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REVIEW

Marine *Streptomyces* as a novel source of bioactive substances

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Abstract Marine actinobacteria are the most economically as well as biotechnologically valuable prokaryotes. Representative genera of marine actinobacteria include *Actinomadura*, *Aeromicrobium*, *Dietzia*, *Gordonia*, *Marinophilus*, *Micromonospora*, *Nonomuraea*, *Rhodococcus*, *Saccharomonospora*, *Saccharopolyspora*, *Salinispora*, *Streptomyces*, *Solwaraspora*, *Williamsia*, *Verrucosispora* and several others. Among the genera of marine actinobacteria, the genus *Streptomyces* is represented in nature by the largest number of species and varieties, which differ greatly in their morphology, physiology, and biochemical activities. Marine *Streptomyces* occur in different biological sources such as fishes, molluscs, sponges, seaweeds and mangroves, besides seawater and sediments. In this review an evaluation is made on the present state of research on marine *Streptomyces* and its perspectives. The highlights include the production of metabolites such as antibiotics, anticancer compounds, enzymes, enzyme inhibitors and pigments by marine *Streptomyces* and their application as single cell protein and as probiotics in aquaculture. The marine environment contains a wide range of distinct *Streptomyces* that are not present in the terrestrial environment. With increasing advancement in science and technology, there would be greater demands in future for new bioactive compounds synthesised by *Streptomyces* from various marine sources.

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Introduction

Actinobacteria represents one of the largest taxonomic units among the 18 major lineages currently recognised within the domain Bacteria, including five subclasses and 14 suborders (Stackebrandt 2000). Among the five subclasses, actinobacteria—bacteria belonging to the Order Actinomycetales (commonly called actinomycetes)—account for approximately 7,000 of the metabolites reported in the *Dictionary of Natural Products*. Actinomycetes have a high GC content in their deoxyribonucleic acid (DNA) and grow as aerial mycelia (Yoshida et al. 2008). They are responsible for the production of about half of the discovered secondary metabolites (Bull 2004; Berdy 2005), notably antibiotics (Strohl 2004), antitumour agents (Olano et al. 2009), immunosuppressive agents (Mann 2001) and enzymes (Pecznska-Czoch and Mordarski 1988; Oldfield et al. 1998). A large number of actinomycetes have been isolated and screened from soil in the past few decades (Williams et al. 1989). Recently, the rate of discovery of new metabolites from terrestrial actinomycetes has decreased, whereas the rate of re-isolation of known compounds has increased (Fenical et al. 1999; Fenical and Jensen 2006). Thus, it is crucial that new groups of actinomycetes from unexplored or underexploited habitats be pursued as sources of novel secondary metabolites.

The diversity of life in the terrestrial environment is extraordinary, but the greatest biodiversity occurs in the oceans (Donia and Hamann 2003). Indeed, the marine environment is a virtually untapped source of novel

actinomycete diversity (Stach et al. 2003; Magarvey et al. 2004) and therefore, of new metabolites (Bull et al. 2005; Fiedler et al. 2005). The distribution of actinomycetes in the sea is largely unexplored and the presence of indigenous marine actinomycetes in the oceans remains elusive. This is partly caused by the lack of effort spent in exploring marine actinomycetes, whereas terrestrial actinomycetes have been, until recently, a successful source of secondary metabolites. Furthermore, scepticism regarding the existence of indigenous populations of marine actinomycetes arises from the fact that the terrestrial bacteria produce resistant spores that are known to be transported from land into sea, where they can remain available but dormant for many years (Bull et al. 2000). Thus, it has been frequently assumed that actinomycetes isolated from marine samples are merely of terrestrial origin.

Recent data from culture-dependent studies have shown that indigenous marine actinomycetes indeed exist in the oceans (Jensen et al. 2005a; Lam 2006). Actinomycete genera identified by cultural and molecular techniques from different marine ecological niches include *Actinomadura*, *Actinosynnema*, *Amycolatopsis*, *Arthrobacter*, *Blastococcus*, *Brachybacterium*, *Corynebacterium*, *Dietzia*, *Frankia*, *Frigoribacterium*, *Geodermatophilus*, *Gordonia*, *Kitasatospora*, *Micromonospora*, *Micrococcus*, *Microbacterium*, *Mycobacterium*, *Nocardioides*, *Nocardiopsis*, *Nonomurea*, *Psuedonocardia*, *Rhodococcus*, *Saccharopolyspora*, *Salinispora*, *Serinicoccus*, *Solwaraspora*, *Streptomyces*, *Streptosporangium*, *Tsukamurella*, *Turicella*, *Verrucosispora* and *Williamsia* (Stach et al. 2004; Jensen et al. 2005b; Ward and Bora 2006; Das et al. 2006a). Marine environmental conditions are extremely different from terrestrial ones; it is surmised that marine actinomycetes have different characteristics from those of terrestrial counterparts and therefore, might produce different types of secondary metabolites. Over the past decade, information on the diversity of actinomycetes in marine habitats has grown considerably, while the somewhat longer held interest in their ability to produce secondary metabolites has continued quite strongly (Stackebrandt et al. 1997).

Marine actinomycetes are a prolific source of secondary metabolites and the vast majority of these compounds are derived from the single genus *Streptomyces*. *Streptomyces* species are distributed widely in marine and terrestrial habitats (Pathom-aree et al. 2006) and are of commercial interest due to their unique capacity to produce novel metabolites. It was also expected that *Streptomyces* species will have a cosmopolitan distribution, as they produce abundant spores that are readily dispersed (Antony-Babu et al. 2008). These filamentous bacteria are well adapted to the marine environment and are able to break down complex biological polymers. The genus *Streptomyces* was classified under the family *Streptomycetaceae*, which includes Gram-positive aerobic members of the order Actinomycetales and suborder *Streptomycineae* within the new class Actinobacteria (Stackebrandt et al. 1997; Anderson and Wellington 2001), with a DNA G + C content of 69–78 mol%. In fact, the genus *Streptomyces* alone accounts for a remarkable 80% of the actinomycete natural products reported to date, a biosynthetic capacity that remains without rival in the microbial world (Watve et al. 2001).

Marine *Streptomyces* are widely distributed in biological sources such as fishes, molluscs, sponges, seaweeds, mangroves, besides seawater and sediments. These organisms are gaining importance not only for their taxonomic and ecological perspectives, but also for their production of novel bioactive compounds like antibiotics, enzymes, enzyme inhibitors, pigments and for their biotechnological application such as probiotics and single cell protein. In this review, the distribution of marine *Streptomyces* in various biological sources, their metabolite production and application in biotechnology are outlined in detail.

Metabolite production by marine *Streptomyces*

About 23,000 antibiotics have been discovered from microorganisms. It has been estimated that approximately 10,000 of them were isolated from actinomycetes (Okami and Hotta 1988). Actinomycetes, mainly the genus *Streptomyces*, have the ability to produce a wide variety of secondary metabolites as bioactive compounds, including antibiotics. The group has an enormous biosynthetic potential that remains unchallenged among other microbial groups. The immense diversity, along with its underutilisation is the fundamental reason for attracting researchers towards it for discovering novel metabolites. The genus *Streptomyces* is represented in nature by the largest number of species among all the genera of actinomycetes and figures over 500 species. The name *Streptomyces* was introduced in 1943 for the aerial mycelia-producing actinomycetes. Actinomycetes comprise about 10% of the bacteria colonising marine aggregates and can be isolated from various marine sources. Many actinomycete isolates from the depths of the oceans contain non-ribosomal polyketide synthase (NRPS) and polyketide synthase (PKS) pathways, the hallmarks of secondary metabolite production (Li and Piel 2002; Salmon et al. 2003).

Terrestrial soils have hitherto been the predominant and widely exploited source, and investigations on marine *Streptomyces* are few and inconclusive, though they are the important sources for new bioactive compounds (Okami 1984). During the last decade, there has been increasing number of novel metabolites possessing potent bioactivity isolated from marine-derived *Streptomyces* (Lam 2006; Wu et al. 2007). Many of them are cytotoxic and come from a wide variety of chemical structures such as

macrolides, α-pyrones, lactones, indoles, terpenes and quinones.

