

Supporting Information

Lineariifolians I-L, four rare sesquiterpene lactone dimers inhibiting NO production from *Inula lineariifolia*†

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Table S1. ¹H NMR (**1**, **2** and **4** for 500 MHz, **3** for 600 MHz, *J* in Hz) Spectroscopic Data for **1-4**

NO	1	2	3	4
1	2.10, t (5.5)	-	-	-
2	3.83, m	2.29, m	2.41, m, 2.22, m	2.37, m, 2.23, m
3	1.75, m, overlapped	2.67, m, 2.49, m	2.63, m, overlapped, 2.47, m	2.55, m, 2.42, m, overlapped
4	4.35, dt (11.4, 6.6×2), 4.13, dt (11.2, 5.5×2)	-	-	-
5	-	5.74, d (8.2)	5.60, d (9.3)	5.36, s
6	4.99, brd (1.0)	5.40, d (8.9)	2.27, m, 2.10, m	4.60, d (9.8)
7	3.31, brd (10.2)	2.76, dd (6.9, 1.6)	2.55, ddd (12.8, 5.9, 2.1)	2.42, m, overlapped
8	4.44, td (10.3×2, 6.1)	5.00, dt (11.8, 6.1×2)	4.94, dt (11.0, 5.7×2)	4.76, dt (5.9×2, 5.0)
9	2.57, m, 1.54, m	2.37, m, 2.21, m	2.07, m	2.25, m, 1.91, m, overlapped
10	2.07, m, overlapped	2.49, m	2.44, m	2.34, m
13	2.27, dd (12.6, 3.8), 1.97, d (12.4)	1.63, d (11.9)	2.41, m, 1.67, d (12.2)	3.00, m, overlapped, 1.91, m, overlapped
14	1.05, d (7.1)	1.19, d (7.0)	1.16, d (7.2)	1.15, d (7.1)
15	1.76, s	2.12, s	2.12, s	2.14, s
2'	3.46, brd (9.2)	4.74, s	4.67, s	4.51, s
3'	2.63, m	2.93, d (1.6)	2.94, d (1.6)	2.89, d (1.4)
6'	2.80, m,	4.78, d (6.7)	4.78, d (6.7)	3.00, m, overlapped,

	2.15, m			2.09, m, overlapped
7'	2.52, m	3.24, ddt (10.4, 6.8, 3.2×2)	3.23, ddt (10.4, 6.9, 3.2×2)	2.81, brt (10.1)
8'	4.22, m	4.24, td (10.1×2, 7.2)	4.25, td (10.2×2, 7.2)	4.19, td (9.5×2, 3.3)
9'	2.35, m, 2.05, m, overlapped	1.87, m	2.21, m, 1.89, m	2.30, m, 1.91, m, overlapped
10'	2.91, brt (7.4×2)	2.62, m	2.62, ddt (16.3, 8.2, 5.7×2)	2.14, m, overlapped
13'	6.18, d (3.0), 5.46, d (3.0),	6.17, d (3.7), 5.92, s	6.16, d (3.7), 5.92, brd (1.2)	6.22, d (3.1), 5.53, d (3.1)
14'	1.19, d (7.2)	1.07, d (7.0)	1.10, d (7.2)	1.02, d (7.3)
15'	1.81, d (1.6)	1.70, s	1.70, s	1.66, d (1.5)
2''	2.07, s	2.00, s	2.02, s	2.09, s
2'''	-	1.96, s	-	-

Table S2. ^{13}C NMR (**1**, **2** and **4** for 125 MHz, **3** for 150 MHz) SpectroscopicData for **1-4**

NO	1	2	3	4
1	54.5	152.1	145.8	143.5
2	68.8	30.1	32.2	30.5
3	35.4	41.3	43.1	42.1
4	62.2	208.8	211.0	207.5
5	141.8	120.2	124.2	132.4
6	121.2	69.0	25.0	66.7
7	49.5	48.8	48.9	52.3
8	80.9	78.7	81.4	78.0
9	39.6	37.8	38.2	36.2
10	29.2	31.3	32.9	32.0
11	57.3	54.0	56.9	55.8
12	184.1	180.1	181.9	178.3
13	33.4	33.3	35.0	35.9
14	22.9	20.5	22.0	21.2
15	25.7	28.4	29.8	29.7
1'	68.2	59.5	61.0	62.5
2'	85.7	81.3	82.6	81.8
3'	52.0	57.9	59.3	57.7
4'	138.8	137.6	139.4	132.9
5'	134.1	140.2	141.3	136.6
6'	25.6	68.7	70.3	26.0
7'	44.4	48.4	49.8	45.2
8'	81.5	76.8	78.3	82.4
9'	36.4	38.0	39.5	35.9
10'	26.3	28.8	30.4	29.9
11'	139.9	140.5	141.9	139.4
12'	169.6	170.4	171.9	170.3
13'	118.6	119.5	121.3	119.5
14'	18.9	15.4	16.9	17.0
15'	13.7	12.3	13.8	14.2
1''	171.4	169.8	171.5	170.2
2''	20.9	20.1	21.5	21.1
1'''	-	170.2	-	-
2'''	-	19.5	-	-

Isolation procedure

General. Column chromatography (CC): silica gel H (10-40 μm) and silica gel (200-300 mesh) (Marine Chemical Factory, Qingdao, P. R. China); Sephadex LH-20 (Pharmacia Fine Chemicals, Piscataway, NJ, USA); RP-C18 gel (40-63 μm ; Daiso, Co., Japan). TLC: silica gel plates (Yantai Jiang You silicone development co., Yantai, P. R. China), visualization by spraying with 10 % H_2SO_4 in EtOH. Semi-preparative HPLC: Agilent 1260 series with a Zorbax SB-C18 (5 μm , 9.4 mm \times 25 cm) column. Melting point: X-4B digital display micro-melting apparatus (Shanghai jingsong instrument product, Shanghai, P. R. China). Optical rotation: Autopol VI (Rudolph Research Analytical, Hackettstown, NJ). CD spectra: Brighttime Chirascan (Applied Photophysics Ltd, UK). UV spectra: Agilent 1260 series DAD detector (Agilent Technologies, US). IR: Thermo Scientific Nicolet 6700 (Thermo Scientific, US). NMR Spectra: Bruker Avance III-500 and Avance III-600 spectrometers (Bruker, Switzerland). MS: Agilent MSD-Trap-XCT (for ESI) and Q-ToF micro mass spectrometer (for HR-ESI).

Plant Material. The aerial parts of *Inula linearifolia* was collected from Liaoning province of China in March 2016, and were authenticated by Professor Bao-Kang Huang, Department of Pharmacognosy, School of Pharmacy, Second Military Medical University. A voucher specimen (No. 201603-IL) is deposited in the Department of Pharmacognosy, Second Military Medical University

Isolation. The air-dried aerial parts of *I. linearifolia* (500 Kg) was extracted three times with 80% ethanol at room temperature to afford a crude extract (12.72 kg), which further partitioned by petroleum ether and CH_2Cl_2 , giving a CH_2Cl_2 -soluble fraction (6.86 kg). The CH_2Cl_2 fraction was segmented by silica gel (petroleum ether/EtOAc 5:1 and 1:1, respectively) to give two fractions. The second fraction (P/E 1:1, 1.70 Kg) was dissolved in 5L EtOAc, and filtered to eliminate the large amount of crystal (Britanin, 1.12 Kg, a major monomer in title plant). The concentrated filtrate (510 g) was chromatographed over MCI gel (MeOH/ H_2O , from 40 to 90%) to give Fr.1-Fr.6. Subsequently, Fr.4-Fr.6 were purified by semi-preparative and preparative HPLC ($\text{CH}_3\text{CN}/\text{H}_2\text{O}$ from 40 to 60%), yielding **1** (157 mg), **2** (12.75 g), **3** (86 mg) and **4** (114 mg).

Compound characterization of 1–4

Lineariifolianoid I (1). Optically active colourless orthorhombic crystal in MeOH; m.p.: 189-192°C; $[\alpha]_D^{25}$ -164.2 (*c* 0.048, CHCl₃); UV (CH₃OH/H₂O) λ_{\max} 210 nm; IR (KBr) ν_{\max} 3396, 2960, 2877, 1770, 1727, 1664, 1644, 1454, 1434, 1403, 1382, 1243, 1160, 1033, 977, 813, 725, 607 cm⁻¹; ¹H- and ¹³C-NMR data, see Table S1-S2; ESIMS *m/z* 577.4 ([M+Na]⁺), 553.3 ([M-H]⁻); positive HRESIMS at *m/z* 577.2788 ([M+Na]⁺, calcd 577.6603).

Lineariifolianoid J (2). Optically active colourless orthorhombic crystal in MeOH; m.p.: 191-193°C; $[\alpha]_D^{25}$ +186.3 (*c* 0.062, CHCl₃); UV (CH₃OH/H₂O) λ_{\max} 210 nm; IR (KBr) ν_{\max} 3633, 3515, 2994, 2971, 2940, 2898, 2636, 2599, 1778, 1739, 1710, 1666, 1643, 1619, 1465, 1438, 1373, 1307, 1274, 1238, 1153, 1056, 1020, 998, 958, 611 cm⁻¹; ¹H- and ¹³C-NMR data, see Table S1-S2; ESIMS *m/z* 633.3 ([M+Na]⁺), 609.3 ([M-H]⁻); positive HRESIMS at *m/z* 633.2678 ([M+Na]⁺, calcd 633.6805).

Lineariifolianoid K (3). Optically active colourless oil; $[\alpha]_D^{25}$ +173.4 (*c* 0.059, CHCl₃); UV (CH₃OH/H₂O) λ_{\max} 220 nm; IR (KBr) ν_{\max} 3478, 2964, 2938, 1766, 1739, 1714, 1666, 1648, 1461, 1444, 1378, 1234, 1157, 1031, 954, 815, 698, 609 cm⁻¹; ¹H- and ¹³C-NMR data, see Table S1-S2; ESIMS *m/z* 575.3 ([M+Na]⁺), 551.3 ([M-H]⁻); positive HRESIMS at *m/z* 575.2625 ([M+Na]⁺, calcd 575.7444).

Lineariifolianoid L (4). Optically active colourless oil; $[\alpha]_D^{25}$ +41.9 (*c* 0.062, CHCl₃); UV (CH₃CN/H₂O) λ_{\max} 220 nm; IR (KBr) ν_{\max} 3446, 2965, 2937, 1881, 1766, 1739, 1716, 1664, 1648, 1444, 1405, 1376, 1238, 1166, 1128, 1052, 1029, 991, 904, 815, 603 cm⁻¹; ¹H- and ¹³C-NMR data, see Table S1-S2; ESIMS *m/z* 575.4 ([M+Na]⁺), 551.3 ([M-H]⁻); positive HRESIMS at *m/z* 575.2634 ([M+Na]⁺, calcd 575.7444).

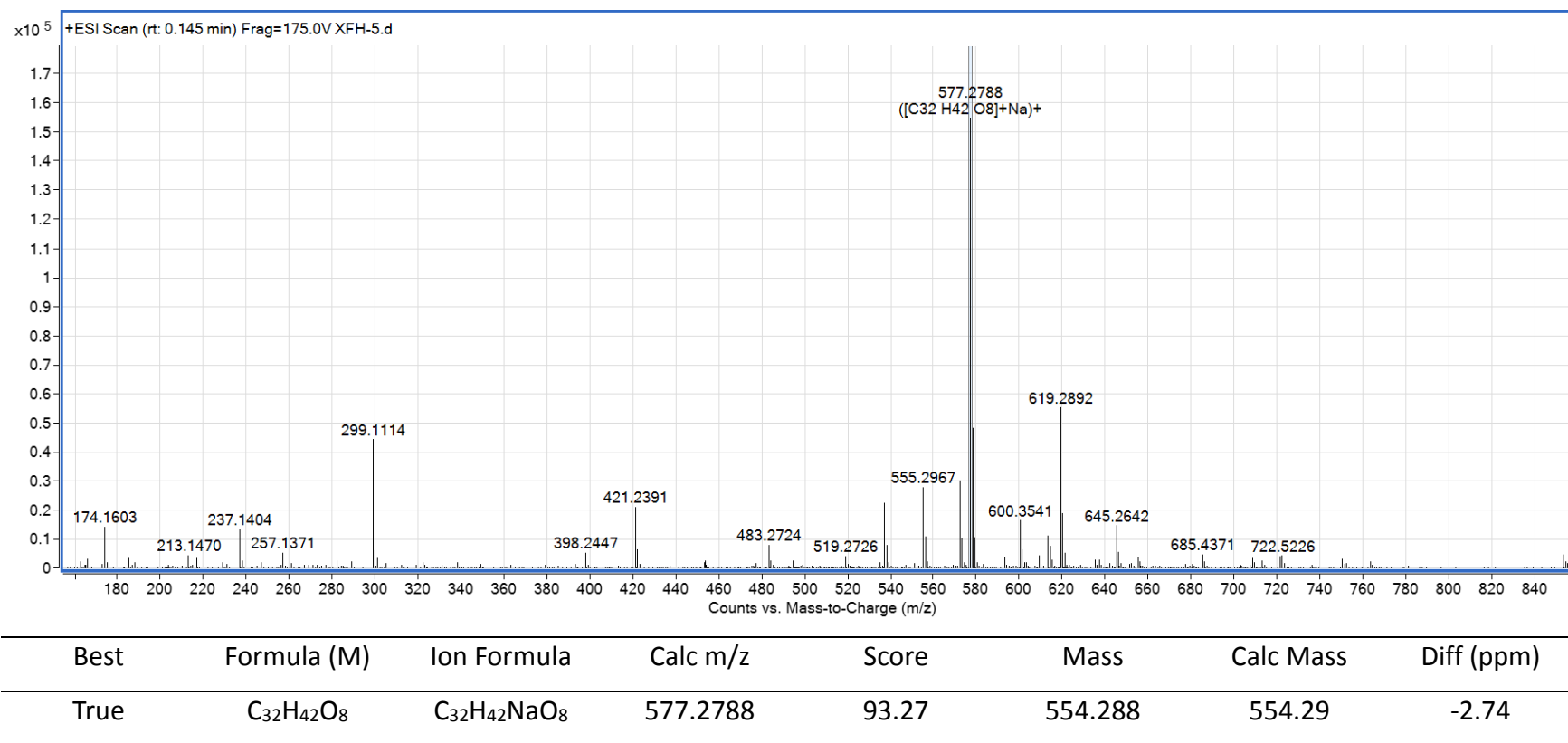


Figure S1. HRESIMS spectrum of Linearifolianoid I (**1**)

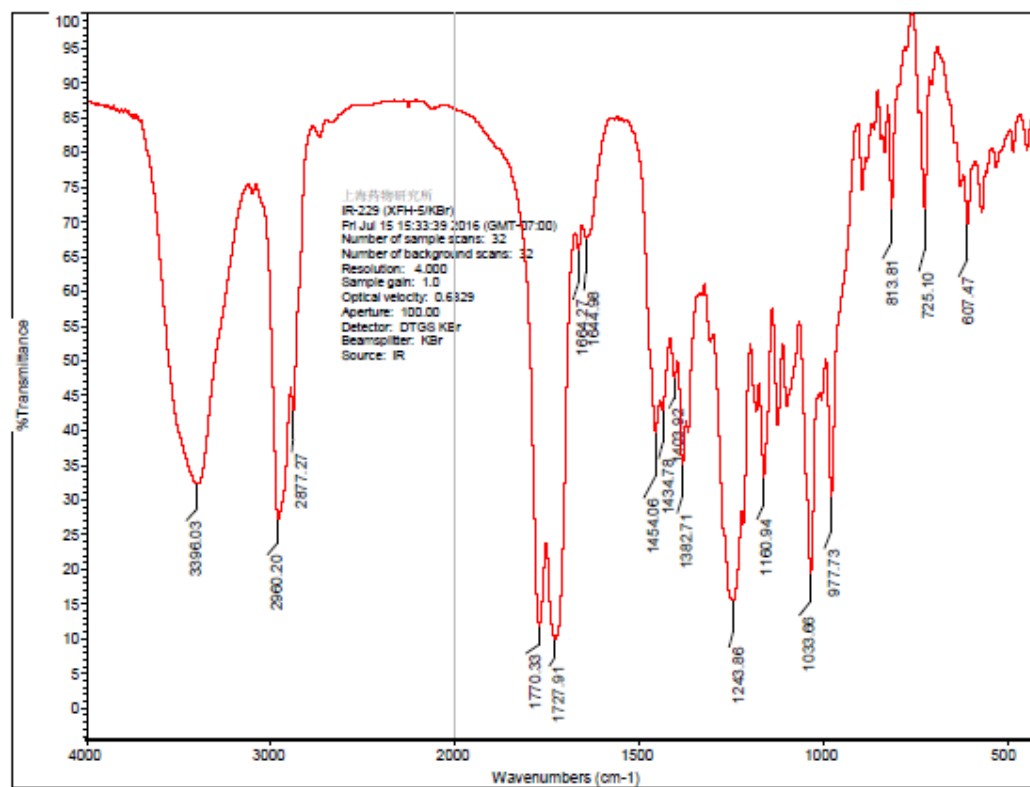


Figure S2. IR spectrum of Linearifolianoid I (**1**)

Rudolph Research Analytical

Monday, 07/18/2016

This sample was measured on an Autopol VI, serial number 90079,
manufactured by Rudolph Research Analytical, Hackettstown, NJ.

LotID : XFH-5
Set Temperature : 20.0
Temp Corr : OFF

n	Average	Std.Dev.	Maximum	Minimum						
6	-164.236	0.8504	-162.500	-164.583						
S.No	Sample ID	Time	Result	Scale	OR ° Arc	WLG	Lg.mm	Conc.	Temp.	Comment
1	XFH-5	09:35:59 AM	-164.583	SR	-0.079	589	100.00	0.048	19.9	
2	XFH-5	09:36:07 AM	-164.583	SR	-0.079	589	100.00	0.048	20.0	
3	XFH-5	09:36:15 AM	-164.583	SR	-0.079	589	100.00	0.048	20.0	
4	XFH-5	09:36:23 AM	-162.500	SR	-0.078	589	100.00	0.048	20.0	
5	XFH-5	09:36:30 AM	-164.583	SR	-0.079	589	100.00	0.048	20.0	
6	XFH-5	09:36:38 AM	-164.583	SR	-0.079	589	100.00	0.048	20.0	

