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Review

A Decade of Antifungal Leads from Natural Products

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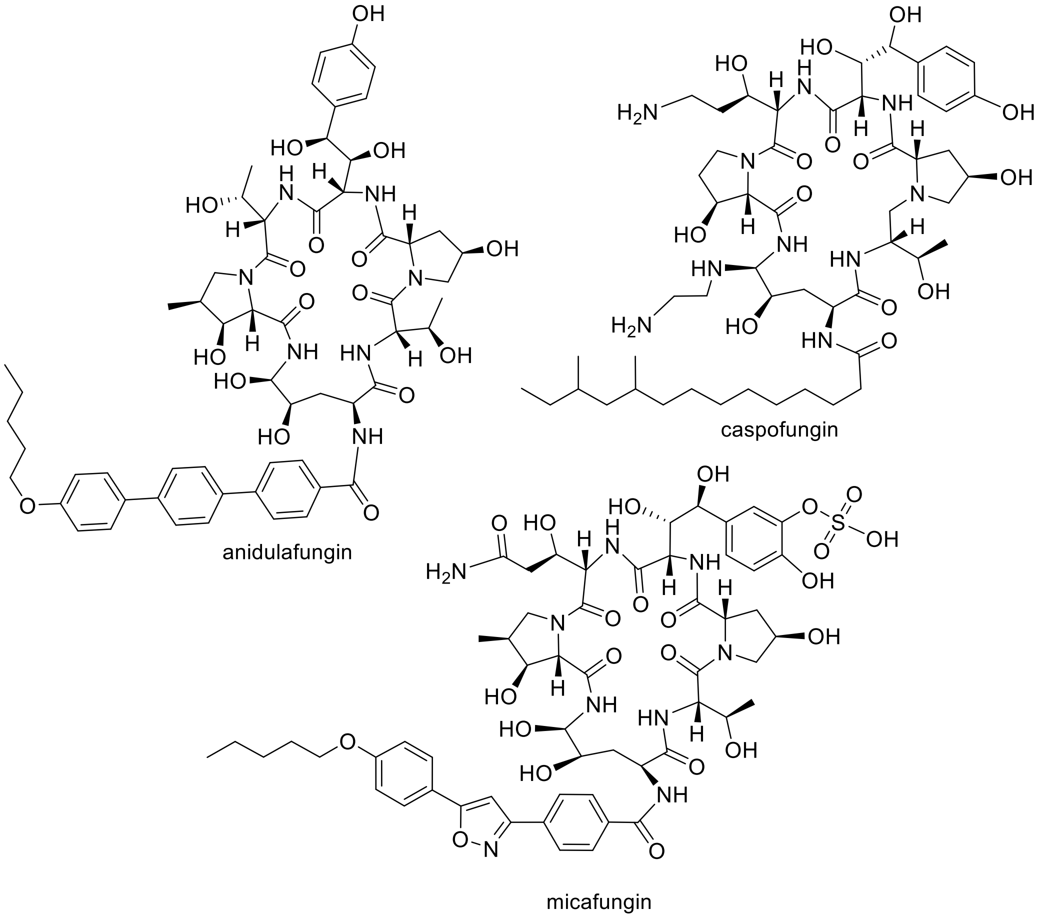
Abstract: In this review, we discuss novel natural products discovered within the last decade that are reported to have antifungal activity against pathogenic species. Nearly a hundred natural products were identified that originate from bacteria, alga, fungi, sponges and plants. Fungi were the most prolific source of antifungal compounds discovered during the period of review. The structural diversity of these antifungal leads encompasses all the major classes of natural products including polyketides, shikimate metabolites, terpenoids, alkaloids and peptides.

Keywords: fungal pathogens; antifungal agents; natural products

1. Introduction

The global increase in antimicrobial resistance among pathogenic bacteria, viruses, fungi and parasites is a serious concern for human healthcare. In the case of fungi, more than one billion individuals worldwide are affected by fungal infections and the associated mortality, over 1.5 million deaths each year, is equivalent to that caused by tuberculosis and more than triple that of malaria [1]. Although relatively rare in healthy individuals, the incidence of superficial and invasive fungal infections has dramatically risen in recent years. This is due to a growing 'at-risk' population with impairments in their immune system, breaches in physical barriers to fungal entry or an altered microbiome. Skin mycoses are predominantly caused by *Trichophyton*, *Microsporum* and *Epidermophyton* genera while *Candida*, *Cryptococcus*, *Aspergillus* and *Pneumocystis* genera, and *Mucorales* are the most common invasive fungal pathogens [2]. Meanwhile, emerging pathogenic fungi that are either new species such as the recently described *Candida auris* [3] or well-known species spreading in their ecological distribution represent additional threats to human health.

The growing challenges posed by fungal diseases are further heightened as antifungal treatment is mainly limited to the azoles and echinocandins. The azoles are the most widely used antifungals and are synthetic compounds that reversibly inhibit cytochrome P450-dependent lanosterol or eburicol 14α-demethylase with moderate specificity for the fungal enzyme over the human counterpart [4]. Nevertheless, they suffer from off-target toxicity as well as issues with fungistatic rather than fungicidal activity in yeast that promotes the development of resistance. The echinocandins are fungal lipopeptide natural products (Figure 1) that are non-competitive inhibitors of 1,3-β-glucan synthase, an enzyme involved in fungal cell wall biosynthesis. While the natural products are not optimal in terms of pharmacokinetics, three semi-synthetic derivatives are approved for clinical use: anidulafungin prepared from echinocandin B, caspofungin prepared from pneumocandin B_0 and micafungin prepared from FR901379 [5]. Although the selectivity of the echinocandin target for fungi provides a good safety profile, these compounds are large peptides, requiring intravenous administration. In addition to the azoles and echinocandins, the polyenes and pyrimidines are two other classes approved for antifungal therapy. The natural product polyenes (Figure 2) are macrolides isolated from various *Streptomyces* strains. The prototypical amphotericin B has been in clinical use for the treatment of systemic fungal infections since the 1950s and is still an important option in critical cases. Several additional polyenes -nystatin, natamycin, hamycin and filipin- have received regulatory approval. As a class, the polyenes have significant nephrotoxicity due to their relatively nonselective mechanisms of ergosterol binding and pore formation within the cell membrane [6,7]. Finally, synthetic pyrimidine antimetabolites such as flucytosine interfere with nucleic acid biosynthesis but resistance restricts their application to combination therapy [8].



anidulafungin

caspofungin

micafungin

Figure 1. Semi-synthetic derivatives of the echinocandin family of natural products approved for antifungal therapy.

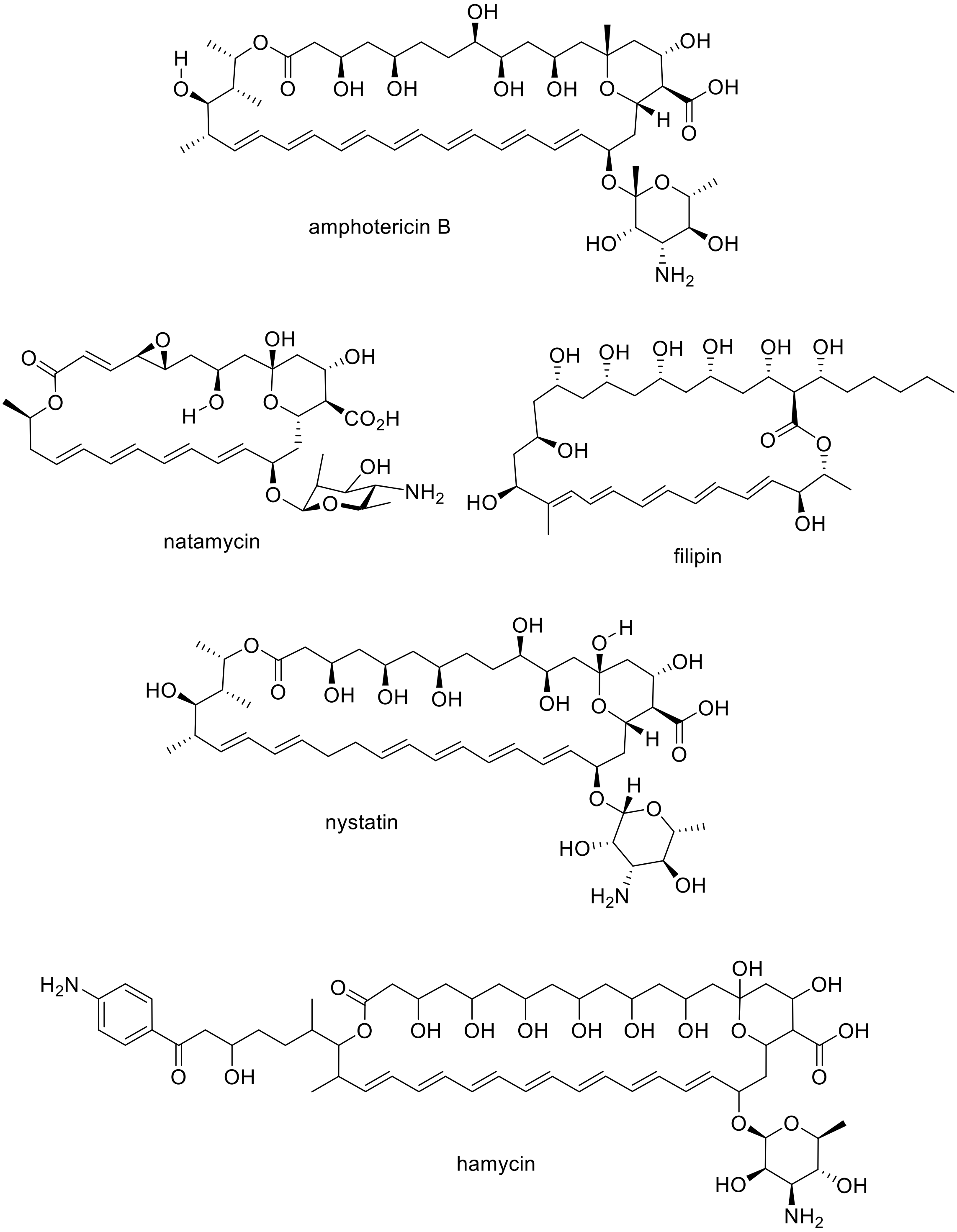


Figure 2. Polyene natural products approved for antifungal therapy.

In summary, the current drugs have numerous limitations including toxicity, drug-drug interactions, poor pharmacokinetics, narrow spectrum of activity and fungistatic versus fungicidal action. These inherent liabilities are exacerbated in immunocompromised patients since their immune system cannot effectively assist in the eradication of the infection, thus requiring complex and prolonged treatment regimens [9]. A further alarming trend is the rising incidence of fungal clinical isolates that are resistant to the currently used antifungals [10,11]. The scale of the problem is highlighted by the fact that the newest class of approved antifungals, the echinocandins, were actually discovered fifty years ago. The American Food and Drug Administration (FDA) has recognized the need for new antifungals by placing *Candida* and *Aspergillus* on their list of qualifying pathogens [12]. Therapies directed against these species will benefit from incentives including an additional five-year marketing exclusivity besides eligibility for designation as a fast-track drug.

2. A pipeline of antifungal natural product leads

While antifungal agents with novel mechanisms of action are in various stages of clinical development, their number is relatively small compared to other therapeutic indications [13]. A pipeline of additional preclinical leads is clearly needed, and natural product screening is an important contributor in this regard. One unique feature of natural products is their high structural diversity, sampling areas of chemical space that are difficult to access through purely synthetic compounds [14,15]. Natural products are also well validated to possess biological activity, with many examples approved as therapeutic agents either in their native form or as semi-synthetic derivatives [16]. For this review, we searched *Natural Product Updates* for publications that reported novel natural products with antifungal activity within the last decade January 2010 - November 2019. From the publications, we selected novel natural products that were active against human pathogenic fungi with a MIC < 10 μg/mL or IC_{50} < 10 μM. In the discussion, we include any information on additional biological activity observed or mechanistic studies on the mode of action. The compounds are classified below according to the type of producing organism.

