Antibiotics from Extremophilic Micromycetes
A. A. Baranova\textsuperscript{a}, V. A. Alferova\textsuperscript{a,c}, V. A. Korshun\textsuperscript{a,b,c}, and A. P. Tyurin\textsuperscript{a,c,1}

\textsuperscript{a} Gause Institute of New Antibiotics, Moscow, 119021 Russia
\textsuperscript{b} Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, 117997 Russia
\textsuperscript{c} National Research University, Higher School of Economics, Moscow, 101000 Russia

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Abstract—Extremophilic microorganisms, which are capable of functioning normally at extremely high or low temperatures, pressure, and in other environmental conditions, have been in the focus of microbiologists’ attention for several decades due to the biotechnological potential of enzymes inherent in extremophiles. These enzymes (also called extremozymes) are used in the production of food and detergents and other industries. At the same time, the inhabitants of extreme ecoinchès remained almost unexplored for a long time in terms of the chemistry of natural compounds. In recent years, the emergence of new antibiotic-resistant strains of pathogens, which affect humans and animals has become a global problem. The problem is compounded by a strong slowdown in the development of new antibiotics. In search of new active substances and scaffolds for medical chemistry, researchers turn to unexplored natural sources. In recent years, there has been a sharp increase in the number of studies on secondary metabolites produced by extremophiles. From the discovery of penicillin to the present day, micromycetes, along with actinobacteria, are one of the most productive sources of antibiotic compounds for medicine and agriculture. Many authors consider extremophilic micromycetes as a promising source of small molecules with an unusual mechanism of action or significant structural novelty. This review summarizes the latest (for 2018–2019) experimental data on antibiotic compounds, which are produced by extremophilic micromycetes with various types of adaptation. Active metabolites are classified by the type of structure and biosynthetic origin. The data on the biological activity of the isolated metabolites are summarized.

Keywords: antibiotics, extremophiles, micromycetes, extreme habitats, resistance, biotechnology

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INTRODUCTION

The resistance of pathogens to antimicrobial agents and the emergence of new pathogens, such as SARS-CoV-2, is a global threat to modern health. The problem caused by improper use and disposal of antimicrobial agents (for self-treatment, in animal husbandry, etc.) is compounded by a strong decline in the rate of development of new antibiotics because of their low investment returns [1, 2]. The development of new anti-infectious agents and methods to combat the resistant microorganisms are a priority at both the international and national level. This problem is recorded in several political documents, i.e., UN Resolution A/RES/71/3 [3], the WHO Global action plan to combat antimicrobial resistance [4], the Strategy for preventing the spread of antimicrobial resistance in the Russian Federation [5].

According to the analysis of the introduction of low-molecular-weight compounds into medical practice in 1981–2019, natural substances and their semisynthetic derivatives and mimetics are an important source of new therapeutic agents. In some areas (for example, the use of antibacterial and anticancer agents), they are the main source of new medicines [6]. Thus, the search and study of compounds from various natural sources remains one of the key directions in the development of new anti-infectious agents.

However, the traditional (phenotypic) approach to screening and revealing active substances is unable to significantly expand the chemical range of secondary metabolites. One of the ways to solve this problem is to study hard-to-reach and little-explored habitats. Recently, there has been a sharp increase in the number of studies of secondary metabolites from extremophiles. Extremophilic microorganisms are capable of functioning normally at extremely high or low temperatures, pressure, and in other environmental con-
conditions. For several decades, microbiologists have paid attention to these organisms because of the biotechnological potential of their enzymes (so-called extremozymes), which are used in the production of food and detergents and other industries. At the same time, the inhabitants of extreme econiches remained nearly unexplored for a long time in terms of the chemistry of natural compounds. Current trends in biotechnology indicate a high potential of the inhabitants of such econiche as producers of new specialized metabolites with a wide variety of properties [7]. As a rule, extremophiles are classified by a broad-spectrum of adaptation factors. For the producers considered in this paper, these factors are temperature, salinity, pressure, solar radiation, and pH level (Fig. 1). Organisms that can adapt to several factors are called polyextremophiles.

Fungi and fungi-like microorganisms are the most numerous eukaryotic organisms on the planet, and their presence in a wide variety of extreme ecosystems makes them important objects for researchers [8]. Since the discovery of penicillin to the present day, micromycetes, along with actinobacteria, are one of the most productive sources of antibiotic compounds for medicine and agriculture [9]. Many authors consider extremophilic micromycetes as a promising source of small molecules with an unusual mode of action or significant structural novelty. This work generalizes the latest literature data (2018–2019) on secondary metabolites of extremophilic micromycetes with antibiotic activity.

Natural compounds including bioactive ones, which were isolated from extremophilic fungi with various types of adaptation, were considered in a recent review of the literature data up to 2017 [10]. There are also several specialized reviews about the biotechnological potential of fungi and other microorganisms with different types of adaptation, i.e., psychrophiles [11, 12], acidophiles [13], and halophiles [14].

Fig. 1. Common adaptation factors for extremophiles.
Several extreme habitats that combine distinct adaptation factors are emphasized in this review. First of all, these are micromycetes isolated from marine habitats at a depth of less than 200 m (from marine sponges, sediments of coastal zones except for the Arctic/Antarctic shelf, shellfish, corals, algae, ascidia, etc.), which are designated further by the descriptor “marine.” Marine ecosystems are very diverse in terms of temperature fluctuations (from −1.5°C in marine ice to 400°C in deep-sea hydrothermal vents), pressure (1–1000 atm), illumination (from total darkness to euphotic zones), and composition and concentration of nutrients [15]. Fungi often associate with various marine invertebrates, algae, and plants, which contribute to nutrient cycling and organic decomposition [16]. Due to the unique features of polyextremophilic adaptation and a wide range of secondary metabolites, marine fungi are an interesting object in terms of expanding the pharmacophore space [7, 17]. High interest in marine micromycetes is reflected in some reviews of the literature data on their biodiversity and the spectrum of metabolites [18–35]. Secondary metabolites of marine micromycetes are mentioned in reviews concerning the biotechnological potential of the entire biodiversity of marine microorganisms [18, 24, 26, 27, 33, 34]. They are also described in several specialized reviews. In recent years, generalized data on active secondary metabolites of micromycete genera, which are common among marine microorganisms, i.e., Phoma [28], Penicillium [21], and Aspergillus [30] have been summarized. A growing number of publications on new biologically active compounds isolated from marine micromycetes have led to reviews of both their active metabolites in general [19, 20, 23, 29], and specific chemical classes of compounds, i.e., anthraquinones [22] and peptides [32].

The “deep-sea” descriptor refers to producers from marine habitats at a depth of 200 m or more (samples of sediments, water, etc.). The deep-sea environment is one of the most extensive ecosystems on the planet because 95% of the Earth’s oceans are more than 1000 m deep. These habitats are characterized by temperatures below 2°C, complete darkness at depths of more than 250 m, and low oxygen levels. Deep-sea fungi are mainly present in seafloor sediments [15, 16]. Antibiotic secondary metabolites of fungi from deep-sea habitats are mentioned in several recent reviews on the biotechnological potential and biodiversity of deep-sea econiche [26], anoxic water fungi [31], and other deep-sea habitats [35].

The “mangrove” descriptor refers to microorganisms isolated from mangrove soils and roots, branches, leaves, and fruits of mangrove plants. Over the past 15 years, the number of secondary metabolites from fungi of mangrove plants has been steadily increasing, which indicates the great potential of this ecological niche. Researchers have recently generalized the data on some bioactive compounds of mangrove soil fungi, endophytes of mangrove plants [27], and secondary metabolites of mangrove fungi of the Talaromyces genus [25].

The “Arctic/Antarctica” descriptor identified micromycetes isolated from seafloor sediments of coastal areas, soils, and soil-like formations of the Arctic and Antarctic zones.

Substances of different types of antibiotic (antiviral, antibacterial, antifungal, cytotoxic, and antihelminthic) activity are grouped by structure type taking into account their biosynthetic origin (peptides, diketopiperazines and related compounds, polyketides, xanthonoids and related compounds, alkaloids, terpenoids, steroids and related compounds, and compounds of mixed and unidentified origin). Polypeptide compounds, due to their large number, are divided into several groups by the type of chemical structure (quinones, chromones, benzophenones, xanthenes, and other polyketides). The configurations of stereocenters are indicated for compounds, which have been studied in this regard in the original works. Planar structural formulas are given for compounds, the relative configuration of which has been determined by the NMR spectra. The structures and numbers of substances previously described and reidentified are grayed out in tables and figures.

### 1. PEPTIDES, DIKETOPIPERAZINES, AND RELATED COMPOUNDS

Among the biologically active metabolites of extremophilic micromycetes, some peptide compounds of various structural types were identified, i.e., a new family of small cyclic peptides (1–5), a series of diketopiperazines and related compounds (6–21), and two types of linear peptides with pronounced cytotoxicity (22–25, 26). Data on the biological activity of compounds are summarized in Table 1.

Cyclic peptides, so-called acremonpeptides A–D (1–4), isolated from marine micromycetes [36] are natural siderophores. The chelating structural fragment of acremonpeptide molecules is of a hydroxamate nature and formed by the N5-hydroxy-N5-acetyl-L-ornithine residues (Fig. 2). The high affinity of these compounds for trivalent metal ions causes acremonpeptide D to also be released as a complex with aluminum(III) ions (5). The moderate antiviral activity of acremonpeptides is of main interest.

In recent years, extremophilic micromycetes have become the source of some new compounds, which belong to the structural class of diketopiperazines. For example, a marine fungus of the Penicillium genus [37] has been the source for 2,5-diketopiperazine called penicillatide B (6), which belongs to the family of previously known peptides isolated from other marine sources [38, 39]. Recently, a new member of the fusaperazine family, fusaperazine F (9), with moderate cytotoxicity, was isolated from an extremophilic micromycete [40]. Interestingly, its well-known ana-
### Table 1. Data on the origin and biological activity of peptide antibiotics

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC_{50}, IC_{50}, MIC | Ref. |
|------|------------------|--------------------------|-------------------|----------------------|------|
| 1–5  | *Acremonium persicinum* SCSIO 115 | Marine | AV | EC_{50} 8.7–16 μM (Herpes Simplex Virus) | [36] |
| 6    | *Penicillium* sp. | Marine | CT | IC_{50} 23.0–50 μM (HCT-116, HepG2, MCF-7) | [37] |
|      |                  |              |     | IC_{50} 38.9–102 μM (HCT-116, HepG2, MCF-7) |      |
| 7    | *Penicillium* sp. | Deep-sea Marine 4762 m | CT | IC_{50} 94.0–114 μM (HCT-116, HepG2, MCF-7) | [37] |
|      | *Penicillium* sp. SCSIO 06720 | Deep-sea Marine 4762 m | AB | MIC 0.10–0.13 μg/mL (Vibrio anguillarum) | [58] |
| 8    | *Penicillium* crustosum HDN153086 | Antarctica | CT | IC_{50} 12.7 μM (K562) | [40] |
| 9    | *Aspergillus ochraceus* | Marine | CT | IC_{50} 3.0 μM (A2780) | [42] |
| 10   | *Aspergillus sydowii* SP-1 | Antarctica | AB | MIC 0.12–1.0 μg/mL (Staphylococcus aureus, MRSA, S. epidermidis, MRSE) | [44] |
| 11   | *Penicillium chrysogenum* MCCC 3A00292 | Deep-sea 2076 m | CT | IC_{50} 7.81–8.34 μM (BEL-7402, BIU-87K562) | [46] |
| 12   | *Talaromyces purpurogenes* | Marine | CT | IC_{50} 8.29–9.71 μM (A-549, HL-60) | [55] |
| 13   | *Penicillium granulatum* MCCC 3A00475 | Deep-sea 2284 m | CT | IC_{50} 19.5 μM (HepG2) | [47] |
| 14   | *Penicillium chrysogenum* MCCC 3A00292 | Deep-sea 2076 m | CT | IC_{50} 7.81–8.34 μM (BEL-7402, BIU-87K562) | [46] |
| 15   | *Trichoderma velutinum* | At an altitude of about 800 m above sea level, India/ Psychrotolerant | CT | IC_{50} 13–33.6 μM (BEL-7402, A-549, MOLT-4, HL-60) | [49] |
| 16   | *Eurotium* sp. SCSIO F452 | Marine | CT | IC_{50} 12.5–15.0 μM (SF-268, HepG2) | [53] |
| 17   | *Eurotium* sp. SCSIO F452 | Marine | CT | IC_{50} 30.1–37.3 μM (HepG2, SF-268) |      |
| 18   | *Penicillium* sp. TJ403-1 | Marine | CT | IC_{50} 18.41–21.77 μM (A-549, HL-60) | [51] |
| 19   | *Eurotium* sp. SCSIO F452 | Marine | CT | IC_{50} 12.5–15.0 μM (SF-268, HepG2) | [53] |
| 20   | *Eurotium* sp. SCSIO F452 | Marine | CT | IC_{50} 30.1–37.3 μM (HepG2, SF-268) |      |
| 21   | *Trichoderma velutinum* | At an altitude of about 800 m above sea level, India/ Psychrotolerant | CT | IC_{50} 30 μM (A549) | [56] |
| 22   | *Trichoderma velutinum* | At an altitude of about 800 m above sea level, India/ Psychrotolerant | CT | IC_{50} 2–30 μM (HL-60, MDA-MB-231, A549) | [56] |
| 23   | *Trichoderma velutinum* | At an altitude of about 800 m above sea level, India/ Psychrotolerant | CT | IC_{50} 16–17 μM (HL-60, MDA-MB-231, A549) | [56] |
| 24   | *Trichoderma velutinum* | At an altitude of about 800 m above sea level, India/ Psychrotolerant | CT | IC_{50} 4–7 μM (HL-60, MDA-MB-231, A549, LS-180) | [56] |
| 25   | *Emericellopsis alkalina* | Lake Zhaltyr, Kulunda steppe, Russia/ Haloalkalophilic | CT | EC_{50} 2.8 μM (HepG2) | [57] |
| 26   | *Emericellopsis alkalina* | Lake Zhaltyr, Kulunda steppe, Russia/ Haloalkalophilic | CT | MIC 4–32.5 μg/mL (Bacillus cereus ATCC 14893, S. aureus FDA 209 P, Listeria monocytogenes EGDe) | [57] |
|      |                  |              |     | MIC 2–4 μg/mL (Candida sp., Aspergillus sp.) |      |
log, fusasperazin E [41], which differs in the geometry of the double bond, was not active. These compounds are typical representatives of the corresponding structural families.

Diketopiperazine waspergillamide B (10) that contains the unusual paranitrobenzoyl group has been obtained for the first time by culturing the marine Aspergillus ochraceus micromycete [42].

In addition to new compounds, some previously known active metabolites of the diketopiperazine class including cyclo-(D-Pro-D-Phe) (7) [38] and cyclo-(D-Pro-L-Phe) (8) were discovered [39]. Their activity spectrum was refined and selective cytotoxicity was found against certain tumor cell lines. The antibacterial activity was also detected for the well-known diketopiperazine cyclo-(L-Trp-L-Phe) (11) [43], which was isolated from a psychrotolerant micromycete [44]. Cyclopenol (12), a known fungal metabolite [45] isolated from a seafloor fungus of the Penicillium chrysogenum species [46] showed moderate cytotoxic activity.

Representatives of the diketopiperazine class of alkaloid nature deserve a special mention. The chemical studies of secondary metabolites of the deep-sea seafloor Penicillium granulatum MC CC 3A00 475 micromycete [47] led to the discovery of a previously undescribed diketopiperazine, roquefortine J (14) along with three known analogs, i.e., the neurotoxins roquefortine C (15) [48], roquefortine F (16) [49], and meleagrin (17) [50]. Weak cytotoxic activity was shown for well-known diketopiperazine alkaloid brevicompane G (18) [52] (structurally resembling the roquefortine family), which was isolated from the Penicillium sp. TJ403-1 coral fungus [51].

Three pairs of enantiomeric spirocyclic diketopiperazine alkaloids, called variecolortins A–C (19–21, Fig. 3) with an unusual spirocyclic scaffold were isolated from the Eurotium sp. SCSIO F452 marine micromycete [53].

Along with new terpenoids that showed noticeable activity, a diketopiperazine alkaloid 6-methoxyspiropyropostatin B (13) isolated from the culture fluid of the Talaromyces purpurigenus strain [54] previously showed the cytotoxic activity [55].

Peptaibols (nonribosomal linear oligopeptides with the reduced C-terminal fragment that contain α-branched amino acids, i.e., α-aminoizobutanoic acid and/or isovaline) are a common type of peptide secondary metabolites of micromycetes among linear peptides. In recent years, two new representatives of this structural type, i.e., lipovulitols A–D (22–25) [56] and emericellipsin A (26) [57] have been isolated from extremophilic micromycetes. Features of lipovulitols B (23) and D (25) are the presence of nonproteinogenic amino acid D-isovaline and the absence of α-aminoisobutanoic acid in their molecules, previously described among all peptaibols. What is especially interesting is that these compounds show a more pronounced cytotoxic activity than analogs (23) and (25) that contain α-aminoisobutanoic acid (lipovulitols A and C). Another peptaibol isolated from an extremophilic micromycete, emericellipsin A (26), has a noticeable antifungal activity and pronounced cytotoxicity. An interesting feature of this compound is the ability to inhibit the formation of bacterial biofilms in the almost complete absence of antibacterial properties.

2. POLYKETIDES, XANTHONOIDS AND RELATED COMPOUNDS

2.1. Quinones

Polyketides, which can be assigned to quinones, were quite widely represented among the secondary metabolites of extremophlic micromycetes isolated during the period covered in this work. Various substituted anthraquinones (27–29, 30–35, 38–41), dimeric anthraquinones (42–44), a series of perylene quinones (45–50, 37), and tricyclic naphthoquinones (51–53) were isolated. Data on the activity of new and known quinones are summarized in Table 2.

