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Secondary Metabolites of Actinomycetes and their Antibacterial, Antifungal and Antiviral Properties

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Abstract

The growing resistance of microorganisms towards antibiotics has become a serious global problem. Therapeutics with novel chemical scaffolds and/or mechanisms of action are urgently needed to combat infections caused by multidrug resistant pathogens, including bacteria, fungi and viruses. Development of novel antimicrobial agents is still highly dependent on the discovery of new natural products. At present, most antimicrobial drugs used in medicine are of natural origin. Among the natural producers of bioactive substances, Actinobacteria continue to be an important source of novel secondary metabolites for drug application. In this review, the authors report on the bioactive antimicrobial secondary metabolites of Actinobacteria that were described between 2011 and April 2018. Special attention is paid to the chemical scaffolds, biological activities and origin of these novel antibacterial, antifungal and antiviral compounds. Arenimycin C, chromopeptide lactone RSP 01, kocurin, macrolactins A1 and B1, chaxamycin D as well as anthracimycin are regarded as the most effective compounds with antibacterial activity. In turn, the highest potency among selected antifungal compounds is exhibited by enduspeptide B, neomaclafungins A-I and kribelloside D, while ahmpatinin ^{i}Bu, antimycin A1a, and pentapeptide 4862F are recognized as the strongest antiviral agents.

Key words: bioactive, secondary metabolites, actinomycetes, antibacterial activity, *Streptomyces* sp.

Introduction

Natural products play a predominant role in the development of new therapeutic agents (Newman and Cragg 2016). Actinobacteria represent the most prominent group of microorganisms, which produce bioactive compounds. They synthesize approximately two-thirds of all naturally derived antibiotics currently used in medicine, veterinary practice and agriculture. Majority of these molecules originate from *Streptomyces* genus (Barka et al. 2016; Chater 2016).

A traditional approach in obtaining novel bioactive agents, especially with unique chemical structures and biological significance, relies on distinct microorganisms isolated from different, often secluded, environments. Actinobacterial strains commonly derive from soil (Guo et al. 2015), but they are also abundantly present in seas and oceans (Hassan et al. 2015; Xu et al. 2017). Moreover, extreme habitats such as caves (Jiang et al. 2015), deserts (Goodfellow et al. 2017) or Antarctic ecosystems (Lee et al. 2012) are recognized as valuable sources of actinomycetes producing novel metabolites of pharmacological importance (Solecka et al. 2013; Singh et al. 2018). Biosynthesis of secondary metabolites depends on the growth conditions of each strain. For years researchers have been applying different modifications in nutrients and physicochemical factors during fermentation processes to optimize the production of bioactive compounds (Rajnisz et al. 2016). Currently, modeling and analysis of fermentation processes is performed by the statistical optimization approach, e.g. response surface methodology, which enables enhanced production of antibiotics, enzymes and probiotics (Latha et al. 2017).

Genome sequencing can also be applied to detect the genes responsible for production of secondary metabolites besides those that were isolated under standard cultivation conditions (Thong et al. 2015). Most

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microbially derived natural products are produced via metabolic pathways encoded by adjacent chromosomal genes: biosynthetic gene clusters (BGCs). BGCs encode enzymes, regulatory proteins and transporters that are necessary to produce, process and export a metabolite (Medema and Fischbach 2015). On average, BGCs encompass 1.64 Mbp (16% of actinomycete coding capacity), encoding 35 secondary metabolites. The largest number of natural products was determined to be encoded by *Kutzneria albida*, *S. bingchenggensis* and *S. rapamycinicus* strains, which devote 2.5–3.09 Mbp (> 20% of coding capacity) to encode 48–53 secondary metabolites (Wink et al. 2017). Most of BGCs are cryptic or poorly expressed under laboratory conditions (Baltz 2011). However, many methods have been developed to activate the actinobacterial secondary metabolism, including combined cultures and use of goadsporins (Onaka 2017). An effective strategy in the development of strains with enhanced secondary metabolism was established with the recent advancement of whole-genome sequencing, systems biology and genetic engineering. In this aspect, the "-omics" technologies (genomics, transcriptomics, proteomics and metabolomics) together with bioinformatic are especially useful tools in inducing the overproduction of actinomycetes secondary metabolites. The past few years were an exciting time for metabolic engineering of actinomycetes as several novel in silico methods to automate the analysis of secondary metabolism in bacterial genomes (e.g. antibiotics & Secondary Metabolite Analysis Shell, antiSMASH) had been introduced (Medema et al. 2011).

In this review, we present secondary metabolites of Actinobacteria, which possess antibacterial, antifungal and antiviral activities. Their origin and chemical features are also reported. We draw special attention to novel agents described from 2011 to April 2018, displaying minimum inhibitory concentrations (MICs) less than or equal to 10 μg/ml. Additionally, we discuss on the previously described compounds that were recently characterized with new properties and function. The present article is a thematic continuation of a review published in 2012 (Solecka et al. 2012).

Antibacterial activity

Nowadays, antibiotic resistance of microorganisms is one of the biggest threats to global health, food security and development. The World Health Organization (WHO) Global Report on the surveillance of antimicrobial resistance has established that bacterial resistance to commonly used drugs in infection treatment has reached alarming levels in many parts of the world (WHO 2014). In 2017, WHO released its first list of most concerning "priority pathogens" for human health – a catalogue of twelve families of bacteria for which new antibiotics are urgently needed (WHO 2017). According to O'Neill's independent review (2016) about 700 000 people around the world die annually due to drug-resistant infections. If current trends continue, such infections could entail the death of 10 million people a year by 2050 (O'Neill 2016). In this context, the discovery of new bioactive compounds, particularly those with new modes of action, is not only needed for modern medicine but absolutely required to avoid future pandemics.

Below authors present the major chemical structural groups of newly discovered compounds with antibacterial activity.

Spirotetronate compounds. Among novel molecules that were reported since 2011 is maklamicin (Fig. 1), a new spirotetronate-class polyketide. It is a polycyclic compound from the culture extract of endophytic *Micromonospora* sp. GMKU326 isolated in Thailand. Maklamicin showed potent antimicrobial activities against Gram-positive bacteria, including *Micrococcus luteus*, *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, and *Enterococcus faecalis* with MIC values of 0.2, 1.7, 6.5, 13, and 13 μg/ml, respectively, and significantly lower activity against *Candida albicans* (MIC = 50 μg/ml). The compound displayed also moderate cancer cell cytotoxicity (Igarashi et al. 2011).

Another newly discovered spirotetronate antibiotic of polyketide origin is nomimicin, which was isolated from the culture extract of *Actinomadura* sp. TP-A0878. The molecule showed antimicrobial activities against *M. luteus*, *C. albicans* and *Kluyveromyces fragilis* with MIC values of 6.3, 12.5 and 12.5 μg/ml, respectively. Moreover, nomimicin displayed weak cytotoxicity against human cancer cells (Igarashi et al. 2012).

