Adociasulfates 1, 7, and 8: New Bioactive Hexaprenoid Hydroquinones from the Marine Sponge *Adocia* sp.

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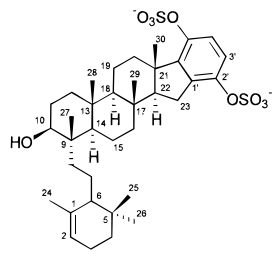
Adociasulfate 1 (**1**), adociasulfate 7 (**2**), and adociasulfate 8 (**3**), which are inhibitors of proton pump activity in hen bone-derived membrane vesicles, were isolated from an extract of the sponge *Adocia* sp. (Chalinidae). Structure elucidation by 2D-NMR spectroscopy revealed that they are novel hexaprenoid hydroquinone sulfates.

Vacuolar H^+-ATPases are a class of multi-subunit ATP-driven proton pumps found in all eukaryotic cells. Vacuolar H^+-ATPases are responsible for proton transport in bone-derived membrane vesicles.[1] The process of osteoclast-mediated bone resorption is directly dependent on H^+-translocating ATPases.[1] Inhibition of osteoclast vacuolar H^+-ATPase proton pumps may provide an effective means of reducing the rate of bone resorption in pathological conditions such as osteoporosis and as a result could be of therapeutic value.

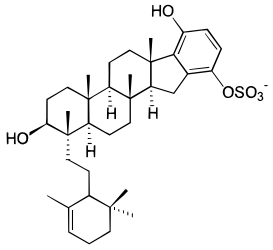
In the present study, three new hexaprenoid hydroquinone sulfates, adociasulfate 1 (**1**), adociasulfate 7 (**2**), and adociasulfate 8 (**3**), which were isolated from the marine sponge *Adocia* sp., inhibited the proton pump. Sulfated hexaprenyl hydroquinones have been previously isolated from marine sponges. These include toxiusol and toxicol A (**4**), B, and C from the Red Sea sponge *Toxiclona toxius*[2] and adociasulfate 2 (**5**) from the Palauan sponge *Adocia* sp.[3] These compounds have been associated with a range of biological activities including inhibition of reverse transcriptase of the human immuno deficiency virus (HIV)[4] and inhibition of kinesin motor proteins.[3]

The methanol extract of the *Adocia* sp. was chromatographed on Sephadex LH-20 (100% methanol), and two active fractions were further separated by C18 MPLC and HPLC to give adociasulfates 1 (**1**), 7 (**2**), and 8 (**3**). It was critical to perform HPLC with sodium chloride in the aqueous phase to increase resolution.

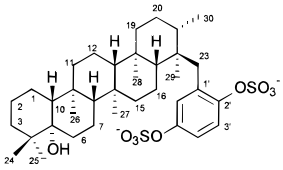
The ^{1}H NMR spectrum of adociasulfate 1 (**1**) (Table 1) showed six tertiary methyl groups at δ 0.68, 0.81, 0.84, 0.90, 0.97, and 1.01 and one olefinic methyl group at δ 1.64. The ^{13}C NMR spectrum contained the resonance of 36 carbons: seven methyl groups, eight unsaturated carbons, and 21 aliphatic carbons. The base peak observed in the negative low-resolution electrospray ionization mass spectrum was $m/z = 346.4$, which suggested a doubly charged molecular ion, given the large number of carbons in the molecule. Negative high-resolution electrospray ionization mass spectroscopy (HRESIMS) showed a molecular ion at m/z 693.3111, establishing a molecular formula of $C_{36}H_{54}O_9S_2$. Disulfated compounds typically show a strong $[M - 2H^+]^{2-}$ peak in the negative ESIMS, accounting for the base peak at m/z 346.4.



