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Pyrroloquinoline derivatives from a Tongan specimen of the marine sponge *Strongylodesma tongaensis*

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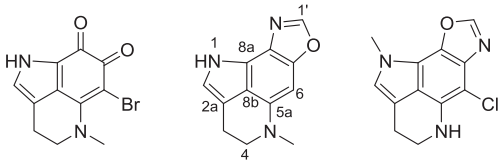
ABSTRACT

Pyrroloquinoline alkaloids are well known bioactive metabolites commonly found from latrunculiid sponges. Two new pyrroloquinoline alkaloids, 6-bromodamirone B (**1**) and makaluvamine W (**2**), were isolated from the Tongan sponge *Strongylodesma tongaensis.* Makaluvamine W (**2**) contains an oxazole moiety, which is rare in this large group of natural products, and is the first example of a pyrroloquinoline with nitrogen substitution at C-8. Both **1** and **2** lacked activity against a human promyelocytic leukemia cell line (HL-60), supporting the premise that an intact iminoquinone moiety plays a key role in the cytotoxicity of this compound class. The chemotaxonomic impact of these makaluvamine-type compounds is also discussed.

Introduction

Latrunculiid sponges have proven to be a prolific source of biologically active metabolites, particularly rich in pyrroloiminoquinone alkaloids [1,2]. This group of natural products contain the pyrrolo[4,3,2-*de*]quinoline core found in the discorhabdins [3–6], damirones [7,8], batzellines [9,10], veiutamine [11] and the makaluvamines [8,12–15]. The pyrroloiminoquinone alkaloids are known for their potent bioactivity toward various tumor cell lines [3,11,14–16], as inhibitors of topoisomerase I and II [11,12,14,16], and for antifungal [12,14] and antimicrobial [5] activities. In our continuing search for novel secondary metabolites from marine organisms, we investigated the crude extract of *Strongylodesma tongaensis* collected within the Vava'u Island group, Kingdom of Tonga, using an NMR-based screen. This chemical investigation of the sponge led to the discovery of two new compounds, 6-bromodamirone B (**1**) and makaluvamine W (**2**), along with the known compounds makaluvamines A, E, F [12], K [8], makaluvone, damirone B [7], makaluvic acid A [17] and tsitsikammamine B [18]. We report herein the isolation, structural elucidation, and biological evaluation of these new alkaloid metabolites.



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Results and discussion

Specimens of *S. tongaensis* were collected using SCUBA from Fakafotulā, Vava'u Island group, Kingdom of Tonga, in 2009.

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A sample of frozen sponge was extracted with MeOH and the extracts were partitioned using a reversed-phase polystyrene-divinylbenzene copolymer (PSDVB) column that was batch-eluted with increasing amounts of Me_2CO in H_2O. These fractions were further purified using normal phase (DIOL) and size-exclusion (LH20) chromatography, with final purification by reversed-phase C18 HPLC, to yield the new compound, 6-bromodamirone B (**1**), along with known compounds makaluvamines A, E, F, K, makaluvone and damirone B. A large scale extraction of the remaining frozen *S. tongaensis* was carried out using the same extraction and fractionation protocols as before, which led to the isolation of an additional new compound, makaluvamine W (**2**), together with the additional known compounds makaluvamine C, makaluvic acid A and tsitsikammamine B.

6-Bromodamirone B (**1**) was obtained as an optically inactive dark purple solid. The observation of a protonated molecule by positive mode HRESIMS indicated a molecular formula of $C_{11}H_9BrN_2O_2$ for **1** ($[M+H]^+$, *m/z* observed 280.9918, calculated 280.9920), requiring eight degrees of unsaturation. The presence of mono-bromination was evident by a $[M+2+H]^+$ peak in a 1:1 ratio. The ^{13}C NMR spectrum revealed 11 resonances, while a multiplicity-edited HSQC experiment confirmed that all hydrogen atoms except one were attached to carbon, including one methyl (δ_C 43.5), two methylenes (δ_C 56.9, 20.5) and one olefinic methine (δ_C 125.7). The remaining seven non-protonated centers were assigned as two α,β-unsaturated carbonyls (δ_C 176.5, 168.8) and five olefinic carbons (δ_C 154.3, 126.8, 125.7, 120.2, 87.9). With eight of the 11 carbons sp^2-hybridised, including the two carbonyls, this suggested that the molecule has three rings.

