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Review Article

Advances in Chemical Studies on Low-Molecular Weight Metabolites of Marine Fungi

M. A. Farooq Biabani, and Hartmut Laatsch

Göttingen, Institut für Organische Chemie, Universität

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Abstract. The world oceans represent a resource of huge dimension, but their microbial diversity is still poorly understood. The chemistry of marine fungi was even a widely neglected part of natural product chemistry until recently. But symbiotic and epibiotic coexistence of fungi with higher forms of life, *e.g.* with sponges, forming highly specialised communities gave rise to an increasing interest in their secondary metabolism. More than 100 metabolites from marine fungi are known now, many of them showing fascinating structures or remarkable biological activities. This review gives a comprehensive summary of most structures and discusses their origin and properties.

Contents

Introduction

Over the past 60 years terrestrial fungi offered an enormous scope for the discovery of novel natural products, many of them being potential targets for biomedical developments. The introduction of penicillin in medicine in 1929 started the era of fungal antibiotics and was followed by other important fungal metabolites like cephalosporins and griseofulvins, some of them being still in clinical use as antibiotics or antitumor agents [1]. Although terrestrial fungi continue to be studied extensively, the rate of discovery of novel metabolites is decreasing, due to replication of known compounds.

Recently, chemists on a world wide basis have paid attention towards the potential of marine microorganisms (*e.g.* bacteria, fungi, blue green algae, dinoflagellates etc.), as an alternative source for isolation of novel metabolites with interesting biological and pharmaceutical properties [2, 3]. The world oceans do indeed represent a microbial broad and microbiologically diverse resource of huge dimension but about which we know relatively little. As it is estimated that less than 5% of marine bacterial and fungal species are known, it is clear that the microbial diversity of oceans is still poorly understood. Recent studies of microbial variety using analysis of rRNA sequences have shown that marine microbial picoplankton contains a high abundance of rare species, virtually none of which have ever been isolated and chemically investigated [4].

Terrestrial fungi have proven to produce a variety of chemically interesting and novel metabolites [5, 6], yet only modest attention has been devoted toward isolation of metabolites from marine fungi. In the area of marine natural products chemistry, only a few early reviews have covered the small number of metabolites derived from marine fungi [7–10]. Rapid progress in the isolation of marine fungal metabolites in the 1994–98 period has prompted us to write a review which tries a comprehensive coverage of secondary metabolites isolated from marine fungi till to date. In this article we discuss only low-molecular weight secondary metabolites, but exclude biopolymers as enzymes, or other products of the primary metabolism.

Marine Fungal Diversity and Taxonomic Groups Found in the Sea

Marine fungi are not taxonomically defined, but are classified according to their habitat and in part to their physiology, with representatives from all taxonomic groups. They are geographically widely distributed and appear to occur in all climates and all salinities, but are often uniquely adapted for life in the sea. Many genera are found only there and to colonise a wide range of marine macroorganisms like algae, mangroves, sponges, the shell of crabs and in the gastrointestinal tract of marine fish. Kohlmeyer *et al.* [11] proposed an ecological definition which has gained general acceptance by taxonomists [12]: *Obligate* marine fungi are those that grow and sporulate exclusively in marine or estuarine habitats; *facultative* marine fungi are isolated from marine environments but can also grow under terrestrial conditions. The majority of marine fungi is isolated from intertidal zones of shores or mangroves, estuarine waters, sediments, muds, sand dunes [13]. Fungi from leaves that fall into the marine environment are probably terrestrial. Also for other facultative marine fungi it is doubtful if they are truly marine, *i.e.* that they are actively metabolising and growing in the sea [14].

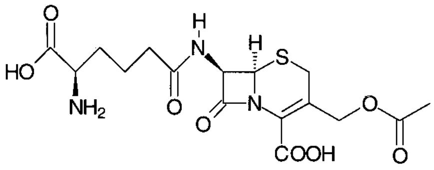
Filamentous ascomycetes and fungi imperfecti are predominating the described marine fungal species. They occur as saprophytes and parasites on sea weed, drift wood and higher marine organisms in littoral and neritic environments [15]. These fungi are not prominent in deep sea environments [16]. The majority of ascomycetes belongs to two groups – the *Halosphaeriales* and the *Loculoascomycetes* (*Pleosporales*). The *Halosphaeriales* form an order largely restricted to the open ocean and coastal waters while the *Loculoascomycetes* are generally found in intertidal habitats, such as mangroves. Lignicolous and mangrove fungi, in particular higher marine fungi have received considerable attention over the last three decades and this is reflected in the higher number of described species [17]. Other taxonomic groups have found less interest.

The first facultative marine fungus, *Spaeria typharum* was reported by Deamazières in 1849, and the first obligate marine fungus, *Sphaeria posidoniae* was published by Durieu and Montagne in 1869. The number of marine fungi discovered during the 1850–1949 period was merely less than twenty. During the 1950–1979 period, the number climbed to nearly five hundred and at present an estimated total of 900 species has been described, most of them belonging to ascomycetes [18]. Schaumann estimated the number of higher fungi to be at least 6000 [14], not including marine yeasts (*Zygomycetes*) and fungi-like protists (lower fungi, *Phycomycetes*). However, published accounts of their chemistry are few, and are concerned chiefly with saline tolerance, nutritional requirements or cellulolytic activities having potential economic as well as biological significance. Marine yeasts also have been described extensively from the biological point of view, but with two exceptions, their chemistry has been investigated only in relation to taxonomy.

Chemical Studies of Fungi from Marine Environments

The first qualitative chemical study concerning the metabolites of marine ascomycetes was published in 1957 by Schafer *et al.* [19], who identified 12 amino acids in *Lulworthia floridana* with paper chromatography. Dietrich *et al.* [20] analyzed in 1958 the oil in a species of *Ceratostomella,* but this was probably a facultative marine fungus. Kirk *et al.* [21] in 1966 identified major constituents of ascospores with various degrees of precision using histochemical methods and confirmed the presence of ergosterol and choline in the mycelia of several ascomycetes and other fungi imperfecti [22]. Findings of the initial phase of these studies demonstrated that the principal amines, sugar alcohols, sterols and triglyceride fatty acids are similar in marine and terrestrial higher fungi [23].

Recent attention is focused on ascomycetes and fungi imperfecti, which include most of the obligate marine fungi. These fungi are not prominent in deep sea environments. More recent chemical studies indicated that marine fungi are like many terrestrial fungi able to produce secondary metabolites in detectable amounts. Other fundamental dissimilarities in secondary metabolism, plus being adapted for life submerged in sea-water, may qualify certain marine fungi for industrial fermentations in which the oceans can provide an inexpensive source of growth medium.



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The only compound from a fungus isolated from a *marine* source that up to now has been established as a medical drug or a source for partial synthetic derivatives is cephalosporin C (**1**). It is produced by cultures of *Acremonium chrysogenum* isolated from sewage taken off the Sardinian coast [24].

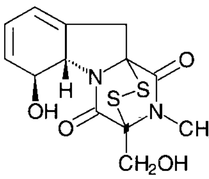
Secondary Metabolites of Fungi Isolated from Sea Sediment

Like the soil, marine sediments are a more nutrient rich micro habitat, but organic content varies greatly from place to place. Sediments from estuaries and bays are obviously nutrient rich and likely to provide a diversity of marine fungi not found in more nutrient limited habitats. Investigation dealing with the secondary metabolites of fungi derived from sea sediments and muds is just beginning, but already a few species showed significant promise.

In 1977, the Okutani group [25] in Japan reported the isolation of the first member of a novel type of dioxopiperazine, gliotoxin (**2**) which is produced by an *Aspergillus sp.* obtained from the bottom mud of Seto island sea. Most substances of this type develop varying antibiotic effects against different test organisms. Gliotoxin displays antibacterial activity specifically against *Staphylococcus aureus* and *Bacillus subtilis,* but is inactive against *Escherichia coli* and *Pseudomonas aeruginosa.* Also other marine microorganisms are known to produce dioxopiperazines. They occur as monomers or dimers and quite often possess sulfur chains of different lengths. Previously, structurally simpler dioxopiperazines have been isolated as secondary metabolites of terrestrial fungi. Gliotoxin was found to be produced also by terrestrial fungi of the genera *Aspergillus, Gliocladium* and *Penicillium*, but gliotoxin was the first antimicrobial compound of this type isolated from the culture broth of a fungus obtained from deep sea sediments.

Melinacidins II–IV (**3a**–**3c**) and gancidin W (**4**) are antimicrobial dioxopiperazines isolated from culture broth of the marine ascomycete *Corollospora pulchella,* separated from the surfaces of sand grains collected from the beach of Miura city, Kanagawa prefecture [26]. The same sulfur-bridged chaetocin derivatives were previously isolated from cultures of *Acrostalagmus cinnabarinus var. melinacidicus.* The sulfur-free gancidin W had been identified before in cultures of a terrestrial microorganism (*Streptomyces gancidus*).

In 1985, another Japanese research group reported the isolation of an antifungal metabolite producing new species in the genus *Zopfiella. Zopfiella marina* Furuya et Udagawa was isolated from the 120 m deep floor mud of the east China Sea [27]. The fungus was found to produce the novel antifungal metabolite zofimarin (**5**) [28] together with zofinol (zopfinol, **6**) [29], a chlorinated phenol with an aliphatic side chain. The deacyl-zofimarin (sordarin) had been isolated previously from the terrestrial microorganism *Sordaria araneosa* [30].



