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Table S1. List of 62 herbs.

Sample #	Common Name	Genus and species
1	Vetivert root	<i>Vetiveria zizanioides</i>
2	Canada snakeroot	<i>Asarum canadense</i>
3	Atractylodes	<i>Atractylodes macrocephala</i>
4	Schizandra berries	<i>Schisandrae chinensis</i>
5	Stone root	<i>Collinsonia canadensis</i>
6	Elecampane	<i>Inula helenium</i>
7	Lady's mantle	<i>Alchemilla vulgaris</i>
8	Butterbur	<i>Petasites frigidus</i>
9	Danshen	<i>Salvia miltiorrhiza</i>
10	Osha root	<i>Ligusticum porteri</i>
11	Cinnamon sticks	<i>Cinnamomum cassia</i>
12	Jujube date	<i>Ziziphus jujuba</i>
13	Rehmannia root	<i>Rehmannia glutinosa</i>
14	Muirá puama	<i>Ptychopetalum olacoides</i>
15	Kava root	<i>Piper methysticum</i>
16	Fo-Ti (He Shou Wu)	<i>Polygonum multiflorum</i>
17	Valerian root	<i>Valeriana officinalis</i>
18	Blue malva	<i>Malva officinalis</i>
19	Boldo	<i>Peumus boldus</i>
20	Alkanet root	<i>Alkanna tinctoria</i>
21	Honeysuckle flowers	<i>Lonicera japonica</i>
22	California poppy	<i>Eschscholzia californica</i>
23	Chinese Licorice	<i>Glycyrrhiza uralensis</i>
24	Chrysanthemum flowers	<i>Chrysanthemum morifolium</i>
25	Horney Goat Weed	<i>Epimedium brevicornum</i>
26	Chaparral	<i>Larrea divaricata</i>
27	Oakmoss	<i>Evernia furfuracea</i>
28	Dong Quai	<i>Angelica sinensis</i>
29	Wakame	<i>Alaria marginata</i>
30	Astragalus	<i>Astragalus membranaceus</i>
31	Magnolia bark	<i>Magnolia officinalis</i>
32	Bai Zhi	<i>Angelica dahurica</i>
33	Peony root	<i>Paeonia lactiflora</i>
34	Chuan Xin Lian	<i>Andrographis paniculata</i>
35	Poke root	<i>Phytolacca americana</i>
36	Ajwain seed	<i>Apium graveolens</i>
37	Deer's Tongue leaf	<i>Trilisa odoratissima</i>
38	Kelp	<i>Nereocystis sp.</i>
39	Eleuthero	<i>Eleutherococcus senticosus</i>
40	Goldthread	<i>Coptis chinensis</i>
41	Bupleurum	<i>Bupleurum chinense</i>
42	Chaste Tree berry	<i>Vitex agnus-castus</i>
43	Codonopsis	<i>Codonopsis pilosula</i>
44	Lycii (Goji berry) berries	<i>Lycium chinense</i>
45	Calamus root	<i>Acorus calamus</i>
46	Quassia	<i>Quassia amara</i>
47	Orris root	<i>Iris germanica var. Florentina</i>
48	Papaya leaf	<i>Carica papaya</i>
49	Angelica	<i>Angelica archangelica</i>
50	Tansy flowering tops	<i>Tanacetum vulgare</i>
51	Corydalis root	<i>Corydalis yanhusuo</i>
52	Isatis	<i>Brassicaceae sp.</i>
53	Pau D'arco	<i>Tabebuia impetiginosa</i>
54	Pygeum	<i>Pygeum africanum</i>
55	Gymnema sylvestre	<i>Gymnema sylvestre</i>
56	Tonka bean	<i>Dipteryx odorata</i>
57	Chuan xiong	<i>Ligusticum wallichii</i>
58	Blue flag	<i>Iris versicolor</i>
59	Job's tears	<i>Coix lacryma-jobi</i>
60	Skullcap	<i>Scutellaria baicalensis</i>
61	Reishi mushroom	<i>Ganoderma lucidum</i>
62	High John the Conqueror	<i>Ipomea jalapa</i>

Table S2. ^1H NMR (600 MHz) data for actinomycin D (**9**) and V (**10**) in CDCl_3

No.	9	10
3	7.59, d (7.7)	7.59, d (7.7)
4	7.35, d (7.8)	7.36, d (7.7)
2'	4.51, dd (7.1, 2.5)	4.58, m
4'	3.53, dd (9.5, 6.0)	3.59, m
5'	2.16, m	2.13, m
6'	1.09, d (6.6) ^b	1.13, d (6.8) ^b
7'	0.85, d (6.6) ^b	0.91, d (6.8) ^b
9'	3.70, m; 3.95, m	3.98, d (19.5); 4.54, m
10'	2.07, 2.23, m	--
11'	1.80, m; 2.61, m	2.34, d (17.5); 3.65 d (17.2)
12'	5.98, d (9.2)	6.56, d (10.0)
14'	2.85, s	2.90, s ^d
15'	3.63, d (17.5); 4.71, d (17.5)	3.71, m; 4.59, m
17'	2.91, s	2.93, s
18'	2.67, d (9.4)	2.66, m ^c
19'	2.61, m	2.64, m
20'	0.72, d (6.6) ^a	0.75, d (6.0) ^a
21'	0.92, d (6.5) ^a	0.95, d (6.0) ^a
23'	5.19, dd (6.5, 2.4)	5.25, dd (5.6, 2.2)
24'	1.22, d (6.3)	1.26, d (6.7)
NH-2'	7.15, d (7.0)	7.17, d (7.3)
NH-4'	8.19, d (6.0)	7.76, d (5.8)
2''	4.61, dd (6.7, 2.5)	4.52, m
4''	3.56, dd (10.0, 6.0)	3.70, m
5''	2.12, m	2.23, m
6''	1.08, d (6.6) ^b	1.15, d (6.8) ^b
7''	0.87, d (6.6) ^b	0.90, d (6.8) ^b
9''	3.67, m; 3.81, m	3.73, m; 3.91m
10''	2.07, 2.23, m	2.21, m; 2.27, m
11''	1.84, m; 2.90, m	1.86, m; another H not detected
12''	5.9, d (9.2)	5.94, d (9.2)
14''	2.85, s	2.89, s ^d
15''	3.60, d (17.5); 4.79, d (17.5)	3.65, d (17.4); 4.71, d (17.5)
17''	2.90, s	2.91, s
18''	2.67, d (9.4)	2.71, m ^c
19''	2.61, m	2.63, m
20''	0.72, d (6.6) ^a	0.74, d (6.0) ^a
21''	0.94, d (6.5) ^a	0.98, d (6.0) ^a
23''	5.15, dd (6.5, 2.4)	5.17, dd (6.2, 2.2)
24''	1.22, d (6.3)	1.12, d (6.6)
NH-2''	7.7, d (6.6)	7.68, d (5.8)
NH-4''	8.01, d (6.2)	8.23, d (6.0)

^{a-d}The data with the same labels in each column may be interchanged.

* The reported NMR data refers to Zhang, X. F.; Ye, X. W.; Chai, W. Y.; Lian, X. Y.; Zhang, Z. Z. *Mar. Drugs* **2016**, *14*, 181

Table S3. ^{13}C NMR (150 MHz) data for actinomycin D (**9**) and V (**10**) in CDCl_3

No.	9	10	No.	9	10
1	129.2	129.3	17'	39.3	39.5
2	132.5	132.2	18''	71.2	71.3
3	125.8	126.2	18'	71.4	71.6
4	130.4	130.5	19''	27.0	27.2
5	127.8	128.1	19'	27.1	27.1
6	140.6	140.7	2''	54.9	55.1
7	145.2	145.2	2'	55.2	54.9
8	113.6	113.8	20''	19.1	19.2
9	179.1	179.2	20'	19.2	19.2
10	147.7	147.5	21''	21.7	21.9
11	101.7	101.9	21'	21.6	21.7
12	145.9	146.1	22''	167.8	167.6
13	15.1	15.2	22'	167.7	167.6
14	7.8	7.9	23''	75.1	74.9
1''	166.6	166.4	23'	75.0	74.8
1'	166.7	166.4	24''	17.8	17.8
10''	22.9	23.1	24'	17.4	17.3
10'	23.1	208.9	3''	169.1	169.2
11''	31.4	31.2	3'	168.7	169.1
11'	31.0	42.0	4''	58.8	57.4
12''	56.6	56.7	4'	58.9	58.8
12'	56.4	54.5	5''	31.9	32.1
13''	173.4	173.7	5'	31.6	31.9
13'	173.4	172.9	6''	19.1	19.1
14''	35.0	35.2	6'	19.1	19.0
14'	35.1	35.0	7''	19.3	19.4
15''	51.4	51.5	7'	19.4	19.3
15'	51.4	51.5	8''	173.7	173.5
16''	166.7	166.7	8'	173.3	174.2
16'	166.4	166.0	9''	47.7	47.6
17''	39.2	39.2	9'	47.4	53.0

* The reported NMR data refers to Zhang, X. F.; Ye, X. W.; Chai, W. Y.; Lian, X. Y.; Zhang, Z. Z. *Mar. Drugs* **2016**, *14*, 181

Table S4. ^1H NMR (600 MHz) data for actinomycin X $_{\beta}$ (**11**) in CDCl_3

No.	δ_{H} (J in Hz)
3	7.65, d (7.7)
4	7.35, d (7.8)
2'	4.83, dd (6.2, 2.2)
4'	3.57, m
6'	1.12, d (6.7) ^d
7'	0.88, d (6.7) ^d
12'	6.07, dd (9.3, 2.7)
14'	2.88, s
15'	3.60, m; 4.54, d (17.6)
17'	2.93, s ^a
18'	2.68, (9.1)
19'	2.66, m
20'	0.74, d (6.7) ^b
21'	0.96, d (6.7) ^b
23'	5.25, m
24'	1.29, d (6.2) ^c
NH-2'	7.46, d (6.2)
NH-4'	7.51, d (6.9)
2''	4.5, d (6.2, 2.5)
4''	3.74, t
6''	1.14, d (6.7) ^d
7''	0.91, d (6.7) ^d
12''	5.99, d (9.2)
14''	2.88, s
15''	3.66, d (17.2); 4.73, d (17.3)
17''	2.94, s ^a
18''	2.72, (9.3)
19''	2.66, m
20''	0.75, d (6.7) ^b
21''	0.97, d (6.7) ^b
23''	5.25, m
24''	1.26, d (6.2) ^c
NH-2''	7.91, d (6.3)
NH-4''	8.19, d (5.6)

^{a-d} The data with the same labels may be interchanged.