The *Streptomyces* strains isolated from different marine sediment samples collected from Tuticorin coast, South India, exhibited inhibitory activity against fish pathogens namely *Aeromonas hydrophila*, *Aeromonas sobria* and *Edwardsiella tarda* (Patil et al. 2001). Around 64 cultures of *Streptomyces* strains were isolated from marine sediment samples of Andaman coast. Among 64 *Streptomyces* sp., 44 isolates showed antibacterial activity and 17 isolates showed antifungal activity. Three isolates showed very promising antagonistic activities against multi-drug resistant pathogens (Sujatha et al. 2005a). Seven strains of *Streptomyces* isolated from marine sediments of South China, were found to produce siderophores which inhibit the growth of *Vibrio* spp. in vitro and act as biocontrol agents in aquaculture (You et al. 2005). Marine *S. griseorubens* isolated from marine sediment of China exhibited anti-tumour activity (Ye et al. 2009). Three *Streptomyces* strains (DKDVIT 1, 2 and 3) isolated from the marine soil samples of Ennore coastal region of Tamil Nadu, India showed antidermatophytic activity (Lakshmipathy and Krishnan 2009).

An antifungal protein (SAP) was found in the culture supernatant of a marine *Streptomyces* sp. strain AP77 isolated from the seawater of Japan, which is specific for *Pythium porphyrae*, a causative agent of red rot disease in *Porphyra* spp (Woo et al. 2002). The water surface microlayer of sea is still poorly explored, although it has been shown to contain a high density of metabolically active bacteria, often called bacterioneuston. *Streptomyces* from the surface microlayer in the Trondheim fjord, Norway, have been isolated and characterised. The strain exhibited antagonistic activity against non-filamentous fungi and Gram-negative and Gram-positive bacteria (Hakvag et al. 2008).

A novel strain *S. xiamenensis* was isolated from the national mangrove reserve in Fujian Province, China. It synthesised compounds such as menaquinones, MK-9(H4) and MK-9(H6) and fatty acids (Xu et al. 2009). *Streptomyces* strain 23-2B was isolated from the marine shellfish *Donax trunculus anatinus* collected from Mediterranean Sea (El-Shatoury et al. 2009). *Streptomyces* 23-2B was particularly noted for its high antitumour activity against Ehrlich's ascites carcinoma with plateau inhibitory effect, promising solid tumour selectivity and high cytotoxicity to human carcinoma of liver (HEPG2), cervix (HELA) and breast (MCF7).

Marine *Streptomyces* sp. (BTL7) was found to be associated with the marine sponge *Dendrilla nigra* and synthesised antibacterial substances. The findings suggested that secondary metabolites of *Dendrilla nigra* might have been synthesised by the associated bacterial endosymbionts (Selvin et al. 2004). About 74% of *Streptomyces* isolates were found to be associated with the sponge *Hymeniacidon perleve* (Zhang et al. 2006). In another report, isolation of marine *Streptomyces* associated with sponges *Callyspongia diffusa* were screened for antimicrobial activity against pathogenic bacteria and fungi (Gandhimathi et al. 2008). An exploration on the functional role of the antagonistic producer strain *S. dendra* sp. nov. MSI051 showed hypothetical factors including the antagonistic potential of MSI051 against biofilm bacteria and a ubiquitous defence enzyme phospholipase A2 (PLA2) in host sponge as well as in bacterial symbiont MSI051. Isolate MSI051 also showed a broad spectrum of antibacterial activity. Polyketide synthase gene type II in MSI051 ultimately evidenced the antagonistic potential. Antimicrobial activity was found to be positively skewed towards biofilm bacteria. All factors imply the functional role of MSI051 in the protection of host sponge against fouling processes (Selvin 2009). Recently about 94 isolates of *Streptomyces* were found to be associated with four marine sponges namely *Callyspongia diffusa*, *Mycale mytilorum*, *Tedania anhelans and Dysidea fragilis* collected from South West coast of India. These strains showed antibacterial and antifungal activities (Dharmaraj and Sumantha 2009).

Marine *Streptomyces* have proven to be efficient producers of bioactive metabolites which have a wide range of activities such as antibacterial, antifungal, antitumour, anticancer, cytotoxic, etc. Depending on the chemical nature, these bioactive substances are classified as follows:

Peptides

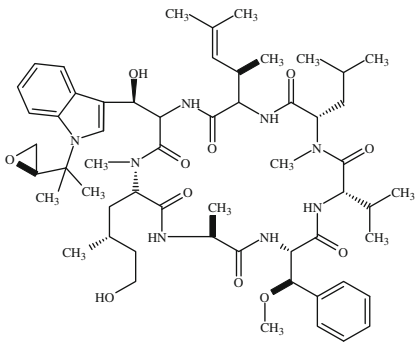
Peptides are short polymers of amino acids. Most of the *Streptomyces* peptides are cyclic and contain further rare structural elements such as chromophores or uncommon amino acids. The peptides include cyclomarin A (**1**), cyclic in nature and produced by an unidentified marine *Streptomyces* sp. Cyclomarins showed anti-inflammatory and antiviral activities (Renner et al. 1999). Piperazimycins A-C (**2**) are cytotoxic hexadepsipeptides isolated from the fermentation broth of a *Streptomyces* sp. Piperazimycin A exhibited potent in vitro cytotoxicity against multiple tumour cell lines (Miller et al. 2007). Another new 3-(4-hydroxybenzyl) piperazine-2, 5-dione was isolated from the marine actinobacterium *Streptomyces* strain KMM7210. The cytotoxic activities of the compounds were estimated from their effects on sperm and eggs of the sea urchin *Strongylocentrotus intermedius* (Sobolevskaya et al. 2007). Allophycocyanin is one of the most important marine active peptides. Previous studies suggested that allophycocyanin could remarkably inhibit the S-180 carcinoma in mice, indicating its potential pharmaceutical use. This was isolated from marine *Streptomyces* strain M097 (Hou et al. 2006). Two cyclic peptides

dehydroxy-nocardamine and desmethylenyl-nocardamine along with nocardamine (**3**) have been isolated from a *Streptomyces* sp. which was obtained from an unidentified marine sponge. These new compounds exhibited weak inhibition against the enzyme sortase B (Lee et al. 2005). Salinamides A and B (**4**) are bicyclic depsipeptides produced by a *Streptomyces* sp. CNB-091 isolated from the jelly fish *Cassiopeia xamachana*. These metabolites are useful as antibiotic and anti-inflammatory agents (Moore et al. 1999). Two new dipeptide derivatives, 8-amino-[1, 4]diazonane-2, 5-dione (**5**) and leucyl-4-hydroxyproline (**6**) were isolated from marine *S. acrimycini* and their biological roles are yet to be determined (Hernandez et al. 2004). Various peptides produced by marine *Streptomyces* are displayed in Fig. 1.

Quinones

Quinones are compounds having a fully conjugated cyclic dione structure. They are common constituents of biologically relevant molecules. Marine *Streptomyces* are especially rich in highly biologically active quinones. Recent examples are the complex C-glycosides himalomycins A (**7**) and B (**8**), anthraquinones with the rare fridamycin E chromophore, a precursor of the anthracycline antibiotics. They were obtained from *Streptomyces* sp. 6921 isolated from marine sediments of Mauritius and exhibited strong antibacterial activity (Maskey et al. 2003). Anthraquinone, 1,8-dihydroxy 2-ethyl 3-methyl anthraquinone was isolated from marine *Streptomyces* sp. FX-58. This compound showed cytotoxic activities (Huang et al. 2006). Tetracenomycin D (**9**) is an anthraquinone antibiotic produced by *S. corchorusii* AUBN (1)/7 (Adinarayana et al. 2006). It showed cytotoxicity against cell line HMO2 (gastric adenocarcinoma) and HepG2 (hepatic carcinoma) and possesses weak antibacterial activities against Gram-positive and Gram-negative bacteria. Komodoquinone A (**10**) and its chromophore, komodoquinone B (**11**) belong to the anthracycline antibiotics. They were isolated from the fermentation broth of *Streptomyces* sp. KS3 and showed neuritogenic activity. They induce cell differentiation in the neuroblastoma cell line, Neuro2A and arrests cell cycle at the G_1 phase (Itoh et al. 2003). The