Among the new and active anthraquinones, we should note similar compounds (38) and (39), the producer of which (Alternaria sp.) was identified as a result of the large-scale screening of strains of marine origin [60]. Despite the similarity of chemical structures, compound (38) showed approximately four times less antibacterial activity than compound (39). At the same time, both compounds showed a similar moderate level of antifungal activity. Another new anthraquinone (30) isolated from a deep-sea micromycete [61] showed a noticeable antibacterial activity. According to molecular docking, these compounds can inhibit topoisomerase IV and AmpC β-lactamase. An interesting example of expanding the chemical space of secondary metabolites and applying the OSMAC strategy (One Strain—Many Compounds [62]) is the production of new anthrachinone from isoversicolorin C (41). Cultivation of the Aspergillus nidulans MA143 mangrove fungus using ethanol stress (in the presence of 0.1% ethanol) [63] resulted in the production of compound (41) along with its close analog, versicolorin C pigment (40) [64].

Other isolated anthraquinones were previously described compounds, for some of which the biological activity was detected or clarified. For example, in addition to the new anthraquinone (30), damnacanthal (31) [65], xanthopurpurin (32) [66], 6-hydroxyrubadin (33) [67], and emodin (34) [68–72] were isolated from the Aspergillus versicolor seafloor micromycete [61]. Emodin (34) was also isolated from a variety of other extremophilic micromycetes, i.e., thermo-
Fig. 2. Cyclic peptides and diketopiperazines.
philic Penicillium sp. RO-11 [73], marine fungi of the Aspergillus genus [74, 75], marine Cochliobolus lunatus SCSIO41401 [76], deep-sea Aspergillus sydowii C1-S01-A7 micromycete [77], marine Penicillium sp. ZZ380 [78], and Aspergillus candidus KUFA0062 [79]. In some cases, new cytotoxic [76] and antitubercular [75] types of bioactivity were revealed for emodin (34). Known emodin-related anthraquinones, i.e., questin (34) [70], physcion (35) [80], and chrysophanic acid (chrysophanol) (36) [79, 81, 82] turned out to be significantly less common.

Dimeric anthraquinones (42) and (43) that contain the unusual C–O–C ether bond have been isolated from the culture fluid of the Aspergillus versicolor marine strain [83]. These new biologically active compounds showed selective antibacterial activity against Staphylococcus aureus. The well-known anthraquinones methylaverantin (27) [84], averantin (28) [84], and averytrin (29) [85] were also isolated. Another example of the dimeric anthraquinone is a well-known mycotoxin, viomellein (44) [86]. The source of this compound was micromycetes of the Aspergillus genus [42] isolated from a sea sponge. Viomellein showed high cytotoxicity against the human ovarian carcinoma A2780 and the mouse lymphoma L5178Y cell lines.

Study of the marine strains of the Alternaria genus (Alternaria sp. SCSIO41014 [87], Alternaria sp. [60], and Alternaria alternata L3111' [88]) led to the identification of some representatives of the structural family of perylene quinones. In particular, two new perylene quinones, i.e., altertoxin VII (45) and a new derivative (46) were isolated [87] along with active structural analogs, i.e., altertoxin I (47) [89], stem-
### Table 2. Data on the origin and biological activity of quinones

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC$_{50}$, IC$_{50}$, MIC | Ref. |
|------|-----------------|--------------------------|------------------|--------------------------|------|
| 27   | *Aspergillus versicolor* | Marine | CT, AB, AF | IC$_{50}$ 0.41–1.17 µg/mL (A549, SK-OV-3, SK-MEL-2, XF498, HCT15) [84] <br> MIC 6.25 µg/mL (*Streptococcus pyogenes* 308A) [84] | [83] |
| 28   | *Aspergillus versicolor* | Marine | CT | IC$_{50}$ 3.04–3.88 µg/mL (A549, SK-OV-3, SK-MEL-2, XF498, HCT15) [84] <br> MIC 0.78, 3.13, 3.13, 3.13, 1.56 µg/mL (*S. pyogenes* 308A, *S. pyogenes* 77A, *S. aureus* SG511, *S. aureus* 285, *S. aureus* 503) [84] | [83] |
| 29   | *Aspergillus versicolor* | Marine | CT | MIC 8–16 µg/mL (*Bacillus subtilis*) [85] <br> MIC 16–32 µg/mL (*Fusarium solani*) [85] | [83] |
| 30   | *Aspergillus versicolor* | Deep-sea 2869 m | AB, CT | IC$_{50}$ 3.9, 7.8, 31.3, 62.5, 15.6 µg/mL (MRSA ATCC 43300, MRSA CGMCC 1.12409, *V. vulnificus* MCCC E1758, *V. rotiferianus* MCCC E385, *V. campbellii* MCCC E333) | [61] |
| 31   | *Aspergillus versicolor* | Deep-sea 2869 m | AB, CT | MIC 6.25, 31.3, 62.5, 125 µg/mL (MRSA ATCC 43300, MRSA CGMCC 1.12409, *V. vulnificus* MCCC E1758, *V. rotiferianus* MCCC E385, *V. campbellii* MCCC E333) | [61] |
| 32   | *Aspergillus versicolor* | Deep-sea 2869 m | AB, CT | MIC 62.5, 125, 62.5, 62.5, 125 µg/mL (MRSA ATCC 43300, MRSA CGMCC 1.12409, *V. vulnificus* MCCC E1758, *V. campbellii* MCCC E333, *V. rotiferianus* MCCC E385) | [61] |
| 33   | *Aspergillus ochraceus* | Marine | CT | IC$_{50}$ 1.3 µg/mL (PRL-3) [67] | [67] |
| 34   | *Aspergillus ochraceus* | Marine | CT | IC$_{50}$ 5 µM (A2780) <br> IC$_{50}$ 5.3 µM (L5178Y) | [42] |
| 38   | *Alternaria* sp. (P8) | Marine | AB, AF | MIC 3.91, 3.91, 7.81 µg/mL (*P. syringae pv. lachrymans*, *Aphelenchus avenae*, *Erwinia carotovora*) <br> MIC 31.3 µg/mL (*Pseudopestalotiopsis theae*) | [60] |
| 39   | *Fusarium napiforme* | Mangrove | AB | MIC 6.3, 6.3 µg/mL (*S. aureus* NBRC 13276, *P. aeruginosa* ATCC 15442) <br> MIC 12.5, 6.3 µg/mL (*S. aureus* NBRC 13276, *P. aeruginosa* ATCC 15442) <br> MIC 6.3, 6.3 µg/mL (*S. aureus* NBRC 13276, *P. aeruginosa* ATCC 15442) | [93] |
| 40   | *Aspergillus nidulans* MA143 | Mangrove | AB | MIC 1, 32, 16, 4, 8, 1 µg/mL (*E. coli*, *Micrococcus luteus*, *V. alginolyticus*, *V. anguillarum*, *Edwardsiella ictaluri*, *V. parahaemolyticus*) <br> MIC 32, 16, 64, 1, 4, 32 µg/mL (*E. coli*, *Micrococcus luteus*, *V. alginolyticus*, *Edwardsiella ictaluri*, *V. parahaemolyticus*) | [63] |
| 41   | *Aspergillus versicolor* | Marine | AB | MIC 3.9, 7.8, 31.3, 62.5, 15.6 µg/mL (MRSA ATCC 43300, MRSA CGMCC 1.12409, *V. vulnificus* MCCC E1758, *V. campbellii* MCCC E333) | [61] |
phyperylenol (50) [60], 6-epi-stemphytriol (48) [90], and alterperylenol (49) [91]. The biological properties of known compounds have been clarified. For example, only alterperylenol (49) but not its analogs (47) and (50) showed cytotoxic properties [88]. The cytotoxicity tests [87] showed a noticeable and selective activity of the previously described compound 6-epistemphytriol (48), which makes it promising for further study as an antitumor agent.

Another structural family of secondary metabolites of extreme micromycetes turned out to be the naphthoquinone derivatives. The new derivatives, 6-hydroxy-astropaquinone B (51) and astropaquinone D (52), and well-known 3-O-methyl-9-O-methylfusarubin (53) [92] were isolated from the cul-
ture fluid of the mangrove *Fusarium napiforme* endophyte [93]. The isolated compounds showed a noticeable phytotoxic effect in addition to moderate antibacterial activity.

### 2.2. Chromones, Benzophenones, and Xanthones

Various aromatic compounds were found among the secondary metabolites of extremophilic micromycetes, i.e., xanthones (54–68) and dihydroxanthones (69–71), chromones and dihydrochromones (72–84), dimeric chromones (85–89), benzoquinones (90–97), and related compounds (98–110). Data on the origin and activity of aromatic polyamides are summarized in Table 3.

Xanthones are common antibiotic secondary metabolites of micromycetes. Several compounds of this class have been isolated from various extremophilic sources (Fig. 6).

Three new antibacterial prenylxanthones, aspergixanthones I-K (58–60), and four known analogs, i.e., aspergixanthone A (57) [97], 15-acetyl thajixanthone hydrate (61), thajixanthone hydrate (62) [98], and 16-chlorothajixanthone (63) [98, 99] were isolated from the marine fungus of the *Aspergillus* genus [96]. New aspergixanthone I (58) showed the greatest activity against the studied bacteria. Another new secondary metabolite of this class was 3-hydroxy pinselin (64) [100], which did not show antibiotic
activity. Some extremophilic micromycetes have become sources of known xanthones. 3,8-Dihydroxy-4-(2,3-dihydroxy-1-hydroxymethylpropyl)-1-methoxyxanthone (55) [101] was isolated from sea-floor fungus Penicillium chrysogenum MCCC 3A00292 [46]. The primary study of metabolites of a fungus of the Pseudopestalotiopsis genus [102] led to the isolation of the previously described dehydrate chloroisosulochrin (65) [103]. The well-known xanthone, cytotoxic stergmatocystin (54) [84], was obtained from the Aspergillus versicolor marine strain [83].

A deep-sea micromycete, Aspergillus sydowii C1S01-A7 [77], is a producer of two new compounds, 2-hydroxy-6-formyl-vertixanthone (66) and 12-O-acetyl-sydovinin A (67), and 22 known compounds including those with antibiotic activity, i.e., xanthones (sydovinin B (68) [104] and yikathin C (56) [105]) and their dihydro derivatives (aspergillusone A (69) [106] and AGI-B4 (70) [107]). A similar spectrum of metabolites was found in the marine fungus of the Aspergillus genus [100], i.e., 12-O-acetyl-AGI-B4 (71) [77] and aspergillusone A (69) [106]. AGI-B4 (70) showed noticeable cytotoxicity and selectivity compared to its structural (e.g., O-acetylated) analogs. Thus, the dihydroxanthone core and the free hydroxyl group at the C-12 position are mandatory structural motifs for ensuring the cytotoxic activity of xanthones of this type (Fig. 6).

In addition to xanthones, chromone core-containing metabolites including previously undescribed compounds were isolated. New coniochaetone M (73) [108] along with the well-known analog, coniochaetone B (72) [78], which showed a low activity [109, 110] were isolated from a marine-derived fungus. Sea-floor micromycete [59] was the source of one new and several known chromones, i.e., coniochaetone L (74), oxalicumone A (80) [111], β-diversonolic ester (81), and penicillocitrin A (82) [112].

Among three new polyketides, (2S)-2,3-dihydro-5,6-dihydroxy-2-methyl-4H-1-benzopyran-4-one (75) with antibacterial properties was isolated from the Colletotrichum gloeosporioides mangrove endophyte [113]. Another new chromone, pseudopestalon (98), was obtained in the initial study of the abovementioned fungus of the Pseudopestalotiopsis genus [102]. The marine fungus of the Penicillium genus was a source of new chromones, i.e., pynochromone (76), spirofu- ranochromone (77), and 7-hydroxy-6-methoxy-4-oxo-3-[(1E)-3-oxobut-1-en-1-yl]-4H-chromene-5-carboxylic acid (83) [114], along with known anhydrofulvic acid (84) [115].

We should also note the mangrove endophyte Cladosporium sp. [116], the source of a new glycosylated chromone (78) and the previously known 7-O-α-D-ribofuranosyl-5-hydroxy-2-propyl-chromone (79) [117], which showed cytotoxic properties.

Another structural family of aromatic polyketides isolated from extremophilic fungi is dimeric chro-
Table 3. Data on the activity and origin of chromons, benzophenones, and xanthones

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC₅₀, IC₅₀, MIC | Ref. |
|------|-----------------|--------------------------|-------------------|------------------|-----|
| 54   | Aspergillus versicolor | Marine CT | IC₅₀ 11.25–17.36 µg/mL (A-549, SK-OV-3, SK-MEL-2, XF498) IC₅₀ 1.86–4.61 µg/mL (A-549, SK-OV-3, SK-MEL-2, XF498, HCT15) | [84] |
| 69   | Aspergillus versicolor | Marine AT | MIC 20 µg/mL (BCG) MIC 40 µg/mL (BCG) | [100] |
| 71   | Aspergillus versicolor MF160003 | Marine | MIC 20 µg/mL (BCG) | [100] |
| 85   | Penicillium oxalicum | Marine CT AB AF | IC₅₀ 0.484–26.6 µM (BGC-823, SGC-7901, HGC-27, EC9706, KYSE450, CNE1, CNE2, SW620, SW480, LOVO, HuH-7, PLC/PRF/5, SKHEP, A549, SKMES-1, SPC-A1, 95D, Jeko-1, Raji, U937, A375, HFF, H22) MIC 3.1 µg/mL (Sarcina lutea ATCC 9341) [119] MIC 12.5 µg/mL (Bacillus subtilis CP1 219) [119] MIC 6.3 µg/mL (Corynebacterium diphtheria P.W.8) [119] MIC 12.5 µg/mL (Micrococcus flavus ATCC 10240) [119] MIC 1.6 µg/mL (Trichophyton metagrophytes IAM 8051) [119] | [118] |
| 88   | Penicillium oxalicum Cladosporium sp. JS1-2 | Marine Mangrove | IC₅₀ 0.833–24.1 µM (BGC-823, SGC-7901, HGC-27, EC9706, KYSE450, CNE1, CNE2, SW620, SW480, LOVO, HuH-7, PLC/PRF/5, SKHEP, A549, SKMES-1, SPC-A1, 95D, Jeko-1, Raji, U937, A375, HFF, H22) | [118] |
| 87   | Penicillium erubescent KUFA0220 | Marine AB AF CT | MIC 64.0, 64.0 µg/mL (Enterococcus faecalis ATCC 29212, MRSA) MIC 12.5, 25.0, 12.5 µg/mL (S. aureus ATCC 27154, E. coli ATCC 25922, Sarcina ventriculi ATCC 29068, P. aeruginosa ATCC 25668) [122] MIC 6.25, 6.25, 12.5 µg/mL (C. albicans ATCC 10231, A. niger ATCC 13496, F. oxysporum f. sp. cubense) [122] IC₅₀ 0.63, 1.05 µg/mL (KB, KBv200) | [118] |
| 84   | Penicillium oxalicum | Marine | MIC 64 µg/mL (Enterococcus faecalis ATCC 29212) | [114] |
| 102  | Penicillium oxalicum | Marine | MIC 64 µg/mL (Enterococcus faecalis ATCC 29212) LD₉₉ 0.1 µg/mL (NS-1) [129] | [114] |
| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC$_{50}$, IC$_{50}$, MIC | Ref. |
|------|------------------|------------------------|------------------|--------------------------|-----|
| 90   | Aspergillus sp. Penicillium citrinum HL-5126 | Marine Mangrove | AB CT AF | MIC 7.53, 15.06, 30.12 μM (P. aeruginosa, V. anguillarum, Aeromonas salmonicida) IC$_{50}$ 63.4, 83.1 μM (HL-60, BEL-7402) | [74] [124] |
|      |                  |                        |                  |                          |     |
| 91   | Pseudopestalotiopsis sp. PSU-AMF45 | Marine | AF | MIC 200 μg/mL (Cryptococcus neoformans ATCC 90112) MIC 200 μg/mL (Cryptococcus neoformans ATCC 90112) | [102] |
| 57   | Aspergillus sp. ZA-01 | Marine | AB CT | MIC 25 μM (V. parahemolyticus, V. anguillarum, V. alginolyticus) IC$_{50}$ 1.8 μM (A-549) | [97] |
| 58   |                  |                        |                  |                          |     |
| 59   |                  |                        |                  |                          |     |
| 60   |                  |                        |                  |                          |     |
| 61   |                  |                        |                  |                          |     |
| 62   |                  |                        |                  |                          |     |
| 63   |                  |                        |                  |                          |     |
| 72   | Penicillium sp. ZZ380 Penicillium citrinum SCSIO 41017 | Marine | AF | Qualitative AF activity (C. albicans, S. fimicola, A. furfuraceus) | [109] |
| 73   | Penicillium citrinum SCSIO 41017 | Marine | CT | IC$_{50}$ 16.0–46.4 μM (SF-268, MCF-7, HepG-2, A549) | [108] |
| 75   | Colletotrichum gloeosporioides | Mangrove | AB | MIC 12.5, 25.0, 25.0 μg/mL (B. cereus, B. subtilis, S. aureus) | [113] |
| 92   | Penicillium citrinum HL-5126 | Mangrove | AB CT | MIC 20.0 μg/mL (S. aureus) IC$_{50}$ 15.7 μg/mL (A549) | [124] |
| 97   | Nigrospora sphaerica | Mangrove | CT AB AF | IC$_{50}$ 9.62 μM (HCT 116) MIC 4.0, 4.0, 4.0, 2.0, 2.0 μg/mL (B. subtilis UBC 344, B. subtilis TISTR 088, S. aureus ATCC 43300, B. cereus TISTR 688, MRSA ATCC 33591, E. coli UBC 8161, P. aeruginosa ATCC 27 853) MIC 2.0, 4.0, 8.0 μg/mL (C. albicans ATCC 90028, C. gloeosporioides UBC 3110, A. niger UBC 9214) | [128] |
**Table 3.** (Contd.)

