Electronic Supplementary Information (ESI)

Genomics-driven discovery of a new cyclodepsipeptide from the guanophilic fungus *Amphichorda guana*

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Author Contributions

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Content

Fig. S28-S32 ^{1}H NMR, ^{13}C NMR, ^{1}H -^{1}H COSY, HSQC, HMBC of **7** in DMSO-*d*6.
Fig. S33-S34 ^{1}H NMR, ^{13}C NMR of **8** in DMSO-*d*6.

4. Supplementary references

1. Supplementary methods

Strains, media and growth conditions

A. guana LC5815 originally grew on bat guano, which is isolated from a unnamed Karst Cave in Guizhou, China[1] by Feng Zhang group. In this study, *A. guana* LC5815 was inoculated on 20 kg rice at 28°C for 30 days to isolate these CDPs. *A. guana* LC5815 and its transformants were grown at 28°C on Potato Dextrose Agar (PDA) for sporulation, transformation with appropriate osmotic stabilizer (sucrose) as required. *Escherichia coli* strain DH5α was propagated in Luria–Bertani (LB) medium with appropriate antibiotics for plasmid DNA.

Genomic DNA isolation, DNA sequencing and de novo assembly

A. guana LC5815 and its transformants were inoculated in PDB medium at 28°C. After 2 days, genomic DNA was isolated by lyophilization and phenol chloroform extraction. The *A. guana* genome was sequenced by the Annoroad company in Beijing, and the PacBio database was assembled by de novo.

Gene cloning, plasmid construction

Plasmids and strains used in this study are listed in Table S1. The oligonucleotide sequences for PCR primers are given in Table S2. PCR amplification was carried out using the TransStart FastPfu DNA polymerase (Transgene Biotech) on a T100TM Thermal cycler from Bio-Rad. The marker gene cassette (*hygromycin*) was amplified by using pAG1-H3 (Table S1) as template and used as marker gene for knockout *AG06652* and *AG03264*. Approximately 1.6 kb fragments upstream and downstream of the target genes were amplified from genomic DNA of *A. guana* using the designated primers (Table S2), respectively. These three amplified PCR fragments were then purified with a Zymoclean Gel DNA Recovery Kit (Zymo research), quantified, and fused using Double-joint PCR[2], respectively. The final PCR product was amplified with the designated primer pairs and purified for fungal transformation. In order to quickly amplify the knockout cassette, the knockout cassettes were cloned into pGEMT vector to give two plasmids in Table S2. These plasmids were verified by enzyme digestion.

Genetic manipulations

A. guana protoplast preparation and transformation were carried out by improved fungal method according to the description by Bok & Kelle[3]. Two samples (8 μg) of the Double-joint PCR cassette were used to delete the core gene of NRPS (*AG06652* and *AG03264*) by using *A. guana* LC5815 as the recipient host (Fig. S4 A). Mutants were verified by diagnostic PCR (Fig. S4 B, C).

Chemical analysis and characterization of compounds

Samples were analyzed by a Waters HPLC system (Waters e2695, Waters 2998, Photodiode Array Detector) using an ODS column (C18, 250 × 4.6 mm, XTerra MS, 5 μm) with a flow rate of 1 mL/min. The fermentation products were extracted with ethyl acetate for three times. The organic solvent was evaporated to dryness with rotary evaporator to obtain 60 g of crude extract. The extract was isolated on a silica gel chromatographic column (CC) using dichloromethane, ethyl acetate, acetone, and methanol to give 4 fractions (Fr. 1-4). The subfraction 3 was further purified by MCI CC eluted with CH_3OH/H_2O (5:5, 7:3, 9:1, and 10:0) to give 4 subfractions (Fr. 3.1 to Fr. 3.4). The Fr. 3.2 was isolated by semi-preparative HPLC with CH_3CN/H_2O (85:15, 2.0 mL/min) to afford compound **6** (25 mg, *t*R 11.9 min), compound **2** (10 mg, *t*R 13.1 min), compound **7** (30 mg, *t*R 17.5 min) and compound **8** (35 mg, *t*R 20.1 min). Compound **5** (100 mg) was crystallized from the methanol solution of Fr. 3.2. The Fr. 3.3 was isolated by semi-preparative HPLC with CH_3CN/H_2O (85:15, 2.0 mL/min) to afford compound **1** (25 mg, *t*R 17.5 min), compound **3** (10 mg, *t*R 19.2 min), compound **4** (30 mg, *t*R 25.6 min).

Analytical methods and equipment overview

An Agilent Accurate-Mass-QTOF LC/MS 6520 instrument was utilized to HR-ESI-MS analysis. NMR spectra (^{1}H, ^{13}C, HSQC, HMBC) were recorded on a Bruker Avance-500 spectrometer, which use TMS as internal standard, and chemical shifts were recorded as δ values. HPLC analysis was performed on a Waters HPLC system (Waters e2695, Waters 2998, Photodiode Array Detector), which use an ODS column (C18, 250 × 4.6 mm, XTerra MS, 5 μm) with a flow rate of 1 mL/min. Semi-preparative HPLC was performed with an ODS column [HPLC (YMC-Pack ODS-A, 10 × 250 mm, 5 μm, 2 mL/min)]. Column chromatography (CC) were performed using silica gel (200-300 mesh, Qingdao Marine Chemical Inc., Qingdao, China), and Sephadex LH-20 (Amersham Biosciences), respectively.

Preparation and Analysis of Marfey's Derivatives[4-6]

Compound **1** (1 mg) was dissolved in 6 N HCl (1 mL) under 110°C for 20 h. After cooling to room temperature, the mixture was evaporated to dryness with rotary evaporator. The resulting mixture and the four amino acid standards L-Pro, L-Phe, L-Val and L-Methyl-Val, each 1 mg were respectively dissolved in H_2O (100 μL), and then treated with 1% (w/v) 1-fluoro-2, 4-dinitrophenyl-5-(L)-alanine amide (FDAA) (200 μL) in acetone and $NaHCO_3$ solution (1.0 M, 50 μL), separately. Finally, each of the mixture was heated up to 45°C for 1 h (stirred every 5 min), and then neutralized with 25 μL of 2 N HCl. Derivatized hydrolysate (10 μL) and standard amino acids (5 μL) were subjected to HPLC [Waters XTerra MS-C18 column (250×4.6 mm i.d., 5 μm, 120 Å) using a linear gradient from 30 to 70% CH_3CN in H_2O (0.1% TFA) 60 min; 0.5 mL/min; 25°C; 340 nm]. HPLC analyses revealed that the hydrolysate of **1** consisted of L-Pro, L-Phe, L-Valand L-Methyl-Val [retention times (min): L-Pro (17.02), L-Phe (27.57) L-Val (22.56) and, L-Methyl-Val (26.14).

Assay of isaridins for antibacterial activity

20 mL LB medium was added 10 μL suspension (10^{10} cfu mL^{-1}) of bacterium (*Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus*), Which were grown for 12 h in liquid medium respectively. After mixing well, the medium containing bacteria was poured into a Petri dish (9 cm in diameter). Sterile filter paper disks (0.625 cm in diameter) were placed onto a Petri dish of soft medium and 10 μL isaridins obtained (1 mg mL^{-1}) were added, respectively. The control consisted of 10 μL Dimethyl sulfoxide (DMSO). After cooling, the plate was incubated at 37℃ for 24 h, and the area of the zone of bacterial inhibition was recorded.[7] MIC of isaridin H (**1**) were tested by the microdilution method[8]. The MIC value was obtained after 24 h for *B. subtilis*.

Assay of isaridins for antifungal activity

The antifungal activity was tested with a 9 cm Petri plate containing 10 mL potato dextrose agar (PDA) medium. The plant pathogenic fungi were grown about 2 cm. Then sterile blank paper disks of the same size (0.625 cm in diameter) were placed around and at a distance of 1 cm away from the rim of the mycelial colony. An aliquot (10 μL) of a 1 mg mL^{-1} solution in DMSO of sample were introduced to a disk. The plates were incubated at 28℃ for 36 h until mycelial growth from the central disk had enveloped peripheral disks containing the control.[9]

The antifungal activities of isaridins were evaluated by measuring the diameter of test and control colonies[10]. The fungitoxicities of isaridins were recorded in terms of mycelial inhibition using the expression:

$$\%\text{Mycelial inhibition} = \frac{\mathrm{MI_c} - \mathrm{MI_t}}{\mathrm{MI_c}} \times 100$$

In this study, MI_c and MI_t are the average diameters of mycelial colonies in control and tested fungi sets. The antifungal activities were recorded in Table S7.

Determination of IC_{50} value of antifungal activity[9]

To determine the IC_{50} value for the antifungal activity of isaridin H (**1**), a 200 μL aliquot of test sample following five concentrations (15.5, 31.3, 62.5, 125 and 250 μg mL^{-1}) were added respectively to 4.8 mL PDA at 55°C, mixed rapidly and poured into a 6 cm Petri plate. Finally, we get test sample concentration of 0.63, 1.25, 2.5, 5.0 and 10.0 μg mL^{-1}. After the agar had solidified, a colony of *Alternaria solani* with a diameter of about 6 mm was selected and placed at the center of the plate. The plates were incubated at 28℃ for 6-7 d. The antifungal activity of isaridin H (**1**) was evaluated every 2 days by comparing the diameter of test and control colonies.

2. Supplementary tables

Table S1 Fungal strains and plasmids used in this study.

Strain/Plasmid	Description	Reference
Amphichorda guana LC5815	wild type	[1]
TYML4.1	Δ*AG06652:: hph*	This study
TYML5.1	Δ*AG03264:: hph*	This study
pYWL169	AG06652 deletion cassette in pGEMT	This study
pYWL170	AG03264 deletion cassette in pGEMT	This study
pAG1-H3	Hygromycin resistance vector	[11]

pXX = plasmid, TXX = original transformant

Table S2 PCR primers sets used in this study.

Primers	Oligonucleotide sequence (5’-3’)	Uses
HYG_F	atcgatgatcaggcctcgac	Maker hygromycin Amplification
HYG_R	gtgcattctgggtaaacgactc	Maker hygromycin Amplification
C20_5F_F	gtcgggatagatggacaagtgc	Amplification of Δ*AG06652* 5’flanking region
C20_5F_R	caatatcatcttctgtcgaggcctgatcatcgatgttgttcattggaaatcccgtgg	Amplification of Δ*AG06652* 5’flanking region
C20delpart-3Ff	ctcctatgagtcgtttacccagaatgcactgtccatctccccagtcgac	Amplification of Δ*AG06652* 3’flanking region
C20delpart-3Fscr	cttgctgatgggagccgtc	Amplification of Δ*AG06652* 3’flanking region
C20_nest_F	gacacatgaataggtaggaggcc	Δ*AG06652* cassette
C20delpart-3Fr	cgtgctgctcatactcgagc	Δ*AG06652* cassette
KOC20rt-f	cctacctcttcgccaagtcg	Diagnostic PCR for *AG06652* deletion
KOC20rt-r	gtccggtacatgcgaacagg	Diagnostic PCR for *AG06652* deletion
HYG_RT_R	ccgagagctgcatcaggtc	Δ*AG06652*/Δ*AG03264* 5F screening
HYG_RT_F	gcgaagcagaagaatagcttagc	Δ*AG06652*/ Δ*AG03264* 3F screening
C31del5F-scr	gcatctgggccatatgctcc	Amplification of Δ*AG03264* 5’flanking region
C31delpart-5Fr	tcatcttctgtcgaggcctgatcatcgatcgacttcgccagatcggaag	Amplification of Δ*AG03264* 5’flanking region
C31delpart-3Ff	ctcctatgagtcgtttacccagaatgcaccggctgatggaacaattcgg	Amplification of Δ*AG03264* 3’flanking region
C31_3F_R	ctcgtaggctgacatggagatg	Amplification of Δ*AG03264* 3’flanking region
C31delpart-5Ff	gtcctctctcaacgcccatg	Δ*AG03264* cassette
C31_nest_R	ggtcccacttcaatcatacgac	Δ*AG03264* cassette
C31del5F-scr-2	ctgagccagtagaatgccttcc	Δ*AG03264* screening
KOC31rt-f	gctcaggagattgcgtcgatg	Diagnostic PCR for *AG03264* deletion
KOC31rt-r	cctacctcacgcctactgtgg	Diagnostic PCR for *AG03264* deletion

Table S3 NRPS encoded in *A. guana* genome.

NO.	Gene ID	Cluster number	Domain structure	Closest BLAST hit (s)	coverage /identity	Accession number
1	M518_02636	11	C-A-T-KS	*Cordyceps militaris* CM01	99/66	XP_006667652.1
2	M518_05788	13	A-T-C-A-T-C	*Aspergillus sclerotiicarbonarius* CBS 121057	100/63	PYI02181.1
3	M518_05949	15	A-T-C-A-T	*Pochonia chlamydosporia* 170	99/48	XP_022285841.1
4	M518_06652	20	A-T-C-A-T-C-A-T-E-C-A-T-E-C-A-T-C-T-C	*Thermothelomyces thermophila* ATCC 42464	97/58	XP_003664570.1
5	M518_06769	21	T-C-A-C-T-C-T-C	*Acremonium chrysogenum* ATCC 11550	100/65	KFH43976.1
6	M518_03264	31	A-T-C-A-T-E-C-A-T-C-A-T-C-A-nMT-T-C-A-nMT-T-C	*Tolypocladium ophioglossoides* CBS 100239	99/65	KND86507.1
7	M518_05188	36	C-A-T-C	*Neonectria ditissima*	91/64	KPM35145.1
8	M518_05529	39	A-T-C-T-C	*Acremonium chrysogenum* ATCC 11550	97/78	KFH48348.1

Table S4 Deduced functions of ORFs in Cluster 20.

Protein ID	Size (aa)	putative function	organism	Coverage/identity (%/%)	Homolog Accession
06647	238	Alpha N-terminal protein methyltransferase-like protein	*Acremonium chrysogenum* ATCC 11550	96/72	KFH43784.1
06648	239	Polysaccharide monooxygenase Cel61a-like protein	*Acremonium chrysogenum* ATCC 11550	99/85	KFH43806.1
06649	377	D-2-hydroxyacid dehydrogenase-like protein	*Acremonium chrysogenum* ATCC 11550	83/88	KFH40610.1
06650	155	hypothetical protein ACRE_086880	*Acremonium chrysogenum* ATCC 11550	98/48	KFH40617.1
06651	1426	ABC transporter	*Metarhizium anisopliae*	97/31	KFG85665.1
06652	2000	non-ribosomal peptide synthetase	*Thermothelomyces thermophila* ATCC 42464	97/58	XP_003664570.1
06653	368	hypothetical protein ACRE_086870	*Acremonium chrysogenum* ATCC 11550	99/61	KFH40618.1
06654	582	nucleoside transporter	*Trichoderma arundinaceum*	98/76	RFU75112.1
06655	378	hypothetical protein ACRE_086850	*Acremonium chrysogenum ATCC 11550*	100/91	KFH40616.1
06656	224	Puromycin N-acetyltransferase 1	*Colletotrichum chlorophyti*	98/61	OLN95332.1

Table S5 Deduced functions of ORFs in Cluster 31.

