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Original Research Article

New cytotoxic fatty acid esters from the black coral, *Antipathes dichotoma*

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Abstract

Purpose: *To isolate new fatty acid esters from Antipathes dichotoma and investigate their cytotoxic effects on HepG2, WI-38, VERO and MCF-7 cells.*
Methods: *Antipathes dichotoma was collected using scuba at a depth of 10 to 20 m from the Red Sea, and the lyophilized sample (1500 g) was exhaustively extracted thrice using a mixture of chloroform and methanol (1:1, v/v). The extract was concentrated using a vacuum rotatory evaporator to obtain a brown gummy paste which was fractionated on a silica gel chromatography column and further purified using preparative thin layer chromatography (PTLC). The chemical structures of the newly isolated compounds were elucidated by spectroscopic methods such as infrared (IR), nuclear magnetic resonance (NMR) and mass spectrometry (MS). The cytotoxicity of the isolated compounds was examined in HepG2, WI 38, VERO and MCF-7 cell lines.*
Results: *Three new aliphatic esters namely, (4Z, 7Z, 10Z, 13Z, 16Z)-1-hydroxynonadeca-4, 7, 10, 13, 16-pentaen-2-yl octanoate (1); (4Z, 7Z, 10Z, 13Z, 16Z)-1-hydroxynonadeca-4, 7, 10, 13, 16-pentaen-2-yl decanoate (2) and 1-hydroxynonadecan-2-yl-octanoate (3) were isolated from A. dichotoma. 1 and 2 displayed moderate cytotoxic activities against the examined cell lines with half-maximal inhibitory concentration (IC_{50}) ranging from 30.1 to 43.0 µg/mL, while compound 3 exhibited poor anti-cancer activity.*
Conclusion: *The results indicate that A. dichotoma is a reservoir of new compounds that have potential anticancer effects.*

Keywords: *Red Sea, Black coral, Antipathes dichotoma, Esters, Cytotoxicity*

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INTRODUCTION

Marine organisms live under tough environmental conditions such as high salinity, high pressure, variable nutrient accessibility and presence of predators [1]. Marine invertebrates produce chemical factors that enable them to evade predation and sense danger because they lack mechanical defense mechanisms [2,3]. These chemical factors have a broad spectrum of pharmaceutical applications [4-10]. Synthetic antimicrobial and antitumor agents produce a range of adverse effects such as bleeding in the gastrointestinal tract (GIT) and ulcer, renal tubular necrosis and cardiovascular diseases

(CVDs), while natural products have gained wide acceptance due to their safety profiles [11].

The zoanthid black coral, *Antipathes dichotoma* belongs to the *Antipathidae* family, and is known among local people as a source of remedies and charms [12]. Black coral of the genus *Antipathes* has been shown to contain carbazole, zoanthoxanthin alkaloids, polyhydroxy sterols and sphingolipids [13]. The carbazole and zoanthoxanthin alkaloids are cytotoxic to human stomach carcinoma SGC-7901 and HepG2 cells; polyhydroxy sterols are cytotoxic to *Artemia salina* [7, 14], and sphingolipids exhibit antimicrobial and antitumor activities [15,16].

Unsaturated fatty acids are widely distributed in plants and marine organisms. Polyunsaturated fatty acids reduce the risk of CVDs. Omega-3 and -6 unsaturated fatty acids slow down/prevent the development of cancers and inhibit arthritis-associated inflammation [17].

The aim of this work was to isolate new fatty acid esters from *Antipathes dichotoma* and investigate their cytotoxic effects on HepG2, WI-38, VERO and MCF-7 cells.

EXPERIMENTAL

General

Silica gel GF 254 was a product of Merck (Germany), AVANCE I000 NMR was a product of Bruker Co., Ltd. (Germany), while MTT assay kit was purchased from Trevigen, (USA). Thin layer chromatography (TLC) and PTLC were carried out using silica gel GF 254. A solution of equal volumes of concentrated sulfuric acid (H_2SO_4) and methanol (CH_3OH) was used as spray reagent. Freeze drying was carried out on VIRITIS Benchtop 4K Series, Model BT4KZL-105. One-dimension and two-dimension (COSY, HSQC and HMBC), NMR (400 MHz) and ^{13}C (100 MHz) spectra were carried out using deuterated chloroform ($CDCl_3$) and TMS (tetramethylsilane) as internal standards. HRESIMS spectra were recorded on liquid chromatography-mass spectrometer-IT (LCMS-IT).

