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REVIEW ARTICLE

Antibiotics from Extremophilic Micromycetes

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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 econiches 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-

Abbreviations: AV, antiviral activity; AB, antibacterial activity; AF, antifungal activity; CT, cytotoxic activity; AP, antiprotozoic activity; AT, antituberculosis activity; Ref., literature references (2018–2019); Cpd, serial number of the compound; MRSA, meticilllin-resistant *Staphylococcus aureus*; MRSE, meticilllin-resistant *S. epidermidis*; EC_{50}, half-maximal effective concentration; IC_{50}, half-maximal inhibitory concentration; MIC, minimum inhibitory concentration; Me, methyl.

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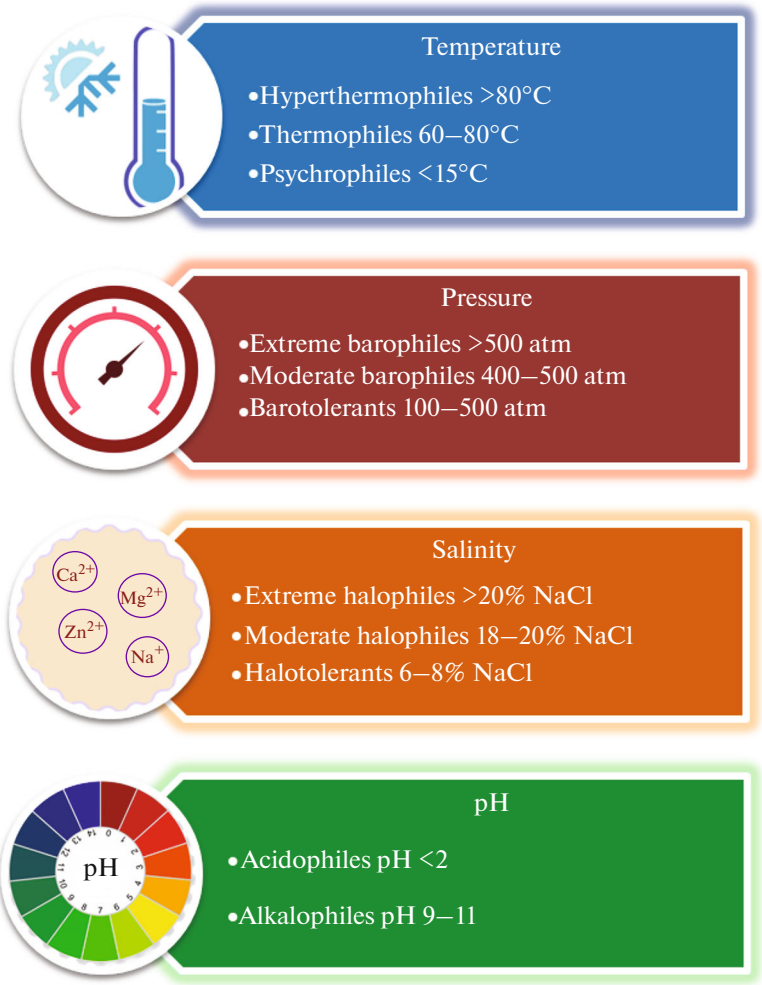


Fig. 1. Common adaptation factors for extremophiles.

ditions. 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].

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, xanthones, 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 N^5-hydroxy-N^5-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 AB	**IC_{50} 23.0–50 μM** (HCT-116, HepG2, MCF-7)	[37]
7				**IC_{50} 38.9–102 μM** (HCT-116, HepG2, MCF-7)	
8	*Penicillium* sp. *Penicillium* sp. SCSIO 06720	Deep-sea Marine 4762 m	CT AB	**IC_{50} 94.0–114 μM** (HCT-116, HepG2, MCF-7) **MIC 0.10–0.13 μg/mL** (*Vibrio anguillarum*) [58]	[37] [59]
9	*Penicillium crustosum* HDN153086	Antarctica	CT	**IC_{50} 12.7 μM** (K562)	[40]
10	*Aspergillus ochraceus*	Marine	CT	**IC_{50} 3.0 μM** (A2780)	[42]
11	*Aspergillus sydowii* SP-1	Antarctica	AB	**MIC 0.12–1.0 μg/mL** (*Staphylococcus aureus*, MRSA, *S. epidermidis*, MRSE)	[44]
12	*Penicillium chrysogenum* MCCC 3A00292	Deep-sea 2076 m	CT	**IC_{50} 7.81–8.34 μM** (BEL-7402, BIU-87K562)	[46]
13	*Talaromyces purpurogenus*	Marine	CT	**IC_{50} 8.29–9.71 μM** (A-549, HL-60) [55]	[54]
14	*Penicillium granulatum* MCCC 3A00475	Deep-sea 2284 m	CT AB	**IC_{50} 19.5 μM** (HepG2)	[47]
15				**Qualitative AB activity (***Bacillus coagulans* IMM 311, *B. licbeniformis* IMM 308, *B. megateriurn* DSM 32, *B. subtilis* IMM 313, *B. cereus* IMM 307, *B. stearotberrnopbilus* DSM 22, *Mycobacterium phlei* IMM 255, *S. aureus* IMM 257, *Micrococcus luteus* DSM 348, *M. caseolyticus*) [48]	
16				**IC_{50} 13–33.6 μM** (BEL-7402, A-549, MOLT-4, HL-60) [49]	
17				**IC_{50} 7 μM** (HepG2)	
18	*Penicillium* sp. TJ403-1	Marine	CT	**IC_{50} 18.41–21.77 μM** (A-549, HL-60)	[51]
20	*Eurotium* sp. SCSIO F452	Marine	CT	**IC_{50} 12.5–15.0 μM** (SF-268, HepG2)	[53]
21				**IC_{50} 30.1–37.3 μM** (HepG2, SF-268)	
22	*Trichoderma velutinum*	At an altitude of about 800 m above sea level, India/ Psychrotolerant	CT	**IC_{50} 30 μM** (A549)	[56]
23				**IC_{50} 2–30 μM** (HL-60, MDA-MB-231, A549)	
24				**IC_{50} 16–17 μM** (HL-60, MDA-MB-231, A549)	
25				**IC_{50} 4–7 μM** (HL-60, MDA-MB-231, A549, LS-180)	
26	*Emericellopsis alkalina*	Lake Zhaltyr, Kulunda steppe, Russia/ Haloalkalophilic	CT AB AF	**EC_{50} 2.8 μM (**HepG2) **MIC 4–32.5 μg/mL** (*Bacillus cereus* ATCC 14893, *S. aureus* FDA 209 P, *Listeria monocytogenes* EGDe) **MIC 2–4 μg/mL** (*Candida sp.*, *Aspergillus* sp.)	[57]

log, fusaperazin 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 brevicompanine 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-methoxyspirotrypostatin B (**13**) isolated from the culture fluid of the *Talaromyces purpurogenus* 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., lipovelutibols A–D (**22**–**25**) [56] and emericellipsin A (**26**) [57] have been isolated from extremophilic micromycetes. Features of lipovelutibols 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 (lipovultibols 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.

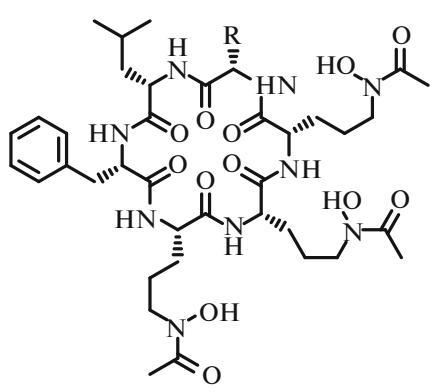
2. POLYKETIDES, XANTHONOIDS AND RELATED COMPOUNDS

2.1. Quinones

Polyketides, which can be assigned to quinones, were quite widely represented among the secondary metabolites of extremophilic 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].

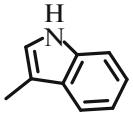
Other isolated anthraquinones were previously described compounds, for some of which the biological activity was detected or clarified. For example, in addition to the new anthraquinone (**30**), damnacanthal (**31**) [65], xanthopurpurin (**32**) [66], 6-hydroxyrubiadin (**33**) [67], and emodin (**34**) [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-

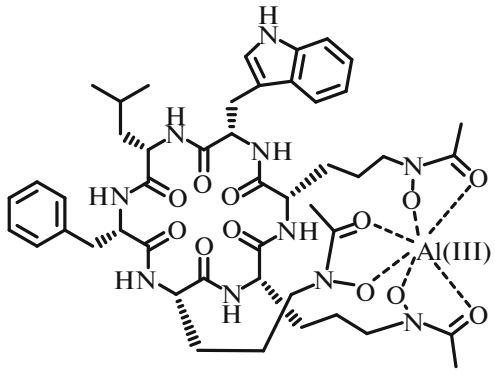


Acremonpeptides A–D
(1) R = CH_2OH
(2) R = Me
(3) R = A
(4) R = B

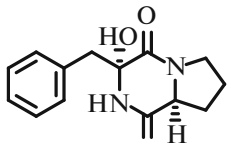
A =

B =

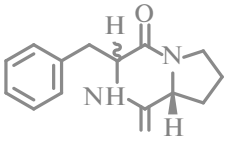




Al(III)-Acremonpeptide D
(5)

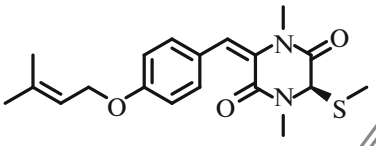


Penicillatide B
(6)

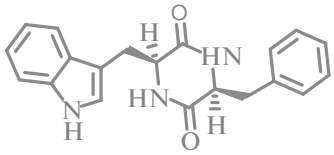


Cyclo-(D-Pro-L-Phe)
(7)

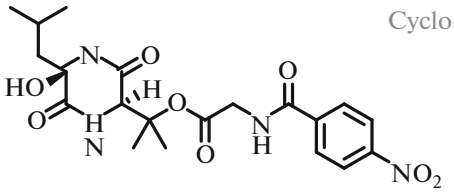
Cyclo-(D-Pro-D-Phe)
(8)



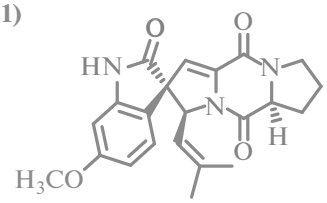
Fusaperazine F
(9)



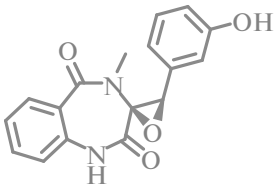
Cyclo-(L-Trp-L-Phe)
(11)



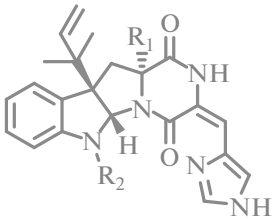
Waspergillamide B
(10)



6-Methoxyspirotryprostatin B
(13)

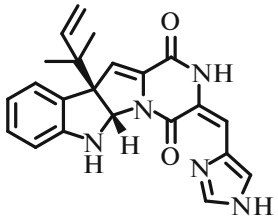


Cyclopenol
(12)

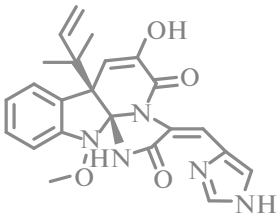


Roquefortine C
(15) R_1 = H, R_2 = H

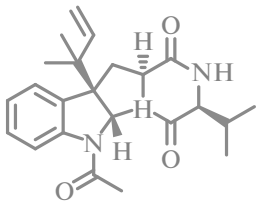
Roquefortine F
(16) R_1 = H, R_2 = OCH_3



Roquefortine J
(14)



Meleagrin
(17)



Brevicompanine G
(18)

Fig. 2. Cyclic peptides and diketopiperazines.

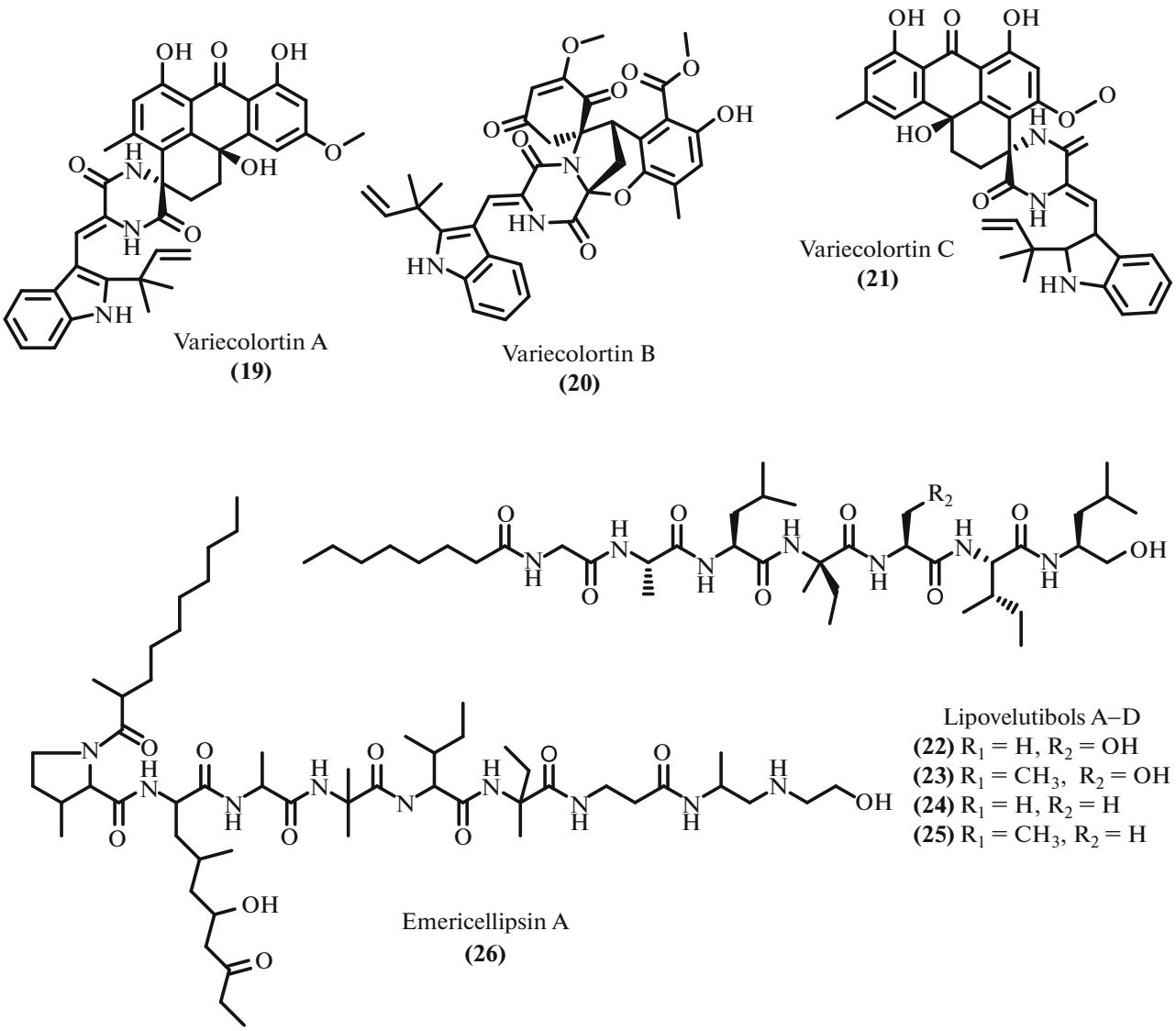


Fig. 3. Linear peptides and mixed diketopiperazines.

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] **MIC 6.25 μg/mL** (*Streptococcus pyogenes* 308A) [84]	[83]
28				**IC_{50} 3.04–3.88 μg/mL** (A549, SK-OV-3, SK-MEL-2, XF498, HCT15) [84] **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]	
29				**MIC 8–16 μg/mL** (*Bacillus subtilis*) [85] **MIC 16–32 μg/mL** (*Fusarium solani*) [85]	
42				**IC_{50} 22.39 μg/mL** (XF498) **Qualitative AB activity** (*S. aureus*)	
43				**Qualitative AB activity** (*S. aureus*)	
44	*Aspergillus ochraceus*	Marine	CT	**IC_{50} 5 μM** (A2780) **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*) **MIC 31.3 μg/mL** (*Pseudopestalotiopsis theae*)	[60]
39				**MIC 15.6, 7.81, 7.81 μg/mL** (*E. carotovora, P. syringae pv. lachrymans, A. avenae*) **MIC 31.3 μg/mL** (*P. theae*)	
51	*Fusarium napiforme*	Mangrove	AB	**MIC 6.3, 6.3 μg/mL** (*S. aureus* NBRC 13276, *P. aeruginosa* ATCC 15442)	[93]
52				**MIC 12.5, 6.3 μg/mL** (*S. aureus* NBRC 13276, *P. aeruginosa* ATCC 15442)	
53				**MIC 6.3, 6.3 μg/mL** (*S. aureus* NBRC 13276, *P. aeruginosa* ATCC 15442)	
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*)	[63]
41				**MIC 32, 16, 64, 1, 4, 32 μg/mL** (*E. coli*, *Micrococcus luteus*, *V. vulnificus*, *V. alginolyticus*, *Edwardsiella ictaluri*, *V. parahaemolyticus*)	
30	*Aspergillus versicolor*	Deep-sea 2869 m	AB CT	**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. rotiferianus* MCCC E385, *V. campbellii* MCCC E333)	[61]
31				**MIC 62.5, 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)	
32				**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)	
33				**IC_{50} 1.3 μg/mL (**PRL-3) [67]	

Table 2. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
34	*Aspergillus versicolor* *Penicillium* sp. *Cochliobolus lunatus* *Aspergillus fumigatus* *Aspergillus sydowii* *Penicillium* sp. *Aspergillus candidus* *Aspergillus* sp.	Deep-sea 2869 m Hot spring deposits (45–65°C), Saudi Arabia/ Thermophile Marine Marine Deep-sea 4950 m Marine Marine Marine	AT AB CT	**MIC 1.25 μg/mL** (BCG) [75] **MIC 15.6, 15.6, 31.3, 62.5 μg/mL** (MRSA ATCC 43300, MRSA CGMCC 1.12409, *V. vulnificus* MCCC E1758, *V. campbellii* MCCC E333, *V. rotiferianus* MCCC E385) [61] **MIC 12.5 μg/mL** (*P. aeruginosa*) [73] **MIC 50 μg/mL** (*S. aureus*, MRSA) [75] **MIC 16.1, 15.4, 15.7 μg/mL** (*V. vulnificus* MCCC E1758, *S. aureus* ATCC 43300 (MRSA), *S. aureus* CGMCC 1.12409 (MRSA)) [77] **MIC 16, 64, 32 μg/mL** (*S. aureus* ATCC 25923, *E. faecalis* ATCC 29212, *S. aureus* ATCC 25923) [71] **IC_{50} 2 μM (**HTB-176) [73] **IC_{50} 1.7–5.6 μM** (HepG-2, SGC7901) [76] **IC_{50} 27.1 μM (**HeLa) [77] **IC_{50} 23.8–65.2 μM (**HL-60, BEL-7402, A-549) [70]	[61] [73] [76] [75] [77] [78] [79] [74]
35	*Aspergillus* sp.	Marine	CT	**IC_{50} 73.2 μM** (HL-60) [70]	[74]
36	*Penicillium sp.* ZZ901	Marine	CT AB	**IC_{50} 34.68 μM** (U87MG glioma cells) **IC_{50} 30.22 μM** (C6)	[94]
45 **48**	*Alternaria* sp. SCSIO41014	Marine	CT	**IC_{50} 8.75–26.58 μg/mL** (K562, SGC-7901, BEL-7402) **IC_{50} 19.67 μg/mL** (K562)	[87]
49	*Alternaria* sp. *Alternaria alternata* L3111'	Marine	AB CT	**MIC 1.95 μg/mL** (*Clavibacter michiganensis*) [60] **IC_{50} 2.4–3.1 μg/mL** (A-549, HCT-116, HeLa) [88]	[60] [88]
47	*Alternaria* sp. SCSIO41014 *Alternaria alternata* L3111'	Marine	AV	**IC_{50} 1.42–2.2 μM** (HIV-1) [95]	[87] [88]
50	*Alternaria* sp. SCSIO41014 *Alternaria* sp. *Alternaria alternata* L3111'	Marine	AF	**MIC 7.81 μg/mL** (*P. theae*) [60] **MIC 125 μg/mL** (*A. brassicicola*) [60]	[87] [60] [88]
37	*Aspergillus candidus* KUFA0062	Marine	AV	**EC_{50} 0.21, 0.02 μg/mL** (Poliovirus type 2, Poliovirus type 3, Coxsackievirus type A21, Coxsackievirus type B4, Human rhinovirus type 2, Ross River virus, Herpes simplex virus type 1) [82]	[79]

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-epi-stemphytriol (**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-

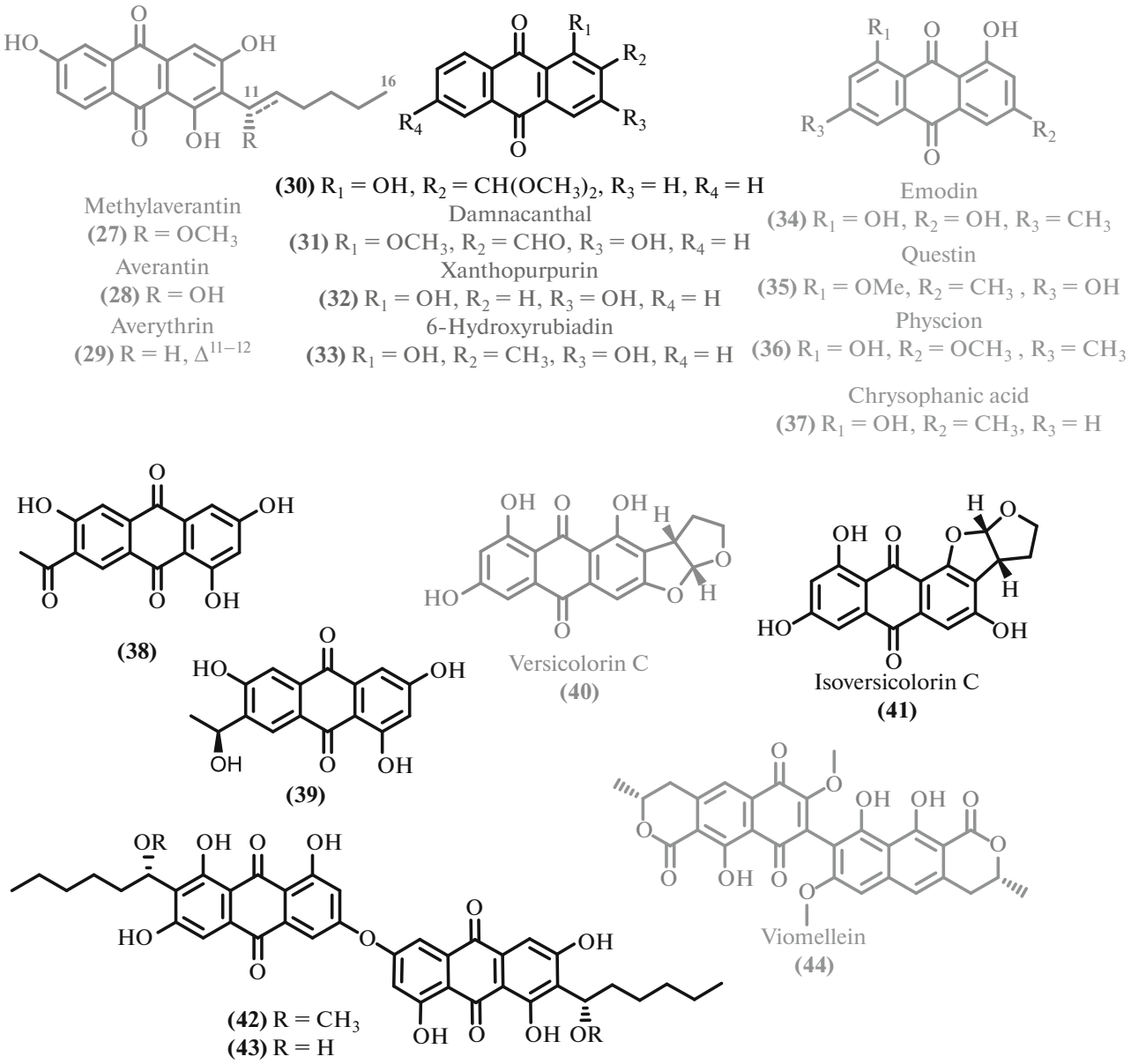


Fig. 4. Anthraquinones and dimeric quinones.

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 dihydroxanthenones (**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-chlorthajixanthone (**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

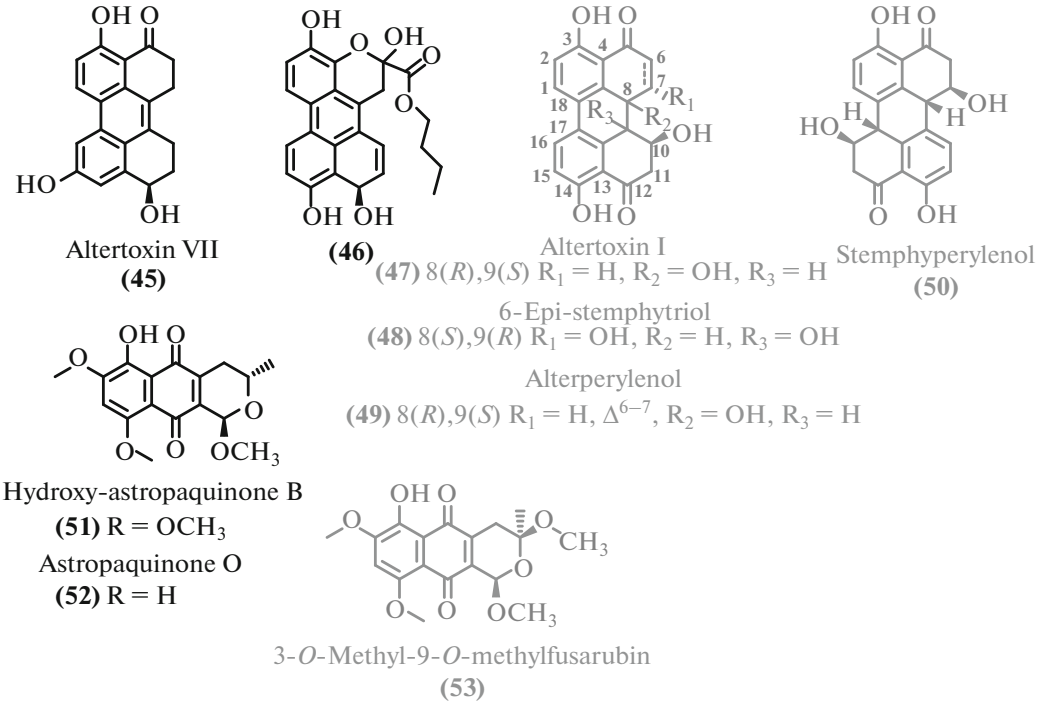


Fig. 5. Perylenequinones and naphtoquionones.

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 seafloor 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* C1-S01-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*-acylated) analogs. Thus, the dihydroxyxanthenone 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. Seafloor 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, (2*S*)-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., pyanochromone (**76**), spirofuranochromone (**77**), and 7-hydroxy-6-methoxy-4-oxo-3-[(1*E*)-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-ribosyl-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	EC_{50}, IC_{50}, MIC	Ref.
54	*Aspergillus versicolor*	Marine	CT	**IC_{50} 11.25–17.36 μg/mL** (A-549, SK-OV-3, SK-MEL-2, XF498) **IC_{50} 1.86–4.61 μg/mL** (A-549, SK-OV-3, SK-MEL-2, XF498, HCT15) [84]	[83]
69 **71**	*Aspergillus versicolor* MF160003	Marine	AT	**MIC 20 μg/mL** (BCG) **MIC 40 μg/mL** (BCG)	[100]
85	*Penicillium oxalicum*	Marine	CT AB AF	**IC_{50} 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* CPI 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	CT	**IC_{50} 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] [121]
87	*Penicillium erubescens* KUFA0220	Marine	AB AF CT	**MIC 64.0, 64.0 μg/mL** (*Enterococcus faecalis* ATCC 29212, MRSA) **MIC 12.5, 25.0, 12.5, 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] **IC_{50} 0.63, 1.05 μg/mL (**KB, KBv200)	
84				**MIC 64 μg/mL** (*Enterococcus faecalis* ATCC 29212) **MIC 6.25, 6.25, 0.78, 6.25, 6.25, 3.13, 1.56, 3.13, 6.25 μg/mL** (*S. cerevisiae* IFO 0203, *C. albicans* IFO 1061, *C. utilis* ATCC 42402, *Schizosaccharomyces pombe* IFO 0342, *Hansenula anomala* IFO 0136, *Rhizopus chinensis* IFO 4745, *Mucor mucedo* IFO 5776, *Penicillium chrysogenum* IFO 4626, *A, niger* ATCC 6275) [115]	[114]
102				**MIC 64 μg/mL** (*Enterococcus faecalis* ATCC 29212) **LD_{99} 0.1 μg/mL (**NS-1) [129]	

Table 3. (Contd.)