Protein ID	**Size (aa)**	**Putative function**	**Organism**	**Coverage/Identity (%/%)**	**Homolog Accession**
03257	456	hypothetical protein ACRE_057260	*Acremonium chrysogenum* ATCC 11550	100/60	KFH43510.1
03258	347	PREDICTED: vacuolar protein sorting-associated protein 37C-like	*Hippocampus comes*	23/39	XP_019735279.1
03259	680	Calcium channel-like protein	*Acremonium chrysogenum* ATCC 11550	95/71	KFH43535.1
03260	474	glycoside hydrolase	*Acremonium chrysogenum* ATCC 11550	83/87	KFH43545.1
03261	293	putative membrane protein-like protein	*Acremonium chrysogenum* ATCC 11550	99/76	KFH45179.1
03262	628	bud emergence protein 1	*Acremonium chrysogenum* ATCC 11550	100/84	KFH45168.1
03263	468	SAC3/GANP domain protein	*Metarhizium brunneum* ARSEF 3297	100/68	XP_014548414.1
03264	2000	Destruxins-like Nonribosomal peptide synthetase	*Metarhizium robertsii* ARSEF 23	99/62	XP_007826232.2
03265	260	aldo-keto reductase family protein	*Metarhizium robertsii* ARSEF 23	93/74	XP_007826234.2
03266	388	Vacuolar protein-sorting-associated protein-like protein	*Acremonium chrysogenum* ATCC 11550	100/88	KFH45140.1
03267	381	CENP-B-like protein 1	*Metarhizium robertsii* ARSEF 23	98/73	XP_007822485.1
03268	70	ATP synthase subunit K-like protein	*Acremonium chrysogenum* ATCC 11550	100/81	KFH45144.1
03269	290	Mitochondrial fission process protein-like protein	*Acremonium chrysogenum* ATCC 11550	99/78	KFH45208.1
03270	309	AN1-type zinc finger protein-like protein	*Acremonium chrysogenum* ATCC 11550	100/85	KFH45196.1

Table S6 A domain specificities prediction of AG06652(NRPS) and AG03264(NRPS).

Protein Identifier	**Adenylation domain start position**	**Adenylation domain end position**	**Substrate (NRPSsp)**	**Substrate (NRPSpredictor3)**
AG06652	309	739	Phe	Gln
AG06652	1441	1834	Pro	Gln
AG06652	2521	2930	Phe	
AG06652	4086	4500	Pro	Gln
AG06652	5678	6075	Pro	Phe
AG03264	295	691	Pro	Ala
AG03264	1371	1769	Phe	Gln
AG03264	2876	3272	Pro	
AG03264	3968	4365	Pro	
AG03264	5063	5479	Leu	Val
AG03264	6578	6984	Leu	Leu

Table S7 List of isolated cyclodepsipeptides.

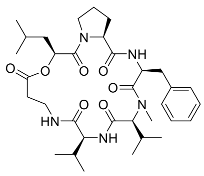
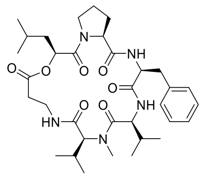
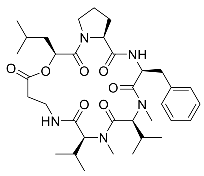
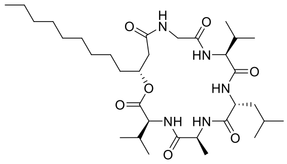
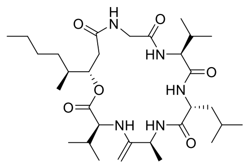
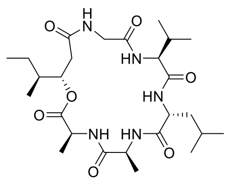
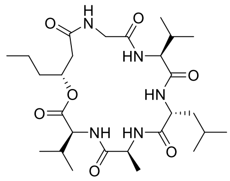
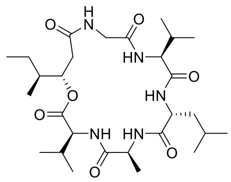
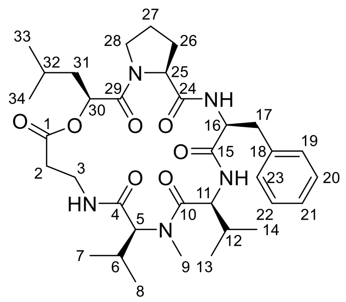
Compound #	Structure	Published/reference name given in this study
1		isaridin H
2		desmethylisaridin E
3		isaridin E
4		isariin A
5		iso-isariin B
6		iso-isariin D
7		isariin E
8		nodupetide

Table S8 Inhibition of mycelial growth in phytopathogens induced by isaridins obtained.

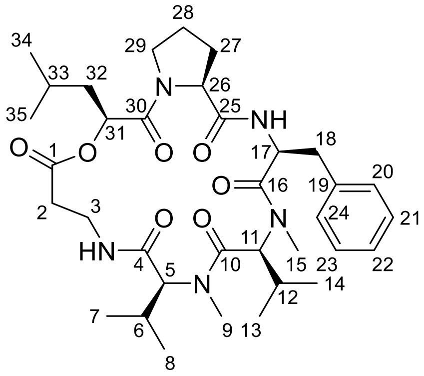
Strain	**Inhibition (%)**		
	(**1**)	(**2**)	(**3**)
Alternaria solani	27.27%	0	31.82%
Botrytis cinerea	45.00%	0	46.67%
Fusarium oxysporum	1.67%	6.67%	0

Table S9 ^{1}H and ^{13}C NMR spectroscopic data for **2** in DMSO-*d*6.



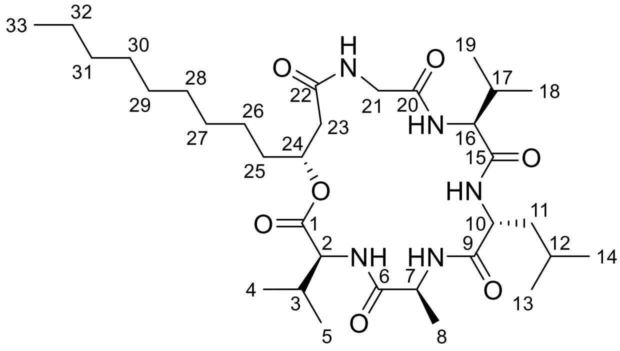
Position	δ_H (J Hz)	δ_C
1		170.9
2	2.77 m	29.7
3	3.66 m	40.7
4		169.6
5	4.55 d (10.9)	60.9
6	1.91 m	26.0
7	0.47 d (6.6)	19.3
8	0.84 d (6.6)	18.4
9	2.48 s	29.7
10		169.5
11	4.88 d (10.6)	57.9
12	2.16 dq (17.2, 6.9)	26.7
13	0.67 d (6.3)	17.8
14	0.79 d (6.3)	19.6
15		171.1
16	5.00	49.8
17	3.10 dd (13.1, 8.9), 2.77 m	37.6
18		137.2
19	7.23 d (8.7)	129.2
20	7.25 d (8.7)	128.3
21	7.20 m	126.5
22	7.25 d (8.7)	128.3
23	7.23 d (8.7)	129.2
24		172.4
25	4.37 dd (8.4, 4.0)	59.2
26	1.98 ddd (15.6, 7.9, 3.9), 1.65 td (11.8, 5.7)	28.9
27	1.81 m	24.4
28	3.59, 3.43 dt (9.7, 6.5)	46.3
29		171.1
30	4.16 brs	67.3
31	1.34 m	42.6
32	1.82 m	21.4
33	0.90 s	23.9
34	0.91 s	23.6

Table S10 ^{1}H and ^{13}C NMR spectroscopic data for **3** in DMSO-*d*6.



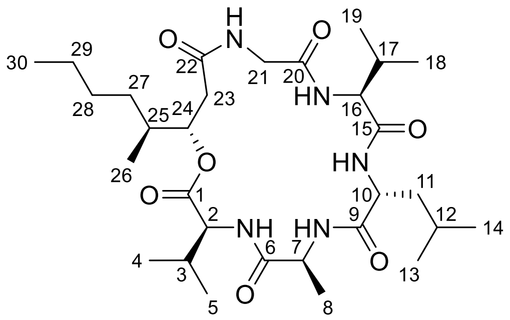
Position	δ_H (J Hz)	δ_C
1		173.7
2	2.71 m, 2.34 m	34.9
3	3.95 m, 3.08 dd (13.7, 5.5)	35.4
4		167.9
5	4.26 m	65.6
6	2.30 m	27.2
7	0.85 d (6.7)	19.4
8	0.80 d (6.7)	19.1
9	2.83 m	28.6
10		168.9
11	5.04 d (10.7)	56.9
12	2.28 m	26.9
13	0.75 d (6.6)	19.9
14	0.79 d (6.6)	18.5
15	2.95 m	29.2
16		173.5
17	4.62 ddd (10.9, 7.6, 5.3)	53.0
18	3.08 m, 2.83 m	34.2
19		136.9
20	7.28 m	129.0
21	7.28 m	128.3
22	7.25 m	126.8
23	7.28 m	128.3
24	7.28 m	129.0
25		171.5
26	4.14 d (8.0)	60.2
27	2.13 m, 1.96 dd (12.3, 5.9)	31.7
28	1.72 m, 1.12 m	21.6
29	3.30 m	46.8
30		168.9
31	5.28 d (11.5)	73.0
32	1.67 m, 1.52 dd (14.2, 9.8)	37.5
33	1.86 m	24.4
34	0.96 d (6.6)	23.1
35	0.95 d (6.6)	19.9

Table S11 ^{1}H and ^{13}C NMR spectroscopic data for **4** in DMSO-*d*6.



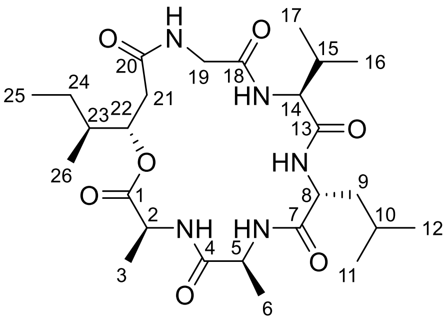
Position	δ_H (J Hz)	δ_C
1		170.8
2	3.96 t (6.6)	58.2
3	2.06 m	29.2
4	0.88 d (7.0)	19.7
5	0.88 d (7.0)	18.9
6		172.0
7	4.20 m	47.9
8	1.21 m	17.3
9		171.2
10	4.04 d (10.7)	51.7
11	1.49 m	38.6
12	1.63 tt (13.2, 6.6)	24.1
13	0.89 d (6.7)	19.1
14	0.81 d (6.7)	20.9
15		171.8
16	4.01 m	58.9
17	1.86 dt (13.4, 6.7)	29.5
18	0.84 d (6.8)	18.7
19	0.89 d (6.8)	23.1
20		169.1
21	4.11 dd (16.9, 7.0), 3.45 dd (16.9, 3.4)	42.0
22		169.3
23	2.46 dd (14.4, 8.5), 2.34 dd (14.4, 2.2)	40.1
24	4.93 q (8.4)	72.0
25	1.54 m, 1.51 m	33.2
26	1.23 m	24.4
27	1.21-1.24 m	28.9
28		28.7
29		28.8
30		28.7
31		31.3
32	1.23 m	22.1
33	0.84 t (6.7)	14.0

Table S12 ^{1}H and ^{13}C NMR spectroscopic data for **5** in DMSO-*d*6.



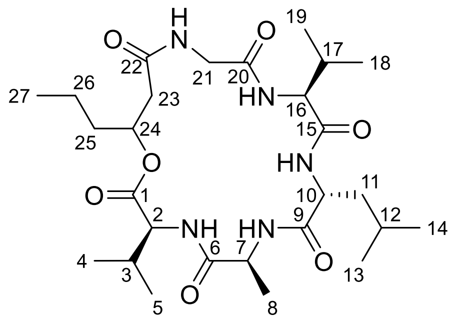
Position	δ_H (J Hz)	δ_C
1		170.8
2	4.07 m	57.7
3	2.07 dt (13.4, 6.7)	29.5
4	0.87 d (6.6)	17.5
5	0.88 d (6.6)	19.0
6		171.9
7	4.19 m	48.0
8	1.22 m	17.3
9		171.3
10	4.03 dd (15.3, 6.8)	51.9
11	1.49 m	38.7
12	1.64 m	24.1
13	0.81 d (8.5)	20.9
14	0.89 d (8.5)	19.1
15		171.7
16	4.03 m	58.8
17	1.86 dt (13.4, 6.7)	29.6
18	0.88 d (6.7)	23.0
19	0.82 d (6.7)	18.7
20		169.1
21	4.09 m, 3.44 dd (17.1, 3.5)	41.9
22		169.8
23	2.54 dd (13.1, 5.2)	37.5
	2.23 d (13.1)	
24	4.91 dd (5.6, 2.1)	75.5
25	1.67 m	36.2
26	1.37 m, 1.02 m	31.2
27	1.25 m, 1.17 m	28.9
28	1.24 m	22.4
29	0.84 d (6.6)	13.9
30	0.82 d (6.6)	14.8

Table S13 ^{1}H and ^{13}C NMR spectroscopic data for **6** in DMSO-*d*6.



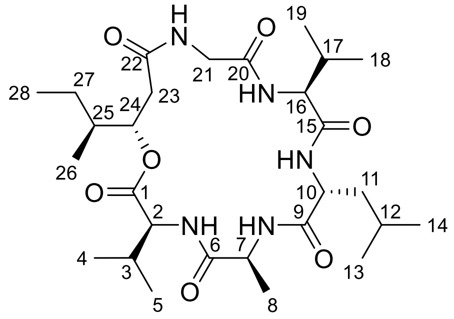
Position	δ_H (J Hz)	δ_C
1		172.2
2	4.13 m	48.8
3	1.30 d (7.3)	17.1
4		172.2
5	4.19 m	48.1
6	1.20 d (7.0)	17.8
7		171.6
8	4.03 m	52.4
9	1.48 ddd (17.3, 9.0, 5.1)	39.1
10	1.63 dt (17.8, 5.8)	24.6
11	0.82 d (6.5)	19.4
12	0.90 d (6.5)	21.6
13		172.2
14	4.11 m	58.7
15	1.86 td (13.7, 6.8)	30.5
16	0.85 d (6.8)	19.1
17	0.89 d (6.8)	23.4
18		169.4
19	4.07 d (6.5), 3.43 dd (16.5, 3.8)	42.8
20		170.2
21	2.54 dd (13.4, 8.6), 2.27 d (13.4)	38.0
22	4.98 d (5.4)	74.8
23	1.55 m	38.5
24	1.38 m, 1.05 m	25.3
25	0.85 d (6.6)	14.6
26	0.82 d (6.6)	11.9

Table S14 ^{1}H and ^{13}C NMR spectroscopic data for **7** in DMSO-*d*6.



