Chapter 12
The Current Status of Novel Anticancer Drugs from Marine Actinobacteria

Panchanathan Manivasagan and Se-Kwon Kim

Abstract Marine actinobacteria are emerging as a valuable resource for bioactive substances encompassing a variety of unique structural classes. Marine actinobacteria are one of the most efficient groups of secondary metabolite producers and are very important from an industrial point of view. Chemotherapy is one of the main treatments used to combat cancer. A great number of anticancer compounds are natural products or their derivatives, mainly produced by microorganisms. In particular, actinobacteria are efficient producers of a large number of bioactive natural products that show a range or biological activities including antimicrobial, anticancer and enzyme inhibition. Marine actinobacteria have attracted special attention in the last ten years for their ability to produce interesting pharmacological lead compounds.

Keywords Marine actinobacteria · Anticancer · Natural products · Bioactive compounds

12.1 Introduction

Marine microorganisms are widely recognized as rich sources of novel natural products [1, 2]. In recent years, numerous novel bioactive compounds discovered from marine actinobacteria have been reported [3–6]. They are responsible for the production of about half of the discovered bioactive secondary metabolites notably antibiotics, antitumor agents, and immunosuppressive agents [7–10].

Marine actinobacteria also constitute an important and potential source of novel bioactive compounds. They produce different types of antibiotics, because the environmental conditions of the ocean differ greatly from terrestrial conditions [11]. Novel actinobacteria with biopharmaceutical potential have been increasingly iso-

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lated from marine habitats [12–15]. A new major marine *Streptomyces* genus have recently been described and shown to produce biological activities, including antibiotics [16, 17]. The antibiotics are entirely new and unique when compared to those from the terrestrial ones.

Around 23,000 bioactive secondary metabolites produced by microorganisms have been reported and over 10,000 of these compounds are produced by actinobacteria, representing 45% of all bioactive microbial metabolites discovered [18]. Among actinobacteria, around 7600 compounds are produced by *Streptomyces* species [18]. Many of these secondary metabolites are potent antibiotics, which has made streptomycetes the primary antibiotic-producing organisms exploited by the pharmaceutical industry [18]. Members of this group are producers, in addition, of clinically useful drugs such as anthracyclines, peptides, aureolic acids, enediynes, antimetabolites, carzinophilin, mitomycins and others [19]. However, the search for novel drugs is still a priority goal for cancer therapy, due to the rapid development of resistance to multiple chemotherapeutic drugs. In addition, the high toxicity usually associated with cancer chemotherapy drugs and their undesirable side effects increase the demand for novel anticancer drugs active against untreatable tumors, with fewer side effects and/or with greater therapeutic efficiency [20]. This book chapter discusses the current status of novel anticancer drugs from marine actinobacteria

12.2 Actinobacteria from Marine Environment

Actinobacteria are Gram-positive, often filamentous, bacteria known for their unsurpassed capacity for the production of secondary metabolites with diverse biological activities. Extensive screening of terrestrial actinobacteria, started in the early 1950s, has yielded many important drug leads, later developed into antimicrobial (amphotericin B, erythromycin, vancomycin), anticancer (daunorubicin, bleomycin, mitomycin) and immunosuppressive (rapamycin) drugs. Despite this apparent success, most of the actinomycete-based screening programs at big pharmaceutical companies have been abandoned in the recent years due to several reasons. One of the reasons was high costs of the internal screening programs, combined with the low number of new drug leads and relatively low profit on such drugs as new anti-infectives [21]. Another reason has been frequent re-discovery of the same compounds, mostly due to the redundancy of the samples, as well as strain isolation and screening technologies [22].

In the recent years, actinobacteria isolated from the marine environment (sediments, sponges, tunicates, neuston, etc.) have attracted considerable attention [23]. True marine actinobacteria are usually considerably more difficult to culture compared to their terrestrial relatives, most likely due to the special growth requirements. However, development of both sampling and cultivation techniques allowed isolation of representatives of several true marine actinomycete genera producing novel compounds with interesting biological activities [12].

