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for

New Insulapeptolides from the Cyanobacterium *Nostoc insulare* as Selective and Potent Inhibitors of Human Leukocyte Elastase

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Table S1: NMR spectroscopic data of compound **2** (300 MHz, CD_3OD)

	C/H no.	d_H (*J* in Hz)[a]	d_C[a]	HMBC	NOESY (selected)
Ile1	1	-	175.2		
	2	5.20, d (3.7)	56.1	1, 3, 4, 5, 6	
	3	2.04, m	40.3		
	4a	1.41, m	28.0	2, 3, 47, 5	
	4b	1.29, m		2, 3, 47, 5	
	47	1.05, t (7.1)	12.4	3, 4	
	5	0.86, d (6.9)	15.2	2, 3, 4	
N-Me-Tyr	6	-	171.9		
	7	5.39, dd (2.8; 11.7)	62.8	6, 8, 15	17
	8a	3.38, m	34.9	7, 9, 10, 11	
	8b	2.78, dd (11.7; 14.6)		7, 9, 10, 11	
	9	-	129.1		
	10	7.13, d (8.4)	131.9	12, 13, 14	15, 17
	11	7.13, d (8.4)	131.9	12, 13, 14	15, 17
	12	6.72, d (8.4)	116.8	9, 10, 11, 14	20, 21
	13	6.72, d (8.4)	116.8	9, 10, 11, 14	20, 21
	14	-	157.8		
N-Me	15	2.87, s	31.8	7, 16	10, 11
Ile2	16	-	172.8		
	17	4.60, d (10.7)	56.6	16, 18, 19, 21, 22, 26	10, 11
	18	1.92, m	34.7		
	19a	1.24, m	25.3		
	19b	0.77, m			
	20	0.76, t (7.0)	10.8	18, 19	12, 13
	21	0.05, d (6.7)	14.8	17, 18, 19	12, 13
Ahp	22	-	171.6		
	23	4.63, m	50.6	22, 24, 27	24b, 25
	24a	2.96, m	22.1		
	24b	1.97, m			23
	25	1.95, m	31.1	26	23, 26
	26	5.14, brs	76.0	22, 24, 17	25
Leu	27	-	174.5		
	28	4.69, m	52.3	27, 29, 30, 33	
	29a	1.99, m	41.1	28, 30, 32	
	29b	1.55, m		28, 30, 32	
	30	2.08, m	24.5		
	31	0.99, d (6.5)	24.3	29, 30, 32	
	32	0.92, d (6.2)	21.6	29, 30, 31	
Hmp	33	-	169.5		

	34	4.52, d (3.3)	66.4	33, 39	35, 36
	35	5.34, t (3.3)	79.2	1, 34, 37	34, 36
	36	2.62, m	39.0		34, 35, 38
	37a	4.34, brt (9.0)	53.5	34, 35, 36, 39	40
	37b	3.55, m		36, 38	
	38	1.20, d (6.5)	11.3	35, 36, 37	36
Cit	39	-	173.6		
	40	4.58, m	52.7	39, 41, 42	37a
	41	1.75, m	29.7	39, 40, 42	46
	42	1.67, m	26.5	41	
	43a	3.24, m	40.5	41, 42, 44	
	43b	3.08, m		41, 42, 44	
	44	-	162.3		
Ac	45	-	173.4		
	46	2.01, s	22.1	45	41

[a] assignments are based on extensive 1D and 2D NMR measurements (HMBC, HSQC, COSY).

Table S2: NMR Spectroscopic data of compound **3** (500 MHz, CD_3OD)

	C/H no.	d_H (*J* in Hz)[a]	d_C[a]	HMBC	ROESY (selected)
Val	1	-	175.0		
	2	4.96, d (4.9)	58.3	1, 3, 4, 5, 6	
	3	2.32, m	33.1		38
	4	0.89, d (6.9)	17.6	2, 3, 5	35
	5	1.04, d (6.9)	20.2	2, 3, 4	15
N, *O*-diMe-Tyr	6	-	171.6		
	7	5.39, dd (2.9; 12.0)	62.5	6, 8, 15	17
	8a	3.39, dd (2.9; 14.8)	34.6	7, 9, 10, 11	
	8b	2.84, dd (12.0; 14.8)		7, 9, 10, 11	
	9	-	130.3		
	10	7.24, d (8.6)	131.9	8, 12, 13, 14	15, 17, 20, 21
	11	7.24, d (8.6)	131.9	8, 12, 13, 14	15, 17, 20, 21
	12	6.87, d (8.6)	115.5	9, 10, 11, 14	20, 21
	13	6.87, d (8.6)	115.5	9, 10, 11, 14	20, 21
	14	-	160.3		
O-Me	47	3.78, s	55.5	14	
N-Me	15	2.89, s	31.5	7, 16	5, 10, 11
Ile	16	-	172.4		
	17	4.58, d (10.7)	56.4	16, 18, 21, 22, 26	7, 10, 11
	18	1.93, m	34.4		
	19a	1.22, m	25.1		
	19b	0.81, m			
	20	0.75, t (7.0)	10.5	18, 19	10, 11, 12, 13
	21	0.00, d (6.6)	14.6	17, 18, 19	10, 11, 12, 13
Ahp	22	-	171.4		
	23	4.64, m	50.6	22, 24, 27	24b/ 25
	24a	2.97, m	22.0		
	24b	1.95, m			23
	25	1.95, m	30.9		23
	26	5.13, brs	75.9	22, 24	
Leu	27	-	174.3		

	28	4.66, m	52.2	27, 33, 34	
	29a	2.00, m	41.0		
	29b	1.56, m			
	30	2.10, m	24.3		
	31	1.00, d (6.3)	24.1	29, 32	
	32	0.93, d (6.3)	21.4	29, 31	34
Hmp	33	-	169.3		
	34	4.53, d (3.5)	66.2	33, 39	32, 35
	35	5.34, t (3.5)	79.1	1	4, 34, 36
	36	2.62, m	38.8		35, 38, 40
	37a	4.32, brt (9.0)	53.2	34, 35, 36, 39	40
	37b	3.57, dd (9.7; 11.0)		36	40
	38	1.20, d (6.7)	11.1	35, 36, 37	3, 36
Cit	39	-	173.3		
	40	4.58, m	52.5	39, 41, 42	36, 37a, 37b
	41a	1.81, m	29.5		46
	41b	1.73, m			46
	42a	1.73, m	26.2		
	42b	1.64, m			
	43a	3.26, m	40.3		
	43b	3.08, m		41, 42, 44	
	44	-	162.1		
Ac	45	-	173.2		
	46	2.01, s	21.9	45	41a, 41b

[a] assignments are based on extensive 1D and 2D NMR measurements (HMBC, HSQC, COSY).

Table S3: NMR Spectroscopic data of compound **4** (300/500 MHz, CD_3OD)

	C/H no.	d_H (*J* in Hz)[a]	d_C[a]	HMBC	ROESY (selected)
Ile1	1	-	175.0		
	2	5.18, d (3.7)	55.9	1, 3, 4, 5, 6	38
	3	2.05, m	40.0		
	4a	1.45, m	27.8	2, 3, 5, 47	15
	4b	1.28, m		2, 3, 5, 47	15
	47	1.05, t (7.3)	12.1	3, 4	15
	5	0.87, d (6.9)	14.9	2, 3, 4	
N, *O*-diMe-Tyr	6	-	171.6		
	7	5.39, m	62.5	6	17
	8a	3.42, m	34.6	9, 10, 11	
	8b	2.85, m		7, 9, 10, 11	
	9	-	130.3		
	10	7.24, d (8.4)	131.9	14	15, 17, 21
	11	7.24, d (8.4)	131.9	14	15, 17, 21
	12	6.87, d (8.4)	115.4	9, 10, 11, 14	20, 21, 48
	13	6.87, d (8.4)	115.4	9, 10, 11, 14	20, 21, 48
	14	-	160.3		
O-Me	48	3.78, s	55.5	14	12, 13
N-Me	15	2.88, s	31.5	7, 16	4a, 4b, 10, 11, 47
Ile2	16	-	172.5		
	17	4.57, d (10.7)	56.2	16, 18, 21, 22, 26	7, 10, 11

	18	1.94, m	34.4		
	19a	1.22, m	25.0		
	19b	0.82, m			
	20	0.75, t (7.0)	10.5	18, 19	12, 13
	21	0.00, d (6.2)	14.6	17, 18, 19	10, 11, 12, 13
Ahp	22	-	171.4		
	23	4.65, m	50.4	22, 24, 27	24b, 25
	24a	2.98, m	22.0		
	24b	1.97, m			23
	25	1.95, m	30.8		23, 26
	26	5.13, brs	75.7	22, 24	25
Leu	27	-	174.3		
	28	4.68, m	52.1	27	
	29a	2.00, m	41.0		
	29b	1.56, m			
	30	2.11, m	24.3		
	31	0.99, d (6.6)	24.0	29, 30, 32	
	32	0.92, d (6.2)	21.4	29, 30, 31	34
Hmp	33	-	169.3		
	34	4.53, d (3.3)	66.2	33	32, 35, 36
	35	5.33, t (3.3)	79.0	1	34, 36
	36	2.64, m	38.7		34, 35
	37a	4.33, brt (9.0)	53.2	35, 36	40
	37b	3.55, m		36	40
	38	1.20, d (6.6)	11.1	35, 36, 37	2
Cit	39	-	173.3		
	40	4.59, m	52.4	39, 41, 42, 45	37a, 37b
	41a	1.83, m	29.5		46
	41b	1.74, m			46
	42a	1.73, m	26.2		
	42b	1.65, m			
	43a	3.24, m	40.3	41, 42	
	43b	3.09, m			
	44	-	162.3		
Ac	45	-	173.2		
	46	2.01, s	21.9	45	41a, 41b

[a] assignments are based on extensive 1D and 2D NMR measurements (HMBC, HSQC, COSY).

Table S4: NMR Spectroscopic data of compound **6** (300 MHz, CD_3OD)

	C/H no.	d_H (J in Hz)[a]	d_C[a]	HMBC	NOESY (selected)
Val	1	-	175.3		
	2	4.44, d (7.0)	59.5	1, 3, 4, 5, 6	
	3	2.15, m	31.9	2, 4, 5	
	4	0.97, d (6.6)	19.3	2, 3, 5	
	5	1.01, d (7.3)	19.7	2, 3, 4	
N-Me-Tyr	6	-	172.1		
	7	5.03, m	63.3	6, 16	
	8a	3.40, m	34.4	7, 9, 10, 11	
	8b	2.79, m		7, 9, 10, 11	
	9	-	129.1		
	10	7.12, d (8.4)	131.8	8, 12, 13, 14	15, 17

	11	7.12, d (8.4)	131.8	8, 12, 13, 14	15, 17
	12	6.74, d (8.4)	116.7	9, 10, 11, 14	19
	13	6.74, d (8.4)	116.7	9, 10, 11, 14	19
	14	-	157.8		
N-Me	15	2.87, s	31.4	7, 16	10, 11
Thr1	16	-	173.2		
	17	4.59, d (7.3)	56.3	16, 18, 19, 20, 24	10, 11
	18	3.71, m	67.1	17, 19	24
	19	0.54, d (6.2)	19.7	17, 18	12, 13
Ahp	20	-	171.6		
	21	4.65, dd (6.6; 12.4)	51.0	20, 25	22b/ 23b
	22a	2.79, m	22.2		
	22b	1.90, m			21
	23a	2.06, m	30.8		24
	23b	1.90, m			21, 24
	24	5.32, brs	77.2	20	18, 23a, 23b
Hphe	25	-	174.1[b]		
	26	4.36, brd (9.9)	54.7		
	27a	2.48, m	33.4		
	27b	2.00, m			
	28a	2.77, m	33.1	29, 30, 31	
	28b	2.66, m		29, 30, 31	
	29	-	142.2		
	30	7.21, d (7.3)	129.8	34	36
	31	7.21, d (7.3)	129.8	34	36
	32	7.29, t (7.3)	129.5	29, 30, 31, 34	
	33	7.29, t (7.3)	129.5	29, 30, 31, 34	
	34	7.21, t (7.3)	127.1	32, 34	
Thr2	35	-	171.6		
	36	4.82, m	57.3	35, 37, 38, 39	30, 31
	37	5.65, m	73.5	1, 35, 38	
	38	1.46, d (6.2)	18.8	36, 37	
Ser	39	-	173.3		
	40	4.69, m	56.8	39, 41, 42	
	41a	4.02, dd (5.4; 11.0)	63.3	39, 40	
	41b	3.93, dd (5.4; 11.0)		39, 40	
Pro	42	-	174.9		
	43	4.55, m	61.3	42, 44, 45, 46	
	44a	2.28, m	30.9	42, 43, 45, 46	
	44b	2.06, m			
	45a	2.13, m	25.9	43, 45, 46	
	45b	2.02, m			
	46a	3.70, m	48.8	44, 45	48a
	46b	3.63, m		44, 45	48a
Ba	47	-	174.6		
	48a	2.41, m	37.3	47, 49, 50	46a, 46b
	48b	2.28, m		47	
	49	1.69, m	19.2	47, 48, 50	
	50	0.99, t (7.3)	14.2	48, 49	

[a] assignments are based on extensive 1D and 2D NMR measurements (HMBC, HSQC, COSY). [b] assignment followed by deduction.

Table S5: NMR Spectroscopic data of compound **7** (300/500 MHz, CD_3OD)

	C/H no.	d_H (J in Hz)[a]	d_C[a]	HMBC	ROESY (selected)
Val	1	-	175.3		
	2	4.44, d (7.6)	59.7	1, 3, 4, 5, 6	8b, 38
	3	2.16, m	31.8	2, 4, 5	38
	4	0.97, d (6.6)	19.3	2, 3, 5	37, 38
	5	1.02, d (7.3)	19.9	2, 3, 4	37, 38
N-Me-Phe	6	-	171.9		
	7	5.13, dd (2.8; 12.3)	63.0	6, 8, 15, 16	17, 18
	8a	3.53, dd (2.8; 14.2)	35.3	9, 10, 11	
	8b	2.90, m		9, 10, 11	2
	9	-	138.4		
	10	7.33, m	130.8	8, 9, 14	17, 18, 19
	11	7.33, m	130.8	8, 9, 14	17, 18, 19
	12	7.33, m	130.0	9	17, 18, 19
	13	7.33, m	130.0	9	17, 18, 19
	14	7.25, m	128.0	10, 11	17, 18, 19
N-Me	15	2.90, s	31.4	7, 16	17, 18
Thr1	16	-	173.1		
	17	4.57, d (7.6)	56.4	16, 18, 19, 20, 24	7, 10, 11, 12, 13, 15, 24
	18	3.66, m	66.9	17, 19	7, 10, 11, 12, 13, 14, 15, 24
	19	0.42, d (6.3)	19.7	17, 18	10, 11, 12, 13, 14
Ahp	20	-	171.6		
	21	4.65, dd (6.3; 12.3)	51.0	20, 22, 25	22b, 23b
	22a	2.81, m	22.2	21, 24	
	22b	1.91, m		20, 24	21
	23a	2.06, m	30.8		24
	23b	1.88, m		21, 24	21, 24
	24	5.31, brs	77.1	17, 20, 22	17, 18, 23a, 23b
Hphe	25	-	174.1		
	26	4.35, brd (9.1)	54.7	25	
	27a	2.49, m	33.4	26, 28, 29	
	27b	2.01, m			
	28a	2.80, m	33.1	26, 27, 29, 30, 31	37
	28b	2.66, m		26, 27, 29, 30, 31	
	29	-	142.1		
	30	7.22, d (7.3)	129.7	34	
	31	7.22, d (7.3)	129.7	34	
	32	7.30, t (7.3)	129.5	29	
	33	7.30, t (7.3)	129.5	29	
	34	7.20, t (7.3)	127.1	30, 31	
Thr2	35	-	171.6		
	36	4.83, brs	57.3	35, 37, 38, 39	
	37	5.64, q (6.6)	73.5	1, 35, 38	4, 5, 28a
	38	1.46, d (6.6)	18.8	36, 37	2, 3, 4, 5
Ser	39	-	173.2		
	40	4.70, t (5.4)	56.8	39, 41, 42	
	41a	4.02, dd (5.4; 11.0)	63.3	39, 40	
	41b	3.93, dd (5.4; 11.0)		39, 40	

Pro	42	-	174.9		
	43	4.56, m	61.3	42, 44, 45, 46	
	44a	2.29, m	30.9	43, 45, 46	
	44b	2.16, m		43, 45, 46	
	45a	2.11, m	25.9	43, 44, 46	
	45b	2.01, m		43, 44, 46	
	46a	3.71, m	48.8	43, 44, 45	48a
	46b	3.63, m		43, 44, 45	48a
Ba	47	-	174.6		
	48a	2.41, m	37.3	47, 49, 50	46a, 46b
	48b	2.28, m		47, 49, 50	
	49	1.69, m	19.2	47, 48, 50	
	50	1.01, t (7.3)	14.2	48, 49	

[a] assignments are based on extensive 1D and 2D NMR measurements (HMBC, HSQC, COSY).

