Supplementary Table 1. HR-MS data for orfamides, canucins, keratinimicins, and keratinicyclins.[a]

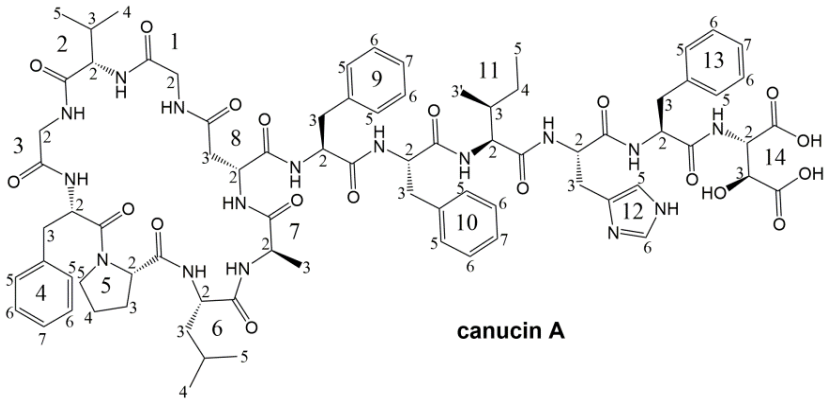
Orfamide	Formula	$[M+H]^+_{calc}$	$[M+H]^+_{obs}$	Δppm
A	$C_{64}H_{114}N_{10}O_{17}$	1295.84362	1295.84380	0.1
B	$C_{63}H_{112}N_{10}O_{17}$	1281.82797	1281.83038	1.9
Canucin	**Formula**	$[M+H]^+_{calc}$	$[M+H]^+_{obs}$	**Δppm**
A	$C_{79}H_{102}N_{16}O_{19}$	1579.75799	1579.75592	1.3
B	$C_{79}H_{102}N_{16}O_{18}$	1563.76308	1563.76242	0.4
Keratinimicin		$[M+H]^+_{calc}$	$[M+H]^+_{obs}$	**Δppm**
A	$C_{84}H_{92}Cl_2N_8O_{33}$	1811.52166	1811.52091	0.4
B	$C_{78}H_{83}Cl_2N_9O_{26}$	1632.48991	1632.49397	2.5
C	$C_{84}H_{90}Cl_2N_8O_{32}$	1793.51109	1793.50422	3.8
D	$C_{84}H_{89}Cl_2N_7O_{34}$	1810.49002	1810.48720	1.6
Keratinicyclin		$[M+H]^+_{calc}$	$[M+H]^+_{obs}$	**Δppm**
A	$C_{77}H_{84}ClN_7O_{32}$	1654.49222	1654.49089	0.8
B	$C_{77}H_{85}ClN_8O_{30}$	1637.51329	1637.51130	1.2
C	$C_{71}H_{75}ClN_8O_{25}$	1475.46046	1475.45782	1.8

[a]$[M+H]^+_{calc}$ and $[M+H]^+_{obs}$ denote calculated and observed $[M+H]^+$, respectively. Δppm denotes the mass error in parts per million.

Supplementary Table 2. NMR assignments for canucin A in CD_3OH. The numbering scheme for canucin A is shown below the table.

Residue		δH[a]	δC[b]	Residue		δH[a]	δC[b]
Gly 1	1	-	169.9	Phe 9	1	-	ND
	2	4.35, 3.66	42.5		2	3.42	58.1
	NH	8.31	-		3	3.54, 3.11	34.7
Val 2	1	-	171.4		4	-	139.7
	2	4.09	56.7		5, 9	7.44	129.5
	3	2.07	33.3		6, 8	7.29	128.0
	4	0.88	18.3		7	7.20	126.0
	5	0.90	16.0		NH	8.67	-
	NH	7.96	-	Phe 10	1	-	ND
Gly 3	1	-	ND		2	3.84	61.2
	2	4.60, 3.756	42.3		3	3.70, 3.04	35.4
	NH	9.02	-		4	-	138.9
Phe 4	1	-	171.6		5, 9	7.18	126.4
	2	4.84	55.3		6, 8	7.25	128.2
	3	3.39, 2.88	35.2		7	7.33	126.5
	4		137.3		NH	7.80	-
	5, 9	7.37	128.5	Ile 11	1	-	171.5
	6, 8	7.33	128.3		2	4.31	58.7
	7	7.25	126.6		3	1.85	37.1
	NH	8.75	-		3’	0.93	15.0
Pro 5	1	-	ND		4	1.13, 0.70	23.1
	2	3.46	63.2		5	0.80	11.2
	3	2.54, 1.91	29.7		NH	8.59	-
	4	2.03, 1.92	24.9	His 12	1	-	172.1
	5	3.88, 3.50	47.6		2	5.40	50.8
Leu 6	1	-	173.0		3	2.92, 2.75	27.6
	2	4.10	57.7		4	-	ND
	3	1.70, 1.82	39.2		5	7.24	119.1
	4	1.24	25.4		6	8.67	133.3
	5	0.44	22.5		NH	8.47	-
	6	0.90	20.24	Phe 13	1	-	ND
	NH	8.02	-		2	4.74	60.7
Ala 7	1	-	172.1		3	4.26, 3.56	38.6
	2	4.51	50.0		4	-	137.0
	3	1.34	17.2		5, 9	7.45	130.0
	NH	8.33	-		6, 8	7.25	130.1
Asp 8	1	-	172.8		7	7.17	126.4
	2	4.56	48.0		NH	8.26	-
	3	2.32	36.7	β-OH-Asp 14	1	-	ND
	4	-	ND		2	4.73	58.1
	NH	7.35			3	4.35	71.3
					4	-	ND
					NH	8.00	

[a]800 MHz, [b]determined by edited HSQC and HMBC, ND: not detected.



canucin A

Supplementary Table 3. Summary of CYANA-derived parameters from calculations of *R* and *S* stereoisomers at the Cβ of Asp14 in canucin A.[a]

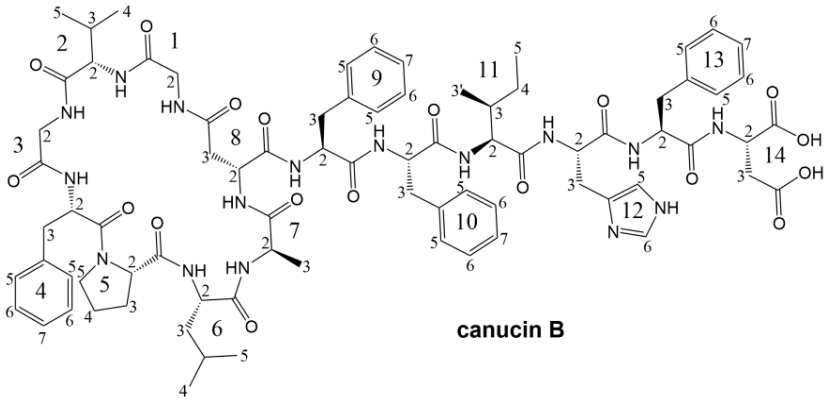
Parameter	R	S
# of distance constraints used for final structure calculation	189	183
average target function (*f*)	0.23 ± 0.00	0.17 ± 8.47E-05
average backbone RMSD to mean	0.03 Å ± 0.01	0.01 Å ± 0.00
average heavy atom RMSD to mean	0.39 Å ± 0.04	0.46 Å ± 0.05
# of violated distance constraints	3	3
# of violated van der Waals constraints	0	0

[a]The mean and standard deviation are listed for the parameters indicated.

Supplementary Table 4. NMR assignments for canucin B in CD_3OH. The numbering scheme for canucin B is shown below the table.

Residue		δH[a]	δC[b]	Residue		δH[a]	δC[b]
Gly	1	-	169.9	Phe	1	-	ND
	2	4.36, 3.66	42.5		2	3.42	58.1
	NH	8.44	-		3	3.54, 3.11	34.8
Val	1	-	174.1		4	-	139.8
	2	4.09	56.7		5, 9	7.44	129.5
	3	2.07	33.3		6, 8	7.29	128.1
	4	0.93	16.1		7	7.20	126.0
	5	0.90	18.3		NH	8.66	-
	NH	8.02	-	Phe	1	-	ND
Gly	1	-	171.5		2	3.82	61.3
	2	4.57, 3.72	42.3		3	3.70, 3.03	35.4
	NH	9.00	-		4	-	138.1
Phe	1	-	ND		5, 9	7.18	126.9
	2	4.84	55.3		6, 8	7.25	128.1
	3	3.37, 2.85	35.2		7	7.30	128.12
	4	-	137.3		NH	7.82	-
	5, 9	7.35	128.4	Ile	1	-	ND
	6, 8	7.31	128.3		2	4.31	58.7
	7	7.23	126.6		3	1.86	37.0
	NH	8.68	-		3'	0.93	15.8
Pro	1	-	171.5		4	1.11, 0.69	23.0
	2	3.50	63.2		5	0.79	11.2
	3	2.54, 1.91	29.7		NH	8.61	-
	4	2.02	24.9	His	1	-	175.3
	5	3.88, 3.50	47.6		2	5.37	50.9
Leu	1	-	172.1		3	2.92, 2.76	27.6
	2	4.13	57.7		4	-	ND
	3	1.75, 1.87	39.6		5	7.15	119.8
	4	1.28	25.4		6	8.53	133.3
	5	0.50	22.6		NH	8.49	-
	6	0.91	20.2	Phe	1	-	173.9
	NH	8.08	-		2	4.76	60.5
Ala	1	-	172.0		3	4.27. 3.50	38.2
	2	4.55	50.0		4	-	136.9
	3	1.33	17.1		5, 9	7.31	129.9
	NH	8.38	-		6, 8	7.23	130.0
Asp	1	-	ND		7	7.17	126.4
	2	4.58	48.1		NH	8.28	-
	3	2.31	36.7	Asp	1	-	ND
	4	-	ND		2	4.29	50.9
	NH	7.34	-		3	2.94, 2.69	36.2
					4	-	ND
					NH	8.04	-

[a]800 MHz, [b]determined by edited HSQC and HMBC, ND: not detected.



canucin B

Supplementary Table 5. Annotation of the canucin biosynthetic gene cluster (*can*).[a]

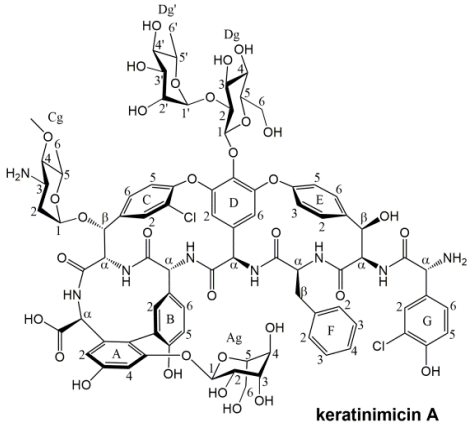
Gene	Length (AA)	Homology-Based Predicted Function
canA	40	leader/core peptide, putative Class II
canB	625	asparagine synthetase
canC	85	PqqD family protein
canD	137	transglutaminase-like superfamily protein
canE	283	TauD/TfdA family dioxygenase

[a]Gene name, the corresponding protein amino acid length, and a homology-predicted function are listed.

