Bioorganic Chemistry 37 (2009) 96–100

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Effect of 6α,7β-dihydroxyvouacapan-17β-oic acid and its lactone derivatives on the growth of human cancer cells

Felipe P.G. Euzébio [a], Flávio J.L. dos Santos [a], Dorila Piló-Veloso [a], Ana Lúcia T.G. Ruiz [b], João Ernesto de Carvalho [b], Dalton L. Ferreira-Alves [c], Ângelo de Fátima [a,*]

[a] Departamento de Química, Instituto de Ciências Exatas, Universidade Federal de Minas Gerais (UFMG), Av. Pres. Antônio Carlos, 6627, Campus Pampulha, 31270-901 Belo Horizonte, MG, Brazil
[b] Centro Pluridisciplinar de Pesquisas Químicas, Biológicas e Agrícolas (CPQBA), Universidade Estadual de Campinas (UNICAMP), CP 6171, 13083-970 Paulínia, SP, Brazil
[c] Departamento de Farmacologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais (UFMG), Av. Pres. Antônio Carlos, 6627, Campus Pampulha, 31270-901 Belo Horizonte, MG, Brazil

ARTICLE INFO

Article history:
Received 6 February 2009
Available online 31 March 2009

Keywords:
Pterodon polygalaeflorus
Furanditerpenes
Antiproliferative activity

ABSTRACT

The furanditerpene 6α,7β-dihydroxyvouacapan-17β-oic acid (**1**) is a natural product biosynthesized by some species from the genus *Pterodon* (Leguminosae). This secondary metabolite has multiple biological activities that include anti-inflammatory, analgesic, plant growth regulatory, anti-edematogenic, photosystem II inhibitory and photosynthesis uncoupler, and antifungal properties. However, few studies on the antiproliferative profile of compound **1** and/or its derivatives have been reported up to date. Here, we describe the isolation of compound **1** from hexane extract of *P. polygalaeflorus* fruits as well as the semisynthesis of three lactone derivatives: 6α-hydroxyvouacapan-7β,17β-lactone (**2**), 6α-acetoxyvouacapan-7β,17β-lactone (**3**), and 6-oxovouacapan-7β,17β-lactone (**4**). Additionally, antiproliferative activity of these compounds against nine human cancer cell lines was investigated. Our results revealed that 6α-hydroxyvouacapan-7β,17β-lactone (**2**) was the most potent furanditerpene against all cancer cell lines studied. The presence of non-substituted hydroxyl group at C-6 and the presence of 7β,17β-lactone ring are important for the antiproliferative activity of these compounds.

1. Introduction

The genus *Pterodon* (Leguminosae) is widely distributed over savannahs of Central and Southern Brazil and comprises five native species: *P. abruptus* Vog, *P. apparicioi* Pedersoli, *P. emarginatus* Benth, *P. polygalaeflorus* Benth, and *P. pubescens* Benth. Alcoholic extracts from the fruits of these plants are used in folk medicine as antirheumatic, anti-inflammatory (sore throat), and pain killer preparations [1]. The fruit oils of the last three species have protective action against infection by *Schistosoma mansoni* [2,3]. Furanditerpene 6α,7β-dihydroxyvouacapan-17β-oic acid (**1**) (Fig. 1) and other correlated vouacapanoids were identified and isolated from these oils [2–5]. Compound **1** and some derivatives were shown to have anti-inflammatory [6], analgesic [7], plant growth regulatory [8–11], anti-edematogenic [12], photosystem II inhibitory and photosynthesis uncoupler [13,14], and antifungal activities [15].

Although compound **1** and correlated vouacapanoids exhibit a broad range of biological activities, the antiproliferative activity of such compounds is still poorly explored. Recently, Vieira et al. showed that compound **1** inhibits the proliferation of human melanoma (SK MEL 37) cells [16]. Spindola et al. (2009) evaluated the antiproliferative activity of five non-lactone vouacapanoids isolated from *P. pubescens* seed oil and found three of them selective for prostate (PC-3) cancer cell line [17]. In this scenario, it is mandatory that any potential cytotoxic compound is evaluated against different cancer cell lines in order to better understand its antiproliferative activity. The present study reports the cytotoxicity of the furanditerpene 6α,7β-dihydroxyvouacapan-17β-oic acid (**1**) and its lactone derivatives 6α-hydroxyvouacapan-7β,17β-lactone (**2**), 6α-acetoxyvouacapan-7β,17β-lactone (**3**), and 6-oxovouacapan-7β,17β-lactone (**4**) on nine human tumor cell lines of various histological origins.

