Supporting Information

Conformation-based design and synthesis of apratoxin A mimetics modified at the α,β-unsaturated thiazoline moiety

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Spectral assignment

NMR spectra

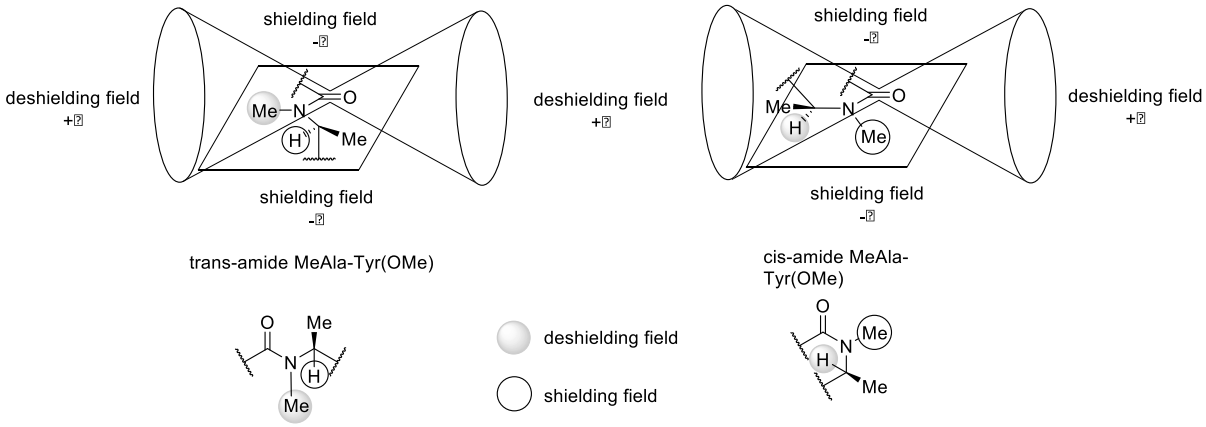
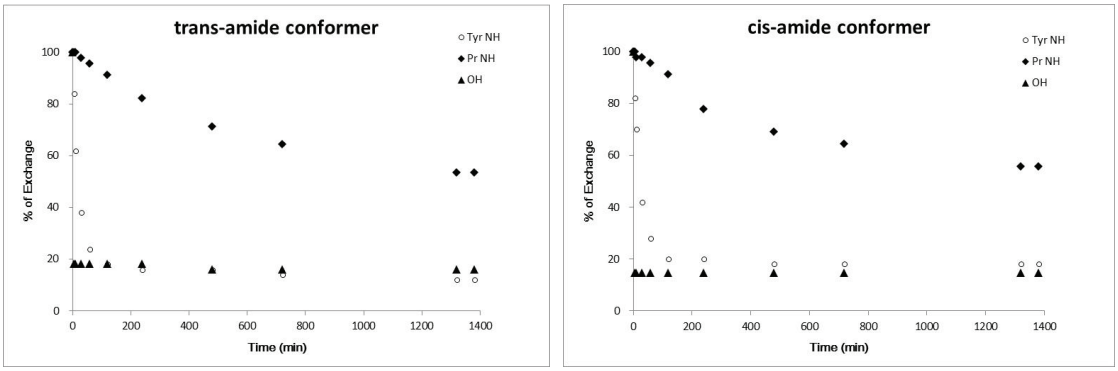


Figure S1. Magnetic anisotropic effect of amides

(A) H-D Exchange experiment



(B) Variable temperature experiment

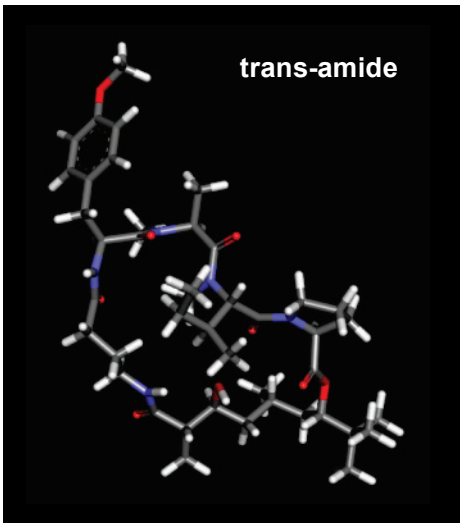
	trans-amide conformer			cis-amide conformer		
	Tyr NH	Pr NH	OH	Tyr NH	Pr NH	OH
$\Delta\sigma$ / ΔT (10^{-3} ppm / K)	4.5	0.5	0.38	2.5	0.43	1.15

(C) Chemical shifts of MeAla-MeIle region

	Apratoxin M1 trans-amide conformer		*E*-dehydroapratoxin A trans-amide	
C / H no.	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
12	2.65 (s, 3 H)	31.0	2.85 (s, 3 H)	30.8
14	3.36 (m, 1 H)	61.2	3.37 (q, *J* = 6.8, 1 H)	60.4
15	1.05 (d, *J* = 6.8, 3 H)	14.4	1.24 (d, *J* = 6.8, 1 H)	13.8
16	2.89 (s, 3 H)	37.2	2.90 (s, 3 H)	36.7
18	5.01 (m, 1 H)	N.D.	5.07 (ddd, *J* = 11.2, 9.7, 5.6, 1 H)	50.6

	Apratoxin M1 cis-amide conformer		*E*-dehydroapratoxin A cis-amide conformer	
C / H no.	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
12	2.82 (s, 3 H)	31.1	2.78 (s, 3 H)	30.0
14	4.74 (q, *J* = 6.3, 1 H)	54.9	4.74 (q, *J* = 6.8, 1 H)	53.8
15	0.66 (d, *J* = 6.6, 3 H)	15.6	0.63 (d, *J* = 6.8, 3 H)	15.3
16	2.55 (s, 3 H)	29.1	2.59 (s, 3 H)	28.8
18	5.31 (ddd, *J* = 10.2, 9.2, 5.7, 1 H)	51.0	5.34 (ddd, *J* = 10.6, 9.2, 4.6, 1 H)	50.2

(D) 3D structure of trans-amide and cis-amide conformers



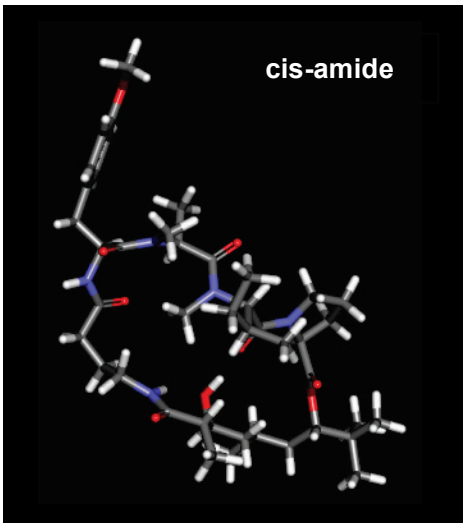
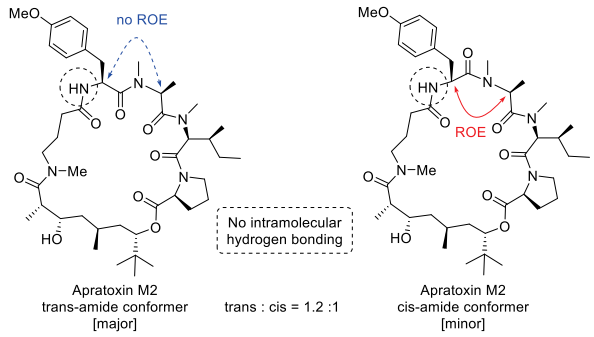
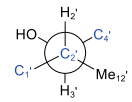
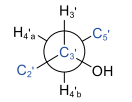
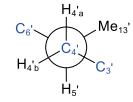
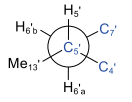
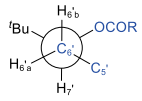


Figure S2. Additional information of the conformational analysis of apratoxin M1 (**4a**). (A) H-D exchange experiment (B) variable temperature experiment (C) Chemical shifts of MeAla-MeIle region of apratoxin M1 (CD_3CN) and (*E*)-dehydroapratoxin A ($CDCl_3$) (D) 3D structure of *trans*-amide and *cis*-amide conformers

(A) *Trans*-amide and *cis*-amide conformers



(B) Conformation of Dtena region confirmed by the NMR data

	trans-amide conformer	cis-amide conformer
	$^3J_{H\text{-}2',H\text{-}3'}$ = 9.4 Hz (Large)	$^3J_{H\text{-}2',H\text{-}3'}$ = 9.7 Hz (Large)
	$^3J_{H\text{-}3',H\text{-}4'a}$ = 2.9 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.0 Hz (Large)	$^3J_{H\text{-}3',H\text{-}4'a}$ = 3.1 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.2 Hz (Large)
	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 11.0 (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 2.9 Hz (Small)	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 11.7 (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 3.2 Hz (Small)
	$^3J_{H\text{-}5',H\text{-}6'a}$ = 11.5 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 2.5 Hz (Small)	$^3J_{H\text{-}5',H\text{-}6'a}$ = 11.4 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 2.8 Hz (Small)
	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 2.0 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 12.5 Hz (Large)	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 2.7 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 12.4 Hz (Large)

(C) Variable temperature experiment

	trans-amide conformer		cis-amide conformer	
	Tyr NH	OH	Tyr NH	OH
$\Delta\sigma$ / ΔT (10^{-3} ppm / K)	4.5	N.D.	2.6	N.D.

(D) Chemical shifts of MeAla-MeIle region

	Apratoxin M2 trans-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.66 (s, 3 H)	31.3
14	3.36 (m, 1 H)	60.8
15	1.03 (d, J = 6.4, 1 H)	14.4
16	2.92 (s, 3 H)	37.5
18	4.99 (m, 1 H)	N.D.

	Apratoxin M2 cis-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.83 (s, 3 H)	31.2
14	4.71 (q, J = 6.6, 1 H)	54.3
15	0.48 (d, J = 6.4, 1 H)	15.2
16	2.53 (s, 3 H)	29.0
18	5.09 (ddd, J = 10.6, 8.7, 5.2, 1 H)	51.3

(E) 3D structure

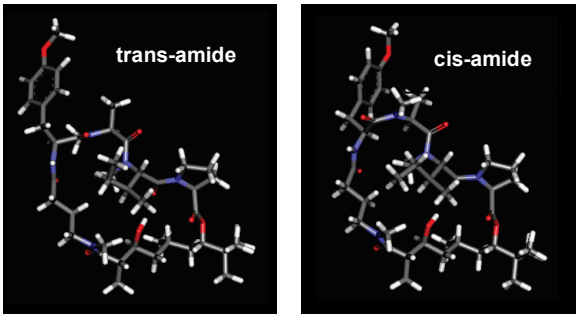
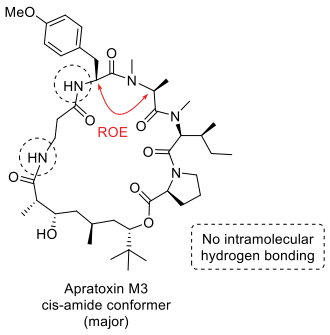


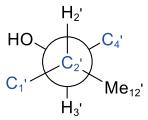
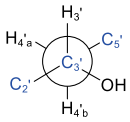
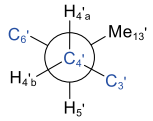
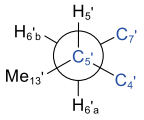
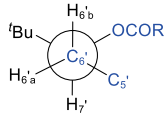
Figure S3. Conformational analysis of apratoxin M2 (**4b**). (A) *trans*-amide and *cis*-amide conformers (B) conformation of Dtena region confirmed by the NMR data (C) variable temperature experiment (D) Chemical shifts of MeAla-MeIle region (E) 3D structure of *trans*-amide and *cis*-amide conformers

(A) *Cis*-amide conformer



Apratoxin M3 cis-amide conformer (major)

(B) Conformation of Dtena region confirmed by the NMR data

	cis-amide conformer
	$^3J_{H\text{-}2',H\text{-}3'}$ = 9.3 Hz (Large)
	$^3J_{H\text{-}3',H\text{-}4'a}$ = 2.8 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.6 Hz (Large)
	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 11.6 Hz (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 3.6 Hz (Small)
	$^3J_{H\text{-}5',H\text{-}6'a}$ = 11.1 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 3.4 Hz (Small)
	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 3.0 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 12.4 Hz (Large)

(C) Variable temperature experiment

	cis-amide conformer		
	Tyr NH	Ethyl NH	OH
$\Delta\sigma$ / ΔT (10^{-3} ppm / K)	2.6	3.3	N.D.

(D) Chemical shifts of MeAla-MeIle region

	Apratoxin M3 cis-amide conformer	
C / H no.	δ_H (*J* in Hz)	δ_C
12	2.84 (s, 3 H)	30.9
14	4.82 (q, *J* = 6.7, 1 H)	54.9
15	0.59 (d, *J* = 6.7, 3 H)	15.2
16	2.50 (s, 3 H)	28.8
18	5.27 (ddd, *J* = 9.5, 9.5, 5.8, 1 H)	50.2

(E) 3D structure

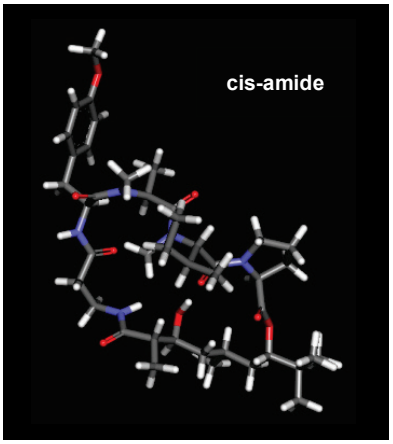
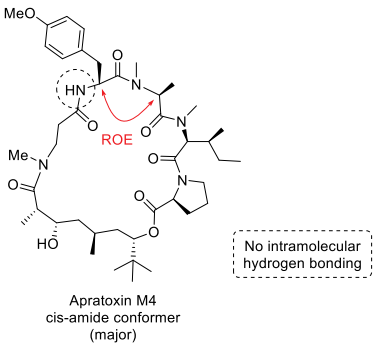


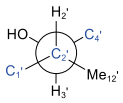
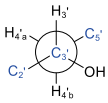
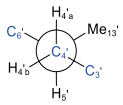
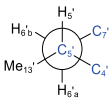
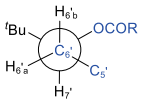
Figure S4. Conformational analysis of apratoxin M3 (**4c**). (A) *cis*-amide conformer (B) conformation of Dtena region confirmed by the NMR data (C) variable temperature experiment (D) chemical shifts of MeAla-MeIle region (E) 3D structure of *trans*-amide and *cis*-amide conformers

(A) *Cis*-amide conformer



Apratoxin M4
cis-amide conformer
(major)

(B) Conformation of Dtena region confirmed by the NMR data

	cis-amide conformer
	$^3J_{H\text{-}2',H\text{-}3'}$ = 9.1 Hz (Large)
	$^3J_{H\text{-}3',H\text{-}4'a}$ = 3.1 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.3 Hz (Large)
	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 10.6 Hz (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 3.3 Hz (Small)
	$^3J_{H\text{-}5',H\text{-}6'a}$ = 12.4 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 3.1 Hz (Small)
	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 3.1 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 11.9 Hz (Large)

(C) Variable temperature experiment

	cis-amide conformer	
	Tyr NH	OH
$\Delta\sigma$ / ΔT (10^{-3} ppm / K)	2.3	N.D.

(D) Chemical shifts of MeAla-MeIle region

	Apratoxin M4 cis-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.86 (s, 3 H)	31.1
14	4.75 (q, J = 6.6, 1 H)	54.0
15	0.39 (d, J = 6.7, 3 H)	14.8
16	2.52 (s, 3 H)	28.6
18	5.25 (dd, J = 9.4, 7.3, 1 H)	50.6

(E) 3D structure

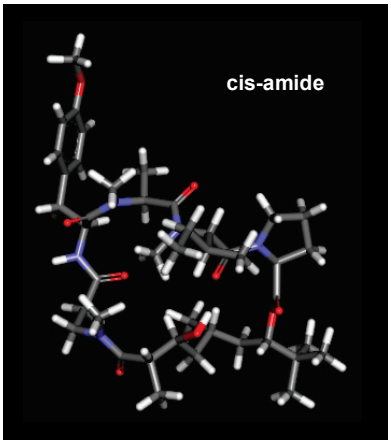
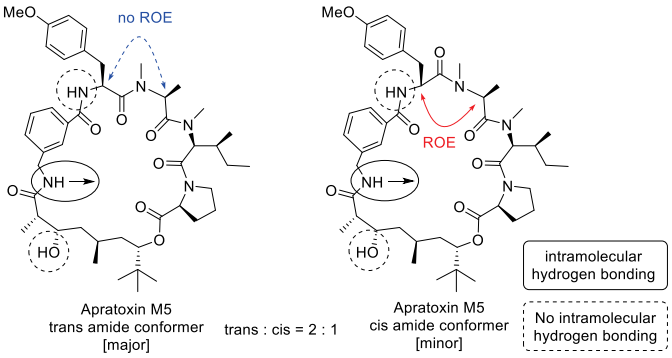
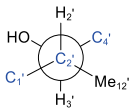
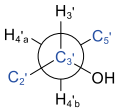
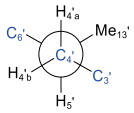
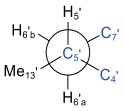
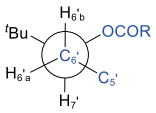


Figure S5. Conformational analysis of apratoxin M4 (**4d**). (A) *cis*-amide conformer (B) conformation of Dtena region confirmed by the NMR data (C) variable temperature experiment (D) chemical shifts of MeAla-MeIle region (E) 3D structure of *trans*-amide and *cis*-amide conformers

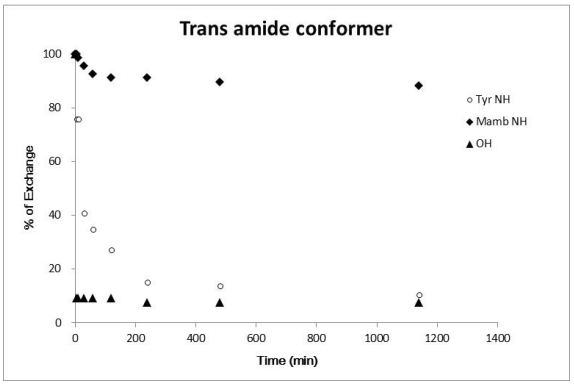
(A) *Trans*-amid and *cis*-amide conformers

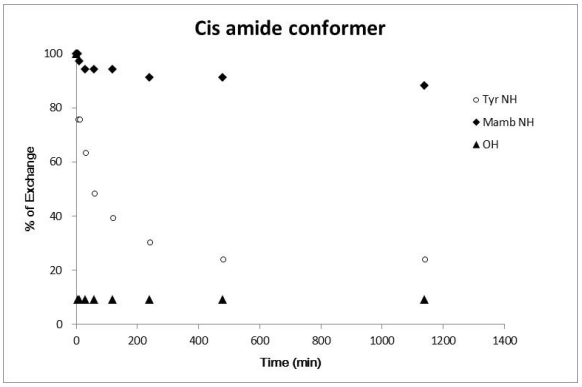


(B) Conformation of Dtena region confirmed by the NMR data

	trans-amide conformer	cis-amide conformer
	$^3J_{H\text{-}2',H\text{-}3'}$ = 10.0 Hz (Large)	$^3J_{H\text{-}2',H\text{-}3'}$ = 9.9 Hz (Large)
	$^3J_{H\text{-}3',H\text{-}4'a}$ = 2.6 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.8 Hz (Large)	$^3J_{H\text{-}3',H\text{-}4'a}$ = 3.1 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.7 Hz (Large)
	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 10.8 Hz (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 4.0 Hz (Small)	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 11.2 Hz (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 3.6 Hz (Small)
	$^3J_{H\text{-}5',H\text{-}6'a}$ = 11.7 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 2.2 Hz (Small)	$^3J_{H\text{-}5',H\text{-}6'a}$ = 11.7 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 2.2 Hz (Small)
	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 2.2 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 12.6 Hz (Large)	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 2.7 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 12.4 Hz (Large)

(C) H-D Exchange experiment





(D) Variable temperature experiment

	trans-amide conformer			cis-amide conformer		
	Tyr NH	Mamb NH	OH	Tyr NH	Mamb NH	OH
$\Delta\sigma$ / ΔT (10^{-3} ppm / K)	N.D.	0.66	N.D.	2.6	N.D.	N.D.

(E) Chemical shifts of MeAla-MeIle region

	Apratoxin M5 trans-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.73 (s, 3 H)	30.7
14	3.39 (m, 1 H)	61.1
15	1.07 (d, J = 6.8, 3 H)	14.4
16	2.94 (s, 3 H)	37.3
18	5.06 (m, 1 H)	51.5

	Apratoxin M5 cis-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.89 (s, 3 H)	31.1
14	4.87 (q, J = 6.5, 1 H)	54.6
15	0.76 (d, J = 6.6, 3 H)	15.1
16	2.61 (s, 3 H)	29.5
18	5.31 (ddd, J = 10.5, 9.0, 6.1, 1 H)	51.5

(F) 3D structure of trans-amide and cis-amide conformers

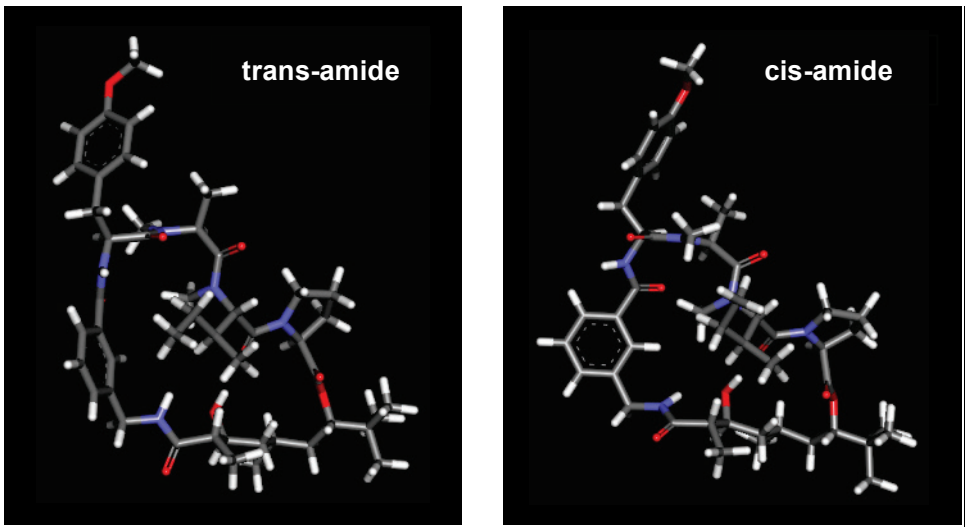
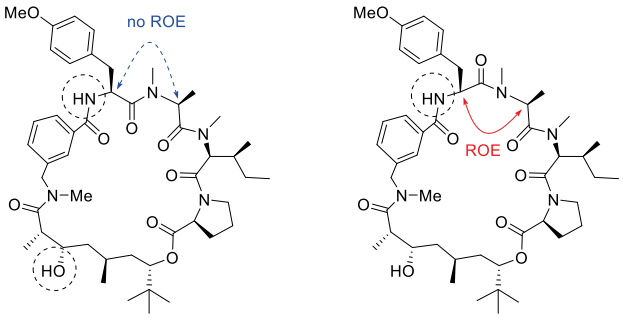
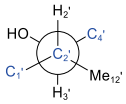
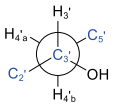
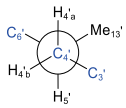
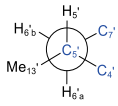
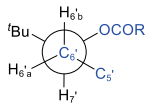


Figure S6. Conformational analysis of apratoxin M5 (**4e**). (A) *trans*-amide and *cis*-amide conformers. (B) conformation of Dtena region confirmed by the NMR data. (C) H-D exchange experiment (D) variable temperature experiment (E) Chemical shifts of MeAla-MeIle region (F) 3D structure of *trans*-amide and *cis*-amide conformers

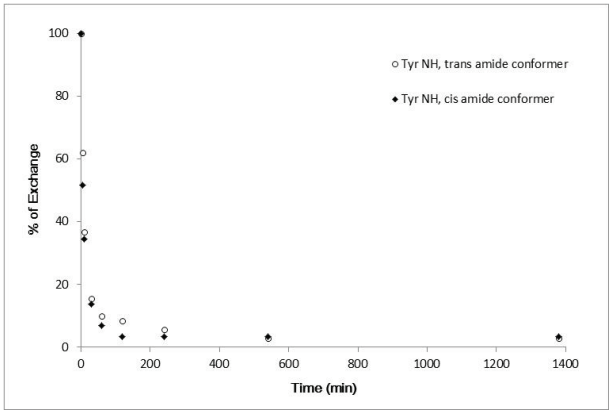
(A) *Trans*-amid and *cis*-amide conformers



(B) Conformation of Dtena region confirmed by the NMR data

	trans-amide conformer	cis-amide conformer
	$^3J_{H\text{-}2',H\text{-}3'}$ = 10.3 (Large)	$^3J_{H\text{-}2',H\text{-}3'}$ = 9.9 (Large)
	$^3J_{H\text{-}3',H\text{-}4'a}$ = 3.3 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.3 Hz (Large)	$^3J_{H\text{-}3',H\text{-}4'a}$ = 3.2 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.6 Hz (Large)
	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 11.3 Hz (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 3.7 Hz (Small)	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 10.8 Hz (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 3.2 Hz (Small)
	$^3J_{H\text{-}5',H\text{-}6'a}$ = 12.1 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 2.7 Hz (Small)	$^3J_{H\text{-}5',H\text{-}6'a}$ = 11.1 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 3.3 Hz (Small)
	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 2.1 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 12.4 Hz (Large)	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 2.5 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 12.5 Hz (Large)

(C) H-D Exchange experiment



(D) Variable temperature experiment

	trans-amide conformer		cis-amide conformer	
	Tyr NH	OH	Tyr NH	OH
$\Delta\sigma$ / ΔT (10^{-3} ppm / K)	4.4	2.3	2.2	N.D.

(E) Chemical shifts of MeAla-MeIle region

	Apratoxin M6 trans-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.74 (s, 3 H)	30.5
14	3.39 (m, 1 H)	61.0
15	1.06 (d, J = 6.8, 3 H)	14.5
16	2.93 (s, 3 H)	37.2
18	5.04 (m, 1 H)	51.6

	Apratoxin M6 cis-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.88 (s, 3 H)	30.8
14	4.82 (q, J = 6.5, 1 H)	54.1
15	0.68 (d, J = 6.6, 3 H)	15.8
16	2.58 (s, 3 H)	29.1
18	5.41 (ddd, J = 10.5, 9.0, 6.1, 1 H)	51.3

(F) 3D structure of trans-amide and cis-amide conformers

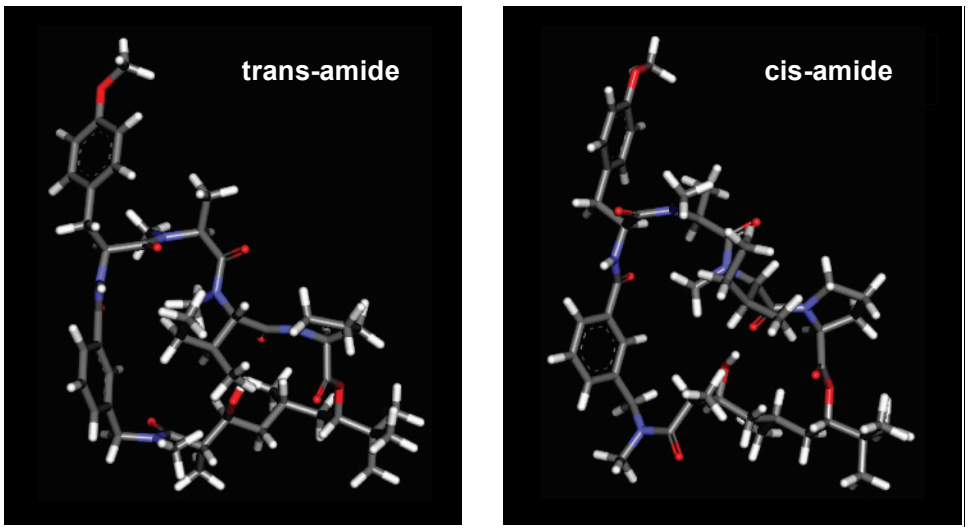
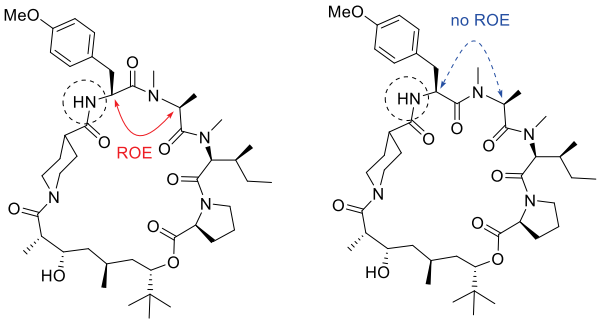


Figure S7. Conformational analysis of apratoxin M6 (**4f**). (A) *trans*-amide and *cis*-amide conformers. (B) conformation of Dtena region confirmed by the NMR data. (C) H-D exchange experiment (D) variable temperature experiment (E) Chemical shifts of MeAla-MeIle region (F) 3D structure of *trans*-amide and *cis*-amide conformers

(A) *Trans*-amid and *cis*-amide conformers

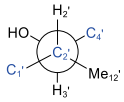
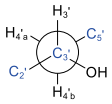
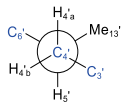
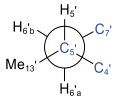
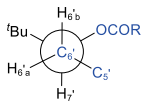


Apratoxin M7
cis-amide conformer
[major]

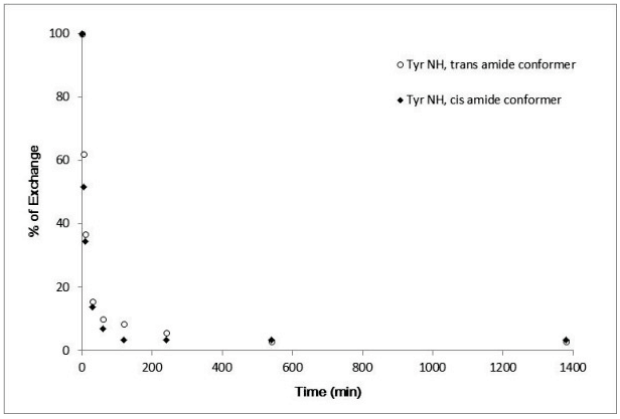
cis : trans = 2 : 1

Apratoxin M7
trans-amide conformer
[minor]

(B) Conformation of Dtena region confirmed by the NMR data

	cis-amide conformer	trans-amide conformer
	$^3J_{H\text{-}2',H\text{-}3'}$ = N.D.	$^3J_{H\text{-}2',H\text{-}3'}$ = N.D.
	$^3J_{H\text{-}3',H\text{-}4'a}$ = 2.7 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 9.1 Hz (Large)	$^3J_{H\text{-}3',H\text{-}4'a}$ = 2.2 Hz (Small) $^3J_{H\text{-}3',H\text{-}4'b}$ = 11.6 Hz (Large)
	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 10.2 Hz (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 3.1 Hz (Small)	$^3J_{H\text{-}4'a,H\text{-}5'}$ = 10.1 Hz (Large) $^3J_{H\text{-}4'a,H\text{-}5'}$ = 3.4 Hz (Small)
	$^3J_{H\text{-}5',H\text{-}6'a}$ = 6.8 Hz (Medium) $^3J_{H\text{-}5',H\text{-}6'b}$ = 5.7 Hz (Medium)	$^3J_{H\text{-}5',H\text{-}6'a}$ = 10.8 Hz (Large) $^3J_{H\text{-}5',H\text{-}6'b}$ = 2.5 Hz (Small)
	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 4.2 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 8.9 Hz (Large)	$^3J_{H\text{-}6'a,H\text{-}7'}$ = 2.2 Hz (Small) $^3J_{H\text{-}6'b,H\text{-}7'}$ = 12.4 Hz (Large)

(C) H-D Exchange experiment



(D) Variable temperature experiment

	cis-amide conformer		trans-amide conformer	
	Tyr NH	OH	Tyr NH	OH
$\Delta\sigma$ / ΔT (10^{-3} ppm / K)	4.4	N.D.	3.7	N.D.