Signature

Figure S3. OR Value of Linearifolianoid I (**1**) in CHCl₃

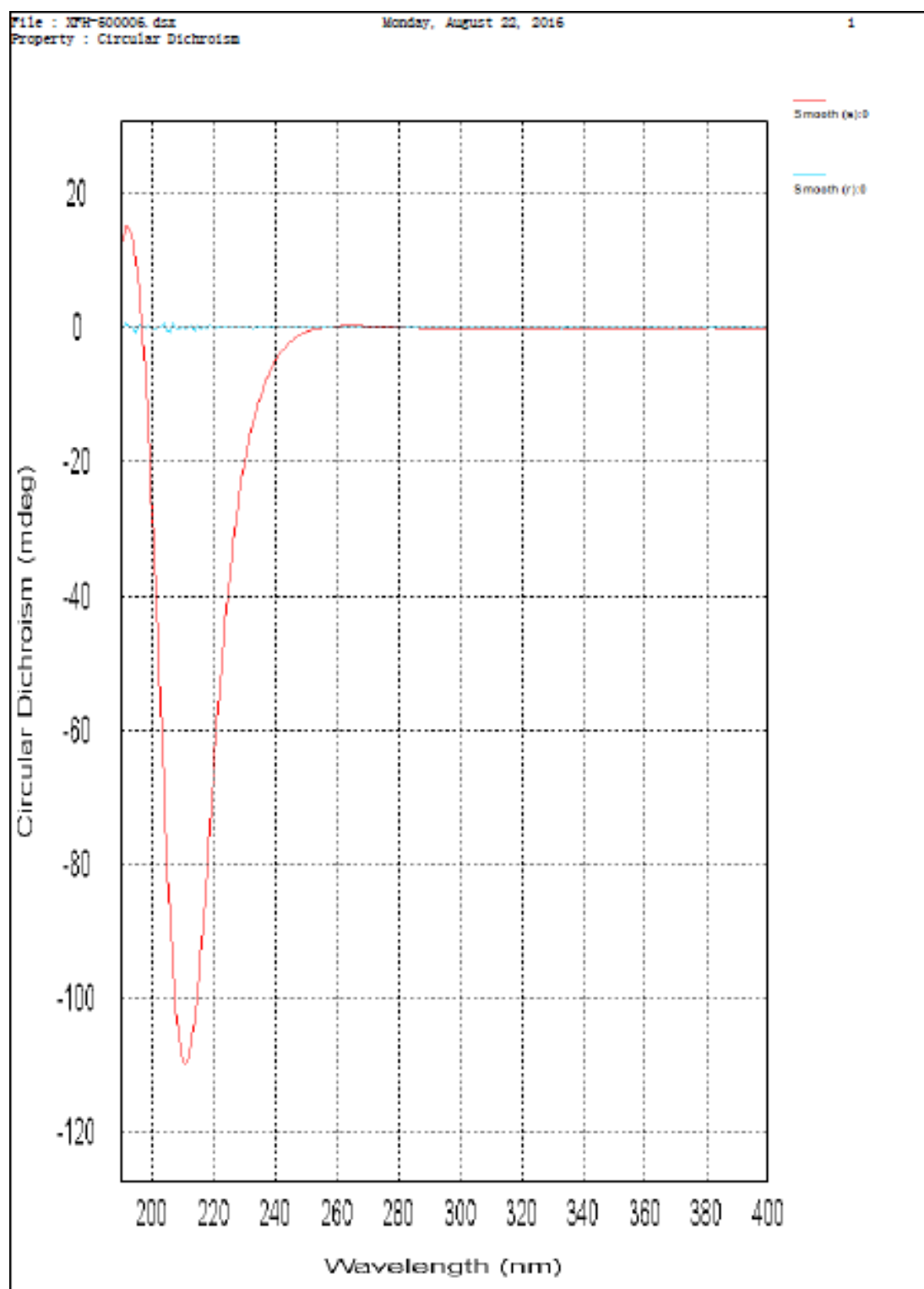


Figure S4. CD spectra of Linearifolianoid I (**1**) in CH₃CN

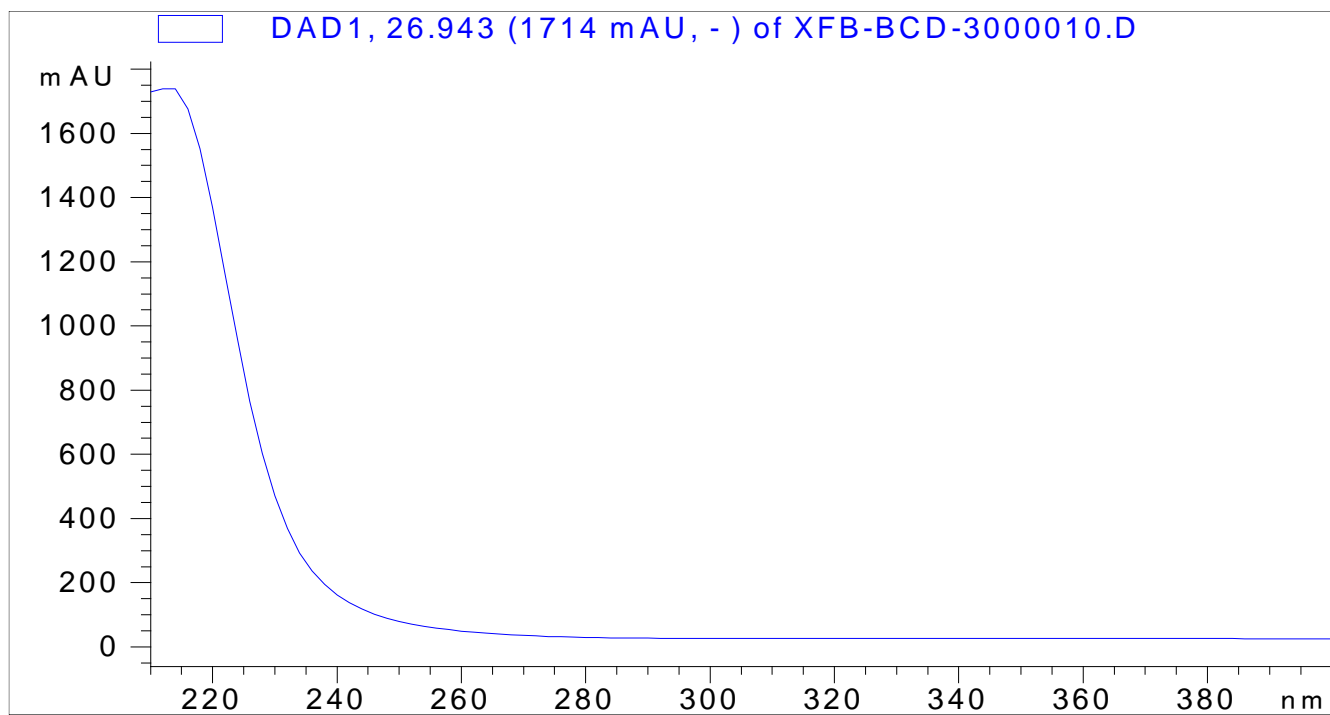


Figure S5. UV spectrum of Linearifolianoid I (**1**) in CH₃OH/H₂O

Compound 1 ¹H NMR

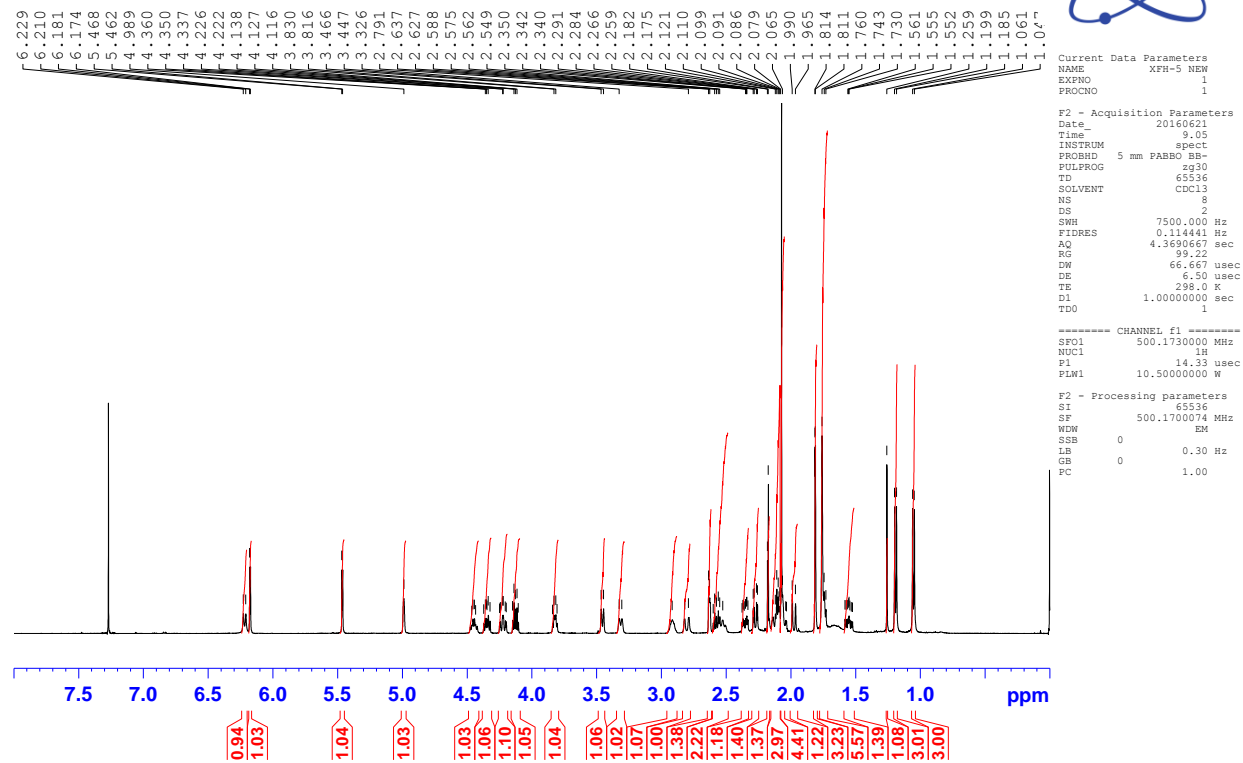
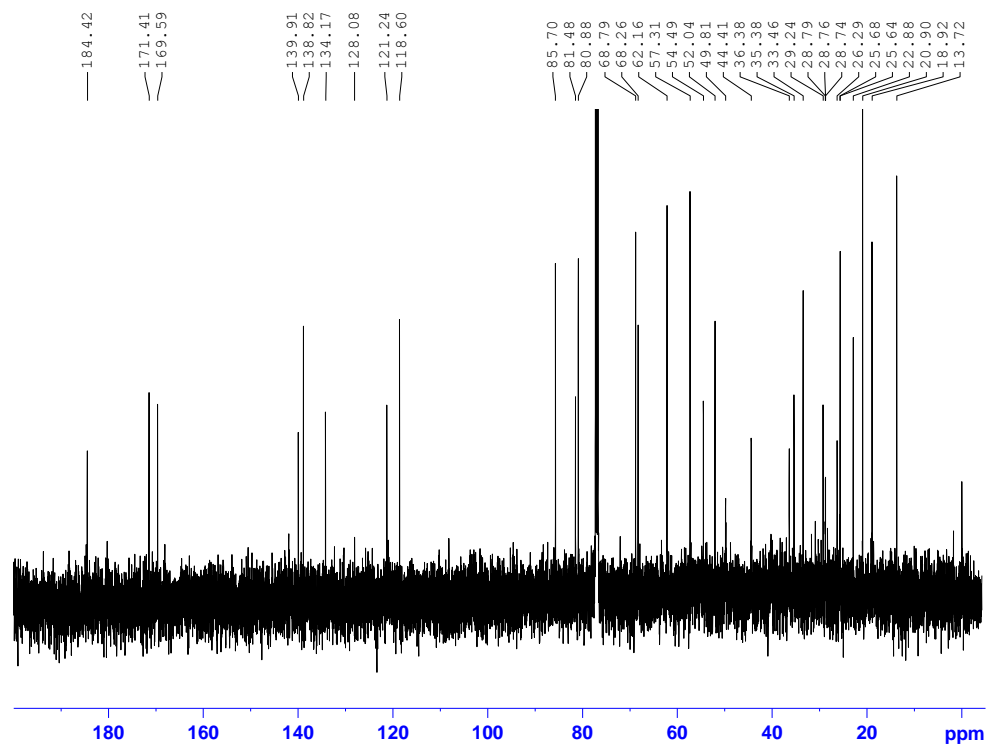


Figure S6. ¹H NMR spectrum of Linearifolianoid I (**1**) in CDCl₃

Compound 1 ¹³C NMR



```
Current Data Parameters
NAME      XFH-5 NEW
EXPNO    2
PROCNO   1

F2 - Acquisition Parameters
Date_    20160621
Time     9.18
INSTRUM  spect
PROBHD   5 mm PABBO BB-
PULPROG  zgpg30
TD       65536
SOLVENT  CDCl3
NS       300
DS       4
SWH      31250.000 Hz
FIDRES   0.476837 Hz
AQ       1.0485760 sec
RG       199.24
SW       16.000 usec
DE       6.50 usec
TE       298.0 K
D1       2.0000000 sec
D11      0.03000000 sec
TDO      1

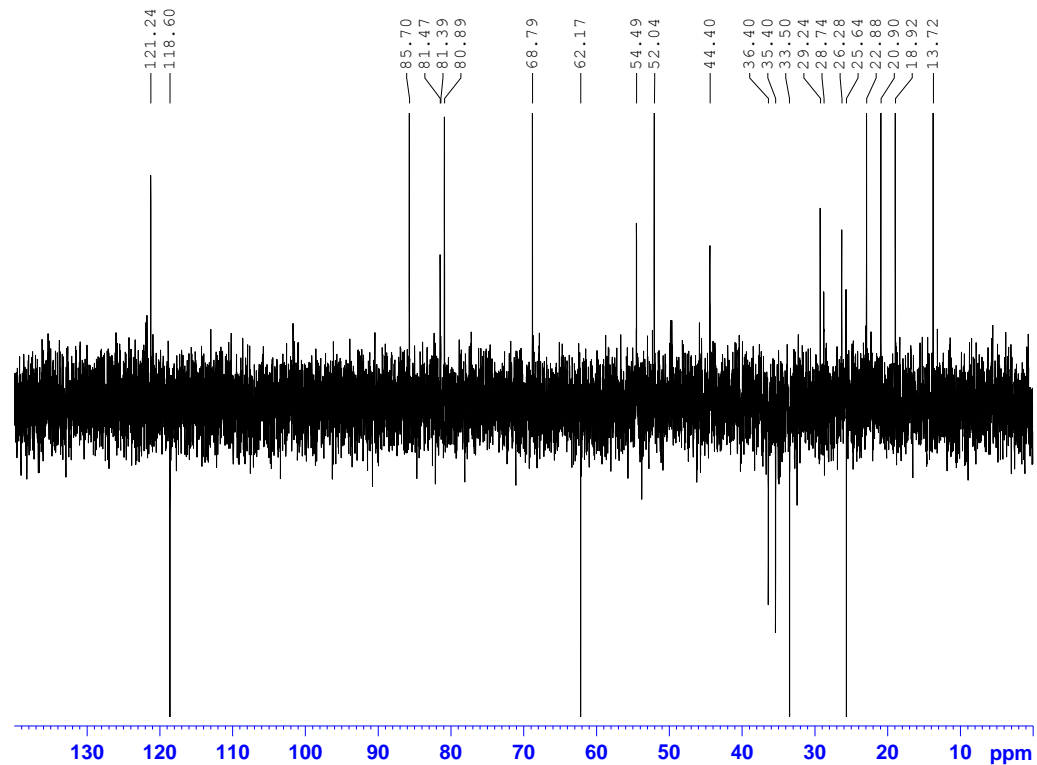
***** CHANNEL f1 *****
SF01    125.7829390 MHz
NUC1     13C
P1       9.00 usec
PLW1    65.00000000 W

***** CHANNEL f2 *****
SF02    500.1720007 MHz
NUC2     1H
CPDPRG2  waltz16
PCPD2    80.00 usec
PLW2    10.50000000 W
PLW12   0.35936001 W
PLW13   0.22999001 W

F2 - Processing parameters
SI       32768
SF       125.7678509 MHz
WDW      EM
SSB      0
LB       1.00 Hz
GB       0
PC       1.40
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Figure S7. ¹³C NMR spectrum of Linearifolanioid I (**1**) in CDCl₃

Compound 1 135 DEPT



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EXPNO     3
PROCNO    1

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PULPROG   deptsp135
TD         65536
SOLVENT   CDCl3
NS         67
DS         4
SWH       31250.000 Hz
FIDRES    0.476837 Hz
AQ         1.0485760 sec
RG         199.24
DW         16.000 usec
DE         6.50 usec
TE         298.0 K
CNST2     145.0000000
D1         2.0000000 sec
D2         0.00344828 sec
D12        0.00002000 sec
TDO        1

===== CHANNEL f1 =====
SFO1      125.7829390 MHz
NUC1       13C
P1         9.00 usec
P13        2000.00 usec
PLW0       0 W
PLW1       65.00000000 W
SPNAM[5]   Crp60comp.4
SFO1S      0 Hz
SPOFFS5    0 Hz
SPW5       8.04430008 W

===== CHANNEL f2 =====
SFO2      500.1715996 MHz
NUC2       1H
CPDPRG(2) waltz16
P3         14.80 usec
P4         29.60 usec
PCPD2      80.00 usec
PLW2       10.50000000 W
PLW12      0.35936001 W

F2 - Processing parameters
SI         32768
SF         125.7678509 MHz
WDW        EM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
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Figure S8. DEPT spectrum of Linearifolianoid I (**1**) in CDCl₃

Compound 1 HSQC

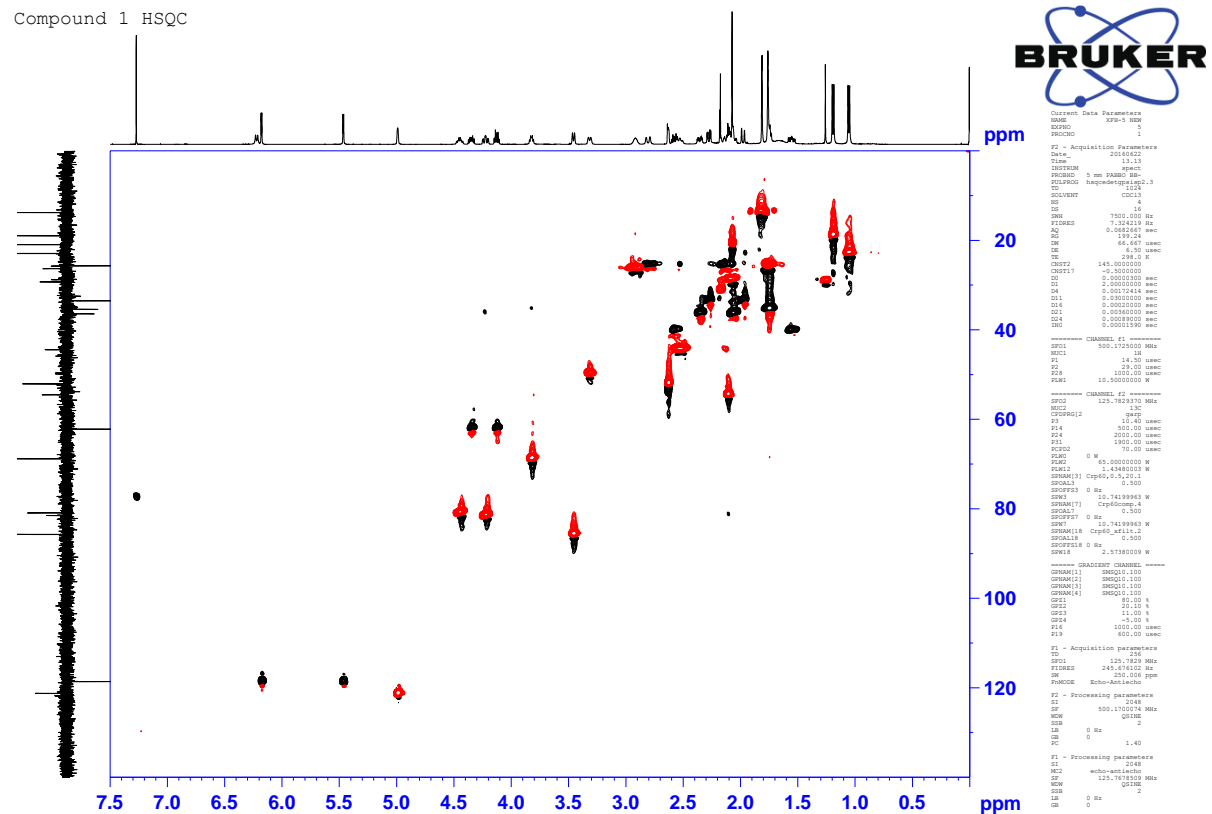
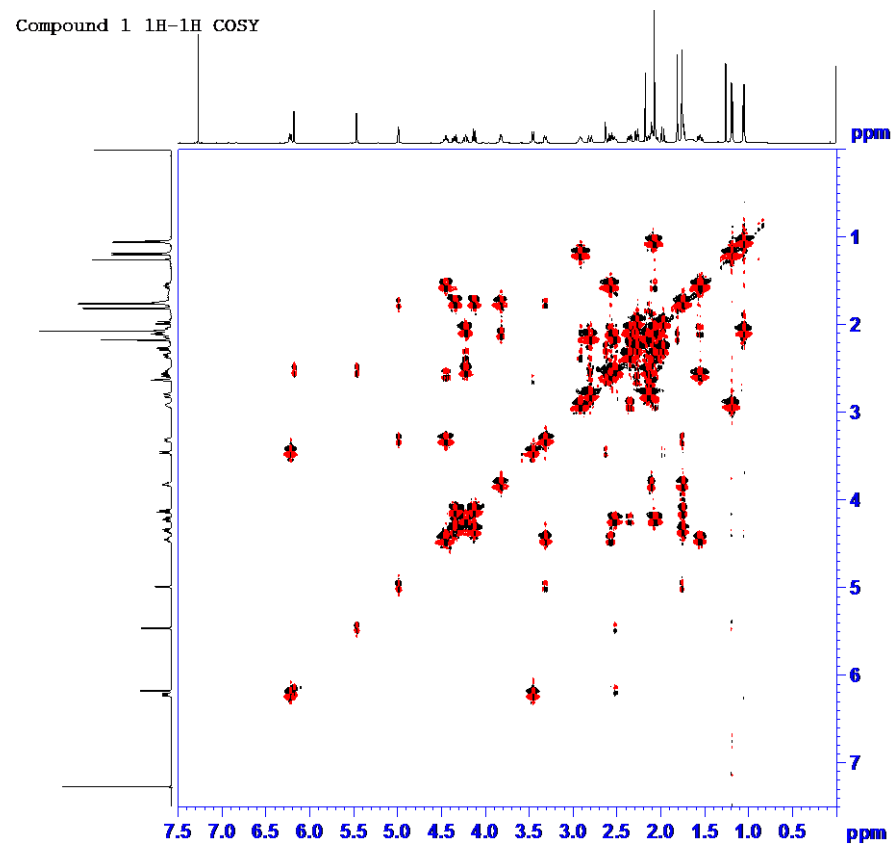


Figure S9. HSQC spectrum of Linearifolianoid I (**1**) in CDCl₃



```

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EXPNO    4
PROCNO   1

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TD        2048
SOLVENT   CDCl3
NS        4
DS        4
SWH        7500.000 Hz
FIDRES    2.662100 Hz
AQ        0.1365333 sec
RG        159.24
DE        66.667 umsec
TE        4.50 umsec
TE2       298.0 K
DQ        0.0004824 sec
DE2       2.0000000 sec
DEL1      0.0300000 sec
DE2       0.0002000 sec
DE3       0.0000000 sec
DRO       0.00013340 sec

===== CHANNEL f1 =====
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PR        29.00 umsec
PD17     2500.00 umsec
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PULPRO1   3.248570010 Hz

===== CHANNEL f2 =====
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GENAM(2)  SMCQ10.100
SFO1      500.1372500 MHz
SFO2      500.1372500 MHz
YF0RES    50.544460 Hz
SF        14.987 ppm
PULPROG   States-TEFI

F2 - Processing parameters
SI        2048
SF        500.1700074 MHz
WDW       USINE
SSB       2
GB        0 Hz
PC        1.40

F1 - Processing parameters
SI        2048
SF        States-TEFI
SF        500.1700074 MHz
WDW       USINE
SSB       2
GB        0 Hz
PC        0
  
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Figure S10. ^1H - ^1H COSY spectrum of Linearifolianoid I (**1**) in CDCl_3

