Chapter 13
Antimicrobial Potential and Metabolite Profiling of Marine Actinobacteria

Jignasha Thumar and Satya P. Singh

Abstract Over 90% volume of the Earth's crust is covered by oceans. Many natural product-based drug discovery programs are being run and funded by developed countries. Marine organisms harbor incredibly diverse natural products with novel pharmaceutical applications. Among all the marine microorganisms, actinomycetes remain the most popular because of their capacity to produce a wide range of secondary metabolites that can be developed into drugs for treatment of wide range of diseases in human, agriculture, and veterinary sectors. Further, these compounds also hold the potential in treatment of life-threatened infections in humans. Numerous antibacterial, antifungal, cytotoxic, neurotoxic, antiviral, and antitumor compounds against new targets including AIDS, anti-inflammation, aging process, and immunosuppression have been characterized from marine actinomycetes. *Streptomyces* is the most prominent genus studied so far in this regard. However, many rare actinomycete genera have also been reported to produce a diverse array of antimicrobial compounds including polyenes, peptides, macrolides, aminoglycosides, polyether, etc. This chapter highlights the metabolite profiling of marine actinomycetes with respect to current status on drug discovery programs. It further stresses on the emergence of discovery of new antimicrobial metabolites, as the replacement of already existing ones, due to serious problem of antibiotic resistance among the human pathogens.

Keywords Marine actinomycetes · Metabolite profiling · Antibiotic resistance · Antimicrobial metabolites · Drug discovery

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Abbreviations

AGS	Human gastric adenocarcinoma cells
DKP	Diketopiperazine
ECD	Electron capture detector
FDA	Food and drug administration
GC-MS	Gas chromatography mass spectrometry
HepG-2	Human liver cancer cell lines
HPLC	High performance liquid chromatography
HRESIMS	High resolution electrospray ionization mass spectrometry
HRTOFMS	High resolution time-of-flight mass spectrometry
IC_{50}	Half-maximal inhibitory concentration
KB	Keratin-forming tumor cell lines
LC-MS	Liquid chromatography mass spectrometry
LU-1	Lung cancer cell lines
MAC	*Mycobacterium avium* complex
MCF-7	Breast cancer cell line
MiaPaca-2	1-Pancreatic carcinoma cell lines
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
NMR	Nuclear magnetic resonance
TLC	Thin layer chromatography
VRE	Vancomycin-resistant *Enterococci*
WHO	World Health Organization

13.1 Introduction

Emergence of antibiotic resistance in pathogens has become an alarming problem over the globe. In addition, the decline in the discovery and development of new antibiotics has created havoc in the health sector (Genilloud 2017; Durand et al. 2019). The development of multiple drug resistance in the pathogenic strains reduced susceptibility to antimicrobial compounds and modification of the target drugs has led to an increase in deaths caused by the infectious diseases worldwide. These pathogenic bacteria possess a number of virulent factors, some encoded in plasmids, bacteriophages, and the bacterial chromosomes. Such organisms can also colonize in a biofilm protecting the cells against therapeutic antibacterial agents (Brander et al. 2005; Lino and Degracious 2006). According to the list on the fetal human pathogens, released by World Health Organization (WHO) in 2017, there are a total of 12 bacterial families having multiple drug resistance (WHO 2017). O'Neill (2016) reported that approximately, 7,00,000 deaths occur every year due to multi-drug-resistant pathogens, and this may increase to ten million per year by 2050, if the current trend continues. Organisms may develop multiple drug resistance by various

mechanisms; such as presence of antibiotic degrading enzymes, antibiotic altering enzymes, and gene transfer processes like conjugation, transformation, and transduction. Therefore, it necessitates the search of naturally occurring novel antimicrobial compounds to curve the increasing menace of the infection (Vasavada et al. 2006; Thumar et al. 2010).

13.2 Antibiotics: Past and Present

Nature is the great treasure of millions of prokaryotes and eukaryotes which includes approximately 0.5 million plant species, 10^{11}–10^{12} microbial species and 1.5 million fungi. Unfortunately, only a small fraction out of it (approximately 250,000–300,000) has been documented (Berdy 2012; Locey and Lennon 2016). The microbial metabolites are used as the main bioactive scaffold for the development of the novel antibiotics instead of using the already known synthetic combinational treasure of molecules to develop novel drugs (Challinor and Bode 2015). The period spanning 1950–1960 is considered as "The golden age of antibiotics." During this time phase, the large-scale cultivation of microorganisms and extraction of secondary metabolites for the identification of novel antimicrobial compounds was carried out. Genus *Streptomyces* alone is identified as the huge source of novel antimicrobial compounds including antibacterial, antifungals, antiprotozoal, and antivirals. US Food and Drug administration (FDA) gave approval to approximately 1211 small molecule drugs during 1981–2014, among which approximately 65% accounted for natural chemicals/compounds (Newman and Cragg 2016; Noman Van 2016).

13.2.1 Antibiotics from Actinomycetes: Research and Developments

During the last 76 years of research on the actinomycetes for novel bioactive metabolites for human welfare, more than 5000 bioactive compounds were explored and investigated. During this period, the actinomycetes research advanced in various dimensions, from isolation and screening techniques to molecular approaches including post-genomic research for metabolites (Demain and Sanchez 2009; Subramani and Aalbersberg 2012). According to a report by Subramani and Sipkema (2019), during 2007–2017, approximately 177 new species of marine actinomycetes were isolated from geographically rare habitats and belonged to 33 families including three novel families and 29 new genera. The single genus *Streptomyces* produces more than 80% of all actinomycetes origin antibiotics (Subramani and Aalbersberg 2013). Ten major classes of antibiotics are produced by actinomycetes including oligomycin-type macrolids, polyene macrolids,

daunomycin-type anthracyclines, non-actin type cyclopolylactones, aminoglycosides, streptothricin, nigericin-type polyethers, cyclopolylactones, quinoxaline-peptides, and actinomycins (Berdy 2012).