2.1 Natural product antifungal leads from bacteria and algae

Actinomycetes are the most prolific source of bacterial natural products, and this remains the case for recently discovered antifungal leads (Figures 3-6, **1**-**29**). In addition, there were three examples isolated from non-actinomycete species (Figure 7, **30**-**35**) and two from algae (Figure 8, **36**-**37**). A strain of *Streptomyces albolongus* YIM 101047 isolated from elephant dung produced a number of bafilomycins in laboratory fermentation. The new example 21-deoxybafilomycin A1 (**1**) and the sesquiterpene (1β,4β,4aβ,8aα)-4,8a-dimethyloctahydronaphthalene-1,4a(2*H*)-diol (**2**) displayed antifungal activity against *Candida parapsilosis* with a MIC of 3.2 μg/mL while being inactive against other species [17]. Genome sequencing of the strain suggested the presence of forty-six putative biosynthetic gene clusters [18]. In the course of biosynthetic labelling experiments, it was discovered that supplementation by acetate produced new metabolites in a *Streptomyces hyaluromycini* MB-PO13 strain. Among these, rubromycin CA1 (**3**) was active against Gram-positive bacteria and *Candida albicans* NBRC 1594 with a MIC of 6.3 μg/mL whereas an analogue with an additional alcohol was inactive [19]. A strain of *Actinoalloteichus* isolated from marine sediment was the source of neomaclafungins A–I (**4**-**12**), a series of macrolides of the oligomycin family of antibiotics. The neomaclafungins were active against *Trichophyton mentagrophytes* with MIC values between 1 and 3 μg/mL, compared to 10 μg/mL for oligomycin A [20].

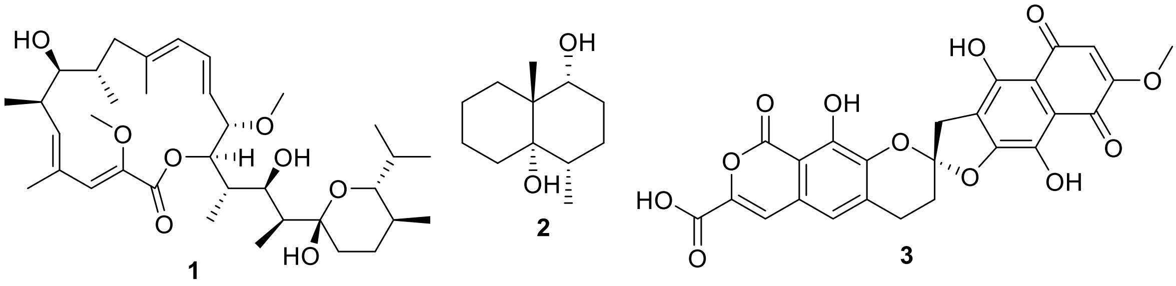


Figure 3. Structures of natural products **1**-**3**

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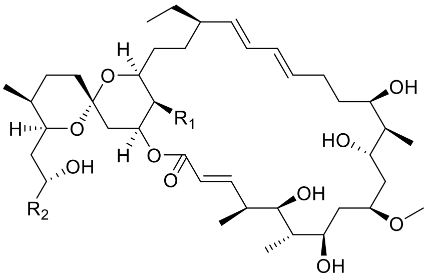
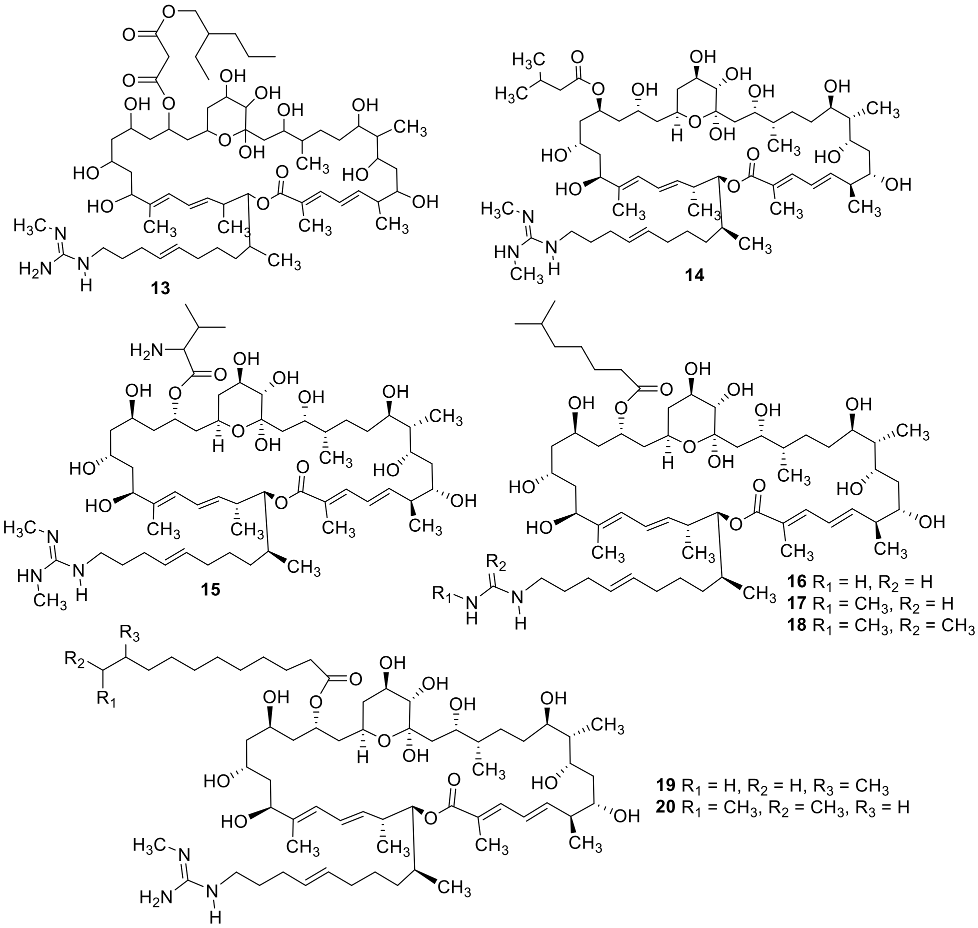


	R$_1$	R$_2$
4	$CH_2CH_2CH_2OH$	CH_3
5	$CH_2CH_2CH(CH_3)OH$	CH_3
6	$CH_2CH_2CH_2OH$	CH_2CH_3
7	$CH_2CH_2CH(CH_3)OH$	CH_2CH_3
8	CH_2CH_3	CH_3
9	$CH_2CH_2CH_3$	CH_3
10	$CH_2CH_2CH_2CH_3$	CH_3
11	$CH_2CH_2CH_3$	CH_2CH_3
12	$CH_2CH_2CH_2CH_2CH_3$	CH_3

Figure 4. Structures of neomaclafungins A-I **4-12**

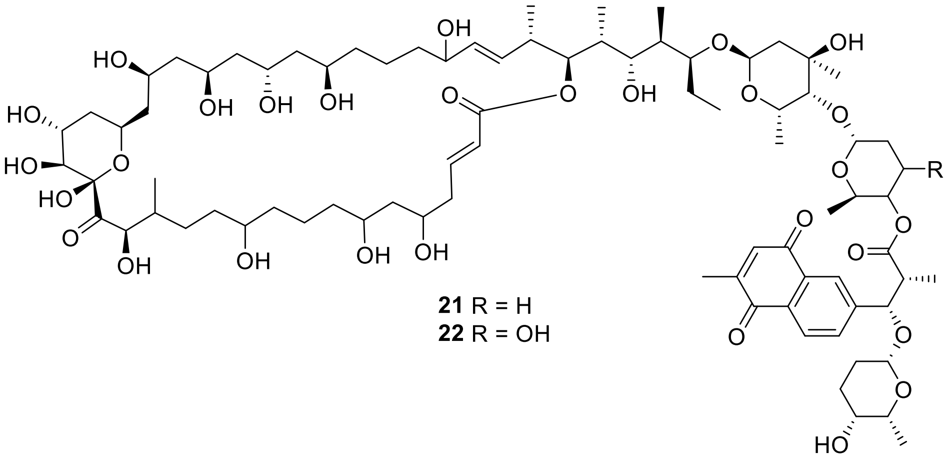
Fermentation of a *Streptomyces* sp. isolated from mangrove rhizosphere soil led to the isolation of a series of azalomycin F natural products (**13-20**) with MIC values of 1.6-6.3 µg/mL against *Candida albicans* as well as having antibacterial and cytotoxic activity [21,22]. Astolides A (**21**) and B (**22**) are polyol macrolides isolated from *Streptomyces hygroscopicus* collected from alkaline soil [23]. The compounds have MICs of 1-2 µg/mL against *Candida albicans*, *Candida tropicalis* and *Aspergillus niger*. Related macrolides caniferolides A-D (**23-26**) were isolated from the marine-derived *Streptomyces caniferus* CA-271066 [24]. Like the astolides, the caniferolides displayed potent antifungal activity with MICs of 0.5-2 µg/mL against *Candida albicans* and 2-8 µg/mL against *Aspergillus fumigatus*, as well as similar levels of cytotoxicity against human tumor cell lines. Caniferolide A was also shown to have in vitro activity against targets relevant to Alzheimer's disease [25]. Enduspeptides A-C (**27-29**) are depsipeptides that differ in the acyl chain attached to the threonine residue and were isolated from a *Streptomyces* sp. The peptides had an IC50 of 2-8 µg/mL against *Candida glabrata* [26].



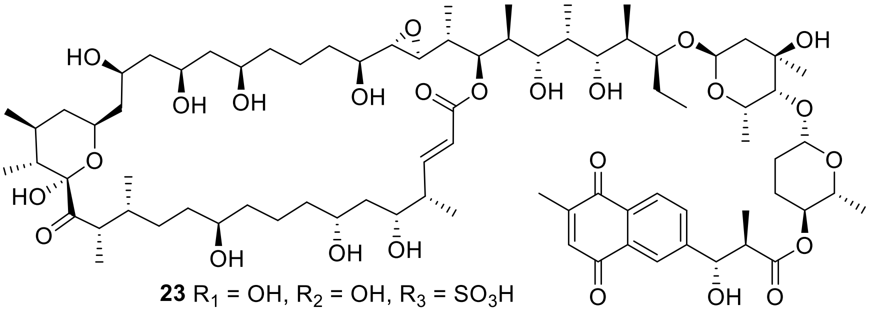
16 R$_1$ = H, R$_2$ = H
17 R$_1$ = CH$_3$, R$_2$ = H
18 R$_1$ = CH$_3$, R$_2$ = CH$_3$

19 R$_1$ = H, R$_2$ = H, R$_3$ = CH$_3$
20 R$_1$ = CH$_3$, R$_2$ = CH$_3$, R$_3$ = H

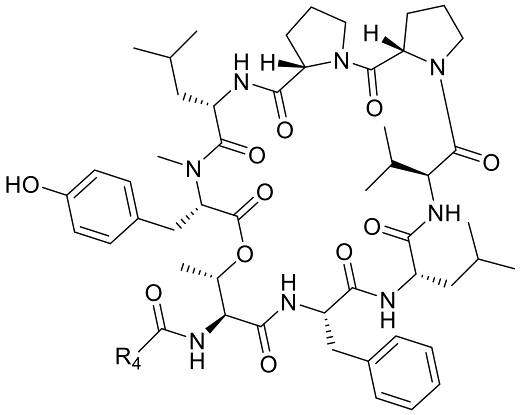
Figure 5. Structures of azalomycin F macrolides **13-20**



21 R = H
22 R = OH



23 R_1 = OH, R_2 = OH, R_3 = SO_3H
24 R_1 = OH, R_2 = OH, R_3 = H
25 R_1 = OH, R_2 = H, R_3 = H
26 R_1 = H, R_2 = OH, R_3 = SO_3H



27 R_4 = CH_2CH_3
28 R_4 = CH_3
29 R_4 = $CH_2CH_2CH_3$

Figure 6. Structures of natural products **21**-**29**

Within the period under review, three antifungal leads were isolated from non-actinomycete bacterial strains. Fermentation of a myxobacterial *Nannocystis* sp. led to the isolation of nannocystin A (**30**) with a novel macrocyclic scaffold. While the compound inhibited *Candida albicans* with a MIC_{50} of 73 nM, it also inhibited human cancer cell lines at a nanomolar level [27]. The mechanism of action involves binding to the eukaryotic translation elongation factor 1α and SAR has been established through the total synthesis of analogues [28]. The burkholdines are lipopeptide antifungal agents previously isolated from *Burkholderia ambifaria* 2.2N, with three new examples Bk-1119, Bk-1213, and

Bk-1215 (**31**-**33**) displaying potent activity against *Candida albicans* and *Aspergillus niger* [29]. Among the burkholdines, Bk-1119 was the most active against *Aspergillus niger* with a MIC of 0.1 μg/mL and also had the best antifungal:hemolytic ratio. Additional analogues were prepared by total synthesis [30]. The Gram-negative bacteria *Chitinophaga pinensis* DSM 28390 produces the novel lantibiotics pinensins A and B (**34**, **35**). Although lantibiotics are typically antibacterial, the pinensins were only weakly so while having MICs of 2-4 μg/mL against yeasts and filamentous fungi [31].

