SUPPORTING INFORMATION

Synthesis, Racemic X-Ray Crystallographic, and Permeability Studies of Bioactive Orbitides from *Jatropha* Species

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List of Tables/Figures

Figure S17. ^{1}H NMR spectrum of D-jatrophidin (**13**) (500 MHz in CD_3CN 20% at 298 K).

Figure S18. TOCSY fingerprint region of D-jatrophidin (**13**) (500 MHz in CD_3CN 20% at 298 K).

Figure S19. *N*-methylated ribifolin analogues assigned by NMR temperature coefficient studies and racemic X-ray structure.

Figure S20. *N*-methylated pohlianin C analogues assigned by NMR temperature coefficient studies and racemic X-ray structure.

Figure S21. ^{1}H NMR spectrum of [NMe-ILG]-ribifolin (**3**) (500 MHz in CD_3CN 70% at 298 K).

Figure S22. TOCSY fingerprint region of [NMe-ILG]-ribifolin (**3**) (500 MHz in CD_3CN 70% at 298 K).

Figure S23. ^{1}H NMR spectrum of [NMe-G]-ribifolin (**4**) (500 MHz in CD_3CN 20% at 298 K).

Figure S24. TOCSY fingerprint region of [NMe-G]-ribifolin (**4**) (500 MHz in CD_3CN 20% at 298 K).

Figure S25. ^{1}H NMR spectrum of [NMe-S]-ribifolin (**5**) (500 MHz in CD_3CN 20% at 298 K).

Figure S26. TOCSY fingerprint region of [NMe-S]-ribifolin (**5**) (500 MHz in CD_3CN 20% at 298 K).

Figure S27. ^{1}H NMR spectrum of [NMe-SG]-ribifolin (**6**) (500 MHz in CD_3CN 20% at 298 K).

Figure S28. TOCSY fingerprint region of [NMe-SG]-ribifolin (**6**) (500 MHz in CD_3CN 20% at 298 K).

Figure S29. ^{1}H NMR spectrum of [NMe-FGGG]-pohlianin C (**9**) (500 MHz in CD_3CN 70% at 298 K).

Figure S30. TOCSY fingerprint region of [NMe-FGGG]-pohlianin C (**9**) (500 MHz in CD_3CN 70% at 298 K).

Figure S31. ^{1}H NMR spectrum of [NMe-IFG]-pohlianin C (**10**) (500 MHz in CD_3CN 70% at 298 K).

Figure S32. TOCSY fingerprint region of [NMe-IFG]-pohlianin C (**10**) (500 MHz in CD_3CN 70% at 298 K).

Figure S33. ^{1}H NMR spectrum of [NMe-FG]-pohlianin C (**11**) (500 MHz in CD_3CN 20% at 298 K).

Figure S34. TOCSY fingerprint region of [NMe-FG]-pohlianin C (**11**) (500 MHz in CD_3CN 20% at 298 K).

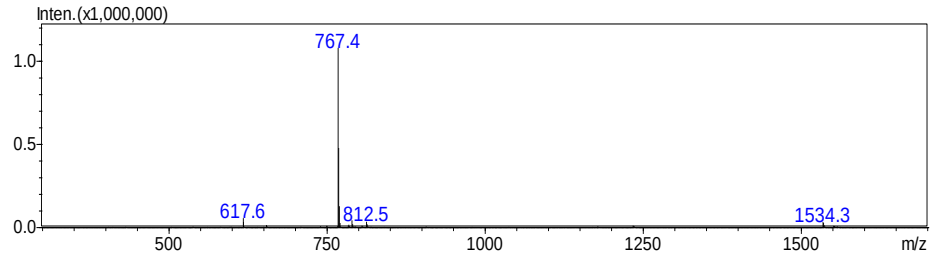
Figure S35. Cytotoxicity evaluation of ribifolin (**1**), pohlianin C (**7**) and jatrophidin (**12**) on Caco-2 cells.

Table S1. Permeability data (Caco-2 and PAMPA) for synthetic peptides.

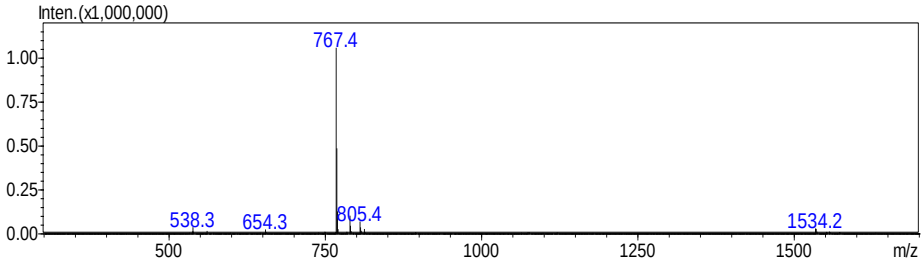
Number	Peptide	$P_{app\text{-}caco}$ (x 10^{-6} cm/s)	$P_{app\text{-}pampa}$ (x 10^{-6} cm/s)
1	ribifolin	0.00	0.00
3	[NMe-ILG]-ribifolin	0.00	0.22
4	[NMe-G]-ribifolin	0.00	0.00
5	[NMe-S]-ribifolin	0.00	0.00
6	[NMe-SG]-ribifolin	0.00	0.00
7	pohlianin C	0.00	0.00
9	[NMe-FGGG]-pohlianin C	0.00	0.00
10	[NMe-IFG]-pohlianin C	0.00	0.00
11	[NMe-FG]-pohlianin C	0.00	0.00
12	jatrophidin	0.00	0.00
control	atenolol	0.00	0.03
control	quinidine	15.16	4.87

Note: limit of detection constraints can also give rise to permeability values of 0.00.

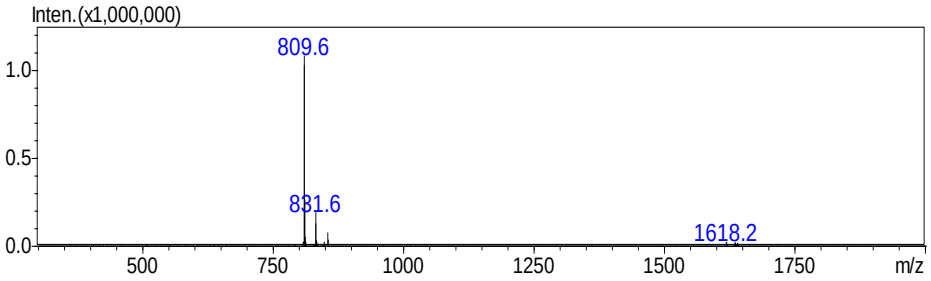
a) ribifolin



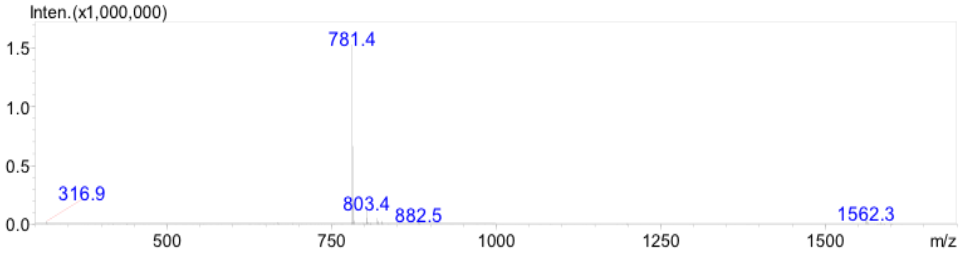
b) D-ribifolin



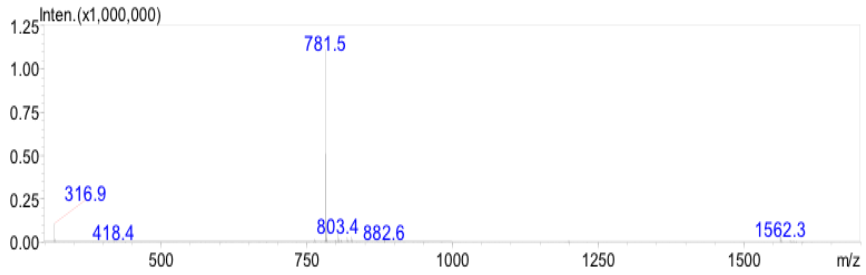
c) [NMe-ILG]-ribifolin



d) [NMe-G]-ribifolin



e) [NMe-S]-ribifolin



f) [NMe-SG]-ribifolin

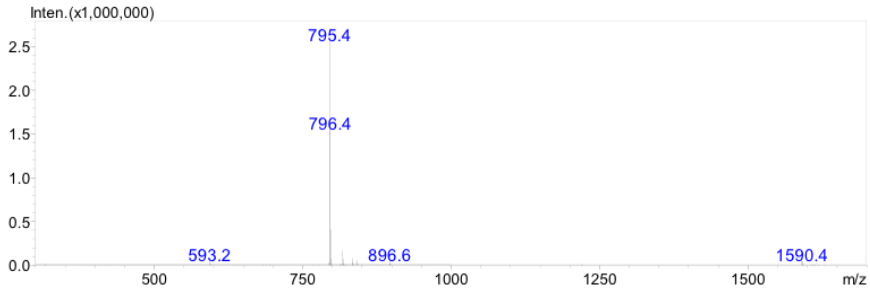
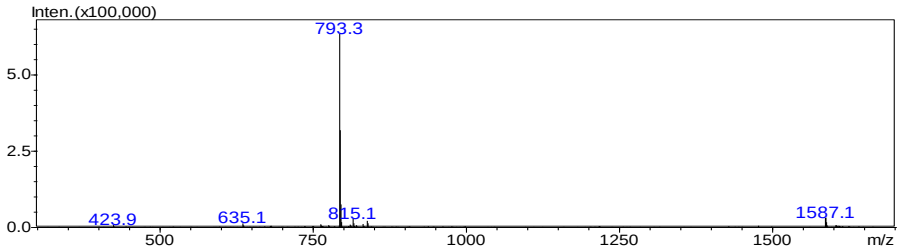
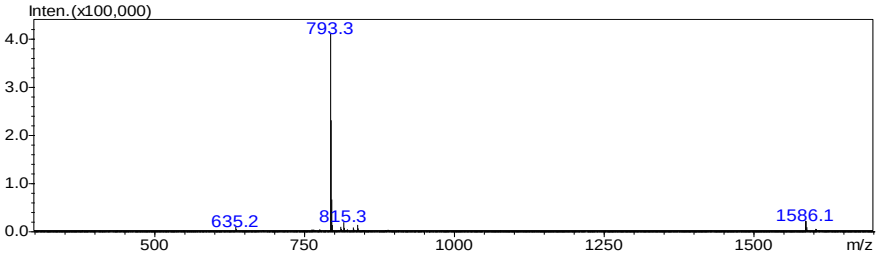


Figure S1. Characterization of ribifolin and synthetic analogues. ESI-MS spectra (positive mode) of a) ribifolin (**1**), b) D-ribifolin (**2**), c) [NMe-ILG]-ribifolin (**3**), d) [NMe-G]-ribifolin (**4**), e) [NMe-S]-ribifolin (**5**) and f) [NMe-SG]-ribifolin (**6**).