(E) Chemical shifts of MeAla-MeIle region

	Apratoxin M7 cis-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.80 (s, 3 H)	31.8
14	4.82 (q, J = 6.6, 1 H)	55.8
15	0.67 (d, J = 6.6, 3 H)	15.9
16	2.53 (s, 3 H)	29.3
18	5.15 (ddd, J = 10.2, 9.0, 5.6, 1 H)	50.6

	Apratoxin M7 trans-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.64 (s, 3 H)	31.7
14	3.34 (m, 1 H)	61.6
15	1.05 (d, J = 6.5, 3 H)	14.6
16	2.88 (s, 3 H)	37.5
18	5.00 (m, 1 H)	51.4

(F) 3D structure of *trans*-amide and *cis*-amide conformers

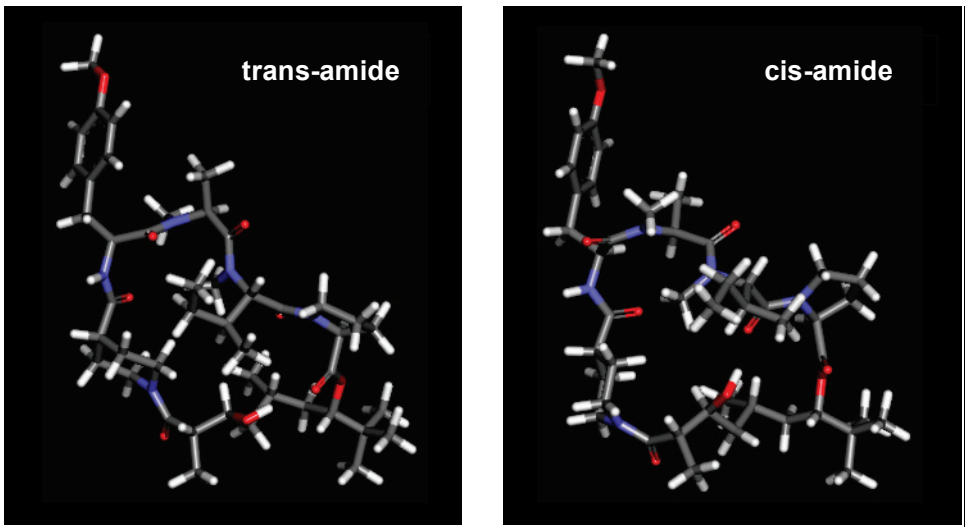


Figure S8. Conformational analysis of apratoxin M7 (**4f**). (A) *trans*-amide and *cis*-amide conformers. (B) conformation of Dtena region confirmed by the NMR data. (C) H-D exchange experiment (D) variable temperature experiment (E) Chemical shifts of MeAla-MeIle region (F) 3D structure of *trans*-amide and *cis*-amide conformers

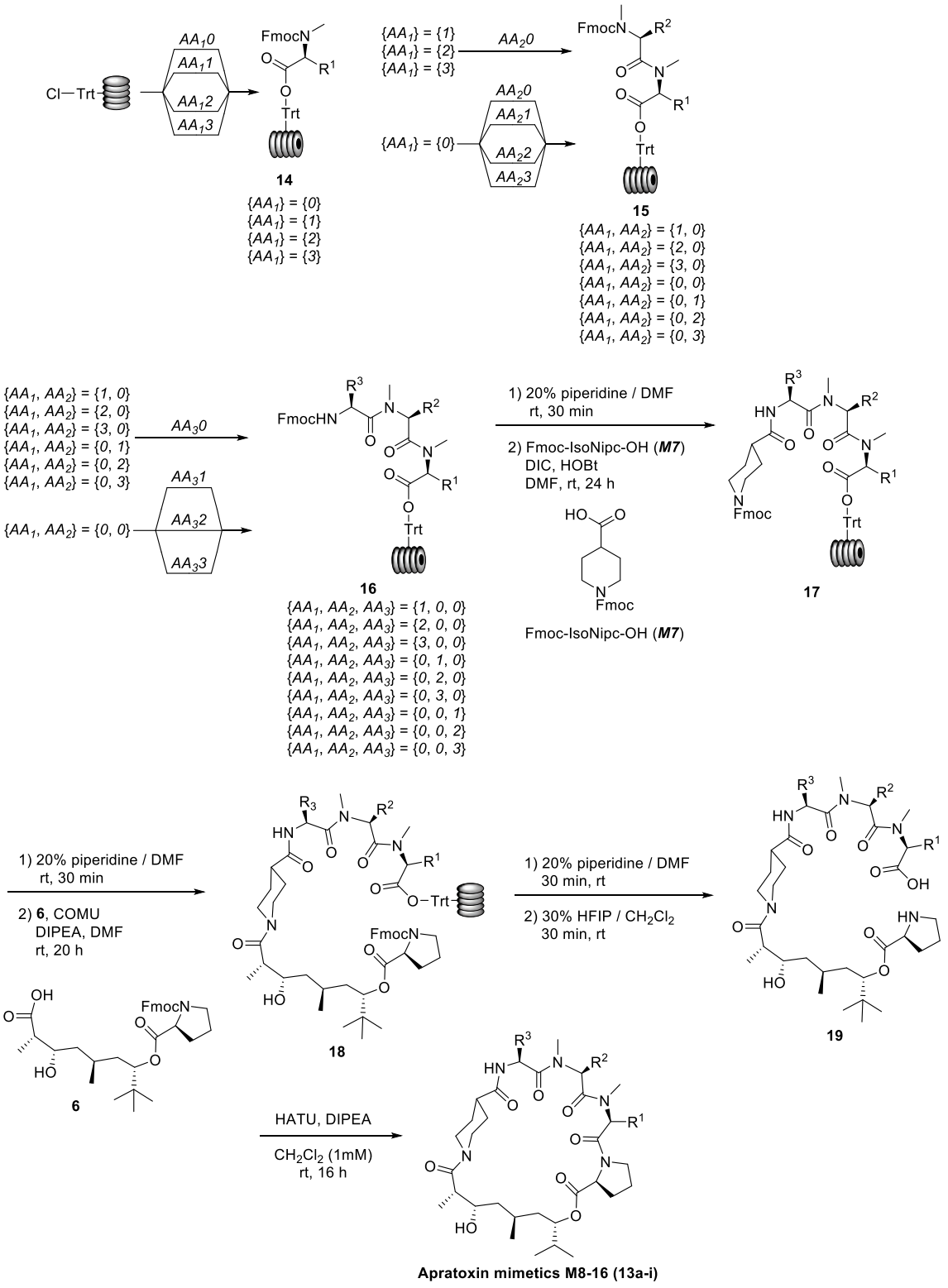


Figure S9. Synthetic scheme of apratoxins M8–M16 (**13a–i**)

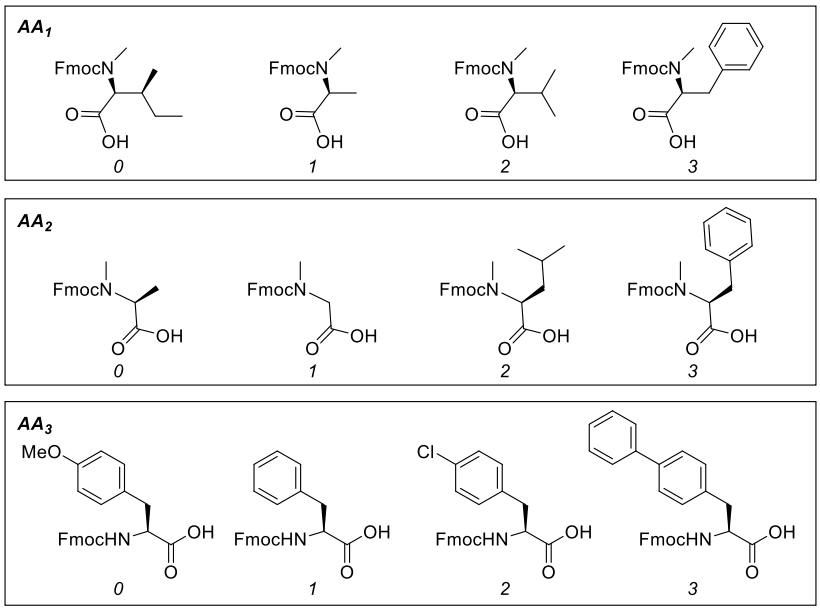


Figure S10. Building blocks AA_1–AA_3 for the synthesis of apratoxins M8–M16 (**13a–i**)

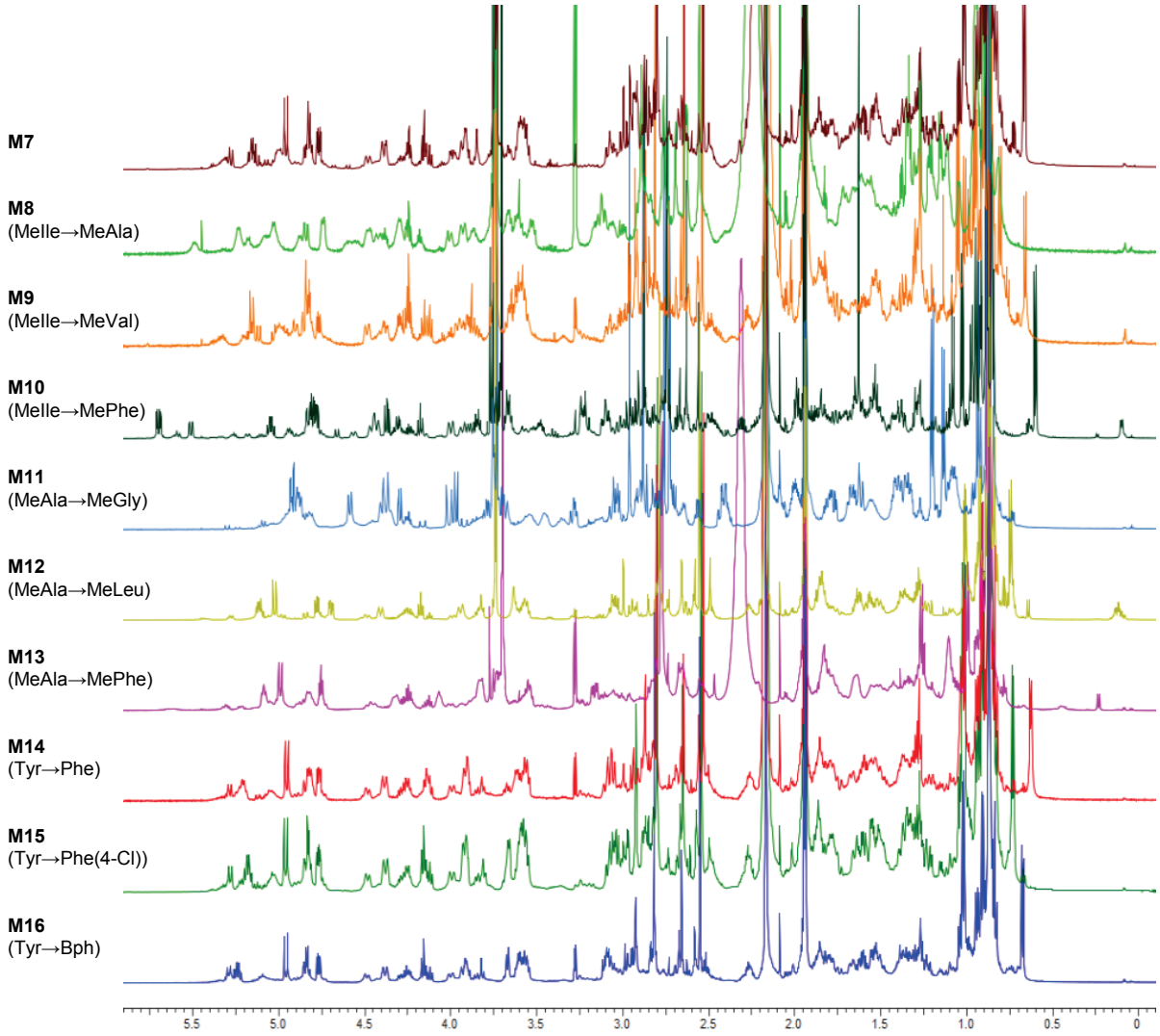
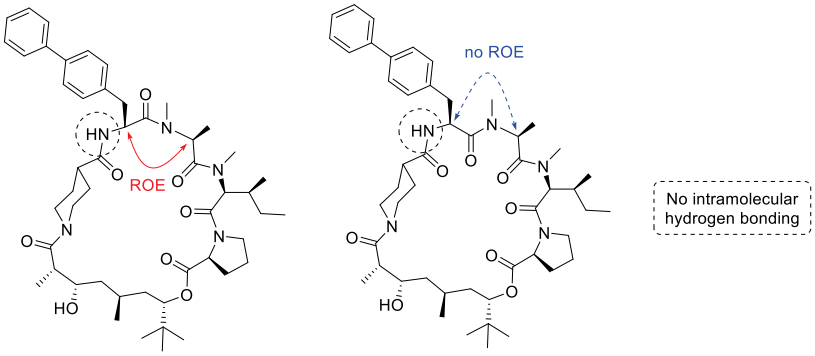


Figure S11. Comparison of ^{1}H NMR spectra of apratoxins M7–M16 (**13a–i**)

(A) *Trans*-amid and *cis*-amide conformers

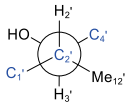
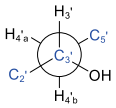
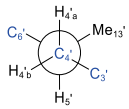
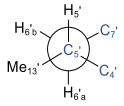
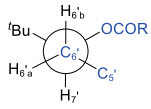


Apratoxin M16
cis-amide conformer
[major]

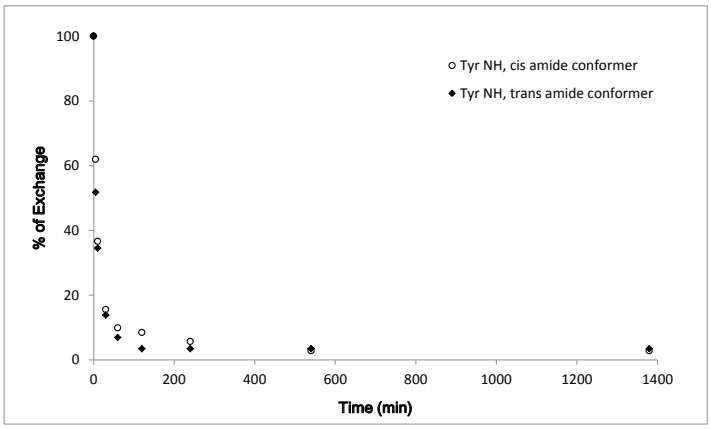
cis : trans = 2 : 1

Apratoxin M16
trans-amide conformer
[minor]

(B) Conformation of Dtena region confirmed by the NMR data

	cis-amide conformer	trans-amide conformer
	$^{3}J_{\text{H-2',H-3'}}$ = N.D.	$^{3}J_{\text{H-2',H-3'}}$ = N.D.
	$^{3}J_{\text{H-3',H-4'a}}$ = 2.6 Hz (Small) $^{3}J_{\text{H-3',H-4'b}}$ = 9.1 Hz (Large)	$^{3}J_{\text{H-3',H-4'a}}$ = 2.6 Hz (Small) $^{3}J_{\text{H-3',H-4'b}}$ = 12.7 Hz (Large)
	$^{3}J_{\text{H-4'a,H-5'}}$ = 10.1 Hz (Large) $^{3}J_{\text{H-4'a,H-5'}}$ = 3.6 Hz (Small)	$^{3}J_{\text{H-4'a,H-5'}}$ = 12.8 Hz (Large) $^{3}J_{\text{H-4'a,H-5'}}$ = 2.5 Hz (Small)
	$^{3}J_{\text{H-5',H-6'a}}$ = 7.1 Hz (Medium) $^{3}J_{\text{H-5',H-6'b}}$ = 5.7 Hz (Medium)	$^{3}J_{\text{H-5',H-6'a}}$ = 11.6 Hz (Large) $^{3}J_{\text{H-5',H-6'b}}$ = 2.5 Hz (Small)
	$^{3}J_{\text{H-6'a,H-7'}}$ = 4.0 Hz (Small) $^{3}J_{\text{H-6'b,H-7'}}$ = 9.0 Hz (Large)	$^{3}J_{\text{H-6'a,H-7'}}$ = 2.7 Hz (Small) $^{3}J_{\text{H-6'b,H-7'}}$ = 12.6 Hz (Large)

(C) H-D Exchange experiment



(D) Variable temperature experiment

	cis-amide conformer		trans-amide conformer	
	Tyr NH	OH	Tyr NH	OH
$\Delta\sigma$ / ΔT (10^{-3} ppm / K)	3.8	N.D.	3.9	N.D.

(E) Chemical shifts of MeAla-MeIle region

	Apratoxin M16 cis-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.81 (s, 3 H)	31.6
14	4.87 (q, J = 6.7, 1 H)	55.7
15	0.67 (d, J = 6.7, 3 H)	15.7
16	2.55 (s, 3 H)	26.2
18	5.24 (ddd, J = 9.6, 8.9, 6.1, 1 H)	50.4

	Apratoxin M16 trans-amide conformer	
C / H no.	δ_H (J in Hz)	δ_C
12	2.66 (s, 3 H)	31.4
14	3.35 (m, 1 H)	61.8
15	1.04 (d, J = 6.7, 3 H)	14.5
16	2.94 (s, 3 H)	37.5
18	5.09 (m, 1 H)	51.1

(F) 3D structure of *trans*-amide and *cis*-amide conformers

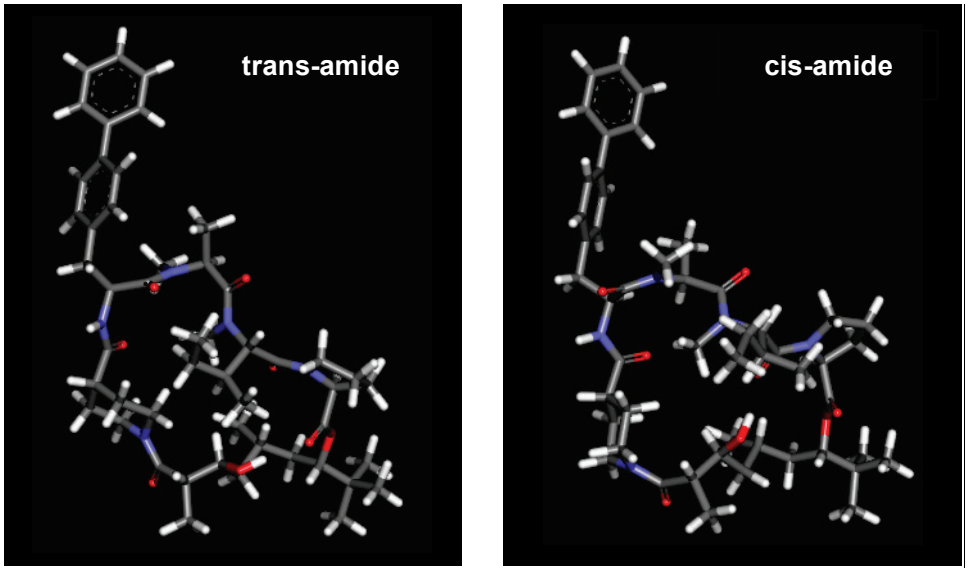
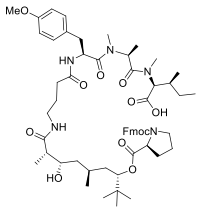
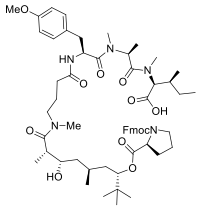
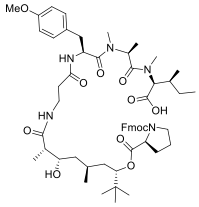
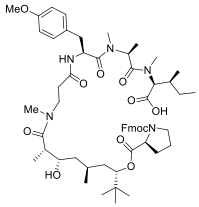
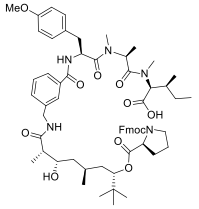
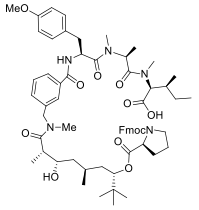
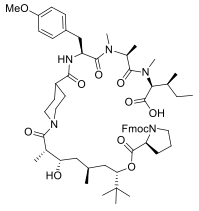


Figure S12. Conformational analysis of apratoxin M16 (**13i**). (A) *trans*-amide and *cis*-amide conformers. (B) conformation of Dtena region confirmed by the NMR data. (C) H-D exchange experiment (D) variable temperature experiment (E) Chemical shifts of MeAla-MeIle region (F) 3D structure of *trans*-amide and *cis*-amide conformers

	structure	molecular formula	obzserved mass (ESI) [M+H]	retention time (min)	purity (%)
M1		$C_{58}H_{81}N_5O_{12}$	1040.86	10.4	96.7
M2		$C_{59}H_{83}N_5O_{12}$	1054.76	10.4	94.0
M3		$C_{57}H_{79}N_5O_{12}$	1026.80	10.4	98.1
M4		$C_{58}H_{81}N_5O_{12}$	1040.78	10.4	94.8
M5		$C_{62}H_{81}N_5O_{12}$	1088.79	10.4	89.8
M6		$C_{63}H_{83}N_5O_{12}$	1102.77	10.6	82.6
M7		$C_{60}H_{83}N_5O_{12}$	1066.90	10.4	91.5

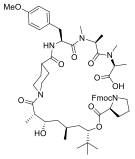
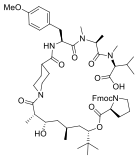
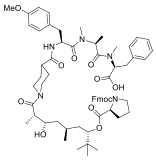
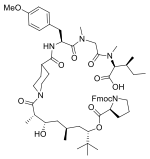
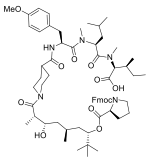
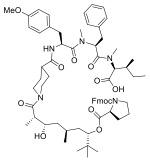
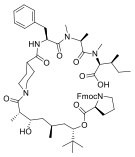
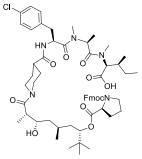
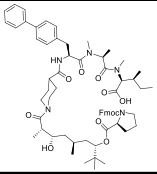
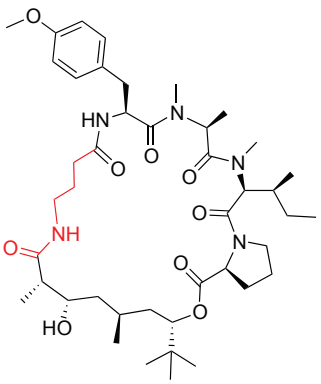
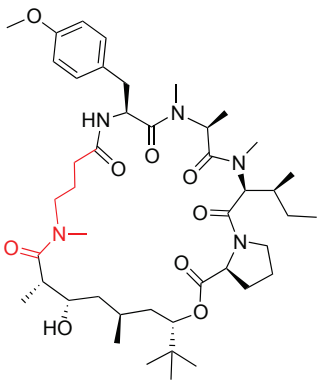
	structure	molecular formula	obzserved mass (ESI) [M+H]	retention time (min)	purity (%)
M8		$C_{57}H_{77}N_5O_{12}$	1024.58	10.1	91.9
M9		$C_{59}H_{81}N_5O_{12}$	1052.69	10.3	85.6
M10		$C_{63}H_{81}N_5O_{12}$	1100.55	10.5	86.3
M11		$C_{59}H_{81}N_5O_{12}$	1052.69	10.4	85.8
M12		$C_{63}H_{89}N_5O_{12}$	1108.69	10.8	86.8
M13		$C_{66}H_{87}N_5O_{12}$	1142.64	10.8	84.2
M14		$C_{59}H_{81}N_5O_{11}$	1036.64	10.6	83.9
M15		$C_{59}H_{80}ClN_5O_{11}$	1070.59	10.8	83.3
M16		$C_{65}H_{85}N_5O_{11}$	1112.76	11.0	71.9

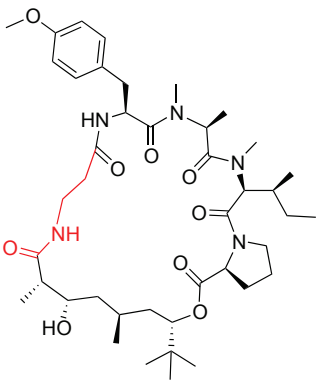
Figure S13. LC-MS analysis of linear Fmoc-hexadepsipeptides obtained by cleavage of **12a–g** and **18**



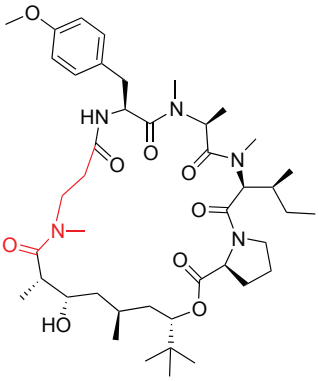
apratoxin M1
Yield 25%
IC_{50} 2.6 μM
trans : cis = 1 : 1



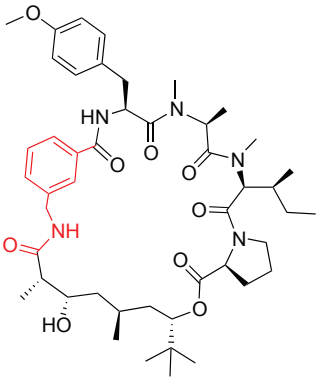
apratoxin M2
Yield 28%
IC_{50} 0.34 μM
trans : cis = 1.2 : 1



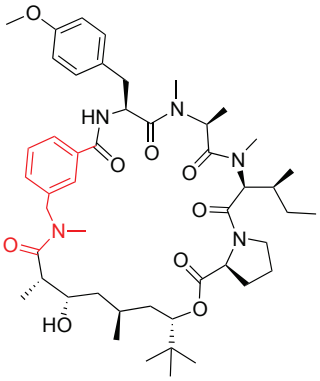
apratoxin M3
Yield 44%
IC_{50} 3.4 μM
trans : cis = 1 : >9



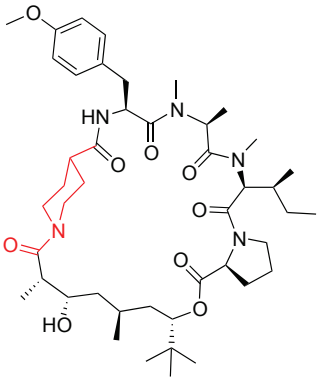
apratoxin M4
Yield 31%
IC_{50} 3.1 μM
trans : cis = 1 : >1.5



apratoxin M5
Yield 23%
IC_{50} 0.82 μM
trans : cis = 2 : 1



apratoxin M6
Yield 30%
IC_{50} 0.22 μM
trans : cis = 2.8 : 1



apratoxin M7
Yield 16%
IC_{50} 0.12 μM
trans : cis = 1 : 2

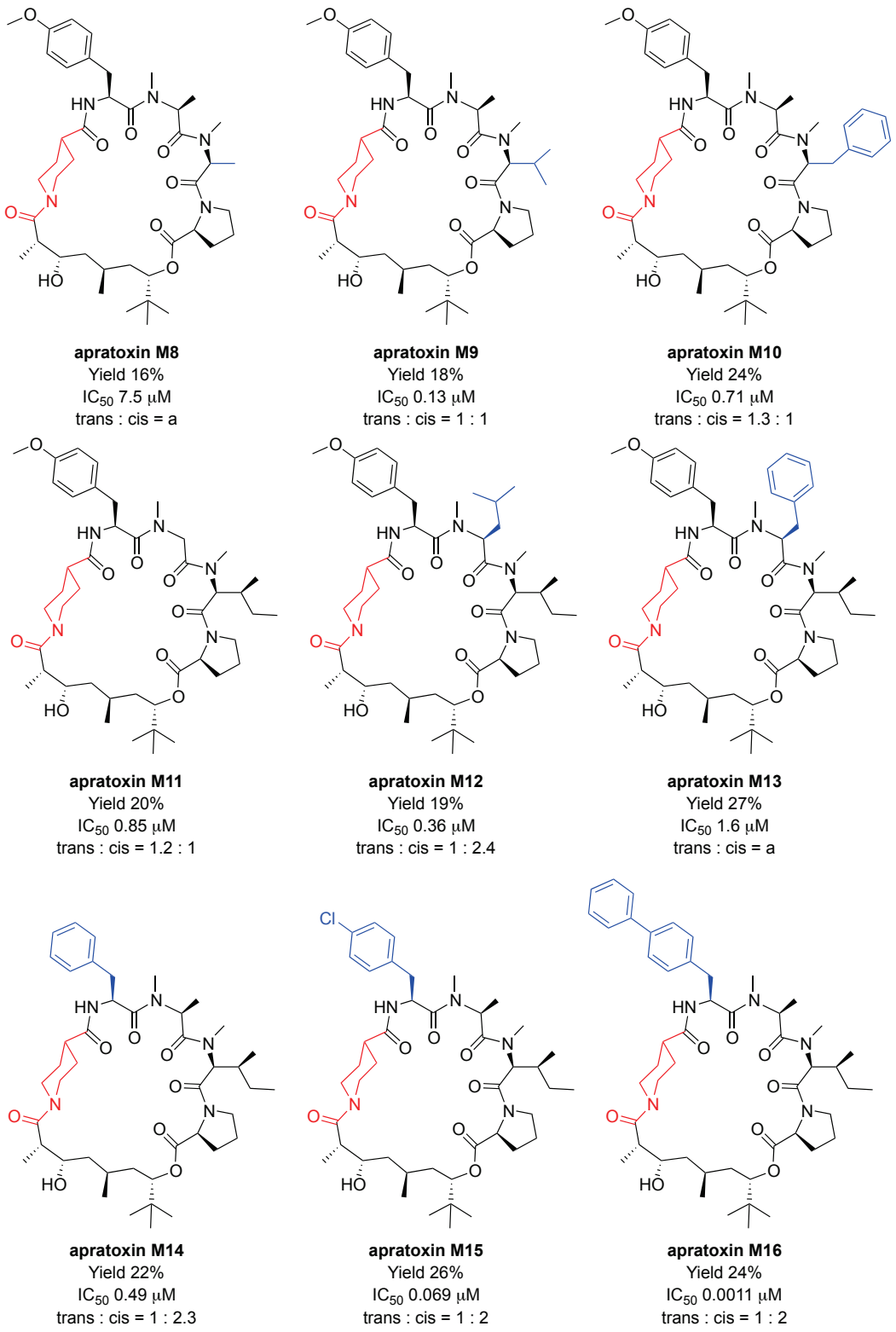
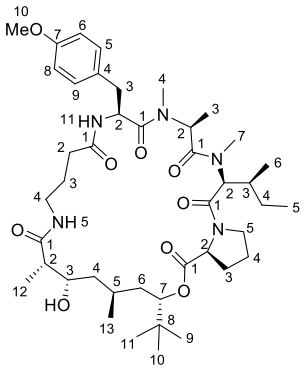
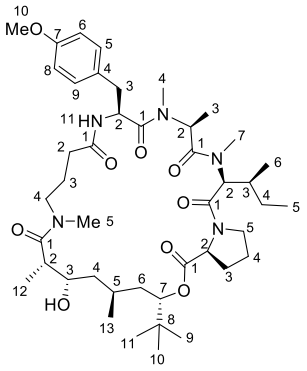


Figure S14. Summary of yields, IC_{50} values against HCT-116 cells, and ratios of trans/cis amide bond orientation in apratoxins M1–M8 (**4a–g**) and M9–M16 (**13a–i**). [a]Not determined due to the broad spectrum



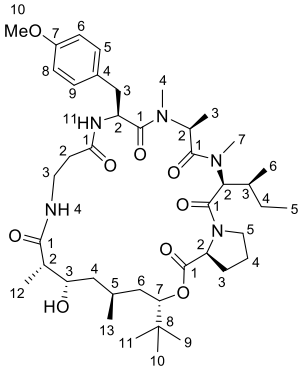
apratoxin M1 (**4a**)

unit	C/H no.	trans-amide conformer **A**		cis-amide conformer **B**	
		δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
Pro	1	-	173.4	-	172.0
	2	4.11 (dd, J = 7.8, 7.8, 1 H)	60.7	4.27 (dd, J = 8.3, 6.5, 1 H)	60.2
	3a	1.78 (m, 1 H)	29.9	1.89 (m, 1 H)	29.9
	3b	2.30 (m, 1 H)	29.9	2.29 (m, 1 H)	29.9
	4a	1.80 (m, 1 H)	25.7	1.90 (m, 1 H)	25.6
	4b	1.87 (m, 1 H)	25.7	1.90 (m, 1 H)	25.6
	5a	3.62 (m, 1 H)	48.5	3.62 (m, 1 H)	48.5
	5b	3.99 (m, 1 H)	48.5	4.02 (m, 1 H)	48.5
N-Me-Ile	1	-	171.2	-	171.1
	2	5.24 (d, J = 11.5, 1 H)	56.7	4.92 (d, J = 11.4, 1 H)	58.6
	3	2.04 (m, 1 H)	33.6	2.06 (m, 1 H)	34.7
	4a	1.21 (m, 1 H)	26.1	0.99 (m, 1 H)	26.2
	4b	1.41 (m, 1 H)	26.1	1.30 (m, 1 H)	26.2
	5	0.87 (m, 3 H)	9.3	0.85 (m, 3 H)	9.9
	6	0.99 (d, J = 7.0, 3 H)	15.3	1.05 (d, J = 7.1, 3 H)	14.2
	7	2.65 (s, 3 H)	31.0	2.82 (s, 3 H)	31.0
N-Me-Ala	1	-	170.9	-	171.2
	2	3.36 (m, 1 H)	61.2	4.74 (q, J = 6.3, 1 H)	54.9
	3	1.05 (d, J = 7.1, 3 H)	14.4	0.66 (d, J = 6.6, 3 H)	15.6
	4	2.89 (s, 3 H)	37.2	2.55 (s, 3 H)	29.1
O-Me-Tyr	1	-	N.D.	-	172.8
	2	5.01 (m, 1 H)	N.D.	5.11 (ddd, J = 10.5, 9.2, 5.7, 1 H)	51.0
	3a	2.78 (m, 1 H)	N.D.	2.99 (dd, J = 13.6, 5.6, 1 H)	39.8
	3b	2.94 (m, 1 H)	N.D.	2.84 (dd, J = 12.7, 9.0, 1 H)	39.8
	4	-	130.2	-	130.2
	5 / 9	7.14 (d, J = 8.9, 2 H)	131.3	7.10 (d, J = 8.9, 1 H)	131.3
	6 / 8	6.83 (d, J = 8.9, 2 H)	114.7	6.82 (d, J = 8.9, 1 H)	114.6
	7	-	159.6	-	159.5
	10	3.74 (s, 3 H)	55.7	3.73 (s, 3 H)	55.7
	11	6.83 (m, 1 H)	-	6.89 (m, 1 H)	-
n-Pr	1	-	173.2	-	N.D.
	2a	2.10 (m, 1 H)	34.1	2.12 (m, 1 H)	33.7
	2b	2.00 (m, 1 H)	34.1	2.12 (m, 1 H)	33.7
	3a	1.71 (m, 1 H)	26.2	1.66 (m, 1 H)	26.2
	3b	1.54 (m, 1 H)	26.2	1.60 (m, 1 H)	26.2
	4a	3.36 (m, 1 H)	39.5	3.07 (m, 1 H)	39.7
	4b	2.81 (m, 1 H)	39.5	3.07 (m, 1 H)	39.7
	5	6.39 (m, 1 H)	-	6.71 (m, 1 H)	-
Dtena	1	-	176.4	-	177.1
	2	1.88 (dq, J = 10.1, 7.1, 1 H)	50.6	2.07 (dq, J = 8.8, 7.1, 1 H)	49.8
	3	3.58 (dddd, J = 11.2, 10.1, 8.2 , 3.1, 1 H)	71.5	3.52 (dddd, J = 11.6, 10.2, 8.8, 3.1, 1 H)	71.8
	4a	1.13 (ddd, J = 14.4, 11.4, 3.1, 1 H)	39.4	1.15 (ddd, J = 14.1, 11.1, 3.1, 1 H)	40.3
	4b	1.45 (ddd, J = 14.1, 11.2, 3.6, 1 H)	39.4	1.32 (ddd, J = 14.1, 11.6, 3.4, 1 H)	40.3
	5	2.09 (ddqdd, J = 12.1, 11.4, 7.1, 3.6, 3.2, 1 H)	26.2	1.99 (ddqdd, J = 11.1, 10.2, 7.1, 3.4, 3.2, 1 H)	25.7
	6a	1.33 (ddd, J = 14.1, 12.1, 2.1, 1 H)	38.3	1.41 (ddd, J = 14.3, 10.2, 2.7, 1 H)	37.6
	6b	1.72 (ddd, J = 14.3, 12.1, 3.2, 1 H)	38.3	1.72 (ddd, J = 14.3, 12.1, 3.2, 1 H)	37.6
	7	4.89 (dd, J = 12.5, 2.1, 1 H)	78.1	4.85 (dd, J = 12.0, 2.7, 1 H)	78.5
	8	-	35.5	-	35.5
	9 / 10 / 11	0.86 (s, 9 H)	26.3	0.86 (s, 9 H)	26.3
	12	0.93 (d, J = 7.1, 3 H)	14.7	1.00 (d, J = 7.0, 3 H)	15.4
	13	0.92 (d, J = 7.1, 3 H)	20.2	0.93 (d, J = 7.1, 3 H)	19.9
	OH	4.43 (d, J = 8.2, 1 H)	-	4.04 (d, J = 10.2, 1 H)	-



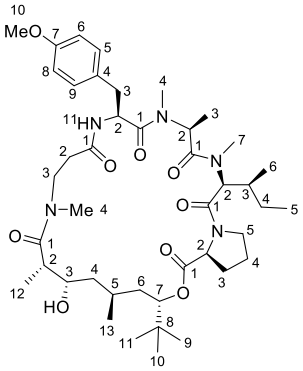
apratoxin M2 (**4b**)

unit	C/H no.	trans-amide conformer **A** (major)		cis-amide conformer **B** (minor)	
		δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
Pro	1	-	173.0		
	2	4.10 (dd, J = 9.3, 7.0, 1 H)	60.8		
	3a	1.78 (m, 1 H)	30.0		
	3b	2.29 (m, 1 H)	30.0		
	4a	2.25 (m, 1 H)	25.7		
	4b	1.87 (m, 1 H)	25.7		
	5a	3.61 (m, 1 H)	48.7		
	5b	4.03 (m, 1 H)	48.7		
N-Me-Ile	1	-	171.6		
	2	5.27 (d, J = 11.0, 1 H)	55.9		
	3	2.04 (m, 1 H)	33.1		
	4a	1.16 (m, 1 H)	26.0		
	4b	1.35 (m, 1 H)	26.0		
	5	0.88 (m, 3 H)	8.9		
	6	0.93 (d, J = 7.0, 3 H)	14.5		
	7	2.66 (s, 3 H)	31.2	2.83 (s, 3 H)	31.2
N-Me-Ala	1	-	171.0		
	2	3.36 (m , 1 H)	60.8	4.71 (q, J = 6.6, 1 H)	54.3
	3	1.03 (d, J = 6.4, 3 H)	14.4	0.48 (d, J = 6.4, 1 H)	15.2
	4	2.92 (s, 3 H)	37.5	2.53 (s, 3 H)	29.0
O-Me-Tyr	1	-	N.D.		
	2	4.99 (m, 1 H)	N.D.	5.09 (ddd, J = 10.6, 8.7, 5.2, 1 H)	51.3
	3a	2.78 (m, 1 H)	37.6		
	3b	2.94 (m, 1 H)	37.6		
	4	-	129.9		
	5 / 9	7.14 (d, J = 8.9, 2 H)	131.4		
	6 / 8	6.83 (d, J = 8.9, 2 H)	114.6		
	7	-	159.5		
	10	3.74 (s, 3 H)	55.8		
	11	6.81 (m, 1 H)	-	6.73 (m, 1 H, s)	-
N-Me-*n*-Pr	1	-	172.8		
	2a	2.09 (m, 1 H)	34.5		
	2b	1.92 (m, 1 H)	34.5		
	3a	1.74 (m, 1 H)	30.1		
	3b	1.56 (m, 1 H)	30.1		
	4a	3.90 (m, 1 H)	49.8		
	4b	2.43 (m, 1 H)	49.8		
	5	3.01 (s, 3 H)	37.6		
Dtena	1	-	176.5	-	
	2	2.58 (dq, J = 9.4, 6.8, 1 H)	43.8	2.62 (dq, J = 9.7, 6.7, 1 H)	
	3	3.66 (m, 1 H)	73.3	3.70 (m, 1 H)	
	4a	1.17 (ddd, J = 14.8, 11.0, 2.9, 1 H)	40.3	1.16 (ddd, J = 14.2, 11.7, 3.1, 1 H)	
	4b	1.48 (ddd, J = 13.8, 11.0, 2.9, 1 H)	40.3	1.36 (ddd, J = 14.1, 11.2, 3.2, 1 H)	
	5	2.04 (ddqdd, J = 11.5, 11.0, 6.8, 2.9, 2.5, 1 H)	25.6	1.89 (ddqdd, J = 11.7, 11.4, 6.7, 3.2, 2.8, 1 H)	
	6a	1.35 (ddd, J = 14.9, 11.5, 2.2, 1 H)	25.6	1.37 (ddd, J = 15.1, 11.4, 2.8, 1 H)	
	6b	1.66 (ddd, J = 14.1, 12.3, 2.5, 1 H)	38.8	1.69 (ddd, J = 14.8, 12.4, 2.8, 1 H)	
	7	4.87 (dd, J = 12.5, 2.0, 1 H)	78.4	4.81 (dd, J = 12.2, 2.7, 1 H)	
	8	-	35.2	-	
	9 / 10 / 11	0.86 (s, 9 H)	26.4	0.86 (s, 9 H)	
	12	0.88 (d, J = 7.1, 3 H)	14.4	0.90 (d, J = 6.7, 3 H)	
	13	0.93 (d, J = 6.8, 3 H)	20.8	0.92 (d, J = 6.7, 3 H)	
	OH	N.D.	-	N.D.	



