SUPPORTING INFORMATION

Positive $GABA_A$ Receptor Modulators from *Acorus calamus* L. and Structural Analysis of (+)-Dioxosarcoguaiacol by 1D and 2D NMR and Molecular Modeling

Janine Zaugg[†], Eva Eickmeier[†], Samad Ebrahimi[†], Igor Baburin[‡], Steffen Hering[‡], and Matthias Hamburger*[,†]

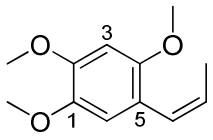
[†]Division of Pharmaceutical Biology, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

[‡]Departement of Pharmacology and Toxicology, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria

*To whom correspondence should be addressed. Tel: +41 61 267 1425. Fax: +41 61 267 1474. E-mail: matthias.hamburger@unibas.ch

Table S1. Spectral characterization data for (**1**) (NMR spectra recorded in $CDCl_3$)

β-Asarone
CAS Nr.: 5273-86-9



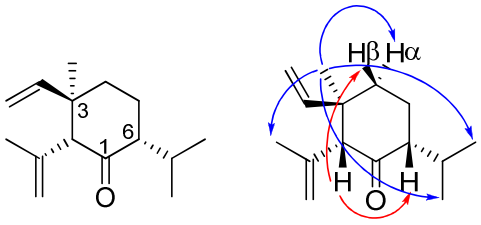
m/z (ESITOFMS) 231. 0998 [M+Na^+] (Calc.: 231.0992)

position	δ_C [a,b]	δ_H (I, m, *J* in Hz)[a]
1	142.6	-
1-OCH_3	56.5	3.57 (CH_3, s)
2	148.9	-
2-OCH_3	55.8	3.6 (CH_3, s)
3	98.4	6.30 (CH, s)
4	151.8	-
4-OCH_3	56.0	3.52 (CH_3, s)
5	118.0	-
5-**CH**=$CHCH_3$	124.9	6.28 (CH, dq, 11.5, 2.0)
5-CH=**CH**CH_3	124.8	5.49 (CH, dq, 11.5, 7.0)
5-CH=CH**CH_3**	14.3	1.61 (CH_3, dd, 7.0, 2.0)
6	115.0	6.64 (CH, s)

[a]Reference data can be found in A. Patra et al., J. Nat. Prod. 1981, 44, 668-669
[b]Calculated ^{13}C shift of HSQC- and HMBC-NMR experiments. Spin systems evaluated by HSQC-NMR experiment

Table S2. Spectral characterization data for (**3**) (NMR spectra recorded in $CDCl_3$)

(+)-Shyobunone
CAS Nr.: 21698-44-2



Relative configuration detected by 1D NOE NMR. Critical correlations highlighted by red and blue arrows.

m/z (ESITOFMS) 243.1722 [M+Na^+] (Calc.: 243.1719)

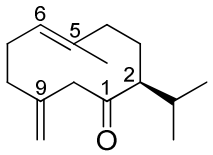
$[\alpha]_D$ (21.4°C) +100° (*c* = 0.19, $CHCl_3$)[a]

position	δ_C [b,c]	δ_H (I, m, *J* in Hz)[c]
1	209.6	-
2	66.9	2.99 (CH, s)
2-**C**CH_2CH_3	139.7	-
2-C**C**$\mathbf{H_2}CH_3$	116.5	4.70 (CH_2, s) 4.93 (CH_2, s)
2-$CCH_2\mathbf{CH_3}$	24.1	1.70 (CH_3, s)
3	46.2	-
3-CH_3	18.9	0.98 (CH_3, s)
3-**C**$\mathbf{H}CH_2$	146.6	5.76 (CH, dd, 11.0, 17.8)
3-$CH\mathbf{CH_2}$	110.7	4.89 (CH_2, dd, 11.0, 1.0) 4.91 (CH_2, dd, 17.8, 1.0)
4	39.3	Hα: 1.56, CH_2, m Hβ: 1.86, CH_2, ddd (5.2, 13.2, 13.2)
5	24.8	1.59 (CH_2, m) 1.96 (CH_2, m)
6	56.4	2.09 (CH, m)
6-**C**$\mathbf{H}(CH_3)_2$	26.3	2.09 (CH, m)
6-$CH(\mathbf{CH_3})_2$	18.3	0.82 (CH_3, d, 6.4)
6-$CH(\mathbf{CH_3})_2$	21.0	0.86 (CH_3, d, 6.4)