| Cpd. | Producer/species          | Extremophile type/origin                  | Activity/ toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|---------------------------|------------------------------------------|--------------------|-------------------------------------|------|
| 94   | *Aspergillus* sp. YQ-13   | Hydrothermal vent sediments, Kueishantao, Taiwan/Thermophile | AB                 | MIC 860.8, 40.93 μg/mL (*P. aeruginosa, B. subtilis*)<br>MIC 394.1, 191.67, 58.21, 58.21 μg/mL (*P. aeruginosa, E. coli, B. subtilis, MRSA*) | [126] |
| 95   |                           |                                          |                    |  | |
| 66   | *Aspergillus sydowii* C1-S01-A7 | Deep-sea 4950 m                      | AB, CT             | MIC 16.3, 16.1 μg/mL (MRSA ATCC 43300, MRSA CGMCC 1.12409)<br>IC<sub>50</sub> 32.7 μM (HepG2)<br>MIC 32.6, 31.8 μg/mL (MRSA ATCC 43300, MRSA CGMCC 1.12409)<br>IC<sub>50</sub> 25.2–42.3 μM (A549, HepG2, HeLa)<br>MIC 32.6 μg/mL (*V. rotiferianus*)<br>IC<sub>50</sub> 1.5 μM (L5178Y) [107] | [77] |
| 67   |                           |                                          |                    |  | |
| 68   |                           |                                          |                    |  | |
| 70   |                           |                                          |                    |  | |
| 56   |                           |                                          |                    |  | |
| 99   | *Penicillium chrysogenum* MCCC 3A00292 | Deep-sea 2076 m                      | CT                 | IC<sub>50</sub> 10.21 μM (BIU-87)<br>IC<sub>50</sub> 15.94 μM (BEL-7402) | [46] |
| 55   |                           |                                          |                    |  | |
| 89   | *Cochliobolus lunatus* SCSIO41401 | Marine                               | CT, AB             | IC<sub>50</sub> 41.3–47.9 μM (SF-268, MCF-7, HepG-2, A549, 786-O)<br>MIC 50.0, 25.0, 13.0 μg/mL (*S. aureus, E. rhizophthiae, P. multocida*)<br>IC<sub>50</sub> 31.36 μg/mL (L6) [123]<br>IC<sub>50</sub> 8.07 μg/mL (*P. falciparum* NF54) [123]<br>MIC 125.0, 62.5, 62.5, 62.5, 62.5, 250.0, 62.5, 125.0, 125.0, 125.0 μg/mL (*B. cereus, L. monocytogene, E. coli ATCC 8739, E. coli ATCC 8739, K. pneumoniae ATCC 11296, K. pneumoniae ATCC 11296, P. stuartii ATCC 29916, P. stuartii ATCC 29916, P. aeruginosa PA01, P. aeruginosa PA01*) [123]<br>IC<sub>50</sub> 0.633 μg/mL (*L. donovani*) [123]<br>IC<sub>50</sub> 28.8 μg/mL (*T. b. rhodesiense*) [123]<br>IC<sub>50</sub> 14.41 μg/mL (*T. cruzi*) [123] | [121] |
| 88   |                           |                                          |                    |  | |
| 98   |                           |                                          |                    |  | |
| 109  | *Penicillium pinophilum* SCAU037 | Mangrove                           | CT                 | IC<sub>50</sub> 0.2, 1.6 μM (HL-60, CCRF-CEM) [131]<br>IC<sub>50</sub> 20.0, 15.1 μg/mL (KB, KBv200) [132]<br>IC<sub>50</sub> 60 μg/mL (HEp-2) [134]<br>Qualitative AF activity (*R. solani* RT23, *R. solani* RT20, *F. solani* (Mart.) Appel et Wollenw., *Cylindrocladium scoparium* Morgan, *Alternaria alternata* (Fries) Keissl.) [133] | [130] |
| 108  |                           |                                          |                    |  | |
| 107  |                           |                                          |                    |  | |
| 97   |                           |                                          |                    |  | |
| 96   |                           |                                          |                    |  | |
| 79   | *Cladosporium* sp. OUCMDZ-302 | Mangrove                           | CT                 | IC<sub>50</sub> 40 μM (HL-60, SMMC-7721, A-549, MCF-7, SW480) [117] | [116] |
mones. Among the new compounds of this class, we can note the previously undescribed pyranochromone dimer (86) isolated from a marine fungus of the *Penicillium* genus [114], which did not show antibiotic properties.

As for the previously described dimeric chromones, the data on biological activity has been expanded for some of them. For example, significant cytotoxic activity was detected for the 4,4′-bound secalonic acid D isomer (85) isolated from marine micromycetes of the *Penicillium* genus [118], which was known primarily for its bactericidal properties [119]. The stereoisomer of secalonic acid D (88) [120], which also showed the cytotoxic activity, was found in a mangrove fungus of the *Cladosporium* genus [121]. Another related compound, secalonic acid A (87) [122], was isolated from a marine fungus of the *Penicillium* genus [114]. The previously described xanthone purpureone (89) [76, 123] showed cytotoxic activity [76].

Along with the xanthones and quinones described above, the study of secondary metabolites of micromycetes revealed structurally similar compounds, primarily benzophenones. For example, a micromycete of mangrove origin belonging to the *Penicillium* genus [124] became the source of two new benzophenones, i.e., the antibacterial penibenzophenone A (92) and the cytotoxic penibenzophenone B (93), along with the well-known benzophenone sulochrine (90) [70, 125].

Another example is the thermophilic micromycete *Aspergillus* sp. YQ-13 [126] isolated from hydrothermal vents. It has been studied in terms of the spectrum of secondary metabolites. A new natural compound, methyl ester of 3-hydroxy-2-(2-hydroxy-6-methoxy-4-methylbenzoyl)-5-methoxy benzoic acid (94), showed low antibacterial activity. At the same time, a

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**Fig. 6. Xanthones and dihydroxanthones.**
A well-known metabolite, 1,2-SECO-trypacidin (95), showed a noticeable activity [127].

A new antibiotic, nigronaphthaphenyl (97), isolated from a mangrove endophyte [128], showed a wide range of biological activity including anti-inflammatory properties and the ability to inhibit alpha-glucosidase, which made it promising for further study.

The study of some extremophilic micromycetes led to the isolation of known benzophenones. Thus, the screening of marine micromycetes for antibacterial activity revealed the producer strain of six known metabolites [74] including benzophenone sulochrine (90) [70, 125]. Another described benzophenone, chloroisosulochrin (91) [103], was isolated in the...
study of secondary metabolites of a fungus of the *Pseu-
dopestalotiopsis* genus [102].

In addition to discovery new benzophenones, the study of secondary metabolites of extremophilic micromycetes has led to the isolation of several structu-
turally similar compounds. A new chromene, 1-hydroxy-12-methoxyctromycin (103), was isolated from a marine fungus of the *Penicillium* genus [114], along with a known analog, citromycin (102) [129].

Seafloor fungus *Penicillium chrysogenum* MCCC 3A00292 [46] produces a series of related compounds, i.e., previously undescribed peniciversioles A–C (99–101), which were studied as cytotoxic agents. Interest-
ingly, peniciversiole A (99) showed cytotoxic proper-
ties in contrast to peniciversioles B and C (100, 101).

Five new funicon derivatives named pinophilones A–E (104–108) were isolated from soil mangrove producer *Penicillium pinophilum* SCAU037 [130] along with eighteen biosynthetically related known compounds. Some of these compounds, i.e., penisim-
pilicissin (109) [131], methoxyvermistatin (110) [132], and 3-O-methylfunicon (96) [133, 134] showed high antibiotic activity.

### 2.3. Other Polyketides

In addition to the compounds described above, extremophilic micromycetes became the source of some other polyketides during the studied period. Sev-
eral structural families can be distinguished among isolated compounds. Isocoumarins (111–120), dihydroisocoumarins (121–127), and other lactones (128–148) can be distinguished among cyclic esters. Most of the new and known metabolites can be assigned to phenols and their derivatives (149–176) and diphenyl esters (177–189). Many isolated metab-
lites were aromatic compounds, i.e., phenalenones (190–198), grisane metabolites (199–201), and azaphilones (202–222). Linear polyketides with vari-
sion side chains (223–245) and other polyketides (246–257) were also obtained.

Isocoumarins and their derivatives are common bio-
active metabolites of micromycetes [135]. New iso-
coumarins were also isolated from mangrove micro-
mycete *Ascomycota* sp. [136], endophyte *Pluechasia indica*. This strain was the source of three new isocou-
marins, i.e., dichlorodiaportin (116), desmethyldi-
chlorodiaportin (117), and desmethylchlorodiaport-
tinol (114), along with several other well-known ana-
logs, i.e., dichlorodiaportinol (115) [137], desmethyldichlorodiaportinol (119) [138], and dichlo-
rodiprotinol (120) [139, 140]. Other isocoumarins with antibiotic activity turned out to have been be previ-
ously described. For example, the chemical study of mangrove endophyte *Phyllosticta capitalensis* [141] afforded the known isocoumarin derivative with anti-
biotic activity, 6,8-dihydroxy-5-methoxy-3-methyl-
1H-isochromen-1-one (118) [142]. When studying the *Alternaria* sp. SCSIO41014 strain [87], researchers obtained the isocoumarin derivatives, i.e., alternariol (111) [143], 5-O-methyl ester of alternariol (112) [143], and altenuisol (113) [144].

Several new compounds isolated from extremo-
philic micromycetes belong to dihydroisocoumarins. A new isocoumarin derivative, pestalotiopisorin B (121) with moderate antibacterial activity, was isolated from the *Pestalotiopsis* strain of mangrove origin [145]. Another new dihydroisocoumarin, nordihydroaltenu-
ene A (123), and known bioactive analogs, i.e., (–)-3-
O-acetylaltenuene (126) [143, 146], altenuin (155) [147], and dihydroaltenuene A (127) [148], were iso-
lated in the study of the *Alternaria* sp. SCSIO41014 strain [87]. Several known dihydrocoumarins were obtained from other sources, (3R,4S)-6,8-Dihydroxy-
3,4,7-trimethylisocoumarin (122) [149] was isolated from a deep-sea micromycete [59]; cladosporin (124) and 5′-hydroxyasperentin (125) [150] were isolated from a marine fungus [151].

In addition to isocoumarin derivatives, a series of lactones of various natures were isolated when studying extremophilic micromycetes (Fig. 10). Of the new lactones, four new unusual sulfur-containing compounds should be noted, which were isolated from the mangrove *Cladosporium* micromycete [152]. The lactones were called thiocladospolids A–D (128, 130–132). Similar known antibiotic pandangolide 3 was also isolated (129) [152, 153]. Comparison of the NMR data of new macrorides and known pandan-
golide 3 (129) allowed to revise its structure and clarify the attachment site of the side sulfide chain. Another new 10-membered lactone decaerestrin Q (135), an analog of decaestrin B (136) [154], was isolated from a marine fungus of the *Pseudopestalotiopsis* genus [102]. Significant cytotoxicity was shown for another structurally original depsidone, curdepsidone A (139), isolated from the strain of the *Curvularia* genus of the marine origin [155]. A new depsidone deriva-
tive, botryorhodine 1 (141), and eight known com-
ounds were isolated from the soil mangrove micro-
mycete *Lasidioploida theobromae* M4.2-2 [156]. Sev-
eral other antibiotics were also found, i.e., antifungal and cytotoxic botryorhodinases A, B, and D (142–144) [157] and compounds (140) and (134) [156, 158]. Mangrove endophyte *Colletotrichum gloeosporioides* [113] became the source of new lactone (148), which showed antimicrobial activity.

The approach to activation of silent biosynthetic clusters of micromycetes deserves a special mention: biosynthesis of a new cytotoxic polyketide, purpuro-
genic acid (145), was observed in a mutant strain of *Penicillium purpurogenum* G59 obtained by exposure of diethyl sulfate [159].

In addition to the new compounds, some previ-
ously described biologically active lactones were ob-
tained. A well-known aromatic lactone, 8-dime-
thoxy-10-methoxy-ventiquinone C (137), was iso-
lated from a fungus of marine origin [108] [77, 160]. 8-
Dimethoxy-10-methoxyventriquinone C (137) was
also isolated from seafloor micromycete Aspergillus
sydowii C1-S01-A7 [77]. Several discovered lactones
have been previously described, including alterlactone
(147) [143] isolated in the study of the Alternaria sp.
SCSIO41014 strain [87], the antibiotic lactone peni-
cillide (138) [161] isolated from mangrove soil pro-
ducer Penicillium pinophilum SCAU037 [130], nod-
ulisporone A (146) [162] found in the study of deep
micromycete [59], and asperdemin (133) [163] iso-
lated from deep-sea fungus Penicillium chrysogenum
MCCC 3A00292 [46].

A significant proportion of antibiotic compounds
isolated from extremophilic micromycetes are phenols
and their derivatives, many of which have been
described for the first time (Fig. 11). The study of sec-
ondary metabolites of the Zopfiella marina strain [164]
of marine origin allowed to identify several previously undescribed compounds, i.e., two derivatives of salicylic aldehyde (161, 165), five dihydroisobenzofurans (171–175), and 5-chloro-3-deoxyizoochracinic acid (176). Of these, only the derivative (161) showed the antibacterial, including antituberculosis, activity.

The spectrum of secondary metabolites of the mangrove fungus of the Dothiorella genus [165] includes some phenols with an antibiotic activity, which primarily belong to the structural family of dothiorelones. New dothiorelones K–M (152–154) and known cytosporon derivatives, i.e., dothiorelones A (149) [166], B (150), and I (151) [167] and cytosporon A (160) were isolated [168].

New polyketides, sarcopodinols A and B (167, 168) were isolated from the Sarcopodium fungus [169], which was found as a result of physical and chemical screening of 60 strains of deep-sea micromycetes. Interestingly, the compound (168) showed a broader spectrum of cytotoxic action as compared to compound (167), which indicates the importance of the 5’-OH group for the activity in some cell lines.

Bioactivity-based separation of a culture liquid extract of a thermophilic micromycete of the Penicillium genus [73], isolated from a hot spring in Saudi Arabia, resulted in a new phenol (162). 5-(2-Hydroxypropyl)-2,6-dimethylresorcinol (159), which did not exhibit biological activity, was isolated from the seafloor micromycete [59].

Mangrove endophytes have also proved to be a valuable source of biologically active compounds of this type. A new polyketide (166) was isolated from the Colletotrichum gloeosporioides strain [113], in addition to the abovementioned benzophenone (75) and lactone (148). The mangrove endophyte Cladosporium sp. [116] became the source of a series of new phenols (163, 164). A new prenylated benzaldehyde dioxoauriglaucin (156) was isolated from mangrove fungus Aspergillus sp. AV-2 [170], along with its several known analogs, of which flavoglaucin (157) [171], previously

**Fig. 9.** Isocoumarins and dihydroisocoumarins.
known primarily as an antioxidant, showed a pronounced cytotoxic activity.

Previously described phenols were also revealed. When studying mangrove fungi of the *Cladosporium* genus [121], known polyketides were obtained, i.e., cladosporol E (170) [172], which previously did not show noticeable activity, and its more active analog cladosporol C (169) [173]. Chemical study of the
Fig. 11. Phenols.
mangrove endophyte *Phyllosticta capitalensis* [141] yielded the known polyketide, 3,4-dihydroxybenzoic acid (158), with antibiotic activity [174, 175].

In addition to phenols, related diphenyl ethers including several new compounds were isolated (Fig. 12). Cultivation of *Penicillium* sp., a marine sponge symbiont, allowed to isolate a new chlorinated diphenyl ether (179) [176]. The rest of diphenyl ethers were the known compounds. The study of the secondary metabolites of a fungus of the *Pseudopestalotiopsis* genus [102] afforded the known polyketides, i.e., pesteic acid (177) and pestalotether A (178) [177]. The seafloor fungus *Penicillium chrysogenum* MCCC 3A00292 [46] produces a series of antibiotic polyketides of different natures, i.e., 3,3′-dihydroxy-5,5′-dimethyldiphenyl ether (183) [178], aspermutarubrol (184) also known as violaceol I [179, 180], violaceol II (180) [180, 181], and aspermutarubrol (184) R$_1$ = R$_2$ = OH [184]. Screening of marine micromycetes for the antibacterial activity gave the producer strain of six known metabolites [74] including polyketide, methyl asterrate (182) [182, 183]. Corresponding asterric acid (181) [184] was isolated from the culture liquid of micromycete of the *Penicillium* genus of mangrove origin [124]. A group of structurally related polyketides, consisting of a new (185) and three known polyketides, i.e., asterric acid (181) [184], methyl asterrate (182) [182, 183], and methyl-3-chloroasterric acid (186) [185]) was isolated from a mangrove fungus of the *Pleosporales* genus [186]. Only the known compound (186) among them exhibited significant activity.

New antibacterial diphenyl ether, diorcinol K (189) was isolated from marine micromycete *Aspergillus* sp. CUGB-F046 [187] along with the known analogs, diorcinols D and I (187, 188) [188, 189].

**Fig. 12.** Diphenyl ethers.
Phenalenons are a fairly rare class of natural compounds [190]. When studying the marine fungus of the *Penicillium* genus [94], six undescribed phenalenon derivatives were isolated, i.e., peniciphenalenins A–F (190–195) with no antibiotic activity (Fig. 13). At the same time, the known structural analogs, i.e., (+)-sclerodin (197) [191], (+)-scleroderolide (198) [192], and (+)-sclerodione (196) [193] exhibited a moderate cytotoxicity.

Spirocyclic metabolites with the grisan skeleton were found as secondary metabolites of extremophilic micromycetes (Fig. 14). The abovementioned producer of some benzophenones and anthraquinones [74] of marine origin along with the mentioned compounds synthesizes (–)-bis-dechlorogeodin (201) [194]. This previously described metabolite showed the antibacterial activity and moderate cytotoxicity. Cultivation of a marine sponge symbiont of the *Penicillium* genus [176] led to the isolation of the well-known spirocyclic antifungal antibiotic griseofulvin (200) [131, 195].

