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Antimalarial Natural Products of Marine and Freshwater Origin

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Abstract

This review highlights recently discovered antimalarial natural products from marine and freshwater sources described in the literature from 2006 to 2008. The structures as well as bioactivities of compounds against the malaria parasites such as *Plasmodium falciparum* are discussed, including for example agelasine, xestoquinone, alisiaquinone, crambescidin, venturamide, dragomabin, gragonamide, viridamide, salinosporamide, chaetoxanthone, nodulisporacid, tumonoic acid, girolline, oroidin, nostocarboline, aerucyclamide and microcylamide 7806 and its revised structure. Synthetic derivatives of natural products are presented including plakortin, isoaaptamine, curcuphenol, pseudopyronine, manzamine and nostocarboline. Consequences of these discoveries for the development of novel natural product agents against malaria are discussed.

Biographical Sketch

Karl Gademann (1972) was educated at ETH Zürich and Harvard University (PhD with Prof. Dr. Dieter Seebach, postdoctoral studies with Prof. Dr. Eric N. Jacobsen, Habilitation associated with Prof. Dr. Erick M. Carreira). He is currently an assistant professor at the Swiss Federal Institute of Technology (EPF Lausanne). He has published over fifty publications, holds two patents and received several awards including the Latsis Prize, Lilly Lecture Award, the Schläfli award of the Swiss Academy of Sciences, and, most recently, the Liebig Lectureship of the German Chemical Society. He was awarded the European Young Investigator grant related to natural product synthesis research. His research interests include the synthesis and chemical biology of natural products.

Joanna Kobylinska was born in 1975 in Skarzysko-Kamienna, Poland. She studied organic chemistry at the Technical University of Wroclaw and carried out her Diploma thesis in 2000 in the group of Prof. Dr. Jacek Skarzewski, working on catalytic enantioselective oxidations. She completed her PhD studies in 2004 in the group of Prof. Dr. Manfred Schlosser at the EPFL (Lausanne, Switzerland) dealing with the organic synthesis and regioselective functionalization of fluorinated aromatics. Currently, she is carrying out postdoctoral studies in the group of Prof. Dr. Karl Gademann at the EPFL working on surface functionalization and modifications.

Introduction

Malaria constitutes the most threatening parasitic infection in humans. Each year, between 300 to 500 million new clinical cases are reported by the world health organization,[1] resulting in annual deaths of about one million people,[2] of which three-quarters of the fatalities are children below 5 years of age.[3] The most exposed continent is Africa, but also South-east Asia, Oceania, and Central and South America are under severe threat. Among the most affected countries are developing nations, which suffer from a weakly developed health care system.

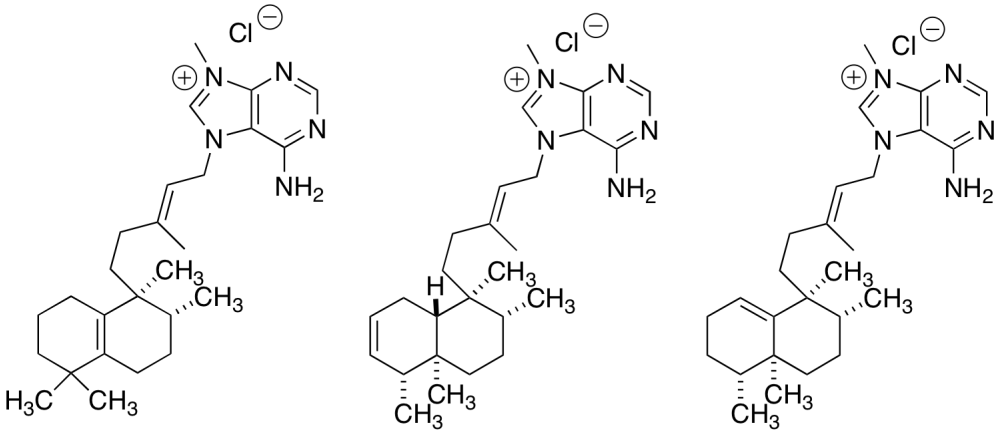
There are four species of *Plasmodium* infecting humans: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, but most of the malaria cases are caused by the protozoan parasite *P. falciparum*.[4] The parasite is transmitted by *Anopheles* mosquitos, and therefore malaria can be controlled to some extent by conventional prevention strategies such as mosquito repellents, mosquito traps, insecticides or biological control. The introduction of efficient vaccines is still problematic, despite recent progress in this area.[5] As a direct consequence, the treatment of choice remains parasite chemotherapy with small molecule drugs both of natural origin or synthetics.[6, 7] In parallel, resistance of the malaria parasite to commonly used drugs such as quinine, chloroquine and mefloquine is emerging,[8] which results is an urgent need to develop new drugs against this disease. Also, an additional option for treatment, which implies reduction of the risk of resistance, offers the combination of two antimalarial drugs. Examples of such drug combinations are the artemisinin-amodiaquine and the artemether-lumefantine combination (Coartem).[9]

Antiplasmodial Agents of Marine and Freshwater Origin

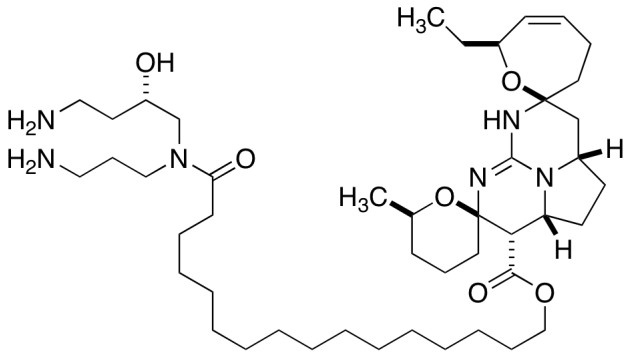
The marine environment, taking more than 70% of the Earth's surface, is a rich source of both biological and chemical diversity. As a consequence, such aqueous environments harbor new compounds with great potential as pharmaceuticals, nutritional supplements, cosmetics and agrochemicals.[10] Many life forms in the marine environment such as algae, sponges, corals, ascidians and fungi have been investigated for their natural product content.[11-13] Many structurally and pharmacologically important substances have been isolated with novel antimicrobial, antitumor, anti-inflammatory, antimalarial, antibiotic or antifouling properties, and they are described in several excellent reviews that have appeared in recent years.[14-24]
In the current review, we give an overview of the bioactive metabolites recently isolated from marine organisms that have shown antiplasmodial activity and discuss their pharmacological potential. In addition, since some freshwater organisms have been found to populate both freshwater and marine environments (e.g. cyanobacteria), are found in brackish mixed environments, or are washed out into the ocean by rivers and streams, we have chosen to include examples from both aquatic domains.
While we do not claim completeness, research efforts published between 2006 and 2008 are discussed in the following chapters.

