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# Diversity of biologically active secondary metabolites in the ascomycete order *Sordariales*

Esteban Charria-Girón [1,2,3] · Frank Surup [2,3] · Yasmina Marin-Felix [2,3]

## Abstract

Ascomycetes belonging to the order *Sordariales* are a well-known reservoir of secondary metabolites with potential beneficial applications. Species of the *Sordariales* are ubiquitous, and they are commonly found in soils and in lignicolous, herbicolous, and coprophilous habitats. Some of their species have been used as model organisms in modern fungal biology or were found to be prolific producers of potentially useful secondary metabolites. However, the majority of sordarialean species are poorly studied. Traditionally, the classification of the *Sordariales* has been mainly based on morphology of the ascomata, ascospores, and asexual states, characters that have been demonstrated to be homoplastic by modern taxonomic studies based on multi-locus phylogeny. Herein, we summarize for the first time relevant information about the available knowledge on the secondary metabolites and the biological activities exerted by representatives of this fungal order, as well as a current outlook of the potential opportunities that the recent advances in omic tools could bring for the discovery of secondary metabolites in this order.

**Keywords** Bioactive compounds · *Diplogelasinosporaceae* · *Lasiosphaeriaceae* · *Naviculisporaceae* · *Podosporaceae* · *Schizotheciaceae* · *Sordariaceae*

## Introduction

Fungi represent one of the best known sources of natural products among living organisms (Bills and Gloer 2016; Atanasov et al. 2021). Recent advances in genomics, molecular biology, bioinformatics, etc. have shed a light on the extensive reservoir of secondary metabolites that they harbor, which might lead to the future discovery of unidentified secondary metabolites (Grigoriev et al. 2011; Winter et al. 2011; Keller 2019). On the other hand, fungi have been extensively exploited for a variety of human purposes ranging from food and beverages to pharmaceutical applications and

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✉ Yasmina Marin-Felix
  Yasmina.MarinFelix@helmholtz-hzi.de

1   Departamento de Ingeniería Bioquímica, Facultad de Ingeniería, Universidad Icesi, Calle 18 No. 122–135, Cali 760031, Colombia

2   Department Microbial Drugs, Helmholtz Centre for Infection Research, Inhoffenstrasse 7, 38124 Braunschweig, Germany

3   Institute of Microbiology, Technische Universität Braunschweig, Spielmannstraße 7, 38106 Braunschweig, Germany

fermentative-industrial processes for the production of vitamins, enzymes, pigments, glycolipids, lipids, polyhydric alcohols, and polysaccharides (Hyde et al. 2019; Dhevagi et al. 2021; Miethke et al. 2021).

Within the phylum *Ascomycota*, the order *Sordariales* is one of the largest and most diverse taxonomic groups within the class *Sordariomycetes*, and contains soil-borne, lignicolous, herbicolous, and coprophilous taxa currently arranged among seven families (Lundquist 1972; Hawksworth 1986; Huhndorf et al. 2004; Marin-Felix et al. 2020). It also represents a source of prolific producers of a great diversity of biologically active secondary metabolites with interesting drug-like properties (Guo et al. 2019; Noumeur et al. 2020). As an example, the antifungal diterpene glycosides, the sordarins, have attracted considerable interest due to their specific action against elongation factor 2 in protein biosynthesis in fungi (Dominguez and Martin 1998; Vicente et al. 2009). Therefore, several sordarin derivatives underwent preclinical investigations in various pharmaceutical companies during the last century, but a successful candidate for clinical development has not yet emerged (Ostrosky-Zeichner et al. 2010).

In this review, we aim to provide for the first time updated information about the vast diversity of secondary metabolites reported for this fungal order in accordance with the most

recent advances in the fungal classification. The recent changes in the taxonomy have resulted in a reallocation of some compounds that were published long time ago to newly established genera and even families. In general, this review covers the secondary metabolites reported in the Dictionary of Natural Products (DNP) database from taxa belonging to this order. Also, the currently valid names of the fungi treated (*fide* MycoBank) are used and the names of outdated or invalidated synonyms that have been used in the old literature are given in brackets where appropriate. Herein, 174 compounds derived from different classes of secondary metabolites have been reported from members of the *Sordariales*, in addition to 189 active compounds reported by Ibrahim et al. (2021) from taxa belonging to the *Chaetomiaceae*. These numbers illustrate an optimistic perspective about the continued discovery of novel bioactive secondary metabolites from representatives of an order that presents a vast taxonomical diversity, reflected in a rich reservoir of natural products, but for which still many taxa remain neglected and require future efforts to unearth their chemical potential.

## Current taxonomical classification of the *Sordariales*

As traditionally defined, the order *Sordariales* has included 7 to 14 families (Hawksworth 1986, Eriksson et al. 2001), until Huhndorf et al. (2004) revised the order based on molecular data, and restricted it to three families, i.e., *Chaetomiaceae*, *Lasiosphaeriaceae*, and *Sordariaceae*. However, these families and their genera, e.g., *Cercophora*, *Chaetomium*, and *Podospora*, were considered polyphyletic (Huhndorf et al. 2004, Cai et al. 2005; Miller and Huhndorf 2005; Kruys et al. 2015).

The *Chaetomiaceae* has been one of the most extensively studied families in the recent years (Wang et al. 2016, 2019a,b). These studies have focused on delimitation of this family and their largest genera *Chaetomium*, *Humicola*, and *Thielavia*, based on polyphasic taxonomy including detailed morphological studies and multi-locus genealogies. This resulted in the introduction of 17 new genera and more than 70 new combinations.

The family *Lasiosphaeriaceae* was the largest family of the order of the redefined *Sordariales* (Huhndorf et al. 2004). This family was considered polyphyletic and was divided in four different lineages in a phylogenetic study (Kruys et al. 2015). The new family *Podosporaceae* was introduced to accommodate one of these lineages distant from the type genus of the family *Lasiosphaeriaceae*, i.e., *Lasiosphaeria* (Wang et al. 2019a). In this same work, the genera *Cladorrhinum* and *Triangularia* were redefined and one of the largest lasiosphaeriaceous genera (*Podospora*) was delimited to the type species *P. fimicola* and another species, i.e., *P. bulbillosa*.

Subsequently, the whole family underwent revision, resulting in the delimitation of *Lasiosphaeriaceae* to the genus *Lasiosphaeria*, and a monophyletic lineage including the type species of *Zopfiella* and other species characterized by ascospores with septate upper cell (except for *Anopodium ampullaceum*) (Marin-Felix et al. 2020). Moreover, other three families were introduced to accommodate three monophyletic lineages, i.e., *Diplogelasinosporaceae*, *Naviculisporaceae*, and *Schizotheciaceae*. Finally, five new genera were introduced; five further genera were redelineated and 26 new combinations were proposed to achieve a more natural classification of taxa included in these families. However, still some taxa remained *incertae sedis* located in phylogenetically unsupported clades that were called *Lasiosphaeriaceae* s. lat., awaiting for a proper fungal classification (Marin-Felix et al. 2020).

On the other hand, the family *Sordariaceae* was the only family considered monophyletic (Huhndorf et al. 2004), but it was demonstrated that the genus *Diplogelasinospora*, which was considered a member of the *Sordariaceae*, was not located in the monophyletic lineage representing the family (Cai et al. 2005). As mentioned above, a new family, the *Diplogelasinosporaceae*, was introduced to accommodate only this genus (Marin-Felix et al. 2020).

Figure 1 illustrates a schematic phylogeny based on the internal transcribed spacer region (ITS), the nuclear rDNA large subunit (LSU), and fragments of ribosomal polymerase II subunit 2 (*RPB2*) and tubulin (*TUB2*) genes, for a better overview of the current division of the order in the different families and not well-delimited lineages.

Recently, a novel phylogenetic reconstruction based exclusively on DNA sequences of the *Sordariales* available in GenBank yield a new interpretation of intra-ordinal relationships (Huang et al. 2021). They also studied some type specimens but did not provide any DNA sequence data from those. As a result, they introduced five new families, i.e., *Bombardiaceae*, *Lasiosphaeridaceae*, *Neoschizotheciaceae*, *Strattoniaceae*, and *Zygospermellaceae*. However, this novel "taxonomic classification" is highly contradictory to previous interpretations, original studies, and therefore, we are reluctant to follow it until further work has confirmed its validity. For instance, the new family *Neoschizotheciaceae* was introduced based on an obvious error of interpretation, because of the erroneous assumption that *Schizothecium* should be a synonym of *Podospora* (Huang et al. 2021). In fact, an extensive explanation of the taxonomic history and the validation of both genera as independent was recently published in two different articles (Ament-Velásquez et al. 2020; Vogan et al. 2021), not considered by Huang et al. (2021). The *Bombardiaceae* was erected even though there is no support in the Bayesian inference, and only 76% bootstrap support in the maximum likelihood. On the other hand, the *Strattoniaceae* was introduced to accommodate the genus *Strattonia*, which remains poorly delimited. Finally,
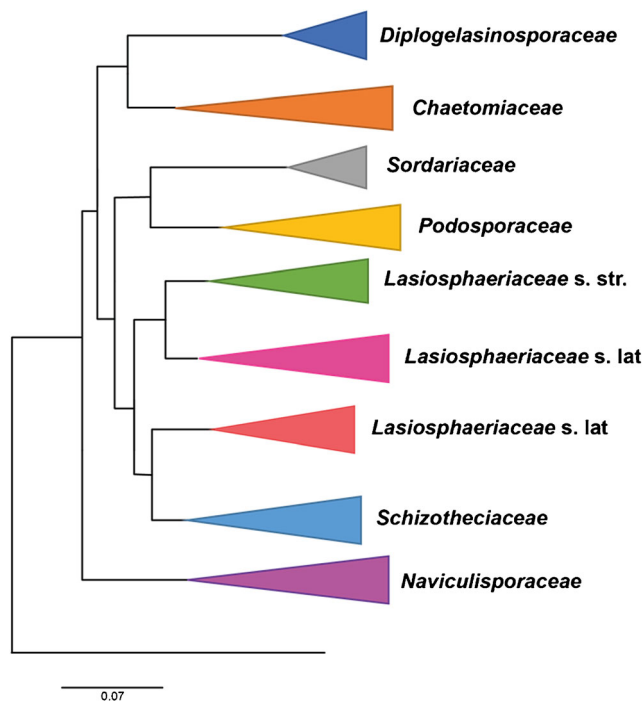
**Fig. 1** Scheme illustrating the phylogenetic relationships between the families and lineages in *incertae sedis* of the *Sordariales* (phylogenetic tree retrieved from Marin-Felix et al. 2020)

the families *Lasiosphaeridaceae* and *Zygospermellaceae* were introduced to accommodate two different lineages with only one and two genera, respectively. However, both lineages were clustered together in previous phylogenetic studies and were closely related to the *Schizotheciaceae*, suggesting that these genera could belong to the latter family (Kruys et al. 2015; Marin-Felix et al. 2020). Generally speaking, this example emphasizes that much new evidence based on original research (rather than by just playing around with data from the public domain) will have to be generated until the taxonomy of the *Sordariales* can finally be stabilized.

Genera of the *Sordariales* have been traditionally classified based on the ascomata, and anamorph morphology, but these characters have proved to be predominantly homoplastic and inconsistent predictors of phylogenetic relationships (Miller and Huhndorf 2004, 2005). This is the main reason why the genera of the *Sordariales* have appeared to be polyphyletic. This problem was firstly observed in different polyphasic studies of *Gelasinospora* and *Neurospora*, which classically have been the largest genera in the *Sordariaceae* (Dettman et al. 2001; García et al. 2004). Both genera belong to the same monophyletic lineage despite their different patterns of ascospore ornamentation, resulting in the merging of *Gelasinospora* with *Neurospora* (García et al. 2004). Instead of the ascospore morphology, the ascomatal wall was demonstrated to be a more useful character for the delimitation of

some genera of the *Sordariales* (Miller and Huhndorf 2005). However, this character is not always useful since it may vary among taxa in the same phylogenetic clade. Moreover, some lineages included fungi with relatively simple ascomatal walls without discriminative characters. Delimitation of the genera based solely on anamorphs is also not useful because many different genera bear similar reduced and simple anamorph morphology. For example, cladorrhinum-like anamorphs are evident in the three genera belonging to the *Podosporaceae*, i.e., *Cladorrhinum*, *Podospora*, and *Triangularia* (Wang et al. 2019a). Even though it seemed that anamorphs could help at least to the delimitation of some families, such as the later mentioned, it is also not always useful for that purpose. Similarly, a cladorrhinum-like anamorph has been reported from the recently described genus *Morinagamyces* (*Schizotheciaceae*) (Harms et al. 2021b). Therefore, the identification of taxa in the *Sordariales* employing only morphological characters is challenging, or even impossible in some cases. A polyphasic approach, combining morphological and other phenotypic data with molecular phylogenetic methods, is currently accepted as the best approach (Miller and Huhndorf 2005; Kruys et al. 2015; Wang et al. 2019a; Marin-Felix et al. 2020). In most cases, comparative sequence-based methods are the best option for the genus and species identification. For this purpose and for phylogenetic reconstructions, the loci most frequently used are the ITS, LSU, *RPB2* and *TUB2*.

Additional problems result from the lack of living material for many, if not most, of taxa described before the DNA era and whose taxonomical position remains uncorroborated by molecular data. Therefore, it is of the utmost importance to recollect fresh material and generate DNA barcodes and cultures to support comprehensive polyphasic studies. Moreover, it is crucial to designate type species and type specimens for those genera and species from which the type material is unavailable or cases when a type was not indicated in the original description. Thus, new type specimens are needed to fix the application of genus and species names.

# Secondary metabolites from species of the *Sordariales*

## *Chaetomiaceae*

As mentioned before, the *Chaetomiaceae* has been extensively studied to achieve a more natural classification of its genera (Wang et al. 2016, 2019a,b). The genera *Chaetomium*, *Humicola*, and *Thielavia*, which have traditionally been the largest genera in the family, have been redefined during the above mentioned studies. The reclassification resulted in the introduction of 17 new genera to accommodate taxa located

distinctly from the monophyletic lineages that included the type species of these genera. Strikingly, many of the entries concern compounds from *Chaetomium* spp. Due to the reorganization of this genus, their classification may be erroneous according to the current taxonomy. Taxa belonging to the *Chaetomiaceae* have played a significant role in a variety of applications including biodeteriotation, agriculture, food production, human and animal health, ecosystems, and biotechnology (Ibrahim et al. 2021). Species belonging to this family also represent a wealth of promising classes of secondary metabolites due to their structural frameworks and interesting bioactivities (Fatima et al. 2016; Zhang et al. 2012). Ibrahim et al. (2021) summarized the chemical diversity found of the family, and therefore we refer to that previous review.

## Diplogelasinosporaceae

This family was recently introduced to accommodate the genus *Diplogelasinospora* (Marin-Felix et al. 2020). *Diplogelasinosporaceae* is characterized by the production of arthroconidia, anamorph not observed in other families of the *Sordariales*.

Due to the fact that this family is rather small, few secondary metabolites have been reported as summarized in Table 1 and illustrated in Fig. 1. For instance, the potential application of the secondary metabolites produced by one representative of the genus *Diplogelasinospora* has been previously studied (Fujimoto et al. 1998a). Among the metabolites produced by the type species, *Diplogelasinospora grovesii*, two macrolide lactone derivates, 10-*epi*-colletodiol (**1**) and its isomer colletodiol (**3**), and a α-pyrone named macrophin (**5**) were found to be the immunosuppressive principles of its crude extract. For the latter compound the half-maximum inhibitory concentration ($IC_{50}$) values against concanavalin A (Con A)- and lipopolysaccharide (LPS)-induced proliferations of mouse spleen lymphocytes were 0.4 and 0.3 μg/mL, respectively. Additionally, 4,8-dimethyl-1,5-dioxacyclooctane-2,6-dione (**2**), and isosclerone (**4**) were also isolated from *D. grovesii* but did not display immunosuppressive properties. These results suggest that the genus could be a rich, but underexplored source of metabolites derived from different biosynthetic pathways, and deserves further studies.

## Lasiosphaeriaceae s. str.

*Lasiosphaeriaceae* represented the largest family included in the order *Sordariales* and it was traditionally considered polyphyletic (Miller and Huhndorf 2004; Kruys et al. 2015). Recently, this family was redefined and delimited to a monophyletic lineage representing the type genus, *Lasiosphaeria*, and a monophyletic clade including the type species of *Zopfiella* and other species characterized by ascospores with septate upper cell (except from *Anopodium ampullaceum*) (Marin-Felix et al. 2020).

The taxa belonging to this redefined family have been largely neglected, and production of secondary metabolites of members of this family has not been reported. The scarce availability of fungi from this family in culture collections due to the difficulty to get these in culture, in particular some of the lignicolous species, could be addressed as possible reasons for this lack of information. Further studies are needed to corroborate the vast chemical diversity found in taxonomically related clades of the order (Fig. 2).

## Lasiosphaeriaceae s. lat.

Several lasiosphaeriaceous taxa remain with an uncertain position at the family level. In the recent revision of the order, these were included in not well-delimited lineages, and therefore these were classified in what was named *Lasiosphaeriaceae* s. lat. (Marin-Felix et al. 2020). The compounds produced by these taxa are herein reported as summarized in Table 2 and illustrated in Fig. 3.

