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Note

Quintaquinone, a Merosesquiterpene from the Yellow Sponge *Verongula* cf. *rigida* Esper

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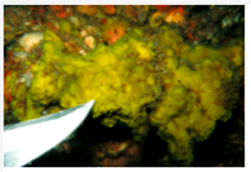
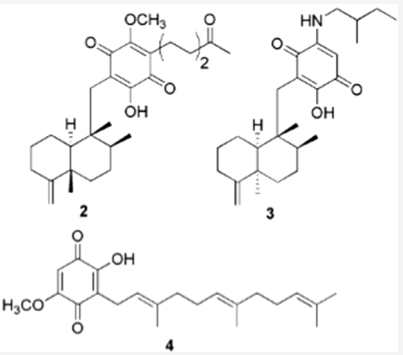
ABSTRACT: A chemical investigation of the sponge *Verongula* cf. *rigida* led to the isolation of 13 merosesquiterpenes, among which quintaquinone (**2**), 5-*epi*-nakijiquinone L (**3**), and 3-farnesyl-2-hydroxy-5-methoxyquinone (**4**) were isolated and reported here for the first time. Particularly, compound **2** is the first member of merosesquiterpenes with a polyketide side chain substituted on C-19. All of the isolated compounds were examined for steroid 5α-reductase inhibitory activity. Cyclospongiaquinone 1 (**5**) showed a strong activity in the same range as that of standard finasteride.



Verongula cf. *rigida*



"Meroterpenes" is a trivial term used to define terpenoid compounds that possess a terpene moiety coupling to a nonterpene unit. Best represented by puupehenone,[1] avarol,[2] and ilimaquinone,[3] the sponge-derived merosesquiterpenes are a subgroup of meroterpenes, most of which possess either a drimane or a 4,9-friedodrimane terpenoid skeleton connected to a polyketide-derived quinone or hydroquinone. Several merosesquiterpenes are biologically active. For example, ilimaquinone (**1**) is cytotoxic against various cancer cell lines, with IC_{50} values in a range of 0.5−25 μM, and has shown other related activities including anti-HIV and antituberculosis activities.[4,5]

Recently, we collected sponge specimens later identified to be *Verongula* cf. *rigida* from the vicinity of Ko Ha Islets, Thailand. The sponge extract inhibited the growth of MCF-7 breast cancer cells (>90%) at 25 μg/mL. This prompted the chemical investigation of the sponge, leading to the isolation of three new compounds, quintaquinone (**2**), 5-*epi*-nakijiquinone L (**3**), and 3-farnesyl-2-hydroxy-5-methoxyquinone (**4**), along with a series of previously reported merosesquiterpenes. In addition to the structure elucidation, the inhibitory activity of the isolated compounds against steroid 5α-reductase, the key enzyme targeted in the treatment of androgenic hyperfunction, is reported here.

The specimens of *V. rigida* were collected during two expeditions in December 2010 and April 2014. The investigation of the 2014 specimen yielded compound **2**, along with the known compounds ilimaquinone (**1**),[3,6] 5-*epi*-ilimaquinone,[6,7] smenospongidine,[6,8] smenospongorine,[6,8] smenodiol,[6] and cyclospongiaquinone 1 (**5**).[9] Two inseparable mixtures of compound **3** and 5-*epi*-smenospongiarine (**6**),[6] and of nakijiquinone L[10] and smenospongiarine,[6,8] were also obtained. (The chemical structures of unnumbered compounds are summarized in the Supporting Information.)

Compound **2** has a molecular formula of $C_{28}H_{40}O_5$ as deduced from the masses of the deprotonated molecule $[M - H]^-$ (*m*/*z* 455.2828) and the sodium adduct $[M + Na]^+$ (*m*/*z* 479.2763) in the ESI mass spectra and from carbon types indicated in the DEPT spectra. Combined with the IR spectroscopic analysis, the unsaturation degree of nine was deduced to be three carbonyls, three olefinic/aromatic double bonds, and three rings.