Significant antibacterial and antitumor activities were demonstrated by lobophorin F, a new spirotetronate molecule isolated from *Streptomyces* sp. SCSIO 01127. The MIC values towards *Bacillus thuringiensis*, *S. aureus* and *E. faecalis* equaled 2, 8, 8 μg/ml, respectively (Niu et al. 2011). Interesting bioactivities were demonstrated by secondary metabolites of *Streptomyces* sp. strain MS1 00061 originating from the South China Sea. The three detected secondary metabolites belong to the lobophorin family, and one of them, lobophorin G, was described for the first time. The others, lobophorin A and B, were previously known as anti-inflammatory agents. Together, these three metabolites exhibited a significant anti-BCG (anti-*Mycobacterium bovis*) effect. Furthermore, they exhibited moderate anti-tuberculosis (anti-*Mycobacterium tuberculosis*) properties and diverse activity towards *B. subtilis* (Chen et al. 2013). Another, novel lobophorin H inhibited the growth of *M. tuberculosis*, *B. subtilis* and *S. aureus* and

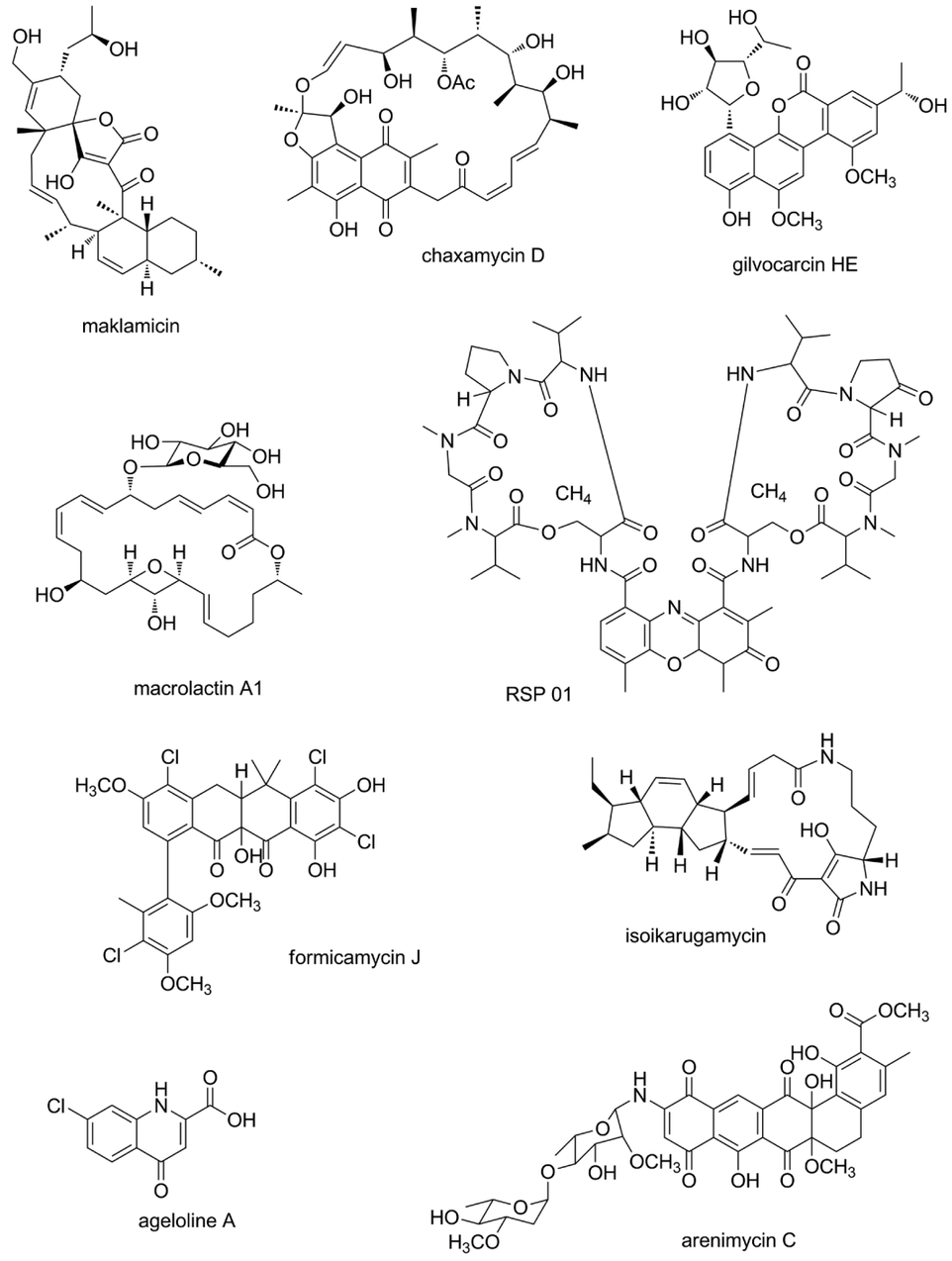

Fig. 1. Chemical structures of compounds with antibacterial activities.

was toxic towards the human CEM-TART cell line (Pan et al. 2013; Lin et al. 2014).

Ansamycin-type compounds. Four new ansamycin-type (aromatic moiety bridged by an aliphatic chain) polyketides, named chaxamycins A-D were isolated from the *Streptomyces* sp. strain C34 from the Chilean hyperarid Atacama Desert soil. Antibacterial activity assays showed chaxamycin D (Fig. 1) to present the strongest activity against *S. aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 (MIC = 0.05 and 1.21 μg/ml, respectively) as well as against a panel of methicillin-resistant *S. aureus* (MRSA) clinical isolates with MICs ranging from 0.06–0.25 μg/ml (Rateb et al. 2011a). The other chaxamycins (A-C) exhibited also the ability to inhibit the intrinsic ATPase activity of the heat shock protein 90 (Hsp) (41–46% of inhibition at 100 μM).

β-diketones, aromatic ketones. Three new bioactive β-diketones were discovered from the culture broth of *S. asenjonii* KNN 42.f isolated from an extreme hyperarid Atacama Desert soil in Northern Chile. In addition to thirteen already known substances, three novel compounds – asenjonamides A, B and C, were also purified.

These new active metabolites were grouped in the β-diketone family of polyketides. The highest antibacterial activity was determined for asenjonamide C, which exhibited MIC = 1.8 μg/ml against methicilin-sensitive *S. aureus* (MSSA), MIC = 3.9 μg/ml against *E. faecium* and MIC = 5.4 μg/ml against *E. coli* (Abdelkader et al. 2018).

