

Biologically active secondary metabolites from Actinomycetes

Review Article

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Abstract: Secondary metabolites obtained from *Actinomycetales* provide a potential source of many novel compounds with antibacterial, antitumour, antifungal, antiviral, antiparasitic and other properties. The majority of these compounds are widely used as medicines for combating multidrug-resistant Gram-positive and Gram-negative bacterial strains. Members of the genus *Streptomyces* are profile producers of previously-known secondary metabolites. Actinomycetes have been isolated from terrestrial soils, from the rhizospheres of plant roots, and recently from marine sediments. This review demonstrates the diversity of secondary metabolites produced by actinomycete strains with respect to their chemical structure, biological activity and origin. On the basis of this diversity, this review concludes that the discovery of new bioactive compounds will continue to pose a great challenge for scientists.

Keywords: Bioactive • Secondary metabolites • Antibacterial properties • Cytotoxicity • *Streptomyces* sp.

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1. Introduction

Bioactive metabolites are products of primary and secondary metabolism of different organisms (plants, animals, fungi, bacteria). They often demonstrate biological activity [1]. Secondary metabolites have diverse and unusual chemical structures, and often a low molecular mass [2,3]. Secondary metabolites, unlike primary metabolites, have no function in the life cycle of cells and are characterize specific groups of organisms [3]. Genetic methods and high throughput screening (HTS) techniques have allowed over one million natural compounds to be described. Of these, 500 000–600 000 products are produced by plants (usually alkaloids, flavonoids, terpenoids, steroids, saccharides, etc.), and 50 000 are of microbial origin [3,4]. About 200 000–250 000 metabolites show signs of bioactivity, more than 22 000 of which are produced by microorganisms [1,3]. Of the 22 500 microbial metabolites, about 17% (3 800) are metabolites of unicellular bacteria (especially *Bacillus* spp. and *Pseudomonas* spp.); 45% (10 100) are products of actinomycetes fermentation; and about 38%

(8 600) are of fungal origin [1,3]. Among filamentous actinomycetes, about 75% (7 600) of metabolites are produced by species of the genus *Streptomyces* [3,4] (Figure 1).

More than 140 actinomycete genera have been described to date. A few of these are responsible for the majority of known essential compounds [5-7]. Other actinomycetes, like *Saccharopolyspora*, *Amycolatopsis*, *Micromonospora* and *Actinoplanes*, also produce bioactive metabolites — but at a lower scale. Actinomycete strains are usually found in terrestrial soils, but have also been isolated from marine sediments and marine sponges [8,9]. In 2008, over 1 000 marine metabolites had been described [10]. These marine metabolites show high structural variety and exhibit a broad range of activities: antimicrobial, antiprotozoal, antiparasitic, antitumour, and antimalarial [9,11]. More than 30 marine-derived compounds are currently under clinical or preclinical trials for their anticancer activity [12].

The *Streptomyces* genome is unusually large for a bacterium. The genome of the most extensively studied *Streptomyces* strain, *Streptomyces coelicolor*

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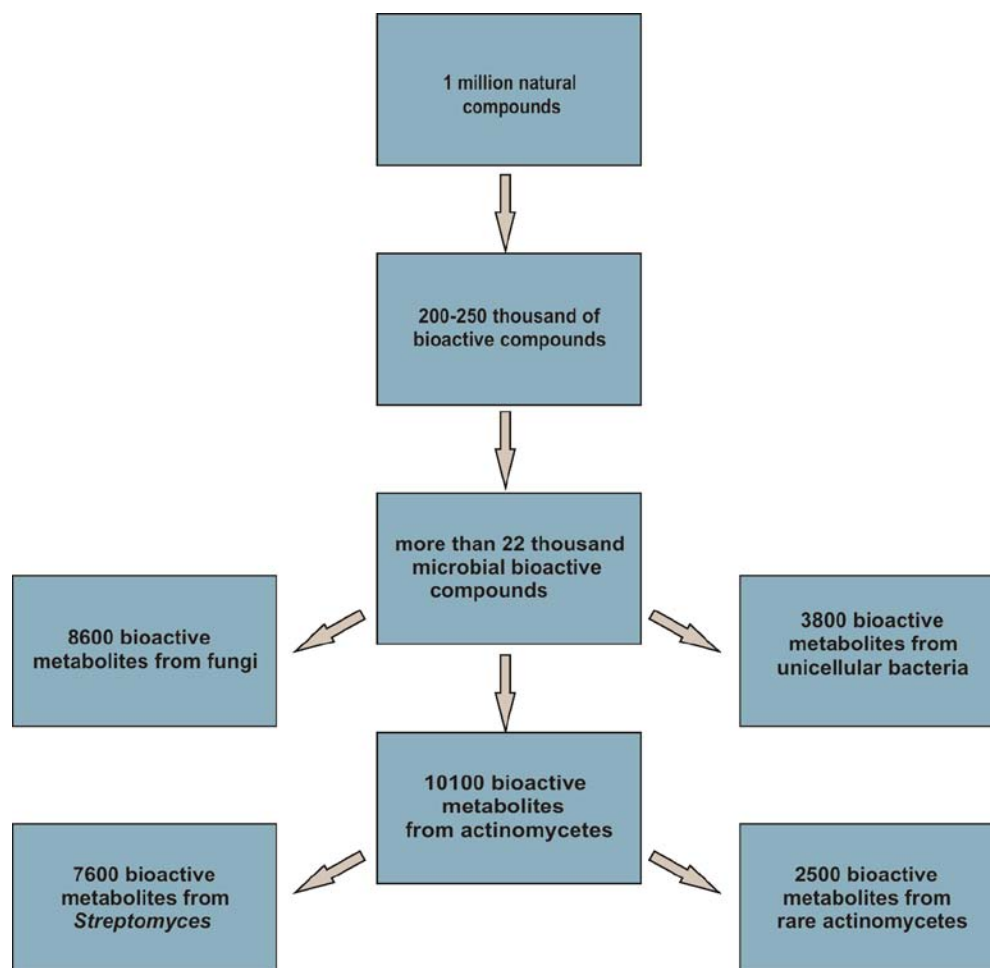


Figure 1. Distribution of the discovered bioactive compounds according to their origin.

(*S. coelicolor*) A3(2) has 8.66 million base pairs (Mbp) of DNA and contains more than 7 800 putative genes. In comparison, the genome of *Escherichia coli* (*E. coli*) K-12 comprises 4.6 Mbp and 4 400 putative genes. The genome of *S. coelicolor* includes more than 20 clusters that encode enzymes involved in the formation of secondary metabolites [13].

A large variety of the metabolites that are currently used are produced in microbial fermentation processes or derived by chemical modifications of microbial products [2]. *Streptomyces* fermentation products are a rich source of compounds that can be applied as new drugs. In this review we discuss the main activities of actinomycete secondary metabolites, their therapeutic applications and chemical features. We will discuss the well-known bioactive compounds produced by actinomycetes and focus on novel and promising discoveries. Moreover, this work compares the activity of novel antibiotics to old ones. We will also highlight how important and structurally unique are the bioactive metabolites of actinomycetes.

2. Bioactivity profile

Many secondary microbial metabolites show antibacterial, antifungal, antiviral, antitumour, antiprotozoal, hypocholesterolemic and other activities. They are commonly used in medicine, veterinary practice, agriculture and industry. About 14 000 compounds of microbial origin exhibit antimicrobial (antibacterial, antifungal, antiprotozoal) activity. Of these, 66% demonstrate activity against Gram-positive bacteria, 30% against Gram-negative bacteria, and 5% against mycobacteria. 34% of compounds exhibit antifungal activity. 21% of those possess activity against yeasts, 11% against phytopathogenic fungi, and 24% against other fungi [3]. Among microbial products, *Streptomyces* fermentation products are the richest source of antibiotics and other industrially-important compounds [14,15]. Examples with antimicrobial activity include β -lactams, tetracyclines, aminoglycosides, glycopeptides, macrolides, aminocyclitols,

cyclic peptides, lincosamides, glycolipopeptides, streptogramins, ansamycins, chloramphenicols, phenylpropanoids [16].