The NMR spectra of **2** (Table 1 and Figure 1) indicate that **2** shares the same chemical skeleton as that of **1**. The differences between **1** and **2** are the absence of H-19 in the ^{1}H NMR spectrum of **2** and its additional mass of 98 mu (equivalent to $C_6H_{10}O$). This corresponds to the aliphatic methylenes and methyl signals of H_2-22−H_3-27, which were elucidated to be an oxo-hexyl unit substituted on C-19 (Figure 1). It should be noted that the signal of 17-OH of **2** was undetectable even in a H-bond-facilitating solvent, e.g., DMSO-d_6 (data not shown), hence limiting the HMBC

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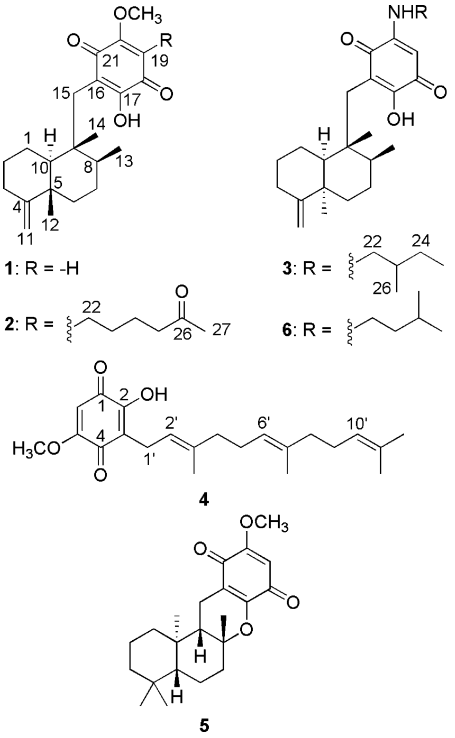

correlations within the quinone ring. The spectroscopic data of **2** therefore can be elucidated to either a *p*- or *o*-quinone as two equally possible structures that cannot be proven spectroscopically without any ambiguity. Here we propose the structure of the *p*-quinone as the most plausible one due to the similarity among the chemicals shifts of **1** and **2**. Compound **2** is a new 19-(oxo-hexyl)-sesquiterpene quinone, named quintaquinone (after Ko Ha Islets, or Islets of Five, the collection site for the sponge). The compound is the first member of the ilimaquinone family possessing a polyketide side chain on C-19, a position not previously found alkylated among the sesquiterpene quinones.

The shielded chemical shifts of C-12 (δ 21.0) and C-14 (δ 17.9),[6,11] resulting from the electronic repulsion general to the 1,3-diaxial functionality, and the coupling constant of H-10 (J = 11.2 Hz) indicated that H-10, C-12, and C-14 adopted axial orientations. Hence, **2** has a *trans*-decalin ring system, the same as **1**. The proposed *trans* ring junction was supported by NOE correlations (Figure 1) and by the characteristic chemical shift of C-4 (δ 160.5)[6,11] deshielded by the σ-orbital of the nearby ring. As the stereogenic centers and relative configuration of **1** and **2** are all equivalent, these allow a direct comparison between the electronic circular dichroism (ECD) spectra of the two compounds for the absolute configuration analysis. Both spectra showed the same Cotton effects at comparable wavelengths (Figure S15, Supporting Information); therefore, **2** was proposed to have the same absolute configuration as that of **1**.

Compound **3** was isolated as a 3:4 mixture with its constitutional isomer, 5-*epi*-smenospongiarine (**6**).[6] Unable to isolate each isomer in decent purity, we decided to elucidate the structures of both compounds simultaneously. The ESI mass spectrum showed the same deprotonated molecules of **3** and **6** at m/z 412.2857 $[M - H]^-$, and a molecular formula of $C_{26}H_{39}NO_3$ was proposed. The unsaturation degree of eight was deduced to be two carbonyls, three olefinic/aromatic double bonds, and three rings.