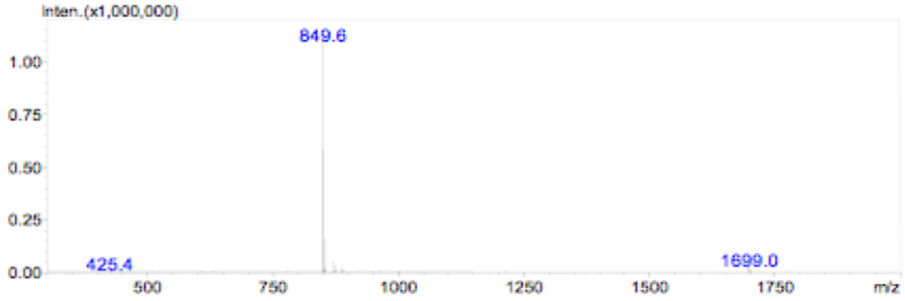
a) pohlianin C



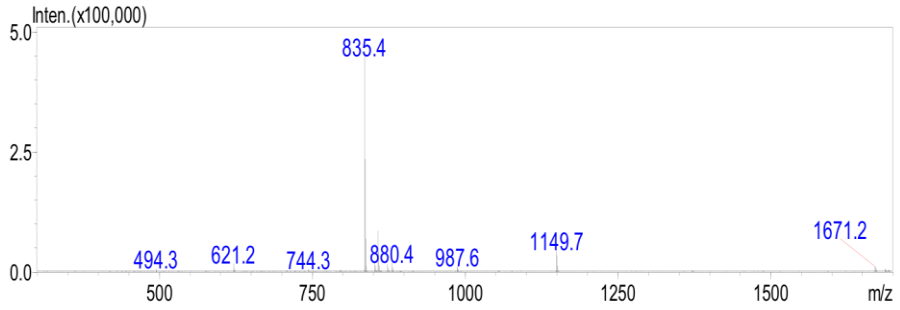
b) D-pohlianin C



c) [NMe-FGGG]-pohlianin C



d) [NMe-IFG]-pohlianin C



e) [NMe-FG]-pohlianin C

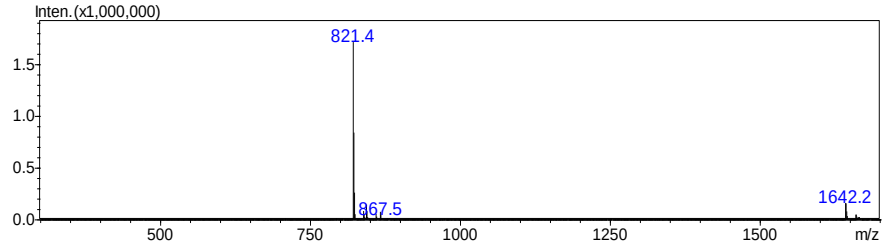
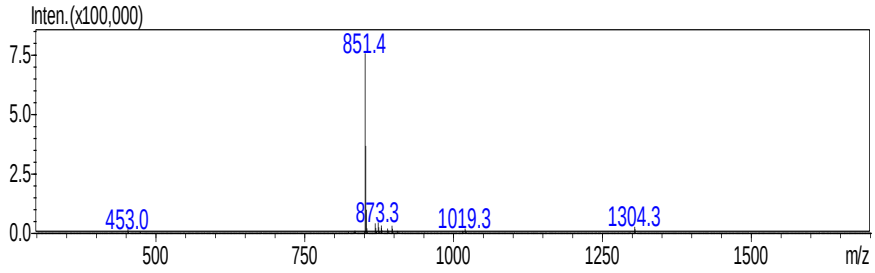


Figure S2. Characterization of pohlianin C and synthetic analogues. ESI-MS spectra (positive mode) of a) pohlianin C (**7**), b) D-pohlianin C (**8**), c) [NMe-FGGG]-pohlianin C (**9**), d) [NMe-IFG]-pohlianin C (**10**) and e) [NMe-FG]-pohlianin C (**11**).

a) jatrophidin



b) D-jatrophidin

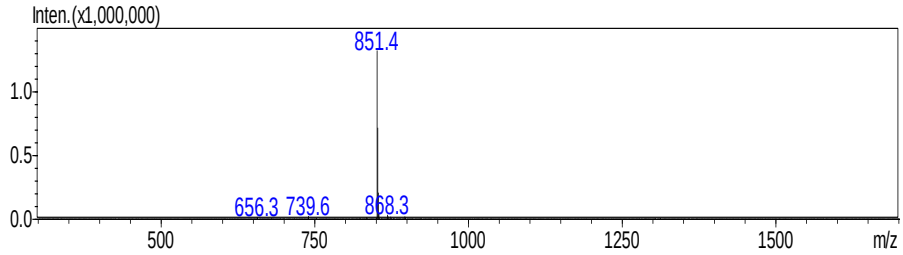
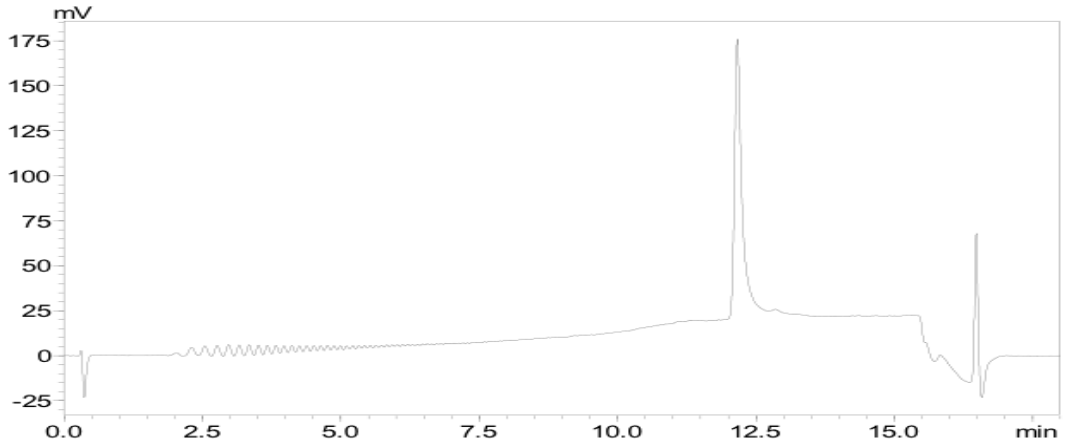


Figure S3. Characterization of jatrophidin and synthetic analogue. ESI-MS spectra (positive mode) of a) jatrophidin (**12**) and b) D-jatrophidin (**13**).

A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75
50
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5.0
7.5
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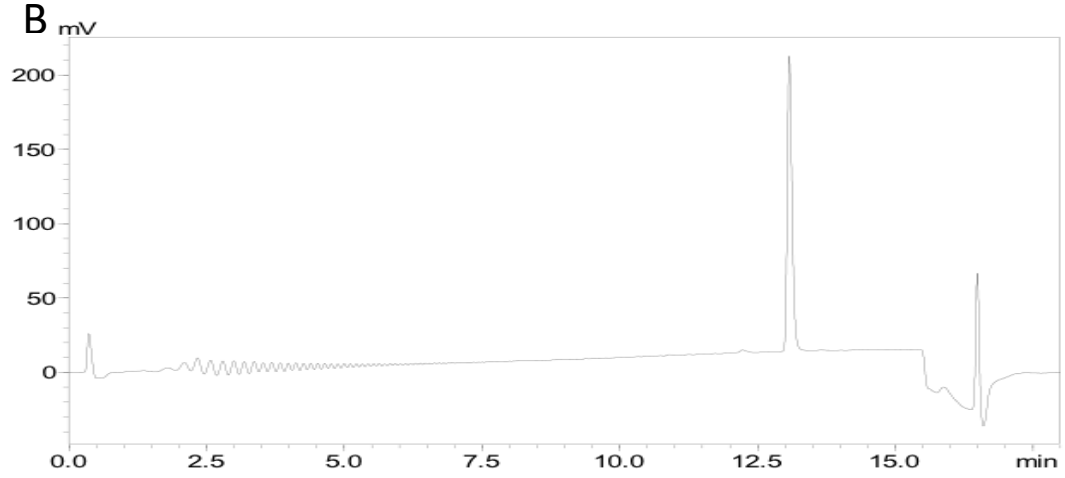
12.5
15.0
min

B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min

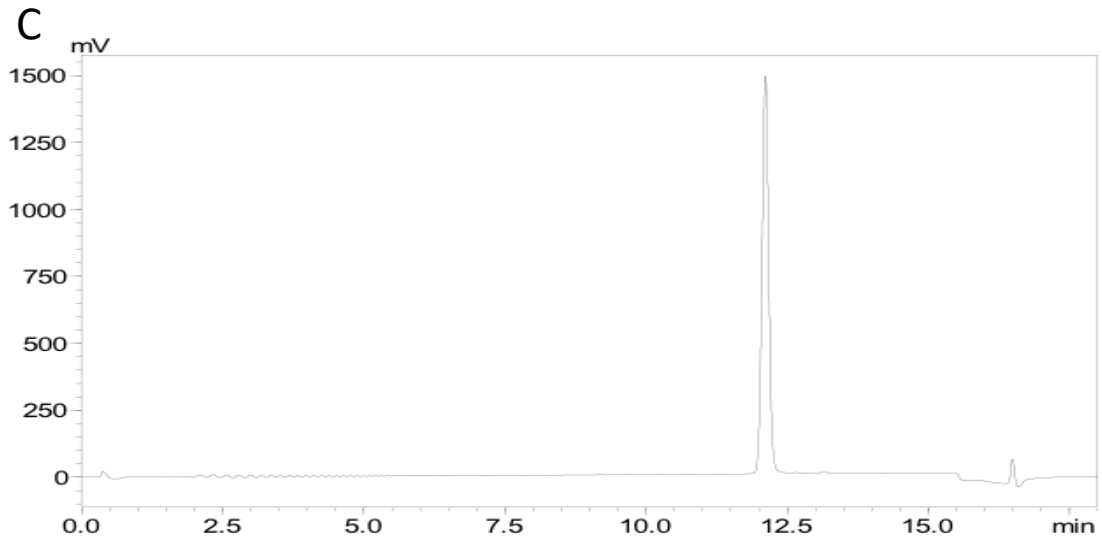

Figure S4. Analytical reversed-phase HPLC chromatograms of the purified peptides a) ribifolin (**1**), b) pohlianin C (**7**) and c) jatrophidin (**12**). Gradient 10-90% B in A in 20 min (solvent A: 0.05% v/v TFA in H_2O; solvent B: 0.05% v/v TFA), flow rate 1 mL min^{-1} and detection at λ = 214 nm.

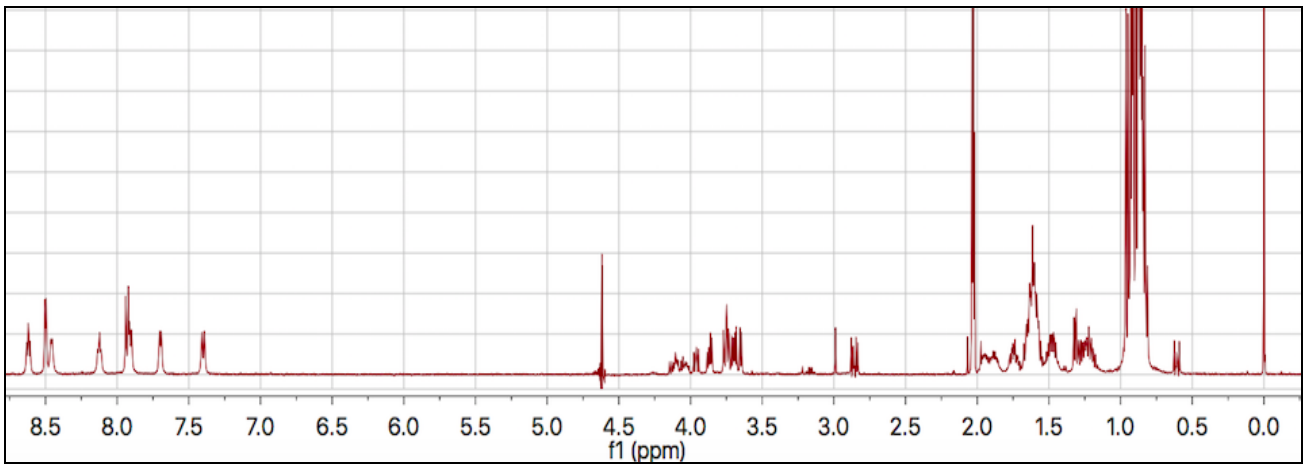

Figure S5. ^1H NMR spectrum of ribifolin (**1**) (500 MHz in CD_3CN 20% at 298 K).

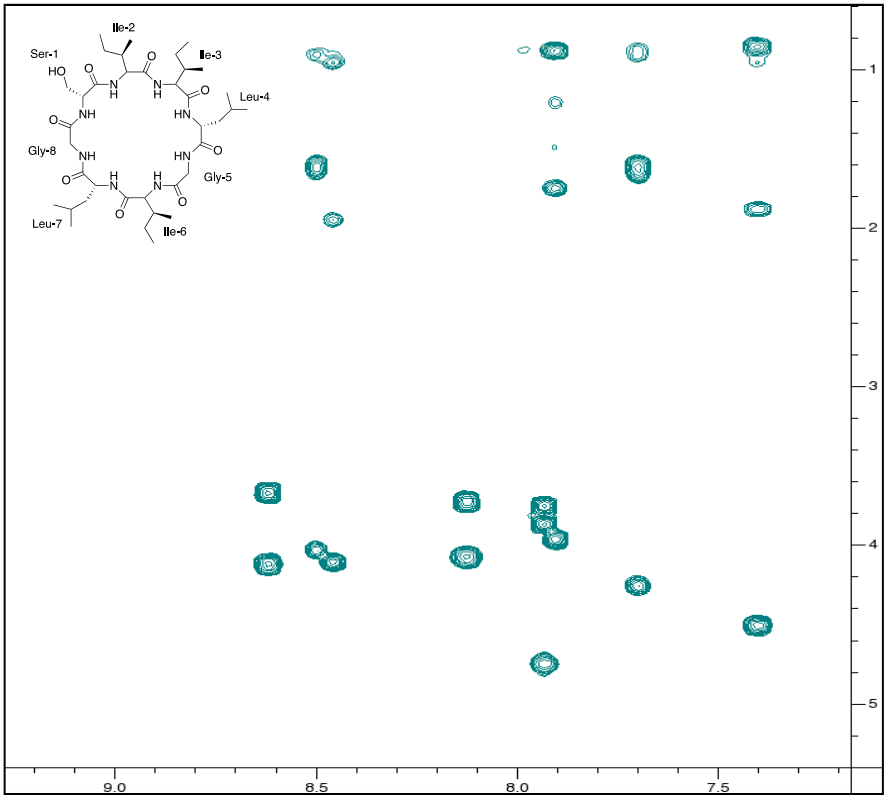

Figure S6. TOCSY fingerprint region of ribifolin (**1**) (500 MHz in CD_3CN 20% at 298 K).

