This is the authors' draft manuscript. Please kindly cite the paper as Awang, K., Loong, X.-M, Leong, K.H., Supratman, U., Litaudon, M., Mukhtar, M.R., Mohamad, K. 2012. Triterpenes and steroids from the leaves of Aglaia exima (Meliaceae). Fitoterapia. 83:1391-1395. The full version of the paper is available at the publisher's website through this link:
http://www.sciencedirect.com/science/article/pii/S0367326X12002808

Triterpenes and Steroids from the Leaves of *Aglaia exima* (Meliaceae)

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ABSTRACT

A study on the leaves of *Aglaia exima* led to the isolation of one new and seven known compounds.; six triterpenoids and two steroids. Their structures were elucidated and analyzed mainly by using spectroscopic methods; 1D and 2D NMR, mass spectrometry, UV spectrometry and X-ray. All the triterpenoids and steroids were measured *in vitro* for their cytotoxic activities against eight cancer cell lines; lung (A549), prostate (DU-145), skin (SK-MEL-5), pancreatic (BxPC-3), liver (Hep G2), colon (HT-29), breast (MCF-7) and (MDA-MB-231). The new cycloartane triterpenoid, cycloart-24-ene-3-one-26-ol **1**, showed potent cytotoxic activity against colon (HT-29) cancer cell line (IC_{50} 11.5 μM).

Keywords: *Aglaia exima*; Meliaceae; Cycloartane; Cytotoxicity; Steroids; Cycloart-24-ene-3-one-26-ol

1. Introduction

The genus *Aglaia* is the largest genus of the family Meliaceae which has a total of 105 species and is widely distributed in subtropical and tropical forest of southern mainland China, Indo-Malaysian region and the Pacific Island [1]. Meliaceae is a family known for the presence of triterpenes which possess interesting biological activities such as hypoglycemia, anticancer, anti-inflamatory, antifeedant, insecticides and antitumor activities [2-3]. In this study, eight compounds, including five cycloartane-type triterpenoids (**1**-**5**); cycloart-24-ene-3β,26-diol **1**, cycloart-24-ene-3*β*,26-diol **2** [7,12], schizandronic acid **3** [9], 24(E)-3*β*-hydroxycycloart-24-ene-26-al **4** [10], vaticinone **5** [8], one dammarane-type triterpenoids; cabraleahydroxylactone **6** [11,13], and two steroids (**7**-**8**); *β*-sitosterol **7** [4,5,6], stigmast-5-ene-28-one **8**, were isolated from the leaves of *Aglaia exima* (Fig. 1). We herein report the isolation and structure elucidation of the new cycloartane; cycloart-24-ene-3β,26-diol **1**, together with the cyctotoxicities of compounds **1**-**7** against eight cancer cell lines, lung (A549), prostate (DU-145), skin (SK-MEL-5), pancreatic (BxPC-3), liver (Hep G2), colon (HT-29) and breast (MDA-MB-231).

Footnote This article is dedicated to Prof. Dr. Atta-ur-Rahman who is a great inspiration to all Natural Products scientists.

