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Jatrophane diterpenoids with multidrug-resistance modulating activity from the latex of *Euphorbia nicaeensis*

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ABSTRACT

Seven previously undescribed jatrophane diterpenoids, nicaeenin A–G, with eight known jatrophane diterpenoids, namely euphodendrophanes A–C, F, N, O, Q, S, were isolated from latex of *Euphorbia nicaeensis* collected in Serbia. The chemical structures of the compounds were determined by spectroscopic analysis including 1D and 2D NMR and HRESIMS experiments.

All but one of the previously undescribed jatrophanes, showed significant potential to inhibit P-glycoprotein (P-gp) activity in two MDR cancer cells (NCI-H460/R and DLD1-TxR). The most powerful were nicaeenin F and nicaeenin G. Moreover nicaeenin G significantly stronger sensitized NCI-H460/R cells to DOX than Dex-VER.

1. Introduction

In the course of investigation into biologically active compounds from *Euphorbia* species (genus comprising more than 2000 species and the largest one in the family Euphorbiaceae), lower diterpenoids of different skeletal types such as jatrophane, tigliane, ingenane, lathyrane and others were isolated, their chemical structures established, and numerous compounds tested for biological activities such as antitumor, cytotoxic, antimicrobial, multidrug-resistance-reversing and other, as summarized in two reviews (Shi et al., 2008; Vasas and Hohmann, 2014).

Latex of *Euphorbia* spp. as an abundant source of bioactive diterpenoids (Esposito et al., 2016) exhibited potent anti-CHICV (Nothias-Scaglia et al., 2015) and anti-HIV (Avila et al., 2010) activities, and inhibited CaCdr1p and/or CaMdr1p efflux pumps of *Candida albicans* (Esposito et al., 2017). *Euphorbia peplus* latex might function as defense metabolites against insect herbivores and pathogens for the plant (Hua et al., 2017). From latex of *Euphorbia trigona* lectines with remarkable cytototoxic activity have been isolated (Vilanueva et al., 2015).

Jatrophanes of a unique trans-bicyclo [10.3.0]pentadecane framework are considered among the most potent modulators of P-glycoprotein (P-gp) *in vitro* that consequently reverse multidrug resistance (MDR) (Hohmann et al., 2002; Corea et al., 2003), while some of them exhibit microtubule interacting activity and induce paclitaxel-like microtubules (Miglietta et al., 2003). Mostly jatrophanes show moderate cytotoxicity against cancer cells (Hegazy et al., 2010; Lanzotti et al., 2015), while in combination with anticancer drugs a promising synergistic increase of anticancer activity on resistant cells was obtained (Pešić et al., 2011). Several jatrophanes acted *in vitro* against human immunodeficiency virus (HIV) (Bedoya et al., 2009) and Chikungunya virus (CHIKV) transmitted to the people by mosquitoes (Nothias-Scaglia et al., 2014).

As a part of our ongoing investigation of naturally occurring diterpenoids from *Euphorbia* species, *Euphorbia nicaeensis* All. (family Euphorbiaceae, genus *Euphorbia* L.) was collected in Serbia. Phytochemical studies of *E. nicaeensis* have been reported dealing with epicuticular wax constituents (Hemmers and Guelz, 1986),

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isolation of tetracyclic triterpenoids (Oksuz et al., 1993), glucocerebrosides (Cateni et al., 2003) and glyceroglycolipids with anti-inflammatory activity (Cateni et al., 2004).

However, the diterpenoid constituents of this plant have not been reported yet. Here we present the isolation of fifteen jatrophanes from latex of *E. nicaeensis*, the structure elucidation of seven previously undescribed jatrophanes along with their MDR reversing activity.

