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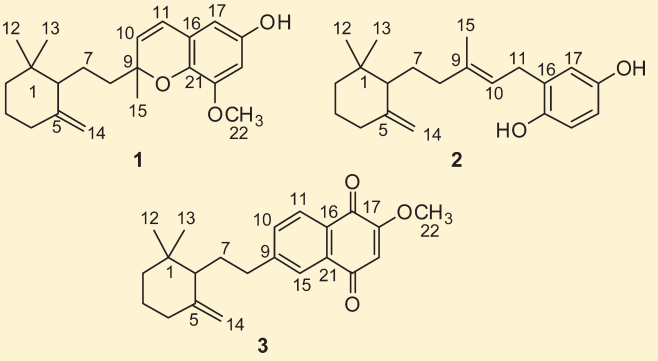
Metachromins U−W: Cytotoxic Merosesquiterpenoids from an Australian Specimen of the Sponge *Thorecta reticulata*

Simon P. B. Ovenden,[†] Jonathan L. Nielson,[‡] Catherine H. Liptrot,[§] Richard H. Willis, Dianne M. Tapiolas, Anthony D. Wright,[⊥] and Cherie A. Motti*

Australian Institute of Marine Science, PMB no. 3, Townsville MC, Townsville, QLD 4810, Australia

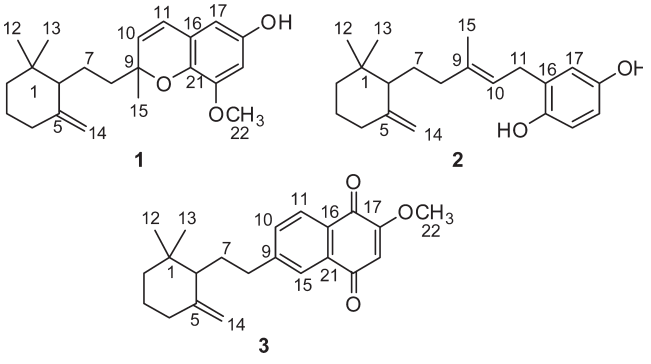
Supporting Information

ABSTRACT: Three new merosesquiterpenoids, metachromins U, V, and W (**1**−**3**), were isolated from a specimen of the marine sponge *Thorecta reticulata* collected off Hunter Island, Tasmania, Australia. Structures of the new compounds were elucidated through extensive NMR investigations and comparison with literature values. The cytotoxicities of **1**−**3** were assessed against a panel of human tumor cell lines (SF-268, H460, MCF-7, and HT-29) and a mammalian cell line (CHO-K1). All compounds were found to have 50% growth inhibition activities in the range 2.1−130 μM, with **2** being the most active (GI_{50} 2.1−10 μM).



Sponges from the family Thorectidae are proficient producers of secondary metabolites, including but not limited to manoalide,[1] aplysinopsin,[2] altohyrtins,[3] cacoxanthenes,[4] smenochromenes,[5] dictazolines,[6] and aignopsanes.[7] Despite this, there are only five reports describing the isolation of alkaloids,[2] carotenoids,[8] furanosesterterpenes,[9,10] and sesquiterpene quinones[11] from the genus *Thorecta*.

While screening EtOH extracts derived from marine macroorganisms for whole cell anticancer activity, an extract of the sponge *Thorecta reticulata* was found to have significant cytotoxicity in the NCI 60 cell line screen and an interesting COMPARE analysis.[12] Bioassay-guided fractionation of a MeOH extract of the sponge led to the isolation of three new merosesquiterpenoids, metachromins U−W (**1**−**3**). Described below are details pertaining to the isolation and structure elucidation of **1**−**3**, as well as their biological activity profiles against a panel of human tumor cell lines (SF-268, H460, MCF-7, and HT-29) and a normal mammalian cell line (CHO-K1).



Metachromin U (**1**) was isolated as a colorless oil with a molecular weight consistent with the molecular formula $C_{22}H_{30}O_3$ and corresponding to eight double-bond equivalents. Analysis of the NMR data for **1** (Table 1) revealed resonances consistent with 1,1-disubstituted (δ_C 151.2, 110.2; δ_H 4.48, d, J = 2.4 Hz, 4.68, d, J = 2.4 Hz) and 1,2-disubstituted double bonds (δ_C 132.9, 124.5; δ_H 5.62, d, J = 9.8 Hz, 6.26, d, J = 9.8 Hz) as well as a tetrasubstituted benzene ring (δ_C 152.6, 150.3, 136.8, 124.2, 106.1, 102.3; δ_H 6.09, d, J = 2.6 Hz, 6.34, d, J = 2.6 Hz). These correlations accounted for six double-bond equivalents and, in the absence of any other sp or sp^2 ^{13}C resonances, showed **1** was tricyclic. Further analysis of the NMR data for **1** (Table 1) revealed resonances consistent with five aliphatic methylenes, three methyl groups attached to quaternary carbons, two aliphatic quaternary carbons, one of which bears an oxygen (δ_C 79.8, 36.3), an aliphatic methine, and a methoxy moiety. The remaining hydrogen was assigned to a hydroxy group on the basis of the presence of a characteristic broad IR O−H absorbance at ν_{max} 3433 cm^{-1}, implying the remaining oxygen was an ether.

