Notes

Jatrophane Diterpenoids from *Euphorbia mongolica* as Modulators of the Multidrug Resistance of L5128 Mouse Lymphoma Cells

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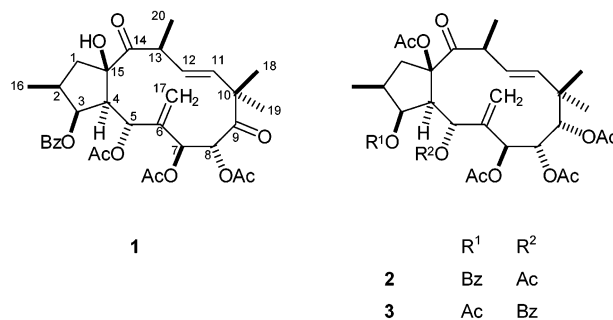
The dried aerial parts of *Euphorbia mongolica* afforded three new acylated polyhydroxy diterpenoids based on the jatrophane framework. The structures were established by means of a combination of 1D and 2D NMR techniques and mass spectrometry as (2*S**,3*S**,4*R**,5*R**,7*S**,8*R**,13*S**,15*R**)-5α,7β,8α-triacetoxy-3β-benzoyloxy-15β-hydroxyjatropha-6(17),11*E*-diene-9,14-dione (**1**), (2*S**,3*S**,4*R**,5*R**,7*S**,8*S**,-9*S**13*S**,15*R**)-5α,7β,8α,9α,15β-pentaacetoxy-3β-benzoyloxyjatropha-6(17),11*E*-dien-14-one (**2**), and (2*S**,3*S**,4*R**,5*R**,7*S**,8*S**,9*S**13*S**,15*R**)-3β,7β,8α,9α,15β-pentaacetoxy-5α-benzoyloxyjatropha-6(17),-11*E*-dien-14-one (**3**). When the isolates were assayed for multidrug resistance-reversing activity in a rhodamine 123 exclusion test using L5178 mouse lymphoma cells, all compounds demonstrated a concentration-dependent effect in inhibiting the efflux pump activity of these tumor cells in the range 11.2−112 μM.

In the past few decades there has been great clinical interest in the development of drugs that overcome multidrug resistance (MDR) to antibiotics in viruses, bacteria, and fungi, and to cytostatic chemotherapeutic agents in cancer cells. Extensive studies have been performed in the search for new effective resistance modulators or chemosensitizers from natural sources.[1−3] Previous investigations revealed that macrocyclic diterpenes isolated from *Euphorbia* species are promising modulators of MDR in tumor cells. Some jatrophane and rearranged jatrophane diterpenes have been found to be able to enhance drug retention in the cells by inhibiting the efflux-pump activity, mediated by P-glycoprotein.[4] To find further efficient anti-MDR agents from the genus *Euphorbia*, the chemical constituents of *E. mongolica* Prokh. (Euphorbiaceae) were investigated.

Euphorbia mongolica is distributed in southeastern parts of Asia and is traditionally used in Mongolia to treat inflammation, warts, and tumors.[5,6] Despite its medicinal uses, the chemical constituents of this species have previously not been described. The present paper reports the isolation, structure determination, and MDR-reversing effect of three new diterpenes (**1−3**) from the aerial parts of *E. mongolica*. The structures of these compounds, including stereochemical aspects, were obtained with the aid of mass spectrometry and extensive 1D and 2D NMR studies.

The CH$_2$Cl$_2$-soluble extract of the dried aerial parts of *E. mongolica* was fractionated by column chromatography on polyamide and purified by vacuum-liquid chromatography, to afford three new jatrophane diterpenoids (**1−3**).

