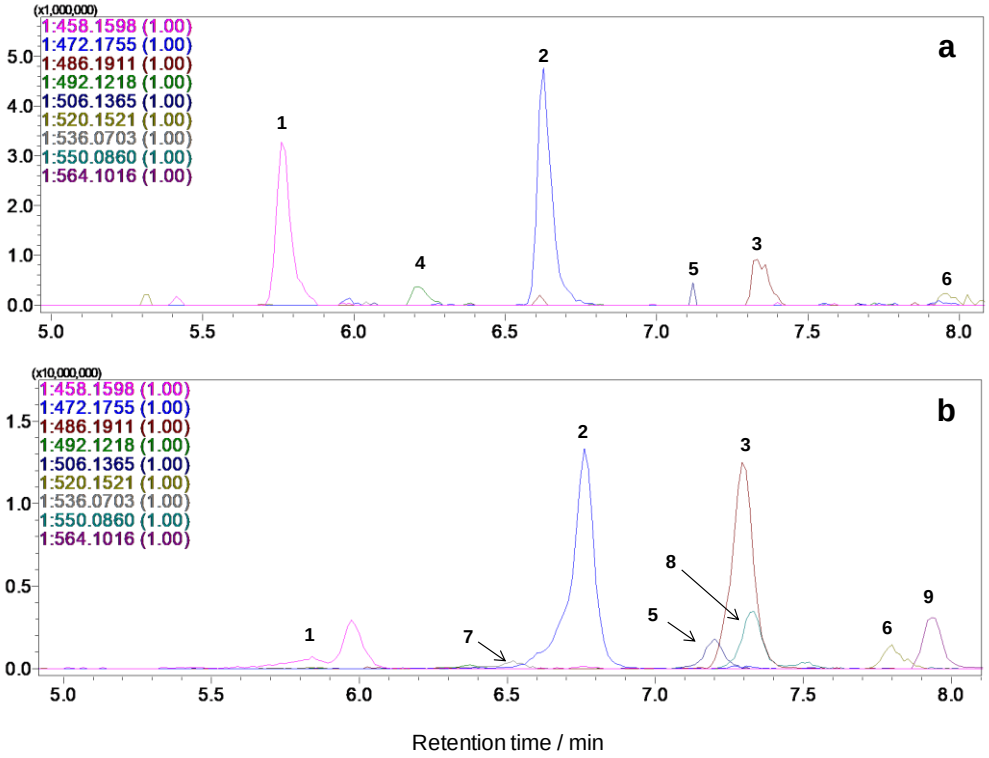
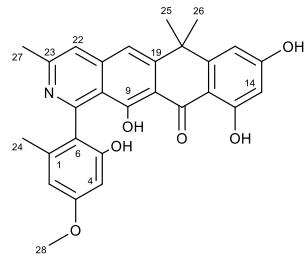
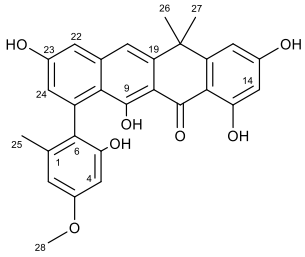
Electronic Supporting information



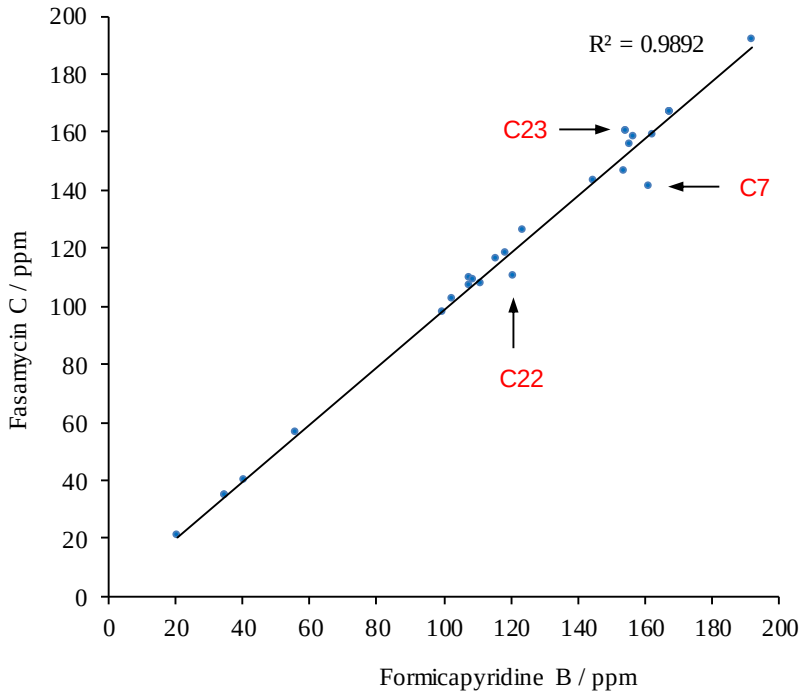
Supplementary Figure 1 | Extracted ion chromatograms for **1**-**9** from LCMS runs of extracts from the WT strain grown on MS agar medium without (a) and with (b) exogenous addition of NaBr (the slight shifts in retention times for **1**-**6** was due to machine maintenance carried out between the experiments).



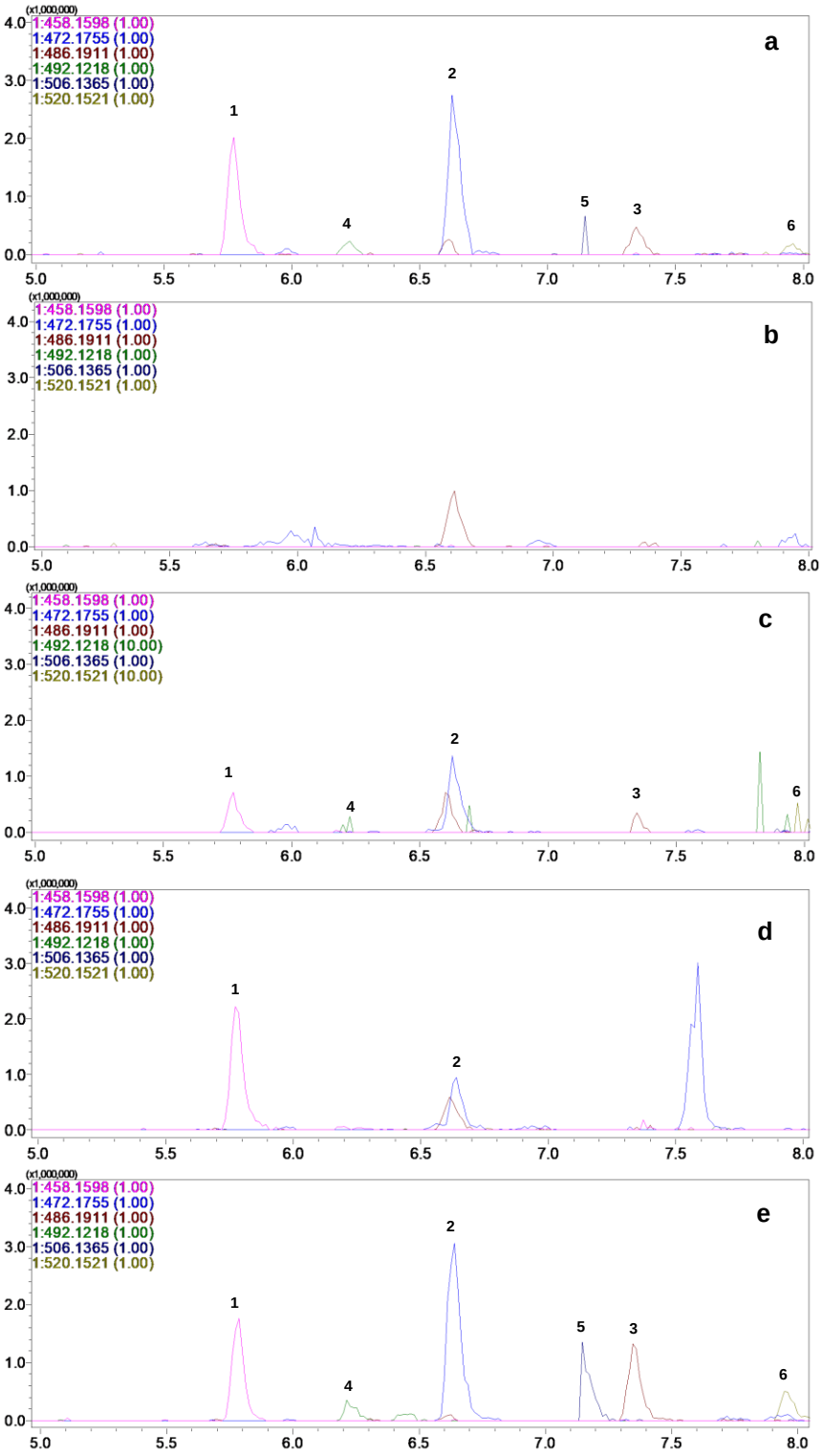
Formicapyridine B (**2**)



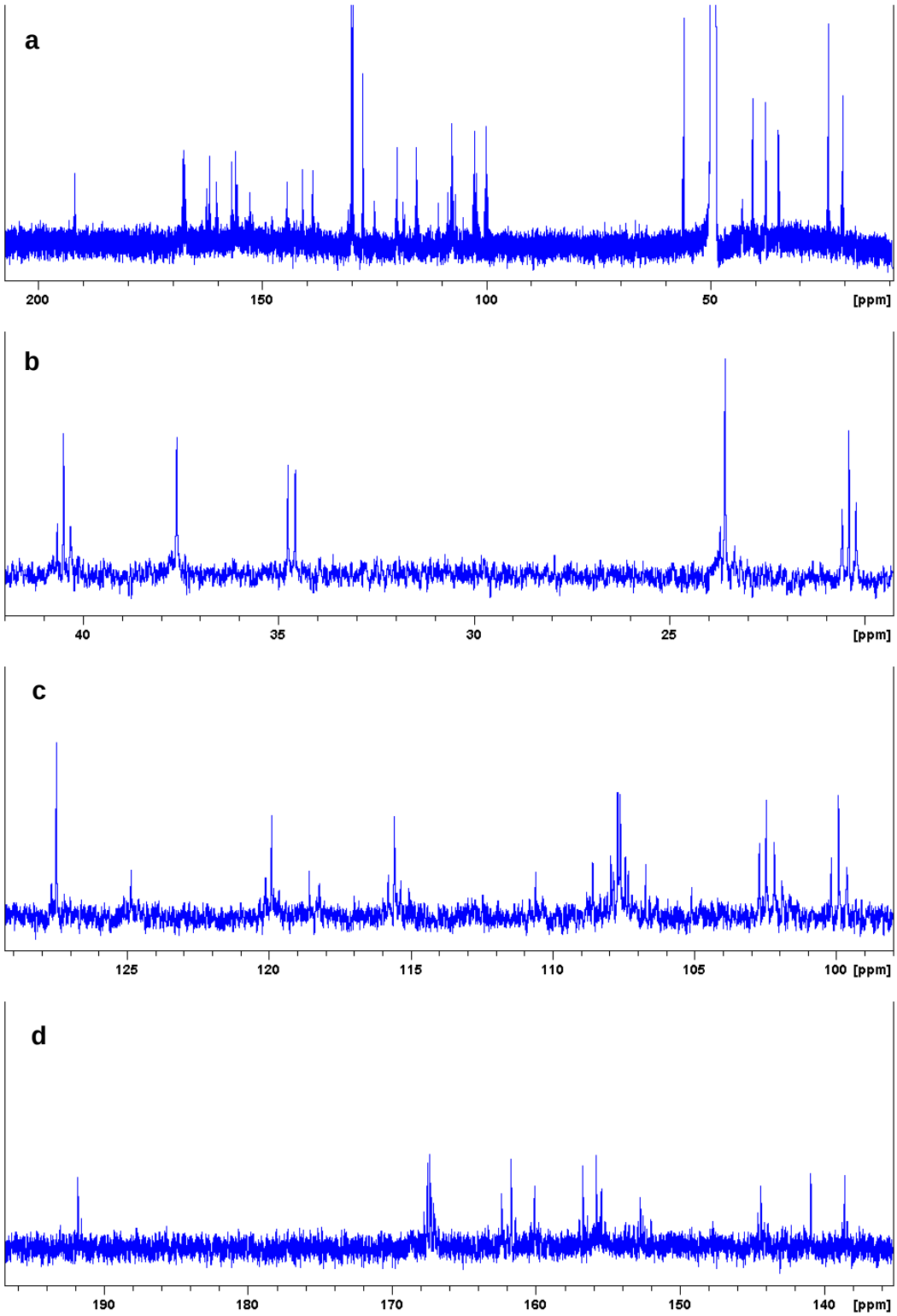
Fasamycin C (**10**)



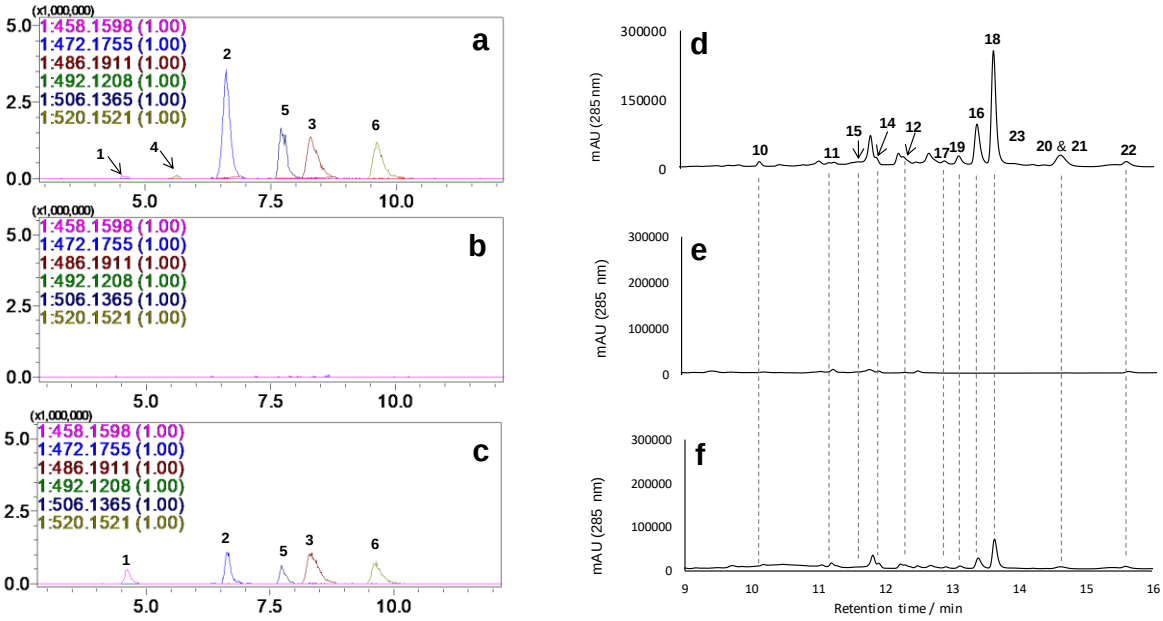
Supplementary Figure 2 | Comparison of the ^{13}C NMR chemical shifts for formicapyridine B (**2**) and fasamycin C (**10**). The chemical shifts for carbons C7, C22 and C23 are highlighted.



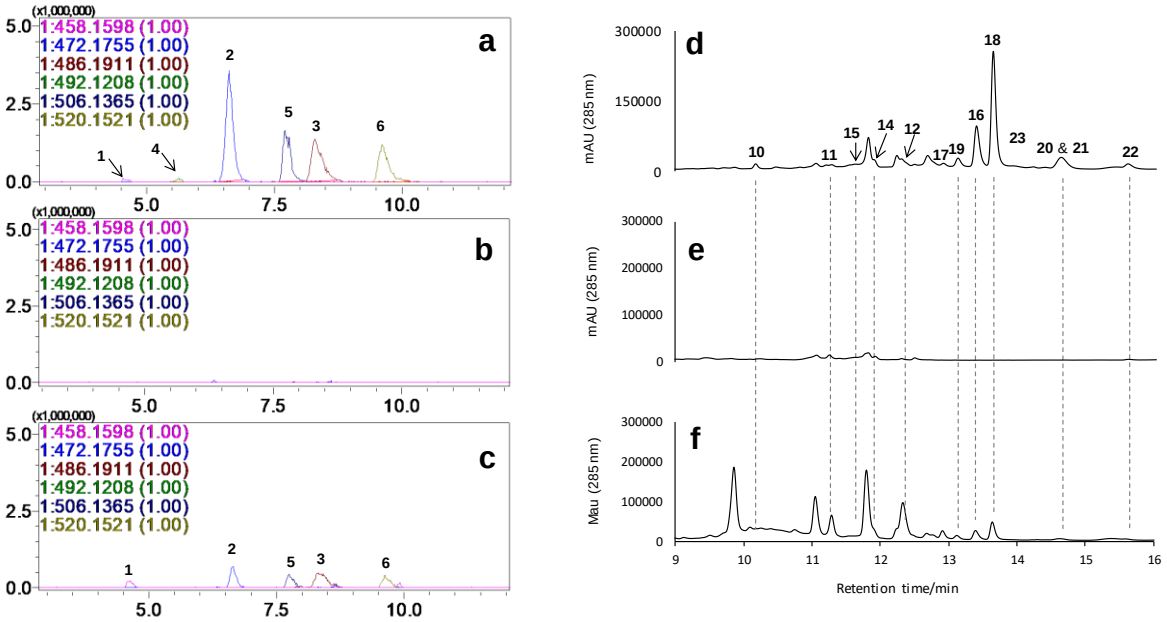
Supplementary Figure 3 | Extracted ion chromatograms for **1**-**6** from LCMS runs of fermentation extracts for: (a) *S. formicae* WT; (b) *S. formicae* Δ*for*; (c) *S. formicae* Δ*for/for*; (d) *S. formicae* Δ*forV*; (e) *S. formicae* Δ*forv/forv*. (The signal abundance of **4** and **6** in (c) was enlarged × 10 for clarity).