S. clavuligerus produces clavulanic acid, an inhibitor of β -lactamases. Moreover, this species produces penicillin N, cephamycin C and holomycin [17]. Cephamycins, which are structurally similar to cephalosporins, are produced by different *Streptomyces* species, e.g. *S. griseus*, *S. viridochromogenes* and *S. fimbriatus* are likely to produce cephamycin A and B; *S. lactamdurans* produces cephamycin C. Interestingly, actinomycete strains that produce cephamycin C (e.g. *S. jumonjinensis*, *S. katsurahamanus*, *S. clavuligerus* and unclassified *Streptomyces* sp.) also produce clavulanic acid [18]. Clavulanic acid was discovered in 1976 and shown to inhibit β -lactamases produced by *Staphylococcus* spp. and β -lactamases carried on plasmids by *E. coli*, *Proteus* spp., *Klebsiella* spp., *Shigella* spp., *Haemophilus* spp. and *Pseudomonas* spp. [1]. Clavulanic acid shows low antibacterial activity, but in combination with other semi-synthetic or synthetic penicillins (amoxicillin - Augmentin, Amoksiklav) acts as a β -lactamase inhibitor and is commonly used in pathogenic treatment. It is also combined with ticarcillin (a penicillin active against *E. coli*, *Proteus* spp., *Salmonella* spp., *Haemophilus* spp., *Pseudomonas* spp. and *Staphylococcus aureus* (*S. aureus*)) and marketed as the commercial drug Timentin [1].

More than 40 natural carbapenems have been isolated from *Streptomyces* spp. fermentation products. These are broad spectrum antibiotics used in clinical treatment and seem to be relatively resistant to β -lactamases. One representative of carbapenems is thienamycin, produced by *S. cattleya*. This compound, like penicillin and cephalosporin, inhibits the biosynthesis of bacterial cell walls. It too is relatively resistant to β -lactamases [16]. The majority of tetracycline antibiotics are produced by *Streptomyces* species. The first antibiotic isolated from this group was chlortetracycline (aureomycin), produced by *S. aureofaciens*. Subsequently, tetracycline (MIC=0.12-1 μ g/ml for *S. aureus* ATCC®29213, MIC=0.5-2 μ g/ml for *E. coli* ATCC®25922) and oxytetracycline have been isolated from *S. rimosus* fermentation broth [19-21].

In 1944, Waksman discovered streptomycin, an aminoglycoside antibiotic, in the culture of *S. griseus* [22]. This compound shows antibacterial properties against Gram-negative bacteria and has a weaker activity against Gram-positive bacteria. It is commonly used in the treatment of tuberculosis [22]. However, it is also nephrotoxic and may cause hearing and balance disturbances. Gentamycin is produced by fermentation processes in *Micromonospora echinospora* and

Micromonospora purpurea [23]. It is a broad spectrum antibiotic, highly active against Gram-negative bacteria. The MIC value for *E. coli* ATCC®25922 is 0.25-1 μ g/ml [21]. Kanamycins A, B and C are aminoglycosides produced by *Streptomyces* spp., including *S. kanamyceticus* (MIC=1-4 μ g/ml for *S. aureus* ATCC®29213 and 1-4 μ g/ml for *E. coli* ATCC®25922) [21]. *S. tenebrarius* produces aminoglycoside antibiotic complex that mainly consists of tobramycin carbamate, kanamycin B carbamate and apramycin [24]. *S. fradiae* produces neomycin [25].

The majority of glycopeptide antibiotics are produced by *Streptomyces* spp. Vancomycin is a product of *Amycolatopsis orientalis* fermentation (MIC=0.5-2 μ g/ml for *S. aureus* ATCC®29213) [21,26]. Teicoplanin is produced by *Actinoplanes teichomyceticus* (MIC=0.25-1 μ g/ml for *S. aureus* ATCC®29213) [21]. The antibacterial properties of vancomycin and teicoplanin stem from the inhibition of peptidoglycan biosynthesis of the bacterial cell wall [27]. These compounds are also used in the treatment of serious infections caused by *S. aureus* and other Gram-positive bacteria, including resistant *Enterococcus* spp. strains. However, vancomycin shows high toxicity, and its use is limited.

Streptomyces spp. also produce macrolide structures, which hinder the growth of bacteria by interacting with their ribosomes. Erythromycin is a metabolite of *Saccharopolyspora erythraea* (MIC=0.25-1 μ g/ml for *S. aureus* ATCC®29213) [21]. *S. ambofaciens* produces spiramycin (rovamycin), that is used in toxoplasmosis treatment [28]. Nystatin also belongs to macrolide polyene antibiotics and possesses a glycoside structure. It is isolated from *S. noursei* and shows strong activity against *Candida albicans* [29]. *S. fradiae* is a potent producer of tylosin, which is a macrolide antibiotic. Tylosin and its derivative-tilmicosin are used as therapeutic antibiotics in food animals [30].

Phosphonomycin is another secondary metabolite that is active against *S. aureus*, *Neisseria* spp. and Gram-negative bacteria. It is produced by *S. wedmorensis* and *S. fradiae*, and inhibits bacterial cell wall biosynthesis [31]. The genome of *S. avermitilis* contains 37 gene clusters that control secondary metabolism. Among secondary metabolites of *S. avermitilis* are avermectin, oligomycin (polyketide macrolides), filipin (polyene macrolide), neopentalenolactone, nacardamine-siderophore [32]. *Micromonospora carbonacea* is another source of antibiotics, producing 3 antibacterial compounds with different chemical structures and mechanisms of action: everninomycin (polysaccharide), chloramphenicol, and thiostreptone (thiopeptide) [16]. Bagremycin A and B were isolated from *Streptomyces* sp. Tü 4128. Both

secondary metabolites demonstrate activity against Gram-positive bacteria and some fungi [33].

3. Antimicrobial properties of novel antibiotics

At present, antibacterial activity of secondary metabolites is of high interest. It is triggered by the extensive need for the discovery of new antibiotics against the widespread of multidrug resistant clinical strains and the therapeutic failure in treatment of resulting infections. Due to their chemical and functional diversity, bioactive metabolites are the subjects of scientific investigations that could lead to new and effective antimicrobial medicines [1,34]. About 70% of all known antibiotics are obtained from actinomycetes, and the majority of those are derived from *Streptomyces* spp. strains [35].

Streptogramins, a group of antimicrobial compounds obtained from *Streptomyces*, are structurally unrelated compounds that inhibit bacterial ribosomal protein synthesis at the peptidyl transfer step. Etamycin, which is the streptogramin antibiotic, was obtained from the terrestrial strain of *S. griseus* in 1960s [36], but its antimicrobial properties were only recently evaluated. Etamycin exhibits potent activity against methicillin-resistant *S. aureus* strains, including community-acquired (CA-MRSA) (MIC=1-2 µg/ml) and hospital-acquired (HA-MRSA) (MIC=8-16 µg/ml). Etamycin also possesses antibacterial activity against *Streptococcus pyogenes* (*S. pyogenes*) and *S. agalactiae* (MIC=8 µg/ml) strains [37]. *S. virginiae* produces two streptogramin antibiotics, virginiamycin M₁ (VM₁) and virginiamycin S (VS). Both compounds show strong synergy [38]. Virginiamycin shows activity against Gram-positive bacteria; furthermore, it regulates the natural bacterial flora in animals and has been applied as a growth promoter. Its use has been limited due to the emergence of virginiamycin-resistant strains [1]. Pristinamycin is another streptogramin-group compound; it is a depsipeptide antibiotics and possesses a lactone peptolide structure. Pristinamycin is derived from *S. pristinaespiralis*. The combination of different streptogramins increases their antibacterial efficacy [39]. Quinupristin/dalfopristin-chemically modified streptogramins have been approved as antibiotics for the treatment of complicated cutaneous infections caused by vancomycin-resistant *Enterococcus faecium* (*E. faecium*) strains and other Gram-positive pathogens [1,39].

