50} (μM)[a]	ΔG_{exp} (kcal/mol)[b]	ΔG_{calc} (kcal/mol)		Binding Features		
			AutoDock	MM/GBSA	Residue	Type	Length (Å)
Erlotinib	nd	---	-7.23	-47.89	Met_{769}	H-bond	2.01
					Cys_{773}	H-bond	2.05
Afatinib	nd	---	-7.68	-55.90	Met_{769}	H-bond	2.09
					Leu_{694}	H-bond	2.10
					Cys_{773}	H-bond	1.90
					Lys_{692}	H-bond	1.91
Gefitinib	nd	---	-7.69	-50.23	Thr_{766}	H-bond	2.08
					Met_{769}	H-bond	2.24
Doxorubicin	0.62	-8.46	-8.94	-54.72	Lys_{721}	H-bond	1.92
					Thr_{766}	H-bond	1.76
					Met_{769}	H-bond	1.82
					Thr_{830}	H-bond	1.92
					Asp_{831}	H-bond	1.94
8	27.3	-6.22	-8.13	-41.18	Thr_{766}	H-bond	1.79
					Asp_{776}	H-bond	1.62
7	43.6	-5.94	-5.82	-36.52	Thr_{766}	H-bond	1.75
					Thr_{830}	H-bond	1.87
6	37.0	-6.04	-6.14	-38.04	Met_{769}	H-bond	1.82
					Asp_{831}	H-bond	1.65
4	91.5	-5.51	-7.17	-31.81	Lys_{721}	H-bond	1.82
Correlation coefficient (R^2)			0.37[c]	0.96[c]			

[a] IC_{50} Values for the tested compounds against A549 cell line.

[b]Calculated based on the experimental IC_{50}.

[c]Erlotinib, afatinib and gefitinib were not considered in the calculated correlation due to the absence of the corresponding experimental IC_{50}.

Figure S1. HR-ESI-FTMS spectrum of Sarcoehrenbergilid A (**1**) in $CDCl_3$.

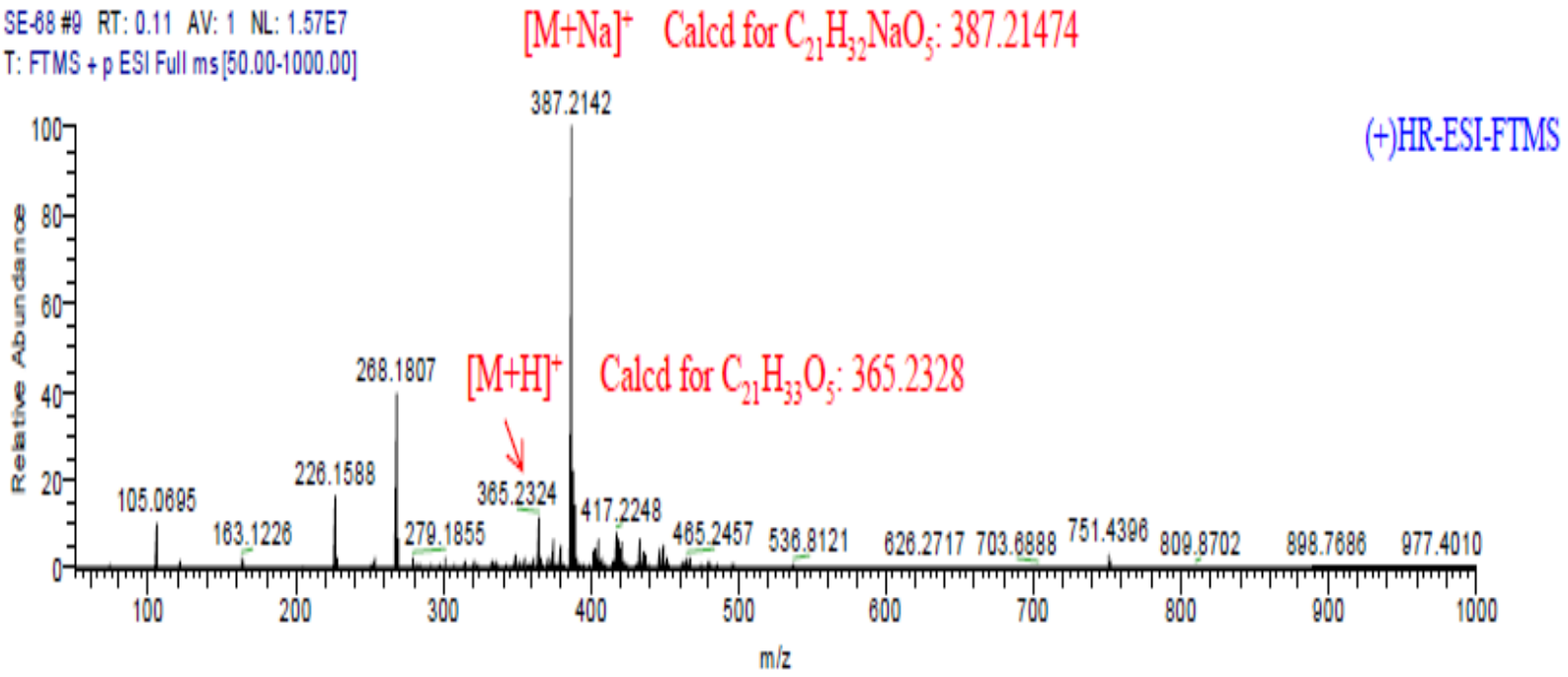


Figure S2. ^{1}H NMR spectrum of Sarcoehrenbergilid A (**1**) in $CDCl_3$.

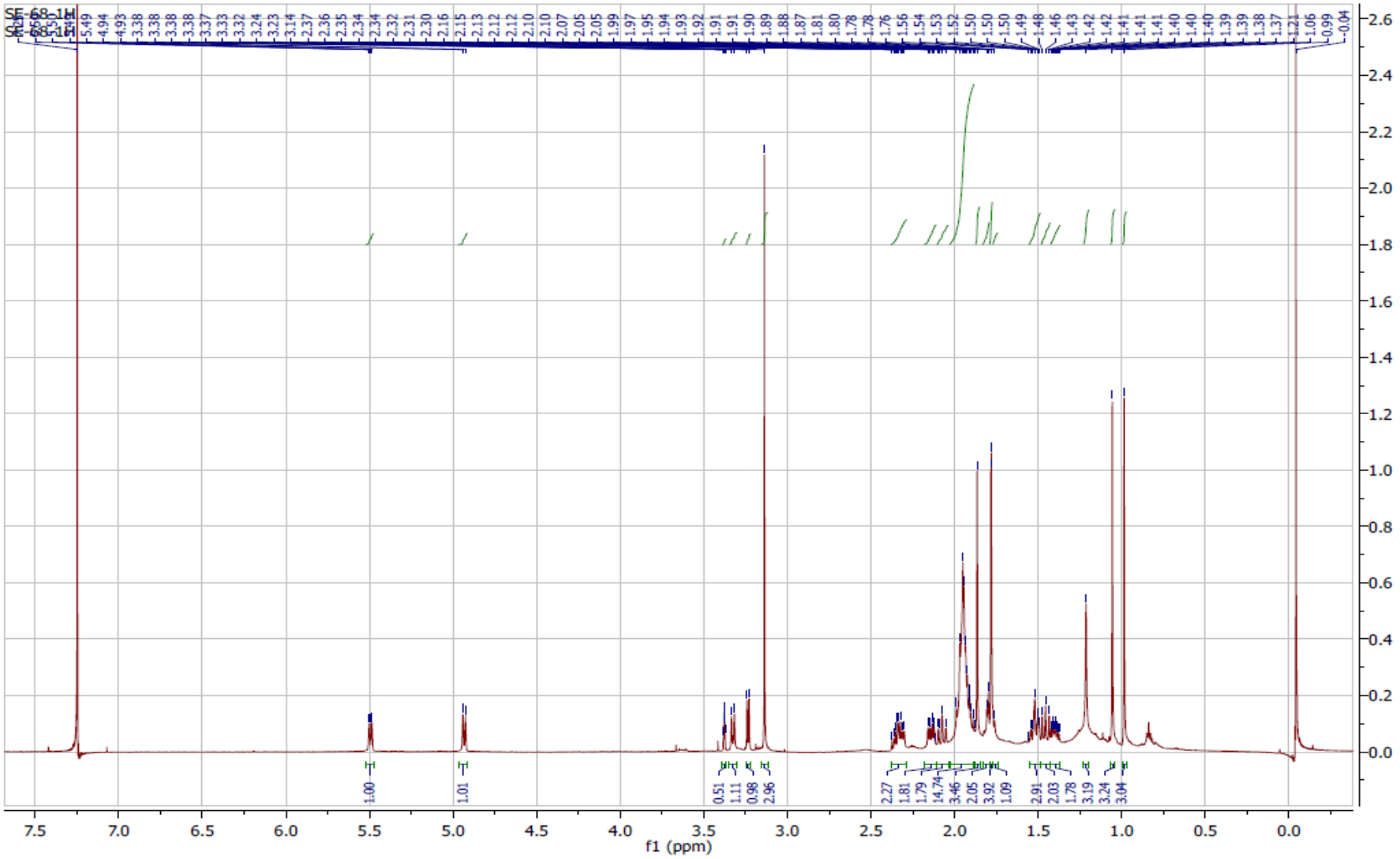


Figure S3. ^{13}C NMR spectrum of Sarcoehrenbergilid A (**1**) in $CDCl_3$.

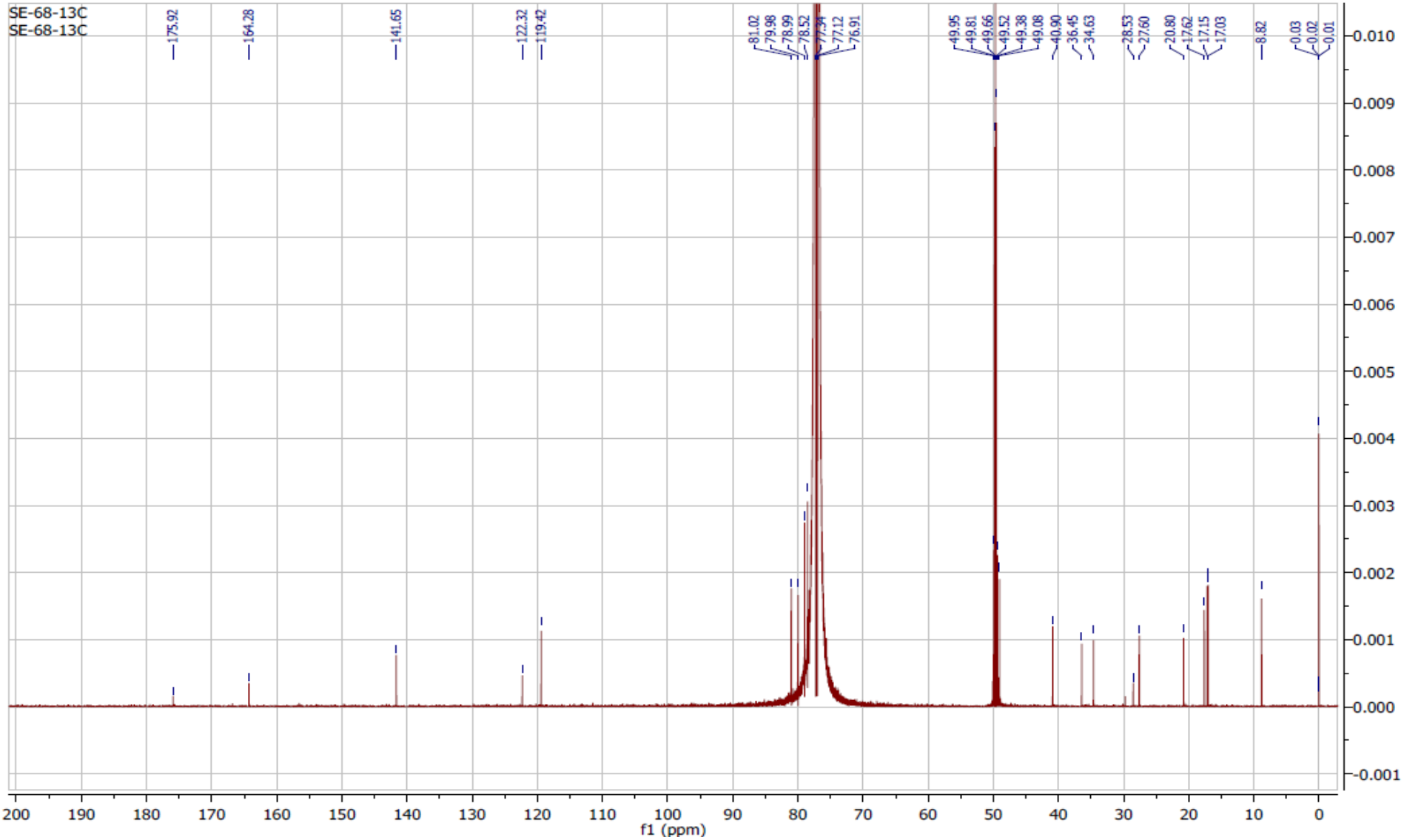


Figure S4. DEPT spectrum of Sarcoehrenbergilid A (**1**) in $CDCl_3$.

