

Chapter 3

Anti-infective Compounds from Marine Organisms



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Abbreviations

Anti-HCMV	Anti-human cytomegalovirus
BCG	Bacille Calmette-Guérin
CH ₂ Cl ₂	Dichloromethane
DKPs	Diketopiperazines
DOPA	2-Amino-3-(3',4'-dihydroxyphenyl) propionic acid
EMA	European Medicines Agency
EtOH	Ethanol

Both the authors Elena Ancheeva and Mona El-Neketi have contributed equally for this chapter. E.A. contributed to the years 2014–2016, Introduction, and Conclusion. M.E. contributed to the years 2010–2013 and combining the chapter in the final form.

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EtOAc	Ethyl acetate
FDA	Food and Drug Administration
HSV	Herpes simplex virus
HAT	Human African trypanosomiasis
HCMV	Human cytomegalovirus
HMPV	Human metapneumovirus
HRV2	Human rhinovirus serotype 2
HRV3	Human rhinovirus serotype 3
HIV-1	Human immunodeficiency virus type 1
Human APOBEC3G	An innate intracellular antiviral factor
H1N1	Influenza A virus subtype H1N1 = hemagglutinin type 1 and neuraminidase type 1
H5N1	Influenza A virus subtype H5N1 = hemagglutinin type 5 and neuraminidase type 1
ICL	Isocitrate lyase
IC ₅₀	Half maximal inhibitory concentration
MeOH	Methanol
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MRSE	Methicillin-resistant <i>Staphylococcus epidermidis</i>
MS/MS	Tandem mass spectrometry
MSSA	Methicillin-sensitive <i>S. aureus</i>
MIC	Minimum inhibitory concentration
NA	Neuraminidase activity (NA)
NMR	Nuclear magnetic resonance
PIV	Parainfluenza virus
PCR	Polymerase chain reaction
RSV	Respiratory syncytial virus
ROESY	Rotating frame Overhauser effect spectroscopy
SAR	Structure-activity relationship
SARS	Severe acute respiratory syndrome
USA	United States of America
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant <i>S. aureus</i>
VCD	Vibrational circular dichroism
Vif	Viral infectivity factor of HIV-1
WHO	World Health Organization

1 Introduction

Natural products play a pivotal role in drug discovery of anti-infectives, as highlighted by the fact that nearly two-thirds of all drugs currently available on the market for treatment of infectious diseases are natural products or derivatives thereof [1]. It is commonly accepted that the success of natural products as a prolific source

of lead structures is due to metabolome evolution of macro- and microorganisms, which resulted in the accumulation of antimicrobial compounds as a response toward antagonistic environmental conditions.

Historically, most of the currently used anti-infectives of natural origin were derived from soil-dwelling microorganisms, such as fungi and actinomycetes, and in limited cases from terrestrial plants (antimalarial agents) [2, 3]. A few notable examples include the β -lactam antibiotic penicillin G from the fungus *Penicillium notatum*, the macrolide erythromycin from the actinomycete *Saccharopolyspora erythraea*, and the antimalarial compound artemisinin from the plant *Artemisia annua* [4]. Most of these agents were introduced between the 1940s and 1960s, during the so-called 'golden era' of antibiotic discovery; however, the development of novel antibiotics dramatically dropped over the past several decades, partially based on the misleading notion that the battle against microbial infections has been won. Moreover, in recent years, the emerging microbial drug resistance against many clinically used anti-infective drugs has jeopardized their treatment efficacy. In particular, according to the World Health Organization (WHO), resistant strains of Gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus* sp.), Gram-negative bacteria (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*), *Mycobacterium tuberculosis*, *Candida* sp., *Plasmodium falciparum*, or HIV, among others, have become a global threat [5]. This antibiotic resistance crisis may lead to extremely severe public health consequences unless adequate global responses, including development of new antimicrobials, are achieved [6]. Thus, the discovery of new antimicrobial agents from nature, preferably with new mechanisms of action, higher selectivity, and less sensitivity to drug-resistance development, remains an important investigation area of natural products research.

Marine-derived natural products occupy a special place in delivering new drugs into the pharmaceutical market, as a rich source of numerous novel chemical entities with pronounced biological activities [7]. This is exemplified by the fact that in the last two decades the number of FDA-/EMA-approved marine drugs (ziconotide, 2004; omega-3-acid-ethyl esters, 2004; eribulin mesylate, 2010; brentuximab vedotin, 2011; and trabectedin, 2015) substantially increased since the discovery of the unusual nucleosides spongothymidine and spongouridine from the sponge *Tethya crypta*, leading to the first marine drugs ara-A (vidarabine) and ara-C (cytarabine) by the late 1950s [8, 9] (Fig. 3.1). Literature data have shown that the majority of these metabolites, including those entering clinical trials, are mainly being developed in the areas of analgesia and cancer [10]. However, following the success of marine-derived natural products in drug discovery, marine organisms have captured wide attention as a promising source for antimicrobial bioprospecting, as highlighted by the considerable rise of publications in recent years dealing with the discovery of anti-infective agents [1, 11].

The present chapter provides an overview of key publications on marine anti-infective compounds from various marine sources between 2010 and 2016, classified primarily according to the spectrum of antimicrobial activity (antibacterial, antifungal, antiviral, antiprotozoal compounds) with further subdivision based on

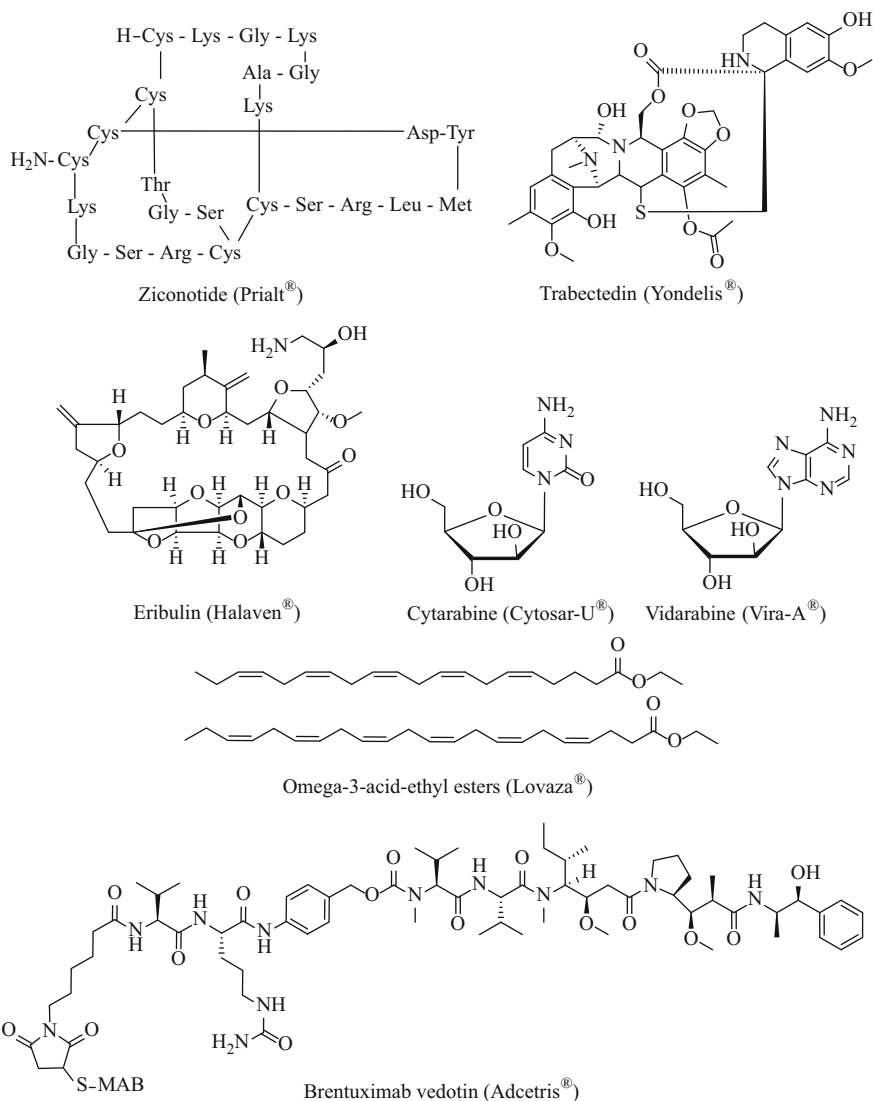


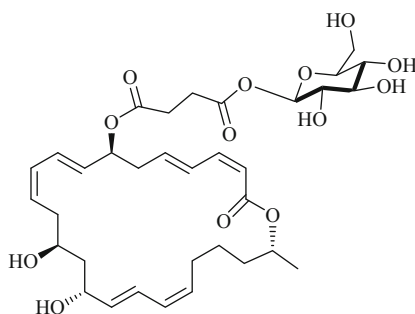
Fig. 3.1 Structures of marine-inspired drugs approved by FDA/EMA

their natural sources including marine microorganisms (bacteria/fungi) and macroorganisms (algae, invertebrates). The examples of new antimicrobials were compiled with focus on their structural features, structure-activity relationships, and mode-of-action studies.

2 Antibacterial Compounds

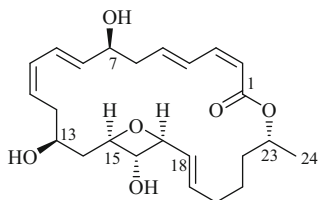
2.1 From Bacteria

Marine microbial metabolites are well known for their chemically diverse structures and for their broad biological activities. Twenty-four-membered macrolactins are frequently produced by *Bacillus* strains and possess antibacterial, anticancer, and antiviral activities. The culture broth of bacterium *Bacillus* sp. 09ID194, isolated from a marine sediment sample collected from Jeodo in Korea's southern reef, was found to produce three macrolides including macrolactins A, Q, and W. Macrolactin W (**1**) showed antibacterial activity against both Gram-positive and Gram-negative pathogenic bacteria: *Bacillus subtilis* (KCTC 1021), *Staphylococcus aureus* (KCTC 1916), *Escherichia coli* (KCTC 1923), and *Pseudomonas aeruginosa* (KCTC 2592) with minimum inhibitory concentration (MIC) value = 64 $\mu\text{g/ml}$ in the serial dilution assay. However, no cytotoxic activity was recorded for **1** against different cancer cell lines, emphasizing its importance as a selective antibacterial drug candidate [12].

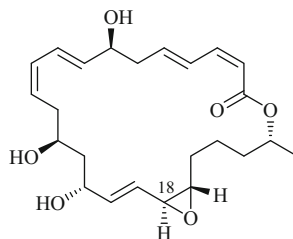


Macrolactin W (**1**)

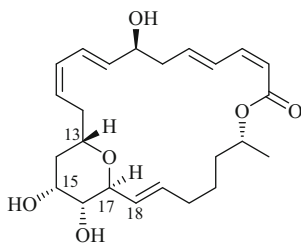
Further investigation of the same bacterial strain afforded three additional new bioactive macrolactins including 15,17-epoxy-16-hydroxy macrolactin A, 18,19-epoxy macrolactin A, and 13,17-epoxy-16-hydroxy macrolactin A (**2–4**) [13]. These macrolides feature an oxetane ring in **2**, an epoxide moiety in **3**, and a tetrahydropyran ring in **4**. The configurations of **2–4** were assigned by calculating the coupling constants, through analysis of ROESY spectra, and by performing the modified Mosher's method. Compounds **2–4** exhibited MICs of 0.06–0.07 $\mu\text{g/ml}$, against *B. subtilis* (KCTC 1021) and *E. coli* (KCTC 1923), and 0.009–0.07 $\mu\text{g/ml}$ against *Saccharomyces cerevisiae* (KCTC 7913) in the broth dilution assay. The presence of an oxygen at C-15 was mandatory for the antibacterial activity [13].



15,17-Epoxy-16-hydroxy macrolactin A (2)

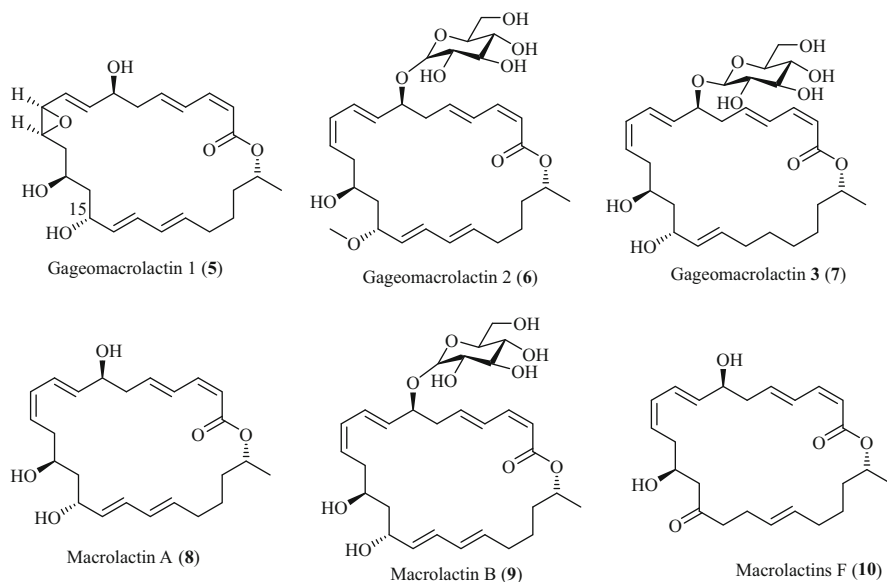


18,19-Epoxy macrolactin A (3)

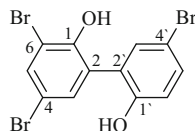
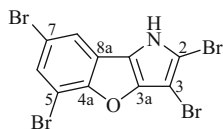


13,17-Epoxy-16-hydroxy macrolactin A (4)

Further macrolactin analogues were obtained from the culture broth of *B. subtilis* strain 109GGC020 isolated from a marine sediment sample obtained from Gageocho, in Korea's southern reef. The new compounds gageomacrolactins (**5**–**7**) and the known macrolactins A (**8**), B (**9**), F (**10**), and W (**1**) exhibited significant broad-spectrum antibacterial and antifungal activities. Compounds **5**–**7** revealed antibacterial activities against Gram-positive (*S. aureus*, *B. subtilis*, and *Bacillus cereus*) and Gram-negative (*E. coli*, *Salmonella typhi*, and *P. aeruginosa*) bacteria with MIC values in the range of 0.008–0.03 $\mu\text{g/ml}$ vs. azithromycin (positive control, MIC 0.008 $\mu\text{g/ml}$). All isolated compounds inhibited also the mycelial growth of the fungi *Aspergillus niger*, *S. cerevisiae*, *Candida acutatum*, and *Candida albicans* with MIC values ranging from 0.016 to 0.204 $\mu\text{g/ml}$ vs. amphotericin B (positive control, MIC 0.018 $\mu\text{g/ml}$). Structure activity relationship (SAR) studies revealed that the hydroxyl function at C-15 of the macrolactone moiety is essential for antimicrobial activity. These results emphasize the impact of macrolactins as potential antibacterial/fungicidal drugs [14].

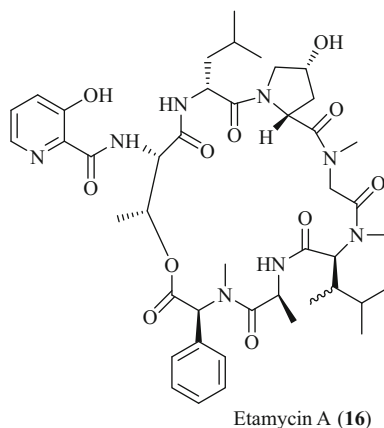
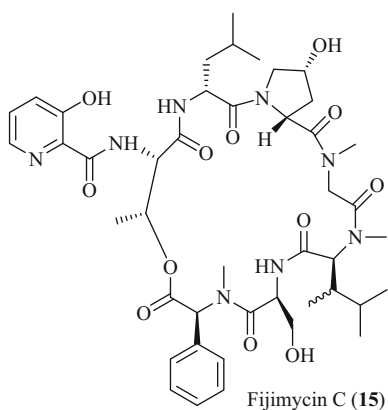
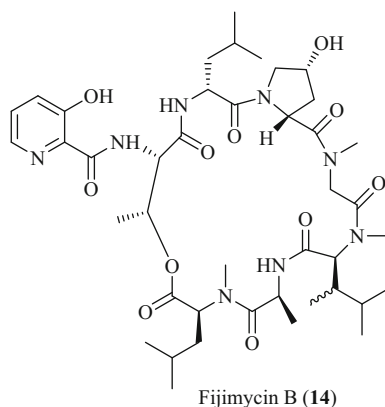
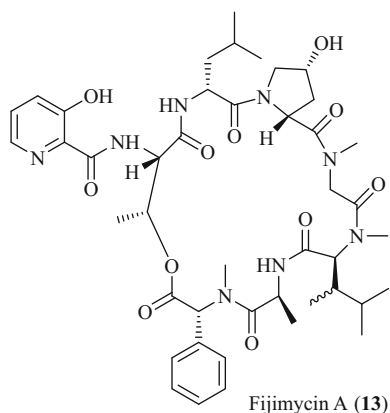


Proteobacteria that are derived from the marine environment are prolific producers of many new and bioactive metabolites. The crude extract of *Pseudoalteromonas* sp. CMMED 290, associated with a nudibranch collected in shallow waters of Kaneohe Bay, Oahu (Hawaii), displayed significant broad-spectrum antibiotic activity against *S. aureus* (ATCC 25923), methicillin-resistant *Staphylococcus aureus* (ATCC 43300), and *E. coli* (ATCC 25922). Chromatographic workup afforded compounds **11** and **12**, which showed potent antimicrobial activity against methicillin-resistant *S. aureus* (MRSA) with MIC values in the low μM range [15]. 2,3,5,7-Tetrabromobenzofuro[3,2-b]pyrrole (**11**) exhibited activity against MRSA (MIC 0.90 $\mu\text{g/ml}$). The mechanism of antimicrobial activity of this compound was suggested to be due to its ability to disrupt the bacterial cell wall membrane, whereas human erythrocytes were not lysed when the compound was applied at the same dose [15].