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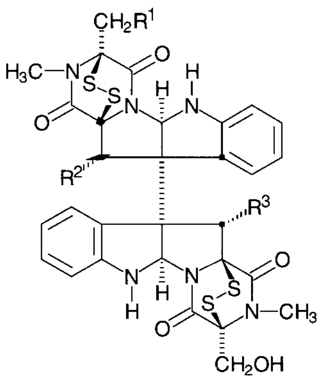
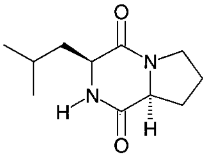


3a-c

	R^1	R^2	R^3
a	H	H	OH
b	OH	OH	H
c	OH	OH	OH



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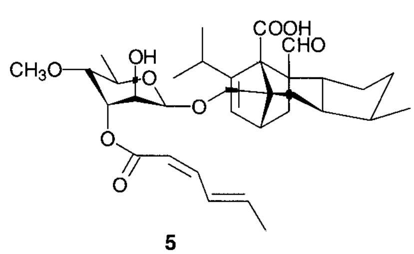

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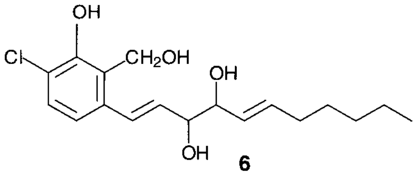

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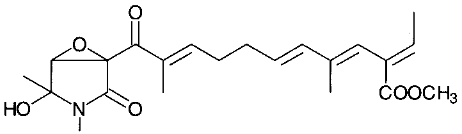

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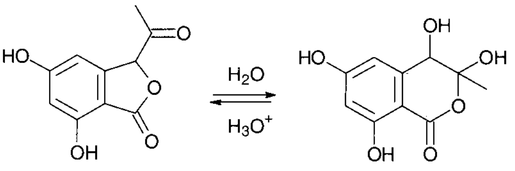
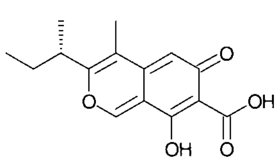
Zofimarin was found in a screening for inhibitors of the HMG-CoA reductase. The pure metabolite exhibited potent antifungal activity especially against *Candida albicans*, but was inactive against bacterial species tested at concentrations up to 100 µg/ml and also inactive in the HMG-CoA reductase test. The compound showed no toxicity at the dose of 50 mg/kg in mice by *i.p.* administration. Most of the strains in the genus *Zopfiella* were isolated from terrestrial environments, thus the marine habitat of *Z. marina* is rare and unique. *Z. marina* is most closely allied to *Z. latipes* and *Z. longicaudata*, but different in shape and colour of ascospore cells.

Osada and co-workers [31] have isolated a novel neuritogenic compound epolactaene (**7**) from a marine fungus. The strain identified as *Penicillium sp.* was isolated from a sea sediment sample collected in the sea bottom of the Uchiura bay, Japan. The structure of the light sensitive molecule, containing an epoxide, γ-lactam, α,β-unsaturated ketone and triene moieties was determined by spectral data. Epolactaene is a new type of neuritogenic compound, causing characteristic changes in the morphology of human neuroblastoma cells (line SH-SY 5Y). When the cells were treated with epolactaene at 2.5–10 µg/ml, neurites were extended from cell bodies in a dose-dependent manner. Epolactaene is the first microbial metabolite effective to the neurite outgrowth of human neuroblastoma cells. It is of interest therefore, if the closely related fusarins from terrestrial *Fusarium moniliforme* [32] show similar activities.

Continuing these investigations, the same group [33] has recently described acetophthalidin (**8**), a novel inhibitor of mammalian cell cycle. The producing strain was identified as *Penicillium sp.* and isolated from a sea sediment sample collected from off-shore bottom near Miho, Sizuoka prefecture, Japan. Acetophthalidin (**8**) completely inhibited the cell cycle progression of a mouse tsFT210 cell line in the M phase at a concentration of 6.25 µg/ml. The labile acetophthalidin (**8**) could not be isolated directly, but Osada and co-workers observed that the fungus produced also the proto-inhibitor 3,4,6,8-tetrahydroxy-3-methyl-3,4-dihydroxy coumarin (**9**) in high yield (966 mg/2.5 l) which could be readily isolated and later on converted into **8** by heating in water at pH 1. The compound **9** had previously been isolated by Ayer *et al.* [34] in 1987 as a metabolite of *Ceratocystis minor*, a fungus associated with the blue stain disease of Canadian pine trees. The acetophthalidin synthesis was achieved by adopting the general synthetic method of substituted coumarins.



8 **9**



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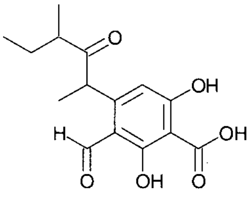

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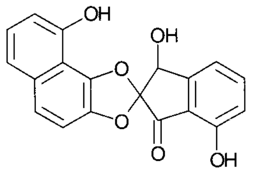

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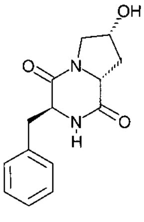

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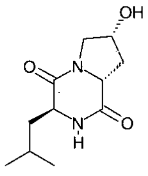

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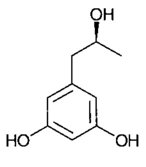


15a
b: C=O instead of CH, OH

In a recent screening of marine fungi from European habitats, extracts from *Kirschsteiniothelia maritima*, *Corollospora maritima*, *Humicola alopallonella*, and *Nia vibrissa* showed pronounced antibiotic activity. From *K. maritima*, the terrestrial metabolite ascochitin (**10**) and the new intermediate of its biosynthesis, M-9/2 (**11**) were isolated [35].

Among the collection of the Sankyo research group at the sea side of Ito-shi, Shizouka, Japan is the unusual black marine yeast, *Hormonema sp.* (*Pullularia sp., Aureobasidium sp.*). Sea water culture of this organism produced a new spiro-indanone derivative with an unprecedented skeleton: Indanonaftol A (**12**) is the first compound reported from a marine yeast [36]. Structure **12** was elucidated by spectroscopic data and chemical degradation. Indanonaftol was slightly active against Gram-positive bacteria.

A second yeast, *Aureobasidium pullulans*, isolated from a marine sponge collected at Okinawa and grown in peptone, yeast extract, glucose broth, produced the new diketopiperazines **13** and **14** containing D-*cis*-4-hydroyproline; **14** was isolated as pair of diastereomers with D- and L-leucine [37]. Dioxopiperazines with *L-trans*-4-hydroxyproline residue had been isolated from rabbit skin tissue previously. The configuration of the amino acids was determined by HPLC on a chiral column. A third new compound from this yeast was (*S*)-orcinotriol (**15a**). Although orcinol derivatives are common in microorganisms, oxygen in β-position of the side chain is very rare and only α-acetylorcinol (**15b**) from the fungus *Cochliobolus lunata*, citreochlorol and citreovirone from *Penicillium citreo-viride* are known. Biological activities have not been reported.

From the same yeast *Aureobasidium pullulans*, a group of closely related cyclopeptides, aureobasidins A-R was isolated. But apparently this strain was isolated from a terrestrial source [38].

Chemical Studies of Fungi Derived from Marine Flora

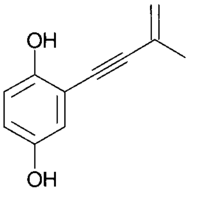
Fungi from Mangroves and other Plants

Open ocean waters are nutrient-deficient, but coastal waters, in particular mangrove areas, have an abundant supply of all kinds of plant materials for colonisation.

Mangrove areas are typical brackish water zones and vary considerably in temperature and salt content of the water. While open oceans have a salinity of about 3.5%, especially in monsoon season in mangroves the salinity can be lower than 0.5%. Fungi have to depend on dissolved organic substances, floating algae and plankton for their nutrient and need special temperatures and salinities. Mangroves can provide these conditions and hence proved to be a rich resource of marine fungi: In a recent study on manglicolous fungi of the Red Sea in upper Egypt, 36 species were isolated from random wood samples, including 26 *Ascomycotina*, 6 *Deuteromycotina*, one *Basidiomycete*, and three unidentified species. The most common species were *Halosphaeria quadricornuta*, *Leptosphaeria australiensis*, and *Periconia prolifica* [39]. A similar result was recorded on mooring posts of oak and larch in Denmark, and even a remarkable substrate specificity of the fungi for the two tree species was found [40] which was also reported from other authors [41]. It is worth mentioning that the occurrence of fungi depends strongly on the incubation period: Six months incubation of driftwood yielded about 70% of the total marine fungi encountered [42].

Among the first metabolites from mangrove basidiomycetes, Kupka *et al.* [43] reported the isolation of siccayne (**16**) from the cultures of *Halocyphina villosa*. This fungus develops its minute cup-shaped fruiting bodies on mangrove roots. Siccayne is a monoprenylated hydroquinone, previously isolated from a terrestrial deuteromycete *Helminthosporium siccans* [44]; some related compounds (eutypine, culpin, frustulosinol or foeniculoxin) have been reported from other sources. Siccayne is moderately active against Gram-positive bacteria and some fungi at concentrations of 10–50 μg/ml. Siccayne inhibits also the uptake of nucleoside precursors into DNA and RNA and shows cytotoxic effects in a chicken embryo fibroblast test and against Ehrlich ascites carcinoma cells.

From an ascomycete *Helicascus kanaloanus* Kohlmeyer (ATCC 18591) found in Hawaiian mangrove, Gloer and co-workers [45] isolated two epimeric new δ-lactones, helicascolide A (**17a**) and B (**17b**), together with the known (*S*)-(+)-ochracin [(*S*)-mellein, **18**]. The structures and relative configurations of these metabolites were assigned by NMR studies, and absolute configurations are proposed based on CD data. Isolation of these relatively simple but uncommon *gem*-dimethyl δ-lactones indicates that marine fungi may possess biosynthetic capabilities which differ in some respect from those of terrestrial fungi. However, up to date no biosynthetic studies were reported.



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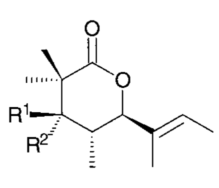
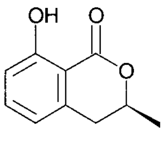


17a: $R^1 = H, R^2 = OH$
b: $R^1 = OH, R^2 = H$



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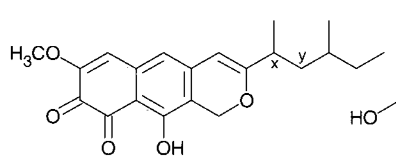
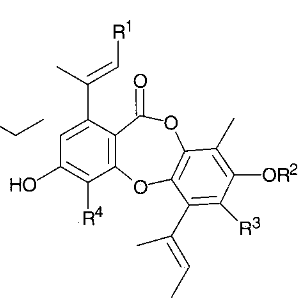
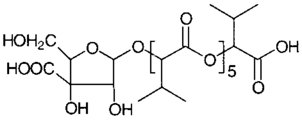


19a
b: x,y = double bond



20a–c:	R^1	R^2	R^3	R^4
a	CO_2H	Me	H	CH_2OH
b	CO_2H	Me	H	CHO
c	Me	H	CO_2H	CHO



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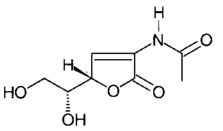


22

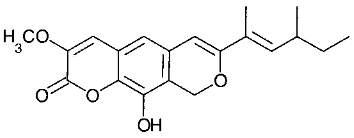
From artificial sea water culture of a halotolerant ascomycete *Passeriniella obiones* (formerly *Leptosphaeria obiones* (Crouan et Crouan Saccoro), Gloer and co-workers [46] also reported the isolation of obionin A (**19a**), one of the rare naturally occurring *o*-quinone derivatives. It represents a regular nonaketide which has been modified by addition of C1 units to its side chain. The marine fungus *P. obiones* was isolated from salt marsh grass *Spartina alterniflora* in the coastal marshlands of Sapelo island, Georgia. *L. obiones* is commonly found in the lower portions of marsh grasses that are regularly immersed by the tides, and has been classified as an obligate marine fungus. Obionin A showed potential CNS activity and inhibited binding of the dopamine D1 selective ligand ^{3}H-SCH-23390 to bovine corpus striatum membrane with an IC_{50} of 2.5 μg/ml.

