The Chemistry of Marine Bacteria

CHAPTER · JANUARY 2012

DOI: 10.1007/978-90-481-3834-0_3

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The Chemistry of Marine Bacteria

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Brian T. Murphy, Paul R. Jensen, and William Fenical

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Abstract

The world's oceans harbor extensive levels of bacterial diversity. Although much of this diversity remains uncharacterized, cultured representatives from a broad range of taxonomic groups are proving to be an important source of novel secondary metabolites. These metabolites include new carbon skeletons as well as compounds with a high degree of halogenation, a relatively common feature of marine-derived secondary metabolites. The bacteria being cultured from marine sources include new taxa, which are proving to be a particularly important source of new chemical entities. This chapter will provide the reader with a brief, though not comprehensive history of the secondary metabolites that

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E. Fattorusso, W. H. Gerwick, O. Taglialatela-Scafati (eds.),
Handbook of Marine Natural Products, DOI 10.1007/978-90-481-3834-0_3,

have been isolated from marine bacteria. The focus is on the taxonomic distribution of the producing strains and interesting structural features and biological activities of the compounds that are being discovered from marine bacteria.

3.1 Introduction

The marine environment is composed of a myriad of ecologically distinct habitats. Thus, it is not surprising that bacteria adapted to life in the marine environment are both diverse, phylogenetically distinct, and maintain survival adaptations that differ from bacteria that occur on land. One of the earliest physiological differences identified among marine-derived bacteria was the requirement of seawater, or more specifically sodium, for growth. Historically, bacteria demonstrating this physiological requirement were defined as obligate marine. However, there is no a priori reason to presume that bacteria lacking this specific marine adaptation should not be considered as part of the autochthonous marine bacterial community. It is common to culture bacteria from marine samples that grow equally well in media prepared with seawater or deionized water. Conversely, bacteria capable of growth on media prepared with salt concentrations equivalent to that of seawater can be readily cultured from nonmarine samples. These strains, it can be presumed, have the potential to grow in both environments. Studies of secondary metabolites from marine-derived bacteria have included strains that appear highly adapted to life in the ocean as well as more cosmopolitan taxa that occur both in the sea and on land. Both groups of bacteria are yielding interesting new secondary metabolites. The following sections highlight select secondary metabolites produced by various taxonomic groups of marine-derived bacteria.

After Alexander Fleming's discovery of penicillin in 1929, terrestrial microorganisms became the focal point for one of the most prolific drug discovery efforts in history. The discoveries of penicillin and later actinomycin (1940) led to the "Great Antibiotic Era" which yielded more than 120 drugs for the treatment of infectious diseases, cancer, elevated cholesterol, immunomodulation, and others. Some of the most important of these discoveries came from studies of the filamentous actinomycete bacteria, which because of their growth forms, were at one time considered to be fungi (hence the suffix "mycetes"). The actinomycetes are responsible for the majority of the antibiotics in clinical use today. From the period 1950 to 1990, most of the pharmaceutical companies invested heavily in microorganism-based drug discovery with financial commitments that reached in the vicinity of $10 B per year. The intensity of these explorations led to discoveries of new microorganisms from virtually all accessible terrestrial environments, from arctic and cold temperate regions to tropical environments. Interestingly, although the world's oceans occupy more than 70% of the surface of the Earth, this massive resource remained unexplored.

It is now clear that bacteria use small organic molecules, or secondary metabolites, for many important adaptive functions including communication and antagonism. The unique environmental conditions experienced by marine bacteria afford

opportunities for the selective production of secondary metabolites that are not observed outside of the marine environment. One clear example of this is the high level of halogenation observed among the secondary metabolites of marine bacterial origin.

This chapter highlights some of the structurally interesting secondary metabolites that have been isolated from cultured marine bacteria. It is beyond its scope to provide a comprehensive review of all metabolites produced by marine bacteria or to report on cyanobacterial metabolites, which will be addressed in another chapter. Instead, an overview of the metabolites produced by various taxonomic groups of heterotrophic marine bacteria is offered, with a few compounds highlighted for each group. For further information on specific topics, the reader is referred to review articles cited in the Bibliography [1–16]. With a few exceptions, articles published after June 2010 are not included.

This chapter begins with unicellular Gram-negative bacteria and ends with filamentous Gram-positive actinomycetes. It is written with a focus on chemistry and includes details about compound biological activity and the environmental source of the producing strains. We chose to organize this chapter following the framework used in Bergey's Manual of Determinative Bacteriology and "The Prokaryotes – A Handbook on the Biology of Bacteria" [17].

3.2 Secondary Metabolites from Gram-Negative Marine Bacteria

Gram-negative bacteria are ubiquitous in marine environments. They are more abundant than their Gram-positive counterparts and are the best studied of the marine bacteria from a taxonomic, ecological, and phylogenetic perspective. In terms of secondary metabolite discovery, fewer compounds have been discovered from Gram-negative marine bacteria, possibly because these bacteria have not been studied as intensively with this goal in mind or that they do not maintain genes involved in secondary metabolism as commonly as Gram-positive forms.

3.2.1 Proteobacteria

The Proteobacteria, formerly known as purple bacteria, constitute the largest and most physiologically diverse bacterial phylum. Indicative of this diversity, the phylum was named after the Greek god Proteus, son of Poseidon, who had the ability to assume different shapes. This phylum comprises the majority of medically and agriculturally significant Gram-negative bacteria. Found within the β-, δ-, and γ-divisions of the Proteobacteria are bacteria that maintain gliding motility. These include a large group of chemically prolific gliding bacteria called the myxobacteria, many of which form fruiting bodies under low-nutrient conditions. In the following two sections, proteobacterial secondary metabolites are organized by class.

3.2.1.1 α- and δ-Proteobacteria

Categorized within the phylum Proteobacteria are the classes α- and δ-Proteobacteria. The mitochondria, found in the eukaryotic cell, are believed to have originated from α-Proteobacteria, a class that is crucial to the regulation of Earth's carbon, sulfur, and nitrogen cycles. The majority of the α-Proteobacteria are rod-shaped. This class includes prokaryotic predators (*Bdellovibrio*), strains that have the ability to glide (myxobacteria), and those that can reduce sulfur. To date, relatively few secondary metabolites have been identified from marine representatives within these classes.

From the cells of an undescribed species of the unicellular marine α-proteobacterium *Agrobacterium*, agrochelin A (**1**), a cytotoxic thiazole alkaloid was isolated [18, 19]. This strain was cultivated from a tunicate collected in the Mediterranean Sea off the east coast of Spain. It displayed inhibitory activity against a panel of tumor cell lines and was shown to form a complex with Zn^{2+} ions. In the search for endothelin-converting enzyme (ECE) inhibitors, B-90063 (**2**), a dimeric oxazole–pyridone analog was isolated from an undescribed species of the marine α-proteobacterium *Blastobacter* [20]. This strain was isolated from the water column on the coast of Ojika Peninsula, Japan, and required seawater for growth. It exhibited antagonistic activities toward endothelins, peptides responsible for the constriction of blood vessels. In addition to the two aforementioned metabolites from α-Proteobacteria, two polyketide-derived metabolites were discovered from two marine-derived myxobacterial strains. An ethylated polyene-substituted pyrone metabolite (phenylnannolone A, **3**) was isolated from the marine δ-proteobacterium *Nannocystis exedens* [21]. Although polyene pyrones have been reported from various terrestrial sources, the presence of an ethyl group on the polyene chain represented a novel deviation from this class of molecules. Biosynthetic studies suggested unprecedented biochemical reactions are employed to form phenylnannolone A. In a program designed to isolate marine myxobacteria, the δ-proteobacterium *Haliangium luteum* was isolated from a marine alga collected in Kanagawa, Japan. This myxobacterium required approximately 2–3% NaCl for growth and the production of the metabolite haliangicin (**4**) [22, 23]. Compound **4** was found to display antifungal activity toward a number of fungi, including the pathogenic strain *Phytophthora capsici* (Fig. 3.1).

3.2.1.2 γ-Proteobacteria

The γ-Proteobacteria consist of over 180 genera and more than 750 species (as of 2007) and are the largest class within the phylum Proteobacteria. This class contains several human and animal pathogens including *Escherichia coli*, *Salmonella typhi* (typhoid fever), *Yersinia pestis* (plague), *Vibrio cholerae* (cholera), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Of all Gram-negative marine bacteria, the γ-Proteobacteria harbor the greatest number of secondary metabolites published in the literature, and these metabolites subsequently exhibit the most structural and functional diversity. Four families within this class, namely, Vibrionaceae, Alteromonadaceae, Pseudoalteromonadaceae, and

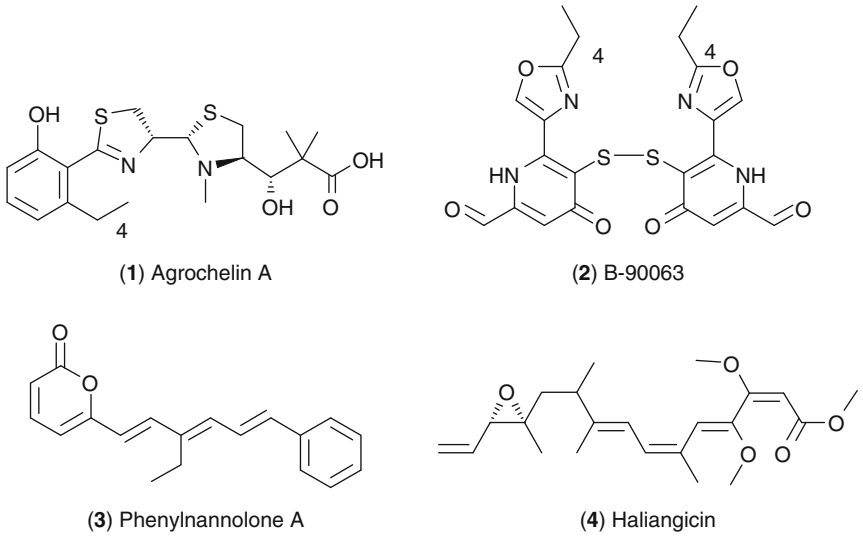


Fig. 3.1 Secondary metabolites from marine α- and δ- Proteobacteria

Pseudomonadaceae, contain genera responsible for the production of the majority of molecules from the Proteobacteria.

Members of the family Vibrionaceae are typically rod-shaped, facultative anaerobes and include several human pathogens such as *V. cholerae*. In the following few examples, indole natural products were isolated from two diverse marine environments. First, an undescribed species of *Vibrio* was isolated from an Okinawan sponge, *Hyrtios altum*. This bacterium produced an unusual indole trimer, trisindoline (**5**) [24]. Similarly, the toxic mucus of the boxfish *Ostracion cubicus* was found to harbor the microbial strain *V. parahaemolyticus*. This fish excretes mucus in response to stress. A structurally similar *bis*-indole (vibrindole A, **6**) was isolated from this strain and exhibited antibacterial activity against a number of pathogenic bacteria [25]. Also isolated from a *Vibrio* sp. colonizing the surface of the soft coral *Sinularia polydactyla* in the Red Sea (Aquaba, Jordan) was aqabamycin E (**7**) [26].