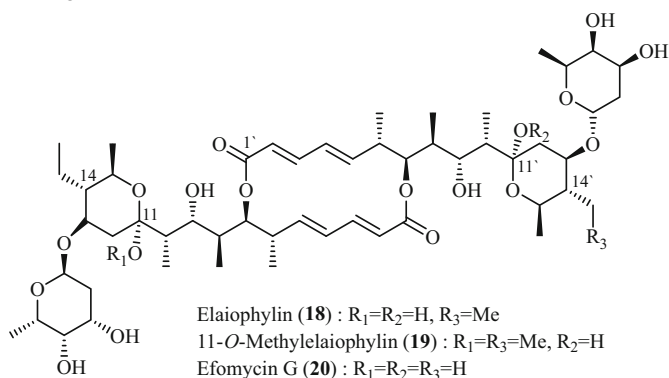
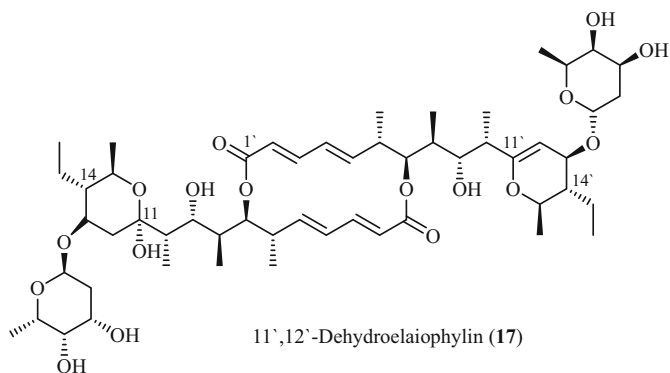


2,3,5,7-Tetrabromobenzofuro[3,2-b]pyrrole (**11**) 4,4',6-Tribromo-2,2'-biphenol (**12**)

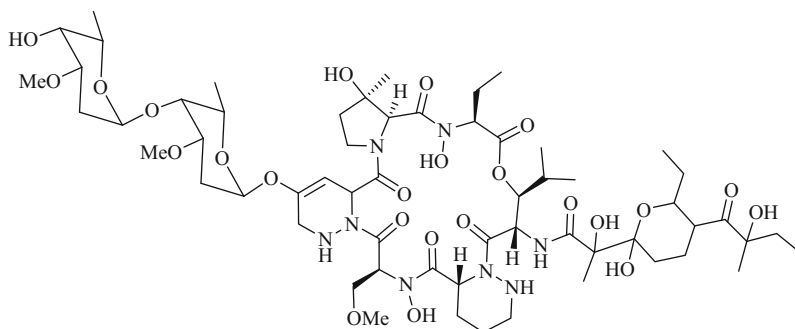
MRSA-caused infections are challenging problems in both community and hospital settings. An extract of the strain *Streptomyces* sp. CNS-575, isolated from a marine sediment sample collected at ca. 0.5 m depth from Nasese shoreline, Viti Levu, Fiji, exhibited potent antibiotic activity against MRSA. Chromatographic workup afforded fijimycins A–C (**13**–**15**), in addition to etamycin A (**16**). The antibacterial activities of these metabolites were assessed against three MRSA strains, the hospital-associated strain (ATCC33591), the sequenced hospital-associated strain (Sanger 252), and the community-associated strain (UAMS1182). Fijimycins A (**13**), C (**15**) and etamycin A (**16**) exhibited strong to medium antibiotic activities against the three MRSA strains with MIC values ranging from 4–32 $\mu\text{g/ml}$. The weak activity of fijimycin B (**14**) against both ATCC33591 and UAMS1182 indicated that the α -phenylsarcosine unit is essential for antibacterial activity. The similar antimicrobial activities of the stereoisomers fijimycin A (**13**) and etamycin A (**16**) suggest that substituting D- for L- α -phenylsarcosine has only negligible effects with regard to the anti-MRSA activities [16].



Streptomyces sp. 7-145 was isolated from a marine sediment sample obtained from Heishijiao Bay, Dalian, People's Republic of China (P.R. China). Wu et al. selected this strain for further investigation based on polymerase chain reaction (PCR) screening, targeted for strains that may produce glycosylated antibiotics. Investigation of the culture broth of the studied *Streptomyces* sp. afforded two new elaiophylins-6-deoxyglycoside derivatives along with four known ones [17]. Among the purified compounds, 11',12'-dehydroelaiophylin (17), elaiophylin, 11-*O*-methylelaiophylin, and efomycin G (18–20) were the most potent ones against different MRSA strains and vancomycin-resistant enterococci (VRE) with MIC values ranging from 1 to 4 $\mu\text{g/ml}$ [17]. In addition, 18 and 20 were also active against methicillin-resistant *Staphylococcus epidermidis* (MRSE) with MICs ranging from 2 to 16 $\mu\text{g/ml}$ [17]. No cross-resistance was observed between 17 and 20 and erythromycin or azithromycin (14- and 15-membered macrolides) confirming that the activity of elaiophylins (16-membered lactone) is not affected by the macrolide resistance mechanism in Gram-positive bacteria. SAR studies revealed that the hemiketal moiety at 11 and 11' positions is important for the antibacterial activity, whereas substitution of the 14' ethyl group with a methyl group reduces the activity, thereby proving the essential role of the alkyl group at positions C-14 or C-14'.



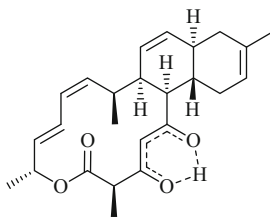
Chemical investigation of a marine bacterium *Streptomyces* sp. (CMB-M0244) derived from a sediment sample collected off South Molle Island, Queensland, Australia, led to the isolation of a first-in-class glyco-hexadepsipeptide-polyketide mollemycin A (**21**) [18]. Mollemycin A (**21**) showed pronounced activity against a panel of Gram-positive bacteria, including *S. aureus* (strains ATCC 25293 and ATCC 9144), *S. epidermidis* ATCC 12228, and *B. subtilis* (strains ATCC 6051 and ATCC 6633), as well as against the Gram-negative bacteria *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 with IC_{50} values ranging from 13 to 65 ng/ml. Moreover, compound **21** was exceptionally potent against drug-sensitive 3D7 and multidrug-resistant Dd2 clones of the Malaria parasite *P. falciparum* with IC_{50} values of 12 and 9 ng/ml, respectively, whereas it exhibited at least 20-fold lower cytotoxicity toward human neonatal foreskin fibroblast cells, verifying this compound as a potential lead antimalarial agent for further investigation [18].



Mollemycin A (**21**)

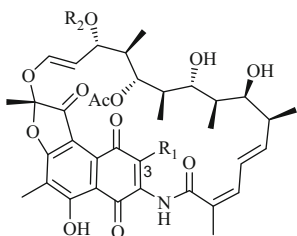
Bioassay-guided fractionation of the EtOAc extract of *Streptomyces* sp. CNH365, isolated from a sediment sample collected off Gaviota State Beach, California, USA, yielded a structurally unique 14-membered macrolide, termed anthracimycin (**22**). Compound **22** exhibited potent activity against a panel of Gram-positive pathogens, including *Bacillus anthracis*, *E. faecalis*, *S. pneumoniae*, as well as methicillin- and vancomycin-resistant strains of *S. aureus* with MIC values less than 0.25 $\mu\text{g/ml}$ [19, 20]. Moreover, **22** showed marked effects on the growth rate of MRSA even at sub-MIC concentrations (1/16 MIC; 0.0078 $\mu\text{g/ml}$), compared to the antibacterial agent vancomycin. Notably, **22** exhibited low mammalian cell cytotoxicity with an IC_{50} value of 70 $\mu\text{g/ml}$ and was shown to exert synergistic effects with the human cathelicidin LL-37 on MRSA growth. Further investigation employing an optimized macromolecular synthesis assay indicated disruption of nucleic acid synthesis from **22** at concentrations near the MIC, thus suggesting that this effect might be related to its mode of action. Following these intriguing results, a murine peritonitis model of infection was employed to ascertain *in vivo* efficacy of **22**. Interestingly, anthracimycin (**22**) at a single i.p. injection dose of 1 or 10 mg/kg, even one hour after MRSA infection, provided sufficient protection against mortality and was well

tolerated by mice, thus suggesting its potential as a novel lead scaffold against MRSA [19].



Anthracimycin (**22**)

Four new rifamycins (ansa macrolides), 3-amino-27-demethoxy-27-hydroxyrifamycin S (**23**), 3-amino-rifamycin S (**24**), and sporolactams A (**25**) and B (**26**), were isolated from the culture broth of the marine-derived bacterium *Micromonospora* sp. RJA4480, derived from a sediment sample collected in Barkley Sound, British Columbia (Canada) [21]. Interestingly, compounds **23** and **24** are the first natural rifamycins to bear a 3-amino group. Moreover, the structures of compounds **25** and **26** feature an unprecedented heterocyclic core connected with a 14-membered ansa bridge, thus forming a novel ansa macrolide template. All isolated compounds (**23–26**), together with two reference compounds 27-demethoxy-27-hydroxyrifamycin S (**27**) and rifamycin S (**28**), both lacking the 3-amino substituent, were evaluated for their antimicrobial activity against MRSA, *E. coli*, and *M. tuberculosis*. Among the isolated compounds, rifamycins **23** and **24** displayed exceptional antibacterial activity (MIC₉₀ values ranging from 0.07 to 0.63 ng/ml), which was higher than that of the reference compounds **27** and **28** (up to 700-fold). Moreover, sporolactam B (**26**) showed selective activity against *M. tuberculosis*, both in broth and in macrophages, with MIC₉₀ values of 44 ng/ml and 2.2–6.5 μg/ml, respectively, comparable to those of **27**. These data implied that the 3-amino substituent as well as 27-O-methylation plays an important role in the antimicrobial potency of these metabolites, probably by favoring their binding to RNA polymerase [21].

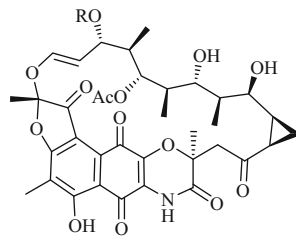


3-Amino-27-demethoxy-27-hydroxyrifamycin S (**23**): R₁=NH₂, R₂=H

3-Amino-rifamycin S (**24**): R₁=NH₂, R₂=Me

27-Demethoxy-27-hydroxyrifamycin S (**27**): R₁=H, R₂=H

Rifamycin S (**28**): R₁=H, R₂=Me

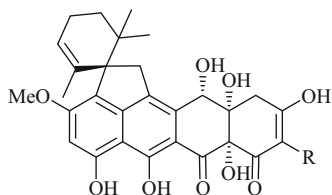


Sporolactam A (**25**): R=H

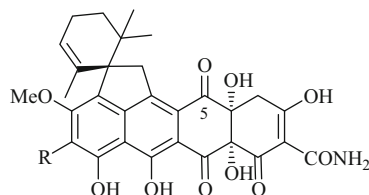
Sporolactam B (**26**): R=Me

2.2 From Fungi

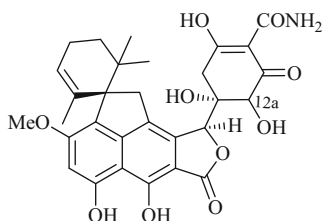
Four new viridicatumtoxins C–F, together with four known metabolites, viridicatumtoxins A (**29**) and B (**30**), spirohexaline (**34**), and previridicatumtoxin (**35**), were reported from the fungus *Paecilomyces* sp. (CMB-MF010), isolated from the inner tissues of a mollusk of the genus *Siphonaria* collected near Shorncliffe, Australia [22]. Viridicatumtoxins are a rare family of fungal polyketides structurally related to the tetracycline class of antibiotics. Notably, viridicatumtoxins A–E (**29**–**33**), as well as compounds **34** and **35**, showed potent activity against MRSA and VRE with IC_{50} values less than 5.5 $\mu\text{g}/\text{ml}$. Among them, the 5-oxo analogue viridicatumtoxin B (**30**) was found to be the most active compound with IC_{50} values of 85 and 23 ng/ml , respectively, possessing significantly higher activity than the positive control oxytetracycline ($IC_{50} = 0.23$ and 5.1 $\mu\text{g}/\text{ml}$, respectively). Moreover, viridicatumtoxin A (**29**) was shown to be remarkably stable when subjected to different acid degradation protocols, suggesting that the viridicatumtoxin framework could potentially be utilized to optimize oral bioavailability and efficacy of tetracycline antibiotics. In a subsequent study, viridicatumtoxin A (**29**) and spirohexaline (**34**) were discovered as inhibitors of recombinant undecaprenyl pyrophosphate (UPP) synthase from *S. aureus* with IC_{50} values of 2.3 and 5.1 $\mu\text{g}/\text{ml}$, respectively [23]. Moreover, these molecules showed only weak inhibitory activities toward catalytically related enzymes, such as octaprenyl pyrophosphate (OPP) synthase of *E. coli* and dehydrodolichyl pyrophosphate (DedolPP) synthase of the yeast *S. cerevisiae*, thus suggesting that these compounds selectively inhibit UPP synthase, which is in agreement with their anti-*S. aureus* activity. In addition, molecular docking studies revealed that **29** and **34** bind to the active site of this enzyme and compete with the natural substrate farnesyl pyrophosphate (FPP), thus corroborating their mode of antibacterial action via inhibition of UPP synthase activity [23].



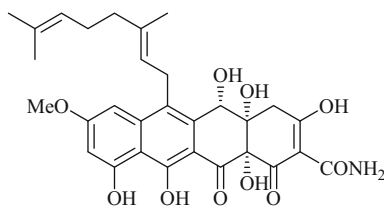
Viridicatumtoxin A (**29**): R=CONH₂
 Spirohexaline (**34**): R=COCH₃



Viridicatumtoxin B (**30**): R=H
 Viridicatumtoxin C (**31**): R=OH

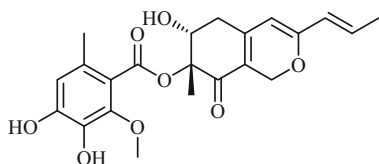


(*R*) 12a: Viridicatumtoxin D (**32**)
 (*S*) 12a: Viridicatumtoxin E (**33**)

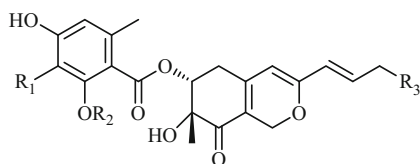


Previridicatumtoxin (**35**)

Azaphilones are produced by several fungal genera including *Aspergillus*, *Monascus*, and *Penicillium*. Six unprecedented azaphilones, comazaphilones A–F, were obtained from extracts of *Penicillium commune* QSD-17, a fungus derived from a marine sediment sample obtained at 210 m depth from the Southern China Sea [24]. Comazaphilone C (**36**) was shown to be active against MRSA, *P. fluorescens*, and *B. subtilis* with MIC values of 16, 64, and 32 µg/ml, respectively. Comazaphilone D (**37**) was active only against MRSA and *P. fluorescens* with MIC values of 32 and 16 µg/ml, respectively, while comazaphilone E (**38**) was active against *P. fluorescens* and *B. subtilis* with MIC values of 32 and 16 µg/ml, respectively. The MIC values of the positive control, ampicillin, ranged from 4 to 8 µg/ml. SAR studies showed that the position of the double bond at C-10 and of the orsellinic acid moiety at C-6 in the azaphilone core structure affects the antibacterial activity of the respective compounds.

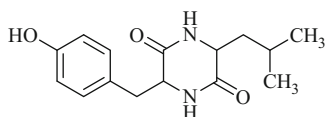


Comazaphilone C (**36**)



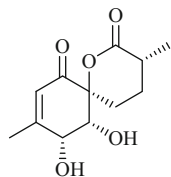
Comazaphilone D (**37**): R₁=R₂=R₃=H
 Comazaphilone E (**38**): R₁=OH, R₂=Me, R₃=H

Infections by pathogenic bacteria are often due to the formation of microbial biofilms. Medical devices are often contaminated with *Staphylococcus epidermidis* biofilms which are involved in the transmission of infections. Scopel et al. succeeded in isolating the dipeptide *cis-cyclo* (Leucyl-Tyrosyl) (**39**) from culture broth of *Penicillium* sp. F37, a fungal strain obtained from the sponge *Axinella corrugata* collected in South Brazil. *Cis-cyclo* (Leucyl-Tyrosyl) (**39**) selectively inhibits up to 85% of biofilm formation, thus pointing to **39** as a promising broad-spectrum drug candidate [25].

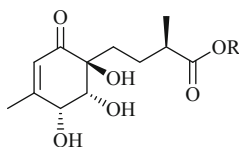


cis-cyclo (Leucyl-Tyrosyl) (**39**)

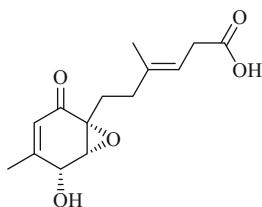
The deep-sea fungus *Penicillium* sp. F23-2, obtained from a deep ocean sediment sample collected at a depth of 5080 m, afforded five new ambuic acid derivatives, penicyclones A–E (**40–44**) [26]. Interestingly, compound **40** possesses an unprecedented spiro- δ -valerolactone moiety. Bioactivity screening of **40–44** revealed significant antibacterial activity against *S. aureus* with MIC values in the range between 0.3 and 1.0 $\mu\text{g/ml}$, whereas no cytotoxic effects were detected against a panel of different cancer cell lines (HeLa, BEL-7402, HEK-293, HCT-116, and A549) at similar concentrations ($\text{IC}_{50} > 12 \mu\text{g/ml}$), suggesting their selective antibacterial activity.



