Herbicidal Quassinoids Isolated from *Ailanthus altissima* Leaves

Short title: A New Herbicide of Quassinoid Series

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ABSTRACT

Bioassay-guided fractionation of the methanolic extract of *Ailanthus altissima* leaves led to the isolation of one new quassinoid, named 6-α-tigloyloxyailanthone (**3**), and three known quassinoids, ailanthone (**1**), 13, 18-dehydroglaucarubinone (**2**), and 6-α-tigloyloxychaparrinone (**4**) by a series of chromatographic methods. The structures of the isolates were established by one-dimensional (1D) and 2D-nuclear magnetic resonance (NMR) analysis along with high-resolution time-of-flight mass spectrometry (HRTOFMS) and chemical methods. In addition, herbicidal activity against five grassy weeds and five broad-leaf weeds was evaluated.

Introduction

Quassinoids are a group of degraded triterpenes found in the family Simaroubaceae that undergo extensive oxidative biodegradation, leaving their carbon skeleton highly oxygenated[1-4]. Quassinoids are classified into five groups according to their basic structure, C-18, C-19, C-20, C-22, and C-25. The C-20 quassinoids have been extensively investigated due to their antileukemic activity discovered in the early 1970s[3, 5] Since 1960, hundreds of quassinoids have been isolated and identified from plants, but they seem harder to synthesize due to the presence of their highly oxygenated carbon framework[2]. Many quassinoids display a wide range of biological activities *in vitro* or *in vivo*, including antitumor[6], antimalarial[7], antiviral[8], anti-inflammatory[9], antifeedant[10], insecticidal[11], antiulcer[12], and herbicidal activities[13]. In our ongoing investigations of structurally unique bioactive agents, such as herbicides derived from traditional plants, systematic phytochemical studies of *Ailanthus*

altissima resulted in the isolation of one new quassinoid (**3**) and three known quassinoids (**1**, **2**, and **4**). In this paper, we describe the isolation, structural elucidation, and evaluation of the herbicidal activities of all isolates obtained.

Experimental details

Plant material

Seeds of 10 weed species (*S. bicolor, E. crus-galli, A. smithii, D. sanguiinalis, P. dichotomiflorum, S. nigrum, A. indica, A. avicennae, X. strumarium, C. japonica*) were germinated in flats in a commercial greenhouse substrate and watered with tap water. The weeds were grown in a greenhouse at 30 ± 3 / 20 ± 3 ºC day/night temperature with a 14-h photoperiod.

Biological activity

The activity assay was performed 12 days after sowing for the foliar application of samples at each concentration with a laboratory spray gun. The herbicidal activity of the foliar application was evaluated by visual injury 14 days after treatment (0, no damage; 100, complete control).

Extraction and isolation

Fresh samples (5 kg) were dipped in MeOH at room temperature and filtered after three days. After concentrating the methanol, the extract was defatted with hexane, then partitioned between EtOAc and H_2O. A portion of the active EtOAc fraction (6 g) was purified by gradient elution on a flash silica gel column using $CHCl_3$:MeOH (50:1, 20:1, 10:1, 5:1, and 100%

MeOH). Fraction II [1.03 g, $CHCl_3$-MeOH (20:1)] and fraction III [1.32 g, $CHCl_3$:MeOH (10:1)], which were active in the bioassay, were further purified by ODS Sep-pak cartridge (Alltech, Deerfield, IL, USA) chromatography eluted with an increasing methanol concentration gradient (0% – 100%) in water. The active fraction was finally purified by reversed-phase HPLC. Preparative HPLC (C_{18}, 5 μm, 20 x 250 mm; COSMOSIL) was performed using 30 – 50% aqueous MeOH, UV detection at 254 nm, a flow rate of 12 mL/min, and gradient elution for 50 min.