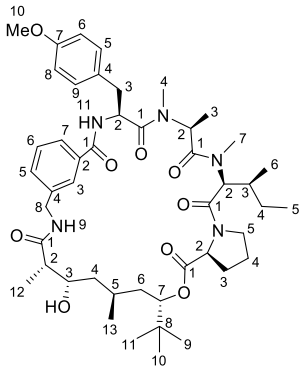
apratoxin M3 (**4c**)

unit	C/H no.	cis-amide conformer (major)	
		δ_H (J in Hz)	δ_C
Pro	1	-	
	2	4.22 (dd, J = 8.2, 8.2, 1 H)	
	3a	1.83 (m, 1 H)	
	3b	2.21 (m, 1 H)	
	4a	1.85 (m, 1 H)	
	4b	1.95 (m, 1 H)	
	5a	3.60 (m, 1 H)	
	5b	4.04 (m, 1 H)	
N-Me-Ile	1	-	
	2	4.89 (d, J = 11.4, 1 H)	
	3	1.90 (m, 1 H)	
	4	1.10 – 0.90 (m, 2 H)	
	5	0.81 (dd, J = 7.4, 7.4, 3 H)	
	6	1.08 (d, J = 6.8, 3 H)	
	7	2.84 (s, 3 H)	30.9
	1	-	
N-Me-Ala	2	4.82 (q, J = 6.7, 1 H)	54.9
	3	0.59 (d, J = 6.7 3 H)	15.2
	4	2.50 (s, 3 H)	28.8
	1	-	
O-Me-Tyr	2	5.27 (ddd, J = 9.5, 9.5, 5.8, 1 H)	50.2
	3a	2.97 (dd, J = 12.7, 9.5, 1 H)	
	3b	2.78 (dd, J = 12.7, 5.8, 1 H)	
	4	-	
	5 / 9	7.11 (d, J = 8.8, 2 H)	
	6 / 8	6.82 (d, J = 8.8, 2 H)	
	7	-	
	10	3.73 (s, 3 H)	
	11	6.89 (br, 1 H)	
Et	1	-	
	2a	2.30 (m, 1 H)	
	2b	2.30 (m, 1 H)	
	3a	3.19 (m, 1 H)	
	3b	3.54 (m, 1 H)	
	4	7.79 (m, 1 H)	
Dtena	1	-	
	2	2.13 (dq, J = 9.3, 7.2, 1 H)	
	3	3.53 (dddd, J = 11.6, 11.2, 9.3, 2.8, 1 H)	
	4a	1.06 (ddd, J = 14.6, 11.6, 3.6, 1 H)	
	4b	1.47 (ddd, J = 14.6, 11.6, 2.8, 1 H)	
	5	1.96 (ddqdd, J = 11.6, 11.1, 6.7, 3.6, 3.4, 1 H)	
	6a	1.35 (ddd, J = 14.6, 11.1, 3.0, 1 H)	
	6b	1.76 (ddd, J = 14.6, 12.4, 3.4, 1 H)	
	7	4.84 (dd, J = 12.3, 3.1, 1 H)	
	8	-	
	9 / 10 / 11	0.87 (s, 9 H)	
	12	0.94 (d, J = 7.2, 3 H)	
	13	0.92 (d, J = 6.7, 3 H)	
	OH	4.31 (d, J = 11.2, 1 H)	



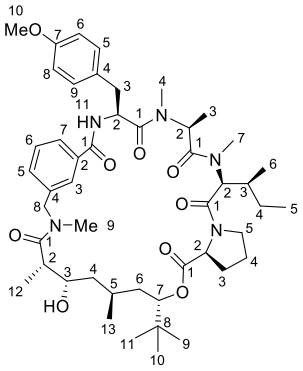
apratoxin M4 (**4d**)

unit	C/H no.	cis-amide conformer (major)	
		δ_H (J in Hz)	δ_C
Pro	1	-	
	2	4.13 (dd, J = 7.7, 7.7, 1 H)	
	3a	1.80 (m, 1 H)	
	3b	2.26 (m, 1 H)	
	4a	1.86 (m, 1 H)	
	4b	1.95 (m, 1 H)	
	5a	3.59 (m, 1 H)	
	5b	4.01 (m, 1 H)	
N-Me-Ile	1	-	
	2	4.85 (d, J = 11.3, 1 H)	
	3	1.94 (m, 1 H)	
	4a	1.01 (m, 1 H)	
	4b	1.30 (m, 1 H)	
	5	0.85 (dd, J = 7.5, 7.5, 3 H)	
	6	1.13 (d, J = 6.8, 3 H)	
	7	2.86 (s, 3 H)	31.1
N-Me-Ala	1	-	
	2	4.75 (q, J = 6.6, 1 H)	54.0
	3	0.39 (d, J = 6.7 3 H)	14.8
	4	2.52 (s, 3 H)	28.6
O-Me-Tyr	1	-	50.6
	2	5.25 (dd, J = 9.4, 7.3, 1 H)	
	3	2.88 (m, 2 H)	
	4	-	
	5 / 9	7.08 (d, J = 8.9, 2 H)	
	6 / 8	6.80 (d, J = 8.9, 2 H)	
	7	-	
	10	3.72 (s, 3 H)	
	11	6.86 (m, 1 H)	
N-Me-Et	1	-	
	2a	2.31 (m, 1 H)	
	2b	2.31 (m, 1 H)	
	3a	2.70 (m, 1 H)	
	3b	2.63 (m, 1 H)	
	4	2.84 (s, 3 H)	
Dtena	1	-	
	2	2.58 (dq, J = 9.1, 7.0, 1 H)	
	3	3.90 (m, 1 H)	
	4a	1.07 (ddd, J = 14.3, 11.3, 3.3, 1 H)	
	4b	1.47 (ddd, J = 13.7, 10.6, 3.1, 1 H)	
	5	1.96 (ddqdd, J = 12.4, 10.6, 6.7, 3.3, 3.1, 1 H)	
	6a	1.36 (ddd, J = 14.2, 11.5, 3.1, 1 H)	
	6b	1.73 (ddd, J = 14.2, 12.4, 3.2, 1 H)	
	7	4.79 (dd, J =11.9, 3.1, 1 H)	
	8	-	
	9 / 10 / 11	0.86 (s, 9 H)	
	12	0.89 (d, J = 7.0, 3 H)	
	13	0.92 (d, J = 6.7, 3 H)	
	OH	3.73 (m, 1 H)	



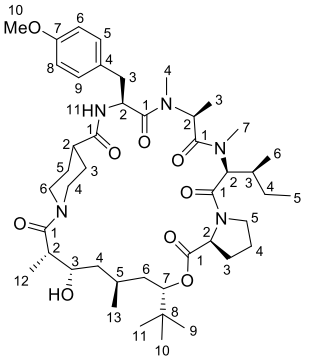
apratoxin M5 (**4e**)

unit	C/H no.	trans-amide conformer **A** (major)		cis-amide conformer **B** (minor)	
		δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
Pro	1	-	173.2		
	2	4.11 (dd, *J* = 8.0, 8.0, 1 H)	60.6		
	3a	1.76 (m, 1 H)	30.1		
	3b	2.27 (m, 1 H)	30.1		
	4a	1.84 (m, 1 H)	25.9		
	4b	1.99 (m, 1 H)	25.9		
	5a	3.55 (m, 1 H)	48.4		
	5b	4.08 (m, 1 H)	48.4		
N-Me-Ile	1	-	171.6		
	2	4.98 (d, *J* = 11.4, 1 H)	57.6		
	3	1.76 (m, 1 H)	33.0		
	4a	0.53 (br, 1 H)	25.0		
	4b	0.59 (br, 1 H)	25.0		
	5	0.15 (m, 3 H)	8.6		
	6	0.74 (br, 3 H)	14.4		
	7	2.73 (br, 3 H)	30.7	2.89 (s, 3 H)	31.1
N-Me-Ala	1	-	171.0		
	2	3.39 (br, 1 H)	61.1	4.87 (q, *J* = 6.96, 1 H)	54.6
	3	1.07 (d, *J* = 6.84, 3 H)	14.4	0.76 (d, *J* = 6.84)	15.1
	4	2.94 (br, 3 H)	37.3	2.61 (s, 3 H)	29.5
O-Me-Tyr	1	-	172.2		
	2	5.06 (br, 1 H)	51.5	5.31 (ddd, *J* = 8.4, 8.4, 6.4, 1 H)	51.5
	3a	3.10 (br, 1 H)	37.2	3.10 (dd, *J* = 13.0, 8.6, 1 H)	37.2
	3b	2.98 (br, 1 H)	37.2	2.98 (dd, *J* = 13.0, 6.1, 1 H)	37.2
	4	-	131.6		
	5 / 9	7.22 (d, *J* = 8.8, 2 H)	131.6		
	6 / 8	6.87 (d, *J* = 8.8, 2 H)	114.7		
	7	-	159.7		
	10	3.75 (s, 3 H)	54.8	3.74 (s, 3 H)	54.8
	11	7.28 (br, 1 H)	-	7.20 (br, 1 H)	-
mamb	1	-	168.6		
	2	-	136.1		
	3	7.64 (m, 1 H)	129.2	7.40 (m, 1 H)	
	4	-	141.4		
	5	7.41 (m, 1 H)	132.8	7.38 (m, 1 H)	
	6	7.34 (m, 1 H)	129.1	7.36 (m, 1 H)	
	7	7.61 (m, 1 H)	126.1	7.45 (m, 1 H)	
	8a	4.85 (dd, *J* = 14.6, 8.6, 1 H)	43.6	4.51 (m, 1 H)	45.8
	8b	3.90 (dd, *J* = 14.6, 4.0, 1 H)	43.6	4.13 (m, 1 H)	45.8
	9	6.59 (br, 1 H)	-	6.90 (br, 1 H)	-
Dtena	1	-	176.7	-	
	2	1.84 (dq, *J* = 10.0, 7.4, 1 H)	50.9	2.07 (dq, *J* = 9.9, 7.0, 1 H)	51.9
	3	3.78 (m, 1 H)	70.2	3.56 (m, 1 H)	71.3
	4a	1.07 (ddd, *J* = 14.4, 10.8, 2.6, 1 H)	38.3	1.08 (ddd, *J* = 14.5, 11.2, 3.1, 1 H)	39.7
	4b	1.52 (ddd, *J* = 14.0, 11.8, 4.0, 1 H)	38.3	1.41 (ddd, *J* = 14.1, 11.7, 3.6, 1 H)	39.7
	5	2.06 (ddqdd, *J* = 11.7, 10.8, 6.9, 4.0, 2.2, 1 H)	24.8	1.94 (ddqdd, *J* = 11.7, 11.2, 6.8, 3.6, 2.2, 1 H)	26.3
	6a	1.31 (ddd, *J* = 14.0, 11.7, 2.5, 1 H)	38.6	1.31 (ddd, *J* = 14.0, 11.7, 2.5, 1 H)	38.6
	6b	1.74 (ddd, *J* = 14.4, 12.2, 2.2, 1 H)	38.6	1.74 (ddd, *J* = 14.4, 12.2, 2.2, 1 H)	38.6
	7	4.92 (dd, *J* =12.6, 2.2, 1 H)	78.0	4.89 (dd, *J* = 12.4, 2.7, 1 H)	78.0
	8	-	35.4	-	35.4
	9 / 10 / 11	0.86 (s, 9 H)	26.2	0.86 (s, 9 H)	26.2
	12	0.97 (d, *J* = 6.94, 3 H)	15.3	0.99 (d, *J* = 6.8, 3 H)	15.5
	13	0.99 (d, *J* = 6.90, 3 H)	19.6	1.01 (d, *J* = 6.8, 3 H)	14.3
	OH	4.27 (m, 1 H)	-	4.25 (m, 1 H)	-



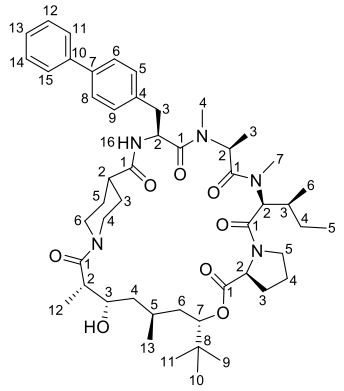
apratoxin M6 (**4f**)

unit	C/H no.	trans-amide conformer **A** (major)		cis-amide conformer **B** (minor)	
		δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
Pro	1	-	173.0		
	2	4.06 (dd, J = 8.0, 8.0, 1 H)	60.8		
	3a	1.74 (m, 1 H)	30.1		
	3b	2.25 (m, 1 H)	30.1		
	4a	1.84 (m, 1 H)	26.2		
	4b	1.99 (m, 1 H)	26.2		
	5a	3.53 (m, 1 H)	48.3		
	5b	4.12 (m, 1 H)	48.3		
N-Me-Ile	1	-	172.0		
	2	4.97 (d, J = 11.4, 1 H)	57.2		
	3	1.72 (m, 1 H)	32.9		
	4a	0.60 (m, 1 H)	25.2		
	4b	0.62 (m, 1 H)	25.2		
	5	0.13 (dd, J = 7.3, 7.3, 3 H)	8.8		
	6	0.72 (m, 3 H)	14.3		
	7	2.74 (s, 3 H)	30.5	2.88 (s, 3 H)	30.8
N-Me-Ala	1	-	170.8	-	171.5
	2	3.39 (m, 1 H)	61.0	4.92 (m, 1 H)	54.1
	3	1.06 (d, J = 6.8, 3 H)	14.5	0.68 (d, J = 6.6, 3 H)	15.8
	4	2.93 (s, 3 H)	37.2	2.58 (s, 3 H)	29.1
O-Me-Tyr	1	-	171.3	-	172.4
	2	5.04 (m, 1 H)	51.6	5.41 (ddd, 10.5, 9.0, 6.1, 1 H)	51.3
	3a	3.08 (m, 1 H)	37.5	3.10 (m, 1 H)	
	3b	2.98 (m, 1 H)	37.5	2.99 (m, 1 H)	
	4	-	131.4		
	5 / 9	7.27 (d, J = 9.1, 2 H)	131.6		
	6 / 8	6.86 (d, J = 9.1, 2 H)	114.6		
	7	-	159.4		
	10	3.75 (s, 3 H)	55.8		
	11	7.32 (m, 1 H)	-		
N-Me-mamb	1	-	168.2		
	2	-	136.2		
	3	7.59 (m, 1 H)	129.3		
	4	-	140.1		
	5	7.43 (m, 1 H)	133.7		
	6	7.36 (m, 1 H)	128.9		
	7	7.63 (m, 1 H)	126.4		
	8a	5.74 (d, J = 14.3, 1 H)	50.3		
	8b	3.38 (d, J = 14.3, 1 H)	50.3		
	9	2.77 (s, 3 H)	34.4	2.98(s, 3 H)	35.2
Dtena	1	-	176.2	-	177.2
	2	2.46 (dq, J = 10.3, 7.0, 1 H)	45.6	2.68 (dq, J = 9.9, 7.0, 1 H)	
	3	3.90 (dddd, J = 11.3, 10.3, 7.4, 3.3, 1 H)	70.8	3.88 (m, 1 H)	
	4a	1.14 (ddd, J = 14.3, 11.3, 3.3, 1 H)	39.0	1.13 (ddd, J = 14.2, 10.8, 3.2, 1 H)	
	4b	1.57 (ddd, J = 14.7, 11.8, 3.7, 1 H)	39.0	1.47 (ddd, J = 14.4, 11.6, 3.2, 1 H)	
	5	2.13 (ddqdd, J = 12.1, 11.3, 6.8, 3.7, 2.7, 1 H)	24.7	1.95 (ddqdd, J = 11.1, 10.8, 6.8, 3.3, 3.2, 1 H)	
	6a	1.33 (ddd, J = 14.0, 12.1, 2.3, 1 H)	38.8	1.34 (ddd, J = 14.4, 11.1, 2.9, 1 H)	
	6b	1.72 (ddd, J = 14.7, 12.1, 2.7, 1 H)	38.8	1.76 (ddd, J = 14.0, 12.4, 3.3 1 H)	
	7	4.89 (dd, J =12.4, 2.1, 1 H)	77.9	4.86 (dd, J =12.5, 2.5, 1 H)	
	8	-	35.2	-	
	9 / 10 / 11	0.86 (s, 9 H)	25.4	0.86 (s, 9 H)	
	12	0.95 (d, J = 7.0, 3 H)	15.0	0.95 (d, J = 7.0, 3 H)	
	13	0.97 (d, J = 6.8, 3 H)	20.2	0.94 (d, J = 6.8, 3 H)	
	OH	4.13 (d, J = 7.4, 1 H)	-	3.82 (m, 1 H)	



apratoxin M7 (**4g**)

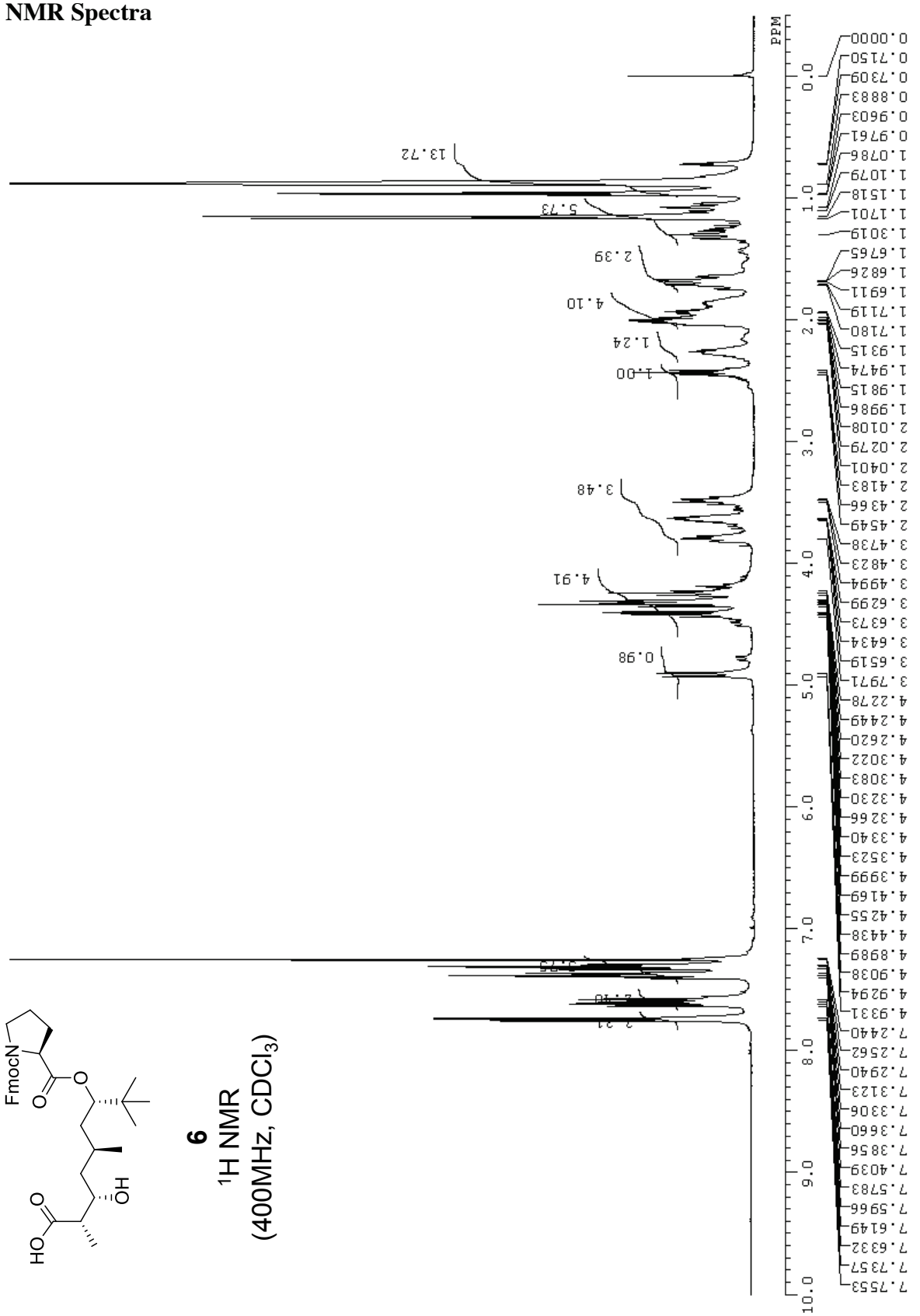
unit	C/H no.	cis-amide conformer **B** (major)		trans-amide conformer **A** (minor)	
		δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
Pro	1	-	172.2		N.D.
	2	4.16 (dd, J = 7.7, 7.7, 1 H)	60.9	4.12 (m, 1 H)	60.7
	3a	1.83 (m, 1 H)	30	1.78 (m, 1 H)	29.9
	3b	2.26 (m, 1 H)	30	2.29 (m, 1 H)	29.9
	4a	1.95 (m, 1 H)	25.9	1.86 (m, 1 H)	26
	4b	1.87 (m, 1 H)	25.9	2.02 (m, 1 H)	26
	5a	3.56 (m, 1 H)	48.5	3.61 (m, 1 H)	48.7
	5b	3.91 (m, 1 H)	48.5	3.67 (m, 1 H)	48.7
N-Me-Ile	1	-	171.1	-	N.D.
	2	4.96 (d, J = 11.7, 1 H)	58.3	5.28 (d, J = 11.2, 1 H)	57.3
	3	1.95 (m, 1 H)	35.0	1.78 (m, 1 H)	34.8
	4a	1.31 (m, 1 H)	26.2	1.28 (m, 1 H)	26.9
	4b	0.88 (m, 1 H)	26.2	0.96 (m, 1 H)	26.9
	5	0.84 (dd, J = 7.5, 7.5, 3 H)	10.1	0.92 (m, 1 H)	26.9
	6	1.02 (d, J = 7.0, 3 H)	14.2	0.90 (d, J = 6.8, 3 H)	14.6
	7	2.80 (s, 3 H)	31.8	2.64 (s, 3 H)	31.7
N-Me-Ala	1	-	170.9	-	170.9
	2	4.82 (q, J = 6.6, 1 H)	55.8	3.34 (m, 1 H)	61.6
	3	0.67 (d, J = 6.6, 3 H)	15.9	1.05 (d, J = 6.5, 3 H)	14.6
	4	2.53 (s, 3 H)	29.3	2.88 (s, 3 H)	37.5
O-Me-Tyr	1	-	172.9	-	172.3
	2	5.15 (ddd, J = 10.2, 9.0, 5.6, 1 H)	50.6	5.00 (m, 1 H)	51.4
	3a	2.80 (m, 1 H)	40.3	2.74 (m, 1 H)	N.D.
	3b	2.99 (m, 1 H)	40.3	2.93 (m, 1 H)	N.D.
	4	-	130.1	-	130.1
	5 / 9	7.10 (d, J = 8.9, 2 H)	131.5	7.15 (d, J = 8.9, 2 H)	131.5
	6 / 8	6.82 (d, J = 8.9, 2 H)	114.8	6.84 (d, J = 8.9, 2 H)	114.8
	7	-	159.7	-	159.7
	10	3.73 (s, 3 H)	55.8	3.74 (s, 3 H)	55.8
	11	6.97 (m, 1 H)	-	6.88 (m, 1 H)	-
piperidine	1	-	174.9	-	N.D.
	2	2.49 (m, 1 H)	41.9	2.49 (m, 1 H)	43
	3a	1.37 (m, 1 H)	32.1	1.54 (m, 1 H)	33.1
	3b	1.62 (m, 1 H)	32.1	1.79 (m, 1 H)	33.1
	4a	3.93 (m, 1 H)	46.4	4.00 (m, 1 H)	46.5
	4b	3.08 (m, 1 H)	46.4	3.08 (m, 1 H)	46.5
	5a	1.54 (m, 1 H)	27.1	1.56 (m, 1 H)	26.8
	5b	1.62 (m, 1 H)	27.1	1.60 (m, 1 H)	26.8
	6a	4.39 (m, 1 H)	41.7	4.48 (m, 1 H)	42.3
	6b	2.67 (m, 1 H)	41.7	2.58 (m, 1 H)	42.3
Dtena	1	-	175.8	-	176.6
	2	2.82 (m, 1 H)	41.9	2.65 (m, 1 H)	44.2
	3	3.59 (m, 1 H)	73.1	3.85 (m, 1 H)	72.8
	4a	1.23 (ddd, J = 14.2, 10.2, 2.7, 1 H)	42.8	1.10 (ddd, J = 13.8, 10.1, 2.2, 1 H)	38
	4b	1.35 (ddd, J = 14.2, 9.1, 3.1, 1 H)	42.8	1.50 (ddd, J = 13.6, 11.6, 3.4, 1 H)	38
	5	1.80 (ddqdd, J = 10.2, 6.8, 6.6, 5.7, 3.1, 1 H)	27.5	2.10 (ddqdd, J = 10.8, 10.1, 6.7, 3.4, 2.5, 1 H)	25.9
	6a	1.53 (ddd, J = 14.4, 6.8, 4.2, 1 H)	38.2	1.38 (ddd, J = 14.1, 10.8, 2.1, 1 H)	39.1
	6b	1.61 (ddd, J = 14.4, 8.9, 5.7, 1 H)	38.2	1.75 (ddd, J = 14.4, 11.1, 2.5, 1 H)	39.1
	7	4.76 (dd, J = 8.9, 4.2, 1 H)	79.8	4.84 (dd, J = 12.4, 2.2, 1 H)	78.6
	8	-	35.7	-	35.7
	9 / 10 / 11	0.88 (s, 9 H)	26.3	0.87 (s, 9 H)	26.3
	12	1.02 (d, J = 7.0, 3 H)	14.3	0.87 (m, 3 H)	15.6
	13	0.91 (d, J = 6.6, 3 H)	20.8	0.94 (d, J = 6.7, 3 H)	20.3
	OH	N.D.	-	N.D.	-

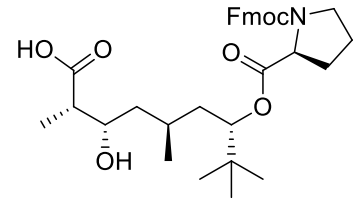


apratoxin M16 (**13i**)

unit	C/H no.	cis-amide conformer **B** (major)		trans-amide conformer **A** (minor)	
		δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
Pro	1	-	172.2		173.0
	2	4.16 (dd, J = 7.9, 7.9, 1 H)	60.7	4.12 (m, 1 H)	60.5
	3a	1.83 (m, 1 H)	30.0	1.79 (m, 1 H)	29.9
	3b	2.26 (m, 1 H)	30.0	2.29 (m, 1 H)	29.9
	4a	1.93 (m, 1 H)	25.9	1.86 (m, 1 H)	26.0
	4b	1.87 (m, 1 H)	25.9	2.02 (m, 1 H)	26.0
	5a	3.56 (m, 1 H)	48.3	3.61 (m, 1 H)	48.6
	5b	3.90 (m, 1 H)	48.3	3.67 (m, 1 H)	48.6
N-Me-Ile	1	-	171.1	-	
	2	4.96 (d, J = 11.3, 1 H)	58.3	5.30 (d, J = 10.9)	57.1
	3	1.96 (m, 1 H)	34.9	1.80 (m, 1 H)	34.9
	4a	1.31 (m, 1 H)	26.3	1.28 (m, 1 H)	26.9
	4b	0.91 (m, 1 H)	26.3	0.96 (m, 1 H)	26.9
	5	0.83 (dd, J = 7.4, 7.4, 3 H)	10.1	0.92 (m, 1 H)	9.7
	6	1.02 (d, J = 6.8, 3 H)	14.3	0.90 (d, J = 6.8, 3 H)	14.6
	7	2.81 (s, 3 H)	31.6	2.66 (s, 3 H)	31.4
N-Me-Ala	1	-	170.9	-	170.9
	2	4.84 (q, J = 6.7, 1 H)	55.7	3.35 (m, 1 H)	61.8
	3	0.67 (d, J = 6.7, 3 H)	15.7	1.04 (d, J = 6.7, 3 H)	14.5
	4	2.55 (s, 3 H)	29.2	2.93 (s, 3 H)	37.5
O-Me-Tyr	1	-	172.7	-	N.D.
	2	5.24 (ddd, J = 9.6, 8.9, 6.1, 1 H)	50.4	5.09 (m, 1 H)	51.1
	3a	3.10 (dd, J = 12.9, 8.9, 1 H)	40.7	3.04 (m, 1 H)	N.D.
	3b	2.93 (dd, J = 12.9, 6.1, 1 H)	40.7	2.91 (m, 1 H)	N.D.
	4-15	7.65-7.52 (m, 4 H)	127.84, 127.90, 128.02, 128.05, 128.41, 128.44,	7.65-7.52 (m, 4 H)	127.84, 127.90, 128.02, 128.05, 128.41, 128.44,
	4-15	7.47-7.42 (m, 2 H)	129.96, 131.07, 131.12, 137.54, 140.43, 140.50,	7.47-7.42 (m, 2 H)	129.96, 131.07, 131.12, 137.54, 140.43, 140.50,
	4-15	7.38-7.27 (m, 3 H)	141.60, 141.64	7.38-7.27 (m, 3 H)	141.60, 141.64
	16	6.99 (d, J = 9.6, 1 H)	-	6.87 (m, 1 H)	-
	1	-	174.9	-	N.D.
	2	2.52 (m, 1 H)	41.9	2.49 (m, 1 H)	43.1
piperidine	3a	1.37 (m, 1 H)	32.3	1.54 (m, 1 H)	33.1
	3b	1.65 (m, 1 H)	32.3	1.78 (m, 1 H)	33.1
	4a	3.92 (m, 1 H)	46.3	4.00 (m, 1 H)	46.4
	4b	3.08 (m, 1 H)	46.3	3.07 (m, 1 H)	46.4
	5a	1.54 (m, 1 H)	27.1	1.55 (m, 1 H)	26.7
	5b	1.64 (m, 1 H)	27.1	1.60 (m, 1 H)	26.7
	6a	4.38 (m, 1 H)	41.8	4.49 (m, 1 H)	42.2
	6b	2.67 (m, 1 H)	41.8	2.57 (m, 1 H)	42.2
	1	-	175.8	-	176.4
	2	2.81 (m, 1 H)	41.9	2.66 (m, 1 H)	44.2
Dtena	3	3.60 (m, 1 H)	73.0	3.85 (m, 1 H)	72.7
	4a	1.23 (ddd, J = 13.6, 10.1, 2.6, 1 H)	42.9	1.10 (ddd, J = 14.2, 12.8, 2.6, 1 H)	38.2
	4b	1.34 (ddd, J = 14.3, 9.1, 3.6, 1 H)	42.9	1.50 (ddd, J = 14.4, 12.7, 2.5, 1 H)	38.2
	5	1.80 (ddqdd, J = 10.1, 7.1, 6.2, 5.7, 3.6, 1H)	27.6	2.11 (ddqdd, J = 12.8, 11.6, 6.8, 2.5, 2.5, 1 H)	26.1
	6a	1.53 (ddd, J = 14.5, 7.1, 4.0, 1 H)	38.2	1.37 (ddd, J = 14.9, 11.6, 2.7, 1 H)	39.1
	6b	1.61 (ddd, J = 14.5, 8.9, 5.7, 1 H)	38.2	1.75 (ddd, J = 14.9, 12.7, 2.5, 1 H)	39.1
	7	4.77 (dd, J = 9.0, 4.2, 1 H)	79.8	4.85 (dd, J = 12.6, 2.7, 1 H)	78.4
	8	-	35.7	-	35.7
	9 / 10 / 11	0.88 (s, 9 H)	26.2	0.88 (s, 9 H)	26.2
	12	1.02 (d, J = 6.8, 3 H)	14.4	0.87 (m, 3 H)	15.6
	13	0.92 (d, J = 6.2, 3 H)	20.8	0.94 (d, J = 6.8, 3 H)	20.3
	OH	3.67 (m, 1 H)	-	N.D.	-

