Supporting Information

Total Biosynthesis of Cotylenin Diterpene Glycosides as 14-3-3 Protein-Protein Interaction Stabilizers

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General

High-resolution electrospray ionization mass spectrometry (HRESIMS) was obtained on Fisher LC-LTQ-Orbitrap XL spectrometer. HPLC-MS analyses were recored on Agilent 1290 Infinity Ⅱ-6545B Q-TOF. NMR spectroscopic data were measured on Bruker AM-600 NMR spectrometer with $CDCl_3$, CD_3OD and CD_3OCD_3 as solvent. Silica gel (100-200 mesh, 200-300 mesh, Qingdao Marine Chemical Inc., China) were used in the chromatography processes. Oligonucleotides for PCRs were purchased from Sangon Biotech (shanghai) Co., Ltd.

Strains

Escherichia coli DH5α was used for cloning and following standard recombinant DNA techniques. *Escherichia coli* BL21 was used for protein expression. *Aspergillus oryzae* NSAR1, a quadruple auxotrophic mutant (*niaD*$^{-}$, *sC*$^{-}$, *adeA*$^{-}$, and *argB*$^{-}$) was used as the host for gene expression. *Talaromyces adpressus* and *Alternaria brassicicola* XXC were grown on potato dextrose agar at 30℃ for 4 days was used for gDNA extraction. *Saccharomyces cerevisiae* RC01, which contains a chromosome-integrated gene encoding a cytochrome P450 reductase (CPR) from *Aspergillus terreus*, was used for P450 gene overexpression[1].

Genomic DNA preparation.

Mycelia of *Talaromyces adpressus* and *Alternaria brassicicola* XXC were grown in potato dextrose agar (PDA) at 30℃ for 4 days, which then were collected and lyophilized with liquid nitrogen. The mycelia were grinded via Tissuelyser (Shanghai Jinxing Co., Ltd, China). Then gnomonic DNA were extracted by fugal gnomonic DNA extraction kit (BioFlux) according to the instruction of the manufacturer.

Plasmid construction.

The primers used in this study were listed in Table S1. The recombinant plasmids were summarized in Table S2.

To construct expression plasmids for *Aspergillus oryzae,* the genes *abnA, abnB, abnC, abnD, abnE, ctyA, ctyB, ctyD, ctyE, ctyF, ctyJ* were amplified from the genomic DNA of *Alternaria brassicicola* XXC and *Talaromyces adpressus* respectively, the sequences of *Pa-orf11* was purchased from Nanjing GenScript Inc., China. Linker region of the fellow plasmids was amplified from pAdeA2. Twelve expression plasmids were constructed as follows. The KpnI digested fragments of pUSA2 plasmid were subjected to Gibson assembly (NEBuilder HiFi DNA Assembly Master Mix, New England BioLabs) with *abnE* to construct pUSA2-*abnE*. pAdeA2-*ctyA*, pAdeA2-*ctyB*, pUARA2-*ctyA,* pUSA2-*ctyE* and pAdeA2-*ctyF* were similarly constructed by Gibson assembly. The KpnI and NheI digested fragments of pAdeA2 plasmid were subjected to Gibson assembly (NEBuilder HiFi DNA Assembly Master Mix, New England BioLabs) with *abnA*, *abnB* and corresponding linker to construct pAdeA2-*abnAB*. The pAdeA2-*ctyBD*, pUSA2-*ctyEJ,* pUARA2-*ctyAJ,* pUARA2-*ctyA-Pa-orf11* and pUARA2-*abnCD* were also constructed by Gibson assembly.

For CtyD, CtyE, CtyJ, Pa-orf11, 14-3-3ζ proteins preparation, *ctyD*, *ctyE*, *ctyJ* were amplified from the genomic DNA of *Talaromyces adpressus*, the sequences of *Pa-orf11*and human 14-3-3 proteins isoforms ζ were purchased from Nanjing GenScript Inc., China. The EcoRI and NcoI

digested fragments of pETM41 plasmid were subjected to Gibson assembly (NEBuilder HiFi DNA Assembly Master Mix, New England BioLabs) with *ctyD* to construct pETM41-*ctyD*. The EcoRI and XhoI digested fragments of pET28a plasmid were subjected to Gibson assembly (NEBuilder HiFi DNA Assembly Master Mix, New England BioLabs) with *ctyE* to construct pET28a-*ctyE*. pET28a-*ctyJ,* pET28a-*Pa-orf11*, *and* pET28a-*14-3-3ζ* were similarly constructed by Gibson assembly.

To express *ctyA* gene in *S. cerevisiae*, the intron-free *ctyA* was amplified from the cDNA of recombinant *AO-ctyA* strain. The SpeI and PmlI digested fragments of XW55 plasmid was subjected to Gibson assembly (NEBuilder HiFi DNA Assembly Master Mix, New England BioLabs) with intron-free *ctyA* to construct XW55-*ctyA*.

Transformation of *A. oryzae*.

Transformation of *A. oryzae* was performed by the protoplast-polyethylene glycol method reported previously to construct the following transformants[2]; *AO-abnABCDE, AO-ctyA*, *AO-ctyB*, *AO-ctyF*, *AO-ctyBD, AO-ctyBDE*, *AO-ctyBDEJ, AO-ctyABDEJ. AO-ctyABDJ, and AO-ctyABD-Pa-orf11.* Plasmids used for the construction of each transformant are summarized in **Table S2.**

Brassicicene I (8) isolated from *AO-abnABCDE.*

Spore suspension of transformant *AO-abnABCDE* was inoculated into MPY medium (3% maltose, 1% hipolypeptone, 0.5% yeast extract, 0.925% $(NH_4)_2SO_4$, 200 mL) in 1000 mL Erlenmeyer flasks. Each culture was added 3 g Amberlite XAD-16 packaged in tea bag. After incubating for 3 to 5 days at 30 ˚C, the Amberlite XAD-16 and liquid part were separated by filtration. Then the liquid part was extracted three times using EtOAc, the Amberlite XAD-16 was soaked with MeOH for three times. All the organic phase was concentrated in vacuo to afford crude extracts (2 g from 4 L of MPY medium), which was loaded on silica gel column chromatography (CC, 200–300 mesh) eluting with petroleum ether (PE)-ethyl acetate (EtOAc) system (100:1→50:1→30:1→15:1→8:1) to yield five fractions (A–E). Brassicicene I (**8**) (60 mg) was obtained from the fraction E.

Brassicicene I (**8**); colorless oil, [α]25 D： +27˚ (c 0.11, CH_3OH). ^1H and ^{13}C NMR data are in good agreement with reported ones[3].

Extraction of the metabolites from the biotransformation *AO-ctyF*, *AO-ctyB, AO-ctyBD, AO-ctyBDE, AO-ctyBDEJ, AO-ctyABDEJ, AO-ctyABDJ, and AO-ctyABD-Pa-orf11*.

Spore suspension of each transformant was inoculated into MPY medium (3% maltose, 1% hipolypeptone, 0.5% yeast extract, 10 mg adenine, 100 mL) in 500 mL Erlenmeyer flasks. Each culture was incubated at 30 ˚C for 1 day. Each culture was added brassicicene I (**8**) (0.05 mmol/L) and was continued to incubate at 30 ˚C for 3 days. If appropriate, the mycelia and culture broth was separated prior to extraction. After the extraction with EtOAc, the extract was concentrated in vacuo to afford crude extracts. The crude extracts were analyzed by LC-MS with Eclipse Plus C18 column (2.1 × 100 mm, 3.5 μm) at the following condition unless otherwise noted; CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. The concentration of CH_3CN was linearly increased from 5% to 98% over 11 min and kept at 100% for 2 min. Flow rate was kept at 0.5 ml min^{-1}. The column temperature was kept at 25 ˚C. Metabolites were analyzed in ESI positive mode.

Extraction of the metabolites from *Aspergillus oryzae NSAR1* and AO-*ctyA.*

Spore suspension of *Aspergillus oryzae NSAR1* and *AO-ctyA* were inoculated into MPY

medium (3% maltose, 1% hipolypeptone, 0.5% yeast extract, 10 mg adenine, 100 mL) in 50 mL Erlenmeyer flasks. Each culture was incubated at 30 ˚C for 1 day. **4** and **3** (0.05 mmol/L) were added to the culture of *AO-ctyA* and *Aspergillus oryzae NSAR1* respectively. Then the culture of *Aspergillus oryzae NSAR1* was continued to incubate at 30 ˚C for 3 days, and the culture of *AO-ctyA* was continued to incubate at 30 ˚C for 1.5, 2.5, 3.5 days. If appropriate, the mycelia and culture broth was separated prior to extraction. After the extraction with EtOAc, the extract was concentrated in vacuo to afford crude extracts. The crude extracts were analyzed by LC-MS with Eclipse Plus C18 column (2.1 × 100 mm, 3.5 μm) at the following condition unless otherwise noted; CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. The concentration of CH_3CN was linearly increased from 5% to 98% over 11 min and kept at 100% for 2 min. Flow rate was kept at 0.5 ml min^{-1}. The column temperature was kept at 25 ˚C. Metabolites were analyzed in ESI positive mode.

Fusicocca 2,10(14)-diene isolated from *AO-ctyF*

The crude extracts (1.1 g from 4 L of MPY medium) were loaded on silica gel column chromatography (CC, 200–300 mesh) eluting with petroleum ether (PE) to yield Fusicocca 2,10(14)-diene (18.3mg) as colorless solid. The NMR data are in good agreement with the reported data[4].

Compound 7 isolated from *AO-ctyB*

The crude extracts (1.5 g from 4 L of MPY medium) were loaded on silica gel column chromatography (CC, 200–300 mesh) eluting with petroleum ether (PE)-ethyl acetate (EtOAc) system (100:1→50:1→20:1→10:1→5:1) to yield five fractions (A–E). Cotylenol (28.2 mg) was obtained from the fraction E.

Compound **7**; colorless solid, HR-ESIMS: calcd. for $C_{21}H_{34}O_4$ $[M+Na]^+$: 373.2349, found: 373.2352. [α]25 D： -88˚ (c 0.11, CH_3OH).

Compound 6 isolated from *AO-ctyBD*

The crude extracts (1.3 g from 4 L of MPY medium) were purified with silica gel column chromatography (DCM:MeOH), stepwise elution from 500:1 to 2:1). Purification of partially purified metabolites with HPLC equipped with ZORBAX SB-C18 (9.4 × 250 mm, 5 μm) at the conditions (27% acetonitrile at a flow rate of 2.0 mL min^{-1}) gave **6** (16.2 mg).

Compound **6**; colorless solid, HR-ESIMS: calcd. for $C_{27}H_{44}O_9$ $[M+Na]^+$: 535.2878, found: 535.2891. [[α]25 D: +61˚ (*c* 0.15, CH_3OH).

Cotylenin E (5) isolated from *AO-ctyABDEJ*

The crude extracts (3.5 g from 8 L of MPY medium) were purified with silica gel column chromatography ((*n*-hexane:EtOAc), stepwise elution from 50:1 to 0:1). Purification of partially purified metabolites with HPLC equipped with ZORBAX SB-C18 (9.4 × 250 mm, 5 μm) at the conditions (32% acetonitrile at a flow rate of 2.0 mL min^{-1}) gave **5** (10.2 mg).

Cotylenin E (5); colorless solid, HR-ESIMS: calcd. for $C_{28}H_{46}O_9$ $[M+Na]^+$: 549.3034, found: 549.3048. [α]25 D +59˚ (*c* 0.15, CH_3OH).

Cotylenin I (4) isolated from *AO-ctyBDEJ*

The crude extracts (1.2 g from 4 L of MPY medium) were purified with silica gel column

chromatography ((*n*-hexane:EtOAc), stepwise elution from 50:1 to 0:1). Purification of partially purified metabolites with HPLC equipped with ZORBAX SB-C18 (9.4 × 250 mm, 5 μm) at the conditions (45% acetonitrile at a flow rate of 2.0 mL min^{-1}) gave **4** (8.8 mg).
Cotylenin I (4); colorless solid, HR-ESIMS: calcd. for $C_{33}H_{54}O_9$ $[M+Na]^+$: 617.3660, found:617.3664. [α]25 D: +94˚ (*c* 0.15, CH_3OH).

Cotylenin F (3) isolated from *AO-ctyABDEJ*

The crude extracts (3.5 g from 8 L of MPY medium) were purified with silica gel column chromatography ((*n*-hexane:EtOAc), stepwise elution from 50:1 to 0:1). Purification of partially purified metabolites with HPLC equipped with ZORBAX SB-C18 (9.4 × 250 mm, 5 μm) at the conditions (39% acetonitrile at a flow rate of 2.0 mL min^{-1}) gave **3** (11.4 mg).
Cotylenin F (3); colorless solid, HR-ESIMS: calcd. for $C_{33}H_{54}O_{11}$ $[M+Na]^+$: 649.3558, found:649.3573. [α]25 D: +26˚ (*c* 0.15, CH_3OH).

Cotylenin C (2) isolated from *AO-ctyABDEJ*

The crude extracts (3.5 g from 8 L of MPY medium) were purified with silica gel column chromatography ((*n*-hexane:EtOAc), stepwise elution from 50:1 to 0:1). Purification of partially purified metabolites with HPLC equipped with ZORBAX SB-C18 (9.4 ×× 250 mm, 5 μm) at the conditions (39% acetonitrile at a flow rate of 2.0 mL min^{-1}) gave **2** (11.4 mg).
Cotylenin C (2); colorless solid, HR-ESIMS: calcd. for $C_{33}H_{52}O_{11}$ $[M+Na]^+$: 647.3402, found:647.3399. [α]25 D: +139˚ (*c* 0.15, CH_3OH).

12 isolated from *AO-ctyABDJ*

The crude extracts (3.5 g from 8 L of MPY medium) were purified with silica gel column chromatography ((*n*-hexane:EtOAc), stepwise elution from 50:1 to 0:1). Purification of partially purified metabolites with HPLC equipped with ZORBAX SB-C18 (9.4 × 250 mm, 5 μm) at the conditions (39% acetonitrile at a flow rate of 2.0 mL min^{-1}) gave **12** (1.8 mg).
12; colorless solid, HR-ESIMS: calcd. for $C_{32}H_{52}O_{10}$ $[M+Na]^+$: 619.3453, found:619.3460. [α]25 D: +83˚ (*c* 0.15, CH_3OH).

Expression and purification of recombinant CtyD, CtyE, CtyJ and Pa-orf11

The pETM41 vector containing *ctyD* and pET28a vectors containing the *ctyE, ctyJ* and *Pa-orf11* gene were prepared previously. The plasmid was transformed into *Escherichia coli* BL21(DE3) competent cell and used for the expression of CtyD, CtyE, CtyJ and Pa-orf11. The cells harboring the plasmids were cultured at 37 °C to an OD600 of 0.6 in Luria-Bertani medium, containing 50 μg/ml kanamycin and 1 mol/L. Isopropyl *β*-Dthiogalactopyranoside (IPTG) was then added to 0.5 mmol/L (final concentration) for target protein expression, and the cultures were continued for 20 h at 16 °C. All purification steps were performed at 4 °C. The cultured cells were resuspended in 50 mmol/L $NaH_2PO_4{\cdot}H_2O$, pH 8.0, containing 10% (v/v) glycerol, 300 mmol/L NaCl, and 10 mmol/L imidazole (Lysis buffer). The cells were lysed by sonication and the insoluble debris was removed by centrifugation at 12,000 g for 30 min. The supernatant was loaded onto a Ni-NTA Resin (Thermo Fisher Scientific) column. The resin was washed with 50 column volumes of Lysis buffer containing 40 mmol/L imidazole, and then the CtyD, CtyE, CtyJ and Pa-orf11 was eluted with Lysis buffer containing 250 mmol/L imidazole. The protein solution was concentrated with Amicon Ultra-15 centrifugal filter devices (10 K MWCO, Millipore). The target protein was eluted with 50 mmol/L HEPES containing 100 mmol/L NaCl and 10% (v/v) glycerol, stored at -80 °C. The purity of the

enzymes was monitored by SDS-PAGE. These results are summarized in Figure S14. The protein concentrations were calculated by measuring the ultraviolet absorption at A_{280}.

In vitro assay of recombinant CtyD

The assay mixture for CtyD contained, in a final volume of 200 μL, 0.25 mmol/L cotylenol, 1 mmol/L UDP-glucose, 5 mmol/L $CaCl_2$. 50 mM Tris–HCl (pH 7.5), and 2 μmol/L CtyD. The mixture was incubated at 30 ℃ for 2 h. Then the reaction was stopped by the addition of methanol (200 μL). LC-MS analysis was performed with an Eclipse Plus C18 column (2.1 × 100 mm, 3.5 μm) at the following condition; CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. The concentration of CH_3CN was linearly increased from 5% to 98% over 11 min and kept at 100% for 2 min. Flow rate was kept at 0.5 ml/min. Metabolites were analyzed in ESI positive mode.

In vitro assay of recombinant CtyE

The assay mixture for CtyE contained, in a final volume of 200 μL, 0.25 mmol/L of compound **6** and **9**, 1 mmol/L S-adenosyl-L-methionine (SAM), 50 mM Tris–HCl (pH 7.5), and 2 μmol/L CtyE. The reaction mixture was incubated at 30 ℃ for 2 h. Then the reaction was stopped by the addition of methanol (200 μL). LC-MS analysis was performed with an Eclipse Plus C18 column (2.1 × 100 mm, 3.5 μm) at the following condition; CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. The concentration of CH_3CN was linearly increased from 5% to 98% over 11 min and kept at 100% for 2 min. Flow rate was kept at 0.5 ml/min. Metabolites were analyzed in ESI positive mode.

In vitro assay of recombinant CtyJ

The assay mixture (200 μL) for CtyJ contained, in a final volume of 200 μL , 0.25 mmol/L compound **6**, 1 mmol/L DMAPP, 5 mmol/L $CaCl_2$, Tris·HCl (50 mM, pH 7.5), and 2 μmol/L CtyJ. This mixture was incubated at 30 ℃ for 2 h, and the reaction was stopped by the addition of methanol (200 μL). LC-MS analysis was performed with an Eclipse Plus C18 column (2.1 × 100 mm, 3.5 μm) at the following condition; CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. The concentration of CH_3CN was linearly increased from 5% to 98% over 11 min and kept at 100% for 2 min. Flow rate was kept at 0.5 ml/min. Metabolites were analyzed in ESI positive mode.

In vitro assay of recombinant Pa-orf11

The assay mixture (200 μL) for CtyJ contained, in a final volume of 200 μL , 0.25 mmol/L compound **6**, 1 mmol/L DMAPP, 5 mmol/L $CaCl_2$, Tris·HCl (50 mM, pH 7.5), and 2 μmol/L CtyJ. This mixture was incubated at 30 ℃ for 2 h, and the reaction was stopped by the addition of methanol (200 μL). LC-MS analysis was performed with an Eclipse Plus C18 column (2.1 × 100 mm, 3.5 μm) at the following condition; CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. The concentration of CH_3CN was linearly increased from 5% to 98% over 11 min and kept at 100% for 2 min. Flow rate was kept at 0.5 ml/min. Metabolites were analyzed in ESI positive mode.

Isolation of each product from *in vitro* enzymatic reactions

Compound 9: To isolate compounds **9** from the *in vitro* enzymatic reactions, the purified CtyJ (final conc. 4 mg/mL) was added to 100 mL reaction buffer (50 mmol/L Tris-HCl buffer pH 7.5) and incubated with 0.25 mmol/L of compounds **6** and 1 mmol/L DMAPP at 30 °C for 4 h. The reaction

was quenched by adding an equivalent volume of MeOH. The samples were centrifuged and clarified with a 0.22 μm filter, and the reaction products were further purified by reverse-phase preparative HPLC (52% aqueous acetonitrile, 2.0 mL/min) using an ZORBAX SB-C18 Column (9.4 × 250 mm, 5 μm)
Compound **9**; colorless solid, HR-ESIMS: calcd. for $C_{32}H_{52}O_9$ $[M+Na]^+$: 603.3504, found:603.3509. [α]25 D: +81˚ (*c* 0.15, CH_3OH).

Compound 10: To isolate compounds **9** from the *in vitro* enzymatic reactions, the purified Pa-orf11 (final conc. 4 mg/mL) was added to 100 mL reaction buffer (50 mmol/L Tris-HCl buffer pH 7.5) and incubated with 0.25 mmol/L of compounds **6** and 1 mmol/L DMAPP at 30 °C for 4 h. The reaction was quenched by adding an equivalent volume of MeOH. The samples were centrifuged and clarified with a 0.22 μm filter, and the reaction products were further purified by reverse-phase preparative HPLC (52% aqueous acetonitrile, 2.0 mL/min) using an ZORBAX SB-C18 Column (9.4 × 250 mm, 5 μm)
Compound **10**; colorless solid, HR-ESIMS: calcd. for $C_{32}H_{52}O_9$ $[M+Na]^+$: 603.3504, found:603.3499. [α]25 D: +37˚ (*c* 0.15, CH_3OH).

Heterologous expression of *ctyA* in *S. cerevisiae* RC01 and feeding experiments

To heterologously express *ctyA* gene in *S. cerevisiae* RC01, plasmids XW55-*ctyA* was transformed to competent cells of *S. cerevisiae* RC01 using Frozen-EZ Yeast Transformation II Kit, and the transformation mixture was cultured on solid SD medium (6.7 g/L YNB, 20 g/L glucose, 100 mL/L amino acid mixture) at 30 °C for 2 days to obtain the transformant. The transformant was inoculated in 2 mL SD medium at 28 °C and 250 rpm for 15 h to get seed culture. 200 μL seed culture was transferred to 20 mL YPD medium (1% yeast extract, 2% tryptone, 2% glucose) at 28°C and 250 rpm for additional 3 days. 20 mL of YPD medium was concentrated to 2 mL by centrifugation and then resuspended. 4μL **4** and **3** (5 mM in DMSO) were added to the culture and cultivated for one day. The mixture was extracted with ethyl acetate and acetone (v:v=3:1). After centrifugation at 12000 g for 5 min, the cells were extracted with acetone followed by evaporation of the organic solvent.The cell-free medium suspension was extracted with EtOAc followed by evaporation of the organic solvent. The extracts were then dissolved in methanol and analyzed by LC-MS. LC-MS analysis was performed with an Eclipse Plus C18 column (2.1 x 100 mm, 3.5 μm) at the following condition; CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. The concentration of CH_3CN was linearly increased from 5% to 98% over 11 min and kept at 100% for 2 min. Flow rate was kept at 0.5 ml min^{-1}. Metabolites were analyzed in ESI positive mode.

Expression, and preparation of CtyA-containing microsomes for in vitro assay.

For expression of CtyA, the cells were grown in YPD medium supplemented with 1% dextrose at 28°C with shaking for 48 hours. The microsomes were prepared according to the protocol described previously[5]. Briefly, the cells were harvested by centrifugation (3,750 rpm at 4 °C for 10 mins) and the cell pellet was washed with 100 mL of TES buffer (50 mM Tris–HCl, pH, 7.5, 1 mM EDTA, 0.6 M sorbitol). The cells were centrifuged as above, resuspended in 100 mL of TES-M (TES supplemented with 10 mM 2-mercaptoethanol), and allowed to incubate at room temperature for 10 min. The yeast cells were centrifuged again at 3,750 rpm for 10 min, and the pellet was resuspended in 90 mL of extraction buffer (1% bovine serum albumin, fraction V, 2 mM 2-mercaptoethanol, 1 mM phenylmethylsulfonyl fluoride, all dissolved in TES). Cell walls were

disrupted by high pressure homogenizer (Scientz-150) at 1200 bar at 4 °C for 40 mins. Finally, microsomes were obtained by differential centrifugation at 10,000g for 30 min at 4°C to remove cellular debris followed by centrifugation at 100,000g for 70 min at 4°C. The microsomal pellets were resuspended in 1.5 mL of TEG-M buffer (50 mM Tris–HCl, pH 7.5, 1 mM EDTA, 20% glycerol, and 1.5 mM 2-mercaptoethanol) and stored frozen at -80 °C.

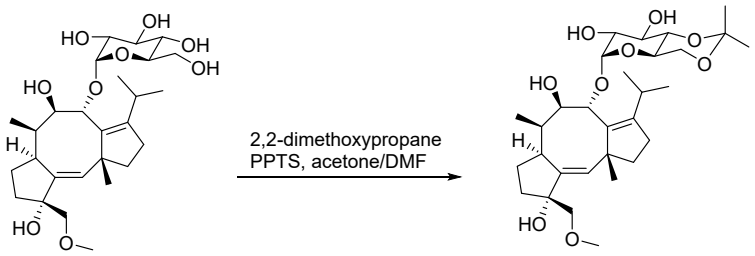
In vitro assays of microsome fraction from yeast expressing CtyA.

For in vitro assays of CtyA, 10 mg/mL (wet weight) microsomal fractions containing CtyA, 0.1 mM substrates **4,** 2 mM NADPH in 100 mM PBS, pH 7.4, were incubated in a total 100 μL reaction. The reaction was incubated at room temperature overnight and extracted with 100 μL ethyl acetate twice. The organic phase was dried and dissolved in MeOH for analysis on LC-MS. LC-MS analysis was performed with an Eclipse Plus C18 column (2.1 × 100 mm, 3.5 μm) at the following condition; CH_3CN and H_2O (each contained 0.1% HCOOH) were used as eluents. The concentration of CH_3CN was linearly increased from 5% to 98% over 11 min and kept at 100% for 2 min. Flow rate was kept at 0.5 ml min^{-1}. Metabolites were analyzed in ESI positive mode.

Expression and purification of recombinant 14-3-3ζ.

The pET28a vectors containing the *14-3-3ζ* gene was prepared previously. The *E. coli* BL21 (DE3) transformed with the cloned vector have been used to inoculate 50ml of Luria-Bertani (LB)-media with 50 μg ml^{-1} kanamycin. The culture was grown for 12 h at 310 K during vigorous shaking. The preculture was used to inoculate a 5 L terrific broth (TB) culture with 50 μg ml^{-1} kanamycin. The culture was put at 310 K shaking at 140 rpm until an OD600 of 0.4-0.6 was reached. Protein expression was started by adding 0.4 mM IPTG to the culture. The culture was incubated at 298 K for 12 h and then harvested by centrifugation. The bacteria pellet was resuspended in 50 ml lysis buffer containing 50 mM Tris/HCl, 300 mM NaCl, 5% glycerol, 10 mM imidazole, 0.5 mM TCEP, and 1 mM PMSF, pH 8.0. The cells were lysed using an ultrasonic cell disruptor. The lysate was cleared by centrifugation at 12000 g for 30 minutes at 277 K. The HIS-tagged 14-3-3ζ protein was purified using Ni-NTA-Resin (Thermo Fisher Scientific) according to the manufacturer's manual. The resin was washed in a buffer containing 50 mM Tris, 500 mM NaCl, 5% glycerol 25 mM imidazole, and 0.5 mM TCEP, pH 8.0. The protein was eluted in a buffer containing 50 mM HEPES, 200 mM NaCl, 5% glycerol, 250 mM imidazole, 0.5 mM TCEP, pH 8.0. The protein solution was further concentrated to a volume of 2 ml with Amicon Ultra-15 centrifugal filter devices (10 K MWCO, Millipore) for gel filtration. The gel filtration was performed using an Äkta Prime and a superdex 75 16/60 gel filtration column (GE Healthcare, Freiburg, Germany). The buffer contained 25 mM HEPES, 100 mM NaCl, 10 mM $MgCl_2$, 1 mM TCEP, pH 8.0. The 14-3-3**ζ** protein was then pooled according to the elution profile and concentrated to 75mg/ml. The protein was aliquoted and flash frozen in liquid nitrogen and stored at 193 K.

Semisynthesis of ISIR-050 from compound 6



6 ISIR-050

To a solution of **6** (10.2 mg, 20 µmol) in a mixture of anhydrous acetone (1 mL) and anhydrous DMF (50 µL) was added PPTS (1 mg, 4 µmol) and 2,2-dimethoxypropane (7.5 µL, 60 µmol). After stirring at rt for 18 h, the resulting mixture was diluted with EtOAc and poured into brine. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, and then dried over sodium sulfate. After filtration, the solvent was removed in vacuo. The resulting residue was purified by flash column chromatography on silica gel to yield ISIR-050 as a colorless solid (8.1 mg, 80%). ISIR-050: ^{1}H-NMR (600 MHz, CDCl3) δ: 5.54 (1H, d, *J* = 2.5 Hz), 5.01 (1H, d, *J* = 3.8 Hz), 3.99 (1H, dd, *J* = 10.1, 4.4 Hz), 3.87 (1H, t, *J* = 9.2 Hz), 3.83 (1H, d, *J* = 10.1 Hz), 3.79-3.72 (2H, m) 3.70-3.67 (2H, m), 3.46 (1H, t, *J* = 9.2 Hz), 3.40 (3H, s), 3.37 (1H, d, *J* = 9.5 Hz), 3.21 (1H,m), 3.11 (1H, d, *J* = 9.5 Hz), 2.95 (1H, td, *J* = 8.3, 2.5 Hz), 2.17-2.12 (2H, m), 2.03 – 1.93 (3H, m), 1.83 (1H, ddd, *J* = 12.0, 5.8, 4.1 Hz), 1.70 (1H,m), 1.48 (3H, s), 1.42 (1H,m), 1.39 (3H, s), 1.30 (1H, m), 1.20 (3H, s), 1.10 (3H, d, *J* = 6.7 Hz), 0.98 (3H, d, *J* = 6.8 Hz). ^{13}C-NMR (150 MHz, CDCl3) δ: 149.9, 139.9, 135.1, 134.7, 101.7, 99.8, 82.1, 78.1, 77.9, 77.5, 74.1, 73.2, 71.8, 63.7, 62.6, 59.5, 52.3, 42.7, 41.5, 40.3, 35.6, 31.8, 29.2, 28.1, 27.0, 26.6, 21.4, 21.0, 19.3, 8.6. HR-ESIMS: m/z calcd for $C_{30}H_{48}O_9$ $[M + Na]^+$ 575.3196, found 575.3181.

Anisotropy measurements.

FAM-QHRY-pS-TPHAFTFNTSSPSSEGSLSQRQRST-pS-TPNVH peptide was purchased from NovoPro Bioscience Inc. FAM-labeled di-phosphorylated peptides were diluted to 20 nM in buffer (10 mM HEPES, 150 mM NaCl, 0.1 % Tween-20, 0.1 % BSA, pH 7.4) and titrated with His-14-3-3ζ in a serial dilution in 384-well plates[6]. The purification of 14-3-3ζ was performed as described before and the concentrated protein was dialyzed against dialysis buffer (25 mM HEPES/NaOH, pH 7.5, 100 mM NaCl, 2 mM $MgCl_2$ and 4 mM 2-Mercaptoethanol). Anisotropy was measured using white light and standard excitation (485 ± 10 nm) and emission (535 ± 12.5 nm) filters in a BioTek Synergy 2 Multimode Plate Reader.

First, the peptides were titrated with His-14-3-3ζ in order to obtain a K_d value and select an appropriate concentration for the subsequent stabilization experiments. For the determination of EC_{50}-values, a solution comprising 20 nM FAM-labelled phosphopeptide and 250 nM His-14-3-3ζ was titrated with the respective compound. The measured anisotropy values were normalized using **10** as a positive control and plotted against logarithmic compound concentration. To obtain EC_{50} values, the resulting curve was fitted to a four-parameter logistic model (4PL) using GraphPad Prism 5.03 for Windows (GraphPad Software, La Jolla, CA).

SUPPLEMENTARY TABLES

Table S1. Oligonucleotides used for construction of plasmids.