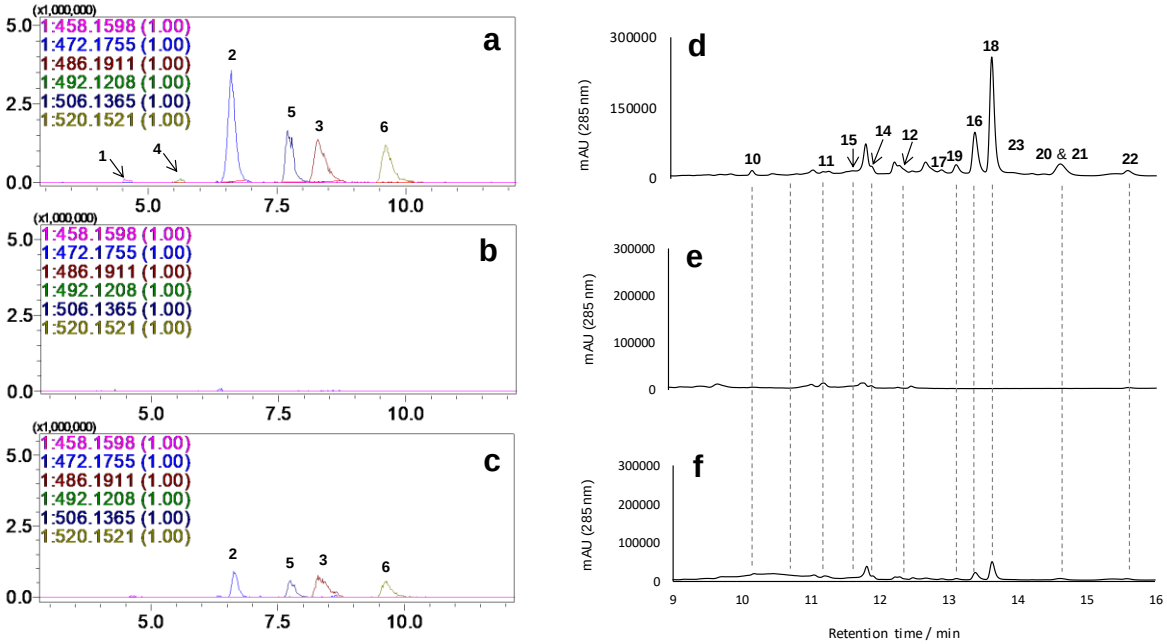
Supplementary Figure 4 | ^{13}C NMR spectra (125 MHz, methanol-d_6) of **2** isolated after growth of *S. formicae* WT in the presence of [1,2-$^{13}C_2$] sodium acetate: (a), full scale; (b)-(d), expanded scale.



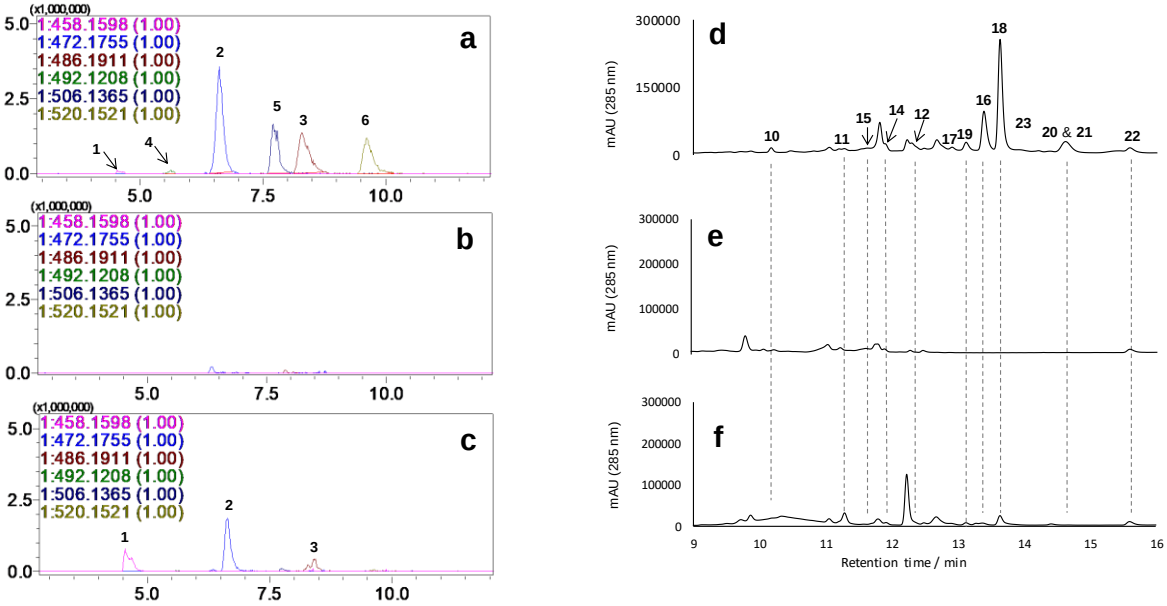
Supplementary Figure 5 | Mutational analysis of *forD*. Extracted ion chromatogram (left) and reconstituted HPLC-UV (285 nm) profiles (right) for extracts of *forD* mutagenesis and complementation experiments: (a) and (d) *S. formicae* wild-type; (b) and (e) *S. formicae* Δ*forD*; (c) and (f) *S. formicae* Δ*forD/forD*.



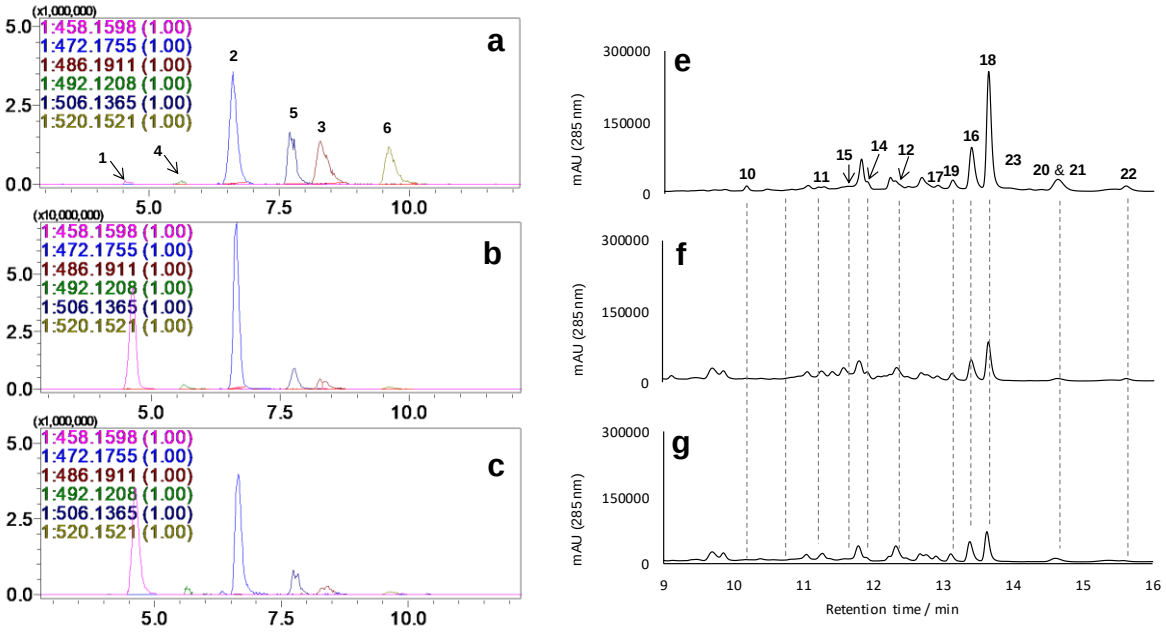
Supplementary Figure 6 | Mutational analysis of *forL*. Extracted ion chromatogram (left) and reconstituted HPLC-UV (285 nm) profiles (right) for extracts of *forL* mutagenesis and complementation experiments: (a) and (d) *S. formicae* wild-type; (b) and (e) *S. formicae* Δ*forL*; (c) and (f) *S. formicae* Δ*forL*/*forL*.



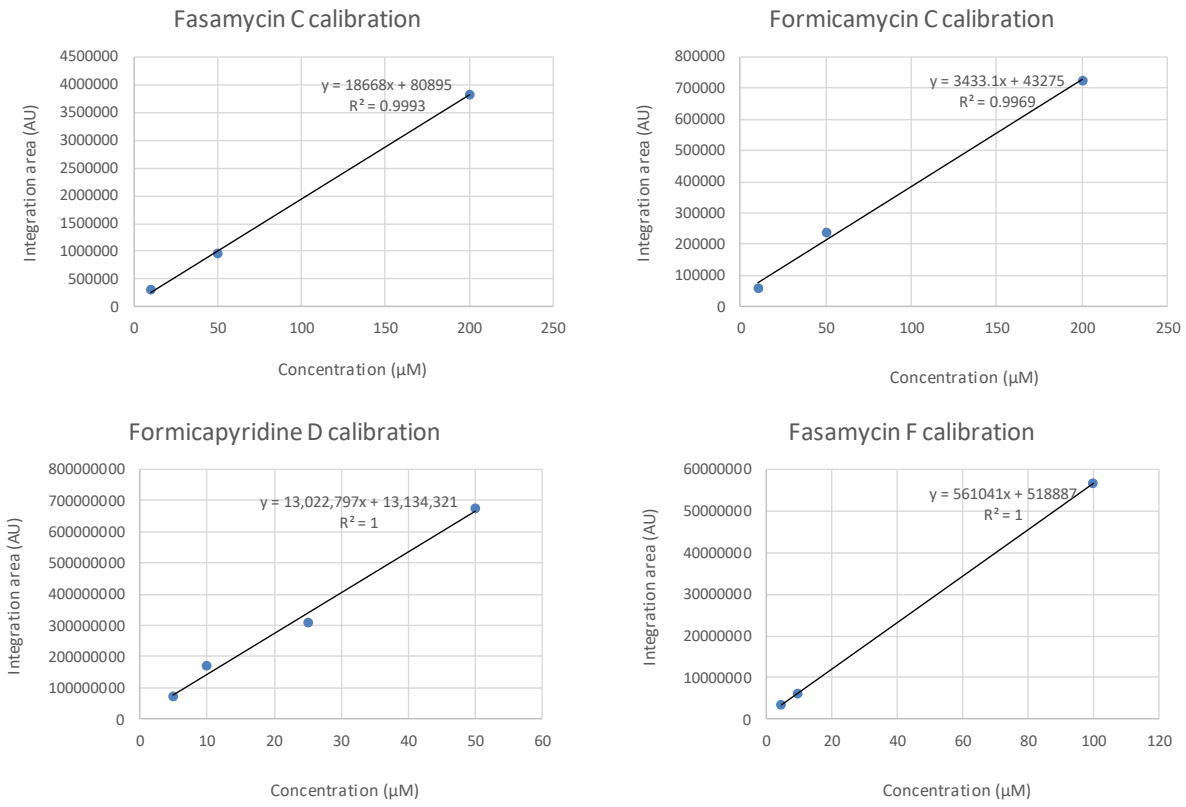
Supplementary Figure 7 | Mutational analysis of *forR*. Extracted ion chromatogram (left) and reconstituted HPLC-UV (285 nm) profiles (right) for extracts of *forR* mutagenesis and complementation experiments: (a) and (d) *S. formicae* wild-type; (b) and (e) *S. formicae* Δ*forR*; (c) and (f) *S. formicae* Δ*forR*/*forR*.



Supplementary Figure 8 | Mutational analysis of *forU*. Extracted ion chromatogram (left) and reconstituted HPLC-UV (285 nm) profiles (right) for extracts of *forU* mutagenesis and complementation experiments: (a) and (d) *S. formicae* wild-type; (b) and (e) *S. formicae* Δ*forU*; (c) and (f) *S. formicae* Δ*forU/forUV*.



Supplementary Figure 9 | Mutational analysis of *forS*. Extracted ion chromatogram (left) and reconstituted HPLC-UV (285 nm) profiles (right) for extracts of *forS* mutagenesis and complementation experiments: (a) and (d) *S. formicae* wild-type; (b) and (e) *S. formicae* Δ*forS*; (c) and (f) *S. formicae* Δ*forS/forS*.



Supplementary Figure 10 | Calibration curves of fasamycin C (10), formicamycin C (16), formicapyridine D (4), and fasamycin F (13).

Supplementary Table 1 | Strains made or used in this study.

Strain	Description	Plasmid	Resistance	Source or Reference
E. coli ET12567	*dam*$^{-}$ *dcm*$^{-}$ *hsdS*$^{-}$	*pUZ8002*	*Cml*^{R}/*Tet*^{R}	Reference 1
E. coli Top10	F– *mcr*A Δ(*mrr-hsd*RMS*mcr*BC) Φ80*lac*ZΔM15 Δ*lac*X74 *rec*A1 *end*A1 *ara*D139 Δ(*ara leu*) 7697 *gal*U *gal*K *rps*L *nup*G			Invitrogen, USA
E. coli DH10ß	F– *mcr*A Δ(*mrr-hsd*RMS*mcr*BC) Φ80*lac*ZΔM15 Δ*lac*X74 *rec*A1 *end*A1 *ara*D139 Δ(*ara leu*) 7697 *gal*U *gal*K *rps*L *nup*G λ–			Invitrogen, USA
S. formicae	Wild-type strain			Reference **Error! Bookmark not defined.**
S. formicae Δ*for*	Formicamycin (*for*) biosynthetic gene cluster (BCG) deleted			Reference **Error! Bookmark not defined.**
S. formicae Δfor:for ΦC31	*for* BGC deleted and complemented with the *for* BGC in trans at ΦC31	*PESAC-13 215-G*	*Kan*^{R}/*Tsr*	Reference **Error! Bookmark not defined.**
S. formicae Δ*forV*	Halogenase (*forV*) gene deleted			Reference **Error! Bookmark not defined.**
S.	Halogenase (*forV*)	pRD004	Hyg^{R}	Reference

formicae Δ*forV:forV pForV*	deleted and complemented at ΦBT1 under the native promoter			**Error! Bookmark not defined.**
S. formicae Δ*forD*	Cyclase (*forD*) gene deleted			This work
S. *formicae* Δ*forD:forD pForD*	Cyclase (*forD*) deleted and complemented at ΦBT1 under the native promoter	pRD012	Hyg^R	This work
S. formicae Δ*forL*	Cyclase (*forL*) gene deleted			This work
S. *formicae* Δ*forL:forL pForL*	Cyclase (*forL*) deleted and complemented at ΦBT1 under the native promoter	pRD013	Hyg^R	This work
S. formicae Δ*forS*	Cyclase (*forR*) gene deleted			This work
S. *formicae* Δ*forS:forS pErmE**	Cyclase (*forR*) deleted and complemented at ΦBT1 under the ErmE* promoter	pRD015	Hyg^R	This work
S. formicae Δ*forR*	Cyclase (*forS*) gene deleted			This work
S. *formicae* Δ*forR:forR-A pErmE**	Cyclase (*forS*) deleted and complemented with *forR* and *forA* (directly downstream) at ΦBT1 under the ErmE* promoter	pRD017	Hyg^R	This work
S. formicae Δ*forU*	Cyclase (*forU*) gene deleted			This work

S. *formicae* Δ*forU:forU-V pErmE**	Cyclase (*forU*) deleted and complemented with *forU* and *forV* (directly downstream) at ΦBT1 under the ErmE* promoter	pRD019	Hyg^R	This work

Supplementary Table 2 | Plasmids and ePACs used in this study.