As previously mentioned, members of the *Sordariales* are commonly coprophilous fungi, which are those that inhabit or are associated with the dung of animals and have provided an excellent example of interspecies competition and a model for studying colonization patterns within fungal ecosystems (Bills et al. 2013). Moreover, the chemical investigation of coprophilous fungal species has led to discovering novel bioactive agents, including antifungals (Bills et al. 2013). Such is the case of the fungi *Bombardioidea anartia*, for which the bioassay-guided fractionation of its crude extract led to the discovery of the γ-lactones, bombardolides A–D (**8–11**), a group of antifungal and antibacterial secondary metabolites (Hein et al. 2001). In the same study, a meta-substituted phenol (**6**) and the known compound asteriquinone B4 (**7**) were also obtained from this strain. Bombardolides A–C and 3-(1′-hydroxypentyl) phenol were active in disk diffusion assays against *Bacillus subtilis*, while only bombardolides A, B and compound **6** were active against *Staphylococcus aureus*. On the other hand, bombardolides B and C exhibited antifungal activity *against Candida albicans*. The biosynthesis of bombardolides remains unclear since this group of compounds does not appear to be regular polyketides due to the absence of a keto acid corresponding to an open chain form. However, it is presumed that these compounds seem most likely to arise via oxidative cleavage of an aromatic polyketide precursor (Hein et al. 2001). Similarly, for a strain of *Podospora appendiculata* originally obtained from deer dung, its chemical investigation afforded three antifungal 2(5*H*)-furanones, named appenolides A–C (**17–19**), active against the yeast *Candida albicans*, and the filamentous fungi *Ascobolus furfuraceus* and *Sordaria fimicola*, which are also coprophilous fungi (Wang et al. 1993). Appenolides B and C

**Table 1** List of compounds isolated from members of the *Diplogelasinosporaceae* (Genera, species, compound class, molecular weights and formulae, and biological activity)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| *Diplogelasinospora* | *grovesii* | 10-*epi*-colletodiol | 1 | Macrodiolide | $C_{14}H_{20}O_6$ (284) | Immunosuppressive | Fujimoto et al. (1998a) |
| | | 4,8-dimethyl-1,5-dioxacyclooctane-2,6-dione | 2 | Macrodiolide | $C_8H_{12}O_4$ (172) | | |
| | | Colletodiol | 3 | Macrodiolide | $C_{14}H_{20}O_6$ (284) | Immunosuppressive | |
| | | Isosclerone | 4 | Naphthalene derivative | $C_{10}H_{10}O_3$ (178) | | |
| | | Macrophin | 5 | alpha-pyrone | $C_{17}H_{20}O_8$ (352) | Immunosuppressive | |

also exhibited antibacterial activity against *Bacillus subtilis*, while appenolide A was biologically inactive against bacteria. Interestingly, naturally occurring furanones represent a rare class of compounds with a diverse variety of biological activities, as antibacterial and phytotoxic (Evidente et al. 1986; Sparapano et al. 1986; Davidson and Ireland 1990; Wang et al. 1993).

*Fimetariella rabenhorstii*, which has been isolated as an endophyte of *Aquilaria sinensis*, was the first example of the occurrence of a compound biogenetically related to the agarwood fragrant chemicals in endophytic fungi of agarwood-producing plants (Tao et al. 2011). Frabenol (13), a sesquiterpenoid alcohol with an uncommon carbon skeleton similar to the major fragrant chemical constituents in agarwood, suggested a method in which potential new sources for producing bioactive fragrant chemicals could be achieved biotechnologically. Although the crude extract of *F. rabenhorstii* demonstrasted to have potential to inhibit the growth of some tumor cell strains in vitro (Li et al. 2009), frabenol was inactive in further assays (Tao et al.

2011). In a different study, this same species was detected in oak trees (*Quercus brantii*) from the Zagros forest, in the west of Iran, as a phytopathogen causing decline and wood necrosis symptoms (Bashiri et al. 2020). Respectively, a chlorinated chromen-4-one named rabenchromenone (15), and a hexasubstituted benzophenone, rabenzophenone (16), were isolated together with coniochaetone A (12) and moniliphenone (14), as phytotoxic constituents of this fungus. Rabenzophenone was the most phytotoxic compound against holm oak and tomato leaves causing significant necrosis (0.7 and 0.5 cm, respectively) in the leaf puncture bioassays. Even though these strains were previously reported as *F. rabenhorstii*, the BLAST search using the sequences of the internal transcribed spacer region (ITS) revealed that they are related to *Coniochaeta* (*Coniochaetales*). This fact is well supported in the case of the phytopathogenic strain by the finding of coniochaetone A, an antifungal secondary metabolite originally reported from the coprophilous fungus *Coniochaeta saccardoi* (Wang et al. 1995). Further
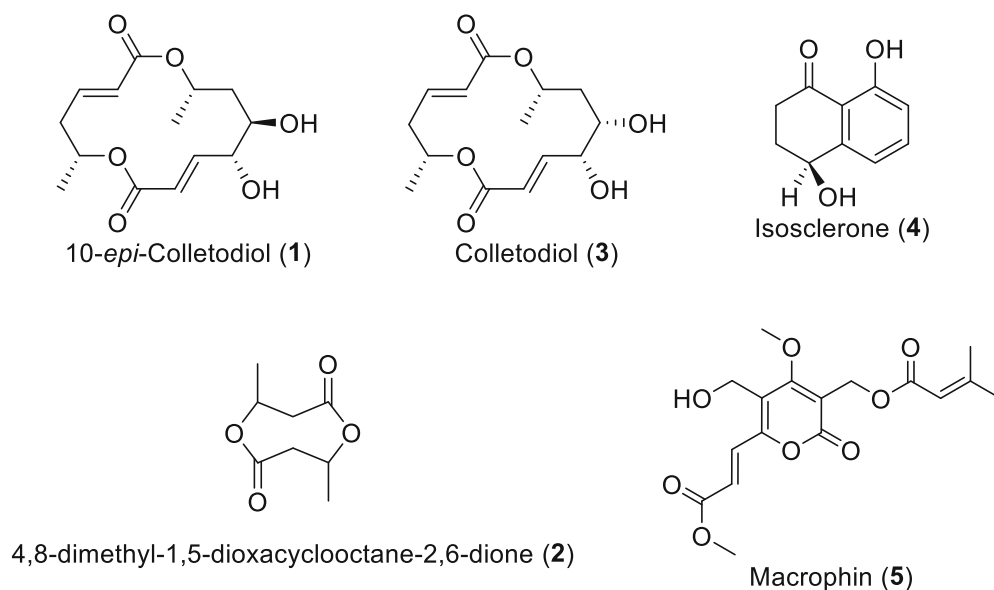


**Fig. 2** Chemical strucutres of compounds isolated from members of the *Diplogelasinosporaceae* (1–5)

10-*epi*-Colletodiol (1)

Colletodiol (3)

Isosclerone (4)

4,8-dimethyl-1,5-dioxacyclooctane-2,6-dione (2)

Macrophin (5)

**Table 2** List of compounds isolated from members of the *Lasiosphaeriaceae* s. lat. (Genera, species, compound class, molecular weights and formulae, and biological activity)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological Activity | Reference |
|---|---|---|---|---|---|---|---|
| *Bombardioidea* | *anartia* | 3-(1′-hydroxypentyl)phenol | 6 | Alkyl phenol | $C_{11}H_{16}O_2$ (180) | Antibacterial | Hein et al. (2001) |
| | | Asteriquinone B4 | 7 | Bis-indolylquinone | $C_{34}H_{34}N_2O_4$ (534) | | |
| | | Bombardolide A | 8 | Furanone polyketide | $C_{10}H_{12}O_3$ (180) | Antibacterial and antifungal | |
| | | Bombardolide B | 9 | Furanone polyketide | $C_{10}H_{14}O_3$ (182) | Antibacterial | |
| | | Bombardolide C | 10 | Furanone polyketide | $C_{10}H_{10}O_4$ (194) | Antibacterial | |
| | | Bombardolide D | 11 | Furanone polyketide | $C_{10}H_{14}O_3$ (182) | Antifungal | |
| *Coniochaeta* | *rabenhorstii* | Coniochaetone A | 12 | Chromone polyketide | $C_{13}H_{10}O_4$ (230) | Antifungal | Bashiri et al. (2020) |
| | | Frabenol | 13 | Sesquiterpenoid | $C_{15}H_{26}O_2$ (238) | | Tao et al. (2011) |
| | | Moniliphenone | 14 | Benzophenone derivative | $C_{16}H_{14}O_6$ (302) | Phytotoxic | Bashiri et al. (2020) |
| | | Rabenchromenone | 15 | Chromone polyketide | $C_{15}H_{11}ClO_6$ (322) | Phytotoxic | |
| | | Rabenzophenone | 16 | Aromatic polyketide | $C_{16}H_{13}ClO_6$ (336) | Phytotoxic | |
| *Podospora* | *appendiculata* | Appenolide A | 17 | Furanone polyketide | $C_{14}H_{20}O_3$ (236) | Antifungal and antibacterial | Wang et al. (1993) |
| | | Appenolide B | 18 | Furanone polyketide | $C_{14}H_{22}O_3$ (238) | Antifungal and antibacterial | |
| | | Appenolide C | 19 | Furanone polyketide | $C_{14}H_{22}O_3$ (238) | Antifungal | |

studies are needed to corroborate whether *F. rabenhorstii* should be transferred to this latter genus or it was a misidentification of the strains in both studies.

### Naviculisporaceae

The *Naviculisporaceae*, which was recently erected, includes four recently introduced genera, i.e., *Areotheca*, *Naviculispora*, *Pseudorhyphophila*, and *Rhypophila*, as well as some species of *Arnium*, whose taxonomic placement still remains unclear (Marin-Felix et al. 2020). Due to the recent introduction of most of the genera belonging to the family, the producers were almost all reported with outdated names following the obsolete taxonomic classification of lasiosphaeriaceous taxa. Updated records about the secondary metabolites reported from this family are summarized in Table 3 and shown in Figs. 4 and 5.

Cercophorins A–C (21–23), three antifungal and cytotoxic isocoumarin derivates, have been isolated from the colonist of porcupine dung, *Cercophora areolata* (now classified as *Areotheca areolata*), whose crude extract showed antifungal activity against *C. albicans* (Whyte et al. 1996; Marin-Felix et al. 2020). In addition, two isocoumarins,

decarboxycitrinone (24) and 4-acetyl-8-hydroxy-6-methoxy-5-methylisocoumarin (20), and a known trichothecene mycotoxin, roridin E (25), were also isolated from this fungus. This latter compound 25 was found to be responsible for most of the anti-*Candida* activity observed in the crude extract. In fact, trichothecenes are a family of terpenoid toxins produced by several genera of fungi, including plant and insect pathogens, which are considered of great concern to food and feed safety (Proctor et al. 2018). Over 150 trichothecene metabolites have been reported from phylogenetically diverse producers, which mostly belong to the *Hypocreales* (*Sordariomycetes*) (Proctor et al. 2018). Therefore, the production of roridin E within a member of the *Sordariales* appears to an anomaly, and requires further studies to confirm this finding.

Sordarin (29) was first isolated from *Sordaria araneosa*, and its taxonomic adscription gave name to this family of antifungal compounds (Hauser and Sigg 1971). Subsequently, *S. araneosa* had been transferred to *Podospora* as *Podospora araneosa* (Cain 1962), and then Vicente et al. (2009) confirmed that this strain was not a member of genus *Sordaria* and was found to be phylogenetically closely related to a number of *Podospora* spp., i.e., *P. myriospora*, *P. decipiens*, and *P. pleiospora*, which now all belong to the recently introduced genus *Rhypophila* (Marin-
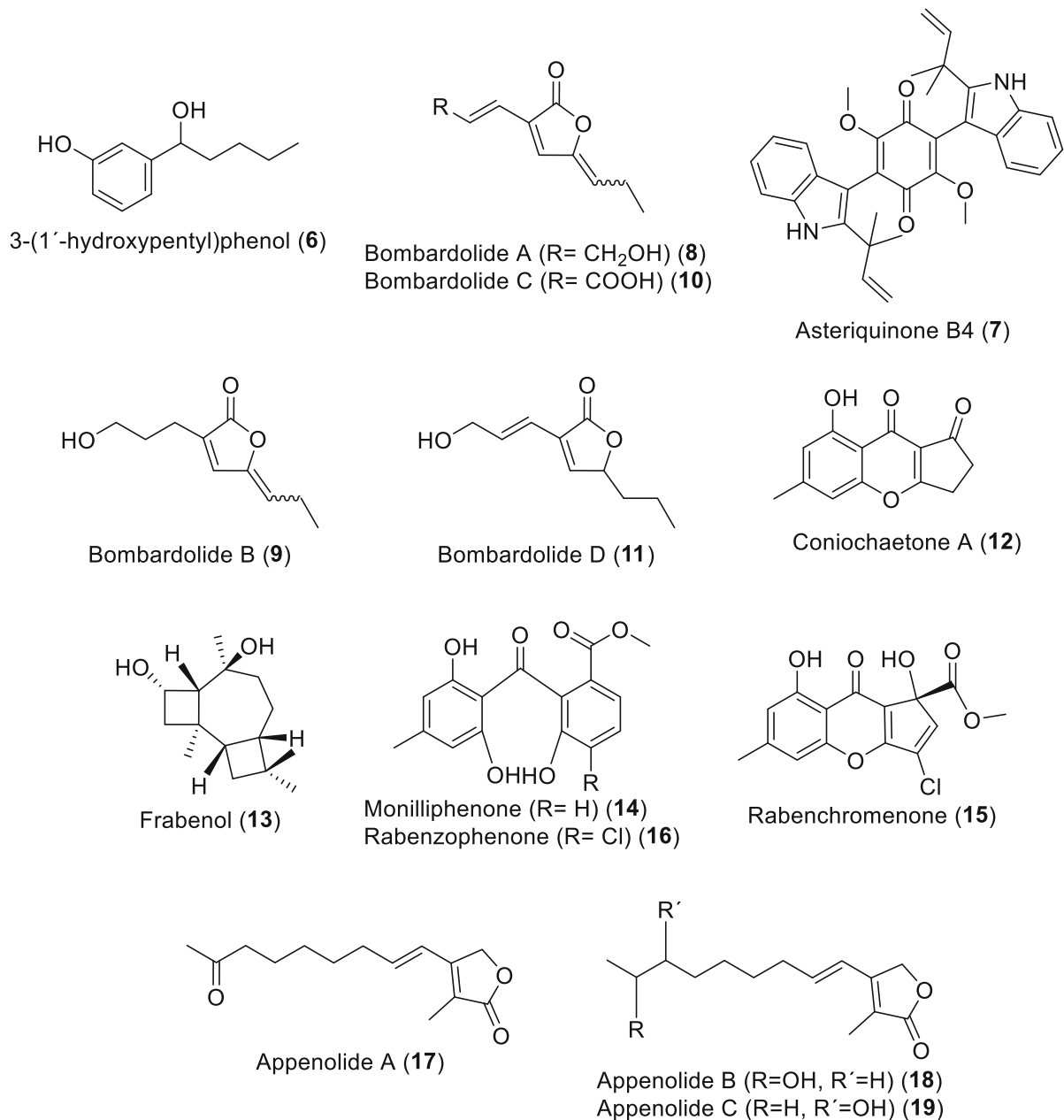
**Fig. 3** Chemical strucutures of compounds isolated from members of the *Lasiosphaeriaceae* s. lat. (**6–19**)

Felix et al. 2020). Sordarins are a class of natural antifungal agents which were found to act at the protein synthesis level through their interaction with the elongation factor 2 in eukaryotes (eEF2) (Dominguez and Martin 1998). This enzyme is responsible for the translocation of transfer RNA and messenger RNA after peptide bond formation during the translation process, thus the inhibition of this step directly triggers cell death (Kudo et al. 2016; Chaichanan et al. 2014). However, sordarins have an attractive mechanism of action since the solely antimycotic activity of these compounds results from the high affinity for fungal eEF2 when compared against that of plants or mammals (Chaichanan et al. 2014). Sordarin type compounds have been mainly found in

*Xylariales*, but they were also reported from some species of the *Sordariales*, *Eurotiales*, and *Microascales* (Vicente et al. 2009). In fact, Harms et al. (2021a) demonstrated that all sordarin producers belonging to the *Sordariales* were nested in the *Naviculisporaceae*, playing the role of potential chemotaxonomic markers of the family (Weber et al. 2005; Harms et al. 2021a). In this sense, apart from sordarin (**29**), other related metabolites including hydroxysordarin (**26**), hypoxysordarin (**27**), and neosordarin (**28**) were isolated from *Rh. araneosa* (Davoli et al. 2002; Daferner et al. 1999). Also, sordarin B (**31**), hydroxysordarin (**26**), and sordaricin (**30**) were found in the culture of the coprophilous species *Rh. pleiospora* (Weber et al. 2005). Sordarins have been also

