Chapter 17
Polyketides from Fungi

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Abstract Fungal secondary metabolites present a huge scaffold of chemical entities. Many of these substances have played important roles not only in nature, but also in human life, as lead compounds of immunosuppressants, antibiotics, anticancer drugs, and cholesterol-lowering medicines, along with other industrial uses. Among fungal natural products, polyketides represent a large group of metabolites defined by their biosynthetic origin, highly programmed by iterative multifunctional proteins. This chapter brings some novelties, especially from 2020 onward, focusing on the main classes of polyketides, new isolated compounds, innovative strategies for synthetic and biosynthetic production. Furthermore, we discuss the current and future biological applications of fungal polyketides in different fields.

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17.1 Historical Overview of the Discovery of Fungal Polyketides

Polyketides comprise a large and structurally diverse group of molecules that constitute one of the most important classes of secondary metabolites originated from bacteria, fungi, plants, and marine organisms. The term polyketide stems from their biosynthetic origin, which derives from the acetate or similar units coupling to malonyl-CoA units to provide long poly-β-keto chains. These chains can afford compounds with a huge structural diversity as macrolide antibiotics and many aromatic compounds, e.g., anthraquinones, tetracyclines, furochromones, pyrones, and benzophenones derivatives, after reactions such as aldol- and Claisen reactions, C- and O-alkylation, enolization, reduction, and decarboxylation. Most fungal metabolites originate from this metabolic pathway and display interesting biological activities or functionalities. However, it is hard to correlate one specific chemical core to a particular bioactivity. The most diverse biological activities have been associated with natural polyketides, supporting the development of a variety of commercial products. Koskinen and Karisalmi (2005) suggested that 1% of the secondary metabolites of polyketide origin may be of interest due to potential drug activities. In the same year, 20% of the blockbuster pharmaceutical drugs were polyketide-derived, according to Weissman and Leadlay (2005).

The first fungal polyketide identified that found industrial application was, probably, mycophenolic acid (**1**) (Fig. 17.1), an immunosuppressive agent which exerts its effect by inhibiting the growth of B and T cells of the immune system. It was first isolated by Bartolomeo Gosio in 1896, from *Penicillium brevicompactum*, and rediscovered and named later by Alsberg and Black (1913), who isolated it from cultures of *Penicillium stoloniferum*. Mycophenolic acid (**1**) can be produced by indigenous strains of *Penicillium glabrum* (Mahmoudian et al. 2021) and is available commercially as the ester prodrug mycophenolate mofetil (**2**) (CellCept®, Roche) or an enteric-coated form as mycophenolate sodium (**3**) (Myfortic®, Novartis) (Budde et al. 2004). Studied since the 1970s, mycophenolate mofetil (**2**) was approved for medical use in the USA in 1995, as an immunosuppressant to prevent organ transplantation rejection, and later, to treat psoriasis (Strathie Page and Tait 2015). Mycophenolic acid (**1**) is also an antimicrobial agent, and, over the years, several other biological properties have been attributed to it, such as antitumor, anti-inflammatory, and more recently, as an antiviral against SARS-CoV-2 (Wang et al. 2021a).

In the middle 1970s, an antimycotic agent named echinocandin B (**4**) (peptide-polyketide mixed biosynthesis) (Fig. 17.1) was concomitantly isolated from *Aspergillus delacroxii* (former *Aspergillus nidulans* var. *echinolatus*) and *Aspergillus rugulosus* (Hüttel 2021). The problems associated to solubility, toxicity, and industrial production were overcome in 2001, with the approval of caspofungin acetate (**5**) (Cancidas®, Merck Sharp & Dohme), a semi-synthetic derivative of the natural product (Fig. 17.1). Later, two other derivatives, micafungin (Mycamine®, Astellas Pharma) (**6**) and anidulafungin (Eraxis™, Pfizer) (**7**) (Fig. 17.1) were approved by

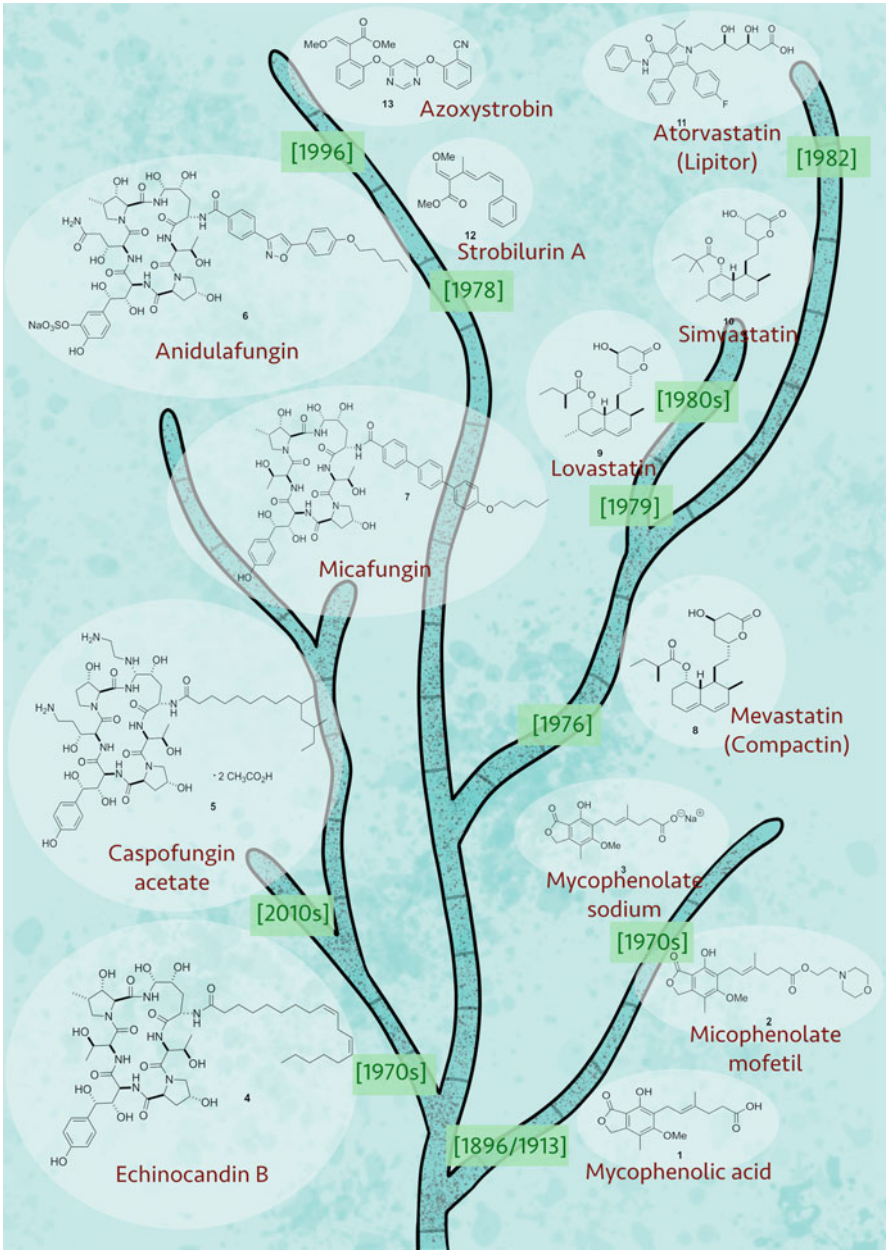


Fig. 17.1 Timeline of the discovery of some fungal polyketides and derivatives with expressive industrial importance: mycophenolic acid (**1**), mycophenolate mofetil (**2**), mycophenolate sodium (**3**), echinocandin B (**4**), caspofungin acetate (**5**), micafungin (**6**), anidulafungin (**7**), mevastatin (compactin) (**8**), lovastatin (mevinolin) (**9**), simvastatin (**10**), atorvastatin (**11**), strobilurin A (**12**), azoxystrobin (**13**)

American and European regulatory agencies (Hüttel 2021). Caspofungin is a prescription drug for several fungal infections, including candidiasis, as well as empirical antifungal therapy in patients with neutropenic fever of unknown origin, because it competitively inhibits 1,3-β glucan synthase, an enzyme that is essential for the synthesis of β-glucan in the fungal cell wall. This metabolite is also efficient in the treatment of invasive aspergillosis in patients that were refractory to amphotericin B (Heinz et al. 2016). According to a report from Transparency Market Research (TMR 2019), the global caspofungin market was valued at US$ 484.20 million in 2018 and is projected to expand at a compound annual grow rate (CAGR) of 0.18% from 2019 to 2027.

Among the most prominent fungal polyketides and their derivatives, the statins currently used to lower serum cholesterol deserve a highlight. Mevastatin (**8**) was the first statin drug, isolated from the ascomycete fungus *Penicillium citrinum* by Endo in the early 1970s, and described as an hypolipidemic agent capable of competitively inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), critical in the biosynthetic pathway of cholesterol (Endo 2017). The clinical trial on mevastatin (**8**) (Fig. 17.1) to reduce cholesterol levels was done in the late 1970s in Japan. At the same time, this compound was isolated in Britain, as an antifungal, and designated as compactin. The C-12 methylated derivative of mevastatin (compactin) (**8**), lovastatin (mevinolin) (**9**) (Fig. 17.1), was independently isolated from *Aspergillus terreus* by Endo and Merck researchers in 1979, and it was the first pharmacological agent able to reduce LDL-cholesterol to unprecedented levels, without serious side effects. Lovastatin (**9**) was approved for commercial use in the USA in 1987 as Mevacor® (Merck) (Endo 2017; Dehnavi et al. 2020). It was followed by the development of simvastatin (**10**), a semi-synthetic version of the natural product, launched in 1992 as Zocor® (Merck). Atorvastatin (**11**) was synthetized in 1985, and clinical trials revealed it as more effective than simvastatin (**10**). Marketed as Lipitor® (Pfizer) (Fig. 17.1) since 1986, atorvastatin (**11**) has been reported as the best-selling drug in the last two decades (Newman and Cragg 2020). Statins have saved millions of lives in patients with coronary problems and nowadays it has been considered as a repurposing drug to fight major human diseases such as cancer (Jiang et al. 2021) and as an adjuvant therapy to treat patients with COVID-19 (Vuorio and Kovanen 2021).

In addition to the use of fungal polyketides in the pharmaceutical industry, another outstanding industrial application can be pointed. Strobilurins are polyketide-derived natural products, usually synthesized by species of the genus *Strobilurus* (basidiomycetes), that consist in important fungicides of broad agricultural use. These metabolites are very efficient in the control of ascomycetes, basidiomycetes, and oomycetes, being applicable in different crops like rice, coffee, wheat and vines, fruits like bananas, and several other vegetables to control and prevent fungal diseases such as water molds, downy mildews, leaf spotting and rusts (Balba 2007; Selim and Khalil 2021). The first natural compound isolated from this class was strobilurin A (**12**) (Fig. 17.1), isolated from *Strobilurus tenacellus* by Schramm et al. (1978). The basic structure of these fungicides contains a methyl (E)-3-methoxy-2-(5-phenylpenta-2,4-dienyl) acrylate moiety, and the derivatives have

different patterns of substituents in the aromatic ring (Balba 2007; Wang et al. 2021b). Despite the great applicability of strobilurins, the natural products were photo-unstable, leading the pesticide industry to synthesize more stable semi-synthetic derivatives, which have reached the world market in 1996. In 2016, strobilurins already accounted for a quarter of the world's fungicide market (US $15.3 billion), with 11 different commercial derivatives (Selim and Khalil 2021). The world's biggest selling fungicide, azoxystrobin (**13**) (Fig. 17.1), is a semi-synthetic derivative of strobilurins, produced and patented by Syngenta (formerly Zeneca Agrochemicals) (Balba 2007; Wang et al. 2021b).

In this chapter, some remarkable fungal polyketides and derivatives will be presented, and their routes of synthesis and applications will be discussed, along with several examples of compounds with pharmacological activities, such as antimicrobial, antiparasitic, anticancer, immunological and metabolism regulators, neuro- and cardioprotectors, as well as polyketides useful in agriculture and environment, such as anti-phytopathogen, and in the food industry, such as pigments. Furthermore, a summary of the new bioactive compounds will be reported, along with their chemical structures, the progress in their biosynthesis research, and their biotechnological potential.

17.2 Polyketides from Fungi: A Chemical Perspective

Although fungal polyketides display a huge structural diversity, it is possible to classify them among three main classes: aromatic polyketides—products from Diels–Alder reactions, macrolides, and polyethers (Simpson and Cox 2008; Crawford and Townsend 2010; Pavesi et al. 2021). Aromatic polyketides from the acylpolymalonate pathway can be as simple as orsellinic acid (OA) (**14**) or highly complex as aflatoxins or tetracyclines. The examples grow geometrically with more interesting compounds if polyketides of mixed biogenetic origins are considered. Diels–Alder reactions are part of many metabolic pathways and can occur in different steps of the biosynthesis. For instance, statins, cytochalasans, and sorbicillinoids, which exhibit diverse biological activities, are fungal polyketides displaying a cyclic aliphatic system arising from enzymatic Diels–Alder reactions (Hantke et al. 2020; Kahlert et al. 2020). Macrolides, macrolactones, and polyesters are known for their large range of biological activity as antibacterial, antifungal, antitumor, and plant-growth regulating (Karpiński 2019). There are other interesting polyketides, that will be presented in this chapter, which did not fit in those three classes, being generally classified as miscellaneous polyketides.

17.2.1 Aromatic Polyketides

Among the simplest aromatic polyketides, orsellinic acid (**14**), 6-methylsalicylic acid (6-MSA) (**15**), and phloracetophenone (**16**) (Fig. 17.2) are the most illustrative.

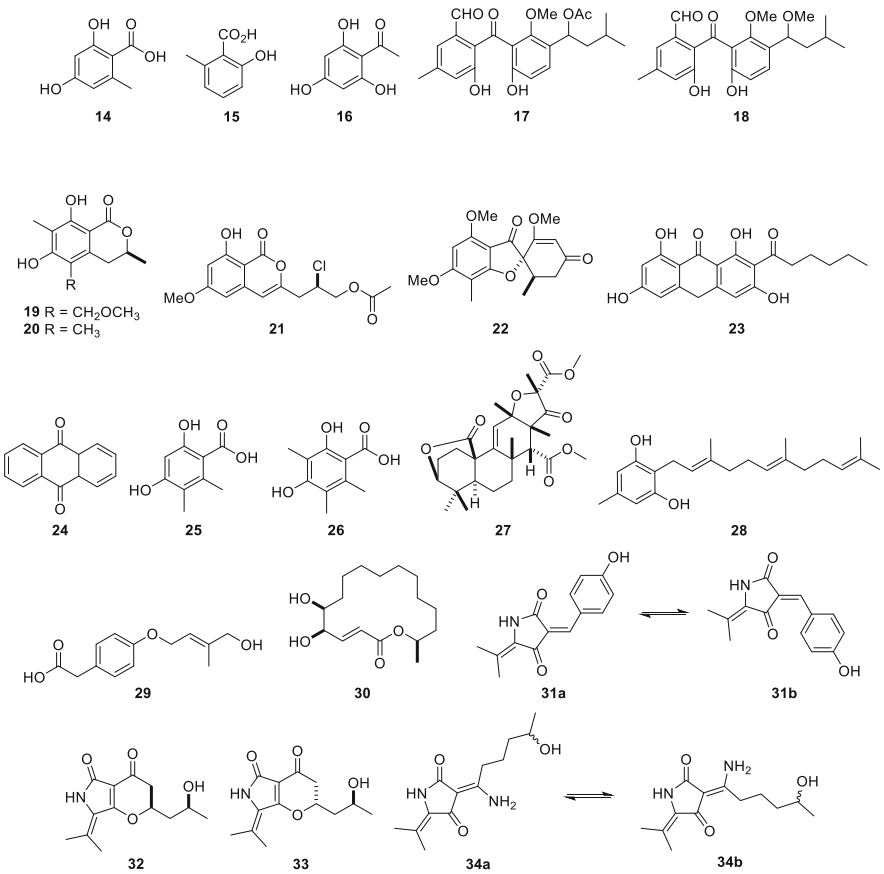


Fig. 17.2 Chemical structures of some aromatic fungal polyketides: orsellinic acid (OA) (**14**), 6-methylsalicylic acid (6-MSA) (**15**), phloracetophenone (**16**), penibenzones A (**17**) and B7 (**18**), (S)-6,8-dihydroxy-5-(methoxymethyl)-3,7-di-methylisochroman-1-one (**19**), (S)-6,8-dihydroxy-3,5,7-tri-methylisochroman-1-one (**20**), (R)-2-chloro-3-(8-hydroxy-6-methoxy-1-oxo-1H-isochromen-3-yl) propyl acetate (**21**), griseofulvin (**22**), norsolorinic acid anthrone (**23**), anthraquinone (**24**), 5-methyl orsellinic acid (5-MOA) (**25**), 3,5-dimethyl orsellinic acid (DMOA) (**26**), aspergillactone (**27**), grifolin B (**28**), 12-hydroxyhomovalencic acid (**29**), (5R,6S,16R,3E)-5,6-dihydroxy-16-methyloxacyclohexadec-3-en-2-one (**30**), and cladosins L−O (**31**–**34**)

They can be produced by several fungi or be part of hybrid polyketides, such as meroterpenes. Endophytic fungi of *Penicillium* genus have provided some examples of new aromatic polyketides as benzophenones [e.g., penibenzones A (**17**) and B (**18**)] and isocoumarins derivatives [e.g., (S)-6,8-dihydroxy-5-(methoxymethyl)-3,7-di-methylisochroman-1-one (**19**), (S)-6,8-dihydroxy-3,5,7-tri-methylisochroman-1-one (**20**), and (R)-2-chloro-3-(8-hydroxy-6-methoxy-1-oxo-1H-isochromen-3-yl) propyl acetate (**21**)] (Xia et al. 2020; Anh et al. 2021). Griseofulvin (**22**) is another benzophenone derivative produced by *Penicillium* species and administered orally as an antibiotic against skin fungal infections (Samuelsson and Bohlin 2009).