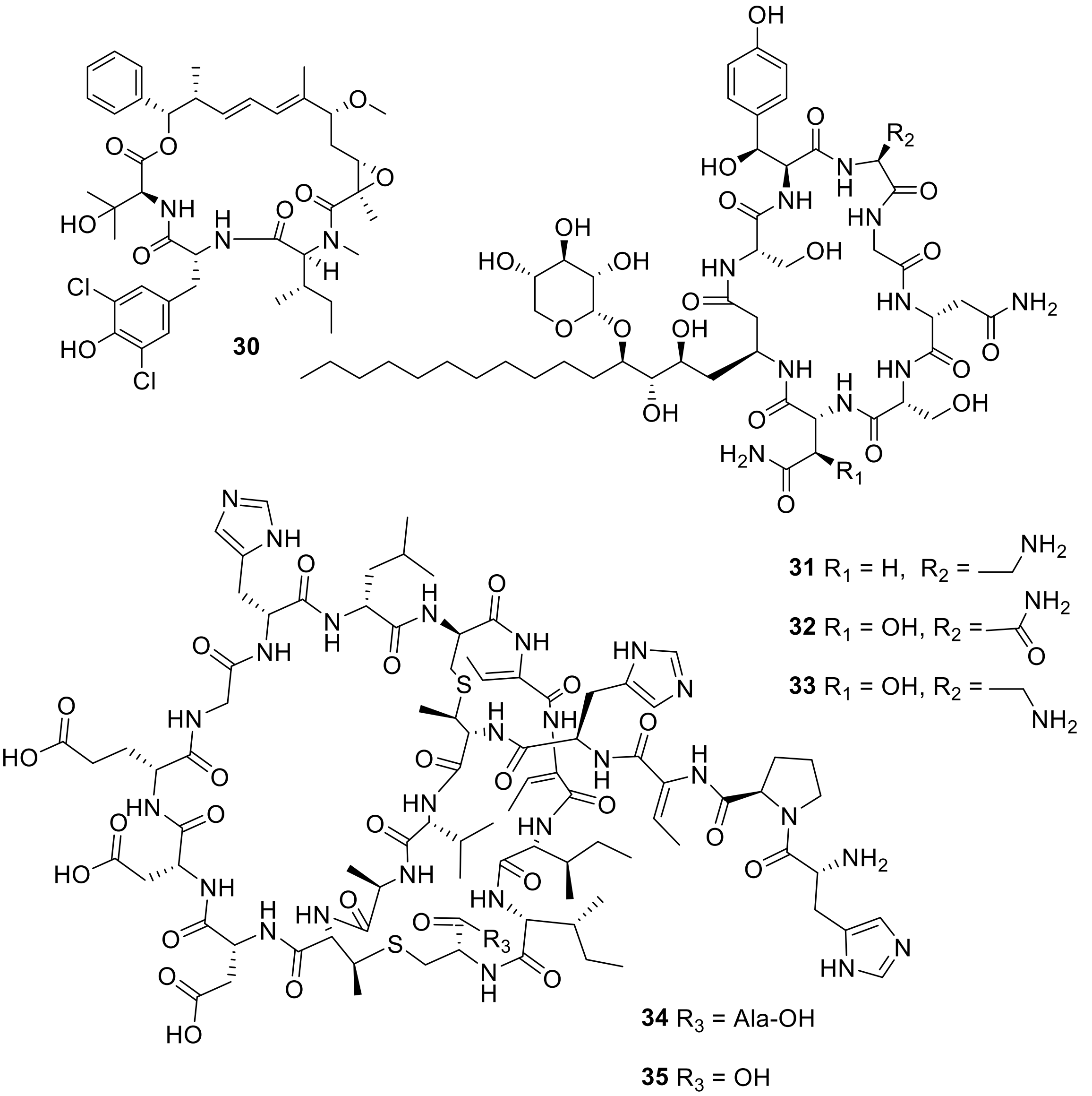


Figure 7. Structures of natural products **30**-**35**

The marine alga *Laurencia* is a prolific producer of secondary metabolites. The sesquiterpene eudesma-4(15),7-diene-5,11-diol (**36**) isolated from a Red Sea sample of *Laurencia obtusa* was antifungal with MIC values of 2-7 μM against *Candida* and *Aspergillus* strains [32]. The prenylated xylene caulerprenylol B (**37**) was isolated from the green alga *Caulerpa racemosa* and had MIC_{80} values of 4 μg/mL against *Candida glabrata* and *Cryptococcus neoformans* while being inactive against *Aspergillus fumigatus* [33].

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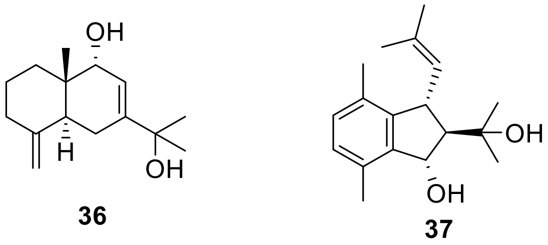
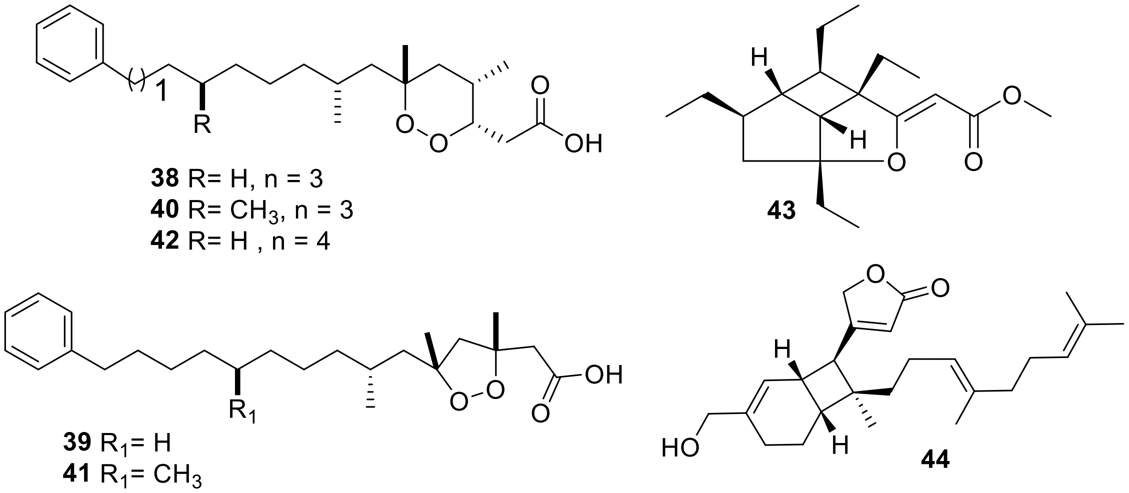


Figure 8. Structures of natural products **36** and **37**

2.2 Natural product antifungal leads from sponges

Marine sponges are an important source of novel natural products, and more than ten examples with antifungal activity were described in this period (Figures 9 and 10, **38**-**55**). Extracts from the symbiotic two-sponge association *Plakortis halichondroides*−*Xestospongia deweerdtae* yielded a number of peroxide natural products, of which plakinic acids I, J, K and L (**38**-**41**) were potent against *Candida* and *Cryptococcus* species with MIC ≤ 0.5 µg/mL [34]. Plakinic acid M (**42**) was active against *Cryptococcus gattii*, *Cryptococcus grubii* and *Candida krusei* with MIC_{90} values of 2.4-3.4 µg/mL but less active against *Candida albicans* [33]. Extraction from the South China Sea sponge *Hippospongia lachne* was the source for hippolachnin A (**43**), a polyketide with an unprecedented scaffold [36]. The compound was potently antifungal with a MIC of 0.4 µg/mL against *Cryptococcus neoformans*, *Trichophyton rubrum* and *Microsporum gypseum*. However, the natural product and analogues obtained by total synthesis were inactive, suggesting the initial report was in error [37]. Bioassay-guided fractionation of the same extract led to isolation of a racemic sesterterpene hippolide J (**44**) [38]. The natural product was resolved into its two enantiomers, and both were highly potent antifungals with MIC_{50} of 0.13–0.25 µg/mL against *Candida* and *Trichophyton* while weakly cytotoxic to the human embryonic kidney HEK293 cell line.



38 R= H, n = 3
40 R= CH_3, n = 3
42 R= H , n = 4

39 R_1= H
41 R_1= CH_3

Figure 9. Structures of natural products **38**-**44**

A new member of the manzamine alkaloids, zamamidine D (**45**), was isolated from an Okinawan marine sponge *Amphimedon* sp. Zamamidine D had an IC_{50} of 2 µg/mL against *Cryptococcus neoformans* but was weakly active against other fungal and bacterial strains tested [39]. From another Okinawan marine sponge *Pseudoceratina* sp., ceratinadin A and B (**46**, **47**) were isolated with MIC values of 4 and 8 µg/mL respectively against *Cryptococcus neoformans* and 2 and 4 µg/mL respectively against *Candida albicans* [40]. From an extract of the sponge *Pseudaxinella reticulata*, several crambescin guanidine containing alkaloids were isolated. Crambescin A2 392 and 406 (**48**, **49**) inhibited

Cryptococcus neoformans with a MIC_{50} of 1.2 and 0.9 µg/mL respectively while being relatively inactive against *Candida albicans* [41]. The enantiomers of two known crambescins, crambescin A2 420 (**50**) and Sch 575948 (**51**) were also isolated with a MIC_{50} of 1.1 and 2.5 µg/mL respectively against *Cryptococcus neoformans*. Among metabolites isolated from the marine sponge *Agelas*, two new diterpene alkaloids from *Agelas citrina*, agelasidine E and F (**52**, **53**), were reported to have MIC values of 8 and 4 µg/mL respectively against *Candida albicans* [42]. Isoagelasine C (**54**), isolated from *Agelas nakamurai*, had a MIC value of 4.7 µg/mL against *Candida albicans* [43]. Ageloxime B (**55**), isolated from *Agelas mauritiana*, had an IC_{50} value of 5.0 µg/mL against *Cryptococcus neoformans* as well as antibacterial activity [44].

