CHAPTER 1

INTRODUCTION

1.1 General introduction

For the rich diversity of living organisms on earth, natural products have long been standing as prime sources of drugs and agents used for medical purposes (Chin et al, 2006). Among all available bioresources, including terrestrial plants, microorganisms and animals, both terrestrial and marine, medicinal plants and herbal medicines have been the most important sources for drugs from nature. Some examples of medicines that have been developed recently based on the traditional uses or folklores include paclitaxol from *Taxus brevifolia*, etoposide from *Podophyllum peltatum*, irinotecan from *Camptotheca acuminata* (Proksch et al, 2003), galantamine from *Galanthus nivalis*, and artemisinin from *Artemisia annua* (Chin et al, 2006).

Despite the stories of success among drugs from terrestrial herbal medicines, the biodiversity consideration still points to the oceans, in which more than 300,000 readily described species and much more undescribed ones reside (Chin et al, 2006). The adaptation to ecological pressures, including competition for fouling spaces, scarcity of certain physical resources, and fierce predation toward sedentary preys, have led to the chemical evolutions among marine organisms to survive such environments. These chemicals have been known to be rich platforms for new biologically active compounds with high potential for further development towards pharmaceutical and medical applications.

Whereas the history of marine natural products is as comparatively short as five decades, the progress in such discipline is intense. This could be attributed to the ease and availability of SCUBA techniques and collecting tools, as well as to the advanced technology for isolation and structure elucidation (Newman and Cragg, 2004; Rawat et al, 2006). Whereas most invertebrates that have been major targets for chemicals investigations, including sponges, tunicates, and soft corals, remain the primary subjects, certain classes of organisms such as marine bacteria have drawn large amount of attention. Also, several terrains that have never been explored now become more accessible and allow marine natural product chemists to expand their horizon to the unimaginable extent.

To date, only a few of compounds that have been developed from marine natural products are readily available in clinic. These include vidarabine and cytarabine, which were derived from arabino nucleosides from the sponge *Cryptotethya crypta*. Another success story include ziconotide, (ω-conotoxin MVIIA), a novel non-opioid analgesic peptide, from *Conus magus*. However, a handful of compounds that are in clinical trials show their potential and possibility for the further advancement into clinical uses. Some examples of compounds that are now entering clinical trials are shown in Table 1.

Table 1 Marine natural products ongoing in clinical trials

Name	Sources	Status (disease)
ecteinascidin 743 (Yondelis™)	*Ecteinascidia turbinata*	Phase III (cancer)
Æ-941 (Neovastat™)	shark cartilage	Phase III (cancer)
bryostatin 1	*Bugula neritina*	Phase II (cancar)
LU-103793 (cematodin)	synthetic derivative of dolastatin15	Phase II (cancer)
TZT-1027 (soblidotin)	synthetic derivative of dolastatin 10	Phase II (cancer)
kahalalide F	*Elysia rufescens*; *Bryopsis* sp.	Phase II (cancer)
ILX651 (synthatodin)	synthetic derivative of dolastatin15	Phase II (cancer)
squalamine	*Squalus acanthias*	Phase II (cancer)
aplidine	*Aplidium albicans*	Phase II (cancer)
CGX-1160 (contulakin-G)	*Conus geographus*	Phase II (pain)
CGX-1007 (conantokin-G)	*Conus geographus*	Phase II (pain and epilepsy)
CGX-100 (conantokin-T)	*Conus geographus*	Phase II (pain)

Table 1 (cont.)

Name	Sources	Status (disease)
AM336 (ω-conotoxin CVID)	*Conus catus*	Phase II (pain)
IPL-576092 (HMR-4011A)	*Petrosia contignata*	Phase II (antiasthma)
IPL-512602	*Petrosia contignata*	Phase II (anti-inflammatory)
discodermolide	*Discodermia dissoluta*	Phase I (cancer)
E7389 (halichondrin B derivative)	*Lissodendoryx* sp.	Phase I (cancer)
ES-285 (spisulosine)	*Spisula polynyma*	Phase I (cancer)
HTI-286 (hemiasterlin derivative)	*Cymbastella* sp.	Phase I (cancer)
KRN-7000	*Agelas mauritianus*	Phase I (cancer)
DMBX (GTS-21)	*Amphiporus lactifloreus*	Phase I (anti Alzheimer's)
IPL-550260	*Petrosia contignata*	Phase I (anti-inflammatory)

Note: Modified from Newman and Cragg. (2004), and Alonso et al. (2003).

1.2 Malaria

Malaria is one of the deadliest parasitic infectious diseases distributing primarily in the less developed countries in the tropical zones, among which Thailand is included. There are four species of *Plasmodium* parasites that can cause malaria in human, including *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, among which *P. falciparum* is the most life threatening species due to the ability to adhere to the vascular endothelium, making the vascular obstruction. The severe symptoms from *P. falciparum* infection include acute renal failure, cerebral malaria, and pulmonary edema, all of which may lead to the death of the patient (Rathbun, 2000). Malaria is transmitted via the bite of various species of *Anopheles* mosquitoes. After the bite, the sporozoites, parasites in sexual stage from the mosquito's salivary gland, are

released into blood circulation of human. The sporozoites in blood circulation then invade the host's liver, becoming tissue schizonts or hypnozoites, and develop into the merozoites or erythrocytic schizonts, the parasites in erythrocytic stage. The hibernation in liver tissue lasts 1-2 weeks, at which time the merozoites are released from liver to bloodstream and infect the erythrocytes. In the erythrocytes, merozoites consume hemoglobin and develop into a ring form and gametophytes, before erupting the erythrocytes into blood stream. Merozoites will re-attach other erythrocytes, while gametophytes, which can develop only in mosquitoes, are await for the next bite. Since the stage of being merozoites in erythrocyte is the active proliferating stage, most of the clinically available drugs are targeting the parasites in this stage. For *P. vivax* and *P. ovale* infection, in which the hibernation stage can last longer, and which may become latent, the un-targetted hypnozoites could cause relapsing malaria. The lack of antimalarial drugs targeting dormant hypnozoites is among one of the needs for area with outbreak of *P. vivax* and *P. ovale* (Anandan, 2003; Rathbun, 2000).

Annually, more than 300 million clinical malarial cases with 1 million deaths, are reported worldwide. Whereas the epidemic spreads mainly in the tropics, rounded to 60% of clinical illnesses are reported in Africa, especially in the sub-Saharan belt. Age-group distribution in African region lays primarily on the children, with more than 90% of deaths reported every year (WHO, 2008). For Thailand, whereas the clinical illnesses and death tolls are not as high, the severity, similar to most South-East and South Asian countries, lays upon the drug-resistant strains of *P. falciparum*. It is, in facts, the South-East Asia, where the multidrug-resistant strains were first reported in the 1950's, and where the most invasive ones are yet found (WHO, 2005).

Normally, the choices of malaria treatment depend on the infecting species. Non-complicated *P. falciparum* infection can be treated with either single or combined drug regimen. The single drug regimen include either quinine (600 mg every 6 hours for 7 days), mefloquine (1250 mg single dose), or artesunate (600 mg divided to 5 days), whereas combined ones involve either quinine (600 mg every 6 hours for 7 days) or mefloquine (1250 mg single dose) combined with tetracycline (200 mg every 6 hours for 7 days) or doxycycline (250 mg/day for 7 days), or artesunate (600 mg divided to 5 days) followed by mefloquine (1250 mg single dose). For *P. vivax* infection, the use of chloroquine (loading dose 1000 mg, 500 mg after

6 hours, then 500 mg/day for 2 days) and primaquine (15 mg/day for 14 day) is adequately effective (WHO, 2006). For the treatment of multi-drug resistant malaria infection, WHO has recommended the ACTs (artemisinin-based combination therapies) guideline, in which the recommended first-line drugs are combination of artesunate (200 mg/day for 3 days) and mefloquine (1000 mg on day 2 and 500 mg on day 3) (WHO, 2006).

1.2.1 Antimalarial drugs from nature

Antimalarial drugs seem to be the best examples of modern medicines that are developed solely from natural products. Quinine and artemisinin derivatives, the only two classes of antimalarial agents effectively used in clinics, have evolved from medicinal plants used in traditional medicines (Krishna et al, 2004). Cinchona bark (*Cinchona succirubra* and related species of *Cinchona*) was used for the treatment of malaria among native Americans and was the source that led to the discovery of quinine, which was then developed to become the mere treatment for malaria since the 1820's. Later derivatives also include mefloquine, chloroquine, hydroxychloroquine, and primaquine (Figure 1). The primary target of quinine and derivatives is heme, to which the quinines can form an un-detoxified complex toxic solely to the parasites (Wright, 2002).

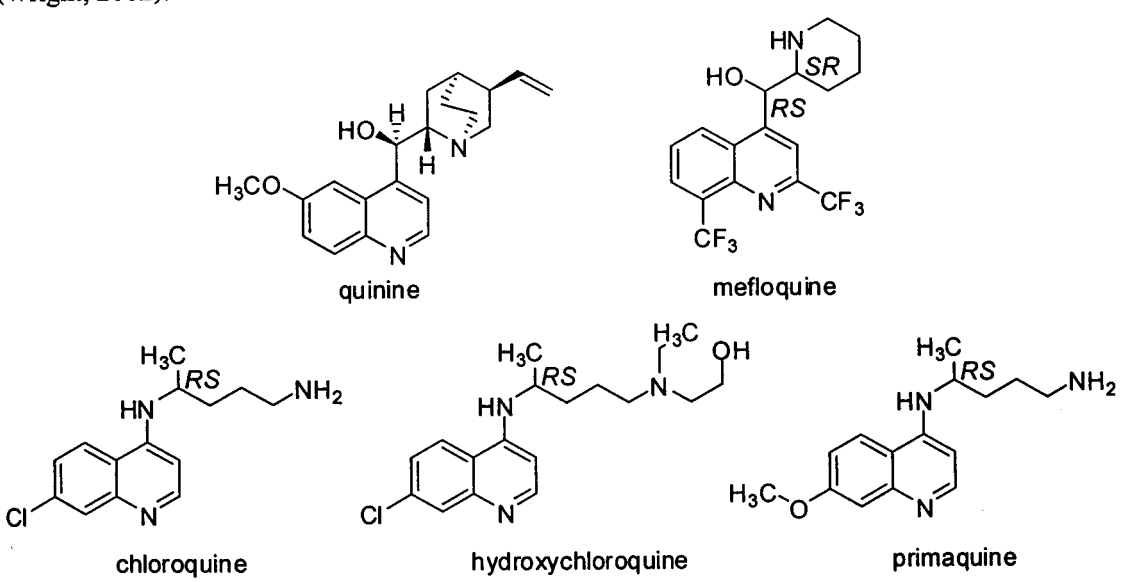


Figure 1 Quinine and its derivatives

Artemisinin, cyclicperoxide diterpene from the Chinese medicinal plant, qinghao (*Atemisia annua*), was discovered in 1971 (Wright, 2002). The compound evolved into various derivatives, mainly to improve solubility (Krishna et al, 2004). These include artesunate, dihydroartemisinin, artemether, and artemotil (Figure 2). The peroxide functionality plays an important role in the antimalarial activity. The oxidation of ferrous in haem by the peroxide leads to the release of free radicals toxic to the parasites (Murakami et al, 2004).