Continued analysis of the NMR data of **1** enabled two partial structures, A and B, to be elucidated (Figure 1). Partial structure A was readily identified through analysis of the ^{1}H−^{1}H coupling constants and the gHMBC data. Important gHMBC correlations from H-17 and H-19 to C-18 and C-21, from H-19 to C-20, and from H_3-22 to C-20 as well as the small coupling constant between H-17 and H-19 (J = 2.6 Hz) confirmed the presence of a 1,2,3,5-substituted benzene ring. Furthermore, the ^{13}C chemical shifts of C-18 (δ_C 152.6), C-20 (δ_C 150.3), and C-21 (δ_C 136.8) were indicative of oxygenated substituents at these positions.

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Table 1. NMR Spectroscopic Data (300 MHz, CD_3OD) for Metachromin U (1)

no.	δ_C, mult.[a]	δ_H (J in Hz)[b]	gHMBC[c]
1	36.3, C		
2	37.6, CH_2	1.50, m	4, 6, 12
		1.20, m	4, 6, 12
3	25.2, CH_2	1.49, m	1, 5
4	33.6, CH_2	1.93, m	2, 3, 5, 14
5	151.2, C		
6	56.0, CH	1.64, t (9.1)	1, 4, 5, 7, 8, 14
7	22.1, CH_2	1.64, m	5, 6, 9
		1.47, m	5, 9
8	40.5, CH_2	1.57, m	7, 9, 15
		1.37, m	7
9	79.8, C		
10	132.9, CH	5.62, d (9.8)	9, 16
11	124.5, CH	6.26, d (9.8)	9, 16, 17, 21
12	29.3, CH_3	0.88, s	1, 2, 6, 13
13	27.4, CH_3	0.80, s	1, 2, 6, 12
14	110.2, CH_2	4.68, d (2.4)	4, 6
		4.48, d (2.4)	4, 6
15	26.7, CH_3	1.33, s	8, 9, 10
16	124.2, C		
17	106.1, CH	6.09, d (2.6)	11, 16, 18, 19, 21
18	152.6, C		
19	102.3, CH	6.34, d (2.6)	17, 18, 20, 21
20	150.3, C		
21	136.8, C		
22	57.0, CH_3	3.77, s	20

[a] 75 MHz. [b] 300 MHz. [c] HMBC correlations are from proton(s) stated to the indicated carbons.

Additional gHMBC correlations from H-10 and H-11 to C-16 and from H-11 to C-21 established the 1,2-disubstituted double bond to be pendant at C-16. Further, gHMBC correlations from H_3-15 to C-8, C-9, and C-10 and NOE-induced enhancement of resonances associated with the olefinic protons H-11 and H-10 caused by irradiation of H_3-15 (δ_H 1.33) allowed partial structure A to be elucidated as shown (Figure 1). The observation of gHMBC correlations from H_3-12 and H_3-13 to C-1, C-2, and C-6, from H_2-14 to C-4 and C-6, and from H_2-3, H-6, and H_2-7 to C-5, and vicinal COSY correlations from H_2-3 to H_2-2 and H_2-4, allowed partial structure B (Figure 1) to be identified as shown. The observation of a gHMBC correlation from H-6 to C-8, as well as a COSY correlation from H_2-7 to H_2-8, established that partial structures A and B were connected between C-7 and C-8. Finally, the magnitude of the $^1H-^1H$ coupling constant for $\Delta^{10,11}$ (J = 9.8 Hz) was consistent with a Z configuration, as would be expected if the double bond was associated with a dihydropyran ring formed via an ethereal bridge between C-9 and C-21. This was supported by the ^{13}C chemical shifts of C-9 (δ_C 79.8) and C-21 (δ_C 136.8). Consequently it was deduced that the hydroxy moiety was positioned at C-18 (δ_C 152.6). Hence, the planar structure of **1** is as shown. Literature analysis established **1** to be structurally similar to the known metachromins B,[13] D,[14] K,[15] and T.[16] The configurations at C-6 and C-9 remain unassigned at this time.