Moreover, significant antimicrobial properties against *S. aureus*, *B. subtilis*, *E. coli* and *C. albicans* (MICs between 0.25–2.5 μg/ml) were determined for a new polyketide glycoside, gilvocarcin HE (Fig. 1), obtained from the ethyl acetate extract of *Streptomyces* sp. QD01-2 (isolate from soil sample collected at Huiquan Square in China). The compound showed also moderate cytotoxicity against the MCF-7, K562 and P388 cell lines, with IC_{50} values of 36, 39 and 45 μM, respectively. Results prove that the vinyl side chain helps to increase the cytotoxicity and antimicrobial activities of gilvocarcin-type glycosides (Hou et al. 2012).

Two new chloroanthrabenzoxocinones antibiotics – zunyimycins B and C – were isolated from the *Streptomyces* sp. FJS31-2 fermentation broth. The strain was isolated from a soil sample from the Fanjing Mountain of Guizhou Province, China. Zunyimycin C presents good antimicrobial activity toward *S. aureus* ATCC 29213 (MIC = 0.94 μg/ml) and five clinical MRSA isolates (MICs between 3.75–8.14 μg/ml) (Lü et al. 2017).

Tetracenediones. Novel polyketides named formicamycins A-L were discovered as secondary metabolite products of the *S. formicae* KY5 strain isolated from Kenyan ants *Tetraponera penzigi*. Formicamycin J (Fig. 1) was shown to inhibit the growth of the clinically relevant pathogens – MRSA and vancomycin-resistant *Enterococcus faecium* (VRE) with MICs of 0.41 and 0.82 μg/ml, respectively. Other tested formicamycins were less potent (Qin et al. 2017).

Lactones. Application of the "one strain-many compounds" approach on the *Streptomyces* strain using a range of cultivation media resulted in the isolation and identification of several new compounds. These included three new chaxalactins A-C from the rare class of macrolactone polyketides detected together with already known deferroxamine E, hygromycin A, and 5"-dihydrohygromycin A. Novel molecules showed strong activity against Gram-positive bacteria, such as *S. aureus*, *L. monocytogenes*, *B. subtilis* (MICs ranging from 0.2 to 6.3 μg/ml) and weaker activity against Gram-negative strains like *V. parahemolyticus* with MIC of 12.5 μg/ml for chaxalactins A and C and 20 μg/ml for chaxalactin B (Rateb et al. 2011b).

In 2013, Jang and colleagues described a new, promising natural product especially effective towards *Bacillus anthracis* (MIC = 0.03 μg/ml). The compound was designated as anthracimycin and was shown to display antibacterial activity also against *E. faecalis*, *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, MSSA, MRSA and vancomycin-resistant *S. aureus* with MICs ranging from 0.03 to 4 μg/ml. Anthracimycin was isolated from the *Streptomyces* sp. strain CNH365 collected from marine sediments near Santa Barbara, California, USA. The compound was classified as a polyketide antibiotic and possesses a 14-membered lactone ring and a chemical structure similar to that observed for the macrolide chlorotonil. The mode of action of anthracimycin is based on the inhibition of DNA/RNA synthesis (Jang et al. 2013). Additionally, *in vivo* experiments revealed that anthracimycin was able to protect mice from MRSA-induced mortality in a murine peritonitis model of infection (Hensler et al. 2014).

An actinomycete strain isolated from marine sediment from Chuuk, Federated States of Micronesia, was discovered to produce two new macrolactins – A1 (Fig. 1) and B1 (polyene cyclic macrolactones), and the previously known lauramide diethanolamine. All of them significantly inhibited the growth of Gram-positive (*B. subtilis*, *S. aureus*) and Gram-negative (*E. coli*, *P. aeruginosa*) bacteria with MICs ranging between 0.015 and 0.125 μg/ml. Furthermore, they also displayed potent anti-yeast effects (MIC towards *S. cerevisiae* – 0.125 μg/ml). Unfortunately, activities of these compounds were weaker compared to azithromycin and amphotericin B, which served as positive controls in the trials (Mondol and Shin 2014).

Cruz et al. described the first hyperchlorinated angucyclinones produced by *Actinoallomurus* sp. ID145698. Due to their unique structural features and wide distribution among *Actinoallomurus*, authors have designated these angucyclinones as allocyclinones. These compounds are characterized by an unusual lactone ring and present up to four halogens per molecule, with one congener representing the first natural product containing a trichloromethyl substitution on an aromatic system. The antibacterial activity of four isolated allocyclinones was determined to increase with the number of chlorine substituents on the methyl group. Allocyclinone A has three additional chlorine atoms at carbon C-13. This compound showed the highest antibacterial activity. The MICs were in the range of 0.25–0.5 μg/ml against *S. aureus*, *S. pyogenes* and *E. faecalis,* except for *E. faecium* (MIC = 4 μg/ml). As expected, none of the evaluated, clinically relevant resistance mechanisms affected the activity of the compounds (Cruz et al. 2017).

The first-time reported compound RSP 01 (Fig. 1) is a bicyclic chromopeptide lactone from the actinomycin group. It was found to be biosynthesized together with the already described RSP02 by *Streptomyces* sp. RAB12 isolated from soil samples collected from the garden near the CSIR-Indian Institute of Chemical Technology, Hyderabad, India. Both RSP 01 and 02 revealed a chemical structure similar to actinomycin D. However, RSP 01 has a ketocarbonyl group at the fourth car-

bon of the proline moiety, which is absent in actinomycin D. Results of bioactivity assays suggest that RSP 01 has a higher antimicrobial potential in comparison with actinomycin D. The MICs values for RSP 01 ranged from 0.007 to 0.06 μg/ml against *S. aureus*, *P. aeruginosa*, *S. typhi* and *B. subtilis* (Rathod et al. 2018).

Macrolides are also recognized as lactones. They belong to a class of natural products that consists of a macrocyclic lactone ring (14-membered or more) to which one or more deoxy sugar moiety can be attached. Two 16-membered macrolides, tylosin analogues, were obtained from a wbIA disruption mutant of *Streptomyces ansochromogenes* (wbIA, an Actinobacteria-specific gene controlling major developmental transition). These novel natural products exhibited moderate activity against Gram-positive bacteria, such as: *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *B. subtilis*, *B. cereus* and *S. aureus* with MIC values in the range of 3.53–58.5 μg/ml. It is noteworthy that tylosin derivatives showed stronger bactericidal effects towards *S. pneumoniae* than tylosin itself (Lu et al. 2015).

A novel 48-membered polyol macrolide, named quadoctomycin, was isolated from *Streptomyces* sp. MM168-141F8. It showed potent antibacterial activity against *S. aureus*. The MIC values were evaluated for three MSSA, five MRSA and six *E. faecalis* strains and ranged between 1–2 μg/ml. In turn, quadoctomycin did not show antimicrobial activity toward Gram-negative bacteria (Sawa et al. 2018).