[a]No reference value could be found in literature. Relative configuration detected by 1D NOE NMR experiments. Important correlations highlighted by red (plain) and blue (dashed) arrows.
[b]Calculated ^{13}C shift of HSQC-NMR and HMBC-NMR experiments. Spin systems evaluated by HSQC- NMR experiment
[c]Reference data can be found in P. Weyerstahl et al. Liebigs Ann. Chem. 1987, 2, 89-101

Table S3. Spectral characterization data for (**4**) (NMR spectra recorded in $CDCl_3$)

(+)-Preisocalamenediol
CAS Nr.: 25645-19-6



m/z (ESITOFMS) 243.1731 [M+Na^+] (Calc.: 243.1719)

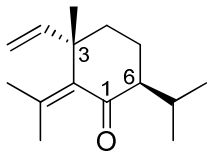
$[\alpha]_D$ (20.3°C) +61.6° (*c* = 0.71, $CHCl_3$)[a]

position	δ_C [b,c]	δ_H (I, m, *J* in Hz)[a]
1	207.2	-
2	60.0	2.20 (CH, ddd, 1.0, 4.9, 10.9)
2-**CH**$(CH_3)_2$	30.5	1.61 (CH, m)
2-CH(**CH_3)$_2$**	19.5	0.82 (CH_3, d, 6.9)
	20.5	0.77 (CH_3, d, 6.9)
3	28.2	1.43 (CH_2, dm, 13.5)
		2.03 (CH_2, m)
4	40.6	1.75 (CH_2, dt, 3.4, 12.8)
		1.98 (CH_2, m)
5	137.9	-
6	125.6	5.15 (CH, dd, 3.0, 10.7)
7	29.2	1.96 (CH_2, m)
		2.11 (CH_2, m)
8	36.7	1.94 (CH_2, m)
		2.27 (CH_2, m)
9	142.6	-
10	53.4	2.85 (CH_2, d, 14.8)
		3.21 (CH_2, d, 14.8)
5-CH_3	15.2	1.30 (CH_3, s)
9=CH_2	116.5	4.77 (CH_2, s)
		4.90 (CH_2, s)

[a]Reference value can be found in C. Zdero et al. Phytochemistry 1989, 28, 531-542
[b]Calculated ^{13}C shift of HSQC- and HMBC-NMR experiments. Spin systems evaluated by HSQC-NMR experiment
[c]Reference data can be found in D.M. Delvalle et al. Planta Med. 1987, 87, 230.

Table S4. Spectral characterization data for (**5**) (NMR spectra recorded in $CDCl_3$)

(-)-Isoshyobunone
CAS Nr.: 21698-46-4



m/z (ESITOFMS) 243.1730 [M+Na^+] (Calc.: 243.1719)

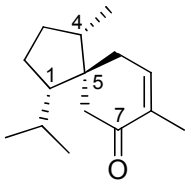
$[\alpha]_D$ (21.5°C) -156° (*c* = 0.61, $CHCl_3$)[a]

position	δ_C [b, c]	δ_H (I, m, *J* in Hz)[b,c]
1	209.4	-
2	140.1	-
3	44.4	-
4	39.3	1.33 (CH_2, ddd, 14.0, 6.8, 3.6)
		1.44 (CH_2, ddd, 14.0, 10.7, 3.3)
5	21.4	1.79 (CH_2, m)
		1.60 (CH_2, m)
6	55.2	2.11 (CH, ddd, 9.0, 9.0, 6.3)
2-**C**(CH_3)	146.6	-
2-C(**CH_3)$_2$**	23.5	1.69 (CH_3, s)
	24.2	1.74 (CH_3, s)
3-CH_3	24.5	1.29 (CH_3, s)
3-**CH**CH_2	146.4	5.83 (CH, dd, 10.4, 17.9)
3-CH**CH_2**	110.7	4.91 (CH_2, dd, 10.4, 1.2)
		4.90 (CH_2, dd, 17.9, 1.2)
6-**CH**(CH_3)$_2$	29.4	2.00 (CH, m)
6-CH(**CH_3)$_2$**	18.4	0.79 (CH3, d, 6.8)
	20.6	0.84 (CH3, d, 6.8)