Supplementary Table 6. NMR assignments for keratinimicin A in DMSO-*d6*. The numbering scheme for keratinimicin A is shown below the table.

	C/H	δH[a]	Multiplicity (Hz)	δC[b]		C/H	δH[a]	Multiplicity (Hz)	δC[b]
	NH	8.54	UM	-		NH	7.42	UM	-
	COOH	-	-	173.2		COOH	-	-	169.5
	α	4.42	d (6.1)	57.6		α	4.45	q (9.8)	56.4
	1	-	-	137.7	F	β	2.69, 2.55	d (7.0, 9.7)	39.4
A	2	6.57	s	109.1		1	-	-	137.0
	3	-	-	157.7		2	6.87	d (7.5)	129.5
	4	6.69	s	102.0		3	6.91	t (7.4)	128.5
	5	-	-	155.2		4	7.03	t (7.3)	126.8
	6	-	-	120.8		NH	ND	-	-
	NH	-	-	-		COOH	-	-	174.3
	COOH	-	-	173.2		α	4.41	d (3.9)	59.0
	α	4.48	d (3.9)	54.2		1	-	-	ND
	1	-	-	ND	G	2	7.44	s	129.3
B	2	7.18	s	136.2		3	-	-	119.2
	3	-	-	120.8		4	-	-	152.9
	4	-	-	155.8		5	6.94	d (8.0)	116.7
	5	6.80	UM	116.2		6	7.21	UM	127.8
	6	6.80	UM	126.2		1	5.18	UM	98.1
	NH	6.92	-	-		2	3.19	t (4.1)	70.4
	COOH	-	-	167.0	Ag	3	3.22	t (8.9)	70.7
	α	4.23	d (11.4)	61.5		4	3.39	t (9.2)	66.9
	β	5.11	UM	74.8		5	3.49	UM	74.2
C	1	-	-	138.8		6	3.49, 3.45	UM	61.2
	2	7.89	s	129.3		1	4.67	UM	94.2
	3	-	-	127.5		2	2.09, 1.48	UM	37.2
	4	-	-	150.0		3	3.23	m	47.2
	5	7.32	d (8.3)	124.2	Cg	3-NH_2	ND	-	-
	6	7.36	d (8.3)	127.8		4	2.57	t (9.6)	86.5
	NH	8.19	UM	-		4-OMe	3.33	s	58.
	COOH	-	-	170.3		5	3.64	m	67.3
	α	5.62	d (8.5)	54.6		6	1.17	d (5.7)	18.7
	1	-	-	133.7		1	5.67	d (7.4)	99.8
D	2	5.17	s	104.9		2	3.62	t (8.2)	77.1
	3	-	-	151.4	Dg	3	3.46	t (8.6)	78.2
	4	-	-	132.4		4	3.22	t (8.9)	70.8
	5	-	-	153.1		5	3.29	m (4.6,10.2)	78.1
	6	5.65	s	108.4		6	3.72	d (10.2)	61.4
	NH	ND	-	-		1'	5.18	UM	100.6
	COOH	-	-	168.5		2'	3.71	t (3.2)	71.1
	α	4.52	t (3.8)	59.7	Dg'	3'	3.5	t (10.2)	71.1
	β	5.2	d (4.1)	71.5		4'	3.2	t (10.2)	72.2
	1	-	-	137.6		5'	4.12	m (6.2)	68.8
E	2	7.78	d (8.3)	128.2		6'	1.08	d (6.0)	18.5
	3	7.22	d (6.3)	122.9					
	4	-	-	155.2					
	5	7.13	d (8.4)	124.1					
	6	7.05	d (8.4)	128.6					

[a]800 MHz, [b]determined by edited HSQC and HMBC, UM: unresolved multiplicity, ND: not detected.



keratinimicin A

Supplementary Table 7. Annotation of the keratinimicin biosynthetic gene cluster (*ker*).

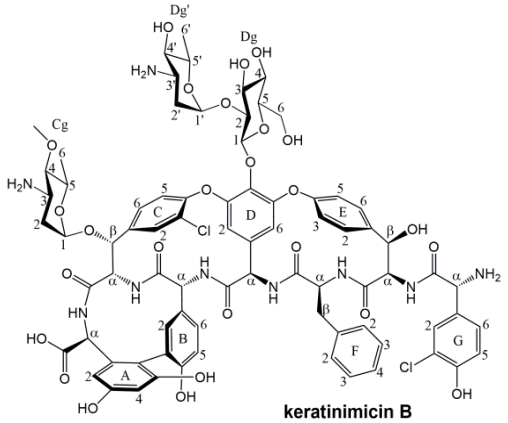
Gene	Length (AA)	Homology-Based Predicted Function
vanH	291	D-lactate dehydrogenase
vanA	348	D-alanine--(R)-lactate ligase
vanX	202	D-Ala-D-Ala dipeptidase VanX
ajrR	340	StrR-like transcriptional regulator
pdh	303	prephenate dehydrogenase
tri	644	ABC transporter
kerA	2082	NRPS (A-T-C-A-T-E)
kerB	1055	NRPS (C-A-T)
kerC	4059	NRPS (C-A-T-E-C-A-T-E-C-A-T)
kerD	1864	NRPS (C-A-T-X-TE)
mbtH	69	MbtH protein
oxyA	401	cytochrome P450
ker1	61	hypothetical protein
oxyB	398	cytochrome P450
oxyC	406	cytochrome P450
khaI	491	Halogenase
gtfA	363	Glycosyltransferase
gtfB	408	Glycosyltransferase
kerM	309	O-methyltransferase
gtfC	408	Glycosyltransferase
ker2	270	PIG-L family deacetylase
gtfD	623	Mannosyltransferase
hpgT	434	Aminotransferase
kph	276	α/β fold hydrolase
kerE	577	AMP-dependent synthetase and ligase
oxyD	396	cytochrome P450
hmaS	350	4-hydroxyphenylpyruvate dioxygenase
hmo	358	4-hydroxymandelate oxidase
ker3	448	cation/H(+) antiporter
kraA	476	NDP-hexose 2,3-dehydratase
kraB	325	NAD-dependent epimerase/dehydratase
kraC	369	Aminotransferase
kraD	205	dTDP-4-keto-6-deoxy-D-glucose epimerase
dpgA	366	type III polyketide synthase
dpgB	209	enoyl-CoA hydratase
dpgC	404	enoyl-CoA hydratase
dpgD	263	enoyl-CoA hydratase
dahp	358	3-deoxy-7-phosphoheptulonate synthase
ker4	188	hypothetical protein

[a]Gene name, the corresponding protein amino acid length, and a homology-predicted function are listed.

Supplementary Table 8. NMR assignments for keratinimicin B in DMSO-*d6*. The numbering scheme for keratinimicin B is shown below the table.

	C/H	δH[a]	Multiplicity (Hz)	δC[b]		C/H	δH[a]	Multiplicity (Hz)	δC[b]
	NH	8.57	UM	-		NH	7.58	d (8.6)	-
	COOH	-	-	173.1		COOH	-	-	169.5
	α	4.46	d (4.7)	57.5		α	4.33	q (8.0)	56.8
	1	-	-	136.9	F	β	2.75, 2.56	d (8.4, 7.8)	40.0
A	2	6.29	s	106.5		1	-	-	ND
	3	-	-	157.6		2	6.83	UM	129.6
	4	6.42	s	102.8		3	6.83	UM	128.6
	5	-	-	ND		4	6.93	t (6.8)	126.7
	6	-	-	118.6		NH	7.52	UM	-
	NH	8.51	UM	-		COOH	-	-	174.3
	COOH	-	-	173.2		α	4.82	UM	57.5
	α	4.51	d (3.4)	54.2		1	-	-	131.2
	1	-	-	ND	G	2	7.52	s	129.4
B	2	7.23	S	136.7		3	-	-	120.0
	3	-	-	ND		4	-	-	153.6
	4	-	-	ND		5	7.04	d (9.0)	116.8
	5	6.78	UM	116.5		6	7.34	UM	128.2
	6	6.77	UM	125.9		1	4.75	UM	93.6
	NH	7.32	d (8.6)	-		2	2.24, 1.76	t (3.2)	34.4
	COOH	-	-	166.9		3	3.57	m	47.3
	α	4.27	t (9.0)	61.4	Cg	3-NH_2	ND	-	-
	β	5.1	U.S.	75.2		4	2.98	t (7.4)	82.5
C	1	-	-	138.8		4-OMe	3.35	s	58.6
	2	7.91	s	129.5		5	3.67	m	67.3
	3	-	-	127.5		6	1.19	d (5.4)	18.5
	4	-	-	149.8		1	5.67	d (7.4)	100.0
	5	7.32	d (8.6)	124.2		2	3.61	t (7.9)	77.2
	6	7.34	UM	128.2		3	3.51	t (6.1)	77.9
	NH	8.06	d (7.5)	-	Dg	4	3.25	t (9.0)	70.6
	COOH	-	-	170.3		5	3.31	m	78.2
	α	5.62	d (8.4)	54.8		6	3.72	d (10.8)	61.4
	1	-	-	133.7		1'	5.41	UM.	95.7
D	2	5.15	s	104.9		2'	2.19, 1.76	d (3.6)	34.2
	3	-	-	151.4		3'	3.21	UM	50.0
	4	-	-	132.2	Dg'	3'-NH_2	ND	-	-
	5	-	-	153.3		4'	3.16	t (9.2)	72.9
	6	5.67	s	108.7		5'	4.28	M	68.4
	NH	ND	-	-		6'	1.14	d (6.0)	18.3
	COOH	-	-	168.5					
	α	4.73	t (3.4)	59.8					
	β	5.09	UM	72.0					
	1	-	-	137.7					
E	2	7.79	d (8.2)	128.4					
	3	7.21	UM	123.1					
	4	-	-	155.1					
	5	7.11	d (7.8)	124.1					
	6	7.02	d (8.8)	128.8					

