Invited Review

Antimalarial Activity: The Search for Marine-Derived Natural Products with Selective Antimalarial Activity[†]

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In this short review, an approach to the isolation of potential antimalarial agents and lead compounds is outlined. A discussion of organism collection, followed by a description of biological testing and isolation methodologies, is also given. For two organisms, details of their secondary metabolite chemistry are reported. From one of these, *Laurencia papillosa*, the two aromatic compounds *p*-hydroxybenzaldehyde (**1**) and *p*-methoxybenzyl alcohol (**2**) were isolated. From the other, the tropical marine sponge *Cymbastela hooperi*, 15 diterpenes (**3−17**), which contain isonitrile, isothiocyanate, and isocyanate functionalities, are reported. Together with the diterpenes, three sesquiterpene hydrocarbons, **18−20**, and the thiol, **21**, were obtained. All structures were established by spectroscopic methods, particularly $^1H-^1H$ and $^1H-^{13}C$ shift-correlated 2D NMR spectroscopy and accurate mass measurement (HREIMS). The majority of isolates demonstrate significant and selective *in vitro* antimalarial activity. For compounds **4−17** a brief description of their possible structure−activity relationships is provided.

In the last two decades, malaria has regained its status as an extremely important threat to the health and economic prosperity of the human race. It is estimated that 1.5×10^9 people live in regions where malaria is endemic and that in excess of 1.5 million people die from this disease each year. The disease is caused by the protozoan parasite, *Plasmodium*, which is transmitted through the bite of the Anopheles mosquito. Since it is almost impossible to remove the vector of transmission, there will always be a need for new antimalarial agents, particularly those that may have a novel mode of action.

One of the noteworthy facts about the disease is its geographical distribution and the corresponding low level of funding malaria research receives. Malaria is currently restricted to mainly economically poor tropical
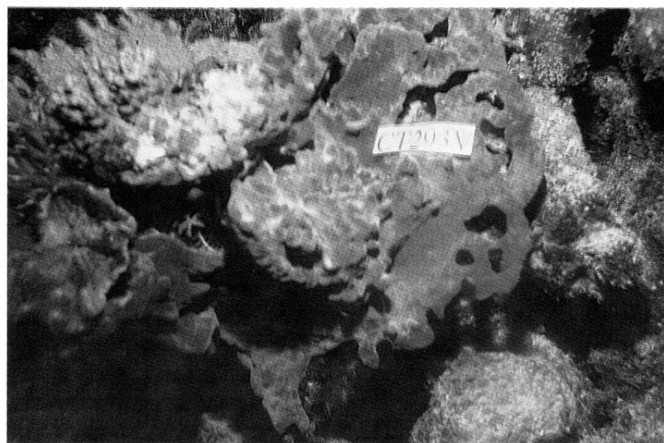

Figure 1. Photograph of the new sponge species *C. hooperi* van Soest, Desqueyroux-Faúndez, Wright, and König (Halichondrida, Axinellidae), CT293V.