* The reported NMR data refers to Zhang, X. F.; Ye, X. W.; Chai, W. Y.; Lian, X. Y.; Zhang, Z. Z. *Mar. Drugs* **2016**, *14*, 181

Table S5. ¹H NMR (600 MHz), and ¹³C NMR (150 MHz) data for berberine (**12**) in MeOH-*d*₄

No.	δ_{H} (J in Hz)	δ_{C} (ppm)
1	7.64, s	105.3
2		148.7
3		150.8
4	6.94, s	108.2
4a		130.7
5	3.24, t (6.4)	27.0
6	4.91, t (6.4)	56.0
8	9.75, s	145.2
8a		122.1
9		144.6
9-OMe	4.18, s	61.3
10		151.0
10-OMe	4.09, s	56.4
11	7.98, d (8.4)	126.8
12	8.10, d (8.3)	123.3
12a		134.0
13	8.69, s	120.3
13a		138.5
13b		120.7
OCH ₂ O	6.09, s	102.5

* The reported NMR data refers to Jung, H. A.; Yoon, N. Y.; Bae, H. J.; Min, B. S.; Choi, J. S. *Arch. Pharm. Res.* **2008**, *31*, 1405-1412.

Table S6. ^1H NMR (600 MHz), and ^{13}C NMR (150 MHz) data for palmatine (**13**) in $\text{MeOH-}d_4$

No.	δ_{H} (J in Hz)	δ_{C} (ppm)
1	7.67, s	109.9
2		150.9
3		153.8
4	7.05, s	112.2
5	3.28, m	27.8
6	4.94, m	56.7
8	9.77, s	146.4
9		145.8
10		151.9
11	8.12, d (8.9)	124.4
12	8.01, d (9.0)	128.1
13	8.81, s	121.3
10-OMe	3.94, s	57.6
12a		135.3
13a		139.8
13b		123.3
2-OMe	3.99, s	57.3
3-OMe	4.11, s	57.0
4a		130.1
8a		120.5
9-OMe	4.21, s	62.5

* The reported NMR data refers to Jung, H. A.; Yoon, N. Y.; Bae, H. J.; Min, B. S.; Choi, J. S. *Arch. Pharm. Res.* **2008**, *31*, 1405-1412.

Table S7. ^1H NMR (600 MHz), and ^{13}C NMR (150 MHz) data for coptisine (**14**) in $\text{MeOH-}d_4$

No.	δ_{H} (J in Hz)	δ_{C} (ppm)
1	7.65, s	106.4
2		149.3
3		150.0
4	6.96, s	109.4
5	3.25, m	28.1
6	4.89, m	57.2
8	9.72, s	145.8
9		145.3
10		152.2
11	7.88, d (8.5)	121.9
12	7.86, d (8.5)	123.1
13	8.74, s	122.3
12a		134.4
13a		139.0
13b		122.5
4a		131.8
8a		113.7
OCH ₂ O	6.47, s	106.2
OCH ₂ O	6.11, s	103.7

* The reported NMR data refers to Jung, H. A.; Yoon, N. Y.; Bae, H. J.; Min, B. S.; Choi, J. S. *Arch. Pharm. Res.* **2008**, *31*, 1405-1412.

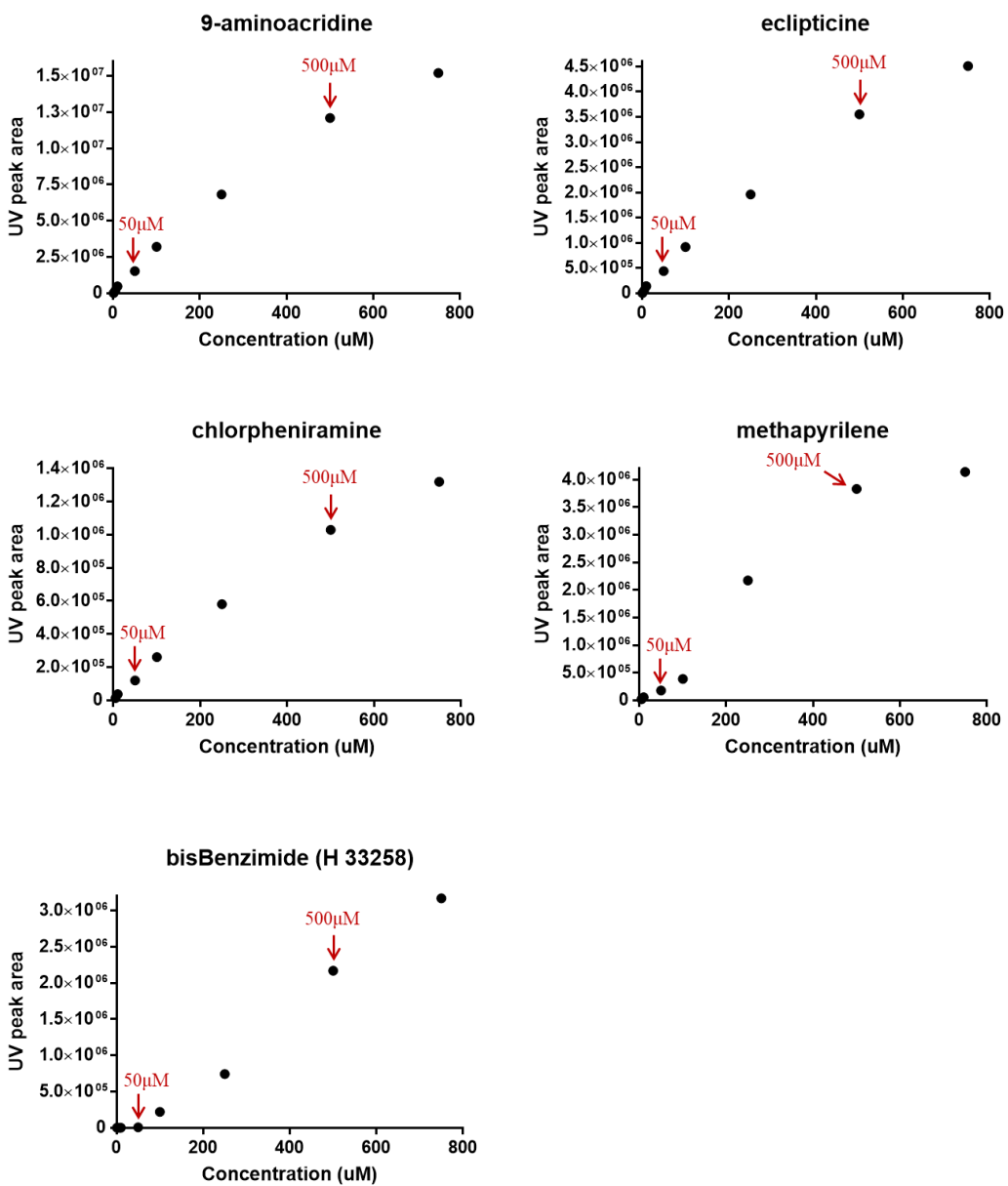


Figure S1. Calibration curve analysis (UV peak area) of 4 intercalators (1-4) and 1 groove binder (5)

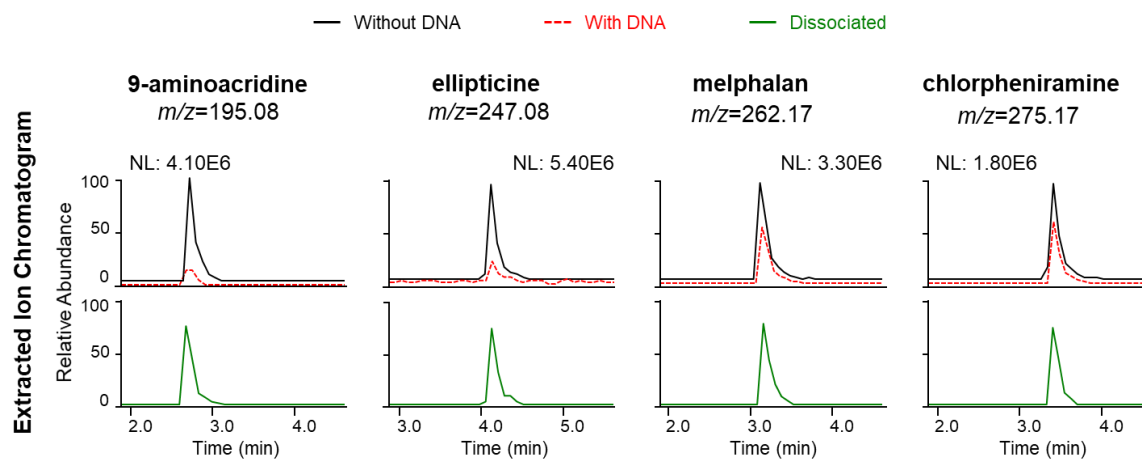


Figure S2. EIC analysis of the 4 individual intercalators (**1-4**) in the assay.

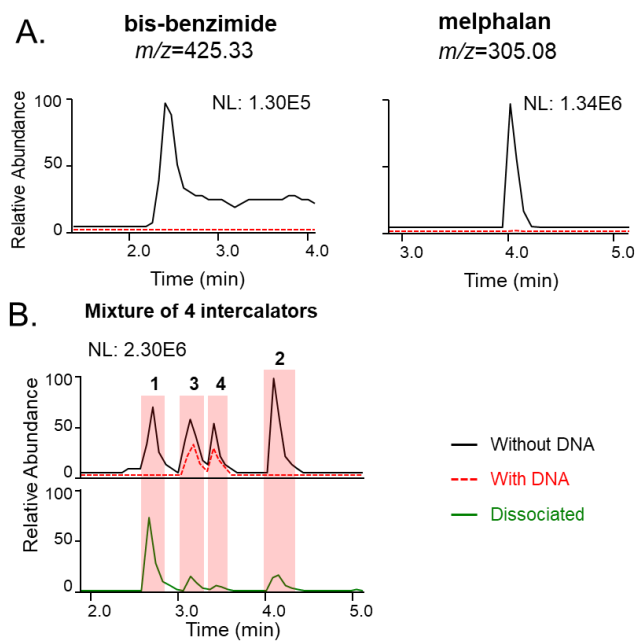


Figure S3. EIC analysis of bisbenzimidazole (H33258) (**5**), melphalan (**7**), and 4 intercalators (**1-4**) mixture.