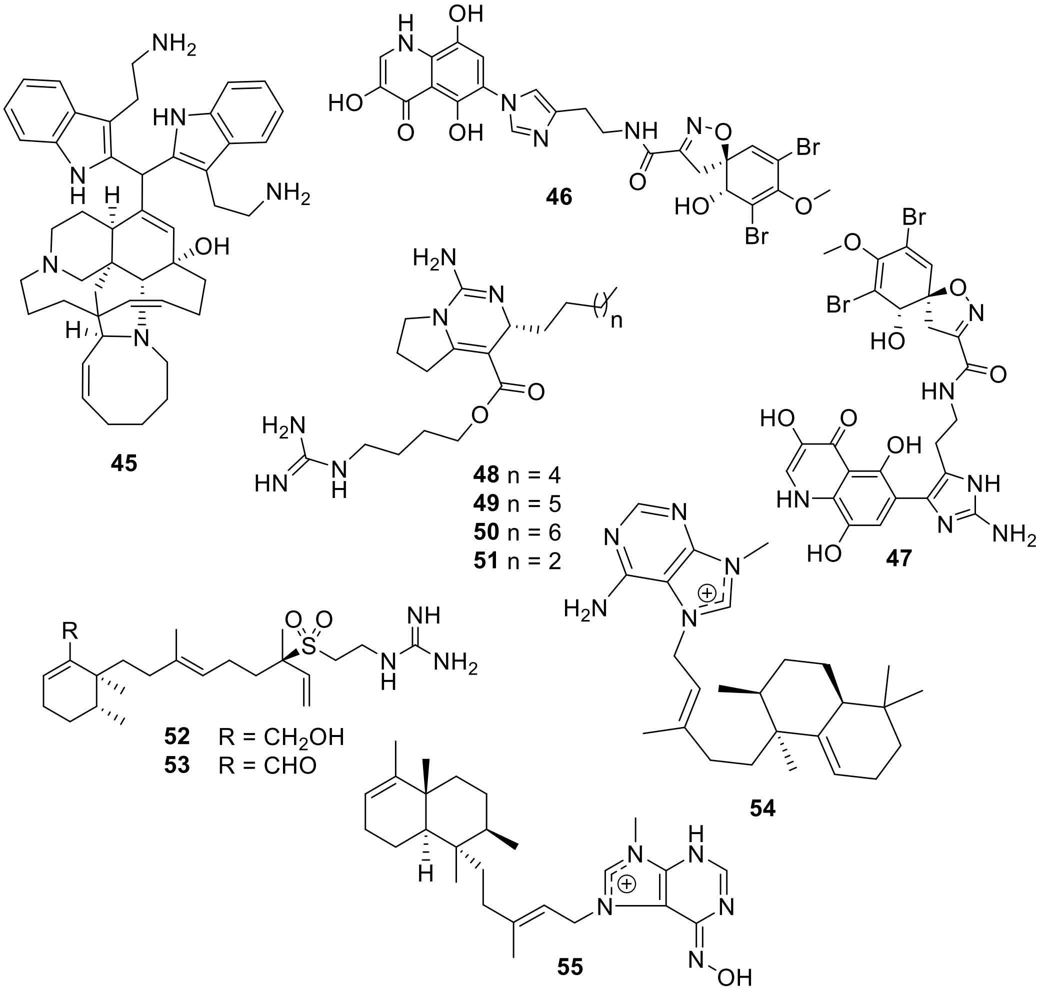


Figure 10. Structures of natural products **45-55**

2.3 Natural product antifungal leads from plants

Plants accounted for nearly ten antifungal leads within the last decade (Figures 11 and 12, **56-64**). The flavonoid (*E*)-6-(2-carboxyethenyl)apigenin (**56**) was isolated from an extract of *Mimosa caesalpiniifolia* Benth., a Brazilian medicinal plant commonly known as "sabiá" or "sansão-do-campo" [45]. The compound inhibits *Candida krusei* with an IC_{50} of 44 nM, although it was inactive against *Candida glabrata*. The isoflavonoid vatacarpan (**57**) with a MIC of 1 µg/mL against *Candida albicans* was isolated by bioassay-guided fractionation from the roots of *Vatairea macrocarpa* (Benth.) Ducke [46]. The biaryl ether laevicarpin (**58**) was isolated from leaves of *Piper laevicarpu*, known as "falsa-pimenteira" in Brazil [47]. Interestingly, the compound was previously prepared synthetically prior to this isolation. Laevicarpin had an IC_{50} of 7.9 µM against *Cryptococcus gattii*, in addition to an IC_{50} of

50 µM against the trypomastigote form of *Trypanosoma cruzi*. The dimeric chalcone kamalachalcone E (**59**) was isolated from the red dye extracted from whole uncrushed fruits of *Mallotus philippinensis* [48]. The chalcone exhibited an IC_{50} of 4-8 µg/mL against two strains of *Cryptococcus neoformans*.

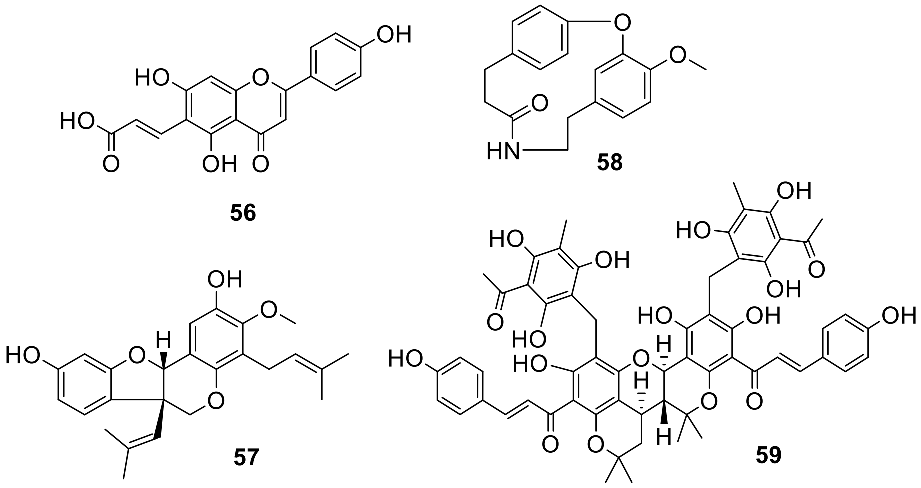


Figure 11. Structures of natural products **56-59**

Investigation of the juvenile leaves of *Eucalyptus maideni* F. Muell led to the discovery of a number of phloroglucinol derivatives, among which eucalmaidial A (**60**) showed antifungal activity against *Candida glabrata* with an IC_{50} of 0.8 µg/mL [49]. A monoterpene indole alkaloid, 16,17-epoxyisositsirikine (**61**), isolated from the evergreen shrub *Rhazya stricta* Decne. had an IC_{50} of 6.3 µg/mL against *Candida glabrata* but was less active against other *Candida* species tested [50]. Erchinine B (**62**), a monoterpene indole alkaloid with an unusual 1,4-diazepine ring embedded was isolated from roots of *Ervatamia chinensis* and had a MIC of 6.3 µg/mL against *Trichophyton rubrum*, with a lower MIC of 0.8 µg/mL against the Gram-positive bacteria *Bacillus subtilis* [51]. An aporphine alkaloid (**63**) was isolated from the bark of a Costa Rican sample of *Beilschmiedia alloiophylla* [52]. The alkaloid had a MIC of 8 µg/mL against *Candida albicans*, as well as antileishmanial activity and inhibition of acetylcholinesterase. The cyclic peptide tunicyclin D (**64**) was isolated from roots of the medicinal herb *Psammosilene tunicoides* W. C. Wu *et*. C. Y. Wu [53]. The peptide exhibited MIC_{80} values of 0.3-16 µg/mL against *Candida* species and 1.0 µg/mL against *Cryptococcus neoformans*.

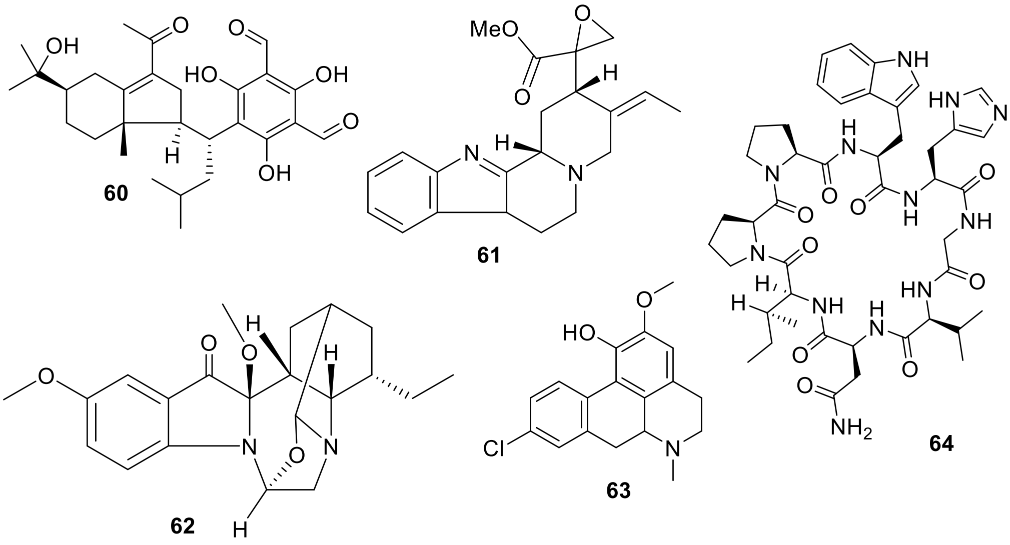


Figure 12. Structures of natural products **60-64**

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2.4 Natural product antifungal leads from fungi

Within the last decade, fungi were the most prolific source of novel antifungal leads (Figures 13-17, **65-98**). An extract of the endophytic species *Pestalotiopsis mangiferae* obtained from the leaves of the plant *Mangifera indica* Linn. yielded an unprecedented epoxyacetal 4-(2,4,7-trioxa-bicyclo[4.1.0]heptan-3-yl) phenol (**65**) with a MIC of 0.04 μg/mL against *Candida albicans* strains and 1.3 μg/mL against the bacterium *Micrococcus luteus* [54]. Two phenalenones, auxarthrone A and D (**66, 67**) were obtained from fermentation extracts of an *Auxarthron pseudauxarthron* strain isolated from rabbit dung [55]. The compounds have MIC values of 3.2 and 6.4 μg/mL against *Cryptococcus neoformans* and *Candida albicans* respectively. Further investigation into these compounds demonstrated that they are unnatural artifacts, arising from reaction of natural products with ketone solvents employed during the extraction. Grifolaone A (**68**) was isolated from the edible mushroom *Grifola frondosa*. Interestingly, the hemiketal lactone was obtained in an optically active form and assigned as the *S* enantiomer [56]. The furanone was a potent inhibitor, MIC of 0.15 μg/mL, of the opportunistic human pathogen *Pseudallescheria boydii* and also had a MIC of 10 μg/mL against *Aspergillus fumigatus*.

The tropolone nemanolone B (**69**) was isolated from fermentation of a *Nemania* sp. fungus and displayed antifungal activity with an IC$_{50}$ of 4.5 μg/mL against *Candida albicans*, and similar levels of activity against the parasite *Plasmodium falciparum* and human tumor cell lines [57]. The quinone pleosporallin E (**70**), isolated from a marine-derived *Pleosporales* sp., inhibited *Candida albicans* with a MIC of 7.4 μg/mL [58]. Five new isocoumarins were isolated from fermentation of an endophytic *Pestalotiopsis* sp. obtained from *Photinia frasery*. Among these, pestalactone C (**71**) inhibited *Candida glabrata* with a MIC$_{50}$ value of 3.5 μg/mL [59]. Aspergillusether D (**72**), isolated from fermentation of *Aspergillus unguis* PSU-RSPG204, inhibited *Cryptococcus neoformans* with a MIC value of 8 μg/mL, and inhibited *Candida albicans* at a lower level [60]. A series of *p*-terphenyl natural products was isolated from a strain of *Floricola striata* inhabiting the lichen *Umbilicaria* sp., among which the quinones floricolin B and C (**73**, **74**) displayed MIC$_{80}$ values of 8 μg/mL against *Candida albicans* [61]. Further investigation of floricolin C suggested a fungicidal action through disruption of mitochondria [62].