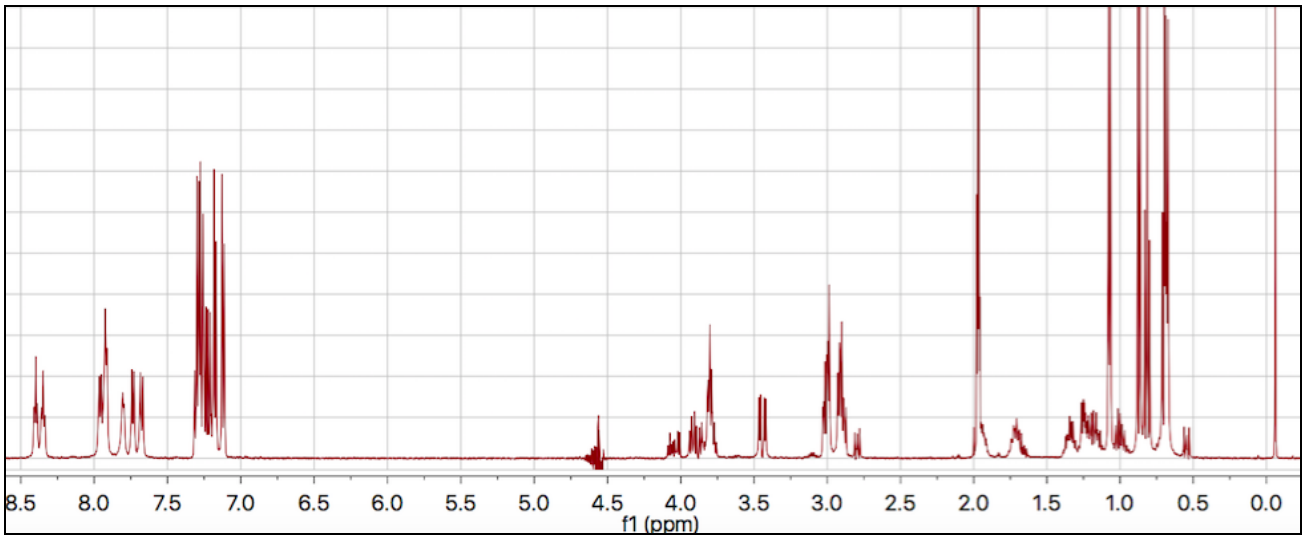

Figure S7. ^1H NMR spectrum of pohlianin C (**7**) (500 MHz in CD_3CN 20% at 298 K).

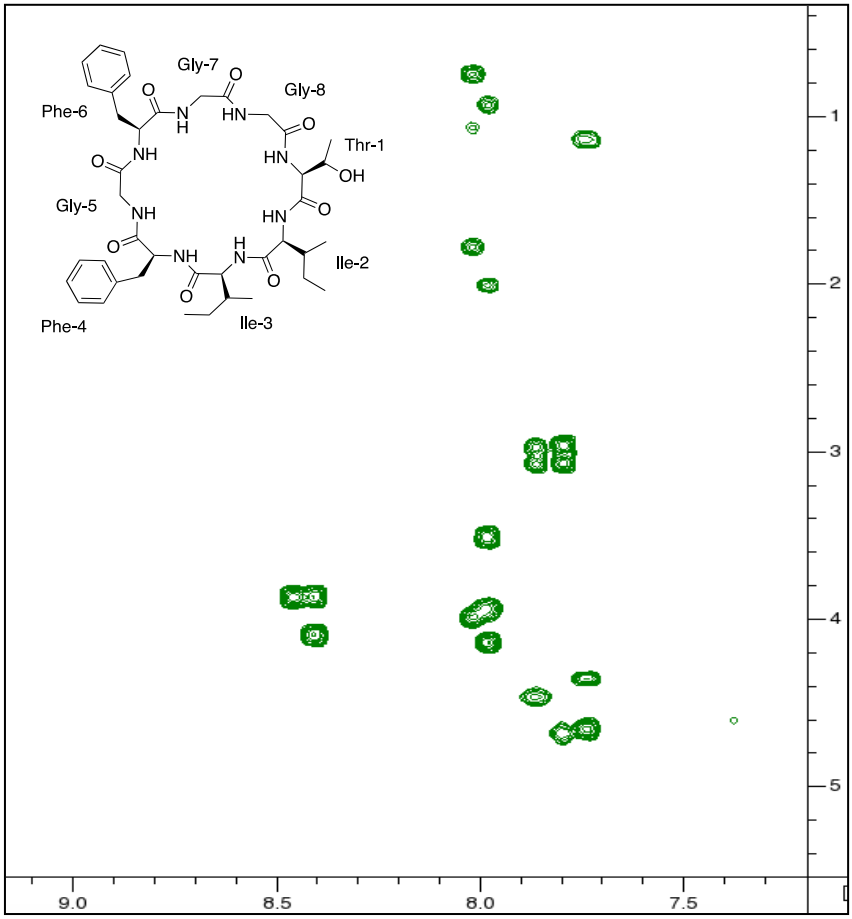

Figure S8. TOCSY fingerprint region of pohlianin C (**7**) (500 MHz in CD_3CN 20% at 298 K).

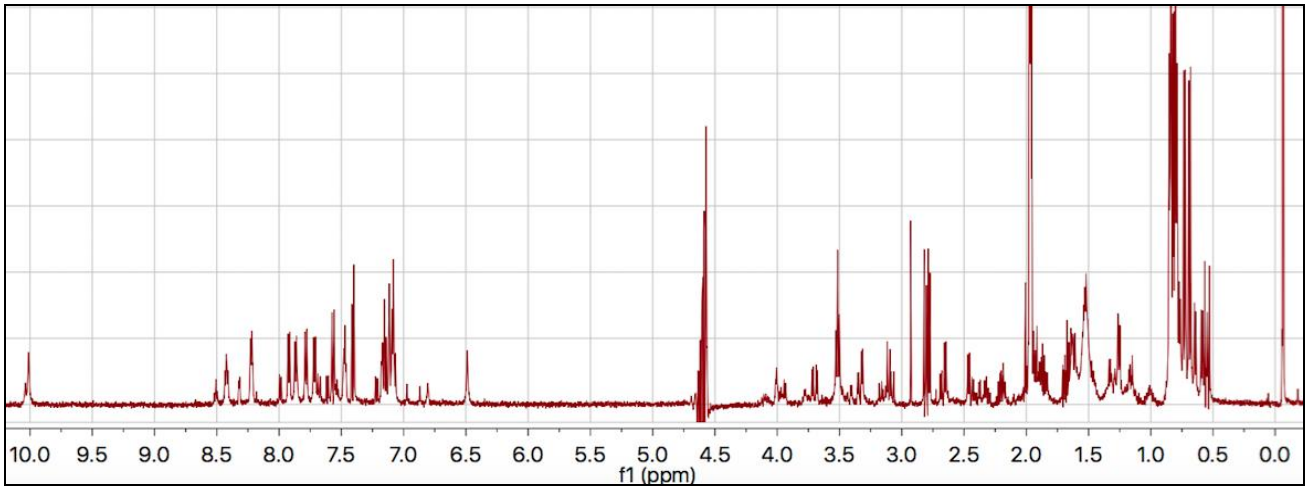

Figure S9. ^1H NMR spectrum of jatrophidin (**12**) (500 MHz in CD_3CN 20% at 298 K).

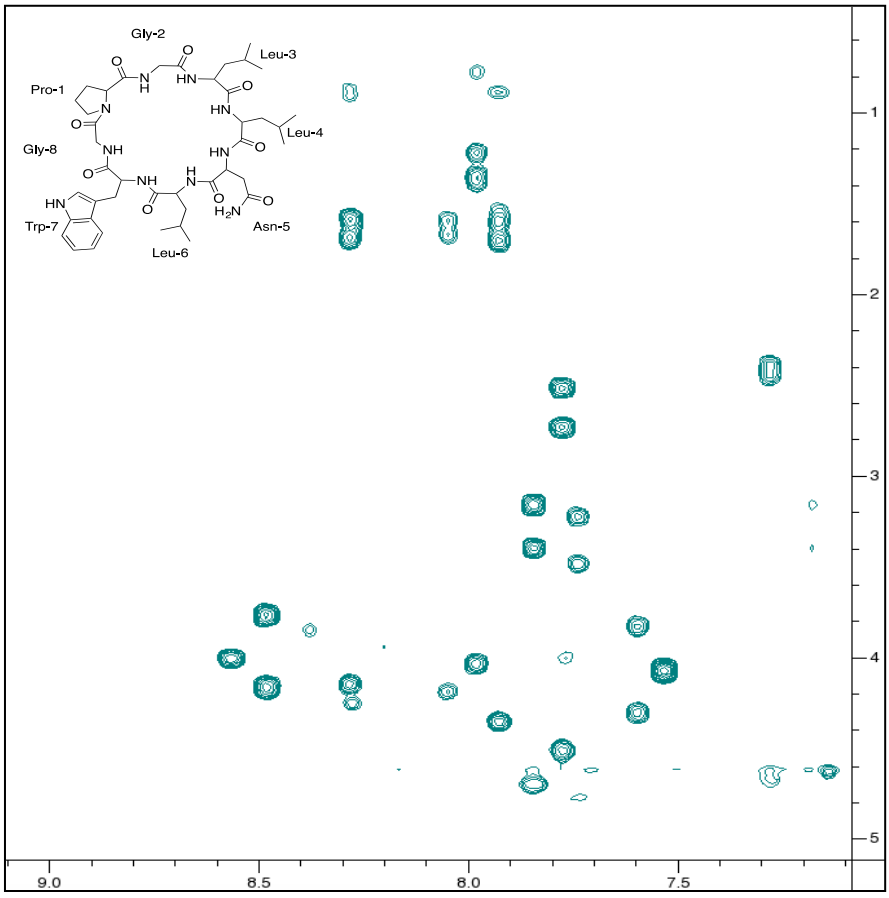

Figure S10. TOCSY fingerprint region of jatrophidin (**12**) (500 MHz in CD_3CN 20% at 298 K).

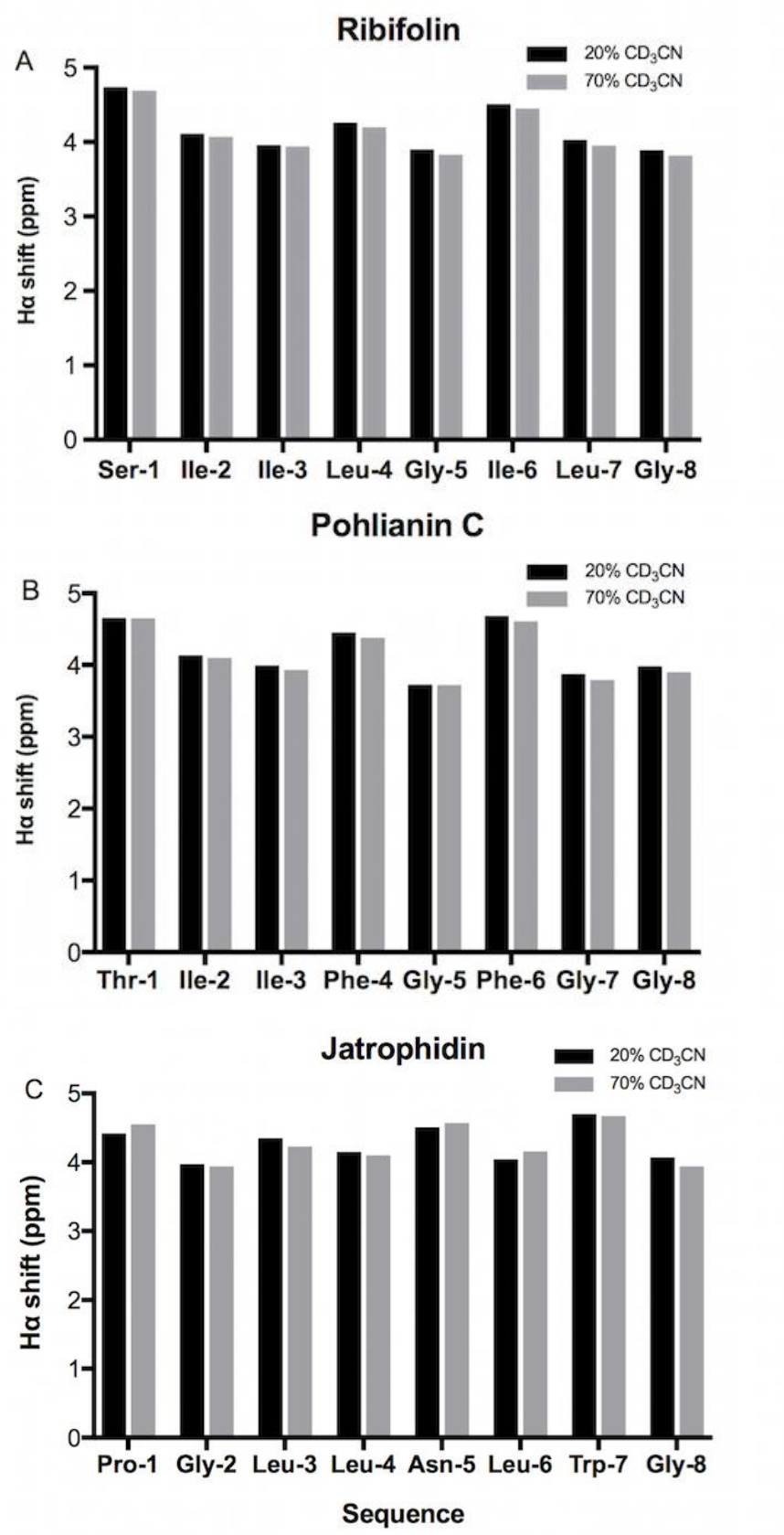

Figure S11. Hα chemical shifts derived using NMR are shown for a) ribifolin (**1**), b) pohlianin C (**7**) and c) jatrophidin (**12**) in acetonitrile/water mixtures (v/v).