Position	δ_H (J Hz)	δ_C
1		170.8
2	3.96 t (6.6)	58.2
3	2.06 dq (13.3, 6.6)	29.2
4	0.88 d (6.6)	17.8
5	0.88 d (6.6)	18.9
6		172.0
7	4.19 m	47.9
8	1.22 d (7.0)	17.3
9		171.2
10	4.04 dd (13.8, 4.8)	51.7
11	1.50 m	38.6
12	1.63 m	24.1
13	0.81 m	20.9
14	0.89 d (6.7)	19.2
15		171.8
16	4.01 m	59.0
17	1.86 td (13.3, 6.7)	29.4
18	0.84 d (6.7)	18.7
19	0.89 d (6.7)	23.1
20		169.2
21	4.12 dd (16.8, 6.9), 3.44 dd (16.8, 3.1)	42.0
22		169.3
23	2.45 dd (14.4, 8.4), 2.35 d (14.4)	40.1
24	4.94 d (6.4)	71.9
25	1.54 dd (13.8, 7.2), 1.45 m	35.4
26	1.27 m	17.9
27	0.85 d (6.7)	13.7

Table S15 ^{1}H and ^{13}C NMR spectroscopic data for **8** in DMSO-*d*6.



Position	δ_H (J Hz)	δ_C
1		170.8
2	4.09 m	57.7
3	2.07 dd (12.2, 6.0)	29.6
4	0.88 d (6.8)	17.6
5	0.88 d (6.8)	18.7
6		171.9
7	4.19 m	48.0
8	1.22 d (6.7)	17.5
9		171.3
10	4.04 d (7.8)	51.9
11	1.48 m	38.7
12	1.63 m	24.2
13	0.88 d (6.8)	21.0
14	0.80 d (6.8)	23.0
15		171.7
16	4.04 m	58.8
17	1.86 m	29.6
18	0.88 d (6.8)	19.0
19	0.83 d (6.8)	19.1
20		169.1
21	4.08 m, 3.45 d (15.2)	42.0
22		169.9
23	2.53 d (14.0), 2.25 d (14.0)	37.8
24	4.92 d (2.8)	75.4
25	1.59 m	38.1
26	1.42 m, 1.06 m	24.5
27	0.84	14.3
28	0.86	11.5

3. Supplementary figures

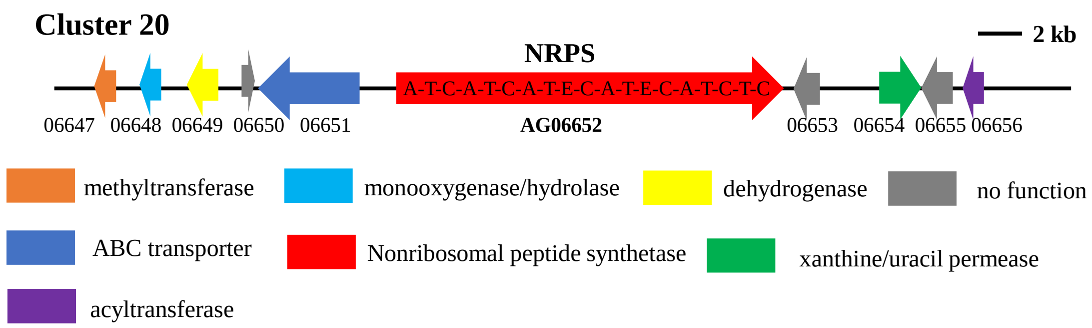


Fig. S1 Organization of cluster 20 in *A. guana*

Nucleotide sequence (5'-3') of *AG06652* in *A. guana*:

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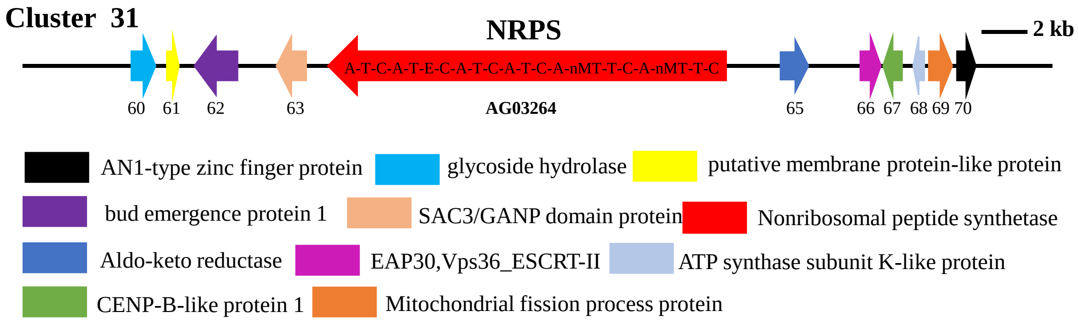

Fig. S2 Organization of cluster 31 in *A. guana*

Nucleotide sequence (5'-3') of *AG03264* in *A. guana*:

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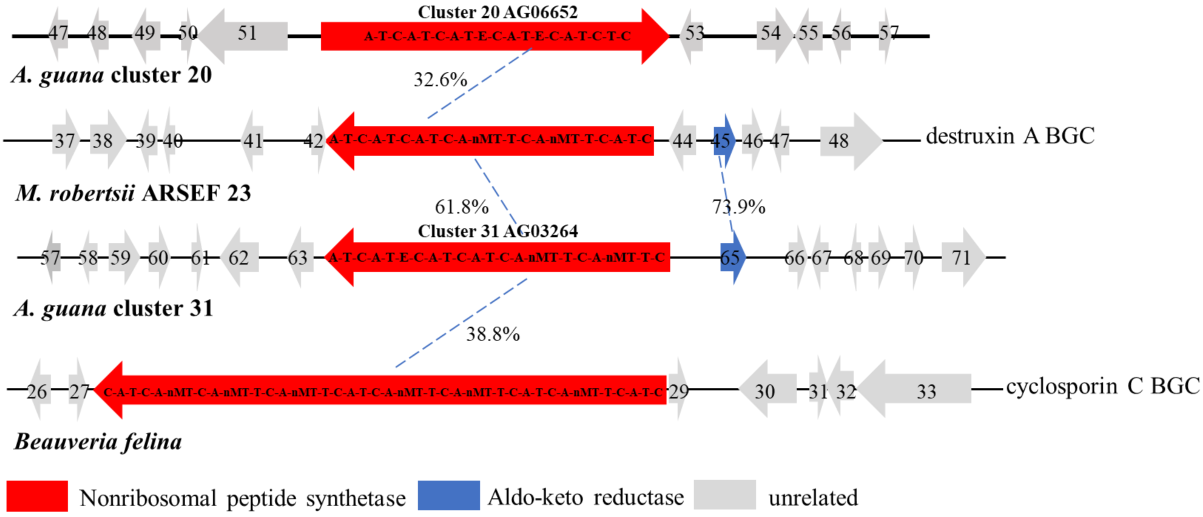

Fig. S3 Comparison of destruxin A biosynthetic gene cluster in *M. robertsii*, cyclosporin C biosynthetic gene cluster in *B. felina* and the putative cyclodepsipeptides biosynthetic gene cluster in *A. guana*. The sequence identities on the amino acid level are given as percent.

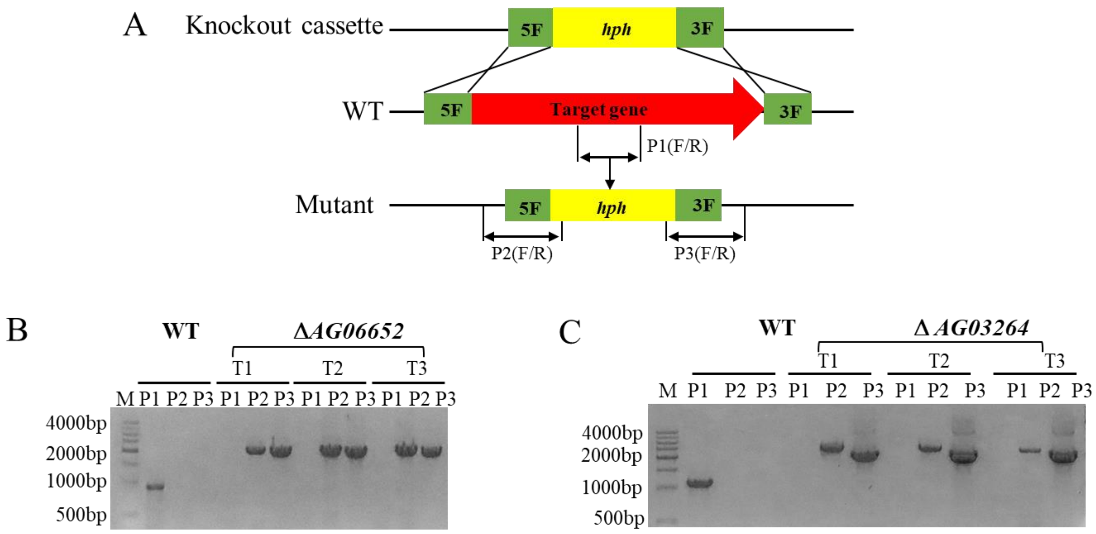

Fig. S4 Generation of *AG06652*(NRPS) and *AG03264*(NRPS) disruption strains. **A.** Schematic illustration for disruption of targeted genes. The *hph* gene in vector pAG1-H3 was used as a selection maker after transformation. Transformation was performed by homologous recombination via PEG mediated protoplast transformation methods. Three pairs of primers including P1F/R, P2F/R and P3F/R were used for transformant screening. **B.** Confirmation of *AG06652* disruption strains by diagnostic PCR, specific bands (ca. 2.0-2.1 kb) were only detected in mutants but not in WT. **C.** Confirmation of *AG03264* disruption strains by diagnostic PCR, specific bands (ca. 1.9-2.3 kb) were only detected in mutants but not in WT.

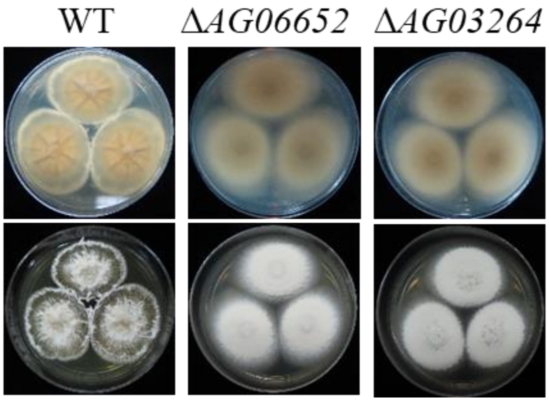

Fig. S5 The phenotypes of the *A. guana* wild-type strain and mutants (Δ*AG06652* and Δ*AG03264*) on PDA plate at 28°C,15 days.

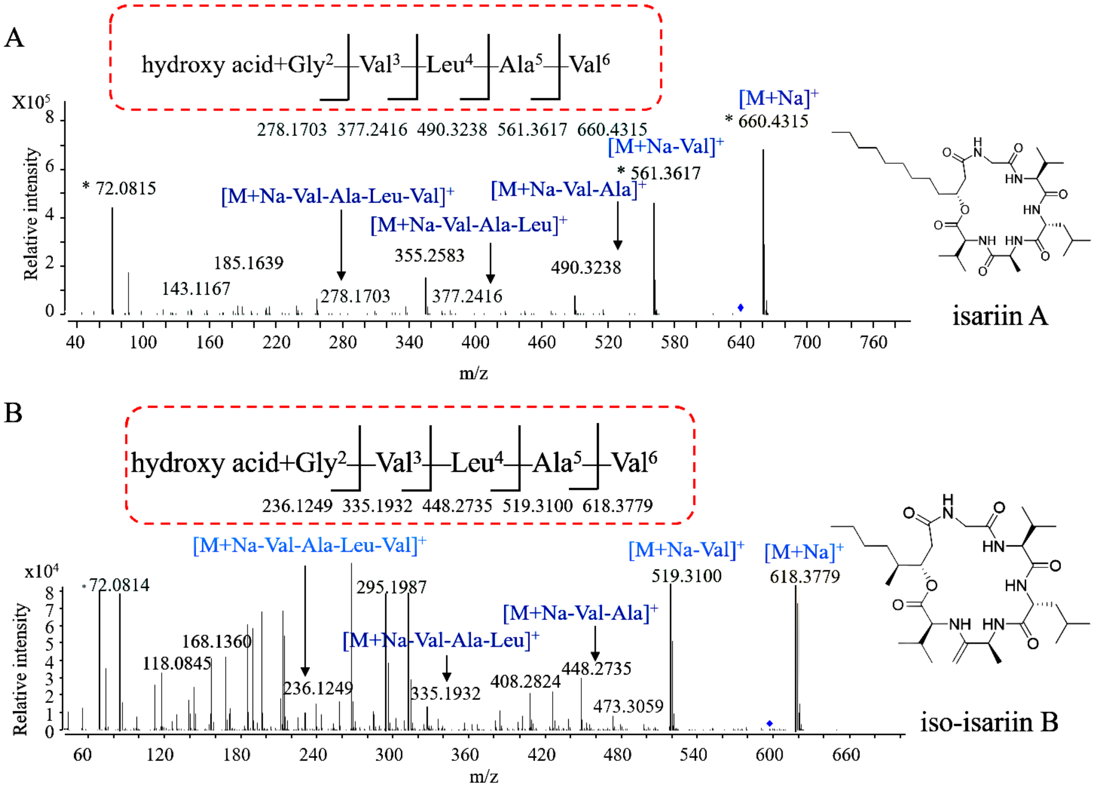

Fig. S6 The putative isariins indicated by the pronounced fragment ions in their LC-MS/MS spectra.