13.2.2 Marine Actinomycetes: The Source of Novel Antimicrobial Compounds

It is believed that till date we could explore only a small portion of marine microbes. Because of limited accessibility and lack of proper leads, many unique biomolecules from different marine microbial communities are waiting to be discovered. The major pharmaceutical companies are at the verge of losing interest from natural products of microbial origin and focusing on alternative discovery approaches, such as combinational chemistry (Koehn and Carter 2005). This paradigm shift is because of the over-exploitation of the microbial resources and continued rediscovery of compounds that are already in use. However, natural product research has renewed the interest because of significant rise in the demand of novel compounds to treat drug-resistant microbial infections (Li and Vedaras 2009). This is mainly due to the low returns from alternative discovery platforms. It included the exploration of microbial wealth from poorly and less attended habitats, a concept based on the assumption that organisms evolve new bioactive metabolites in order to adapt to the unusual/extreme environments (Letzel et al. 2013). In the light of this knowledge, marine actinomycetes have recently focused attention with emphasis on their bio-catalytic potential and pharmaceutically important secondary metabolites (Sharma et al. 2020; Rathore et al. 2021).

Actinomycetes are a group of industrially important microorganisms because of their capability to produce a range of commercially viable products in various sectors; including agriculture, healthcare, veterinary, food, and nutrition (Sisi et al. 2020; Thakrar and Singh 2019; Thumar and Singh 2009). As per the records until October, 2016, the domain Bacteria includes 30 currently recognized phyla, the Actinobacteria being one of the largest phyla with 6 families, about 18 orders, almost 63 families and more than 370 genera (Subramani and Sipkema 2019). Despite a critical role in biogeochemical cycles, the actinomycetes also produce a variety of enzymes (Thumar and Singh 2007a, b; Chen et al. 2020) and therapeutic compounds (Sisi et al. 2020). There are approximately 500,000 naturally occurring biological compounds, from which approximately.

70,000 are microbially derived molecules and 29% are solely derived from actinomycetes. Actinomycetes are Gram-positive, high G + C (>55%) bacteria which were earlier misbelieved as an intermediate link between bacteria and fungi. Being saprophytic in nature, they are the dominant group of soil microflora involved in recycling of organic matter. The metabolites obtained from actinomycetes range from enzymes, antitumor agents, immunity-modifiers, enzyme inhibitors, cytotoxic molecules to vitamins, and nutritional material.

Approximately, 70% of the surface of planet Earth is covered by oceans, accounting for nearly 97% of total water and possessing 80% of the life. There are 15 exclusively marine phyla out of total 33 known animal phyla (Margulis and Chapman 2009). The marine habitats vary in their ecological pressure with respect to available nutrients, pressure, light, oxygen, predation, competition for space, etc. In order to survive under such extreme conditions, marine organisms have developed unique survival strategies, such as secretion of potent and novel secondary metabolites (Skropeta and Wei 2014). Various unexplored or underexplored ecosystems are the most promising sources of novel actinomycetes (Dhakal, et al. 2017). Many of these compounded are afforded by marine actinomycetes belonging to deep sea sediments, marine sponges, marine invertebrates, plants, and coral reefs (Zhang et al. 2005; Thomas et al. 2010; Vynne et al. 2011; Blunt et al. 2013; Viegelmann et al. 2014).

13.2.2.1 Bioactive Compounds from Marine Actinomycetes with Novel Pharmaceutical Potential

Research on pharmaceutically active metabolites from marine actinomycetes is emerging as a hot spot since a decade. A significant number of varied and novel molecules have been isolated from marine-derived actinomycetes. A new molecule, 3-(4-hydroxybenzyl) piperazine-2,5-dione was obtained from a marine *Streptomyces* sp. (Sobolevskaya et al. 2007). Molecular structure of the compound was drawn on the basis of NMR and mass spectroscopy. Its cytotoxic activity was checked on sperm and eggs of the sea urchin *Strogylocentrotus intermedius*.

Actinomycetes exhibit a tremendous taxonomic diversity ranging from the most typical genus *Streptomyces* to rare and exotic non-*Streptomyces* genera including *Dietzia, Salinispora, Marinophilus, Rhodococcus, Solwaraspora, Salinibacterium, Williamsia, Verrucosispora, and Aeromicrobium*, and thereby, increasing the possibilities of new potent bioactive metabolites (Valliappan et al. 2014). There are many compounds from marine actinomycetes, which have been selected for the pharmaceutical trial based on their strong potential. For instance, Diazepinomicin—a dibenzodiazepine alkaloid extracted from *Micromonospora* strain, which exhibited significant antitumor activities. Further, it is also nominated for clinical trials in phase II for the treatment of human glioblastoma cancer (Charan et al. 2004; Mason et al. 2012).

Salinispora is a newly described genus of obligate actinomycetes and also a rich source of such compounds (William and Jensen 2006; Williams et al. 2007a). Diverse categories of secondary metabolites such as cyanosporaside A, saliniketal A and B (Williams et al. 2007b) and sporolide A (Buchanan et al. 2005) have been discovered from this actinomycete on the basis of numerous chemical investigations. Recent studies highlighted *Salinispora* and its extraordinary biosynthetic diversity (Jensen et al. 2015). Interestingly, Salinosporamide A, a β-lactone-γ-lactam obtained from *Salinispora tropica* could enter clinical trials soon after its discovery to cure multiple myeloma.

13.3 Metabolite Profiling of Marine Actinobacteria

Majority of the drug discovery programs are oriented around actinobacteria because of their abundant resourcefulness for discovery of numerous lead metabolites. Further, the emergence of unique metabolic pathways provides them an ability to synthesize diverse categories of bioactive metabolites which are rarely available in terrestrial habitats. Marine actinomycetes hold an important position in drug discovery programs in comparison to terrestrial counter parts, mainly because of their unique metabolic pathways and rich molecular library (Yang et al. 2019). Many new biologically active compounds have been isolated from marine actinomycetes from the year 2015 to 2021 as highlighted in Table 13.1.