[a]Reference value can be found in M. Niwa et al. Chem. Lett. 1977, 12, 1415-1418
[b]Calculated ^{13}C shift of HSQC- and HMBC-NMR experiments. Spin systems evaluated by HSQC-NMR experiment
[c]Reference data can be found in P. Weyerstahl et al. Liebigs Ann. Chem. 1987, 2, 89-101

Table S5. Spectral characterization data for (**6**) (NMR spectra recorded in $CDCl_3$)

(-)-Acorenone
CAS Nr.: 5956-05-8



m/z (ESITOFMS) 243.1730 [M+Na^+] (Calc.: 243.1719)

$[\alpha]_D$ (21.5°C) -27° (*c* = 0.37, $CHCl_3$)[a]

position	δ_C [a, b]	δ_H (I, m, *J* in Hz)[a, c]
1	56.9	1.24 (CH, m)
1-**CH**$(CH_3)_2$	28.9	1.49 (CH, o, 6.5)
1-CH(**CH_3)$_2$**	21.5	0.73 (CH_3, d, 6.8)
	24.0	0.84 (CH_3, d, 6.8)
2	25.4	1.24 (CH_2, m) 1.60 (CH_2, m)
3	29.9	1.14 (CH_2, m) 1.57 (CH_2, m)
4	47.0	1.57 (CH, m)
4-CH_3	16.1	0.70 (CH_3, d, 6.8)
5	47.9	-
6	38.8	2.16 (CH_2, d, 16.6) 2.21 (CH_2, d, 16.6)
7	200.3	-
8	134.6	-
8-CH_3	15.6	1.63 (CH_3, s)
9	144.4	6.54 (CH, s)
10	37.4	2.01 (CH_2, dm, 19.9) 2.53 (CH_2, dm, 19.9)

[a]Reference value can be found in S.W. Baldwin et al., Tetrahedron Lett. 1982, 23, 1235-1238
[b]Calculated ^{13}C shift of HSQC- and HMBC-NMR experiments. Spin systems evaluated by HSQC-NMR experiment
[c]Reference data can be found in W. Rascher et al., Tetrahedron, 33, 575-577