Natural metabolites also include cyclic lipopeptides such as daptomycin, a compound produced by *S. roseosporus* that is used to treat infections caused

by Gram-positive bacteria, skin infections, diabetic foot infections, and burned skin; and in the treatment of patients who do not tolerate other potent antibiotics for these type of infections [40]. Daptomycin shows antibacterial activity against penicillin-resistant *S. pneumoniae*, vancomycin-resistant *S. aureus*, methicillin-resistant *S. aureus* and other multidrug-resistant strains [41]. The mechanism of daptomycin activity involves irreversible binding to bacterial cell membranes, leading to their depolarization. It also disturbs the gradient of ion concentrations and causes the efflux of K⁺ ions.

One of the newly discovered antibacterial mechanisms of action is the inhibition of bacterial fatty acid biosynthesis. Fatty acids are essential for bacterial energy storage and are a part of the composition of cells. Soil-derived *S. platensis* MA 7327, isolated from Eastern Cape, South Africa, produces platensimycin; whereas *S. platensis* MA 7339 from Spanish soil was discovered to produce platencin (1) (Figure 2). The selective inhibition of bacterial fatty acid synthesis grants both compounds strong activity against Gram-positive bacteria, methicillin-resistant *S. aureus* strains (MIC=1 µg/ml for platencin and MIC=0.5 µg/ml for platensimycin), and vancomycin-resistant *E. faecium* (MIC<0.06 µg/ml for platencin, MIC=0.01 µg/ml for platensimycin) [42].

Amycolatopsis fastidiosa produces nocathiacins and thiazomycins, which exhibit antibacterial activity [43]. Thiazomycin and thiazomycin A (2) are thiazolyl peptides (thiopeptides) that are potent against Gram-positive bacteria (MIC=0.002~0.064 µg/ml for thiazomycin, 0.002~0.25 µg/ml for thiazomycin A) (Figure 2) [42,44]. Thiazomycins inhibit bacterial growth by selectively inhibiting protein biosynthesis. Thiazomycin does not show cross-resistance to clinically available antibiotics (β-lactams, vancomycin, quinolones, oxazolidinone) [45].

A novel isoquinoline alkaloid JS-1 (3) (C₁₀H₉NO₄) was isolated by Solecka *et al.* [46] from *Streptomyces* sp. 8812 fermentation broth (Figure 3). It shows antibacterial activity by inhibiting DD-peptidases. DD-carboxypeptidases/transpeptidases are enzymes involved in bacterial cell wall biosynthesis. This new compound is most active against *Bordetella bronchiseptica* and *S. aureus*, including MRSA strains. JS-1 does not possess any hemolytic or genotoxic properties, so its antibacterial activity can be increased by potential modifications [46,47].

Another new compound, pargamycin A (PRGA) (4), was isolated from a soil-derived actinomycete strain, *Amycolatopsis* sp. ML1-hF4 (Figure 4). It is a cyclic peptide antibiotic which demonstrates a higher

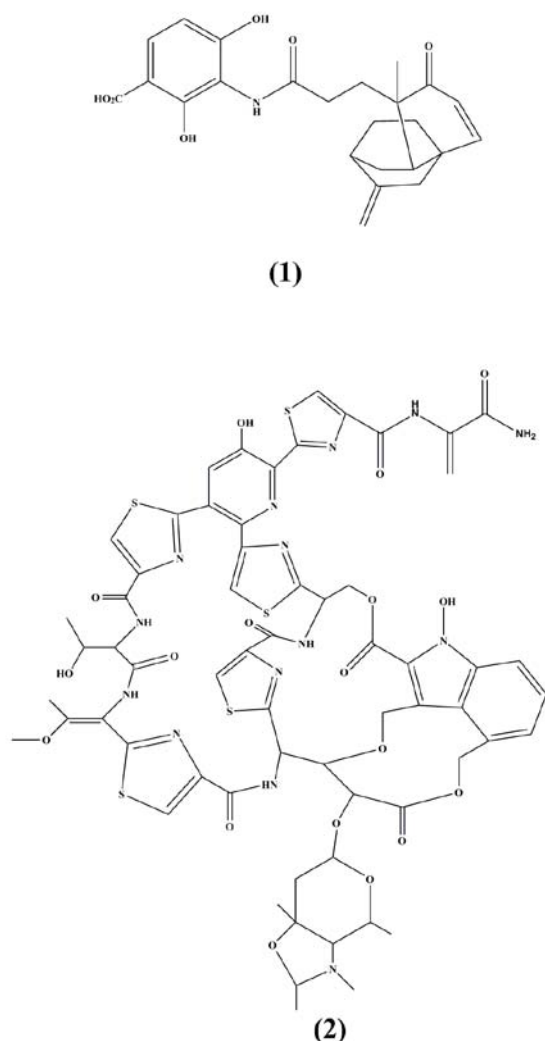


Figure 2. Chemical structure of platencin (1) and thiazomycin A (2).

MIC value against MRSA than against VRE strains. The mechanism of action involves the rapid disruption of bacterial membrane function [48]. Some bisindole pyrroles, specifically lynamycins, specifically lynamycins A-E (5), were isolated from a marine-derived *Marinispora* strain (Figure 4). These compounds show broad-spectrum activity against both Gram-negative and Gram-positive bacteria cells, including methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium* [10,49]. Lynamycins present also antitumour and antiangiogenic properties [11].

In 2009, Carlson *et al.* [50] reported isolation of tirandamycin C (6) and D from *Streptomyces* sp. 307-9, which demonstrated strong activity against vancomycin-resistant *Enterococcus faecalis* (Figure 5). These compounds were classified as dienoyl tetramic acids [50]. Tirandamycin impairs the transcription process by

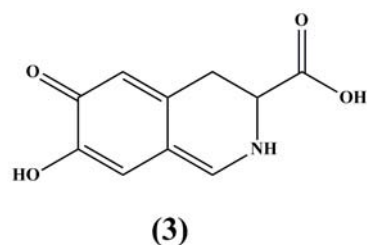


Figure 3. Chemical structure of JS-1 (3).

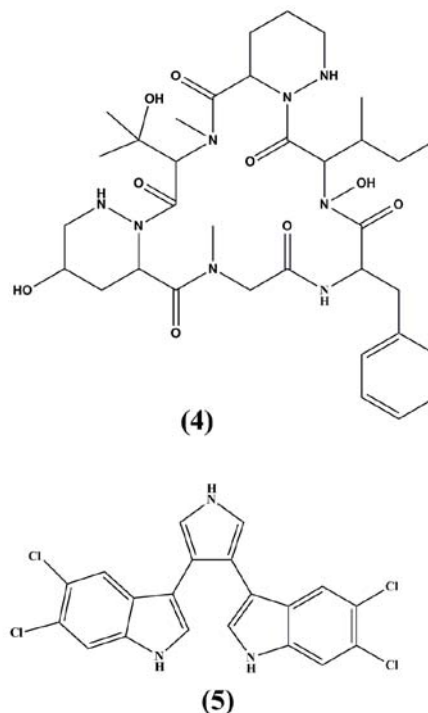


Figure 4. Chemical structure of pargamycin A (4) and lynamycin C (5).

inhibiting the bacterial ribonucleic acid polymerase [51].

Marinomycines, polyketide-derived polyenes, are compounds derived from the novel genus *Marinispora* (MAR-2). Marinomycin A (7) shows strong *in vitro* antitumour (against six to eight melanoma cell lines) and antibacterial properties (Figure 4). It exhibits a MIC value of 0.1–0.6 μM toward methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium* [8,51].