A recent report from the same group [47] describes auranticin A (**20a**) and an oxidized analogue B (**20b**) which further underscores the potential of mangrove fungi to produce new secondary metabolites. The auranticins were isolated from cultures of mangrove fungus *Preussia aurantiaca* and exhibited antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis*. The depsidone **20c** from *Sirodesmium diversum* is closely related, and many other depsidones have been isolated from lichens. Continuing these investigations, the same group has isolated the very unusual diacid hymenoscyphin A (**21**) from the salt marsh fungus

Hymenoscyphus sp. Hymenoscyphin shows toxicity against brine shrimp at 10 µg/ml and consists of unusual repeating α-hydroxy isobutyric acid groups.

Although marine ascomycetes such as *Leptosphaeria sp.* are significant inhabitants of shallow marine environments, their distribution on living surfaces in the ocean remains unclear. Several investigations of *Leptosphaeria sp.* are reported making this marine fungus to the most widely studied one. The first novel secondary metabolite from a marine fungus was leptosphaerin (**22**) from *Leptosphaeria oraemaris* [48] demonstrating that this group of organisms is able to use its own biosynthetic pathways. The structure was established by X-ray crystallography and stereoselective synthesis [49–51]. Leptosphaerin is a unique 2-aminohexose derivative that has undergone substantial oxidative modification. Its absolute configuration suggests a biogenetic origin in *D*-glucose, perhaps *via* transamidation of fructose.

The plant *Arundo donax* collected in the mouth of the Sarno river near the bay of Naples has yielded another strain of *Leptosphaeria oraemaris*. Extracts of this culture produced structurally different nonaketide-derived lactones, leptosphaerolide (**23**) and traces of leptosphaerodione (**19b**) [52]. The most abundant compound in the extracts was the acetone adduct **24**; but as this derivative is also formed by treatment of **19b** with acetone, this may be an artefact. Leptosphaerodione (**19b**) may be a biosynthetic intermediate, and forms **23** *via* a rearrangements of the *o*-quinone. The production of secondary metabolites is highly dependent on the culture conditions and the origin of the strains, and none of the metabolites previously isolated from *L. obiones* [48, 53] was obtained now.



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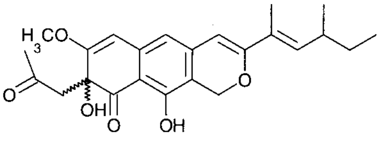

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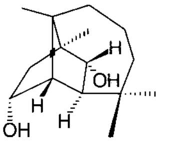

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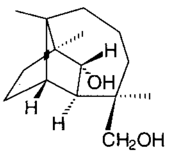

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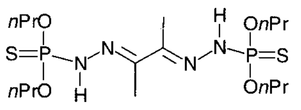

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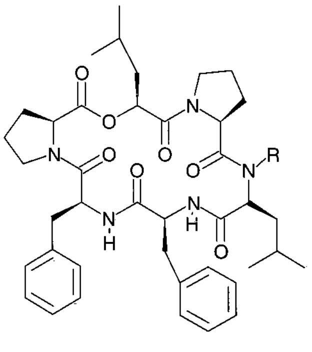
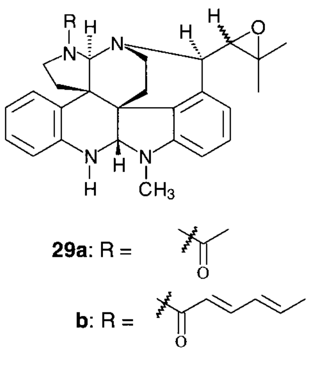


28a: R = Me
b: R = H



29a: R =
b: R =

To assess the degree of interspecies chemical competition of fungi, Strongman *et al.* [53] compared the antifungal activity of 27 lignicolous fungi collected from submerged wood surfaces and found four strains showing inhibitory properties. Further cultivation of one of the active *Leptosphaeria oraemaris* strains afforded the sesquiterpene diol culmorin (**25**). The latter had been previously isolated from *Fusarium* spp. and several other terrestrial species and identified as an antimycotically acting principle responsible for interspecies competition. These results indicated that chemical defence is an important adaptation mechanism of fungi competing for limited substrates.

Alam and co-workers reported [54] the isolation of the new culmorin analogue isoculmorin (**26**) from *Kallichroma tethys* (Kohlmeyer and Kohlmeyer). The tricyclic sesquiterpene structure of isoculmorin was determined by X-ray crystallography. The same group as well previously reported three substances from the mycelium of *Lignincola laevis*. The main constituent, an unusual dimerised phosphorohydrazide thioate with the proposed structure **27** was found to be responsible for strong cytotoxic effects against mouse murine leukaemia cell line (L 1210) at a level of 0.25 µg/ml. This was the first report of isolation of a new cytotoxic compound from marine fungal extracts. It was supposed that **27** is a biotransformation product of a pesticide present in the sea water. However, in-depth chemical literature survey did not reveal pesticides with comparable chemical structures. The minor components from *Lignincola laevis* were identified as 7-hydroxyergosterol and a common ceramide **69b** [55].

As part of their program aimed at the discovery of ecologically relevant natural products, Fenical *et al.* [56] described two new cyclodepsipeptides, exumolides A (**28a**) and B (**28b**). Both compounds exhibited phytotoxic activity against the unicellular marine microalga *Dunaliella sp.* (Chlorophyta) in a range of 20 µg/ml. The fungal isolate was obtained from decaying plant material collected subtidally in the Bahama region, and identified as a member of the genus *Scytalidium* by fatty acid methyl ester analysis.

Strains of *Thraustochytrium spp.* (fungi-like protists, *Labyrinthulomycota*) isolated from decaying mangrove leaves have been shown to produce *in vitro* significant amounts of a lipid with 22 : 6 docosahexenoic acid (DHA) comprising over 60% of total lipids [57]. Recent use of long chain polyunsaturated acids for the treatment and alleviation of a wide range of human disorders and as a dietary supplement has lead to commercial interest in microbial lipids as an alternative source for these compounds to fish oils.

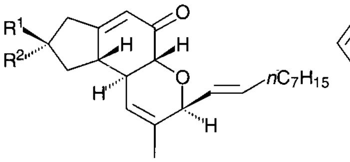
In the past decade, the mangrove habitat has proved to be a rich source of new species and these now form the second largest ecological sub-group of marine fungi. Some species of mangrove fungi can be considered as extremophiles as they grow and reproduce attached to sand grains in low nutrient beach soils. Even the common intertidal colonisers for instance mangrove trees, must also be able to tolerate extreme fluxes in external environmental factors. Chemical investigations of mangrove fungi in search of biologically active natural products began only few years ago hence there is still an enormous task ahead.

Fungi from Marine Algae

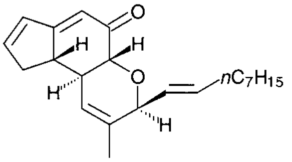
Marine algae have nutrient-rich surfaces and a diverse array of polysaccharides; they usually harbour many microorganisms, which is expressed by the fact that algae have been favourite research targets for isolation of fungi in recent years. Relatively few species of fungi associated with marine algae have been chemically explored and that circumstance also is reflected by the fact that few secondary metabolites have been isolated from these sources. Although much of the chemical evidence is fragmentary, the results obtained to date suggest that future chemical research of algae associated fungi will be exciting and rewarding.

Investigation of secondary metabolites from fungi associated with marine algae was initiated by Pedersén *et al.* [58], who detected four bromo compounds in an axenically cultured fungus, most probably *Mycosphaerella ascophylli*. The marine ascomycete lived as an endophyte in the brown alga *Ascophyllum nodosum* and grew out slowly on nutrient agar medium from pieces of algal thallus, which had been surface sterilised by treatment with ethyl alcohol and conc. calcium hypochlorite solution. The mycelial extract afforded bromo compounds, one of them being identified as 3,5-dibromo-*p*-hydroxybenzyl alcohol. Previously, such bromophenols as 2,3-dibromo-4,5-dihydroxybenzyl alcohol have been identified only in marine algae [59], in sea water [60] and in the culture filtrate of a blue-green alga [61].

On screening for novel cytotoxic metabolites from fungi, Numata and co-workers [62] reported the isolation of two cytotoxic alkaloids, the communesins A (**29a**) and B (**29b**) from the cultured mycelium of a *Penicillium sp.* originally isolated from the marine alga *Enteromorpha intestinalis*. The structure of communesins was elucidated by spectroscopic analysis. Communesins exhibited moderate cytotoxic activity against cultured P-388 lymphocytic leukaemia cells with ED_{50} = 3.5 and 0.45 μg/ml, respectively. Although communesins A and B differ only in the structure of the acyl group, they exhibit roughly a 10-fold variation in their cytotoxicity.