Trypacidin (199), which was well-known for high cytotoxicity [196], was isolated from the strain of the *Aspergillus* genus [75].

Azaphilons are the common class of aromatic secondary fungal metabolites with a wide spectrum of biological activity [197]. Some representatives of this family including the halogenated analogs were isolated from extremophilic micromycetes (Fig. 14). According to the ASMAC strategy, the cultivation of this fungus was carried out in the presence of 5% NaBr, which allowed to obtain another two brominated azaphilons, i.e., bromophilons A and B (210, 211). Stereomers (210) and (211) contain a unique for azaphilons structural motif, the aromatic side chain. Interestingly, bromophilon B (211) appeared to be noticeably more toxic than its isomer bromophilon A (210).

At the same time, several structurally close azaphilons were isolated from another fungus also of the marine origin of the *Penicillium* genus [198]. Newly isolated compounds, penicilazaphilons D and E (205, 206), did not exhibit a significant biological activity. Previously described (+)-sclerotiorin (207) [199], on the contrary, demonstrated a noticeable antiviral activity.

Another source of halogenated azaphilons was mangrove micromicete *Diaporthe* sp. SCSIO 41011 [200]. Six new oxidized chloroazaphilon derivatives, isochromophilons A–F (212–215, 202, 203), were isolated from the culture liquid of this strain, and isochromophilon D (215) showed the highest cytotoxicity. In addition to new compounds, several known analogs with antibiotic activity were isolated, i.e., epi-isochromophilon II (204) [200, 201], epi-isochromophilon III (216) [201], and isochromophilon III (217) [201]. Known azaphilons, pinophilin B (209) [202] and Sch 725680 (208) [202, 203], were isolated from mangrove producer *Penicillium pinophilum* SCAU037 [130].

Along with new compounds, known spirocyclic azaphilon mycotoxin H1 (218) [78, 204] was obtained.
when studying a mangrove fungus of the *Cladosporium* genus [121]. Similar compounds, new polyketide xerucitrinin A (219), xerucitrin acid A (220) [205], and penicitrinins A (221) and F (222) [206], were obtained from a fungus of marine origin [108].

Many polyketides that contained linear structure or long weakly branched chains including polyunsaturated ones (Fig. 16) were discovered among secondary metabolites of extremophilic micromycetes.

The systematic screening of marine microorganisms for the antibacterial activity revealed the strain of the *Aspergillus* genus [75], which produced sphingofungin I (239) and known polyketides including similar in structure sphingofungin D (240) [207]. Two new glycosilated alkylresorcin, resorcinosides A and B (244, 245), were isolated from the *Penicillium janthinellum* fungus [208]. Compounds 244 and 245 are the first representatives of the structural family of resorcinols, which are glycosylated at the alkyl, and not the aromatic, part of the molecule. Substituted resorcinol B (245) showed pronounced cytotoxic activity against several cell lines, whereas resorcinol A (244) was almost inactive (GI_{50} > 50 μM). New polyketidic metabolites, porosulfenolons A–D (234, 235, 237a,b) were obtained from the culture liquid of the *Aspergillus porosus* strain of marine origin [209]. Two latter compounds are in a dynamic equilibrium under ambient conditions (linear 237a and cyclic 237b forms). Psychrophilic micro-mycete isolated from *Penicillium crustosum* HDN153086 [40] in the Antarctic region appeared to produce a new polypeptide compound of unusual structure (238), which exhibited no biological activity. Another known linear polyketide, radicolinic acid (236) [210] was isolated from a seafloor fungus *Penicillium chrysogenum* MCC 3A00292 [46].

Mangrove micromycete of the *Fusarium solani* genus H918 [211], along with antibiotic I233B (241) [212], produces a series of previously undescribed polyketides, fusarisolins A–E (242, 243, 229–231). Despite the absence of a pronounced antibiotic activity, the molecules of these compounds contain the rare structural motifs, such as β- and γ-lactone cycles in fusarisolins A (242) and B (243), respectively. Another mangrove endophyte *Cladosporium* sp. [116] became a source of linear polyketides (232, 233).

The combined cultivation of two micromycetes of extremophilic origin resulted in an unusual range of bioactive secondary metabolites. Four new alkylaromatic polyketides, penixylarines A–D (223–226), and two known [214] biosynthetic analogs, 5-(12-hydroxyheptadecyl)resorcinol (227) and 5-(12-sulfoheptadecyl)resorcinol (228), were obtained from the combined culture of a deep-sea Antarctic fungus of *Penicillium crustosum* PRB-2 and a mangrove fungus *Xylaria* sp. HDN13-249 [213]. It should be noted that compounds (223) and (224) are biosynthetically only when two producers are cocultured, while metabolites (225–228) can be produced by the *Xylaria* sp. Monoculture, although in significantly lower amounts.

The structures of other polyketide secondary metabolites are shown in Fig. 17. Some of these compounds have been described for the first time. In addition to new halogenated azaphilones, the cultivation of a marine sponge symbiont of the *Penicillium* genus [176] led to the isolation of the known mycotoxin, penicillic acid (249) [215–218]. A series of penicillic acid derivatives have also been isolated from marine micromycetes [42]. Cocultivation of this micromycete with *Bacillus subtilis* according to the OSMAC strategy resulted in obtaining two new derivatives of penicillic acid, i.e., ochraspergillic acids A and B (253, 254), in addition to penicillic acid itself (249).

A new macrolide, curvulide A (257), with moderate antibacterial activity and cytotoxicity was isolated from a marine micromycete of the *Curvularia* sp. genus [219]. A new hybrid polyketide, cladodionen (252) was isolated from another fungus *Cladosporium* sp. OUCMDZ-1635 of marine origin [220]. Compound (252) is the equilibrium mixture of two geometric isomers (252a, 252b). Cladodionen (252) exhibited pronounced cytotoxic activity.

A thermophilic micromycete of the *Penicillium* genus [73] was isolated from hot springs in Saudi Arabia using bioactivity-based separation of a culture liquid extract, from which a new polyketide was obtained (246).

When studying a mangrove fungus of the *Cladosporium* genus [121], new active 1,1'-dioxin-2,2'-dipropionic acid (247) was obtained.

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**Fig. 14.** Grisane-type compounds.
Several well-known antibiotics of various structures were also isolated. In particular, trichodimerol \((256)\) was isolated from the seafloor micromycete \([59]\) \([221]\). A marine psychrotrophic fungus \textit{Aspergillus protuberus} \([222]\), which was selected by screening of some cultivated polyextremofilic microorganisms of the Barents Sea for the antibacterial activity, was the source of the known antibacterial polyketide of the sorbicilllonoids group, bisvertinolone \((255)\) \([223]\).

Seafloor fungus \textit{Penicillium chrysogenum} MCCC 3A00292 \([46]\) produces the known metabolites, decumbenos A and B \((250, 251)\) \([224]\), which were studied as cytotoxic agents.

Fig. 15. Azaphions.
Fig. 16. Linear polyketides.
The study of some isolates of marine micromycetes allowed to identify a producer of the well-known antibiotic terrein (248) [131, 225], with high productivity [226]. The selection of strains was based on the screening of the antimicrobial and cytotoxic activities of isolates.

### 3. ALKALOIDS

In the study of extremophilic micromycetes, more than seventy heterocyclic compounds were isolated, which can be assigned to alkaloids.

Penicipyrrodiether A (259), which was a new biosynthetic adduct of two known fungal metabolites, GKK1032B (258) [228] with a derivative of phenol A showed a pronounced antibacterial activity and cytotoxicity [229]. Interestingly, compound (258) was also isolated from another marine micromycete, Penicillium erubescens KUFA0220 [114, 230], and also turned out to be the most active antibiotic secondary metabolite among listed above. Seven new pyrrospirones C–I (260–268) with a similar structure were isolated from marine fungus Penicillium sp. ZZ380 [78]. These pyrrospirones significantly differed in their biological activity. For example, only pyrrospiron G (266) showed the pronounced cytotoxicity against four cell lines. Pyrrospirones C (260), F (264), and I (267) exhibited the antibacterial activity including against resistant Gram-positive and Gram-negative bacteria.

Extremophilic micromycetes became the source of some alkaloids containing the indole core and its derivatives (Figs. 19, 20).

Indole-diterpene-type alkaloids (Fig. 19) were isolated from micromycetes of various origins. A marine fungus of the Aspergillus genus [231] became the source of four new indole diterpene-type alkaloids, asperindoles A–D (279–282). Only one of them, compound (279), showed cytotoxic activity. When studying the Tolypocladium sp. XL115 [232] strain isolated from the soil of a coal mine, ten new prenylated diterpene alkaloids, called tolipocladins A–J (269–

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**Fig. 17.** Other polyketides.
were obtained. Compounds (269, 276) showed significant antimicrobial activity.

The structures of other indole alkaloids are summarized in Fig. 20. Two new alkaloids, i.e., 4-epi-seco-shornephinic acid A (300) and its methyl ester (299), along with the well-known biosynthetically bound analog, shornephine A (303) [233], that contained a rare diketomorpholine motif were isolated from the endophyte of seaweed [234].

Previously undescribed alkaloids, candidusine D (296) and preussin C (329), were isolated from marine fungus Aspergillus candidus KUFA0062 [79] along with related compounds. Only petromurine C (295) [235] and preussin (328) [236] among the latter exhibited significant activity. The other compounds, i.e., asterquinol D (296) and cumbicins A, B, and D (298, 304) [235], showed weak cytotoxicity.

Deep-sea micromycete Aspergillus fumigatus SCSIO 41012 [237] turned out to be the source of many antibiotic secondary metabolites. Two new alkaloids, fumigatosids E (283) and F (284), and previously described their structural analogs, fumiquinazoline C (285) and G (286) [238], and epi-aszonalenin A (288) [239] were isolated.

An interesting example of the successful application of cocultivation of two marine micromycetes (in addition to the above mentioned method [213]) to diversify the spectrum of secondary metabolites of micromycetes is the isolation of five new indole alkaloids, i.e., 17-hydroxy notoamide D (287), 17-O-ethylnotoamide M (292), 10-O-acetylscerotoamide (289), 10-O-ethylscerotoamide (290), and 10-O-ethylnotoamide R (293) [240].

The study of the relationship between the structure and cytotoxic activity of new indole alkaloid misszrinine A (291) isolated from marine Aspergillus sp. SCSIO XWS03F03 [241] showed a significant effect of the functionalization of indole nitrogen on biological properties.

Original indole diterpenes, penicillindoles A–C (305–307), were isolated from mangrove fungus Eupenicillium sp. HJ002 [242]. Penicillindoles A (305) and B (306) that contained no additional cycle showed a noticeable cytotoxic activity. Compound (305) that contained the OH group at position 19 appeared to be more active than its carbonyl analog (306).

Two new oxyindole epimeric diterpenes, anthicolourins G (301) and H (302), were significantly different in their biological activity. Only epimer (302) showed moderate activity.

Some isolated alkaloids can be considered as derivatives of maleimide and pyrrolidone (Fig. 21). Three new macrocyclic alkaloids, ascomylactams A–C (308–310) were isolated from mangrove endophyte Didymella sp. CYSK-4 [244], along with the known analogs, phomapyrrolidones A and C (311, 312) [245], structure of which was refined. Two new stereoisomeric alkaloids, cladosporitins A (313) and B (314), were isolated from the culture fluid of the mangrove micromycete Cladosporium sp. HNWSW-1.
Fig. 19. Tolypocladins and asperindoles.

**Antibiotics from Extremophilic Micromycetes**

Some isolated alkaloids can be assigned to pyridone derivatives (Fig. 22). Seafloor micromycete *Arthrinium* sp. UJNMF0008 [248] produces a series of eight alkaloids, artpirons D–K ([316–323]), that contain unusual structural motifs, and a known analog, apiosporamide ([324]) [249].

Systematic screening of marine micromycetes for a wide range of antibacterial activity revealed a strain of the *Aspergillus* genus [75], which produced a new alkaloid, chaetominine A ([326]), along with known chaetominine ([325]) [250].

Thermophilic micromycete [126] isolated from hydrothermal vents was found to produce several antibiotic compounds, the most active of which were the known alkaloids, leporin A ([327]) (previously described as an insecticide [251]) and chaetominine ([325]) [250].

Known alkaloid penicidone C ([330]) [252] was isolated from soil mangrove producer *Penicillium pinophilum* SCAU037 [130]. When studying a mangrove fungus of the *Cladosporium* genus [121], moderately active new alkaloid 2-acetoxymethyl-3,5,6-trimethyl pyrazine ([331]) was isolated along with polyketides. New alkaloid acremol C ([332]) with a moderate antibacterial activity was isolated from Antarctic soil fungus *Aspergillus sydowii* SP-1 [44]. The authors of [253] suggest that this compound may be identical to the previously described acremol B, which contains the isopropyl group at position 2’, not 1’. Another pyrazine alkaloid flavacol ([333]) was re-isolated from mangrove *Aspergillus* sp. SCSIO41211 [254].

**4. Terpenoids, Steroids, and Related Compounds**

A significant part of the secondary metabolites of extremophilic micromycetes can be assigned to terpenoids, steroids, or related compounds. Sesquiterpenes and sesquiterpenoids ([334–393]) (Figs. 24, 25),...
Fig. 20. Indoles and their derivatives.
diterpenes and diterpenoids (394–420) (Fig. 26), steroids, sterols, and their derivatives (421–457) were isolated (Figs. 27, 28).

Many previously undescribed sesquiterpenoids were isolated, and many of them did not show biological activity. For example, three new inactive sesquiterpenes of pestalotiopsin I–K (334–336) were isolated from \textit{Pseudopestalotiopsis} sp. PSU-AMF45 [102]. A new sesquiterpene (337) that did not show the antibiotic activity was isolated from a mangrove fungus of the \textit{Pleosporales} genus [186].

Six new sesquiterpenes (338-342) and four known sesquiterpenes (343–346) [256], which belonged to the ophioboline family, were isolated from marine endophyte \textit{Aspergillus flocculosus} [255]. All the isolated compounds showed strong cytotoxic activity.

Nitrobenzoic sesquiterpenes are rarely found among natural compounds. Three new nitrobenzoyl-sesquiterpenes, insulicolides B and C and 14-O-acetylinsulicolide A (351, 352, 349), and known active analogs (350, 353, 354) [258, 259] were isolated from marine fungus \textit{Aspergillus ochraceus} Jcma1F17 [257].

Three new sesquiterpenes of the eremophylane type were isolated from marine fungus \textit{Cochliobolus lunatus} SCSIO41401 [76]. The isolated compounds belong to the structural family of dendryphiellins; they were called dendryphiellins H–J (355, 347, 348). Two of these compounds (347, 348) exhibited high cytotoxic activity, whereas compound (355) was not active, which indicated the critical importance of the side chain of dendryphiellins for the implementation of their biological properties.

The spectrum of secondary metabolites of mangrove endophyte \textit{Cytospora} sp. was studied [260]. The authors of [261] isolated bicyclic sesquiterpene, seirircardin D (356), with no biological activity and determined the structure of eight known metabolites. The antibacterial activity was shown for (22\textit{E},24\textit{R})-5,8-epidioxy-5\textit{\alpha},8\textit{\alpha}-ergosta-6,9(11),22-trien-3\textit{\beta}-ol (357).

Two known terpenes with moderate antibacterial activity, (7\textit{S})-(+)-hydroxydonic acid (358) [262] and (7\textit{S}, 11\textit{S})-(+)-12-hydroxydonic acid (359) [263], were isolated from Antarctic soil fungus \textit{Aspergillus sydowii} SP-1 [44].

Mangrove endophyte \textit{Aspergillus} sp. xy02 [264] became the source of seven new phenolic bisbolanic sesquiterpenes (360–364, 366, 367), which showed weak antibacterial activity. Interestingly, epimers (361) and (362) were found to be completely inactive [264]. Terpene (367) that contained the \textit{E}-double bond instead of the \textit{Z}-double bond as in (366) was also inactive. Some previously described analogs, i.e.,

\begin{itemize}
  \item Ascomylactam A (308)
  \item Ascomylactam B (309)
  \item Ascomylactam C (310) 16(R)
  \item Phomapyrrolidone A (311)
  \item Phomapyrrolidone B (312)
  \item Cladosporitin A (313)
  \item Cladosporitin B (314)
  \item Talaroconvolutin A (315)
\end{itemize}

\textbf{Fig. 21.} Pyrrolidone and maleimide derivatives.
Engiodontiumon I (365) [265], hydroxysydonic acid (359) [262, 263], and (–)-(7S)-10-hydroxysydonic acid (368) [263, 264], were active.

Four new sesquiterpenoids, penicieudesmols A–D (369–372), were isolated from a mangrove endophyte of the *Penicillium* genus; however only one of them showed weak cytotoxicity [266].

Six sesquiterpenoids, piltunins A–F (373–378) were isolated from marine fungus *Penicillium piltunense* KMM 4668 [151] along with the known structural analog, penigrisacide D (385) [267].

In addition to diterpene alkaloids, nine new sesquiterpenoids (379–384, 386–388) were isolated from the culture liquid of mangrove endophyte *Aspergillus versicolor* [243]. Two of these compounds, i.e., 7-deoxy-7,14-didehydro-12-acetoxy-sydonic acid (386) and its isomer 7-deoxy-7,8-didehydro-12-acetoxy-sydonic acid (387), showed a weak cytotoxic activity.

A new abscisic acid analog, cladosacid (393), was isolated from fungus *Cladosporium* sp. OUCMDZ-1635 of marine origin [220].