**Table 3** List of compounds isolated from members of the *Naviculisporaceae* (Genera, species, compound class, molecular weights and formulae, and biological activity)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| *Areotheca* | *areolata* | 4-acetyl-8-hydroxy-6-methoxy-5-methylisochroman-1-one | 20 | Isocoumarin | $C_{13}H_{14}O_5$ (250) | | Whyte et al. (1996) |
| | | Cercophorin A | 21 | Isocoumarin | $C_{20}H_{16}O_9$ (400) | | |
| | | Cercophorin B | 22 | Isocoumarin | $C_{20}H_{16}O_{10}$ (416) | | |
| | | Cercophorin C | 23 | Isocoumarin | $C_{20}H_{16}O_{10}$ (416) | | |
| | | Decarboxycitrinone | 24 | Isocoumarin | $C_{12}H_{12}O_4$ (220) | | |
| | | Roridin E | 25 | Polyketide-Sesquiterpenoid-hybride | $C_{29}H_{38}O_8$ (514) | Antifungal | |
| *Rhypophila* | *araneosa* | Hydroxysordarin | 26 | Diterpenoid | $C_{27}H_{40}O_9$ (508) | Antifungal | Davoli et al. (2002) |
| | | Hypoxysordarin | 27 | Diterpenoid | $C_{36}H_{50}O_{11}$ (658) | Antifungal | Daferner et al. (1999) |
| | | Neosordarin | 28 | Diterpenoid | $C_{36}H_{50}O_{11}$ (658) | Antifungal | Davoli et al. (2002) |
| | | Sordarin | 29 | Diterpenoid | $C_{27}H_{40}O_8$ (492) | Antifungal | Hauser and Sigg (1971) |
| | *pleiospora* | Hydroxysordarin | 26 | Diterpenoid | $C_{27}H_{40}O_9$ (508) | Antifungal | Weber et al. (2005) |
| | | Sordaricin | 30 | Diterpenoid | $C_{20}H_{28}O_4$ (332) | Antifungal | |
| | | Sordarin B | 31 | Diterpenoid | $C_{27}H_{40}O_8$ (492) | Antifungal | |
| *Pseudorhypophila* | *mangenotii* | 7-*O*-acetylmultiplolide A | 32 | Macrolactone | $C_{12}H_{16}O_6$ (256) | Antifungal | Harms et al. (2021a) |
| | | 8-*O*-acetylmultiplolide A | 33 | Macrolactone | $C_{12}H_{16}O_6$ (256) | Antifungal | |
| | | Hypoxysordarin | 27 | Diterpenoid | $C_{36}H_{50}O_{11}$ (658) | Antifungal | |
| | | Sordarin | 29 | Diterpenoid | $C_{27}H_{40}O_8$ (492) | Antifungal | |
| | | Sordarin B | 30 | Diterpenoid | $C_{27}H_{40}O_8$ (492) | Antifungal | |
| | | Zopfinol | 34 | Salicylalcohol derivative | $C_{18}H_{25}ClO_4$ (340) | Antibacterial and antifungal | |
| | | Zopfinol B | 35 | Salicylalcohol derivative | $C_{18}H_{26}O_4$ (306) | | |
| | | Zopfinol C | 36 | Salicylalcohol derivative | $C_{18}H_{27}ClO_4$ (342) | Antibacterial and antifungal | |
| | | Zopfinol D | 37 | Salicylalcohol derivative | $C_{18}H_{28}O_4$ (308) | Antibacterial | |
| | *marina* | 3-deoxyisoochracinic acid | 38 | Salicylalcohol derivative | $C_{10}H_{10}O_4$ (194) | | Chokpaiboon et al. (2018) |
| | | 5-chloro-3-deoxyisoochracinic acid | 39 | Salicylalcohol derivative | $C_{10}H_9ClO_4$ (228) | | |
| | | Dihydroisobenzofuran 1 | 40 | Salicylalcohol derivative | $C_{18}H_{24}O_3$ (288) | | |
| | | Dihydroisobenzofuran 2 | 41 | Salicylalcohol derivative | $C_{18}H_{26}O_4$ (306) | | |
| | | Dihydroisobenzofuran 3 | 42 | Salicylalcohol derivative | $C_{18}H_{28}O_5$ (324) | | |
| | | Dihydroisobenzofuran 4 | 43 | Salicylalcohol derivative | $C_{18}H_{28}O_6$ (340) | | |
| | | Dihydroisobenzofuran 5 | 44 | Salicylalcohol derivative | $C_{18}H_{26}O_5$ (322) | | |
| | | Hydroxymethylphenol | 45 | Salicylalcohol derivative | $C_{12}H_{12}O_4$ (230) | | |

**Table 3** (continued)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| | | Salicylaldehyde derivative 1 | 46 | Salicylaldehyde derivative | $C_{18}H_{24}O_3$ (288) | Antibacterial and cytotoxic | |
| | | Salicylaldehyde derivative 2 | 47 | Salicylalkohol derivative | $C_{12}H_{10}O_4$ (228) | | |
| | | Zofimarin | 48 | Diterpen derivative | $C_{33}H_{46}O_9$ (586) | Antifungal | Hanadate et al. (2009) |
| | | Zopfinol | 34 | Salicylalcohol derivative | $C_{18}H_{25}ClO_4$ (340) | Antibacterial and antifungal | Kondo et al. (1987) |

isolated from the type strain of *Pseudorhyphophila mangenotii*, a closely related genus to *Rhyphophila* (Harms et al. 2021a). Moreover, the gene cluster responsible for the biosynthesis of these compounds was recently identified (Kudo et al. 2016), and further details can be found in the omics section.

The genus *Pseudorhypophila* was introduced by Harms et al. (2021a) to accommodate *Triangularia mangenotii* and different species of *Zopfiella*, i.e., *Z. marina*, *Z. pilifera*, and *Z. submersa*, that nested in a monophyletic clade based on the phylogenetic study combined to chemotaxonomic data in a so-called polythetic taxonomic approach. For instance, among the compounds produced by the type strain of *Prh. mangenotii*, which included the known zopfinol (**34**) and its derivatives zopfinol B–D (**35**–**37**), and the 10-membered lactones 7-*O*-acetylmultiplolide A (**32**) and 8-*O*-acetylmultiplolide A (**33**) were also isolated (Harms et al. 2021a). From the mentioned metabolites, only zopfinol and its derivates **36** and **37** exhibited weak antibacterial activity against *B. subtilis* (MIC = 33.3, 33.3, and 66.7 μg/mL) and *St. aureus* (MIC = 66.7, 33.3, and 66.7 μg/mL). Also, zopfinol C presented weak inhibition against *Rhodotorula glutinis*, while compounds **34** and **36** showed weak antifungal activity against *Mucor hiemalis*. In contrast, sordarin (**29**) and hypoxysordarin (**27**) showed antifungal activity against *C. albicans*, even though the MIC of **27** was twice the value of **29** in the same assays. Hypoxysordarin showed a much stronger antifungal activity against *M. hiemalis*. Compounds **34**, **36**, and **37** showed weak cytotoxic activity against KB 3.1 and L929 mammalian cell lines. The 10-membered lactones, 7-*O*-acetylmultiplolide A and 8-*O*-acetylmultiplolide A, were lacking antimicrobial activity against the array of microorganisms tested in this study. However, 8-*O*-acetylmultiplolide A had displayed antifungal activity against several fungal strains as previously reported by Wu et al. (2008). In contrast, compound 7-*O*-acetylmultiplolide A was found mostly inactive, even though both compounds differ only in the position of the acetoxy group, demonstrating its critical role in the exhibited biological activities. *Pseudorhypophila marina* (syn. *Zopfiella marina*) also produces zopfinol and the strong antifungal zofimarin (**48**), which acts at the protein synthesis level in a similar way to that exhibited by sordarins (Kondo et al. 1987; Ogita et al. 1987). The structure of zofimarin is related to sordarin, since it has an acyl group attached to the pyran ring of the tetracyclic aglycon common to all sordarins (Hanadate et al. 2009). The chemical investigation of this fungus also afforded a 5-chloro-3-deoxyisoochracinic acid (**39**), five dihydroisobenzofuran (**40**–**44**) derivatives, a hydroxymethylphenol (**45**), and two salicylaldehyde derivatives (**46**) and (**47**), together with a known 3-deoxyisoochracinic acid (**38**) (Chokpaiboon et al. 2018). Compound **46** showed activity against *Mycobacterium tuberculosis* with an MIC value of 25 μg/mL and displayed antibacterial activity against *Bacillus cereus* with an MIC
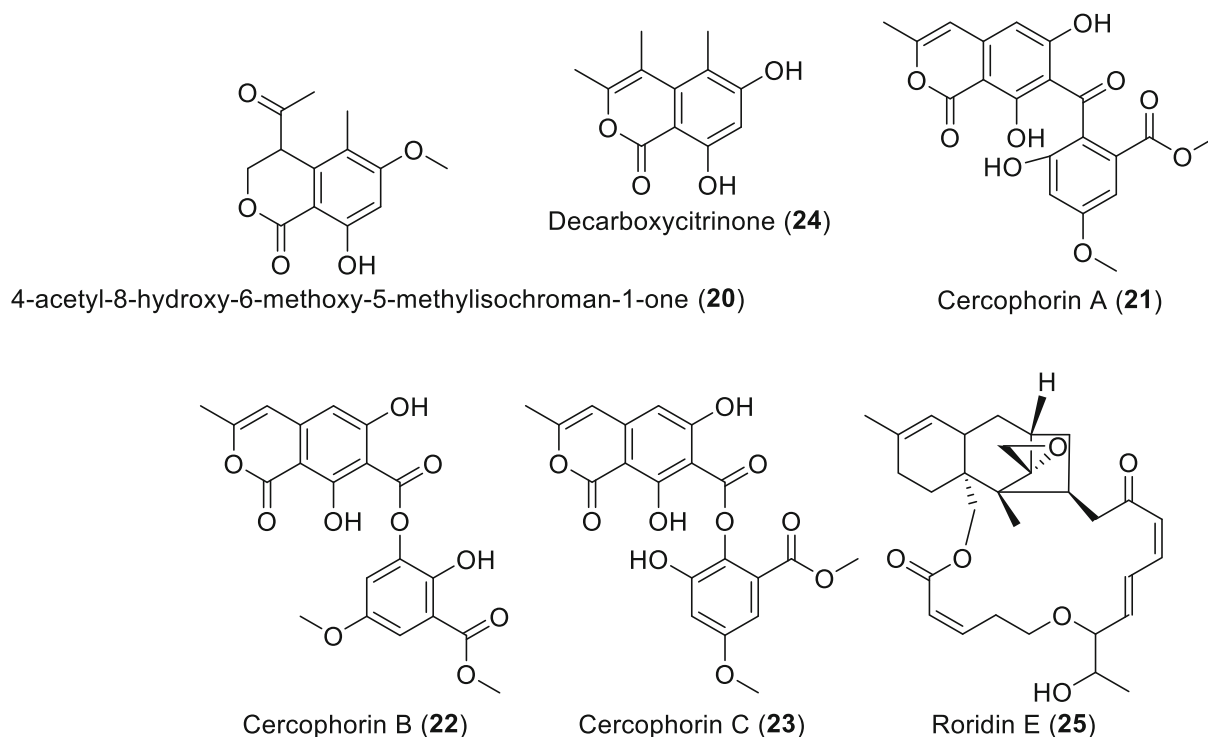
Fig. 4 Chemical strucutures of compounds isolated from members of the *Naviculisporaceae* (**20–25**)

value 12.5 µg/mL, but it was inactive against *Plasmodium falciparum* at 10 µg/mL. It was also active against Vero cells (African green monkey kidney fibroblasts) with an $IC_{50}$ value of 13.6 µg/mL. Furthermore, the production of secondary metabolites by the new genus *Pseudorhypophila* could play a useful role as chemotaxonomic markers in a similar extent to the sordarins in the *Naviculisporaceae* family, since the zopfinol is produced by different species of *Pseudorhypophila*, but it was not reported in any other taxon (Harms et al. 2021a).

## Podosporaceae

The *Podosporaceae* includes the recently redefined genera *Chladorrhinum*, *Podospora*, and *Triangularia* (Wang et al. 2019; Marin-Felix et al. 2020). As a result of the correct delimitation of these genera, a high number of species changed their taxonomic placement. Therefore, the producers of the compounds reported from this family were wrongly identified or named based on an obsolete fungal classification, and amended information is summarized on Table 4 and illustrated in Figs 6 and 7.

Benzoquinones derivates are frequently isolated as bioactive components of fungi and plants (Chiung et al. 1993). In this sense, two unprecedented benzonquinones with antifungal, antibacterial, and cytotoxic activities were obtained from the coprophilous fungus *Podospora anserina*, now transferred to the genus *Triangularia* as *T. anserina* (Wang et al. 1997). Anserinones A (**66**) and B (**67**) were found to be different

from naturally precedents in the identity of the substituents and substitution patterns and active against other coprophilous fungi and Gram-positive bacteria in disk assays. Moreover, they exhibited cytotoxic activity against NCI's 60 human tumor cell line panel with $IC_{50}$ values of 1.9 and 4.4 µg/mL, respectively. An endophytic strain of *Podospora*, which ITS sequence showed high similitude to *T. anserina* (> 99.6%) produced two xanthones, secosterigmatocystin (**68**) and sterigmatocystin (**69**), together with an anthraquinone derivate, 13-hydroxyversicolorin B (**65**) (Matasyoh et al. 2011). Sterigmatocystin was the first known naturally occurring compound to contain the bisdihydrofuran ring system and is a known carcinogenic polyketide (Terao, 1983; Veršilovskis and Saeger, 2010; Rank et al. 2011). It is produced by species in several fungal genera and is an intermediate of more potent aflatoxins, which are extensively studied as fungal metabolites with relevant biological function and biosynthetic understanding (Rank et al. 2011; Shen et al. 2019; Li et al. 2020; Shen et al. 2022). The mosquito larvicidal activity of compounds **65** and **69** was evaluated against third instar larvae of *Anopheles gambiae*, a malaria mosquito (Matasyoh et al. 2011). Compound **69** exhibited potent activity with a lethal concentration ($LC_{50}$ and $LC_{90}$) values of 13.3 and 73.5 µg/mL, respectively, which in comparison with the commercial larvicide pylarvex® showed close mortality percentages at the same concentration.

Emestrin (**49**), a macrocyclic epidithiodioxopiperazine derivate, was obtained from *Triangularia striata* (syn. *Emericella striata*) (Seya et al. 1985). Emestrin exhibited
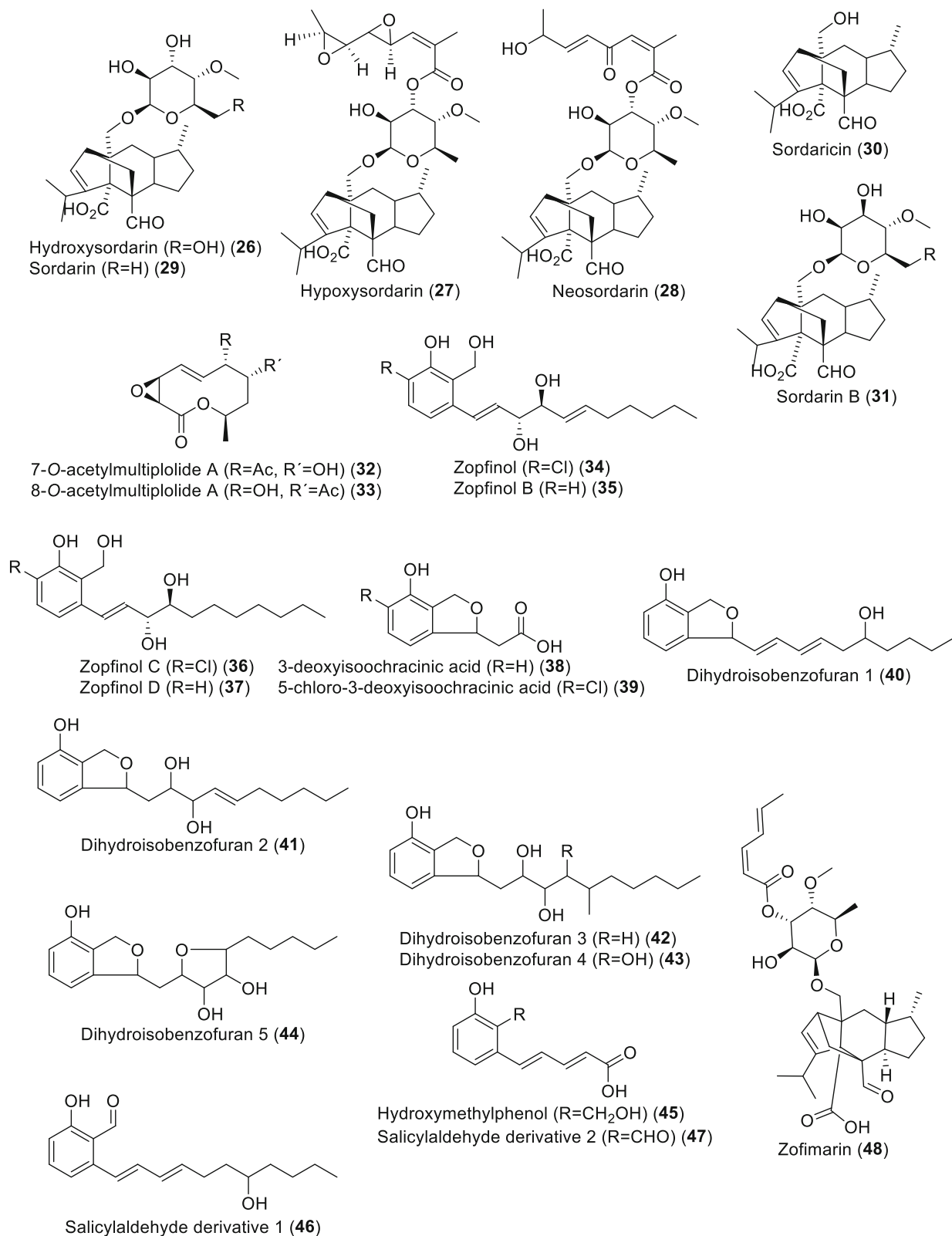
**Fig. 5** Chemical strucutures of compounds isolated from members of the *Naviculisporaceae* (**26–48**)