Compound 1 HMBC

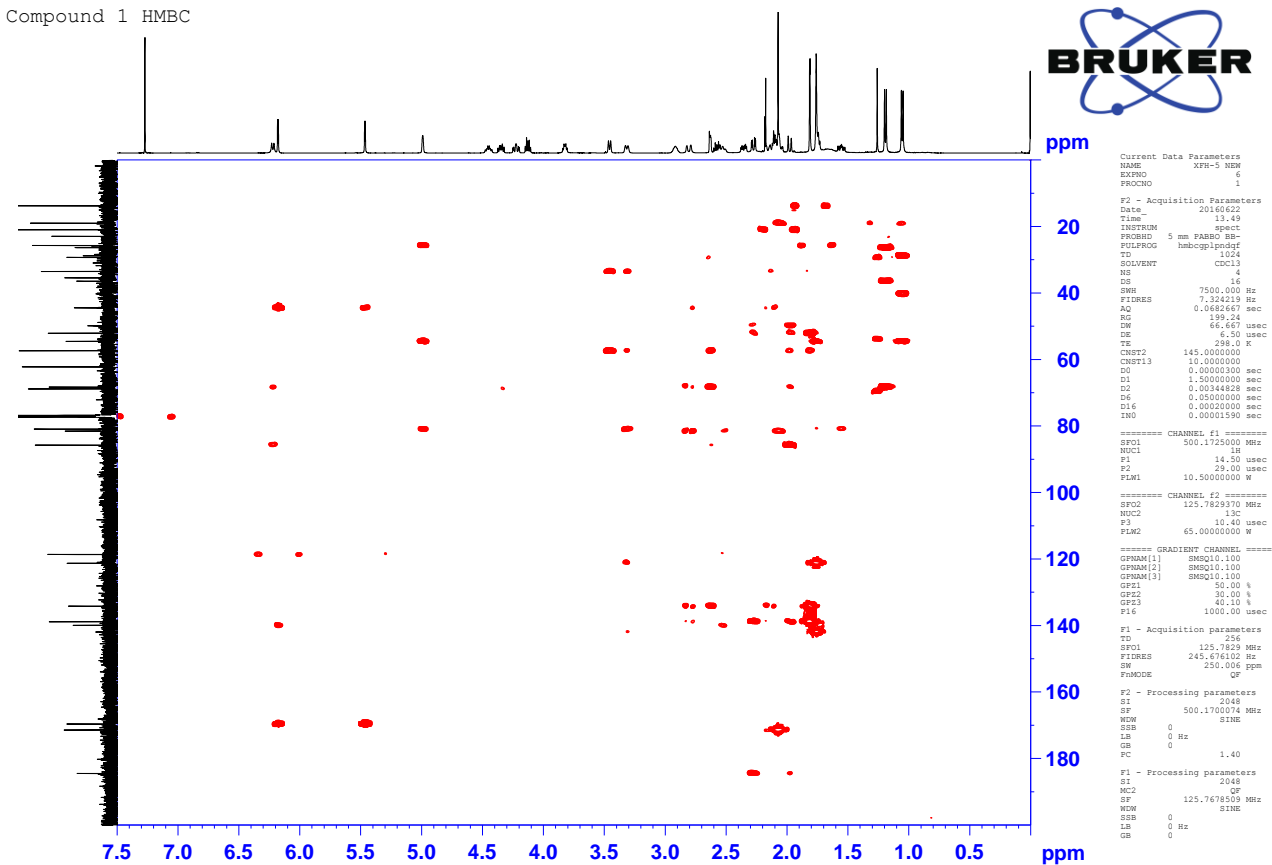


Figure S11. HMBC spectrum of Linearifolianoid I (**1**) in CDCl₃

Compound 1 NOESY

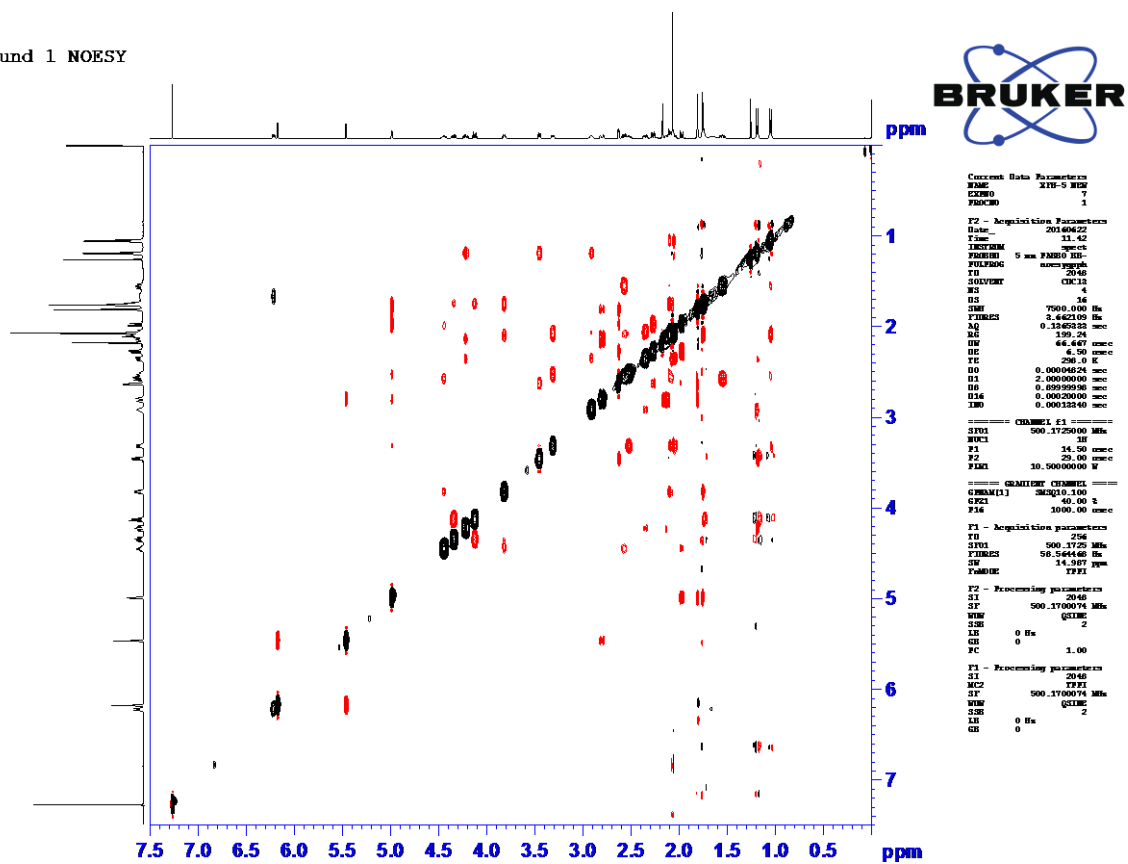


Figure S12. NOESY spectrum of Linearifolianoid I (1) in CDCl₃

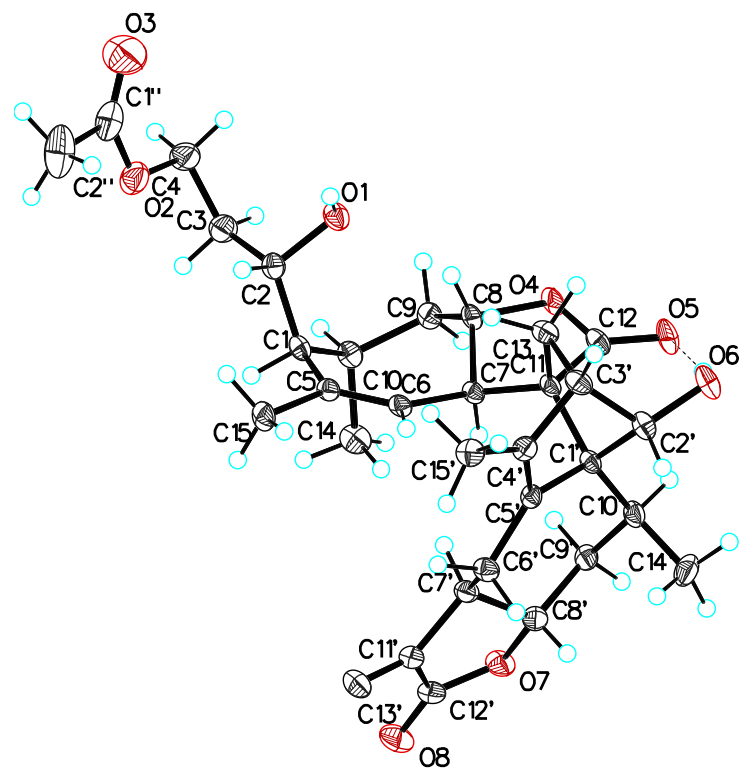
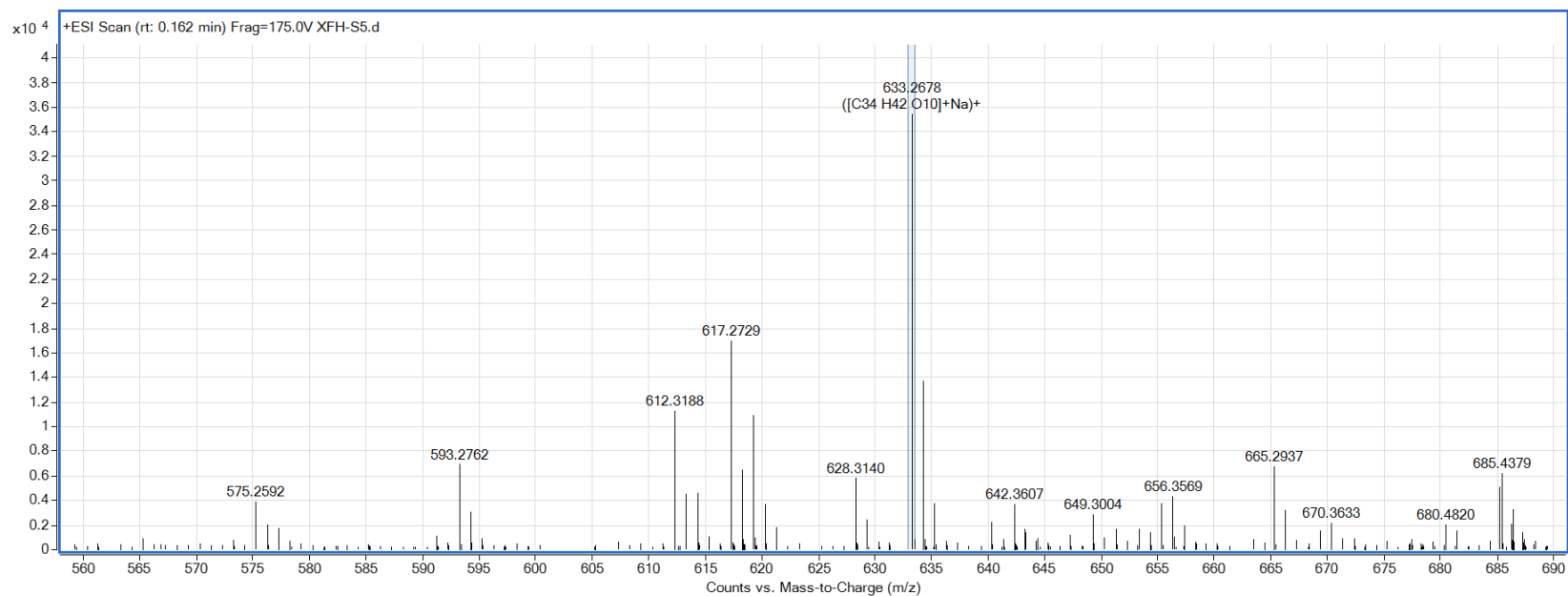


Figure S13. X-ray structure of Linearifolianoid I (**1**)



Best	Formula (M)	Ion Formula	Calc m/z	Score	Mass	Calc Mass	Diff (ppm)
True	C ₃₄ H ₄₂ O ₁₀	C ₃₄ H ₄₂ NaO ₁₀	633.2678	96.8	610.2778	610.28	-1.79

Figure S14. HRESIMS spectrum of Linearifolianoid J (**2**)

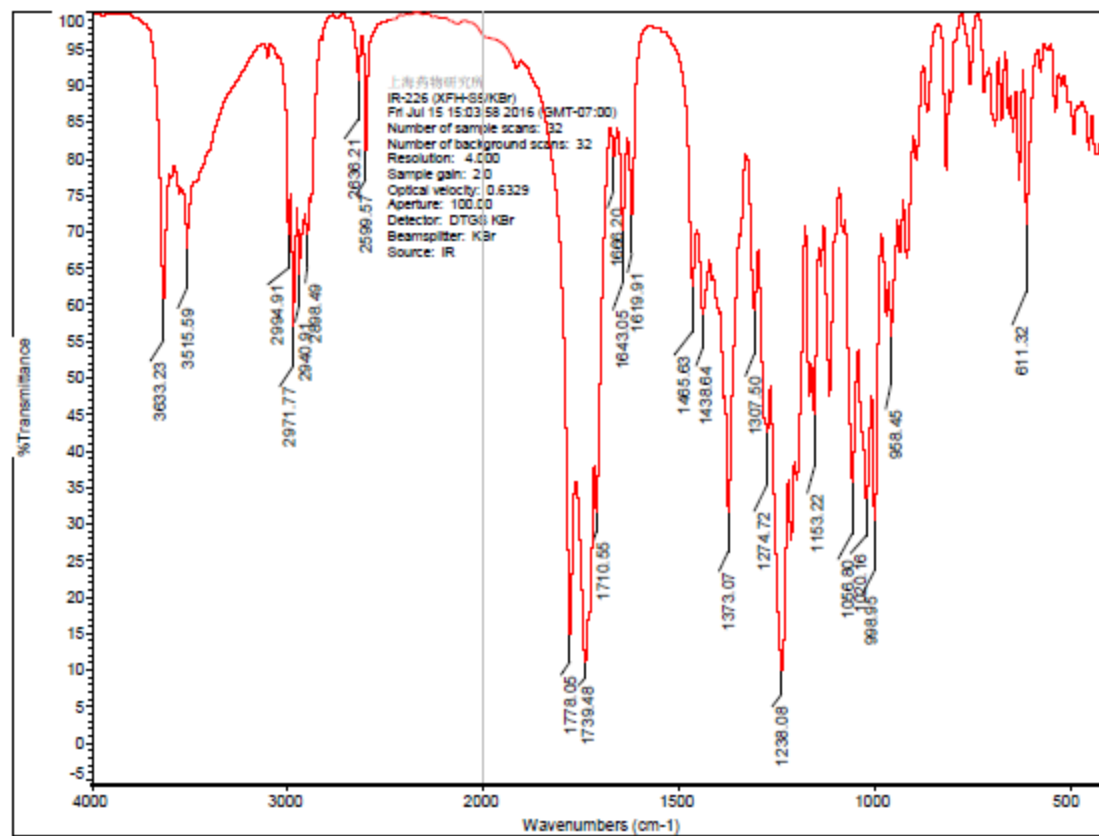


Figure S15. IR spectrum of Linearifoliod J (2)

Rudolph Research Analytical

Tuesday, 07/19/2016

This sample was measured on an Autopol VI, serial number 90079,
manufactured by Rudolph Research Analytical, Hackettstown, NJ.

LotID : XFH-S5
Set Temperature : 20.0
Temp Corr : OFF

n	Average	Std.Dev.	Maximum	Minimum						
6	186.291	0.8835	187.097	185.484						
S.No	Sample ID	Time	Result	Scale	OR ° Arc	WLG	Lg.mm	Conc.	Temp.	Comment
1	XFH-S5	02:59:05 PM	187.097	SR	0.116	589	100.00	0.062	19.9	
2	XFH-S5	02:59:13 PM	187.097	SR	0.116	589	100.00	0.062	19.9	
3	XFH-S5	02:59:20 PM	185.484	SR	0.115	589	100.00	0.062	19.9	
4	XFH-S5	02:59:27 PM	185.484	SR	0.115	589	100.00	0.062	19.9	
5	XFH-S5	02:59:35 PM	185.484	SR	0.115	589	100.00	0.062	20.0	
6	XFH-S5	02:59:42 PM	187.097	SR	0.116	589	100.00	0.062	20.0	

Signature

Figure S16. OR value of Linearifolianoid J (**2**) in CHCl₃

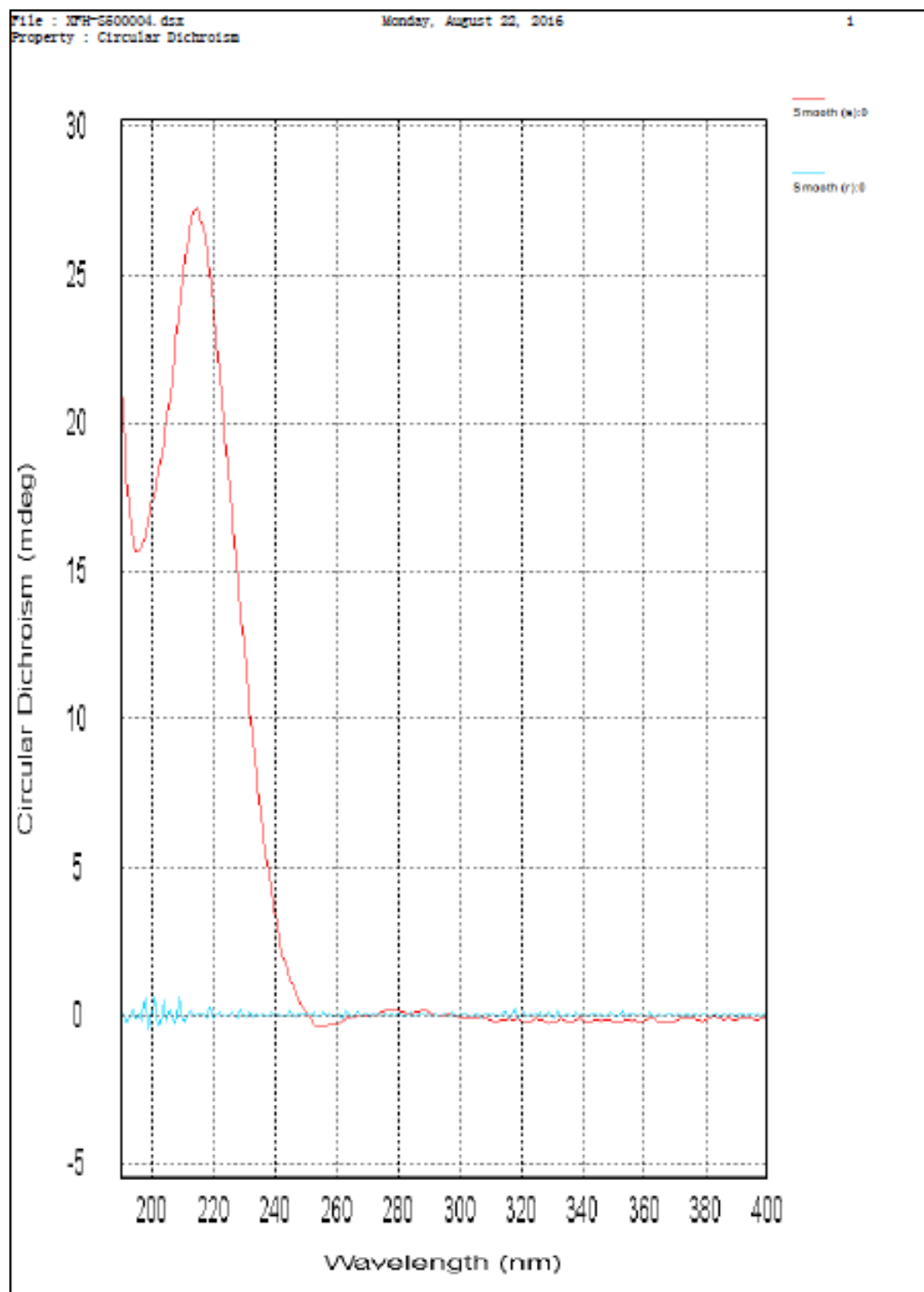


Figure S17. CD spectra of Linearifolianoid J (2) in CH₃CN

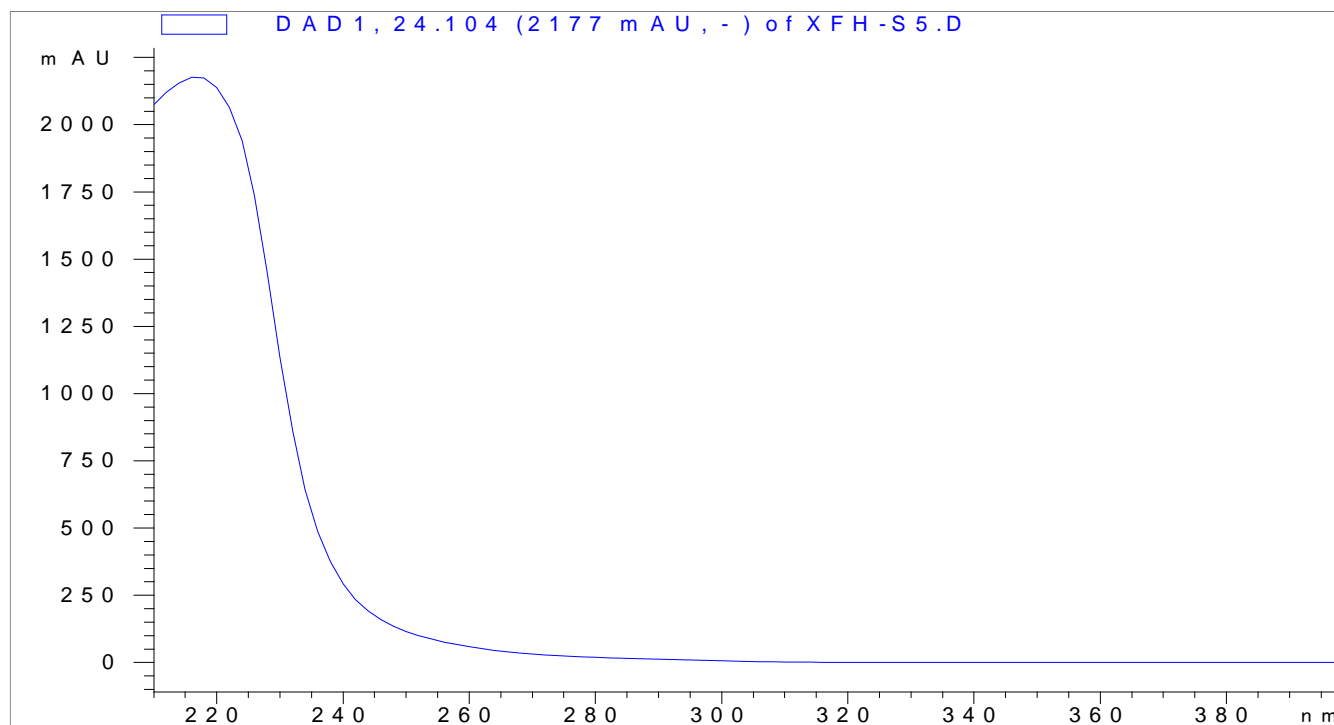
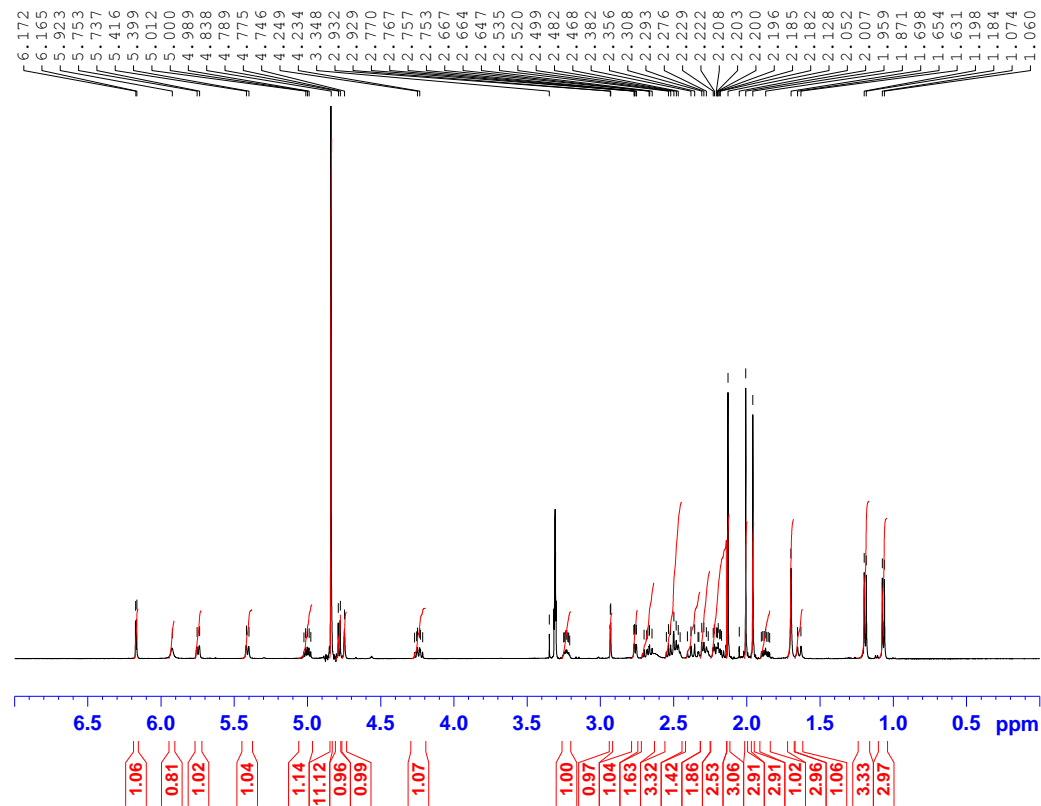