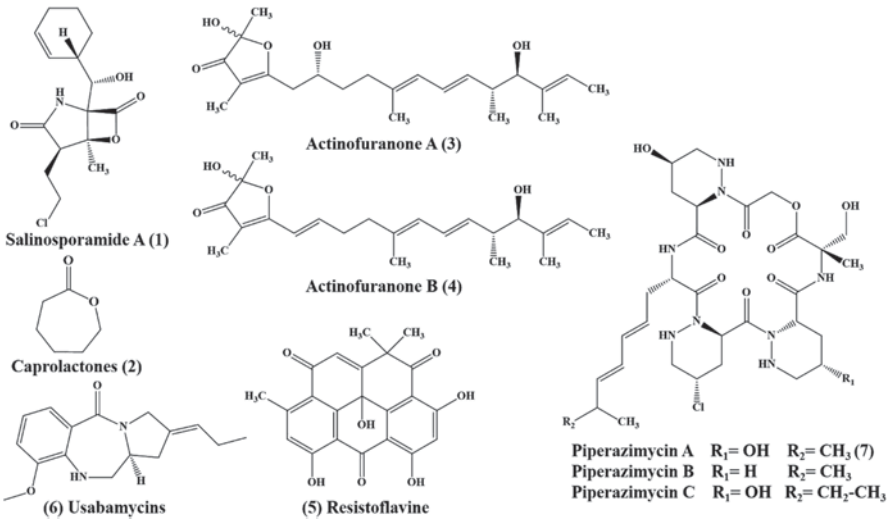

Fig. 12.1 Chemical structures of salinosporamide A, caprolactones, actinofuranone A, actinofuranone B, resistoflavine, usabamycins and piperazimycins

12.3 Anticancer Activity

Cancer still remains one of the most serious human health problems and breast cancer is the second most universal cause of cancer deaths in women. Therapeutic methods for cancer treatment are surgery, radiotherapy, immunotherapy and chemotherapy and these techniques are individually useful in particular situations and when combined, they offer a more efficient treatment for tumor. Many of the antitumor compounds from marine drugs are derived from marine actinobacteria and these metabolites play an important role in identification of pharmaceutical compounds. Currently, it appears that there have been only a few studies focusing on finding bioactive compounds derived from marine actinobacteria to be used as anticancer agents, as well as agents against infectious organisms.

Pure active compounds extracted from the marine actinobacterium, *Salinispora tropica* have shown inhibitory effects in many malignant cell types [24]. In particular, Salinosporamide A **(1)** (Fig. 12.1) is a novel rare bicyclic beta-lactone gamma-lactam isolated from an obligate marine actinobacterium, *Salinispora tropica* [25, 26]. Salinosporamide A is an orally active proteasome inhibitor that induces apoptosis in multiple myeloma cells with mechanisms distinct from the commercial proteasome inhibitor anticancer drug Bortezomib [27]. It is being developed by Nereus Pharmaceuticals, Inc. (as NPI-0052) and was scheduled to enter clinical studies for treatment of cancer in humans in 2006. NPI-0052 is currently being evaluated in multiple phase I trials for solid tumors, lymphoma and multiple myeloma (http://www.nereuspharm.com/NPI-0052.shtml). NPI-0052 represents the first clinical candidate for the treatment of cancer produced by saline fermentation of an obligate marine actinobacterium [28].

Prudhomme et al. [24] tested Salinosporamide A for its utility as an anticancer and antimalarial drug. It was shown to have inhibitory activity against parasite development *in vitro* (*Plasmodium falciparum*) and *in vivo* (*P. yoelii*). The exact mode by which salinosporamide A inhibits *Plasmodium* erythrocytic development is unknown; however, it is likely due to the inhibition of the proteasome complex. It is interesting to note that chloroquine resistant strains are still sensitive to Salinosporamide A. Targeting the proteasome system has a huge therapeutic implication as it can restrain growth and survival of most cell types [24]. These attributes, taken with the fact that it is already in phase I clinical trials as an antitumor agent, make it an excellent candidate for alternative therapies, such as antibacterial, antiparasitic, antifungal or antiviral treatments.