A member of a rare actinomycete genus *Verrucosipora* produces a family of polycyclic polyketides. One of these compounds, abyssomicin, is isolated from *Verrucosipora maris* AB-18-032 [52]. It demonstrates antibacterial properties by inhibiting *para*-aminobenzoic acid biosynthesis [8,53]. As such, its activity impairs folic acid biosynthesis at an earlier stage than known synthetic sulfa drugs [54]. Abyssomicin C demonstrates strong antibacterial activity against Gram-

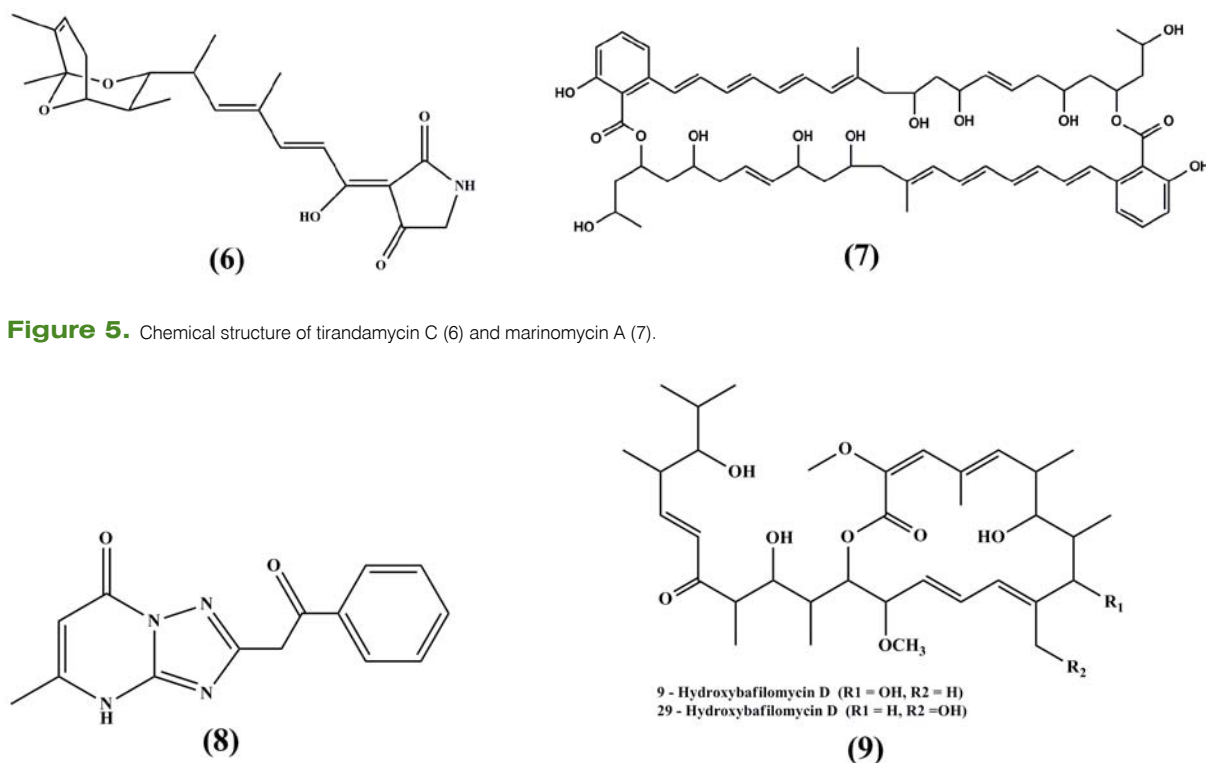


Figure 5. Chemical structure of tirandamycin C (6) and marinomycin A (7).

Figure 6. Chemical structure of essramycin (8) and bafilomycin D analogs (9).

positive bacteria, including multiresistant *S. aureus* strains [53].

Albidopyrone, a novel α -pyrone-containing secondary metabolite, was isolated from *Streptomyces* sp. NTK 227. Albidopyrone inhibits protein-tyrosine phosphatase B [55]. *Micromonospora rifamycinica* produces rifamycin S and its geometric isomer, both of which are antibiotics directed against Gram-positive bacteria, including MRSA. The MIC value for both compounds against eight clinical MRSA isolates ranges from <0.03 to 8 $\mu\text{g/ml}$. Both possess the molecular formula $\text{C}_{37}\text{H}_{45}\text{NO}_{12}$ [56].

The nucleosidyl-peptide antibiotics sansamycin F and G have been isolated from *Streptomyces* sp. SS fermentation broth. Sansamycin F showed weak antibacterial activity against *Pseudomonas aeruginosa* (MIC=16 $\mu\text{g/ml}$). Both compounds show activity against *Mycobacterium tuberculosis* H₃₇Rv (MIC>16 $\mu\text{g/ml}$) [57].

Amycolamicin was isolated from *Amycolatopsis* sp. MK575-fF5 culture broth. It has a distinctive chemical structure, containing the trans-decalin, tetramic acid, two unusual sugars and pyrrole carbonic acid. Amycolamicin shows bactericidal activity towards a wide variety of bacteria, including methicillin-resistant *S. aureus* (MIC₉₀=0.39 $\mu\text{g/ml}$) and vancomycin-resistant enterococci (MIC₉₀= 0.2-0.78 $\mu\text{g/ml}$) [58]. *Nocardia* sp.

ALAA 2000 was discovered to produce ayamycin, a monocyclic nitrated aromatic compound, which exhibits antibacterial and antifungal activity [59,60]. Pyrrolomycin A, another recently-discovered nitrated compound, is produced by *Actinosporangium vitaminophilum* SF-2080. It demonstrates activity against Gram-positive and Gram-negative bacteria as well as some fungi [60]. Aureothin, alloaureothin, spectinabilin (neoaureothin) and luteoreticulic acid (griseulin) are structurally related nitrophenyl pyrones which express various bioactivities and are produced by *Streptomyces* spp. [60]. Aureothin demonstrates anti-*Helicobacter pylori*, antitumour and antifungal activity, whereas luteoreticulic acid possesses mosquitoicidal and nematocidal properties [60].

Essramycin (8), a triazolopyrimidine, is a secondary metabolite of *Streptomyces* sp. Merv8102. It exhibits potent antibacterial activity, and has a broad spectrum activity against *E. coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *S. aureus* and *Micrococcus luteus* (*M. luteus*) (Figure 6) [61]. However, Tee *et al.* reported that the synthetically derived compound did not demonstrate any biological activity in comparison to its natural isolates [61].

Bafilomycins are secondary metabolites of *Streptomyces* spp., which exhibit antimicrobial, antifungal, antitumour, and antiparasitic activities [62].

Bafilomycins A₁, A₂, B₁, B₂, C₁ and C₂ were isolated from fermentation broth of *S. griseus* strains (TÜ1922, TÜ2437, TÜ2599) [63]. Their antibacterial activity was evaluated and the obtained data has shown that these macrolide antibiotics are active against Gram-positive bacteria in order A<B<C of antibacterial strength [63]. New bafilomycins, 9-hydroxybafilomycin D (9) and 29-hydroxybafilomycin D (9) were isolated from *Streptomyces* sp. YIM56209 and determined to express antitumour activity (Figure 6). Novel bafilomycin D analogs exhibit less toxicity than other bafilomycins and are therefore used in clinical treatments [62].

Some lipoxazolidinones (A (10), B, C) were obtained from a marine actinomycete strain NPS008920 that belongs to the recently-described genus *Marinispora* (Figure 7). These 2-alkylidene-5-alkyl-4-oxazolidinones, lipoxazolidinone A (C₁₉H₃₁NO₃), lipoxazolidinone B (C₂₀H₃₃NO₃) and lipoxazolidinone C (C₁₈H₂₉NO₃), demonstrate broad antibacterial activity. Lipoxazolidinone A is the most potent and active against Gram-positive bacteria (MIC=0.5–5 µg/ml) and against *Haemophilus influenzae* strains (MIC=12 µg/ml). Compounds with these chemical structures (2-alkylidene-4-oxazolidinone) are unique in nature and are a potential source of new antibiotics [64].

Fujianmycin C (11) is a bioactive member of the angucyclinone family and was obtained from *Streptomyces* sp. B6219 (Figure 7) [1]. Other compounds, fujianmycin A and B, which were isolated along with fujianmycin C, were known previously. Data showed that fujianmycin C exhibits antibacterial activity against *Bacillus subtilis*, *S. aureus* and *E. coli* [65].