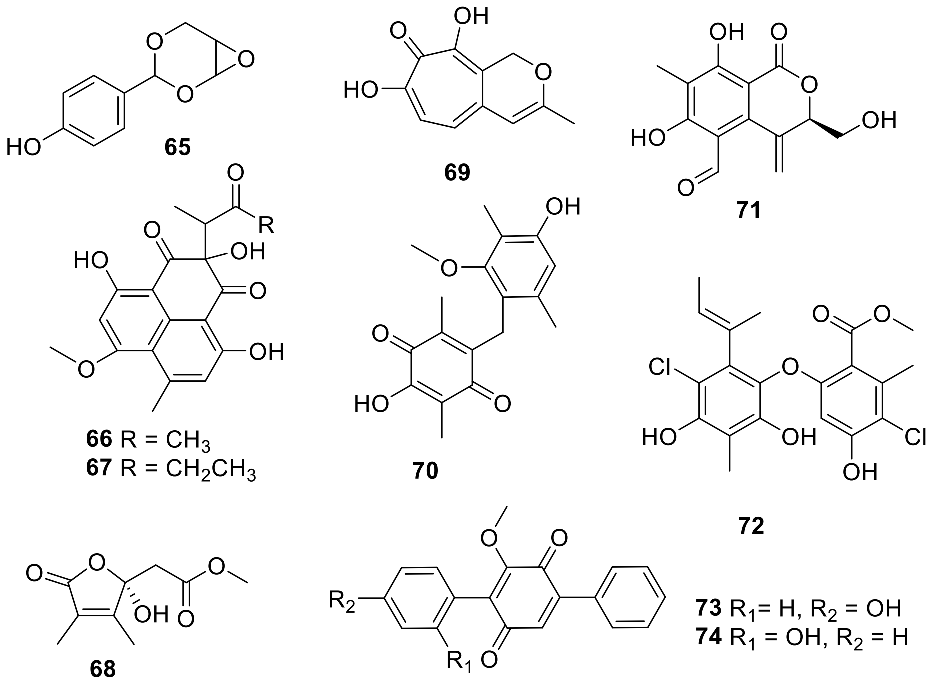

Figure 13. Structures of natural products **65-74**

Extended fermentation (365 days) of a marine-derived strain of *Aioliomyces pyridodomos* led to the appearance of new metabolites, of which onydecalin C (**75**) had a MIC of 2 μg/mL against *Histoplasma capsulatum* [63]. The same strain, in a more conventional fermentation period (25 days), produced aintennol A (**76**) with an IC_{50} of 8 μg/mL against *Histoplasma capsulatum* [64]. Genome mining for potential Diels-Alderase enzymes identified a potential candidate in the sequence of *Penicillium variabile*. The putative biosynthetic gene cluster was engineered into an *Aspergillus nidulans* expression host, enabling the isolation of varicidin A (**77**) with a MIC_{50} value of 8 μg/mL against *Candida albicans* [65]. The *N*-demethylated analogue, varicidin B, was two-fold less active. In the same manner, the ilicicolin H biosynthetic gene cluster including a putative Diels-Alderase from a producing strain, *Neonectria* sp. DH2, was heterologously expressed in *Aspergillus nidulans*. In addition to ilicicolin H, a shunt metabolite ilicicolin J (**78**) was isolated with a MIC of 6.3 μg/mL against *Candida albicans* [66]. Heterologous expression was also employed to confirm the biosynthetic gene cluster involved in the production of the burnettramic acids A and B (**79** and **80**) in *Aspergillus burnettii* FRR 5400 [67]. Burnettramic acid A had a MIC value < 1 μg/mL against *Candida albicans* and *Saccharomyces cerevisiae* while burnettramic acid B was slightly less active with values of 1-2 μg/mL.

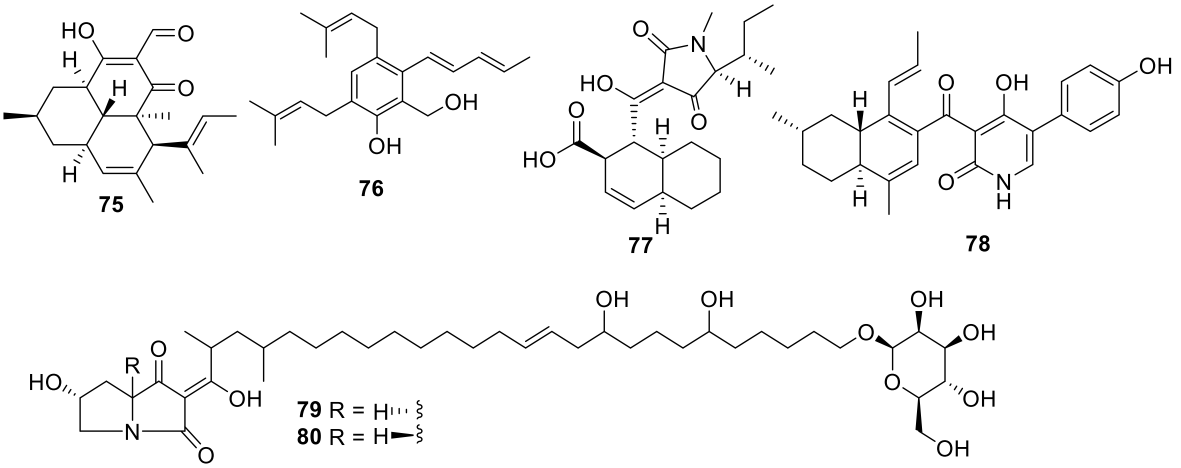

Figure 14. Structures of natural products **75-80**

Co-culture of two extremophilic fungal strains of *Penicillium fuscum* (Sopp) Raper & Thom and *Penicillium camembertii/clavigerum* Thom isolated from a single sample of surface water from Berkeley Pit Lake led to the production of novel metabolites. Berkeleylactone A (**81**) displayed modest antifungal activity with an IC_{50} of 6 μg/mL against *Candida glabrata* and higher antibacterial activity [68]. Fermentation of a Saudi strain of *Petriella setifera* led to the identification of the triterpene glycoside amnomopin (**82**) with MIC values of 0.5-2 μg/mL against *Candida* species [69]. Sclerodol B (**83**), a triterpene from extracts of the endophyte *Scleroderma* UFSM Sc1(Persoon) Fries obtained from *Eucalyptus grandis* had a MIC of 6.3 μg/mL against *Candida krusei* with weaker activity against other species [70]. A strain of the marine-derived fungus *Stachybotrys chartarum* produced several novel diterpenoids, of which atranone Q (**84**) had a MIC of 8 μg/mL against *Candida albicans* and weaker antibacterial activity [71].

An endophytic *Penicillium* sp. isolated from grass produced picolinic acid derivatives in fermentation. Penicolinate B and C (**85**, **86**) had MIC values of 1.5 and 3.7 μg/mL, respectively, against *Candida albicans* [72]. The didymellamide series of pyridone alkaloids was isolated from cultures of the marine-derived fungus *Stagonosporopsis cucurbitacearum* and *Coniochaeta cephalothecoides* [73,74]. Didymellamide A, F and G (**87-89**) were antifungal with MIC values of 3 μg/mL against *Candida* species. The fermentation also yielded (+)-*N*-hydroxyapiosporamide (**90**), the enantiomer of the previously isolated natural product, with a MIC value of 6.3 μg/mL against *Candida albicans*.

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Fermentation of a *Cyathus* cf. *striatus* basidiomycete led to the isolation of the alkaloid pyristriatin A (**91**) with a MIC of 8.3 µg/mL against *Rhodotorula glutinis* and similar levels of activity against Gram-positive bacteria and human tumor cell lines [75].

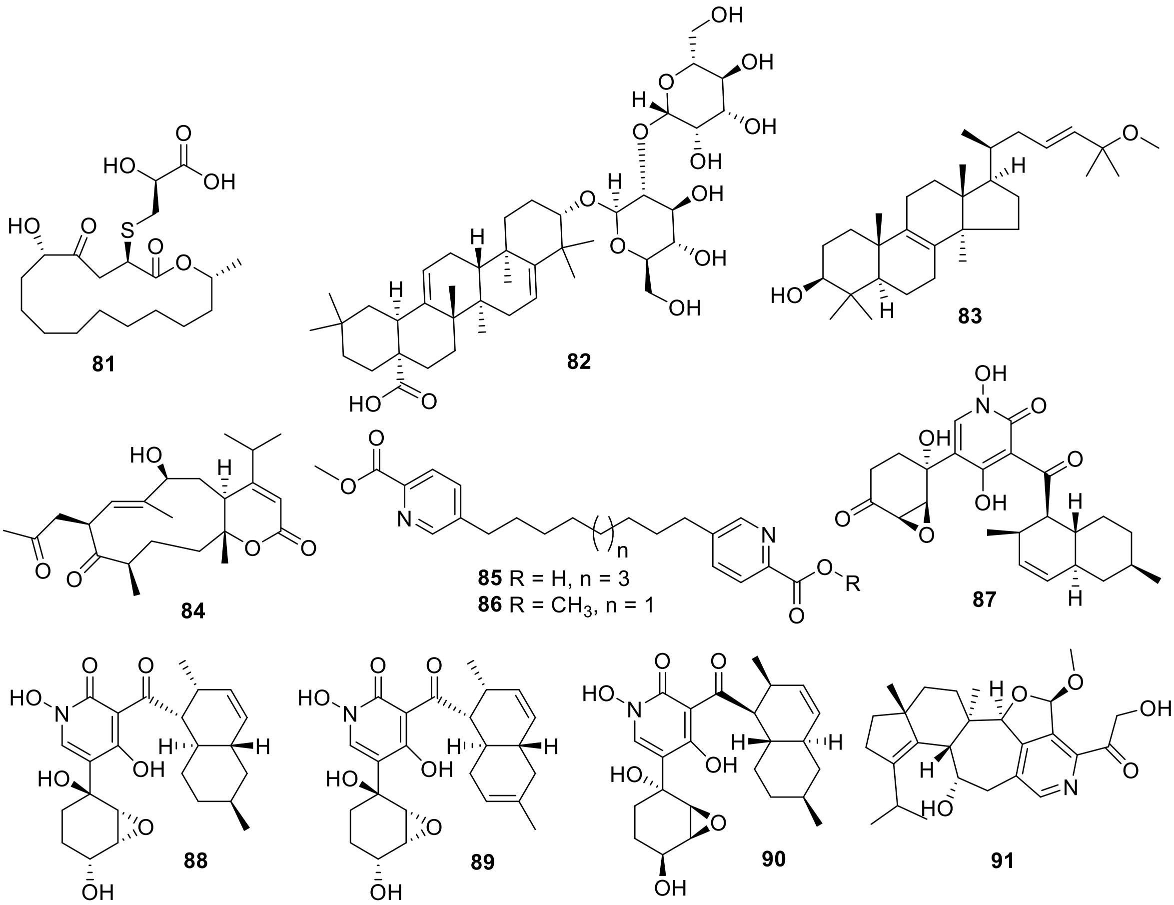

Figure 15. Structures of natural products **81-91**

The alkalophilic extremophile fungus *Emericellopsis alkalina* VKPM F-1428 was the source of the peptaibol emericellipsin A (**92**), which exhibited antifungal MIC values of 2-4 µg/mL against *Candida* and *Aspergillus* species as well as activity against Gram-positive bacteria. Bioassay-guided fractionation of extracts of *Colispora cavincola* isolated from plant litter led to the discovery of the linear peptides cavinafungin A and B (**93**, **94**) [76]. The cavinafungins inhibited *Candida* species with a MIC of 0.5–4 µg/mL and *Aspergillus fumigatus* at 8 µg/mL. However, the antifungal effects were lost in the presence of mouse serum. Cavinafungin A also potently inhibits the Zika and dengue virus, with the mechanism of action attributed to inhibition of the host signal pepdidase [77]. The antifungal activity of *Phaeosphaeria* sp. F-167,953 was ascribed to the lipodepsipeptide phaeofungin (**95**) with some structural similarity to the previously known phomafungin [78]. Phaeofungin had a MIC of 4 µg/mL against *Trichophyton mentagrophytes* and lower activity against other fungi tested.