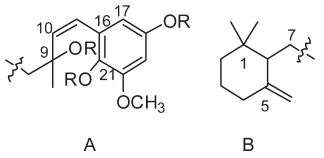

Figure 1. Partial structures A and B of metachromin U (**1**).

Metachromin V (**2**) was isolated as a colorless oil with a molecular weight consistent with the molecular formula $C_{21}H_{30}O_2$ and corresponding to seven double-bond equivalents. Immediately apparent in the NMR data for **2** (Table 2) was the same terminal cyclohexane moiety as present in **1**. Also evident in the NMR data for **2** were resonances consistent with a 2-substituted 1,4-dihydroxy benzene ring (δ_C 149.0, 148.0, 128.0, 116.8, 116.6, 113.8; δ_H 6.68, d, J = 8.4 Hz, 6.61, d, J = 2.6 Hz, 6.58, dd, J = 8.4, 2.6 Hz) and a trisubstituted double bond (δ_C 120.6, 139.0; δ_H 5.27, t, J = 7.2 Hz). These observations accounted for all of the double-bond equivalents, indicating the presence of an aliphatic linkage between the two rings.

Analysis of the COSY and gHMBC data for **2** enabled the aliphatic linkage between the two rings to be established. Observed COSY correlations from H_2-7 to H-6 and H_2-8 and from H-10 to H_2-11, as well as gHMBC correlations from H_2-11 to C-16, C-17, and C-21 and from H_2-7 and H_2-8 to C-6, established the planar structure of **2** as shown. The structure of **2** was similar to those for the known compounds metachromins A[13] and C.[17] Comparison of the ^{13}C NMR data for C-15 of **2** (δ_C 16.6) with those of metachromins A (δ_C 16.4) and C (δ_C 16.2) established an E geometry about $\Delta^{9,10}$. The configuration at C-6 remains unassigned.

Metachromin W (**3**) was isolated as a yellow oil with a molecular weight consistent with the molecular formula $C_{22}H_{26}O_3$ and corresponding to 10 double-bond equivalents. Analysis of the NMR data for **3** (Table 2) readily identified the same terminal cyclohexane moiety found in both **1** and **2**. Further comparison of the NMR data of **3** with those of **2**, however, revealed several significant differences. As for **2**, there were NMR resonances in the spectra of **3** consistent with the presence of a 1,3,4-trisubstituted benzene ring (Table 2). However, the absence of an O−H absorption in the IR spectrum and the presence of an absorption at 331 nm in the UV spectrum of **3** together with ^{13}C resonances for C-17 (δ_C 179.8) and C-20 (δ_C 185.2) indicated the presence of a quinone, rather than the hydroxylated benzene moiety found in **2**. Important gHMBC correlations from H-19 to C-17, C-18, C-20, and C-21, from H-11 to C-17 and C-21, and from H-15 to C-16 and C-20 supported the presence of a napthaquinone moiety in **3**. A gHMBC correlation from a methoxy methyl (δ_C 56.3; δ_H 3.90, s) to C-18 positioned the methoxy functionality at C-18. Observed COSY correlations from H-6 to H_a-7 and from H_2-7 to H_2-8 and a gHMBC correlation from H-15 to C-8 established that the cyclohexane and the methoxynapthaquinone moieties were joined by an ethylene bridge. Hence, the planar structure of **3** is as shown. The configuration at C-6 remains unassigned.

Metachromins U−W (**1**−**3**) were screened against four human tumor cell lines [MCF-7 (breast), SF-268 (CNS), H-460 (lung), and HT-29 (colon)], as well as a mammalian cell line [Chinese hamster ovary (CHO-K1) cells] (Table 3). All three compounds were found to be cytotoxic against all cell lines, with **2** being the most active. Surprisingly, **3**, possessing a napthaquinone functionality known to impart significant cytotoxic properties to various molecules,[18−20] was significantly less active than both **1** and **2**. Indeed, **1**−**3** all have significant structural features