Among the secondary metabolites of micromycetes, diterpenes and diterpenoids were no less common than sesquiterpenes and their derivatives (Fig. 26). In some cases, diterpenoids were isolated along with sesquiterpene metabolites. A new sesquiterpenoid 9,10-diolhinokic acid (389) and the diterpenoid roussoellol C (404) and the well-known dankansterone (405) [268, 269] were found among secondary metabolites of marine fungus *Talaromyces purpurogenus* [54]. The cultivation of marine fungus *Trichoderma erinaceum* F1-1 [270] led to the isolation of four new (close to known) terpenoids of different structures, diterpenoid (420) and sesquiterpenoids (390–392), which did not show biological activity [303].

Three new diterpenoids of the dolabellanic type, stachatranones А–С (394–396), and three new atranones Q–S (397–399) were isolated from marine fungus *Stachybotrys chartarum* [271]. New atranones have a significantly new structure. Atranone Q (397) is the first C23 atranone that contains the propan-2-one motif attached to the dolabellane core through the C–
C bond. Antranone R (398) is the first representative of C_{24} antranones that contains the condensed 2-methyltetrahydrofuran–3-carboxylate cycle at the C-5–C-6 position (Fig. 26; the noted fragments are highlighted in red).

Separation of toxic fractions of the culture liquid extract of the marine Aspergillus porosus strain [209] led to the release of the known phytotoxin, sphaeropsidin A (401) [272, 273], which recently attracted interest as a cytotoxic agent [274]. Interestingly, the second isolated analog, which is very similar in structure to the known aspergiloid E (400) [273], has a significantly lower activity.

Fungus Penicillium sp. TJ403-1 isolated from the marine coral [51] turned out to be a producer of several cytotoxic spiroditerpenoids of the brevione family. New brevione O (403) did not show valuable pharmacological properties, while the well-known brevione I (402) [275] was active against several tumor cell lines.

Seven new diterpenoids of the pimarane type, libertellenones O–S (410–414) and eutypeellenones A and B (406, 407), were isolated from the culture liquid of soil Arctic fungus Eutypella sp. D-1 [276] along with known libertellenones H and J (408, 409) [277].

All isolated compounds showed cytotoxic activity. The high diversity of structures allowed to establish some structure–activity relationships. For example, methoxylation at the C-10 position is favorable for the cytotoxic action, while the reversal of the C-13 configuration and hydroxylation at the C-14 position reduce the activity.

Five new 20-nor-isopimarane diterpenoids including the set of four diastereomers, aspewenitones I–L (415–418), and the methylated derivative, aspewentine M (419), were isolated from marine fungus Aspergillus wentii SD-310 [278].

Another structural family of isolated secondary metabolites is steroids and related compounds. New sterols are rare among secondary metabolites of microorganisms, which makes it interesting to detect the new sterol, 3,7-diketo-cephalosporin P1 (421), in the culture liquid of the deep-sea Aspergillus fumigatus SCSIO 41012 [237]. In addition to the new sterol, two known compounds of this class were isolated, i.e., helvolic acid (424) [279, 280] and 22-acetylisocyclocitrin A (435) [281]. Interestingly, new sterol (421) showed a noticeable specific activity against Acinetobacter baumannii. Helvolic acid (424) and its seven new derivatives (422, 423, 425–430) were isolated from marine fungus Aspergillus fumigatus HNMF0047 [282]. Compounds (422–424) exhibited maximal antibiotic activity.

Seaweed endophyte Aspergillus alabamensis EN-547 [234] was the source of a new steroid of ergostane type, 28-acetoxy-12β,15α,25-trihydroxyergosta-4,6,8(14),22-tetraen-3-one (431), which demonstrated a weak aqntimicrobial activity.

20-Acetoxy-16α-methylpreg-17α,19-dihydroxy-(9,11)-epoxy-4-en-3,18-dione (433) and previously described toxic terpenoid, terretonin (439) [283], were isolated from the marine Penicillium citrinum SCSIO 41017 strain [108].

Two new terpenoids, asperterpenes N (436) and O (437) were isolated from seaweed endophyte Aspergillus terreus EN-539 [284] along with related known compounds, terretonins A [285] and G (440) [286], the stereoconfiguration of which was clarified. As before [286], terretonin (444), demonstrated weak antibacterial activity [284]. Later, new terpenoid, terretonin O (442), was isolated from thermophilic Aspergillus terreus TM8 and marine Aspergillus terreus LGO13 [287]. Presumably, compound (442) is a biosynthetic precursor of the recently isolated terretonins M (441) [288] and N (443) [289]. These compounds are oxidized at the C-11 position, which is not typical...
A new ergostan, sarocladione (444), is the first steroid that contains the unique 5,10:8,9-diketo motif. This compound was isolated from deep-sea fungus *Sarocladium kilniense* [290]. In addition to sarocladione (444), twenty known compounds were isolated, and some of them showed the antibiotic properties. A high cytotoxic activity was detected for β-sitostenone (438) [291] and 4,6-dihydroxyeudesmane (456) [292]. 22E-7α-Methoxy-5α,6α-epoxyergosta-8(14),22-dien-3β-ol (455) [293], diosgenin (457) [294], and gramisterol (432) [291] demonstrated a moderate activity. Among the known sterols, we should also note β-sitosterol (454) [295] isolated from seafloor *Aspergillus sydowii* C1-S01-A7 [77]. Mangrove *Aspergillus* sp. SCSIO41211 [254] was the source of new steroid (434) that did not show activity.

Active secondary metabolites of deep-sea micro-mycete *Penicillium granulatum* MC 3A00 475 [47] include several compounds of the steroid nature, i.e., isonuatigenin I (453) [296], penicysteoid A (446) [297], and anicequol (445) [298].

Five new ergostans, penicysteoids D-H (448–452) were obtained from the deep-sea strain of *Penicillium granulatum* MCCC 3A00475 [299] along with fourteen known steroids, some of which exhibited the cytotoxic activity (primarily penicysteoids A and C (446, 447) [297, 300].
Fig. 25. Sesquiterpenes and sesquiterpenoids.
Fig. 26. Diterpenes and diterpenoids.
5. COMPOUNDS OF MIXED AND UNIDENTIFIED ORIGIN

In addition to the compounds summarized in the previous chapters, antibiotic secondary metabolites have been identified, which are difficult to classify unambiguously into one of the abovementioned classes of compounds. In some cases, it is obvious that

**Fig. 27.** Steroids and their derivatives.
the biosynthesis of these compounds requires the joint work of enzyme machinery of different classes (polyketide synthases, nonribosomal peptide synthases, fatty acid synthases, sterol biosynthesis enzymes, the shikimate pathway, etc.). Sometimes (especially for structurally simple compounds), there are not enough data for the biogenetic attribution.

When studying the antimicrobial activity of the extract culture of marine micromycete *Penicillium* ZZ1283 [301], eighteen metabolites were isolated and their structures were determined. One of them turned out to be previously undescribed compound, purpureide D (458), which was a conjugate of drimane-type sesquiterpene and amino acid N-acetyl-L-valine.

Two known micotoxins, ochratoxins A (464) and B (465) [302, 303], that contained the peptide and polyketide fragments were isolated from marine fungus *Aspergillus ochraceus* [42]. Ochratoxins A ethyl ester (461) and its antibiotic activity were studied when isolated from mangrove fungus *Aspergillus* sp. SCSIO41211 [254].

Producer *Trichoderma erinaceum* F1-1 [270] of marine origin mentioned in Section 4 significantly changed the spectrum of synthesized secondary metabolites when cultured on a medium in the presence of L-tryptophan. Instead of terpenoids, eighteen aromatic compounds were isolated in this case, including six new compounds, trichoderolides A–F (462–467), of which only compound (463) showed weak cytotoxicity. The known cytotoxic aromatic compounds, i.e., 3,3’-dimethoxy-5,5’-dimethylidiphenyl ether (468) [304], 3-0-methylidiorcinol (469) [305], and isolated from a natural source for the first time 4’-[(2-hydroxy-1,3-propanyl)bis(oxy-4,1-phenylene(1-methylethylidene))bisphenol (470) [306] were also obtained.

Chemical study of the extract of marine fungus *Truncatella angustata* [307] led to the isolation of previously undescribed prenylated cyclohexanols, two of which (471, 472) showed antiviral activity.

*Penicillilactone A* (473) was isolated from marine fungus *Penicillium* sp. LS54 [308], which was the first natural compound that contained the 7-membered lactone cycle condensed with the furan ring.
Table 4. Data on the origin and biological activity of polypeptides of various structural types

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC$_{50}$, IC$_{50}$, MIC | Ref. |
|------|------------------|--------------------------|-------------------|---------------------------|------|
| 257  | Curvularia sp.   | Marine CT AB             |                   | EC$_{50}$ 12.46 µM (BEL7402/5-Fu) | [219] |
|      |                  |                          |                   | MIC 62.5 µM (P. gingivalis)     |      |
| 161  | Zopfiella marina | Marine AT AB CT          |                   | MIC 25 µg/mL (M. tuberculosis H37Ra) | [164] |
|      |                  |                          |                   | MIC 12.5 µg/mL (B. cereus)      |      |
|      |                  |                          |                   | IC$_{50}$ 13.6 µg/mL (Vero)     |      |
| 199  | Aspergillus fumigatus MF029 | Marine AB AT AF | MIC 50, 50, 12.5, 1.25 µg/mL (MRSA, S. aureus, B. subtilis) | [75] |
|      |                  |                          |                   | MIC 1.25 µg/mL (BCG)           |      |
|      |                  |                          | MIC 8, 32, 8, 16 µg/mL (Cryptococcus neoformans MY 1051, C. neoformans MY 1146, C. neoformans MY 2061, C. neoformans MY 2062) | [207] |
|      |                  |                          | MIC 128 µg/mL (C. albicans MY 1028, MY 1055, MY 1750) | [207] |
|      |                  |                          | MIC 128, 16, 128 µg/mL (C. parapsilosis MY 1010, C. pseudotropicalis MY 2099, C. tropicalis MY 1012, S. cerevisiae MY 1976) | [207] |
|      |                  |                          | MIC 64 µg/mL (A. flavus MF 383) |      |
| 201  | Aspergillus sp.  | Marine AB CT             | MIC 15.15, 30.30, 7.53 µM (V. anguillarum, A. salmonicida, P. aeruginosa) | [74] |
|      |                  |                          | IC$_{50}$ 3.56 – 10.69 µM (Jurkat, A549, HeLa) |      |
| 248  | Aspergillus terreus S020 | Marine CT | MIC 12.13, 22.53 µM (HCT-116, HepG2) | [226] |
|      |                  |                          | IC$_{50}$ 1.1–66.8 µM (MCF-7, PANC-1, HepG2) |      |
| 111  | Alternaria sp.   | Marine CT AB             | EC$_{50}$ 1.7 µg/mL (L5178Y) | [143] |
| 112  | SCSIO41014      |                          | EC$_{50}$ 7.8 µg/mL (L5178Y) | [143] |
|      |                  |                          | EC$_{50}$ 6.8 µg/mL (L5178Y) | [143] |
|      |                  |                          | EC$_{50}$ 0.67 µM (Soybean cell) | [147] |
| 126  |                  |                          | MIC 45 µg/mL (S. aureus ATCC 25923) | [146] |
| 113  |                  |                          | IC$_{50}$ 85.4 µM (FabI S. aureus) | [144] |
|      |                  |                          | MIC 8–32 µg/mL (S. aureus RN4220, S. aureus (MRSA) CCARM, S. aureus (QRSA) CCARM 3505, B. cereus KCTC 1661) | [144] |
| 127  | Qualitative AB activity (S. aureus ATCC 29213, Bacillus subtilis ATCC 6051) | Marine | | | |
|      |                  |                          | IC$_{50}$ 1.1–66.8 µM (MCF-7, PANC-1, HepG2) | [148] |
| 147  |                  |                          | MIC 31.25 µg/mL (S. aureus) | [148] |
|      |                  |                          | MIC 17.1 µg/mL (C. albicans ATCC 24433) | [146] |
|      |                  |                          | MIC 35.5 µg/mL (Trichophyton rubrum 28189) | [146] |
|      |                  |                          | EC$_{50}$ 10 µg/mL (L5178Y) | [143] |
| 196  | Penicillium sp.  | Marine CT AB             | IC$_{50}$ 60.93 µM (U87MG glioma cells) | [94] |
|      | ZZ901            |                          | IC$_{50}$ 60.81 µM (C6 glioma cells) |      |
|      |                  |                          | MIC 23, 35 µg/mL (MRSA, E. coli) |      |
| 197  |                  |                          | IC$_{50}$ 55.99 µM (U87MG glioma cells) | [94] |
|      |                  |                          | IC$_{50}$ 44.65 µM (C6 glioma cells) |      |
| 198  |                  |                          | IC$_{50}$ 37.26 µM (U87MG glioma cells) | [94] |
|      |                  |                          | IC$_{50}$ 23.24 µM (C6 glioma cells) |      |
|      |                  |                          | MIC 7, 9 µg/mL (MRSA, E. coli) |      |
| 207  | Penicillium sclerotior- | Marine AV | IC$_{50}$ 19.5–132 µM (HSV, EV71, RSV1) | [198] |
| run GDST-2013-0415 | |                          | | | | |
| Cpd. | Producer/species                     | Extremophile type/origin | Activity/toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|-------------------------------------|--------------------------|-------------------|--------------------------------------|------|
| 210  | *Penicillium canescens*             | Marine                   | CT                | IC<sub>50</sub> 13.9 μM (L5178Y)     |      |
| 211  |                                     |                          | AF                |                                      |      |
| 200  |                                     |                          | AB                |                                      |      |
| 249  |                                     |                          |                   | IC<sub>50</sub> 2.7, 8.9 μM (A2780, L5178Y) |      |
|      |                                     |                          |                   | IC<sub>50</sub> 20, 35 μM (HeLa, SCC-114) [131] |      |
|      |                                     |                          |                   | IC<sub>50</sub> 11.6 μg/mL (C. gloeosporioides) [195] |      |
|      |                                     |                          |                   | IC<sub>50</sub> 2.68 μg/mL (A. solani) [195] |      |
|      |                                     |                          |                   | IC<sub>50</sub> 8.9 μM (L5178Y)       | [176]|
|      |                                     |                          |                   | MIC 11.1 μg/mL (Agrobacterium tumefaciens, Clavibacter michiganensis subsp. michiganensis, Pectobacterium carotovorum subsp. carotovorum, Pseudomonas syringae pv. Actinidae, Xanthomonas arboricola pv. Pruni, X. axonopodis pv. citri) [218] |      |
|      |                                     |                          |                   | MIC 37 μg/mL (Acidovorax avenue subsp. cattlyae, Burkholderia glumae, X. euversicatoria, Streptomyces scabies) [218] |      |
|      |                                     |                          |                   | MIC 12.3 μg/mL (X. oryzae pv. oryzae) [218] |      |
| 212  | *Diaporthe* sp. SCSIO 41011         | Mangrove                 | CT                | IC<sub>50</sub> 27–45 μM (ACHN, 786-O, -RC-2) |      |
| 214  |                                     |                          | AP                |                                      | [200]|
| 215  |                                     |                          |                   | IC<sub>50</sub> 38, 44 μM (786-O, OS-RC-2) |      |
| 204  |                                     |                          |                   | IC<sub>50</sub> 8.9–14 μM (ACHN, 786-O, OS-RC-2) |      |
| 216  |                                     |                          |                   | IC<sub>50</sub> 10–38 μM (ACHN, 786-O, OS-RC-2) |      |
| 217  |                                     |                          |                   | IC<sub>50</sub> 48, 4.9 μM (786-O, OS-RC-2) |      |
|      |                                     |                          |                   | IC<sub>50</sub> 6.2–10.6 μg/mL (KB, NCI-H187, MCF-7) [201] |      |
|      |                                     |                          |                   | IC<sub>50</sub> 7.8 μg/mL (Plasmodium falciparum) [201] |      |
|      |                                     |                          |                   | IC<sub>50</sub> 8.5–30.2 μg/mL (KB, NCI-H187, MCF-7) [201] |      |
| 145  | *Penicillium purpuro-genum* G59     | Marine                   | CT                | IC<sub>50</sub> 124.3, 329.9 μM (HL-60, K562) |      |
| 177  | *Pseudopestalotiopsis* sp. PSU-AMF45| Marine                   | AF                | MIC 200 μg/mL (Cryptococcus neoformans ATCC90112) |      |
| 136  |                                     |                          |                   | MIC 200 μg/mL (Cryptococcus neoformans ATCC90112) | [102]|
| 245  | *Penicillium janthinellum*          | Marine                   | CT                | GI<sub>50</sub> 9.3–31 μM (NUGC-3, HCT-15, NCI- H23, ACHN, PC-3, MDA-MB-231) |      |
| 139  | *Curvularia* sp. IFB-Z10            | Marine                   | CT                | IC<sub>50</sub> 9.85, 2.46 μM (BEL7402, BEL7402/5-FU) |      |
| 124  | *Penicillium piltnense* KMM 4668    | Marine                   | CT                | IC<sub>50</sub> 71.74 μM (22Rv1) |      |
| 125  |                                     |                          | AF                | IC<sub>50</sub> 30 μM (P. viticola) | [151]|
| 252  | *Cladosporium* sp. OUCMDZ-1635      | Marine                   | CT                | IC<sub>50</sub> 9.1–19.1 μM (MCF-7, HeLa, HCT-116, HL-60) |      |
| 255  | *Aspergillus protuberus* MUT 3638   | Marine                   | AB                | MIC 30 μg/mL (S. aureus) | [222]|
| 148  | *Colletothrichum gloeosporioides*   | Mangrove                 | AB                | MIC 25, 12.5, 12.5, 12.5 μg/mL (B. cereus, B. subtilis, S. aureus, S. albus) | [113]|
| 166  |                                     |                          |                   | MIC 25 μg/mL (B. cereus, B. subtilis, S. aureus) |      |
| Cpd. | Producer/species             | Extremophile type/origin | Activity/toxicity | EC₅₀, IC₅₀, MIC                  | Ref. |
|------|-----------------------------|-------------------------|-------------------|---------------------------------|------|
| 154  | *Dothiorella* sp. ML002     | Mangrove                | AB CT AV          | MIC 50 µg/mL (*S. aureus*)      |      |
| 151  |                             |                         |                   | MIC 50 µg/mL (*S. aureus*)      | [165]|
| 149  |                             |                         |                   | IC₅₀ 25–30 µg/mL (HEp-2, HepG2) | [166]|
| 153  |                             |                         |                   | MIC 50 µg/mL (*S. aureus*)      |      |
| 160  |                             |                         |                   | IC₅₀ 436–600 µg/mL (*S. epidermidis, E. coli, P. aeruginosa, M. smegmatis*) | [168]|
| 150  |                             |                         |                   | MIC 500 µg/mL (TMV)             | [227]|
| 121  | *Pestalotiopsis* sp.        | Mangrove                | AB                | MIC 12.5, 50 µg/mL (*E. coli, P. aeruginosa*) | [145]|
| 116  | *Ascomycota* sp. CYSK-4    | Mangrove                | AB AF CT          | MIC 50 µg/mL (*S. aureus, E. coli, Klebsiella pneumoniae*) |      |
| 119  |                             |                         |                   | MIC 25, 25, 25, 50 µg/mL (*S. aureus, B. subtilis, E. coli, K. pneumoniae, Acinetobacter calcoaceticus*) | [136]|
| 120  |                             |                         |                   | MIC 25 µg/mL (*S. aureus, B. subtilis*) |      |
| 115  |                             |                         |                   | MIC 150 µg/mL (*R. solani*)     |      |
| 134  | *Lasiodiplodia theobromae* M4.2-2 | Mangrove            | CT AB             | MIC 25, 25, 25 µg/mL (*S. aureus ATCC 29213, S. aureus ATCC 700699 and E. faecium ATCC 35667)* | [156]|
| 140  |                             |                         |                   | IC₅₀ 7.3 µM (L5178Y)            |      |
| 142  |                             |                         |                   | IC₅₀ 96.97 µM (HeLa)           | [157]|
| 143  |                             |                         |                   | IC₅₀ 36.41 µM (HeLa)           | [157]|
| 118  | *Phyllosticta capitalensis* | Mangrove                | AB                | MIC 25 µg/mL (*P. aeruginosa*)  | [141]|
| 158  |                             |                         |                   | MIC 25 µg/mL (*P. aeruginosa*)  |      |
| 247  | *Cladosporium* sp. JS1-2   | Mangrove                | AB CT             | MIC 25, 25, 12.5 µg/mL (*S. aureus, E. coli, B. cereus*) | [121]|
| 170  |                             |                         |                   | MIC 1.56, 12.5 µg/mL (*S. aureus, M. luteus*) |      |
| 169  |                             |                         |                   | MIC 6.25, 12.5 µg/mL (*S. aureus, M. luteus*) |      |
| 218  | *Penicillium* sp. ZZ380     | Marine                  | AB                | MIC 6.25, 12.5, 12.5 µg/mL (*S. aureus, E. coli, B. cereus*) | [78] |
|      | *Cladosporium* sp. JS1-2   | Mangrove                |                   |                                 | [121]|