In 2017, Khalil et al. reported on the identification of amycolatopsins A, B and C, the representatives of a rare family of glycosylated polyketide macrolides that are related to the apoptolidin, and novel metabolites of ammocidin structure class derived from the southern Australian soil isolate, *Amycolatopsis* sp. MST-108494. Only amycolatopsins A and C were active towards *M. bovis* and *M. tuberculosis,* reaching IC_{50} values of 0.5–7.0 μg/ml. In turn, all three compounds showed cytotoxicity against mammalian NCIH-460 and SW620 cells (Khalil et al. 2017).

Lactams. *Streptomyces zhaozhouensis* CA-185989 from marine sediment collected near Utonde, Equatorial Guinea was found to produce new bioactive secondary metabolites from the class of polycyclic tetramic acid macrolactams, isoikarugamycin (Fig. 1) and 28-N-methylikarugamycin. These novel compounds demonstrated potent antibacterial and antifungal activities and were shown to be active towards *S. aureus*, *C. albicans* and *A. fumigatus* presenting MICs between 1 and 8 μg/ml (Lacret et al. 2014).

Quinones. Heterologous expression of specific gene clusters (corresponding to two eDNA-derived KSβ sequence tags) in *Streptomyces albus* enabled the isolation of new polyketides, arenimycins C (Fig. 1) and D with potent antibacterial activities. Arenimycins C and D belong to benzo[α]naphthacene quinones and were shown to be active towards MRSA USA300 (MIC = 0.098 and 0.19 μg/ml, respectively) and *B. subtilis* RM125 (MIC = 0.0015 and 0.39 μg/ml, respectively) (Kang and Brady 2014).

Identification of pseudonocardians A-C, new diazaanthraquinone analogs, substantiated the potential of marine actinomycetes as a source of novel drugs. These two compounds derived from *Pseudonocardia* sp. SCSIO 01299 collected from the deep-sea sediment of the South China Sea. The activity profile revealed that pseudonocardians A and B were notably potent against bacterial strains as well as tumor cell lines. The MIC values towards *S. aureus*, *E. faecalis* and *B. thuringensis* ranged between 2–4 μg/ml (Li et al. 2011).

Another group of quinones – pyranonaphthoquinone antibiotics, known as selective inhibitors of the serine-threonine kinase AKT (protein kinase B), has been enlarged in 2015 to include a new member – xiakemycin A. The compound was isolated from the culture broth of *Streptomyces* sp. CC8-201 originating from the soil of a Chinese karst cave. In a panel of antibacterial and antiproliferative assays, xiakemycin A demonstrated activity towards Gram-positive bacteria (*S. aureus*, *S. epidermidis*, *E. faecalis* and *E. faecium*) with MICs ranging from 2 to 16 μg/ml (Jiang et al. 2015).

In 2013, Song et al. reported the isolation of four new sesquiterpenoid naphthoquinones, marfuraquinocins A-D, from the fermentation broth of *Streptomyces niveus* SCSIO 3406 (South China Sea, sediment sample). All compounds were evaluated for their potential antibacterial and cytotoxic properties. Marfuraquinocins A, C and D were active towards *S. aureus* ATCC 29213 with equivalent MICs of 8 μg/ml. Additionally, marfuraquinocins C and D exhibited antibacterial activity against the methicillin-resistant *S. epidermidis* clinical isolate shhs-E1 with the same MIC values (8 μg/ml) (Song et al. 2013).

Xin and colleagues discovered also other quinone derivatives with antibacterial and antitumor properties that is produced by actinomycetes as secondary metabolites. Among them were new modified anthraquinones – fradimycins A and B (capoamycin-type agents) isolated from marine *Streptomyces fradiae* PTZ0025. These two substances were active against *S. aureus* with MICs of 6 and 2 μg/ml, respectively. Moreover, these compounds displayed cytotoxicity towards human cancer cell lines (Xin et al. 2012).

Quinolones. Interesting bioactivity was observed for a newly recognized chlorinated quinolone of actinomycetes origin (*Streptomyces* sp. SBT345) obtained from the Mediterranean sponge, *Agelas oroides*. This novel natural product designated as ageloline A (Fig. 1), showed antichlamydial and antioxidant effects. Ageloline inhibited the growth of *Chlamydia trachomatis*

inclusion with IC_{50} value of 2.1 μg/ml. Moreover, the compound was shown not only to reduce oxidative stress, but also to decrease genomic damage induced by the 4-nitroquinoline-1-oxide, an oxidative stress inducer (Cheng et al. 2016).

Xanthones. Another promising substance with antimicrobial potential is buanmycin, a new pentacyclic xanthone isolated from the culture of a marine *Streptomyces* strain from a tidal mudflat in Buan (Republic of Korea). Buanmycin was shown not only to display strong inhibitory activity against both Gram-positive (*S. aureus*, *B. subtilis*, *K. rhizophila*) and Gram-negative bacteria (*Salmonella enterica*, *P. hauseri*) with MICs 0.42–12.5 μg/ml, but also to inhibit the *S. aureus* sortase A, an enzyme that plays key role in adhesion and host invasion by Gram-positive bacteria (with IC_{50} value of 43.2 μM in comparison to IC_{50} = 104.4 μM for the p-hydroxymercuribenzoic acid, the positive control compound). Additionally, buanmycin exhibited potent cytotoxicity with submicromolar IC_{50} values as well as moderate antifungal activity towards *C. albicans* (MIC = 12.5 μg/ml) (Moon et al. 2014). Four novel xanthones (citreamicin θ A (Fig. 2), citreamicin θ B, citreaglycon A and dehydrocitreaglycon) were obtained by Liu et al. from a marine *Streptomyces caelestis* strain. All these compounds demonstrated potent activity towards *S. haemolyticus*, *S. aureus* and *B. subtilis* with MIC values in the range of 0.25–16 μg/ml. However, citreamicin θ A and citreamicin θ B were definitely more active than the other metabolites, probably due to the five-member nitrogen heterocycle in their structures. Additionally, they also showed cytotoxicity against HeLa cells (Liu, Xu et al. 2012).

Aminocoumarins. The combined approach of phylogenetic and chemical analyses of the *Streptomyces* community from marine sediments of British Columbia in Canada allowed discovering a range of structurally diverse actinomycetes secondary metabolites. Four of them were determined as new novobiocin analogues. Two of them, desmethylnovobiocin and 5-hydroxynovobiocin (Fig. 2) were active against MRSA ATCC 33591 with MIC values of 16 and 8 μg/ml, respectively. Novobiocin is known to target the bacterial gyrase by inhibiting ATP hydrolysis (Maxwell and Lawson 2003). Structure-activity relationships (SAR) studies demonstrated that analogues bearing different substituents at 3"-carbamoyl and 4"-OMe noviose moieties, or a 5-H hydroxybenzoate ring exhibited a dramatic decrease or complete elimination of inhibitory activity against MRSA (Dalisay et al. 2013).