Structural analysis

Melting points were measured on a Fisher melting point apparatus and uncorrected. Optical rotations were measured on a Perkin Elmer 341-LC polarimeter. NMR spectra were recorded on a Bruker 900 and 700 spectrometer with standard pulse sequences, operated at 900 and 700 MHz for ^{1}H NMR and 226 and 176 MHz for ^{13}C NMR. Chemical shifts, measured in ppm, were referenced to solvent peaks (δ_H 2.50 and δ_C 39.5 for DMSO-d_6**)**. HR-TOF-MS spectra were recorded in the positive ESI mode on a Waters Synapt G2 at the Korea Basic Science Institute.

Compound 1 (ailanthone)

^{1}H NMR (DMSO-d_6, 900 MHz) δ: 8.23 (1H, s, 11-OH), 7.08 (1H, d, J = 2.8 Hz, 1-OH), 5.99 (1H, d, J = 0.9 Hz, H-3), 5.40 (1H, d, J = 4.5 Hz, 12-OH), 5.05 (1H, d, J = 0.9 Hz, H_a-21), 5.02 (1H, d, J = 0.9 Hz, H_b-21), 4.55 (1H, t, J = 2.8 Hz, H-7), 4.28 (1H, s, H-1), 3.81 (1H, d, J = 9.0 Hz, H_a-20), 3.27 (1H, d, J = 9.0 Hz, H_b-20), 3.67 (1H, d, J = 3.6 Hz, H-12), 2.88 (1H, d, J = 10.8 Hz, H-5), 2.98 (1H, dd, J = 18.0, 14.4 Hz, H_a-15), 2.81 (1H, s, H-9), 2.77 (1H, dd, J = 13.5,

5.4, H-14), 2.44 (1H, dd, J = 18.0, 5.4 Hz, H_b-15), 2.03 (2H, m, H-6), 1.93 (3H, s, H-18), 1.06 (3H, s, H-19) ppm; ^{13}C NMR (225 MHz, DMSO-d_6): 197.1 (C2), 169.1 (C16), 162.4 (C4), 146.6 (C13), 125.0 (C3), 117.6 (C21), 108.8 (C11), 82.4 (C1), 79.0 (C12), 77.5 (C7), 71.1 (C20), 46.1 (C14), 44.5 (C8 and C10), 43.3 (C9), 41.2 (C5), 34.3 (C15), 25.1 (C6), 22.4 (C18), and 9.5 (C19) ppm; HRTOFMS (positive ESI mode) *m/z* 399.1415 $[M + Na]^+$ (calcd for $C_{20}H_{24}O_7$+Na, 399.1420).

Compound 2 (13, 18-dehydroglaucarubinone)

^{1}H NMR (DMSO-d6, 700 MHz) δ: 8.33 (1H, s, 11-OH), 7.16 (1H, d, J = 2.1 Hz, 1-OH), 5.99 (1H, q, J = 0.7 Hz, H-3), 5.64 (1H, br s, H-15), 5.35 (1H, br s, 12-OH), 5.11 (1H, s, 2'-OH), 5.09 (1H, d, J = 1.4 Hz, Ha-21), 4.99 (1H, br s, H_b-21), 4.70 (1H, t, J = 2.8 Hz, H-7), 4.42 (1H, d, J = 2.1 Hz, H-1), 3.81 (1H, d, J = 8.4 Hz, H_a-20), 3.67 (1H, d, J = 4.9 Hz, H-12), 3.32 (1H, dd, J = 8.4 Hz, H_b-20), 3.08 (1H, d, J = 11.9 Hz, H-5), 3.04 (1H, d, J = 11.4 Hz, H-14), 2.97 (1H, s, H-9), 2.06 (2H, m, H-6), 1.93 (3H, s, H-18), 1.70 (1H, dq, J = 140.0, 7.0 Hz, H_a-3'), 1.53 (1H, dq, J = 140.0, 7.0 Hz, H_b-3'), 1.30 (3H, s, H-5'), 1.06 (3H, s, H-19), 0.81 (3H, t, J = 7.0 Hz, H-4') ppm; ^{13}C NMR (176 MHz, DMSO-d_6): 197.0 (C2), 174.2 (C1'), 166.7 (C16), 162.4 (C4), 142.4 (C13), 124.8 (C3), 119.8 (C21), 108.6 (C11), 82.1 (C1), 78.7 (C12), 77.8 (C7), 73.9 (C2'), 70.7 (C20), 68.2 (C15), 50.2 (C14), 46.4 (C8), 44.5 (C10), 44.0 (C9), 40.7 (C5), 32.8 (C3'), 25.8(C5'), 24.6 (C6), 22.2 (C18), 9.5 (C19), and 8.0 (C4') ppm; HRTOFMS (positive ESI mode) *m/z* 499.1944 $[M + Na]^+$ (calcd for $C_{25}H_{32}O_9$+Na, 499.1944) and *m/z* 975.3983 $[2M + N]^+$ [calcd for $(C_{25}H_{32}O_9)_2$+Na, 975.3990].