<i>m/z</i>	1255.75
RT (min)	8.64
annotation	actinomycin D
cosine score	0.96
<i>m/z</i> error (Da)	0.11
reference Spectrum ID	CCMSLIB00000006871

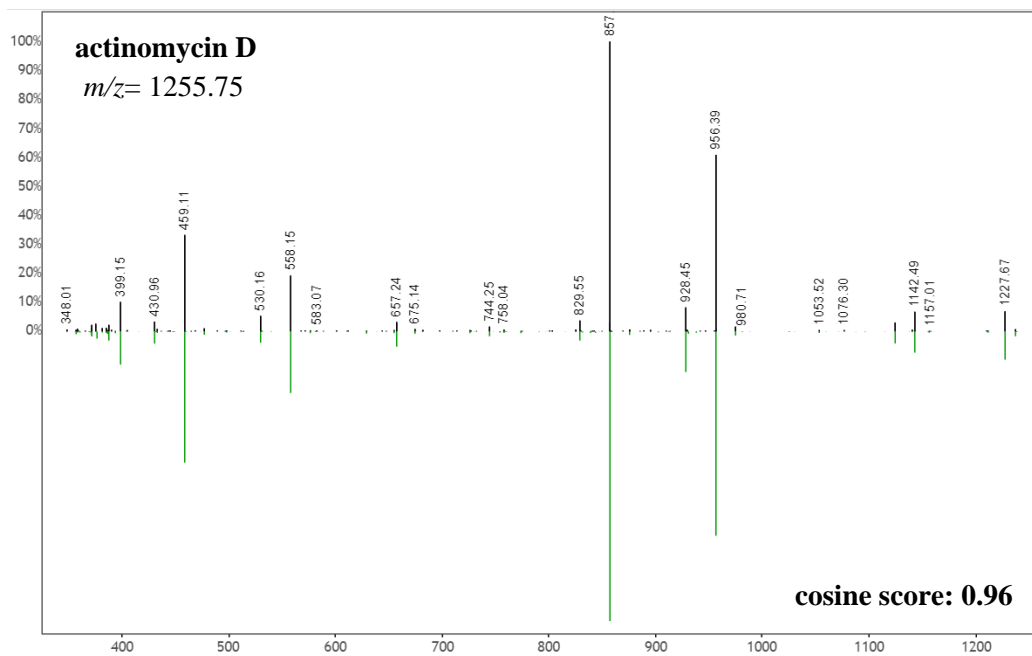


Figure S4. Annotation and mirror plot of actinomycin D (9) using GNPS.

<i>m/z</i>	1269.67	1271.75
RT (min)	8.64	7.77
annotation	actinomycin D +14 Da	actinomycin D +16 Da
cosine score	0.92	0.91
<i>m/z</i> error (Da)	0.1	0.12
reference Spectrum ID	CCMSLIB00000081798	CCMSLIB00000006871

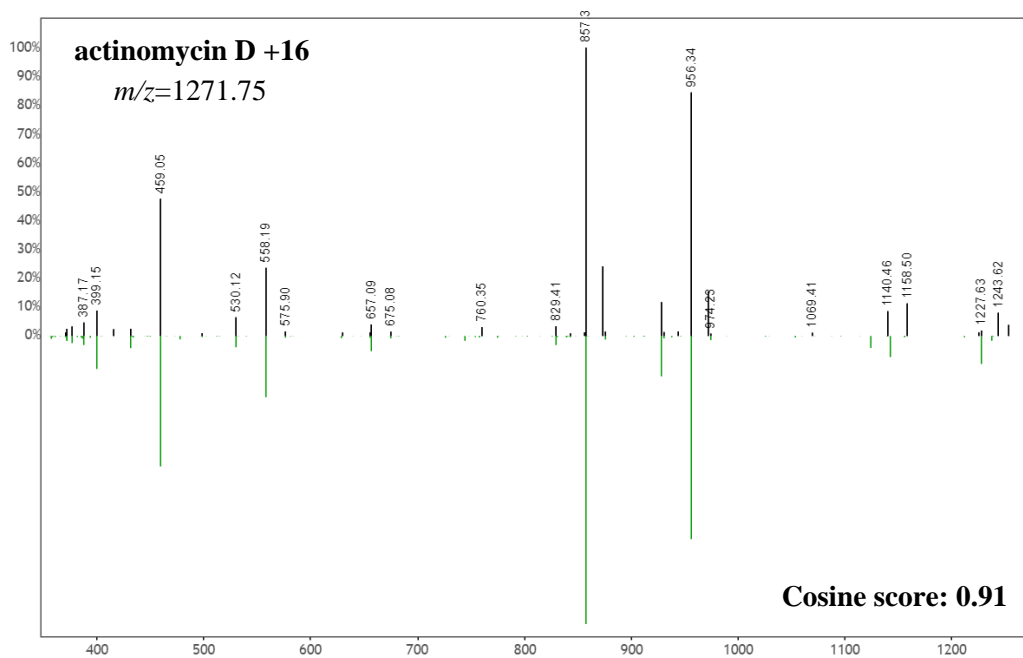
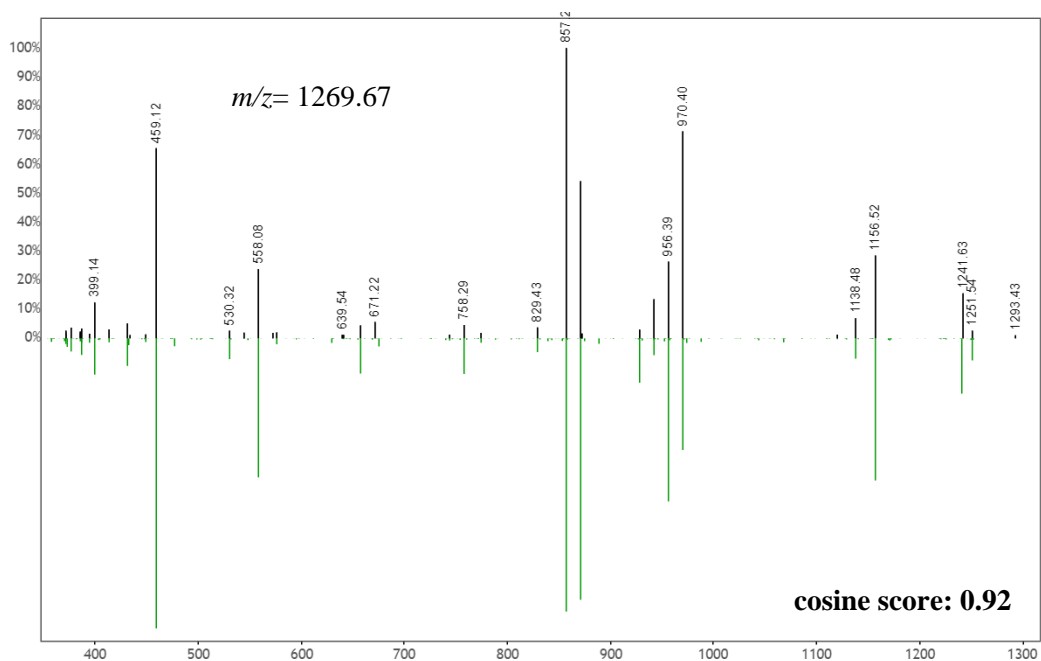


Figure S5. Annotation and mirror plots of the two analogues of actinomycin D (9) using GNPS.