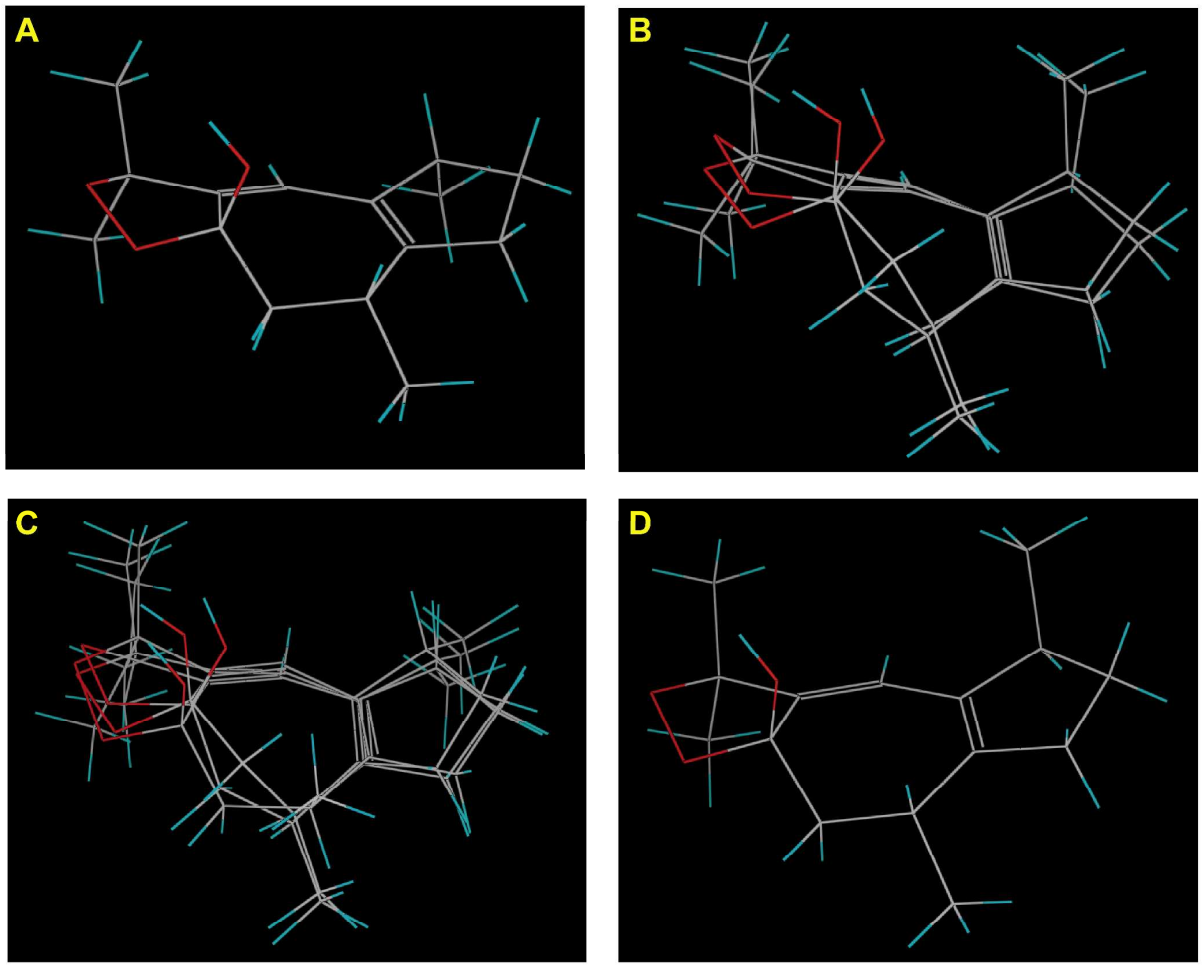


Figure S1: Predominant conformers of the four possible stereoisomers of (+)-dioxosarcoguaiacol (**2**) within a 1 kcal/mol energy window from the particular global minimum. Conformational analysis was performed at the OPLS_2005 level in chloroform. A: 4*R**8*S**10*R**, B: 4*S**8*S**10*S**, C: 4*R**8*S**10*S**, D: 4*S**8*S**10*R**

Table S6. Comparison of NMR Data ($^3J_{HH}$-Coupling Constants and NOESY Correlations) with Geometrically Optimized Conformers of the Four Stereoisomers of (+)-Dioxosarcoguaiacol (**2**)

NMR observations	**Matching geometrically optimized conformers**[a]			
	4R*8S*10R*	4S*8S*10R*	4R*8S*10S*	4S*8S*10S*
$J_{2b,3b}$ = 0 Hz , NOESY: H-3b ↔ H-2a	**yes**	yes	yes	yes
$J_{9b,10}$ = 5.2 Hz, $J_{9a,10}$ = 13.4 Hz	**yes**	yes	yes	yes
NOESY: H-6 ↔ H-12,13	**yes**	yes	no	no
NOESY: H-2a ↔ H-15	**yes**	yes	no	no
NOESY: H-3a ↔ H-4, H-3b ↔ H-14	**yes**	no	no	yes

[a]Conformers were found by conformational analysis in $CHCl_3$ and further geometrically optimized based on Density function theory (DFT) on the B3LYP/6-31G* level in gas-phase.