Primer name	Primer sequence (5′→3′)
pAdeA2-*AbnA* -F	TTCGAATCGATTTGAGCTAGCATGAAATACCAATTTTCCATCA
pAdeA2-*AbnA* -R	CACTAGTGCGGCCGCTAGCTCAAAGCTTGAGCATCATTAG
pAdeA2-*AbnB* -F	CGGAATTCGAGCTCGGTACCATGGCTACAACCTTTACACA
pAdeA2-*AbnB* -R	ACTACAGATCCCCGGGTACCCTACTCCTTGTTTTTTCTAACGA
Linker-F	GGTACCCGGGGATCTGTAGT
Linker-R	GCTAGCTCAAATCGATTCGA
pUARA2-*AbnC*-F	TCGAATCGATTTGAGCTAGCATGGCTTCCATACTATGGAC
pUARA2-*AbnC* -R	GTCACTAGTGCGGCCGCTAGCTATTTCGTTCTCGGAGCGA
pUARA2-*AbnD*-F	CGGAATTCGAGCTCGGTACCATGGCAGTCCAAGAGACAGA
pUARA2-*AbnD*-R	ACTACAGATCCCCGGGTACCTTATGCATTCTGTGCCGCAG
pUSA2-*AbnE*-F	CGGAATTCGAGCTCGGTACCATGGCTTCCACCAGTTCCAC
pUSA2-*AbnE*-R	ACTACAGATCCCCGGGTACCTTAATGAGCCACCGCTGTTG
pAdeA2-*ctyA* -F	CCGAATTCGAATCGATTTGAGCTAGCATGTATCTTTTGATGATACTGGC
pAdeA2-*ctyA* -R	CCCGGGTCACTAGTGCGGCCGCTAGCTTAATGCTGTCGTTTAATCAACC
pAdeA2-*ctyB* -F	GCTCCGAATTCGAATCGATTTGAGCTAGCATGCCAAACATTATGGCTTC
pAdeA2-*ctyB* -R	CGGGTCACTAGTGCGGCCGCTAGCTTAAGCAGGTAAGATGTTAATCTCC
pAdeA2-*ctyD* -F	GCAAGCTCCGGAATTCGAGCTCGGTACCATGAATTACCCCCCATTTCCT
pAdeA2-*ctyD* -R	CACGAGCTACTACAGATCCCCGGGTACCTTATTTCCGGTGCTCCAATGG
pUSA2-*ctyE* -F	CAAGCTCCGAATTCGAATCGATTTGAGCTAGCATGGCCGCAATGAACAC
pUSA2-*ctyE* -R	ACCCGGGTCACTAGTGCGGCCGCTAGCTTAATCCTTCGTAAGGTCCCAC
pAdeA2-ctyF-F	CGAATTCGAATCGATTTGAGCTAGCATGGATTATCTTTACTCAACAGTT
PAdeA2-ctyF-R	ACCCGGGTCACTAGTGCGGCCGCTAGCTCAGATGCGTAGGAACTC
pUSA2-*ctyJ* -F	CAGCAAGCTCCGGAATTCGAGCTCGGTACCATGTCTGAATCGACGTACA
pUSA2-*ctyJ* -R	TCACGAGCTACTACAGATCCCCGGGTACCTCAACGGTTCATATCCAAGG
pETM41-*ctyD*-F	GAGAATCTTTATTTTCAGGGCGCCATGGTGAATTACCCCCCATTTCCTA
pETM41-*ctyD*-R	TTGTCGACGGAGCTCGAATTCGGATCCGGTACTTTCCGGTGCTCCAATG
pET28a-*ctyE*-F	GTGGACAGCAAATGGGTCGCGGATCCGAATTCATGGCCGCAATGAACAC
pET28a-*ctyE*-R	TTTGTTAGCAGCCGGATCTCACTCGAGTTAATCCTTCGTAAGGTCCCAC
pET28a-*ctyJ*-F	GCGGATCCGAATTCGAGCTCCGTCGAATGTCTGAATCGACGTACAATCT
pET28a-*ctyJ*-R	CAGTGGTGGTGGTGGTGGTGCTCGAGTCAACGGTTCATATCCAAGGTCT
pET28a-Pa-*orf11*-F	TGGACAGCAAATGGGTCGCGGATCCGAATTCATGGCAAACGTGGTTCTG
pET28a-Pa-*orf11*-R	TGTTAGCAGCCGGATCTCACTCGAGCTAGTATATCTGGTCTCTAGCCAC
pET28a-*14-3-3ζ*-F	CAGCAAATGGGTCGCGGATCCGAATTCATGGATAAAAACGAACTGGTTC
pET28a-*14-3-3ζ*-R	CTTTGTTAGCAGCCGGATCTCACTCGAGTTAGTTTTCACCACCTTCACC
XW55-*ctyA*-F	ATAAGGATGATGATGATAAGACTAGTATGTATCTTTTGATGATACTGGC
XW55-*ctyA*-R	TAGTGATGGTGATGGTGATGCACGTGTTAATGCTGTCGTTTAATCAACC

Table S2. Summary of the transformants in this study.

Transformants	plasmids		
	AdeA	*ArgB*	*sC*
AO-abnABCDE	pAdeA2-*abnAB*	pUARA2-*abnCD*	pUSA2-*abnE*
AO-ctyA	pAdeA2-*ctyA*		
AO-ctyB	pAdeA2-*ctyB*		
AO-ctyF	pAdeA2-ctyF		
AO-ctyBD	pAdeA2-*ctyBD*		
AO-ctyBDE	pAdeA2-*ctyBD*		pUSA2-*ctyE*
AO-ctyBDEJ	pAdeA2-*ctyBD*		pUSA2-*ctyEJ*
AO-ctyABDEJ	pAdeA2-*ctyBD*	pUARA2-*ctyA*	pUSA2-*ctyEJ*
AO-ctyABDJ	pAdeA2-*ctyBD*	pUARA2-*ctyAJ*	
AO-ctyABDPa-orf11	pAdeA2-*ctyBD*	pUARA2-*ctyA-Pa-orf11*	

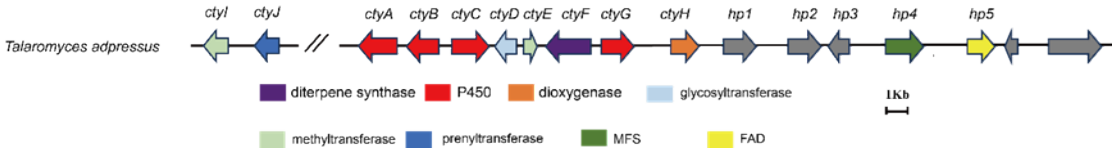
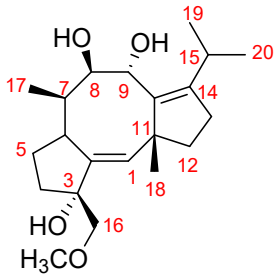


Table S3. Comparative analysis of gene clusters of *cty, orf, abn.*

Gene	corresponding *Pa* gene （UniProtKB/identity %）	corresponding *abn* gene (identity %）	Predicted function
ctyA	*Pa-orf12*(L0MYS8/30.8%)	*abnK*(23.5%)	P450
ctyB	*Pa-orf7* (L0MYS5/54.0%)		P450
ctyC	*Pa-orf5* (L0N063/67.1%)	*abnB* (63.0%)	P450
ctyD	*Pa-orf6* (L0MZK0/54.3%)		*O*-glycosyltransferase
ctyE			Methyltransferase
ctyF	*Pa-orf1* (A2PZA5/55.8%)	*abnA* (47.2%)	Fusicoccadiene synthase
ctyG	*Pa-orf3* (L0MXJ1/60.8%)	*abnC* (51.5%)	P450
ctyH	*Pa-orf2* (E0D7H6/51.9%)	*abnD* (61.4%)	Alpha-ketoglutarate-dependent dioxygenase
ctyI	*Pa-orf8*(L0MXX3/24.8%)	*abnE* (53.9%)	*O*-methyltransferase
ctyJ	*Pa-orf11* (H7CE84/43.4%)		*O*-glucose prenyltransferase
hp1			Manganese transporter
hp2			Arylsulfotransferase
hp3			No hits
hp4			MFS
hp5			FAD binding

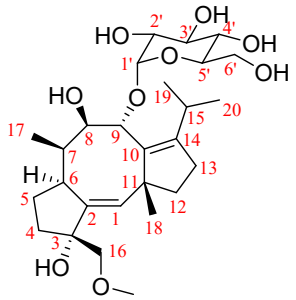
Our group identified the *abn* BGC previously[7].

Table S4. NMR data of compound 7 in $CDCl_3$.



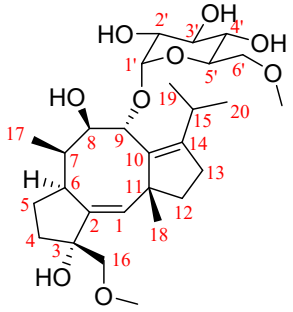
No.	**7**	
	δ_H, mult, (*J* in Hz)	δ_C, type
1	5.51, d, (2.6)	134.4, CH
2		139.7, C
3		82.1, C
4	1.27-1.33, m	31.7, CH2
	1.92-2.03, m	
5	1.92-2.03, m	35.4, CH2
6	2.93, td, (8.6, 2.6)	40.3, CH
7	1.41, m	41.7, CH
8	3.93, dd, (10.0, 4.4)	77.4, CH
9	4.06, d, (10.0)	67.9, CH
10		136.9, C
11		51.9, C
12	1.68, ddd, (12.0, 10.0 8.4)	42.6, CH2
	1.84, ddd, (12.0, 6.9, 2.2)	
13	2.06-2.17, m	27.2, CH2
14		150.5, C
15	3.26, p, (6.8)	28.2, CH
16	3.08, dd, (9.5, 1.3)	77.6, CH2
	3.35, d, (9.5)	
17	0.8, d, (7.2)	8.5, CH3
18	1.21, s	26.6, CH3
19	0.95, d, (6.9)	21.6, CH3
20	1.03, d, (6.7)	20.4, CH3
OMe	3.40, s	59.4, CH3

Table S5. NMR data of compound 6 in CD_3OD.



No.	**6**	
	δ_H, mult, (*J* in Hz)	δ_C, type
1	5.49, d, (2.5)	135.6, CH
2		141.2, C
3		83.3, C
4	2.00, 1.38, m	32.6, CH_2
5	1.96, 1.40, m	35.7, CH_2
6	2.99, m	41.7, CH
7	1.90, m	42.8, CH
8	3.99, dd, (10.0, 4.2)	78.5, CH
9	3.89, d, (10.0)	79.7, CH
10		136.8, C
11		53.1, C
12	2.15, m	43.6, CH_2
13	1.85, 1.67, m	27.5, CH_2
14		150.7, C
15	3.28, m	29.2, CH
16	3.35, 3.11 d, (10.0)	78.5, CH_2
17	0.84, d, (7.2)	9.0, CH_3
18	1.26, s	26.9, CH_3
19	1.10, d, (6.6)	22.0, CH_3
20	0.99, d, (6.9)	20.9, CH_3
1‘	4.94, d, (3.8)	103.6, CH
2‘	3.43, dd, (9.7,3.7)	73.8, CH
3‘	3.69, m	75.0, CH
4‘	3.42, m	71.2, CH
5‘	3.73, m	73.7, CH
6‘	3.66, m	62.1, CH_2
OMe	3.37, s	59.5, CH_3

Table S6. NMR data of compound 5 in CD_3OD and CD_3COCD_3.

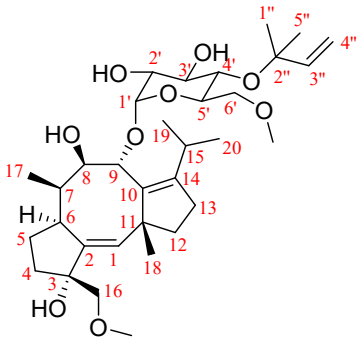


No.	**Reported**[8, 9]		**this work**		
	δ_H, mult, (*J* in Hz) CD_3COCD_3	δ_C, type CD_3OD	δ_H, mult, (*J* in Hz) CD_3COCD_3 (match the key signals)	δ_H, mult, (*J* in Hz) CD_3OD	δ_C, type CD_3OD
1	5.50, d, (2.5)	135.6, CH	5.51, d, (2.5)	5.49, d, (2.5)	135.6, CH
2		141.2, C			141.2, C
3		83.2, C			83.4, C
4		32.3, CH_2		2.00, 1.38, m	32.6, CH_2
5		35.5, CH_2		1.96, 1.40, m	35.7, CH_2
6		41.4, CH		2.99, m	41.7, CH
7		42.5, CH		1.90, m	42.8, CH
8		79.0, CH		3.99, dd, (10.0, 4.2)	78.9, CH
9		79.6, CH		3.89, d, (10.0)	79.7, CH
10		137.8, C			136.7, C
11		53.1, C			53.1, C
12		43.3, CH_2		2.15, m	43.6, CH_2
13		27.0, CH_2		1.85, 1.67, m	27.5, CH_2
14		150.2, C			150.7, C
15		28.5, CH		3.28, m	29.2, CH
16		78.5, CH_2		3.35, 3.11 d, (10.0)	78.1, CH_2
17		8.7, CH_3		0.84, d, (7.2)	8.9, CH_3
18	1.27, s	26.1, CH_3	1.28, s	1.26, s	26.6, CH_3
19	1.01, d, (6.5)	21.5, CH_3	1.08, s	1.10, d, (6.6)	22.0, CH_3
20	0.94, d, (6.5)	20.6, CH_3	0.96, s	0.99, d, (6.9)	20.9, CH_3
1′	4.91, d, (3.5)	103.5, CH	4.90, d, (3.5)	4.90, d, (3.8)	103.7, CH
2′		73.4, CH		3.43, dd, (9.7, 3.8)	72.9, CH
3′		75.2, CH		3.69, t, (9.3)	75.0, CH
4′		71.7, CH		3.34, m	71.5, CH
5′		72.7, CH		3.77, m	72.8, CH
6′		73.4, CH_2		3.59, dd, (10.6, 4.5)	73.7, CH_2
				3.52, dd, (10.8, 2.3)	
OMe	3.33, s	59.6, CH_3	3.34, s	3.37, s	59.5, CH_3
	3.27, s	59.6, CH_3	3.28, s	3.34, s	59.5, CH_3

5: ^{1}H NMR (600 MHz, Acetone-d_6) δ 5.51 (d, *J* = 2.5 Hz, 1H), 4.90 (d, *J* = 3.8 Hz, 1H), 3.93 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.85 (d, *J* = 10.0 Hz, 1H), 3.79 (m 1H), 3.74 (t, *J* = 9.2 Hz, 1H), 3.53 (m, 2H), 3.44

(m, 2H), 3.38 (d, *J* = 9.9 Hz, 1H),3.34 (s, 3H), 3.32 (m, 1H), 3.28 (s 3H), 3.05 (dd, *J* = 9.9, 1.1 Hz, 1H), 2.97 (td, *J* = 8.6, 2.5 Hz, 1H), 2.09, (m, 2H), 1.90-1.96(m,3H), 1.78 (m, 1H), 1.70 (m, 1H), 1.32 (m, 2H), 1.28 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 7.2 Hz, 3H).

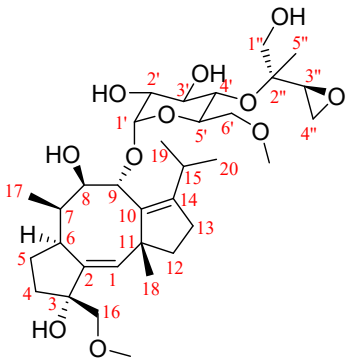
Table S7. NMR data of compound 4 in CD_3OD.



No.	**Reported**[9]	**this work**	
	δ_C, type	δ_H, mult, (*J* in Hz)	δ_C, type
1	135.3, CH	5.48, d, (2.5)	135.5, CH
2	141.4, C		141.2, C
3	83.2, C		83.4, C
4	32.5, CH_2	2.00, m	32.6, CH_2
		1.38, m	
5	35.7, CH_2	1.96, m	35.7, CH_2
		1.40, m	
6	41.6, CH	2.99, m	41.7, CH
7	42.6, CH	1.90, m	42.8, CH
8	78.7, CH	3.97, dd, (10.0, 4.2)	78.8, CH
9	79.5, CH	3.86, d, (10.0)	79.6, CH
10	136.5, C		136.7, C
11	53.0, C		53.1, C
12	43.6, CH_2	2.15, m	43.7, CH_2
13	27.4, CH_2	1.85, m	27.5, CH_2
		1.67, m	
14	150.5, C		150.7, C
15	29.1, CH	3.28, m	29.2, CH
16	77.3, CH_2	3.35, d, (10.0)	77.4, CH_2
		3.11, d, (10.0)	
17	9.0, CH_3	0.84, d, (7.2)	9.0, CH_3
18	26.7, CH_3	1.26, s	26.7, CH_3
19	21.9, CH_3	1.10, d, (6.6)	21.9, CH_3
20	21.1, CH_3	0.98, d, (6.9)	21.1, CH_3
1′	103.2, CH	4.87, d, (3.8)	103.3, CH
2′	72.7, CH	3.39, m	72.8, CH
3′	73.6, CH	3.63, m	73.8, CH
4′	74.9, CH	3.35, m	75.0, CH
5′	72.7, CH	3.70, m	72.8, CH
6′	72.1, CH_2	3.62, 3.51, m	72.2, CH_2
1′′	27.6, CH_3	1.32, s	27.6, CH_3
2′′	78.0, C		78.1, C

3''	146.4, CH	6.05, dd, (17.5, 10.8)	146.6, CH
4''	112.8, CH_2	5.12, dd, (17.5, 1.4)	112.8, CH_2
		5.01, dd, (10.9, 1.4)	
5''	27.9, CH_3	1.31, s	27.9, CH_3
OMe	59.5, CH_3	3.37, s	59.5, CH_3
	59.1, CH_3	3.30, s	59.1, CH_3

Table S8. NMR data of compound 3 in CD_3OD and CD_3COCD_3.

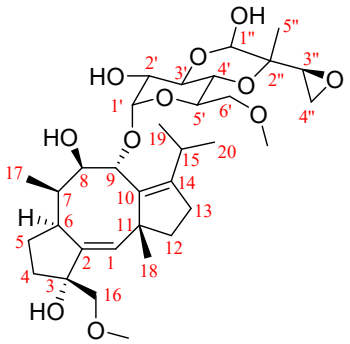


No.	Reported[9, 10]		this work		
	δ_H, mult, (*J* in Hz) CD_3COCD_3	δ_C, type CD_3OD	δ_H, mult, (*J* in Hz) CD_3COCD_3 (match the key signals)	δ_H, mult, (*J* in Hz) CD_3OD	δ_C, type CD_3OD
1	5.56, d, (2.5)	135.6, CH	5.51, d, (2.6)	5.49, d, (2.5)	135.4, CH
2		141.5, C			141.3, C
3		83.4, C			83.4, C
4		32.7, CH_2		1.30, 1.94, m	32.6, CH_2
5		35.9, CH_2		1.37, 2.00, m	35.7, CH_2
6		41.7, CH		2.98, m	41.7, CH
7		42.8, CH		1.89, m	42.7, CH
8		79.1, CH		3.97, dd, (10.0, 4.2)	79.0, CH
9		79.7, CH		3.86, d, (10.1)	79.6, CH
10		137.0, C			136.7, C
11		53.2, C			53.1, C
12		43.7, CH_2		1.67, 1.88, m	43.7, CH_2
13		27.5, CH_2		2.08-2.20, m	27.5, CH_2
14		150.8, C			150.7, C
15		29.1, CH		3.28, m	29.2, CH
16		78.2, CH_2		3.36, d, (10.0)	78.0, CH_2
				3.11, d, (10.0)	
17	0.83,	9.0, CH_3	0.83, d (7.2)	0.84, d, (7.2)	8.9, CH_3
18	1.26, s	26.8, CH_3	1.26, s	1.25, s	26.8, CH_3
19	1.09	21.9, CH_3	1.09, d, (6.6)	1.10, d, (6.6)	21.8, CH_3
20	0.97	21.1, CH_3	0.97, d, (6.9)	0.99, d, (6.9)	21.0, CH_3
1′	4.94, d, (3.0)	103.4, CH	4.88, d, (3.8)	4.86, d, (4.0)	103.4, CH
2′		72.5, CH		3.61, m	72.5, CH
3′		73.7, CH		3.44, dd, (9.7, 3.8)	73.5, CH
4′		75.4, CH		3.75, m	75.4, CH
5′		72.5, CH		3.68, m	72.4, CH
6′		71.7, CH_2		3.36, 3.74, m	71.5, CH_2
1′′		67.9, CH_2		3.56, 3.60, m	67.9, CH_2
2′′		78.2, C			78.1, C
3′′	2.4-3.1, m	57.3, CH	2.95, dd, (4.0, 2.7)	2.98, m	57.3, CH

4''	2.4-3.1, m	44.5, CH_2	2.60, dd, (5.6, 4.0) 2.78, dd, (5.6, 2.7)	2.81, dd, (5.6, 2.7) 2.66, dd, (5.5, 4.1)	44.5, CH_2
5''	1.17, s	16.6, CH_3	1.16, s	1.20, s	16.6, CH_3
OMe	3.37	59.6, CH_3	3.34, s	3.37, s	59.5, CH_3
	3.31	59.3, CH_3	3.28, s	3.32, s	59.2, CH_3

3: ^{1}H NMR (600 MHz, Acetone-d_6) δ 5.51 (d, *J* = 2.6 Hz, 1H), 4.88 (d, *J* = 3.8 Hz, 1H), 3.92 (dd, *J* = 10.0, 4.2 Hz, 1H), 3.86 – 3.77 (m, 2H), 3.72 – 3.65 (m, 2H), 3.63 – 3.57 (m, 2H), 3.54 – 3.46 (m, 2H), 3.38 (d, *J* = 9.8 Hz, 1H), 3.38 (m, 1H) 3.34 (s, 3H), 3.28 (s, 3H), 3.28 (m,1H), 3.05 (d, *J* = 9.9 Hz, 1H), 2.95 (dd, *J* = 4.0, 2.7 Hz, 2H), 2.78 (dd, *J* = 5.6, 2.6 Hz, 1H), 2.60 (dd, *J* = 5.6, 4.0 Hz, 1H), 2.14 – 2.07 (m, 2H), 2.01 – 1.86 (m, 3H), 1.84 – 1.75 (m, 1H), 1.73 – 1.62 (m, 1H), 1.38 – 1.28 (m, 2H), 1.26 (s, 3H), 1.16 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 7.2 Hz, 3H).

Table S9. NMR data of compound 2 in CD_3OD and CD_3COCD_3.

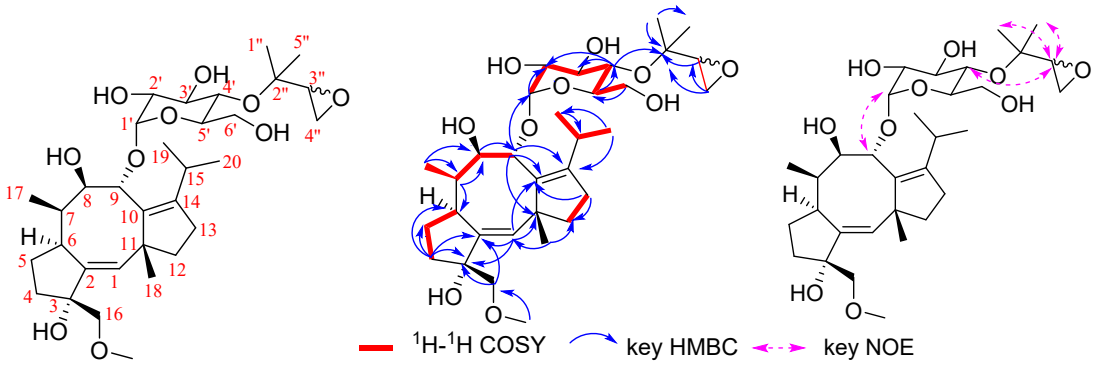


No.	Reported[8, 9]		this work		
	δ_H, mult, (*J* in Hz) CD_3COCD_3	δ_C, type CD_3OD	δ_H, mult, (*J* in Hz) CD_3COCD_3 (match the key signals)	δ_H, mult, (*J* in Hz) CD_3OD	δ_C, type CD_3OD
1	5.57, d, (2.5)	135.5, CH	5.51, d, (2.5)	5.48, d, (2.5)	135.5, CH
2		141.1, C			141.1, C
3		83.4, C			83.2, C
4		32.7, CH_2		1.30, 1.94, m	32.6, CH_2
5		35.8, CH_2		1.37, 2.00, m	35.7, CH_2
6		41.7, CH		2.98, m	41.7, CH
7		42.7, CH		1.89, m	42.7, CH
8		79.0, CH		3.88, d, (10.1)	79.0, CH
9		79.8, CH		3.98, dd, (10.1, 4.2)	79.7, CH
10		136.7, C			136.7, C
11		53.2, C			53.1, C
12		43.8, CH_2		1.70, 1.87, m	43.7, CH_2
13		27.6, CH_2		2.14, m	27.5, CH_2
14		150.6, C			150.6, C
15		29.3, CH		3.30, m	29.2, CH
16		78.1, CH_2		3.36, 3.11, d, (10.0)	78.1, CH_2
17	0.83	9.1, CH_3	0.83, d, (7.2)	0.83, d, (7.2)	8.9, CH_3
18	1.27	26.6, CH_3	1.27, s	1.26, s	26.5, CH_3
19	1.08	22.1, CH_3	1.12, d, (6.6)	1.13, d, (6.6)	22.2, CH_3
20	0.96	21.2, CH_3	0.98, d, (6.6)	1.01, d, (7.0)	21.0, CH_3
1′	4.99, d, (3.0)	103.6, CH	4.94, d, (3.0)	4.93, d, (3.6)	103.6, CH
2′		71.2, CH		3.81, m	71.2, CH
3′		77.9, CH		3.73, t, (9.5)	77.9, CH
4′		70.8, CH		3.69, dd, (10.0, 3.5)	70.8, CH
5′		68.1, CH		3.40, t, (9.5)	68.1, CH
6′		72.0, CH_2		3.46, m	71.9, CH_2
1′′	4.78, d, (6.0)	97.2, CH	4.75, s	4.71, s	97.2, CH
2′′		75.4, C			75.4, C
3′′	2.4-3.1, m	57.1, CH	2.97, dd, (4.1, 2.6)	3.03, m	57.1, CH
4′′	2.4-3.1, m	44.1, CH_2	2.58, 2.77, m	2.66, 2.83, m	43.9, CH_2

5''	1.27	13.3, CH_3	1.26, s	1.29, s	13.1, CH_3
OMe	3.37, s	59.8, CH_3	3.34, s	3.37, s	59.7, CH_3
	3.29, s	59.7, CH_3	3.27, s	3.32, s	59.5, CH_3

2: ^{1}H NMR (600 MHz, Acetone-d_6) δ 5.51 (d, *J* = 2.5 Hz, 1H), 4.94 (d, *J* = 3.1 Hz, 1H), 4.75 (s, 1H), 3.94 (dd, *J* = 10.1, 3.9 Hz, 1H), 3.89 – 3.79 (m, 2H), 3.76 – 3.70 (m, 1H), 3.52 – 3.39 (m, 3H), 3.37 (m, 2H), 3.34 (s, 3H), 3.32 – 3.29 (m, 1H), 3.27 (s, 3H), 3.07 – 3.02 (m, 1H), 2.97 (m, 2H), 2.77 (ddd, *J* = 13.3, 5.6, 2.7 Hz, 1H), 2.58 (ddd, *J* = 13.0, 5.7, 4.1 Hz, 1H), 2.12 – 2.07 (m, 2H), 1.94 (m, 3H), 1.78 (m, 1H), 1.74 – 1.65 (m, 1H), 1.38 – 1.29 (m, 2H), 1.27 (s, 3H), 1.26 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 7.2 Hz, 3H).

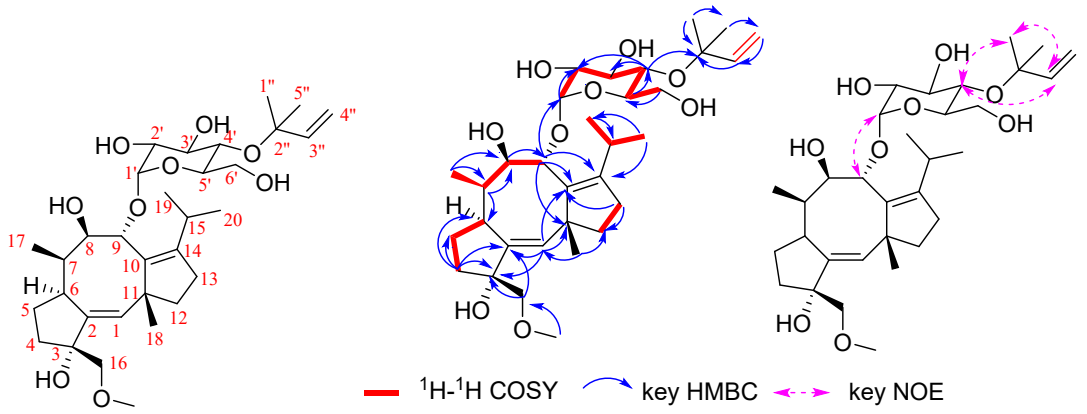
Table S10. NMR data of compound 12 in CD_3OD.



No.	12			
	δ_H, mult, (*J* in Hz)	δ_C, type	Key HMBC correlations	Key COSY correlations
1	5.49, d, (2.5)	135.5, CH	C2, C3, C6, C10, C18	H6
2		141.3, C		
3		83.4, C		
4	2.00, m	35.7, CH_2	C2, C3, C6, C16	H5
	1.38, m			
5	1.96, m	32.6, CH_2	C2, C3, C4, C6	H4
	1.40, m			
6	2.99, td, (8.5, 2.5)	41.7, CH	C2, C5, C7, C8, C17	H1, H5
7	1.90, m	42.8, CH	C2, C5, C6, C8, C17	H8, H17
8	3.97, dd, (10.0, 4.3)	79.7, CH	C7, C9, C10, C17	H7
9	3.87, d, (10.0)	78.6, CH	C7, C8, C10, C11, C14 C1′	H8
10		136.8, C		
11		53.1, C		
12	2.14, m	27.5, CH_2	C10, C11, C13, C14	H13
13	1.86, m	43.7, CH_2	C10, C11, C12, C14	H12
	1.67, m			
14		150.6, C		
15	3.28, m	29.2, CH	C10, C14	H19, H20
16	3.36, d, (10.0)	78.1, CH_2	C3, C4, OMe	
	3.11, d, (10.0)			
17	0.84, d, (7.2)	9.0, CH_3	C7, C8	H7
18	1.25, s	26.9, CH_3	C1, C10, C11, C12	
19	1.09, d, (6.6)	21.8, CH_3	C14, C15, C20	H15
20	0.99, d, (6.9)	21.0, CH_3	C14, C15, 19	H15
1′	4.91, d, (3.8)	103.4, CH	C9, C2′	H2′
2′	3.42, m	73.9, CH		H1′, H3′
3′	3.66, m	75.0, CH	C2′, C4′	H2′
4′	3.66, m	72.3, CH	C5′, C6′, C2′′	H3′
5′	3.61, m	73.7, CH	C3′	H4′
6′	3.8, dd, (11.6, 2.7)	61.5, CH_2	C5′	H5′
	3.62, m			
1′′	1.25, s	24.0, CH_3	C2′′, C3′′, C4′′, C5′′	

2''		75.9, C		
3''	3.14, dd, (4.2, 2.9)	59.1, CH	C1'', C2'', C5''	H4''
4''	2.70, dd, (5.1, 2.9)	45.2, CH_2	C2'', C3''	H3''
	2.67, dd, (5.1, 4.2)			
5''	1.24, s	23.8, CH_3	C1'', C2'', C3'', C4''	
OMe	3.37, s	59.5, CH_3		

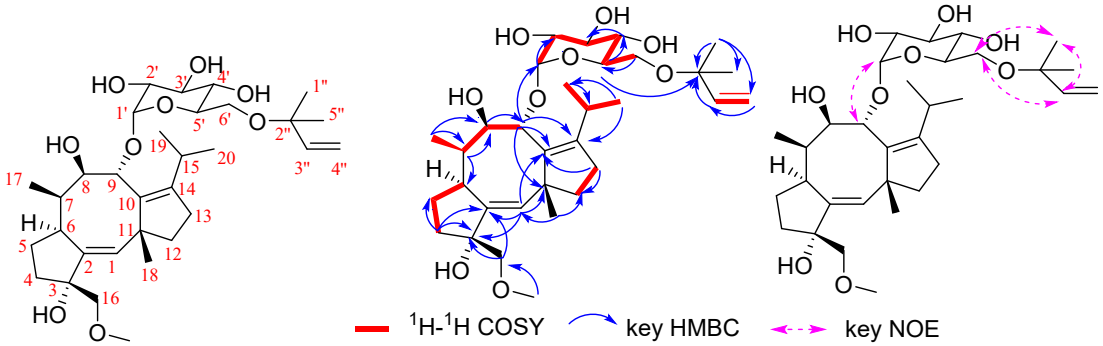
Table S11. NMR data of compound 9 in CD_3OD.