Caprolactones **(2)** (Fig. 12.1) are new antibiotics isolated from *Streptomyces* sp. showing moderate phytotoxicity and promising activity against cancer cells with concomitant low general cytotoxicity [29]. Two new polyketides, actinofuranones A **(3)** and B **(4)** (Fig. 12.1), were isolated from the culture extract of a marine-derived *Streptomyces* strain, designated as CNQ766. It showed weak *in vitro* cytotoxicity against mouse splenocyte T-cells and macrophages with IC_{50} values of 20 μg/mL and were inactive against human colon carcinoma HCT-116 cells [30]. Resistoflavine **(5)** (Fig. 12.1) is a cytotoxic compound, isolated from *S. chibaensis* $AUBN_1/7$. It showed cytotoxic activity against human gastric adenocarcinoma HMO2 and hepatic carcinoma HePG2 cell lines [31]. Usabamycins **(6)** (Fig. 12.1) are new anthramycin-type analogues isolated from *Streptomyces* sp. NPS853. Usabamycins show weak inhibition of HeLa cell growth and selective inhibition of serotonin (5-hydroxytrypamine) $5\text{-}HT_{2B}$ uptake [32].

Piperazimycins (**7**) (Fig. 12.1) are cyclic hexadepsipeptides isolated from the fermentation broth of a *Streptomyces* sp. strain CNQ-593, isolated from marine sediments at a depth of approximately 20 m near the island of Guam. Cytotoxic activities of piperazimycins were initially evaluated *in vitro* against the human colon carcinoma HCT-116 cell line. All compounds exhibited significant cytotoxicity with an average GI_{50} of 76 ng/mL for each. Piperazimycin A also showed potent biological activity when evaluated against the NCI's cancer cell line panel, with mean GI_{50}, TGI and LC_{50} values for all the cell lines of 100 nM, 300 nM and 2 μM, respectively. Overall, piperazimycin A exhibited a nearly 3-fold more potent activity against solid tumors (average LC_{50} of 13.9 μM) than against the leukemia cell lines tested (average LC_{50} of 31.4 μM). It was most active against the melanoma (average LC_{50} of 0.3 μM), central nervous system (average LC_{50} of 0.4 μM) and prostate cell lines (average LC_{50} of 0.6 μM) cancers [33].

Neomarinones **(8)** (Fig. 12.2) are sesquiterpenoid naphthoquinones with a mixed polyketide-terpenoid origin [34]. Neomarinone, isomarinone, hydroxydebromomarinone and methoxydebromomarinone were produced by the actinobacterial isolate CNH-099 obtained from sediments at 1 m depth in Batiquitos Lagoon, North of San Diego, California. These compounds showed moderate *in vitro* cytotoxicity, (IC_{50} of 8 μg/mL) against human colon carcinoma HCT-116 cells. In addition, neomarinone generated a mean IC_{50} value of 10 μM in the NCI's 60 cancer cell line panel [35, 36]. Nonactin **(9)** (Fig. 12.2), a cyclic polyether also known as macrotetrolide,