13.3.1 Antibacterial Activities

Antibacterial substances are significant in the control of infectious diseases which may cause deaths due to drug resistance among the pathogens. The microbial pathogens have developed resistance against various antibacterial compounds. Marine actinobacteria are being used to develop effective newer drugs without any side effects (Table 13.1)

13.3.1.1 Antibacterial Compounds from Marine-Derived Streptomyces sp.

Reports say that out of 100% bioactive metabolites isolated from actinomycetes till date, more than 70% were derived from *Streptomyces* and rest from other rare actinomycete species. Until recently, a range of antibacterial compounds have been reported from marine-derived *Streptomyces* sp. Hassan et al. (2015) identified Salinamide F **(1),** from the culture broth of *Streptomyces* sp., having antibacterial activity against a range of bacterial pathogens including *Enterococcus faecalis, Enterobacter cloacae, Haemophilus influenzae,* and *Neisseria gonorrhoeae.* Chemical analysis of Salinamide F by HRTOFMS revealed its molecular formula $C_{51}H_{71}N_7O_{16}$. Similarly, aranciamycins I and J **(2)** from *Streptomyces sp.* CMB0150 showed moderate-to-severe activity against *Mycobacterium tuberculosis*, Gram-positive *Bacillus subtilis*, and human cancel cell lines with IC_{50} values 0.7–1.7 μM, >1.1 μM and >7.5, respectively (Khalil et al. 2015). *Streptomyces* sp.SNM5 has been reported to produce Hormaomycins B and C **(3)** under altered cultural conditions (Bae et al. 2015a). Very similar to this, rocheicoside A **(5)**—a cytosine type nucleotides discovered from *Streptomyces rochei* 06CM016 demonstrated significant antimicrobial activity (Aksoy et al. 2016). Similarly, Lacret and co-workers (2016) reported napyradiomycin MDN-0170 **(7)** from *Streptomyces zhaozhouensis* CA-271078 with antibacterial (against methicillin-resistant

Table 13.1 Novel bioactive metabolites from marine actinomycetes (From year 2015–2021)

Sr. no.	The organism	Name of the compound	Biological activity	Reference
01	*Streptomyces* sp.	Salinamide F	Antibacterial	Hassan et al. (2015)
02	*Streptomyces* sp. CMB0150	Aranciamycins I and J	Antibacterial	Khalil et al. (2015)
03	*Streptomyces* sp.SNM5	Hormaomycins B and C	Antibacterial	Bae et al. (2015a)
04	*Streptomyces* sp.	Mohangamides A and B	Antifungal	Bae et al. (2015b)
05	*Streptomyces rochei* 06CM016	Rocheicoside A	Antibacterial and antifungal	Aksoy et al. (2016)
06	*Streptomyces zhaozhouensis* CA-185989	Ikarugamycin derivatives	Antifungal	Lacret et al. (2015)
07	*Streptomyces zhaozhouensis* CA-271078	Napyradiomycin MDN-0170	Antibacterial and antifungal	Lacret et al. (2016)
08	*Streptomyces* sp. SCSGAA 0027	Nahuoic acids B-E	Antibacterial	Nong et al. (2016)
09	*Nocardiopsis* sp. SCSIO 10419, SCSIO 04583, SCSIO KS107	α-pyrones (1–8)	Antibacterial	Zhang et al. (2016)
10	*Streptomyces* sp. 182SMLY	Polycyclic anthraquinones	Antibacterial	Liang et al. (2016)
11	*Micromonospora* sp. 5–297	Tetrocarcins N and O	Antibacterial	Tan et al. (2016)
12	*Nocardiopsis* sp. G057	Compounds 1–12	Antibacterial and antifungal	Thi et al. (2016a)
13	*Micromonospora* sp. G019	Quinoline alkaloid and 1,4- dioxane derivative	Antibacterial	Thi et al. (2016b)
14	*Verrucosispora* sp. MS 100047	1-Hydroxy-2, 5-dimethyl benzoate	Antibacterial	Huang et al. (2016)
15	*Streptomyces* sp.*IMB094*	Neo-actinomycins A and B	Antibacterial and antifungal	Wang et al. (2017)
16	*Streptomyces* sp.SUK 25	Diketopiperazine derivatives	Antibacterial and cytotoxic	Alshaibani et al. (2017)
17	*Streptomyces* sp. HZP-2216E	N-arylpyrazinone	Antibacterial and cytotoxic	Zhang et al. (2017a)
18	*Streptomyces* sp. HZP-2216E	Indolizinium alkaloids and Bifilomycins	Antibacterial and cytotoxic	Zhang et al. (2017b)
19	*Streptomyces* sp. EGY1	Sharkquinone	Antitumor	Abdelfattah et al. (2017)
20	*Streptomyces* sp. M-207	Lobophorin K	Antibacterial and cytotoxic	Brana et al. (2017)
21	*Streptomyces chartreusis* NA02069	Streptazolins A and B	Antibacterial	Yang et al. (2017)

(continued)

Table 13.1 (continued)