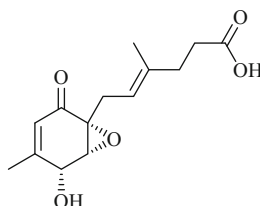
Penicyclone A (**40**)



Penicyclone B (**41**): R = H
Penicyclone C (**42**): R = Me



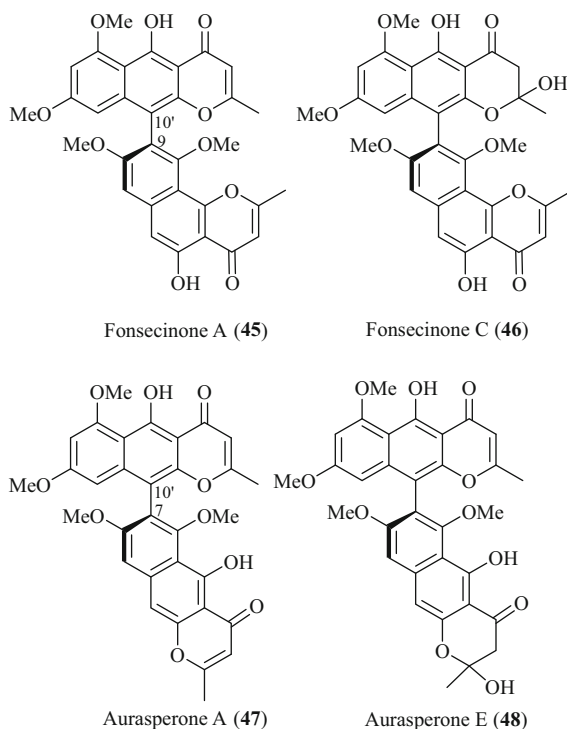
Penicyclone D (**43**)



Penicyclone E (**44**)

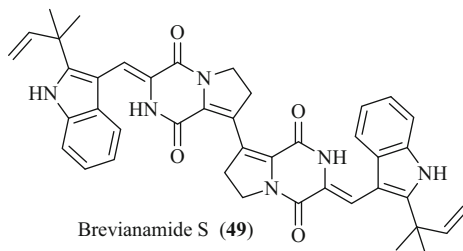
With the purpose to identify novel antibiotics from microbial sources, a series of naphtho- γ -pyrones were isolated from the fungus *Aspergillus* sp. Z120 that was obtained from the Marine Culture Collection of China [27]. Among them, the

asperpyrone-type metabolites fonsecinones A (**45**) and C (**46**), formed via a C-10'-C-9 linkage, displayed significant antibacterial activity toward extended spectrum beta-lactamase (ESBL)-producing *E. coli* (MIC = 4.3 $\mu\text{g/ml}$), followed by the dimeric naphtho- γ -pyrones aurasperones A (**47**) and E (**48**) with C-10'-C-7 linkages (MIC = 8.5 $\mu\text{g/ml}$), equipotent to the inhibitory effects of the positive controls amikacin and ceftriaxone, respectively. Subsequent molecular docking-based target identification studies were employed revealing the bacterial enoyl-acyl carrier protein reductase (FabI), a key enzyme in the bacterial fatty acid synthesis, as a possible antibacterial target for compounds **45**–**48**. To further confirm these results, all compounds were subjected to a FabI inhibition assay and were shown to inhibit FabI in a concentration-dependent manner, thus indicating that this effect is likely related to the mode of action of these metabolites [27].

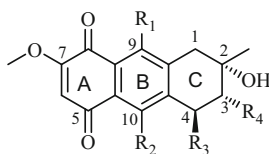


Diketopiperazines (DKPs) are widespread in nature and show diverse biological activities, such as disruption of biofilm formation [28]. *Aspergillus versicolor* MF030 was isolated from the Bohai Sea sediment (P.R. China). Fermentation of the strain yielded brevianamide S (**49**), a rare natural dimeric DKP having antitubercular activity, and three monomeric DKPs brevianamides T, U, and V, along with the known brevianamides N and K and deoxybrevianamide E. Among the isolated metabolites, **49** exhibited antibacterial activity against bacille Calmette-Guérin (BCG) with a MIC value of 6.25 $\mu\text{g/ml}$, versus the positive control isoniazid (MIC, 0.05 $\mu\text{g/ml}$). In spite of the moderate effect of **49**, its selectivity toward BCG

makes brevianamide **S** a potential new drug candidate as a next-generation antibiotic for the treatment of *Mycobacterium tuberculosis* [29].



The fungus *Nigrospora* sp. isolated from fresh tissue of an unidentified sea anemone, collected from the Weizhou coral reef in the South China Sea (P.R. China), afforded two new hydroanthraquinone derivatives 4a-*epi*-9 α -methoxy-dihydrodeoxybostrycin and 10-deoxybostrycin together with seven known anthraquinones nigrosporin B, α -hydroxydihydrodesoxybostrycin, α -hydroxyhalorosellinia A, bostrycin, 4-deoxybostrycin, 3,5,8-trihydroxy-7-methoxy-2-methylanthracene-9,10-dione, and austrocortirubin as well as ten further acetylated derivatives. All isolated compounds were evaluated for their antibacterial activity against different bacterial strains. 10-Deoxybostrycin (**50**) and nigrosporin B (**51**), along with the acetylated compound 3-acetoxy-4-deoxybostrycin (**52**), displayed pronounced antibacterial activity. Compound **52** showed the strongest activity against *B. cereus* (ATCC 11077) and *Vibrio anguillarum* (ATCC 19019) with MIC values of 17.7 and 35.5 ng/ml, respectively. Nigrosporin B (**51**) revealed high antibiotic activity against *B. subtilis* (ATCC 6633) and *B. cereus* (ATCC 11077), with MIC values of 94.9 ng/ml against both bacteria. The MIC value of the positive control ciprofloxacin amounted to 414.2 ng/ml. SAR studies revealed that the cycloaliphatic ring C is essential for the activity [30].



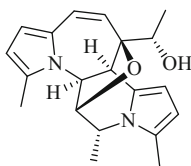
10-Deoxybostrycin (**50**) : $R_1 = R_3 = R_4 = \text{OH}$; $R_2 = \text{H}$

Nigrosporin B (**51**) : $R_1 = R_3 = \text{H}$, $R_2 = R_4 = \text{OH}$

3-Acetoxy-4-deoxybostrycin (**52**) : $R_1 = R_2 = \text{OH}$, $R_3 = \text{H}$, $R_4 = \text{OAc}$

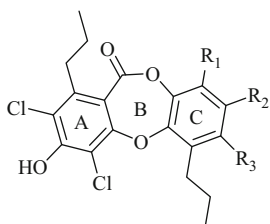
A structurally unprecedented alkaloid, curvulamine (**53**), was reported from the fungus *Curvularia* sp. IFB-Z10, isolated from the fish *Pennahia argentata* [31]. Isotope-feeding and enzyme inhibition studies suggested that the unique carbon framework of **53** is derived from two unprecedented oligoketide extender units that are formed via decarboxylative condensation between a tetraketide acyl-CoA substrate and the amino acid alanine. Notably, curvulamine (**53**) exhibited potent antibacterial activity toward a panel of patient-derived pathogens, including

Veillonella parvula, *Streptococcus* sp., *Peptostreptococcus* sp., and *Bacteroides vulgatus* with MIC values of 0.12 $\mu\text{g/ml}$, being more active than the antimicrobial agent tinidazole, which was used as a positive control (MICs, 0.12–0.5 $\mu\text{g/ml}$).

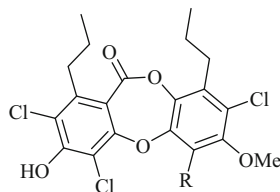


Curvulammine (**53**)

Chemical investigation of the fungus *Spiromastix* sp. MCCC 3A00308 that was isolated from deep-sea sediment collected in the South Atlantic Ocean (2,869 m depth) led to the discovery of two new classes of compounds with antimicrobial properties, the antibacterial chlorodepsidones, spiromastixones A–O, and the antiviral aromatic lactones, spiromastilactones A–M (see Sect. 4.1) [32, 33]. Spiromastixones F–J (**54**–**58**) displayed potent inhibitory effects against MRSA (MIC range from 1.92 to 14.9 $\mu\text{g/ml}$) as well as against methicillin-resistant *Staphylococcus epidermidis* (MRSE) strains (MIC range from 0.86 to 14.9 $\mu\text{g/ml}$). Likewise, **54** showed activity against vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* with MICs of 1.9 $\mu\text{g/ml}$. In addition, spiromastixones G (**55**), J (**58**), K (**59**), and L (**60**) showed pronounced antibacterial effects against the Gram-positive strains *S. aureus*, *Bacillus thuringiensis*, and *B. subtilis* with MIC values less than 2 $\mu\text{g/ml}$, comparable to those of the positive control penicillin G. However, all compounds were found to be inactive against the Gram-negative bacterium *E. coli* (MIC > 128 $\mu\text{g/ml}$), suggesting their selective antibacterial action. Moreover, comparison of the antibacterial properties of the isolated spiromastixones revealed that increase of chlorine substitution as well as O-methylation in ring C are essential structural features for the antibacterial activity of these compounds [32]. Thus, the pronounced growth inhibition effects of **54**–**60** toward several Gram-positive bacteria, including drug-resistant clinical isolates, render these metabolites attractive for further antibiotic development.



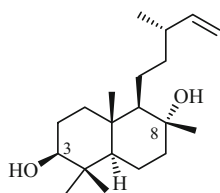
Spiromastixone F (**54**): $R_1=\text{H}$, $R_2=\text{OH}$, $R_3=\text{Cl}$
 Spiromastixone G (**55**): $R_1=\text{H}$, $R_2=\text{OMe}$, $R_3=\text{Cl}$
 Spiromastixone H (**56**): $R_1=\text{Cl}$, $R_2=\text{OH}$, $R_3=\text{H}$
 Spiromastixone I (**57**): $R_1=R_3=\text{Cl}$, $R_2=\text{OH}$
 Spiromastixone J (**58**): $R_1=R_3=\text{Cl}$, $R_2=\text{OMe}$



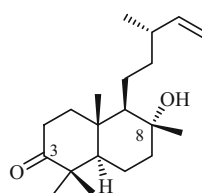
Spiromastixone K (**59**): $R=\text{H}$
 Spiromastixone L (**60**): $R=\text{Cl}$

2.3 From Algae

Green algae are a prolific source of bioactive constituents. A prominent member of this group is *Ulva fasciata* Delile (family Ulvaceae), commonly known as “sea lettuce,” which grows in coastal regions of Asia-Pacific [34]. Numerous compounds such as terpenes, polyphenolic compounds, and steroids were reported from *U. fasciata* [35]. These compounds include two potent antibacterial agents, labda-14-ene-3 α ,8 α -diol (**61**) and labda-14-ene-8 α -hydroxy-3-one (**62**) [36]. Both compounds were active against *Vibrio parahaemolyticus* and *Vibrio harveyi* (MIC, 30 μ g/ml each). SAR studies revealed that electronegative hydroxyl or carbonyl group(s) are essential for proton exchange reactions with basic amino acyl residues in the active sites of virulent enzymes of these pathogenic bacteria.

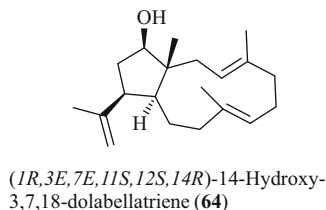
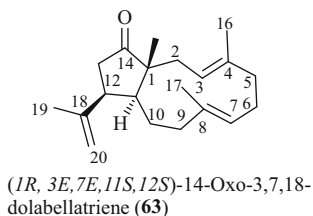


Labda-14-ene-3 α ,8 α -diol (**61**)



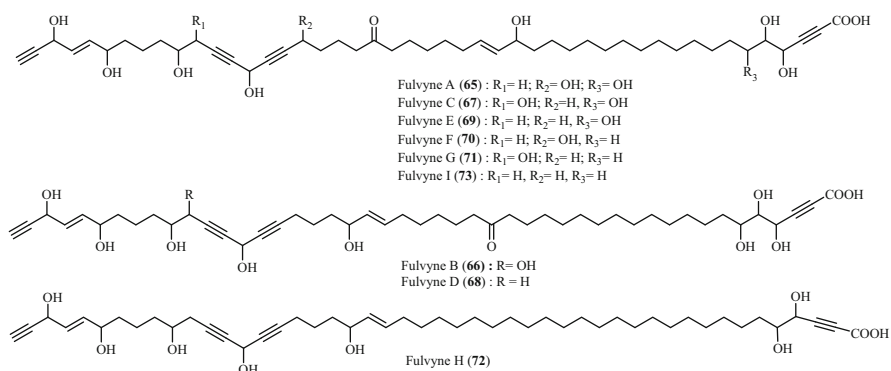
Labda-14-ene-8 α -hydroxy-3-one (**62**)

Brown algae are commonly found in the tropical and subtropical waters, especially in the Atlantic, Pacific, and Indian Oceans, the Caribbean and Mediterranean Sea, and in the Sea of Japan. Secondary metabolites that are frequently isolated from brown algae are sesquiterpenes and diterpenes which have been shown to exhibit antibacterial, antiviral, cytotoxic, algicidal, antifouling, antifeedant, and/or ichthyotoxic activities [37]. Chromatographic separation of the $\text{CH}_2\text{Cl}_2/\text{MeOH}$ extract of the brown alga *Dilophus spiralis* (collected at Elafonisos Island, Greece) yielded seventeen diterpenes featuring a dolabellane skeleton. These compounds showed weak to moderate activity against six strains of *S. aureus* including a standard laboratory strain (ATCC 25923), two epidemic MRSA strains (EMRSA-15 and EMRSA-16), a macrolide-resistant variant (RN4220), and two multi-drug-resistant effluxing strains (SA1199B and XU212). Reduction of (1*R*,3*E*,7*E*,11*S*,12*S*)-14-oxo-3,7,18-dolabellatriene (**63**) which was devoid of antibacterial activity using NaBH_4 yielded the C-14 epimeric alcohol (1*R*,3*E*,7*E*,11*S*,12*S*,14*R*)-14-hydroxy-3,7,18-dolabellatriene (**64**). Interestingly, the semisynthetic compound **64** showed antibacterial activity against all tested strains of *S. aureus*, with MIC values in the range of 2–4 μ g/ml. The hydroxyl group at C-14 was crucial for antibacterial activity, whereas the presence of the ketone functionality at C-14 as found in the natural product rendered the compound inactive [38].

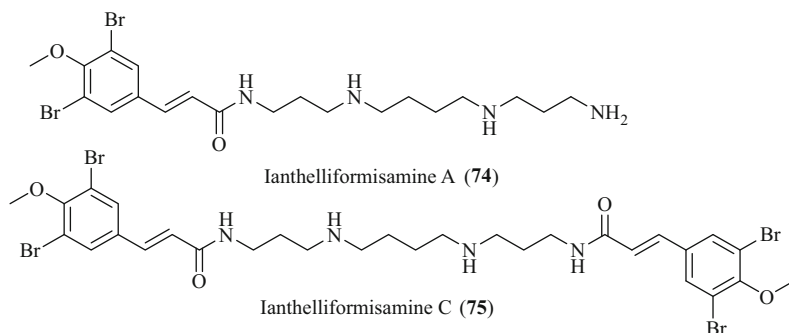


2.4 From Invertebrates

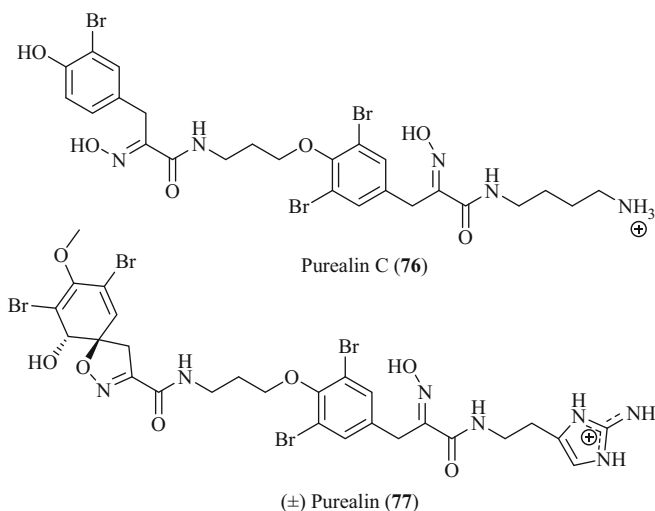
Haliclona sponges are well-known sources of polyacetylenic lipids. *Haliclona fulva* is a Mediterranean sponge, collected at the Gulf of Naples (Italy). Chromatographic workup of its butanolic extract revealed nine highly oxygenated acetylenes fulvynes A–I (**65**–**73**), whose structures include long linear alkyl chains with a rare propargylic acid terminal moiety and poly-oxygenated carbons. All isolated compounds exhibited potent antibacterial activity against a chloramphenicol-resistant strain (PY79) of *B. subtilis* with MICs in the range of 9.7–49.7 $\mu\text{g/ml}$ [39].



Three new bromotyrosine analogues ianthelliformisamine A–C along with the known aplysamine I and araplysillin I were isolated from the sponge *Suberea ianthelliformis* collected at North Stradbroke Island, Australia. Only ianthelliformisamines A and C (**74**, **75**) exhibited antibacterial activity against the Gram-negative bacterium *P. aeruginosa* with MICs of 18.2 and 14.7 $\mu\text{g/ml}$, respectively, while **75** showed activity against *S. aureus* with a MIC of 7.33 $\mu\text{g/ml}$. The spermine nucleus in **74** and **75** is essential for the antibiotic activity against *P. aeruginosa* [40].