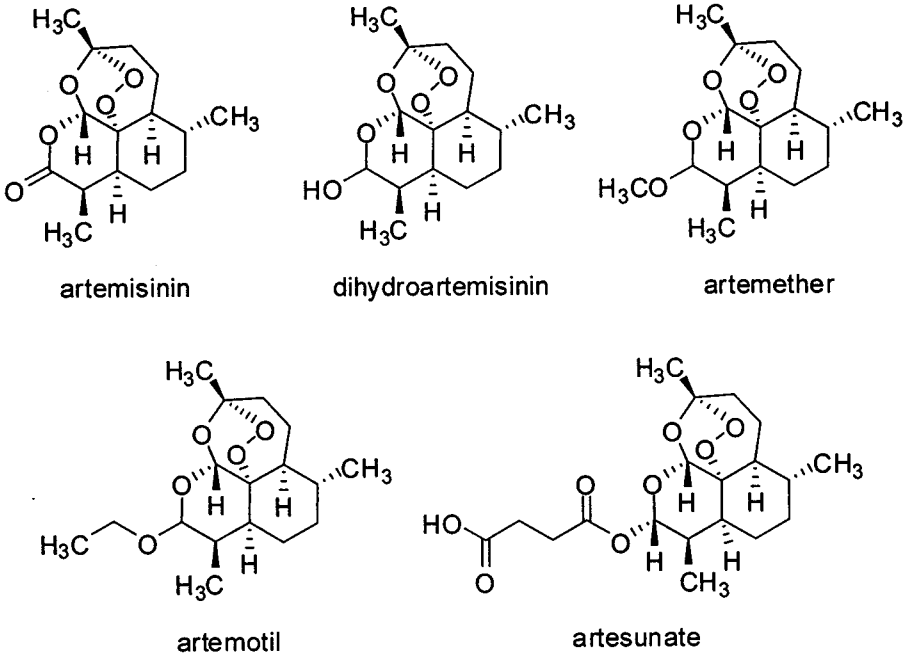


Figure 2 Artemisinin and its derivatives

1.2.2 Antimalarial compounds from marine natural products

Whereas the uses of quinine and artemisinin derivatives seem to contain malarial epidemic to the certain extent. The worldwide outbreaks of drug-resistant *Plasmodium* urge the need for the development of new antimalarial drugs to complement the currently used medicines and/or to counteract with newly evolved strains of *Plasmodium* parasites. Various groups of natural products such as quassinoids and nimbolides showed good tendency, although never been advanced to the further stages primarily due to the strong toxicity and/or inadequate efficacy.

Marine natural products are among the rich bioresources that have been explored for the new antimalarial agents, especially against the drug-resistant strains of *Plasmodium* (Donia and Harmann, 2003). Various groups of compounds of marine origins, ranging from

β-carboline alkaloids to functionalized terpenoids, were reported active against *P. falciparu*, well as other *Plasmodium* species. Some of these compounds were even advanced to pre-clinical investigations, although being dropped later due to the lack of sufficient potency. Listed in Table 2 are compounds from marine natural products that were reported with antimalarial activity.

Table 2 Antimalarial compounds derived from marine natural products

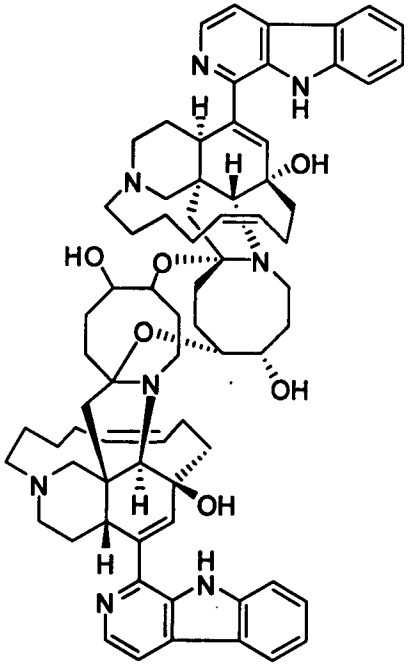
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
manzamine alkaloids			
neo-kauluamine 	undescribed genus (sponge)	1700 ng/mL (D6 clone) 2800 ng/mL (W2 clone)	El Sayed et al, 2001b; Rao et al, 2004

Table 2 (cont.)

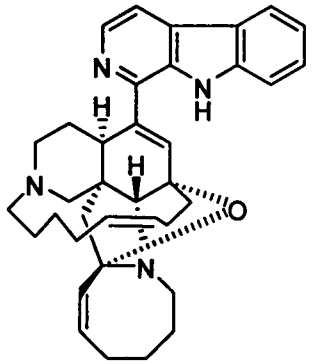
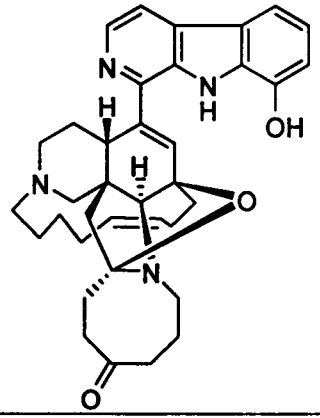
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
12,34-oxamanzamine A 	undescribed genus (01IND51) (sponge)	4760 ng/mL (D6 clone)	Yousaf et al, 2002
ent-12,34-oxamanzamine F 	undescribed genus (01IND35) (sponge)	840 ng/mL (D6 clone) 1100 ng/mL (W2 clone)	Yousaf et al, 2002

Table 2 (cont.)

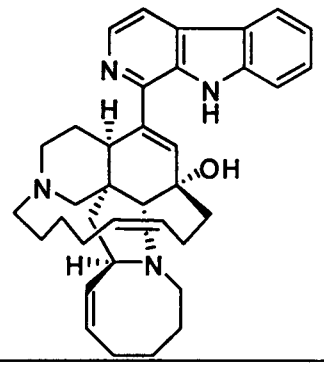
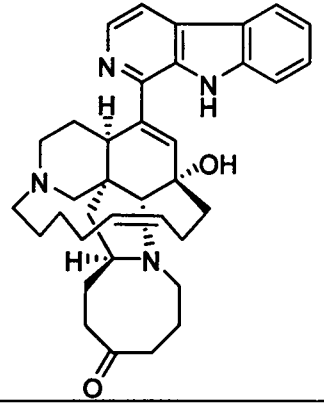
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
manzamine A 	undescribed genus (01IND51, 01IND76) (sponge)	4.5 ng/mL (D6 clone) 8.0 ng/mL (W2 clone)	Rao et al, 2003
manzamine E 	undescribed genus (01IND35) (sponge)	3400 ng/mL (D6 clone) 4760 ng/mL (W2 clone)	Rao et al, 2003

Table 2 (cont.)

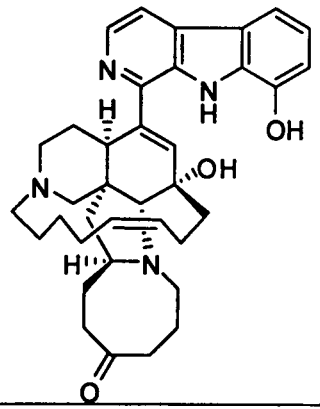
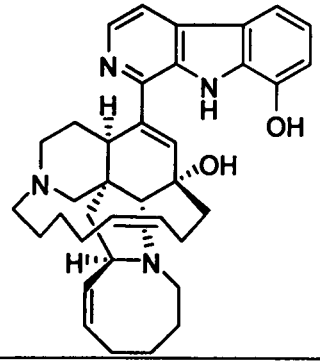
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
manzamine F 	undescribed genus (01IND 51 and 01IND76) (sponge)	780 ng/mL (D6 clone) 1700 ng/mL (W2 clone)	Rao et al, 2003
(+)-8-hydroxymanzamine A 	*Acanthostrongylophora* sp. (sponge)	6.0 ng/mL (D6 clone) 8.0 ng/mL (W2 clone)	Rao et al, 2004

Table 2 (cont.)

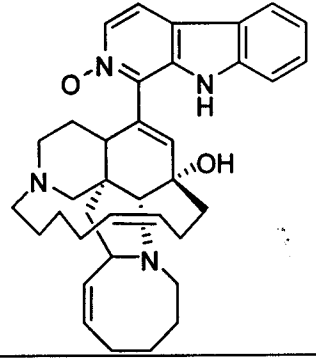
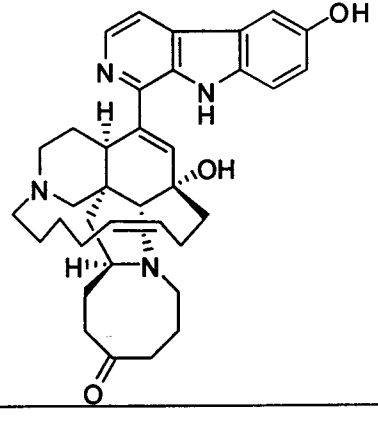
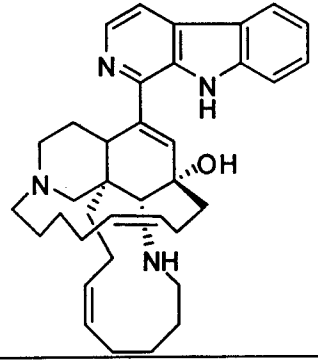
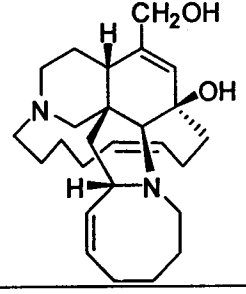
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
manzamine A *N*-oxide 	*Acanthostrongylophora* sp. (sponge)	11 ng/mL (D6 clone) 13 ng/mL (W2 clone)	Rao et al, 2004
6-hydroxymanzamine E 	*Acanthostrongylophora* sp. (sponge)	780 ng/mL (D6 clone) 870 ng/mL (W2 clone)	Rao et al, 2004

Table 2 (cont.)

Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
manzamine J 	*Acanthostrongylophora* sp. (sponge)	1300 ng/mL (D6 clone) 750 ng/mL (W2 clone)	Rao et al, 2004
ircinol A 	*Acanthostrongylophora* sp. (sponge)	2400 ng/mL (D6 clone) 3100 ng/mL (W2 clone)	Rao et al, 2004

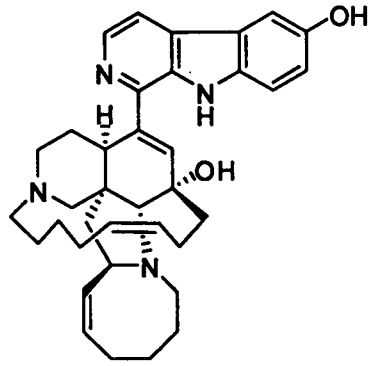
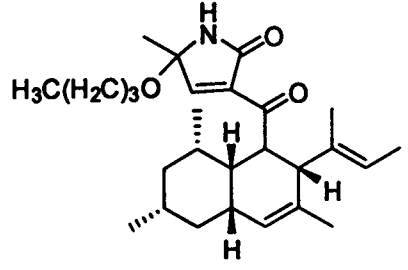
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
manzamine Y 	*Acanthostrongylophora* sp. (sponge)	420 ng/mL (D6 clone) 850 ng/mL (W2 clone)	Rao et al, 2006
pyrrole alkaloids			
ascosalipyrrolidinone A 	*Ascochyta salicorniae* (fungus)	378 ng/mL (NF54 clone) 736 ng/mL (K1 clone)	Osterhage et al, 2000

Table 2 (cont.)

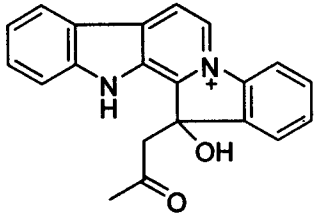
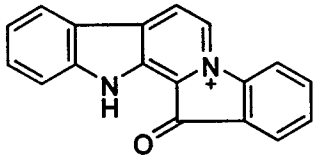
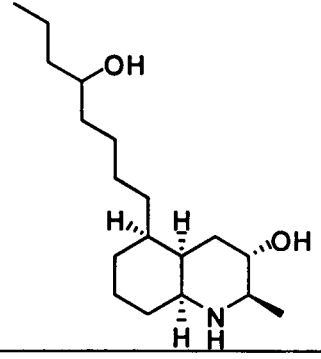
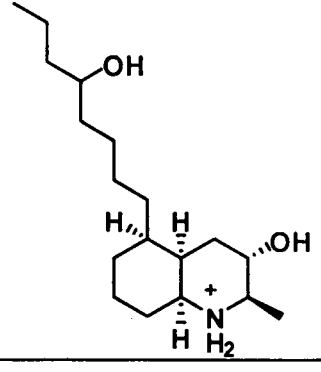
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
bis-indole alkaloids			
homofascaplysin A 	*Hyrtios* cf. *erecta* (sponge)	24 ng/mL (NF54 clone) 14 ng/mL (K1 clone)	Kirsch et al, 2000
fascaplysin 	*Hyrtios* cf. *erecta* (sponge)	34 ng/mL (NF54 clone) 50 ng/mL (K1 clone)	Kirsch et al, 2000

Table 2 (cont.)

Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
decahydroquinoline alkaloids			
lepadin D 	*Didemnum* sp. (tunicate)	10.0 µg/mL (NF54 clone) 6.1 µg/mL (K1 clone)	Wright et al, 2002
quaternary nitrogen derivative of lepadin D 	*Didemnum* sp. (tunicate)	10.0 µg/mL (NF54 clone) 4.0 µg/mL (K1 clone)	Wright et al, 2002

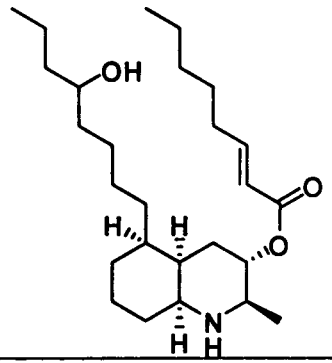
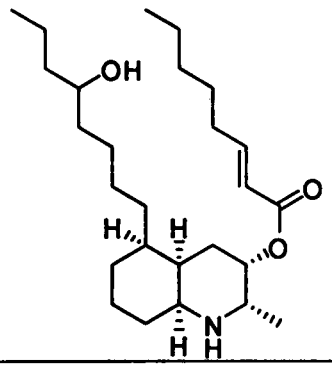
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
lepadin E 	*Didemnum* sp. (tunicate)	0.9 µg/mL (NF54 clone) 0.4 µg/mL (K1 clone)	Wright et al, 2002
lepadin F 	*Didemnum* sp. (tunicate)	0.3 µg/mL (NF54 clone) 0.2 µg/mL (K1 clone)	Wright et al, 2002

Table 2 (cont.)

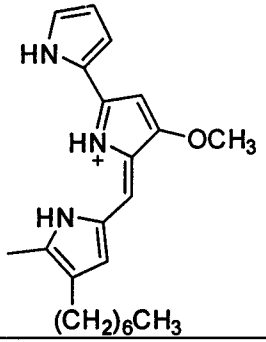
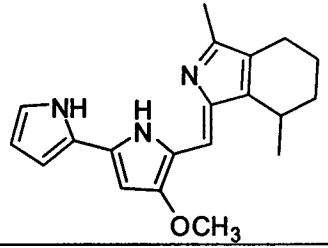
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
prodigiosin-type polypyrrole alkaloids			
hyptyl prodigiosin 	undescribed proteobacteria (proteobacteria)	0.07 µM (3D7 clone)	Mayer and Hamann, 2005
cycloprodigiosin 	*Pseudoalteromonas denitrificans* (bacteria)	11 nM (FCR-3 clone)	Laurent and Pietra, 2006

Table 2 (cont.)

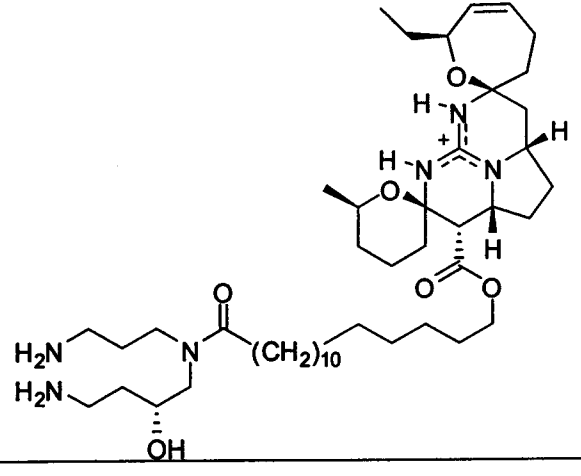
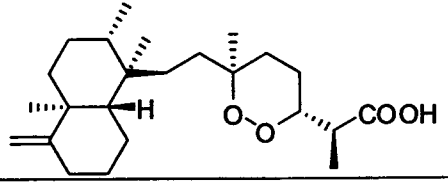
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
crambesidin alkaloid			
crambescidin 800 	*Mycophora* sp. (sponge)	160 nM (3D7 clone)	Lazaro et al, 2006
cyclic peroxides			
sigmosceptrellin B 	*Diacarnus erythraeanus* (sponge)	1200 ng/mL (D6 clone) 3400 ng/mL (W2 clone)	El Sayed et al, 2001a

Table 2 (cont.)

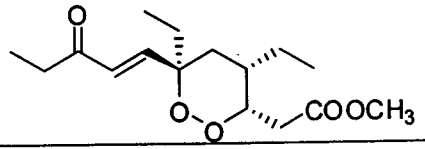
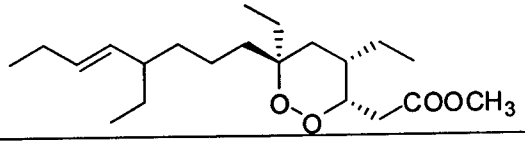
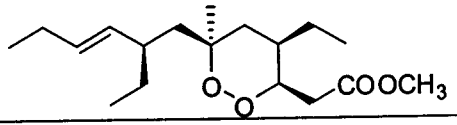
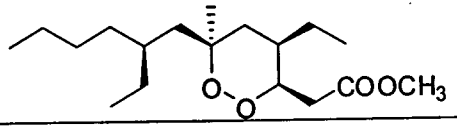
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
plakortide I 	*Plakortis* sp. (sponge)	570 ng/mL (W2 clone)	Hu et al, 2001
plakortide F 	*Plakortis* sp. (sponge)	480 ng/mL (D6 clone) 390 ng/mL (W2 clone)	Gochfeld and Hamann, 2001
plakortin 	*Plakortis simplex* (sponge)	1263 nM (D10 clone) 735 nM (W2 clone)	Fattorusso et al, 2002
dihydroplakortin 	*Plakortis simplex* (sponge)	1117 nM (D10 clone) 760 nM (W2 clone)	Fattorusso et al, 2002

Table 2 (cont.)

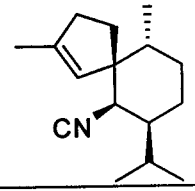
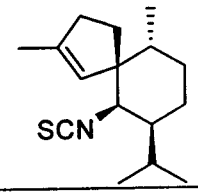
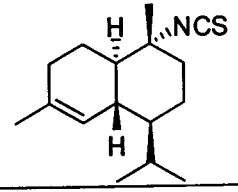
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
isonitrile and related functionalized terpenoids			
axisonitrile 3 	*Acanthella klethra* (sponge)	142 ng/mL (D6 clone) 16.5 ng/mL (W2 clone)	Angerhofer and Pezzuto, 1992
axisothiocyanate 3 	*Acanthella klethra* (sponge)	12340 ng/mL (D6 clone) 3110 ng/mL (W2 clone)	Angerhofer and Pezzuto, 1992
10-isothiocyano-4-cadinene 	*Phakellia carduus* (sponge)	1.5 µg/mL (NF54 clone) 1.5 µg/mL (K1 clone)	Wright, 2003

Table 2 (cont.)