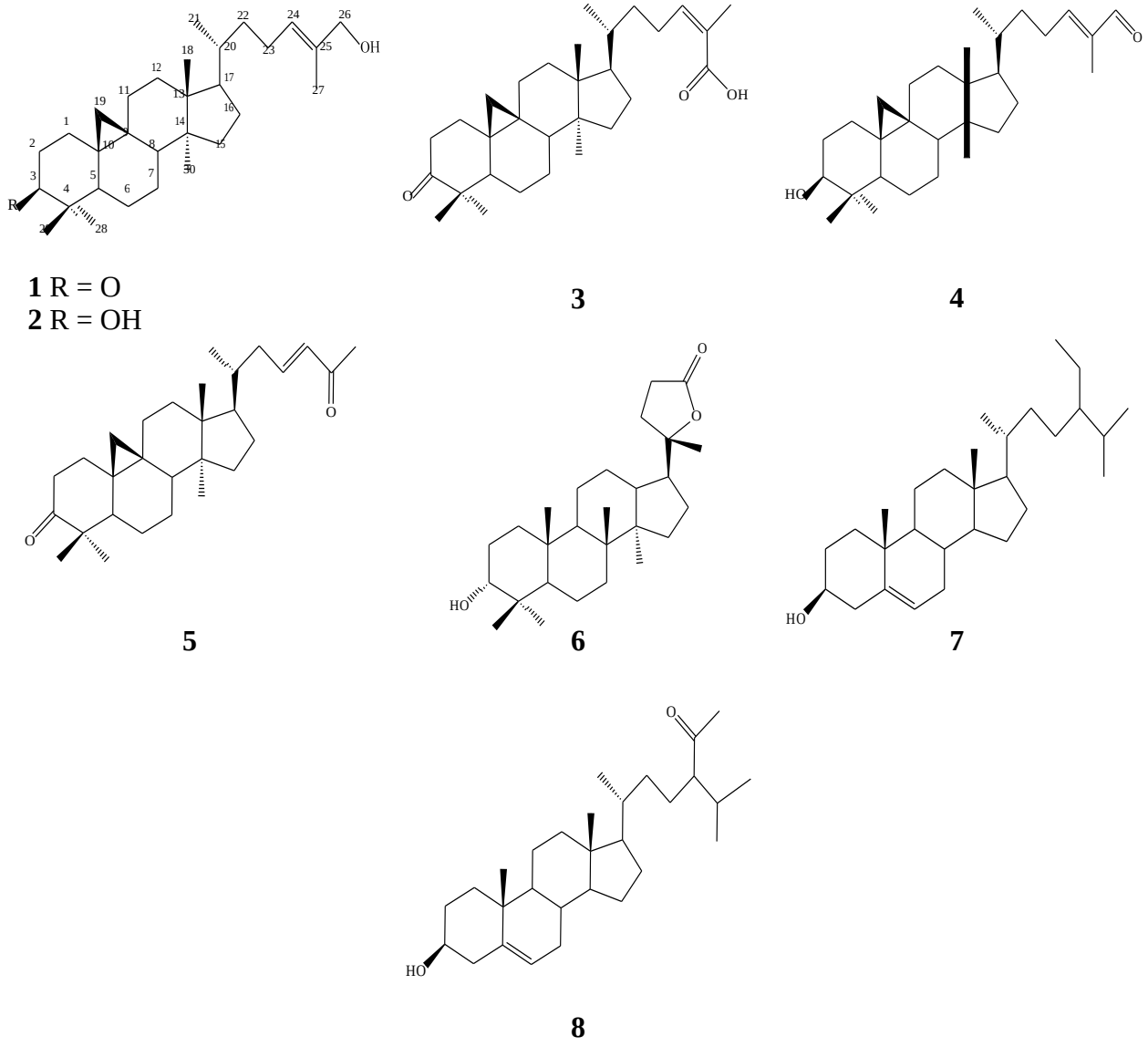

Fig. 1. The molecular structure of compounds **1**-**8**

2. Experimental

2.1 General

The specific rotations were determined on Jasco P-1020 Polarimeter. UV spectra were measured by using Shimazu UV- 160A ultraviolet-visible spectrometer with methanol. IR spectra were recorded by Perkin Elmer 1600 Series FT-NMR. ^{1}H, ^{13}C, DEPT, HSQC and HMBC NMR spectra were measured on JEOL JNM- LA 400 FT-NMR and JEOL ECA 400. Mass spectra were obtained by Shimadzu LCMS-IT-TOF Liquid Chromatograph Mass Spectrometer. Solvents were distilled prior to use, and spectroscopic grade solvents were employed. Column chromatography (CC) was carried out on Merck silica gel 60 (70-230 mesh and 230-400 mesh)

and TLC on silica gel Merck 60 GF_{254}. Spots on the plates were detected under UV light and visualized by spraying with vanillin reagent then followed by heating.