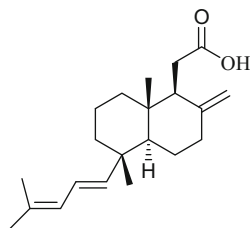


Further bromotyrosine derivatives were isolated from two marine sponges of the genus *Pseudoceratina* collected off Port Campbell, Victoria, southern Australia. Chromatographic workup of the first sponge afforded twelve bromotyrosine derivatives, including the new derivatives aplysamine-7, (–)-purealin B, purealin C (76), and purealin D and two new enantiomers (–)-purealidin R and (–)-aerophobin-2 along with five known compounds, while the second *Pseudoceratina* sponge yielded the first reported racemic bromotyrosine-analogue (±)-purealin (77) as a new compound along with the known purealidin A. Among the isolated compounds, only purealin C (76) and (±)-purealin (77) revealed significant broad-spectrum antibacterial activity against different *S. aureus* and *B. subtilis* bacterial strains with MIC values ranging from 0.6 to 5.4 μg/ml [41].



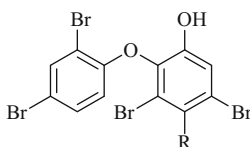
The new antibacterial bicyclic terpene derivative clathric acid (78) was obtained from the methanolic extract of the sponge *Clathria compressa*, collected at Panama City, Florida (USA), along with two new *N*-acyl taurine derivatives clathrimides A and B. Only clathric acid (78) exhibited antibacterial activity against different Gram-positive bacterial strains including *S. aureus* (ATTC 6538P), MRSA

(ATTC 33591), and vancomycin-resistant *S. aureus* (VRSA) with MIC values of 32, 64, and 64 $\mu\text{g/ml}$, respectively [42].



Clathric acid (**78**)

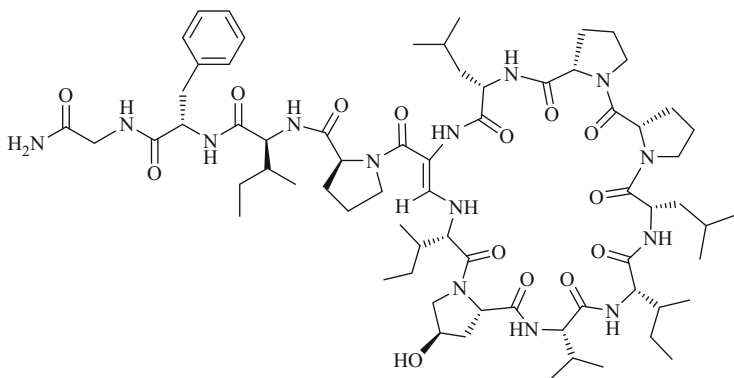
Bioassay-guided isolation of the MeOH extract of the Indo-Pacific marine sponge *Dysidea granulosa* afforded the polybrominated diphenyl ethers 2-(2',4'-dibromophenoxy)-3,5-dibromophenol (**79**) and 2-(2',4'-dibromophenoxy)-3,4,5-tribromophenol (**80**) [43]. The in vitro antibacterial potency of **79** and **80** was evaluated toward a panel of 14 foodborne and clinical human pathogens. Notably, both compounds were found to be potent inhibitors of the Gram-positive bacteria *B. cereus*, *Listeria monocytogenes*, and MRSA with MIC values of 0.1 $\mu\text{g/ml}$. Moreover, **79** exerted a broader spectrum of activity, effectively inhibiting the Gram-negative bacterium *Klebsiella pneumoniae* (MIC = 0.1 $\mu\text{g/ml}$), comparable or even more active than the antimicrobial agents ciprofloxacin (MIC = 0.125 $\mu\text{g/ml}$), cefoxitin (MIC = 0.25 $\mu\text{g/ml}$), and imipenem (MIC = 0.25 $\mu\text{g/ml}$), which were used as positive controls. These results suggested that the 3,5-dibromophenol substitution of **79** plays an important role in mediating antimicrobial activity, and thus this metabolite represents a potential lead scaffold for drug development against MRSA- and *K. pneumoniae*-associated infections, which are difficult to treat with currently available antibiotics [43].



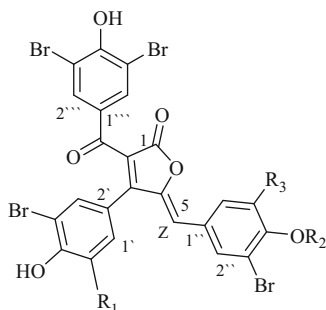
2-(2',4'-Dibromophenoxy)-3,5-dibromophenol (**79**): R=H

2-(2',4'-Dibromophenoxy)-3,4,5-tribromophenol (**80**): R=Br

A unique class of proline-rich peptides, callyaerins A–M, were obtained from the Indonesian marine sponge *Callyspongia aerizusa* [44]. Callyaerins feature an unusual core structure comprising a cyclic peptide part and a linear peptide side chain, which are connected through a rare, non-proteinogenic (Z)-2,3-diaminoacrylic acid (DAA) moiety. Among the isolated compounds, callyaerin A (**81**) exhibited the strongest activity against *M. tuberculosis* with a MIC₉₀ of 2.7 $\mu\text{g/ml}$. In addition, **81** was found to be inactive against THP-1 (human acute monocytic leukemia) and MRC-5 (human fetal lung fibroblast) cells (IC₅₀ >10 $\mu\text{g/ml}$), highlighting its potential as a promising antitubercular lead compound.

Callyaerin A (**81**)

Marine tunicates are a prolific source for biologically active secondary metabolites such as peptides and alkaloids having anticancer, antiviral, and antifungal or antibacterial activities [45, 46]. Lyophilized specimens of the colonial tunicate *Pseudodistoma antinboja* collected at a depth of 10–15 m off the shore of Tongyeong City, South Sea, Korea, were extracted with 50% MeOH/ CH₂Cl₂ yielding nine butenolides. Only cadiolides C–G (**82–86**) displayed antibacterial activity against a panel of Gram-positive strains including methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) strains with MIC ranging from 0.13 to 12.5 µg/ml. Among the tested compounds, cadiolide C (**82**) was the most potent one, showing equal or even stronger activity compared to the well-known antibiotic drug vancomycin (MIC, 0.5–1 µg/ml). The location of bromine atoms was found to be important for the antibiotic activity of the investigated compounds. The free phenolic group enhances the activity, whereas its methylation reduces the activity as shown for **85** which is less active than **82** while permethylation resulted in a complete loss of activity [47].



Cadiolide C (**82**) : R₁=R₂=R₃=H

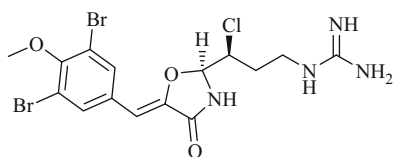
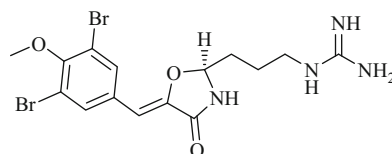
Cadiolide D (**83**) : R₁=Br, R₂=R₃=H

Cadiolide E (**84**) : R₁=R₂=H, R₃=Br

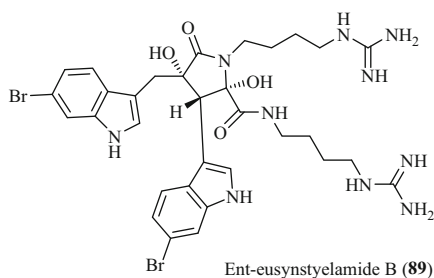
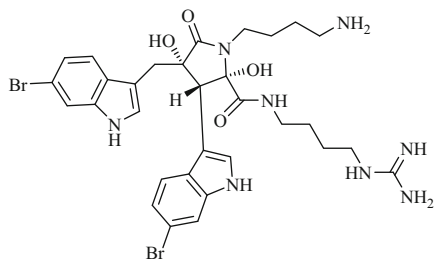
Cadiolide F (**85**) : R₁=H, R₂=Me, R₃=H (E/Z)

Cadiolide G (**86**) : R₁=Br, R₂=H, R₃=Br

The colonial ascidian, *Synoicum* sp., is a prominent source of numerous secondary metabolites showing a variety of biological activities. Examples include cytotoxic palmerolide A, ecdysteroids, a tetrahydrocannabinol derivative, prunolides A–C, a number of rubrolides, the antidiabetic tiruchanduramine, and the anti-inflammatory halogenated furanone *E/Z*-rubrolide O. *S. pulmonaria* is abundant in the Arctic-boreal waters of the North Sea and in the deep cold waters of West Scotland and Northern Ireland [48]. The sub-Arctic ascidian *S. pulmonaria*, obtained off the Norwegian coast, afforded novel brominated guanidinium oxazolidinones named synoxazolidinones A and B (**87** and **88**) [49]. The 4-oxazolidinone ring present in compounds **87** and **88** is rare in natural products. Synoxazolidinone A (**87**) showed promising antibacterial activity against the Gram-positive *S. aureus* as well as against MRSA with MIC values of 10 $\mu\text{g/ml}$ in both cases. Moreover, **87** featured a MIC value of 6.25 $\mu\text{g/ml}$ when tested against the Gram-positive bacterium *Corynebacterium glutamicum*. Synoxazolidinone B (**88**) displayed lower activities against MRSA (MIC of 30 $\mu\text{g/ml}$). This weaker activity of **88** compared to **87** corroborates the importance of the chlorine substituent for the antibacterial activity [49].

Synoxazolidinone A (**87**)Synoxazolidinone B (**88**)

The Arctic bryozoan *Tegella* cf. *spitzbergensis* yielded four brominated eusynstyelamide alkaloids including ent-eusynstyelamide B and eusynstyelamides D–F. Ent-eusynstyelamide B (**89**) is the enantiomer of the known brominated tryptophan metabolite eusynstyelamide B [50]. These compounds were tested against several bacteria including *S. aureus*, *E. coli*, *P. aeruginosa*, *C. glutamicum*, and MRSA. Ent-eusynstyelamide B and eusynstyelamide F (**89** and **90**) exhibited antibacterial activity with MIC values as low as 6.25 $\mu\text{g/ml}$ against *S. aureus* (ATTC 9144) and MIC values of 12.5 and 6.25 $\mu\text{g/ml}$ against *C. glutamicum* (ATTC 13032), whereas the MIC value against *E. coli* (ATCC 25922) was 12.5 $\mu\text{g/ml}$. Moreover, (**89**) exhibited a MIC value of 20 $\mu\text{g/ml}$ against MRSA (ATCC 33591).

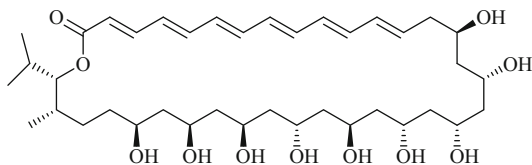
Ent-eusynstyelamide B (**89**)Eusynstyelamide F (**90**)

3 Antifungal Compounds

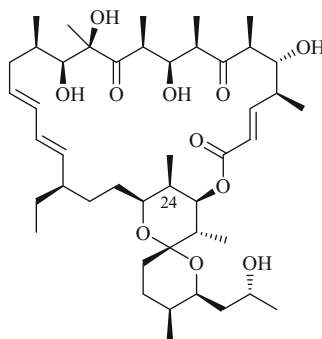
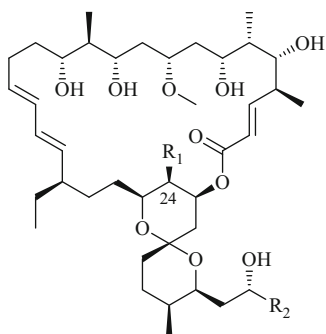
3.1 From Bacteria

Actinobacteria are prolific sources for many important antibiotics such as aminoglycosides, erythromycin, tetracyclines, or vancomycin [51]. *Streptomyces* sp. CN Q3 43 was isolated from a sediment sample collected at North Cat Cay at the Bahamas and cultivated on seawater-based medium. Chromatographic workup of the extract yielded two polyene polyol (36-membered) macrocyclic lactones bahamaolides A and B. Bahamaolide A (**91**) showed antifungal activity against various pathogenic fungi with a MIC value of 12.5 $\mu\text{g/ml}$ and exhibited strong inhibitory activity against *C. albicans* isocitrate lyase (ICL) with an IC_{50} value of 7.65 $\mu\text{g/ml}$ which is almost equal to that of 3-nitro-propionate ($\text{IC}_{50} = 6.84 \mu\text{g/ml}$) which was used as a positive control [52].

Chromatographic workup of the culture broth of *Actinoalloteichus* sp. NPS702, obtained from sediment of Usa Bay, Kochi Prefecture, Japan, afforded nine new 26-membered macrolides of the oligomycin class including neomaclafungins A–I (**92–100**) along with oligomycin A (**101**). Compounds **92–100** revealed potent antifungal activity against *Trichophyton mentagrophytes* (ATCC 9533), with MIC values ranging from 1 to 3 $\mu\text{g/ml}$, whereas oligomycin A (**101**) was the least potent compound encountered (MIC = 10 $\mu\text{g/ml}$) [53].



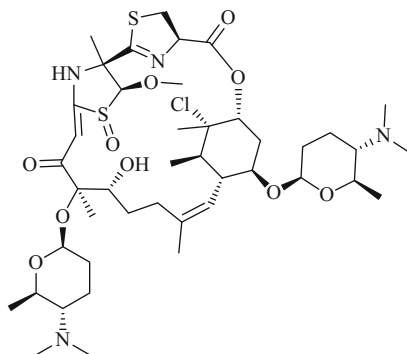
Bahamaolide A (91)



Oligomycin A (101)

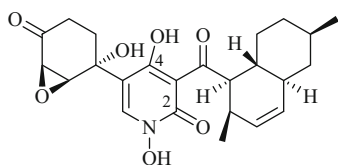
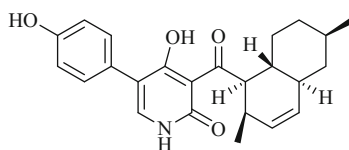
	R ₁	R ₂
Neomaclafungin A (92):	CH ₂ CH ₂ CH ₂ OH	CH ₃
Neomaclafungin B (93):	CH ₂ CH ₂ CH(CH ₃)OH	CH ₃
Neomaclafungin C (94):	CH ₂ CH ₂ CH ₂ OH	CH ₂ CH ₃
Neomaclafungin D (95):	CH ₂ CH ₂ CH(CH ₃)OH	CH ₂ CH ₃
Neomaclafungin E (96):	CH ₂ CH ₃	CH ₃
Neomaclafungin F (97):	CH ₂ CH ₂ CH ₃	CH ₃
Neomaclafungin G (98):	CH ₂ CH ₂ CH ₂ CH ₃	CH ₃
Neomaclafungin H (99):	CH ₂ CH ₂ CH ₃	CH ₂ CH ₃
Neomaclafungin I (100):	CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	CH ₃

Chemical investigation of a marine-derived actinobacterium *Actinomadura* sp., obtained from the ascidian *Ecteinascidia turbinata*, led to the isolation of a novel polyketide forazoline A (**102**) [54]. Interestingly, **102** exhibited *in vivo* efficacy in a murine model of infection with *C. albicans* at concentrations ranging from 0.125 to 2.5 mg/kg, comparable to those of amphotericin B, without any apparent toxicity. A chemical genomic approach with the yeast *S. cerevisiae* indicated that **102** possibly dysregulates phospholipid homeostasis, thus affecting the cell membrane integrity. To further evaluate this hypothesis, membrane permeability studies were employed, which showed that **102** causes permeabilization of fungal membranes in a dose-dependent manner, corroborating its putative mode of action. Moreover, **102** was found to exert a synergistic effect with the clinically used antifungal agent amphotericin B and thus represents a potential lead scaffold for further development of anti-*C. albicans* agents [54].

Forazoline A (**102**)

3.2 From Fungi

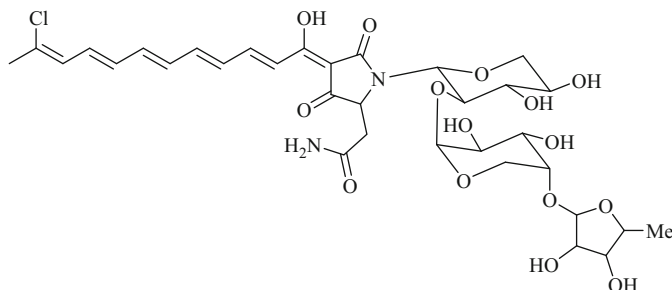
Deep-seated candidiasis is a fungal infection that is commonly treated with azoles. However, recent years have seen an increasing number of reports on resistance of *Candida* strains against azole derivatives [55]. This calls for the discovery of new antifungal drugs targeted against azole-resistant *C. albicans* strains. Four new alkaloids featuring a 4-hydroxy-2-pyridone moiety including didymellamides A–D were obtained from the fungus *Stagonosporopsis cucurbitacearum*, isolated from an unidentified sponge collected at Atami-shi, Shizuoka Prefecture, Japan. Didymellamide A (**103**) exhibited broad antifungal activity against azole-resistant strains as well as against azole-sensitive *C. albicans*, *C. glabrata*, and *Cryptococcus neoformans* with MIC values of 1.6–3.1 $\mu\text{g/ml}$, respectively, while didymellamide B (**104**) was only activity against *C. neoformans* with a MIC value of 6.3 $\mu\text{g/ml}$ [56].