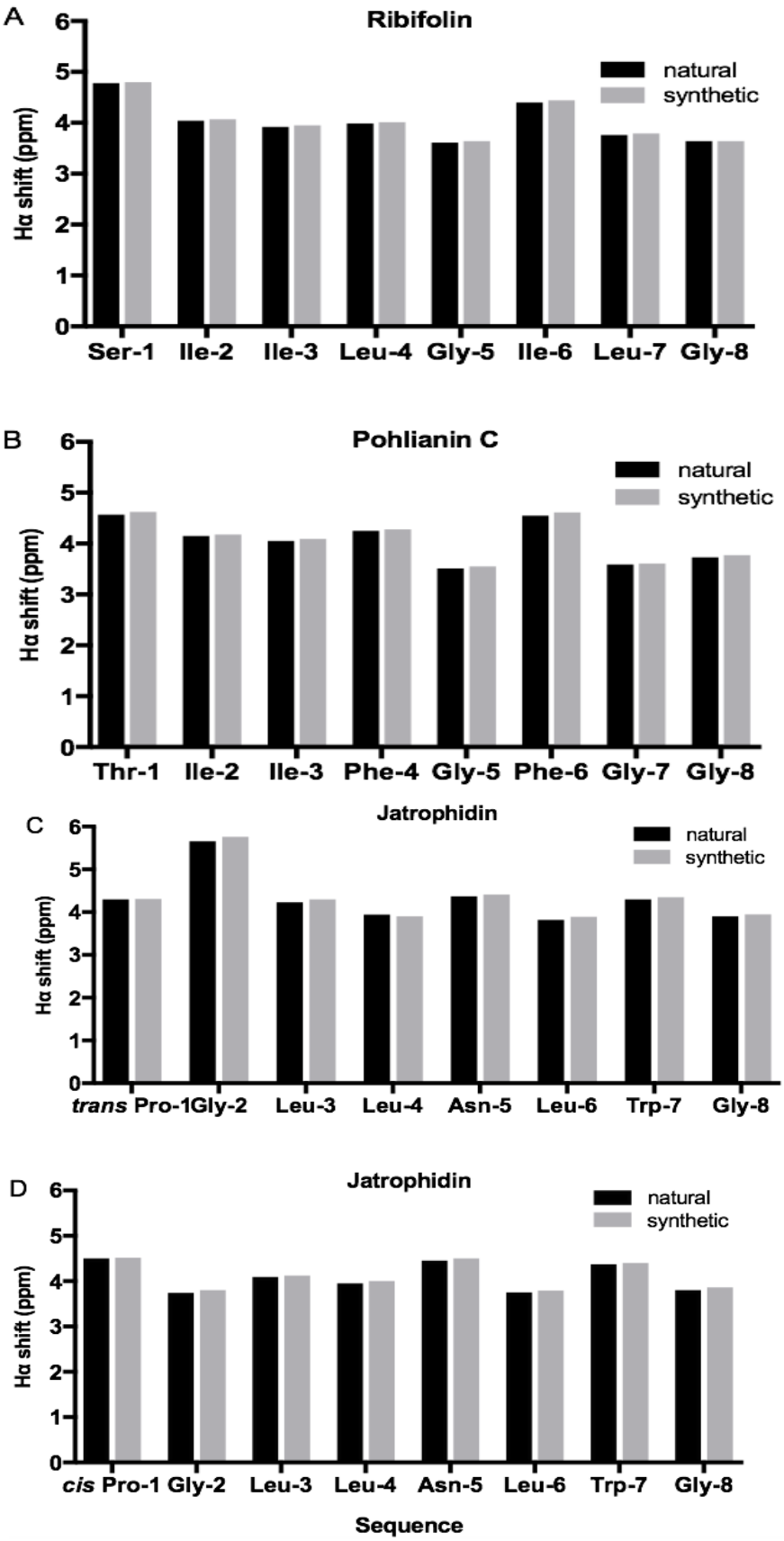

Figure S12. Hα chemical shifts derived using NMR in DMSO-d_6 are compared for the native and syntethic forms of a) ribifolin (**1**), b) pohlianin C (**7**), c) and d) jatrophidin (**12**).

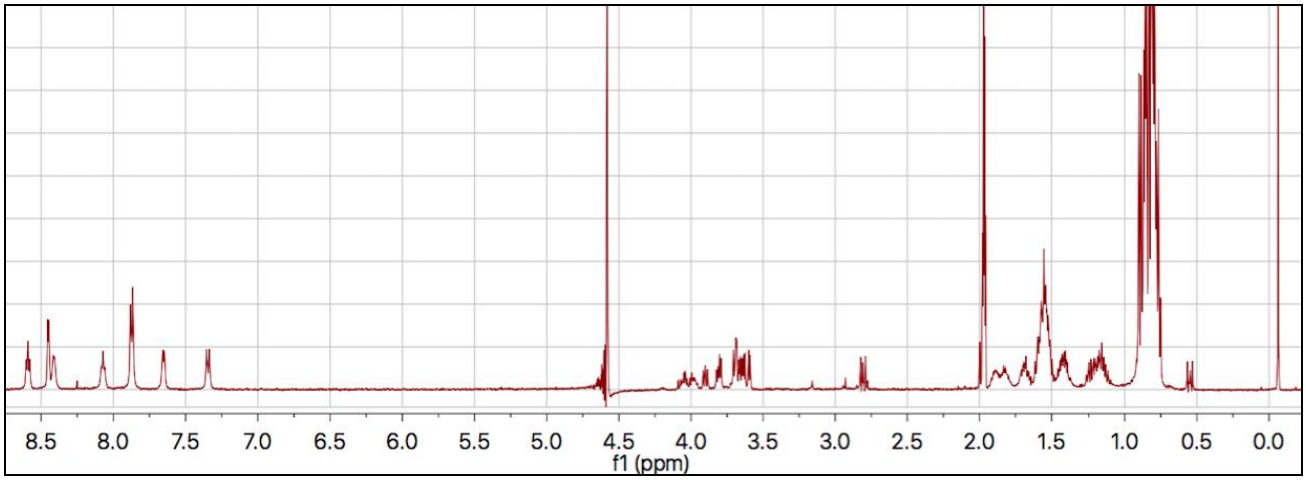

Figure S13. ^{1}H NMR spectrum of D-ribifolin (**2**) (500 MHz in CD_3CN 20% at 298 K).

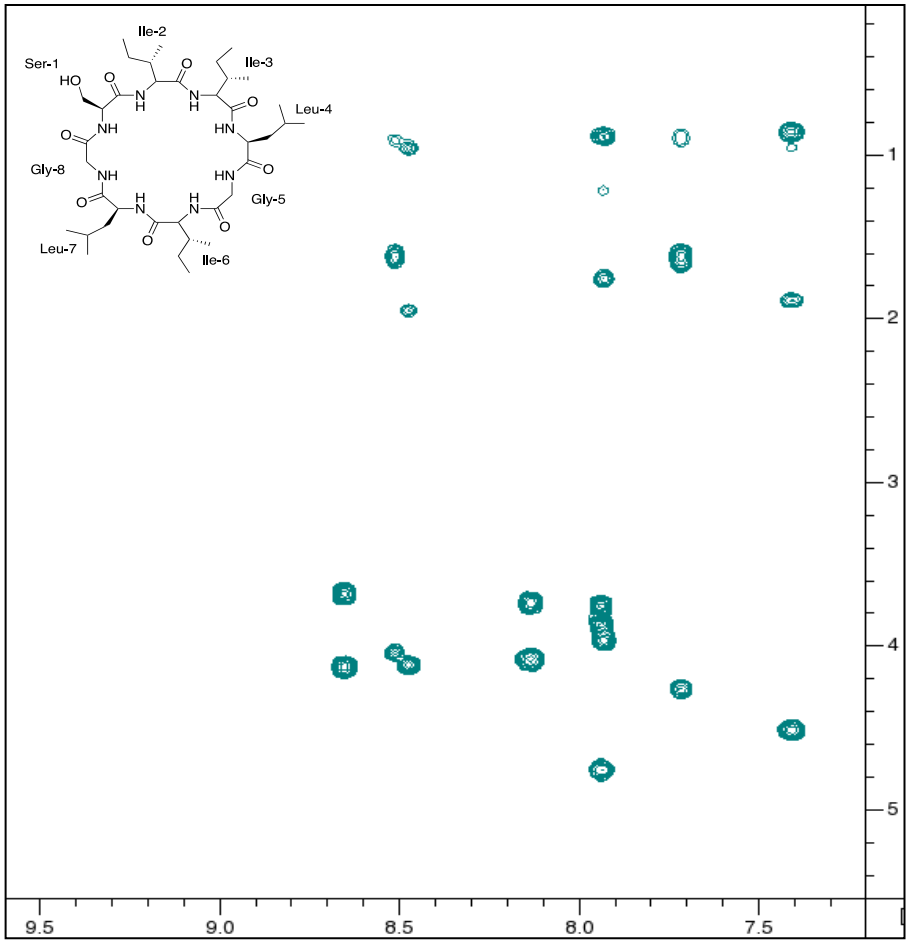

Figure S14. TOCSY fingerprint region of D-ribifolin (**2**) (500 MHz in CD_3CN 20% at 298 K).

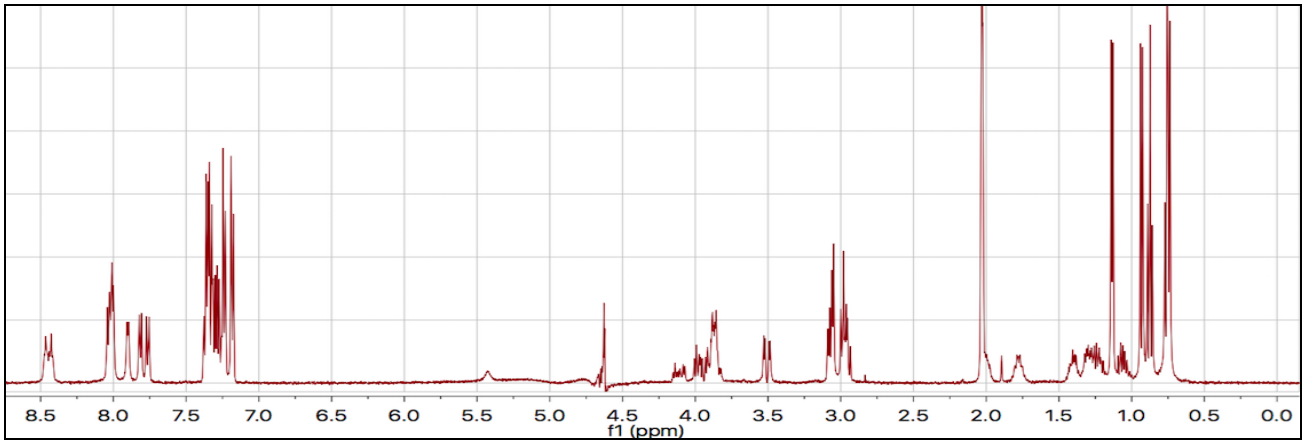

Figure S15. ^{1}H NMR spectrum of D-pohlianin C (**8**) (500 MHz in CD_3CN 20% at 298 K).