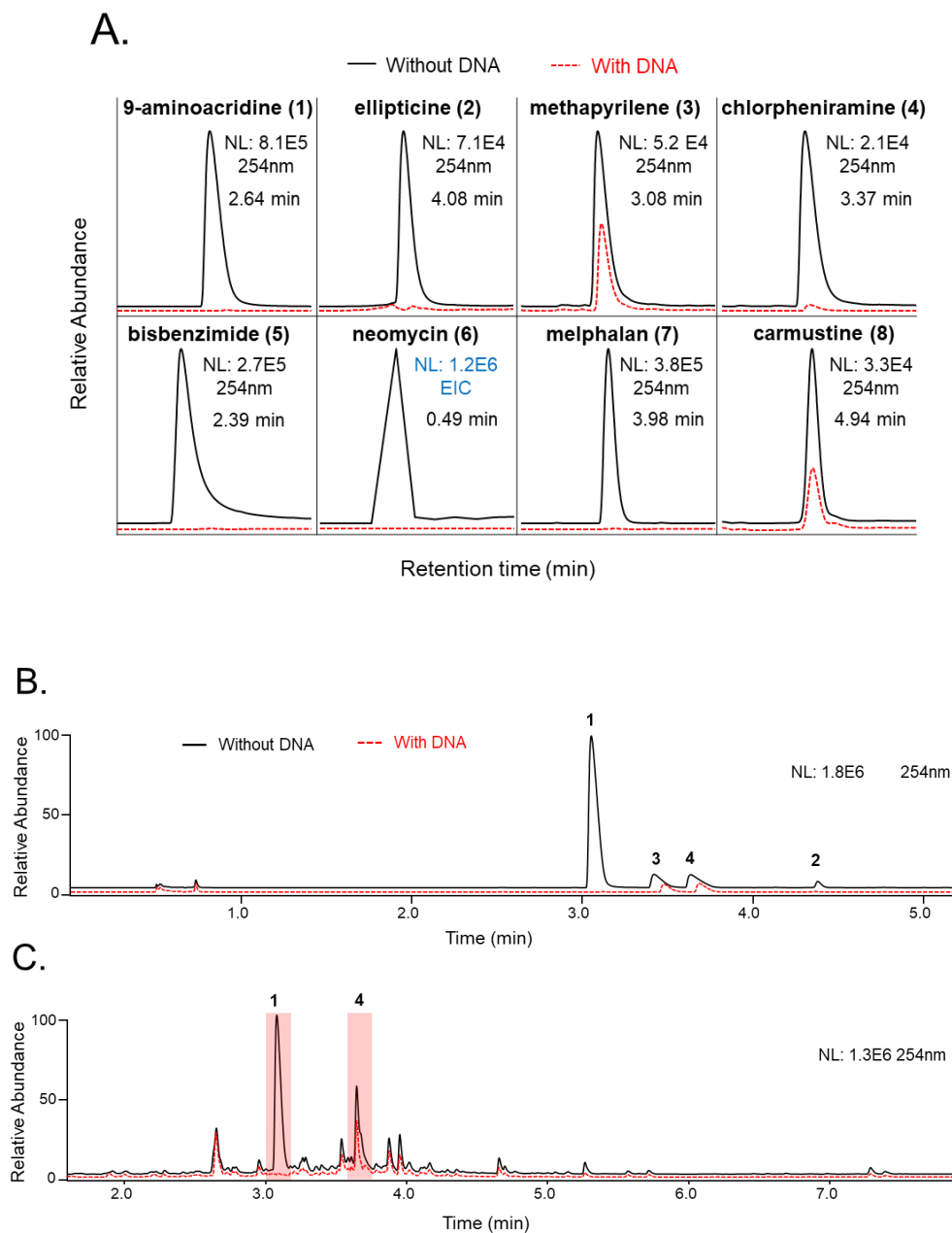


Figure S6. Results of the high throughput LLAMAS development. **A)** Performance of the 8 DNA binding agents including: 4 intercalators [9-aminoacridine (**1**), 34 μM], ellipticine (**2**), 54 μM], methapyrilene (**3**), 45 μM], and chlorpheniramine (**4**), 34 μM], 2 groove binders [bisBenzimidazole (H 33258) (**5**), 125 μg μM], and neomycin (**6**), 157 μM], and 2 covalent binders [melphalan (**7**), 44 μM] and carmustine (**8**), 62 μM] in the assay. The DNA binding capability of neomycin was confirmed by analysis of the EIC trace (m/z of 615.09-615.51); while other compounds were examined by using PDA-derived data. **B)** Performance of the mixture of 4 DNA intercalators (**1-4**) in the assay. **C)** DNA intercalators 9-aminoacridine (**1**) and ellipticine (**4**) were successfully detected in a complex mixture of wild herbaceous plant extract [spike-in ratio, 1:5:250 (w:w:w)].

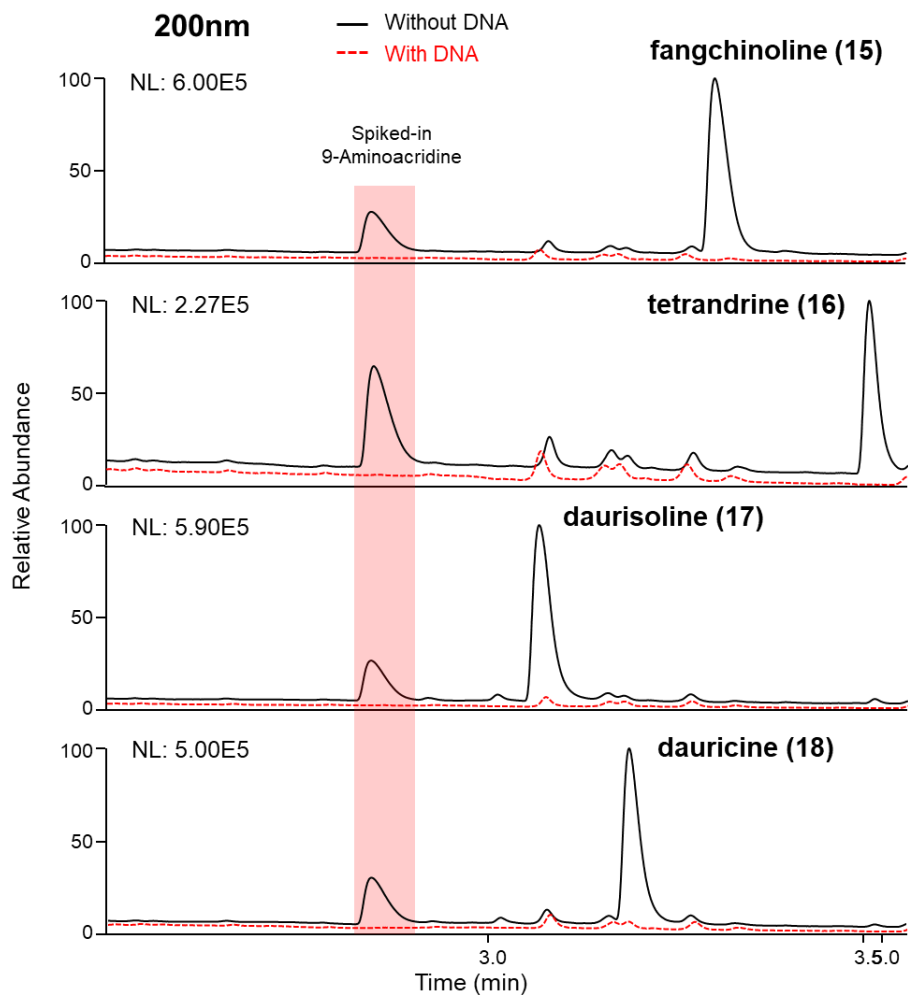


Figure S7. Confirmation of the DNA binding activities of fangchinoline (**15**), tetrandrine (**16**), daurisolone (**17**), and dauricine (**18**). UV chromatogram (monitored at λ 200 nm) revealed that the compounds were retained by the DNA.

Figure S8. ^1H NMR (600 MHz) spectrum of actinomycin D (**9**) in CDCl_3

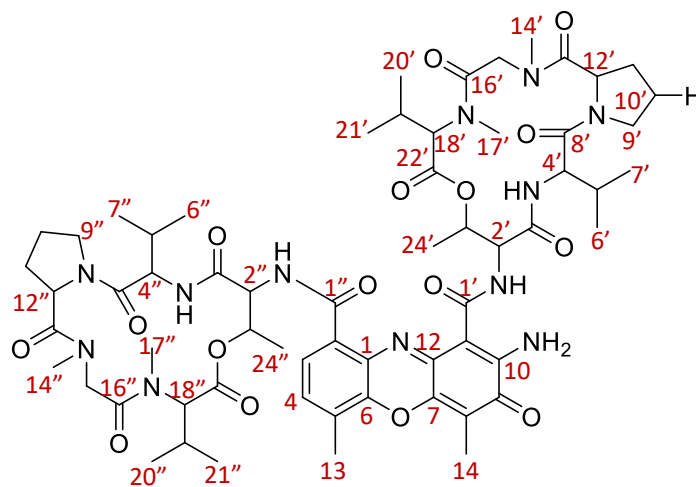
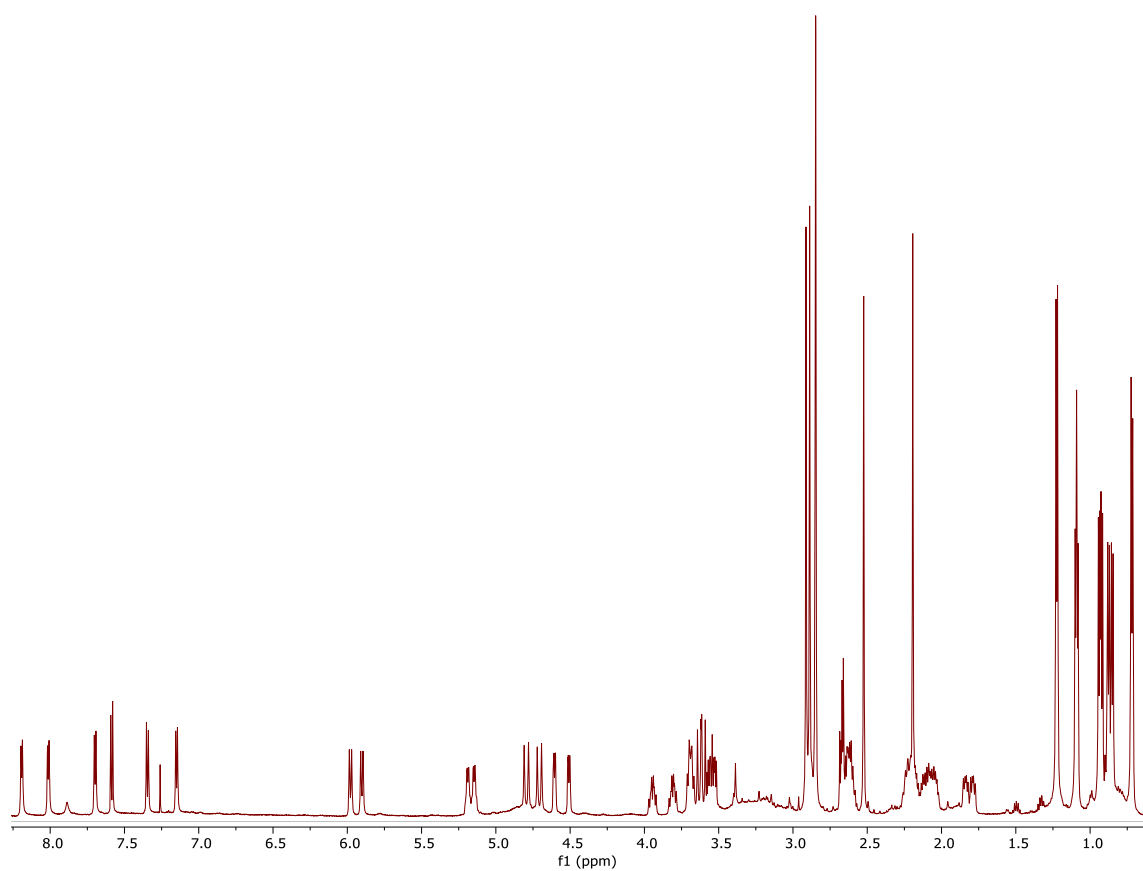