Figure S18. UV spectrum of Linearifolianoid J (**2**) in CH₃OH/H₂O

Compound 2 ¹H NMR



```
Current Data Parameters
NAME      CLP-XPB-S5
EXPNO    1
PROCNO   1

F2 - Acquisition Parameters
Date_    20160722
Time     7.48
INSTRUM  spect
PROBHD   5 mm PABBO BB-
PULPROG  zg30
TD       65536
SOLVENT  MeOD
NS       8
DS       2
SWH      7500.000 Hz
FIDRES   0.114441 Hz
AQ       4.3690667 sec
RG       120.22
DW       66.667 usec
DE       6.50 usec
TE       298.0 K
D1       1.00000000 sec
TDO      1

===== CHANNEL f1 =====
SF01    500.1730000 MHz
NUC1    1H
P1      14.33 usec
PLW1    10.50000000 W

F2 - Processing parameters
SI      65536
SF      500.1700100 MHz
WDW     EM
SSB     0
LB      0.30 Hz
GB      0
PC      1.00
```

Figure S19. ¹H NMR spectrum of Linearifolianoid J (2) in CD₃OD

Compound 2 ¹³C NMR

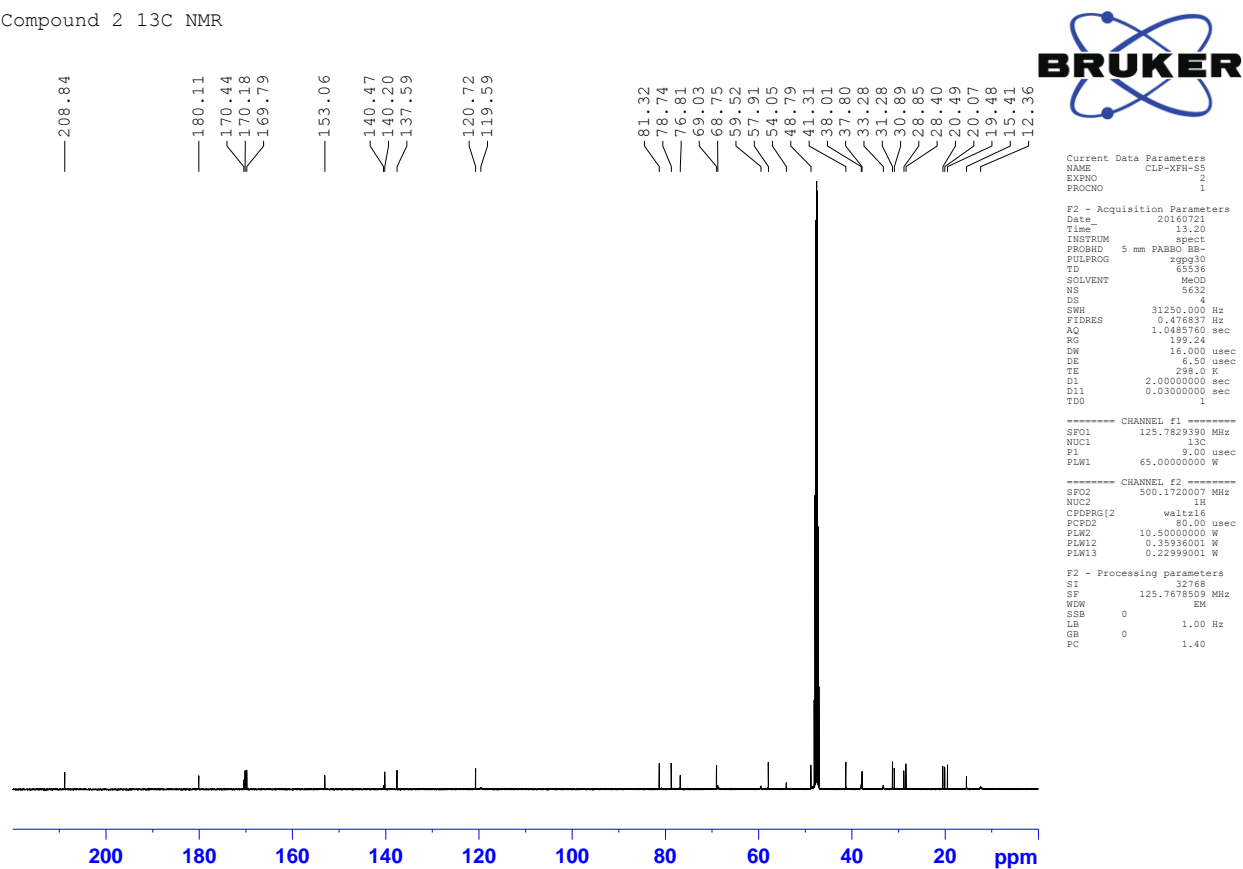
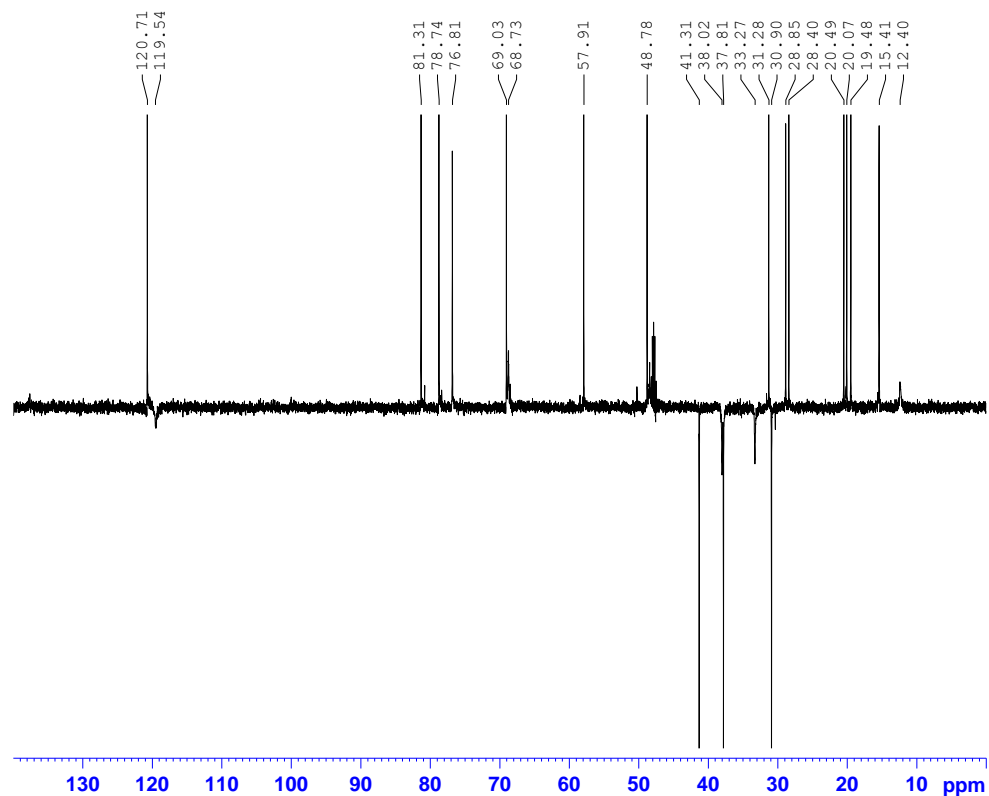


Figure S20. ¹³C NMR spectra of Lineariifolianoid J (**2**) in CD₃OD

Compound 2 135 DEPT



```
Current Data Parameters
NAME      CLP-KF4-55
EXPNO     3
PROCNO    1

F2 - Acquisition Parameters
Date_     20160722
Time      0.32
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   deptsp135
TD        65536
SOLVENT   MeOD
NS         13824
DS         4
SWH        31250.000 Hz
FIDRES     0.476837 Hz
AQ         1.0485760 sec
RG         199.24
DW         16.000 usec
DE         6.50 usec
TE         298.0 K
CNST2     145.000000
D1         2.00000000 sec
D2         0.00344828 sec
D12        0.00002000 sec
TDO        1

===== CHANNEL f1 =====
SFO1      125.7829390 MHz
NUC1       13C
P1         9.00 usec
P13        2000.00 usec
PLW0       0 W
PLW1       65.00000000 W
SPNAM[5]   Crp60comp.4
SFOALS     0.500
SFOFFS5    0 Hz
SPW5       8.04430008 W

===== CHANNEL f2 =====
SFO2      500.1715996 MHz
NUC2       1H
CPDPRG[2]  waltz16
P3         14.80 usec
P4         29.60 usec
PCPD2     80.00 usec
PLW2      10.50000000 W
PLW12     0.35936001 W

F2 - Processing parameters
SI         32768
SF         125.7678509 MHz
WDW        EM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
```

Figure S21. DEPT spectra of Linearifolianoid J (2) in CD₃OD

Comound 2 HSQC

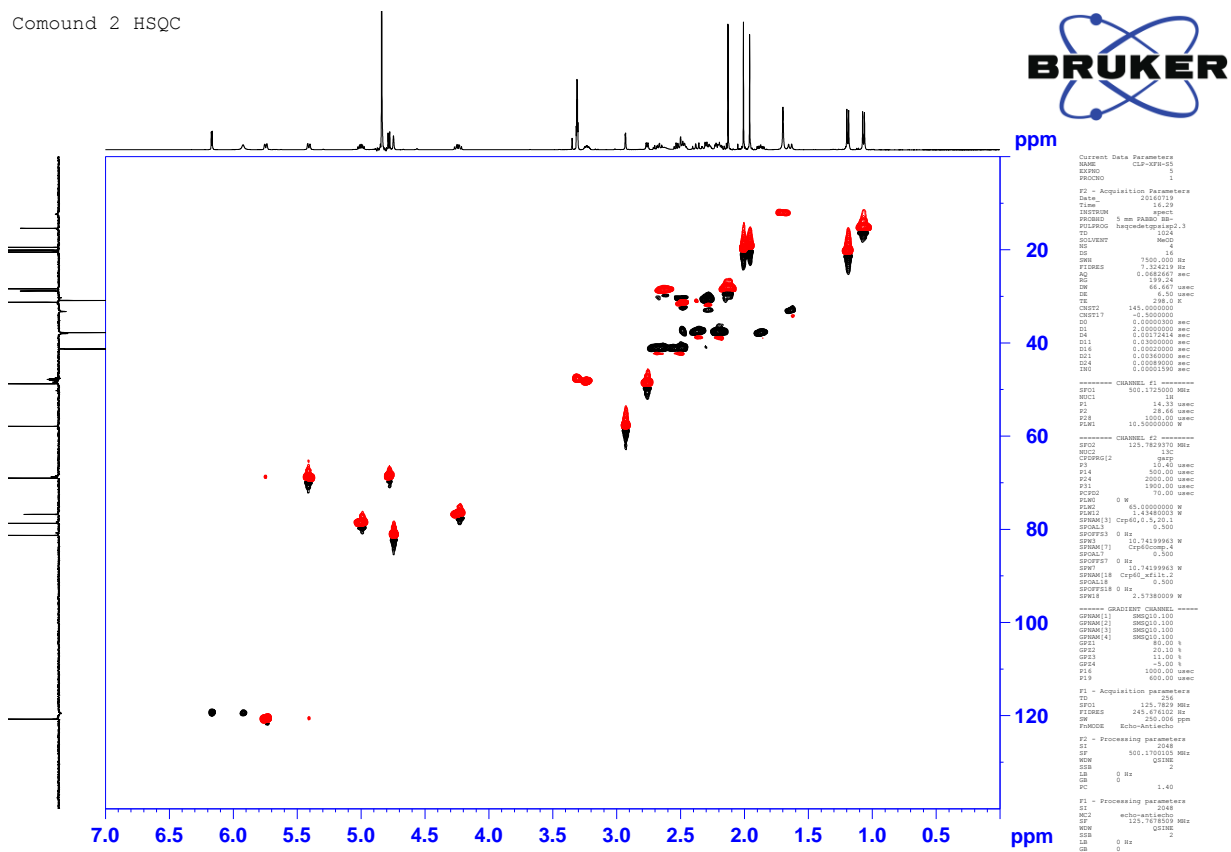
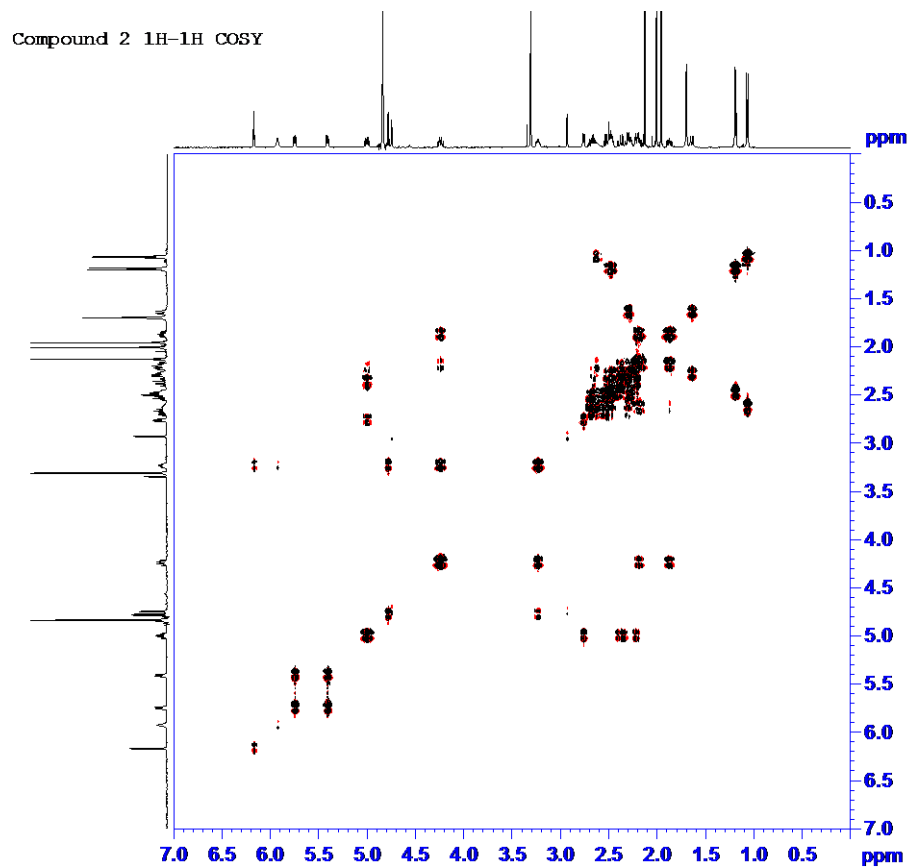


Figure S22. HSQC spectrum of Linearifolianoid J (2) in CD₃OD



```

Current Data Parameters
NAME      CLR-231-05
EXPNO    4
PROCNO    1

F2 - Acquisition Parameters
Date_     20160719
Time      11.36
INSTRUM   spect
PROBHD    5 mm HBBBO BB-
PULPROG   coyygpg1pgpp
TD        2048
SOLVENT   MeOD
NS        4
DS        16
SWH        7500.000 Hz
FIDRES    0.662109 Hz
AQ         0.1360333 sec
RG         159.24
BW         65.667 usec
DE         6.50 usec
TE        298.0 K
DQ         0.0009845 sec
DL         2.0000000 sec
DL1        0.0000000 sec
DL2        0.0002000 sec
DL3        0.0002000 sec
DRO        0.0013340 sec

----- CHANNEL f1 -----
NUC1      500.172000 MHz
P1        18
PL1       14.23 usec
PL2       21.66 usec
PL3       2500.00 usec
PL12      10.5000000 W
PL13      3.1835000 W

----- GRABBER CHANNEL -----
GRAB1(1)  SENS10.100
GRAB1(2)  SENS10.100
GR12      10.00 %
GR13      20.00 %
GR14      1000.00 usec

F1 - Acquisition parameters
TD        256
SF        500.1725 MHz
FIDRES    58.564463 Hz
SR        15.507 ppm
NAME      States-TFPI

F2 - Processing parameters
SI        2048
SF        500.1700105 MHz
WDW       QFTIME
SSB       2
GB        0 Hz
PC        1.40

F1 - Processing parameters
SI        2048
SF        States-TFPI
WDW       QFTIME
SSB       2
GB        0 Hz
PC        0
  
```

Figure S23. ¹H-¹H COSY spectrum of Linearifolianoid J (2) in CD₃OD

Compound 2 HMBC

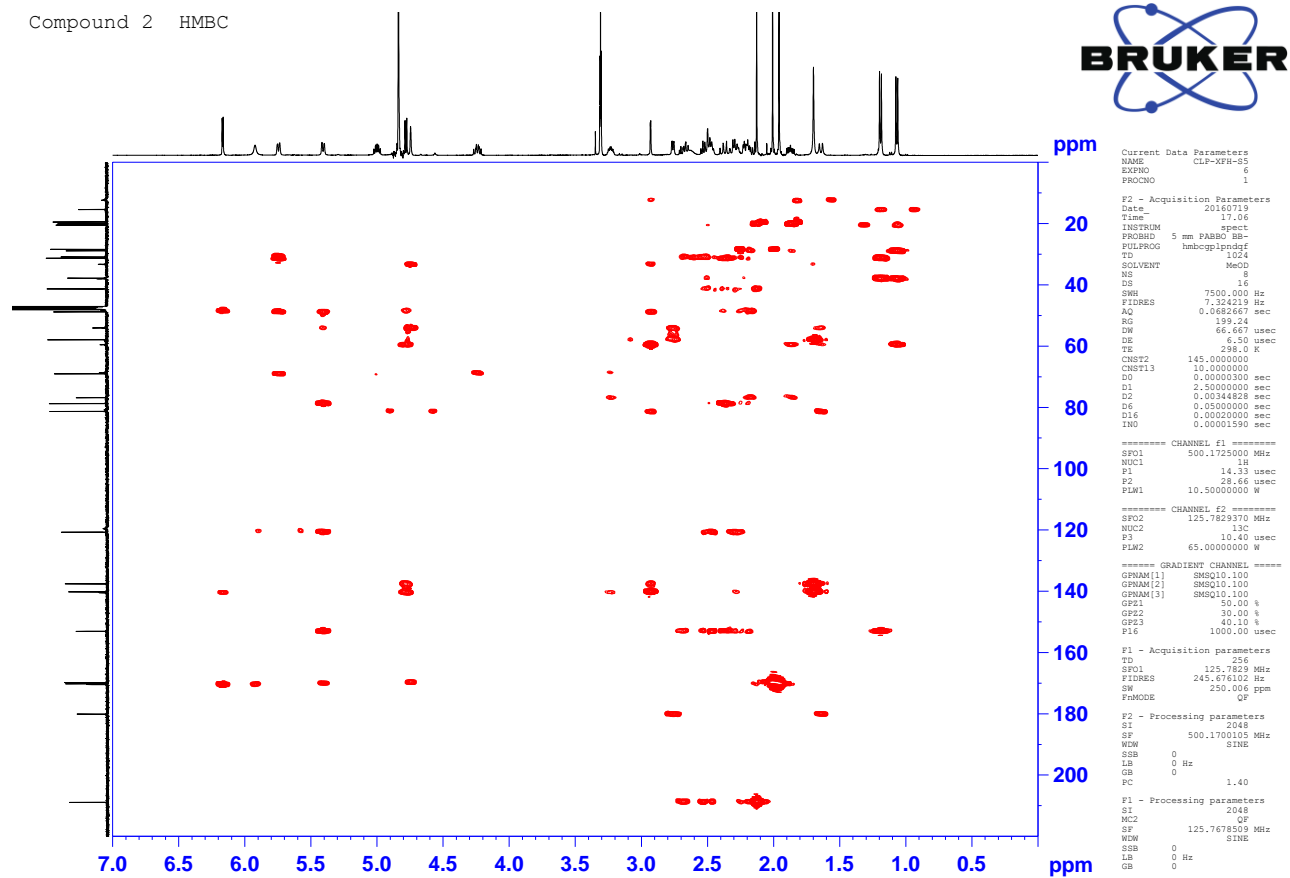
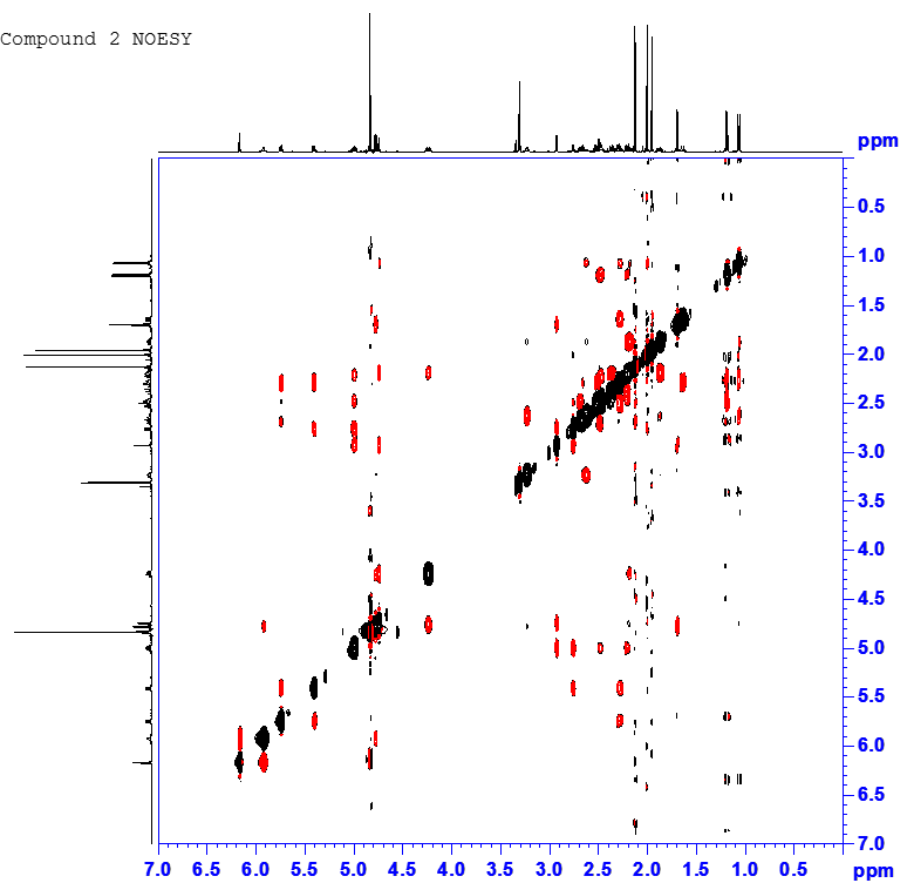