Table 2. NMR Spectroscopic Data (600 MHz, $CDCl_3$) for Metachromin V (2) and Metachromin W (3)

no.	δ_C, mult.[a]	δ_H (J in Hz)[b]	gHMBC[c]	δ_C, mult.[a]	δ_H (J in Hz)[b]	gHMBC[c]
		2			3	
1	34.5, C			34.9, C		
2	36. 3, CH_2	1.46, m	1, 3, 4, 6, 12	35.8, CH_2	1.48, m	1, 3, 4, 12, 13
		1.21, m	3, 4		1.24, m	1, 3, 4
3	23.7, CH_2	1.51, m	1, 2, 4, 5	23.6, CH_2	1.55, m	
4	32.0, CH_2	1.99, m	2, 3, 5, 14	32.5, CH_2	2.09, m	3
5	148.0, C			148.7, C		
6	53.9, CH	1.67, ddd (3.5, 11.1, 11.1)	1, 4, 5, 7, 8, 12, 13, 14	53.7, CH	1.79, m	1, 2, 5, 7, 8, 12, 14
7	24.7, CH_2	1.58, m	6, 8, 9	28.1, CH_2	1.82, m	5
		1.44, m	1, 5, 6, 8, 9		1.74, m	6
8	38.4, CH_2	2.02, m	5, 6, 7, 9, 10	CH_2	2.74, m	7, 15
		1.82, m	6, 7, 9, 10, 15		2.49, m	7, 15
9	139.0, C			150.6, C		
10	120.6, CH	5.27, t (7.2)	8, 11, 15, 16	133.0, CH	7.50, dd (1.7, 7.9)	8, 15, 16
11	29.8, CH_2	3.31, d (7.2)	9, 10, 16, 17, 21	126.6, CH	8.04, d (7.9)	9, 17, 21
12	28.4, CH_3	0.91, s	1, 2, 6, 13	28.3, CH_3	0.92, s	1, 2, 6, 13
13	26.2, CH_3	0.83, s	1, 2, 6, 12	26.4, CH_3	0.84, s	1, 2, 6, 12
14	108.9, CH_2	4.74, d (2.3)	4, 5, 6	109.3, CH_2	4.86, d (1.6)	4, 6
		4.53, d (2.3)	4, 5, 6		4.62, d (1.6)	4, 6
15	16.6, CH_3	1.75, s	8, 9, 10	125.5, CH	7.89, d (1.7)	8, 10, 16, 20
16	128.0, C			129.0, C		
17	116.8, CH	6.61, d (2.6)	11, 19, 21	179.8, C		
18	149.0, C			160.5, C		
19	113.8, CH	6.58, dd (2.6, 8.4)	17, 20, 21	109.4, CH	6.14, s	17, 18, 20, 21
20	116.6, CH	6.68, d (8.4)	16, 18	185.2, C		
21	148.0, C			132.0, C		
22				56.3, CH_3	3.90, s	18

[a] 150 MHz. [b] 600 MHz. [c] HMBC correlations are from proton(s) stated to the indicated carbons.

Table 3. GI_{50} (μM) Data for Compounds 1−3 against the Human Tumor Cell Lines SF-268, MCF-7, H460, and HT-29 and the Mammalian Cell Line CHO-K1

compound	SF-268[a]	MCF-7[b]	H460[c]	HT-29[d]	CHO-K1[e]
1	32	29	37	30	27
2	5.1	3.2	5.1	10	2.1
3	104	107	50	130	89
staurosporine	0.044	11	3.6	3.6	0.13
paclitaxel	0.012	0.012	0.024	0.012	5.9

[a] SF-268, central nervous system-glioblastoma cells. [b] MCF-7, breast-pleural effusion adenocarcinoma cells. [c] H460, lung-large cell carcinoma cells. [d] HT-29, colon-recto-sigmoid colon adenocarcinoma cells. [e] CHO-K1, subclone of Chinese hamster ovary cells.

in common with the known biologically active merosesquiterpenoids, metachromins A−M[13−15,17,21] and S and T.[16] Interestingly, metachromins N−R,[16,21] which contain both quinone and phenol moieties, are reported as being inactive, most likely due to the bulky nature of their quinone substituents.

EXPERIMENTAL SECTION

General Experimental Procedures. General experimental details have been previously reported.[22,23] NMR spectra for **1** were measured on a Bruker Avance 300 MHz NMR spectrometer. NMR spectra for **2** and **3** were measured on a Bruker Avance 600 MHz NMR spectrometer with a cryoprobe.

Animal Material. The sponge *Thorecta reticulata* (order Dictyoceratida, family Thorectidae) was collected east of Hunter Island, North West Tasmania (40°27′6″ S, 144°7′7″ E), at a depth of 6 m, in February 1991 and frozen. Collection was conducted under the Department of Sea Fisheries Tasmania permit number 7/1/14/63. A voucher specimen (accession number G311976) has been lodged with the Queensland Museum.