The proposed molecular formula of **1** was identical to makaluvone, while its uncluttered ^1H NMR spectrum was similar to both those of co-isolated makaluvone and damirone B. In contrast, the pyrrole *N*-methyl of makaluvone appeared absent, replaced instead by methyl substitution at secondary amine N-5. The structure of **1** was assembled using 2D-NMR spectroscopic data as well as by direct comparison with makaluvone [12] and damirone B [7]. The olefinic methine CH-2 (δ_H 7.02; δ_C 125.7) showed HMBC correlations to C-2a (δ_C 120.2), C-8a (δ_C 126.8 and C-8b (δ_C 125.7). The unusually large $^1J_{CH}$ coupling constant (194 Hz) of CH-2 suggested the attachment of a heteroatom, likely nitrogen, which was supported by the observed correlation from H-2 to NH-1 (δ_N −224.1) in a ^1H–^{15}N CIGAR experiment, establishing the existence of a pyrrole moiety – a common feature of the damirones and makaluvamines. A weak correlation between H-2 and the methylene triplet CH_2-3 (δ_H 2.85; δ_C 20.5), which in turn coupled to CH_2-4 (δ_H 3.79; δ_C 56.9), established the only spin system evident in the COSY spectrum. Several long-range correlations from H_2-3 to C-2, C-2a and C-8b, and from H_2-4 to C-2a, C-3, C-5a and CH_3-5 (δ_H 3.75; δ_C 43.5), and from *N*-5-Me to C-4, C-5a and N-5 (δ_N −279.5) were observed in the HMBC spectrum establishing the partial structure of 6-bromodamirone B (Fig. 1).

With eight of the 11 carbons and all nine protons accounted for, a fragment containing three carbons, two oxygens and one bromine atom remained to be assigned. Since all the protons were accounted for, and long range HMBC correlations were not observed to the remaining quaternary carbons, given their experimental chemical shifts were close to those reported for makaluvanone [12], makaluvamine O [15] and the damirones [7,8], the retention of a 1,2-diketone moiety was suggested. Supporting this assignment was the fact that four of the eight degrees of unsaturation were yet to be assigned. The olefinic carbon C-6 was determined as the site of bromination, judging from its shielded sp^2 chemical shift at δ_C 87.9, while the 1,2-diketone carbons were assigned as δ_C 168.8 (C-7) and δ_C 176.5 (C-8). Therefore, the structure of 6-bromodamirone B is proposed to be **1**, a regioisomer of makaluvone.

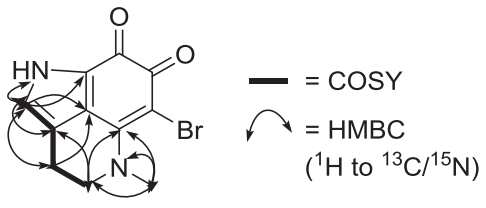


Fig. 1. Key COSY and HMBC correlation used to determine the majority of the structure of 6-bromodamirone B (**1**).

Makaluvamine W (**2**) was isolated as an optically inactive brown/purple solid. Positive ion HRESIMS analysis of a protonated molecule at *m/z* 214.0977 indicated a molecular formula of $C_{12}H_{11}N_3O$ (calculated *m/z* 214.0975) and requiring nine degrees of unsaturation. The ^{13}C and ^1H NMR spectra (d_6-DMSO) revealed the presence of 12 distinct carbons and 11 protons, respectively. A multiplicity-edited HSQC experiment confirmed the attachment of 10 protons to carbon, indicating the presence of one exchangeable proton, including one methyl (δ_C 38.1), two methylenes (δ_C 52.0, 22.6) and three olefinic methines (δ_C 149.1, 115.1, 82.4). The remaining six carbons (δ_C 149.4, 142.0, 123.6, 118.0, 115.8, 110.4) were all assigned as non-protonated olefinic carbons.