Collection and processing of *Antipathes dichotoma*

Antipathes dichotoma samples were collected using scuba at a depth of 10 to 20 meter from the Red Sea coast at Haqel, Saudi Arabia. A voucher specimen (No. B.C. 2009.77) was prepared and kept at the Faculty of Marine Sciences, KAU. The samples were then transferred to the laboratory and immediately frozen and lyophilized. The lyophilized sample (1500 g) was exhaustively extracted thrice using a mixture of chloroform and methanol (1:1, v/v) at room temperature. The extract was concentrated using a vacuum rotatory evaporator to obtain a brown gummy paste.

A portion of the brown gummy residue (30 g) was well mixed with silica gel (60G) until homogenization. The obtained homogenous mixture was applied to Si-gel column for chromatographic separation of the extract constituents. After adsorption of the analyte material, elution process started with *n*-haxane and the polarity was gradually raised by adding volumes of ethylacetate followed by chloroform and finally methanol. The TLC was carried out using proper solvent system for elution and a spray reagent and/or ultraviolet light for visualization of spots. Further purification of promising spots was carried out by means of PTLC.

The column eluted fractions with solvent system *n*-hexane: ethylacetate (90:10, v/v), yielded 40.1 mg (dry wt.), which was then further purified by PTLC and using the same column elution system. PTLC purification yielded two bands: a) a brownish color band with spray reagent at R_f= 0.67, extraction and drying afforded oily material assigned for compound **1** (8.1 mg); b) the second band displayed also a brownish color with spray reagent at R_f= 0.75, extraction and drying afforded oily material assigned for compound **2** (10.0 mg). The column eluted fractions with solvent system *n*-hexane: ethylacetate (80:20, v/v), yielded 44.1 mg (dry wt.), which was then further purified by PTLC and using the same column elution system. PTLC purification yielded an orange band after spraying with 50% H_2SO_4 R_f= 0.42, extraction and drying afforded oily material assigned for compound **3** (7.7 mg).

Hydrolysis and methanolysis

The isolated compounds (5 mg) were refluxed with 1.0 M HCl in 90% aq. MeOH (5 ml) for 24 h. the resultant was fractionated between H_2O and Et_2O. The upper layer (Et_2O layer) was dried over anhydrous Na_2SO_4, and then directly injected in the GC-MS (QP 2014-mass spectrometry).

Cytotoxicity bioassays

Four cancer cell lines were selected as targets to estimate the bioactivity of the isolated new compounds **1**-**3** which are HepG2 (human hepatocellular liver carcinoma), WI 38 (human

lung fibroblast cell line), VERO (normal adult African green monkey kidney) (VERO) and MCF-7 (human caucasian breast adeno-carcinoma). The cytotoxicity evaluation was carried out using MTT assay, and percentage viability was determined using trypan blue dye exclusion technique [5]. 5-fluorouracil (positive control).

Statistical analysis

Graph Pad InStat software, version 3.05 was employed for statistical analysis. Data are expressed as mean SEM (n = 3), and were analyzed by ANOVA. $P < 0.05$ was considered statistically significant.

RESULTS

Spectra of isolated compounds

Elucidation of chemical structures was achieved after extensive analysis of their spectroscopic data and comparison with those reported in the literature.

***(4Z, 7Z, 10Z, 13Z, 16Z)-1-hydroxynonadeca-4,7,10,13,16-pentaen-2-yl octanoate* (1)**

Yellowish oil; $[\alpha]^{20}_D$ = -5.8 (CH_2Cl_2; *c* = 0.2); IR υ_{max} (neat) 3507 (OH), 1718 (ester C=O), 1675 (C=C), 1400 cm^{-1}; proton and carbon NMR δ (Table 1); HRESI-MS data *m/z* 416.3298 $[M]^+$ (calculated for $C_{27}H_{44}O_3$ 416.3290).

***(4Z, 7Z, 10Z, 13Z, 16Z)-1-hydroxynonadeca-4,7,10,13,16-pentaen-2-yl decanoate* (2)**

Colorless oil; $[\alpha]^{20}_D$ = -5.4 (CH_2Cl_2; *c* = 0.2); IR υ_{max} (neat) 3509 (OH), 1714 (ester C=O), 1679(C=C), 1400 cm^{-1}; proton and carbon NMR δ (Table 1); HRESI-MS data *m/z* 444.3611 $[M]^+$ (calculated for $C_{29}H_{48}O_3$ 444.3603).