NMR Spectra

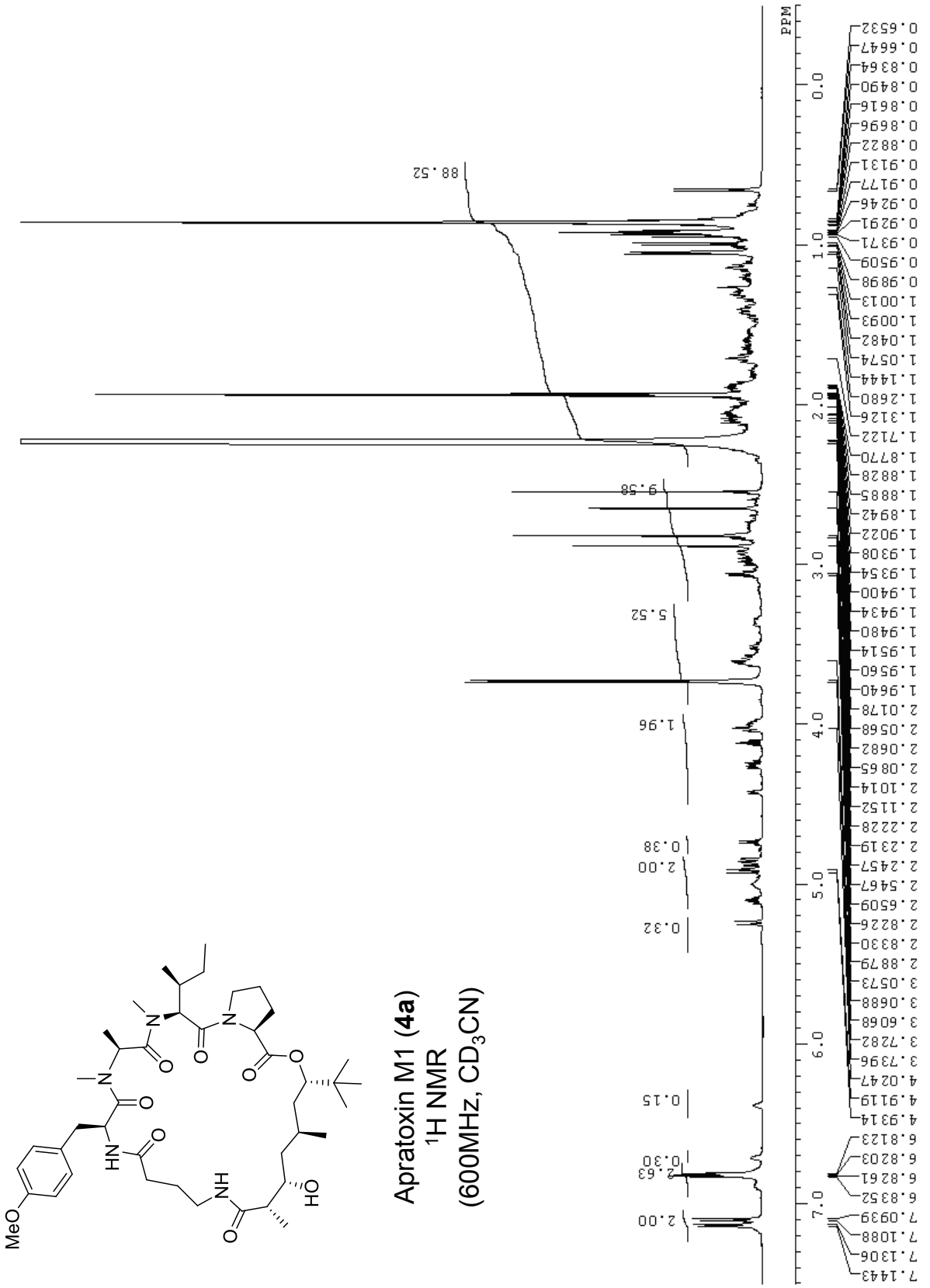

FmocN
O
O
OH
HO
O
6
^{1}H NMR
(400MHz, CDCl$_3$)
PPM
13.72
5.73
2.39
4.10
1.24
1.00
3.48
4.91
0.98

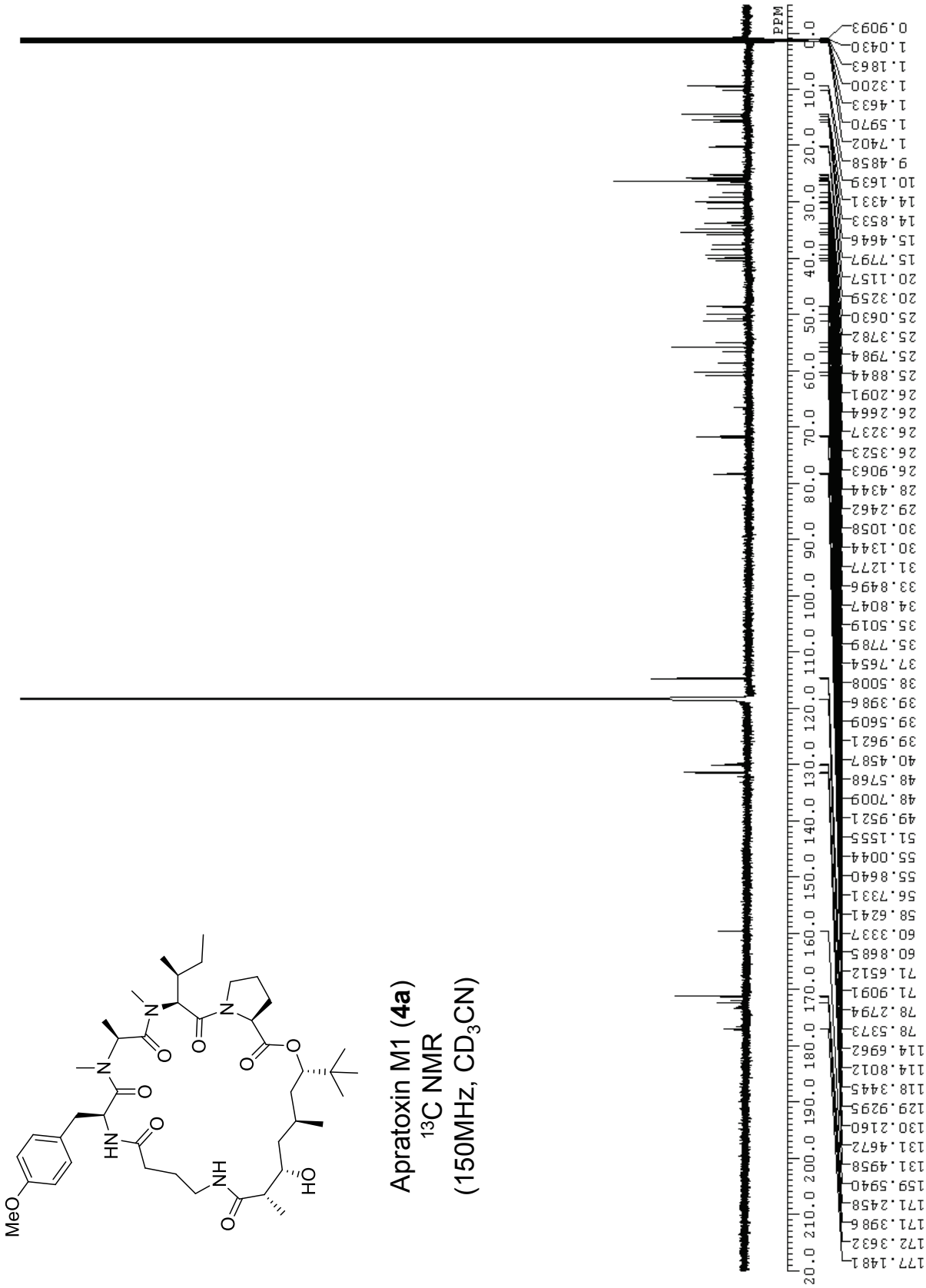


6

^{13}C NMR

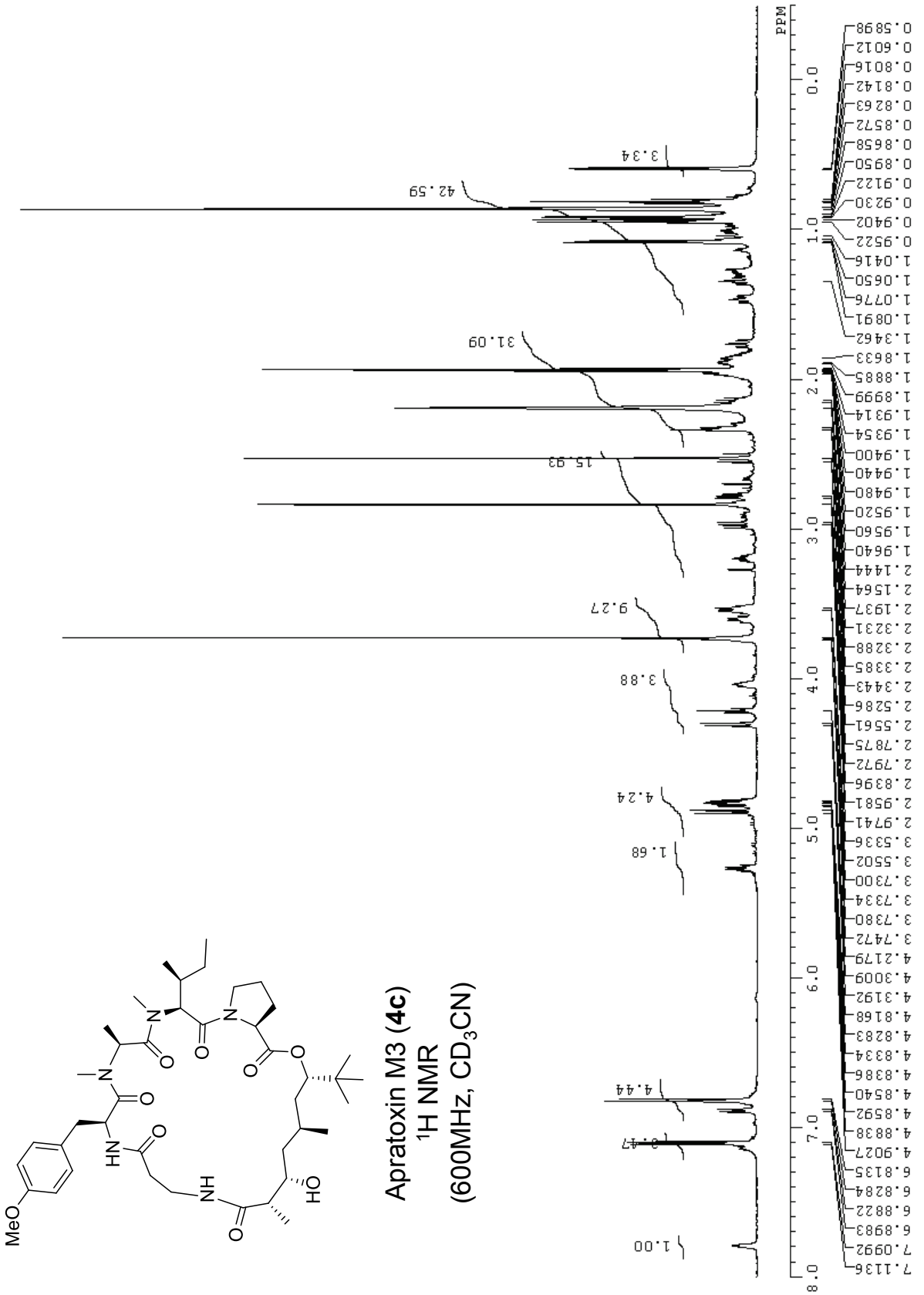
(100MHz, $CDCl_3$)

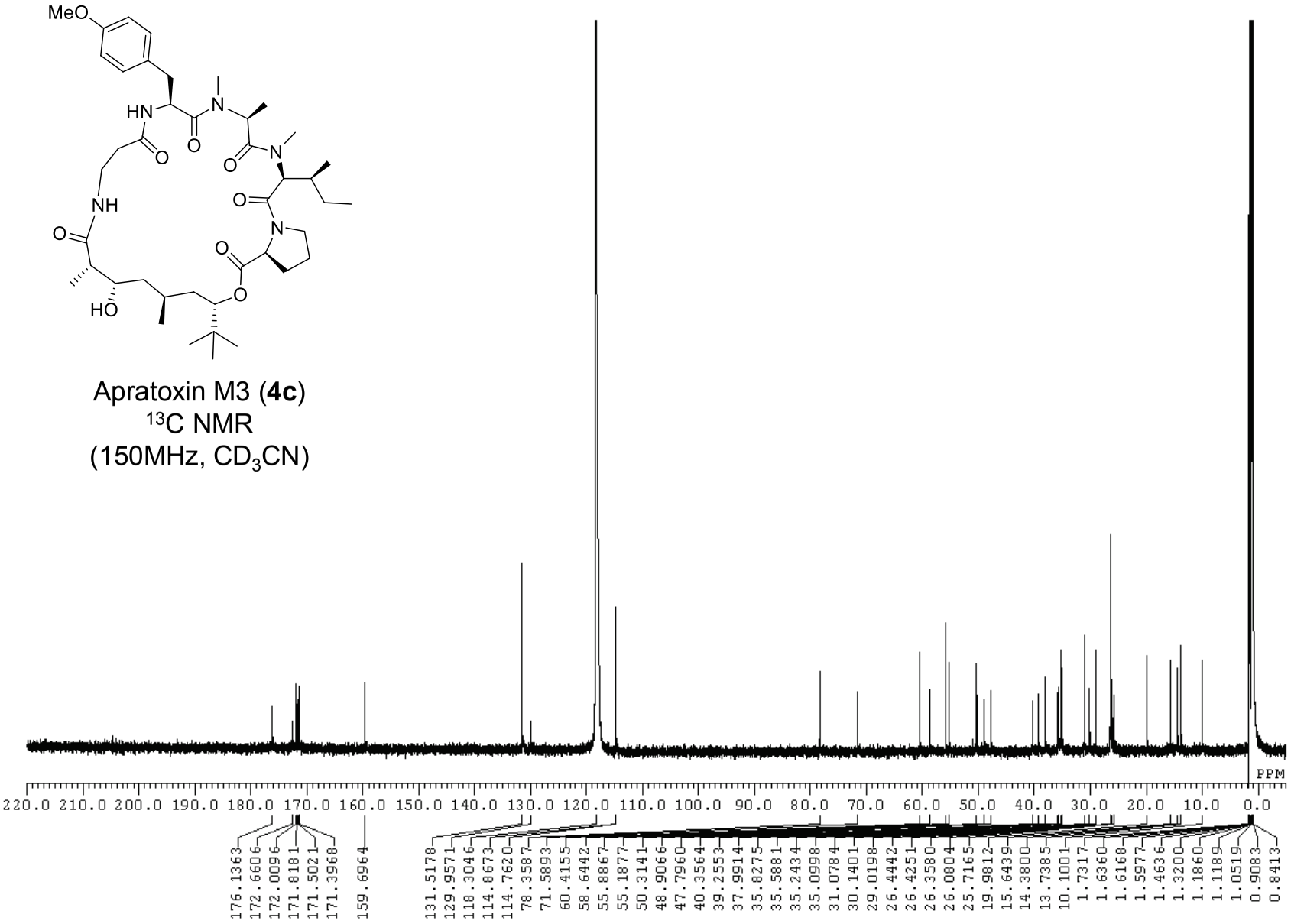

Apratoxin M1 (4a)
1H NMR
(600MHz, CD3CN)
MeO
HN
NH
HO
N
O
PPM
88.52
9.58
5.52
1.96
0.38
2.00
0.32
0.15
2.63
0.30
2.00

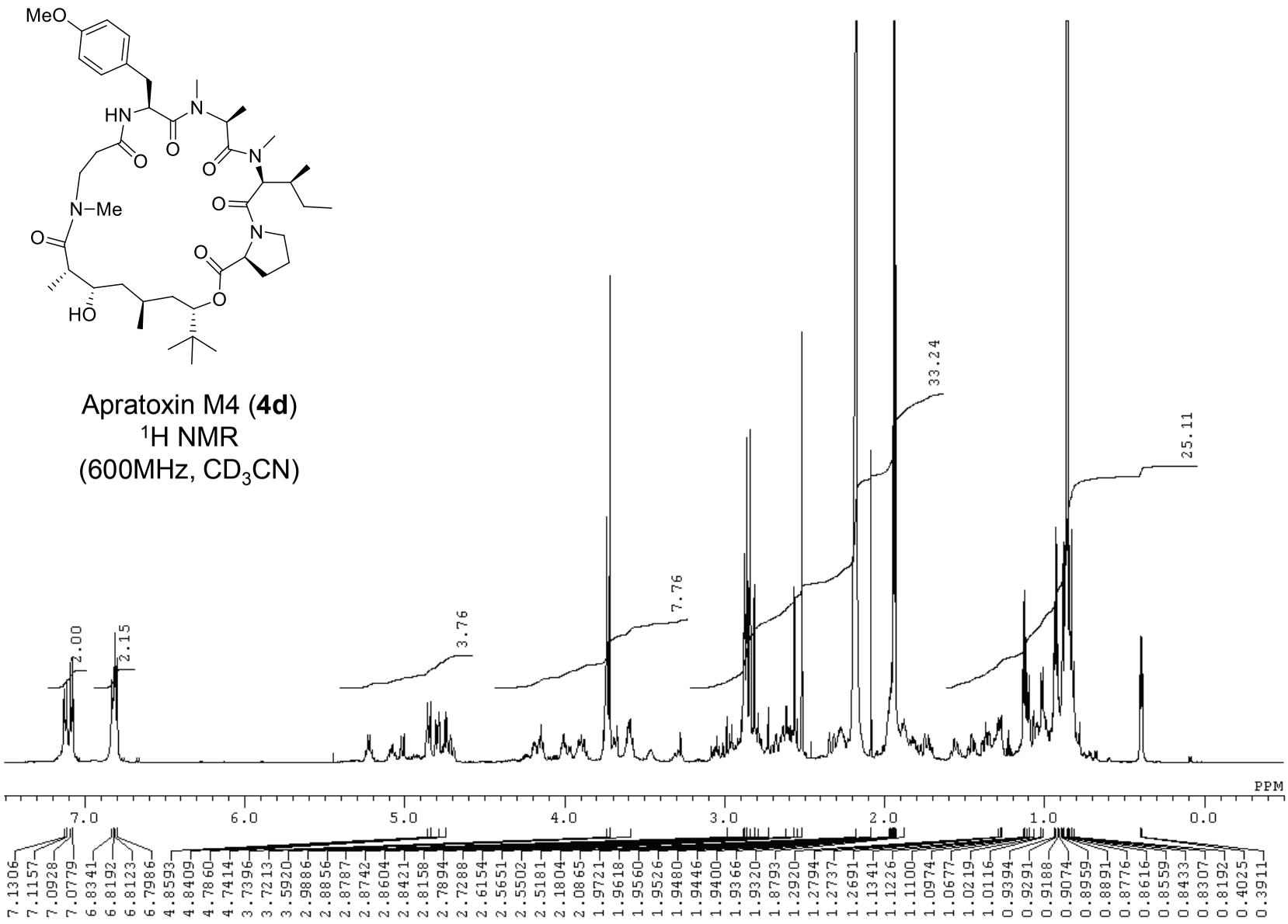

Apratoxin M1 (4a)
13C NMR
(150MHz, CD3CN)
MeO
HN
NH
HO
O
N
PPM
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
170.0
180.0
190.0
200.0
210.0
220.0
0.9093
1.0430
1.1863
1.3200
1.4633
1.5970
1.7402
9.4858
10.1639
14.4331
14.8533
15.4646
15.7797
20.1157
20.3259
25.0630
25.3782
25.7984
25.8844
26.2091
26.2664
26.3237
26.3523
26.9063
28.4344
29.2462
30.1058
30.1344
31.1277
33.8496
34.8047
35.5019
35.7789
37.7654
38.5008
39.3986
39.5609
39.9621
40.4587
48.5768
48.7009
49.9521
51.1555
55.0044
55.8640
56.7331
58.6241
60.3337
60.8685
71.6512
71.9091
78.2794
78.5373
114.6962
114.8012
118.3445
129.9295
130.2160
131.4672
131.4958
159.5940
171.2458
171.3986
172.3632
177.1481

Apratoxin M2 (4b)
1H NMR
(600MHz, CD3CN)
MeO
HN
N–Me
OH
O
N
2.00
2.83
3.55
9.78
13.03
57.55
PPM
7.1443
7.1306
7.1008
7.0871
6.8341
6.8203
5.2771
5.2577
4.1014
3.7408
3.7362
3.7282
3.2806
3.2737
3.0138
3.0001
2.9635
2.9463
2.9291
2.8810
2.8375
2.8204
2.6681
2.5548
2.5364
2.1701
2.0613
2.0522
2.0476
2.0304
1.9560
1.9526
1.9480
1.9446
1.9400
1.9366
1.9320
1.9205
1.9137
1.8976
1.8919
1.8862
1.3733
1.3619
1.3550
1.1718
1.0688
1.0585
1.0482
1.0367
0.9371
0.9349
0.9257
0.9211
0.9097
0.8982
0.8868
0.8788
0.8650
0.8547
0.8398
0.8272
0.8147
0.4907
0.4804

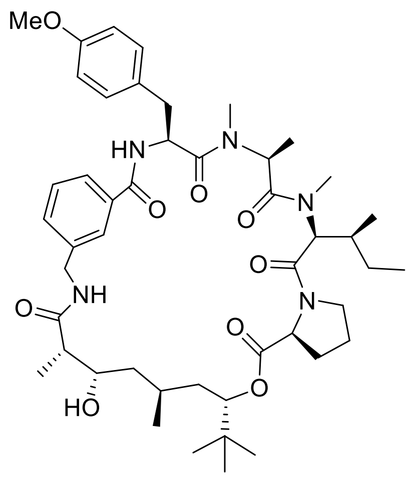
Apratoxin M2 (4b)
13C NMR
(150MHz, CD3CN)
MeO
HN
N–Me
HO
O
N
PPM
0.8329
0.8998
0.9762
1.0430
1.1767
1.2149
1.3200
1.4537
1.4919
1.5970
1.7307
8.9892
10.4314
14.4044
14.4426
14.5095
14.6241
15.2736
20.8894
20.9276
24.9484
25.6742
25.7220
25.9035
26.1327
26.3237
26.3714
26.3905
29.0743
30.1440
31.2709
31.3474
33.1142
35.3682
35.4159
35.5688
36.3424
37.6986
38.3958
38.8255
40.4110
48.6150
48.8442
49.9234
51.3751
54.3550
55.8544
55.8926
55.9881
58.5191
60.2191
60.9163
73.3322
78.4513
78.6997
114.6771
114.8967
118.3063
129.9964
131.4385
131.4958
159.5749
172.0098
172.5065
173.1368


Apratoxin M3 (4c)
1H NMR
(600MHz, CD3CN)
MeO
HN
NH
N
O
OH
PPM
1.00
0.47
4.44
1.68
4.24
3.88
9.27
15.93
31.09
42.59
3.34

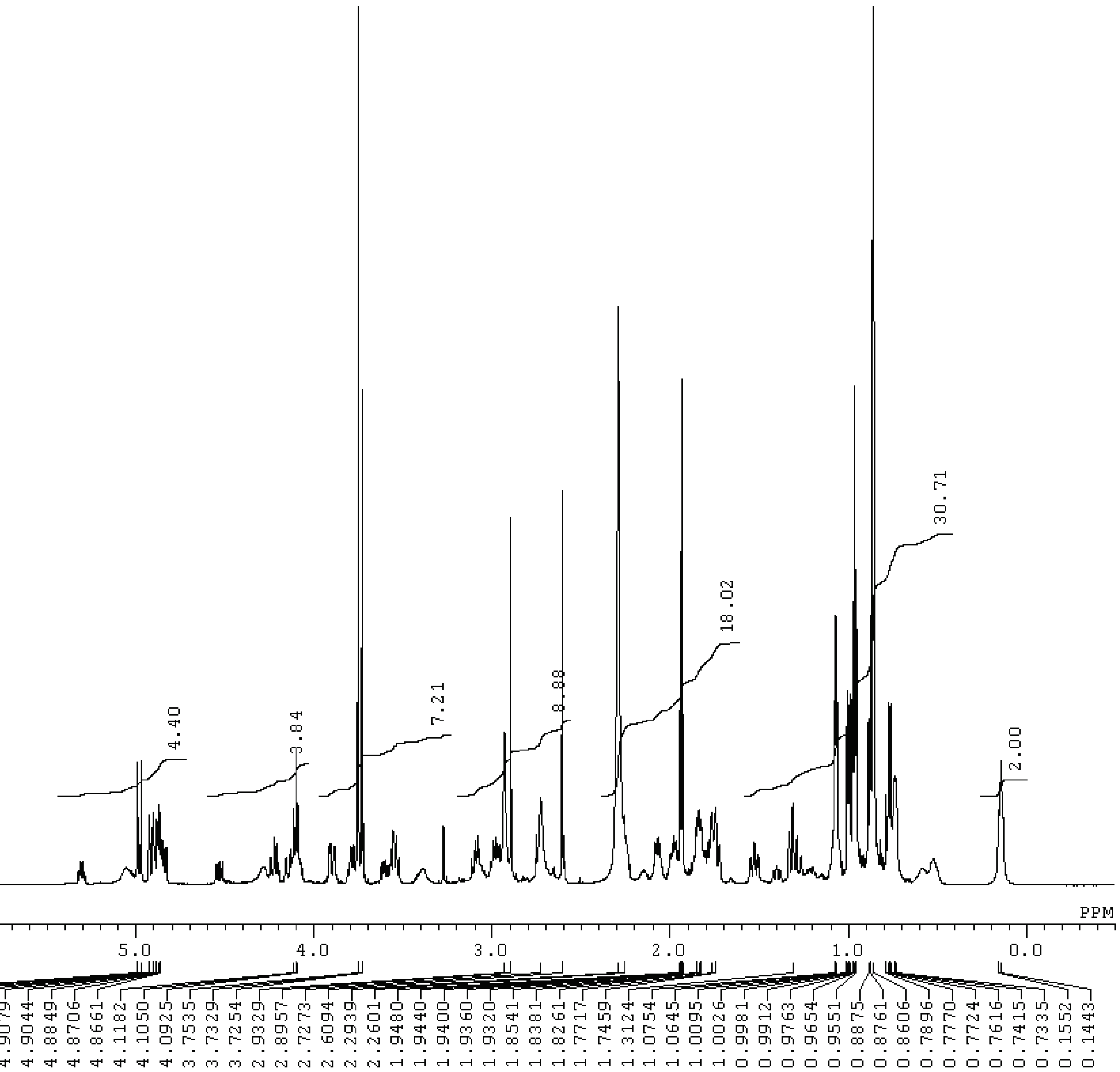

MeO
HN
N
O
O
N
O
NH
O
N
O
O
HO
O
Apratoxin M3 (4c)
13C NMR
(150MHz, CD3CN)
PPM
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0
176.1363
172.6606
172.0096
171.8181
171.5021
171.3968
159.6964
131.5178
129.9571
118.3046
114.8673
114.7620
78.3587
71.5893
60.4155
58.6442
55.8867
55.1877
50.3141
48.9066
47.7960
40.3564
39.2553
37.9914
35.8275
35.5881
35.2434
35.0998
31.0784
30.1401
29.0198
26.4442
26.4251
26.3580
26.0804
25.7165
19.9812
15.6439
14.3800
13.7385
10.1001
1.7317
1.6360
1.6168
1.5977
1.4636
1.3200
1.1860
1.1189
1.0519
0.9083
0.8413

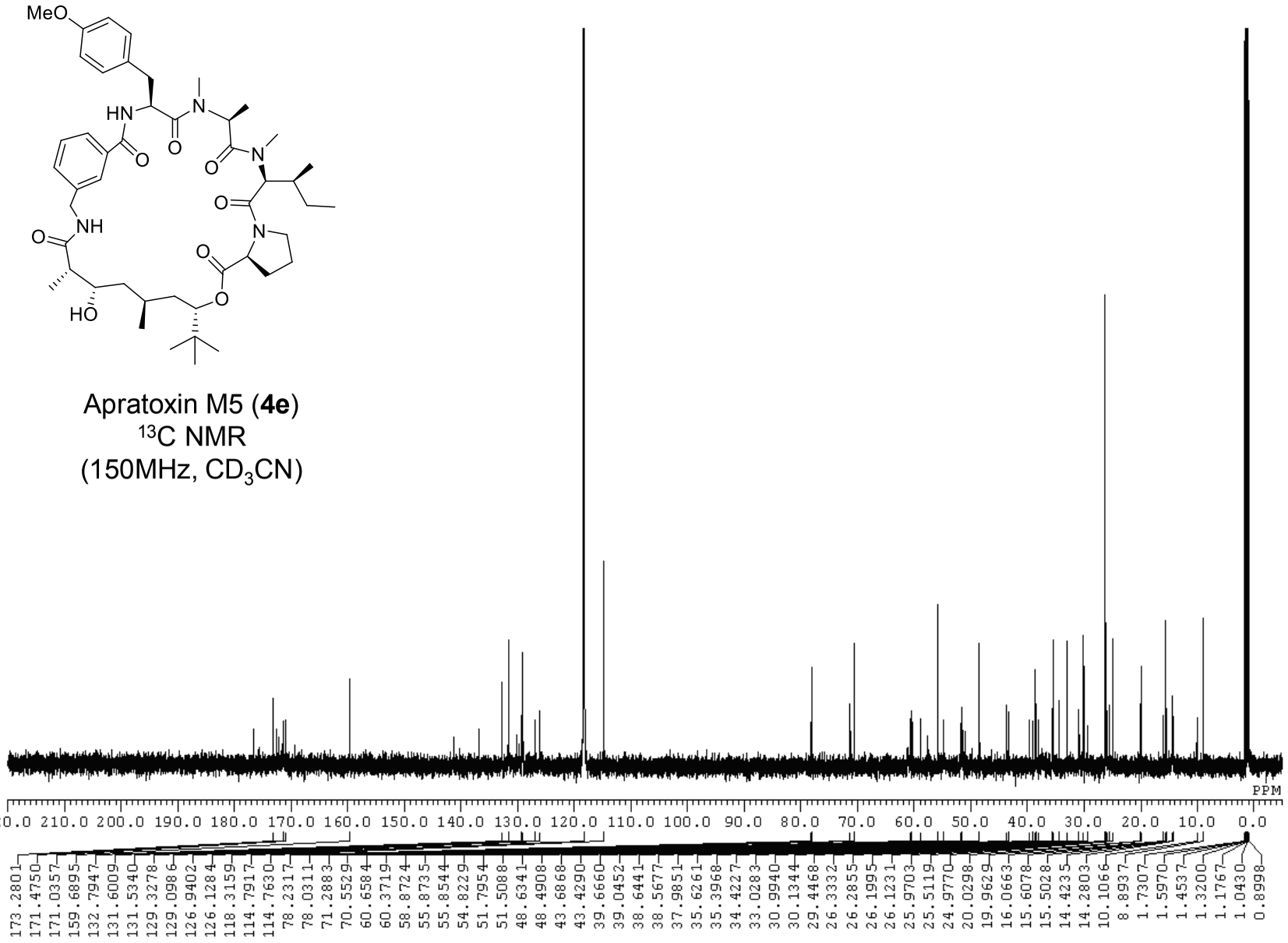

MeO
HN
N
O
N–Me
HO
Apratoxin M4 (4d)
1H NMR
(600MHz, CD3CN)
2.00
2.15
3.76
7.76
33.24
25.11
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

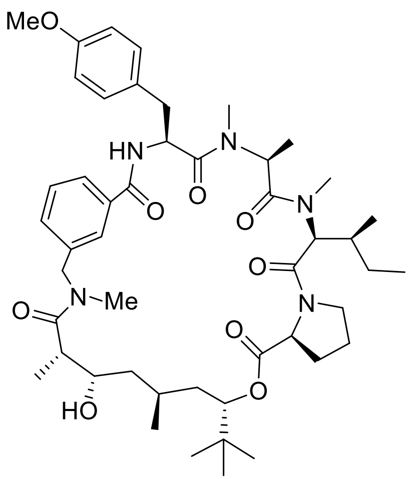
Apratoxin M4 (4d)
13C NMR
(150MHz, CD3CN)
MeO
HN
N–Me
HO
O
N
PPM
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
170.0
180.0
190.0
200.0
210.0
220.0
0.8425
0.9093
0.9762
1.0430
1.1194
1.1576
1.1863
1.3200
1.3964
1.4346
1.4633
1.5970
1.7402
10.2117
10.4505
14.5477
14.6050
14.8629
15.0539
16.2764
16.5247
20.3450
25.8175
25.8462
26.1327
26.2186
26.3141
26.4765
27.3361
28.8833
30.1249
30.3350
30.8985
31.5479
32.6462
33.7637
34.7283
35.8457
38.0997
38.3671
40.5256
41.6430
45.4346
48.8442
51.1555
54.4791
55.8353
55.9117
58.6528
60.5056
60.6011
71.4125
78.5277
78.6997
114.7248
114.9254
118.3159
129.8913
131.4767
131.5149
159.7277
171.4655
171.5992
172.0003
172.4778



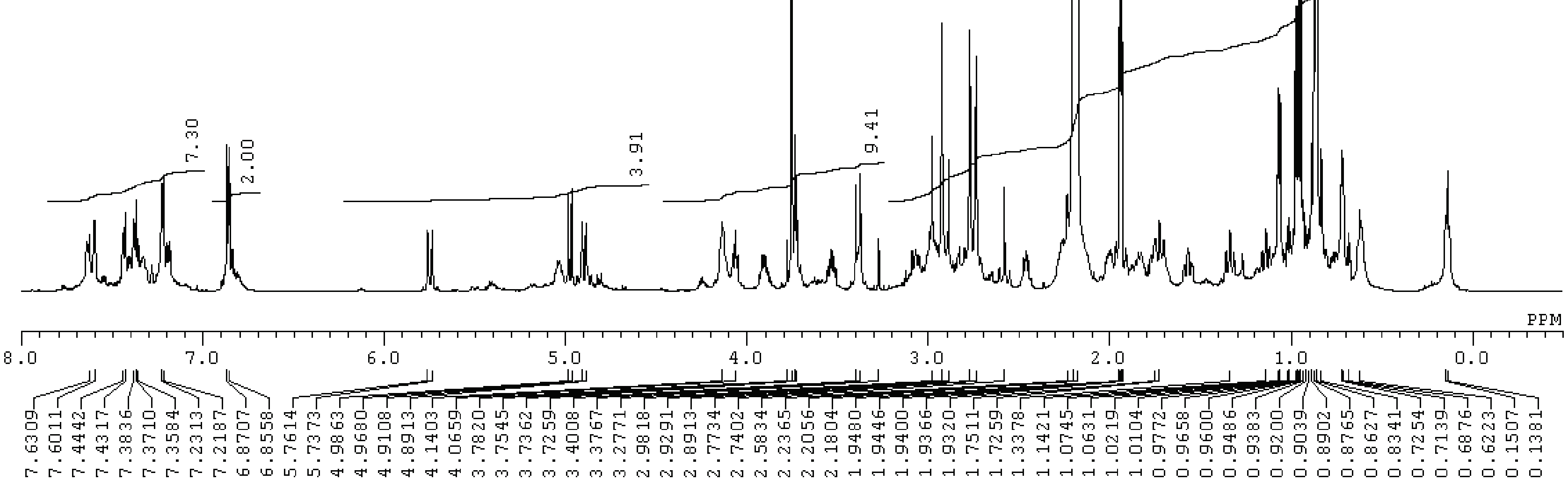
Apratoxin M5 (**4e**)
^{1}H NMR
(600MHz, CD_3CN)