and subtropical regions of the world where the people can ill-afford to pay for the high technology facilities needed to do adequate research into these types of problems. It is hoped that in the not-too-distant future, funding for malaria research will come to reflect the
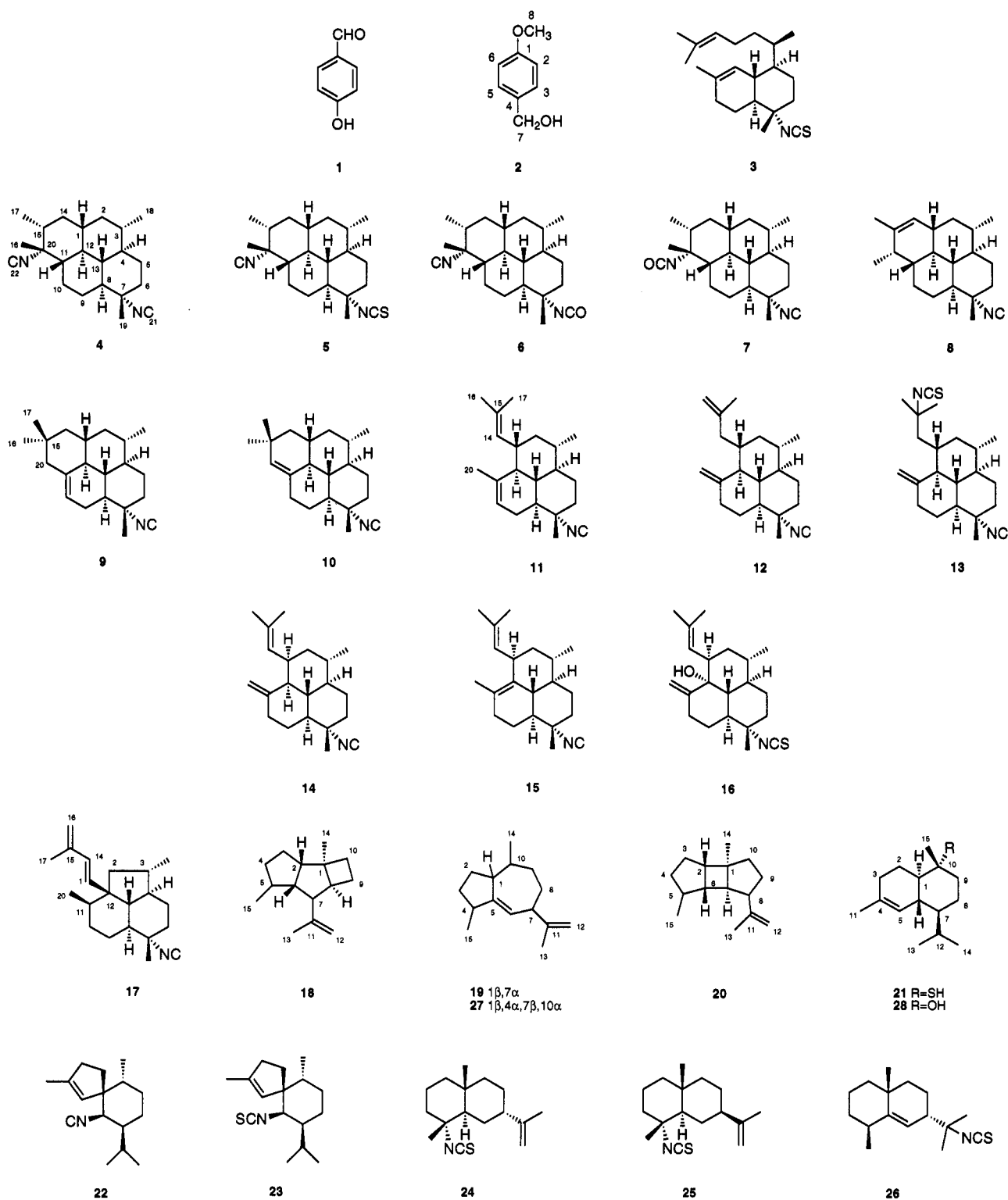

Chart 1

severe threat that this disease represents to the world's population as a whole, more than is currently the case.

Some years ago, a small sample of the sponge *Acanthella klethra* Pulitzer-Finali was collected from the Palm Islands group, north of Townsville, Queensland, Australia. From the dichloromethane (CH₂Cl₂) solubles of this sponge, five sesquiterpenes (**22–26**, Chart 1), two of which were new natural products (**24** and **25**), and one of which, axisonitrile-3 (**22**), had potent *in vitro* antimalarial activity and no detectable cytotoxic properties, were isolated.[1, 2]

On the basis of these findings, it was decided to pursue the isolation and identification of other compounds that contained –NC or similar functionalities. As a result of these investigations, CH₂Cl₂ extracts of three marine sponges, two soft corals, and one marine alga were shown to demonstrate significant and selective *in vitro* antimalarial activity. To date, two of these extracts have been investigated in detail. From the first of these, which derived from the marine red alga *Laurencia papillosa* (J. Agardh) Greville (Rhodomelaceae, Rhodophyta), two aromatic compounds, *p*-hydroxy-