In a program designed to discover bioactive metabolites from poorly studied taxa, the antibacterial cyclic depsipeptide unnarmicin A (**8**) was isolated from cultures of a bacterium of the genus *Photobacterium*, family Vibrionaceae [27]. The strain was isolated from the water column near Okinawa, Japan. Unnarmicin A exhibited inhibitory activity toward a few α-Proteobacterial strains of the genus *Pseudovibrio* that are common culturable strains from the marine environment. Antimicrobial activity against Gram-positive bacteria (*Bacillus subtilus*) and microalgae (*Prorocentrum micans*) was discovered in association with the unusual magnesium-containing metabolite magnesidin A (**9**) [28, 29]. Magnesidin A is produced by *Vibrio gazogenes*, a pink-colored bacterium isolated from the marine

alga *Caulerpa peltata*, though it originally appeared several years earlier as an impure mixture from a marine *Pseudomonas* sp.

One final example of a natural product isolated from the family Vibrionaceae is that of a rare boron-containing small molecule involved in cell-to-cell bacterial communication known as quorum sensing. AI-2 (**10**) is a fused, bicyclic boronic acid anion that acts as an autoinducer, or an extracellular signaling molecule. AI-2 was first identified in the marine bacterium *Vibrio harveyi*, but its structure eluded the scientific community until it was cocrystallized with its sensor protein target LuxP [30]. AI-2 was found to be one of two molecules that regulate bioluminescence in *V. harveyi* and is one of a growing number of signaling molecules isolated from marine microorganisms. It is now accepted that communication among microbes via secondary metabolites is essential to a variety of processes from bioluminescence to biofilm formation, and even secondary metabolite production (Fig. 3.2).

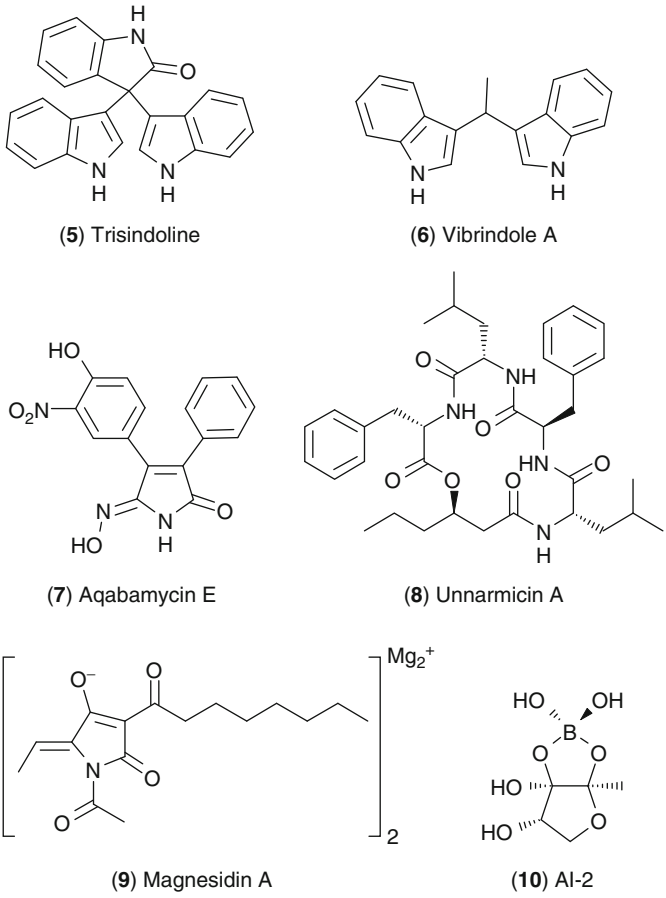


Fig. 3.2 Secondary metabolites from marine γ-Proteobacteria (Vibrionaceae)

As of 2007, the family Pseudomonadaceae contained approximately 15 genera characterized by straight or curved rods. It was from a marine strain of *Pseudomonas bromoutilis* that the first marine microbial natural product, pentabromopseudilin (**11**), was identified in 1966 [31]. This antibiotic contains an unusual framework, possessing a small carbon skeleton while the majority of its molecular mass is derived from bromine. Pentabromopseudilin was known to possess biological activity; however, it was not until 2009 that its specific mechanism of action was identified. It was shown to potently inhibit myosin, a motor protein that facilitates the transport of other important proteins such as tubulin [32]. The potential therapeutic applications of selective myosin inhibitors include the treatment of cancer, heart failure, and malaria.

Within the family Alteromonadaceae is the genus *Alteromonas*, which was originally described in 1972 in order to encompass a number of Gram-negative *Pseudomonas*-like strains isolated from the marine environment. A tripeptide-derived metabolite, **12**, with a novel β-aminopimelic acid component was isolated from a partly classified bacterium falling within the genera *Pseudomonas*/*Alteromonas* [33]. This bacterium was found associated with the common black sea sponge *Dysidea fragilis*. Another sponge associate, an undescribed species of *Alteromonas*, was shown to produce the macrocyclic lactam alteramide A (**13**) [34]. This bacterium was isolated from a sample of the sponge *Halichondria okadai* collected in Kanagawa, Japan, and the resulting metabolite displayed cytotoxicity toward a number of cancer cell lines. An additional *Alteromonas* species that has yet to undergo complete taxonomic identification is *Alteromonas* cf. *rava*. Isolated from seawater, this bacterium produced thiomarinol B (**14**), which displayed antibacterial activity against various Gram-negative and Gram-positive bacteria [35]. This metabolite is a hybrid structure of two previously known antibiotic classes: the pseudomonic acids and the pyrrothines. Finally, an undescribed species of *Alteromonas* was found to colonize the surface of shrimp embryos (*Palaemon macrodactylus*). This bacterium was found to produce a small molecule (isatin, **15**) that chemically defended the embryos from the common crustacean fungal pathogen *Lagenidium callinectes* [36]. This remains a rare example of the functional elucidation of a secondary metabolite within the ecological niche of its producing microorganism.

Within the family Pseudoalteromonadaceae is the genus *Pseudoalteromonas*, which is the source of a large number of marine natural products. Among them is a brominated korormicin derivative (**16**) isolated from a *Pseudoalteromonas* strain collected from the surface of an undescribed species of the macroalga *Halimeda* from the Palauan Sea [37]. The original metabolite korormicin inhibited Na^+-translocating NADH-quinone reductase, a process of Na^+ ion translocation that is prevalent in Gram-negative bacteria [38]. This property suggested that korormicin may be useful as an antibiotic against any bacterial strain requiring a sodium pump for survival. The marine strain *Pseudoalteromonas maricaloris*, which was isolated as an epibiont of the Australian sponge *Fascaplysinopsis reticulata*, produced a brominated cyclic peptide (bromoalterochromide A′, **17**) that possessed a unique peptidic chromophore [39]. This, and related peptides, exhibited cytotoxicity

toward developing eggs of the sea urchin *Strongylocentrotus intermedius*, thus suggesting a possible ecological role for the metabolites.

An unidentified species of *Halomonas* from the family Pseudomonadaceae, collected from a water sample in the East Frisian Wadden Sea, Germany, produces the metabolite HPPD-1 (**18**) [40]. It is a diarylpyrrole that exhibited chemopreventive properties. This study provided a nice example of the optimization of growth conditions to boost production of target metabolites. Since laboratory culture conditions do not perfectly represent the environment in which the bacterium previously existed, experimenting with different culture conditions may greatly alter the ability of a microorganism to produce secondary metabolites. One final example of a natural product from a *Halomonas* sp. is the amphiphilic siderophore loihichelin A (**19**) [41]. The producing strain was studied as part of an effort to explore reduced Fe-, Mn-, or S-requiring microorganisms from basaltic rocks. The strain was isolated at approximately 1,700 m from partially weathered surfaces of submarine basalts at the Loihi Seamount, an active Hawaiian volcano laden with Fe(II)-rich hydrothermal fluids. The loihichelins differ from other peptidic siderophores by an increased hydrophilicity due to their longer peptide and shorter fatty acid chains. Their role in nutrient acquisition and interactions with basaltic rock is the topic of ongoing studies (Fig. 3.3).

3.2.2 Bacteroidetes

The phylum Bacteroidetes contains some bacteria that are also considered gliding bacteria. They are typically chemoheterotrophs, found in a diversity of environments, and play important roles in the breakdown of high-molecular-weight dissolved organic matter. There are relatively few studies involving the isolation of natural products from genera within the phylum Bacteroidetes; a few examples are presented below.

Although some bacteria contain terpenoid biosynthetic pathways for the production of carotenoid pigments, bacteria only rarely produce terpenoid secondary metabolites. There are a couple of notable exceptions. From the gliding bacterium *Saprospira grandis* (Saprospiraceae), which captures and digests other bacteria, four diterpenoids of the neoverrucosane class, Fig. 3.4 (**20**), were isolated [42]. From an undescribed species of *Rapidithrix* (family Flammeovirgaceae), which also maintains gliding motility, a new linear hybrid NRPS–PKS peptide antibiotic called ariakemicin A (**21**) was isolated [43]. This compound exhibited selective antibiotic activity against Gram-positive bacteria and was especially potent against the pathogen *Staphylococcus aureus*.

The unusual metabolites **22**–**25** have also been isolated from two strains of *Cytophaga* (BIO137 and BIO138) within the family Flexibacteriaceae [44]. Strains BIO137 and BIO138 were isolated from biofilms in the North Sea. These new naturally occurring polysulfides were the result of an effort to identify volatile molecules that are typically overlooked in natural product studies. The investigators used gas chromatography coupled with mass