No.	9			
	δ_H, mult, (*J* in Hz)	δ_C, type	Key HMBC correlations	Key COSY correlations
1	5.49, d, (2.5)	135.5, CH	C2, C3, C6, C10, C18	H6
2		141.2, C		
3		83.4, C		
4	2.00, m	35.7, CH_2	C2, C3, C6, C16	H5
	1.38, m			
5	1.96, m	32.6, CH_2	C2, C3, C4, C6	H4
	1.40, m			
6	2.99, m	41.7, CH	C2, C5, C7, C8, C17	H1, H5
7	1.90, m	42.8, CH	C2, C5, C6, C8, C17	H8, H17
8	3.97, dd, (10.0, 4.2)	79.7, CH	C7, C9, C10, C17	H7
9	3.88, d, (10.0)	78.6, CH	C7, C8, C10, C11, C14 C1'	H8
10		136.7, C		
11		53.1, C		
12	2.15, m	27.5, CH_2	C10, C11, C13, C14	H13
13	1.85, m	43.7, CH_2	C10, C11, C12, C14	H12
	1.67, m			
14		150.7, C		
15	3.28, m	29.2, CH	C10, C14	H19, H20
16	3.35, d, (10.0)	78.1, CH_2	C3, C4, OMe	
	3.11, d, (10.0)			
17	0.84, d, (7.2)	9.0, CH_3	C7, C8	H7
18	1.26, s	26.9, CH_3	C1, C10, C11, C12	
19	1.10, d, (6.6)	21.9, CH_3	C14, C15, C20	H15
20	0.98, d, (6.9)	21.1, CH_3	C14, C15, 19	H15
1'	4.91, d, (3.8)	103.3, CH	C9, C2'	H2'
2'	3.41, dd, (9.7, 3.8)	73.9, CH		H1', H3'
3'	3.66, m	75.0, CH	C2', C4'	H2'
4'	3.54, m	72.6, CH	C5', C6', C2''	H3'
5'	3.62, m	73.9, CH	C3'	H4'
6'	3.72, dd, (11.9, 3.3)	61.5, CH_2	C5'	H5'

	3.63, m			
1''	1.33, s	27.8, CH_3	C2'', C3'', C4'', C5''	
2''		77.4, C		
3''	6.09, dd, (17.5, 10.8)	146.7, CH	C1'', C2'', C5''	H4''
4''	5.13, dd, (17.5, 1.4)	112.8, CH_2	C2'', C3''	H3''
	5.01, dd, (10.9, 1.4)			
5''	1.33, s	27.9, CH_3	C1'', C2'', C3'', C4''	
OMe	3.37, s	59.5, CH_3		

Table S12. NMR data of compound 10 in CD_3OD.



No.	10			
	δ_H, mult, (*J* in Hz)	δ_C, type	Key HMBC correlations	Key COSY correlations
1	5.48, d, (2.5)	135.5, CH	C2, C3, C10, C11, C18	H6
2		141.1, C		
3		83.3, C		
4	2.01, m	35.7, CH_2	C2, C3, C5, C6	H5
	1.38, m			
5	1.96, m	32.6, CH_2	C2, C3, C4, C6	H4
	1.33, m			
6	2.99, m	41.7, CH	C2, C5, C7, C8, C17	H1, H5
7	1.90, m	42.8, CH	C2, C5, C6, C8, C17	H8, H17
8	3.99, dd, (10.1, 4.2)	79.7, CH	C7, C9, C10, C17	H7
9	3.88, d, (10.0)	78.9, CH	C7, C8, C10, C11, C14 C1′	H8
10		136.7, C		
11		53.2, C		
12	2.15, m	27.5, CH_2	C10, C11, C13, C14	H13
13	1.85, m	43.6, CH_2	C10, C11, C12, C14	H12
	1.73, m			
14		150.6, C		
15	3.26, m	29.2, CH	C10, C14, C19, C20	H19, H20
16	3.36, d, (10)	78.1, CH_2	C2, C3, C4, OMe	
	3.11, d, (10)			
17	0.84, d, (7.2)	8.9, CH_3	C7, C8	H7
18	1.28, s	27.0, CH_3	C10, C11, C12	
19	1.11, d, (6.6)	22.0, CH_3	C14, C15, C20	H15
20	0.98, d, (6.9)	21.0, CH_3	C14, C15, 19	H15
1′	4.90, d, (3.8 Hz)	103.71, CH	C9, C2′, C3′	H2′
2′	3.43, dd, (9.7, 3.9)	73.7, CH		H1′
3′	3.69, t, (9.3)	75.1, CH	C5′	H2′
4′	3.29, m	72.2, CH	C3′, C6′	H3′
5′	3.75, m	73.0, CH	C4′	H4′, H6′
6′	3.53, dd, (10.3, 2.7)	63.8, CH_2	C5′, C2′′	H5′
	3.45, m			

1''	1.26, s	26.3, CH_3	C2'', C3'', C4'', C5''	
2''		76.7, C		
3''	5.84, dd (17.7, 10.9)	145.1, CH	C1'', C2'', C5''	H4''
4''	5.16, dd, (17.7, 1.2)	114.4, CH_2	C2'', C3''	H3''
	5.10, dd, (10.9, 1.2)			
5''	1.26, s	26.3, CH_3	C1'', C2'', C3'', C4''	
OMe	3.37, s	59.5, CH_3	C2, C4, C16	

Table S13. Gene sequences used in this work.

Gene name	Sequence (5' to 3', with intron)
CtyA	ATGTATCTTTTGATGATACTGGCGCTTGCCATCTACCATATAACGAGCAGTGTTTTTGCTTTCCTT AACAATCTTGATACAGCTAAGAAGATTGGGCTTCCCATTGTTATTAGCCCAGTCTCGCGTATAAA CCCAGCATGGATGATCTTCCAAAAGCAGCTCGTGCCGCTATTAACCAAACTACCCTTTGGACTAG GCTCCTTCACGAGGTACAATACTATGAATTGGTGGTTTATTGAGAAACATCGGATCCATCAACAA TATGGTAAAGTATTCATACACGTCTCGCCGGGGCTTAATGAGCTGCATTGTGCAGACCCATTTGT CAATCAGCAAATTTTTTCAAGACGAAGGGACTTTGAAAAGCCGCCAAACCTCTTAAGTCAGTTGC ACAAGCCTGATCAAGTTCTTGGGGGAGTGAGTGGACTGACAATTAGCAGAAGCTACGAGAATC TACGGCGATAGCGTCACAACAGTATGTGTGCTATTTTCCTTTGGTTTAAATAGCTTGTTTATGCA GAGAATTATCACTAACATATTCGAATTACTACTCCGCTAAAGGTCACGGGCCCAGACTGGCAAC GCCACCGCCGTATCACAACTTCCCCGTTCAATGAGCGGAACAACAAGTTAGTTTGGAATGAGGC TATTCGCCAAACAATTCAAGTGGGAGCATATTGGTGTGATCACGGATCAGCCGGGTTCGAAACC GCTACTCAGGACTGGTCGACGGTAACGCTAAATATACTTGCAACCGCTGCACTTGGGGAGTCAT GGGACTTTCGCGGAATGTCAAATGGGCAGCAGAGTGAGAGCAACGCTGGGTCCGAGATGATG ACTTACCGCGATTCTCTCTTTACGCTAGCTGGCAACGTCCGTATGCTAGTTCTTACCCCGACCTGG CTCTATTCGGTTCCTCTCTCGTGGCTTCCCAATGGGCTTCGACAGTTTGTTTCCGCATACAAGCAG TTCGAACAGCACATGAAGCAGATGGTACAAAAGAAGAAGGAGCAAATTTCCAGGGGTGAGGCC GTCGATGCTACACTCTTGAGCACGCTGATTCTGAAATCTGAAGAATCGCGCCTTGACCAATCATC AGAATCACCAGCTAGCAATGGAACTGTGACTAGGATAGGTGCTGCCAGTGTTGGGTTATCGGAT GAAGAGTTATACGGTAATCTGTTTACTTACAATGTTGCGGGACATGAAACAACCGCCAGTACTCT GGGGTTTTCCATGTACCTTCTAGCTGCATTTCCAAACTGGCAAAACTGGGTCTTCGAAGAACTCG ATCTTATTTACGGACCCTATTCGAACACAAAGGACCTAGTCTATGAGGATGTATACCCTCGGTTA AAGCGCTGCCTCGCGATCATGGTATATGCCTTCCTGCTTTGATTTGATCATGCTGCTCTATTTGTT ACTAACAACATTTGAAAAGTTGGAGACTCTCAGATTATATGGTCCTATACACAGCGTCTATAAAG CTACTATAGGTGCTCACGGCCAGGATCTTGTAATCGACGGCCGGACTGTTCACATCCCTCCGAAT ACCTATGTTCTTCCGAATATAATCGCCTCACATACGTTGCCCGAATTCTGGGGTGACGACCATCT AGACTGGAACCCTAGCCGTTGGATTGAATCCGCCTCCACCACCCTCGAACACAACCTCAGTGACA AACCCGTATCCTCAAAGCCAGGAGGTGAAGAGATACGTACCCCGCCAAAAGGAAAAGATACGT ACCTTCCTTGGTCGGGAGGTGGACGCGTCTGTCCGGGCAGGAAGTTCTCACAAGTCGAATTTGT CGCGGCAATCTCAGTCCTGCTATGGGAATATGTAATTGAAGTCGTTCCCCGTCCCGGACGAGAG ACTGTGCAAGAGGCCCGACAGAGGTGTCTCGCTGTCATTCAAGACAGCGAGTCACAGATCACGC TGCAGATGAAGAACCCTACGTCTGTGAGGCTTAGGTTGATTAAACGACAGCATTAA
CtyB	ATGCCAAACATTATGGCTTCCATGTATTACCTCGTGACGAGTCATGACTTTCCAGCCGTGCCAGT CATTGCCGTCTCTTTTGCCGTACTTTGGTTCTCAAGCAAATACCTTTTTCATCTCTACAAGTTATCC TGCTTTCCCCTGGTAAATGATGGGGGGGTTTTTGGGATTTTCTCTACCAGAGCCCGCAATGAATT CATTACGGACTGCGCTACCCTGATCCGCCGAGGCTTTTCCCTAGTCAGTGAGTCAACAAACAACA GAGAATCTTGATTGACTTGTGCAGAATCCAGATGCCTTCCGTGTCCGAACCGACTTCAACGAAGT CGTCGTTTTGGCCCCATATTTCGCCGAGACAATTAGGGGCGAGCAACGACTCTCAGCGGGCATG TACACAGAAACTGTGGGTATTGGATCCTCTTGTTTCATCCTGGCATTGACATGTGTTCTTAGGAG TTGATGGGTTATATCCCAGGCTTTGAACCATTTGCATTTGCTGGGACACACCGCAATCTCTTACA CGATGTCATCACATCTAGGTTGAACCGTGCCTTGCGTGAGCAGTTACATCGAGCCTGGACAGAA AAACCAAACTCTAATTAACTCGGATTGGTAGCAAAGATGGTCAATTATATTTCCGTCGAGGCAAC AGACTCTCTCAGGAGAAGTTGGACAAATGAAACCGGTTCGTTGTTGTGGTTCCAAGTACGCAAT TTTGTGACCTAGGTAACTAACAACATCCAGAATGGCACAAAATTCCCCTGTACCAGGAGGCACT GATGCTGGTAGCTCAGGCCTCAATCCGTGTATTCTTGGGGCCAGAGCTCTGTCGTCATCGGCGA TGGGTGGAAATTAACTCACAGTATACGGTTGTCGCGCTGGGTGCTGTCAACGCGTTACGCAGAT GGCCCAGGTCTCTTATTCCACTGGTTCACTGGCTACACCCGCAGGTGAAGGCAACGCGAGCTCT CTTGAACGAGGCACGGGCTCTTCTTCAGCCTATTCACGAGAAACGGGCGCGTGAAATTGATGCA GATCCTGCAACACAGACCGATGCACTTGGATGGTTCGAGGAAGTAGCTGAACGACAGCCATAT GATCCGACGGTTGCGCAGCTCACTTTTGCGGTAGCAGCAATTCATTCTACAACAGACCTATTATG CCAGGTGCTTATAGACCTGGCTAACCACCCCGACATTATCCAGGAACTGAGGAAGGAGTTGGTA GATGTCCTGACGCGGGAGGGCTGGCAGCAATCCGCTTTCGGTCATCTCAAGCTCATGGACAGTG TAATGAAGGAGTCCCAGCGTCTCAAGCCTATAAGTCGAGGTAAGTCATTTCCATGTACGCAATC AACACACTGGCTGACTTGCTTCAGTGTTTAATAAACGCGTTGCCATGGACGATATCGAATTGAGC

	GAAAGCGTAAAGATTCCAAAGGGAGCCTACGTAGTTGTTTCGGCACATAATATGATGGACCCCA ACATTTATCCAGAGCCGTTCAAGTTCGACGCCTATCGTTTCATTAAGAGGGCGCAGGTGCCAGA CCTCGCGAGGTTCAGCAGCTTCTCAGCTGTCAGTCTCGAGCACACAGGCTTTGGCTTTGGCAAAC ATGCCTGCCCCGGTCGCACGTATGTCACTCTCGAACTGAAGATATTGCTGTCTCACATTATCCTCA AGTATGACTGGAGGTTATCAGACGGGTACAAGCCCAAGGTCTTTAACAACGGGTTTGACAGTGT GACCGACGTTACCGCACAGCTTTTGATCCGGAGGCGAAAAGAGGAGATTAACATCTTACCTGCT TAA
CtyC	ATGAGCCTGTTTTACAACGTTCTCGATGGCCTCTCGTTAAGAGACATCGTCTTCTTAGCGGTGCC CACCACATTTGTTTGCTACTTCATTACGGTACTTATTTATCGGCTTTACTTCCATCCTCTGGCGAAA TTCCCAGGTCCCAAAATCGCAGCAGGAACATATCTCTATGAAATAGCGTGGGACTATTTTGGTCA TGGAGCCTATCTCTTCGAGTGCGAGCGAATGCATGCGAAATACGGTTATATATGCACCTGTCCTT TCCTTTCCACCTGGTCAACTAACTGCTCTTTGTGTAGGACCAATTATACGTGTGAATCCTTCCGAA CTCTCGATCAAGGACCCAGAGTACTACAACACATTGTATGTTACAGGGGCAATTAGGAAAACAA ATGCCTGGCCTCACTTTGGAGATGGCATGGACTTTAACGGTATTTCCTCCCGTATTGAGTCTGCT CAATCTAGCGAGAAAGACACCACTGCTTACTTCAGCAGGGTCGCATGGAATGACTGTAGACCAT GATCACCACCGCCGGCGTCGCAAGCCCATGGAACCGTTCTTCTCACAAGCTGGAGTTAGTCGGA TTGAGCCACTTCTGCATGATCTTGTCCAGACGTTGGTTGCAAGACTGTATGAGTACCAAGGAACT GGCAAGCCAGTCAGACTGGACCATGTCTTCGCGGCTCTAGCAGGGGACGTTGTTAGTGCAATCT GTATCGAGAATCCCCAGATATCTTTCCTTCGCGACCCAGAATTTAGCCCCCACTGGTAAGTGTTA CTTCCTTGGGCCGTGGTTAACCCTTGGTAACTCCCGTATACATGCGAAAACAGGTACGATCTATT TCACACACTTATTTGCTCGATGCCTATTTTCATGAACTTCACCTGGATCATACAGTAAGTAACTTC TAATGCCTCCCAGACGATCTACCCACTGACTAAAGCACGTGGTGTTCAGGGTCGTCAGACTAATT CCTGCATGGTTGCTCAAGAGACTGGATCCAAGAAGTCAAATGTTCCGAGACTGGAGAAGTGTG AGATAATTTGAAGTTCACCGTTTTGCATCATTGAAAATATACTACAGAAATATTGACTGGTAAAC TCAATTCAACCTGCAGATGTCGCTCGATCACATTATTGAAGCCAAACGTCGCAAAACTTGCGGAA TTGTGCGCGACGACGGCAACTTCAAATACAACACTTTATTTGACCATTTGGTCACTTCCGACCTAC CTGAGTCGGAACTTTCAGTGGAGCGCTTGGCATCAGAAGCTCAGGTAATCATGGGAGCTGGTAC AGTTACTACAGCCCGGTCCATGGATCACCTAGTTGTTCACATCCTGCTCAATGAGGGCATTCGTC AACGACTCTGCGAGGAGTTGAGGGAGCCCATGGCCAATTTTCCTGAAAAAATGCCAAGCTACAA AGTCCTTGAGCAGCTTCCGTATCTACAGGCGTGCATCAAAGAAGGTCTCCGGTGAGTACCGCAC ACCATGTTTTAATCGCTGCCAACAGGAATCACTGATTTGTCTTGGAAGGCTGAGTCACGGAATCA TGCACCGTCTGCCACGTTGCTCGCCCAACGTCGAACTTCAATACAATGAATGGACTATTCCGAAG GGTGTGAGTGTCATTAGGTCTGATAGAGTCTTCATACATAGGATCGCTAACATGTTTCCAACAAA AACCCCAATAGACCCCAGTTGGTATGTCGGCCTACTATATGCATACAGATCCCGACGTCTTTGAA AGCCCATTTGTGTTTAGACCAGAGAGGTGGCTGGAGGGAGTCACTGCGGAGATGCAGCGTAAC TACGTCCCATTCACAAAAGGCTCACGAGGCTGCCTAGGAATAAAGTAAGTATATTTTAATCCATC TACTTTGCTGTATGTGAGTCTAGTTAACTGGTACAGTCTGGCTTATGCCGAGATGTCAATGGTTT TCGCGGCTCTTTTCTCTCCCAACGGACCGAAATTAAAACTATACCAGACTGATGCAACAGACGCC GACCCGGCCTGTGCATTTCTTTTACCATTGCCACGACTAGATAGCAAGGGTATCAGGGTCACTAT CGAATAA
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CtyF	ATGGATTATCTTTACTCAACAGTTGTTGACCCTTCCAACTACGAGACCGAAGGTCTCTGTGATGG TATTGATGTCCGGAAAAGCAACTACACTGAGCTTGAGGATCGAGGCGCCATCCGCACCCATCAG GATTGGACTAAGTATATCCGGGATTGTCGTGGATATCGCGGGACTCTTGGGCCAGAGTATAGCT TTATGTCTGTTGCCGTTCCAGAGTGCATTCCAGATCGTCTGGAGATTATCTCTTACGCAAACGAG TTCGCCTTCCTCCATGATGGTAAGTTGTTCCCAAGCTAGATAAAGACTTGCTTATTGTATTATAGA TGTCACGGAATTCGTTGATCATGAACTTGTAAGTTGAGGTTTCGAAACGGTTAGAGACCTGTGC TTACACGCTAGCTGGCAGGGAGGTATCGAGAATGACGACATGATGGAAGGTTTCCTAGAAGGT GCACAGTCTGGGTTCATTAATCCAGAAAAGGTTGAGACAAGACGTATAGGGAAGAAGCAGATC CAGTCCAAGCTCTTACTGGAGATGGTGGCCATCGACCGTGAGTGCGCCCTGGTGACAATGAAG GCTTGGGCGAAGTTCCTGGAGGTCGGGTCCAGCCGACAGCATGATACACGTTTCACTTCACTCA AGACATACTTGCCTTACCGTATAATGGATGTTGGCGAAATGTAAGTAGGATTTCACTCTTAACAG TATCTCATATTTACATCGGAAACCTGTTCAGGAACTGACTGGGGTATACAGGTTTTGGTATGGG GTAGTTACTTTCGGCATGGGCTTACACATCCCCGACCATGAGATGGATACCTGCCGCGATCTAAT GGCGCCGGCTTGGATTGCTGTTTGCCTTCAGAATGACCTATATTCATGGCCCAAAGAGCAGCAG GCGGCCCACAGTCGTGGCGAGGACCATGTTGTGAACGCGATCTGGGTTCTAATGCAAGAGCAT AACGTTGATGTCGATGGAGCCGTTAAAATTTGTCGAGACCTTATCAAGCGGTATGTTGCCCAATA TGTCCTTATTGTTAAGGAGAACAAGGACAATGAGCTCCTCTCTAAGGACCTCCGAAAGTACATTG AGGCAATGCAATACAGTATCTCTGGCAACGTTGTCTGGAGCCGCACATGTCCACGATACAATCC GCATGCCTCGTTTAACAAGACGCAGCTGGACTGGATGCACAACGGGATCCCAGCGCTGGACTCT TCCAGCAGTACCCAGAGGTCTTTGAAACAAGACTCGAGCTCCACCAGCCCAGAGCCGTCGAACG TAACCTCACCGTTACTTGACATGGACCTGTGGATGTTGACAGAAATGGACAATCGTCATCTACAA CACAGTGAAGCTTTTCCTAGCGTATGTAGATACTGGTCGCTACATACTATCCGGCAGCCAGGAG AACAACAAAGCTAACATAACTACTATATTTTAAGGATGTCGTTGAAACTCCATATCACTATATAT GTTCTTTACCATCGAAAGGTGTTCGCGATCGGTTTATAGACGCAATGAACCATTGGTTCGAGGCC CCACGTGGAACTTTGGACGAGGTCAAGAAAGTCATCAATACGCTACACAACTCATCGCTCATGT GAGATCCCGAATGCCCGTACGGCTCTTAACTCTAAGAGGTTTGCTCTAATGATTGAATCATAGAT TGGACGACTTCCAAGACGGCTCGCCATTACGACGAGGCAAACCGGCTGCTCATACCATCTTCGG TCCTGCACAGGCAGTTAACTCATCGAGTTATTTTATCGTCAAGGCTATTGCGCACATTCAAAGCT TTTCAAGACCTGTGGACTTGAAGTTTGCCATAGGTAAGCATTTGGAACTTCCTTATTGAGATTTTC CGTTCGCTAATAGTCCCTTTCCCCCTCTTTAACAGAGAAAATTTTGGAAATGTTTCAAGGCCAAGC AATGGATCTACACTGGACATACAATATCGCCTGTCCCTCTATCAACGAGTATAAAAACATGATCA GAAAAAGTAAGGGAGCTTGCTTTCCGATGCTGAAAATTTTGGATCCTGAGTGATTAATGAAAAT AGAAACCGGTGCTCTATTTGGGCTAGCCAGCTACCTCATTGGAACTCATTCACCCGTCGCCATGA CGAGCGACACGCTCACGGCCACGGATAGAATGACAGCACTCCTAGGCCTGTATTTCCAGATCCG CGATGACTACCAGAACCTAATGTCTACTGATGTGAGTTACTTGTTGTCTCCGATATCCTATACAAT AATCTAAAATTCATAGAAAAAACTCCTTCTAATTTACTTCTAGTACACTGACCAGAAAGGCTTCTG CGAAGATTTGGATGAAGGGAAATACTCCTTGCCCCTGATTCATGCTCTCGAGACCCACCCGAGC AACCTGTCGCTAAGAAATATTTTATCGACACGGCATGTGCATGGGCAGCTGACCCGCAAACAGA AAGAGTTTGTGCTGGAGGAAATCAAAGCATGCAACAGCTTGGGTTGGACAAAATTGGTTCTCGC CGACTTGCACTCCCAGGTTGTGGCAGAGATCGACAAGTTGGACAAGGTTTTTGACAAGGAAAAC TTTGAGATCAAGACTCTCATGGAGTTCCTACGCATCTGA
CtyG	ATGGATGCAGTTTTTTTTGGAAAGATGGACCAGATTCCTCTTGTCGGGCTTTGGGGTATTGTAAG TAACCTACCAGCTTGGATATTGCGCACTAATCACCACTTGCACTTCAGGCCCTTCTTTTGATCCTT

	GGGCAGGGACTGTACAATATCTACTTCCACCCAGCTAAAGACTTCCCCGGTCCTTACCTTGCAAA GGCAACACGTCTATACTACTCATACTACCGAAGCACCGGACAACTCGAGTTTAAGACCAAAGAG CTTCATGATAAATATGGCCAAGTTGTGCGGCTTGCACCGGATGAATGTATGATCTTCTGCACCTT CTACTCTAAGACATCTTTGGAGTTTCATGAATGCTGATGTAGGACTGGTATCTGCCCCTATCAGT GAGCTTCAATGGTGGTACAGCATGGGACGATATATATGGGTTCAAAACTAAGAAATCGTCTGGA AAGAATCTAATGTAAGCGAGCTTAGCGGGTGAATTTGCATGCTTATTTGTCTAATATCTCGATAG GAAAGACCCTCACTTTTATATAGGTGCCACGGCGCCGAATGGCGAGAAGAATTTGGTAAGCTTT ATCTGTGGATTTCTCTCAATGCACATTCCAGCTAAGCCCATATAATCAAAATCTTACAGGGAGCA TCTGGGGATCTTGACCATGCTCGAATCCGAGGCGTTCTTTCATATGCTTTCTCCGACAAAGCCCT CTACTCTCAAGAAGTAACTCTCATCAGCCACATCGACCATCTTATCCGACGGCTACATGCGCTTA ATGGACAGGCCACTGATGGAGTGCGCTGGCTACACCACTGCACCTACGATATCATCACGGACCT AGCCCTCGGGCAGAGCGCTAACACACTTGCCTGTGACACATGGAGCCCTCAAGCACACCTCATT TTTGAAAGTATCAAGGAAGGTATTGTGTTCGTTGAGATATTGCGGTTCTTGCCCTTCAAGAACCA TATCCTTACCTTCTTCATGAAGATGTTTGGCACTGTTATGCGTCAGAATTTCGATCAGGCTGTCGA AAGAGCCCGCAAACGCATGGAGACACAGGATATAAACAAGCCCGACTTCATATCCTACATTCTG CGAGCCAACGAGTCAGCCCGGGCTCTGACATCGAAGGAGATTACAGCCAATACTGCGCTTCTCC TTGACGCCGGTTCTGAAACCACTGCTTCTCTACTTTCAGGTATATAGAATGATCTCCTTCAATTCG CTCCTACCCTAACCTATCTAGGATGCCTGTTTTACCTTGCCAAGAATCCAGATGTCTTGAGCAAAC TAAGCCAAGTCATCCGCGAAAGATTCGCCCAGGAAAACGAAATGGACTCTAAGAGCCTAGCACA ACTCCCGTACCTCACAGCCGTCCTCAATGAGTCTTTACGCATTTACCCATCCGTGGCATCATCAAC ACCACGCTTGACACCACTGGGTGGGTCTAAAAGTACGTCAAATCAGGTTTGAGTTACTTCACCCC CGTTCTACAGACCACGAGGCGGGTGACTTCAAAATGAAAGCTAACTTTTGGTCTATCTGCAGTC GATAATCGCTTTGTTCCGGGTAACATCATTGTTGCAGTGAATCAGTATGCTGCGTACAGGTCCGA GGATAATTTCGCTGATCCCTACTCCTTTATTCCTGAGCGTTGGCTTAGTGGTAACAATGATAAGC GCTTTGTCAATGACAAGCCTTCCGTTCTGCAGCCTTTCTCAATTGGGCCTCGGAACTGCCTTGGA AGGAAGTATGTATCCTGCCTATCTAGCTCCGGTGTTTCTTCACAATGTGTTATGCATGTATGATTT ATTACAAACTGACTGTATTTGCTAGTCTTGCTTGGCTCGAGATGCGTCTGGTATTAGGCCGTCTA TTGTGGAACTTTGACTTGGAACTCACTGAGGAGTCTCAAAATTGGCACGCCGTGCAAAAGACAT GGTTTATTTGGGATAAGCCTGATCTCATGATGCGATTCAAGGCACGACAGACCTTGCCAATTACT AGCAGTGAGTGA
CtyH	ATGGATTCTAAATCGACGTTTGATATTGTGCCACTAGACCATGGCCCTGATTCCAAGGCTAATGT GAGTTGGGCTTTGTTTTCTTCTCATTACTCGGCATGCTAACCTAAAGTCCCTGCAAGTTTGGAGCT GCAATCTATGGGCTTGATCTGGGCAATATCACAGGTAAAAATGACACTACTCGGAACCTTGAAA TATTTAGGAAAAGATGTATTCTGACTAAAGATAGATGATGAACTTGCACGACTACGGAATGCAG TCATGCAGTATAAGGTGGTCATTGTGAAGAAGCAGTTCTCGCTGGCCCCAAAGAAAAATTGGGA GTTGTTGCAACGGCTTGACCCTGAGGCAGCTTCATACAACACGGAAGAGTTTGGTAAACTGTTC CACCCGACTGGACAAGGCATTATTGTAAGACTCATCTCATCCGGTCAAAGTATGCCCATTCTCTG CTAACAGATACGTTTATTAGGAAAAATTAAGGGTCGCCACTGTACCTGATGCCGGCCAAATTCAT CTCATCGGCAAAGGATACCAAGGGGATGATCATTATGGCATGAAGAAGCTCAACCTTGGCGAG GCATTTGCCAACGGCTACTATTCGAAGCCGTTATCCGAAGAAGCATTCGAGCAAGGCGTAACTC GTTTCCAATCATGGCACATGGATGGCCCTCTGTATAAAGTGAATCCTCCTATGATTAGCTCGTTTC GCATCATCAAATTTCCGGTAGGCGAACAAGAGGTCGACTGGGCCGACGGCTCTGGGTTCAAGA AGCGGGTCCCCGCGGGGCGCACTGCCTTCTTCAGTACATCTCAATTGTACAGTCTATTTTCCGAC GAAGAGAAGAAAATGGCGGATCACAGCTGGGTGGAATATATGTTCTATCCATACGAGTGGATT CGCGGCTGCCATGGGAACCCCAATGGATTAGGTGTGGCATCTGAGGGTCAAGAGGTACCTGAT GAGCAGTTAGCCGAGCTGGCTCCAGACAGGCACCCTTCATGGACCCGGGTGGTGAGAAGACCC TTACTCTCCAACAATATTCATTCTATGCACCATTAAAAGCACTTGGGTTCGTATCGCTAACTAGGT TATGCCTCAATGATCACAGCTCCCGATGGTATGGGTGAACCCAACGACTGGTGAGAAGGCATTC CAGGTGCAGCCTAACTGTGTGCGCCGAGTTTTCGTCAGACACAACGCCAACGATTCGCCTAAGG TTATCGAGGATGTGGCAGAGGTGCGAGATTTCCTGAATCGCCTGCAGACCCGCATTGTCAGGCC TGAGTACATCTATGCTGGCCCCGAAGACGAAGGAGATCATTTGCTGTGGTTTAACTGGGGCCTT ATGCATAGTAGGATTGATTATCCCATTAAGTTTGGACCCAGAATTACACACCAGGGTTGGATCCC TTCCAGCCGTGCACCTACTGGTCCAGTTCCGATTCCTCAAAATATCTAG
CtyI	ATGGCCGAGATTACACAGCAATTAAACAAGGTTGTGGCCATGGTTGATGACCTTGCTAGCAAGG CAGATGTCACTGGGCGACGGACCATCCAGGACATACTGATGAAACTCCAACACTCACTCGAGAC TCCTTTCGAGACAACCATGAGGATGTATGACTGGCATCACCGGTCCATGGTTGTTAGAATGGGT TCAGATCTCCAGATCTTCAAGTTCCTATCTGAGAGCCCCAACCCACTGACAGTGGACGATCTTGC

	CAAACGCAACGGCGCCGCGCCGCAGCTTCTTGGTCAGTAGTCATATTCCGCGCCTATCGCATAA AATAATCTTATGGTTCCTCTTATATTACTTTGATTCTGATACCGTCAACGACCAGGCCGCATATTG AGATATCTTGCATCAGAGGACATGATTGACGAGGTCGATCAGGACACATTCACTGCAAATAAAA CGAGCAGGTGGTTTGCAACCGATGACATGGATGGTGGGATTCATCTCTCGTAAGTGTAGCTCCC ATATCCCAAGGCTGACGTGTTAAAAACACTATTGTCTTTCACGGCATCTTTGAAATGTACGCGTG ACTAACGTCAACTCTTGCTCGACCTAGCTTTGATGTGTGTGGCCGTACATACCAAGCACTTCCTG ATTTTCTGCTCGAAAAAGGCTATCAGAATATCACTTCCAACACCGACACTGCCTTCAACAAGGCG TGGGACACACAGGATCCCTGTTTCTACTGGCTCCGTAACCAGCCTAAGTTCTTCAAGTACCTACA CCATGCACTACAACTCCAGCATCGTGAAGATTACTTAACAAAGTTCCCATTGGAGTCATATCTCG GAGACTTTGCAGCTCAGGCTACTGCGGACACCCAAGCAGTATTATTCGTTGATGTTGGGGGAAG CTTCGGCGTGCAGTGTAAGGGGTTGAAGGCCAAATACCCGCACCTAGCTGGACGTGTAATCCTA CAAGACATGAAGGAAACCATTGATCTAGTAAGGGAAGATCCAATTCCTGGCGTTGAGCTCATGG CCCAGGACTTTTTCCAGCCCCAAGTTGTCAAGGGTAAGCAAACAGCAGAAATGTTCCTTTCCTTG GAGAGATAAGAGTAAGGATAACTGACGGAGGCTGCTTTTCTTAAATACTCAGGAGCCAAGTTCT ACTACCATCGTAATATCTTCCATGATTATCCCGACAACCGCGTTCTGGTACTGCTGGAAAATCTCC TACCGGCCCTCAGTCCCAGCTCTCTTATTCTCATCGATGATAAAGTTTTGCCAAACAAGGGCGTA CACCGACATGTCACAATGATGGACATAGCTATGCTGGCACAGACAGGCTCCTTGGAGCGGACCA TCGACCAGTGGAAGACTCTTCTAGACCAGGGTGGTTGCAAGATCCTCGACATCGTGACGTATTC GGATGAGCACGACTCTATCTTGGTCGTGGCCCCTAAGAGTAGCGAGTTGAAGTTCTGA
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SUPPLEMENTARY FIGURES

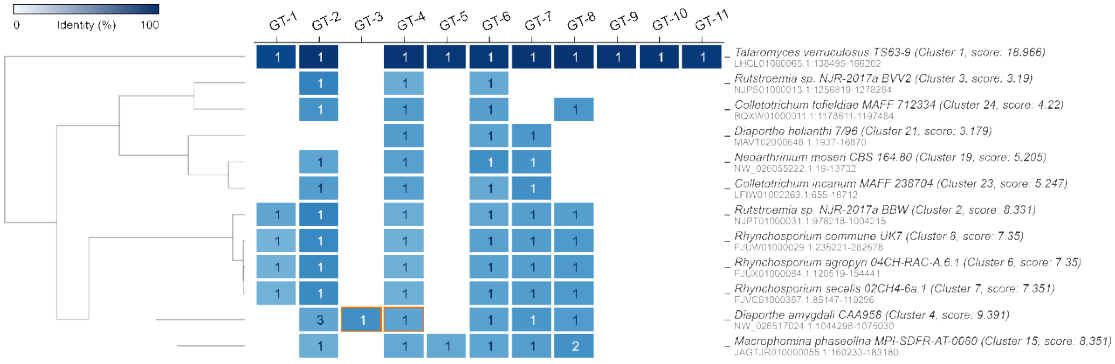


Figure S 1. The profile of cblaster, the first line was a highly similar but longer biosynthetic gene cluster (BGC) in the *Talaromyces verruculosus* TS63-9 strain.