Plasmids and ePACs	**Description**	**Source or Reference**
pCRISPomyces-2	Streptomyces plasmid for expression of codon-optimized Cas9 and a single guide RNA	Reference 2
pUZ8002	Non-transmissible RK2 derivative with a mutation in *oriT*	Reference 3
pESAC13-215-G	ePAC clone harbouring the *For* BGC integrative ΦC31	Reference**Error! Bookmark not defined.**1
pMS82	ΦBT1 *attP-int* derived integration vector for the conjugal transfer of DNA from *E. coli* to *Streptomyces* (Hyg^R)	Reference 4
pIJ10257	Plasmid for the conjugal transfer of DNA (under control of the ermE* constitutive promoter) from E. coli to Streptomyces spp. Integrates specifically at the ΦBT1 attachment site (HygR)	Reference 5
pRD004	PMS82 pForV ForV complementation plasmid	This work
pRD012	PMS82 pForD ForD	This work

	complementation plasmid	
pRD013	PMS82 pForL ForL complementation plasmid	This work
pRD015	pIJ10257 ForR-ForA complementation plasmid	This work
pRD017	pIJ10257 ForS complementation plasmid	This work
pRD019	pIJ10257 ForU-ForV complementation plasmid	This work

Supplementary Table 3 | PCR primers used in this study.

Primer name	Sequence	Description
pCRISP-2 For TEST	AGGCTAGTCCGTTATCAACTTGAAA	Detection of pCRISP and cloning inserts around XbaI site forward
pCRISP-2 Rev TEST	TCGCCACCTCTGACTTGAGCGTCGA	Detection of pCRISP and cloning inserts around XbaI site reverse
Spacer primer	atacggctgccagataaggc	Detection of gRNA insert at BbsI site via sequencing
pms82 Rev	gccagtggtatttatgtcaacaccgcc	Detection of Pms82 and cloning inserts around HINDIII site reverse
FOR pMS82	gcaacagtgccgttgatcgtgctatg	Detection of Pms82 and cloning inserts around HINDIII site forward
RD206 ForD 1.1 For	gctcggttgccgccgggcgtttttaTCTAGAccagttcggccacggactgc	pCRISPomyces-2 template 1 left flank ForD
RD207 ForD 1.2 Rev	GCTGCTGCGACCAGGCGAGCTCGCcacggtcaggctcccttcg	pCRISPomyces-2 template 1 right flank ForD
RD208 ForD 2.1 For	GCGAGCTCGCCTGGTCGCAGCAGCgtatgagcgccaccgaggcc	pCRISPomyces-2 template 2 left flank

		ForD
RD209 ForD 2.2 Rev	gcaacgcggccttttacggttcctggccTCTAGAccaacggccagacggcgcgtc	pCRISPomyces-2 template 2 right flank ForD
RD209 ForD gRNA For	ACGCtggatgcgcatgaacgcgaa	ForD gRNA forward
RD210 ForD gRNA Rev	AAACttcgcgttcatgcgcatcca	ForD gRNA reverse
RD211 ForD Test Int For	ccacgctggtcgaacagtgc	Confirmation of ForD deletion external for
RD212 ForD Test Int Rev	gcgagtctgaccaggcgctc	Confirmation of ForD deletion external rev
RD213 ForD Test Ext For	cgtcctggtcaccgacgagg	Confirmation of ForD deletion internal for
RD214 ForD Test Ext Rev	gcatggcgcaggtgcacacc	Confirmation of ForD deletion internal rev
RD215 ForL 1.1 For	gctcggttgccgccgggcgtttttaTCTAGAgcagcacgccgaccagcacg	pCRISPomyces-2 template 1 left flank ForL
RD216 ForL 1.2 Rev	GCTGCTGCGACCAGGCGAGCTCGCtagtcccgccatggcggacc	pCRISPomyces-2 template 1 right flank ForL
RD217 ForL 2.1 For	GCGAGCTCGCCTGGTCGCAGCAGCcatggacgaactccctttcgcc	pCRISPomyces-2 template 2 left flank ForL
RD218 ForL 2.2 Rev	gcaacgcggccttttacggttcctggccTCTAGAgctaaggaggtggccgagg	pCRISPomyces-2 template 2 right flank ForL
RD219 ForL gRNA For	ACGCgagccccaactgccttggta	ForL gRNA forward
RD220 ForL gRNA Rev	AAACtaccaaggcagttggggctc	ForL gRNA reverse
RD221 ForL Test Int For	cgagggcgagcagcaggcg	Confirmation of ForL deletion external for
RD222 ForL Test Int Rev	cggcacgcgagttcggtggc	Confirmation of ForL deletion external rev

RD223 ForL Test Ext For	cgctcggtcgccacggcc	Confirmation of FoL deletion internal for
RD224 ForL Test Ext Rev	ccgcgtgatgacagatgcgcc	Confirmation of ForL deletion internal rev
RD235 ForR 1.1 For	gctcggttgccgccgggcgtttttaTCTAGAct tcggcaagcagttcttcg	pCRISPomyces-2 template 1 left flank ForR
RD236 ForR 1.2 Rev	GCTGCTGCGACCAGGCGAGCTC GCggtcatggttctccttgtcc	pCRISPomyces-2 template 1 right flank ForR
RD237 ForR 2.1 For	GCGAGCTCGCCTGGTCGCAGCA GCacatgacccggcaggtcgcc	pCRISPomyces-2 template 2 left flank ForR
RD238 ForR 2.2 Rev	gcaacgcggccttttacggttcctggccTCTA GAccgagccgtgcgcgttgacg	pCRISPomyces-2 template 2 right flank ForR
RD239 ForR gRNA For	ACGCcgtagaggaactcctcggagta	ForR gRNA forward
RD240 ForR gRNA Rev	AAACtactccgaggagttcctctacg	ForR gRNA reverse
RD241 ForR Test Int For	gcacatacgccatcaggtcgc	Confirmation of ForR deletion external for
RD242 ForR Test Int Rev	ggtccatgcgttgggcctcg	Confirmation of ForR deletion external rev
RD243 ForR Test Ext For	cggcgagcgggtcttcgac	Confirmation of ForR deletion internal for
RD244 ForR Test Ext Rev	cgtgccggtcgttctgcttgg	Confirmation of ForR deletion internal rev
RD245 ForS 1.1 For	gctcggttgccgccgggcgtttttaTCTAGAg aggagcacctcaccatgacg	pCRISPomyces-2 template 1 left flank ForS
RD246 ForS 1.2 Rev	GCTGCTGCGACCAGGCGAGCTC GCgctcatacggtgccctccac	pCRISPomyces-2 template 1 right flank ForS
RD247 ForS 2.1 For	GCGAGCTCGCCTGGTCGCAGCA GCtgatccgacccaacggggac	pCRISPomyces-2 template 2 left flank

		ForS
RD248 ForS 2.2 Rev	gcaacgcggccttttacggttcctggccTCTAGAgaagcgccggtgatcatgacg	pCRISPomyces-2 template 2 right flank ForS
RD249 ForS gRNA For	ACGCgggtttgtggacgtaggtga	ForS gRNA forward
RD250 ForS gRNA Rev	AAACtcacctacgtccacaaaccc	ForS gRNA reverse
RD251 ForS Test Int For	cctcgtcgaggacagcacgg	Confirmation of ForS deletion external for
RD252 ForS Test Int Rev	cgatgcgtacgtcgacgttgc	Confirmation of ForS deletion external rev
RD253 ForS Test Ext For	gcctcttgcgcggcttgagc	Confirmation of ForS deletion internal for
RD254 ForS Test Ext Rev	cgcgtcgaagcaggagacgg	Confirmation of ForS deletion internal rev
RD265 ForU 1.1 For	gctcggttgccgccgggcgtttttaTCTAGAcgtagtactcgccgcggttc	pCRISPomyces-2 template 1 left flank ForU
RD266 ForU 1.2 Rev	GCTGCTGCGACCAGGCGAGCTCGCgatgagtgaccagcagcgcc	pCRISPomyces-2 template 1 right flank ForU
RD267 ForU 2.1 For	GCGAGCTCGCCTGGTCGCAGCAGCcatgtggagctgccctcactc	pCRISPomyces-2 template 2 left flank ForU
RD268 ForU 2.2 Rev	gcaacgcggccttttacggttcctggccTCTAGAgcttcttgccgccgacgttg	pCRISPomyces-2 template 2 right flank ForU
RD269 ForU gRNA For	ACGCgtggccctcttgagctacgt	ForU gRNA forward
RD270 ForU gRNA Rev	AAACacgtagctcaagagggccac	ForU gRNA reverse
RD271 ForU Test Int For	ggtccactgcggcaggtcg	Confirmation of ForU deletion external for
RD272 ForU Test Int Rev	gcgcggttcctcgtcgagcg	Confirmation of ForU deletion external rev

RD273 ForU Test Ext For	ggtcacgaagtcgacgtcgg	Confirmation of ForU deletion internal for
RD274 ForU Test Ext Rev	cggtagccgtggtaggtgagg	Confirmation of ForU deletion internal rev
RD307 ForD pMS82 pF	gccgagaaccTAGGATCCAAGCTTgtg gagctgccctcactctc	ForD pMS82-promotor for complementation forward
RD308 ForD pMS82 pR	cgttctcggtgagctcgggcacggtgaggtgctc ctcctg	ForD promotor-gene for complementation reverse
RD309 ForD pMS82 gF	caggaggagcacctcaccgtgcccgagctcac cgagaacg	ForD promotor-gene for complementation forward
RD310 ForD PMS82 gR	CTGGTACCATGCATAGATCTAAG CTTcctcggtggcgctcatacgg	ForD gene-pMS82 for complementation reverse
RD311 ForL pMS82 pF	gccgagaaccTAGGATCCAAGCTTgat tcttcggcgcacgacag	ForL pMS82-promotor for complementation forward
RD312 ForL pMS82 pR	cgacgatcaacgtggtgtgcataccggctcccat cggttgc	ForL promotor-gene for complementation reverse
RD313 ForL pMS82 gF	gcaaccgatgggagccggtatgcacaccacgtt gatcgtcg	ForL promotor-gene for complementation forward
RD314 ForL pMS82 gR	CTGGTACCATGCATAGATCTAAG CTTctactcgacggggactacgc	ForL gene-pMS82 for complementation reverse
RD512 ForR-ForA ErmE* F	AAAAAcatatgatgaccacgcacaccgtgc	ForRA complementation under ErmE* forward pIJ10257
RD513 ForR-ForA ErmE* R	AAAAAaagctttcacctcagctccctccggtc	FoRA complementation under ErmE* reverse pIJ10257
RD516 ForS ErmE* F	AAAAAcatatgatgagccaggaggagccgc	ForS complementation under ErmE* forward

		pIJ10257
RD517 ForS ErmE* R	AAAAAaagctttcagaggggtgctgccgtg	ForS complementation under ErmE* reverse pIJ10257
RD518 ForU-ForV ErmE* F	AAAAAcatatgatggccgagatctccgccg	ForU-V complementation under ErmE* forward pIJ10257
RD519 ForU-ForV ErmE* R	AAAAAaagcttcgctctgctcctgtgccgtc	ForU-V complementation under ErmE* reverse pIJ10257

Supplementary Table 4 | Growth media used in this study

Media	**Recipe (per litre)**	**Water**	**pH**
LB	10 g tryptone 5 g yeast extract 10 g NaCl (omitted when selecting with Hygromycin) +/- 20 g agar	Deionised	7.5
MS	20 g soy flour 20 g mannitol 20 g agar	Tap	As made
MYM	4 g maltose 4 g yeast extract 10 g malt extract 18g agar	50:50 Tap:Deisonised	7.3

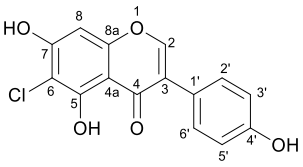
Supplementary Table 5 | Antibiotics (and concentrations) used in this study.

Antibiotic	**Final concentration used for selection (µg/ml)**
Apramycin	50
Hygromycin	50
Kanamycin	50
Chloramphenicol	30
Nalidixic Acid	25

Supplementary Note 1 | Compound structure elucidation data for 6-chlorogenistein

An isomer of 6-chlorogenistein – identified based on based on UV and MS characteristics, and likely to be a chlorination regioisomer - was identified in the LCMS trace but was not isolated due to low levels of production. The NMR data for 6-chlorogenistein has been reported previously[6], and is in accordance with the data reported here.

Supplementary Figure 11 | Chemical structure of 6-chlorogenistein



Molecular formula: $C_{15}H_9O_5Cl$

Isolated yield: 2 mg

UV (PDA): λ_{max} = 259 nm

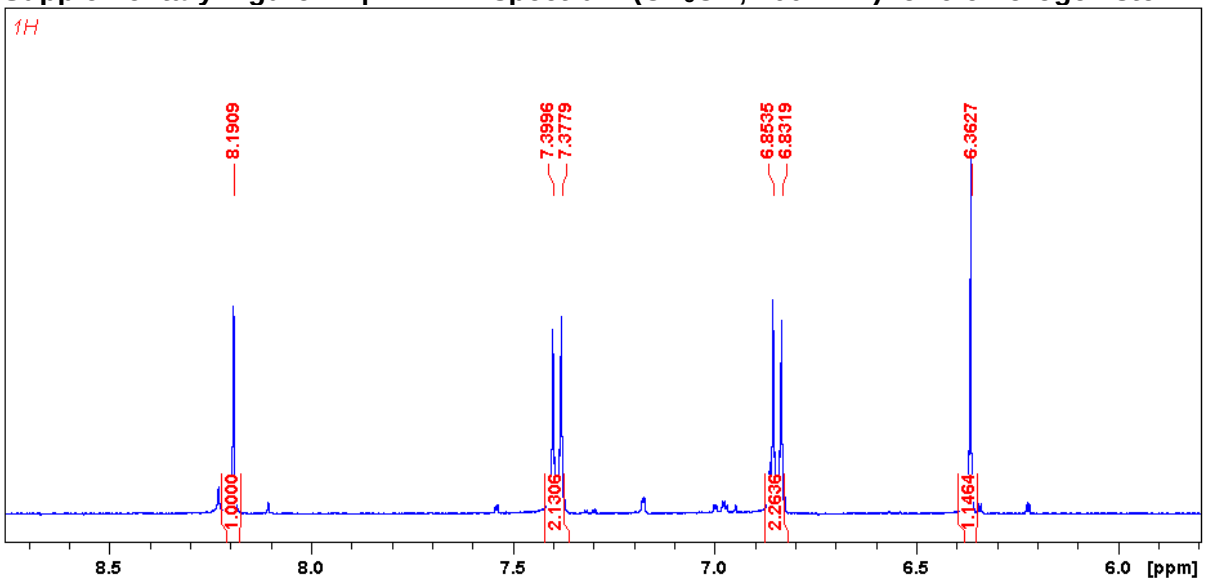
HRMS (ESI) *m/z*: calculated $[M + H]^+$ = 305.0211; observed $[M + H]^+$ = 305.0212, Δ = 0.33 ppm

Supplementary Table 6 | NMR data for 6-chlorogenistein in CD_3OD at 400 MHz for ^1H and 100 MHz for ^{13}C.