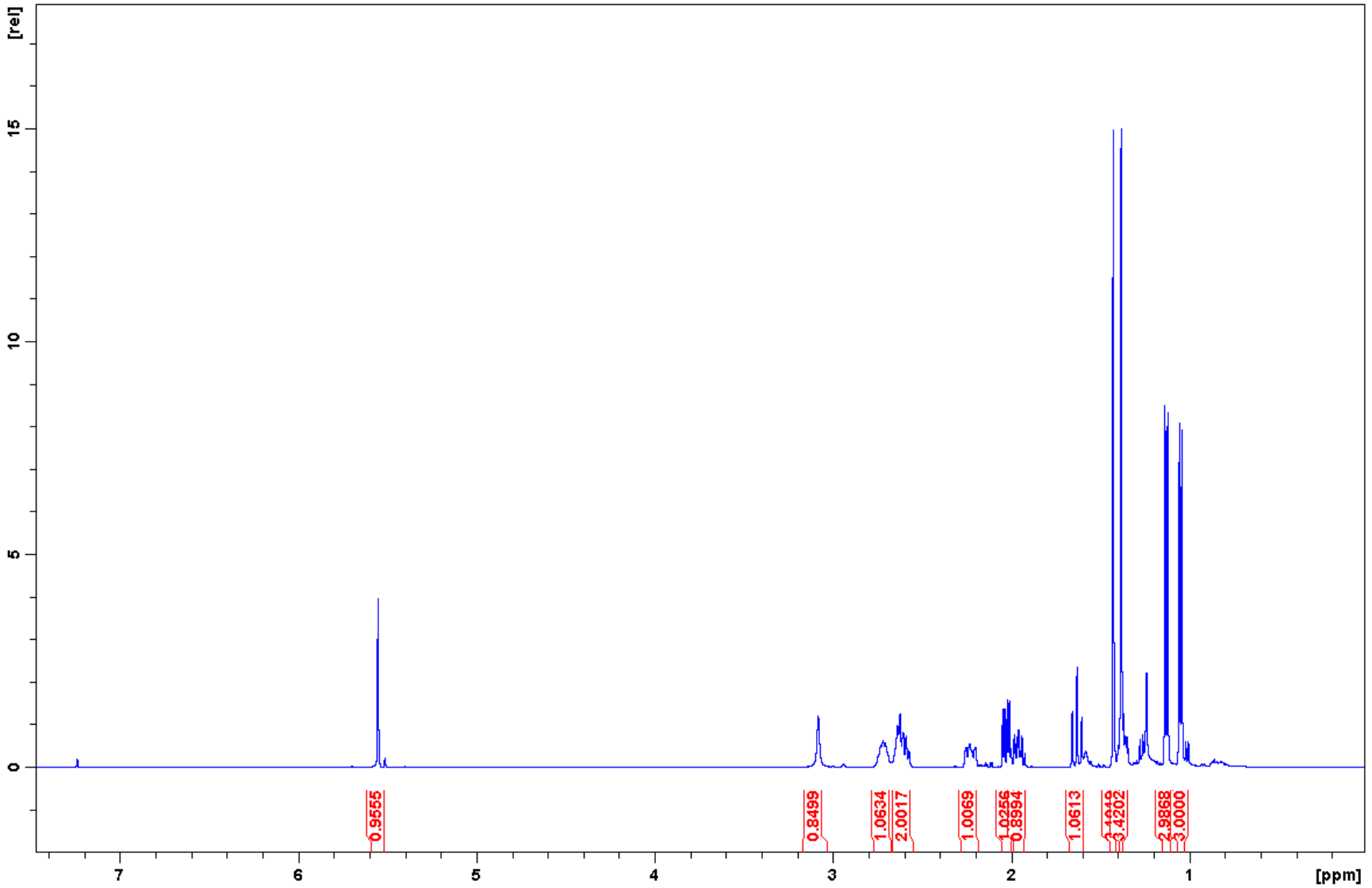


Figure S2. ^{1}H-NMR spectrum of (**2**) (NS: 64, DS: 2, $CDCl_3$).