Figure S9. ^{13}C NMR (600 MHz) spectrum of actinomycin D (**9**) in CDCl_3

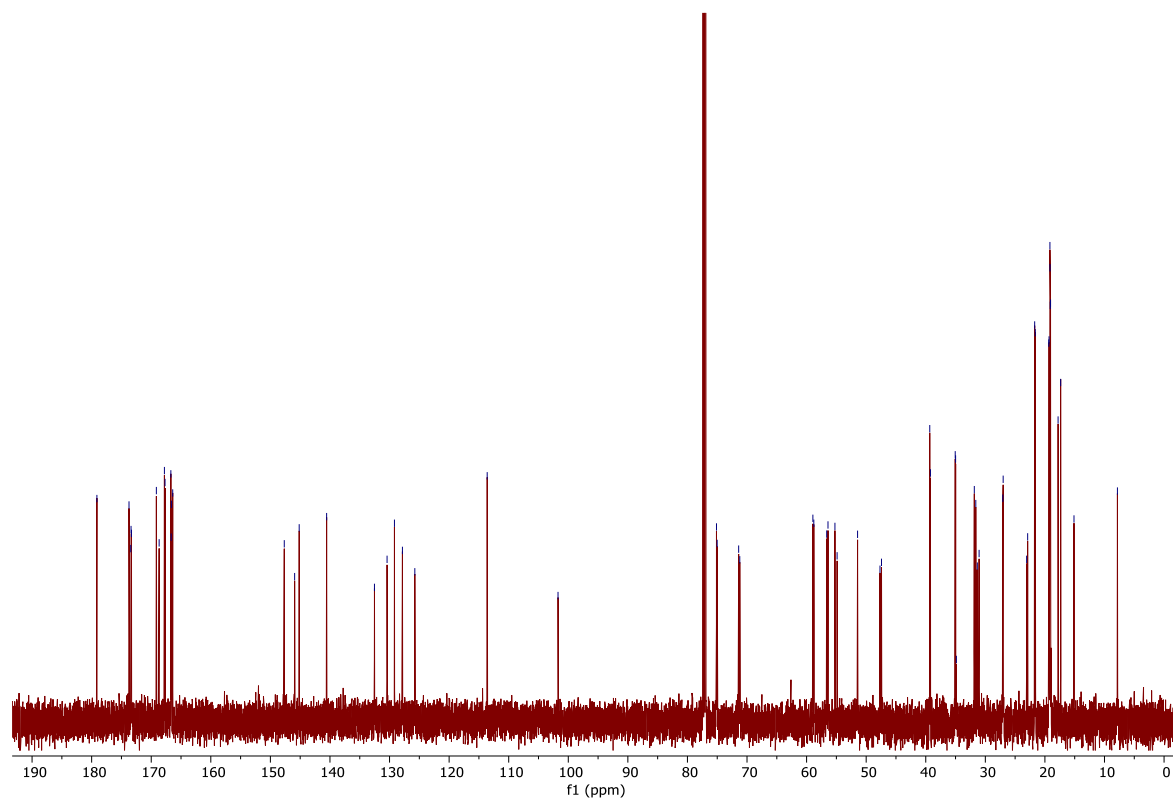


Figure S10. ^1H NMR (600 MHz) spectrum of actinomycin V (**10**) in CDCl_3

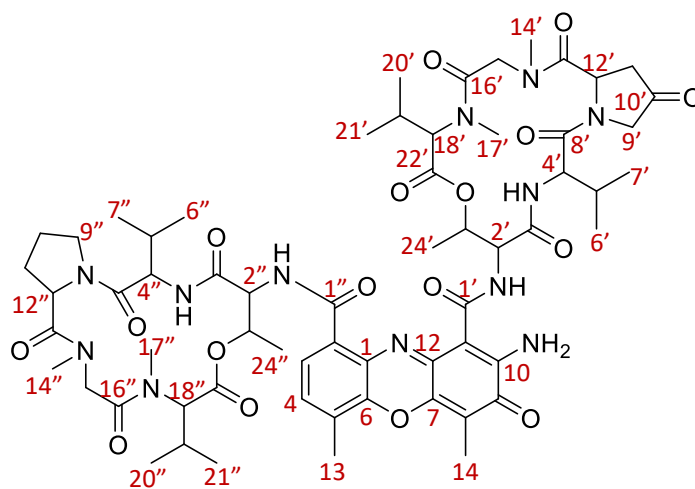
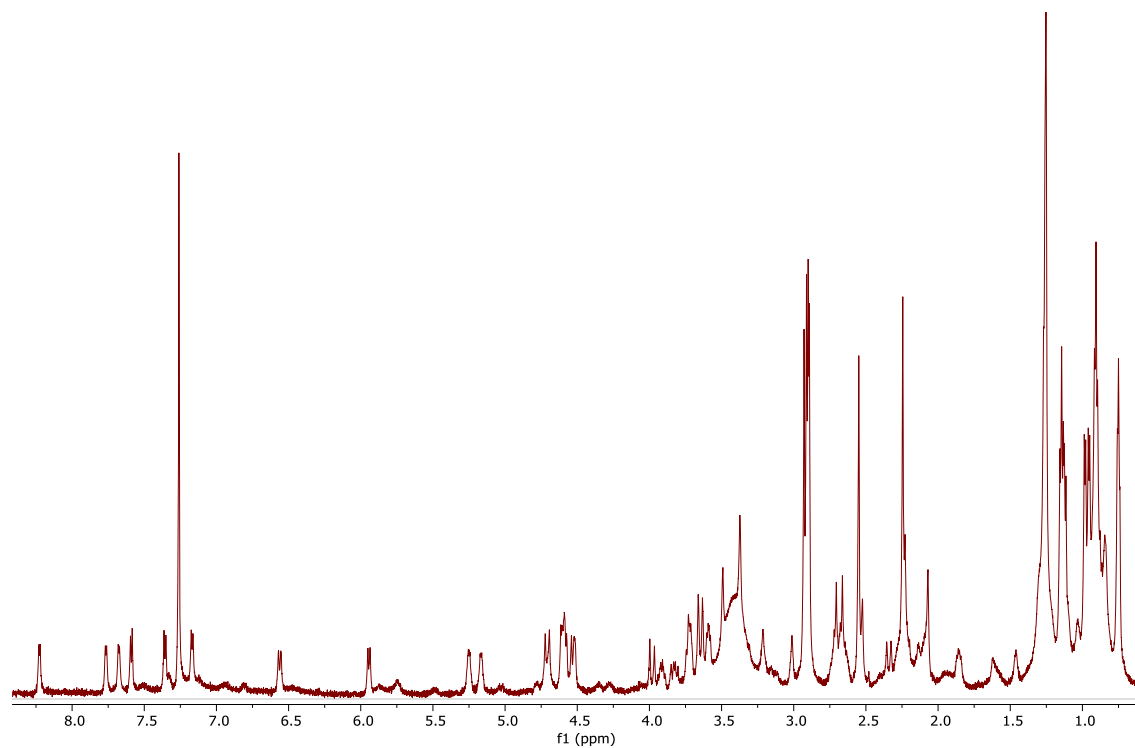