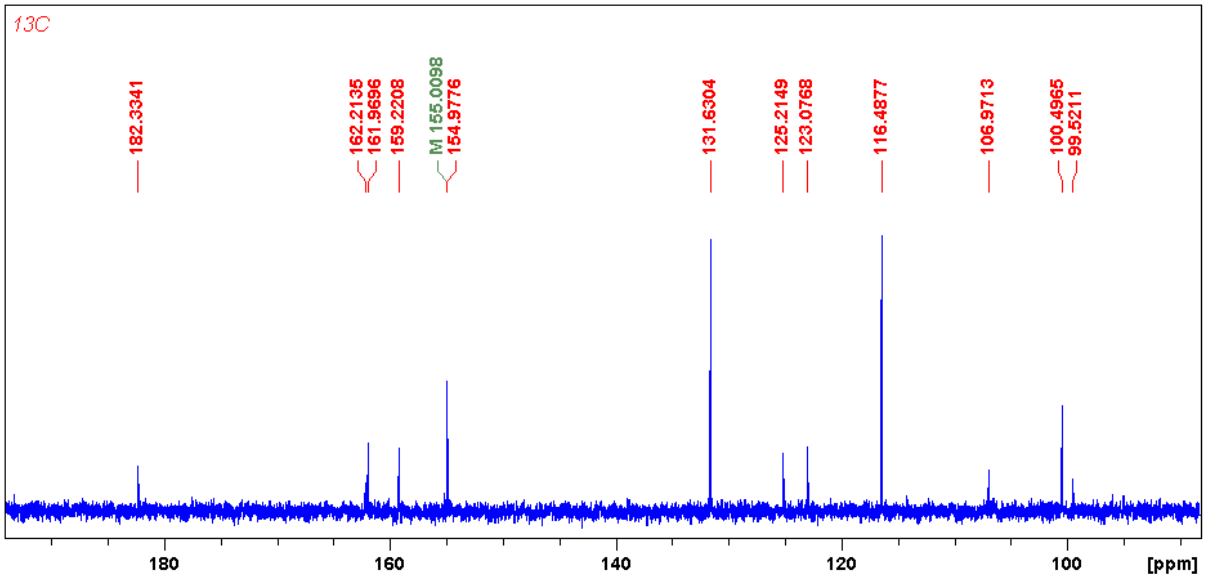
Position	δ_C ppm	δ_H ppm (no. of protons, multiplicity, J in Hz)	HMBC
2	155.0	8.2	
3	123.1		2, 2', 6'
4	182.3		2
4a	107.0		8
5	162.2		
6	99.5		8
7	162.0		8
8	100.5	6.4	
8a	155.0		2
1'	125.2		2, 3', 5'
2'	116.5	6.8	6'
3'	131.6	7.4	5'
4'	159.2		2', 3', 5', 6'

5’	131.6	7.4	3’
6’	116.5	6.9	2’

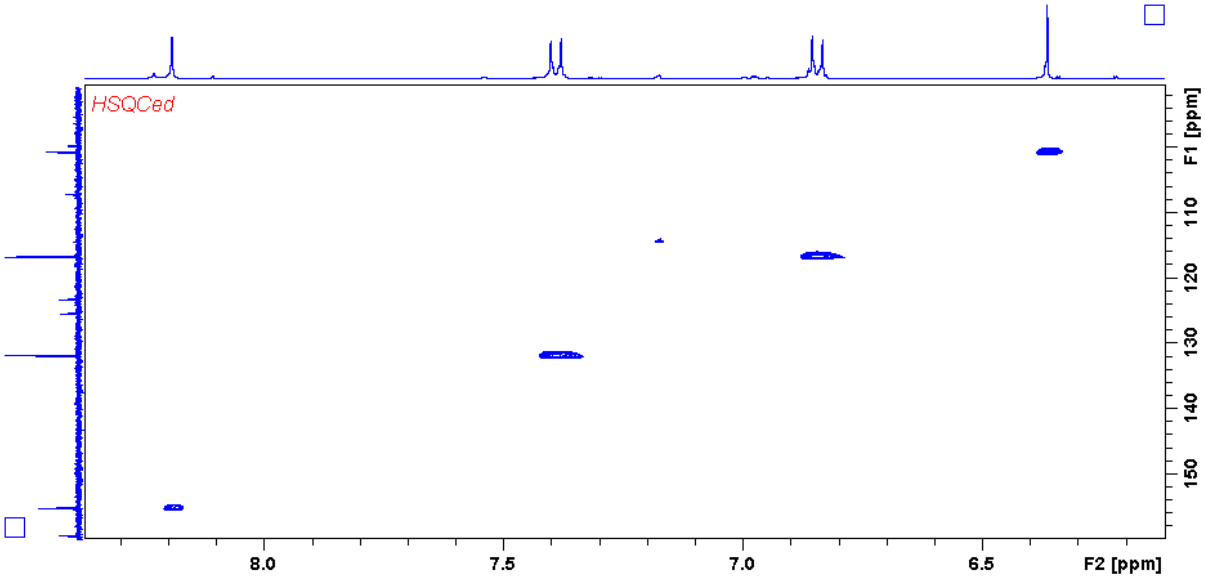
Supplementary Figure 12 | ^{1}H NMR spectrum (CD_3OD, 400 MHz) for 6-chlorogenistein.



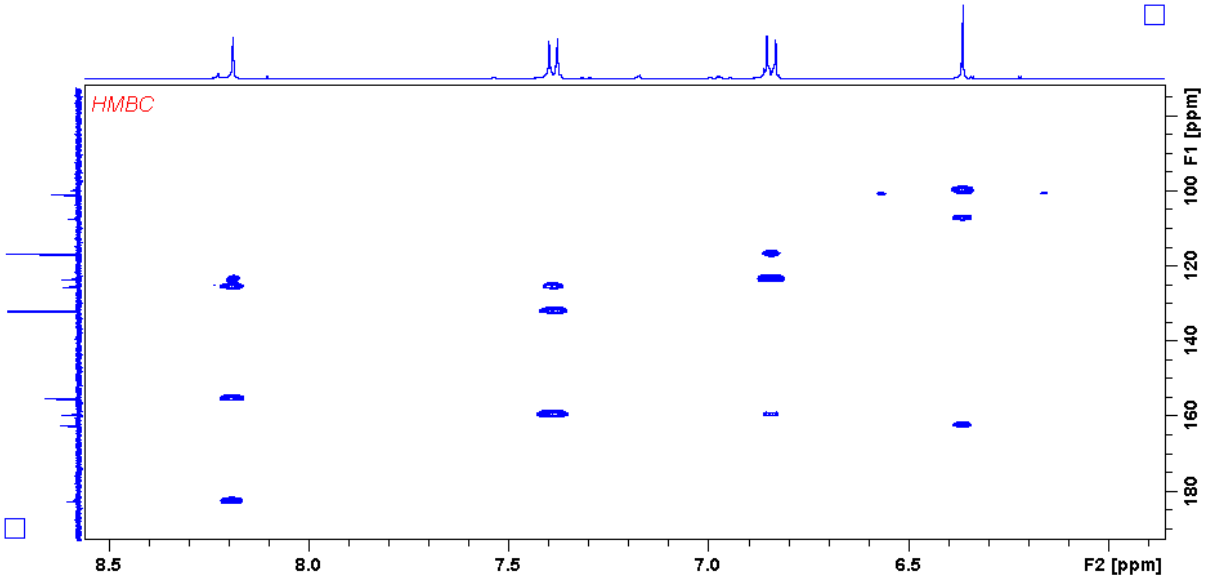
Supplementary Figure 13 | ^{13}C NMR spectrum (CD_3OD, 100 MHz) for 6-chlorogenistein.



Supplementary Figure 14 | HSQC spectrum (CD_3OD) for 6-chlorogenistein.



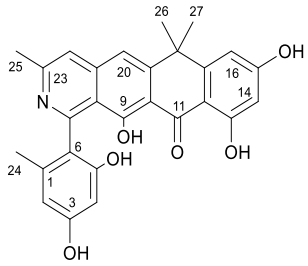
Supplementary Figure 15 | HMBC spectrum (CD_3OD) for 6-chlorogenistein.



Supplementary Note 2 | Formicapyridine A-F (1-6) and fasamycin F (13) structure elucidation data.

COMPOUND 1 (formicapyridine A)

Supplementary Figure 16 | Chemical structure of compound 1



Molecular formula: $C_{27}H_{23}NO_6$

Isolated yield: 1 mg

UV (PDA): λ_{max} = 228, 249, 272, and 391 nm

Optical activity: $[\alpha]_D^{20}$ = +9.890

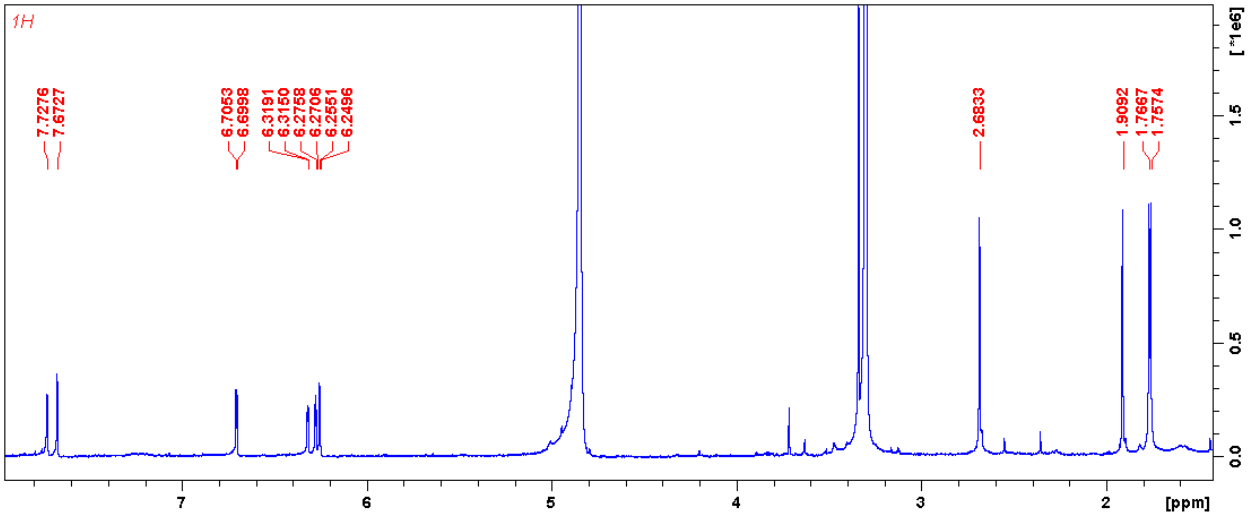
HRMS (ESI) *m/z*: calculated $[M + H]^+$ = 458.1598; observed $[M + H]^+$ = 458.1600, Δ = 0.44 ppm

Supplementary Table 7 | NMR data for compound 1 in CD_3OD at 400 MHz for ^1H and 100 MHz for ^{13}C.

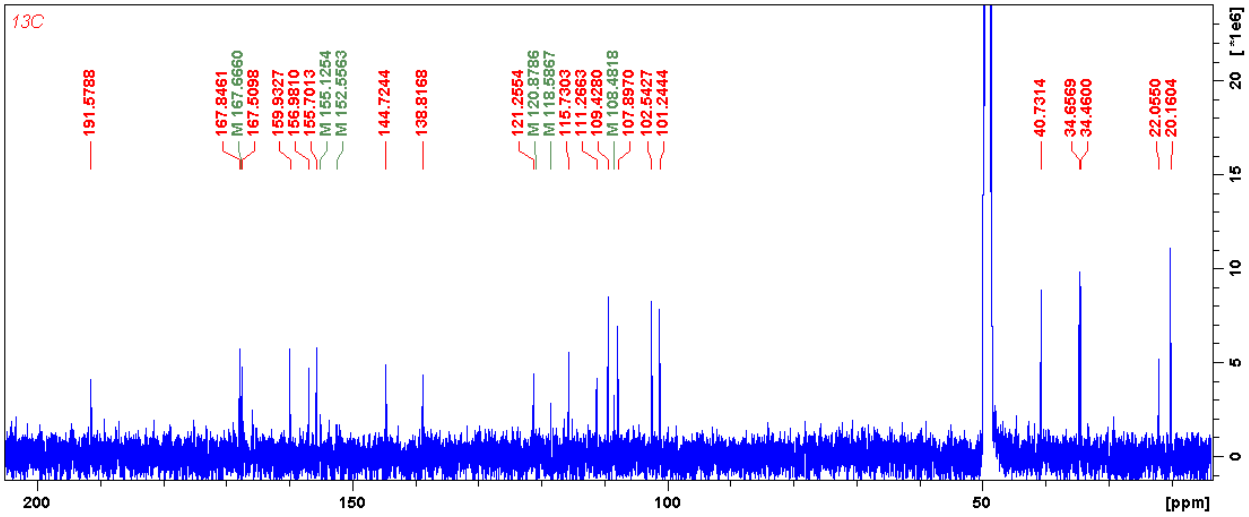
Position	δ_C ppm	δ_H ppm (no. of protons, multiplicity, J in Hz)	HMBC	NOESY
1	138.8		24	
2	109.4	6.3 (1H, d, 1.64)	24	24
3	not detected			
4	101.2	6.3 (1H, d, 1.64)		
5	157.0			
6	120.9		2, 4, 24	
7	159.9			
8	118.6		20, 22	
9	167.5			
10	111.3		20	
11	191.6			
12	108.5		14	
13	167.7		14	

14	102.5	6.3 (1H, d, 2.21)	16	
15	167.8			
16	107.9	6.7 (1H, d, 2.21)	14	26, 27
17	155.7		26, 27	
18	40.7		20, 26, 27	
19	155.1		26, 27	
20	115.7	7.7 (1H, s)	22	26, 27
21	144.7			
22	121.3	7.7 (1H, s)	20, 25	25
23	152.6		25	
24	20.2	1.9 (3H, s)		2
25	22.1	2.7 (3H, s)		6
26	34.5	1.8 (3H, s)	27	16, 20
27	34.7	1.8 (3H, s)	26	16, 20

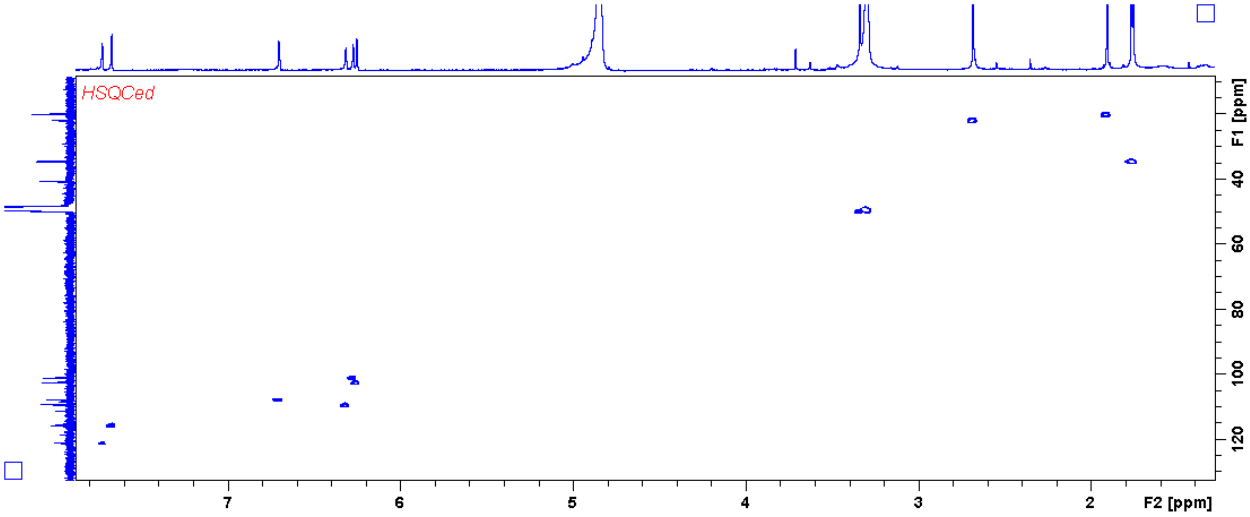
Supplementary Figure 17 | ^{1}H NMR spectrum (CD_3OD, 400 MHz) for compound 1.



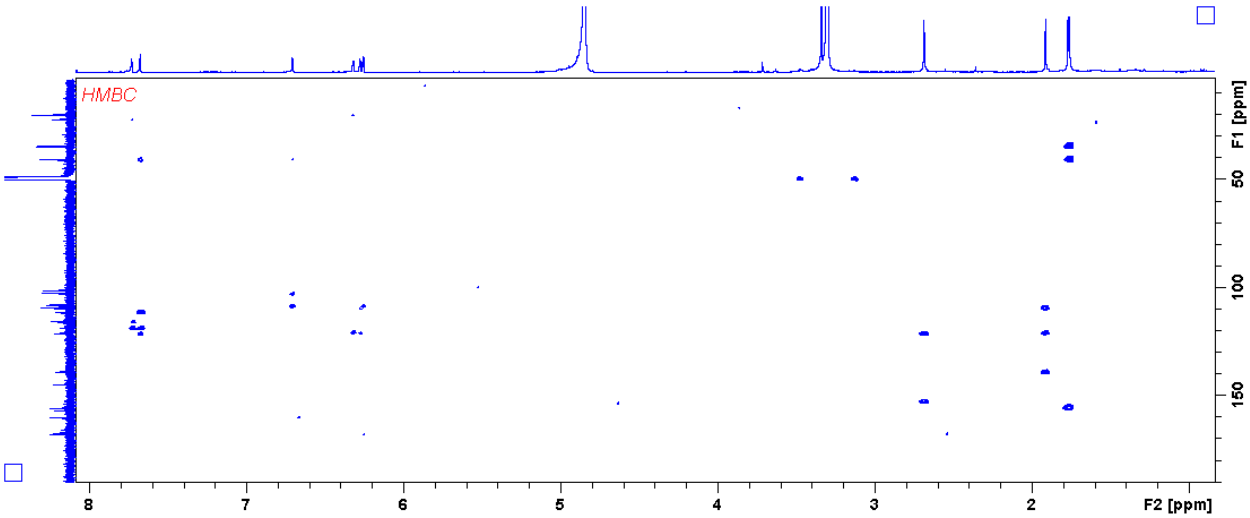
Supplementary Figure 18 | ^{13}C NMR spectrum (CD_3OD, 100 MHz) for compound 1.