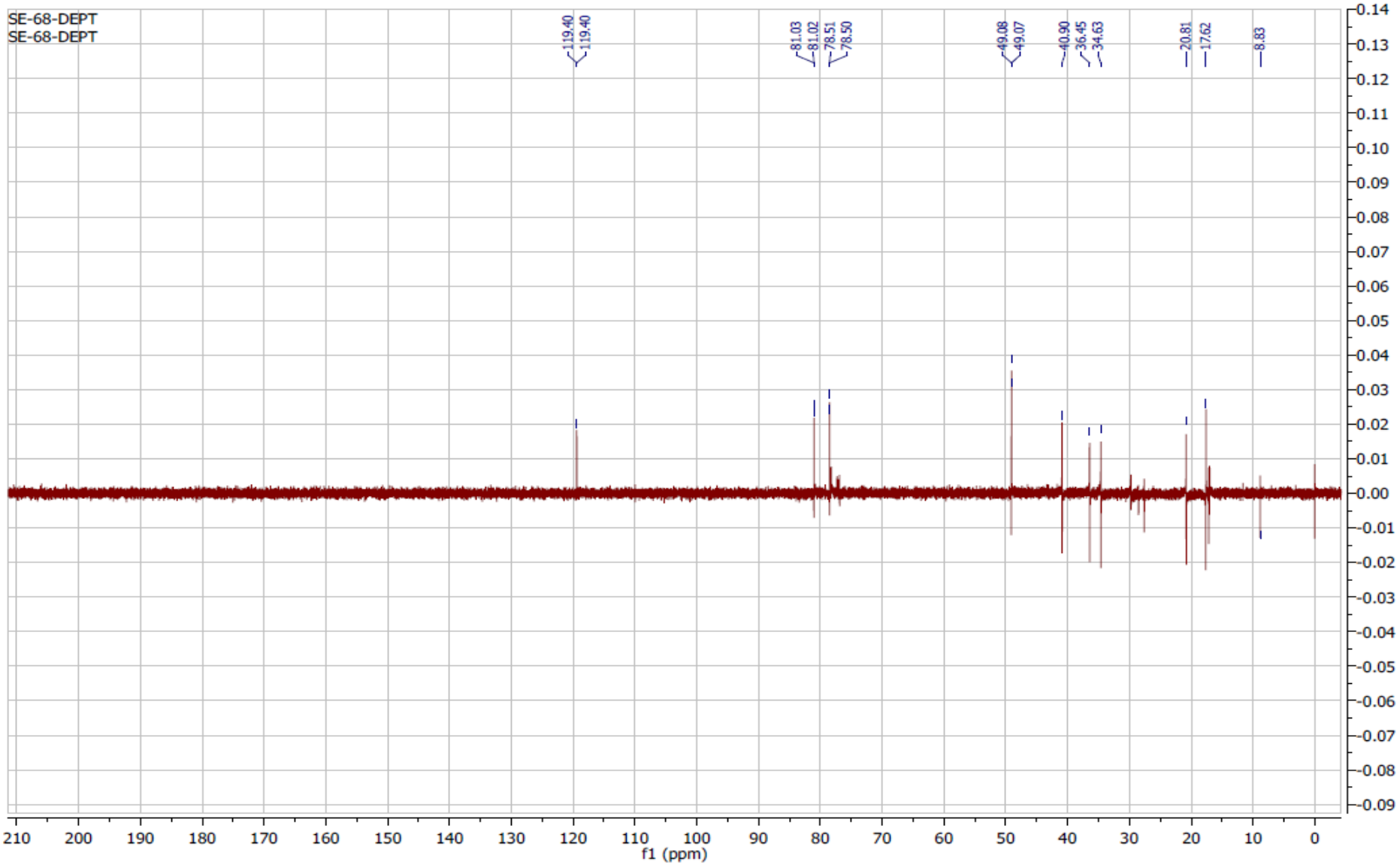
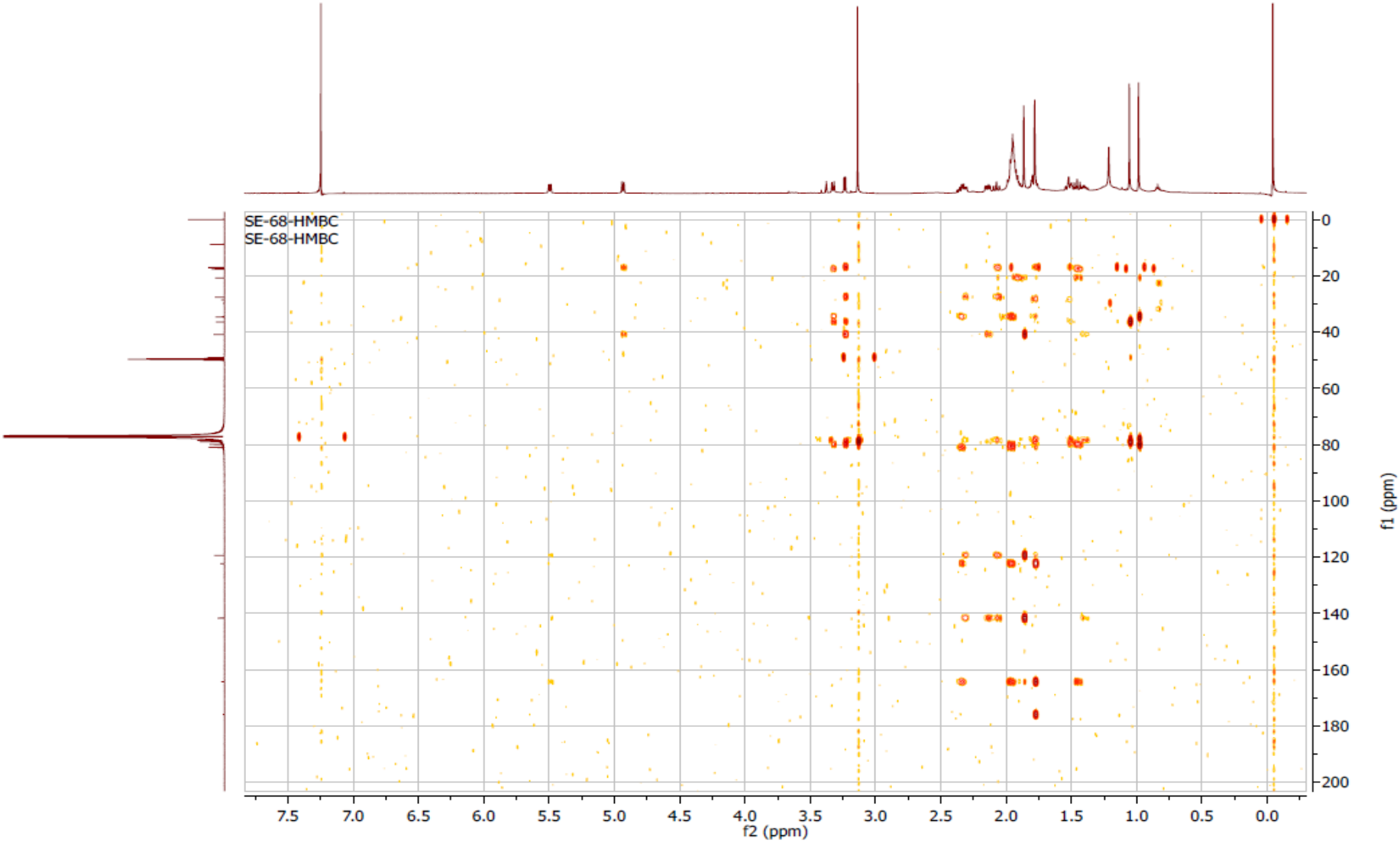


Figure S5. HMBC spectrum of Sarcoehrenbergilid A (**1**) in $CHCl_3$.



Figure

Fig. S6. ^{1}H, ^{1}H COSY spectrum of Sarcoehrenbergilid A (**1**) in $CDCl_3$.

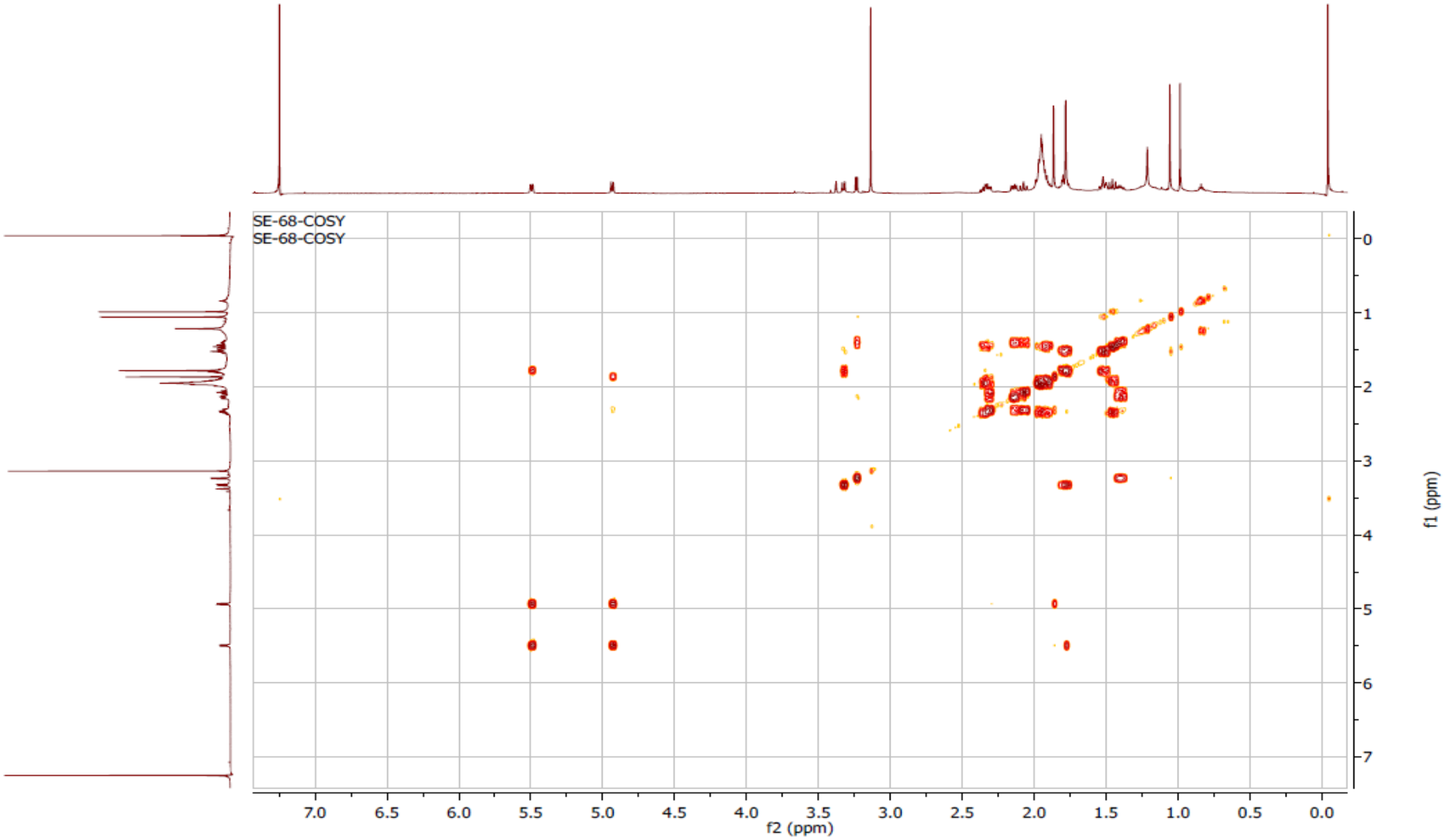


Figure S7. NOESY spectrum of Sarcoehrenbergilid A (**1**) in $CDCl_3$.