Several alkaloids were identified from marine sources in the last years. A survey of different invertebrates was conducted by Mendiola et al.,[25] in order to classify these sources for antiplasmodial activity. Seven extracts from different marine species, three species of Chordata, two species of Echinodermata, one species of Cnidaria and one species of Porifera, collected on the northwest Cuban coast from Havana to Puerto Esperanza were reported to display moderate antimalarial activity.[25] Among them, three ascidians produced *in vitro* IC_{50} values lower than 30μg/ml, and *in vivo*, the crude extracts caused partial reduction of *Plasmodium berghei* parasitaemia in mice.[25] Alkaloids and polyketides were found to be the major substances with antimalarial activity isolated from chordata, but the studied aqueous extracts of three ascidians were mixtures of compounds.
Although agelasidae sponges have been widely investigated, they still represent a source of new marine metabolites.[10] Three new diterpene alkaloids, agelasine J (**1**), agelasine K (**2**), and agelasine L (**3**), were recently isolated from the marine sponge

Agelas cf. *mauritiana* from the Solomon Islands.[26a] Agelasine J (**1**) was obtained previously by Nakamura et al. by semisynthesis from agelasine A or B under acidic conditions.[26b] All three compounds displayed moderate activity on *P. falciparum* with IC_{50} = 6.6, 8.3 and 18 μM for agelasines J, K and L, respectively, and a low cytotoxicity on MCF7 cells with IC_{50} values of 33, 30 and 80 μM, was determined. The molecular target of these substances was not yet investigated.[26a]



From a *Mycophora sp.* Sponge, crambescidin 800 (**4**) was isolated,[27] which had been previously reported,[28] and few analogues had been prepared. Crambescidin 800 (**4**) showed *in vitro* activity against chloroquine(CQ)-resistant FCR3 *P. falciparum* (IC_{50} = 240 nM) and CQ-sensitive 3D7 strains, (IC_{50} = 160 nM). The most active analogue **5** had *in vitro* activity against *P. falciparum* strain 3D7 comparable to quinine as well, but slightly less than that of crambescidin 800 (IC_{50} = 490 nM). [27] The mode of action has not been investigated, but similar compounds have been shown to be channel blockers or ATPase inhibitors.[27]



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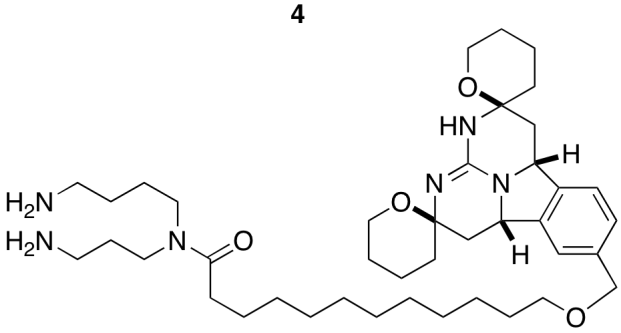

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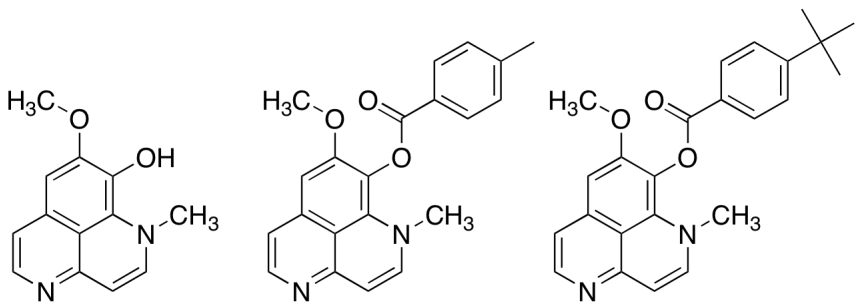
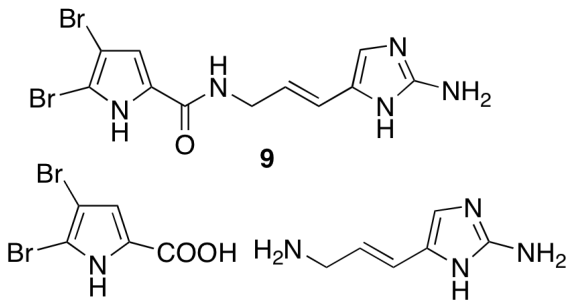
Novel isoaaptamine analogues[29] were prepared by coupling acyl halides to the C9 position of isoaaptamine (**6**), first isolated from a sponge of the genus *Suberites* by Fedoreev,[30] later by two other groups from the sponge *Aaptos aaptos*,[31, 32] and recently from a sponge belonging to the genus *Hymeniacidon*.[33] The compound **6** displayed remarkable activity against the W2 clone and good activity against the D6 clone of *P. falciparum*, with an IC_{50} values of 380 and 1100 ng/mL, respectively. All nineteen synthesized derivatives resulting from various acyl halides coupled at C9 position of isoaaptamine (**6**) have had a negative impact on the activity against the W2 clone. However, the activity against the D6 clone in many derivatives increased, and the most potent were compounds **7** and **8**, with IC_{50} = 230 and 240 ng/mL, respectively.[29]



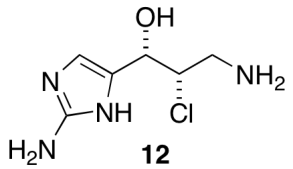
6 **7** **8**

Recently Tasdemir et al.[34] reported isolation of six pure metabolites and some

complex fatty acid mixtures (FAMA-FAMG) from the Turkish marine sponge *Agelas oroides* which showed promising P*f*FabI inhibitory and antiplasmodial activity. Among the metabolites, (*E*)-oroidin (**9**) was isolated as free base and identified as the most potent enzyme P*f*FabI inhibitor with IC_{50} = 0.77 μM. The kinectic analysis revealed an uncompetitive binding mechanism with respect to substrate and cofactor, indicating that the compound **9** is exclusively binding to the enzyme-substrate complex or enzyme-cofactor complex.[34] This mechanism is identical to the one observed for triclosan towards FabI of various species.[35, 36] Oroidin base (**9**) was assayed for its *in vitro* inhibitory activity on multidrug resistant K1 strain of *P. falciparum* and it exhibited an IC_{50} value of 3.9 μg/mL in the whole cell parasite assays. Oroidin (**9**) is a condensation product of the imidazol portion, 3-amino-1-(2-aminoimidazoyl)-prop-1-ene (**10**), which has no effect on P*f*FabI, but has unspecific effect on the malaria parasite, and 4,5-dibromopyrrole-2-carboxylic acid **11**, which is not toxic, but has limited antimalarial and P*f*FabI inhibition activities. A previous report[37] described oroidin (as TFA salt) to be inactive towards the D6 and W2 strains of *P. falciparum*, however, a more recent study reported a moderate antimalarial effect with an IC_{50} = 1.2 μg/mL.[38]



Benoit-Vical and co-workers[39] evaluated the effects of a natural product girolline (**12**) and some of its synthetic analogues *in vitro* and *in vivo* against *P. falciparum* and *P. vinckei petteri*, respectively. This 2-aminoimidazol derivative was originally isolated from a New-Caledonian sponge *Cymbastela cantharella,*[40] and this compound was demonstrated for its antitumor properties.[41-43] More recently the compound **12** has been also isolated from another species of the marine sponge *Axinella brevistyla* collected in western Japan.[44]

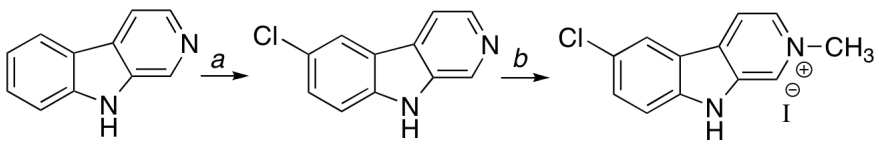


12

The IC_{50} value of girolline (**12**) on the CQ-resistant strain FcM29 was determined to be 130 nM, and with artemisinin or chloroquine the compound inhibited parasitic growth by 100%. Several synthetic analogues were shown to possess IC_{50} values higher than 50 μM. Girolline (**12**) showed also very high activity in an *in vivo* *Plasmodium vinckei petteri* assays, and even although the compound displays some toxicity,[42] it might considered as a natural compound with very promising activity against malaria.[39] The mode of action of this compound is debated in the literature, and Benoit-Vical et al. suggest its mechanism to be related to the inhibition of protein synthesis.[39]