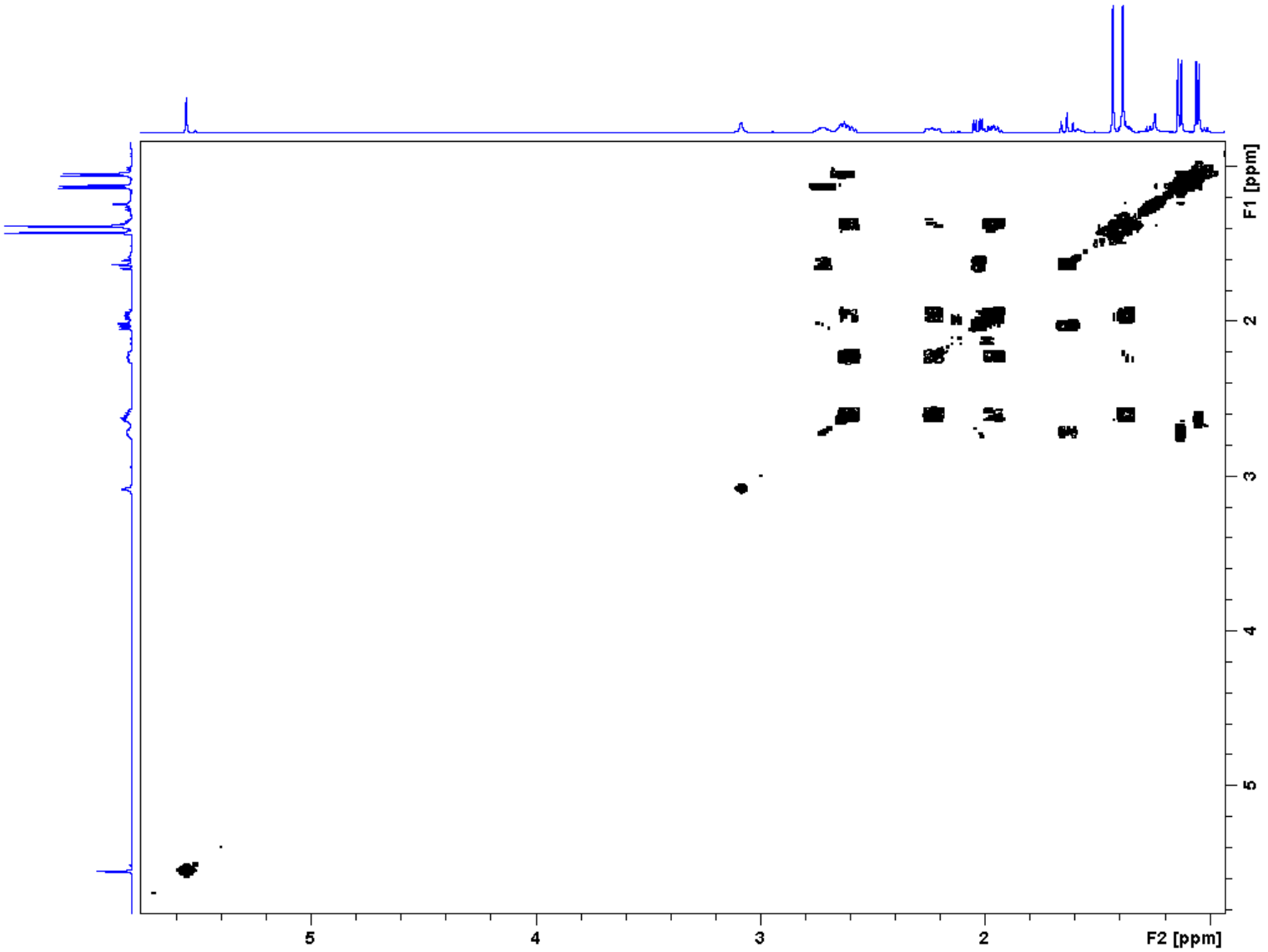


Figure S3. COSY-NMR spectrum (*cosygpqf*, NS: 4, DS: 8) of (**2**) in $CDCl_3$.