Despite certain overlapping resonances, the NMR signals in a 3:4 ratio allowed **3** to be set apart from **6**. The resemblances among the resonances of the two compounds (Table 1) indicated that both shared identical skeletons. Compounds **3** and **6** differ only at the 20-*N*-side chain, where the isopentyl subunit of **6**, characterized by the geminal dimethyl doublet (δ 0.55, H_3-25 and H_3-26), was replaced by a (β-methyl)-butyl end in **3**, as indicated by one doublet (δ 0.44, H_3-26) and one triplet (δ 0.55, H_3-25) methyl. In contrast to the *trans*-decalin ring system of **1** and **2** discussed above, the chemical shifts of the equatorial methyls C-12 (both **3** and **6**, δ 33.8) and exomethylenes C-4 (both **3** and **6**, δ 153.9)[6,11] indicate that **3** and **6** have a *cis* ring junction. This was supported by the NOE correlations observed in the NOESY spectrum. Compound **3** is proposed to be a new epimer, 5-*epi*-nakijiquinone L (Figure S3, for COSY, HMBC, and NOESY correlations of **3**).

The investigation of the 2010 specimen yielded compound **4**, along with **1**, **5**, smenodiol,[6] and dactylospontriol.[6] The molecular formula of **4** was proposed to be $C_{22}H_{30}O_4$, according to the protonated species $[M + H]^+$ at m/z 359.2211 in the ESI mass spectrum. This required an unsaturation degree of eight, equivalent to two carbonyls, five olefinic/aromatic double bonds, and one ring.

A trisubstituted *p*-quinone subunit similar to that of **1** was first recognized in the NMR spectra of **4** (Table 2). The characteristic ^{13}C chemical shifts and HMBC correlations allowed a hydroxy, methoxy, and alkyl groups to be placed on C-2, C-5, and C-3 of the quinone moiety, respectively. Based on the COSY and HMBC analysis (Figure 2), the alkyl substituent on C-3 was elucidated to be a typical farnesyl side chain. Compound **4** was proposed to be a new noncyclized merosesquiterpene, 3-farnesyl-2-hydroxy-5-methoxyquinone. The *E* configuration at $\Delta^{2'}$ and $\Delta^{6'}$ was determined based on the characteristic chemical shifts of 3′-CH_3 and 7′-CH_3 (δ 16.5 and 16.7, respectively) and was confirmed by the NOE correlations.

Apart from **4**, there has been only one other acyclic sesquiterpene quinone reported to date.[12] The presence of **4** together with other drimane and 4,9-friedodrimane derivatives suggested that **4** is a putative biosynthetic intermediate preceding the cyclization and modification of the other cyclic sesquiterpene quinones.

All of the isolated compounds were subjected to the steroid 5α-reductase inhibition assay. The primary function of the enzyme steroid 5α-reductase is to metabolize testosterone to 5-dihydrotestosterone, which is responsible for the development of male gender identity. Inhibition of 5α-reductase is therefore a therapeutic target for the treatment of androgenic hyperfunction, including prostatic hyperplasia, male-pattern hair loss, and excessive body hair in women. Among the isolated meroterpenes, only **5** was active (IC_{50} 0.73 ± 0.05 μM) in the same range as that of standard finasteride (IC_{50} 0.76 ± 0.03 μM), whereas all other compounds were inactive (≤50% inhibition at 100 μM). Although it is the only compound tested as active, the tetracyclic structure of **5** with the quinone moiety is distinguishable. This structural feature mimics the androgenic substrates with the 3-oxo functionality and suggests its necessity in the enzyme inhibition. This agrees well with the hypothetical SAR of other 5α-reductase inhibitors.[13,14]

The cytotoxicities of all of the isolated compounds were tested, and the activities agreed with the previous reports (Table S1).[5,6] With the IC_{50} values higher than 10 μM, all of

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Table 1. NMR Data of Compounds 2, 3, and 6 (500 MHz for ^{1}H, Benzene-d_6)