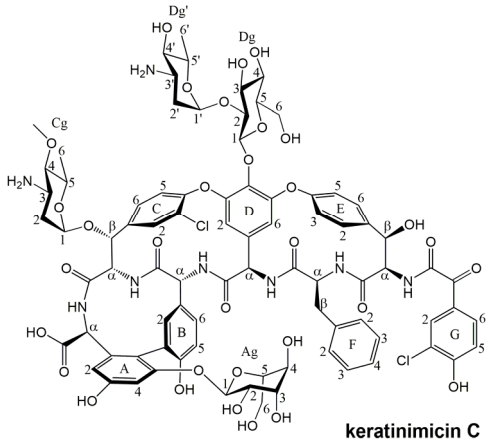
[a]800 MHz, [b]determined by edited HSQC and HMBC, UM: unresolved multiplicity, ND: not detected.



Supplementary Table 9. NMR assignments for keratinimicin C in DMSO-*d6*. The numbering scheme for keratinimicin C is shown below the table.

C/H		δH[a]	Multiplicity (Hz)	δC[b]	C/H		δH[a]	Multiplicity (Hz)	δC[b]
A	NH	8.47	UM	-	F	NH	7.3	-	-
	COOH	-	-	173.3		COOH	-	-	169.5
	α	4.42	d (6.1)	57.6		α	4.5	q (9.2)	55.5
	1	-	-	137.7		β	2.61, 2.57	d (6.9, 7.0)	40.0
	2	6.53	s	109.0		1	-	-	136.3
	3	-	-	157.6		2	6.79	d (7.7)	129.1
	4	6.66	s	102.7		3	6.86	t (7.3)	128.3
	5	-	-	155.1		4	6.99	t (7.2)	126.4
	6	-	-	121.2		COOH	-	-	172.0
B	NH	8.5	UM	-	G	CO	-	-	183.2
	COOH	-	-	174.5		1	-	-	124.5
	α	4.45	UM	54.1		2	7.98	s	131.9
	1	-	-	ND		3	-	-	115.6
	2	7.22	s	136.2		4	-	-	152.9
	3	-	-	121.5		5	6.34	d (6.6)	119.6
	4	-	-	155.8		6	7.69	d (8.5)	132.9
	5	6.82	d (8.2)	115.9	Ag	1	5.15	UM	98.0
	6	6.8	UM	125.8		2	3.11	UM	70.0
C	NH	7.19	UM	-		3	3.16	t (8.2)	70.6
	COOH	-	-	167.2		4	3.36	t (9.4)	66.9
	α	4.23	t (7.5)	61.23		5	3.49	t (7.7)	74.1
	β	5.07	UM	74.8		6	3.45,3.49	UM	61.2
	1	-	-	138.7	Cg	1	4.72	UM	93.4
	2	7.86	s	129.1		2	2.16, 1.63	UM	35.0
	3	-	-	127.7		3	3.5	t (8.8)	46.9
	4	-	-	149.9		3-NH_2	ND	-	-
	5	7.3	d (7.8)	123.9		4	2.78	UM	83.5
	6	7.32	d (10.5)	127.3		4-OMe	3.33	s	58.1
D	NH	7.79	d (7.6)	-		5	3.67	UM	67.0
	COOH	-	-	170.5		6	1.18	d (5.7)	18.3
	α	5.61	d (9.4)	54.1	Dg	1	5.63	d (7.5)	99.6
	1	-	-	133.5		2	3.59	t (8.2)	77.3
	2	5.1	s	104.3		3	3.48	t (7.7)	77.5
	3	-	-	151.6		4	3.21	t (8.7)	70.4
	4	-	-	132.2		5	3.31	UM	77.8
	5	-	-	153.2		6	3.72, 3.45	d (10.5)	61.3
	6	5.58	s	108.1		1'	5.39	UM	95.5
E	NH	7.62	d (7.9)	-		2'	2.14, 1.67	UM	34.3
	COOH	-	-	167.8		3'	3.16	m (8.2)	49.5
	α	4.77	t (3.8)	59.3	Dg'	3'-NH_2	ND	-	-
	β	5.24	d (2.6)	71.2		4'	3.06	UM	73.1
	1	-	-	137.3		5'	4.23	UM	68.4
	2	7.62	d (7.9)	128.1		6'	1.08	d (6.0)	18.5
	3	7.2	d (7.8)	122.7					
	4	-	-	155.2					
	5	7.13	d (7.9)	123.9					
	6	7.07	d (8.1)	128.4					

[a]800 MHz, [b]determined by edited HSQC and HMBC, UM: unresolved multiplicity, ND: not detected.

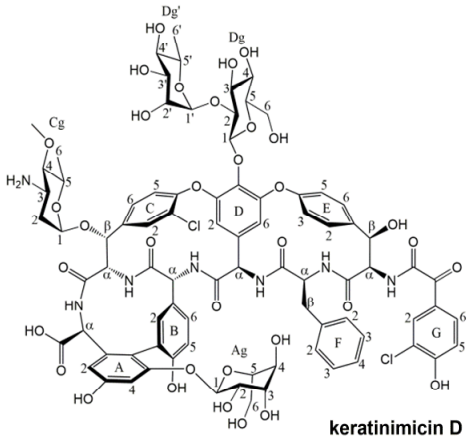


keratinimicin C

Supplementary Table 10. NMR assignments for keratinimicin D in DMSO-*d6*. The numbering scheme for keratinimicin D is shown below the table.

C/H		δH[a]	Multiplicity (Hz)	δC[b]	C/H		δH[a]	Multiplicity (Hz)	δC[b]
	NH	8.32	UM	-		NH	ND	-	-
	COOH	-	-	ND		COOH	-	-	ND
	α	4.43	d (5.1)	57.3		α	4.5	q (8.2)	55.8
	1	-	-		F	β	2.59	d (6.3)	40.3
A	2	6.48	s	108.6		1	-	-	ND
	3	-	-			2	6.78	d (7.6)	129.3
	4	6.69	s	103.2		3	6.84	t (7.5)	128.5
	5	-	-	ND		4	6.98	t (7.4)	126.6
	6	-	-	ND		COOH	-	-	ND
	NH	8.55	UM	-		CO	-	-	ND
	COOH	-	-	ND		1	-	-	ND
	α	4.44	UM	54.3	G	2	7.96	s	131.4
	1	-	-	-		3	-	-	ND
B	2	7.23	s	136.2		4	-	-	ND
	3	-	-	ND		5	6.3	d (6.3)	119.8
	4	-	-	ND		6	7.67	d (8.6)	128.3
	5	6.83	d (7.5)	116.2		1	5.16	UM	98.3
	6	6.81	d (8.8)	126.2		2	3.12	UM	70.2
	NH	ND	-	-	Ag	3	3.2	t (8.7)	70.8
	COOH	-	-	ND		4	3.37	UM	67.1
	α	4.25	d (11.5)	61.5		5	3.48	t (7.7)	74.3
	β	5.07	UM	74.4		6	3.47	UM	61.4
C	1	-	-	ND		1	4.73	UM	93.7
	2	7.86	s	129.3		2	2.16, 1.61	UM	35.3
	3	-	-	ND		3	3.49	UM	47.3
	4	-	-	ND	Cg	3-NH_2	ND	-	-
	5	7.28	d (8.3)	124.1		4	2.55	UM	86.7
	6	7.32	d (8.4)	127.5		4-OMe	3.34	s	58.5
	NH	ND	-	-		5	3.65	m	67.3
	COOH	-	-	ND		6	1.19	d (5.6)	18.5
	α	5.59	d (9.0)	54.3		1	5.63	d (7.4)	99.8
	1	-	-	ND		2	3.59	t (8.3)	77.6
D	2	5.09	s	104.4	Dg	3	3.45	UM	77.8
	3	-	-	ND		4	3.15	d (9.1)	70.9
	4	-	-	ND		5	3.31	m	78.1
	5	-	-	ND		6	3.73, 3.44	UM	61.5
	6	5.55	s	108.3		1'	5.13	UM	100.8
	NH	7.83	d (8.5)	-		2'	3.72	UM	71.0
	COOH	-	-	ND		3'	3.48	UM	71.1
	α	4.77	dd (8.4,4.6)	59.6	Dg'	4'	3.21	t (9.4)	72.4
	β	5.23	d (3.3)	71.4		5'	4.08	m	68.8
	1	-	-	ND		6'	1.08	d (6.1)	18.4
E	2	7.61	d (8.5)	128.3					
	3	7.21	dd (7.8,1.6)	123.0					
	4	-	-	ND					
	5	7.13	dd (7.8,1.7)	124.1					
	6	7.06	d (8.3)	128.7					

[a]800 MHz, [b]determined by edited HSQC and HMBC, UM: unresolved multiplicity, ND: not detected.