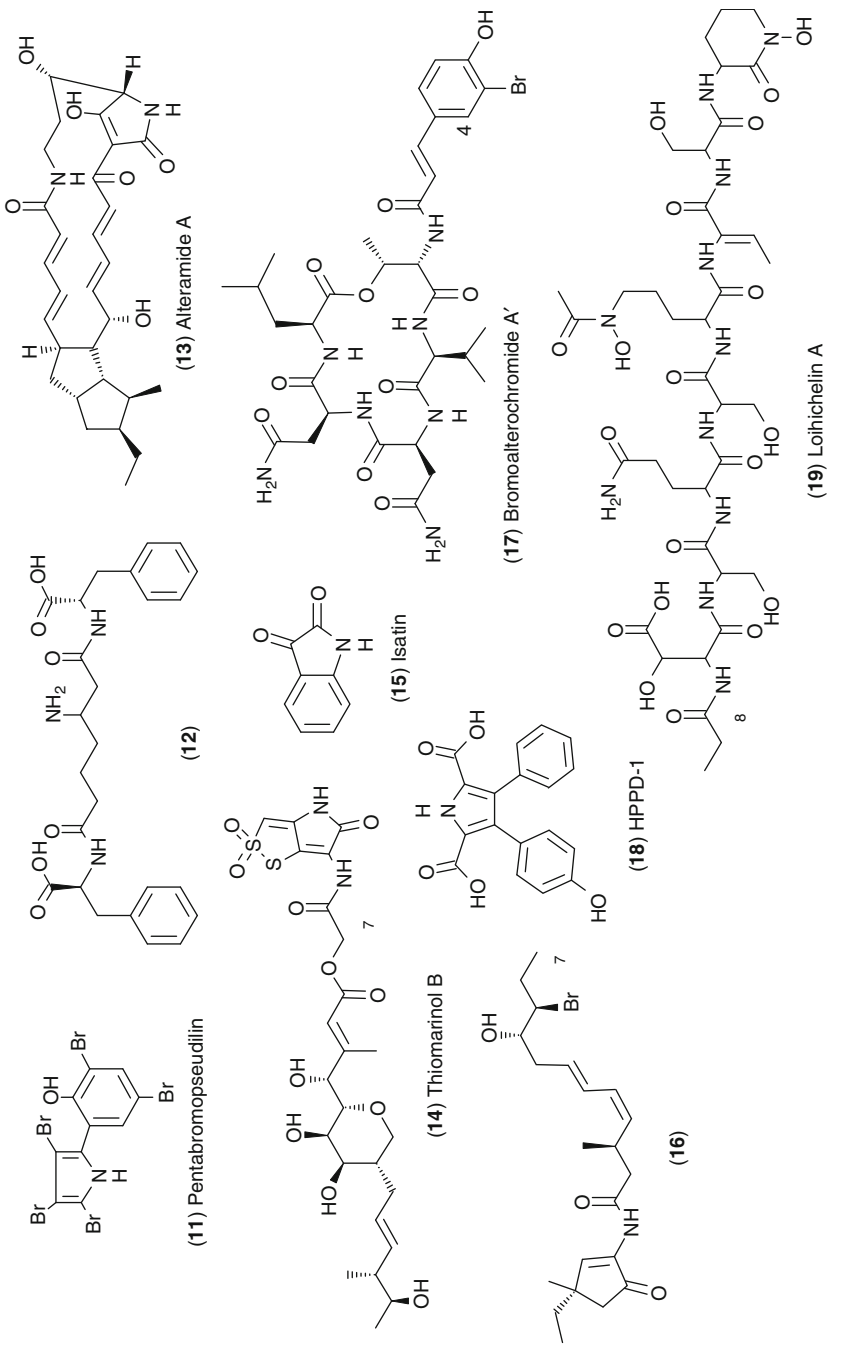


Fig. 3.3 Secondary metabolites from marine γ-Proteobacteria

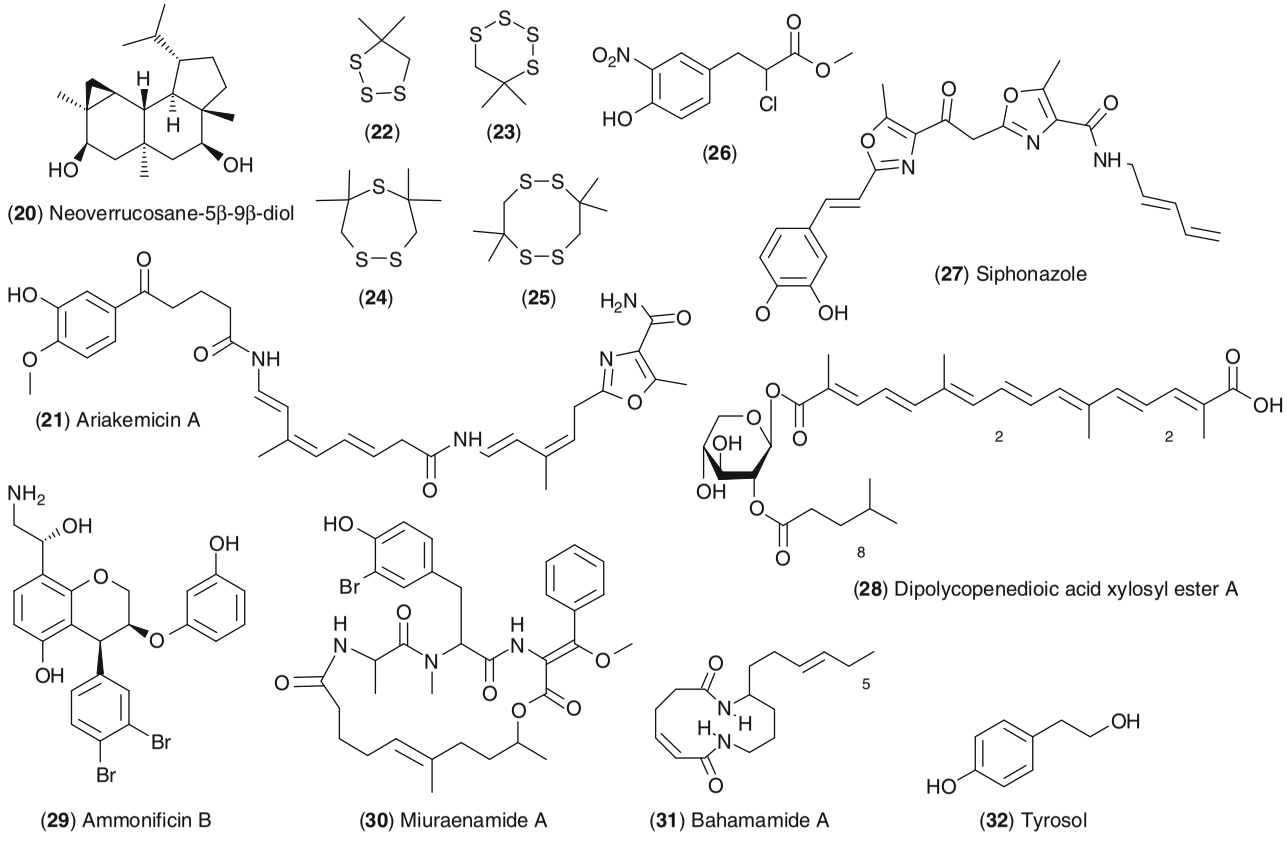


Fig. 3.4 Secondary metabolites from remaining marine Gram-negative bacteria

spectrometry to analyze the volatile components of these strains, and the result was the identification of seven unique thiacycloalkanes, four of which are presented here. Additional metabolites from this family include 25 aromatic nitro derivatives isolated in small yields from the psychrotolerant (ability to survive in cold temperatures) bacterium *Salegentibacter* sp., one of which is presented here (**26**) [45]. These were isolated as a result of efforts to explore secondary metabolite production by marine microorganisms in Arctic and Antarctic habitats.

3.2.3 Chloroflexi

The phylum Chloroflexi is highly diverse and can be divided into five major subdivisions. It is predominantly represented by Gram-negative, filamentous strains with unusual cell envelopes containing either no or little peptidoglycan in their cell walls. It is also the only phylum that consists entirely of bacteria that possess gliding motility. In an effort to expand upon what little is known about the capacity of strains from this phylum to produce secondary metabolites, siphonazole (**27**), a new class of natural products containing both oxazole and aromatic moieties, was isolated from a *Herpetosiphon* sp. [46].

3.2.4 Verrucomicrobia

The phylum Verrucomicrobia, which was established in 2001, is composed of strains that exhibit coccoid or rod-shaped morphologies. They have been observed in environments ranging from the cold sediment of the Arctic Ocean to the tissues of the giant tubeworm *Riftia pachyptila*, an organism found near deep-sea hydrothermal vents. A novel glycosylated polyene named dipolycopenedioic acid xylosyl ester A (**28**) was isolated from the strain *Rubritalea squalenifaciens* within the family Verrucomicrobiaceae [47]. This strain was isolated from the marine sponge *Halichondra okadai*. This molecule was isolated as part of a search for rare carotenoid-like molecules from pigmented marine bacteria.

3.2.5 Aquificae

Within the phylum Aquificae is the order *Aquificales*, members of which are chemolithoautotrophic thermophiles. The bacterium *Thermovibrio ammonificans*, within the family Desulfurobacteriaceae, was isolated from a deep-sea hydrothermal vent on the East Pacific Rise. *T. ammonificans* is a thermophilic, anaerobic strain that produced the dibrominated hydroxyethylamine chroman derivative ammonificin B (**29**) [48]. To date, this is the only known secondary metabolite isolated from this group of bacterial extremophiles.

3.2.6 Undescribed Gram-Negative Marine Bacteria

Taxonomic information has not always been provided from bacterial strains from which natural products have been reported, although there is a movement underway to at least require the deposition of a partial 16 S rRNA gene sequence in association with the report of a bacterial natural product. The following three examples are of metabolites isolated from undescribed Gram-negative marine bacteria. From a slightly halophilic myxobacterial strain (SMH-27-4) isolated from a shallow water sediment collected off the Miura Peninsula, Japan, the antibiotic depsipeptide miuraenamide A (**30**) was isolated [49]. This was part of ongoing attempts to explore the secondary metabolite potential of slow-growing marine-derived strains. Compound **30** exhibited selective inhibition of the phytopathogenic fungus *Phytophthora* sp. and most likely targeted the electron transfer system of the mitochondrial respiratory chain. Bahamamide A (**31**), a 12-membered ring *bis*-amide that is not commonly observed in nature, was isolated from strain CNE-852 [50]. This strain was isolated from a sediment sample collected in the Bahamas. In an unusual example of symbiosis, embryo surfaces of the American lobster (*Homarus americanus*) were colonized almost entirely by a rod-shaped Gram-negative epibiotic bacterial strain, SGT-76. This strain produced the simple antifungal molecule tyrosol (**32**), which inhibited the growth of the common crustacean pathogenic fungus *Lagenidium callinectes*, thus suggesting a potential ecological function for the natural product and its producing bacterium [51] (Fig. 3.4).

3.3 Secondary Metabolites from Gram-Positive Marine Bacteria

Marine Gram-positive bacteria have been poorly studied by marine microbiologists relative to their Gram-negative counterparts. This may in part be due to the general observation that they are numerically less abundant in most marine habitats. Like terrestrial Gram-positive bacteria, however, marine strains have proven to be a rich source of secondary metabolites. In fact, the majority of natural products that have been characterized from marine bacteria are from Gram-positive strains. Representative compounds and producing organisms are described below.

3.3.1 Firmicutes

The name Firmicutes is derived from the Latin words “firmus” and “cutis,” which mean “strong” and “skin,” respectively. These bacteria are generally unicellular and contain a low G + C content. Within the phylum Firmicutes is the family Bacillaceae, which is typically comprised of rod-shaped cells capable of producing endospores. This family produces the majority of the secondary metabolites reported from the phylum, predominantly because of the chemical capacity of the

genus *Bacillus*. *Bacillus* is one of just under 40 genera in the family Bacillaceae and includes pathogenic strains such as *B. anthracis*, the causative agent of anthrax. Terrestrial bacilli are well-known producers of antibiotics as evidenced by bacitracin, polymyxin, tyrocidin, and gramicidin. As might be expected, marine-derived *Bacillus* strains are also proving to be a rich source of novel secondary metabolites.