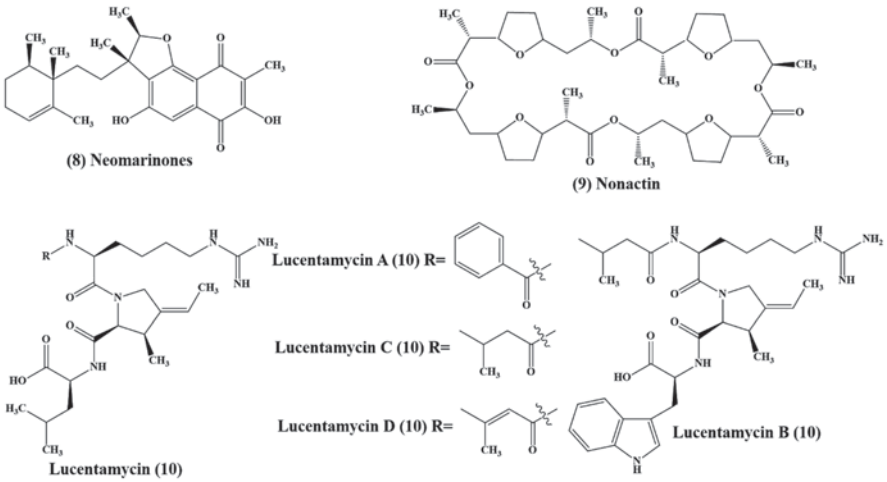

Fig. 12.2 Chemical structures of neomarinones, nonactin and lucentamycins

has been isolated from cultures of *Streptomyces* sp. KORDI-3238, isolated from deep-sea sediments collected at Ayu Trough in the Western Pacific Ocean [37]. Biosynthesis of gene cluster of nonactin has previously been isolated and characterized from *Streptomyces griseus* DSM40695 [38], revealing that it is synthesized by a non-iteratively acting type II PKS that involves five ketosynthases and lacks the acyl carrier protein. Nonactin exhibited significant cytotoxicity against the multidrug-resistant human erythroleukemia cell line K-562 [39].

Lucentamycins **(10)** (Fig. 12.2), 3-methyl-4-ethylideneproline-containing peptides, are produced by *Nocardiopsis lucentensis* strain CNR-712, isolated from the sediments of a shallow saline pond from the island of Little San Salvador, in the Bahamas. Lucentamycins A and B showed significant *in vitro* cytotoxicity against human colon carcinoma HCT-116 cell line with IC_{50} values of 0.20 and 11 μM, respectively. However, lucentamycins C and D were not cytotoxic in the same assay, suggesting that the presence of an aromatic ring is essential for the biological activity of this class of compounds [40].

Mansouramycin C **(11)** (Fig. 12.3) is an isoquinolinequinones antibiotic isolated from *Streptomyces* sp. Cytotoxicity profiling of the mansouramycins in a panel of up to 36 tumor cell lines indicated significant cytotoxicity of several derivatives, with pronounced selectivity for non-small cell lung cancer, breast cancer, melanoma and prostate cancer cells [41]. Four new polyketides, salinipyrones A **(12)** (Fig. 12.3) and B **(13)** (Fig. 12.3), and pacificanones A **(14)** and B **(15)** (Fig. 12.3) have been isolated from cultures of the obligate marine actinobacteria *Salinispora pacifica* CNS-237, found in the sediments collected from the Palau island, Western Pacific Ocean. Biological activity of these compounds is currently being examined in diverse bioassays. In the initial screening, salinipyrones and the pacificanones displayed no significant activity in a cancer cytotoxicity assay using HCT-116 human colon cancer cells. In an isolated mouse splenocyte model of allergic inflam-

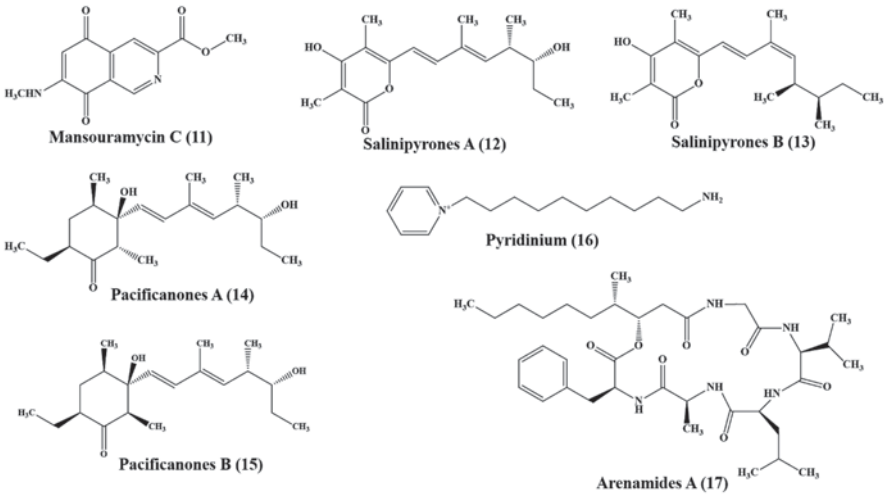

Fig. 12.3 Chemical structures of mansouramycin C, salinipyrones A, salinipyrones B, pacificanones A, pacificanones B, pyridinium and arenamides A

mation, salinipyrone A displayed moderate inhibition of interleukin-5 production by 50 % at 10 μg/mL without measurable human cell cytotoxicity [42].