2. Materials and methods

2.1. Chemistry

2.1.1. General procedures

Reagents and solvents were used as supplied. Flash chromatography was performed with columns packed with 70–230 mesh silica gel. ^{1}H NMR and ^{13}C NMR data were recorded on a Bruker DRX 400 AVANCE (9.40 T) spectrometer. Chemical shifts are reported in

* Corresponding author. Fax: +55 31 3409 5700.
E-mail address: adefatima@qui.ufmg.br (Â.de Fátima).

0045-2068/$ - see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.bioorg.2009.03.004

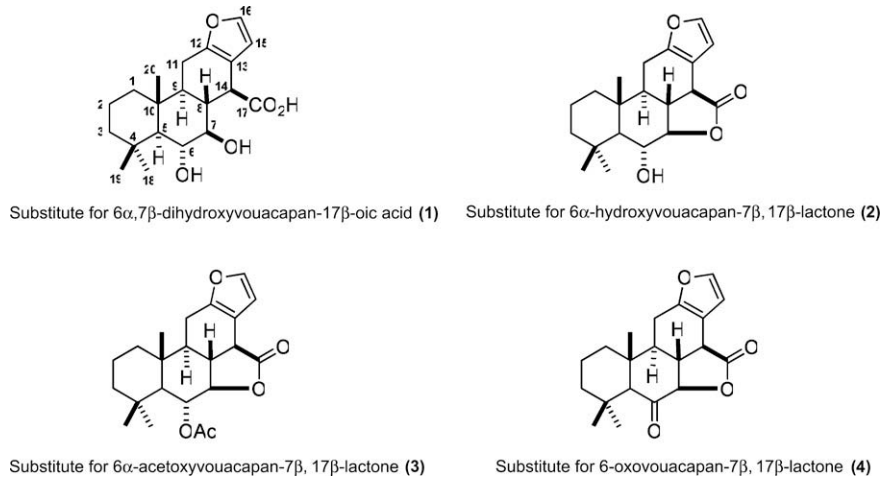

Fig. 1. Structure of furanditerpene **1** and its lactone derivatives **2**–**4**.

δ [ppm relative to $(CH_3)_4Si$]. For ^1H NMR, the chemical shifts were followed by multiplicity (bs, broad singlet; bd, broad doublet; d, doublet; dd, double doublet; ddd, double double doublet; dt, double triplet; dtd, double triplet of doublets; m, multiplet; qt, quartet of triplets; s, singlet; t, triplet; td, triplet of doublets) and coupling constant *J* reported in Hertz (Hz). The NMR techniques 1D and 2D (COSY, NOESY, HMQC, HMBC) were employed to the assignments.

2.1.2. Isolation of 6α,7β-dihydroxyvouacapan-17β-oic acid (1)

Compound **1** was isolated from the hexane extract of *P. polygalaeflorus* fruits as described in the literature [4]. ^1H-NMR (400 MHz, DMSO-d6): δ_H = 0.92 (s, 3H, CH_3-20); 0.89–0.99 (m, 1H, H-1_{ax}); 0.96 (d, 1H, J_{5-6} = 11.1, H-5); 1.14 (s, 3H, CH_3-18); 1.15 (td, 1H, $J_{3ax-3eq} = J_{3ax-2ax}$ = 13.2, $J_{3ax-2eq}$ = 3.5, H-3_{ax}); 1.01 (s. 3H, CH_3-19); 1.27–1.42 (m, 3H, H-2_{eq}, H-3_{eq}, H-9); 1.43–1.54 (m, 1H, H-2_{ax}); 1.58 (bd, 1H, $J_{1eq-1ax}$ = 13.4, H-1_{eq}); 2.27 (ddd, 1H, $J_{11ax-11eq}$ = 16.2, J_{11ax-9} = 11.2, $J_{11ax-15}$ = 2.5, H-11_{ax}); 2.54 (dd, 1H, $J_{11eq-11ax}$ = 16.2, J_{11eq-9} = 5.3, H-11_{eq}); 3.05 (dd, 1H, J_{7-8} = 10.0, J_{7-6} = 9.1, H-7); 3.15 (bd, 1H, J_{14-8} = 8.8, H-14); 3.35 (bs, OH-7); 3.52 (dd, 1H, J_{6-5} = 11.1, J_{6-7} = 9.1, H-6); 4.12 (bs, OH-6); 6.58 (dd, 1H, J_{15-16} = 1.8, $J_{15-11ax}$ = 2.5, H-15); 7.42 (d, 1H, J_{16-15} = 1.8, H-16); 11.83 (bs, OH-17). ^{13}C NMR (100 MHz, DMSO-d6) δ_C = 15.1 (C-20), 18.1 (C-2), 21.5 (C-11), 22.2 (C-19), 33.1 (C-4), 37.7 (C-10), 39.5 (C-18), 38.7 (C-1), 40.7 (C-8), 43.4 (C-3), 46.3 (C-14), 47.5 (C-9), 55.2 (C-5), 73.0 (C-6), 81.6 (C-7), 108.6 (C-15) 114.3 (C-13), 141.2 (C-16), 150.2 (C-12), 175.2 (C-17).