Sr. no.	The organism	Name of the compound	Biological activity	Reference
22	*Micromonospora* sp. RJA4480	Ansa microlides (1–4)	Antibacterial	Williams et al. (2017)
23	*Micromonospora harpali* SCSIO GJ089	Spirotetronate aglycones	Antibacterial	Gui et al. (2017)
24	*Kribella* sp. MI481-42F6	Kribellosides	Antifungal	Igarashi et al. (2017)
25	*Actinomadura* sp. DSMS-114	Methylbenz[a]anthracene-7, 12-quinone	Antibacterial	Kurata et al. (2017)
26	*Thermoactinomyces vulgaris* ISCAR 2354	Thermoactinoamide A	Antibacterial	Teta et al. (2017)
27	Actinomycete HF-11225	Nivelactum B	Antibacterial	Chen et al. (2018)
28	*Streptomyces pratensis*	New angucycline-type antibiotics	Antibacterial	Akhter et al. (2018)
29	*Streptomyces coeruleorubidus* GRG 4	Bis (2-Ethylhexyl) phthal-ate (BEP)	Antibacterial and antitumor	Rajivgandhi et al. (2018)
30	*Streptomyces* sp. LHW52447	Actinomycins D1-D4	Antibacterial	Jiao et al. (2018)
31	*Streptomyces cyaneofuscatus* M-169	Anthramycin B	Antibacterial	Rodriguez et al. (2018)
32	*Streptomyces seoulensis* A 01	Streptoceomycin 1	Antibacterial	Zhang et al. (2018a)
33	*Streptomyces sp. ZZ745*	Bagremycins (F-G)	Antibacterial	Zhang et al. (2018b)
34	*Streptomyces xinghaiensis* SCSIO S15077	Tunicamycin E	Antibacterial and antifungal	Zhang et al. (2018c)
35	*Streptomyces* sp. IMB7–145	Niphimycins C-E	Antibacterial and antifungal	Hu et al. (2018)
36	*Nocardiopsis* sp.	Terretonin N-1	Antibacterial	Hamed et al. (2018a)
37	*Streptomyces mutabilis* sp. MII	Borrelidin B	Anticancer	Hamed et al. (2018b)
38	*Micromonospora carbonacea* LS276	Tetrocarcin Q	Antibacterial	Gong et al. (2018)
39	*Streptomyces chartreusis* XMA39	Medermycin, Streptoxepinmycin A-D	Antibacterial and antifungal	Jiang et al. (2018)
40	*Nocardiopsis* sp. CNQ-115	Fluvirucin	Antibacterial	Leutou et al. (2018)
41	*Lechevalieria aerocolonigenes* K 10–0216	Pyrizomicins A and B	Antibacterial and antifungal	Kimura et al. (2018)
42	*Kocuria marina* CMGS2	Kocumarin	Antibacterial	Uzair et al. (2018)

(continued)

Table 13.1 (continued)

Sr. no.	The organism	Name of the compound	Biological activity	Reference
43	*Streptomyces* sp. G212	Novel metabolites	Antibacterial and antifungal	Cao et al. (2019a)
44	*Streptomycetes* sp. G248	Lavandulylated flavanoids	Antibacterial	Cao et al. (2019b)
45	*Streptomycetes* sp. strain 271,078	Napyradiomycins	Antibacterial and cytotoxic	Carretero-Monila et al. (2019)
46	*Streptomycetes albolongus* CA-186053	Medermycin analog MDN-0171	Antibacterial	Lacret et al. (2019)
47	*Streptomycetes puniceus*	Diketopiperazines	Antifungal	Kim et al. (2019)
48	*Streptomyces* sp. ZZ741	Streptoglutirimides	Antifungal, antibacterial, and cytotoxic	Zhang et al. (2019a)
49	*Streptomyces* sp. SCSIO 41	Aranciamycin and Isotirandamycin	Cytotoxic and antibacterial	Cong et al. (2019)
50	*Streptomyces althioticus* MSM3	Desertomycin G	Antitumor and antibacterial	Brana et al. (2019)
51	*Streptomyces* sp. OPMA 1730	Nosiheptides, Griseoviridin, and Etamycin	Antibacterial	Hosoda et al. (2019)
52	*Streptomyces sp.* ZZ820	Streptoprenylindoles A-C	Antibacterial	Yi et al. (2019)
53	*Streptomyces atratus* SCSIOZH16	Atratumycin	Antibacterial	Sun et al. (2019)
54	*Salinispora arenicola* BRA-213	Salinapththoquinones	Antibacterial	Da Silva et al. (2019)
55	*Verucosispora* sp. SCSIO	Kendomycins	Antibacterial	Zhang et al. (2019b)
56	*Streptomyces* sp. G246	Lavandulylated flavanoids	Antibacterial and antifungal	Cao et al. (2020)
57	*Streptomyces* sp.EG1	Mersaquinone	Antibacterial	Kim et al. (2020)
58	*Streptomyces* sp.4506	Lobophorin L and M	Antibacterial	Luo et al. (2020)
59	*Streptomyces* sp.	*n*-hexadecanoic acid, tetradecanoic acid, and pentadecanoic acid	Antifungal	Sangkanu et al. (2021)

Staphylococcus aureus) and antifungal properties (against *Aspergillus niger* and *Candida albicans*). The compound was studied with respect to its structure on the basis of molecular modeling in combination with nOe—nuclear overhauser effect NMR spectroscopy—and coupling constant analysis. *Streptomyces* sp. SCSGAA 0027 yielded nahuoic acids B-E **(8)**; a novel nahuoic acid with SETD8 inhibition activity. Compound 1–5 showed antibiofilm activity against *Shewanella onedensis* MR-1 biofilms (Nong et al. 2016).

Neo-actinomycins A and B **(15)** were extracted from *Streptomyces* sp. IMB094 which displayed strong antibacterial activity against VRE (vancomycin-resistant *Enterococci*). Structure elucidation by spectroscopic analysis confirmed the presence of tetracyclic 5H-oxazolo (4,5-b) phenoxazine (Wang et al. 2017). *Streptomyces* sp. SUK 25 produced five active diketopiperazine (DKP) derivatives **(16)** which displayed significant activities against multi-drug-resistant *Staphylococcus aureus* (Alshaibani et al. 2017). Streptazolins A and B **(21)** were isolated, together with already reported streptazolin, from *Streptomyces chartreusis* NA02069, which displayed weak anti-*Bacillus subtilis* activity with MIC value of 64 μM. While compound A inhibited acetylcholinesterase (AchE) activity under in vitro conditions with IC_{50} value 50.6 μM, compound B was not active at all (Yang et al. 2017). Novel angucycline-type antibiotics 1 and 2 **(28)** from *Streptomyces pratensis* NA-ZhouA1 showed antibacterial activities against *Klebsiella pneumoniae*, *Escherichia coli,* and MRSA (methicillin-resistant *Staphylococcus aureus*) (Akhter et al. 2018). Bis (2-ethylhexyl) phthalate (BEP) **(29)** produced by *Streptomyces coeruleorubidus* GRG 4, inhibited CR (colistin resistant) *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* (Rajivgandhi et al. 2018). Recently, Jiao et al. (2018) reported actinomycins D1–D4 **(30)** from the culture broth of Streptomyces sp. LHW52447. They exhibited strong antibacterial activities against MRSA (MIC- 0.125–0.25 μg/ml).