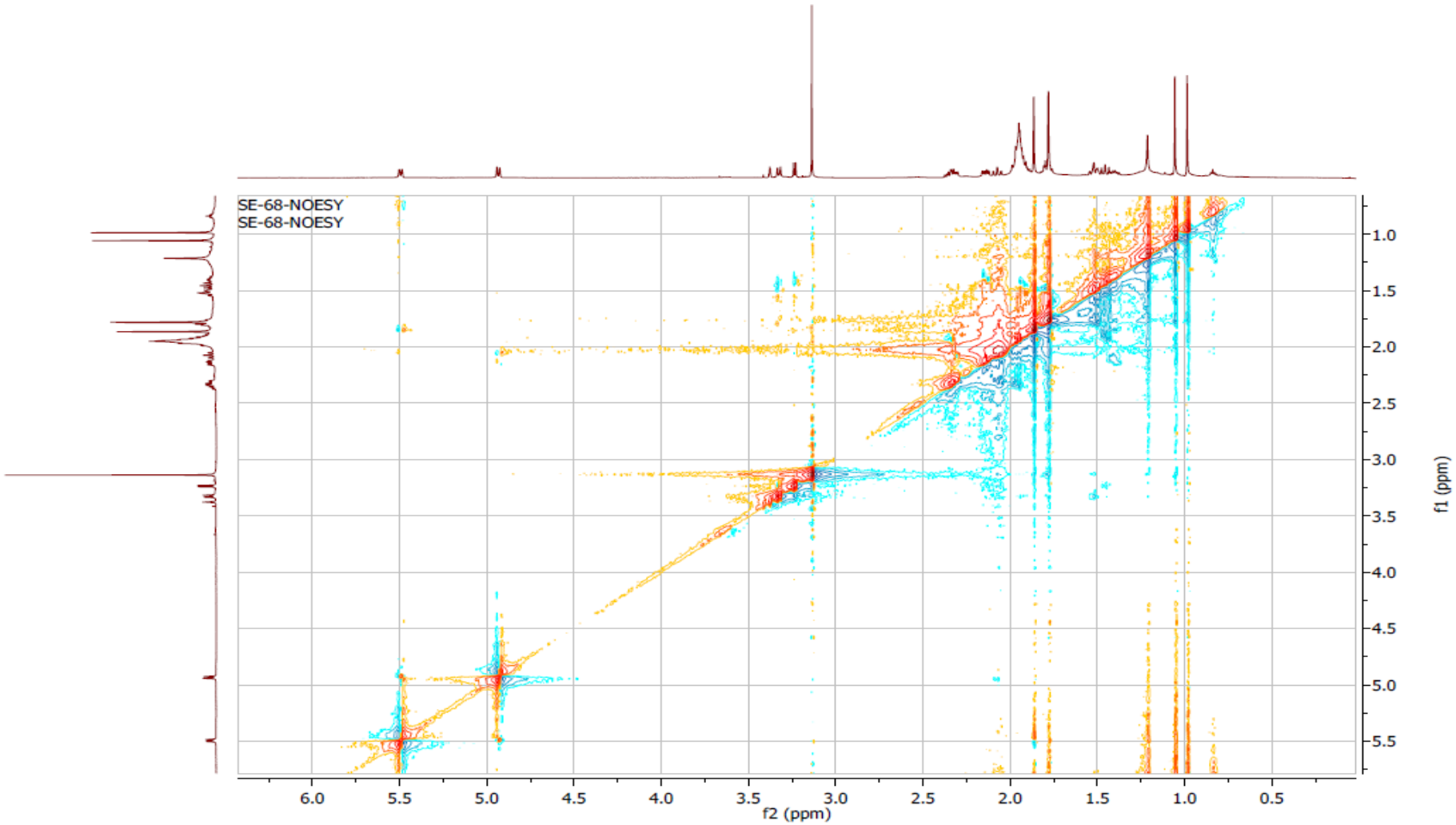


Figure S8. HR-ESI-FTMS spectrum of Sarcoehrenbergilid B (**2**).

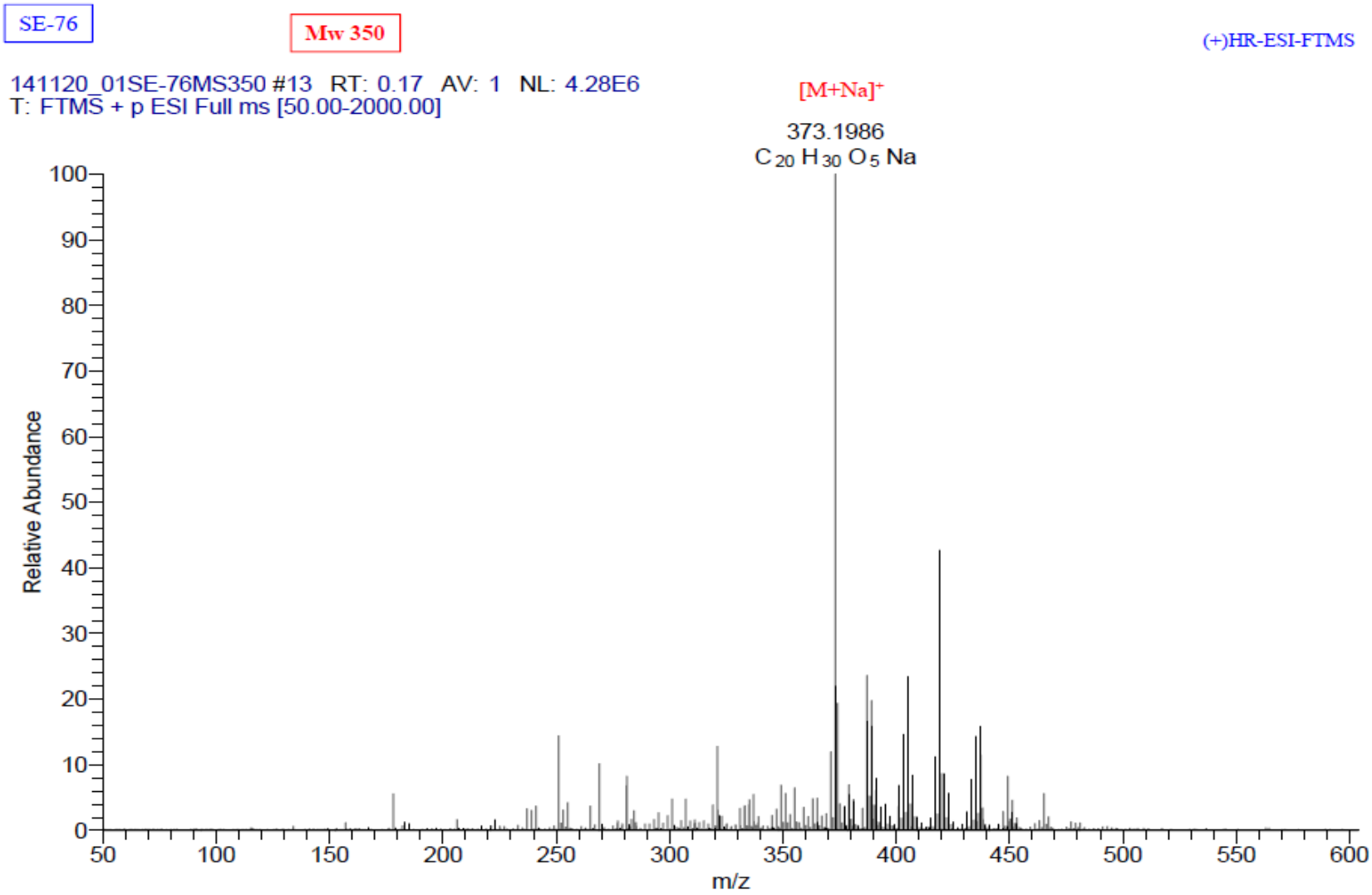


Figure S9. ^{1}H NMR spectrum of Sarcoehrenbergilid B (**2**) in $CDCl_3$.

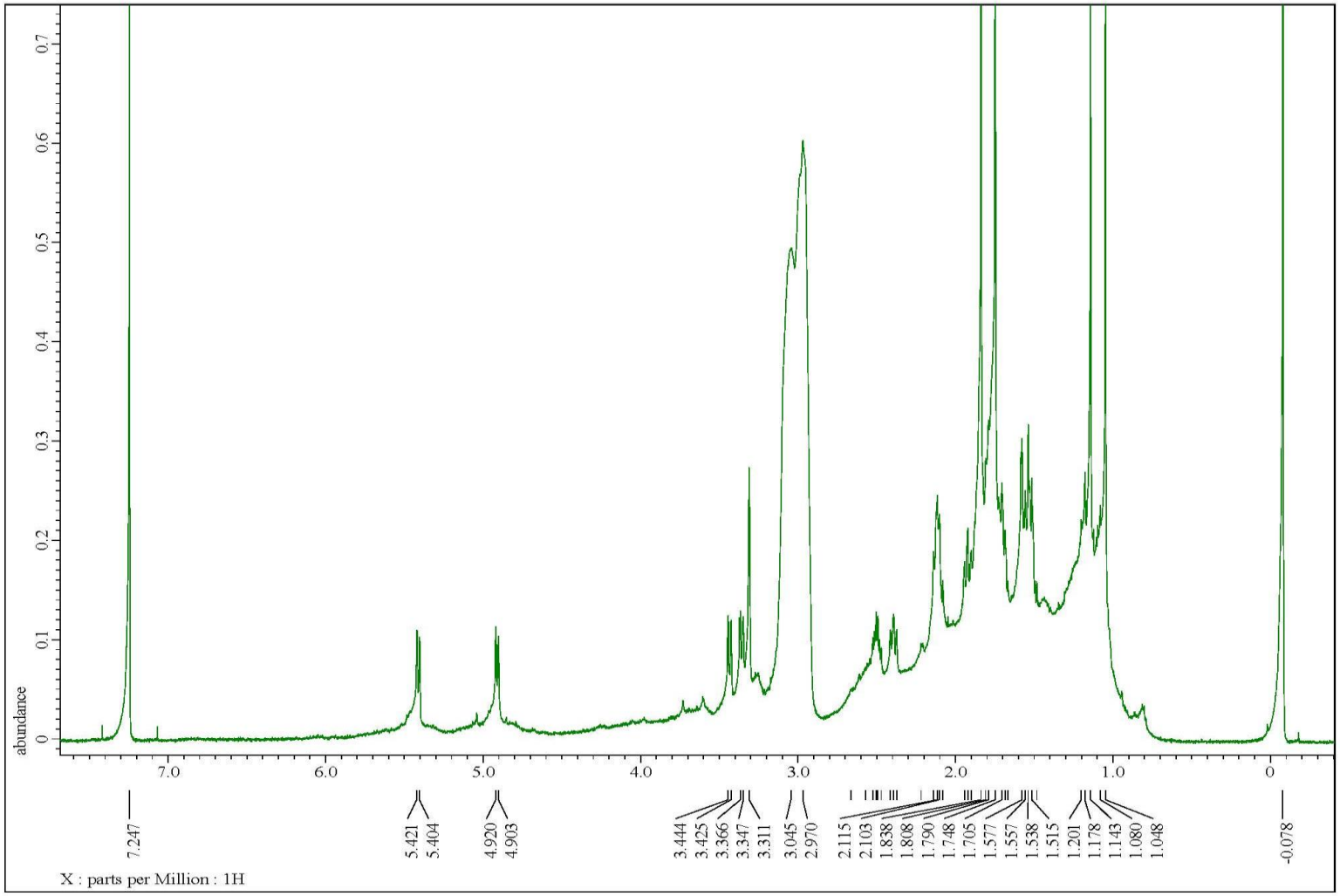


Figure S10. ^{13}C NMR spectrum of Sarcoehrenbergilid B (**2**) in $CDCl_3$.