2.1.3. Preparation of 6α-hydroxyvouacapan-7β,17β-lactone (2) and 6α-acetoxyvouacapan-7β,17β-lactone (3)

Compounds **2** and **3** were prepared according to Rubinger et al. [18], with some modifications. Lactones **2** and **3** were obtained in quantitative yields from the treatment of **1** with acetic anhydride and sodium acetate in tetrahydrofurane at 45 °C for 1 h and 3 h, respectively. Compound 2**:** ^1H-NMR (400 MHz, $CDCl_3$): δ_H = 1.02 (s, 3H, CH_3-20); 1.12 (td, 1H, $J_{1ax-1eq} = J_{1ax-2ax}$ = 12.9, $J_{1ax-2eq}$ = 3.3, H-1_{ax}); 1.13 (s, 3H, CH_3-19); 1.24 (s, 3H, CH_3-18); 1.22-1.33 (m, 1H, H-3_{ax}); 1.25 (d, 1H, J_{5-6} = 9.7, H-5); 1.41–1.50 (m, 2H, H-2_{ax}, H-3_{eq}); 1.52–1.69 (m, 2H, H-1_{eq}, H-2_{eq}); 2.05 (bs, OH-6); 2.52 (ddd, 1H, $J_{11ax-11eq}$ = 17.5, J_{11ax-9} = 8.8, $J_{11ax-15}$ = 2.5, H-11_{ax}); 2.54 (ddd, 1H, $J_{11eq-11ax}$ = 16.2, J_{11eq-9} = 5.3, $J_{11ax-15}$ = 1.8, H-11_{eq}); 4.08–4.17 (m, 2H, H-6, H-7); 3.25 (ddd, 1H, J_{14-8} = 13.3, J_{14-15} = 2.4, J_{14-16} = 1.8, H-14); 6.69 (bd, 1H, J_{15-16} = 2.0, H-15); 7.30 (bd, 1H, J_{16-15} = 2.0, H-16). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 15.6 (C-20), 18.1 (C-2), 21.8 (C-11), 22.9 (C-19), 34.2 (C-4), 40.7 (C-10), 36.9 (C-18), 39.2 (C-1), 45.6 (C-8), 41.7 (C-14), 44.2 (C-3), 44.1 (C-9), 58.0 (C-5), 72.0 (C-6), 87.9 (C-7), 107.7 (C-15) 113.6 (C-13), 141.7 (C-16), 152.4 (C-12), 173.8 (C-17). Compound **3**: ^1H-NMR (400 MHz, $CDCl_3$): δ_H = 1.07 (s, 3H, CH_3-20); 1.15 (td, 1H, $J_{1ax-1eq} = J_{1ax-2ax}$ = 13.3, $J_{1ax-2eq}$ = 3.6, H-1_{ax}); 1.00 (s, 3H, CH_3-19); 1.08 (s, 3H, CH_3-18); 1.29 (td, 1H, $J_{3ax-3eq} = J_{3ax-2ax}$ = 13.9, $J_{3ax-2eq}$ = 4.3, H-3_{ax}); 1.48 (d, 1H, J_{5-6} = 10.8, H-5); 1.42–1.50 (m, 2H, H-2_{ax}, H-3_{eq}); 1.53–1.61(m, 1H, H-2_{eq}), 1.62–1.72 (m, 1H, H-1_{eq}) 2.54 (ddd, 1H, $J_{11ax-11eq}$ = 17.4, J_{11ax-9} = 8.7, $J_{11ax-15}$ = 2.2, H-11_{ax}); 2.68 (ddd, 1H, $J_{11eq-11ax}$ = 17.4, J_{11eq-9} = 8.1, $J_{11ax-15}$ = 1.5, H-11_{eq}); 3.23 (ddd, 1H, J_{14-8} = 13.3, J_{14-15} = 2.2, J_{14-16} = 1.5, H-14); 4.15 (dd, 1H, J_{7-8} = 11.1, J_{7-6} = 9.3, H-7); 5.5 (dd, 1H, J_{6-5} = 10.8, J_{6-7} = 9.3, H-6); 6.57 (bd, 1H, J_{15-16} = 2.0, H-15); 7.29 (bd, 1H, J_{16-15} = 2.0, H-16). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 15.4 (C-20), 18.0 (C-2), 21.6 (C-COO in C-6) 21.8 (C-11), 22.9 (C-19), 33.8 (C-4), 41.1 (C-10), 36.5 (C-18), 39.1 (C-1), 45.7 (C-8), 41.6 (C-14), 44.1 (C-3), 44.2 (C-9), 57.2 (C-5), 71.8 (C-6), 85.1 (C-7), 107.7 (C-15) 113.6 (C-13), 141.7 (C-16), 152.2 (C-12), 169.7 (O–C=O in C-6), 173.2 (C-17).