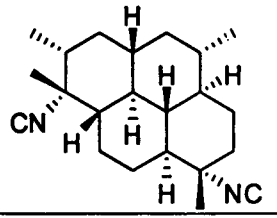
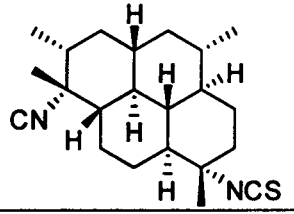
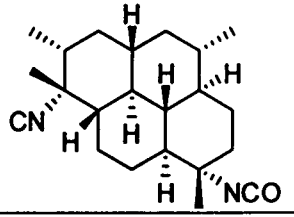
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
diisocyanoadociane 	*Cymbastela hooperi* (sponge)	4.7 ng/mL (D6 clone) 4.3 ng/mL (W2 clone)	König and Wright, 1996
20-isocyano-7-isothiocyanatoisocycloamphilectane 	*Cymbastela hooperi* (sponge)	45.1 ng/mL (D6 clone) 28.5 ng/mL (W2 clone)	König and Wright, 1996
20-isocyano-7-isocyanatoisocycloamphilectane 	*Cymbastela hooperi* (sponge)	74.9 ng/mL (D6 clone) 56.1 ng/mL (W2 clone)	König and Wright, 1996

Table 2 (cont.)

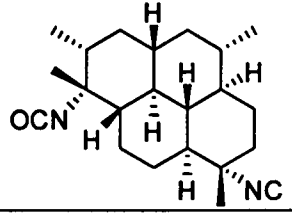
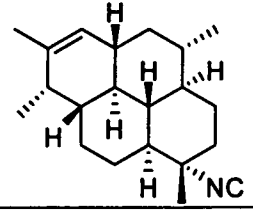
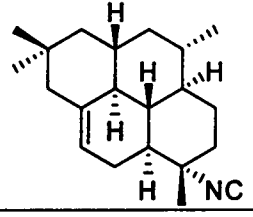
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
20-isocyanato-7-isocyano-isocycloamphilectane 	*Cymbastela hooperi* (sponge)	3.2 ng/mL (D6 clone) 2.5 ng/mL (W2 clone)	König and Wright, 1996
7-isocyanoisocycloamphilect-14-ene 	*Cymbastela hooperi* (sponge)	62.5 ng/mL (D6 clone) 29.5 ng/mL (W2 clone)	König and Wright, 1996
7-isocyanocycloamphilect-10-ene 	*Cymbastela hooperi* (sponge)	84.9 ng/mL (D6 clone) 28.4 ng/mL (W2 clone)	König and Wright, 1996

Table 2 (cont.)

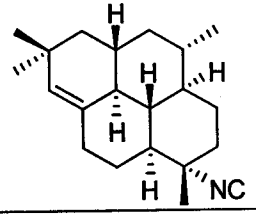
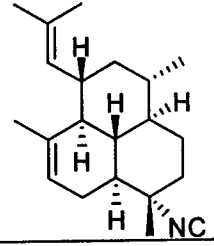
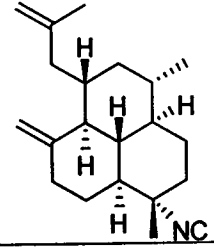
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
7-isocyanocycloamphilect-11(20)-ene 	*Cymbastela hooperi* (sponge)	74.1 ng/mL (D6 clone) 23.8 ng/mL (W2 clone)	König and Wright, 1996
7-isocyanoamphilecta-10,14-diene 	*Cymbastela hooperi* (sponge)	302 ng/mL (D6 clone) 133 ng/mL (W2 clone)	König and Wright, 1996
7-isocyanocycloamphilecta-11(20),15-diene 	*Cymbastela hooperi* (sponge)	520 ng/mL (D6 clone) 242 ng/mL (W2 clone)	König and Wright, 1996

Table 2 (cont.)

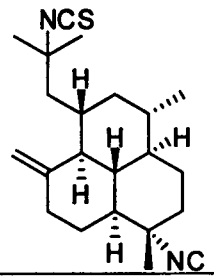
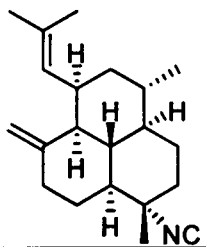
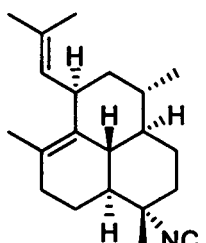
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
7-isocyano-15-isothiocyanatoamphilect-11(20)-ene 	*Cymbastela hooperi* (sponge)	470 ng/mL (D6 clone) 109 ng/mL (W2 clone)	König and Wright, 1996
7-isocyanoamphilecta-11(20),14-diene 	*Cymbastela hooperi* (sponge)	14.1 ng/mL (D6 clone) 9.3 ng/mL (W2 clone)	König and Wright, 1996
7-isocyanoamphilecta-11,14-diene 	*Cymbastela hooperi* (sponge)	58.5 ng/mL (D6 clone) 25.6 ng/mL (W2 clone)	König and Wright, 1996

Table 2 (cont.)

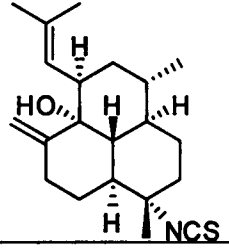
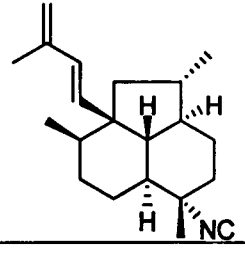
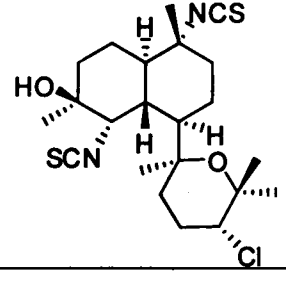
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
12-hydroxy-7-isothiocyanatoamphilecta-11(20),14-diene 	*Cymbastela hooperi* (sponge)	797 ng/mL (D6 clone) 423 ng/mL (W2 clone)	König and Wright, 1996
7-isocyanoneoamphilecta-1(14),15-diene 	*Cymbastela hooperi* (sponge)	90.0 ng/mL (D6 clone) 29.7 ng/mL (W2 clone)	König and Wright, 1996
10-epikalihinol I 	*Acanthella* sp. (sponge)	>1800 nM (FCR-3 clone)	Miyaoka et al, 1998

Table 2 (cont.)

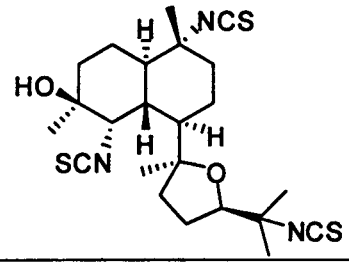
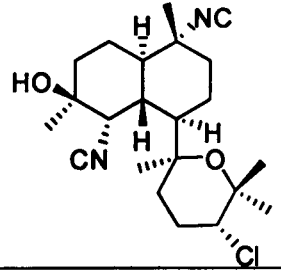
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
5,10-bisisothiocyanatokalihinol G 	*Acanthella* sp. (sponge)	2600 μM (FCR-3 clone)	Miyaoka et al, 1998
kalihinol A 	*Acanthella* sp. (sponge)	1.2 nM (FCR-3 clone)	Miyaoka et al, 1998

Table 2 (cont.)

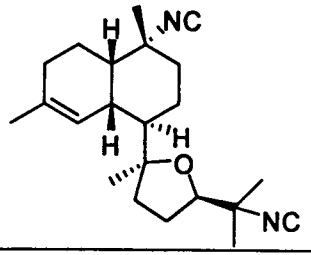
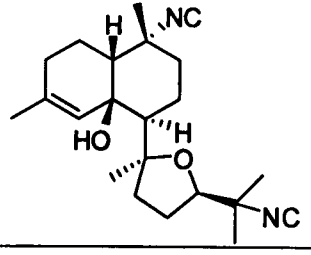
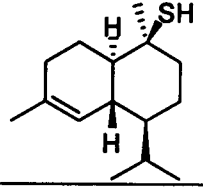
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
kalihinene 	*Acanthella* sp. (sponge)	10 nM (FCR-3 clone)	Miyaoka et al, 1998
6-hydroxykalihinene 	*Acanthella* sp. (sponge)	80 nM (FCR-3 clone)	Miyaoka et al, 1998
other terpenes			
T-cadinithiol 	*Cymbastela hooperi* (sponge)	3.6 µg/mL (D6 clone)	König and Wright, 1997

Table 2 (cont.)

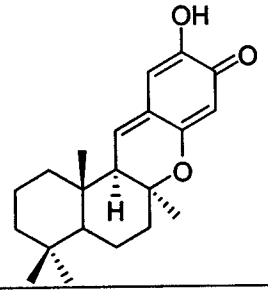
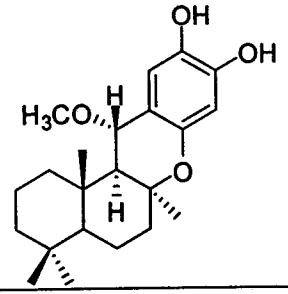
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
puupehenone 	*Hyrtios* sp. (sponge)	0.6 μg/mL (F32 clone) 2.1 μg/mL (FCB1 clone) 1.5 μg/mL (PFB clone)	Bourguet-Kondracki et al, 1999
15α-methoxypuupehenol 	*Hyrtios* sp. (sponge)	0.4 μg/mL (F32 clone) 1.4 μg/mL (FCB1 clone) 1.2 μg/mL (PFB clone)	Bourguet-Kondracki et al, 1999

Table 2 (cont.)