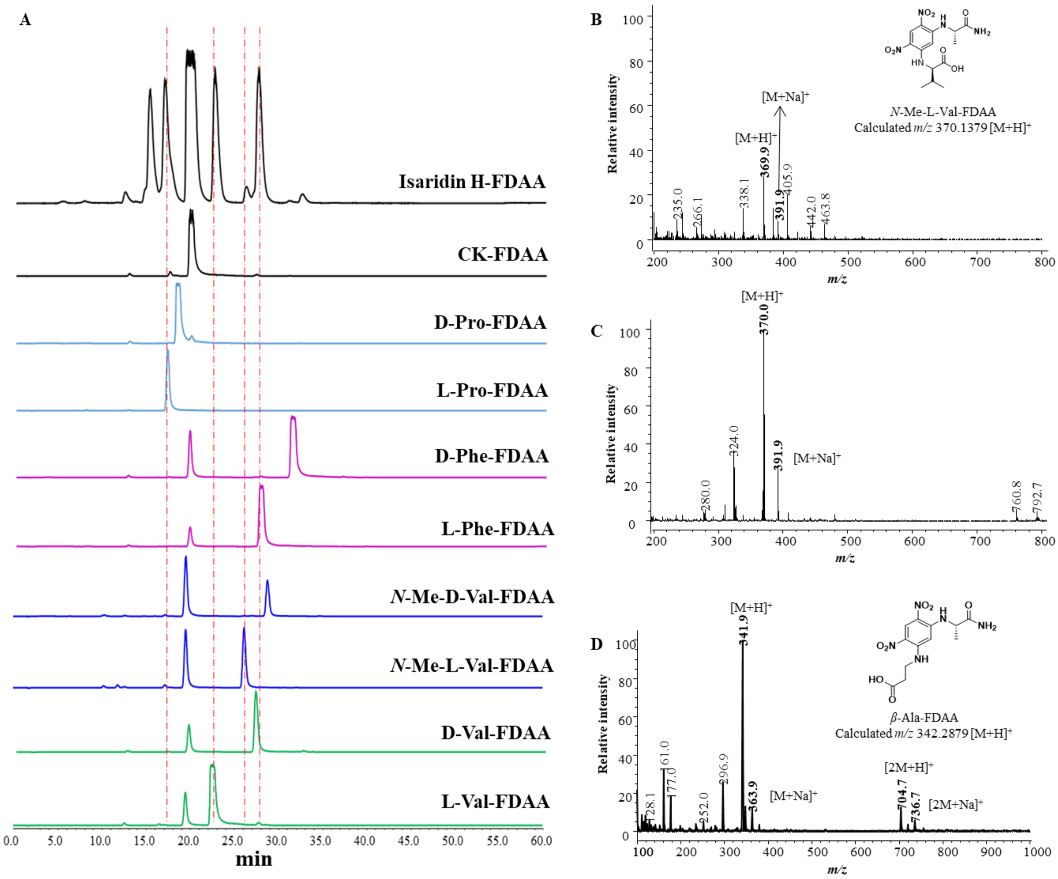

Fig. S7 The amino acid absolute configuration of compound **1** confirmed by the advanced Marfey's method and detected by HPLC and LC-MS. **A.** The HPLC analysis for Marfey's reaction products of compound **1**. **B.** The MS spectrum of the Marfey's reaction product of *N*-Me-L-Val standard. **C.** The MS spectrum of *N*-Me-L-Val-FDAA in the Marfey's reaction products of compound **1**. **D.** The MS spectrum of *β*-Ala-FDAA in the Marfey's reaction products of compound **1**.

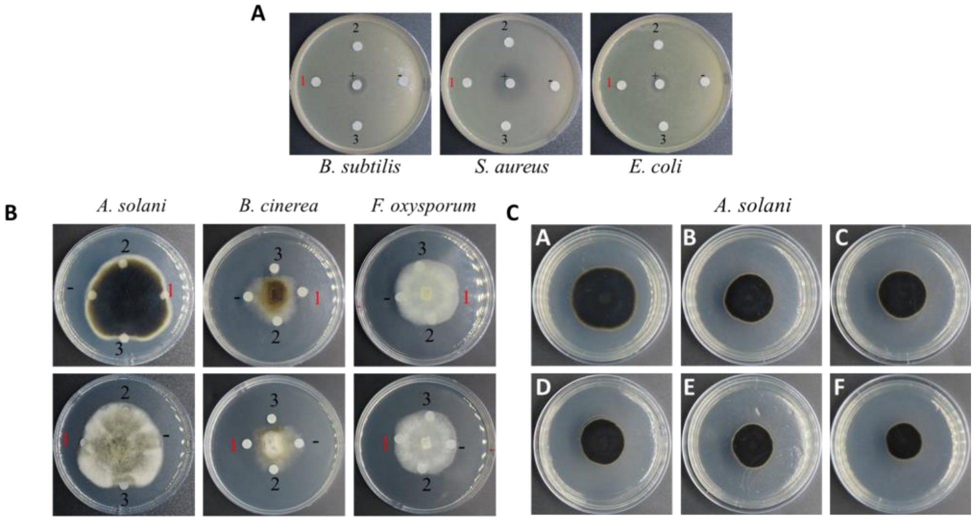

Fig. S8 Assay of isaridins (**1, 2, 3**) for antibacterial and antifugal activity. **A.** Antibacterial activities of isaridins against *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus*. Control (Ampicillin, DMSO) **B.** Antifungal activities of isaridins against *Alternaria solani*, *Botrytis cinerea*, *Fusarium oxysporum*. Control (DMSO) **C.** Inhibition of mycelial growth in *A. solani* by isaridin H (**1**). A-F represent control (100% DMSO) and 0.63, 1.25, 2.5, 5 and 10 μg/mL sample, respectively.

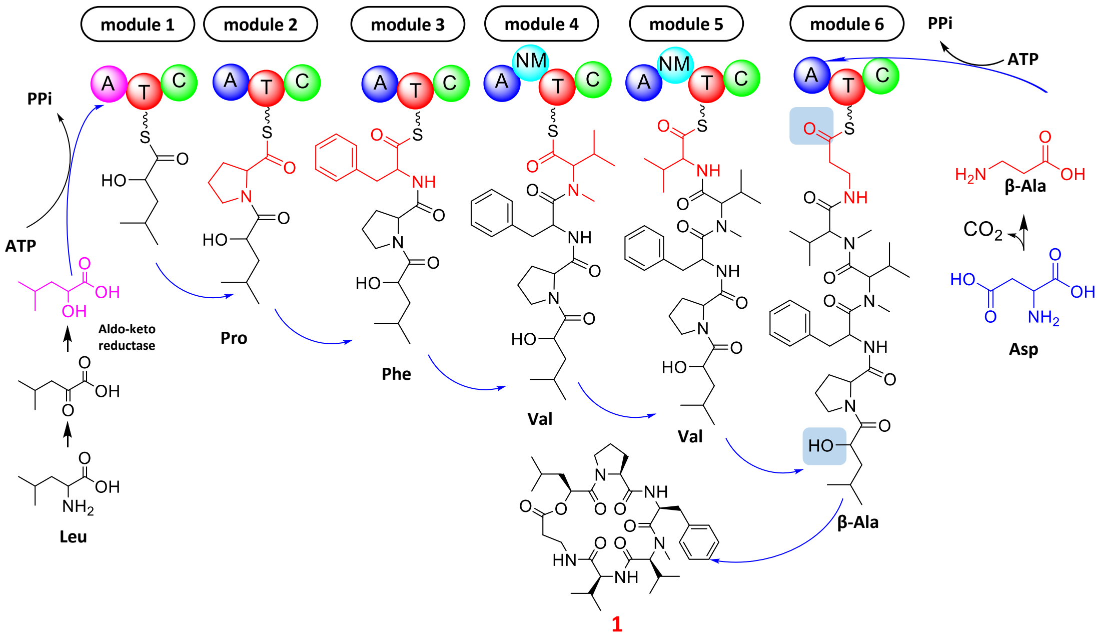

Fig. S9 Proposed isaridin H (1) biosynthetic model in *A. guana*.

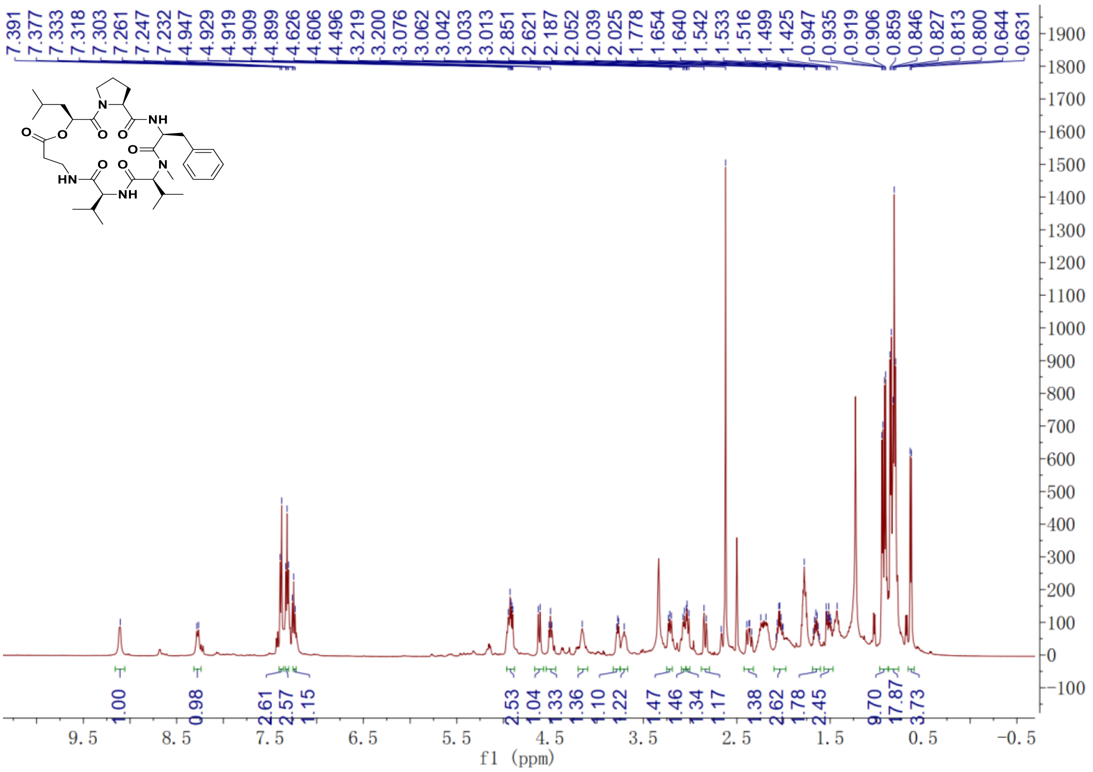

Fig. S10 ^{1}H NMR spectrum of **1** in DMSO-*d*6.

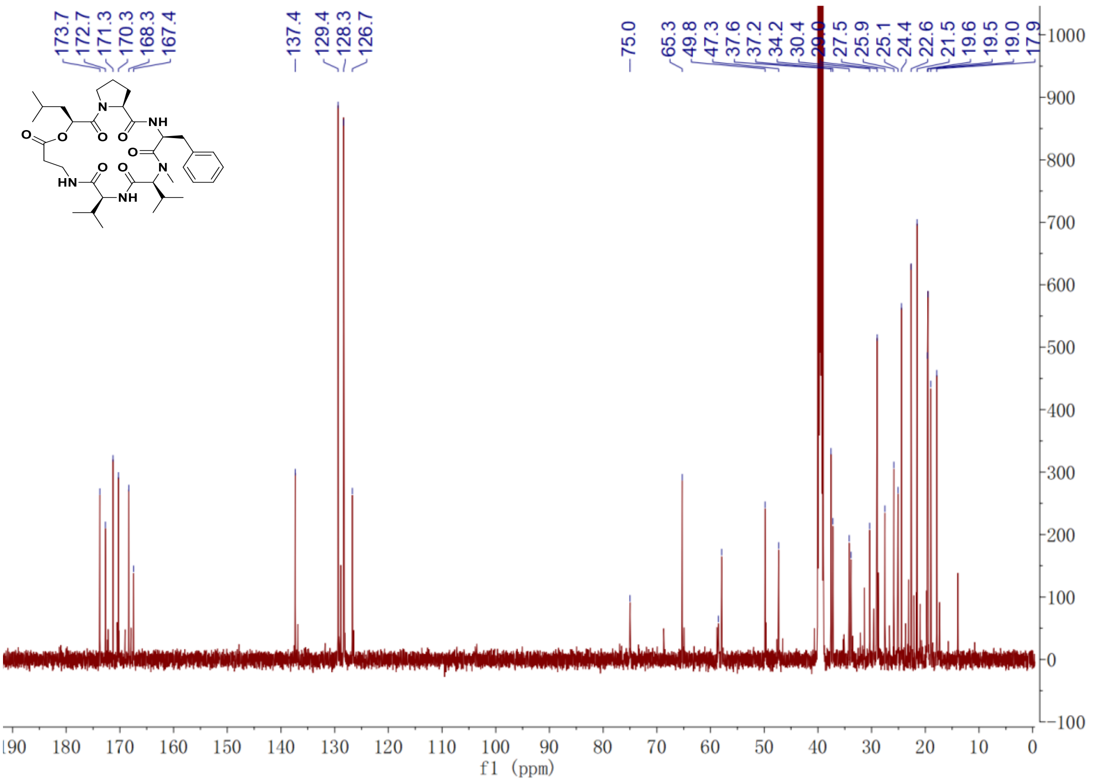

Fig. S11 ^{13}C NMR spectrum of **1** in DMSO-*d*6.

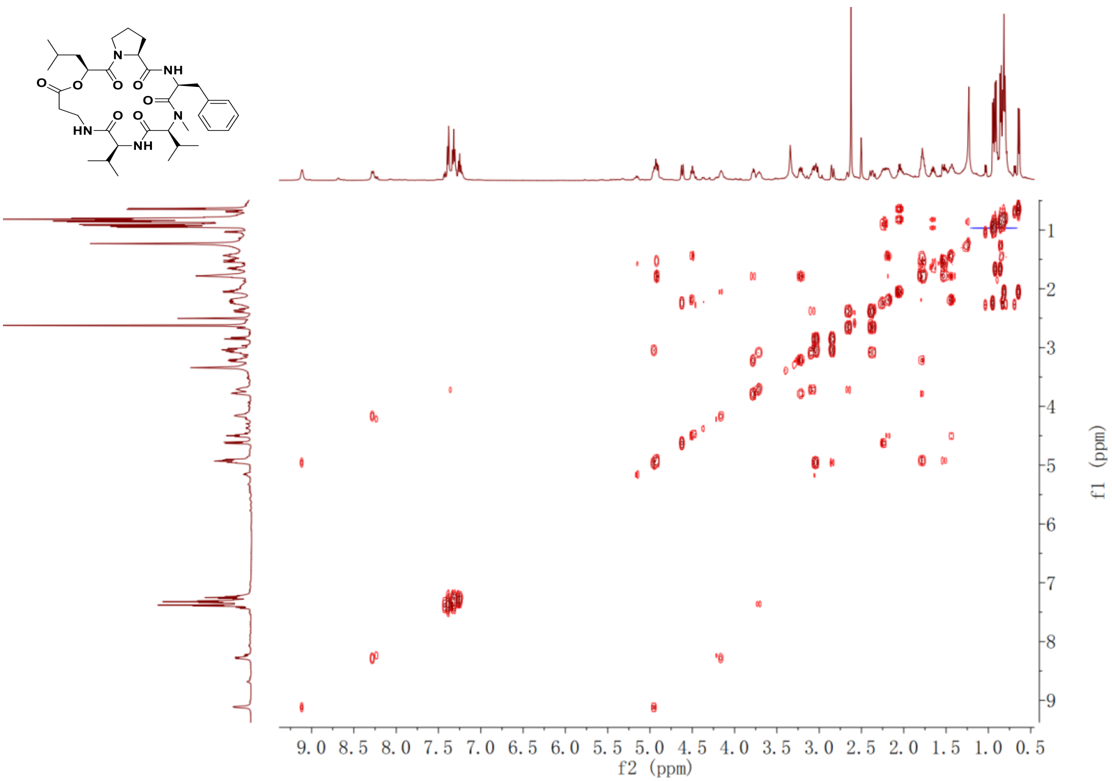

Fig. S12 ^{1}H -^{1}H COSY spectrum of **1** in DMSO-*d*6.