Pyridinium **(16)** (Fig. 12.3) is a salt antibiotic isolated from *Amycolatopsis alba.* The compound showed potent cytotoxic activity against cancer cell lines of cervix (HeLa), breast (MCF-7) and brain (U87MG) *in vitro* and also exhibited antibacterial activity against Gram-positive and Gram-negative bacteria [43]. This new α-pyrone containing secondary metabolite was detected by HPLC–DAD analysis in a culture filtrate extract of *Streptomyces* sp. NTK 227, a strain isolated from the Atlantic Ocean sediments and found to be a member of the *Streptomyces albidoflavus* 16S rRNA gene clade.

Three new cyclohexadepsipeptides, arenamides A-C **(17)** (Fig. 12.3), were isolated from the fermentation broth of a marine actinobacterial strain identified as *Salinipora arenicola* CNT-088 which was obtained from the marine sediments at a depth of 20 m off the Great Astrolab Reef, in the Kandavu Island chain, Fiji. Arenamides A and B exhibited weak *in vitro* cytotoxicity against human colon carcinoma HCT-116 with IC_{50} values of 13.2 and 19.2 μg/mL, respectively [44]. In addition, arenamides have been associated to chemoprevention of carcinogenesis by suppression of NF*κ*B activation. NF*κ*B regulates the expression of a number of genes, the products of which are involved in tumorigenesis [45, 46]. Effect of arenamides on NF*κ*B activity was studied with stably transfected 293/NF*κ*B-Luc human embryonic kidney cells, induced by treatment with tumor necrosis factor (TNF). Arenamides A and B blocked TNF-induced activation in a dose- and time dependent manner with IC_{50} values of 3.7 and 1.7 μM, respectively [44].

Albidopyrone **(18)** (Fig. 12.4) showed moderate inhibitory activity against protein-tyrosine phosphatase B [47]. Two new cytotoxic antibiotics, piericidins C7 and C8 **(19)** (Fig. 12.4), were isolated from a marine *Streptomyces* sp. [48].

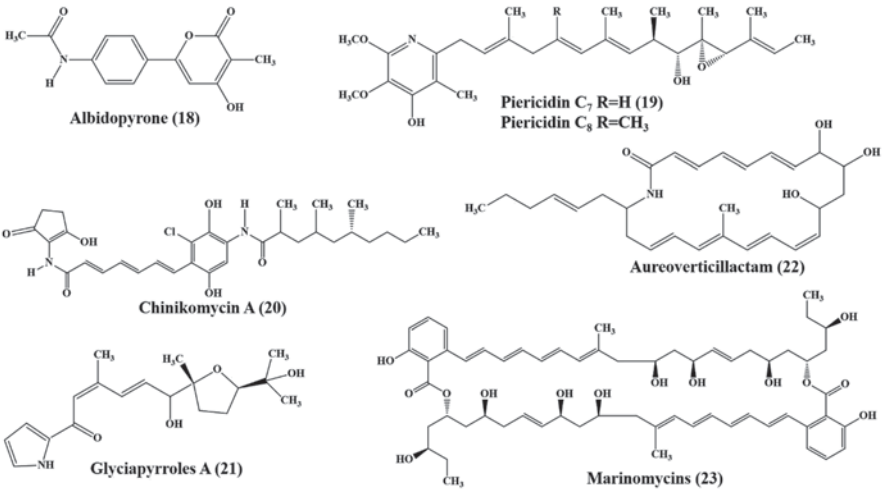

Fig. 12.4 Chemical structures of albidopyrone, piericidins, chinikomycin A, glyciapyrroles A, aureoverticillactam and marinomycins