2.2 Plant material

The leaves of *Aglaia exima* was collected from H.S. Kg. Kepayang, Pahang, Malaysia on November 1997 and identified by Mr. Teo Leong Eng (University Malaya). Voucher specimen (KL 4762) has been deposited at the Herbarium of Department of Chemistry, University of Malaya, Kuala Lumpur, Malaysia.

2.3 Plant extraction

Dried ground leaves (1 kg) of *Aglaia exima* were extracted exhaustively with hexane at room temperature for 4 days and then filtered. The solution was decanted and then evaporated to give a residue of 25 g hexane extracts. 15 g of the hexane crude was subjected to column chromatography over silica gel using a gradient mixture of hexane and ethyl acetate as eluent. A total of 123 fractions were obtained and Fr. 54 gave crystals which is compound **7** (34.2 mg). Further isolation of Fr. 67 (ethyl acetate-hexane 86:14, 0.72 g) by CC with silica gel gave **5** (6.5 mg), **1** (19.1 mg), **4** (25.6 mg) and **8** (5.1 mg). Fr. 94 to Fr. 100 (ethyl acetate- hexane 60:40 50:50 20:80, 1.5398 g) were combined and further isolated by CC on silica gel to furnish **3** (16.3 mg) and **6** (2.9 mg). Of 123 fractions, Fr. 92 was collected as crystals which were then recrystallized by ethyl acetate to give a colorless crystal **2** (93.6 mg).

*2.5 Spectroscopic data of compound*s

Compound **1**. Colorless amorphous solid, $[\alpha]_D^{27.7}$ +29.7^o (c 0.00209, CH_2Cl_2); IR (KBr): 3445, 2942, 1705; UV (MeOH): 237 nm; HRESI-MS: *m/z* 463.3813 $[M+Na]^+$ calculated *m/z* 463.3678, ^{1}H- and ^{13}C- NMR data: see Table 1

Compound **8**. Colorless crystal; $[\alpha]_D^{27.4}$ -75.0^o (c 0.00008, CH_2Cl_2); IR (KBr): 3419, 2934, 2852, 1713 cm^{-1}; UV (MeOH): 208 nm; EI-MS (*m/z* rel int): 428 *m/z*; ^{1}H- and ^{13}C- NMR data: see Table 1

2.6 In vitro assay for cytotoxic activity

2.6.1 Cell lines

The hexane extract of the leaves from *A. exima* was investigated for cytotoxic activity against eight cancer cell lines; lung (A549), prostate (DU-145), skin (SK-MEL-5), pancreatic (BxPC-3), liver (Hep G2), colon (HT-29), breast (MCF-7) and (MDA-MB-231). These cancer cell lines were chosen from the National Cancer Institute (NCI) list of 60 cancer cell lines for drug screening and drug treatment conditions were done according to the NCI recommendations (Boyd, 1995). The human cancer cell lines were obtained from American Type Culture Collection (ATCC) (Manassas, VA, USA). Dulbecco's modified Eagle's medium (DMEM), 100 mM non-essential amino acids, phosphate buffer solution (pH 7.2), 50 µg/ml gentamycin and 2.5 µg/ml amphotericin B were purchased from Invitrogen Corporation (Carlsbad, CA, USA). 200 mM L-glutamine, foetal bovine serum, 0.25% trypsin-EDTA, dimethyl sulphoxide (DMSO),

cisplatin and vinblastine sulphate were purchased from Sigma–Aldrich (St. Louis, MO, USA). MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium, inner salt] assay kit (CellTiter 96® AQ_{ueous} One Solution) was obtained from Promega (Madison, WI, USA).