Furthermore, four polyketide dimers characterized by 6/6/8 tricycle carbon skeleton, incorporating an unusual bicycle [5.3.1] hendecane core, were identified in *P. canescens* ATCC 1049. Although these structures showed modest antitumor activity as compared to taxol or cisplatin, they are examples of the extremely enriching chemical diversity of fungal polyketides (Zang et al. 2020).

Anthrone, anthraquinone, and naphthopyrone are very representative of fungal polyketide metabolites. They are biosynthesized by several genera, including *Aspergillus,* known producers of highly carcinogenic compounds on foodstuffs such as cereals, beans, peanuts, coconuts, and almonds. Norsolorinic acid anthrone (**23**) and anthraquinone (**24**) (Fig. 17.2) are intermediates in the biosynthetic pathway of aflatoxins B1 and B2 (Samuelsson and Bohlin 2009).

Meroterpenoids (Fig. 17.2) are hybrid partially originated from terpenoids and display a broad range of structural diversity and biological activity. One of the largest meroterpenoids subgroups is composed of polyketide-terpenoid hybrid molecules. For instance, OA (**14**), 5-methyl orsellinic acid (5-MOA) (**25**), and 3,5-dimethyl orsellinic acid (DMOA) (**26**) are common polyketide parts of different meroterpene structures. Moreover, the genus *Aspergillus* is a great contributor to marine-derived fungal meroterpenoids. Aspergillactone (**27**), a DMOA-based meroterpene, exhibiting antibacterial activity against drug-resistant clinical isolates of *Helicobacter pylori* and *Staphylococcus aureus*, was isolated from *Aspergillus* sp. CSYZ-1 (Cen et al. 2021). *Aspergillus unguis* 158SC-067 and *A. flocculosus* 01NT-1.1.5 afforded a new resorcinol-meroterpene called grifolin B (**28**), a new homovalencic acid derivative, 12-hydroxyhomovalencic acid (**29**), and (5R,6S,16R,3E)-5,6-dihydroxy-16-methyloxacyclohexadec-3-en-2-one (**30**), a cytotoxic compound isolated from a natural source for the first time, along with seven known compounds (Anh et al. 2021).

Cladosin is a class of hybrid polyketides also produced by endophytic fungi. These compounds originated from the fusion of amino acids and polyketide units, and commonly isolated from the endophytic fungus *Cladosporium sphaerospermum* (Pan et al. 2020). *C. sphaerospermum* WBS017 afforded four new hybrid polyketides of cladosins L−O (**31–34**), which showed moderate antibacterial and antifungal activity (Pan et al. 2020) (Fig. 17.2).

17.2.2 Polyketides by Enzymatic Diels–Alder Reactions

Aromatic and cyclohexane rings can be built not only by Claisen and aldol reactions but also by enzymatic Diels–Alder reactions. Among the polyketides whose scaffold was originated from a [4 + 2] cycloaddition, the statins, such as lovastatin (**9**) (Fig. 17.1) and simvastatin (**10)** are good examples (Fig. 17.3). They arise from two polyketide chains, joined through an ester linkage with the decalin ring, formed by the Diels–Alder reaction, displaying a γ-lactone ring and other functional groups substituents (Campbell and Vederas 2010; Wang et al. 2021c).

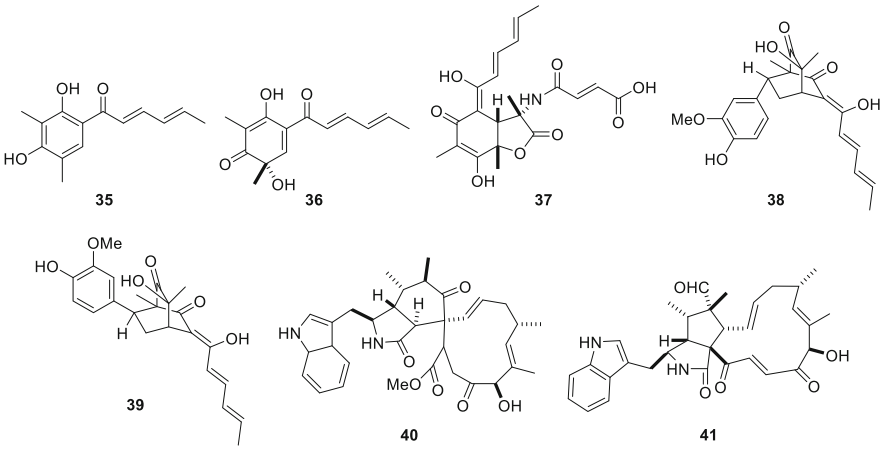


Fig. 17.3 Chemical structures of some fungal polyketides with Diels–Alder origin: sorbicillin (**35**), sorbicillinol (**36**), sorbicillactone A (**37**), sorbicatechol A (**38**) and B (**39**), spiropchaeglobosin A (**40**), and pchaeglobosal B (**41**)

Hybrid sorbicillinoids are another interesting class of biologically active and structurally diverse fungal polyketides arising from enzymatic Diels–Alder reaction. Sorbicillinoids are hexaketides derived from a cyclization on the carboxylate terminus. The first representative sorbicillin (**35**) was isolated from *Penicillium notatum* by Cram and Tishler in 1948 (Fig. 17.3). Up to now, more than 90 sorbicillinoids produced by terrestrial and marine fungi are known (Kahlert et al. 2020) and classified into four sub-classes. The hybrid sorbicillinoids are biosynthesized from either a Diels–Alder reaction or a Michael reaction of a monomeric sorbicillinoid diene and a second non-sorbicillinoid dienophile (Meng et al. 2016; Kahlert et al. 2020). The sorbicillinoids display a variety of biological activities including cytotoxic, antioxidant, antiviral, and antimicrobial. For instance, sorbicillinol (**36**) and sorbicillactone A (**37**) (Fig. 17.3) demonstrated a great cytotoxicity against cancer cell lines, and sorbicatechol A and B (**38–39**) displayed antiviral activities (Meng et al. 2016).

Finally, cytochalasans represent an interesting class of hybrid tricyclic polyketides containing an 11- to 16-membered macrocycle ring fused to an octahydro-isoindole derived from amino acids (e.g., phenylalanine, tyrosine, tryptophan, leucine, or alanine). These compounds exhibit a wide range of activities such as phytotoxic, antitumor, antiviral, antiangiogenic, immunomodulatory, and nematicidal (Peng et al. 2020). *Chaetomium globosum* P2-2-2 afforded four novel chaetoglobosins with an unprecedented system of fused rings. Among them spiropchaeglobosin A (**40**) was remarkable for its unique spiro [5.10]hexadecane system, which distinguished it from all known cytochalasans. Moreover, the new compound pchaeglobosal B (**41**) exhibited significant cytotoxicity against cancer cell lines (Peng et al. 2020) (Fig. 17.3).

17.2.3 Macrolides and Polyesters

Macrolides (Fig. 17.4) are an interesting group of 10–22-membered lactones originated from acetate or propionate polyketides and produced by bacteria and fungi. The polyketide chain can have a portion which might cyclize to an aromatic ring originating olivetolic acid (**42**), a 6-alkyl-substituted 2,4-dihydroxybenzoic acid, also known as a β-resorcylic acid, frequently present in fungal polyketide macrolactones, including the well-known zearalenone (**43**), besides hypothemycin (**44**) and radicicol (**45**) (Okorafor et al. 2021). Compound **43** is a 14-membered β-resorcylic lactone containing all types of oxidation levels seen during the fatty acid extension cycle. Also, this polyketide is a toxin produced by the fungus *Gibberella zeae* and several *Fusarium* species, displaying a high antifungal activity (Cox et al. 2018).

Another interesting macrolide groups are those which lack the β-resorcylic moiety forming the lactone. They are often biosynthesized by endophytic marine fungi of genera *Cladosporium*, *Curvularia*, *Hypoxylon*, *Paraphaeosphaeria*, *Penicillium*, *Phomopsis*, and *Sphaeropsidales* (Karpiński 2019; Zhang et al. 2020a). Besides, these macrolides presented antimicrobial, anticancer, chemopreventive, antibacterial, and/or antifungal activities. The mangrove-derived fungus *Cladosporium cladosporioides* MA-299 provided the new macrolide cladocladosin A (**46**), with an unprecedented bicycle 5/9 ring system, along with the two new sulfur-containing macrolides thiocladospolides F and G (**47–48**) (Fig. 17.4). The three compounds demonstrated antimicrobial activity against human and aquatic pathogenic bacteria (Zhang et al. 2020a).

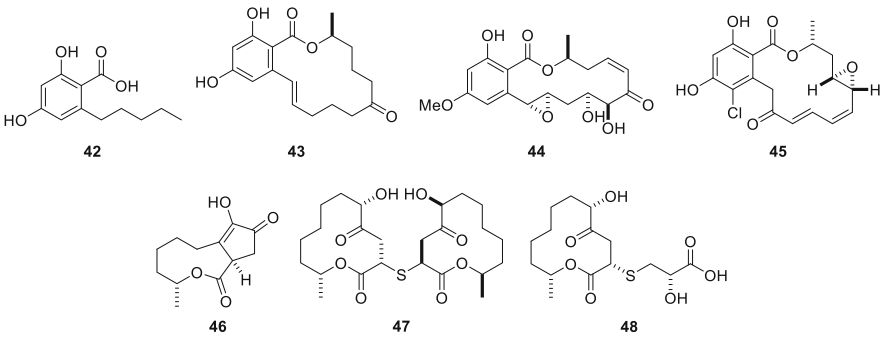


Fig. 17.4 Chemical structures of some fungal macrolide and polyester polyketides: olivetolic acid (**42**), zearalenone (**43**), hypothemycin (**44**), radicicol (**45**), cladocladosin A (**46**), thiocladospolides F (**47**) and G (**48**)

17.3 Routes of Synthesis of Polyketides Derived from Fungi

17.3.1 Fungal Polyketide Biosynthesis: The Most Recent Insights

The biosynthesis of fungal polyketides was previously reviewed by Simpson and Cox (2008) and recently considered by Cox et al. (2018). The genes encoding enzymes of a given biosynthetic pathway are frequently found adjacent in the genome and co-regulated, being denominated biosynthetic gene clusters (BGC). The biosynthesis of polyketides is catalyzed by modular polyketide synthases (PKS), which are enzymes with many domains. A set of ketoacylsynthase (KS), acyltransferase (AT), and acyl carrier protein (ACP) domains are mandatory in PKS to catalyze all chain extension cycles (iterative PKS). Besides, several additional domains, such as ketoreductase (KR), dehydratase (DH), enoyl reductase (ER), thioesterase (TE), and C-methyl transferase (CMeT) can be involved in a β-ketothioester processing, which performs specific operations in the chain-elongating process, usually acting in an iterative way, and the degree of reduction can vary into different units.

Genetic engineering provided tools to determine the PKS cluster genes, and their sequencing allowed to group them into three different classes, according to their architecture and mechanism of action (Fig. 17.5). Fungi present only types I and III PKS. Iterative type I modular PKS, present in most fungi, display modules which catalyze two-carbon linear extension, carrying out different actions in the β-keto group during the different cycles of chain elongation. In this sense, they are classified according to the degree of reduction of their products into non-reducing (NR) PKS, partially reducing (PR) PKS, and highly reducing (HR) PKS. HRPKS perform a cryptic biosynthetic pathway to selectively reduce β-keto moieties after each extension step into a β-alcohol, alkene, or alkane through KR, DH, and ER domains (Xu et al. 2020). Additionally, a hybrid synthetase composed by an HR-PKS fused to a non-ribosomal peptide synthetase (NRPS) leads to polyketides such as congeners of the benzendiol lactones, polylactones, sorbicillinoids, and some azaphilones (Xu et al. 2020). Moreover, these HRPKS-NRPS systems also produce polyketides fused to an amino acid by an amide bond, as found in the cytochalasans. Even though fungal type III PKS are structurally the simplest PKS, they present very complex mechanisms, producing chalcones, stilbenes, and small aromatic

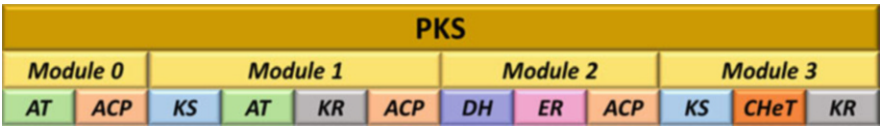


Fig. 17.5 Generic model for a polyketide synthase (PKS) and its modules and domains: acyltransferase (AT), acyl carrier protein (ACP), ketoacylsynthase (KS), ketoreductase (KR), dehydratase (DH), enoyl reductase (ER), and C-methyl transferase (CMeT) (Simpson and Cox 2008; Cox et al. 2018)

compounds (Schuemann and Hertweck 2009; Cox et al. 2018). The largest structural diversity of polyketides is also due to an impressive set of post-PKS modifications performed by cytochrome P450 monooxygenases, dehydrogenases, methyltransferases, as well as pathway regulators and transporters (Schuemann and Hertweck 2009).

The advance of the sequenced genome allows identifying BGC and comparing the PKS genes with known ones linked to natural products or to a specific biosynthetic step. Normally, most filamentous fungi can contain between 10 and 50 PKS genes (Cox et al. 2018), although a description of the fungal genome can reach up to 80 BGC (Meng et al. 2022). Moreover, this gene can be cloned and introduced in a heterologous host, in which not only the biosynthetic pathway can be deeply investigated, but also provides a convenient platform to generate a supply of useful secondary metabolites. Gene knockout, transcriptional activation, epigenetic regulation of fungal BGC, and combinatorial biosynthesis have also been revolutionizing the conventional fungal natural products discovery and production (Xu et al. 2020; Du and Li 2021).

Subcellular compartmentalization of secondary metabolism pathway enzymes also plays an important role in the biosynthesis of fungi. In fact, an isolated reaction occurs in an organelle where the substrates are highly concentrated, providing an optimal physiochemical environment for enzymatic catalysis. Moreover, the efficiency of precursor supply and intermediate channeling might be improved, preventing the loss of intermediates by off-target pathways, and the negative effects of toxic intermediates/products on the other cellular networks (Du and Li 2021). Therefore, more attention should be paid to the compartmentalization of biosynthetic steps to better understand the physiological and biochemical mechanisms of fungal biosynthesis.