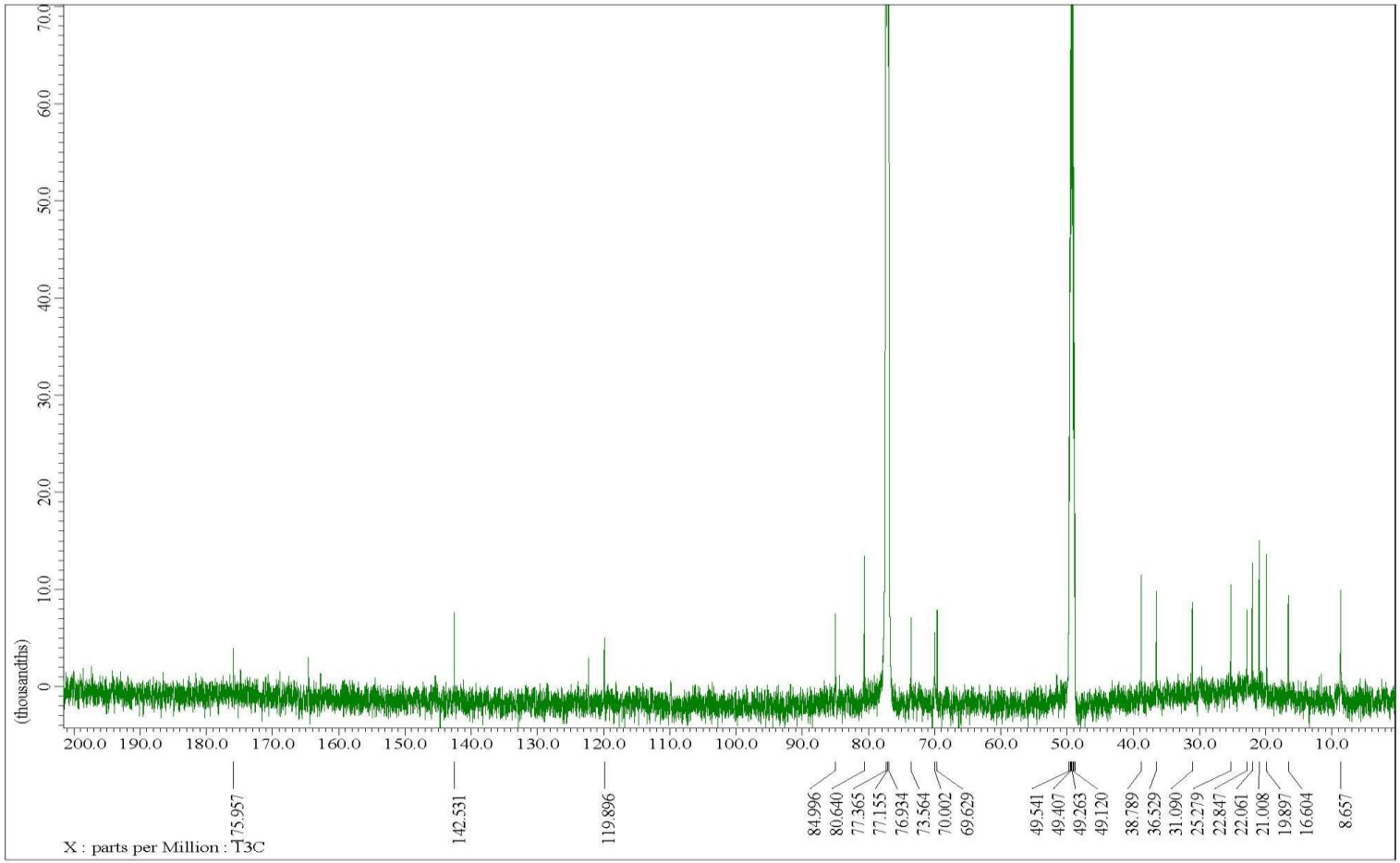


Figure S11. ^{1}H-^{1}H COSY spectrum of Sarcoehrenbergilid B (**2**) in $CDCl_3$.

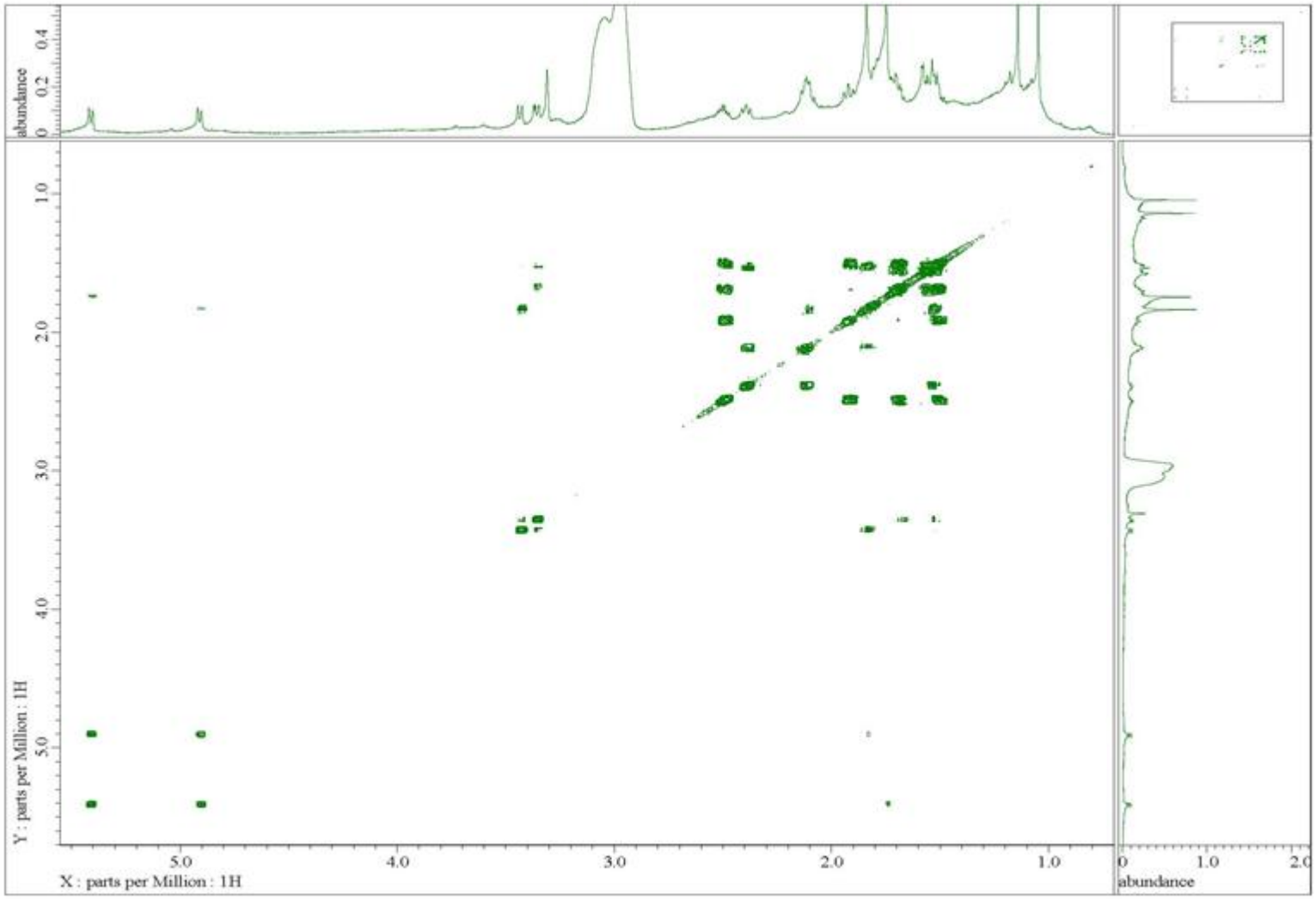


Figure S12. HSQC spectrum of Sarcoehrenbergilid B (**2**) in $CDCl_3$.

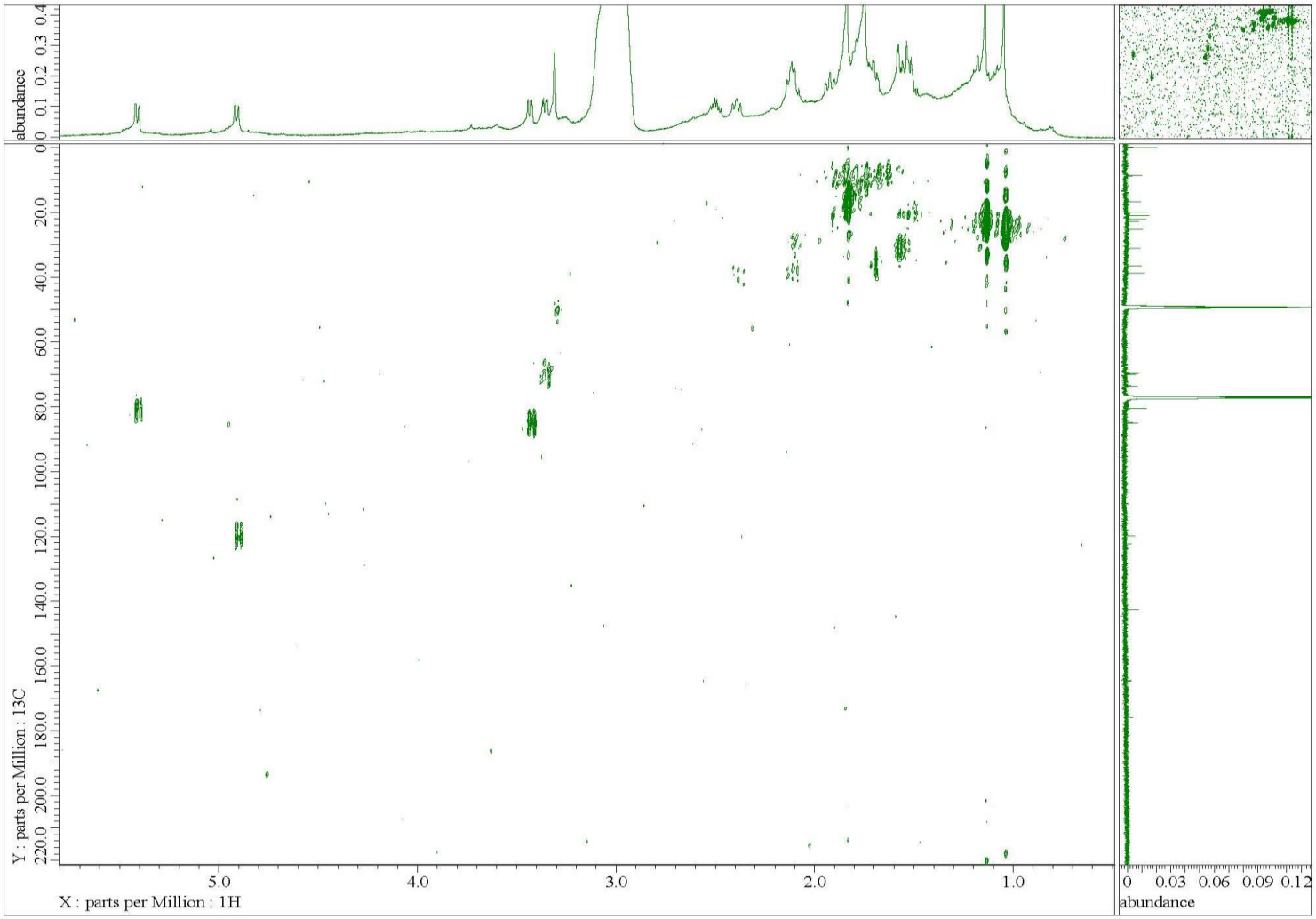


Figure S13. HMBC spectrum of Sarcoehrenbergilid B (**2**) in $CDCl_3$.

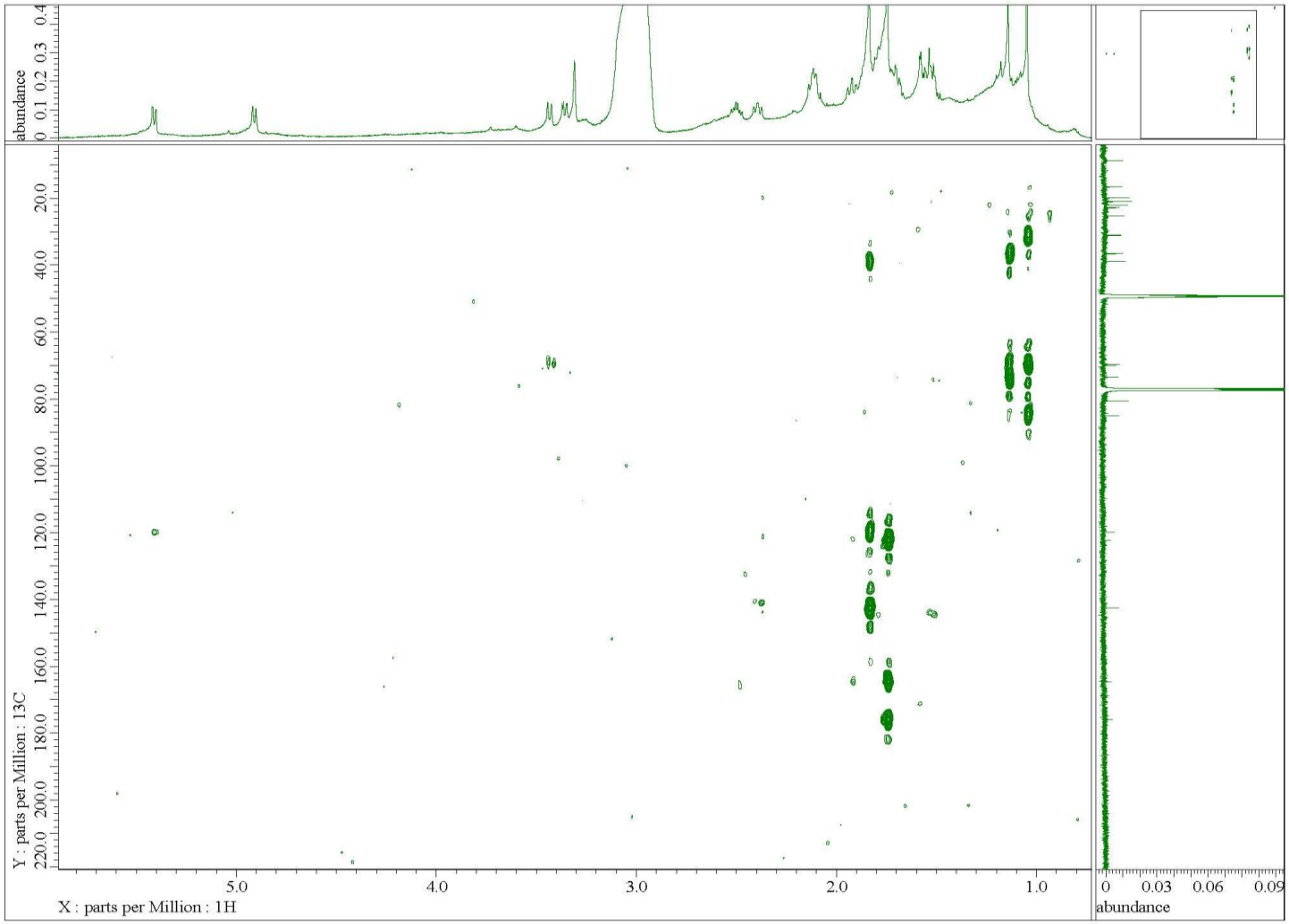


Figure S14. NOESY spectrum of Sarcoehrenbergilid B (**2**) in $CDCl_3$.