Table 4. (Contd.)
| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC₅₀, IC₅₀, MIC | Ref. |
|------|-----------------|------------------------|------------------|------------------|-----|
| 208  | *Penicillium pinophilum* SCAU037 | Mangrove | AB AF CT | IC₅₀ 23.5, 2.6 μM (*M. smegmatis, S. aureus*)<br>MIC 64 μg/mL (*S. aureus*) [203]<br>MIC 8–64 μg/mL (*S. cerevisiae PM503, C. albicans C43*) [203]<br>IC₅₀ 6.7–7.8 μM (Hep-2, RD) [161]<br>IC₅₀ 62–68.8 μM (A549, BALL-1, HCT116, HeLa, NUGC-3) [202]<br>IC₅₀ 90.4–99 μM (A549, BALL-1, HCT116, HeLa, NUGC-3) [202] | [130] |
| 209  | *Penicillium pinophilum* SCAU037 | Mangrove | AB AF CT | IC₅₀ 2.6–2.8 μM (Caco-2) | [170] |
| 138  | *Aspergillus* sp. AV-2 | Mangrove | CT | IC₅₀ 2.87 μM | [170] |
| 241  | *Fusarium solani* H918 | Mangrove | AF | ED₅₀ 55 μM (*P. theae*) | [211] |
| 128  | *Cladosporium cladosporioides* MA-299 | Mangrove | AB AF | MIC 2 μg/mL (*C. glecosporioides*)<br>MIC 1, 8 μg/mL (*E. tarda, E. ictarda*)<br>MIC 2 μg/mL (*C. glecosporioides*)<br>MIC 32 μg/mL (*P. piricola Nose*)<br>MIC 1 μg/mL (*Fusarium oxysporum f. sp. cucumerinum*)<br>MIC 1 μg/mL (*E. ictarda*)<br>MIC 1 μg/mL (*C. glecosporioides*)<br>MIC 32 μg/mL (*P. piricola Nose*)<br>MIC 32 μg/mL (*Fusarium oxysporum f. sp. cucumerinum*) | [152] |
| 129  | *Cladosporium cladosporioides* MA-299 | Mangrove | AB AF | MIC 2 μg/mL (*C. glecosporioides*)<br>MIC 1, 8 μg/mL (*E. tarda, E. ictarda*)<br>MIC 2 μg/mL (*C. glecosporioides*)<br>MIC 32 μg/mL (*P. piricola Nose*)<br>MIC 1 μg/mL (*Fusarium oxysporum f. sp. cucumerinum*)<br>MIC 1 μg/mL (*E. ictarda*)<br>MIC 1 μg/mL (*C. glecosporioides*)<br>MIC 32 μg/mL (*P. piricola Nose*)<br>MIC 32 μg/mL (*Fusarium oxysporum f. sp. cucumerinum*) | [152] |
| 224  | Cocultivation *Penicillium crustosum* PRB-2 and *Xylaria* sp. HDN13-249 | Antarctica | AB | MIC 100 μM (*B. subtilis*)<br>MIC 6.25, 12.5 μM (*M. phlei, V. parahemolyticus*)<br>MIC 25 μM (*M. phlei*)<br>MIC 12.5, 25 μM (*M. phlei, V. parahemolyticus*) | [213] |
| 246  | *Penicillium* sp. RO-11 | Hot spring deposits (45–65°C), Saudi Arabia/Thermophile | AB CT | MIC 9.3, 7.4 μg/mL (*Enterobacter xiangfangensis, P. aeruginosa*)<br>MIC 6.3, 5.7 μg/mL (*Escherichia fergusonii, P. aeruginosa*)<br>IC₅₀ 22 μM (HTB-176) | [73] |
| 162  | *Sarcopodium* sp. FJK-0025 | Deep-sea 200 m | CT | IC₅₀ 47 μg/mL (Jurkat)<br>IC₅₀ 37–66 μg/mL (Jurkat, HL-60, Panc1) | [169] |
| 233  | *Cladosporium* sp. OUCMDZ-302 | Mangrove | CT | IC₅₀ 10 μM (H1975) | [116] |
| 236  | *Penicillium chrysogenum* MCC 3A00292 | Deep-sea 2076 m | CT | IC₅₀ 7.70–13.75 μM (BIU-87, ECA109, BEL-7402) | [210] |
| Cpd. | Producer/species        | Extremophile type/origin | Activity/toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|-------------------------|--------------------------|-------------------|---------------------------------------|-----|
| 183  | *Penicillium chrysogenum* MCCC 3A00292 | Deep-sea 2076 m          | CT, AB, AF        | IC<sub>50</sub> 16.41 μM (BIU-87)      | [46] |
|      |                         |                          |                   | MIC 200 μg/mL (*E. coli*) [179]         |     |
|      |                         |                          |                   | MIC 50–200 μg/mL (*B. subtilis, S. aureus, M. lysodeikiticus*) [179] |     |
|      |                         |                          |                   | MIC 19.531 μg/mL (*S. aureus, S. saprophyticus, MRSA*) [180] |     |
|      |                         |                          |                   | MIC 19.531, 156.25, 78.125 μg/mL (*B. subtilis, B. cereus, Salmonella thyphimurium, Shigella sonnei*) [180] |     |
|      |                         |                          |                   | IC<sub>50</sub> 9.95 μM (ECA109)       | [46] |
|      |                         |                          |                   | MIC 39.062, 78.125, 39.062 μg/mL (*S. aureus, MRSA, B. subtilis, B. cereus, Salmonella thyphimurium, Shigella sonnei*) [180] |     |
|      |                         |                          |                   | MIC < 9.765 μg/mL (*C. albicans*) [180] |     |
| 184  | *Penicillium chrysogenum* MCCC 3A00292 | Deep-sea 2076 m          | CT, AB, AF        | IC<sub>50</sub> 12.49 μM (ECA109)     | [46] |
| 180  | *Aspergillus sp.* Pleosporales sp. SK7 Mangrove | CT, AB, AF        | IC<sub>50</sub> 30.2–45 μg/mL (HepG2, HL-60, MOLT-3) | [182] |
| 182  | *Penicillium chrysogenum* MCCC 3A00292 | Deep-sea 2076 m          | CT, AB, AF        | IC<sub>50</sub> 18.9 μg/mL (K562)      | [149] |
|      | *Penicillium sp.* SCSIO 06720 Mangrove | CT, AB, AF        | IC<sub>50</sub> 18.9 μg/mL (K562) | [149] |
|      | *Aspergillus sp.* SCSIO 06720 Mangrove | CT, AB, AF        | IC<sub>50</sub> 18.9 μg/mL (K562) | [149] |
| 181  | *Penicillium citrinum* HL-5126 Mangrove | CT, AB, AF        | IC<sub>50</sub> 21.6 μg/mL (HeLa) | [124] |
| 186  | *Pleosporales sp.* SK7 Mangrove | CT, AB, AF        | IC<sub>50</sub> 25.96 μg/mL (MDA-MB-435) | [186] |
| 189  | *Aspergillus sp.* CUGB-F046 Mangrove | CT, AB, AF        | MIC 3.125 μg/mL (*S. aureus, MRSA*) | [189] |
| 187  | *Aspergillus sp.* CUGB-F046 Marine | AB, CT, AF | MIC 6.25 μg/mL (*S. aureus, MRSA*) | [189] |
|      |                         |                          |                   | IC<sub>50</sub> 31.5–48.9 μM (HeLa, K562) | [189] |
|      |                         |                          |                   | IC<sub>50</sub> 23.2–36.3 μg/mL (PC3, A549, A2780, MDA-MB231, HEPG2) | [189] |
|      |                         |                          |                   | MIC 32.0 μg/mL (*C. albicans*) [189] |     |
| 188  | *Aspergillus sp.* CUGB-F046 Marine | AB, CT, AF | MIC 6.25 μg/mL (*S. aureus, MRSA*) | [189] |
|      |                         |                          |                   | IC<sub>50</sub> 29.8–31.6 μg/mL (PC3, HEPG2) | [189] |
|      |                         |                          |                   | MIC 8.0 μg/mL (*C. albicans*) [189] |     |
Chemical study of mangrove endophyte *Phyllosticta capitalensis* [141] yielded two known compounds of mixed biosynthetic origin, i.e., meroterpenoids guignardones A (474) and J (475), which showed antibacterial activity [309].

Two new furandion derivatives with moderate antifungal activity, asperfurandiones A and B (476, 477) were isolated from the marine strain of *Aspergillus versicolor* [310].

A new derivative of pentenoic acid, 1,1'-dioxin-2,2'-propanoic acid (478) was obtained from the mangrove endophyte *Cladosporium* sp. JS 1-2 [121] and showed moderate antibacterial activity.

*Talaromyces assiutensis* JTY2 [311] of mangrove origin became the source of three new metabolites, i.e., the cyclopentenone derivative of talarocyclopenta A (479), the pyrogallol ester of talaracyclopent B (480), and the new itaconic acid derivative of talarocyclopenta C (481), two of which (479, 480) showed the antibacterial activity.

Three new lactones, penicilactones A–C (482–484), were obtained from mangrove *Penicillium* sp. TGM112 [312]. Interestingly, only compound (482) of all the isomers showed antibacterial properties.

Two new pairs of epimeric acetaminophen derivatives of penicilqueis A–D (485–488), which showed promising activity against phytopathogenic fungi, were isolated from the *Penicillium herquei* JX4 culture [313].

Another new polycyclic cytotoxic metabolite, alternatone A (489) was isolated from the marine strain of the *Alternaria* genus [88].

Mangrove endophyte *Cladosporium* sp. JJM22 [314] was the source of two new metabolites (495, 496) and several known ones, only one of which (497) [315] showed the antibacterial activity.

The marine strain of *Aspergillus terreus* LGO13 [287] produces the terpenoids described above and several known metabolites with the antibiotic activity, i.e., butyrolactones I–III (490–492) [316] and aspulvinone O (498) [317]. A deep-sea micromycete of the same species, *Aspergillus terreus* SCSIO FZQ028 [318], became the source of several structurally similar butenolides including a new compound, (±)-asperteretal F (494), and its recently described close analog asperteretal E (493) [319] that contained 2-benzyl-3-phenyl-substituted lactone. Another five known metabolites including the abovementioned butyrolactone III (492) were isolated. Antibacterial activity was shown in asperteretal E (493) and aspernolide A (499) [320].

Cultivation of marine fungus *Aspergillus versicolor* MCC 3A00080 [321] in the presence of the histone deacetylase inhibitor, vorinostat (N-hydroxy-N'...
### Table 5. Data on the origin and biological activity of alkaloids

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|------------------|-------------------------|-------------------|--------------------------------------|-----|
| 259  | *Penicillium* sp. ZZ380 | Marine | AB, CT | MIC 5 μg/mL (MRSA) IC<sub>50</sub> 11.32–29.1 μM (U87-MG, U251, SHG-44, C6) | [229] |
| 258  | *Penicillium* sp. ZZ380 *Penicillium erubescens* KUFA0220 | Marine | AB, CT | MIC 8, 16, 32, 8, 32 μg/mL (*E. faecalis* ATCC 29212, *E. faecium* ATCC 19434, *S. aureus* ATCC 29213, *E. faecalis* B3/101 (VRE), *E. faecium* 1/6/63 (VRE)) [114] MIC 48.35 μM (*M. tuberculosis* H<sub>37</sub>Ra) [230] IC<sub>50</sub> 17.14–29.55 μM (KB, MCF-7, Vero) [230] | [229] [114] |
| 260  | *Penicillium* sp. ZZ380 | Marine | CT, AB | IC<sub>50</sub> 10.03–22.12 μM (U87-MG, U251, SHG-44, C6) MIC 4.0, 5.0 μg/mL (MRSA, *E. coli*) | |
| 261  |                  |             |      | IC<sub>50</sub> 9.95–22.39 μM (U87-MG, U251, SHG-44, C6) MIC 12.0, 3.0 μg/mL (MRSA, *E. coli*) | |
| 262  |                  |             |      | IC<sub>50</sub> 15.76–26.64 μM (U87-MG, U251, SHG-44, C6) MIC 10.0, 11.0 μg/mL (MRSA, *E. coli*) | |
| 264  |                  |             |      | IC<sub>50</sub> 8.93–22.82 μM (U87-MG, U251, SHG-44, C6) MIC 2.0, 3.0 μg/mL (MRSA, *E. coli*) | [78] |
| 266  |                  |             |      | IC<sub>50</sub> 1.06–8.52 μM (U87-MG, U251, SHG-44, C6) | |
| 267  |                  |             |      | IC<sub>50</sub> 12.89–23.92 μM (U87-MG, U251, SHG-44, C6) MIC 19.0, 4.0 μg/mL (MRSA, *E. coli*) | |
| 268  |                  |             |      | IC<sub>50</sub> 7.44–19.18 μM (U87-MG, U251, SHG-44, C6) MIC 4.0, 2.0 μg/mL (MRSA, *E. coli*) | |
| 292  | Cocultivation *Aspergillus sulphureus* and *Isaria felina* | Marine | CT | IC<sub>50</sub> 10.0 μM (22Rv1) | [240] |
| 299  | *Aspergillus* alabamensis EN-547 | Marine | AB | MIC 64.0, 32.0, 32.0, 64.0 μg/mL (*E. coli, Ed. ictaluri, M. luteus, V. alginolyticus) | [234] |
| 300  |                  |             |      | MIC 16.0, 64.0, 64.0 μg/mL (*E. coli, Ed. ictaluri, M. luteus*) | |
| 303  |                  |             |      | MIC 32, 64, 32 μg/mL (*E. coli, Ed. ictaluri, M. luteus, V. alginolyticus*) | |
Table 5. (Contd.)