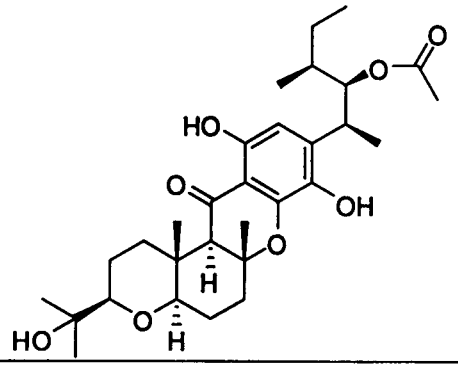
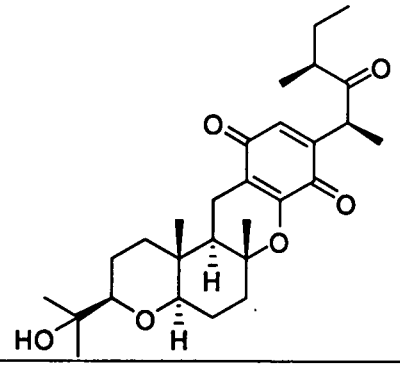
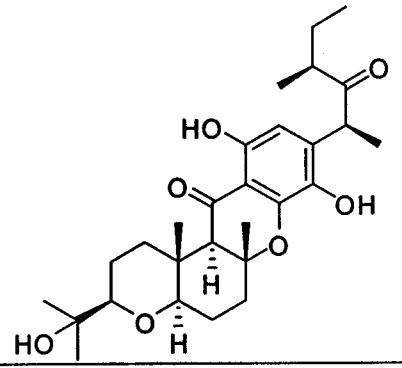
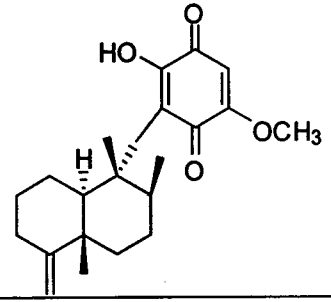
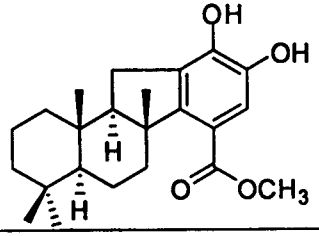
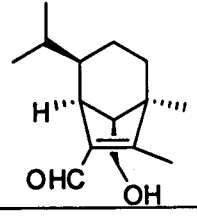
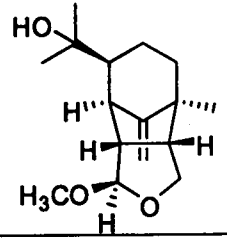
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
isocochlioquinone A 	*Drechslera dematioidea* (fungus)	3303 ng/mL (NF54 clone) 1412 ng/mL (K1 clone)	Osterhage et al, 2002
cochlioquinone B 	*Drechslera dematioidea* (fungus)	3411 ng/mL (NF54 clone) 2611 ng/mL (K1 clone)	Osterhage et al, 2002

Table 2 (cont.)

Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
isocohlioquinone C 	*Drechslera dematioidea* (fungus)	9261 ng/mL (NF54 clone) 6945 ng/mL (K1 clone)	Osterhage et al, 2002
ilimaquinone 	*Dactylospongia elegans* (sponge)	949 ng/mL (NF54 clone) 1743 ng/mL (K1 clone)	Goclik et al, 2000

Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
pelorol 	*Dactylospongia elegans* (sponge)	1911 ng/mL (NF54 clone) 786 ng/mL (K1 clone)	Goclik et al, 2000
helminthosporol 	*Drechslera dematioidea* (fungus)	6705 ng/mL (NF54 clone) 4711 ng/mL (K1 clone)	Osterhage et al, 2002
drechslerine E 	*Drechslera dematioidea* (fungus)	3651 ng/mL (NF54 clone) 5095 ng/mL (K1 clone)	Osterhage et al, 2002

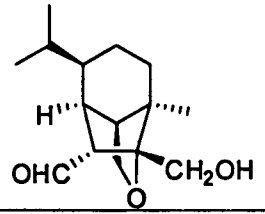
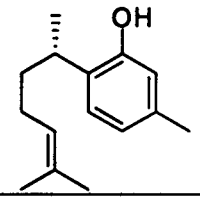
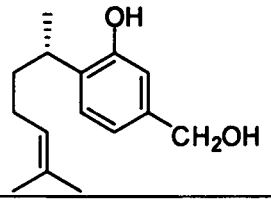
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
drechslerine G 	*Drechslera dematioidea* (fungus)	4244 ng/mL (NF54 clone) 2904 ng/mL (K1 clone)	Osterhage et al, 2002
(*S*)-(+)-curcuphenol 	*Didiscus oxeata* (sponge)	3600 ng/mL (D6 clone) 1800 ng/mL (W2 clone) (reported in MIC)	El Sayed et al, 2002
(*S*)-(+)-15-hydroxycurcuphenol 	*Didiscus oxeata* (sponge)	3800 ng/mL (D6 clone) 2900 ng/mL (W2 clone) (reported in MIC)	El Sayed et al, 2002

Table 2 (cont.)

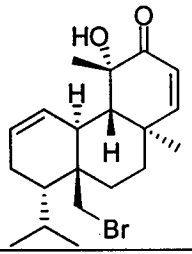
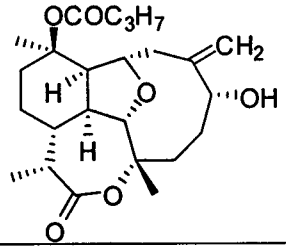
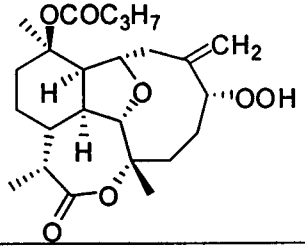
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
sphaerococcenol A 	*Sphaerococcus coronopifolius* (alga)	1 μM (FCB1 clone)	Etahiri et al, 2001
briarellin D 	*Briareum polyanthes* (gorgonian coral)	13 μg/mL (unidentified strain)	Ospina et al, 2003
briarellin D hydroperoxide 	*Briareum polyanthes* (gorgonian)	9 μg/mL (unidentified strain)	Ospina et al, 2003

Table 2 (cont.)

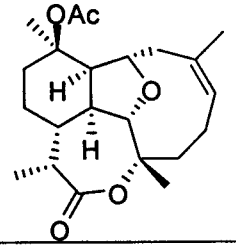
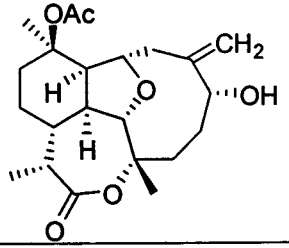
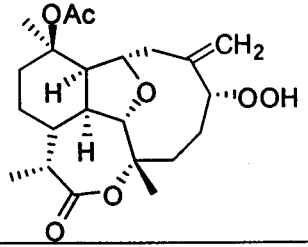
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
briarellin J 	*Briareum polyanthes* (gorgonian)	50 μg/mL (unidentified strain)	Ospina et al, 2003
briarellin K 	*Briareum polyanthes* (gorgonian)	15 μg/mL (unidentified strain)	Ospina et al, 2003
briarellin K hydroperoxide 	*Briareum polyanthes* (gorgonian)	9 μg/mL (unidentified strain)	Ospina et al, 2003

Table 2 (cont.)

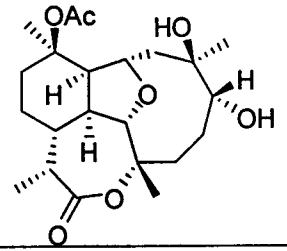
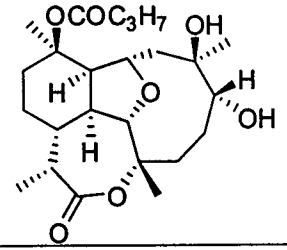
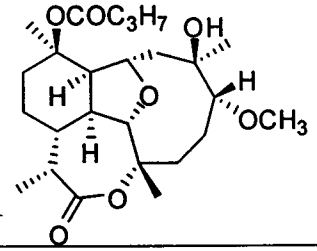
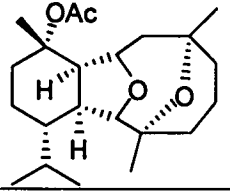
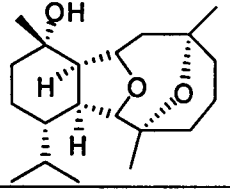
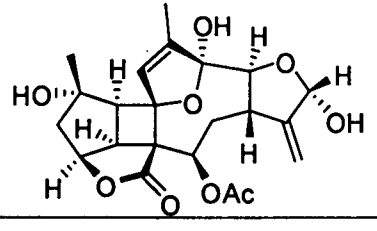
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
briarellin M 	*Briareum polyanthes* (gorgonian)	22 µg/mL (unidentified strain)	Ospina et al, 2003
briarellin O 	*Briareum polyanthes* (gorgonian)	24 µg/mL (unidentified strain)	Ospina et al, 2003
briarellin P 	*Briareum polyanthes* (gorgonian)	14 µg/mL (unidentified strain)	Ospina et al, 2003

Table 2 (cont.)

Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
polyanthellin A 	*Briareum polyanthes* (gorgonian)	16 µg/mL (unidentified strain)	Ospina et al, 2003
polyanthellin A derivative 12 	*Briareum polyanthes* (gorgonian)	16 µg/mL (unidentified strain)	Ospina et al, 2003
bielschowskysin 	*Pseudopterogorgia kallos* (gorgonian)	10 µg/mL (D6 clone) 10 µg/mL (W2 clone)	Marrero et al, 2004

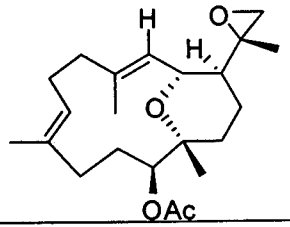
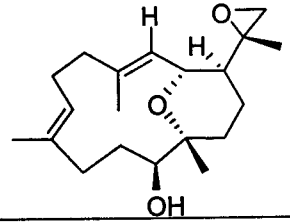
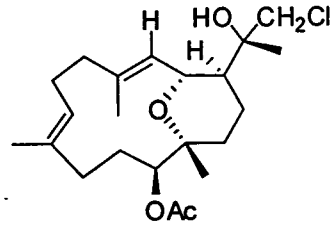
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
11-acetyloxy-2,12,15,17-diepoxy-(3*E*,7*E*)-cembra-3,7-diene 	*Enicea* sp. (gorgonian)	23 µg/mL (W2 clone)	Wei et al, 2004
11-hydroxy-2,12,15,17-diepoxy-(3*E*,7*E*)-cembra-3,7-diene 	*Enicea* sp. (gorgonian)	15 µg/mL (W2 clone)	Wei et al, 2004
11-acetyloxy-15-hydroxy-17-chloro-2,12-epoxy-(3*E*,7*E*)-cembra-3,7-diene 	*Enicea* sp. (gorgonian)	16 µg/mL (W2 clone)	Wei et al, 2004

Table 2 (cont.)