Compound 3 (6-α-tigloyloxyailanthone)

^{1}H NMR (DMSO-d_6, 700 MHz) δ: 8.15 (1H, s, 11-OH), 7.28 (1H, d, J = 2.8 Hz, 1-OH), 6.91 (dq, J = 7.7, 2.1 Hz, H3'), 6.02 (1H, s, H-3), 5.55 (1H, d, J = 4.2 Hz, 12-OH), 5.49 (1H, dd, J = 11.9, 2.8 Hz, H-6), 5.02 (1H, d, J = 1.4 Hz, H_a-21), 5.01 (1H, s, H_b-21), 4.63 (1H, d, J = 2.8 Hz, H-7), 4.39 (1H, s, H-1), 3.91 (1H, d, J = 8.4 Hz, H_a-20), 3.69 (1H, t, J = 4.9 Hz, H-12), 3.46 (1H, d, J = 11.9 Hz, H-5), 3.39 (1H, dd, J = 8.4 Hz, H_b-20), 3.01 (1H, dd, J = 18.4, 13.3 Hz, H_a-15), 2.85 (1H, dd, J = 13.3, 5.6 Hz, H-14), 2.83 (1H, s, H-9), 2.47 (1H, dd, J = 18.4, 5.6 Hz, H_b-15), 1.94 (3H, s, H-18), 1.829 (3H, s, H5'), 1.823 (3H, d, J = 4.2 Hz, H4'), 1.21 (3H, s, H-19) ppm; ^{13}C NMR (176 MHz, DMSO-d_6): 196.6 (C2), 168.2 (C16), 165.9 (C1'), 161.2 (C4), 146.1 (C13), 139.2 (C3'), 127.9 (C2'), 127.6 (C3), 117.5 (C21), 109.0 (C11), 82.4 (C1), 79.1 (C12), 77.5 (C7), 70.2 (C20), 67.3 (C6), 47.2 (C10), 46.1 (C14), 45.2 (C8), 44.1 (C5), 42.0 (C9), 34.0 (C15), 24.7 (C18), 14.4 (C4'), 11.9 (C5'), and 10.9 (C19) ppm; HRTOFMS (positive ESI mode) *m/z* 497.1785 $[M + Na]^+$ (calcd for $C_{25}H_{30}O_9$+Na, 497.1788) and *m/z* 971.3670 $[2M + N]^+$ [calcd for $(C_{25}H_{30}O_9)_2$+Na, 971.3678].

Compound 4 (6-a-tigloyloxychaparrinone)