Figure S24. HMBC spectrum of Linearifolianoid J (**2**) in CD₃OD

Compound 2 NOESY



```
Current Data Parameters
NAME      CLP-NFU-S5
EXPNO     7
PROCNO    1

F2 - Acquisition Parameters
Date_     20160719
Time      15.15
INSTRUM   spect
PROBHD    5 mm FAMB0 BB-
PULPROG   noesypph
ID        2048
SOLVENT   MeOD
NS         4
DS         16
SWH        7500.000 Hz
FIDRES     3.662109 Hz
AQ         0.1365323 sec
RG         199.24
DH         66.667 usec
DE         6.50 usec
TE         298.0 K
DQ         0.0004848 sec
D1         2.0000000 sec
DS         0.88899998 sec
D16        0.0002000 sec
IN0        0.00013340 sec

===== CHANNEL f1 =====
SFO1      500.1725000 MHz
NUC1      1H
P1        14.22 usec
P2        25.66 usec
PLW1      10.50000000 W

===== GRADIENT CHANNEL =====
SFO1M1    SMSQ10.100
PFG1      40.00 t
P16       1000.00 usec

F1 - Acquisition parameters
ID        256
SFO1      500.1725 MHz
FIDRES    58.864468 Hz
SW        14.387 ppm
FAMODE    7PFI

F2 - Processing parameters
SI        2048
SF        500.1700105 MHz
WDW       QSI
SSB       2
LB        0 Hz
GB        0
PC        1.00

F1 - Processing parameters
SI        2048
MC2       7PFI
SF        500.1700105 MHz
WDW       QSI
SSB       2
LB        0 Hz
GB        0
```

Figure S25. NOESY spectrum of Linearifolianoid J (2) in CD₃OD

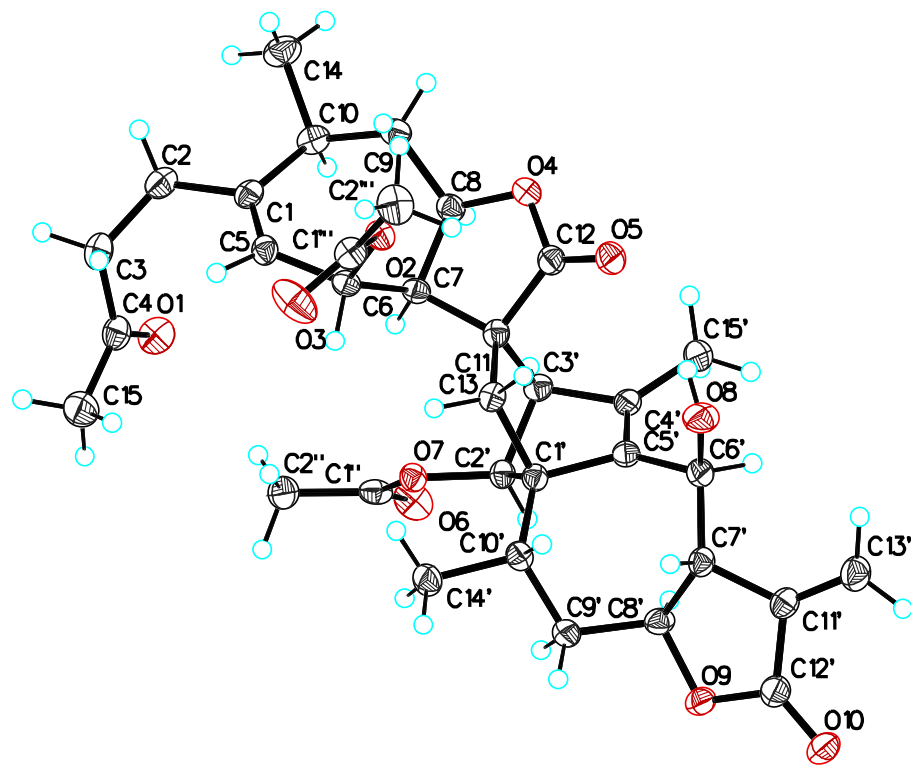
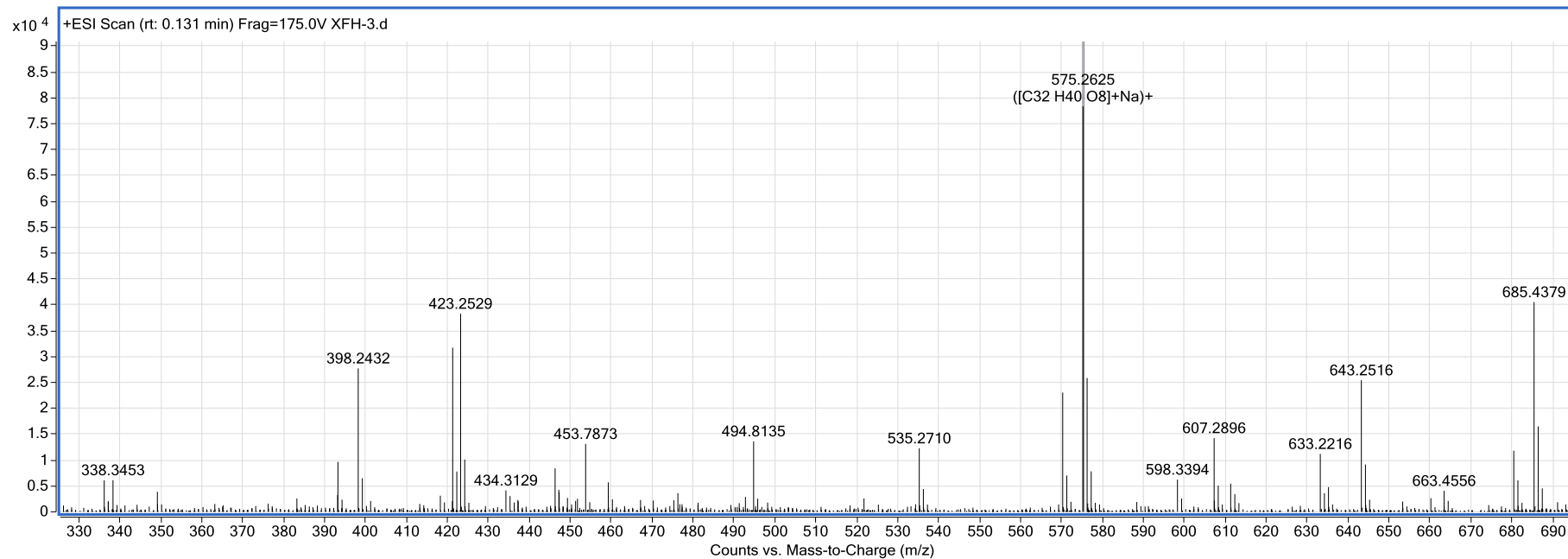


Figure S26. X-ray structure of Linearifolianoid J (2)



Best	Formula (M)	Ion Formula	Calc m/z	Score	Mass	Calc Mass	Diff (ppm)
True	C ₃₂ H ₄₀ O ₈	C ₃₂ H ₄₀ NaO ₈	575.2625	93.28	552.2723	552.27	-2.15

Figure S27. HRESIMS spectrum of Linearifolianoid K (**3**)

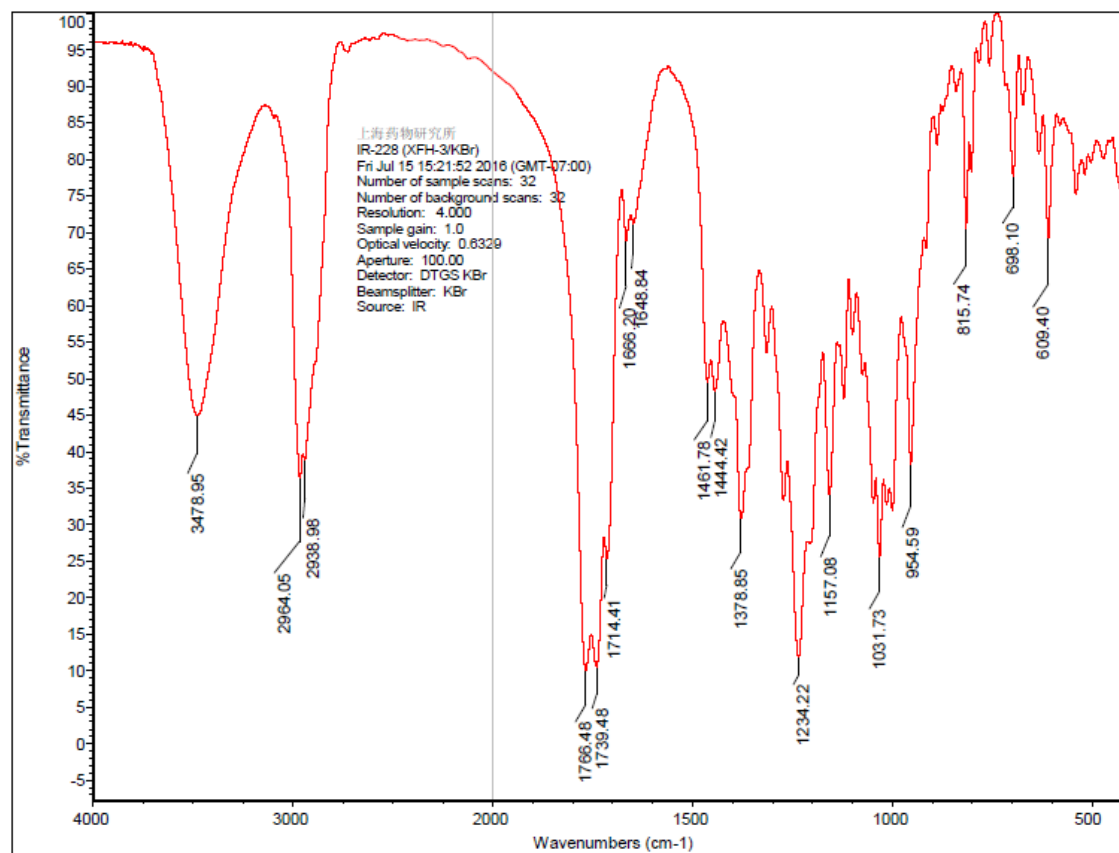


Figure S28. IR spectrum of Linearifolianoid K (3)

Rudolph Research Analytical

Tuesday, 07/19/2016

This sample was measured on an Autopol VI, serial number 90079,
manufactured by Rudolph Research Analytical, Hackettstown, NJ.

LotID : XFH-3

Set Temperature : 20.0

Temp Corr : OFF

n	Average	Std.Dev.	Maximum	Minimum
6	173.446	0.8753	174.576	172.881

S.No	Sample ID	Time	Result	Scale	OR ° Arc	WLG	Lg.mm	Conc.	Temp.	Comment
1	XFH-3	03:02:35 PM	172.881	SR	0.102	589	100.00	0.059	20.0	
2	XFH-3	03:02:43 PM	172.881	SR	0.102	589	100.00	0.059	20.0	
3	XFH-3	03:02:51 PM	172.881	SR	0.102	589	100.00	0.059	20.0	
4	XFH-3	03:02:58 PM	172.881	SR	0.102	589	100.00	0.059	20.0	
5	XFH-3	03:03:06 PM	174.576	SR	0.103	589	100.00	0.059	20.0	
6	XFH-3	03:03:14 PM	174.576	SR	0.103	589	100.00	0.059	20.0	