Our group has recently isolated nostocarboline (**13**), an acetyl- and butyryl-cholinesterase, and trypsin inhibitor from the cyanobacterium *Nostoc* 78-12A.[45-47] The compound itself inhibits *Plasmodium* with high selectivity in nanomolar concentrations, and additionally, dimerization of nostocarboline leads to very potent and selective antiplasmodial agents.[48] Nostocarboline (**74**) was synthesized starting from norharmane via chlorination at C-6 and methylation according to published procedures.[45, 46]

Scheme 1. Preparation of nostocarboline (**13**) from norharmane. Reagents and conditions: (a) NaOCl, EtOH, 0 °C, 30 min, then rt, 5 h, 75%; (b) CH_3I, *i*-PrOH, reflux, 4 h, 94%.



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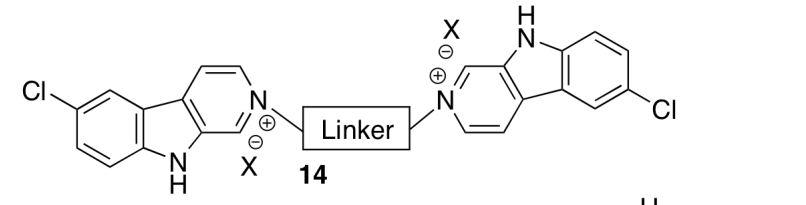
6-Cl-norharmane was also the starting material for the synthesis of ten nostocarboline symmetrical homo-dimers of general formular **14**. Alkenyl, alkynyl, aryl, biaryl and alkyl linkers of various lenghts were employed for the corresponding dimers, which

were obtained in a two-step process and in good yields (60 – 95%).

Nostocarboline (**13**) as well as dimers such as **16-20** were evaluated against *P. falciparum* K1. Nostocarboline (**13**) displayed antimalarial activity against the K1 strain with an IC_{50} = 194 nM, and in addition it showed very weak cytotoxicity (>100 μM), giving rise to a 600 fold selectivity of *Plasmodium* over rat myoblast L6 cells. The best results against *P. falciparum* were obtained for dimers with long and flexible linkers, and compounds **16-20** displayed IC_{50} values below 100 nM, and the most active compound **19** containing a $(CH_2)_{10}$ linker displayed an IC_{50} = 14 nM against *P. falciparum* K1. Cytotoxicity against the L6 rat myoblast cell line was determined as well, and the values varied between 5-60 μM. Cytotoxicity increased with linker length, thus decreasing selectivity for longer linkers. Compounds **16** and **17** with five and six atom linkers are considered optimal in this series. Compound **16** displayed high potency (IC_{50} = 18 nM) and an excellent selectivity of >2500-fold against the L6 cell line. The mode of action of these compounds is currently under investigation.



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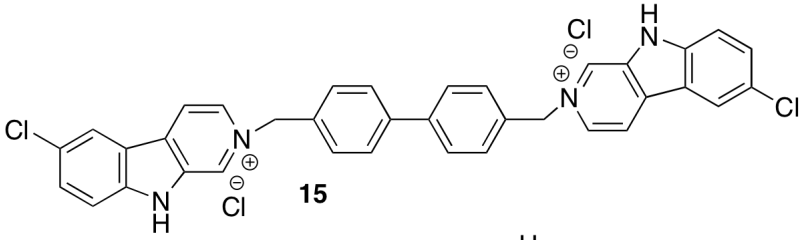

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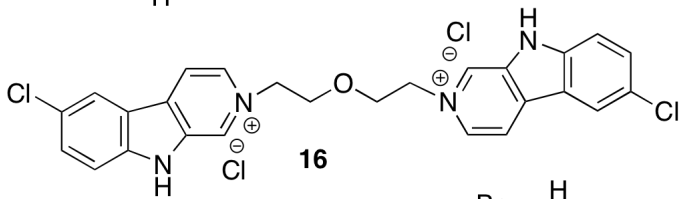

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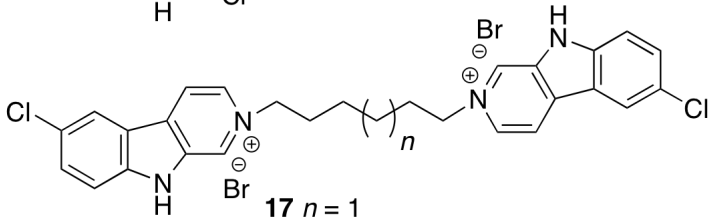
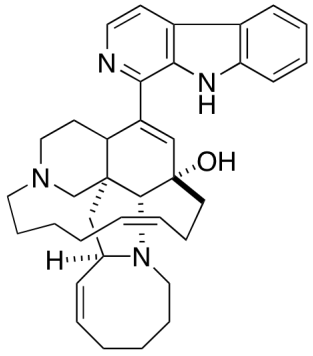


17 *n* = 1
18 *n* = 3
19 *n* = 5
20 *n* = 7

A remarkable example of a marine compound with potential activity against *P. falciparum* is manzamine A (**21**), a unique beta-carboline alkaloid. The compound was first isolated from the Okinawan sponge of the genus *Haliclona*,[49] since then more than 60 manzamine and related alkaloids have been isolated from 16 species of sponges belonging to nine different genera.[50, 51] More than 90% of the asexual erythrocytic stages of *Plasmodium berghei* were inhibited after a single intraperitoneal injection of manzamine A (**21**) into infected mice. Such suppressive activity is comparable to that of chloroquine and superior to that of artemisinin at the same dose.[52]

One of the common manzamine alkaloids is 8-hydroxy-manzamine A (**22**) that has been isolated from sponges of the genera *Amphimedon*, *Xestospongia*, *Acanthostrongylophora*, and *Pachypellina*. [53-55] Despite highly promising antimalarial activity, toxicity remains a major problem with respect of the potential for alkaloids such as **21** and **22** as drugs.



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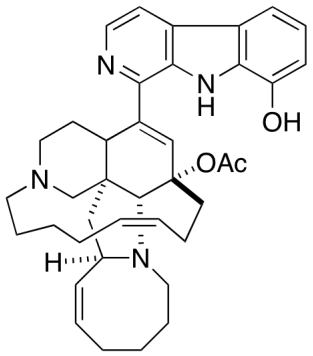
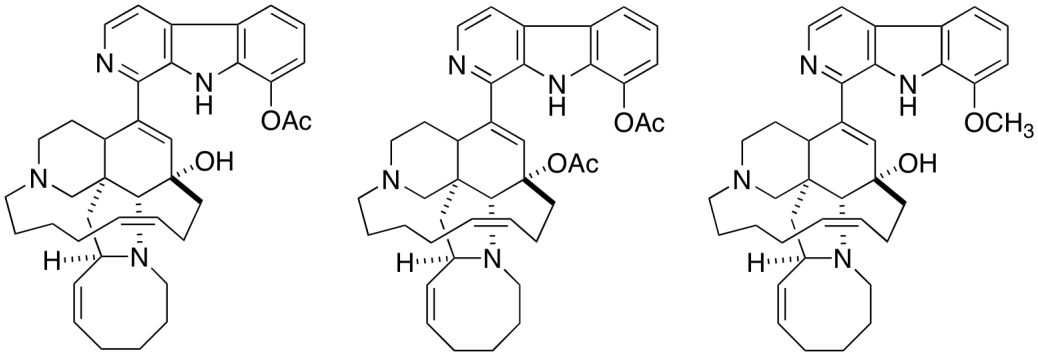