4. Anticancer activity of actinomycete metabolites, now and in the past

Actinomycin D was one of the first natural metabolites to be used in tumour treatment. It was isolated from *S. antibioticus*. Actinomycin D acts by binding DNA at the transcription initiating complex and preventing the

transcript's elongation by RNA polymerase. Actinomycin D is still used in treatment of Wilms tumors in children, but its many side-effects have limited its application [1,66].

Other anticancer antibiotic groups include anthracyclines, daunorubicin (daunomycin), doxorubicin (adriamycin), which were obtained in the 1960s during the biosynthesis process of *S. peuceticus*. Epirubicin is one of the more recently identified anthracycline group compounds; it was approved by the FDA in 1999 and has a better therapeutic profile than doxorubicin due to less-adverse effects. It is used in treatment of breast cancer, ovarian cancer, lung cancer and leukemia [67]. Bleomycin is another antitumour compound. This metabolite of *S. verticillus* was approved for clinical treatment by the FDA in 1973 [68]. Mitomycins produced by *S. caespitosus* show high antitumour activity. However, their use is limited in therapy due to their toxicity [69]. Streptozotocin, produced by *S. achromogenes*, shows selective toxicity against pancreatic β cells. It was approved by the FDA in 1982 as a pancreatic islets cell antitumour drug [1,70]. Calicheamycins are antitumour compounds isolated from *Micromonospora echinospora*. They act by cleaving DNA in its double-stranded condition. They are highly toxic, but if linked to antibody that selectively delivers drugs to cancer cells, they show only antitumour toxicity [1,71].

Recently, a new compound, 11-methoxy-17-formyl-17-demethoxy-18-O-21-O-dihydrogeldanamycin (12) – was isolated from *S. hygroscopicus* A070101 (Figure 7). This is an analogue of geldanamycin, which shows significant toxicity against human cancer cell lines (e.g. breast cancer MCF-7, lung carcinoma COR-L23, skin melanoma SK-MEL-2) [72].

From a marine actinomycete, *S. chibaensis* AUBN₁/7, Gorajana *et al.* isolated resitoflavine, a quinone-related antibiotic [73]. It possesses cytotoxicity against HMO2 (gastric adenocarcinoma) and HePG2 (hepatic carcinoma) cell lines. Moreover, it shows weak antibacterial activity against *Bacillus subtilis*, *Bacillus pumilus*, *S. aureus* and *Proteus vulgaris* [73].

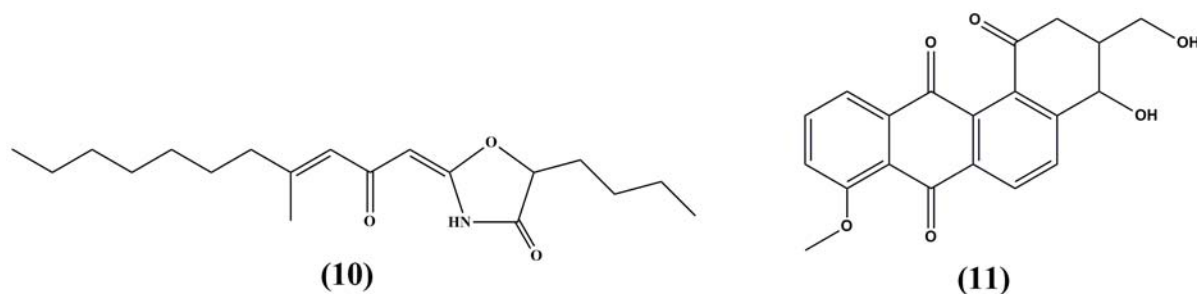


Figure 7. Chemical structure of lipoxazolidinone A (10), fujianmycin C (11).

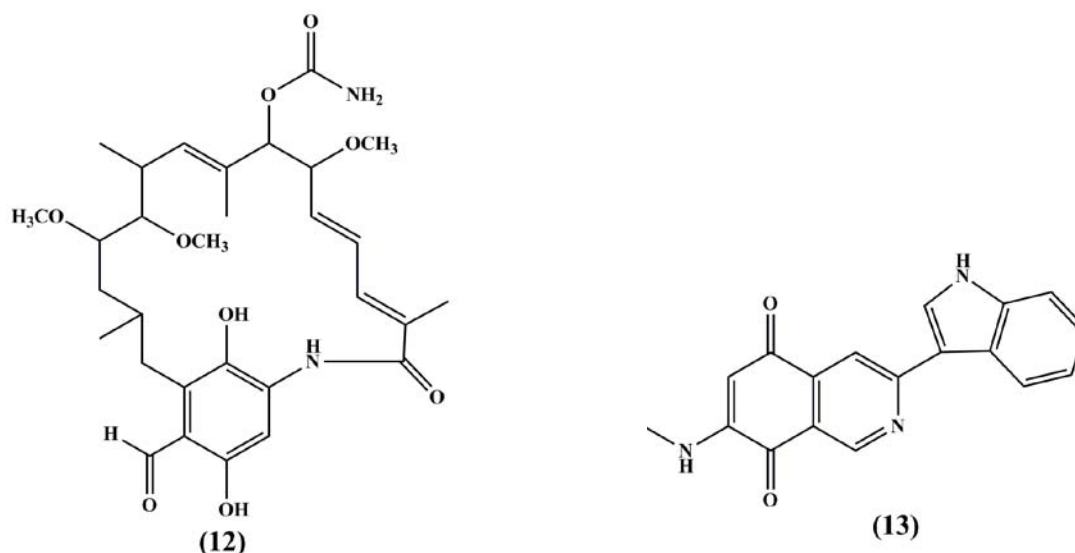


Figure 8. Chemical structure of a new geldanamycin analogue (12) and a member of mansouramycins (13).

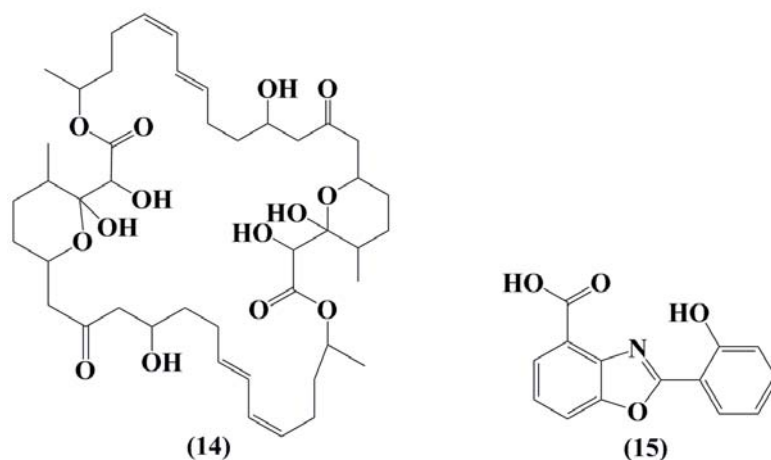


Figure 9. Chemical structure of tartrolon D (14) and carboxamycin (15).

Marinomycin A, daryamide C, lucentamycins (A,B), mansouramycins (13) and tatrolons (Figure 8) are other antitumour compounds that have been obtained from actinomycete strains found in marine sediments [11]. In 2007 Cho *et al.* [74] isolated novel compounds, lucentamycins A-D. Their chemical structure includes 3-methyl-4-ethylideneproline-containing peptides. They were isolated from marine *Nocardioopsis lucentensis* (strain CNR-712). Lucentamycin A and B show potent activity against HCT-116 human colon carcinoma cells [11,74]. Mansouramycins A-D are isoquinolinequinones isolated from the marine-derived Mei37 isolate of *Streptomyces* sp. They show antitumour activity against lung cancer, breast cancer, melanoma and prostate cancer cells [11,75]. Tartrolons, compounds

with a macrodiolide structure, also possess interesting bioactive properties. Tartrolon D (14) was isolated from *Streptomyces* sp. MDG-04-17-069 (Figure 9). It shows cytotoxicity against human tumour cell lines: lung (A549), colon (HT29) and breast (MDA-MB-231) [10,76].