Fig. 1 Peptides



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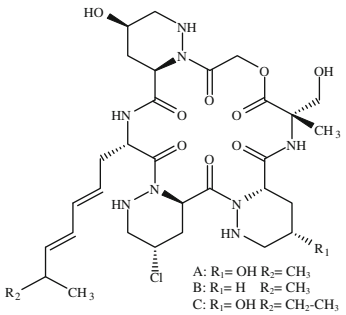

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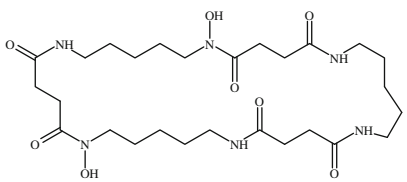

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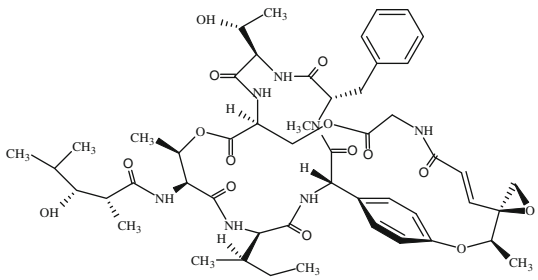

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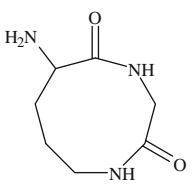

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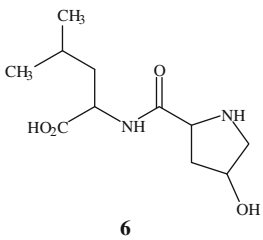

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benzopyrene quinones include resistomycin and resistoflavine. Resistomycin (**12**) is produced by *S. corchorusii* AUBN (1)/7 (Shiono et al. 2002). This is an inhibitor of HIV-1 protease. Resistoflavine (**13**) is produced by *S. chibaensis* AUBN (1)/7 (Kock et al. 2005; Gorajana et al. 2006). The structures of the quinones discussed above are displayed in Fig. 2.

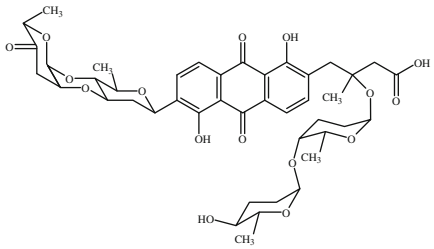
Macrolides

The macrolides are a group of drugs (typically antibiotics) whose activity stems from the presence of a macrolide ring, a large macrocyclic lactone ring to which one or more deoxy sugars may be attached. Generally, macrolides are protein synthesis inhibitors. The *Streptomyces* sp. M491, a marine actinobacterium produces a macrolide antibiotic named chalcomycin (**14**) and also some terpenes (Wu et al. 2007). Another macrolide antibiotic designated as chalcomycin B (**15**) was isolated from the culture broth of a marine *Streptomycete* isolate B7064 (Asolkar et al. 2002). The chemical structures of macrolides are shown in Fig. 3.

Terpenes

Terpenes are a large and varied class of hydrocarbons. They are the major biosynthetic building blocks within nearly every living creature. Terpenes are derived biosynthetically from units of isoprene, which has the molecular formula C_5H_8. As chains of isoprene units are built up, the resulting terpenes are classified sequentially by size as hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes, and tetraterpenes. The *Streptomyces* sp. NPS008187 isolated from marine sediment collected in Alaska, synthesised three new pyrrolosesquiterpenes, glyciapyrroles A (**16**), B (**17**) and C (**18**). They exhibited

Fig. 2 Quinones



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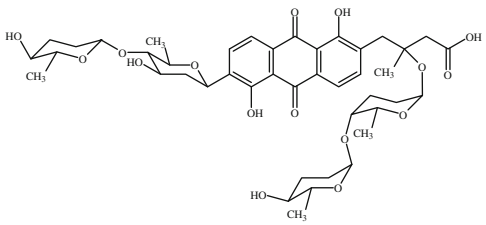

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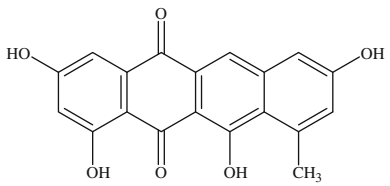

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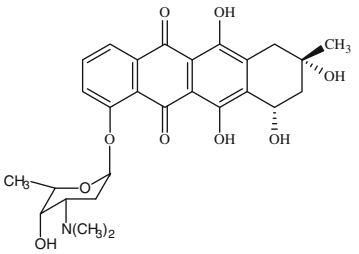

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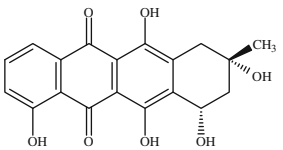

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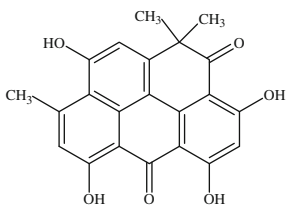

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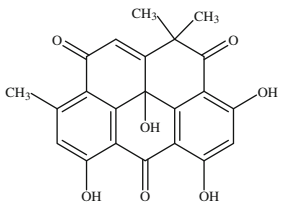

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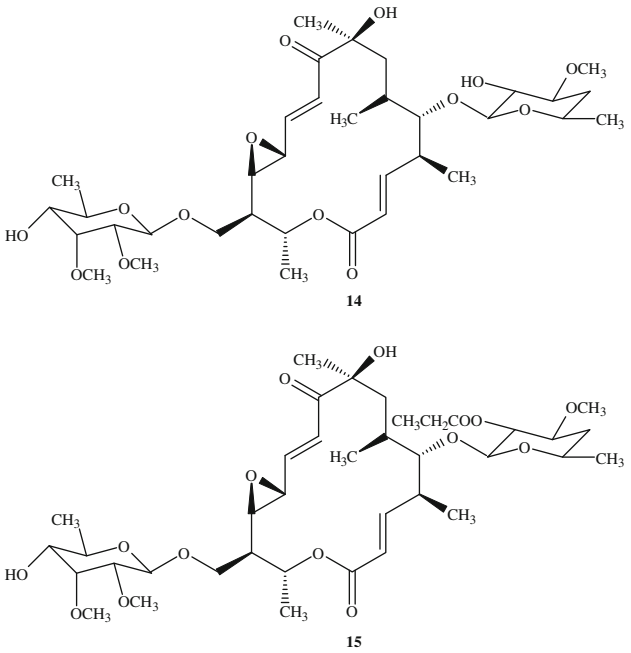


Fig. 3 Macrolides

antibacterial activity (Macherla et al. 2005). Azamerone (**19**), a novel meroterpenoid was isolated from the saline culture of marine-derived *Streptomyces*. Azamerone is composed of an unprecedented chloropyranophthalazinone core with a 3-chloro 6-hydroxy 2, 2, 6-trimethylcyclohexylmethyl side chain. It appears to be the first natural product with a phthalazione ring (Cho et al. 2006a). A new sesquiterpene known as selina-4(14),7(11)-diene-8,9-diol (**20**) was isolated from *Streptomyces* sp.QD518. This compound showed anticancer properties (Wu et al. 2006). Amorphane sesquiterpenes namely 10α,11-dihydroxyamorph-4-ene (**21**), 10α,15-dihydroxyamorph-4-en-3-one (**22**) and 5α,10α, 11-trihydroxyamorphan-3-one(**23**) are produced by *Streptomyces* sp. M491. The bioactivity of amorphane is unknown (Wu et al. 2007). T-Muurolol sesquiterpenes were isolated from *Streptomyces* strain M491 derived from marine sediment Qingdao coast, China. These sesquiterpenes of the T-muurolol family were tested for their cytotoxycity against 37 human tumour cell lines, but only 15-hydroxy-T-muurolol (**24**) showed moderate cytotoxic activity (Ding et al. 2009). The chemical structures of terpenes are diagrammatically shown in Fig. 4.