2.1.4. Preparation of 6-oxovouacapan-7β,17β-lactone (4)

Compound **4** was synthesized from oxidation of compound **2** as reported elsewhere [13,19]. ^1H NMR (400 MHz, $CDCl_3$) δ_H = 0.89 (s, 3H, CH_3-20); 0.93 (s, 3H, CH_3-18); 1.13 (td, 1H, $J_{3ax-3eq} = J_{3ax-2ax}$ = 13.3, $J_{3ax-2eq}$ = 3.5, H-3_{ax}); 1.31 (m, 1H, H-1_{ax}); 1.28 (s, 3H, CH_3-19); 1.43 (m, 1H, H-3_{eq}); 1.53 (m, 1H, H-2_{eq}); 1.65 (qt, 1H, $J_{2ax-2eq} = J_{2ax-1ax} = J_{2ax-3ax}$ = 13.3, $J_{2ax-1eq} = J_{2ax-3eq}$ = 3.5, H-2_{ax}); 1.67 (dtd, 1H, $J_{1eq-1ax}$ = 12.8, $J_{1eq-2ax} = J_{1eq-2eq}$ = 3.2, $J_{1eq-3eq}$ = 1.3, H-1_{eq}); 2.20 (dt, 1H, $J_{8-9} = J_{8-14}$ = 13.0, J_{8-7} = 12.0, H-8); 2.37 (dt, J_{9-8} = 13.0, $J_{9-11ax} = J_{9-11eq}$ = 8.3, H-9); 2.46 (d, 1H, J_{5-7} = 0.9, H-5); 2.56 (ddd, 1H, $J_{11ax-11eq}$ = 17.6, J_{11ax-9} = 8.3, $J_{11ax} = J_{11ax-14}$ = 2.1, H-11_{ax}), 2.75 (ddd, 1H, $J_{11eq-11ax}$ = 17.6, J_{11eq-9} = 8.3, $J_{11eq-14}$ = 2.1, H-11_{eq}); 3.73 (dt, 1H, J_{14-8} = 13.0, $J_{14-11ax} = J_{14-11\ eq}$ = 2.1, H-14), 5.16 (dd, 1H, J_{7-8} = 12.0, J_{7-5} = 0.9, H-7), 6.52 (d, 1H, J_{15-16} = 1.9, H-15), 7.55–7.57 (m, 1H, H-16). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 14.5 (C-20), 17.5 (C-2), 21.3 (C-11), 22.0 (C-19), 32.3 (C-20), 32.3 (C-4), 37.6 (C-1), 40.8 (C-14), 41.9 (C-3), 43.1 (C-9), 45.7 (C-10), 49.2 (C-8), 61.7 (C-5), 82.6 (C-7), 107.3 (C-15) 113.0 (C-13), 142.1 (C-16), 151.9 (C-12), 172.4 (C-17), 200.2 (C-6).