Terpenoids. Three new meroterpenoids – napyradiomycins, together with six already known analogues were isolated as secondary metabolites of the *Streptomyces* sp. strain SCSIO 10428 derived from the Xieyang Island (Beihai, Guangxi province, China). Among them were 4-dehydro-4a-dechloronapyradiomycin A1, 3-dechloro-3-bromonapyradiomycin A1 and 3-chloro-6, 8-dihydroxy-8-α-lapachone, of which the second compound displayed the widest bioactivity range. Antibacterial assays revealed that 3-dechloro-3-bromonapyradiomycin A1 is active towards *S. aureus*, *B. subtilis* and *B. thuringensis* with MIC values at the level of 0.5–1 μg/ml. The compound showed also cytotoxicity against four human cancer cell lines (Wu et al. 2013).

A new secondary metabolite, actinomadurol (Fig. 2), was isolated from rare actinomycete strain, *Actinomadura* KC191. The structure of the compounds revealed a unique 19-norditerpenoid-carbon backbone, which provided a novel scaffold for antibiotic discovery. This molecule displayed significant inhibitory activity towards various bacterial strains, such as *B. subtilis* ATCC 6633, *S. aureus* ATCC 6538p, *K. rhizophila* NBRC 12708, *P. hauseri* NBRC 3851 and *S. enterica* ATCC 14028 with MIC values of 0.39 to 3.12 μg/ml (Shin et al. 2016).

Peptides. A promising scaffold for the treatment of Gram-positive bacterial infections is kocurin (PM181104) (Fig. 2), a new thiazozyl peptide obtained from *Kocuria palustris* F-276,345. This metabolite displays much lower MICs (0.008–0.512 μg/ml) towards *B. subtilis* and drug-resistant strains of *S. aureus*, *E. faecium* or *E. faecalis* than the standard antibiotic, linezolid. The most likely mode of action of this agent is inhibition of bacterial growth by blocking its protein biosynthesis at the translation stage. Furthermore, *in vivo* studies revealed that kocurin protected mice from organ-specific infections or even from systemic infections (Mahajan et al. 2013).

Pargamicins B, C and D are new cyclic peptide metabolites, which were isolated from the fermentation broth of a soil actinomycete strain, *Amycolatopsis* sp. ML1-hF4. The structure of pargamicin A was determined in 2008. Pargamicins are structurally unique cyclic peptides consisting of N-methyl-3-hydroxy valine, 4-hydroxy piperazic acid (4-OH-Pip), sarcosine, phenylalanine, N-hydroxy isoleucine (NOH-Ile) and piperazic acid (Pip). The only structural difference between pargamicins is in the Pip(NOH-Ile) moiety. However, despite this structural similarity, antimicrobial activities of pargamicins showed remarkable differences. Pargamicins A and C exhibited potent antibacterial activity against Gram-positive bacteria, including MRSA and VRE. The MIC values of pargamicin C towards MSSA and MRSA were in the range between 2 and 4 μg/ml, while towards *E. faecium* and *E. faecalis* – in the range from 0.5 to 1 μg/ml. In turn, the antibacterial activity of pargamicin B and D against these bacteria was weaker. Both agents demonstrated MIC values equal 8 μg/ml towards *E. faecium* and *E. faecalis*. When assayed against MSSA and MRSA strains it revealed MICs in the range

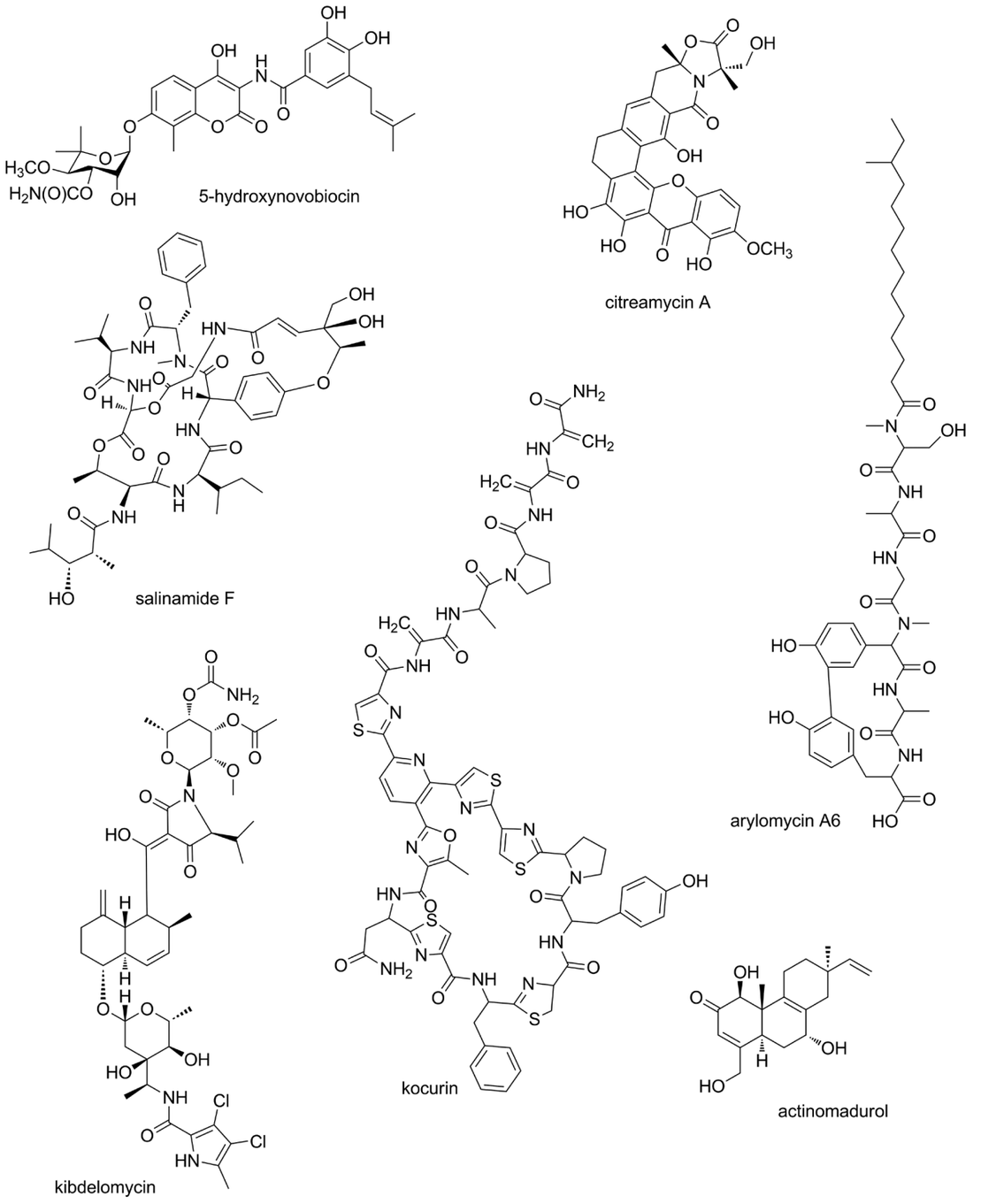

Fig. 2. Chemical structures of compounds with antibacterial activities.

of 8–16 and 32–64 μg/ml for pargamicin B and D, respectively (Hashizume et al. 2017).