2. Results and discussion

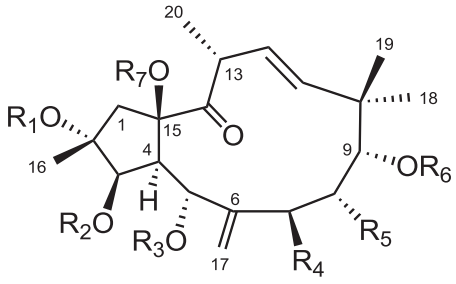
2.1. Structural and stereochemical studies

Chemical study on the lyophilized latex of *E. nicaeensis* afforded seven unreported jatrophane diterpenoids (**1**–**4**, **6**–**8**) and eight previously isolated jatrophanes (**5**, and **9**–**15**) (Aljančić et al., 2011; Jadranin et al., 2013) (Fig. 1). The structures of previously undescribed compounds and relative configurations were established on the basis of spectroscopic analysis including 1D and 2D NMR (^{1}H–^{1}H COSY, NOESY, ^{1}H-^{13}C HSQC, HMBC) and HRESIMS experiments. Each of known compounds isolated were identified by the comparison of the spectral data with the published ones.

Compound **1**, $[\alpha]^{20}_D$ −7.14 (*c* 0.1, MeOH), was isolated as a colorless amorphous solid with the molecular formula $C_{32}H_{41}O_{10}N$, as deduced by the ^{13}C NMR data and HRESIMS ion at *m/z* 600.2803 $[M+H]^+$ (calcd. 600.2790), indicating deficit of 12 hydrogen atoms. Four ester residues were readily identified as three acetates and a nicotinate (Table 1). The remaining 20 carbon signals in the diterpenoid core were recognized by DEPT and ^{13}C NMR spectra.

An exomethylene 6,17-double bond was elucidated from the correlations in the COSY spectrum between H-17a/H-7 and H-17b/H-7 (Fig. S4, Supporting Information) as well as HMBC correlation of C-7 and H-17a (Fig. S6, Supporting Information). Data from HSQC and ^{1}H NMR pointed out to disubstituted double bond with *E* geometry ($J_{11,12}$ = 15.8 Hz).

Three spin coupling fragments (**A**–**C**) were established by the



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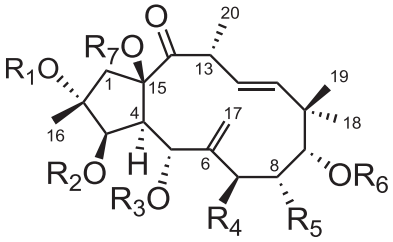

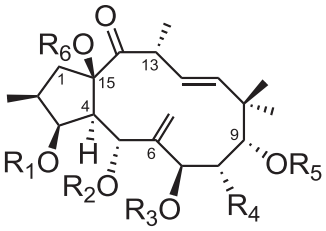

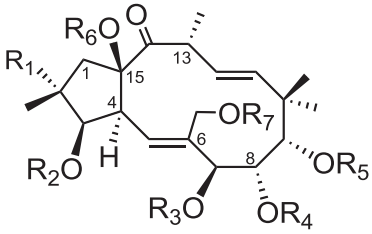

2–5 **6–12** **13–15**

	R_1	R_2	R_3	R_4	R_5	R_6	R_7
1	H	Ac	Ac	H	H	Nic	Ac
2	Ac	Pr	Ac	OiBu	OAc	Nic	H
3	Nic	iBu	Ac	OiBu	OAc	Ac	H
4	Nic	Pr	Ac	OiBu	OAc	Ac	H
5 (Euphodendrophane O)	Ac	iBu	Ac	OiBu	OAc	Nic	H
6	Pr	Ac	Ac	H	Nic	Ac	-
7	Ac	Ac	iBu	OAc	Nic	Ac	-
8	Pr	Ac	iBu	ONic	Ac	H	-
9 (Euphodendrophane A)	Pr	Ac	iBu	OAc	Nic	H	-
10 (Euphodendrophane B)	iBu	Ac	iBu	OAc	Nic	H	-
11 (Euphodendrophane C)	Pr	Ac	iBu	OAc	Nic	Ac	-
12 (Euphodendrophane N)	Ac	Ac	iBu	OAc	Nic	H	-
13 (Euphodendrophane F)	OAc	Ac	iBu	Ac	Nic	Ac	Ac
14 (Euphodendrophane Q)	OAc	Pr	iBu	Ac	Nic	Ac	Ac
15 (Euphodendrophane S)	OAc	Ac	iBu	Ac	Bz	Ac	Ac

Ac-acetyl, Bz-benzoyl, iBu-isobutanoyl, Nic-nicotinoyl, Pr-propanoyl

Fig. 1. Jatrophanes from latex of *E. nicaeensis*.