2.2. Biological activities

2.2.1. Antiproliferative activity

The human cancer cell lines UACC-62 (melanoma), MCF-7 (breast), NCI-ADR/RES (ovarian expressing the resistance phenotype for adryamycin), 786–0 (kidney), NCI-H460 (lung, non-small cells), PC-3 (prostate), OVCAR-03 (ovarian), HT-29 (colon), and K562 (erythromyeloblastoid leukemia) were kindly provided by

Frederick Cancer Research & Development Center – National Cancer Institute – Frederick, MA, USA. Stock cultures were grown in 5 mL of RPMI 1640 (GIBCO BRL, Life Technologies) supplemented with 5% fetal bovine serum and 50 μg/mL gentamicine. Cells (100 μL cells/well) were exposed to various concentrations of furanditerpenes **1–4** (0.25–250 μg/mL) in DMSO (0.1% v/v) at 37 °C and 5% CO_2 for 48 h. Then, trichloroacetic acid solution (50%, v/v) was added, the plates incubated at 4 °C for 30 min, washed and dried. Cell proliferation was determined by spectrophotometric quantification (540 nm) of cellular protein content using sulforhodamine B assay [20]. Doxorubicin (DOX; 0.25–25 μg/mL) was used as a positive control. Three measurements were obtained at time zero (T_0) at the beginning of incubation and 48 h post-incubation for compound-free (C) and tested (T) cells. Cell proliferation was determined according to the equation $100 \times [(T - T_0)/C - T_0]$. Cytostatic effect was observed when $C > T \geqslant T_0$ while cytocidal effect occurred when $T < T_0$. GI_{50} (concentration of test substance that elicits 50% of cell growth inhibition) and TGI (concentration of test substance that elicits 100% of cell growth inhibition) values were determined by non-linear regression analysis using Origin software, version 7.5.

3. Results and discussion

3.1. Chemistry

The furanditerpene 6α,7β-dihydroxyvouacapan-17β-oic acid (**1**) was isolated from *P. polygalaeflorus* Benth fruits according to the procedure described by Mahajan and Monteiro [4]. Lactones **2** and **3** were obtained in quantitative yields from the treatment of compound **1** with acetic anhydride and sodium acetate in tetrahydrofurane at 45 °C for 1 h and 3 h, respectively. The lactone **4** was synthesized as reported elsewhere [19]. NMR spectral data of each compound are in agreement with the corresponding data published in the literature [4,13,18,19].

3.2. Biological activities

In the present study we have evaluated the effect of compound **1** and its derivatives 6α-hydroxyvouacapan-7β,17β-lactone (**2**), 6α-acetoxyvouacapan-7β,17β-lactone (**3**), and 6-oxovouacapan-7β,17β-lactone (**4**) on the proliferation of cancer cells of various histological origins (melanoma, UACC-62; breast, MCF-7; ovarian expressing the resistance phenotype for adryamycin, NCI-ADR/RES; kidney, 786–0; lung non-small cells, NCI-H460; prostate, PC-3; ovarian, OVCAR-03; colon, HT-29, and erythromyeloblastoid leukemia, K562). Cell proliferation was determined by spectrophotometric measurements using sulforhodamine B as a protein-binding dye and DOX (0.25–250 μg/mL) as a positive control. Compounds **1–4** were used at concentrations in the range of 0.25–250 μg/mL. The compound concentrations that elicit cell growth inhibition by 50% (GI_{50}) or 100% (TGI) were determined after 48 h of cell treatment.

Compounds **2** and **4** exhibited antiproliferative activity against the tested cancer cells in a concentration-dependent fashion (Fig. 2). The furanditerpene **2** was more active than compound **4** against the cancer cell lines studied (Fig. 2B and D). Compounds **1** and **2** were cytotoxic to six cancer cell lines when used at 250 μg/mL; the former was cytostatic against HT-29, K562, and MCF-7 cells while the latter was cytostatic against HT-29, K562,