Table S6: NMR Spectroscopic data of compound **8** (300/500 MHz, CD_3OD)

	C/H no.	d_H (*J* in Hz)[a]	d_C[a]	HMBC	ROESY (selected)
Ile	1	-	175.2		
	2	4.73, d (6.3)	57.4	1, 3, 4, 5, 6	8b
	3	2.00, m	38.1	2, 4, 5, 51	
	4a	1.44, m	27.5	2, 3, 5, 51	
	4b	1.28, m		2, 3, 5, 51	
	51	1.00, m	11.5	3, 4	
	5	0.92, d (6.6)	15.8	2, 3, 4	37
N-Me-Phe	6	-	171.9		
	7	5.14, dd (2.8; 12.0)	63.0	6, 8, 9, 15, 16	17, 18
	8a	3.51, dd (2.8; 14.2)	35.4	7, 9, 10, 11	
	8b	2.88, m		7, 9, 10, 11	2
	9	-	138.8		
	10	7.33, m	130.9	8, 9, 14	17, 18, 19
	11	7.33, m	130.9	8, 9, 14	17, 18, 19
	12	7.33, m	130.0	9	17, 18, 19
	13	7.33, m	130.0	9	17, 18, 19
	14	7.25, m	128.0	10, 11	17, 18, 19
N-Me	15	2.89, s	31.4	7, 16	17, 18
Thr1	16	-	173.2		
	17	4.56, d (7.3)	56.2	16, 18, 19, 20, 24	7, 10, 11, 12, 13, 14, 15, 24
	18	3.63, m	67.0	17, 19	7, 10, 11, 12, 13, 14, 15, 24
	19	0.42, d (6.3)	19.6	17, 18	10, 11, 12, 13, 14
Ahp	20	-	171.7		
	21	4.65, dd (6.6; 12.3)	51.0	20, 22, 25	22b, 23b
	22a	2.78, m	22.3		
	22b	1.92, m		24	21
	23a	2.06, m	30.8		24
	23b	1.88, m		21, 24	21, 24
	24	5.32, brs	77.1	17, 20, 22	17, 18, 23a, 23b
Hphe	25	-	173.9		
	26	4.39, brd (9.5)	54.5	25	
	27a	2.49, m	33.4	28	

	27b	2.00, m			
	28a	2.79, m	33.0	26, 27, 29, 30, 31	37
	28b	2.64, m		26, 27, 29, 30, 31	
	29	-	142.2		
	30	7.22, d (7.3)	129.7	28, 34	
	31	7.22, d (7.3)	129.7	28, 34	
	32	7.29, t (7.6)	129.5	29	
	33	7.29, t (7.6)	129.5	29	
	34	7.20, t (7.6)	127.1	30, 31	
Thr2	35	-	171.6		
	36	4.82, brs	57.3	35, 37, 38, 39	
	37	5.62, q (6.6)	73.6	1, 35, 38	5, 28a
	38	1.45, d (6.6)	18.7	36, 37	
Ser	39	-	173.2		
	40	4.69, t (5.4)	56.8	39, 41, 42	
	41a	3.98, dd (5.4; 11.0)	63.3	39, 40	
	41b	3.91, dd (5.4; 11.0)		39, 40	
Pro	42	-	174.9		
	43	4.55, m	61.3	42, 44, 45	
	44a	2.29, m	30.9	42, 43, 45, 46	
	44b	2.16, m		42, 43, 45, 46	
	45a	2.13, m	25.9	43, 44, 46	
	45b	2.01, m		43, 44, 46	
	46a	3.71, m	48.8	44, 45	48a
	46b	3.63, m		44, 45	48a
Ba	47	-	174.6		
	48a	2.40, m	37.3	47, 49, 50	46a, 46b
	48b	2.27, m		47, 49, 50	
	49	1.69, m	19.2	47, 48, 50	
	50	1.01, m	14.2	48, 49	

[a] assignments are based on extensive 1D and 2D NMR measurements (HMBC, HSQC, COSY).

Figure S1: A) ^{1}H NMR spectrum of **1** (MeOD; 500 MHz)

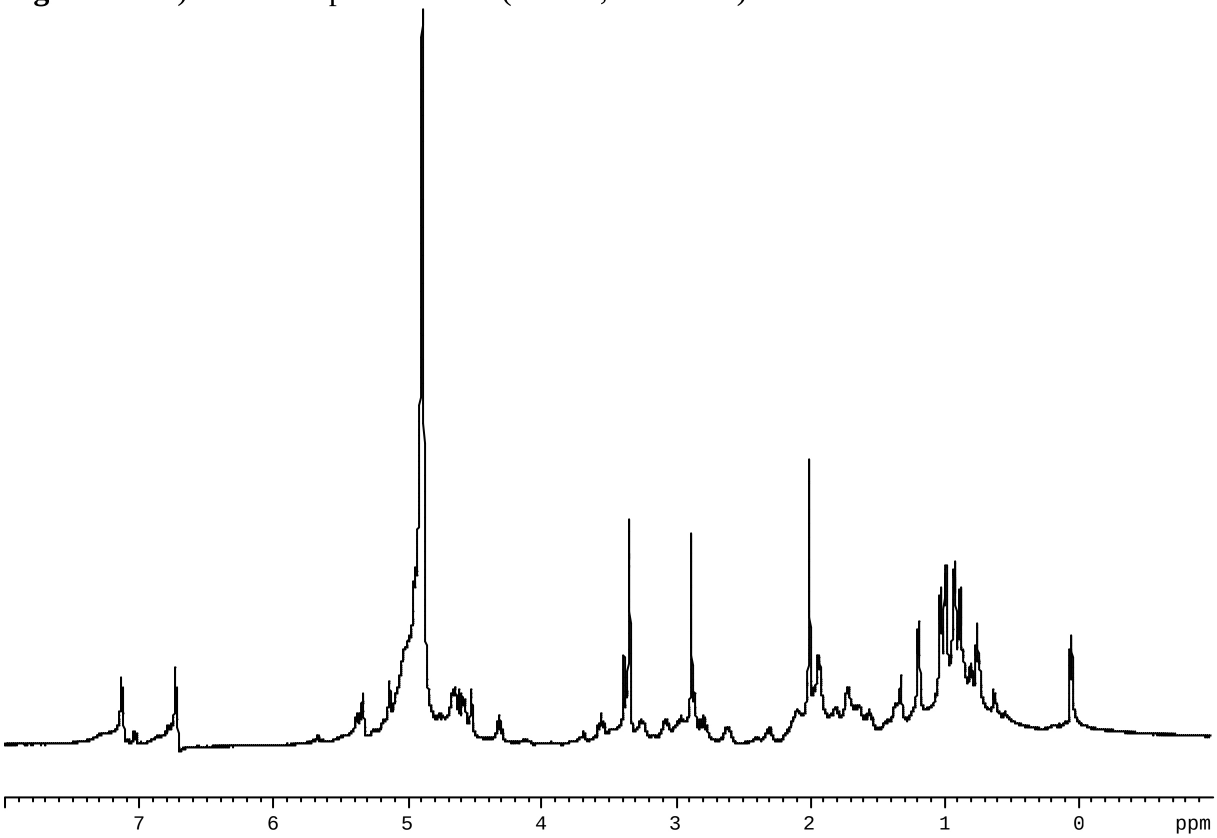

Figure S1: B) ^{13}C NMR spectrum of **1** (MeOD; 125 MHz)

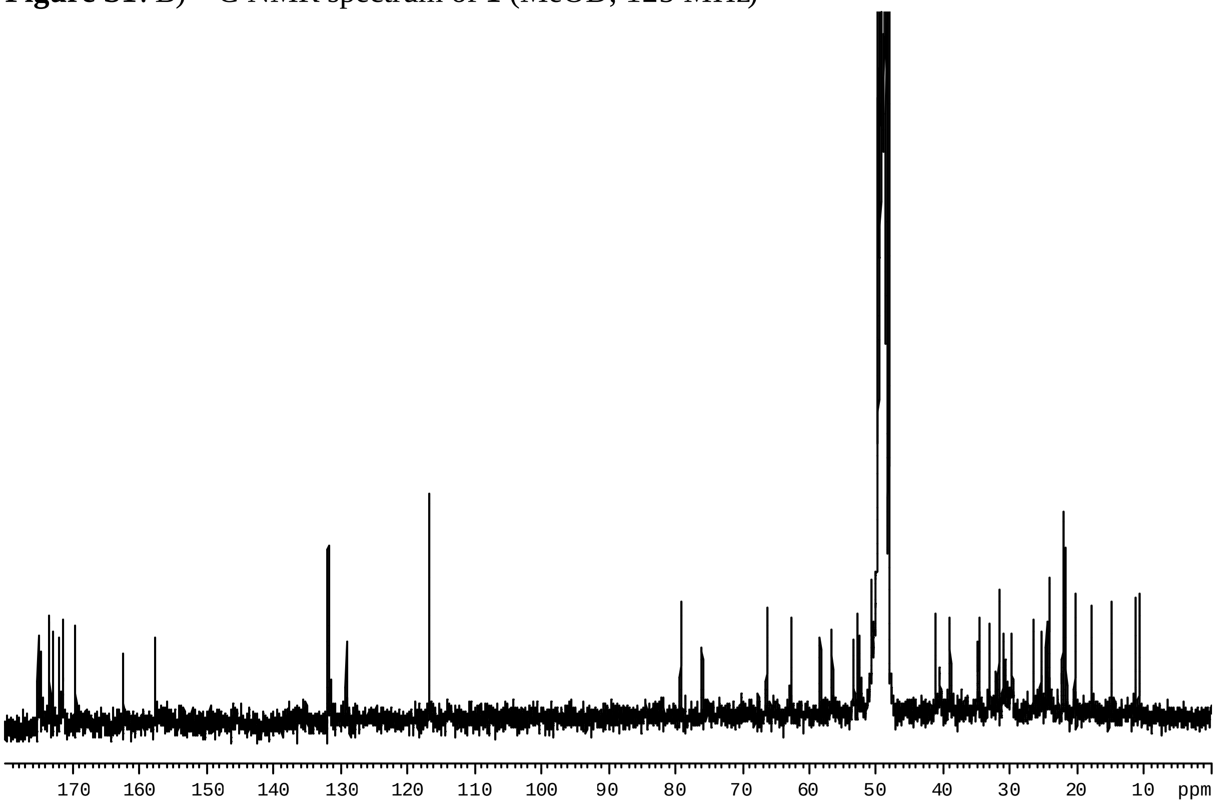

Figure S1: C) HSQC spectrum of **1** (MeOD; 500 MHz)

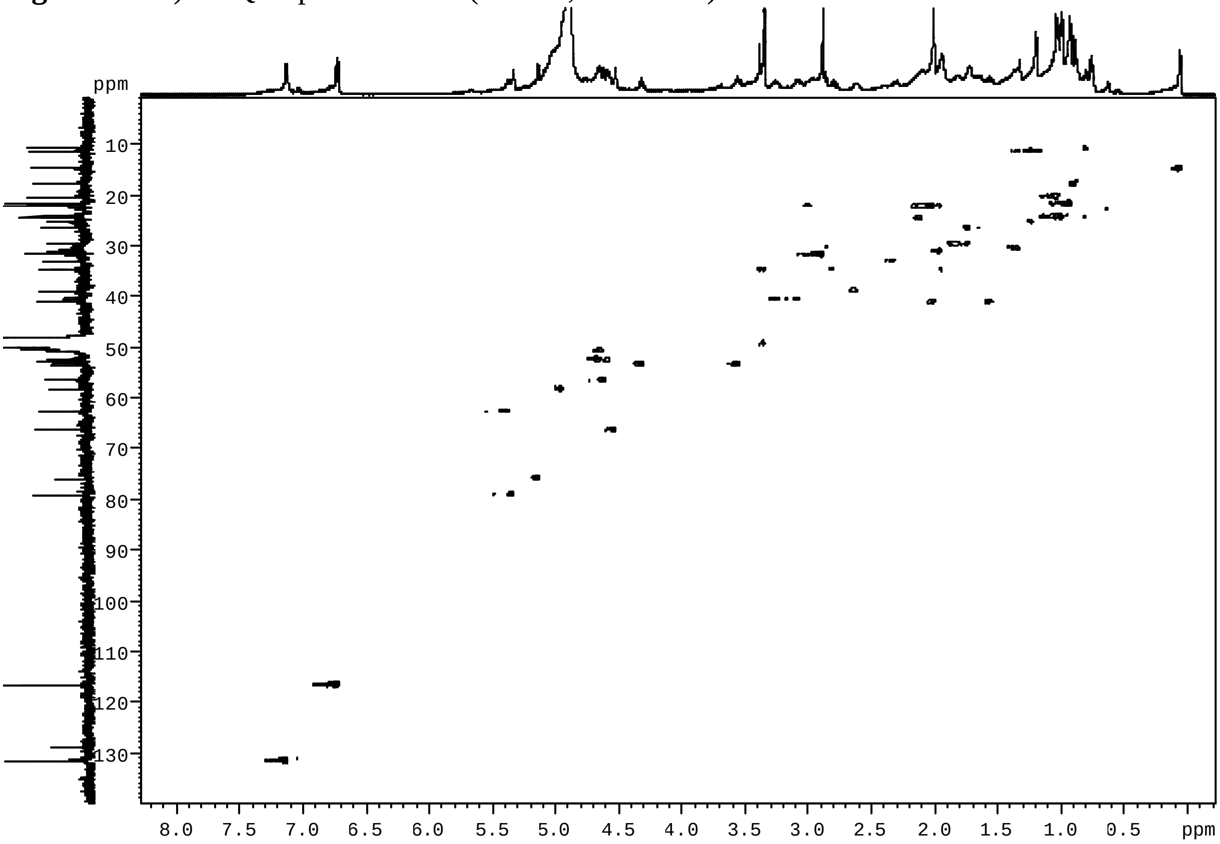

Figure S1: D) COSY spectrum of **1** (MeOD; 500 MHz)