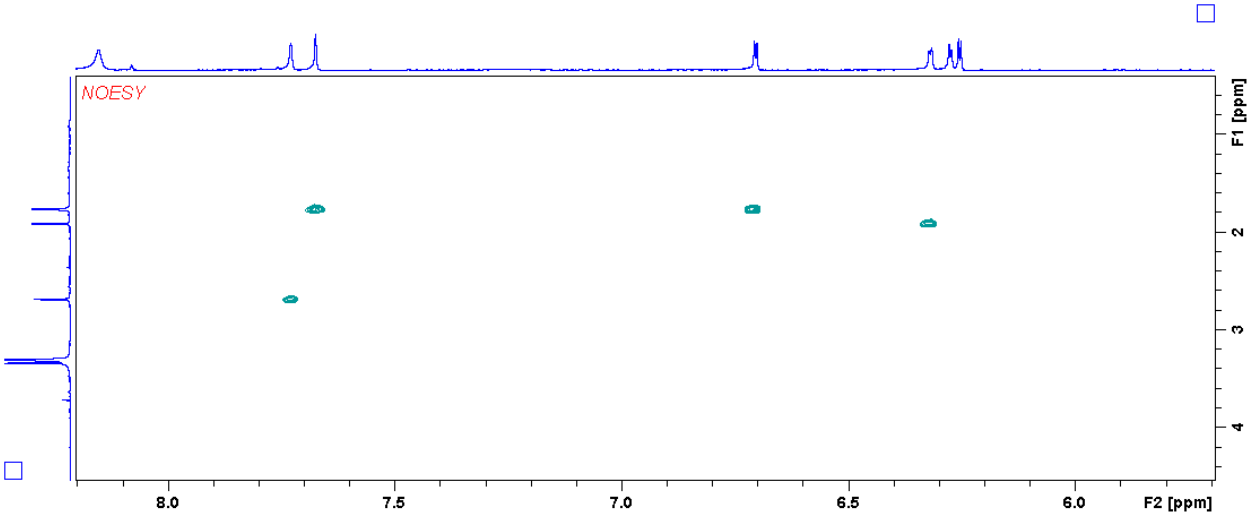
Supplementary Figure 19 | HSQC spectrum (CD_3OD) for compound 1.



Supplementary Figure 20 | HMBC spectrum (CD_3OD) for compound 1.

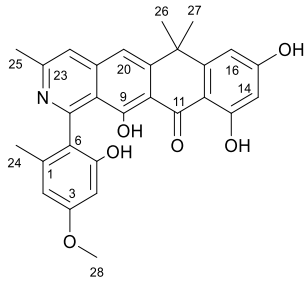


Supplementary Figure 20 | NOESY spectrum (CD_3OD) for compound 1.



COMPOUND 2 (formicapyridine B)

Supplementary Figure 22 | Chemical structure of compound 2



Molecular formula: $C_{28}H_{25}NO_6$

Isolated yield: 1 mg

UV (PDA): λ_{max} = 229, 249, 272, and 392 nm

Optical activity: $[\alpha]_D^{20}$ = +7.692

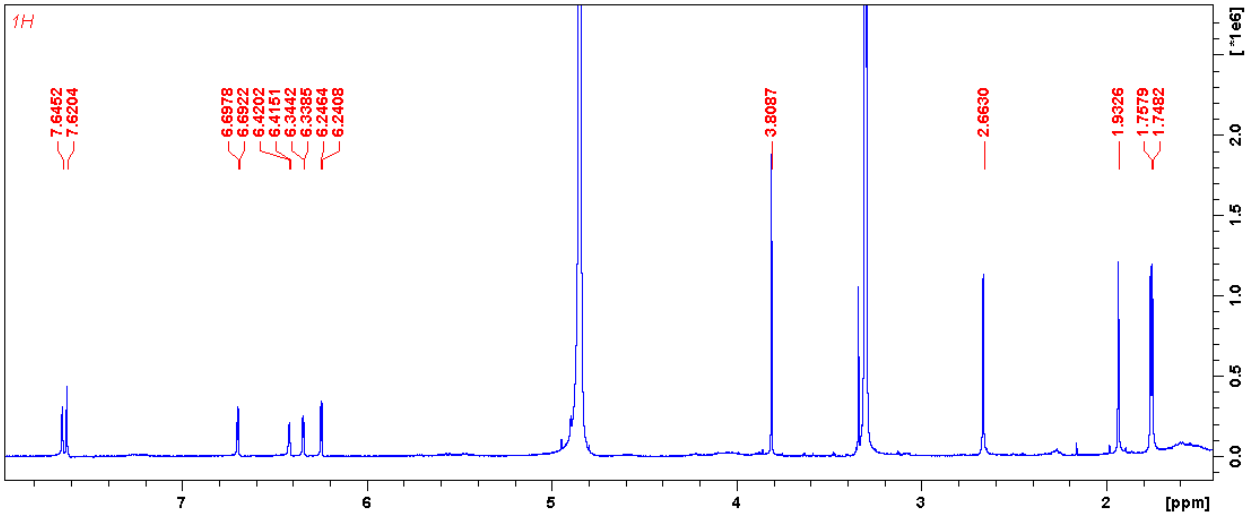
HRMS (ESI) *m/z*: calculated $[M + H]^+$ = 472.1755; observed $[M + H]^+$ = 472.1753, Δ = -0.42 ppm.

Supplementary Table 8 | NMR data for compound 2 in CD_3OD at 400 MHz for ^1H and 100 MHz for ^{13}C.

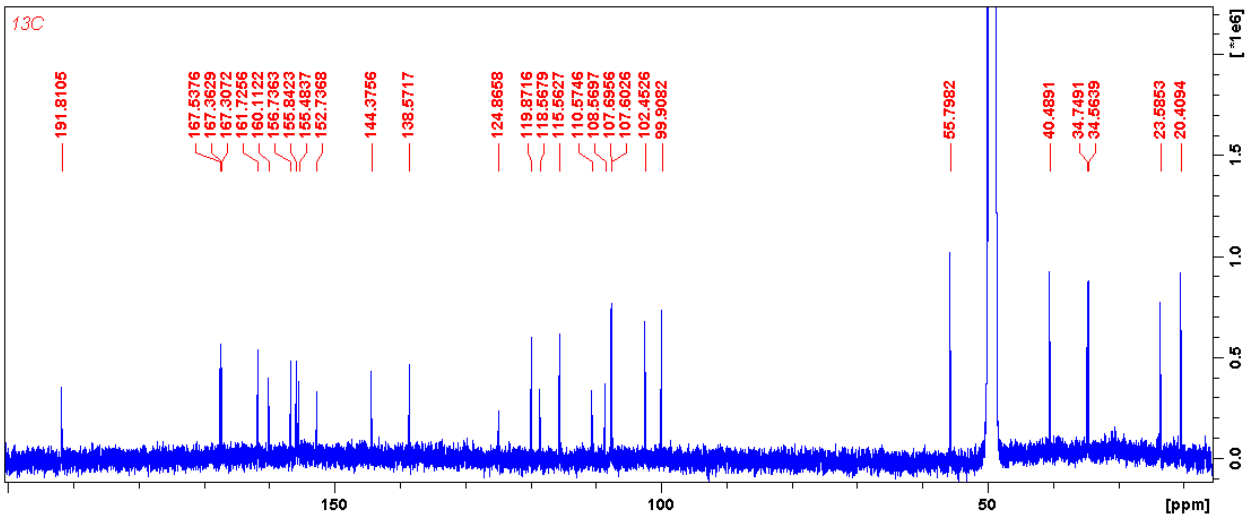
Position	δ_C ppm	δ_H ppm (no. of protons, multiplicity, J in Hz)	^1H – ^1H COSY	HMBC	NOESY
1	138.6			24	
2	107.7	6.4 (1H, d, 2.27)	4	4, 24	24, 28

3	161.7			4, 28	
4	99.9	6.3 (1H, d, 2.27)	2	2	28
5	156.7			4	
6	124.9			2, 4, 24	
7	160.1				
8	118.6			20, 22	
9	167.3				
10	110.6			20	
11	191.8				
12	108.6			14, 16	
13	167.5			14	
14	102.5	6.2 (1H, d, 2.25)	16	16	
15	167.4			14, 16	
16	107.6	6.7 (1H, d, 2.25)	14	14	26, 27
17	155.8			26, 27	
18	40.5			16, 20, 26, 27	
19	152.7			26, 27	
20	115.6	7.6 (1H, s)		22	26, 27
21	144.4			20	
22	119.9	7.6 (1H, s)		20, 25	25
23	155.5			22, 25	
24	20.4	1.9 (3H, s)		2	2
25	23.6	2.7 (3H, s)		22	22
26	34.6	1.8 (3H, s)		27	16. 20
27	34.8	1.7 (3H, s)		26	16, 20
28	55.8	3.8 (3H, s)			2, 4

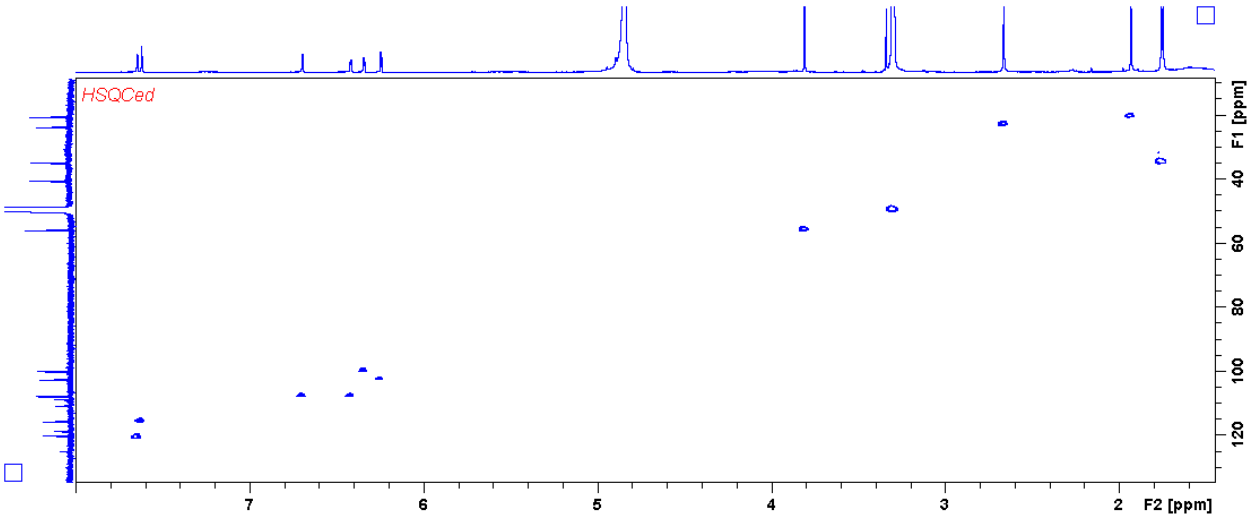
Supplementary Figure 23 | ^{1}H NMR spectrum (CD_3OD, 400 MHz) for compound 2.



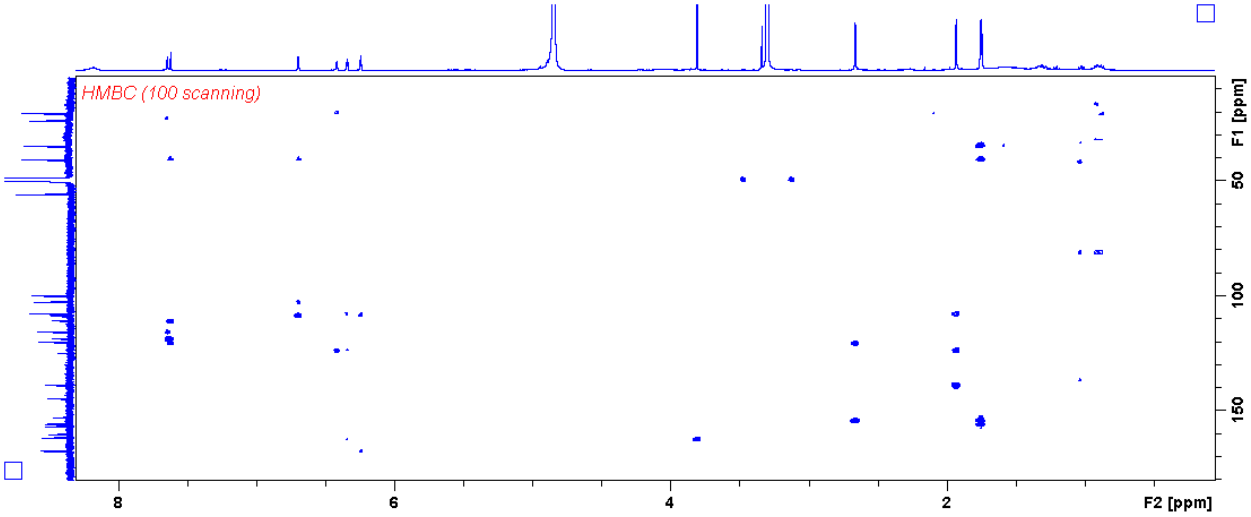
Supplementary Figure 24 | ^{13}C NMR spectrum (CD_3OD, 100 MHz) for compound 2.



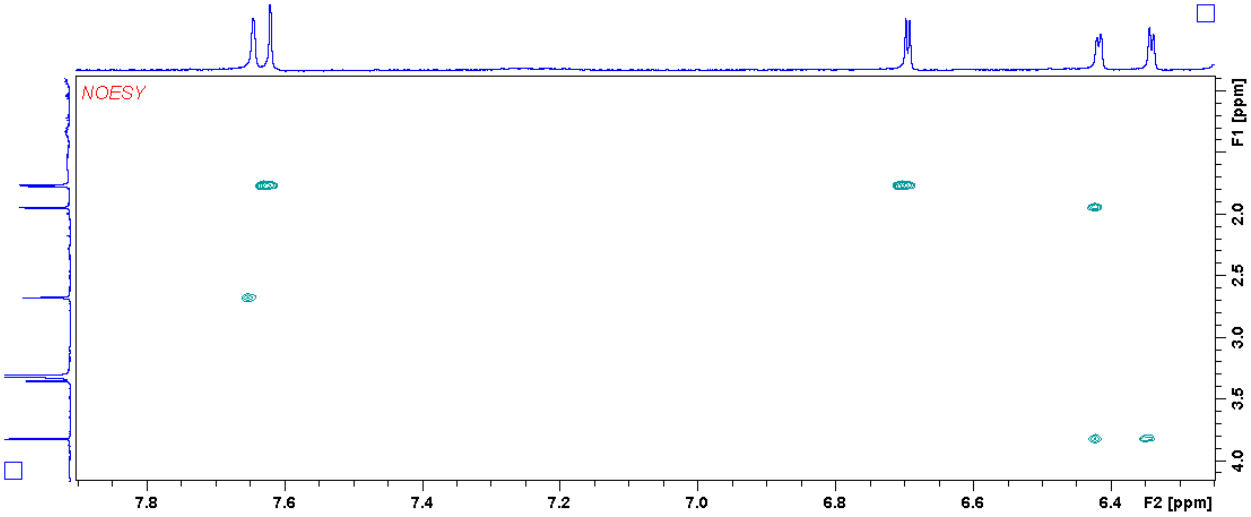
Supplementary Figure 25 | HSQC spectrum (CD_3OD) for compound 2.



Supplementary Figure 26 | HMBC spectrum (CD_3OD) for compound 2.

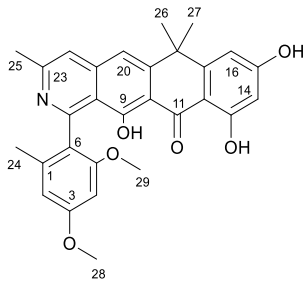


Supplementary Figure 27 | NOESY spectrum (CD_3OD) for compound 2.