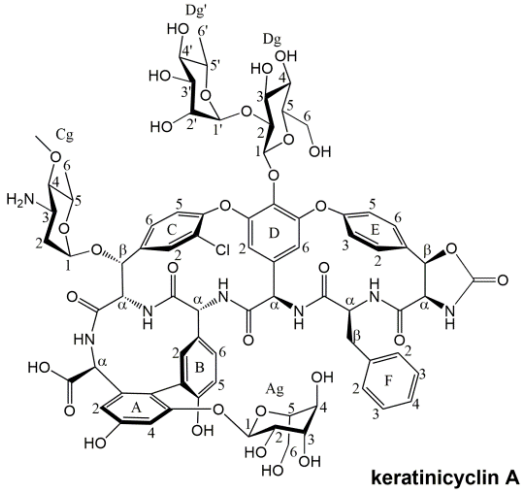


keratinimicin D

Supplementary Table 11. NMR assignments for keratinicyclin A in DMSO-*d6*. The numbering scheme for keratinicyclin A is shown below the table.

	C/H	δH[a]	Multiplicity (Hz)	δC[b]		C/H	δH[a]	Multiplicity (Hz)	δC[b]
	NH	8.7	d (4.4)	-		NH	8.16	UM	-
	COOH	-	-	173.2		COOH	-	-	166.5
	α	4.49	d (5.8)	57.3		α	4.74	UM	62.8
	1	-	-	137.3		β	5.93	d (8.4)	77.1
A	2	6.52	s	108.9		1	-	-	137.6
	3	-	-	158.0	E	2	7.29	d (8.5)	127.5
	4	6.71	s	102.7		3	7.00	d (8.8)	123.5
	5	-	-	155.6		4	-	-	158.7
	6	-	-	121.5		5	7.22	d (8.0)	122.0
	NH	8.65	d (3.5)	-		6	7.12	d (8.1)	128.8
	COOH	-	-	ND		NHCO		-	160.1
	α	4.59	d (3.9)	54.2		NH	7.84	d (9.2)	-
	1	-	-	132.8		COOH	-	-	169.5
B	2	7.23	s	136.4		α	4.34	q (7.8, 9.2)	57.6
	3	-	-	119.2	F	β	2.75, 2.58	d (10.7)	39.9
	4	-	-	156.0		1	-	-	137.0
	5	6.84	d (8.1)	116.2		2	6.85	d (7.4)	129.9
	6	6.82	UM	126.3		3	6.8	t (7.4)	128.5
	NH	7.2	-	-		4	6.97	t (7.2)	127.1
	COOH	-	-	167.7		1	5.2	UM	98.3
	α	4.29	d (11.3)	61.6		2	3.18	t (3.1)	70.4
	β	5.11	UM	75.2	Ag	3	3.24	t (3.6,9.7)	71.0
C	1	-	-	138.8		4	3.39	t (9.7)	67.1
	2	7.89	s	129.5		5	3.48	UM	74.4
	3	-	-	127.5		6	3.49, 3.45	d (7.5)	61.2
	4	-	-	150.0		1	4.76	t (4.0)	93.9
	5	7.26	d (8.2)	124.0		2	2.17, 1.65	UM	35.2
	6	7.35	d (8.0)	128.1		3	3.52	m (8.3)	47.3
	NH	8.13	d (8.5)	-	Cg	3-NH_2	ND	-	-
	COOH	-	-	170.2		4	2.8	t (9.9)	83.7
	α	5.56	d (8.6)	54.1		4-OMe	3.35	s	58.6
	1	-	-	133.7		5	3.68	m (6.0)	67.3
D	2	5.11	s	105.0		6	1.2	d (5.5)	18.8
	3	-	-	151.4		1	5.63	d (7.5)	99.5
	4	-	-	132.4		2	3.59	t (8.4)	77.7
	5	-	-	153.1	Dg	3	3.41	t (9.0)	78.1
	6	5.51	s	112.6		4	3.14	t (9.0)	71.1
						5	3.22	m (8.7)	78.7
						6	3.72, 3.37	d (9.4, 6.2)	62.0
						1'	5.13	UM	101.2
					Dg'	2'	3.71	t (3.3)	71.0
						3'	3.49	t (9.2)	71.4
						4'	3.2	t (9.4)	72.5

[a]800 MHz, [b]determined by edited HSQC and HMBC, UM: unresolved multiplicity, ND: not detected.

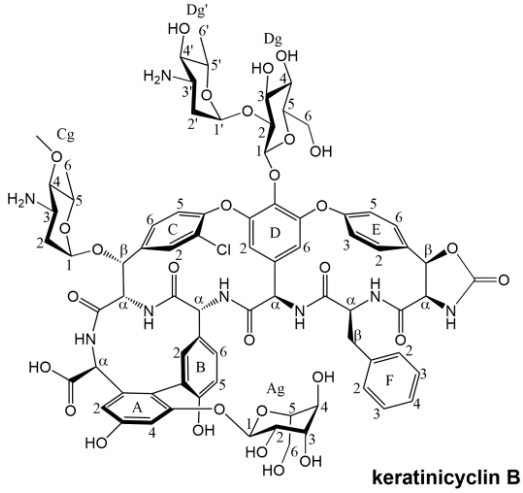


keratinicyclin A

Supplementary Table 12. NMR assignments for keratinicyclin B in DMSO-*d6*. The numbering scheme for keratinicyclin B is shown below the table.

	C/H	δH[a]	Multiplicity (Hz)	δC[b]		C/H	δH[a]	Multiplicity (Hz)	δC[b]
	NH	8.67	d (4.8)	-		NH	8.19	UM	-
	COOH	-	-	173.2		COOH	-	-	ND
	α	4.49	d (5.8)	57.5		α	4.75	UM	62.6
	1	-	-	-		β	5.93	d (8.4)	76.8
A	2	6.29	s	106.5		1	-	-	ND
	3	-	-	ND	E	2	7.3	dd (1.5,9.1)	127.5
	4	6.42	s	102.7		3	7.00	dd (1.6,9.1)	123.3
	5	-	-	ND		4	-	-	ND
	6	-	-	ND		5	7.22	d (7.1)	121.8
	NH	8.64	d (3.2)			6	7.14	dd (1.4,7.4)	128.6
	COOH	-	-	ND		NHCO		-	ND
	α	4.59	d (3.4)	54.0		NH	7.85	d (9.1)	-
	1	-	-	ND		COOH	-	-	ND
B	2	7.23	s	136.3		α	4.35	q (8.7)	57.3
	3	-	-	ND	F	β	2.76, 2.6	t (10.3),d (7.1)	39.7
	4	-	-	ND		1	-	-	ND
	5	6.84	d (8.9)	116.2		2	6.86	d (7.7)	129.6
	6	6.82	dd (2.8,9.0)	126.2		3	6.8	t (7.3)	128.5
	NH	ND	-	-		4	6.98	t (7.2)	126.9
	COOH	-	-	167.4		1	5.19	UM	98.4
	α	4.29	d (10.6)	61.6		2	3.18	t (3.0)	70.2
	β	5.13	UM	75.0	Ag	3	3.25	t (9.0)	70.8
C	1	-	-	ND		4	3.4	t (9.3)	67.0
	2	7.9	s	129.3		5	3.5	m	74.2
	3	-	-	ND		6	3.48,3.46	UM	61.1
	4	-	-	ND		1	4.75	UM	93.6
	5	7.28	d (8.2)	124.1		2	2.19, 1.66	UM	35.0
	6	7.35	d (7.4)	127.9		3	3.53	m	47.1
	NH	8.13	d (8.6)	-	Cg	3-NH_2	ND	-	-
	COOH	-	-	ND		4	2.83	t (9.6)	83.4
	α	5.57	d (8.6)	54.0		4-OMe	3.34	s	58.4
	1	-	-	ND		5	3.69	m	67.3
D	2	5.13	s	104.8		6	1.2	d (5.3)	18.6
	3	-	-	ND		1	5.64	d (7.4)	99.3
	4	-	-	ND		2	3.59	t (8.4)	77.4
	5	-	-	ND		3	3.43	t (9.4)	77.8
	6	5.53	s	112.4	Dg'	4	3.16	t (9.0)	70.7
						5	3.23	m	78.4
						6	3.72, 3.39	d (10.8)	61.6
						1'	5.37	UM	95.8
						2'	2.14, 1.69	UM	34.6
					Dg'	3'	3.2	m	49.8
						3'-NH_2	ND	-	-
						4'	3.06	t (8.4)	73.2

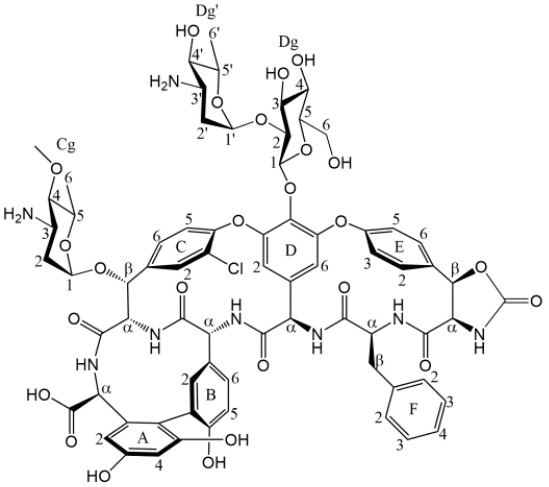
[a]800 MHz, [b]determined by edited HSQC and HMBC, UM: unresolved multiplicity, ND: not detected.



Supplementary Table 13. NMR assignments for keratinicyclin C in DMSO-*d6*. The numbering scheme for keratinicyclin C is shown below the table.