Didymellamide A (**103**)Didymellamide B (**104**)

3.3 From Invertebrates

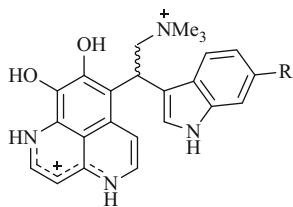
Sponges of the genus *Melophlus* are well-known sources for chemically diverse bioactive secondary metabolites such as tetramic acid derivatives [57]. The unprecedented tetramic acid glycoside aurantoside K (**105**) was isolated from *Melophlus* sp. collected at the Fiji Islands, Melanesia. The compound showed pronounced

antifungal activity against amphotericin-resistant *C. albicans* and wild-type *C. albicans* with MIC values of 31.25 and 1.95 $\mu\text{g/ml}$, respectively [58].

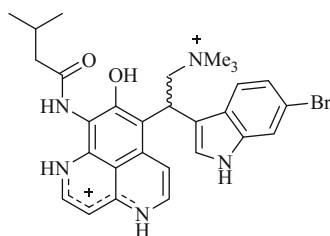


Aurantoside K (**105**)

Aptamine-type alkaloids are heteroaromatic alkaloids with a 1*H*-benzo[de][1,6]naphthyridine ring system showing a wide range of bioactivities including antimicrobial, antiviral, antioxidant, and cytotoxic activities [59, 60]. Seven new compounds including six new aptamine alkaloids were isolated from an Okinawan marine sponge *Suberites* sp. collected from Unten Port, Nakijin, Okinawa, Japan. Among the purified compounds, nakijinamine A (**106**) displayed antifungal activity against *C. albicans*, *C. neoformans*, and *T. mentagrophytes* with MIC values of 0.25, 0.5, and 0.25 $\mu\text{g/ml}$, respectively, as well as antibacterial activity against *S. aureus*, *B. subtilis*, and *M. luteus* with MIC values of 16, 16, and 2 $\mu\text{g/ml}$, respectively. Nakijinamines B (**107**) and F (**108**) exhibited antifungal activity against *C. albicans* (MIC value of 8 $\mu\text{g/ml}$, for both compounds) [61].

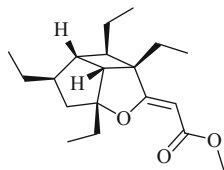


Nakijinamine A (**106**): R = Br
Nakijinamine B (**107**): R = H



Nakijinamine F (**108**)

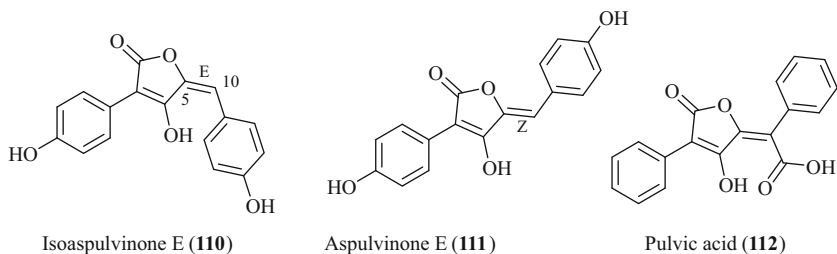
The sponge *Hippospongia lachne* collected in the South China Sea (P.R. China) is a promising source for antifungal drugs. Bioassay-guided fractionation of the EtOH extract of *H. lachne* yielded the polyketide hippolachnin A (**109**), featuring a rare four-membered carbon ring. Hippolachnin A exhibited potent antifungal activity against the pathogenic fungi *C. neoformans*, *Trichophyton rubrum*, and *Microsporum gypseum*, with MIC values of 0.13 $\mu\text{g/ml}$, respectively [62].

Hippolachnin A (**109**)

4 Antiviral Compounds

4.1 From Fungi

Influenza type A, caused by the virus subtype H1N1, is a life-threatening disease which leads to 20–50 million deaths worldwide [63]. Until now, very few drugs are available to treat H1N1 viral infections [64]. Gao et al., in 2013, succeeded in obtaining three antiviral butenolides including isoaspulvinone E (**110**), aspulvinone E (**111**), and pulvic acid (**112**) from the fungus *Aspergillus terreus* Gwq-48, isolated from mangrove rhizosphere at the coast of Fujian province (P.R. China). The compounds exhibited significant anti-influenza A H1N1 activities with IC₅₀ values of 32.3, 56.9, and 29.1 µg/ml, respectively, compared to the positive controls ribavirin (IC₅₀ 24.6 µg/ml) or zanamivir (IC₅₀ 28.4 ng/ml). In addition, compound **110** showed anti-H1N1 viral neuraminidase activity (NA). Docking of **110** and **111** into NA active sites indicated that the *E* double bond Δ⁵⁽¹⁰⁾ is essential for activity [65].

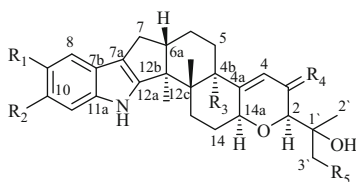


Further anti-H1N1 metabolites were isolated from the culture broth of the fungus *Penicillium camemberti* OUCMDZ-1492, obtained from marine sediment at mangrove roots of *Rhizophora apiculata* collected from Hainan Province (P.R. China). Chromatographic workup yielded six new indole-diterpenoids along with five known compounds. Among the isolated compounds, 3-deoxo-4b-deoxypaxilline (**113**), 4a-demethylpaspaline-4a-carboxylic acid (**114**), 4a-demethylpaspaline-3,4,4a-triol (**115**), 9,10-diisopentenylpaxilline (**116**), (6*S*,7*R*, 10*E*,14*E*)-16-(1*H*-indol-3-yl)- 2, 6, 10, 14- tetramethylhexadeca-2,10,14-triene-6,7-diol (**117**), emindole SB (**118**), 21-isopentenylpaxilline (**119**), paspaline (**120**), and paxilline (**121**) revealed significant activity against the H1N1 virus with IC₅₀ values ranging

from 3.32–32.8 $\mu\text{g/ml}$ compared to the positive control ribavirin 27.6 $\mu\text{g/ml}$. The most potent compound was **119**, while **120** was the least active one. SAR studies indicated that:

1. The anti-H1N1 activity of hexacyclic indole-diterpenoids increased due to the presence of a methylene group as in **113**, a carboxy/or hydroxy group at position 4a as in **114** and **115**, a hydroxy group at position 4b as in **121**, and an isopentenyl group at position 9 as in **119**.
2. The anti-H1N1 activity decreased by phenyl isoprenylation as in **116**.
3. The pronounced activity of **117** with the aliphatic diterpene moiety and of **118** with the pentacyclic indole-diterpene proved that the cyclic diterpenoid nucleus has a limited effect on the activity.

Moreover, the presence of 3-oxo and 4b-hydroxy, together with 9-isopentenyl substituents in **119**, was responsible for the highest anti-H1N1 activity among the separated compounds [66].

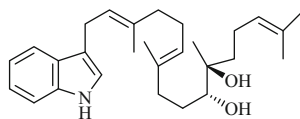


3-Deoxy-4b-deoxypaxilline (**113**) : $R_1=R_2=R_3=R_5=H$, $R_4=H_2$

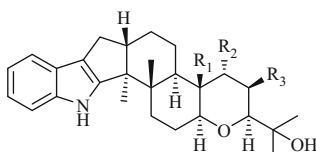
9,10-Diisopentenylpaxilline (**116**) : $R_1=R_2=$, $R_3=OH$, $R_4=O$, $R_5=H$

21-Isopentenyl-paxilline (**119**) : $R_1=$, $R_2=R_5=H$, $R_3=OH$, $R_4=O$

Paxilline (**121**) : $R_1=R_2=R_5=H$, $R_3=OH$, $R_4=O$



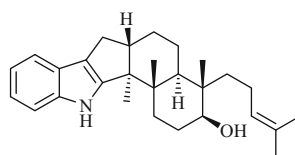
(6*S*,7*R*, 10*E*,14*E*)-16- (1*H*-Indol-3-yl)-
2, 6, 10, 14-tetramethylhexadeca-
2,10,14-triene-6,7-diol (**117**)



4a-Demethylpaspaline-4a-carboxylic acid (**114**) : $R_1=CO_2H$, $R_2=R_3=H$

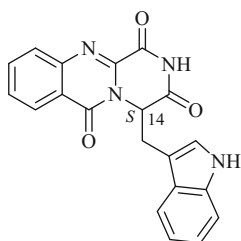
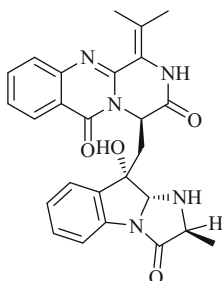
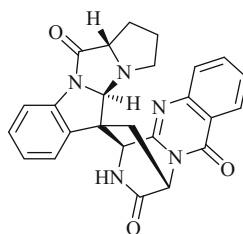
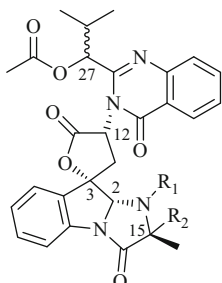
4a-Demethylpaspaline-3,4,4a-triol (**115**) : $R_1=R_2=R_3=OH$

Paspaline (**120**) : $R_1=CH_3$, $R_2=R_3=H$



Emindole SB (**118**)

The fungus *Cladosporium* sp. PJX-41 was isolated from mangrove sediment in Guangzhou (P.R. China). Chromatographic workup afforded six new indole alkaloids, five of them being gyantrypine analogues. Six alkaloids including (14*S*)-oxogyantrypine (**122**), norquinadoline A (**123**), deoxynortryptoquivaline (**124**), deoxytryptoquivaline (**125**), tryptoquivaline (**126**), and quinadoline B (**127**) showed antiviral activity against influenza virus A (H1N1), with IC_{50} values ranging from 30.4 to 48.6 $\mu\text{g/ml}$ comparable to the positive control ribavirin that exhibited an IC_{50} value of 21.2 $\mu\text{g/ml}$ [67].

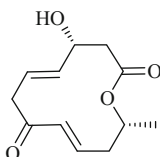
(14-*S*) Oxoglyantryptine (**122**)Norquinadoline A (**123**)Quinadoline B (**127**)

Deoxynortryptoquivaline (**124**) : $R_1=H$, $R_2=H$; (2*R*, 3*S*, 12*R*, 15*S*, 27*S*)

Deoxytryptoquivaline (**125**) : $R_1=H$, $R_2=CH_3$; (2*R*, 3*S*, 12*R*, 27*S*)

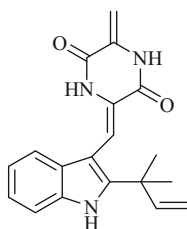
Tryptoquivaline (**126**) : $R_1=OH$, $R_2=CH_3$; (2*S*, 3*S*, 12*R*, 27*S*)

The potent antiviral metabolite, balticolid (**128**), was isolated from an unidentified fungus collected at the coast of the Greifswalder Bodden, Baltic Sea, Germany [68]. Balticolid (**128**) displayed strong activity against influenza A virus and herpes simplex virus (HSV) type I with an IC_{50} value of 0.10 $\mu\text{g/ml}$ but was nontoxic to eukaryotic cells when investigated at similar concentrations.

Balticolid (**128**)

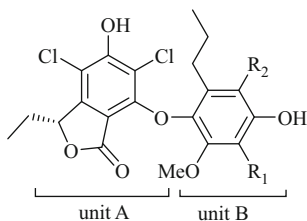
Bioassay-guided fractionation of a crude extract of the deep-sea-derived fungus *Eurotium rubrum* F33, isolated from sediment collected from the South Atlantic Ocean (2067 m depth), afforded a series of prenylated indole diketopiperazine alkaloids with antiviral activity toward the influenza virus strain A/WSN/33 (H1N1) [69]. All compounds were tested against H1N1 propagated in Madin-Darby canine kidney (MDCK) cells and the known compound neoechinulin B (**129**) exhibited the strongest antiviral activity with an IC_{50} value of 8.8 $\mu\text{g/ml}$. Moreover, **129** was found to exert high potency against oseltamivir- or amantadine- and ribavirin-resistant

influenza clinical isolates with IC_{50} values ranging from 5.4 to 7.1 $\mu\text{g/ml}$, respectively. However, **129** showed lack of cytotoxicity against MDCK cells, highlighting its selective antiviral activity. Subsequent mode-of-action studies, employing hemagglutination inhibition, surface plasmon resonance, and polykaryon assays, revealed that **129** binds to the HA1 subunit of hemagglutinin glycoprotein, blocking its interaction with the sialic acid receptor, and thus inhibits the attachment of H1N1 virus to host cells. Interestingly, **129** was found to inhibit influenza virus (strain A/WSN/33) propagation without causing viral resistance, as shown in a multi-passage experiment, employing a plaque formation assay (even after a fifth passage), in contrast to clinically used anti-influenza drugs, such as amantadine [69]. Hence, these results demonstrated that **129** may serve as a useful lead compound for the development of new anti-influenza agents.



Neoechinulin B (**129**)

Further investigation of the fungus *Spiromastix* sp. MCCC 3A00308 (see Sect. 2.2) afforded an array of new aromatic lactones with various chlorine atom substituents, spiromastilactones A–M [33]. Bioactivity assays of these compounds revealed that most of the derivatives, bearing a pseudo-depsidone skeleton, possess antiviral activity. Spiromastilactones D (**130**) and E (**131**) showed the strongest antiviral activity against A/WSN/33 (H1N1) influenza virus propagated in MDCK cells with IC_{50} values of 2.8 and 5.3 $\mu\text{g/ml}$, respectively, similar to those of the positive controls oseltamivir (3.1 $\mu\text{g/ml}$) and amantadine (1.97 $\mu\text{g/ml}$). These findings allowed to conclude that monochlorination of ring B, in contrast to dichlorination, is important for expression of the strong antiviral activity of these metabolites. Moreover, formation of the pseudo-depsidone scaffold is essential for mediating antiviral properties, since the respective monomers spiromastilactone A (unit A) and divaric acid (unit B) were inactive. The most active compound, spiromastilactone D (**130**), exhibited a broad antiviral spectrum toward influenza A and B viruses, including oseltamivir- or amantadine-resistant clinical isolates, and therefore was chosen for further mode-of-action and molecular docking studies. Accordingly, **130** was shown to potentially bind to the hemagglutinin protein (HA1) subunit, adjacent to the sialic acid receptor binding pocket, thus disrupting the HA-sialic acid receptor interaction, which is crucial for the attachment of influenza viruses to host cells. Moreover, **130** was found to inhibit viral genome replication, probably via interfering with the viral ribonucleoprotein complex [33], verifying this metabolite as a potential anti-influenza lead structure for further development.

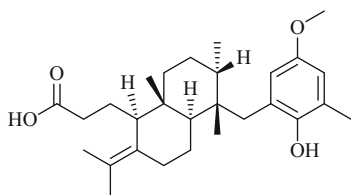
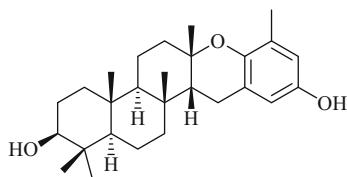
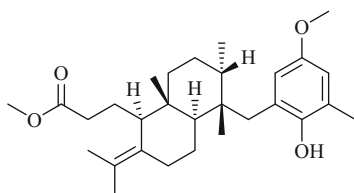


Spiromastilactone D (**130**): $R_1 = H$, $R_2 = Cl$
 Spiromastilactone E (**131**): $R_1 = Cl$, $R_2 = H$

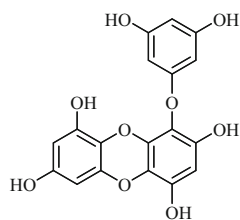
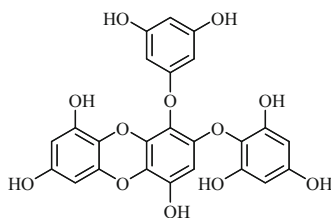
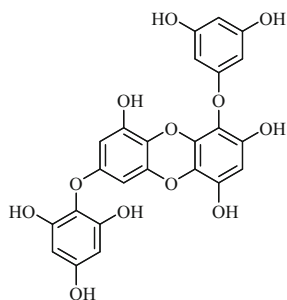
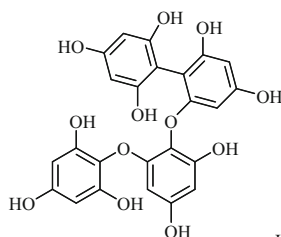
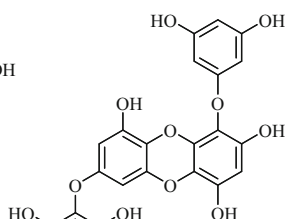
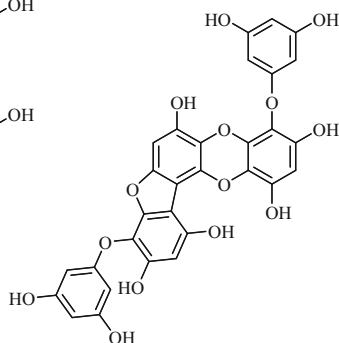
4.2 From Algae

Paramyxoviridae type viruses include both human metapneumovirus (HMPV), respiratory syncytial virus (RSV), and parainfluenza virus (PIV) [70]. Among them, HMPV is the most dangerous one as it can cause significant morbidity especially in infants and in elderly patients [71]. The brown seaweed *Styopodium zonale* which is common along the Brazilian coast accumulates mainly meroditerpenes, with several of them exhibiting antiviral activity. Two meroditerpenoids atomaric acid¹ (**132**) [72] and epitaondiol (**133**) were obtained from *S. zonale*, and the methyl ester of atomaric acid (**134**) was prepared by semi-synthesis [73]. Compounds **132–134** exhibited antiviral activity against HMPV replication and showed selectivity indices of >56.81, 49.26, and 12.82, respectively. Epitaondiol (**133**) exhibited potent anti-HMPV activity ($IC_{50} = 1.01 \mu\text{g/ml}$) compared to atomaric acid methyl ester (**134**; $IC_{50} = 2.66 \mu\text{g/ml}$) and its parent compound atomaric acid (**132**) ($IC_{50} = 3.52 \mu\text{g/ml}$). Each compound exerted its effect by a unique mechanism: atomaric acid interacts with viral particles outside of the host cells thus preventing infection of the cell cultures. The compound has no effect on cellular receptors or on viral penetration. The meroditerpene epitaondiol (**133**) inhibits the penetration of viral particles into cells but without affecting the post-penetration stages or interacting with cellular receptors. The methyl ester of atomaric acid inhibits penetration of viral particles without exhibiting any effect on the post-penetration events and cellular receptors. These compounds showed selective antiviral activity with low cytotoxic activity against LLC-MK2 cells, thus highlighting their potential to inhibit HMPV in vitro [73].