COMPOUND 3 (formicapyridine C)

Supplementary Figure 28 | Chemical structure of compound 3



Molecular formula: $C_{29}H_{27}NO_6$

Isolated yield: 2 mg

UV (PDA): λ_{max} = 228, 249, 272, and 391 nm

Optical activity: $[\alpha]_D^{20}$ = +8.791

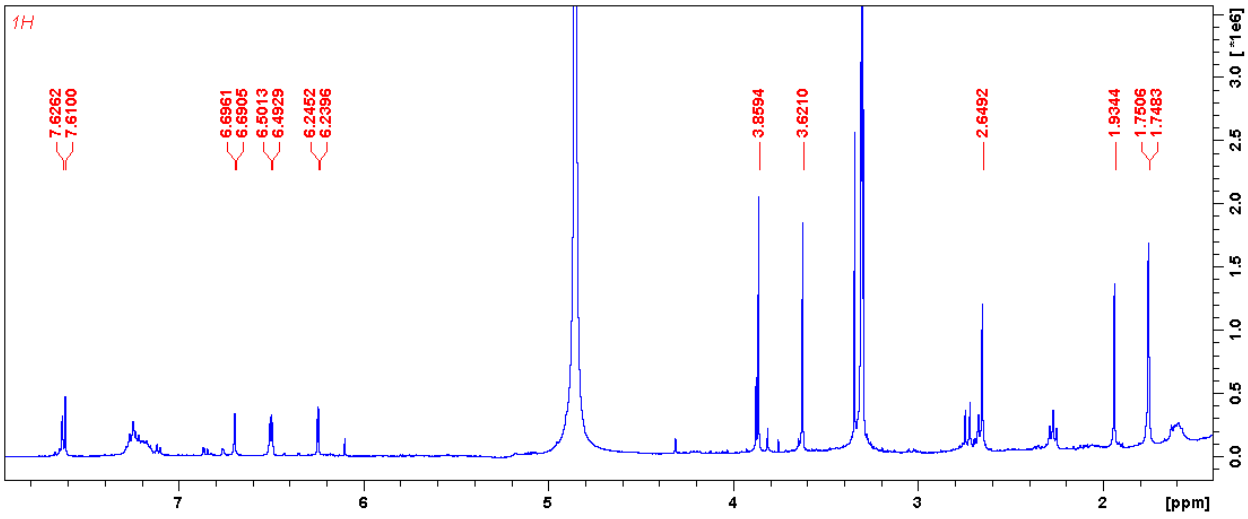
HRMS (ESI) *m/z*: calculated $[M + H]^+$ = 486.1911; observed $[M + H]^+$ = 486.1905, Δ = -1.23 ppm.

Supplementary Table 9 | NMR data for compound 3 in CD_3OD at 400 MHz for ^1H and 100 MHz for ^{13}C.

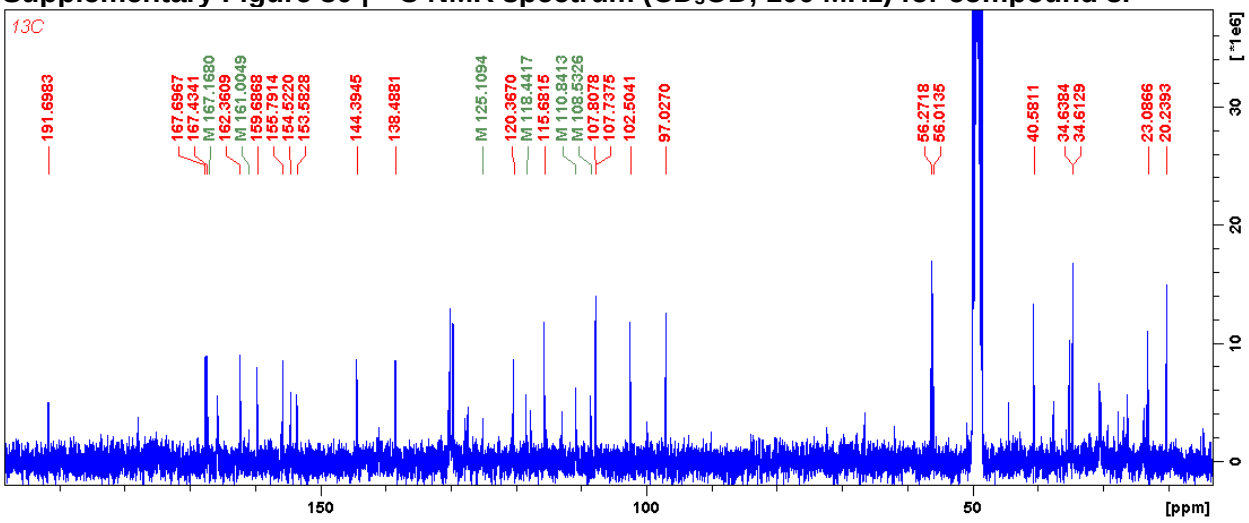
Position	δ_C ppm	δ_H ppm (no. of protons, multiplicity, J in Hz)	HMBC	NOESY
1	138.5		25	
2	107.7	6.5 (1H, d, 2.33)	4, 24	28
3	162.4		4, 28	
4	97.0	6.5 (1H, d, 2.33)	2	28, 29
5	159.7		4, 29	
6	125.1		4, 25	
7	161.0			
8	118.4		20	
9	167.2			
10	110.8		20	
11	191.9			
12	108.5		14, 16	
13	167.4		14	
14	102.5	6.2 (1H, d, 2.30)	16	
15	167.7		16	
16	107.8	6.7 (1H, d, 2.30)		26, 27
17	155.8		26, 27	
18	40.6		16, 20, 26, 27	
19	153.6		26, 27	
20	115.7	7.6 (1H, s)	22	26, 27
21	144.4		20	
22	120.4	7.6 (1H, s)	20, 25	25
23	154.5		22, 25	
24	20.2	1.9 (3H, s)	2	2
25	23.1	2.6 (3H, s)	22	22
26	34.6	1.7 (3H, s)	27	16, 20

27	34.6	1.8 (3H, s)	26	16, 20
28	56.0	3.9 (3H, s)		2, 4
29	56.3	3.6 (3H, s)		4

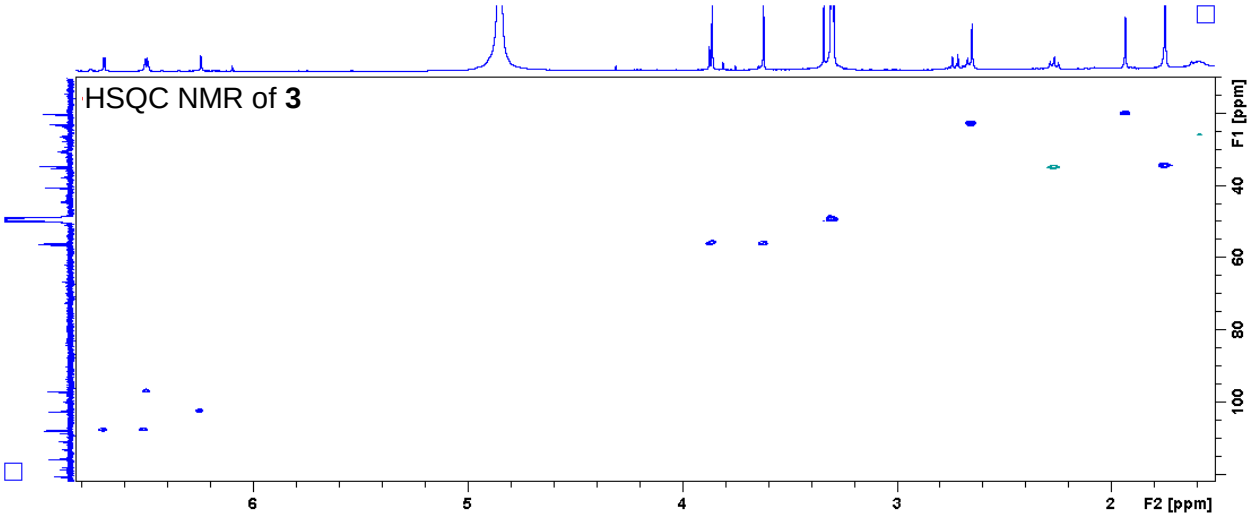
Supplementary Figure 29 | ^{1}H NMR spectrum (CD_3OD, 400 MHz) for compound 3.



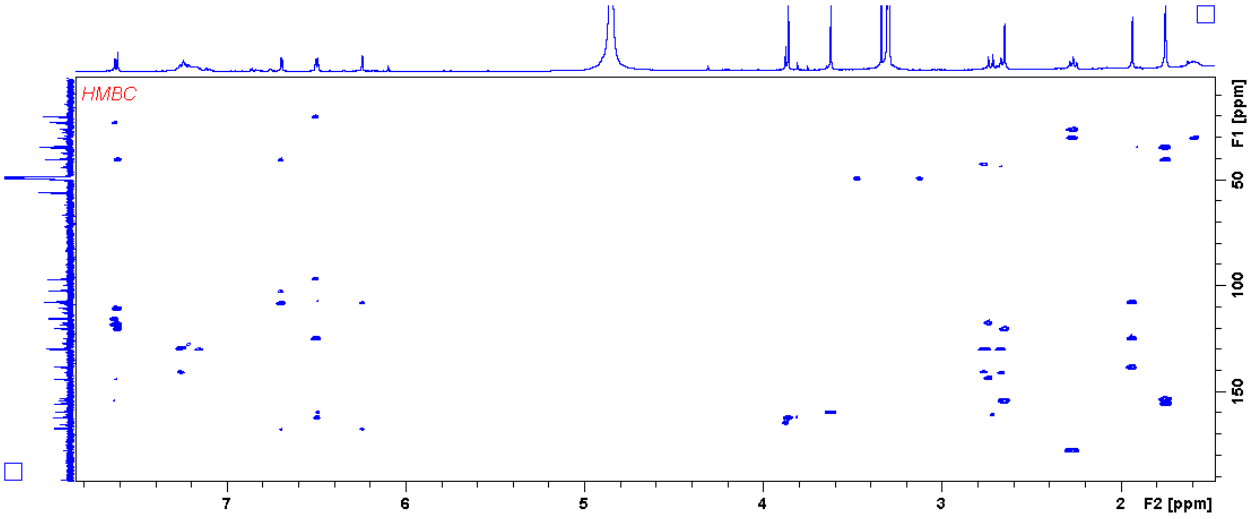
Supplementary Figure 30 | ^{13}C NMR spectrum (CD_3OD, 100 MHz) for compound 3.



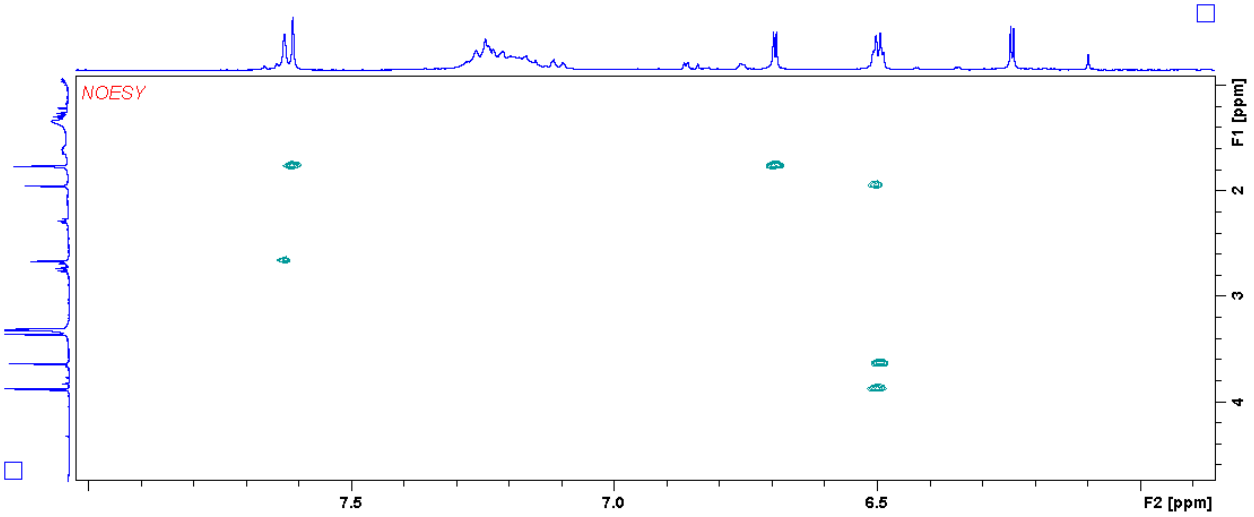
Supplementary Figure 31 | HSQC spectrum (CD_3OD) for compound 3.



Supplementary Figure 32 | HMBC spectrum (CD_3OD) for compound 3.

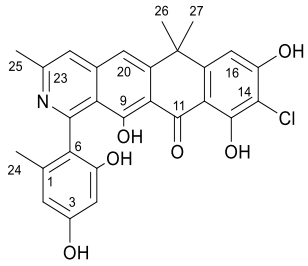


Supplementary Figure 33 | NOESY spectrum (CD_3OD) for compound 3.



COMPOUND 4 (formicapyridine D)

Supplementary Figure 34 | Chemical structure of compound 4



Molecular formula: $C_{27}H_{22}NO_6Cl$

Isolated yield: 0.7 mg

UV (PDA): λ_{max} = 228, 252, and 391 nm

Optical activity: $[\alpha]_D^{20}$ = +10.989

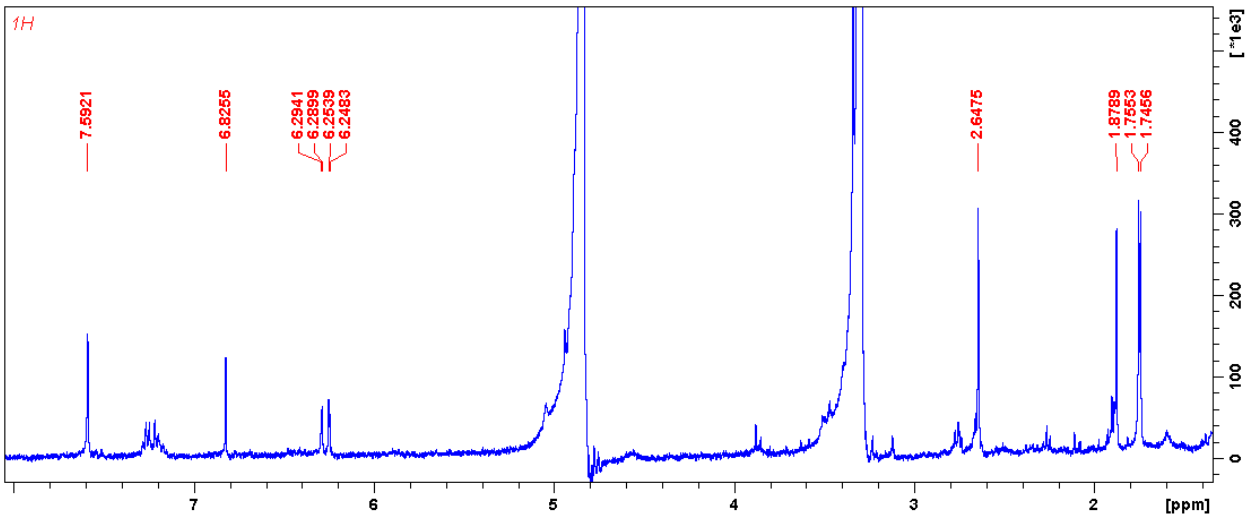
HRMS (ESI) *m/z*: calculated $[M + H]^+$ = 492.1218; observed $[M + H]^+$ = 492.1208, Δ = 2.03 ppm.

Supplementary Table 10 | NMR data for compound 4 in CD_3OD at 400 MHz for ^1H.

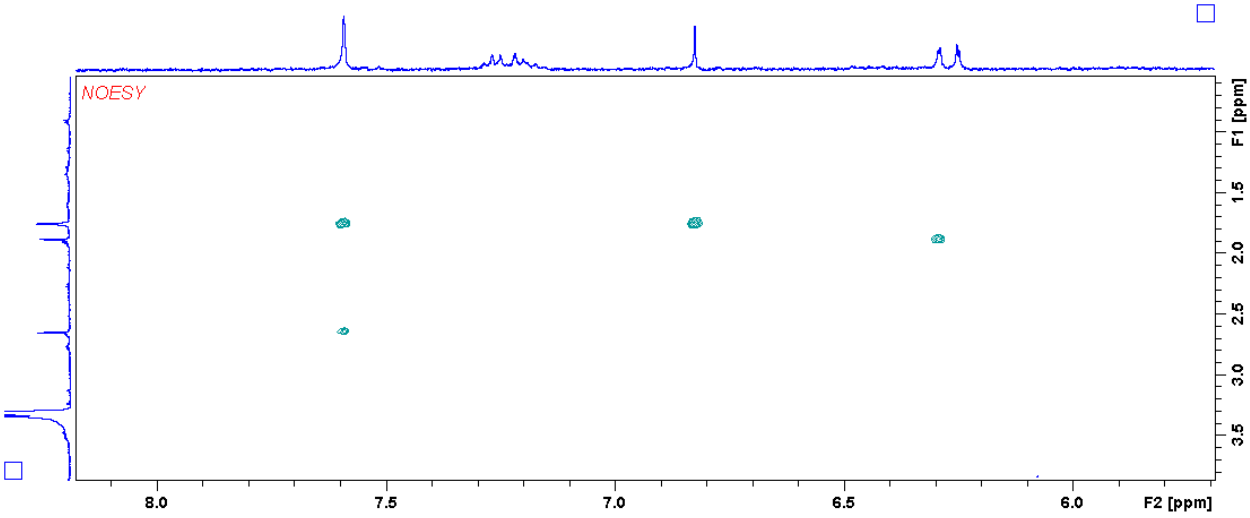
Position	δ_H ppm (no. of protons, multiplicity, J in Hz)	NOESY
2	6.2929 (1H, d, 2.32)	24
4	6.2511 (1H, d, 2.32)	
16	6.8255 (1H, s)	26, 27

20	7.5921 (1H, s)	26, 27
22	7.5921 (1H, s)	25
24	1.8789 (3H, s)	2
25	2.6475 (3H, s)	22
26	1.7456 (3H, s)	16, 20
27	1.7456 (3H, s)	16, 20

Supplementary Figure 35 | ^{1}H NMR spectrum (CD_3OD, 400 MHz) for compound 4.