Signature

Figure S29. OR Value of Linearifolianoid K (**3**) in CHCl₃

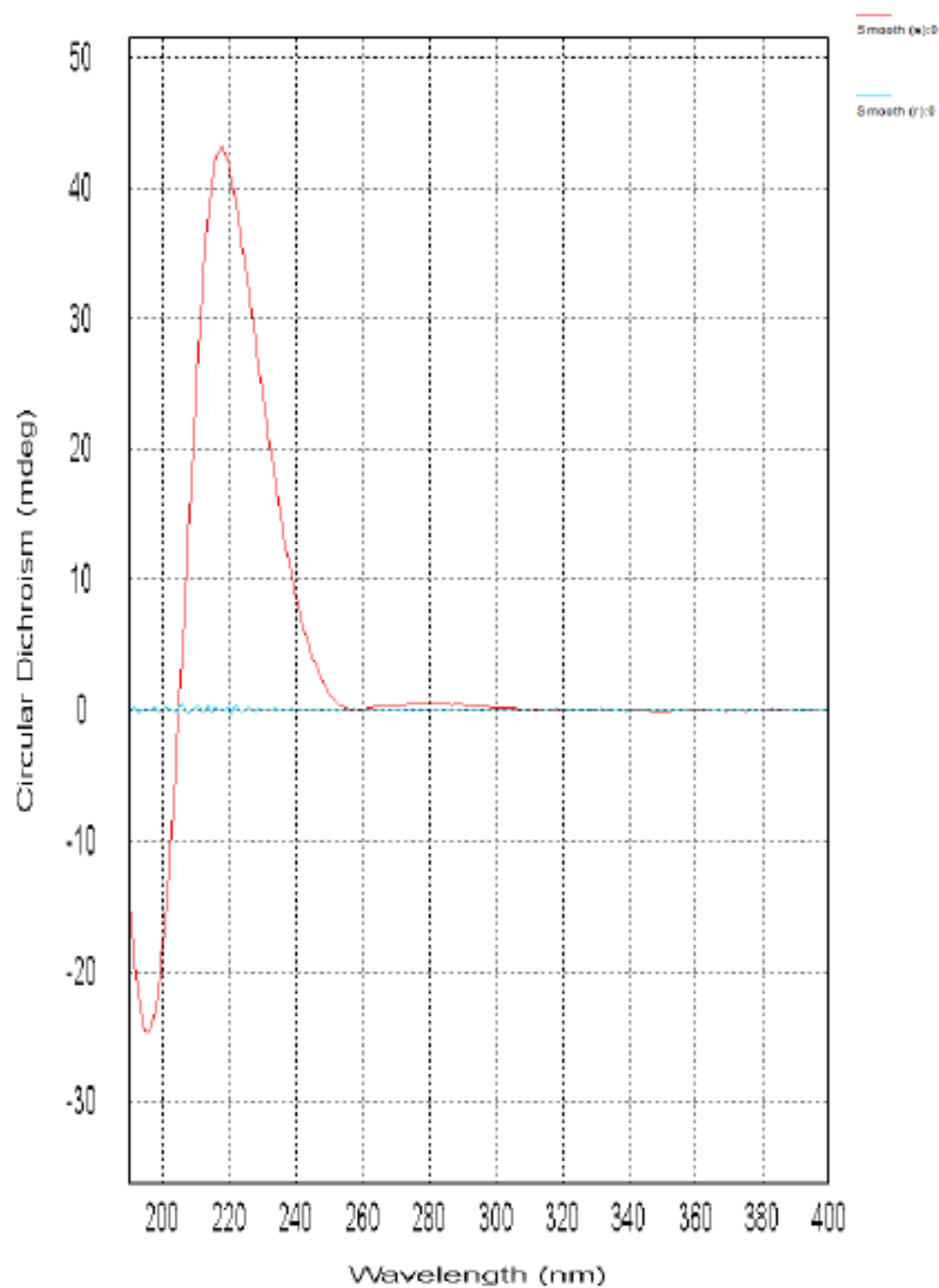


Figure S30. CD spectra of Linearifolianoid K (**3**) in CH₃CN

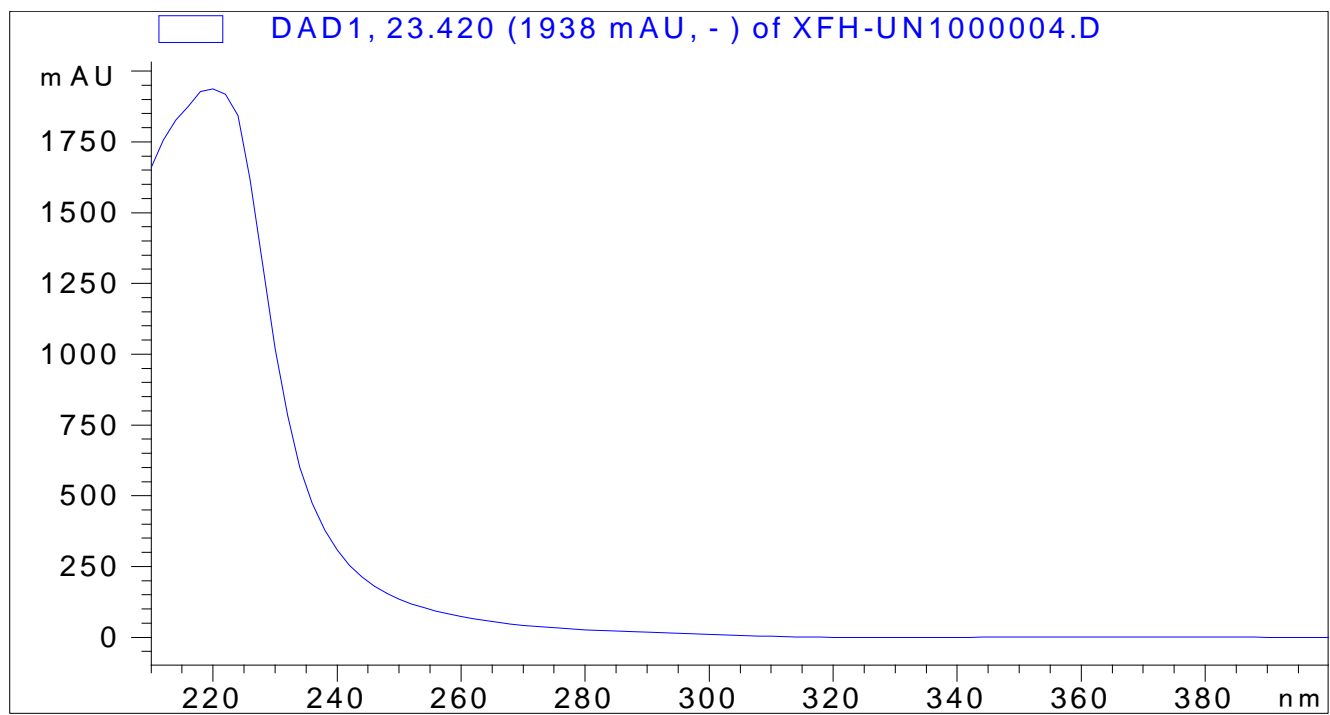


Figure S31. UV spectrum of Linearifolianoid K(3) in CH₃OH/H₂O

Compound 3 1H NMR

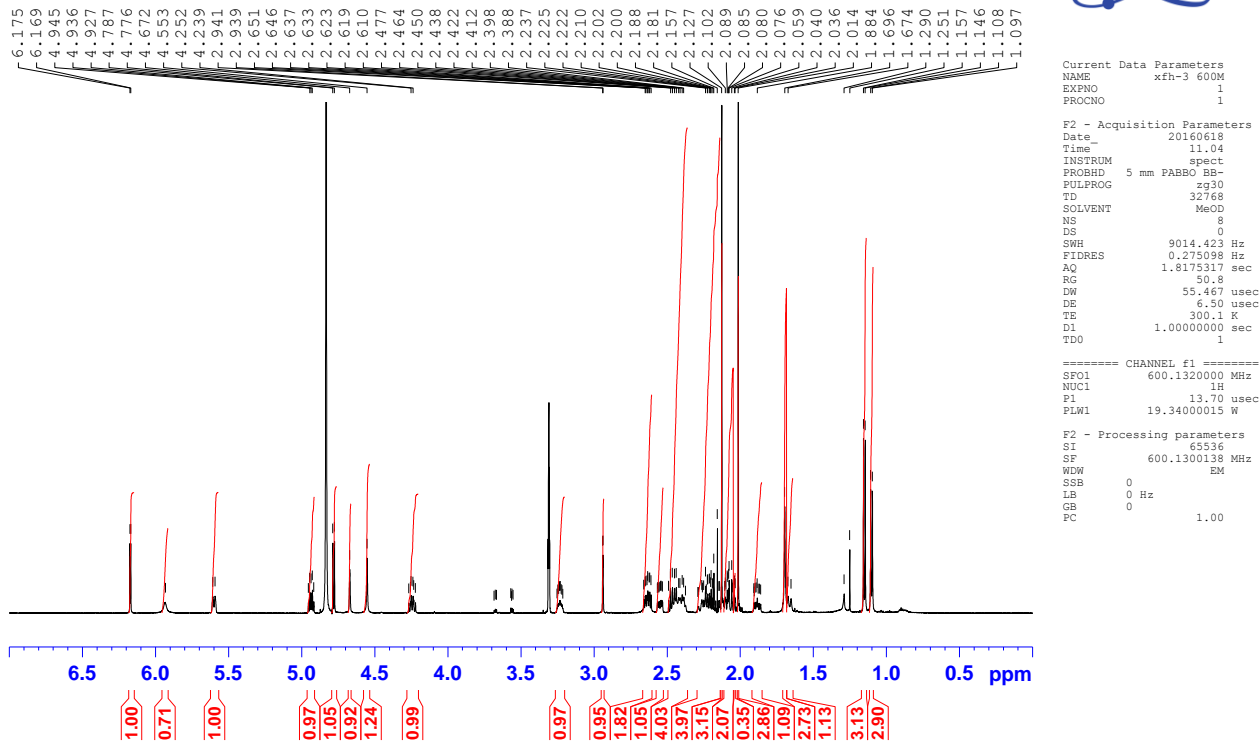
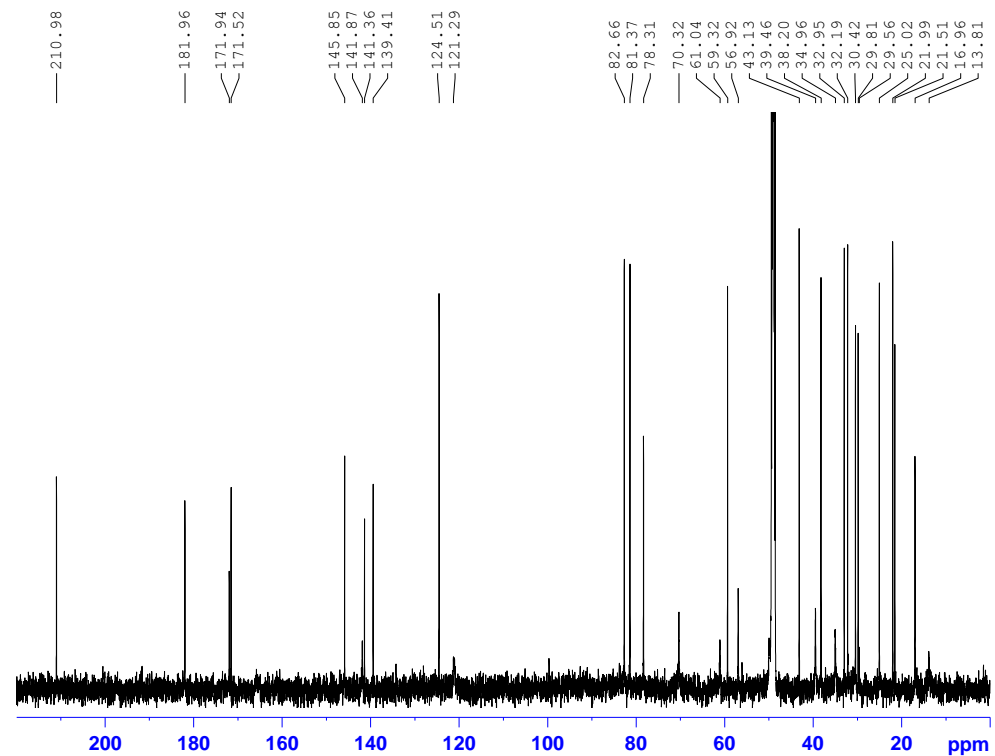


Figure S32. ¹H NMR spectrum of Linearifolianoid K (**3**) in CD₃OD

Compound 3 13 NMR



```
Current Data Parameters
NAME      xfh-3 60M
EXPNO    2
PROCNO   1

F2 - Acquisition Parameters
Date_    20160618
Time     19.21
INSTRUM  spect
PROBHD   5 mm PABBO BB-
PULPROG  zgpg30
TD        37874
SOLVENT  MeOD
NS        3538
DS        4
SWH      37878.789 Hz
FIDRES   1.000126 Hz
AQ        0.4999368 sec
RG        2050
DW        13.200 usec
DE        6.50 usec
TE        300.0 K
D1        1.00000000 sec
d11       0.03000000 sec
TDO       1

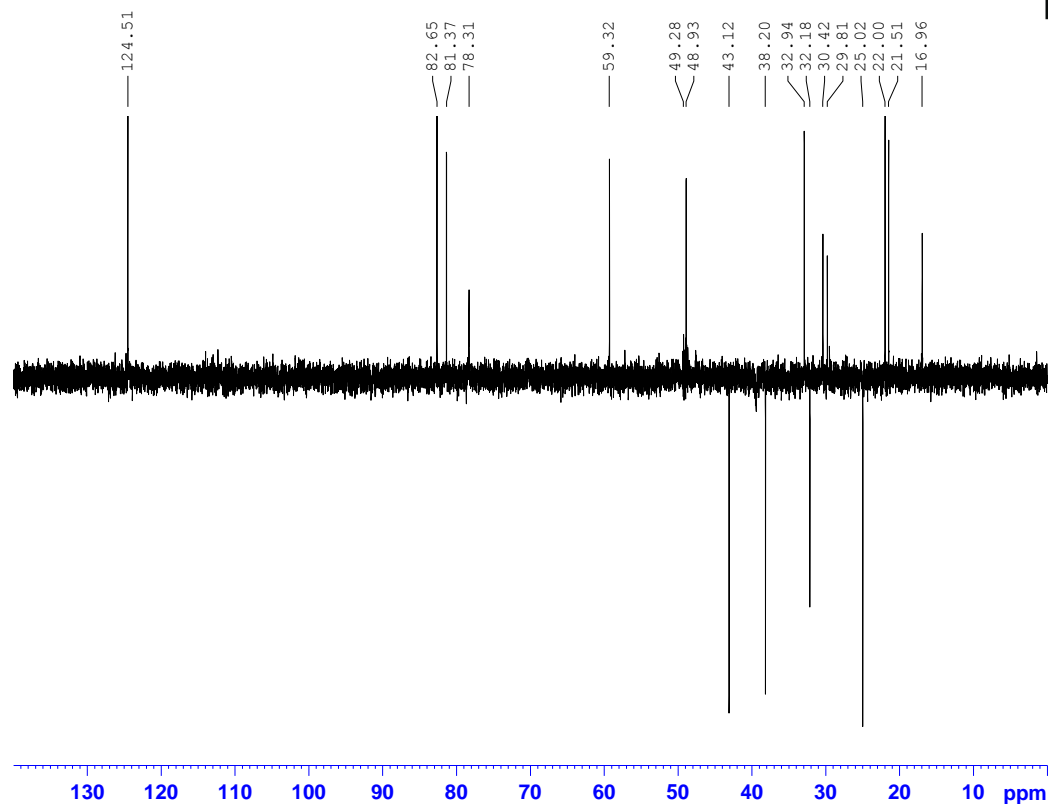
===== CHANNEL f1 =====
SFO1     150.9178990 MHz
NUC1     13C
P1       9.00 usec
PLW1     41.50000000 W

===== CHANNEL f2 =====
SFO2     600.1324005 MHz
NUC2     1H
CPDPRG2  waltz16
PCPD2    70.00 usec
PLW2     19.34000015 W
PLW12    1.01040006 W
PLW13    0.49509999 W

F2 - Processing parameters
SI       65536
SF       150.9025983 MHz
WDW      EM
SSB      0
LB       3.00 Hz
GB       0
PC       1.40
```

Figure S33. ¹³C NMR spectra of Linearifolianoid K (3) in CD₃OD

Compound 3 135 DEPT



```
Current Data Parameters
NAME      xfh-3 600M
EXPNO    3
PROCNO   1

F2 - Acquisition Parameters
Date_    20160618
Time     19.34
INSTRUM  spect
PROBHD   5 mm PABBO BB-
PULPROG  dept135
TD        36054
SOLVENT  MeOD
NS        512
DS        4
SWH       37878.789 Hz
FIDRES    1.050613 Hz
AQ        0.4759128 sec
RG        2050
LW        13.200 usec
DE        6.50 usec
TE        300.0 K
CNS22    145.000000
D1        1.00000000 sec
D2        0.00344828 sec
D12       0.00002000 sec
TDO       1

----- CHANNEL f1 -----
SF01     150.9178990 MHz
NUC1      13C
P1        9.00 usec
P2        18.00 usec
PLW1     41.50000000 W

----- CHANNEL f2 -----
SF02     600.1324005 MHz
NUC2      1H
CPDPRG2  waltz16
P3        15.00 usec
P4        32.00 usec
PCPD2    70.00 usec
PLW2     19.34000015 W
PLW12    1.01040006 W

F2 - Processing parameters
SI        65536
SF        150.9025983 MHz
WDW       EM
SSB       0
LB        1.00 Hz
GB        0
FC        1.40
```

Figure S34. DEPT spectra of Linearifolianoid K (3) in CD₃OD

Compound 3 HSQC

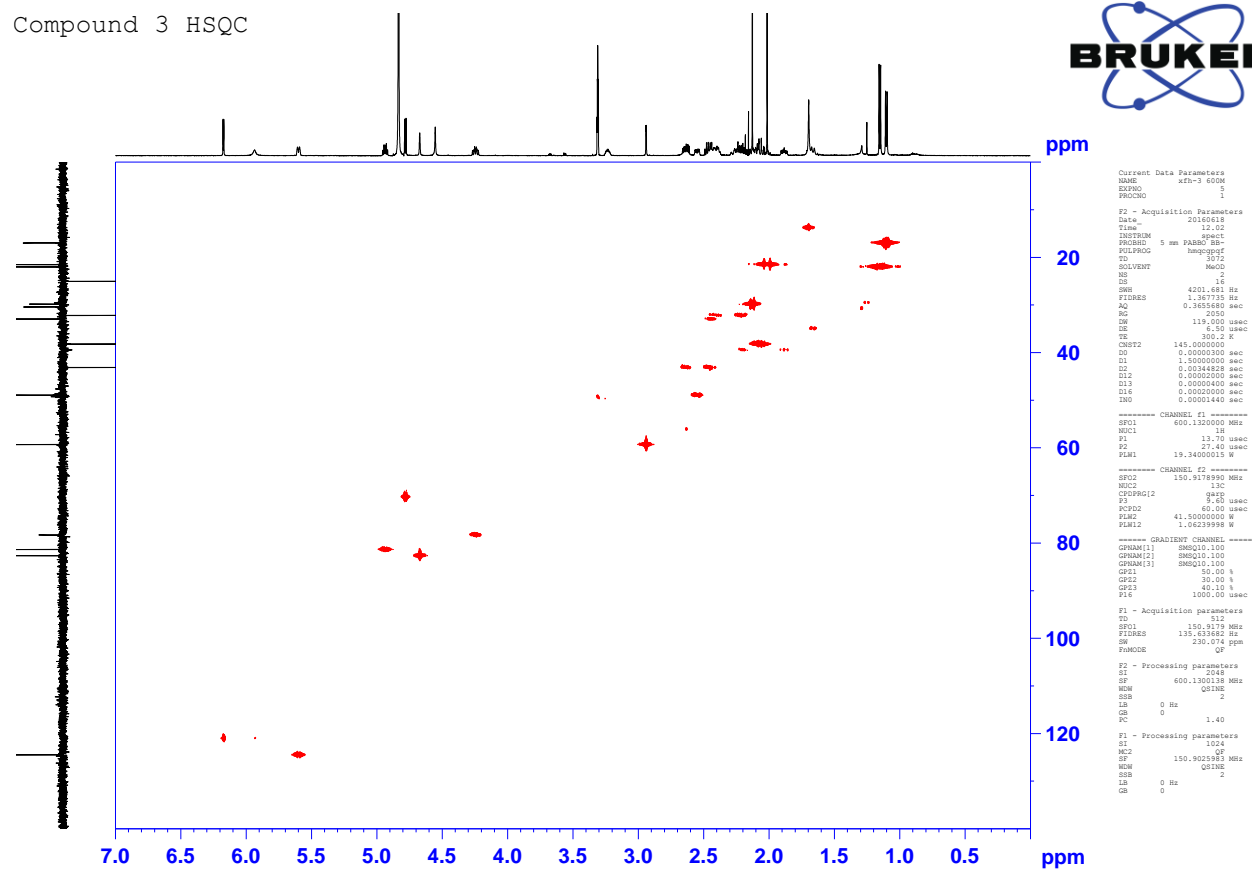


Figure S35. HSQC spectrum of Linearifolianoid K (**3**) in CD₃OD

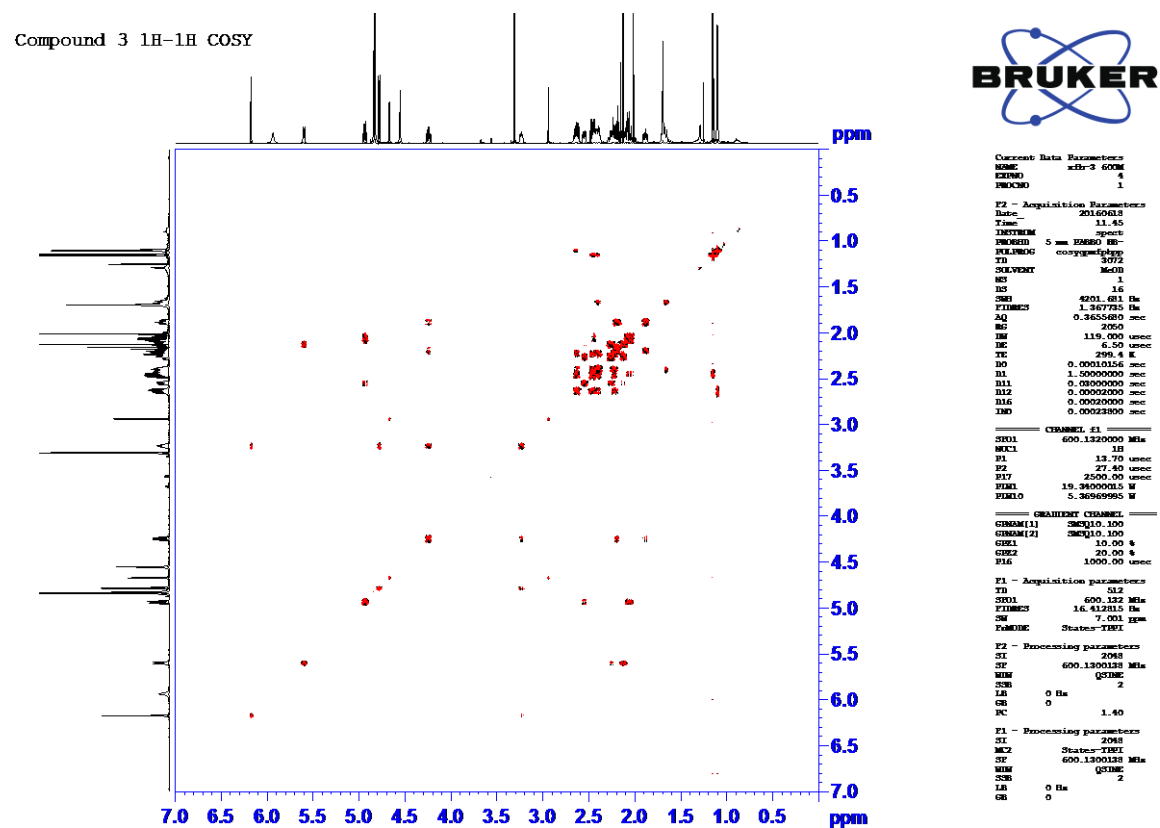


Figure S36. ¹H-¹H COSY spectrum of Linearifolianoid K (**3**) in CD₃OD

Compound 3 HMBC

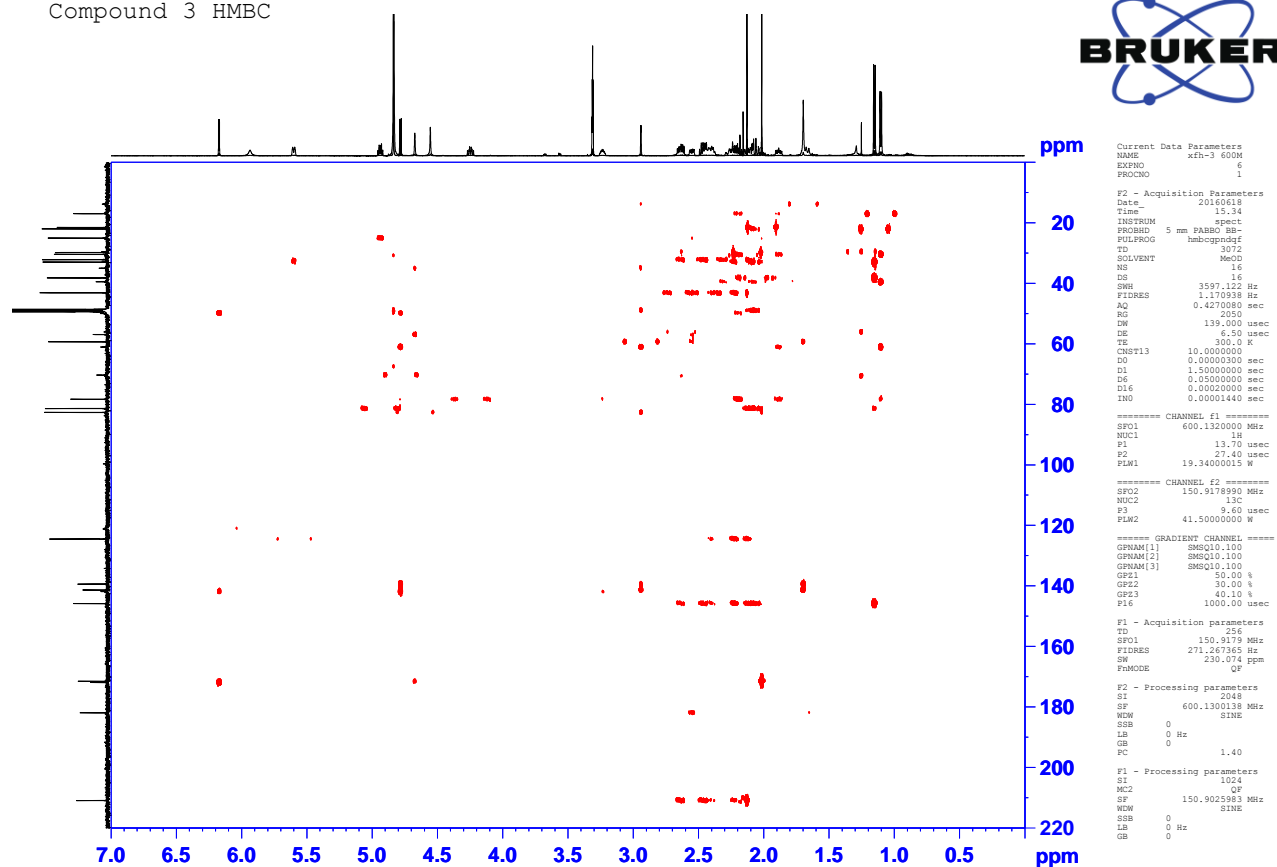
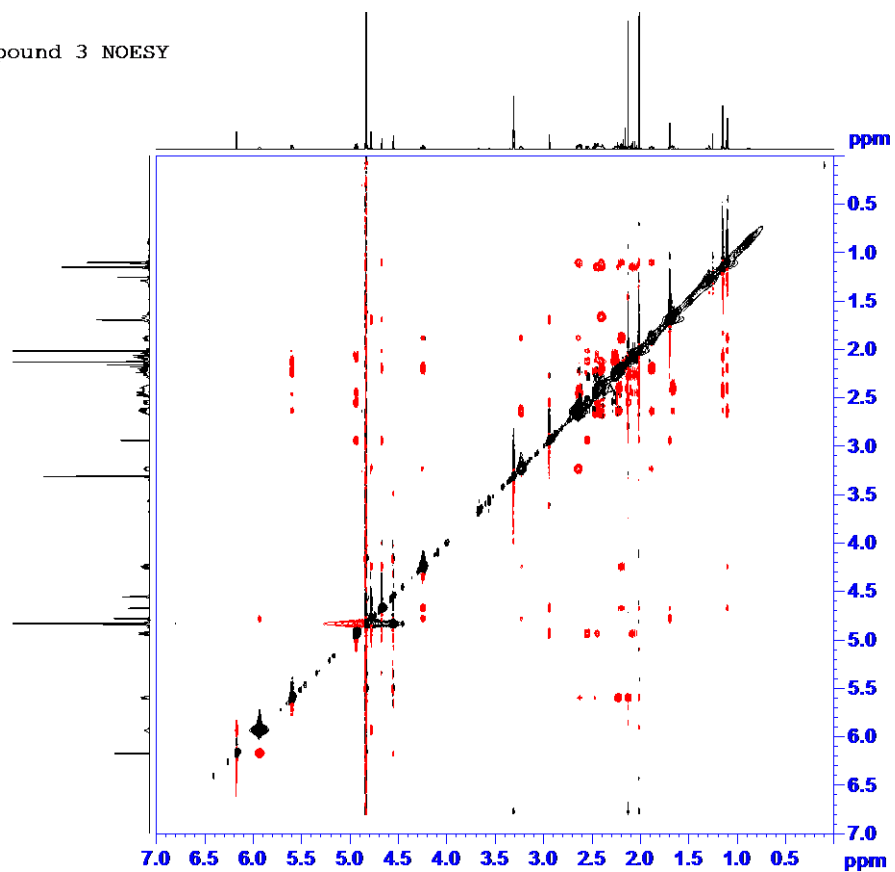