Biological activity of piericidins was examined using rat glial cells transformed with the adenovirus E1A gene (RG-E1A-7), Neuro-2a mouse neuroblastoma cells, C6 rat glioma cells and 3Y1 rat normal fibroblast. Adenovirus E1A gene product inactivated the retinoblastoma tumor suppressor protein that plays an important role in cell-cycle and apoptosis control in mammalian cells and is inactivated during the development of a wide variety of cancers [49]. Piericidins C7 and C8 showed selective cytotoxicity against RG-E1A-7 cells (IC_{50} of 1.5 nM and 0.45 nM, respectively), and inhibited the growth of Neuro-2a cells (IC_{50} of 0.83 nM and 0.21 nM, respectively) without cytotoxic cell death. On the other hand, C6 rat glioma cells and 3Y1 rat normal fibroblast were not affected by piericidins [50].

Chinikomycins **(20)** (Fig. 12.4) are two novel antitumor antibiotics isolated from *Streptomyces* sp. They exhibited antitumor activity against different human cancer cell lines, but were inactive in antiviral, antimicrobial and phytotoxicity test [51]. Glyciapyrroles A **(21)** (Fig. 12.4) is a new pyrrolosesquiterpenes antibiotic isolated from *Streptomyces* sp. (NPS008187). Glyciapyrroles A possesses potent antitumor activity against the pair tumor cell lines at concentration up to 1 mM [17]. Aureoverticillactam **(22)** (Fig. 12.4) is a 22-membered macrocyclic lactam produced by *Streptomyces aureoverticillatus* NPS001583 isolated from marine sediments. Aureoverticillactam was found to possess moderate growth inhibitory activity against human colorectal adenocarcnioma HT-29, Jurkat leukemia and mouse melanoma B16F10 cell lines [4]. Marinomycins **(23)** (Fig. 12.4) are new antitumor antibiotics isolated from *Marinispora* sp. Marinomycins show significant antimicrobial activities against drug resistant bacterial pathogens and demonstrate impressive and selective cancer cell cytotoxicities against six of the eight melanoma cell lines in the National Cancer Institute's 60 cell line panel. The discovery of these new compounds from a new, chemically rich genus further documents that marine actinobacteria are a significant resource for drug discovery [52].

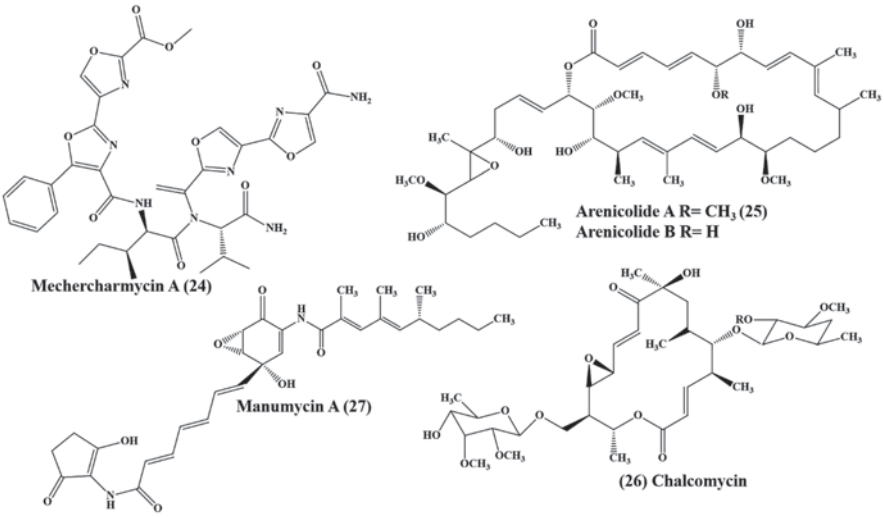

Fig. 12.5 Chemical structures of mechercharmycin A, arenicolides, chalcomycinand manumycin A