Figure S11. ^{13}C NMR (600 MHz) spectrum of actinomycin V (**10**) in CDCl_3

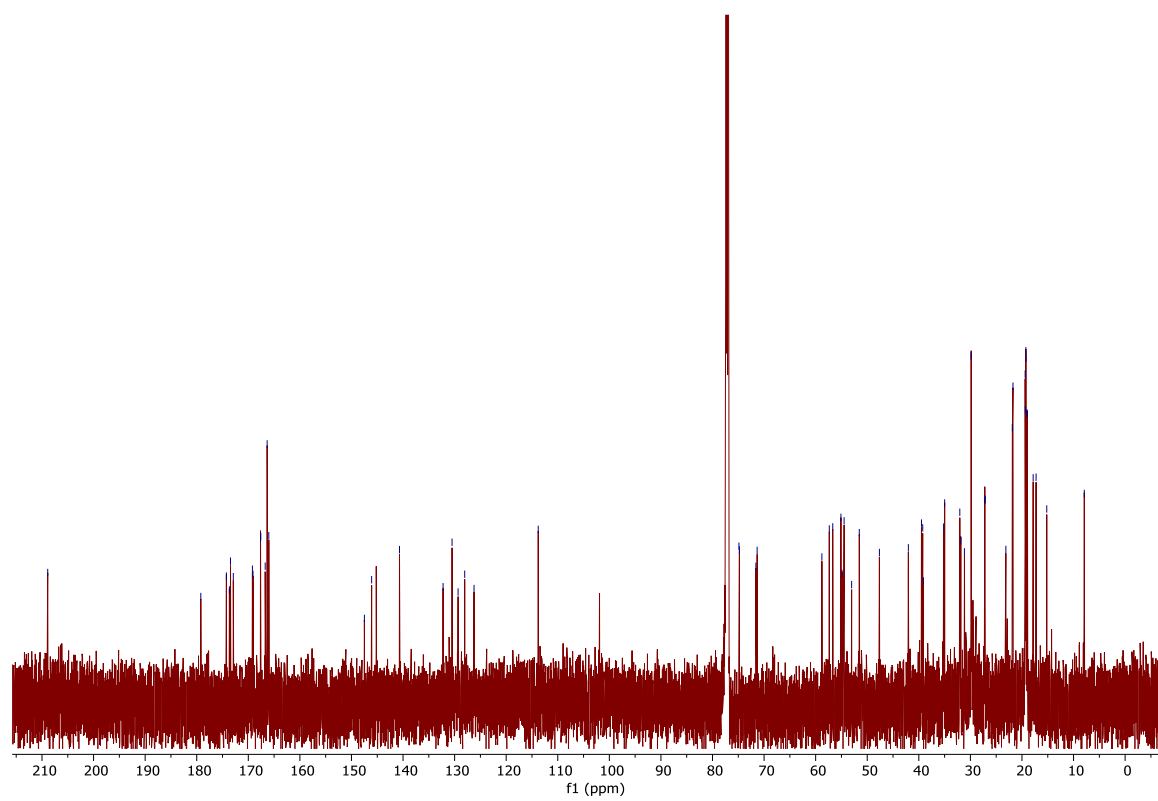


Figure S12. ^1H NMR (600 MHz) spectrum of actinomycin X_{0β} (**11**) in CDCl₃

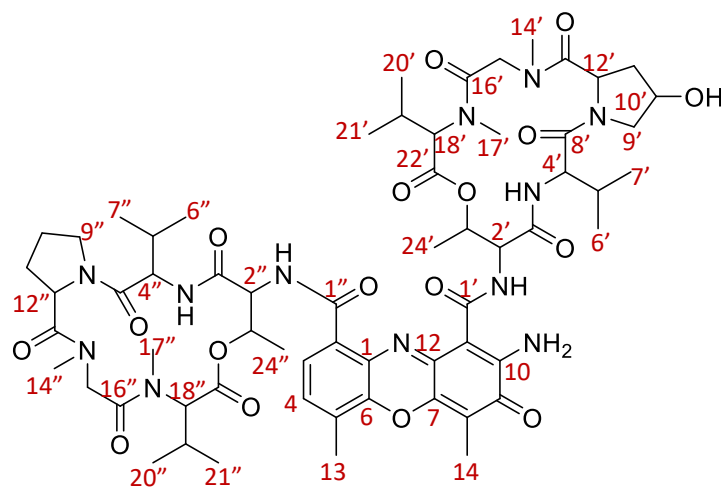
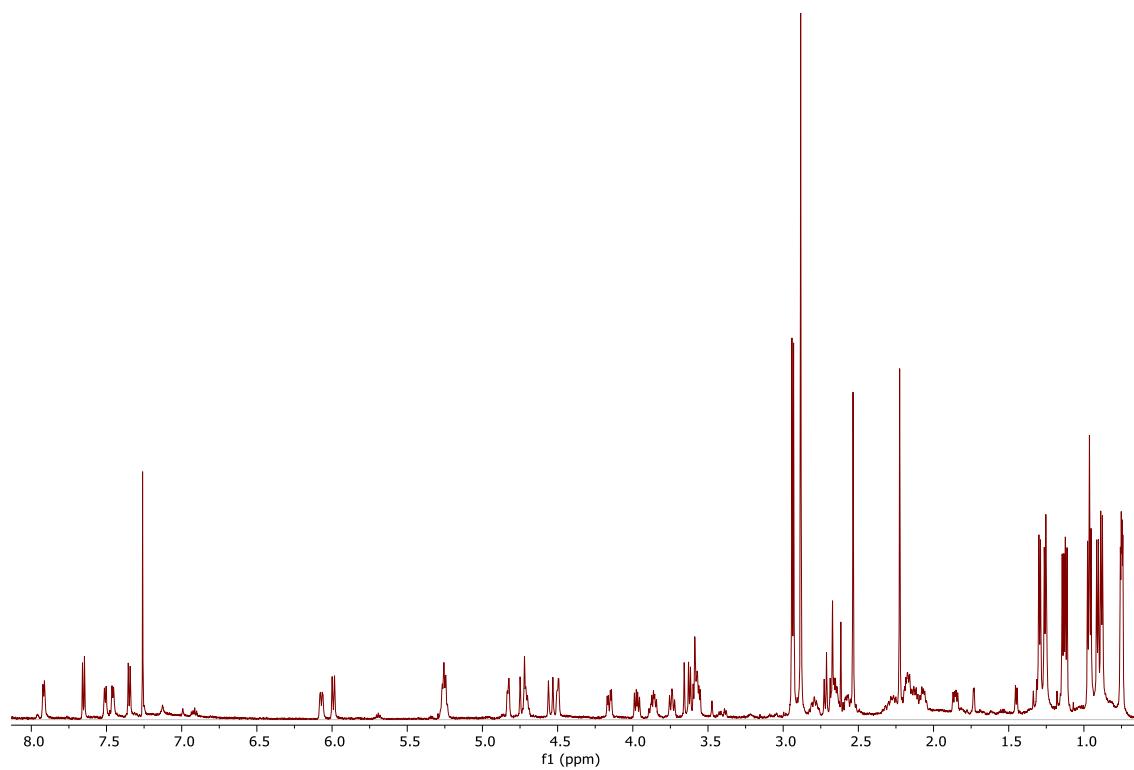


Figure S13. ^1H NMR (600 MHz) spectrum of berberine (**12**) in $\text{MeOH-}d_4$

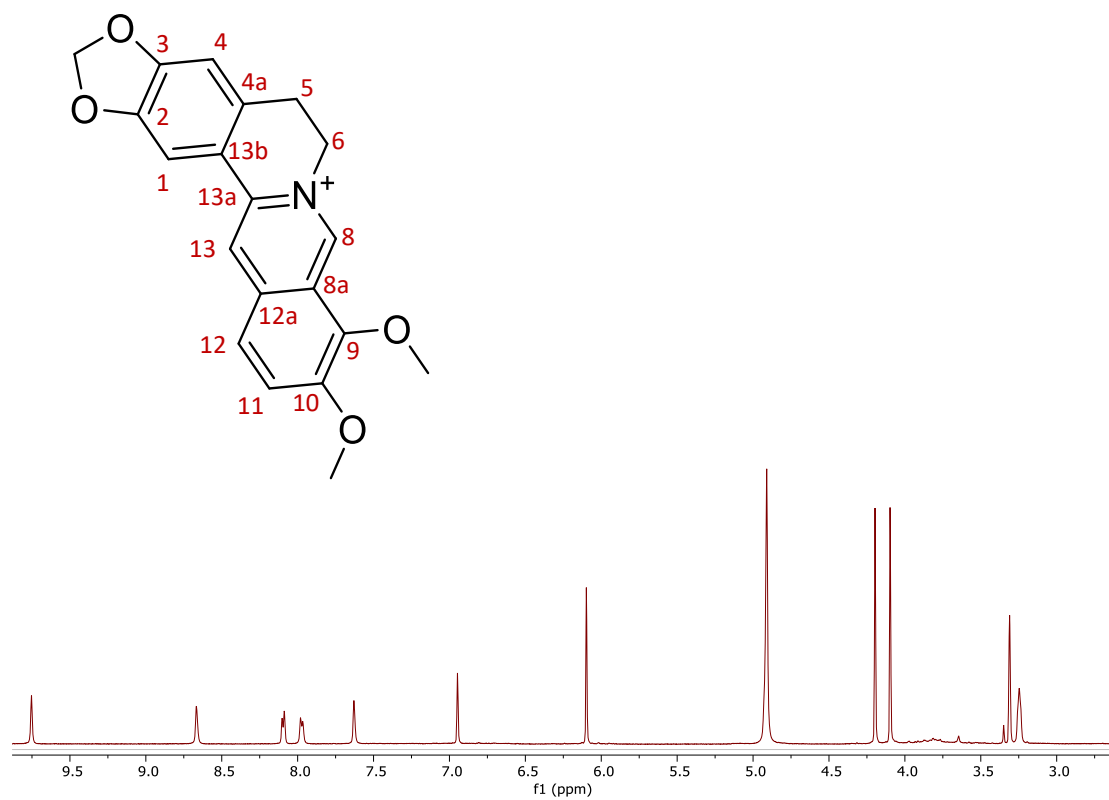


Figure S14. ^{13}C NMR (600 MHz) spectrum of berberine (**12**) in $\text{MeOH-}d_4$

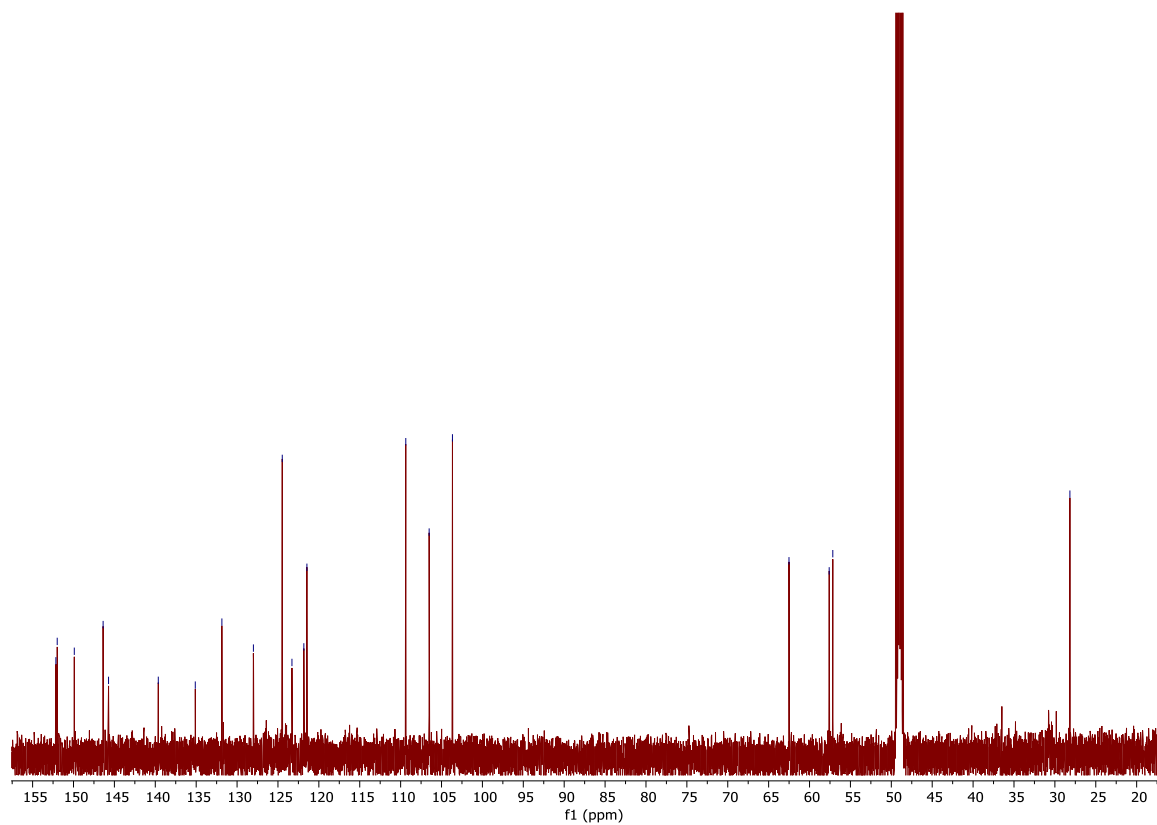


Figure S15. ^1H NMR (600 MHz) spectrum of palmatine (**13**) in $\text{MeOH-}d_4$