| Cpd. | Producer/species                      | Extremophile type/origin | Activity/toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|--------------------------------------|--------------------------|-------------------|---------------------------------------|------|
| 328  | *Aspergillus candidus* KUFA 0062     | Marine                   | CT, AB, AF        | IC<sub>50</sub> 12.3–74.1 μM (HepG2, HT29, HCT116, A549, A375, MCF7, U251, T98G) | [79] |
|      |                                      |                          | MIC 32.0 μg/mL (S. aureus ATCC 29213, E. faecalis ATCC 29212) | | |
|      |                                      |                          | MBC 64.0 μg/mL (VRE E. faecalis B3/101) | | |
|      |                                      |                          | MIC 3.1–25 μg/mL (Candida sp.) [236] | | |
|      |                                      |                          | MIC 1.6–12.5 μg/mL (T. menta SC2637, T. rubrum SC9199, M. canis SC9327, A. fumigatus SC 2100) [236] | | |
| 329  | *Aspergillus* sp.                    | Marine                   | CT                | IC<sub>50</sub> 57.2–215.7 μM (HepG2, HT29, HCT116, A549, A375, MCF7, U251) | [231] |
| 296  | *Aspergillus* sp. SCSIO XWS03F03     | Marine                   | CT                | IC<sub>50</sub> 64.0 μM (HL60) | [241] |
| 297  |                                      |                          | IC<sub>50</sub> 3.1 μM (HL60) | | |
| 298  |                                      |                          | IC<sub>50</sub> 4.9 μM (LNCA P) | | |
| 304  | *Cladosporium* sp. JS1-2             | Mangrove                 | AB                | IC<sub>50</sub> 4.86–69.4 μM (PC-3, 22Rv1, LNCA P) | [231] |
| 308  | *Didymella* sp. CYSK-4              | Mangrove                 | CT, AT            | IC<sub>50</sub> 4.4–6.8 μM (MDA-MB-435, MDA-MB-231, SNB19, HCT116, NCI-H460, PC-3) | [244] |
| 309  |                                      |                          | IC<sub>50</sub> 4.5–20.0 μM (MDA-MB-435, MDA-MB-231, SNB19, HCT116, NCI-H460, PC-3) | | |
| 310  |                                      |                          | IC<sub>50</sub> 4.2–7.8 μM (MDA-MB-435, MDA-MB-231, SNB19, HCT116, NCI-H460, PC-3) | | |
| 311  |                                      |                          | IC<sub>50</sub> 4.5–6.6 μM (MDA-MB-231, HCT116) | | |
| 312  |                                      |                          | IC<sub>50</sub> 12–29 μM (MDA-MB-435, MDA-MB-231, SNB19, HCT116, NCI-H460, PC-3) | [245] |
|      |                                      |                          | IC<sub>50</sub> 17.7 μM (Vero) | | |
|      |                                      |                          | MIC 20.1–40.1 μg/mL (MABA, LORA) | | |
| 313  | *Cladosporium* sp. HNWSW-1           | Mangrove                 | CT                | IC<sub>50</sub> 14.9–26.7 μM (Hela; BEL-7042, K562, SGC-7901) | [246] |
| 314  |                                      |                          | IC<sub>50</sub> 25.6–41.7 μM (BEL-7042, K562, SGC-7901) | | |
| 315  |                                      |                          | IC<sub>50</sub> 26.7 μM (Hela, BEL-7042) | | |
| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC₅₀, IC₅₀, MIC | Ref. |
|------|-----------------|-------------------------|------------------|------------------|-----|
| 269  | *Tolypocladium* sp. | Mine soil, Lianyuan, China | AB CT | MIC 6.25, 25, 25, 6.25, 25, 25 µg/mL (*Alternaria fragariae, Corynespora cassiicola, Alternaria alternate, Botrytis cinereal Pers, C. personata, Verticillium dahliae Kleb, Sclerotinia sclerotiorum*), MIC 25.0, 12.5 µg/mL (*B. cereus, MRSA*), IC₅₀ 16.32–37.8 µM (Huh7, LN229, HCT116, MGC803, A549, MDA231) | |
| 270  | | | | MIC 25, 25, 50 µg/mL (*A. fragariae, B. cinereal Pers, C. personata*), MIC 50 µg/mL (MRSA), IC₅₀ 56.35–128.5 µM (Huh7, LN229, HCT116, MGC803, A549, MDA231) | |
| 271  | | | | MIC 25, 12.5, 50 µg/mL (*A. fragariae, C. cassiicola, C. personata*), IC₅₀ 192.8–196.8 µM (Huh7, HCT116) | |
| 272  | | | | MIC 50, 25, 50 µg/mL (*A. fragariae, C. cassiicola, A. alternate, B. cinereal Pers, C. personata, V. dahliae Kleb, S. sclerotiorum*), MIC 100.0 µg/mL (*B. cereus*), IC₅₀ 84.94–114.8 µM (Huh7, LN229, HCT116, MGC803, A549, MDA231) | |
| 273  | | | | MIC 6.25, 12.5, 12.5 µg/mL (*A. fragariae, C. cassiicola, C. personata*), IC₅₀ 198.6 µM (A549) | [232] |
| 274  | | | | MIC 25.0, 12.5 µg/mL (*A. fragariae, C. cassiicola*), IC₅₀ 54.29–157.2 µM (Huh7, LN229, HCT116, MGC803, A549, MDA231) | |
| 275  | | | | MIC 6.25, 50, 25, 100 µg/mL (*A. fragariae, A. alternate, B. cinereal Pers, C. personata*), IC₅₀ 39.94–154.1 µM (Huh7, LN229, HCT116, MGC803, A549, MDA231) | |
| 276  | | | | MIC 25.0 µg/mL (*C. personata*), MIC 12.5 µg/mL (*B. cereus*), MIC 25.0 µg/mL (MRSA, *M. lysodeikticus, Bact. para-typhosum, B. subtilis, E. aerogenes, S. typhi, P. vulgaris*), IC₅₀ 31.49–64.49 µM (Huh7, LN229, HCT116, MGC803, A549, MDA231) | |
| 277  | | | | MIC 50 µg/mL (*A. fragariae*), MIC 100 µg/mL (*B. cereus*), IC₅₀ 50.95–129.1 µM (Huh7, LN229, HCT116, MGC803, A549, MDA231) | |
| 278  | | | | MIC 25 µg/mL (*A. fragariae*), IC₅₀ 174.2 µM (A549) | |
| 332  | *Aspergillus sydowii* SP-1 | Antarctica | AB | MIC 4.0, 8.0, 32.0, 16.0 µg/mL (*S. epidermidis, S. aureus, MRSA, MRSE*) | [44] |
phenyloctanediamide), induced the biosynthesis of a new secondary metabolite of versiperol A (513), which showed weak antibacterial activity.

Three new derivatives of itaconic acid isolated from marine *Aspergillus niger* were named asperitaconic acids А–С (500–502) [322]. The described compounds did not show noticeable cytotoxicity but demonstrated a moderate antibacterial activity. A new secondary metabolite, 1-(2',6'-dimethyl-phenyl)-2-3-propyl-1,2-dihydropyridazine-3,6-dione (512), which is the derivative of maleic hydrazide, was isolated from mangrove fungus *Aspergillus* sp. AV-2

Table 5. (Contd.)

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|------------------|--------------------------|-------------------|-------------------------------------|-----|
| 327  | *Aspergillus* sp. | Hydrothermal vent sediment, Kueishantao, Taiwan/Thermophile Marine | AB | MIC 8.75, 5.42, 19.67, 1.33, 11.91 µg/mL (P. aeruginosa, E. coli, S. aureus, B. subtilis, MRSA) | [126] [75] |
| 325  | *Aspergillus fumigatus* | | | MIC 21.13, 2.51, 3.72, 0.89, 6.25 µg/mL (P. aeruginosa, E. coli, S. aureus, B. subtilis, MRSA) IC<sub>50</sub> 21.0–28.0 µM (SW1116, K562) | [250] |
| 283  | *Aspergillus fumigatus* | Deep-sea 3614 m | AB | MIC 12.5, 6.25, 25.0, 6.25, 12.5 µg/mL (A. baumanii ATCC 9606, A. baumanii ATCC 15122, Fusarium oxysporum f. sp. cucumerinu, S. aureus ATCC 16339, K. pneumonia ATCC 14578) | [126] [75] |
| 284  | | | | MIC 6.25 µg/mL (A. baumanii ATCC 19606) | |
| 286  | | | | MIC 6.25, 12.5, 0.78, 25.0 µg/mL (A. baumanii ATCC 15122, S. aureus ATCC 16339, Fusarium oxysporum f. sp. cucumerinu, S. aureus ATCC 29213, K. pneumonia ATCC 14578) | |
| 285  | | | | MIC 12.5, 1.5, 0.78, 25.0 µg/mL (Fusarium oxysporum f. sp. cucumerinu, S. aureus ATCC 16339, S. aureus ATCC 29213, K. pneumonia ATCC 14578) | |
| 288  | | | | MIC 50.0, 6.25, 12.5 µg/mL (A. baumanii ATCC 1606, A. baumanii ATCC 15122, Fusarium oxysporum f. sp. cucumerinu) | |
| 318  | *Arthrinium* sp. | Deep-sea 3858 m | AB | IC<sub>50</sub> 11.4, 8.97 µM (M. smegmatis ATCC607, S. aureus ATCC25923) | |
| 319  | | | | IC<sub>50</sub> 42.8 µM (S. aureus ATCC25923) | |
| 320  | | | | IC<sub>50</sub> 19.4, 8.37 µM (M. smegmatis ATCC607, S. aureus ATCC25923) | |
| 321  | | | | IC<sub>50</sub> 35.3, 14.1 µM (M. smegmatis ATCC607, S. aureus ATCC25923) | |
| 324  | | | | IC<sub>50</sub> 2.20, 1.66 µM (M. smegmatis ATCC607, S. aureus ATCC25923) IC<sub>50</sub> 19.3, 11.7 µM (U2OS, MG63) | [248] |
| 330  | *Penicillium pinophilum* | Mangrove | CT | IC<sub>50</sub> 15.1–20 µg/mL (KB, KBv200) IC<sub>50</sub> 44.3–80.8 µM (SW1116, K562, KB, HeLa) | [130] |
| 333  | *Aspergillus* sp. | Mangrove | CT | IC<sub>50</sub> 0.15–22.9 µM (H1975, U937, K562, BGC823, MOLT-4, MCF-7, A549, HL60, Huh-7) | |
| 305  | *Eupenicillium* sp. | Mangrove | CT | IC<sub>50</sub> 1.5–23.3 µM (A549, HeLa, HepG-2) IC<sub>50</sub> 18.6–47.2 µM (A549, HeLa, HepG-2) | |
| 302  | *Aspergillus versicolor* | Mangrove | CT | IC<sub>50</sub> 43.7 µM (HeLa) | |

A new secondary metabolite, 1-(2',6'-dimethyl-phenyl)-2-3-propyl-1,2-dihydropyridazine-3,6-dione (512), which is the derivative of maleic hydrazide, was isolated from mangrove fungus *Aspergillus* sp. AV-2
Table 6. Data on the origin and biological activity of terpenoids and related compounds

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC₅₀, IC₅₀, MIC | Ref. |
|------|-----------------|-------------------------|-------------------|-----------------|-----|
| 454  | *Aspergillus sydowii* C1-S01-A7 | Deep-sea 4950 m | CT | IC₅₀ 50 µg/mL (HepG2) | [77] |
| 421  | *Aspergillus fumigatus* SCSIO 41012 | Deep-sea 3614 m | AB | MIC 50 µg/mL (*A. baumanii* ATCC 19606) | [237] |
|      |                  |                        |                  | MIC 12.5, 3.125 µg/mL (*A. baumanii* ATCC 15122, *K. pneumonia* ATCC 14578) |       |
|      |                  |                        |                  | MIC 1.5 µg/mL (*F. oxysporum* f. sp. *Momordicae*) |       |
|      |                  |                        |                  | MIC 100 µg/mL (*S. epidermidis*) [281] |       |
|      |                  |                        |                  | MIC 100 µg/mL (*Enterococcus durans*) [281] |       |
| 424  | *Aspergillus fumigatus* SCSIO 41012 *Aspergillus fumigatus* HNMF0047 | Deep-sea 3614 m Marine | AB | MIC 25, 12.5 µg/mL (*S. aureus* ATCC 16339, 29213) [237] |       |
|      |                  |                        |                  | MIC 2, 4 µg/mL (MRSA ATCC 33591, *B. subtilis* UBC 344) [279] |       |
|      |                  |                        |                  | MIC 5.8 µg/mL (*S. aureus*) [280] |       |
|      |                  |                        |                  | MIC 4.6 µg/mL (*P. aeruginosa*) [280] |       |
|      |                  |                        |                  | MIC 16, 8 µg/mL (*S. aureus, Streptococcus agalactiae*) |       |
| 422  | *Aspergillus fumigatus* HNMF0047 | Marine | AB | MIC 16 µg/mL (*S. aureus, S. agalactiae*) | [282] |
|      |                  |                        |                  | MIC 8, 2 µg/mL (*S. aureus, S. agalactiae*) |       |
| 395  | *Stachybotrys chartarum* | Marine | AB | MIC 16 µg/mL (*A. baumanii*) | [271] |
| 397  |                  |                        | AF               | MIC 16 µg/mL (*E. faecalis*) |       |
|      |                  |                        |                  | MIC 32 µg/mL (MRSA) |       |
|      |                  |                        |                  | MIC 8 µg/mL (*C. albicans*) |       |
| 401  | *Aspergillus porosus* | Marine | AB | IC₅₀ 32.6, 35.3 µM (*S. aureus* ATCC 25923, *S. aureus* ATCC BAA-41) | [209] |
|      |                  |                        | CT | IC₅₀ 4.9 µM (HCT-116 ATCC CCL-247) |       |
|      |                  |                        | AF | MIC 10–100 µg/mL (*Botrytis cinerea, Seiridium cardinal, Seiridium cupressi, Colletotrichum acutatum, F. oxysporum, F. solani, Fusicoccum amygdale, Penicillium expansum, Pyrenozaeta hypocersici, Sclerotinia minor, Sclerotinia wlerotiorum, Verticillium dahliae*) [272] |       |
|      |                  |                        |                  | IC₅₀ 6.74–10.68 µM (KB, SGC-7901, SW1116, A549) [273] |       |
| 400  |                  |                        |                  | IC₅₀ 71.6, 77.8 µM (*S. aureus* ATCC 25923, *S. aureus* ATCC BAA-41) |       |
|      |                  |                        |                  | IC₅₀ 32.7 µM (HCT-116 ATCC CCL-247) |       |
| 431  | *Aspergillus alabamensis* EN-547 | Marine | AB | MIC 32, 64 µg/mL (*Ed. ictaluri, V. alginolyticus*) | [234] |
Table 6. (Contd.)

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|------------------|-------------------------|-------------------|-------------------------------------|------|
| 338  | *Aspergillus flocculosus* | Marine | CT | IC<sub>50</sub> 0.14–0.24 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) | [255] |
|      |                   |                         |                   | IC<sub>50</sub> 0.44–0.63 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) |      |
|      |                   |                         |                   | IC<sub>50</sub> 0.88–1.40 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) |      |
|      |                   |                         |                   | IC<sub>50</sub> 1.07–1.50 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) |      |
|      |                   |                         |                   | IC<sub>50</sub> 1.53–2.01 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) |      |
|      |                   |                         |                   | IC<sub>50</sub> 0.19–0.43 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) |      |
|      |                   |                         |                   | IC<sub>50</sub> 0.16–0.36 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) |      |
|      |                   |                         |                   | IC<sub>50</sub> 8 μM (CLL) |      |
| 341  |                   |                         |                   | IC<sub>50</sub> | 0.20–0.30 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) |      |
| 342  |                   |                         |                   | IC<sub>50</sub> | 0.19–0.42 μM (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) |      |
| 343  | *Talaromyces purpurogens* | Marine | CT | IC<sub>50</sub> 12.6–35.7 μM (HL-60, A549) | [54] |
| 344  | *Penicillium sp. TJ403-1* | Marine | CT | IC<sub>50</sub> 6.5–25.8 μM (SW480, HL-60, A549, MCF-7) | [51] |
| 345  | *Aspergillus ochraceus* Jcma1F17 | Marine | CT | IC<sub>50</sub> 4.92–8.6 μM (HL-60, A549, HEP3B) | [257] |
| 349  |                   |                         | CT | IC<sub>50</sub> 7.44–32.5 μM (MCF-7, A549) | [275] |
| 350  |                   |                         | AV | IC<sub>50</sub> 23–30 μM (ACHN, OS-RS-2, 786-O) | [258] |
| 351  |                   |                         | AV | IC<sub>50</sub> 2.3–5.3 μM (ACHN, OS-RS-2, 786-O) |      |
| 352  |                   |                         | AV | IC<sub>50</sub> 11–14 μM (ACHN, OS-RS-2, 786-O) |      |
| 353  |                   |                         | AV | IC<sub>50</sub> 0.89–1.5 μM (ACHN, OS-RS-2, 786-O) |      |
| 354  |                   |                         | AV | IC<sub>50</sub> 2.11–6.35 μM (H1975, U937, K562, BGC823, Molt-4, MCF-7, A549, HeLa, HL60, Huh-7) |      |
|      |                   |                         | AV | IC<sub>50</sub> 4.3–11 μM (ACHN, OS-RS-2, 786-O) |      |
|      |                   |                         | AV | IC<sub>50</sub> 1.95–17 μM (H1975, U937, K562, BGC823, Molt-4, MCF-7, A549, HeLa, HL60, Huh-7) |      |
|      |                   |                         | AV | IC<sub>50</sub> 17, 9.4 μM (H3N2, EV71) |      |
|      |                   |                         | AV | IC<sub>50</sub> 20–30 μM (ACHN, OS-RS-2, 786-O) |      |
| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|------------------|--------------------------|-------------------|-------------------------------|-----|
| 347  | Cochliobolus lunatus SCSIO 41401 | Marine | CT AB | IC<sub>50</sub> 1.41–4.3 μM (ACHN, 786-O, OS-RC-2, HepG-2, SGC7901) IC<sub>50</sub> 3.1–27 μM (ACHN, 786-O, HepG-2, SGC7901) MIC 1.5–13 μg/mL (S. aureus, Erysipelothrix rhusiopathiae, Pasteurella multocida) | [76] |
| 348  | Penicillium citrinum SCSIO 41017 | Marine | CT AF | IC<sub>50</sub> 13.5–18 μM (SF-268, MCF-7, HepG-2, A549) MIC 125–250 μg/mL (C. asiaticum, C. acutatum) | [108] |
| 433  | Aspergillus terreus EN-539 | Marine | AB | MIC 32, 8 μg/mL (M. luteus, S. aureus) | [284] |
| 442  | Aspergillus terreus TM8 Aspergillus terreus LGO13 | Soil of Egypt (optimum growth 45–50°C)/ Thermophile Marine | AB AF | MIC 250 μg/mL (S. aureus ATCC 6538-P, P. aeruginosa ATCC 27853) MIC 250 μg/mL (S. aureus ATCC 6538-P, B. cereus ATCC 11778, C. albicans ATCC 10231) Qualitative AB activity (E. coli DSMZ 1058, B. subtilis DSMZ 704, P. agarici DSMZ 11810, M. luteus DSMZ 1605, S. warneri DSMZ 20036) | [287] |
| 386  | Aspergillus versicolor | Mangrove | CT | IC<sub>50</sub> 83.8 μM (HeLa) IC<sub>50</sub> 53.5 μM (HeLa) | [243] |
| 387  | Cytospora sp. | Mangrove | AB | MIC 233.3, 58.3, 58.3 μg/mL (MRSA, B. subtilis, P. aeruginosa) | [260] |
| 361  | Aspergillus sp. xy02 | Mangrove | AB | IC<sub>50</sub> 32.2 μM (S. aureus ATCC 25923) | [264] |
| 362  | Penicillium sp. J-54 | Mangrove | CT | IC<sub>50</sub> 90.1 μM (K-562) | [266] |
| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC50, IC50, MIC | Ref. |
|------|-----------------|--------------------------|------------------|----------------|------|
| 410  | *Eutypella* sp. D-1 | Arctic                   | CT               | IC50 2–6 μM (HeLa, MCF-7, HCT-116, PANC-1, SW1990) | [276] |
| 411  |
| 412  | *Eutypella* sp. D-1 | Arctic                   | IC50 1–3.6 μM (HeLa, MCF-7, HCT-116, PANC-1, SW1990) |
| 413  | *Eutypella* sp. D-1 | Arctic                   | IC50 0.8–2.1 μM (HeLa, MCF-7, HCT-116, PANC-1, SW1990) |
| 414  | *Eutypella* sp. D-1 | Arctic                   | IC50 26.6 μM (PANC-1) |
| 417  | *Eutypella* sp. D-1 | Arctic                   | IC50 29.4 (HCT-116) |
| 418  | *Eutypella* sp. D-1 | Arctic                   | IC50 10.3–13.1 μM (HeLa, MCF-7, HCT-116, PANC-1, SW1990) |
| 419  | *Eutypella* sp. D-1 | Arctic                   | IC50 6–8.4 μM (HeLa, MCF-7, HCT-116, PANC-1, SW1990) |
| 421  | *Eutypella* sp. D-1 | Arctic                   | IC50 0.3–1.8 μM (HeLa, MCF-7, HCT-116, PANC-1, SW1990) |
| 422  | *Eutypella* sp. D-1 | Arctic                   | IC50 3–44.1 μM (U251, SW-1990, SG7901, MCF-7, Huh-7, HeLa, H460) [277] |
| 358  | *Aspergillus sydowii* SP-1 | Antarctica Mangrove | AB AF            | MIC 0.5, 1, 0.25, 0.5 μg/mL (S. aureus, MRSA, S. epidermidis, MRSE) [44] |
|      | *Aspergillus sp. xy02* | Antarctica Mangrove     |                 | IC50 34 μM (S. aureus ATCC 25923) [264] |
|      |                 |                          |                 | MIC 0.5 μg/mL (S. aureus, V. parahemolyticus) [263] |
|      |                 |                          |                 | MIC 32 μg/mL (Gaeumannomyces graminis) [263] |
| 446  | *Penicillium granulatum* MCCC 3A00475 | Deep-sea 2284 m | CT AF           | IC50 8.2 μM (HepG2) [47] |
|      |                 |                          |                 | IC50 4.1–12.5 μM (A549, SHG-44, HepG2, BIU-87, ECA-109, Hela-S3, PANC-1, BEL-7402) [299] |
|      |                 |                          |                 | IC50 15–40 μg/mL (HeLa, SW1990, NCI-H460) [297] |
|      |                 |                          |                 | Qualitative AF activity (*Aspergillus niger*) [297] |
| 453  | *Penicillium granulatum* MCCC 3A00475 | Deep-sea 2284 m | CT              | IC50 8.6 μM (HepG2) [47] |
|      |                 |                          |                 | IC50 1.2 μM (DLD-1 cells on polyHEMA-coated) [298] |
|      |                 |                          |                 | IC50 40 μM (DLD-1 cells on uncoated plates) [298] |
Compounds that contain the N–N bond are quite rare among natural compounds [323] but they are widely represented among synthetic biologically active compounds, especially pyridazine derivatives [324].