Heterologous and engineering expression, and genome mining strategies were used by Zhang et al. (2020b) to investigate the biosynthesis of thermolides, fungal polyketide-nonribosomal peptide (PK-NRP) hybrid macrolactones produced by extreme thermophilic fungi *Talaromyces thermophilus* NRRL 2155. The study showed that the *Thm* gene cluster (*Thm*ABCE) is critical for the synthesis. Two separate single-module HRPKS (*Thm*A) and NRPS (*Thm*B) enzymes collaborate to synthesize the core macrolactone backbone type PK-NRP. Also, the NRPS *Thm*B-C_T domain catalyzes the key macrocyclization step in PK-NRP intermediate release via ester bond formation, representing a novel function of fungal NRPS C domains. These strategies not only dramatically enhanced the yields of thermolides, but also significantly increased its structural complexity and diversity, such as the synthesis of the first *L*-phenylalanine-based thermolides A (**49**) and B (**50**) (Fig. 17.6).

Co-expression, feeding experiments, knockout of genes, and heterologous expression are other successful tools for understanding the biosynthesis of dimeric or hybrid sorbicillinoids. The study of Kahlert et al. (2020) in *Trichoderma reesei* QM6a identified the gene SorD, recognized for encoding the first flavin-dependent monooxygenase enzyme operating in the biosynthesis of dimeric, hybrid, and epoxy sorbicillinoids in vivo. This monooxygenase acts in the dimerization of highly

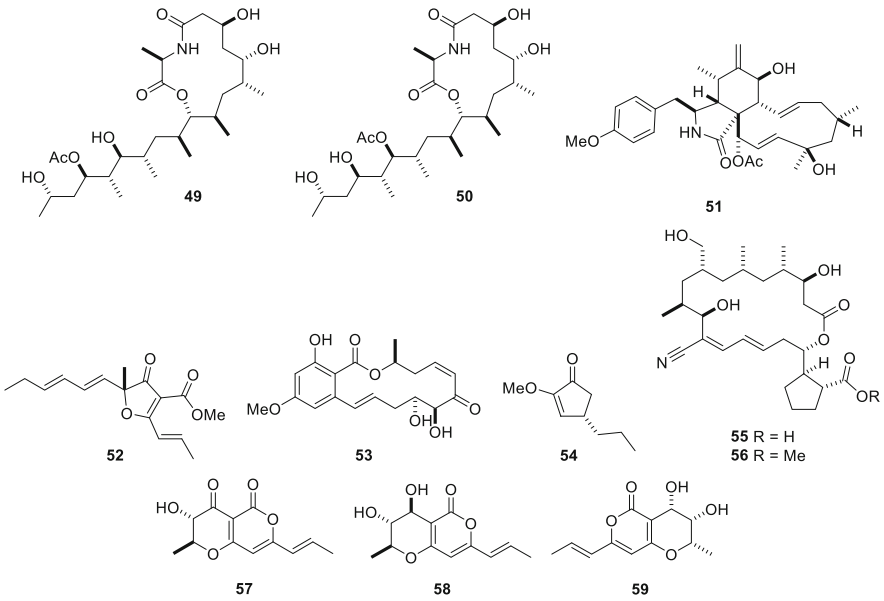


Fig. 17.6 Some polyketides elucidated by novel biosynthetic strategies: thermolides A (**49**) and B (**50**), pyrichalasin H (**51**), gregantin A (**52**), (5*Z*)-7-oxozeaenol (**53**), asperterrein (**54**), borrelidins J (**55**) and K (**56**), radicinin (**57**), radicinol (**58**), and 3-epiradicinol (**59**)

reactive sorbicillinoids (**36–39**), catalyzing an intermolecular Diels–Alder e/or Michael-addition, as well as in the epoxidation of sorbicillinol (**36**) (Fig. 17.3).

Directed gene knockout and complementation strategy were also carried out by Hantke et al. (2020) to investigate the function of the gene PyiF in the formation of cytochalasins, as well as to study if the closely related homologous protein ORF3 (62% identity to PyiF protein), from cryptic gene cluster ACE1 BGC in *P. oryzae* Guuy11, was also able to produce these polyketides. Their results strongly suggested that PyiF protein and ORF3 catalyze the long-proposed intramolecular Diels–Alder reaction, forming the tricyclic core structure of pyrichalasin H (**51**) (Fig. 17.6).

Another interesting approach to elucidating the biosynthetic mechanism to furnish the intriguing molecular skeleton of the alkylated furanone gregantin A (**52**) (Fig. 17.6) was reported by Wang et al. (2020a). Genome sequence of *Penicillium* sp. sh18 identified the gene cluster *grg* as responsible for the biosynthesis. Heterologous expression of the five enzyme-coding genes in *Aspergillus oryzae* successfully reconstituted the gregantin A (**52**) biosynthesis. Isotope-incorporation experiments indicated that compound **52** was biosynthesized by fusion of two polyketide chains synthesized by a single PKS, GrgA. In vitro enzymatic reactions confirmed that hydrolase GrgF was responsible for the fusion of the C11 and C4 carbon chains to produce strobilurin A (**12**) (Fig. 17.1). Finally, X-ray structural analysis and mutational experiments using GrgF provided a plausible mechanism for the chain fusion reaction (Wang et al. 2020a).

17.3.1.1 Enhancing the Biosynthesis of Fungal Polyketides

Fungi, as well as any other living being, tend to adapt to the conditions imposed by their natural habitats and develop tools to ensure their survival in that specific environment. These tools are basically metabolic alterations, which, for example, activate the biosynthesis of defense metabolites when dispute for space or food with other microorganisms takes place (Oliveira et al. 2021). These defense mechanisms become unnecessary to the extent that fungi are isolated and stored ex situ, in culture media containing enough amounts of carbon, nitrogen, macro, and microelements, as well as water (Oliveira et al. 2019). In vitro, fungal metabolism tends to decrease, with the deactivation of unnecessary biosynthetic routes. However, fungal metabolism is adjustable, due to the susceptibility of these organisms to the different conditions to which they are subjected. Therefore, physical, chemical, and biological modifications during the fermentation process can reactivate silenced biosynthetic routes (Peng et al. 2021). The various processes used for metabolic activation result, in general, from biotic or abiotic stress imposed on the fungus during its development. Biotic stress consists of the addition of microbial genetic material to the culture medium and the response tends to be the production of antimicrobial metabolites (Oliveira et al. 2021). Abiotic stress consists of physical (luminosity, agitation) or chemical (pH, nutrient type) alterations of the culture medium or during fungal development. In this case, the metabolites produced are not necessarily antimicrobials. Biotic and abiotic stress are relatively ways to activate metabolic production without the need for complex genetic modifications (Peng et al. 2021).

The general term used to describe improvement in the fermentation parameters is OSMAC (One Strain Many Compounds). This strategy was utilized to produce large amounts of the macrolactones hypothemycin (**44**) and (5*Z*)-7-oxozeaenol (**53**) (Fig. 17.6), using selected strains of the fungus *Setophoma* sp., to be used as feedstock for preparing synthetic analogs of resorcyclic acid lactones (RAL) in an economic way (Al Subeh et al. 2021). These fungal secondary metabolites are RAL with a *cis*-enone moiety, which show irreversible inhibitory activity against protein kinases, with selectivity toward transforming growth factor beta-activated kinase 1 (TAK1).

The secondary metabolites produced by fungi under stress are not normally produced by the species, under non-stressful conditions, as reported for the co-cultivation of *Aspergillus terreus* and *Paecilomyces lilacinus*. The interaction of these two fungi led to the production of asperterrein (**54**), a new antibacterial substance not detected in extracts where the two species developed individually (Li et al. 2020). In the same way, co-culture of a sponge-derived actinomycete *Streptomyces rochei* and a gorgonian-derived fungus *Rhinocladiella similis* was shown to induce the production of borrelidins J (**55**) and K (**56**), another antibacterial compounds, only expressed in the co-culture (Yu et al. 2019).

Abiotic stress has also been reported as a useful tool to enhance the biosynthesis of fungal polyketides. The chemical stress caused to the phytopathogenic fungus *Curvularia lunata* by the addition of sodium and calcium chloride, and

glycyrrhetinic acid, led to enhanced production of the polyketides radicinin (**57**), radicinol (**58**), and 3-epiradicinol (**59**) in up to 30 times. The salts were more effective stressing agents, probably because they trigger osmotic stress and, consequently, water uptake, leading to imbalance ionic environment inside the cells (Srivastava et al. 2021).

17.3.2 Synthetic Preparation of Polyketides and Derivatives

There are many strategies being applied to synthetically obtain polyketides with industrial and environmental interest. The advantage of exploring these routes of synthesis mainly relies in the search for improved yields and quicker processes for scaling-up.

The natural polyketide 6-pentyl-2*H*-pyrone-2-one (**60**) and other natural products are generated from the marine-derived fungi *Trichoderma reesei* (TR–13–01) and *T. atroviride* (TA–13–01), which were isolated from the marine sponge *Niphates* sp. (Khan et al. 2021). The high antimicrobial activity of this pyranone encouraged Khan et al. (2021) to synthesize this natural product and some analogs (**61** and **62**), seeking to prepare compounds to prevent marine biofouling, a widespread phenomenon in oceans worldwide. The development of nontoxic antifouling paint, in contrast of organotin and copper-based paints, reduces the environmental impact caused by increasing human activities in open and coastal waters. The activity of the synthesized compounds was evaluated in barnacle cyprid settlement assays, biofilm formation, and antimicrobial assays against marine bacteria, indicating 6-pentyl-2*H*-pyrone-2-one (**60**) as a good prototype entity with antifouling potential. The synthesized pyranone derivatives **61** and **62** demonstrated higher antifouling potential. The pyrone analogs were synthesized using two different alkynes, through a gold-catalyzed coupling reaction employing silver trifluoromethane sulphonate (AgOTf) as a catalyst in dichloromethane, during 12 h (Fig. 17.7).

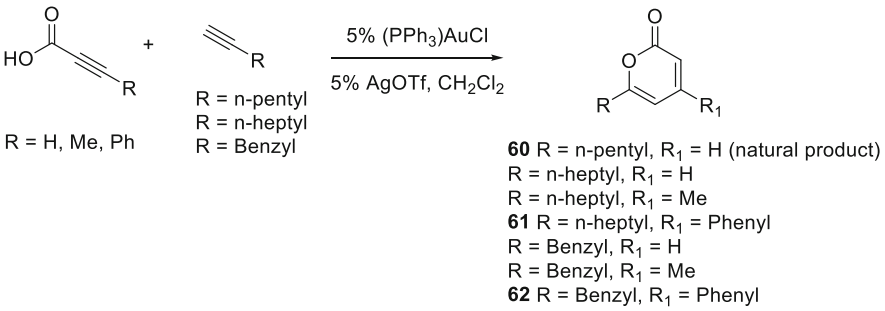
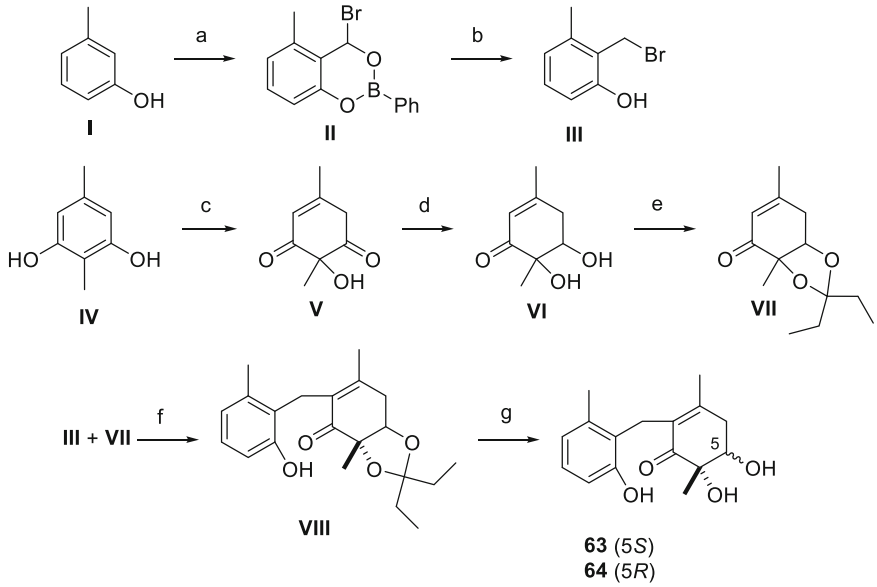


Fig. 17.7 Synthesis of the natural polyketide 6-pentyl-2*H*-pyrone-2-one (**60**) and its derivatives (**61** and **62**) (modified from Khan et al. 2021)

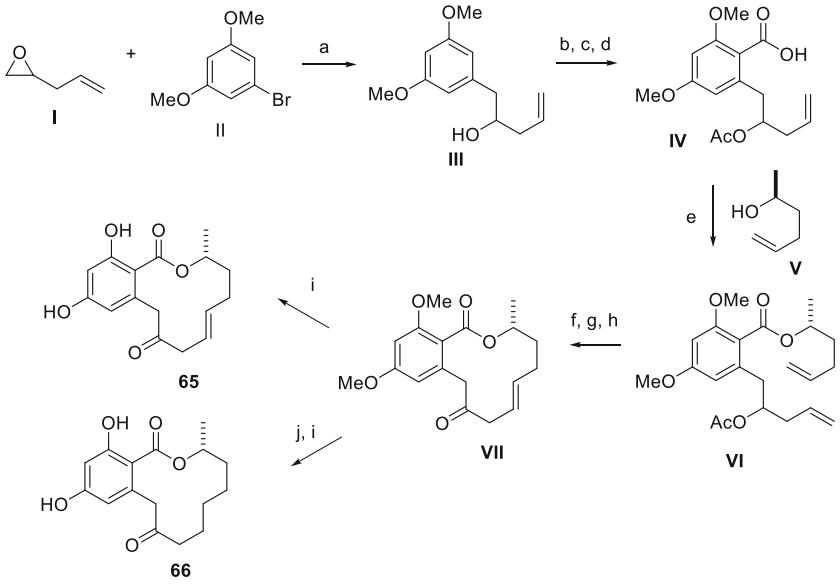


a) $PhB(OH)_2$, BrCHO; b) *terc*-$BuNH_2.BH_3$, $AlCl_3$; c) SIBX; d) [(*S*) or (*R*)-BINAP-Ru], H_2; e) 3-pentenone, TsOH, THF; f) $PhS(CH_2)_2OH$, $CsCO_3$, CH_3CN/*tert*-BuOH (1:1), 24h, 80 °C; g) TFA, H_2O, THF.

Fig. 17.8 Synthesis of the natural microketides A (**63**) and B (**64**) (modified from Wu 2021)

The C-11 epimeric polyketides microketides A (**63**) and B (**64**) were originally isolated from the marine gorgonian-derived fungus *Microsphaeropsis* sp. RA10-14. Both presented antimicrobial activity against several fungi and bacteria (Liu et al. 2020), motivating their synthesis through a convergent strategy, from two precursors (Fig. 17.8) (Wu 2021). The first precursor (III) was prepared by an *ortho*-specific alkylation of phenols, and the second precursor (VII) was synthesized oxidizing and then reducing the phenols. After using Noyori asymmetric hydrogenation to reduce intermediate V producing compound VI, which was protected as an acetonide (VII), a Morita–Baylis–Hillman reaction between the precursors III and VII provided microketides A (**63**) and B (**64**) after deprotection of compound VIII.