Extraction and Isolation. Freeze-dried animal material (12.5 g dry weight) was exhaustively extracted with MeOH (3 × 1 L) and subjected to reversed-phase (RP) C18 vacuum liquid chromatography (0%, 20%, 50%, 70%, 90%, and 100% MeOH in H_2O and 1:1 CH_2Cl_2/MeOH). The bioactivity was confined to the 90% MeOH fraction. This fraction was preadsorbed onto C18 RP silica gel and subjected to preparative RP HPLC [250 mm × 21 mm, 5 μ Phenomenex Luna C18 column, 9.5 mL/min, gradient elution from 10% MeCN/H_2O (+ 0.1% formic acid) to 75% MeCN/H_2O (+ 0.1% formic acid) over 30 min, then with 100% MeCN for 15 min] to generate three active fractions. The first active fraction yielded metachromin U (**1**) (14.9 mg, 0.12% of dry weight). The two remaining active fractions were further purified using semipreparative RP HPLC [150 mm × 10 mm, 5 μ Phenomenex Luna phenyl hexyl column, 4 mL/min, gradient elution from 60% MeOH/H_2O (+ 0.1% formic acid) to 100% MeOH (+ 0.1% formic acid) over 10 min, followed by isocratic elution with 100% MeOH (+ 0.1% formic acid) for a further 10 min] to yield metachromins V (**2**, 1.6 mg, 0.013% of dry weight) and W (**3**, 0.5 mg, 0.004% of dry weight). Metachromins U, V, and W (**1**−**3**) were the only

compounds found to be responsible for the observed cytotoxic activity of the MeOH extract.

Metachromin U (1): brown oil; $[\alpha]^{21}_{D}$ +28 (*c* 0.2, MeOH); UV (PDA, MeCN/H_2O) λ_{max} 222, 266, 275, 334 nm; IR (neat) ν_{max} 3433 (O−H s, br), 2931 (alkyl C−H s, br), 1620 (alkenyl C=C w), 1588 (aromatic C=C m) cm^{-1}; ^1H (300 MHz, CD_3OD) and ^{13}C (75 MHz, CD_3OD) NMR data see Table 1; HRESIMS *m*/*z* 365.2080 $[M + Na]^+$ (calcd for $C_{22}H_{30}O_3Na$, 365.2087; Δ 1.9 ppm).

Metachromin V (2): colorless oil; $[\alpha]^{21}_{D}$ 0 (*c* 0.1, $CHCl_3$); UV (PDA, MeCN/H_2O) λ_{max} 227, 292 nm; IR (neat) ν_{max} 3371 (O−H s, br), 2931 (alkyl C−H s, br), 1625 (alkenyl C=C w), 1541 (aromatic C=C m) cm^{-1}; ^1H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz, $CDCl_3$) NMR data see Table 2; HRESIMS *m*/*z* 337.2121 $[M + Na]^+$ (calcd for $C_{21}H_{30}O_2Na$, 337.2138; Δ 5.0 ppm).

Metachromin W (3): yellow oil; $[\alpha]^{21}_{D}$ −60 (*c* 0.03, $CHCl_3$); UV (PDA, MeCN/H_2O) λ_{max} 221, 247, 255, 280, 331 nm; IR (neat) ν_{max} 2932 (alkyl C−H s, br), 1681 (quinone C=O m), 1605 (alkenyl C=C w), 1554 (aromatic C=C m) cm^{-1}; ^1H (600 MHz, $CDCl_3$) and ^{13}C (150 MHz, $CDCl_3$) NMR data see Table 2; HRESIMS *m*/*z* 361.1773 $[M + Na]^+$ (calcd for $C_{22}H_{26}O_3Na$, 361.1774; Δ 0.2 ppm).

Bioassay. Whole cell bioassay experimental details have been previously reported.[22,23] Staurosporine and paclitaxel were used as positive controls in all five cell lines with a GI_{50} range of 12 nM to 11 μM.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra for all isolated compounds are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +61 7 4753 4143. Fax.: +61 7 4772 5852. E-mail: c.motti@aims.gov.au.

Present Addresses

[†]Defense Science & Technology Organisation, 506 Lorimer Street, Fishermans Bend, Victoria, 3207, Australia.

[‡]ACD Laboratories UK, Building A, Trinity Court, Wokingham Road, Bracknell, Berkshire, RG42 1PL, England.

[§]Advanced Analytical Centre, James Cook University, Townsville, QLD 4811, Australia.

[⊥]College of Pharmacy, University of Hawaii at Hilo, 34 Rainbow Drive, Hilo, Hawaii 96720, USA.

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