antifungal activity against *C. albicans* and *Cryptococcus neoformans* and antibacterial activity against both *Escherichia coli* and *St. aureus* (Herath et al. 2013; Oberhofer et al. 2021). Particularly, potent antifungal

activity of this compound against *Penicillium expansum* and *Fusarium graminearum* (reported under the outdated name *Gibberella zeae*) has been also reported (Seya et al. 1986). Together with this compound, aurantioemestrin (**79**), dethiosecoemestrin (**80**), emestrin B (**81**), and violaceid acid (**83**), biogenetically related metabolites, were also isolated from the same strain (Seya et al. 1985; Kawahara et al. 1986; Nozawa et al. 1987). Chemical investigations led to the hypothesis that aurantioemestrin is chemically degraded to dethiosecoemestrin, which is later desulfurized and oxidatively converted to emestrin or violaceic acid (Kawahara et al. 1986). Moreover, compound **80** exhibited antibacterial effects in disk assays against *B. subtilis* (Seya et al. 1985). In addition, in this study, the tremorgenic mycotoxin from *Penicillium paxilli*, paxilline (**82**), was also reported as metabolite of *T. striata*. Onodera et al. (2004) found eight emestrin-type metabolites from *Cladorrhinum* sp. with potent antiproliferative activities against DU145 human prostate cancer cell line together with the known compounds, emestrin, emestrin B, and secoemestrin C (**58**). It is noting that the initial classification of this fungus was solely made based on morphological data, but the anamorph before known as *Cladorrhinum*, now are located in three different genera, i.e., *Cladorrhinum*, *Podospora*, and *Triangularia*. This kind of anamorph is characteristic of taxa belonging to the *Podosporaceae*, except from *Morinagamyces*. Therefore, emestrins producers are here considered as members of the *Podosporaceae*, but a precise identification at genus and species level from molecular data is needed. In this study, the active metabolites corresponded to MPC1001 (**50**), an *O*-methyl derivate of the 15-membered antimicrobial emestrin, and its analogs MPC1001B–H (**51**–**57**). Mostly, natural products exerting polythiodioxopiperazine moieties exhibit a broad range of biological activities, with antibiotic and antifungal as the most commonly observed ones (Brewer et al. 1996). In this case, MPC1001 and the analogues **51**–**57** containing both macrocyclic skeletons and polysulfide bridges over dioxopiperadine rings showed an $IC_{50}$ between 9.3 and 450 nM against DU145 human prostate cancer cell line. Particularly, the decrease in the bioactivity in MPC1001E ($IC_{50}$ = 83 nM), MPC1001G ($IC_{50}$ = 350 nM), and MPC1001G ($IC_{50}$ = 450 nM) suggested that the lack of the macrocyclic ring and polysulfide bonds affected substantially the exhibited antitumor activity (Onodera et al. 2004). Moreover, the production of emestrin-type compounds has been also found in another strain identified as *P. australis* (Li et al. 2016b), but whose molecular data demonstrated its location in the genus *Cladorrhinum*. In this study, 11 emestrin-type epipolythiodioxopiperazine metabolites were obtained, including four analogs (**60**–

**63**). Among these, emestrin C (Also named MPC1001) and MPC1001C were highly active against *Cr. neoformans* with MIC values of 0.8 and 1.6 μg/mL, respectively, but these lacked any antibacterial activity. Also, both the trisulfur-bridged emestrin D and the tetrasulfur-bridged emestrin E (**59**) displayed weaker activity against *Cr. neoformans* with at least a 4-fold higher MIC value. The rest of the macrocycle ring-opened compounds were inactive in the same assays, which emphasized the essential role of the macrocyclic ring and polysulfide structures for the inhibition of *Cryptococcus*. Studies on rat liver revealed a possible relation between antifungal and cytotoxic activities of emestrins and inhibition of ATP synthesis in the mitochondria (Kawai et al. 1989). However, the selective action of emestrins on *Cr. neoformans* remains unclear, since ATP synthesis and mitochondrial function are conserved features between fungi and other eukaryotic organisms.

Six immunosuppressive components have been isolated from *Z. longicaudata*, which was also transferred to *Triangularia* as *T. longicaudata* (Fujimoto et al. 2004; Wang et al. 2019a). Among the isolated metabolites, the anthraquinone namely omega-acetylcarviolin (**77**), and three known anthraquinones, 1-*O*-methylemodin (**73**), carviolin (roseo-purpurin) (**75**), and omega-hydroxyemodin (citreorosein) (**78**), were found. Also, the steroids, 25-hydroxyergosta-4,6,8(14),22-tetraen-3-one (**74**), and ergosta-4,6,8(14),22-tetraen-3-one (**76**) were obtained. Moderate immunosuppressive activity of these compounds was found against Con A-induced and LPS-induced proliferations of mouse spleen lymphocytes compared to the exhibited activity of the known anthraquinones, emodin, questin, and rubrocristin. Two patents have been created based on the compounds produced by *Apiosordaria effusa* SANK 15083, apiodionen (**71**) and preapiodionen (**72**), which are useful as anti-neoplastic agents with inhibitory properties on topoisomerases I and II in animals or as anti-inflammatory agents, which display a chemiluminescence inhibition effect (Takahashi et al. 1992). According to the molecular data, this species should be transferred to the genus *Triangularia*. During the screening for antibiotics of fungal origin, four strains of *Sordariales* identified as *T. bambusae*, *T. matsushimae* (syn. *Zopfiella matsushimae*), *T. tetraspora* (syn. *Lacunospora tetraspora*), and *Triangularia* sp. (syn. *Apiosordaria* sp.) were newly found to produce botryodiplodin (**70**) (Nakagawa et al. 1979). This compound was found to be mostly active against *Botrytis cinerea*, *Trichophyton mentagrophytes* (syn. *Trichophyton interdigitale*), and *Microsporum gypseum* with MIC values of 12.5, 25, and 25 μg/mL, respectively, but it did not show activity against Gram-positive and Gram-negative bacteria.

Even though different metabolites have been reported from species that were once classified in *Podospora*, but none of

**Table 4** List of compounds isolated from members of the *Podosporaceae* (Genera, species, compound class, molecular weights and formulae, and biological activity)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| *Cladorrhinum* sp. | | Emestrin | 49 | Epipolythiodiketopiperazine | $C_{27}H_{22}N_2O_{10}S_2$ (598) | Antiproliferative | Onodera et al. (2004) |
| | | MPC1001 | 50 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_{10}S_2$ (612) | Antiproliferative | |
| | | MPC1001 B | 51 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_9S_2$ (596) | Antiproliferative | |
| | | MPC1001 C | 52 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_9S_2$ (596) | Antiproliferative | |
| | | MPC1001 D | 53 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_{10}S_3$ (644) | Antiproliferative | |
| | | MPC1001 E | 54 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_{10}S_4$ (676) | Antiproliferative | |
| | | MPC1001 F | 55 | Epipolythiodiketopiperazine | $C_{29}H_{26}N_2O_{11}S$ (610) | Antiproliferative | |
| | | MPC1001 G | 56 | Epipolythiodiketopiperazine | $C_{28}H_{22}N_2O_9S$ (562) | Antiproliferative | |
| | | MPC1001 H | 57 | Epipolythiodiketopiperazine | $C_{28}H_{22}N_2O_{10}$ (546) | Antiproliferative | |
| | | Secoemestrin C | 58 | Epipolythiodiketopiperazine | $C_{27}H_{22}N_2O_{10}S_4$ (662) | | Li et al. (2016b) |
| | | MPC1001 | 50 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_{10}S_2$ (612) | | |
| | | MPC1001 D | 53 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_{10}S_3$ (644) | | |
| | | Emestrin E | 59 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_{10}S_4$ (676) | | |
| | | Emestrin H | 60 | Epipolythiodiketopiperazine | $C_{20}H_{22}N_2O_4S_2$ (418) | | |
| | | Emestrin I | 61 | Epipolythiodiketopiperazine | $C_{29}H_{30}N_2O_7S_2$ (582) | | |
| | | Emestrin J | 62 | Epipolythiodiketopiperazine | $C_{27}H_{24}N_2O_7S_2$ (552) | | |
| | | Emestrin K | 63 | Epipolythiodiketopiperazine | $C_{29}H_{30}N_2O_6S_2$ (566) | | |
| | | MPC1001 C | 52 | Epipolythiodiketopiperazine | $C_{28}H_{24}N_2O_9S_2$ (596) | Antiproliferative | |
| | | MPC1001 F | 55 | Epipolythiodiketopiperazine | $C_{29}H_{26}N_2O_{11}S$ (610) | Antiproliferative | |
| | | MPC1001 H | 57 | Epipolythiodiketopiperazine | $C_{28}H_{22}N_2O_{10}$ (546) | Antiproliferative | |
| | | Secoemestrin D | 64 | Epipolythiodiketopiperazine | $C_{27}H_{24}N_2O_8S_4$ (632) | Cytotoxic | |
| *Triangularia* | *anserina* | 13-hydroxyversicolorin B | 65 | Anthraquinone | $C_{18}H_{12}O_8$ (356) | Larvicidal | Matasyoh et al. (2011) |
| | | Anserinone A | 66 | 1,4-Benzoquinone | $C_{11}H_{12}O_4$ (208) | Antibacterial and antifungal | Wang et al. (1997) |
| | | Anserinone B | 67 | 1,4-Benzoquinone | $C_{11}H_{14}O_4$ (210) | Antibacterial and antifungal | |
| | | Secosterigmatocystin | 68 | Xanthone | $C_{18}H_{18}O_8$ (362) | | Matasyoh et al. (2011) |
| | | Sterigmatocystin | 69 | Xanthone | $C_{18}H_{12}O_6$ (324) | Carcinogenic, mutagenic and larvicidal | |
| | *bambusae* | Botryodiplodin | 70 | Tetrahydrofuran derivative | $C_7H_{12}O_3$ (144) | Antifungal | Nakagawa et al. (1979) |
| | *effusa* | Apiodionen | 71 | PKS-NRPS hybride | $C_{13}H_{15}NO_3$ (233) | Anti-neoplastic and anti-inflamatory | Takahashi et al. (1992) |
| | | Preapiodionen | 72 | PKS-NRPS hybride | $C_{13}H_{19}NO_5$ (269) | Anti-neoplastic and anti-inflamatory | |
| | *longicaudata* | 1-*O*-methylemodin | 73 | Anthraquinone | $C_{16}H_{12}O_5$ (284) | Immunosuppressive | Fujimoto et al. (2004) |
| | | 25-hydroxyergosta-4,6,8(14),22-tetraen-3-one | 74 | Steroid | $C_{28}H_{40}O_2$ (408) | Immunosuppressive | |
| | | Carviolin | 75 | Anthraquinone | $C_{16}H_{12}O_6$ (300) | Immunosuppressive | |

**Table 4** (continued)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| | | Ergosta-4,6,8(14),22-tetraen-3-one | 76 | Steroid | $C_{28}H_{40}O$ (392) | Immunosuppressive | Nakagawa et al. (1979) |
| | | Omega-acetylcarviolin | 77 | Anthraquinone | $C_{18}H_{14}O_7$ (342) | Immunosuppressive | |
| | | Omega-hydroxyemodin | 78 | Anthraquinone | $C_{15}H_{10}O_6$ (286) | Immunosuppressive | |
| | *matsushimae* | Botryodiplodin | 70 | Small polyketide | $C_7H_{12}O_3$ (144) | Antifungal | Kawahara et al. (1986) |
| | *striata* | Aurantioemestrin | 79 | Diketopiperazine | $C_{27}H_{20}N_2O_9S$ (342) | | |
| | | Dethiosecoemestrin | 80 | Diketopiperazine | $C_{27}H_{22}N_2O_{10}$ (532) | Antibacterial | |
| | | Emestrin | 49 | Epipolythiodiketopiperazine | $C_{27}H_{22}N_2O_{10}S_2$ (598) | Antibacterial and antifungal | Seya et al. (1985) |
| | | Emestrin B | 81 | Epipolythiodiketopiperazine | $C_{27}H_{22}N_2O_{10}S_3$ (630) | Antibacterial | Nozawa et al. (1987) |
| | | Paxilline | 82 | Alkaloid | $C_{27}H_{33}NO_4$ (435) | Tremorgenic | Kawahara et al. (1986) |
| | | Violaceid acid | 83 | Biaryl ether | $C_{15}H_{12}O_6$ (288) | | |
| | *tetraspora* | Botryodiplodin | 70 | Small polyketide | $C_7H_{12}O_3$ (144) | Antifungal | Nakagawa et al. (1979) |

them belongs to this genus in the current definition. Considering the high diversity of metabolites that were observed during the evaluation of its two related genera, it should be worthwhile to focus on these taxa.

## Schizotheciaceae

Even though the *Schizotheciaceae*, which was recently introduced (Marin-Felix et al. 2020), is nowadays one of the largest families in the *Sordariales*, their taxa have been neglected, existing few studies about their secondary metabolite production (Table 5; Fig. 8).

During an ongoing evaluation of rare and interesting members of *Sordariomycetes* to find novel biologically active secondary metabolites, *Jugulospora vestita* was found to produce seven xanthone-anthraquinone active heterodimers (**84–90**), together with the known xanthoquinodin B4 (**91**) (Shao et al. 2020). All the compounds were active against Gram-positive bacteria with MIC values ranging between 0.2 and 8.3 µg/mL and displayed cytotoxic activity against KB 3.1, L929, A459, SK-OV-3, PC-3, A431, and MCF-7 mammalian cell lines. Additionally, xanthoquinodin B11 showed moderate fungicidal activity against *M. hiemalis* (MIC = 2.1 µg/mL), *Wickerhamomyces anomalus* (syn. *Pichia anomala*) (MIC = 8.3 µg/mL), and *R. glutinis* (MIC = 2.1 µg/mL). Moreover, the seven metabolites were also obtained from different strains belonging to *Jugulospora rotula*, including the type strains of *Apiosordaria globosa* and *A. hispanica*, which were synonymized to *J. rotula* by Marin-Felix et al. (2020) based on morphological and molecular data. This draws attention to the potential of these compounds as possible chemotaxonomic markers in the genus (Shao et al. 2020).

On the other hand, the genus *Morinagamyces* was recently introduced to accommodate the fungus *A. vermicularis* based on the phylogenetic analysis of the sequences of the ITS, LSU, *RPB2*, and *TUB2* genes (Harms et al. 2021b). In addition, *Morinagamyces vermicularis* was reported to produce a depsipeptide named morinagadepsin (**93**), and the known metabolite chaetone B (**92**). Compound **93** displayed cytotoxic properties against the mammalian cell lines KB3.1 and L929, but no antimicrobial activity against the fungi and bacteria tested was observed. In the same assays, compound **92** was weakly cytotoxic against the cell line L929 but did not show any antimicrobial activity.