The 1D and 2D-NMR experimental data (see Table 1) of **2** strongly indicated the presence of a pyrrolo[4,3,2-*de*]quinoline moiety, including the usual mutually coupled methylene triplets at δ_H 2.97 (CH_2-3: δ_C 22.6) and δ_H 3.25 (CH_2-4: δ_C 52.0), the pyrrole methine proton at δ_H 6.84 (CH-2: δ_C 115.1) and an olefinic proton resonance at δ_H 6.46 (CH-6: δ_C 82.4). The data also revealed the presence of an unusual sp^2-hybridised methine CH-1′ (δ_H 8.36: δ_C 149.1) with a very large heteronuclear coupling constant ($^1J_{CH}$ = 235 Hz), suggesting the structure of **2** to be distinct from the common makaluvamines/damirones.

Pyrrole methine CH-2 (δ_H 6.84; δ_C 115.1) displayed a series of HMBC correlations to C-2a (δ_C 110.4), C-8a (δ_C 123.6), C-8b (δ_C 115.8) and NH-1 (δ_N −248.1), leading to the construction of the pyrrole ring. The exchangeable proton NH-1 (δ_H 11.4) showed a COSY correlation to H-2 and HMBC correlations to four olefinic carbons; CH-2, C-2a, C-8a and C-8b, supporting this assignment. The COSY spectrum revealed a long-range correlation between H-2 and H_2-3 (δ_H 2.97; δ_C 22.6), which subsequently showed a vicinal COSY correlation to H_2-4 (δ_H 3.25; δ_C 52.0), revealing the only spin system in the molecule. HMBC correlations from H_2-3 to CH-2, C-2a, C-8b and CH_2-4, and from H_2-4 to C-2a, CH_2-3, CH_3-5 (δ_H 2.91; δ_C 38.1) and C-5a (δ_C 142.0), and from H-6 to C-5a, C-8b, C-7 (δ_C 149.4) and C-8 (δ_C 118.0), established the presence of the *N*-substituted pyrrolo[4,3,2-*de*]quinoline core (Fig. 2).

However, there were significant changes in the chemical shifts associated with the iminoquinone ring, including the apparent absence of the α,β-diketone frequently found in damirone-type alkaloids. The pyrrolo[4,3,2-*de*]quinolone core accounted for seven degrees of unsaturation. The remaining unassigned nitrogen and oxygen atoms necessitated the inclusion of the sp^2-hybridised methine CH-1′ and the final two degrees of unsaturation. Therefore, an oxazole substructure was proposed that was consistent with the observed oxidation state and large $^1J_{CH}$ value (235 Hz) [19,20]. This accounted for the final nitrogen and the oxygen atoms and was confirmed through the observed correlation from H-1′ to a nitrogen resonance at δ_N −135.8 in the ^1H–^{15}N CIGAR experiment, supporting the presence of an oxazole ring. The HMBC spectrum showed strong correlations from H-1′ to both C-7 and C-8, and a weak correlation to C-6 connected the substructure to the remainder of the molecule.

A subsequent search of the MarinLit database identified citharoxazole (**3**), an unprecedented pyrroloiminoquinone featur-

Table 1
^{13}C (150 MHz) and ^{1}H (600 MHz) NMR data for 6-bromodamirone B (**1**) and Makaluvamine W (**2**).[a]

Position	**1**[b]				**2**[c]			
	$\delta_{C/N}$	mult.	$^{1}J_{CH}$ (Hz)	δ_H mult. (*J*, Hz)	$\delta_{C/N}$	mult.	$^{1}J_{CH}$ (Hz)	δ_H mult. (*J*, Hz)
1	−224.1	NH			−248.1	NH		11.4 s
2	125.7	CH	194	7.02 s	115.1	CH	184	6.84 s
2a	120.2	C			110.4	C		
3	20.5	CH_2	132	2.85 t (7.0)	22.6	CH_2	129	2.97 t (5.9)
4	56.9	CH_2	142	3.79 t (7.0)	52.0	CH_2	137	3.25 t (5.9)
5	−279.5	N			−321.2	N		
5-Me	43.5	CH_3	139	3.75 s	38.1	CH_3	135	2.91 s
5a	154.3	C			142.0	C		
6	87.9	C			82.4	CH	163	6.46 s
7	168.8	C			149.4	C		
8	176.5	C			118.0	C		
8a	126.8	C			123.6	C		
8b	125.7	C			115.8	C		
9					−135.8	N		
1′					149.1	CH	235	8.36 s

[a] For full NMR data, see the Supporting Information.
[b] Acquired in CD_3OD.
[c] Acquired in DMSO d_6.