Anthramycin B **(31)**, a potent anti-tubercular compound against *Mycobacterum tuberculosis* (MIC 0.03 μg/ml) has been isolated from *Streptomyces cyaneofuscatus* M-169. The structure elucidation of the compound revealed the presence of lactone carbonyl on first carbon and oxygenated enol on third carbon. Further, the ability of the organism to produce anthramycin B at very high quantities (17.7 mg/L) was evident during the studies (Rodriguez et al. 2018). A rare macrodilactone named Streptoceomycin 1 **(32)** with anti-microaerophilic bacterial activity has been extracted from *Streptomyces seoulensis* A 01. When characterized to unfold the structural details, it was found to possess a pentacyclic ring along with the ether bridge (Zhang et al. 2018a). Two Bagremycins analogs; F and G **(32)** were obtained from *Streptomyces* sp. ZZ745. Both the compounds were highly active against *Escherichia coli* and showed the MIC values 41.8 (F) and 61.7 (G) μM, respectively (Zhang et al. 2018b). Same way, *Streptomyces xinghaiensis* SCSIOS15077 is reported to produce tunicamycin E by Zhang et al. (2018c). Very high to moderate activities against *Bacillus thuringiensis* W102 and *Bacillus thuringiensis* BT01 were evident based on the MIC values (range: 0.0008–2 μg/ml). Further, four new naphthoquinones named Medermycin **(39)** and Streptoxepinmycin A-D were found in the extracts of *Streptomyces chartreusis* XMA39 (Jiang et al. 2018). These compounds afforded the antibacterial compounds against *E. coli* and MRSA along with antifungal activities against *Candida albicans*.

Cao et al. (2019a) reported novel metabolites **(43)** with antibacterial and antifungal activities from marine-derived *Streptomycetes sp.* G212. Nuclear magnetic resonance (NMR) and other analysis confirmed the presence of three new lavandulylated flavonoids (44) which showed significant inhibitory activities against multi-drug-resistant *Mycobacterium tuberculosis* H37Rv. Recently, Carretero-Monila et al. (2019) reported four new napyradiomycins (1–3, 5) **(45)** from

Streptomycetes sp. strain 271,078 with detailed characterization. While compound 1 had a functionalized prenyl side chains of napyradiomycin—A series, compound 2 and 3 harbored rings of chlorocyclohexane resembling to napyradiomycin B. The authors further identified compound 5 to be a new class of napyradiomycins on the basis of its cyclic ether ring and designated the compound as napyradiomycin D1. All the compounds also displayed remarkable inhibitory activities against *Mycobacterium tuberculosis*, *Staphylococcus aureus,* and cytotoxic activity against human liver cancer cell lines (Hepatoma G2). Lacret and co-workers (2019) isolated a new Medermycin analog MDN-0171 **(46)** from marine-derived *Streptomycetes albolongus* CA-186053 which showed potent activity against MRSA (methicillin-resistant *Staphylococcus aureus*) and *E. coli*. Streptoglutirimides A-J **(48)** with antibacterial (methicillin-resistant *Staphylococcus aureus*; MIC: 08–12 μg/ml), antifungal (*Candida albicans;* MIC: 08–20 μg/ml) and cytotoxic (human glioma U87MG and U251 cells with IC_{50} values 1.5–3.8 μM) activities was reported by Zhang et al. (2019a). They elucidated the structure of these compounds based on their HRESIMS data, ECD calculations, X-ray diffraction experiments, and NMR spectroscopic analysis.

Mycobacterium is a multi-drug-resistant organism and is known to cause serious diseases in humans including *Mycobacterium avium* complex (MAC). Cultivation of *Streptomyces* sp. OPMA 1730 yielded Griseoviridin, Nosiheptides, and Etamycin **(51)**. Interestingly, these compounds showed portent activities against *Mycobacterium avium* and *M. intracellulare* with MIC in the range of 0.024–1.5 μg/ml (Hosoda et al. 2019). Streptoprenylindoles A-C **(52)** was isolated from *Streptomyces* sp. ZZ820, which reflected the antibacterial activity against MRSA (Yi et al. 2019). Recently, Sun et al. (2019) reported atratumycin **(53)** from *Streptomyces atratus* SCSIOZH16 with broad spectrum antibacterial activity. The organic extract of sponge-derived *Streptomyces* sp. G246 yielded two new lavandulylated flavonoids **(56)**. These metabolites had a broad spectrum antibacterial activity against a range of Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative bacteria (*Enterococcus faecalis*, *Salmonella enterica*, *Pseudomonas aeruginosa*) (Cao et al. 2020). Similarly, Kim and co-workers (2020) reported mersaquinone **(57)** from *Streptomyces sp.* EG1 which displayed antibacterial activity against MRSA (MIC- 3.36 μg/ml). Luo et al. (2020) reported two new spirotetronates **(58)** natural products from marine *Streptomyces* sp.4506 with strong antibacterial activities.