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	R^1	R^2
2	Bz	Ac
3	Ac	Bz

Compound **1** was obtained as colorless crystals. The HRESIMS data in combination with NMR data on **1** indicated the molecular formula C$_{33}$H$_{40}$O$_{11}$ on the basis of the *m/z* 745.1630 [M + Cs]$^+$ ion (calcd for *m/z* 745.1625, Δ −0.7 ppm). From the ^{1}H NMR and JMOD spectra, four ester residues were identified as one benzoate [δ$_H$ 8.13 d, 7.46 t, and 7.56 t; δ$_C$ 165.8, 133.1, 129.9, 129.8, and 128.4] and three acetate groups (δ$_H$ 1.72, 2.04, and 2.10 s; δ$_C$ 170.3, 169.9, 168.8, 2 × 20.7, and 20.4) (Table 1). The UV spectrum of **1** also exhibited the characteristic absorptions of a benzoyl group at 240, 274, and 282 nm. Further, the JMOD (*J*-modulated spin−echo experiment) spectrum, supported by ^{1}H−^{1}H COSY and HSQC correlations, showed the presence of a C$_{20}$-containing diterpene skeleton.[7,8] The diterpene core was found to contain two keto functions according to the carbon resonances at δ$_C$ 204.5 and 212.3 ppm, one olefin group (δ$_C$ 136.4 and 132.2 ppm) and one *exo*-methylene, as indicated by the signals at δ$_C$ 137.9 and δ$_H$ 5.65 brs and 5.53 brs.[9−11] From the ^{1}H−^{1}H COSY and HMQC spectra, three sequences of correlated protons were identified: −CH$_2$−CH(CH$_3$)−CH(OR)−CH− (fragment A), −CH(OR)−CH(OR)− (fragment B), and −CH=CH−CH-(CH$_3$)− (fragment C with *E* olefin *J* = 16.0 Hz) (R = ester group). These structural fragments were linked to quaternary carbons, tertiary methyls, and a methine group by

Table 1. NMR Data of Compounds **1**−**3** [500 MHz (^{1}H), 125 MHz (^{13}C), CDCl$_3$, δ (ppm) (J = Hz)]

	1		**2**		**3**	
position	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1α	2.48 dd (14.3, 8.5)	46.4	2.85 dd (15.7, 9.2)	43.4	2.79 dd (15.6, 9.0)	43.2
1β	1.97 dd (14.3, 12.2)		2.26 dd (15.7, 10.4)		2.15 dd (15.6, 10.6)	
2	2.38 m	38.8	2.54 dddd (10.4, 9.2, 6.7, 3.5)	37.9	2.48 m	38.1
3	5.83 d (5.0)	77.5	5.78 t (3.5)	76.4	5.71 t (3.7)	76.2
4	2.88 brd (5.0)	50.7	3.10 t (3.5)	50.1	3.07 t (3.7)	49.9
5	5.36 s	73.0	5.41 d (3.5)	68.9	5.65 m	69.2
6		137.9		141.9		142.1
7	5.93 s	64.4	5.66 s	68.0	5.65 s	68.0
8	5.35 s	73.0	5.06 s	69.8	5.11 s	70.1
9		204.5	4.94 s	80.5	4.95 s	80.6
10		49.4		40.3		40.5
11	6.02 d (16.0)	136.4	5.82 d (16.0)	135.9	5.82 d (15.8)	135.6
12	5.82 dd (16.0, 10.2)	132.2	5.62 dd (16.0, 9.2)	130.5	5.65 dd (15.8, 9.2)	131.0
13	3.64 dq (10.2, 6.5)	43.9	3.60 dq (9.2, 6.6)	44.6	3.56 dq (9.2, 7.0)	44.8
14		212.3		204.2		204.0
15		84.9		92.5		92.3
16	1.07 d (6.5)	13.9	1.05 d (6.7)	14.3	1.01 d (6.7)	14.4
17a[a]	5.65 brs		5.15 s	115.9	5.20 s	115.6
17b	5.53 brs		5.06 s		5.17 s	
18	1.34 s	25.4	1.26 s	23.4	1.30 s	23.4
19	1.25 s	23.8	0.94 s	25.7	0.95 s	25.8
20	1.43 d (6.5)	21.0	1.33 d (6.6)	19.9	1.30 d (7.0)	19.9
Acetyls						
CO-3						169.7[c]
COMe-3					2.05 s	21.5[b]
CO-5		168.8		168.2		
COMe-5	1.72 s	20.7	1.60 s	20.4		
CO-7		170.3		170.1		169.9[c]
COMe-7	2.04 s	20.7	2.16 s	21.3	2.02 s	21.3[b]
CO-8		169.9		169.7		170.0[c]
COMe-8	2.10 s	20.4	2.02 s	20.6	2.02 s	20.7[b]
CO-9				169.5		169.6[c]
COMe-9			2.08 s	20.6	2.06 s	20.6[b]
CO-15				169.5		169.8[c]
COMe-15			2.18 s	21.4	1.76 s	21.2[b]
OBz						
CO		165.8		165.3		164.3
1′		129.9		130.3		130.0
2′, 6′	8.13 d (7.4)	129.8	8.09 d (7.2)	129.6	8.07 d (7.3)	129.8
3′, 5′	7.46 t (7.8)	128.4	7.45 t (7.7)	128.3	7.42 t (7.8)	128.2
4′	7.56 t (7.4)	133.1	7.58 t (7.4)	133.1	7.56 t (7.4)	133.1
OH-15	4.26 s					