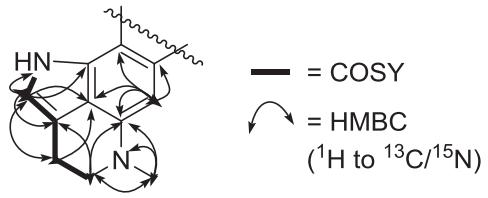
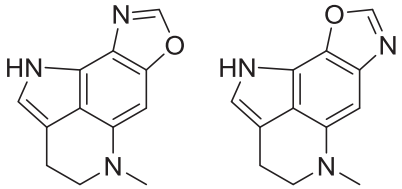


Fig. 2. Key COSY and HMBC correlation used to assign the majority of the structure of makaluvamine W (**2**).

ing a benzoxazole moiety, isolated from the Mediterranean latrunculid sponge *Latrunculia citharistae* [19]. The large $^{1}J_{CH}$ value (235 Hz) observed for CH-1′ in makaluvamine W (**2**) was exactly the same as the reported value for citharoxazole [19], confirming the presence of the oxazole moiety. However, the NMR spectroscopic data reported for the oxazole portion of citharoxazole did not match that of **2**, suggesting changes to its constitutional structure.

With all carbons and degrees of unsaturation accounted for, two possible constitutions (**2a** and **2b**) could be proposed regarding the relative placement of the N and O atoms (Fig. 3). Although H-6 showed HMBC correlations to C-5a, C-7, C-8 and C-8b, there was no direct evidence to which carbon the oxygen and nitrogen atoms were attached (C-7 and C-8) around the aromatic ring. One of the inherent challenges associated with interpreting HMBC spectra is the inability to differentiate between $^{2}J_{CH}$ and $^{3}J_{CH}$. However, certain functional groups have very diagnostic correlation patterns. For example, in aromatic rings $^{n}J_{CH}$ values differ meaning $^{3}J_{CH}$ (~7–8 Hz) correlations are typically stronger than $^{2}J_{CH}$ (~1–3 Hz)