22

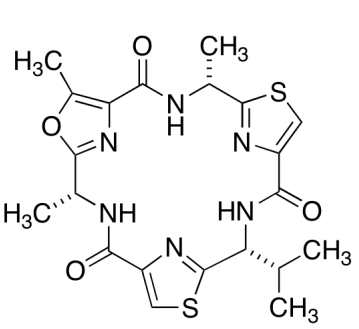
Three acetylated 8-hydroxymanzamine A (**22**) analogues **23**, **24** and **25** were prepared by modification at the 8-position in an effort to generate manzamine prodrugs with improved antimalarial activity and reduced GI toxicity.[56] These synthetic analogues exhibited antimalarial activity against the chloroquine-sensitive (D6) and the chloroquine-resistant (W2) strains of *Plasmodium falciparum* with values ranging from 9 to 1300 ng/mL. The most significant *in vitro* antimalarial activity displayed analogue **23**, with an IC_{50} = 9.6 ng/mL against the D6 strain, and IC_{50} = 30 ng/mL against the W2 strain, what is comparable to 8-hydroxymanzamine A (**22**). Analogue **24**, which contains acetoxy groups at both the 8- and 12-positions, was the least potent compound, with IC_{50} values of 1300 and 1200 ng/mL against the D6 and W2

clones, respectively. Analogues **23** and **25** exhibited toxicity to the normal Vero cell line, while the diacetate **24** did not show cytotoxicity at the highest tested concentration of 4700 ng/mL. Analogue **23** was also evaluated for *in vivo* antimalarial activity against *Plasmodium berghei* sensitive strain, but appeared being rather toxic.[56] Interesting results of quaternary manzamine derivatives similar to nostocarboline (**13**) were reported.[57] All these examples **1**-**25** support the notion that alkaloids still represent an important class for the discovery of novel antimalarial agents.



23 **24** **25**

Several peptides were isolated over the last years that display antiplasmodial activity. Gerwick and coworkers have recently isolated antimalarial venturamides A (**26**) and B (**27**) from a Panamanian *Oscillatoria sp.*.[58] These modified cyclic hexapeptides showed moderate selectivity for the parasite versus mammalian host cells. Venturamide A (**26**) showed *in vitro* activity against *P. falciparum* (IC_{50} = 8.2 μM), with only mild cytotoxicity to mammalian Vero cells (IC_{50} = 86 μM). Venturamide B (**27**) also showed low micromolar antimalarial activity against *P. falciparum* (IC_{50} = 5.6 μM) and mild cytotoxicity to mammalian Vero cells (IC_{50} = 56 μM). The mode of action of these compounds is yet unknown.



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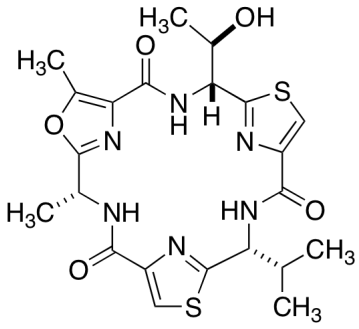
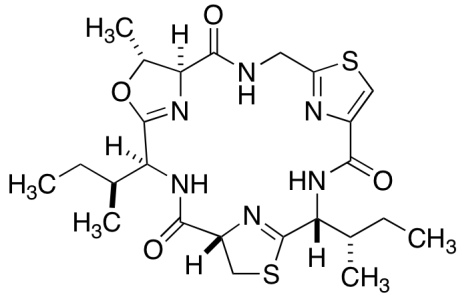


27

Four new haxacyclopeptides, aerucyclamides A[59] (**28**), B [59] (**29**), C [60] (**30**) and D [60] (**31**) were isolated from cyanobacterium *Microcystis aeruginosa* PCC 7806 and their structural characterization, synthesis and biological evaluation have been reported. [59, 60] These peptides are the actual metabolites produced by ribosomal peptide synthesis in *M. aeruginosa* PCC 7806, it has been predicted by a parallel study.[61]



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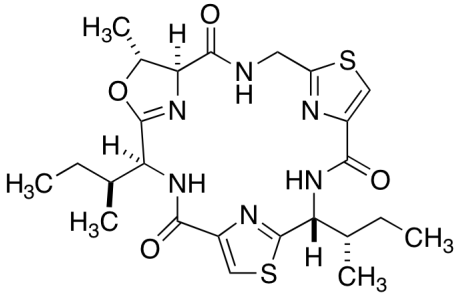

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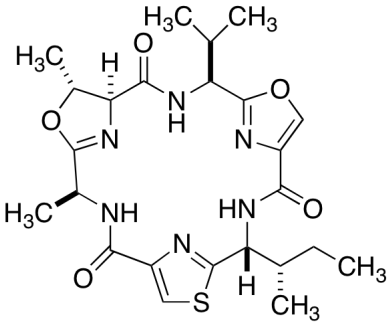

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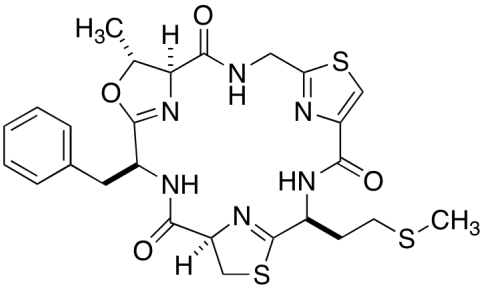
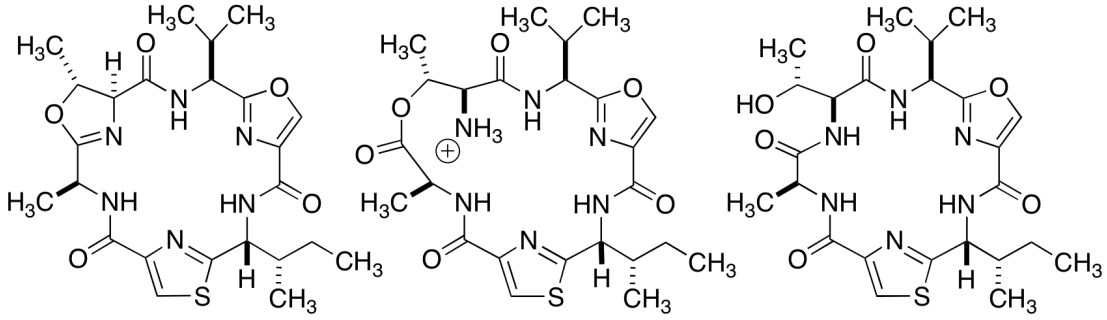


31

Aerucyclamide A (**28**) is a rare example of a cyclamide that features oxazoline, thiazoline, and thiazole moieties in one compound. Aerucyclamide B (**29**) is an oxidative derivative of **28**, and can be obtained synthetically through oxidation of aerucyclamide A (**28**) (MnO_2, benzene). Surprisingly, the structure of aerucyclamide