	2		3		6	
position	δ_C, type	δ_H (J in Hz)	δ_C, type	δ_H (J in Hz)	δ_C, type	δ_H (J in Hz)
1 ax	23.8, CH_2	1.45, overlapped	23.4, CH_2	1.97, m	23.4, CH_2	1.97, m
1 eq		2.28, overlapped		2.40, overlapped		2.40, overlapped
2 ax	29.6, CH_2	1.40, overlapped	25.8, CH_2	1.67, overlapped	25.8, CH_2	1.67, overlapped
2 eq		1.93, br d (12.8)		1.87, m		1.87, m
3 ax	33.8, CH_2	2.35, br ddd (13.2, 12.1, 6.4)	32.8, CH_2	2.47, overlapped	32.8, CH_2	2.47, overlapped
3 eq		2.14, br dd (13.2, 11.6)		2.15, br dd (13.4, 3.4)		2.15, br dd (13.4, 3.4)
4	160.5, C		153.9, C		153.9, C	
5	42.1, C		40.2, C		40.2, C	
6 ax	37.5, CH_2	1.42, overlapped	38.7, CH_2	1.15, overlapped	38.7, CH_2	1.15, overlapped
6 eq		1.55, br d (16.9)		2.06, dd (14.6, 6.4)		2.06, dd (14.6, 6.4)
7 ax	28.8, CH_2	1.35, overlapped	28.8, CH_2	1.65, overlapped	28.8, CH_2	1.65, overlapped
7 eq		1.42, overlapped		1.28, m		1.28, m
8	39.1, CH	1.32, ddq (12.2, 1.6, 6.0)	40.2, CH	1.45, overlapped	40.2, CH	1.45, overlapped
9	43.8, C		45.1, C		45.1, C	
10	51.3, CH	0.94, dd (11.2, 1.8)	49.2, CH	1.45, overlapped	49.2, CH	1.41, overlapped
11 a	103.6, CH_2	4.59, br s	106.6, CH_2	4.84, br s	106.6, CH_2	4.84, br s
11 b		4.55, br s		4.81, br s		4.81, br s
12	21.0, CH_3	1.04, s	33.8, CH_3	1.13, s	33.8, CH_3	1.14, s
13	18.7, CH_3	1.13, d (6.0)	19.2, CH_3	1.20, d (5.8)	19.2, CH_3	1.21, d (5.8)
14	17.9, CH_3	0.86, s	19.4, CH_3	1.03, s	19.4, CH_3	1.04, s
15 a	33.0, CH_2	2.67, d (13.6)	33.6, CH_2	2.71, d (13.6)	33.6, CH_2	2.72, d (13.6)
15 b		2.50, d (13.6)		2.65, d (13.6)		2.66, d (13.6)
16	117.5, C		114.1, C		114.1, C	
17	153.1, C		157.9, C		157.9, C	
18	183.6, C		178.6, C		178.5, C	
19	126.3, C		92.4, CH	5.28, s	92.3, CH	5.25, s
20	159.1, C		150.6, C		150.4, C	
21	184.2, C		183.7, C		183.7, C	
22 a	23.1, CH_2	2.30, overlapped	48.6, CH_2	2.27, overlapped	41.1, CH_2	2.27, overlapped
22 b				2.08, overlapped		2.08, overlapped
23	28.4, CH_2	1.26, quint (6.0)	34.1, CH	0.95, ddd (8.7, 6.8, 6.4)	36.8, CH_2	0.71, dt (8.1, 7.2)
24 a	24.2, CH_2	1.45, overlapped	27.4, CH_2	0.87, dd (12.4, 6.5)	26.2, CH	1.67, br d (10.5)
24 b				0.67, ddd (12.4, 12.4, 6.5)		
25	43.2, CH_2	1.86, t (7.3)	11.5, CH_3	0.55, t (6.4)	22.5, CH_3	0.55, d (6.3)
26	206.2, C		17.3, CH_3	0.44, d (6.5)	22.5, CH_3	0.55, d (6.3)
27	29.7, CH_3	1.61, s				
20-OCH_3	61.6, CH_3	3.78, s				
20-NH				6.10, br s		5.92, br s

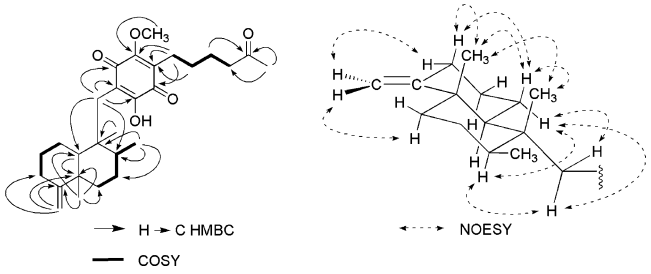

Figure 1. COSY, HMBC, and NOE correlations of 2.

the new compounds were considered inactive. Noticeably between 1 and its 5-epimer and, to a comparable extent, between 3 and 6 and their epimeric counterparts the compounds with a *trans*-decalin subunit were approximately twice as active as were the *cis* ones, suggesting the impact of their relative and absolute configurations on the cytotoxicity.