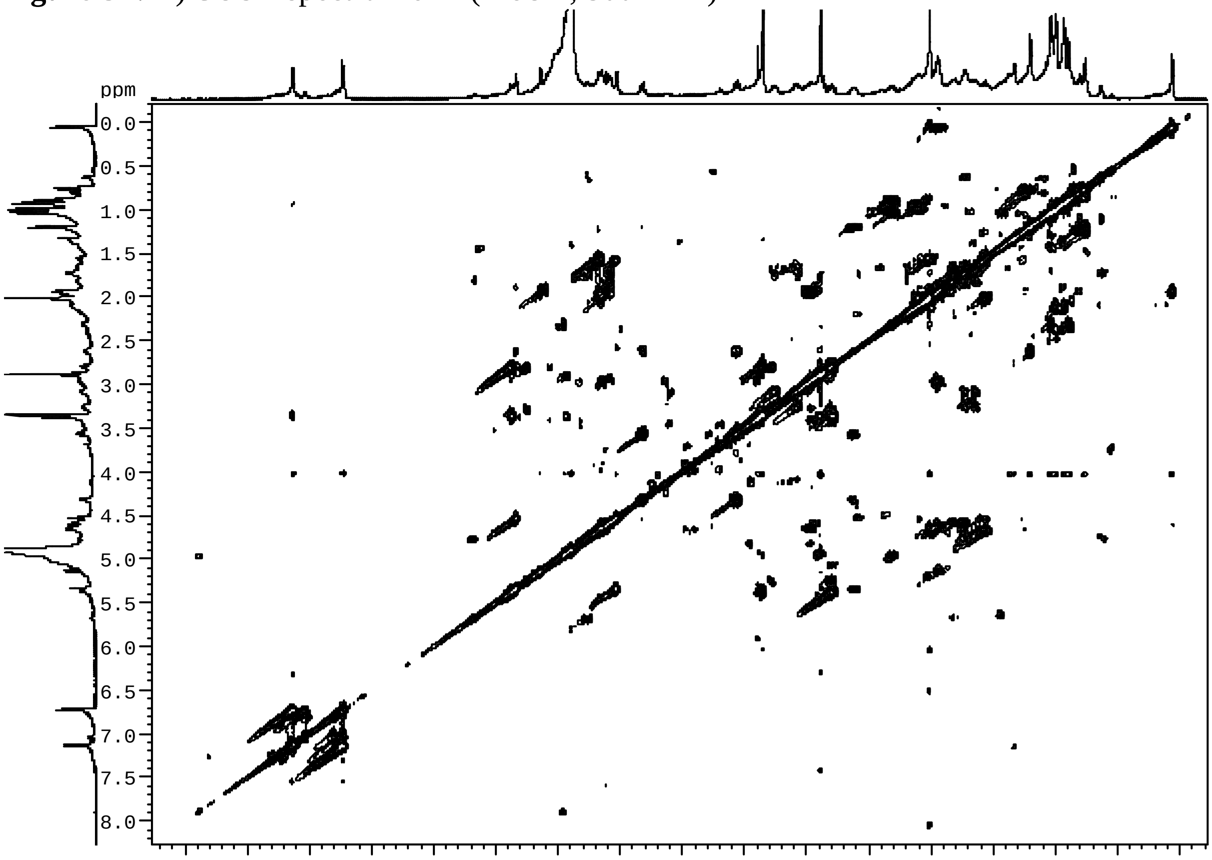

Figure S1: E) HMBC spectrum of **1** (MeOD; 500 MHz)

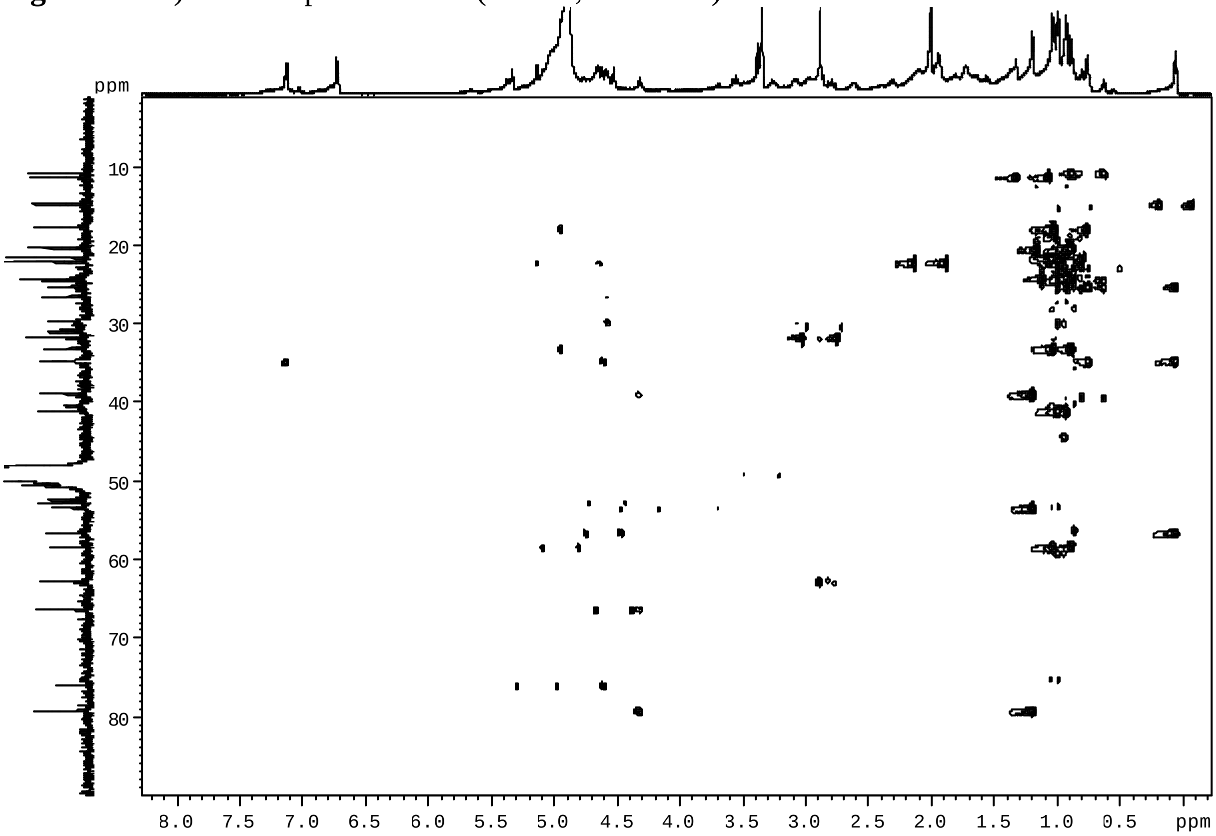

Figure S1: E) HMBC spectrum of **1** (MeOD; 500 MHz)

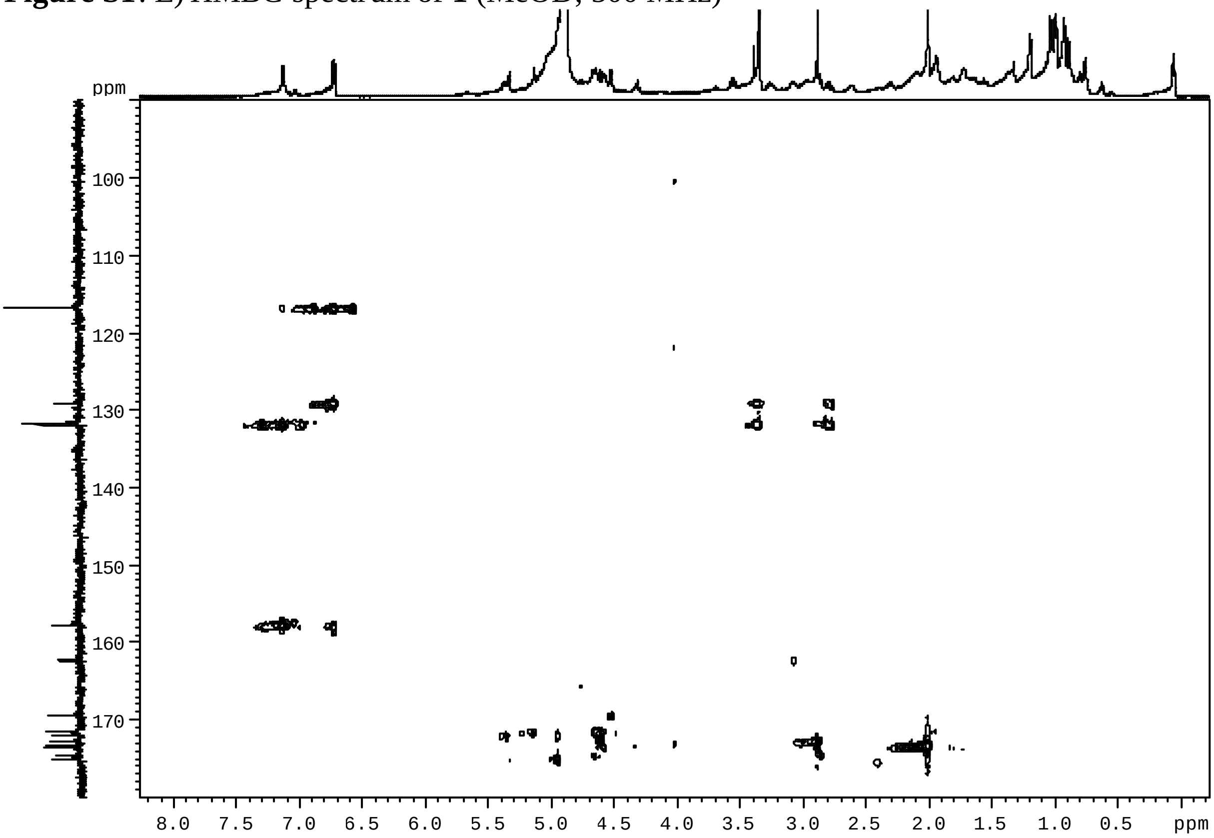

Figure S1: F) ROESY spectrum of **1** (MeOD; 500 MHz)

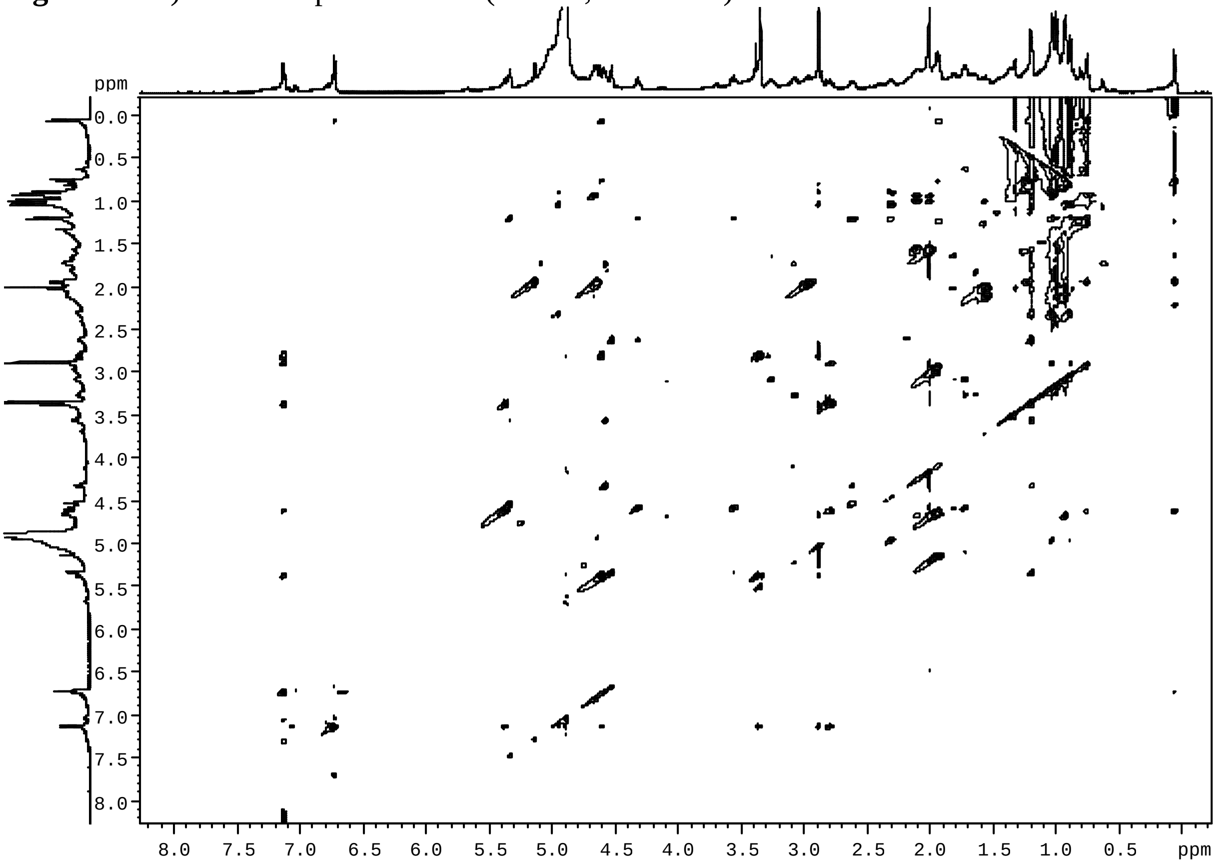

Figure S2: A) ^{1}H NMR spectrum of **2** (MeOD; 300 MHz)

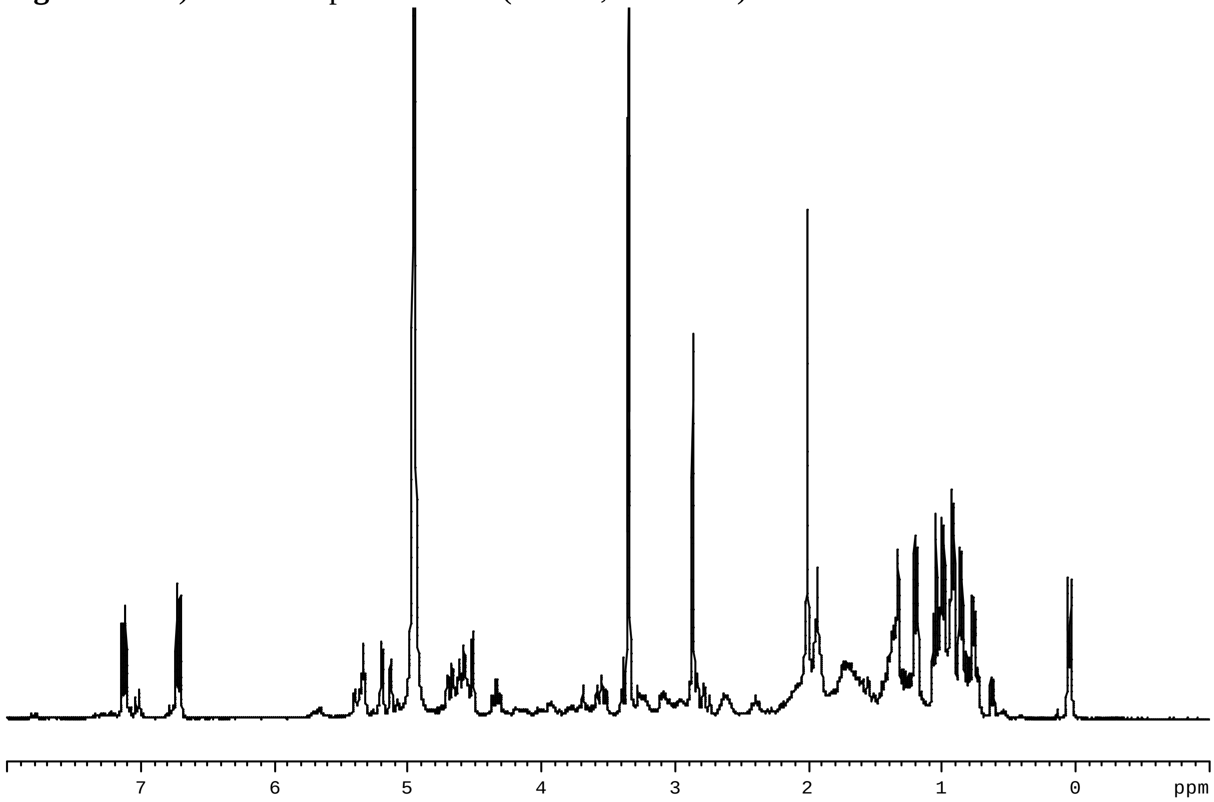

Figure S2: B) ^{13}C NMR spectrum of **2** (MeOD; 75 MHz)