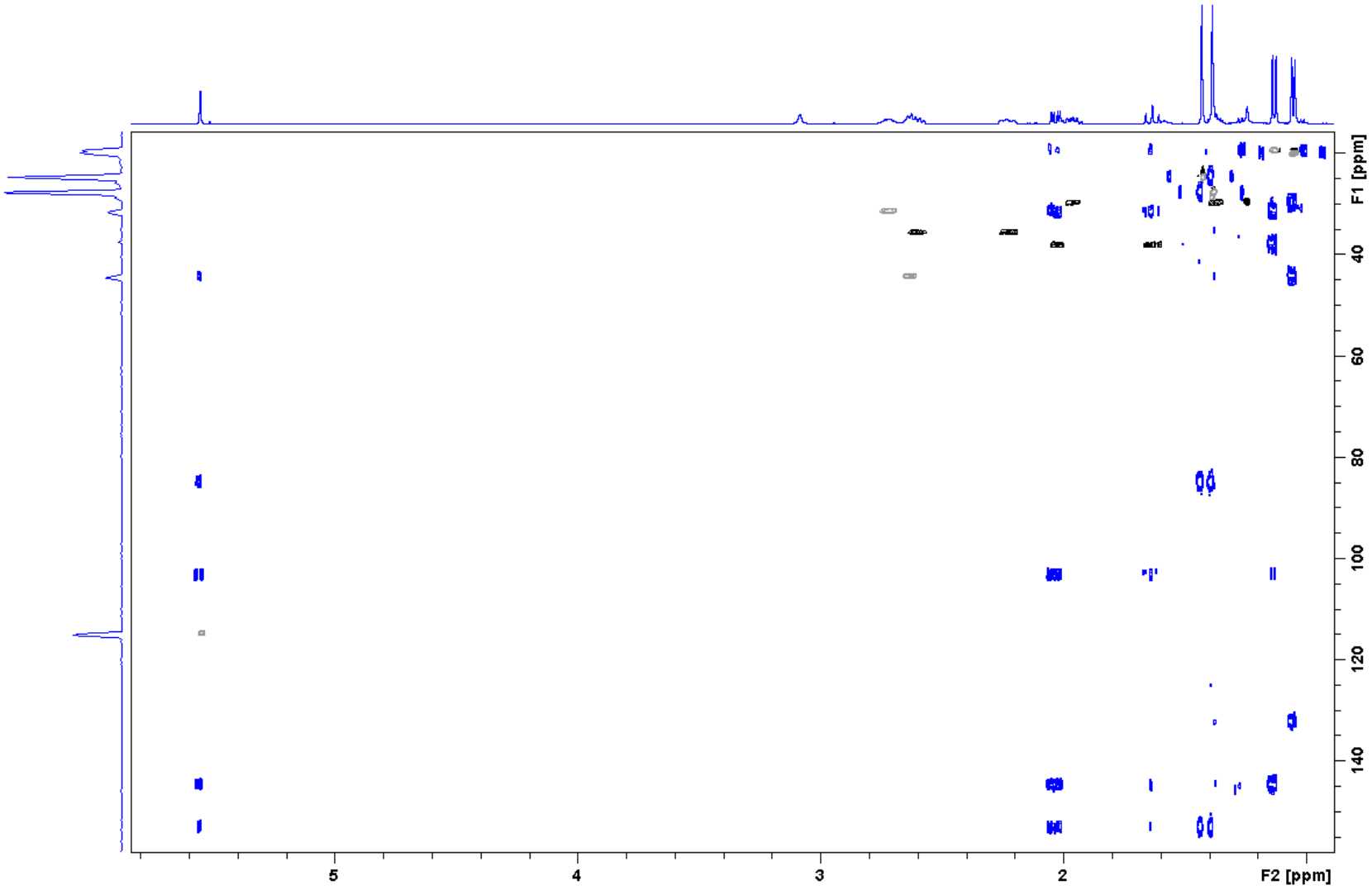


Figure S4. Overlay of DEPTedited HSQC-NMR spectrum (*hsqcedetgp*, NS: 8, DS: 16; black/grey) and HMBC spectrum (*hmbcgp*, NS: 128, DS: 16, optimized for 10 Hz; blue) of (**2**) in $CDCl_3$.