In summary, the investigation of the sponge *V.* cf. *rigida* led to the isolation of 13 sesquiterpene quinones, with 2−4 reported here for the first time. Among the isolated compounds, compound 5 had a strong inhibitory activity against steroid 5α-reductase. Studies on the computational model of the binding site of 5 and on the effects of 1 and its derivatives on DNA damage are now underway.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on a Jasco P1020 polarimeter. UV spectra were recorded on a Thermo Scientific Genesys6 spectrophotometer. ECD spectra were performed on a Jasco J715 spectropolarimeter. IR spectra were recorded on a Bruker Vertex70. All the NMR experiments were performed on an NMR Varian Unity Inova 500 MHz spectrometer, referencing the operating solvent, benzene-d_6 (δ_H 7.16 for residual C_6HD_5, δ_C 128.39), as an internal standard. ESI mass spectra were recorded on a Waters Alliance 2690 Micromass LCT. Silica gel 60 (230−400 mesh; Scharlau) was used for flash and vacuum chromatographies, and Sephadex LH20 (18−111 μm; GE Healthcare) was for size-exclusion chromatographies. HPLC was performed on a Waters 1525 binary solvent delivery system, equipped with a

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Table 2. NMR Data of Compound 4 (500 MHz for ^{1}H, Benzene-d_6)

position	δ_C, type	δ_H (J in Hz)
1	183.2, C	
2	151.3, C	
3	118.4, C	
4	181.1, C	
5	161.4, C	
6	102.3, CH	5.13, s
1′	22.6, CH_2	3.30, d (7.1)
2′	120.7, CH	5.48, tq (7.1, 1.2)
3′	137.5, C	
4′	40.5, CH_2	2.04, overlapped
5′	27.6, CH_2	2.15, overlapped
6′	125.0, CH	5.22, tq (6.9, 1.4)
7′	135.4, C	
8′	40.5, CH_2	2.03, overlapped
9′	27.3, CH_2	2.14, overlapped
10′	125.4, CH	5.22, tq (6.9, 1.4)
11′	131.4, C	
12′	26.2, CH_3	1.67, d (1.10)
5-OCH_3	55.8, CH_3	2.72, s
3′-CH_3	16.5, CH_3	1.82, br s
7′-CH_3	16.7, CH_3	1.55, s
11′-CH_3	18.1, CH_3	1.54, s

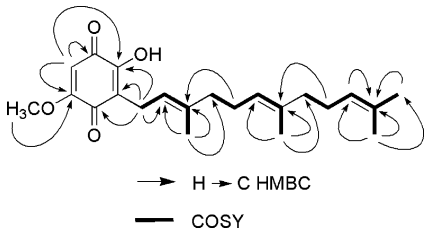

Figure 2. COSY and HMBC correlations of **4**.

Waters 2998 photodiode array detector and a Rheodyne 7125 injection port, and operated with Empower 3 software.

Sponge Materials. The sponge specimens were collected from the vicinity of Ko Ha Islets, Krabi Province, Thailand (7.4336, 98.8981) in December 2010 and in April 2014. The sponge was identified morphologically by one of us (S.P.) and by means of phylogenetic analysis[15] to be *Verongula* cf. *rigida* Esper (1794). The voucher specimens (AP10-017-02 and AP14-001-01) were deposited at the Institute of Marine Science, Burapha University, and at Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Prince of Songkla University. (See the Supporting Information for the extended morphological description and experimental section on the phylogenetic analysis.)