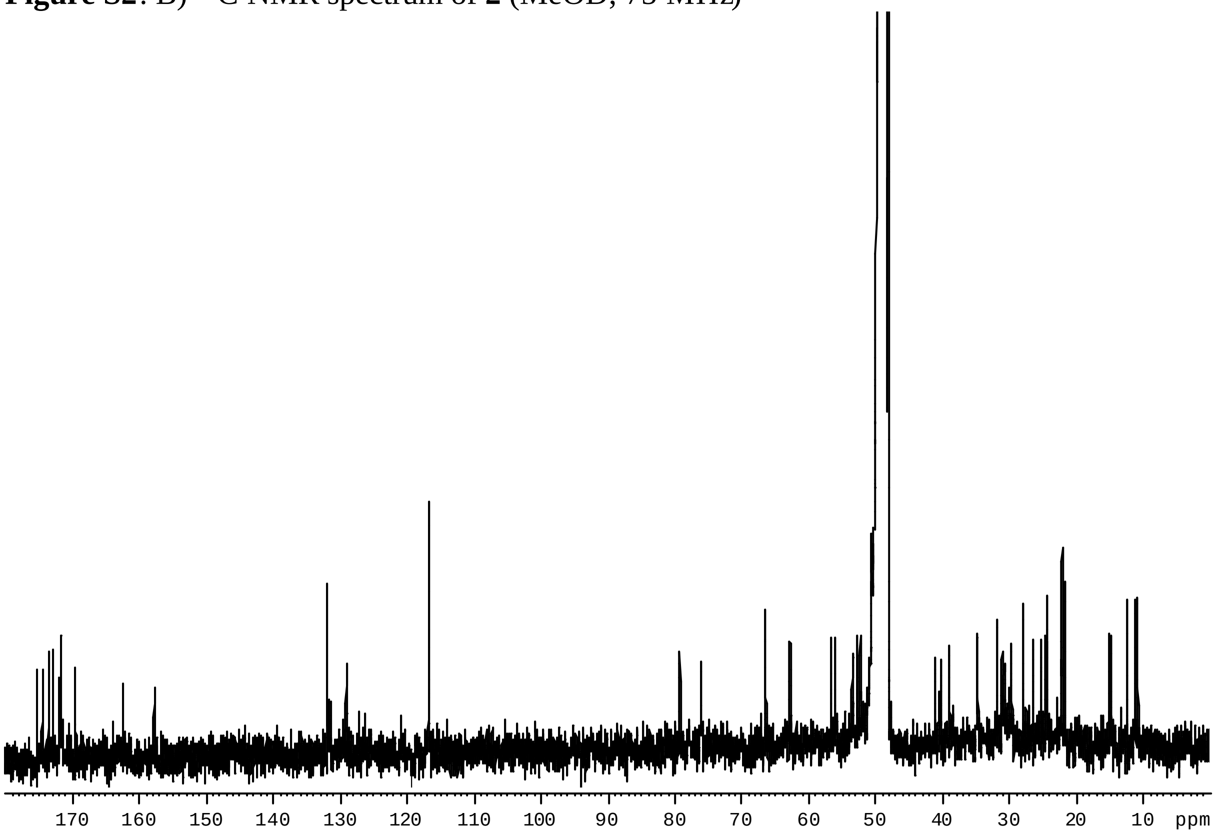

Figure S3: ^{1}H NMR spectrum of **3** (MeOD; 500 MHz)

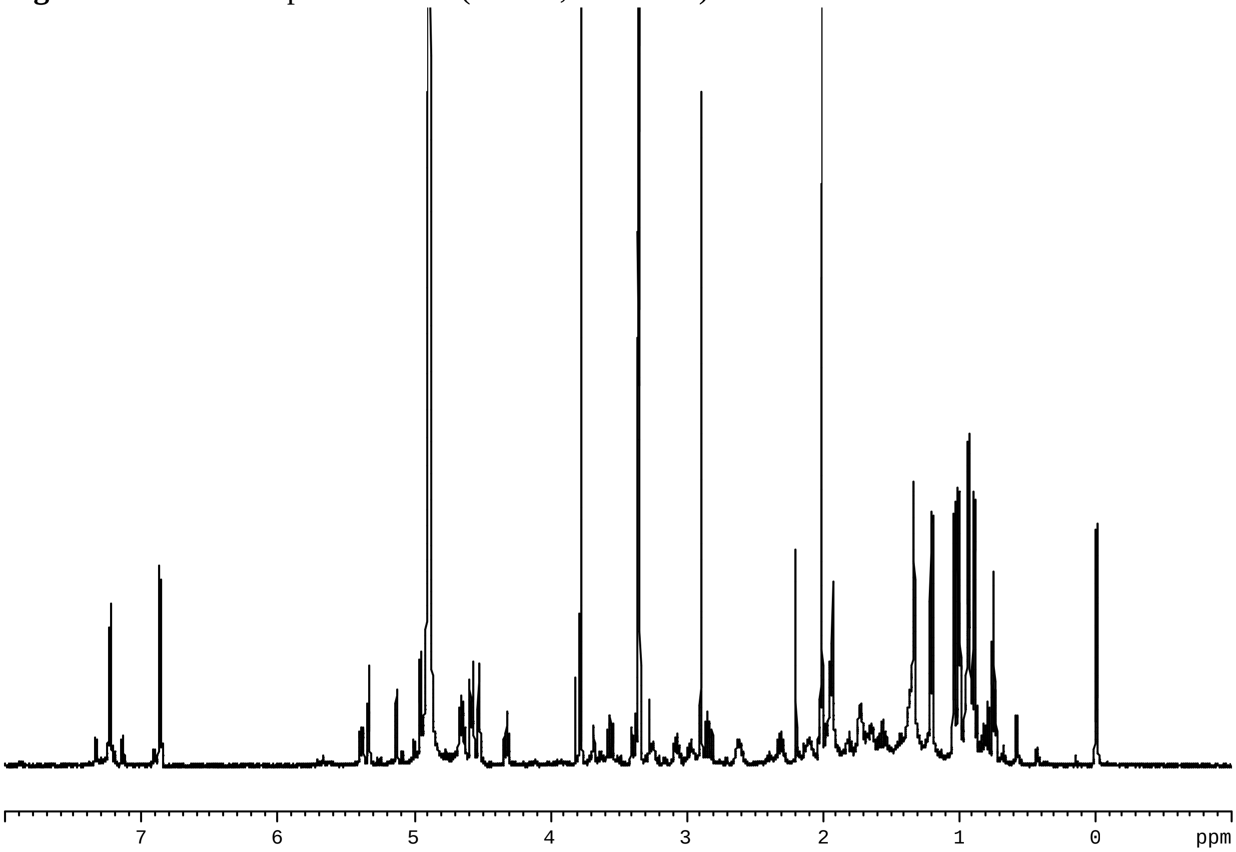

Figure S4: ^{1}H NMR spectrum of **4** (MeOD; 300 MHz)

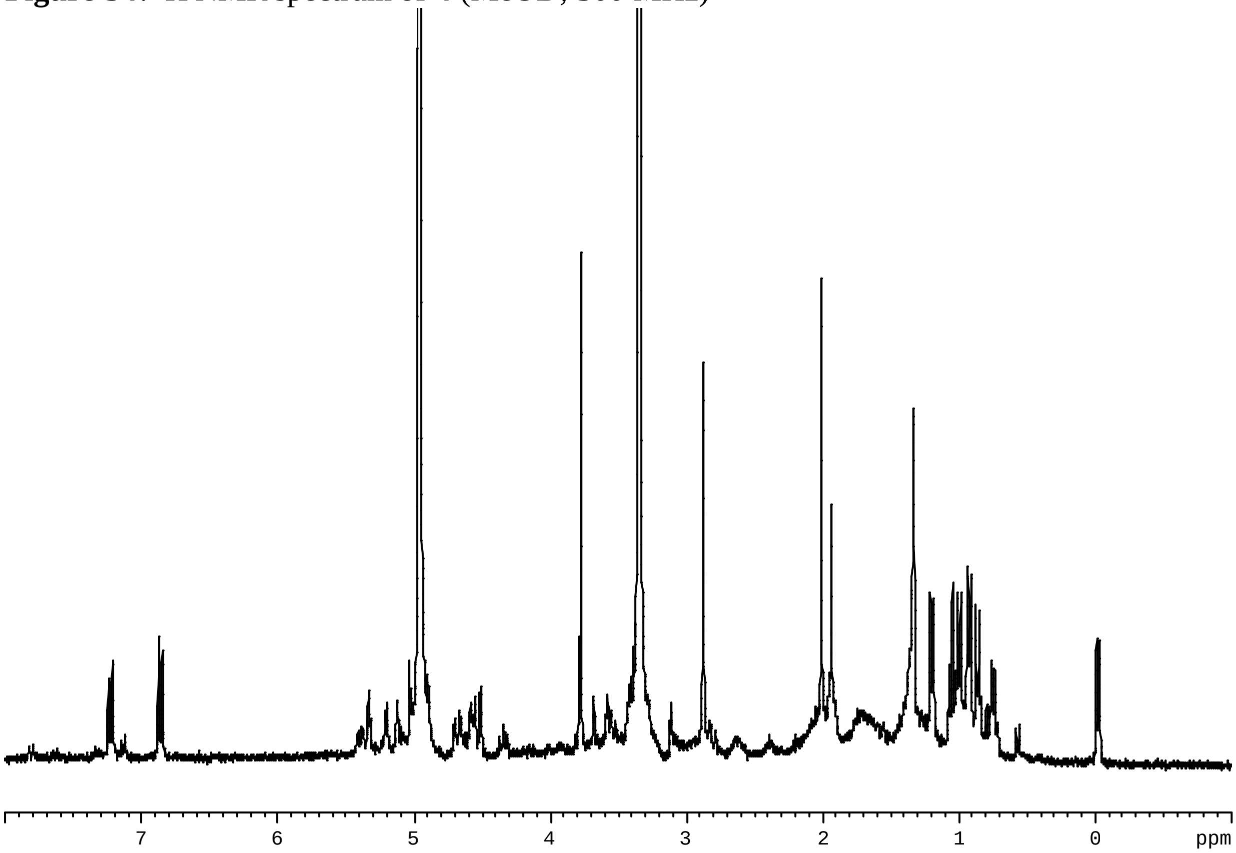

Figure S5: A) ^{1}H NMR spectrum of **5** (MeOD; 500 MHz)

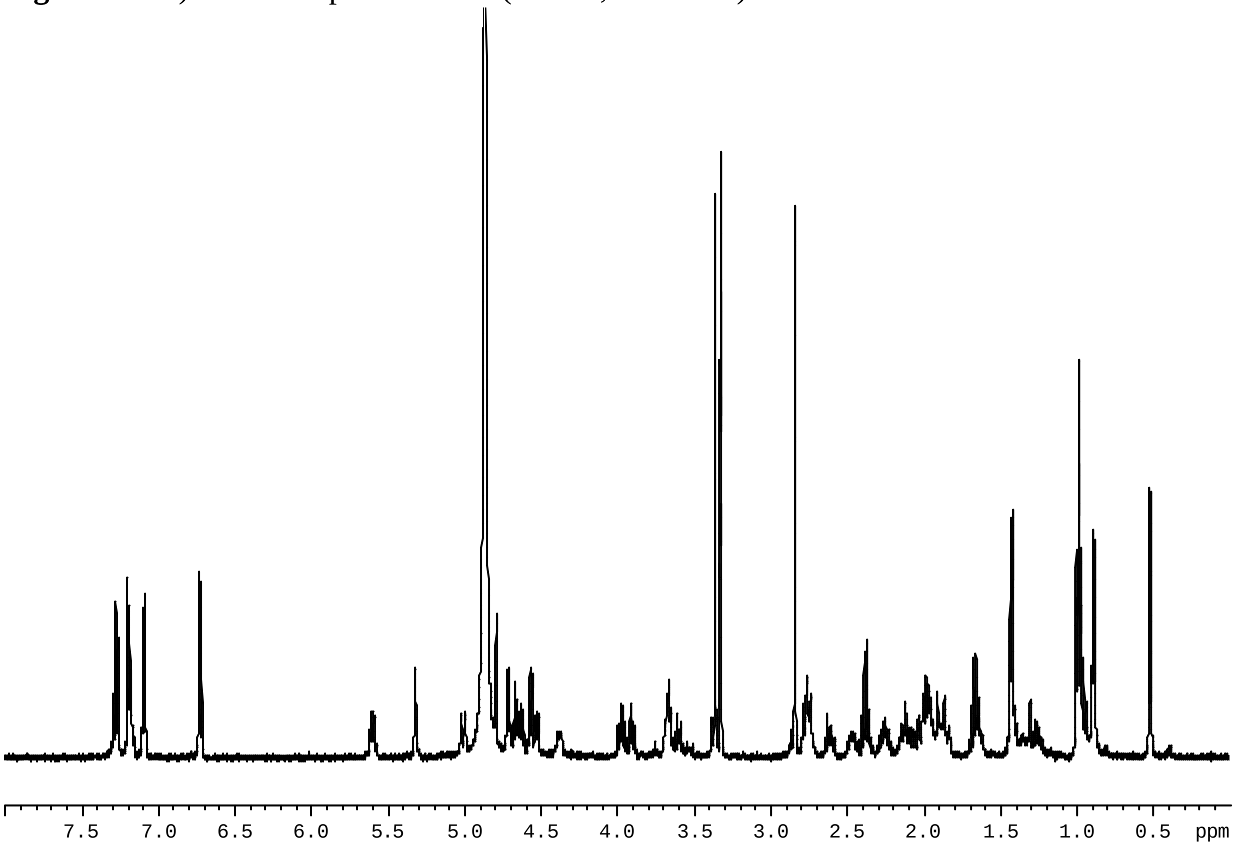

Figure S5: B) ^{13}C NMR spectrum of **5** (MeOD; 125 MHz)

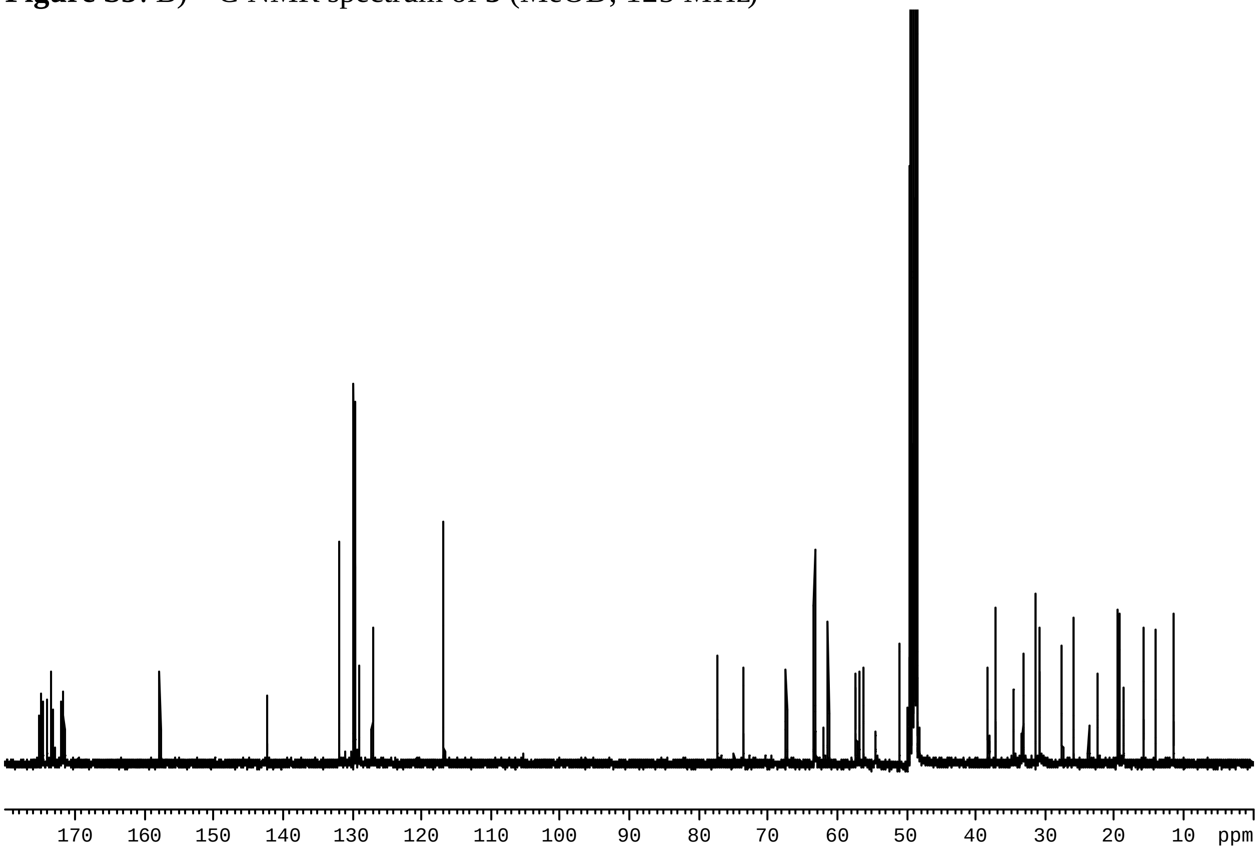

Figure S5: C) HSQC spectrum of **5** (MeOD; 500 MHz)