[a] ^{13}C NMR signal of C-17 of **1** was not observed. [b,c] Signals may be interchanged.

interpretation of the long-range ^{1}H−^{13}C correlations detected in the HMBC (heteronuclear multiple bond correlation) spectrum. The two- and three-bond correlations between the quaternary carbon at δ_C 84.9 (C-15) and the protons at δ_H 1.97 (H-1), 5.83 (H-3), and 4.26 (OH-15) indicated that fragment A and this carbon form a five-membered ring, substituted with one methyl, one ester, and one hydroxy group. The long-range couplings of the keto group at δ_C 212.3 (C-14) with the protons at δ_H 2.48, 1.97 (H-1), 3.64 (H-13), 1.43 (H-20), and 4.26 (OH-15) demonstrated the connection of fragment C through a keto group to the five-membered ring. Similarly, the HMBC correlations of the carbons at δ_C 49.4 (C-10) and 204.5 (C-9) with the protons at δ_H 5.82 (H-12), 6.02 (H-11), 1.34 (H-18), 1.25 (H-19), 5.35 (H-8), and 5.93 (H-7) proved the linkage of structural parts C and B and two methyl groups through quaternary carbons. Moreover, two- and three-bond correlations were observed between the signals at δ_C 137.9 (C-6) and δ_H 5.35 (H-8), 5.93 (H-7), and 5.36 (H-5), revealing that the complete structure of **1** involves a jatrophane skeleton substituted with ester groups at positions C-3, C-5, C-7, and C-8, with a hydroxy group at C-15, and keto groups at C-9 and C-14. The HMBC spectrum also provided information on the locations of the three acetyl groups and one benzoyl group. The long-range correlations of the carbonyl carbons (δ_C 170.3, 169.9, 168.8, and 165.8) and

oxymethine protons (δ_H 5.93, 5.35, 5.36, and 5.83) clearly showed the presence of the acetyl groups at C-5, C-7, and C-8 and the benzoyl group at C-3.

The relative configurations of the stereogenic centers of **1** were assessed by inspection of the NOESY spectrum (Table 1). Thus, the proton at the ring junction (H-4), to which the α configuration was conventionally assigned,[10] displayed correlations with H-2, H-3, H-7, and H-13, indicating their α position. The nuclear Overhauser effects observed between H-16 and H-1β and between H-1β and OH-15 revealed the β position of the hydroxy group at C-15. Further diagnostic NOESY cross-peaks were those of the macrocyclic protons with geminal methyl groups and especially the correlations between H-11/H-19, H-12/H-18, and H-18/H-8. As a result of the NOE between H-4/H-11, it was concluded that H-11 and H-19 are on the α face of the macrocycle, while H-12 and H-18 are on the β face, and consequently H-8 is in the β position. The stereochemistry of C-5 was deduced from the interactions between OAc-5/H-3, H-17b/OH-15, and H-17b/H-5, indicating a β-oriented H-5. On the basis of the above evidence, the structure of this compound was elucidated as **1**, and complete, unambiguous ^{1}H and ^{13}C NMR chemical shift assignments were determined as listed in Table 1.