2.6.2 Cytotoxic assay

Cell lines were cultured in DMEM media supplemented with 2 mM L-glutamine, 10% foetal bovine serum, 50 µg/ml gentamycin and 2.5 µg/ml amphotericin B, maintained in a 37 ºC humid atmosphere of 5% CO_2 cell incubator. Samples and drug standards (cisplatin and vinblastine sulphate) were dissolved in DMSO and immediately diluted with DMEM media to yield a final DMSO concentration of less than 0.5% v/v.

Cells were plated into 96-well microplates at 5,000–10,000 cells per well and maintained in the cell incubator for 24 hour. Then, 100 µL of samples were introduced in triplicates to a final concentration of 15–200 µM, with the exception of sample **1** that was further diluted down to 4 µM in BxPC-3 and HT-29 cell lines. Drug standards were also introduced to a final concentration of 0.03 - 2000 µM (cisplatin) and 0.002 - 100 µM (vinblastine sulphate). Cells were further incubated for 48 hours and then, cell viability was determined according to the manufacturer protocol of a commercial MTS assay kit (CellTiter 96 AQ_{ueous}® One Solution, Promega). Culture media were carefully refreshed with 100 µL of DMEM media, followed by 20 µL per well of MTS reagent. Microplates were returned to the incubator for 1 to 2 hours and absorbance of the formazan product was read on a microplate reader at 490nm with 690nm as the background wavelength (Infinite 200, Tecan, Männedorf, Swizerland). IC_{50} of samples and drug standards were determined using dose-response curves in Prism 5.02 software (GraphPad Software Inc., La Jolla, CA, USA).

3. Results and discussion

Compound **1**, was obtained as colorless amorphous solid, $[\alpha]_D^{27.7}$ +29.7^o (c 0.00209, CH_2Cl_2). The HR-ESI-MS spectrum showed an $[M+Na]^+$ pseudomolecular ion peak at m/z 463.3813 (calcd 463.3678) which corresponded to the molecular formula of $C_{30}H_{48}O_2$. The IR spectrum showed absorption peaks at 3445, 2942, 1705cm^{-1} suggesting the presence of hydroxyl, alkyl and carbonyl groups respectively. The cycloartane nature of **1** was deduced by the appearance of a pair of very shielded doublets at δ 0.58 and 0.79 (J = 4.4 Hz). The olefinic proton (H-24) resonated as a broad triplet at δ 5.36 (J= 7.1 Hz).). In addition, the oxymethylene protons which were attached to C-26 appeared as a broad singlet at δ 3.94. The ^{13}C NMR and DEPT spectra showed peaks corresponding to thirty carbons; six methyl, twelve methylene, five methine, and seven quaternary carbons. The peak at δ 216.7 is assignable to the ketonic carbonyl, C-3. In addition, the signals of the double bond carbons (C-24, C-25) appeared at δ 127.0 and δ 134.3 respectively. The methylene carbon C-26 of the side chain resonated downfield at δ 69.0 since it is attached to a hydroxyl group. The HMBC spectrum showed correlations of H-24 with C-26 and C-27, H-26 with C-24, C-25 and C-27 thus confirming the position of the double bond at C-24 and C-25 respectively. Furthermore, the location of the hydroxyl group on C-26 was also established by the HMBC correlations of H_2-26 with C-24, 25 and C-27. Thorough analysis of the DEPT, COSY, HSQC and HMBC spectra allowed the complete assignment of all protons and carbons (Table 1). Therefore, compound **1** was elucidated as cycloart-24-ene-3β,26-diol.

Compounds **2-7** were isolated by comparison of their NMR data with literature values, known compounds **2-7** were identified as cycloart-24-ene-3*β*,26-diol **2** [7,12], schizandronic acid **3** [9], 24(E)-3*β*-hydroxycycloart-24-ene-26-al **4** [10], vaticinone **5** [8], cabraleahydroxylactone **6** [11,13] and *β*-sitosterol **7** [4,5,6]. Compound **8** is a new natural product. It was previously synthesized by Ikekawa *et.al.* The complete proton and carbon assignments of **8** are listed in Table 1.