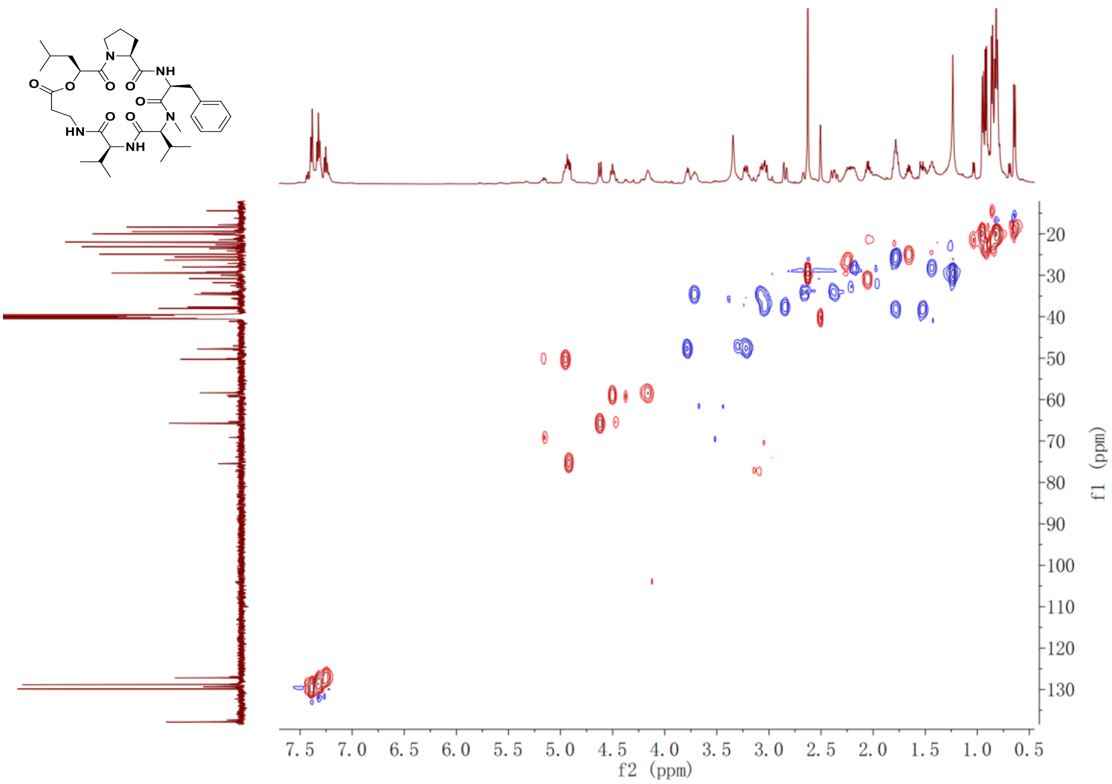

Fig. S13 HSQC spectrum of **1** in DMSO-*d*6.

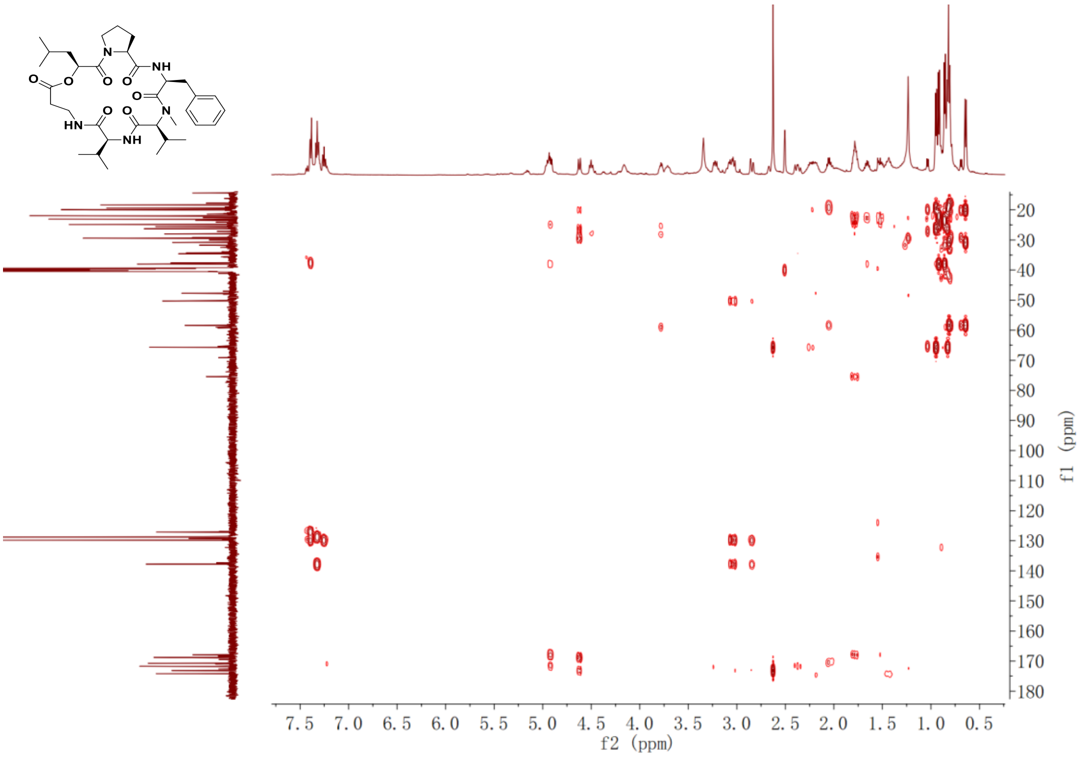

Fig. S14 HMBC spectrum of **1** in DMSO-*d*6.

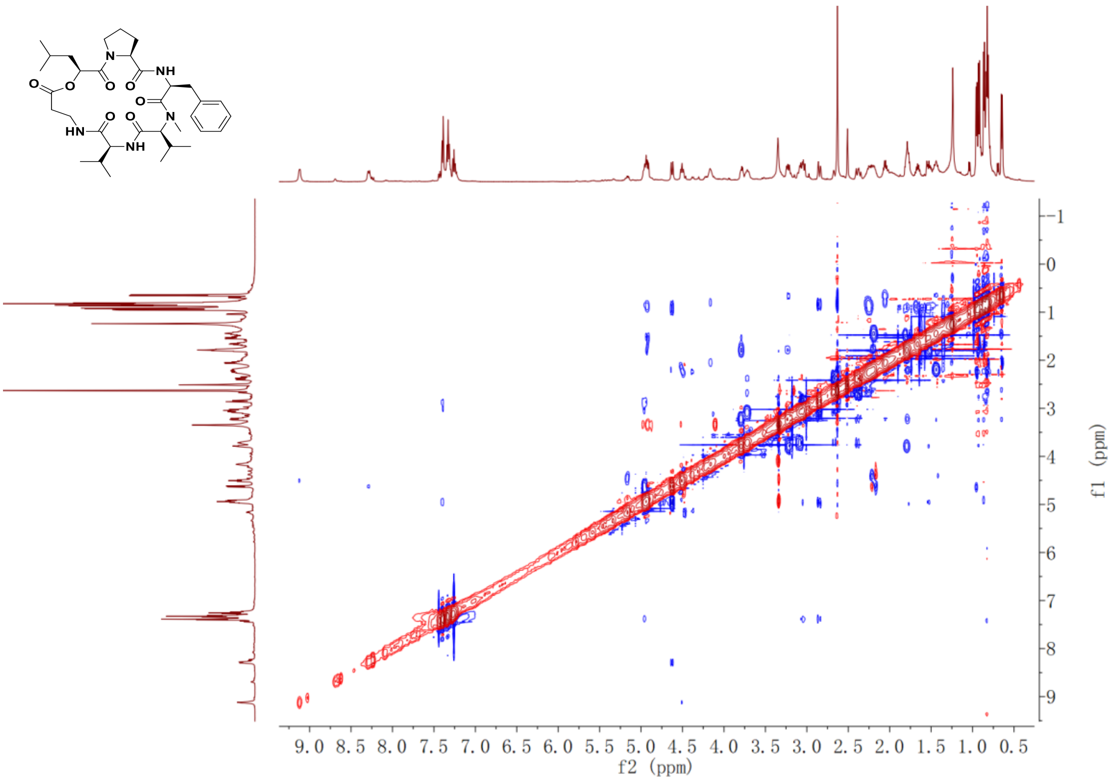

Fig. S15 ROESY spectrum of **1** in DMSO-*d*6.

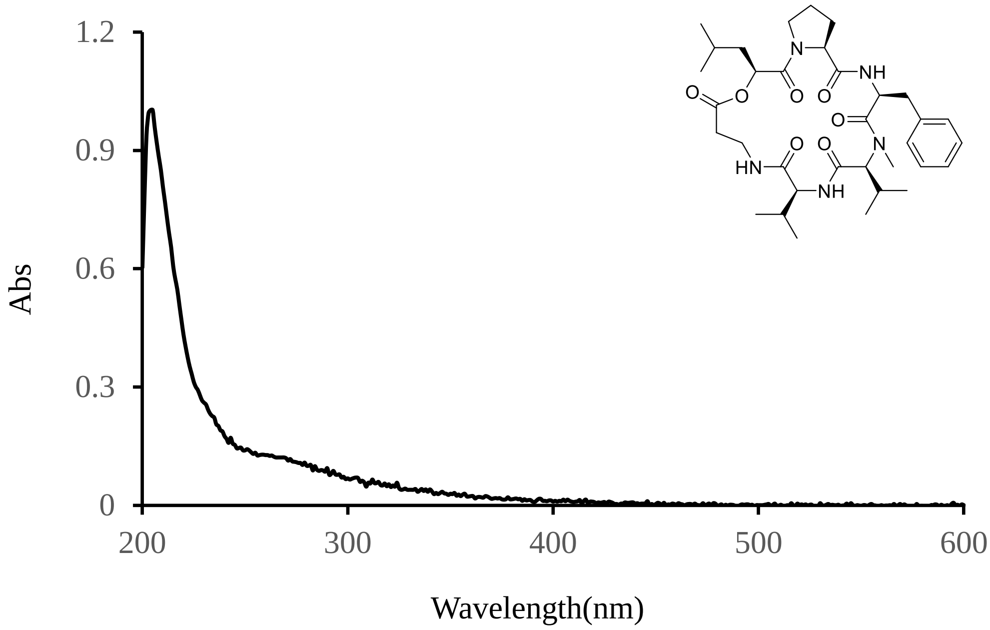

Fig. S16 UV spectrum of **1**.

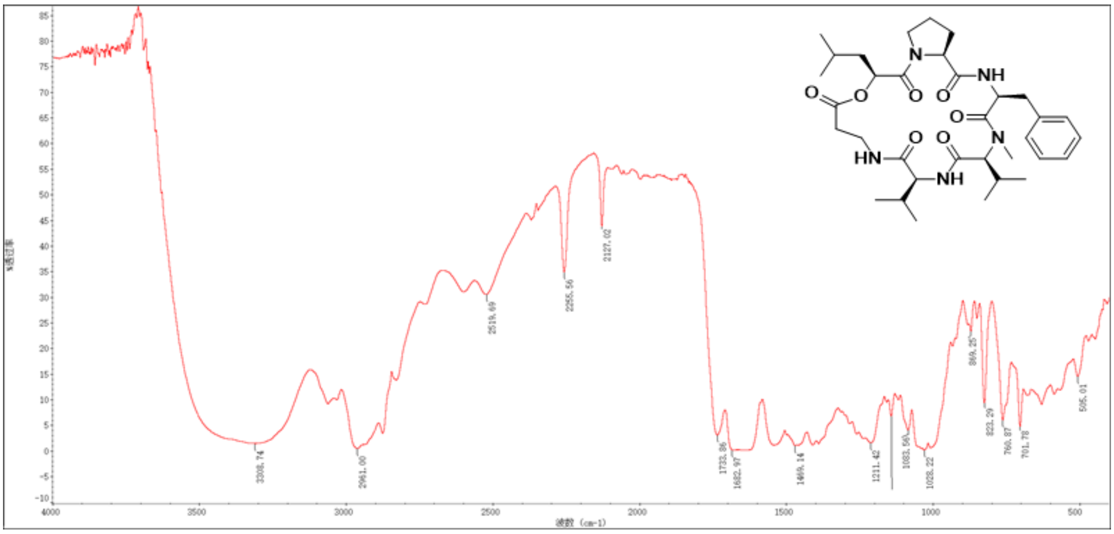

Fig. S17 IR spectrum of **1**.

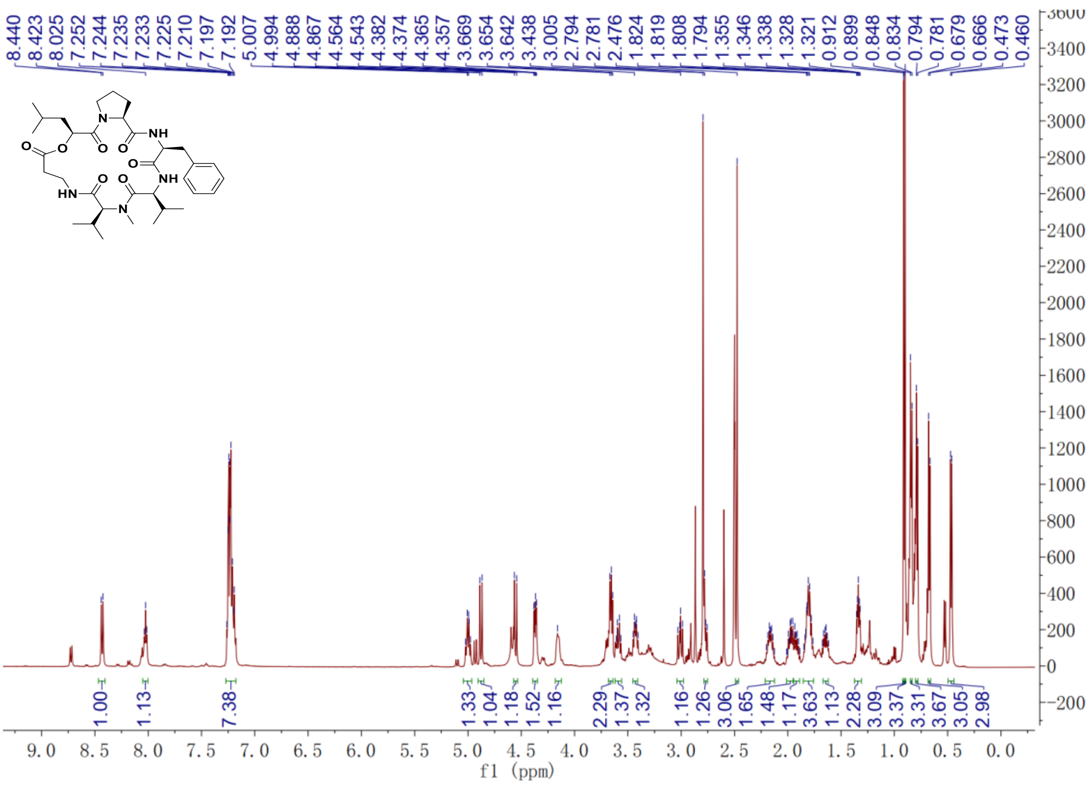

Fig. S18 ^{1}H NMR spectrum of **2** in DMSO-*d*6.