C (**30**) matched the one reported for microcyclamide 7806A (**32**) despite different data. Structure **32** was postulated as the actual metabolite of ribosomal peptide synthesis by Ziemert et al.[61] Therefore, we suggested a structure revision of microcyclamide 7806A (**32**),[60] based on chemical, physical and spectroscopic evidence. The revised structure **33** for microcyclamide 7806A[60] includes an ester involving the Thr group and the ammonium residue instead of the oxazoline ring. Moreover, microcyclamides 7806A (**32**) and B (**34**) can be obtained under acidic conditions frequently used in HPLC purifications (CF3CO2H in H2O) from aerucyclamide C (30). This chemical transformation supports the hypothesis that both microcyclamides 7806A (**32**) and B (**34**) are isolation artifacts, and that the aerucyclamides A-D (**28-31**) are the actual metabolites produced via ribosomal peptide synthesis in *Microcystis aeruginosa* PCC 7806.[60]

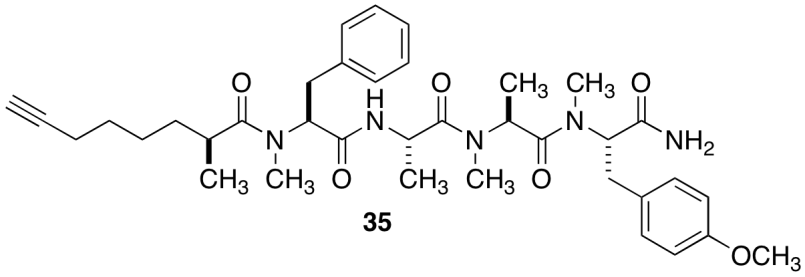


Microcylamide 7806A Original Structure (**32**) | Microcylamide 7806A Revised Structure (**33**) | Microcylamide 7806B (**34**)

All four cyclamide derivatives **28-31** were biologically evaluated for antiplasmodial activity. The most active compound was aerucyclamide B (**29**), displaying a submicromolar IC_{50} value of 0.7 μM against the chloroquine-resistant strain K1 of *Plasmodium falciparum*. In addition, this compound displays a large selectivity for the parasite with respect to the L6 rat myoblast cell line, where an IC_{50} value of 120 μM was determined. Interestingly, a reduction of the thiazole to a thiazoline (structural modification from **29** to **28**) decreases the antiplasmodial activity by 1 order of magnitude. Similar low micromolar activities displayed aerucyclamides C (**30**) and D (**31**) (IC_{50} = 2.3 and 6.3 μM, respectively). All compounds displayed very weak (for **29** and **30**) or no toxicity to the L6 rat myoblast cell line under the conditions evaluated. Therefore, such cyclamides **28-31** as well as venturamides A (**26**) and B (**27**) can be considered interesting lead structures for further development.

Gerwick and coworkers reported two other marine cyanobacterial metabolites.[62] New

linear alkynoic lipopetides, dragomabin (**35**) and dragonamide B (**36**), have been isolated from a red Panamanian strain of the marine cyanobacterium *Lyngbya majuscula* from different sites in the Bocas del Toro region.[62]



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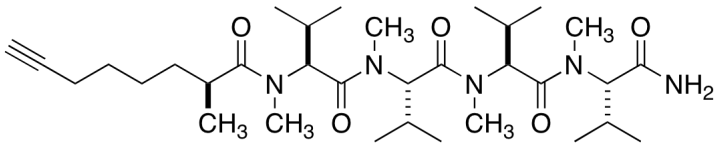
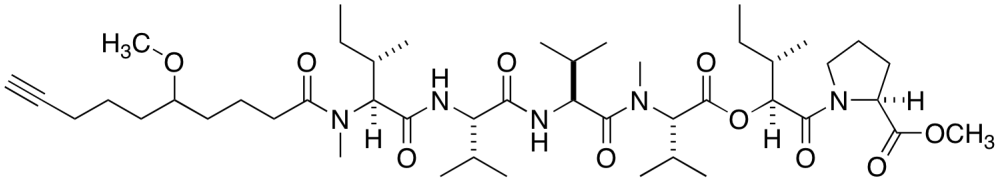


36

Dragomabin (**35**) showed good antimalarial activity (IC_{50} = 6 μM) against chloroquine-resistant *Plasmodium falciparum*, whereas the nonaromatic analogue, dragonamide B (**36**) was inactive in this assay.

An investigation of a marine cyanobacterium *Oscillatoria nigro-viridis* from Panama led to the isolation of two novel bioactive lipopeptides, viridamides A (**37**) and B (**38**).[63] Viridamide A (**37**) was tested against a series of relevant tropical pathogens and cancer cell lines, and it displayed significant activity against the parasitic protozoan *P. falciparum* (IC_{50} = 5.8 μM), but also displayed strong activity against *Trypanosoma cruzi* and *Leishmania mexicana.*



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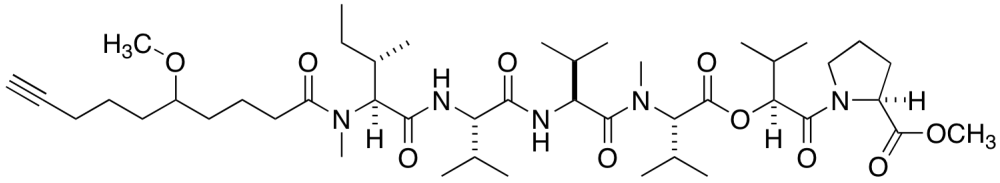
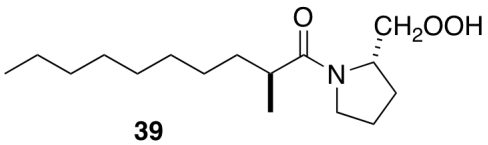


38

The marine cyanobacterium *Blennothrix cantharidosmum* was a source for six new acyl proline derivatives, tumonoic acids D-I (**39-44**), plus the known tumonoic acid A and lyngbyastatins as the active metabolites.[64] The tumonoic acids were originally isolated from a *Lyngbya majuscula* / *Schizothrix calcicola* assemblage, as well as collection of *L. majuscula*, all collected in Guam,[65] but phylogenetic investigation using 16S rRNA suggests that these compounds could also originate from *Lyngbya*/*Blennothrix* assemblages. The new compounds were tested in an array of assays, but only tumonoic acid I (**44**) displayed antimalarial activity with an IC_{50} = 2 μM, none of the other naturally occurring analogues showed any activity in this assay at a concentration of up to10 μg/mL. The target of these compounds is unknown.[64]



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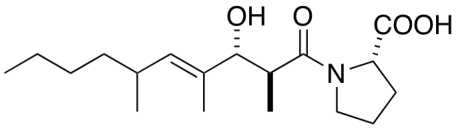

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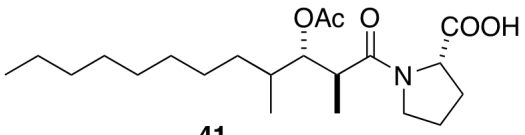

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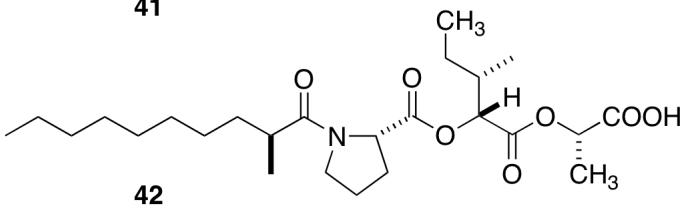