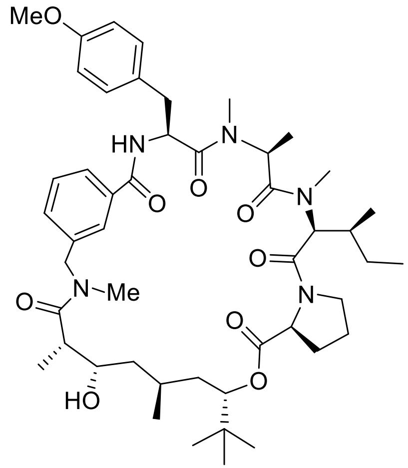



MeO
HN
N
O
NH
HO
Apratoxin M5 (4e)
13C NMR
(150MHz, CD3CN)
PPM
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0
173.2801
171.4750
171.0357
159.6895
132.7947
131.6009
131.5340
129.3278
129.0986
126.9402
126.1284
118.3159
114.7917
114.7630
78.2317
78.0311
71.2883
70.5529
60.6584
60.3719
58.8724
55.8735
55.8544
54.8229
51.7954
51.5088
48.6341
48.4908
43.6868
43.4290
39.6660
39.0452
38.6441
38.5677
37.9851
35.6261
35.3968
34.4227
33.0283
30.9940
30.1344
29.4468
26.3332
26.2855
26.1995
26.1231
25.9703
25.5119
24.9770
20.0298
19.9629
16.0663
15.6078
15.5028
14.4235
14.2803
10.1066
8.8937
1.7307
1.5970
1.4537
1.3200
1.1767
1.0430
0.8998

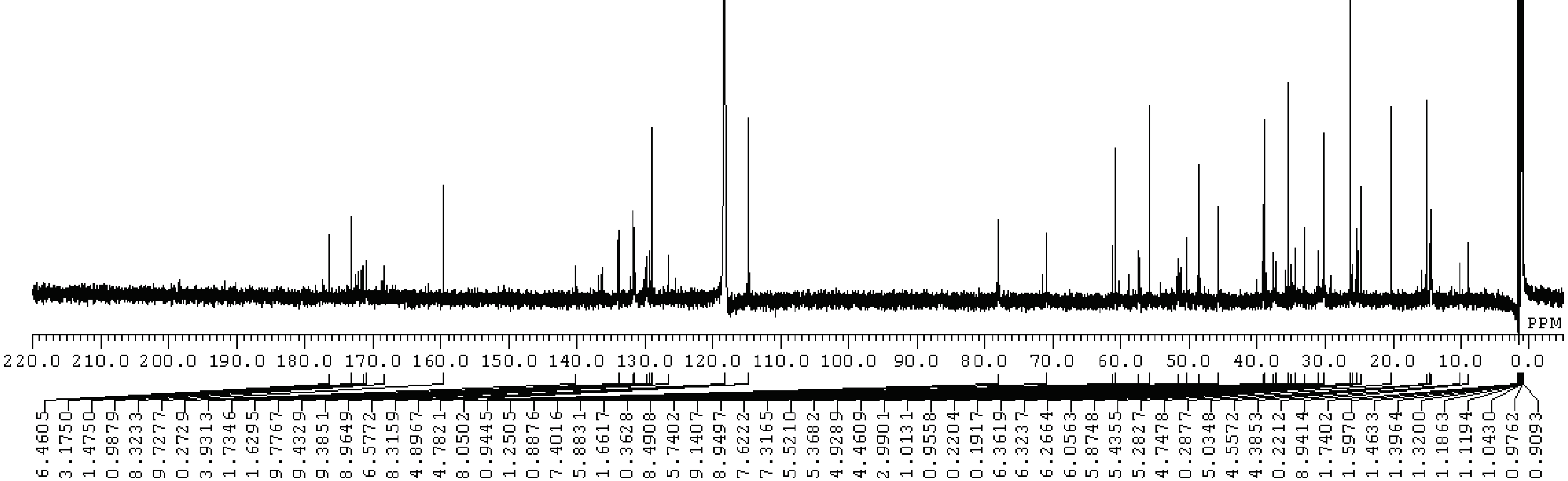


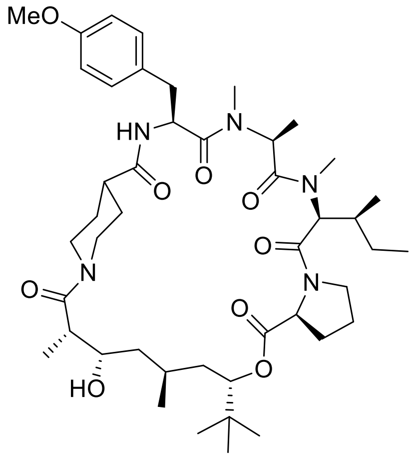
Apratoxin M6 (**4f**)
^{1}H NMR
(600MHz, CD_3CN)



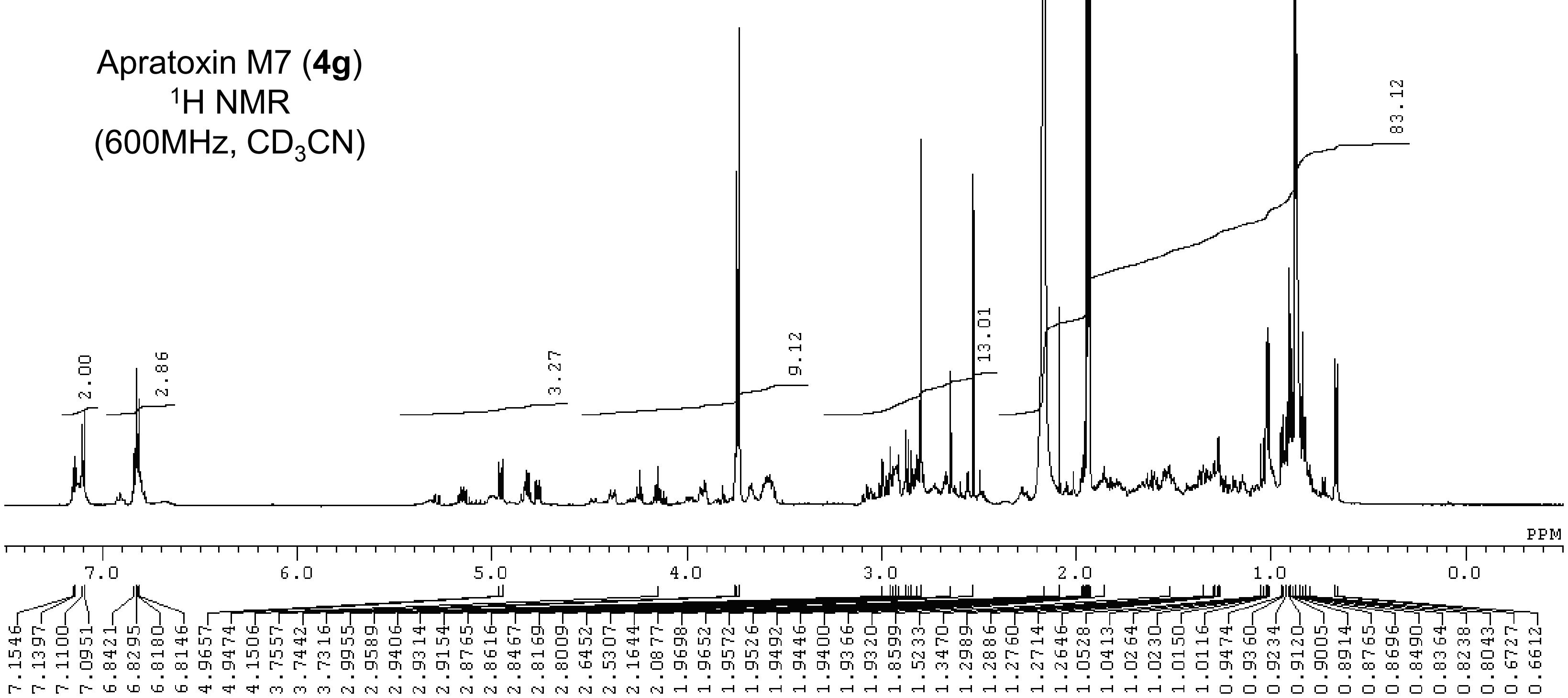


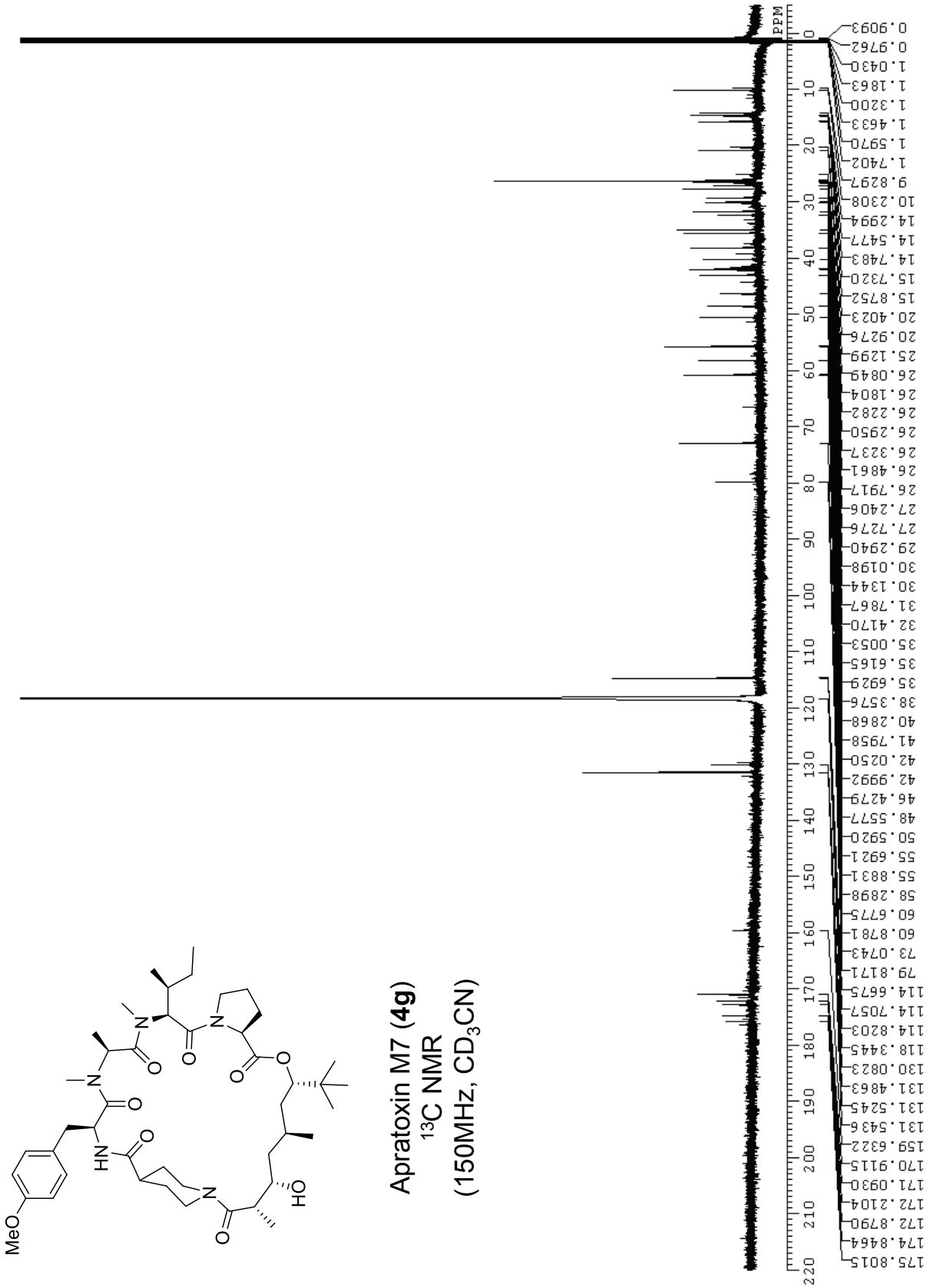
Apratoxin M6 (**4f**)
^{13}C NMR
(150MHz, CD_3CN)

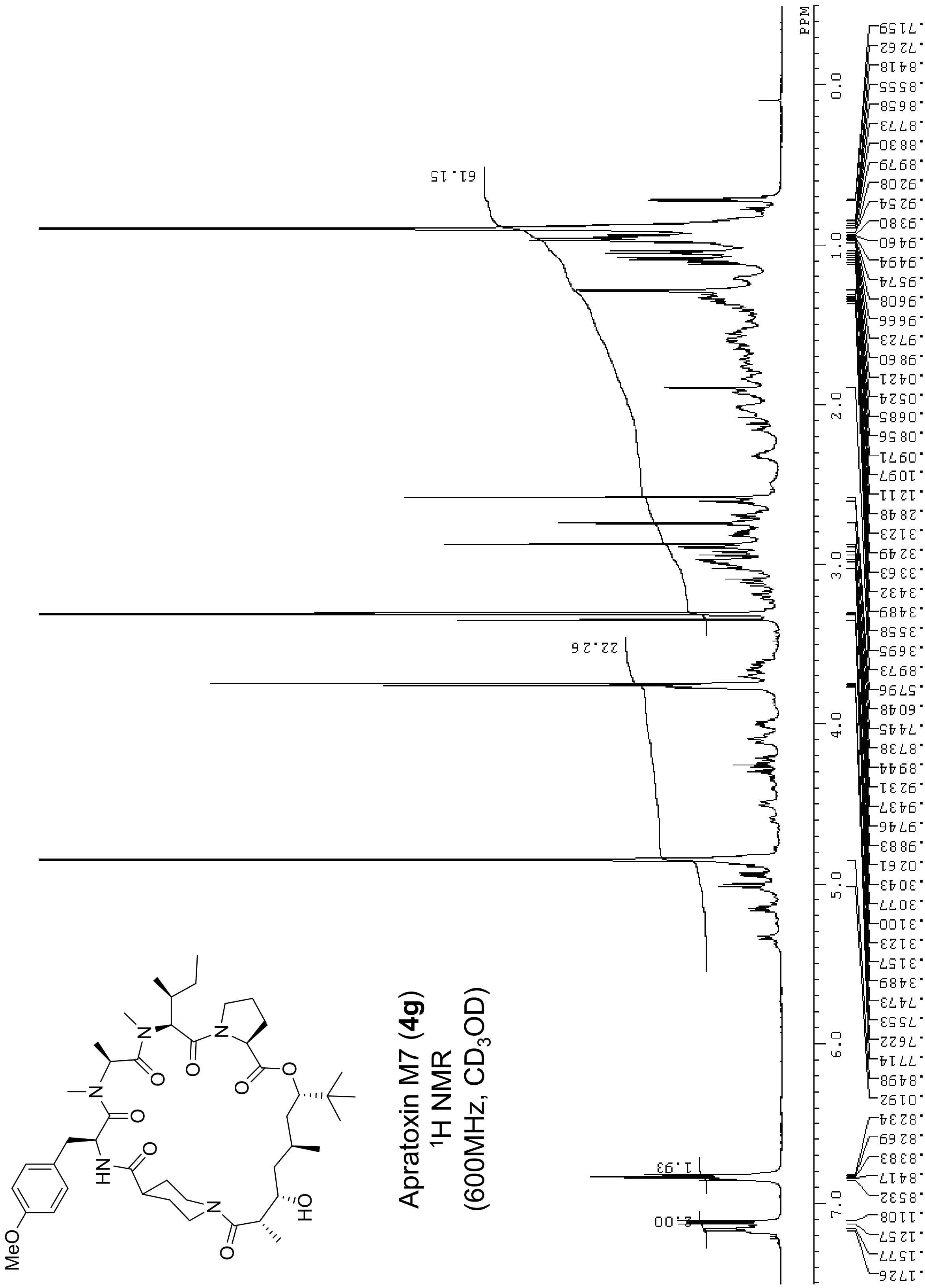


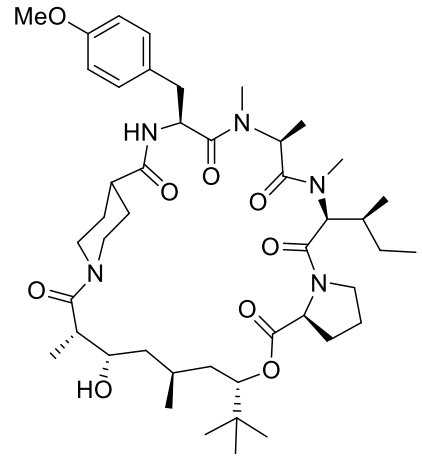


Apratoxin M7 (**4g**)
^{1}H NMR
(600MHz, CD_3CN)

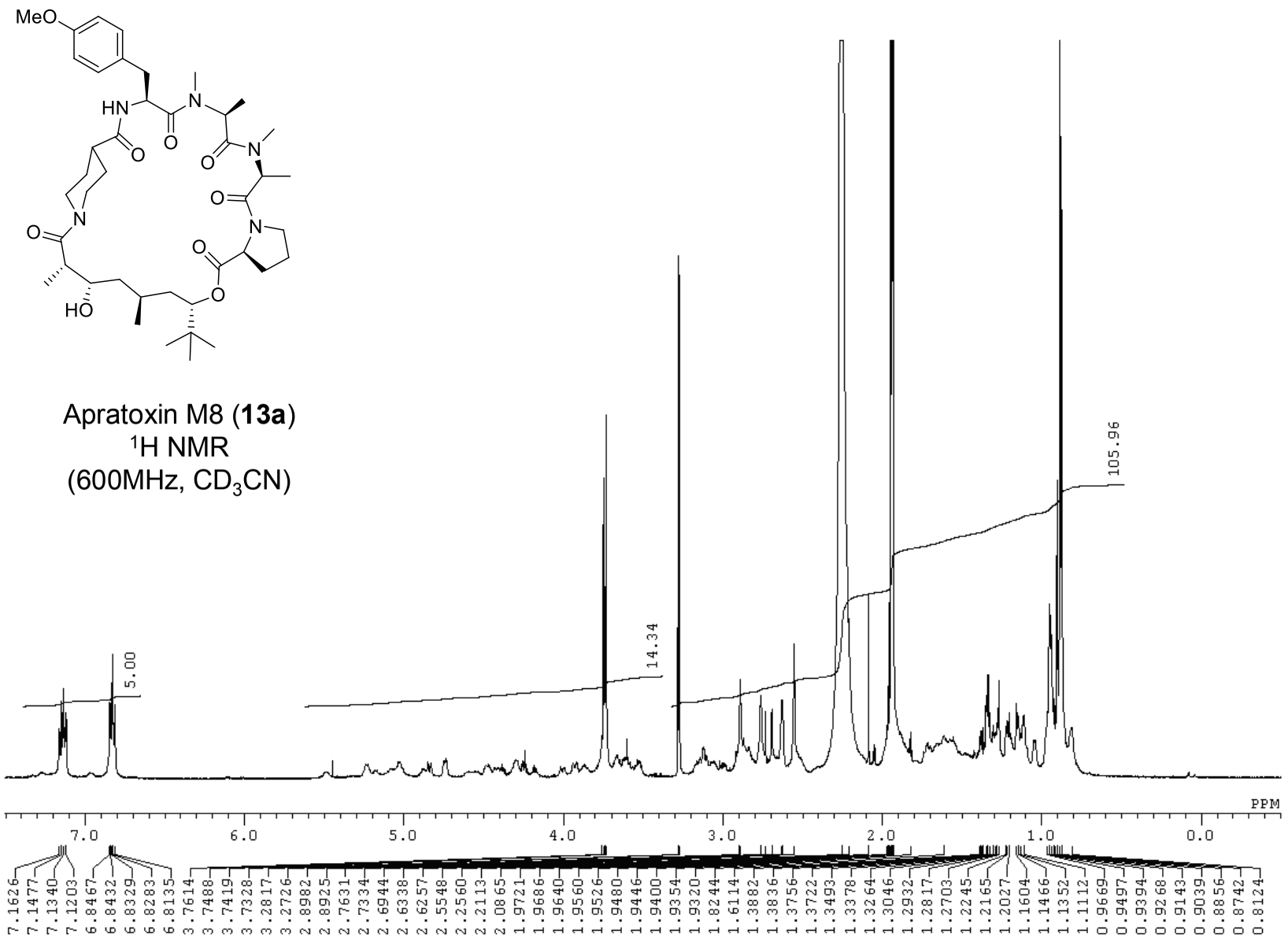


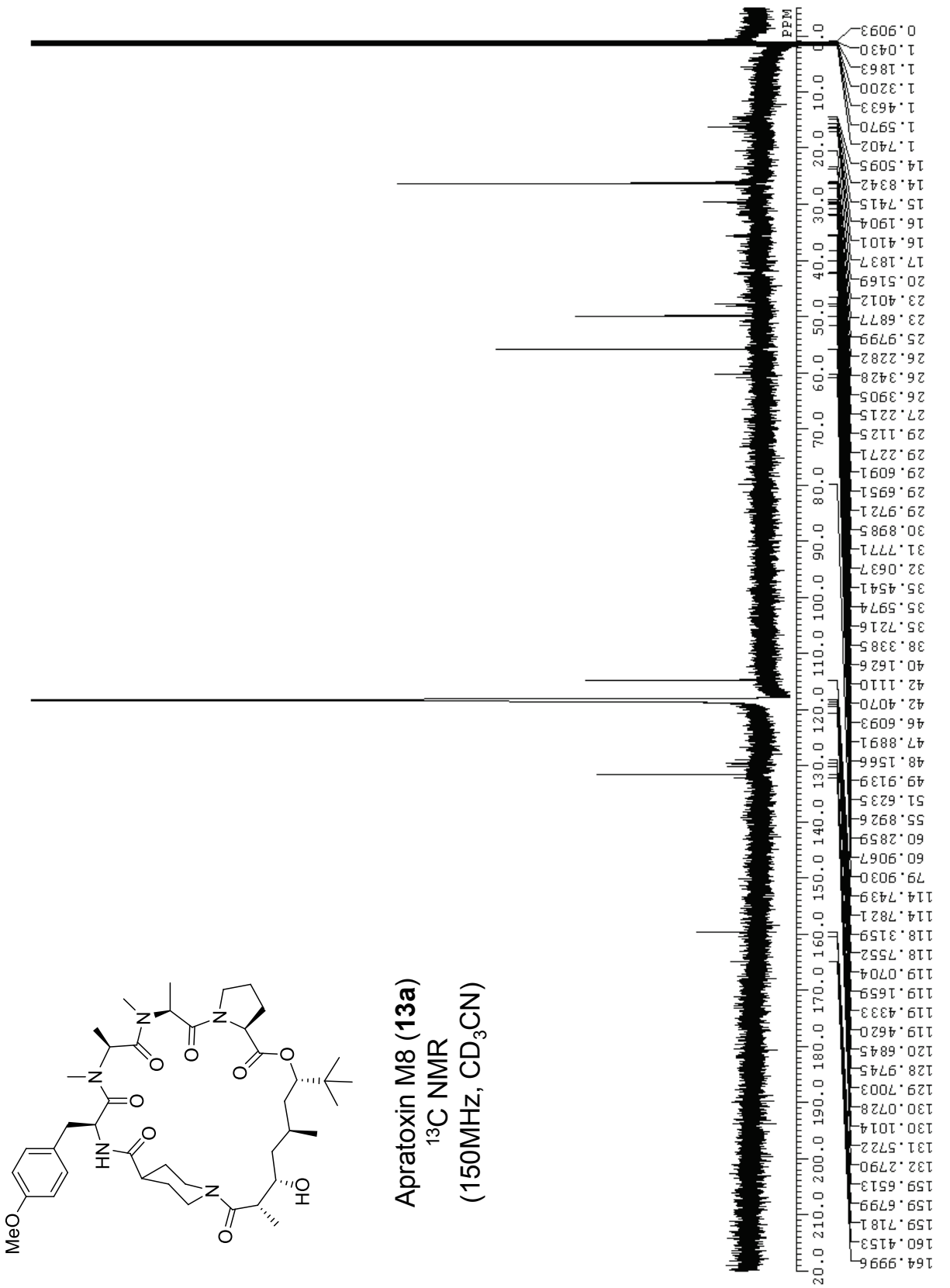

Apratoxin M7 (4g)
13C NMR
(150MHz, CD3CN)
MeO
HN
HO
PPM

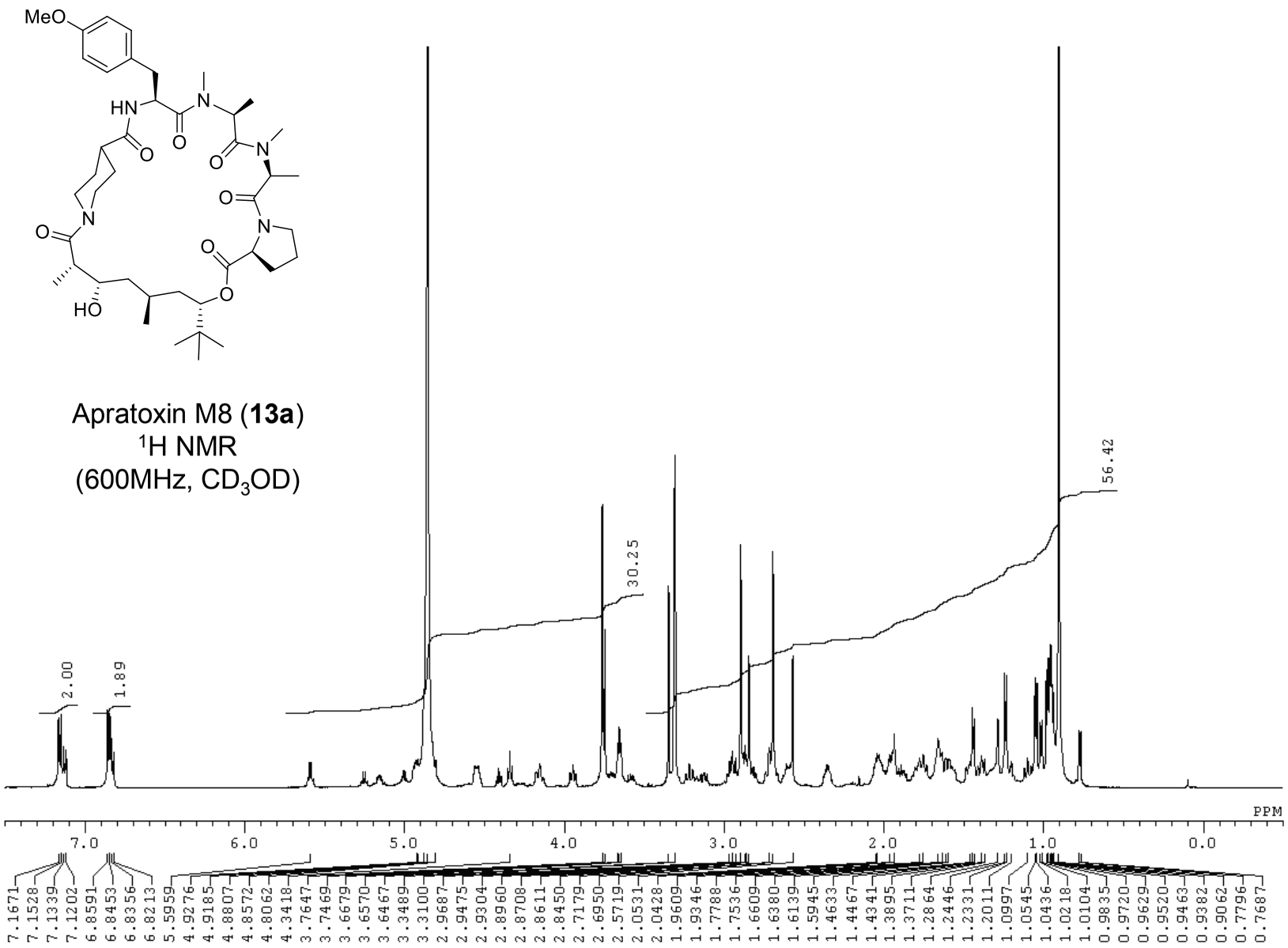

Apratoxin M7 (4g)
1H NMR
(600MHz, CD3OD)
MeO
HN
N
O
OH
PPM
61.15
22.26
1.93
2.00

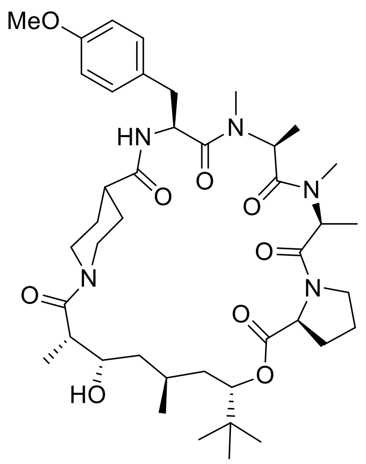


Apratoxin M7 (**4g**)
^{13}C NMR
(150MHz, CD_3OD)

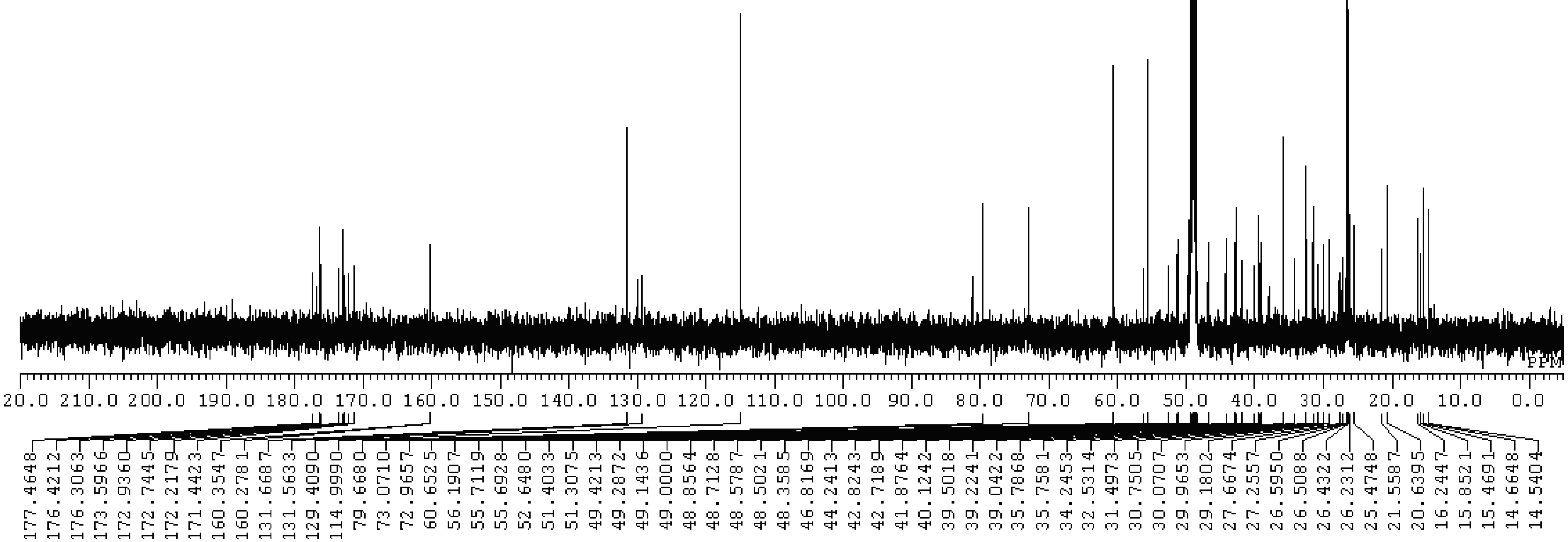

MeO
HN
N
O
HO
Apratoxin M8 (13a)
1H NMR
(600MHz, CD3CN)
5.00
14.34
105.96
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
7.1626
7.1477
7.1340
7.1203
6.8467
6.8432
6.8329
6.8283
6.8135
3.7614
3.7488
3.7419
3.7328
3.2817
3.2726
2.8982
2.8925
2.7631
2.7334
2.6944
2.6338
2.6257
2.5548
2.2560
2.2113
2.0865
1.9721
1.9686
1.9640
1.9560
1.9526
1.9480
1.9446
1.9400
1.9354
1.9320
1.8244
1.6114
1.3882
1.3836
1.3756
1.3722
1.3493
1.3378
1.3264
1.3046
1.2932
1.2817
1.2703
1.2245
1.2165
1.2027
1.1604
1.1466
1.1352
1.1112
0.9669
0.9497
0.9394
0.9268
0.9143
0.9039
0.8856
0.8742
0.8124

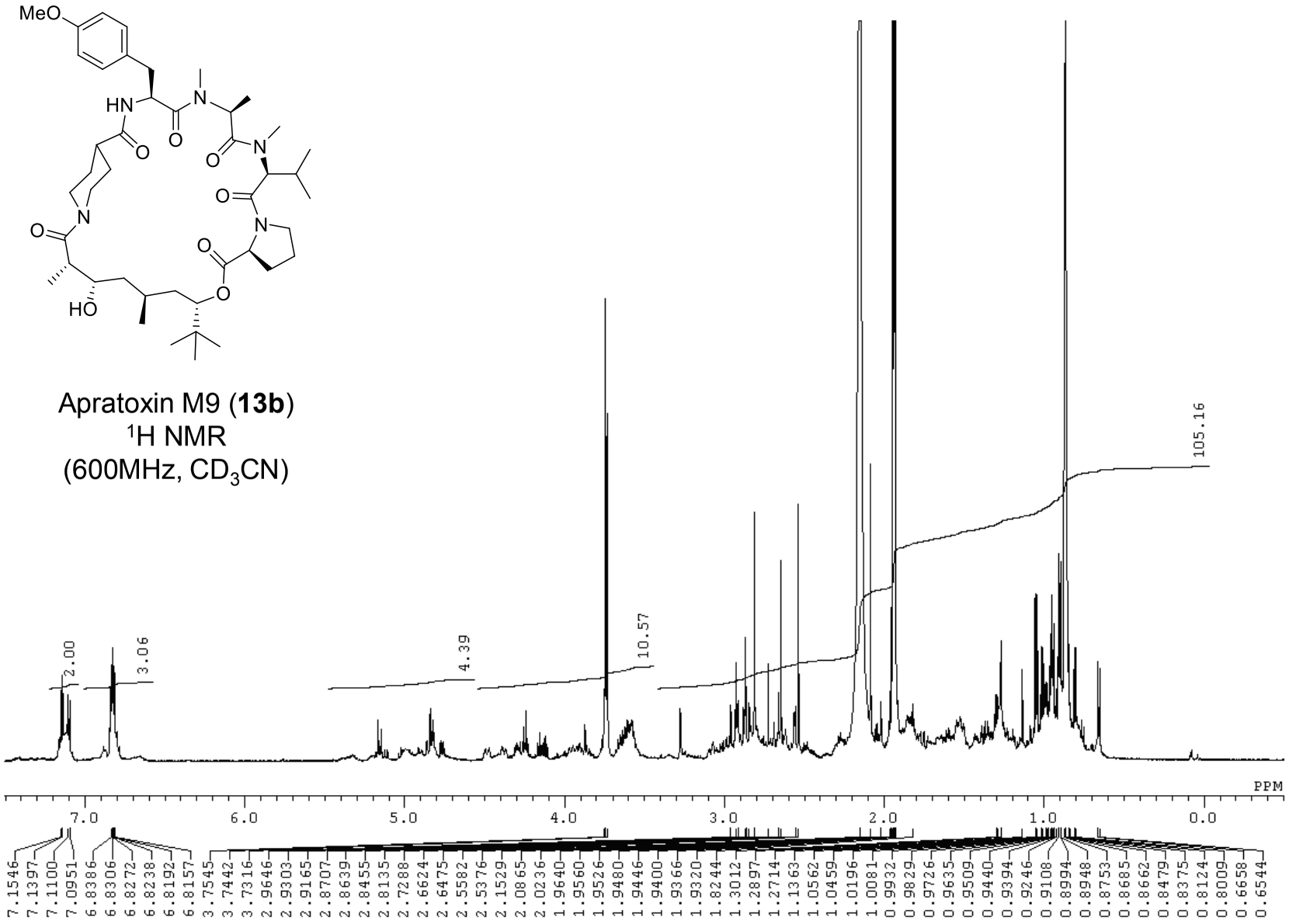

Apratoxin M8 (13a)
13C NMR
(150MHz, CD3CN)
MeO
HN
N
O
OH
PPM

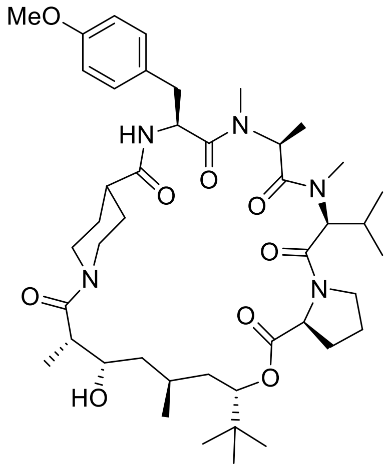

MeO
HN
N
O
HO
Apratoxin M8 (13a)
1H NMR
(600MHz, CD3OD)
2.00
1.89
30.25
56.42
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