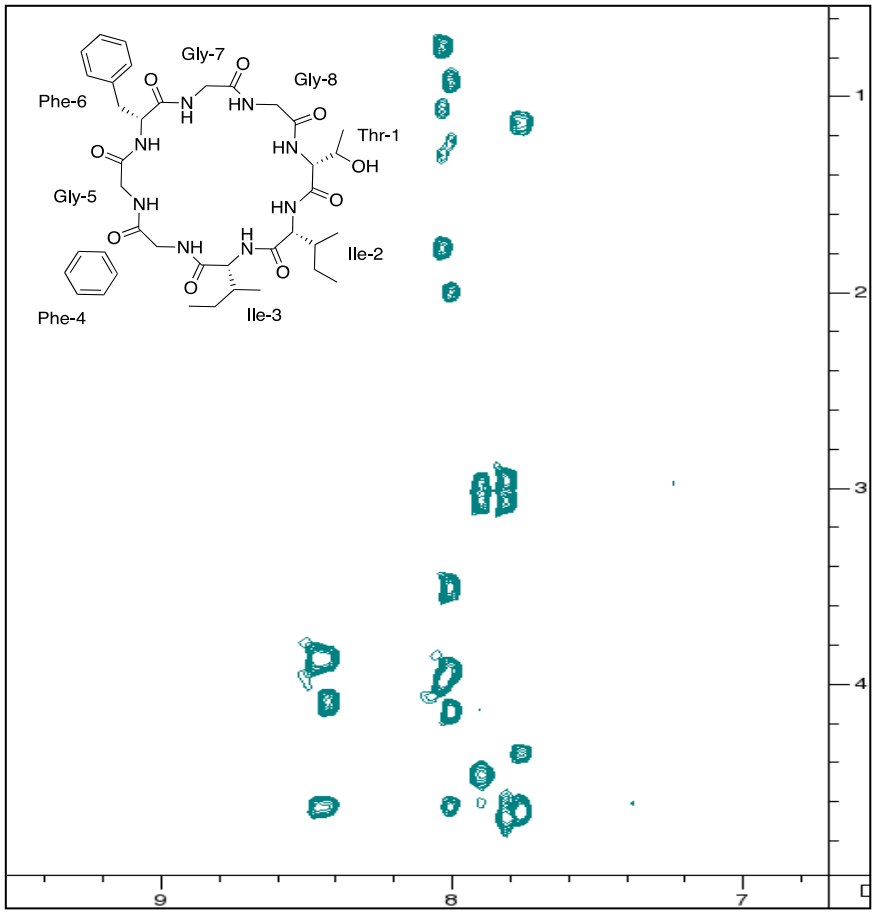

Figure S16. TOCSY fingerprint region of D-pohlianin C (**8**) (500 MHz in CD_3CN 20% at 298 K).

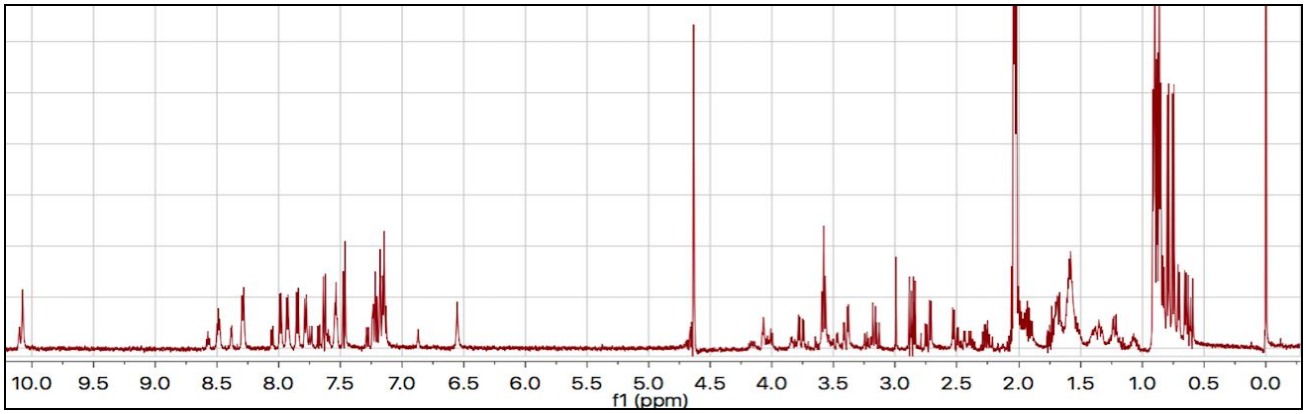

Figure S17. ^{1}H NMR spectrum of D-jatrophidin (**13**) (500 MHz in CD_3CN 20% at 298 K).

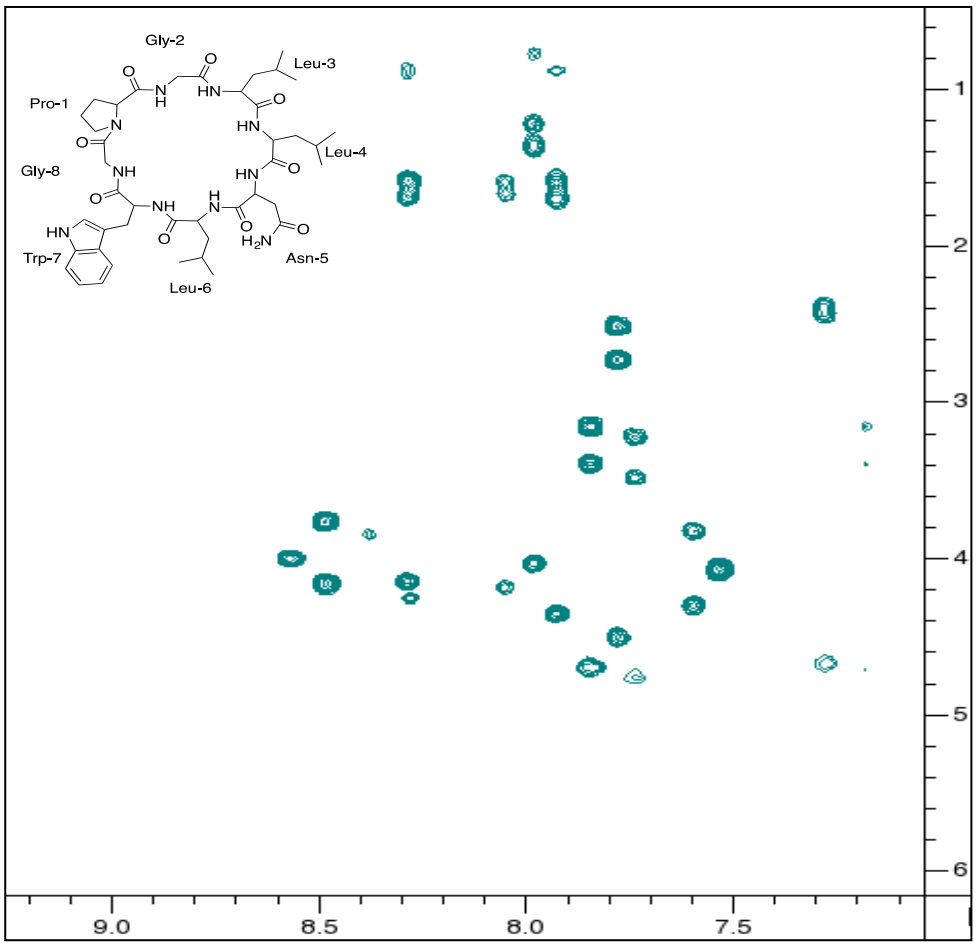

Figure S18. TOCSY fingerprint region of D-jatrophidin (**13**) (500 MHz in CD_3CN 20% at 298 K).

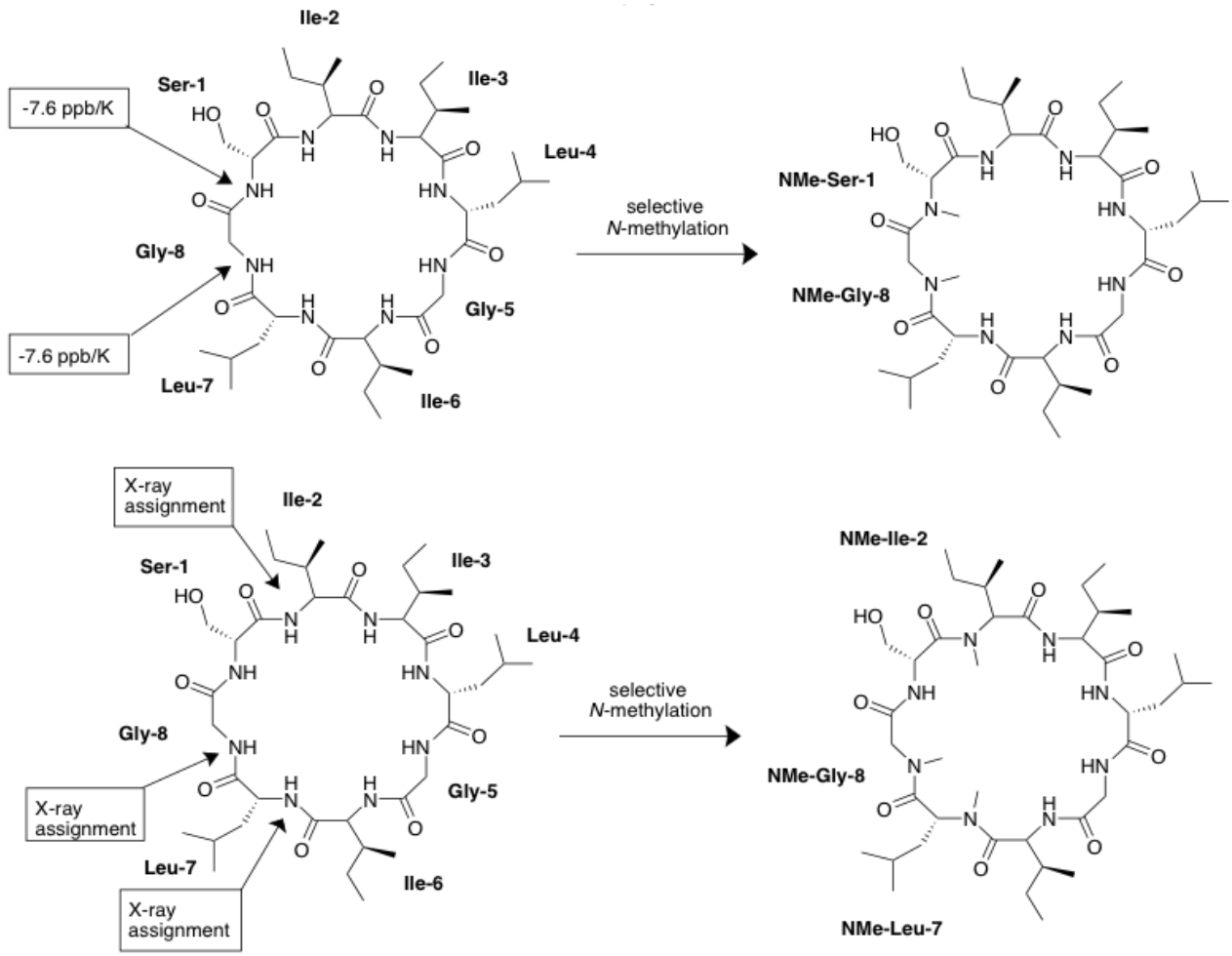

Figure S19. *N*-methylated ribifolin analogues assigned by NMR temperature coefficient studies and racemic X-ray structure.