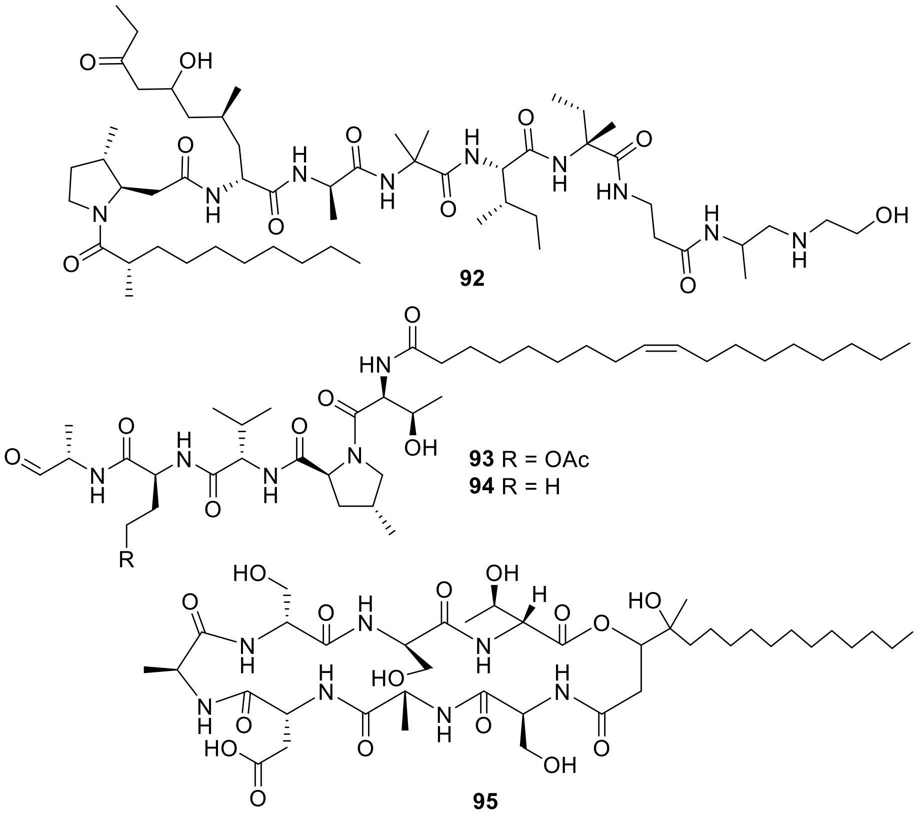

Figure 16. Structures of natural products **92-95**

High-throughput screening by Astellas Pharmaceuticals against a silkworm model of *Aspergillus fumigatus* infection led to bioassay-guided fractionation activity of an extract of *Acremonium persicinum* MF-347833. The siderophore hexapeptide ASP2397 (**96**) was discovered as an aluminum chelate with exceptional potency against *Aspergillus fumigatus*, with a MIC of 0.2 μg/mL and efficacy at 3.2 mg/kg in a mouse in vivo model [79]. The metal-free form AS2488059 (**97**) as well as the congener AS2524371 (**98**) were also isolated, and the target was identified as a fungal siderophore transporter [80,81]. The compound was out-licensed to Vical and renamed VL-2397, reaching Phase II clinical trials that were recently discontinued.

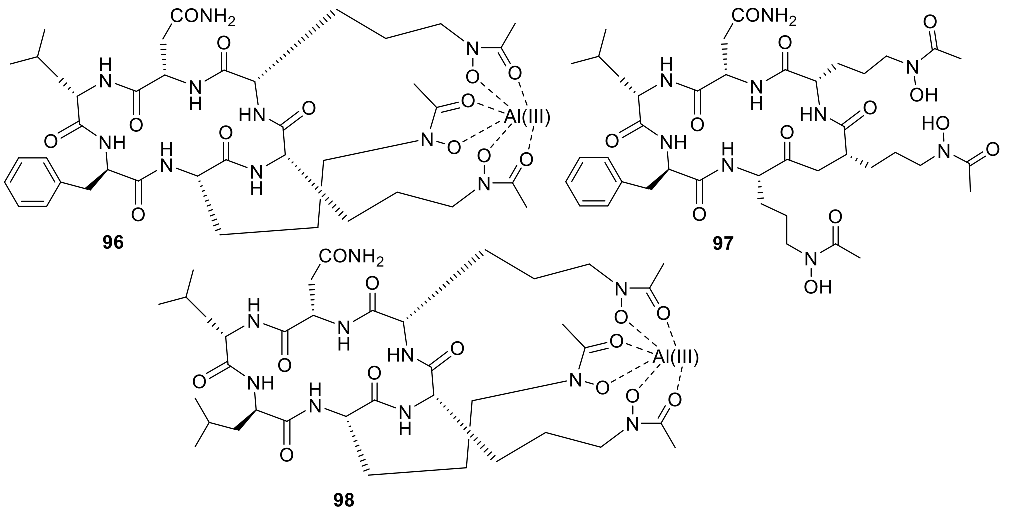

Figure 17. Structures of natural products **96-98**

3. Discussion

Between 2010-2019, we identified nearly a hundred novel natural products reported with antifungal activity against human pathogens. The compounds originate from a variety of sources comprising bacteria, alga, fungi, sponges and plants with fungi being the most prolific source of antifungal compounds. The techniques employed range from classical phytochemical studies with plants to high-throughput screening of extract collections and modern microbiological strategies such as co-cultivation and heterologous expression of biosynthetic gene clusters. All the major classes of natural products including polyketides, shikimate metabolites, terpenoids, alkaloids and peptides are represented. As the majority of examples in this review involve the initial disclosure of activity, further investigations are needed to assess the therapeutic potential of highly active compounds as well as their selectivity as antifungal agents. Meanwhile, it is interesting to observe the physicochemical space occupied by these natural product leads (Table 1). Although the compounds are diverse in their structural features, they are largely compliant with the typical guidelines for small molecule drug-like chemical space. While many of the natural products are large in molecular weight, resulting in an average of 569, other properties like hydrogen bonding potential, molecular flexibility and polarity often remain within the recommended limits.

Compound	MW	clogP	HBD	HBA	nrot	TPSA
1	607	4.8	3	8	10	115
2	198	2.1	2	2	2	41
3	508	2.9	4	12	5	186
8	751	7.0	5	10	10	155
17	1123	7.6	13	18	26	312
21	1580	0.9	15	29	33	472
28	987	4.7	6	19	11	253
30	817	4.3	4	12	9	167
31	1200	-5.7	23	32	36	546
35	2144	-0.4	26	55	30	876
36	236	2.4	2	2	3	41
37	274	3.0	2	2	4	41
42	419	7.7	1	4	14	56
44	385	6.2	1	3	9	47
45	713	8.1	7	7	10	110
46	667	0.7	6	13	10	188
48	393	3.1	6	8	13	130
53	438	5.0	4	6	12	121
54	423	2.0	2	5	5	61
55	439	2.3	2	6	5	70
56	340	1.9	4	7	6	124
57	423	6.0	2	5	7	68
58	297	2.7	1	4	1	48
59	1065	8.0	11	18	23	319

60	487	6.5	4	7	12	132
61	352	3.0	0	5	3	64
62	370	0.5	0	6	3	51
63	281	2.5	1	3	2	33
64	901	-0.1	10	21	9	303
65	194	1.3	1	4	2	51
66	358	3.0	3	7	6	121
68	200	-1.6	1	5	4	73
69	206	-1.0	2	4	2	67
70	316	3.5	2	5	5	84
71	264	0.8	3	6	5	104
72	427	7.9	3	6	8	96
74	306	4.7	1	4	4	64
75	329	6.8	1	3	3	54
76	327	6.7	2	2	9	41
77	376	3.3	2	6	5	95
78	432	5.4	3	5	4	87
79	770	3.2	8	13	35	218
81	405	2.3	3	7	6	146
82	779	6.4	8	13	14	216
83	457	9.5	1	2	6	30
84	391	2.7	1	5	3	81
85	399	5.1	1	6	14	89
87	444	1.4	3	8	6	128
90	446	3.5	4	8	7	131
91	442	3.5	2	6	6	89
92	1064	4.9	10	20	38	294
93	792	6.6	5	14	31	200
95	904	-2.0	13	23	23	368
97	891	-2.5	11	23	21	339
Average	569	3.4	5	10	11	155

Table 1. Physicochemical properties of antifungal natural products. MW = molecular weight, clogP = calculated log P, HBD = hydrogen bond donors, HBA = hydrogen bond acceptors, nrot = number of rotated bonds, TPSA = total polar surface area in Å^2. The values were taken from SciFinder (https://scifinder-n.cas.org), based on calculations using Advanced Chemistry Development (ACD/Labs) Software V11.02. In certain cases where the data was absent in SciFinder, values were calculcated using the Molinspiration website (https://www.molinspiration.com/).

For natural products where a series of related compounds was reported, one representative example was selected. Shaded cells indicate values above the recommended guidelines for small molecule drug-like chemical space (MW ≤ 500, Clog P ≤ 5, HBD ≤ 5, HBA ≤ 10, nrot ≤ 10, TPSA ≤ 140).

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References

1. Bongomin, F.; Gago, S.; Oladele, R.; Denning, D. Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision. *J. Fungi* **2017**, *3*, 57.
2. Pianalto, K.; Alspaugh, J. New Horizons in Antifungal Therapy. *J. Fungi* **2016**, *2*, 26.
3. Jeffery-Smith, A.; Taori, S.K.; Schelenz, S.; Jeffery, K.; Johnson, E.M.; Borman, A.; Manuel, R.; Brown, C.S. Candida auris: a Review of the Literature. *Clin. Microbiol. Rev.* **2018**, *31*, e00029-17.
4. Allen, D.; Wilson, D.; Drew, R.; Perfect, J. Azole antifungals: 35 years of invasive fungal infection management. *Expert Rev. Anti. Infect. Ther.* **2015**, *13*, 787–798.
5. Patil, A.; Majumdar, S. Echinocandins in antifungal pharmacotherapy. *J. Pharm. Pharmacol.* **2017**, *69*, 1635–1660.
6. Zotchev, S.B. Polyene macrolide antibiotics and their applications in human therapy. *Curr. Med. Chem.* **2003**, *10*, 211–23.
7. Gray, K.C.; Palacios, D.S.; Dailey, I.; Endo, M.M.; Uno, B.E.; Wilcock, B.C.; Burke, M.D. Amphotericin primarily kills yeast by simply binding ergosterol. *Proc. Natl. Acad. Sci.* **2012**, *109*, 2234–2239.
8. Vermes, A.; Guchelaar, H.J.; Dankert, J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *J. Antimicrob. Chemother.* **2000**, *46*, 171–9.
9. Perfect, J.R. The impact of the host on fungal infections. *Am. J. Med.* **2012**, *125*, S39–S51.
10. Geddes-McAlister, J.; Shapiro, R.S. New pathogens, new tricks: Emerging, drug-resistant fungal pathogens and future prospects for antifungal therapeutics. *Ann. N. Y. Acad. Sci.* **2019**, *1435*, 57–78.
11. Revie, N.M.; Iyer, K.R.; Robbins, N.; Cowen, L.E. Antifungal drug resistance: evolution, mechanisms and impact. *Curr. Opin. Microbiol.* **2018**, *45*, 70–76.
12. Food and Drug Administration. Establishing a list of qualifying pathogens under the Food and Drug Administration Safety and Innovation Act. Final rule. *Fed. Regist.* **2014**, *79*, 32464–32481.
13. Perfect, J.R. The antifungal pipeline: a reality check. *Nat. Rev. Drug Discov.* **2017**, *16*, 603–616.
14. Ortholand, J.Y.; Ganesan, A. Natural products and combinatorial chemistry: Back to the future. *Curr. Opin. Chem. Biol.* **2004**, *8*, 271–280.
15. Ganesan, A. The impact of natural products upon modern drug discovery. *Curr. Opin. Chem. Biol.* **2008**,

Peer-reviewed version available at *Pharmaceuticals* **2019**, *12*, 182; doi:10.3390/ph12040182

12, 306–317.