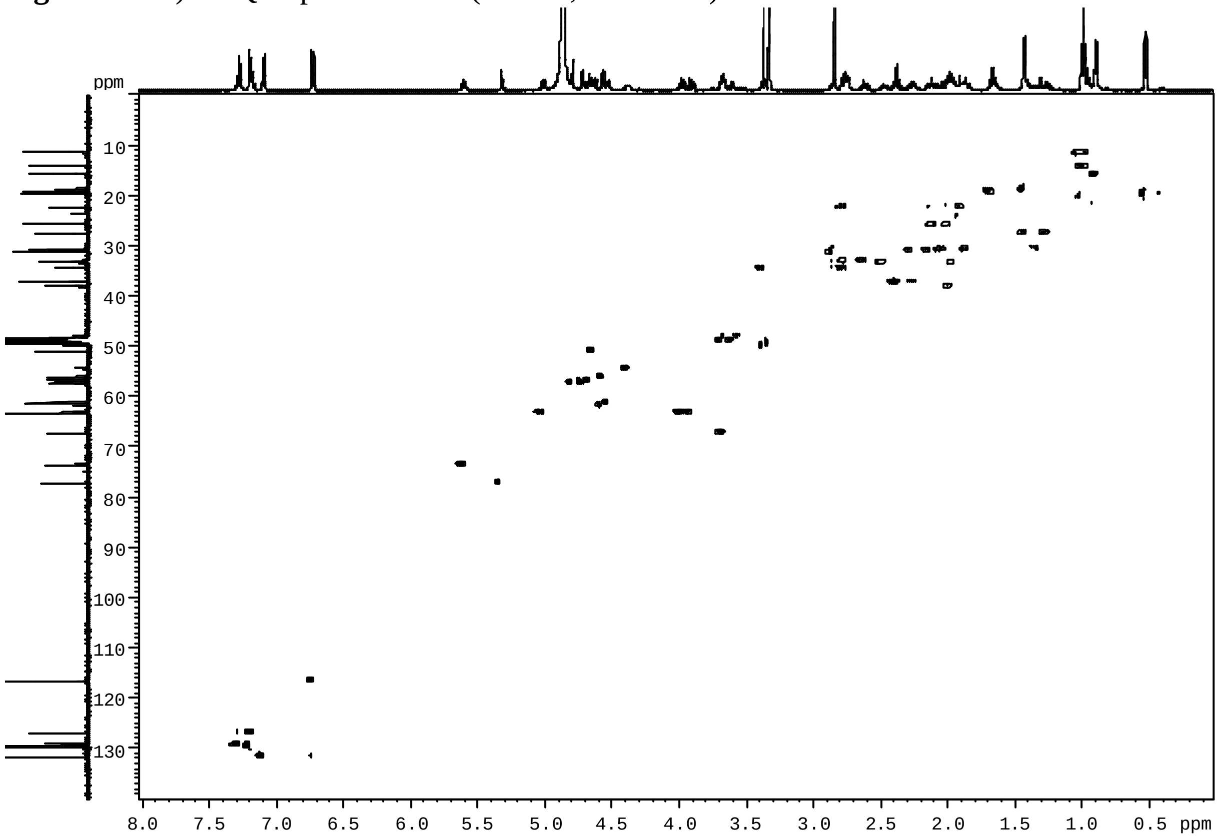

Figure S5: D) COSY spectrum of **5** (MeOD; 500 MHz)

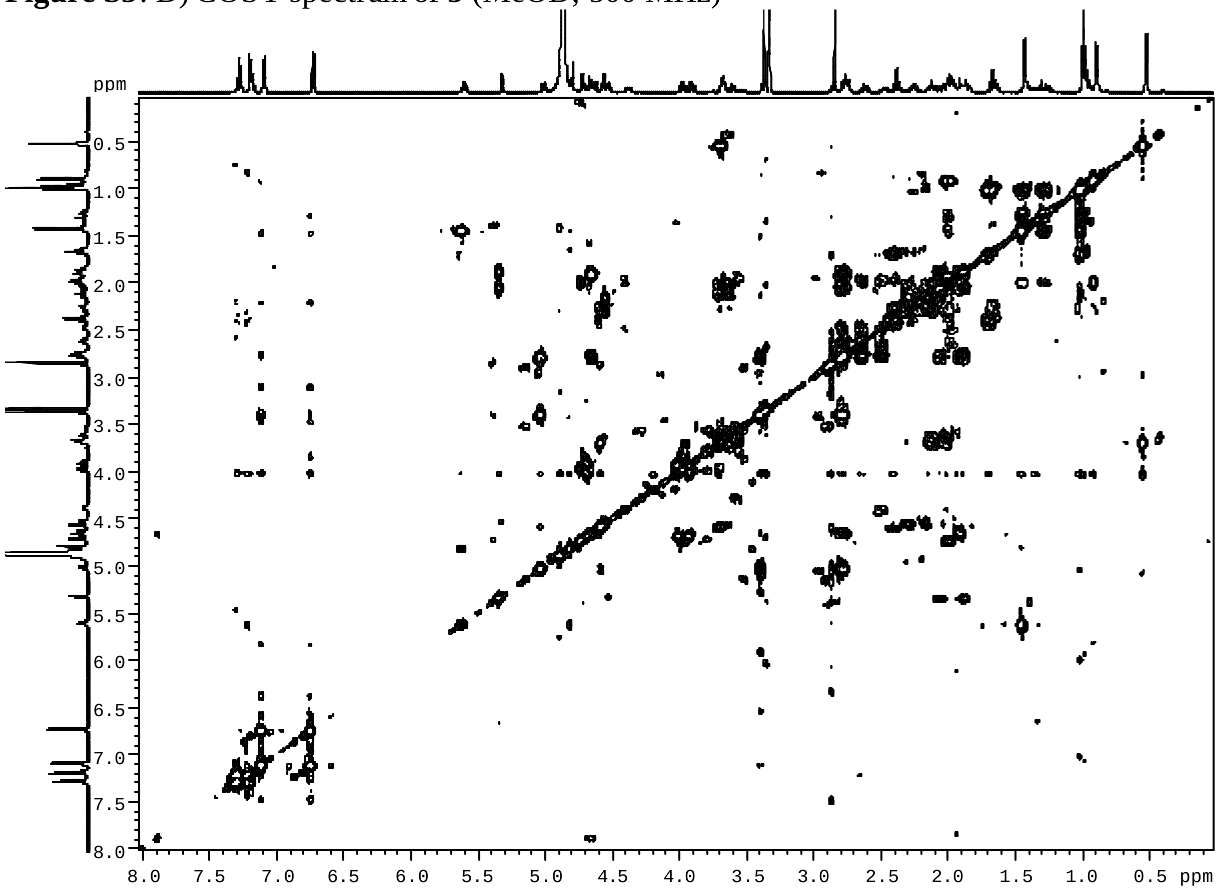

Figure S5: E) HMBC spectrum of **5** (MeOD; 500 MHz)

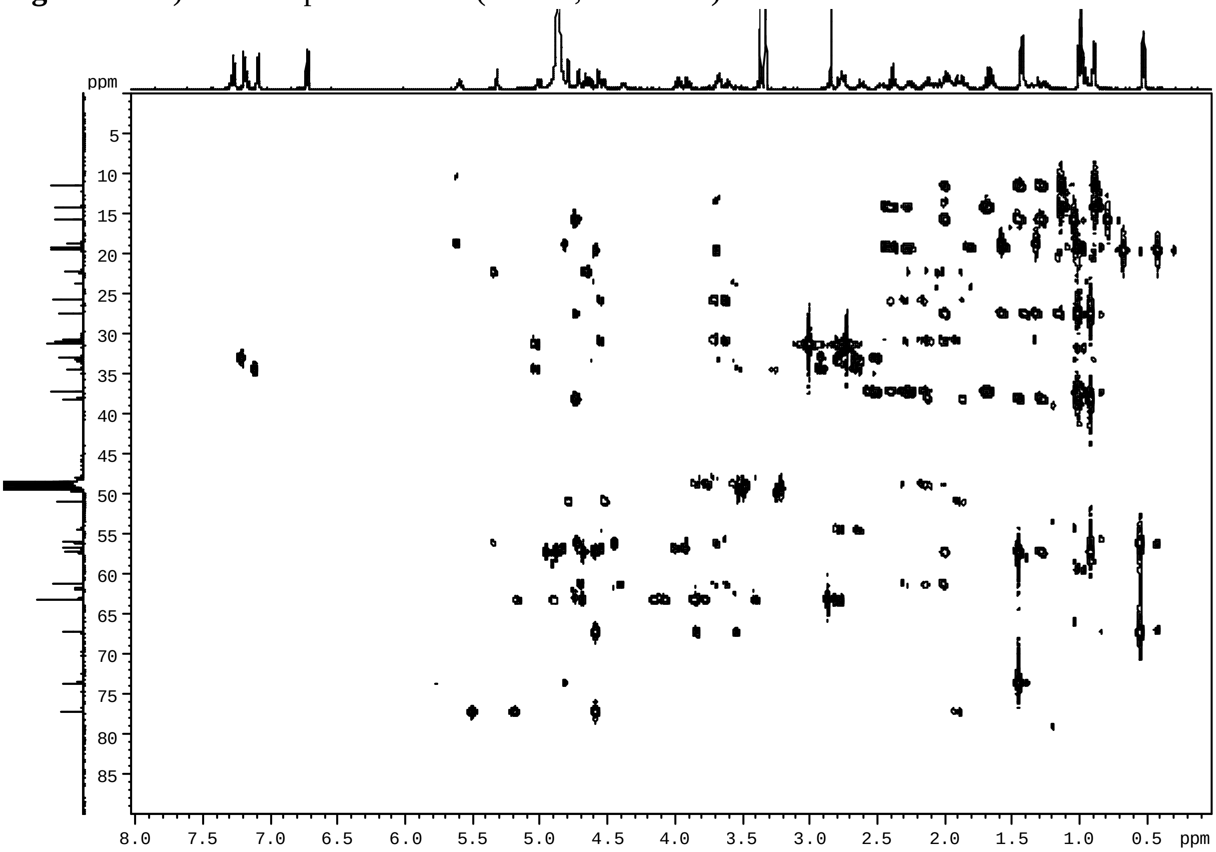

Figure S5: E) HMBC spectrum of **5** (MeOD; 500 MHz)

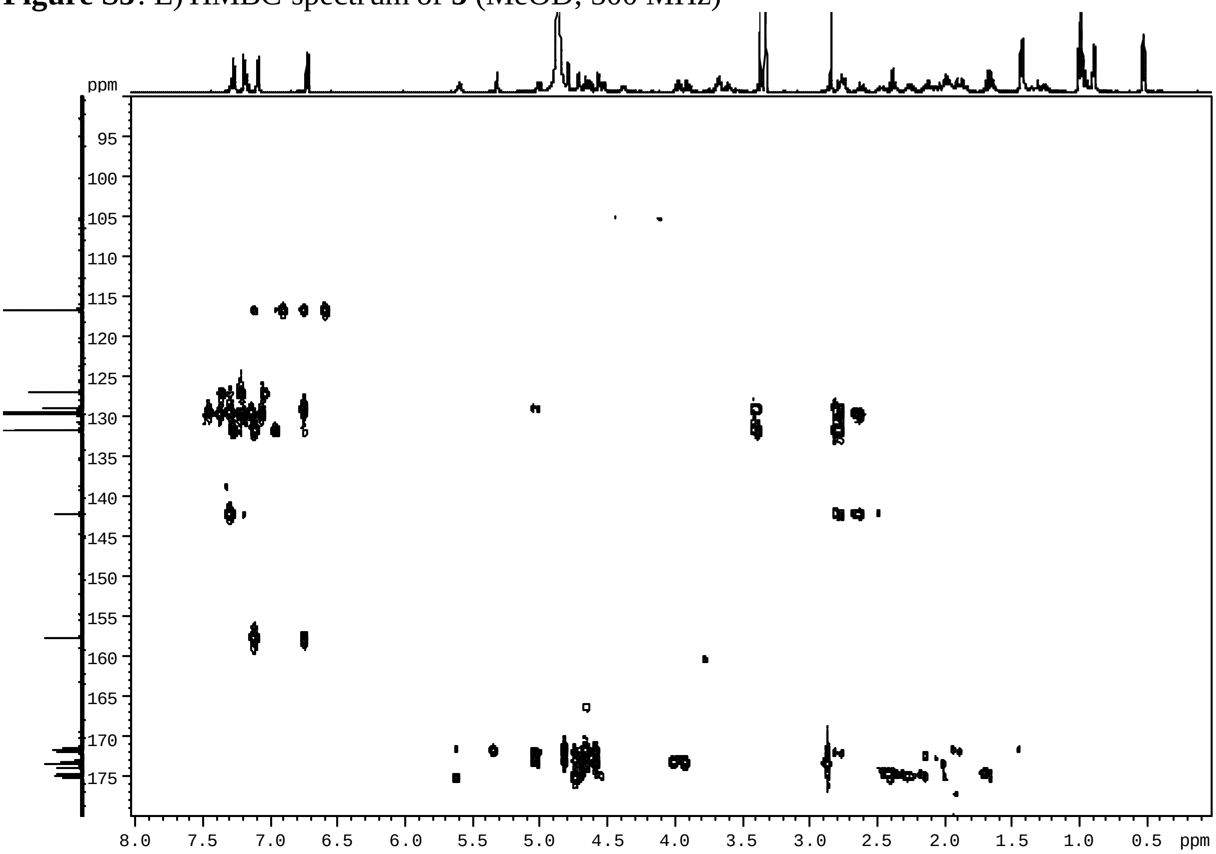

Figure S5: F) ROESY spectrum of **5** (MeOD; 500 MHz)

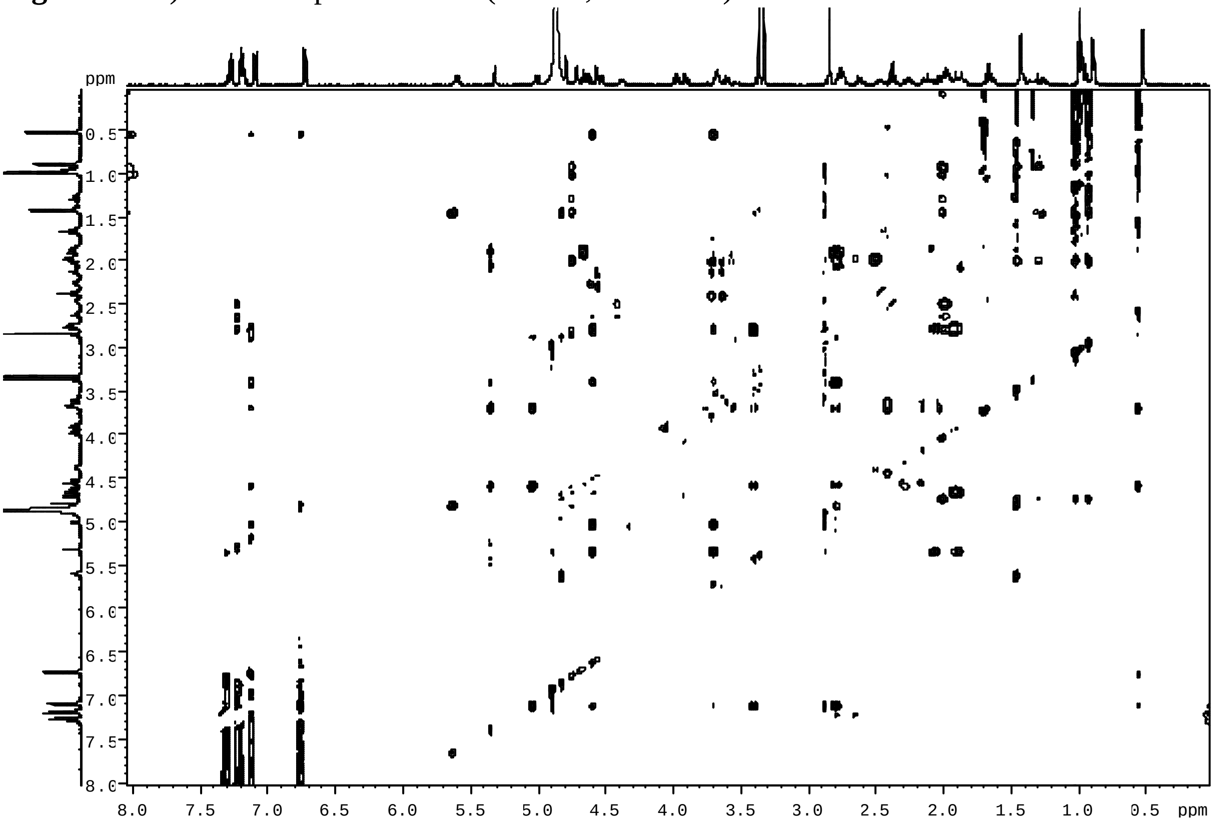

Figure S6: A) ^{1}H NMR spectrum of **6** (MeOD; 300 MHz)