Tetraterpenes include carotenoids which are ubiquitous pigments synthesised by plants, fungi, algae, and bacteria. Industrially, carotenoids are used in pharmaceuticals, nutraceuticals, animal feed additives, as well as colorants in cosmetics and foods. Scientific interest in dietary carotenoids has increased in recent years because of their beneficial effects on human health, such as lowering the risk of cancer and enhancement of immune system function, which are attributed to their antioxidant potential. Carotenoid synthesis in prokaryotes occurs in a constitutive, light-induced or cryptic manner. Whereas the majority of microbes reported produce carotenoids constitutively, some organisms belonging to *Myxococcus*, *Streptomyces*, *Mycobacterium*, *Agromyces* and *Sulfolobus* form these pigments when the cells are illuminated. To date, the carotenoid production in *Streptomyces* has been performed with terrestrial strains like *S. griseus* (Schumann et al. 1996; Lee et al. 2001), *S. setonii* (Kato et al. 1995) and *S. coelicolor* A3 (2) (Takano et al. 2005). There was a recent report on the production of carotenoids by marine *Streptomyces* strain AQBWWS1 isolated from marine sponge *Callyspongia diffusa* (Dharmaraj et al. 2009).

Polyketides

Polyketides are a large and structurally diverse group of natural products synthesised by multifunctional or mono- or bi-functional enzymes called polyketide synthases (PKSs) by repetitive condensations of small carboxylic acid units in a manner similar to fatty acid synthesis (Staunton and Weissman 2001). Many of them are of industrial and medical importance. Some of the polyketides of industrial importance like doramectin, epirubicin and compounds like aurantimycin, chartreusin, concanamycin, kirromycin, lysolipin, polyketomycin were used for medical treatments (Weber et al. 2003). Generally in bacteria the genes required for the biosynthesis of a given polyketide are usually clustered.

The *Streptomyces* sp. JP95 isolated from the marine ascidian *Aplidium lenticulum* at Heron Island, Australia was found to biosynthesise the polyketide, griseorhodin A (**25**) and the biological role of the compound has not yet been determined (Li and Piel 2002). A marine inhabitant known as *S. psammoticus* produces a polyketide antibiotic SBR-22 (Sujatha et al. 2005b). It showed antibacterial activity against methicillin-resistant *Staphylococcus aureus*. Daryamides A (**26**), B (**27**) and C (**28**) are cytotoxic polyketides isolated from culture broth of a *Streptomyces* strain, CNQ-085 (Asolkar et al. 2006). These bioactive compounds showed weak to moderate cytotoxicity against the human colon carcinoma cell line HCT-116 and very weak antifungal activities against *Candida albicans*. Actinofuranones A (**29**) and B (**30**) were isolated from the fermentation broth of a marine bacterium related to *Streptomyces* genus. Actinofuranones A and B showed weak in vitro cytotoxicity against mouse splenocyte T-cells and macrophages (Cho et al. 2006b). Recently three new polyketides, phaeochromycins F (**31**), G, H were obtained from the culture broth of marine *Streptomyces* sp. DSS-18. These compounds exhibited cytotoxic effect (Li et al.

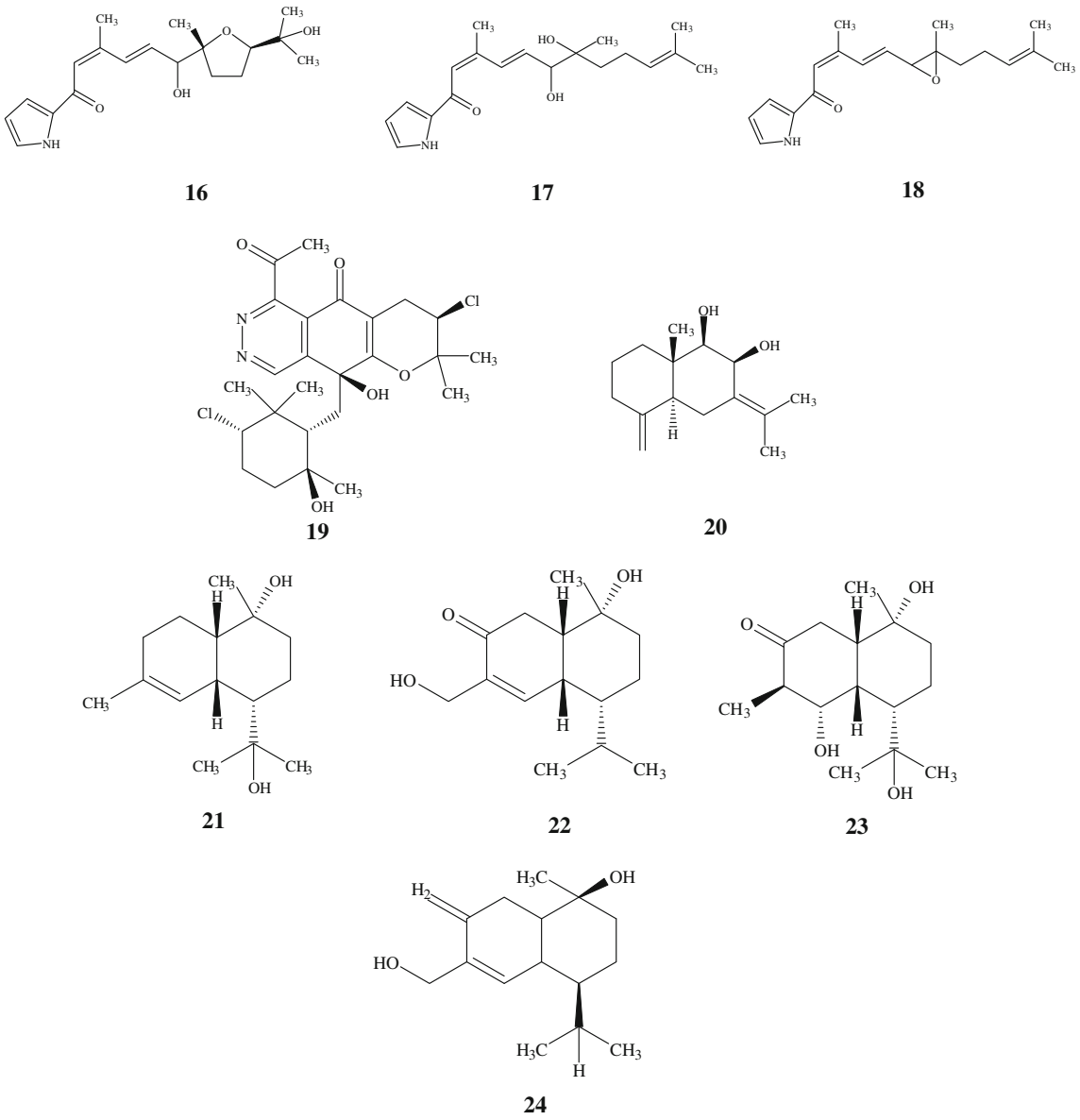


Fig. 4 Terpenes

2008). The structure of polyketide compounds are displayed in Fig. 5.

Enzymes

Marine *Streptomyces* strains (PDK2, PDK7) isolated from South Indian coast, produced L-asparaginase and exhibited cytotoxic effect on JURKAT cells (Acute T cell leukemia) and K562 cells (chronic myelogenous leukemia) (Dhevagi and Poorani 2006). *S. aurantiacus* isolated from Bhitarkanika mangrove ecosystem of Orissa, India exhibited different extracellular activity like phosphate solubilisation, lipase and L-asparaginase production (Gupta et al. 2007). *Streptomyces* marine isolates S3, S4 and K8 showed the production of extracellular anti-leukemic enzyme L-asparaginase obtained by solid-state and submerged fermentation (Basha et al. 2009). The *S. clavuligerus* strain isolated from the western coast of India, exhibited the production of alkaline protease (Thumar and Singh 2007). Thermostable alkaline protease was characterised from marine *S. fungicidicus* MML1614 (Ramesh et al. 2009).