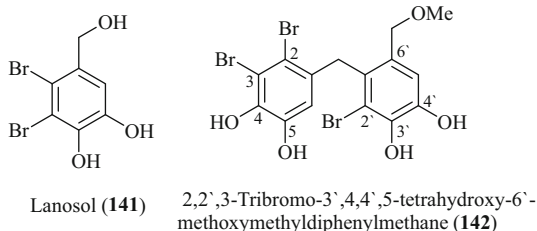
¹The structures of atomaric acid is drawn incorrectly in the original manuscript [72], and it is drawn correctly in this chapter.

Atomaric acid (**132**)Epitaondiol (**133**)Methyl ester of atomaric acid (**134**)

Severe acute respiratory syndrome (SARS) is a severe pneumonia caused by a novel human coronavirus (SARS-CoV); its SARS-CoV 3CL^{pro} plays a crucial role in viral replication [74]. Betulinic acid [75], indigo, aloe emodin [76], the biflavonoids amentoflavones [77], and quinone-methide triterpenoids [78] are among its naturally occurring inhibitors. Park et al. [79], succeeded in isolating nine phlorotannins from the ethanol extract of *Ecklonia cava*, an edible brown alga. Six of the isolated compounds showed anti-SARS-CoV 3CL^{pro} activity including the phlorotannin derivatives eckol (**135**), 2-phloroeckol (**136**), 7-phloroeckol (**137**), fucodiphloroethol G (**138**), dieckol (**139**), and phlorofucofuroeckol A (**140**) with IC₅₀ values of 2.0–20.9 µg/ml. Dieckol (**139**) was the most potent derivative encountered, with an IC₅₀ value of 2.0 µg/ml, compared to 18.1 µg/ml for the positive control hesperetin [79].

Eckol (**135**)2-Phloroeckol (**136**)7-Phloroeckol (**137**)Fucodiphloroethol G (**138**)Dieckol (**139**)Phlorofucufuroeckol A (**140**)

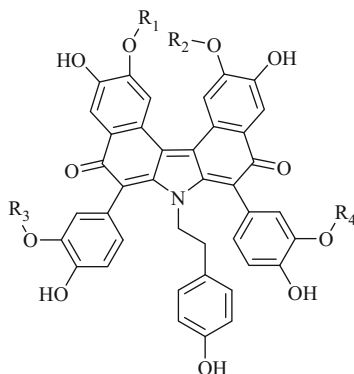
Chromatographic workup of the red alga *Neorhodomela aculeata* collected at the port of Namae, South Korea, afforded the new compound lanosol along with five known polybromocatechols. Two of the isolated compounds exhibited antiviral activity: 2,3-dibromo-4,5-dihydroxybenzyl alcohol (lanosol, **141**) and polybromocatechol (2,2',3-tribromo-3',4,4',5-tetrahydroxy-6'-methoxymethyl-diphenylmethane, **142**). Compound **141** exhibited antiviral activity against HRV2 with an IC_{50} value of 2.50 $\mu\text{g/ml}$, while compound **142** revealed anti-HRV2 activity, with an IC_{50} value of 7.11 $\mu\text{g/ml}$, and anti-HRV3 activity with an IC_{50} value of 4.69 $\mu\text{g/ml}$. The positive control ribavirin exhibited IC_{50} s of 2.15 and 5.09 $\mu\text{g/ml}$ against HRV2 and HRV3, respectively. Compounds **141** and **142** were not cytotoxic making them potential drug candidates for new antiviral drugs against two different human rhinoviruses [80].



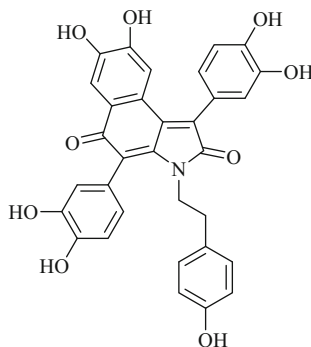
4.3 From Invertebrates

DOPA (2-amino-3-(3',4'-dihydroxyphenyl) propionic acid) is a key biogenetic precursor for many structurally unique alkaloids. Naturally occurring alkaloids with pyrrole core structures are examples of DOPA-derived alkaloids and are characterized by different substitution patterns [81]. Based on the cyclic condensation and substitution pattern of the pyrrole ring, these compounds are classified as lamellarins, lukianols, polycitrins, polycitons, storniamides, and ningalins. DOPA-derived alkaloids were found to exert several pharmacological activities, such as cytotoxicity, HIV-1 integrase inhibition, and multidrug resistance reversal activity in addition to immunomodulatory activity [82]. Fifteen new DOPA-derived pyrrole alkaloids, baculiferins A–O, were isolated from the marine sponge *Ietrochota baculifera* collected in the South China Sea (P.R. China) [82]. All compounds were found to feature one to three *O*-sulfate units. Among the isolated compounds, baculiferins C, E–H, and K–N (**143–151**) exhibited potent inhibitory activity against HIV-1 III_B virus with IC₅₀ values ranging from 1.4 to 8.6 µg/ml. Interestingly, these compounds showed weak to moderate activity against the tumor cell lines HCT-8, Bel-7402, BGC-823, A549, and A2780.

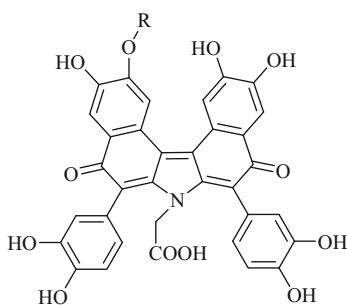
The binding activities of these compounds to HIV-1 targets including recombinant gp41 (a transmembrane protein of HIV-1), Vif (viral infectivity factor of HIV-1), and human APOBEC3G (an innate intracellular antiviral factor) were evaluated to elucidate the mechanism of their anti-HIV activities. Baculiferins containing *N*-acetyl groups (**149** and **150**) were found to show the highest binding affinities toward both Vif (RU >1800) and APOBEC3G (RU >2170). The binding activity of these compounds suggested that the antiviral activity of the compounds is due to their interaction with the targets Vif, APOBEC3G, and/or gp41 [82].



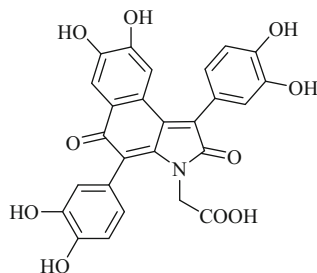
Baculiferin C (**143**) : R₁=R₂=H, R₃=R₄=SO₃H
 Baculiferin E (**144**) : R₁=R₃=SO₃H, R₂=R₄=H
 Baculiferin F (**145**) : R₁=R₄=SO₃H, R₂=R₃=H
 Baculiferin G (**146**) : R₁=R₃=R₄=SO₃H, R₂=H
 Baculiferin H (**147**) : R₁=R₂=R₃=SO₃H, R₄=H



Baculiferin K (**148**)

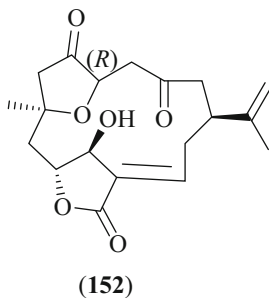


Baculiferin L (**149**) : R=H
 Baculiferin M (**150**) : R=SO₃H

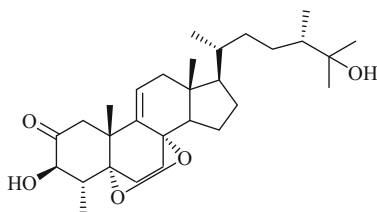
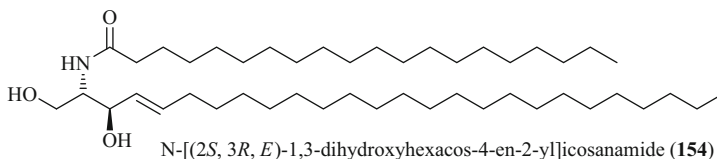
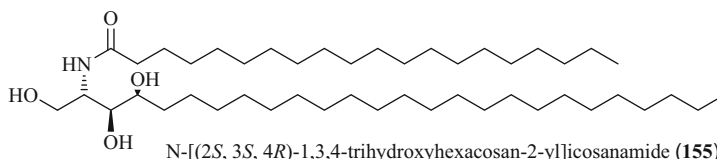
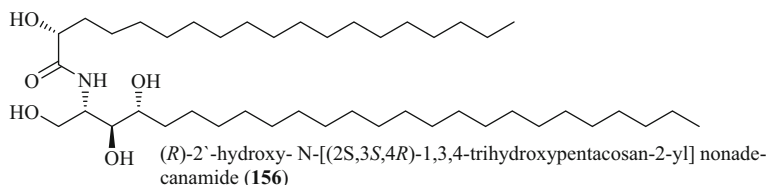


Baculiferin N (**151**)

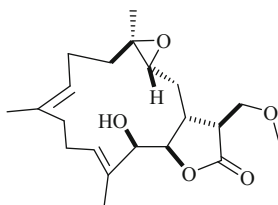
Soft corals of the genus *Sinularia* (Alcyoniidae) are well-known sources of macrocyclic norcembranoids. Many of these macrocyclic norcembranoids were found to exhibit a wide array of bioactivities such as antifungal and cytotoxic properties. *Sinularia gyrosa* collected along the coast of the Dongsha Atoll off Taiwan was shown to yield several of these metabolites [83]. Purification of the acetone extract of this soft coral gave rise to seven new norcembranoids, gyrosanoids A–G, and in addition to known norcembranoids [84]. Among these metabolites, compound (**152**) was found to show significant antiviral activity against human cytomegalovirus (HCMV) with an IC₅₀ value of 1.9 μg/ml.



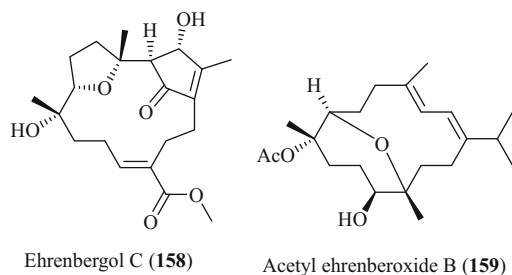
Sinularia candidula, collected in the Egyptian Red Sea, afforded an unprecedented polyhydroxylated sterol, 3 β -25-dihydroxy-4-methyl-5 α ,8 α -epidioxy-2-ketoergost-9-ene (**153**) together with three new ceramide derivatives *N*-[(2*S*,3*R*,*E*)-1,3-dihydroxyhexacos-4-en-2-yl]icosanamide (**154**), *N*-[(2*S*,3*S*,4*R*)-1,3,4-trihydroxyhexacosan-2-yl]icosanamide (**155**), and (*R*)-2'-hydroxy-*N*-[(2*S*,3*S*,4*R*)-1,3,4-trihydroxypentacosan-2-yl] nonadecanamide (**156**). All isolated compounds (**153–156**) exhibited selective antiviral activity against H5N1 avian influenza strain using the plaque inhibition assay possessing virus titer reductions of 55.16%, 48.81%, 10.43%, and 15.76%, respectively, at concentrations less than or equal to 1 ng/ml [85].

3β-25-dihydroxy-4-methyl-5α,8α-epidioxy-2-ketogost-9-ene (**153**)N-[(2*S*, 3*R*, *E*)-1,3-dihydroxyhexacos-4-en-2-yl]icosanamide (**154**)N-[(2*S*, 3*S*, 4*R*)-1,3,4-trihydroxyhexacosan-2-yl]icosanamide (**155**)*(R)*-2'-hydroxy- N-[(2*S*,3*S*,4*R*)-1,3,4-trihydroxypentacosan-2-yl] nonadecanamide (**156**)

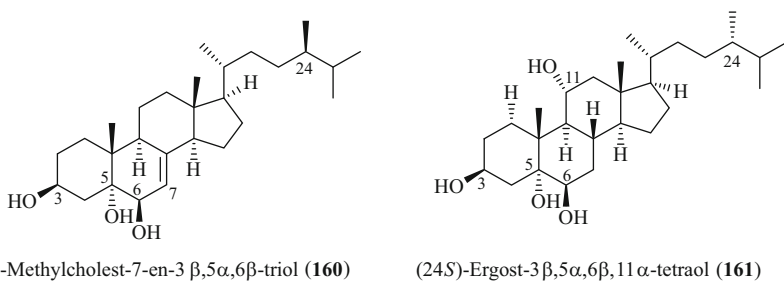
Further anti-HCMV compounds were obtained from species of the soft coral genus *Lobophytum* collected at the Dongsha Atoll (Taiwan) which is well known for producing a large variety of bioactive secondary metabolites including cytotoxic, antibacterial, anti-inflammatory, and HIV-inhibitory compounds [86, 87]. Chromatographic workup of an extract of *L. durum* gave rise to five new cembranolides durumolides M–Q, of which durumolide Q (**157**) exhibited significant antiviral activity against HCMV with an IC_{50} value of 5.2 $\mu\text{g/ml}$ [88].

Durumolide Q (**157**)

Further anti-HCMV metabolites were obtained from the soft coral *Sarcophyton ehrenbergi* collected at San-hsian-tai, Taiwan. Purification of its acetone extract yielded two new antiviral diterpenoids, ehrenbergol C and acetyl ehrenberoxide B (**158** and **159**). The compounds exhibited selective antiviral activity toward HCMV, with IC_{50} values of 20 and 8.0 $\mu\text{g/ml}$, respectively [89].



Chromatographic workup of a *Sarcophyton* sp. collected in the South China Sea (P.R. China) yielded three new polyhydroxylated steroids along with seven known steroid derivatives. The isolated compounds featured a 3β , 5α , 6β -trihydroxylated steroidal moiety. Compounds **160** ($24R$)-methylcholest-7-en- $3\beta,5\alpha,6\beta$ -triol and **161** ($24S$)-ergost- $3\beta,5\alpha,6\beta$, 11α -tetraol displayed antiviral activity against H1N1 (Influenza A virus) with IC_{50} values = 19.6 and 36.7 $\mu\text{g/ml}$, respectively, which is equal to or even more active than those of the positive control ribavirin / IC_{50} value of 24.6 $\mu\text{g/ml}$ [90].

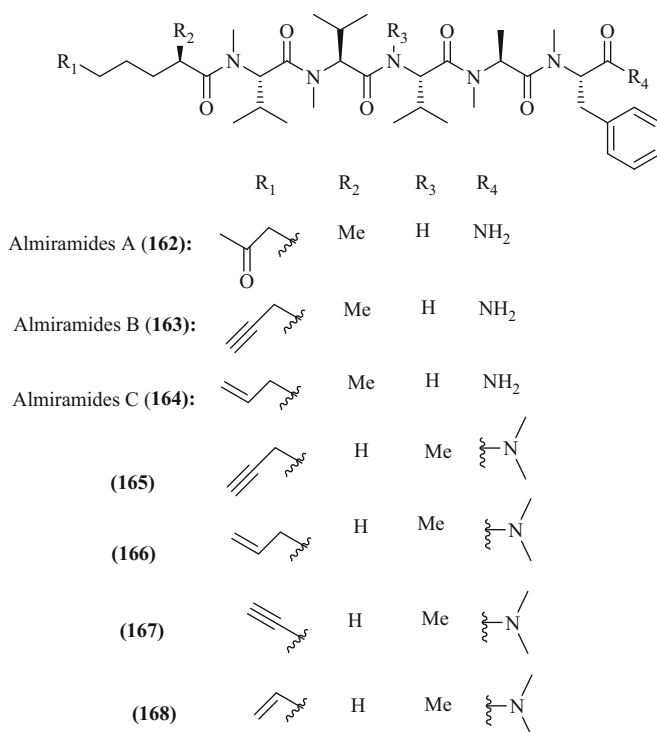


5 Antiprotozoal Compounds

5.1 From Bacteria

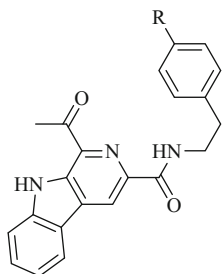
Leishmaniasis (also known as Leishmaniosis) is one of the most dangerous diseases in tropical regions such as India, Sudan, and Brazil. The disease is caused by more than twenty species of taxonomically related intracellular parasites of the genus *Leishmania* and is characterized by cutaneous, mucosal, and visceral manifestations. Main symptoms include ulcerative skin lesions and the destruction of the mucous membranes of the nose, mouth, and throat [91]. An extract of the cyanobacterium

Lyngbya majuscula obtained from mangrove roots in the Bocas del Toro National Marine Park, Bocas del Toro Province, on the north coast of Panama exhibited strong in vitro activity in two complementary screens against the tropical parasite *Leishmania donovani*, the causative agent of visceral leishmaniasis. Chromatographic workup of the extract yielded the *N*-methylated linear lipopeptides almiramides B–C (**162**–**164**), which showed potent anti-leishmanial activity with IC₅₀ values in the range of 1.4–1.7 µg/ml, respectively. The semisynthetic products (**165**–**168**) showed IC₅₀ values in the range of 2.0–4.9 µg/ml with improved therapeutic indices compared to the natural products [92].