Compound **2** was isolated as colorless crystals with the molecular formula $C_{37}H_{46}O_{13}$, as established by the quasi-

Table 2. Reversal of Multidrug Resistance (MDR) of L5178 Mouse Lymphoma Cells by Compounds **1**−**3**[a]

compound	conc, μM	FSC	SSC	FL-1	fluorescence activity ratio
PAR control		487.60	198.82	953.44	
MDR control		497.63	236.10	12.09	
verapamil	23	492.01	225.08	158.90	13.14
1	11.2	503.35	244.67	148.64	12.29
	112	525.91	242.38	277.08	22.92
2	11.2	503.09	244.85	31.46	2.60
	112	513.78	244.79	217.81	18.02
3	11.2	502.40	244.67	33.71	2.79
	112	516.46	240.49	354.21	29.29

[a] Abbreviations: FSC = forward scatter count of cells in the samples. SSC = side scatter count of the cells in the samples. FL-1 = mean fluorescence intensity of the cells. Fluorescence activity ratio: values were calculated by using the equation given in the Experimental Section. PAR control: parental cell without MDR gene. MDR control: parental cell transfected with human MDR1 gene.

molecular ion peak at m/z 831.1983 [M + Cs]$^+$ (calcd for $C_{37}H_{46}O_{13}Cs$ m/z 831.1993, Δ +1.2 ppm) in the HRESIMS. The ^{1}H NMR and JMOD spectra showed similarities to those of compound **1**, but **2** contained five acetate groups and one benzoate group (Table 1), and only one keto group (δ_C 204.2 ppm). Extensive studies of the ^{1}H−^{1}H COSY, HSQC, and HMBC spectra resulted in the unequivocal assignments of the proton and carbon resonances and revealed that compound **2** is based on the jatrophane skeleton with an 11E double bond (J = 16.0 Hz) and a 6(17) exocyclic methylene group. The locations of the ester groups were confirmed through the observation of HMBC cross-peaks between the carbonyl carbons and the ester-bearing methine protons. Thus, the benzoyl group was placed at C-3 and the acetyl groups at C-5, C-7, C-8, and C-9. One additional acetyl group (δ_H 2.18 s), situated on quaternary carbon C-15, was allocated via the C−O−CO−CH_3 four-bond coupling, observed as a weak signal in the HMBC spectrum. The position of the keto group at C-14 was evident from its heteronuclear long-range correlations with H-1, H-4, H-12, H-13, and H-20. The stereochemical aspects were studied by means of a NOESY experiment. Starting from the H-4α reference point,[10] NOE-enhanced signals were detected between proton pairs H-4/H-2, H-4/H-3, H-4/H-7, H-3/H-7, H-4/H-13, and H-13/H-1α, suggesting the α orientation of these protons. Similar to **1**, it was found that H-11 is directed below and H-12 above the plane of the macrocycle, while H-19 is in the α and H-18 in the β position with regard to the NOESY correlations between H-11/H-13, H-11/H-19, and H-12/H-18. Moreover, the NOE effect between H-18 and H-8 and between H-12 and H-5 demonstrated the β-oriented H-8 and H-5. Further important NOEs of the ester groups were observed, such as H-7/OAc-9 and H-2′,6′/OAc-15, which provided evidence of the 15β and 9α configurations of the acetyl groups. In conclusion, the structure of **2** was elucidated as 5α,7β,8α,9α,15β-pentaacetoxy-3β-benzoyloxyjatropha-6(17),11E-dien-14-one.