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) [70] **MIC >50 μg/mL** (*T. metagrophytes* IFO-5811, *Candida albicans* IAM-4966, *Pyricularia orysae* IFO-5279, *A. fumigatus* IAM-2004, *Helminthosporium sesamum* IAM-5012) [125]	[74] [124]
91	*Pseudopestalotiopsis* sp. PSU-AMF45	Marine	AF	**MIC 200 μg/mL** (*Cryptococcus neoformans* ATCC 90112)	[102]
65				**MIC 200 μg/mL** (*Cryptococcus neoformans* ATCC 90112)	
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]	[96]
58				**MIC 1.56, 1.56, 3.12 μM** (*V. parahemolyticus*, *V. anguillarum*, *V. alginolyticus*)	
59				**MIC 6.25, 25.0, 25.0 μM** (*V. parahemolyticus*, *V. anguillarum*, *V. alginolyticus*)	
60				**MIC 3.12, 25.0, 12.5 μM** (*V. parahemolyticus*, *V. anguillarum*, *V. alginolyticus*)	
61				**MIC 12.5, 25.0, 12.5 μM** (*V. parahemolyticus*, *V. anguillarum*, *V. alginolyticus*)	
62				**MIC 6.25, 6.25, 12.5 μM** (*V. parahemolyticus*, *V. anguillarum*, *V. alginolyticus*)	
63				**MIC 25.0, 6.25, 25.0 μM** (*V. parahemolyticus*, *V. anguillarum*, *V. alginolyticus*)	
72	*Penicillium* sp. ZZ380 *Penicillium citrinum* SCSIO 41017	Marine	AF	**Qualitative AF activity** (*C. albicans, S. fimicola, A. furfuraceus*) [109]	[78] [108]
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*)	[124]
93				**IC_{50} 15.7 μg/mL (**A549)	
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_{50}, IC_{50}, MIC	Ref.
94 **95**	*Aspergillus* sp. YQ-13	Hydrothermal vent sediments, Kueishantao, Taiwan/Thermophile	AB	**MIC 860.8, 40.93 μg/mL (***P. aeruginosa*, *B. subtilis*) **MIC 394.1, 191.67, 58.21, 58.21 μg/mL (***P. aeruginosa*, *E. coli*, *B. subtilis*, MRSA)	[126]
66 **67** **68** **70** **56**	*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) **IC_{50} 32.7 μM** (HepG2) **MIC 32.6, 31.8 μg/mL** (MRSA ATCC 43300, MRSA CGMCC 1.12409) **IC_{50} 25.2–42.3 μM** (A549, HepG2, HeLa) **MIC 32.6 μg/mL** (*V. rotiferianus*) **IC_{50} 1.5 μM (**L5178Y) [107] **IC_{50} 37.7 μM** (A549)	[77]
99 **55**	*Penicillium chrysogenum* MCCC 3A00292	Deep-sea 2076 m	CT	**IC_{50} 10.21 μM (**BIU-87) **IC_{50} 15.94 μM (**BEL-7402)	[46]
80 **81** **82**	*Penicillium sp.* SCSIO 06720	Deep-sea 4762 m	CT AB AF	**IC_{50} 11.7–99.0 μM** (A375, A549, HeLa, HepG2, SW-620, L-02) [111] **MIC 10.4, 46.9 μg/mL** (*S. aureus* ATCC 29213, MRSA-shh-1) **IC_{50} 40.0, 50.0 μg/mL** (A549, HeLa) [112]	[59]
89	*Cochliobolus lunatus* SCSIO41401	Marine	CT AB	**IC_{50} 41.3–47.9 μM** (SF-268, MCF-7, HepG-2, A549, 786-O) **MIC 50.0, 25.0, 13.0 μg/mL** (*S. aureus*, *E. rhusiophthiae*, *P. multocida*) **IC_{50} 31.36 μg/mL** (L6) [123] **IC_{50} 8.07 μg/mL** (*P. falciparum* NF54) [123] **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*, *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] **IC_{50} 0.633 μg/mL** (*L. donovani*) [123] **IC_{50} 28.8 μg/mL** (*T. b. rhodesiense*) [123] **IC_{50} 14.41 μg/mL** (*T. cruzi*) [123]	[121]
109 **110** **96**	*Penicillium pinophilum* SCAU037	Mangrove	CT	**IC_{50} 0.2, 1.6 μM** (HL-60, CCRF-CEM) [131] **IC_{50} 20.0, 15.1 μg/mL** (KB, KBv200) [132] **IC_{50} 60 μg/mL** (HEp-2) [134] **Qualitative AF activity** (*R. solani* RT23 *R. solani* RT20, *F. solani* (Mart.) Appel et Wollenw., *Cylindrocladium scoparium* Morgan, *Alternaria alternata* (Fries) Keissl.) [133]	[130]
79	*Cladosporium* sp. OUCMDZ-302	Mangrove	CT	**IC_{50} 40 μM** (HL-60, SMMC-7721, A-549, MCF-7, SW480) [117]	[116]

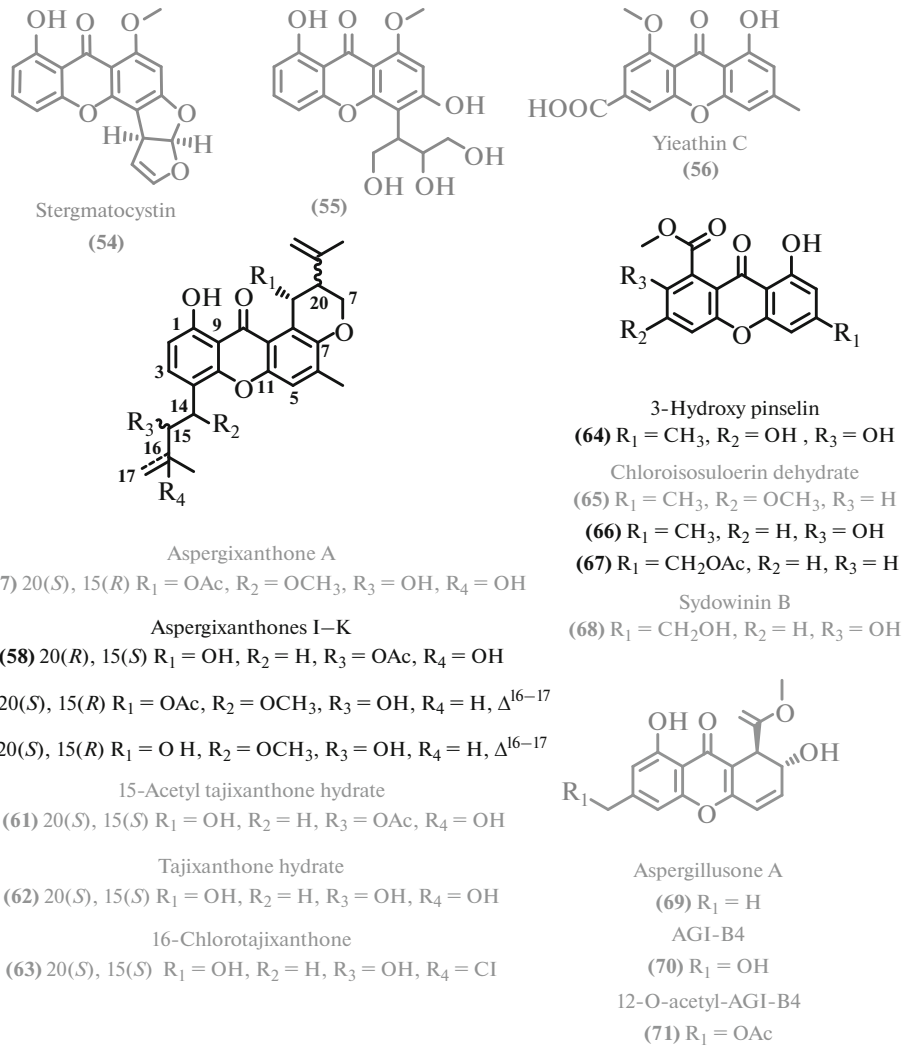


Fig. 6. Xanthones and dihydroxanthones.

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

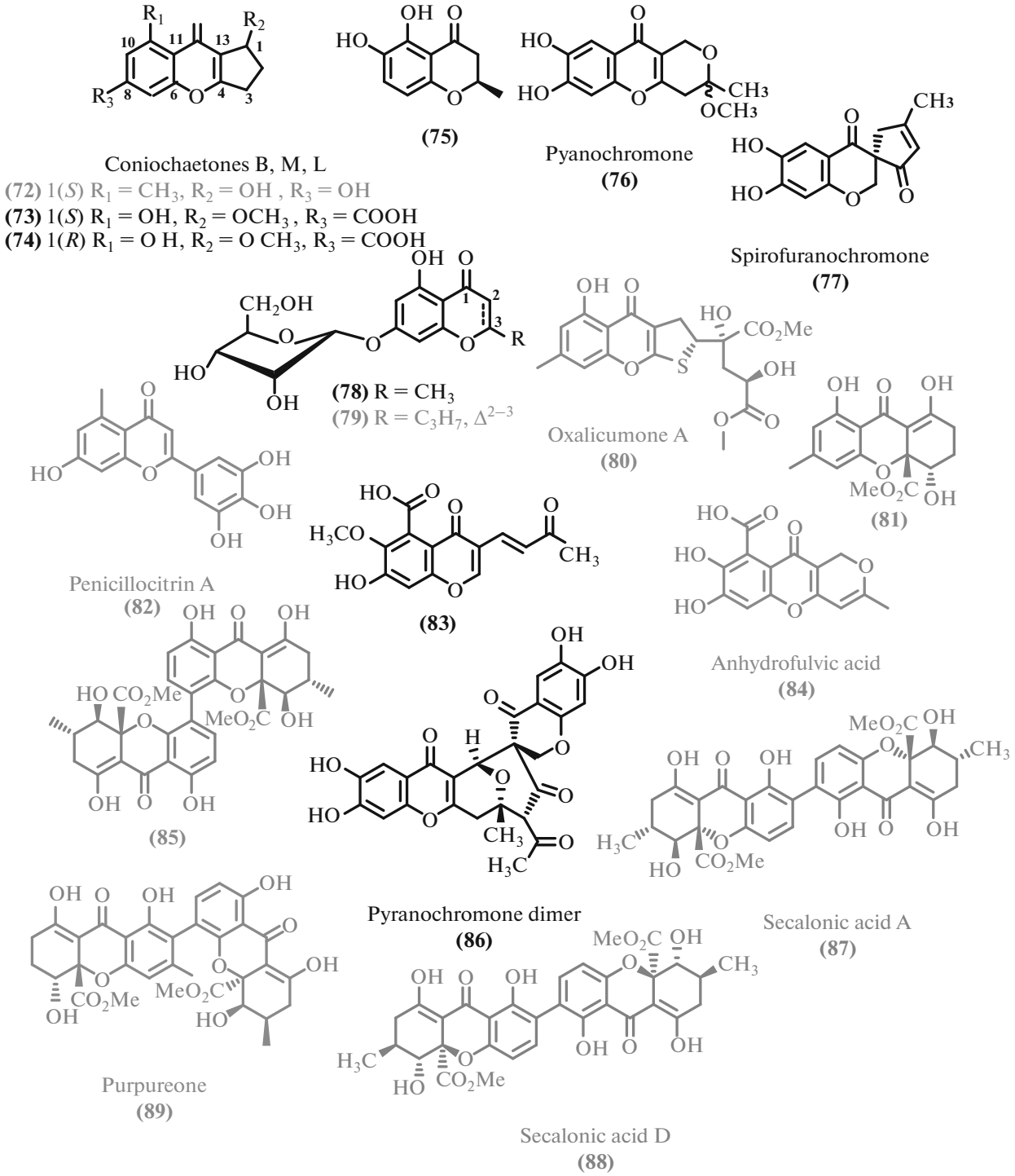


Fig. 7. Chromones and dimeric compounds.

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 *Pseudopestalotiopsis* genus [102].

In addition to discovery new benzophenones, the study of secondary metabolites of extremophilic micromycetes has led to the isolation of several structurally similar compounds. A new chromene, 1-hydroxy-12-methoxycitromycin (**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. Interestingly, peniciversiole A (**99**) showed cytotoxic properties 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., penisimplicissin (**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. Several 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 metabolites were aromatic compounds, i.e., phenalenones (**190**–**198**), grisane metabolites (**199**–**201**), and azaphilones (**202**–**222**). Linear polyketides with various side chains (**223**–**245**) and other polyketides (**246**–**257**) were also obtained.

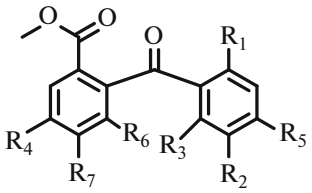
Isocumarins and their derivatives are common bioactive metabolites of micromycetes [135]. New isocoumarins were also isolated from mangrove micromycete *Ascomycota* sp. [136], endophyte *Pluchea indica*. This strain was the source of three new isocoumarins, i.e., dichlorodiaportin (**116**), desmethyldichlorodiaportin (**117**), and desmethyldichlorodiaportinol (**114**), along with several other well-known analogs, i.e., dichlorodiaportinol (**115**) [137], desmethyldichlorodiaportin (**119**) [138], and dichlorodiaportin (**120**) [139, 140]. Other isocoumarins with antibiotic activity turned out to have been be previously described. For example, the chemical study of mangrove endophyte *Phyllosticta capitalensis* [141] afforded the known isocoumarin derivative with antibiotic activity, 6,8-dihydroxy-5-methoxy-3-methyl-1*H*-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 extremophilic micromycetes belong to dihydroisocoumarins. A new isocumarin derivative, pestalotiopisorin B (**121**) with moderate antibacterial activity, was isolated from the *Pestalotiopsis* strain of mangrove origin [145]. Another new dihydroisocoumarin, nordihydroaltenuene A (**123**), and known bioactive analogs, i.e., (–)-3-*O*-acetylaltenuene (**126**) [143, 146], altenusin (**155**) [147], and dihydroaltenuene A (**127**) [148], were isolated in the study of the *Alternaria* sp. SCSIO41014 strain [87]. Several known dihydrocoumarins were obtained from other sources. (3*R*,4*S*)-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].

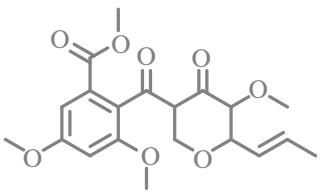
In addition to isocumarin derivatives, a series of lactones of various natures were isolated when studying extremophilic micromycetes (Fig. 10). Of the new lactones, four new unusual sulfur-containing compounds should be noted, which were isolated from the mangrove *Cladosporium* micromycete [152]. The 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 macrolides and known pandangolide 3 (**129**) allowed to revise its structure and clarify the attachment site of the side sulfide chain. Another new 10-membered lactone decarestrictine Q (**135**), an analog of decarestrictin 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 derivative, botryorhodine I (**141**), and eight known compounds were isolated from the soil mangrove micromycete *Lasiodiplodia theobromae* M4.2-2 [156]. Several other antibiotics were also found, i.e., antifungal and cytotoxic botryorhodines 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, purpurogenic 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 previously described biologically active lactones were obtained. A well-known aromatic lactone, 8-dimethoxy-10-methoxy-ventiquinone C (**137**), was iso-

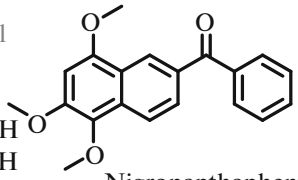


Sulochrin
(90) R_1 = OH, R_2 = H, R_3 = OH, R_4 = OH, R_5 = CH_3, R_6 = OCH_3, R_7 = H



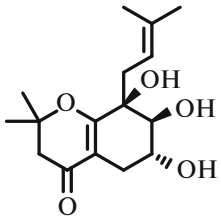
3-*O*-Methylfunicon
(96)

Chloroisosulochrin
(91) R_1 = OH, R2 = H, R_3 = OH, R_4 = OCH_3, R_5 = CH_3, R_6 = OH, R_7 = Cl

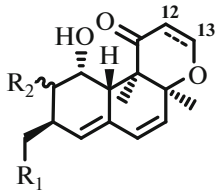


Penibenzophenones A, B
(92) R_1 = OH, R_2 = Cl, R_3 = OCH_3, R_4 = CH_3, R_5 = OCH_3, R_6 = OH, R_7 = H
(93) R_1 = OCH3, R_2 = H, R_3 = OH, R_4 = CH_3, R_5 = OCH_3, R_6 = OH, R_7 = H
(94) R_1 = OCH_3, R_2 = H, R_3 = OH, R_4 = OCH_3, R_5 = CH_3, R_6 = OH, R_7 = H
(95) R_1 = OCH_3, R_2 = H, R_3 = OH, R_4 = OH, R_5 = CH_3, R_6 = OCH3, R_7 = Cl

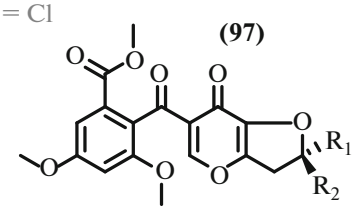
Nigronapthaphenyl
(97)



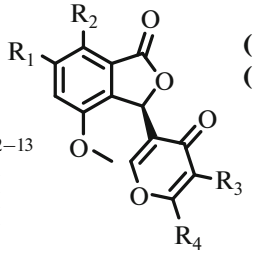
Pseudopestalone
(98)



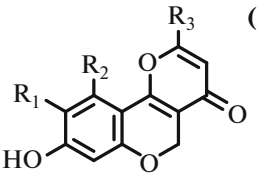
Peniciversioles A–C
(99) R_1 = OH, R_2 = H, Δ^{12-13}
(100) R_1 = OH, R_2 = H
(101) R_1 = H, R_2 = OH



Pinophilones A, B
(104) R_1 = H, R_2 = Me
(105) R_1 = Me, R_2 = H



Pinophilones C–E
(106) R_1 = OH, R_2 = R_3 = H, R_4 = *n*Pr
(107) R_1 = OH, R_2 = H, R_3 = OMe, R_4 = *n*Pr
(108) R_1 = OH, R_2 = OMe, R_3 = H, R_4 = propenyl



Citromycin
(102) R_1 = OH, R_2 = H, R_3 = Me

1-Hydroxy-12-methoxycitromycin
(103) R_2 = OMe, R_2 = H, R_3 = Me

Penisimplicissin
(109) R_1 = OMe, R_2 = R_3 = H, R_4 = Me

Methoxyvermistatin
(110) R_1 = OMe, R_2 = H, R_3 = OMe, R_4 = propenyl

Fig. 8. Benzophenones and other related compounds.

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 penicillide (**138**) [161] isolated from mangrove soil producer *Penicillium pinophilum* SCAU037 [130], nodulisporone A (**146**) [162] found in the study of deep micromycete [59], and asperdemin (**133**) [163] isolated 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 secondary metabolites of the *Zopfiella marina* strain [164]

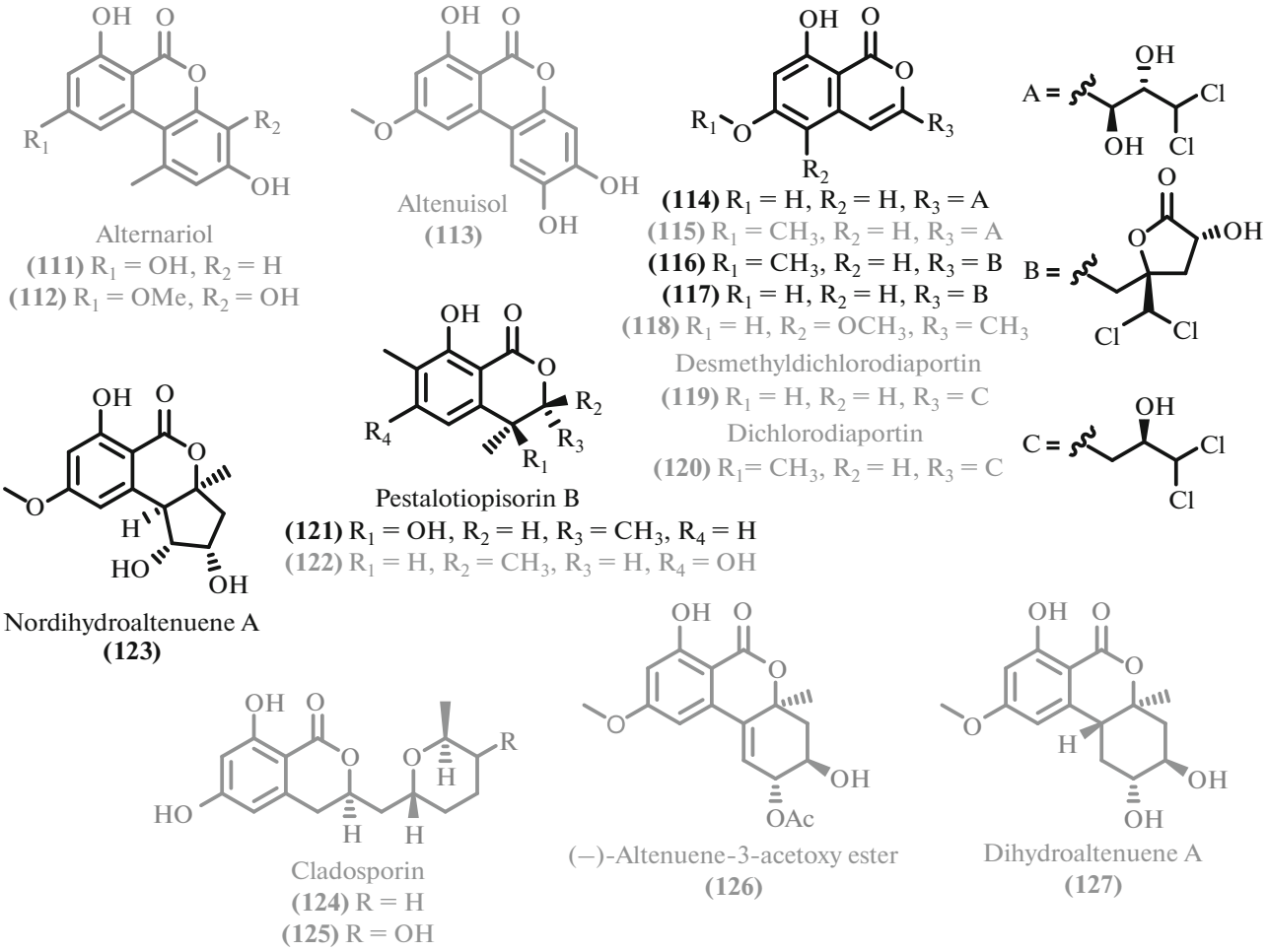


Fig. 9. Isocoumarins and dihydroisocoumarins.

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 sea-floor 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 dioxoauroglaucin (**156**) was isolated from mangrove fungus *Aspergillus* sp. AV-2 [170], along with its several known analogs, of which flavoglaucin (**157**) [171], previously

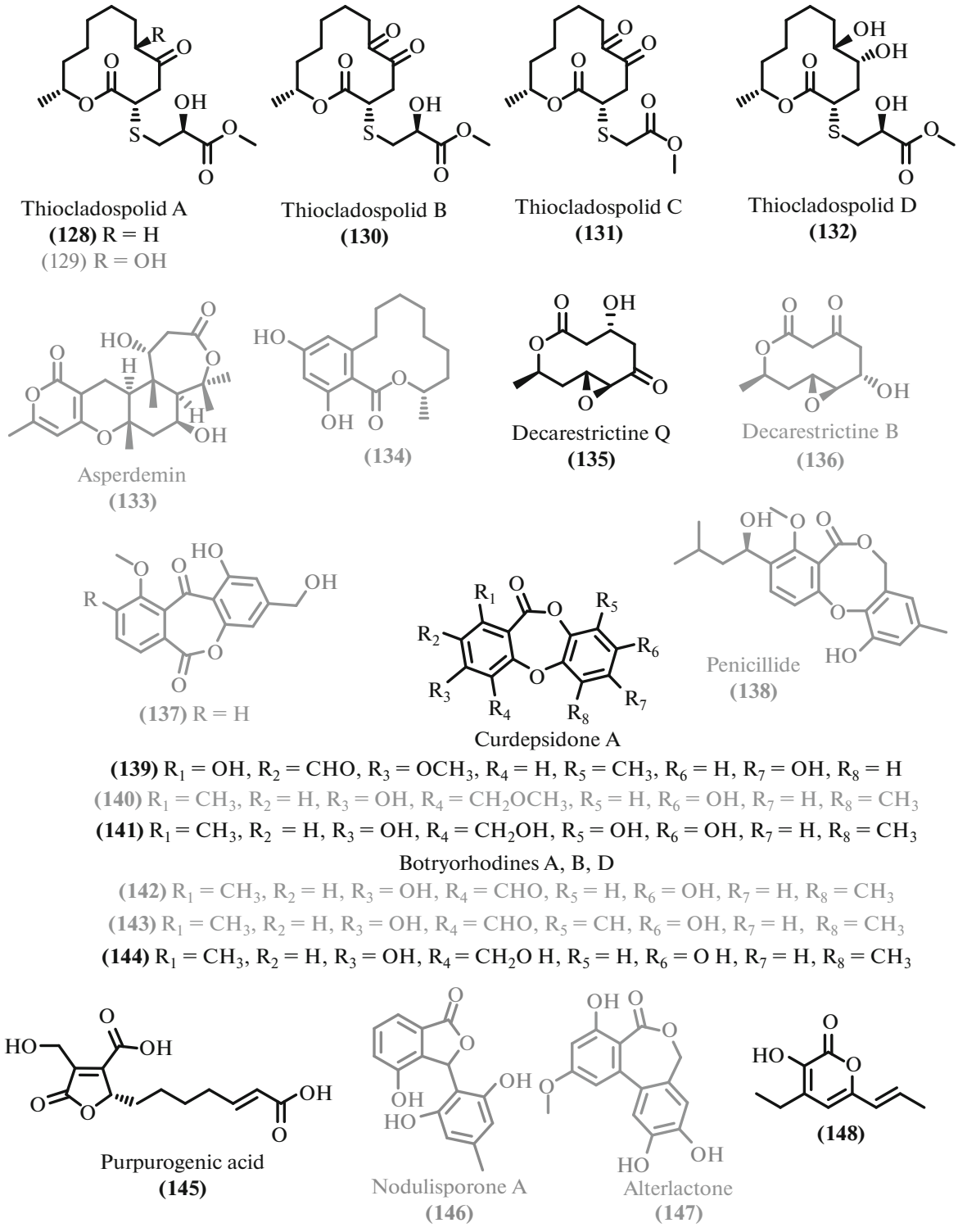


Fig. 10. Lactones.

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

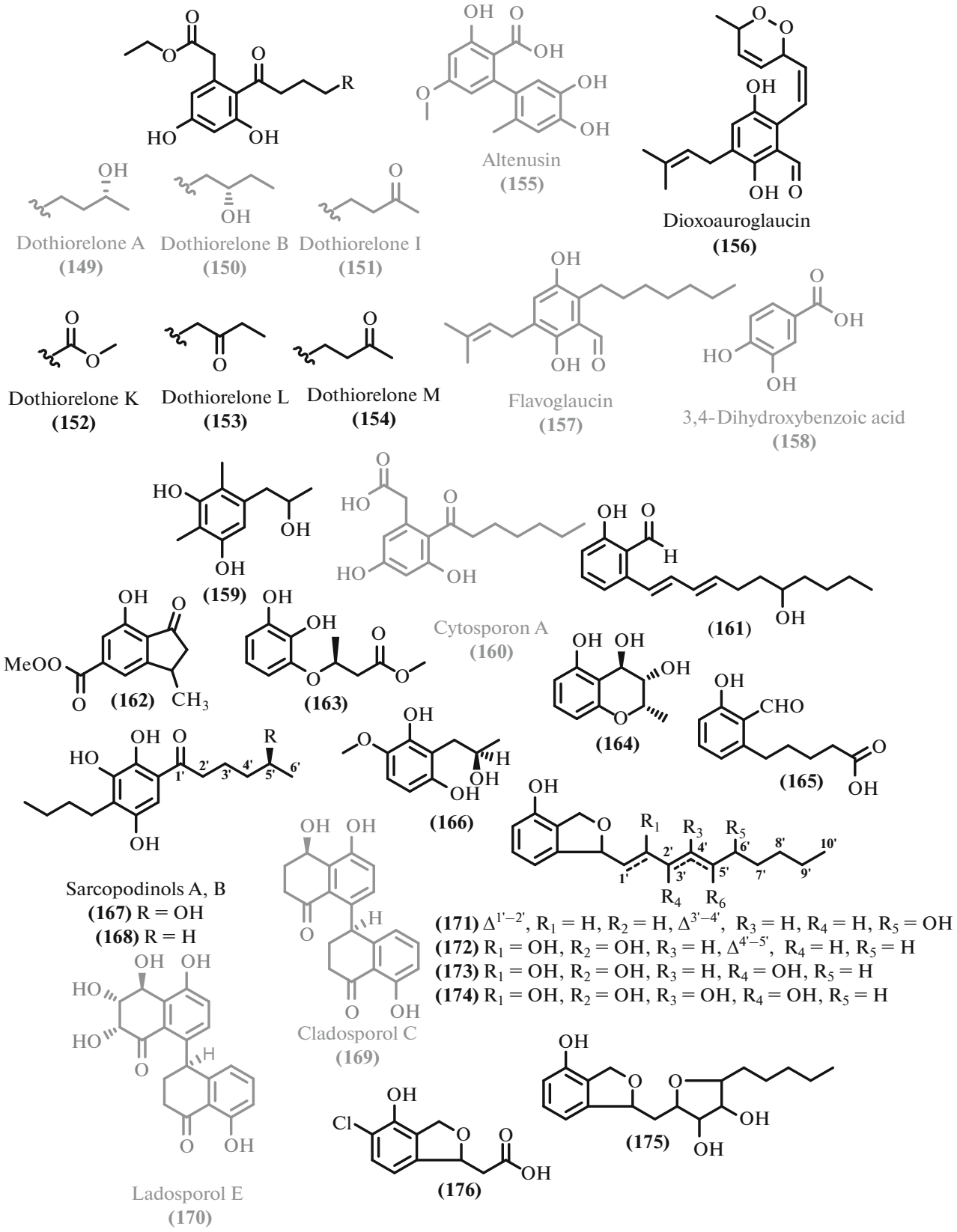


Fig. 11. Phenols.

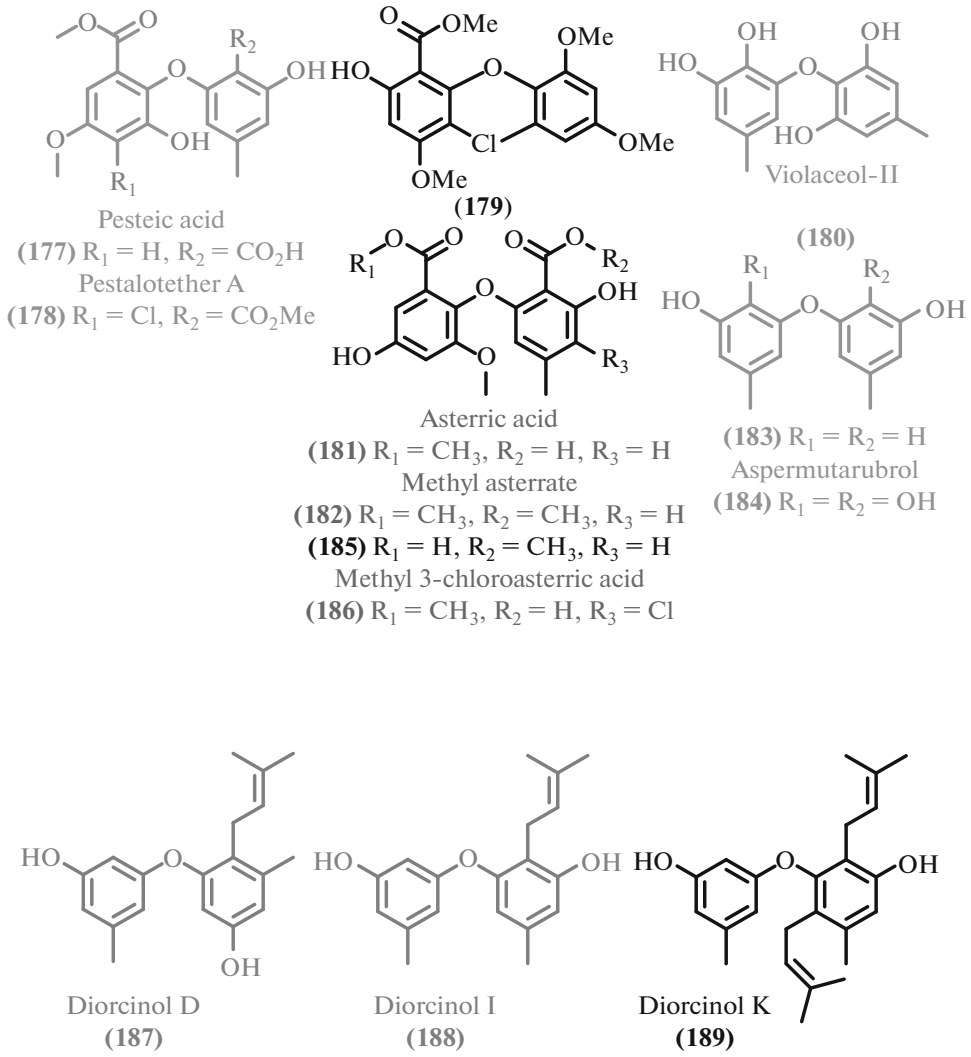


Fig. 12. Diphenyl ethers.

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 asperdemin (**133**) [163]. 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].

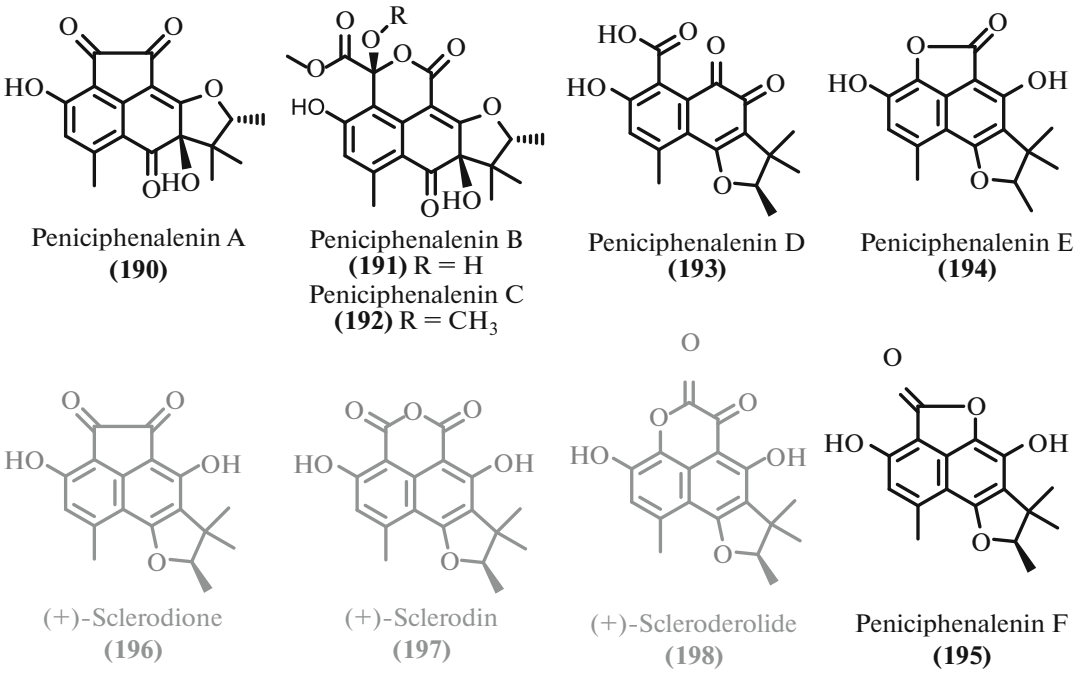


Fig. 13. Phenalenon derivatives.