Table 1
^{1}H and ^{13}C NMR of Compound **1** and **8** in $CDCl_3$

Position	δH (p p m)	δC (p p m)	δH (p p m)	δC (p p m)
1	1.48 (*m*)	33.4	1.06 (*m*)	37.3
	1.78 (*m*)		1.79 (*m*)	
2	2.30 (*m*)	37.4	1.80 (*m*)	31.7
	2.70 (*ddd*, J_1= 7.3 Hz, J_2= 13.9 Hz, J_3= 21.2 Hz)			
3	-	216.7	3.50 (*m*)	71.9
4	-	50.2	2.21 (*m*)	42.4
5	1.52 (*m*)	48.4	-	140.8
6	1.50 (*m*)	21.5	5.32 (*d*, *J*= 6.9 Hz)	121.8
7	1.22 (*m*)	28.1	1.44 (*m*)	32.0
	1.84 (*m*)		1.92 (*m*)	
8	1.64 (*m*)	47.8	1.44 (*m*)	32.0
9	-	21.1	0.89 (*m*)	50.1
10	-	25.9	-	36.5
11	1.10 (*m*)	26.7	1.40 (*m*)	21.1
	1.98 (*m*)		1.44 (*m*)	
12	1.60 (*m*)	32.8	1.10 (*m*)	39.8
			1.96 (*m*)	
13	-	45.3	-	42.4
14	-	48.7	0.96 (*m*)	55.9
15	1.02 (*m*)	35.9	0.98 (*m*)	24.3
			1.52 (*m*)	
16	1.86 (*m*)	24.5	1.14 (*m*)	28.2
	2.02 (*m*)		1.74 (*m*)	
17	-	52.2	1.04 (*m*)	55.8
18	1.00 (s)	18.1	0.70 (*s*)	11.9
19	0.58 (*d*, *J*= 4.4 Hz)	29.5	1.00 (*s*)	20.1
	0.79 (*d*, *J*= 4.4 Hz)			
20	1.02 (*m*)	35.9	1.32 (*m*)	35.9
21	0.91 (*d*, *J*= 6.1Hz)	18.2	0.91 (*d*, *J*= 2.0 Hz)	18.5
22	1.24 (*m*)	35.5	0.88 (*m*)	33.9
			1.20 (*m*)	
23	1.08 (*m*)	25.8	1.32 (*m*)	25.4
	1.30 (*m*)		1.54 (*m*)	
24	5.36 (*t*, J_1= 7.1 Hz)	127.0	2.11 (*d*, *J*= 6.9 Hz)	60.6
25	-	134.3	1.78 (*m*)	30.2
26	3.94 (*s*)	69.0	0.87 (*d*, *J*= 2.2 Hz)	21.3
27	1.68 (s)	13.6	0.89 (*d*, *J*= 2.2 Hz)	20.1
28	1.05 (s)	22.2	-	213.5
29	1.10 (s)	20.7	2.09 (*s*)	30.0
30	0.91 (s)	19.3		