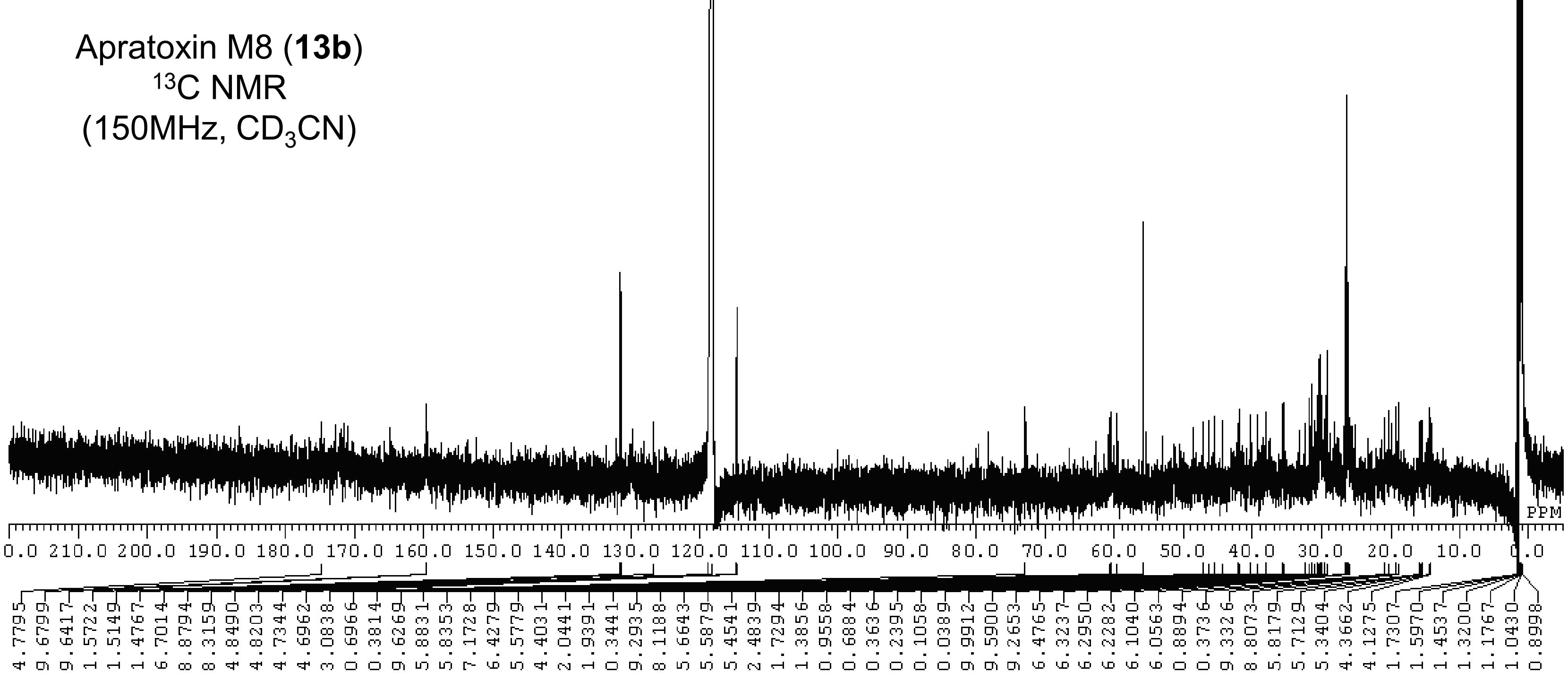


Apratoxin M8 (**13a**)
^{13}C NMR
(150MHz, CD_3OD)

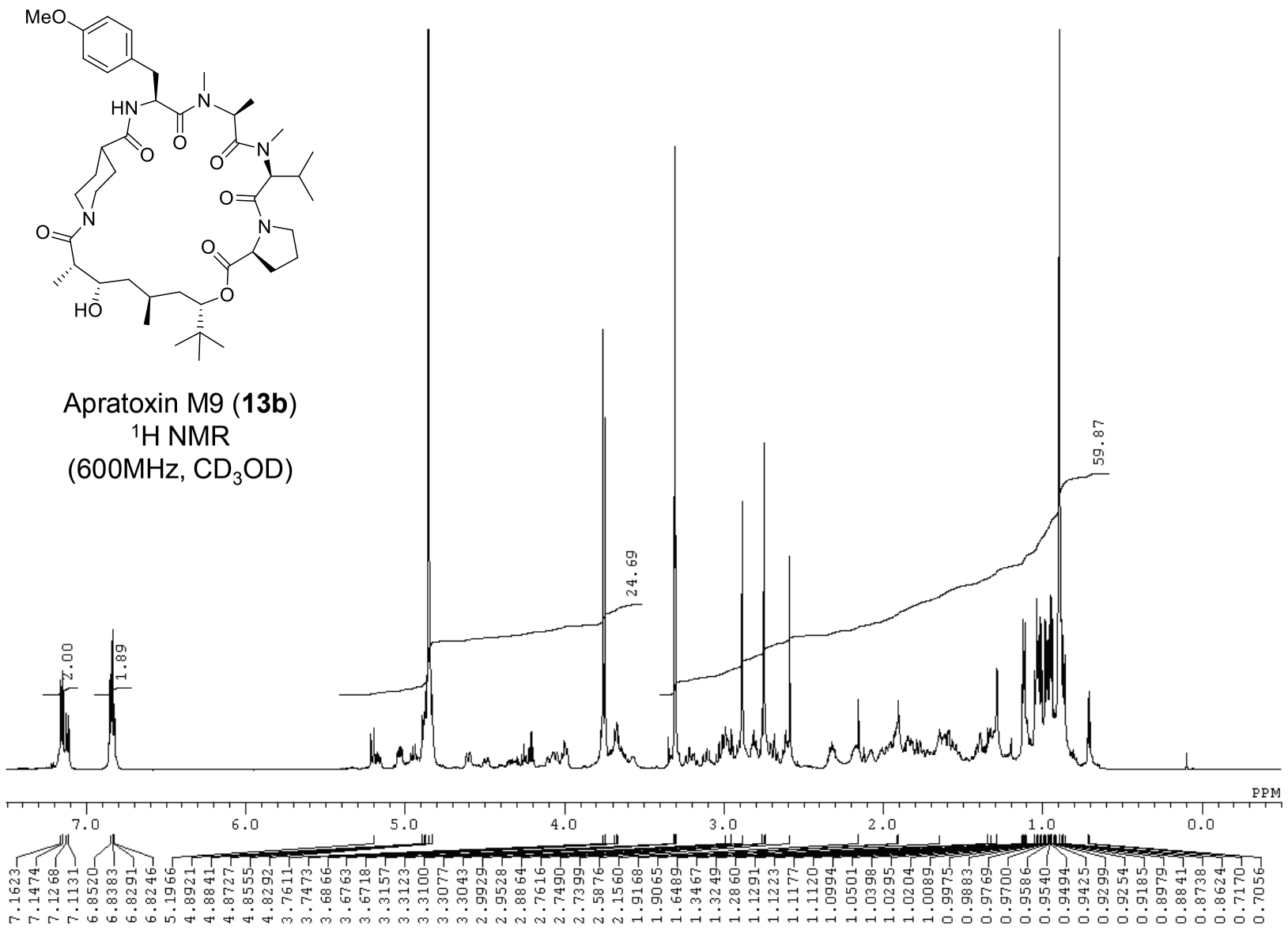


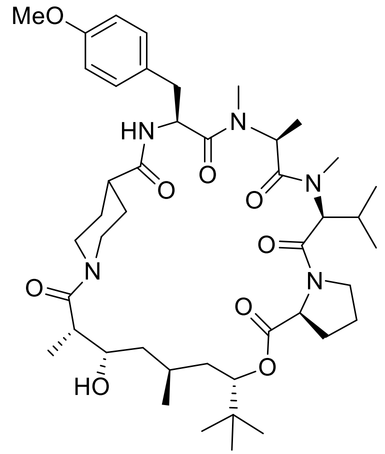

MeO
HN
O
N
HO
Apratoxin M9 (13b)
1H NMR
(600MHz, CD3CN)
2.00
3.06
4.39
10.57
105.16
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0



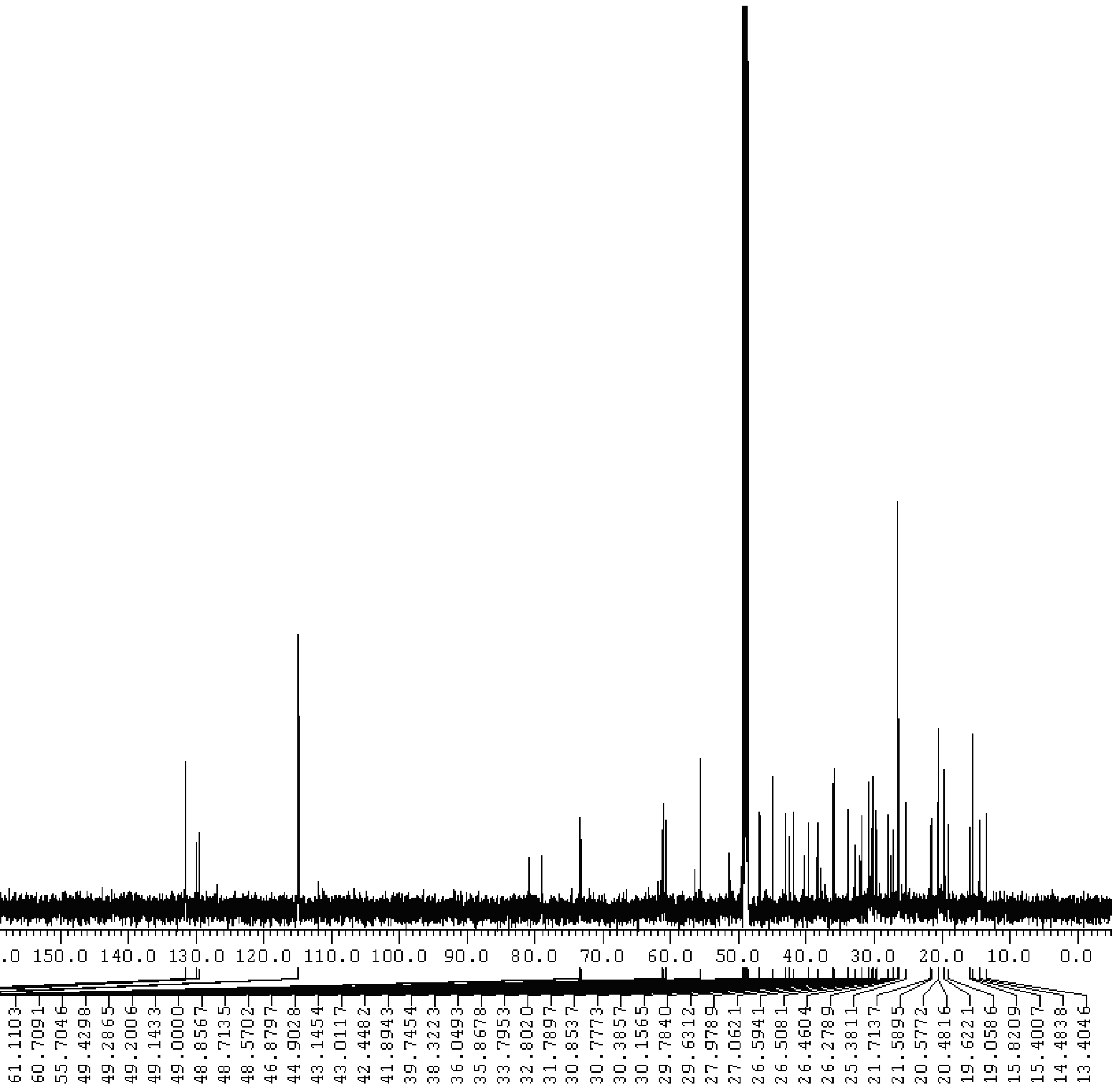


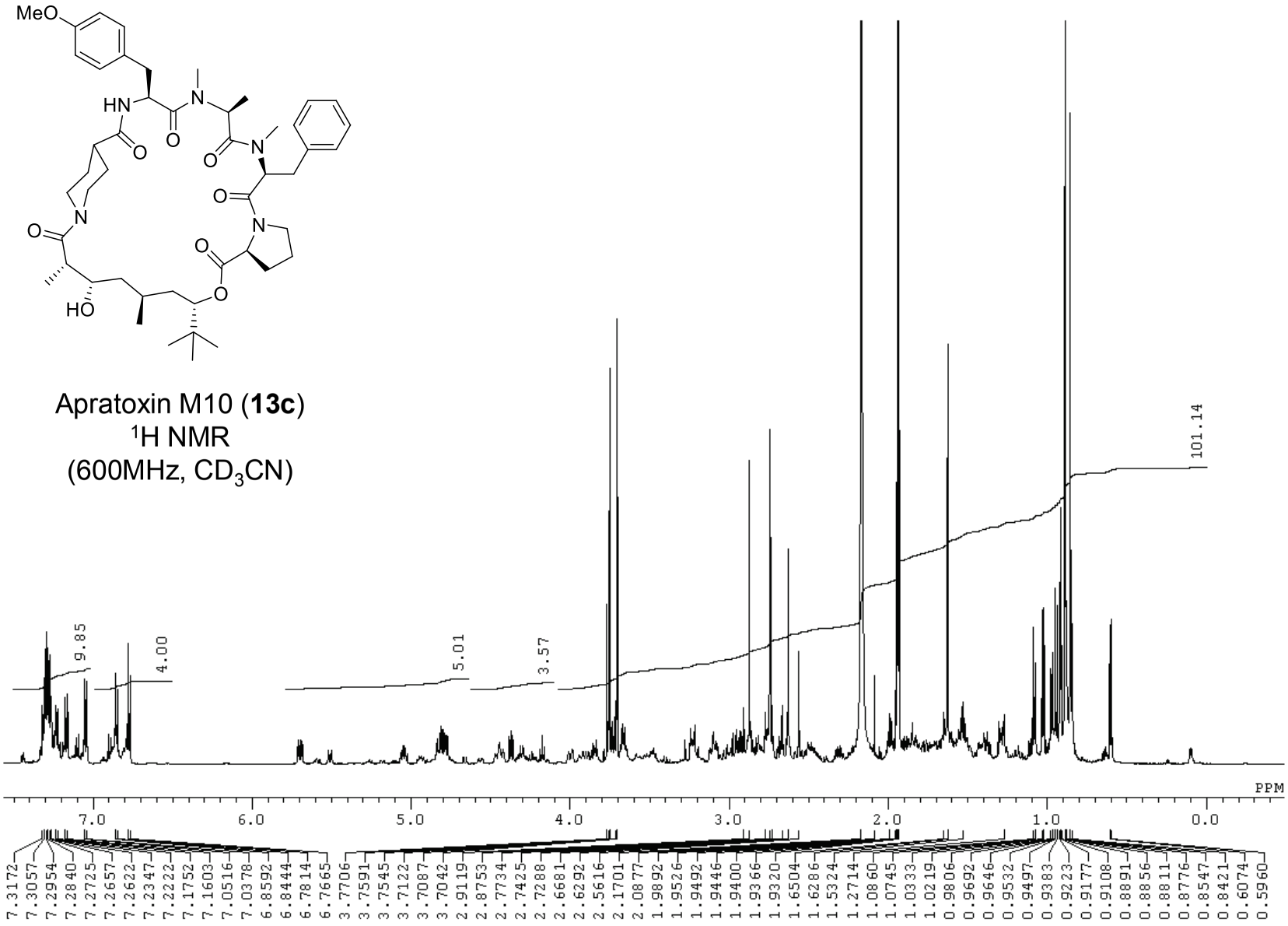
Apratoxin M8 (**13b**)
^{13}C NMR
(150MHz, CD_3CN)

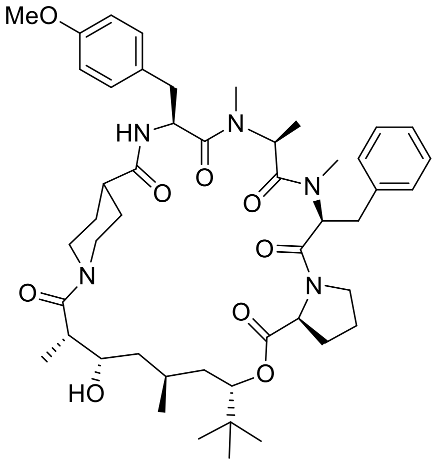

MeO
HN
N
O
HO
Apratoxin M9 (**13b**)
^{1}H NMR
(600MHz, CD_3OD)
2.00
1.89
24.69
59.87
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0



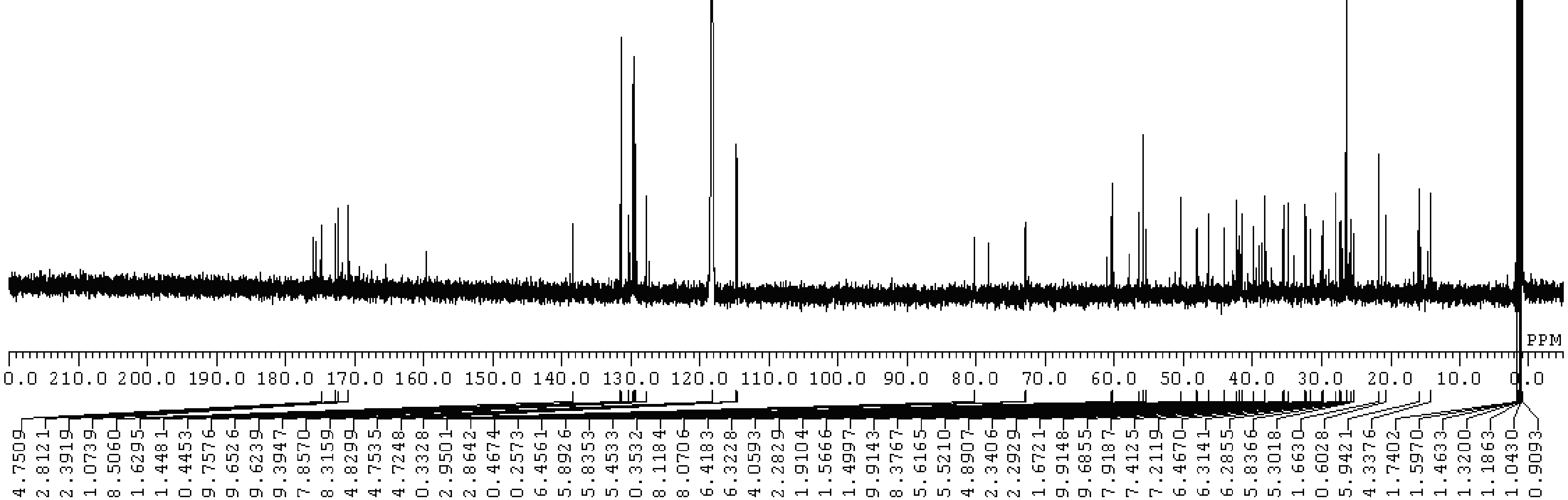
Apratoxin M8 (**13b**)
^{13}C NMR
(150MHz, CD_3OD)

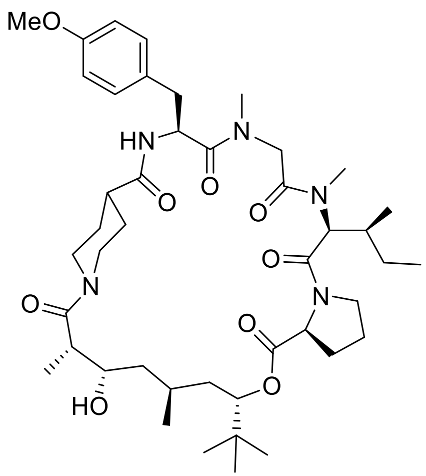



MeO
HN
N
O
HO
Apratoxin M10 (**13c**)
^{1}H NMR
(600MHz, CD_3CN)
9.85
4.00
5.01
3.57
101.14
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

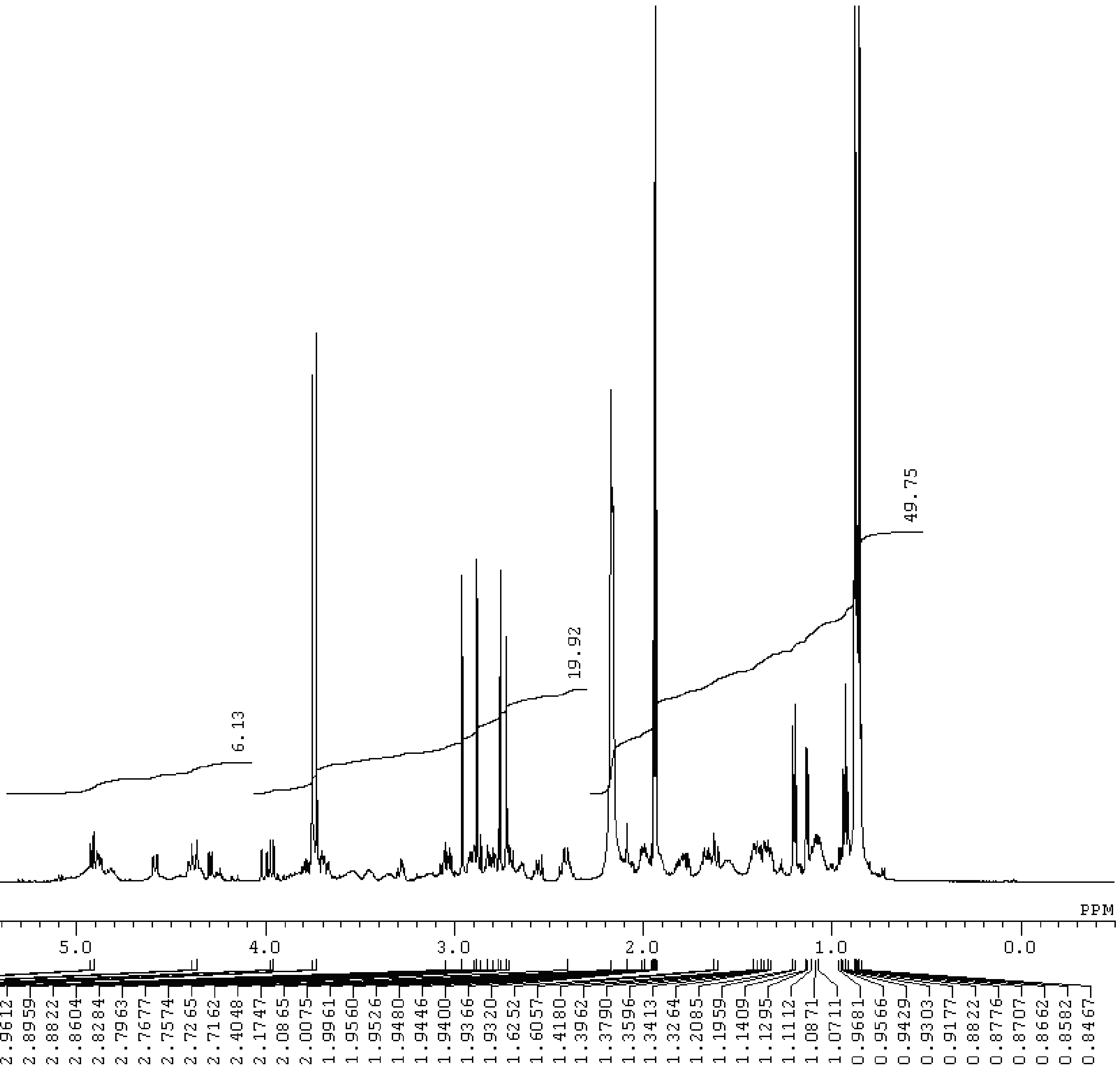


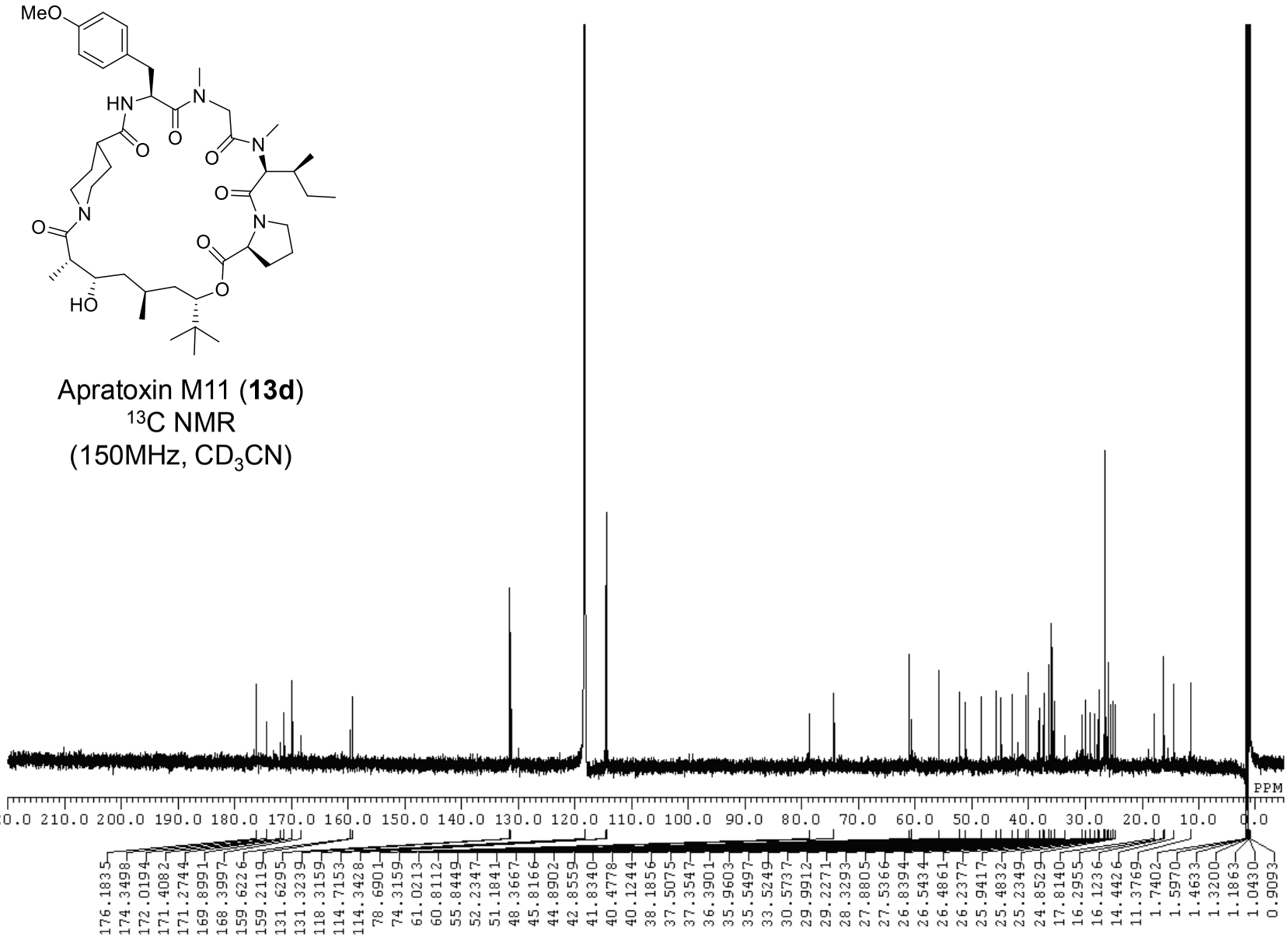
Apratoxin M10 (**13c**)
^{13}C NMR
(150MHz, CD_3CN)

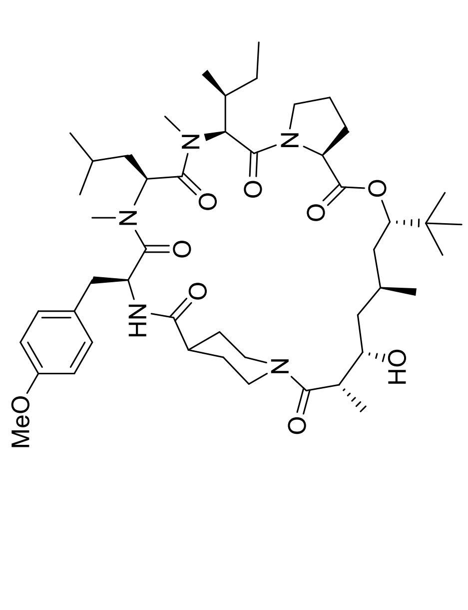


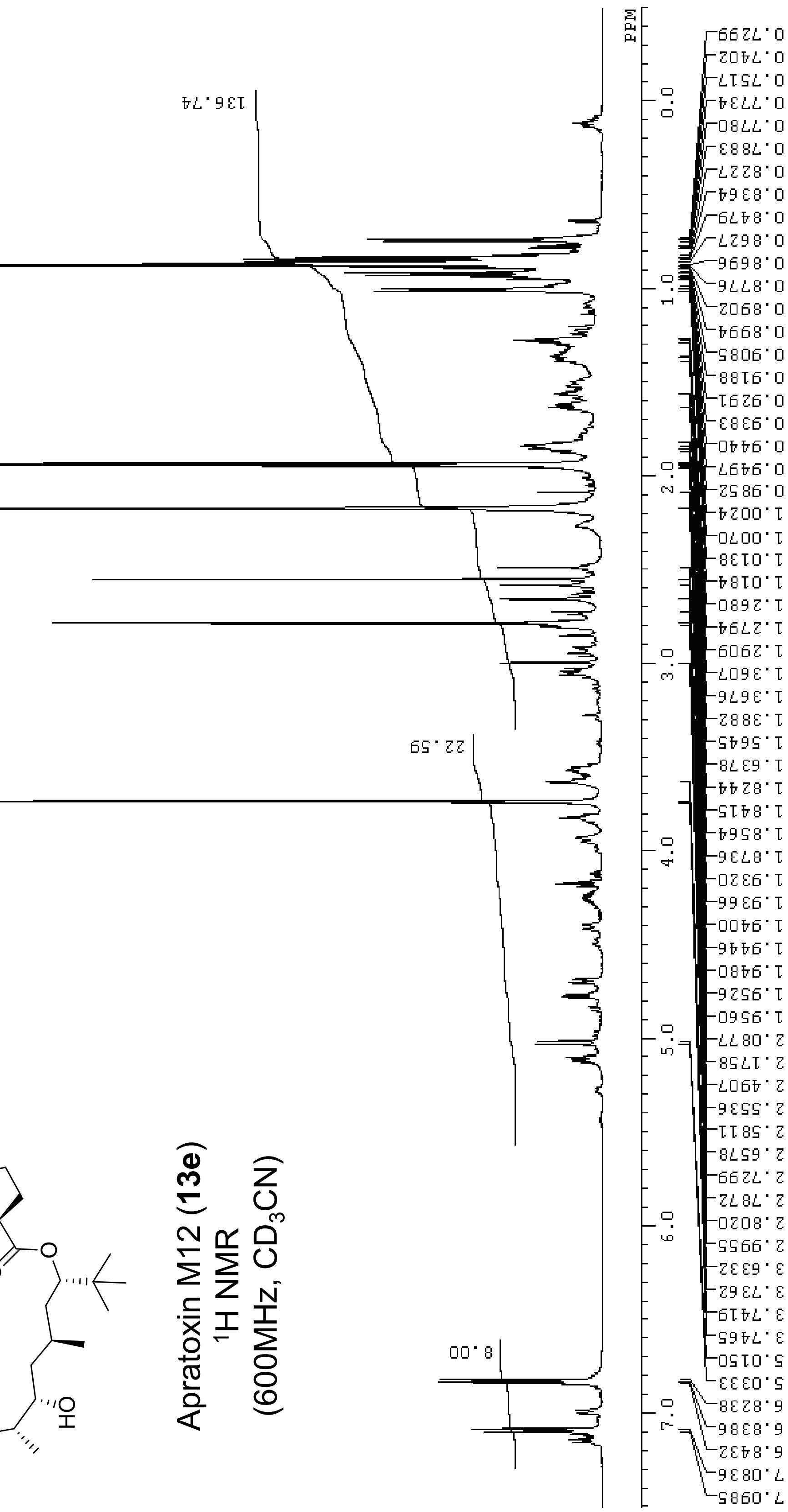


Apratoxin M11 (**13d**)
^{1}H NMR
(600MHz, CD_3CN)

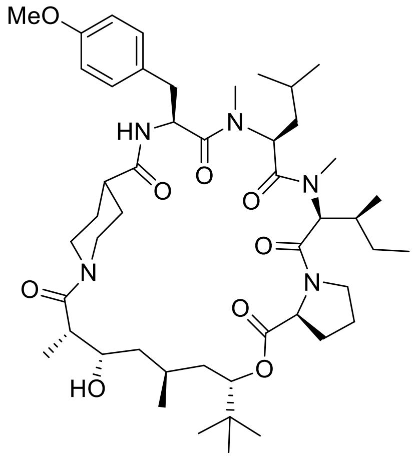



MeO
HN
N
O
HO
Apratoxin M11 (**13d**)
^{13}C NMR
(150MHz, CD_3CN)
PPM
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0
176.1835
174.3498
172.0194
171.4082
171.2744
169.8991
168.3997
159.6226
159.2119
131.6295
131.3239
118.3159
114.7153
114.3428
78.6901
74.3159
61.0213
60.8112
55.8449
52.2347
51.1841
48.3667
45.8166
44.8902
42.8559
41.8340
40.4778
40.1244
38.1856
37.5075
37.3547
36.3901
35.9603
35.5497
33.5249
30.5737
29.9912
29.2271
28.3293
27.8805
27.5366
26.8394
26.5434
26.4861
26.2377
25.9417
25.4832
25.2349
24.8529
17.8140
16.2955
16.1236
14.4426
11.3769
1.7402
1.5970
1.4633
1.3200
1.1863
1.0430
0.9093