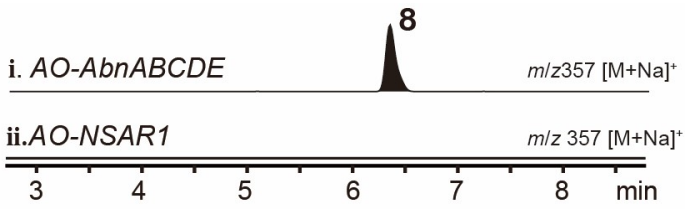


Figure S 2. EIC chromatography profile of *AO-AbnABCDE* and *AO-NSAR1*.

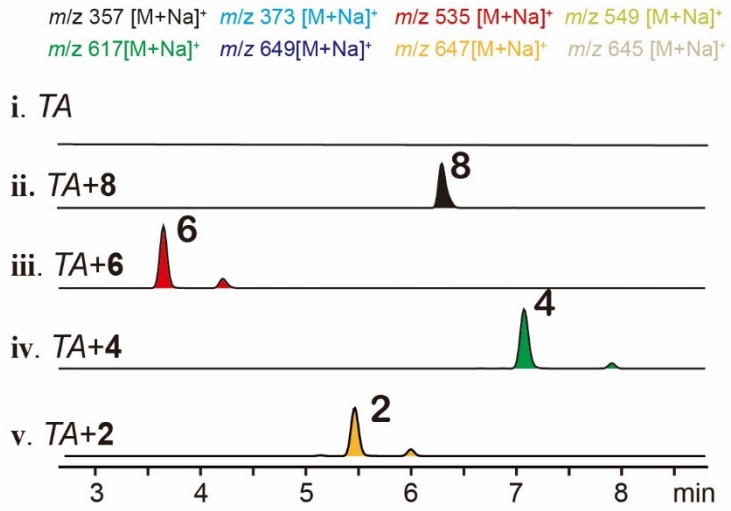


Figure S 3. EIC chromatography profile of *Talaromyces adpressus* fed with **8, 6, 4,** and **2**. No new generated cotylenin was detected.

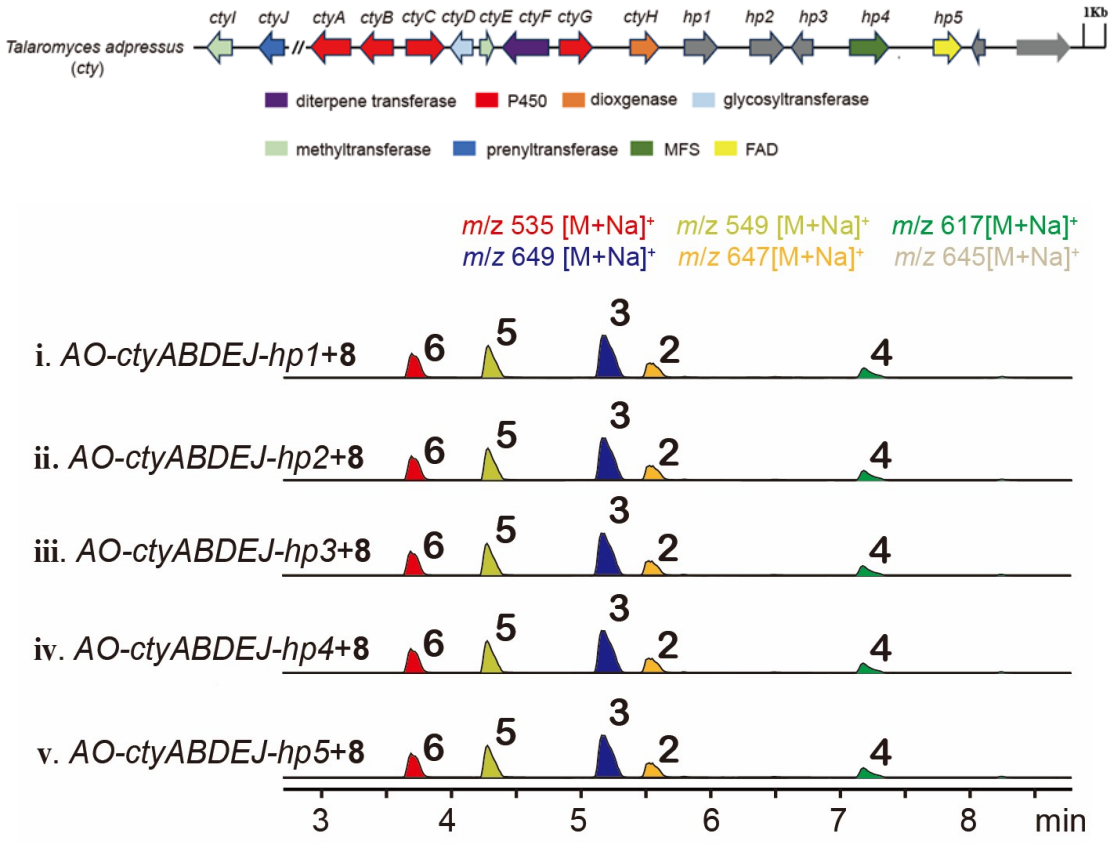


Figure S 4. EIC chromatography profile of the other unknown function gene were co-transformed with *ctyABDEJ* and fed with compound **8**. No further oxidation product *m/z* 645 [M+Na$^+$] was found.

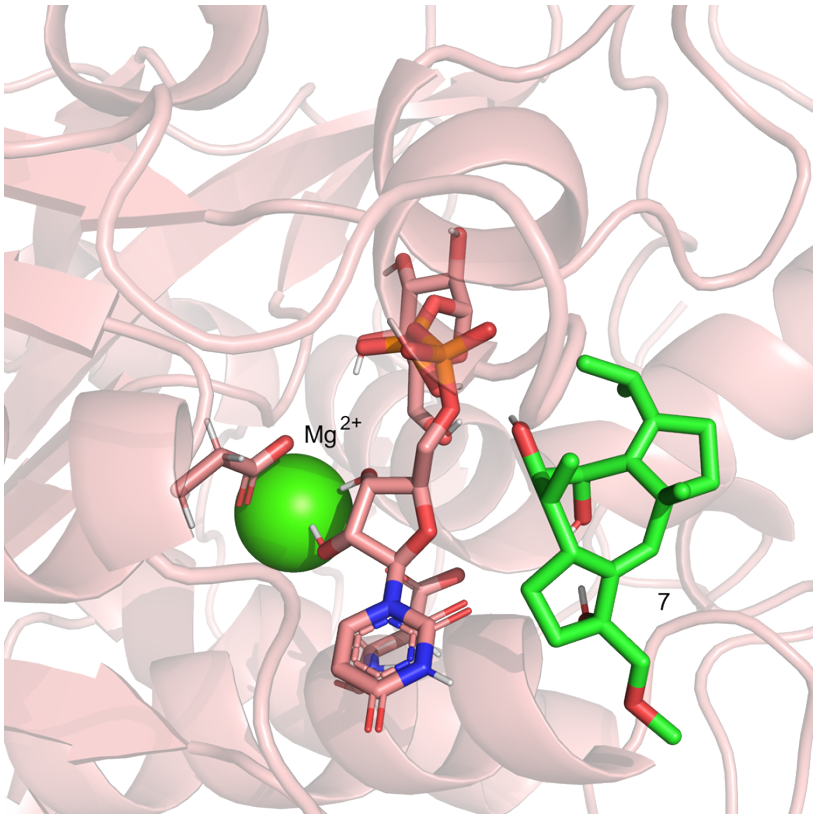


Figure S 5. The molecular docking between CtyD and its substrate **7**. CtyD was modeled on Alphafold2.

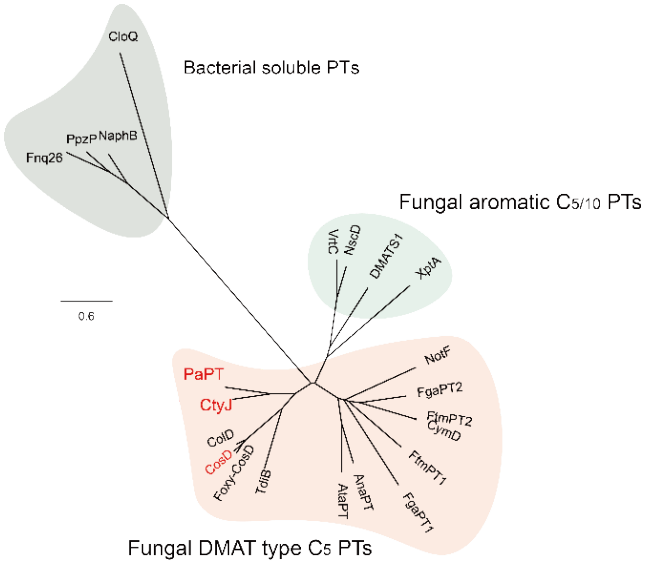


Figure S 6. Phylogenetic analysis of CtyJ and its homologues with other well-documented fungal and bacterial soluable prenyltransferases shows that it is clustered into fungal DMAT-type C5 prenyltransferase clade. PaPT (H7CE84), a DMAT implicated in the FC biosynthetic pathway, exhibits a close phylogenetic relationship with CtyJ. Additionally, another DMAT enzyme involved in the modification of the sugar moiety for cosmosporaside C, denoted as CosD, has been recently reported[11].

The accession number of DMAT-type PTs used in this phylogenetic analysis were listed below. PaPT (H7CE84), FgaPT2 (AAX08549.1), FgaPT1 (XP_756136.1), FtmPT2 (XP_747179.1), AnaPT (A1DN10.1), CymD (KAG2001332.1), TdiB (ABU51603), NscD (NFIA_112230), VrtC (ADI24928.1), Fnq26 (CAL34104.1), PpzP (C4PWA1.1), NaphB (1ZB6_A), CloQ (Q8GHB2.1), NotF (E0Y3X1.1), FtmPT1 (AAX56314), DMATS1 (S0EH60.1), XptA (KAI8293691.1), AtaPT (5KCG_A), Foxy-CosD (XP_018252512.1), ColD (RDW88426.1).

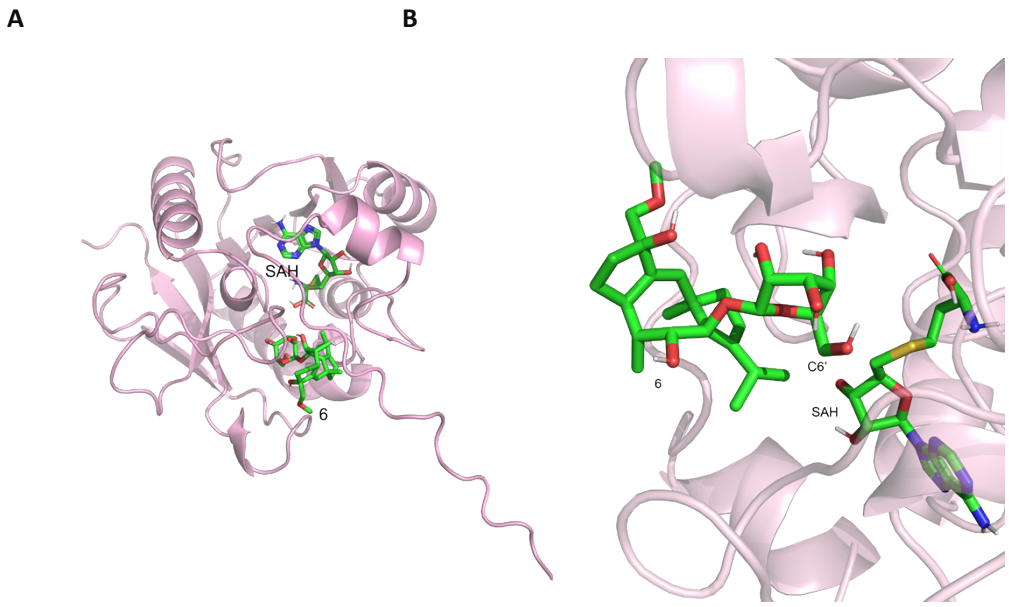


Figure S 7. The molecular docking between CtyE and its substrate **6**. **A**): The aglycone portion of **6** situated outside the cavity and the glycosyl part positioned within the reaction pocket, in proximity to the cofactor SAH. **B**) shows the docking scenario within the reaction pocket between **6** and SAH, where the C-6' hydroxyl group of the **6** glycoside is oriented towards the sulfur atom of SAH.

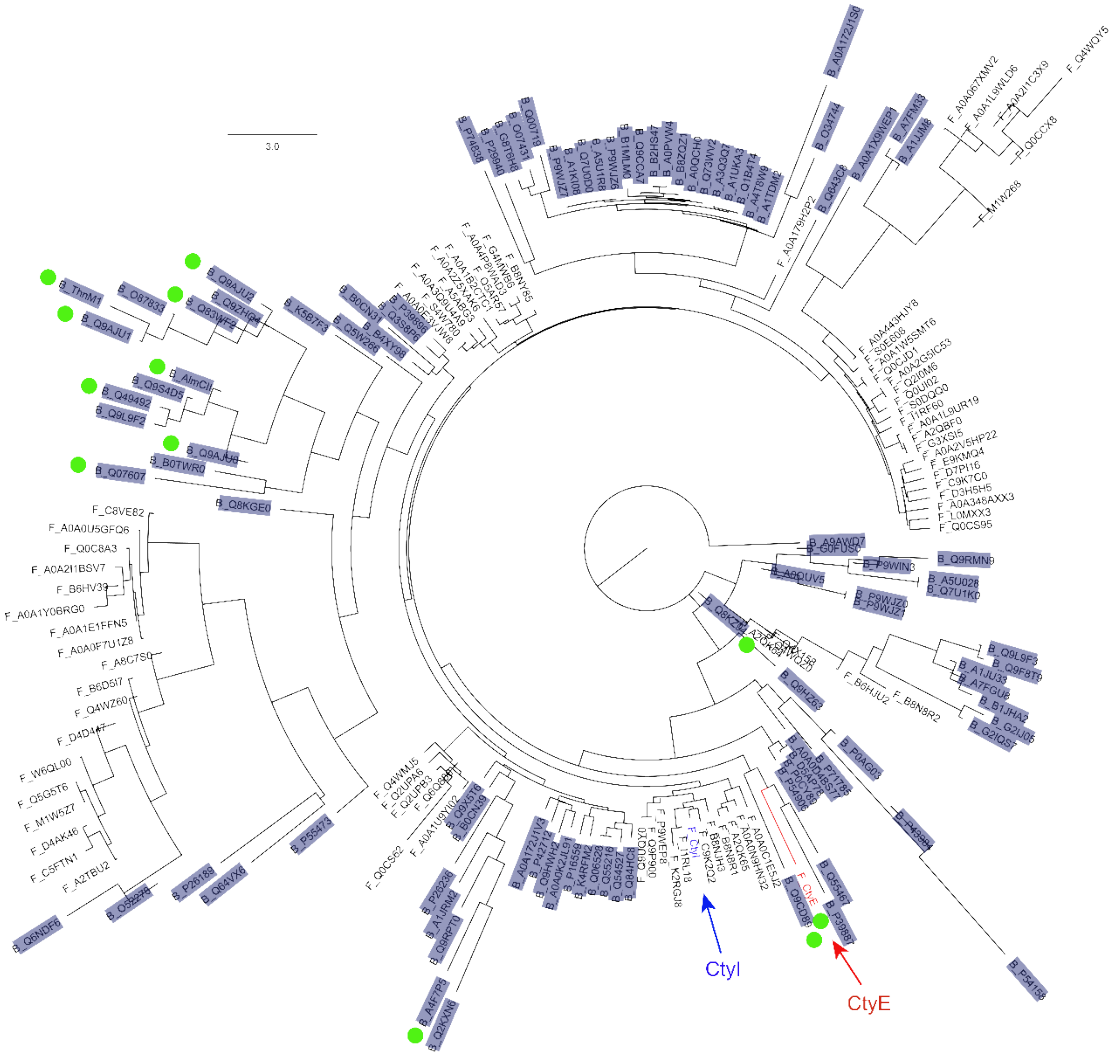


Figure S 8. A phylogenic tree of methyltransferases from bacterial and fungal origins, mainly focusing on the modifications of secondary metabolites. Highlighted within the tree are two key methyltransferases from the *cty* cluster, CtyE and CtyI, indicated by red and blue arrows, respectively. Enzymes originating from bacteria are denoted with a prefix 'B_' in their UniProt identifiers and are highlighted in gray. Enzymes from fungi are marked with a 'F_' prefix before their UniProt numbers, without highlighting. Additionally, enzymes involved in methylations to sugars are further annotated with green dots next to their names, including RebM (Q8KZ94), ML0127 (Q9CD89), EryG (A4F7P5), DapA (Q07607), ElmMIII (Q9AJU0), MycF (Q49492), AlmC Ⅱ (G0LWU9), ElmM Ⅱ (Q9AJU1), OleY (O87833), MycE (Q83WF2), ElmMI (Q9AJU2).

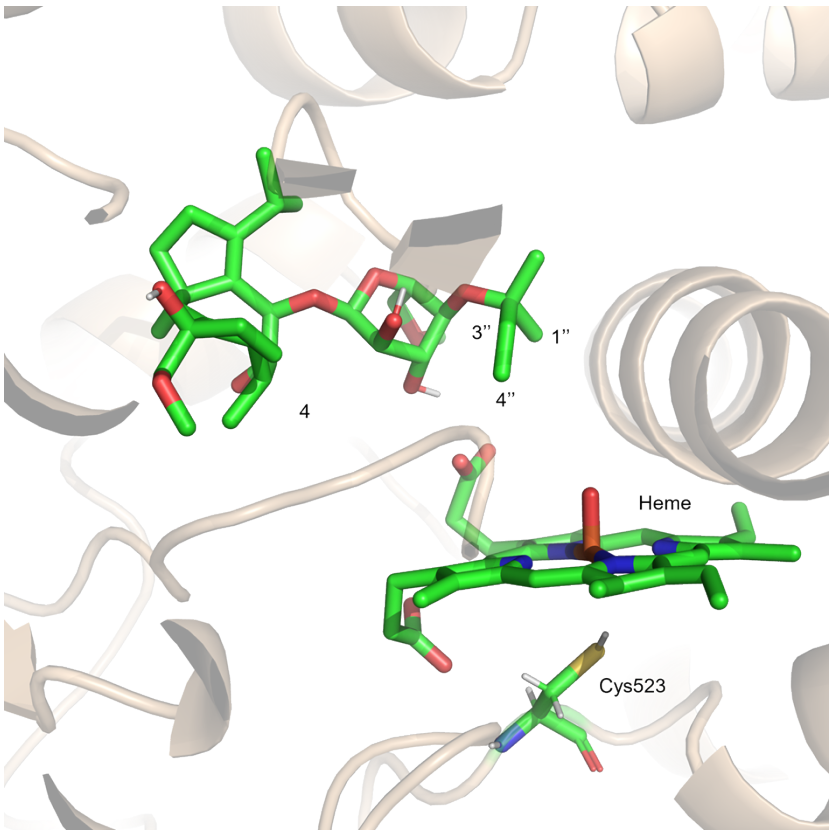
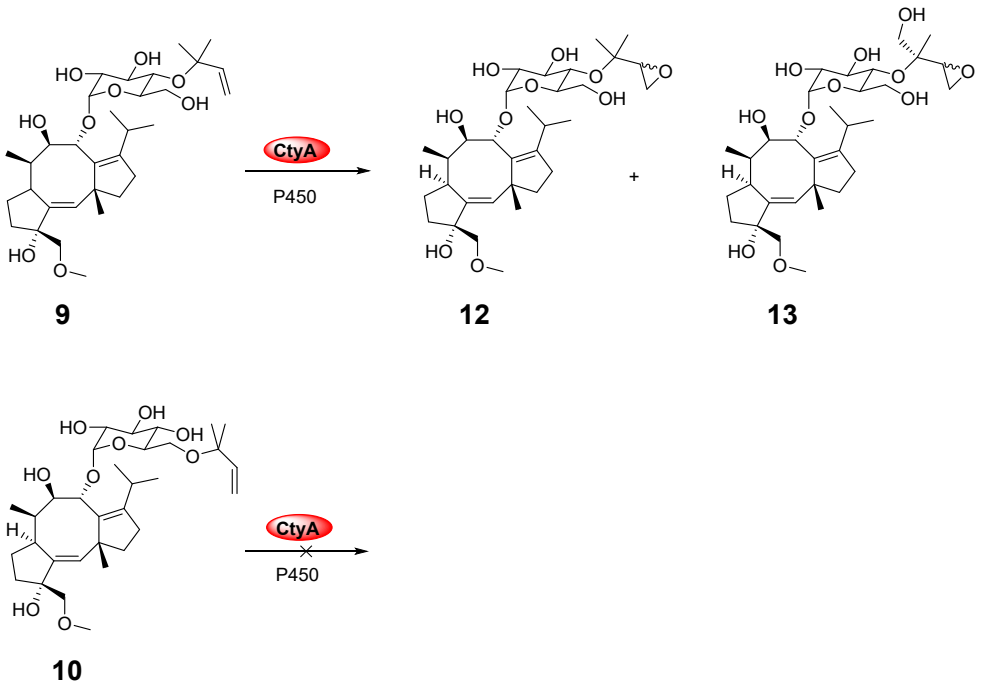


Figure S 9. the molecular docking scenario of CtyA with the substrate **4** and the coenzyme Heme. In CtyA, the Cys523 residue coordinates with the Fe in Heme. The reverse prenyl group on the glycoside of the substrate **4** is oriented towards the iron center of Heme.



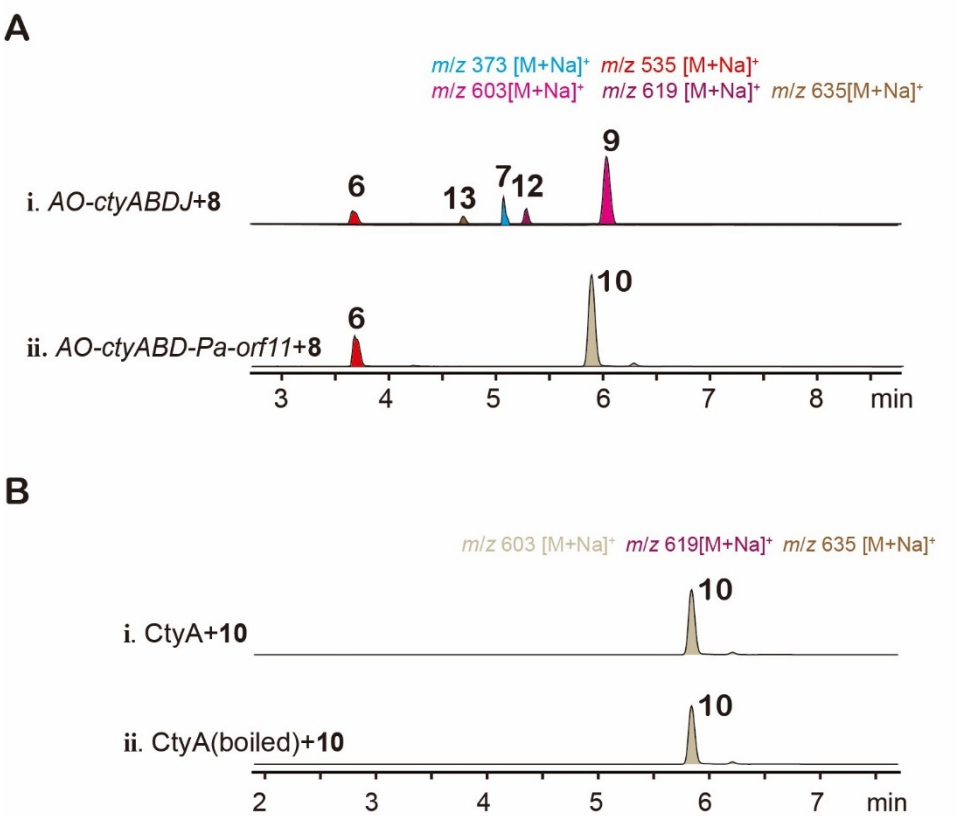


Figure S 10. A) EIC chromatography profile of *AO-ctyABDJ* and *AO-ctyABD-Orf11* fed with **8. B)** EIC chromatography of microsome fraction from yeast expressing CtyA reacting with **10**.

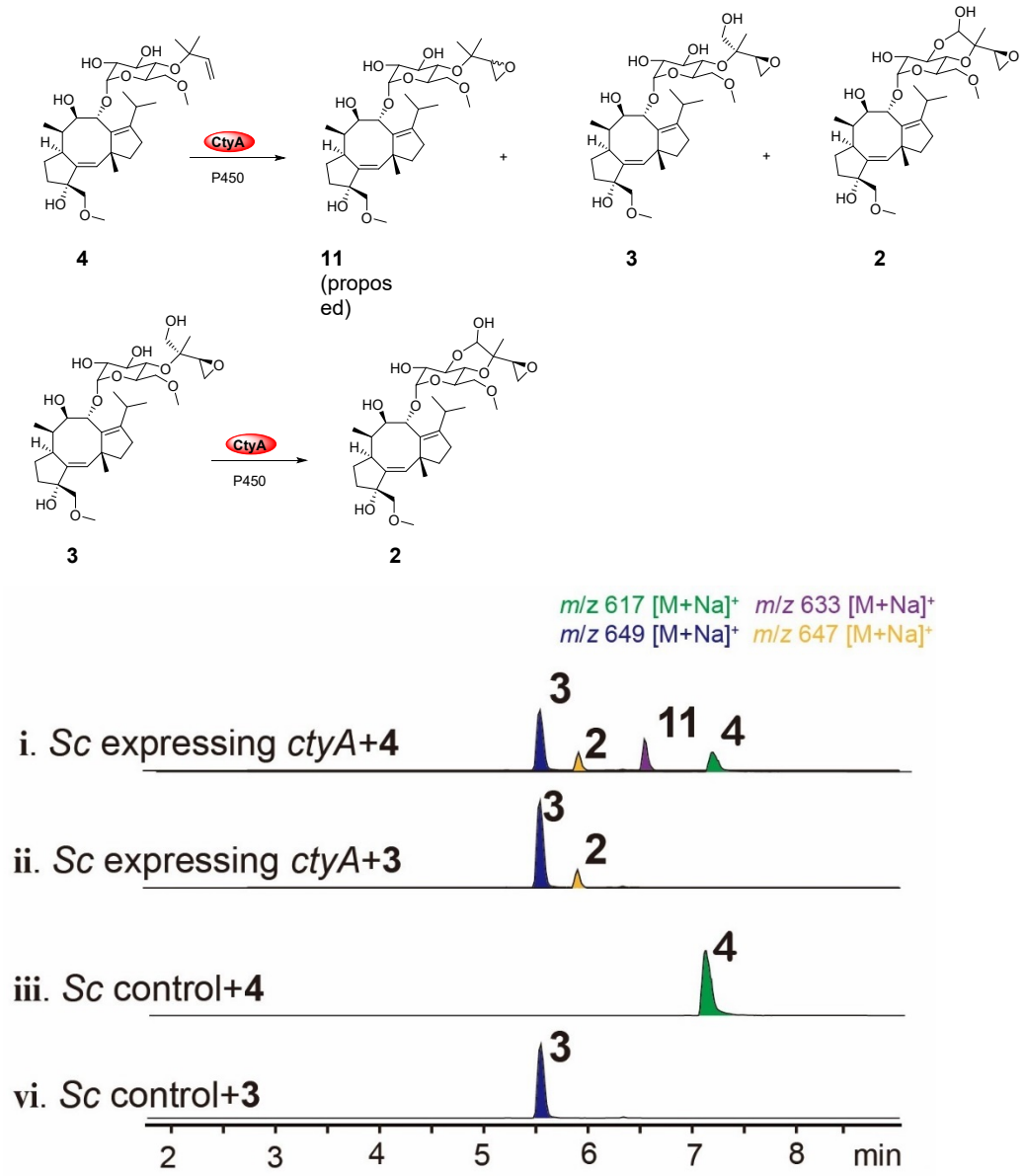


Figure S 11. EIC chromatography profile of *Sc* expressing *ctyA* fed with **4** and **3**. **i** and **iii**) *Sc* expressing *ctyA* fed with **4**. **ii** and **iv**) *Sc* expressing *ctyA* fed with **3**

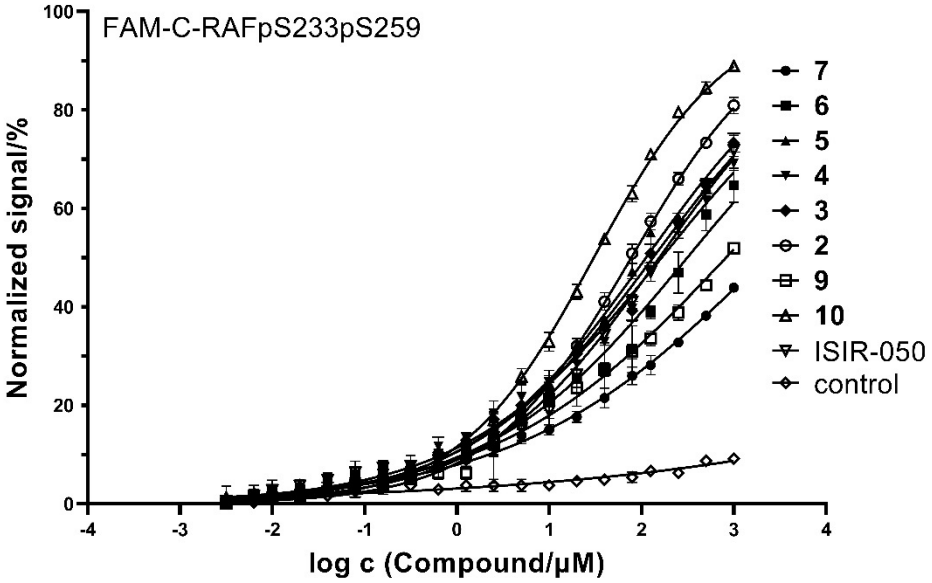


Figure S 12. FP measurements of FAM-labeled C-RAF phosphopeptide (20 nM in 10 mM HEPES,150 mM NaCl, 0.1% Tween-20, 0.1% BSA, pH 7.4) and 14-3-3ζ (0.25 µM) titrated with different cotylenins to obtain EC_{50} values. Error bars indicate the mean ± SD of at least three experiments.