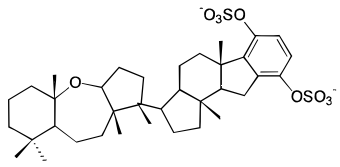
(1) Adociasulfate-1



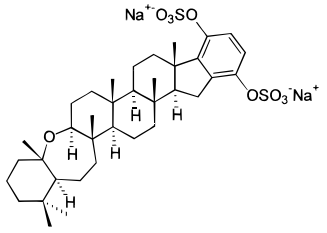
(2) Adociasulfate-7



(3) Adociasulfate-8



(4) Toxicol A



(5) Adociasulfate-2

The 10 units of unsaturation implied by the molecular formula suggested an aromatic ring, a double bond, and five rings. A series of HMBC correlations from the four methyl groups C27−C30 (δ 0.68, 0.84, 0.97, 1.01) allowed a tetracyclic system to be assigned. This was supported by a series of COSY correlations from H19 to H20 and H22 to H23 and from the C10 hydroxyl group to the

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Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR Data for Adociasulfate 1 (1) and Adociasulfate 7 (2) and HMBC, COSY, and ROESY Correlations for Adociasulfate 1 (1) in DMSO-d_6

	adociasulfate 1 **(1)**					adociasulfate 4 **(2)**	
pos.	^{13}C NMR	^{1}H NMR	$^2J_{CH}$ and $^3J_{CH}$	COSY	ROESY (500 ms)[a]	^{13}C NMR	^{1}H NMR
1	136.6					136.4	
2	118.9	5.22 (s)		H3, H6, H24		119.2	5.21 (s)
3	22.5	1.88 (brs)		H2, H4a, H4b	H26	22.5	1.88 (brs)
4	31.0	1.07 (m)	C3	H3, H4b		31.0	1.07 (m)
		1.38 (m)	C3, C5, C6, C25, C26	H3, H4a			1.39 (m)
5	32.2					32.2	
6	49.4	1.28 (m)		H2	H26	49.4	1.28 (m)
7	23.4	1.00 (m)		H7b, H8a		23.4	1.02 (m)
		1.33 (m)		H7a, H8a			1.38 (m)
8	37.5	1.13 (m)	C9, C10, C27	H8b		37.5	1.13 (m)
		1.59 (m)		H7a, H7b, H8a			1.61 (m)
9	40.8					40.9	
10	70.8	3.28 (m)	C27	H11, 10-OH		70.8	3.28 (m)
11	27.2	1.50 (m)		H10, 10-OH	H27, H28	27.2	1.52 (m)
12	37.8	0.89 (m)				37.8	0.89 (m)
		1.62 (m)			H27		1.61 (m)
13	36.5					36.5	
14	49.4	0.92 (m)	C9, C13, C27, C28		H15a, H18	49.4	0.93 (m)
15	17.2	1.02 (m)			H14	17.2	1.01 (m)
		1.35 (m)					1.35 (m)
16	41.2	1.01 (m)				41.2	1.03 (m)
		1.58 (m)			H28		1.59 (m)
17	36.8					36.8	
18	61.2	0.87 (m)			H14	61.2	0.85 (m)
19	17.8	1.49 (m)		H20	H29	17.9	1.48 (m)
		1.56 (m)	C21	H20			1.56 (m)
20	37.2	1.55 (m)				37.2	1.56 (m)
		2.41 (m)	C18, C21, C22	H19a, H19b	H30		2.41 (m)
21	46.6					46.5	
22	63.7	1.51 (m)	C17, C18, C21, C23, C29, C30	H23a, H23b	H23b	64.0	1.49(m)
23	25.5	2.39 (dd, J = 14.4, 14.4 Hz)	C21, C22, C1′	H22, H23b, H3′	H23b, H29, H30	24.9	2.32 (dd, J = 13.2, 13.2 Hz)
		2.59 (dd, J = 6.6, 14.4 Hz)	C21, C22, C1′, C2′, C6′	H22, H23a, H3′	H22, H23a		2.45 (dd, J = 6.0, 13.2 Hz)
24	23.0	1.64 (brs)	C1, C2, C6	H2, H3		23.0	1.63 (brs)
25	27.5	0.90 (s)	C4, C5, C6, C26		H26	27.5	0.90 (s)
26	27.4	0.81 (s)	C4, C5, C6, C25		H3, H6, H25	27.4	0.81 (s)
27	17.3	0.68 (s)	C8, C9, C10, C14		H11, H12b, H28, 10-OH	17.4	0.68 (s)
28	16.4	0.84 (s)	C12, C13, C14, C18		H11, H16b, H27, H29	16.5	0.84 (s)
29	16.9	0.97 (s)	C16, C17, C18, C22		H16, H19a, H23a, H28	17.0	0.97 (s)
30	20.5	1.01 (s)	C20, C21, C22, C6′		H20B, H23a	20.5	1.01 (s)
1′	134.8					136.4	
2′	144.7					144.8	
3′	118.5	7.08 (d, J = 9.0 Hz)	C1′, C2′, C5′	H23a, H23b, H4′	H4′	118.8	6.99 (d, J = 9.0 Hz)
4′	118.8	6.87 (d, J = 9.0 Hz)	C1′, C2′, C6′	H3′	H3′	112.3	6.36 (d, J = 9.0 Hz)
5′	145.1					148.8	
6′	144.1					141.3	
OH		4.04 (d, J = 5.4 Hz)	C9, C10	H10, H11			4.04 (d, J = 5.2 Hz)