Depsipeptides. Investigations of microorganisms from unique environments, such as the sand beach on Jeju, a volcanic island in the Republic of Korea, led to discovery of ohmyungsamycins A and B produced by *Streptomyces* sp. These new cyclic depsipeptides bear unusual amino acid units (N-methyl-4-methoxytrytophan, β-hydroxyphenylalanine, and N,N-dimethylvaline). The two molecules displayed various inhibitory activities against both Gram-positive and Gram-negative bacteria, including *B. subtilis*, *Kocuria rhizophila* and *Proteus hauseri* (MICs = 1.56–49.5 μg/ml). Ohmyungsamycin A is much more potent than ohmyungsamycin B with regard to its cytotoxicity and antibacterial properties (Um et al. 2013).

In 2014, a new bicyclic depsipeptide, salinamide F (Fig. 2), isolated from marine-derived *Streptomyces* sp. CNB-091, was described. The activity profile of salinamide F revealed that it is active towards *E. coli* D21f2tolC, *Haemophilus influenzae*, *E. faecalis* and *Neisseria gonorrhoeae* with MIC values of 0.20, 12.5, 12.5 and 25 μg/ml, respectively. Moreover, it showed significant inhibition of Gram-positive and Gram-negative bacterial RNA polymerase with IC_{50} = 4 μM for *S. aureus* RNAP and 2 μM for *E. coli* RNAP (Hassan et al. 2015).

New natural products discovered by Sun and colleagues, named fijimycins A and C, exhibited activity against three different MRSA strains with MICs in the range of 4–32 μg/ml. These novel etamycin-class depsipeptides were identified from the fermentation broth of *Streptomyces* sp. CNS-575 strain (Nasese, Fiji) (Sun et al. 2011).

Lipopeptides. The use of ultra-performance liquid chromatography coupled with tandem quadrupole and time of flight high-resolution mass spectrometry (UPLC-Q-TOF-HRMS) led to the identification of two lipopeptides from *Streptomyces parvus* HCCB10043. One of them, arylomycin A6 (Fig. 2), was a novel compound and showed antibacterial activity towards *Staphylococcus epidermidis* HCCB20256 with the MIC of 1 μg/ml (Rao et al. 2013).

Other chemical compounds. In 2011, Phillips and coworkers from Merck Research Laboratories, Merck & Co. reported on a compound named kibdelomycin (Fig. 2), which constituted the first structural class of DNA gyrase inhibitors discovered during 60 years of research. This secondary metabolite is a hexacyclic polyketide-peptide hybrid with a dichloropyrrole moiety produced by *Kibdelosporangium* sp. MA7385. The mode of action of kibdelomycin is similar to the coumarin antibiotic – novobiocin, as it targets two subunits of topoisomerase IV and DNA gyrase A. This broad spectrum antibiotic shows activity against MRSA (MIC = 0.5 μg/ml) as well as against *S. pneumoniae* (MIC = 1 μg/ml), *E. faecalis* (MIC = 2 μg/ml) and the Gram-negative pathogen, *Haemophilus influenzae* (MIC = 2 μg/ml) (Phillips et al. 2011). The recent studies performed with clinical strains have revealed potent activity of kibdelomycin against *Acinetobacter baumanii* (MIC = 0.125 μg/ml). There was no cross-resistance observed with other gyrase inhibitors in assays with novobiocin- and ciprofloxacin-resistant *S. aureus* strains (Singh et al. 2015).

Antifungal activity

Among the novel antifungal secondary metabolites produced by actinomycetes is sceliphrolactam. This previously unreported compound was isolated in 2011 from *Streptomyces* sp. associated with the black and yellow mud dauber, *Sceliphron caementarium*, collected in Wisconsin (United States). The structure, which consists of polyunsaturated and polyoxygenated 26-membered macrocyclic lactam is extremely sensitive to light, high temperatures and Lewis acids. Despite its liability, sceliphrolactam demonstrated potent antifungal activity against amphotericin B-resistant *C. albicans* with MIC of 4 μg/ml (Oh et al. 2011).

Other three novel members (15-glycidylfilipin III; 16α, 17α-epoxyfilipin V; 16β, 17β-epoxyfilipin V) of the polyene macrolide class were isolated from the cultures of a soil actinomycete, *S. lavenduligriseus*. Among them, only 15-glycidylfilipin III exhibited strong inhibition of mycelia growth of *C. albicans* with MIC value of 6.25 μg/ml compared to MIC = 3.13 μg/ml for the control, nystatin. The other compounds displayed considerably weaker fungicidal effects (MIC = 200 μg/ml) which ruled out the hypothesis that microbial secondary metabolites with an epoxide function are more toxic or have stronger cytostatic properties than analogs without the epoxide function (Yang et al. 2016).

In 2017, a *Streptomyces* sp. strain was isolated from a soil sample collected from a coal mine at a depth of 20 cm in Nanchang, Jiangxi, People's Republic of China. Six new cyclic octa depsipeptides, enduspeptides A-F, were produced by this strain. The most potent antifungal activities against *C. glabrata* ATCC 90030 with IC_{50} values of 5.33, 1.72 and 8.13 μg/ml were shown by enduspeptides A, B (Fig. 3) and C, respectively (Chen et al. 2017).

Four new Cet1p RNA 5'-triphosphatase inhibitors, designated kribellosides A-D (Fig. 3) were isolated as secondary metabolites of a rare Actinobacteria, *Kribella* MI481-42F6, found in a soil sample collected at Nerima-ku, Tokyo, Japan. These novel alkyl glyceryl ether compounds inhibited the activity of RNA 5'-triphosphatase from *Saccharomyces cerevisiae in vitro* with IC_{50} of 5–8 μM and showed antifungal activity with MICs ranging from 3.12 to 100 μg/ml against *S. cerevisiae* (Igarashi et al. 2017).