^{1}H NMR (DMSO-d_6, 700 MHz) δ: 8.0 (1H, s, 11-OH), 7.19 (1H, d, J = 2.8 Hz, 1-OH), 6.91 (dq, J = 7.7, 2.1 Hz, H3'), 6.0 (1H, s, H-3), 5.49 (1H, dd, J = 11.9, 2.8 Hz, H-6), 5.14 (1H, d, J = 4.9 Hz, 12-OH), 4.56 (1H, d, J = 2.8 Hz, H-7), 4.30 (1H, d, J = 2.8 Hz, H-1), 3.93 (1H, d, J = 8.4 Hz, H_a-20), 3.64 (1H, dd, J = 8.4 Hz, H_b-20), 3.39 (1H, d, J = 11.9 Hz, H-5), 3.21 (1H, t, J = 4.9 Hz, H-12), 2.72 (1H, dd, J = 18.2, 13.3 Hz, H_a-15), 2.61 (1H, s, H-9), 2.40 (1H, dd, J = 18.2, 5.6 Hz, H_b-15), 2.09 (1H, m, H-13), 2.05 (1H, m, H-14), 1.94 (3H, s, H-18), 1.82 (3H, br s, H5'), 1.81 (3H, d, J = 7.7 Hz, H4'), 1.22 (3H, s, H-19), 0.85 (3H, d, J = 7.0 Hz, H-21) ppm; ^{13}C NMR (176 MHz, DMSO-d_6): 196.5 (C2), 168.9 (C16), 165.8 (C1'), 161.2 (C4), 139.0 (C3'), 127.8 (C2'), 127.5 (C3), 109.1 (C11), 82.5 (C1), 78.1 (C12), 77.6 (C7), 69.3 (C20), 67.3 (C-6),

47.1 (C10), 45.7 (C8), 44.1 (C5), 41.8 (C9), 40.6 (C14), 30.2 (C13), 29.3 (C15), 24.5 (C18), 14.3 (C4'), 12.5 (C21), 11.8 (C5'), and 10.8 (C19) ppm; HRTOFMS (positive ESI mode) *m/z* 499.1944 $[M + Na]^+$ (calcd for $C_{25}H_{32}O_9$+Na, 499.1944) and *m/z* 975.3983 $[2M + N]^+$ [calcd for $(C_{25}H_{32}O_9)_2$+Na, 975.3990].

Results and Discussion

The MeOH extract of *Ailanthus altissima* leaves at 10 mg/mL showed 100% control of *Sorghum bicolor, Digitaria sanguinalis, Aeschynomene indica, and Abutilon avicennae,* and > 90% control of *Echinochlia crus-galli, Panicum dichotomiflorum, Xanthium strumarium, and Calystegia japonica*. Herbicidal activity against *Agropyron smithii* was slightly weaker (Table 1).

Table 1. Herbicidal activity of foliar application of methanol extracts from *Ailanthus altissima* to several weeds in a greenhouse condition.

Rates (mg/mL)	Herbicidal activity (%)									
	SOR	ECHC	AGRS	DIGS	PAN	SOL	AESI	ABUT	XAN	CAG
10	100	95	30	100	98	70	100	100	90	95
5	40	40	20	100	70	60	100	80	40	70
2.5	40	30	10	90	20	20	98	98	40	70
1	40	30	10	70	20	20	95	98	40	70

SORBI ; *Sorghum bicolor*, ECHCG ; *Echinochloa crus-galli*, AGRSM ; *Agropyron smithii*, DIGSA ; *Digitaria sanguinalis*, PANDI ; *Panicum dichotomiflorum*, SOLNI ; *Solanum nigrum*, AESIN ; *Aeschynomene indica*, ABUTH ; *Abutilon avicennae*, XANSI ; *Xanthium strumarium*, CAGHE ; *Calystegia japonica.*

The main characteristic was its quick action upon foliar application. External symptoms began to appear within 24 h of exposure, and the weeds were completely controlled five days after treatment. MeOH extract showing herbicidal activity was purified by ethyl acetate fractionation and a series of chromatographic techniques, including silica gel column, C18 Sep-pak cartridge, Sephadex LH20, and preparative high-performance liquid chromatography (HPLC). Four quassinoids, **1-4** (Figure 1, Figs. S1~4), were isolated from the MeOH extract of *Ailanthus altissima* leaves and showed herbicidal activity of 98, 95, 85, and 75%, respectively, when applied to *D. sanguiinalis* at a concentration of 10 μg/mL (Table 2, Figure 2).

Table 2. Herbicidal activity of isolated compounds against *Digitaria sanguinalis*.

	Herbicidal activity at 10 μg/mL (%)
Compound 1	98
Compound 2	95
Compound 3	85
Compound 4	75

Fig 1. Structures of compounds 1-4.