[a] Mixing time in milliseconds.

methylene protons at δ 1.50 (H11) and the methine proton at δ 3.28 (H10). HMQC-TOCSY correlations from the methine proton at δ 0.92 (H14) to carbons at 17.2 (C15) and 41.2 (C16) ppm also supported the assignment of the tetracyclic system. HMBC correlations from the aromatic proton at δ 6.87 (H4′) to carbons at 144.1 (C6′) and 144.7 (C2′) ppm and from the aromatic proton at δ 7.08 (H3′) to carbons at 134.8 (C1′), 144.7 (C2′), and 145.1 (C5′) ppm, combined with correlations from the geminal methylene protons at δ 2.39 and 2.59 (H23) to the aromatic carbons at 134.8 (C1′), 144.1 (C6′), and 144.7 (C2′) ppm, allowed the connection of that aromatic ring to the tetracyclic system.

The three remaining methyl groups, two geminal and one olefinic, were assigned to an isolated ring system. This assignment was supported by COSY correlations from the olefinic proton at δ 5.22 (H2) to the methylene protons at δ 1.88 (H3) and methine proton at δ 1.28 (H6). The connection of this ring system to the tetracyclic system was based on correlations from three different NMR experiments. The HMBC experiment showed correlations from the methylene proton at δ 1.13 (H8a) to carbons at 40.9 (C9), 70.8 (C10), and a methyl group at 17.3 ppm (C27), the HMQC-TOCSY showed correlations from the methine proton at δ 1.28 (H6) to carbons at 23.4 (C7) and 37.5 ppm (C8), and the COSY showed correlations from the geminal methylene protons at δ 1.00 and 1.33 (H7) to the methylene proton at δ 1.13 (H8a). Table 2 compares the ^{1}H and ^{13}C chemical shifts of **1** for positions 17−30 and 1′−6′ with toxicol A (**4**). All chemical shifts for this fragment are in close agreement despite their NMR spectra being recorded in different solvents.

ROESY correlations from the hydroxy group at C10, via methyl H27, methyl H28, methyl H29, methylene H23b, and methyl H30, established that all methyl groups were on the β face of the molecule. H14 and H18 were on the α face of the molecule as these protons correlated to each other and to none of the methyl groups.

Table 2. Selected ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR Data for Adociasulfate 1 (1) in DMSO-d_6 and ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR Data for Toxicol A (4) in $CDCl_3$+CD_3OD (1:10)

	adociasulfate 1 (**1**)		toxicol A (**4**)	
position	^{13}C	^{1}H	^{13}C	^{1}H
17	36.8		37.0	
18	61.2	0.87 (m)	61.2	n/r[a]
19	17.8	1.49 (m) 1.56 (m)	18.2	n/r
20	37.2	1.55 (m) 2.41 (m)	37.1	2.42 (m)
21	46.6		47.3	
22	63.7	1.51 (m)	64.0	n/r
23	25.5	2.39 (dd, J = 14.4, 14.4 Hz) 2.59 (dd, J = 6.6, 14.4 Hz)	25.7	2.48 (t, J = 14 Hz) 2.68 (dd, J = 6, 14 Hz)
29	16.9	0.97 (s)	16.9	0.87 (s)
30	20.5	1.01 (s)	19.7	0.99 (s)
1′	134.8		137.4	
2′	144.7		146.2	
3′	118.5	7.08 (d, J = 9.0 Hz)	119.5	6.95 (d, J = 9 Hz)
4′	118.8	6.87 (d, J = 9.0 Hz)	118.9	7.14 (d, J = 9 Hz)
5′	145.1		145.0	
6′	144.1		144.6	

[a] Chemical shifts not reported.