Compound **3** was crystallized from MeOH as colorless crystals. Its molecular formula was determined by means of HRESIMS and NMR as $C_{37}H_{46}O_{13}$. The ^{1}H NMR and JMOD spectra of **3** were very similar to those of **2**, indicating the presence of the same diterpene polyol and ester groups and differing only in the esterification pattern. Comparison of the ^{1}H NMR data on **2** and **3** revealed that the C-5 acetoxy moiety was replaced by a benzoyloxy group with respect to the downfield-shifted H-5 signal (**2**, δ_{H-5} 5.41; **3**, δ_{H-5} 5.65). Additionally, the presence of the acetoxy

goups at C-3, C-7, C-8, and C-9 was suggested by the long-range correlations of the carbonyl ^{13}C NMR signals (Table 1). As in the case of **1** and **2**, the stereochemistry of **3** was determined on the basis of NOESY measurements. The NOE effects (Table 3) demonstrated the same configuration of **3** as that of **2**. Unfortunately, the overlapping signals of H-5, H-7, and H-12 (δ_H 5.65 m, 3H) did not allow stereochemical conclusions from the NOESY spectrum concerning C-5, C-7, and C-9. However, the chemical shifts and coupling constants of H-5 and H-7−H-9 for **3** were very close to those for **2** and for 3β,5α,8α,9α,15β-pentaacetoxy-7β-benzoyloxyjatropha-6(17),11E-dien-14-one (δ_{H-5} 5.71, δ_{H-7} 6.13, δ_{H-8} 5.18, δ_{H-9} 4.94; $J_{4,5}$ = 7.6, $J_{7,8}$ = 0, $J_{8,9}$ = 0 Hz), a compound isolated from *E. turczaninowii*.[11] Thus, **3** could be characterized as containing 5α-, 7β-, and 9α-oriented acetyl groups, as found previously in many jatrophane polyesters.[9,12] These observations permitted the assignment of this compound as **3**.

The MDR-reversing activities of compounds **1**−**3** were investigated using a rhodamine 123 exclusion test. All compounds displayed a significant effect in inhibiting the efflux-pump activity of multidrug-resistant L5178 mouse lymphoma cells as compared with that of the positive control verapamil. The results obtained at 11.2 and 112 μM concentrations indicated a concentration-dependent activity, as expressed by the fluorescence activity ratio increasing at higher concentration (Table 2).

Experimental Section

General Experimental Procedures. Melting points are uncorrected. Optical rotations were determined with a Perkin-Elmer 341 polarimeter. UV spectra were recorded on a Shimadzu UV-2101 PC spectrometer. NMR spectra were recorded in CDCl$_3$ on a Bruker Avance DRX 500 spectrometer, at 500 MHz (^{1}H) and 125 MHz (^{13}C), with TMS as internal standard. Two-dimensional data were acquired and processed with standard Bruker software. HRESIMS measurements were carried out on a Perkin-Elmer Q-STAR Pulsar Q-TOF mass spectrometer equipped with an electrospray ionization source. For vacuum-liquid chromatography, silica gel (Kiesel-gel GF$_{254}$ 15 μm, Merck) was used. Chromatographic fractions were monitored by TLC on silica gel plates (Merck 5554) visualized by spraying with concentrated H$_2$SO$_4$, followed by heating.

Plant Material. *Euphorbia mongolica* was collected at Govi Gurvan-Sajhan, Omnogovi, Mongolia, in June 2001, and identified by Dr. S. Sanzhir (Institute of Medicinal Research, Sector of Pharmacy, Ulaanbaatar, Mongolia). A voucher specimen (No. 539) has been deposited in the Herbarium of the Department of Pharmacognosy, University of Szeged, Szeged, Hungary.