30a: R^1 = OH, R^2 = H
b: R^1 = H, R^2 = OH



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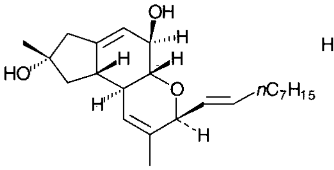
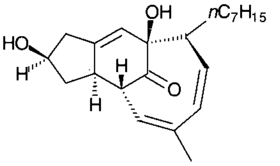
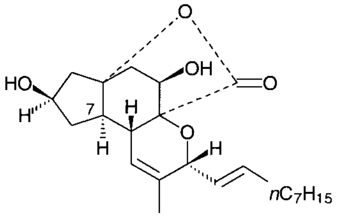


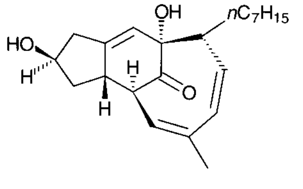
32



33



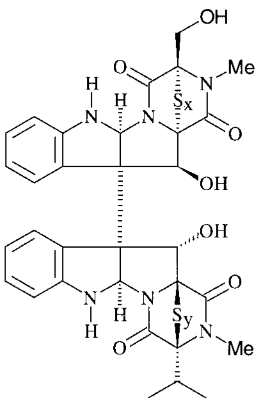
34a
b: opposite config. at C-7



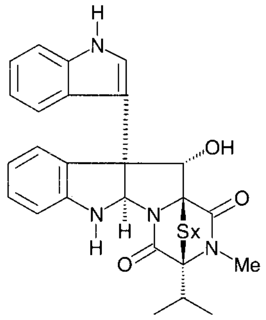
35

The same *Penicillium sp.* cultivated under different nutrient conditions has led to the isolation of four new compounds [63], penostatins A–D (**30a–32**). Penostatins A–D exhibited cytotoxic activities with ED_{50} 0.8, 1.2, 1.1, and 11.5 μg/ml, respectively in the P388 lymphocytic leukaemia test system in cell culture. From the same source, the penostatins F-I (**33–35**) were isolated recently [64]. It is surprising that all asymmetric centres of compound **33** except for C-5 had the opposite absolute configuration to those of isomer **35**. Such examples have never before been reported. The cytotoxic activities were in the range of 0.5–1.4 μg/ml. Both groups don't have terrestrial counterparts.

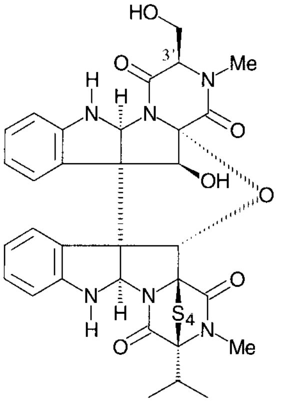
The same group has also reported the isolation of a series of dimeric epipolysulfanyldioxopiperazines, leptosins A–C (**36a–36c**), D–F (**37a–37c**) [65], the G group (G, G_1, G_2: **36d–36f**), H (**36g**) [66], I and J (**38a, 38b**) [67], and the K group (K, K_1, K_2: **39a–39c**) [68]



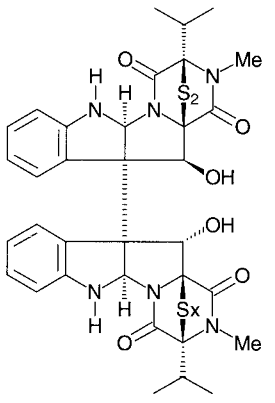
36a–g	a	b	c	d	e	f	g
x	4	3	2	4	3	2	2
y	2	2	2	3	3	3	4



37a: x = 2
b: x = 3
c: x = 4



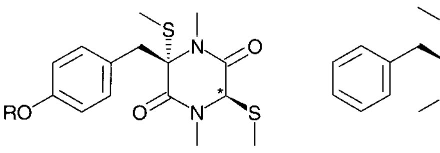
38a
b: opposite config. at C3'



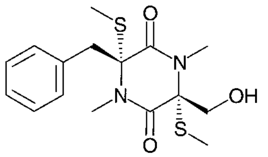
39a: x = 2
b: x = 3
c: x = 4

from *Leptosphaeria sp.* The strain was originally separated from the marine brown alga *Sargassum tortile* C. Agard (Sargassaceae) collected in the Tanabe Bay of Japan. The leptosins are structurally related to the melinacidins (**3a**–**3c**) and to the previously isolated terrestrial metabolites chaetocin, chetomin, chetracin A [69] and verticillins (A: 2 Me instead of 2 *i*-Pr in **39a**) [70]. The stereo structures, with configurations different from those of related compounds were elucidated by spectroscopic techniques and some chemical transformations. All compounds exhibited potent cytotoxicity against P388 lymphocytic leukaemia cells, among them the dimeric epipolysulfanyldioxopiperazines showed more potent activity than the monomeric indolyl epipolysulfanyldioxopiperazines **37a**–**37c**. The number of sulfur atoms in dioxopiperazine rings did not influence the activity. Compounds **36a** and **36c** showed significant antitumor activity against sarcoma 180 ascites (T/C 260 and 293) at doses of 0.5 mg $kg^{-1}$and 0.25 mg kg^{-1}, respectively.

Penicillium waksmanii Zaleski OUPS-N133 from *Sargassum ringgoldianum* as well produced a number of sulfur-containing dioxopiperazines **40a**–**40c** [71]. The metabolite **40b** is a diastereomer and double bond isomer of cis-bis(methylthio)silvatin (**40d**) from *Penicillium brevi-compactum* [72]. From *Gliocladium virens*, a **40c** diastereomer with shifted double bond is known as well. Additionally to the known pyrones pyrenocine A (**42**) and B (**43a**), the new pyrenocines D (**44**) and E (**43b**) were isolated from *P. waksmanii*. As expected from other related pyrones, also the pyrenocines showed significant cytotoxicity (< 1 μg/ml) [71].



40a–d	R
a	H
b	CH=CH-*i*-Pr
c	CH=CH–CHMe–CH$_2$OH
d	CH$_2$–CH=CMe$_2$ opposite config at*



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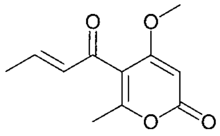
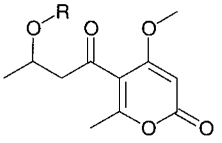
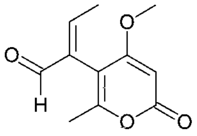


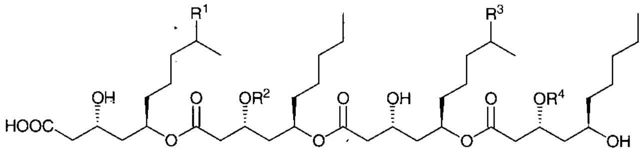
42



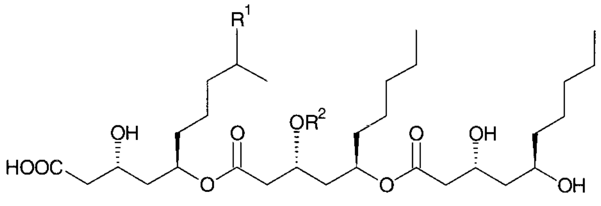
43a: R = H
b: R = Me



44



45a–c	R^1	R^2	R^3	R^4
a	H	Ac	H	H
b	H	Ac	H	*β*-*D*-mannosyl
c	OH	H	OH	H

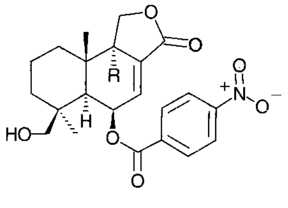


46a–c	R^1	R^2
a	H	Ac
b	OH	H
c	H	H

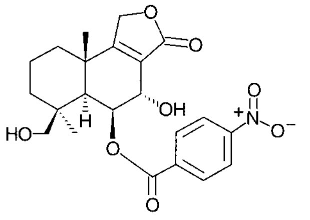
Obligate marine fungi are frequently isolated from both living and decaying marine algae and drift wood even in depths. Investigations of the obligate marine deuteromycete *Asteromyces cruciatus* F. et Moreau ex Hennebert from living and dead algae in the lower Chesapeake Bay [73] yielded as single major product gliovictin (**41**) beside triglycerides and sterols. Gliovictin was previously isolated from terrestrial fungi of the genera *Helminthosporium* and *Penicillium* and is related to **40a**, but has a different stereochemistry.

More recently novel conjugates of di- and trihydroxydecanoic acid tetramers named halymecins A (**45a**), B (**45b**), D (**45c**) and trimers C (**46a**) and E (**46b**) were identified by Chen *et al.* [74]. Halymecins A, B, D were isolated from the sea water culture of a *Fusarium sp.* separated from a marine alga *Halymenia dilatata,* collected at the Palau islands. The 3,5-dihydroxydecanoic acid trimers **46a** and **46b** came from another marine *Acremonium sp.* isolated from an unidentified marine alga, collected from Aburatsubo at Kanagawa prefecture, Japan. The stereo structures of halymecins were determined by extensive 2D-NMR studies as well as mass spectral data and chemical degradation. The 3,5-dihydroxydecanoic acid substructure is not known from terrestrial sources. Halymecin A showed strong antimicroalgal activity against the diatom *Skeletonema costatum* and was active against green algae *Brachiomonas submarina* and dinoflagellate *Prorocentrum micans.*

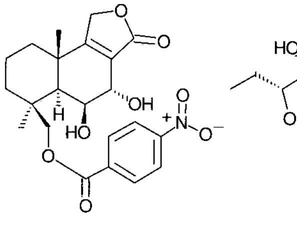
Finally, there is a very recent report which further underlines the potential of algae associated fungi to produce unique metabolites. Christopherson's and co-workers comprehensive study of a marine fungus resulted in the isolation of new nitrobenzoyloxy-substituted sesquiterpenes from various isolates of *Aspergillus insulicola* [75]. The strains were fermented on two different yeast extract/sucrose media (CYA, YES), and SB medium (potato starch, soybean meal, sea salts). Two strains grown on CYA and SB produced the nitrobenzoyloxy-substituted tricyclic sesquiterpene insulicolide A (**47a**), the known neurotoxin asteltoxin (**50**), and also the terrestrial metabolites penicillic acid, 4-hydroxymellein, xanthomegnin, viomellein, and vioxanthin. Insulicolide A resembles the BCD rings of the steroid skeleton. Its structure was characterised by X-ray crystallography and is closely related to the astellolides A and B isolated from *Aspergillus variecolor* [76] and drimane sesquiterpene esters from *Aspergillus ustus* var. *pseudodeflectus* [77]. It was later on found also in terrestrial isolates of *A. sclerotiorum* and *A. bridgeri*, but not in any other species related to the genus *Petromyces* (formerly *A. ochraceus* group). The *p*-nitrobenzoic acid has not been reported for terrestrial antibiotics so far.



47a: R = OH
b: R = H



48



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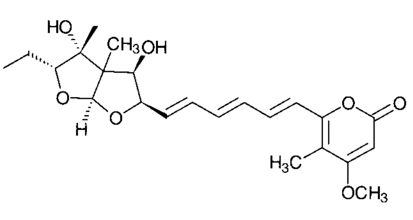


50

Insulicolide A (9a,14-dihydroxy-6β-*p*-nitrobenzoylcinnamolide, **47a**) and three closely related sesquiterpenes (14-hydroxy-6β-*p*-nitrobenzoylcinnamolide, **47b**; 7a,14-dihydroxy-6β-*p*-nitrobenzoylconfertifolin, **48**; 6β,7a-dihydroxy-14-*p*-nitrobenzoylconfertifolin, **49**) were recently described as metabolites of *Aspergillus versicolor* isolated from a Caribbean green alga *Penicillus capitatus* by Fenical *et al.* [78]. They showed significant activity against HTC-116 human colon carcinoma cells in vitro and moderately selective cytotoxicity toward various renal tumor cell lines.