***1-hydroxynonadecan-2-yl-octanoate* (3)**

Colorless oil; $[\alpha]^{20}_D$ = -3.9 (CH_2Cl_2; *c* = 0.2); IR υ_{max} (neat) 3508 (OH), 1724 (ester C=O), 1679(C=C), 1400 cm^{-1}; proton and carbon NMR δ (Table 1); HRESI-MS data *m/z* 442.4030 $[M]^+$ (calculated for $C_{27}H_{54}O_4$ 442.4022).

Cytotoxicity

The cytotoxic effects of all isolated compounds against HepG2, WI38, VERO and MCF-7 cancer cell lines are shown in table 2. Compounds **1** and **2** displayed moderate cytotoxic activities toward the four examined cell (IC_{50} is 69.1- 84.0 µg/mL) as presented in Table 1, while compound **3** showed weak activity. It is apparent the presence of multiple isolated double bonds enhanced the biological activity of the compound under evaluation.

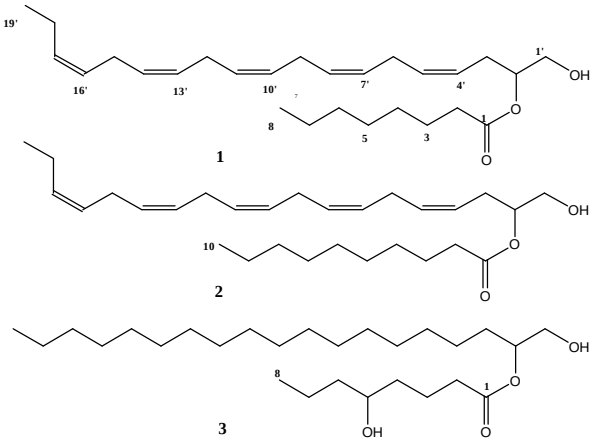

Figure 1: Compounds isolated from *A. dichotoma*

DISCUSSION

Compound **1** was isolated as an optically active yellowish oil. HR-ESIMS and ^{13}C NMR allowed the determination of its molecular formula as $C_{27}H_{44}O_3$, with parent peak detected at *m/z* 416.3298 $[M]^+$, referring to six sites of unsaturation. Hydrolysis and methanolysis [13] of compound **1** afforded the octanoic acid methyl ester $[CH_3(CH_2)_6$ COOMe, $M]^+$ at *m/z* 158 confirmed by base peak fragment $CH_3(CH_2)_6$ CO, $M\text{-OMe}]^+$at *m/z* 127 in the GC-MS. Consequently, the rest fragment of the molecule contains nineteen carbon atoms with five unsaturations. Again, the twenty seven carbon atoms (Table 1) have been recognized in the ^{13}C NMR spectrum, these carbon signals was further categorized with the aid of ^1H NMR spectrum and DEPT 135 experiment into two CH_3 groups, thirteen CH_2, an sp^3 oxygenated carbon (δ_C 68.9 ppm), ten sp^2 carbons, one carbonyl ester (δ_C 174.0). Therefore, compound **1** is acyclic aliphatic ester. The IR absorption at 3280 cm^{-1} and from both δ ^1H and ^{13}C NMR data δ_H/ δ_C (5.25/68.9) confirmed the occurrence of hydroxyl function.

2D NMR (HMQC) spectrum allowed all the carbon – proton association. The chemical structure of **1** was identified by analysis of COSY and HMBC spectra; signals from proton nuclear magnetic resonance were interpreted as follow: the first group constitutes 10 resonances assigned for ten olefinic protons (δ_H: 5.34- 5.44, m, H-4`, 5`, 7`, 8`, 10`, 11`, 13`, 14`, 16` and –H-17`) and a carbinol proton (δ_H 5.25, m, H-2`).