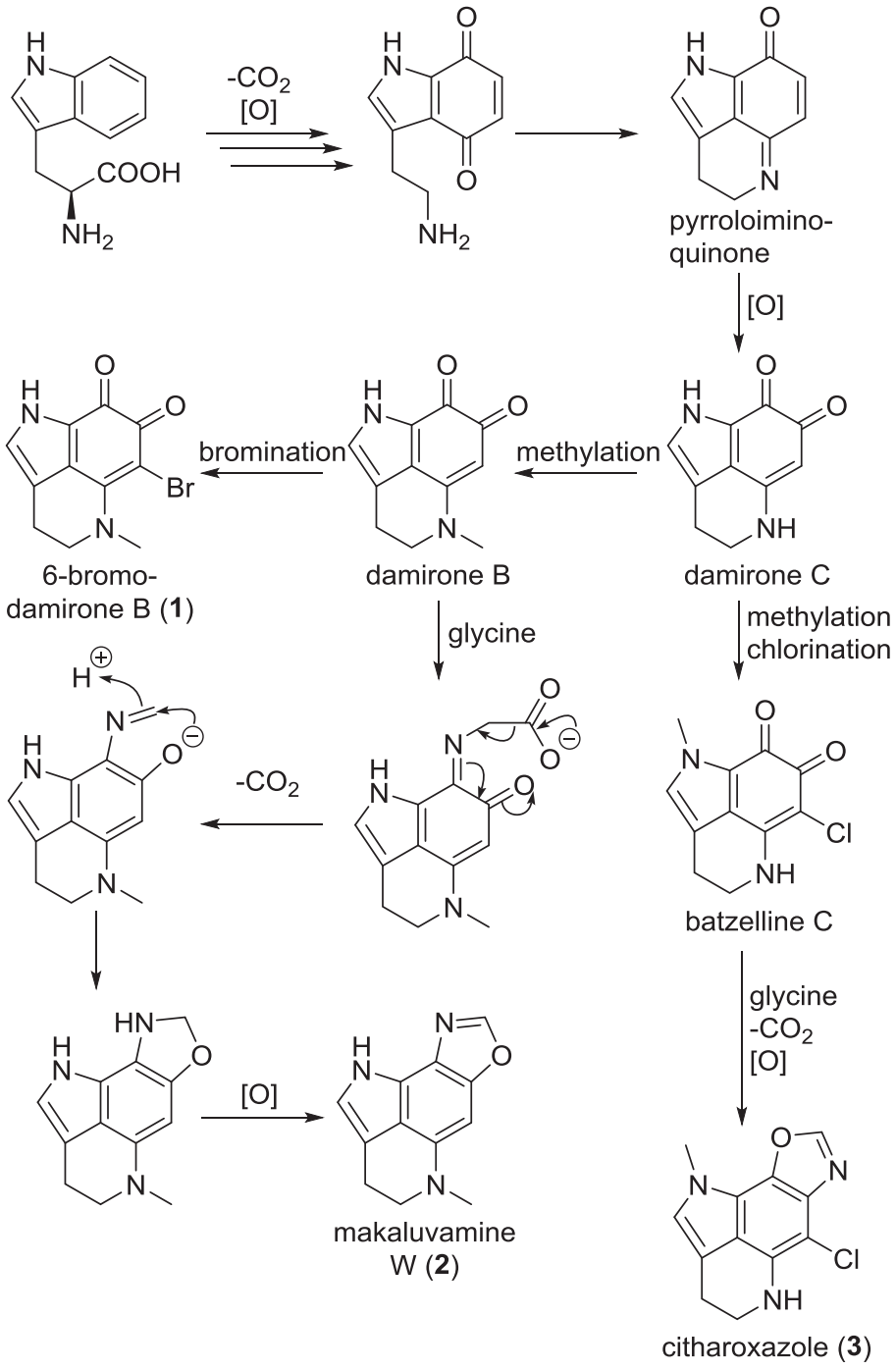
2a **2b**

Fig. 3. Possible constitutions (**2a** and **2b**) of makaluvamine W.

correlations so such ambiguity ($^{3}J_{CH}$ *vs* $^{2}J_{CH}$) is easily resolved in these cases [21–25]. Therefore, the placement of the oxazole ring was assigned from the strength of the HMBC correlation intensity from H-6, with weak HMBC correlations from H-6 to C-5a and C-7 and stronger correlations to C-8 and C-8b, thus proposing structure **2a** as the probable structure and only the second example of a makaluvamine-type structure containing an oxazole to be reported from this family of natural products. This is consistent with the absence of a $^{1}H–^{15}N$ correlation from H-6 to N-9 in the CIGAR experiment. To the best of our knowledge, makaluvamine W (**2**) is also the first example of a pyrroloquinoline-type secondary metabolite with nitrogen substitution at C-8.

Biosynthetically, one potential proposal for the formation of **2** is that increased electron density at C-7, due to resonance from N-5 in damirone B as the most likely biogenic precursor to **2**, would favor Schiff base formation with decarboxyglycine at C-8, giving rise to the oxazole regioisomer **2a** proposed here. Conversely, the presence of a chlorine atom would increase electron density at C-8 in biosynthetic precursor batzelline C [10], giving rise to the regioisomer proposed for citharoxazole **3** (Scheme 1) [19,20].

To confirm this assignment, computational assessment of the two possible structures **2a** and **2b** was used, in conjunction with Goodman's DP4 probability [26–29]. As the isolation of **2** utilized formic acid in the final step, there was also a possibility of the molecule being protonated due to the presence of the basic nitrogen groups (Fig. 4). All these possibilities (Figs. 3 and 4) were modelled and analyzed computationally to confirm the structure proposed. After optimization, the NMR data for all the six molecules (**2a**, **2b**, **2a-1**, **2a-2**, **2b-1**, and **2b-2**) were calculated at the *m*PW1PW91/aug-cc-pVTZ/SMD_{DMSO} level of theory. Methanol was used to reference the NMR chemical shift values as described by Sarotti and Pellegrinet [30] because of its better accuracy and precision than using TMS as a reference standard. DP4 analysis of non-protonated **2a** and **2b** as well as protonated isomers **2a-1**, **2a-2**, **2b-1** and **2b-2** indicated 100% probability of regioisomer **2a** as the best fit between experimental and calculated data (Supplementary Information). Upon removing neutral molecules **2a** and **2b** to leave protonated **2a-1**, **2a-2**, **2b-1**, and **2b-2**, DP4 analysis of the calculated and experimental NMR data showed that structure **2a-2** had a 62.4% probability of being correct with **2a-1** 37.6% (Supplementary Information) likely, thus ruling out **2b-1** and **2b-2**. Thus, with the fact that makaluvamine W was isolated using acid and inclusion of both the neutral and the protonated analogues in the calculations and irrespective of whether or not