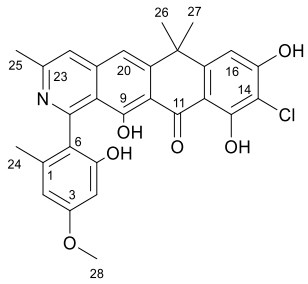


Supplementary Figure 36 | NOESY spectrum (CD_3OD) for compound 4.



COMPOUND 5 (formicapyridine E)

Supplementary Figure 37 | Chemical structure of compound 5



Molecular formula: $C_{28}H_{24}NO_6Cl$

Isolated yield: 1 mg

UV (PDA): λ_{max} = 218, 252, and 391 nm

Optical activity: $[\alpha]_D^{20}$ = +12.088

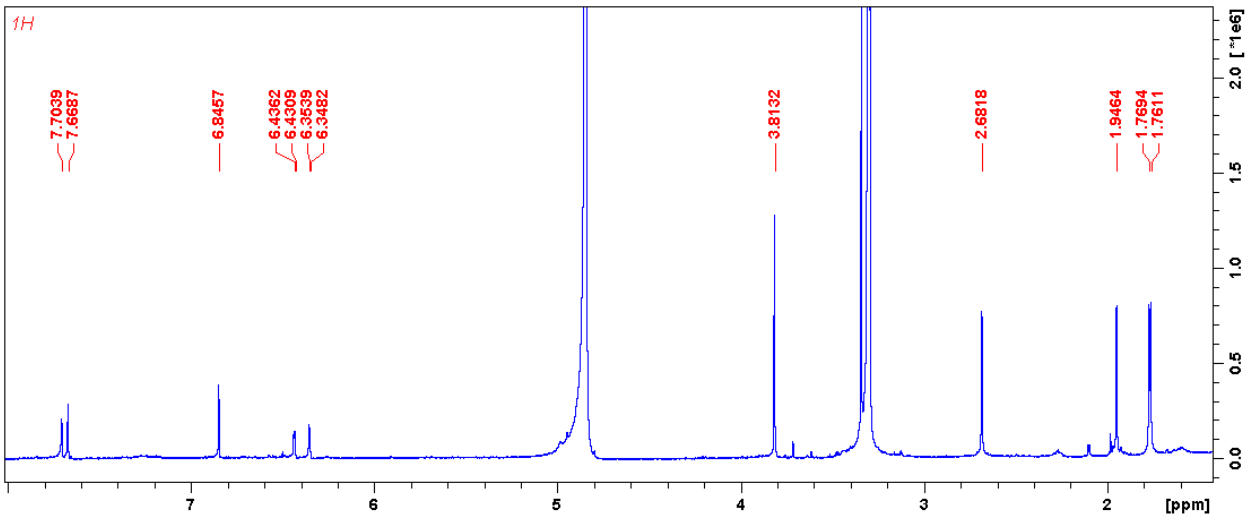
HRMS (ESI) *m/z*: calculated $[M + H]^+$ = 506.1365; observed $[M + H]^+$ = 506.1362, Δ = -0.59 ppm.

Supplementary Table 11 | NMR data for compound 5 in CD_3OD at 400 MHz for ^1H and 100 MHz for ^{13}C.

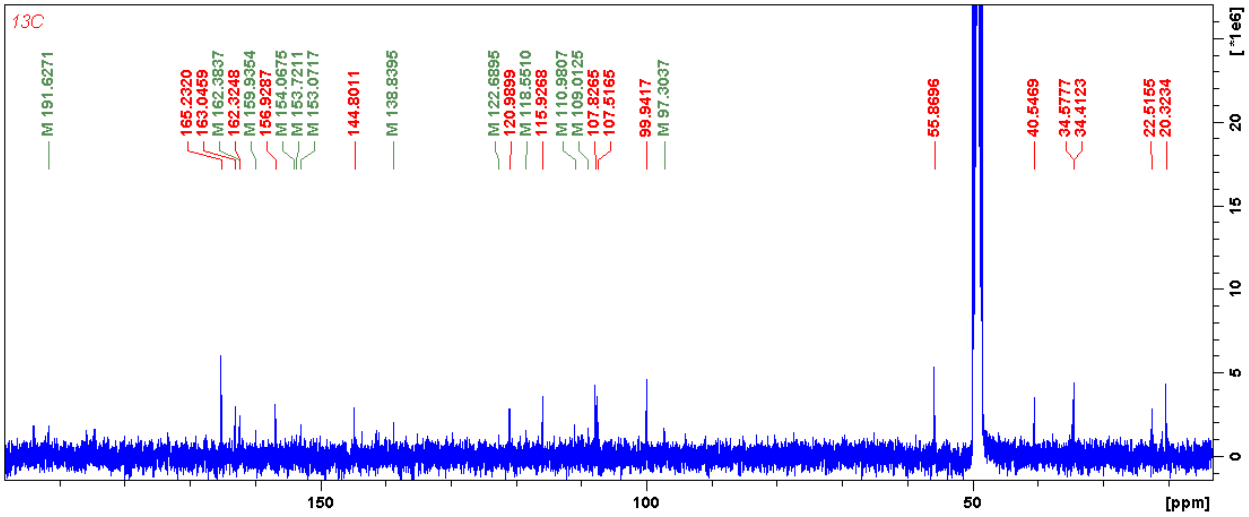
Position	δ_C ppm	δ_H ppm (no. of protons, multiplicity, J in Hz)	HMBC	NOESY
1	138.8		24	
2	107.8	6.4 (1H, d, 2.22)	24	24, 28
3	162.4		28	
4	99.9	6.3 (1H, d, 2.22)		28
5	156.9			
6	122.7		2, 24	
7	159.9			
8	118.6		20, 22	
9	162.3			
10	111.0		20	
11	191.6			
12	109.0		16	
13	165.2			
14	97.3			
15	163.0			

16	107.5	6.8 (1H, s)		26, 27
17	154.1		26, 27	
18	40.5		16, 20, 26, 27	
19	153.1		26, 27	
20	115.9	7.7 (1H, s)	22	26, 27
21	144.8			
22	121.0	7.7 (1H, s)	20, 25	25
23	153.7		25	
24	20.3	1.9 (3H, s)	22	2
25	22.5	2.7 (3H, s)		22
26	34.4	1.7 (3H, s)	27	16, 20
27	34.6	1.7 (3H, s)	26	16, 20
28	55.9	3.8 (3H, s)		2, 4

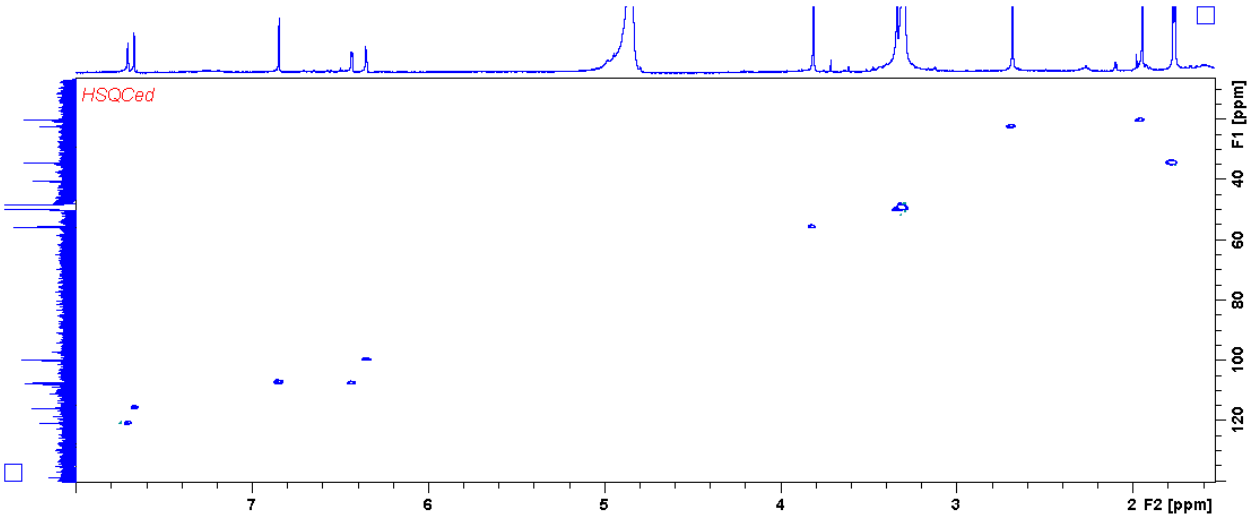
Supplementary Figure 38 | ^{1}H NMR spectrum (CD_3OD, 400 MHz) for compound 5.



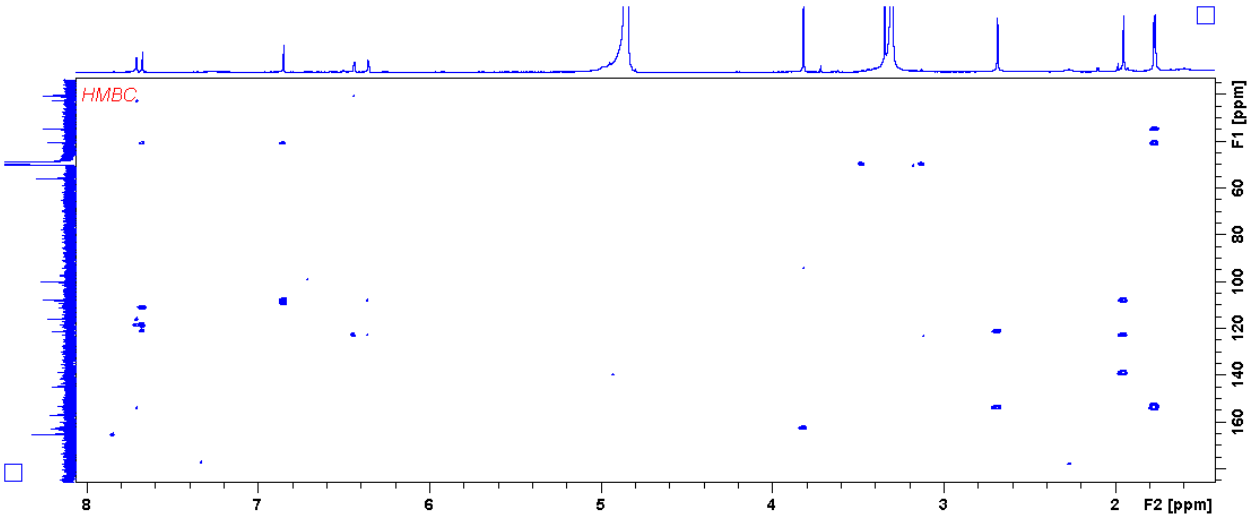
Supplementary Figure 39 | ^{13}C NMR spectrum (CD_3OD, 100 MHz) for compound 5.



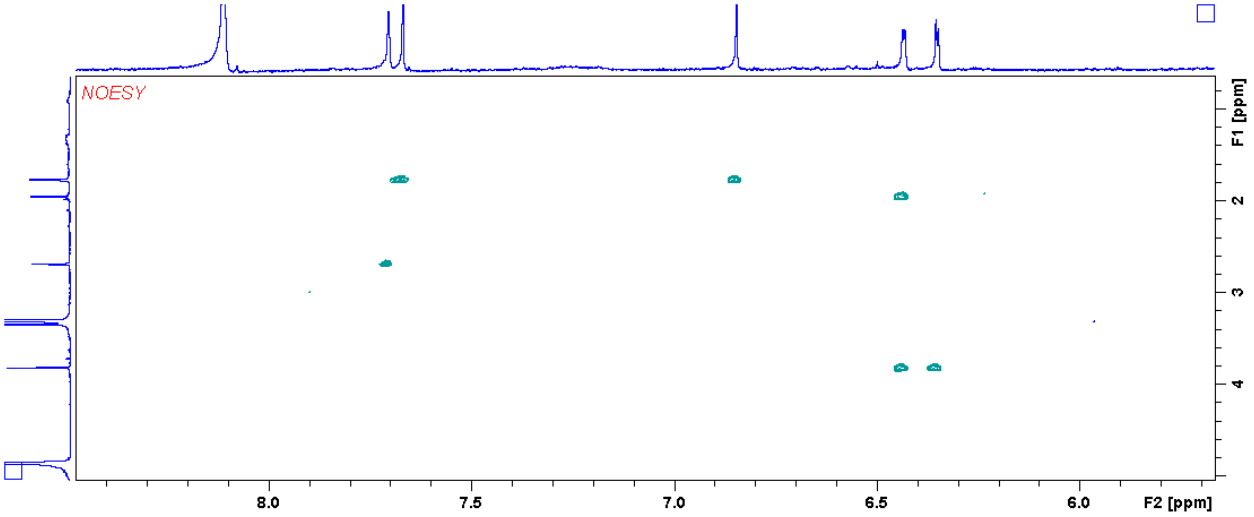
Supplementary Figure 40 | HSQC spectrum (CD_3OD) for compound 5.



Supplementary Figure 41 | HMBC spectrum (CD_3OD) for compound 5.

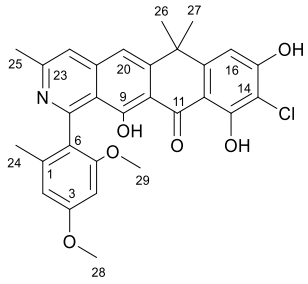


Supplementary Figure 42 | NOESY spectrum (CD_3OD) for compound 5.



COMPOUND 6 (formicapyridine F)

Supplementary Figure 43 | Chemical structure of compound 6



Molecular formula: $C_{29}H_{26}NO_6Cl$

Isolated yield: 0.6 mg

UV (PDA): λ_{max} = 231, 252, and 391 nm

Optical activity: $[\alpha]_D^{20}$ = +12.821

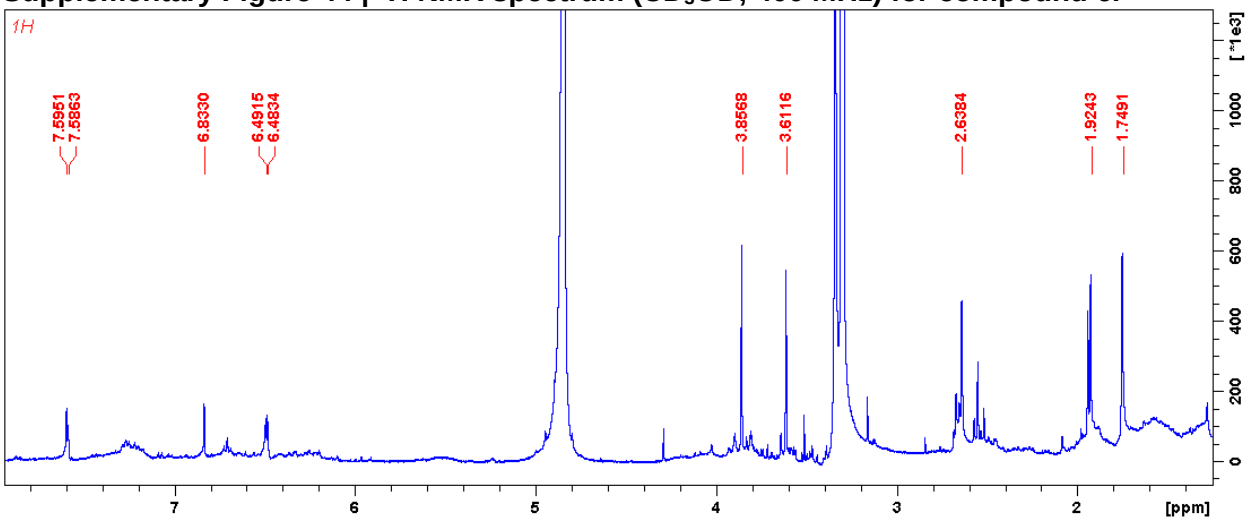
HRMS (ESI) *m/z*: calculated $[M + H]^+$ = 520.1521; observed $[M + H]^+$ = 520.1525, Δ = 0.77 ppm.