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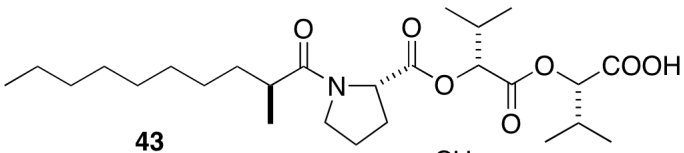

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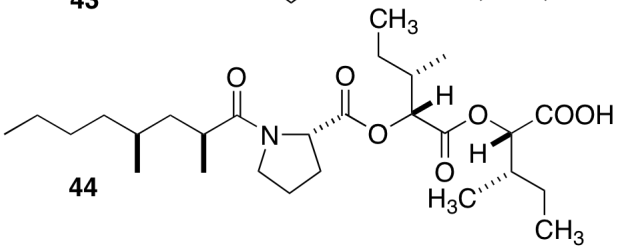
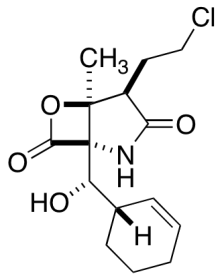


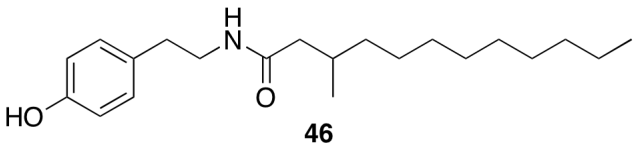
44

In addition to these peptides, several amino acid derivatives were isolated and characteriyed. Salinosporamide A (**45**) was initially discovered and described in 2003 by Fenical and co-workers from the marine actinomycete *Salinispora tropica*[66] and belongs to a family of compounds possessing a densely functionalized γ-lactam-β-lactone bicyclic framework. These compounds are potent anticancer agents due to proteasome inhibition. Compound **45** was evaluated by Prudhomme *et al.*,[67] who found this lactam **45** to be a highly potent inhibitor of the human malaria parasite both *in vitro* (IC_{50} = 11.4 nM) and *in vivo* (ca. 90 % reduction in parasitemia at 130 μg/kg (s.c.) in mice, *P. yoelii*). More promisingly, salinosporamide A (**45**) is currently in phase I clinical trials against the treatment of refractory multiple myeloma.



45

Eight compounds, including four new natural products, were isolated from the marine octocoral *Muricea austera* collected in the Pacific coast of Panama.[68] Two natural tyramine derivatives, **46** and **47**, showed moderate antiplasmodial activity (IC_{50} = 45 and 38 μM), and a series of synthetic derivatives with fatty acid moieties showed antiplasmodial activity very similar to those of their natural analogues.[68]



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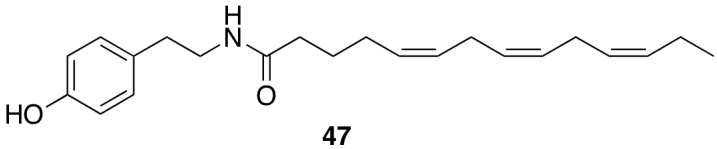
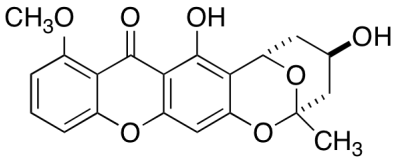


47

Another class of natural products with antiplasmodial activity encompasses hydroxyaromatic compounds. Three new natural products chaetoxanthones A (**48**), B (**49**) and C (**50**) were isolated from marine-derived fungus *Chaetomium* sp..[69] Compounds **48** and **49** are substituted with a dioxane/tetrahydropyran moiety rarely found in natural products, and compound **50** was identified as a chlorinated xanthone substituted with a tetrahydropyran ring. The new xanthones were tested in a series of *in vitro* bioassays for their antiprotozoal activities and cytotoxic potency. Among the isolated xanthones only chaetoxanthone B (**49**), which was probably isolated as racemate based on CD spectroscopic evidence, showed selective antiprotozoal activity against *P. falciparum* with an IC_{50} = 0.5 μg/mL (at least 7.5-fold enhanced potency compared to the other tested protozoans) without being cytotoxic toward cultured eukaryotic L6-cells (IC_{50} > 90 μg/mL). The mode of action of xanthones toward *Plasmodium* parasites was investigated in detail in earlier studies,[70, 71] and

these compounds are considered to inhibit heme polymerization. Thus, the detoxification of harmful hematin is hampered which results in the death of the parasitic cells.[70, 71]



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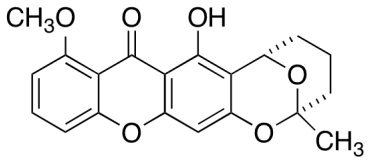
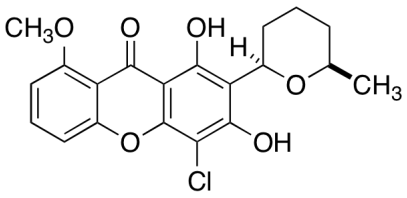
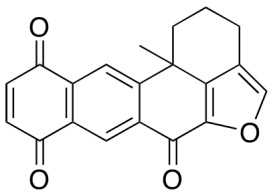


rac-**49**



50

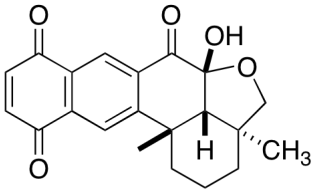
Previously described xestoquinone[72-80] (**51**) was re-isolated from the marine sponge *Xestospongia* collected in Vanuatu in South Pacific.[36] The selectivity of the protein kinase inhibitory activity of xestoquinone against a panel of *P. falciparum* protein kinases was evaluated.[81] Xestoquinone (**51**), the most potent and the most abundant Pfnek-1[82] inhibitor, showed a moderate *in vitro* antiplasmodial activity against a FCB1 *P. falciparum* strain (IC_{50} = 3 μM) and exhibited a cytotoxic activity on MCF7 cells with an IC_{50} value of 20 μM, but it only exhibited weak *in vivo* activity at 5 mg/kg in *Plasmodium berghei* NK65 infected mice and was toxic at higher doses.



51

Four new bioactive compounds, alisiaquinones A, B and C (**52**, **53** and **54**) and alisaquinol (**55**), were isolated from a New Caledonian deep-water sponge.[83] They are

related to xestoquinone (5**1**),[76, 84] methoxyxestoquinone,[79] adociaquinone[80] and xestoquinol,[39, 76, 84] respectively, but show an unusual substitution pattern on the furan ring. These new meroterpenes displayed mild activity with micromolar range on two enzymatic targets of importance for the control of malaria, the plasmodial kinase Pfnek-1 and a protein farnesyl transferase (PFT) as well as on different chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*.[83] Alisiaquinones A (**52**) and B (**53**) and alisiaquinol (**55**) displayed similar activities *in vitro* on *Plasmodium falciparum*, but the IC_{50} values were not determined on Pfnek-1. Alisiaquinone A (**52**) was slightly less cytotoxic and had low selectivity index. Alisoquinone C (**54**), bearing the taurine substituent, displayed a submicromolar activity on *Plasmodium falciparum* and a competitive selectivity index on the different plasmodial strains, especially on the chloroquine-resistant strain PfFcMC29. For alisaquinones A (**52**) and C (**54**) also the *in vivo* activity was investigated, but they displayed a relatively high level of toxicity.