From an undescribed deep-sea sediment bacterium (later isolated from a marine strain of *Bacillus amyloliquefaciens*), a novel 24-membered lactone (macrolactin A, **33**) representing a new class of macrolides was isolated [52, 53]. Macrolactin A exhibited considerable antibacterial activity and also antiviral activity against *Herpes simplex*. To date, there have been at least 18 macrolactins isolated, and nearly all have been produced by marine *Bacillus* strains (*B. marinus*, *B. subtilis*, *B. polyfermenticus*, *B. amyloliquefaciens*, and *Bacillus* spp.) [54].

A *Bacillus cereus* strain isolated from the Japanese sponge *Halichondria japonica* was found to produce a cyclic peptide (YM-266183, **34**) composed of a pyridine ring, six thiazole rings, and a number of unusual amino acids [55]. This peptide displayed antibacterial activity selective against a number of Gram-positive drug-resistant strains. Another *B. cereus* strain, isolated from the sea snail *Littorina* sp., was found to produce the potently cytotoxic cyclic peptide homocereulide (**35**) [56], while a strain of *B. silvestris* isolated from a crab collected off Chile was found to produce the antibacterial cyclic peptide bacillistatin 1 (**36**) [57]. Cyclic peptides were also isolated from two undescribed *Bacillus* strains, one sediment-derived strain produced the cyclic heptapeptide halobacillin (**37**), and one collected in Papua New Guinea produced the antibiotic cyclic decapeptide loloatin A (**38**) [58].

Another undescribed *Bacillus* species, isolated from the tissues of a tube worm collected in waters off Papua New Guinea, produced the unique nonribosomal peptide bogorol A (**39**) [59]. This linear, cationic peptide is thought to kill bacteria quickly by physically disrupting the cell membrane, and this structural class was proclaimed as a new template for cationic peptide antibiotics. Using the bogorol family of antibiotics, methods for determining the amino acid sequence of cationic peptides was subsequently described [60].

In a feeding study, an undescribed *Bacillus* sp. produced the antibiotic selenohomocysteine (**40**) when grown in a medium containing seleno-DL-methionine [61]. Compound **40** was antibacterial against the Gram-positive bacterial strain *Micrococcus luteus*. In another study, *B. subtilis* was isolated from the intestines of a sardine (*S. melanosticta*) collected off Japan and shown to produce the isocoumarin metabolite bacilosarcin A (**41**) [62]. Although no antibiotic activity was observed, it did contain an unprecedented bicyclic ring system combined with an otherwise common terrestrial metabolite.

In general, marine bacilli have been implicated in the production of cyclic peptides or polyketide-derived macrolides that possess antibacterial activity. The occurrence of macrolactins is, to this date, highly conserved among the genus *Bacillus*.

Of the non-*Bacillus* strains of the family Bacillaceae, a strain of *Halobacillus halophilus* produced the novel C_{30} carotenoid (**42**) in a study aimed at isolating

carotenoids from pigmented bacteria [63]. *Halobacillus salinus* was shown to produce secondary metabolites that inhibit quorum-sensing-controlled phenotypes in Gram-negative bacteria [64]. This strain was isolated from a sea grass sample collected off the coast of Rhode Island. In cocultivation experiments, the bacterium was found to excrete a metabolite that inhibited bioluminescence in *Vibrio harveyi*. Subsequently, the phenethylamide derivative *N*-(2′-phenylethyl)-isobutyramide (**43**) was isolated and hypothesized to competitively inhibit typical Gram-negative bacterial signaling molecules (*N*-acyl homoserine lactones) and thereby act as bacterial quorum-sensing agonists.

An additional family within the phylum Firmicutes is the Thermoactinomycetaceae. All members of this taxon contain *meso*-diaminopimelic acid (meso-A_2pm) in their cell wall and are generally classified as aerobic, chemoorganotrophic microorganisms. From an undescribed species of the genus *Thermoactinomyces*, the potent antitumor thiopeptide mechercharmycin A (**44**) was discovered [65]. The producing strain was isolated from sea mud collected from Mercherchar in the Republic of Palau. In later studies, this molecule along with its analogs were shown to induce apoptosis in certain cancer cells [66] (Fig. 3.5a, b).

3.3.2 Actinobacteria (Actinomycetes)

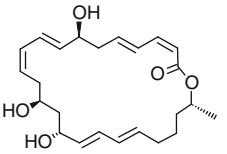
In 1875, the first actinomycete genus *Strepthrotrix* was described, although because of its filamentous morphology, it was originally reported to be a fungus. To differentiate actinomycetes from fungi, the order Actinomycetales was proposed in 1917. Actinomycetes are high G + C content Gram-positive bacteria and are physiologically and morphologically quite diverse. A majority of these bacteria produce branching filaments and form mycelia. There are approximately 50 families containing 195 validated genera (as of 2007) within the phylum Actinobacteria, although only a few families account for more than half of microbial antibiotics discovered to this date, most of which are produced by the genus *Streptomyces*.

3.3.2.1 Streptomycetaceae

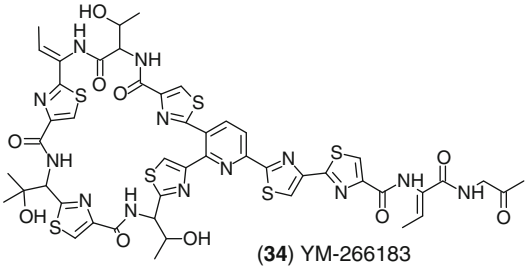
Within the family Streptomycetaceae, members of the genus *Streptomyces* are the source of the majority of secondary metabolites isolated from marine-derived bacteria. Although the genus *Streptomyces* is common in terrestrial soils, recent studies have revealed that phylogenetically distinct marine groups can be resolved within this highly diverse genus. The following section presents a compilation of unique structures that may be either of rare occurrence or completely unprecedented from terrestrial bacteria. Descriptions of their chemical and biological properties will be brief, as the focus is intended to be on the diversity of the structures isolated. Additional metabolites discovered from marine-derived *Streptomyces* sp. can be found in Table 3.1 and Figs. 3.6 and 3.7 [67–85].

An undescribed *Streptomyces* species (Merv8102) isolated from a sediment sample collected in the Mediterranean Sea along the Egyptian coastline produced

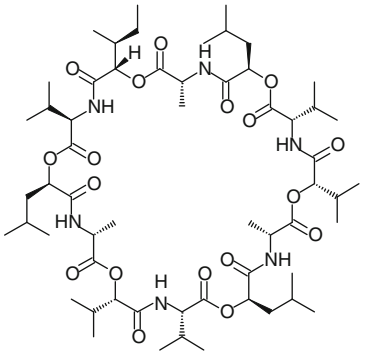
a



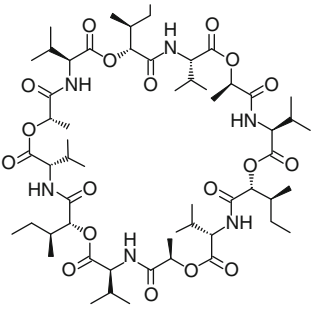
(**33**) Macrolactin A



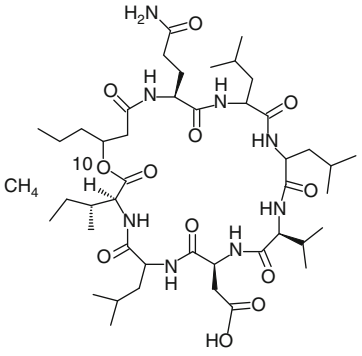
(**34**) YM-266183



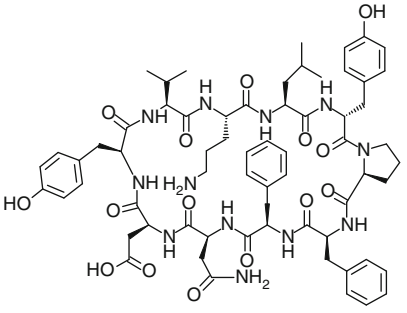
(**35**) Homocereulide



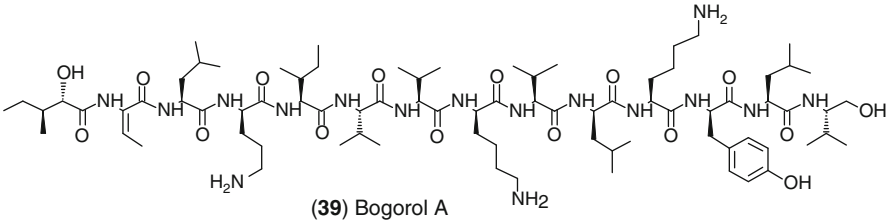
(**36**) Bacillistatin 1



(**37**) Halobacillin



(**38**) Loloatin A



(**39**) Bogorol A

Fig. 3.5 (continued)

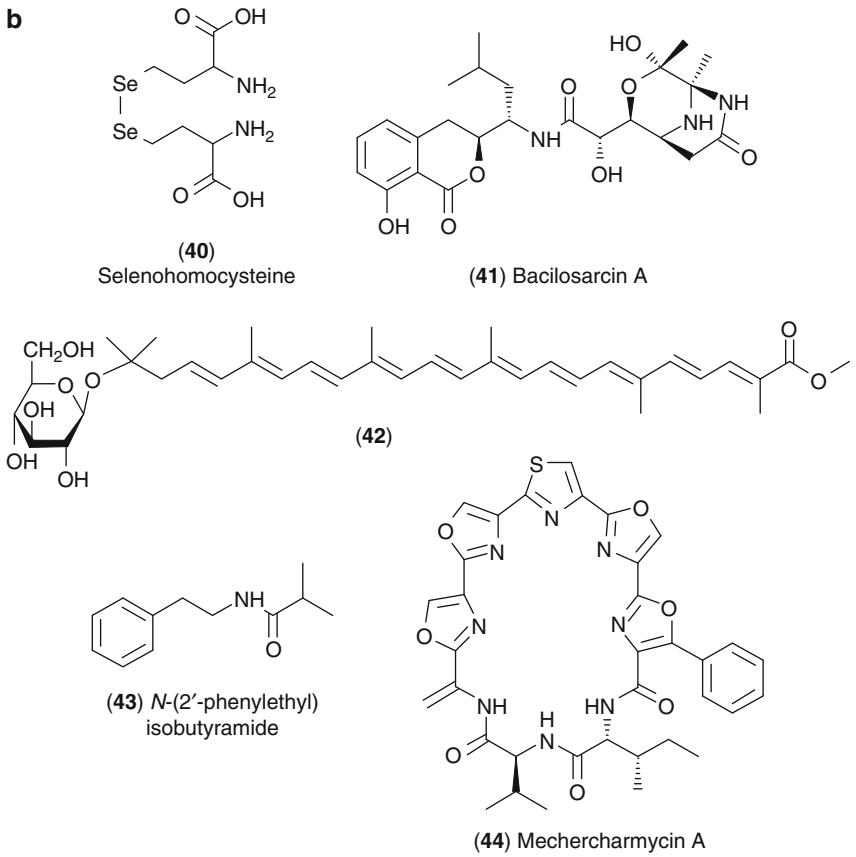


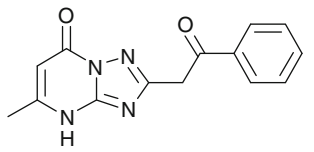
Fig. 3.5 Secondary metabolites from marine Bacillaceae

the first reported naturally occurring triazolopyrimidine antibiotic (essramycin, **45**) [86]. Gutingimycin (**46**), a complex guanine/trioxacarcin A conjugate, was also isolated from an undescribed *Streptomyces* species [87]. The compound was cytotoxic and showed antibacterial activity against a variety of Gram-positive and Gram-negative strains. The biological activity of this complex metabolite was hypothesized to be the result of nucleophilic attack on bacterial DNA resulting in strand cleavage thus offering a potential explanation for its potent cytotoxicity.