The molecular formula of adociasulfate 7 (**2**) was determined to be $C_{36}H_{54}O_6S$ by HRESIMS, showing a molecular ion peak of m/z 613.3548 corresponding to $[M - H^+]^-$ in the negative ESI mass spectrum. The base peak observed in the negative LRESIMS (m/z 613.4) indicated a singly charged molecular ion corresponding to $[M - H^+]^-$, as expected for a monosulfate. The aromatic ortho-coupled proton doublets in the ^{1}H NMR spectrum showed an upfield shift of 0.51 ppm for H4′ compared with 0.09 ppm for H3′, indicating a hydroxyl group on C5′ compared with a sulfate in adociasulfate 1 (**1**). ^{13}C NMR experiments confirmed this with an observed upfield shift of 6.5 ppm for C4′ and a downfield shift of 3.7 ppm for C5′ compared with adociasulfate 1. All other chemical shifts (Table 1) were in close agreement with those of adociasulfate 1, which confirmed the structure as **2**.

Adociasulfate 8 (**3**) showed a base ion peak in the negative LRESIMS (m/z = 347.4), which suggested a doubly charged molecular ion $[M - 2H^+]^{2-}$ and a molecular formula of $C_{36}H_{56}S_2O_9$. There was no molecular ion observed in the HRESIMS; however, a peak at m/z = 535.4026, which represented the fragment $[C_{36}H_{56}S_2O_9 - 2SO_3 - H^+]^-$, was consistent with the molecular formula. The ^{1}H NMR spectrum of **3** revealed six methyl singlets, one methyl doublet, and three aromatic protons, of which two were ortho coupled with the third appearing as a singlet. The multiplicity of these signals indicated a 1,2,4-trisubstituted aromatic ring. No other signal downfield of 2.6 ppm was observed, indicative of a saturated system. The ^{13}C NMR spectrum contained the resonances of 36 carbon atoms, which consisted of seven methyls, six aromatics, an oxygen-bearing carbon atom at 74 ppm, and 23 other saturated carbon atoms. A DEPT experiment confirmed the presence of seven methyl groups, 12 methylenes, eight methines, and nine quaternary carbon atoms. There were nine double-bond equivalents, which indicated an aromatic ring and five rings.

The carbon framework was elucidated from HMBC and COSY NMR experiments (Table 3). The attachment of the aromatic ring to the methylene carbon at 36.5 ppm

Table 3. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR Data and HMBC, COSY, and ROESY Correlations for Adociasulfate 8 (3) (in DMSO-d_6)