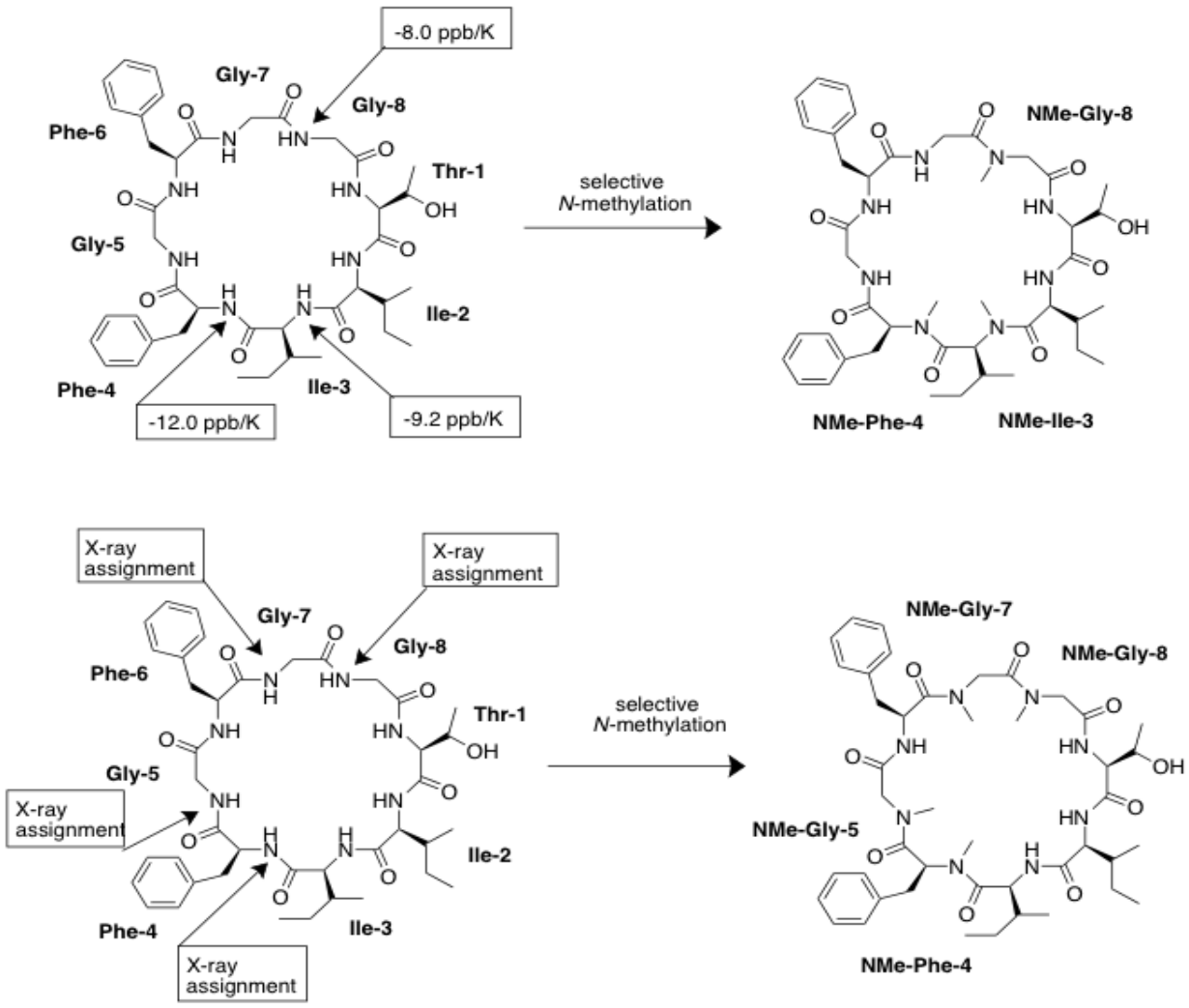

Figure S20. *N*-methylated pohlianin C analogues assigned by NMR temperature coefficient studies and racemic X-ray structure.

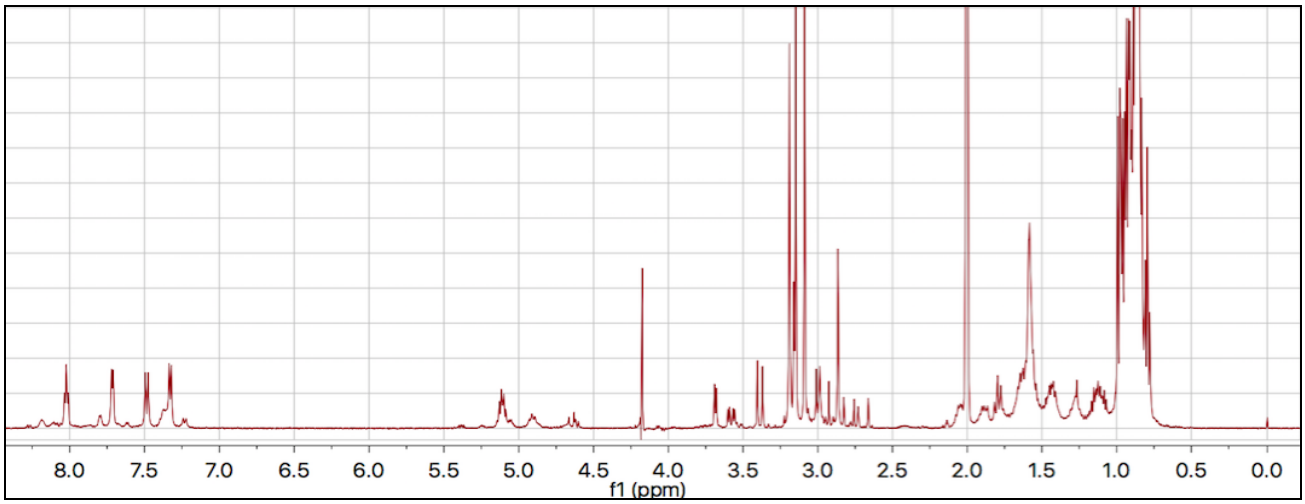

Figure S21. ^{1}H NMR spectrum of [NMe-ILG]-ribifolin (**3**) (500 MHz in CD_3CN 70% at 298 K).

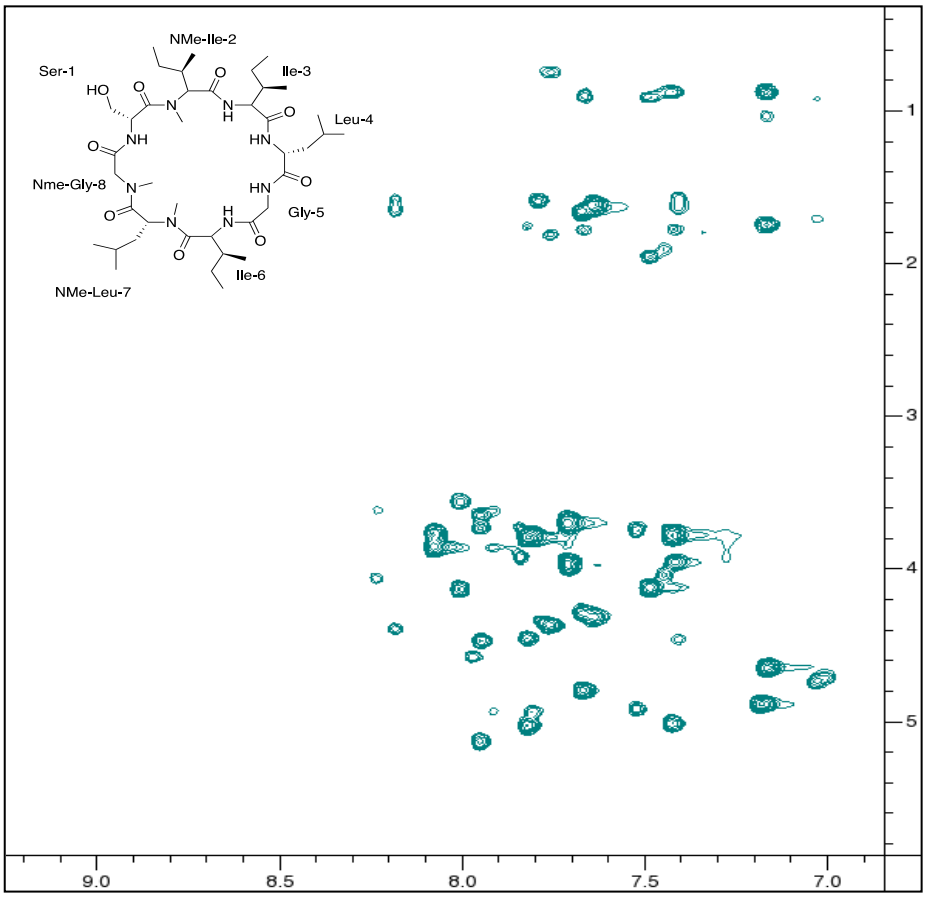

Figure S22. TOCSY fingerprint region of [NMe-ILG]-ribifolin (**3**) (500 MHz in CD_3CN 70% at 298 K).

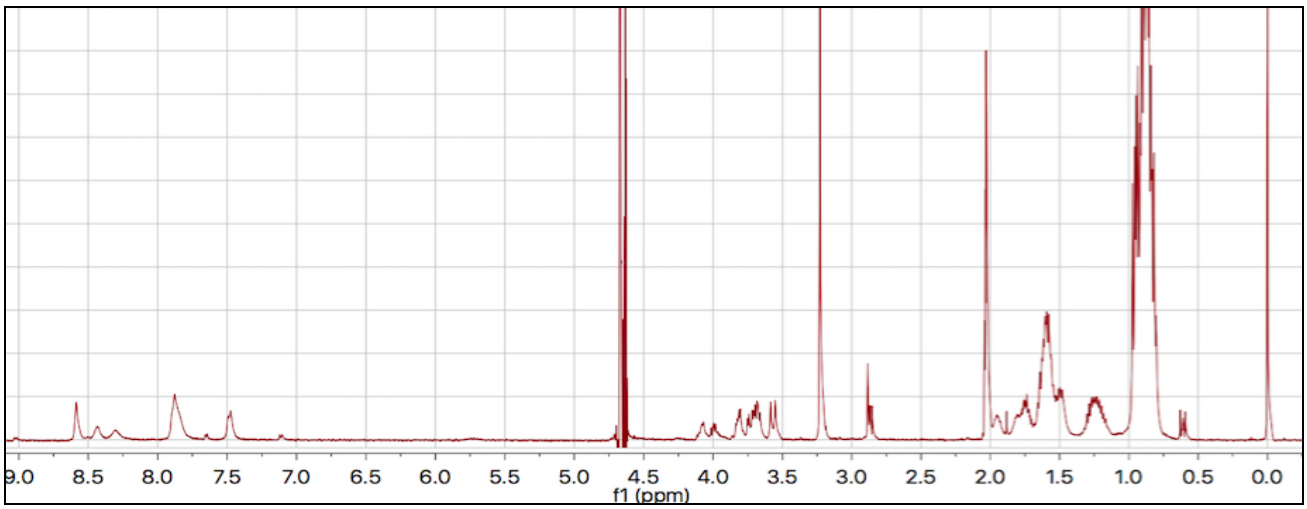

Figure S23. ^{1}H NMR spectrum of [NMe-G]-ribifolin (**4**) (500 MHz in CD_3CN 20% at 298 K).

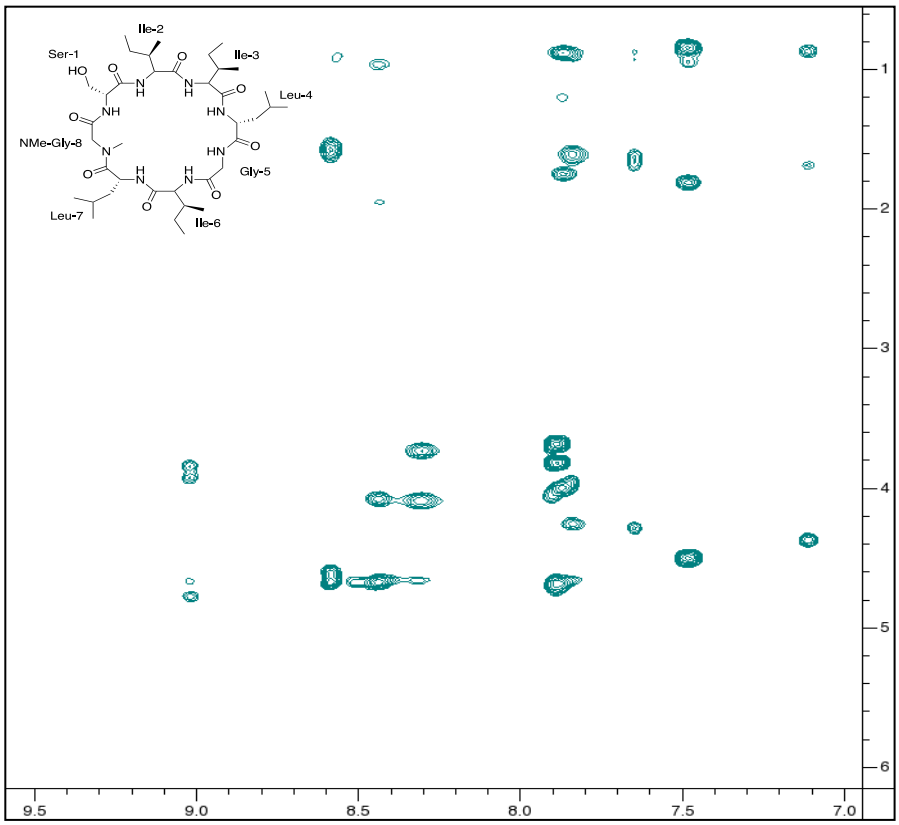

Figure S24. TOCSY fingerprint region of [NMe-G]-ribifolin (**4**) (500 MHz in CD_3CN 20% at 298 K).