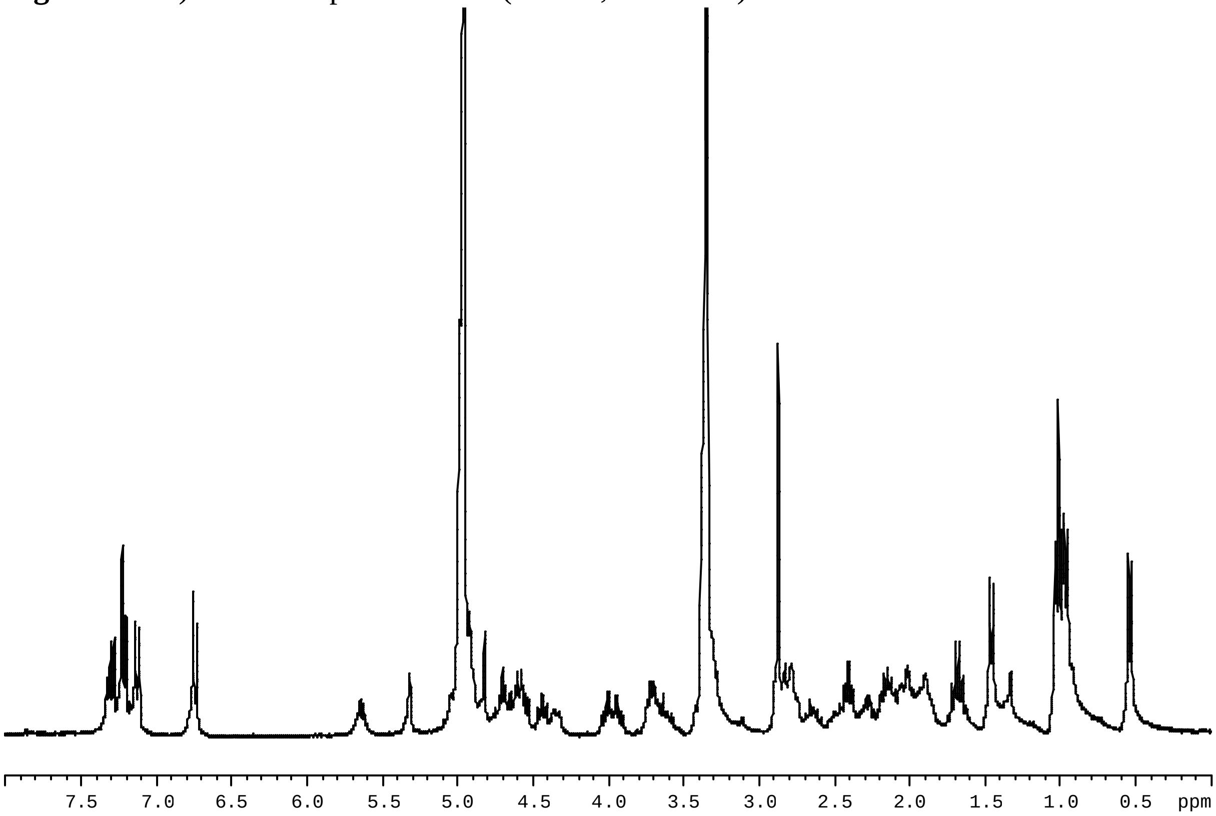

Figure S6: B) ^{13}C NMR spectrum of **6** (MeOD; 75 MHz)

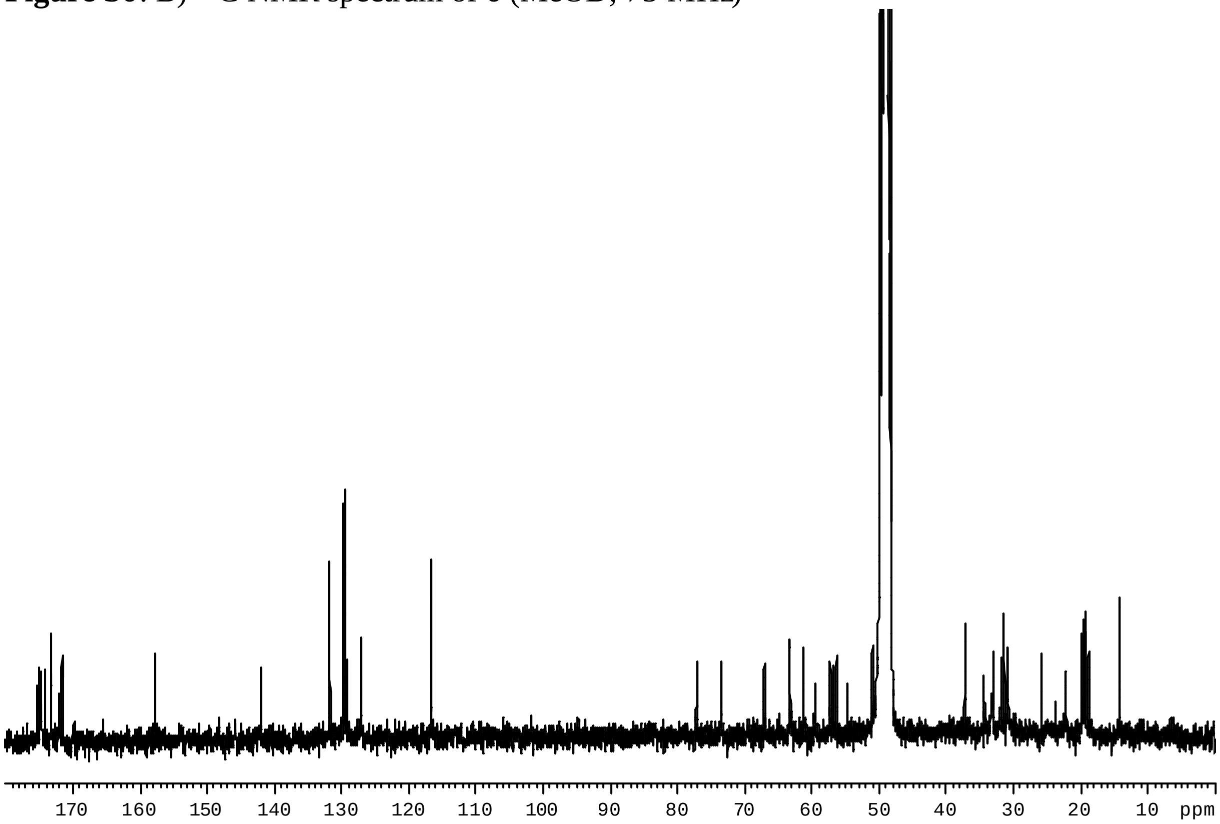

Figure S7: A) ^{1}H NMR spectrum of **7** (MeOD; 500 MHz)

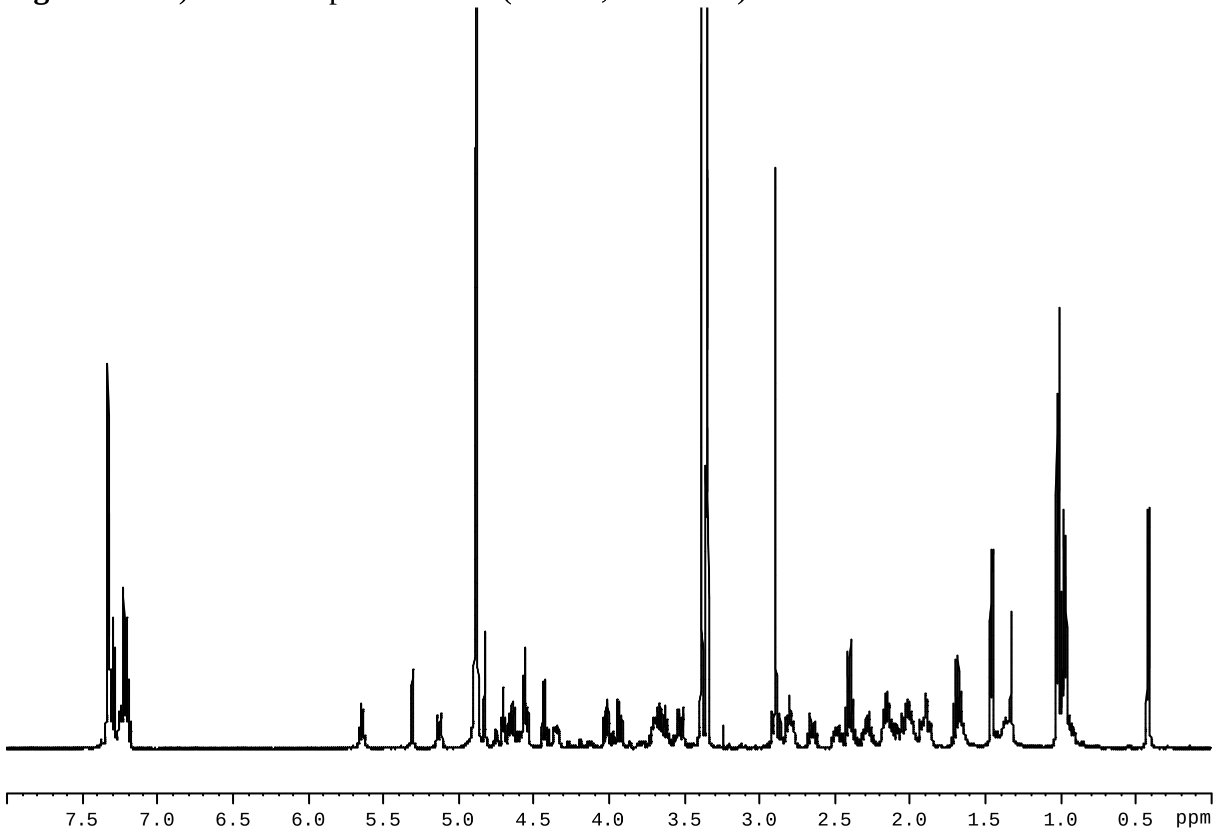

Figure S7: B) ^{13}C NMR spectrum of **7** (MeOD; 75 MHz)

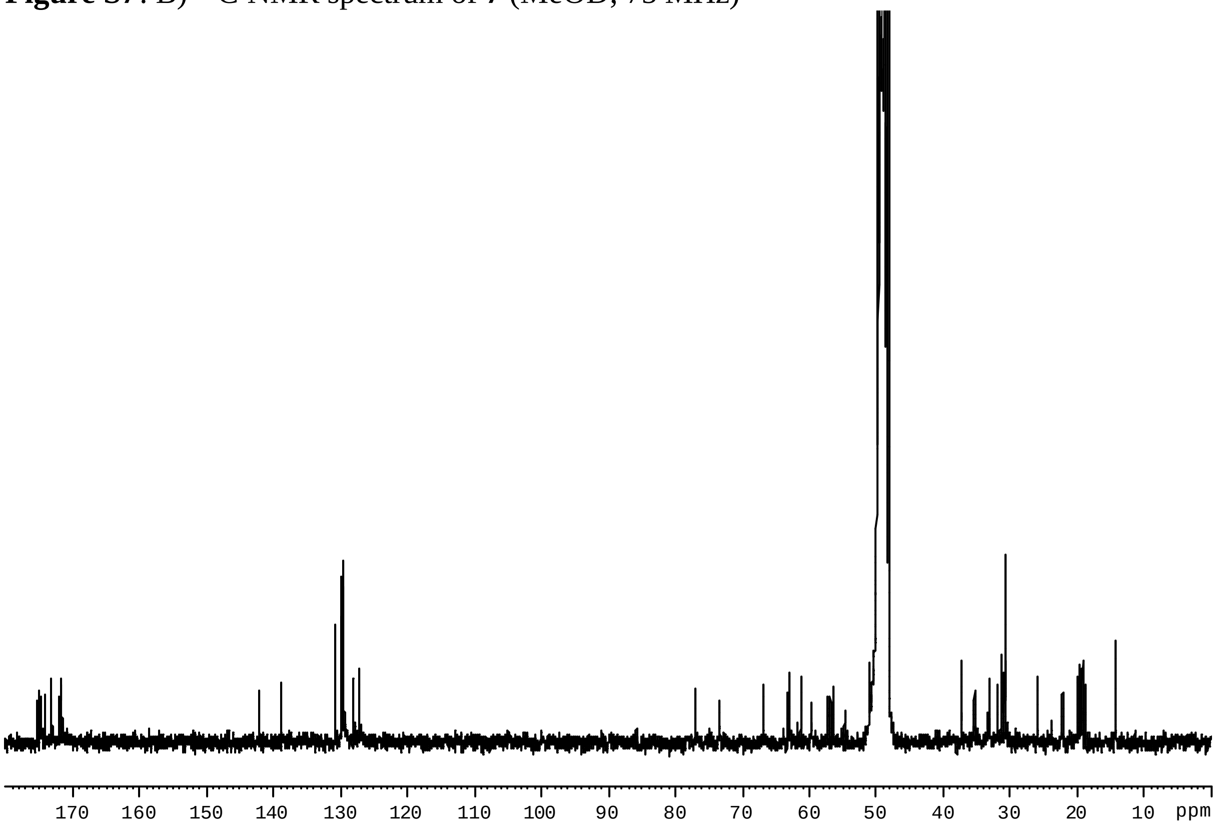

Figure S8: A) ^{1}H NMR spectrum of **8** (MeOD; 500 MHz)

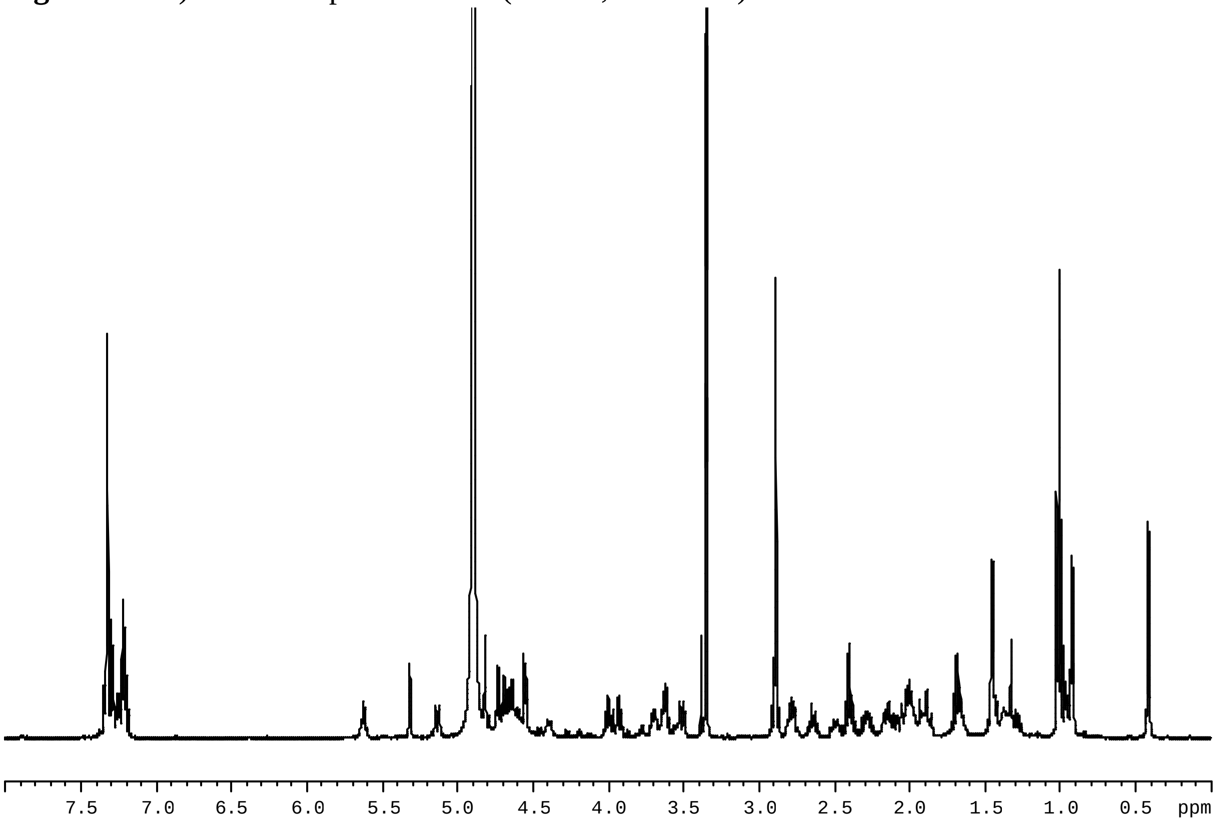

Figure S8: B) ^{13}C NMR spectrum of **8** (MeOD; 75 MHz)