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 azaphiolons, 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

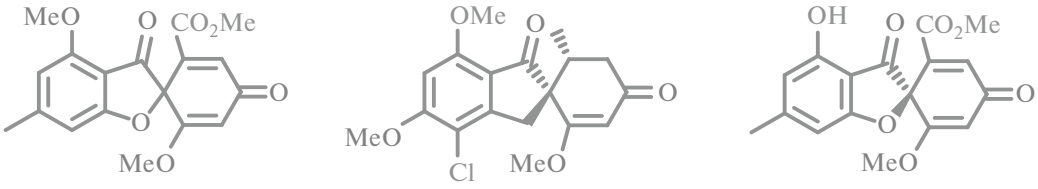


Fig. 14. Grisane-type compounds.

when studying a mangrove fungus of the *Cladosporium* genus [121]. Similar compounds, new polyketide xerucitrinin A (**219**), xerucitrinic 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 estremophilic micropicetes.

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 alkylresorcins, 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 cytotoxicity against several cell lines, whereas resorcinol A (**244**) was almost inactive ($GI_{50} > 50$ μM). New polyketidic metabolites, porosulfenols 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 micromycete isolated from *Penicillium crustosum* HDN153086 [40] in the Antarctic region appeared to produce a new polyene compound of unusual structure (**238**), which exhibited no biological activity. Another known linear polyketide, radiclonic acid (**236**) [210] was isolated from a seafloor fungus *Penicillium chrysogenum* MCCC 3A00292 [46].

Mangrove micromycete of the *Fusarium solani* genus H918 [211], along with antibiotic 1233B (**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 biosyinthesized 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, curvulaide 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.

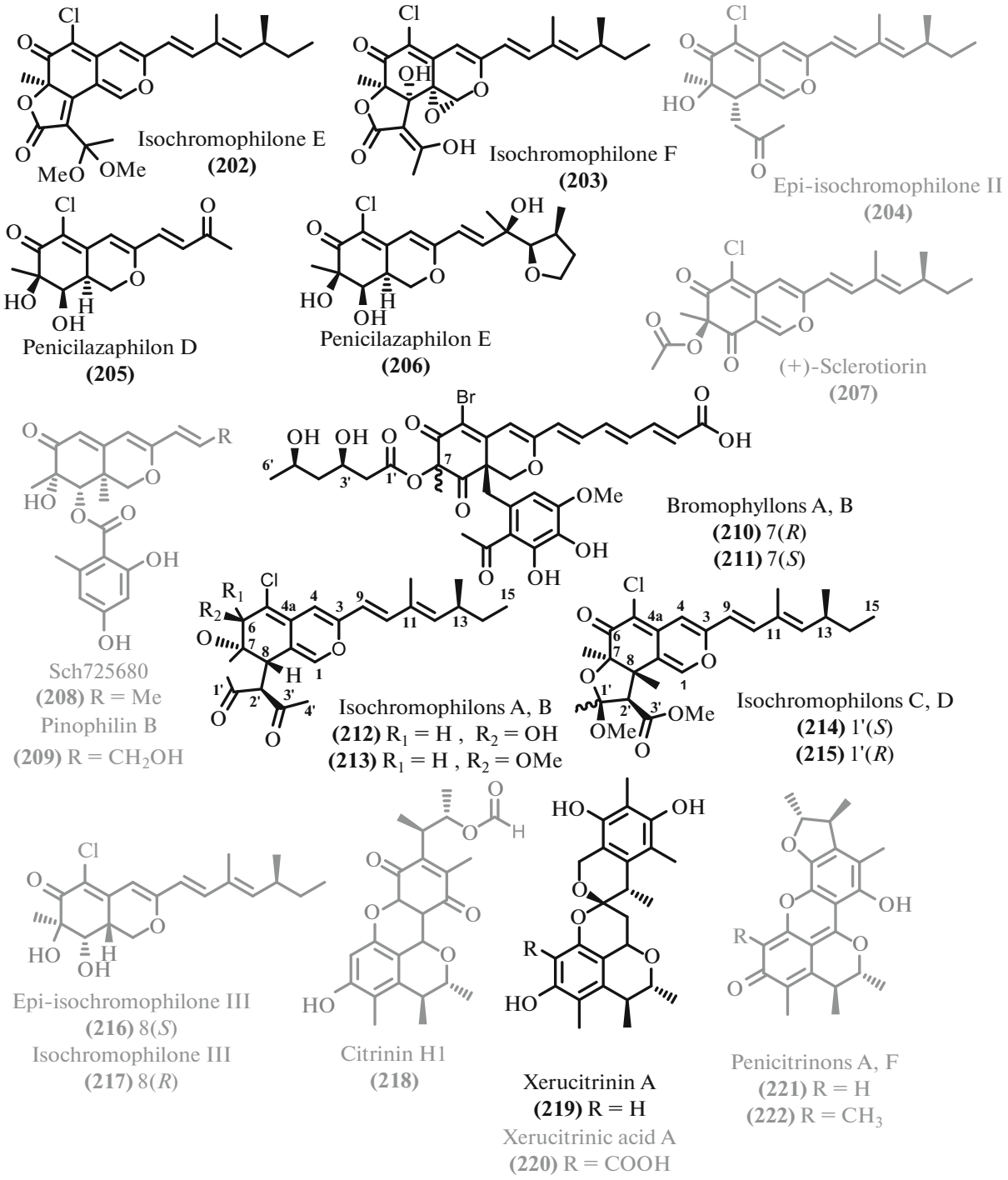


Fig. 15. Azaphions.

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 *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 sorbicillonoids group, bisvertinolone (**255**) [223].

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

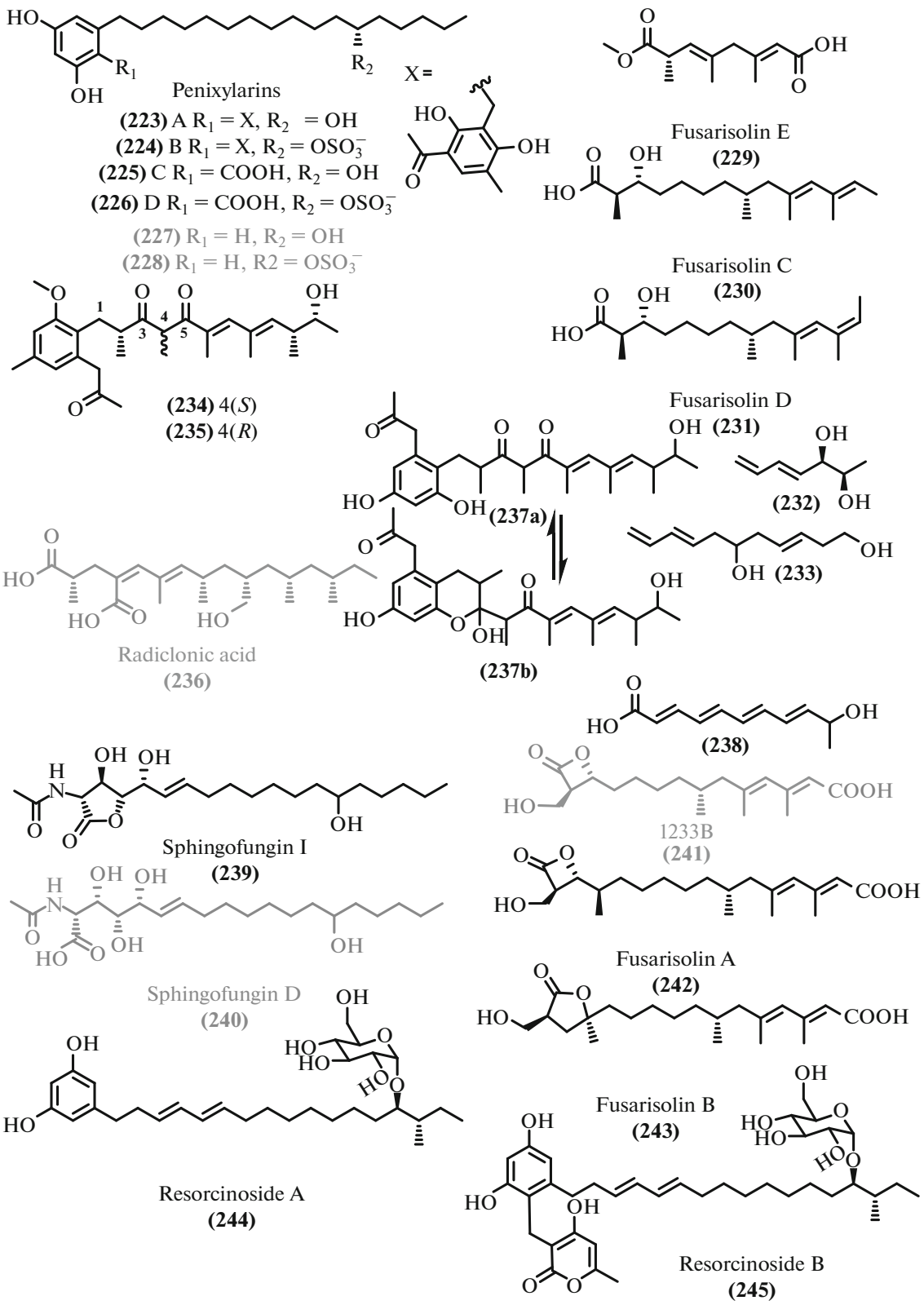


Fig. 16. Linear polyketides.

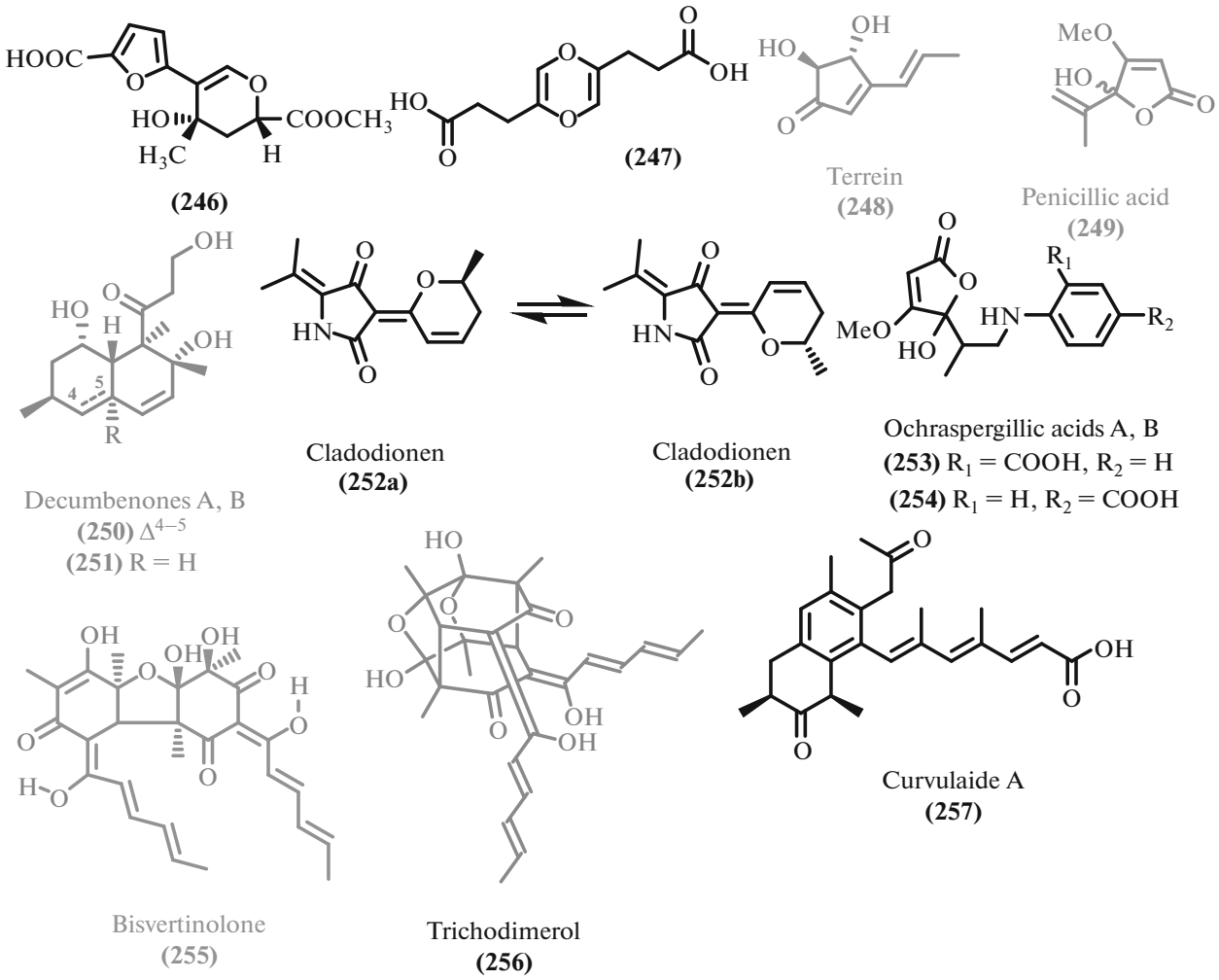


Fig. 17. Other polyketides.

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 pyrrospirone 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–**

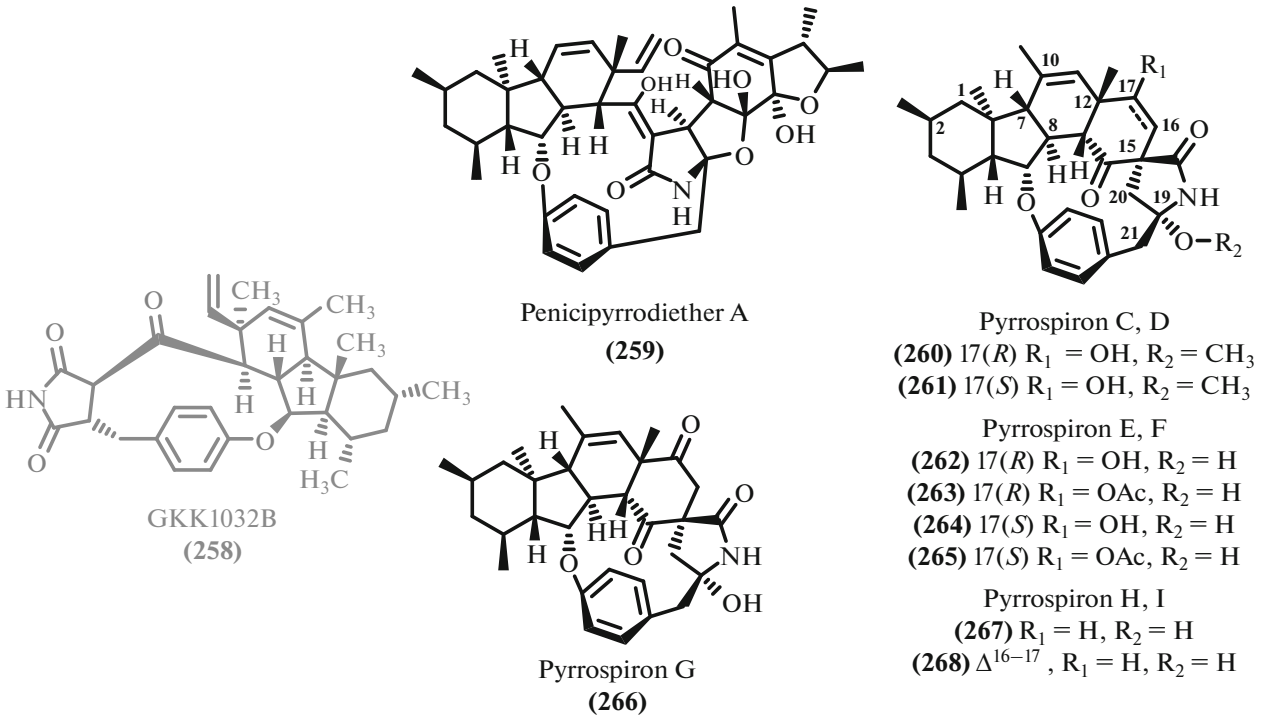


Fig. 18. GKK1032B, penicipyrrodiether A, and pyrrospirones.

278), 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 (**327**, **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, fumiquinazolines 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-hydroxynotoamide D (**287**), 17-*O*-ethylonotoamide M (**292**), 10-*O*-acetylsclerotoamide (**289**), 10-*O*-ethylsclerotoamide (**290**), and 10-*O*-ethylnotoamide R (**293**) [240].

The study of the relationship between the structure and cytotoxic activity of new indole alkaloid misszrtine 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, anthcolorins 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

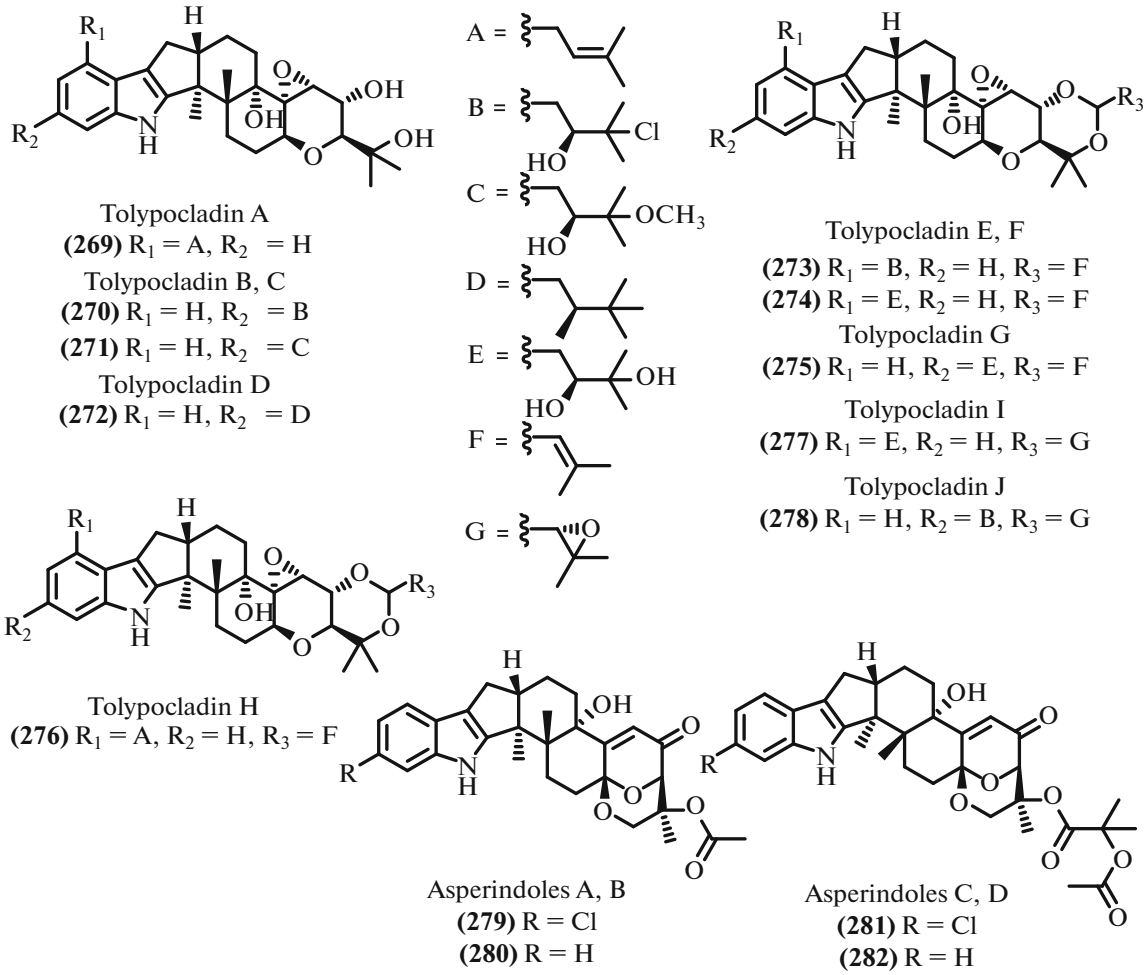


Fig. 19. Tolipocladins and asperindoles.

[246], along with a known analog, talaroconvolutin A (**315**) [247]. Interestingly, despite the same planar structure, only cladosporitin B (**314**) showed noticeable cytotoxicity.

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 acremolin 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 acremolin 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),

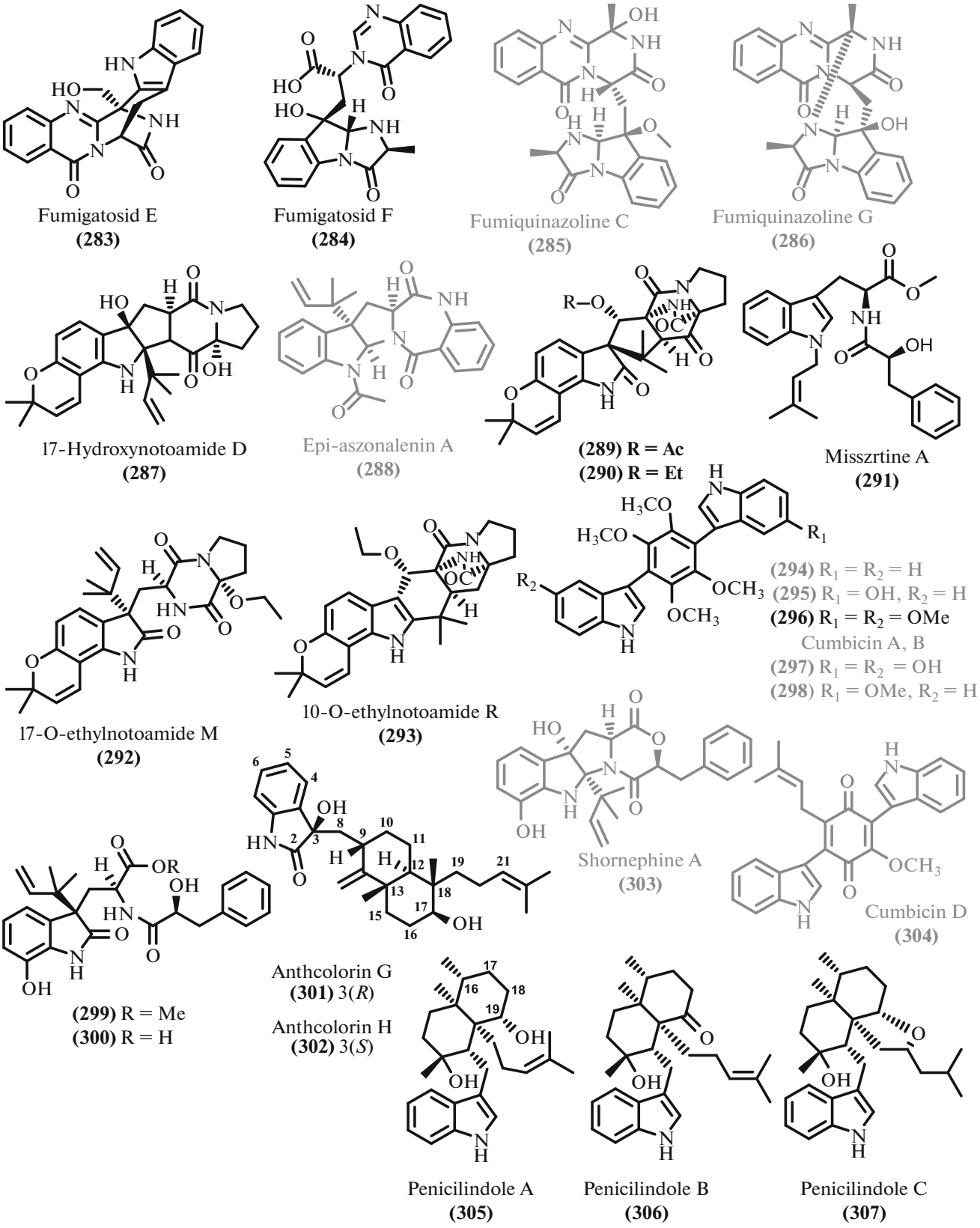


Fig. 20. Indoles and their derivatives.

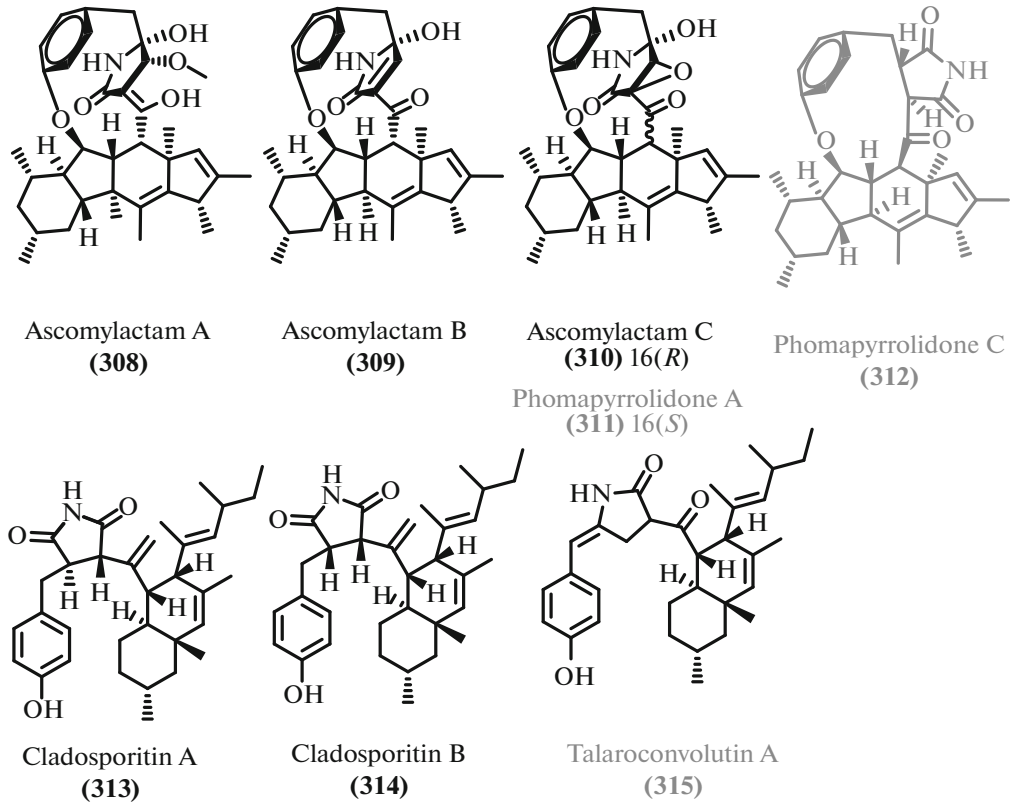


Fig. 21. Pyrrolidone and maleimide derivatives.

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 *Pseudopestalotiopsis* sp. PSU-AMF45 [102]. A new sesquiterpene (**337**) that did not show the antibiotic activity was isolated from a mangrove fungus of the *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 *Aspergillus flocculosus* [255]. All the isolated compounds showed strong cytotoxic activity.

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

Three new sesquiterpenes of the eremophylane type were isolated from marine fungus *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 *Cytospora* sp. was studied [260]. The authors of [261] isolated bicyclic sesquiterpene, seiricardine D (**356**), with no biological activity and determined the structure of eight known metabolites. The antibacterial activity was shown for (22*E*,24*R*)-5,8-epidioxy-5α,8α-ergosta-6,9(11),22-trien-3β-ol (**357**).

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

Mangrove endophyte *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 *E*-double bond instead of the *Z*-double bond as in (**366**) was also inactive. Some previously described analogs, i.e.,

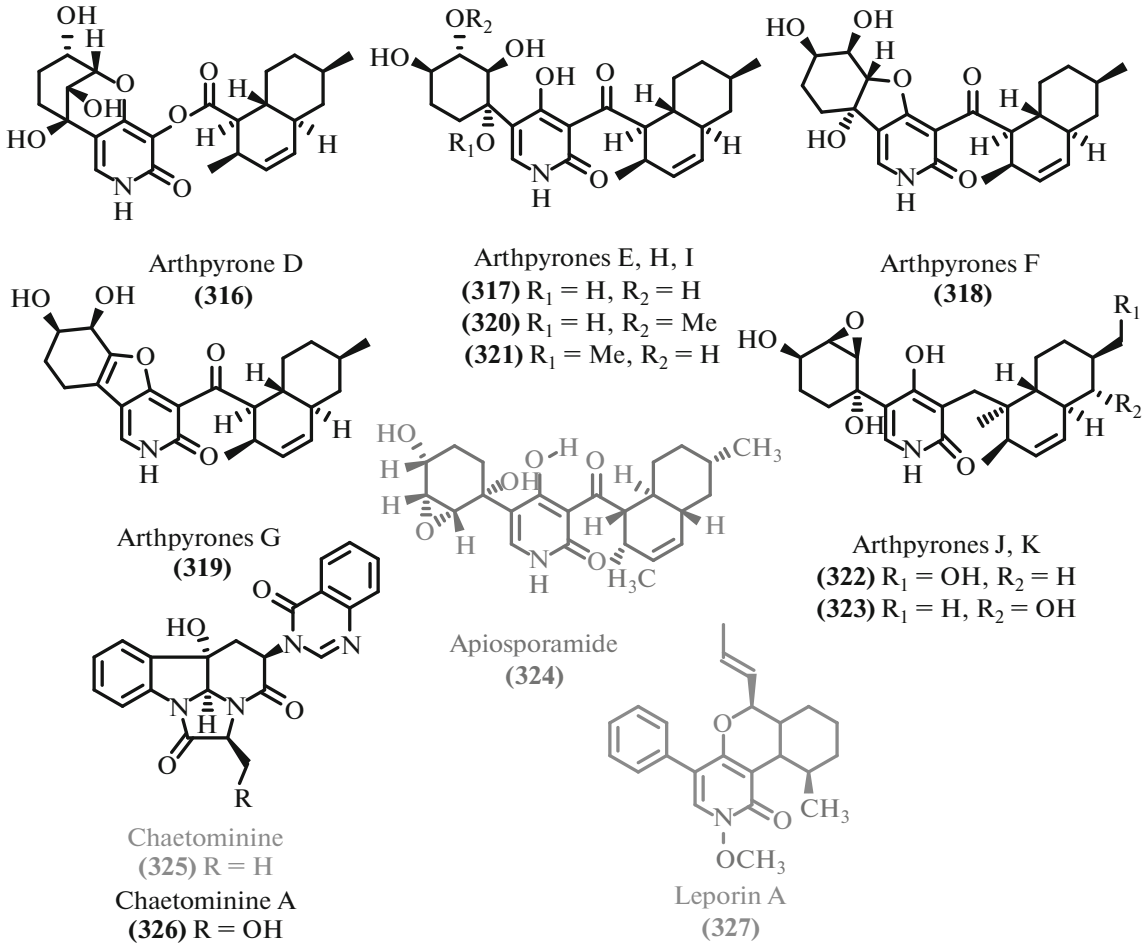


Fig. 22. Pyridone derivatives.

engiodontiumon I (**365**) [265], hydroxysydonic acid (**359**) [262, 263], and (–)-(7*S*)-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 dankasterone (**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 A–C (**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 C_{23} atranone that contains the propan-2-one motif attached to the dolabellane core through the C–

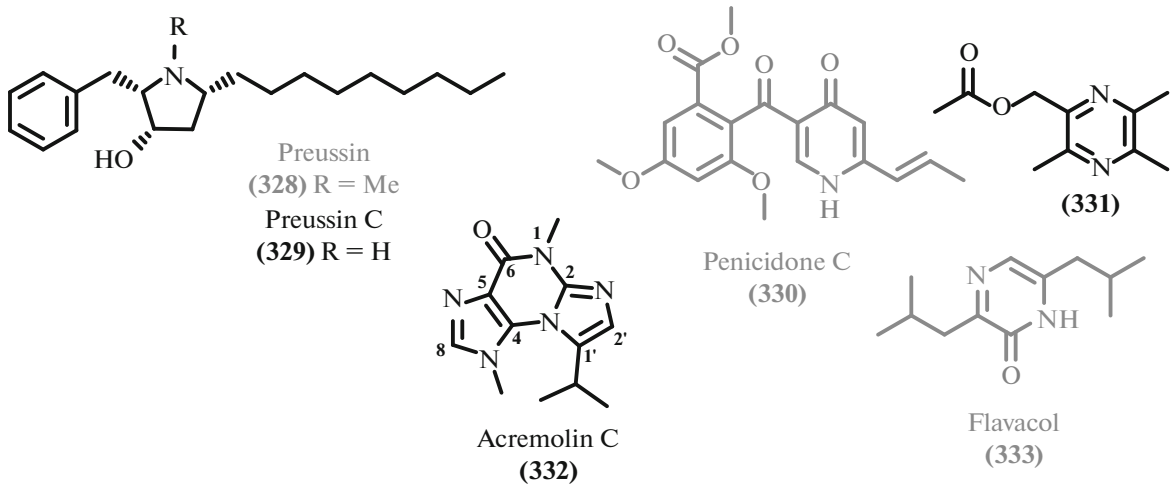


Fig. 23. Other alkaloids.