pos.	^{13}C NMR	^{1}H NMR	$^2J_{CH}$ and $^3J_{CH}$	COSY	ROESY[a]
1	20.3	1.38 (m)	C5		
		1.27 (m)		H2a	H10
2	21.9	1.41 (m)		H2b, H3a	H1b
		1.29 (m)		H3a, H3b	
3	36.4	1.66 (m)	C5	H3b	H3b
		0.87 (m)	C5	H3a	
4	38.4				
5	73.9				
6	33.0	1.67 (m)	C5		H6b, H26
		1.30 (m)	C5, C8	H6a	
7	16.5	1.47 (m)			
		1.32 (m)		H6a	
8	60.7	0.62 (brd, J = 11.4 Hz)	C9, C10, C11, C27, C26	H7a, H7b	H10, H13
9	37.1				
10	50.9	1.11 (brd, J = 11.0 Hz)	C1, C9, C7	H1a, H1b	H8, H11b
11	41.3	1.63 (m)	C8	H12a, H12b	
		0.81 (m)		H11a, H12a	
12	16.6	1.35 (m)	C18		H12b
		1.22 (m)		H11a, H13	
13	60.7	0.55 (brd, J = 12.3 Hz)	C11, C14, C18, C27, C28	H12a, H12b	H17,H8
14	37.2				
15	41.1	1.72 (brd, J = 13.4 Hz)	C14	H15b, H16a, H16b	
		0.90 (m)			
16	18.3	1.97 (brd, J = 13.2 Hz)	C14	H15a, H15b, H16b, H17	H16b, H23a
		1.39 (m)		H15a	H6′, H23a
17	50.4	0.78 (m)		H16a, H16b	
18	37.2				
19	38.5	1.51 (m)		H19b, H20a, H20b	H19b
		0.52 (m)			
20	27.1	1.30 (m)		H20b	
		1.23 (m)		H20a	H21
21	35.4	1.33 (m)			H6′
22	41.1				
23	36.5	2.54 (d, J = 14.0 Hz)	C17, C21, C22, C1′, C6′	H23b	H23b
		2.40 (d, J = 14.0 Hz)	C17, C21, C22, C1′, C6′	H23a	H29, H30
24	24.6	0.76 (s)	C3, C4, C5, C25		H25
25	24.0	0.89 (s)	C3, C4, C5, C24		H26
26	16.6	0.90 (s)	C8, C9, C10, C11		H27
27	17.9	0.81 (s)	C8, C13, C14, C15		
28	16.1	0.77 (s)	C13, C17, C19, C18		
29	17.4	0.72 (s)	C17, C21, C22, C23		H30
30	17.5	0.91 (d, J = 6.2 Hz)	C20, C21, C22		H29
1′	125.5				
2′	148.8				
3′	115.3	6.57 (d, J = 8.1 Hz)	C1′, C5′	H4′	
4′	113.2	6.41 (d, J = 8.1 Hz)	C2′, C6′	H3′	
5′	148.8				
6′	118.6	6.42 (s)	C23, C4′, C2′		

[a] Mixing time in milliseconds.

(C23) was based on HMBC correlations from the geminal methylene protons H23a and H23b (δ 2.41 and 2.52) to C1′ and C6′. These protons also showed HMBC correlations to carbons C17, C21, C22, and C29, which supported the assignment. A crucial contribution to the structure elucidation was a series of HMBC correlations from the

seven methyl groups, which together with COSY correlations allowed a pentacyclic ring system to be assigned. HMBC correlations from the methyl singlet at δ 0.72 (C29) to C17, C21, C22, and C23 and from the methyl doublet at δ 0.91 (C30) to C20, C21, and C22 established part of the ring attached to the aromatic ring. Methyl protons on C28 (δ 0.77) showed HMBC correlations to C13, C17, C18, and C19 supporting the D/E ring fusion and COSY correlations between protons on C19 and C20 completed the assignment of ring E. Methyl protons (δ 0.81) on C27 showed HMBC correlations to C8, C14, C15, and importantly C13, which supported the C/D ring fusion. COSY correlations between protons on C15 and C16 and C16 and C17 allowed the assignment of ring D. COSY correlations from protons on C13 through C11 and HMBC correlations from methyl protons (δ 0.90) on C26 to C9, C10, C11, and C8 completed the assignment of ring C and supported the fusion of rings B and C. The two remaining methyl singlets at δ 0.89 (C25) and δ 0.76 (C24) both showed HMBC correlations to C3, C4, and C5 and to each other, indicative of a geminal dimethyl moiety. COSY correlations between protons H3 and H2 and between H1 and H2 and H1 and H10, along with a series of COSY correlations from protons on C6 through to C8, which also provided a link to ring C, were important in assigning the A/B unit. These COSY correlations along with the HMBC correlations from methyl protons on C26 and the geminal methyls, C24 and C25, established a 10 carbon unit. HMBC correlations from protons on carbons C1 and C3 to the oxygen-bearing C5 supported the assignment of the A/B 6:6 fused system. Examples of this fused ring system with a hydroxy group at the ring junction C5 have been reported elsewhere. [5,6]

ROESY data established an all trans stereochemistry. Correlations were observed between ring junction protons H10 and H8, H8 and H13, and H13 and H17. No correlations were observed between these protons and the adjacent methyl groups, which indicated trans geometries across ring junctions and hence an all-chair configuration throughout the ring system.