Extraction and Isolation. The dried plant material (166 g) was percolated with MeOH (6700 mL) at room temperature. The MeOH extract was subjected to solvent partitioning to yield CH$_2$Cl$_2$- and H$_2$O-soluble phases. The organic phase (12.59 g) was chromatographed on a polyamide column (48 g) with mixtures of MeOH and H$_2$O (3:2 and 4:1, each 1000 mL) as eluents. The fraction obtained with MeOH−H$_2$O (3:2) was fractionated by VLC (vacuum-liquid chromatography), using a gradient system of cyclohexane−EtOAc−EtOH (70:10:0, 70:20:0, 70:20:1, 70:20:2, and 70:30:3). From fractions 22−26, compound **1** was crystallized (20.4 mg). Fractions 32−38 were subjected repeatedly to silica gel chromatography, using a gradient system of CH$_2$Cl$_2$−acetone (100:0, 99:1, 98:2, 97:3, 95:5, and 90:10). After crystallization, fractions 34−43 and 44−55 yielded compounds **2** (13.9 mg) and **3** (5.8 mg), respectively.

(2S^*,3S^*,4R^*,5R^*,7S^*,8R^*,13S^*,15R^*)-5α,7β,8α-Triacetoxy-3β-benzoyloxy-15β-hydroxyjatropha-6(17),11E-diene-9,14-dione (1): colorless needles; mp 178−180 °C; [α]$^{25}_D$ +95°

(*c* 0.10, CHCl₃); UV λ_{max} (log ϵ) (MeOH) 240 (3.71), 274 (2.93), 282 (2.88); ¹H and ¹³C NMR data, see Table 1; HRESIMS *m/z* 745.1630 [M + Cs]⁺ (calcd for $C_{33}H_{40}O_{11}Cs$ *m/z* 745.1625, Δ −0.7 ppm).

(2*S**,3*S**,4*R**,5*R**,7*S**,8*S**,9*S**13*S**,15*R**)-5α,7β,8α,9α,- 15β-Pentaacetoxy-3β-benzoyloxyjatropha-6(17),11*E*-dien- 14-one (2): colorless needles; mp 198−199 °C; [α]²⁵_D +64° (*c* 0.20, CHCl₃); UV λ_{max} (log ϵ) (MeOH) 240 (3.66), 274 (2.91), 281 (2.85); ¹H and ¹³C NMR data, see Table 1; HRESIMS *m/z* 831.1983 [M + Cs]⁺ (calcd for $C_{37}H_{46}O_{13}Cs$ *m/z* 831.1993, Δ +1.2 ppm).

(2*S**,3*S**,4*R**,5*R**,7*S**,8*S**,9*S**13*S**,15*R**)-3β,7β,8α,9α,- 15β-Pentaacetoxy-5α-benzoyloxyjatropha-6(17),11*E*-dien- 14-one (3): colorless crystals; mp 198−202 °C; [α]²⁵_D +31° (*c* 0.175, CHCl₃); UV λ_{max} (log ϵ) (MeOH) 240 (3.69), 274 (2.93), 281 (2.87); ¹H and ¹³C NMR data, see Table 1; HRESIMS *m/z* 831.1991 [M + Cs]⁺ (calcd for $C_{37}H_{46}O_{13}Cs$ *m/z* 831.1993, Δ +0.2 ppm).

Assay for MDR-Reversal Activity. Anti-MDR effects were investigated in a rhodamine 123 exclusion experiment using L5178 mouse lymphoma cells infected with the pHa MDR1/A retrovirus, as detailed in ref 4. The fluorescence of the cell population was measured by flow cytometry with a Beckton Dickinson FACScan instrument. Verapamil was used as a positive control. The fluorescence activity ratio was calculated from the drug accumulation of treated MDR and untreated MDR cells related to parental treated per untreated drug-sensitive cells. An activity ratio (*R*) was calculated on the basis of the measured fluorescence values via the following equation:

$$\text{fluorescence activity ratio } (R) = \frac{\text{MDR treated/MDR control}}{\text{parental treated/parental control}}$$

Supporting Information Available: Details of the NMR experiments performed on compounds **1**, **2**, and **3** are summarized in Tables 1−3. Included is Figure 1, presenting selected ¹H−¹H COSY and HMBC correlations of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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