16. Newman, D.J.; Cragg, G.M. Natural Products as Sources of New Drugs from 1981 to 2014. *J. Nat. Prod.* **2016**, *79*, 629–661.
17. Ding, N.; Jiang, Y.; Han, L.; Chen, X.; Ma, J.; Qu, X.; Mu, Y.; Liu, J.; Li, L.; Jiang, C.; et al. Bafilomycins and Odoriferous Sesquiterpenoids from Streptomyces albolongus Isolated from Elephas maximus Feces. *J. Nat. Prod.* **2016**, *79*, 799–805.
18. Yin, M.; Li, G.; Jiang, Y.; Han, L.; Huang, X.; Lu, T.; Jiang, C. The complete genome sequence of Streptomyces albolongus YIM 101047, the producer of novel bafilomycins and odoriferous sesquiterpenoids. *J. Biotechnol.* **2017**, *262*, 89–93.
19. Harunari, E.; Imada, C.; Igarashi, Y. Konamycins A and B and Rubromycins CA1 and CA2, Aromatic Polyketides from the Tunicate-Derived Streptomyces hyaluromycini MB-PO13 T. *J. Nat. Prod.* **2019**, *82*, 1609–1615.
20. Sato, S.; Iwata, F.; Yamada, S.; Katayama, M. Neomaclafungins A–I: Oligomycin-Class Macrolides from a Marine-Derived Actinomycete. *J. Nat. Prod.* **2012**, *75*, 1974–1982.
21. Yuan, G.; Lin, H.; Wang, C.; Hong, K.; Liu, Y.; Li, J. 1H and 13C assignments of two new macrocyclic lactones isolated from Streptomyces sp. 211726 and revised assignments of Azalomycins F3a, F4aand F5a. *Magn. Reson. Chem.* **2011**, *49*, 30–37.
22. Yuan, G.; Hong, K.; Lin, H.; She, Z.; Li, J. New Azalomycin F Analogs from Mangrove Streptomyces sp. 211726 with Activity against Microbes and Cancer Cells. *Mar. Drugs* **2013**, *11*, 817–829.
23. Alferova, V.A.; Novikov, R.A.; Bychkova, O.P.; Rogozhin, E.A.; Shuvalov, M. V.; Prokhorenko, I.A.; Sadykova, V.S.; Kulko, A.B.; Dezhenkova, L.G.; Stepashkina, E.A.; et al. Astolides A and B, antifungal and cytotoxic naphthoquinone-derived polyol macrolactones from Streptomyces hygroscopicus. *Tetrahedron* **2018**, *74*, 7442–7449.
24. Pérez-Victoria, I.; Oves-Costales, D.; Lacret, R.; Martín, J.; Sánchez-Hidalgo, M.; Díaz, C.; Cautain, B.; Vicente, F.; Genilloud, O.; Reyes, F. Structure elucidation and biosynthetic gene cluster analysis of caniferolides A–D, new bioactive 36-membered macrolides from the marine-derived Streptomyces caniferus CA-271066. *Org. Biomol. Chem.* **2019**, *17*, 2954–2971.
25. Alvariño, R.; Alonso, E.; Lacret, R.; Oves-Costales, D.; Genilloud, O.; Reyes, F.; Alfonso, A.; Botana, L.M. Caniferolide A, a Macrolide from Streptomyces caniferus , Attenuates Neuroinflammation, Oxidative Stress, Amyloid-Beta, and Tau Pathology in Vitro. *Mol. Pharm.* **2019**, *16*, 1456–1466.
26. Chen, Y.; Liu, R.-H.; Li, T.-X.; Huang, S.-S.; Kong, L.-Y.; Yang, M.-H. Enduspeptides A-F, six new cyclic depsipeptides from a coal mine derived Streptomyces sp. *Tetrahedron* **2017**, *73*, 527–531.

27. Hoffmann, H.; Kogler, H.; Heyse, W.; Matter, H.; Caspers, M.; Schummer, D.; Klemke-Jahn, C.; Bauer, A.; Penarier, G.; Debussche, L.; et al. Discovery, Structure Elucidation, and Biological Characterization of Nannocystin A, a Macrocyclic Myxobacterial Metabolite with Potent Antiproliferative Properties. *Angew. Chemie Int. Ed.* **2015**, *54*, 10145–10148.

28. Liu, Q.; Yang, X.; Ji, J.; Zhang, S.-L.; He, Y. Novel nannocystin A analogues as anticancer therapeutics: Synthesis, biological evaluations and structure-activity relationship studies. *Eur. J. Med. Chem.* **2019**, *170*, 99–111.

29. Lin, Z.; Falkinham, J.O.; Tawfik, K.A.; Jeffs, P.; Bray, B.; Dubay, G.; Cox, J.E.; Schmidt, E.W. Burkholdines from Burkholderia ambifaria : Antifungal Agents and Possible Virulence Factors. *J. Nat. Prod.* **2012**, *75*, 1518–1523.

30. Konno, H.; Abumi, K.; Sasaki, Y.; Yano, S.; Nosaka, K. Structure activity relationship study of burkholdine analogues toward simple antifungal agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3199–202.

31. Mohr, K.I.; Volz, C.; Jansen, R.; Wray, V.; Hoffmann, J.; Bernecker, S.; Wink, J.; Gerth, K.; Stadler, M.; Müller, R. Pinensins: The First Antifungal Lantibiotics. *Angew. Chemie Int. Ed.* **2015**, *54*, 11254–11258.

32. Alarif, W.M.; Al-Footy, K.O.; Zubair, M.S.; Halid PH, M.; Ghandourah, M.A.; Basaif, S.A.; Al-Lihaibi, S.S.; Ayyad, S.-E.N.; Badria, F.A. The role of new eudesmane-type sesquiterpenoid and known eudesmane derivatives from the red alga Laurencia obtusa as potential antifungal–antitumour agents. *Nat. Prod. Res.* **2016**, *30*, 1150–1155.

33. Liu, A.-H.; Liu, D.-Q.; Liang, T.-J.; Yu, X.-Q.; Feng, M.-T.; Yao, L.-G.; Fang, Y.; Wang, B.; Feng, L.-H.; Zhang, M.-X.; et al. Caulerprenylols A and B, two rare antifungal prenylated para-xylenes from the green alga Caulerpa racemosa. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2491–2494.

34. Dalisay, D.S.; Quach, T.; Molinski, T.F. Liposomal Circular Dichroism. Assignment of Remote Stereocenters in Plakinic Acids K and L from a Plakortis − Xestospongia Sponge Association. *Org. Lett.* **2010**, *12*, 1524–1527.

35. Jamison, M.T.; Dalisay, D.S.; Molinski, T.F. Peroxide Natural Products from Plakortis zyggompha and the Sponge Association Plakortis halichondrioides – Xestospongia deweerdtae : Antifungal Activity against Cryptococcus gattii. *J. Nat. Prod.* **2016**, *79*, 555–563.

36. Piao, S.-J.; Song, Y.-L.; Jiao, W.-H.; Yang, F.; Liu, X.-F.; Chen, W.-S.; Han, B.-N.; Lin, H.-W. Hippolachnin A, a New Antifungal Polyketide from the South China Sea Sponge Hippospongia lachne. *Org. Lett.* **2013**, *15*, 3526–3529.

37. Timmerman, J.C.; Wood, J.L. Synthesis and Biological Evaluation of Hippolachnin A Analogues. *Org. Lett.* **2018**, *20*, 3788–3792.

Peer-reviewed version available at *Pharmaceuticals* **2019**, *12*, 182; doi:10.3390/ph12040182

38. Jiao, W.-H.; Hong, L.-L.; Sun, J.-B.; Piao, S.-J.; Chen, G.-D.; Deng, H.; Wang, S.-P.; Yang, F.; Lin, H.-W. (±)-Hippolide J - A Pair of Unusual Antifungal Enantiomeric Sesterterpenoids from the Marine Sponge Hippospongia lachne. *European J. Org. Chem.* **2017**, *2017*, 3421–3426.

39. Kubota, T.; Nakamura, K.; Kurimoto, S.; Sakai, K.; Fromont, J.; Gonoi, T.; Kobayashi, J. Zamamidine D, a Manzamine Alkaloid from an Okinawan Amphimedon sp. Marine Sponge. *J. Nat. Prod.* **2017**, *80*, 1196–1199.

40. Kon, Y.; Kubota, T.; Shibazaki, A.; Gonoi, T.; Kobayashi, J. Ceratinadins A–C, new bromotyrosine alkaloids from an Okinawan marine sponge Pseudoceratina sp. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4569–4572.

41. Jamison, M.T.; Molinski, T.F. Antipodal Crambescin A2 Homologues from the Marine Sponge Pseudaxinella reticulata . Antifungal Structure–Activity Relationships. *J. Nat. Prod.* **2015**, *78*, 557–561.

42. Stout, E.P.; Yu, L.C.; Molinski, T.F. Antifungal Diterpene Alkaloids from the Caribbean Sponge Agelas citrina: Unified Configurational Assignments of Agelasidines and Agelasines. *European J. Org. Chem.* **2012**, *2012*, 5131–5135.

43. Chu, M.-J.; Tang, X.-L.; Qin, G.-F.; Sun, Y.-T.; Li, L.; de Voogd, N.J.; Li, P.-L.; Li, G.-Q. Pyrrole Derivatives and Diterpene Alkaloids from the South China Sea Sponge Agelas nakamurai. *Chem. Biodivers.* **2017**, *14*, e1600446.

44. Yang, F.; Hamann, M.T.; Zou, Y.; Zhang, M.-Y.; Gong, X.-B.; Xiao, J.-R.; Chen, W.-S.; Lin, H.-W. Antimicrobial Metabolites from the Paracel Islands Sponge Agelas mauritiana. *J. Nat. Prod.* **2012**, *75*, 774–778.

45. Dias Silva, M.J.; Simonet, A.M.; Silva, N.C.; Dias, A.L.T.; Vilegas, W.; Macías, F.A. Bioassay-Guided Isolation of Fungistatic Compounds from Mimosa caesalpiniifolia Leaves. *J. Nat. Prod.* **2019**, *82*, 1496–1502.

46. Santana, D.B.; da Costa, R.C.; Araújo, R.M.; de Paula, J.E.; Silveira, E.R.; Braz-Filho, R.; Espindola, L.S. Activity of Fabaceae species extracts against fungi and Leishmania: vatacarpan as a novel potent anti-Candida agent. *Rev. Bras. Farmacogn.* **2015**, *25*, 401–406.

47. da Silva A. Maciel, D.; Freitas, V.P.; Conserva, G.A.A.; Alexandre, T.R.; Purisco, S.U.; Tempone, A.G.; Melhem, M.S.C.; Kato, M.J.; Guimarães, E.F.; Lago, J.H.G. Bioactivity-guided isolation of laevicarpin, an antitrypanosomal and anticryptococcal lactam from Piper laevicarpu (Piperaceae). *Fitoterapia* **2016**, *111*, 24–28.

48. Kulkarni, R.R.; Tupe, S.G.; Gample, S.P.; Chandgude, M.G.; Sarkar, D.; Deshpande, M. V.; Joshi, S.P. Antifungal dimeric chalcone derivative kamalachalcone E from Mallotus philippinensis. *Nat. Prod. Res.* **2014**, *28*, 245–250.