The macrocyclic lactones of RAL class are polyketides isolated from a range of fungal strains like *Lasiodiplodia theobromae*, *Penicillium* sp., and *Syncephalastrum racemosum* (Das and Reddy 2021). RAL were synthetically obtained, since this class of metabolites exhibits a large spectrum of biological activities (Das and Reddy 2021). The synthesis of these compounds was described (Fig. 17.9) starting with a Grignard reagent, obtained from aryl bromide (II), which opened the epoxide (I), gave the corresponding secondary alcohol (III), that was protected before reacting with a benzoic acid, prepared via Vilsmeier–Haack formylation, followed by Pinnick oxidation giving intermediate IV. The latter was coupled with the chiral alcohol (V) under Mitsunobu reaction condition. Using Grubb's II catalyst, a ring-closing



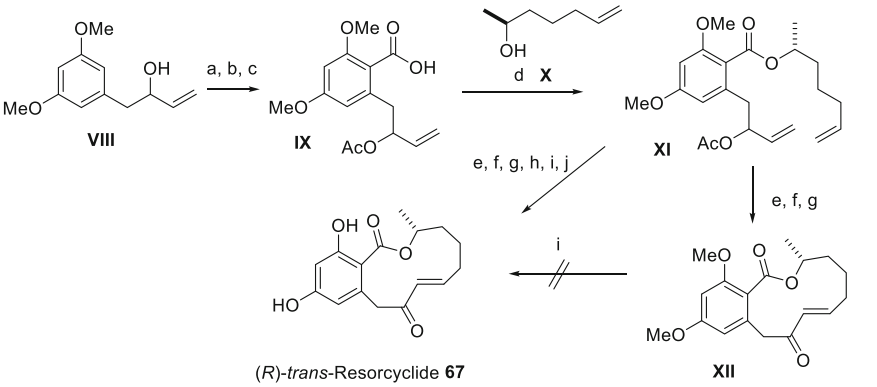
a) Mg, THF, 1h, CuI, -78 °C to rt, 12h, 86%; b) Et_3N, Ac_2O, DMAP, CH_2Cl_2, 1h; c) $POCl_3$, DMF, 4h; d) NaH_2PO_4, $NaClO_2$, DMSO, H_2O, 5 °C to rt, 53% (two steps); e) PPh_3, DIAD, THF, 0 °C to rt, 12h; f) Grubbs' II, CH_2Cl_2, reflux, 30 min, 65%; g) K_2CO_3, MeOH, 0 °C to rt, 1h; h) DMP, CH_2Cl_2, 0 °C to rt, 4h, 63% (two steps); i) AlI_3, TBAI, phloroglucinol, benzene, 5-7 °C, 34%; j) H_2 (ballon), 10% Pd/C, EtOH, 5h.

Fig. 17.9 Synthesis of (*R*)-penicimenolide (**65**) and (*R*)-dihydroresorcyclide (**66**) (modified from Das and Reddy 2021)

metathesis allowed the obtaining of macrolactone (VII) from diene (VI). After deprotection of compound VII, a Dess–Martin oxidation and removal of the methyl groups, the (*R*)-penicimenolide (**65**) was achieved (34% yield). The macrolactone (VII) was hydrogenated and demethylated, to furnish RAL12 fungal polyketide (*R*)-dihydroresorcyclide (**66**).

The polyketide (*R*)-trans-resorcyclide (**67**) was also prepared synthetically (Fig. 17.10), starting from 3,5-dimethoxybenzaldehyde, which was converted in the allyl alcohol (VIII) (Gualandi et al. 2014). After protection of the hydroxyl group, formylation (Vilsmeier–Haack reaction), followed by oxidation (Pinnick reaction), gave the compound IX. Esterification of IX using the alcohol (X), under Mitsunobu conditions, provide the diene (XI). A further sequence of metathesis, deprotection, and oxidation steps furnished the dimethylated macrolactone (XII). To overcome the problem of removing the methyl groups from intermediate XII, the double bond was masked though the formation of a selenide intermediate, which was totally demethylated using AlI_3, and then the selenide was oxidated and eliminated in a one-pot reaction, to finally furnish (*R*)-trans-resorcyclide (**67**).

The polyketide 5′-methoxy-6-methyl-[1,1′-biphenyl]-3,3′,4-triol (**68**) (Fig. 17.11) was isolated from *Ulocladium* sp., *Nigrospora sphaerica*, *Phialiphora* sp., *Penicillium pinophilum* SD-272, *Alternaria* sp., and from the endophytic fungus



a) Et_3N, Ac_2O, DMAP, CH_2Cl_2, 1h; b) $POCl_3$, DMF, 4h; c) NaH_2PO_4, $NaClO_2$, DMSO, H_2O, 5 °C to rt, 5h, 58% (two steps); d) PPh_3, DIAD, THF, 0 °C to rt, 12h, 62%; e) Grubbs' II, CH_2Cl_2, reflux, 45 min, 61%; f) K_2CO_3, MeOH, 0 °C to rt, 1h; g) DMP, CH_2Cl_2, 0 °C to rt, 4h, 60% (two steps); h) Ph_2Se_2, $NaBH_4$, EtOH, AcOH, THF, rt, 10 min, 84%; i) AlI_3, TBAI, phloroglucinol, benzene, 5-7 °C; j) H_2O (30%), AcOH, THF, H_2O, 0 °C, 2h, 54% (two steps).

Fig. 17.10 Synthesis of (*R*)-trans-resorcyclide (**67**) (modified from Gualandi et al. 2014)

Botryosphaeria dothidea in *Melia azedarach*. It shows relevant DPPH radical scavenging activities, with determined half maximal inhibitory concentration (IC_{50}) values of 18.7 ± 0.2 μM and 148 ± 3 μM, respectively, and exhibits inhibitory activity against three tyrosine kinases (EGFR, VEGFR-1, and c-Met) (Warmuth et al. 2021). For the chemical preparation of **68**, a convergent synthesis was conceived, employing a Suzuki cross coupling to join two intermediates, a boronate and an arylbromide. For the synthesis of the first intermediate (Fig. 17.11a), it was envisaged the use of a silyl protecting group, *tert*-butyldimethylsilyl group (TBS), suitable for all steps. The 4-methylcatechol was used as starting material which was protected with TBSCl in the presence of 4-(dimethylamino)pyridine and imidazole to furnish the disilylated compound (I). Using *N*-bromosuccinimide (NBS) in acetonitrile, the bromide (III) was obtained in excellent yield. The formation of boronate (V) was finished treating III with butyllithium and trapping with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The other electrophilic intermediate necessary to couple with boronic compound (IX) was prepared from the commercial 1-bromo-3,5-dimethoxybenzene (VII), which was mono-demethylated by using BBr_3 to give the phenol (VIII), that, in its turn, protected with TBS group to give IX (Fig. 17.11b). Finally, the Suzuki coupling led to the product XI with 98% yield (Fig. 17.11c). However, the desilylation of XI failed giving a mixture of products hard to separate. Because of this, several issues post-reaction had to be addressed before reaching the final product, changing the protect group (silyl to benzyl), allowing to obtain product **68** from compound XII, in the last step, with 88% yield.

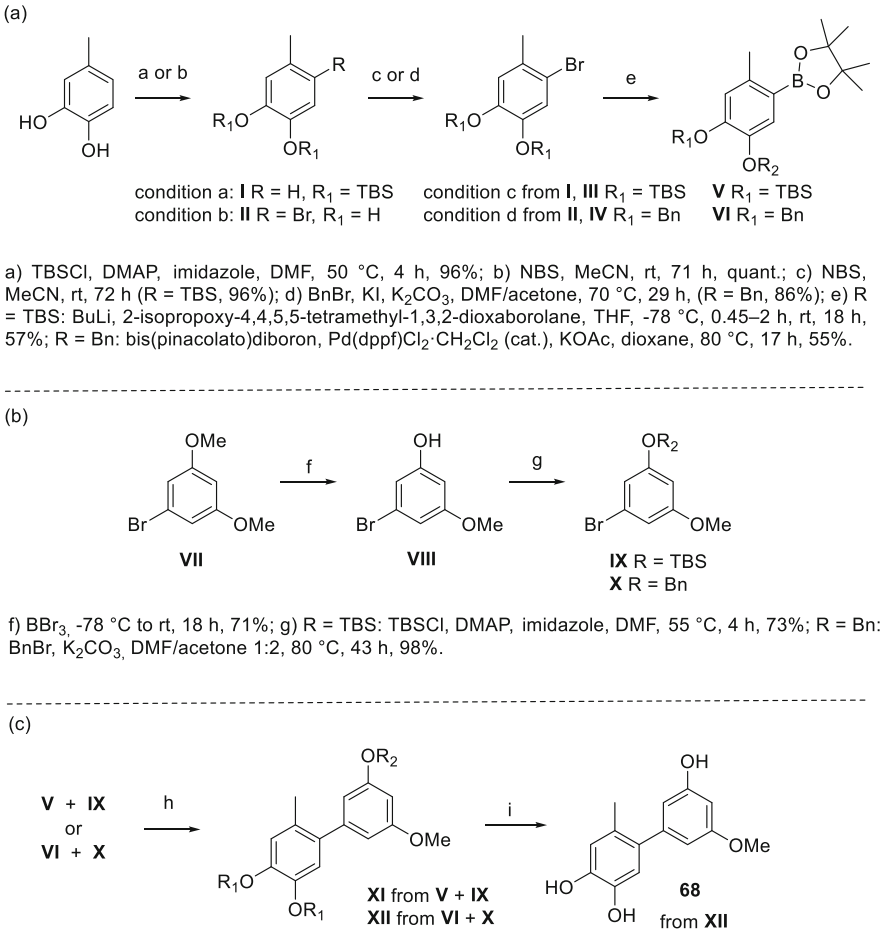


Fig. 17.11 Synthesis of 5′-Methoxy-6-methyl-[1,1′-biphenyl]-3,3′,4-triol (**68**): (**a**) preparation of intermediates boronates (V and VI); (**b**) preparation of intermediate aryl bromide (IX and X); (**c**) obtention of polyketide (**68**) from a Suzuki reaction between the boronate (V and VI) and aryl bromide (IX and X) after deprotection of (XII) (modified from Warmuth et al. 2021)

17.4 Overview of Fungi Polyketides as Lead Compounds for Biotechnological Applications

Polyketides originated from fungi and their synthetic/semi-synthetic derivatives have biological properties as antibiotic, antifungal, antiparasitic, immunosuppressant, anti-cholesterol, antitumoral, antidiabetic, insecticide, among other applications. Many fungal polyketides also have coloring properties that can be explored as

food pigments. In this topic, several biologically active polyketides from fungal origin are presented, and the scope of their biological action, source, biotechnological potential, and recent achievements are discussed.

17.4.1 Antimicrobial

17.4.1.1 Antibacterial

Fungi of the genus *Aspergillus* are prolific in the production of polyketides with antimicrobial activity. A strain of *Aspergillus niger*, isolated in Egypt as an endophytic from the marine alga *Laurencia obtuse*, produced six metabolites, including a new pentacyclic polyketide named RF-3192C (**69**), active against three bacteria species (*Pseudomonas aeruginosa*, *Bacillus subtilis*, and *S. aureus*) and the yeast *Saccharomyces cerevisiae*, in a trial using disc diffusion method (Mahmoud et al. 2021). Although the crude extract was active against *Candida albicans*, the metabolites isolated were inactive against this yeast and *C. albicans* inhibition may be related to a non-isolated metabolite or to synergic interactions (Table 17.1, Fig. 17.12). On the other side, the crude extract was unable to inhibit the growth of *P. aeruginosa*, while the activity of isolated RF-3192C (**69**) (inhibition zone, IZ, 15 mm) against this bacterium was comparable to positive control gentamycin (IZ 18 mm) (Mahmoud et al. 2021). The polyketide glycoside isotorachrysone 6-O-α-d-ribofuranoside (**70**), recovered from a culture of another Egyptian *Aspergillus* species, *A. ochraceopetaliformis*, showed broad antimicrobial activity in both disc diffusion and microdilution assays against *S. aureus, Staphylococcus epidermidis, P. aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae, Escherichia coli, C. tropicalis,* and *C. glabrata* (IZ 11–17 mm; Minimum inhibitory concentration, MIC, 0.09–0.90 mg/mL) (Asmaey et al. 2021). *Aspergillus unguis* PSU-MF16, isolated from the sponge *Dysidea* sp. in Thailand, was reported to produce several metabolites, including six new polyketides. The diphenyl ether (**71**) was active against *S. aureus*, *Microsporum gypseum*, and a methicillin-resistant *S. aureus* (MRSA) strain (MIC 16 μg/mL) (Saetang et al. 2021). From the fifteen polyketides recovered from *Aspergillus versicolor*, isolated from Chinese deep-sea sediment, the metabolite 3,7-dihydroxy-1,9-dimethyldibenzofuran (**72**) stood out for being able to inhibit *S. aureus* and *Aeromonas salmonicida* (MIC 13.7 μM) (Yang et al. 2020) (Table 17.1, Fig. 17.12).

Two new 3,4-dihydroisocoumarins, 3 *R*-8-methoxy-3-(4-oxopentyl) isochroman-1-one (**73**), and 3 *R*-7-hydroxy-8-methoxy-3-(4-oxopentyl) isochroman-1-one (**74**) isolated from a *Penicillium* sp., collected from the Xinren coal area of Guizhou province in China, probably biosynthesized from malonyl-CoA and acetyl-CoA via a linear polyketide synthesis pathway, with further functionalization, were active against *C. albicans* and *S. epidermidis* (50–100 μg/mL). Other two 3,4-dihydroisocoumarins isolated from the same species, 5,6-dihydroxy-3*R*-(4S-hydroxypentyl)-isochroman-1-one (**75**) and 3 R-(7,8-dihydroxy-1-

Table 17.1 Fermentation parameters and scope of antibacterial activity of some fungal polyketides

Metabolite (#) [Activity]	Fungal species [Fermentation parameters]	Reference
Cladosin L (**31**) [*S. aureus* MIC 25–50 μM]	*Cladosporium sphaerospermum* WBS017 [100 g rice in 100 mL demineralized water; static conditions]	Pan et al. (2020)
RF-3192C (**69**) [*P. aeruginosa*: IZ 15 cm; *B. subtilis*: IZ 12 cm; *S. cerevisiae*: IZ 9 cm; *S. aureus*: IZ 7 cm]	*Aspergillus niger* SB4 [Rice medium: 100 g commercial rice in 100 mL 50% seawater; 14 days, 37 °C]	Mahmoud et al. (2021)
Isotorachrysone 6-O-α-d-ribofuranoside (**70**) [*S. aureus*, *S. epidermidis*, *P. aeruginosa*, *K. pneumoniae*, *E. cloacae*, *E. coli*, *C. tropicalis,* and *C. glabrata*: IZ 11–17 mm, MIC 0.09–0.90 mg/mL]	*Aspergillus ochraceopetaliformis* ASAI [100 g commercial rice in 150 mL 50% seawater;14 days, 35 °C]	Asmaey et al. (2021)
Diphenyl ether (**71**) [*S. aureus*, MRSA, and *Microsporum gypseum*: MIC 16 μg/mL]	*Aspergillus unguis* PSU-MF16 [Potato dextrose broth; 4 weeks, room temperature]	Saetang et al. (2021)
3,7-Dihydroxy-1,9-dimethyldibenzofuran (**72**) [*S. aureus* MIC 13.7 μM; *Aeromonas salmonicida* MIC 13.7 μM]	*Aspergillus versicolor* SH0105 [80 g rice in 80 mL seawater; 60 days, 25 °C]	Yang et al. (2020)
3 *R*-8-methoxy-3-(4-oxopentyl) isochroman-1-one (**73**) 3 *R*-7-hydroxy-8-methoxy-3-(4-oxopentyl) isochroman-1-one (**74**) [*C. albicans* MIC 50 μg/mL; *S. epidermidis* MIC 100 μg/mL]	*Penicillium* sp. XR046 [Solid rice medium]	Xu et al. (2019)
5,6-dihydroxy-3*R*-(4S-hydroxypentyl)-isochroman-1-one (**75**) 3 R-(7,8-dihydroxy-1-oxoisochroman-3-yl) propanoic acid (**76**) [*B. subtilis* MIC 100 μg/mL]		
Pseudophenone A (**77**) [*X. citri* MIC_{50} 36.16–44.19 μM; *S. aureus* MIC_{50} 47.44 μM; *A. salmonicida* MIC_{50} 36.90 μM; *P. fulva* MIC_{50} 35.64 μM]	*Pseudogymnoascus* sp. HSX2#-11 [Potato Dextrose Agar; 45 days, 16 °C]	Shi et al. (2021)
Pseudophenone A benzoic acid derivative (**78**) [*X. citri* MIC_{50} 40.83 μM; *S. aureus* MIC_{50} 56.93 μM; *A. salmonicida* MIC_{50} 26.86 μM; *P. fulva* MIC_{50} 37.61 μM]		
Arthproliferin A (**79**) [*S. aureus* MIC 78 μg/mL]	*Stachybotrys chartarum* SCSIO41201 [rice 200 g, NaCl 0.5 g, distilled water 200 mL; static conditions and daylight, 50 days, 25 °C]	Yang et al. (2021)

(continued)

Table 17.1 (continued)

Metabolite (#) [Activity]	Fungal species [Fermentation parameters]	Reference
(2*S*)-2,3-dihydro-5,6-dihydroxy-2-methyl-4H-1-benzopyran-4-one (**80**) [*B. cereus* MIC 12.5 μg/mL]	*Colletotrichum gloeosporioides* [50 g rice in 50 mL seawater; 30 days, static conditions, room temperature]	Luo et al. (2019)
4-ethyl-3-hydroxy-6-propenyl-2H-pyran-2-one (**81**) [*S. aureus* and *S. albus* MIC 12.5 μg/mL]		
Daldispone B (**82**) [*S. aureus* MIC 32 μg/mL; *E. faecalis* MIC 16 μg/mL; *B. cereus* MIC 32 μg/mL]	*Daldinia* sp. CPCC 400770 [80 g rice in 120 mL distilled water; 40 days, 30 °C]	Gu et al. (2021)
Koninginin W (**83**) [*E. coli* MIC 128 μg/mL, *B. subtilis* MIC 128 μg/mL; *S. typhimurium* MIC 64 μg/mL]	*Trichoderma koningiopsis* YIM PH30002 [Fermentation parameters not provided]	Wang et al. (2021d)

Notes: IZ inhibition zone (disc diffusion assay), MIC Minimum inhibitory concentration (microdilution assay), MRSA methicillin-resistant *S. aureus*

oxoisochroman-3-yl) propanoic acid (**76**), were the only metabolites active against *B. subtilis*. The activity of the latter was related to the ortho-dihydroxy function in the benzene ring, which is not present in the structures of (**73** and **74**) (Xu et al. 2019) (Table 17.1, Fig. 17.12).