Fig 2. Herbicidal activity against *Digitaria sanguinalis* at same concentration of 10 μg/mL.

Among these, **3** was a new compound, and the characterization and spectroscopic analysis of this compound were performed by data comparison with literature values[14]. The ^{1}H and ^{13}C NMR (nuclear magnetic resonance) data for these compounds are shown in the experimental section. The ^{1}H (Table 3) and ^{13}C NMR (Table 4) signals assignments were aided by ^{1}H-^{1}H COSY (correlation spectroscop Y), HSQC (heteronuclear single quantum correlation) and HMBC (heteronuclear multiple bond correlation) experiments. The other compounds were

155 identified as ailanthone (**1**)[15], 13, 18-dehydroglaucarubinone (**2**)[15,16], and 6-α-

156 tigloyloxychaparrinone **(4)[**17,18].

157 **Table 3. ^{1}H-NMR Data (DMSO-d_6) for compounds 1-4.**

	Compound			
Proton	1	2	3	4
H-1	4.28(s)	4.42 (d, 2.1)	4.39 (s)	4.30 (d, 2.8)
H-3	5.99 (d, 0.9)	5.99 (q, 0.7)	6.02 (s)	6.0 (s)
H-5	2.88 (d, 10.8)	3.08 (d, 11.4)	3.46 (d, 11.9)	3.39 (d, 11.9)
H-6	2.03 (m)	2.06 (m)	5.49 (dd, 11.9, 2.8)	5.49 (dd, 11.9, 2.8)
H-7	4.55 (t, 2.8)	4.70 (t, 2.8)	4.63 (d, 2.8)	4.56 (d, 2.8)
H-9	2.81 (s)	2.97(s)	2.83(s)	2.61(s)
H-12	3.67 (d, 3.6)	3.67 (d, 4.9)	3.69 (d, 3.5)	3.21 (t, 4.9)
H-13	-	-	-	20.9 (m)
H-14	2.77 (dd, 13.5, 5.4)	3.04 (d, 11.4)	2.85 (dd, 13.3, 5.6)	2.05 (m)
Ha-15	2.98 (dd, 18.4, 13.5)	5.64 (br s)	3.01 (dd, 18.4, 13.3)	2.72 (dd, 18.2, 13.3)
Hb-15	2.44 (dd, 18.4, 5.4)	-	2.47 (dd, 18.4, 5.6)	2.40 (dd, 18.2, 5.6)
H-18	1.93 (s)	1.93 (s)	1.94 (s)	1.94 (s)
H-19	1.06 (s)	1.06 (s)	1.21 (s)	1.22 (s)
Ha-20	3.81 (d, 9.0)	3.81 (d, 8.4)	3.91 (d, 8.4)	3.93 (d, 8.4)
Hb-20	3.27 (d, 9.0)	3.32 (d, 8.4)	3.39 (d, 8.4)	3.64 (d, 8.4)
Ha-21	5.05 (d, 0.9)	5.09 (d, 1.4)	5.02 (d, 1.4)	-
Hb-21	5.02 (d, 0.9)	4.99 (br s	5.01 (br s)	-
Ha-3'	-	1.70 (dq, 14.0, 7.0)	6.91 (dq, 7.7, 2.1)	6.91 (dq, 7.7, 2.1)
Hb-3'	-	1.53 (dq, 14.0, 7.0)	-	-
H-4'	-	0.81 (t, 7.0)	1.823 (d, 4.2)	1.81 (d, 7.7)
H-5'	-	1.30 (s)	1.829 (s)	1.82 (br s)
1-OH	7.08 (s)	7.16 (d, 2.1)	7.28 (s)	7.19 (d, 2.8)
11-OH	8.23 (s)	8.33 (s)	8.15 (s)	8.0 (s)
12-OH	5.40 (d, 4.5)	5.35 (br s)	5.55 (d, 4.2)	5.14 (d, 4.9)

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160 **Table 4.** ^{13}C-NMR Data (DMSO-d_6) for compounds **1-4**.

