Antimalarial Activity of Sesquiterpenes from the Marine Sponge Acanthella klethra

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ANTIMALARIAL ACTIVITY OF SESQUITERPENES FROM THE MARINE SPONGE *ACANTHELLA KLETHRA*

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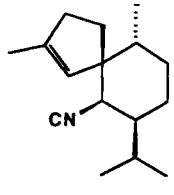
ABSTRACT.—Five sesquiterpenoids containing isonitrile or isothiocyanate groups were isolated from the sponge *Acanthella klethra*. Compounds **1** and **2** were identified as axisonitrile 3 and the corresponding isothiocyanate derivative, respectively. Compounds **3–5** were found to be eudesmane sesquiterpenes. None of these compounds was cytotoxic toward cultured KB-3 cells, but varying degrees of activity were observed with cultured *Plasmodium falciparum*. Compound **1** demonstrated greatest promise as an antimalarial agent.

In an ongoing collaborative effort to discover new biologically active natural products, we have isolated five sesquiterpenoids containing isonitrile or isothiocyanate moieties from the sponge *Acanthella klethra* Pulitzer-Finali (Axinellidae), collected from Pelorus Island, Queensland, Australia. As was recently reported (1), compound **1** was shown to be the bicyclic spirosesquiterpene axisonitrile 3, and compound **2** was found to be axisothiocyanate 3 by spectroscopic methods (nmr, ir, ms) (1,2). The eudesmane compounds **3–5** are similar to acanthellin 1 (3), and compounds **4** and **5** are novel isolates whose structures have recently been reported (1).

Compounds **1–5** as well as four known antimalarial drugs were evaluated for antimalarial activity against cultured *Plasmodium falciparum* (chloroquine-sensitive D6 and chloroquine-resistant W2 strains) using a microdilution technique



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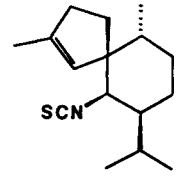

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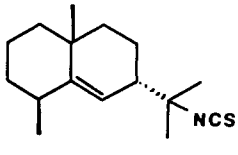

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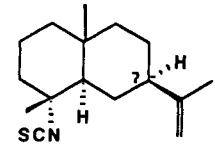

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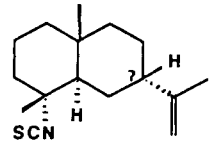

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that monitors incorporation of radioactive hypoxanthine (4–6). The cytotoxic potential of each of these compounds was also determined using cultured KB-3 cells as previously described (4,7) (Table 1).

TABLE 1. Evaluation of the Cytotoxic and Antimalarial Activity of Pure Isolates from *Acanthella klethra*.

Compound	KB cells	*Plasmodium falciparum* strain	
	IC_{50}[a]	D6	W2
		IC_{50}	IC_{50}
Chloroquine	17,400	1.95	22.8
Quinine	>20,000	10.2	23.8
Mefloquine	3,500	8.2	0.49
Artemisinin	>20,000	4.1	0.71
1	>20,000	142	16.5
2	>20,000	12340	3110
3	>20,000	2240	610
4	>20,000	4000	550
5	>20,000	>10,000	>10,000

[a]IC_{50} values are expressed in ng/ml.

None of the five isolates exhibited cytotoxicity toward KB-3 cells at the highest concentration tested. However, compounds **1–4** were found to demonstrate dose-dependent in vitro anitimalarial activity against *P. falciparum*. As described previously (4,8), the ratio of observed cytotoxic and antimalarial IC_{50} values (the selectivity index) affords an indication of selective toxicity toward the malarial parasite. In this context, the most potent antimalarial activity was observed with compound **1**, and its selectivity for the chloroquine-resistant strain of *P. falciparum* compares favorably to that of the known drugs. The isonitrile group appears to be crucial for activity since the corresponding isothiocyanate derivative **2** is 500-fold less active than **1**. The eudesmane isothiocyanate isolates **3** and **4** have lower antimalarial potential than compound **1** but still show moderate activity against the chloroquine-resistant strain of *P. falciparum*. A reversal of the stereochemical configuration at the C-7 position of **4** and **5** was also observed to have a significant effect on the antimalarial activity.

This is the first report in which the antimalarial potential of a compound bearing an isonitrile group has been demonstrated. Isonitriles are rarely encountered in nature; most are produced by marine organisms (9,10), and many of these are terpenes. Sponges of the orders Axinellida, Halichondrida, and Lithistida have proven to be particularly rich sources of isonitriles and their corresponding isothiocyanate and formamide derivatives (2,11). Furthermore, these compounds have been reported to mediate a host of biological responses including antibiotic (12,13), ichthyotoxic and antifeedant (14,15), cytotoxic (16), and anthelminthic (11,17) activities. As demonstrated by the current report, the favorable selectivity index of **1**, as well as its ability to inhibit the growth of the chloroquine-resistant W2 strain with greater efficacy than with the D6 strain, suggests that additional studies are warranted to define the antimalarial potential of this structural class.

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