Chemical Studies of Fungi Derived from Fauna

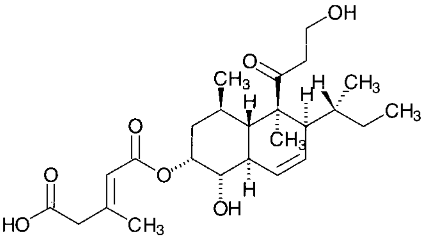
Fungi Associated with Marine Sponges and Tunicates

In the last few years sponges became the dominant source of novel bioactive compounds. The increase in studies explains in large part the growing diversity of structural types reported from marine sponges. Sponges may have a wider range of biosynthetic capabilities than any other group of marine invertebrates. But it is widely accepted now, that at least a part of spongal metabolites is produced by associated or symbiotic microorganisms.

A first literature precedent of metabolites from sponge-associated fungi appeared in 1993. Kitagawa and coworkers [79] reported a new polyketide trichoharzin (**51**) from an imperfect fungus *Trichoderma harzianum* Rifai. The fungus was separated from a marine sponge *Micale cecilia* collected at Amami Island, Kagoshima prefecture, grown in the Wickerham medium prepared with sea water. *Trichoderma harzianum* Rifai is a widespread soil fungus and is known to produce antibiotics active against other microscopic fungi. Trichoharzin is an octaketide with an alkylated decalin skeleton and esterified with 3-methylglutaconic acid. The latter is a rare acid and known to occur only in some lichen chromones and the terrestrial fungal metabolites, helicusins [80]. The free acid was isolated from the terrestrial fungus *Cephalosporium aphidicola* [81]. The skeleton of trichoharzin is related to betaenones, previously isolated from the culture filtrate of *Phoma betae* Fr., a casual fungus of leaf spot disease of sugar beat. It is noteworthy also to mention that the chemical constituents of *T. harzianum* grown in fresh water medium differed significantly from those grown in sea water.

Another *Trichoderma harzianum* strain from the sponge *Halichondria okadai* collected in Japan produced trichodenones A–C (**52–54**), harzialactones A and B (**55**, **56**), and (*R*)-mevalonolactone (**57**) [82]. The stereostructure of the harzialactones was revealed by comparison with antafumicins A and B (**58a**, **58b**). The cyclopentenones **52–54** showed significant cytotoxicity against cultured P388 cells with ED_{50} values of 0.21–1.45 µg/ml.

In the early nineties, Crews and co-workers initiated a program to explore chemically prolific sponge-derived fungi. They reported soon three novel halogenated sesquiterpenoids, chloriolin A–C (**59–60b**) along with two known metabolites, from an unidentified *Hyphomycete* isolated from the Indo-pacific sponge *Jaspis aff. johnstoni* [83]. Chloriolins are bi- and tricyclic sesquiterpenes of the coriolin class. The structures were established by 2D-NMR experiments, synthetic transformations and X-ray crystallography. The other two hirsutene derivatives, coriolin B (**61a**) and dihydrocoriolin C (**61b**, both without the "Cl" in the name) had been reported earlier from the terrestrial wood rotting fungus *Coriolus consors*. Chloriolin B was potent against two human tumor cell lines and exhibited IC_{50} values of 0.7 µg (breast) and 0.5 µg (neuroblastoma). Chloriolin A and C, however, did not show any disease oriented biological activity in the NCI screening, despite a large number of reactive functionalities in the molecules.



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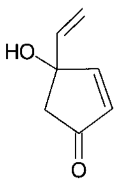

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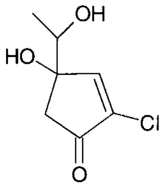

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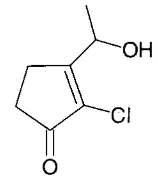

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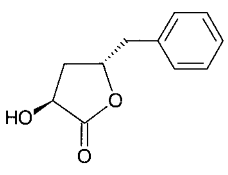

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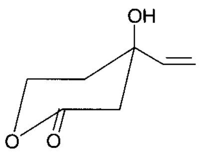

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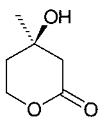

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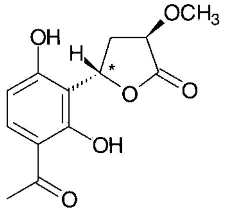
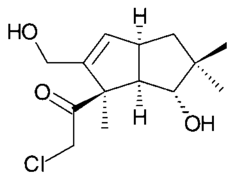


58a
b: config. at* opposite



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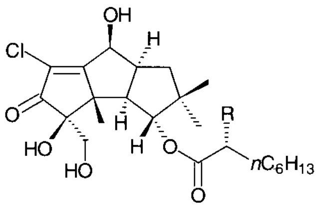
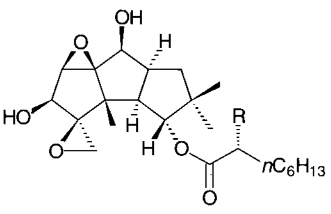


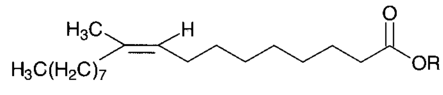
60a: R = OH
b: R = H



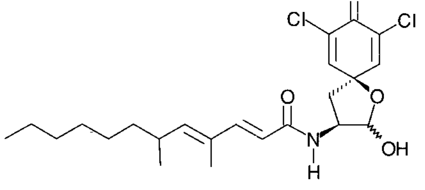
61a: R = H
b: R = OH

In a continuing investigation the Crews group also reported [84] an unidentified fungus or mixture of two different fungi obtained from aseptic sections of an encrusting sponge *Stylotella sp.* collected at Somosomo strait near Taveuni, Fiji. The ethyl acetate extract of the filtered broth yielded two new α-pyrone metabolites, demethyl nectriapyrone A (pestalopyrone, **62a**) and nectriapyrone B (**62b**). These pyrones are structurally related to previously reported nectriapyrone A (**62a**, R^1 = Me) isolated from the terrestrial fungus *Gyrostroma missouriense*, with helicascolides **17a**, **17b** and tetraacetic acid lactones isolated from *Penicillium stipitatum*. Similarities with these structures strongly suggests that they all arise from a common tetraketide core.

Similarly, a recent addition to the marine halogenated fungal metabolites were the first chlorine containing polyketides, chlorocarolide A (**63a**) and B (**63b**) isolated from the salt water culture of *Aspergillus ochraceus* separated from the Indo-pacific sponge *Jaspis cf. coriacea*. An appealing structural analogy is evident between the chlorocarolides and carolic acid (**64**), a tetronic acid derived from *Penicillium charlessi* [85]. Chlorocarolides have also structural similarities with those of the litsenolides from the roots of *Litsea japonica* and the mahubenolides from the trunk wood of *Clinostemon mahuba*. In addition to chlorocarolide A and B, several other known polyketide compounds were reported from the same fungus including (–)-(*R*)-mellein (*R*-**18**), penicillic acid (**65**) and (+)-hexylitaconic acid (**66**). It is noteworthy that these compounds have been isolated earlier from a terrestrial culture of *A. ochraceus*. Mellein is a widespread metabolite and was also reported from other terrestrial fungi, *e.g. Aspergillus melleus*. The structures of these compounds were determined by comparing spectral properties of identical gross structures. The relative stereochemistry at the four chiral centers of both chlorocarolide diastereomers was determined by comparing experimental ^3J coupling constants versus calculated values [86]. Further contributing to this emerging subject, the same group more recently reported the isolation of a new mildly antibiotic polyketide 14,15-secocurvularin (**67**) [87] from an unidentified fungus derived from inside of the encrusting sponge *Spirastrella vagabunda*. 14,15-Secocurvularin has close structural resemblance to curvularin class of compounds. Curvularin (atoms 14, 15 connected in **67**) was previously isolated from four different fungal genera, *Curvularia, Cochliobolus, Penicillium* and *Alternaria*.



70a,b	R
a	H
b	$-CH_2CH(OH)CH_2OH$



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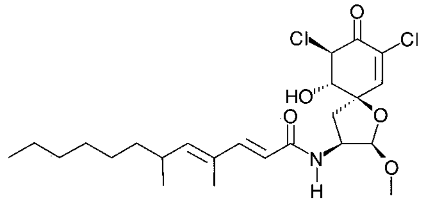

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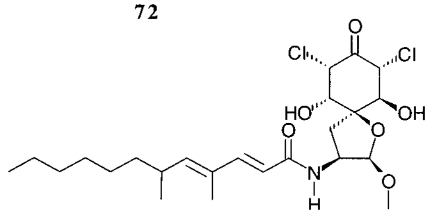

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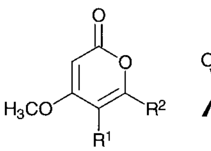
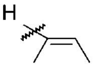
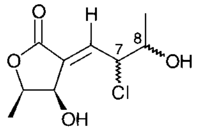
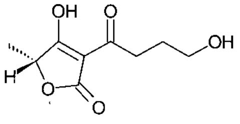


62a: $R^1 = H$
$R^2 =$ 

b: $R^1 = CH_3$
$R^2 = Et$



63a: 7*R*, 8*R*
b: 7*S*, 8*S*



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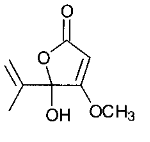
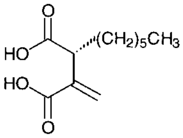


65



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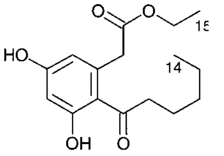

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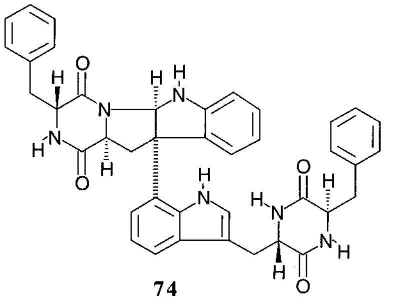

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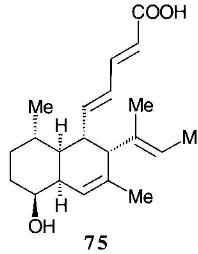