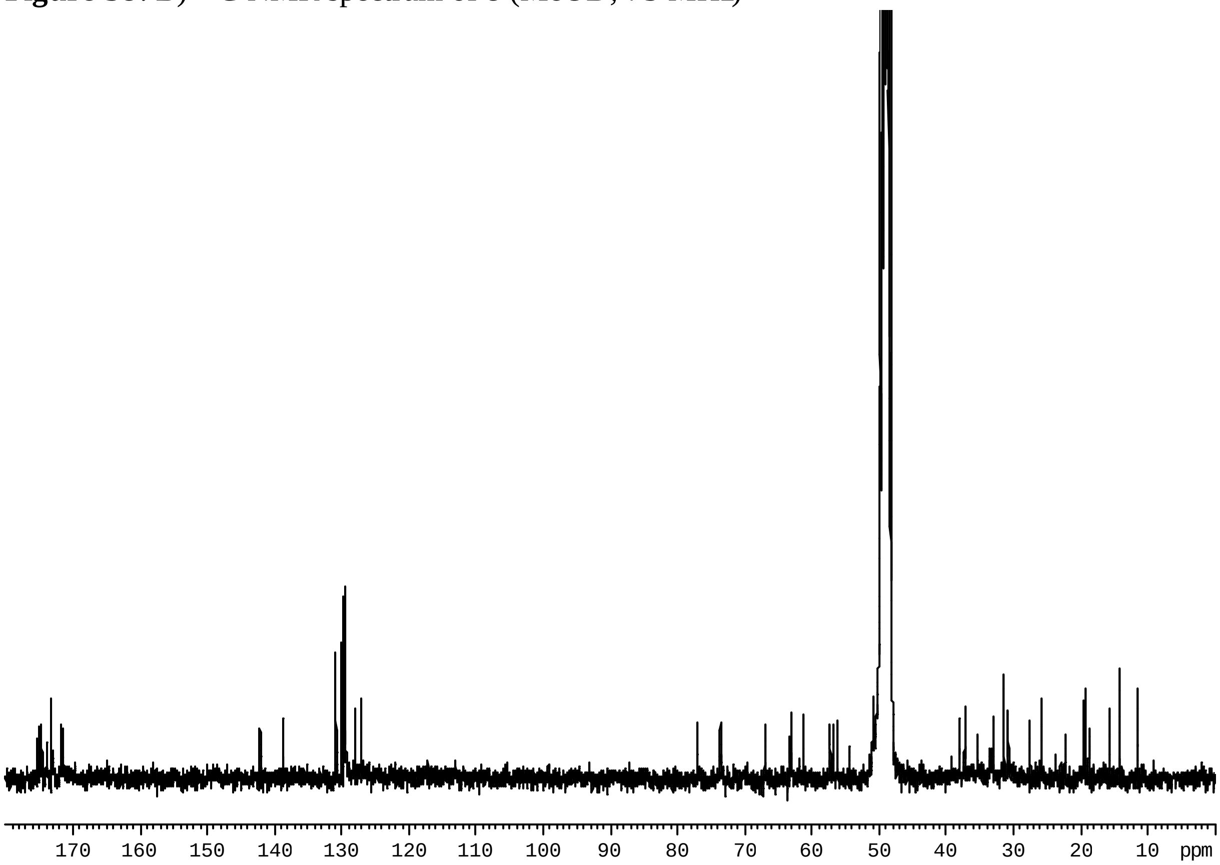

Figure S9: Selective ROESY experiments for determination of the relative configuration of Hmp (compound **1**, MeOD, 500 MHz).

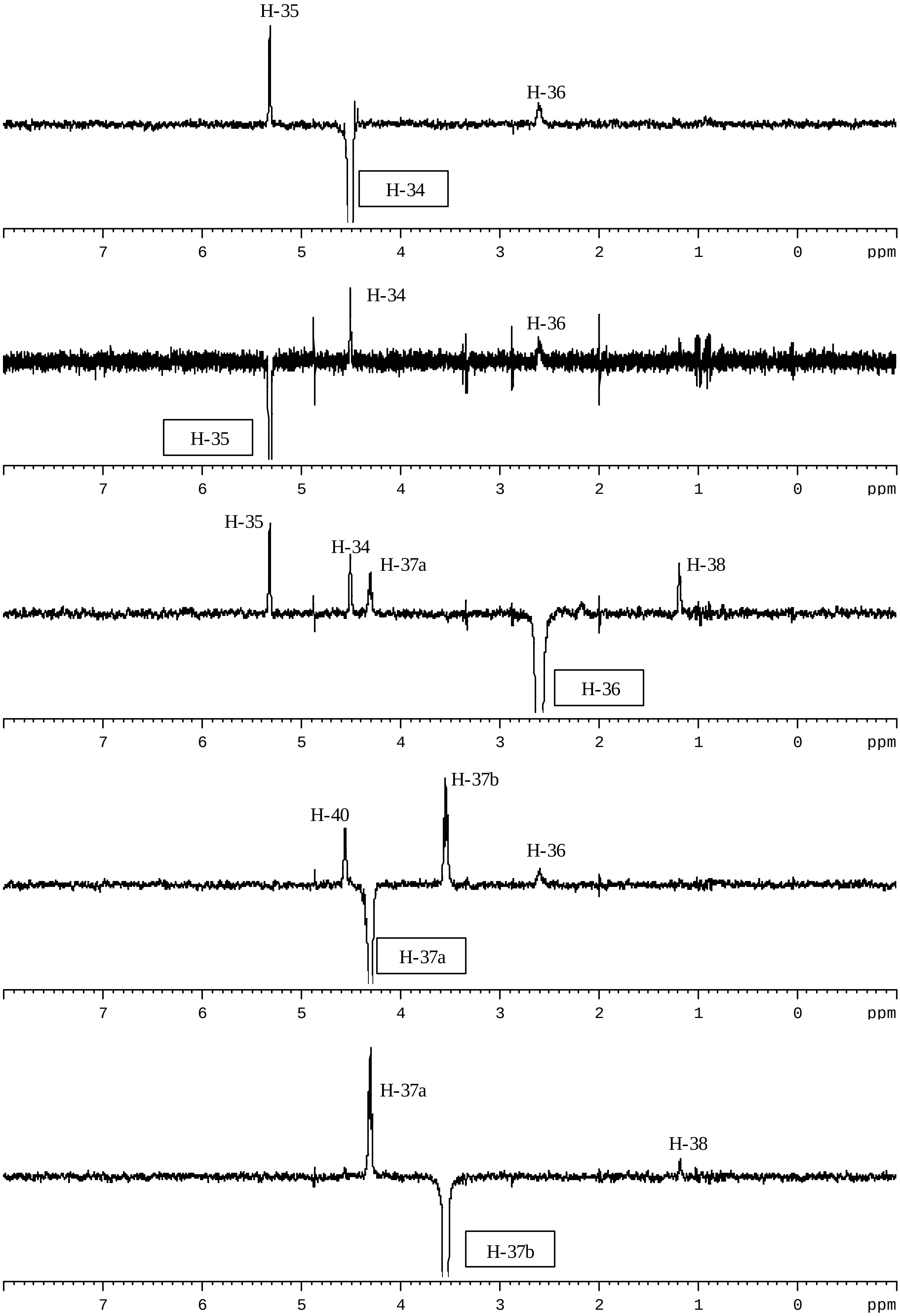

Figure S10: Determination of the absolute configuration of the unusual amino acid Hmp after derivatisation (advanced Marfey´s method) of a hydrolysate of compound **1**. Shown are the LC-MS runs (extracted ions in the negative mode 438.0-438.5) of the L-FDLA-Hmp adduct (upper chromatogram) and of a mixture of L-FDLA-Hmp and D-FDLA-Hmp adducts (lower chromatogram).

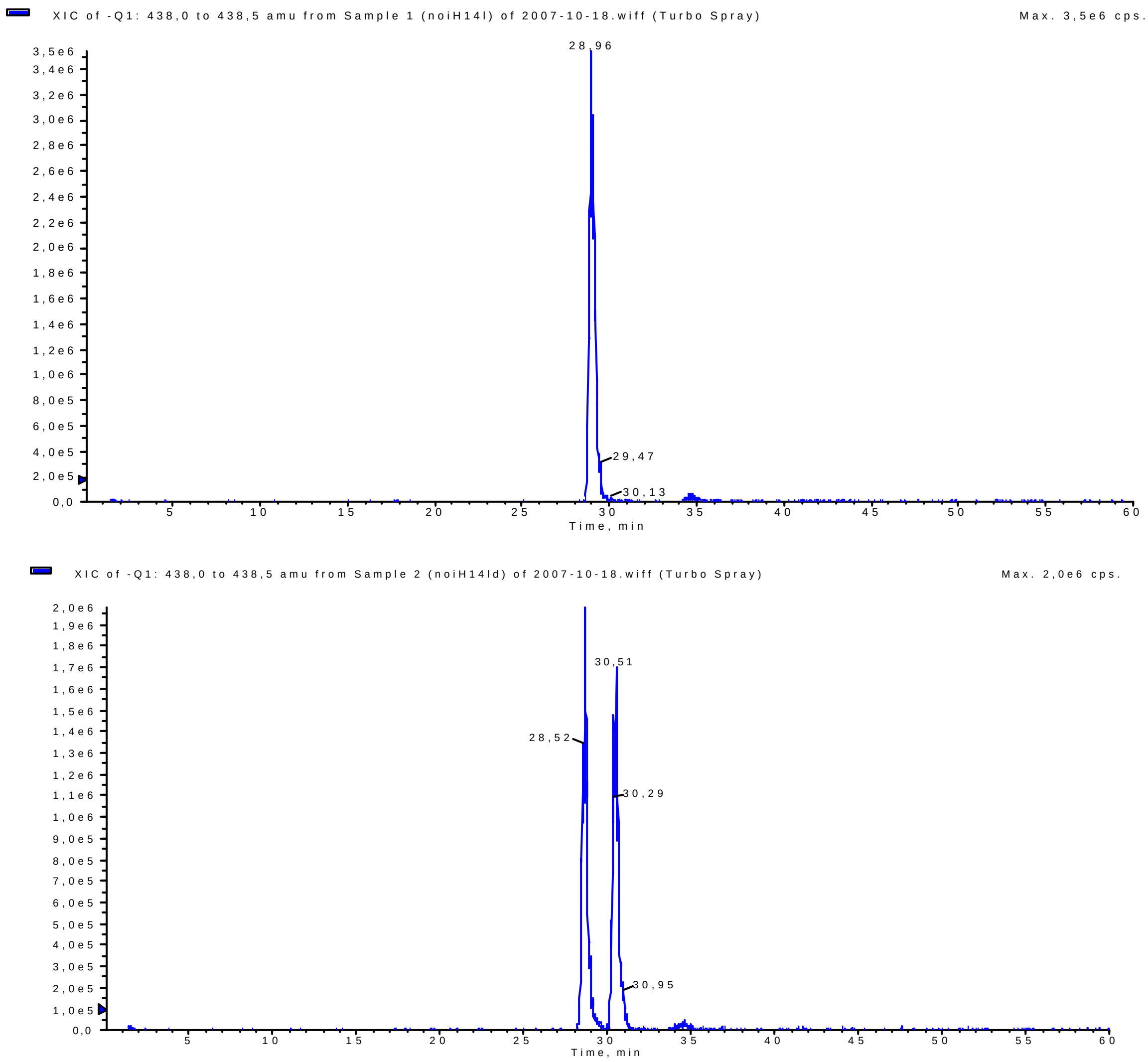

Figure S11: Chiral GC-MS run of the derivatised hydrolysate of compound **1**. The extracted ions are EI+ 166.20 for citrulline, EI+ 342.20 for *N*-methyl-tyrosine, EI+ 182.30 for isoleucine/ leucine and EI+ 168.20 for valine. These values are deduced from comparison with standard amino acids. Retention times of standards: L-Cit 33.24 min, D-Cit 32.90 min, L-Ile 16.30 min, D-Ile 15.88 min, L-*allo*-Ile 15.97 min, D-*allo*-Ile 15.47 min, L-Leu 18.04 min, D-Leu 17.22 min, L-Val 14.01 min, D-Val 13.54 min, L-*N*-Me-Tyr 32.46 min, *D*-N-Me-Tyr 32.50 min.

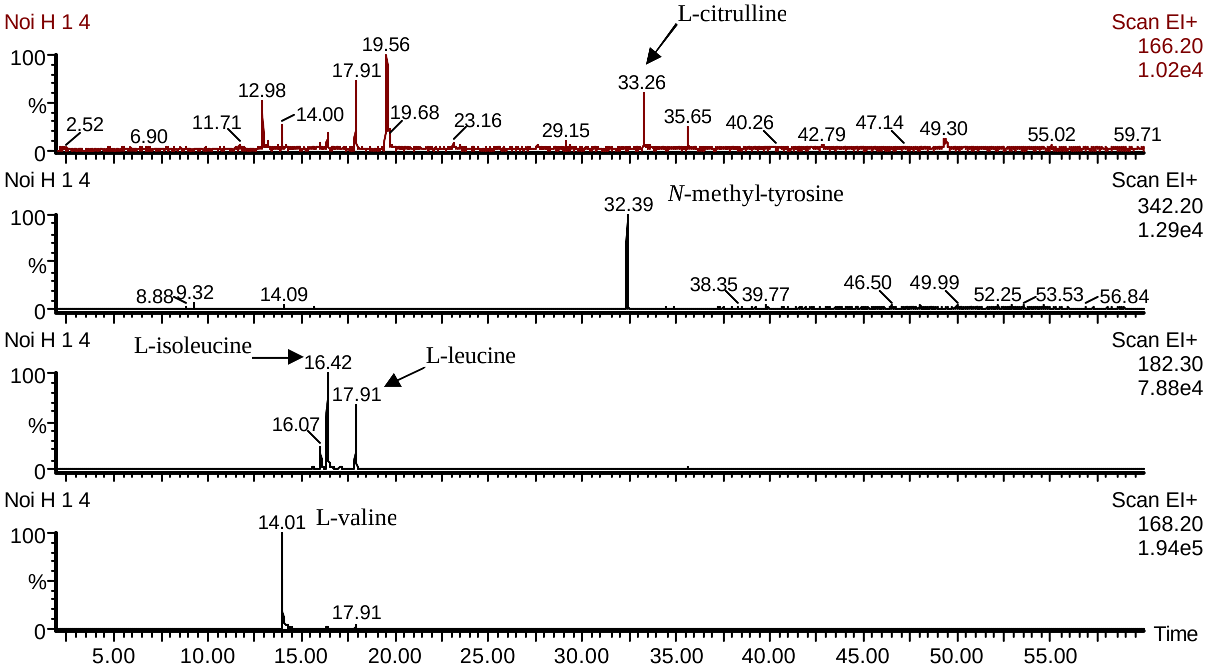

Figure S12: Relative activity of HLE in the presence crude extract (MeOH/DCM: 1/2) of *Nostoc insulare* (**noi**); determined IC_{50} value = 9.0 ± 0.6 µg/mL. The data are mean values of duplicate measurements.