A broad screening with five phytopathogenic bacteria (*Xanthomonas citri* pv. *malvacearum*, *X. citri*, *Pseudomonas syringae*, *Dickeya chrysanthemi*, and *Erwinia amylovora*), four animal pathogenic bacteria (*E. coli*, *S. aureus*, *P. aeruginosa*, and *B. subtilis*), and eight marine fouling bacteria (*P. fulva*, *Aeromonas hydrophila*, *A. salmonicida*, *Vibrio anguillarum*, *V. harveyi*, *Photobacterium halotolerans*, *P. angustum*, and *E. cloacae*) was conducted with pseudophenone A (**77**) and its benzoic acid derivative (**78**) (Table 17.1, Fig. 17.12), both isolated from the psychrophilic pathogenic Antarctic fungus *Pseudogymnoascus* sp. Interestingly, these compounds did not show cytotoxicity against five human cancer cell lines (Shi et al. 2021).

Antimicrobial polyketides with complex structural features have been frequently reported from fungi associated to marine organisms. A comprehensive screening of more than 200 strains of symbiotic and epiphytic fungi isolated from the soft coral *Sinularia* sp., collected in the South China Sea, led to the isolation of the fungal strain *Stachybotrys chartarum* (Yang et al. 2021). This species furnished four new polyketide derivatives, arthproliferins A–D, along with other thirteen metabolites. Arthproliferin A (**79**) was inactive against *Acinetobacter baumannii*, *K. pneumoniae*, *E. coli*, *Aeromonas hydrophila*, and *Enterococcus faecalis*, but displayed moderate inhibitory activity against *S. aureus* (MIC 78 μg/mL) (Table 17.1, Fig. 17.12).

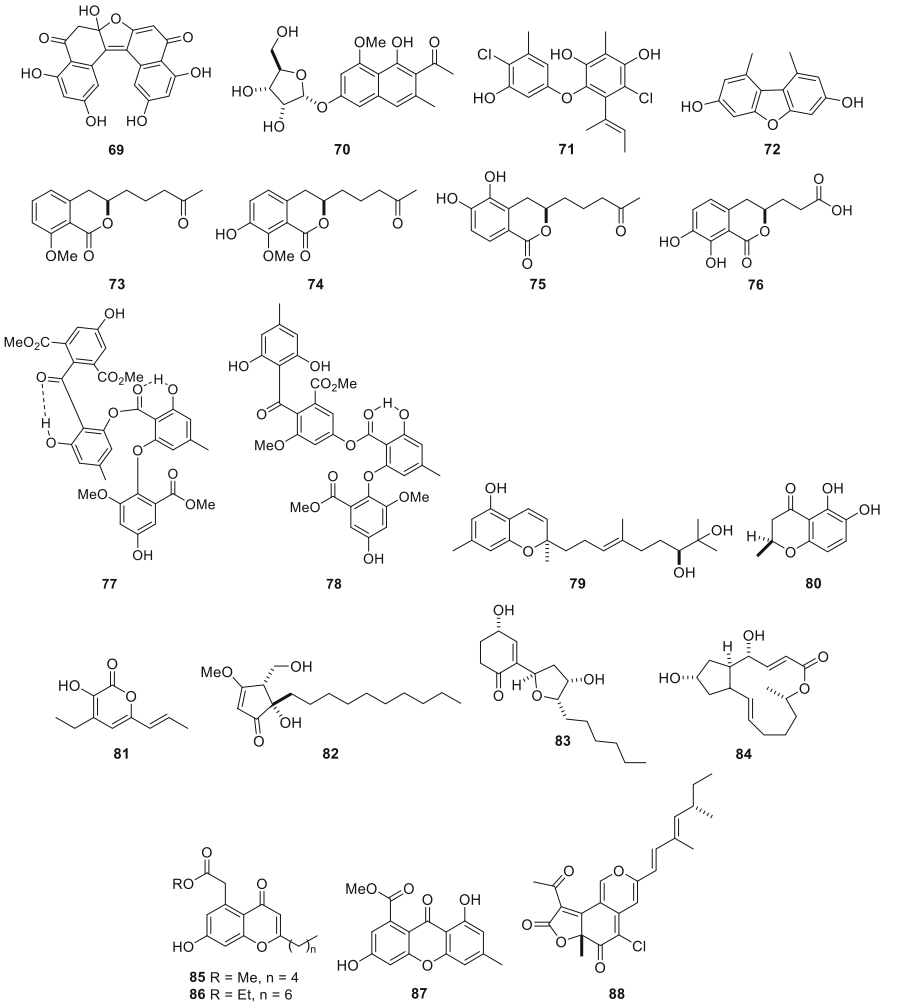


Fig. 17.12 Fungal polyketides and derivatives with antimicrobial applications: RF-3192C (**69**), isotorachrysone 6-O-α-d-ribofuranoside (**70**), diphenyl ether (**71**), 3,7-dihydroxy-1,9-dimethyldibenzofuran (**72**), 3 *R*-8-methoxy-3-(4-oxopentyl) isochroman-1-one (**73**), 3 *R*-7-hydroxy-8-methoxy-3-(4-oxopentyl) isochroman-1-one (**74**), 5,6-dihydroxy-3*R*-(4S-hydroxypentyl)-isochroman-1-one (**75**), 3 R-(7,8-dihydroxy-1-oxoisochroman-3-yl) propanoic acid (**76**), pseudophenone A (**77**) and its benzoic acid derivative (**78**), arthproliferin A (**79**), (2*S*)-2,3-dihydro-5,6-dihydroxy-2-methyl-4H-1-benzopyran-4-one (**80**), 4-ethyl-3-hydroxy-6-propenyl-2H-pyran-2-one (**81**), daldispone B (**82**), koninginin W (**83**), brefeldin A (**84**), pestalotiopsone F (**85**), pestalotiopsone B (**86**), 3,8-dihydroxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**87**), and 5-chloroisorotiorin (**88**)

The already mentioned polyketide asperterrein (**54**), obtained in special conditions of co-culture (see Sect. 17.3.2), was able to inhibit the bacteria *Alternaria brassicae*, *E. coli*, *Physalospora piricola*, and *S. aureus* (MIC 4–64 μg/mL) (Li et al. 2020). Another example is borrelidin J (**55**), which demonstrated significant activity against methicillin-resistant *S. aureus* (MIC 0.195 μg/mL) (Yu et al. 2019). Radicinin (**57**), obtained under stressing culture conditions, was also identified as an antibacterial agent active against the phytopathogenic *Xylella fastidiosa* (Aldrich et al. 2015).

Other fungal species capable of producing antibacterial polyketides include *Cladosporium sphaerospermum* (Pan et al. 2020), *Colletotrichum gloeosporioides* (Luo et al. 2019), *Daldinia* sp. (Gu et al. 2021), *Trichoderma koningiopsis* YIM PH30002 of *Panax notoginseng* (Wang et al. 2021d) (Table 17.1, Fig. 17.12).

17.4.1.2 Antifungal

Griseofulvin (**22**) (Fig. 17.2) and echinocandins (Fig. 17.1) are, respectively, polyketide and peptide-polyketide mixed drugs acting on fungi. Griseofulvin (**22**) was first discovered by Oxford et al. in 1939 and tested as an antifungal agent in humans in the 1950s. Since then, more than 400 analogs have been synthesized (Petersen et al. 2017). It is a secondary metabolite of the fungus *Penicillium griseofulvum* with selective inhibitory activity in the assembly of microtubules, and thus the first example of a product from one fungus being used to attack another (Odds 2003). Griseofulvin (**22**) (GRIS-PEG®, Bausch Health) is indicated for the treatment of dermatophyte infections tinea corporis (ringworm of the body), tinea pedis (athlete's foot), tinea cruris (ringworm of the groin and thigh), tinea barbae (barber's itch), tinea capitis (ringworm of the scalp), and tinea unguium (onychomycosis, ringworm of the nails).

Echinocandin B (**4**) was first discovered in 1974 by a group from Ciba-Geigy AG (Switzerland) as a metabolite of *Aspergillus delacroxii* (former *Aspergillus nidulans* var. *echinulatus*) and *Aspergillus rugulosus* (Hüttel 2021). Currently, strains of more than 20 fungal species are reported to produce echinocandins, of which echinocandin B (**4**) from diverse *Aspergillus* (Emericella) is the most common product. Echinocandins are cyclic non-ribosomal hexapeptides equipped with a lipophilic side chain. They are produced by filamentous fungi (Ascomycota) of the classes Leotiomycetes (mostly Helotiales) and Eurotiomycetes (Aspergillaceae). Echinocandins are potent antifungal compounds, due to their strong inhibitory effect on 1,3-β-D-glucan synthase, an enzyme required for the biosynthesis of β(1,3)-D-glucan, one of the main polysaccharides of the fungal cell wall. A fungistatic effect is observed as result of limited cell growth due to inhibition of cell wall synthesis. While a fungicidal effect is the result of the cellular destruction due to changes in the integrity of fungal cell wall, leading to loss of mechanical strength and failure to maintain intracellular osmotic pressure (Hashemian et al. 2020).

The semi-synthetic derivatives of echinocandins include caspofungin acetate (**5**) (Cancidas®), micafungin (**6**) (Mycamine®), and anidulafungin (**7**) (Eraxis™) and

they are first-line antimycotics for the treatment of invasive mycosis (Denning 2002; Patil and Majumdar 2017). Caspofungin acetate (**5**) is the first member of echinocandins that was approved by the U.S. Food and Drug Administration (FDA) against fungal infection in 2001. It is indicated in adults and pediatric patients for treatment of invasive candidiasis, aspergillosis, and invasive aspergillosis in patients that were refractory to amphotericin B (Heinz et al. 2016; Fisher et al. 2019). Caspofungin (**5**) may have fungicidal effects on *Candida* spp. and fungistatic effect against filamentous fungi such as *Aspergillus* species (Horan-Saullo and Alexander 2016).

Micafungin sodium (**6**) is a semi-synthetic lipopeptide echinocandin, synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. It is indicated for treatment of esophageal candidiasis, candidemia, and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation. Micafungin (**6**) has also strong inhibitory effects against both adhesion and biofilm formation of different *Candida* species, like *C. guilliermondii*, *C. tropicalis*, and *C. parapsilosis* (Zuo et al. 2021). These *Candida* species had varied biofilm-forming capabilities and are very important pathogens in catheter-related candidemia patients.

Anidulafungin (**7**) is indicated for the treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in adults and pediatric patients.

17.4.1.3 Antivirals

Fungal secondary metabolites are likewise a potential and valuable source in drug screening for the development of antiviral agents. Many fungal polyketides are under in vitro screening with promising results. For instance, mycophenolic acid (**1**) (Fig. 17.1) became a promising drug candidate against HIV-1 (Chapuis et al. 2000), vesicular stomatitis Indiana virus, hepatitis C virus (Henry et al. 2006), Dengue virus (Takhampunya et al. 2006), Zika virus (Barrows et al. 2016), and SARS-CoV-2 (Kato et al. 2020).

Likewise, brefeldin A (**84**), isolated from *Penicillium* sp. FKI-7127, has shown antiviral activity against Dengue virus (subtypes 1–4) and Zika virus, besides Japanese encephalitis virus, demonstrated by focus reduction assay in Vero cell (Raekiansyah et al. 2017). It is also a potent inhibitor of poliovirus RNA replication (Crotty et al. 2004).

Among 28 aromatic polyketides from the mangrove-associated fungus *Diaporthe* sp. SCSIO 41011, pestalotiopsone F (**85**), pestalotiopsone B (**86**), 3,8-dihydroxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**87**), and 5-chloroisorotiorin (**88**) displayed pronounced anti-IAV activities against three virus subtypes, including A/Puerto Rico/8/34 H274Y (H1N1), A/FM-1/1/47 (H1N1), and A/Aichi/2/68 (H3N2) (Luo et al. 2018).

17.4.2 Antiparasitic

Three new polyketides active against malaria were recently isolated from the basidiomycete fungus *Favolaschia* sp. BCC 18686 [X (**89**), Y (**90**) and Z (**91**), Fig. 17.13)] (Kornsakulkarn et al. 2020). Other 14 new compounds, in addition to another nine known, were also isolated from the same strain. These polyketides were subjected to biological assays for antiplasmodial activity using *Plasmodium falciparum* (strain K1) and showed discrete values of IC_{50} (X > 45 μM, Y > 38 μM, and Z > 43 μM).

Fungal polyketide-nonribosomal peptide (PK-NRP) hybrid macrolactones, such as the thermolides A (**49**) and B (**50**) (Fig. 17.6), are produced by extreme thermophilic fungi and exhibit strong nematocidal activity (Zhang et al. 2020b). Structurally, thermolides are thirteen-membered lactam-bearing macrolactones that possess a polyketide chain featuring eleven chiral centers and an unnatural amino acid D-alanine or D-valine. The activities of thermolides A (**49**) and B (**50**) are comparable to those of commercial avermectins (Guo et al. 2012), and they are therefore considered valuable nematocidal agents for biological control in agriculture (Degenkolb and Vilcinskas 2016; Zhai et al. 2016).

The polyketide ravenelin (**92**) (Fig. 17.13) was isolated from the biomass extracts of *Exserohilum rostratum* fungus, and its antiplasmodial and trypanocidal activities were evaluated (Pina et al. 2021). Compound **92** was tested in vitro against cultures of *P. falciparum* 3D7, a chloroquine-sensitive strain, and against the epimastigote and intracellular amastigote forms of *Trypanosoma cruzi*. The compound showed antiplasmodial (IC_{50} 3.4 μM) and trypanocidal activities (IC_{50} 5.0 μM and 9.0 μM, respectively, for epi and amastigote forms) in the low micromolar range.

17.4.3 Antidiabetic/Hypoglycemic and Hypolipidemic

Polyketides are promising in the development of antidiabetic drugs. A major effect of polyketides in diabetes-associated conditions occurs via protein tyrosine phosphatase PTP1B, a protein that is also a target for developing anti-obesity and

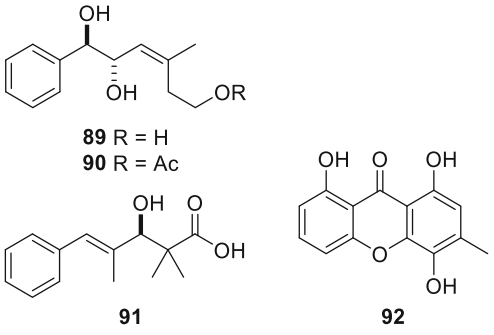


Fig. 17.13 Antiparasitic polyketides from fungi: compounds X (**89**), Y (**90**), and Z (**91**) from *Favolaschia* sp. BCC 18686, and ravenelin (**92**)

antitumor drugs. The inhibition of PTP1B has a positive influence in alleviating insulin resistance, therefore compounds able to inhibit this enzyme may have positive results in patients with type 2 diabetes.