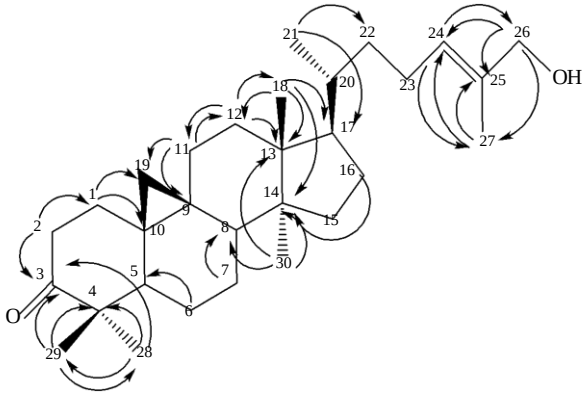

Fig. 2. Selected HMBC correlations of Compound **1**

Colon (HT-29) cancer cell line was found to be very susceptible towards cycloart-24-ene-3-one-26-ol **1** with IC_{50} values of 11.48 µg/ml. Meanwhile, cycloart-24-ene-3-one-26-ol **1** revealed moderate to skin (SK-MEL-5) and breast (MCF-7). Cycloart-24-ene-3β,26-diol **2** shows moderate effect against liver (Hep G2) and colon (HT-29), weak against lung (A549), skin (SK-MEL-5), breast (MCF-7) and (MDA-MB-231). Vaticinone **5** revealed moderate inhibitory effect towards colon (HT-29) and weak towards skin (SK-MEL-5). At last, 24(E)-3*β*-hydroxycycloart-24-ene-26-al **4** has moderate effect against breast (MDA-MB-231) and weak against skin (SK-MEL-5). schizandronic acid **3**, cabraleahydroxylactone **6**, *β*-sitosterol **7** and stigmast-5-ene-28-one **8** exhibited no significant inhibitory effects with IC_{50} values over 200 µM.

Table 2.
Cytotoxicity of Eight Compounds for Eight Cancer Cell Lines[a]

Name of Compounds	A549	DU-145	SK-MEL-5	BxPC-3	Hep G2	HT-29	MCF-7	MDA-MB-231
Cycloart-24-ene-3-one-26-ol **1**	-	-	96.6	-	-	11.5	86.2	-
Cycloart-24-ene-3*β*,26-diol **2**	172.4	-	157.8	-	75.1	99.3	127.7	195.2
Schizandronic acid **3**	-	-	-	-	-	-	-	-
24(E)-3*β*-hydroxycycloart-24-ene-26-al **4**	-	-	117.8	-	-	-	-	94.4
Vaticinone **5**	-	-	105.7	-	-	96.8	-	-
Cabraleahydroxylactone **6**	-	-	-	-	-	-	-	-
β- sitosterol **7**	-	-	-	-	-	-	-	-
Stigmast-5-ene-28-one **8**	-	-	-	-	-	-	-	-

[a] Results are expressed as IC_{50} values in µM . Blank indicates IC_{50} more than 200 µM

Table 3.
Cyctotoxicity of Drug Standards against Eight Cancer Cell Lines

Drug standards (Mean ± SD, n=3)	Cisplatin	Vinblastine
Lung (A549)	36.17 ± 3.00 µM	29.01 ± 6.46 µM
Prostate (DU-145)	12.54 ± 0.50 µM	4.75 ± 1.13 µM
Skin (SK-MEL-5)	68.86 ± 1.13 µM	1.71 ± 0.24 µM

Pancreatic (BxPC-3)	22.10 ± 0.31 µM	2.03 ± 1.05 µM
Liver (Hep G2)	15.20 ± 1.04 µM	0.35 ± 0.41 µM
Colon (HT-29)	70.19 ± 2.21 µM	0.98 ± 0.33 µM
Breast (MCF-7)	90.11 ± 2.11 µM	28.11 ± 3.20 µM
Breast (MDA-MB-231)	306.73 ± 3.45 µM	35.32 ± 3.42 µM

Acknowledgement

This work was supported by grant from the Institute of Research Management and Monitoring (IPPP) (PS344/2009C) and Fundamental Research Grant Scheme (FRGS). We thank D. M. Nor (University of Malaya) for the collection of plant material and Mr. Teo Leong Eng for the botanical identification. This work was carried out within the framework of an official agreement between University of Malaya (Malaysia) and CNRS.

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.