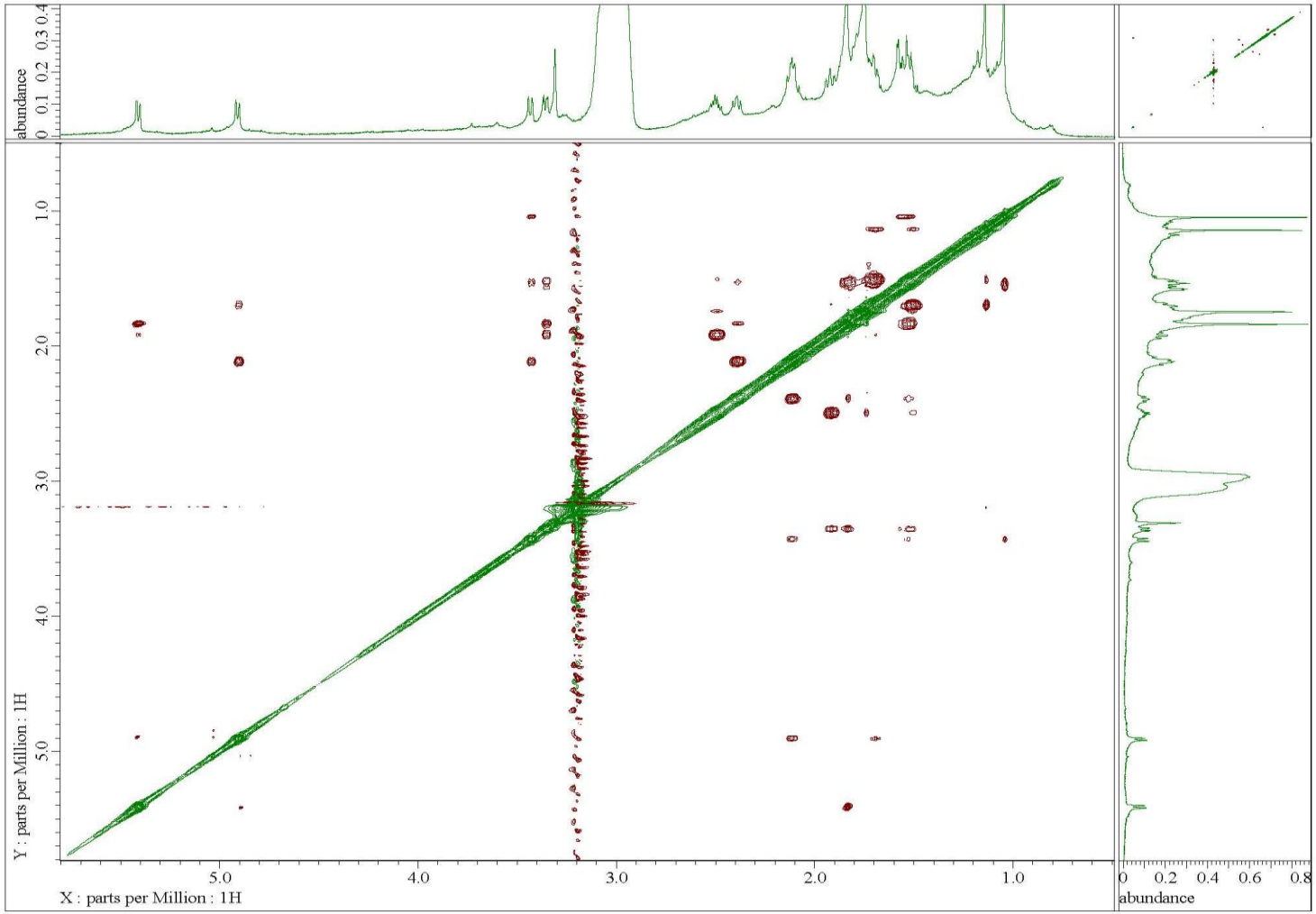


Figure S15. HR-ESI-FTMS spectrum of Sarcoehrenbergilid C (**3**).

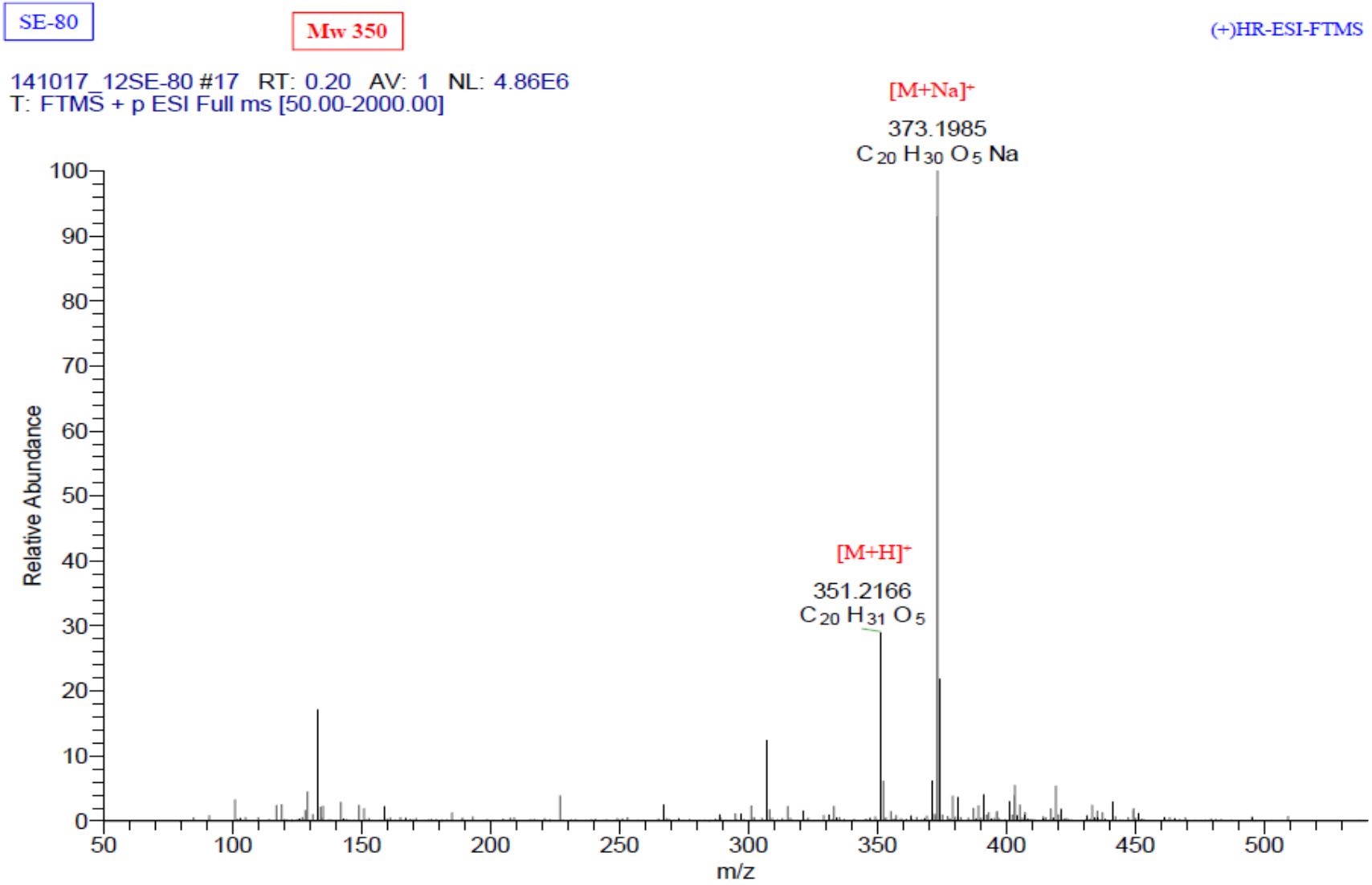


Figure S16. ^{1}H NMR spectrum of Sarcoehrenbergilid C (**3**) in $CDCl_3$.

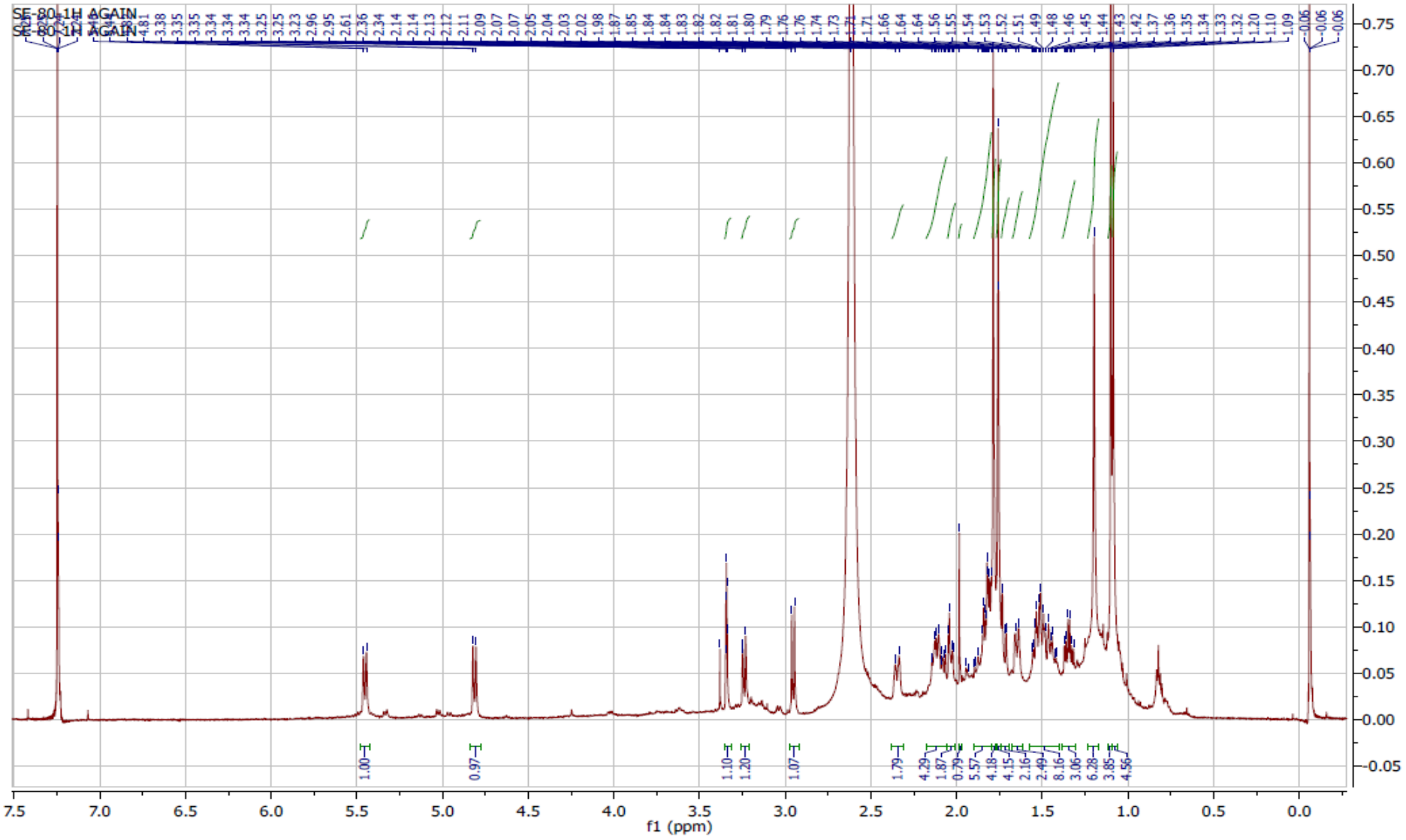


Figure S17. ^{13}C NMR spectrum of Sarcoehrenbergilid C (**3**) in $CDCl_3$.