Mohangamides A and B were purified from culture broth of marine *Streptomyces* sp. SNM55 obtained from the Mohang mud flat collected in the Buan, Republic of Korea. These unique dilactone-tethered pseudodimeric peptides bear two unusual acyl chains and 14 amino acid residues. The biological activities of these novel compounds were primarily evaluated against *C. albicans* isocitrate lyase (ICL), which is a key enzyme of the glyoxylate cycle and enables microorganisms to grow on acetate, ethanol, or fatty acids in host environments. Mohangamides A and B displayed inhibition against ICL with an IC_{50} value of 4.4 μM and 20.5 μM, respectively. These compounds did not show significant antifungal activity when fungi were fed with glucose. Interestingly,

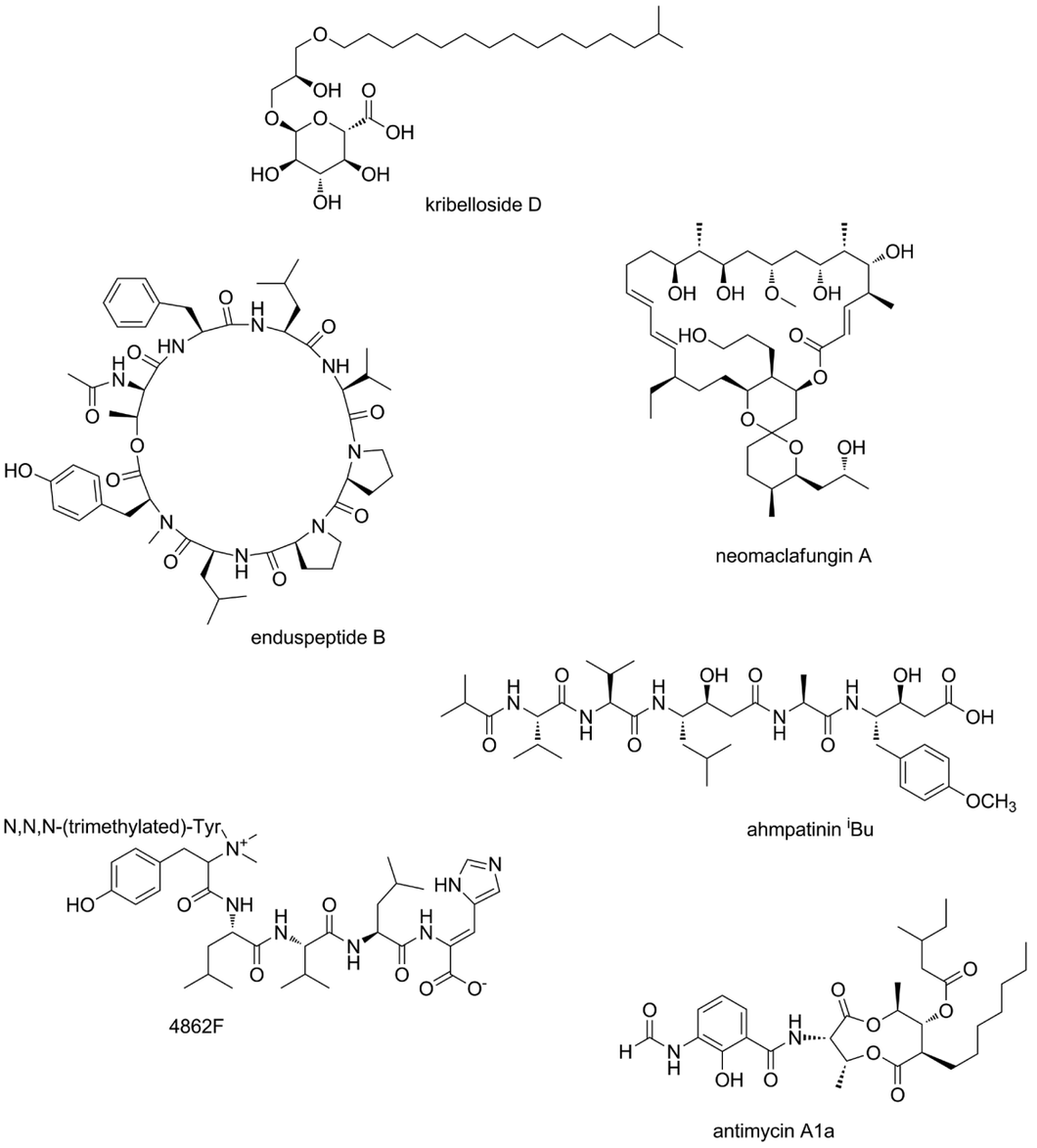

Fig. 3. Chemical structures of compounds with antifungal and antiviral activities.

mohangamide A inhibited *C. albicans* that was grown on 2% sodium acetate (Bae et al. 2015).

Neomaclafungin A (Fig. 3) was the main metabolite from the fermentation broth of *Actinoalloteichus* sp. NPS702 that was isolated from the marine sediment collected from Usa Bay, Kochi Prefecture, Japan. Besides neomaclafungin A, also other neomaclafungins (B-I) were isolated, but in lower concentrations. All novel compounds possess a macrolide ring similar to that of maclafungin, but with different moieties substituted in C-24 and C-33 position. The MIC values for these new neomaclafungins (A-I) against dermatophyte *Trichophyton mentagrophytes* ATCC 9533 were between 1–3 μg/ml (Sato et al. 2012).

Antiviral activity

The study of a marine actinomycetes strain, *Streptomyces kaviengensis*, isolated from the coast of New Ireland (Papua New Guinea) enabled Raveh and coworkers to identify a novel metabolite with significant antiviral activity. The compound, antimycin A1a (Fig. 3), was found to be an antimycin A derivative and shows high potency against the Western equine encephalitis virus with IC_{50} value of less than 4 nM and selectivity index of greater than 550. Analysis of its mechanism of action revealed disruption of mitochondrial electron transport and pyrimidine biosynthesis. Moreover, the previously known antimycin A demonstrated

a broad spectrum activity towards a wide range of RNA viruses, including members of the *Togaviridae*, *Flaviviridae*, *Bunyaviridae*, *Picornaviridae*, and *Paramyxoviridae* families (Raveh et al. 2013).

Promising chemical skeletons with antiviral properties are displayed by xiamycins C-E, produced by *Streptomyces* sp. #HK18 from the topsoil of a Korean solar saltern. New compounds were elucidated as carbazole-bearing indolosesquiterpenoids. Among them, xiamycin D exhibited the strongest effect on porcine epidemic diarrhea virus (PEDV) with replication with value of EC_{50} equaling 0.93 μM (cytotoxicity = 56.03 μM; selectivity index = 60.31). Additionally, the inhibitory activity of xiamycin D was confirmed by quantitative real-time PCR after amplification of fragments of the genes encoding essential structural proteins (GP6 nucleocapsid, GP2 spike, and GP5 membrane) for PEDV replication and by Western blotting of PEDV GP2 spike and GP6 nucleocapsid proteins (Kim et al. 2016).