Carboxamycin (15) was isolated from *Streptomyces* sp. NTK 937 from sediments of the Canary Basin (Figure 9). It shows antitumour activity against gastric adenocarcinoma cell lines (AGS), hepatocellular carcinoma (HepG2) and breast carcinoma (MCF7) as well as antibacterial properties against Gram-positive bacteria [66,77]. *Dermacoccus abyssi*, actinomycete strains isolated from the Mariana Trench sediment, produces phenazine-type secondary metabolites (dermacozines (16)) that possess antitumour (against

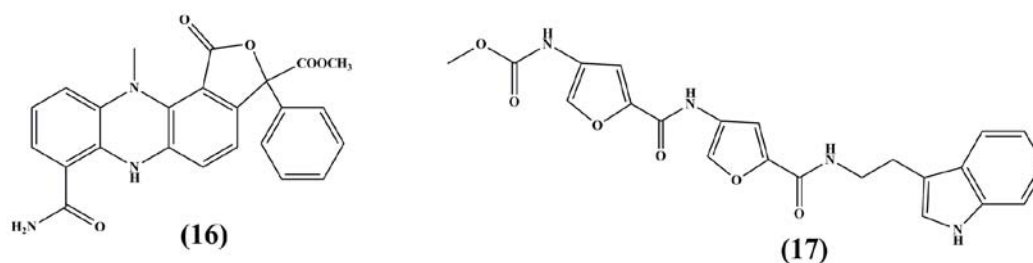


Figure 10. Chemical structure of dermacozine D (16) and proximicin C (17).

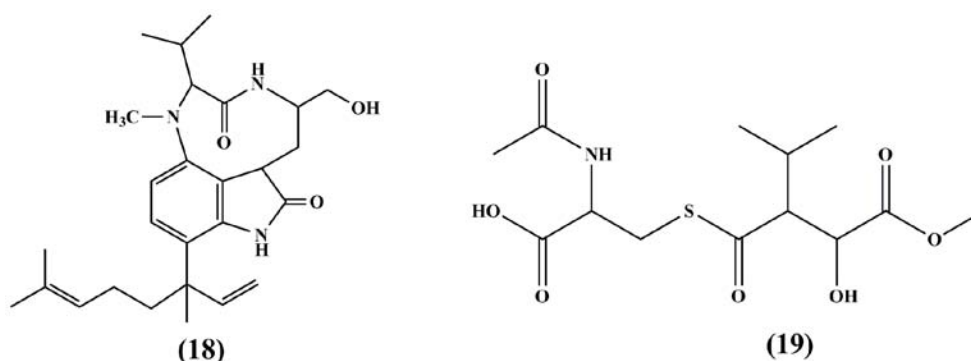


Figure 11. Chemical structure of JBIR-31 (18) and JBIR-69 (19).

leukaemia cell line K562), antiprotozoal and free radical scavenging activity (Figure 9) [78].

Proximicins (17), isolated from *Verrucosispora* MG-37 strains from marine sediment samples, are novel aminofuran-type antibiotics (Figure 10). They demonstrate weak antibacterial activity, but show high cytotoxicity against certain human tumour cell lines (gastric adenocarcinoma (AGS) and hepatocellular carcinoma (Hep G2)). Weaker cytotoxicity is exhibited against breast tumour cells [79].

A novel teleocidin analog, JBIR-31(18) compound, was recently isolated from *Streptomyces* sp. NBRC 105896 found in a marine sponge (Figure 11). Data showed weak cytotoxic activity against human cervical carcinoma HeLa cells and human malignant pleural mesothelioma (MPM) ACC-MESO-1 cells [80].

Another compound, JBIR-69 (19), was isolated from *Streptomyces* sp. OG05 from a soil sample (Figure 10). It was evaluated for antitumour activity. JBIR-69 possesses weak anticancer properties against human acute myelogenous leukemia HL-60 cells and does not demonstrate antibacterial activity against *Micrococcus luteus*, *E. coli* or *Schizosaccharomyces pombe* [81]. An angucycline representative, JBIR-88, and a novel butenolide, JBIR-89, are produced respectively by *Streptomyces* sp. RI104-LiC106 and RI104-LiB101. Both compounds exhibit cytotoxicity against HeLa and ACC-MESO-1 cells and demonstrate anti-*Micrococcus luteus* activity [82].

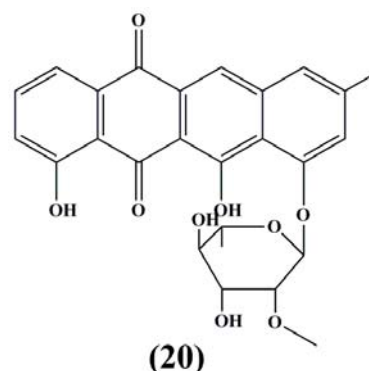


Figure 12. Chemical structure of tetracenoquinocin (20).

Novel anthracyclines, tetracenoquinocin (20) and 5-iminoaranciamycin, were isolated from *Streptomyces* sp. Sp080513GE-26 derived from marine sponge (Figure 12). The molecular formula for tetracenoquinocin was established as $C_{26}H_{24}O_9$. Both compounds showed anticancer activity against two cancer cell lines [83].

Streptomyces sp. strain HB202, isolated from another marine sponge, *Halichondria panicea*, produces a cytotoxic polyketide, mayamycin. This benz[α]anthracene exhibits cytotoxic properties against 8 human cancer cell lines and demonstrates antibacterial activity, including antibiotic resistant strains [84].

5. Antifungal activity

Amphotericin B, one of the most known actinomycete metabolites, is a macrolide polyene antibiotic that was isolated in 1955 from *S. nodosus* broth [85]. It is an antifungal antibiotic with a broad spectrum of activity, but its many side effects limit its clinical application [85].

Two classes of antifungal nucleosides competitively inhibit fungal chitin synthase: polyoxins and nikkomycins [86,87]. Polyoxins are secondary metabolites of *S. cacaoi* var. *asoensis* that exhibit antifungal activity. Isolated in 1960s, they were shown to possess activity against phytopathogenic fungi (e.g. *Alternaria kikuchiana*, *Piricularia oryzae*) [86]. Nikkomycins (nikkomycin Z) are more potent against *Candida albicans* than polyoxins. Nikkomycins are produced by *S. tendae* and *S. ansochromogenes*. Nikkomycins were isolated in 1970s from *S. tendae* and were proven to be active against *Rhizopus carcinans* and *Botrytis cinerea* [86]. Nikkomycin X and Z belong to peptidyl nucleoside antibiotics and are produced by *S. ansochromogenes*. Nikkomycins acts as inhibitors of chitin synthase in fungi and insects [88]. Nikkomycin Z and X are structurally very similar; yet, the first one is more promising as an antifungal agent than nikkomycin X. Therefore, high selective nikkomycin Z production was obtained by Liao *et al.* by genetic manipulations and precursor feeding [88].

Oligomycins are products of *S. diastaticus* fermentation, but are also produced by *S. diastatochromogenes* (oligomycin A (21) first described for this species in 1954), *S. libani*, and *S. avermitilis* (Figure 13). Oligomycins A and C are macrolide antibiotics that demonstrate strong antifungal

activity against *Aspergillus niger*, *Alternaria alternata*, *Botrytis cinerea* and *Photophthora capsici*. They do not exhibit any antibiotic activity [89].

S. hygroscopicus is responsible for rapamycin (sirolimus) production. Rapamycin was first isolated from soil-derived actinomycete strains on Easter Island [90]. Rapamycin exhibits antifungal activity against *Candida* spp. It shows more potent antifungal properties in murine systemic candidiasis in comparison with amphotericin B [91].