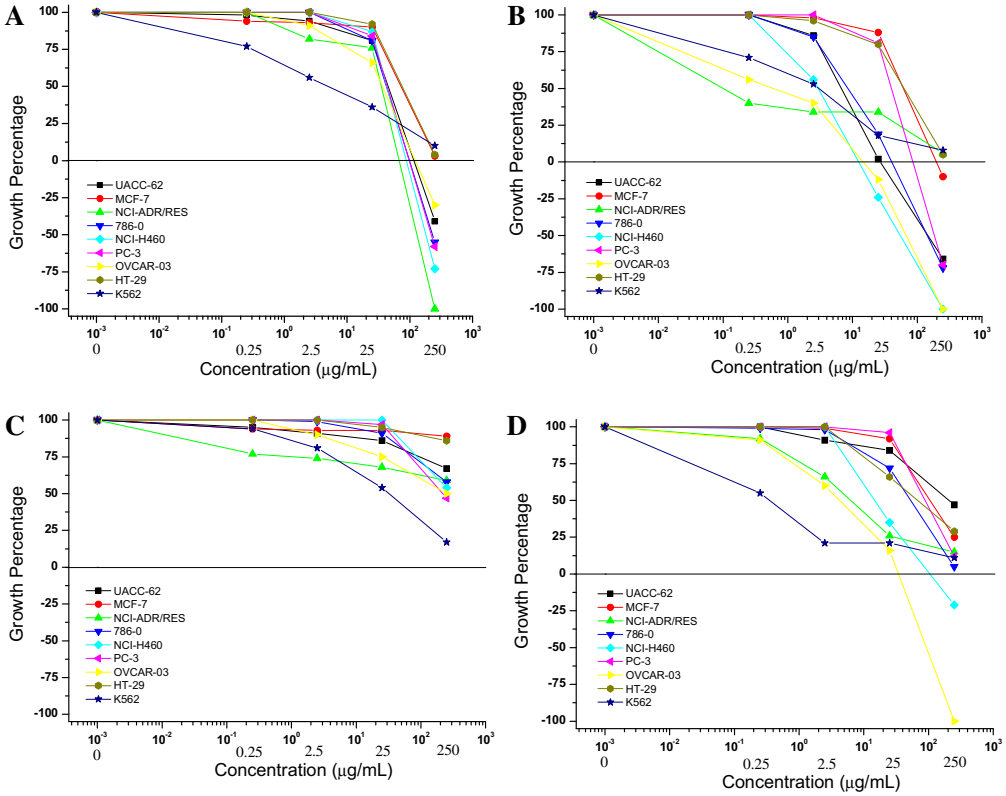

Fig. 2. Effect of furanditerpenes on the proliferation of cancer cells. Human cancer cells were treated with furanditerpene **1** (**A**), furanditerpene **2** (**B**), furanditerpene **3** (**C**) or furanditerpene **4** (**D**). After 48 h of exposure, cell growth was analyzed according to the described in Section 2. UACC-62, melanoma cells; MCF-7, breast cancer cells; NCI-ADR/RES, adryamycin-resistance ovarian cancer cells; 786-0, kidney cancer cells; NCI-H460, lung, non-small cancer cells; PC-3, prostate cancer cells; OVCAR-03, ovarian cancer cells; HT-29, colon cancer cells; K562, erythromyeloblastoid leukemia cells. Data are geometric means of a representative experiment done in triplicate. Standard errors were lower than 5%.

Table 1
Comparison of antiproliferative activity, in μg/mL, of 6α,7β-dihydroxyvouacapan-17β-oic acid (**1**), 6α-hydroxyvouacapan-7β,17β-lactone (**2**), 6α-acetoxyvouacapan-7β,17β-lactone (**3**), and 6-oxovouacapan-7β,17β-lactone (**4**) against human cancer cell lines.

Compound	UACC-62		MCF-7		NCIADR/RES		786-0		NCI-H460		PC-3		OVCAR-03		HT-29		K562	
	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI	GI_{50}	TGI
1	30.4	130.9	61.2	>250	26.8	43.2	30.4	110.6	31.6	97.1	31.6	111.3	27.4	130.1	68.0	>250	4.6	>250
2	5.2	30.0	27.7	213.7	0.3	>250	8.8	37.3	2.5	12.4	30.8	91.9	0.5	8.8	52.5	>250	2.1	>250
3	>250	>250	>250	>250	>250	>250	>250	>250	>250	>250	231.5	>250	>250	>250	>250	>250	27.4	>250
4	218.7	>250	122.2	>250	6.7	>250	43.9	>250	23.1	112.7	102.9	>250	3.9	25.3	71.5	>250	0.4	>250
DOX	0.2	0.5	0.5	>25	1.6	>25	0.2	4.6	0.2	4.3	0.9	5.1	0.3	2.3	1.2	>25	7.4	>25

GI_{50} is the concentration of compound (μg/mL) that elicits the inhibition of cell growth by 50%; TGI is the concentration of compound (μg/mL) that elicits total inhibition of cell growth; DOX refers to the positive control drug doxorubicin. Data are geometric means of a representative experiment done in triplicate.

and NCI-ADR/RES (Fig. 2A and B). At the same concentration (250 μg/mL), compound **4** was cytotoxic to OVCAR.03 and NCI-H460 only. Compound **3** does not present effect against any of the cell lines assayed (GI_{50} > 250 μg/mL), except for K562 with a marginal activity (GI_{50} = 27.4 μg/mL) (Fig. 2C).