	C/H	δH[a]	Multiplicity (Hz)	δC[b]		C/H	δH[a]	Multiplicity (Hz)	δC[b]
	NH	8.52	UM	-		NH	8.14	UM	-
	COOH	-	-	173.3		COOH	-	-	166.2
	α	4.44	d (5.8)	57.7		α	4.75	d (9.0)	62.6
	1	-	-	137.3		β	5.93	d (8.2)	76.8
A	2	6.34	s	106.6		1	-	-	132.4
	3	-	-	157.5	E	2	7.31	dd (2.1,8.5)	127.5
	4	6.39	s	102.7		3	7.02	d (3.1,9.0)	123.4
	5	-	-	ND		4	-	-	158.7
	6	-	-	118.6		5	7.22	dd (2.3)	121.8
	NH	8.75	d (3.4)			6	7.12	dd (1.7,8.2)	128.6
	COOH	-	-	ND		NHCO		-	159.7
	α	4.58	d (4.3)	54.1		NH	7.84	d (9.8)	-
	1	-	-	126.4		COOH	-	-	169.5
B	2	7.27	s	136.6		α	4.31	q (7.8, 9.2)	57.6
	3	-	-	122.4	F	β	2.76, 2.60	d (10.6)	39.9
	4	-	-	155.9		1	-	-	137.0
	5	6.76	d (8.6)	116.5		2	6.88	d (7.5)	129.6
	6	6.82	dd (1.8,8.6)	125.7		3	6.94	t (7.6)	128.5
	NH	6.91	-	-		4	7.02	t (7.4)	126.7
	COOH	-	-	ND		1	4.69	UM	94.0
	α	4.32	t (8.7)	61.5		2	2.12, 1.54	UM	36.7
	β	5.13	UM	74.8		3	3.31	dd (10.2)	47.3
C	1	-	-	138.8	Cg	3-NH2	ND	-	-
	2	7.93	s	129.4		4	2.65	t (9.7)	85.7
	3	-	-	127.5		4-OMe	3.34	s	58.3
	4	-	-	149.9		5	3.65	UM	67.8
	5	7.26	d (8.6)	124.1		6	1.18	d (5.8)	18.7
	6	7.38	dd (1.7,8.0)	127.9		1	5.65	d (7.6)	99.2
	NH	8.24	d (8.7)	-		2	3.59	t (8.1)	77.5
	COOH	-	-	170.0	Dg	3	3.43	UM	78.0
	α	5.64	d (8.9)	54.2		4	3.15	t (9.5)	70.8
	1	-	-	134.5		5	3.23	m (6.0)	78.5
D	2	5.17	s	104.8		6	3.73, 3.38	d (10.3)	61.9
	3	-	-	ND		1'	5.35	UM	96.1
	4	-	-	133.1		2'	2.1, 1.6	UM	35.4
	5	-	-	ND	Dg'	3'	3.11	UM	49.8
	6	5.52	s	112.4		3'-NH2	ND	-	-
						4'	2.94	t (10.1)	74.5
						5'	4.17	m (6.4,8.8)	68.5

[a]800 MHz, [b]determined by edited HSQC and HMBC, UM: unresolved multiplicity, ND: not detected.



keratinicyclin C

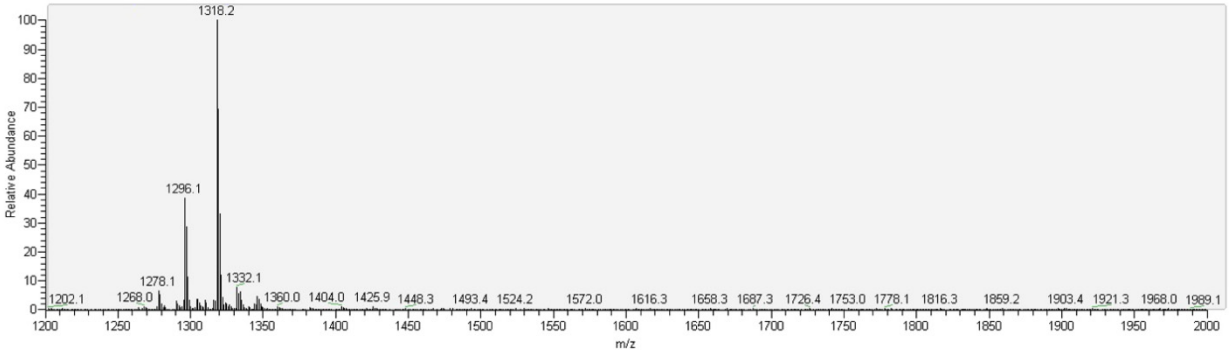
Supplementary Table 14. MIC values (in μM) for keratinimicins and keratinicyclin B against select pathogenic Gram-negative bacteria and viruses.

Strain	Keratini-micin A	Keratini-micin C	Keratini-cyclin B	Control drug[a]
Bacterium				
E. coli	>35	>35	>39	>44 (V), 0.1 (C)
K. pneumoniae	>35	>35	>39	>44 (V), 0.1 (C)
E. cloacae	>35	>35	>39	>44 (V), 0.1 (C)
P. aeruginosa	>35	>35	>39	>44 (V), 3.0 (C)
A. baumannii	>35	>35	>39	>44 (V), 3.0 (C)
V. cholerae	>35	>35	>39	>44 (V), 0.8 (C)
B. fragilis	>35	>35	>39	11.7 (M)
Virus				
Influenza B	–[b]	–	>92	6.1 (O)
HSV-1	–	–	>92	97 (A)
HSV-2	–	–	>92	32 (A)
Vaccinia	–	–	>92	–
Rhinovirus	–	–	>92	204 (R)

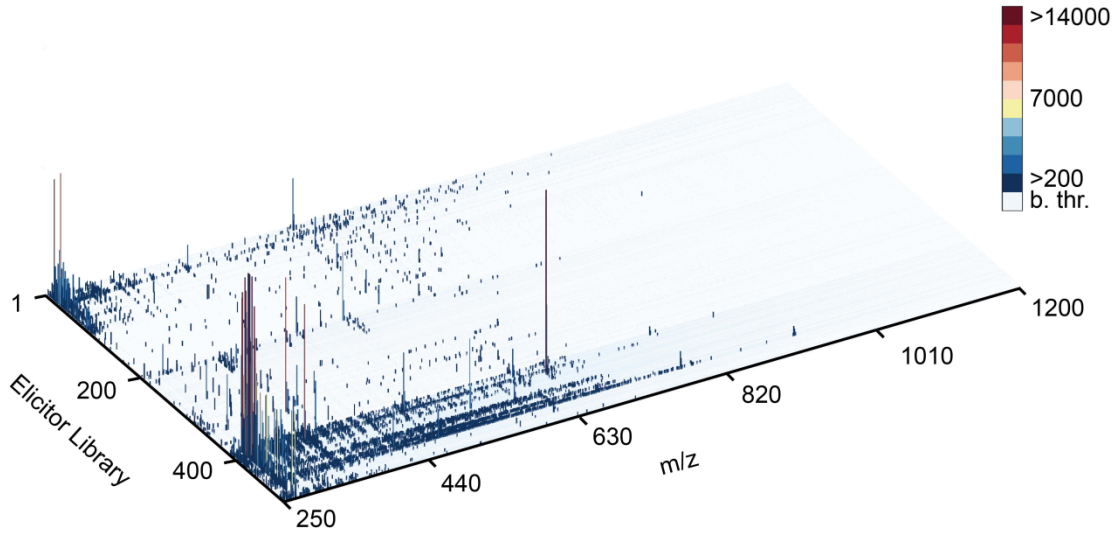
[a]Control drugs are abbreviated as follows: V, vancomycin; C, ciprofloxacin, M, metronidazole; O, oseltamivir; A, acyclovir; R, ribavirin.

[b]Not determined.

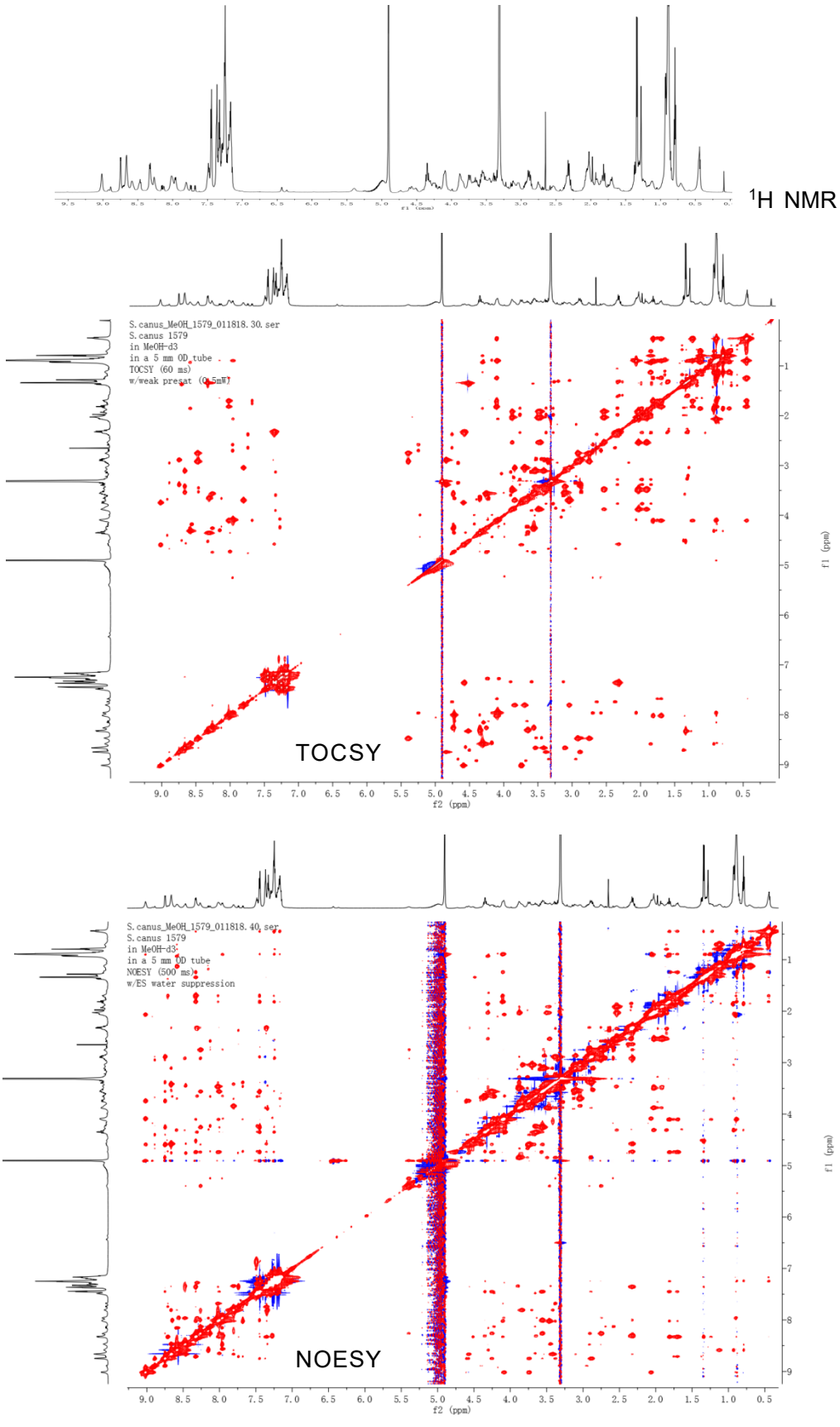
Supplementary Fig. 1. Direct LAESI-IMS output from a well containing orfamide. For each strain, 502 such spectra were compiled (one per elicitor), the observed signals extracted using GMSU-LAESI software, which gave all m/z values and the corresponding intensities per well, and the three-dimensional dataset (elicitor vs. m/z vs. intensity) then plotted in MatLab (see Supplementary Methods for details).