Marine *Streptomyces* sp. DA11 isolated from South China, found to be associated with sponge *Craniella australiensis*, produced the enzyme chitinase and showed antifungal activities against *Aspergillus niger* and *Candida albicans* (Han et al. 2009). Chitin, a linear β-1,4-linked homopolymer of *N*-acetylglucosamine, is one of the three most abundant polysaccharides in nature besides cellulose

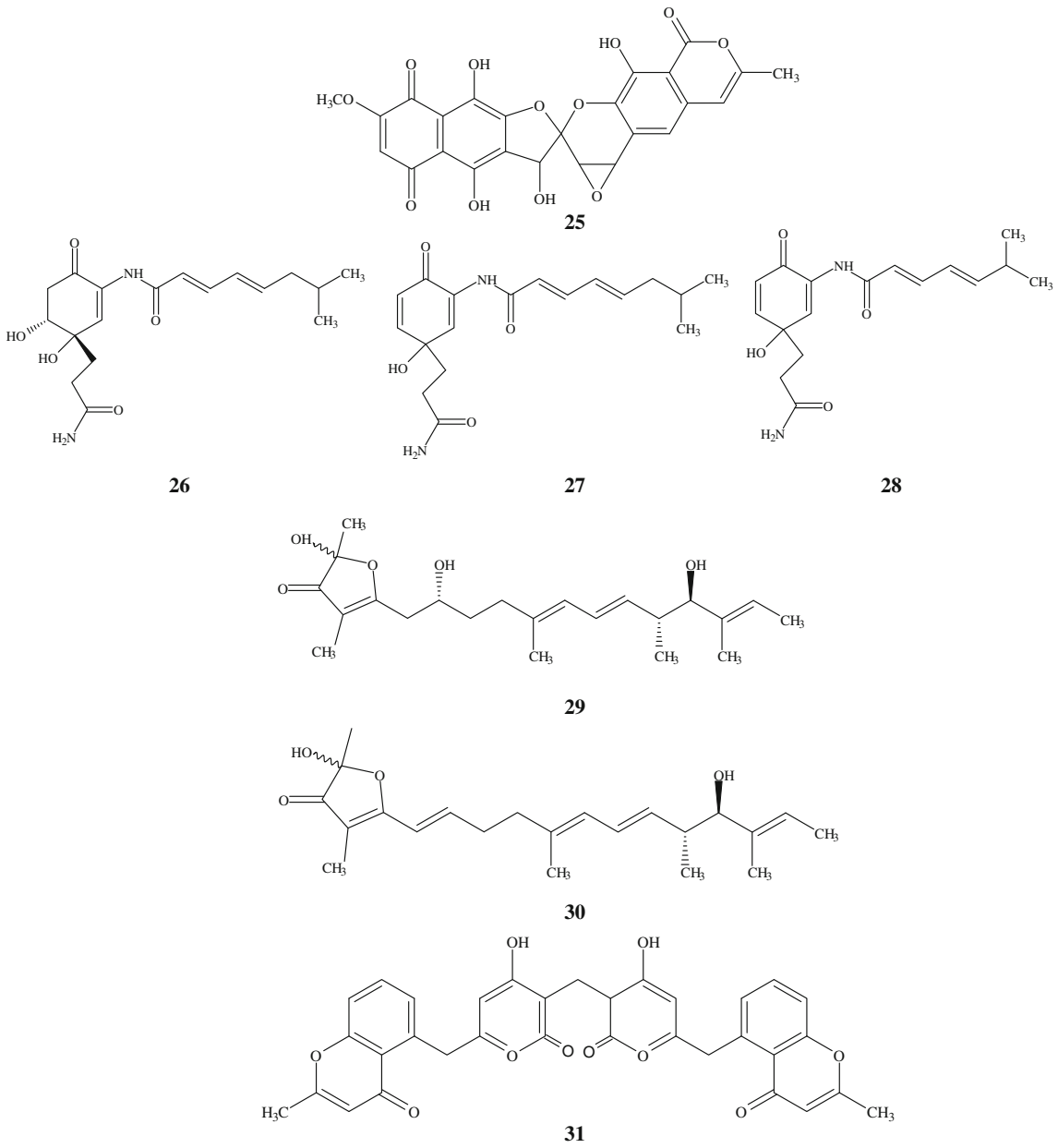


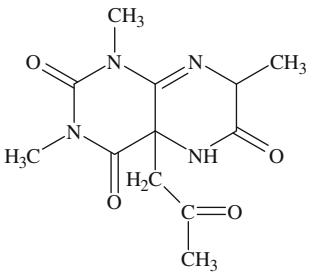
Fig. 5 Polyketides

and starch. The antifungal activity and highly biocompatible quality make chitinase and its derivatives particularly useful for biomedical applications, such as wound healings, cartilage tissue engineering, drug delivery, and nerve generation (Shi et al. 2006; Yan et al. 2006). The biodegradable and antifungal properties of chitinase are also useful for environmental and agricultural uses, food technology and cosmetics (Goosen 1997; Rabea et al. 2003; Lin and Lin 2005).

An alginate-degrading bacterium classified as *Streptomyces* sp. ALG-5 was isolated from marine seaweeds of South Korea (Kim et al. 2009). Alginate lyases catalyse the degradation of alginate through β-elimination of the glycosidic bond. More than 50 alginate lyases with various substrate specificities have been isolated from algae, marine invertebrates and a wide range of microorganisms. Most alginate lyases exhibit endo-cleaving activity.

Enzyme inhibitors

Enzyme inhibitors are molecules that bind to enzymes and decrease their activity. The binding of an inhibitor can stop a substrate from entering the enzyme's active site and/or hinder the enzyme from catalysing its reaction. Inhibitor binding is either reversible or irreversible. Irreversible inhibitors usually react with the enzyme and change it



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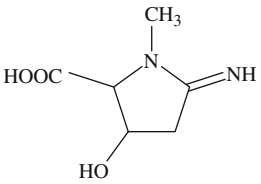

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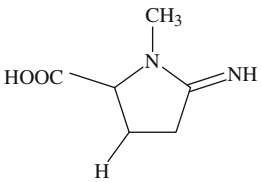

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Fig. 6 Enzyme inhibitors

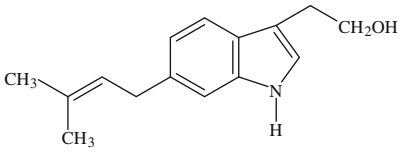
chemically. These inhibitors modify key amino acid residues needed for enzymatic activity. In contrast, reversible inhibitors bind non-covalently and different types of inhibition are produced depending on whether these inhibitors bind the enzyme, the enzyme-substrate complex, or both. A few enzymes inhibitors have been reported from marine *Streptomyces*. An α-amylase inhibitor was isolated from *S. corchorusii* subsp. *rhodomarinus.* subsp. nov (Imada and Simidu 1988). Pyrizinostatin (**32**) is an inhibitor of pyroglutamyl peptidase, isolated from culture of *Streptomyces* sp. SA-2289 (Aoyagi et al. 1992). Pyrostatin A (**33**) and B (**34**) are inhibitors of N-acetyl *β*-glucosaminidase, produced by *Streptomyces* sp. SA-3501 (Aoyama et al. 1995; Imada 2004, 2005). The chemical structures of these compounds are shown in Fig. 6.

Indole compounds

Three new cytotoxic 3,6-disubstituted indoles A (**35**), B (**36**) and C (**37**) (Fig. 7) obtained from *Streptomyces* sp. BL-49-58-005 were found to be associated with Mexican marine invertebrate (Jose et al. 2003).

Piericidins

Piericidins C_7 (**38**) and C_8 (**39**) are the two new members of the piericidin family, isolated from a marine *Streptomyces* sp. Piericidins C_7 and C_8 (Fig. 8) showed selective



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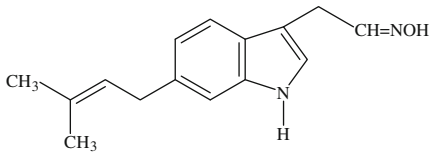

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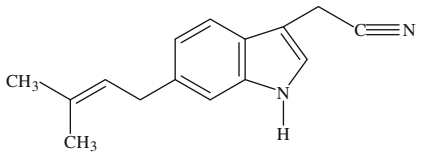

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Fig. 7 Indole compounds

cytotoxicity against rat glia cells transformed with the adenovirus E1A gene and Neuro2A mouse neuroblastoma cells (Hayakawa et al. 2007).