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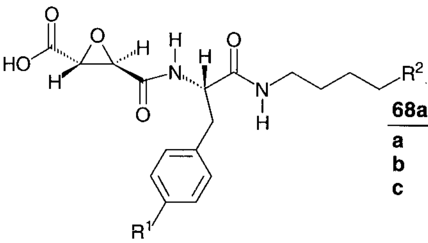
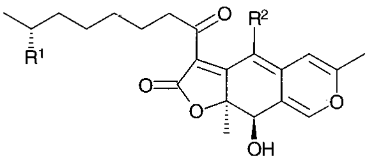
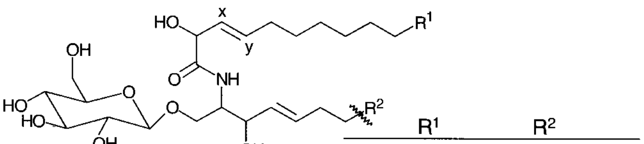


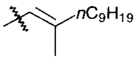
68a–c	R^1	R^2
a	H	NH_2
b	OH	NH_2
c	OH	CH_2NH_2



76a–d	R^1	R^2
a	OH	CHO
b	H	CHO
c	OH	H
d	H	H



69

	R^1	R^2
69a	nC_8H_{17}	 nC_9H_{19}
b	nC_6H_{13}	$nC_{15}H_{31}$

x,y = single bond

Microascus longirostris SF-73 was isolated from a marine sponge, collected at Harrington point, Otago harbour, New Zealand. The methanol extract of the mycelium has yielded three metabolites, cathestatins A, B (**68a**, **68b**), which are closely related to terrestrial estatins A and B (**68a**, **68b** with R^2 = guanidino residue) from terrestrial *Myceliophthora thermophila* [88]. The homologue cathestatin C (**68c**) has been new and unreported [89]. Among these metabolites cathestatin A and B exhibited potent and irreversible *in vitro* inhibition against the cysteine proteases papain, with IC_{50} values in lower nanomolar range. However, this class of protease inhibitors possessing an epoxysuccinate functional group is reported to induce hepatic injury, thereby limiting their potential as new medicinal agent, but they may become useful tools for biological research.

In a search for new antibacterial metabolites from marine fungi, Doshida *et al.* reported the isolation of exophilin A (**46c**) [90]. Compound **46c** is another new acyclic aliphatic lactone from the marine fungus *Exophiala pisciphila* which was isolated from a marine sponge *Mycale adhaerens*. The structure was determined as a trimer of (3*R*,5*R*)-3,5-dihydroxydecanoic acid by spectral methods and chemical degradation. Exophilin A showed moderate antimicrobial activity against Gram-positive bacteria in a range of 12.5–50 μg/ml.

Recent investigation of *Microsphaeropsis olivacea* (Bonord.) Höhn, isolated from a marine sponge *Agelus sp.* collected off Sombrero Key East, Florida has produced cerebroside, being identified as *N*-2'-hydroxy-3'*E*-octadecenoyl-1-*O*-*β*-*D*-glucopyranosyl-9-methyl-4*E*,8*E*-sphingadiene (**69a**) [91]. Later, from the same species an unusual methyl branched unsaturated linear fatty acid, 10-methyl-9*Z*-octadecenoic acid (**70a**) and its monoglyceride **70b** were isolated. The structure and location of the double bond was established by MS spectral and partial chemical fragmentation [92]. The isolation of cerebrosides from *M. olivacea* is the first account of the isolation of a cerebroside from a Coelomycete. Cerebrosides are of interest because of their cytotoxic activity, their synergism with the known glucan synthetase inhibitor aculeacin, and their important biological role as cell surface antigens and receptors.

The spirocyclic gymnastatins A–C (**71–73**) were formed by *Gymnascella dankaliensis*, isolated from the sponge *Halichondria japonica* [93]. All three compounds exhibited moderate cytotoxic activity in the P388 lymphocyte leukemia test in cell culture (ED_{50} A: 0.018, B: 0.108, C: 0.106 mg/ml). The chlorohydrin **73** may be obtained biosynthetically by reaction of bis-epoxid aranorosin [94] with hydrochloric acid and methanol.

From an *Aspergillus niger* saltwater culture, obtained from the Caribbean Hyrtios sponge, the unique unsymmetrical dioxopiperazine dimer asperazine (**74**) was isolated. The structure was determined by mea~~ns~~ of spectroscopic methods. Asperazine displayed remarkable cytotoxicity and an interesting leukaemia selectivity [95]. Inhibitors of microtubule assembly like taxol have found world-wide interest as antitumor agents. A new antimitotic metabolite from the sea is phomopsidin (**75**), a constituent from a *Phomopsis sp.* strain TUF 95F47 isolated from a coral reef in Pohnpei [96]. It is closely related to TB-toxin from *Talaromyces bacillosporus*, where the carboxy group is bound as a hexahydrophthalimide [97].

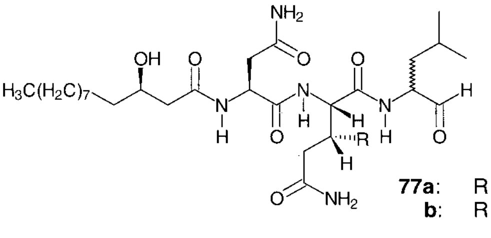
Fungi isolated from tunicates are rare. Recently four new pigments from *Pithomyces sp.* separated from the Indo-Pacific tunicate *Oxycorynia fascicularis* were isolated and named pitholides A–D (**76a–76d**) [98]. Their azaphilone chromophor resembles that of rotiorin [99], bulgarialactone C [100], and that of *Monascus* pigments [101].

Fungi from Marine Fish and Crab

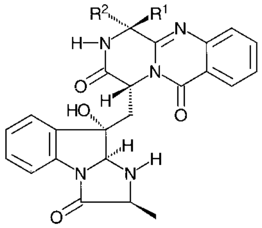
The most productive marine ecosystems are based to a great extent upon detritus, formed by the decay of sea grasses, salt marsh vegetation and mangroves. A diverse flora of obligate and facultative marine fungi is associated with each of these higher plants. The subtle nutritional relationship of numerous marine animals to these decay fungi and other heterotropic microorganisms is well illustrated in the joint study of a red mangrove (*Rizophora mangle*) ecosystem conducted by Heald and Odum [102, 103]. They showed that fishes, molluscs, and arthropods ingest large quantities of decaying mangrove leaves, but digest only the adsorbed micro flora rather than the ligno-cellulosic leaf particles. In this connection, the origin of marine fungi associated with the gasterointestine of marine fishes and crabs has to be discussed under a new perspective. Also the significance of microbial epibionts on marine crustaceans and other invertebrates is not well understood [104].

Two lipophilic cytotoxic tripeptides, fellutamide A (**77a**) and B (**77b**) were isolated from *Penicillium fellutanum* Biourge, a fungus separated from the gastrointestinal tract of the marine fish *Apogon endekataenia* Bleeker (kosuji-ishimochi in Japanese) collected off Manazuru beach, Kanagawa Japan [105], and also from terrestrial sources. Fellutamide structures have been determined by spectral analysis. These metabolites showed potent cytotoxicity against murine leukaemia cells and human epidermoid carcinoma, P388, with IC_{50} 0.2 and 0.1 μg/ml respectively and L1210 IC_{50} 0.8 and 0.7 μg/ml respectively; against KB cells, IC_{50} was 0.5 and 0.7 μg/ml *in vitro*.

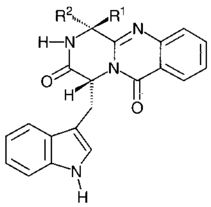
Fumiquinazolines A (**78a**), B (**78b**), C (**80**), D (**81**), E (**78c**), F (**79a**), and G (**79b**) were isolated from the mycelium of the fungus *Aspergillus fumigatus* which co-existed in the salt water fish *Pseudolabrus japonicus*. The content of the gastrointestinal tract was applied onto the surface of nutrient agar layered in a petri dish. Serial transfers of one of the resulting colonies provided a pure strain of *A. fumigatus*. The structures of its metabolites were determined by spectroscopic and X-ray diffraction analyses [106]. Biogenetically, these molecules are tri- or tetrapeptides derived from anthranilic acid, tryptophane and alanine. The fumiquinazolines must therefore be derived from *D*-tryptophane. Fumiquinazolines A-G exhibited moderate cytotoxicities (ED_{50} 6.1, 16.0, 52.0, 13.5, 13.8, 14.6, and 17.7 μg/ml respectively).

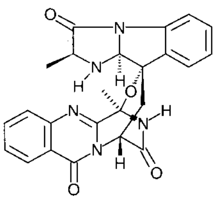


77a: R = OH
b: R = H



78a–c	R¹	R²
a	Me	H
b	H	Me
c	Me	OMe





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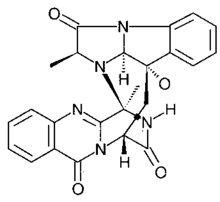


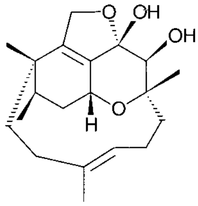
81

79a–c	R¹	R²
a	Me	H
b	H	Me
c	*i*-Pr	H

Terrestrial microorganisms *A. clavatus* and *A. fumigatus* are known to produce the structurally related tryptoquivalines, but these were not detected in the marine variety of *A. fumigatus*. Fiscalin B (**79c**) from the terrestrial fungus *Neosartorya fischeri* [107] is related to fumiquinazoline F (**79a**) except for the substitution of a methyl group at C1 by an isopropyl group. The fiscalins inhibit the binding of substance P (SP) to intact human U-373 MG cells and therefore this type of compounds might deliver novel analgetic or anti-inflammatory agents [107].

Aureobasidium pullulans isolated from the intestine of the marine fish *Hexagrammos otakii*, produced an extracellular malic acid containing polysaccharide. It was homogenous in both ultracentrifugal and electrophoretic analyses and was composed of glucose and malic acid in a molar ratio of 1:1 [108].