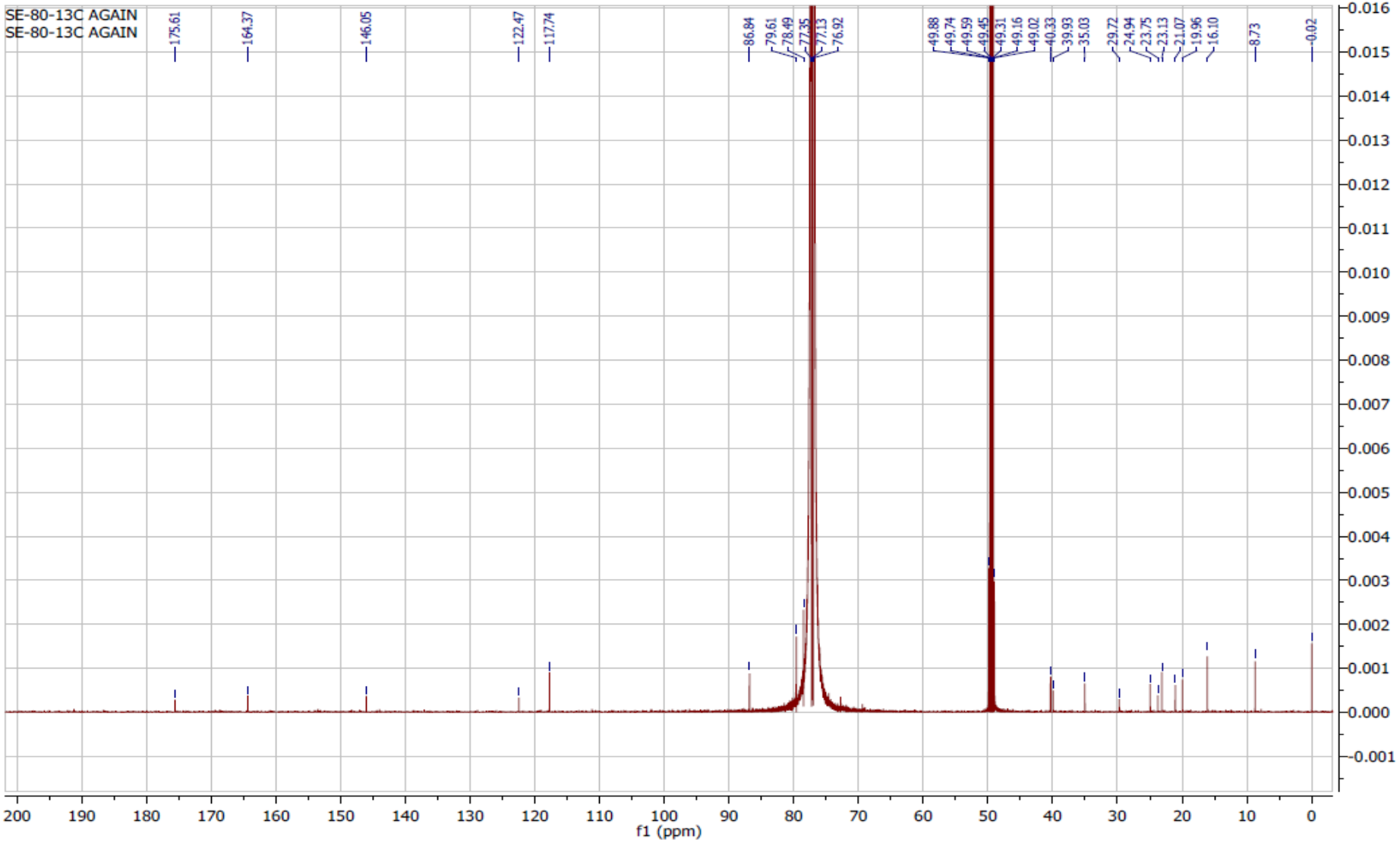


Figure S18. DEPT spectrum of Sarcoehrenbergilid C (**3**) in $CDCl_3$.

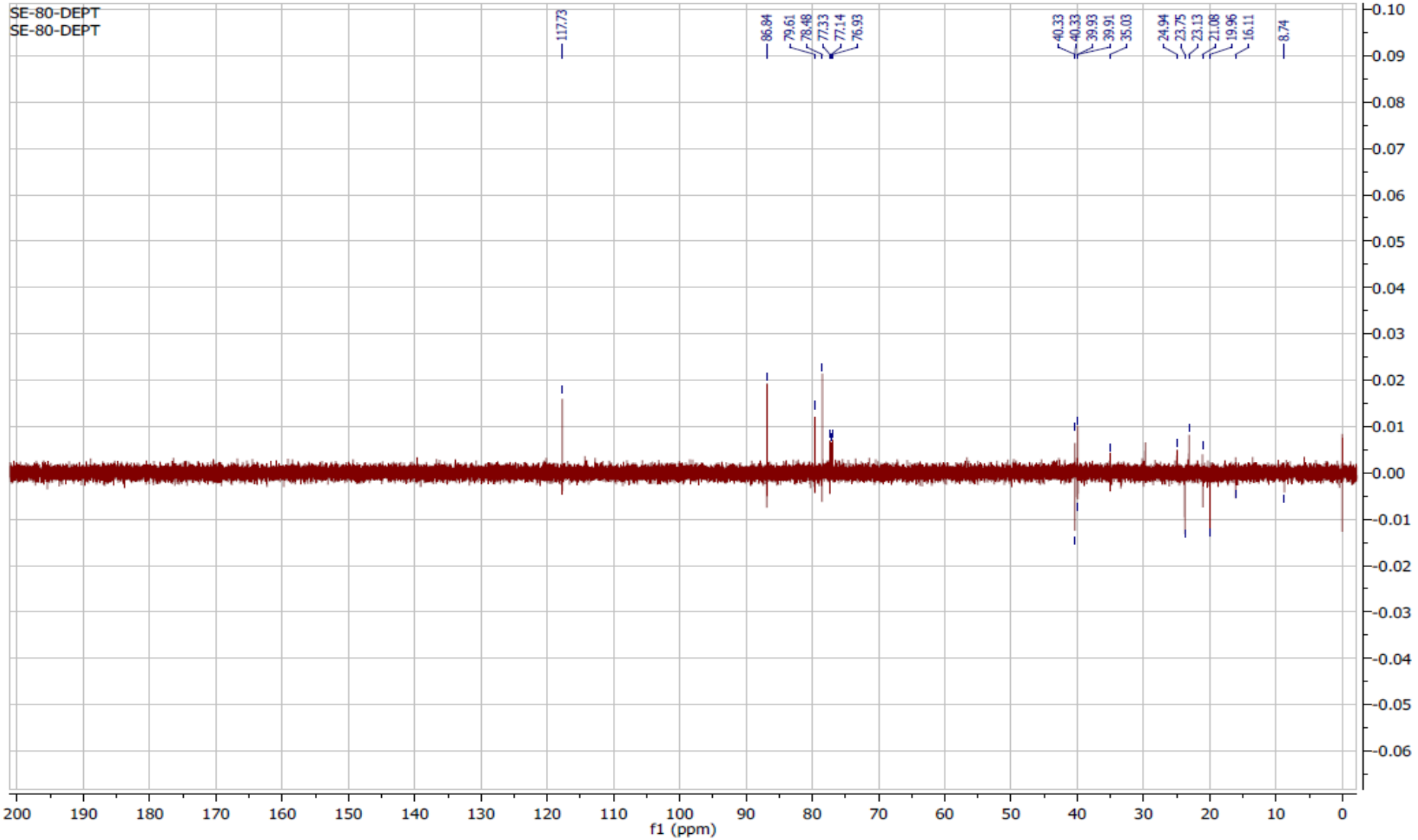


Figure S19. HSQC spectrum of Sarcoehrenbergilid C (**3**) in $CDCl_3$.

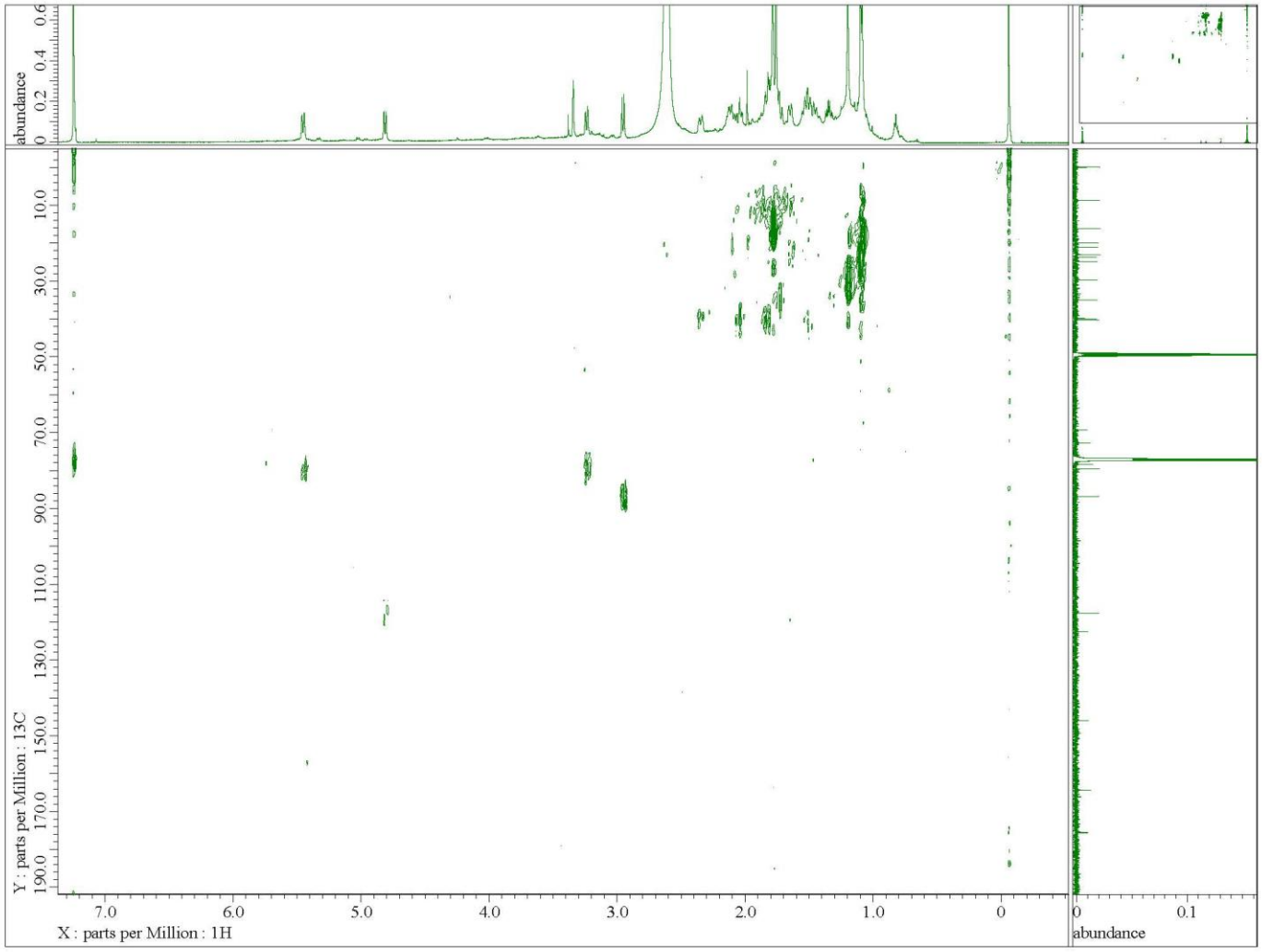


Figure S20. HMBC spectrum of Sarcoehrenbergilid C (**3**) in $CDCl_3$.