Trioxacarcins

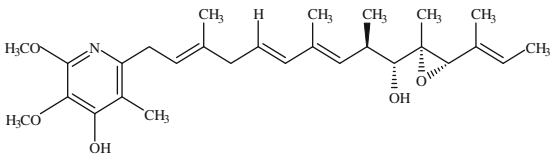
Trioxacarcins are complex compounds showing high antibacterial activity against Gram-positive and Gram-negative bacteria, and some of them possess high antitumour and antimalarial activities as well. Trioxacarcin A exhibited antifungal activities. Trioxacarcin A, B and C (**40**) (Fig. 8) were obtained from *S. ochraceus* and *S. bottropensis* (Maskey et al. 2004). Some of these compounds possess extremely high antiplasmodial activity, which is comparable to that shown by artemisinin, the most active compound against the pathogen of malaria.

Methylpyridine

Streptokordin is a new cytotoxic compound of the methylpyridine class isolated from the culture broth of *Streptomyces* sp. KORDI-3238 (Jeong et al. 2006). It exhibited significant cytotoxicity against several human cancer cell lines but showed no growth inhibition against bacteria and fungi.

Marinopyrroles

Marine *Streptomyces* strain CNQ-418 obtained from a marine sediment sample collected near La Jolla, California (Hughes et al. 2008), produced marinopyrroles A (**41**) and B (**42**) (Fig. 8) which were densely halogenated, axially chiral metabolites that contain an uncommon bispyrrole



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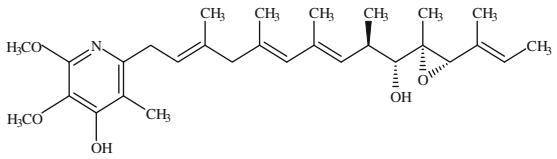

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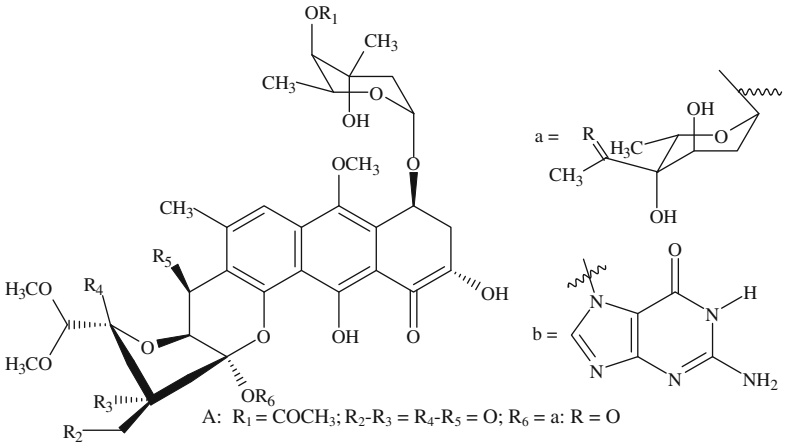

A: $R_1 = COCH_3$; R_2-R_3 = R_4-R_5 = O; R_6 = a: R = O

B: $R_1 = COCH_3$; $R_2 = R_3$ = OH; R_4-R_5 = O; R_6 = a: R = O

C: $R_1 = COCH_3$; R_2-R_3 = R_4-R_5 = O; R_6 = a: R = OH, H

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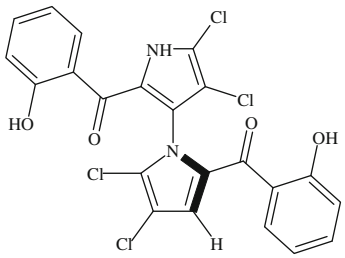

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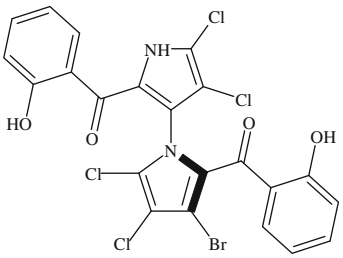

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Fig. 8 Piericidins, Trioxacarcins, Marinopyrroles

structure. The marinopyrroles possess potent antibiotic activities against methicillin resistant-*Staphylococcus aureus* (MRSA).

Sisomicin

Marine *Streptomyces* strain GB-2 isolated from coastal soil of China produced the antibacterial substance sisomicin (**43**) (Fig. 9) (Lu et al. 2009).

Triazolopyrimidine

The *Streptomyces* sp. Merv8102 derived from sediment samples of Paltium coast on the Mediterranean Sea of Egypt produced a novel triazolopyrimidine antibiotic, essramycin (**44**) (Fig. 9). The compound is antibacterially active with MIC of 2–8 μg/ml against Gram-positive and Gram-negative bacteria, while it showed no antifungal activity (El-Gendy et al. 2008b).

Esters

Bonactin (**45**) (Fig. 9), an antimicrobial ester, isolated from the *Streptomyces* sp. BD21-2 obtained from marine sediment sample collected at Hawaii displayed antimicrobial activity against both Gram-positive and Gram-negative bacteria as well as antifungal activity (Schumacher et al. 2003).

Caprolactones

Two new caprolactones R-10-methyl-6-undecanolide and (6R, 10S)-10-methyl-6-dodeconolide are produced by a

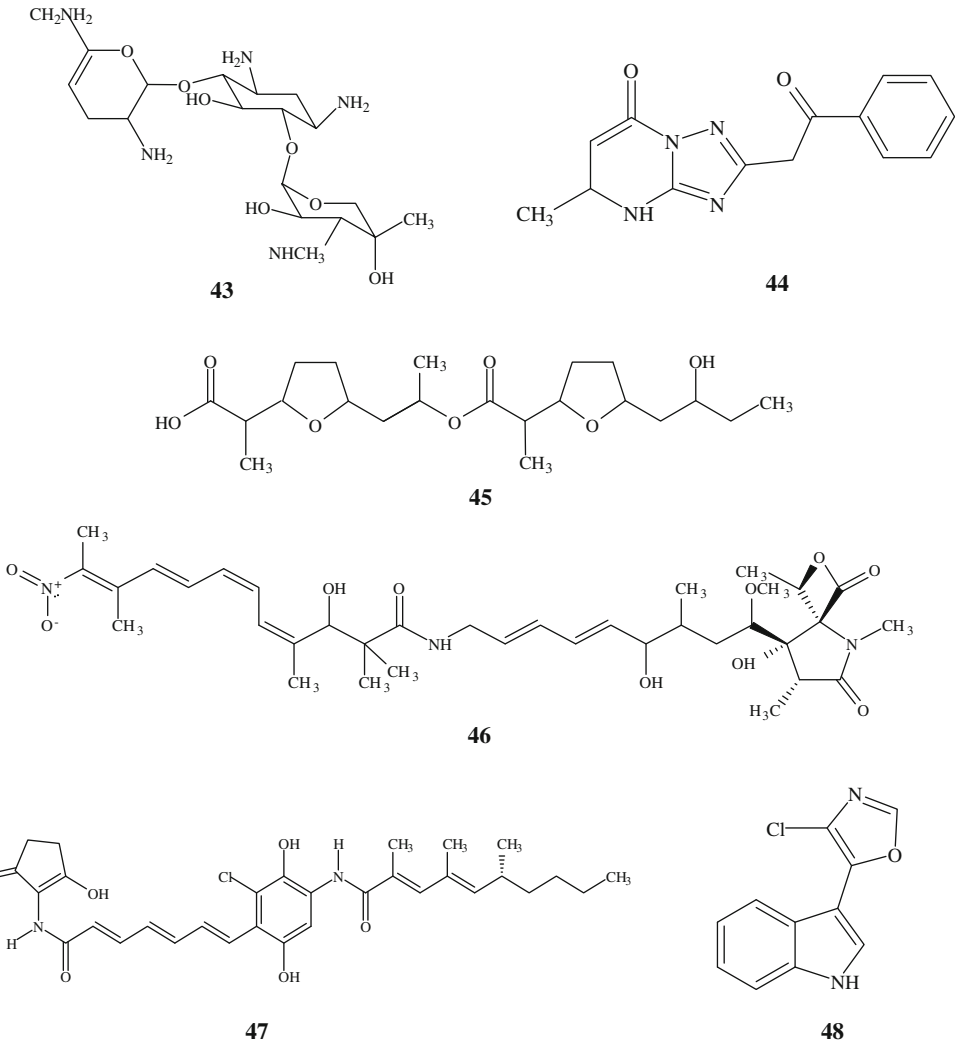

Fig. 9 Sisomicin, Essramycin, Bonactin, Lajollamycin, Chinikomycin A, Streptochlorin

marine *Streptomyces* sp. B6007. These caprolactones showed moderate phytotoxicity and low cytotoxocity against cancer cells (Stritzke et al. 2004).