Supplementary Table 12 | NMR data for compound 6 in CD_3OD at 400 MHz for ^1H.

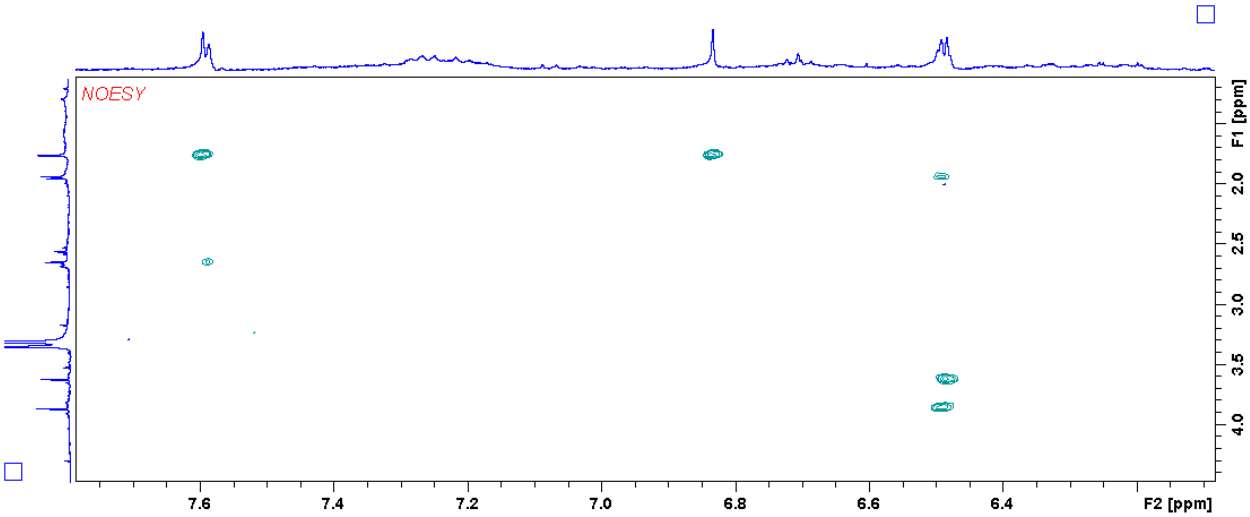
Position	δ_H ppm (no. of protons, multiplicity, J in Hz)	NOESY
2	6.4915 (1H, d, 2.33)	24
4	6.4834 (1H, d, 2.33)	29
16	6.833	26, 27

20	7.5951	26, 27
22	7.5863	25
24	1.9243 (3H, s)	2
25	2.6384 (3H, s)	22
26	1.7491 (3H, s)	16, 20
27	1.7491 (3H, s)	16, 20
28	3.8568 (3H, s)	2
29	3.6116 (3H, s)	4

Supplementary Figure 44 | ^{1}H NMR spectrum (CD_3OD, 400 MHz) for compound 6.

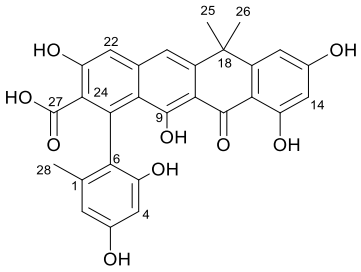


Supplementary Figure 45 | NOESY spectrum (CD_3OD) for compound 6.



COMPOUND 15 (fasamycin F)

Supplementary Figure 46 | Chemical structure of compound 13



Molecular formula: $C_{28}H_{22}O_9$

Isolated yield: 3.4 mg

UV (PDA): λ_{max} = 247, 287, 353, and 414 nm

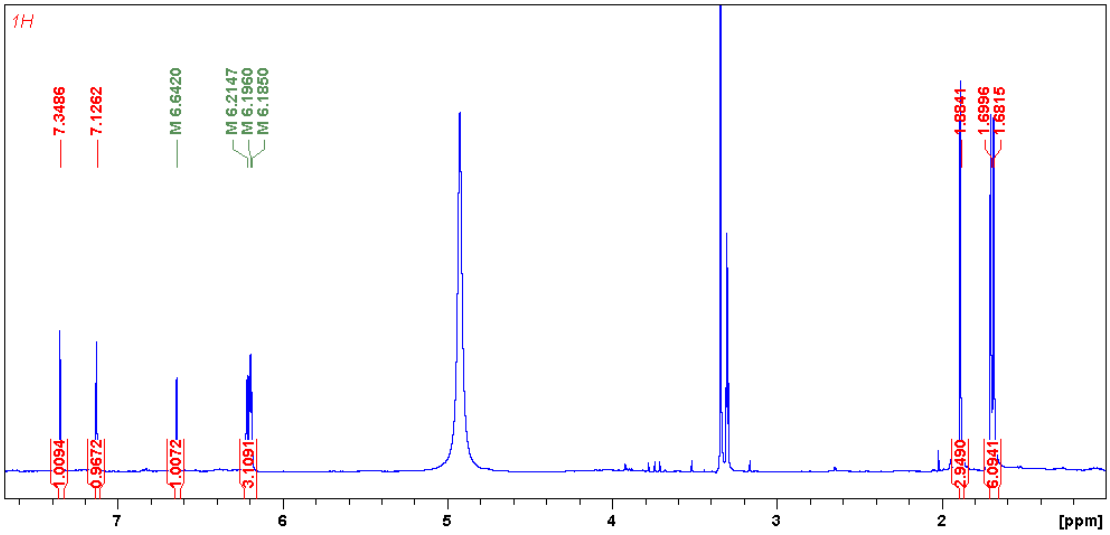
HRMS (ESI) *m/z*: calculated $[M + H]^+$ = 503.1337; observed $[M + H]^+$ = 503.1326, Δ = -0.29 ppm.

Supplementary Table 13 | NMR data for compound 13 in CD_3OD at 400 MHz for ^1H and 100 MHz for ^{13}C.

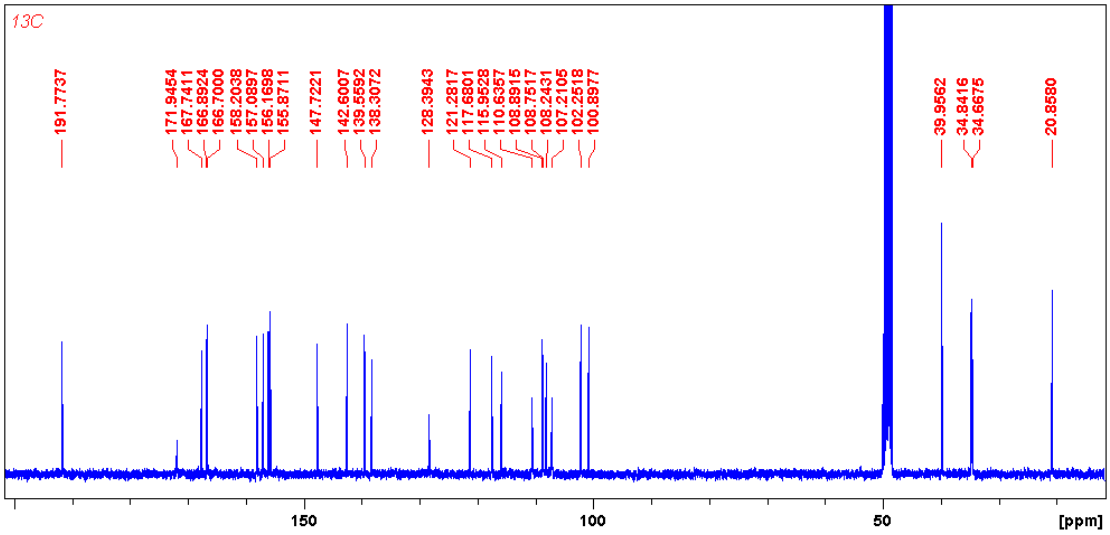
Position	δ_C ppm	δ_H ppm (no. of protons, multiplicity, J in Hz)	COSY	HMBC	NOESY
1	139.56			28	
2	108.89	6.2 (1H, d, 2.30)	4	4, 28	28
3	158.20				
4	100.90	6.2 (1H, d, 2.30)	2	2	
5	156.17			4	
6	121.28			2, 28	
7	138.31				
8	117.68			20, 22	
9	167.74				
10	108.24			20	
11	191.77				
12	108.75			16	
13	166.89			14	
14	102.25	6.2 (1H, d, 2.22)	16	16	
15	166.70			14, 16	

16	107.21	6.6 (1H, d, 2.22)	14	14	25, 26
17	155.87			25, 26	
18	39.96			16, 20, 25, 26	
19	147.72			25, 26	
20	115.95	7.3 (1H, s)		22	25, 26
21	142.60				
22	110.64	7.1 (1H, s)		20	
23	157.09			22	
24	128.39			22	
25	34.67	1.7 (3H, s)		26	16, 20
26	34.84	1.7 (3H, s)		25	16, 20
27	171.95				
28	20.86	1.9 (3H, s)		2	2

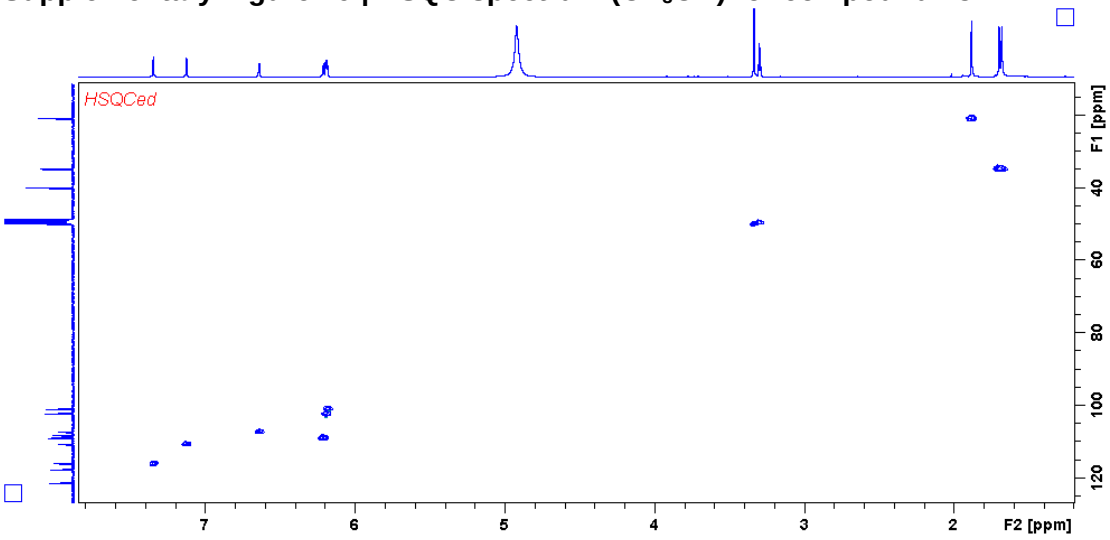
Supplementary Figure 47 | ^{1}H NMR spectrum (CD_3OD, 400 MHz) for compound 13.



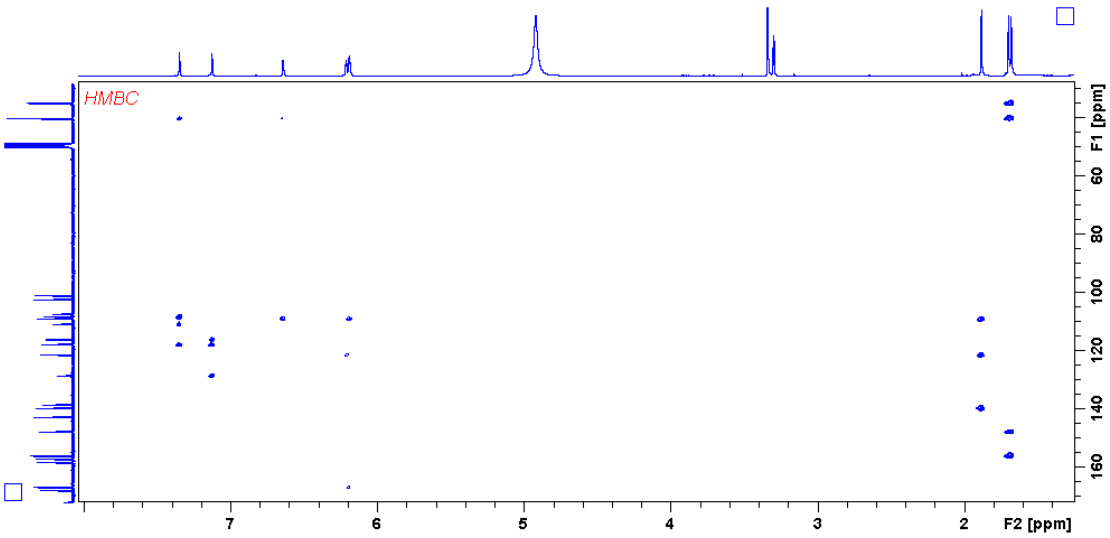
Supplementary Figure 48 | ^{13}C NMR spectrum (CD_3OD, 100 MHz) for compound 13.



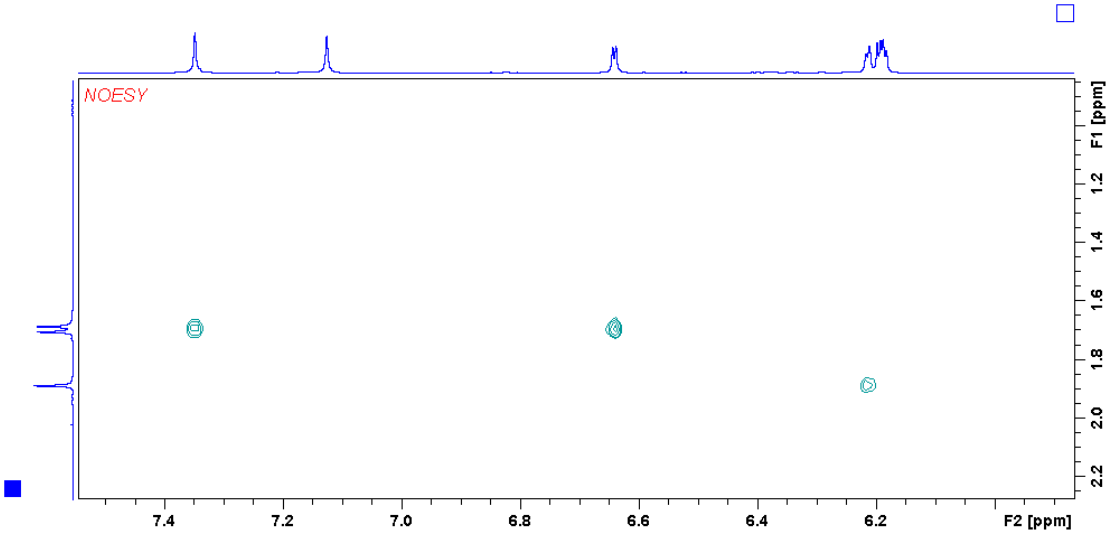
Supplementary Figure 49 | HSQC spectrum (CD_3OD) for compound 13.



Supplementary Figure 50 | HMBC spectrum (CD_3OD) for compound 13.



Supplementary Figure 51 | NOESY spectrum (CD_3OD) for compound 13.



References

1 MacNeil, D. J., Gewain, K. M., Ruby, C. L., Dezeny, G., Gibbons, P. H., MacNeil, T. Analysis of *Streptomyces avermitilis* genes required for avermectin biosynthesis utilizing a novel integration vector. *Gene*. **111**, 61-68 (1992).

2 Cobb, R. E., Wang, Y. & Zhao, H. High-efficiency multiplex genome editing of *Streptomyces* species using and engineered CRISPR/Cas system. *ACS Synth. Biol*. **4**, 723-728 (2015).

3 Kieser, T., Bibb, M. J., Buttner, M. J., Chater, K. F., Hopwood, D. A. *Practical Streptomyces Genetics* (The John Innes Foundation Press, Norwich, 2000).

4 Gregory, M. A., Till, R., Smith, M. C. M. Integration Site for *Streptomyces* Phage φBT1 and Development of Site-Specific Integrating Vectors. *J Bacteriol.* **185**, 5320-5323 (2003).

5 Hong, H. J., Hutchings, M. I., Hill, L. M., Buttner, M. J. The Role of the Novel Fem Protein VanK in Vancomycin Resistance in *Streptomyces coelicolor*. *J. Biol. Chem.* **280**, 13055-13061 (2005).

6 Konig, W. A., Krauss, C., Zahner, H. Metabolites from Microorganisms, 6-Chlorogenistein and 6,3'-Dichlorogenistein. *Helv. Chim. Acta*. **60**, 2071–2078 (1977).