Table 1. Cytotoxicity to KB Cells and *P. falciparum* Clones D6 and W2 of CH$_2$Cl$_2$ Extracts Which Yielded Survival Rates of Less Than 50% in Preliminary Screening

compd or extract tested	KB cells IC$_{50}$[a]	clone D6		clone W2	
		IC$_{50}$	SI[b]	IC$_{50}$	SI
chloroquine	17 400	1.6	10 610	29.9	580
quinine	>20 000	11.1	>1800	87.4	>230
mefloquine	3500	7.2	490	3.6	970
artemisinin	>20 000	6.2	>3220	7.1	>2820
CT293B	>20 000	>10 000		>10 000	
CT293G	>20 000	>10 000		>10 000	
CT293N	>20 000	9680	2	9960	2
CT293Q	>20 000	7810	2.5	9050	2.2
CT293R	NT	>10 000		>10 000	
CT293V	>20 000	210	95	310	64.5
CT293W	>20 000	>10 000		>10 000	
CT293X[c]	>20 000	>10 000		>10 000	
CT293Y	>20 000	8460	2.4	7050	2.8
CT293Z	NT	>10 000		>10 000	
CT293ZZ	>20 000	8710	2.3	9100	2.2
CT193D	NT	>10 000		>10 000	
CT193K	NT	6860		>10 000	
CT193M	NT	>10 000		>10 000	

[a] Expressed in ng/mL. [b] Selectivity index (SI) is defined as the ratio of KB cell cytotoxicity to *P. falciparum* cytotoxicity (antimalarial activity). [c] MeOH extract.

benzaldehyde (**1**) and *p*-methoxybenzyl alcohol (**2**), were isolated. From the second active CH$_2$Cl$_2$ extract, this time from a sample of the new sponge species, *Cymbastela hooperi* van Soest, Desqueyroux-Faúndez, Wright, and König (Axinellidae, Halichondrida)[3] (Figure 1), a series of new diterpene metabolites, 12 in all (**3, 5–11, 13**, and **15–17**), were isolated.[4] Together with these compounds, three sesquiterpene hydrocarbons, **18–20**, and the thiol, **21**, were also obtained.[5] In the current review, the approach to the isolation of potential antimalarial agents and lead compounds is presented. An initial discussion of organism collection philosophy, followed by a description of biological testing and isolation methodologies, is given. For the two CH$_2$Cl$_2$ extracts that were studied in more detail, a summary of their secondary metabolite chemistry is provided. A brief description of the possible structure–activity relationships for compounds **4–17** is presented.

Examples of Isolation of Biologically Active Compounds

In order to facilitate the planned natural products investigations, two major collection trips, one to Australia and one to the Caribbean, were undertaken. From Australia, 27 organisms, and from the Caribbean, 17 organisms, were sampled. Organisms selected for collection were never taken in totality. In the specific case of sponges, a section of the sponge was left so that the specimen could regrow. For soft corals, gorgonians, tunicates, nudibranchs, and algae, samples were taken only when it was evident that such collection would have no major impact on the local population. The total wet (frozen) weight of all collected material (44 samples) did not exceed 40 kg.

At completion of sampling a small piece (~1 g) of each specimen was taken, freeze-dried, and then exhaustively extracted with CH$_2$Cl$_2$ followed by MeOH. Resultant extracts were submitted to antimalarial and cytotoxicity testing.[6, 7] The results of these bioassays (see Table 1) indicated six (CT293N, CT293Q, CT293V, CT293Y, CT293ZZ, and CT193K) of the CH$_2$Cl$_2$ extracts to have

Table 2. General Spectroscopic Features of –NC, –NCS, and –NCO Functionalities

func-tionality	UV, λ_{max}	IR, ν_{max} (cm^{-1})	^{13}C NMR (ppm)
–NC	<190	~2130, sharp	~152, broad or triplet ($J \approx 4$ Hz)
–NCS	~225 ($\epsilon \approx 1000$)	~2130, broad	~122, singlet
–NCO	~250 ($\epsilon \approx 1000$)	~2130, broad	~130, broad

antimalarial potential. To date, two of these have been investigated for their chemical profiles: the marine red alga *Laurencia papillosa* (CT193K) (IC$_{50}$ ≈ 7000 ng/mL), and the sponge *Cymbastela hooperi* (CT293V) (IC$_{50}$ = 210 ng/mL).

Following the biological activity assessment of the CH$_2$Cl$_2$ and MeOH extracts a strict bioassay-guided approach to fractionation and isolation was pursued. Each sample was freeze-dried and then exhaustively extracted with CH$_2$Cl$_2$ followed by MeOH to yield a quantity (see refs 4 and 5 and the Experimental Section) of CH$_2$Cl$_2$-soluble material.