A new cytotoxic substance named mechercharmycin A **(24)** (Fig. 12.5) was isolated from marine-derived *Thermoactinomyces* sp. YM3-251. Mechercharmycin A exhibited relatively strong antitumor activity, whereas mechercharmycin B exhibited no such activity [53]. A higher number of type I polyketide derived compounds with antitumor activity have been isolated from marine actinobacteria. Once such compound is arenicolides **(25)** (Fig. 12.5), 26-membered polyunsaturated macrolactones, produced by the obligate marine actinobacteria *S. arenicola* strain CNR-005, isolated from the marine sediments, at a depth of 20 m from the coastal around the island of Guam. In particular, arenicolide A was found to exhibit moderate cytotoxicity toward the human colon adenocarcinoma cell line HCT-116 with an IC_{50} of 30 μg/mL [54]. Chalcomycin **(26)** (Fig. 12.5), a 16-membered macrolide, is produced by *Streptomyces* sp. M491 isolated from the Qingdao coast (China). Chalcomycin has been found to inhibit protein synthesis in HeLa human cervix carcinoma cell line [55, 56].

Manumycins constitute a class of compounds with antibiotic, cytotoxic, and other biological activities. It has been reported that manumycin A **(27)** (Fig. 12.5) and its analogues inhibit Ras farnesyl transferase and the growth of *Ki*-ras-activated murine fibrosarcoma in mice [57]. The side chains in manumycins appear to be a typical polyketide-derived moiety, differing with respect to their combinations of starter and elongation units. The central cyclohexene ring may be derived from the polyketide as in the case of manumycins or from some modified amino acid like 3-amino-5-hydroxybenzoic acid. Manumycin A and chinikomycins A and B (the quinone form of chinikomycin A) were isolated from *Streptomyces* sp. M045 derived from the sediments of Jiaozhou Bay in China [51].

Aureolic acid **(28)** (Fig. 12.6) (Chromomycin B, A_2 and A_3) are a new antitumor antibiotics isolated from *Streptomyces* sp. WBF16. These compounds showed

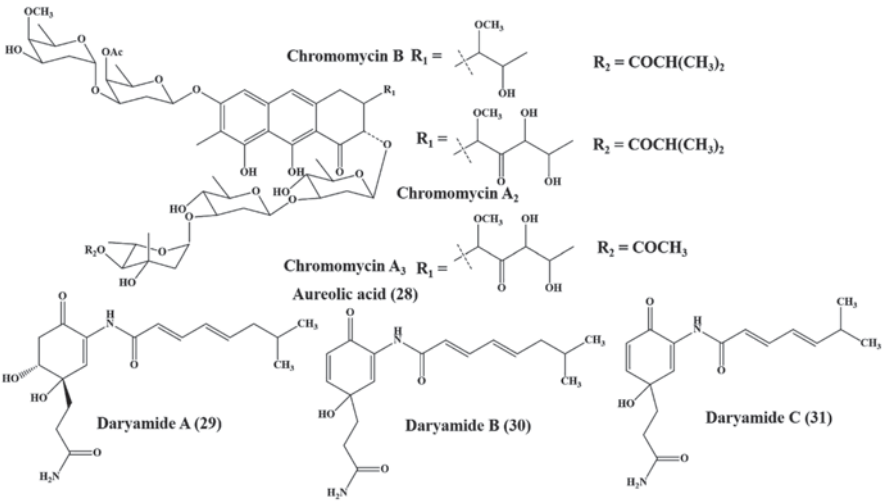

Fig. 12.6 Chemical structure of aureolic acid, daryamides A, daryamides B and daryamides C

strong cytotoxicity against SGC7901, HepG2, A549, HCT116 and COC1 and HUVEC [58]. Daryamides are new antitumor-antibiotics isolated from marine-derived *Streptomyces* strain CNQ-085. Daryamides A **(29)** (Fig. 12.6), B **(30)** and C **(31)** (Fig. 12.6) were subjected to cytotoxicity evaluation against the human colon carcinoma cell line HCT-116. Daryamide A exhibited significantly more potent cancer cell cytotoxicity, with an IC_{50} of 3.15 μg/mL, than daryamides B and C and very weak antifungal activity against *Candida albicans* [59].