	Compound			
Carbon	1	2	3	4
C-1	82.4	82.1	82.4	82.5
C-2	197.1	197.0	196.6	196.5
C-3	125.0	124.8	127.6	127.5
C-4	162.4	162.4	161.1	161.2
C-5	41.2	40.7	44.1	44.1
C-6	25.1	24.6	67.3	67.3
C-7	77.5	77.8	77.6	77.6
C-8	44.5	46.4	45.2	45.7
C-9	43.3	44.0	42.0	41.8
C-10	44.5	44.5	47.2	47.1
C-11	108.8	108.6	109.0	109.1
C-12	79.0	78.7	79.1	78.1
C-13	146.6	142.4	146.1	30.2
C-14	46.1	50.2	46.1	40.6
C-15	34.3	68.2	34.0	29.3
C-16	169.1	166.7	168.2	168.9
C-17	22.4	22.2	24.7	24.5
C-18	9.5	9.5	10.9	10.8
C-19	71.1	70.7	70.2	69.3
C-20	117.6	119.8	117.5	12.5
C-1'	-	174.2	165.9	165.8
C-2'	-	73.9	127.9	127.8
C-3'	-	32.8	139.2	139.0
C-4'	-	8.0	14.4	14.3
C-5'	-	25.8	11.9	11.8

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162 Compound **3** was obtained as a white solid. The molecular formula was established as

163 $C_{25}H_{32}O_9$ based on a quasi-molecular ion at m/z 497.1785 $[M + Na]^+$ (calcd 497.1788) in its

164 HRTOFMS. The ^{1}H NMR spectrum of **3** displayed signals for two olefinic protons [δ_H 6.91 (1H,

165 dq, J = 7.7, 2.1, H-3'), 6.02 (1H, s, H-3)], an exo-methylene [δ_H 5.02 (1H, d, J = 2.1, H_a-21),

166 5.01 (1H, s, H_b-21)], four oxygenated methines [δ_H 5.49 (1H, dd, *J* = 11.9, 2.8, H-6), 4.63 (1H, d,
167 *J* = 2.8, H-7), 4.39 (1H, s, H-1), 3.69 (1H, d, *J* = 3.5, H-12)], one oxygenated methylene [δ_H 3.91
168 and 3.39 (each 1H, d, *J* = 8.4, H-20)], one methylene proton [δ_H 3.01 (1H, dd, *J* = 18.4, 13.3, H_a-
169 15) and 2.40 (1H, dd, *J* = 18.4, 5.6, H_b-15)] and four methyl groups [δ_H 1.94 (3H, s, H-18), 1.829
170 (3H, br s, H-5'), 1.823 (3H, d, *J* = 7.7, H-4'), and 1.21 (3H, s, H-19)](Fig S9). The ^{13}C NMR
171 spectrum exhibited 25 carbon signals, including three carbonyl signals, six olefinic carbon
172 signals, one hemiketal carbon signal, four methyl carbon signals, two methylene carbon signals,
173 seven methine carbon signals, and two quaternary carbon signals(Fig S10). Comparison of the
174 NMR data of **3** with those of ailanthone (**1**) revealed that the two compounds possessed the same
175 quassinoid moiety, except that the C6 position in ailanthone (**1**) was substituted with a tigloyloxy
176 group in **3**. The ^1H-^1H COSY between H-3' (δ_H 6.91) and H-4' (δ_H 1.823) and the HMBC
177 correlation between H-3' (δ_H 6.91), H-5' (δ_H 1.829), and C1' (δ_C 165.8) and H-4' (δ_H 1.81) and
178 C-2' (δ_C 127.8) confirmed the existence of a tigloyloxy group and that it was connected to the C6
179 position of **3**, established by a long-range correlation between δ_H 5.49 (H-6 of quassinoid moiety)
180 and carboxylic carbon (δ_C 165.9, C1' of tigloyloxy group) in the HMBC spectrum of **3**(Figs.
181 S11, 12, 13)**.** The correlations between H-9 and H-1/H-5 and between H-7 and H-14 in the
182 ROESY spectrum(Fig S14) suggested that the configuration of **3** was the same as that of
183 ailanthone (**1**). And the ROESY correlation between H-3' and H-5' indicated that the geometry
184 of the double-bond of the tigloyloxy group was Z-form. Thus, the structure of compound **3** was
185 determined to be 6-α-tigloyloxyailanthone. The relative stereochemistry of **3** was confirmed
186 from its 2D-ROESY NMR spectrum. The NOE correlations are shown by arrows in Figure 3
187 (2D-ROESY).