Extraction and Isolation. The sponge specimen from the 2010 expedition (1.8 kg, wet weight) was extracted with 1:1 MeOH/EtOAc (2.5 L) and EtOAc (2.5 L × 3). The solvents were removed, and the dried extract was partitioned consecutively with hexane, CH_2Cl_2, and *n*-BuOH. The hexane extract was fractionated with Sephadex LH20 (EtOAc), SiO_2 (2:98 MeOH/CH_2Cl_2), normal-phase HPLC (SiO_2, Vertisep GES Silica, 250 × 10 mm, 10 μm; 85:15 hexane/EtOAc, 2.0 mL/min), and reversed-phase HPLC (C18, MightSill RP-18 GPII, 250 × 4.6 mm, 5 μm; 8:2 MeCN/water; 1.0 mL/min) to yield compound **4** (3 mg, t_R 13 min).

The sponge specimen from the 2014 expedition (325 g, dry weight) was consecutively and exhaustively extracted with hexane (3 L × 5), CH_2Cl_2 (3 L × 4), and MeOH (3 L × 4). The hexane extract was chromatographed over a SiO_2 column (stepped gradient from 100:0 to 0:100 hexane/EtOAc), a Sephadex LH20 column (4:1 MeOH/EtOAc), a SiO_2 column (85:15 hexane/$CHCl_3$), and RP-HPLC (C18 MightSill RP-18 GPII, 250 × 4.6 mm, 5 μm; 85:15 MeCN/water, 1.0 mL/min), and compounds **2** (2 mg, t_R 16 min) and **3** (as a 3:4 mixture with **6**, 2 mg, t_R 29 min) were obtained. Along with the isolation of the new compounds described above, a series of previously reported compounds were isolated. The isolation is described in the Supporting Information.

*Quintaquinone (**2**):* yellow solid, $[\alpha]^{26}_D$ −7.53 (*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ε) 292 (3.98) nm; ECD (*c* 0.37, MeOH) λ ($\Delta\varepsilon$) 313 (−0.48), 224 (−1.77), 200 (4.09) nm; IR (neat) ν_{max} 3344, 3084, 2959, 1713, 1645, 1611 cm^{-1}; ^{1}H and ^{13}C NMR, Table 1; ESIMS *m*/*z* 479.2763 $[M + Na]^+$ (calcd for $C_{28}H_{40}O_5Na$, 479.2763); *m*/*z* 455.2838 $[M - H]^-$ (calcd for $C_{28}H_{30}O_5$, 455.2787).

*5-Epi-nakijiquinone L (**3**) and 5-epi-smenospongiarine (**6**):* red solid, UV (MeOH) λ_{max} (log ε) 325 (3.74) nm; ECD (*c* 0.8, MeOH) λ ($\Delta\varepsilon$) 324 (−0.29), 267 (0.12), 211 (−2.16) nm; IR (neat) ν_{max} 3277, 2956, 1595 cm^{-1}; ^{1}H and ^{13}C NMR, Table 1; ESIMS *m*/*z* 412.2857 $[M - H]^-$ (calcd for $C_{26}H_{38}NO_3$, 412.2842).

*3-Farnesyl-2-hydroxy-5-methoxyquinone (**4**):* brown solid; UV (MeOH) λ_{max} (log ε) 215 (3.95), 283 (4.08) nm; IR (neat) ν_{max} 3350, 2951, 1645, 1606 cm^{-1}; ^{1}H and ^{13}C NMR, Table 2; HR-ESIMS *m*/*z* 359.2211 $[M + H]^+$ (calcd for $C_{22}H_{31}O_4$, 359.2214).

5α-Reductase Inhibitory Assay. The enzyme 5α-reductase tested in this investigation was a whole-cell isolated enzyme harvested from LNCaP cells. The assay was performed following the protocol readily described.[16] Finasteride was used as a positive standard (IC_{50} 0.76 ± 0.03 μM).

Antiproliferative Assay. The antiproliferative activity in this investigation was determined by the MTT (on PC-3 cell line)[17] and SRB colorimetric assays (on HeLa and MCF-7 cell lines)[18] as previously described. Docetaxel (IC_{50} 0.5 μM against PC-3 cell lines) and camptothecin (IC_{50} 0.67 μM against HeLa cells) were used as positive controls.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.9b00886.

Supplementary experimental section and all the relevant spectra of compounds **2**, **3** (as a mixture with **6**), and **4** (PDF)

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Notes

The authors declare no competing financial interest.

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