A strain of *Podospora curvicolla*, recently transferred to the genus *Pseudoechria* as *Pse. curvicolla* (Marin-Felix et al. 2020), was isolated from the surface of a sclerotium of *Aspergillus flavus* in the search of anti-*Aspergillus* agents (Che et al. 2004a). Three highly modified γ-lactones namely curvicollides A–C (**94–96**) were obtained from this fungus. Among these metabolites, curvicollide A displayed antifungal activity in disk assays against *As. flavus* and *Fusarium fujikuroi* (syn. *F. verticillioides,* Crous et al. 2021) in a
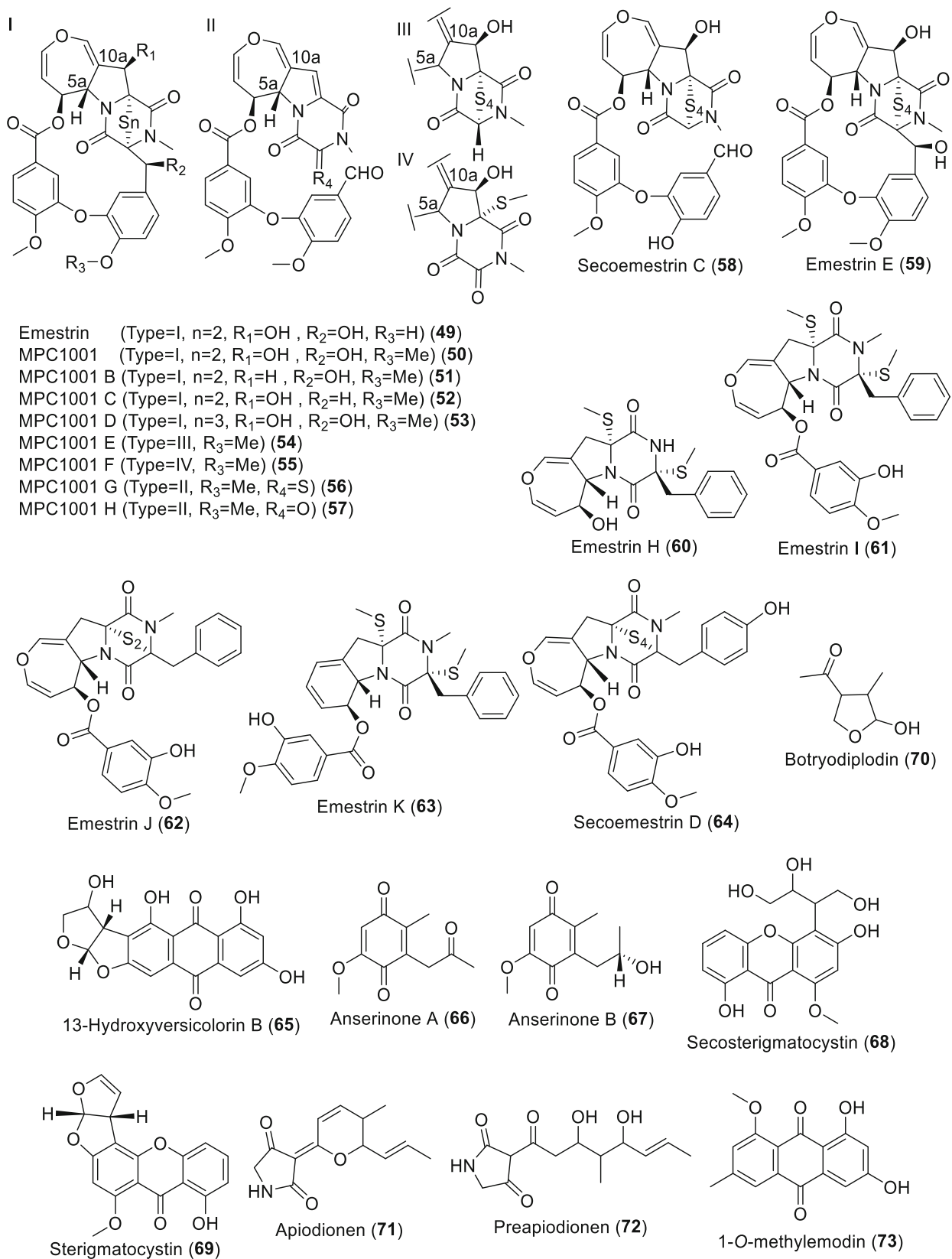
Secoemestrin C (**58**)

Emestrin E (**59**)

Emestrin    (Type=I, n=2, R$_1$=OH , R$_2$=OH, R$_3$=H) (**49**)
MPC1001    (Type=I, n=2, R$_1$=OH , R$_2$=OH, R$_3$=Me) (**50**)
MPC1001 B (Type=I, n=2, R$_1$=H , R$_2$=OH, R$_3$=Me) (**51**)
MPC1001 C (Type=I, n=2, R$_1$=OH , R$_2$=H, R$_3$=Me) (**52**)
MPC1001 D (Type=I, n=3, R$_1$=OH , R$_2$=OH, R$_3$=Me) (**53**)
MPC1001 E (Type=III, R$_3$=Me) (**54**)
MPC1001 F (Type=IV, R$_3$=Me) (**55**)
MPC1001 G (Type=II, R$_3$=Me, R$_4$=S) (**56**)
MPC1001 H (Type=II, R$_3$=Me, R$_4$=O) (**57**)

Emestrin H (**60**)

Emestrin I (**61**)

Emestrin J (**62**)

Emestrin K (**63**)

Secoemestrin D (**64**)

Botryodiplodin (**70**)

13-Hydroxyversicolorin B (**65**)

Anserinone A (**66**)

Anserinone B (**67**)

Secosterigmatocystin (**68**)

Sterigmatocystin (**69**)

Apiodionen (**71**)

Preapiodionen (**72**)

1-O-methylemodin (**73**)

**Fig. 6** Chemical strucutures of compounds isolated from members of the *Podosporaceae* (**49–73**)
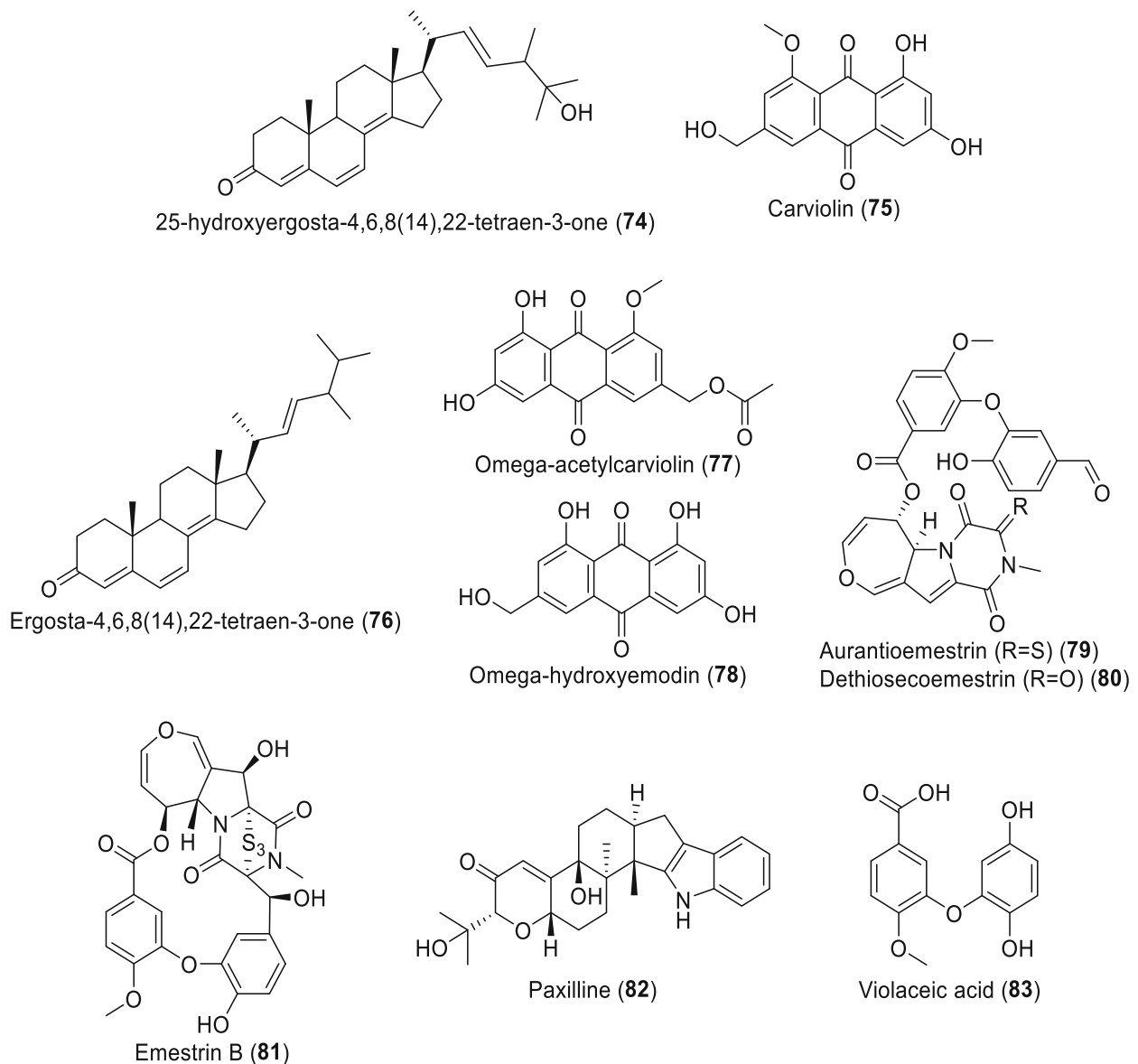
Fig. 7 Chemical strucutures of compounds isolated from members of the *Podosporaceae* (74–83)

comparable extent with the antifungal control, i.e., nystatin. The above compounds are rather rare between γ-lactones due to the identity and complexity of their side chains and substitutions in the lactone ring. The above findings led to the hypothesis that they might arise from the condensation of two polyketide units, rather than one single precursor (Che et al. 2004a).

## Sordariaceae

Numerous studies of the secondary metabolites produced by taxa of this family have been conducted in the past as summarized in Table 6 and illustrated in Figs 9, 10, and 11, while other families remain untapped or almost so, as it is the case of

*Lasiosphaeriaceae* s. str. and *Diplogelasinosporaceae*.alpha-pyrone

Several species of *Neurospora* (syn. *Gelasinospora*) produce a variety of secondary metabolites, which are of potential use as anticancer pharmaceuticals due to their immunosuppressants characteristics (Fujimoto et al. 1995a,b). The α-pyrone polyketides, named multiforisins A–F (106–111), were originally isolated from *Neurospora multiformis* (Fujimoto et al. 1995a, b). Even so, multiforisins G–I (97–99) together with multiforisin A have also been obtained from *N. heterospora*, *N. longispora*, and *N. multiformis*, which suggest their suitability as chemotaxonomic markers for the genus (Fujimoto et al. 1999). Interestingly, multiforisins are active at a slightly lower concentration than those that show cytotoxic properties (Fujimoto, 2018). For example, multiforisins A, G,

**Table 5**  List of compounds isolated from members of the *Schizotheciaceae* (Genera, species, compound class, molecular weights and formulae, and biological activity)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| *Jugulospora* | *vestita* | Xanthoquinodin A11 | 84 | Xanthone-anthraquinone heterodimer | $C_{35}H_{32}O_{12}$ (644) | Antibacterial and cytotoxic | Shao et al. (2020) |
| | | Xanthoquinodin B10 | 85 | Xanthone-anthraquinone heterodimer | $C_{35}H_{32}O_{12}$ (644) | Antibacterial and cytotoxic | |
| | | Xanthoquinodin B11 | 86 | Xanthone-anthraquinone heterodimer | $C_{35}H_{32}O_{12}$ (644) | Antibacterial, antifungal and cytotoxic | |
| | | Xanthoquinodin B12 | 87 | Xanthone-anthraquinone heterodimer | $C_{35}H_{33}O_{13}$ (661) | Antibacterial and cytotoxic | |
| | | Xanthoquinodin B13 | 88 | Xanthone-anthraquinone heterodimer | $C_{33}H_{28}O_{12}$ (616) | Antibacterial and cytotoxic | |
| | | Xanthoquinodin B14 | 89 | Chromanone anthraquinone heterodimer | $C_{35}H_{32}O_{12}$ (644) | Antibacterial and cytotoxic | |
| | | Xanthoquinodin B15 | 90 | Xanthone-anthraquinone heterodimer | $C_{35}H_{34}O_{13}$ (662) | Antibacterial and cytotoxic | |
| | | Xanthoquinodin B4 | 91 | Xanthone-anthraquinone heterodimer | $C_{31}H_{26}O_{11}$ (574) | Antibacterial and cytotoxic | |
| *Morinagamyces* | *vermicularis* | Chaetone B | 92 | Bisary- Polyketide | $C_{17}H_{16}O_5$ (300) | Cytotoxic | Harms et al. (2021b) |
| | | Morinagadepsin | 93 | Depsipeptide | $C_{31}H_{56}N_4O_6$ (580) | Cytotoxic | |
| *Pseudoechria* | *curvicolla* | Curvicollide A | 94 | Linear polyketide | $C_{26}H_{40}O_5$ (432) | Antifungal | Che et al. (2004a) |
| | | Curvicollide B | 95 | Linear polyketide | $C_{26}H_{40}O_5$ (432) | | |
| | | Curvicollide C | 96 | Linear polyketide | $C_{26}H_{40}O_4$ (416) | | |

and H whose $IC_{50}$ values against Con A-induced (0.6–1.8 μg/mL) and LPS-induced proliferations of mouse spleen lymphocytes (0.6–1.2 μg/mL), displayed higher $IC_{50}$ values against human leukemic HL-60 cells (1–5 μg/mL) (Fujimoto et al. 1995, 1999). *Neurospora kobi* biosynthesized the sesterterpetriol, kobiin (**101**), the main immunosuppressive principle of its crude extract, with $IC_{50}$ values against Con A-induced and LPS-induced proliferations of mouse spleen lymphocytes of 7 and 3.5 μg/mL, respectively. Together with this terpenoid, three 2-furanones, kobifuranones A–C (**102**–**104**), were also isolated from this fungus as immunosuppressive compounds. Also, the known compound, *p*-hydroxybenzaldehyde (**105**), was for the first time isolated from *N. kobi* (Fujimoto et al. 1998b). In addition, from *N. pseudoreticulata* two 4,9-dioxonaphto[2,3-c] furans, (**112**) and (**113**), with monoamine oxidase (MAO) inhibitory activity were found together with the known anthraquinone chrysophanol (**114**), which was previously isolated from *Talaromyces islandicus* (syn. *Penicillium islandicum*) (Fujimoto et al. 1995). On the other hand, the xanthones, 1,9a-dihydronidulalin A (**115**), 1-hydroxy-3-methylxanthone (**116**), nidulin A (**117**) and B (**118**), have been isolated from *N. santi-florii*. Only nidulin A displayed significant immunosuppressive activity, demonstrating that the suppressive effects of substituted xanthones against the proliferation of human lymphocytes are ascribable to the positions of substituents on the xanthone nucleus (Fujimoto et al. 2006).

*Neurospora crassa* has been a cornerstone biological system for genetics, biochemistry, molecular biology, and a model organism for studying fungal growth and development (Galagan et al. 2003; Borkovich et al. 2004). Additionally, the composition of the carotenoids and sterols produced by *Neurospora* spp. has been extensively characterized (Aasen and Jensen 1965; Goldie and Subden 1973; Renaud et al. 1978). Neurosporaxanthin (**122**) was isolated from various *Neurospora* species, including *N. sitophila* and *N. crassa*, as a carotenoid acid, an uncommon class of natural carotenoid (Aasen and Jensen 1965). In a similar extent, *N. crassa* has been useful for the study of siderophores production, which are ubiquitous iron-complexing agents with low molecular masses that sequester this biologically relevant nutrient (Horowitz et al. 1976; Tóth et al. 2009). The tetraglycosylated glycosphingolipid, neurosporaside (**121**), was isolated from *N. crassa* (Constantino et al. 2011). Its structure is unique in that the sugar moiety linked to the ceramide is formed by a chain of three β-galactopyranoside residues, with a glucopyranoside α-linked to the outer galactopyranoside. Previous studies on the glycosphingolipid composition of *N. crassa* reported only β-glucopyranosylceramide to be present (Park et al. 2005). Terricollenes A–C (**123**–**125**), terricolyne (**1268**), 1-*O*-acetylterricolyne (**119**), and 1-*O*-methylterricolyne (**120**) were isolated from the fungus *N. terricola* (Zhang et al. 2009). Compounds (**123**–**125**) are allenyl phenyl ethers, whereas compounds **119**, **120**, and
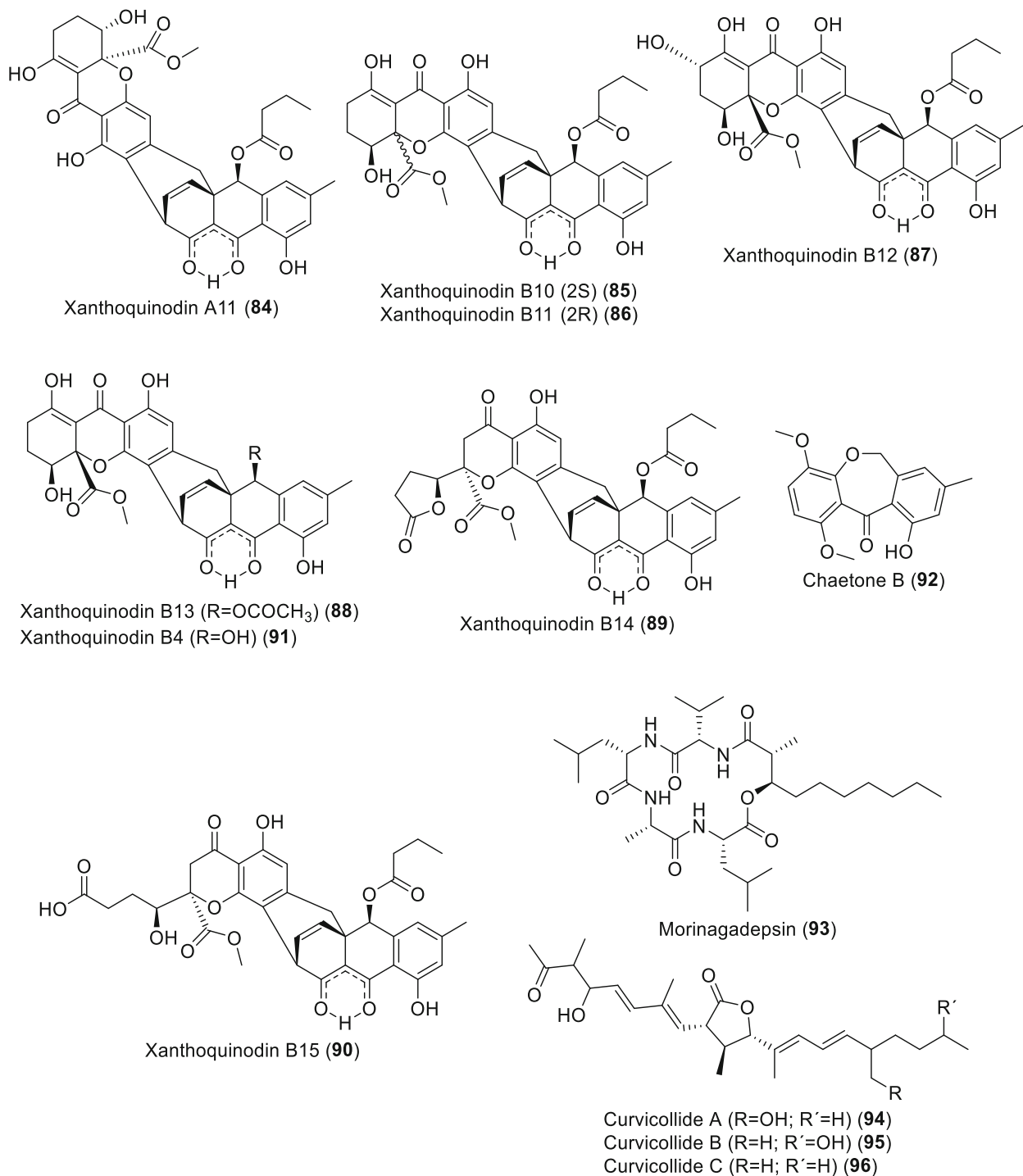
Xanthoquinodin A11 (**84**)

Xanthoquinodin B10 (2S) (**85**)
Xanthoquinodin B11 (2R) (**86**)

Xanthoquinodin B12 (**87**)

Xanthoquinodin B13 (R=OCOCH₃) (**88**)
Xanthoquinodin B4 (R=OH) (**91**)

Xanthoquinodin B14 (**89**)

Chaetone B (**92**)

Morinagadepsin (**93**)

Xanthoquinodin B15 (**90**)

Curvicollide A (R=OH; R´=H) (**94**)
Curvicollide B (R=H; R´=OH) (**95**)
Curvicollide C (R=H; R´=H) (**96**)

**Fig. 8** Chemical strucutures of compounds isolated from members of the *Schizotheciaceae* (**84–96**)

**126** are alkynyl phenyl ethers. Out of the six metabolites, terricolene A showed modest cytotoxicity against the human tumor cell lines HeLa and MCF-7. Two α-pyrone derivatives, namely udagawanones A (**130**) and B (**131**), along with the known compounds (Z)-4-hydroxy3-(3-hydroxy-3-methylbut-1-en-1-yl)benzoic acid (**127**), isosclerone (**4**), cyclo-(*L*-Leu-*L*-Pro) (**128**), and cyclo-(*L*-Pro-*L*-Tyr) (**129**), were isolated from an endophytic strain of *N. udagawae* (Macabeo et al. 2020).