L. papillosa **(CT193K)**. After fractionation of the CH$_2$Cl$_2$-solubles of the marine red alga *L. papillosa* (CT193K) by vacuum liquid chromatography (VLC), an assessment of the individual activities of the fractions was made (see refs 6 and 7). From these results, it was evident that six fractions (F3, F5, and F8–F11) warranted further investigation. This was only possible, however, for fraction F5 due to very small amounts of material contained in the majority of the other fractions (<5 mg). After repeated normal-phase HPLC of this fraction, the two aromatic compounds **1** and **2** were isolated and their biological activities assessed (see Table 3). This is the first report of **1** having, albeit weak, selective *in vitro* antimalarial activity (see Table 3) and of **2** as a marine-derived natural product. ^{1}H-NMR analysis of all fractions from the initial VLC indicated that other active fractions contain small amounts of compounds typical of the genus *Laurencia*,[8] which suggests that other *Laurencia* metabolites might have some antimalarial activity.

C. hooperi **(CT293V)**. In a fashion similar to that applied to the algal specimen, the sample of the sponge *C. hooperi* (CT293V) was worked up.[4] After fractionation of the CH$_2$Cl$_2$-solubles, 11 fractions were obtained, the antimalarial activities of which were assessed. The biological activity data indicated VLC fractions 4 and 5 to have the most pronounced antimalarial activity. Further investigation revealed **4**,[9–11] a modified (iso-)-cycloamphilectane-based compound, to be the main component. Next, VLC fraction 2 was selected for chemical profiling, as it contained no **4**, and it represented a reasonable quantity of material (>0.5 g) and demonstrated good *in vitro* antimalarial activity. It was found to contain 13 diterpenes (**5–17**).[4] Of these, compound **17** is the first member of a new structural class, while compound **16** is the first member of its class to contain an oxygen-based functionality, and 11 substances were new natural products (**5–11, 13**, and **15–17**). Furthermore, for marine-derived natural products, a number of compounds contained unprecedented combinations of functionalities (**5–7, 13**, and **16**). All of the functional groups found in these compounds were quite readily identified on the basis of their spectroscopic characteristics, as outlined in Table 2 and in the review by Chang and Scheuer.[12]

To establish several structural deductions unequivocally, single-crystal X-ray crystallographic analysis was undertaken for compounds **8**, **10**, **14**, and **15**.[13]

The remaining VLC fractions with antimalarial activity were not further investigated, as they were shown by ¹H-NMR and TLC analysis to contain different combinations of compounds **4–17**. The biologically inactive VLC fraction 1 appeared to be promising chemically, however, since its ¹H-NMR spectrum showed many interesting resonances. After repeated HPLC separations, this fraction yielded four sesquiterpenes, three as hydrocarbons (**18–20**), one as a thiol (**21**), and one diterpene isothiocyanate (**3**).[4,5] All structures were solved using extensive 1D and 2D NMR measurements and mass spectrometry. Even though the full details of the isolation and structure elucidation for **3** and **18–21** will not be given here, a few aspects concerning them individually and as a group will follow.

Compound **21** is certainly a representative of a class of marine-derived natural products with an unusual functionality. Its ground structure was readily and unambiguously deduced on the basis of an INADEQUATE NMR measurement. The determination of the relative stereochemistry and the nature of the functional group at C-10 were, however, not so easily resolved. The positive EIMS of **21** contained the $[C_{15}H_{24}]^+$ fragment ion as the base peak and no other obvious ions (>1%) at greater mass. Consequently, an elemental analysis was required to establish its molecular formula as $C_{15}H_{26}S$ and the functional group at C-10 to be a free thiol [SH, exchangeable resonance at δ 1.30 (s)], a functionality that has rarely been encountered in marine organisms. Stereochemically, **21** was deduced to have the same relative configuration as **28** [(−)-α-cadinol[14]] on the basis of ¹³C-NMR and optical rotation data comparison.

The final sesquiterpene isolated from the first VLC fraction was **18**, a compound without precedent in the marine natural products literature and only the second example in nature of a compound possessing the tricyclo-[6.2.0.3²,⁶]decane ring system; the other, also a sesquiterpene, but clearly of different biosynthetic origin, was reported from a laboratory-cultured slime mold.[15] Compound **3**, also isolated from the first VLC fraction, has the same planar structure as 10-isothiocyanatobiflora-4,15-diene.[16] Close inspection of its ¹³C-NMR data and optical rotation revealed clearly, however, that this compound and **3** were different stereochemically. Comparison with compounds having structures similar to **3** allowed its relative configuration to be assigned as shown in the structural representation.