Figure S37. HMBC spectrum of Linearifolianoid K (3) in CD₃OD

Compound 3 NOESY



```

Current Data Parameters
NAME      xEh-3 600M
EXPNO     7
PROCNO    1

F2 - Acquisition Parameters
Date_     20160618
Time      14.08
INSTRUM   spect
PROBHD    5 mm PARBO BB-
PULPROG   noesyzgpg
TD         3272
SOLVENT   MeOD
NS         16
DS         16
SWH        4201.681 Hz
FIDRES     1.367735 Hz
AQ         0.3655690 sec
RG         128
RW         119.000 usec
DE         6.54 usec
TE         300.1 K
DQ         0.00010156 sec
D1         1.50000000 sec
D2         0.60000002 sec
D16        0.00020000 sec
TD0        0.00020000 sec

===== CHANNEL f1 =====
SFO1       600.132000 MHz
NUC1       1H
P1         13.70 usec
P2         27.40 usec
PR1        19.34000015 W

===== GRADIENT CHANNEL =====
CHRM1[1]   SMSQ10.100
CPC1       40.00 *
P16        1000.00 usec

F1 - Acquisition parameters
TD         256
SFO1       600.132 MHz
FIDRES     32.825638 Hz
SN         7.001 ppm
FAMODE     TQPI

F2 - Processing parameters
SI         2048
SF         600.1300138 MHz
WDW         Q5LINE
SSB         2
LB         0 Hz
GB         0
PC         1.00

F1 - Processing parameters
SI         1024
WC2        TQPI
SF         600.1300138 MHz
WDW         Q5LINE
SSB         2
LB         0 Hz
GB         0
    
```

Figure S38. NOESY spectrum of Linearifolianoid K (**3**) in CD₃OD

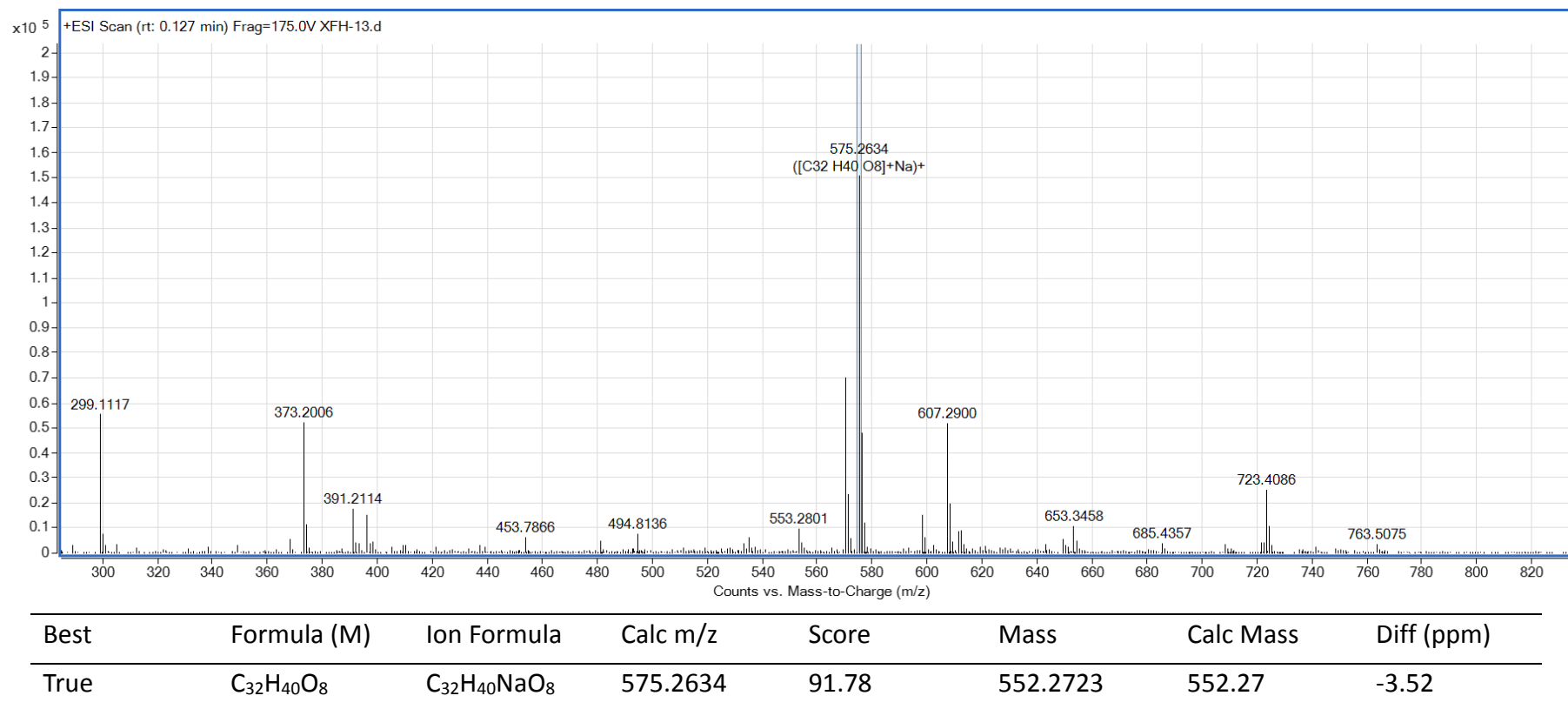


Figure S39. HRESIMS spectrum of Linearifolianoid L (4)

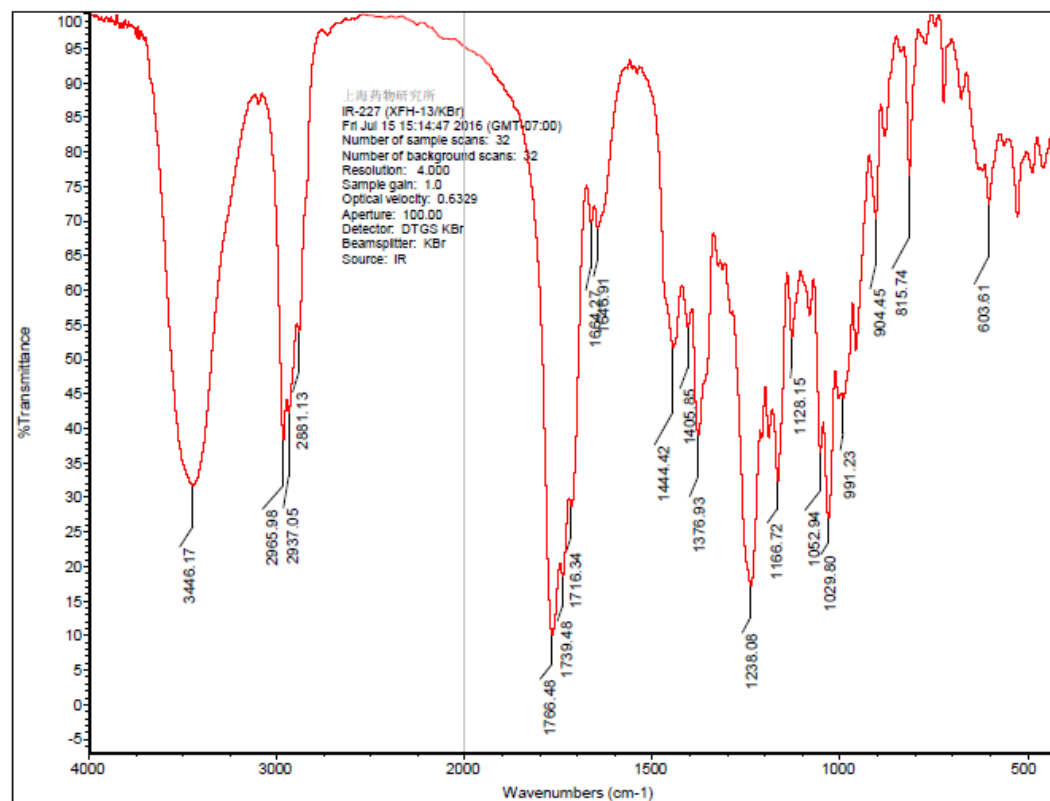


Figure S40. IR spectrum of Linearifolianoid L (4)

Rudolph Research Analytical

Tuesday, 07/19/2016

This sample was measured on an Autopol VI, serial number 90079,
manufactured by Rudolph Research Analytical, Hackettstown, NJ.

LotID : XFH-13
Set Temperature : 20.0
Temp Corr : OFF

n	Average	Std.Dev.	Maximum	Minimum						
6	41.935	0.0000	41.935	41.935						
S.No	Sample ID	Time	Result	Scale	OR °Arc	WLG	Lg.mm	Conc.	Temp.	Comment
1	XFH-13	03:06:11 PM	41.935	SR	0.026	589	100.00	0.062	20.1	
2	XFH-13	03:06:19 PM	41.935	SR	0.026	589	100.00	0.062	20.1	
3	XFH-13	03:06:27 PM	41.935	SR	0.026	589	100.00	0.062	20.1	
4	XFH-13	03:06:35 PM	41.935	SR	0.026	589	100.00	0.062	20.1	
5	XFH-13	03:06:43 PM	41.935	SR	0.026	589	100.00	0.062	20.1	
6	XFH-13	03:06:50 PM	41.935	SR	0.026	589	100.00	0.062	20.1	

Signature

Figure S41. OR Value of Linearifolianoid L (**4**) in CHCl₃

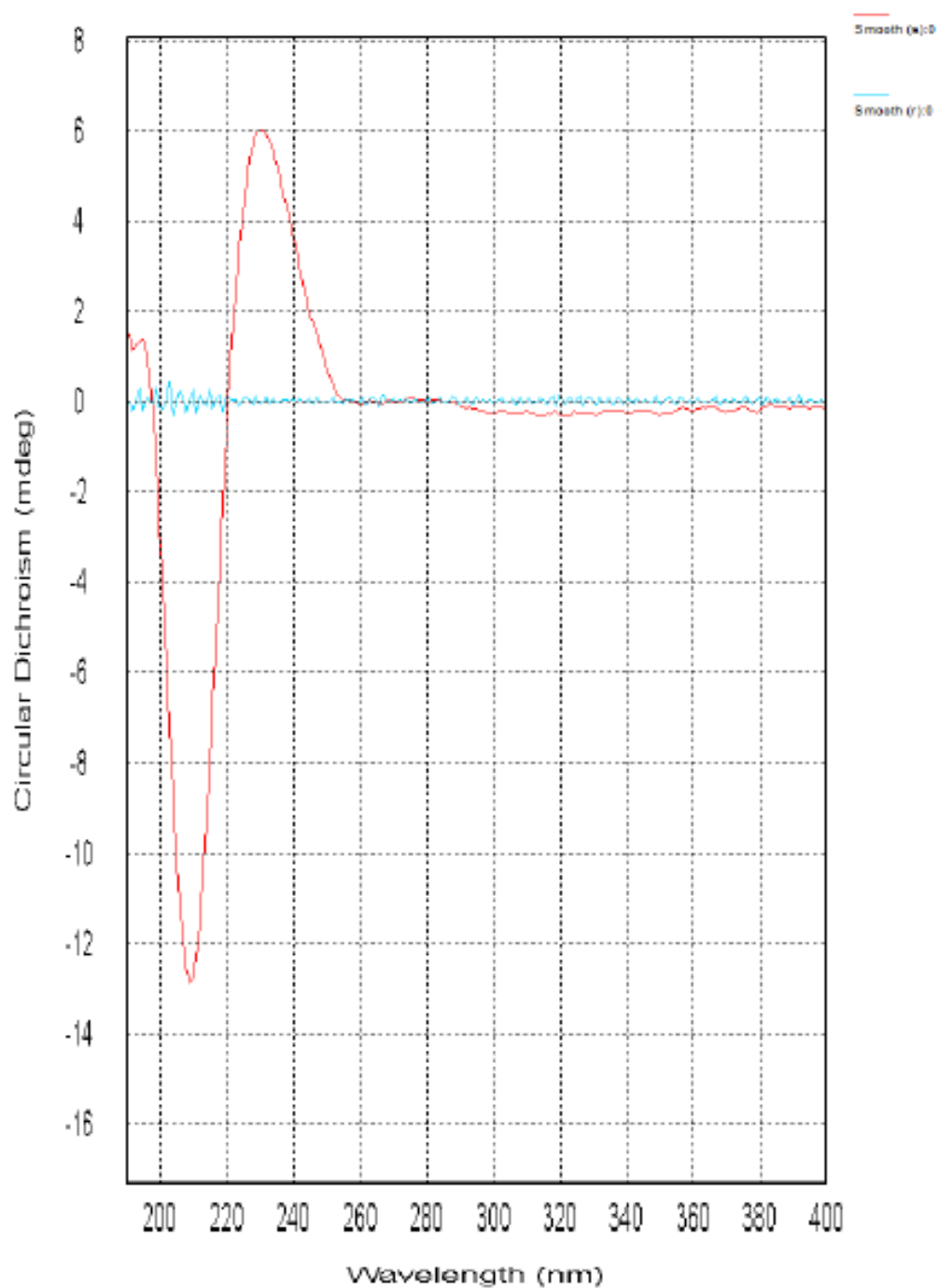


Figure S42. CD spectra of Linearifolianoid L (4) in CH₃CN

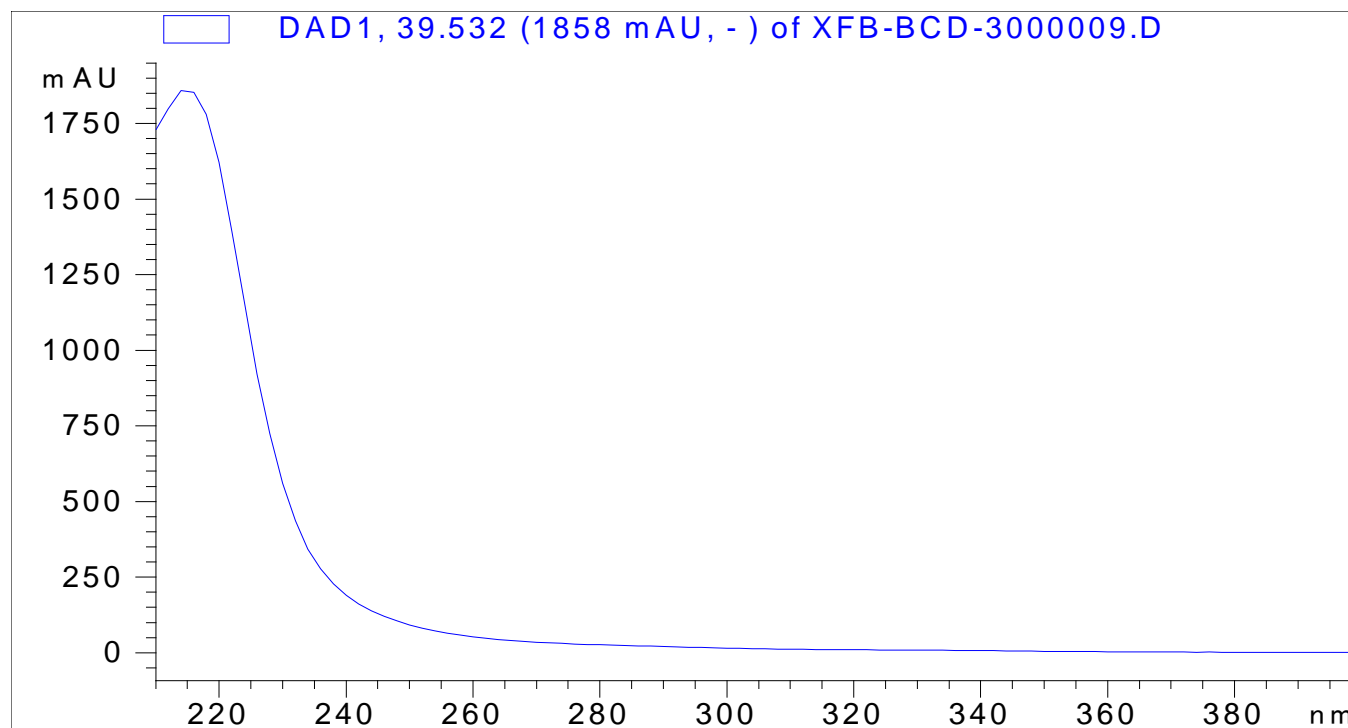
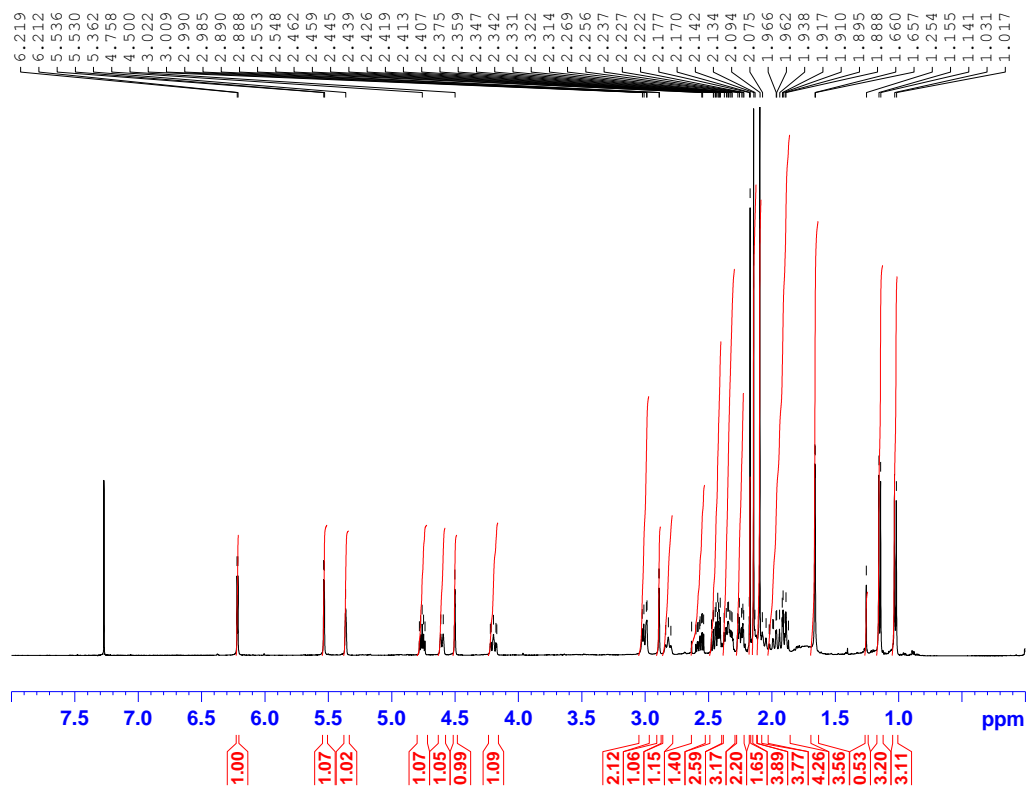


Figure S43. UV spectrum of Linearifolianoid L (**4**) in CH₃CN/H₂O

Compound 4 1H NMR



```
Current Data Parameters
NAME      XFX-13 NEW
EXPNO     1
PROCNO    1

F2 - Acquisition Parameters
Date_     20160706
Time      11.06
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zg30
TD         65536
SOLVENT   CDCl3
NS         8
DS         2
SWH        7500.000 Hz
FIDRES     0.114441 Hz
AQ         4.3690667 sec
RG         120.22
DM         66.667 usec
DE         6.50 usec
TE         298.0 K
D1         1.00000000 sec
TDO        1

----- CHANNEL f1 -----
SFO1      500.1750000 MHz
NUC1      1H
PI         14.33 usec
PLM1      10.50000000 W

F2 - Processing parameters
SI         65536
SF         500.1700074 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
```