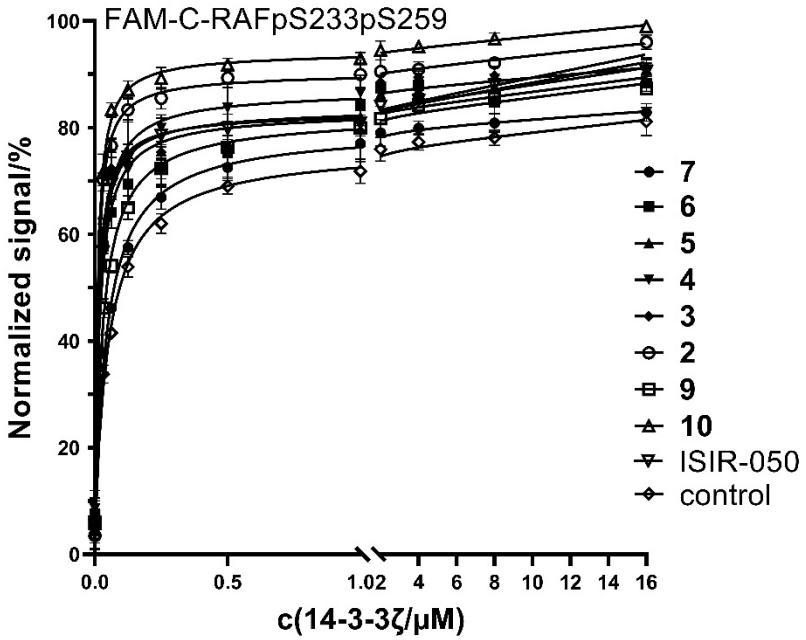


Figure S 13. FP measurements of FAM-labeled C-RAF phosphopeptide (20 nM in 10 mM HEPES,150 mM NaCl, 0.1% Tween-20, 0.1% BSA, pH 7.4) in the absence (control) or presence of 150 µM of the different cotyienins titrated with 14-3-3ζ to obtain the apparent K_d of the 14-3-3ζ/ FAM-labeled C-RAF phosphopeptide interaction. Error bars indicate the mean ± SD of at least three experiments.

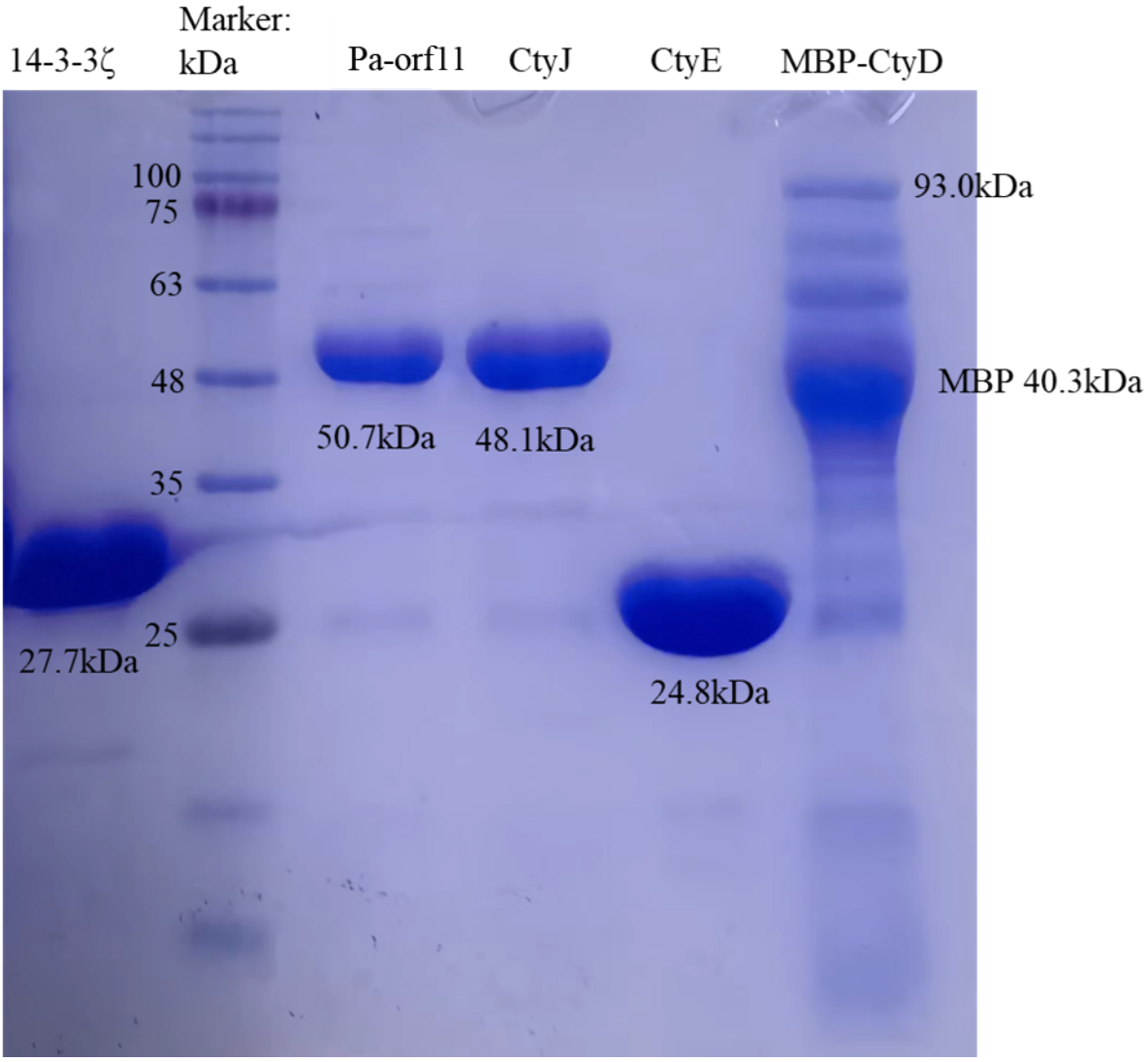


Figure S 14. SDS-PAGE of MBP-CtyD, CtyE, CtyJ, Pa-orf11 and 14-3-3ζ purified from *E. coil* BL21.

Figure S 15. ^{1}H NMR spectrum of compound Fusicocca 2,10(14)-diene in $CDCl_3$ (600 MHz)

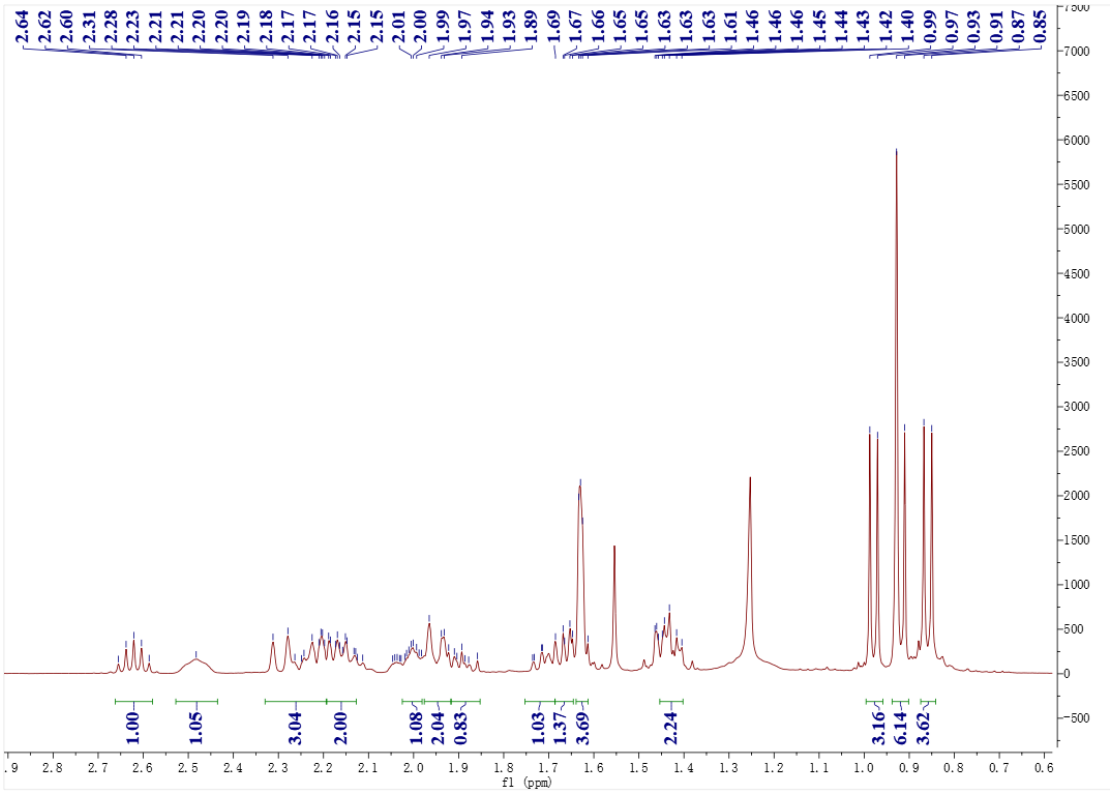


Figure S 16. ^{1}H NMR spectrum of compound **8** in $CDCl_3$ (600 MHz)

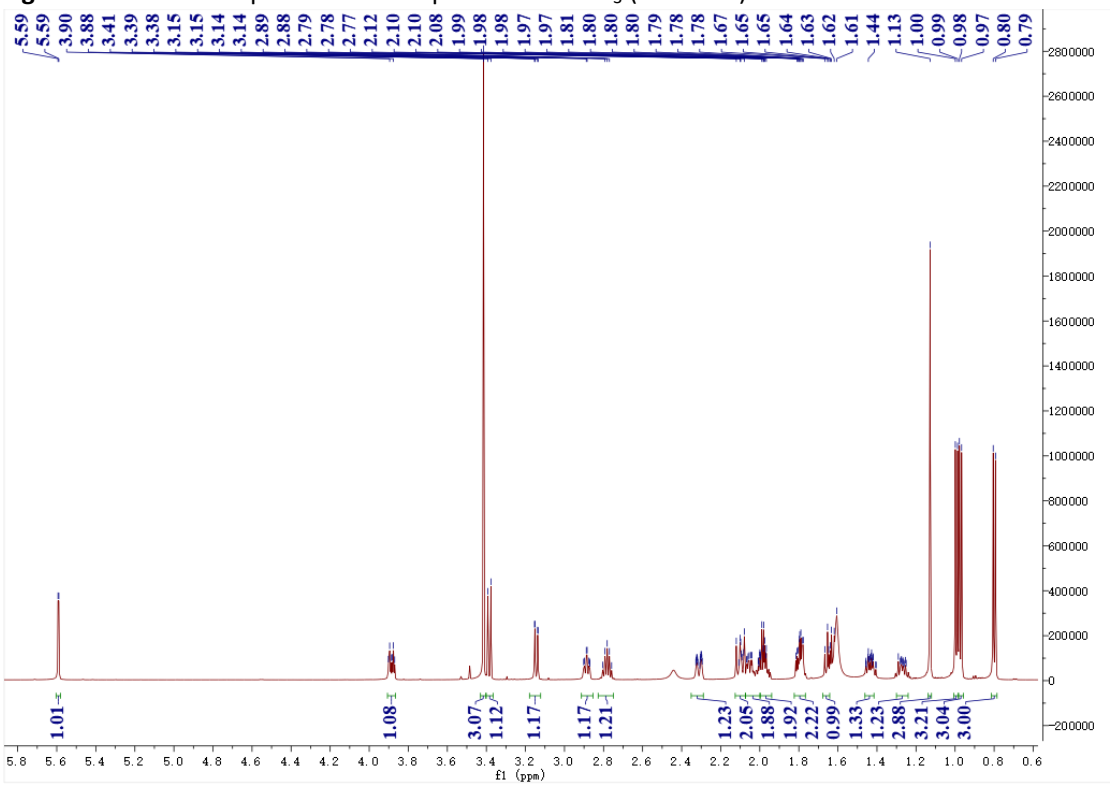


Figure S 17. ^{1}H NMR spectrum of compound **7** in $CDCl_3$ (600 MHz)

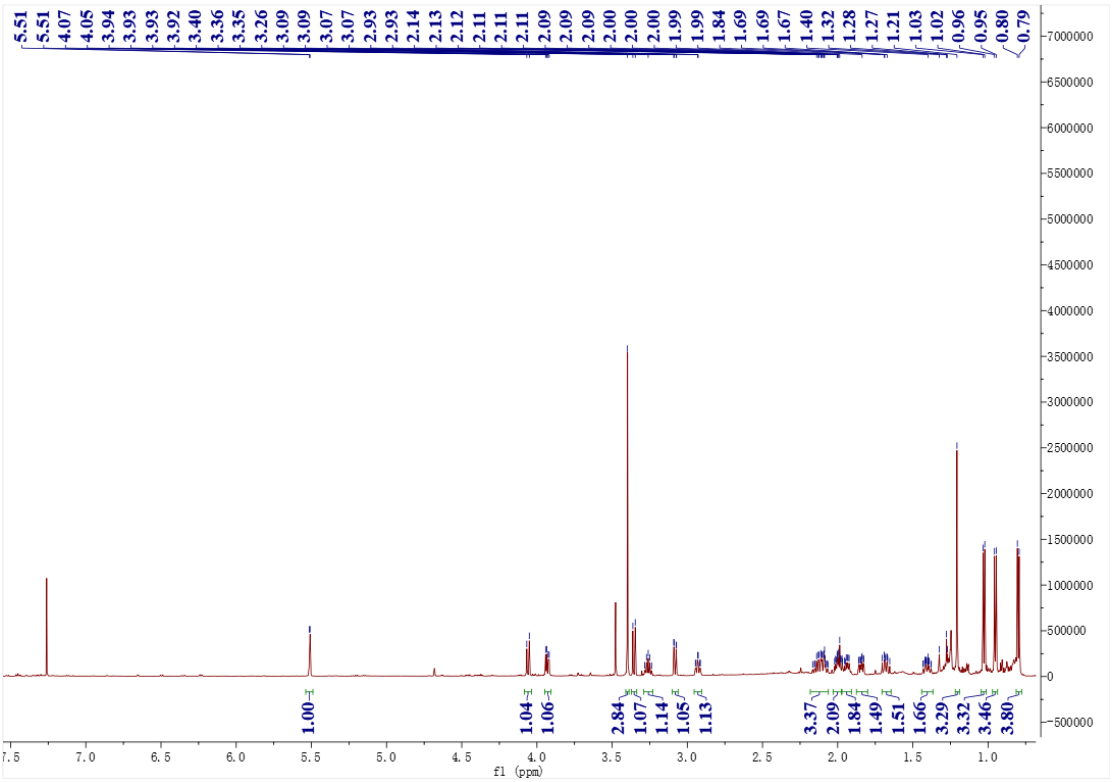


Figure S 18. ^{13}C NMR spectrum of compound **7** in $CDCl_3$ (150 MHz)

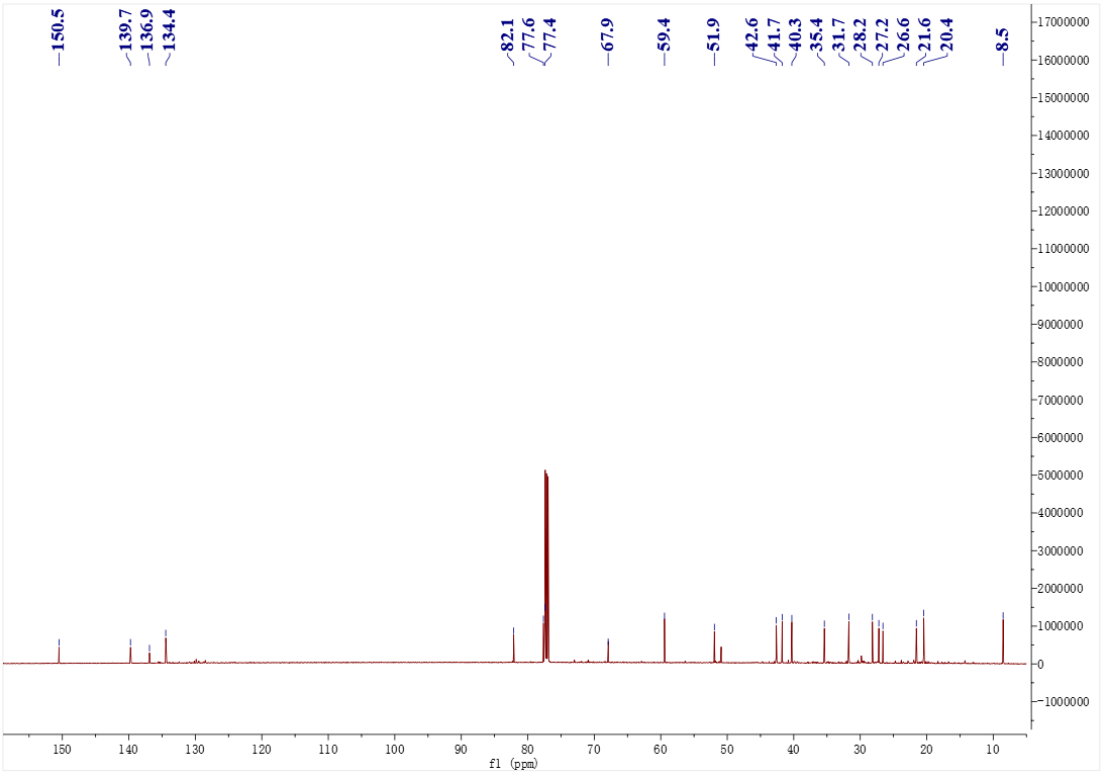


Figure S 19. ^{1}H NMR spectrum of compound **6** in CD_3COCD_3 (600 MHz)

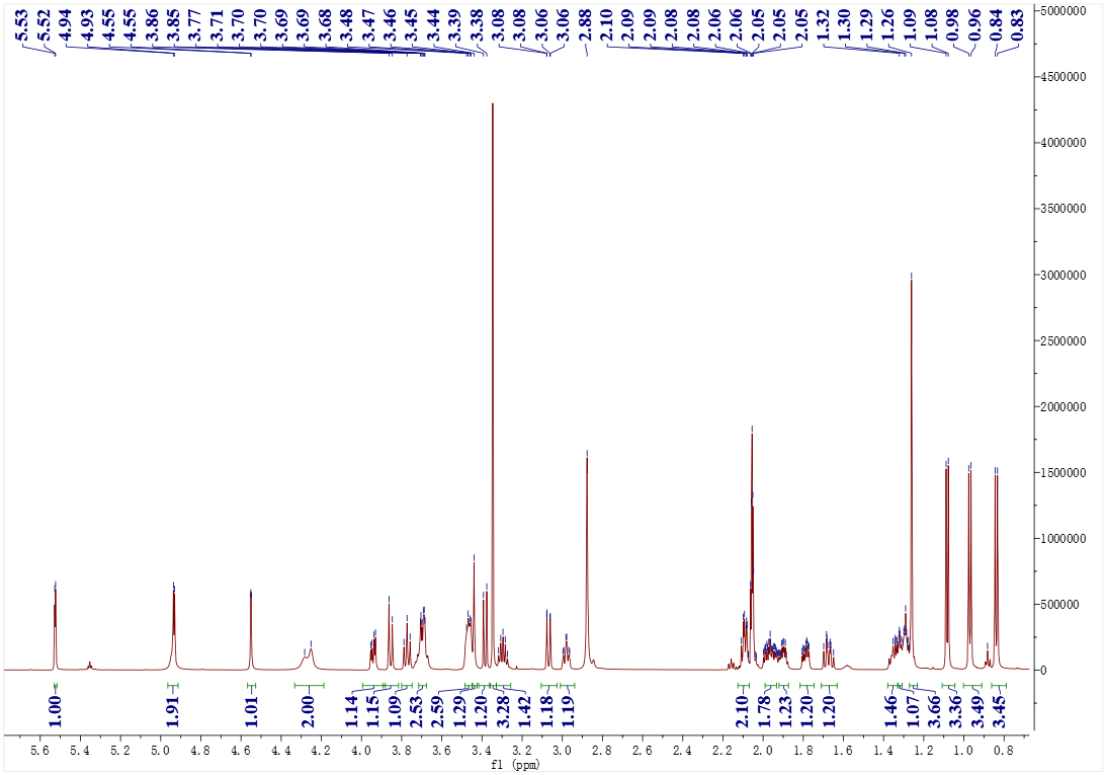


Figure S 20. ^{1}H NMR spectrum of compound **6** in CD_3OD (600 MHz)

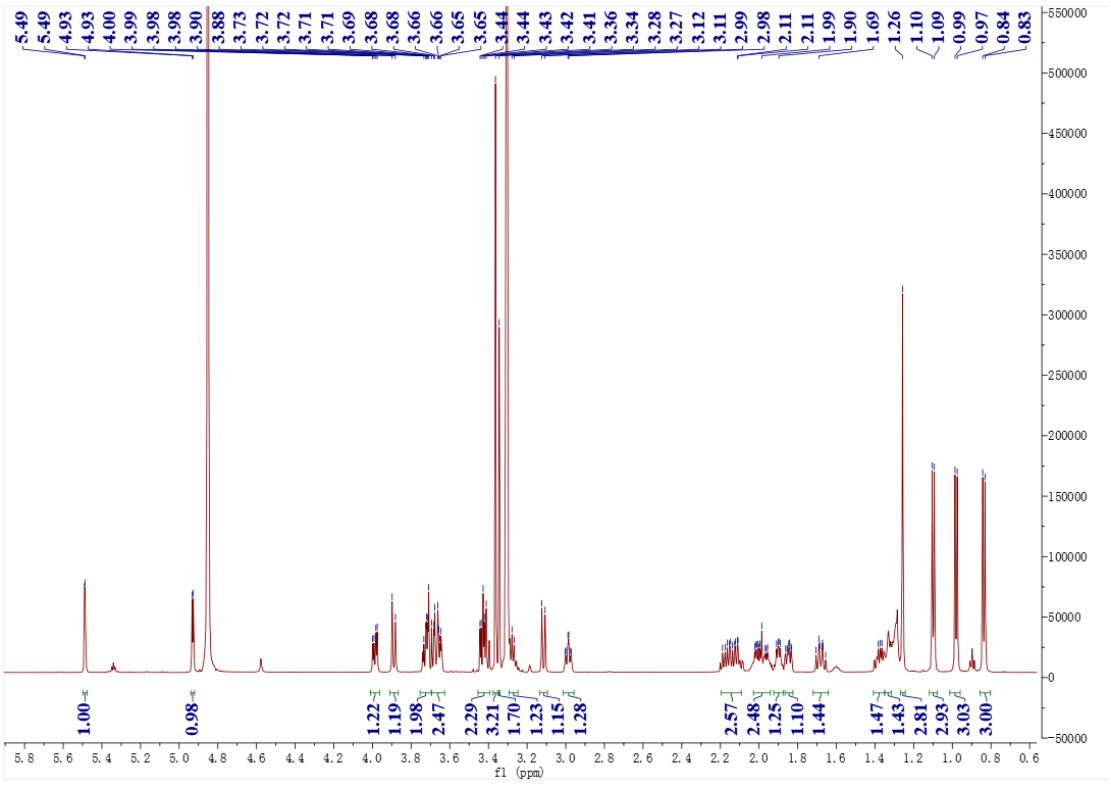


Figure S 21. ^{13}C NMR spectrum of compound **6** in CD_3OD (150 MHz)

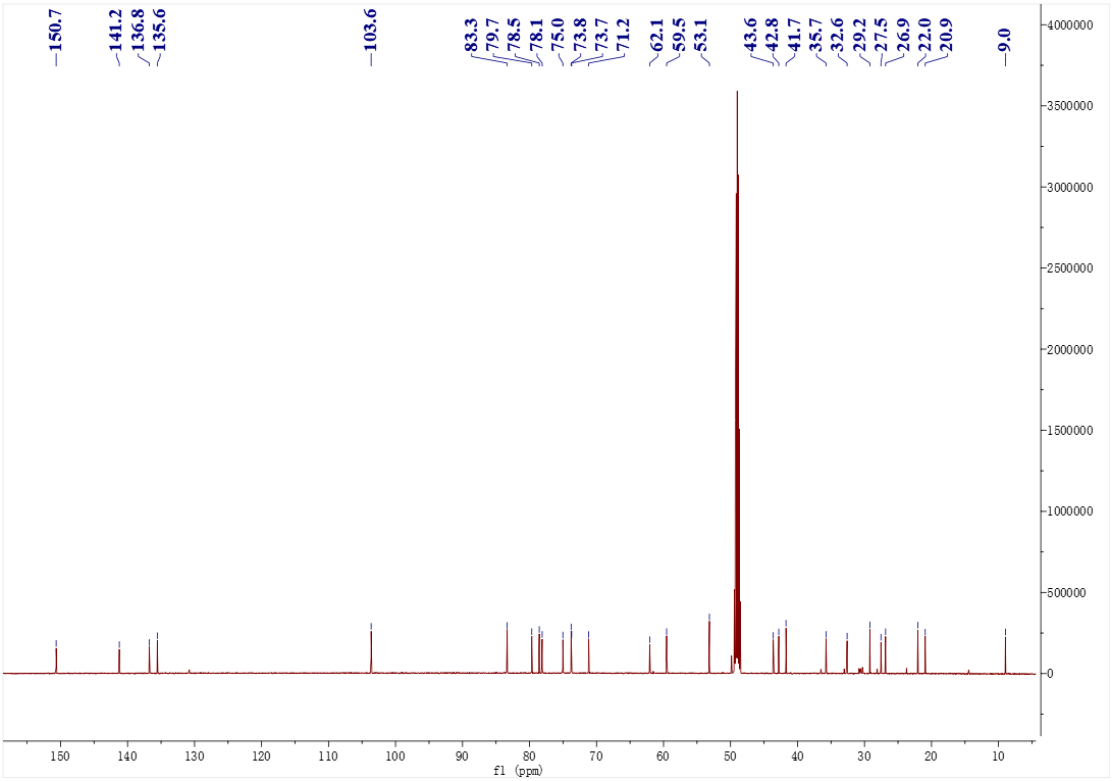


Figure S 22. ^{1}H NMR spectrum of compound **5** in CD_3COCD_3 (600 MHz)

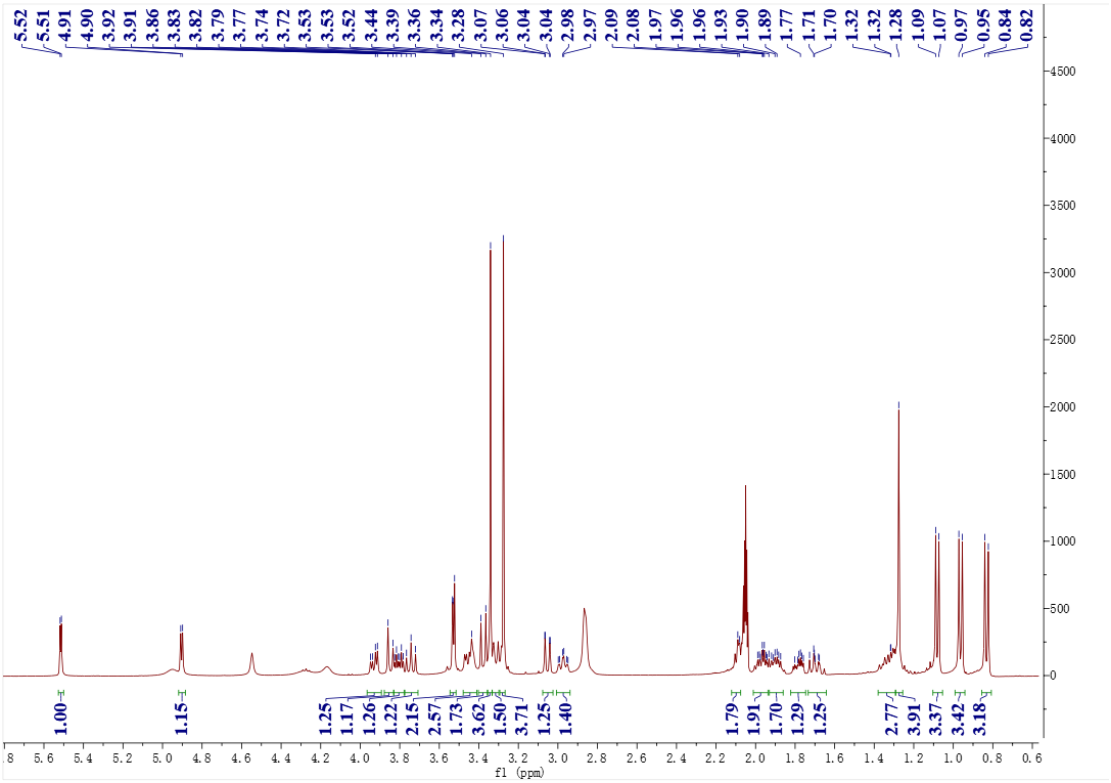


Figure S 23. ^{1}H NMR spectrum of compound **5** in CD_3OD (600 MHz)