13.3.1.2 Antibacterial Compounds from Marine-Derived NOCARDIOPSIS sp.

Genus *Nocardiopsis* is known for its biotechnologically versatile and ecologically important nature. Many species of *Nocardiopsis* have been reported to belong to hyper saline locations. Diverse antibacterial compounds including terphenyls, alkaloids, polyketides, quinoline alkaloids, amines, proteins, thiopeptides, and phenzines have been studied from this genus. Eight new α-pyrones **(9)** were obtained from

Nocardiopsis sp. SCSIO 10419, SCSIO 04583, and SCSIO KS107. They displayed antibacterial activity against *Bacillus cereus* and *Micrococcus luteus* (Zhang et al. 2016). The structure analysis revealed that the side chain was important to decide the characteristic high wavelength ECD transition. Similarly, *Nocardiopsis* sp. G057 afforded the secretion of 12 compounds each with different chemical properties (**12).** While antibacterial activity of compound 1 was evident against *E. coli* (MIC 16 μg/ml), compound 2 and 3 displayed the activity against both, Gram-positive and Gram-negative bacteria and the yeast *candida albicans,* respectively (Thi et al. 2016a).

Terpenes have emerged as an interesting group of bioactive metabolites these days, may be because of their diverse skeletal compositions. Soil-state fermentation of *Nocardiopsis* sp. yielded a highly oxygenated terretonin N-1 **(36)**—a unique tetracyclic 6-hydroxymeroterpenoid. While its antibacterial activity against Gram-positive *Staphylococcus warneri* was very significant, very low activity was detected against Gram-negative *E.coli* (7 mm) (Hamed et al. 2018a). Recently, Fluvirucin B6 **(40)**—a 14-membered macrolactum was extracted from *Nocardiopsis sp.*CNQ-115. Surprisingly, it exhibited weak antibacterial activity against Gram-positive *Bacilli* and no effect at all on Gram-negative bacteria (Leutou et al. 2018).

13.3.1.3 Antibacterial Compounds from Marine-Derived Micromonospora sp.

Genus *Micromonospora* has been established as a vigorous model for the drug discovery module since its discovery before 100 years. It is still emerging as an untapped resource of many drug leads because of its unique chemical diversity. *Micromonospora* sp. 5–297 produced two new tetrocarcins N- and O-glycosidic spirotetronate antibiotics (**11**). Structural analysis revealed that tetrocarcin O is the derivative of tetrocarcin N. Both the compounds were able to inhibit the growth of *Bacillus subtilis* with MIC ranging from 02 μg/ml (tetrocarcin N) to 64 μg/ml (tetrocarcin O). Similarly, *Micromonospora* sp.G019 secreted quinoline alkaloid as well as 1,4-dioxine derivative **(13)**. While quinoline alkaloid showed antibacterial activity against human pathogens including *Enterococcus faecalis*, *Salmonella enterica,* and *Escherichia coli*, the 1, 4-dioxane derivative was effective against *Enterococcus faecalis* and *Candida albicans* (MIC- 32 μg/ml and 64 μg/ml, respectively) (Thi et al. 2016b). Ansa microlides 1–4 **(22)** were obtained from *Micromonospora* sp. RJA4480. These four antibiotics showed very high antibacterial activity against prominent human pathogens including methicillin-resistant *Staphylococcus aureus*, *Escherichia coli*, and *Mycobacterium tuberculosis* having MIC values of 0.0009, 0.0003, and 0.0009 (compound 1); 0.0001, 0.00083, and 0.0009 μg/ml (compound 2); 0.8, 1.8, and 7.0 μg/ml (compound 3); 0.06, 0.40, and 1.80 (compound 4) μg/ml, respectively (Williams et al. 2017).

Two spirotetronate aglycones **(23)**, 22-dehydroxymethyl-kijanolide and 8-hydroxy-22-dehydroxymethyl-kijanolide, were separated from *Micromonospora harpali* SCSIO GJ089. Both the compounds displayed very high activity against *Bacillus subtilis* and *B. thuringiensis* with MIC values ranging from 0.016 to 8.0 μg/

ml (Gui et al. 2017). The fermentation broth of *Micromonospora carbonacea* LS276 yielded a new spirotetrone Tetrocarcin Q **(38).** Bearing a glycosyl group, the compound possessed moderate potency (MIC; 12.5 μM), when tested against *Bacillus subtilis* ATCC 63501. Presence of a unique sugar (2-deoxy-allose) at C-9 position of the compound was reported for the first time from spirotetronate glycosides (Gong et al. 2018).

13.3.1.4 Antibacterial Compounds from Other Marine-Derived Actinomycetes

As stated earlier, there are only a few rare non-*Streptomyces* actinomycete genera have been identified from marine sources in recent past. Bulk cultivation of *Verrucosispora* sp. MS 100047 afforded the production of a new glycerol 1-hydroxy-2, 5-dimethyl benzoate—a salicylic acid derivative **(14)**. It exhibited selective activity against methicillin-resistant *Staphylococcus aureus* (MRSA) with MIC 12.5 μg/ml. In addition; the compound also displayed significant antitubercular activity (Huang et al. 2016). Kurata et al. (2017) reported the extraction and structure elucidation of *Actinomadura* sp. DS-MS-1145 derived, 6, dihydrol-1-8, dihydroxy-3-methylbenz(a)anthracene-7, 12-quinone **(25).** The purified compound possessed very strong activity when tested against Gram-positive *Staphylococcus aureus*. However, scare activities were evident against Gram-negative, *E. coli*; yeast, *Candida albicans* and fungi, *Aspergillus brasiliensis*. The molecular formula of the compound was $C_{19}H_{14}O_4$ with the molecular weight 306.0966 (Kurata et al. 2017). Thermoactinoamide A **(26)**—a lipophilic cyclopeptide antibiotic was obtained from thermophilic bacteria—*Thermoactinomyces vulgaris* ISCAR 2354. The cyclic hexapeptide displayed potent activity against *Staphylococcus aureus* with MIC value 35 μM (Teta et al. 2017). Nivelactum B **(27)** was obtained from actinomycete HF-11225, which displayed antibacterial activities against a range of pathogens.