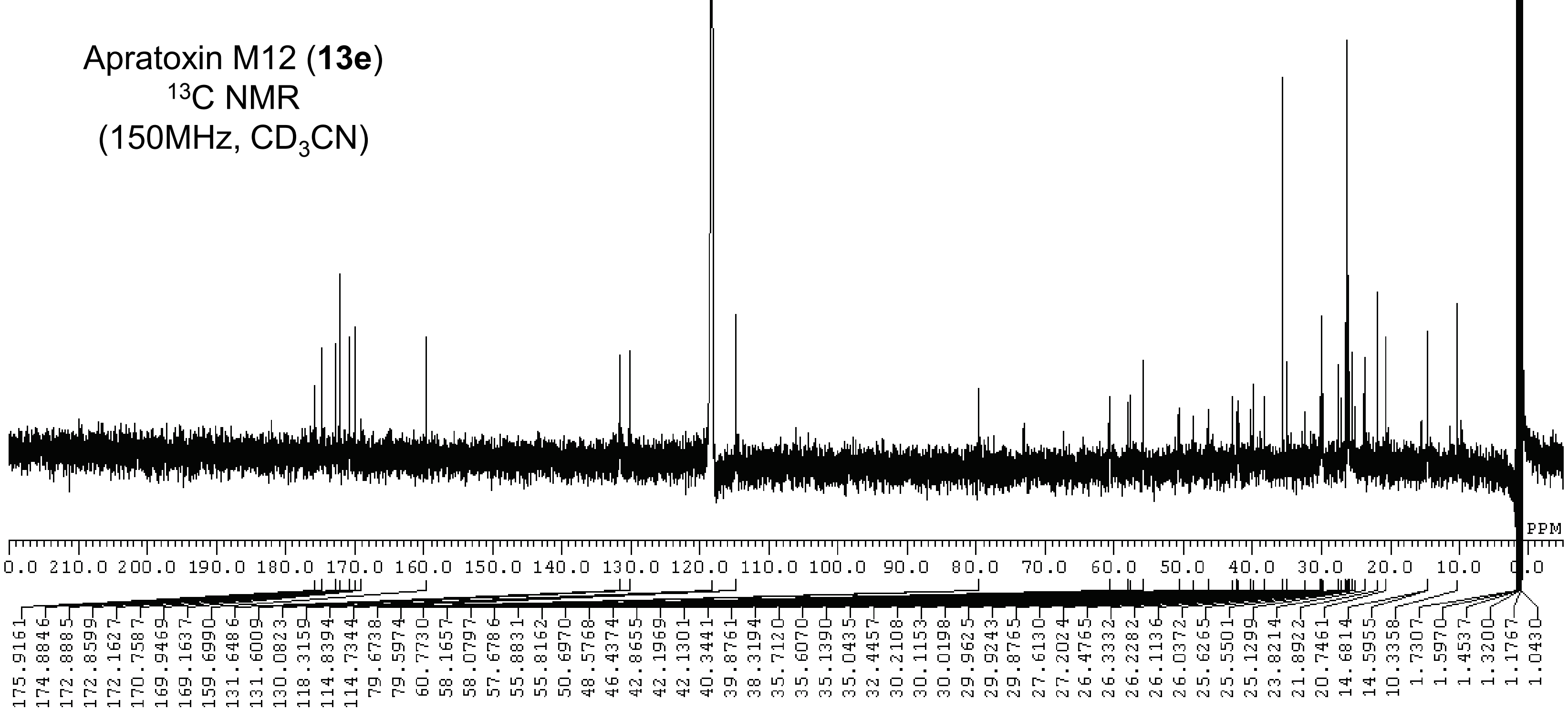


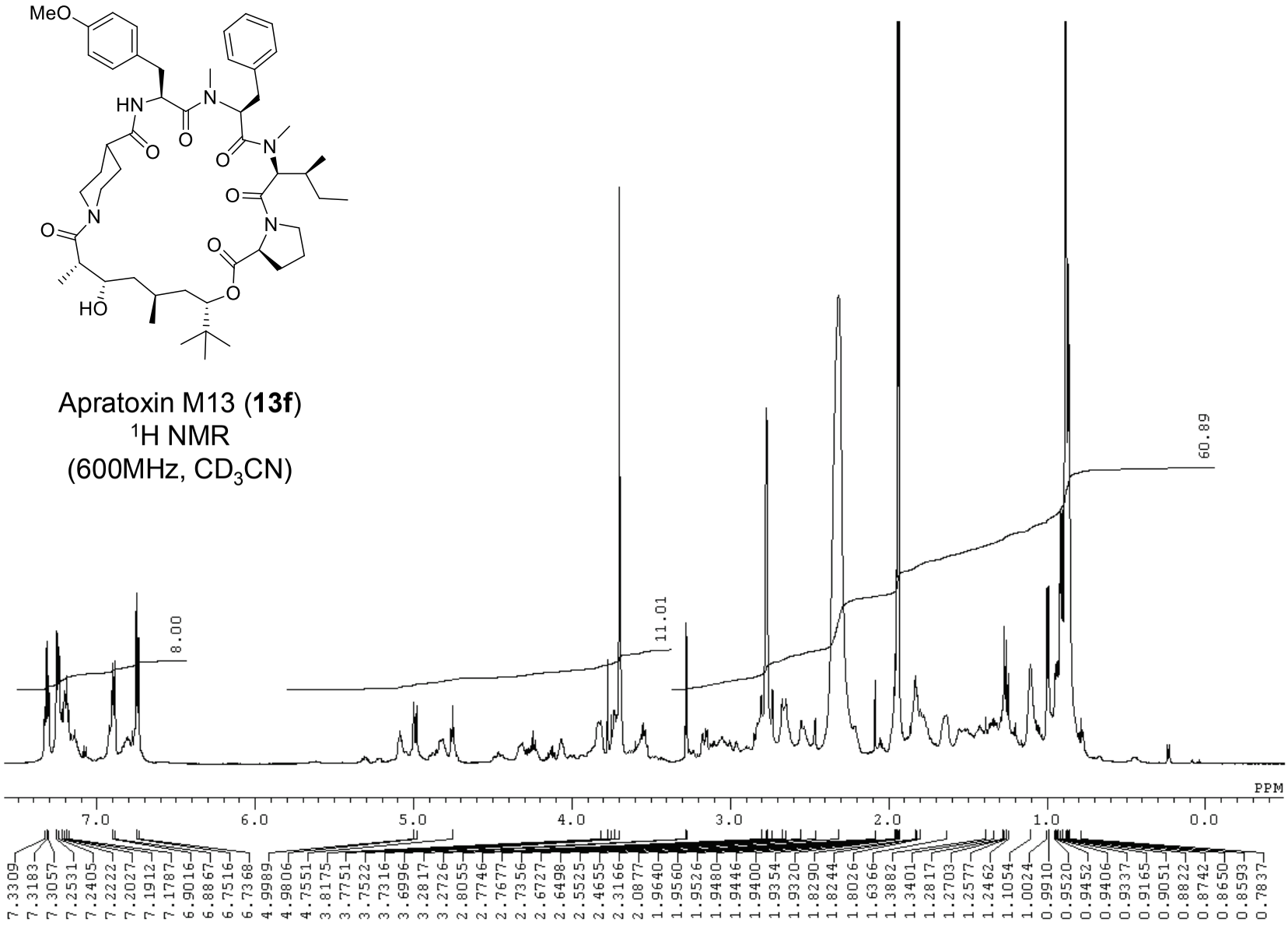


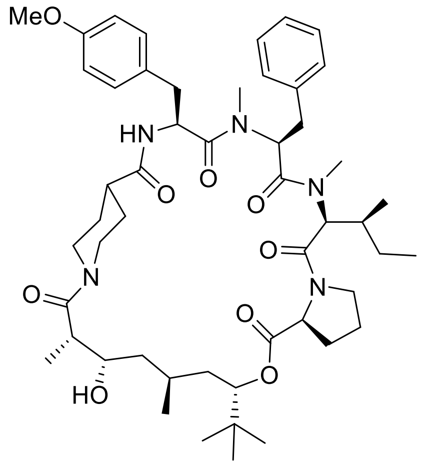
Apratoxin M12 (**13e**)
^{1}H NMR
(600MHz, CD_3CN)



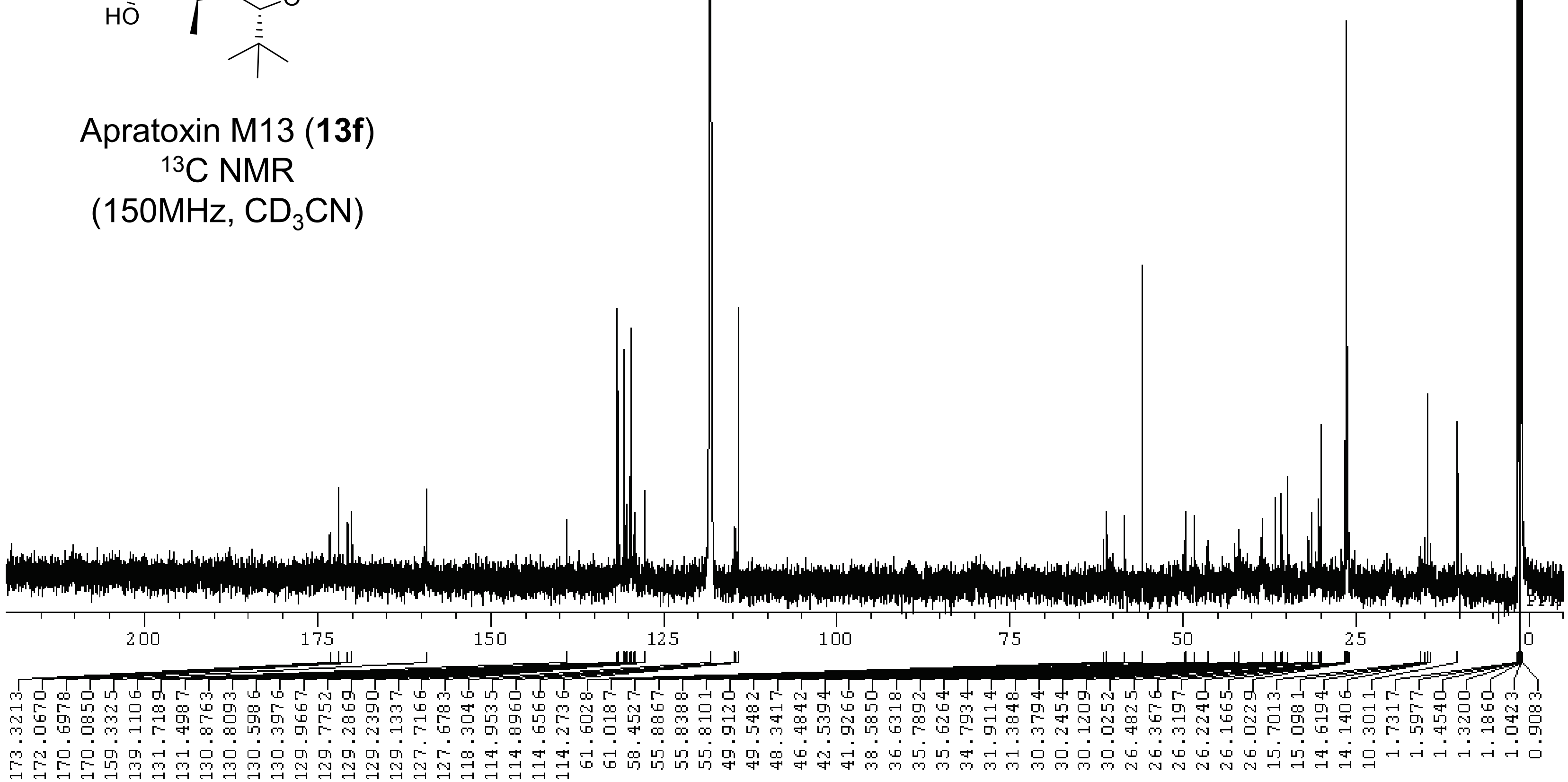
Apratoxin M12 (**13e**)
^{13}C NMR
(150MHz, CD_3CN)

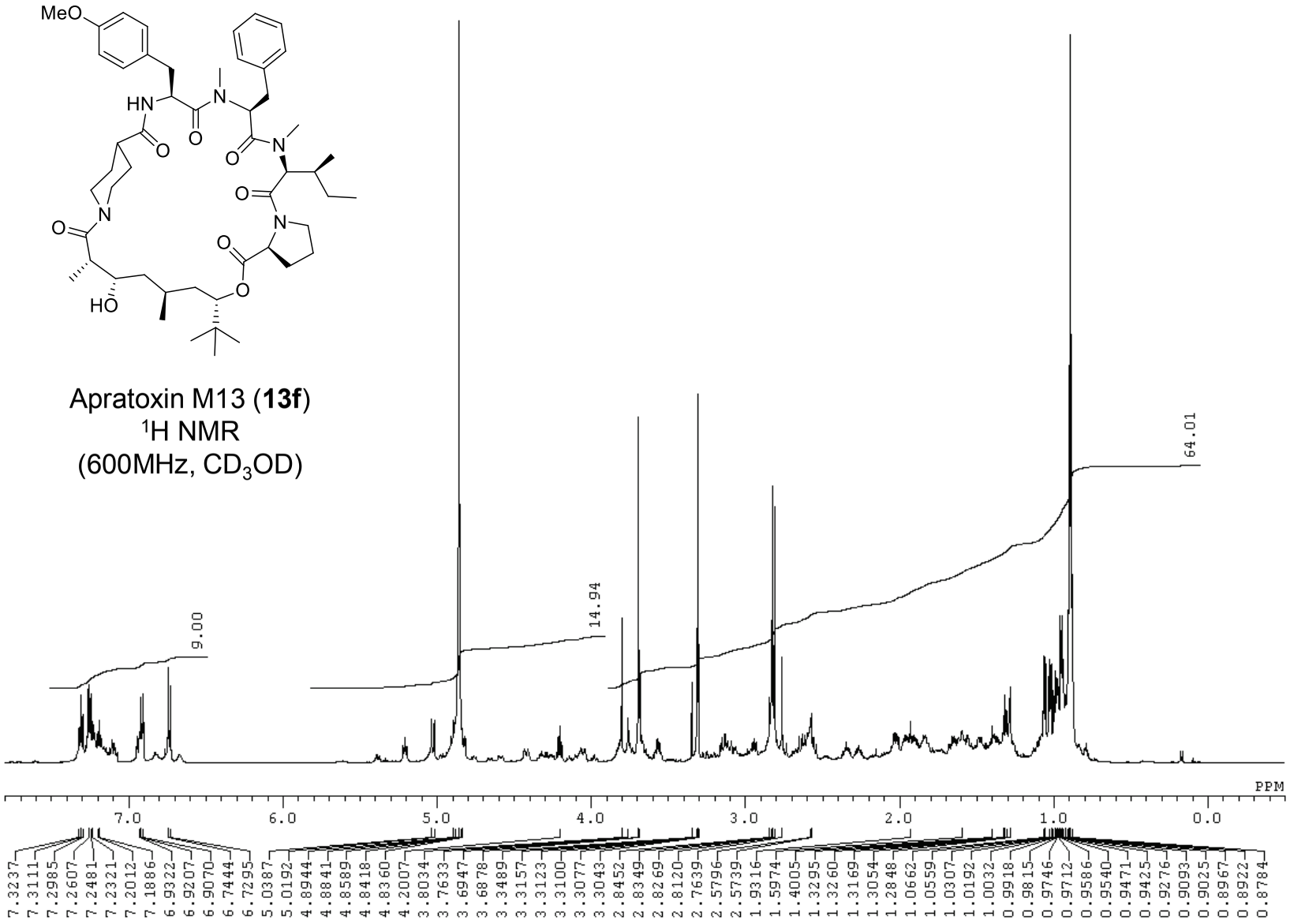


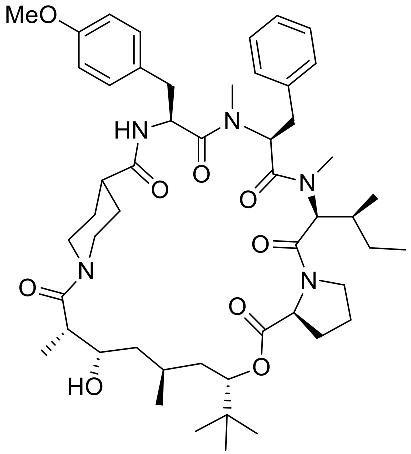

MeO
HN
N
O
N
O
O
N
O
N
O
O
O
HO
Apratoxin M13 (13f)
1H NMR
(600MHz, CD3CN)
8.00
11.01
60.89
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
7.3309
7.3183
7.3057
7.2531
7.2405
7.2222
7.2027
7.1912
7.1787
6.9016
6.8867
6.7516
6.7368
4.9989
4.9806
4.7551
3.8175
3.7751
3.7522
3.7316
3.6996
3.2817
3.2726
2.8055
2.7746
2.7677
2.7356
2.6727
2.6498
2.5525
2.4655
2.3166
2.0877
1.9640
1.9560
1.9526
1.9480
1.9446
1.9400
1.9354
1.9320
1.8290
1.8244
1.8026
1.6366
1.3882
1.3401
1.2817
1.2703
1.2577
1.2462
1.1054
1.0024
0.9910
0.9520
0.9452
0.9406
0.9337
0.9165
0.9051
0.8822
0.8742
0.8650
0.8593
0.7837



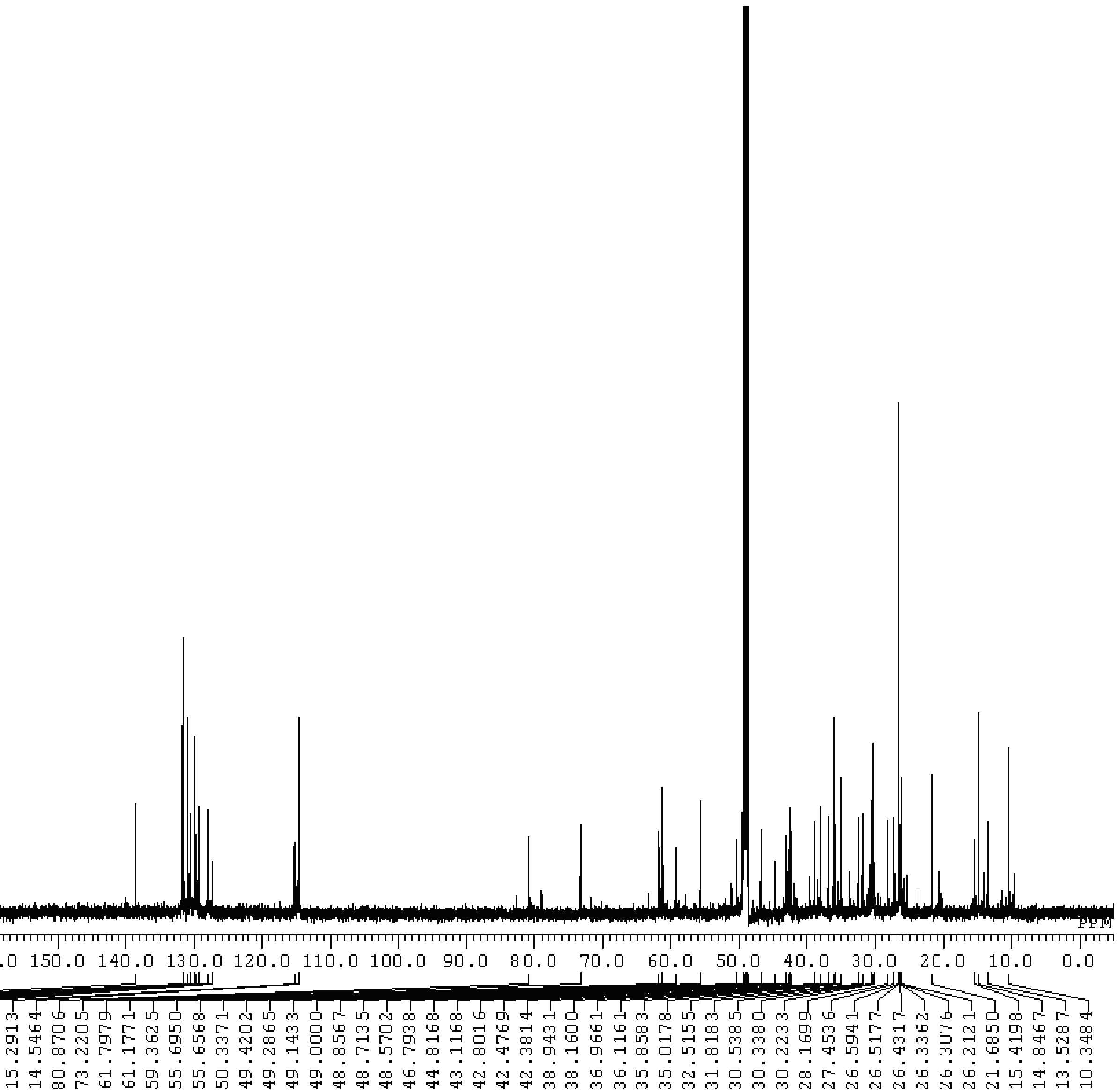
Apratoxin M13 (**13f**)
^{13}C NMR
(150MHz, CD_3CN)

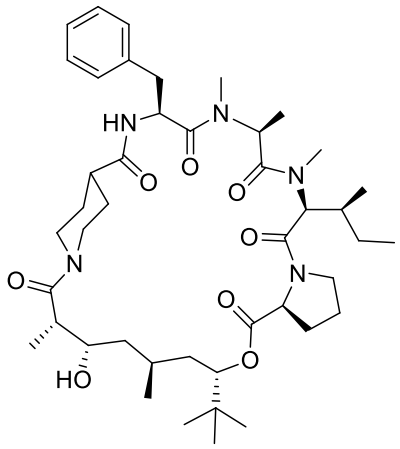



MeO
HN
N
O
HO
Apratoxin M13 (13f)
1H NMR
(600MHz, CD3OD)
9.00
14.94
64.01
PPM
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

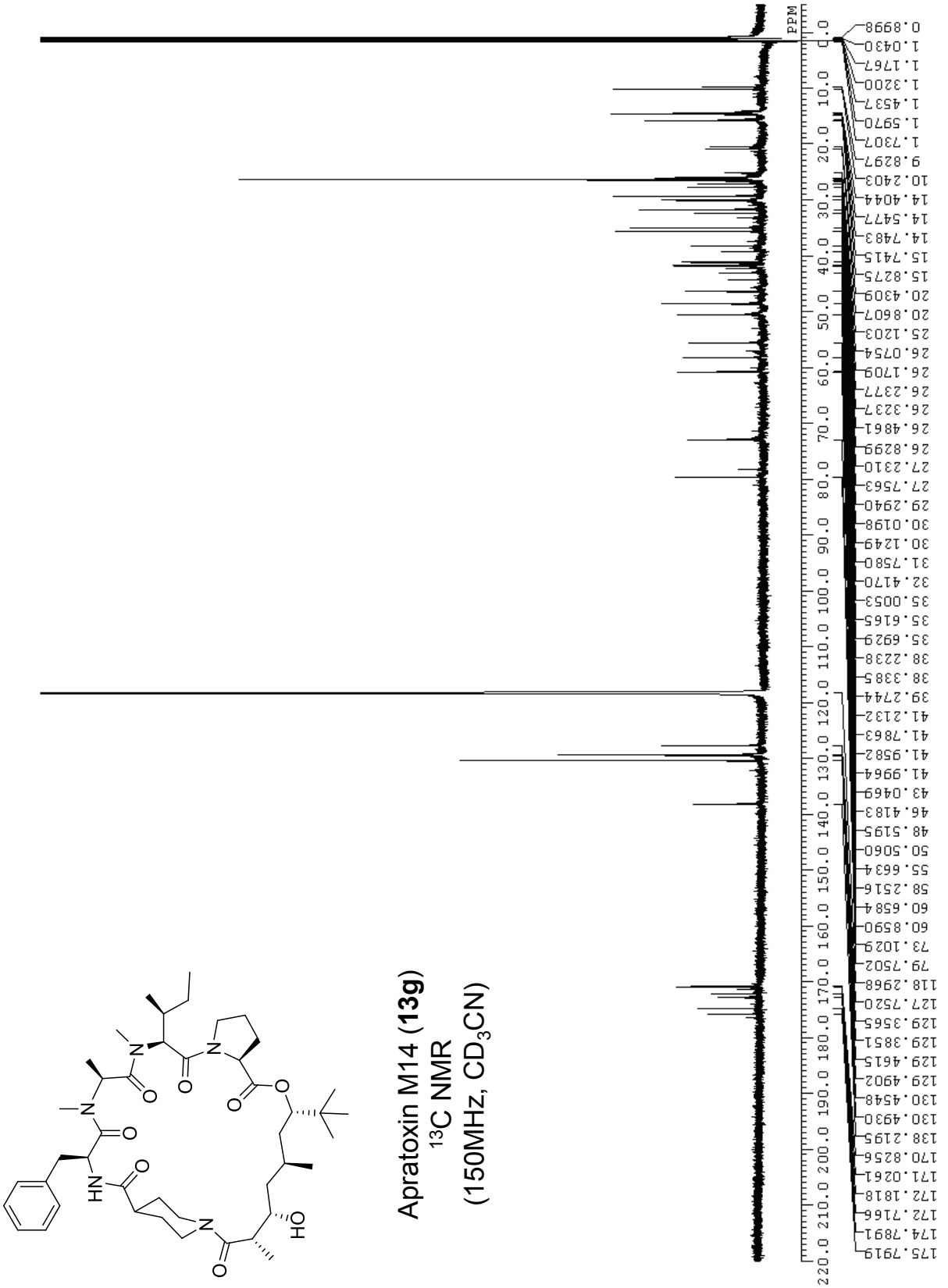


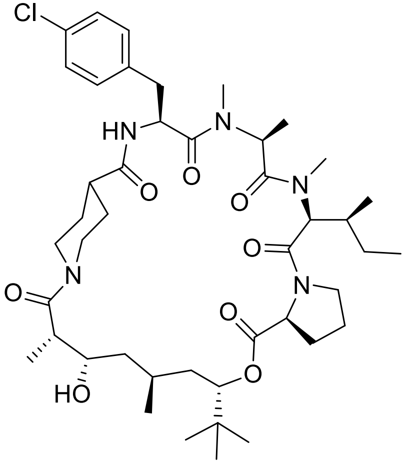
Apratoxin M13 (**13f**)
^{13}C NMR
(150MHz, CD_3OD)



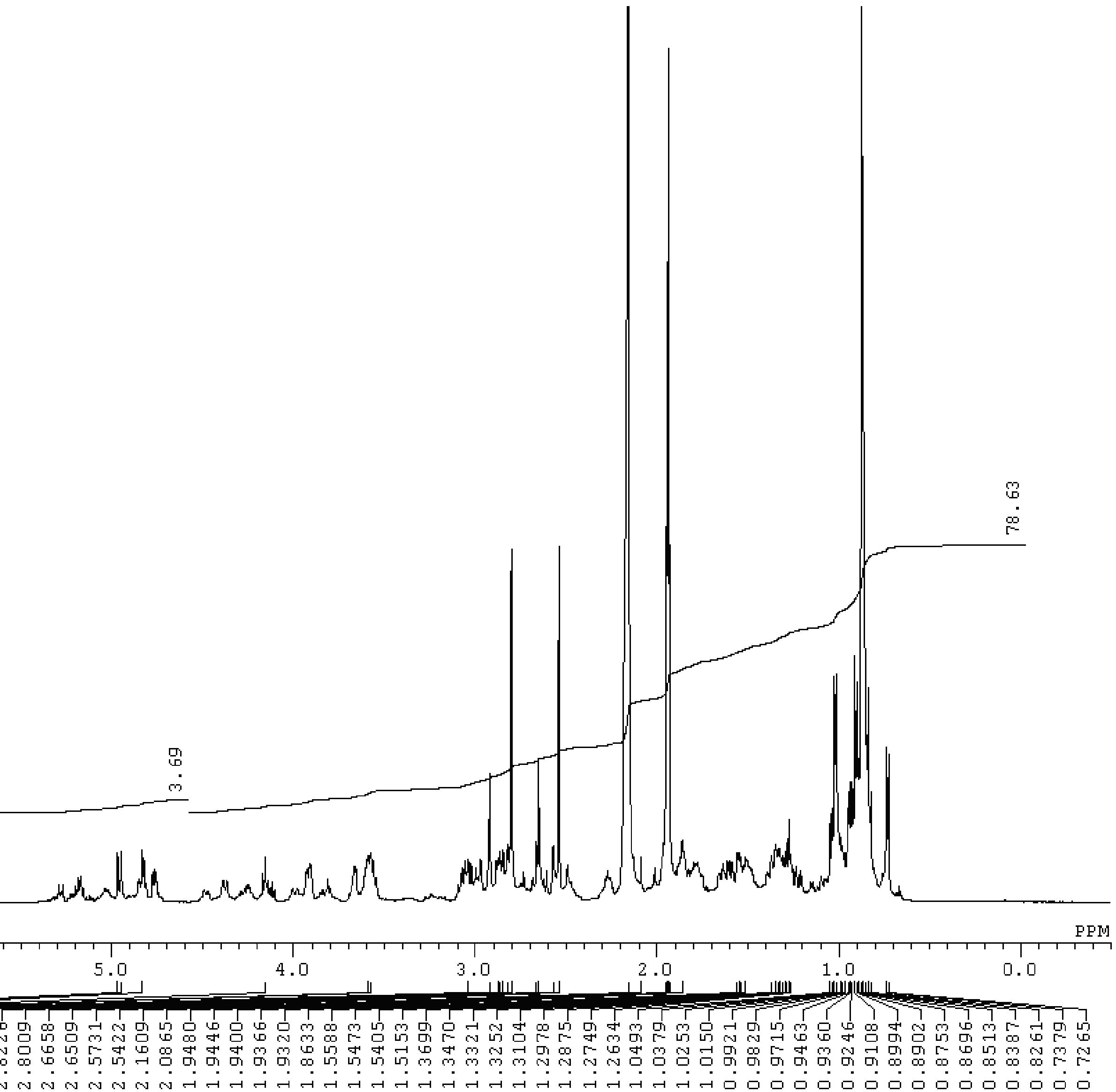


Apratoxin M14 (**13g**)
^{1}H NMR
(600MHz, CD_3CN)


Apratoxin M14 (13g)
13C NMR
(150MHz, CD3CN)
PPM
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
130.0
140.0
150.0
160.0
170.0
180.0
190.0
200.0
210.0
220.0
0.8998
1.0430
1.1767
1.3200
1.4537
1.5970
1.7307
9.8297
10.2403
14.4044
14.5477
14.7483
15.7415
15.8275
20.4309
20.8607
25.1203
26.0754
26.1709
26.2377
26.3237
26.4861
26.8299
27.2310
27.7563
29.2940
30.0198
30.1249
31.7580
32.4170
35.0053
35.6165
35.6929
38.2238
38.3385
39.2744
41.2132
41.7863
41.9582
41.9964
43.0469
46.4183
48.5195
50.5060
55.6634
58.2516
60.6584
60.8590
73.1029
79.7502
118.2968
127.7520
129.3565
129.3851
129.4615
129.4902
130.4548
130.4930
138.2195
170.8256
171.0261
172.1818
172.7166
174.7891
175.7919



Apratoxin M15 (**13h**)
^{1}H NMR
(600MHz, CD_3CN)



Apratoxin M15 (13h)
13C NMR
(150MHz, CD3CN)
PPM
0.9093
1.0430
1.1863
1.3200
1.4633
1.5970
1.7402
9.8201
10.2308
14.3662
14.5477
14.7292
15.7511
16.0663
20.4214
20.9085
25.1299
26.0754
26.1804
26.2377
26.3237
26.3619
26.4861
26.8299
27.2406
27.7563
29.3322
30.0294
30.1440
31.5384
31.7867
32.3979
35.0053
35.6165
35.7025
38.3003
39.2840
40.3345
41.7576
41.9773
43.0469
44.3458
46.4088
48.5481
48.7201
50.2291
55.6252
58.2994
60.6775
60.8590
72.8164
73.1029
79.7598
118.3159
129.3087
129.3851
132.2217
133.1195
137.1403
170.7683
171.0548
172.1818
172.4205
174.8273
175.7728

Apratoxin M16 (13i)
1H NMR
(600MHz, CD3CN)
10.00
10.47
71.79
PPM
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
7.6286
7.6263
7.6125
7.6057
7.5931
7.5885
7.5748
7.5599
7.5461
7.4523
7.4477
7.4397
7.4259
7.3630
7.3607
7.3492
7.3355
7.3218
7.2897
7.2760
4.9669
4.9486
4.1564
2.9864
2.9245
2.8387
2.8181
2.6727
2.6578
2.5822
2.5513
2.1678
2.0877
1.9560
1.9526
1.9480
1.9446
1.9400
1.9366
1.9320
1.8564
1.5267
1.2691
1.2565
1.0493
1.0379
1.0264
1.0150
0.9887
0.9784
0.9486
0.9371
0.9303
0.9188
0.9131
0.9028
0.8948
0.8742
0.8696
0.8604
0.8501
0.8375
0.8250
0.6807
0.6693

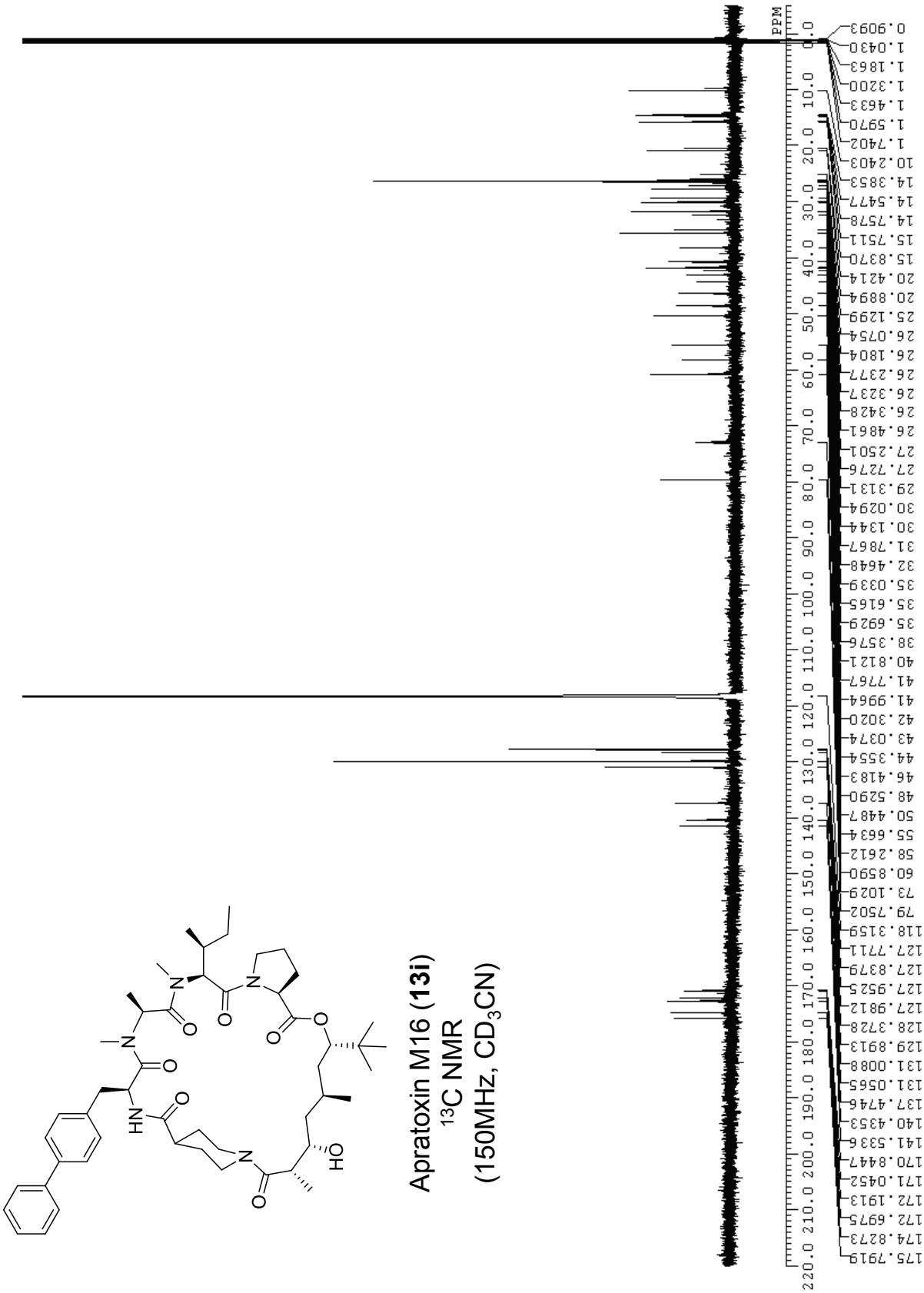

Apratoxin M16 (13i)
13C NMR
(150MHz, CD3CN)
PPM
0.9093
1.0430
1.1863
1.3200
1.4633
1.5970
1.7402
10.2403
14.3853
14.5477
14.7578
15.7511
15.8370
20.4214
20.8894
25.1299
26.0754
26.1804
26.2377
26.3237
26.3428
26.4861
27.2501
27.7276
29.3131
30.0294
30.1344
31.7867
32.4648
35.0339
35.6165
35.6929
38.3576
40.8121
41.7767
41.9964
42.3020
43.0374
44.3554
46.4183
48.5290
50.4487
55.6634
58.2612
60.8590
73.1029
79.7502
118.3159
127.7711
127.8379
127.9525
127.9812
128.3728
129.8913
131.0088
131.0565
137.4746
140.4353
141.5336
170.8447
171.0452
172.1913
172.6975
174.8273
175.7919

Table S1. A panel of 10 cancer cell lines for growth inhibition assay.