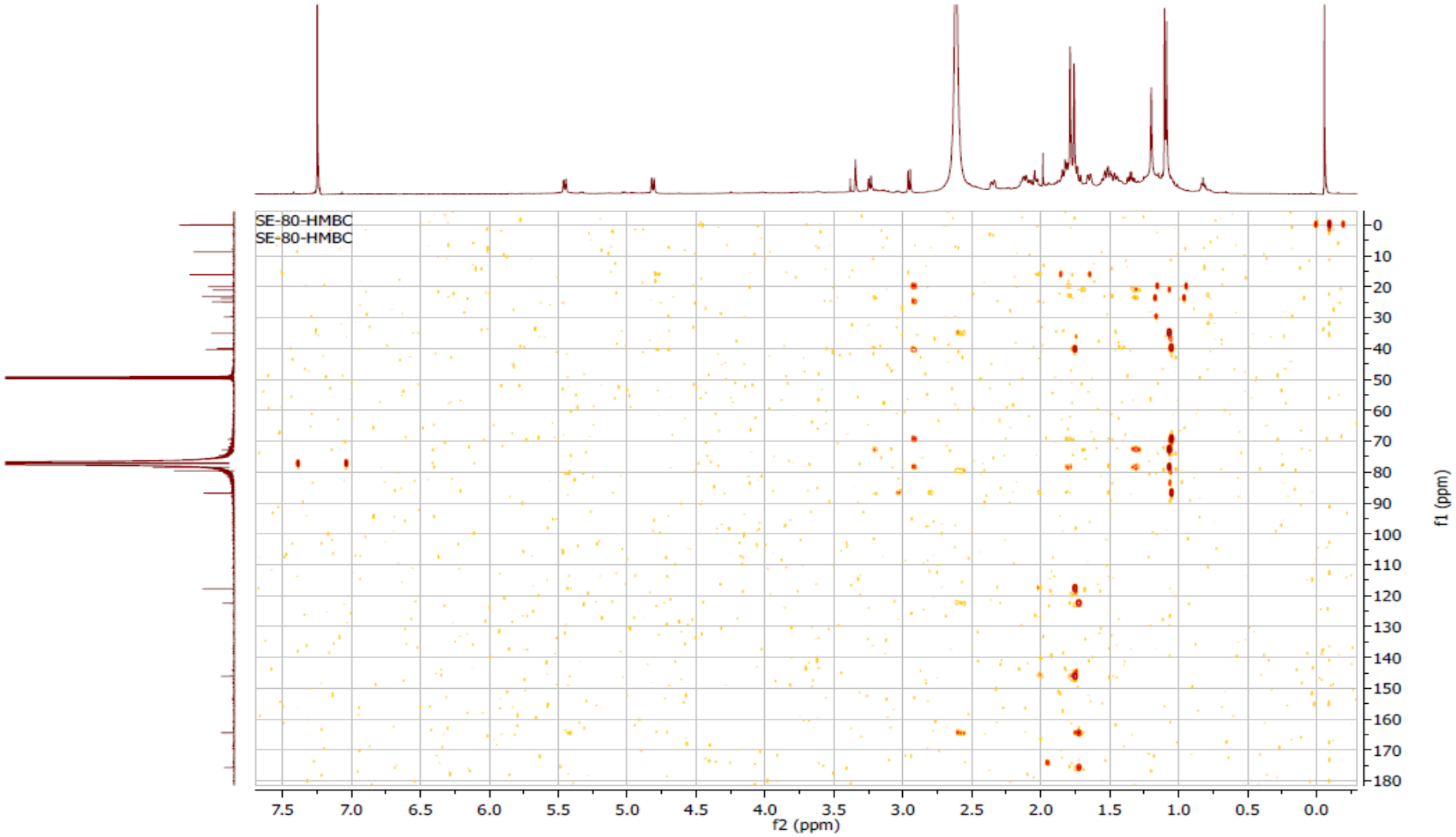


Figure S21. NOESY spectrum of Sarcoehrenbergilid C (**3**) in $CDCl_3$.

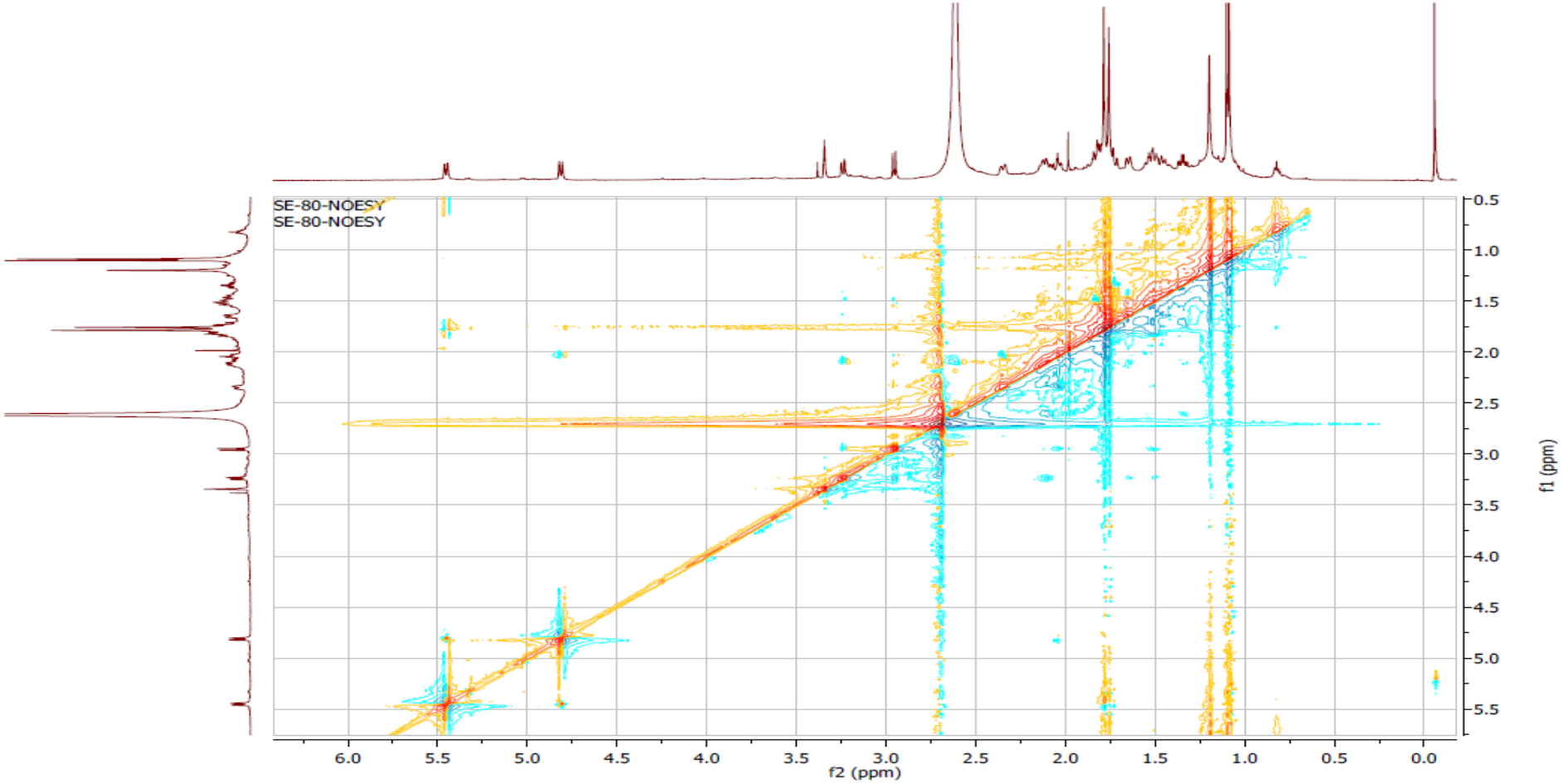
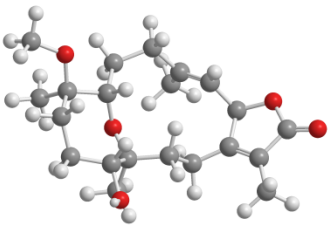
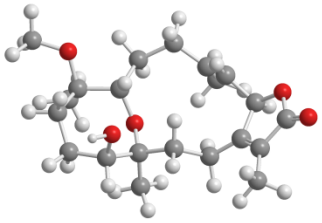


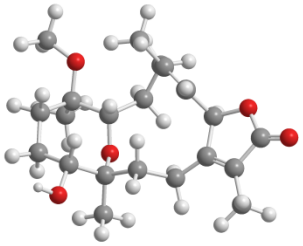
Figure S22. Optimized structure and relative free energy of conformers of **1** with Boltzmann population higher than 1%.



Compound 1a

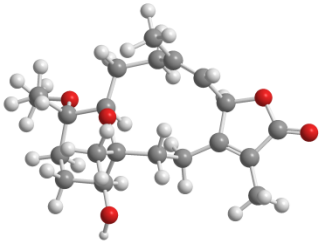


conformer 1b
Δ*G*=+2.8 kj/mol

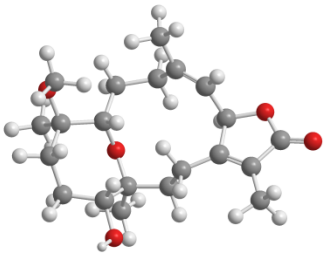


conformer 1c
Δ*G*=+3.1 kj/mol

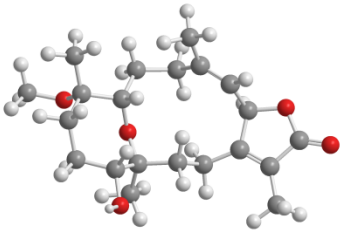
conformer 1d
Δ*G*=+3.2 kj/mol



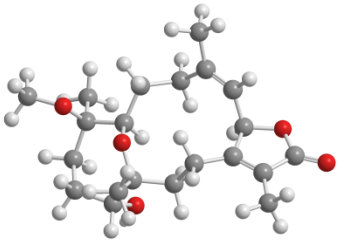
conformer 1e
Δ*G*=+4.2 kj/mol



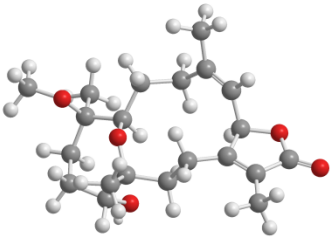
conformer 1f
Δ*G*=+4.3 kj/mol



conformer 1g
Δ*G*=+5.3 kj/mol

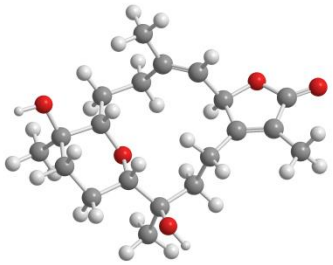


conformer 1h
Δ*G*=+7.0 kj/mol

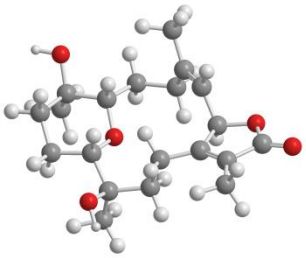


conformer 1i
Δ*G*=+7.4 kj/mol

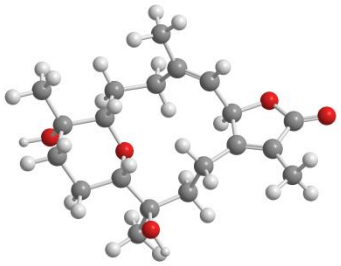
Figure S23. Optimized structure and relative free energy of conformers of **2** with Boltzmann population higher than 1%.



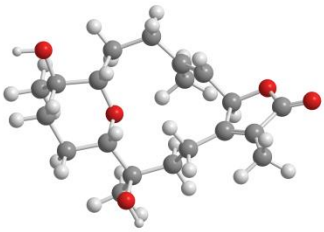
Compound 2a



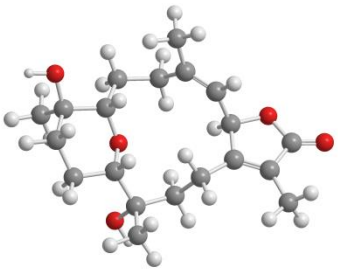
conformer 2b
Δ*G*=+0.2 kj/mol



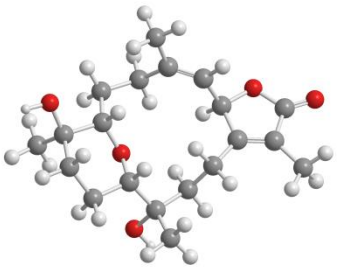
conformer 2c
Δ*G*=+1.5 kj/mol



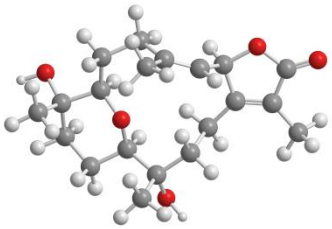
conformer 2d
Δ*G*=+4.4 kj/mol



conformer 2e
Δ*G*=+6.6 kj/mol



conformer 2f
Δ*G*=+6.8 kj/mol



conformer 2g
Δ*G*=+7.4 kj/mol

Figure S24. Optimized structure and relative free energy of conformers of **3** with Boltzmann population higher than 1%.