The culture broth of very rare actinomycete *Lechevalieria aerocolonigenes* K 10-0216 yielded Pyrizomicins A and B **(41)**, which exhibited strong activity against a range of pathogenic bacteria. Interestingly, the results of NMR and mass spectroscopy proposed them as the new thiazolyl pyridine compounds (Kimura et al. 2018). A unique ultraviolet (UV) bioactive kocumarin **(42)** was obtained from *Kocuria marina* CMGS2 isolated from a sea weed *Pelvetia canaliculata*. It showed potent activity against pathogenic bacteria including MRSA (range of MIC; 15–20 μg/ml) and fungal isolates (minimum fungal inhibitory concentration; 15–25 μg/ml). The chemical structure elucidation studies confirmed the compound to be 4-[(Z)-2 phenyl ethenyl] benzoic acid (Uzair et al. 2018). Salinaphthoquinones **(54)** with broad spectrum antimicrobial activities were obtained from *Salinispora arenicola* BRA-213 (Da Silva et al. 2019). The solvent extracts of *Verucosispora* sp. SCSIO 07399 yielded three new analogs (B-D) of kendomycin **(55)** with very good antibacterial activities. The compounds were very effective against six Gram-positive bacteria with 0.5–8.0 μg/ml (range) of MIC values (Zhang et al. 2019b).

13.3.2 Antifungal Activities

While numerous antibiotics have been isolated from a range of marine microorganisms, studies to discover potent compounds against fungal pathogen are still at the limit. Marine actinobacteria can be a hidden treasure for the exploration of many antifungal metabolites. As discussed in the Table 13.1 Bae et al. (2015b), reported mohangamides A and B **(4)** from *Streptomyces* sp. which strongly inhibited *Candida albicans* isocitrate lyase. When studied by chromatographic and spectroscopic analysis, the compound showed a novel structure with dilactone-ethered pseudodimeric peptides having 14 different amino acids and two unusual acyl chains. Similarly, Ikarugamycin derivatives **(6)** from *Streptomyces zhaozhouensis* CA-185989 showed remarkable antifungal activities, when tested against *Candida albicans* (MIC; 2–4 μg/ml) and *Aspergillus fumigatus* (MIC; 4–8 μg/ml) (Lacret et al. 2015). Antifungal cocktail included three new tetramic acid macrolactams (polycyclic) with four already identified compounds. Further, the authors claimed that compound-1 from the above mixture was a newly isolated natural compound by them and hence, was given the trivial name isokarugamycin. Capping enzymes are different in terms of the structure and function in yeast, when compared to mammalian system. Cultivation of *Kribbella* sp. MI481-42F6 yielded Kribellosides **(24)**—RNA 5′-triphosphatase inhibitor which belong to the alkyl glyceryl ethers. Kribellosides inhibited *Saccharomyces cerevisiae* and secured the minimum inhibitory concentration in the range of 3.12–100 μg/ml. In addition, it also suppressed the activity of intracellular RNA 5'triohosphatase, named Cet1p from the same organism (Igarashi et al. 2017). Interestingly, tunicamycin E **(34)** with moderate antifungal activities (MIC; 02–1 μg/ml) against fuconazole-resistant *Candida albicans* ATCC96901 has been reported for the first time from *Streptomyces xinghaiensis* SCSIOS15077, isolated from the marine mud sample (Zhang et al. 2018c).

Antifungal activities of five Diketopiperazines **(47)** from marine *Streptomycetes puniceus,* against *Candida albicans,* were explained by Kim et al. (2019). Cyclo (L-Phe-L-Val) was a potent inhibitor with 27 μg/ml half-maximal inhibitory concentration. Streptoglutirimides A-J having antifungal (*Candida albicans;* MIC: 08–20 μg/ml), antibacterial (MRSA; MIC: 08–12 μg/ml), and cytotoxic (against human glioma U87MG and U251 cells with IC_{50} values 1.5–3.8 μM) activities was reported from *Streptomyces sp.* ZZ741 by Zhang et al. (2019a). They elucidated the structure of these compounds based on their HRESIMS data, ECD calculations, X-ray diffraction experiments, and NMR spectroscopic analysis.

Most recently, Sangkanu et al. (2021) extracted and identified n-hexadecanoic acid, tetradecanoic acid, and pentadecanoic acid **(59)** from *Streptomyces* sp. All the compounds were capable enough to inhibit *Talaromyces marneffei*—a thermally dimorphic pathogenic fungus.

13.3.3 Anticancer Activities

Mankind has witnessed many serious health problems such as cancer. Cao et al. (2019a) emphasised that the second most common reason of deaths in human females is breast cancer. While a number of metabolites with anticancer properties are known in recent years, there is need for extensive efforts in this direction. The immense development in the cancer research has geared up the search for anticancer compounds from natural resources. In this direction, many marine actinobacteria are also being studied with respect to their potential to produce antitumor, anticancer, and cytotoxic compounds. The literature suggests that only limited studies have focused on finding bioactive metabolites (Table 13.1) as anticancer agents from marine actinobacteria.