Another new structure was obtained from a *Streptomyces* strain cultured from a sediment sample collected in the Sea of Cortez, Baja California Sur, Mexico. Culture of this organism produced the angucycline-like cytotoxic quinone marmycin B (**47**) [88]. This was the first report of an angucycline with both C- and N-glycoside linkages, which resulted in a novel hexacyclic skeleton. From subunits of a common metabolite, new members of a novel chemical scaffold were

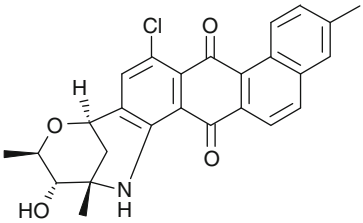
Table 3.1 Additional secondary metabolites produced by marine *Streptomyces* spp.

Compound	Source	Properties	Reference
(**56**) Aburatubolactam A	*Streptomyces* sp.	Polycyclic macrolactam exhibiting diverse bioactivity	Bae et al. [67]
(**57**) Altemicidin	*Streptomyces* sp.	Monoterpene alkaloid with rare azaindene skeleton	Takahashi et al. [68]
(**58**) Aureoverticillactam	*S. aureoverticillactus*	22-Membered cytotoxic macrocyclic lactam	Mitchell et al. [69]
(**59**) Bioxalomycin α1	*Streptomyces* sp.	Complex aromatic, polycyclic alkaloid	Bernan et al. [70]
(**60**) Caboxamycin	*Streptomyces* sp.	A deep-sea benzoxazole antibiotic active against *B. Subtilis*	Hohmann et al. [71]
(**61**) Chinikomycin A	*Streptomyces* sp.	Chlorinated, aromatic manumycin derivatives; antitumor activity	Li et al. [72]
(**62**) Daryamide A	*Streptomyces* sp.	Cytotoxic and weak antifungal metabolite	Asolkar et al. [73]
(**63**) Glaciapyrrole A	*Streptomyces* sp.	Rare pyrrole-sesquiterpene metabolite	Macherla et al. [74]
(**64**) Halawanone A	*Streptomyces* sp.	Of the isochromane class of quinone antibiotics	Ford et al. [75]
(**65**) Halichomycin	*S. hygroscopicus*	16-Membered macrolactam isolated from fish; cytotoxic agent	Takahashi et al. [76]
(**66**) JBIR-34	*Streptomyces* sp.	Strain was selected on the basis of a screen for unique NRPS genes	Motohashi et al. [77]
(**67**) Lajollamycin	*S. nodosus*	Rare spiro-β-lactone-γ-lactam unit; antitumor and antibiotic activity	Manam et al. [78]
(**68**) Mansouramycin D	*Streptomyces* sp.	Compound class showed cytotoxicity toward a panel of tumor cells	Hawas et al. [79]
(**69**) Marineosin A	*Streptomyces* sp.	Cytotoxic; hypothesized to derive from novel prodigiosin pathway	Boonlarppradab et al. [80]
(**70**) Salinamide A	*Streptomyces* sp.	Complex bicyclic hexadepsipeptide; anti-inflammatory activity	Trischman et al. [81]
(**71**) Splenosin A	*Streptomyces* sp.	Inhibitor of pro-inflammatory cytokine production (antiasthma)	Strangman et al. [82]
(**72**) SS-228Y	*Chainia purpurogena* (e.g., *Streptomyces*)	Antibiotic; one of the earliest bioactive molecules isolated from a marine actinomycete	Okazaki et al. [83]
(**73**) Streptokordin	*Streptomyces* sp.	Cytotoxic metabolite of the methylpyridine class	Jeong et al. [84]
(**74**) Teleocidin A_1	*Streptomyces* sp.	Isolated from marine-obligate *Streptomyces*, a sponge colonizer	Izumikawa et al. [85]

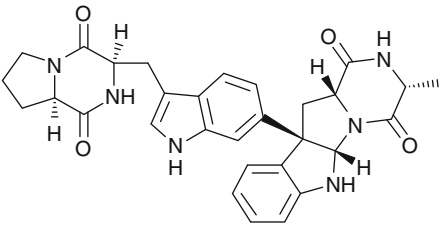


(**45**) Essramycin

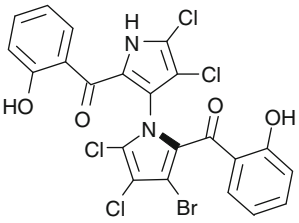
(**46**) Gutingimycin



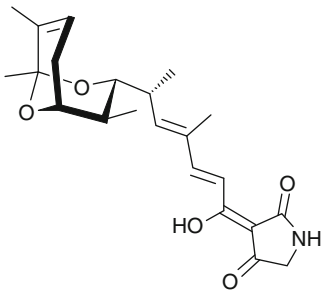
(**47**) Marmycin B



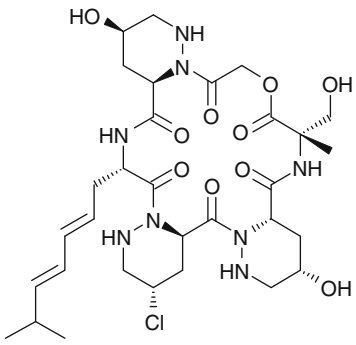
(**48**) Naseseazine A



(**50**) Marinopyrrole B



(**49**) Tirandamycin C



(**51**) Piperazimycin A

Fig. 3.6 (continued)

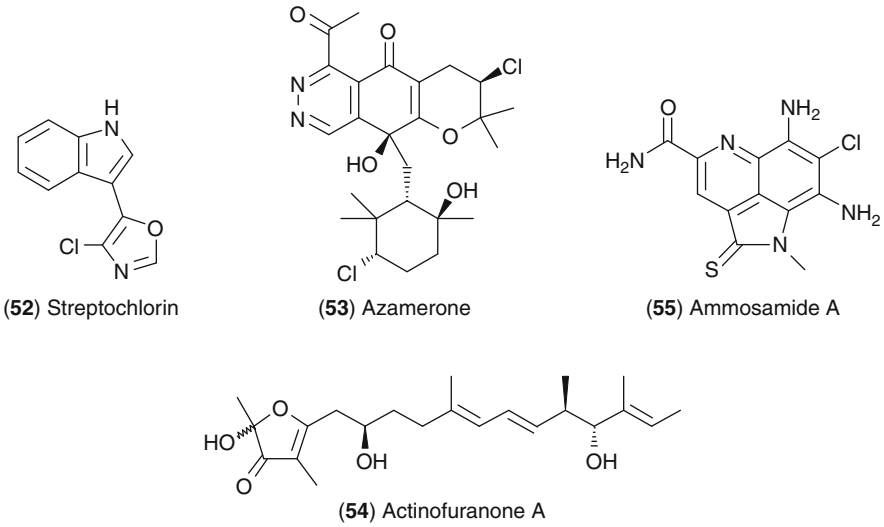
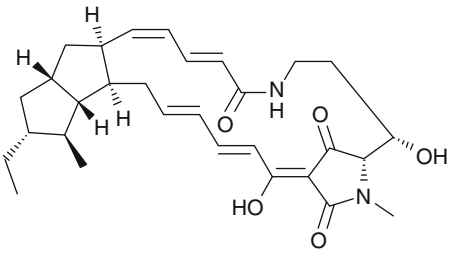


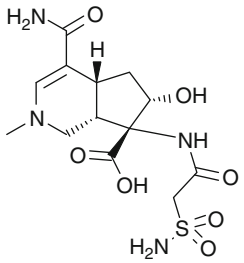
Fig. 3.6 Structures of secondary metabolites from marine *Streptomyces*

observed from a *Streptomyces* strain cultured from a Fijian marine sediment [89]. Naseseazine A (**48**) and two other classes of dimeric diketopiperazines (asperazines and pestalazines, produced by fungi; not shown here) were hypothesized to result from indole resonance from which nucleophilic attack yielded differing regioselective substitution patterns around the nucleophile's aromatic ring [89]. In a study that afforded the known antibiotic tirandamycin C (**49**), the authors employed a method commonly used to isolate unstable secondary metabolites [90]. Mesh bags of sterilized organic XAD resin were added directly to the microbial fermentation in order to capture metabolites as they were produced. This served to prevent compound degradation or enzymatic conversion within the broth and facilitate the extraction process. Tirandamycin C is a tetramic acid derivative with a 2,4-pyrrolidinedione and is predicted to be produced by hybrid polyketide-nonribosomal peptide biosynthetic machinery [91].