Table 1 shows that compound **2** was more potent than compound **1** against all cancer cell lines studied, except prostate cells (PC-3), in which both compounds exhibited similar potencies. By comparing GI_{50} values, compound **2** was 55- and 89-fold more potent than compound **1** in inhibiting the growth of ovarian cancer (OVCAR-03) cells and adryamycin-resistant ovarian cancer cells (NCI-ADR/RES), respectively. Additionally, compound **2** inhibited by 50% the growth of non-small lung cancer cells (NCI-H460) and melanoma cells (UACC-62) at a concentration 12- and 6-fold lower than that of compound **1**, respectively. The GI_{50} values for compound **2** against kidney (786–0) and breast (MCF-7) cancer cells were, respectively, 3- and 2-fold lower than those determined for compound **1** against the same cell lines (Table 1).

Interestingly, compound **2** was 5-fold more potent than the reference drug doxorubicin (DOX) in inhibiting the growth of adryamycin-resistant ovarian (NCI-ADR/RES) cancer cells. In addition, compound **2** was as potent as DOX against ovarian (OVCAR-03) cancer cells. Compound **2** was also more potent than compound **1** and DOX against erythromyeloblastoid leukemia (K562) cells (2- and 3-fold, respectively). It is noteworthy that compound **4** was the most potent growth inhibitor of erythromyeloblastoid leukemia (K562) cells, reducing the cell growth by 50% at a concentration that is 19-fold lower (0.4 μg/mL) than the concentration of DOX necessary to promote a similar effect (Table 1). Compound **4** also presented significant antiproliferative activity against ovarian (OVCAR-03; GI_{50} = 3.9 μg/mL) and adryamycin-resistant ovarian (NCI-ADR/RES; GI_{50} = 6.7 μg/mL) cancer cells while the activity against non-small lung (NCI-H460) was weak (Table 1). Although the number of tested compounds is reduced to establish a structure-activity relationship, it seems that the substitution at C-6 is more relevant than the lactone ring for the antiproliferative activity of these furanditerpenes. Thus, the most active compounds against the majority of the cell lines (**1** and **2**) present a hydroxyl group at C-6. Moreover, the most selective one (**4**) showed a carboxyl group at the same position. On the other hand, compound **3**, which was inactive against all cell lines, also presents a lactone moiety.

Compound **2** completely inhibited the cell growth of five cancer lines when employed at concentrations lower than 100 μg/mL. TGI values for compound **2** were in the range of 8.8–91.9 μg/mL against ovarian (OVCAR-3), non-small lung (NCI-H460), melanoma (UACC-62), kidney (786-0), and prostate (PC-3) cancer cells. Compound **1**, when used at 43.2 μg/mL, was able to completely inhibit the growth of adrymycin-resistant ovarian (NCI-ADR/RES) cancer cells while a higher concentration of this compound (97.1 μg/mL) was required to cause a similar effect on non-small lung (NCI-H460) cancer cells (Table 1). Compound **4** was able to completely abolish OVCAR-03 cells growth at a concentration of 25.3 μg/mL (Table 1). Concentration higher than 230 μg/mL is necessary for compound **3** to cause total growth inhibition of all cell lines studied.

4. Conclusion

The furanditerpene 6α,7β-dihydroxyvouacapan-17β-oic acid (**1**) and its derivatives 6α-hydroxyvouacapan-7β,17β-lactone (**2**), and 6-oxovouacapan-7β,17β-lactone (**4**) presented interesting antiproliferative activities against the human cancer cell lines studied. Erythromyeloblastoid leukemia cells (K562) were highly sensitive to compound **4** while ovarian cancer cells (NCI-ADR/RES and OVCAR-03) were highly sensitive to compound **2** (also exhibited high selectivity). These results point out the furanditerpene **2** as the most promising lead compound among the other furanditerpenes for further studies especially with ovarian cancer cells. The synthesis of new correlated vouacapanoids and studies on their mechanism of action on cancer cells are in progress in our laboratories.