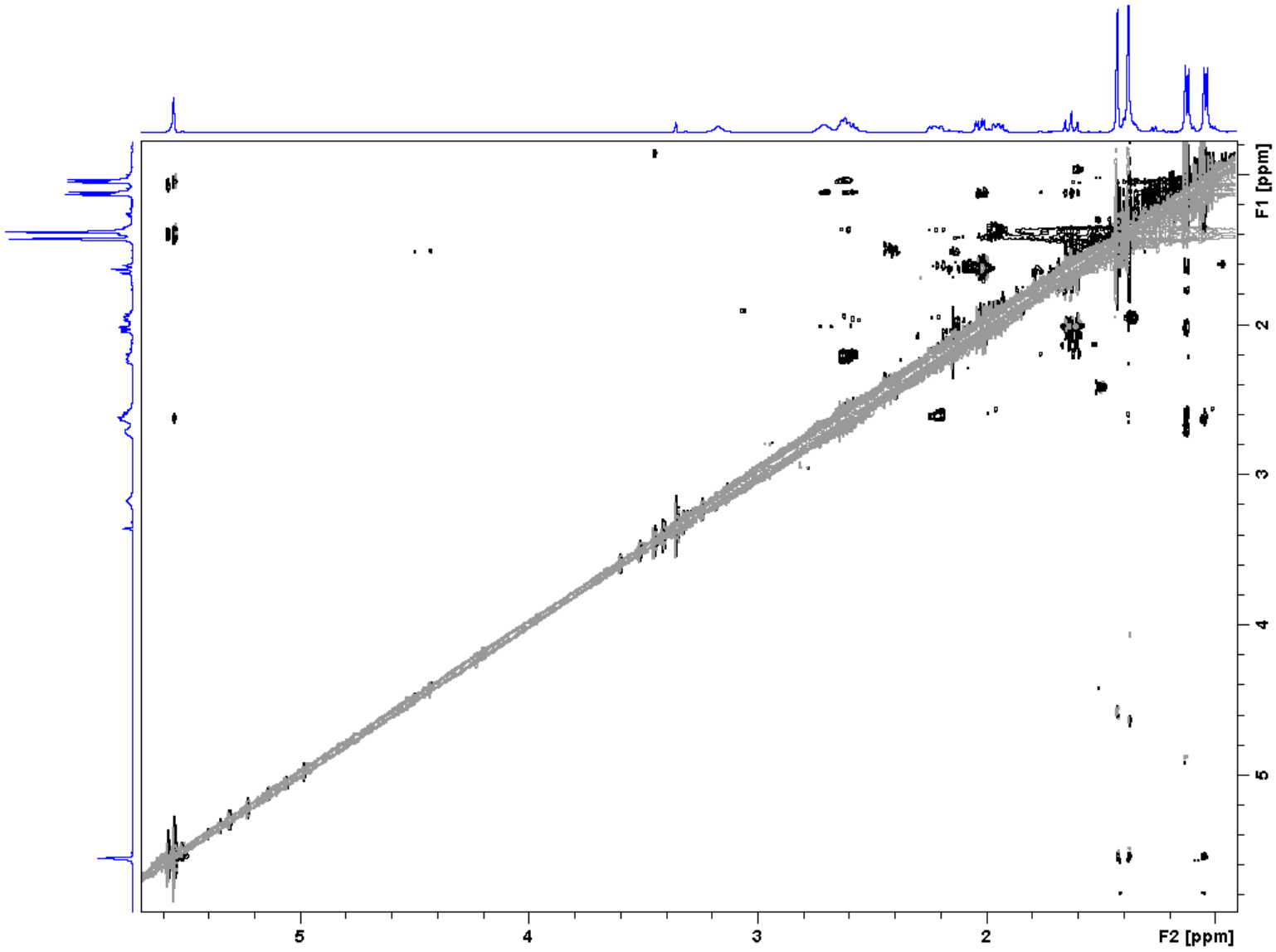


Figure S5. NOESY NMR spectrum (*noesygpphpp*, NS: 32, DS: 16, mixing time 0.75 s) of (**2**) in $CDCl_3$.