Cultivation of *Streptomyces* sp. 182SMLY produced two new polycyclic anthraquinones **(10)**. Proliferation and progression of glioma—a type of cancer in the glial cells of brain, was suppressed by these compounds (identified as streptoanthraquinone and N-acetyl-N-demethylmayamycin) with IC_{50} values >14–31 and 6.4–5 μM, respectively (Liang et al. 2016). *Nocardiopsis* sp. G057 was identified to produce 12 new compounds (**12).** These compounds displayed strong cytotoxic activity against keratin-forming tumor (KB) cell lines, lung cancer cell lines (LU-1), human liver cancer cell lines (HepG-2), and breast cancer cell line (MCF-7). However, compound 1 and 2 displayed poor effect ($IC_{50;}$ 128 μg/ml) against KB and LU cell lines even at high concentrations (Thi et al. 2016a). *Streptomyces* sp. IMB094-derived neo-actinomycins A and B **(15)** exhibited strong cytotoxic activities against adenocarcinomic human alveolar (A549) and human colon cancer cell lines (HCT116) with IC_{50} values 65.8 and 38.7 nM, respectively (Wang et al. 2017). Five active diketopiperazine (DKP) derivatives **(16)** were obtained from endophytic *Streptomyces sp*. SUK 25 which displayed low toxicity against human hepatoma HepaRG cell line (Alshaibani et al. 2017). Marine green algae *Ulva pertusa* associated *Streptomyces* sp. HZP-2216E secreted N-arylpyrazinone derivative **(17)** which selectively inhibited the cell division of malignant glioma cells. In addition, Streptoarylpyrazinone A was identified as a rare compound existing as a zwitterion from natural sources (Zhang et al. 2017a). Very similar to this, a novel indolizinium alkaloid, named streptopertusacin A, **(18)** was reported in the extracts of *Streptomyces* sp. HZP2216E. Chemical degradation, electronic circular calculations and nOe confirmed it to be a novel compound. Interestingly, it not only inhibited methicillin-resistant *Staphylococcus aureus*, but also affected of human glioma cells with great potency (Zhang et al. 2017b). Marine coral *Lophelia pertusa* – derived *Streptomyces* sp. M-207 afforded to produce Lobophorin K **(20)**. The compound managed to show very strong activity against two human cell lines; 1-pancreatic carcinoma (MiaPaca-2) and 2-breast adenocarcinoma (Brana et al. 2017). The activity of the compounds on human cell lines may establish *Streptomyces* sp. M-207 as the potential candidate for the treatment of highly prevailing breast cancer. Nivelactum B (1), a new macrolactum derivative **(27)** with antifungal activities has been demonstrated from marine-derived

actinomycete HF-11225, which showed weak cytotoxic and antifungal activity (Chen et al. 2018). Sponge- associated *Streptomyces* sp. LHW52447 produce four actinomycins D1-D4 **(30)** that possess an oxazole unit into the central phenoxazinone chromohpore. When studied for the cytotoxicity potential, D1-D4 showed the activity against WI-38 human diploid lung fibroblasts (Jiao et al. 2018).

Niphimycins C-E was produced by *Streptomyces* sp. IMB7–145 **(35)**. Hu et al. (2018) proposed their full configuration on the basis of studies on their biosynthetic gene clusters in ketoreductase and enoylreductase domains. The cytotoxicity of niphimycins C, E, and F was evident against cancerous human HeLa cell lines (IC_{50} range: 3.0–9.0 μM). N-acetylborrelidin B **(37)**—a naturally new microlide antibiotic was obtained from *Streptomyces mutabilis* sp. MII which demonstrated a potent cytotoxic effect even in crude extract against carcinoma cell lines of human cervix (KB-3-1) under in vitro conditions (Hamed et al. 2018b). The fermentative cultivation of *Streptomyces sp.* SCSIO 41 afforded aranciamycin and isotirandamycin **(49)**, which displayed in vitro cytotoxic activities against K560 cell lines with IC_{50} values; 22, 1.8, and 12.1 μM, respectively (Cong et al. 2019).

13.3.4 Antitumor Activities

Among various treatment strategies to combat cancer, chemotherapy remains the main and the most efficient treatment. Marine actinomycetes have been recently focused with respect to their metabolic and physiological abilities with the potential to produce antitumor compounds (Table 13.1) (Olano et al. 2009). Abdelfattah et al. (2017) reported a new ana-quinonoid tetracene, Sharkquinone **(19)** from the ethyl acetate extracts of *Streptomyces* sp. EGY1. Quantum chemical calculations and detailed spectral analysis revealed the structure of the compound, which displayed strong ability to overcome necrosis factor-related apoptosis in human gastric adenocarcinoma (AGS) cells. *Streptomyces coeruleorubidus* GRG 4 afforded to produce bis (2-ethylhexyl) phthalate (BEP) **(29)** which displayed very strong activity antitumor activities. It inhibited the proliferation and progression of human lung cancer cells in 24 h of treatment at the concentration of 100 μg/ml along with oxidative damage. Compound was extracted in methanol followed by TLC and HPLC analysis. Presence of carbonyl group was confirmed followed by GC-MS and LC-MS that further confirmed the compound to be BEP (Rajivgandhi et al. 2018).

Desertomycin G **(50)** was obtained from *Streptomyces althioticus* MSM3. It was first time reported to show antitumor activity against colorectal adenocarcinoma cells (DLD-1) and human breast cancer adenocarcinoma (MCK-7) cell lines. Desertomycin G also displayed moderate antibacterial activity against *Clostridium perfringens, Bacteroide fragilis*, *Haemophilus influenzae,* and *Neisseria meningitidis* (Brana et al. 2019).

13.4 Conclusion

The world is at urgent need of new drugs, especially antibiotics, where the unexplored and underexplored sources remain the natural products. New methodologies, such as genome sequencing in conjunction with molecular genetics, bioinformatics, and understanding of the regulatory and biosynthetic pathways would lead to develop rare molecules for diverse uses including pharmaceuticals. Several analytical approaches such as molecular networking, peptidogenomics and glycogenomics are clubbed with advance mass spectra-based analysis and investigations, making it possible to search strains that eliminate the randomness in the traditionally associated approaches. In the exploration of new resources for the novel bioactive molecules, the marine environment catches more attention because of the tremendous physiological variations among the organisms and also the metabolites of pharmaceutical interest. Expensive studies on the metabolite profiling of marine actinomycetes opened the hidden treasure of the capabilities, these fraction of microorganisms hold, with respect to the production of natural products with antibacterial, antifungal, antiviral, and antitumor properties. They are even diverse with respect to their structural skeletons including polyketides, caprolactones, lynamicins, sterols, terpenoids, cyclic hexapeptides, and nitrogen-containing compounds (e.g., alkaloids and peptides). However, the blending of traditional knowledge and modern analytical will certainly lead to the discovery of many new antimicrobial metabolites to combat the novel infectious agents.

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