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, aspewentines 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-acetylisocyclocitrinol 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, asperterpens 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

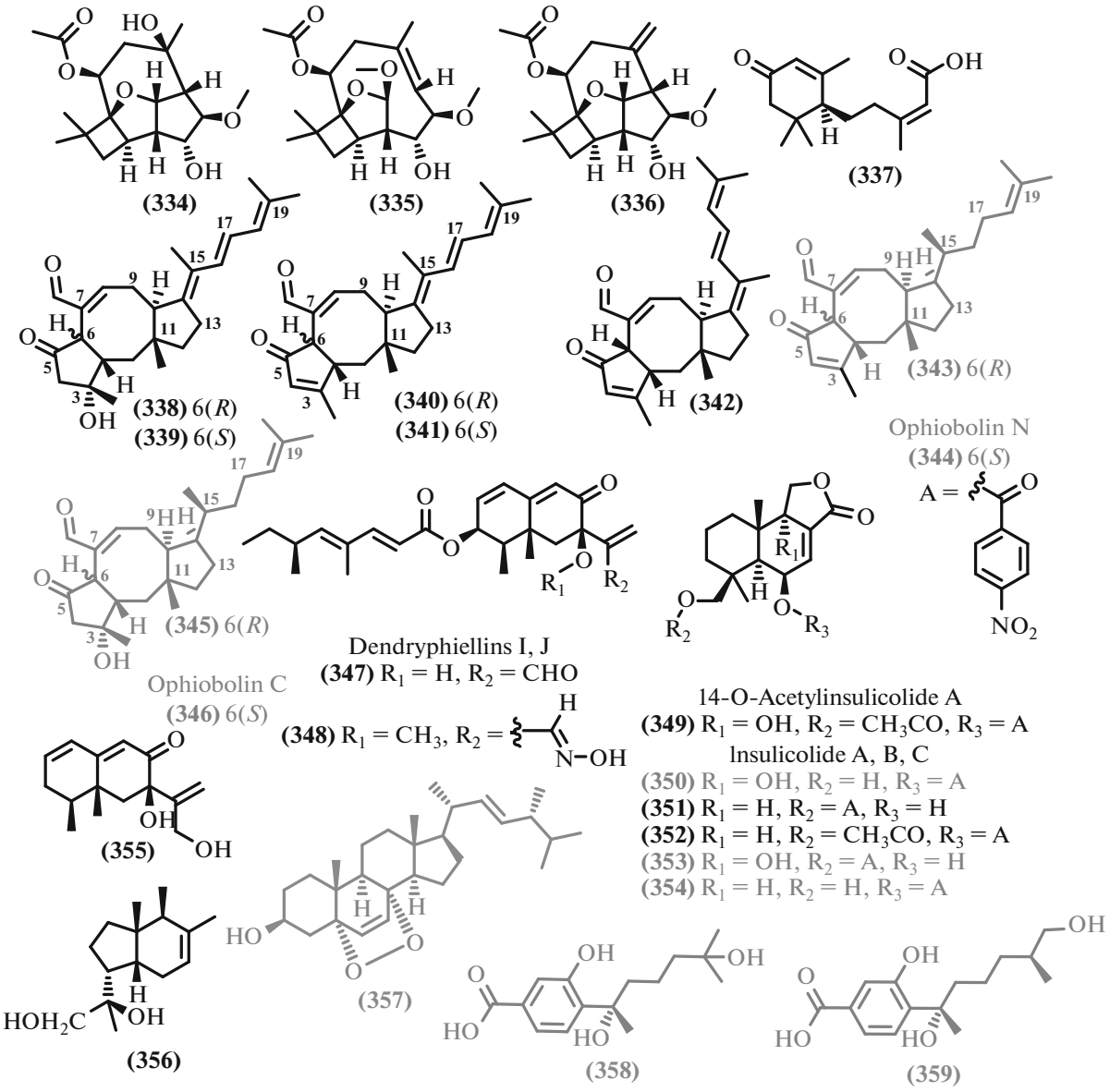


Fig. 24. Sesquiterpenes and sesquiterpenoids.

for this class of compounds but their antibacterial activity is very low.

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 kiliense* [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]. 22*E*-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 micromycete *Penicillium granulatum* MC 3A00 475 [47] include several compounds of the steroid nature, i.e., isonuatigenin I (**453**) [296], penicysteroid A (**446**) [297], and anicequol (**445**) [298].

Five new ergostans, penicysteroids 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 penicysteroids A and C (**446**, **447**) [297, 300].

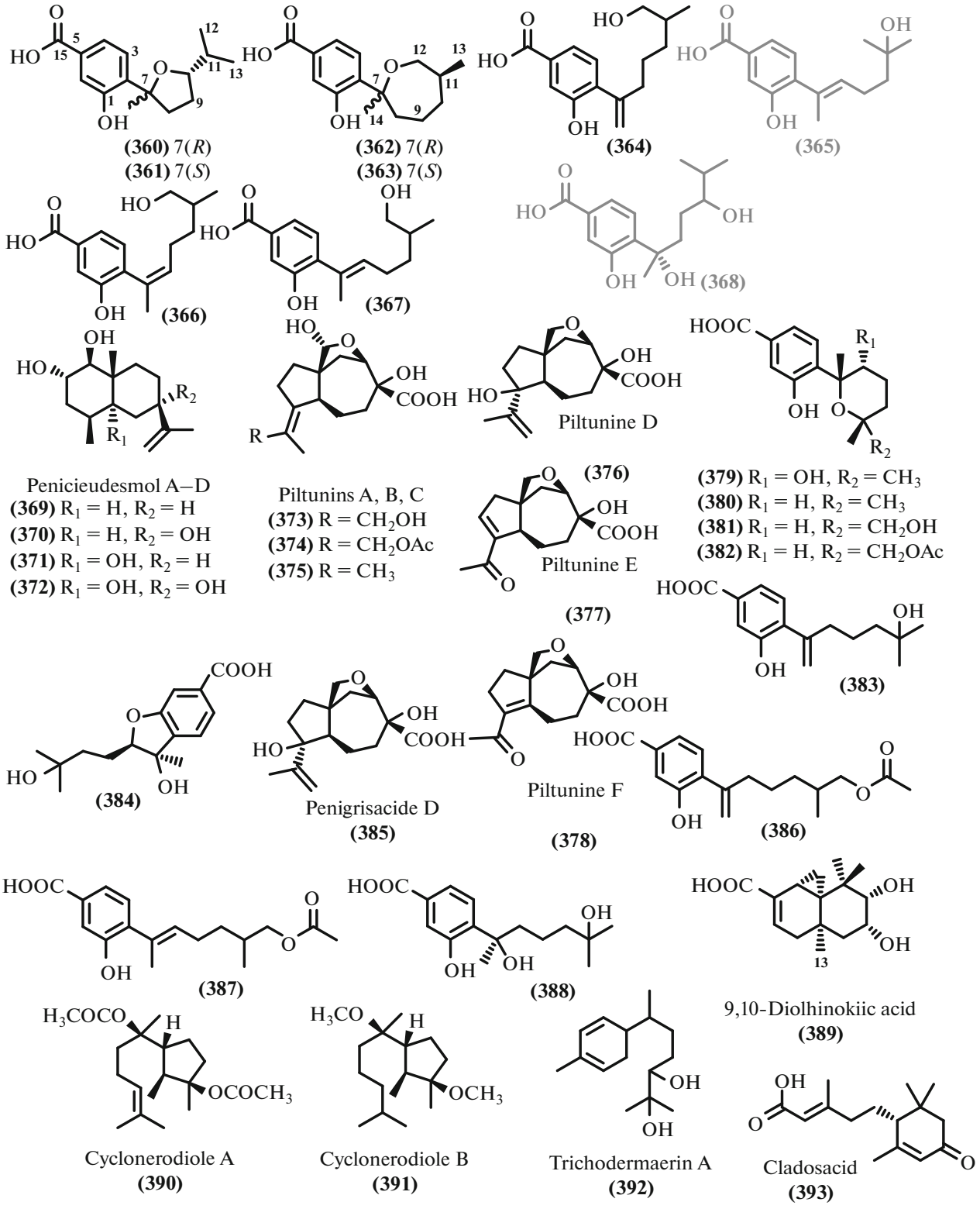


Fig. 25. Sesquiterpenes and sesquiterpenoids.

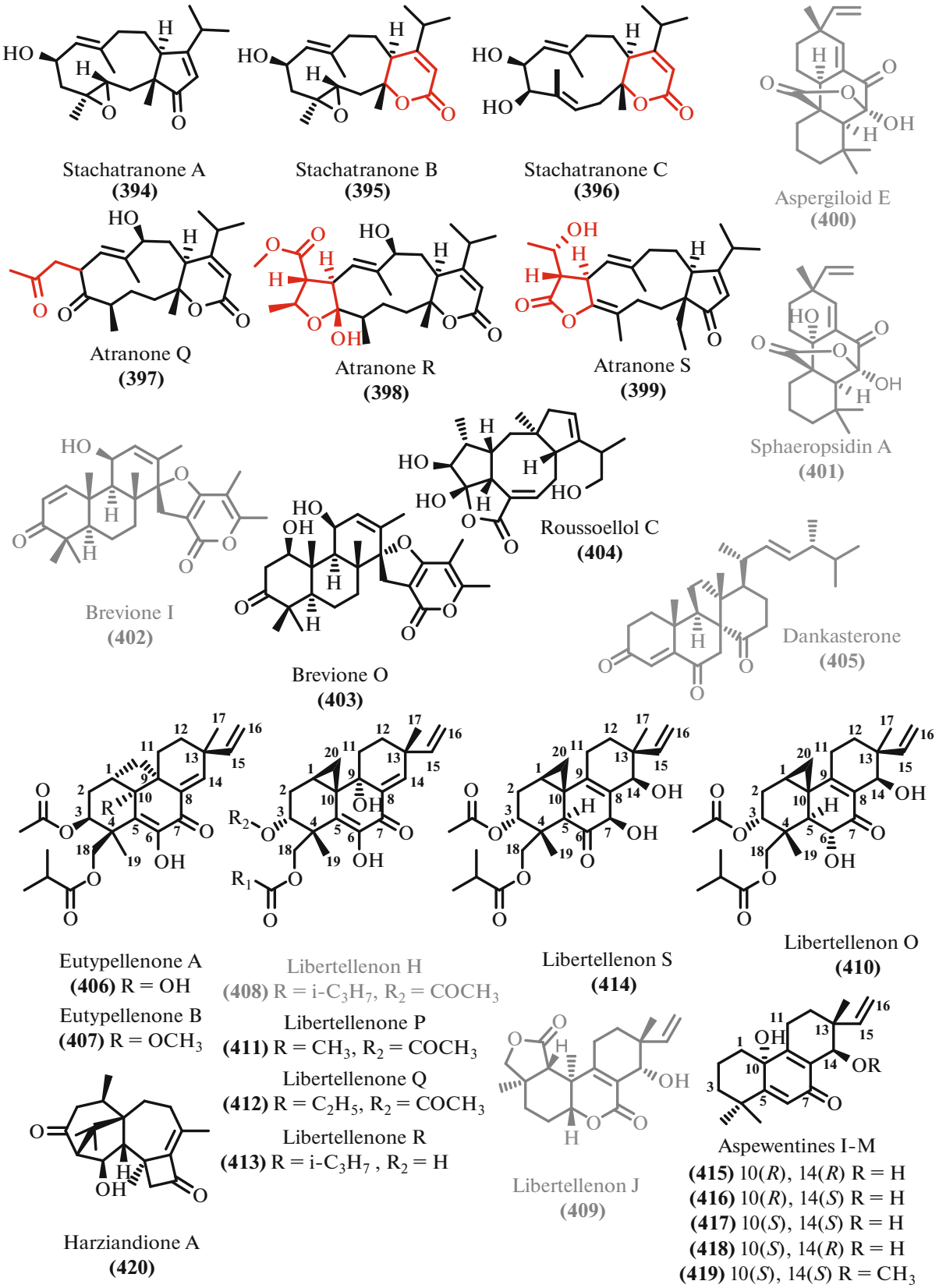


Fig. 26. Diterpenes and diterpenoids.

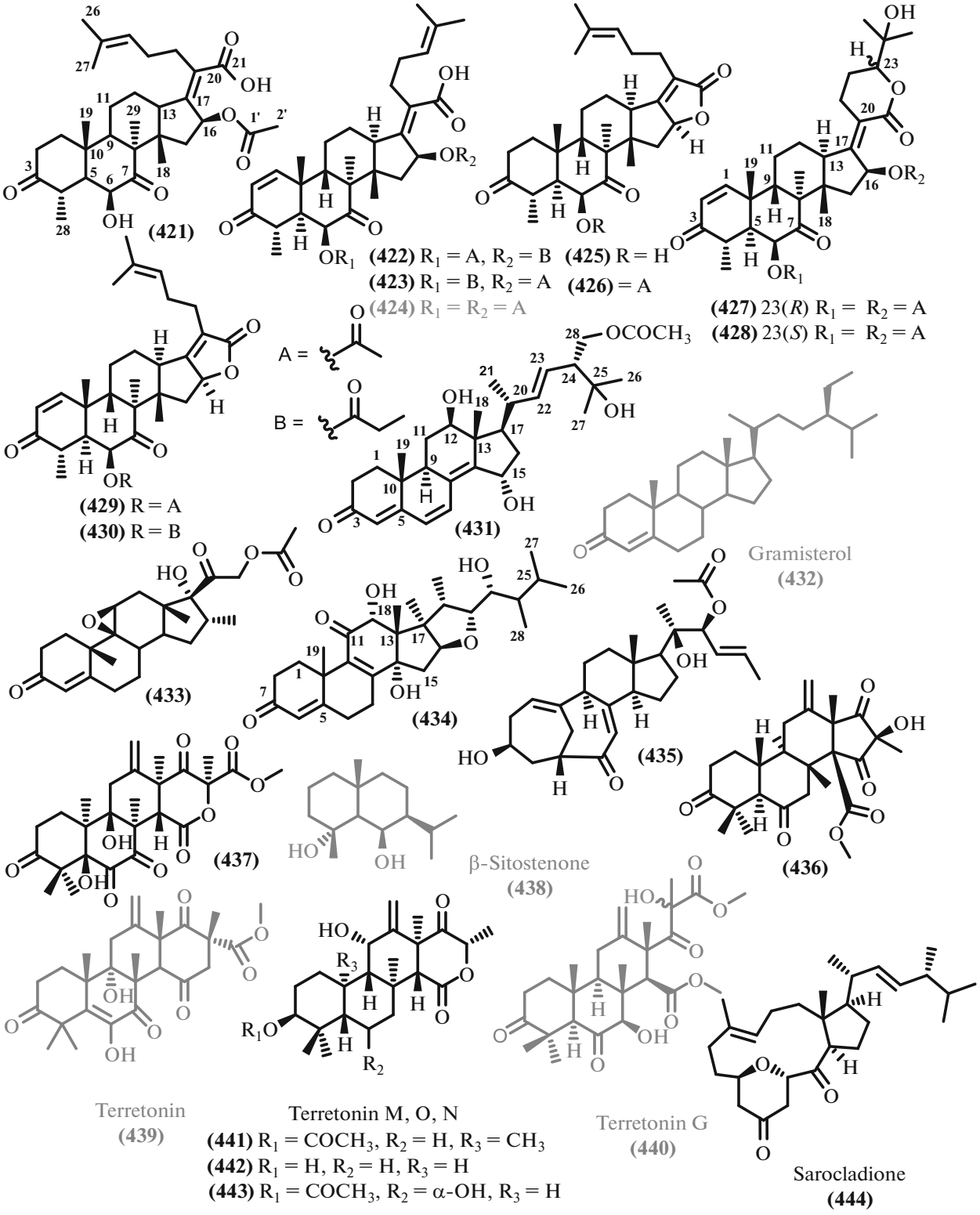


Fig. 27. Steroids and their derivatives.

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

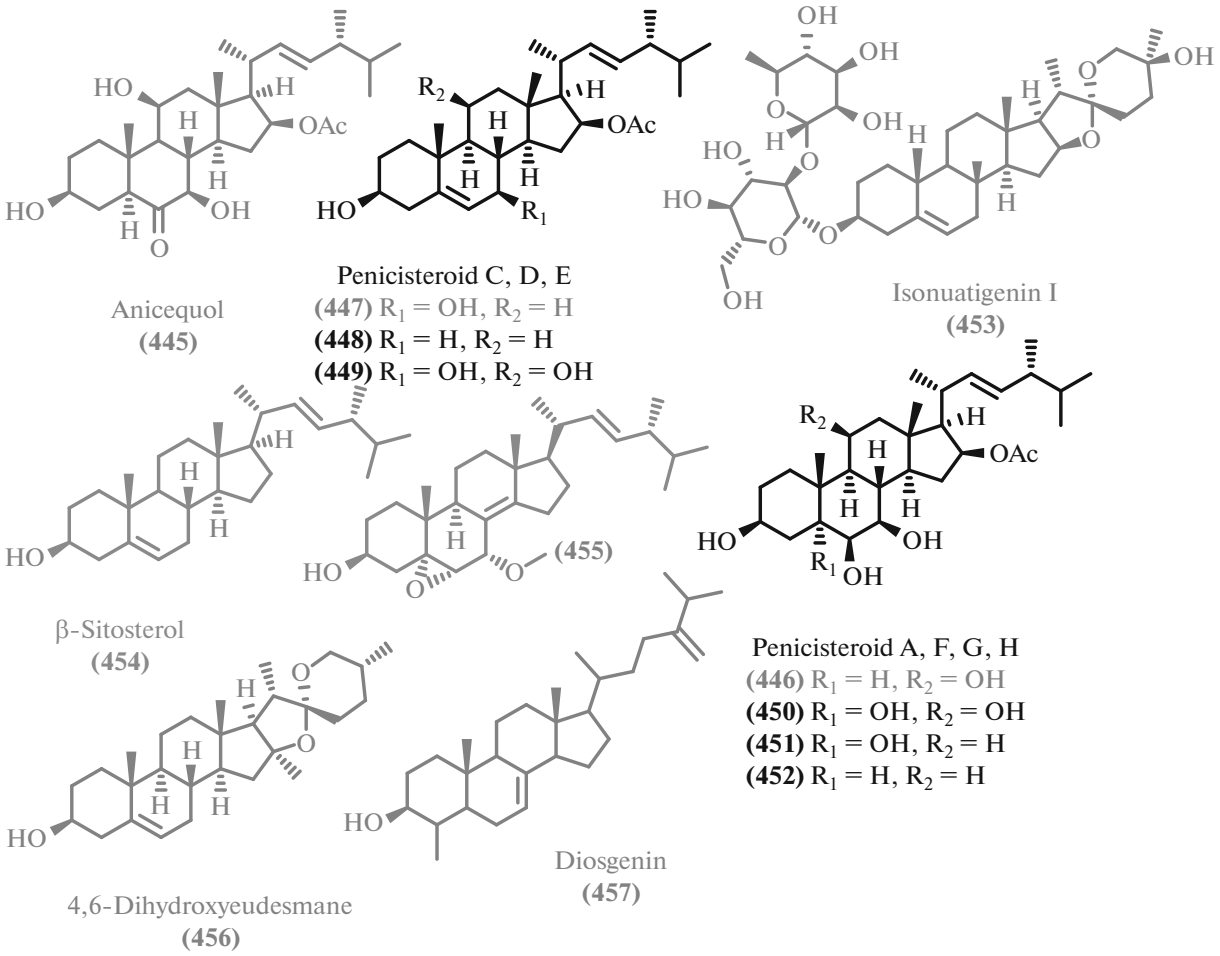


Fig. 28. Sterols and their derivatives.

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, purpuride 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'-dimethyldiphenyl ether (**468**) [304], 3-*O*-methyldiorcinol (**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	**IC_{50} 12.46 μM** (BEL7402/5-Fu) **MIC 62.5 μM** (*P. gingivalis*)	[219]
161	*Zopfiella marina*	Marine	AT AB CT	**MIC 25 μg/mL** (*M. tuberculosis* H37Ra) **MIC 12.5 μg/mL** (*B. cereus*) **IC_{50} 13.6 μg/mL** (Vero)	[164]
199 **240**	*Aspergillus fumigatus* MF029	Marine	AB AT AF	**MIC 50, 50, 12.5, 1.25 μg/mL** (MRSA, *S. aureus*, *B. subtilis*) **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, 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)	[75]
201	*Aspergillus* sp.	Marine	AB CT	**MIC 15.15, 30.30, 7.53 μM** (*V. anguillarum*, *A. salmonicida*, *P. aeruginosa*) **IC_{50} 3.56 – 10.69 μM** (Jurkat, A549, HeLa)	[74]
248	*Aspergillus terreus* S020	Marine	CT	**IC_{50} 12.13, 22.53 μM** (HCT-116, HepG2) **IC_{50} 1.1–66.8 μM** (MCF-7, PANC-1, HepG2) [131]	[226]
111 **112** **155** **126** **113** **127** **147**	*Alternaria* sp. SCSIO41014	Marine	CT AB	**EC_{50} 1.7 μg/mL** (L5178Y) [143] **EC_{50} 7.8 μg/mL** (L5178Y) [143] **EC_{50} 6.8 μg/mL** (L5178Y) [143] **EC_{50} 0.67 μM** (Soybean cell) [147] **MIC 45 μg/mL** (*S. aureus* ATCC 25923) [146] **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] **Qualitative AB activity** (*S. aureus* ATCC 29213, *Bacillus subtilis* ATCC 6051) [148] **MIC 31.25 μg/mL** (*S. aureus*) **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]	[87]
196 **197** **198**	*Penicillium* sp. ZZ901	Marine	CT AB	**IC_{50} 60.93 μM** (U87MG glioma cells) **IC_{50} 60.81 μM** (C6 glioma cells) **MIC 23, 35 μg/mL** (MRSA, *E. coli*) **IC_{50} 55.99 μM** (U87MG glioma cells) **IC_{50} 44.65 μM** (C6 glioma cells) **IC_{50} 37.26 μM** (U87MG glioma cells) **IC_{50} 23.24 μM** (C6 glioma cells) **MIC 7, 9 μg/mL** (MRSA, *E. coli*)	[94]
207	*Penicillium sclerotiorum* GDST-2013-0415	Marine	AV	**IC_{50} 19.5–132 μM** (HSV, EV71, RSV1)	[198]

Table 4. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
210	*Penicillium canescens*	Marine	CT AF AB	**IC_{50} 13.9 μM** (L5178Y)	[176]
211				**IC_{50} 2.7, 8.9 μM** (A2780, L5178Y)	
200				**IC_{50} 20, 35 μM** (HeLa, SCC-114) [131] **IC_{50} 11.6 μg/mL** (*C. gloeosporioides*) [195] **IC_{50} 2.68 μg/mL** (*A. solani*) [195]	
249				**IC_{50} 8.9 μM** (L5178Y) **IC_{50} 7.8–29.4 μM** (POS1, AT6-1, L929) [217] **MIC 111.1 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 avenae* 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 AP	**IC_{50} 27–45 μM** (ACHN, 786-O, -RC-2)	[200]
214				**IC_{50} 38, 44 μM** (786-O, OS-RC-2)	
215				**IC_{50} 8.9–14 μM** (ACHN, 786-O, OS-RC-2)	
204				**IC_{50} 10–38 μM** (ACHN, 786-O, OS-RC-2)	
216				**IC_{50} 48, 4.9 μM** (786-O, OS-RC-2) **IC_{50} 6.2–10.6 μg/mL (**KB, NCI-H187, MCF-7) [201] **IC_{50} 7.8 μg/mL** (*Plasmodium falciparum*) [201]	
217				**IC_{50} 8.5–30.2 μg/mL** (KB, NCI-H187, MCF-7) [201]	
205				**IC_{50} 3.0–4.4 μM** (ACHN, 786-O, OS-RC-2)	
145	*Penicillium purpurogenum* G59	Marine	CT	**IC_{50} 124.3, 329.9 μM** (HL-60, K562)	[159]
177	*Pseudopestalotiopsis* sp. PSU-AMF45	Marine	AF	**MIC 200 μg/mL** (*Cryptococcus neoformans* ATCC90112)	[102]
178				**MIC 200 μg/mL** (*Cryptococcus neoformans* ATCC90112)	
136				**IC_{50} 0.01 μM** (HEP-G2) [154]	
245	*Penicillium janthinellum*	Marine	CT	**GI_{50} 9.3–31 μM** (NUGC-3, HCT-15, NCI- H23, ACHN, PC-3, MDA-MB-231)	[208]
139	*Curvularia sp.* IFB-Z10	Marine	CT	**IC_{50} 9.85, 2.46 μM** (BEL7402, BEL7402/5-FU)	[155]
124	*Penicillium piltunense* KMM 4668	Marine	CT AF	**IC_{50} 71.74 μM** (22Rv1)	[151]
125				**IC_{50} 30 μM** (*P. viticola*)	
252	*Cladosporium* sp. OUCMDZ-1635	Marine	CT	**IC_{50} 9.1–19.1 μM (**MCF-7, HeLa, HCT-116, HL-60)	[220]
255	*Aspergillus protuberus* MUT 3638	Marine	AB	**MIC 30 μg/mL** (*S. aureus*)	[222]
148	*Colletotrichum 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*)	

Table 4. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
154	*Dothiorella* sp. ML002	Mangrove	AB CT AV	**MIC 50 μg/mL** (*S. aureus*)	[165]
151				**MIC 50 μg/mL** (*S. aureus*)	
149				**IC_{50} 25–30 μg/mL** (HEp-2, HepG2) [166]	
153				**MIC 50 μg/mL** (*S. aureus*)	
160				**IC_{50} 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*)	[136]
119				**MIC 25, 25, 25, 25, 50 μg/mL** (*S. aureus*, *B. subtilis*, *E. coli*, *K. pneumoniae*, *Acinetobacter calcoaceticus*)	
120				**MIC 25 μg/mL** (*S. aureus*, *B. subtilis*) **MIC 25–50 μg/mL** (*E. coli*, *Klebsiella pneumoniae*, *Acinetobacter calcoaceticus*) **MIC 150 μg/mL** (*R. solani*)	
115				**IC_{50} 17.8 μg/mL** (MCF-7) [137] **IC_{50} 39.6 μg/mL** (HepG2) [137]	
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				**IC_{50} 7.3 μM** (L5178Y)	
142				**IC_{50} 96.97 μM** (HeLa) [157] **GI_{50} 1.67 μM** (HUVEC) [157] **GI_{50} 0.84 μM** (K-562) [157] **MIC 26.03, 191.60 μM** (*A. terreus*, *F. oxysporum*) [157]	
143				**IC_{50} 36.41 μM** (HeLa) [157] **GI_{50} 0.07 μM** (HUVEC) [157] **GI_{50} 0.003 μM** (K-562) [157] **MIC 49.7, 238.8 μM** (*A. terreus*, *F. oxysporum*) [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*) **MIC 8–32 μg/mL** (*E. coli*, *V. harveyi*, *M. luteus*) [173] **IC_{50} 4–14 μM** (H446, A549) [173]	
218	*Penicillium* sp. ZZ380 *Cladosporium* sp. JS1-2	Marine Mangrove	AB	**MIC 6.25, 12.5, 12.5 μg/mL** (*S. aureus*, *E. coli*, *B. cereus*)	[78] [121]

Table 4. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
208	*Penicillium pinophilum* SCAU037	Mangrove	AB AF CT	**IC_{50} 23.5, 2.6 μM** (*M. smegmatis*, *S. aureus*) **MIC 64 μg/mL** (*S. aureus*) [203] **MIC 8–64 μg/mL** (*S. cerevisiae* PM503, *C. albicans* C43) [203]	
138				**IC_{50} 6.7–7.8 μM** (Hep-2, RD) [161]	[130]
209				**IC_{50} 62–68.8 μM** (A549, BALL-1, HCT116, HeLa, NUGC-3) [202] **IC_{50} 90.4–99 μM** (A549, BALL-1, HCT116, HeLa, NUGC-3) [202]	
157	*Aspergillus* sp. AV-2	Mangrove	CT	**IC_{50} 2.87 μM (**Caco-2)	[170]
241	*Fusarium solani* H918	Mangrove	AF	**ED_{50} 55 μM** (*P. theae*)	[211]
128	*Cladosporium cladosporioides* MA-299	Mangrove	AB AF	**MIC 2 μg/mL** (*C. glecosporioides*) **MIC 1, 8 μg/mL** (*Edwardsiella tarda*, *E. ictarda*)	
129				**MIC 2, 8 μg/mL** (*C. glecosporioides*, *Bipolaris sorokiniana*)	
130				**MIC 2 μg/mL** (*C. glecosporioides*) **MIC 32 μg/mL** (*P. piricola Nose*) **MIC 1 μg/mL** (*Fusarium oxysporum* f. sp. *cucumerinum*)	
131				**MIC 1 μg/mL** (*C. glecosporioides*) **MIC 32 μg/mL** (*P. piricola Nose*) **MIC 32 μg/mL** (*Fusarium oxysporum* f. sp. *cucumerinum*)	[152]
132				**MIC 1 μg/mL** (*E. ictarda*) **MIC 1 μg/mL** (*C. glecosporioides*) **MIC 32 μg/mL** (*P. piricola Nose*) **MIC 32 μg/mL** (*Fusarium oxysporum* f. sp. *cucumerinum*)	
224	Cocultivation *Penicillium crustosum* PRB-2 and *Xylaria* sp. HDN13-249	Antarctica Mangrove	AB	**MIC 100 μM** (*B. subtilis*)	
225				**MIC 6.25, 12.5 μM** (*M. phlei*, *V. parahemolyticus*)	[213]
227				**MIC 25 μM** (*M. phlei*)	
228				**MIC 12.5, 25 μM** (*M. phlei*, *V. parahemolyticus*)	
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*)	
162				**MIC 6.3, 5.7 μg/mL** (*Escherichia fergusonii*, *P. aeruginosa*) **IC_{50} 22 μM** (HTB-176)	[73]
167	*Sarcopodium* sp. FKJ-0025	Deep-sea 200 m	CT	**IC_{50} 47 μg/mL** (Jurkat)	[169]
168				**IC_{50} 37–66 μg/mL** (Jurkat, HL-60, Panc1)	
233	*Cladosporium* sp. OUCMDZ-302	Mangrove	CT	**IC_{50} 10 μM** (H1975)	[116]
236	*Penicillium chrysogenum* MCCC 3A00292	Deep-sea 2076 m	CT	**IC_{50} 7.70–13.75 μM** (BIU-87, ECA109, BEL-7402)	[210]

Table 4. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
183	*Penicillium chrysogenum* MCCC 3A00292	Deep-sea 2076 m	CT AB AF	**IC_{50} 16.41 μM** (BIU-87)	[46]
184				**MIC 200 μg/mL** (*E. coli*) [179] **MIC 50–200 μg/mL** (*B. subtilis*, *S. aureus*, *M. lysodeikticus*) [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 sonneii*) [180]	
180				**IC_{50} 9.95 μM** (ECA109) **MIC 39.062, 78.125, 39.062, 312.5 μg/mL** (*S. aureus*, MRSA, *B. subtilis*, *B. cereus*, *Salmonella thyphimurium*, *Shigella sonneii*) [180] **MIC < 9.765 μg/mL** (*C. albicans*) [180]	
133				**IC_{50} 12.95 μM** (BEL-7402)	
182	*Aspergillus* sp. *Pleosporales* sp. SK7	Marine Mangrove	CT	**IC_{50} 30.2–45 μg/mL** (HepG2, HL-60, MOLT-3) [182]	[74] [186]
250	*Penicillium chrysogenum* MCCC 3A00292	Deep-sea 2076 m	CT	**IC_{50} 12.49 μM** (ECA109)	[46]
251				**IC_{50} 15.6 μM** (ECA109)	
122	*Penicillium* sp. SCSIO 06720	Deep-sea 4762 m	CT AF	**IC_{50} 18.9 μg/mL** (K562) [149]	[59]
256				**MIC 32, 32, 64 μg/mL** (*P. oryzae*, *C. albicans*, *A. niger*) [221]	
146				**Qualitative AF activity** (*C. albicans*, *T. harzianum*) [162]	
181	*Penicillium citrinum* HL-5126	Mangrove	AB CT	**IC_{50} 21.6 μg/mL** (HeLa)	[124]
219	*Penicillium citrinum* SCSIO 41017	Marine	CT AB AV	**IC_{50} 13.0–49.3 μM** (SF-268, MCF-7, HepG-2, A549)	[108]
220				**IC_{50} 16.1–55.4 μM** (SF-268, MCF-7, HepG-2, A549) **MIC 12.5 μg/mL** (*B. cereus*) [205]	
221				**IC_{50} 1.3–47.9 μM** (SF-268, MCF-7, HepG-2, A549)	
222				**IC_{50} 16.41–115.3 μM** (SF-268, MCF-7, HepG-2, A549) **IC_{50} 14.5 μM** (EV71) [206]	
137	*Penicillium citrinum* SCSIO 41017 *Aspergillus sydowii* C1-S01-A7	Marine Deep-sea 4950 m	AB	**MIC 32.4 μg/mL** (MR *S. aureus* ATCC 43300, MR *S. aureus* CGMCC) [77]	[108] [77]
186	*Pleosporales* sp. SK7	Mangrove	CT	**IC_{50} 25.96 μM** (MDA-MB-435)	[186]
189	*Aspergillus* sp. CUGB-F046	Marine	AB CT AF	**MIC 3.125 μg/mL** (*S. aureus*, MRSA)	[187]
187				**MIC 6.25 μg/mL** (*S. aureus*, MRSA) **IC_{50} 31.5–48.9 μM** (HeLa, K562) [188] **IC_{50} 23.2–36.3 μM** (PC3, A549, A2780, MDA-MB231, HEPG2) [189] **MIC 32.0 μg/mL** (*C. albicans*) [189]	
188				**MIC 6.25 μg/mL** (*S. aureus*, MRSA) **IC_{50} 29.8–31.6 μM** (PC3, HEPG2) [189] **MIC 8.0 μg/mL** (*C. albicans*) [189]	

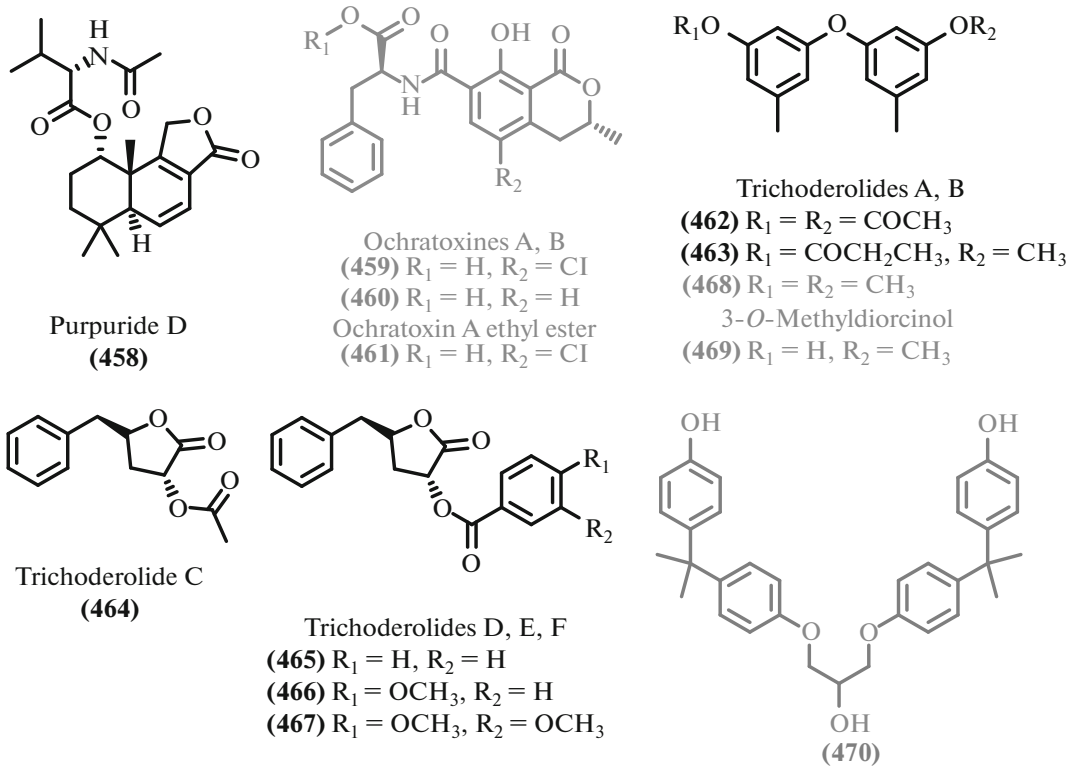


Fig. 29. Purpuride, ochratoxins, and trichoderolides.