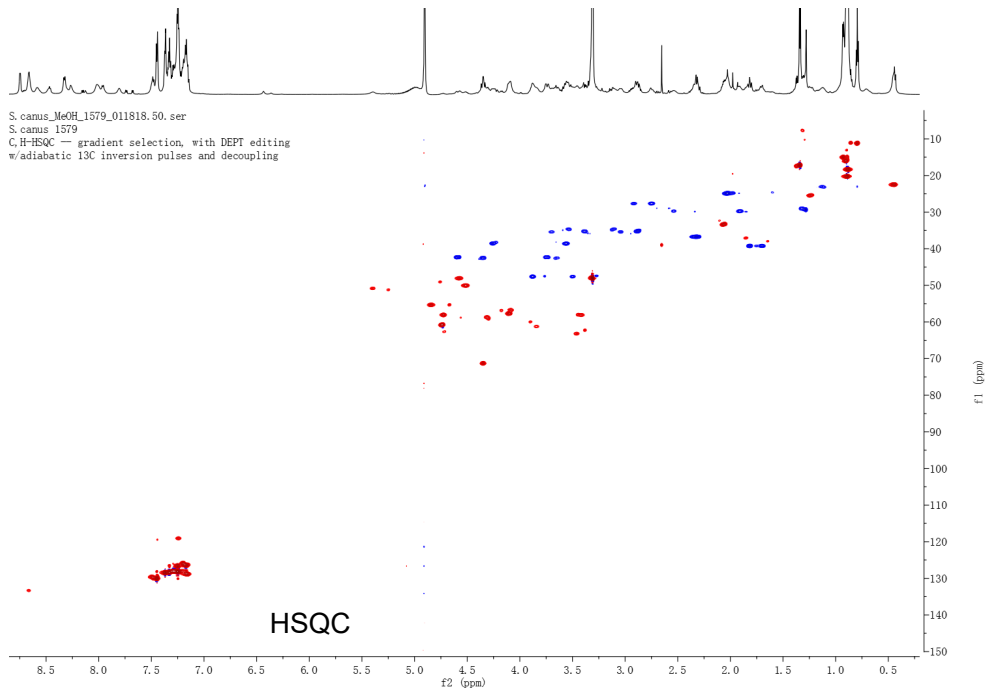


Supplementary Fig. 2. Secondary metabolome of *S. canus*, as detected by LAESI-MS in response to 502 elicitors in the m/z range of 250-1200. b. thr. designates below threshold of detection. The HiTES-IMS screen was carried out in a single replicate.



Supplementary Fig. 3. NMR spectra of canucin A in CD_3OH. Full 1D/2D NMR datasets on canucins were collected once.