188 **Fig 3. 2D ROESY (NOE) correlation of 3.**

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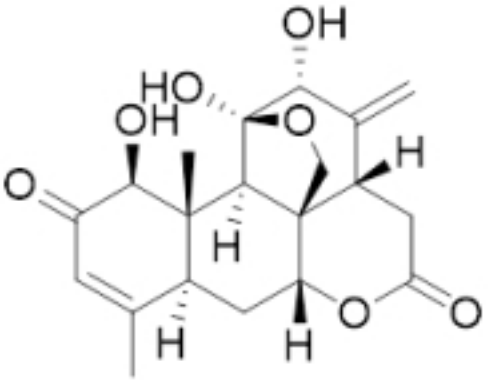
Supporting Information

Structures and spectra of compound 1, 2, 3 and 4.



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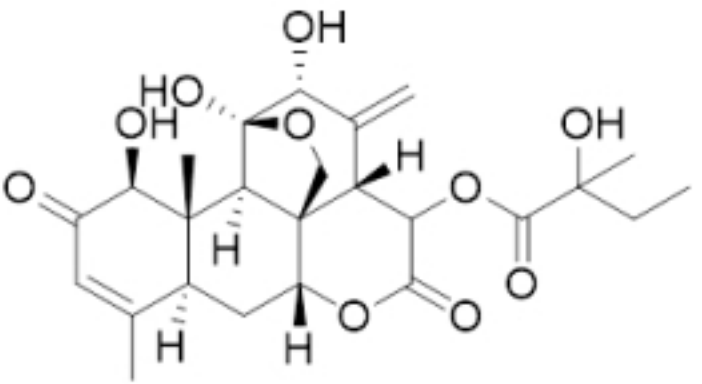

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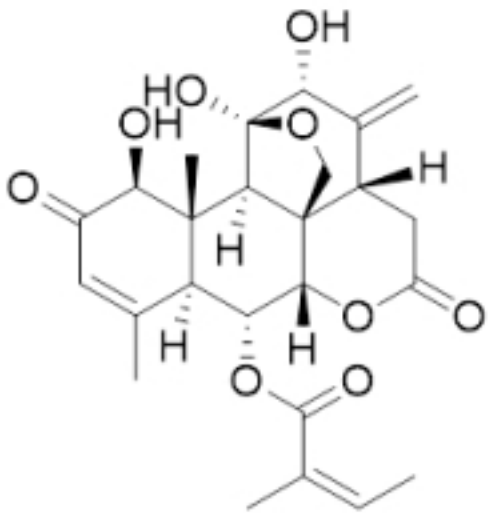

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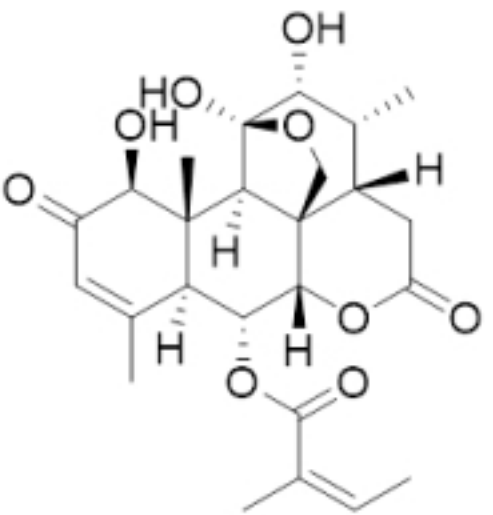