Peer-reviewed version available at *Pharmaceuticals* **2019**, *12*, 182; doi:10.3390/ph12040182

49. Tian, L.-W.; Xu, M.; Li, X.-C.; Yang, C.-R.; Zhu, H.-J.; Zhang, Y.-J. Eucalmaidials A and B, phloroglucinol-coupled sesquiterpenoids from the juvenile leaves of Eucalyptus maideni. *RSC Adv.* **2014**, *4*, 21373–21378.

50. Ahmed, A.; Li, W.; Chen, F.-F.; Zhang, J.-S.; Tang, Y.-Q.; Chen, L.; Tang, G.-H.; Yin, S. Monoterpene indole alkaloids from Rhazya stricta. *Fitoterapia* **2018**, *128*, 1–6.

51. Yu, H.-F.; Qin, X.-J.; Ding, C.-F.; Wei, X.; Yang, J.; Luo, J.-R.; Liu, L.; Khan, A.; Zhang, L.-C.; Xia, C.-F.; et al. Nepenthe-Like Indole Alkaloids with Antimicrobial Activity from Ervatamia chinensis. *Org. Lett.* **2018**, *20*, 4116–4120.

52. Mollataghi, A.; Coudiere, E.; Hadi, A.H.A.; Mukhtar, M.R.; Awang, K.; Litaudon, M.; Ata, A. Anti-acetylcholinesterase, anti-α-glucosidase, anti-leishmanial and anti-fungal activities of chemical constituents of Beilschmiedia species. *Fitoterapia* **2012**, *83*, 298–302.

53. Tian, J.; Shen, Y.; Yang, X.; Liang, S.; Shan, L.; Li, H.; Liu, R.; Zhang, W. Antifungal Cyclic Peptides from Psammosilene tunicoides. *J. Nat. Prod.* **2010**, *73*, 1987–1992.

54. Subban, K.; Subramani, R.; Johnpaul, M. A novel antibacterial and antifungal phenolic compound from the endophytic fungus Pestalotiopsis mangiferae. *Nat. Prod. Res.* **2013**, *27*, 1445–1449.

55. Li, Y.; Yue, Q.; Jayanetti, D.R.; Swenson, D.C.; Bartholomeusz, G.A.; An, Z.; Gloer, J.B.; Bills, G.F. Anti-Cryptococcus Phenalenones and Cyclic Tetrapeptides from Auxarthron pseudauxarthron. *J. Nat. Prod.* **2017**, *80*, 2101–2109.

56. He, X.; Du, X.; Zang, X.; Dong, L.; Gu, Z.; Cao, L.; Chen, D.; Keyhani, N.O.; Yao, L.; Qiu, J.; et al. Extraction, identification and antimicrobial activity of a new furanone, grifolaone A, from Grifola frondosa. *Nat. Prod. Res.* **2016**, *30*, 941–947.

57. Kornsakulkarn, J.; Saepua, S.; Suvannakad, R.; Supothina, S.; Boonyuen, N.; Isaka, M.; Prabpai, S.; Kongsaeree, P.; Thongpanchang, C. Cytotoxic tropolones from the fungus Nemania sp. BCC 30850. *Tetrahedron* **2017**, *73*, 3505–3512.

58. Chen, C.J.; Zhou, Y.Q.; Liu, X.X.; Zhang, W.J.; Hu, S.S.; Lin, L.P.; Huo, G.M.; Jiao, R.H.; Tan, R.X.; Ge, H.M. Antimicrobial and anti-inflammatory compounds from a marine fungus Pleosporales sp. *Tetrahedron Lett.* **2015**, *56*, 6183–6189.

59. Song, R.-Y.; Wang, X.-B.; Yin, G.-P.; Liu, R.-H.; Kong, L.-Y.; Yang, M.-H. Isocoumarin derivatives from the endophytic fungus, Pestalotiopsis sp. *Fitoterapia* **2017**, *122*, 115–118.

60. Phainuphong, P.; Rukachaisirikul, V.; Phongpaichit, S.; Preedanon, S.; Sakayaroj, J. Diphenyl ethers and indanones from the soil-derived fungus Aspergillus unguis PSU-RSPG204. *Tetrahedron* **2017**, *73*, 5920–5925.

61. Li, W.; Gao, W.; Zhang, M.; Li, Y.-L.; Li, L.; Li, X.-B.; Chang, W.-Q.; Zhao, Z.-T.; Lou, H.-X. p -Terphenyl

Derivatives from the Endolichenic Fungus Floricola striata. *J. Nat. Prod.* **2016**, *79*, 2188–2194.

62. Zhang, M.; Chang, W.; Shi, H.; Li, Y.; Zheng, S.; Li, W.; Lou, H. Floricolin C elicits intracellular reactive oxygen species accumulation and disrupts mitochondria to exert fungicidal action. *FEMS Yeast Res.* **2018**, *18*.

63. Lin, Z.; Phadke, S.; Lu, Z.; Beyhan, S.; Abdel Aziz, M.H.; Reilly, C.; Schmidt, E.W. Onydecalins, Fungal Polyketides with Anti- Histoplasma and Anti-TRP Activity. *J. Nat. Prod.* **2018**, *81*, 2605–2611.

64. Lin, Z.; Kakule, T.B.; Reilly, C.A.; Beyhan, S.; Schmidt, E.W. Secondary Metabolites of Onygenales Fungi Exemplified by Aioliomyces pyridodomos. *J. Nat. Prod.* **2019**, *82*, 1616–1626.

65. Tan, D.; Jamieson, C.S.; Ohashi, M.; Tang, M.-C.; Houk, K.N.; Tang, Y. Genome-Mined Diels–Alderase Catalyzes Formation of the cis -Octahydrodecalins of Varicidin A and B. *J. Am. Chem. Soc.* **2019**, *141*, 769–773.

66. Lin, X.; Yuan, S.; Chen, S.; Chen, B.; Xu, H.; Liu, L.; Li, H.; Gao, Z. Heterologous Expression of Ilicicolin H Biosynthetic Gene Cluster and Production of a New Potent Antifungal Reagent, Ilicicolin J. *Molecules* **2019**, *24*, 2267.

67. Li, H.; Gilchrist, C.L.M.; Lacey, H.J.; Crombie, A.; Vuong, D.; Pitt, J.I.; Lacey, E.; Chooi, Y.-H.; Piggott, A.M. Discovery and Heterologous Biosynthesis of the Burnettramic Acids: Rare PKS-NRPS-Derived Bolaamphiphilic Pyrrolizidinediones from an Australian Fungus, Aspergillus burnettii. *Org. Lett.* **2019**, *21*, 1287–1291.

68. Stierle, A.A.; Stierle, D.B.; Decato, D.; Priestley, N.D.; Alverson, J.B.; Hoody, J.; McGrath, K.; Klepacki, D. The Berkeleylactones, Antibiotic Macrolides from Fungal Coculture. *J. Nat. Prod.* **2017**, *80*, 1150–1160.

69. Awaad, A.S.; Al-Aonazi, N.K.; Al-Othman, M.R.; Zain, M.E.; El-Meligy, R.M.; El-Sayed, N. Anticandidal Activity of Extracts and a Novel Compound, Amnomopin, Isolated From Petriella setifera. *Phyther. Res.* **2017**, *31*, 1504–1508.

70. Morandini, L.M.B.; Neto, A.T.; Pedroso, M.; Antoniolli, Z.I.; Burrow, R.A.; Bortoluzzi, A.J.; Mostardeiro, M.A.; da Silva, U.F.; Dalcol, I.I.; Morel, A.F. Lanostane-type triterpenes from the fungal endophyte Scleroderma UFSMSc1 (Persoon) Fries. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1173–1176.

71. Yang, B.; He, Y.; Lin, S.; Zhang, J.; Li, H.; Wang, J.; Hu, Z.; Zhang, Y. Antimicrobial Dolabellanes and Atranones from a Marine-Derived Strain of the Toxigenic Fungus Stachybotrys chartarum. *J. Nat. Prod.* **2019**, *82*, 1923–1929.

72. Intaraudom, C.; Boonyuen, N.; Suvannakad, R.; Rachtawee, P.; Pittayakhajonwut, P. Penicolinates A–E from endophytic Penicillium sp. BCC16054. *Tetrahedron Lett.* **2013**, *54*, 744–748.

73. Haga, A.; Tamoto, H.; Ishino, M.; Kimura, E.; Sugita, T.; Kinoshita, K.; Takahashi, K.; Shiro, M.; Koyama,

Peer-reviewed version available at *Pharmaceuticals* **2019**, *12*, 182; doi:10.3390/ph12040182

K. Pyridone Alkaloids from a Marine-Derived Fungus, Stagonosporopsis cucurbitacearum , and Their Activities against Azole-Resistant Candida albicans. *J. Nat. Prod.* **2013**, *76*, 750–754.

74. Han, J.; Liu, C.; Li, L.; Zhou, H.; Liu, L.; Bao, L.; Chen, Q.; Song, F.; Zhang, L.; Li, E.; et al. Decalin-Containing Tetramic Acids and 4-Hydroxy-2-pyridones with Antimicrobial and Cytotoxic Activity from the Fungus Coniochaeta cephalothecoides Collected in Tibetan Plateau (Medog). *J. Org. Chem.* **2017**, *82*, 11474–11486.

75. Richter, C.; Helaly, S.E.; Thongbai, B.; Hyde, K.D.; Stadler, M. Pyristriatins A and B: Pyridino-Cyathane Antibiotics from the Basidiomycete Cyathus cf . striatus. *J. Nat. Prod.* **2016**, *79*, 1684–1688.

76. Ortíz-López, F.J.; Monteiro, M.C.; González-Menéndez, V.; Tormo, J.R.; Genilloud, O.; Bills, G.F.; Vicente, F.; Zhang, C.; Roemer, T.; Singh, S.B.; et al. Cyclic Colisporifungin and Linear Cavinafungins, Antifungal Lipopeptides Isolated from Colispora cavincola. *J. Nat. Prod.* **2015**, *78*, 468–475.

77. Estoppey, D.; Lee, C.M.; Janoschke, M.; Lee, B.H.; Wan, K.F.; Dong, H.; Mathys, P.; Filipuzzi, I.; Schuhmann, T.; Riedl, R.; et al. The Natural Product Cavinafungin Selectively Interferes with Zika and Dengue Virus Replication by Inhibition of the Host Signal Peptidase. *Cell Rep.* **2017**, *19*, 451–460.

78. Singh, S.B.; Ondeyka, J.; Harris, G.; Herath, K.; Zink, D.; Vicente, F.; Bills, G.; Collado, J.; Platas, G.; González del Val, A.; et al. Isolation, Structure, and Biological Activity of Phaeofungin, a Cyclic Lipodepsipeptide from a Phaeosphaeria sp. Using the Genome-Wide Candida albicans Fitness Test. *J. Nat. Prod.* **2013**, *76*, 334–345.

79. Nakamura, I.; Kanasaki, R.; Yoshikawa, K.; Furukawa, S.; Fujie, A.; Hamamoto, H.; Sekimizu, K. Discovery of a new antifungal agent ASP2397 using a silkworm model of Aspergillus fumigatus infection. *J. Antibiot. (Tokyo).* **2017**, *70*, 41–44.

80. Nakamura, I.; Yoshimura, S.; Masaki, T.; Takase, S.; Ohsumi, K.; Hashimoto, M.; Furukawa, S.; Fujie, A. ASP2397: A novel antifungal agent produced by Acremonium persicinum MF-347833. *J. Antibiot. (Tokyo).* **2017**, *70*, 45–51.

81. Nakamura, I.; Ohsumi, K.; Takeda, S.; Katsumata, K.; Matsumoto, S.; Akamatsu, S.; Mitori, H.; Nakai, T. ASP2397 Is a Novel Natural Compound That Exhibits Rapid and Potent Fungicidal Activity against Aspergillus Species through a Specific Transporter. *Antimicrob. Agents Chemother.* **2019**, *63*.