Figure S44. ¹H NMR spectrum of Linearifolianoid L (**4**) in CDCl₃

Compound 4 ¹³C NMR

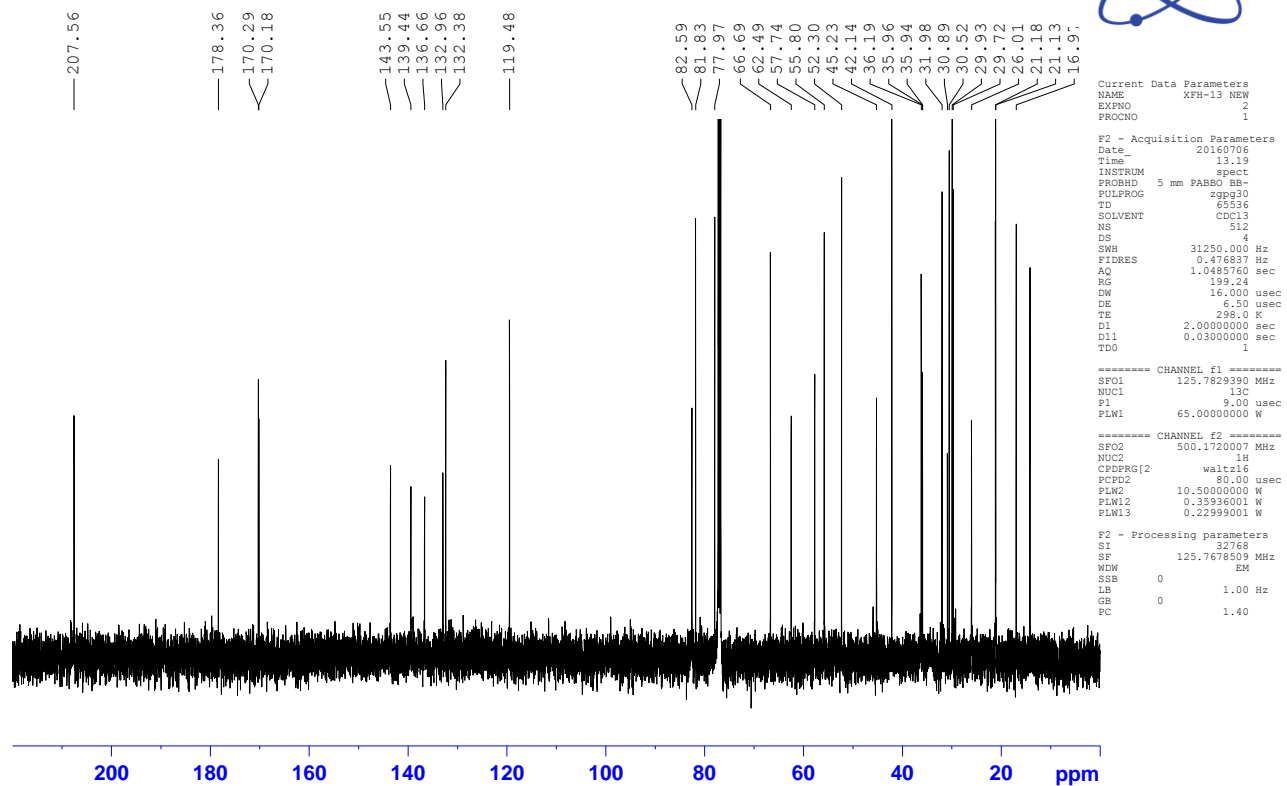


Figure S45. ¹³C NMR spectra of Lineariifolianoid L (4) in CDCl₃

Compound 4 135DEPT

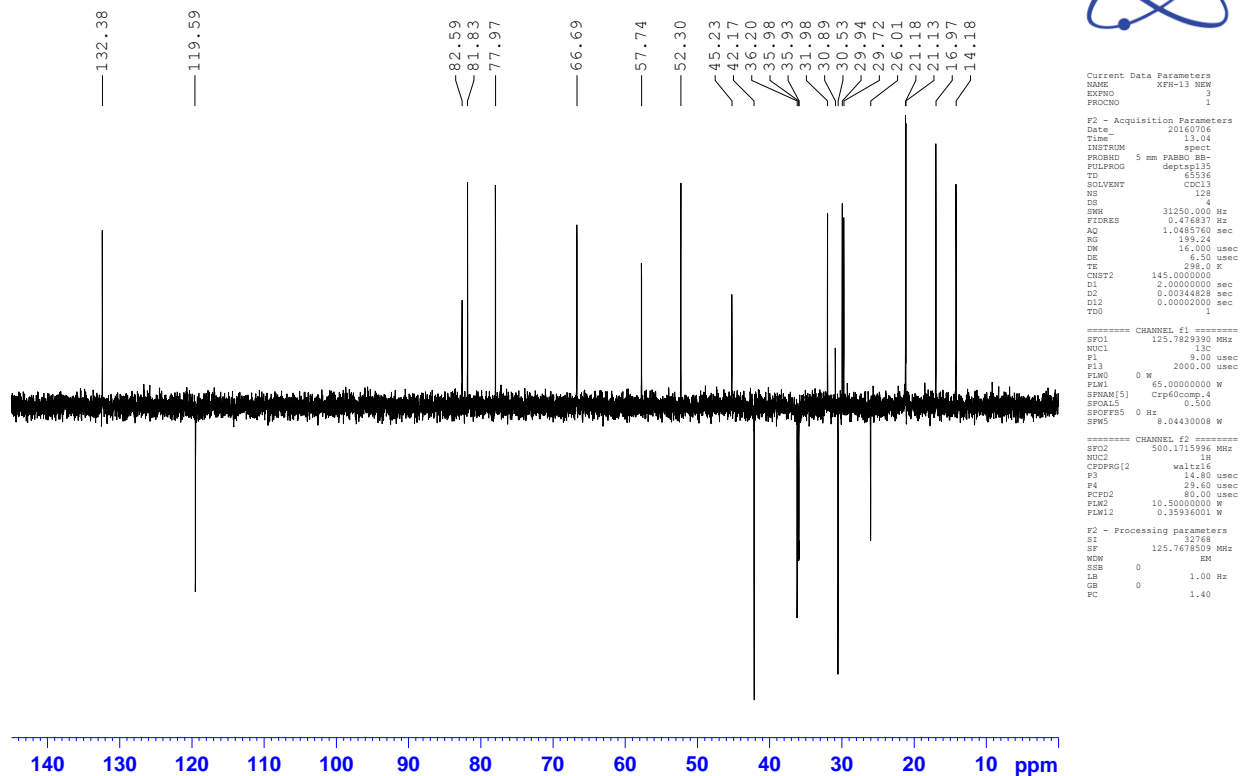


Figure S46. DEPT spectra of Linearifolianoid L (4) in $CDCl_3$

Compound 4 HSQC

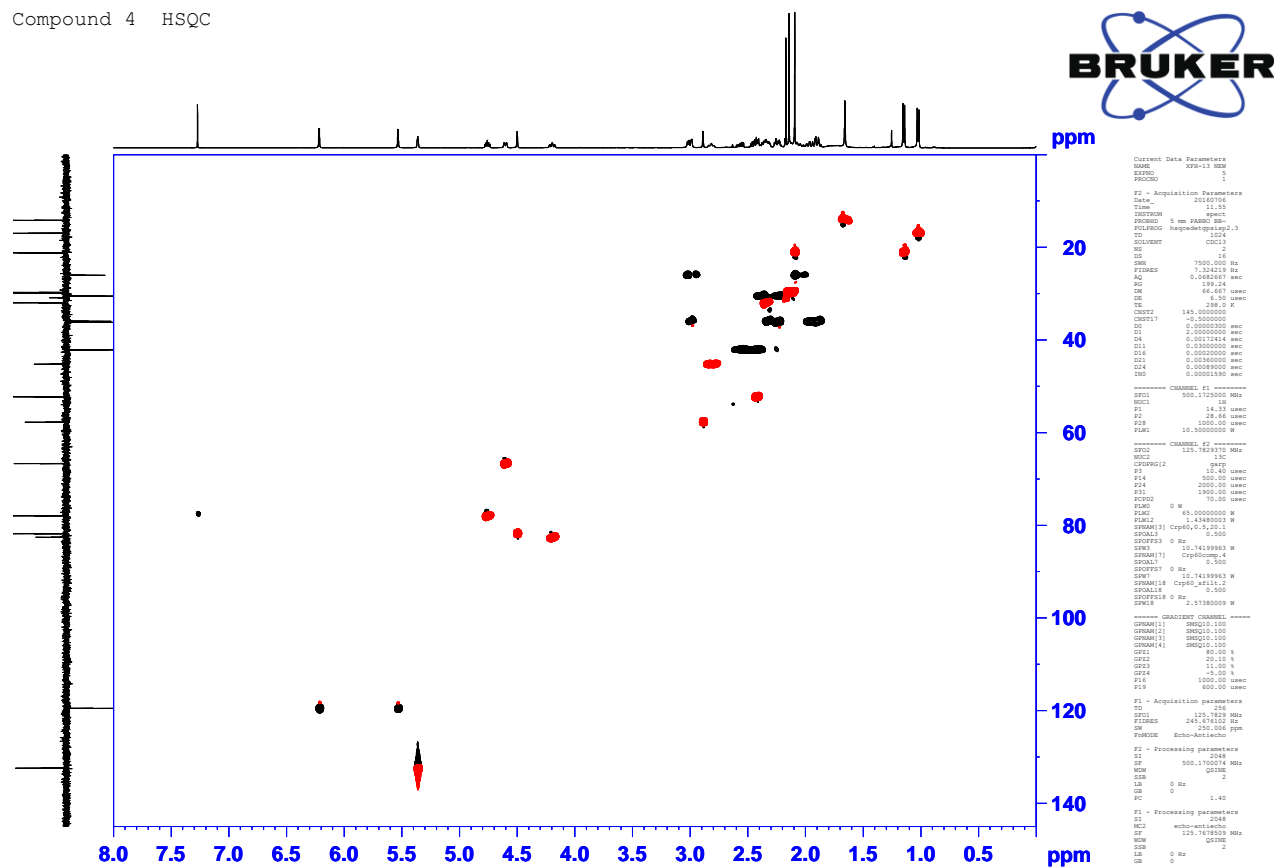
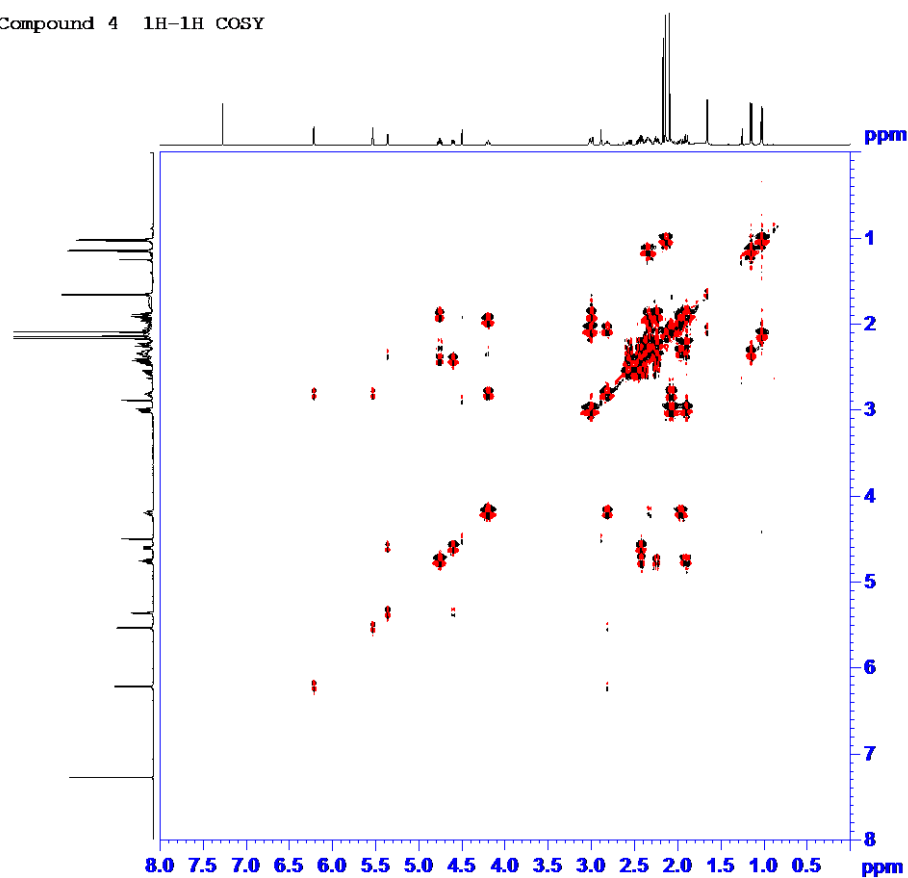


Figure S47. HSQC spectrum of Linearifolianoid L (4) in CDCl₃

Compound 4 1H-1H COSY



```

Current Data Parameters
NAME      KFT-13 NEW
EXPNO    4
PROCNO    1

F2 - Acquisition Parameters
Date_     20160706
Time      11.35
INSTRUM   spect
PROBHD    5 mm HARB0 BP-
PULPROG   conygpw14pp
TD         2048
SOLVENT   CDCl3
NS         2
DS         16
SFO1      7500.000 Hz
FIDRES    3.662109 Hz
AQ         0.1165333 sec
RG         199.24
WE         66.667 usec
IE         6.50 usec
TE         298.0 K
DQ         0.0000485 sec
RL         2.0000000 sec
RL1        0.0000000 sec
RL2        0.0002000 sec
RL3        0.0002000 sec
LWD        0.0013340 sec

===== CHANNEL f1 =====
SFO1      500.1725000 MHz
NUC1       1H
P1         14.33 usec
P2         23.66 usec
PLP        2500.00 usec
PLM1       10.5000000 Hz
PLM2       3.13859999 Hz

===== GRADIENT CHANNEL =====
GMRM(1)   MRQ10.100
GMRM(2)   MRQ10.100
GRF1       10.00 %
GRF2       20.00 %
RL6        1000.00 usec

F1 - Acquisition parameters
TD         256
SFO1      500.1725 MHz
FIDRES    58.564463 Hz
SR         14.987 ppm
F2NAME     States-TFPI

F2 - Processing parameters
SI         2048
SF         500.1700074 MHz
WDW        ODRMC
SSB        2
LB         0 Hz
GB         0
PC         1.40

F1 - Processing parameters
SI         2048
MC2       States-TFPI
SF         500.1700074 MHz
WDW        ODRMC
SSB        2
LB         0 Hz
GB         0
  
```

Figure S48. ^1H - ^1H COSY spectrum of Linearifolianoid L (4) in CDCl_3

Compound 4 HMBC

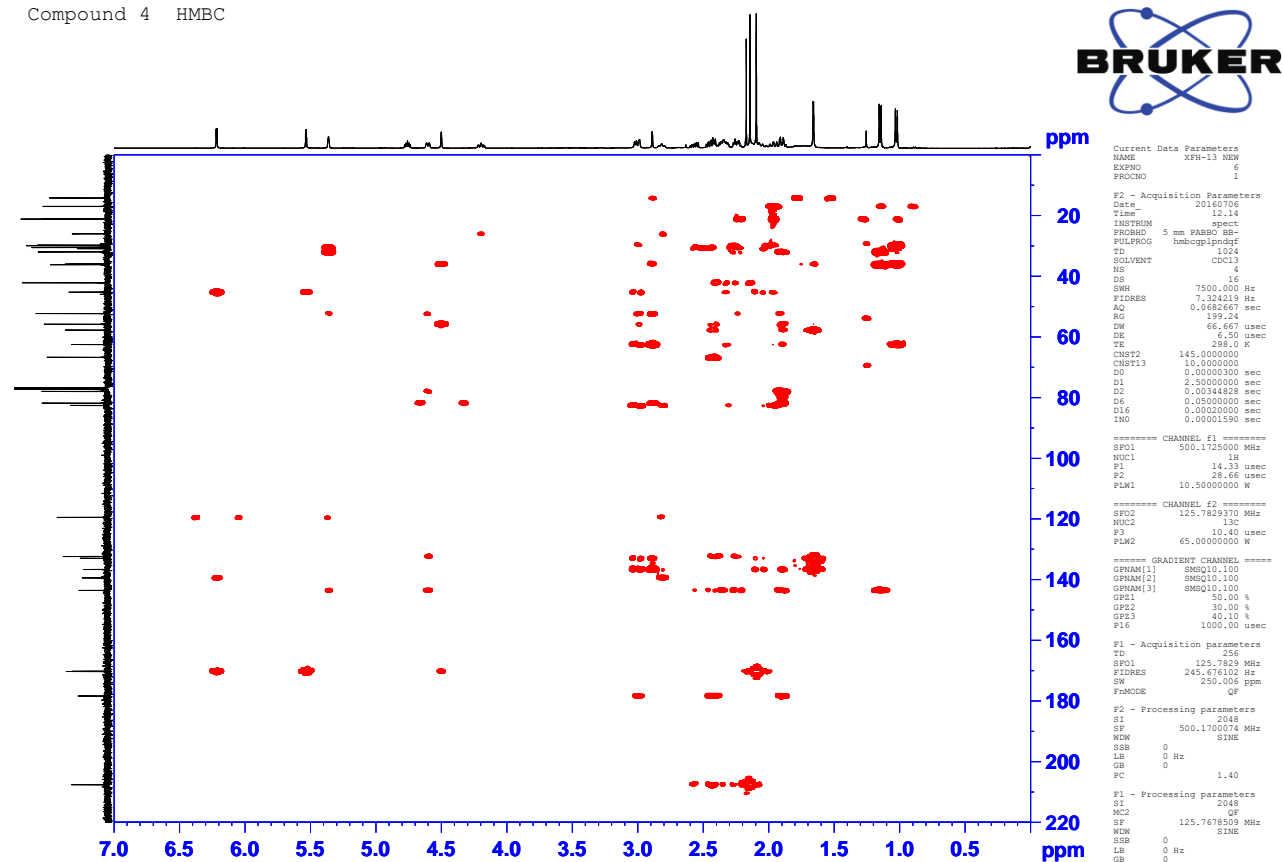
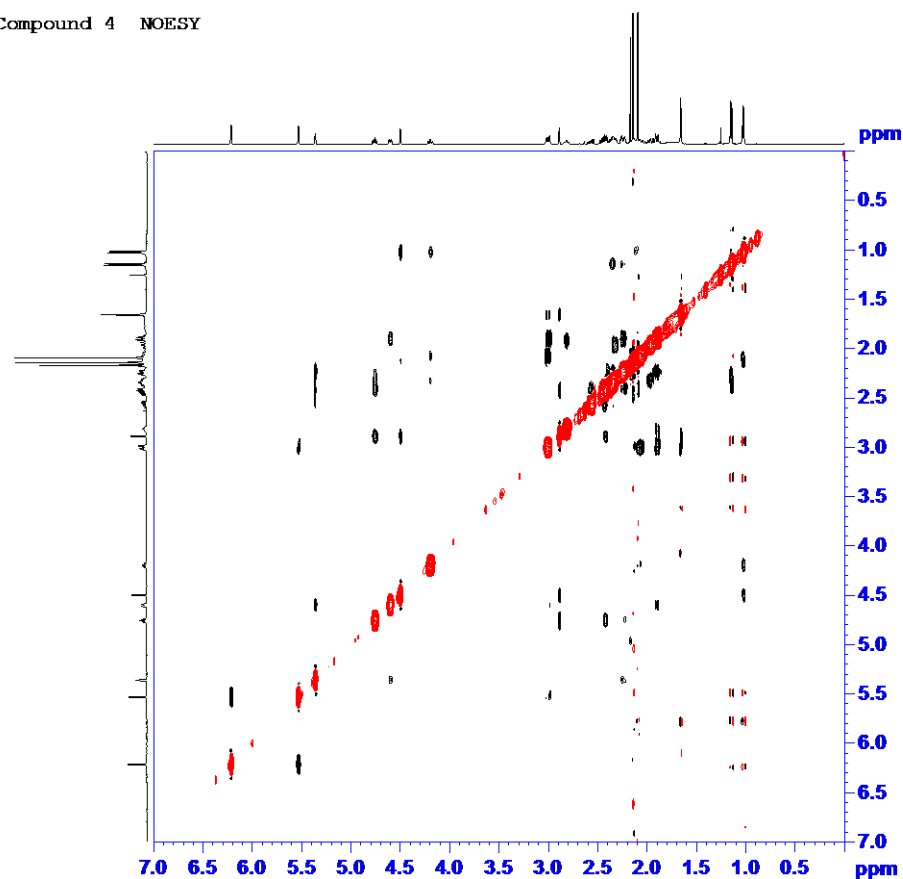


Figure S49. HMBC spectrum of Linearifolianoid L (4) in CDCl₃

Compound 4 NOESY



```

Current Data Parameters
NAME      XFI-13 NEW
EXPNO    7
PROCNO   1

F2 - Acquisition Parameters
Date_    20160706
Time     11.08
INSTRUM  spect
PROBHD   5 mm PABBO BB-
PULPROG  noesyppgh
TD       2048
SOLVENT  CDCl3
NS       2
DS       16
SWH      7500.000 Hz
FIDRES   3.662105 Hz
AQ       0.1365333 sec
RG       139.24
DW       65.667 usec
DE       6.50 usec
TE       298.0 K
D0       0.0000000 sec
D1       2.0000000 sec
D8       0.89999998 sec
D16      0.00020000 sec
DRO      0.00013340 sec

===== CHANNEL f1 =====
SFO1    500.1725000 MHz
NUC1     1H
P1       14.33 usec
P2       28.66 usec
PLW1    10.50000000 W

===== GRADIENT CHANNEL =====
GPRM1(L) SMS10.100
SP21     40.00 %
P16      1000.00 usec

F1 - Acquisition parameters
TD       256
SFO1    500.1725 MHz
FIDRES   58.564468 Hz
SW       14.997 ppm
F0MODE   TDDI

F2 - Processing parameters
SI       2048
SF       500.1700074 MHz
RG       QSTEME 2
SSB      0 Hz
LB       0
GB       0
PC       1.00

F1 - Processing parameters
SI       2048
MC2      TDDI
SF       500.1700074 MHz
RG       QSTEME 2
SSB      0 Hz
LB       0
GB       0
    
```

Figure S50. NOESY spectrum of Lineariifolianoid L (**4**) in CDCl₃

Measurement of LPS-Induced NO Production

RAW 264.7 cells were seeded in 96-well culture plates at 5×10^5 cells/well at 37 °C for 12 h in DMEM medium. The cells were pretreated with different concentrations of samples for 12 h and then incubated for 24 h with or without 1 $\mu\text{g}/\text{mL}$ LPS. The nitrite concentration in the culture supernatant was measured using Griess reagent (1% sulfanilamide, 0.1% N-1-naphthylenediamine dihydrochloride and 2.5% phosphoric acid). The absorbance was measured at 540 nm after incubation for 15 min. The nitrite levels in the samples were calculated from a standard curve created using known concentrations of sodium nitrite. Cell viability was measured by a MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay (Beyotime, China).

RAW 264.7 cells were purchased from ATCC. Dulbecco's modified Eagle's medium (DMEM) and fetal bovine serum were purchased from Gibco Invitrogen (Carlsbad, CA, USA). LPS, Griess reagent was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Table S3. IC₅₀ values (μM) of **1-4** from *Inula lineariifolia* against LPS-induced nitric oxide (NO) production

NO	1	2	3	Mean \pm SD IC ₅₀ (μM)
Compound 1	1.098	1.023	0.9517	1.024 \pm 0.059
Compound 2	2.366	1.517	1.484	1.789 \pm 0.48
Compound 3	9.738	10.41	10.01	10.02 \pm 0.27
Compound 4	10.54	10.09	9.869	10.16 \pm 0.27
Aminoguanidine	2.98	3.14	3.09	3.06 \pm 0.081

- Aminoguanidine was positive control.
- Compounds **1-4** were not exhibited significantly cytotoxic at the concentrations required for inhibition NO production (as determined by MTT assay).