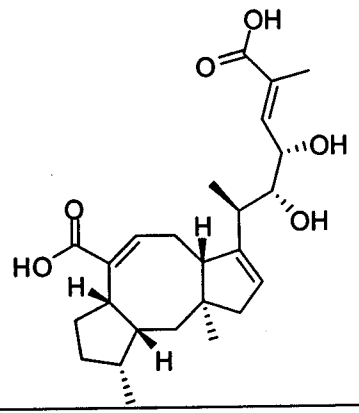
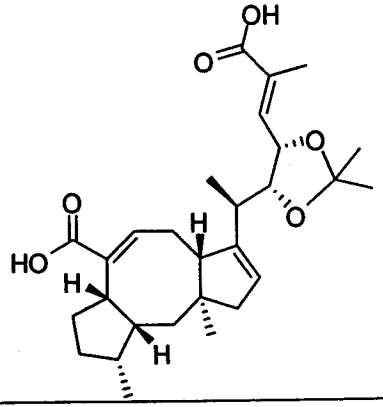
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
halorosellinic acid 	*Halorosellinia oceanica* BCC5149 (fungus)	13 µg/mL (K1 clone)	Chinworrungsee et al, 2001
halorosellinic acetonide 	*Halorosellinia oceanica* BCC5149 (fungus)	19 µg/mL (K1 clone)	Chinworrungsee et al, 2001

Table 2 (cont.)

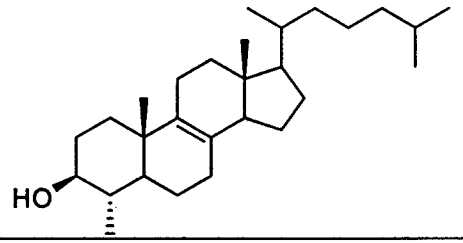
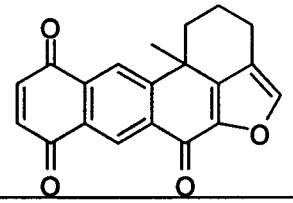
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
sterol			
4α-metyl-5α-cholest-8-en-3β-ol 	*Agelas oroides* (sponge)	5.3 μg/mL (D6 clone) 3.3 μg/mL (W2 clone)	König et al, 1998
quinones			
xestoquinone 	*Xestospongia* sp. (sponge)	3 μM (FCB1 clone)	Laurent et al, 2006

Table 2 (cont.)

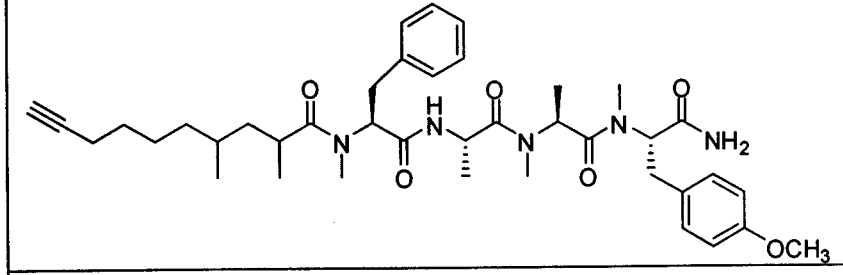
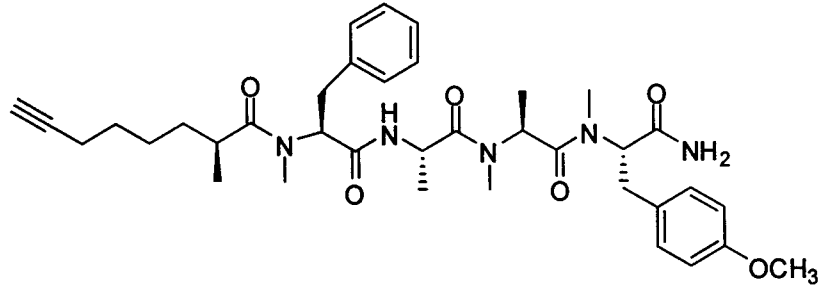
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
peptides			
carmabin A 	*Lyngbya majuscula* (cyanobacteria)	4.3 μM (W2 clone)	McPhail et al, 2007
dragomabin 	*Lyngbya majuscula* (cyanobacteria)	6.0 μM (W2 clone)	McPhail et al, 2007

Table 2 (cont.)

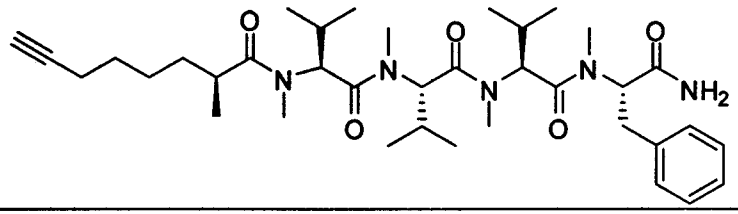
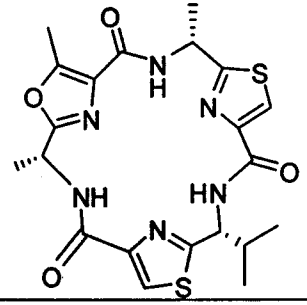
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
dragonamide A 	*Lyngbya majuscula* (cyanobacteria)	7.7 μM (W2 clone)	McPhail et al, 2007
venturamide A 	*Oscillatoria* sp. (cyanobacteria)	8.2 μM (W2 clone)	Linington et al, 2007

Table 2 (cont.)

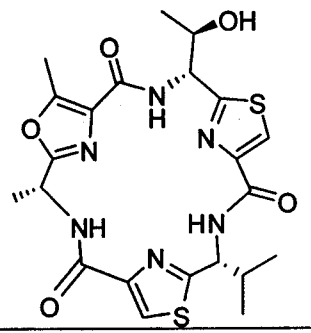
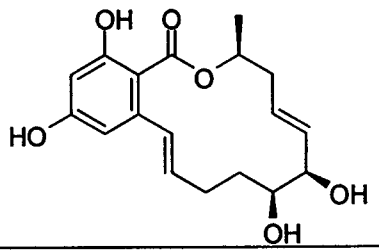
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
venturamide B 	*Oscillatoria* sp. (cyanobacteria)	5.6 μM (W2 clone)	Linington et al, 2007
macrolides			
aigialomycin D 	*Aigialus pavus* BCC531 (fungus)	6.6 μg/mL (K1 clone)	Isaka et al, 2002

Table 2 (cont.)

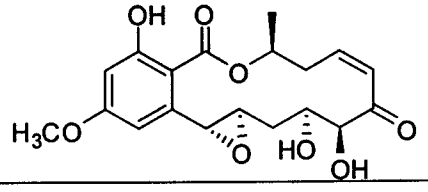
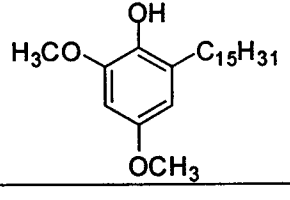
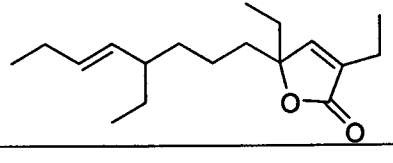
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
hypothemycin 	*Aigialus pavus* BCC531 (fungus)	2.2 µg/mL (K1 clone)	Isaka et al, 2002
miscellaneous compounds			
hierridin B 	*Phormidium ectocarpi* (cyanobacteria)	5.2 µg/mL (D6 clone) 3.7 µg/mL (W2 clone)	Papendorf et al, 1997
plakortone 	*Plakortis* sp. (sponge)	4200 ng/mL (D6 clone)	Gochfeld and Hamann, 2001

Table 2 (cont.)

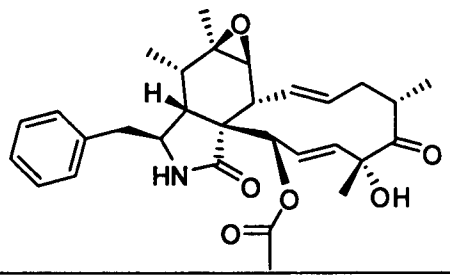
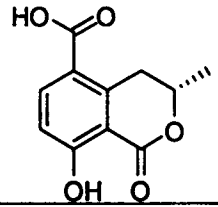
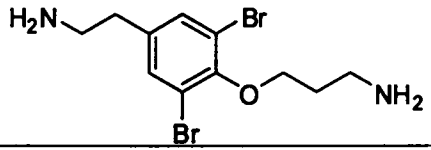
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
cytochalasin Q 	*Halorosellinia oceanica* BCC5149 (fungus)	17 μg/mL (K1 clone)	Chinworrungsee et al, 2001
5-carboxymellein 	*Halorosellinia oceanica* BCC5149 (fungus)	4 μg/mL (K1 clone)	Chinworrungsee et al, 2001
moloka'iamine 	unidentified Hawaiian verongid sponge	6.8 μM (D6 clone)	Laurent and Pietra, 2006

Table 2 (cont.)