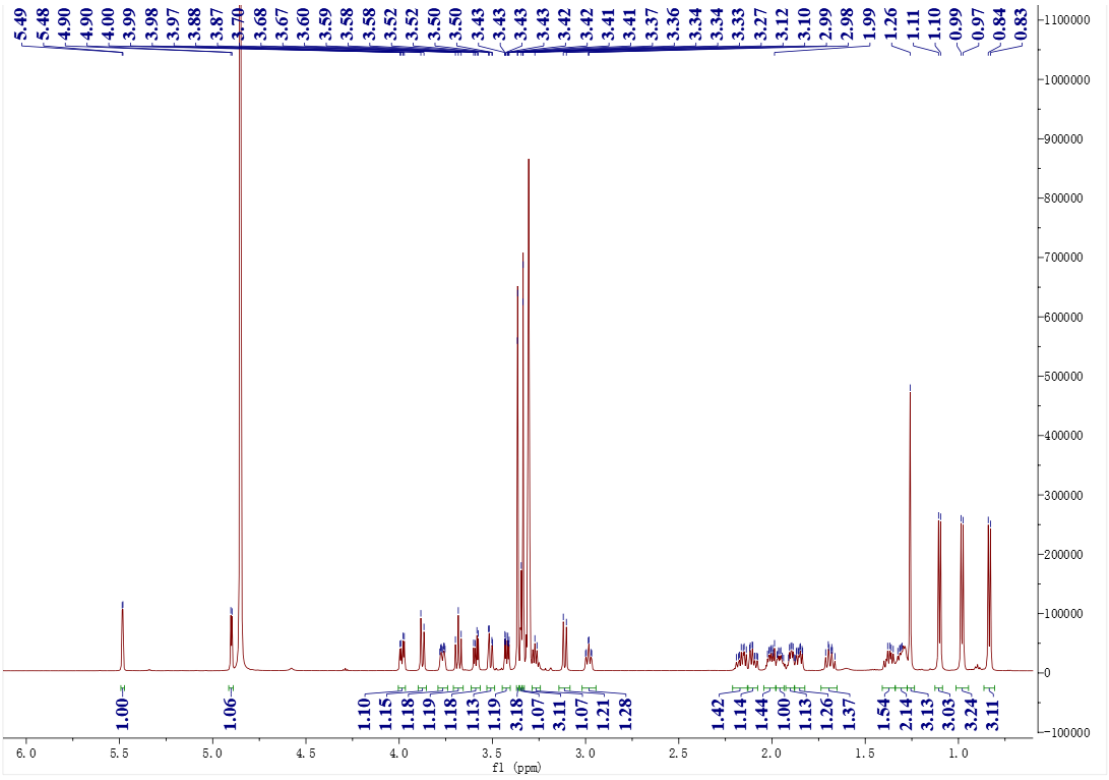


Figure S 24. ^{13}C NMR spectrum of compound **5** in CD_3OD (150 MHz)

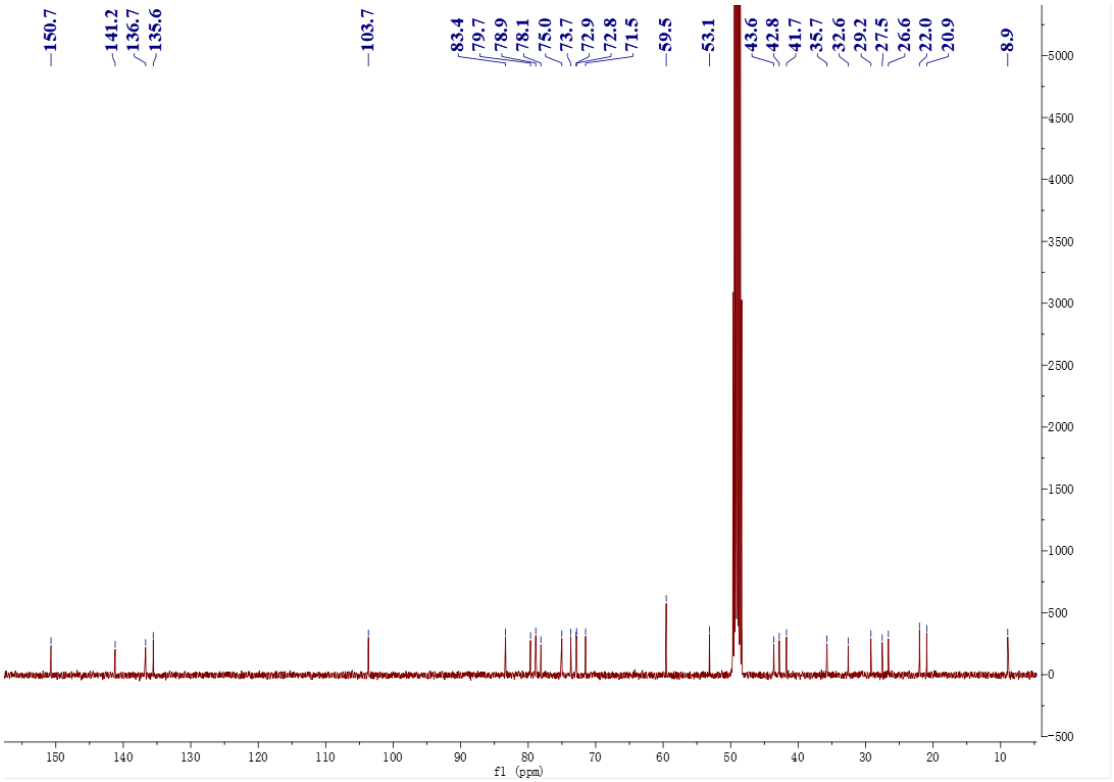


Figure S 25. HSQC spectrum of compound **5** in CD_3OD (600 MHz)

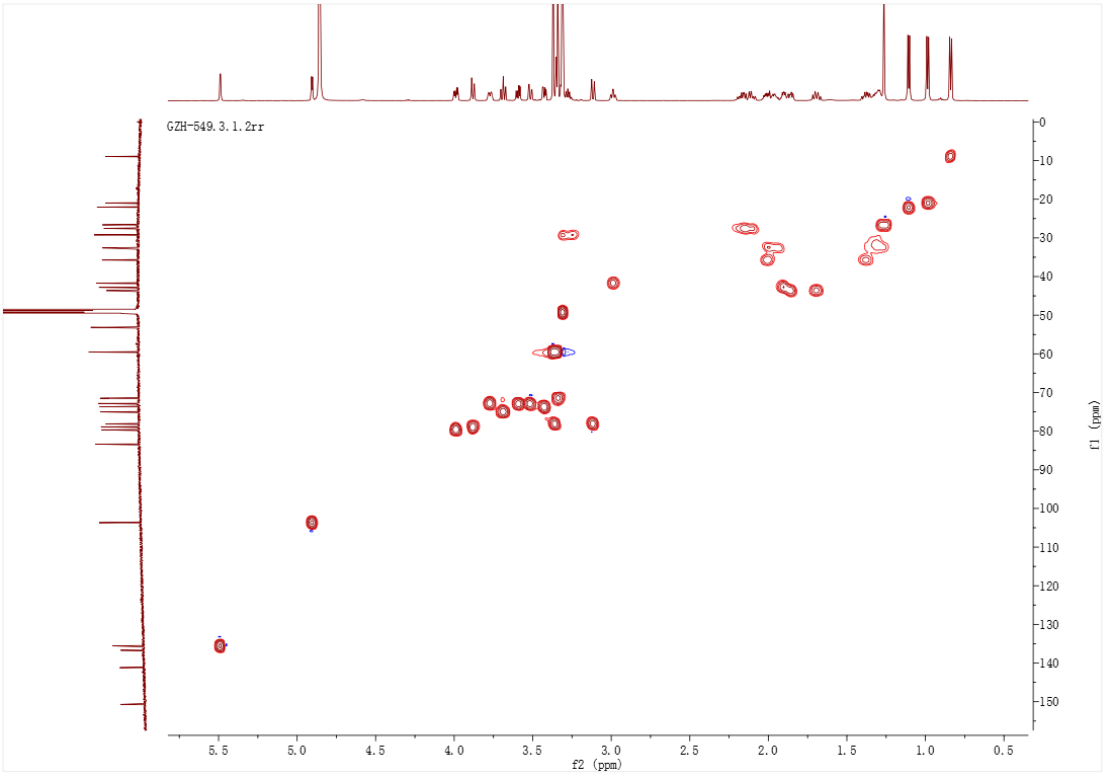


Figure S 26. ^{1}H NMR spectrum of compound **4** in CD_3COCD_3 (600 MHz)

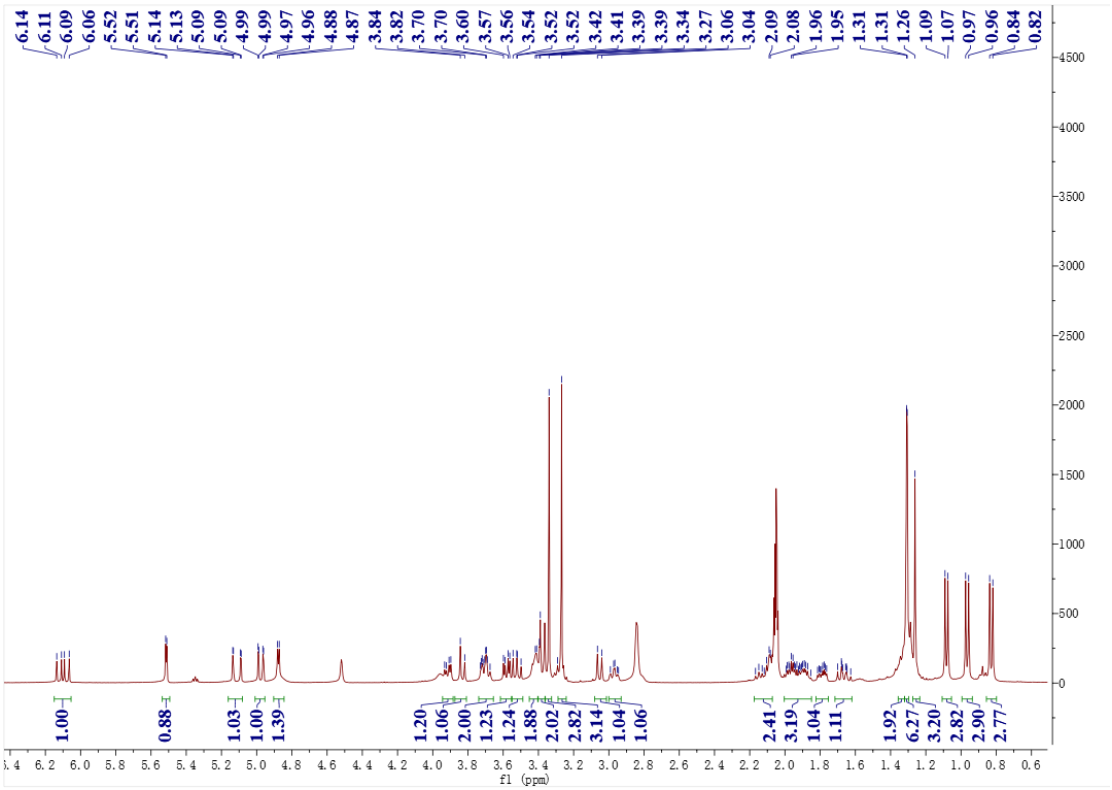


Figure S 27. ^{1}H NMR spectrum of compound **4** in CD_3OD (600 MHz)

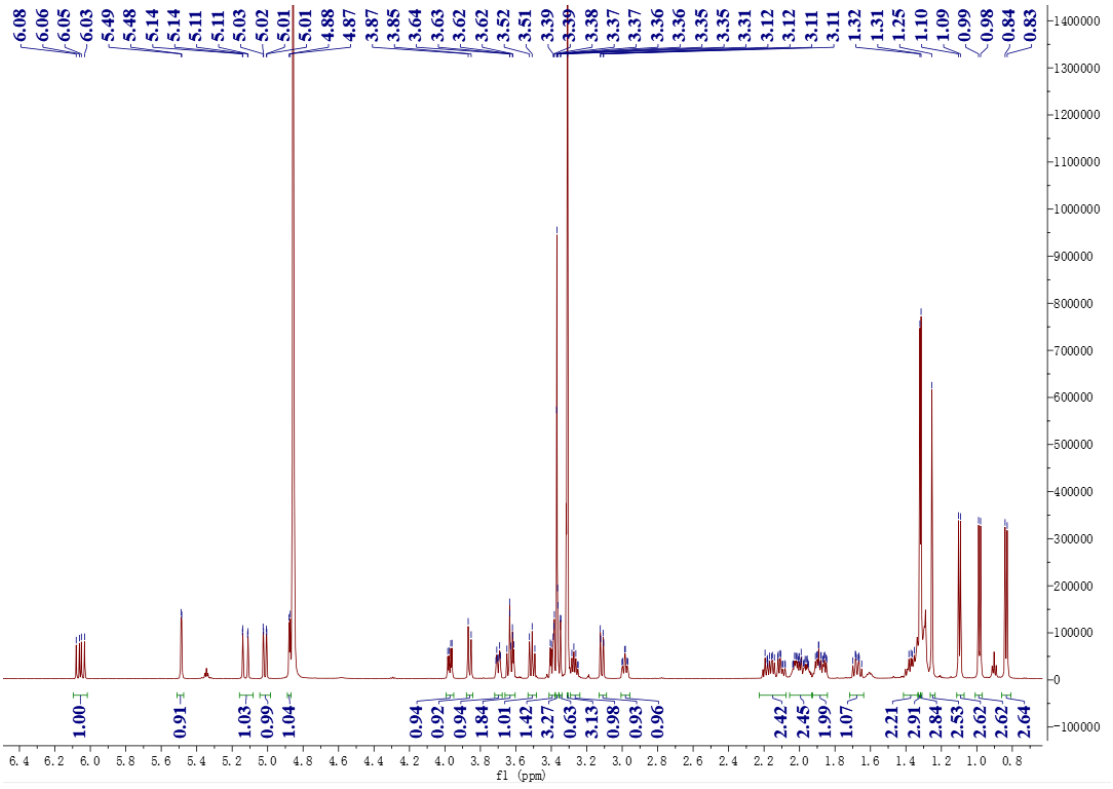


Figure S 28. ^{13}C NMR spectrum of compound **4** in CD_3OD (150 MHz)

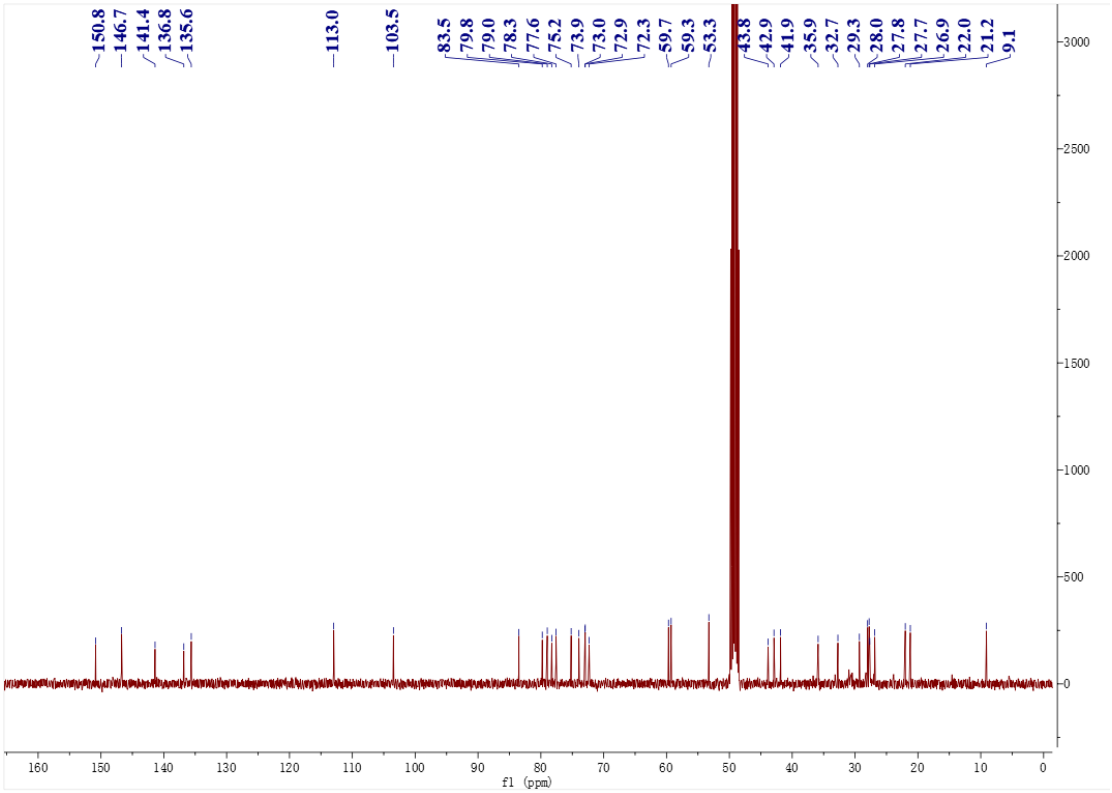


Figure S 29. ^{1}H NMR spectrum of compound **3** in CD_3COCD_3 (600 MHz)

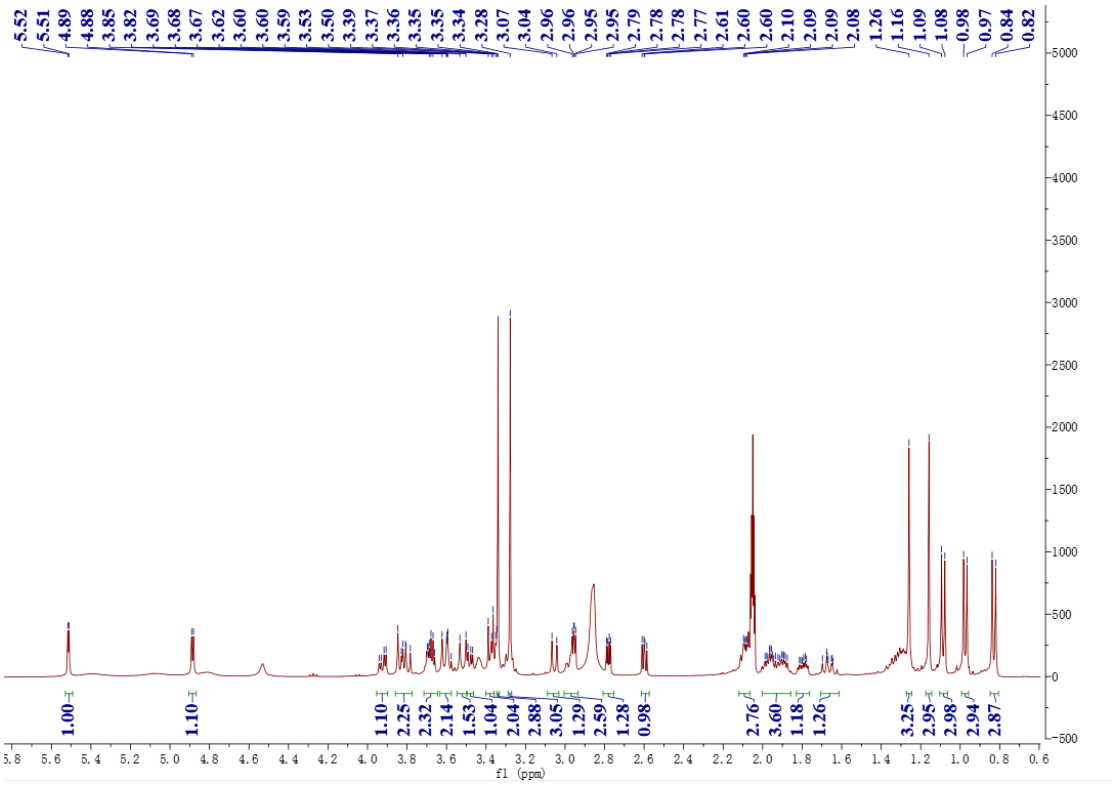


Figure S 30. ^{1}H NMR spectrum of compound **3** in CD_3OD (600 MHz)

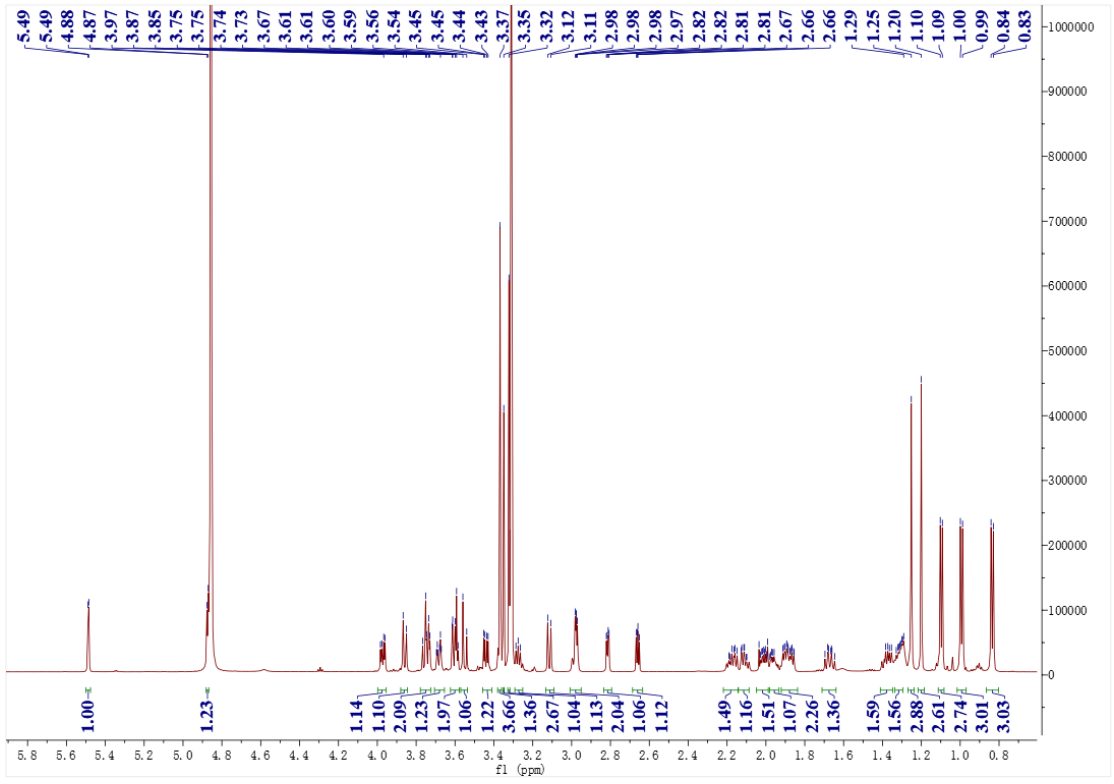


Figure S 31. ^{13}C NMR spectrum of compound **3** in CD_3OD (150 MHz)

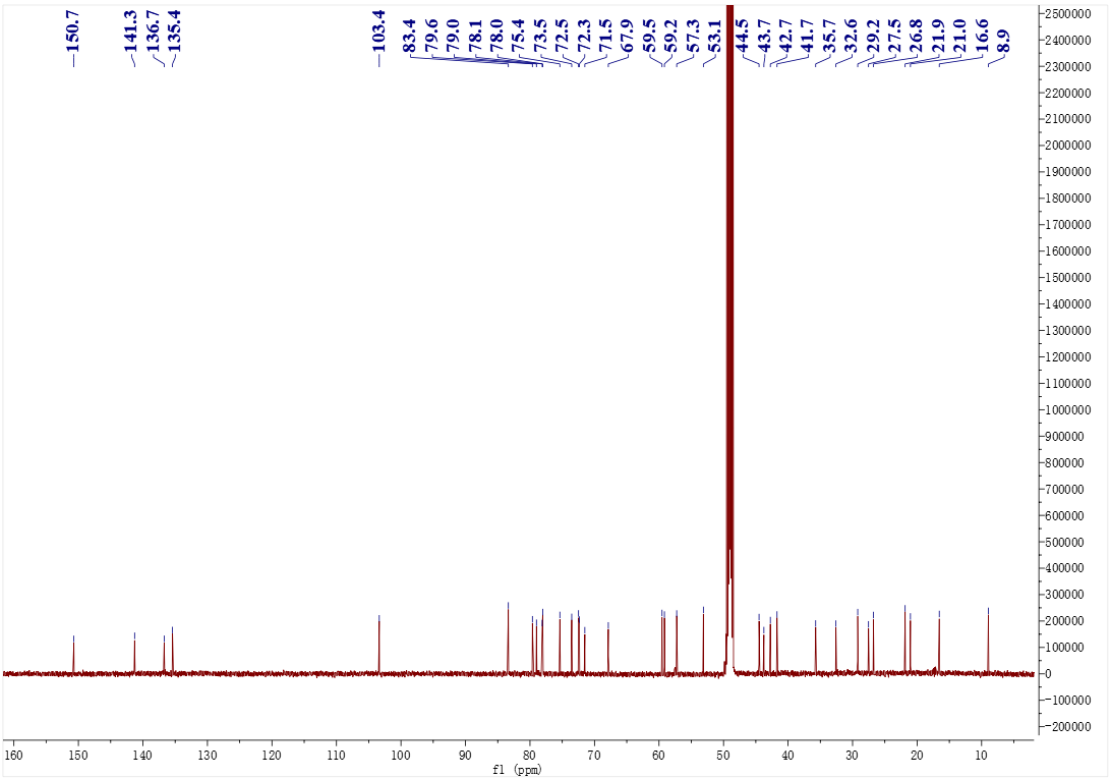


Figure S 32. HSQC spectrum of compound **3** in CD_3OD (600 MHz)

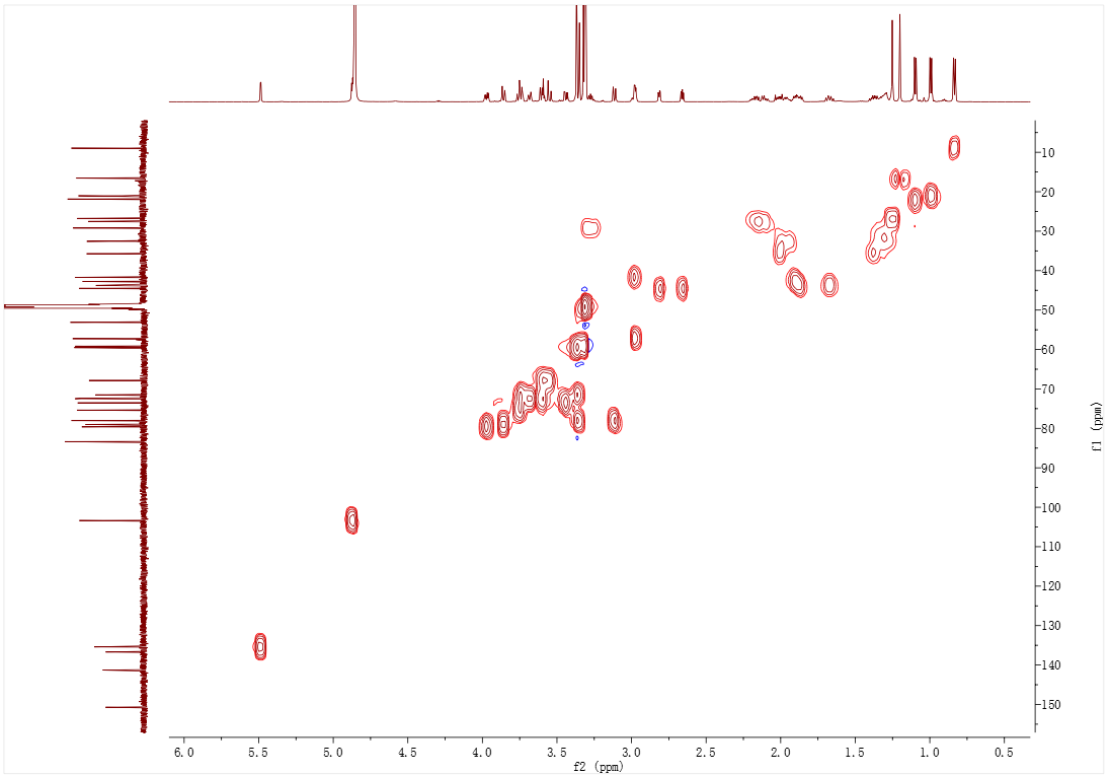


Figure S 33. ^{1}H NMR spectrum of compound **2** in CD_3COCD_3 (600 MHz)

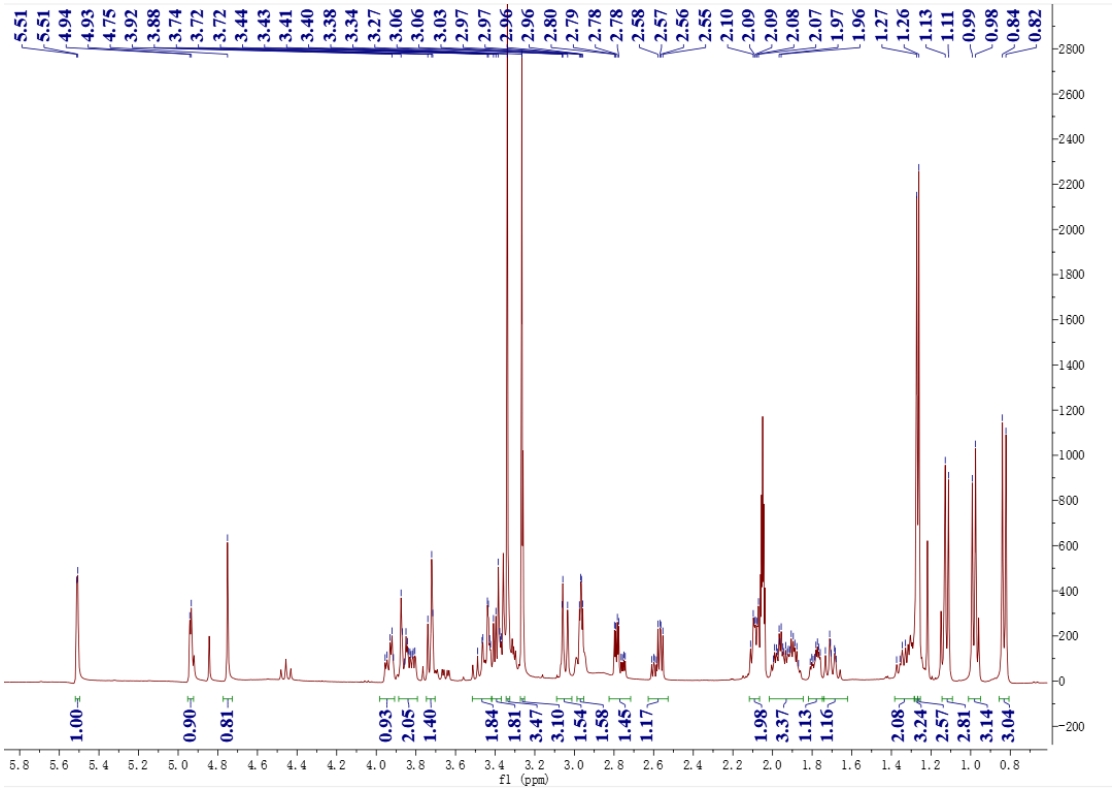


Figure S 34. ^{1}H NMR spectrum of compound **2** in CD_3OD (600 MHz)