Many polyketides produced by fungi of *Penicillium* genus, able to inhibit PTP1B have been described (Fig. 17.14), such as penipyrol C (**93**), a molecule with a rare γ-butyrolactone moiety linked to α-pyrone ring. This metabolite, isolated from the mangrove species *Penicillium* sp. HDN-11-131, induced the regeneration of pancreatic β cells in a zebrafish model; decrease of total glucose level was also detected for this metabolite (Wang et al. 2021e). Penicanesin D (**94**), an acyl phloroglucinol pyrone, is a highly oxygenated aromatic polyketide produced by the soil species *Penicillium canescens* CGMCC 3.79658. This metabolite, elicited by OSMAC approach, presented modest PTP1B inhibition at 50 μM (58.7%) (Zang et al. 2022). The polyketides 5-((*R*,1*Z*,3*E*)-6-hydroxy-1,3-heptadien-1-yl)-1,3-benzenediol (**95**), 4-carboxy-5-((*R*,1*Z*,3*E*)-6-hydroxy-1,3-heptadien-1-yl)-1,3-benzenediol (**96**), and 4-carboxy-5-((1*Z*,3*E*)-1,3-heptadien-1-yl)-1,3-benzenediol (**97**) were isolated from the marine fungal species *Penicillium* sp. TW58-16. These metabolites were suggested to be further studied as antidiabetic agents due to their strong α-glucosidase inhibitory activity (73.2%, 55.6%, and 74.4%, respectively, at 400 μM) (Gou et al. 2021).

Fungal species from other genera have also been described as PTP1B inhibitors (Fig. 17.14), as is the case of the marine-derived strain *Aspergillus* sp. SF-5929, from where the polyketides (±)-tylopilusin D (**98**) and funalenone (**99**) were recovered (IC_{50} 8.1 and 6.1 μM, respectively) (Kim et al. 2020). The hypoglycemic activity of butyrolactone I (**100**), a polyketide produced by several strains of *Aspergillus terreus,* led to the synthesis of butanolide derivatives, after modification of the butyrolactone side chain. Studies using molecular docking simulation compared to experimental results over PTP1B inhibition of the butanolide derivatives pointed that the chiral center at C-4 has deep influence in PTP1B inhibition (Hong et al. 2020).

Neglectine A (**101**), a metabolite bearing a bis-tetrahydrofuran ring, was isolated from endophytic fungus *Pestalotiopsis neglecta*, was able to inhibit PTP1B (IC_{50} 6.7 μg/mL) (Gao et al. 2019a). Other interesting PTP1B inhibitors comprise (+)-palitantin (**102**), isolated from the Antarctic fungus *Geomyces* sp. 3-1 (IC_{50} 7.9 μM) (Yu et al. 2021), and chrysopyrones A (**103**) and B (**104**), metabolites of the deep-sea fungus *Penicillium chrysogenum* SCSIO 07007 (IC_{50} 9.32 and 27.8 μg/mL, respectively) (Han et al. 2020) (Fig. 17.14).

A comprehensive review on antidiabetic fungal agents, with focus on fungal metabolites able to inhibit PTP1B, is available at Nazir et al. (2021), while the review of Hussain et al. (2021) emphasizes the α-glucosidase inhibitors.

Another group of drugs associated to the treatment of diabetes consists of competitive inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonate (Endo 2017). This mechanism is associated with statins, the most effective and best-tolerated agents for treating dyslipidemia, highly prescribed to diabetic individuals. As pointed before, statins are a group of exceptionally successful drugs that lower cholesterol levels in blood,

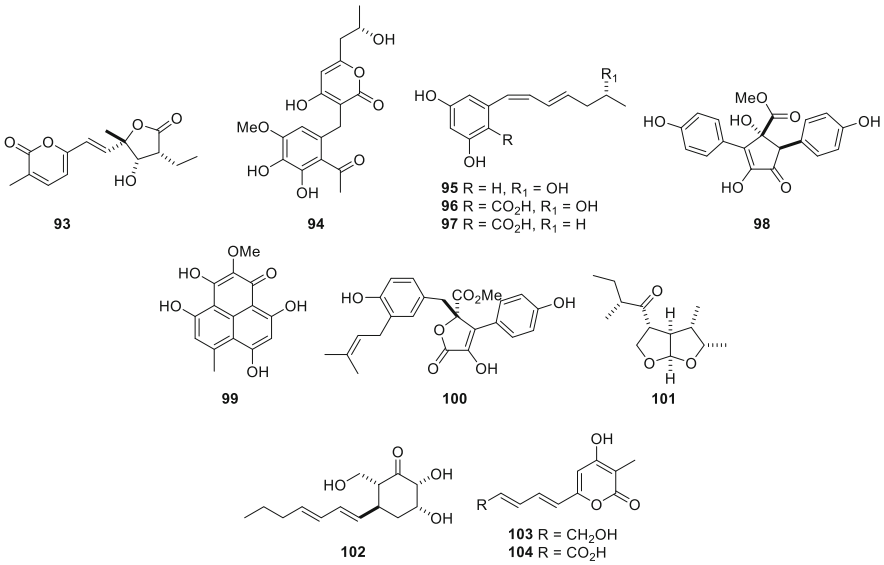


Fig. 17.14 Fungal polyketides with antidiabetic/hypoglycemic effect: penipyrol C (**93**), penicanesin D (**94**), 5-((R,1Z,3E)-6-hydroxy-1,3-heptadien-1-yl)-1,3-benzenediol (**95**), 4-carboxy-5-((R,1Z,3E)-6-hydroxy-1,3-heptadien-1-yl)-1,3-benzenediol (**96**), 4-carboxy-5-((1Z,3E)-1,3-heptadien-1-yl)-1,3-benzenediol (**97**), (±)-tylopilusin D (**98**), funalenone (**99**), butyrolactone I (**100**), neglectine A (**101**), (+)-palitantin (**102**), chrysopyrones A (**103**) and B (**104**)

widely used in the prevention and management of cardiovascular disease, decreasing the risk of heart attack or stroke (Barrios-González et al. 2020). The remarkable safety of statins derives from their unique mechanism of action. When statin is ingested, the drug is routed primarily to the liver, where it inhibits HMG-CoA reductase, lowering cholesterol production. This decrease in liver cholesterol triggers a compensatory feedback loop that increases the number of receptors for low density lipoprotein (LDL), displayed on the hepatocyte membrane. These LDL receptors grab onto LDL and remove it from blood (Endo 2017).

Natural statins, like compactin (**8**) and lovastatin (**9**) (Fig. 17.1), are produced as secondary metabolites, by direct fungal fermentation following a polyketide pathway, predominantly by *Aspergillus* and *Penicillium* species (Subhan et al. 2017). Pravastatin (**105**) (Fig. 17.15) is derived from compactin by biotransformation, and simvastatin (**10**) (Fig. 17.3) is a semi-synthetic derivative of lovastatin (Tobert 2003). Chemically synthesized statins include atorvastatin (**11**) (Fig. 17.1), rosuvastatin, fluvastatin, and pitavastatin (Endo 2017).

Other polyketides are being proposed for hypercholesterolemia treatment, for example, zaragozic acid A (squalestatin) (**106**), B (**107**) (Fig. 17.15), C, D and D2, isolated from different fungi sources, such as *Sporormiella intermedia*, *Leptodontium elatius*, and *Cladosporium cladosporioides* (Lebe and Cox 2019). They are characterized by a 2,8-dioxobicyclic[3.2.1]octane-3,4,5-tricarboxyclic acid core connected to two lipophilic polyketides or fatty acid derived chains (Liu et al. 2017). Their structure comprises two benzoic acids extended with acetate-derived

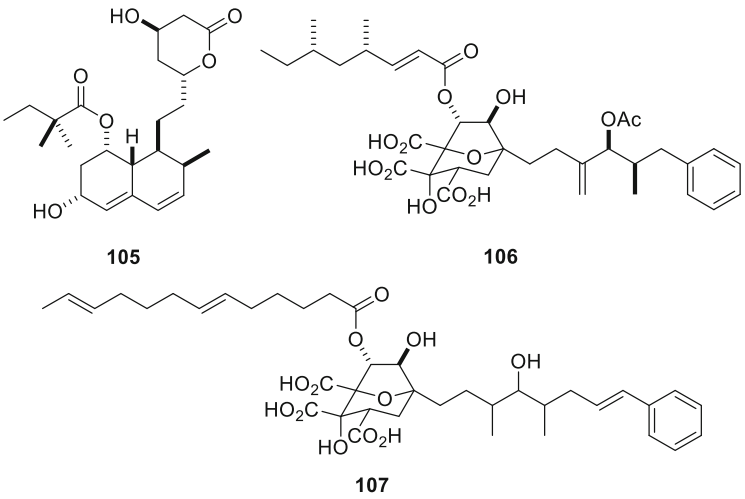


Fig. 17.15 Chemical structure of some fungal polyketides with hypolipidemic activity: the semi-synthetic statin pravastatin (**105**), and zaragozic acids A (**106**) and B (**107**). Other statins are presented on Figs. 17.1 and 17.3

chains and an oxaloacetate unit from the Krebs cycle. Zaragozic acids are inhibitors of fungal and mammalian squalene synthase, the first committed enzyme in sterol synthesis, and an alternative potential target to control cholesterol blood levels (Dufresne et al. 1993; Bergstrom et al. 1995; Rimondi et al. 2021).

17.4.4 Anti-Inflammatory and Immunosuppressant

Besides the effect of lowering LDL and cholesterol, statins (Figs. 17.1, 17.3 and 17.15) present cholesterol-independent pleiotropic effects. This topic remains controversial, however, there is consistent evidence that statins affect downstream steps of the mevalonate pathway, thus influencing inflammation, immunomodulation, the nitric oxide production, the coagulation cascade, and other biochemical processes (Steffens and Mach 2004; Undas et al. 2005; Kagami et al. 2009; Oesterle et al. 2017; Rimondi et al. 2021). The anti-inflammatory effects of statins make them promising candidates for the future treatment of inflammatory and immune-mediated disorders.

In fact, statins were recommended as a first-line therapy for atherosclerotic cardiovascular disease (ASCVD) risk reduction, based on high-quality data regarding the consistent reduction of events with their regular use, in primary and secondary prevention of atherosclerosis (Adhyaru and Jacobson 2018). Chronic inflammation has been recognized as one of the most important pathophysiological mechanisms of initiation and progression of atherosclerosis, thus, the suppression of inflammatory response by statins contributes to their generally positive action in

atherosclerosis and represents an important part of the vasculo- and athero-protective effect of this drug class (Satny et al. 2021).

The pleiotropic effects proposed for statins, that may contribute to reduce ASCVD, are plaque stabilization with increased fibrous cap thickness and macrocalcification, reduced platelet aggregation, decreased oxidative stress by reducing reactive oxygen species, improved vascular tone by increasing nitric oxide, and anti-inflammatory effects with reduction of interleukins and decreased leukocyte-endothelial adhesion (Almeida and Budoff 2019). The cytokines secreted by adipose tissue, so-called adipokines, have been proved to play a critical role in inflammation, and atherosclerosis development and vulnerability. Up to now, robust evidence implicates a significant statin-induced reduction of pro-inflammatory adipokines IL-6, TNF-α and visfatin (Kadoglou et al. 2021).

Additionally, due to their anti-inflammatory and immunomodulatory features, statins have been studied as complementary therapy for various autoimmune diseases, like multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis, psoriasis, and antiphospholipid syndrome (Dehnavi et al. 2020). The underlying mechanisms, the precise doses required to exert immunomodulatory effects, as well as the doses that trigger a statin-mediated autoimmune response as a side effect of dyslipidemia therapy, remain unclear.

Atorvastatin (**11**) and simvastatin (**10**) are among the most studied drugs to treat autoimmune diseases. Simvastatin (**10**) has shown beneficial effects on reducing the rate of brain atrophy and slowing the deterioration of disability in progressive multiple sclerosis, independently of serum cholesterol reduction (Eshaghi et al. 2019). Evidence suggests this may be due to its effect on vascular function and cell protection. Several clinical trials have shown benefits or no significant difference in clinical outcomes of patients treated with statins alone or in combination with other drugs (Dehnavi et al. 2020). Although, the USA Food and Drug Administration (FDA) has not yet approved statins for multiple sclerosis treatment.

Several other fungal polyketides have anti-inflammatory and immunosuppressive properties. Mycophenolic acid (**1**), already cited due to its historical role as an immunomodulatory agent, has also anti-inflammatory properties. Its ester derivative, mycophenolate mofetil (**2**) (Fig. 17.1) is a prodrug with improved bioavailability, efficacy, and has better side-effect profile. This ester is mostly hydrolyzed in the upper gastrointestinal tract, to the active drug, mycophenolic acid, a selective, noncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH is an important enzyme in the de novo pathway of guanine nucleotide synthesis (Ransom 1995). Mycophenolate mofetil (**2**) depletes guanosine nucleotides preferentially in T and B lymphocytes to inhibit their proliferation. Considering that clonal expansion of lymphocytes is a hallmark of the adaptive immunity, mycophenolate mofetil inhibits cellular and humoral immune response. It also inhibits the glycosylation and expression of adhesion molecules, and the recruitment of lymphocytes and monocytes into sites of inflammation (Allison 2005).

Mycophenolate mofetil (**2**) is recommended for prophylaxis of solid organ transplant rejection, typically used in combination with glucocorticoids, as part of

the immunosuppressive induction therapy for transplanted patients. It is also a mainstay of the therapy in lupus nephritis and a second-line immunosuppressive agent in various immunological diseases (e.g., renal vasculitis, idiopathic nephrotic syndrome, scleroderma, and myasthenia gravis) (Morren and Li 2020; Walters et al. 2020; Lugani et al. 2021; Martini et al. 2021). Mycophenolate mofetil (**2**) and enteric-coated mycophenolate sodium (**3**) (EC-MPS) are drugs approved for the immunosuppressive therapy in solid organ transplantation, but the use is off label for all immunological diseases (Ehren et al. 2021).

Moreover, evidence is accumulating that mycophenolate mofetil (**2**) has clinical utility to treat other autoimmune diseases, like systemic lupus erythematosus (Trindade et al. 2021). This compound has been also trialed for a first-line treatment of immune thrombocytopenia, in addition to a glucocorticoid, and results showed greater response, besides a lower risk of refractory or relapsed immune thrombocytopenia, in comparison to the standard glucocorticoid monotherapy (Bradbury et al. 2021).

In addition, experimental models have confirmed that mycophenolic acid (**1**) reduces the production of lymphocyte-derived cytokines, such as interferon-gamma and tumor necrosis factor alpha, pro-inflammatory cytokines produced by monocytes, along with the inhibition of primary humoral responses. In turn, mycophenolate mofetil (**2**) is an effective treatment for induction and maintenance of remission of antineutrophil cytoplasmic antibody-associated vasculitis (AAV) (Koukoulaki and Iatrou 2019).

17.4.5 Neuroprotective

Neurodegenerative diseases are currently a serious and complex public health problem. Humanity has reached new levels of health and well-being, along with an increase in life expectancy. However, well-being in old age has been greatly affected by neurodegenerative diseases that limit various cognitive functions, along with several other progressive symptoms that contribute to the withering of the individual as the age advances (Takahashi et al. 2020). Awareness of the severity of these diseases has prompted a large portion of the population to create healthy habits to delay the onset of degenerative diseases. New drugs for the treatment of patients with different degrees of degeneration are still needed, even with palliative effects. Neuroprotective compounds, to be ingested as medicines or nutraceuticals, are also necessary. These agents can work as hormones, neurotransmitter modulators, neurotrophic factors, antioxidants, or anti-inflammatory agents. In this way, a significant number of fungal polyketides are under study to understand their role in several aspects of neuroprotection (Tong et al. 2021; Wu et al. 2021).

Currently, virtual screening has been widely used in the search for new acetylcholinesterase inhibitors, with the advantage of allowing screening of large chemical databases, including synthetic derivatives, in the search for novel scaffolds (David et al. 2021). Diketopiperazine alkaloids are classical fungal polyketide, produced by

a variety of species, such as the mangrove-sediment-derived fungus *Aspergillus* sp. SCSIO41407 (Cai et al. 2021), and the Antarctic fungus *Penicillium* sp. SCSIO 05705 (Hu et al. 2021). In some studies, acetylcholinesterase inhibition is confirmed by molecular docking studies, as in the study of Sallam et al. (2021), working with metabolites isolated from a marine endophyte species *Cladosporium cladosporioides*, isolated from the leaves of the mangrove *Avicennia marina*. Endophyte fungal species isolated from plants from *Huperzia* sp. have been described as good sources of acetylcholinesterase inhibitors, since these herbs, used in the traditional Chinese medicine, produce huperzine A (**108**), a metabolite known due to its protective brain effects (Cao et al. 2021; Xiao et al. 2022) (Fig. 17.16).