Table 1: ^1H and ^{13}C NMR data

Position	1		2		3	
	δ_C [b]	δ_H [c]	δ_C	δ_H	δ_C	δ_H
1	174.0		174.0		174.5	
2	34.0	2.2 m	34.1	2.2 m	34.2	2.2 m
3	25.6	1.3-1.33 m	25.6	1.3-1.33 m	25.6	1.3-1.33 m
4	29.7		29.7		31.9	
5	29.3		29.6		65.2	
6	29.9		29.9		29.3	
7	22.7		29.9		22.7	
8	14.2	0.88, t, 7.2	29.9		14.2	0.88, t, 7.2
9			22.7			
10			14.2	0.88, t, 7.2		
1`	62.1	4.2, dd, 6.0, 12.0 4.3, dd, 6.0, 12.0	62.1	4.2, dd, 6.0, 12.0 4.3, dd, 6.0, 12.0	63.2	4.2, dd, 6.0, 12.0 4.3, dd, 6.0, 12.0
2`	68.9	5.25, m	68.8	5.25, m	70.2	
3`	34.0	2.33-2.35, m	34.1	2.33-2.35, m	31.6	2.33-2.35, m
4`	127.0	5.35, m	127.0	5.35, m	24.9	1.2-1.4, m
5`	130.0	5.35, m	130.0	5.35, m	29.3	
6`	31.9	2.80, m	31.9	2.80, m	29.7	
7`	129.7	5.35, m	129.9	5.35, m	29.4	
8`	128.5	5.35, m	128.4	5.35, m	29.7	
9`	31.9	2.80, m	31.8	2.80, m	29.4	
10`	128.3	5.35, m	127.8	5.35, m	29.7	
11`	128.4	5.35, m	128.4	5.35, m	29.5	
12`	31.9	2.80, m	31.5	2.80, m	29.7	
13`	128.2	5.35, m	128.3	5.35, m	29.4	
14`	128.1	5.35, m	128.1	5.35, m	29.7	
15`	31.9	2.80, m	31.5	2.80, m	29.5	
16`	128.5	5.35, m	128.2	5.35, m	29.7	
17`	132.0	5.35, m	132.0	5.35, m	29.7	
18`	24.8	2.10, m	24.9	2.10, m	22.8	
19`	**14.2**	**0.88, t, 7.2**	**14.2**	**0.88, t, 7.2**	**14.2**	**0.88, t, 7.2**

Table 2: *In- vitro* cytotoxic effect of the isolated compounds

Compound no.	IC_{50} (µg/ml)[a]			
	HepG2[b]	***WI-38***	***VERO***	***MCF-7***
1	39.2 ± 2.03	43.0± 2.35	36.4± 2.14	42.5± 1.93
2	30.1± 2.00	33.3± 1.95	37.3± 1.65	30.9± 1.67
3	123.2± 3.01	105.0± 3.22	110.5± 4.00	96.6± 2.45
5-Fu[c]	8.6± 1.01	3.2 ±0.90	6.5 ±1.00	2.3 ±0.66

[a] *IC_{50},* (µg/ml): very strong = 1-10; strong = 11-25; moderate =26-50; weak = 51-100; very weak = 100-200 and non-toxic > 200 µg/ml)

Further confirmation came from correlations with ^{13}C signals (δ_C 127.0, C-4`), (130.0, C-5`), (129.7, C-7`), (128.5, C- 8`), (128.3, C-10`), (128.4, C- 11`), (128.2, C- 13`), (128.1, C- 14`), (128.5, C- 16`), (132.0, C- 17`), and (68.9, C-3`) employing HSQC spectral analysis. From the COSY spectrum of **1**, a large spin system between $H_3$-19 with $H_2$-18, $H_2$-18 with H-17`, H-17` with H-16`, H-16` with H-15` was observed.

HMBC displayed correlations between the resonances of between H-19` and those of C-18`, 17` and 16`; H-18` and C-16`, 17` and 19`; H-17` and C-15` and C-16` and C-18`. On these bases the fragment A was established. The second group contains 6 resonances in the low frequency region, 12 methylene protons (δ_H 2.38, m, H_2-2; 1.64, m, H_2-3; 1.22-1.30, m, H_2-4, H_2-5, H_2-6, H_2-7); along with methyl protons (δ_H 0.88, t, 7.2 Hz, H_3-8). Further confirmation came from the correlation with ^{13}C signals (δ_C 34.0, C-2), (25.5, C-3), (29.7, C-4), (29.3, C-5), (31.9, C-6), (22.7, C-7) employing HSQC spectral analysis.

Applying a similar data treatment, a ^1H–^1H spin system between H_3-8 with H_2-7; H_2-6 with H_2-7 and H_2-5 ; H_2-4 with H_2-5and H_2-3 and H_2-2 with H_2-3 were observed. HMBC displayed correlations between the resonances of between H_3-8` and those of C-7, C-6 and C-5; between $H_2$-5 and those of C-6 and C-4 and C-3, between H-2 and C-3 and C-4. On these bases the fragment B was established. The connection between the two fragments (A and B) was established based on the strong HMBC correlation between C-1` and H-2, H-3 and H_2-1.

Finally, **1** was identified as a new fatty acid ester; 4*Z*, 7*Z*, 10*Z*, 13*Z*, 16*Z*)-1-hydroxynonadeca-4, 7, 10, 13, 16-pentaen-2-yl octanoate.