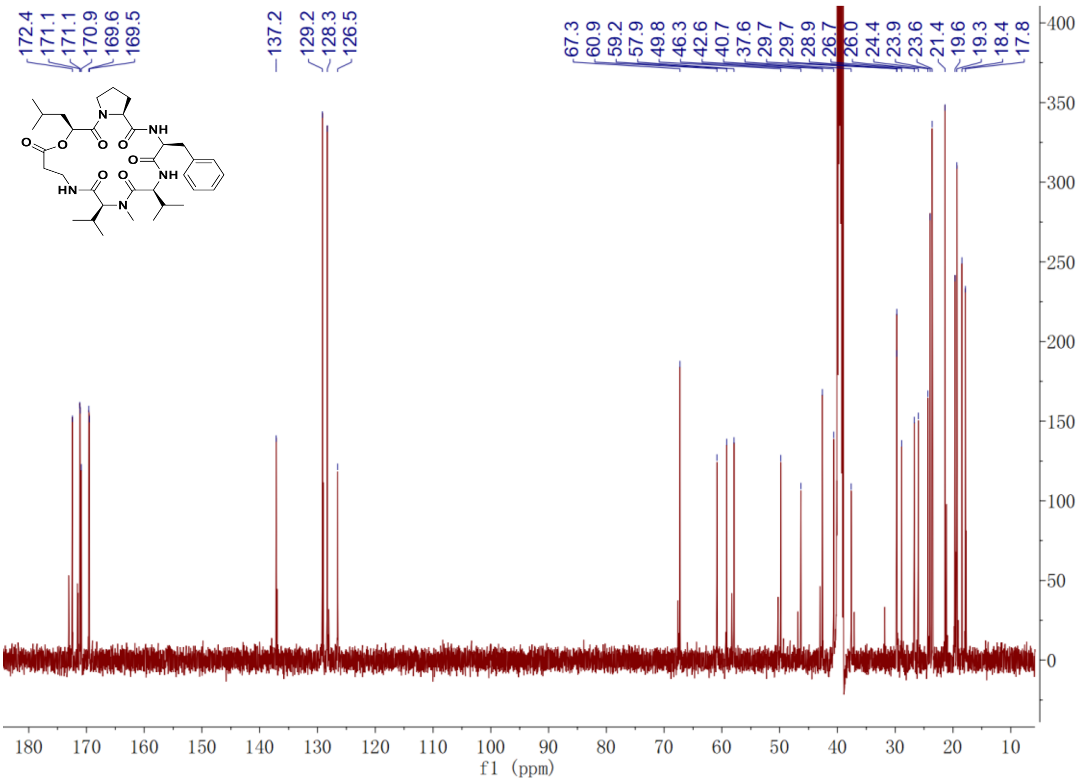

Fig. S19 ^{13}C NMR spectrum of **2** in DMSO-*d*6.

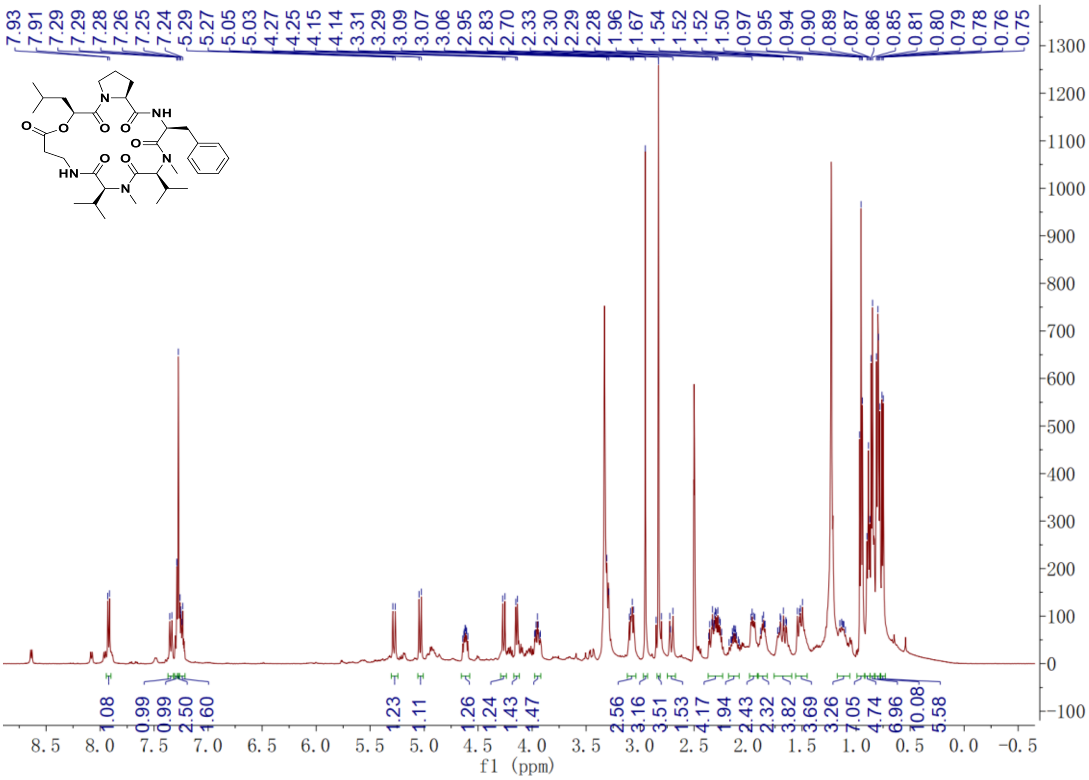

Fig. S20 ^{1}H NMR spectrum of **3** in DMSO-d6.

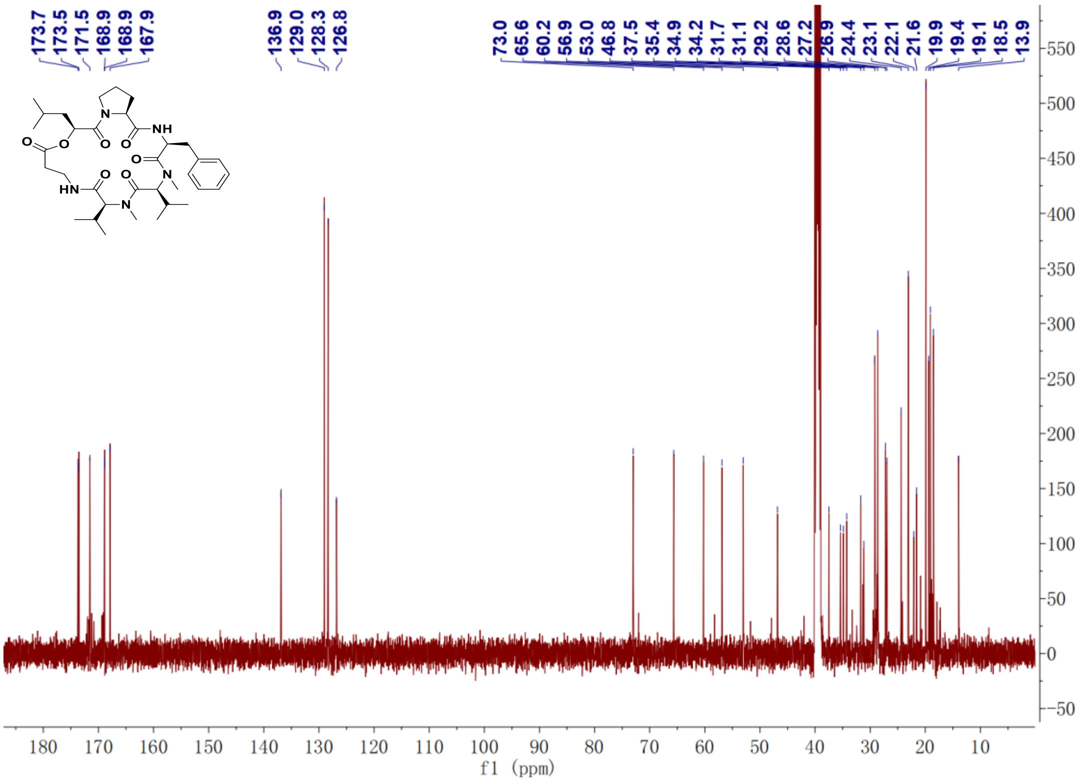

Fig. S21 ^{13}C NMR spectrum of **3** in DMSO-*d*6.

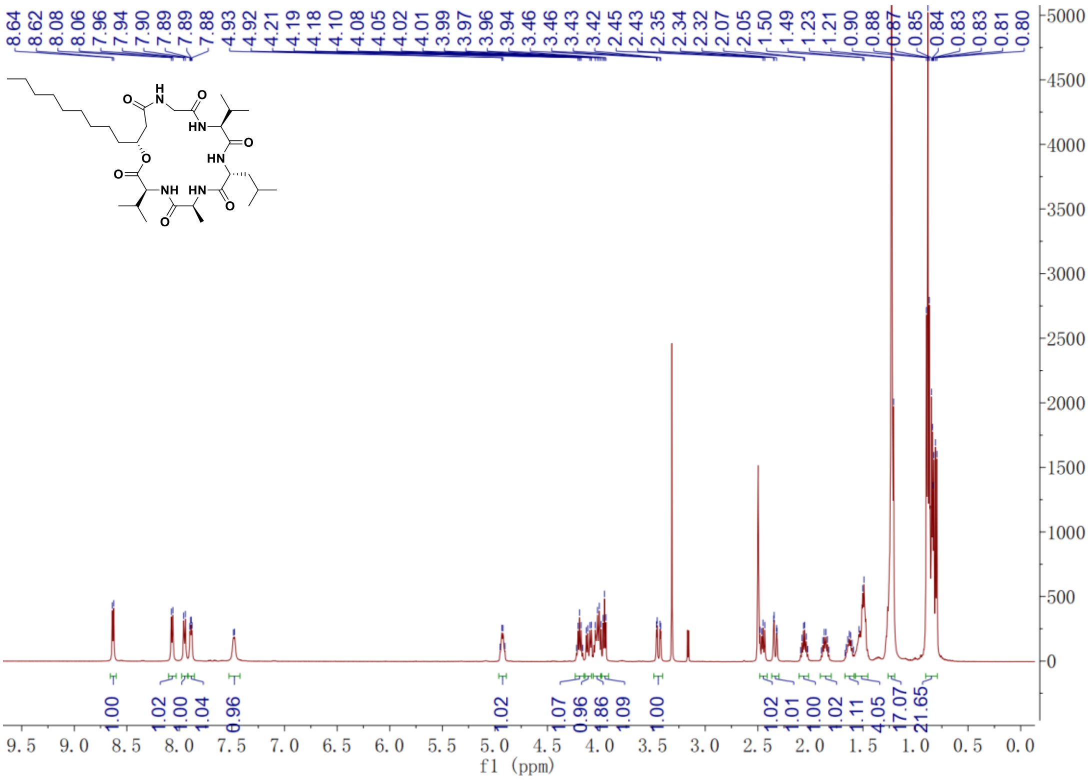

Fig. S22 ^{1}H NMR spectrum of **4** in DMSO-*d*6.

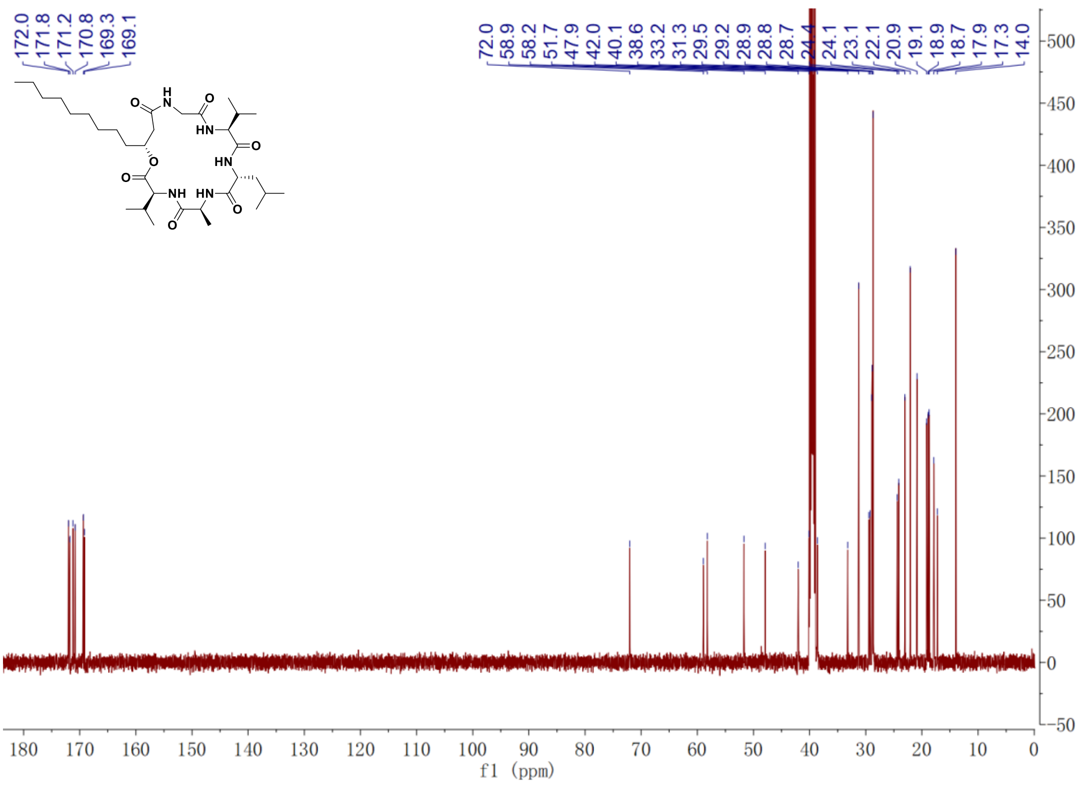

Fig. S23 ^{13}C NMR spectrum of **4** in DMSO-*d*6.