The occurrence of microbial epibionts on marine crustaceans and other invertebrates has been documented repeatedly, but the ecological context and significance of these relationships are still not fully understood [109]. Only a few of these life communities have been chemically investigated so far. Among the pharmacologically more interesting compounds isolated from marine fungi are the phomactins A (**82**) [110], B (**83**), B_1 (**84**), B_2 (**85**) [111], C (**86a**), D (**87**) [112] and E-G [113] (**86b**, **88**, **89**), reported by researchers of the Sankyo group, Japan, as a new type of specific and potent platelet activating factor antagonists. The compounds were separated from the culture broth of a marine deuteromycete *Phoma sp.* which was originally isolated from the shell of a crab which turned black. Hence this phenomenon was commonly termed "the black mat syndrome". The crab (*Chionoecetes opilio*) was collected off the coast of Fukui prefecture Japan. The strain *Phoma sp.* grew 20 mm in diameter in 7 days and 38 mm in 14 days on oatmeal agar at 25 °C as colonies with a velvet appearance and greenish grey colour. On oatmeal agar prepared with artificial sea water, it formed pycnidia in which conidia were produced. Fermentation was carried out at 23 °C for 12 days in two 600 litres tanks, and the culture filtrate was extracted with ethyl acetate. Platelet Activating Factor (PAF, 1-*O*-alkyl-[(2*R*)-acetyl-glyceryl]-3-phosphoryl choline) assay-directed purification of the extracts on silica gel and reverse phase chromatography gave phomactins. The structure of these



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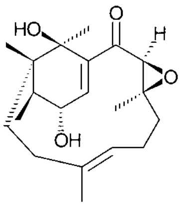

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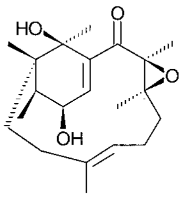

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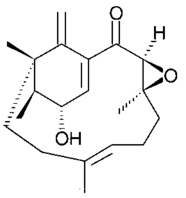

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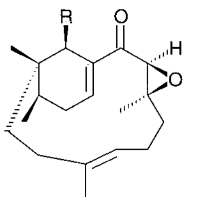
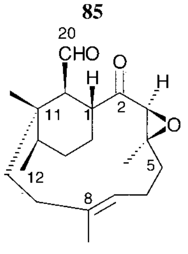


86a: R = CHO
b: R = OH



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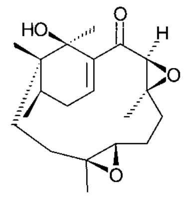

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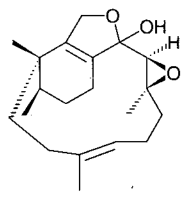

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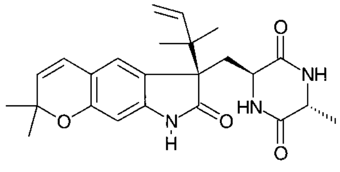

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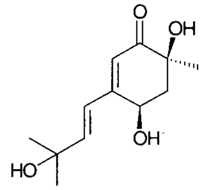


91

compounds was determined by combined spectral methods, absolute stereochemistry by the advanced mosher's method and circular dichroism. These diterpenoids are similar to three compounds isolated from another *Phoma sp.* separated from leaf litter [114], but don't have similarities to other metabolites.

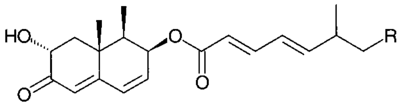
Phomactin D (**87**) was identified as the most potent PAF antagonist in the phomactin series with inhibition of platelet aggregation at IC_{50} 0.80 µM, inhibition of binding at IC_{50} 0.12 µM. The other compounds antagonised the PAF action at higher concentrations, but all seem to act in a unprecedented way. In continuing investigations, the same group later reported structure activity relationships of phomactin derivatives [115]. Enhancing the lipophilicity at C-7/8 by acetoxy or (methoxycarbonyl)oxy residues, a 3-isoxazolyloxy residue at C-20 and the 2-β-OH configuration at C-2 instead of carbonyl all increased the inhibitory activity over that of the lead compound phomactin D (**87**).

In these cases, crab shells seem not only to act as a solid support for surface-populating organisms, but may be a source of activating factors and special nutrient components. Fenical has found that many marine bacteria and fungi do not grow or even survive on terrestrial nutrient broths and require specially adapted compositions: The unique antibiotically active fungal metabolite copiosamide (**90**) *e.g.* was formed only on a medium containing 5 g pepton, 5 g yeast extract, 10 g glucose, and 2 g crab meal per litre [116]. Under similar conditions, Fenical isolated the cytotoxic (HCT-116, ED_{50} = 1.6 µg/ml) longicaulenone (**91**) from an *Acremonium* sp. CNC-457.

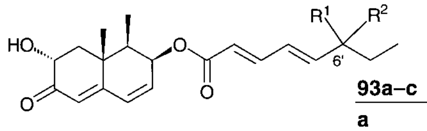
Miscellaneous

Investigating extracts from cultures of the marine deuteromycete *Dendryphiella salina* (Sutherland), Pietra and co-workers [117] reported the isolation of dendryphiellin A (**92a**), the first member of a series of unprecedented tris-*nor*-sesquiterpenoids, esterified with branched C9 carboxylic acids. The minor metabolites dendryphiellin B – D (**93a**–**93c**) vary only in the side chains. Dendryphiellins A – D are tris-*nor*-eremophilanes, where the isopropyl group at C7 is replaced by an OH group. The fully intact sesquiterpenoid ester dendryphiellin E (**94a**) was proving this classification. Additionally, dendryphiellin F (**94b**) & G (**95**) and two freely occurring dendryphiellic acids A (**96a**) and B (**97**) were characterised, and **94b** was realised as an artefact [118]. This fungus also produced 2,6-dimethoxybenzoquinone, a quinone widespread in woody tissues [119].

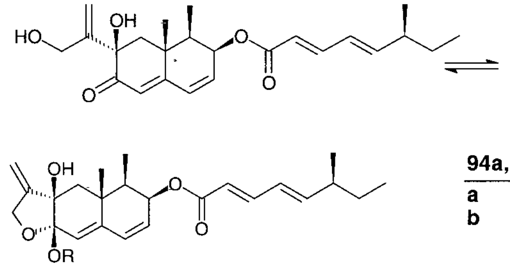
Truncated eremophilane skeletons are unprecedented in fungi, but have been isolated from the terrestrial



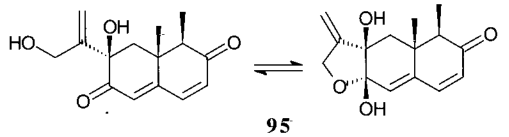
92a: R = CH_2OH
b: R = COOH



93a–c	R^1	R^2
a	OH	CH_3
b	H	CH_3 (6'S)
c	H	CH_2OH (6'R)



94a,b	R
a	H
b	Et



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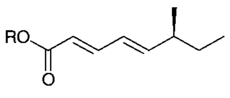

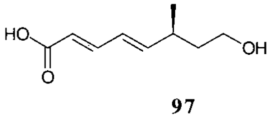

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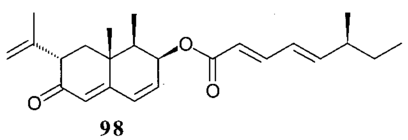
96a,b	R
a	H
b	$CH_3CH(OH)CH_2OH$



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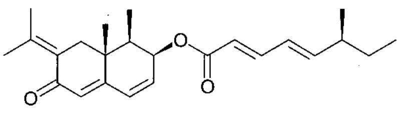
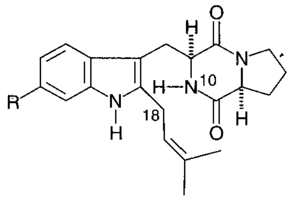


99

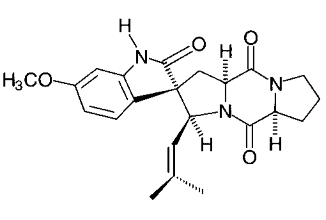
herb *Senecio humillimus* (Compositae) and from the Chinese plant *Nardostachys chenensis* (Valerianaceae). Intact eremophilanes of marine origin are also rare, but have been found in the soft coral *Lamnalia africana* collected around the western Caroline islands. An example for an intact fungal eremophilane is bipolal (CHO instead of CH_2OH in **94a**) isolated from the terrestrial fungus *Bipolaris sp.* [120]; it is also related to petasol from *Drechslera gigantea* [121].

Continuing studies of extracts of *D. salina*, later the same group reported the isolation of novel significant metabolites: the glyceryl ester **96b** of dendryphiellic acid A, two eremophilanes [dendryphiellin E1 (**98**) and E2 (**99**)] and a tri-*nor*-eremophilane (dendryphiellin A1, **92b**) besides the fluorescent steroid (22*E*)-ergosta-4,6,8 (14),22-tetraen-3-one which was already isolated from terrestrial basidiomycetes [122]. The ester chain is part of saponins of the terrestrial plant *Acer negundo*, and is of a structural type that has never been encountered in fungi.

Tryprostatins A (**100a**) and B (**100b**) have been isolated as secondary metabolites of the marine *Aspergillus fumigatus* BM939 [123]. They completely inhibit cell cycle progression of tsFT210 cells in the G2/M phase at a final concentration of 12.5 µg/ml for tryprostatin B and 50 µg/ml for tryprostatin A. Both tryprostatins contain a 2-isoprenyltryptophane moiety and a proline residue, the latter of which is located in the dioxopiperazine unit. Tryprostatins are structurally related to fumitremorgins, but ring C has been cleaved between the positions designated C18 and N10. Large scale fermentation of the tryprostatins producing fungus also afforded two



100a: R = OMe
b: R = H



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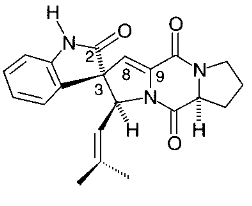

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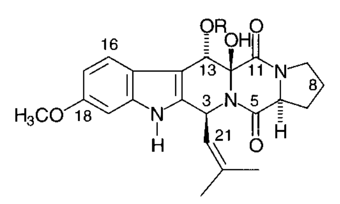
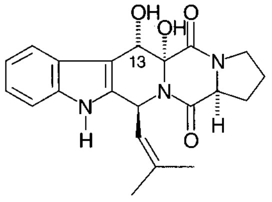


103a: R = H
b: R = CH_3



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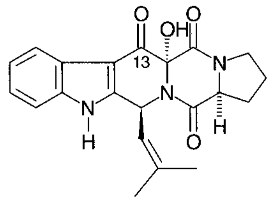

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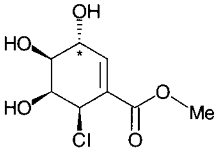
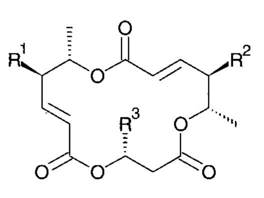
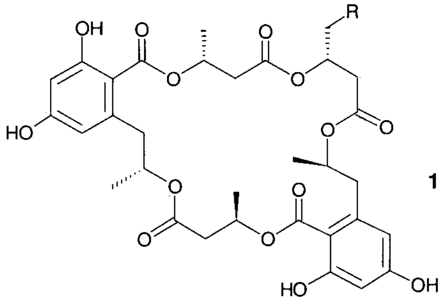