New cytotoxic meroterpenoids, eutypellacytospors A–D (507–510), were isolated from Arctic fungus Eutypella sp. D11 [325]. These compounds are conjugates of polyketide (cytosporin D) and sesquiterpenoids (decipienolides A and B). A small difference in the activity of the C-21 epimers (507) and (509) indicates a slight influence of the configuration of this optical center.

The meroterpenoid austinol (511) [326], which was isolated among secondary metabolites from a thermophilic fungus of the Penicillium genus [73], showed a noticeable antibacterial activity.

The chemical study of the extract of deep-sea fungus Penicillium sp. YPGA11 [327] led to the isolation of four new antibacterial meroterpenoids farnesylcyclohexenones, peniginsengins B–E (503–506), that contained rare motifs for natural compounds, i.e., 1-methylcyclohexene cycle and (4E,8E)-4,8-dimethyldec-4,8-dienoic acid.

**CONCLUSIONS**

The search for new antibiotics is an increasingly urgent task in the context of the spread of drug resistance. Different strategies were used in different periods to search for natural biologically active compounds. The most productive was the Waksman platform, which consists in the cultivation of soil microorganisms with a wide range of antibiotic activ-

### Table 6. (Contd.)

| Cpd. | Producer/species | Extremophile type/origin | Activity/toxicity | EC<sub>50</sub>, IC<sub>50</sub>, MIC | Ref. |
|------|------------------|--------------------------|-------------------|---------------------------------|------|
| 449  | *Penicillium granulatum* MCCC 3A00475 | Deep-sea 2284 m | CT | IC<sub>50</sub> 5.5–8.3 μM (A549, SHG-44) IC<sub>50</sub> 4.8–14.4 μM (A549, SHG-44, HepG2, BIU-87, ECA-109, Hela-S3, PANC-1, BEL-7402) | [299] |
| 451  |                  |                          |                   | IC<sub>50</sub> 4.4–9.2 μM (A549, HepG2, BIU-87, ECA-109, Hela-S3) |      |
| 452  |                  |                          |                   | IC<sub>50</sub> 4.4–9.9 μM (A549, SHG-44, ECA-109, Hela-S3, PANC-1) | [300] |
| 447  |                  |                          |                   | Qualitative AF activity (C. albicans ATCC 10231, S. cerevisiae ATCC 9080) | [300] |
| 385  | *Penicillium griseofulvum* | Deep-sea 1420 m | CT | IC<sub>50</sub> 28.7 μM (ECA-109) | [267] |
| 415  | *Aspergillus wentii* SD-310 | Deep-sea 2038 m | AB, AF | MIC 8, 32, 8 μg/mL (E. tarda, P. aeruginosa, V. harveyi, V. parahaemolyticus) | [278] |
| 416  |                  |                          |                   | MIC 32, 8, 8 μg/mL (E. coli, E. tarda, V. harveyi, V. parahaemolyticus) |      |
| 417  |                  |                          |                   | MIC 32 μg/mL (Aeromonas hydrophilica, V. anguillarum) |      |
| 418  |                  |                          |                   | MIC 32, 32 μg/mL (E. tarda, V. harveyi) |      |
| 419  |                  |                          |                   | MIC 32, 32 μg/mL (V. anguillarum, V. harveyi) |      |
| 432  | *Sarocladium kiliense* | Deep-sea 5070 m | CT | IC<sub>50</sub> 25.8 μM (HeLa-S3) | [290] |
| 438  |                  |                          |                   | IC<sub>50</sub> 9.2 μM (HeLa-S3) |      |
| 457  |                  |                          |                   | IC<sub>50</sub> 44.2 μM (HeLa-S3) |      |
| 456  |                  |                          |                   | IC<sub>50</sub> 9.3 μM (HeLa-S3) |      |
| 455  |                  |                          |                   | IC<sub>50</sub> 30.1 μM (HeLa-S3) |      |
|      |                  |                          |                   | IC<sub>50</sub> 70 μM (A549) [293] |      |
Table 7. Data on the origin and biological activity of compounds of mixed and unidentified origin

| Cpd. | Producer/species         | Extremophile type/origin | Activity/toxicity               | EC\textsubscript{50}, IC\textsubscript{50}, MIC | Ref. |
|------|--------------------------|--------------------------|---------------------------------|-----------------------------------------------|------|
| 458  | Penicillium sp. ZZ1283   | Marine                   | AB                              | MIC 4, 3 μg/mL (S. aureus, E. coli)            | [301]|
|      |                          |                          |                                 | MIC 8 μg/mL (C. albicans)                      |      |
| 459  | Aspergillus ochraceus     | Marine                   | CT                              | IC\textsubscript{50} 0.8–1.0 μg/mL (BME-UV1, MDCK) [328] IC\textsubscript{50} 17–87 μM (IHKE) [329] IC\textsubscript{50} 0.3 μM (Hep G2) [330] IC\textsubscript{50} 3 μM (A2780) | [42] |
| 460  |                          |                          |                                 |                                               |      |
| 461  | Aspergillus sp. SCSIO4121 | Mangrove                 | CT                              | IC\textsubscript{50} 0.031–23.2 μM (H1975, U937, K562, BGC823, MOLT-4, MCF-7, A549, Hela, HL60, Huh-7) [254] | [254]|
| 463  | Trichoderma erinaceum F1-1 | Marine                   | CT                              | IC\textsubscript{50} 31.9 μM (MDA-MB-435) [270] |      |
| 468  |                          |                          |                                 |                                               |      |
| 469  |                          |                          |                                 |                                               |      |
| 470  |                          |                          |                                 |                                               |      |
| 471  | Truncatella angustata    | Marine                   | AV                              | IC\textsubscript{50} 39 μM (HIV-1)             | [307]|
| 472  | Penicillium sp. LS54.    | Marine                   | AB                              | IC\textsubscript{50} 16.1 μM (HIV-1)           | [308]|
| 473  |                          |                          |                                 |                                               |      |
| 476  | Aspergillus versicolor DJ013 | Marine                  | AF                              | MIC 64 μg/mL (G. graminis, C. neoformans, C. albicans) | [310]|
| 477  |                          |                          |                                 |                                               |      |
| 478  | Cladosporium sp. JS1-2   | Mangrove                 | AB                              | MIC 25, 25, 12.5 μg/mL (S. aureus, E. coli, B. cereus) | [121]|
| 479  | Talaromyces assiutensis JTY2 | Mangrove               | AB                              | MIC 20, 40 μg/mL (S. aureus, E. coli)           | [311]|
| 480  |                          |                          |                                 |                                               |      |
| 482  | Penicillium sp. TGM112   | Mangrove                 | AB                              | MIC 5, 2.5, 5, 2.5, 2.5 μg/mL (M. tetragenus, S. aureus, S. albus, B. cereus, B. subtilis, E. coli) | [312]|
| 485  | Penicillium herquei JX4  | Mangrove                 | AF                              | MIC 25, 50, 25, 100, 200, 50, 50 μg/mL (Alternaria brassicicola, P. parasitica var. nicotianae, Colletotrichum capsici, B. oryzae, Diaporthe medusaeae Nitschke, Ceratocystis paradoxa Mareau, P. theae, Alternaria citri) | [313]|
| 486  |                          |                          |                                 |                                               |      |
| 487  |                          |                          |                                 |                                               |      |
| 488  |                          |                          |                                 |                                               |      |
### Table 7. (Contd.)

| Cpd. | Producer/species | Extremophile type/origin | Activity/ toxicity | EC$_{50}$, IC$_{50}$, MIC | Ref. |
|------|------------------|--------------------------|-------------------|--------------------------|-----|
| 497  | *Cladosporium* sp. JJM22 | Mangrove | AB | IC$_{50}$ 20 μM (*S. aureus, B. cereus, MRSA, E. coli, V. alginolyticus, V. parahemolyticus*)<br>MIC 200 μg/mL (*S. aureus, MRSA, M. gypseum SH-MU-4*) [315] | [314] |
| 490  | *Aspergillus terreus* LGO13 | Marine | AB | MIC 125, 250 μg/mL (*S. aureus ATCC 6538-P, B. cereus ATCC 11778*)<br>MIC 250 μg/mL (*C. albicans ATCC 10231*)<br>0.576–1 mM (MCF-7/AGR, U251, SW620, H522, M14, SKOV3, DU145, A498) [316] | [287] |
| 491  | | | AF | Qualitative AF activity (*C. albicans ATCC 10231*)<br>0.626–1 mM (MCF-7/AGR, U251, SW620, H522, M14, SKOV3, DU145, A498) [316] | [318] |
| 492  | | | CT | MIC 250.0 μg/mL (*B. cereus ATCC 11778*)<br>0.16–1 mM (MCF-7/AGR, U251, SW620, H522, M14, SKOV3, DU145, A498) [316] | [287] |
| 493  | *Aspergillus terreus* SCSIO FZQ028 | Deep-sea 1718 m | AB | Qualitative AB activity (*S. aureus, B. thuringiensis, B. subtilis, E. coli*) | [321] |
| 499  | | | Qualitative AB activity (*S. aureus, B. thuringiensis, B. subtilis, E. coli*) | | |
| 500  | *Aspergillus niger* | Marine | AB | MIC 16 μg/mL (*S. aureus*)<br>MIC 32 μg/mL (*S. aureus*)<br>MIC 32 μg/mL (*S. aureus*) | [322] |
| 501  | | | | | |
| 502  | | | | | |
| 503  | *Aspergillus versicolor* MCCC 3A00080 | Deep-sea 2721 m | AB | MIC 8 μg/mL (*S. aureus*) | [321] |
| 474  | *Phyllosticta capitata-lensis* | Mangrove | AB | MIC 25.5 μg/mL (*P. aeruginosa*) [309]<br>MIC 50, 50 μg/mL (*MRSA, P. aeruginosa*)<br>MIC 89.3 μg/mL (*B. subtilis*) [309] | [141] |
| 475  | | | | | |
| 504  | *Penicillium* sp. RO-11 | Hot spring deposits (45–65°C), Saudi Arabia/Thermophile | AB | MIC 1.4, 2.5, 0.13 μg/mL (*S. aureus, Escherichia fergusonii, P. aeruginosa*)<br>IC$_{50}$ 10 μM (HTB-176) | [73] |
| 505  | | | CT | | |
| 506  | *Penicillium* sp. PGA11 | Deep-sea 4500 m | AB | MIC 32, 8 μg/mL (*S. aureus ATCC 43300, S. aureus ATCC 25913*)<br>MIC 16 μg/mL (*S. aureus ATCC 25913*)<br>MIC 64, 32 μg/mL (*S. aureus ATCC 43300, S. aureus ATCC 25913*) | [327] |
This approach allowed to identify of the majority of currently known antibiotics including those used in medicine and veterinary medicine. However, the chances of revealing new compounds by this method after the 1970s became negligible because of the problem of rediscovering known antibiotics (rediscovery problem). At the same time, the need for new antibiotic agents is only growing because of the spread of resistance, which has led to the emergence of alternative approaches, such as omics methods (metabolomics, genomics, and reverse genomics) and target-oriented high-performance screening [1].
However, none of the developed strategies has led to a breakthrough in the search for antibiotics. One of the ways to overcome the crisis in the search for natural compounds is to study difficult-to-cultivate and rare microorganisms including the inhabitants of extreme ecosystems [332, 333]. To assess the prospects for this approach, we have analyzed all secondary metabolites of extreme micromycetes, which are new or known compounds with antibiotic activity isolated over the period 2018—2019.

From a taxonomic point of view, most micromycetes that have become sources of new and/or known active compounds belong to the common *Aspergillus* and *Penicillium* genera. Representatives of other taxa have much smaller proportions.
From a biogenetic point of view, most of the metabolites were polyketides (45%) of various structures. Peptides and related compounds were very rare for extremophilic micromycetes (5%). The distribution of metabolites by structural families is shown in Fig. 36.

Many metabolites (about one third (37%) of all compounds, 190 out of 513), the structure of which was established in the covered period, were previously described antibiotics, and the spectrum of biological activity was clarified for some of them. The antibiotic activity was shown in 53% (179 compounds) of the previously undescribed metabolites (323 compounds, 63% of the total). At the same time, about half of all active metabolites (369) were new. It can be assumed that these statistics do not cover all known antibiotics isolated during the period studied because the data often do not reach publication in the case of isolation of the known compounds.

Despite the short coverage period (2018–2019), many new natural compounds mentioned in the review became the object of the full synthesis. In par-
ticular, peptaibols lipovelutibols B (24) and D (26) and their lipophilic analogs were obtained by the solid-phase method [334]. Terpenoids insulicilide (354) and 14-$O$-acetylinsulicilide (355) and their analogs were synthesized by the enantioselective metal-catalyzed assembly of the driman core followed by oxidative degradation and functionalization [335]. We should also mention the counter synthesis of the indole alkaloid misszrtina A (294) [241].

The generalized data show that many new secondary metabolites were isolated from extremophilic micromycetes, although known antibiotic compounds make up a high proportion. In other words, only studying extreme and hard-to-reach habitats does not solve the rediscovery problem of known antibiotics. Many of the known compounds isolated according to the bioactivity screening have been obtained from different producers many times. For example, antibiotic anthraquinone emodin (35) was developed and characterized seven times during the period considered [61, 73–79]. The use of the modern omics approaches and prioritization and dereplication strategies [336] can significantly increase the efficiency of the study of natural compounds including those from extremophilic econiches, thus avoiding the resource overuse for the isolation of known compounds. In this case, extremophilic microorganisms may have a high potential as sources of new drugs because of the high diversity of chemical structures and biological activities of secondary metabolites of these microorganisms.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving animals or humans as research subjects.

Conflict of Interests

The authors state that they have no conflict of interest.

ADDITIONAL INFORMATION

Review article of the winners of the Russian Foundation of Basic Research competition “Expansion”, 2019.

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