Macrocyclic lactam

Aureoverticillactam, a novel 22-atom macrocyclic lactam was isolated from *S. aureoverticillaris*. It showed cytotoxicity against various tumour cell lines (Mitchell et al. 2004). Lajollamycin (**46**) (Fig. 9), a nitro-tetraene spiro β-lactone γ-lactam antibiotic isolated from *S. nodosus* (NPS007994) collected in marine sediment of California showed antimicrobial activity against both drug-sensitive and resistant Gram-positive bacteria and inhibited the growth of B16-F10 tumour cells in vitro (Manam et al. 2005).

Manumycin derivatives

Chinikomycins A (**47**) and B (Fig. 9) are chlorine-containing aromatic manumycin derivatives. They exhibit antitumour activity against different human cancer cell lines, but are inactive as antiviral, antimicrobial and phytotoxic agents. These compounds are produced by *Streptomyces* strain MO45 (Li et al. 2005).

Streptochlorin

Streptochlorin (**48**) (Fig. 9) was isolated from the fermentation broth of a marine *Streptomyces* strain 04DH110. Streptochlorin exhibited significant antiproliferative activity against human cultured cell lines (Jae et al. 2007).

Chartreusin

The marine Streptomycete isolates B5525 and B5342 produced chartreusin 2″-monoacetate (**49**) (Fig. 10). Chartreusin was not only antibacterially active, but also showed antitumour activity against different human cell lines (Maskey et al. 2002).

Butenolides

Butenolides, a family of α,β-unsaturated lactones, are often encountered among fungi, bacteria, and gorgonians. Their saturated analogues act as signalling substances in bacteria and enhance spore formation of Streptomycetes or induce metabolite production. Four types of butenolides were found in the extracts from the Streptomycete strains B 5632 and B 3497 (Mukku et al. 2000). The butenolides include (4*S*)-4,10-dihydroxy-10-methyl-undec-2-en-1,4-olide (**50**), (4*S*)-4,10-dihydroxy-10-methyl-dodec-2-en-1,4-olide (**51**) and the mixture of 3 and 4, (4*S*)-4,11-dihydroxy-10-methyl-dodec-2-en-1,4-olides (**52**) (Fig. 10).

Alkaloids

Aburatubolactams A (**53**), B (**54**) and C (**55**) (Fig. 10) were isolated from the marine *Streptomyces* sp. SCRC-A20. They were able to inhibit superoxide anion generation. Superoxide anions are thought to be closely associated with inflammation, cancer, and aging (Bae et al. 1996; Yamada et al. 1999).

Flavonoids

Flavonoids are polyphenolic compounds extremely common in higher plants, but very rare as bacterial metabolites. Actinoflavoside, a novel glycoside composed of a rare 2, 3, 6-trideoxy-3-amino-ribopyranoside (ristosamine) amino sugar and an aglycone reminiscent of the plant flavonoids, was isolated from the culture broth of a marine *Streptomyces* strain CNB-689 (Jiang et al. 1997). The structure of actinoflavoside was established by spectroscopic analysis and by chemical degradation. Actinoflavoside possesses a 5-hydroxymethyl flavonone skeleton which is different from all other flavonones known. Actinoflavoside showed only weak antibacterial activity against Gram-positive bacteria, including *Staphylococcus pneumonia*, *S. pyrogenes*, *S. aureus* and *Micrococcus luteus*. Some marine *Streptomyces* synthesise benzopyrone derivatives such as 7-methylcoumarin and the flavonoids, rhamnazin and cirsimaritin (El-Gendy et al. 2008a).

Isoflavonoids occur as phytochemicals of many plants. Marine *Streptomyces* sp. 060524 isolated from the South China Sea, capable of hydrolysing the glycosidic bond of isoflavone glycosides was isolated by detecting its β-glucosidase activity. Five isoflavone aglycones were isolated from culture filtrates and identified as genistein, glycitein, daidzein, 3′,4′,5,7-tetrahydroxyisoflavone and 3′,4′,7-trihydroxyisoflavone. The isoflavone glycoides showed strong cytotoxicity against K562 human chronic leukemia (Hu et al. 2009).

Other substances

Marine-derived *Streptomyces* 3320 strain collected from marine sediment of Jiaozhou Bay, China showed antitumour activity. Ten compounds, cyclo-(Ala-Leu), cyclo-(Ala-Ile), cyclo-(Ala-Val), cyclo-(Phe-Pro), cyclo-(Phe-Gly), cyclo-(Leu-Pro), 1-methyl 2,3,4-tetrahydro-carboline 3-carboxylic acid, N-(4-hydroxyphenethyl) acetamide, 4-methyoxy l-(2-hydroxy) ethylbenzene and uridine, were isolated from the fermented broth of *Streptomyces* 3320. Among these, compounds 6, 7, 8 and 10 showed potent cytotoxicity against the tsFT210 cells. Compounds 8, 10 also exhibited apoptosis inducing activity. Compounds 6, 7, 8 and 10 are the principal bioactive constituents responsible for the antitumour activities of marine *Streptomyces* 3320 (Hong et al. 2006). An antifungal compound, 4′-phenyl 1-napthyl phenyl acetamide was characterised from *Streptomyces* sp. DPTB16 isolated from Cuddalore coastal soil, Tamil Nadu, India (Dhanasekaran et al. 2008). Three isolates of *Streptomyces* (LA3L1, LA3L2 and LA3L4) were found to be symbiotic with both New Zealand and Malaysian marine invertebrates (Mahyudin 2008). *Streptomyces* sp. (LA3L2) showed good cytotoxicity and a new cytotoxic metabolite was isolated from a large scale extract of *Streptomyces* sp. (LA3L2). This metabolite was characterised as *S*-methyl-2,4-dihydroxy-6-isopropyl-3,5-dimethylbenzothioate and the compound was reported to contain the *S*-methylbenzothioate group. The other two *Streptomyces* sp. yielded three known cytotoxic metabolites. These were thiazostatin B from *Streptomyces* sp. (LA5L4) and chromomycin A2, chromomycin A3 and chromomycin 02-3D from *Streptomyces* sp. (LA3L1).

Biotechnological application of marine *Streptomyces*

Single cell protein

Streptomyces are known to produce secondary metabolites that enhance the growth of juvenile fish, shrimp and prawn. There have been reports on the application of marine *Streptomyces* as a SCP source, incorporated in the formulated feed and supplemented to juvenile prawns weighing about 0.130–0.160 g/body weight. The ingredients of the control feed consisted of fishmeal (14.76 g), groundnut oil cake (14.76 g), rice bran (35.24 g) with tapioca flour