However, metabolites with other mechanisms of neuroprotective activity have also been described (Fig. 17.16). The cytoprotective effect of terphenyllin (**109**), 3″-hydroxyterphenyllin (**110**), and 3′-hydroxyterphenyllin (**111**) against rotenone- and paraquat-induced oxidative stress in neuro-2a cells was reported by Yurchenko et al. (2021). The hydroxyl groups at C-3 and C-4 positions in the structures of these *p*-terphenyl polyketides, isolated from *Aspergillus candidus* KMM 4676, were claimed to modulate the activity, which is also influenced by the strong activity in ROS scavenging. Phomopsol (**112**), an unusual N-oxide alkaloid isolated from a mangrove endophyte species of *Phomopsis* sp., was also reported as a neuroprotective agent against corticosterone-induced injury in PC12 cells, as determined by MTT assays (Li et al. 2019).

Hispidin (**113**) (Fig. 17.16), produced by various mushrooms from the genus *Phellinus* and *Inonotus*, is another good candidate as a neuroprotective compound. This antioxidant compound was reported to activate the JNK-pathway and Nrf2 signaling. In addition, **113** can act in Parkinson and Alzheimer diseases, inhibiting BACE 1, which is responsible for stimulating the release of β-amyloid, a toxic

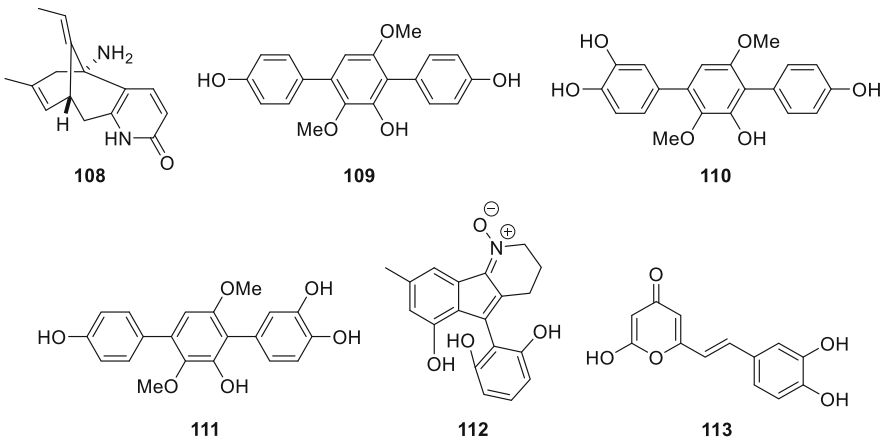


Fig. 17.16 The neuroprotective fungal polyketides huperzine A (**108**), terphenyllin (**109**), 3″--hydroxyterphenyllin (**110**), 3′-hydroxyterphenyllin (**111**), phomopsol (**112**), and hispidin (**113**)

peptide, in the brain. Several other effects of hispidin (**113**) were reviewed by Palkina et al. (2021).

17.4.6 Anticancer

For decades, fungal metabolites have been researched as lead compounds for the development of chemotherapeutics directed toward many types of cancer diseases. Considering the diversity of structures and biological properties presented by polyketides, this group offers new chemotherapeutical approaches to overcome issues that commonly affect the success of cancer treatment, such as drug resistance, insufficient selectivity to tumor cell, and side effects.

Marine fungi are revealed as a rich source of bioactive polyketides, including against cancer. Among polyketides of the 12-membered macrolide class, obtained by Sun et al. (2013) from the marine fungus *Dendrodochium* sp., isolated from the South China Sea *Holothuria nobilis* Selenka, ten structurally diverse dendrodolides were able to elicit in vitro cytotoxic effects against human tumor cell lines from hepatoma origin [dendrodolides A-D, H, I, and K (**114–117, 120–122**)] or colorectal carcinoma [dendrodolides C, E, G, I, K, and L (**116, 118, 119, 121–123**)] (Table 17.2, Fig. 17.17).

Emodin (**124**) and questin (**125**) are polyketones and quinones, isolated from the sea-cucumber-associated fungus *Aspergillus terreus*, which demonstrated cytotoxic effects on human oral epithelial cancer cells (KB) and multidrug-resistant KB cells (KBv200) (Xia et al. 2014a). Found in another sea-cucumber-associated fungus of the genus *Fusarium*, javanicin (**126**), norjavanicin (**127**), and fusarubin (**128**) were also able to inhibit KB and KBv200 cell lines (Xia et al. 2014b) (Table 17.2, Fig. 17.17).

Penicitrinone A (**129**), a polyketide derivative of citrinin, isolated from marine-derived *Penicillium purpurogenum* (G59 strain) by Wu et al. (2015), demonstrated cytotoxicity to human cancer cell lines from leukemias, uterus, and gastric carcinomas. The same compound was later obtained from *Penicillium citrinum* (SCSIO 41017) by Salendra et al. (2021), eliciting inhibitory effects toward the human breast cancer cell line MCF-7, comparable to taxol positive control (Table 17.2, Fig. 17.17).

Among the anticancer anthraquinones, one example is the polyketide 1,3-dihydroxy-6-methyl-7-methoxyanthraquinone (**130**), isolated from the marine thermophilus fungus *Thermomyces lanuginosus*. According to Sobolevskaya et al. (2021), it was responsible of reducing cell viability of a human drug-resistant prostate cancer cell line, with lower effects on non-tumoral control cell line. The compound (**130**) also elicited the reproductive death of those cancer cells, as revealed in colony formation assay (Table 17.2, Fig. 17.17).

Sulochrin (**131**) is another marine-derived fungal metabolite with in vitro anticancer activities. It was isolated from *Aspergillus falconensis* by El-Kashef et al. (2021), using the OSMAC approach, among other 10 polyketide compounds.

Table 17.2 Fungal polyketides with anticancer effect

Metabolite	Fungal Source	Activity	Reference
Pchaeglobosal B (**41**)	Endophytic *Chaetomium globosum* (P2-2-2)	Cytotoxicity to MCF-7, HepG2, HT29, A549, and CT26 (IC_{50} 1.04–9.90 μM) Apoptosis induced on CT26 (at 3-4 μM) and HT29 cells (at 12–15 μM), with cell cycle arrest at S phase on CT26 cells, and at G0/G1 phase on HT29 cells	Peng et al. (2020)
Zaragozic acid A (**106**)	*Sporormiella intermedia*, *Exserohilum khartoumense*	Inhibition of squalene synthase (IC_{50} 0.5 nM) and Ras FPTase (IC_{50} 250 nM)	Dufresne et al. (1993)
		Blockage of cholesterol synthesis and proliferation inhibition on LNCaP (40 μM)	Brusselmans et al. (2007)
Zaragozic acid D, and D_2	*Amauroascus niger* MF5683	Inhibition of squalene synthase (IC_{50} 6 nM and 2 nM, respectively) and Ras FPTase (IC_{50} 100 nM)	Dufresne et al. (1993)
Hispidin (**112**)	Fungus *Phellinus linteus* and *Inonotus* sp	Dose-dependent cytotoxicity to human cancer cell lines SCL1, Capan-1, BxPC-3, AsPC-1, A549, SGC-7901, HepG2, and HCT116, and to murine cancer cell line CMT-93	Gonindard et al. (1997), Lim et al. (2014), Nguyen et al. (2016), Chandimali et al. (2018)
		Dose-dependent increase of apoptosis (25.23–40.4% at 50–200 μg/mL) in CMT-93 cells, with cell cycle arrest at sub-G1 phase, increased expression of apoptotic proteins (intrinsic and extrinsic pathways), and high levels of ROS	Lim et al. (2014)

(continued)

Table 17.2 (continued)

Metabolite	Fungal Source	Activity	Reference
		Dose-dependent increase of apoptosis on BxPC-3 and AsPC-1. Suppressive effects on BxPC-3 $CD44^+$ cells (CSC), enhanced with gemcitabine: cell cycle arrest at G1 phase, apoptosis, inhibition of cell proliferation, migration and invasion, low expression of stem cell markers	Chandimali et al. (2018)
		Selective induction of autophagic and necrotic pathways in cancer cells (SGC-7901, A549, and HepG2 cells), through microtubule depolymerization and lysosomal membrane permeabilization	Lv et al. (2017)
		Low cytotoxic effects on non-tumoral cells MRC5 and GES-1	Gonindard et al. (1997), Lv et al. (2017)
		Protective effect against H_2O_2-induced apoptosis in non-tumoral H9c2, with ROS reduction, inhibition of pro-apoptotic proteins, and activation of Akt/GSK-3β and ERK1/2 signaling pathways	Kim et al. (2014)
Dendrodolides A-D, H, I, and K (**114–117, 120–122**)	Marine *Dendrodochium* sp.	Cytotoxicity to SMMC-7721 (IC_{50} 14.7–24.8 μg/mL)	Sun et al. (2013)
Dendrodolides C, E, G, I, K, and L (**116, 118, 119, 121–123**)		Cytotoxicity to HCT116 (IC_{50} 5.7–26.5 μg/mL)	
Emodin (**124**)	Marine *aspergillus terreus*	Cytotoxicity to KB (IC_{50} 32.97 μg/mL) and multidrug-resistant KBv200 (IC_{50} 16.15 μg/mL)	Xia et al. (2014a)

(continued)

Table 17.2 (continued)

Metabolite	Fungal Source	Activity	Reference
Questin (**125**)		Cytotoxicity to KB and multidrug-resistant KBv200 ($IC_{50} > 50$ μg/mL for both)	
Javanicin (**126**)	Marine *fusarium* sp.	Cytotoxicity to KB (IC_{50} 2.9 μg/mL) and multidrug-resistant KBv200 (IC_{50} 5.91 μg/mL)	Xia et al. (2014b)
Norjavanicin (**127**)		Cytotoxicity to KB (IC_{50} 10.6 μg/mL) and multidrug-resistant KBv200 (IC_{50} 12.12 μg/mL)	
Fusarubin (**128**)		Cytotoxicity to KB (IC_{50} 9.61 μg/mL) and multidrug-resistant KBv200 (IC_{50} 6.74 μg/mL)	
Penicitrinone A (**129**)	Marine *penicillium purpurogenum* (G59)	Cytotoxicity to K562, HL-60, HeLa, and BGC-823 (IC_{50} 34.8–61.5 μM)	Wu et al. (2015)
	Marine *Penicillium citrinum* (SCSIO 41017)	Cytotoxicity to MCF 7 (IC_{50} 1.3 μM); positive control taxol (IC_{50} 1.4 μM)	Salendra et al. (2021)
1,3-dihydroxy-6-methyl-7-methoxyanthraquinone (**130**)	*Thermomyces lanuginosus* KMM 4681	Selective cytotoxicity to drug-resistant 22Rv1 (35% viability at 100 μM) in comparison to non-cancer PNT-2 (65% viability at 100 μM) Inhibition of colony formation of 22Rv1 (70% at 50 μM)	Sobolevskaya et al. (2021)
Sulochrin (**131**)	*Aspergillus falconensis*	Affinity to CDK-2 ($\Delta G = -25.03$ kcal/Mol), TOP-2 (−12.11 kcal/Mol), and MMP-13 (−33.83 kcal/Mol), indicated by molecular docking experiments Cytotoxicity to L5178Y (IC_{50} 5.1 μM) Inhibition of cell	El-Kashef et al. (2021)

(continued)

Table 17.2 (continued)

Metabolite	Fungal Source	Activity	Reference
		migration to MDA-MB-231 (70 μM)	
4,5-dihydroxy-6-(6′--methylsalicyloxy)-2-hydroxymethyl-2-cyclohexenl-one (**132**)	*Epicoccum sorghinum* from sorghum	Cytotoxicity to A549, HepG2, and MDA-MB-231 (IC_{50} 1.86–18.31 μM); doxorubicin positive control (IC_{50} 0.2–0.47 μM)	Chang et al. (2021)
Gentisyl alcohol (**133**)			
6-(hydroxymethyl)-benzene-1,2,4-triol (**134**)			
Cytochalasin E (**135**)	*Aspergillus clavatus*	Inhibition of angiogenesis and autophagy on A549 cells, when associated to bortezomib chemotherapy	Takanezawa et al. (2018)
Myceliothermophin F (**136**) (polyketide-amino acid hybrid)	*Thermothelomyces thermophilus*	Cytotoxicity to DLD-1, Hep3B, HepG2, and HGC-27 (IC_{50} 0.33–0.89 μg/mL)	Gao et al. (2019b)
Globosuxanthone F (**137**)	Marine *Pleosporales sp.* NBUF144	Cytotoxicity to CCRF-CEM (IC_{50} 0.46 μM)	Zhou et al. (2021)
Alterperylenol (**138**)	Endophytic *Alternaria* sp. MG1	Cytotoxicity to NCI-H1299 (98%) and HT-1080 (96.2%) at 20 μM	Tian et al. (2021)
Fusaketide A (**139**) and B (**140**)	Entomogenous *fusarium equiseti*	Cytotoxicity to MCF-7, MGC-803, HeLa and Huh-7 (IC_{50} 2.4–69.7 μg/mL) Dose-dependent inhibition of migration and invasion, and apoptosis induction by fusaketide B on MGC-803	Liu et al. (2021)

Notes: **Human cancer cell lines:** KB—oral epidermal carcinoma; KBv200—multidrug-resistant derived from KB; K562—chronic myelogenous leukemia; HL-60—acute promyelocytic leukemia; CCRF-CEM—acute lymphatic leukemia; HeLa—uterus adenocarcinoma; SGC-7901—endocervical adenocarcinoma; LNCaP, 22Rv1—prostate carcinoma; BGC-823, MGC-803—gastric carcinoma; MCF-7, MDA-MB-231—triple-negative breast carcinoma; A549—lung adenocarcinoma; HepG2, SMMC-7721, Huh-7—hepatocarcinoma; HCT116—colorectal carcinoma; HT29—colorectal adenocarcinoma; A549—lung carcinoma; SCL1—skin squamous cell carcinoma; Capan-1, BxPC-3, AsPC-1—pancreatic adenocarcinoma;. **Murine cancer cell lines:** CT26, CMT-93—colorectal carcinoma; L5178Y—lymphoma. **Non-tumoral cell lines:** MRC5—human pulmonary fibroblasts; H9c2—rat embryonic cardiomyoblasts; PNT-2—human prostate cells; GES-1—human gastric epithelial cells. **Enzymes**: CDK-2—human cyclin-dependent kinase 2; TOP-2—human DNA topoisomerase II; MMP-13—matrix metalloproteinase 13. CSC—cancer stem cells. ROS—reactive oxygen species

Molecular docking studies indicated favorable interactions of sulochrin (**131**) to human cyclin-dependent kinase 2 (CDK-2), DNA topoisomerase II (TOP-2), and matrix metalloproteinase 13 (MMP-13), enzymes directly related to tumorigenesis pathways. In addition, in vitro assays revealed that sulochrin (**131**) was cytotoxic to mouse lymphoma cells and inhibit the migration of triple-negative breast cancer cells (Table 17.2, Fig. 17.17).

Exploring other biological effects of secondary metabolites from the sorghum contaminant fungus *Epicoccum sorghinum*, already known to produce potent mycotoxins, Chang et al. (2021) isolated and identified the chemical structures of three polyketides, 4,5-dihydroxy-6-(6′-methylsalicyloxy)-2-hydroxymethyl-2-cyclohexenl-one (**132**), gentisyl alcohol (**133**), and 6-(hydroxymethyl)benzene-1,2,4-triol (**134**), which demonstrated cytotoxicity to human cancer cell lines from lung adenocarcinoma, hepatoma, and breast carcinoma (Table 17.2, Fig. 17.17).