Table

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Schizandronic acid **3**	-	-	-	-	-	-	-	-
24(E)-3*β*-hydroxycycloart-24-ene-26-al **4**	-	-	117.8	-	-	-	-	94.4
Vaticinone **5**	-	-	105.7	-	-	96.8	-	-
Cabraleahydroxylactone **6**	-	-	-	-	-	-	-	-
β- sitosterol **7**	-	-	-	-	-	-	-	-
Stigmast-5-ene-28-one **8**	-	-	-	-	-	-	-	-

[a]Results are expressed as IC_{50} values in μM . Blank indicates IC_{50} more than 200 μM

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Liver (Hep G2)	15.20 ± 1.04 µM	0.35 ± 0.41 µM
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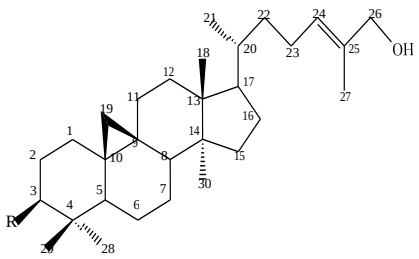
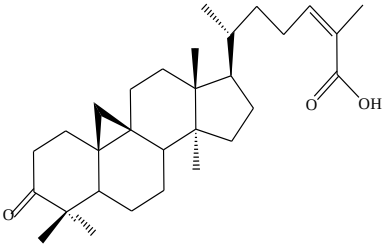
Breast (MCF-7)	90.11 ± 2.11 µM	28.11 ± 3.20 µM
Breast (MDA-MB-231)	306.73 ± 3.45 µM	35.32 ± 3.42 µM

Figure



1 R = O
2 R = OH



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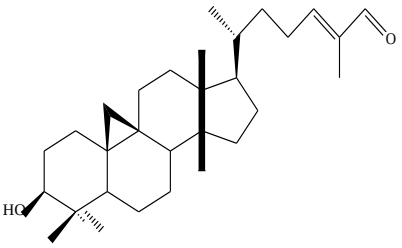

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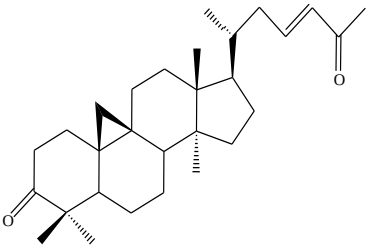

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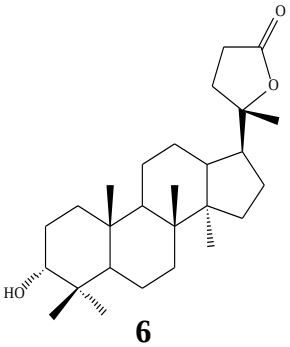

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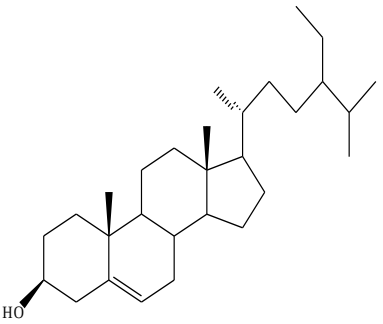

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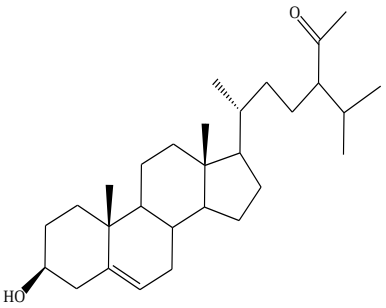

8

Fig. 1. The molecular structure of compounds **1**-**8**

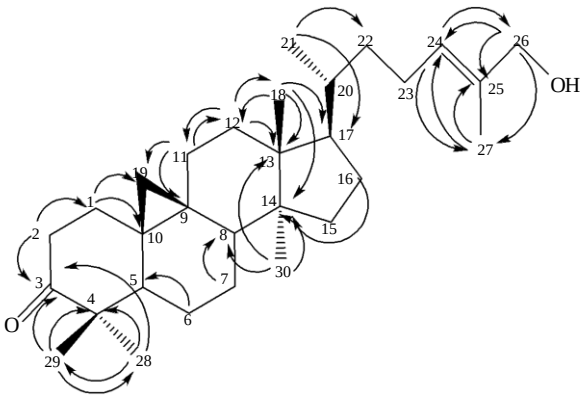

Fig. 2. Selected HMBC correlations of Compound **1**