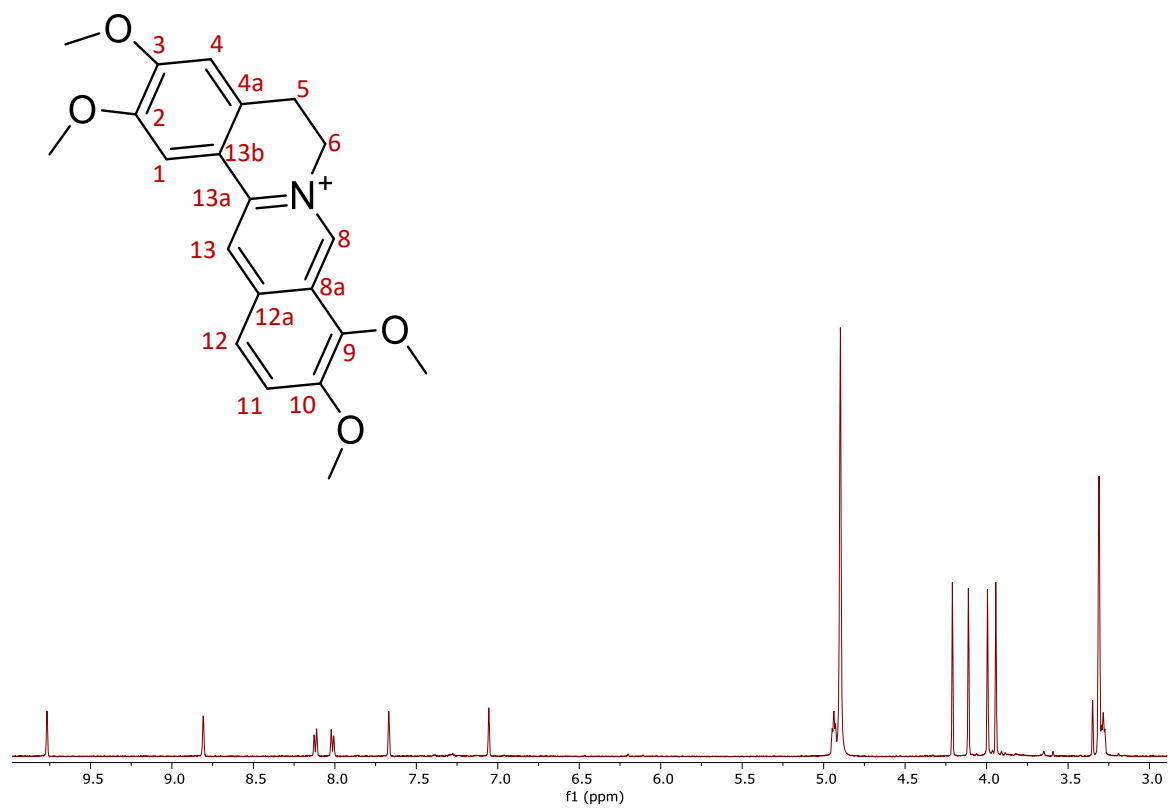


Figure S16. ^{13}C NMR (600 MHz) spectrum of palmatine (**13**) in $\text{MeOH-}d_4$

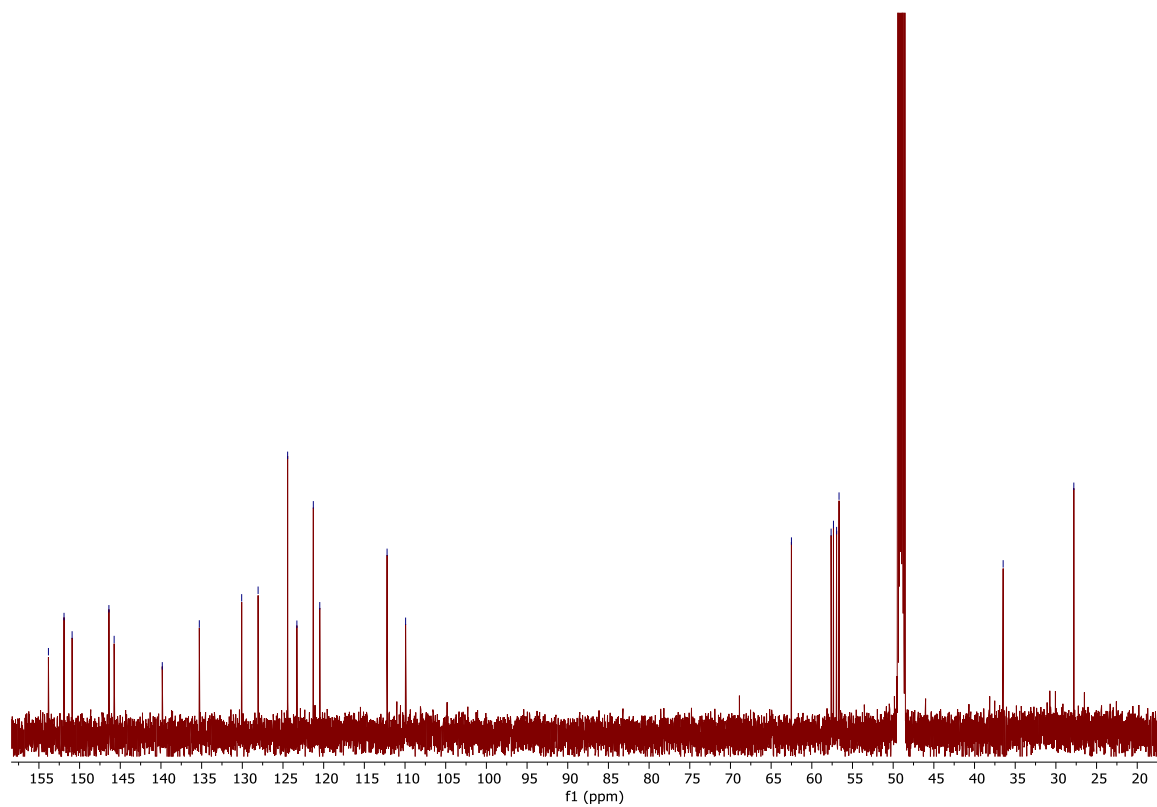


Figure S17. ^1H NMR (600 MHz) spectrum of coptisine (**14**) in $\text{MeOH-}d_4$

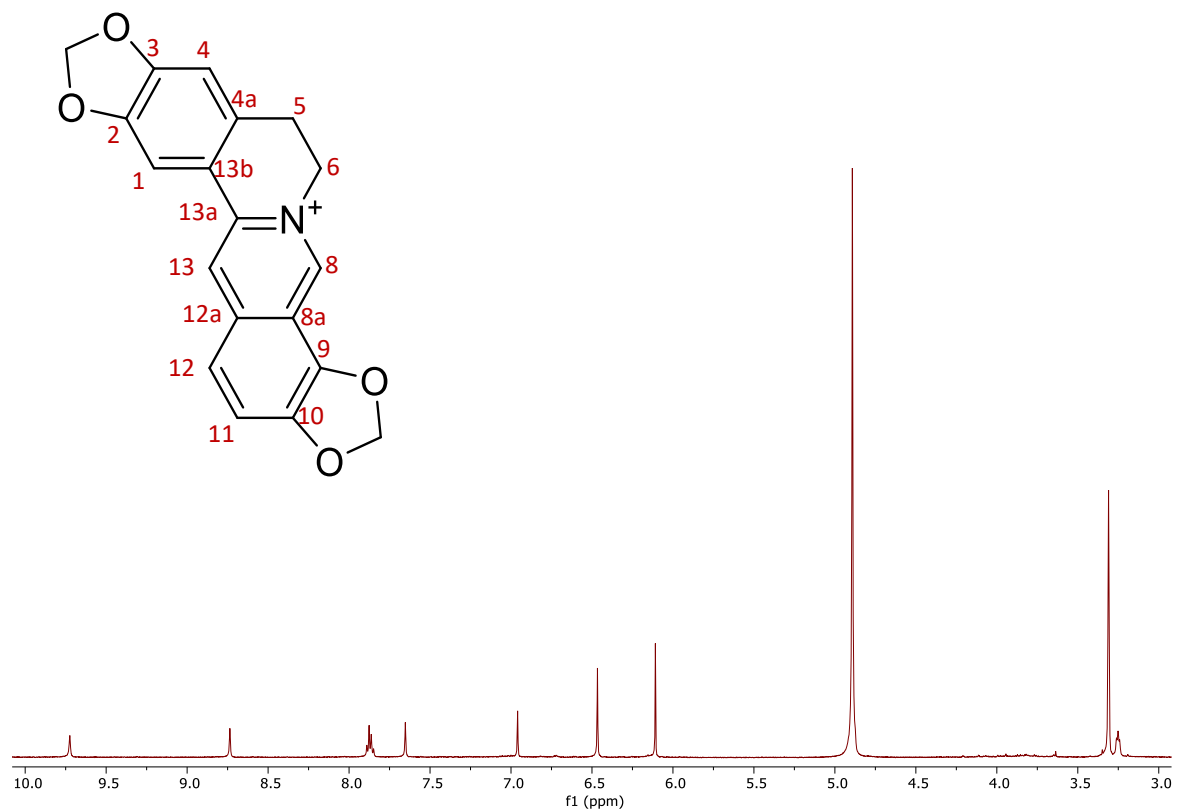


Figure S18. ^{13}C NMR (150 MHz) spectrum of coptisine (**14**) in $\text{MeOH-}d_4$