Adociasulfate 1 (**1**) reduced the proton pump activity in hen bone-derived membrane vesicles with $IC_{50} = 3.6$ μM, compared with that of bafilomycin A_1, 6.19 nM. It also inhibited proton pumping in brain-derived vesicles with $IC_{50} = 4.69$ μM, compared with that of bafilomycin A_1, 1.89 nM. The monosulfate (**2**) was also active ($IC_{50} =$ 30 μM, bone and brain) with a 10-fold decrease in potency compared to the bisulfate (**1**), while adociasulfate 8 (**3**) was again less active (55% inhibition at 100 μM).

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Experimental Section

Animal Material. The sponge sample *Adocia* sp. was collected by scuba diving at Mermaid Cove, Lizard Island, Australia, and a voucher sample (G304214) is lodged at the Queensland Museum, Brisbane, Australia.

Extraction and Isolation. The freeze-dried sponge material (4.8 g) was ground and exhaustively extracted with methanol to afford 1.6 g of crude extract. The methanol crude extract was fractionated by Sephadex LH-20 (100% methanol), which afforded two active fractions. The first fraction (196 mg) was separated by C18 MPLC and semipreparative HPLC using a gradient elution from 50% methanol in 0.2 M NaCl to 100% methanol over 20 min with adociasulfate 1 **(1)** (4.2 mg) eluting at 11 min. The second fraction was also separated by C18 MPLC and HPLC using gradient elution from 80% methanol in 0.2 M NaCl to 100% methanol over 15 min with adociasulfate 8 **(3)** (8 mg) eluting at 9 min and adociasulfate 7 **(2)** (1.7 mg) at 10.5 min.

Adociasulfate 1 (1): white powder (4.2 mg, 0.08% dry wt); $[\alpha]^{26}_D$ −34° (*c* 0.10, MeOH); UV (MeOH) λ_{max} (ϵ) 263.8 nm (313); IR ν_{max} (film) 3470, 2933, 1475, 1239, 1047, 816 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; (−)-LRESIMS *m/z* 346.4 $[C_{36}H_{54}O_9S_2 - 2H^+]^{2-}$ (100); (−)-HRESIMS *m/z* 715.2925 $[C_{36}H_{54}O_9S_2 - 2H^+ + Na^+]^-$ (calcd 715.2956), 693.3111 $[C_{36}H_{54}O_9S_2 - H^+]^-$ (calcd 693.3136), 346.1523 $[C_{36}H_{54}O_9S_2 - 2H^+]^{2-}$ (calcd 346.1532).

Adociasulfate 7 (2): white powder (1.7 mg, 0.03% dry wt); $[\alpha]^{26}_D$ +5° (*c* 0.17, MeOH); UV (MeOH) λ_{max} (ϵ) 276.3 nm (336); IR ν_{max} (film) 3412, 2926, 1286, 1050 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; (−)-LRESIMS *m/z* 613.4 $[C_{36}H_{54}SO_6 - H^+]^-$ (100); (−)-HRESIMS *m/z* 613.3548 $[C_{36}H_{54}SO_6 - H^+]^-$ (calcd 613.3568).

Adociasulfate 8 (3): white powder (8 mg, 0.16% dry wt); $[\alpha]^{26}_D$ +18° (*c* 0.19, MeOH); UV (MeOH) λ_{max} (ϵ) 295.5 nm (982); IR ν_{max} (film) 3326, 2933, 1611, 1383, 1135 cm^{-1}; ^1H and ^{13}C NMR, see Table 3; (−)-LRESIMS *m/z* 347.4 $[C_{36}H_{56}S_2O_9 - 2H^+]^{2-}$ (100); (−)-HRESIMS *m/z* 535.4026 $[C_{36}H_{56}S_2O_9 - 2SO_3 - H^+]^-$ (calcd 535.4137).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all title compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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