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 antibiotic 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_{50}, IC_{50}, MIC	Ref.
259	*Penicillium* sp. ZZ380	Marine	AB CT	**MIC 5 μg/mL** (MRSA) **IC_{50} 11.32–29.1 μM** (U87-MG, U251, SHG-44, C6)	[229]
258	*Penicillium* sp. ZZ380 *Penicillium erubescens* KUFA0220	Marine 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* $H_{37}Ra$) [230] **IC_{50} 14.71–29.55 μM** (KB, MCF-7, Vero) [230]	[229] [114]
260	*Penicillium* sp. ZZ380	Marine	CT AB	**IC_{50} 10.03–22.12 μM** (U87-MG, U251, SHG-44, C6) **MIC 4.0**, **5.0 μg/mL** (MRSA, *E. coli*)	[78]
261				**IC_{50} 9.95–22.39 μM** (U87-MG, U251, SHG-44, C6) **MIC 12.0**, **3.0 μg/mL** (MRSA, *E. coli*)	
262				**IC_{50} 15.76–26.64 μM** (U87-MG, U251, SHG-44, C6) **MIC 10.0**, **11.0 μg/mL** (MRSA, *E. coli*)	
264				**IC_{50} 8.93 – 22.82 μM** (U87-MG, U251, SHG-44, C6) **MIC 2.0**, **3.0 μg/mL** (MRSA, *E. coli*)	
266				**IC_{50} 1.06–8.52 μM** (U87-MG, U251, SHG-44, C6)	
267				**IC_{50} 12.89–23.92 μM** (U87-MG, U251, SHG-44, C6) **MIC 19.0**, **4.0 μg/mL** (MRSA, *E. coli*)	
268				**IC_{50} 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_{50} 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**, **32 μg/mL** (*E. coli*, *Ed. ictaluri*, *M. luteus*, *V. alginolyticus*)	

Table 5. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
328	*Aspergillus candidus* KUFA 0062	Marine	CT AB AF	**IC_{50} 12.3–74.1 μM** (HepG2, HT29, HCT116, A549, A375, MCF7, U251, T98G) **MIC 32.0 μg/mL** (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212) **MIC 32 μg/mL** (MRSA, VRE) **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]	[79]
329				**IC_{50} 57.2–215.7 μM** (HepG2, HT29, HCT116, A549, A375, MCF7, U251)	
296				**IC_{50} 73.2–212.5 μM** (HepG2, HT29, HCT116, A549, A375, MCF7, U251)	
295				**IC_{50} 34.8–94.8 μM** (HepG2, HT29, HCT116, A549, A375, MCF7) **IC_{50} 33.2 μg/mL** (NS-1 ATCC TIB-18) [235]	
294				**IC_{50} 28 μg/mL** (NS-1 ATCC TIB-18) [235]	
297				**IC_{50} 43 μg/mL** (NS-1 ATCC TIB-18) [235]	
298				**IC_{50} 72.9–146.4 μM** (HepG2, HT29, HCT116, A549, A375) **IC_{50} 59 μg/mL** (NS-1 ATCC TIB-18) [235]	
304				**IC_{50} 26 μg/mL** (NS-1 ATCC TIB-18) [235]	
279	*Aspergillus* sp.	Marine	CT	**IC_{50} 4.86–69.4 μM** (PC-3, 22Rv1, LNCaP)	[231]
291	*Aspergillus* sp. SCSIO XWS03F03	Marine	CT	**IC_{50} 3.1 μM** (HL60) **IC_{50} 4.9 μM** (LNCaP)	[241]
331	*Cladosporium* sp. JS1-2	Mangrove	AB	**MIC 12.5 μg/mL** (*S. aureus*)	[121]
308	*Didymella* sp. CYSK-4	Mangrove	CT AT	**IC_{50} 4.4–6.8 μM** (MDA-MB-435, MDA-MB-231, SNB19, HCT116, NCI-H460, PC-3)	[244]
309				**IC_{50} 4.5–20.0 μM** (MDA-MB-435, MDA-MB-231, SNB19, HCT116, NCI-H460, PC-3)	
310				**IC_{50} 4.2–7.8 μM** (MDA-MB-435, MDA-MB-231, SNB19, HCT116, NCI-H460, PC-3) **IC_{50} 4.5–6.6 μM** (MDA-MB-231, HCT116)	
311				**IC_{50} 12–29 μM** (MDA-MB-435, MDA-MB-231, SNB19, HCT116, NCI-H460, PC-3) **IC_{50} 17.7 μM** (Vero) [245] **MIC 20.1–40.1 μg/mL** (MABA, LORA) [245]	
312				**IC_{50} 19.4 μM** (Vero) [245] **MIC 5.2–13.4 μg/mL** (MABA, LORA) [245]	
314	*Cladosporium* sp. HNWSW-1	Mangrove	CT	**IC_{50} 25.6–41.7 μM** (BEL-7042, K562, SGC-7901)	[246]
315				**IC_{50} 14.9–26.7 μM** (Hela, BEL-7042)	

Table 5. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
269	*Tolypocladium* sp.	Mine soil, Lianyuan, China	AB CT	**MIC 6.25, 25, 25, 6.25, 25, 6.25, 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) **IC_{50} 16.32–37.8 μM** (Huh7, LN229, HCT116, MGC803, A549, MDA231)	[232]
270				**MIC 25, 25, 50 μg/mL** (*A. fragariae*, *B. cinereal* Pers, *C. personata*) **MIC 50 μg/mL** (MRSA) **IC_{50} 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*) **IC_{50} 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*) **IC_{50} 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*) **IC_{50} 198.6 μM** (A549)	
274				**MIC 25.0, 12.5 μg/mL** (*A. fragariae*, *C. cassiicola*) **IC_{50} 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*) **IC_{50} 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. paratyphosum*, *B. subtilis*, *E. aerogenes*, *S. typhi*, *P. vulgaris*) **IC_{50} 31.49–64.49 μM** (Huh7, LN229, HCT116, MGC803, A549, MDA231)	
277				**MIC 50 μg/mL** (*A. fragariae*) **MIC 100 μg/mL** (*B. cereus*) **IC_{50} 50.95–129.1 μM** (Huh7, LN229, HCT116, MGC803, A549, MDA231)	
278				**MIC 25 μg/mL** (*A. fragariae*) **IC_{50} 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]

Table 5. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
327	*Aspergillus* sp. YQ-13	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]
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)	[75]
				IC_{50} 21.0–28.0 μM (SW1116, K562) [250]	
283	*Aspergillus fumigatus* SCSIO 41012	Deep-sea 3614 m	AB AF	**MIC 12.5, 6.25, 25.0, 6.25, 12.5 μg/mL** (*A. baumanii* ATCC 19606, *A. baumanii* ATCC 15122, *Fusarium oxysporum* f. sp. *cucumerinu*, *S. aureus* ATCC 16339, *K. pneumonia* ATCC 14578)	[237]
284				**MIC 6.25 μg/mL** (*A. baumanii* ATCC 19606)	
286				**MIC 6.25, 12.5, 12.5, 12.5, 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 19606, *A. baumanii* ATCC 15122, *Fusarium oxysporum* f. sp. *cucumerinu*)	
318	*Arthrinium* sp. UJNMF0008	Deep-sea 3858 m	AB CT	**IC_{50} 11.4, 8.97 μM** (*M. smegmatis* ATCC607, *S. aureus* ATCC25923)	[248]
319				**IC_{50} 42.8 μM** (*S. aureus* ATCC25923)	
320				**IC_{50} 19.4, 8.37 μM** (*M. smegmatis* ATCC607, *S. aureus* ATCC25923)	
321				**IC_{50} 35.3, 14.1 μM** (*M. smegmatis* ATCC607, *S. aureus* ATCC25923)	
324				**IC_{50} 2.20, 1.66 μM** (*M. smegmatis* ATCC607, *S. aureus* ATCC25923)	
				IC_{50} 19.3, 11.7 μM (U2OS, MG63) [249]	
330	*Penicillium pinophilum* SCAU037	Mangrove	CT	**IC_{50} 15.1–20 μg/mL** (KB, KBv200)	[130]
				IC_{50} 44.3–80.8 μM (SW1116, K562, KB, HeLa) [252]	
333	*Aspergillus* sp. SCSIO41211	Mangrove	CT	**IC_{50} 0.15–22.9μM** (H1975, U937, K562, BGC823, MOLT-4, MCF-7, A549, HL60, Huh-7)	[254]
305	*Eupenicillium* sp. HJ002	Mangrove	CT	**IC_{50} 1.5–23.3 μM** (A549, HeLa, HepG-2)	[242]
306				**IC_{50} 18.6–47.2 μM** (A549, HeLa, HepG-2)	
302	*Aspergillus versicolor*	Mangrove	CT	**IC_{50} 43.7 μM** (HeLa)	[243]

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 A–C (**500**–**502**) [322]. The described compounds did not show noticeable cytotoxicity but demonstrated a moderate antibacterial activity.

A new secondary metabolite, 1-(2',6'-dimethylphenyl)-2-*n*-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	EC_{50}, IC_{50}, MIC	Ref.
454	*Aspergillus sydowii* C1-S01-A7	Deep-sea 4950 m	CT	**IC_{50} 50 μg/mL** (HepG2)	[77]
421	*Aspergillus fumigatus* SCSIO 41012	Deep-sea 3614 m	AB AF	**MIC 50 μg/mL** (*A. baumanii* ATCC 19606)	[237]
435				**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 agalactie*)	[237] [282]
422	*Aspergillus fumigatus* HNMF0047	Marine	AB	**MIC 16 μg/mL** (*S. aureus*, *S. agalactie*)	[282]
423				**MIC 8, 2 μg/mL** (*S. aureus*, *S. agalactie*)	
395	*Stachybotrys chartarum*	Marine	AB AF	**MIC 16 μg/mL** (*A. baumanii*)	[271]
397				**MIC 16 μg/mL** (*E. faecalis*) **MIC 32 μg/mL** (MRSA) **MIC 8 μg/mL** (*C. albicans*)	
401	*Aspergillus porosus*	Marine	AB CT AF	**IC_{50} 32.6, 35.3 μM** (*S. aureus* ATCC 25923, *S. aureus* ATCC BAA-41) **IC_{50} 4.9 μM** (HCT-116 ATCC CCL-247) **MIC 10–100 μg/mL** (*Botrytis cinerea*, *Seiridium cardinal*, *Seiridium cupressi*, *Colletotrichum acutatum*, *F. oxysporum*, *F. solani*, *Fusicoccum amygdule*, *Penicillium expansum*, *Pyrenochaeta lycopersici*, *Sclerotinia minor*, *Sclerotinia wlerotiorum*, *Verticillium dahliae*) [272] **IC_{50} 6.74–10.68 μM** (KB, SGC-7901, SW1116, A549) [273]	[209]
400				**IC_{50} 71.6, 77.8 μM** (*S. aureus* ATCC 25923, *S. aureus* ATCC BAA-41) **IC_{50} 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_{50}, IC_{50}, MIC	Ref.
338	*Aspergillus flocculosus*	Marine	CT	**IC_{50} 0.14–0.24 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231)	[255]
339				**IC_{50} 0.44–0.63 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231)	
340				**IC_{50} 0.88–1.40 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231)	
341				**IC_{50} 1.07–1.50 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231)	
342				**IC_{50} 1.53–2.01 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231)	
345				**IC_{50} 0.19–0.43 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231)	
346				**IC_{50} 0.16–0.36 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231) **IC_{50} 8 μM** (CLL) [256]	
343				**IC_{50} 0.20–0.30 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231)	
344				**IC_{50} 0.19–0.42 μM** (HCT-15, NUGC-3, NCI-H23, ACHN, PC-3, MDA-MB-231)	
389	*Talaromyces purpurogenus*	Marine	CT	**IC_{50} 12.6–35.7 μM** (HL-60, A549)	[54]
404				**IC_{50} 6.5–25.8 μM** (SW480, HL-60, A549, MCF-7)	
405				**IC_{50} 7.9–23.8 μM** (SW480, HL-60, A549, MCF-7) **ED_{50} 2.2 μg/mL** (P-388) 10.1039/a903840j **GI_{50} 1.8–15.8 μM** (38 Human cancer cell lines) [269]	
402	*Penicillium* sp. TJ403-1	Marine	CT	**IC_{50} 4.92–8.6 μM** (HL-60, A549, HEP3B) **IC_{50} 7.44–32.5 μM** (MCF-7, A549) [275]	[51]
351	*Aspergillus ochraceus* Jcma1F17	Marine	CT AV	**IC_{50} 23–30 μM** (ACHN, OS-RS-2, 786-O)	[257]
349				**IC_{50} 2.3–5.3 μM** (ACHN, OS-RS-2, 786-O)	
352				**IC_{50} 11–14 μM** (ACHN, OS-RS-2, 786-O)	
350				**IC_{50} 0.89–1.5 μM** (ACHN, OS-RS-2, 786-O) **IC_{50} 2.11–6.35 μM** (H1975, U937, K562, BGC823, Molt-4, MCF-7, A549, HeLa, HL60, Huh-7) [258]	
353				**IC_{50} 4.3–11 μM** (ACHN, OS-RS-2, 786-O) **IC_{50} 1.95–17 μM** (H1975, U937, K562, BGC823, Molt-4, MCF-7, A549, HeLa, HL60, Huh-7) **IC_{50} 17, 9.4 μM** (H3N2, EV71) [258]	
354				**IC_{50} 20–30 μM** (ACHN, OS-RS-2, 786-O)	

Table 6. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
347	*Cochliobolus lunatus* SCSIO 41401	Marine	CT AB	**IC_{50} 1.41–4.3 μM** (ACHN, 786-O, OS-RC-2, HepG-2, SGC7901)	
348				**IC_{50} 3.1–27 μM** (ACHN, 786-O, HepG-2, SGC7901) **MIC 1.5–13 μg/mL** (*S. aureus*, *Erysipelothrix rhusiopathiae*, *Pasteurella multocida*)	[76]
433	*Penicillium citrinum* SCSIO 41017	Marine	CT AF	**IC_{50} 13.5–18 μM** (SF-268, MCF-7, HepG-2, A549)	[108]
439				**MIC 125–250 μg/mL** (*C. asianum*, *C. acutatum*)	
440	*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)	
443				**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) [289]	[287]
386	*Aspergillus versicolor*	Mangrove	CT	**IC_{50} 83.8 μM** (HeLa)	[243]
387				**IC_{50} 53.5 μM** (HeLa)	
357	*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_{50} 32.2 μM** (*S. aureus* ATCC 25923)	
362				**IC_{50} 36 μM** (*S. aureus* ATCC 25923)	
364				**IC_{50} 41.9 μM** (*S. aureus* ATCC 25923)	
365				**IC_{50} 33.4 μM** (*S. aureus* ATCC 25923) **MIC 256 μg/mL** (*B. subtilis*) [265]	[264]
368				**IC_{50} 36.3 μM** (*S. aureus* ATCC 25923) **MIC 8, 32 μg/mL** (*V. harveyi*, *V. parahemolyticus*) [263] **MIC 32 μg/mL** (*S. aureus*, *A. hydrophilia*) [263]	
370	*Penicillium* sp. J-54	Mangrove	CT	**IC_{50} 90.1 μM** (K-562)	[266]

Table 6. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
410	*Eutypella* sp. D-1	Arctic	CT	**IC_{50} 2.2–6 μM** (HeLa, MCF-7, HCT-116, PANC-1, SW1990)	[276]
411				**IC_{50} 1–3.6 μM** (HeLa, MCF-7, HCT-116, PANC-1, SW1990)	
412				**IC_{50} 0.8–2.1 μM** (HeLa, MCF-7, HCT-116, PANC-1, SW1990)	
413				**IC_{50} 26.6 μM** (PANC-1)	
414				**IC_{50} 29.4** (HCT-116)	
406				**IC_{50} 10.3–13.1 μM** (HeLa, MCF-7, HCT-116, PANC-1, SW1990)	
407				**IC_{50} 6–8.4 μM** (HeLa, MCF-7, HCT-116, PANC-1, SW1990)	
408				**IC_{50} 0.3–1.8 μM** (HeLa, MCF-7, HCT-116, PANC-1, SW1990)	
409				**IC_{50} 3.31–44.1 μM** (U251, SW-1990, SG7901, MCF-7, Huh-7, HeLa, H460) [277]	
358	*Aspergillus sydowii* SP-1 *Aspergillus* sp. xy02	Antarctica Mangrove	AB AF	**MIC 0.5, 1, 0.25, 0.5 μg/mL** (*S. aureus*, MRSA, *S. epidermidis*, MRSE)	[44] [264]
359				**MIC 0.5, 1, 0.25, 0.5 μg/mL** (*S. aureus*, MRSA, *S. epidermidis,* MRSE) [44] **IC_{50} 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	**IC_{50} 8.2 μM** (HepG2) [47] **IC_{50} 4.1–12.5 μM** (A549, SHG-44, HepG2, BIU-87, ECA-109, Hela-S3, PANC-1, BEL-7402) [299] **IC_{50} 15–40 μg/mL** (HeLa, SW1990, NCI-H460) [297] **Qualitative AF activity** (*Aspergillus niger*) [297]	[47] [299]
453	*Penicillium granulatum* MCCC 3A00475	Deep-sea 2284 m	CT	**IC_{50} 8.6 μM** (HepG2)	[47]
445				**IC_{50} 1.2 μM** (DLD-1 cells on polyHEMA-coated) [298] **IC_{50} 40 μM** (DLD-1 cells on uncoated plates) [298]	

Table 6. (Contd.)

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
449	*Penicillium granulatum* MCCC 3A00475	Deep-sea 2284 m	CT	**IC_{50} 5.5–8.3 μM** (A549, SHG-44)	[299]
451				**IC_{50} 4.8–14.4 μM** (A549, SHG-44, HepG2, BIU-87, ECA-109, Hela-S3, PANC-1, BEL-7402)	
452				**IC_{50} 4.4–9.2 μM** (A549, HepG2, BIU-87, ECA-109, Hela-S3)	
447				**IC_{50} 4.4–9.9 μM** (A549, SHG-44, ECA-109, Hela-S3, PANC-1) **Qualitative AF activity** (*C. albicans* ATCC 10231, *S. cerevisiae* ATCC 9080) [300] **Qualitative AB activity** (*S. aureus* ATCC 6538-P, *B. cereus* ATCC 11778, *B. subtilis* ATCC 6633) [300]	
385	*Penicillium griseofulvum*	Deep-sea 1420 m	CT	**IC_{50} 28.7 μM** (ECA-109)	[267]
415	*Aspergillus wentii* SD-310	Deep-sea 2038 m	AB AF	**MIC 8, 32, 8, 8 μg/mL** (*E. tarda*, *P. aeruginosa*, *V. harveyi*, *V. parahaemolyticus*)	[278]
416				**MIC 32, 8, 8, 8 μg/mL** (*E. coli*, *E. tarda*, *V. harveyi, V. parahaemolyticus*)	
417				**MIC 32 μg/mL** (*Aeromonas hydrophilia*, *V. anguillarum*)	
418				**MIC 32, 32 μg/mL** (*E. tarda*, *V. harveyi*)	
419				**MIC 32, 32 μg/mL** (*V. anguillarum*, *V. harveyi*) **MIC 4 μg/mL** (*F. graminearum*)	
432	*Sarocladium kiliense*	Deep-sea 5070 m	CT	**IC_{50} 25.8 μM** (HeLa-S3)	[290]
438				**IC_{50} 9.2 μM** (HeLa-S3)	
457				**IC_{50} 44.2 μM** (HeLa-S3)	
456				**IC_{50} 9.3 μM** (HeLa-S3)	
455				**IC_{50} 30.1 μM** (HeLa-S3) **IC_{50} 70 μM** (A549) [293]	

[170]. 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, eutypellacytosporins 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 (4*E*,8*E*)-4,8-dimethyldeca-4,8-dienoic acid.

CONCLUSIONS

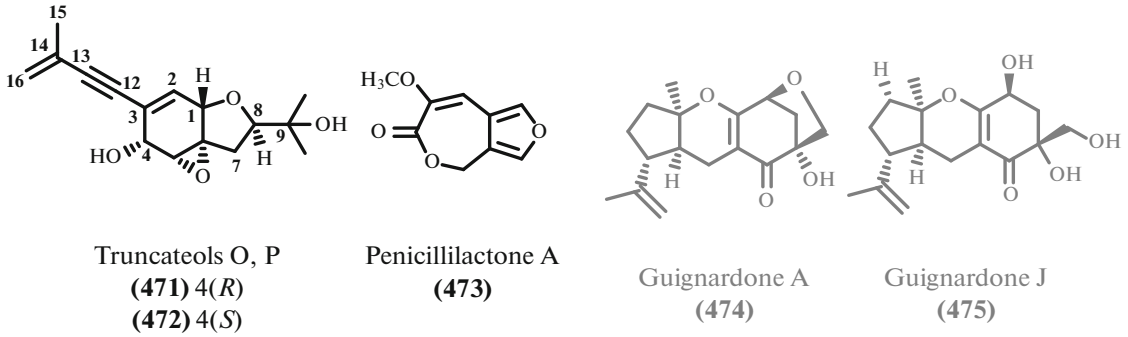
The search for new antibiotics is an increasingly urgent task in the context of the spread of drug resistance. Different strategies were used in different periods to search for natural biologically active compounds. The most productive was the Waksman platform, which consists in the cultivation of soil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

Table 7. Data on the origin and biological activity of compounds of mixed and unidentified origin

Cpd.	Producer/species	Extremophile type/origin	Activity/ toxicity	EC_{50}, IC_{50}, MIC	Ref.
458	*Penicillium* sp. ZZ1283	Marine	AB AF	**MIC 4, 3 μg/mL** (*S. aureus*, *E. coli*) **MIC 8 μg/mL** (*C. albicans*)	[301]
459	*Aspergillus ochraceus*	Marine	CT	**IC_{50} 0.8–1.0 μg/mL** (BME-UV1, MDCK) [328] **IC_{50} 17–87 μM** (IHKE) [329] **IC_{50} 0.3 μM** (Hep G2) [330]	[42]
460				**IC_{50} 3 μM** (A2780)	
461	*Aspergillus* sp. SCSIO41211	Mangrove	CT	**IC_{50} 0.031–23.2 μM (**H1975, U937, K562, BGC823, MOLT-4, MCF-7, A549, Hela, HL60, Huh-7)	[254]
463	*Trichoderma erinaceum* F1-1	Marine	CT	**IC_{50} 31.9 μM** (MDA-MB-435)	[270]
468				**IC_{50} 12.5 μM** (MDA-MB-435)	
469				**IC_{50} 41.4 μM** (MDA-MB-435)	
470				**IC_{50} 22.3, 18.4 μM** (MDA-MB-435, A549)	
471	*Truncatella angustata*	Marine	AV	**IC_{50} 39 μM** (HIV-1)	[307]
472				**IC_{50} 16.1 μM** (HIV-1)	
473	*Penicillium* sp. LS54.	Marine	AB	**MIC 8 μg/mL** (*V. harveyi*)	[308]
476	*Aspergillus versicolor* DJ013	Marine	AF	**MIC 64 μg/mL** (*G. graminis, C. neoformans, C. albicans*)	[310]
477				**MIC 64 μg/mL** (*G. graminis, C. neoformans, C. albicans*)	
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				**MIC 5, 2.5, 5, 2.5, 2.5, 1.25 μg/mL** (*M. tetragenus, S. aureus, S. albus, B. cereus, B.subtilis, E. coli*)	
482	*Penicillium* sp. TGM112	Mangrove	AB	**MIC 6.25 μg/mL** (*S. aureus*)	[312]
485	*Penicillium herquei* JX4	Mangrove	AF	**MIC 25, 50, 25, 100, 200, 50, 50, 50 μg/mL** (*Alternaria brassicicola*, *P. parasitica var. nicotianae*, *Colletotrichum capsici, B. oryzae*, *Diaporthe medusaea Nitschke*, *Ceratocystis paradoxa Mareau*, *P. theae, Alternaria citri*)	[313]
486				**MIC 25, 50, 25, 100, 100, 50, 25, 50 μg/mL** (*Alternaria brassicicola*, *P. parasitica var. nicotianae*, *Colletotrichum capsici, B. oryzae*, *Diaporthe medusaea Nitschke*, *Ceratocystis paradoxa Mareau*, *P. theae, Alternaria citri*)	
487				**MIC 50, 100, 25, 200, 200, 100, 50, 25 μg/mL** (*Alternaria brassicicola*, *P. parasitica var. nicotianae*, *Colletotrichum capsici, B. oryzae*, *Diaporthe medusaea Nitschke*, *Ceratocystis paradoxa Mareau*, *P. theae, Alternaria citri*)	
488				**MIC 50, 100, 50, 200, 200, 100, 50, 25 μg/mL** (*Alternaria brassicicola*, *P. parasitica var. nicotianae*, *Colletotrichum capsici, B. oryzae*, *Diaporthe medusaea Nitschke*, *Ceratocystis paradoxa Mareau*, *P. theae, Alternaria citri*)	

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*) **MIC 200 μg/mL** (*S. aureus,* MRSA, *M. gypseum* SH-MU-4) [315]	[314]
490	*Aspergillus terreus* LGO13	Marine	AB AF CT	**MIC 125, 250 μg/mL** (*S. aureus* ATCC 6538-P, *B. cereus* ATCC 11778) **MIC 250 μg/mL** (*C. albicans* ATCC 10231) **0.576–1 mM** (MCF-7/AGR, U251, SW620, H522, M14, SKOV3, DU145, A498) [316]	[287]
491				**Qualitative AF activity** (*C. albicans* ATCC 10231) **0.626–1 mM** (MCF-7/AGR, U251, SW620, H522, M14, SKOV3, DU145, A498) [316]	
492				**MIC 250.0 μg/mL** (*B. cereus* ATCC 11778) **0.16–1 mM** (MCF-7/AGR, U251, SW620, H522, M14, SKOV3, DU145, A498) [316]	
498				**MIC 62.5, 250, 250 μg/mL** (*S. aureus* ATCC 6538-P, *S. cerevisiae* ATCC 9080, *B. cereus* ATCC 11778) **MIC 250 μg/mL** (*C. albicans* ATCC 10231)	
493	*Aspergillus terreus* SCSIO FZQ028	Deep-sea 1718 m	AB	**Qualitative AB activity** (*S. aureus, B. thuringiensis, B. subtilis, E. coli*)	[318]
499				**Qualitative AB activity** (*S. aureus, B. thuringiensis, B. subtilis, E. coli*)	
500	*Aspergillus niger*	Marine	AB	**MIC 16 μg/mL** (*S. aureus*)	[322]
501				**MIC 32 μg/mL** (*S. aureus*)	
502				**MIC 32 μg/mL** (*S. aureus*)	
513	*Aspergillus versicolor* MCCC 3A00080	Deep-sea 2721 m	AB	**MIC 8 μg/mL** (*S. aureus*)	[321]
474	*Phyllosticta capitalensis*	Mangrove	AB	**MIC 25.5 μg/mL** (*P. aeruginosa*) [309]	[141]
475				**MIC 50, 50 μg/mL** (MRSA, *P. aeruginosa*) **MIC 89.3 μg/mL** (*B. subtilis*) [309]	
507	*Eutypella* sp. D-1	Arctic	CT	**IC_{50} 7.3–17.1 μM** (DU145, SW1990, Huh7, PANC-1)	[325]
508				**IC_{50} 4.9–11.0 μM** (DU145, SW1990, Huh7, PANC-1)	
509				**IC_{50} 9.6–13.5 μM** (DU145, SW1990, Huh7, PANC-1)	
510				**IC_{50} 7.5–13.4 μM** (DU145, SW1990, Huh7, PANC-1)	
511	*Penicillium* sp. RO-11	Hot spring deposits (45–65°C), Saudi Arabia/ Thermophile	AB CT	**MIC 1.4, 2.5, 0.13 μg/mL** (*S. aureus*, *Escherichia fergusonii*, *P. aeruginosa*) **IC_{50} 10 μM** (HTB-176)	[73]
504	*Penicillium* sp. YPGA11	Deep-sea 4500 m	AB	**MIC 32, 8 μg/mL** (*S. aureus* ATCC 43300, *S. aureus* ATCC 25913)	[327]
505				**MIC 16 μg/mL** (*S. aureus* ATCC 25913)	
506				**MIC 64, 32 μg/mL** (*S. aureus* ATCC 43300, *S. aureus* ATCC 25913)	



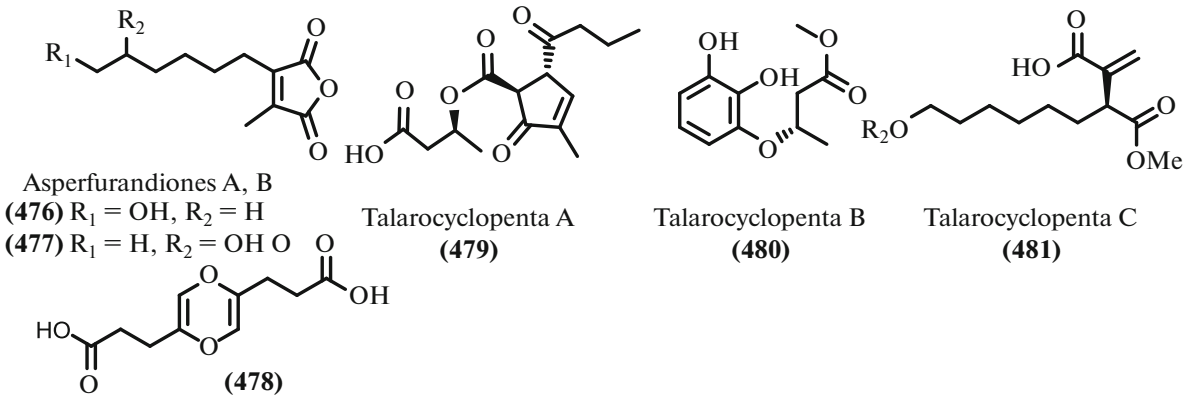
Truncateols O, P
(471) 4(*R*)
(472) 4(*S*)

Penicillilactone A
(473)

Guignardone A
(474)

Guignardone J
(475)

Fig. 30. Trunkateols, penicillacton A, and guignardones.