Compounds having carbon skeletons similar to those of **19** and **20** are most frequently encountered in brown alga,[17,18] and not sponges. In this respect, the data presented represent a unique occurrence of such structural types in sponges. In its own right, **19** is not an unusual natural product as it is very similar to the known compound γ-gurjunene (**27**).[19] On the other hand, **20**, as a sesquiterpene hydrocarbon, is structurally unprecedented in the marine literature, although not in the natural products literature. A series of diterpenes based on the same ring system has been isolated from brown algae,[17] and two sesquiterpenes having the same skeleton are reported from the essential oil of *Geranium bourbon*,[20–22] but there are no

Scheme 1. Proposed Biosynthetic Relationship between **19** Type and **18** and **20** Types
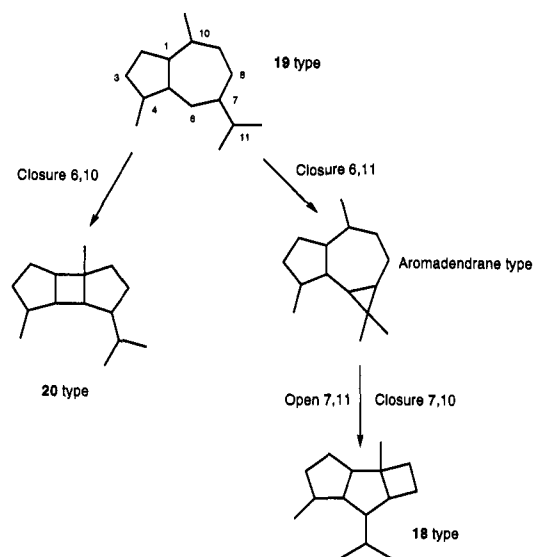
reports in the marine literature of the sesquiterpene equivalents, and certainly not from sponges.

Biosynthetically, compounds **18** and **20** can be considered as being derived from a common precursor having the same planar structure as **19**, as is shown in Scheme 1. When it is considered that an aromadendrane-type compound is probably the direct precursor of **18**, it is somewhat surprising that more representatives of this class of sesquiterpene have not been encountered in nature.

Structure–Activity Relationships (SARs) of Compounds 4–17

At the completion of the isolation and structure elucidation phase of this study, a sample of each pure compound was submitted to biological testing. The biological activity of each compound was first assessed *in vitro* against two clones of the malaria parasite, *Plasmodium falciparum*, and then against the mammalian KB cell line, so as to facilitate the calculation of an experimental selectivity index (SI)[6] in order to assess whether the observed antiplasmodial activity was a specific or general toxic effect, the results of which are presented in Table 3. Of all the samples tested, compounds **4** and **7** had the most potent ($IC_{50} \approx 4$ ng/mL) and selective (SI > 1000) *in vitro* antimalarial activity.

The isolates from VLC fractions 2 and 4, that is compounds **4–17**, could be associated structurally into four groups: six amphilectanes, three with the C_4 side chain α-oriented (**11–13**) and three with it β-oriented (**14–16**), two cycloamphilectanes (**9**, **10**), and five isocycloamphilectane (**4–8**) derivatives, as well as the first ever described neoamphilectane (**17**). These structural correlations and the results of the bioassays (Table 3) indicated some clear structure–activity relationships (SAR), possibly due to a receptor-based mode of action of these compounds. On this basis a more detailed analysis of possible SAR was undertaken using computer-based molecular modeling methodologies.

As **4** was one of the two most active compounds, and since its absolute configuration and X-ray crystal structure were known, it was used as the basis structure for

Table 3. Cytotoxicity of Compounds **1–21** to KB Cells and *P. falciparum* Clones D6 and W2