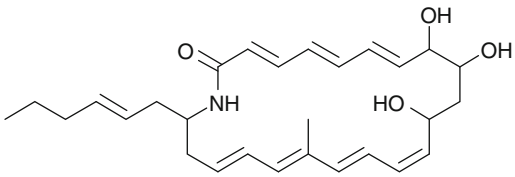
From a marine-derived *Streptomyces* strain that required seawater for growth, marinopyrrole B (**50**) was isolated [92]. This was the first report of a natural product bearing a *N*-, C-2-linked bispyrrole structure. In addition to cytotoxic activity, the marinopyrrole class of molecules displayed significant inhibition against MRSA and with further development may represent a novel pharmacophore for the treatment of this drug-resistant pathogen [93]. The marinopyrroles were also used to develop a streamlined approach toward cellular target elucidation of bioactive natural products [94]. Such an approach serves to increase the efficiency of drug discovery by elucidating the target of a potential drug candidate early in the discovery process; this is especially relevant for metabolites that interact with undesirable targets. In this study, an acyl dye transfer protocol enabled transfer of



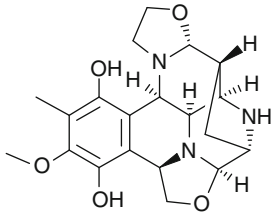
(**56**) Aburatubolactam A



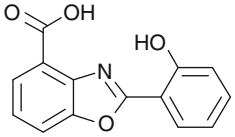
(**57**) Altemicidin



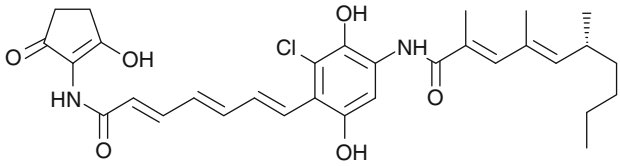
(**58**) Aureoverticillactam



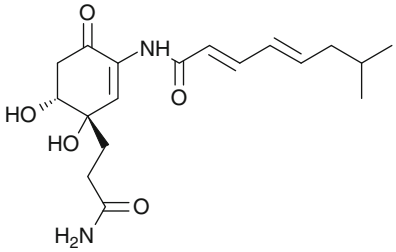
(**59**) Bioxalomycin α_1



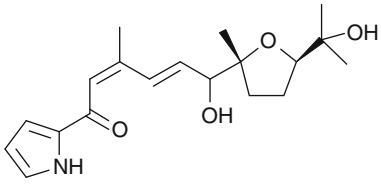
(**60**) Caboxamycin



(**61**) Chinikomycin A

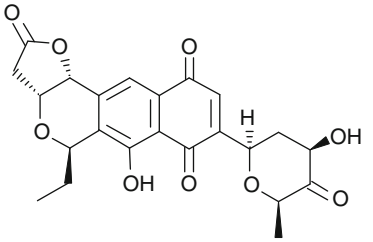


(**62**) Daryamide A

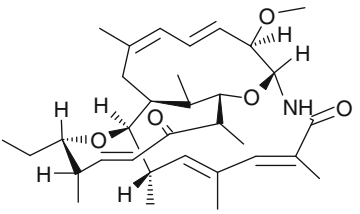


(**63**) Glaciapyrrole A

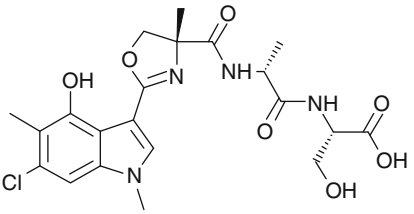
Fig. 3.7 (continued)



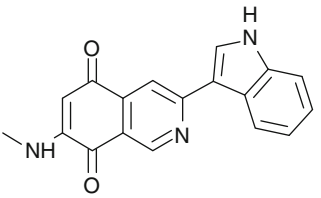
(**64**) Halawanone A



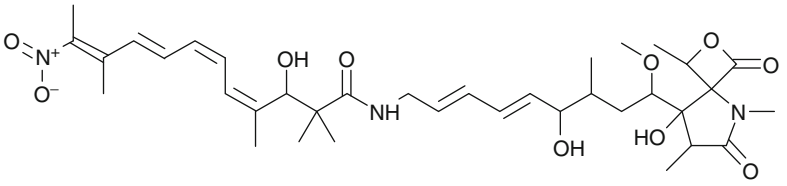
(**65**) Halichomycin



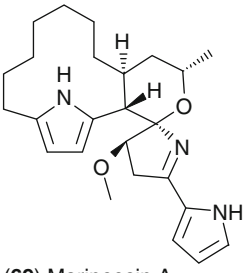
(**66**) JBIR-34



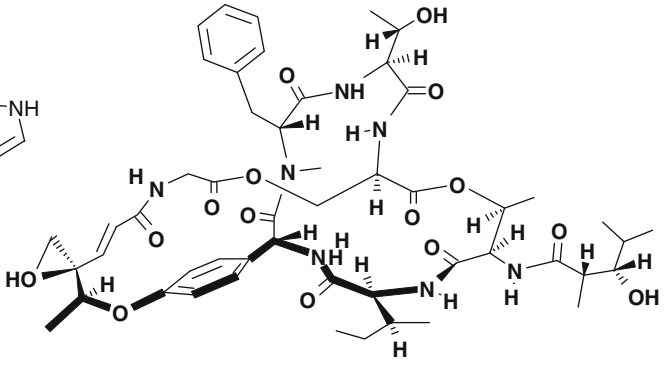
(**68**) Mansouramycin D



(**67**) Lajollamycin



(**69**) Marineosin A



(**70**) Salinamide A

Fig. 3.7 (continued)

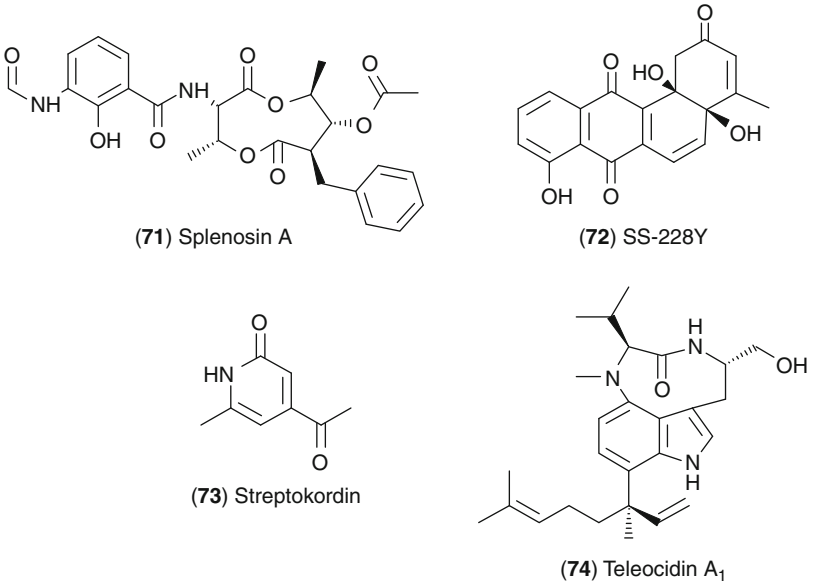


Fig. 3.7 Additional secondary metabolites from marine *Streptomyces*

an immunoaffinity fluorescent tag from the natural product to the protein target. After immunoprecipitation and mass spectral analyses, the protein target of the marinopyrrole class of natural products was determined to be actin.

A sediment-derived *Streptomyces* sp. collected in Guam produced the cyclic hexadepsipeptide piperazimycin A (**51**) [95]. The compound includes a number of rare amino acids. Screening of this molecule against the National Cancer Institute's (NCI) 60-cancer cell line panel revealed that it displayed broad, nanomolar-level cytotoxicity. Sediment from Ayajin Bay, East Sea, Korea, afforded an undescribed species of *Streptomyces*. This strain produced the small molecule streptochlorin (**52**), an indole-substituted chlorinated oxazole [96]. Streptochlorin was found to exhibit antiangiogenic properties through the inhibition of NFκB, a transcription factor implicated in the progression of certain cancers [97]. Azamerone (**53**) was isolated from a strain that is believed to belong to a new marine species within the genus *Streptomyces* [98]. Azamerone was found to have an unprecedented chloropyranophthalazinone core. This was the first report of a phthalazinone ring system in a natural product. Compound **53** is of mixed polyketide–terpene biosynthetic origin and belongs to the class of metabolites known as meroterpenoids. Thus far, the production of this class of compounds appears to be a trait that is a characteristic of a new group of marine-derived *Streptomyces*, which has tentatively been called MAR4. Also isolated from a related strain was actinofuranone A (**54**), a molecule of polyketide origin [99].

A final example of *Streptomyces* metabolites, the ammosamides, were produced by an undescribed *Streptomyces* species cultured from a deep-sea sediment (1,618 m)

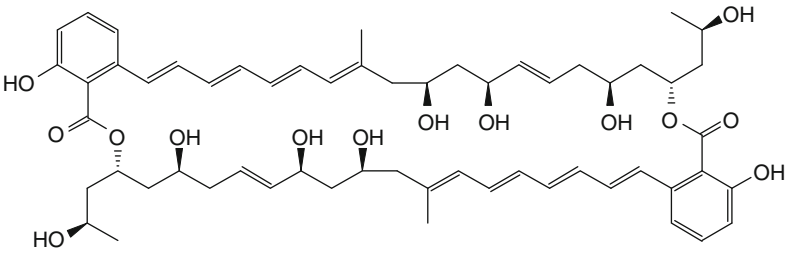
collected in the Bahamas [100]. The cytotoxic agent ammosamide A (**55**) resembled a few other microbial and sponge-derived metabolites, but it was the first natural product to contain a thio-γ-lactam moiety. Using fluorescent labeling techniques, it was determined that the ammosamides target the cytoskeletal protein myosin, an entity involved in cell cycle progression that is of particular interest in the treatment of cancer [101].

A number of new marine lineages have been observed closely related to the genus *Streptomyces* based on 16 S rRNA sequence analysis. Among these is a deeply rooted clade that was originally called MAR2 and subsequently given the informal genus name "*Marinispora*." The first chemical study of a member of the genus "*Marinispora*" resulted in the isolation of the marinomycins, 44-membered ring macrolides with an unusual substitution pattern of polyol and polyene functionalities when compared to typical polyene macrolides such as amphotericin. Marinomycin A (**75**) showed selective cytotoxicity toward eight melanoma cell lines in the NCI 60 cell line panel and also displayed strong antibacterial activity toward a few drug-resistant bacterial pathogens [102]. Similarly, a study of a "*Marinispora*" strain collected from a sediment sample collected at a depth of 51 m off the coast of La Jolla, California, resulted in the isolation of several 34-membered ring macrolides called the marinisporolides [103]. Marinisporolide A (**76**) contains a bicyclic spiro-bis-tetrahydropyran ketal unit, the only examples of spiroketal-polyenol-polyol macrolides isolated from nature. Like the marinomycins, the marinisporolides are photoreactive and photoisomerize in sunlight to yield olefin isomers. From a sediment sample collected from Cocos Lagoon, Guam, three oxazolidinones were isolated (lipoxazolidinone A–C) from a member of the marine taxon "*Marinispora*" [104]. Lipoxazolidinone A (**77**) exhibited broad-spectrum antibiotic activity, and it was suggested that the oxazolidinone ring system was essential for their bioactivity. Also exhibiting broad-spectrum antibiotic activity were the lynamicins (lynamicin A, **78**), isolated from a "*Marinispora*" sp. cultured from a sediment sample collected from Mission Bay in San Diego, California [105]. These are novel, chlorinated *bis*-indole pyrroles that most importantly show activity against MRSA and vancomycin-resistant *Enterococcus faecium* (VREF) (Fig. 3.8).

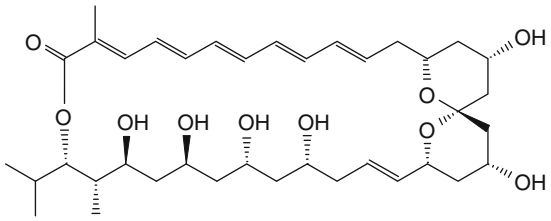
3.3.2.2 Micromonosporaceae

Described in 1938, the Micromonosporaceae is an actinomycete family comprised of more than 20 genera. Within this family are two genera, *Micromonospora* and *Salinispora*, which exemplify the capacity of marine bacteria to produce structurally intriguing secondary metabolites. The genus *Salinispora* is unique among the true marine actinomycete genera described to date in that strains fail to grow when seawater is replaced with deionized water in the culture medium. The genus is currently composed of three species: *S. arenicola*, *S. tropica*, and "*S. pacifica*" (proposed name).