Compound (**130**) exhibited moderate to weak antimicrobial activities, but both metabolites exhibited cytotoxic effects against HeLa cells.

In addition, *trans*-sordarial (**100**), a simple aromatic polyketide originally isolated from *S. macrospora* with no bioactivity previously reported, has been obtained from three *Neurospora* species, i.e., *N. heterospora*, *N. longispora*, and *N. santi-florii*, as an immunosuppressive metabolite against

**Table 6** List of compounds isolated from members of the *Sordariaceae* (Genera, species, compound class, molecular weights and formulae, and biological activity)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| *Gelasinospora* | *heterospora* | Multiforisins G | 97 | alpha-pyrone | $C_{13}H_{16}O_6$ (268) | Immunosuppressive | Fujimoto et al. (1999) |
| | | Multiforisins H | 98 | alpha-pyrone | $C_{13}H_{16}O_6$ (268) | Immunosuppressive | |
| | | Multiforisins I | 99 | alpha-pyrone | $C_{11}H_{14}O_5$ (226) | | |
| | | *trans*-Sordarial | 100 | Salicylaldehyde derivative | $C_{12}H_{14}O_4$ (222) | Immunosuppressive | |
| | *kobi* | Kobiin | 101 | Sesterterpenoid | $C_{25}H_{40}O_3$ (388) | Immunosuppressive | Fujimoto et al. (1998b) |
| | | Kobifuranone A | 102 | Furanone | $C_{11}H_{16}O_3$ (196) | Immunosuppressive | |
| | | Kobifuranone B | 103 | Furanone | $C_{11}H_{14}O_3$ (194) | Immunosuppressive | |
| | | Kobifuranone C | 104 | Furanone | $C_{11}H_{14}O_4$ (210) | Immunosuppressive | |
| | | p-hydroxybenzaldehyde | 105 | Small aromatic aldehyde | $C_7H_6O_2$ (122) | | |
| | *longispora* | Multiforisins A, G-I | 106, 97-9-9 | alpha-pyrone | $C_{11}H_{12}O_5$ (224) | Immunosuppressive (A, G-H) | Fujimoto et al. (1999) |
| | | *trans*-Sordarial | 100 | Salicylaldehyde derivative | $C_{12}H_{14}O_4$ (222) | Immunosuppressive | |
| | *multiforis* | Multiforisins A | 106 | alpha-pyrone | $C_{11}H_{12}O_5$ (224) | Immunosuppressive | Fujimoto et al. (1995) |
| | | Multiforisins B | 107 | alpha-pyrone | $C_{14}H_{18}O_6$ (266) | Immunosuppressive | |
| | | Multiforisins C | 108 | alpha-pyrone | $C_{13}H_{14}O_7$ (298) | Immunosuppressive | |
| | | Multiforisins D | 109 | alpha-pyrone | $C_{22}H_{22}O_9$ (430) | | |
| | | Multiforisins E | 110 | alpha-pyrone | $C_{22}H_{22}O_9$ (430) | Immunosuppressive | |
| | | Multiforisins F, G-I | 111, 97-9-9 | alpha-pyrone | $C_{12}H_{14}O_5$ (238) | Immunosuppressive | |
| | *pseudoreticulata* | 1,3-dihydro-5-hydroxy-7-methoxy-4,9-dioxonaphto[2,3-c]furan | 112 | Naphthoquinone derivative | $C_{13}H_8O_5$ (246) | Monoamine oxidase inhibitors | Fujimoto et al. (1995) |
| | | 5-hydroxy-7-methoxy-4,9-dioxonaphto[2,3-c]furan | 113 | Naphthoquinone derivative | $C_{13}H_{10}O_5$ (244) | Monoamine oxidase inhibitors | |
| | | Chrysophanol | 114 | Anthraquinone | $C_{15}H_{10}O_4$ (254) | | |
| | *santi-florii* | 1,9a-dihydronidulalin A | 115 | Xanthone | $C_{16}H_{16}O_6$ (304) | Immunosuppressive | Fujimoto et al. (2006) |
| | | 1-hydroxy-3-methylxanthone | 116 | Xanthone | $C_{15}H_{10}O_4$ (226) | Immunosuppressive | |
| | | Nidulalin A | 117 | Xanthone | $C_{16}H_{14}O_6$ (302) | | |
| | | Nidulalin B | 118 | Xanthone | $C_{16}H_{16}O_5$ (288) | Immunosuppressive | |
| | | *trans*-Sordarial | 100 | Simple aromatic polyketide | $C_{12}H_{14}O_4$ (222) | Immunosuppressive | |
| *Neurospora* | *crassa* | 1-O-acetylterricolyne | 119 | Alkynyl phenyl ether | $C_{13}H_{14}O_4$ (234) | | Zhang et al. (2009) |
| | | 1-O-methylterricolyne | 120 | Alkynyl phenyl ether | $C_{12}H_{14}O_3$ (206) | | |
| | | Neurosporaside | 121 | Glycosphingolipid | $C_{66}H_{125}NO_{25}$ (1332) | | Constantino et al. (2011) |

**Table 6** (continued)

| Genus | Species | Number | Compound class | Compounds | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| | | 122 | Carotenoid | Neurosporaxanthin | $C_{35}H_{46}O_2$ (498) | | Aasen and Jensen (1965) |
| | | 123 | Allenyl phenyl ether | Terricollene A | $C_{17}H_{22}O_7$ (338) | | Zhang et al. (2009) |
| | | 124 | Allenyl phenyl ether | Terricollene B | $C_{17}H_{22}O_7$ (338) | Cytotoxic | |
| | | 125 | Allenyl phenyl ether | Terricollene C | $C_{11}H_{12}O_2$ (176) | | |
| | | 126 | Alkynyl phenyl ether | Terricolyne | $C_{11}H_{12}O_3$ (192) | | |
| | udagawae | 127 | Benzoic acid derivate | (Z)-4-hydroxy-3-(3-hydroxy-3-methylbut-1-en-1-yl)benzoic acid | $C_{12}H_{12}O_3$ (204) | | Macabeo et al. (2020) |
| | | 128 | Diketopiperazine | Cyclo-(L-Leu-L-Pro) | $C_{11}H_{18}N_2O_2$ (210) | | |
| | | 129 | Diketopiperazine | Cyclo-(L-Pro-L-Tyr) | $C_{14}H_{16}N_2O_3$ (260) | | |
| | | 4 | Bisnaphthalene | Isosclerone | $C_{10}H_{10}O_3$ (178) | | |
| | | 130 | alpha-pyrone | Udagawanone A | $C_{11}H_{14}O_4$ (210) | Antibacterial, antifungal and cytotoxic | |
| | | 131 | alpha-pyrone | Udagawanone B | $C_{10}H_{10}O_4$ (194) | | |
| Sordaria | gondaensis | 132 | Indole diketopiperazine | 13-oxofumitremorgin | $C_{27}H_{31}N_3O_5$ (477) | Immunosuppressive | Fujimoto et al. (2000) |
| | | 133 | Indole diketopiperazine | Fumitremorgin B | $C_{27}H_{33}N_3O_5$ (479) | Immunosuppressive | |
| | | 134 | Prenylated diketopiperazine | Tryprostatin B | $C_{21}H_{25}N_3O_2$ (351) | Immunosuppressive | |
| | macrospora | 135 | Simple aromatic polyketide | 12-methoxy sordariol | $C_{13}H_{18}O_4$ (238) | | Li et al. (2016a) |
| | | 136 | Simple aromatic polyketide | Bisordariols A | $C_{24}H_{30}O_7$ (430) | Antioxidant | |
| | | 137 | Simple aromatic polyketide | Bisordariols B | $C_{25}H_{32}O_7$ (444) | Antioxidant | |
| | | 138 | Simple aromatic polyketide | Bisordariols C | $C_{24}H_{30}O_7$ (430) | Antioxidant | |
| | | 139 | Simple aromatic polyketide | Bisordariols D | $C_{25}H_{32}O_7$ (444) | | |
| | | 140 | Simple aromatic polyketide | cis-Sordariol | $C_{12}H_{16}O_4$ (224) | | Bouillant et al. (1989) |
| | | 141 | Naphtalene polyketide derivative | Cyclosordariolone | $C_{12}H_{12}O_4$ (220) | | |
| | | 142 | Naphtalene polyketide derivative | Heptacyclosordariolone | $C_{12}H_{14}O_4$ (222) | | |
| | | 143 | Simple aromatic polyketide | Isobenzofuranyl sordariol derivate A | $C_{12}H_{16}O_4$ (224) | | Bouillant et al. (1988) |
| | | 144 | Simple aromatic polyketide | Isobenzofuranyl sordariol derivate B | $C_{12}H_{16}O_4$ (224) | | |

**Table 6** (continued)

| Genus | Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|---|
| | | trans-Sordarial | 100 | Simple aromatic polyketide | $C_{12}H_{14}O_4$ (222) | | Bouillant et al. (1989) |
| | | trans-Sordariol | 145 | Simple aromatic polyketide | $C_{12}H_{16}O_4$ (224) | | Bouillant et al. (1988) |
| | | Xylarinol A | 146 | Simple aromatic polyketide | $C_{10}H_8O_3$ (176) | | Li et al. (2016a) |

Con A-induced and LPS-induced proliferations of mouse spleen lymphocytes with $IC_{50}$ values of 6.5 and 5.1 µg/mL, respectively (Fujimoto, 2018).

The secondary metabolites produced by *Sordaria* have attracted attention due to the discovery of brand-new carbon skeletons within the genera (Bouillant et al. 1988). *Sordaria* was reported to produce salicylaldehyde-type aromatic polyketides, such as *cis*- and *trans*-sordariol (**140** and **145**), and its derivates, *trans*-sordarial (**100**) and heptacyclosordariolone (**142**), which possess linear 1,2-diols in their side chains (Bouillant et al. 1988; Li et al. 2016a). Cyclosordariolone (**141**), a compound originally isolated from *S. macrospora* (Bouillant et al. 1989), displayed moderate to weak activities with minimum inhibitory concentration (MIC) values of 9.3 µg/mL for *B. subtilis*, 15.5 µg/mL for *Pseudomonas agarici*, and 16.9 µg/mL for *Micrococcus luteus*. The sordariol dimers produced by *S. macrospora*, bisordariols A–D (**136**–**139**), exhibited potent ABTS radical cation scavenging activities with half-maximum effective concentration ($EC_{50}$) values lower than 14.5 µM, compared to the positive control trolox ($EC_{50}$ = 26.7) (Li et al. 2016a). On the other hand, the derivate of sordariol, 12-methoxy sordariol (**135**), its isobenzofuranyl derivatives (**143** and **144**), and xylarinol A (**146**) did not show antioxidant potential in the same assay. Additionally, three different dioxopiperazine-type compounds including 13-oxofumitremorgin B (**132**) and its known derivates, fumitremorgin B (**133**), tryprostatin B (**134**), were isolated from *S. gondaensis* as immunosuppressive constituents (Fujimoto et al. 2000).

## Taxa whose classification is not verified based on state-of-the-art methods

The taxonomic placement of many of taxa belonging to the order *Sordariales* is still unceratin as a result of the lack of molecular data. Thus, secondary metabolites produced by those species whose taxonomic classification is unknown are included in this section (Table 7; Figs. 12 and 13). Also, fungal strains belonging to polyphyletic genera without adequate identification to species level are also listed here due to the impossibility of confidently classify them in the different families. Finally, due to the difficulty of identifying taxa at species level based only on morphological characters, report from strains whose identification is not verified using molecular data are also here considered unclassified until further studies.

Communiols A–H (**151**–**158**) have been obtained as polyketide-derived metabolites from two geographically distinct isolates of the coprophilous fungus *Podospora communis* (Che et al. 2004b; Che et al. 2005). From these compounds, only communiols A–C (**151**–**153**) showed antibacterial properties against *B. subtilis* and *St. aureus* and none of them was found active against *C. albicans*. These compounds are an
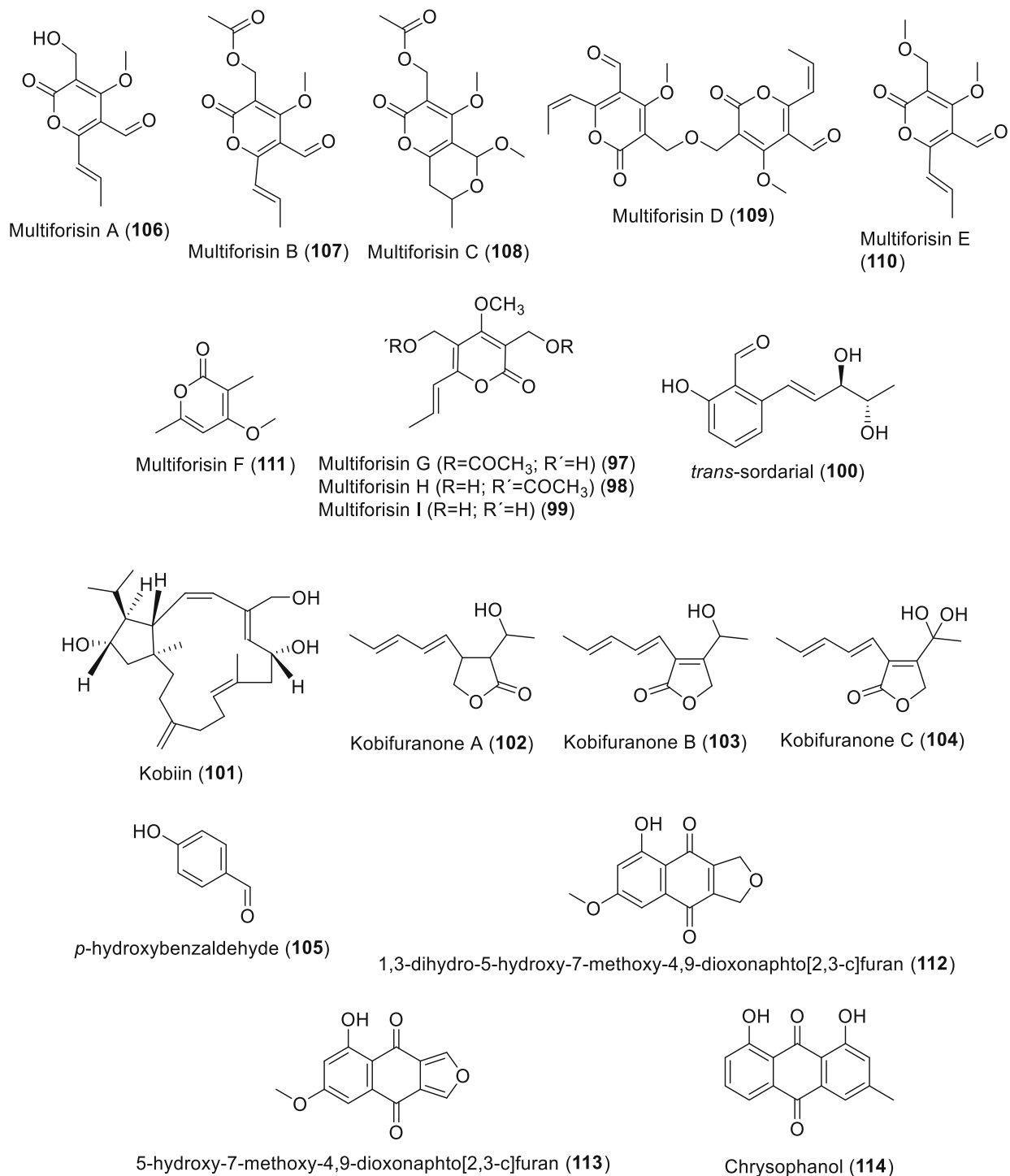
Multiforisin A (**106**)