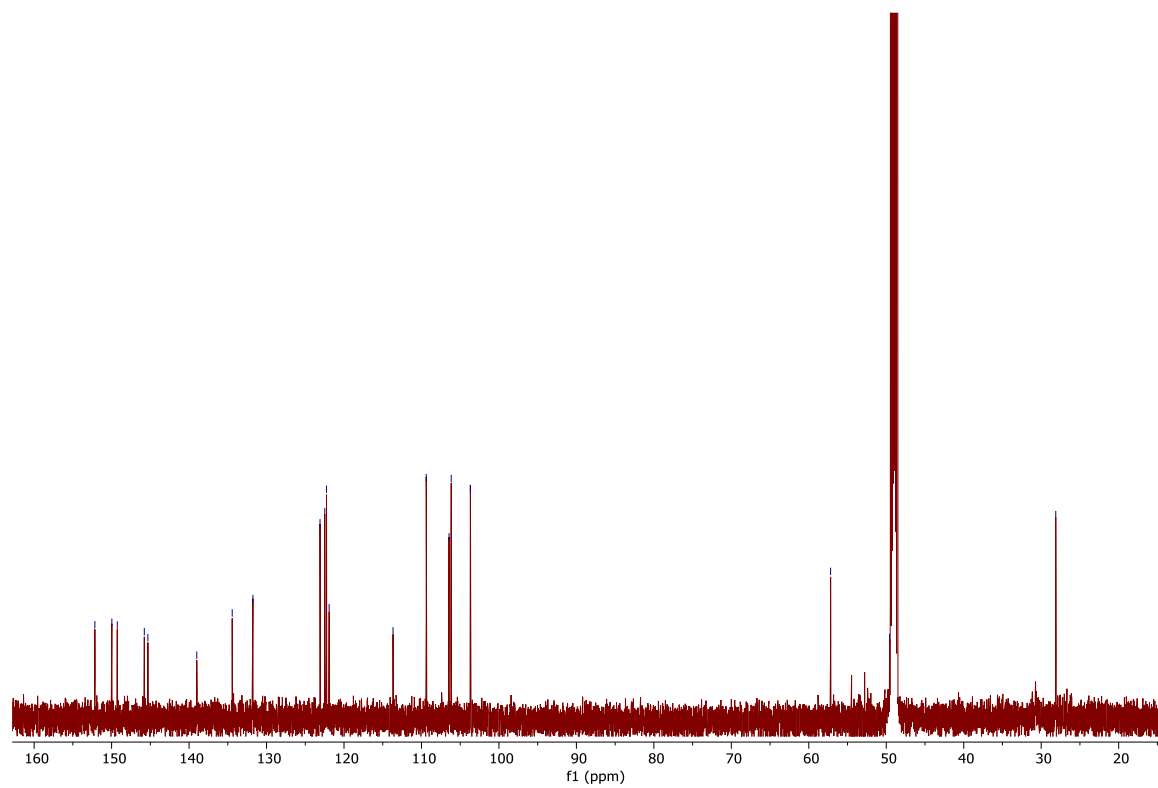


Figure S19. ^1H NMR (500 MHz) spectrum of fangchinoline (**15**) in CDCl_3

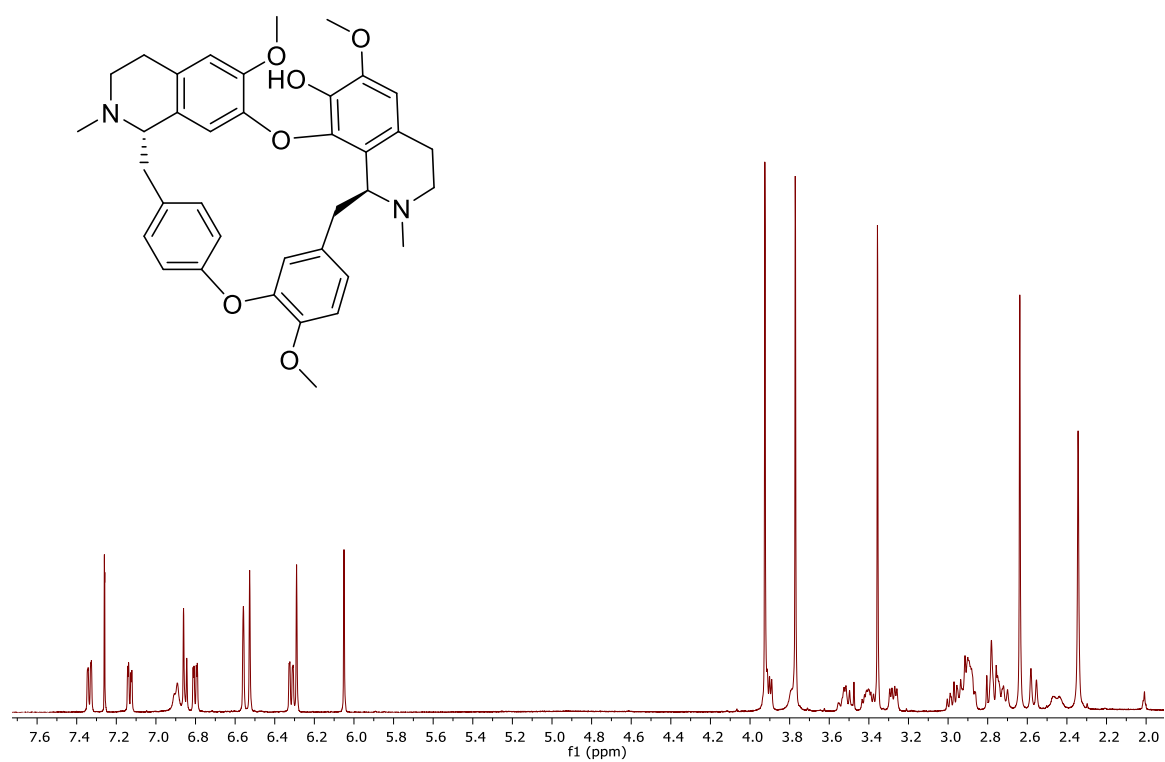


Figure S20. ^1H NMR (500 MHz) spectrum of tetrandrine (**16**) in CDCl_3

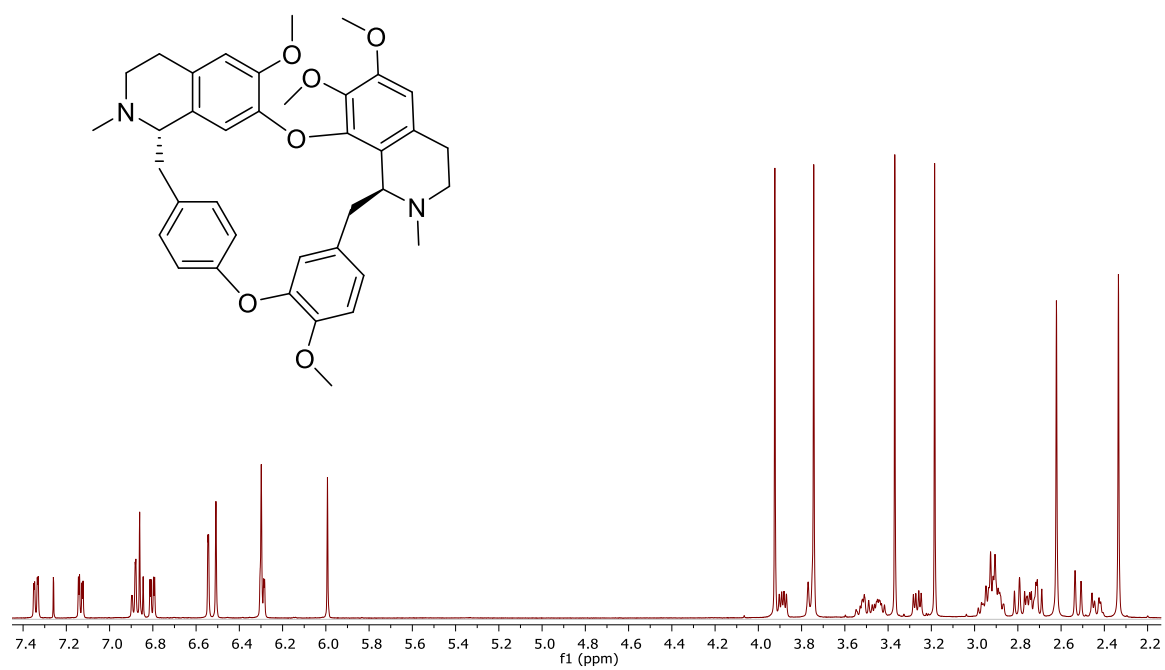


Figure S21. ^1H NMR (500 MHz) spectrum of daurisoline (**17**) in CDCl_3

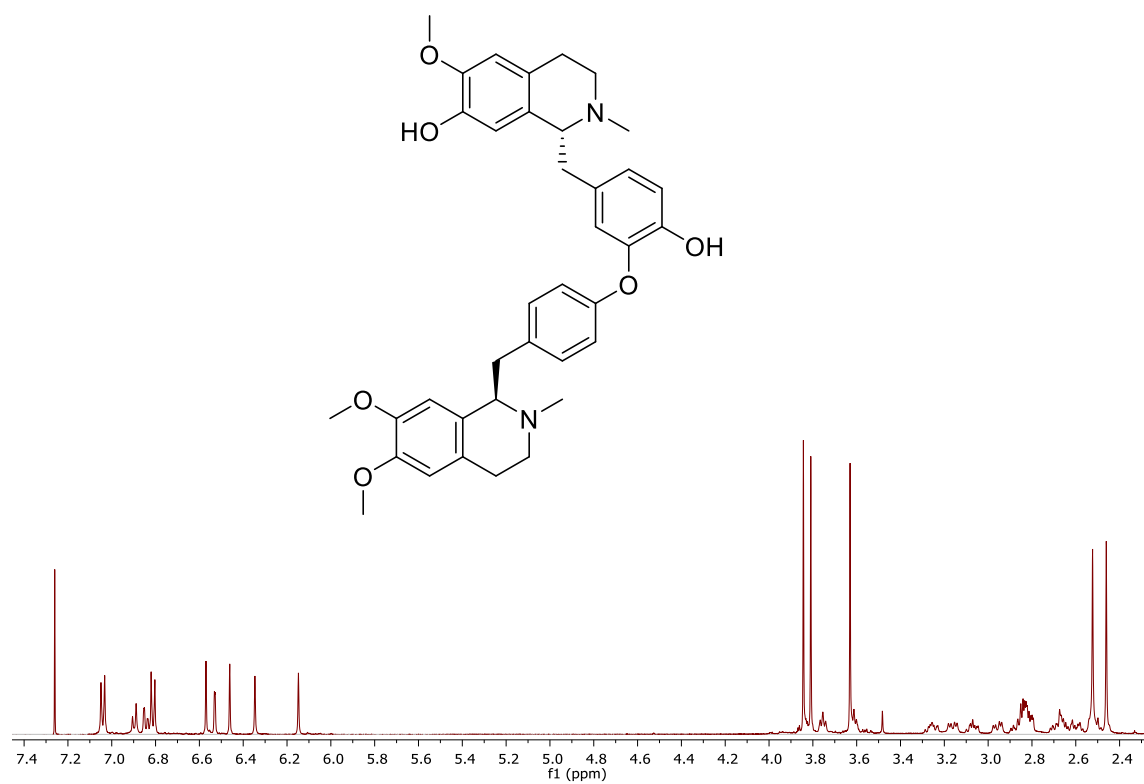


Figure S22. ^1H NMR (500 MHz) spectrum of dauricine (**18**) in CDCl_3