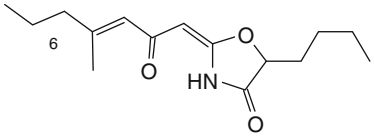
Salinosporamide A (**79**) is undoubtedly the most significant natural product to be isolated from a *Salinispora* species (*S. tropica*) [106]. The producing strain was isolated from a sediment sample collected in the Bahamas. The compound is



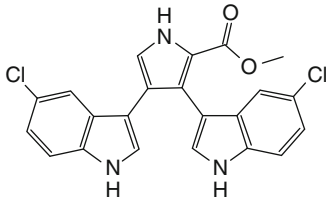
(**75**) Marinomycin A



(**76**) Marinisporolide A



(**77**) Lipoxazolidinone A



(**78**) Lynamicin A

Fig. 3.8 Secondary metabolites from "*Marinispora*"

structurally similar to the β-lactone omuralide. However, the conspicuous halogenation of the ethyl side chain provides an essential structural element that is required for the potent, irreversible binding to the 20 S proteasome, a validated target in cancer chemotherapy. This natural product is currently in Phase I clinical trials for the treatment of various cancers. Interestingly, it is the natural product itself, not any of the synthetic and semisynthetic analogs that were considered during preclinical development, that was taken into the clinic, further emphasizing "the beauty and power of a selection process offered only by nature [107]." In order to produce quantities sufficient for clinical development and commercialization, several steps of the bacterial fermentation process were optimized to increase production of **79** from a few mg/L (original laboratory conditions) to 450 mg/L [108–110]. This represented the first manufacture of a substance in clinical trials by saline fermentation and emphasized the advantages and flexibility of producing a drug candidate through microbial fermentation.

The discovery of salinosporamide A has also inspired molecular engineering of the pathway in an effort to produce new derivatives. One such example is the

engineered production of fluorosalinisporamide A (**80**) by *S. tropica* [111]. Though fluorinated natural products are rare, they account for 15% of pharmaceutical products on the market. To create the fluorinated version of the compound, a *S. tropica* mutant was generated in which the fluorination gene *flA*, taken from *Streptomyces cattleya*, was used to replace the *salL* chlorinase gene normally found in *S. tropica*. This mutant produced **80** in the presence of inorganic fluoride, thus emphasizing an avenue by which a host organism may be genetically engineered to produce novel analogs of a biomedically important secondary metabolite.

Other secondary metabolites from *S. tropica* include salinilactam (**81**) and the polycyclic macrolide sporolide A (**82**) [112, 113]. The biosynthetic pathway for salinilactam production was originally identified during the analysis of the *S. tropica* strain CNB-440 genome sequence. Bioinformatic analysis played a key role in assigning the final structure of this compound, thus illustrating the value of combining genomic analyses with natural product isolation and identification. Sporolide A is a remarkable polycyclic chlorinated macrolide that is composed of a highly oxidized carbon skeleton (23 out of its 24 carbons are oxygenated or sp^2 hybridized). The majority of this skeleton has never been reported in any chemical or biological study. The chlorinated cyclopenta[*a*]indene ring was shown to emerge from an unstable nine-membered enediyne precursor via the nucleophilic addition of chloride, a process that has been verified in laboratory experiments [114]. Sequence analysis of the *S. tropica* genome uncovered two biosynthetic loci that encoded for enediyne polyketide synthases (PKSEs), one of which strongly correlated with the formation of the proposed sporolide precursor. This biosynthetic study highlights the breadth of information available when genomic analyses are coupled with traditional drug discovery efforts.

Three cyclic heptapeptides (cyclomarins A-C) were found to be produced by *S. arenicola* (and earlier from a *Streptomyces* species) [115, 116]. Cyclomarin A (**83**), the major metabolite, was composed of four unusual amino acids and displayed in vitro and in vivo anti-inflammatory activity. An *S. arenicola* strain from a Fijian sediment collection was shown to produce the cyclohexadepsipeptide arenamide A (**84**) [117]. This metabolite displayed chemopreventive properties, inhibiting NFκB and nitric oxide production. From another *S. arenicola* strain, a 26-membered macrolide (arenicolide A, **85**) in addition to the unusual polyketide saliniketal (**86**) was isolated [118, 119]. Saliniketal contains a novel bicyclic ring system and was shown to inhibit ornithine decarboxylase induction, an important target for cancer chemoprevention. Both metabolites **85** and **86** were isolated from an *S. arenicola* strain cultured from sediment samples collected from the coastal waters off Guam. Arenimycin (**87**) was isolated from an *S. arenicola* strain found in association with the ascidian *Ecteinascidia turbinata*, collected from a mangrove channel at Sweetings Cay, Grand Bahama Island [120]. This program focused on the screening of actinomycetes against a rifampin-resistant strain of the pathogen MRSA. Arenimycin exhibited strong inhibition of this pathogen, although potent cytotoxicity prevented further exploration of its antibiotic activities.

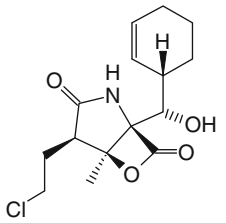
From a strain of "*S. pacifica*" isolated from a sediment sample collected in the waters off Palau, the simple polyketide salinipyrone A (**88**) was isolated [121].

This metabolite is thought to be derived from a mixed precursor polyketide biosynthesis involving acetate, propionate, and butyrate building blocks. Also produced by a "*S. pacifica*" strain isolated from a sediment sample collected at a depth of 500 m off Palau is cyanosporaside A (**89**) [122]. The cyano-containing halogenated aglycone was found to possess a novel 3-keto-pyranohexose sugar. Like sporolide A (**82**), cyanosporaside A is thought to be the cyclization product of an enediyne precursor (Fig. 3.9).

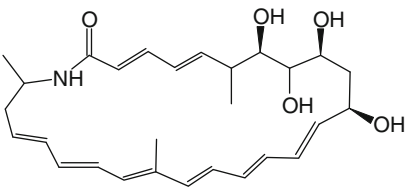
A *Micromonospora* strain cultured from the ascidian *Didemnum proliferum* produced diazepinomicin (**90**), whose unique dibenzodiazepine skeleton was the first to be reported in the peer-reviewed literature [123]. This metabolite was discovered as a result of a program designed to screen microbes for cytotoxic agents that can be linked to monoclonal antibodies targeting tumor-specific antigens. A halophilic strain of the same genus, *Micromonospora lomaivitiensis*, was isolated from the ascidian *Polysyncraton lithostrotum*. This bacterium produced two dimeric diazobenzofluorene glycosides (lomaiviticins A (**91**) and B) that exhibited potent cytotoxicity [124]. The structural architecture of the lomaiviticins is somewhat similar to the kinamycin antibiotics, although they are unique in the sense of their greater complexity. The antitumor agent thiocoraline (**92**) was isolated from a culture of *Micromonospora marina*, isolated from a soft coral from the Indian Ocean [125]. Thiocoraline A is a symmetric, octadepsipeptide that resembles the quinoxaline antibiotics echinomycin and triostin A, although thiocoraline contains a thioester in its backbone and two glycine residues in place of alanine residues. The latter trait has been proposed to afford improved DNA intercalation [126, 127]. A *Micromonospora* sp., isolated from an Indian Ocean coral, was found to produce the spiroketal-containing macrolide IB-96212 (**93**), which displayed cytotoxic properties [128].

The genus *Verrucosispora* within the family Micromonosporaceae has also proven to be chemically prolific. *Verrucosispora maris*, isolated from a sediment sample from the Sea of Japan (depth 289 m), produced the abyssomicins (abyssomicin C, **94**) and proximicins, the latter of which are characterized by 4-amino-furan-2-carboxylic acid cores [129, 130]. Abyssomicin C was the first natural product found to inhibit *p*-aminobenzoic acid biosynthesis (*p*ABA), a new target for antibiotic drug discovery. Its bioactivity, unique structure, and novel mechanism of action serve as an example of the potential for marine taxa to produce interesting, biomedically significant molecules. This discovery was the result of a program designed to screen microorganisms for inhibitors of the *p*ABA pathway. Proximicin A (**95**) was found to contain a previously unknown γ-amino acid and displayed cytotoxicity toward a few tumor cell lines.

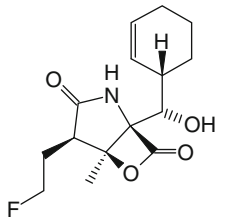
A strain of *Verrucosispora gifthornensis* cultured from an unidentified ascidian collected off Hiroshima, Japan, was found to produce the terpenoid gifthornelone A (**96**) [131]. This isopimaradiene derivative was the result of a program specifically designed to discover novel terpenoids from actinomycetes; its structural similarity to known steroidal androgen antagonists such as dihydrotestosterone led to the discovery of antagonistic activity against an androgen receptor.



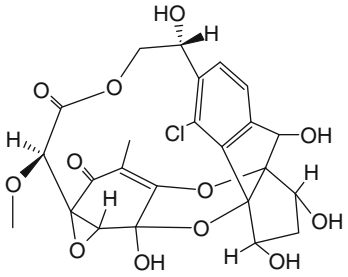
(**79**) Salinosporamide A



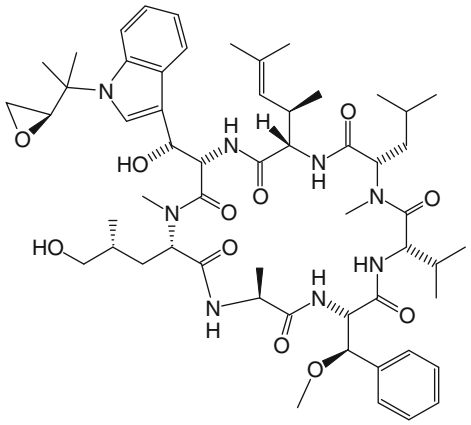
(**81**) Salinilactam



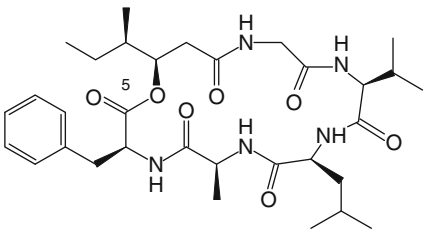
(**80**) Fluorosalinosporamide A



(**82**) Sporolide A



(**83**) Cyclomarin A



(**84**) Arenamide A

Fig. 3.9 (continued)