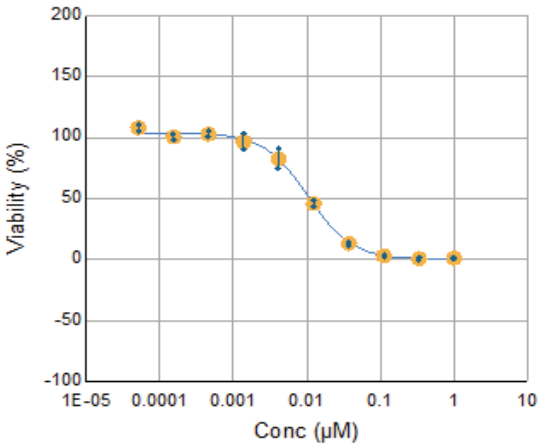
cancer cell line	**tissue**	**resource[a] (resource No.)**	**culture medium[b]**	**number of cells (cells/well)**
HCT-116	colon	ECACC (CCL-247)	M5A, 10% FBS	1×10^3
BxPC-3	pancreas	ATCC (CRL-1687)	RPMI, 10% FBS	2×10^3
A549	lung	JCRB (JCRB0076)	DMEM, 2 mM glutamine	1×10^3
HuH-7	liver	JCRB (JCRB0403)	DMEM, 10% FBS	2×10^3
MKN74	stomach	JCRB (JCRB0255)	RPMI, 10% FBS	2×10^3
U-87 MG	brain	ATCC (HTB-14)	EMEM, 10% FBS	2×10^3
SK-OV-3	ovary	ATCC (HTB-77)	M5A, 10% FBS	2×10^3
HEC-6	uterus	JCRB (JCRB1118)	EMEM, 15% FBS	2×10^3
786-O	kidney	ATCC (CRL-1932)	RPMI, 10% FBS	1×10^3
MCF7	breast	JCRB (JCRB0134)	EMEM, NEAA, 1 mM SP, 0.01 mg/ml insulin, 10% FBS	3×10^3

[a]Abbreviations: ATCC, American Type Culture Collection; JCRB, Japanese Collection of Research Bioresources; ECACC, European Collection of Authenticated Cell Cultures.

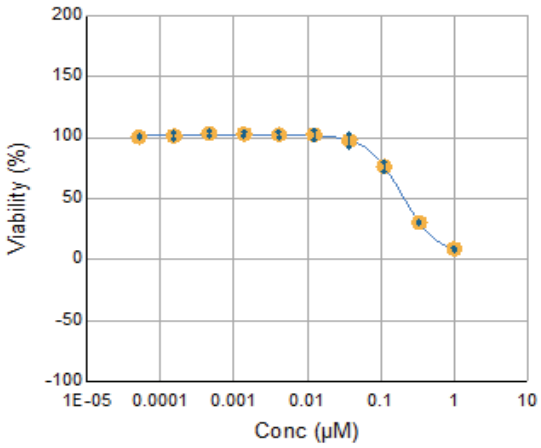
[b]All the media include 100 units/mL penicillin and 100 μg/mL streptomycin.

HCT-116

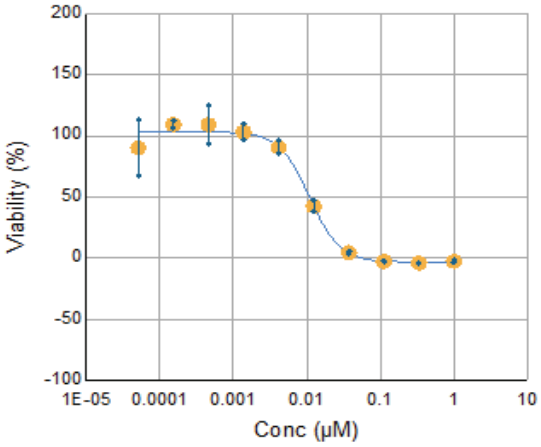
(A) apratoxin A



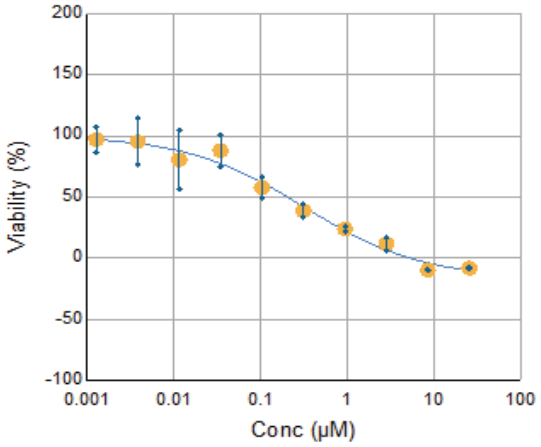
(B) apratoxin A15



(C) apratoxin M16

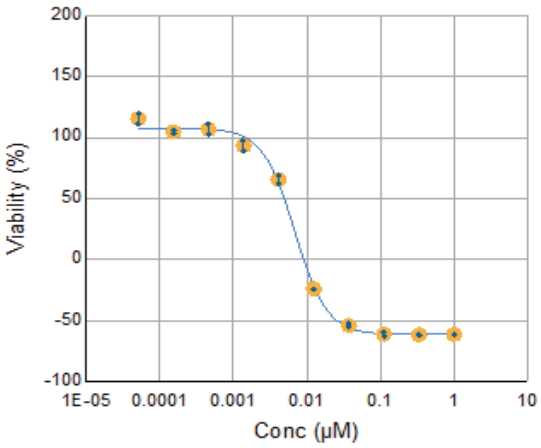


(D) mitomycin C

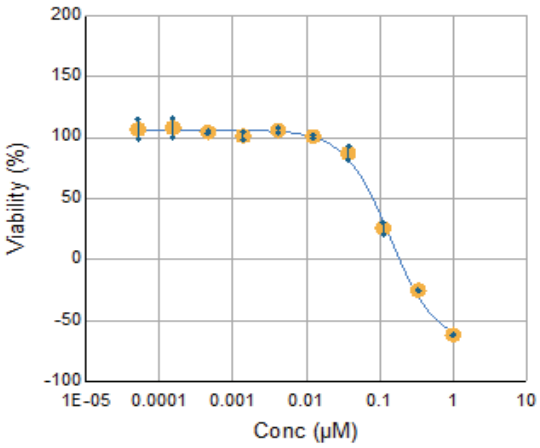


BxPC-3

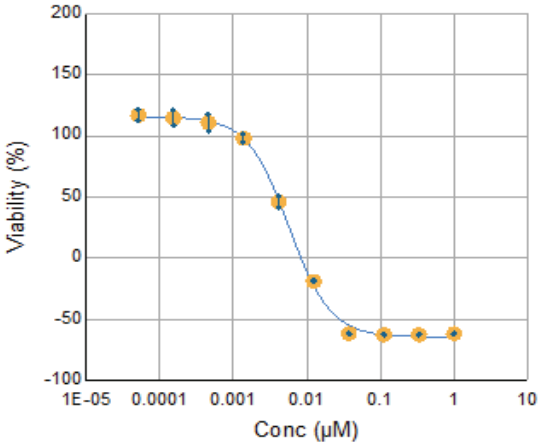
(A) apratoxin A



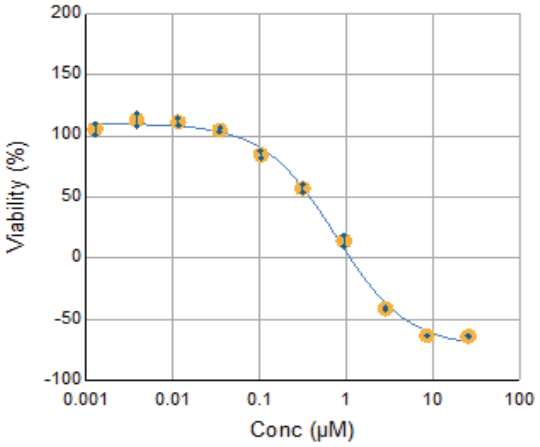
(B) apratoxin A15



(C) apratoxin M16

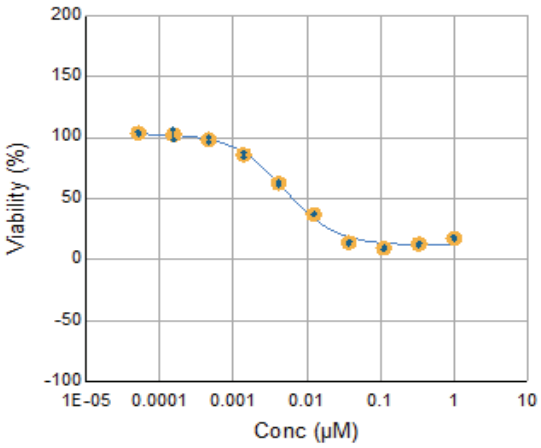


(D) mitomycin C

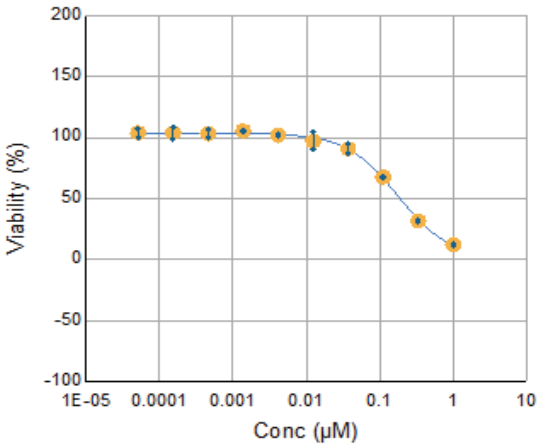


A549

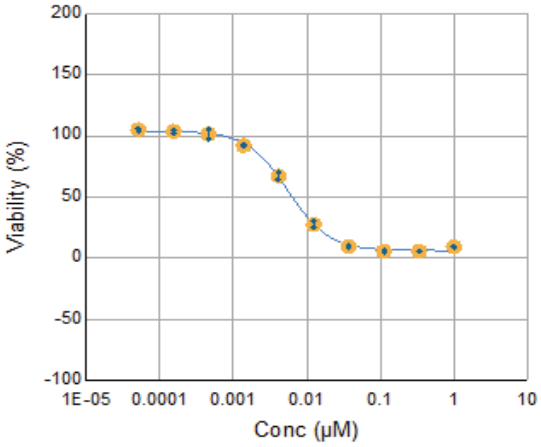
(A) apratoxin A



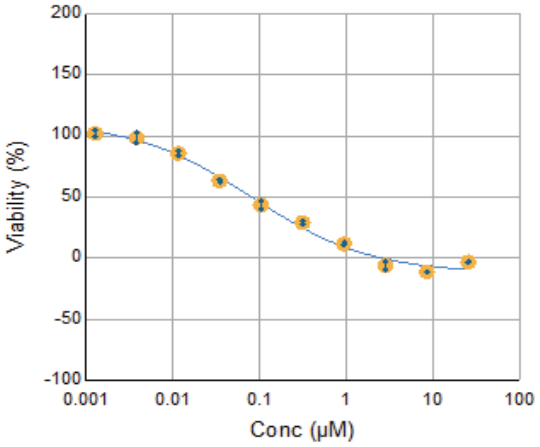
(B) apratoxin A15



(C) apratoxin M16

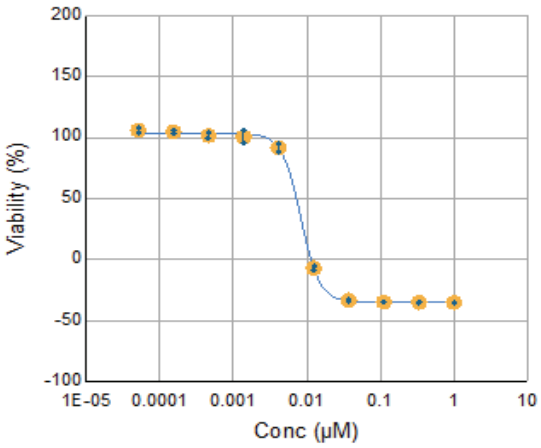


(D) mitomycin C

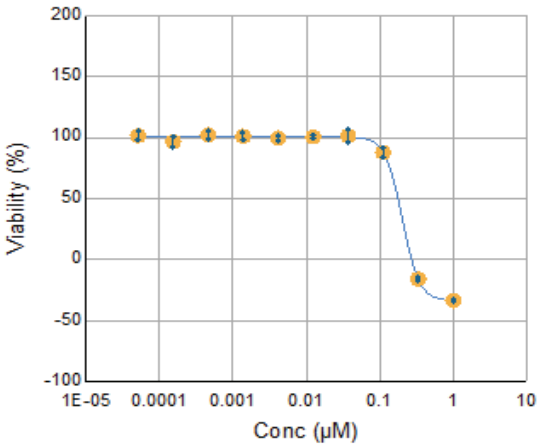


HuH-7

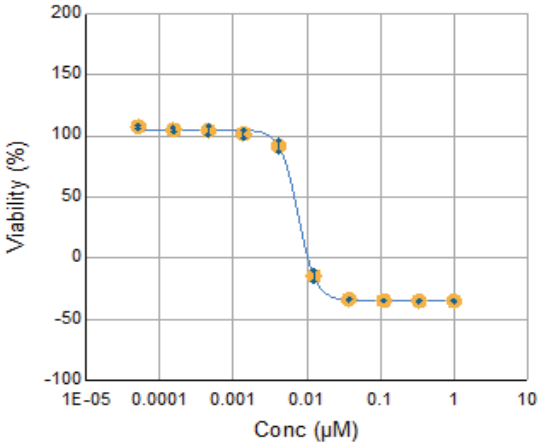
(A) apratoxin A



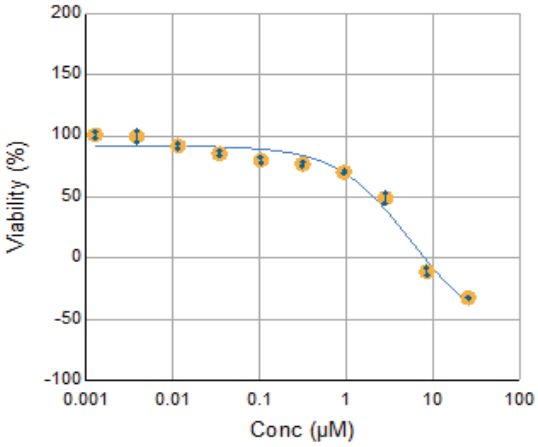
(B) apratoxin A15



(C) apratoxin M16

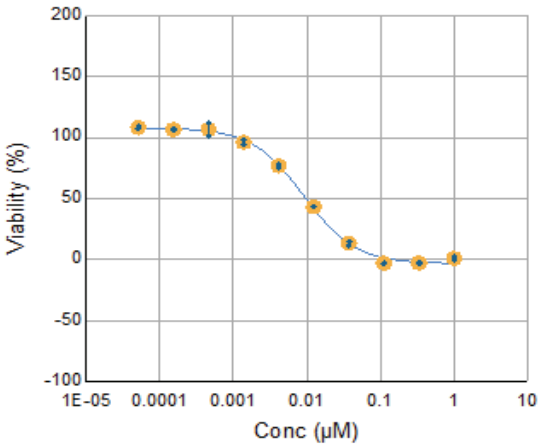


(D) mitomycin C

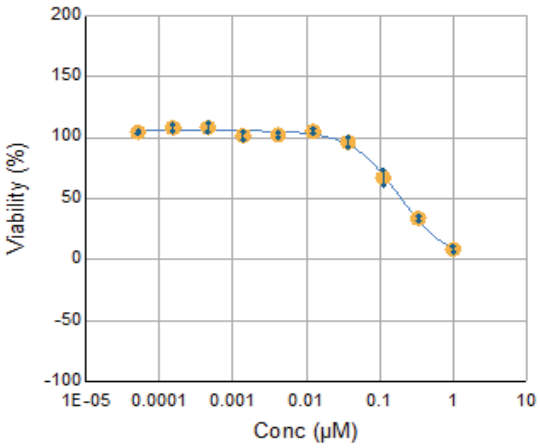


MKN74

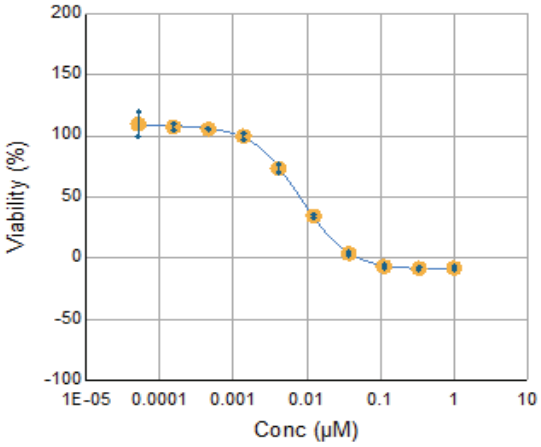
(A) apratoxin A



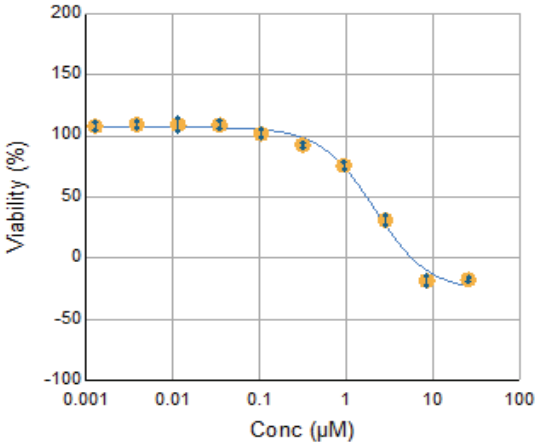
(B) apratoxin A15



(C) apratoxin M16

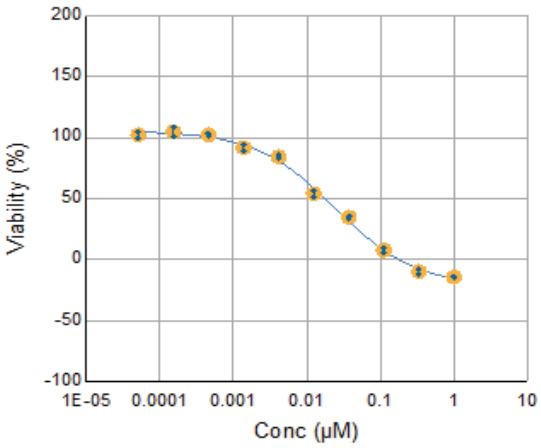


(D) mitomycin C

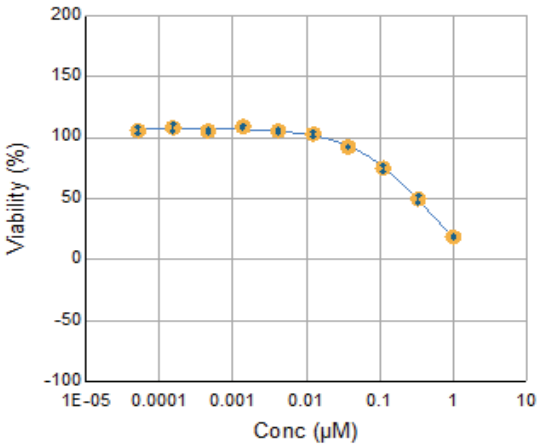


U-87MG

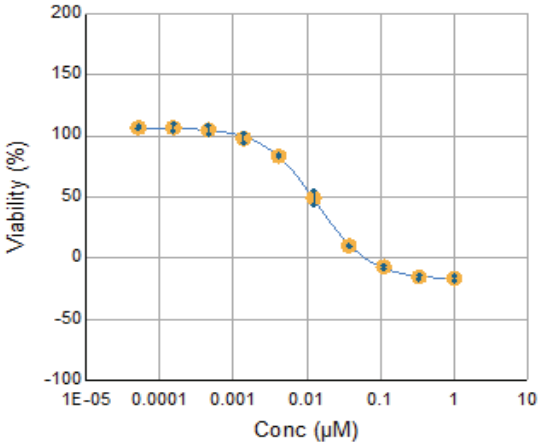
(A) apratoxin A



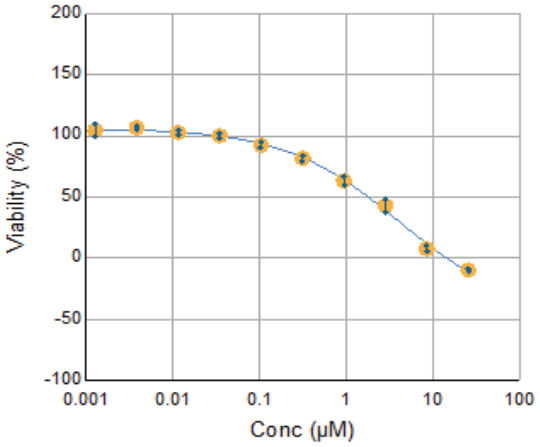
(B) apratoxin A15



(C) apratoxin M16

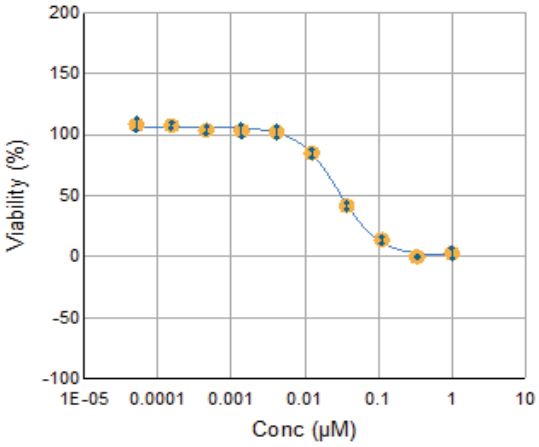


(D) mitomycin C

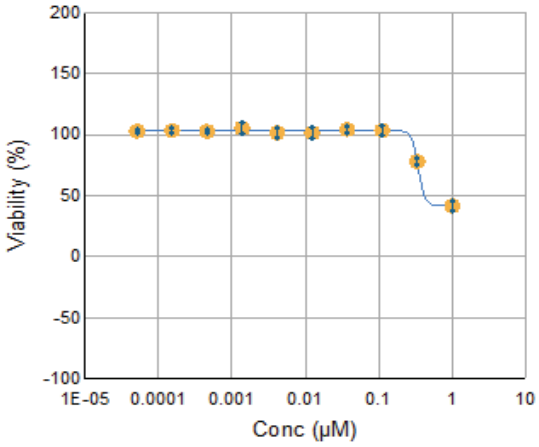


SK-OV-3

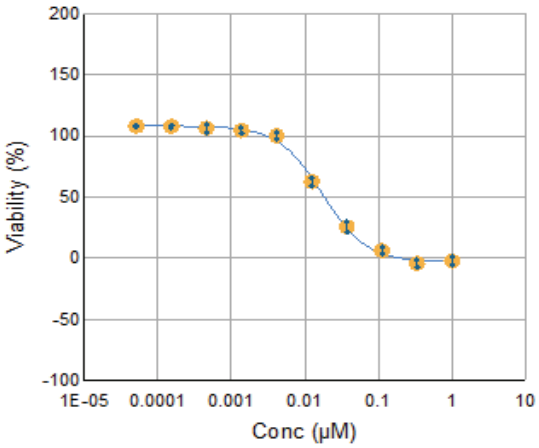
(A) apratoxin A



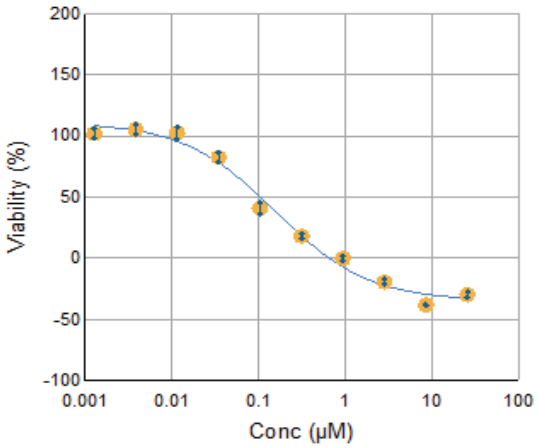
(B) apratoxin A15



(C) apratoxin M16

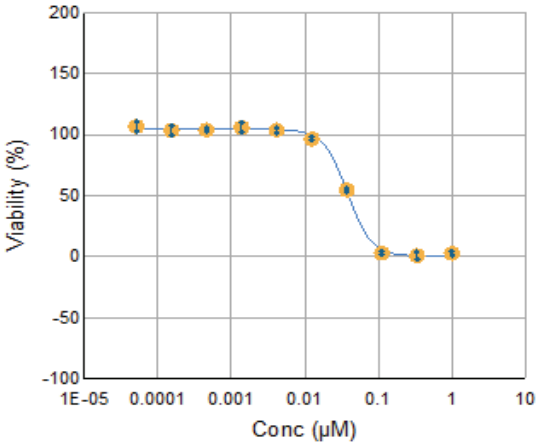


(D) mitomycin C

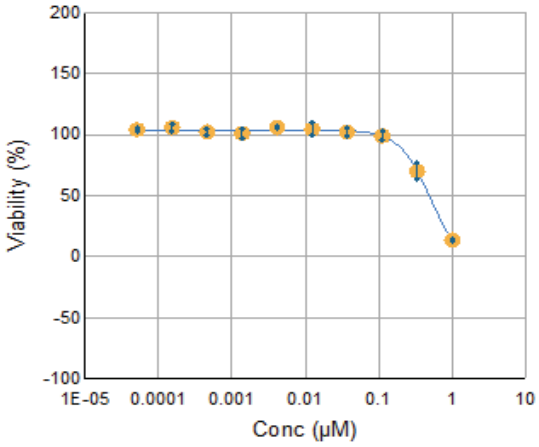


Hec-6

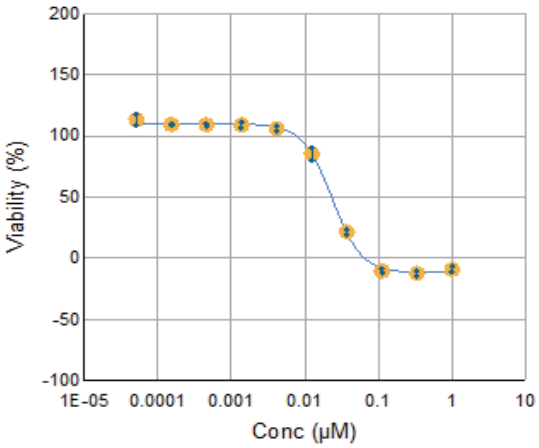
(A) apratoxin A



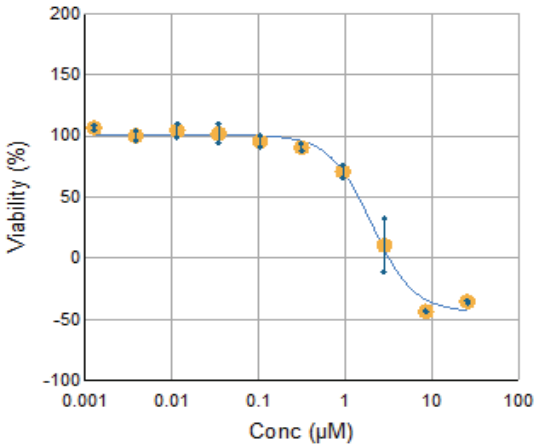
(B) apratoxin A15



(C) apratoxin M16

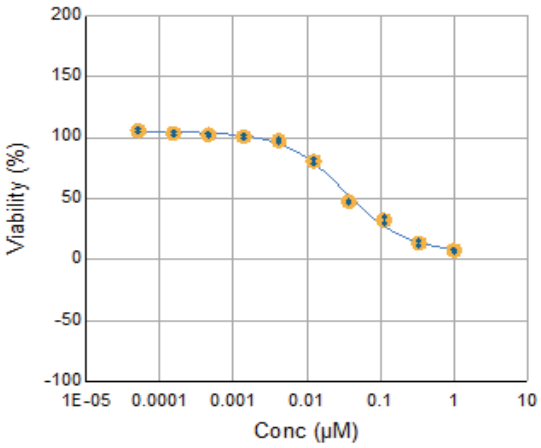


(D) mitomycin C

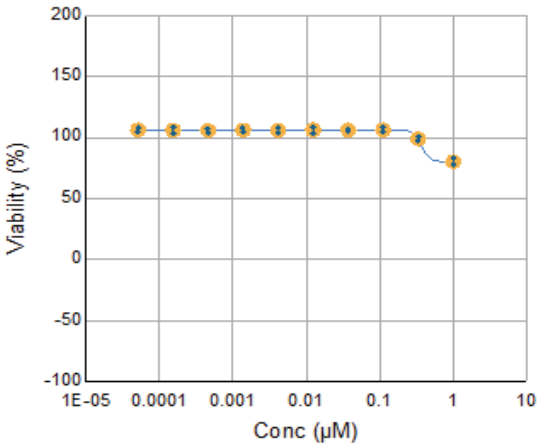


786-O

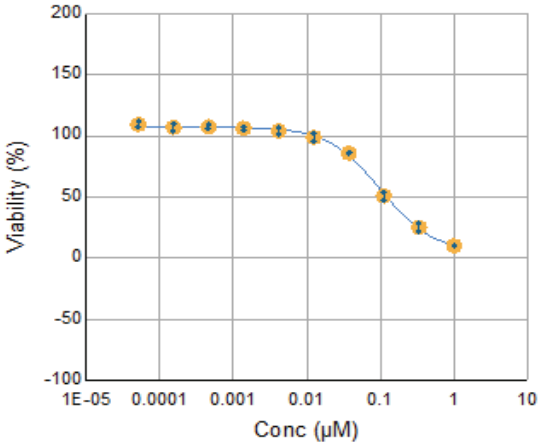
(A) apratoxin A



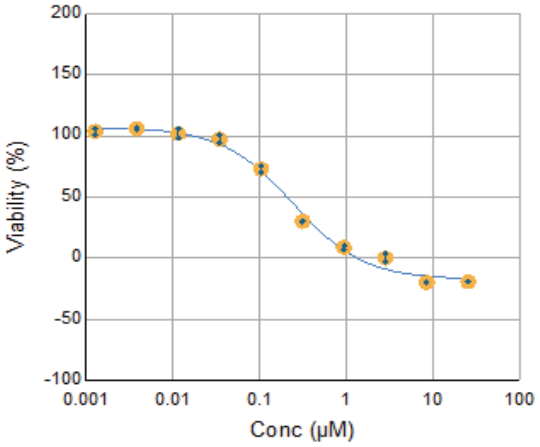
(B) apratoxin A15



(C) apratoxin M16

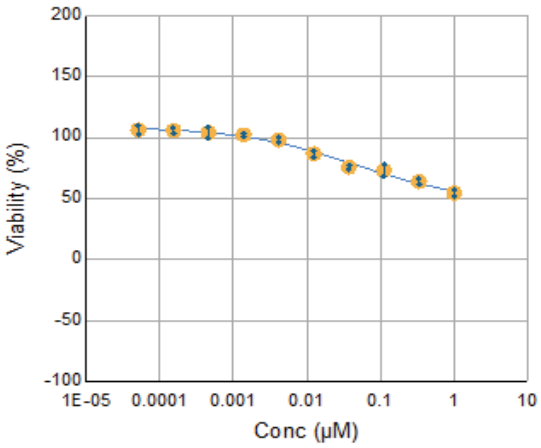


(D) mitomycin C

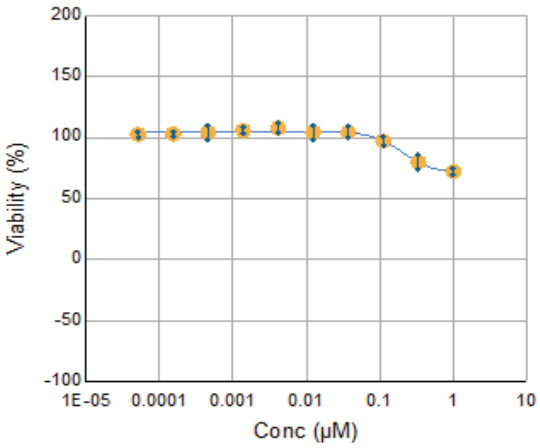


MCF-7

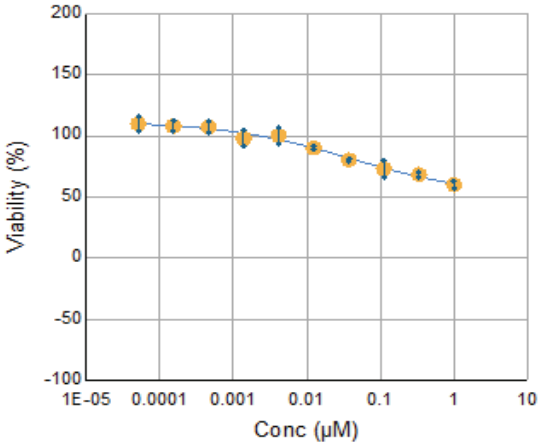
(A) apratoxin A



(B) apratoxin A15



(C) apratoxin M16



(D) mitomycin C