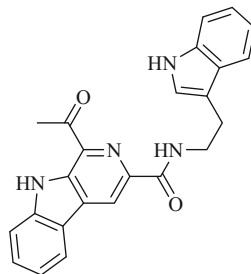


Malaria is a serious infectious disease especially in Central and South America, Southeast Asia, Sub-Saharan Africa, the Middle East, and India which is caused by *Plasmodium* parasites. It is estimated that 0.8–1.2 million people die every year due to malaria [93]. Four new β -carboline alkaloids, including marinacarboline A–D (**169**–**172**), and two new indolactam alkaloids, 13-*N*-demethyl-methylpendolmycin (**173**) and methylpendolmycin-14-*O*- α -glucoside (**174**), were obtained from the culture broth of marine actinomycete *Marinactinospora thermotolerans* SCSIO 00652 isolated from sea sediment sample in the northern South China Sea (P.R. China) obtained at a depth of 3865 m. The new compounds **169**–**174** exhibited

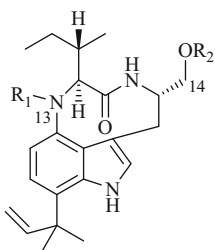
antiplasmodial activities against the malaria parasite *P. falciparum* lines 3D7 and Dd2, with IC_{50} values ranging from 0.74 to 14.0 $\mu\text{g/ml}$ [94].



Marinacarboline A (**169**) : R=OMe
 Marinacarboline B (**170**) : R=OH
 Marinacarboline C (**171**) : R=H



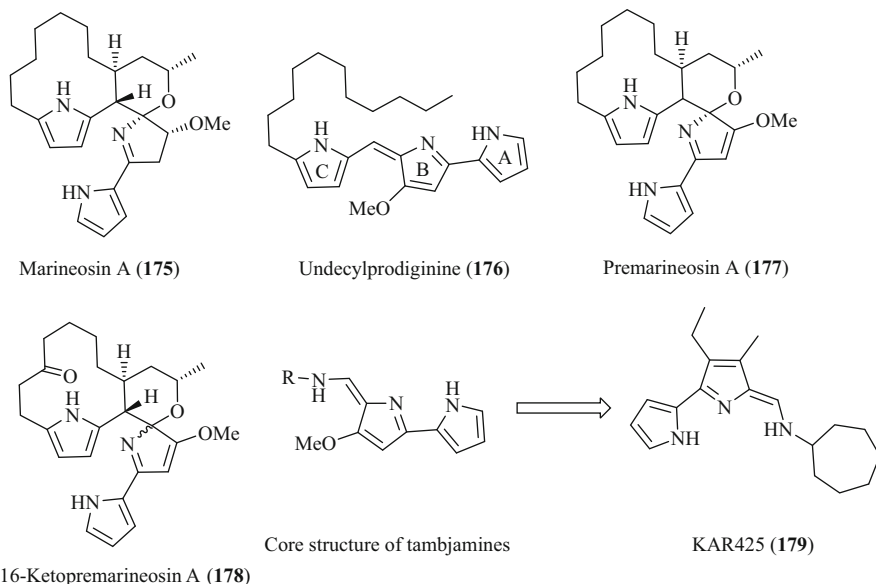
Marinacarboline D (**172**)



13-N-Demethyl-methylpendolmycin (**173**) : $R_1=H$, $R_2=H$
 Methylpendolmycin-14- O - α -glucoside (**174**) : $R_1=Me$, $R_2=Glu$

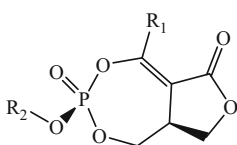
In 2008, an intriguing prodigiosin-related compound, marineosin A (**175**), was isolated from the actinomycete *Streptomyces* sp. CNQ-617, derived from sediment collected off shore of La Jolla, California [95]. Biosynthetic studies assisted to identify the corresponding *mar* gene cluster, leading to **175** that appeared to be homologically similar to the *red* gene cluster described for the soil-dwelling *S. coelicolor*, responsible for the formation of undecylprodigionine (**176**) with additional steps requiring the spiroaminal functionality formation [96]. During further investigation, the antimalarial potency of **175** as well as of two further biosynthetic intermediates, premarineosin A (**177**) and 16-ketopremarineosin A (**178**), isolated from a mutant strain of *S. venezuelae*, was observed. Accordingly, the IC_{50} values of **175**, **177**, and **178** against *P. falciparum* (strains D6, Dd2, and 7G8) were detected at the nanomolar range between 0.6 and 84 ng/ml , being comparable or even more potent than those of the positive control chloroquine. Notably, the most active compound, premarineosin A (**177**), demonstrated high SIs (347 and 2779) against chloroquine-resistant *P. falciparum* strains Dd2 and 7G8, respectively. The remarkable antimalarial activity of this fascinating group of secondary metabolites inspired extensive medicinal chemistry and SAR studies. Accordingly, Kancharla and coworkers

screened a library of B-ring functionalized prodiginins and 94 new synthesized tambjamine derivatives [97]. Naturally occurring tambjamines are found almost exclusively in marine invertebrates (i.e., nudibranchs, bryozoans, and ascidians), and their structures resemble those of prodiginosins, bearing an enamine moiety instead of a pyrrole moiety (ring C) as in the latter [98]. This study revealed that the bipyrrrole scaffold of tambjamines has improved bioactivity profiles with regard to in vitro/in vivo antimalarial efficacy and selectivity. In particular, the analogue KAR425 (**179**) was shown to be an excellent antimalarial lead, being active against the multidrug-resistant strains Dd2 and 7G8 with IC_{50} values of 16 and 18 ng/ml, respectively, while possessing significantly lower cytotoxicity toward HepG2 cells ($IC_{50} = 5711$ ng/ml; SI = 348 and 321, respectively). Moreover, in a subsequent in vivo study, **179** exhibited 100% protection of mice infected with *Plasmodium yoelii* until day 28 when administered orally during 4 days at doses of 25 and 50 mg/kg or after a single-administration dose of 80 mg/kg, whereas no signs of toxic effects were observed. It is also worth noting that the proposed synthesis of KAR425 (**179**) includes the use of inexpensive and accessible precursors, such as cycloheptanamine, and does not involve challenging chemical reactions [97]. Thus, tambjamines and prodiginins have proven to be privileged scaffolds for library design and for development of novel antimalarial agents.



A novel antimalarial compound, salinipostin A (**180**), was discovered by Schulze et al. as a result of a screening program directed toward the search for lead compounds among bacterial marine natural products [99]. This unusual derivative was isolated from *Salinispora* sp., obtained from a marine sediment sample, collected near Keawekahuka Bay, Hawaii, at a depth of 15 m. Salinipostin A (**180**) exhibited potent activity against the chloroquine-resistant W2 strain of

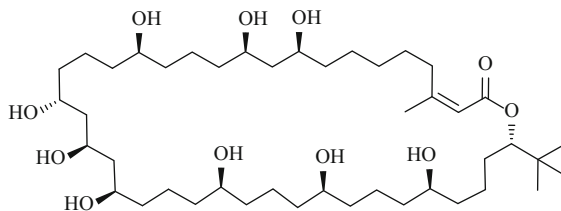
P. falciparum with an EC₅₀ value of 0.024 ng/ml, demonstrating a remarkable selectivity index (SI > 1000). Furthermore, a series of related derivatives salinipostins B–K (**181–190**) were isolated during chemical investigation of *Salinispora* sp., which allowed to explore the structure-activity relationships of this new intriguing class of antimalarials. The chemical structures of **180–190** were unambiguously elucidated by detailed MS/MS as well as by 1D and 2D NMR analysis, including ³¹P NMR, and their absolute configuration was deduced by means of VCD. Evaluation of the antimalarial activity of **180–190**, which share a common bicyclic phosphotriester motif, revealed a broad range of EC₅₀ values between 0.024 (for **180**) and 21.4 μg/ml (for **189**), hinting at the important impact of the side chains (R₁ and R₂) on the antiparasitic effect of these compounds. Accordingly, derivatives with longer vinyl and/or branched R₁ chains as well as with a pentadecyl moiety at R₂, such as salinipostins A, F, and I (**180**, **185**, and **188**, respectively), showed significantly higher activity than the rest of the analogues. Interestingly, none of the compounds displayed cytotoxicity toward mammalian HEK293T cells, indicating their high selectivity against *P. falciparum*. Further biological studies on *P. falciparum* revealed that morphological and developmental changes in the parasite culture, caused by the treatment with the most potent compound salinipostin A (**180**), differ from those that appear as a result of the treatment with chloroquine, suggesting a novel mode of action for **180**. Moreover, growth stage specificity of **180** was evaluated with the respective wash in/wash out experiments that indicated early stages of the parasite life cycle, especially the ring stage, to be the most sensitive ones. A further attempt to generate resistant parasite populations toward **180** failed, thus suggesting that this compound is less susceptible to drug-resistance development than other currently available antimalarial drugs, possibly by targeting fundamental processes in *Plasmodium* growth [99].



- Salinipostin A (**180**): R₁ = Bu, R₂ = C₁₅H₃₁
 Salinipostin B (**181**): R₁ = Bu, R₂ = C₁₄H₂₉
 Salinipostin C (**182**): R₁ = Bu, R₂ = C₁₃H₂₇
 Salinipostin D (**183**): R₁ = *iso*Bu, R₂ = C₁₄H₂₉
 Salinipostin E (**184**): R₁ = *iso*Bu, R₂ = C₁₃H₂₇
 Salinipostin F (**185**): R₁ = Pr, R₂ = C₁₅H₃₁
 Salinipostin G (**186**): R₁ = Pr, R₂ = C₁₄H₂₉
 Salinipostin H (**187**): R₁ = Pr, R₂ = C₁₃H₂₇
 Salinipostin I (**188**): R₁ = Et, R₂ = C₁₅H₃₁
 Salinipostin J (**189**): R₁ = Et, R₂ = C₁₄H₂₉
 Salinipostin K (**190**): R₁ = Et, R₂ = C₁₃H₂₇

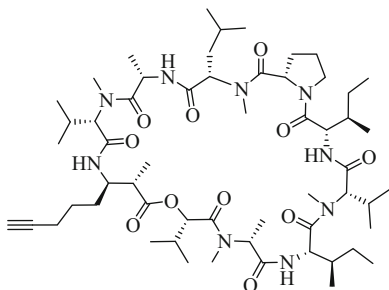
An unprecedented polyhydroxylated macrolide with a 40-membered lactone ring, bastimolide A (**191**), was isolated from the recently described tropical marine cyanobacterium *Okeania hirsute*, collected from the Caribbean coast of Panama [100]. Chemical conversion of **191** to the respective nona-*p*-nitrobenzoate and subsequent X-ray analysis allowed the assignment of its absolute configuration. Bioassay screening against several causative agents of neglected parasitic tropical diseases revealed significant antimalarial activity for **191** at nanomolar

concentrations toward a broad spectrum of drug-resistant *P. falciparum* strains (TM90-C2A, TM90-C2B, W2, and TM91-C235). The respective IC_{50} values were between 63 and 213 ng/ml, whereas only moderate cytotoxicity against Vero and mammalian MCF-7 cells was observed ($IC_{50} = 1.7$ and $2.5 \mu\text{g/ml}$, respectively), with the respective SIs ranging from 7.8 to 56 depending on the tested strain. In addition, **191** exhibited antiparasitic activity against *Trypanosoma cruzi* and *Leishmania donovani* with IC_{50} values of 5.1 and $2.4 \mu\text{g/ml}$, correspondingly [100].

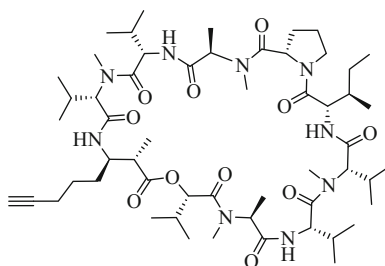


Bastimolide A (**191**)

Two new cyclic depsipeptides, companeramides A (**192**) and B (**193**), were isolated from a cyanobacterial assemblage collected from Coiba Island, Panama [101]. Interestingly, the structures of **192** and **193** contain the unusual amino acids 3-amino-2-methyl-7-octynoic acid (Amoya) and hydroxy isovaleric acid (Hiva), rarely encountered in nature. Both compounds exerted in vitro activity against *P. falciparum* strains D6, Dd2, and 7G8 at low (sub)micromolar concentrations (IC_{50} values between 0.23 and $1.19 \mu\text{g/ml}$). Compounds **192** and **193** were also tested for cytotoxicity against several human cancer cell lines and were found to be nontoxic at concentrations of 1.08 and $1.06 \mu\text{g/ml}$, respectively. The cytotoxicity and selectivity of these compounds at higher concentrations is yet to be studied.



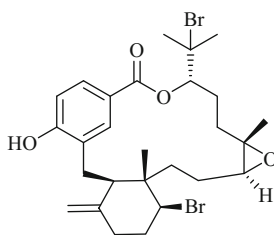
Companeramide A (**192**)



Companeramide B (**193**)

5.2 From Algae

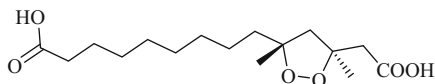
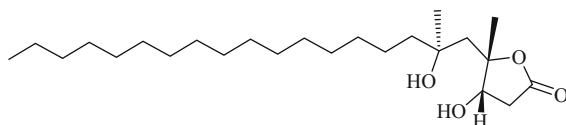
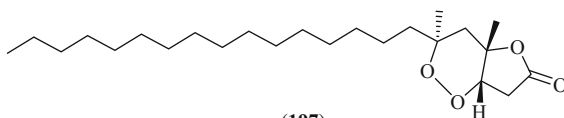
Callophycus serratus is a marine red alga that was found to produce antimalarial metabolites [102]. It is found at depths of 3–20 m throughout the tropical and subtropical Pacific Ocean. Four new bromophycolides, R–U, were obtained from the Fijian red algae *C. serratus* [102]. These natural products feature a diterpene-benzoate macrolide core structure. Bromophycolide S (**194**) showed antimalarial activity against the malaria parasite *P. falciparum* at submicromolar concentrations (IC_{50} value of 0.52 $\mu\text{g/ml}$).



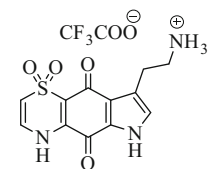
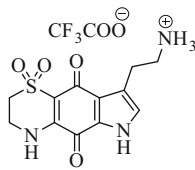
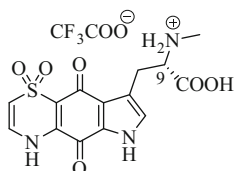
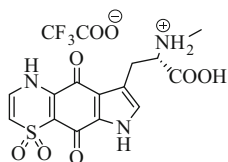
Bromophycolide S (**194**)

5.3 From Invertebrates

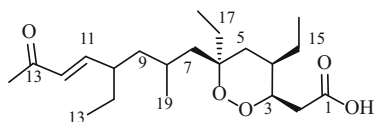
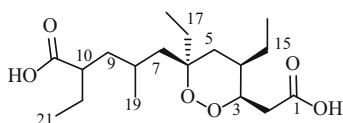
Sponges of the family Plakinidae are known for the accumulation of polyketides featuring cyclic peroxides. Several sponge-derived peroxides showed activity against the protozoan parasites *P. falciparum*, *Leishmania chagasi*, *Trypanosoma brucei brucei*, and *Trypanosoma cruzi* [103]. The Puerto Rican sponge *Plakortis halichondrioides* was found to yield 5-membered-ring polyketide endoperoxides. Antimalarial assessment against *P. falciparum* revealed that epiplakinidioic acid (**195**) showed potent activity with a MIC value of 0.3 $\mu\text{g/ml}$. Semisynthetic derivatives **196** and **197** were found to show comparable antimalarial activity with MIC values of 0.6 and 0.3 $\mu\text{g/ml}$, respectively [104].

Epiplakinidioic acid (**195**)**(196)****(197)**

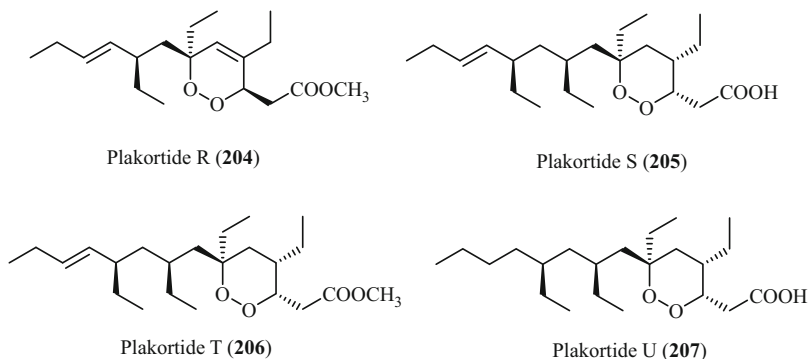
Further investigation of sponges from the genus *Plakortis* resulted in the isolation of unprecedented antimalarial compounds. *Plakortis lita* was collected from the Tydeman Reef, Queensland, Australia, and subjected to bioassay-guided fractionation, thus affording four unprecedented thiazine-derived alkaloids, thiaplakortones A–D isolated as trifluoroacetic acid salts. Thiaplakortone A (**198**) was the most potent compound showing inhibition of chloroquinone-sensitive (3D7) and chloroquinone-resistant (Dd2) *P. falciparum* lines with IC_{50} values of 1.9–20.0 ng/ml, respectively. The weak cytotoxicity of **198** against the HEK293 human cell line corresponds to selectivity indices of 76 and 591 against the 3D7 and Dd2 strains. Moreover, thiaplakortones B–D (**199–201**) showed activity against chloroquinone-sensitive (3D7) and chloroquinone-resistant (Dd2) *P. falciparum* lines with IC_{50} values ranging from 27.1 to 91.7 ng/ml for **199**, from 60.0 to 108.4 ng/ml for **200**, and from 55.8 to 97.9 ng/ml for **201**. Thus, the selectivity of thiaplakortone A (**198**) as well as its high efficacy against *P. falciparum* emphasizes its possible role as a novel antimalarial drug candidate. The structure-activity relationship revealed that (1) the thiazine moiety does not influence the antimalarial activity and (2) the 2-methylaminopropanoic acid chain decreases the antimalarial activity as indicated in **200** and **201**, while the ethylamine side chain increases the activity as seen in **198** [105].