Scheme 1. Plausible biogenesis of 6-bromodamirone B (**1**), makaluvamine W (**2**) and citharoxazole (**3**).

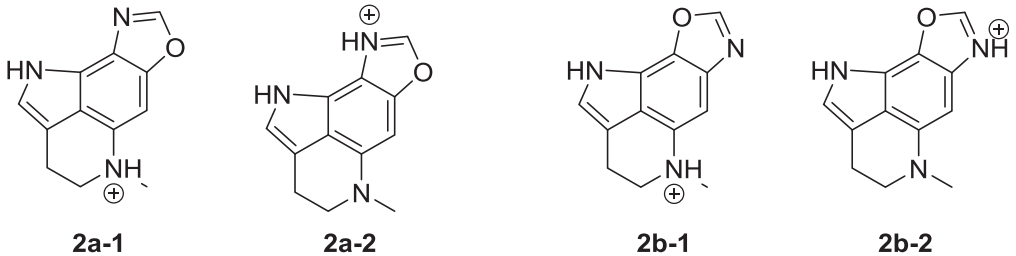


Fig. 4. Possible protonation sites of the potential regioisomers of makaluvamine W (**2**).

we included protonation state, including the possible site of protonation, DP4 analysis with all permutations identified the same isomer as being the parent scaffold, i.e. **2a**, and in agreement with our proposal. The detailed computed NMR data can be found in the Supporting information.

All the isolated metabolites were assessed for cytotoxic activity against the human promyelocytic leukemia cell line HL-60, although makaluvic acid, damirone B, and both new metabolites 6-bromodamirone B (**1**) and makaluvamine W (**2**) were found to be inactive (IC_{50} > 49, 50, 36, 47 μM, respectively). By contrast, tsitsikammamine B, and makaluvamines C, F and K all exhibited moderate cytotoxicity in the same assay (IC_{50} = 1.6, 2.6, 3.0, 4.5 μM, respectively), while makaluvamines A (IC_{50} = 30.4 μM) and E (IC_{50} = 20.3 μM) were less potent. These results are entirely consistent with previous observations indicating the requirement for an intact iminoquinone functionality to impart potent bioactivity [14,17].

The genus *Strongylodesma* appears to have avoided significant chemical investigation in the past. To date, only three other reports of natural products from the genus have been published [31–33], all of which were from South African specimens. Our current study is consistent with the chemistry reported from *S. aliwaliensis*, which was found to contain various makaluvamines and makaluvone [31,32], but is distinctive from *S. algoaensis* which was the source of various discorhabdin congeners [33]. Within their revision of the genus *Strongylodesma*, Samaai et al. note that specimens of *Strongylodesma* have previously been misidentified and have been placed within the genera *Batzella, Damiria*, *Histodermilla*, *Negombata* and *Zyzzya*, all of which have been reported as sources of pyrroloiminoquinone secondary metabolites [34]. Given the relative lack of distinctive morphological and physical identifiers to differentiate members of these genera, our current report underscores the importance of chemotaxonomy to assist in the taxonomic assignment of these rare, but chemically productive, marine sponges.

Conclusion

Two new makaluvamine/damirone-type alkaloids have been isolated from a Tongan specimen of the marine sponge *Strongylodesma tongaensis*. The structures of these molecules were determined by spectroscopic means, and the unusual presence of an oxazole moiety in **2** is consistent with a proposed biogenesis from the Schiff base reaction of damirone B with decarboxyglycine. The structure of **2** was confirmed using computational methods. Both new compounds were essentially inactive, again consistent with the requirement of an intact iminoquinone functionality required by these metabolites to be bioactive.

Declaration of Competing Interest

None.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data (full experimental details, NMR assignments and spectra) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.06.014.

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