Antagonistic activity against fungal pathogens is usually related to various antifungal substances produced by *Streptomyces* spp. as well as to extracellular hydrolytic enzymes (chitinase, β -1,3-glucanase). Chitinase and β -1,3-glucanase are involved in the lysis of the fungal cell wall (e.g. *Fusarium oxysporum*, *Sclerotinia minor*). In the work of Prapagdee *et al.* [92] some unknown extracellular metabolites and a chitinase enzyme of *S. hygroscopicus* were isolated. They were active against *Colletotrichum gloeosporioides* and *Sclerotium rolfsii*. *S. aureofaciens* also produces some antifungal compounds [92]. Taechowisan *et al.* examined the antifungal properties of *S. aureofaciens* culture broth by using *Colletotrichum musae* and *Fusarium oxysporum*. *S. aureofaciens* was isolated from the root tissues of *Zingiber officinale* (Zingiberaceae) and determined to produce two compounds 5,7-dimethoxy-4-phenylcoumarin ($C_{17}H_{14}O_5$) and 5,7-dimethoxy-4-*p*-methoxyl-phenylcoumarin, of antifungal properties [93].

Marinisporolide A and B are polyketide-derived macrolide members obtained from *Marinispora* genus. Polyene macrolides, like nystatin and amphotericin B, often present strong antifungal activity. Although

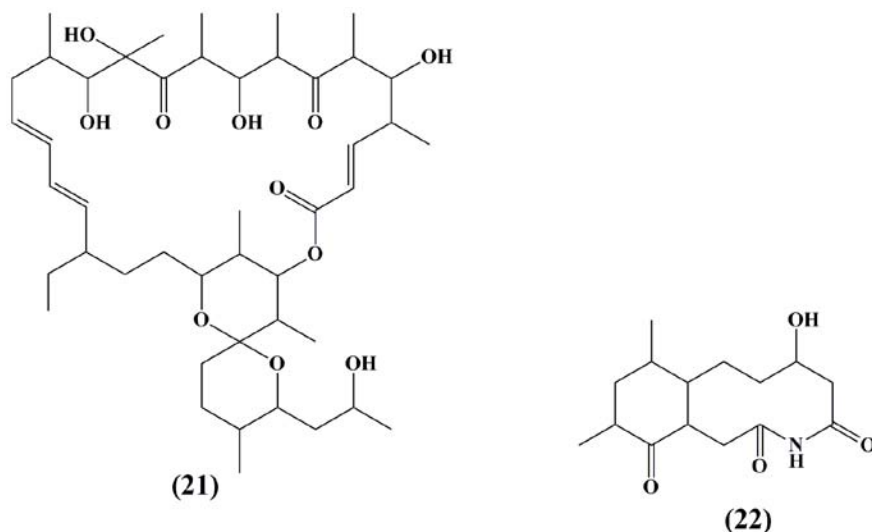


Figure 13. Chemical structure of oligomycin A (21) and 210-A (22).

marinisporolides A and B possess a polyene-polyols structure, they show weak antifungal activity [94].

S. noursei Da07210 is known to produce a novel antibiotic named 210-A (22), which shows potent antifungal activity against *Fusarium oxysporum* f. sp. cubense race four (Figure 13). This compound also demonstrates antitumour activity against human hepatocarcinoma cells and S180 murine sarcoma [95].

Several secondary bioactive metabolites (23) were obtained from *Streptomyces* TK-VL_333 (Figure 14). Among them, 1*H*-indole-3-carboxylic acid (*T₁*) showed antifungal activity against *Candida albicans*, *Epidermophyton floccosum*, *Aspergillus niger* and *Fusarium oxysporum*. It also exhibited antimicrobial activity (Figure 14) [96].

6. Antiparasitic properties

Milbemycins are 16-membered macrolides isolated from *S. hygroscopicus* subsp. *aureolacrimosus*. They exhibit potent, broad spectrum antihelminthic, insecticidal and acaricidal properties [97].

Avermectins are antiparasitic compounds produced by soil-derived *S. avermitilis*. These macrocyclic lactones are active against arthropod parasites of domestic animals [98].

Two novel compounds were isolated from *S. nanchangensis*: nanchangmycin, the polyether that expresses activity against chicken coccidial parasites; and 16-membered macrolide meilingmycin, which shows antiparasitic activities similar to those exhibited by avermectin. Both products are active against harmful nematodes and insects [99].

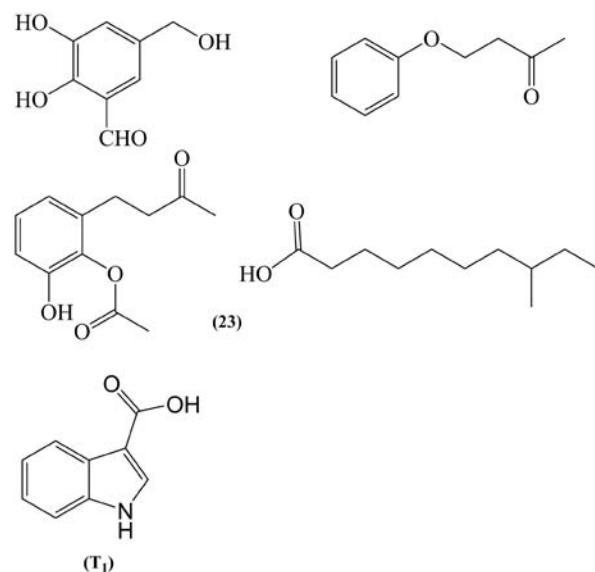


Figure 14. Chemical structure of compounds from *Streptomyces* TK-VL_333 (23).

Previously known tetracycline B and some structurally novel tetracycline derivatives (24) isolated from *S. axinella* PO1001 express antiparasitic activities against *Trypanosoma brucei* (Figure 15) [100].

Valinomycin, staurosporine and butenolide are antiparasitic compounds isolated from *Streptomyces* spp. Valinomycin is a cyclodepsipeptide isolated from many soil actinomycetes, such as, *S. fulvissimus*, *S. roseochromogenes* or *S. griseus* var. *flexipartum* as well as from marine species. Staurosporine is an indolocarbazole alkaloid isolated from *Streptomyces* sp. strain 11. Both compounds exhibit activity against *Leishmania major* and *Trypanosoma brucei brucei*. Butenolide, which is a α,β -unsaturated lactone, possesses activity against *Trypanosoma* sp. [7].

Two new nucleotide antibiotics, named sinefungin VA and dehydrosinefungin V, have been isolated from *Streptomyces* sp. K05-0178 culture broth, recently. They possess antitrypanosomal activity. Sinefungin VA consists of adenosine and ornithylvalylalanine, whereas dehydrosinefungin V consists of 4',5'-dehydroadenosine and ornithylvaline. Sinefungin VA showed potent antitrypanosomal activity with IC_{50} value of 0.0026 μ g/ml and no cytotoxicity against MRC-5-cells was observed [101].