Asperfurandiones A, B
(476) R_1 = OH, R_2 = H
(477) R_1 = H, R_2 = OH

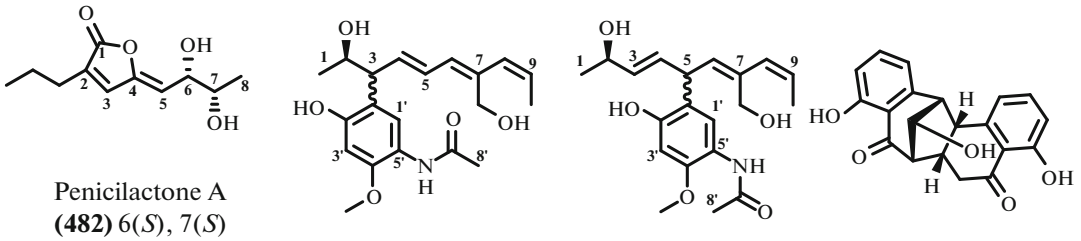
(478)

Talarocyclopenta A
(479)

Talarocyclopenta B
(480)

Talarocyclopenta C
(481)

Fig. 31. Asperfurandiones and talarocyclopentas.



Penicilactone A
(482) 6(*S*), 7(*S*)
Penicilactone B
(483) 6(*S*), 7(*R*)
Penicilactone C
(484) 6(*R*), 7(*S*)

Penicilquei A
(485) 3(*R*)
Penicilquei B
(486) 3(*S*)

Penicilquei C
(487) 5(*R*)
Penicilquei D
(488) 5(*S*)

Alternatone A
(489)

Fig. 32. Penicilactons, penicilqueis, and alternaton A.

ity [331]. 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].

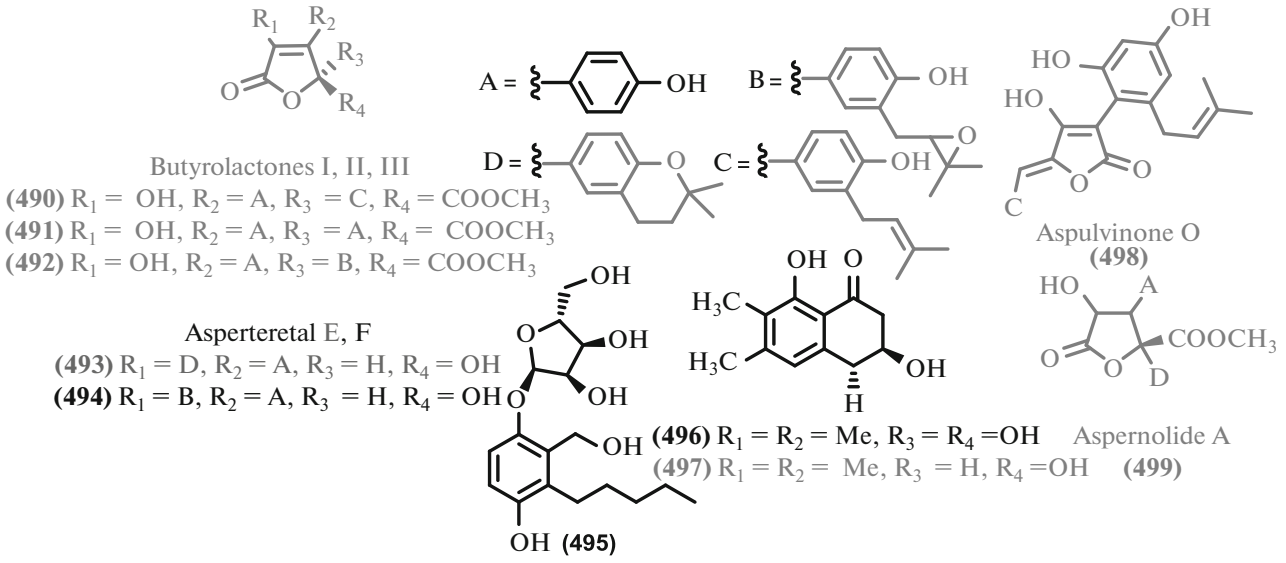


Fig. 33. Butyrolactones and phenols.

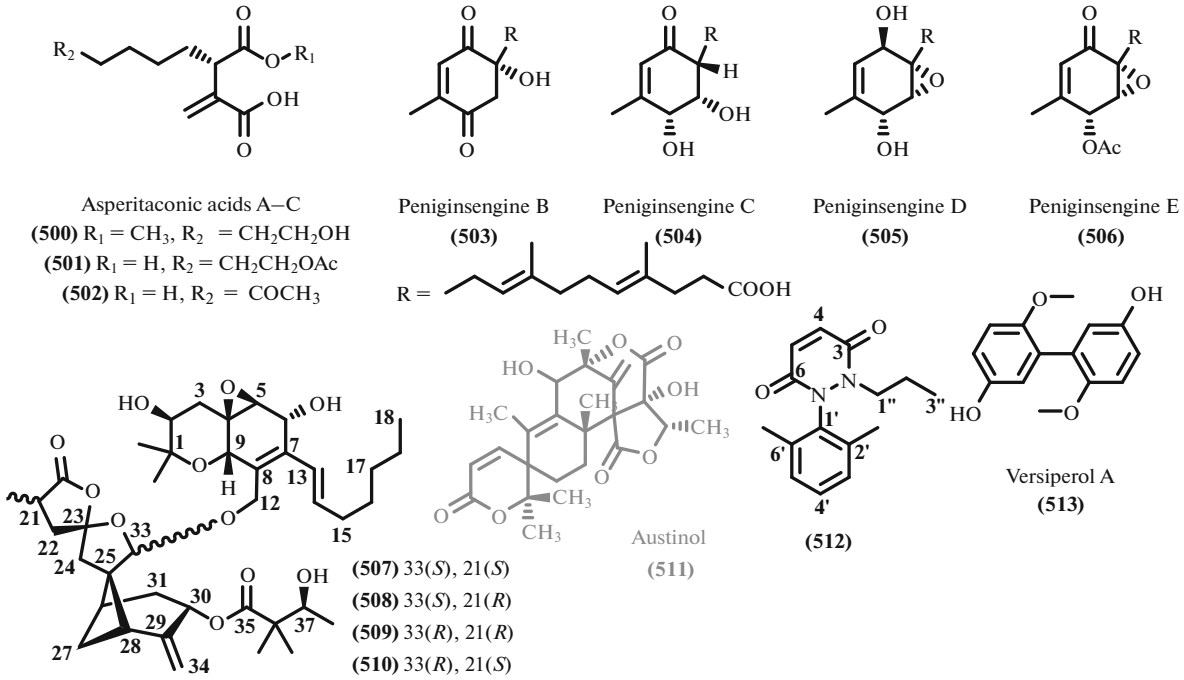


Fig. 34. Meroterpenoids and other metabolites of mixed origin.

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.

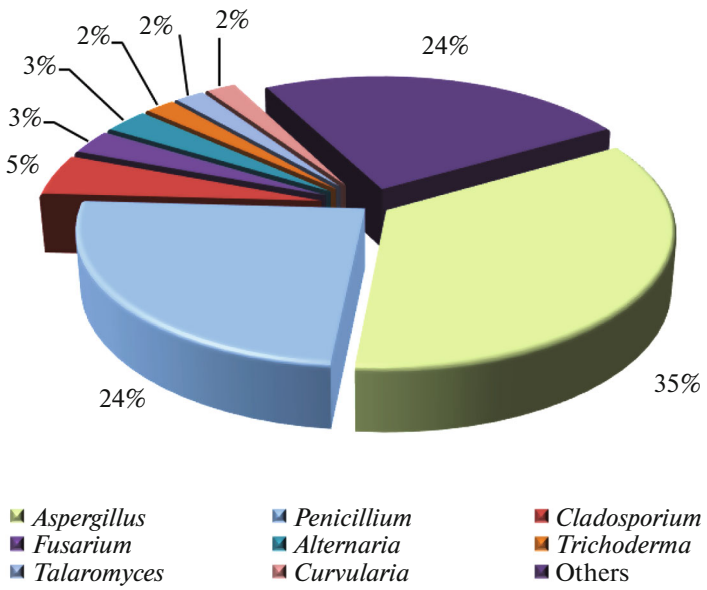


Fig. 35. Distribution of extremophilic micromycetes by genera.

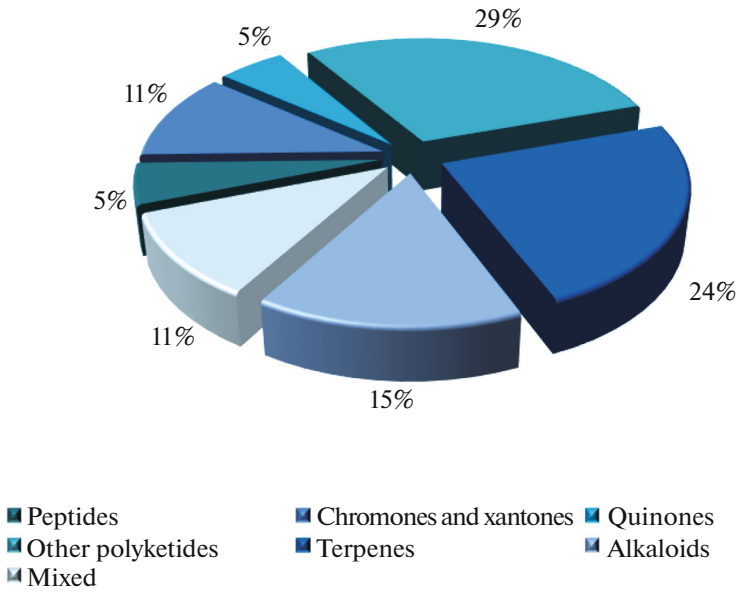


Fig. 36. Structural families of metabolites isolated from extremophilic micromycetes.

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-

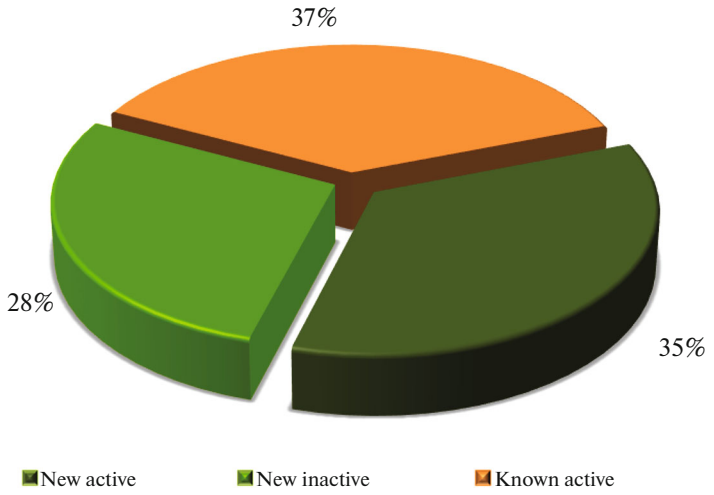


Fig. 37. Distribution of activity of new and previously described metabolites of extremophilic micromycetes.

ticular, peptaibols lipovelutibols B (**24**) and D (**26**) and their lipophilic analogs were obtained by the solid-phase method [334]. Terpenoids insulicolide (**354**) and 14-*O*-acetylinsulicolide (**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.

REFERENCES

1. Ribeiro da Cunha, B., Fonseca, L.P., and Calado, C.R.C., *Antibiotics*, 2019, vol. 8, p. 45. https://doi.org/10.3390/antibiotics8020045
2. Dougan, G., Dowson, C., and Overington, J., *Drug Discov. Today*, 2019, vol. 24, pp. 452–461. https://doi.org/10.1016/j.drudis.2018.11.015
3. Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance, United Nations Resolution A/RES/71/3 (adopted October 5, 2016). https://undocs.org/ru/A/RES/71/3.
4. *Global Action Plan to Combat Antimicrobial Resistance*, Geneva: World Health Organization, 2015, pp. 15–29.
5. Strategy for Preventing the Spread of Antimicrobial Resistance in the Russian Federation for the Period up to 2030, Order of the Government of the Russian Federation dated September 25, 2017, no. 2045-r, pp. 2–14.
6. Newman, D.J. and Cragg, G.M., *J. Nat. Prod.*, 2020, vol. 83, pp. 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285
7. Sayed, A.M., Hassan, M.H.A., Alhadrami, H.A., Hassan, H.M., Goodfellow, M., and Rateb, M.E., *J. Appl. Microbiol.*, 2020, vol. 128, pp. 630–657. https://doi.org/10.1111/jam.14386

8. Keller, N.P., *Nat. Rev. Microbiol.*, 2019, vol. 17, pp. 167–180. https://doi.org/10.1038/s41579-018-0121-1
9. Schueffler, A. and Anke, T., *Nat. Prod. Rep.*, vol. 31, pp. 1425–1448. https://doi.org/10.1039/C4NP00060A
10. Zhang, X., Li, S.-J., Li, J.-J., Liang, Z.-Z., and Zhao, C.-Q., *Mar. Drugs*, 2018, vol. 16, p. 194. https://doi.org/10.3390/md16060194
11. Wickneswary, N., Abu, BakarM., and Khalid, R., *Malaysian J. Chem.*, 2016, vol. 18, pp. 100–105.
12. Tian, Y., Li, Y.-L., and Zhao, F.-C., *Mar. Drugs*, 2017, vol. 15, p. 28. https://doi.org/10.3390/md15030028
13. Stierle, A.A. and Stierle, D.B., *Nat. Prod. Commun.*, 2014, vol. 9, pp. 1037–1044. https://doi.org/10.1177/1934578X1400900738
14. Corral, P., Amoozegar, M.A., and Ventosa, A., *Mar. Drugs*, 2019, vol. 18, p. 33. https://doi.org/10.3390/md18010033
15. Tiquia-Arashiro, S.M. and Grube, M., *Fungi in Extreme Environments: Ecological Role and Biotechnological Significance*, Springer Int. Publ., 2019. https://doi.org/10.1007/978-3-030-19030-9
16. Giddings, L.-A. and Newman, D.J., Bioactive compounds from extremophilic marine fungi, in *Fungi in Extreme Environments: Ecological Role and Biotechnological Significance*, Tiquia-Arashiro, S.M. and Grube, M., Eds., Springer Int. Publ., 2019, pp. 349–382. https://doi.org/10.1007/978-3-030-19030-9_18
17. Zhang, X., Li, S.-J., Li, J.-J., Liang, Z.-Z., and Zhao, C.-Q., *Mar. Drugs*, 2018, vol. 16, p. 194. https://doi.org/10.3390/md16060194
18. Gribble, G., *Mar. Drugs*, 2015, vol. 13, pp. 4044–4136. https://doi.org/10.3390/md13074044
19. Xu, L., Meng, W., Cao, C., Wang, J., Shan, W., and Wang, Q., *Mar. Drugs*, 2015, vol. 13, pp. 3479–3513. https://doi.org/10.3390/md13063479
20. Jin, L., Quan, C., Hou, X., and Fan, S., *Mar. Drugs*, 2016, vol. 14, p. 76. https://doi.org/10.3390/md14040076
21. Ma, H.-G., Liu, Q., Zhu, G.-L., Liu, H.-S., and Zhu, W.-M., *J. Asian Nat. Prod. Res.*, 2016, vol. 18, pp. 92–115. https://doi.org/10.1080/10286020.2015.1127230
22. Fouillaud, M., Venkatachalam, M., Girard-Valenciennes, E., Caro, Y., and Dufosse, L., *Mar. Drugs*, 2016, vol. 14, 64. https://doi.org/10.3390/md14040064
23. Imhoff, J., *Mar. Drugs*, 2016, vol. 14, p. 19. https://doi.org/10.3390/md14010019
24. El-Hossary, E.M., Cheng, C., Hamed, M.M., El-Sayed, HamedA.N., Ohlsen, K., Hentschel, U., and Abdelmohsen, U.R., *Eur. J. Med. Chem.*, 2017, vol. 126, pp. 631–651. https://doi.org/10.1016/j.ejmech.2016.11.022
25. Nicoletti, R., Salvatore, M., and Andolfi, A., *Mar. Drugs*, 2018, vol. 16, p. 12. https://doi.org/10.3390/md16010012
26. Tortorella, E., Tedesco, P., Palma Esposito, F., Fanuary, G., Fani, R., Jaspars, M., and de Pascale, D., *Mar. Drugs*, 2018, vol. 16, p. 355. https://doi.org/10.3390/md16100355
27. Ancheeva, E., Daletos, G., and Proksch, P., *Mar. Drugs*, 2018, vol. 16, p. 319. https://doi.org/10.3390/md16090319
28. Rai, M., Gade, A., Zimowska, B., Ingle, A.P., and Ingle, P., *Appl. Microbiol. Biotechnol.*, 2018, vol. 102, pp. 9053–9066. https://doi.org/10.1007/s00253-018-9329-2
29. Deshmukh, S.K., Prakash, V., and Ranjan, N., *Front. Microbiol.*, 2018, vol. 8, p. 2536. https://doi.org/10.3389/fmicb.2017.02536
30. Wang, K.-W. and Ding, P., *Mini-Rev. Med. Chem.*, 2018, vol. 18, pp. 1072–1094. https://doi.org/10.2174/1389557518666180305160856
31. Barone, G., Varrella, S., Tangherlini, M., Rastelli, E., Dell'Anno, A., Danovaro, R., and Corinaldesi, C., *Diversity*, 2019, vol. 11, p. 113. https://doi.org/10.3390/d11070113
32. Youssef, F.S., Ashour, M.L., Singab, A.N.B., and Wink, M., *Mar. Drugs*, 2019, vol. 17, p. 559. https://doi.org/10.3390/md17100559
33. Carroll, A.R., Copp, B.R., Davis, R.A., Keyzers, R.A., and Prinsep, M.R., *Nat. Prod. Rep.*, 2019, vol. 36, pp. 122–173. https://doi.org/10.1039/c8np00092a
34. Sun, W., Wu, W., Liu, X., Zaleta-Pinet, D.A., and Clark, B.R., *Mar. Drugs*, 2019, vol. 17, p. 339. https://doi.org/10.3390/md17060339
35. Arifeen, M., Ma, Y.-N., Xue, Y.-R., and Liu, C.-H., *Mar. Drugs*, 2019, vol. 18, p. 9. https://doi.org/10.3390/md18010009
36. Luo, M., Zang, R., Wang, X., Chen, Z., Song, X., Ju, J., and Huang, H., *J. Nat. Prod.*, 2019, vol. 82, pp. 2594–2600. https://doi.org/10.1021/acs.jnatprod.9b00545
37. Youssef, D. and Alahdal, A., *Molecules*, 2018, vol. 23, p. 394. https://doi.org/10.3390/molecules23020394
38. Adamczeski, M., Reed, A.R., and Crews, P., *J. Nat. Prod.*, 1995, vol. 58, pp. 201–208. https://doi.org/10.1021/np50116a007
39. Van, G., Dai, Sh., Chen, M., Vu, Kh., Shi, L., Lyuo, S., and Li, S., *Khim. Prirodn. Soed.*, 2010, vol. 46, no. 4, pp. 491–493.
40. Liu, C.-C., Zhang, Z.-Z., Feng, Y.-Y., Gu, Q.-Q., Li, D.-H., and Zhu, T.-J., *Nat. Prod. Res.*, 2019, vol. 33, pp. 414–419. https://doi.org/10.1080/14786419.2018.1455045
41. Guimarães, D.O., Borges, W.S., Vieira, N.J., de Oliveira, L.F., da Silva, C.H.T.P., Lopes, N.P., Dias, L.G., Durán-Patrón, R., Collado, I.G., and Pupo, M.T., *Phytochemistry*, 2010, vol. 71, pp. 1423–1429. https://doi.org/10.1016/j.phytochem.2010.05.012
42. Frank, M., Özkaya, F., Müller, W., Hamacher, A., Kassack, M., Lin, W., Liu, Z., and Proksch, P., *Mar. Drugs*, 2019, vol. 17, p. 99. https://doi.org/10.3390/md17020099
43. Kimura, Y., Tani, K., Kojima, A., Sotoma, G., Okada, K., and Shimada, A., *Phytochemistry*, 1996, vol. 41,

pp. 665–669.
https://doi.org/10.1016/0031-9422(95)00693-1

44. Li, W., Luo, D., Huang, J., Wang, L., Zhang, F., Xi, T., Liao, J., and Lu, Y., *Nat. Prod. Res.*, 2018, vol. 32, pp. 662–667.
https://doi.org/10.1080/14786419.2017.1335730
45. Hodge, R.P., Harris, C.M., and Harris, T.M., *J. Nat. Prod.*, 1988, vol. 51, pp. 66–73.
https://doi.org/10.1021/np50055a008
46. Niu, S., Xia, M., Chen, M., Liu, X., Li, Z., Xie, Y., Shao, Z., and Zhang, G., *Mar. Drugs*, 2019, vol. 17, p. 686.
https://doi.org/10.3390/md17120686
47. Niu, S., Wang, N., Xie, C.-L., Fan, Z., Luo, Z., Chen, H.-F., and Yang, X.-W., *J. Antibiot.*, 2018, vol. 71, pp. 658–661.
https://doi.org/10.1038/s41429-018-0046-y
48. Kopp, B. and Rehm, H.J., *Eur. J. Appl. Microbiol. Biotechnol.*, 1979, vol. 6, pp. 397–401.
https://doi.org/10.1007/BF00499170
49. Du, L., Li, D., Zhu, T., Cai, S., Wang, F., Xiao, X., and Gu, Q., *Tetrahedron*, 2009, vol. 65, pp. 1033–1039.
https://doi.org/10.1016/j.tet.2008.11.078
50. Kawai, K., Nozawa, K., Nakajima, S., and Iitaka, Y., *Chem. Pharm. Bull.*, 1984, vol. 32, pp. 94–98.
https://doi.org/10.1248/cpb.32.94
51. Yang, B., Sun, W., Wang, J., Lin, S., Li, X.-N., Zhu, H., Luo, Z., Xue, Y., Hu, Z., and Zhang, Y., *Mar. Drugs*, 2018, vol. 16, p. 110.
https://doi.org/10.3390/md16040110
52. Du, L., Yang, X., Zhu, T., Wang, F., Xiao, X., Park, H., and Gu, Q., *Chem. Pharm. Bull.*, 2009, vol. 57, pp. 873–876.
https://doi.org/10.1248/cpb.57.873
53. Zhong, W., Wang, J., Wei, X., Chen, Y., Fu, T., Xiang, Y., Huang, X., Tian, X., Xiao, Z., Zhang, W., Zhang, S., Long, L., and Wang, F., *Org. Lett.*, 2018, vol. 20, pp. 4593–4596.
https://doi.org/10.1021/acs.orglett.8b01880
54. Wang, W., Wan, X., Liu, J., Wang, J., Zhu, H., Chen, C., and Zhang, Y., *Mar. Drugs*, 2018, vol. 16, p. 150.
https://doi.org/10.3390/md16050150
55. Zhang, M., Wang, W.-L., Fang, Y.-C., Zhu, T.-J., Gu, Q.-Q., and Zhu, W.-M., *J. Nat. Prod.*, 2008, vol. 71, pp. 985–989.
https://doi.org/10.1021/np700737g
56. Singh, V.P., Yedukondalu, N., Sharma, V., Kushwaha, M., Sharma, R., Chaubey, A., Kumar, A., Singh, D., and Vishwakarma, R.A., *J. Nat. Prod.*, 2018, vol. 81, pp. 219–226.
https://doi.org/10.1021/acs.jnatprod.6b00873
57. Rogozhin, E., Sadykova, V., Baranova, A., Vasilchenko, A., Lushpa, V., Mineev, K., Georgieva, M., Kul'ko, A., Krasheninnikov, M., Lyundup, A., Vasilchenko, A., and Andreev, Y., *Molecules*, 2018, vol. 23, 2785.
https://doi.org/10.3390/molecules23112785
58. Fdhila, F., Vázquez, V., Sánchez, J.L., and Riguera, R., *J. Nat. Prod.*, 2003, vol. 66, pp. 1299–1301.
https://doi.org/10.1021/np030233e
59. Guo, C., Lin, X.-P., Liao, S.-R., Yang, B., Zhou, X.-F., Yang, X.-W., Tian, X.-P., Wang, J.-F., and Liu, Y.-H., *Nat. Prod. Res.*, 2020, vol. 34, pp. 1197–1205.
https://doi.org/10.1080/14786419.2018.1553880
60. Zhao, D.-L., Wang, D., Tian, X.-Y., Cao, F., Li, Y.-Q., and Zhang, C.-S., *Mar. Drugs*, 2018, vol. 16, 36.
https://doi.org/10.3390/md16010036
61. Wang, W., Chen, R., Luo, Z., Wang, W., and Chen, J., *Nat. Prod. Res.*, 2018, vol. 32, pp. 558–563.
https://doi.org/10.1080/14786419.2017.1329732
62. Bode, H.B., Bethe, B., Höfs, R., and Zeeck, A., *ChemBioChem*, 2002, vol. 3, pp. 619–627.
https://doi.org/10.1002/1439-7633(20020703)3:7<619::AID-CBIC619>3.0.CO;2-9
63. Yang, S.-Q., Li, X.-M., Xu, G.-M., Li, X., An, C.-Y., and Wang, B.-G., *J. Antibiot.*, 2018, vol. 71, pp. 778–784.
https://doi.org/10.1038/s41429-018-0063-x
64. Hatsuda, Y., Hamasaki, T., Ishida, M., and Yoshikawa, S., *Agric. Biol. Chem.*, 1969, vol. 33, pp. 131–133.
https://doi.org/10.1080/00021369.1969.10859290
65. Endale, M., Ekberg, A., Alao, J., Akala, H., Ndakala, A., Sunnerhagen, P., Erdelyi, M., and Yenesew, A., *Molecules*, 2013, vol. 18, pp. 311–321.
https://doi.org/10.3390/molecules18010311
66. Chung, M.-I., Jou, S.-J., Cheng, T.-H., Lin, C.-N., Ko, F.-N., and Teng, C.-M., *J. Nat. Prod.*, 1994, vol. 57, pp. 313–316.
https://doi.org/10.1021/np50104a020
67. Moon, M.K., Han, Y.-M., Lee, Y.-J., Lee, L.H., Yang, J.H., Kwon, B.-M., and Kim, D.K., *Arch. Pharm. Res.*, 2010, vol. 33, pp. 1747–1751.
https://doi.org/10.1007/s12272-010-1106-4
68. Yan, L., Sen', Z., Li, Zh.-Kh., and Pan', I.-M., *Khim. Prir. Soed.*, 2016, vol. 52, no. 5, pp. 760–761.
69. Wells, J.M., Cole, R.J., and Kirksey, J.W., *Appl. Microbiol.*, 1975, vol. 30, pp. 26–28.
70. Liu, D., Yan, L., Ma, L., Huang, Y., Pan, X., Liu, W., and Lv, Z., *Arch. Pharm. Res.*, 2015, vol. 38, pp. 1038–1043.
https://doi.org/10.1007/s12272-014-0371-z
71. May, Zin W.W., Buttachon, S., Dethoup, T., Pereira, J.A., Gales, L., Inácio, Â., Costa, P.M., Lee, M., Sekeroglu, N., Silva, A.M.S., Pinto, M.M.M., and Kijjoa, A., *Phytochemistry*, 2017, vol. 141, pp. 86–97.
https://doi.org/10.1016/j.phytochem.2017.05.015
72. Hawas, U.W., El-Beih, A.A., and El-Halawany, A.M., *Arch. Pharm. Res.*, 2012, vol. 35, pp. 1749–1756.
https://doi.org/10.1007/s12272-012-1006-x
73. Orfali, R. and Perveen, S., *J. Chem.*, 2019, vol. 2019, 7162948.
https://doi.org/10.1155/2019/7162948
74. Said, G., Khou, Sh.-M., Lyu, Sh., Chao, Zh., Dzyan, Ya.-Ya., Zhen, Dzh.-E., and Shao, Ch.-L., *Khim. Prir. Soed.*, 2019, vol. 55, no. 3, pp. 457–459.
75. Song, Z., Liu, Y., Gao, J., Hu, J., He, H., Dai, S., Wang, L., Dai, H., Zhang, L., and Song, F., *Nat. Prod. Res.*, 2019.
https://doi.org/10.1080/14786419.2019.1660331
76. Fang, W., Wang, J., Wang, J., Shi, L., Li, K., Lin, X., Min, Y., Yang, B., Tang, L., Liu, Y., and Zhou, X., *J.*

Nat. Prod., 2018, vol. 81, pp. 1405–1410. https://doi.org/10.1021/acs.jnatprod.8b00015