Multiforisin B (**107**)　Multiforisin C (**108**)

Multiforisin D (**109**)

Multiforisin E (**110**)

Multiforisin F (**111**)

Multiforisin G (R=COCH₃; R´=H) (**97**)
Multiforisin H (R=H; R´=COCH₃) (**98**)
Multiforisin I (R=H; R´=H) (**99**)

*trans*-sordarial (**100**)

Kobiin (**101**)

Kobifuranone A (**102**)　Kobifuranone B (**103**)　Kobifuranone C (**104**)

*p*-hydroxybenzaldehyde (**105**)

1,3-dihydro-5-hydroxy-7-methoxy-4,9-dioxonaphto[2,3-c]furan (**112**)

5-hydroxy-7-methoxy-4,9-dioxonaphto[2,3-c]furan (**113**)

Chrysophanol (**114**)

**Fig. 9** Chemical strucutres of compounds isolated from members of the *Sordariaceae* (**97–114**)

example of mono- and bis-tetrahydrofurans, rare among fungal natural products, although molecules with more extensive furanoid rings are relatively common (Abraham and Arfmann 1989; Che et al. 2004b; Bills et al. 2013). Even when the chemical structures of communiols are diverse, they seem to share similar biogenetic origins, as part of a polyketide pathway (Che et al. 2004b). Also, the chemical

investigation of the coprophilous fungi *Podospora decipiens* afforded the discovery of an antifungal polyketide derived metabolite named decipinin A (**161**), together with two tetracyclic sesquiterpenoids, decipienolides A (**159**) and B (**160**) (Che et al. 2002). Decipinin A showed activity in disk assays against *F. verticillioides*, while compound **161** and the epimeric
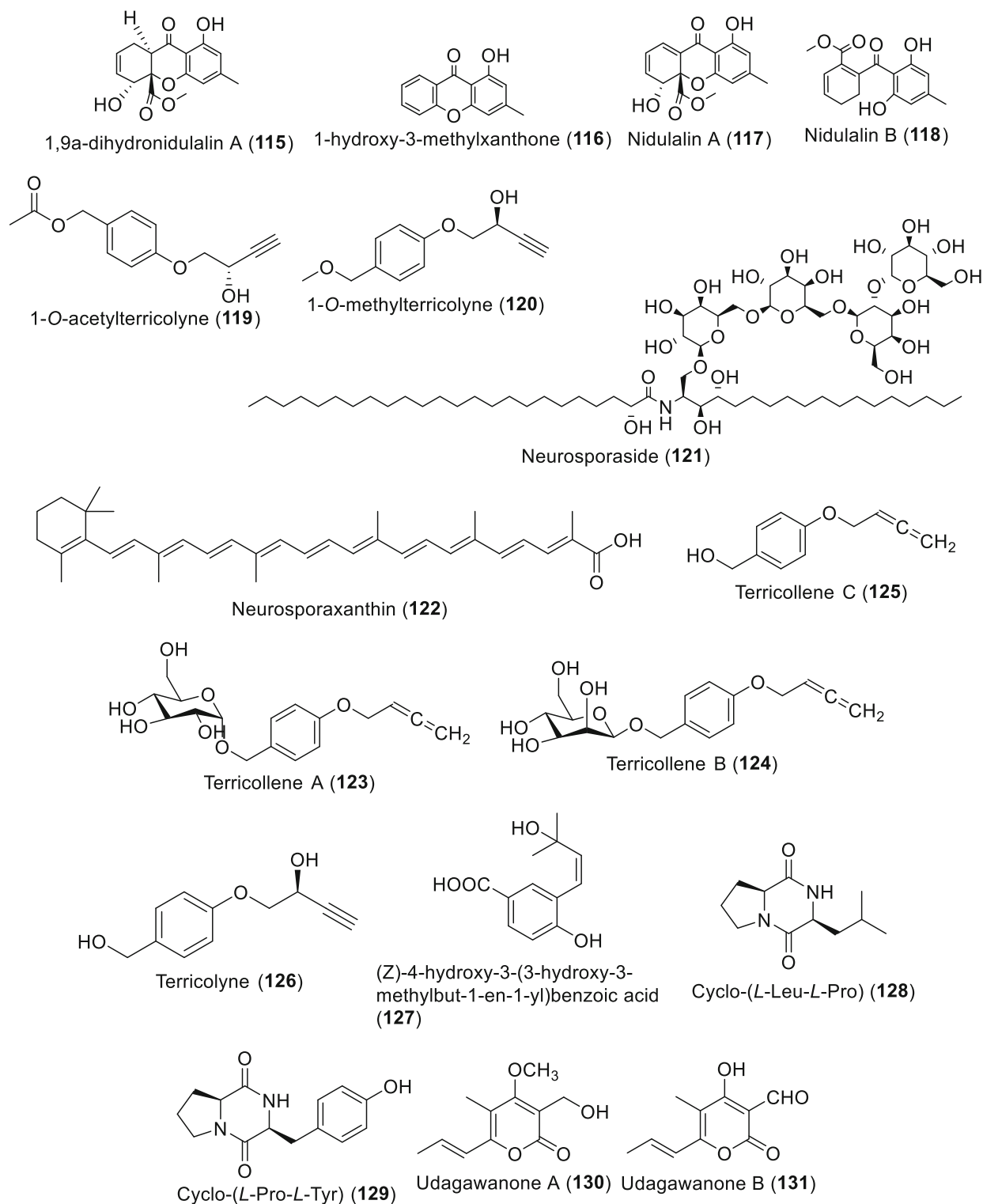
Fig. 10 Chemical strucutres of compounds isolated from members of the *Sordariaceae* (115–131)

mixture of **159** and **160** were active against the Gram-positive bacterium *B. subtilis*.

The chemical investigation of the coprophilous fungus *Cercophora sordarioides* resulted in the isolation of the known metabolite, anthrinone (**149**), and three related compounds, 1-dehydroxyarthrinone (**147**), 3a,9a-deoxy-3a-hydroxy-1-dehydroxyarthrinone (**148**), and cerdarin (**150**) (Whyte et al. 1997). Compounds **147**, **149**, and **150** inhibited the growth of the early successional coprophilous fungi *Asc. furfuraceus* in disk assays. Cerdarin also caused complete

13-oxifumitremorgin (**132**)    Fumitremorgin B (**133**)    Tryprostatin B (**134**)

12-methoxysordariol (**135**)    Bisordariol A (R=H) (**136**)    Bisordariol C (**138**)
                                 Bisordariol A (R=CH₃) (**137**)

Bisordariol D (**139**)    cis-sordariol (**140**)    Cyclosordariolone (**141**)
                           trans-sordariol (**145**)

Heptacyclosordariolone (**142**)    Isobenzofuranyl derivates of sordariol (**143** & **144**)    Xylarinol A (**146**)
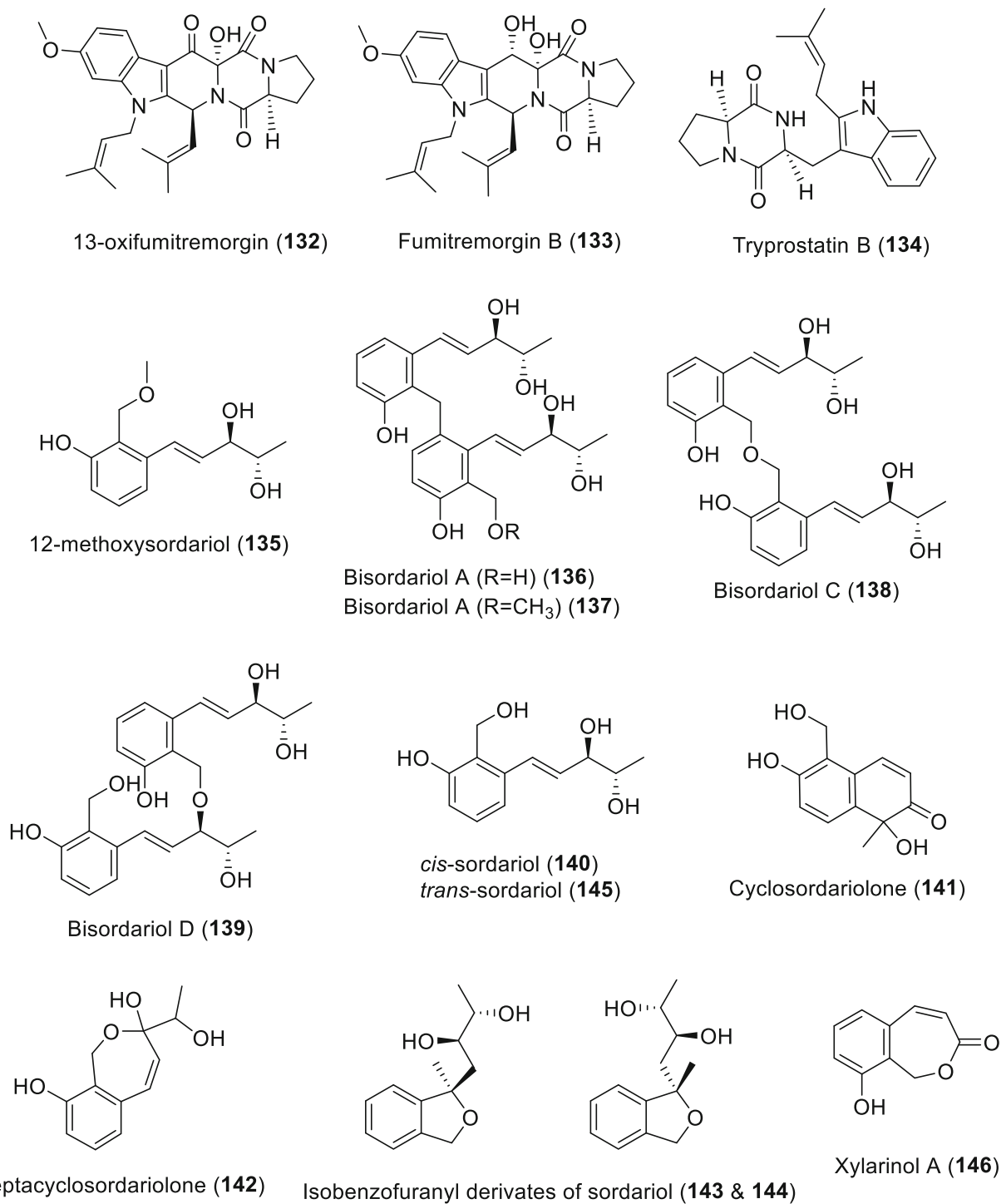
**Fig. 11** Chemical strucutures of compounds isolated from members of the *Sordariaceae* (**132–146**)

inhibition of *S. fimicola* at the evaluated concentration compared to the low inhibition of compounds **147** and **149**. In addition, compounds **147** and **149** exhibited activity against the Gram-positive bacteria, *B. subtilis* and *St. aureus*, while compounds **147** and **150** exhibited activity against *C. albicans* Only compounds **147** and **149** presented limited cytotoxicity

in the NCI 60-tumor cell line bioassay panel, with average IC₅₀ values of 1.0 and 9.4 μg/mL, respectively.

Sphingosine kinase inhibitors have acquired clinical relevance, since sphingosine-1-phosphate (SPP) generation has been implicated in pathogenic states such as angiogenesis, arteriosclerosis, thrombosis, and inflammation

**Table 7** List of compounds isolated from not classified members of the *Sordariales* (Genera, species, compound class, molecular weights and formulae, and biological activity)

| Species | Compounds | Number | Compound class | Molecular formula and weight | Biological activity | Reference |
|---|---|---|---|---|---|---|
| *Cercophora sordarioides* | 1-dehydroxyarthrinone | 147 | Naphthoquinone polyketide | $C_{13}H_{12}O_6$ (264) | Antibacterial, antifungal and cytotoxic | Whyte et al. (1997) |
| | 3a,9a-deoxy-3a-hydroxy -1-dehydroxyarthrinone | 148 | Naphthoquinone polyketide | $C_{13}H_{14}O_6$ (266) | Antifungal | |
| | Anthrinone | 149 | Naphthoquinone polyketide | $C_{13}H_{12}O_7$ (280) | Antibacterial, antifungal and cytotoxic | |
| | Cerdarin | 150 | Naphthoquinone polyketide | $C_{14}H_{12}O_6$ (276) | Antifungal | |
| *Podospora communis* | Communiol A | 151 | Tetrahydrofuran derivative | $C_{11}H_{20}O_4$ (216) | Antibacterial | Che et al. (2004b) |
| | Communiol B | 152 | Tetrahydrofuran derivative | $C_{11}H_{18}O_4$ (214) | Antibacterial | |
| | Communiol C | 153 | Tetrahydrofuran derivative | $C_9H_{16}O_4$ (188) | Antibacterial | |
| | Communiol D | 154 | Tetrahydrofuran derivative | $C_{11}H_{20}O_4$ (216) | | |
| | Communiol E | 155 | Tetrahydrofuran derivative | $C_{11}H_{20}O_3$ (200) | | Che et al. (2005) |
| | Communiol F | 156 | Tetrahydrofuran derivative | $C_{11}H_{18}O_3$ (198) | | |
| | Communiol G | 157 | Tetrahydrofuran derivative | $C_{11}H_{18}O_3$ (198) | | |
| | Communiol H | 158 | Tetrahydrofuran derivative | $C_{11}H_{16}O_4$ (212) | | |
| *Podospora decipiens* | Decipienolide A | 159 | Sesquiterpenoid derivative | $C_{21}H_{30}O_6$ (378) | Antibacterial and antifungal | Che et al. (2002) |
| | Decipienolide B | 160 | Sesquiterpenoid derivative | $C_{21}H_{30}O_6$ (378) | Antibacterial | |
| | Decipinin | 161 | Azaphilone polyketide | $C_{31}H_{36}O_{12}$ (600) | Antibacterial | |
| *Zopfiella curvata* | Zopfiellin | 162 | Dimeric maleic anhydride | $C_{21}H_{26}O_7$ (390) | Antifungal | Watanabe et al. (1994) |
| *Zopfiella inermis* | S-15183 A | 163 | Azaphilone polyketide | $C_{25}H_{36}O_5$ (416) | Sphingosine kinase inhibitor | Kono et al. (2001) |
| | S-15183 B | 164 | Azaphilone polyketide | $C_{27}H_{40}O_5$ (444) | Sphingosine kinase inhibitor | |
| *Zopfiella latipes* | Zopfiellamide A | 165 | 3-decalinoyltetramic acid | $C_{25}H_{35}NO_6$ (445) | Antibacterial and antifungal | Daferner et al. (2002) |
| | Zopfiellamide B | 166 | 3-decalinoyltetramic acid | $C_{26}H_{37}NO_6$ (459) | Antibacterial and antifungal | |
| *Zopfiella* sp. | Zopfielliamide A | 167 | 3-decalinoyltetramic acid | $C_{25}H_{35}NO_5$ (429) | Antibacterial | Yi et al. (2021) |
| | Zopfielliamide B | 168 | 3-decalinoyltetramic acid | $C_{25}H_{35}NO_5$ (429) | Antibacterial | |
| | Zopfielliamide C | 169 | 3-decalinoyltetramic acid | $C_{22}H_{27}NO_4$ (369) | | |
| | Zopfielliamide D | 170 | 3-decalinoyltetramic acid | $C_{22}H_{27}NO_5$ (385) | Antibacterial | |
| *Zopfiella* sp. | Zopfiellasin A | 171 | Cytochalasin | $C_{29}H_{37}NO_5$ (479) | Antibacterial | Zhang et al. (2021) |
| | Zopfiellasin B | 172 | Cytochalasin | $C_{29}H_{37}NO_5$ (479) | | |
| | Zopfiellasin C | 173 | Cytochalasin | $C_{29}H_{37}NO_6$ (495) | Antibacterial | |
| | Zopfiellasin D | 174 | Cytochalasin | $C_{29}H_{37}NO_6$ (495) | | |