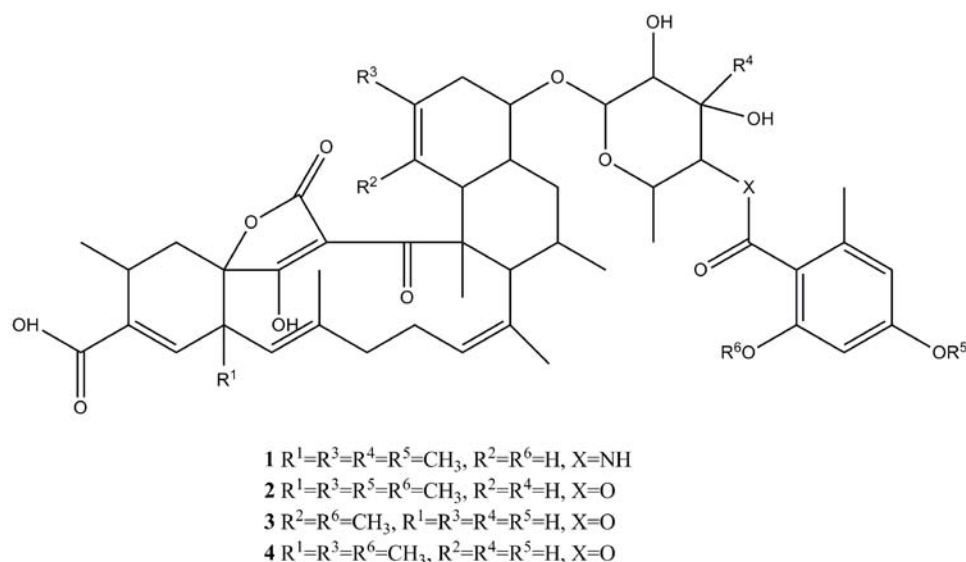
7. Antiviral properties

In 1971, tunicamycin (TM) was isolated from *S. lyososuperficus* nov. sp. fermentation broth by Takatsuki and Tamura *et al.* [102]. Tunicamycins are fatty acyl nucleoside products which contain uracyl. Compounds similar to TM, streptovirudin and corynetoxin, were isolated later also from actinomycete strains. Streptovirudin was isolated from *S. griseoflavus* subsp. *thuringiensis*. Both compounds possess similar activities against enveloped viruses, and streptovirudin is also a potent inhibitor of the *Bacillus* genus. Corynetoxins were isolated in 1982 from *Corynebacterium rathayi* [86].

An anti-influenza virus compound, JBIR-68 (25), with a unique skeleton (5'-O-Geranyl-5,6-dihydrouridine) has been isolated from *Streptomyces* sp. RI18, recently (Figure 15). It noticeably inhibits the influenza virus growth, but the mechanism of the antiviral activity is not clear [103].

8. Other activities

Streptomyces secondary metabolism products can also serve to inhibit the activity of different enzymes: for example, clavulanic acid or acarbose (an α -glucosidase



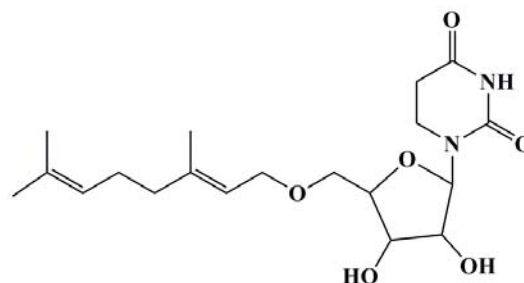
(24)

Figure 15. Chemical structure of tetromycins 1-4 (24).

inhibitor). Acarbose was isolated from *Actinoplanes* sp. SE50 [104]. Lipstatins are pancreatic lipase inhibitors produced by *S. toxytricini*, which limit intestinal fat absorption. The lipstatin molecule includes an unusual β -lactone structure that is responsible for irreversible lipase inhibition. Lipstatins are used in diabetes and obesity treatment and are available on the market as a component of a drug termed orlistat [105].

Tacrolimus, sirolimus (rapamycin) and cyclosporine A are bioactive *Streptomyces* metabolites with immunosuppressive activity. Only one of them, sirolimus, does not have nephrotoxic properties; this compound is thus often used after kidney transplantations. It belongs to the macrolide family and was isolated for the first time from *S. hygroscopicus*. It is widely used as an immunosuppressive and antiproliferative compound [106]. Tacrolimus (FK-506) is produced by *S. tsukubaensis* [107]. This substance was approved in 1994 by the FDA as an immunosuppressive agent after transplantation of liver and other organs. Tacrolimus is used topically in atopic dermatitis.

Spinosyns (A, D) are insecticides produced by *Saccharopolyspora spinosa*. Their mechanism of activity is based on interaction with neurotransmitters and receptors in the brain. Other compounds belonging to spinosyns were isolated as metabolite products of *Saccharopolyspora pogona*. *Saccharopolyspora spinosa* fermentation products consist of a mixture of spinosyn A, which is the major component, and spinosyn D, 6-methyl-spinosyn A, which is present in minor amount. Both compounds possess selective



(25)

Figure 16. Chemical structure of JBIR-68 (25).

activity against target insects and lower toxicity than other insecticides [108].

Actinomycetes are also isolated from manure, compost and fodder, where they take part in decomposition processes. Furthermore, *S. griseus* and *Thermomonospora viridis* (*Saccharomonospora viridis*) decrease odorous gas emission from swine manure [109].

S. griseofuscus was found to produce physostigmine, an alkaloid acetylcholinesterase inhibitor, which improves memory function both in the brain of healthy humans and Alzheimer's disease patients [110]. Flaviogeranin (26) ($C_{22}H_{26}O_5$), isolated from *Streptomyces* sp. RAC226, was proven to possess some neuroprotective properties (Figure 17) [111]. Tumescenamides A (27) and B were isolated from *S. tumescens* YM23-260 fermentation broth (Figure 17). Tumescenamide A was shown to induce upregulation of the insulin-degrading enzyme

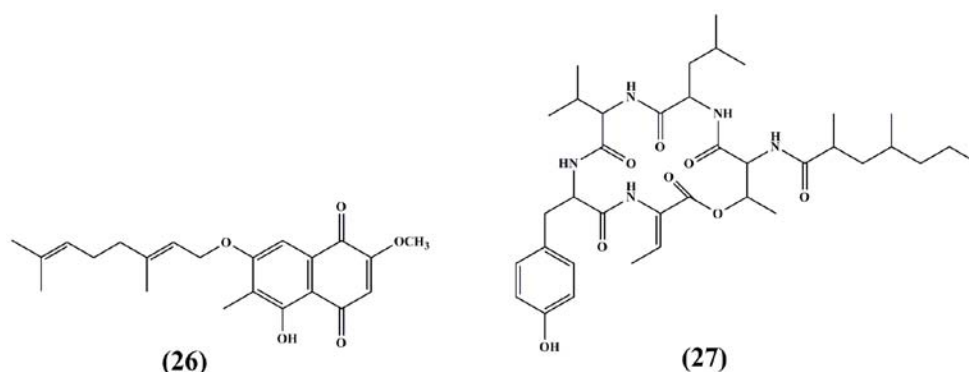


Figure 17. Chemical structure of flaviogeranin (26) and tumescenamides A (27).

(IDE) and can be a promising compound in Alzheimer's disease treatment [112].

9. Conclusions

Microbial secondary metabolites are the source of compounds with unique chemical structures. A large variety of structurally original compounds are produced during microbial fermentation processes. They are known to show various activities, not only antibacterial and antitumour, but also antifungal, antiviral, antiparasitic, immunosuppressive, enzyme-inhibiting, and even neuroprotective: they can play a fundamental part in Alzheimer's disease treatment. The original structures of natural bioactive metabolites provide unique candidates for new medicines. Secondary metabolites with antibacterial activity are widely used in treatment of infectious diseases. However, the majority of novel actinomycete metabolites isolated in the previous five to ten years are likely to possess weaker bioactivity than well-known, older compounds. MIC values of recently discovered antibacterial molecules isolated from actinomycetes are likely to be higher than for well-known antibiotics isolated in the 1950s and 1960s. From a numerical perspective, it is rare to discover a compound with high antibacterial activity. For example, from 10 million tested actinomycete strains isolated from soil samples, one strain will produce

daptomycin, 50 erythromycin, 150 vancomycin, 1000 tetracyclin and actinomycin, and 100 000 streptomycin [113]. Until now, the largest number of bioactive compounds was isolated from soil, which is an easily accessible environment. Current research seeks new strains from less accessible places, such as seas and oceans. Advanced research techniques allow to the combination of chromatographic methods with spectroscopy by exploiting on-line libraries of naturally-derived compounds and HTS. Compounds that have been known for a long time are also being re-screened for new activities. The original structure of bioactive compounds provided by nature is often difficult or impossible to develop in chemical laboratories. But chemical modifications of bioactive compounds deriving from nature often improve their bioactivity, representing a connection between chemistry and biology.

The appearance of multidrug-resistant strains and the demand for improved tumour treatment encourage a continuous search for new natural bioactive metabolites.

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