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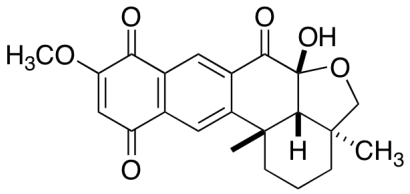

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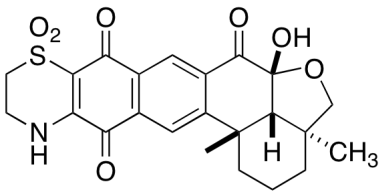

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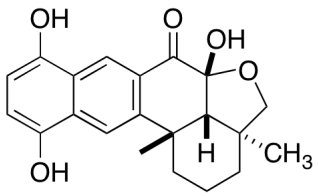
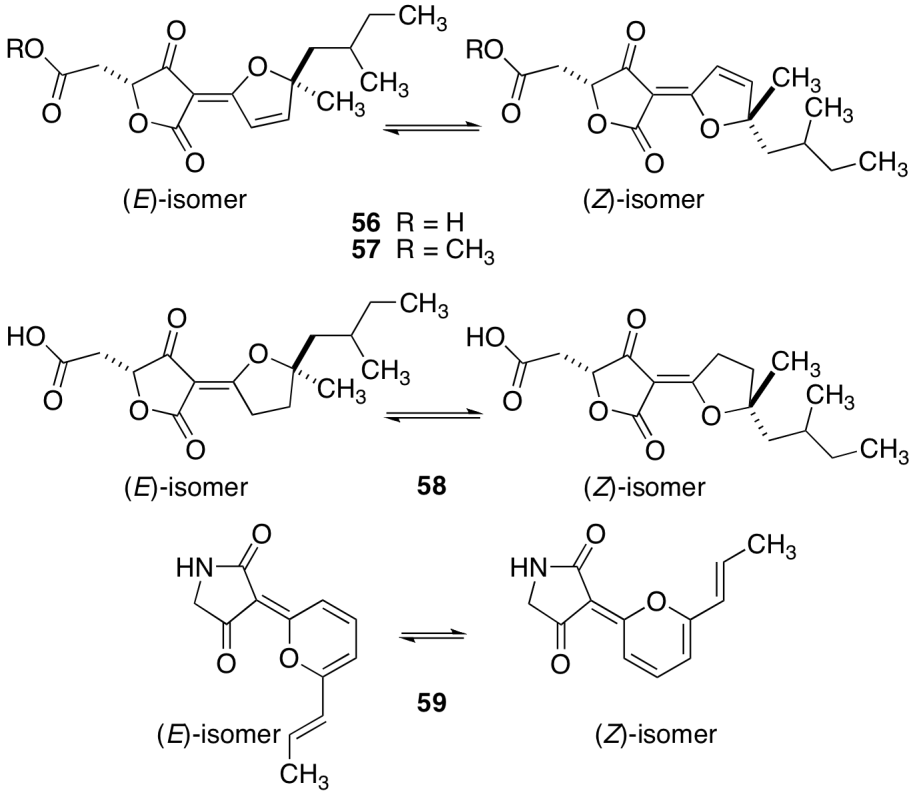


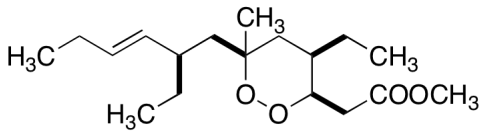
55

A new tetronic acid, nodulisporacid A (**56**), isolated from a marine-derived fungus *Nodulisporium* sp. CRIF1 exhibited moderate antiplasmodial activity.[85] This compound was identified as a truncated derivative of lowdenic acid[86] and a known tetramic acid, vermelhotin (**59**), obtained from an unidentified fungus CRI247-01 (a member of the order Pleosporoles),[85] and was previously obtained as a single *E*-isomer from another unidentified fungus.[87] Both compounds **56** and **59** revealed

spontaneous inter-conversion between *E*- and *Z*-isomers, forming an equilibrium *E*/*Z* mixture with the ratio of 1:1 for nodulisporacid A (**56**) and 1:2 for vermelholtin (**59**). Nodulisporacid A (**56**), the two synthetic derivatives (**57** and **58**), as well as vermelhotin (**59**) exhibited good antiplasmodial activity with IC_{50} values between 1-10 μM, with the latter compound displaying moderate cytotoxicity.[85] Previously, vermelhotin (**59**) was tested against fungi and bacteria, but it showed no antifungal and antibacterial activities.[87]



Natural products are prime candidates for the synthesis of analogues, which might be more effective and less toxic than the parent natural products. A series of semisynthetic derivatives[88] of a remarkably simple 1,2-dioxane derivative, plakortin (**60**) was prepared. Plakortin (**60**) itself was isolated from the Caribbean sponge *Plakortis simplex*, and together with its 9,10-dihydro analogue **61**, and two other analogues 3-epiplakortin (**62**) and plakortide Q (**63**) display submicromolar activities *in vitro* against chloroquine-resistant strains of *P. falciparum*.[89-91]



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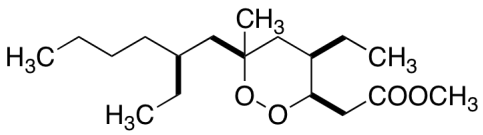

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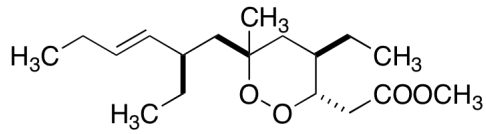

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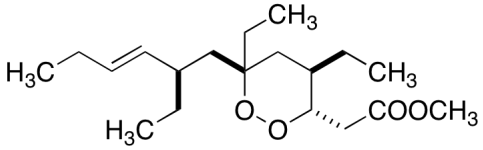
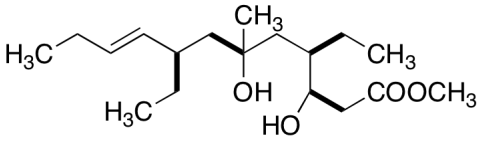


63

The authors[88] confirmed the crucial role of the endoperoxide functionality in the antimalarial activity of plakortin derivatives, since diol (**64**) was completely ineffective. The reduction of the ester function to the corresponding hydroxy (**65**), methoxy (**66**) or acetoxy (**67**) derivatives did not affect activity and selectivity for the tested strains of *Plasmodium falciparum*. A much more pronounced effect on the antimalarial activity are imparted by changes on the alkyl side chain.[88]



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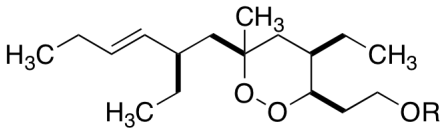
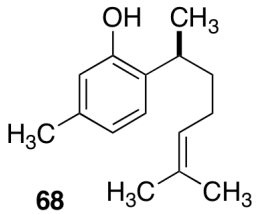


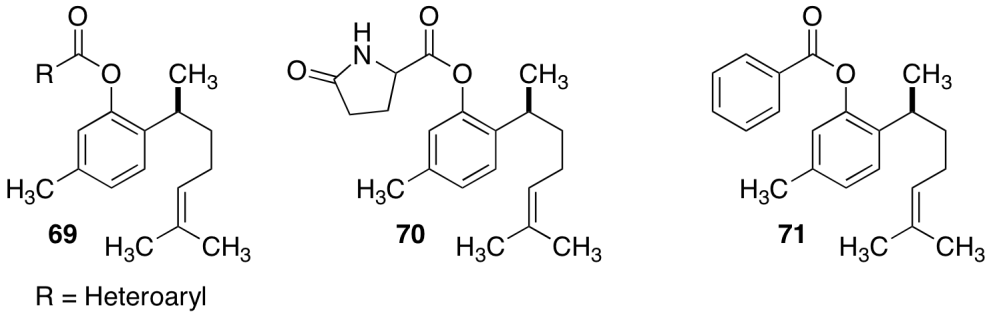
65 R=H
66 R=CH_3
67 R=$COCH_3$

The biologically active marine sesquiterpene phenol (S)-(+)-curcuphenol (**68**) has been isolated from the Jamaican sponges *Didiscus oxeata*, *Didiscus flavus*, *Myrmekioderma styx* and *Epipolasis* sp.[92-94] The compound display *in vitro* antimalarial activity against *P. falciparum*, chloroquine-resistant W2 clone, with an IC_{50} = 16.5 μM,[92] but it has no antimalarial activity against the chloroquine-sensitive D6 clone.