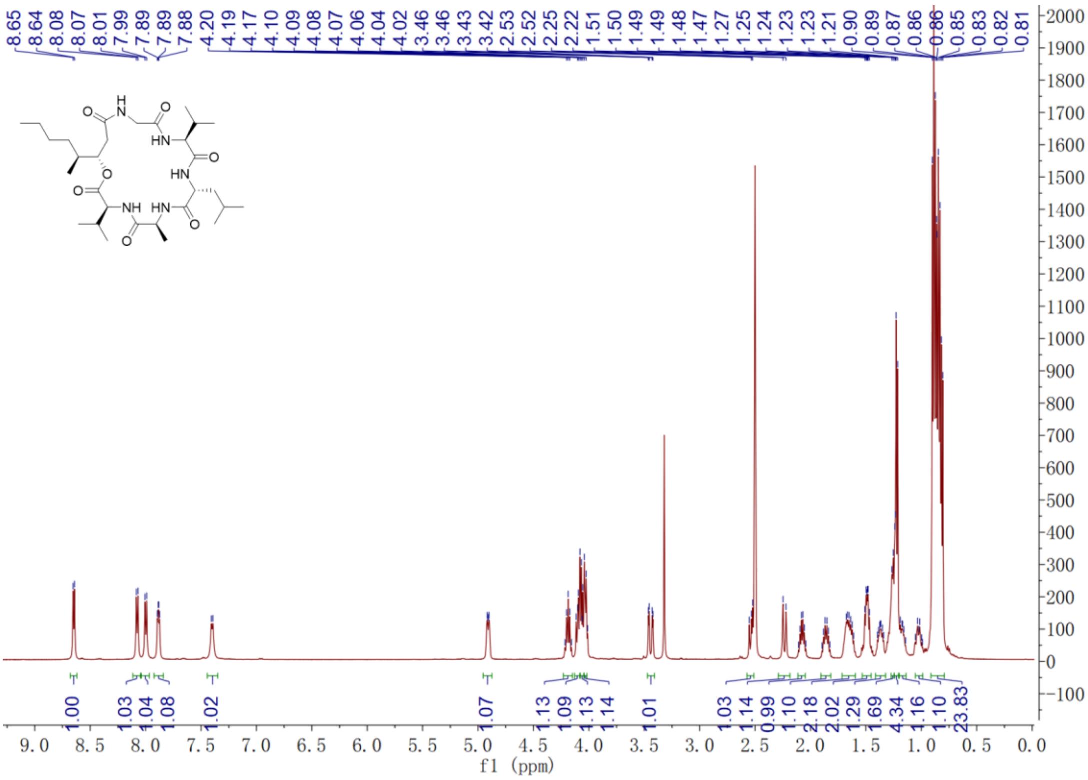

Fig. S24 ^{1}H NMR spectrum of **5** in DMSO-*d*6.

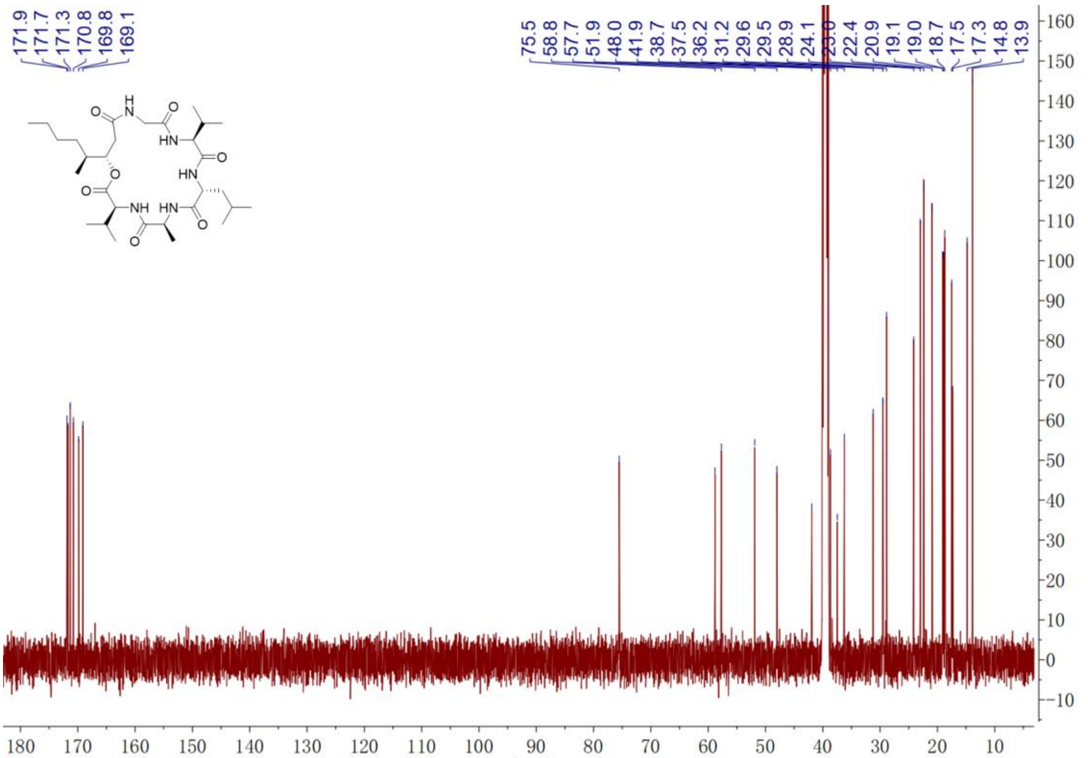

Fig. S25 ^{13}C NMR spectrum of **5** in DMSO-*d6*.

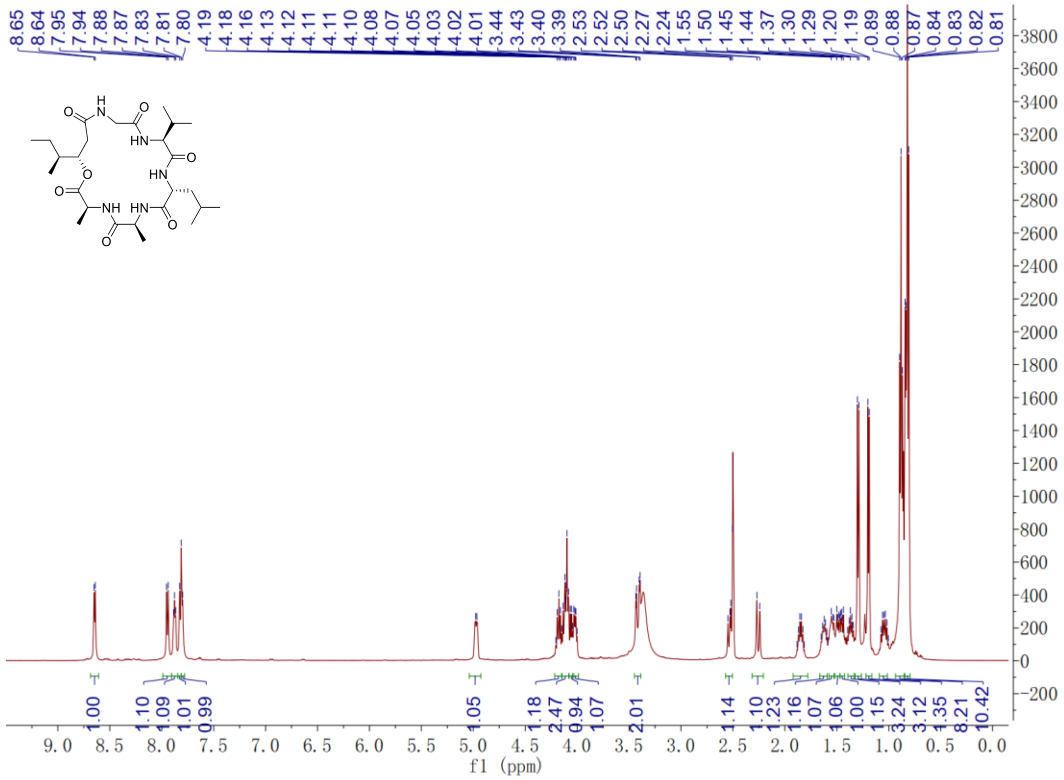

Fig. S26 ^{1}H NMR spectrum of **6** in DMSO-*d*6.

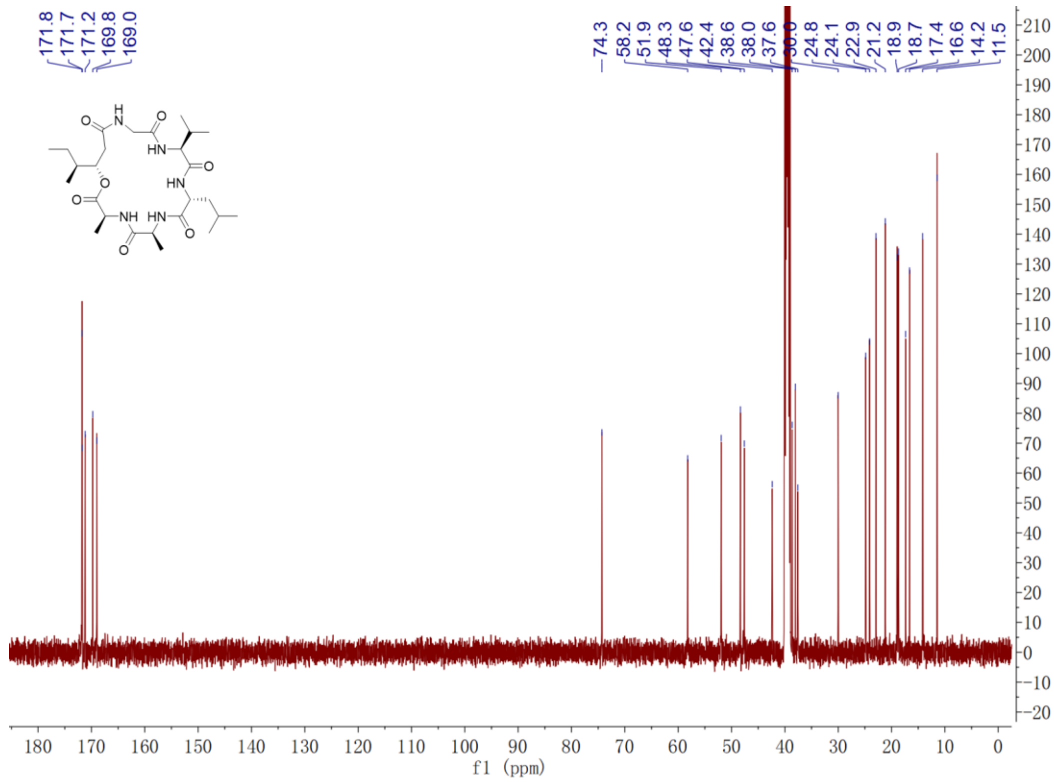

Fig. S27 ^{13}C NMR spectrum of **6** in DMSO-*d6*.

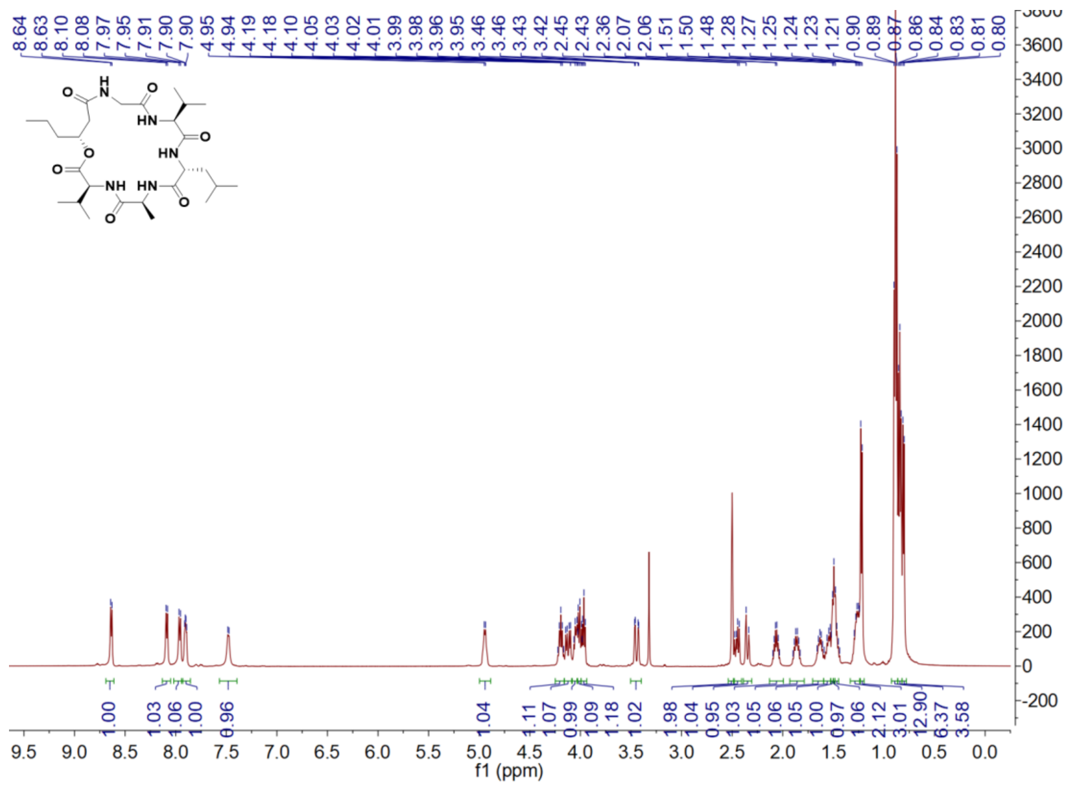

Fig. S28 ^{1}H NMR spectrum of **7** in DMSO-*d*6.

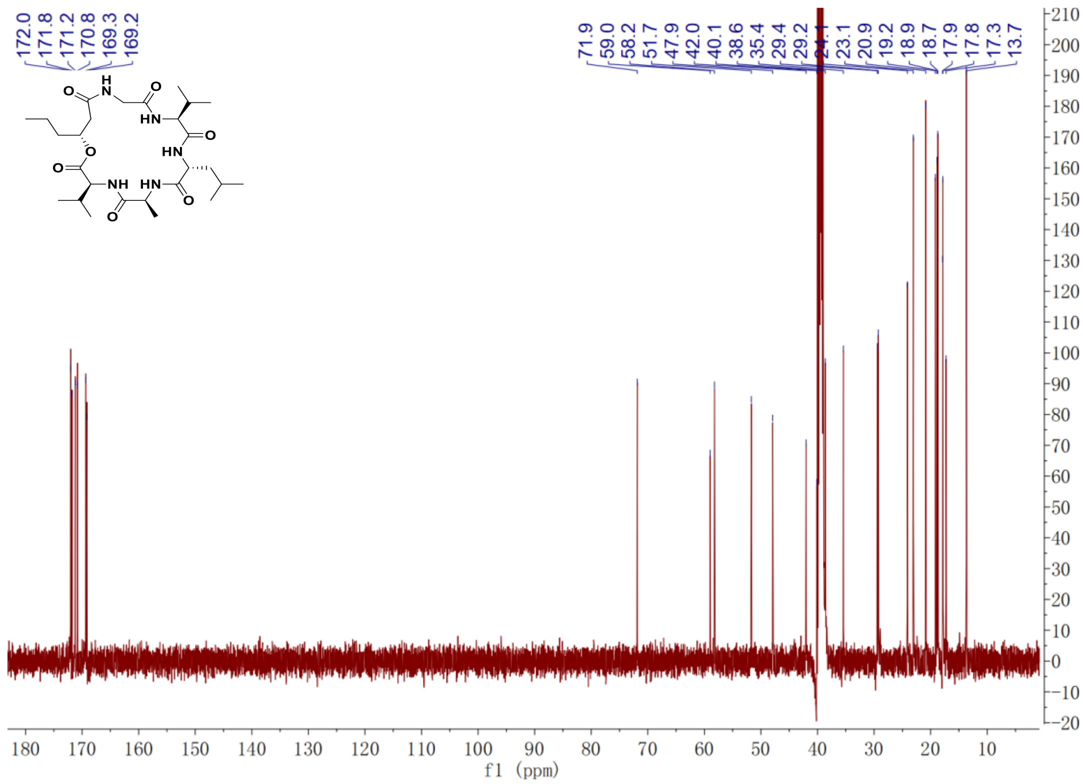

Fig. S29 ^{13}C NMR spectrum of **7** in DMSO-*d*6.