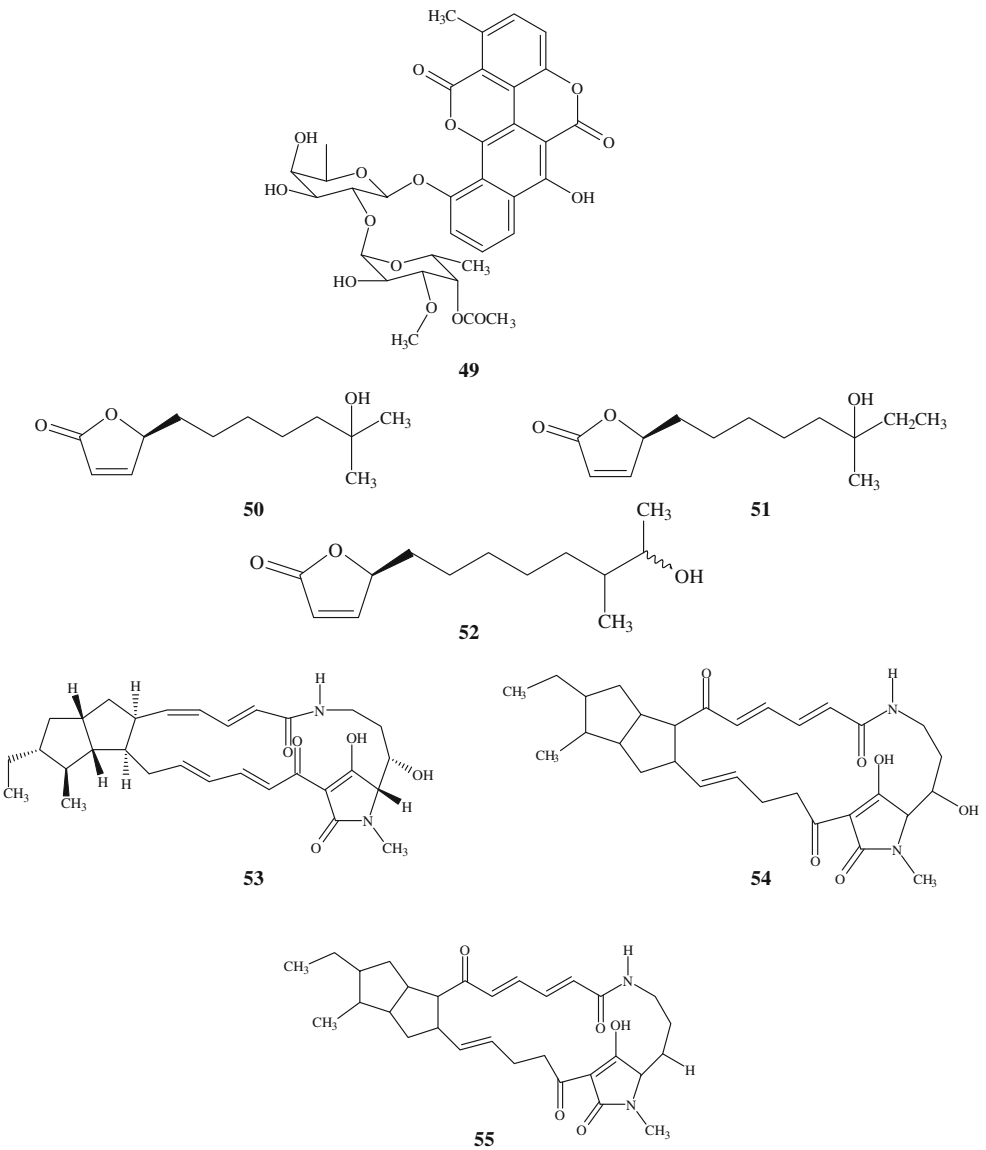

Fig. 10 Chartreusin 2″-monoacetate, Butenolides (1, 2, 3–4), Aburatubolactams A, B and C

(35.24 g) as binder, whereas the SCP incorporated feed consist of fishmeal + *Streptomyces* cells (14.76 g + 165 mg) and the rest were the same as control feed. After 50 days of feeding trials, the growth parameters like feed conversion efficiency, feed conversion ratio and protein content were analysed. The prawns fed with *Streptomyces*-incorporated feed showed improved growth (140.54%), feed conversion efficiency (45%), and higher protein content (54.72%), whereas the prawns fed with control feed showed less growth of 89.52%, food conversion efficiency (20%) and protein content of 35.02%. The feed conversion ratio will be less for the SCP fed-prawns (2.217) than the control (5.015). Hence, among unconventional protein sources, single cell protein (SCP) of microbial origin appears to be a promising substitute for fishmeal, which can replace up to 25–50% fishmeal in aquaculture operations (Manju and Dhevendaran 1997).

Probiotics

Despite the source of several novel antibiotics, marine *Streptomyces* spp. have been given less attention as probiotics in aquaculture. However, it was recommended that marine *Streptomyces* are promising candidates to be utilised in marine aquaculture. You et al. (2005) described the potential of *Streptomyces* against the shrimp pathogen *Vibrio* spp. and recommended marine *Streptomyces* as potential probiotic strains due to their ability to degrade macromolecules such as starch and protein in culture pond water, to produce antimicrobial agents and to form heat- and desiccation-resistant spores. More recently, there were a few studies on the possible use of marine *Streptomyces* in disease prevention against aquatic pathogens. Das et al. (2006b) reported a preliminary study on the use of *Streptomyces*-incorporated feed as probiotic source for the

growth of black tiger shrimp. Cells of *Streptomyces* were incorporated at different concentrations (0, 2.5, 5.0, 7.5, and 10.0 g/kg feed) in the formulated feeds, supplemented for 25 days and growth was monitored. At a concentration of 10 g, shrimp fed with *Streptomyces*-incorporated feed showed high growth in terms of length (15.79%) and weight (57.97%) when compared with the control [length (4.08%) and weight (32.77%)]. The growth of the tiger shrimp, *Penaeus monodon*, also increased with an increase in the concentration of *Streptomyces* in the supplemented feed.

Kumar et al. (2006) reported the antiviral property of marine *Streptomyces* against White Spot Syndrome Virus (WSSV) in penaeid shrimps. WSSV infection can cause cumulative mortality up to 100% within 3–10 days, thereby causing considerable economic loss to the shrimp farmers. Antibiotic extracts were obtained from the fermentation broth of twenty-five isolates of marine *Streptomyces* (isolated from the coastal waters of Southwest coast of India), incorporated in the formulated feeds and supplemented to the post-larvae (PL-20) of the black tiger shrimp *Penaeus monodon* for 2 weeks and challenged with WSSV. The pattern of post-challenge survival % (PCS %) in the 27 treatments (25 experimental and two controls) exhibited a wide range of variation from 11 to 83% during the course of the experiment. PCS % was lowest in the controls (C_1—4.3%, C_2—5.2%) on day 7. However, six probiotic feeds (SA 2, SA 8, SL 27, SL 33, SL 39, and SL 85) supplemented to post-larvae shrimp recorded the highest PCS % ranging between 50 and 83%. Also, severity of the infection observed on days 3, 4 and 5 in post-larvae shrimp fed with other diets was not visible in these groups. In this case, positive effect was obtained by the antibiotic extract incorporated in the feed against WSSV infected penaeid shrimps.

You et al. (2007) reported the activity of marine *Streptomyces* as a potential organism against biofilms produced by *Vibrio* spp. Nearly 88 isolates of marine *Streptomyces* extracts were screened against biofilms produced by various *Vibrio* species. Among these, 35 inhibited the biofilm formation of *Vibrio harveyi*, *Vibrio vulnificus*, and *Vibrio anguillarum* at a concentration of 2.5% (v/v). Thirty-three of the *Streptomyces* extracts dispersed the mature biofilm and six extracts inhibited the quorum-sensing system of *V. harveyi* by attenuating the signal molecules, *N*-acylated homoserine lactones' activity. The marine *Streptomyces* strain A66 was able to attenuate the biofilms and also inhibit their quorum-sensing system. It is suggested that the *Streptomyces* strain A66 is a promising candidate to be used in marine aquaculture and is also recommended for the prevention of diseases caused by *Vibrio* spp.

Conclusions

The marine environment has a vast biological diversity and has been recognised as a potential source of a large number of novel chemical entities. The bioactive substances derived from marine *Streptomyces* are just beginning to be realised. In order to improve the future exploitation of bioactive substances from marine *Streptomyces* and to make the process technically and economically feasible, there are numerous parameters to follow, and these include the application of appropriate isolation media (with optimal salinity, pressure, temperature, and nutrient concentration) for the various sources from the depths of the ocean and primary screening of the fermentation broths extracts using classical methods to define the metabolites combined with techniques such as high pressure liquid chromatography with diode array detection (HPLC–DAD) for metabolite profiling, structural information through mass spectrometry and nuclear magnetic resonance (NMR) and two-dimensional (2D) NMR spectra arrays. Furthermore, molecular techniques like genome sequencing of the most promising strains and identification of cryptic biosynthetic gene clusters would greatly enhance the ability to isolate their metabolic products. There are also several techniques to maximise gene expression that include physicochemically informed (PCI) screening of the gene clusters, gene knockouts, comparative metabolic profiling, heterologous expression, in vitro reconstitution and genomisotopic approaches. The strong interplay of classical natural product chemistry with modern microbial genetics and bioinformatics will help to overcome supply and sustainability issues from the past and to promote bioactive substances from marine *Streptomyces* to a well-recognised alternative for future drug discovery programs.

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