compd tested	KB cells $IC_{50}{}^a$	clone D6		clone W2	
		IC_{50}	SI^b	IC_{50}	SI
chloroquine	17 400	3.8	4600	50.5	340
quinine	>20 000	19.4	>1030	54.6	>370
mefloquine	3500	11.5	300	3.8	920
artemisinin	>20 000	2.8	>7140	2.1	>9400
1	>20 000	7330	>2.7	5560	>3.6
2	>20 000	>10 000		>10 000	
3	>20 000	>10 000		>10 000	
4	4700	4.7	1000	4.3	1100
5	1600	45.1	35	28.5	56
6	2000	74.9	27.0	56.1	36.0
7	4300	3.2	1340	2.5	1710
8	18 200	62.5	290	19.5	930
9	>20 000	84.9	>240	28.4	>700
10	14 500	74.1	200	23.8	610
11	>20 000	302	>66.2	133	>150
12	>20 000	520	>38.5	242	>82.6
13	>20 000	470	>42.6	109	>183
14	3200	14.1	230	9.3	340
15	15 200	58.5	260	25.6	590
16	5300	797	6.6	423	12.0
17	19 100	90.0	210	29.7	640
18	>20 000	>10 000		>10 000	
19	>20 000	>10 000		8460	>2.3
20	>20 000	>10 000		>10 000	
21	>20 000	3610	>5.5	2890	>6.9

^{a} Expressed in ng/mL. ^{b} Selectivity index (SI) is defined as the ratio of KB cell cytotoxicity to *P. falciparum* cytotoxicity (antimalarial activity).

SAR. Its structure was extracted from the Cambridge Structure Database (CSD) and minimized using the PM3 (Parameterisation Method 3) Hamiltonian within MOPAC 6.0.[23] This minimized structure (ligand) was then used as a template from which all other ligands were constructed and then similarly minimized. In addition, PM3 electrostatic potential-derived charges were generated for compounds **4, 6, 7, 9–12, 14–16**, and **20** with the ESP option. SYBYL (v. 5.2)[24] was used for manipulation of the molecules and generation of molecular electrostatic potential maps (MEPs). The best steric superimposition of ligands was achieved by fitting C-7, the nitrogen of the function at C-7, and either C-8 or C-6, which are common to all of the ligands. The corresponding MEPs were then generated. The range of values of isopotential contours selected for display were those for which, from the analysis of the electron density file, a significant number of points were associated, −5 to +5 kcal/mol. All visualizations were carried out on a Silicon Graphics XS24 or INDY workstation, and semiempirical calculations were performed using an IBM RS/6000 Model 550.

In order to identify the structural reasons for the varied biological activities (pharmacophore) within this series of compounds, the steric and electrostatic properties of the ligands were then compared with those of compound **4**. All initial comparisons were made by making superimpositions of the respective minimized ligands onto minimized **4**. The results of these analyses indicated several compounds (**11–13**) to have reduced activity as a result of unfavorable steric influences, in particular the α-orientation of the C$_4$ side chain. Such influences were also considered important in the reduced activities of **3** and **16**. For the remaining compounds (**5, 6, 8–10, 14, 15**, and **17**) it was not sufficient to invoke steric arguments to account for the reduced activities, so molecular electrostatic potential maps were
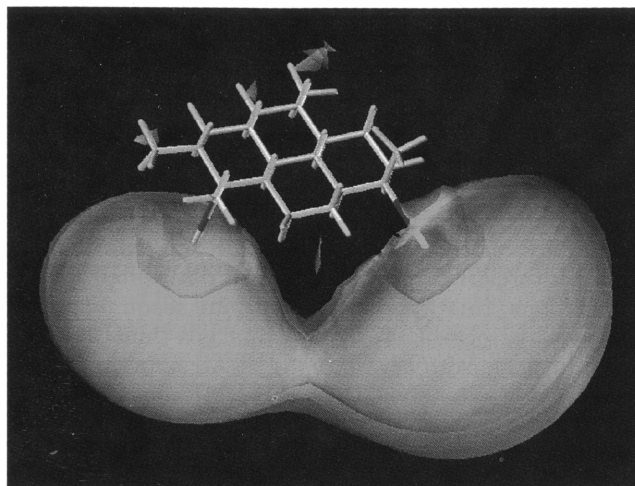