The biological mechanisms of action of some polyketides on cancer are very diverse and reveal potential new targets and strategies for cancer chemotherapy. For example, zaragozic acid A (**106**) (Fig. 17.15, Table 17.2), as well as zaragozic acids D and D2, inhibits the human enzyme Ras farnesyl-protein transferase (FPTase), responsible for the first step of post-translational processing of Ras, a protein expressed by the *ras* oncogene, related to tumorigenesis (Dufresne et al. 1993). Zaragozic acids are also potent inhibitors of squalene synthase, an enzyme with a critical role in de novo synthesis of cholesterol on cancer cells. In fact, zaragozic acid A (**106**) was able to inhibit cholesterol synthesis and membrane exposure, as well as proliferation of androgen-responsive prostate cancer cells (Brusselmans et al. 2007).

Among the fungal PKS-NRPS hybrid cytochalasans, several compounds have been related to anticancer activities. Cytochalasin E (**135**), isolated from *Aspergillus clavatus*, exhibited a potent angiogenesis inhibitory activity, as well as the ability to prevent autophagy, enhancing the effect of the chemotherapeutic bortezomib on human lung cancer A549 cells (Takanezawa et al. 2018). Pchaeglobosal B (**41**) (Table 17.2, Fig. 17.3), a cytochalasan isolated from endophytic *Chaetomium globosum* (P2-2-2), exhibited significant cytotoxic activity against cell lines representative from human breast, liver, colorectal, and lung cancer, and murine colorectal carcinoma, with IC_{50} ranging from 1.04 to 9.90 μM. Moreover, the compound induced death by apoptosis on CT26 and HT29 cell lines, by eliciting cell cycle arrest at early phases of mitosis (Peng et al. 2020).

Nevertheless, hispidin (**113**), already cited in previous sections (Table 17.2, Fig. 17.16), is probably one of the most promising fungal polyketides with anticancer activity, as well as other interesting biological properties such as antioxidant, hypoglycemic, anti-inflammatory, neuroprotective, and antiviral, besides strong evidences of low toxicity to humans (Palkina et al. 2021). Several cancer cell lines from different origins were found to be sensitive to hispidin (**113**), like those from carcinoma of human keratinocytes, pancreatic ductal adenocarcinoma, lung carcinoma, and endocervical adenocarcinoma, as well as human and murine colon carcinoma (Gonindard et al. 1997; Lim et al. 2014; Nguyen et al. 2016; Lv et al. 2017). In counterpart, **113** showed low cytotoxicity on non-tumoral cell lines, such as human pulmonary fibroblasts and gastric epithelial cells (Gonindard et al. 1997;

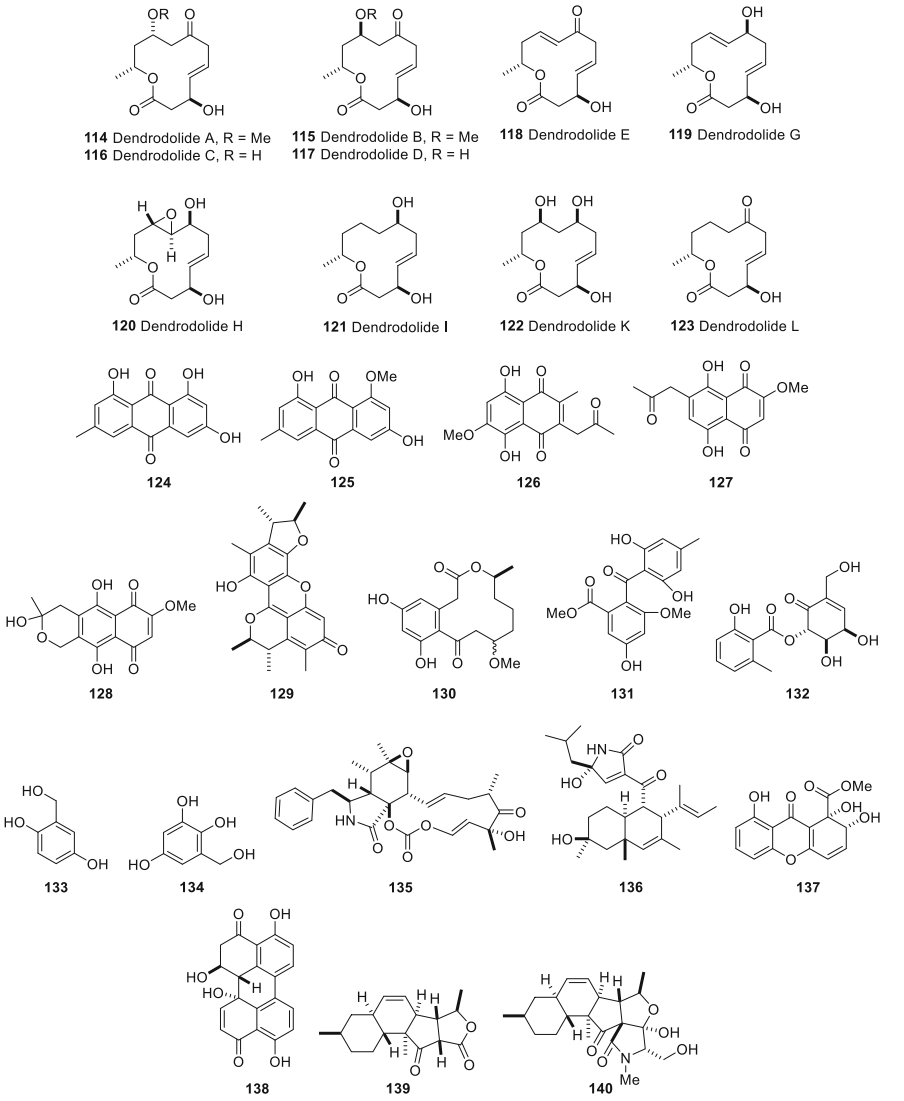


Fig. 17.17 Some prominent fungal polyketides with anticancer potential: dendrodolides A-D, E, G, H, I, K, and L (**114–123**), emodin (**124**), questin (**125**), javanicin (**126**), norjavanicin (**127**), fusarubin (**128**), penicitrinone A (**129**), 1,3-dihydroxy-6-methyl-7-methoxyanthraquinone (**130**), Sulochrin (**131**), 4,5-dihydroxy-6-(6′-methylsalicyloxy)-2-hydroxymethyl-2-cyclohexenl-one (**132**), gentisyl alcohol (**133**), 6-(hydroxymethyl)benzene-1,2,4-triol (**134**), cytochalasin E (**135**), myceliothermophin F (**136**), globosuxanthone F (**137**), alterperylenol (**138**), Fusaketide A (**139**) and B (**140**)

Lv et al. 2017), and even protective effects against oxidative stress and apoptosis on rat embryonic cardiomyoblasts (Kim et al. 2014). The selective mechanisms of action of hispidin (**113**) on cancer cells have been related to a potent inhibition of protein kinase C (IC_{50} 2 x 10^{-6} mol/L), which is involved on signal-transduction pathways (Gonindard et al. 1997), and to the induction of intrinsic and extrinsic apoptosis pathways, mediated by the generation of reactive oxygen species (ROS) (Lim et al. 2014), as well as autophagic and necrotic pathways (Lv et al. 2017). Other promising results were presented by Chandimali et al. (2018), studying cancer stem cells (CSC), known to be responsible for metastasis and chemoresistance in pancreatic adenocarcinoma and other aggressive cancer types. Hispidin (**113**) was able to significantly inhibit stemness of BxPC-3 $CD44^+$ CSC, enhancing the effects of gemcitabine-associated treatment.

Other examples of polyketides with anticancer activities, such as the polyketide-amino acid hybrid metabolite myceliothermophin F (**136**), globosuxanthone F (**137**), alterperylenol (**138**), fusaketide A (**139**) and B (**140**), are indicated on Table 17.2.

17.4.7 Other Biotechnological Uses of Polyketides

Fungal polyketides have other important uses in diverse areas, herein exemplified in the control of phytopathogens and in food industry. These are very different applications, but the outcomes are very promising. Starting with their use in agriculture to control several organisms, natural polyketides are eco-friendly alternatives for biological control of organisms that causes global losses of over 20% of many crops worldwide (Xu et al. 2021). The chemical structures of some fungal polyketides active against some major phytopathogens are shown in Fig. 17.18 and the corresponding spectrum of activity are presented in Table 17.3.

Regarding the use of fungal polyketides as pigments, the azaphilones (Fig. 17.19) play an important role in this field, standing out for their yellow [monascin (**150**)], orange [rubropunctatin (**151**)], and red [rubropunctamine (**152**)] colors. These polyketides contain a pyrone–quinone core, a chiral quaternary center, and hydroxyl groups as substituents. Orange-colored azaphilones, such as rubropunctatin (**151**), usually possess a heterocycle containing a pyranyl oxygen that is susceptible to aminophilic reactions, where the pyran oxygen atom is exchanged for a nitrogen atom derived from peptides, nucleic acids, proteins, and others. This exchange alters the absorption of the pigment, that goes from orange to red, as occurs on rubropunctamine (**152**), frequently also altering its biological properties (Pimenta et al. 2021).

Other biological activities include nitric oxide (NO) production, antioxidant activity, inhibition of biofilm formation, phytotoxicity, insecticidal action, and the inhibition of several enzymes committed to distinct metabolic pathways, as extensively reviewed by Wang et al. (2020b), Zheng et al. (2021) and others.

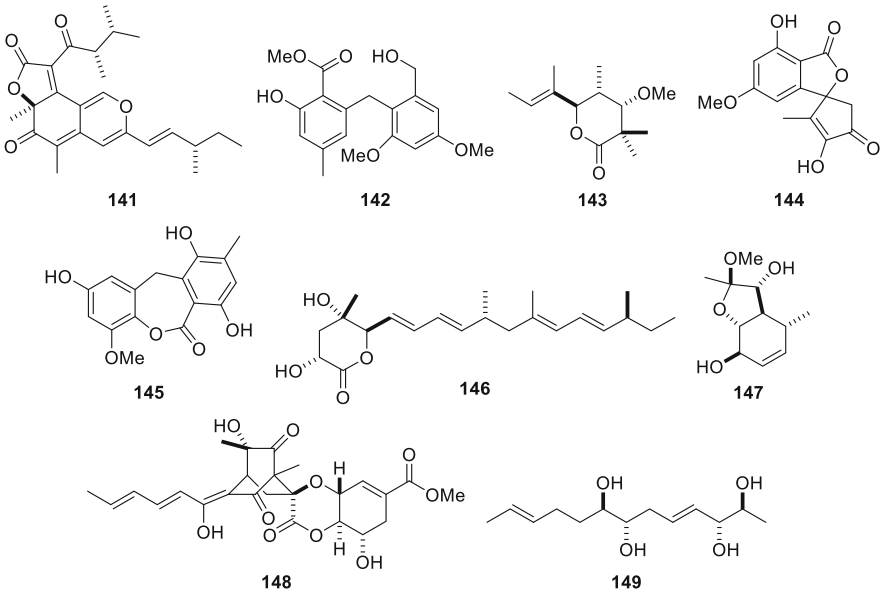


Fig. 17.18 Structures of fungal polyketides with anti-phytopathogenic activities: chaetoviridin A (**141**), epicoccether K (**142**), helicascolide F (**143**), isotalaroflavone (**144**), methyleurotinone (**145**), nafuredin C (**146**), paraverrucsin A (**147**), spirosorbicillinol D (**148**), and triharzianin B (**149**)

17.5 Final Considerations

Polyketides have been widely produced as bioactive fungal metabolites, such as cytochalasans, isoindole macrocyclic derivatives, hybrid peptide-polyketide cyclic depsipeptides, and other uncommon compounds with unprecedented carbon skeletons. Among the fungi that stand out as natural sources of these remarkable products, terrestrial endophytic fungi have been extensively studied, but marine fungi are also prominent contributors. In the review of Zheng et al. (2021), 69 new polyketides, produced by endophytic fungi isolated from different host plants, were reported only in the period of 2017–2019. According to Wang et al. (2020b), 221 new polyketides with specific antimicrobial activities have been isolated from marine fungi, accounting for 81.2% of all the natural products from these organisms, reported from 1998 to 2019.

The pharmaceutical use of fungal polyketides has been recognized early and some of them conquered a prominent position on the world stage, increasing human life expectancy with applications such as dyslipidemic agents, antibiotics, immunosuppressants, antiparasitic, as well as other biotechnological uses, such as anti-phytopathogens and insecticides. Moreover, polyketides have demonstrated to inhibit a range of cancer cells, showing good prospects for the development of new anticancer drugs. The chemistry and biosynthesis of this class have been widely

Table 17.3 Fungal polyketides with anti-phytopathogenic activities

Metabolite	Fungal Source	Phytopathogen Target	Reference
Strobilurin A (**12**)	*Strobilurus tenacellus*, *Oudemansiella mucida*, and *Bolinea lutea*	Ascomycetes, basidiomycetes, and oomycetes	Wang et al. (2021b)
Dendrodolide E (**118**)	*Plenodomus influorescens* and *Pyrenochaeta nobilis*	*Xanthomonas campestris* and *Phytophthora infestans*	Oppong-Danquah et al. (2020)
Chaetoviridin A (**141**)	*Chaetomium globosum*	*Sclerotium rolfsii, Macrophomina phaseolina, Sclerotinia sclerotiorum,* and *Fusarium oxysporum*	Kumar et al. (2021)
Epicoccether K (**142**)	*Epicoccum sorghinum* derived from *Myoporum bontioides*	*P. italicum* and *F. graminearum*	Junjie et al. (2021)
Helicascolide F (**143**)	*Talaromyces assiutensis* JTY2	*Alternaria brassicicola, Phytophthora parasítica var. nicotianae, Colletotrichum capsici, Bipolaris oryzae, Diaporthe medusaea* Nitschke, and *Ceratocystis paradoxa* Moreau	Li et al. (2021)
Isotalaroflavone (**144**)	*Alternaria alternata ZHJG5* derived from *Cercis chinensis*	*Xanthomonas oryzae* pv. Oryzicola (Xoc) and Rs.	Zhao et al. (2021)
Methyleurotinone (**145**)	*Eurotium rubrum*	*Pectobacterium carotovorum subsp. Carotovorum, Pseudomonas syringae pv. Syringae, Rhizobium radiobacter*, and *Ralstonia solanacearum*	Saad et al. (2021)
Nafuredin C (**146**)	*Trichoderma harzianum* D13	*Botrytis cinérea, Magnaporthe grisea, Phytophthora parasítica, Pestalozzia theae,* and *Valsa mali*	Zhao et al. (2020)
Paraverrucsin A (**147**)	*Paraphaeosphaeria verruculosa*	*C. gloeosporioides, D. glomerata, N. oryzae,* and *P. verruculosa*	Hu et al. (2020)
Spirosorbicillinol D (**148**)	*Trichoderma longibrachiatum*	*Phytophthora infestans*	Ngo et al. (2021)
Triharzianin B (**149**)	*Trichoderma harzianum*	*Aspergillus fumigatus, Trichoderma edulis,* and *Tricholoma matsutake*	Wang et al. (2021f)

studied, and the advances in genetic engineering have allowed the manipulation of biosynthetic pathways, providing a convenient platform to supply new and useful lead compounds. New semi-synthetic and synthetic derivatives have been prepared to increase therapeutic capacity or develop industrial-scale production. This scenario is encouraging, especially given the novelties in the biotechnological exploration of fungi specimens and secondary metabolites from unexpected ecological niches.

By the other side, as demonstrated in this review, a variety of newly identified fungal polyketides, with unprecedent biological mechanisms of action, are still on

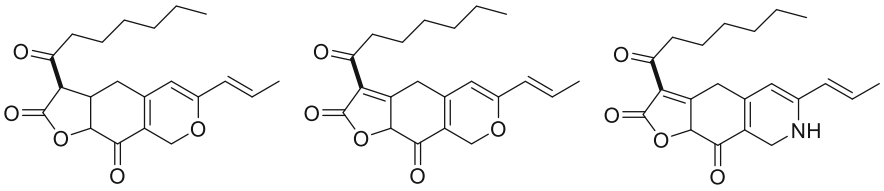


Fig. 17.19 Representative fungal polyketide azaphilones used as pigments: monascin (**150**), rubropunctatin (**151**), and rubropunctamine (**152**)

pre-clinical studies. Attempts should be done to evaluate the in vivo therapeutical effects of these natural compounds and derivatives, as well as the absence of significant side effects, to move forward to clinical trials and to the market as commercial products.

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