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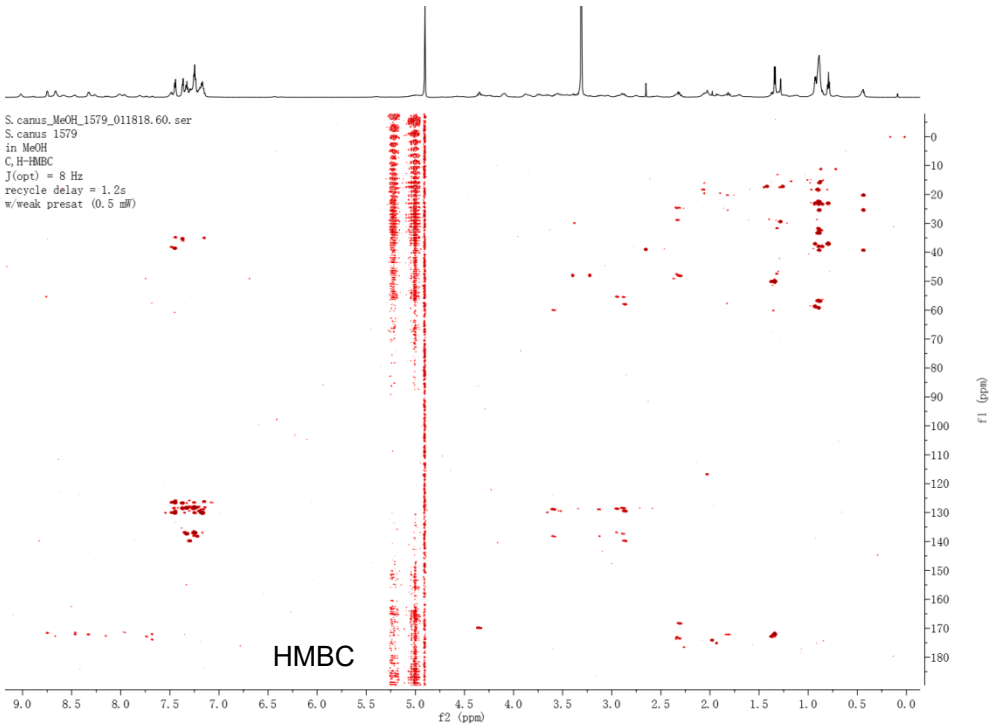
S. canus 1579
C,H-HSQC — gradient selection, with DEPT editing
w/adiabatic 13C inversion pulses and decoupling
HSQC
f2 (ppm)
f1 (ppm)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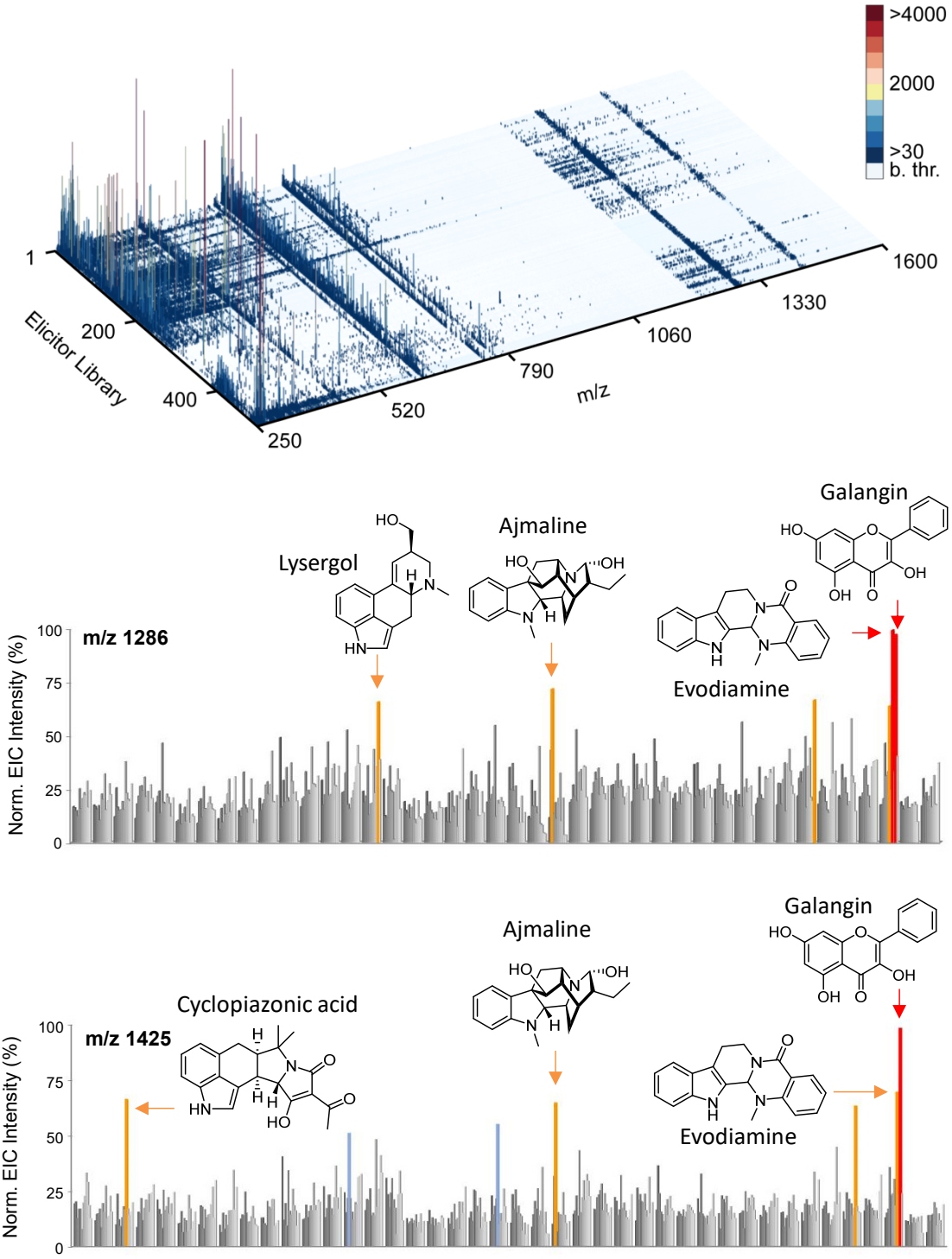
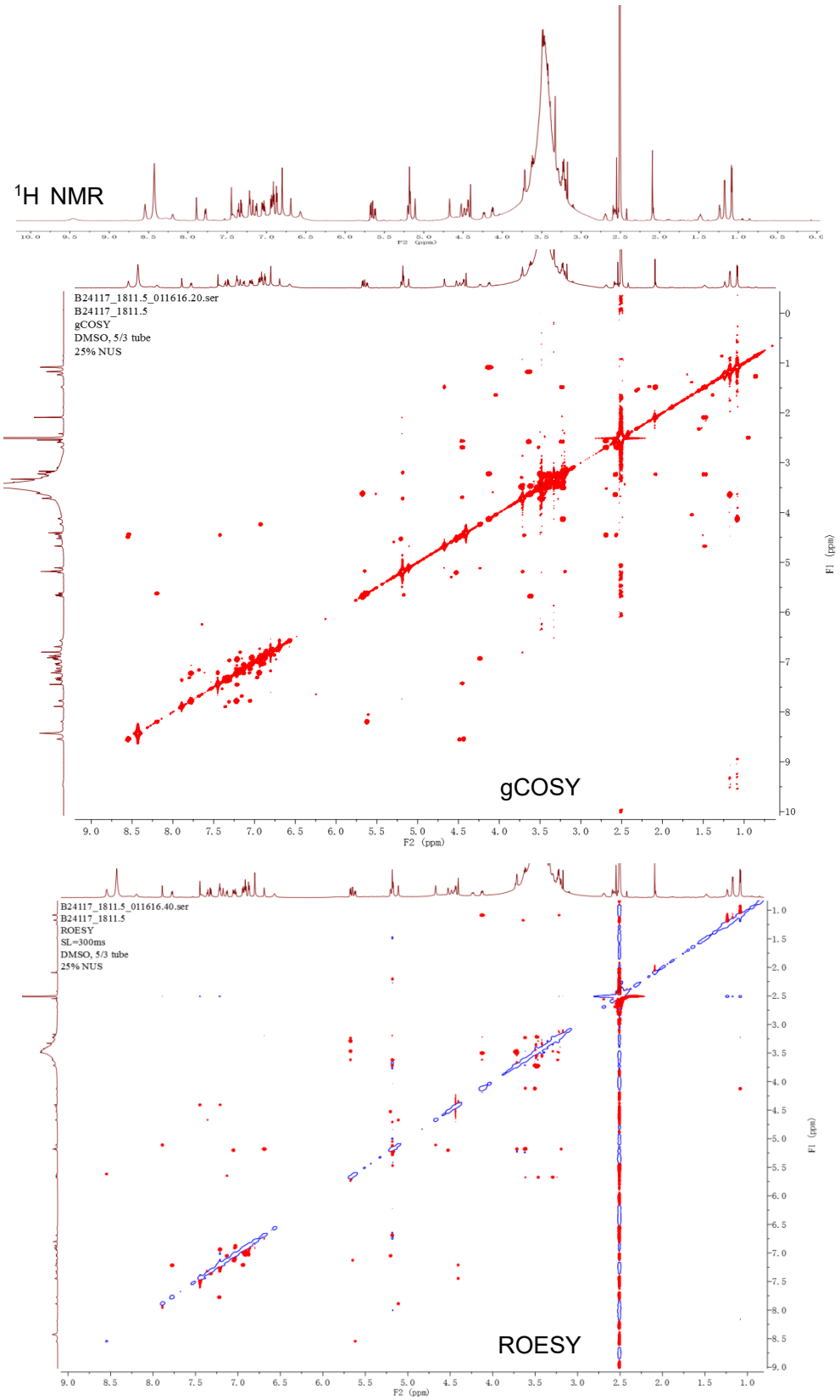
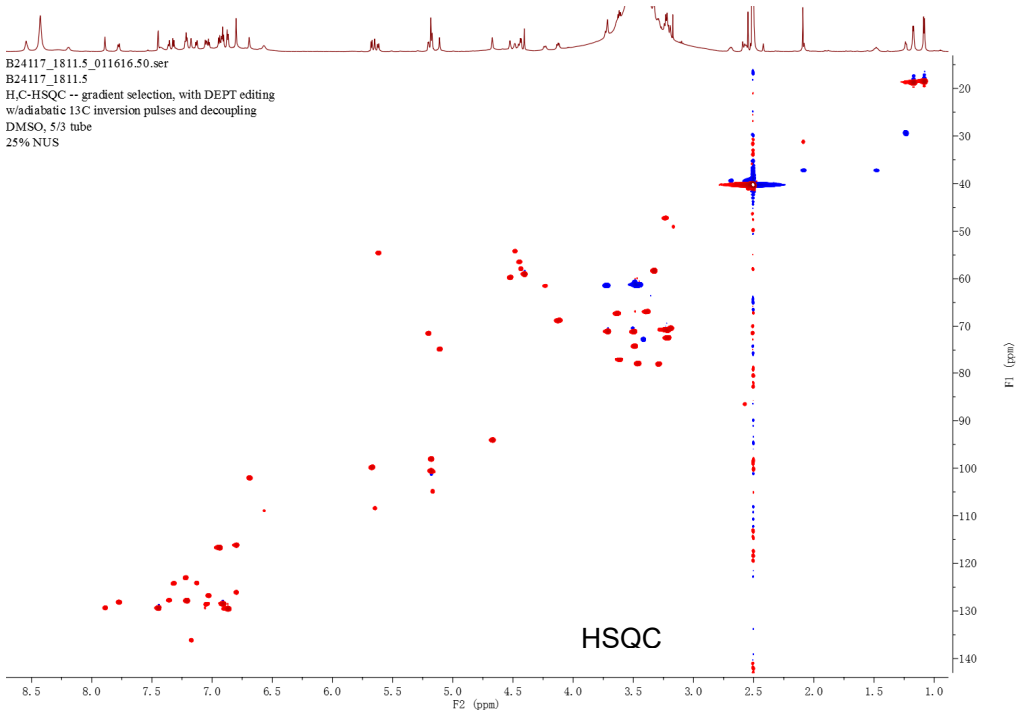
S. canus 1579
in MeOH
C,H-HMBC
J(opt) = 8 Hz
recycle delay = 1.2s
w/weak presat (0.5 mW)
HMBC
f2 (ppm)
f1 (ppm)

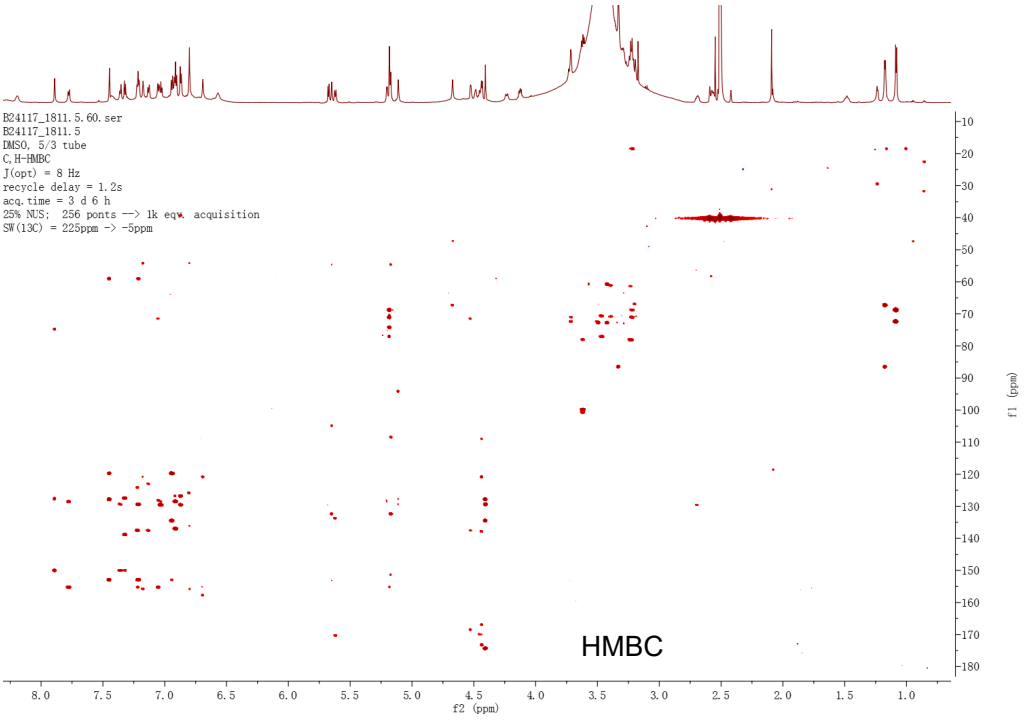
Supplementary Fig. 4. Secondary metabolome of *A. keratiniphila* as detected by LAESI-MS in response to 502 elicitors. (Top) Shown is the m/z range 250-1600; b. thr. designates below threshold of detection. Note that a lower threshold was used for signals in the range of m/z 1100-1500 (as described in Supplementary Methods) to highlight production of two cryptic metabolites with m/z 1286 and 1425). 2D components of the 3D plot focusing on m/z 1286 (middle) and 1425 (bottom) are also shown along with the best elicitors. The HiTES-IMS screen was carried out in a single replicate.