77. Wang, W., Gao, M., Luo, Z., Liao, Y., Zhang, B., Ke, W., Shao, Z., Li, F., and Chen, J., *Nat. Prod. Res.*, 2019, vol. 33, pp. 3077–3082. https://doi.org/10.1080/14786419.2018.1519561
78. Song, T., Chen, M., Chai, W., Zhang, Z., and Lian, X.-Y., *Tetrahedron*, 2018, vol. 74, pp. 884–891. https://doi.org/10.1016/j.tet.2018.01.015
79. Buttachon, S., Ramos, A., Inácio, Â., Dethoup, T., Gales, L., Lee, M., Costa, P., Silva, A., Sekeroglu, N., Rocha, E., Pinto, M., Pereira, J., and Kijjoa, A., *Mar. Drugs*, 2018, vol. 16, p. 119. https://doi.org/10.3390/md16040119
80. Danielsen, K., Aksnes, D.W., and Francis, G.W., *Magn. Reson. Chem.*, 1992, vol. 30, pp. 359–360. https://doi.org/10.1002/mrc.1260300414
81. Lee, M.S., Cha, E.Y., Sul, J.Y., Song, I.S., and Kim, J.Y., *Phytother. Res.*, 2011, vol. 25, pp. 833–837. https://doi.org/10.1002/ptr.3323
82. Semple, S.J., Pyke, S.M., Reynolds, G.D., and Flower, R.L.P., *Antiviral Res.*, 2001, vol. 49, pp. 169–178. https://doi.org/10.1016/S0166-3542(01)00125-5
83. Li, J.L., Jiang, X., Liu, X., He, C., Di, Y., Lu, S., Huang, H., Lin, B., Wang, D., and Fan, B., *Fitoterapia*, 2019, vol. 133, pp. 1–4. https://doi.org/10.1016/j.fitote.2018.11.015
84. Lee, Y.M., Li, H., Hong, J., Cho, H.Y., Bae, K.S., Kim, M.A., Kim, D.-K., and Jung, J.H., *Arch. Pharm. Res.*, 2010, vol. 33, pp. 231–235. https://doi.org/10.1007/s12272-010-0207-4
85. Liu, K., Zheng, Y., Miao, C., Xiong, Z., Xu, L., Guan, H., Yang, Y., and Zhao, L., *Nat. Prod. Res.*, 2014, vol. 28, pp. 2334–2337. https://doi.org/10.1080/14786419.2014.935941
86. Sedmera, P., Volc, J., Weijer, J., Vokoun, J., and Musilek, V., *Collect. Czech. Chem. Commun.*, 1981, vol. 46, pp. 1210–1216. https://doi.org/10.1135/cccc19811210
87. Pang, X., Lin, X., Wang, P., Zhou, X., Yang, B., Wang, J., and Liu, Y., *Mar. Drugs*, 2018, vol. 16, 280. https://doi.org/10.3390/md16080280
88. Zhao, D.-L., Cao, F., Wang, C.-Y., Yang, L.-J., Shi, T., Wang, K.-L., Shao, C.-L., and Wang, C.-Y., *J. Nat. Prod.*, 2019, vol. 82, pp. 3201–3204. https://doi.org/10.1021/acs.jnatprod.9b00905
89. Boutin, B., Peeler, J., and Twedt, R., *J. Toxicol. Environ. Health*, 1989, vol. 26, pp. 75–81. https://doi.org/10.1080/15287398909531234
90. Gao, S.-S., Li, X.-M., and Wang, B.-G., *Nat. Prod. Commun.*, 2009, vol. 4, p. 1477–1480. https://doi.org/10.1177/1934578X0900401107
91. Okuno, T., Natsume, I., Sawai, K., Sawamura, K., Furusaki, A., and Matsumoto, T., *Tetrahedron Lett.*, 1983, vol. 24, pp. 5653–5656. https://doi.org/10.1016/S0040-4039(00)94165-0
92. Kornsakulkarn, J., Dolsophon, K., Boonyuen, N., Boonruangprapa, T., Rachtawee, P., Prabpai, S., Kongsaeree, P., and Thongpanchang, C., *Tetrahedron*, 2011, vol. 67, pp. 7540–7547. https://doi.org/10.1016/j.tet.2011.07.078
93. Supratman, U., Hirai, N., Sato, S., Watanabe, K., Malik, A., Annas, S., Harneti, D., Maharani, R., Koseki, T., and Shiono, Y., *Nat. Prod. Res.*, 2019. https://doi.org/10.1080/14786419.2019.1650358
94. Li, Q., Zhu, R., Yi, W., Chai, W., Zhang, Z., and Lian, X.-Y., *Phytochemistry*, 2018, vol. 152, pp. 53–60. https://doi.org/10.1016/j.phytochem.2018.04.021
95. Bashyal, B.P., Wellensiek, B.P., Ramakrishnan, R., Faeth, S.H., Ahmad, N., and Gunatilaka, A.A.L., *Bioorg. Med. Chem.*, 2014, vol. 22, pp. 6112–6116. https://doi.org/10.1016/j.bmc.2014.08.039
96. Zhu, A., Zhang, X.-W., Zhang, M., Li, W., Ma, Z.-Y., Zhu, H.-J., and Cao, F., *Mar. Drugs*, 2018, vol. 16, p. 312. https://doi.org/10.3390/md16090312
97. Zhu, A., Yang, M.-Y., Zhang, Y.-H., Shao, C.-L., Wang, C.-Y., Hu, L.-D., Cao, F., and Zhu, H.-J., *Sci. Rep.*, 2018, vol. 8, p. 10621. https://doi.org/10.1038/s41598-018-28996-5
98. González-Andrade, M., Rivera-Chávez, J., Sosa-Peinado, A., Figueroa, M., Rodríguez-Sotres, R., and Mata, R., *J. Med. Chem.*, 2011, vol. 54, pp. 3875–3884. https://doi.org/10.1021/jm200167g
99. Figueroa, M., González, M., Rodríguez-Sotres, R., Sosa-Peinado, A., González-Andrade, M., Cerda-García-Rojas, C.M., and Mata, R, *Bioorg. Med. Chem.*, 2009, vol. 17, pp. 2167–2174. https://doi.org/10.1016/j.bmc.2008.10.079
100. Song, Z., Gao, J., Hu, J., He, H., Huang, P., Zhang, L., and Song, F., *Nat. Prod. Res.*, 2020, vol. 34, pp. 2907–2912. https://doi.org/10.1080/14786419.2019.1597355
101. Maes, C.M. and Steyn, P.S., *J. Chem. Soc., Perkin Trans.*, 1984, pp. 1137–1140. https://doi.org/10.1039/p19840001137
102. Putra, H.N., Rukachaisirikul, V., Saithong, S., Phongpaichit, S., Preedanon, S., Sakayaroj, J., Hadsadee, S., and Jungsuttiwong, S., *Tetrahedron*, 2019, vol. 75, p. 130530. https://doi.org/10.1016/j.tet.2019.130530
103. Takahashi, I., Kawano, T., and Kimura, Y., *Z. Naturforsch.*, 2001, vol. 56b, pp. 797–803. https://doi.org/10.1515/znb-2001-0813
104. Hamasaki, T., Sato, Y., and Hatsuda, Y., *Agric. Biol. Chem.*, 1975, vol. 39, pp. 2341–2345. https://doi.org/10.1080/00021369.1975.10861955
105. Sun, R.-R., Miao, F.-P., Zhang, J., Wang, G., Yin, X.-L., and Ji, N.-Y., *Magn. Reson. Chem.*, 2013, vol. 51, pp. 65–68. https://doi.org/10.1002/mrc.3903
106. Trisuwan, K., Rukachaisirikul, V., Kaewpet, M., Phongpaichit, S., Hutadilok-Towatana, N., Preedanon, S., and Sakayaroj, J., *J. Nat. Prod.*, 2011, vol. 74, pp. 1663–1667. https://doi.org/10.1021/np200374j
107. Elnaggar, M.S., Ebada, S.S., Ashour, M.L., Ebrahim, W., Müller, W.E.G., Mándi, A., Kurtán, T., Singab, A., Lin, W., Liu, Z., and Proksch, P., *Tetrahedron*, 2016, vol. 72, pp. 2411–2419. https://doi.org/10.1016/j.tet.2016.03.073
108. Salendra, L., Lin, X., Chen, W., Pang, X., Luo, X., Long, J., Liao, S., Wang, J., Zhou, X., Liu, Y., and

Yang, B., *Nat. Prod. Res.*, 2019. https://doi.org/10.1080/14786419.2019.1610757

109. Wang, H., Gloer, J.B., Scott, J.A., and Malloch, D., *Tetrahedron Lett.*, 1995, vol. 36, pp. 5847–5850. https://doi.org/10.1016/0040-4039(95)01174-G
110. Khamthong, N., Rukachaisirikul, V., Phongpaichit, S., Preedanon, S., and Sakayaroj, J., *Tetrahedron*, 2012, vol. 68, pp. 8245–8250. https://doi.org/10.1016/j.tet.2012.07.060
111. Sun, Y.-L., Bao, J., Liu, K.-S., Zhang, X.-Y., He, F., Wang, Y.-F., Nong, X.-H., and Qi, S.-H., *Planta Med.*, 2013, vol. 79, pp. 1474–1479. https://doi.org/10.1055/s-0033-1350805
112. Li, X., Zhang, L., Liu, Y., Guo, Z., Deng, Z., Chen, J., and Xuantu Zou, K., *Nat. Prod. Commun.*, 2013, vol. 8, p. 1934578X1300800. https://doi.org/10.1177/1934578X1300800510
113. Luo, Y.-P., Zheng, C.-J., Chen, G.-Y., Song, X.-P., and Wang, Z., *J. Antibiot.*, 2019, vol. 72, pp. 513–517. https://doi.org/10.1038/s41429-019-0178-8
114. Kumla, D., Pereira, J., Dethoup, T., Gales, L., Freitas-Silva, J., Costa, P., Lee, M., Silva, A., Sekeroglu, N., Pinto, M., and Kijjoa, A., *Mar. Drugs*, 2018, vol. 16, 289. https://doi.org/10.3390/md16080289
115. Fujita, K.-I., Nagamine, Y., Ping, X., and Taniguchi, M., *J. Antibiot.*, 1999, vol. 52, pp. 628–634. https://doi.org/10.7164/antibiotics.52.628
116. Wang, L., Han, X., Zhu, G., Wang, Y., Chairoungdua, A., Piyachaturawat, P., and Zhu, W., *Front. Chem.*, 2018, vol. 6, 344. https://doi.org/10.3389/fchem.2018.00344
117. Zhao, G.-Y., Fan, J.-Y., Hua, C.-P., Yan, W., Chen, C.-J., Lu, Y.-H., Jiao, R.-H., and Tan, R.-X., *RSC Adv.*, 2015, vol. 5, pp. 5657–5663. https://doi.org/10.1039/C4RA12851F
118. Chen, L., Li, Y.-P., Li, X.-X., Lu, Z.-H., Zheng, Q.-H., and Liu, Q.-Y., *J. Antibiot.*, 2019, vol. 72, pp. 34–44. https://doi.org/10.1038/s41429-018-0104-5
119. Ving, L. and Mcinnes, A., *Secalonic Acids and Their Use*, DE 3002761, 1980.
120. Zhang, J., Tao, L., Liang, Y., Yan, Y., Dai, C., Xia, X., She, Z., Lin, Y., and Fu, L., *Cell Cycle*, 2009, vol. 8, pp. 2444–2450. https://doi.org/10.4161/cc.8.15.9170
121. Bai, M., Zheng, C.-J., Tang, D.-Q., Zhang, F., Wang, H.-Y., and Chen, G.-Y., *J. Antibiot.*, 2019, vol. 72, pp. 779–782. https://doi.org/10.1038/s41429-019-0206-8
122. Liu, F., Cai, X.-L., Yang, H., Xia, X.-K., Guo, Z.-Y., Yuan, J., Li, M.-F., She, Z.-G., and Lin, Y.-C., *Planta Med.*, 2010, vol. 76, pp. 185–189. https://doi.org/10.1055/s-0029-1186047
123. Lenta, B.N., Ngatchou, J., Frese, M., Ladoh-Yemeda, F., Voundi, S., Nardella, F., Michalek, C., Wibberg, D., Ngouela, S., Tsamo, E., Kaiser, M., Kalinowski, J., and Sewald, N., *Z. Naturforsch. B*, 2016, vol. 71, pp. 1159–1167. https://doi.org/10.1515/znb-2016-0128
124. Zheng, C.-J., Liao, H.-X., Mei, R.-Q., Huang, G.-L., Yang, L.-J., Zhou, X.-M., Shao, T.-M., Chen, G.-Y., and Wang, C.-Y., *Nat. Prod. Res.*, 2019, vol. 33, pp. 1127–1134. https://doi.org/10.1080/14786419.2018.1460832
125. Inamori, Y., Kato, Y., Kubo, M., Kamiki, T., Takemoto, T., and Nomoto, K., *Chem. Pharm. Bull.*, 1983, vol. 31, pp. 4543–4548. https://doi.org/10.1248/cpb.31.4543
126. Tao, Q., Ding, C., Auckloo, B.N., and Wu, B., *Nat. Prod. Commun.*, 2018, vol. 13, pp. 571–573. https://doi.org/10.1177/1934578X1801300514
127. Lu, C.-H., Huang, Y.-J., and Shen, Y.-M., *Chin. J. Nat. Med.*, 2005, vol. 3, pp. 269–271.
128. Ukwatta, K.M., Lawrence, J.L., and Wijayarathna, C.D., *Mycology*, 2019, vol. 10, pp. 222–228. https://doi.org/10.1080/21501203.2019.1620892
129. Capon, R.J., Stewart, M., Ratnayake, R., Lacey, E., and Gill, J.H., *J. Nat. Prod.*, 2007, vol. 70, pp. 1746–1752. https://doi.org/10.1021/np0702483
130. He, F., Li, X., Yu, J.-H., Zhang, X., Nong, X., Chen, G., Zhu, K., Wang, Y.-Y., Bao, J., and Zhang, H., *Fitoterapia*, 2019, vol. 136, 104177. https://doi.org/10.1016/j.fitote.2019.104177
131. Bladt, T., Frisvad, J., Knudsen, P., and Larsen, T., *Molecules*, 2013, vol. 18, pp. 11338–11376. https://doi.org/10.3390/molecules180911338
132. Xia, X.-K., Huang, H.-R., She, Z.-G., Cai, J.-W., Lan, L., Zhang, J.-Y., Fu, L.-W., Vrijmoed, L.L.P., and Lin, Y.-C., *Helv. Chim. Acta*, 2007, vol. 90, pp. 1925–1931. https://doi.org/10.1002/hlca.200790200
133. De Stefano, S., Nicoletti, R., Milone, A., and Zambardino, S., *Phytochemistry*, 1999, vol. 52, pp. 1399–1401. https://doi.org/10.1016/S0031-9422(99)00320-9
134. Stammati, A., Nicoletti, R., De Stefano, S., Zampaglioni, F., and Zucco, F., *Altern. Lab. Anim.*, 2002, vol. 30, pp. 69–75. https://doi.org/10.1177/026119290203000107
135. Noor, A.O., Almasri, D.M., Bagalagel, A.A., Abdallah, H.M., Mohamed, S.G.A., Mohamed, G.A., and Ibrahim, S.R.M., *Molecules*, 2020, vol. 25, p. 395. https://doi.org/10.3390/molecules25020395
136. Chen, Y., Liu, Z., Liu, H., Pan, Y., Li, J., Liu, L., and She, Z., *Mar. Drugs*, 2018, vol. 16, p. 54. https://doi.org/10.3390/md16020054
137. Li, C., Gong, B., Cox, D., Li, C., Wang, J., and Ding, W., *Pharmacogn. Mag.*, 2014, vol. 10, pp. 153–158. https://doi.org/10.4103/0973-1296.127367
138. Aly, A.H., Edrada-Ebel, R., Wray, V., Muller, W.E.G., Kozytska, S., Hentschel, U., Proksch, P., and Ebel, R., *Phytochemistry*, 2008, vol. 69, pp. 1716–1725. https://doi.org/10.1016/j.phytochem.2008.02.013
139. Wensheng, L., Jiaxin, X., Fenqi, L., Li, X., and Chunyuan, L., *Pharmacogn. Mag.*, 2016, vol. 12, pp. 259–261. https://doi.org/10.4103/0973-1296.192204
140. Larsen, T.O. and Breinholt, J., *J. Nat. Prod.*, 1999, vol. 62, pp. 1182–1184. https://doi.org/10.1021/np990066b

141. Xu, Z., Xiong, B., and Xu, J., *Nat. Prod. Res.*, 2019. https://doi.org/10.1080/14786419.2019.1656624
142. Chen, S., Liu, Y., Liu, Z., Cai, R., Lu, Y., Huang, X., and She, Z., *RSC Adv.*, 2016, vol. 6, pp. 26412–26420. https://doi.org/10.1039/C6RA02566H
143. Aly, A.H., Edrada-Ebel, R., Indriani, I.D., Wray, V., Muller, W.E.G., Totzke, F., Zirrgiebel, U., Schächtele, C., Kubbutat, M.H.G., Lin, W.H., Proksch, P., and Ebel, R., *J. Nat. Prod.*, 2008, vol. 71, pp. 972–980. https://doi.org/10.1021/np070447m
144. Kim, N., Sohn, M.-J., Koshino, H., Kim, E.-H., and Kim, W.-G., *Bioorg. Med. Chem. Lett.*, 2014, vol. 24, pp. 83–86. https://doi.org/10.1016/j.bmcl.2013.11.071
145. Xu, Z., Wu, X., Li, G., Feng, Z., and Xu, J., *Nat. Prod. Res.*, 2020, vol. 34, pp. 1002–1007. https://doi.org/10.1080/14786419.2018.1539980
146. Wang, Y., Yang, M.-H., Wang, X.-B., Li, T.-X., and Kong, L.-Y., *Fitoterapia*, 2014, vol. 99, pp. 153–158. https://doi.org/10.1016/j.fitote.2014.09.015
147. Souza, G., De Mithöfer, A., Daolio, C., Schneider, B., and Rodrigues-Filho, E., *Molecules*, 2013, vol. 18, pp. 2528–2538. https://doi.org/10.3390/molecules18032528
148. Jiao, P., Gloer, J.B., Campbell, J., and Shearer, C.A., *J. Nat. Prod.*, 2006, vol. 69, pp. 612–615. https://doi.org/10.1021/np0504661
149. Khan', Zh., Mei, V., Zhao, E., Den, Yu., and Dai, Kh., *Khim. Prir. Soed.*, 2009, vol. 45, no. 6, pp. 676–677.
150. Wang, X., Radwan, M.M., Taráwneh, A.H., Gao, J., Wedge, D.E., Rosa, L.H., Cutler, H.G., and Cutler, S.J., *J. Agricult. Food Chem.*, 2013, vol. 61, pp. 4551–4555. https://doi.org/10.1021/jf400212y
151. Afiyatullov, S.S., Zhuravleva, O.I., Antonov, A.S., Leshchenko, E.V., Pivkin, M.V., Khudyakova, Y.V., Denisenko, V.A., Pislyagin, E.A., Kim, N.Y., Berdyshev, D.V., von Amsberg, G., and Dyshlovoy, S.A., *Mar. Drugs*, 2019, vol. 17, 647. https://doi.org/10.3390/md17110647
152. Zhang, F.-Z., Li, X.-M., Yang, S.-Q., Meng, L.-H., and Wang, B.-G., *J. Nat. Prod.*, 2019, vol. 82, pp. 1535–1541. https://doi.org/10.1021/acs.jnatprod.8b01091
153. Jadulco, R., Proksch, P., Wray, V., Sudarsono, Berg, A., and Gräfe, U., *J. Nat. Prod.*, 2001, vol. 64, pp. 527–530. https://doi.org/10.1021/np000401s
154. Grabley, S., Granzer, E., Hütter, K., Ludwig, D., Mayer, M., Thiericke, R., Till, G., Wink, J., Philipps, S., and Zeeck, A., *J. Antibiot.*, 1992, vol. 45, pp. 56–65. https://doi.org/10.7164/antibiotics.45.56
155. An, F.-L., Liu, W.-H., Wei, X.-C., Pan, Z.-H., and Lu, Y.-H., *Nat. Prod. Commun.*, 2018, vol. 13, pp. 865–866. https://doi.org/10.1177/1934578X1801300720
156. Umeokoli, B.O., Ebrahim, W., El-Neketi, M., Müller, W.E.G., Kalscheuer, R., Lin, W., Liu, Z., and Proksch, P., *Nat. Prod. Res.*, 2019, vol. 33, pp. 2215–2222. https://doi.org/10.1080/14786419.2018.1496430
157. Abdou, R., Scherlach, K., Dahse, H.-M., Sattler, I., and Hertweck, C., *Phytochemistry*, 2010, vol. 71, pp. 110–116.
158. Aldridge, D.C., Galt, S., Giles, D., and Turner, W.B., *J. Chem. Soc. C: Org.*, 1971, pp. 1623–1627. https://doi.org/10.1039/j39710001623
159. Xia, M.-W., Yang, Y., Xu, R., Li, C.-W., and Cui, C.-B., *Nat. Prod. Res.*, 2019, vol. 33, pp. 89–94. https://doi.org/10.1080/14786419.2018.1434644
160. Carvalho, M.R., Barbosa, L.C., Queiróz, J.H., and Howarth, O.W., *Tetrahedron Lett.*, 2001, vol. 42, pp. 809–811. https://doi.org/10.1016/S0040-4039(00)02154-7
161. Zhao, D.-L., Shao, C.-L., Zhang, Q., Wang, K.-L., Guan, F.-F., Shi, T., and Wang, C.-Y., *J. Nat. Prod.*, 2015, vol. 78, pp. 2310–2314. https://doi.org/10.1021/acs.jnatprod.5b00575
162. Hayasaka, S., Koseki, T., Murayama, T., Kwon, E., and Shiono, Y., *Z. Naturforsch. B*, 2011, vol. 66, pp. 961–964. https://doi.org/10.1515/znb-2011-0915
163. Yurchenko, A.N., Smetanina, O.F., Kalinovskii, A.I., Pivkin, M.V., Dmitrenok, P.S., and Kuznetsova, T.A., *Izv. Akad. Nauk, Ser. Khim.*, 2010, vol. 59, no. 4, pp. 834–838.
164. Chokpaiboon, S., Unagul, P., Nithithanasilp, S., Komwijit, S., Somyong, W., Ratiarpakul, T., Isaka, M., and Bunyapaiboonsri, T., *Nat. Prod. Res.*, 2018, vol. 32, pp. 149–153. https://doi.org/10.1080/14786419.2017.1342083
165. Zheng, C.-J., Huang, G.-L., Liao, H.-X., Mei, R.-Q., Luo, Y.-P., Chen, G.-Y., and Zhang, Q.-Y., *Bioorg. Chem.*, 2019, vol. 85, pp. 382–385. https://doi.org/10.1016/j.bioorg.2019.01.015
166. Khuan, Zh., Guo, Zh., Yan, Zh., Iin, S., Li, S., Luo, V., She, Zh., and Lin', E., *Khim. Prir. Soed.*, 2009, vol. 45, no. 5, pp. 528–530.
167. Kornsakulkarn, J., Somyong, W., Supothina, S., Boonyuen, N., and Thongpanchang, C., *Tetrahedron*, 2015, vol. 71, pp. 9112–9116. https://doi.org/10.1016/j.tet.2015.10.015
168. Beekman, A.M. and Barrow, R.A., *Aust. J. Chem.*, 2015, vol. 68, pp. 1583–1592. https://doi.org/10.1071/CH15144
169. Matsuo, H., Nonaka, K., Nagano, Y., Yabuki, A., Fujikura, K., Takahashi, Y., Omura, S., and Nakashima, T., *Biosci. Biotechnol. Biochem.*, 2018, vol. 82, pp. 1323–1326. https://doi.org/10.1080/09168451.2018.1467264
170. Elissawy, A.M., Ebada, S.S., Ashour, M.L., El-Neketi, M., Ebrahim, W., and Singab, A.B., *Phytochem. Lett.*, 2019, vol. 29, pp. 1–5. https://doi.org/10.1016/j.phytol.2018.10.014
171. Ishikawa, Y., Morimoto, K., and Hamasaki, T., *J. Am. Oil Chem. Soc.*, 1984, vol. 61, pp. 1864–1868. https://doi.org/10.1007/BF02540819
172. Zhang, Z., He, X., Liu, C., Che, Q., Zhu, T., Gu, Q., and Li, D., *RSC Adv.*, 2016, vol. 6, pp. 76498–76504. https://doi.org/10.1039/C6RA14640F
173. Li, H.-L., Li, X.-M., Mandi, A., Antus, S., Li, X., Zhang, P., Liu, Y., Kurtán, T., and Wang, B.-G., *J.*

Org. Chem., 2017, vol. 82, pp. 9946–9954. https://doi.org/10.1021/acs.joc.7b01277

174. Reichling, J., Suschke, U., Schneele, J., and Geiss, H.K., *Nat. Prod. Commun.*, 2006, vol. 1, pp. 1003–1012. https://doi.org/10.1177/1934578X0600101116
175. Reddy, M., Gupta, S., Jacob, M., Khan, S., and Ferreira, D., *Planta Med*., 2007, vol. 73, pp. 461–467. https://doi.org/10.1055/s-2007-967167
176. Frank, M., Hartmann, R., Plenker, M., Mandi, A., Kurtán, T., Özkaya, F.C., Muller, W.E.G., Kassack, M.U., Hamacher, A., Lin, W., Liu, Z., and Proksch, P., *J. Nat. Prod.*, 2019, vol. 82, pp. 2159–2166. https://doi.org/10.1021/acs.jnatprod.9b00151
177. Klaiklay, S., Rukachaisirikul, V., Tadpetch, K., Sukpondma, Y., Phongpaichit, S., Buatong, J., and Sakayaroj, J., *Tetrahedron*, 2012, vol. 68, pp. 2299–2305. https://doi.org/10.1016/j.tet.2012.01.041
178. Itabashi, T., Nozawa, K., Nakajima, S., and Kawai, K., *Chem. Pharm. Bull.*, 1993, vol. 41, pp. 2040–2041. https://doi.org/10.1248/cpb.41.2040
179. Taniguchi, M., Kaneda, N., Shibata, K., and Kamikawa, T., *Agricult. Biol. Chem*., 1978, vol. 42, pp. 1629–1630. https://doi.org/10.1080/00021369.1978.10863223
180. Nuankeaw, K., Chaiyosang, B., Suebrasri, T., Kanokmedhakul, S., Lumyong, S., and Boonlue, S., *Mycoscience*, 2020, vol. 61, pp. 16–21. https://doi.org/10.1016/j.myc.2019.10.001
181. Yamazaki, M. and Maebayashi, Y., *Chem. Pharm. Bull.*, 1982, vol. 30, pp. 514–518. https://doi.org/10.1248/cpb.30.514
182. Chomcheon, P., Wiyakrutta, S., Sriubolmas, N., Ngamrojanavanich, N., Mahidol, C., Ruchirawat, S., and Kittakoop, P., *Phytochemistry*, 2009, vol. 70, pp. 121–127. https://doi.org/10.1016/j.phytochem.2008.10.007
183. Fang, M.J., Fang, H., Li, W.J., Huang, D.M., Wu, Z., and Zhao, Y.F., *Nat. Prod. Res.*, 2012, vol. 26, pp. 1224–1228. https://doi.org/10.1080/14786419.2011.559947
184. Hargreaves, J., Park, J., Ghisalberti, E.L., Sivasithamparam, K., Skelton, B.W., and White, A.H., *J. Nat. Prod.*, 2002, vol. 65, pp. 7–10. https://doi.org/10.1021/np0102758
185. Fang, S.-T., Wang, Y.-J., Ma, X.-Y., Yin, X.-L., and Ji, N.-Y., *Nat. Prod. Res.*, 2019, vol. 33, pp. 3127–3133. https://doi.org/10.1080/14786419.2018.1522314
186. Wen, S., Fan, W., Guo, H., Huang, C., Yan, Z., and Long, Y., *Nat. Prod. Res.*, 2020, vol. 34, pp. 2919–2925. https://doi.org/10.1080/14786419.2019.1598993
187. Xu, X., Yang, H., Xu, H., Yin, L., Chen, Z., and Shen, H., *Nat. Prod. Res.*, 2018, vol. 32, pp. 821–825. https://doi.org/10.1080/14786419.2017.1363754
188. Gao, H., Zhou, L., Cai, S., Zhang, G., Zhu, T., Gu, Q., and Li, D., *J. Antibiot.*, 2013, vol. 66, pp. 539–542. https://doi.org/10.1038/ja.2013.40
189. Li, X.-B., Zhou, Y.-H., Zhu, R.-X., Chang, W.-Q., Yuan, H.-Q., Gao, W., Zhang, L.-L., Zhao, Z.-T., and Lou, H.-X., *Chem. Biodiversity*, 2015, vol. 12, pp. 575–592. https://doi.org/10.1002/cbdv.201400146
190. Cooke, R.G. and Edwards, J.M., *Fortschritte der Chemie organischer Naturstoffe* (Progress in the Chemistry of Organic Natural Products), Herz, W., Grisebach, H., and Kirby, G.W., Eds., Vienna: Springer Vienna, 1981, pp. 153–190. https://doi.org/10.1007/978-3-7091-8611-4_4
191. Homma, K., Fukuyama, K., Katsube, Y., Kimura, Y., and Hamasaki, T., *Agric. Biol. Chem*., 1980, vol. 44, pp. 1333–1337. https://doi.org/10.1271/bbb1961.44.1333
192. Ayer, W.A. and Hiratsuka, Y., *Rev. Latinoam. Quim*., 1982, vol. 13, pp. 84–87.
193. Ayer, W.A., Hoyano, Y., Pedras, M.S., and van Altena, I., *Can. J. Chem*., 1986, vol. 64, pp. 1585–1589. https://doi.org/10.1139/v86-262
194. Tanaka, Y., Matsuzaki, K., Zhong, C.-L., Yoshida, H., Kawakubo, T., Masuma, R., Tanaka, H., and Omura, S., *J. Antibiot*., 1996, vol. 49, pp. 1056–1059. https://doi.org/10.7164/antibiotics.49.1056
195. Bai, Y.-B., Gao, Y.-Q., Nie, X.-D., Tuong, T.-M.-L., Li, D., and Gao, J.-M., *J. Agricult. Food Chem*., 2019, vol. 67, pp. 6125–6132. https://doi.org/10.1021/acs.jafc.9b00606
196. Gauthier, T., Wang, X., Sifuentes, Dos., Santos, J., Fysikopoulos, A., Tadrist, S., Canlet, C., Artigot, M.P., Loiseau, N., Oswald, I.P., and Puel, O., *PLoS One*, 2012, vol. 7, e29906. https://doi.org/10.1371/journal.pone.0029906
197. Gao, J.-M., Yang, S.-X., and Qin, J.-C., *Chem. Rev*., 2013, vol. 113, pp. 4755–4811. https://doi.org/10.1021/cr300402y
198. Wang, C.-Y., Hao, J.-D., Ning, X.-Y., Wu, J.-S., Zhao, D.-L., Kong, C.-J., Shao, C.-L., and Wang, C.-Y., *RSC Adv*., 2018, vol. 8, pp. 4348–4353. https://doi.org/10.1039/C7RA13327H
199. Pairet, L., Wrigley, S.K., Chetland, I., Reynolds, E.E., Hayes, M.A., Holloway, J., Ainsworth, A.M., Katzer, W., Cheng, X.-M., Hupe, D.J., Charlton, P., and Doherty, A.M., *J. Antibiot*., 1995, vol. 48, pp. 913–923. https://doi.org/10.7164/antibiotics.48.913
200. Luo, X., Lin, X., Tao, H., Wang, J., Li, J., Yang, B., Zhou, X., and Liu, Y., *J. Nat. Prod.*, 2018, vol. 81, pp. 934–941. https://doi.org/10.1021/acs.jnatprod.7b01053
201. Hemtasin, C., Kanokmedhakul, S., Moosophon, P., Soytong, K., and Kanokmedhakul, K., *Phytochem. Lett.*, 2016, vol. 16, pp. 56–60. https://doi.org/10.1016/j.phytol.2016.03.004
202. Myobatake, Y., Takeuchi, T., Kuramochi, K., Kuriyama, I., Ishido, T., Hirano, K., Sugawara, F., Yoshida, H., and Mizushina, Y., *J. Nat. Prod.*, 2012, vol. 75, pp. 135–141. https://doi.org/10.1021/np200523b
203. Yang, S.-W., Chan, T.-M., Terracciano, J., Patel, R., Patel, M., Gullo, V., and Chu, M., *J. Antibiot.*, 2006, vol. 59, pp. 720–723. https://doi.org/10.1038/ja.2006.96
204. Trivedi, A.B., Hirota, M., Doi, E., and Kitabatake, N., *J. Chem. Soc., Perkin Trans. 1*, 1993, pp. 2167–2171. https://doi.org/10.1039/p19930002167
205. Sadorn, K., Saepua, S., Boonyuen, N., Laksanacharoen, P., Rachtawee, P., and Pittayakhajonwut, P.,