Compound **2** was isolated as an optically active yellowish oily substance. HR-MS and ^{13}C NMR allowed the determination of its molecular formula as $C_{29}H_{48}O_3$, with parent peak detected as *m/z* 444.3611 $[M]^+$, referring to six unsaturations. Hydrolysis and methanolysis of compound **2** afforded the octanoic acid methyl ester $[CH_3(CH_2)_8$ COOMe, $M]^+$ at *m/z* 186 confirmed by base peak fragment $[CH_3(CH_2)_8$ CO, M-OMe$]^+$ at *m/z* 155 in the GC-MS. Therefore, the twenty nine carbon atoms (Table 1) were recognized in the ^{13}C NMR spectrum which were further categorized with the aid of ^1H NMR spectrum and DEPT 135 experiment into two CH_3 groups, fifteen CH_2, an sp^3 oxygenated methylene carbon (δ_C 68.8 ppm), ten sp^2 CH carbons, one carbonyl ester (δ_C 174.0). Therefore, compound **2** is acyclic aliphatic ester.

The IR absorption at 3280 cm^{-1} and from both δ ^1H and ^{13}C NMR data δ_H/ δ_C (5.25/68.8) confirmed the occurrence of hydroxyl function.

After extensive comparison between compounds **1** and **2**, compound **2** is 28 amu more than 1, indicating that 2 has two more methylene groups. Finally, literature survey assigned that **2**, is a new fatty acid ester; (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*)-1-hydroxynonadeca-4,7,10,13,16-pentaen-2-yl decanoate (**2**)**.**

Compound **3** was isolated as optically active yellowish oil. HR-MS and ^{13}C NMR allowed the determination of its molecular formula as $C_{27}H_{44}O_3$, with parent peak detected as *m/z* 444.3611 $[M]^+$, referring to six unsaturations. Hydrolysis and methanolysis of compound **3** afforded the octanoic acid methyl ester $[CH_3(CH_2)_6$ COOMe, $M]^+$ at *m/z* 158 confirmed by base peak fragment $CH_3(CH_2)_6$ CO, M-OMe$]^+$at *m/z* 127 in the GC-MS. Twenty seven carbon atoms (Table 1) have been recognized in the ^{13}C NMR spectrum, these further categorized with the aid of ^1H NMR spectrum and DEPT 135 experiment into two methyl groups, fifteen methylene, three sp^3 oxygenated a methine carbon (δ_C 68.8), ten sp^2 CH carbons, one carbonyl ester (δ_C 174.0). Therefore, compound **3** is acyclic aliphatic ester.

The molecular formula of **3**, $C_{27}H_{54}O_4$, was deduced from HREIMS *m/z* 442.4030 $[M]^+$. Hydrolysis and methanolysis [16] of compound **3** afforded the octanoic acid methyl ester $[CH_3(CH_2)_6$ CO_3Me, $M]^+$ at *m/z* 174 confirmed by base peak fragment $CH_3(CH_2)_6$ CO_2, M-OMe$]^+$at *m/z* 143 in the GC-MS. The ^1H, ^{13}C and DEPT NMR spectra of **3** displayed 27 carbon atoms (*cf exp*.), including 2 methyl groups, 22 methylenes (one of them oxygenated), 2 sp^3 methines (oxygenated), one carbonyl ester (δ_C 175.0). Therfore, the compound is an aliphatic ester. A hydroxyl function was evidenced IR (λ_{max} 3280 cm^{-1}) and ^{13}C NMR data.

From 2D NMR spectral measurements, the structure of **3** exhibited the absence of the downfield resonance of **3**, which indicated absence olefinic protons, but it showed the presence of two oxygenated methines (δ_H 4.15, H-2; δ_H 4.18, H-3`), corresponding to $^{13}C$ signals at $\delta_C$ 70.2 (C-2) and 65.1 (C-3`) through HSQC measurement. The COSY spectrum of **3** established the location of the hydroxyl groups (Figure 1). Finally, metabolite **3** is a new fatty acid ester; 1-hydroxynonadecan-2-yl-octanoate.

Compounds **1** and **2** displayed moderate cytotoxic effects toward all examined cell lines (IC_{50} is 69.1- 84.0 µg/mL) as presented in Table 1, while compound **3** showed weak activity. It is apparent the presence of multiple isolated double bonds enhanced the biological activity of the compound under evaluation.

CONCLUSION

The findings of this study indicate that *A. dichooma* is a reservoir of new compounds that have potential anticancer effects. However, *in vivo* investigations are required to ascertain their usefulness.

DECLARATIONS

Acknowledgement

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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