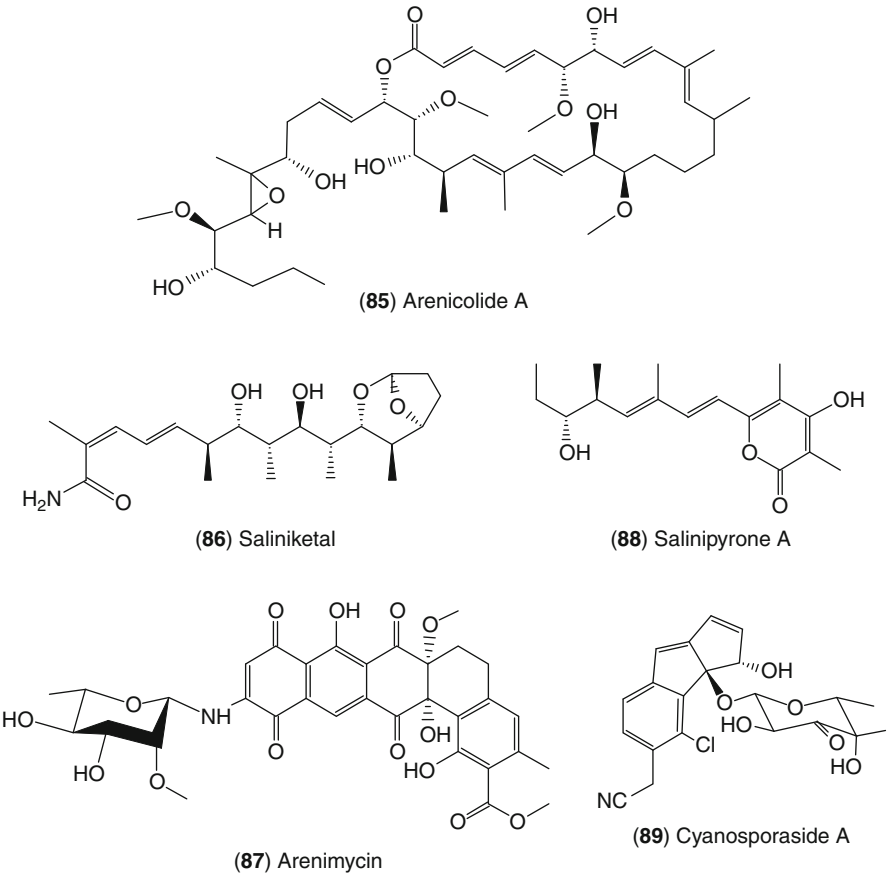
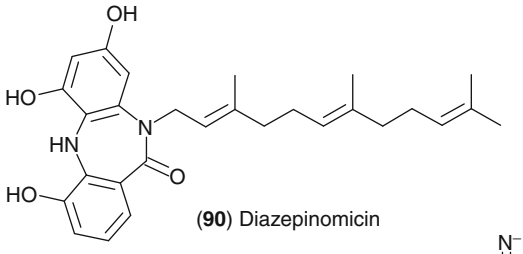


Fig. 3.9 Secondary metabolites from *Salinispora*

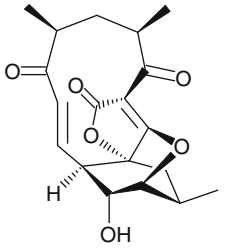
3.3.2.3 Additional Families of Actinobacteria

The family Nocardiopsaceae was created in 1996 in order to accommodate a number of phylogenetically related strains of *Nocardiopsis*. Two peptides, MKN-349A (**97**) and lucentamycin A (**98**), were reported from marine-derived strains of *Nocardiopsis* [132, 133]. Lucentamycin A is a cytotoxic substance isolated from *Nocardiopsis lucentensis*, cultured from a strain isolated from a shallow saline pond in the Bahamas. It was the first report of a ethylideneproline amino acid unit in nature. Kahakamide A (**99**) is a rare *N*-glycosyl indole antibiotic isolated from *N. dassonvillei* cultured from a marine sediment collected from Kauai, Hawaii [134]. It displayed antibacterial activity against *B. subtilis*.

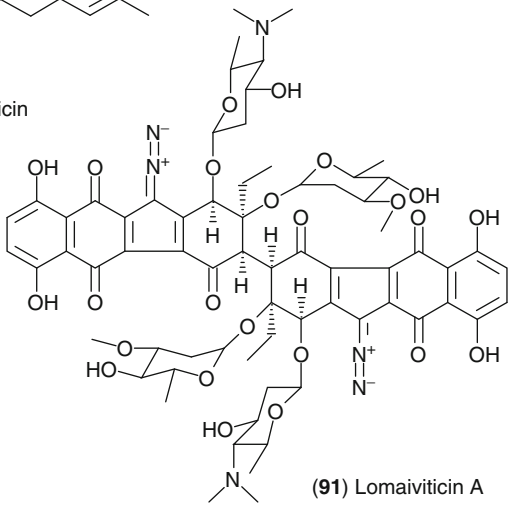
The family Pseudonocardiaceae is composed of fewer than 20 genera. Within this family is the genus *Saccharopolyspora*. A *Saccharopolyspora* strain was cultured from a sample of the sponge *Haliclona* sp. and found to produce



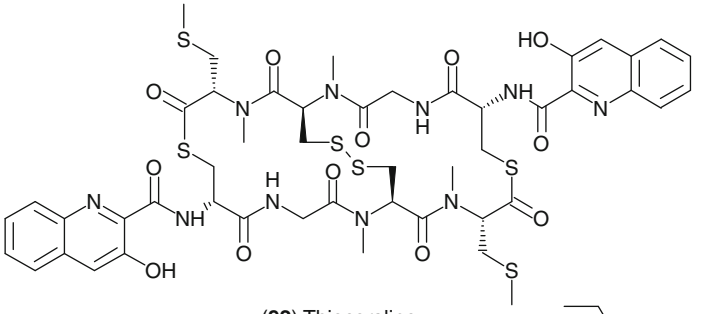
(**90**) Diazepinomicin



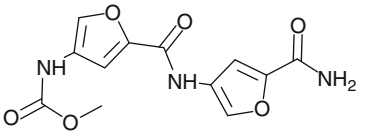
(**94**) Abyssomicin C



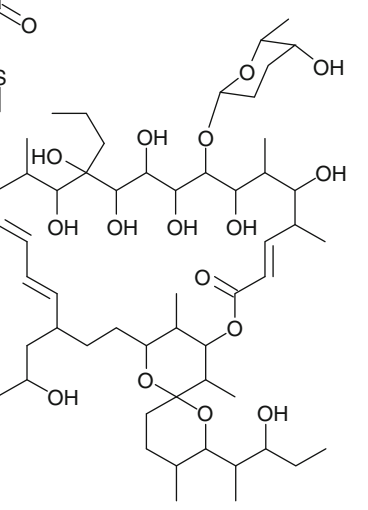
(**91**) Lomaiviticin A



(**92**) Thiocoraline

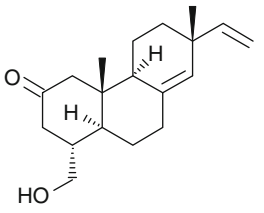


(**95**) Proximicin A

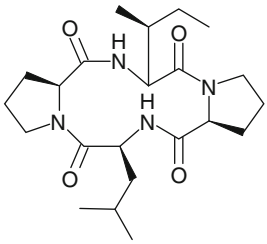


(**93**) IB-96212

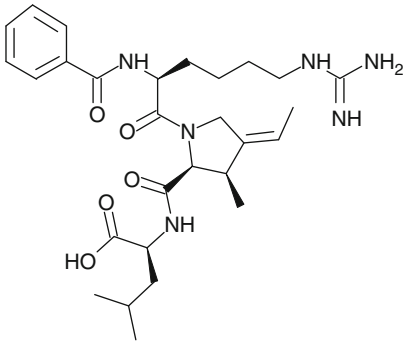
Fig. 3.10 (continued)



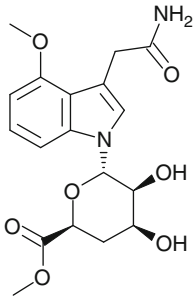
(**96**) Gifhornenolone A



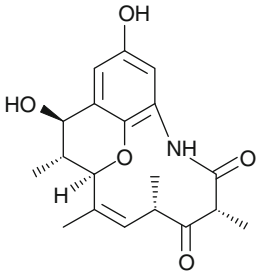
(**97**) MKN-349A



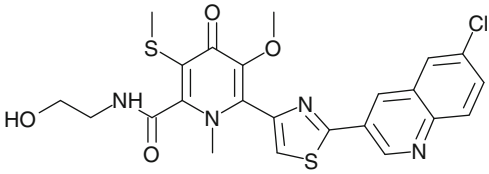
(**98**) Lucentamycin A



(**99**) Kahakamide A



(**100**) Cebulactam A1



(**101**) Lodopyridone

Fig. 3.10 Secondary metabolites from marine Micromonosporaceae

cebulactam A1 (**100**) [135]. This study included the first report of an obligate marine *Saccharopolyspora*. Another actinomycete that was reported to have an obligate requirement of seawater for growth was the *Saccharomonospora* strain CNQ-490. This strain was isolated at a depth of 45 m from a sediment sample collected in the La Jolla Canyon off San Diego, CA. In culture, this strain produced lodopyridone (**101**), a quinoline alkaloid of an unprecedented carbon skeleton

whose combination of heterocyclic units (oxygenated 4-pyridone, thiazole, and chlorinated quinoline) is unlike any secondary metabolite observed to this date [136] (Fig. 3.10).

3.4 Conclusions

Bacteria produce small molecules that are not essential for survival but that may enhance fitness or provide survival advantage. These secondary metabolites not only serve as both initiators and regulators of diverse ecological processes, but they can also be used to treat or probe the causes of human disease. Modern medicine has long relied on microbial natural products to treat infectious disease, cancer, and other recalcitrant ailments. However, the arsenal of small molecule drug candidates has shrunk in part due to a paradigm shift by the pharmaceutical industry away from microbial natural products in favor of other drug discovery platforms. There is now however an ongoing resurgence of interest in natural product drug discovery. This interest is fueled by the availability of new and more precise techniques in analytical chemistry and the recognition that nature remains the best resource for the types of new small molecule organic scaffolds around which pharmaceutical agents have historically been developed. Included among current natural product discovery efforts are studies of new populations of bacteria, including those that reside in the marine environment. Marine-derived bacteria include new taxonomy groups as well as species that also occur on land. Collectively, these bacteria are yielding a wealth of new structures including agents that are advancing through various stages of clinical development, solidifying the importance of exploring new habitats and resources in the search for novel bacterial secondary metabolites.

3.5 Study Questions

1. Although often similar in appearance, how are bacteria different from fungi?
2. What family of bacteria is recognized as the most prolific producers of bioactive compounds? What is the most important genus?
3. What is the fundamental difference between Gram-positive and Gram-negative bacteria?
4. What was the first truly marine genus of bacteria to be described?
5. When and by whom was penicillin discovered?
6. The ocean comprises what percentage of the Earth's surface?
7. Which bacterial group, Gram-positive or Gram-negative, produces the most antibiotics?

Acknowledgments The authors thank the National Institutes of Health (Grant # RO1 GM85770 to PRJ), and in particular the National Cancer Institute (Grant # R37 CA044848 to WF), for their support in developing the field of marine microbial natural products chemistry.

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