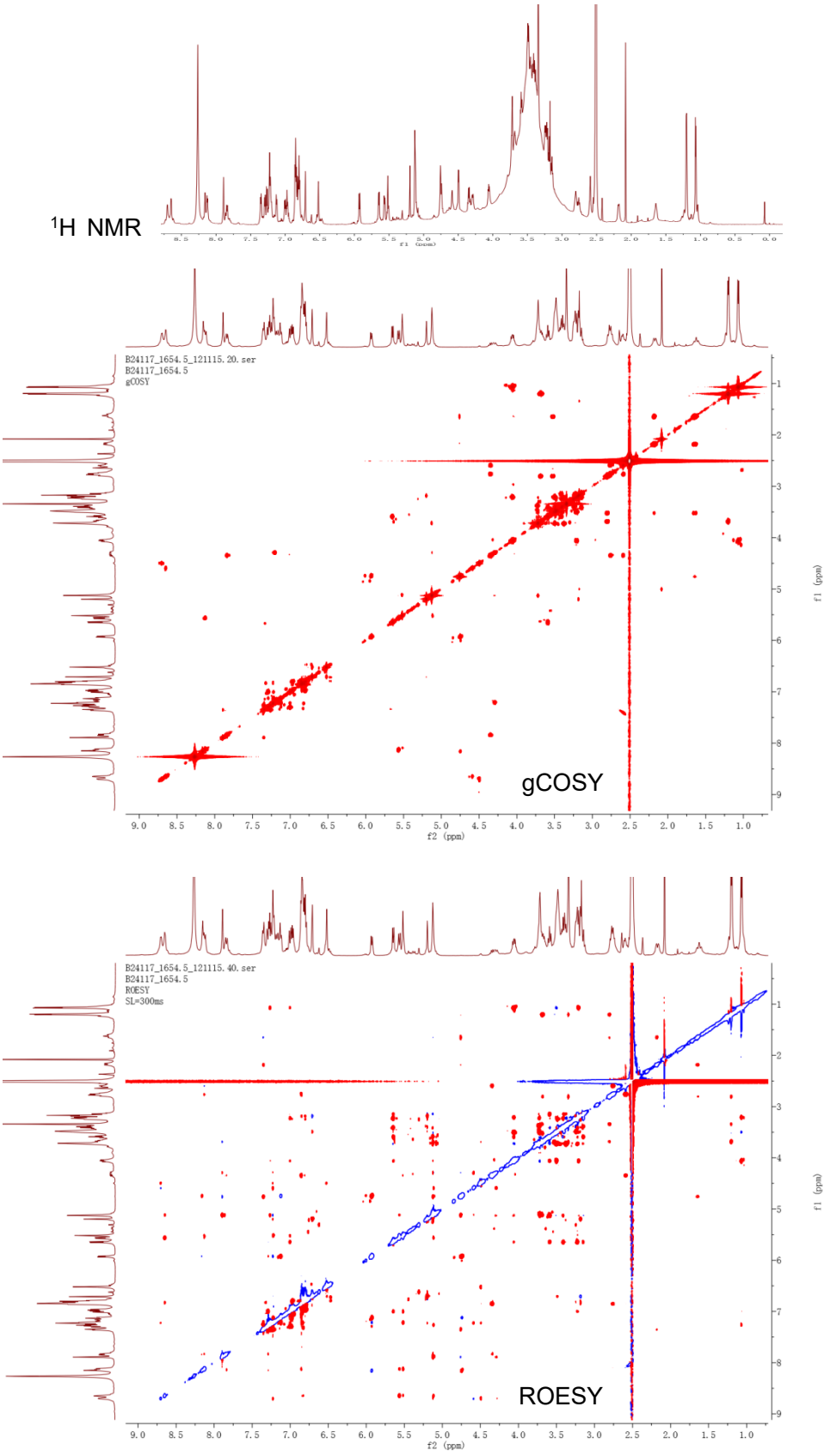
Supplementary Fig. 5. NMR spectra of keratinimicin A in DMSO-*d6*. Full 1D/2D NMR datasets on keratinimicins were collected once.

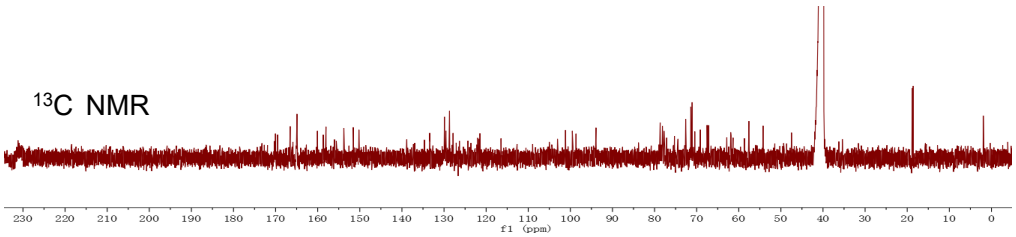


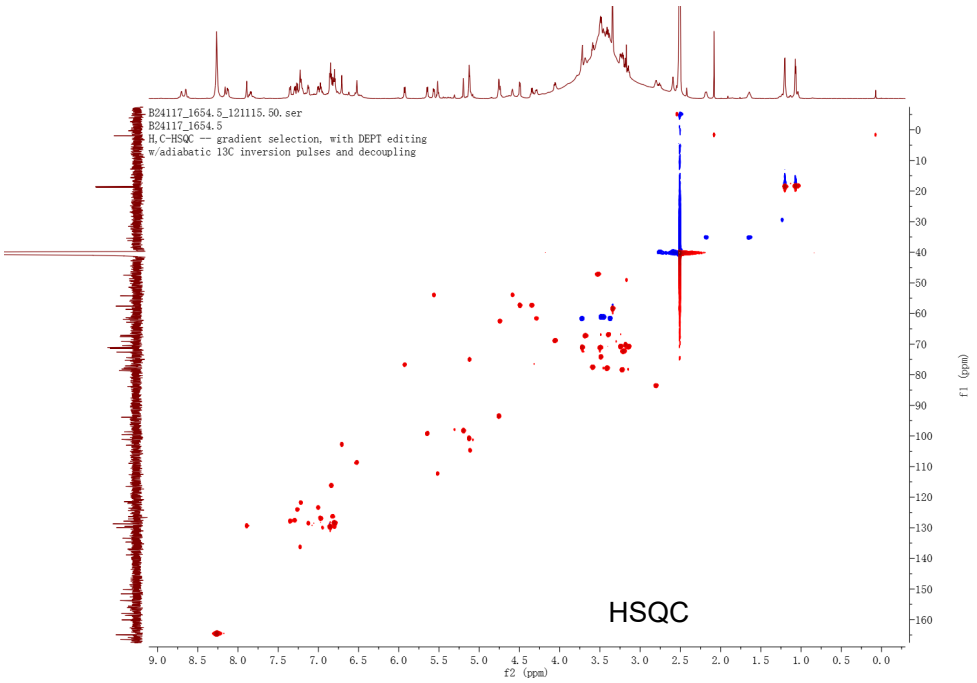

B24117_1811.5_011616.50.ser
B24117_1811.5
H,C-HSQC -- gradient selection, with DEPT editing
w/adiabatic 13C inversion pulses and decoupling
DMSO, 5/3 tube
25% NUS
HSQC
F2 (ppm)
F1 (ppm)

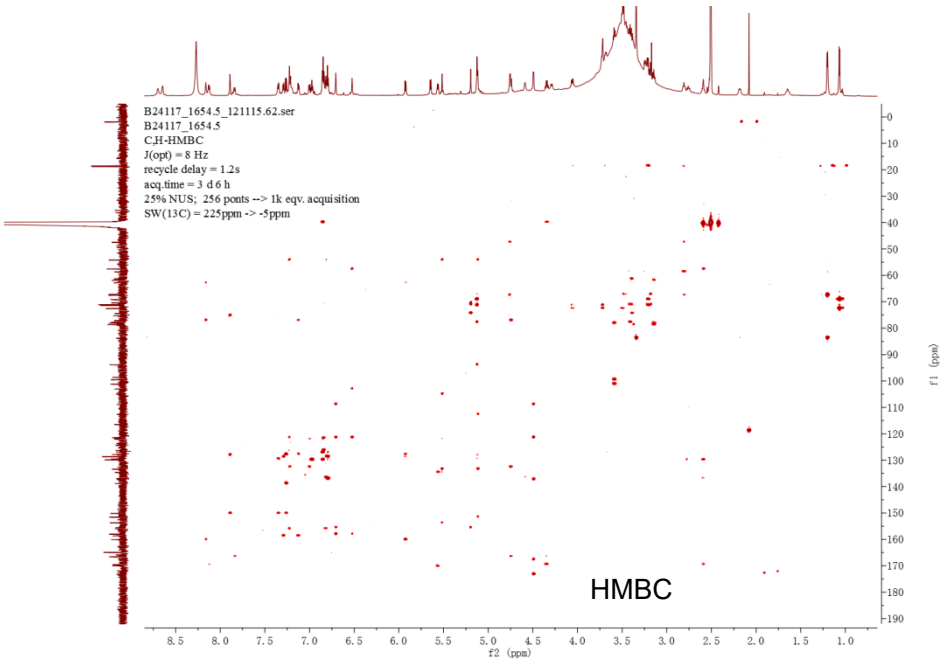

B24117_1811.5.60.ser
B24117_1811.5
DMSO, 5/3 tube
C,H-HMBC
J(opt) = 8 Hz
recycle delay = 1.2s
acq.time = 3 d 6 h
25% NUS; 256 ponts --> 1k eqv. acquisition
SW(13C) = 225ppm -> -5ppm
HMBC
f2 (ppm)
f1 (ppm)

Supplementary Fig. 6. NMR spectra of keratinicyclin A in DMSO-*d6*. Full 1D/2D NMR datasets on keratinicyclins were collected once.




^{13}C NMR
f1 (ppm)


B24117_1654.5_121115.50.ser
B24117_1654.5
H,C-HSQC -- gradient selection, with DEPT editing
w/adiabatic 13C inversion pulses and decoupling
HSQC
f2 (ppm)
f1 (ppm)


B24117_1654.5_121115.62.ser
B24117_1654.5
C,H-HMBC
J(opt) = 8 Hz
recycle delay = 1.2s
acq.time = 3 d 6 h
25% NUS; 256 ponts --> 1k eqv. acquisition
SW(13C) = 225ppm -> -5ppm
HMBC
f2 (ppm)
f1 (ppm)