(Yatomi et al. 1995; Bornfeldt et al. 1995; Choi et al. 1996; Lee et al. 1999). However, mostly sphingosine kinase inhibitors are sphingosine (SPH) analogs with high structure similarity, resulting in the inhibition of several other physiological functions. Therefore, more specific inhibitors for SPH kinase are highly desired.
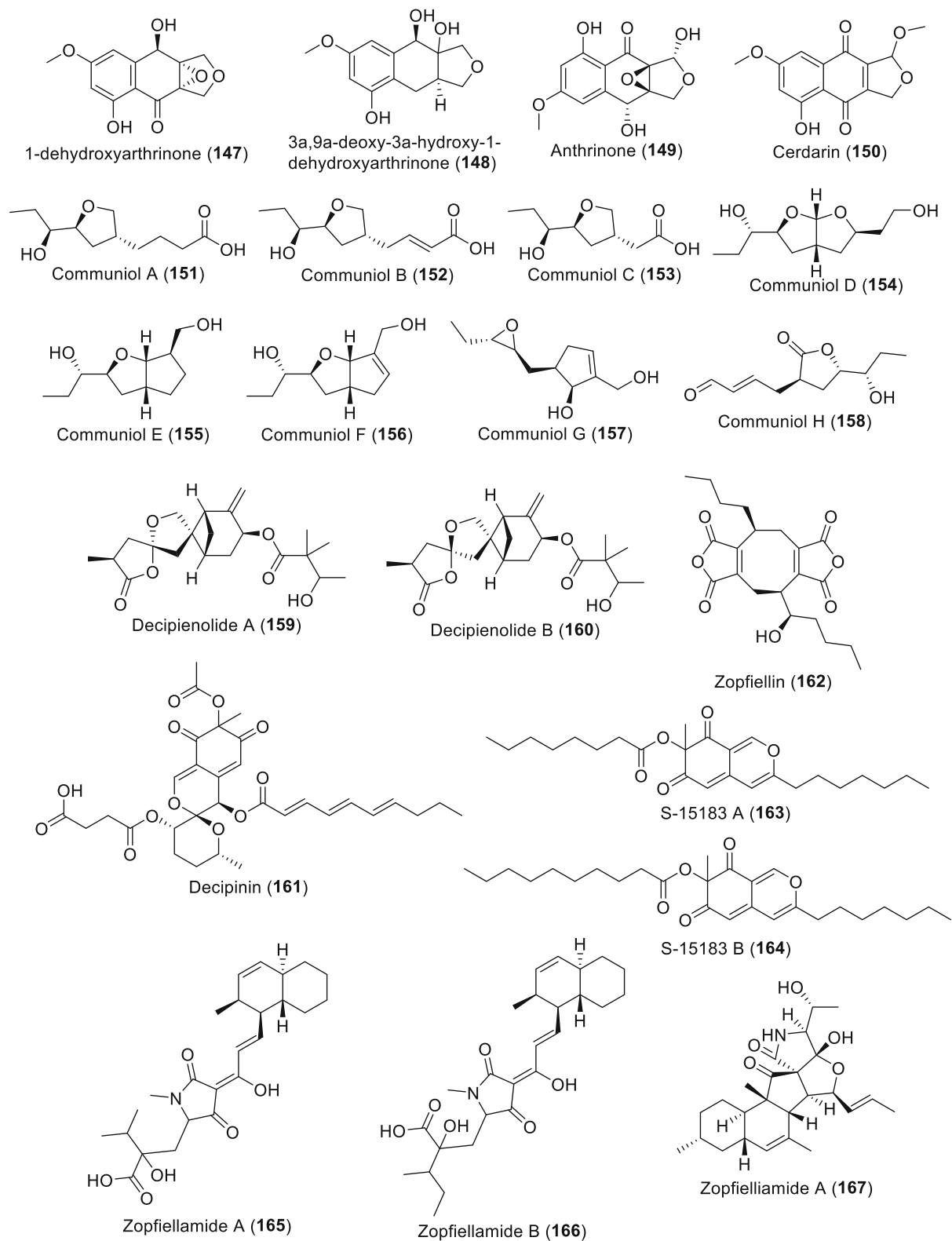
Fig. 12 Chemical strucutures of compounds isolated from not classified members of the *Sordariales* (147–167)

Consequently, two active compounds in a culture broth of *Zopfiella inermis* were found to be azaphilone-type metabolites (Kono et al. 2001). The compounds, S-15183 A (163) and B (164), inhibited sphingosine kinase from rat liver with $IC_{50}$ values of 2.5 and 1.6 μM, respectively. Moreover, S-15183a also inhibited endogenous SPH
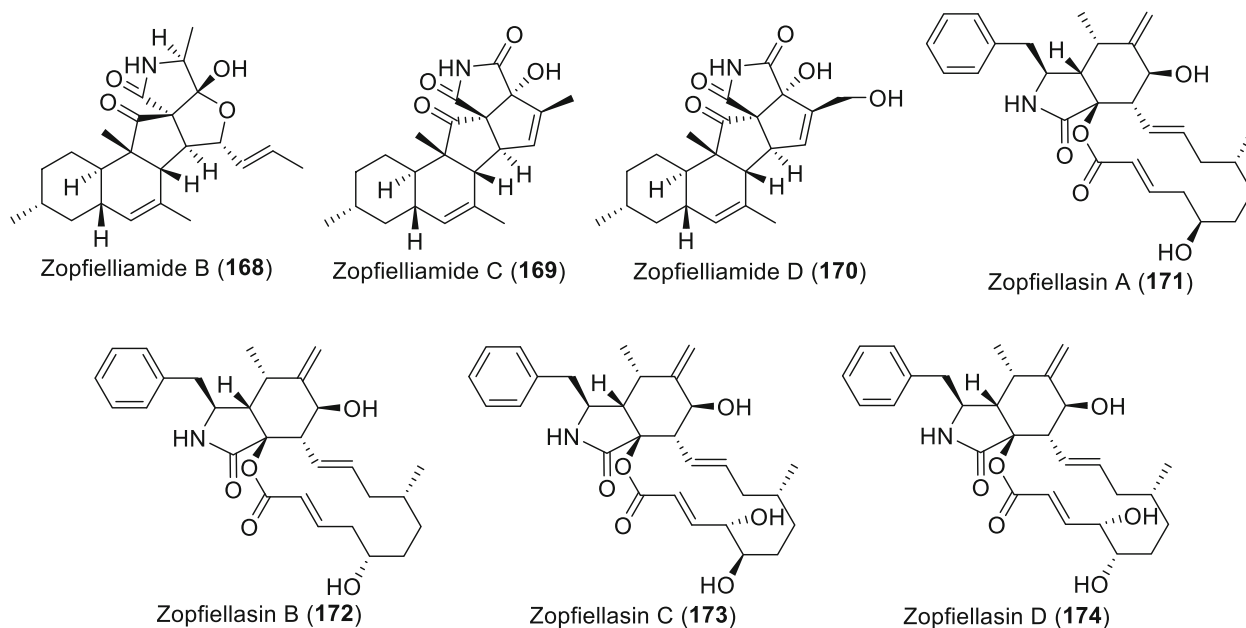
**Fig. 13** Chemical strucutres of compounds isolated from not classified members of the *Sordariales* (**168–174**)

kinase activity in intact platelets and did not show inhibitory activity toward any other sphingolipid metabolic enzymes.

The antimicrobial metabolites, zopfiellamide A (**165**) and B (**166**), were obtained from the submerged culture of the marine fungus *Z. latipes* (Daferner et al. 2002). Moderate antibacterial effects against several Gram-positive bacteria and toward the Gram-negative *Acinetobacter calcoaceticus* were detected, with MIC values between 2 and 10 μg/mL for zopfiellamide A. Zopfiellamide B had MIC values 5 times higher, suggesting the role of the extra methyl group in **166** on the exhibited antimicrobial properties. Among the tested fungi, only the yeasts *Eremothecium coryli* and *Saccharomyces cerevisiae* were inhibited by these metabolites, with MIC values of 2 μg/mL for both compounds. Additionally, no cytotoxic effects were observed for either compound, at concentrations up to 100 μg/mL. *Zopfiella* sp. an endophytic fungus isolated from kiwi plant (*Actinidia chinensis*) showed inhibition of the growth of *Pseudomonas syringae*, a well-known pathogen that causes kiwi fruit canker disease (Yi et al. 2021). Therefore, the chemical investigation of this strain led to the identification of four rare 3-decalinoyltetramic acid derivates namely zofielliamides A–D (**167–170**). All zofielliamides, except for zofielliamide C, showed weak antibacterial activity against this pathogen with MIC values between 32 and 64 μg/mL. Despite the diverse biological activities found in 3-decalinoyltetramic acids, this study was the first time that antibacterial activity against *Ps. syringae* was reported for this type of compounds.

Zopfiellin (**162**), a cyclooctanoid compound produced by *Z. curvata*, has been attributed diverse antimicrobial properties, from which antifungal activity against *Bt. cinerea*, *Sclerotinia sclerotiorum*, and *As. niger* was identified at the micromolar range (Watanabe et al. 1994). The above led to the further study of the mechanism of action of this antifungal agent. As a result, fungal growth inhibition caused by zopfiellin was found to be mediated by the pH of the growth medium and its maximum inhibitory activity obtained between pH 5 and 5.5 (Futagawa et al. 2002a). The above tends to be associated with the intramolecular ring closure from a tetracarboxylate to an anhydride form at a pH value below six (Futagawa et al. 2002b). Currently, the mode of action of zopfiellin is still unknown; however, Futagawa et al. (2002b) also studied the possible relation between the antifungal activity and physiological processes involving oxaloacetate metabolism. Two pairs of epimeric cytochalasins, zopfiellasins A–D (**171–174**), were isolated from the fungus *Zopfiella* sp. during the search for antibacterial agents against *Ps. syringae* produced by kiwi-associated fungi (Zhang et al. 2021). Compounds **171** and **173** exhibited weak activity against this pathogen with MIC values of 25 and 50 μg/mL, respectively. Interestingly, it was the first report on the inhibition of *Ps. syringae* for cytochalasin derivatives. Indeed, this family of fungal secondary metabolites that bind to actin and modify its polymerization in eukaryotic cells, therefore most of the biological activities exhibited by cytochalasans can be traced to its role as selective and strong actin inhibitor (Wang et al. 2020). However, none other biological activities apart from inhibition of *Ps. syringae* were evaluated by the authors, and further efforts are necessary to assess other kind of activities for these natural products.

# Omics overview and outlook

Several fungi from this order have attracted attention for their potential use in different biotechnological applications, especially members of the *Chaetomiaceae* and *Podosporacae* (Martin et al. 2019; Ibrahim et al. 2021). For example, the coprophilous fungus *T. anserina* (syn. *P. anserina*) is a singular example of the evolving enzymatic machinery exhibited by dung-colonizing fungi (Xie et al. 2015). This species together with *N. crassa* have been extensively used as a model system due to the ease of molecular genetic manipulations and the success in constructing multiple deletion strains (Espagne et al. 2007). In fact, recent advances in knowledge on the biosynthetic pathways for secondary metabolites and development of tools for analyzing and manipulating the increasing number of fungal genomes have represented a new avenue in modern natural products drug discovery (Atanasov et al. 2021). For instance, for the *Hypoxylaceae* (*Xylariales*), one of the most diverse orders in the *Sordariomycetes*, the genome for 13 representative species of *Hypoxylum* and one relative (*Xylaria hypoxylon)* were recently sequenced using third-generation sequencing methods that have become available (Wibberg et al. 2021). This achievement has provided an important starting point for the establishment of a stable phylogeny of this order, as well as studies on evolution, ecological behavior and biosynthesis of natural products. In this last matter, the analysis of these genomes led to the identification of 375 gene cluster families from which only 10 of them were conserved across these fungi (Kuhnert et al. 2021). Despite the high predicted potential, the known repertory of natural products from the family demonstrated no obvious link for most of the biosynthetic gene clusters. The above brings to light new opportunities to find unprecedented natural products once these silent gene clusters become accessible, and therefore a long journey is still needed to translate this capacity into potentially useful outcomes.

In the case of the order *Sordariales*, a small number of studies have inspected the genomic diversity in the biosynthetic pathways exhibited by these fungi. Currently, 47 genomes are available on the national center for biotechnology information (NCBI) website (https://www.ncbi.nlm.nih.gov), of which up to 33 correspond to the family *Sordariaceae*, mostly to the genus *Neurospora*. The rest of the available genomes belong to representatives of *Chaetomiaceae* and *Podosporaceae*, which as above mentioned represent some of the most studied families in terms of secondary metabolites production and biotechnological applications. *Chaetomium globosum* is a well-known producer of chaetoglobosins and azaphilones, but no biosynthetic gene cluster responsible for those compounds had been assigned until the identification of the chaetoviridin/ chaetomugilin biosynthetic gene cluster (Winter et al. 2012). Moreover, successful genetic engineering of *Ch. globosum* allowed the disruption of transcriptional regulators associated with epigenetic silencing of secondary metabolite biosynthetic pathways, leading to the identification of six gene clusters responsible for the biosynthesis of 11 natural products previously known to be produced by *Ch. globosum*, including one cytochalasan and six azaphilone-type compounds (Nakazawa et al. 2013). On the other hand, although the antifungal sordarin has been known for almost fifty years, the respective identification of the gene cluster involved in the biosynthesis of this was only achieved on the last decade (Kudo et al. 2016). Thus, a contiguous 67 kb gene cluster consisting of 20 open reading frames encoding a putative diterpene cyclase, a glycosyltransferase, a type I polyketide synthase, and six cytochrome P450 monooxygenases were identified, but even when a plausible biosynthetic pathway for sordarin was proposed, further analysis should be realized since the transformation mechanism from the cycloaraneosene derivative to the sordaricin skeleton remains unclear (Kudo et al. 2016).

The enormous number of BGCs identified during the recent years has illustrated a theoretical potential to produce unknown natural products, but in parallel has drawn attention to the exiting gap between the predicted genomic capacity and the diversity of observed metabolites in fungal cultures (Atanasov et al. 2021; Medema and Fischbach 2015). Moreover, it is expected that in the following years the number of gene cluster from known compounds will be elucidated. That is why, in order to cope with this bottleneck, several analytical methods for in-depth characterization of natural product profiles have also improved significantly. Metabolomics approaches can provide accurate information on the metabolite composition in crude extracts, accelerate dereplication of known compounds, and to annotate unknown analogues and new chemical scaffolds (Hoffmann et al. 2018). These pipelines are useful as complementary tools to compare and contrast genomics originated predictions with the reality of secondary metabolite production. Such approaches have been successfully implemented for important groups of metabolite producers such as myxobacteria, demonstrating that there is an existing correlation between taxonomic distance and the production of distinct secondary metabolites families without the necessity of genomic knowledge (Hoffmann et al. 2018). Therefore, the possibilities to discover novel natural products are markedly increasing when focusing on underexploited taxa, rather than studying additional representatives within the same genus. As a proof of concept, the authors employed these principles to report the discovery and structure elucidation of rowithocin, a myxobacterial secondary metabolite with an uncommon, phosphorylated polyketide scaffold.

In contrast, regarding fungal chemodiversity, fewer examples of metabolomics based approaches have been developed. Some studies have focused on filamentous fungi and yeasts of the genus *Saccharomyces*, *Penicillium*, *Aspergillus*, and *Fusarium* due to their significance for different industrial applications, and their role as pathogens (Smedsgaard and

Nielsen 2005; Villas-Bôas et al. 2005; Jewett et al. 2006). Integrative use of metabolite profiling allowed the classification of the terverticillate penicillica where direct infusion ESI-MS was a very efficient approach (Smedsgaard and Frisvad 1997; Smedsgaard et al. 2004). Also, there are several examples regarding the use of LC-MS data in conjunction with phylogenetic data for a better resolution of genera with uncertain placement. Such is the case of the genus *Annuhypoxylon* (*Xylariaceae*), since the evidence provided from phylogenetic, chemotaxonomic, and morphological data allowed the raising of various varieties to species level (Kuhnert et al. 2017). In addition, modern in-depth untargeted metabolomics approaches which incoporate molecular networking (MN) have been employed for comparative analysis of co-cultures of marine-adapted fungi with phytopatogenic bacteria and subsequently allowed prioritization of two co-cultures for purification and characterization of marine fungal metabolites with crop-protective activity (Oppong-Danquah et al., 2018). However, such approaches are missing regarding past studies within the order *Sordariales*, which despite its observed chemodiversity requires further efforts to unearth its real potential. Therefore, the use of metabolomics tools as part of intelligent and effective screening can accelerate the identification and classification of filamentous fungi, as well as the discovery of novel compounds when used in combination with genomics, proteomics, etc.

## Conclusions

Taxonomical classification of the taxa belonging to the *Sordariales* has been extensively revised during recent years because of the increasing availability of molecular data, leading to the recent redistribution of large genera that were before scattered in different families. The present paper was intended to coordinate modern taxonomic classification with the available information on biologically active compounds isolated to provide a better understanding of the chemical diversity of the different groups within the order.

The distribution of compound families among the highly diverse taxa in the *Sordariales* is still unknown in a detailed extent. But as demonstrated here, the linkage of the available data on the secondary metabolites of these taxa with phylogenetic approaches is of substantial utility in this order since a high number of taxa remains *incertae sedis*, awaiting for a more natural classification. Such an example is the introduction of *Pseudorhypophila* combining both molecular and chemotaxonomic data, in what is called a polyphasic study. However, the establishment of correlations between the taxonomical classification and the production of secondary metabolites remains a challenge due to the scarce information on the production of secondary metabolite from a large number of taxa.

Herein, total of 174 secondary metabolites of taxa belonging to the order *Sordariales* are herein reported. Based on the variety of secondary metabolites from a limited number of tested taxa, the perspective on the potential opportunities for the discovery of new bioactive compounds seems to be reasonable. Indeed, still information about the production of secondary metabolites from families such as *Lasiosphaeriaceae* s. str. remains entirely unknown. The incorporation of available high-throughput genome mining tools and evolving analytical methods for the characterization of natural products driven by metabolomics-based approaches in existing pipelines will represent a step-forward in the progress of future drug discovery campaigns.

**Data availability** Data sharing not applicable to this article as no datasets were generated or analzed during the current study.

## Declarations

**Conflict of interest** The authors declare no conflict of interest.

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