Thiaplakortone A (**198**)Thiaplakortone B (**199**)Thiaplakortone C (**200**)Thiaplakortone D (**201**)

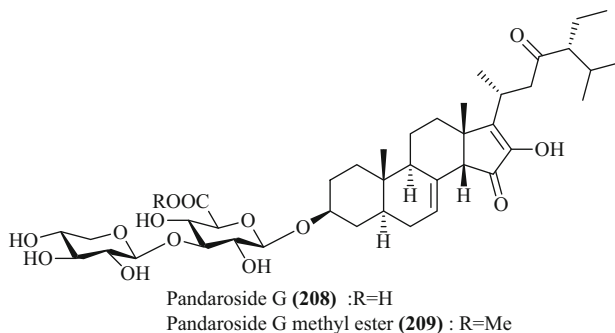
Bioassay-guided fractionation of the Australian marine sponge *Plakortis* sp. [106], previously reported as a prolific source for antimalarial drugs [104, 105], yielded two new cyclic polyketide peroxides, 11,12-didehydro-13-oxo-plakortide Q (**202**) and 10-carboxy-11,12,13,14-tetranorplakortide Q (**203**). Antitrypanosomal assay showed potent activity of **202** against *T. brucei brucei* with IC₅₀ values of 18.04 ng/ml. Compound **203**, which features a carboxyl group in the side chain, showed a 20-fold decrease in activity when compared to **202**.

11, 12-Didehydro-13-oxo-plakortide Q (**202**)10-Carboxy-11,12,13,14-tetranorplakortide Q (**203**)

Plakortides R–U (**204–207**) were isolated from the sponge *Plakinastrella mamillaris* collected at the Fiji Islands, Melanesia, South Pacific Ocean. Plakortide U (**207**) was the most potent compound encountered and exhibited antiplasmodial activity against the chloroquine-resistant FcM29 *P. falciparum* strain with an IC₅₀ value of 0.3 µg/ml, while plakortides R–T (**204–206**) showed moderate activity with IC₅₀ values of 1.62–19.1 µg/ml. No cytotoxic activity was recorded for the isolated compounds [107].

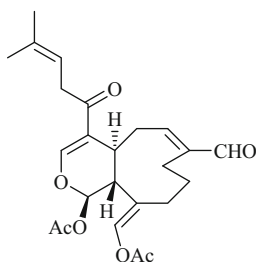


Human African trypanosomiasis (HAT) or African sleeping sickness is caused mainly by two subspecies of protozoan parasites, *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. The disease if not being treated is usually fatal. More than 60 million people in poor regions of Africa are endangered by this disease as stated by the WHO [108]. The Caribbean sponge *Pandaros acanthifolium* yielded twelve steroidal glycosides, including pandarosides E–J along with their corresponding methyl esters. The metabolites feature an unusual oxidized D-ring and a cis C/D ring junction. Pandaroside G (**208**) and its methyl ester (**209**) strongly inhibited the growth of *T. brucei rhodesiense* with IC₅₀ values of 0.6 and 0.03 µg/ml, respectively, and of *L. donovani* with IC₅₀ values of 0.99 and 0.04 µg/ml, respectively [109].



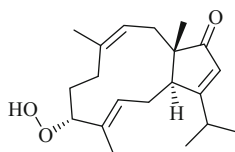
Cristaxenicin A (**210**) is a diterpenoid, isolated from the deep-sea Gorgonian *Acanthoprimnoa cristata* collected from Yakushima-Shinsono, Kagoshima Prefecture, southern Japan. Cristaxenicin A (**210**) exhibited antiprotozoal activity against both *Leishmania amazonensis* and *Trypanosoma congolense* with IC₅₀ values of

0.11–0.04 $\mu\text{g/ml}$, respectively, versus that of the positive control amphotericin B, which showed IC_{50} values of 0.019 and 0.813 $\mu\text{g/ml}$, respectively [110].



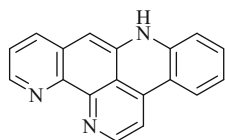
Cristaxenicin A (**210**)

Gorgonian octocorals of the genus *Eunicea*, which are abundant in the Caribbean Sea, is considered to be a rich source for antimalarial compounds. Numerous natural products have been isolated from members of this genus, and most of them exhibit unique structural features and pronounced biological activities. Chromatographic workup of a Colombian gorgonian coral of the genus *Eunicea* afforded eighteen diterpenes of the dolabellane type. Testing the inhibitory activity of these diterpenoids toward *P. falciparum* W2 (chloroquine-resistant) revealed that most of these compounds were active with IC_{50} values ranging from 9.4 to 59.6 μM . In particular, dolabellanone **9** (**211**) showed a pronounced activity with an IC_{50} value of 9.4 μM (2.99 $\mu\text{g/ml}$) [111].

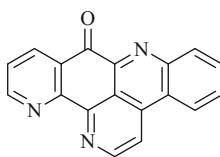


Dolabellanone 9 (**211**)

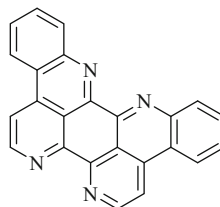
Chromatographic workup of the Australian ascidian *Polysyncraton echinatum* led to the isolation of three pyridoacridine alkaloids, including 12-deoxyascididemin (**212**), ascididemin (**213**), and eilatin (**214**). Compounds **212–214** are potent inhibitors of *T. brucei* with IC_{50} values of 0.02, 0.009, and 0.47 $\mu\text{g/ml}$, respectively [108].



12-Deoxyascididemin (**212**)

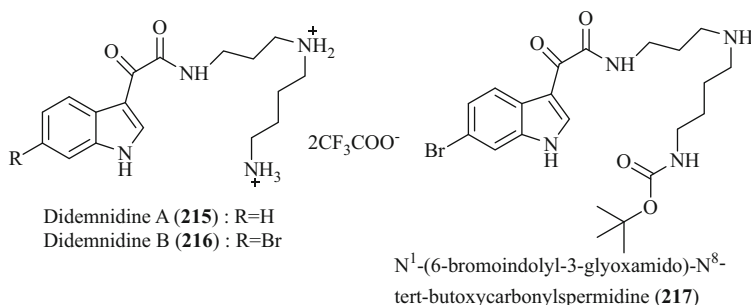


Ascididemin (**213**)



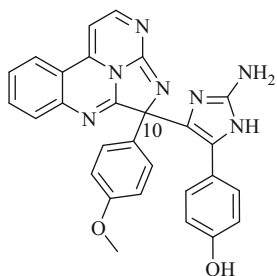
Eilatin (**214**)

Two new alkaloids named didemnidines A (**215**) and B (**216**) were isolated from the methanol extract of the marine organism, *Didemnum* sp. ascidian, obtained from Tiwai Wharf at 7 m depth, Tiwai Point, Southland, New Zealand. Compounds **215** and **216** feature an indole-3-glyoxylamide moiety connected to the N-1 position of spermidine which is rare in marine organisms. Didemnidine B (**216**) was active against the malaria parasite *P. falciparum* (IC₅₀ 5.9 µg/ml). The semisynthetic compound N¹-(6-bromoindolyl-3-glyoxamido)-N⁸-tert-butoxycarbonylspermidine (**217**) showed an IC₅₀ value against *P. falciparum* of 4.2 µg/ml and against *T. brucei rhodesiense* of 4.9 µg/ml, respectively [112].

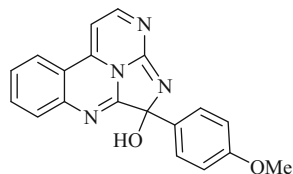


Chemical investigation of the marine ascidian *Eudistoma* sp. led to the isolation of three unusual related alkaloids, eudistidines A–C [113]. Among them, eudistidine C (1:1 mixture of **218a** and **218b**) represents a highly complex alkaloid, bearing fused pyrimidine and imidazole rings, a guanidine, as well as amidine moieties. The proton-deficient nucleus of eudistidine C was unambiguously assigned with the help of a new sensitive NMR pulse sequence LR-HSQMBC (long-range heteronuclear single-quantum multiple-bond correlation), allowing the detection of ⁴J_{CH} and ⁵J_{CH} correlations [114]. Total synthesis of eudistidine C confirmed the structure of this alkaloid, and a series of aryl-substituted (at C-10) derivatives were obtained. Eudistidine C epimers (**218a** and **218b**), eudistidine B (**219**), and their synthetic congeners (**220–224**) exhibited significant antiparasitic activity against chloroquine-sensitive D6 and chloroquine-resistant W2 *P. falciparum* strains with IC₅₀ values in the range from 0.26 to 3.4 µg/ml [113]. The antimalarial potency of these compounds was investigated employing a plasmodial lactate dehydrogenase activity assay with artemisinin and chloroquine as positive controls. Interestingly, **218a** showed an up to 1.7-fold stronger antimalarial activity toward both *P. falciparum* strains in comparison with its epimer **218b**. Among the tested compounds, **219** and its synthetic derivative **224** exhibited the most potent antiplasmodial effect against D6 and W2 strains with MIC values of 0.46 and 0.36 µg/ml (for **219**) and 0.48 and 0.26 µg/ml (for **224**), respectively. Moreover, a subsequent cytotoxicity assay against Vero cells (monkey kidney fibroblasts) revealed no apparent activity for **218a,b–224**, suggesting their selective antimalarial activity. Additionally, compounds **218b**, **220**, **221**, and **224** were found to inhibit the binding of the oncogenic transcription factor HIF-1α (hypoxia-inducible factor 1) to p300 [113]. Thus,

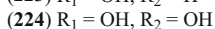
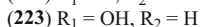
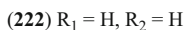
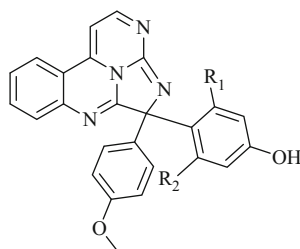
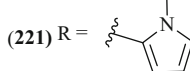
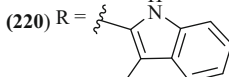
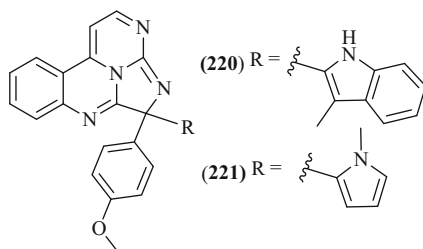
eudistidines C (**218a,b**) and B (**219**), as well as their synthetic analogues, carrying the tetracyclic eudistidine-like scaffold, represent a novel class of lead structures for the development of potent and selective antimalarial agents.



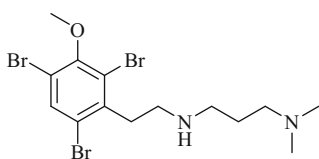
Eudistidine C (+)-R (**218a**)
Eudistidine C (-)-S (**218b**)



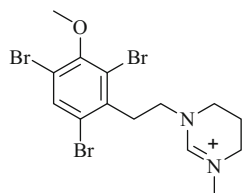
Eudistidine B (**219**)



Convolutamines I (**225**) and J (**226**) were obtained from the marine bryozoan *Amathia tortuosa* collected at the Bass Strait, Tasmania, Australia. Compounds **225** and **226** were shown to be active against the parasite *T. brucei brucei* with IC₅₀ values of 0.52 and 6.44 μg/ml, respectively [115] (Table 3.1).



Convolutamines I (**225**)



Convolutamines J (**226**)

Table 3.1 Summary of promising marine anti-infective compounds with identified/postulated modes of action (or molecular targets)

Source	Compound name	Mode of action/ molecular target	Spectrum of activity	Reference
<i>Pseudoalteromonas</i> sp. CMMED 290, associated with a nudibranch	2,3,5,7-Tetrabromobenzofuro [3,2-b]pyrrole (11)	Disrupts the bacterial cell wall membrane whereas human erythrocytes were not lysed upon application of the same dose of 11	Antibacterial; against MRSA (ATCC 43300)	[15]
<i>Streptomyces</i> sp. CNH365, isolated from a sea sediment sample	Anthracimycin (22)	Disrupts nucleic acid synthesis	Gram-positive bacteria, including MRSA	[19]
Fungus <i>Paecilomyces</i> sp. (-CMB-MF010), associated with a mollusk <i>Siphonaria</i> sp.	Viridicatumtoxin A (29), Spirohexaline (34)	Inhibits recombinant undecaprenyl pyrophosphate (UPP) synthase from <i>S. aureus</i>	MRSA and VRE	[22 23]
Marine fungus <i>Aspergillus</i> sp. Z120	Fonsecinones A (45) and C (46), Aurasperones A (47) and E (48)	Enoyl-acyl carrier protein reductase (FabI), a key enzyme in the bacterial fatty acid synthesis (postulated antibacterial target)	ESBL-producing <i>E. coli</i>	[27]
<i>Streptomyces</i> sp. CN Q3 43, isolated from a sea sediment sample	Bahamaolide A (91)	Inhibits the activity of <i>Candida albicans</i> isocitrate lyase (ICL)	Anti-fungal; especially <i>Candida albicans</i>	[52]
Actinobacterium <i>Actinomadura</i> sp., obtained from the ascidian <i>Ecteinascidia turbinata</i>	Forazoline A (102)	Dysregulates phospholipid homeostasis (postulated)	Anti-fungal; <i>C. albicans</i>	[54]
<i>Aspergillus terreus</i> Gwq-48, isolated from mangrove rhizosphere	Isoaspulvinone E (110)	Anti- H1N1 viral neuraminidase activity (NA)	Anti-viral; especially anti-influenza A H1N1	[65]
Deep-sea-derived fungus <i>Eurotium rubrum</i> F33	Neoechinulin B (129)	Binds to the HA1 subunit of hemagglutinin glycoprotein	Anti-influenza A H1N1	[69]
Deep-sea-derived fungus <i>Spiromastix</i> sp. MCCC 3A00308	Spiromastilactone D (130)	Binds to the HA1 subunit of hemagglutinin glycoprotein	Anti-influenza A H1N1	[33]

(continued)

Table 3.1 (continued)

Source	Compound name	Mode of action/ molecular target	Spectrum of activity	Reference
Brown seaweed <i>Styopodium zonale</i>	Atomaric acid (132)	Interacts with viral particles outside of the host cells thus preventing infection of the cell cultures; inhibits post-penetration stage. The compound has no effect on cellular receptors or on viral penetration	Antiviral; HMPV	[73]
	Epitaondiol (133)	Inhibits the penetration of viral particles into cells without affecting the post-penetration stages or interacting with cellular receptors		
	Methyl ester of atomaric acid (134)			
Marine sponge <i>Iotrochota baculifera</i>	Baculiferins L (149) and M (150)	Binding activities to HIV-1 targets including both Vif (viral infectivity factor of HIV-1) and human APOBEC3G (an innate intracellular antiviral factor)	Antiviral; HIV-1 III B virus	[82]

6 Conclusions

Natural products have been the most successful source of lead compounds for the treatment of infectious diseases since the dawn of the antibiotic era. In recent years, the emergence of resistant microbial strains against virtually all major classes of known anti-infectives poses a worldwide health threat, and thus further mining of natural sources for novel anti-infective agents is eminent [116]. Marine macro- and microorganisms have not been systematically investigated as a source of novel anti-infective agents, despite the fact that more than three-quarters of the Earth's surface is covered by the seas and oceans. Nevertheless, continued interest in the quest for structurally unprecedented bioactive secondary metabolites in combination with recent advances in sampling techniques has opened new avenues for the exploration of this fascinating ecological niche [7, 117]. Indeed, over the last decade, increased marine bioprospecting efforts were observed, particularly aimed at the deep-sea

environment, providing novel leads [118]. As a matter of fact, the potent proteasome inhibitor salinosporamide A, from the marine sediment actinomycete *Salinispora tropica*, has recently entered phase I clinical trials as an anticancer agent [119]. Undoubtedly, the marine environment represents an untapped source of bioactive chemical entities, many of which featuring new carbon frameworks without any terrestrial counterparts. This structural richness may give rise to potential scaffolds for the exploration of new biological targets, thus offering the advantage of the discovery of anti-infective leads with novel mechanisms of action tackling the global challenge posed by antibiotic resistance [120]. Several metabolites from various marine sources (i.e., sponges, bacteria, and fungi), described in this review, have already been identified as lead structures against both drug-sensitive and drug-resistant pathogens, such as the antiviral spiromastilactones (**130** and **131**), the antibacterial anthracimycin (**22**), or the antimalarial thiaplakortones (**198–201**) and salinipostins (**180–190**) possessing activities at (sub)micromolar concentrations [20, 33, 99, 105]. Hence, given the enormous potential of marine natural products in drug development, as demonstrated by the success stories of several marketed marine-derived drugs (i.e., Halaven®, Adcertis®, Yondelis®), it becomes increasingly apparent that the oceans hold great promises as the next source of novel anti-infective agents.

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