Acknowledgments

The authors are thankful to Dr. Luzia V. Modolo for critical reading of the manuscript. This work was supported by FAPEMIG (Fundação de Amparo a Pesquisa no Estado de Minas Gerais) and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico).

References

[1] M.P. Correa, Dicionário das plantas úteis do Brasil e das plantas exóticas cultivadas, Imprensa Nacional/MA-IBDF, Rio de Janeiro, 1978.
[2] W.B. Mors, M. Fascio, J.H. Monteiro, B. Gilbert, J. Pellegrino, Science 157 (1967) 950.
[3] M. Fascio, W.B. Mors, B. Gilbert, J.R. Mahajan, M.B. Monteiro, D. Santos-Filho, W. Vichnewski, Phytochemistry 15 (1976) 201.
[4] J.R. Mahajan, M.B.J. Monteiro, Chem. Soc. Perkin Trans I (1973) 520.
[5] S.G. Ruggiero, B.L. Rodrigues, N.G. Fernandes, G.M. Stefani, D. Piló-Veloso, Acta Cryst. C53 (1997) 982.
[6] E.A. Nunan, M.G. Carvalho, D. Piló-Veloso, R.M.M. Turchetti-Maia, D.L. Ferreira-Alves, Braz. J. Med. Biol. Res. 15 (1982) 450.
[7] I.D.G. Duarte, D.L. Ferreira-Alves, D. Piló-Veloso, M.J. Nakamura-Craig, Ethnopharmacology 55 (1996) 13.
[8] A.J. Demuner, L.C.A. Barbosa, D. Piló-Veloso, D.L. Ferreira-Alves, O.W. Howarth, J. Nat. Prod. 59 (1996) 770.
[9] A.J. Demuner, L.C.A. Barbosa, D. Piló-Veloso, D.L. Ferreira-Alves, O.W. Howarth, Aust. J. Chem. 51 (1998) 61.
[10] V.J. Belinelo, G.T. Reis, G.M. Stefani, D.L. Ferreira-Alves, D. Piló-Veloso, J. Braz. Chem. Soc. 13 (2002) 830.
[11] M.M.M. Rubinger, P.A. Castelo-Branco, S. Guilardi, E.M.R. Souza, M.T.P. Gambardella, E.L. Borges, D.L. Ferreira-Alves, D. Piló-Veloso, J. Braz. Chem. Soc. 15 (2004) 219.
[12] M.C.C. Silva, C.R.M. Gayer, C.S. Lopes, N.O. Calixto, P.A. Reis, C.P.B. Passaes, M.C.S. Paes, R. Dalmau, K.C.C. Sabino, A.R. Todeschini, M.G.P. Coelho, J. Pharm. Pharmacol. 54 (2004) 135.
[13] B. King-Díaz, F.J.L. Santos, M.M.M. Rubinger, D. Piló-Veloso, B. Lotina-Hennsen, Z. Naturforsh 61C (2006) 227.
[14] B. King-Díaz, A. Pérez-Reyes, F.J.L. Santos, D.L. Ferreira-Alves, D. Piló-Veloso, S.U. Carvajal, B. Lotina-Hennsen, Pestic. Biochem. Phys. 84 (2006) 109.

[15] P.A. Castelo-Branco, F.J.L. Santos, M.M.M. Rubinger, D.L. Ferreira-Alves, D. Piló-Veloso, B. King-Díaz, B. Lotina-Hennsen, Z. Naturforsh 63C (2008) 251.
[16] C.R. Vieira, M.F. Marques, P.R. Soares, L. Matuda, C.M.A. Oliveira, L. Kato, C.C. Silva, L.A. Guillo, Phytomedicine 15 (2008) 528.
[17] H.M. Spindola, J.E. de Carvalho, A.L.T.G. Ruiz, R.A.F. Rodrigues, C. Denny, I.M.Q. Sousa, J.Y. Tamashiro, M.A. Foglio, J. Braz. Chem. Soc. 20 (2009) 569.
[18] M.M.M. Rubinger, D. Piló-Veloso, G.M. Stefani, D.L. Ferreira-Alves, J. Braz. Chem. Soc. 2 (1991) 124.
[19] P.A. Castelo-Branco, M.M.M. Rubinger, J.M. Resende, A.A. Silva, D.L. Ferreira-Alves, D. Piló-Veloso, J. Chem. Res. 6 (2006) 351.
[20] A. Monks, D. Scudeiro, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Campbell, J. Mayo, M. Boyd, J. Nat. Can. Inst. 83 (1991) 757.