Figure 2. Negative MEPs (molecular electrostatic potential maps) of **4** (green), **5** (yellow), and **6** (white) overlaid on each other and onto the minimized structure of **4**. The range of values of isopotential contours selected for display are −5 to +5 kcal/mol.
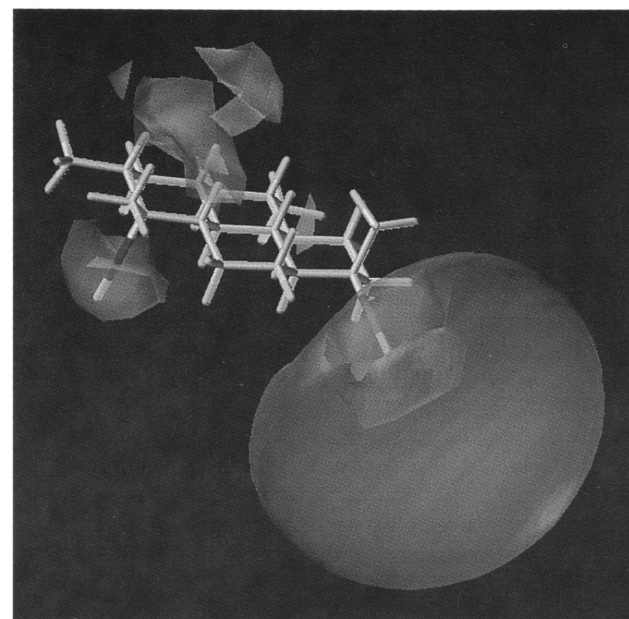

Figure 3. Negative MEPs **14** (yellow) overlaid onto the minimized structure of **4**. The range of values of isopotential contours selected for display are −5 to +5 kcal/mol.

compared. From initial MEP comparisons it appeared that regions associated with positive and neutral potential had little if any influence on the observed activities and were thus removed from further consideration, enabling a more detailed comparison of regions of negative potential to be made. In Figure 2 the negative MEPs of **4** (green), **5** (yellow), and **6** (white) are shown overlaid on each other and onto the minimized structure of **4**. From this figure it is evident that with an increase in negative potential in the region of the C-7 functional group, all other things being equal, there is a corresponding loss in activity. This process was repeated for the majority of other ligands, with the conclusion that the molecules having the ability to mimic the MEP of **4**, especially the lobes of electron density associated with isonitrile groups, are more active than those that cannot. Comparison of the negative MEPs of compounds **14** (Figure 3) and **15** (Figure 4) further support this proposal. The MEP of
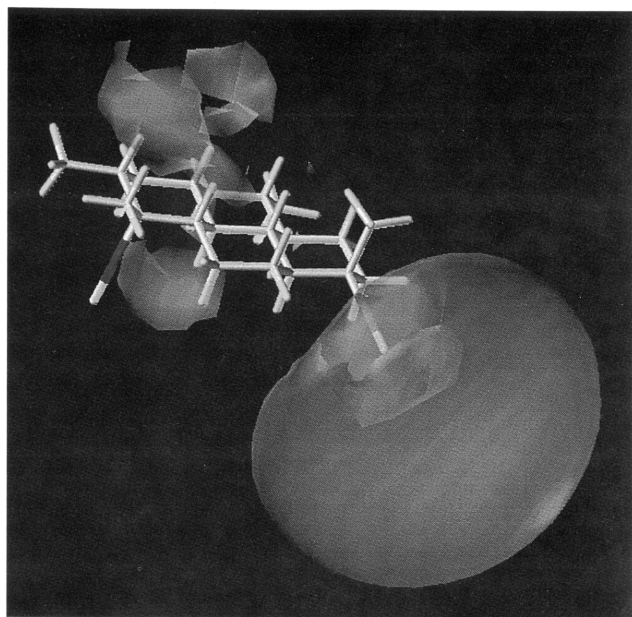
Figure 4. Negative MEPs **15** (yellow) overlaid onto the minimized structure of **4**. The range of values of isopotential contours selected for display are −5 to +5 kcal/mol.

14 best mimics that of **4**, and hence, the molecules have a similar activity. Migrating the $\Delta^{11,20}$ *exo*-double bond to $\Delta^{11,12}$, however, as in **15**, causes the negative potential associated with it to move away from the favored region with the concomitant loss of activity. Steric effects may also play a role, though at the current stage of investigation it is not possible to clearly separate them from electrostatic factors, except in the cases of **11−13**. It was also concluded that the maps cannot be used quantitatively to predict ligand activity, but are useful in a qualitative sense as they give some indication of regions where it is or is not favorable to have negative electrostatic potential. Probably our most interesting finding was that the negative electrostatic potential associated with the isonitrile function at C-20 in **4** can be increased, as in the case of **7**, with no reduction in observed activity. As this work is still ongoing, and the fact that other proposals concerning the SAR of these compounds and our chosen methods of analysis are still being investigated and refined, little more can be said in detail at this stage.