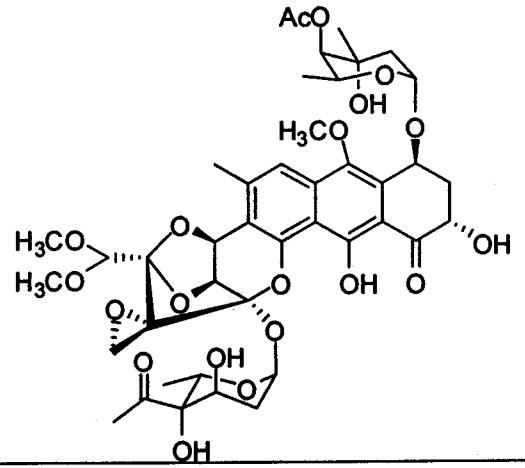
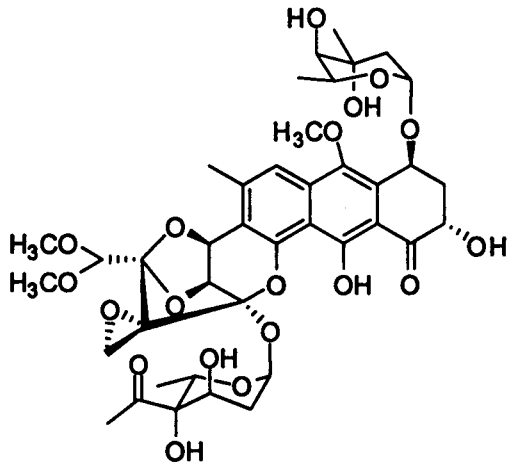
Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
trioxacarcin A 	*Streptomyces* sp. B8652 BCC5149 (bacterium)	1.6 ng/mL (NF54 clone) 1.5 ng/mL (K1 clone)	Mayer et al, 2007

Table 2 (cont.)

Name/Structure	Source	Antimalarial activity against *P. falciparum* (IC_{50})	References
trioxacarcin D 	*Streptomyces* sp. B8652 BCC5149 (bacterium)	1.7 ng/mL (NF54 clone) 2.3 ng/mL (K1 clone)	Mayer et al, 2007

1.2.3 Isonitrile diterpenes

Among the compounds listed in Table 2, of particular interest are isonitrile terpenoids (pages 21-28), which are one of the major foci in this report. Exclusive to marine invertebrates, the major sources of isonitrile terpenoids, as well as of other terpenoids with related functionalities such as isocyanate and isothiocyanate, are sponges of the orders Axinellida, Halichondrida, and Lithistida (Angerhofer and Pezzuto, 1992). As seen in Table 2, most of these terpenoids exhibited antimalarial activity with IC_{50}'s ranging from 2.5 to 3110 ng/mL. Some other biological activities associated with terpenoids bearing isonitrile, isocyanate or isothiocyanate, include antibacterial, ichthyotoxic, and antifeedant activities (Angerhofer and Pezzuto, 1992).

1.2.4 Sterol peroxides

Although rare, the peroxide functionality is not uncommon. Up to 600 naturally occurring peroxides have been isolated from various sources, ranging from terrestrial plants to marine organisms and microorganisms (Dembitsky, 2008). Some of the famous biologically active peroxides are the artemisinins from *Artemisia annua*, which are currently used as antimalarial drugs in clinic (see section 1.1). For the marine natural products, some examples of bioactive peroxides include cyclic peroxides, are shown in Table 2 (pages 19-20). For the steroidal compounds, peroxy functional groups are not uncommon either. Steroidal peroxides, which are another part of interest in this report, can also be found in a wide range of organisms. The sterol peroxides isolated from marine natural products reported to date are shown here in Table 3.

Table 3 Sterol peroxides from marine natural products

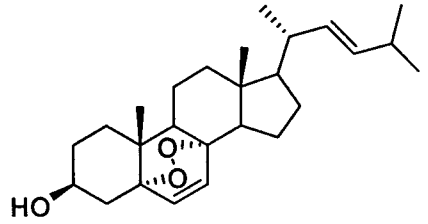
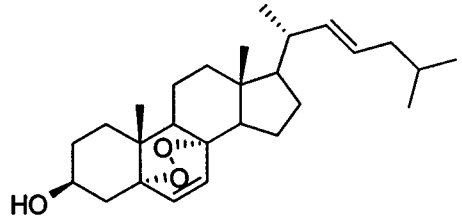
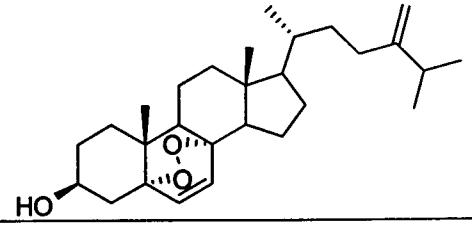
Name/Structure	Sources	Reference
5α,8α-epidioxy-24-norcholesta-6,22-diene-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981
5α,8α-epidioxycholesta-6,22-diene-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981
5α,8α-epidioxy-24-methylcholesta-6,24(28)-diene-3β-ol 	*Ascidia nigra* (tunicate) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981

Table 3 (cont.)

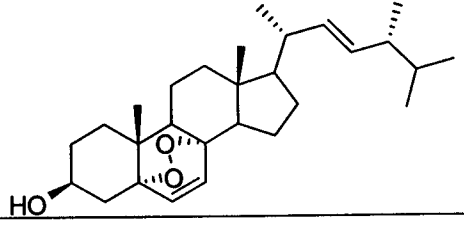
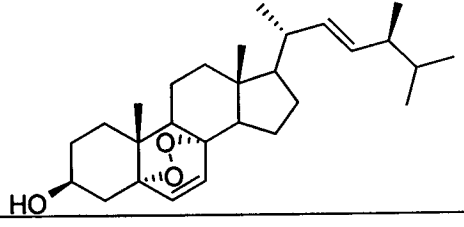
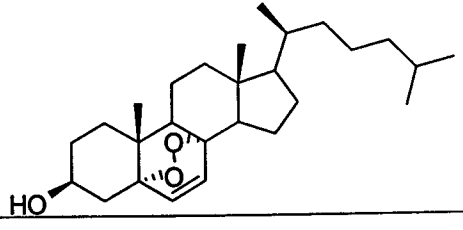
Name/Structure	Sources	Reference
5α,8α-epidioxy-24(*R*)-methylcholesta-6,22-diene-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981
5α,8α-epidioxy-24(*S*)-methylcholesta-6,22-diene-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981
5α,8α-epidioxycholesta-6-en-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge) *Aplysia dactylomela* (sea hare)	Gunatilaka et al, 1981

Table 3 (cont.)

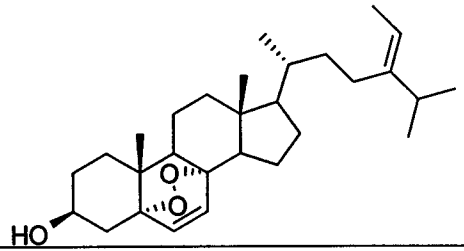
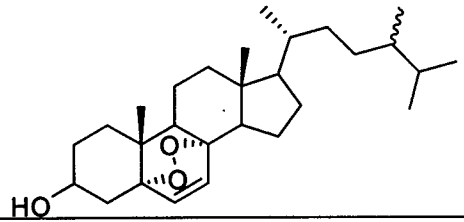
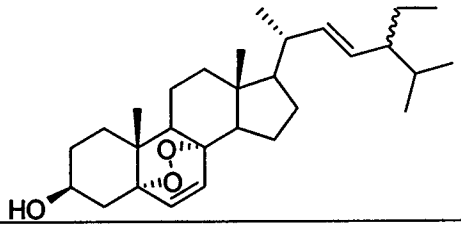
Name/Structure	Sources	Reference
5α,8α-epidioxy-24-ethylcholesta-6,24(28)-diene-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral)	Gunatilaka et al, 1981
5α,8α-epidioxy-24ξ-methylcholesta-6-en-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge) *Aplysia dactylomela* (sea hare)	Gunatilaka et al, 1981
5α,8α-epidioxy-24ξ-ethylcholesta-6,22-dien-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981

Table 3 (cont.)

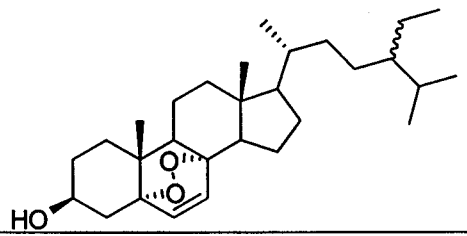
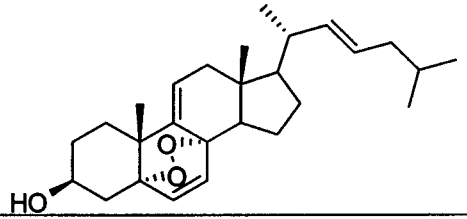
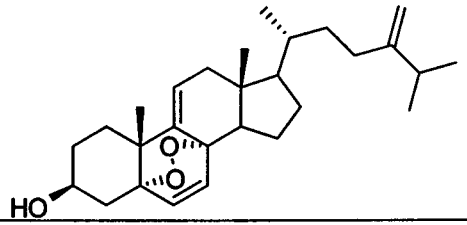
Name/Structure	Sources	Reference
5α,8α-epidioxy-24ξ-ethylcholesta-6-en-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge) *Aplysia dactylomela* (sea hare)	Gunatilaka et al, 1981
5α,8α-epidioxycholesta-6,9(11),22-trien-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981
5α,8α-epidioxy-24-methylcholesta-6,9(11),24(28)-trien-3β-ol 	*Ascidia nigra* (tunicate)	Gunatilaka et al, 1981

Table 3 (cont.)

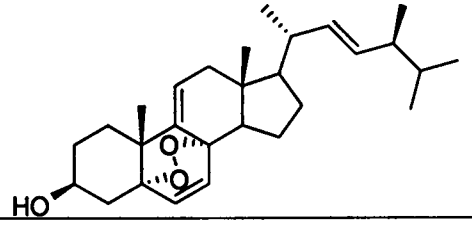
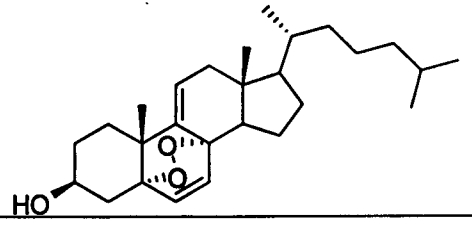
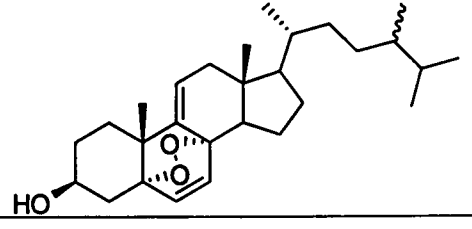
Name/Structure	Sources	Reference
5α,8α-epidioxy-24(*S*)-methylcholesta-6,9(11),22-trien-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981
5α,8α-epidioxycholesta-6,9(11)-diene-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge) *Aplysia dactylomela* (sea hare)	Gunatilaka et al, 1981
5α,8α-epidioxy-24ξ-methylcholesta-6,9(11)-dien-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981

Table 3 (cont.)