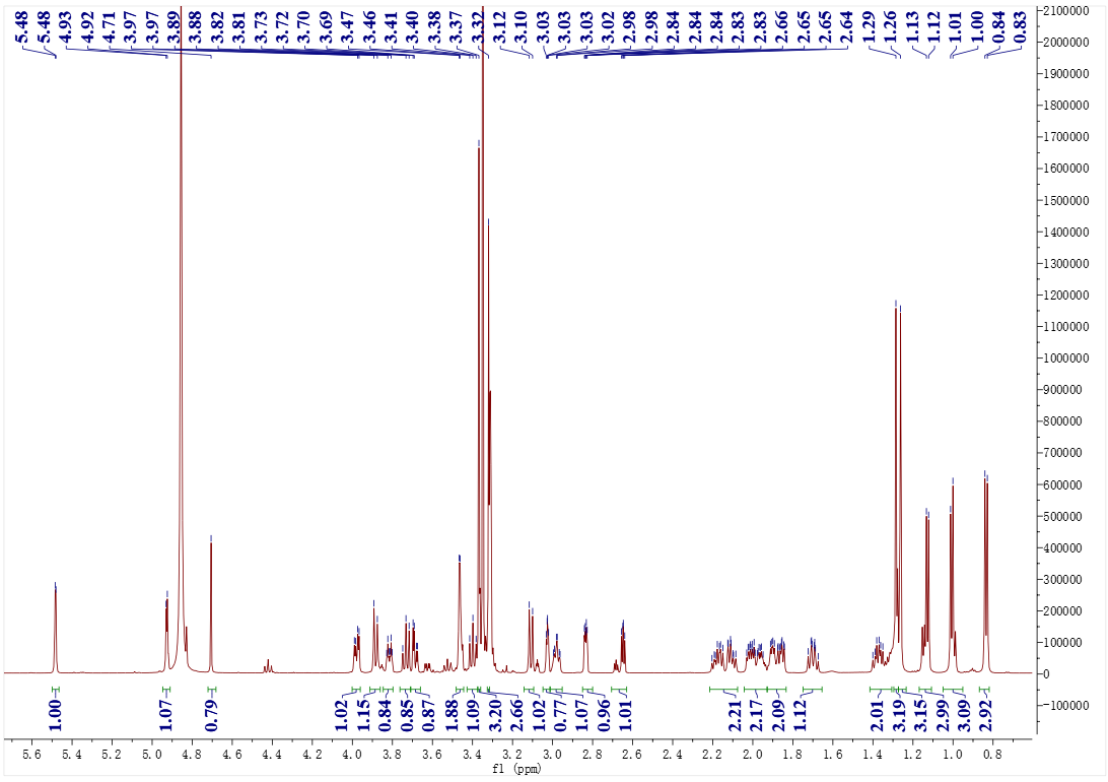


Figure S 35. ^{13}C NMR spectrum of compound **2** in CD_3OD (150 MHz)

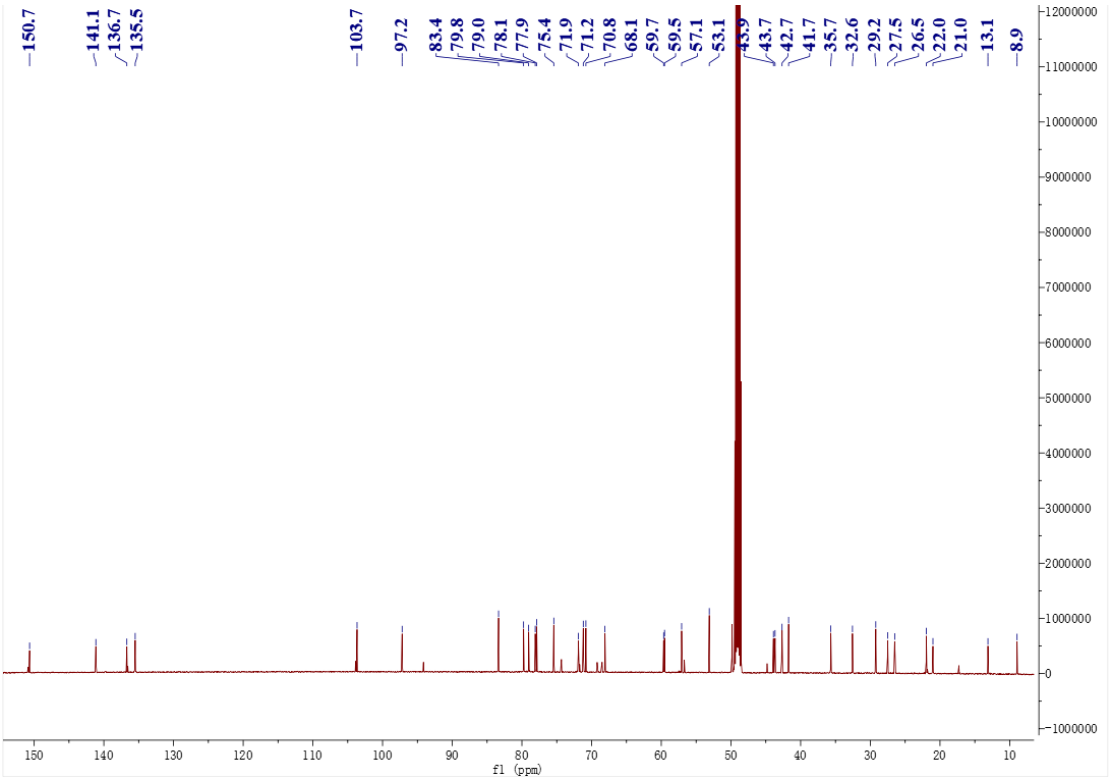


Figure S 36. HSQC spectrum of compound **2** in CD_3OD (600 MHz)

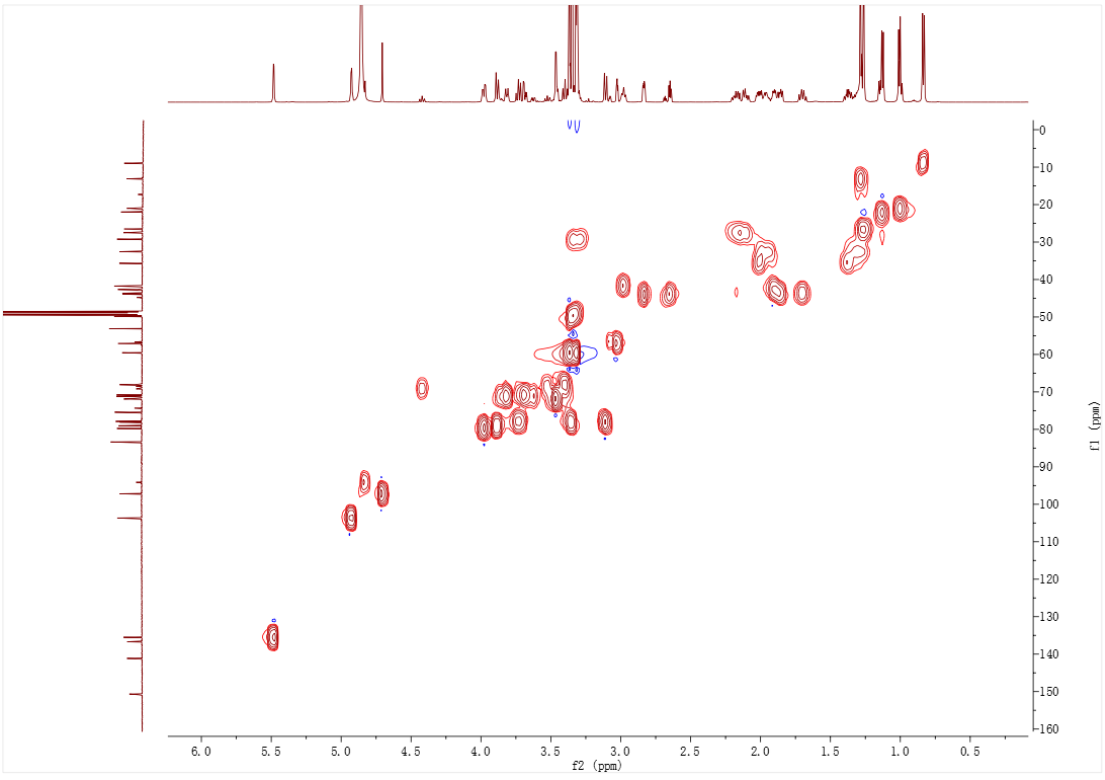


Figure S 37. ^{1}H NMR spectrum of compound **12** in CD_3OD (600 MHz)

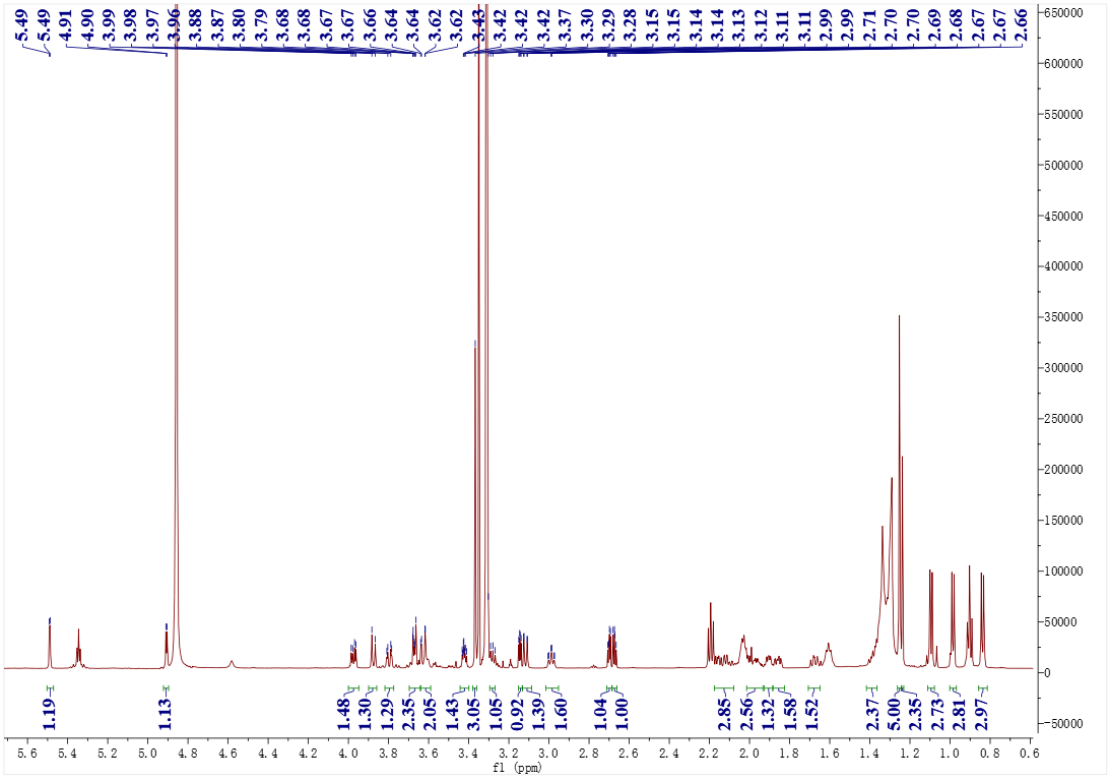


Figure S 38. ^{13}C NMR and DEPT spectrum of compound **12** in CD_3OD (150 MHz)

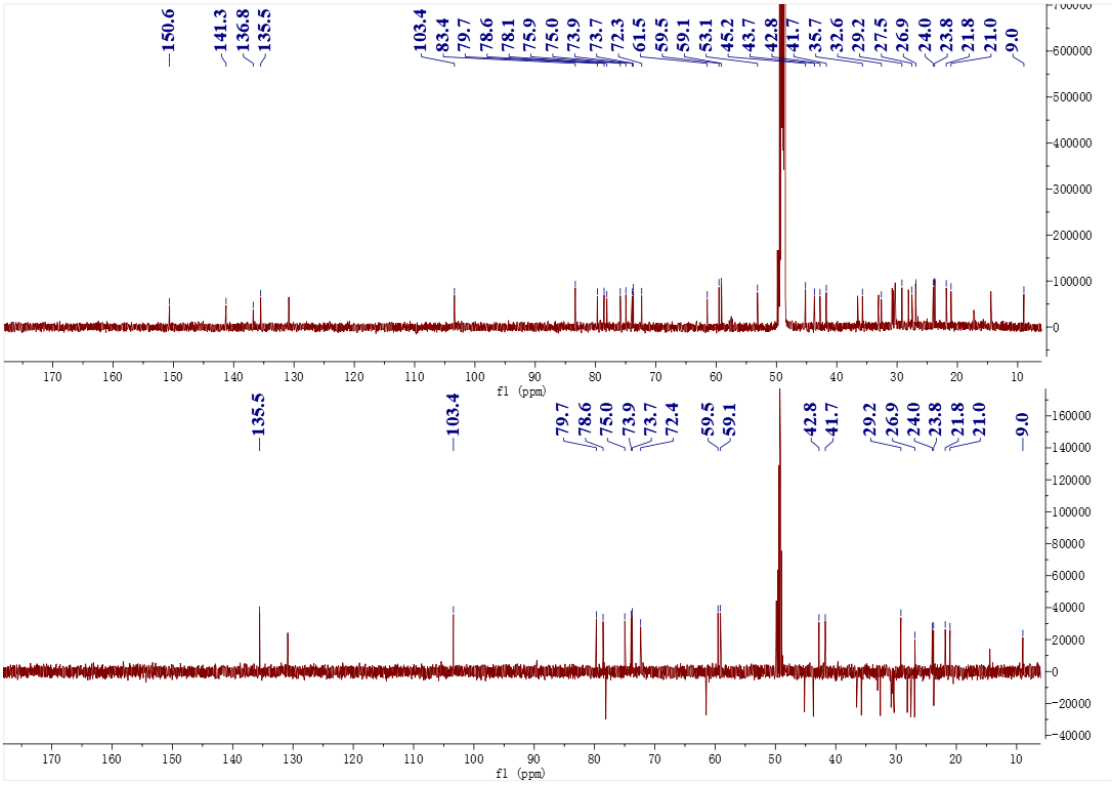


Figure S 39. HSQC spectrum of compound **12** in CD_3OD (600 MHz)

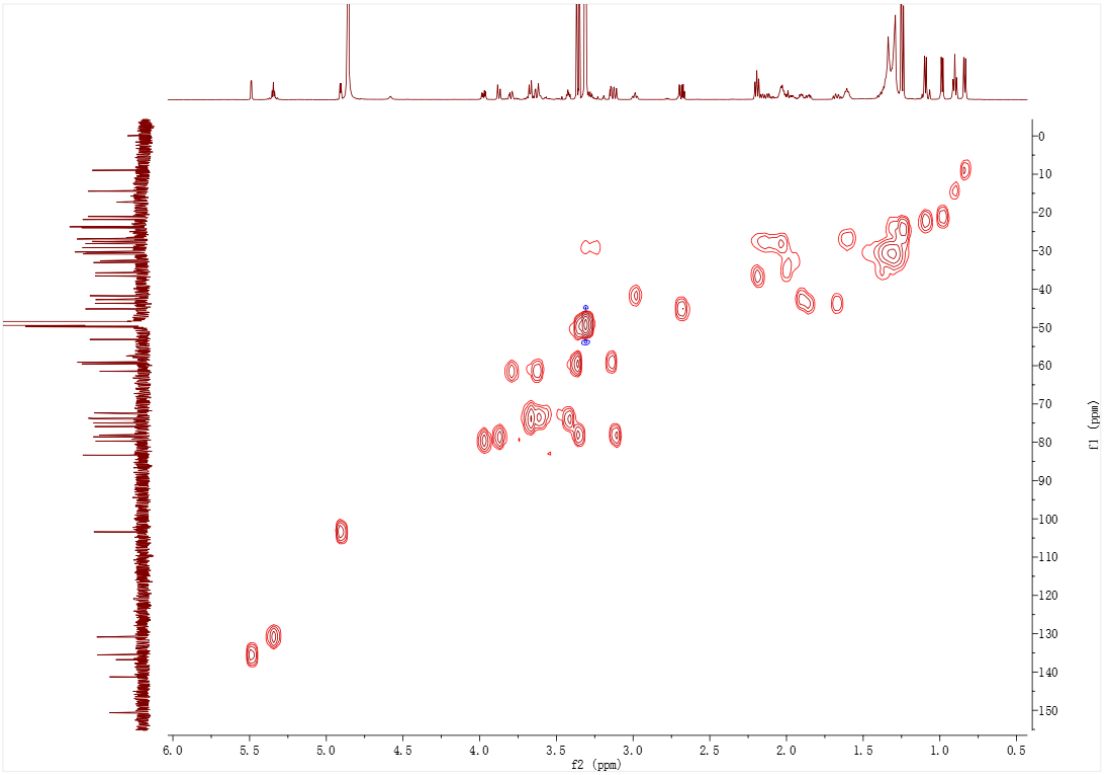


Figure S 40. HMBC spectrum of compound **12** in CD_3OD (600 MHz)

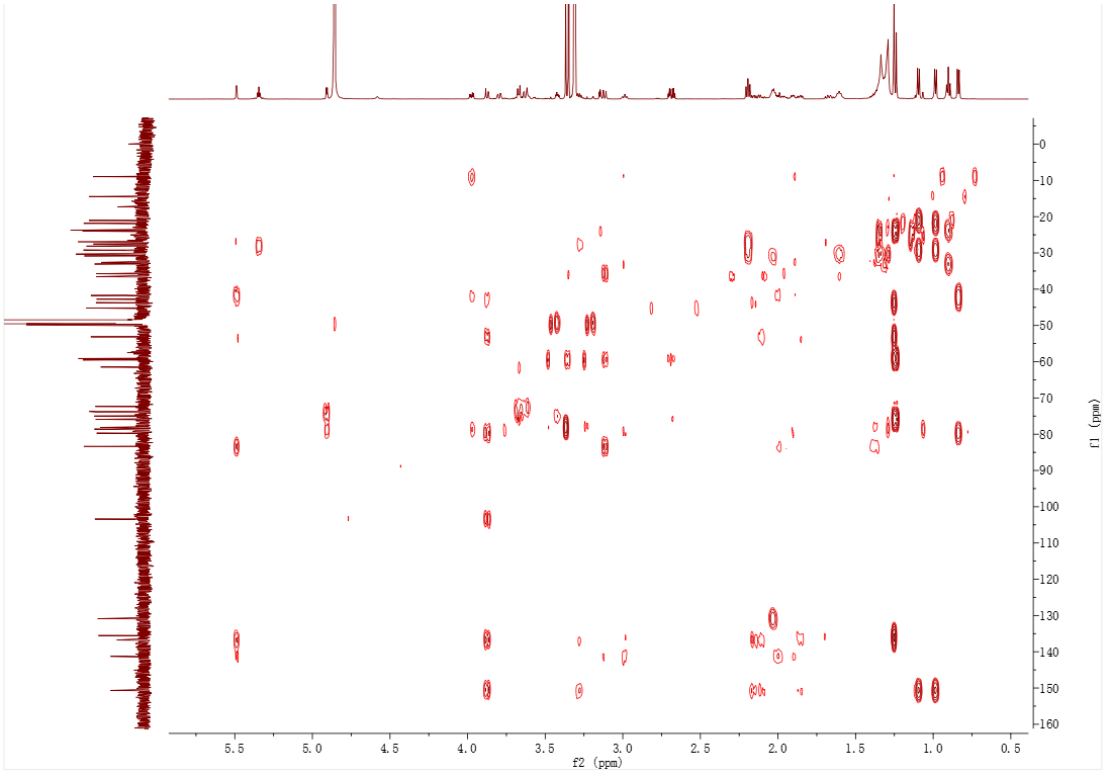


Figure S 41. ^{1}H-^{1}H COSY spectrum of compound **12** in CD_3OD (600 MHz)

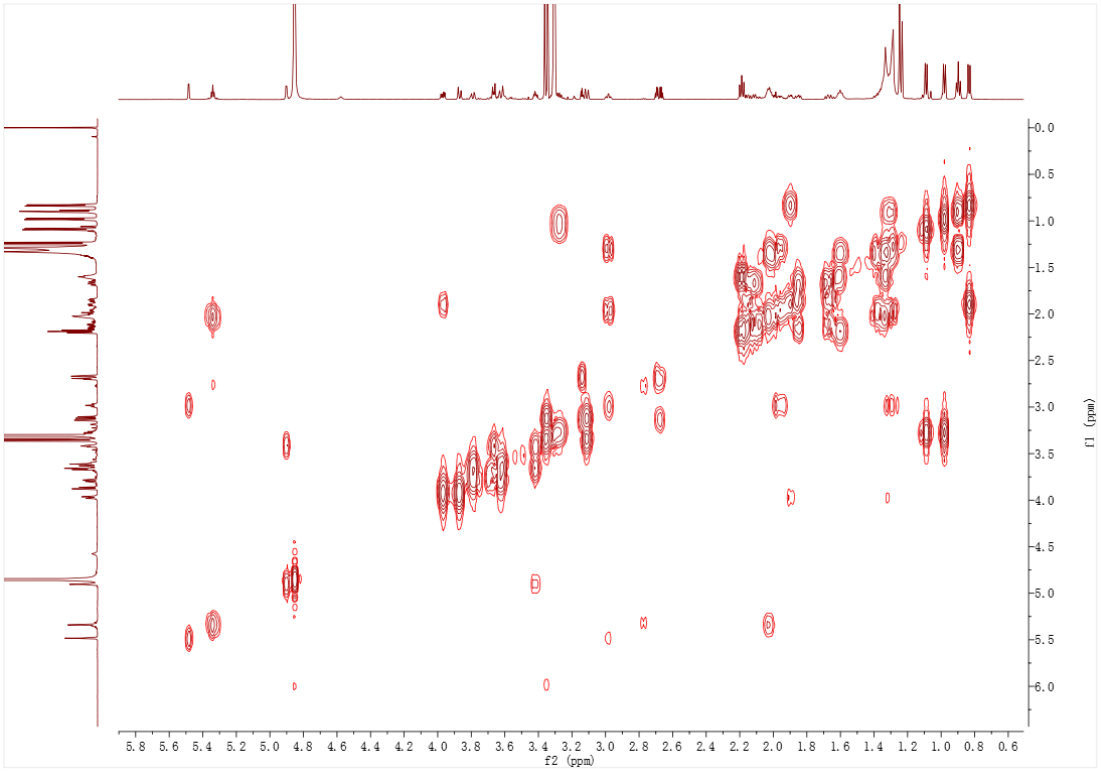


Figure S 42. NOESY spectrum of compound **12** in CD_3OD (600 MHz)

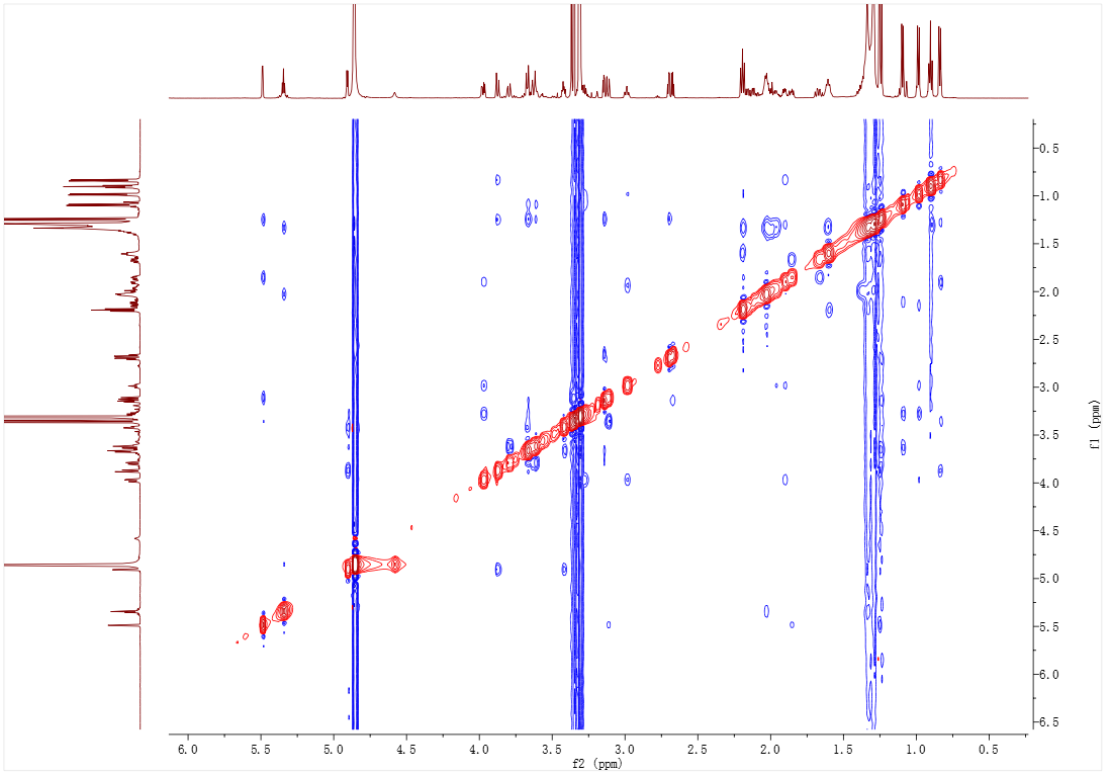


Figure S 43. ^{1}H NMR spectrum of compound **9** in CD_3OD (600 MHz)

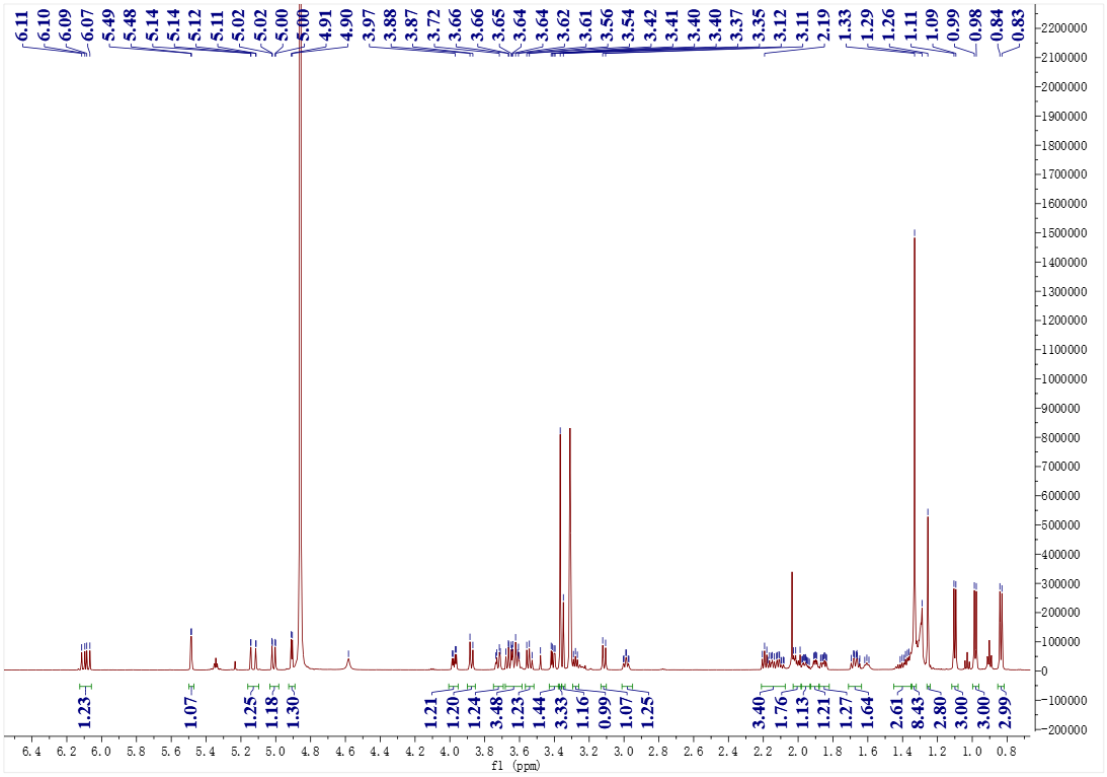


Figure S 44. ^{13}C NMR and DEPT spectrum of compound **9** in CD_3OD (150 MHz)

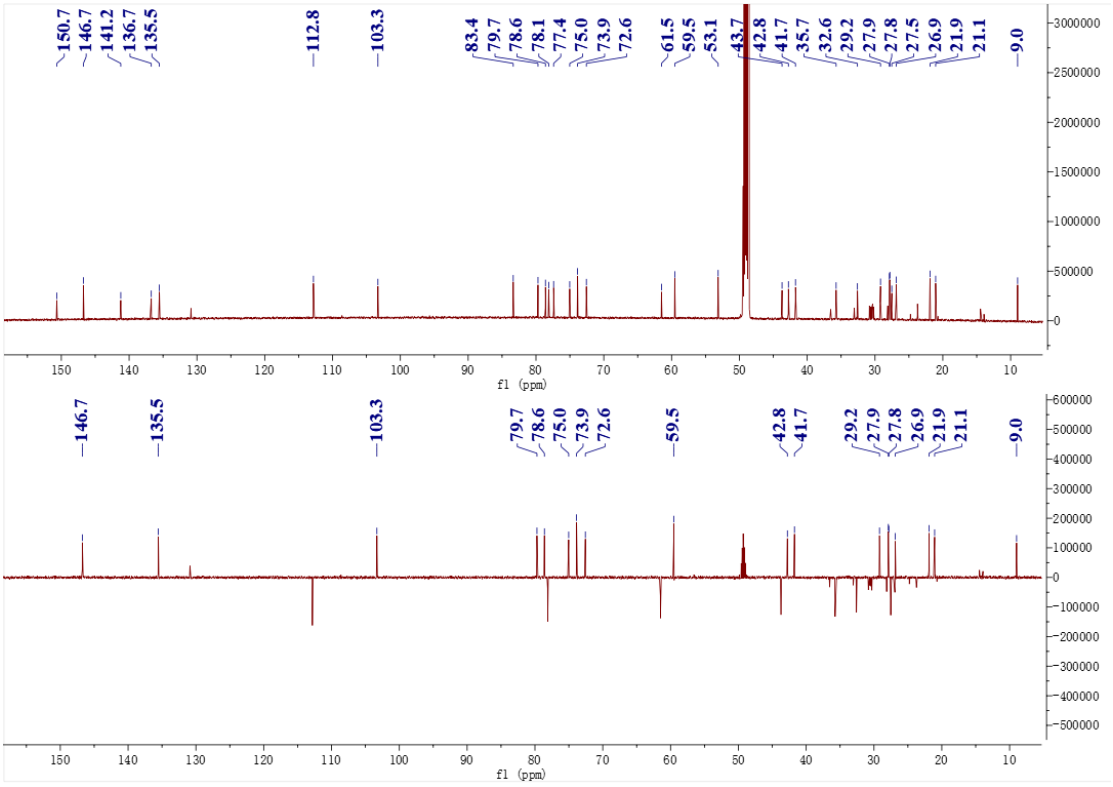


Figure S 45. HSQC spectrum of compound **9** in CD_3OD (600 MHz)

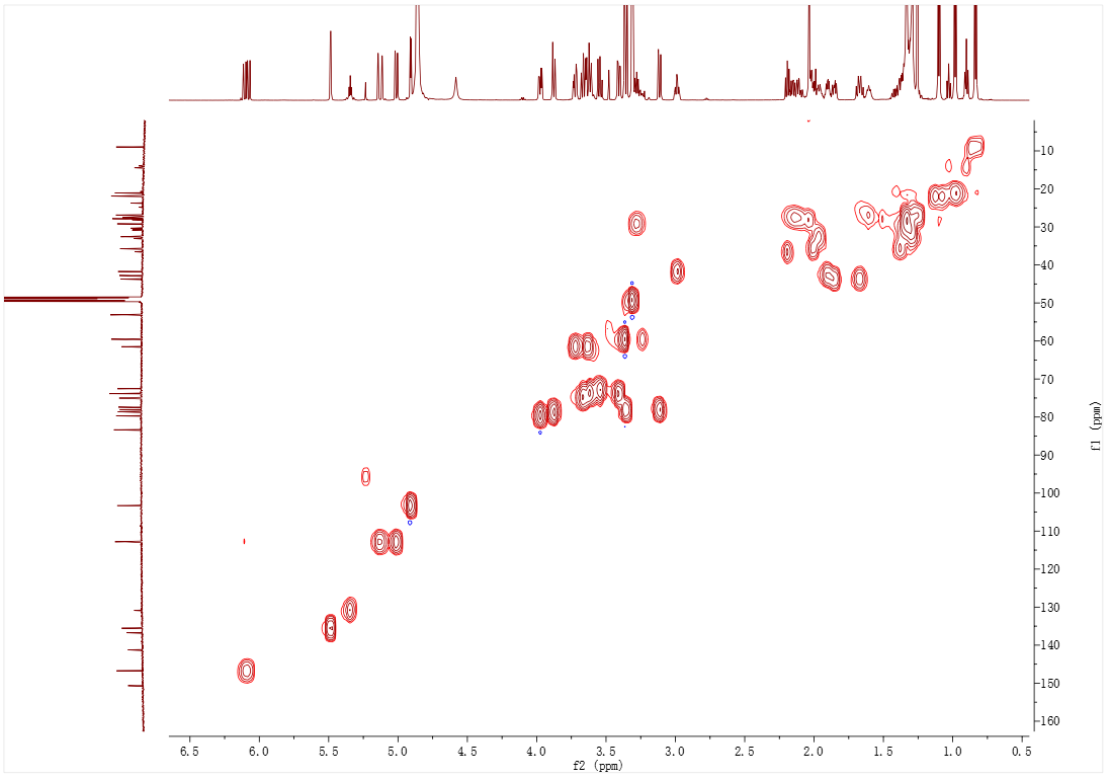


Figure S 46. HMBC spectrum of compound **9** in CD_3OD (600 MHz)