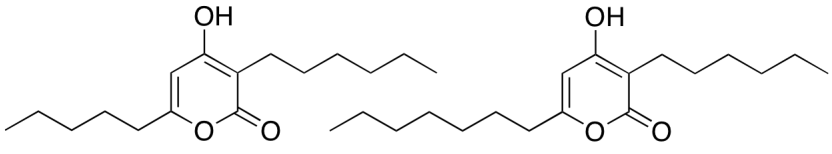
68

Hamann et al.[95] reported the preparation and evaluation for activity against several infectious diseases, of twenty semisynthetic analogues of (*S*)-(+)-curcuphenol (**68**). They were prepared in yields greater than 90% by esterification of (*S*)-(+)-curcuphenol (**68**) with a variety of carboxylic acids in a presence of N,N`-dicyclohexylcarbodiimide (DCC) or 4-dimethylaminopyridine (DMAP). There was significant increase in activity against W2 clones in nine analogues of general structure **69** and IC_{50} = 1.6 μM for **70** and **71** was measured, but no increase in activity against the D6 clone was observed.



69 **70** **71**

Total syntheses of the 2-pyrone-containing marine microbial metabolites pseudopyronines A (**72**) and B (**73**), recently reported as weak antibiotics,[96, 97] as well as a number of analogues have been achieved via a methodology based upon the condensation of β-oxo carboxylic acids.[98] The compounds **72** and **73** were originally isolated from fermentation of *Pseudomonas* sp. F92S91, which was itself isolated from a sponge collected in Fiji.

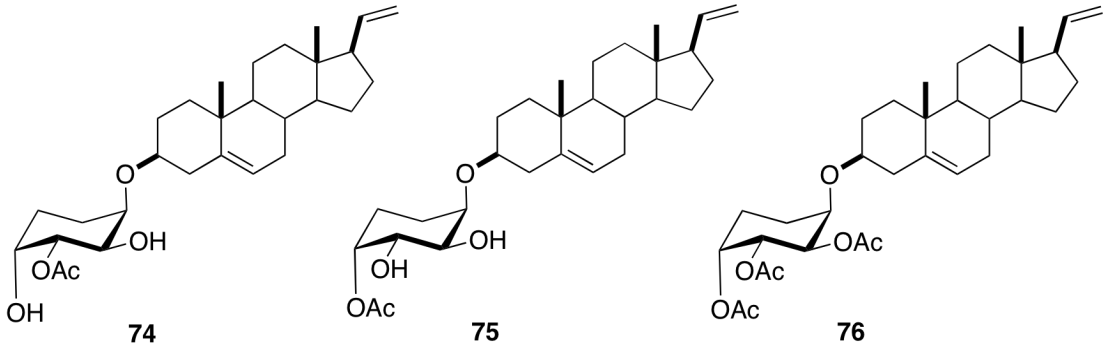


72 **73**

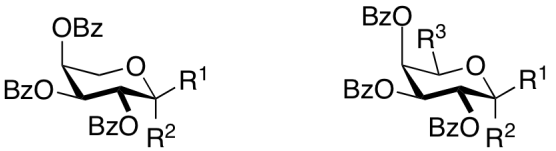
Fatty acids (FAs) are essential for all living organisms, they play crucial roles in the function and viability of cells providing components for biological membranes, acting as chemicals messengers and facilitating the storage of energy. Both natural products, **72** and **73**, inhibited PfFabI, the enoyl-ACP-reductase of *P. falciparum* with IC_{50} = 12 and 4 μg/mL, respectively and additionally pseudopyronine B (**72**) inhibited PfFabG,

a β-ketoacyl-ACP-reductase. The enzyme inhibitory activities of compounds **72** and **73** were well correlated with their *in vitro* growth inhibitory potential on *P. falciparum* whole cells, providing evidence that the PfFab pathway may be the potential cellular target of these compounds.[98]

Several carbohydrates or glycosylated structures were also reported in the literature. Glycosides **74** and **77**, showed moderate antiplasmodial activity (IC_{50} = 67 and 80 μM), which could be somewhat increased in the triacetylated derivative **76** (IC_{50} = 28 μM).[68]



The same authors[68] synthesized and evaluated the antiplasmodial activity of a series of arabinopyranosides, where two compounds, **77** and **78** (IC_{50} = 35 and 21 μM), were found to be active against *Plasmodium falciparum*, and were found being more active than the natural arabinopyranosides **74** and **75**. Antiplasmodial activity was also reported for simple sugar derivatives, with the same configuration as that of D-arabinopyranose, such as the D-fucosides **79** and **80** (IC_{50} = 43 and 36 μM) and D-galactoside **81** (IC_{50} = 21μM).

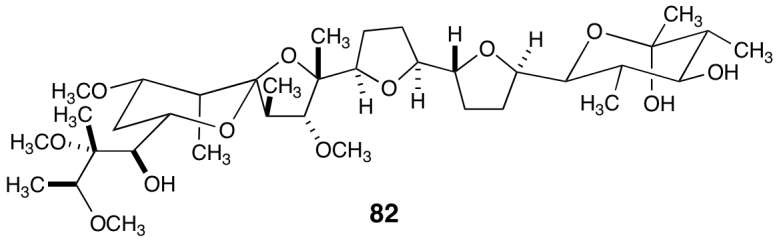


77 R^1 = H; R^2 = OCH_3
78 R^1 = OCH_3; R^2 = H

79 R^1 = H; R^2 = OMe; R^3 = CH_3
80 R^1 = OCH_3; R^2 = H; R^3 = CH_3
81 R^1 = H; R^2 = OCH_3; R^3 = CH_2OBz

A new antimalarial polyether type metabolite **82** was isolated from the marine microorganism *Streptomyces* sp. H668.[99] The antimalarial activity of **28** was

evaluated against both the chloroquine-susceptible (D6) and chloroquine-resistant (W2) clones of *P. falciparum*. Compound showed *in vitro* antiprotozoal activity with IC_{50} values ranging from 100 to 200 ng/mL without significant cytotoxicity to Vero cells. The polyether metabolite **82** is also rather specific to the parasite displaying no toxicity at 4.75 μg/mL.



82

Conclusion

The present review highlighted various efforts on antimalarial agents that have been documented over the last three years thus clearly demonstrating the high scientific activity of the field. Many new interesting lead structures have been discovered, and valuable structure/activity information has been gathered through total or semi-synthesis. Some compounds are currently evaluated in the clinic, and it is hoped that more efficient marine natural products will join the fight against malaria in the future.

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