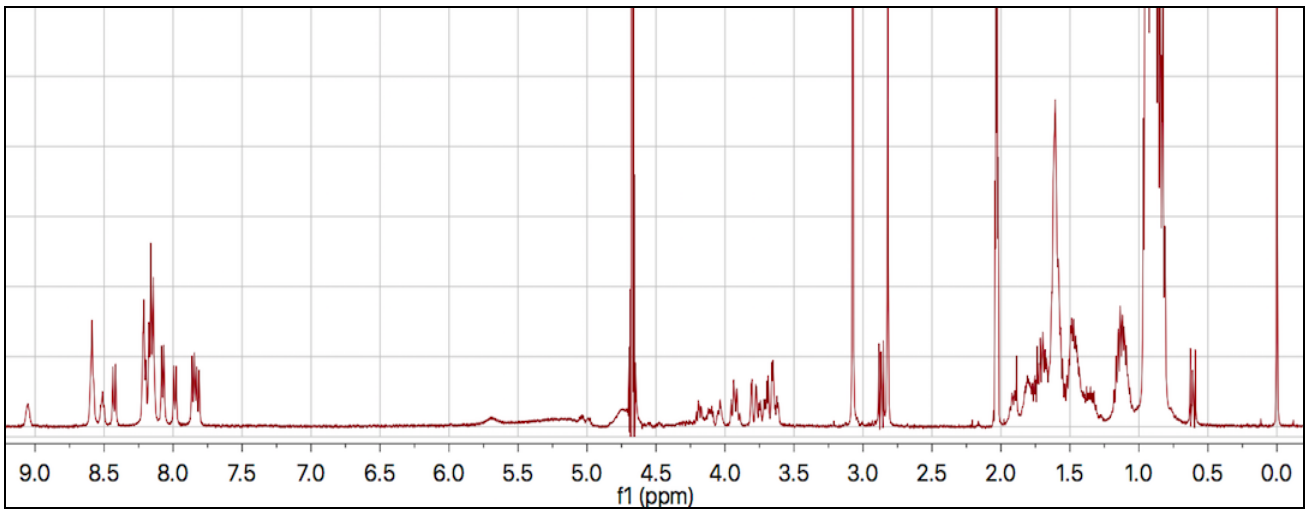

Figure S25. ^{1}H NMR spectrum of [NMe-S]-ribifolin (**5**) (500 MHz in CD_3CN 20% at 298 K).

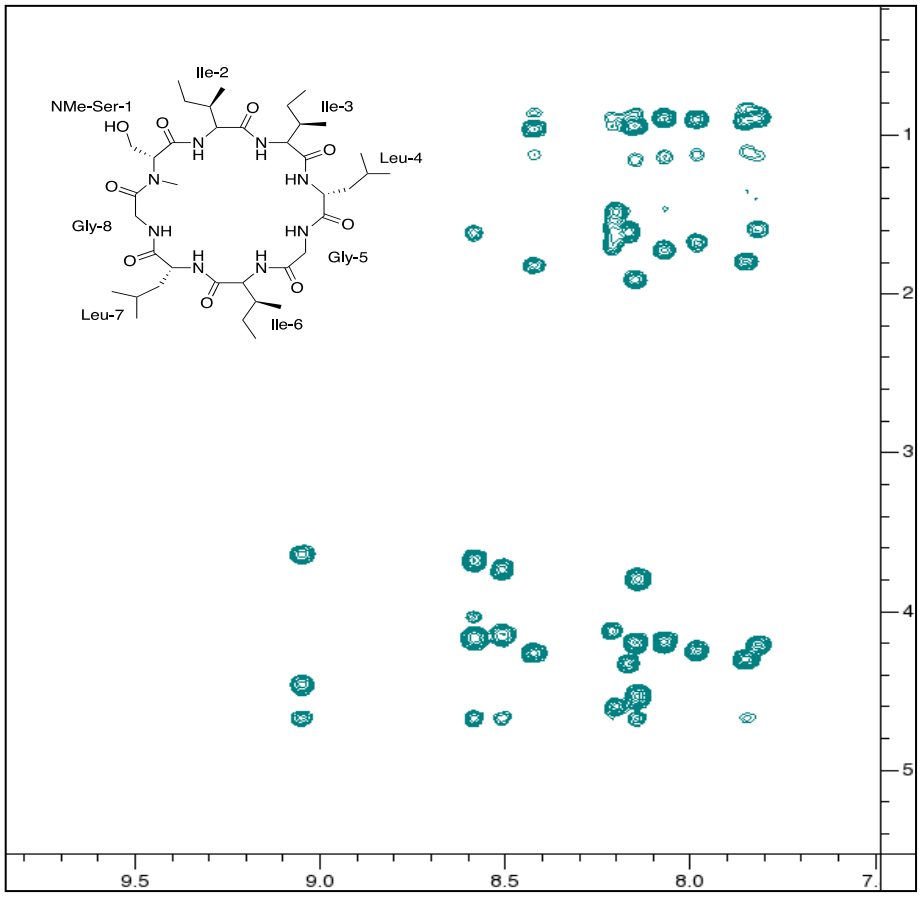

Figure S26. TOCSY fingerprint region of [NMe-S]-ribifolin (**5**) (500 MHz in CD_3CN 20% at 298 K).

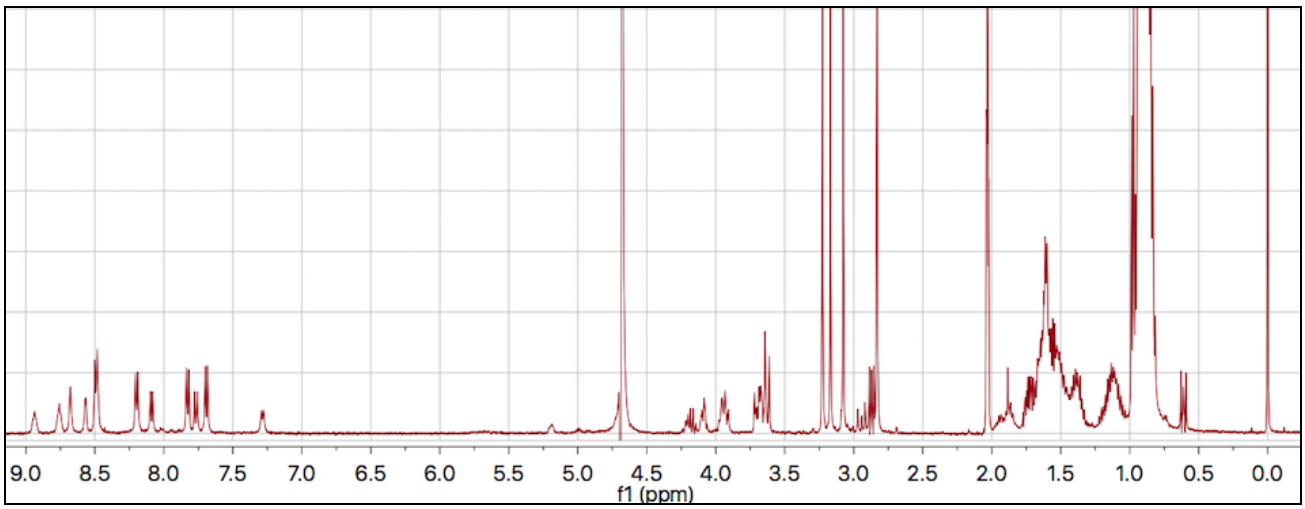

Figure S27. ^1H NMR spectrum of [NMe-SG]-ribifolin (**6**) (500 MHz in CD_3CN 20% at 298 K).

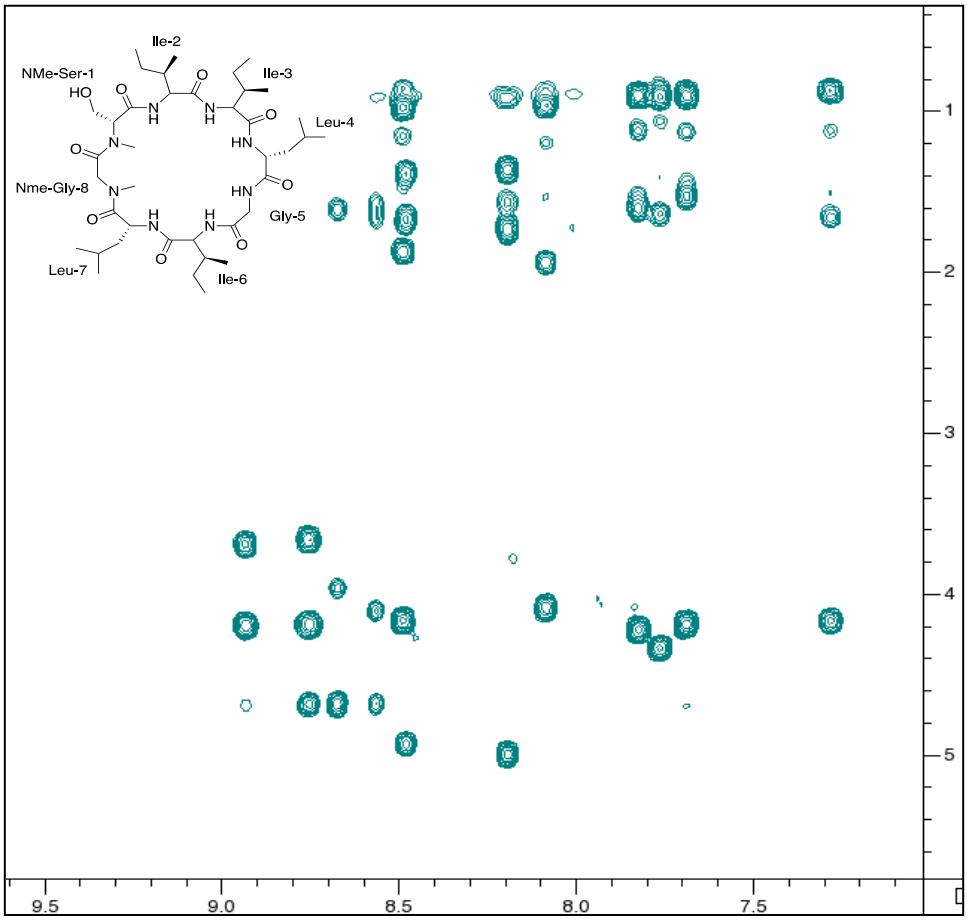

Figure S28. TOCSY fingerprint region of [NMe-SG]-ribifolin (**6**) (500 MHz in CD_3CN 20% at 298 K).

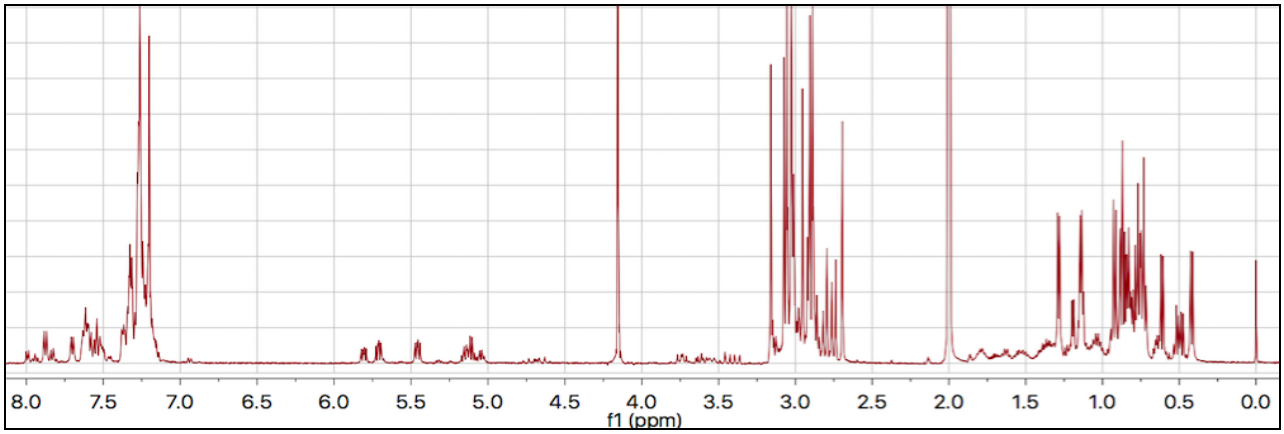

Figure S29. ^1H NMR spectrum of [NMe-FGGG]-pohlianin C (**9**) (500 MHz in CD_3CN 70% at 298 K).