Experimental Section

General Experimental Procedures. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter using hexane as solvent. IR spectra were measured on a Perkin-Elmer 781 infrared spectrometer as liquid films or as KBr disks. UV spectra were recorded in hexane on a Perkin-Elmer Lambda 3 UV/vis spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured on Bruker spectrometers operating at 300, 400, or 600 MHz basic frequencies, with AM, AMX, ARX, and/or DRX configurations. Mass spectral measurements were made on VG Tribrid, Finnigan-MAT 4515 (coupled to a Carlo-Erba Mega 5160 gas chromatograph), and/or Finnigan MAT 8430 mass spectrometers. HPLC was carried out with a Waters Associates M-6000A chromatography pump connected to a Rheodyne HPLC injector and a Knauer differential refractometer. HPLC columns were from Knauer (250 mm × 8 mm, LiChrosorb Si60, 5 μm, and 250 mm × 8 mm, Spherisorb ODS II, 5

μm) and Merck (250 mm × 10 mm, LiChrospher Si60, 10 μm, 250 mm × 4 mm, LiChrospher Si60, 5 μm, and 250 mm × 10 mm, LiChrosorb RP-18, 7 μm, LiChrospher 100 RP-18, 5 μm, 250 mm × 10 mm, LiChrospher 100 diol, 10 μm, and 120 mm × 4 mm, LiChrospher 100 diol, 5 μm). Silica (TLC-Silica 60GF 15 μm, Merck) was used for vacuum−liquid chromatography, while aluminum-backed sheets coated with silica 60F$_{254}$, 0.2 mm thick (Merck), were used for TLC. All solvents were distilled prior to use.

Plant Material. *L. papillosa* (Hudson) Lamouroux (Rhodophyceae, Rhodomelaceae) was collected at depth of 0.5 m, on July 1, 1993, from the coast of the Caribbean island of Dominica.

Extraction and Isolation. A freeze-dried sample of the marine red alga *L. papillosa* (204 g) was exhaustively extracted with 2.5 L of dichloromethane (CH_2Cl_2) followed by MeOH (2 L). The CH_2Cl_2-solubles from these two extracts (2.72 g, 1.3%) were then chromatographed over silica gel (VLC), using hexane containing increasing proportions of ethyl acetate as eluent, to afford 11 fractions, each of approximately 90 mL. Biological screening, thin-layer chromatography, and ^{1}H-NMR spectral analysis indicated several of these fractions to be of further interest, but only fraction 5 to be of an adequate sample size to warrant further investigation. HPLC separation [acetone:hexane (3:17), normal phase silica] of fraction 5 yielded compounds **1** and **2**.

Compound **1** was isolated as an oil (2.6 mg, 0.0013%) and had spectroscopic data identical to the data for a commercial sample of *p*-hydroxybenzaldehyde.

Compound **2** was isolated as an oil (8.6 mg, 0.0042%): IR ν_{max} (film) 3315, 2930, 1615, 1515, 1450, 1215, 1075, 715 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 300 MHz) δ 3.37 (3H, s, H-8), 4.39 (2H, s, H-7), 6.78 (2H, d, J = 8.6 Hz, H-2 and 6), 7.20 (2H, d, J = 8.6 Hz, H-3 and H-5); ^{13}C-NMR (CDCl$_3$, 75.5 MHz) δ 57.7 (q, C-8), 74.4 (t, C-7), 115.2 (dx2, C-2 and 6), 129.7 (dx2, C-3 and 5), 130.1 (s, C-4), 155.4 (s, C-1); EIMS m/z 138 (M$^+$, 47), 137 (29), 107 (100), 95 (5), 78 (11), 77 (21); HREIMS m/z 138.0669 (calcd for C$_8$H$_{10}$O$_2$ 138.0681). Its data were comparable to those of a commercially available sample of *p*-methoxybenzyl alcohol.

For the sponge *C. hooperi* (CT293V) and compounds **3−20** see the primary literature.[4,5]

Conclusions

The marine environment clearly contains compounds that should serve as useful lead structures in the development of new classes of antimalarial drugs. Judicious use of the bioassays as employed in this work can clearly lead to compounds having antimalarial properties, as in the present case, with substances containing −NC, −NCS, and −NCO functionalities. It is also evident from the strategies employed by our group over the years that it is not necessary to collect large quantities of potentially endangered marine plants and animals in order to obtain meaningful and detailed biological and chemical information. It is hoped sincerely that the results of our investigations will in some way lead to the discovery of a new treatment for malaria.

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