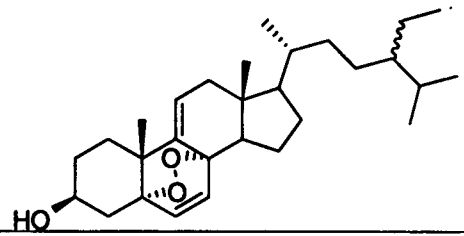
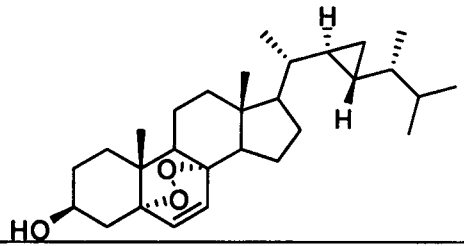
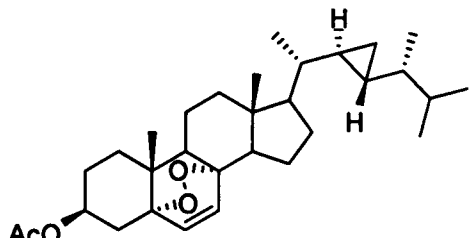
Name/Structure	Sources	Reference
5α,8α-epidioxy-24ξ-ethylcholesta-6,9(11)-dien-3β-ol 	*Ascidia nigra* (tunicate) *Dendrogyrus cylindrus* (pillar coral) *Thalysias juniperina* (sponge)	Gunatilaka et al, 1981
5α,8α-epidioxy-22,23-methylene-24-methylcholest-6-en-3β-ol 	*Sinularia* sp. (soft coral)	Sheu et al, 2000
5α,8α-epidioxy-22,23-methylene-24-methylcholest-6-en-3β-acetate 	*Sinularia* sp. (soft coral)	Sheu et al, 2000

Table 3 (cont.)

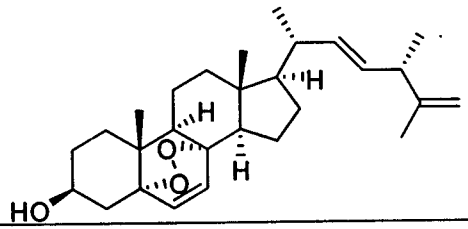
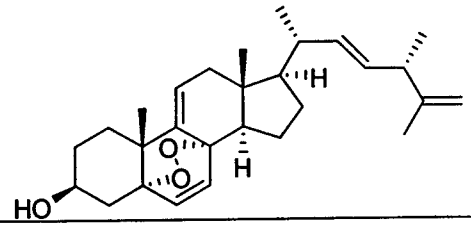
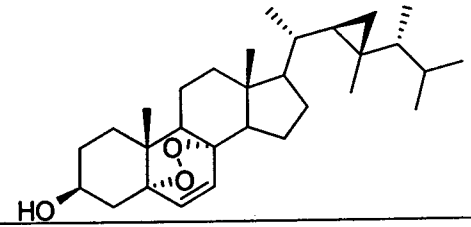
Name/Structure	Sources	Reference
axinysterol 	*Axinyssa* sp. (sponge)	Iwashima et al, 2002
9(11)-dehydroaxinysterol 	*Axinyssa* sp. (sponge)	Iwashima et al, 2002
5α,8α-epidioxygorgosta-6-en-3β-ol 	*Sinularia flexibilis* (soft coral)	Yu et al, 2006

Table 3 (cont.)

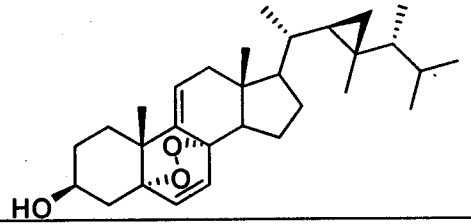
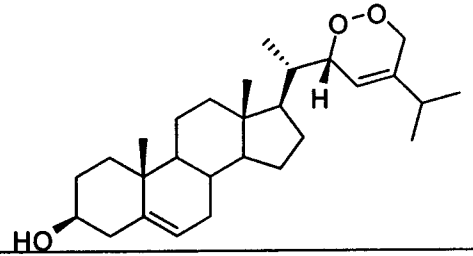
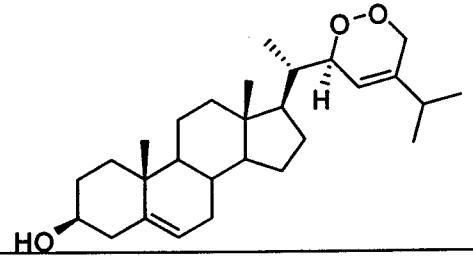
Name/Structure	Sources	Reference
5α,8α-epidioxygorgosta-6,9(11)-dien-3β-ol 	*Sinularia flexibilis* (soft coral)	Yu et al, 2006
22α,28-epidioxycholesta-5,23(*E*)-dien-3β-ol 	*Sinularia flexibilis* (soft coral)	Yu et al, 2006
22β,28-epidioxycholesta-5,23(*E*)-dien-3β-ol 	*Sinularia flexibilis* (soft coral)	Yu et al, 2006

Table 3 (cont.)

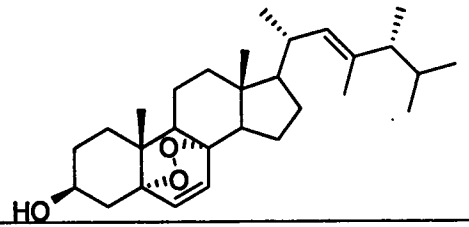
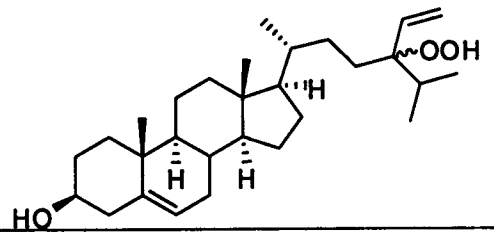
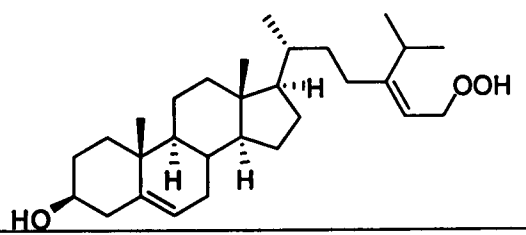
Name/Structure	Sources	Reference
5α,8α-epidioxy-23,24-dimetylcholestra-6,22-dien-3β-ol 	*Sinularia flexibilis* (soft coral)	Yu et al, 2006
24-hydroperoxy-24-vinylcholesterol 	*Ceratodictyon spongiosum* (red alga) *Sigmadocia symbiotica* (symbiotic sponge)	Dembitsky, 2008
29-hydroperoxystigmasta-5,24(28)-dien-3β-ol 	*Ceratodictyon spongiosum* (red alga) *Sigmadocia symbiotica* (symbiotic sponge)	Dembitsky, 2008

Table 3 (cont.)

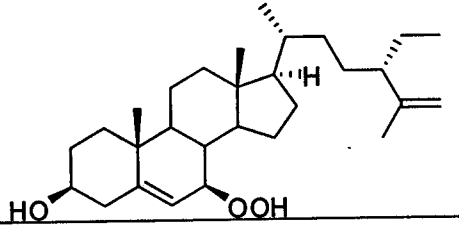
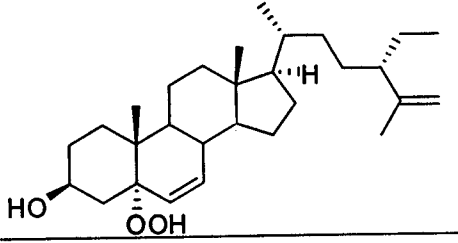
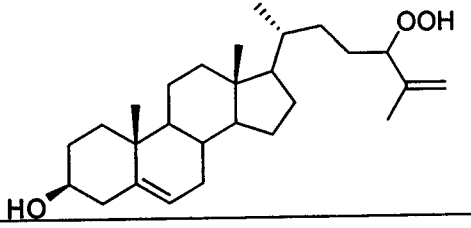
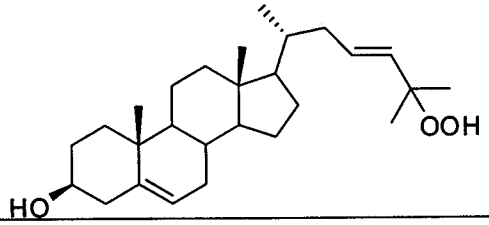
Name/Structure	Sources	Reference
(24*S*)-24-ethyl-7-hydroperoxycholesta-5,25-dien-3β-ol 	*Codium arabicum* (green alga)	Dembitsky, 2008
(24*S*)-24-ethyl-5-hydroperoxycholesta-6,25-dien-3β-ol 	*Codium arabicum* (green alga)	Dembitsky, 2008
24-hydroperoxycholesta-5,25-dien-3β-ol 	*Galaxaura marginata* (red alga)	Dembitsky, 2008

Table 3 (cont.)

Name/Structure	Sources	Reference
25-hydroperoxy-25-dimethyl-5,23-dien-3β-ol 	*Galaxaura marginata* (red alga)	Dembitsky, 2008

1.3 Objectives

This research is focusing on the antimalarial compounds from the Thai sponge *Ciocalapata* sp. (class Demospongiae, order Halichondrida, family Halichondriidae). The sponge was collected from Kho-Tao, Surat Thani Province, Thailand, in April 2002. The preliminary screening showed the potent activity of methanolic extract with an IC_{50} of 0.8 μg/mL against *Plasmodium falciparum* K1 strain. The aims of this work are,

(i) to isolate the antimalarial compounds from the sponge *Ciocalapata* sp.,

(ii) to elucidate the chemical structures of the isolated compounds, and

(iii) to study the antimalarial activity of the isolated compounds as mentioned in (ii).