4

Figure1

Figure2

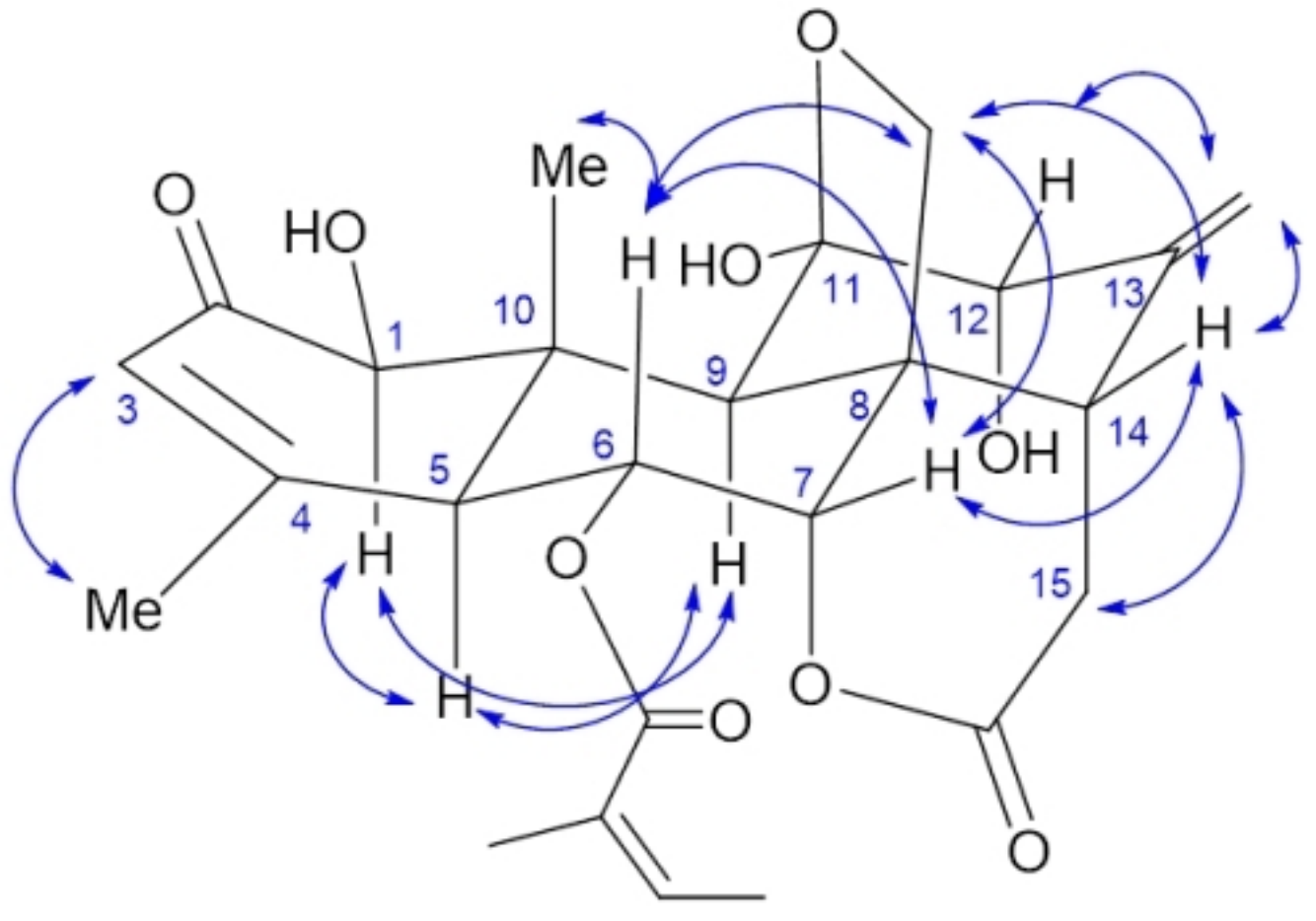

Figure3