RSC Adv., 2016, vol. 6, pp. 94510–94523. https://doi.org/10.1039/C6RA21898A

206. Chen, S., Wang, J., Wang, Z., Lin, X., Zhao, B., Kaliaperumal, K., Liao, X., Tu, Z., Li, J., Xu, S., and Liu, Y., *Fitoterapia*, 2017, vol. 117, pp. 71–78. https://doi.org/10.1016/j.fitote.2017.01.005
207. Vanmiddlesworth, F., Giacobbe, R.A., Lopez, M., Garrity, G., Bland, J.A., Bartizal, K., Fromtling, R.A., Polishook, J., Zweerink, M., Edison, A.M., Rozdilsky, W., Wilson, K.E., and Monaghan, R.L., *J. Antibiot.*, 1992, vol. 45, pp. 861–867. https://doi.org/10.7164/antibiotics.45.861
208. Choi, B.-K., Phan, T.H.T., Hwang, S., Oh, D.-C., Kang, J.S., Lee, H.-S., Ngo, T.D.N., Tran, T.T.V., and Shin, H.J., *J. Nat. Prod.*, 2019, vol. 82, pp. 3186–3190. https://doi.org/10.1021/acs.jnatprod.9b00776
209. Neuhaus, G.F., Adpressa, D.A., Bruhn, T., and Loesgen, S., *J. Nat. Prod.*, 2019, vol. 82, pp. 2780–2789. https://doi.org/10.1021/acs.jnatprod.9b00416
210. Sassa, T., Takemura, T., Ikeda, M., and Miura, Y., *Tetrahedron Lett.*, 1973, vol. 14, pp. 2333–2334. https://doi.org/10.1016/S0040-4039(01)96211-2
211. Niu, S., Tang, X.-X., Fan, Z., Xia, J.-M., Xie, C.-L., and Yang, X.-W., *Mar. Drugs*, 2019, vol. 17, 125. https://doi.org/10.3390/md17020125
212. Höller, U., Wright, A.D., Matthee, G.F., Konig, G.M., Draeger, S., Aust, H.-J., and Schulz, B., *Mycol. Res.*, 2000, vol. 104, pp. 1354–1365. https://doi.org/10.1017/S0953756200003117
213. Yu, G., Sun, Z., Peng, J., Zhu, M., Che, Q., Zhang, G., Zhu, T., Gu, Q., and Li, D., *J. Nat. Prod.*, 2019, vol. 82, pp. 2013–2017. https://doi.org/10.1021/acs.jnatprod.9b00345
214. Kanoh, K., Adachi, K., Matsuda, S., Shizuri, Y., Yasumoto, K., Kusumi, T., Okumura, K., and Kirikae, T., *J. Antibiot.*, 2008, vol. 61, pp. 192–194. https://doi.org/10.1038/ja.2008.29
215. Madhyastha, M.S., Marquardt, R.R., Masi, A., Borsa, J., and Frohlich, A.A., *J. Food Protect.*, 1994, vol. 57, pp. 48–53. https://doi.org/10.1038/ja.2008.29
216. Al-Fakih, A.A. and Almaqtri, W.Q.A., *Mycology*, 2019, vol. 10, pp. 191–209. https://doi.org/10.1080/21501203.2019.1604576
217. Vansteelandt, M., Blanchet, E., Egorov, M., Petit, F., Toupet, L., Bondon, A., Monteau, F., Le Bizec, B., Thomas, O.P., Pouchus, Y.F., Le Bot, R., and Grovel, O., *J. Nat. Prod.*, 2013, vol. 76, pp. 297–301. https://doi.org/10.1021/np3007364
218. Nguyen, H.T., Yu, N.H., Jeon, S.J., Lee, H.W., Bae, C.-H., Yeo, J.H., Lee, H.B., Kim, I.-S., Park, H.W., and Kim, J.-C., *Lett. Appl. Microbiol.*, 2016, vol. 62, pp. 488–493. https://doi.org/10.1111/lam.12578
219. Liu, W.-H., Ding, Y., Ji, X., An, F.-L., and Lu, Y.-H., *J. Antibiot.*, 2019, vol. 72, pp. 111–113. https://doi.org/10.1038/s41429-018-0110-7
220. Zhu, G., Kong, F., Wang, Y., Fu, P., and Zhu, W., *Mar. Drugs*, 2018, vol. 16, 71. https://doi.org/10.3390/md16020071
221. Li, M.-F., Li, G.-H., and Zhang, K.-Q., *Metabolites*, 2019, vol. 9, 58. https://doi.org/10.3390/metabo9030058
222. Corral, P., Esposito, F.P., Tedesco, P., Falco, A., Tortorella, E., Tartaglione, L., Festa, C., D'Auria, M.V., Gnavi, G., Varese, G.C., and De Pascale, D., *Mar. Biotechnol.*, 2018, vol. 20, pp. 502–511. https://doi.org/10.1007/s10126-018-9821-9
223. Trifonov, L.S., Hilpert, H., Floersheim, P., Dreiding, A.S., Rast, D.M., Skrivanova, R., and Hoesch, L., *Tetrahedron*, 1986, vol. 42, pp. 3157–3179. https://doi.org/10.1016/S0040-4020(01)87382-8
224. Fujii, Y., Asahara, M., Ichinoe, M., and Nakajima, H., *Phytochemistry*, 2002, vol. 60, pp. 703–708. https://doi.org/10.1016/S0031-9422(02)00196-6
225. Won-Gon, K., Ryoo, I.-J., Park, S.-H., Kim, D.-S., Lee, S., Park, K.-C., and Yoo, I.-D., *J. Microbiol. Biotechnol.*, 2005, vol. 15, pp. 891–894.
226. Asfour, H.Z., Awan, Z.A., Bagalagel, A.A., Elfaky, M.A., Abdelhameed, R.F.A., and Elhady, S.S., *Biomolecules*, 2019, vol. 9, 480. https://doi.org/10.3390/biom9090480
227. Tan, Q.-W., Fang, P.-H., Ni, J.-C., Gao, F., and Chen, Q.-J., *Molecules*, 2017, vol. 22, 2073. https://doi.org/10.3390/molecules22122073
228. Pastre, R., Marinho, A.M.R., Rodrigues-Filho, E., Souza, A.Q.L., and Pereira, J.O., *Química Nova*, 2007, vol. 30, pp. 1867–1871. https://doi.org/10.1590/S0100-40422007000800013
229. Song, T., Chen, M., Ge, Z.-W., Chai, W., Li, X.-C., Zhang, Z., and Lian, X.-Y., *J. Org. Chem.*, 2018, vol. 83, pp. 13395–13401. https://doi.org/10.1021/acs.joc.8b02172
230. Rukachaisirikul, V., Satpradit, S., Klaiklay, S., Phongpaichit, S., Borwornwiriyapan, K., and Sakayaroj, J., *Tetrahedron*, 2014, vol. 70, pp. 5148–5152. https://doi.org/10.1016/j.tet.2014.05.105
231. Ivanets, E., Yurchenko, A., Smetanina, O., Rasin, A., Zhuravleva, O., Pivkin, M., Popov, R., von Amsberg, G., Afiyatullov, S., and Dyshlovoy, S., *Mar. Drugs*, 2018, vol. 16, p. 232. https://doi.org/10.3390/md16070232
232. Xu, L.-L., Hai, P., Zhang, S.-B., Xiao, J.-F., Gao, Y., Ma, B.-J., Fu, H.-Y., Chen, Y.-M., and Yang, X.-L., *J. Nat. Prod.*, 2019, vol. 82, pp. 221–231. https://doi.org/10.1021/acs.jnatprod.8b00589
233. Khalil, Z.G., Huang, X., Raju, R., Piggott, A.M., and Capon, R.J., *J. Org. Chem.*, 2014, vol. 79, pp. 8700–8705. https://doi.org/10.1021/jo501501z
234. Yang, S.-Q., Li, X.-M., Li, X., Chi, L.-P., and Wang, B.-G., *Mar. Drugs*, 2018, vol. 16, p. 114. https://doi.org/10.3390/md16040114
235. Lacey, H.J., Vuong, D., Pitt, J.I., Lacey, E., and Piggott, A.M., *Aust. J. Chem.*, 2016, vol. 69, pp. 152–160. https://doi.org/10.1071/CH15488
236. Johnson, J.H., Phillipson, D.W., and Kahle, A.D., *J. Antibiot.*, 1989, vol. 42, pp. 1184–1185. https://doi.org/10.7164/antibiotics.42.1184
237. Limbadri, S., Luo, X., Lin, X., Liao, S., Wang, J., Zhou, X., Yang, B., and Liu, Y., *Molecules*, 2018,

vol. 23, p. 2379.
https://doi.org/10.3390/molecules23092379

238. Takahashi, C., Matsushita, T., Doi, M., Minoura, K., Shingu, T., Kumeda, Y., and Numata, A., *J. Chem. Soc., Perkin Trans. 1*, 1995, pp. 2345–2353.
https://doi.org/10.1039/P19950002345
239. Rank, C., Phipps, R.K., Harris, P., Frisvad, J.C., Gotfredsen, C.H., and Larsen, T.O., *Tetrahedron Lett.*, 2006, vol. 47, pp. 6099–6102.
https://doi.org/10.1016/j.tetlet.2006.06.086
240. Afiyatullov, S.Sh., Zhuravleva, O.I., Antonov, A.S., Berdyshev, D.V., Pivkin, M.V., Denisenko, V.A., Popov, R.S., Gerasimenko, A.V., von Amsberg, G., Dyshlovoy, S.A., Leshchenko, E.V., and Yurchenko, A.N., *J. Antibiot.*, 2018, vol. 71, pp. 846–853.
https://doi.org/10.1038/s41429-018-0072-9
241. Zhou, R., Liao, X., Li, H., Li, J., Feng, P., Zhao, B., and Xu, S., *Front. Chem.*, 2018, vol. 6, p. 212.
https://doi.org/10.3389/fchem.2018.00212
242. Zheng, C.-J., Bai, M., Zhou, X.-M., Huang, G.-L., Shao, T.-M., Luo, Y.-P., Niu, Z.-G., Niu, Y.-Y., Chen, G.-Y., and Han, C.-R., *J. Nat. Prod.*, 2018, vol. 81, pp. 1045–1049.
https://doi.org/10.1021/acs.jnatprod.7b00673
243. Elsbaey, M., Tanaka, C., and Miyamoto, T., *Phytochemistry Lett.*, 2019, vol. 32, pp. 70–76.
https://doi.org/10.1016/j.phytol.2019.04.023
244. Chen, Y., Liu, Z., Huang, Y., Liu, L., He, J., Wang, L., Yuan, J., and She, Z., *J. Nat. Prod.*, 2019, vol. 82, pp. 1752–1758.
https://doi.org/10.1021/acs.jnatprod.8b00918
245. Wijeratne, E.M.K., He, H., Franzblau, S.G., Hoffman, A.M., and Gunatilaka, A.A.L., *J. Nat. Prod.*, 2013, vol. 76, pp. 1860–1865.
https://doi.org/10.1021/np400391p
246. Wang, P., Cui, Y., Cai, C., Chen, H., Dai, Y., Chen, P., Kong, F., Yuan, J., Song, X., Mei, W., and Dai, H., *Mar. Drugs*, 2018, vol. 17, p. 4.
https://doi.org/10.3390/md17010004
247. Suzuki, S., Hosoe, T., Nozawa, K., Kawai, K., Yaguchi, T., and Udagawa, S., *J. Nat. Prod.*, 2000, vol. 63, pp. 768–772.
https://doi.org/10.1021/np990371x
248. Bao, J., Zhai, H., Zhu, K., Yu, J.-H., Zhang, Y., Wang, Y., Jiang, C.-S., Zhang, X., Zhang, Y., and Zhang, H., *Mar. Drugs*, 2018, vol. 16, p. 174.
https://doi.org/10.3390/md16050174
249. Alfatafta, A.A., Gloer, J.B., Scott, J.A., and Malloch, D., *J. Nat. Prod.*, 1994, vol. 57, pp. 1696–1702.
https://doi.org/10.1021/np50114a012
250. Jiao, R.H., Xu, S., Liu, J.Y., Ge, H.M., Ding, H., Xu, C., Zhu, H.L., and Tan, R.X., *Org. Lett.*, 2006, vol. 8, pp. 5709–5712.
https://doi.org/10.1021/ol062257t
251. TePaske, M.R., Gloer, J.B., Wicklow, D.T., and Dowd, P.F., *Tetrahedron Lett.*, 1991, vol. 32, pp. 5687–5690.
https://doi.org/10.1016/S0040-4039(00)93530-5
252. Ge, H.M., Shen, Y., Zhu, C.H., Tan, S.H., Ding, H., Song, Y.C., and Tan, R.X., *Phytochemistry*, 2008, vol. 69, pp. 571–576.
https://doi.org/10.1016/j.phytochem.2007.07.014
253. Banert, K. and Tantillo, D.J., *Nat. Prod. Res.*, 2019, vol. 33, pp. 3011–3015.
https://doi.org/10.1080/14786419.2018.1509330
254. Tao, H., Li, Y., Lin, X., Zhou, X., Dong, J., Liu, Y., and Yang, B., *Nat. Prod. Commun.*, 2018, vol. 13, pp. 1629–1631.
https://doi.org/10.1177/1934578X1801301214
255. Choi, B.-K., Trinh, P.T.H., Lee, H.-S., Choi, B.-W., Kang, J.S., Ngoc, N.T.D., Van, T.T.T., and Shin, H.J., *Mar. Drugs*, 2019, vol. 17, 346.
https://doi.org/10.3390/md17060346
256. Bladt, T., Dürr, C., Knudsen, P., Kildgaard, S., Frisvad, J., Gotfredsen, C., Seiffert, M., and Larsen, T., *Molecules*, 2013, vol. 18, pp. 14629–14650.
https://doi.org/10.3390/molecules181214629
257. Tan, Y., Yang, B., Lin, X., Luo, X., Pang, X., Tang, L., Liu, Y., Li, X., and Zhou, X., *J. Nat. Prod.*, 2018, vol. 81, pp. 92–97.
https://doi.org/10.1021/acs.jnatprod.7b00698
258. Fang, W., Lin, X., Zhou, X., Wan, J., Lu, X., Yang, B., Ai, W., Lin, J., Zhang, T., Tu, Z., and Liu, Y., *Med. Chem. Commun.*, 2014, vol. 5, pp. 701–705.
https://doi.org/10.1039/C3MD00371J
259. Belofsky, G., Jensen, P., Renner, M., and Fenical, W., *Tetrahedron*, 1998, vol. 54, pp. 1715–1724.
https://doi.org/10.1016/S0040-4020(97)10396-9
260. Deng, Q., Li, G., Sun, M., Yang, X., and Xu, J., *Nat. Prod. Res.*, 2018, vol. 34, pp. 1404–1408.
https://doi.org/10.1080/14786419.2018.1512993
261. Zhou, J., Li, G., Deng, Q., Zheng, D., Yang, X., and Xu, J., *Nat. Prod. Res.*, vol. 32, 2018, pp. 2968–2972.
https://doi.org/10.1080/14786419.2017.1395431
262. Hamasaki, T., Nagayama, K., and Hatsuda, Y., *Agric. Biol. Chem.*, 1978, vol. 42, pp. 37–40.
https://doi.org/10.1080/00021369.1978.10862919
263. Li, X.-D., Li, X.-M., Xu, G.-M., Zhang, P., and Wang, B.-G., *J. Nat. Prod.*, 2015, vol. 78, pp. 844–849.
https://doi.org/10.1021/acs.jnatprod.5b00004
264. Wang, P., Yu, J.-H., Zhu, K., Wang, Y., Cheng, Z.-Q., Jiang, C.-S., Dai, J.-G., Wu, J., and Zhang, H., *Fitoterapia*, 2018, vol. 127, pp. 322–327.
https://doi.org/10.1016/j.fitote.2018.02.031
265. Yao, Q., Wang, J., Zhang, X., Nong, X., Xu, X., and Qi, S., *Mar. Drugs*, 2014, vol. 12, pp. 5902–5915.
https://doi.org/10.3390/md12125902
266. Qiu, L., Wang, P., Liao, G., Zeng, Y., Cai, C., Kong, F., Guo, Z., Proksch, P., Dai, H., and Mei, W., *Mar. Drugs*, 2018, vol. 16, p. 108.
https://doi.org/10.3390/md16040108
267. Xing, C.-P., Xie, C.-L., Xia, J.-M., Liu, Q.-M., Lin, W.-X., Ye, D.-Z., Liu, G.-M., and Yang, X.-W., *Mar. Drugs*, 2019, vol. 17, p. 507.
https://doi.org/10.3390/md17090507
268. Amagata, T., Doi, M., Tohgo, M., Minoura, K., and Numata, A., *Chem. Commun.*, 1999, pp. 1321–1322.
https://doi.org/10.1039/a903840j
269. Amagata, T., Tanaka, M., Yamada, T., Doi, M., Minoura, K., Ohishi, H., Yamori, T., and Numata, A., *J. Nat. Prod.*, 2007, vol. 70, pp. 1731–1740.
https://doi.org/10.1021/np070165m

270. Guo, Y.-W., Gong, B.-Q., Yuan, J., Li, H.-J., Mahmud, T., Huang, Y., Li, J.-F., Yang, D.-P., and Lan, W.-J., *J. Nat. Prod.*, 2019, vol. 83, pp. 79–87. https://doi.org/10.1021/acs.jnatprod.9b00710

271. Yang, B., He, Y., Lin, S., Zhang, J., Li, H., Wang, J., Hu, Z., and Zhang, Y., *J. Nat. Prod.*, 2019, vol. 82, pp. 1923–1929. https://doi.org/10.1021/acs.jnatprod.9b00305

272. Evidente, A., Sparapano, L., Motta, A., Giordano, F., Fierro, O., and Frisullo, S., *Phytochemistry*, 1996, vol. 42, pp. 1541–1546. https://doi.org/10.1016/0031-9422(96)00206-3

273. Yan, T., Guo, Z., Jiang, R., Wei, W., Wang, T., Guo, Y., Song, Y., Jiao, R., Tan, R., and Ge, H., *Planta Med.*, 2013, vol. 79, pp. 348–352. https://doi.org/10.1055/s-0032-1328260

274. Lallemand, B., Masi, M., Maddau, L., De Lorenzi, M., Dam, R., Cimmino, A., Moreno y Banuls, L., Andolfi, A., Kiss, R., Mathieu, V., and Evidente, A., *Phytochemistry Lett.*, 2012, vol. 5, pp. 770–775. https://doi.org/10.1016/j.phytol.2012.08.011

275. Li, Y., Ye, D., Shao, Z., Cui, C., and Che, Y., *Mar. Drugs*, 2012, vol. 10, pp. 497–508. https://doi.org/10.3390/md10020497

276. Yu, H.-B., Wang, X.-L., Zhang, Y.-X., Xu, W.-H., Zhang, J.-P., Zhou, X.-Y., Lu, X.-L., Liu, X.-Y., and Jiao, B.-H., *J. Nat. Prod.*, 2018, vol. 81, pp. 1553–1560. https://doi.org/10.1021/acs.jnatprod.8b00039

277. Lu, X.-L., Liu, J.-T., Liu, X.-Y., Gao, Y., Zhang, J., Jiao, B.-H., and Zheng, H., *J. Antibiot.*, 2014, vol. 67, pp. 171–174. https://doi.org/10.1038/ja.2013.104

278. Li, X.-D., Li, X., Li, X.-M., Xu, G.-M., Liu, Y., and Wang, B.-G., *Mar. Drugs*, 2018, vol. 16, p. 440. https://doi.org/10.3390/md16110440

279. Ratnaweera, P.B., Williams, D.E., de Silva, E.D., Wijesundera, R.L.C., Dalisay, D.S., and Andersen, R.J, *Mycology*, 2014, vol. 5, pp. 23–28. https://doi.org/10.1080/21501203.2014.892905

280. Yang, M.-H., Li, T.-X., Wang, Y., Liu, R.-H., Luo, J., and Kong, L.-Y., *Fitoterapia*, 2017, vol. 116, pp. 72–76. https://doi.org/10.1016/j.fitote.2016.11.008

281. Amagata, T., Amagata, A., Tenney, K., Valeriote, F.A., Lobkovsky, E., Clardy, J., and Crews, P., *Org. Lett.*, 2003, vol. 5, pp. 4393–4396. https://doi.org/10.1021/ol0356800

282. Kong, F.-D., Huang, X.-L., Ma, Q.-Y., Xie, Q.-Y., Wang, P., Chen, P.-W., Zhou, L.-M., Yuan, J.-Z., Dai, H.-F., Luo, D.-Q., and Zhao, Y.-X., *J. Nat. Prod.*, 2018, vol. 81, pp. 1869–1876. https://doi.org/10.1021/acs.jnatprod.8b00382

283. Springer, J.P., Dorner, J.W., Cole, R.J., and Cox, R.H., *J. Org. Chem.*, 1979, vol. 44, pp. 4852–4854. https://doi.org/10.1021/jo00394a023

284. Li, H.-L., Li, X.-M., Li, X., Yang, S.-Q., and Wang, B.-G., *Phytochem. Lett.*, 2019, vol. 32, pp. 138–142. https://doi.org/10.1016/j.phytol.2019.05.017

285. Li, G.-Y., Li, B.-G., Yang, T., Yin, J.-H., Qi, H.-Y., Liu, G.-Y., and Zhang, G.-L., *J. Nat. Prod.*, 2005, vol. 68, pp. 1243–1246. https://doi.org/10.1021/np0501738

286. Fukuda, T., Kurihara, Y., Kanamoto, A., and Tomoda, H., *J. Antibiot.*, 2014, vol. 67, pp. 593–595. https://doi.org/10.1038/ja.2014.46

287. Hamed, A., Abdel-Razek, A.S., Omran, D.A., El-Metwally, M.M., El-Hosari, D.G., Frese, M., Soliman, H.S.M., Sewald, N., and Shaaban, M., *Nat. Prod. Res.*, 2020, vol. 34, pp. 965–974. https://doi.org/10.1080/14786419.2018.1544977

288. Shaaban, M., El-Metwally, M.M., Abdel-Razek, A.A., and Laatsch, H., *Nat. Prod. Res.*, 2018, vol. 32, pp. 2437–2446. https://doi.org/10.1080/14786419.2017.1419230

289. Hamed, A., Abdel-Razek, A., Frese, M., Stammler, H., El-Haddad, A., Ibrahim, T., Sewald, N., and Shaaban, M., *Molecules*, 2018, vol. 23, p. 299. https://doi.org/10.3390/molecules23020299

290. Fan, S.-Q., Xie, C.-L., Xia, J.-M., Xing, C.-P., Luo, Z.-H., Shao, Z., Yan, X.-J., He, S., and Yang, X.-W., *Org. Biomol. Chem.*, 2019, vol. 17, pp. 5925–5928. https://doi.org/10.1039/C9OB01159E

291. Li, W.-H., Chang, S.-T., Chang, S.-C., and Chang, H.-T., *Nat. Prod. Res.*, 2008, vol. 22, pp. 1085–1093. https://doi.org/10.1080/14786410802267510

292. Rosenberger, M. and Neukom, C., *J. Org. Chem.*, 1982, vol. 47, pp. 1782–1785. https://doi.org/10.1021/jo00348a043

293. Gao, H., Hong, K., Chen, G.-D., Wang, C.-X., Tang, J.-S., Yu, Y., Jiang, M.-M., Li, M.-M., Wang, N.-L., and Yao, X.-S., *Magn. Reson. Chem.*, 2009, vol. 48, pp. 38–43. https://doi.org/10.1002/mrc.2536

294. Talapatra, S.K., Bhaumik, A., and Talapatra, B., *Phytochemistry*, 1992, vol. 31, pp. 2431–2434. https://doi.org/10.1016/0031-9422(92)83293-8

295. Tong, Z.-B., Cui, X.-H., Wang, J., Zhang, C.-L., Zhang, Y.-Y., and Ren, Z.-J., *Nat. Prod. Res.*, 2017, vol. 31, pp. 2564–2567. https://doi.org/10.1080/14786419.2017.1320785

296. Chen, S. and Snyder, J.K., *J. Org. Chem.*, 1989, vol. 54, pp. 3679–3689. https://doi.org/10.1021/jo00276a033

297. Gao, S.-S., Li, X.-M., Li, C.-S., Proksch, P., and Wang, B.-G., *Bioorg. Med. Chem. Lett.*, 2011, vol. 21, pp. 2894–2897. https://doi.org/10.1016/j.bmcl.2011.03.076

298. Igarashi, Y., Sekine, A., Fukazawa, H., Uehara, Y., Yamaguchi, K., Endo, Y., Okuda, T., Furumai, T., and Oki, T., *J. Antibiot.*, 2002, vol. 55, pp. 371–376. https://doi.org/10.7164/antibiotics.55.371

299. Xie, C.-L., Zhang, D., Xia, J.-M., Hu, C.-C., Lin, T., Lin, Y.-K., Wang, G.-H., Tian, W.-J., Li, Z.-P., Zhang, X.-K., Yang, X.-W., and Chen, H.-F., *Mar. Drugs*, 2019, vol. 17, p. 178. https://doi.org/10.3390/md17030178

300. Abdel-Razek, A.S., Hamed, A., Frese, M., Sewald, N., and Shaaban, M., *Steroids*, 2018, vol. 138, pp. 21–25. https://doi.org/10.1016/j.steroids.2018.06.005

301. Kaleem, S., Ge, H., Yi, W., Zhang, Z., and Wu, B., *Nat. Prod. Res.*, 2019. https://doi.org/10.1080/14786419.2019.1680669

302. Bayman, P., Baker, J.L., Doster, M.A., Michailides, T.J., and Mahoney, N.E., *Appl. Environ. Microbiol.*, 2002, vol. 68, pp. 2326–2329. https://doi.org/10.1128/AEM.68.5.2326-2329.2002

303. Wang, Y., Wang, L., Liu, F., Wang, Q., Selvaraj, J., Xing, F., Zhao, Y., and Liu, Y., *Toxins*, 2016, vol. 8, p. 83. https://doi.org/10.3390/toxins8030083
304. Sargent, M.V. and Stransky, P.O., *J. Chem. Soc., Perkin Trans.*, 1982, pp. 1605–1610. https://doi.org/10.1039/p19820001605
305. Wang, J., Lu, Z., Liu, P., Wang, Y., Li, J., Hong, K., and Zhu, W., *Planta Med.*, 2012, vol. 78, pp. 1861–1866. https://doi.org/10.1055/s-0032-1315395
306. Budde, K., Quella, F., Mathes, A., Melchior, W., Müller, H., Nuyken, O., and Spiegel, S., *Angew. Makromol. Chem.*, 1992, vol. 194, pp. 103–117. https://doi.org/10.1002/apmc.1992.051940109
307. Zhao, Y., Liu, D., Proksch, P., Zhou, D., and Lin, W., *Phytochemistry*, 2018, vol. 155, pp. 61–68. https://doi.org/10.1016/j.phytochem.2018.07.017
308. Liu, Y., Ding, L., Fang, F., and He, S., *Nat. Prod. Res.*, 2019, vol. 33, pp. 2466–2470. https://doi.org/10.1080/14786419.2018.1452012
309. Li, T.-X., Yang, M.-H., Wang, X.-B., Wang, Y., and Kong, L.-Y., *J. Nat. Prod.*, 2015, vol. 78, pp. 2511–2520. https://doi.org/10.1021/acs.jnatprod.5b00008
310. Ding, L., Xu, P., Li, T., Liao, X., He, S., and Xu, S., *Nat. Prod. Res.*, vol. 33, 2019, pp. 3404–3408. https://doi.org/10.1080/14786419.2018.1480622
311. Cai, J., Zhou, X.-M., Yang, X., Tang, M.-M., Liao, Q.-Y., Meng, B.-Z., Liao, S., and Chen, G.-Y., *Bioorg. Chem.*, 2019, p. 103362. https://doi.org/10.1016/j.bioorg.2019.103362
312. Bai, M., Huang, G.-L., Mei, R.-Q., Wang, B., Luo, Y.-P., Nong, X.-H., Chen, G.-Y., and Zheng, C.-J., *Mar. Drugs*, 2019, vol. 17, p. 433. https://doi.org/10.3390/md17080433
313. Zhou, X.-M., Zheng, C.-J., Song, X.-M., Tang, M.-M., Yang, J.-Y., Yang, X., Peng, S.-J., Cai, J., and Chen, G.-Y., *Fitoterapia*, 2019, vol. 139, p. 104400. https://doi.org/10.1016/j.fitote.2019.104400
314. Wu, J.-T., Zheng, C.-J., Zhang, B., Zhou, X.-M., Zhou, Q., Chen, G.-Y., Zeng, Z.-E., Xie, J.-L., Han, C.-R., and Lyu, J.-X., *Nat. Prod. Res.*, 2019, vol. 33, pp. 34–40. https://doi.org/10.1080/14786419.2018.1431634
315. Kongyen, W., Rukachaisirikul, V., Phongpaichit, S., and Sakayaroj, J., *Nat. Prod. Res.*, 2015, vol. 29, pp. 1995–1999. https://doi.org/10.1080/14786419.2015.1022542
316. Rao, K.V., Sadhukhan, A.K., Veerender, M., Ravikumar, V., Mohan, E.V.S., Dhanvantri, S.D., Sitaramkumar, M., Moses Babu, J., Vyas, K., and Om Reddy, G., *Chem. Pharm. Bull.*, 2000, vol. 48, pp. 559–562. https://doi.org/10.1248/cpb.48.559
317. Sun, W., Luan, S., Qi, C., Tong, Q., Yan, S., Li, H., and Zhang, Y., *Cell Commun. Signal.*, 2019, vol. 17, 111. https://doi.org/10.1186/s12964-019-0425-4
318. Zeng, Q., Zhong, W.-M., Chen, Y.-C., Xiang, Y., Chen, X.-Y., Tian, X.-P., Zhang, W.-M., Zhang, S., and Wang, F.-Z., *Nat. Prod. Res.*, 2020, vol. 34, pp. 1984–1991. https://doi.org/10.1080/14786419.2019.1569658
319. Sun, Y., Liu, J., Li, L., Gong, C., Wang, S., Yang, F., Hua, H., and Lin, H., *Bioorg. Med. Chem. Lett.*, 2018, vol. 28, pp. 315–318. https://doi.org/10.1016/j.bmcl.2017.12.049
320. Parvatkar, R.R., D'Souza, C., Tripathi, A., and Naik, C.G., *Phytochemistry*, 2009, vol. 70, pp. 128–132. https://doi.org/10.1016/j.phytochem.2008.10.017
321. Zhu, J.X., Ding, L., and He, S., *Nat. Prod. Res.*, 2019, vol. 33, pp. 1191–1195. https://doi.org/10.1080/14786419.2018.1465423
322. Ding, L., Li, T., Liao, X., He, S., and Xu, S., *J. Antibiot.*, 2018, vol. 71, pp. 902–904. https://doi.org/10.1038/s41429-018-0079-2
323. Blair, L.M. and Sperry, J., *J. Nat. Prod.*, 2013, vol. 76, pp. 794–812. https://doi.org/10.1021/np400124n
324. Wermuth, C.G., *MedChemComm*, 2011, vol. 2, pp. 935–941. https://doi.org/10.1039/C1MD00074H
325. Zhang, Y.-X., Yu, H.-B., Xu, W.-H., Hu, B., Guild, A., Zhang, J.-P., Lu, X.-L., Liu, X.-Y., and Jiao, B.-H., *J. Nat. Prod.*, 2019, vol. 82, pp. 3089–3095. https://doi.org/10.1021/acs.jnatprod.9b00700
326. Hayashi, H., Mukaihara, M., Murao, S., Arai, M., Lee, A.Y., and Clardy, J., *Biosci., Biotechnol., Biochem.*, 1994, vol. 58, pp. 334–338. https://doi.org/10.1271/bbb.58.334
327. Cheng, Z., Xu, W., Liu, L., Li, S., Yuan, W., Luo, Z., Zhang, J., Cheng, Y., and Li, Q., *Mar. Drugs*, 2018, vol. 16, p. 358. https://doi.org/10.3390/md16100358
328. Giromini, C., Rebucci, R., Fusi, E., Rossi, L., Saccone, F., and Baldi, A., *Cell Biol. Toxicol.*, 2016, vol. 32, pp. 249–258. https://doi.org/10.1007/s10565-016-9332-2
329. Rottkord, U., Röhl, C., Ferse, I., Schulz, M.-C., Rückschloss, U., Gekle, M., Schwerdt, G., and Humpf, H.-U., *Arch. Toxicol.*, 2017, vol. 91, pp. 1461–1471. https://doi.org/10.1007/s00204-016-1799-3
330. Cramer, B., Harrer, H., Nakamura, K., Uemura, D., and Humpf, H.-U., *Bioorg. Med. Chem.*, 2010, vol. 18, pp. 343–347. https://doi.org/10.1016/j.bmc.2009.10.050
331. Brown, E.D. and Wright, G.D., *Nature*, 2016, vol. 529, pp. 336–343. https://doi.org/10.1038/nature17042
332. Lewis, K., *Nature*, 2012, vol. 485, pp. 439–440. https://doi.org/10.1038/485439a
333. Lewis, K., *Nat. Rev. Drug Discov.*, 2013, vol. 12, pp. 371–387. https://doi.org/10.1038/nrd3975
334. Cameron, A.J., Davison, E.K., An, C., Stubbing, L.A., Dunbar, P.R., Harris, P.W.R., and Brimble, M.A., *J. Org. Chem.*, 2020, vol. 85, pp. 1401–1406. https://doi.org/10.1021/acs.joc.9b02348
335. Lai, Y., Zhang, N., Zhang, Y., Chen, J.-H., and Yang, Z., *Org. Lett.*, 2018, vol. 20, pp. 4298–4301. https://doi.org/10.1021/acs.orglett.8b01733
336. Wolfender, J.-L., Litaudon, M., Touboul, D., and Queiroz, E.F., *Nat. Prod. Rep.*, 2019, vol. 36, pp. 855–868. https://doi.org/10.1039/C9NP00004F

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