Diazepinomicin **(32)** (Fig. 12.7) is an unique farnesylated dibenzodiazepinone produced by a *Micromonospora* strain [3]. It possesses antibacterial, anti-inflammatory and antitumor activity. It has a broad spectrum of *in vitro* cytotoxicity and has demonstrated *in vivo* activity against glioma, breast and prostate cancer in mouse models. Chlorinated dihydroquinones **(33)** (Fig. 12.7) are novel antibiotics produced by a new marine *Streptomyces* sp [15]. The compounds formally possess new carbon skeletons, but are related to several previously reported metabolites of the napyradiomycin class. Structures of the new molecules possess significant antibacterial and cancer cell cytotoxicities. Caboxamycin **(34)** (Fig. 12.7) is a new benzoxazole antibiotic and was detected by HPLC-diode array screening in extracts of *Streptomyces* sp. NTK 937, another strain which was isolated from the sediments collected from the Canary Basin. The compound, caboxamycin was named after the first letters of the collection site from where the organism was isolated and from letters drawn from its chemical structure. Caboxamycin showed inhibitory activity against both Gram-positive bacteria and against the tumor cell lines gastric adenocarcinoma (AGS), hepatocellular carcinoma (Hep G2) and breast carcinoma cells (MCF7). The antibiotic also showed an inhibitory activity against the enzyme phosphodiesterase [60].

Chandrananimycin A **(35)** (Fig. 12.7) is a novel antibiotic isolated from *Actinomadura* sp. Chandrananimycin A possesses potent antifungal activity against

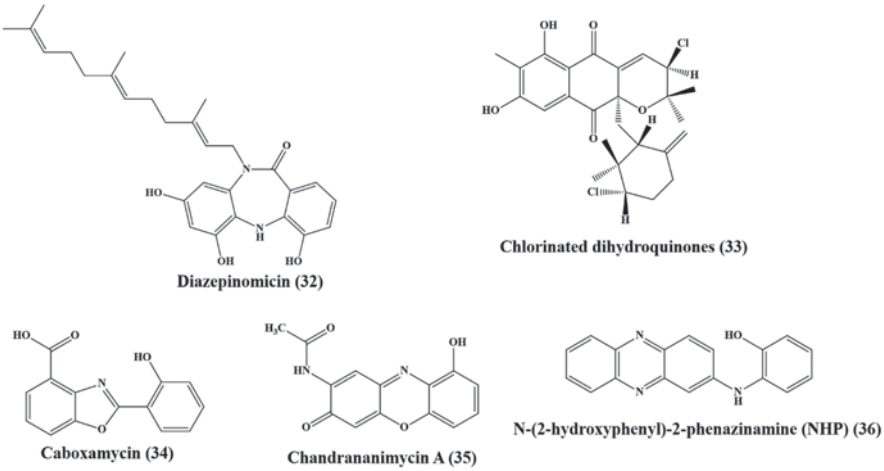

Fig 12.7 Chemical structures of diazepinomicin, chlorinated dihydroquinones, caboxamycin, chandrananimycin A and N-(2-hydroxyphenyl)-2-phenazinamine (*NHP*)

Mucor miehei. It also exhibits antialgal activity against the microalgae *Chlorella vulgaris* and *C. sorokiniana* and antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis,* along with anticancer activity [61]. N-(2-hydroxyphenyl)-2-phenazinamine (NHP) **(36)** (Fig. 12.7) is a new antibiotic isolated from *Nocardia dassonvillei*. The new compound showed significant antifungal activity against *Candida albicans,* with a MIC of 64 μg/mL and high cancer cell cytotoxicity against HepG2, A549, HCT-116 and COC1 cells [62].

12.4 Conclusions

Actinobacteria and, in particular the genus *Streptomyces*, have been well known during the last seventy years as prolific producers of novel bioactive compounds, anticancer drugs included. With the increasing development of oceanographic studies leading to the isolation of new actinobacteria from marine sources, new prolific genera in the production of useful compounds have been found, such as *Salinispora*. However, the Ocean, without any doubt, is keeping a myriad of new actinobacteria providing novel structural diversity to be discovered and used. In addition, the continuous effort for unravel the biosynthesis of the already known compounds and the isolation and characterization of their biosynthesis gene clusters will lead to the development of new anticancer compounds, hopefully with improved therapeutic properties, by using combinatorial biosynthesis approaches.

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