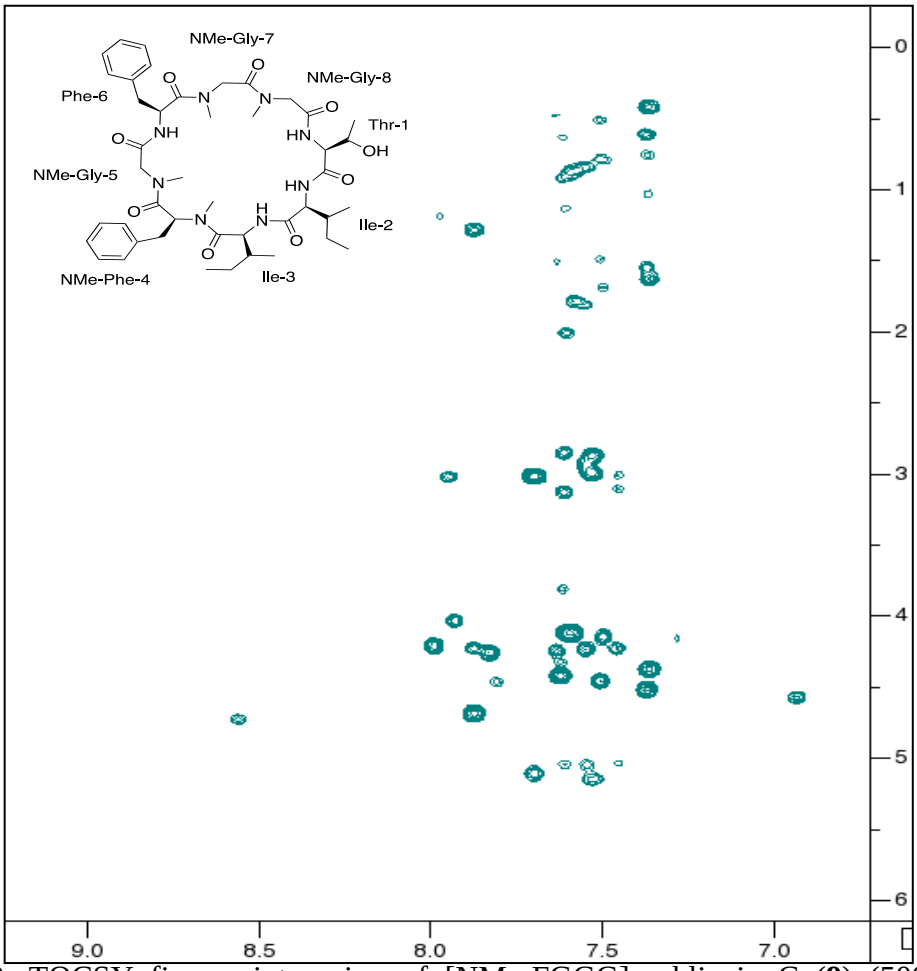

Figure S30. TOCSY fingerprint region of [NMe-FGGG]-pohlianin C (**9**) (500 MHz in CD_3CN 70% at 298 K).

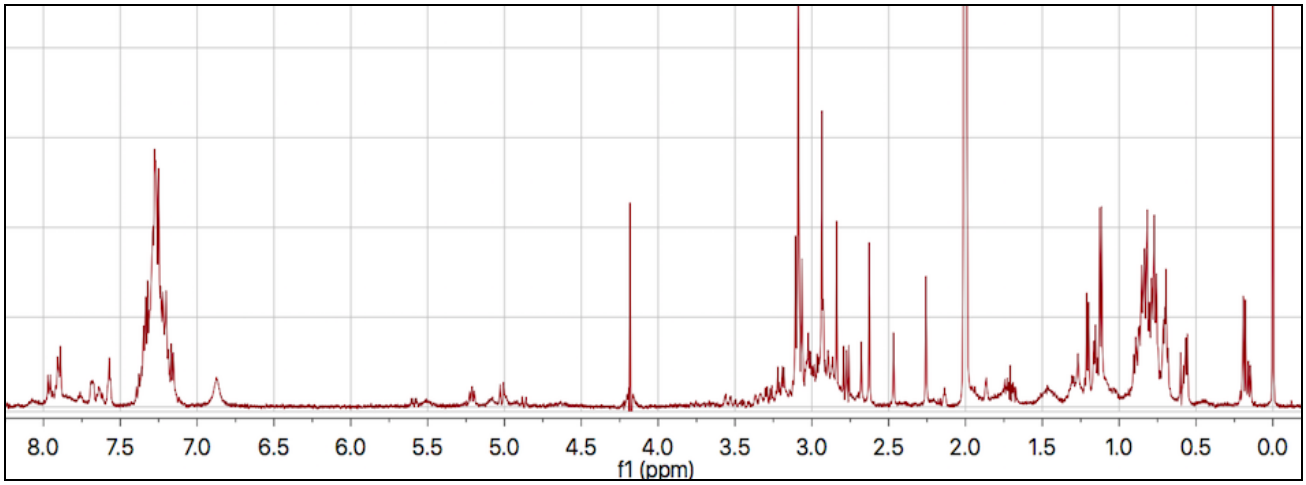

Figure S31. ^1H NMR spectrum of [NMe-IFG]-pohlianin C (**10**) (500 MHz in CD_3CN 70% at 298 K).

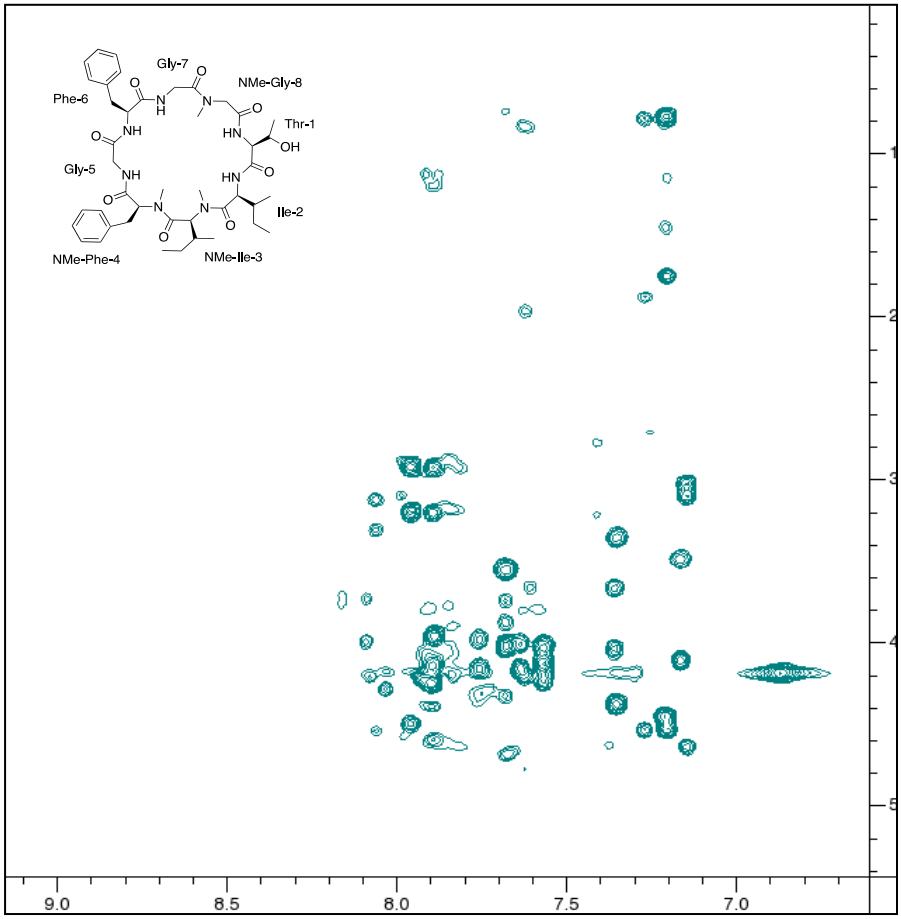

Figure S32. TOCSY fingerprint region of [NMe-IFG]-pohlianin C (**10**) (500 MHz in CD_3CN 70% at 298 K).

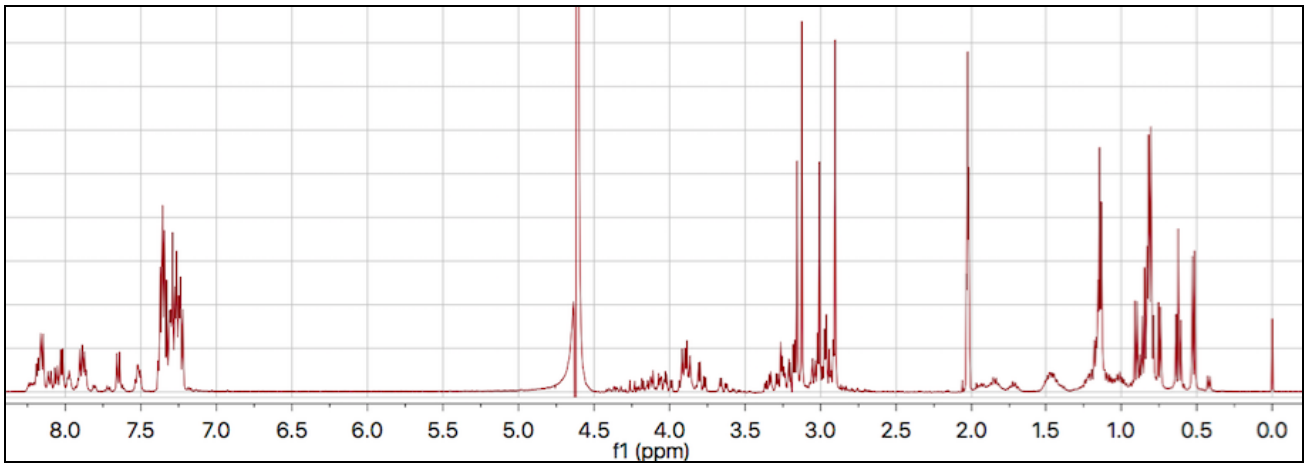

Figure S33. ^1H NMR spectrum of [NMe-FG]-pohlianin C (**11**) (500 MHz in CD_3CN 20% at 298 K).

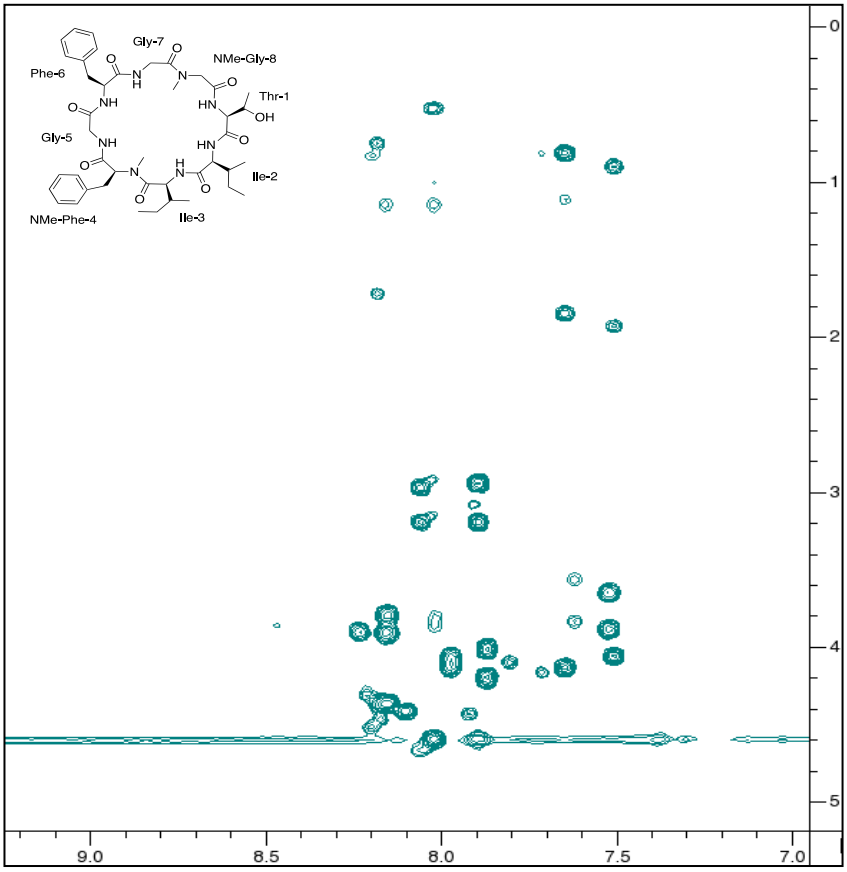

Figure S34. TOCSY fingerprint region of [NMe-FG]-pohlianin C (**11**) (500 MHz in CD_3CN 20% at 298 K).

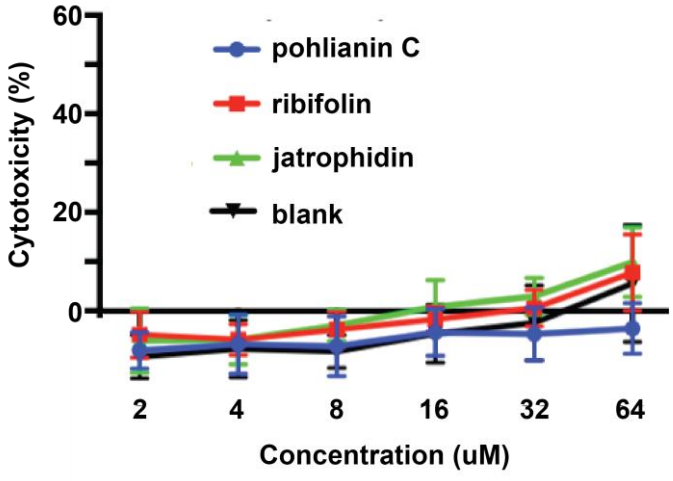

Figure S35. Cytotoxicity evaluation of ribifolin (**1**) (red), pohlianin C (**7**) (blue) and jatrophidin (**12**) (green) on Caco-2 cells. Cytotoxicity is relative to the positive control (0.1% Triton-X). The blank is the negative control and is made of 1% DMSO.