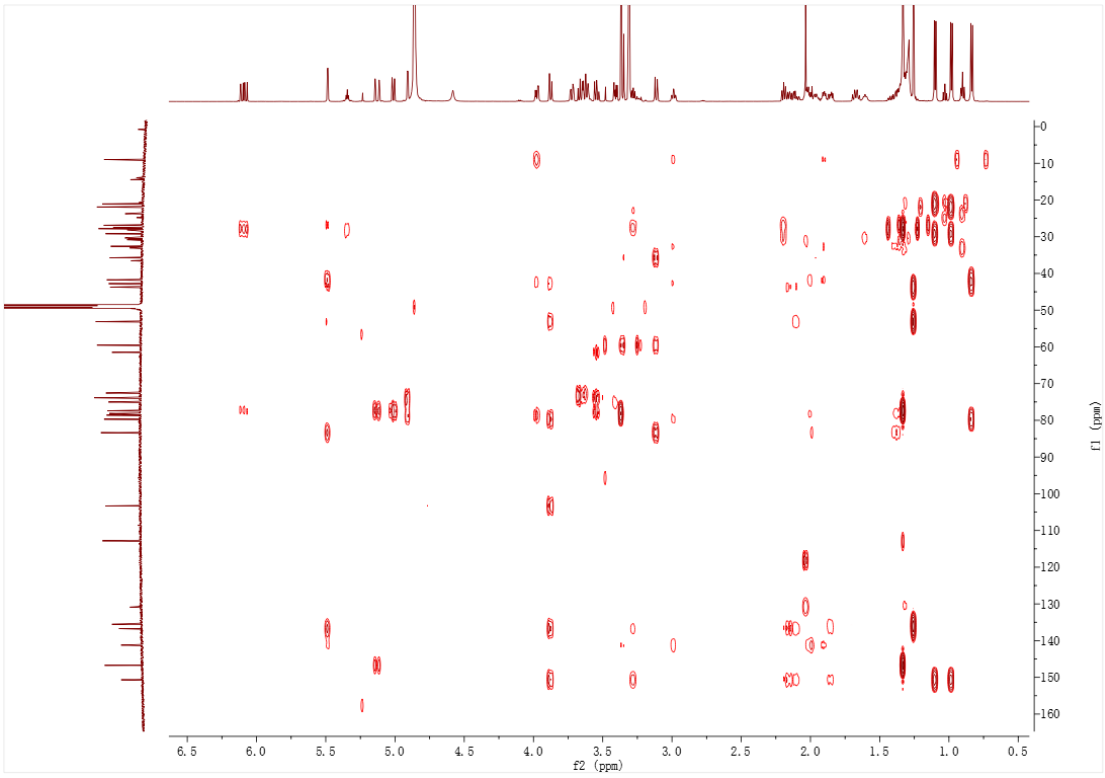


Figure S 47. ^{1}H-^{1}H COSY spectrum of compound **9** in CD_3OD (600 MHz)

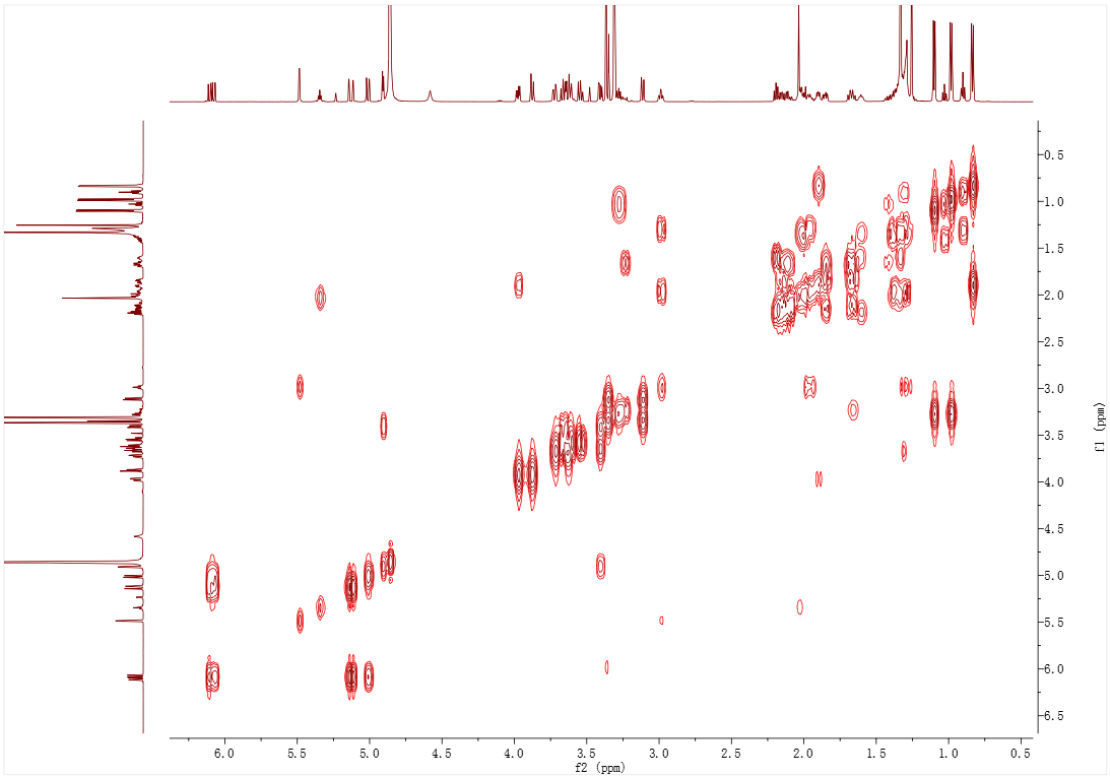


Figure S 48. NOESY spectrum of compound **9** in CD_3OD (600 MHz)

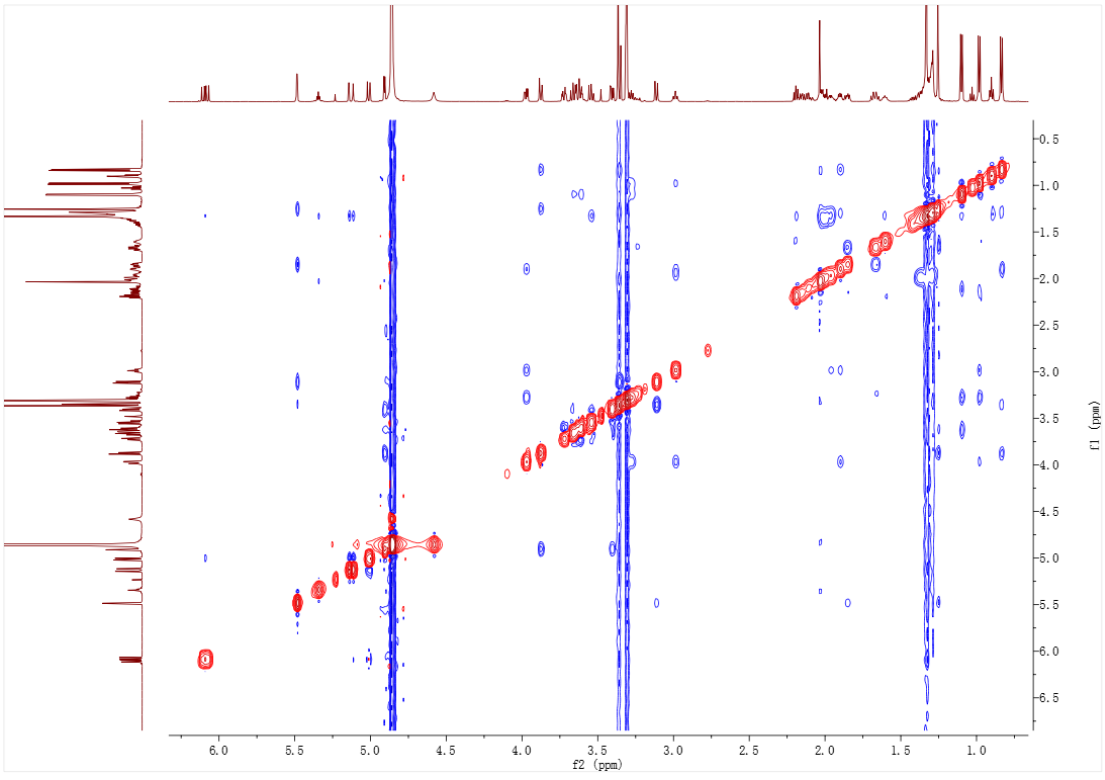


Figure S 49. ^{1}H NMR spectrum of compound **10** in CD_3OD (600 MHz)

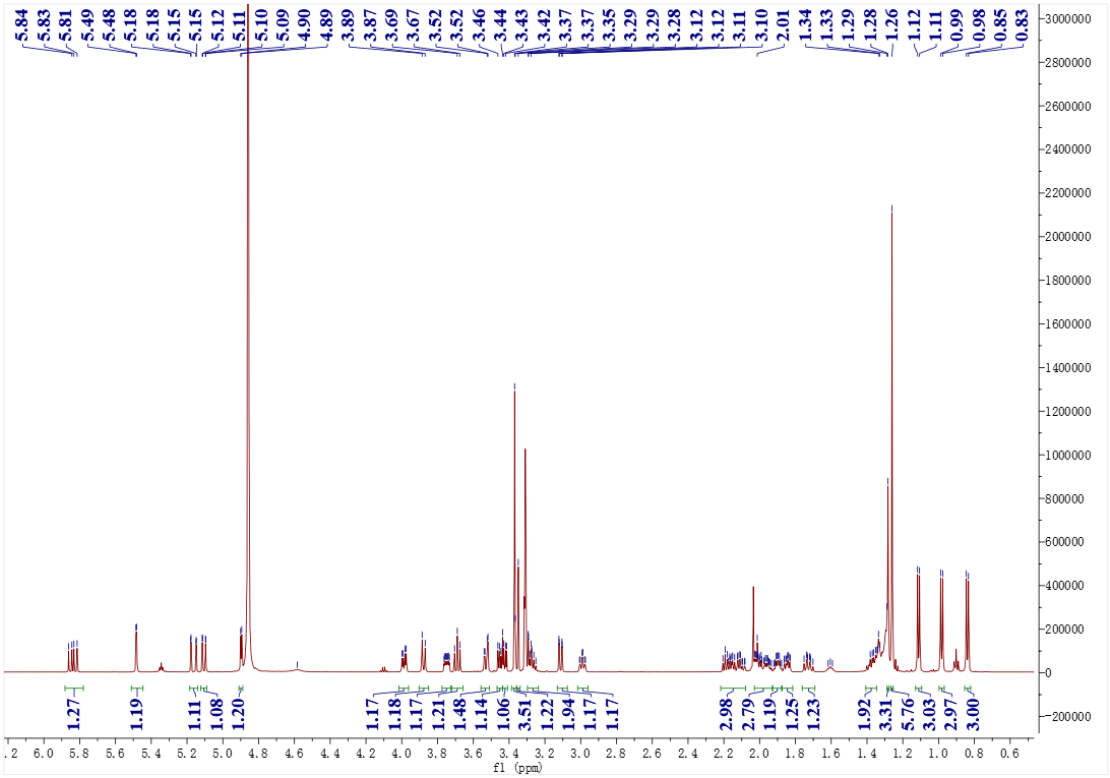


Figure S 50. ^{13}C NMR and DEPT spectrum of compound **10** in CD_3OD (150 MHz)

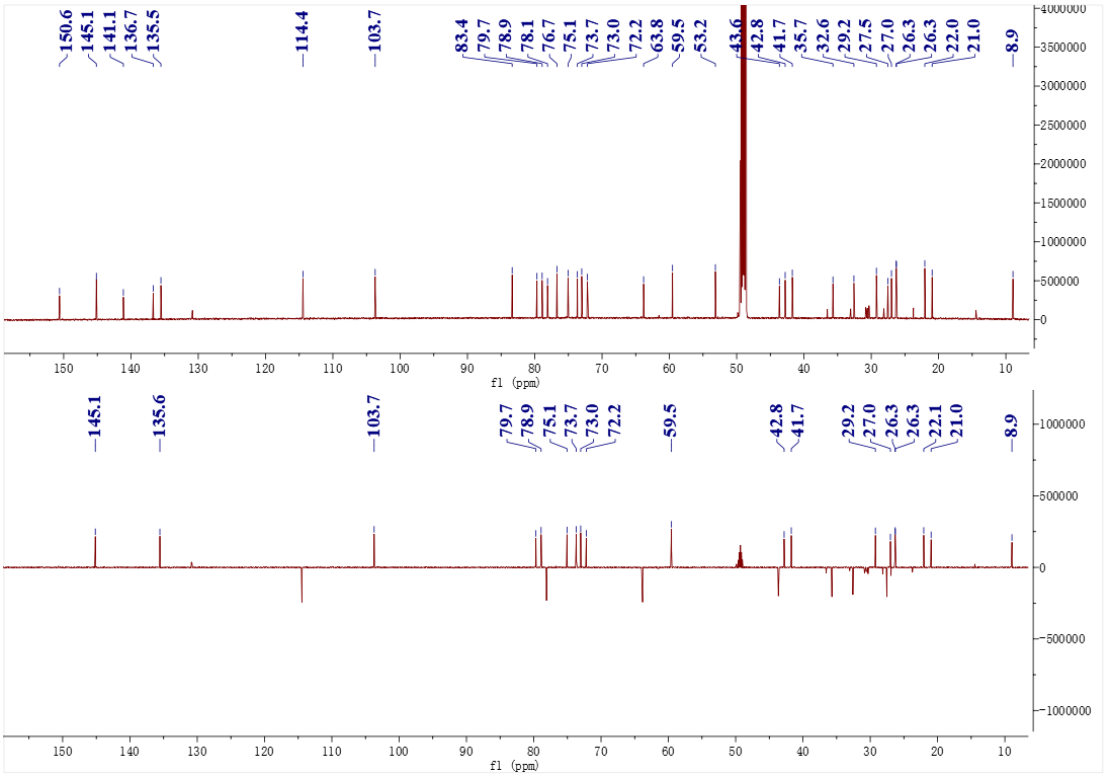


Figure S 51. HSQC spectrum of compound **10** in CD_3OD (600 MHz)

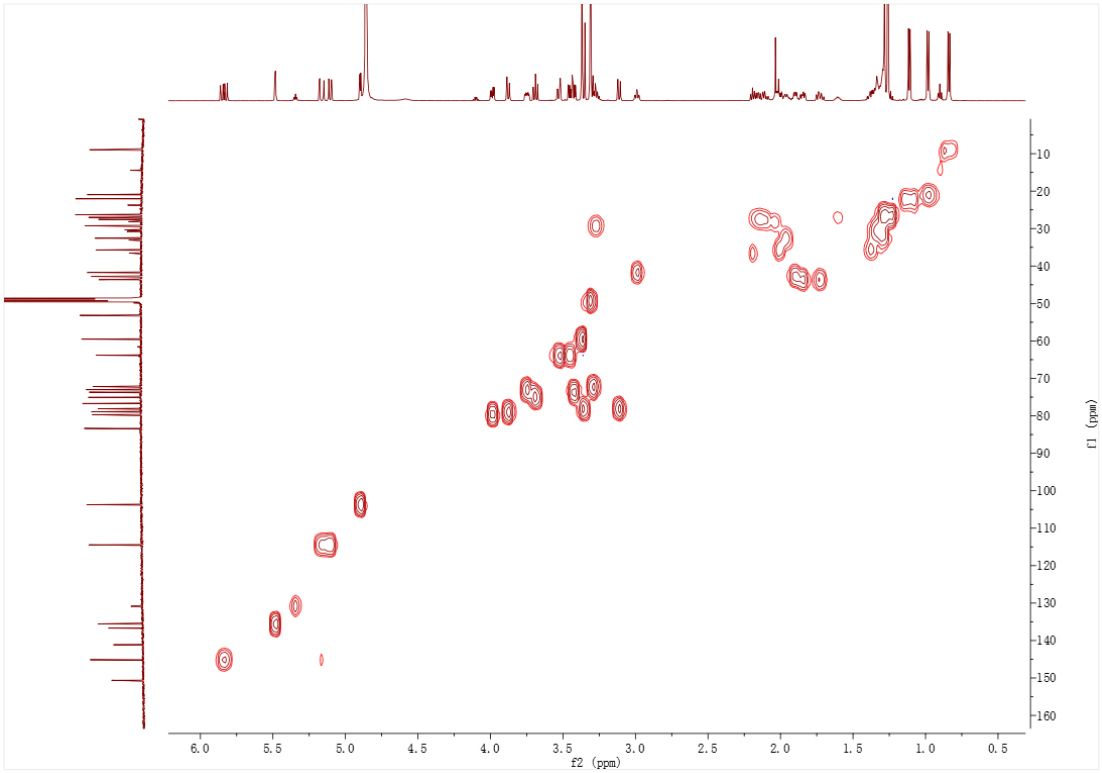


Figure S 52. HMBC spectrum of compound **10** in CD_3OD (600 MHz)

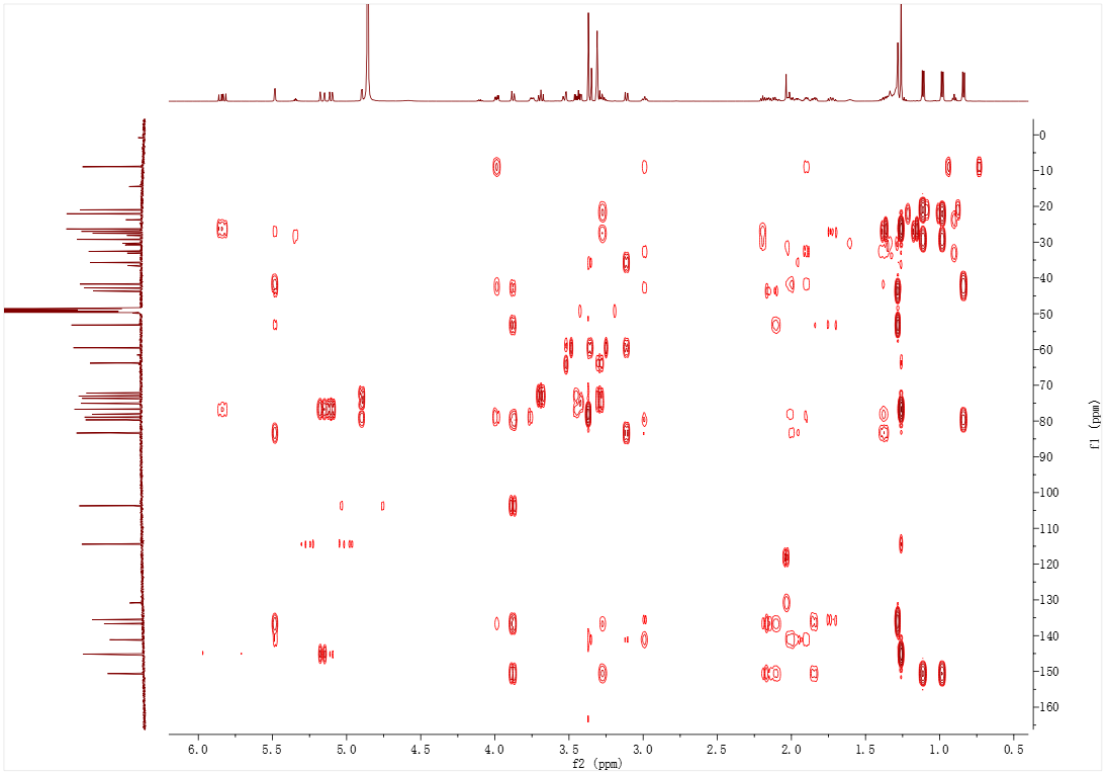


Figure S 53. ^{1}H-^{1}H COSY spectrum of compound **10** in CD_3OD (600 MHz)

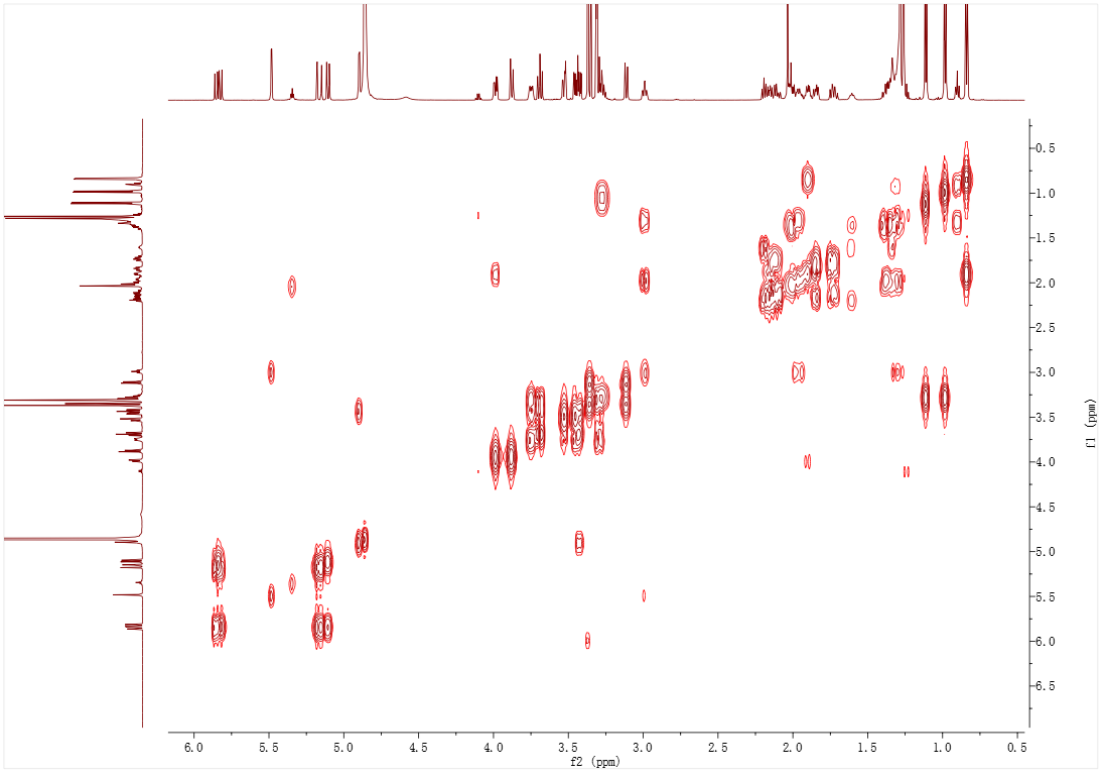


Figure S 54. NOESY spectrum of compound **10** in CD_3OD (600 MHz)

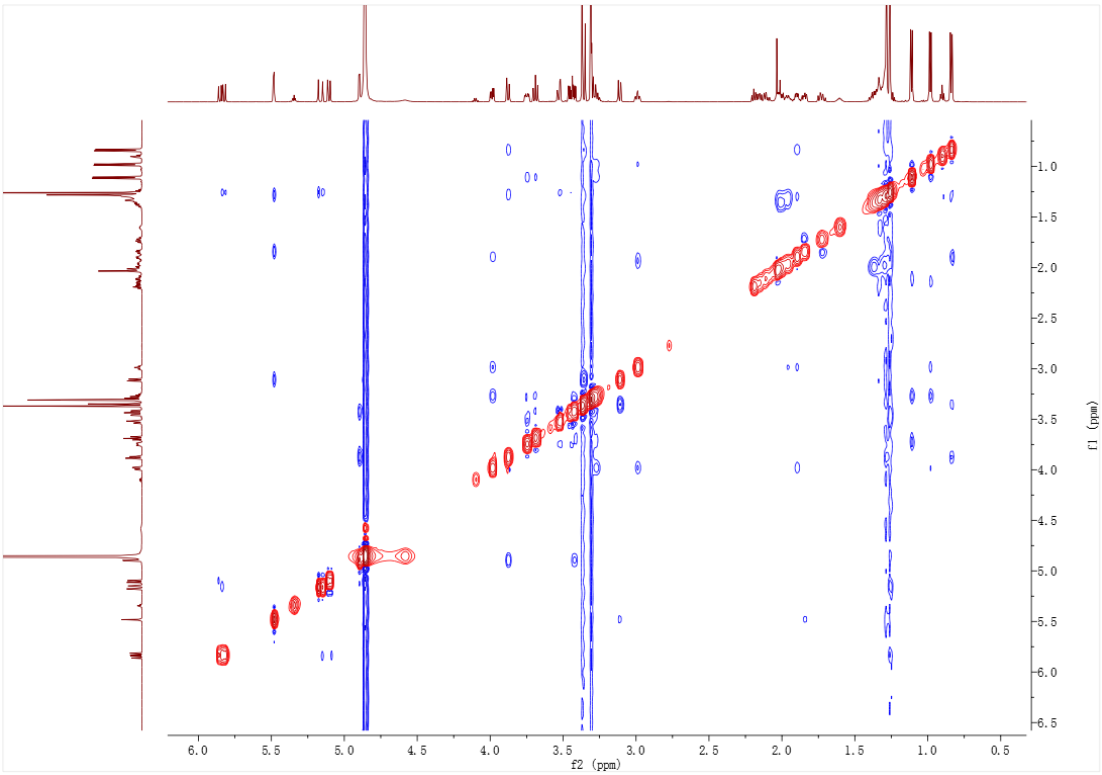


Figure S 55. ^{1}H NMR spectrum of ISIR-050 in $CDCl_3$ (600 MHz)

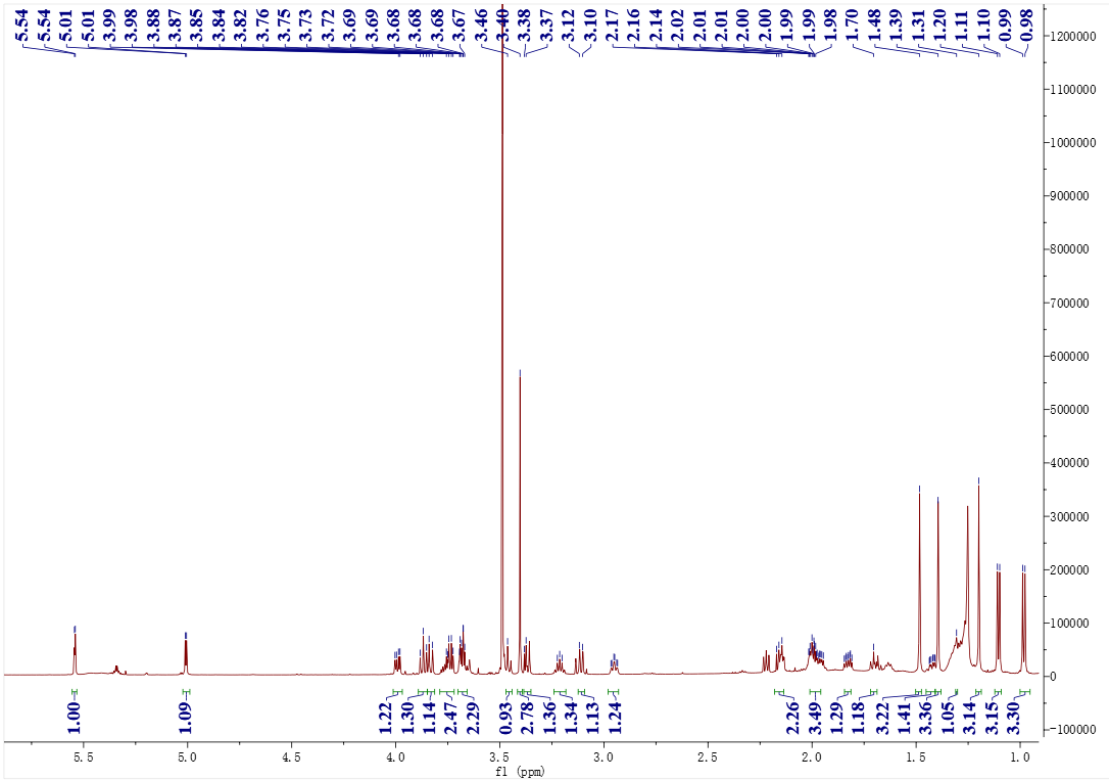
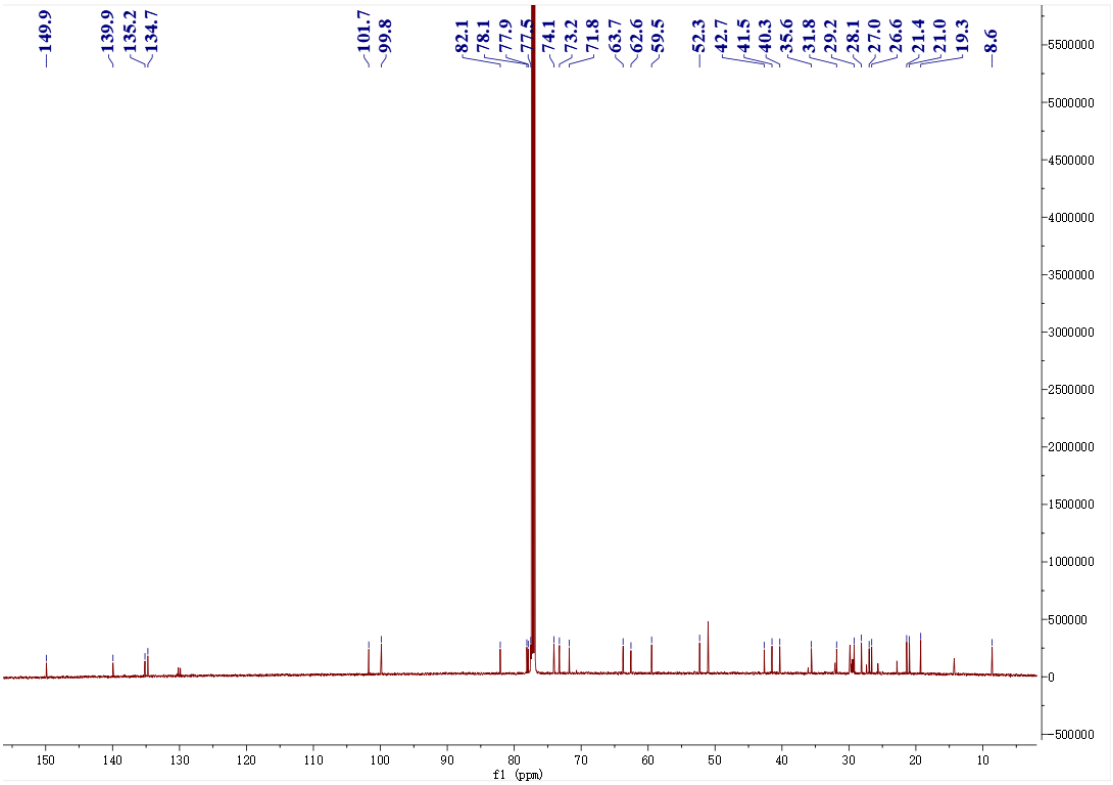


Figure S 56. ^{13}C NMR spectrum of ISIR-050 in $CDCl_3$ (150 MHz)



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