106a:
b: opposite config. at*

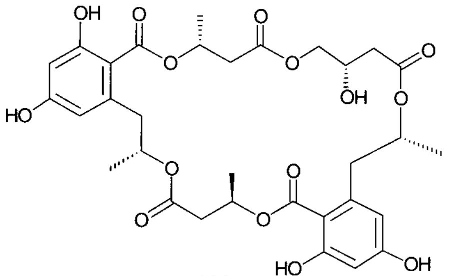


107a–d	R^1	R^2	R^3
a	OH	OH	Me
b*	H	OH	Me
c*	OH	H	Me
d*	OH	H	CH_2COCH_3

* stereostructure unknown



108a: R = OH
b: R = H



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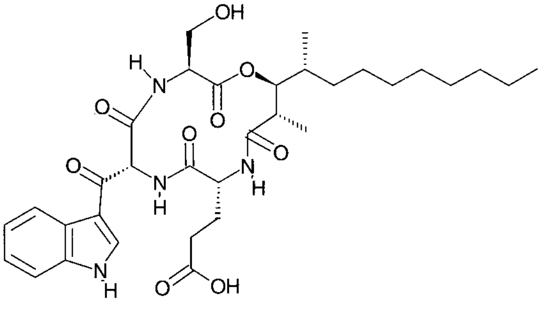


110

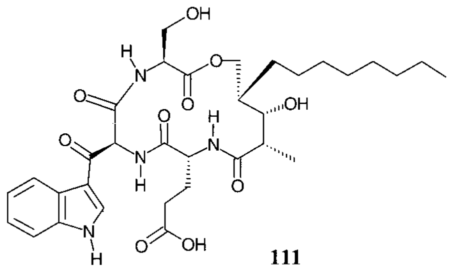
novel dioxopiperazine alkaloids, spirotryprostatins A (**101**) and B (**102**) [124]. Spirotryprostatins have a unique structural skeleton with a spiro ring system composed from a γ-lactam fused to a benzene ring and a five-membered hetero ring fused to a dioxopiperazine moiety, which are composed from a tryptophane unit, a proline residue and an isoprenyl group. The tryptophane unit has been modified by dihydrogenation at C2/C3 and further oxidation at C2 position in both spirostatins and modified further by dehydrogenation at C8/C9 positions to form an enamine ring in **102**. Spirostatins are the first examples of a novel class of natural dioxopiperazines with an unique spiro ring skeleton. To the cell cycle progression of tsFT210 cells, **102** exhibited stronger inhibitory activity than **101**.

Also cyclotryprostatins A–D (**103a–105**) are G2/M phase inhibitors of mammalian cell cycle. These derivatives were isolated from the fermentation broth of the same *Aspergillus fumigatus* strain BM939 [125]. They have a pentacyclic ring skeleton involving a 2,5-dioxopiperazine ring, which is composed from a tryptophane unit, a proline residue and an isoprenyl group. Cyclotryprostatin D is unique in carrying a ketocarbonyl at C-13. Cyclotryprostatins A and C (**103a**, **104**) seem to be identical with compounds prepared by Kodato *et al.* during the synthesis of fumitremorgin B [126], a product of a terrestrial *Aspergillus fumigatus* strain.

In contrast to terrestrial habitats, all *marine* surfaces are covered with a dense layer of associated microorganisms, which in some cases are part of the defence mechanisms of the hosting organisms. A *Periconia byssoides* strain isolated from a sea hare (*Aplysia kurodai*) proved to be a rich strain of novel metabolites [127]: Two diastereomeric antitumor-active pericosines A and B (**106a**, **106b**) were isolated together with the macrosphelides E–H (**107a–107d**). The macrosphelides A–D had been described previously as antimicrobially and cytotoxically inactive cell cell adhesion inhibitors from terrestrial *Microsphaeropsis* sp. [128, 129]. Macrosphelides C (**107b**) and D (**107a**), diastereomers of E and F, were recently found also in *Periconia byssoides*, a marine fungus obtained from an *Aplysia* sp. [130].

The macrocyclic polylactone BE-26263 was formed by *Scedosporium apiospermum* and found in a test for estrogen binding inhibitors [131]. This compound was shown to be identical with the terrestrial metabolite BK-223-C (**108b**) which was previously isolated from *Penicillium verruculosum* together with BK-223-A (= NG-012, **108a**) and B (**109**) [132, 133]. BK-223-A – C are nerve growth factor potentiators and are active against plant pathogenic fungi including *Botrytis cinerea*, *Phoma lingam*, *P. betae* and others. Also the metabolites 15G256α and 15G256β from *Hypoxylon oceanicum* LL-15G256 proved to be identical with **108a** and **108b**. Amongst the lipodepsipeptides 15G256γ-ε (**110–112**), compounds also isolated from the latter source, **110** may be identical with arthrichitin, a metabolite with unpublished stereochemistry from the terrestrial fungus *Arthrinium phaeospermum*. The stereo centre of the 3-keto tryptophane moiety is labile, and equilibration occurs in aqueous solution, resulting in a different configuration of **110** and **111/112**. From other terrestrial *Hypoxylon* sp., cytochalasins, butyrolactones, coumarins, diterpenes, naphthalenones, and naphthoquinones have been isolated, but none of them is reported to inhibit cell wall formation of fungi.

Cytochalasans are spirotricyclic branched polyketides isolated from a wide range of terrestrial fungi, and forming a group of more than 50 compounds with antibiotic and strong cytotoxic properties [134]. Most of these metabolites possess carbonyl groups at C20 and C23 which might cyclize with ammonia forming pyrrole moieties.



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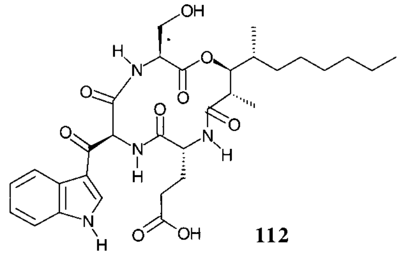

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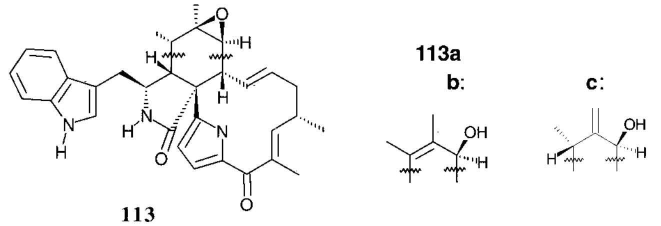

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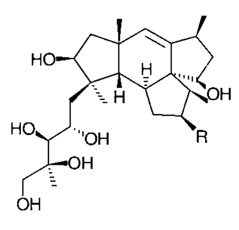
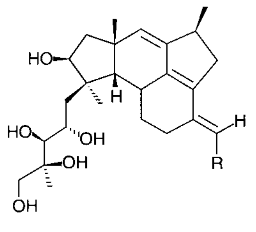
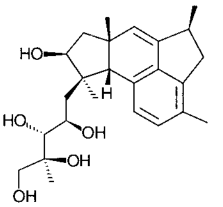




114a: R = H
b: R = OH

115a: R = Br
b: R = Cl



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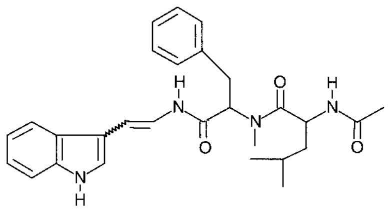
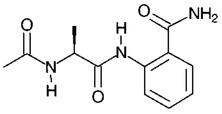


117a: double bond Z
b: double bond E



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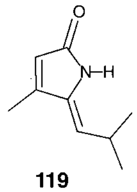

119

Recently, such condensation products of chaetoglobosins C, G, and D, the penochalasins A–C (**113a–c**) have been isolated from a marine *Penicillium* sp. [135].

Most of the very recent structures from marine fungi came from W. Fenical and his group [136]. From the marine *Fusarium heterosporum* CNC 477, a number of unique metabolites was isolated: The cytotoxic mangicols A and B (**114a**,**b**) possess a spirotricyclic skeleton which is unique under all natural products, plants included. They seem to be the precursors of neomangicols A–C (**115a**,**b**, **116**) from the same fungus and may be described as hexahydroacenaphthenes and dihydroacenaphthenes, rsp. Also this skeleton had not been found before. On the same occasion [136], Fenical reported the structures **117a**,**b** of aspergillamides A and B, new tryptamine-derived N-acetyl dipeptides with cytotoxic properties.

An interesting dipeptide from acetylalanine and anthranilamide, the antibiotically inactive NI-15501-A (**118**), was isolated from a salt water *Penicillium* sp. [137], and pulchellalactam (**119**), a CD45 protein tyrosine phosphatase inhibitor, was found in *Corollospora pulchella* [138].

Conclusions

Marine fungi produce metabolites with a remarkable variety of structural classes, unconventional chemical structures, and assorted substituent patterns. All of these structural variations pose interesting biomedical questions that promise to hold the attention of chemists for some time to come. Pietra and co-workers [139] cultivated 1500 marine fungi and 1450 terrestrial fungal strains for evaluation of their antimicrobial activity. A range of different nutrient media was used in order to achieve best growth and metabolite production. More antimicrobially active strains (n = 25) were found among marine than terrestrial fungi (n = 16). Only three of the metabolites isolated from terrestrial strains turned out to be new compounds, compared with 15 new compounds from marine strains. Biological activity of marine metabolites was mostly directed against fungi such as *Candida albicans* or *Botrytis cinerea*, while terrestrial fungal metabolites were active predominantly against Gram-negative bacteria.

Although most metabolites from marine fungi are closely related to constituents of their terrestrial relatives, there are some unique examples indicating that marine fungi may possess biosynthetic capabilities which differ in some respects from those of terrestrial fungi, **12**, **21**, **22**, **27**, **29a**,**b**, **30–33**, **45–49**, the phomac-tins **82–89**, **90**, **114**, and **115** being the most striking examples. Based on these findings and literature survey [140], we believe that marine fungi are rapidly becoming recognised as potentially useful sources of compounds with biomedical interest.

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Address for correspondence:
Prof. Dr. Hartmut Laatsch
Universität Göttingen, Institut für Organische Chemie
Tammannstraße 2
D-37077 Göttingen
Fax +49(0)551-399660
e-mail HLAATSC@gwdg.de