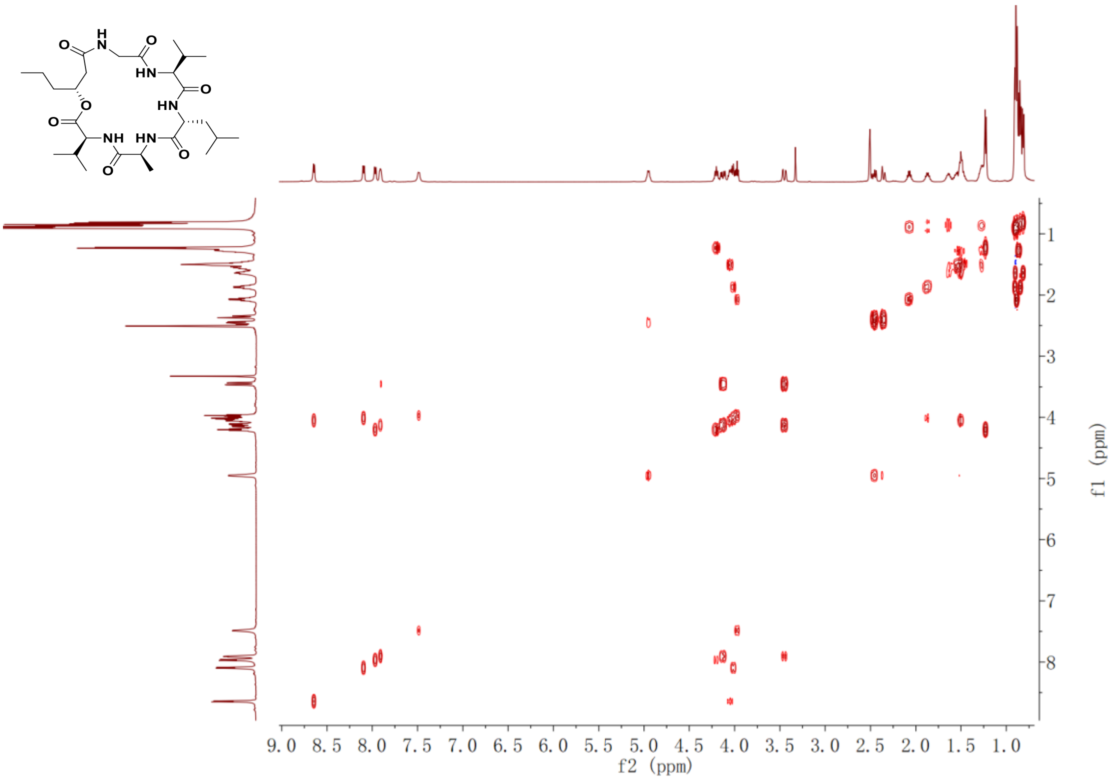

Fig. S30 ^{1}H -^{1}H COSY spectrum of **7** in DMSO-*d6*.

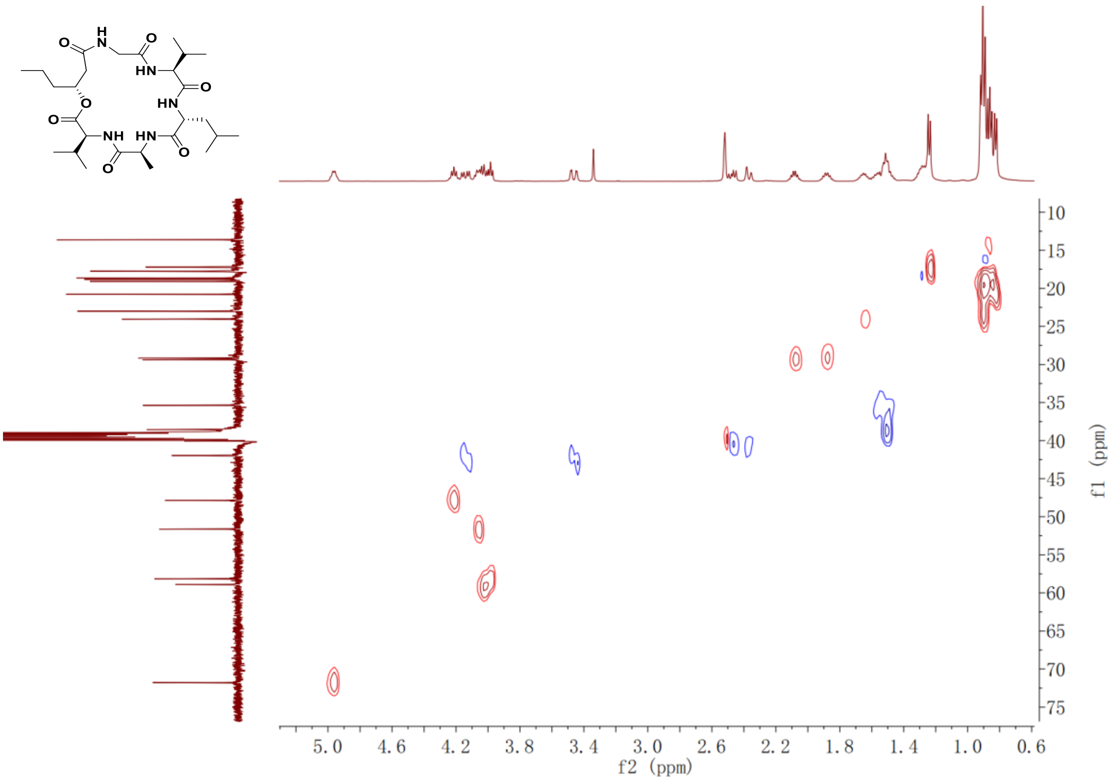

Fig. S31 HSQC spectrum of **7** in DMSO-*d6*.

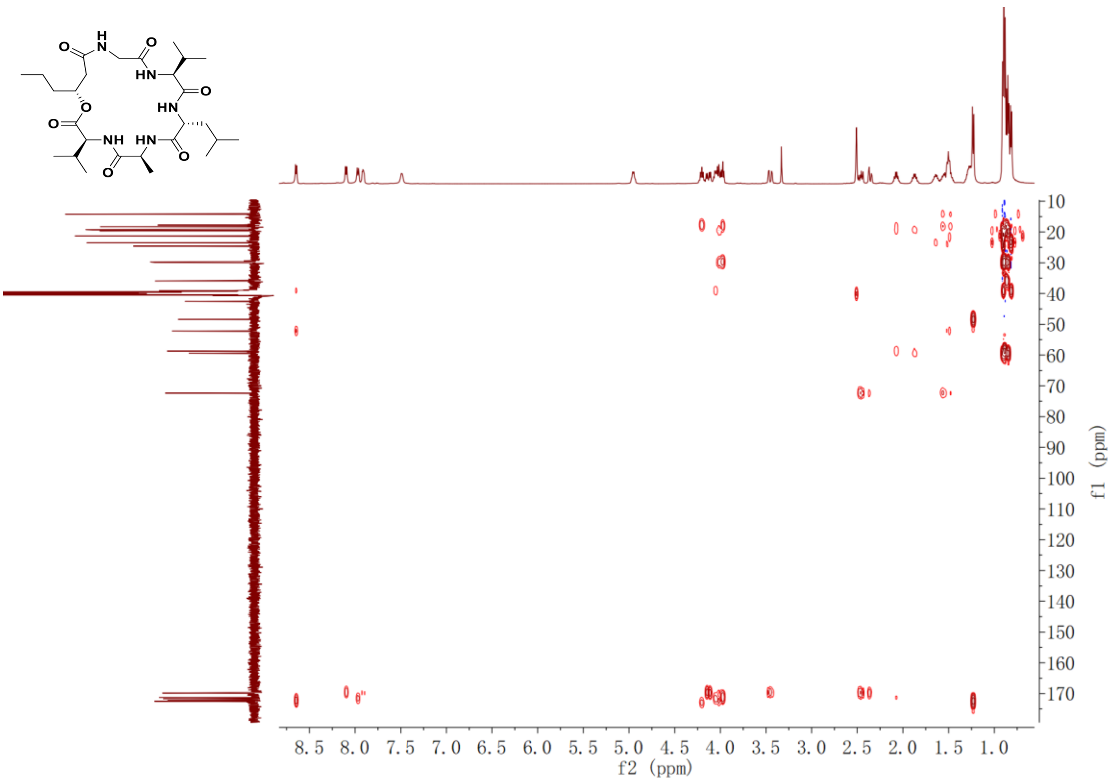

Fig. S32 HMBC spectrum of **7** in DMSO-*d6*.

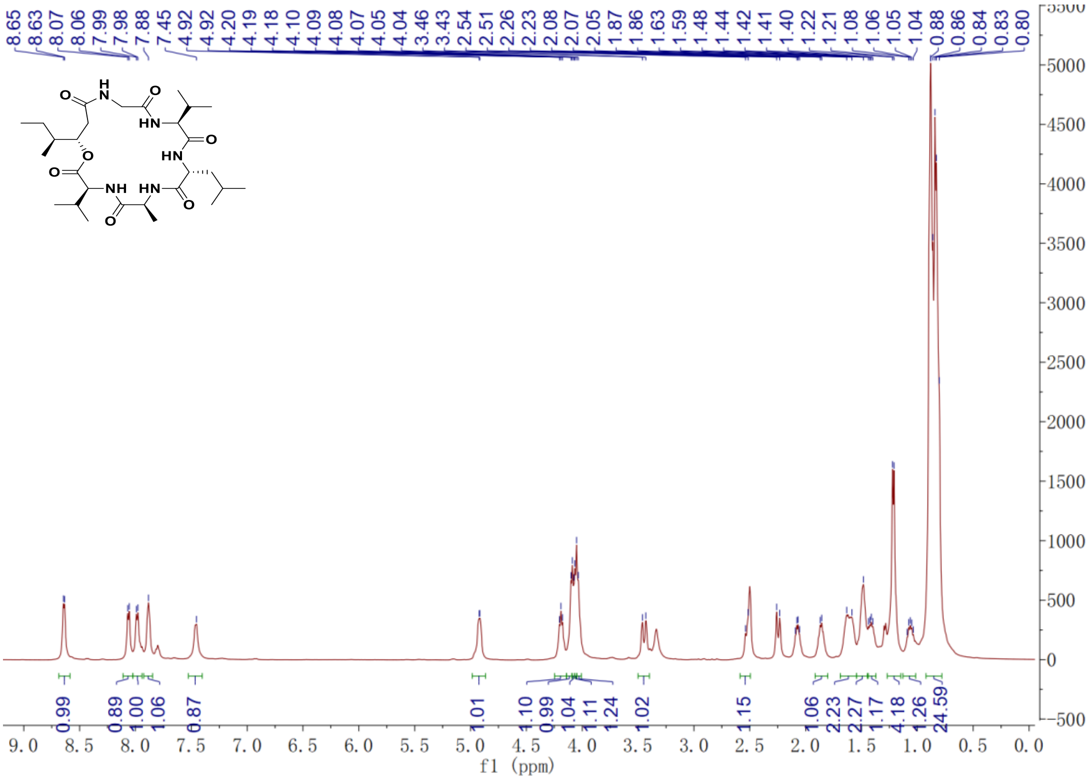

Fig. S33 ^{1}H NMR spectrum of **8** in DMSO-*d*6.

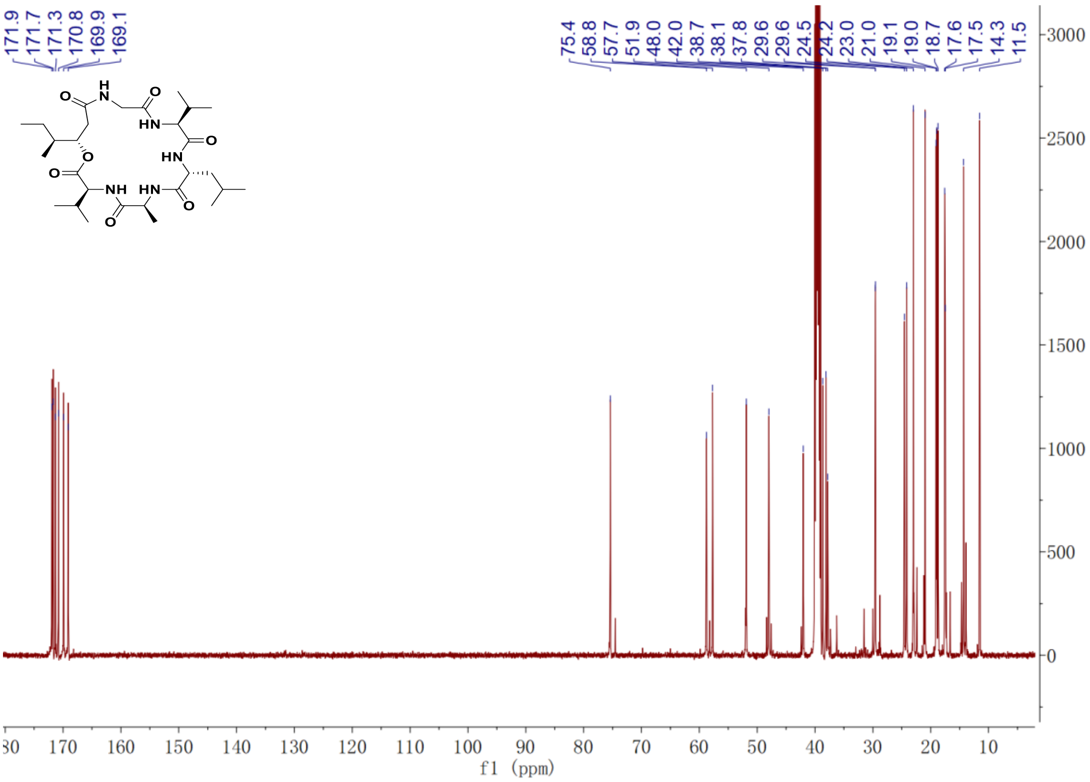

Fig. S34 ^{13}C NMR spectrum of **8** in DMSO-*d*6.

4. Supplementary references

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