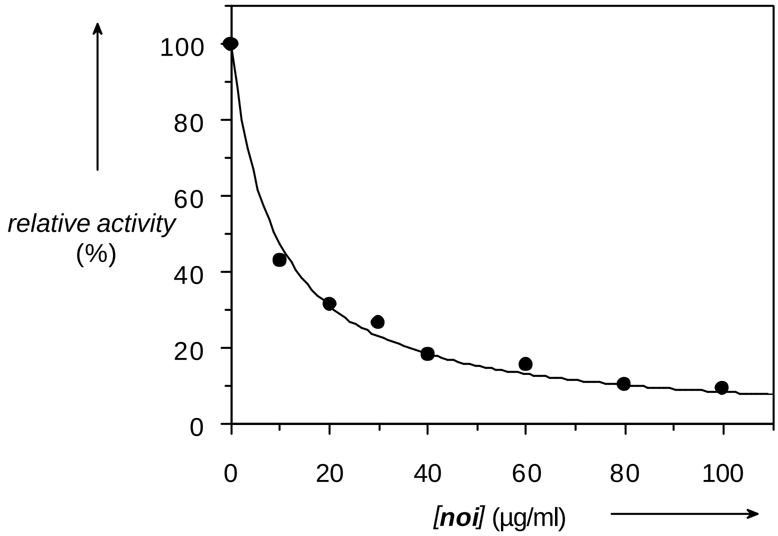

Table S7: Relative HLE activities (%) or IC_{50} values (µg/mL) of the VLC derived fractions of a crude extract (MeOH/DCM: 2/1) of *Nostoc insulare.* Values with standard error were calculated from duplicate experiments at five different concentrations, those without standard error are values from duplicate experiments at a single concentration of 10 µg/mL.

fraction	rel. enzyme act. (%) or IC_{50} (µg/mL)[a]
noi b	9.7 ± 0.8 µg/mL
noi c	98 %
noi d	112 %
noi e	91 %
noi f	91 %
noi g	113 %
noi h	47 %
noi i	1.7 ± 0.1 µg/mL

[a] The last two fractions were purified to yield compounds **1**-**8**. The active fraction **noi b** was not further purified due to not promising LC-MS results and the low weight of the fraction. HPLC-MS (ESI) measurements were conducted employing an Agilent 1100 Series HPLC including DAD (250 nm), with reversed phase C_{18} column (Macherey-Nagel Nucleodur 100, 125 mm x 2 mm, 5 µm) coupled with an API 2000, Triple Quadrupole, LC/MS/MS, Applied Biosystems/MDS Sciex and ESI source. Solvent system: from MeOH/H_2O 10/90 to MeOH/H_2O 100/0 in 20 min, MeOH 100 % for 10 min, with added NH_4Ac, 2 mmol.

Figure S13: Incubation experiments to determine the activity of HLE in the presence (•) and absence (?) of compound **4**. To 900 µL of assay buffer (50 mM sodium phosphate buffer, 500 mM NaCl, pH 7.8) 20 µL of a HLE solution (50 µg/mL) and 80 µL of a solution of **4** (50 µM in DMSO) or 80 µL DMSO were added. The mixtures were incubated at 25 °C and aliquots of 50 µL were added in a cuvette containing 894 µL of assay buffer and 50 µL of a solution of MeOSuc-Ala-Ala-Pro-Val-NHNp (2 mM in assay buffer with 10 % DMSO) and 6 µL DMSO. Final concentrations were as follows: 50 ng/mL HLE, 100 µM MeOSuc-Ala-Ala-Pro-Val-NHNp, 200 nM compound **4** and 1.5 % DMSO. Reactions were followed at 25 °C for 10 min at 405 nm. The data are mean values of duplicate measurements.

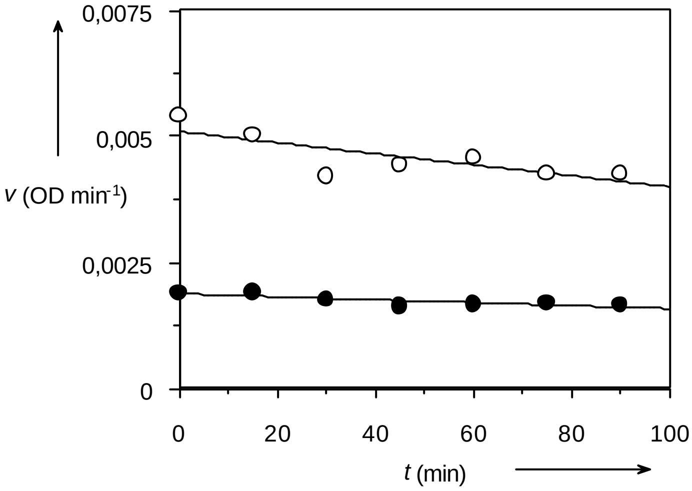

Figure S14: Alignment NoiN1 with NosA (http://www.ncbi.nlm.nih.gov/blast/Blast.cgi)

```
 gb|AAF15891.2|AF204805_1  NosA [Nostoc sp. GSV224]
Length=4379

 Score =  421 bits (1081),  Expect = 5e-116, Method: Compositional matrix adjust.
 Identities = 213/353 (60%), Positives = 257/353 (72%), Gaps = 28/353 (7%)

Query  1     AGGAYVPLDPNYPPERLNYMVADSQMSVILTHSSLLPHLSATLQQAQTKIICWDRDIETI  60
             AGGAY+PLDP YP ERL++M+ D+Q+SV+LT    LL  L+    Q Q K++C D D + I
Sbjct  3808  AGGAYLPLDPEYPTERLHFMLEDAQVSVLLTQQKLLDRLA----QHQAKLVCLDTDWQLI  3863

Query  61    ASQSLDNPINSVQPANLAYVIYTSGSTGQPKAVLIQHSALLNLLFWHLNNFEVKLSDRAT  120
             +  S DN I   Q ANLAYVIYTSGSTGQPK VLI H  LLNL+FWH N F++    D+AT
Sbjct  3864  SQSSQDNLITETQAANLAYVIYTSGSTGQPKGVLIAHQGLLNLVFWHQNTFKITTLDKAT  3923

Query  121   QLAGTAFDAAVWELWPYLVVGASIYLMKSEFLLSPKTLQEQLISQNITISFIPTPLAEKL  180
             QLAGTAFDAAVWELWPYL  GASIYL+KSEFL S   L++ LIS+ ITISF+PTPLA++L
Sbjct  3924  QLAGTAFDAAVWELWPYLTAGASIYLVKSEFLSSLVKLRDWLISKKITISFLPTPLAQEL  3983

Query  181   CLLAWP-ENTALRTILTGGDKLNYYPSETLPFKFFNNYGPTENTVVTTSVQILPGKFASK  239
               L WP E+ ALRTILTGGDKL+ YPS+ +P +  NNYGPTENTVVTTS  ++  +
Sbjct  3984  LSLEWPTESLALRTILTGGDKLHQYPSDLVPSQLVNNYGPTENTVVTTSGLVVAKEQDQI  4043

Query  240   LPPIGRPIANTQVYILDRYLQPVPVGVPGELHIGGVGLARGYLNRPELTAEKFISHPFQA  299
              P IGR IANTQ+YILD  LQ VP+G+PGELHI GVGLA+GYLNRPELT EKFI +PF+
Sbjct  4044  SPSIGRAIANTQIYILDNNLQLVPIGIPGELHIAGVGLAKGYLNRPELTTEKFIPNPFKR  4103

Query  300   NY-----------------------KLYKTGDLARYLPDGNVEFLGRIETRLK  329
             +                        +LYKTGDLARYLPDGN+E+LGRI+ ++K
Sbjct  4104  SREAGEQGSRGAKILPNSQSLVPSPRLYKTGDLARYLPDGNIEYLGRIDNQVK  4156
```

Figure S15: Alignment NoiN1 with NosC
(http://www.ncbi.nlm.nih.gov/blast/Blast.cgi)

```
    gb|AAF17280.1|  NosC [Nostoc sp. GSV224]
Length=3317

 Score =  418 bits (1074),  Expect = 3e-115, Method: Compositional matrix adjust.
 Identities = 211/345 (61%), Positives = 252/345 (73%), Gaps = 20/345 (5%)

Query  1    AGGAYVPLDPNYPPERLNYMVADSQMSVILTHSSLLPHLSATLQQAQTKIICWDRDIETI  60
            AGGAY+PL  +YP ERL  M+ D+Q+SV+LT    L+  L      Q     +C D D + I
Sbjct  605  AGGAYLPLASDYPTERLRLMLEDAQVSVLLTQQKLIDRLPEHTAQR----VCLDADWQVI  660

Query  61   ASQSLDNPINSVQPANLAYVIYTSGSTGQPKAVLIQHSALLNLLFWHLNNFEVKLSDRAT  120
            +  S DN I   Q  NLAYVIYTSGSTGQPK VLI H  LLNL+FWH    F++    D+AT
Sbjct  661  SQLSQDNLIPETQATNLAYVIYTSGSTGQPKGVLIAHQGLLNLVFWHQRTFKITTLDKAT  720

Query  121  QLAGTAFDAAVWELWPYLVVGASIYLMKSEFLLSPKTLQEQLISQNITISFIPTPLAEKL  180
            QLAGTAFDAAVWELWPYL  GASIYL+K E LLSP  LQ+ L S+ ITISF+PTP+AE+L
Sbjct  721  QLAGTAFDAAVWELWPYLTAGASIYLVKPEILLSPVDLQDWLESKKITISFLPTPMAEQL  780

Query  181  CLLAWPENTALRTILTGGDKLNYYPSETLPFKFFNNYGPTENTVVTTSVQILP-GKFASK  239
              L WPE+T LRT+LTGGDKL+ YPS  LPF+  NNYGPTENTVV+TS  ++  G+  +
Sbjct  781  LSLEWPESTTLRTMLTGGDKLHRYPSGLLPFQVVNNYGPTENTVVSTSGLVVSNGRDNNI  840

Query  240  LPPIGRPIANTQVYILDRYLQPVPVGVPGELHIGGVGLARGYLNRPELTAEKFISHPFQA  299
             PPIGRPIAN ++YILD YLQPVPVGVPGELHIGG GLARGYLNRP+LT EKFIS+PF+
Sbjct  841  SPPIGRPIANVEIYILDSYLQPVPVGVPGELHIGGAGLARGYLNRPQLTQEKFISNPFKR  900

Query  300  NY--------------KLYKTGDLARYLPDGNVEFLGRIETRLK  329
            +               +LYKTGDLARYLPDG +E+LGRI+ ++K
Sbjct  901  SRGAGEQRSRGETFNSNRLYKTGDLARYLPDGTIEYLGRIDNQVK  945
```

Figure S16: Alignment NoiF with NosF
(http://www.ncbi.nlm.nih.gov/blast/Blast.cgi)

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>   gb|AAF17284.1|  NosF [Nostoc sp. GSV224]
Length=273

 Score =  499 bits (1284),  Expect = 1e-139, Method: Compositional matrix adjust.
 Identities = 247/272 (90%), Positives = 254/272 (93%), Gaps = 0/272 (0%)

Query  1    LEDLQIAFIGGGTMGEMIISRLLSTKIVEKPDLIIVSEPLSTRCLHLEREYGVRTTTSNI  60
            LEDLQIAFIGGGTMGEMIISRLLSTKIV K DLIIVS+P+S RCLHLEREYGVRTTTSNI
Sbjct  2    LEDLQIAFIGGGTMGEMIISRLLSTKIVPKADLIIVSDPVSARCLHLEREYGVRTTTSNI  61

Query  61   EAVQGASIVILAVKPQVLVEVMAMLKDKISPDTLVISIVGGVSIPSLCQGLNHSAVVRTM  120
            EAV G SIVILAVKPQ+L EV+ MLKDKI P+ LVISIV G SI SLCQGLNH AVVRTM
Sbjct  62   EAVLGVSIVILAVKPQILAEVLGMLKDKIPPNALVISIVSGASISSLCQGLNHPAVVRTM  121

Query  121  PNIAVQVGHGTTVWSSSPSVTQIQRSHTQAILQALGKEFVTQNEHYLDMATALSSAGTGF  180
            PNIAVQVGHGTTVWS+S SVT+IQRSHTQ ILQALGKEF TQNEHYLDMATALSSAGTGF
Sbjct  122  PNIAVQVGHGTTVWSASSSVTEIQRSHTQIILQALGKEFATQNEHYLDMATALSSAGTGF  181

Query  181  VFLYIEAMIDAGVQMGLTRTQAQELTLHTIAGSVELMFQTDEHPAVLRNKVTSPGGVTAA  240
            VFLYIEAMIDAGVQMGLTRTQAQELTLHTIAGSVELMFQT EHPAVLRNKVTSPGGVTAA
Sbjct  182  VFLYIEAMIDAGVQMGLTRTQAQELTLHTIAGSVELMFQTHEHPAVLRNKVTSPGGVTAA  241

Query  241  GLYELEKGGMRTVISNAVLTALSRTQQLGNIS  272
            GLYELEKGGMRTVISNAVL ALSRTQQLGNIS
Sbjct  242  GLYELEKGGMRTVISNAVLAALSRTQQLGNIS  273
```

Figure S17: Alignment NoiF with NcpE (NcpE is responsible for the last step of the biosynthesis of (2S, 4S)-4-methylproline in nostocyclopeptide A1–2 (J. E. Becker, R. E. Moore, B. S. Moore, *Gene* 2004, *325*, 35–42) (http://www.ncbi.nlm.nih.gov/blast/Blast.cgi)

```
    gb|AAO23328.1|  NcpE [Nostoc sp. ATCC 53789]
Length=273

 Score =  471 bits (1213),  Expect = 2e-131, Method: Compositional matrix adjust.
 Identities = 233/270 (86%), Positives = 246/270 (91%), Gaps = 0/270 (0%)

Query  1    LEDLQIAFIGGGTMGEMIISRLLSTKIVEKPDLIIVSEPLSTRCLHLEREYGVRTTTSNI  60
            LEDLQIAFIGGGTMGEMI++RLLSTKIV KPDLIIVS+P+S RCLHLE EYGV TTT NI
Sbjct  2    LEDLQIAFIGGGTMGEMIMARLLSTKIVPKPDLIIVSDPVSARCLHLESEYGVSTTTCNI  61

Query  61   EAVQGASIVILAVKPQVLVEVMAMLKDKISPDTLVISIVGGVSIPSLCQGLNHSAVVRTM  120
            EAV GASIVILAVKPQVL EV+A+LK KISPD LVISIV G SIP LC+GLNH AVVRTM
Sbjct  62   EAVVGASIVILAVKPQVLAEVLAILKGKISPDALVISIVSGASIPYLCEGLNHPAVVRTM  121

Query  121  PNIAVQVGHGTTVWSSSPSVTQIQRSHTQAILQALGKEFVTQNEHYLDMATALSSAGTGF  180
            PNIAVQVGHGTTVWS+S SVT+IQRSHTQ ILQALGKEF TQNEHYLDMATALSSAGTGF
Sbjct  122  PNIAVQVGHGTTVWSASSSVTEIQRSHTQVILQALGKEFPTQNEHYLDMATALSSAGTGF  181

Query  181  VFLYIEAMIDAGVQMGLTRTQAQELTLHTIAGSVELMFQTDEHPAVLRNKVTSPGGVTAA  240
            +FLYIEAMIDAGVQMGLTRTQAQELTLHTIAGSVELMFQTDEH + L   + TSPGGVTA
Sbjct  182  IFLYIEAMIDAGVQMGLTRTQAQELTLHTIAGSVELMFQTDEHASSLTKQGTSPGGVTAV  241

Query  241  GLYELEKGGMRTVISNAVLTALSRTQQLGN  270
            GLYELEKGGMRT+ISNAVL ALSRTQQLG
Sbjct  242  GLYELEKGGMRTLISNAVLAALSRTQQLGT  271
```

Figure S18: Biosynthesis of MePro ((2*S*, 4*S*)-4-methyl-proline; H. Luesch, D. Hoffmann, J. M. Hevel, J. E. Becker, T. Golakoti, R. E. Moore, *J. Org. Chem.* **2003**, *68*, 83–91) and proposed biosynthesis of Hmp ((2*S*, 3*R*, 4*R*)-3-hydroxy-4-methyl-proline). MeP5C = (3*S*, 5*S*)-3-methyl-?^{1}-pyrroline-5-carboxylic acid.