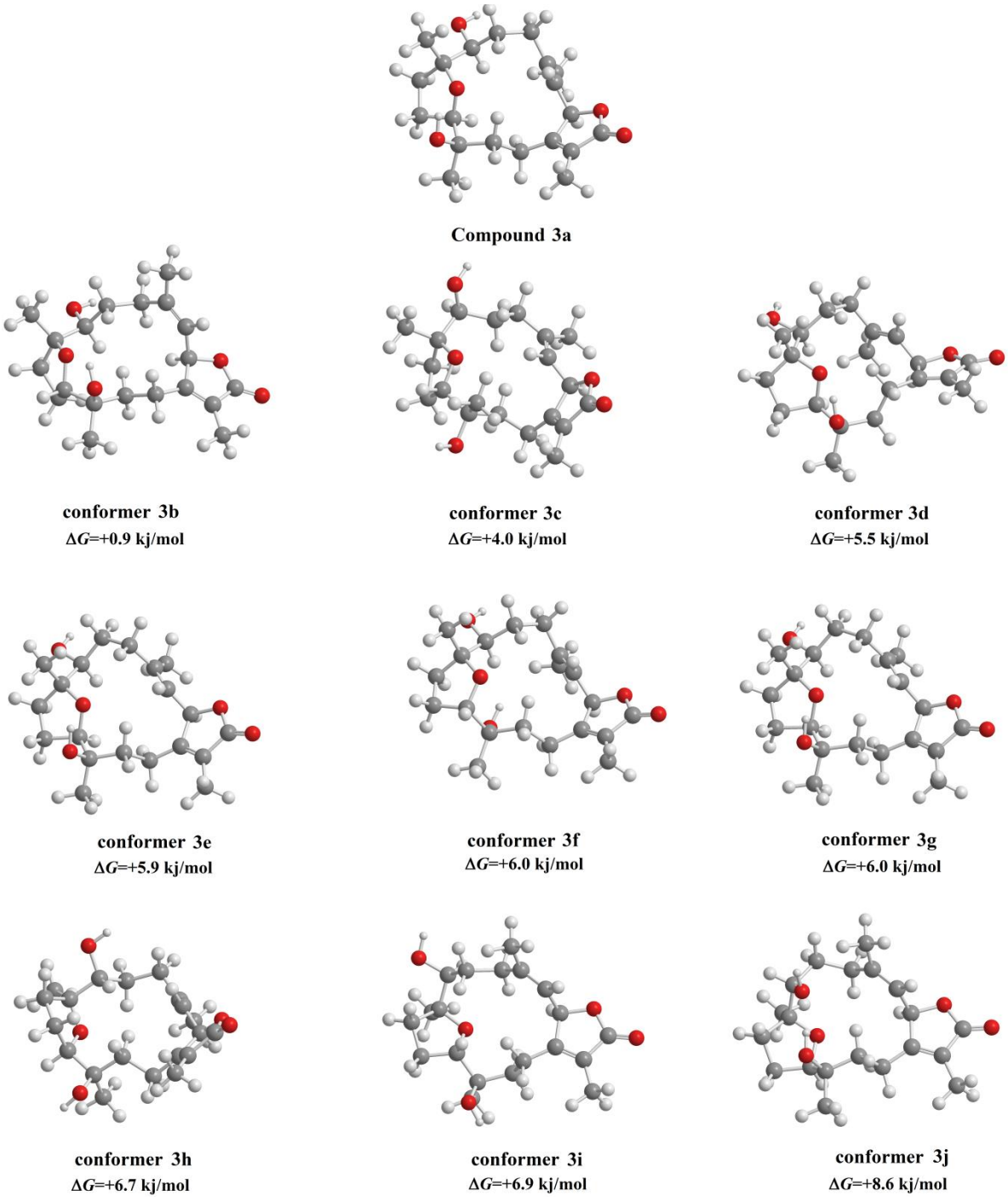


Figure S25. Anti-proliferative A549 response curves with **1-8** based on MTT-reduction assay.

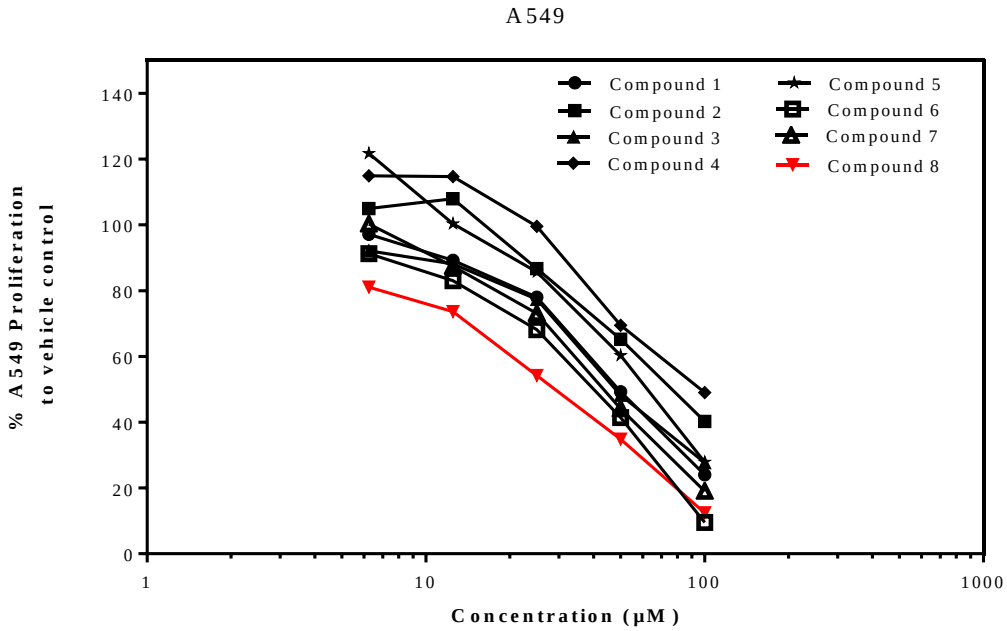


Figure S26. Anti-proliferative Caco-2 response curves with **1**-**8** based on MTT-reduction assay.

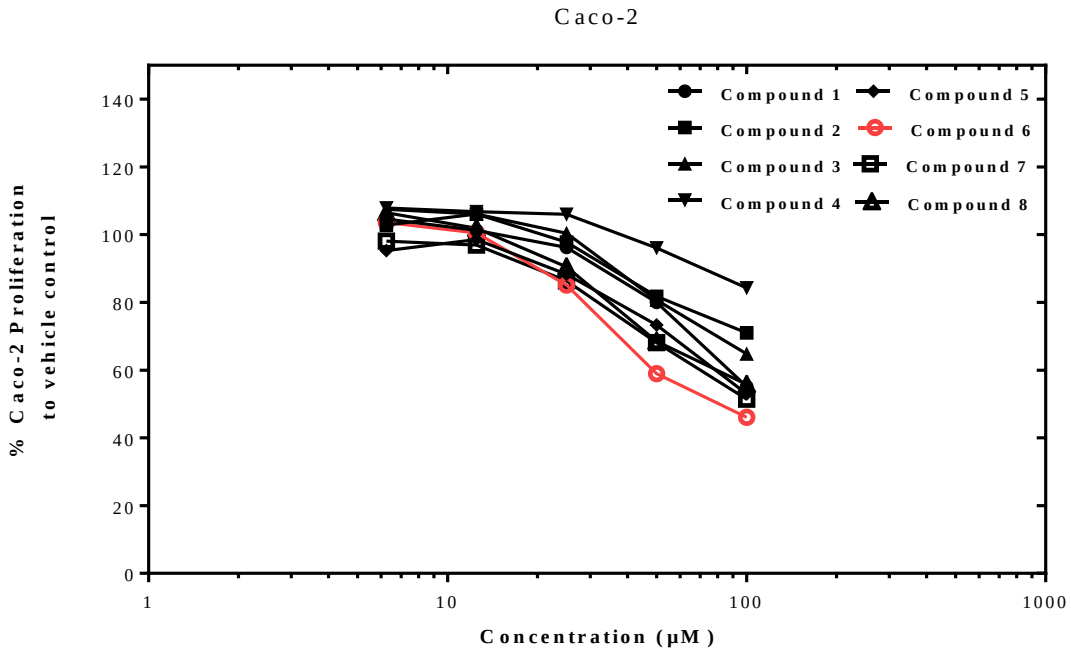


Figure S27. Anti-proliferative HepG2 response curves with **1**-**8** based on MTT-reduction assay.

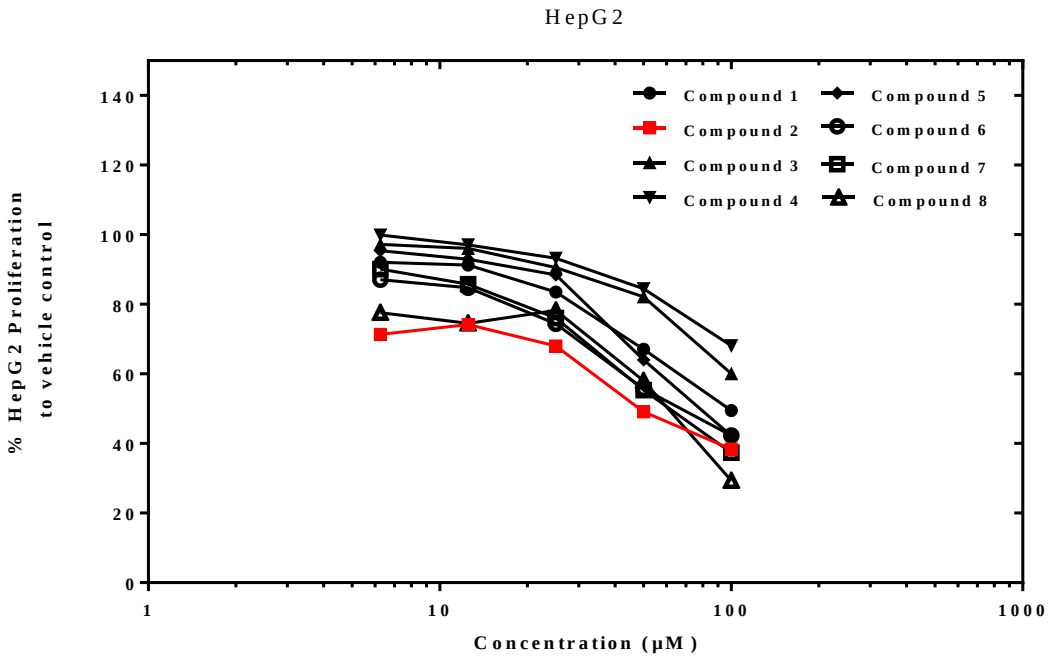


Figure S28. Calculated (i) Autodock and (ii) MM/GBSA binding energies of compounds with EGFR kinase domain relative to the experimental binding energies for the tested compounds against A549 cell line.

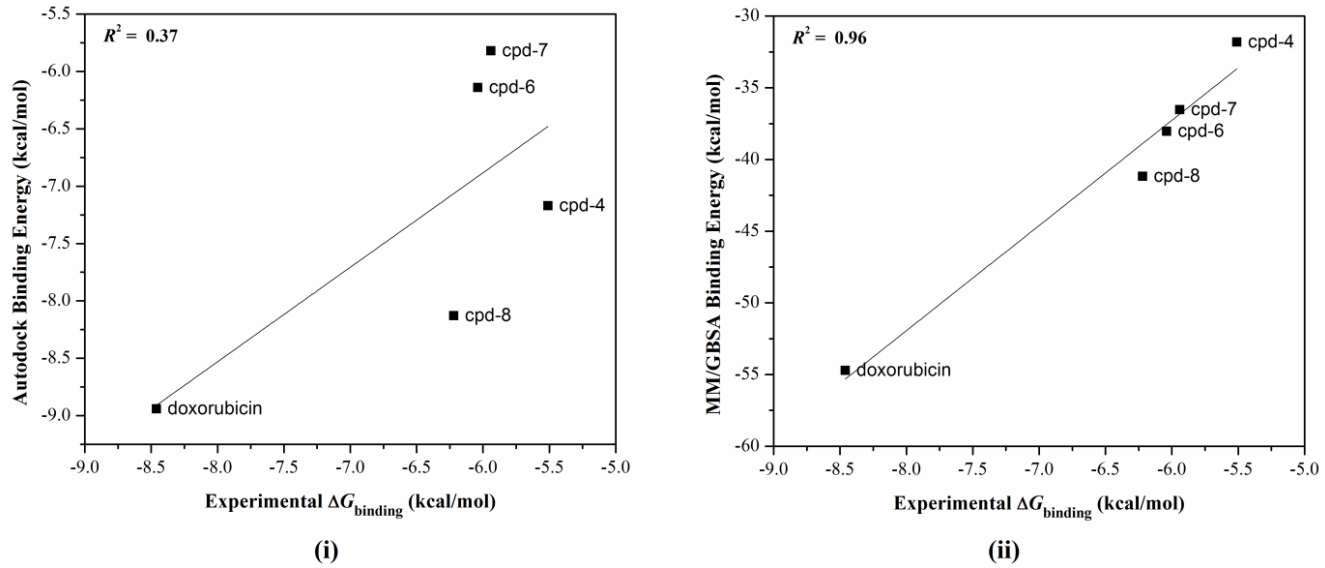


Figure S29. Hydrogen bond distance between **8** and carboxylate oxygen atom of Asp_{776} inside EGFR active site over a 2.5 ns simulation time.