HIV-1 protease is essential in the life cycle of HIV and has been used as a promising target for AIDS therapy. Several novel potent inhibitors of this protease have been reported recently. In 2013, a new inhibitor of HIV-1 protease, 4862F (Fig. 3) was isolated from the culture broth of *Streptomyces albosporus* I03A-04862. It was elucidated as *N,N,N*-(trimethylated)-Tyr-L-Leu-L-Val-L-Leu-(dehydrated)-His and determined to display inhibitory activity against HIV-1 protease with an IC_{50} value of 15.26 nM (Liu, Gan et al. 2012).

Ahmpatinin ^{i}Bu (Fig. 3) is a linear peptide and a novel pyrrolidine derivative with an unusual amino acid, 4-amino-3-hydroxy-5-(4-methoxyphenyl) pentanoic acid. It was produced by *Streptomyces* sp. CPCC 202950 cultured on sterile soaked rice. Ahmpatinin ^{i}Bu showed significant inhibitory activity against HIV-1 protease resulting in IC_{50} = 1.79 nM (Chen et al. 2018).

Functional diversity of microbial natural products is favorable in regards to exploring for drugs against the Zika virus (ZIKV). The spread of ZIKV into North and South America in 2013 has caused infections of millions of people (Saiz and Martín-Acebes 2017). In 2015, WHO declared a public health emergency due to Zika (Blázquez and Saiz 2016). Lately, a great effort has been put to determine drug candidates directed to viral targets or against cellular targets (host-targeting antivirals). This approach included screening of libraries with different compounds and repurposing drugs already used in clinical practice for other diseases (Bae et al. 2015). Among them, daptomycin (IC_{50} = 1 μM) and nanchangmycin (IC_{50} = 0.1 μM) showed a previously not described anti-ZIKV activity (Barrows et al. 2016; Pascoalino et al. 2016; Rausch et al. 2017). Both of these drugs are bioactive secondary products of *Streptomyces* spp., for which antiviral activity was unrecognized before. Daptomycin is a lipopeptide antibiotic used in the treatment of infections caused by Gram-positive bacteria. It was found in the culture broth of *S. roseosporus*. In turn, nanchangmycin is produced by *S. nanchangensis* and was shown to have insecticidal activity against silkworms and antibacterial activity *in vitro.*

Summary

In this review we report on more than a hundred of natural products of cultured actinomycetes, which exhibit antibacterial, antifungal or antiviral activities. Some of these compounds, besides antimicrobial properties show also cytotoxicity towards different tumor cell lines. The majority of presented agents are novel molecules described between 2011 and April 2018. Only a few of them had a known structure or were synthesized earlier but isolated for the first time from natural sources within these last seven years. Moreover, the majority of described compounds were discovered using a traditional approach of screening for metabolites in the actinobacterial fermentation broth. Most of them inhibited the growth of Gram-positive bacteria, which is in accordance with previous results (Butler et al. 2017). Over 70% of the reported metabolites were produced by various *Streptomyces* sp. strains; the other compounds were produced by the following Actinobacteria: *Amycolatopsis*, *Pseudonocardia, Kibdelosporangium, Actinoalloteichus* (family Pseudonocardiaceae), *Micromonospora* (family Micromonosporaceae), *Actinomadura, Actinoallomurus* (family Thermomonosporaceae), *Actinokineospora* (family Actinosynnemataceae), *Kocuria* (family Micrococcaceae), *Actinomyces* (family Actinomycetaceae), *Kribella* (family Nocardioidaceae) and *Nocardia* (family Nocardiaceae). About 40% of the described metabolites were biosynthesized by species originating from marine ecosystems, about 43% were obtained from terrestrial actinomycetes, while 2% of the metabolites were produced by endophytic strains. Others have unknown origin.

The largest number of novel natural products (53) were produced by bacteria collected from Asia (China, South China Sea, Republic of Korea, Thailand, Japan and India), while bacteria from Australia and Oceania (Australia, Micronesia, Papua New Guinea and Fiji), North America (USA, Canada and Bahamas) and finally from South America (Chile) produced equally 10 new compounds. The other bioactive compounds derived from actinomycetes isolated in Africa and Europe.

Chemical structures of the newly discovered metabolites proved to be quite heterologous. Among them were spirotetronates, ansamycin-type compounds, lactones and lactams, glycosylated lactones – macrolides, quinones, peptides and others. Among all new molecules described here, the best activities displayed

arenimycin C (MICs between 0.0015–0.00985 μg/ml against *B. subtilis* and MRSA), bicyclic chromopeptide lactone RSP 01 (MICs between 0.007–0.06 μg/ml against *S. aureus* and *B. subtilis*) and kocurin (MICs in the range of 0.008–0.512 μg/ml against *S. aureus*, *E. faecium* and *E. faecalis*). Furthermore, quite promising properties were shown for chaxamycin D (MICs in the range of 0.06–0.25 μg/ml against *S. aureus* and *E. coli*) and anthracimycin (MICs in the range of 0.03–4.0 μg/ml against *B. anthracis*, *E. faecalis*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus*). Among the identified antifungal compounds, enduspeptide B, neomaclafungins A-I and kribelloside D exhibited the highest activity towards fungi (MICs 1.72, 1–3 and 3.12 μg/ml, respectively). Ahmpatinin ^{i}Bu, antimycin A1a, and pentapeptide 4862F were found to be the strongest antiviral agents with IC_{50} values of 15.26, < 4 and 1.79 nM, respectively.

All antibacterial, antifungal and antiviral agents presented in this review demonstrate the huge potential of actinomycetes as leader producers of novel bioactive molecules, regarded as promising candidates for clinical evaluation in drug development.

The discovery, development and introduction of a new antibiotic to the pharmaceutical industry are very laborious and complicated processes. The chemical structures of antibiotics, especially those derived from nature are complex. They consist of many stereocenters, rotatable bonds, proton donors and acceptors. Optimization of the molecule structure (its function in biological conditions), scale up of metabolites biosynthesis for industrial purposes as well as long time needed for toxicological and clinical studies makes all this procedures very expensive and time consuming. For these reasons, from an economic point of view, pharmaceutical companies prefer developing drugs for chronic diseases rather than for short-term treatments. One the other hand, rapidly increasing resistance of microorganisms makes contemporary bioactive agents less effective in combating different diseases or useless at all. It is also related with excessive and improper use of antibiotics in medicine, veterinary practice and agriculture. In this context, not to remain helpless in terms of bacterial infections, the discovery of new bioactive compounds is absolutely necessary. Both approaches, traditional way relying on distinct microorganisms isolated from different environments, as well as innovative strategy using the "-omics" technologies together with bioinformatics, are still the valid approaches in searching for novel bioactive agents. Especially, molecules with two modes of action and directed against novel targets are extremely desirable (Ziemska et al. 2013). Another possibilities arise from synthetic or semisynthetic modifications of natural products or searching for novel bioactivities among previously known compounds (such strategies significantly reduce research costs). Finally, a special attention should be placed on the education of the society on the wise and proper use of antibiotics in agriculture as well as in treatment of human and animal diseases.

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